SIGMATROPIC REARRANGEMENTS OF DIVINYLCYCLOPROPANES AND CYCLIZATIONS INVOLVING β-ELIMINATION OF SULFONYL RADICALS

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Sigmatropic Rearrangements of Divinylcyclopropanes and Cyclizations Involving β-Eliminations of Sulfonyl Radicals

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The first chapter of this dissertation describes the synthesis and reactions of a family of 1,1-divinylcyclopropanes, including the discovery and studies of several sigmatropic rearrangement cascades. Also discussed is the radical [3+2] cyclization of 1,1-divinylcyclopropanes with the potential for memory of chirality.

The second chapter deals with the elimination of sulfonyl radicals during radical cyclizations of ene-sulfonamides. A family of polycyclic imines and a family of oxindole products were synthesized from polycyclic ene-sulfonamide precursors.

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LIST OF ABBREVIATIONS

Ac	acetyl
AIBN	2,2'-azobis(2-methylpropionitrile) (azobisisobutyronitrile)
BDE	bond dissociation energy
Bn	benzyl
Boc	*tert*-butyloxylcarbonyl
BuLi	*n*-butyllithium
calcd	calculated
CE	Cope-ene
COSY	correlation spectroscopy
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*-dicyclohexylcarbodiimide
DCM	dichloromethane
DIBAL-H	diisobutylaluminum hydride
DIEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMSO	dimethyl sulfoxide
DVCP	divinylcyclopropane
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	enantiomeric excess
er	enantiomeric ratio
EI	electron impact
ESI	electrospray ionization
EtOAc	ethyl acetate
equiv	equivalent(s)
GC	gas chromatography
h	hour
HMDS	bis(trimethylsilyl)amide (hexamethyldisilazide)
HMQC	heteronulcear multiple quantum coherence
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
IR	infrared spectroscopy
LDA	lithium disopropylamine
LRMS	low resolution mass spectrometry
LTMP	lithium tetramethylpiperadide
*m*CPBA	*meta*-chloroperbenzoic acid
min	minute
MOM	methoxymethyl

mp	melting point
MW	molecular weight
NMR	nuclear magnetic resonance
Py	pyridine
ppm	parts per million
rt	room temperature
TBAF	tetrabutylammonium fluoride
Tf	trifluoromethylsulfonyl (triflyl)
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TMS	trimethylsilyl
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
Ts	4-methylphenylsulfonyl (tosyl)
UV	ultraviolet
VCP-CP	vinylcyclopropane-cyclopentene

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1.0 SIGMATROPIC REARRANGEMENTS OF DIVINYLCYCLOPROPANES

1.1 INTRODUCTION

1.1.1 Reactions of vinylcyclopropanes

Vinylcyclopropanes are an important class of compounds that undergo a variety of useful transformations.[1-4] The most common reaction of vinylcyclopropanes is isomerization to cyclopentenes, called the vinylcyclopropane-cyclopentene (VCP-CP) rearrangement.[5-8] The parent VCP-CP rearrangement, shown in Figure 1-1, was independently reported by Vogel and by Overberger in 1960 by flash vacuum pyrolysis at 510 °C of vinylcyclopropane **1.1** to give cyclopentene **1.2**.[9-10]

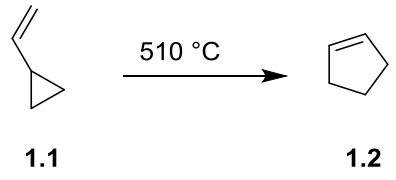


Figure 1-1 The parent vinylcyclopropane-cyclopentene rearrangement

The general features of the VCP-CP rearrangement are 1) thermal activation that requires high temperatures, over 500 °C for some substrates; 2) predictable cyclopropane C–C bond cleavage, dependant on substituents of initial vinylcyclopropane;[11] 3) high regio- and stereo-

selectivity possible in many cases;[12-13] 4) high compatibility with thermally stable functional groups; and 5) substrate-dependant but predictable competing reaction pathways are possible.

The VCP-CP rearrangement usually proceeds by cleavage of the most substituted cyclopropane C–C bond with substrate-dependant selectivity in the recombination to give cyclopentenes. Figure 1-2 shows the thermal isomerization of two substrates: one with moderate product regioselectivity and one with high product regioselectivity. Enantio-pure vinylcyclopropane **(+)-1.3** was thermolyzed at 297 °C to give a 65:8:22:5 mixture of cyclopentene enantiomers of **1.4** and **1.5** shown in Figure 1-2.[12] This represents a modest diastereospecificity shown by the 2.7:1 ratio of **1.4**:**1.5** but a high enantiospecificity shown by the 8.1:1 ratio of **(–)-1.4**:**(+)-1.4**. This example is representative of isomerizations that can give multiple regio- and stereo-isomers. In contrast, thermal isomerization of *trans*-vinylcyclopropane **1.6** gave cyclopentene **1.7** with no trace of cyclopentene **1.8**. This example is representative of the high regioselectivity often seen in isomerization of di-substituted vinylcyclopropanes with conjugating groups like phenyl.

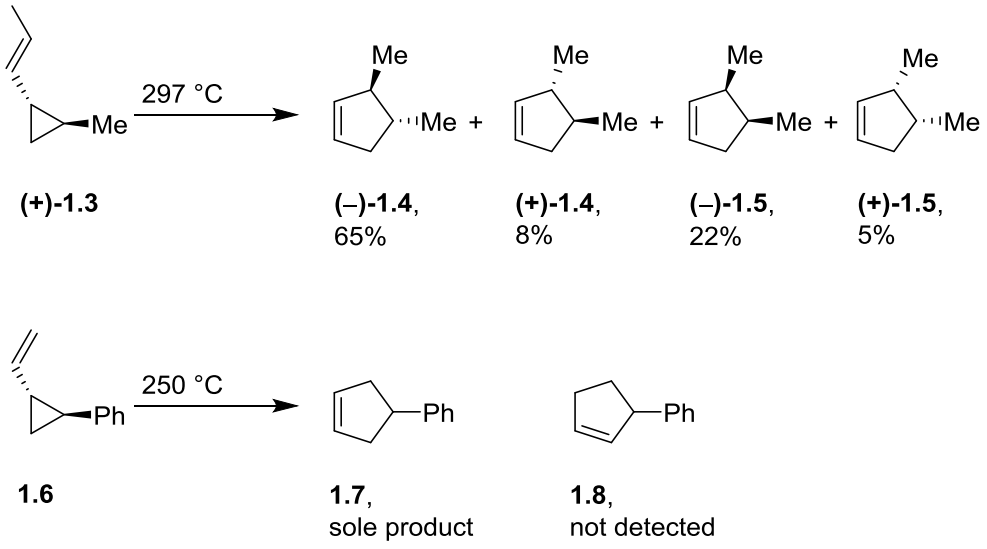
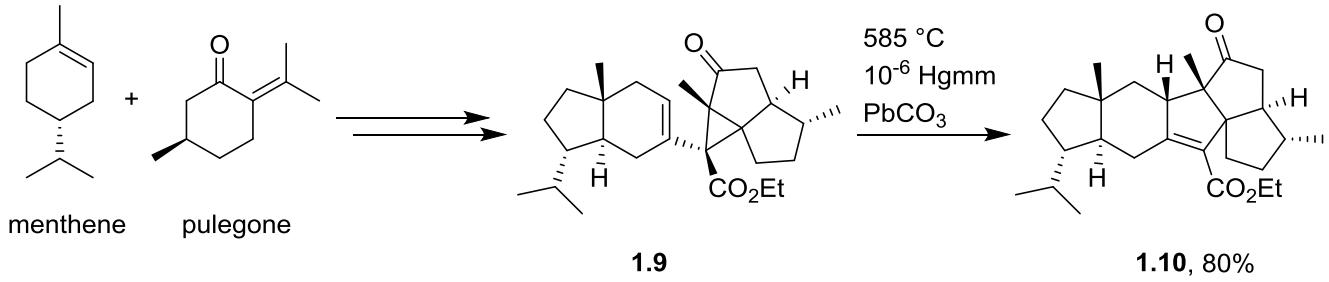


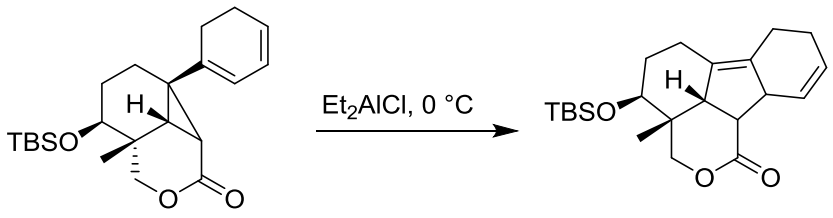
Figure 1-2 Selectivity in the VCP-CP rearrangement

Because it represents a general route to substituted cyclopentenes, the VCP-CP rearrangement has been used as a key transformation in the synthesis of natural products; a typical example is shown in Scheme 1-1.[14] Enantio-pure vinylcyclopropane **1.9** was prepared by through 11 total steps from pulegone and menthene. Distilling vinylcyclopropane **1.9** at 585 °C over vycor glass, that had been treated with lead (II) carbonate, produced angular triquinane derivative **1.10** in 80% yield. This intermediate was transformed in three additional steps to (–)-retigeranic acid.



Scheme 1-1 Formation of triquinane 1.10 by VCP-CP rearrangement

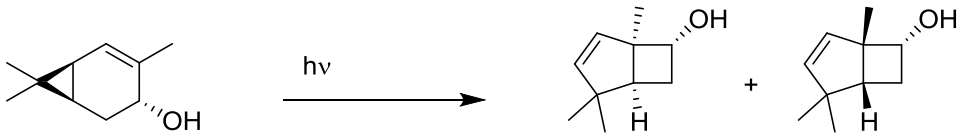
In addition to thermolysis, the VCP-CP rearrangement of suitable substrates can be achieved by Lewis acids,[15] transition metal catalysts,[16-20] and photolysis.[21-25] An example of the Lewis acid-assisted VCP-CP rearrangement is shown in Scheme 1-2; addition of diethylaluminum chloride to vinylcyclopropane **1.11** at 0 ℃ produced cyclopentene **1.12** in 80% isolated yield.



1.11 **1.12** 80%

Scheme 1-2 Lewis acid mediated VCP-CP rearrangement of lactone 1.11

An example of the photolytic VCP-CP rearrangement is shown in Scheme 1-3. UV irradiation of enantio-enriched cyclopropane **1.13** in petroleum ether with toluene as a photosensitizer afforded cyclopentene **1.14** in 53% recovered along with 22% of diastereomer **1.15**.[26] The examples shown in Scheme 1-2 and Scheme 1-3 show that suitable substrates are able to undergo the VCP-CP rearrangement without the use of high temperatures.



1.13 **1.14** 53% **1.15** 22%

Scheme 1-3 Photo-assisted VCP-CP rearrangement

The mechanism of the thermal VCP-CP isomerization generally proceeds by homolytic ring opening of a substituted vinylcyclopropane **1.16** to give the most substituted diradical intermediate **1.16**; recombination gives the more thermodynamically stable cyclopentene **1.17**, constituting a formal [1,3]-sigmatropic rearrangement.[6, 11, 27] Whether the isomerization occurs by a two-step non-concerted mechanism or one-step concerted mechanism has been debated; the high enantiospecificity in the transformation of vinylcyclopropane **1.3** to cyclopentene **1.4** shown

in Scheme 1-2 suggests that the transformation does not have a long-lived diradical intermediate. However Woodward and Hoffman suggested a two step process with a diradical intermediate based on orbital symmetry arguments: if the isomerization of vinylcyclopropane **1.16** shown in Figure 1-3 is concerted, then the *antarafacial*, *retention* (*ar*) and *suprafacial*, *inversion* (*si*) pathways are the symmetry-allowed pathways. However, Figure 1-3 shows that the products of *suprafacial*, *retention* (*si*) and *antarafacial*, *inversion* pathways are major products of thermal isomerization of vinylcyclopropane **1.16**. That the symmetry-forbidden pathways are major pathways suggests a non-concerted process.[27] The observations of moderate enantiospecificity along with the observation of production of symmetry-forbidden products have been combined to suggest a "not-obviously-concerted reaction involving rotational preference within the framework of continuous diradical" pathway."[11]

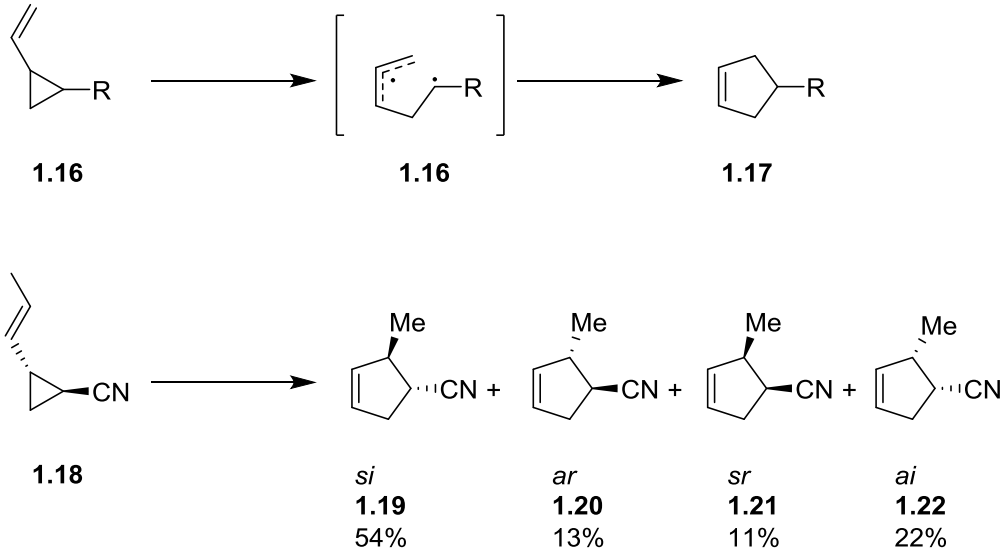


Figure 1-3 Evidence for a non-concerted diradical process

Thermolysis of vinylcyclopropanes can also produce non-cyclopentene products by competing pathways, shown in Figure 1-4. Equation 1 in Figure 1-4 shows the conversion of the

parent vinylcyclopropane **1.1** to cyclopentene **1.2** and 1,4-pentadiene **1.23** in 95% and 5% respectively.[10] Linear diene **1.23** was proposed to form by a 1,2-hydrogen shift of the diradical formed during pyrolysis. Vinylcyclopropylmethyl compounds with an α-hydrogen *cis* to the vinyl group can undergo a [1,5]-sigmatropic shift, called the retro-ene reaction, to give a straight chain 1,4-diene.[28-30] A retro-ene reaction is shown in equation 2 of Figure 1-4; vinylcyclopropane **1.24** was transformed into 1,4-hexadiene **(1*E*,4*Z*)-1.25** as a single alkene isomer by thermolysis at 164 °C.[31]

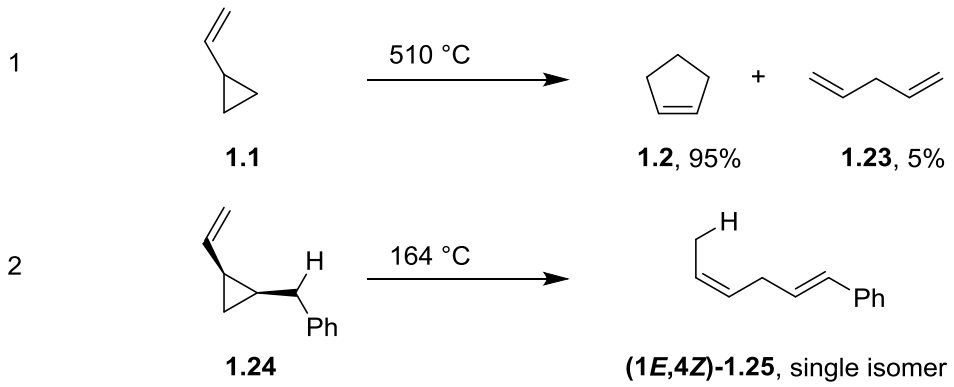


Figure 1-4 The parent retro-ene reaction and a substituted retro-ene reaction

1.1.2 Reactions of divinylcyclopropanes

Like vinylcyclopropanes, divinylcyclopropanes are useful synthetic intermediates. Divinylcyclopropanes can be *vicinal* 1,2-divinylcyclopropanes, which can be *cis* or *trans*; or they can be *geminal*, that is 1,1-divinylcyclopropanes. The typical reaction of 1,2-divinylcyclopropanes is a thermal Cope rearrangement to give a 1,4-cyclohepta-diene,.[32-37] The parent ring-opening Cope rearrangement is shown in Figure 1-4; *cis*-1,2-divinylcycloropane **1.26**

was prepared quickly at 5 °C and isolated at –40 °C.[38] The compound was persistent at –20 °C but at 0 °C underwent conversion to 1,4-cycloheptadiene **1.27**. The corresponding *trans*-1,2-divinylcyclopropane **1.28** required heating to 170 °C for conversion to cycloheptadiene **1.27** to occur.[39] It was proposed that at this temperature the cyclopropyl ring of **1.28** undergoes a reversible ring opening-ring closing process to give *cis* isomer **1.26** which rapidly forms cycloheptadiene **1.27**.[40-42]

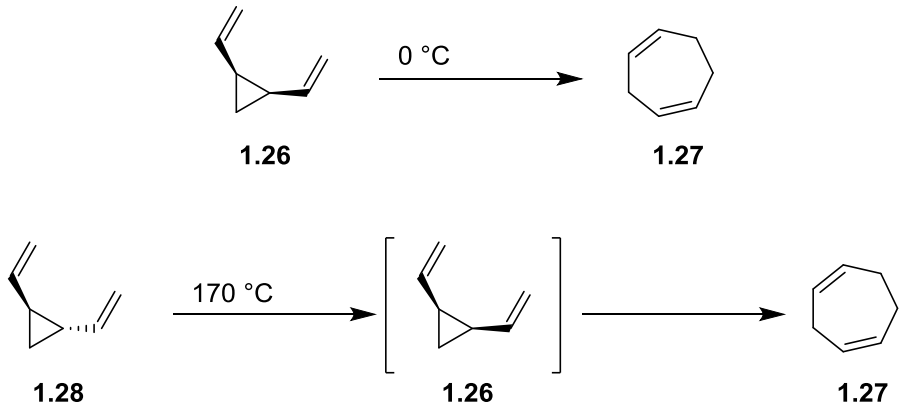


Figure 1-5 The parent divinylcyclopropane-cycloheptene rearrangement

Seven-membered rings can be difficult to access[43-45] and represent pharmaceutically interesting molecular scaffolds;[46-48] the 1,2-divinylcyclopropyl Cope rearrangement represents a useful route to cycloheptenes. The Stolz group reported in 2003 that vinylcyclopropyl diazoketones underwent a cascade Wolff-Cope rearrangement by sonication in the presence of silver benzoate and triethylamine in good yields.[49] Figure 1-4 shows the treatment of diazoketone **1.28** with AgOBz and NEt_3 to give cycloheptadienone **1.30** in 95% as a single diastereomer. The rearrangement was proposed to go through ketene intermediate **1.29**, which underwent a ring-opening Cope rearrangement to give cycloheptadiene **1.30** as a single isomer.

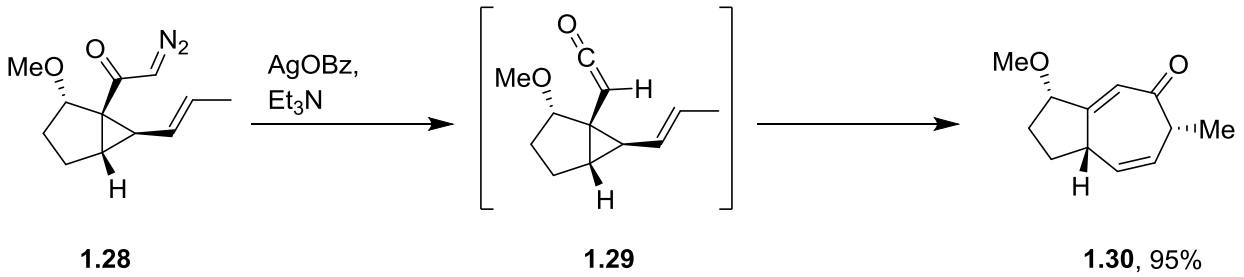


Figure 1-6 Cascade Wolff-cyclopropyl Cope rearrangement

In an example involving a ring-opening Cope rearrangement of a phenylvinylcyclopropane, the Stephenson group reported an iridium catalyzed cascade reaction of cyclopropyl bromide **1.31** to give cycloheptene **1.33** in 69% yield.[50] Diphenylcyclopropyl bromide **1.31** was irradiated with visible light in the presence of $Ir(ppy)_2(dtbbpy)PF_6$ and Et_3N causing reductive 5-*exo* cyclization to generate the vinylcyclopropane intermediate **1.32**. A Cope rearrangement followed by [1,3]-hydrogen transfer provided tricycle **1.33** in 69% isolated yield. Thus, the ring-opening Cope rearrangement may also occur on phenyl rings.

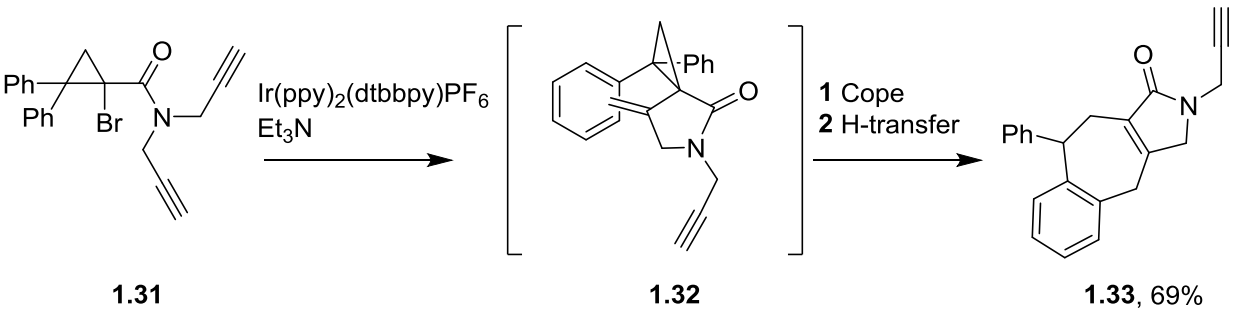


Figure 1-7 Cascade cyclization-Cope rearrangement of cyclopropyl bromide 1.31

In contrast to their *vicinal* counterparts, 1,1-divinylcyclopropanes are less studied, with only few preparations and reactions reported in the literature. The parent *gem*-divinylcyclopropane **1.34** has been made: by reduction and elimination of cyclopropanediacetic

acid **1.35**[51-52] and by tosyl hydrazine mediated reduction-elimination of 1,1-diacetylcyclopropane **1.36**.[53-54] Substituted *gem*-divinylcyclopropanes have few reported syntheses: 9-methylenedispiro[2.2.2.2]dec-4-ene **1.37** was reported as a minor product from fragmentation of azo **1.38**. Divinylcyclopropane **1.39** was obtained from a silver-catalyzed cycloisomerization of 1,6-enyne **1.40**. In an example of a *gem*-divinylcyclopropane with neither vinyl group constrained in a ring, *gem*-divinylcyclopropane carboxylate **1.41** was synthesized by hydrogenation, TEMPO oxidation and methyl Wittig olefination of cyclopropyl dibenzylether **1.42**.[55] Overall, the currently known routes to *vic*-divinylcyclopropanes show limited scope.

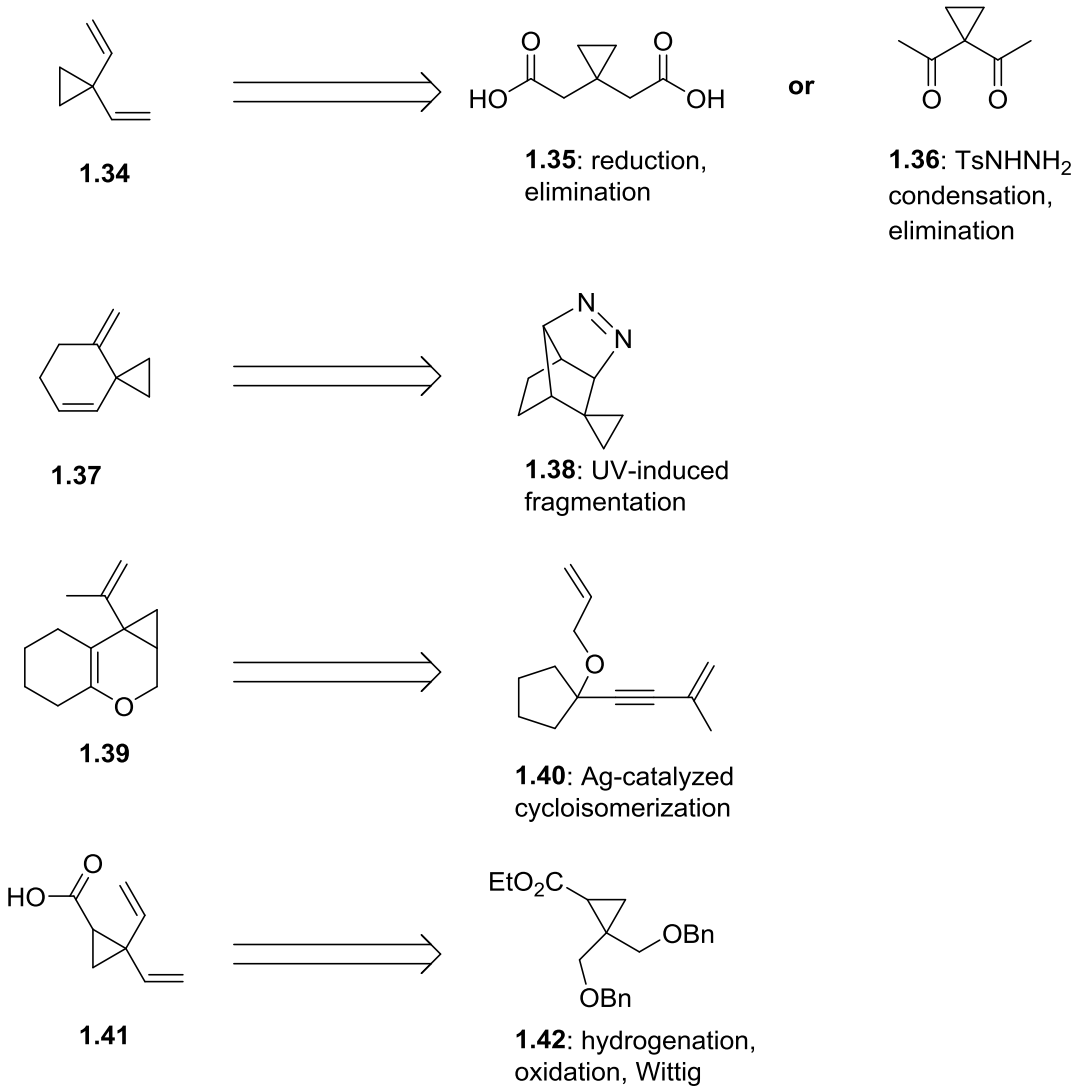
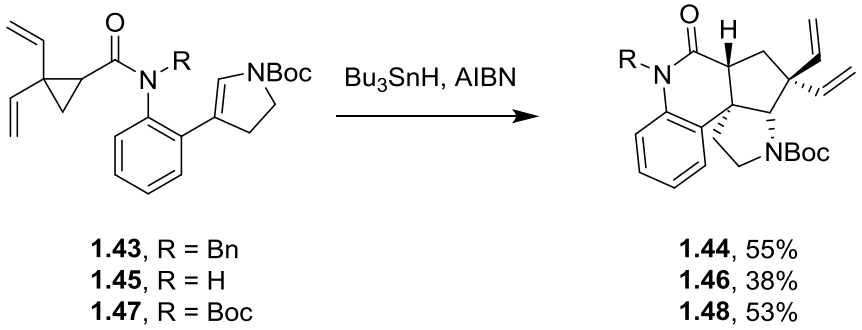


Figure 1-8 Current approaches to *gem*-divinylcyclopropanes

1,1-Divinylcyclopropanes are good substrates for radical [3+2] cyclizations. In 2011 Zhang and Curran showed that the radical [3+2] strategy could be applied to the synthesis of (±)-meloscine.[55] Scheme 1-4 shows the transformation of divinylcyclopropane **1.43** into divinylcyclopentane **1.44** in 55% yield as a single stereoisomer by treatment with tributylstannane and AIBN in refluxing toluene. The removal of the *N*-benzyl group proved to be a roadblock in the synthesis, so the cycloaddition was performed on unprotected amide **1.45** the

bis-Boc-protected analog **1.47** to give analogous N–H and N–Boc tetracycles **1.46** and **1.48** in 38% and 53%, respectively.[56] The synthesis of (±)-meloscine was completed in only 4 additional transformations of the N–H analog **1.46**.



1.43, R = Bn
1.45, R = H
1.47, R = Boc

1.44, 55%
1.46, 38%
1.48, 53%

Scheme 1-4 Radical [3+2] cyclization in the synthesis of (±)-meloscine

1.1.3 Memory of chirality

Memory of chirality was first reported in 1981 by Seebach[57] and later defined as a concept by Fuji to describe the retention of enantiomeric excess in reactions which go through intermediates without point chirality.[58] The chiral information in the starting material is transiently stored in the intermediates as axial[59-61] or planar chirality,[62] or as cyclic structure with sufficiently large barriers to inversion.[63-66] For instance, Fuji reported that asymmetric aryl ketones, prepared in enantio-enriched form, could be treated with base followed by an alkylating reagent to give products with significant enantiomeric excess.[58, 67-68] Figure 1-9 shows the methylation of ketones **1.49** and **1.51** to give α-methyl ketones **1.50** and **1.52** with 66% and 0% *ee* respectively. The enolate intermediates formed do not possess point chirality but are proposed to have transient axial chirality which leads to stereoinversion in the products. The phenyl ring in ketone **1.51** leads to a low barrier of enolate rotation, leading to racemic products.

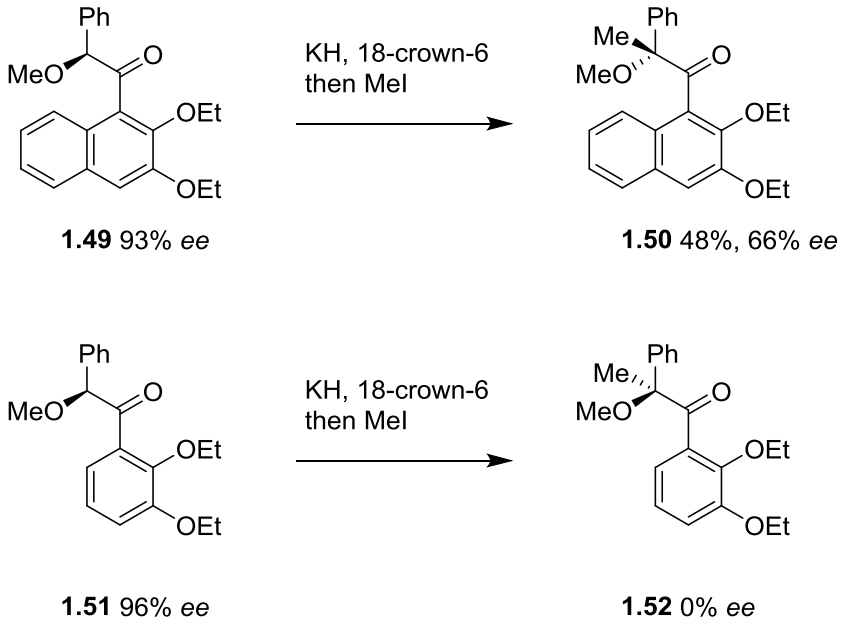


Figure 1-9 Memory of chirality involving axially chiral intermediates

Memory of chirality has been exploited during radical cyclization processes. Cyclodecenol **1.53** was prepared with 86% *ee*, treated with oxalyl chloride and *N*-hydroxy pyridine thione to generate a mixed oxalate *in situ*. When irradiated with UV light, this produced bicyclo[5.3.0]decane **1.54** in 51% yield and 68% *ee*. The key intermediate proposed was radical **1.55**, which underwent 5-*exo*-trig cyclization to give chiral radical **1.56** faster than ring inversion to a racemic radical, shown in Figure 1-10.[65]

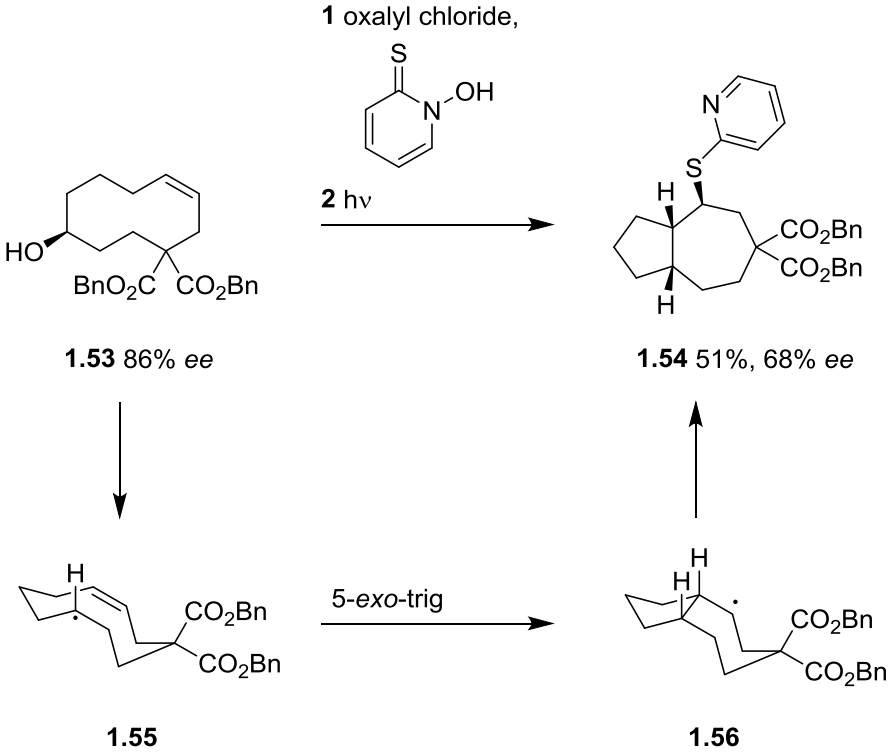


Figure 1-10 Memory of chirality in an intramolecular radical cyclization

Memory of chirality can also occur in reactions with multiple intermediates, such as the radical rebound cascade cyclizations. Scheme 1-5 shows the formation of pyrrolidone **1.58** from allyl amide **1.57** in modest 18% yield with an *ee* of 56% in the product.[61] The reaction is likely to proceed by bromide abstraction by tributyltin radical to give vinyl radical **1.59** followed by [1,5]-hydrogen transfer to give α-acyl radical **1.60**. 5-*exo*-trig cyclization of **1.60** gives methyl radical **1.61** which ultimately abstracts hydrogen from tributylstannane to give the product **1.58**.

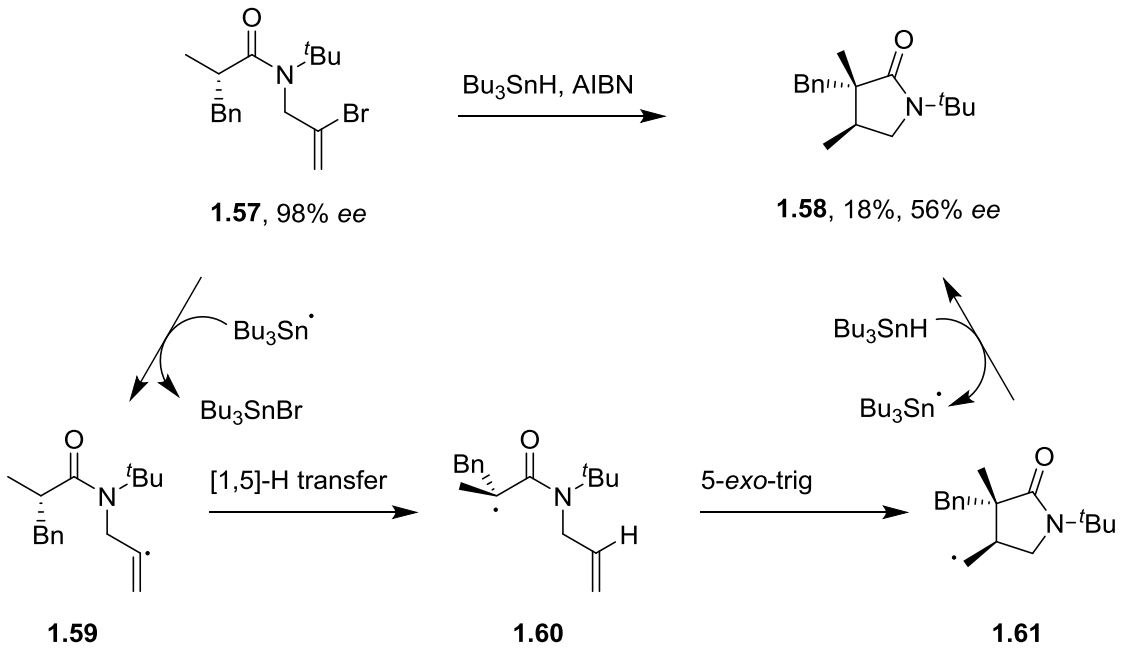


Figure 1-11 Memory of chirality in a radical rebound cyclization

1.2 RESULTS AND DISCUSSION

1.2.1 Synthesis of divinylcyclopropane amide 1.62

Inspired by the potential for memory of chirality in alkaloid synthesis, we set an initial goal to test the memory of chirality in radical [3+2] cyclizations of *gem*-divinylcyclopropanes. Tertiary radical amides may be more prone to cyclize with memory than secondary radical amides. Figure 1-12 shows a secondary α-acyl chiral radical amide **1.63** and a tertiary α-acyl chiral radical amide **1.66**. The secondary radical **1.63** may quickly rotate to give a conjugation stabilized achiral radical intermediate **1.64**; rotation back to a cyclization-competent conformation leads to racemization of radical **1.63** and thus racemic cyclized radical **1.62**. The

tertiary radical **1.66** experiences steric strain meaning **1.67** may rotate more slowly and thus be more likely to cyclize to intermediate **1.65** with memory of chirality.

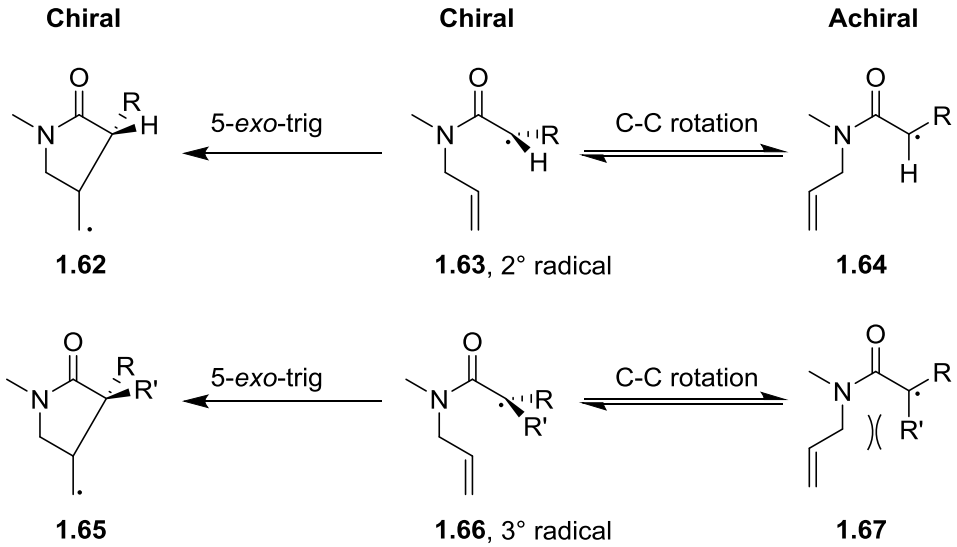


Figure 1-12 Memory of chirality in 2° and 3° radical cyclizations

Because tertiary radicals may be more likely to lead to memory of chirality, we chose amide **1.62** as our initial target to study radical cascade cyclizations, shown in Figure 1-13. To access this target we chose a strategy based on copper mediated S_N2' displacement of a phosphate leaving group.[69] Allyl phosphate **1.63** will be made by cyclopropanation of allenyl phosphate **1.64** with diazoacetate **1.65**.[70]

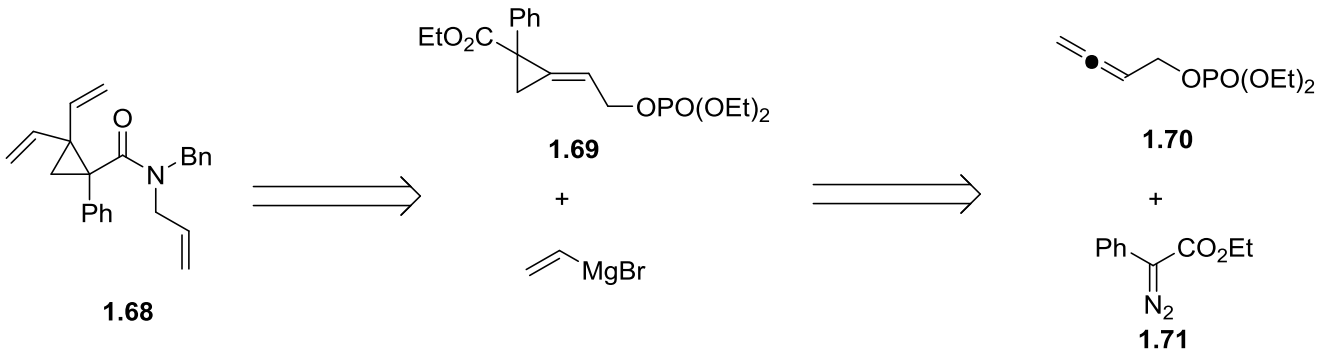
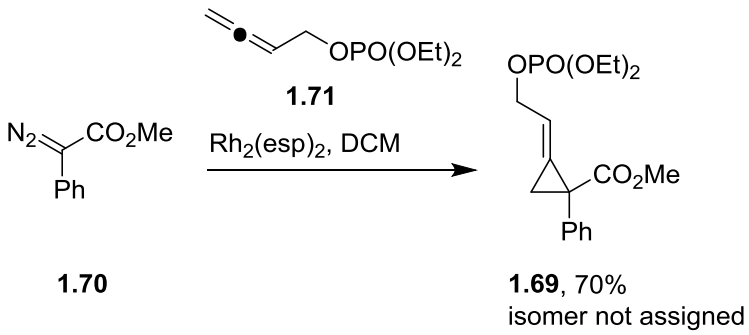


Figure 1-13 Retrosynthetic plan for amide 1.68

The planned allene cyclopropanation represents a synthetic challenge because the measured relative rates of cyclopropanations with metal carbenoids suggests only modest regioselectivity in the cyclopropanation of dienes.[71] However, work by Davies suggested that chemoselective cyclopropanation of the external bond of an allene could be achieved with rhodium catalysis.[70] The cyclopropanation of allene phosphate **1.70**[72] was achieved with ethyl phenyldiazoacetate **1.71**[73] and $Rh_2(esp)_2$ to give methylenecyclopropane **1.69** in 70% yield as a single unassigned alkene isomer after chromatography, shown in Scheme 1-5.



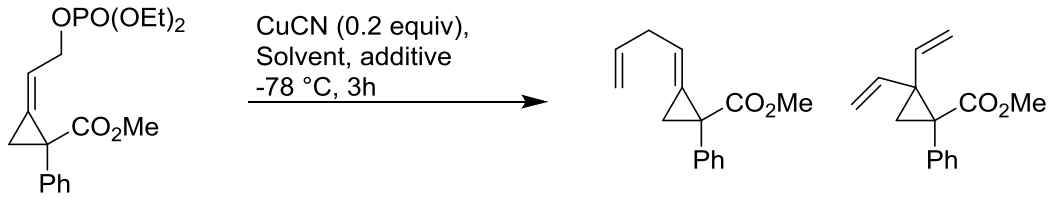
Scheme 1-5 Synthesis of methylenecyclopropane 1.69

The next step in the synthesis of amide **1.68** was a copper-mediated phosphate displacement, which required a screening of conditions to achieve acceptable yields of divinylcyclopropane **1.73**. Initial experiments involved mixing allyl phosphate **1.69** with vinylmagnesium bromide and a copper source at low temperature. Copper sources such as CuBr and CuCl•dipp[74] (dipp = 1,3-bis(2,6-diisopropylphenyl)-1*H*-imidazol-3-ium-2-ide) afforded little or no divinylcyclopropane products.

However, CuCN proved to be an effective catalyst for S_N2' substitution; the reaction conditions screened are shown in Table 1-1. A typical experiment is represented by Entry 1; vinylmagnesium bromide was mixed with copper cyanide in THF at 0 °C forming a dark mixture, then the mixture was cooled to –78 °C. A solution of allyl phosphate **1.69** in THF was added dropwise at –78 °C, and the resultant mixture was stirred for 3 h. After low temperature aqueous quench, the mixture was allowed to warm to room temperature and subjected to standard extraction, drying and evaporation procedures. The resultant residue was analyzed by ^{1}H NMR spectroscopy. Conveniently, phosphate **1.69**, cyclopropane **1.72** and 1,1-divinylcyclopropane **1.73** had diagnostic resonances at δ 2.46, 3.00 and 2.26 ppm, respectively. Analysis of the mixture described above revealed a 9:27:64 mixture of starting material **1.69** to S_N2 product methylenecyclopropane **1.72** to S_N2' product *gem*-divinylcyclopropane **1.73**.

When the reaction was performed with the addition of flame dried LiCl to the copper mixture before addition of phosphate **1.69**, the resultant residue contained a 18:21:60 mixture of **1.69**:**1.72**:**1.73**, entry 2. Changing the solvent to toluene with LiCl as an additive the observed ratio of **1.69**:**1.72**:**1.73** was 52:12:34, entry 3. Using diethyl ether as the solvent with the addition of lithium chloride resulted in a 47:13:40 ratio of **1.69**:**1.72**:**1.73**, entry 4. These results show that THF is a better solvent for **1.73** formation than Et_2O or toluene and that addition of lithium chloride improves the ratio of S_N2' **1.73** to S_N2 **1.72**.

Table 1-1 Optimization of S_N2' synthesis of divinylcyclopropane 1.67



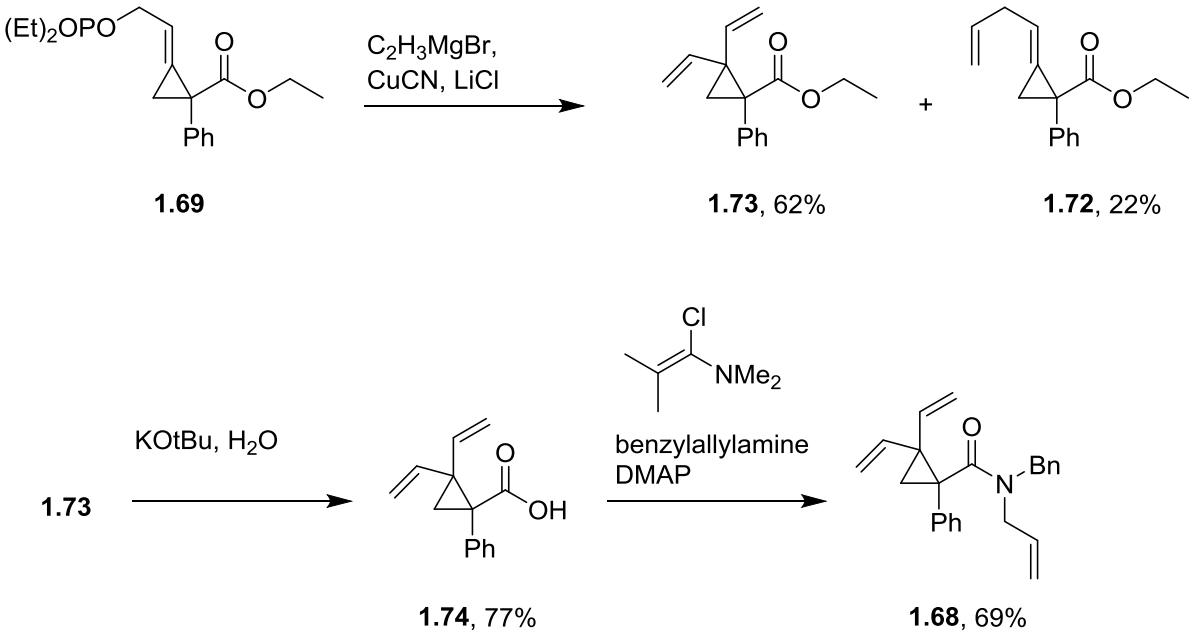
1.69 **1.72** **1.73**

entry	solvent	additive	**1.69**:**1.72**:**1.73**
1	THF	none	9 : 27 : 64
2	THF	LiCl (0.2 equiv)	18 : 21 : 60
3	PhMe	LiCl (0.2 equiv)	52 : 12 : 34
4	Et_2O	LiCl (0.2 equiv)	47 : 13 : 40

The preparative scale reaction of methylenecyclopropane **1.69** with vinyl magnesium bromide was conducted in the presence of CuCN and LiCl in THF to give divinylcyclopropane **1.73** in 62% yield after careful chromatographic separation, Scheme 1-6. The methylenecyclopropane isomer **1.72** was isolated in 22%. In larger scale experiments, chromatographic fractions containing both **1.72** and **1.73** were recovered and, initially, had to be re-purified.

Conversion of ester **1.73** to amide **1.68** required hydrolysis and amide formation, shown in Scheme 1-7. The hydrolysis of ester **1.73** was incomplete after stirring 7 days in the presence of excess LiOH in either THF/H_2O or THF/H_2O/MeOH. Treatment of **1.73** with a slurry of 6 equiv KOtBu and 3 equiv water in diethyl ether for 2 h gave the acid **1.74** in 77% yield after

purification.[75] After hydrolysis, the S_N2 and S_N2' acid isomers were more easily separated by chromatography than the corresponding esters. Accordingly, chromatography fractions from the S_N2' reaction that contained both **1.72** and **1.73** were no longer subjected to subsequent chromatography but directly hydrolyzed and then separated to give pure acid **1.74**. Acid **1.74** was treated with the Ghosez reagent, 1-chloro-*N*,*N*,2-trimethyl-1-propenylamine,[76] followed by benzylallylamine and DMAP to give benzylallylamide **1.68** in 69% yield.



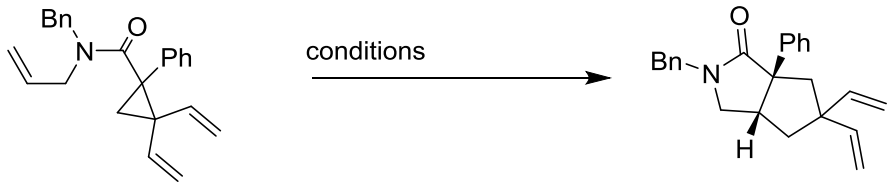
Scheme 1-6 Synthesis of amide 1.68

With amide **1.68** in hand, the radical [3+2] cyclization was attempted with several reagents, with representative results shown in Table 1-2. A number of reaction conditions provided little or no target product **1.75**. For example, entry 1 shows that treatment of amide **1.68** with tributylstannane (1.0 equiv) and triethylborane (0.1 equiv) in the presence of oxygen resulted in a complex mixture with no bicycle **1.75** present, as judged by TLC and ^{1}H NMR

spectroscopy. Treating amide **1.68** with tributylstannane and AIBN in refluxing benzene did not result in isolation of amide **1.75**.

Bicycle **1.75** was first observed after treatment of amide **1.68** with tributylstannane (1.0 equiv) and the room temperature radical initiator v-70[77] (1.0 equiv, v-70 = 2,2'-azobis(4-methoxy-2.4-dimethylvaleronitrile)) in benzene at 30 °C, shown in entry 3. Silica gel chromatography provided fused bicycle **1.75** in 24% yield. Key ^{1}H NMR spectral features used to identify the structure of bicycle **1.75** include signals for 10 aromatic protons; six total alkene signals, two signals corresponding to internal alkene protons at δ 5.85 ppm, each coupled to two terminal alkene peaks at δ 5.04 and 4.89 ppm; two benzylic signals at δ 4.52 and 3.29 ppm; and 7 additional alkyl signals. The signals in the ^{13}C NMR spectrum are an amide carbonyl resonance at δ 177.0 ppm, 12 total aromatic and vinyl resonances, and 7 total resonances corresponding to alkyl carbons. A better yield of **1.75** was obtained by UV irradiation of amide **1.68** in the presence of diphenyl disulfide (1.0 equiv); bicycle **1.75** was recovered in 50% isolated yield, shown in entry 4. A separate control experiment showed that UV irradiation of **1.68** without a mediator resulted in no conversion of the starting material.

Table 1-2 Radical [3+2] cyclization of amide 1.68



1.68 **1.75**

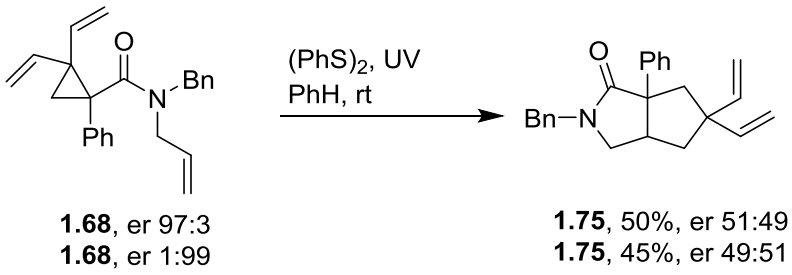
entry	conditions	yield
1	Bu_3SnH, Et_3B, O_2 PhH, rt	0%
2	Bu_3SnH, AIBN PhH, 80 °C	0%
3	Bu_3SnH, v-70, PhH, 30 °C	24%
4	$(PhS)_2$, UV PhH, rt	50%[a]

a: no conversion without $(PhS)_2$

1.2.2 Memory of chirality in [3+2] reactions of divinylcyclopropane 1.68

In preparation for the memory of chirality experiment, benzylallyl amide **1.68** and bicycle **1.75** were analyzed by chiral HPLC using an (*S*,*S*)-Whelk-O 1 25 cm x 4.6 mm column using 5% iPrOH in hexanes for amide **1.68** and 15% iPrOH for bicycle **1.75** with fluorescence monitoring at 231 mm. Both pairs of enantiomers showed good separation. Enantiomers of amide **1.68** were then resolved by preparative chiral HPLC using a (*S*,*S*)-Whelk-O 1 25 cm x 21.1 mm inner diameter column eluting with 5% iPrOH in hexanes at 5.0 mL/min. The first eluting isomer was isolated with 97:3 er, the second eluting isomer was isolated with 1:99 er, as measured by analytical chiral HPLC. The enriched enantiomers were separately subjected to UV

irradiation in the presence of diphenyl disulfide, shown in Scheme 1-7. The first eluting enantiomer **1.68** gave bicycle **1.75** in 50% yield, *er* 51:49. The second eluting enantiomer of **1.68** gave bicycle **1.75 i**n 45% yield, *er* 49:51. In other words, there was no memory of chirality.



Scheme 1-7 Memory of chirality in radical [3+2] cyclizations of amide 1.68

The results in Scheme 1-7 suggest that radical **1.76**, depicted in Figure 1-14, has fast bond rotation, and therefore racemization, relative to the rate of the initial 5-*exo* cyclization. For reference, the rate constant of 5-*exo* cyclizations is known to be approximately 10^6–10^7 s^{-1}.[78-79] The bond rotation in radical **1.76** is apparently much faster. The prime condition for memory of chirality is not met in the radical cyclization of divinylcyclopropane **1.68**.

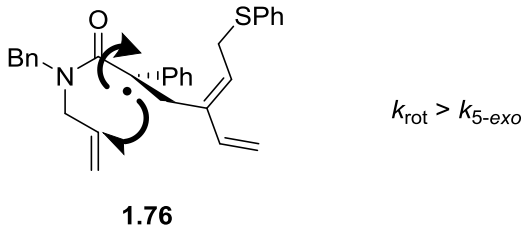
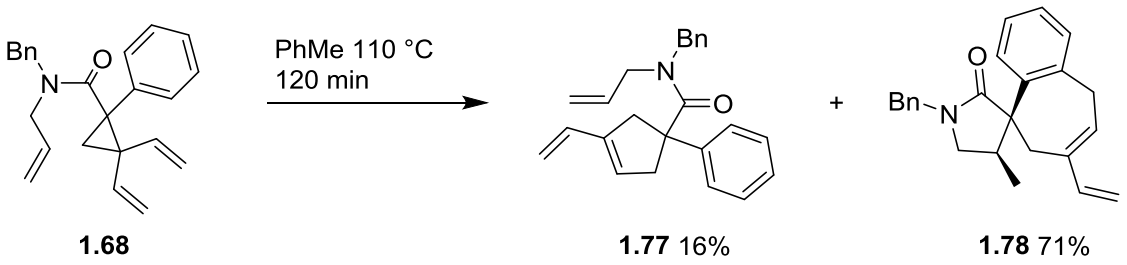


Figure 1-14 Intermediate 1.70 in the radical annulation of cyclopropane 1.62

1.2.3 Discovery of sigmatropic cascade reaction

When analyzing the various cyclization reaction mixtures of racemic amide **1.68** by TLC, two byproducts were consistently observed along with target product **1.75**. The amounts of these products appeared to increase in reactions employing elevated temperature. We began to suspect these byproducts were the results of thermal pathways rather than radical pathways. To test this hypothesis, we heated cyclopropyl amide **1.68** in toluene without any added radical initiator or mediator. The resultant mixture did not contain amide **1.68**. Instead a 6:1 mixture of two new compounds was cleanly formed, as judged by ^{1}H NMR spectroscopy. These products were easily separable by silica gel chromatography. The minor product, vinylcyclopentene **1.77**, was isolated in 16% as a 2:1 mixture of amide rotamers. Vinylcyclopentene **1.77** is the product of the vinylcyclopropane-cyclopentene rearrangement.[8]

The major product was a spiro-fused benzo[7]annulene **1.78**, which was isolated in 71% yield as a single isomer. The spectra of amide **1.78** have several striking features: it appears as a single isomer and all signals are down field of the cyclopropyl signals of the starting cyclopropane at δ 1.94 and 1.75 ppm in the ^{1}H NMR spectrum. Other ^{1}H spectral features include 4 signals corresponding to the vinyl protons, two of which are geminal (terminal) protons. The aromatic region contains signals for 9 protons, and a doublet at δ 0.55 ppm with relative integration of three protons indicates the presence of a shielded methyl group coupled to a single proton which appeared at δ 2.63 ppm. The shift of the methyl group is the result of shielding by the α-phenyl ring, indicating their *cis* relationship. The key ^{13}C features show an amide resonance at δ 177.9 ppm, 14 aromatic and vinyl resonances and 7 alkyl resonances including an upfield methyl resonance at δ 16.6 ppm.



Scheme 1-8 Thermal rearrangement of amide 1.68

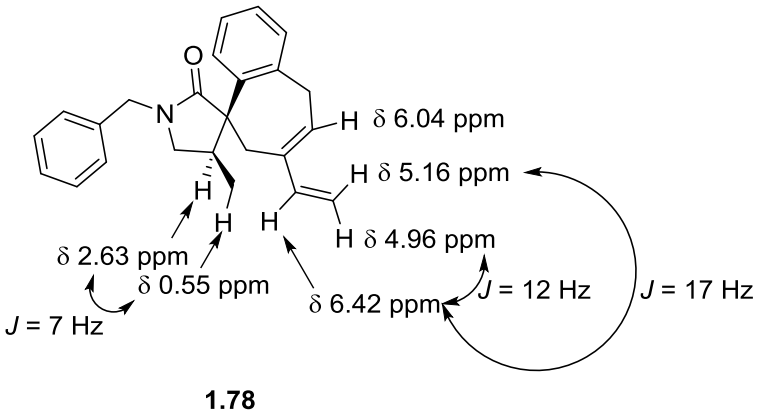


Figure 1-15 Key resonances used to assign structure of amide 1.78

The proposed mechanism of transformation from cyclopropane **1.68** to benzo[7]annulene **1.78** is a Cope-ene cascade, shown in Figure 1-16. Amide **1.68** exists as a 1:1 mixture of amide rotamers *E*-**1.68** and *Z*-**1.68** which interconvert, shown in Figure 1-16**A**. Each rotamer can undergo a reversible [3,3]-Cope rearrangement. The rotamers of divinylcyclopropane **1.68** give rotamers of cyclohexadiene **1.79**; *E*-**1.68** gives *E*-**1.79** and *Z*-**1.68** gives *Z*-**1.73**. If the lifetime of cyclohexadiene **1.79** is sufficient, rotamers *E*-**1.79** and *Z*-**1.79** may interconvert. The release of strain energy of the cyclopropane in **1.68** compensates at least partially for the loss of benzene aromatization energy.

Figure 1-16**B** shows an intramolecular Alder-ene reaction occurs in *Z*-**1.79** between the proximal allylic arm of the amide, the enophile, and the cyclohexadienyl hydrogen, the ene, to

give tricycle **1.78**. This restores aromaticity to the benzene ring and sets the quaternary center of the [5,7] spiro-ring system as a single diastereomer with the methyl group and the aryl group *cis*. The isomer *E*-**1.79** cannot undergo the ene reaction because the enophile component is distal to the ene component. However, it can rotate to *Z*-**1.79** or revert to *E*-**1.68**. In this way, full convergence to **1.78** is possible.

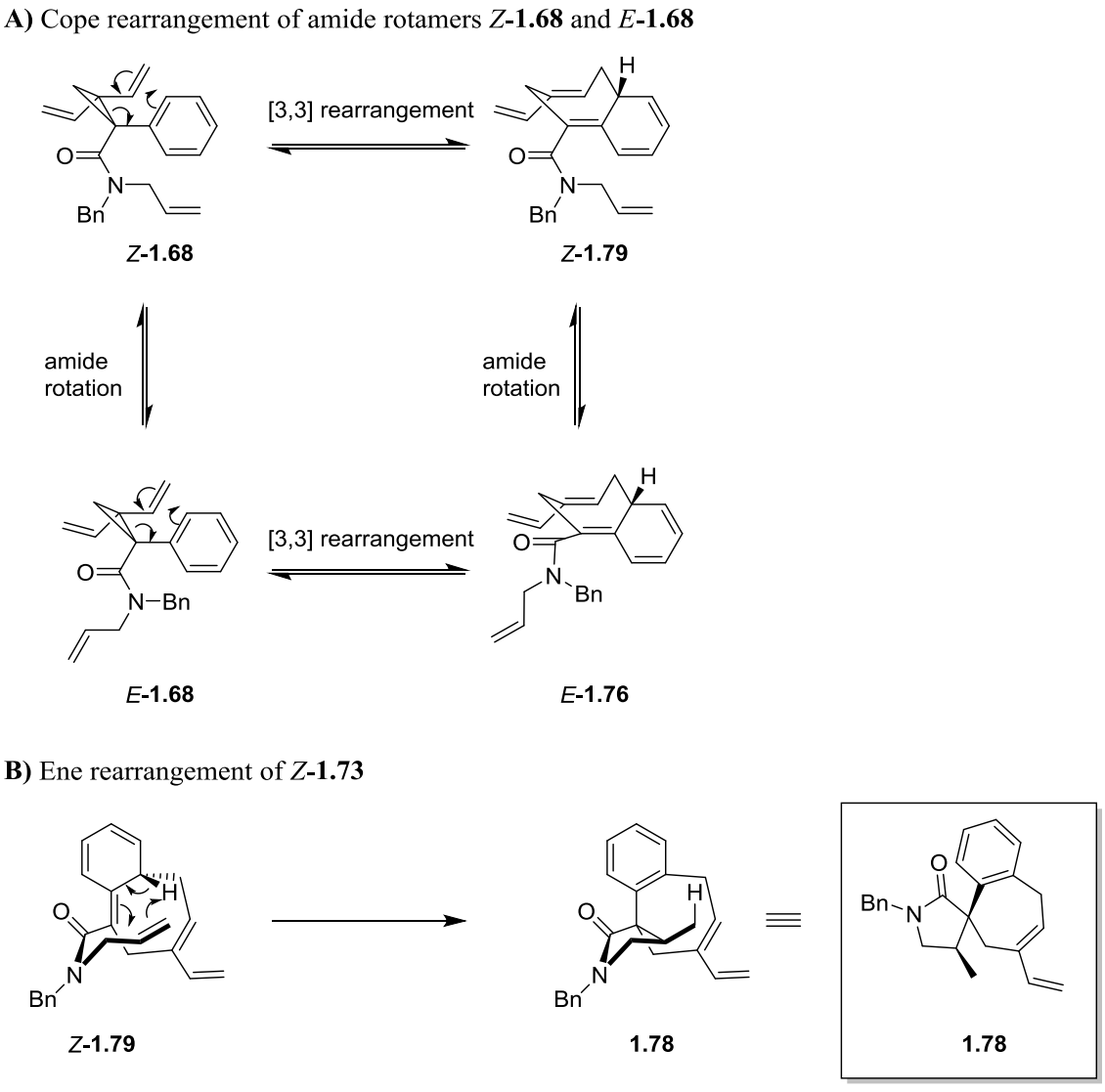


Figure 1-16 Mechanism of Cope-ene cascade

The results shown in Scheme 1-8 suggest that 1,1-divinylcyclopropanes may have interesting sigmatropic rearrangement chemistry in an accessible temperature regime. To test whether *gem*-divinylcyclopropanes primarily react by sigmatropic rearrangements, a family of analogs of divinylcyclopropane **1.68** was synthesized and their transformations were studied under standard conditions of refluxing for 2 h in toluene. The family members are classed into tables based on the major products observed, Table 1-3 and Table 1-4.

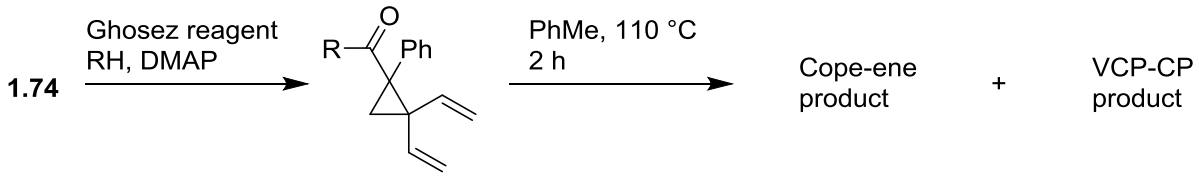
Divinylcyclopropanes that primarily underwent the Cope-ene (CE) cascade are shown in Table 1-3. Diallylamide **1.80** was synthesized in 82% yield by treating cyclopropyl acid **1.74** with Ghosez's reagent followed by diallylamine and DMAP. Similarly, benzylpropargylamide **1.83** and benzyl-(trimethylsilyl)propargyl amide **1.86** were obtained in 69% and 78% yield, respectively, from acid **1.74**. When diallylamide **1.80** was refluxed in toluene for 2 h, a mixture of CE/VCP-CP products in a 5:1 ratio was observed by ^{1}H NMR analysis of the reaction mixture. Flash chromatography provided tricycle **1.81** in 65% yield; tricycle **1.81** had the characteristic spectral features used to identify tricycle **1.78**. In addition, vinylcyclopentene **1.82** was isolated in 10% yield.

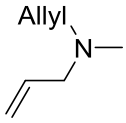
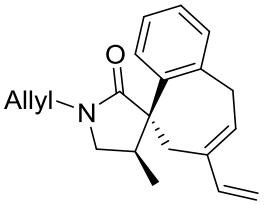
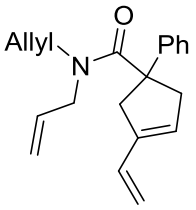
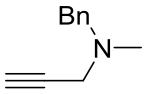
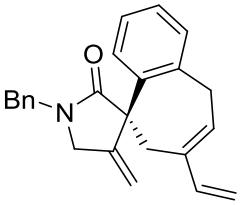
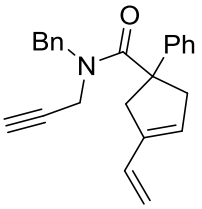
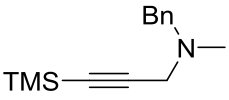
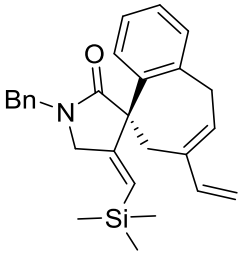
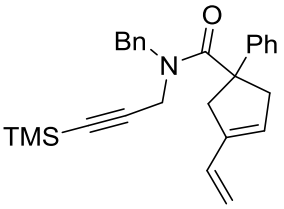
Heating benzylpropargylamide **1.83** produced a 5:1 mixture of CE/VCP-CP products and cycloheptene **1.84** was obtained in 73% isolated yield. Vinylcyclopentene **1.85** was formed in an estimated 15% yield based on the ratio of the two products and the isolated yield of **1.84**. Vinylcyclopentene **1.85** was recovered in only trace amounts, likely due to loss of product during chromatography. However, the recovered **1.85** matched the material seen in the ^{1}H NMR spectrum of the crude reaction mixture.

Heating trimethylsilylpropargyl amide **1.88** in toluene at 110 °C resulted in a 4.5:1 mixture of CE/VCP-CP products; silyl alkene **1.87** was obtained as a single alkene isomer in 53% isolated yield after flash chromatography with 12% yield of vinylcyclopentene **1.88** again

based on the ratio of the two products and the yield of **1.87**. Vinylcyclopentene was also recovered in only trace amounts. The observation of only a single diastereomer of benzannulene **1.81** and a single isomer of alkene **1.87** is consistent with the proposed mechanism shown in Figure 1-14. In the case of **1.87**, only the *E*-vinyl-silyl isomer can form by the ene reaction.

Table 1-3 Scope of Cope-ene cascade



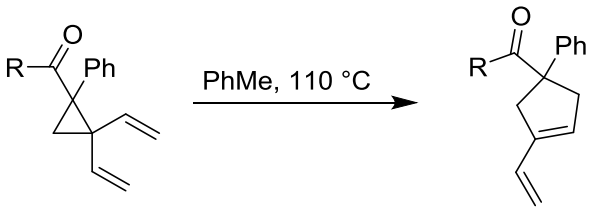
Entry	R =		
1			
	1.80, 82%	**1.81**, 65%	**1.82**, 10%
2			
	1.83, 69%	**1.84**, 73%	**1.85**, 15%[a]
3			
	1.86, 78%	**1.87**, 53%	**1.86**, 12%[a]

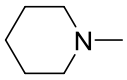
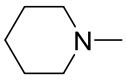
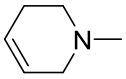
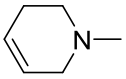
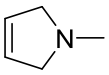
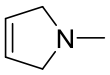
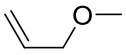
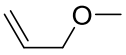
a: ^{1}H NMR yield

Table 1-4 shows the results of thermal reactions of *gem*-divinylcyclopropanes that primarily undergo the vinylcyclopropane-cyclopentene rearrangement. Amides were synthesized in 77–89% yield using the Ghosez reagent as previously outlined. Substrates that cannot undergo the ene part of the Cope-ene cascade reaction because they lack an appropriate enophile are shown in entries 1–3. Ethyl ester **1.73** was heated in refluxing toluene for 2 h. Then the product mixture was analyzed by ^{1}H NMR spectroscopy. Vinylcyclopentene **1.89** was observed as a single product. This was isolated in 87% yield after flash chromatography. Similarly, the cyclopropylcarboxylic acid **1.74** provided 86% of cyclopentenylcarboxylic acid **1.90** as the sole reaction product. Amide **1.91** was refluxed in toluene to produce vinylcyclopentene **1.92** in 90% isolated yield. These results demonstrate that when the ene part of the Cope-ene cascade is not possible due to absence of an enophile, the Cope path does not produce a stable product. Instead, *gem*-divinylcyclopropanes thermolyze at moderate temperatures of 110 °C to give vinylcyclopentenes in good yields.

Vinylcyclopropanes that contain a potential enophile but primarily give vinylcyclopentenes are represented in entries 4–6. Heating amide **1.93** formed cyclopentene **1.94** isolated in 80% yield, as the sole product as judged by ^{1}H NMR of the crude reaction mixture. Similarly, entry 5 shows the transformation of cycloropylamide **1.95** into vinylcyclopentene **1.96**, recovered in 91% isolated yield. Entry 6 shows the reactivity of ester **1.97** as reported in the thesis of Dr. Hanmo Zhang.[80] This substrate gave cyclopentene **1.98** in 73% yield as the sole reaction product. Cyclopropanes **1.93**, **1.95** and **1.97** likely undergo the reversible ring opening Cope rearrangement. However, the enophile is not suitably placed for the ene reaction, either by confinement in a ring structure or as an unreactive ester rotamer. This constraint again funnels the product down the VCP-CP pathway.

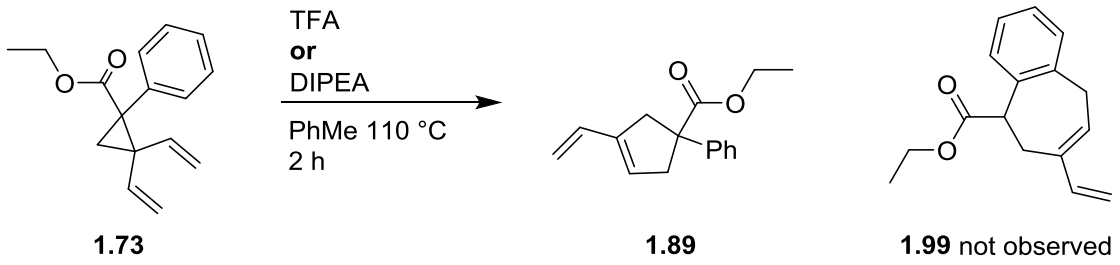
Table 1-4 Scope of VCP-CP reaction



Entry	R	R
1	EtO—	EtO—
	1.73	**1.89**, 87%
2	HO—	HO—
	1.74	**1.90**, 86%
3		
	1.91	**1.92**, 90%
4		
	1.93	**1.94**, 91%
5		
	1.95	**1.96**, 80%
6		
	1.97	**1.98**, 73%[a]

a: data taken from ref 84

To learn whether the VCP-CP rearrangement was promoted by either acid or base, we heated ester **1.73** under the standard conditions in the presence of TFA (2 equiv) in one experiment and in the presence of DIPEA (2 equiv) in a second experiment, shown in Scheme 1.9. The results were similar to standard experiments; vinylcyclopentene **1.89** was formed cleanly as the sole product, benzannulene **1.99** was not detected. Apparently acid or base do not affect the course of the standard VCP-CP pathway.



Scheme 1-9 Reaction of 1.73 under acidic or basic conditions

The results in Table 1-3 and Scheme 1-4 show that the VCP-CP rearrangement of *gem*-divinylcyclopropanes occurs readily under an easily accessible temperature regime. For comparison, a sample of representative cyclopentenes synthesized from vinylcyclopropanes are shown in Figure 1-17 along with the temperature at which they were formed.[5, 8] For instance, diphenylcyclopentene **1.101** was formed by heating to 310 °C.[81] Likewise, **1.100**–**1.103** were synthesized at temperatures from 220–450 °C. Apparently, the addition of a vinyl substituent to a vinylcyclopropane facilitates the VCP-CP isomerization.

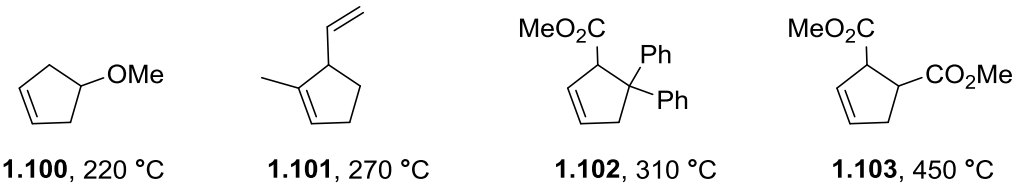
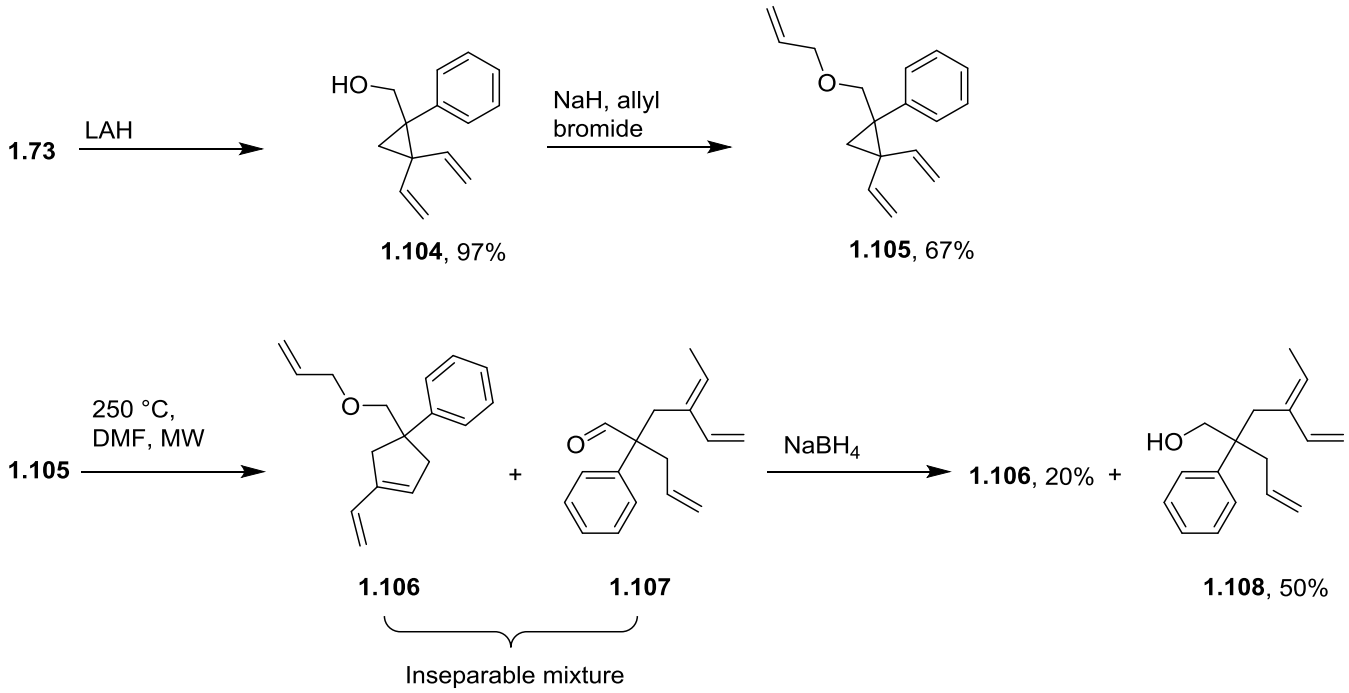


Figure 1-17 Benchmark products of VCP-CP rearrangements of vinylcyclopropanes

1.2.4 Thermal rearrangement of cyclopropylmethoxy compounds

Entry 6 in Table 1-4 showed that ester **1.97** gave vinylcyclopentene **1.98** without trace of the product of a Cope-ene pathway. The Cope rearrangement is likely happening reversibly when substrate **1.97** is heated (see Figure 1-16), the ester apparently holds the allyl group into a conformation that cannot undergo the ene reaction.[82] We know this because **1.97** undergoes the VCP-CP rearrangement at the same temperatures as structurally similar amide **1.688** undergoes the Cope-ene cascade.

Allyl ethers are not subject to the same rotamer effects as allyl esters. To learn whether an allyl ether can undergo the Cope-ene cascade we performed the reactions shown in Scheme 1-10. Reduction of ester **1.73** with lithium aluminum hydride provided cyclopropanemethanol **1.104** in 97% yield. Allylation of **1.104** by treatment with NaH followed by allyl bromide gave allyl ether **1.105** in 67% yield. The allyl ether **1.105** was much more thermally stable than the corresponding ester **1.73**; heating at 110 °C in toluene for 3 days did not cause detectable conversion to a new product. However, microwave heating **1.105** in DMF or 1,2-dichlorobenzene at 250 °C for 5 min resulted in full consumption of the starting material to give two products, as judged by ^{1}H NMR analysis of the reaction mixture. The minor product was vinylcyclopentene **1.106** with spectral properties similar to ester **1.89**. The major product unexpectedly had an aldehyde resonance at 9.77 ppm and was assigned as linear alkene **1.107**. These products were inseparable by silica gel chromatography. To enable purification, the product mixture was suspended in ethanol and treated with sodium borohydride. This produced an easily separated mixture of primary product allyl ether **1.106**, isolated in 20% and alcohol **1.108**, in 50% yield as a secondary product.



Scheme 1-10 Discovery of retro-ene/Claisen cascade

Cyclopentene **1.106** forms by the VCP-CP pathway. The proposed formation of aldehyde **1.107** by a retro-ene Claisen rearrangement is shown in Figure 1-17. A retro-ene reaction of vinylcyclopropane **1.105** gives the linear allyl vinyl ether **1.108**. Ether **1.108** undergoes a Claisen rearrangement to give aldehyde **(*E*)-1.107** as a single alkene isomer.

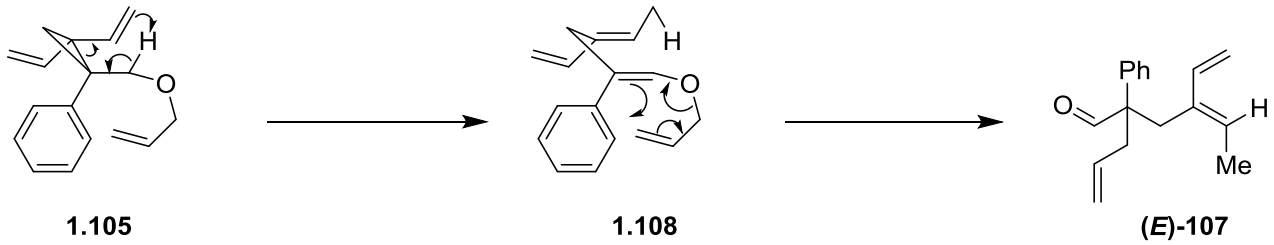
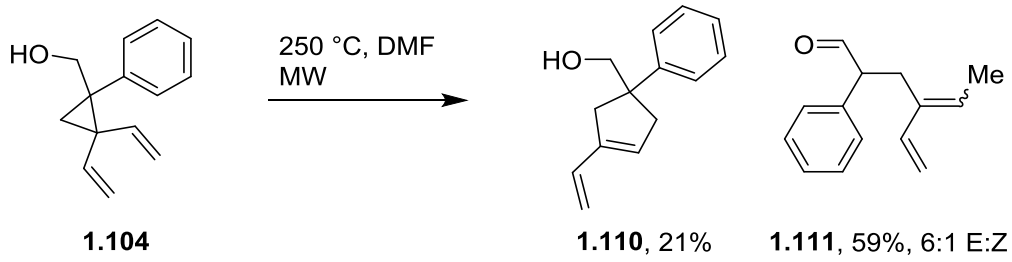


Figure 1-18 Mechanism of retro-ene-Claisen cascade of compound 1.105

The precursor to **1.105**, cyclopropanemethanol **1.104**, can undergo both the VCP-CP rearrangement and the retro-ene reaction but the retro-ene reaction cannot be followed by a Claisen rearrangement. To test whether the Claisen rearrangement affected the retro-ene and VCP-CP reaction, alcohol **1.104** was heated in DMF at 250 °C under microwave conditions as described above. A mixture of three compounds was produced in 6:2.5:1 ratio. The intermediate product vinylcyclopentene **1.110** was easily separated from the major and minor products, isolated in 21% yield. The ^{1}H- and ^{13}C NMR spectra of the intermediate product were analogous to ether **1.110** but lacked the resonances corresponding to the allyl group. The major and minor products were *cis-trans* isomers of **1.111** and were recovered in 59% combined yield in a 6:1 ratio.



Scheme 1-11 Thermal rearrangement of divinylcyclopropylmethanol 1.104

NOE experiments with the isomer mixture of **1.111** showed the major product to be (*E*)-1.**111**. Key NOE interactions used to assign the isomers are shown in Figure 1-19. This is consistent with the mechanism of the retro-ene reaction shown in Figure 1-18, which proceeds with the vinyl group in the *endo* position. The enol product after this retro-ene reaction undergoes tautomerization to give aldehyde (*E*)-**1.111** as the major product.

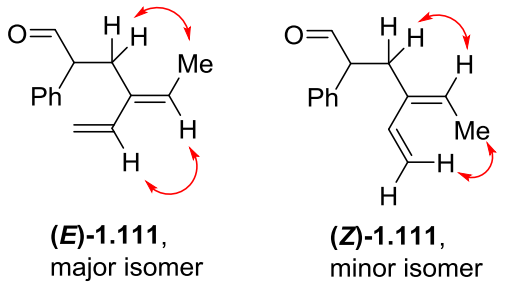


Figure 1-19 NOE interactions of (*E*)-1.111 and (*Z*)-1.111

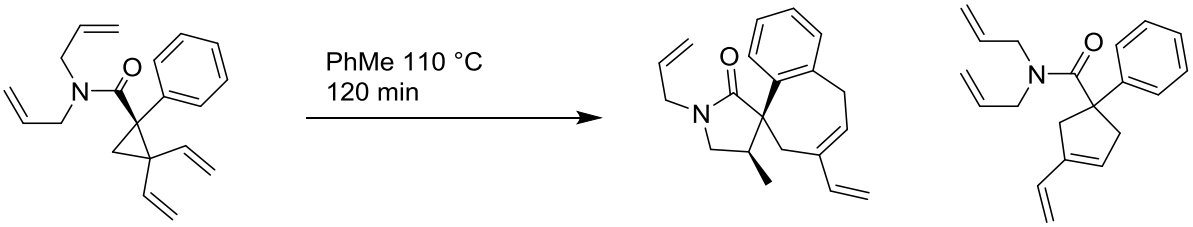
The results in Scheme 1-13 and Scheme 1-14 show that 1,1-divinylcyclopropanes with δ-hydrogen atoms primarily reaction under the retro-ene regime to give enols as primary products and also give vinylcyclopentenes as minor products. This also demonstrates that carbonyl groups activate vinylcyclopropanes for sigmatropic rearrangement. The downstream Claisen rearrangement has little effect on the relative or absolute yields of the competing retro-ene and VCP-CP pathways.

1.2.5 Transfer of chirality in the Cope-ene cascade

Due to the defined transition state geometries of sigmatropic rearrangements, the Cope-ene rearrangement of vinylcyclopropanes is a stereospecific process.[83-85] However, the vinylcyclopropane precursors also form diradical intermediates, whose bonds may rotate and give stereorandom products. To test whether the competing radical pathway affected the stereochemical outcome of the Cope-ene process, thermolysis of enantio-enriched vinylcyclopropane **1.80** was conducted.

In preparation for the transfer of chirality experiment, diallyl amide **1.80** and tricycle **1.81** were analyzed by chiral HPLC using a (*S*,*S*)-Whelk-O 1 25 cm x 4.6 mm column using 5% iPrOH in hexanes with fluorescence monitoring at 231 mm; both materials showed good

separation. Enantiomers of amide **1.80** were then resolved by preparative chiral HPLC using a (*S*,*S*)-Whelk-O 1 25 cm x 21.1 mm inner diameter column eluting with 5% iPrOH in hexanes. The first eluting isomer was isolated with 97:3 *er*, the second eluting isomer was isolated with 5:95 er as measured by analytical chiral HPLC. The enriched enantiomers were separately heated for 2 h in toluene at reflux; the resultant solution was diluted with hexanes, filtered and analyzed by chiral HPLC. The product peaks were identified by comparing the retention times to those of the purified racemic benzannulene **1.81** and vinylcyclopentene **1.82**. Vinylcyclopropane **1.82** with an initial *er* of 96:4 gave rise to benzannulene **1.81** with *er* 58:42 and cyclopentene **1.82** with *er* 50:50. Vinylcyclopropane **1.80** with an initial *er* of 1:99 gave rise to benzannulene **1.81** in with *er* 35:65 and cyclopentene **1.82** with er 50:50.



Scheme 1-12 Memory of chirality in Cope-ene cascade

HPLC analysis of the reaction mixture at partial conversion revealed the starting material was racemizing under the reaction conditions. Figure 1-20 shows the mechanism for this interconversion. Cyclopropane **1.80** opens to diradical intermediate **1.113**,[86-88] rotation of one or more sigma bonds followed by ring closing gradually results in racemization. Even if enantiomers of **1.80** undergo the Cope-ene cascade to give **1.112** stereospecifically, the *er* of benzannulene **1.81** is lowered due to racemization of starting material.

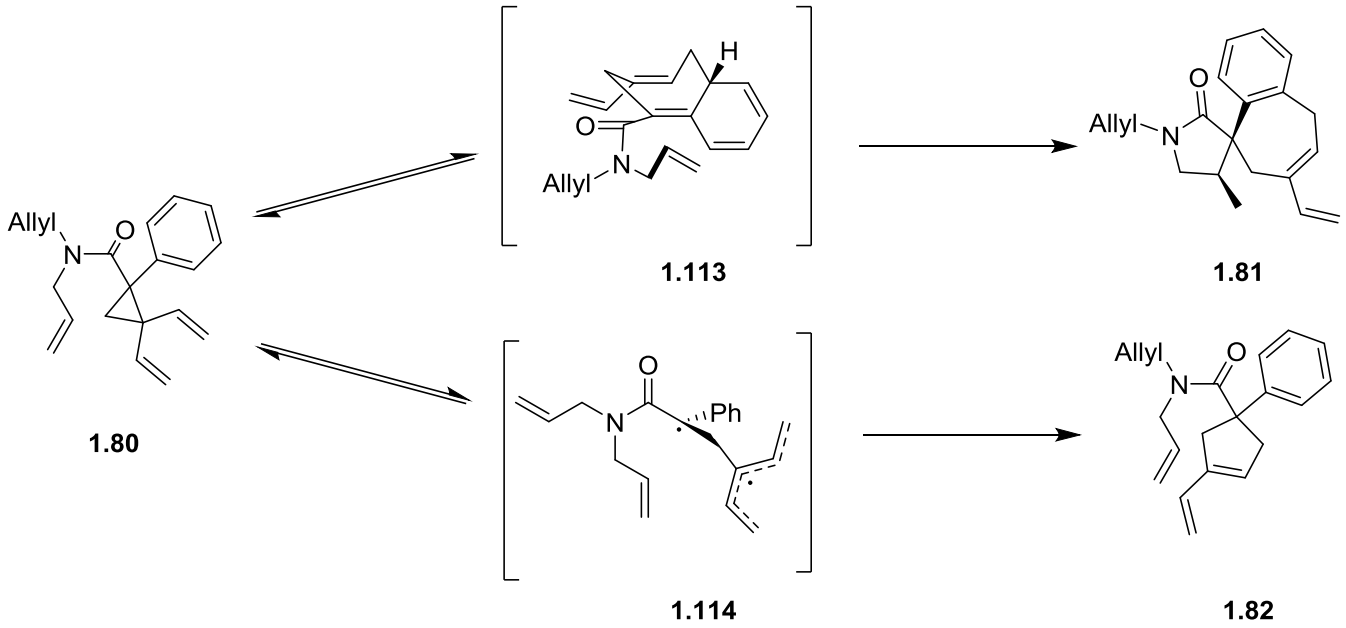


Figure 1-20 Reversibility and racemization in the Cope-ene and VCP-CP pathways

1.2.6 Summary

We have discovered a variety of rearrangements of *gem*-divinylcyclopropanes and have described factors that can be used to predict the reaction pathway. DVCPs with β-phenyl groups undergo a reversible ring opening Cope rearrangement in an easily accessed temperature regime to produce methylenecyclohexadienes. Ene-competent DVCPs, that is, substrates that possess a suitably positioned alkene or alkyne can undergo an irreversible ene reaction to produce benzo[7]annulenes such as **1.78** as stable products. Yields of these products range from 53–73%. Ene-incompetent substrates, those that either lack an enophile or have an enophile that is not in a suitable conformation, react primarily to give vinylcyclopentenes such as **1.98** in good yields at

relatively low temperatures. DVCPs with δ-hydrogen atoms react primarily by the retro-ene reaction and undergo downstream reactions such as Claisen rearrangement or tautomerization to give linear dienes such as **1.107** in moderate yields. Finally, when exposed to UV irradiation at room temperature in the presence of a radical mediator such as $(PhS)_2$, DVCPs undergo [3+2] cyclization to give divinylcyclopentanes such as **1.75** in moderate yields.

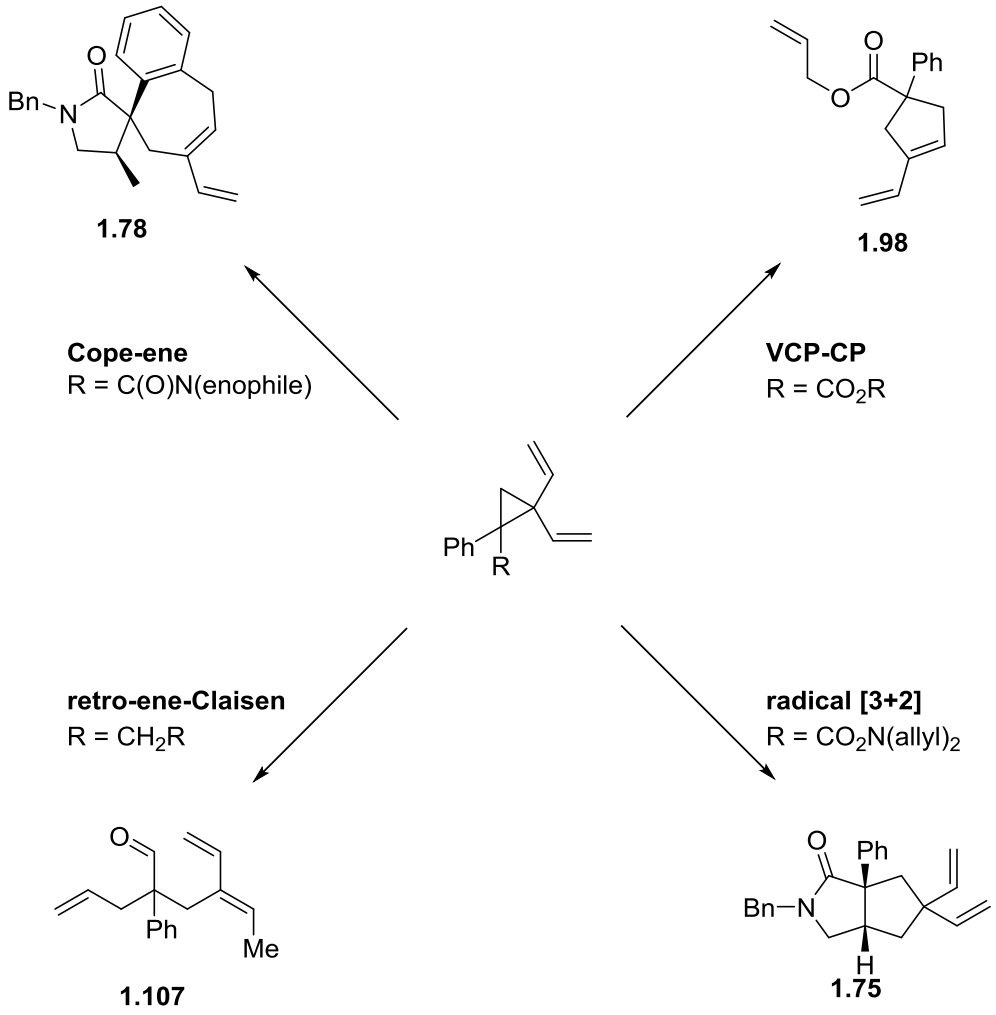


Figure 1-21 Diverse products obtained from reactions of 1,1-divinylcyclopropanes

In summary, the VCP-CP rearrangement of divinylcyclopropanes is general and occurs under mild conditions. However, with the correct substrate design, either the Cope-ene cascade or retro-ene reactions predominate to give benzo[7]annulenes and diene-aldehydes, respectively. Finally, with selection of the correct reaction conditions, polycyclic divinylcyclopentanes can be accessed in moderate yields.

1.3 EXPERIMENTAL

Reactions were performed in oven-dried glassware under an argon atmosphere. Chemicals and solvents were purchased from commercial suppliers and used as received. Dichloromethane, diethyl ether, THF and toluene were dried by passing through an activated alumina column.[89-90]

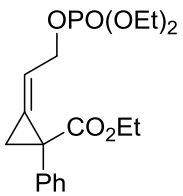
Reactions were followed by TLC to completion, unless stated otherwise. TLC analysis was performed by illumination with a UV lamp (254 nm) or staining with ethanolic anisaldehyde and heating. Flash chromatographies were performed with a Combiflash Rf automated flash chromatography instrument from Teledyne ISCO with normal phase RediSep Rf columns containing 230-400 mesh silica gel.

^{1}H NMR spectra were recorded on Bruker Avance 300, 400, 500 and 600 MHz instruments in $CDCl_3$, chemical shifts were measured relative to tetramethylsilane (δ 0.00 ppm) or residual solvent peak (δ 7.26 ppm). ^{13}C NMR spectra were recorded on Bruker Avance 75, 100, 125, 150 MHz instrument in $CDCl_3$, chemical shifts were measured relative to residual

solvent peak (δ 77.0 ppm). Unless otherwise noted, NMR spectra were recorded at 293 K. The following abbreviations were used to describe coupling: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. IR spectra were recorded as thin films ($CHCl_3$) or neat on NaCl plates on a Nicolet Avatar 360 FTIR spectrometer. Melting ranges were determined using a Mel-Temp II apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 Polarimeter using a 1 dm cell length. All quoted optical rotation values are corrected for 100% ee samples, and have the units (deg cm^2 g^{-1}). Mass spectra were obtained on a Q-Tof Ultima API high-resolution mass spectrometer.

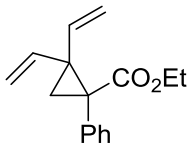
Analytical normal phase HPLC analysis was conducted using a Regis Technologies, Inc. (S,S)-Whelk-O1; 25 cm x 4.6 mm I.D. eluting with hexanes : iPrOH at 1.0 mL/min, 5—10 μL per injection. Semi-prep normal phase HPLC analysis was conducted using a Regis Technologies, Inc. (S,S)-Whelk-O 1; 25 cm x 21.1 mm I.D. eluting with hexanes : iPrOH at 5.0 mL/min, 0.5—1 mL per injection. All HPLC injections were monitored with a Waters model 440 UV detector at wavelength 270 nm.

All microwave-mediated reactions were carried out using a Biotage Initiator™ Exp or an Anton Paar monowave 300 microwave synthesizer. The microwave parameters were set to variable power, constant temperature, with the fixed hold time set to on. The microwave reactions were carried out in 0.5 - 2 mL Biotage microwave vials.



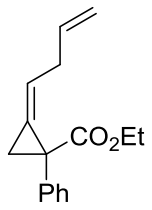
Ethyl 2-(2-(diethoxyphosphoryloxy)ethylidene)-1-phenylcyclopropane-carboxylate

(1.69): A solution of ethyl diazophenylacetate **1.71**[91] (1.30 g, 6.79 mmol) in dichloromethane (3 mL) was added dropwise to a solution of allenyl phosphate **1.70** (1.00 g, 4.85 mmol) and $Rh_2(esp)_2$ (11 mg, 0.015 mmol) in dichloromethane (10 mL). The reaction mixture was refluxed for 2 h, the solvent was evaporated. The residue was purified by flash chromatography (70% EtOAc/hexanes) to provide the title compound (1.25 g, 70%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.30 (m, 5H), 6.35 (tt, *J* = 6.4 Hz, 2.4 Hz, 1H), 4.76 (t, *J* = 7.6 Hz, 2H), 4.18-4.06 (m, 6H), 2.49 (d, *J* = 9.2 Hz, 1H), 1.79 (d, *J* = 9.2 Hz, 1H), 1.39-1.30 (m, 6H), 1.21 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 137.4, 131.5, 129.1, 128.2, 127.5, 114.8 (d, $J_{C\text{-}P}$ = 6.7 Hz), 66.6 (d, $J_{C\text{-}P}$ = 5.4 Hz), 63.9 (d, $J_{C\text{-}P}$ = 5.7 Hz), 63.8 (d, $J_{C\text{-}P}$ = 5.7 Hz), 61.5, 32.1, 19.2, 16.1 (d, $J_{C\text{-}P}$ = 6.7 Hz), 14.1; FTIR (thin film, $CHCl_3$, cm^{-1}) 3085, 3060, 2981, 2904, 1723, 1637, 1447, 1366, 1296, 1241, 1196, 1061, 1027, 933, 914; HRMS (TOF ES) calcd for $C_{18}H_{25}O_6NaP$ *m/z* 391.1286 $[M+Na]^+$, found: 391.1266.

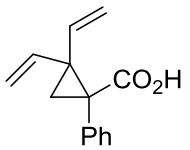


Ethyl 1-phenyl-2,2-divinylcyclopropanecarboxylate (1.73): A vinylmagnesium bromide solution (1 M in THF, 20.4 mL) was added to a suspension of CuCN (145 mg, 1.63 mmol) and flame dried LiCl (138 mg, 3.3 mmol) in THF (20 mL) at 0 °C. After 15 min, the reaction mixture was cooled to −78 °C, and a solution of methylene-cyclopropane **1.69** (3.0 g, 8.1 mmol) in THF (5 mL) was added via syringe pump over a period of 20 min. The reaction mixture was stirred at this temperature for 2 h, before a saturated aqueous NH_4Cl solution was added. The mixture was extracted with EtOAc, and the combined organic layer was dried over $MgSO_4$ and evaporated. The residue contained a 3:1 mixture of closely eluting S_N2'/S_N2

regioisomers (judged by ^{1}H NMR analysis) and was purified by flash chromatography (3–5% Et_2O in hexanes) to afford the title compound (1.31 g, 62%) as a colorless oil along with S_N2 product **1.72** (400 mg, 22%) as a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.38 (m, 2H), 7.31-7.25 (m, 3H), 6.04 (dd, *J* = 17.0 Hz, 10.5 Hz, 1H), 5.29-5.20 (m, 3H), 4.98 (d, *J* = 17.0 Hz, 1H), 4.91 (d, *J* = 10.5 Hz, 1H), 4.13-4.06 (m, 1H), 4.03-3.96 (m, 1H), 2.27 (d, *J* = 5.0 Hz, 1H), 1.62 (d, *J* = 5.0 Hz, 1H), 1.17 (t, *J* = 7.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 138.3, 136.2, 135.2, 131.5, 127.8, 127.3, 117.6, 115.3, 61.1, 43.5, 38.0, 21.7, 14.2; FTIR (thin film, $CHCl_3$, cm^{-1}) 3085, 3060, 2982, 1723, 1631, 1447, 1366, 1293, 1241, 1195, 1108, 1064, 1029, 993, 915; HRMS (TOF ES) calcd for $C_{16}H_{19}O_2$ *m/z* 243.1385 $[M+H]^+$, found: 243.1392.



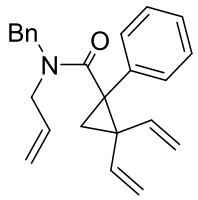
Ethyl 2-(but-3-en-1-ylidene)-1-phenylcyclopropane-1-carboxylate (1.72): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.35 (m, 2H), 7.33–7.22 (m, 3H), 6.15 (tt, *J* = 8.5 Hz, 2.0 Hz, 1H), 5.93 (qt, *J* = 9.1 Hz, 6.4 Hz, 1H), 5.09 (dq, *J* = 17.2 Hz, 1.6 Hz, 1H), 5.03 (dq, *J* = 10.1 Hz, 1.5 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.01 (tt, *J* = 3.2 Hz, 1.7 Hz, 1H), 2.41 (dq, *J* = 8.5 Hz, 2.0 Hz, 1H), 1.65 (dq, *J* = 8.5 Hz, 1.9 Hz, 1H), 1.18 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 138.4, 136.1, 129.0, 128.1, 127.2, 1127.1, 117.7, 115.5, 61.1, 35.5, 32.0, 19.7, 14.1; FTIR (thin film, $CHCl_3$, cm^{-1}) 3085, 3060, 2982, 1723, 1631, 1447, 1366, 1293, 1241, 1195, , 1064, 1029, 993,; HRMS (TOF ES) calcd for $C_{16}H_{19}O_2$ *m/z* 243.1385 $[M+H]^+$, found: 243.1390.



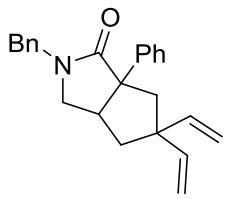
1-Phenyl-2,2-divinylcyclopropanecarboxylic acid (1.74): A solution of ester **1.73** (360 mg, 1.48 mmol) in Et_2O (2 mL) was added to pre-mixed KO^{t}Bu (1.41 g, 12.60 mmol)/H_2O (75 μL, 4.15 mmol) in Et_2O (20 mL). The reaction mixture was stirred at room temperature for 12 h, and another portion of KO^{t}Bu (0.71 g, 6.30 mmol) was added. After 4 h, the reaction mixture was diluted with water and washed with dichloromethane. 6 N HCl was added dropwise until the pH reached below 3 as measured by pH strip. The aqueous solution was extracted with dichloromethane. The combined organic layer was dried over $MgSO_4$ and concentrated under vacuum to afford the crude acid. Flash chromatography (20% EtOAc in hexanes) gave the title compound (310 mg, 77%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.27 (m, 5H), 6.07 (dd, *J* = 17.2 Hz, 10.4 Hz, 1H), 5.30 (dd, *J* = 17.2 Hz, 10.4 Hz, 1H), 5.29 (d, *J* = 10.8 Hz, 1H), 5.24 (d, *J* = 17.6 Hz, 1H), 4.98 (d, *J* = 17.2 Hz, 1H), 4.92 (d, *J* = 10.8 Hz, 1H), 2.26 (d, *J* = 5.2 Hz, 1H), 1.69 (d, *J* = 5.2 Hz, 1H)); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.2, 137.8, 135.6, 134.7, 131.5, 127.9, 127.5, 118.3, 115.9, 42.7, 39.4, 22.6; FTIR (neat, cm^{-1}) 3086 (br), 3027, 2604 (br), 1690, 1417,1295, 1221, 992, 916, 700; HRMS (EI) calcd for $C_{14}H_{15}O_2$ *m/z* 215.1072 $[M+H]^+$, found 215.1072.

General Procedure A: Ghosez reagent (1.05 equiv) was added to a solution of acid **1.74** (1.0 equiv) in DCM (0.4 M) at 0 °C, the mixture was stirred at this temperature for 30 min. Amine (2.0 equiv), DIPEA (1.5 equiv), and DMAP (0.1 equiv) were added, the mixture was warmed to room temperature and stirred 2 h. The mixture was quenched with aqueous NH_4Cl, the phases were separated and the aqueous phase extracted with EtOAc. The combined organic

phase was washed with brine, dried over $MgSO_4$, filtered and evaporated. The residue was subjected to flash chromatography (generally 5-10% EtOAc in hexanes) to give the stated product.



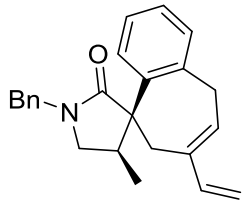
***N*-allyl-*N*-benzyl-1-phenyl-2,2-divinylcyclopropane-1-carboxamide (1.68)**: General procedure A was applied to *N*-allyl-*N*-benzylamine to give the product (74 mg, 69%) as a clear oil: ^{1}H NMR ($CDCl_3$, 400 MHz) (1.2:1 mixture of rotamers) δ 7.50–7.41 (m, 2H), 7.34–7.14 (m, 6H), 7.08–7.02 (m, 1H), 6.80–6.72 (m, 1H), 6.29–6.13 (m, 1H), 5.65–5.55 (m, 0.45 H), 5.54–5.42 (m, 1H), 5.35–5.24 (m, 0.55 H), 5.24–4.91 (m, 6H), 4.90–4.80 (m, 1H), 4.61–4.48 (m, 1H), 4.36 (d, *J* = 14.7 Hz, 0.55 H), 4.13–4.04 (m, 0.58 H), 3.99–3.81 (m, 1H), 3.56 (dd, *J* = 15.1 Hz, 6.1 Hz, 0.45 H), 1.96 (d, *J* = 5.5 Hz, 0.54 H), 1.92 (d, *J* = 5.5 Hz, 0.44 H), 1.77 (d, *J* = 5.6 Hz, 0.63 H), 1.74 (d, *J* = 5.5 Hz, 0.42 H); ^{13}C NMR ($CDCl_3$, 100 MHz) (1.2:1 mixture of rotamers) δ 170.1, 170.0, 138.6 (overlapping resonances), 137.9, 137.8, 137.3, 136.5, 136.5, 136.3, 133.2, 132.5, 129.7, 129.6, 128.5, 128.4, 128.3, 128.3, 128.1, 127.3, 127.1, 127.0, 126.9, 118.1, 117.2, 115.6, 115.5, 114.8 (overlapping resonances), 50.0, 49.0, 46.7, 46.6, 43.0, 42.9, 37.6, 37.5, 21.7, 21.6; FTIR (neat, cm^{-1}) 3083, 3027, 2918, 1637, 1450, 1413, 1266, 1242, 125, 993, 917, 735; HRMS (EI) calcd for $C_{24}H_{26}NO$ *m/z* 344.2014 $[M+H]^+$, found 344.2039.



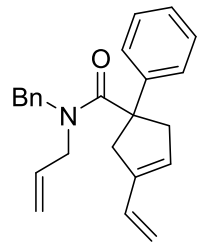
2-Benzyl-6a-phenyl-5,5-divinylhexahydrocyclopenta[c]pyrrol-1(2*H*)-one (1.75): Amide **1.68** (10 mg, 0.03 mmol) and $(PhS)_2$ (3.8 mg, 0.03 mmol) were dissolved in C_6D_6 (2.9 mL) in a quartz NMR tube, placed in front of UV wand. After 2 h, TLC and ^{1}H NMR show full conversion. Flash chromatography (20% EtOAc in hexanes) provided the title compound (5 mg, 50%) as a clear oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39–7.15 (m, 10H), 5.83, (dd, *J* = 18.0 Hz, 10.4, Hz, 1H), 5.78 (dd, *J* = 18.2 Hz, 10.6 Hz, 1H), 5.04–4.97 (m, 3H), 4.89 (d, *J* = 17.5 Hz, 1H), 4.51 (d, *J* = 14.4 Hz, 1H), 4.29 (d, *J* = 14.5 Hz, 1H), 3.50 (dd, *J* = 9.7 Hz, 7.7 Hz, 1H), 3.02 (t, *J* = 7.4 Hz, 1H), 2.96 (d¸ *J* = 10.4 Hz, 1H), 2.79 (d, *J* = 13.8 Hz, 1H), 2.30 (d, *J* = 13.87 Hz, 1H), 2.15 (dd, *J* = 12.5 Hz, 8.1 Hz, 1H), 1.70 (dd, *J* = 13.0 Hz, 8.0 Hz, 1H) ; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.0, 143.6, 143.5, 143.2, 136.2, 128.6, 128.5, 128.3, 127.6, 126.7, 126.2, 113.3,113.2, 60.7, 52.7, 50.0, 47.6, 47.2, 43.7, 42.1, 29.7; FTIR (neat, cm^{-1}) 2917, 2849, 1684, 1494, 1443, 1268, 919, 698; HRMS (EI) calcd for $C_{24}H_{26}NO$ *m/z* 344.2014 $[M+H]^+$, found 334.1992.

Reaction of enantio-enriched amide 1.68: Amide **1.68** was resolved by semipreparative runs on a Whelk column eluting with 5% iPrOH in hexanes. Each enantiomer, 1st 97.5:2.5 er, 2nd 4.6: 95.4 er, was separately subjected to conditions described above; the products were isolated in comparable yields then analyzed using analytical Whelk column eluting with 15% iPrOH in hexanes. The HPLC traces of the isolated products were compared to the racemic standard, retention times for the product **1.75** eluting with 15% iPrOH in hexanes were 11 and 47 min. The product er for the 1st eluting enantiomer was 48.5:51.5, the product er for the 2nd eluting enantiomer was 51.5:48.5.

General Procedure B: The divinylcyclopropane substrate was heated in D_8-PhMe at 110 °C for 120 minutes, the reaction progress was followed by ^{1}H NMR. The residue after evaporation was subjected to flash chromatography (10-20% EtOAc in hexanes) to give the stated product.

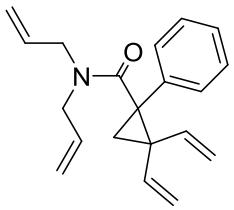


1'-Benzyl-4'-methyl-7-vinyl-6,9-dihydrospiro[benzo[7]annulene-5,3'-pyrrolidin]-2'-one (1.78): General procedure B was applied to divinylcyclopropane **1.68** (31 mg, 0.09 mmol) to give the product (22 mg, 71%%) as a clear oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39-7.32 (m, 5H), 7.11-7.06 (m, 4H), 6.42 (dd, *J* = 17.0 Hz, 12.0 Hz, 1 H), 6.04 (t, *J* = 2.0 Hz, 1H), 5.16 (d, *J* = 17.0 Hz, 1H), 4.96 (d, *J* = 12.0 Hz, 1H), 4.69 (d, *J* = 14.0 Hz), 4.49 (d, *J* = 14.0 Hz, 1H), 3.80 (dd, *J* = 17.0 Hz, 6.0 Hz, 1H), 3.44 (dd, *J* = 17.5 Hz, 6.0 Hz, 1H), 3.34 (dd, *J* = 10.0 Hz, 8.0 Hz, 1H), 3.24 (d, *J* = 16.0 Hz, 1 H), 2.83 (dd, *J* = 10.0 Hz, 6.0 Hz, 1H), 2.63 (hex, *J* = 7.0 Hz, 1 H), 2.56 (d, *J* = 15.5 Hz, 1H), 0.55 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.9, 140.2, 138.3, 137.5, 136.5, 130.8, 130.2, 129.3, 128.7, 127.8, 126.8, 126.7, 126.3, 111.2, 53.9, 47.0, 35.8, 35.7, 33.8, 16.6; FTIR (neat, cm^{-1}) 2926, 2872, 1682, 1493, 1427, 1259, 902, 703; HRMS (EI) calcd for $C_{24}H_{26}NO$ *m/z* 344.2014 $[M+H]^+$, found 344.1991.

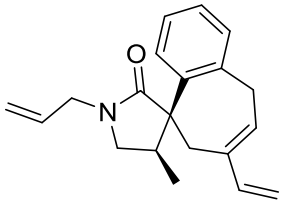


***N*-allyl-*N*-benzyl-1-phenyl-3-vinylcyclopent-3-ene-1-carboxamide (1.77)**: General procedure B was applied to divinylcyclopropane **1.68** to give the product (5 mg, 16%) as a clear oil: ^{1}H NMR ($CDCl_3$, 400 MHz) (2:1 rotamers) δ 7.35–7.14 (m, 9.35H), 6.93 (app d, *J* = 6.4 Hz, 0.65H), 6.53 (dd, *J* = 16.9 Hz, 11.0 Hz, 1H), 5.86–5.73 (m, 0.35H), 5.66 (s, 0.65H), 5.63 (s, 0.35H), 5.29 (ddd, *J* = 16.6 Hz, 10.5 Hz, 5.6 Hz, 0.65H), 5.17–5.91 (m, 4H), 4.61 (s, 1.3H), 4.10 (s, 0.7H), 3.92 (d, *J* = 5.3 Hz, 0.65H), 3.62–3.40 (m, 3.35H), 2.90–2.69 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) (2:1 rotamers) δ 175.4, 175.2, 146.0, 145.8, 139.9, 137.6, 132.9, 132.4, 129.0, 128.8, 128.6, 128.4, 127.3, 127.2, 127.0, 126.5, 124.6, 118.5, 117.9, 114.4, 57.9, 57.8, 50.6, 49.7, 48.1, 47.7, 45.6, 45.4, 43.2, 43.2; FTIR (neat, cm^{-1})3027, 2924, 2851, 1634, 1443, 1401, 1228, 700; HRMS (EI) calcd for $C_{24}H_{26}NO$ *m/z* 344.2014 $[M+H]^+$, found 344.1991.

Structure confirmation of vinylcyclopentene 1.77: Vinylcyclopentenecaboxylic acid **1.74** (5 mg, 0.02 mmol) was dissolved in DCM, cooled to 0 °C. Ghosez reagent (4 µL, 1 equiv) was added, the mixture was stirred 30 min. Benzylallylamine (13 µL, 2.5 equiv) was added followed by DMAP (1 mg, 0.3 equiv), the mixture was stirred 16 h. Aqueous NH_4Cl was added to the mixture, the aqueous layer was extracted twice with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and then volatile compounds were removed under vacuum. Flash chromatography (5% EtOAc in hexanes) gave the product (4 mg, 50%) as a clear oil, the characterization was identical to material obtained above.

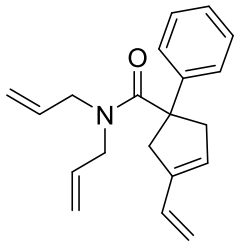


***N*,*N*-diallyl-1-phenyl-2,2-divinylcyclopropane-1-carboxamide (1.80)**: General procedure A was applied to *N*,*N*-diallylamine (86 µL, 0.79 mmol) to give the product (84 mg, 82%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.2 Hz, 2H), 7.33-7.25 (m, 3H), 6.16 (dd, *J* = 17.2 Hz, 10.4 Hz, 1H), 5.62 (ddt, *J* = 17.2 Hz, 10.8 Hz, 5.6 Hz, 1H), 5.52 (dd, *J* = 17.2 Hz, 10.8 Hz, 1H), 5.35 (ddt, *J* = 17.2 Hz, 10.8 Hz, 5.6 Hz, 1H), 5.19-4.92 (m, 8H), 4.25 (dd, *J* = 16.0 Hz, 4.8 Hz, 1H), 4.03 (dd, *J* = 16.0 Hz, 4.8 Hz, 1H), 3.87 (dd, *J* = 16.0 Hz, 5.6 Hz, 1H), 3.67 (dd, *J* = 14.8 Hz, 6.0 Hz, 1H), 1.97 (d, *J* = 5.6 Hz, 1H), 1.76 (d, *J* = 5.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 138.6, 137.8, 136.6, 133.3, 132.8, 129.7, 128.3, 127.1, 117.8, 116.9, 115.7, 114.7, 49.3, 46.5, 42.9, 37.5, 21.7; FTIR (thin film, $CHCl_3$) 3082, 3010, 2983, 2922, 1637, 1637, 1451, 1410, 1245, 1209, 993, 920 cm^{-1}; HRMS (TOF ES) calcd for $C_{20}H_{23}NONa$, *m/z* 316.1677 $[M+Na]^+$, found: 316.1664.



(3'*R*,4'*R*)-1'-Allyl-4'-methyl-7-vinyl-6,9-dihydrospiro[benzo[7]annulene-5,3'-pyrrolidin]-2'-one (1.81): General procedure B was applied to divinylcyclopropane **1.80** (48 mg, 0.162 mmol) to provide the title compound (31 mg, 65%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17-7.09 (m, 4H), 6.46 (dd, *J* = 17.5 Hz, 11.0 Hz, 1H), 6.07 (tt, *J* = 6.0 Hz, 1.0 Hz, 1H), 5.87 (ddt, *J* = 17.0 Hz, 10.0 Hz, 6.5 Hz, 1H), 5.31 (dq, *J* = 17.0 Hz, 1.5 Hz, 1H), 5.29

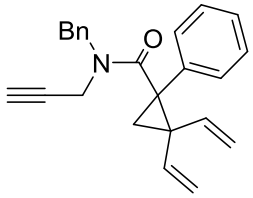
(dq, *J* = 10.0 Hz, 1.5 Hz, 1H), 5.22 (d, *J* = 17.0 Hz, 1H), 5.02 (d, *J* = 11.0 Hz, 1H), 4.11 (ddt, *J* = 15.0 Hz, 6.5 Hz, 1.5 Hz, 1H), 4.01 (ddt, *J* = 15.0 Hz, 6.5 Hz, 1.5 Hz, 1H), 3.83 (dd, *J* = 17.5 Hz, 6.5 Hz, 1H), 3.48 (m, 1H), 3.47 (dd, *J* = 10.0 Hz, 8.0 Hz, 1H), 3.22 (dd, *J* = 15.5 Hz, 1.0 Hz, 1H), 2.98 (dd, *J* = 10.0 Hz, 6.0 Hz, 1H), 2.69 (ddq, *J* = 8.0 Hz, 7.0 Hz, 6.0 Hz, 1H), 2.59 (d, *J* = 16.0 Hz, 1H), 0.62 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 HMz, $CDCl_3$) δ 177.8, 140.3, 138.2, 137.6, 137.5, 132.4, 130.9, 130.2, 129.2, 126.8, 126.4, 118.6, 111.2, 54.1, 51.6, 45.6, 35.8, 35.7, 33.9, 16.7; FTIR (thin film, $CHCl_3$) 2926, 1683, 1438, 1263, 992, 927, 760 cm^{-1}; HRMS (TOF ES) calcd for $C_{20}H_{24}NO$ *m/z* 294.1858 $[M+H]^+$, found: 294.1848.



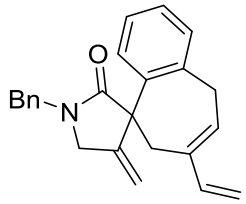
N,N-diallyl-1-phenyl-3-vinylcyclopent-3-ene-1-carboxamide (1.82): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.34 (m, 5H), 6.39 (dd, *J* = 17.6 Hz, 10.9 Hz, 2H), 5.93 (s, 2H), 5.28–5.12 (m, 6H), 4.60 (dd, *J* = 16.1 Hz, 7.2 Hz, 2H), 4.48 (dd, *J* = 12.4 Hz, 3.9 Hz, 2H), 3.06–2.94 (m, 2H), 2.85–2.77 (m, 2H); ^{13}C NMR (100 HMz, $CDCl_3$) δ 174.2, 140.1, 138.9, 138.0, 128.6, 128.3, 127.7, 124.9, 114.3, 63.9, 45.1, 32.1; FTIR (thin film, $CHCl_3$) cm^{-1} 3025, 2924, 2850, 1633, 1443, 1407, 1232, 700; HRMS (TOF ES) calcd for $C_{20}H_{24}NO$ *m/z* 294.1858 $[M+H]^+$, found: 294.1850.

Thermal reaction of enantio-enriched amide 1.80: Amide **1.80** was resolved by semipreparative runs on a Whelk column. Each enantiomer, 1st 96:4 *er*, 2nd 1:99 *er*, was separately subjected to General Procedure B; the reaction mixture was diluted, filtered and

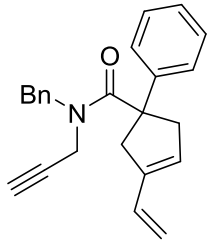
directly analyzed by chiral HPLC. The HPLC traces of the isolated products were compared to the racemic standard, retention times for the product eluting with15% iPrOH in hexanes were 6.7 and 7.2 min for **1.82** and 18.2 and 19.2 min for **1.81**. The *er* of product **18.1** for the 1st eluting enantiomer was 65:35, the *er* of **1.81** for the 2nd eluting enantiomer was 35:65.



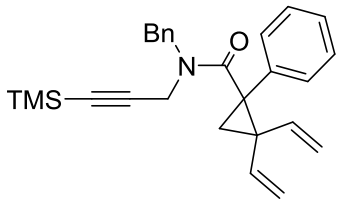
***N*-benzyl-*N*-propargyl-1-phenyl-2,2-divinylcyclopropane-1-carboxamide (1.83)**: General procedure A was applied to *N*-benzyl-*N*-propargylamine (31 µL, 0.23 mmol) to give the title compound (55 mg, 69%) as a clear oil: ^{1}H NMR ($CDCl_3$, 500 MHz) (1:1 mixture of rotamers) δ 7.48-7.42 (m, 2H), 7.33-7.06 (m, 8H), 6.74 (d, *J* = 6.5 Hz, 1H), 6.22-6.10 (m, 1H), 5.56-5.35 (m, 1H), 5.24-4.79 (m, 5H), 4.60 (d, *J* = 15.4 Hz, 0.5H), 4.42 (d, *J* = 14.7 Hz, 0.5H), 4.17 (d, *J* 17.7 Hz, 0.5H), 4.02 (d, *J* = 16.8 Hz, 0.5H), 3.90-3.80 (m, 1H), 2.20-1.74 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) (1:1 mixture of rotamers) δ 170.1, 169.5, 138.5, 138.2, 137.5, 137.4, 136.6, 136.2, 135.8, 135.5, 132.6, 131.3, 129.7, 129.4, 128.9, 128.7, 128.6, 128.5, 128.4, 128.3, 127.6, 127.5, 127.3, 127.3, 127.2, 127.1, 117.8, 116.0, 115.0, 114.9, 78.5, 78.2, 73.0, 71.5, 50.0, 47.2, 42.7, 37.7, 37.2, 36.4, 33.2, 23.8, 21.9, 21.4, 18.3; FTIR (neat, cm^{-1}) 3302, 3054, 2985, 1642, 1449, 1418, 1266, 1204, 1078, 997, 913; HRMS (EI) calcd for $C_{24}H_{24}NO$ *m/z* 342.1858 $[M+H]^+$, found 342.1855.



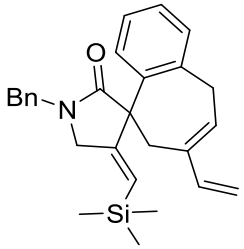
1'-Benzyl-4'-methylene-7-vinyl-6,9-dihydrospiro[benzo[7]annulene-5,3'-pyrrolidin]-2'-one (**1.84)**: General procedure B was applied to divinylcyclopropane **1.83** (15 mg, 0.029 mmol), ^{1}H NMR of the crude residue shows the title compound with a minor compound **1.85**, the product of the VCP-CP reaction, in a 5:1 ratio. Flash chromatography (20% EtOAc in hexanes) provided the title compound (11 mg, 73%) as a clear oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41-7.33 (m, 5H), 7.10-7.07 (m, 3H), 6.81 (app t, *J* = 3.2 Hz, 1H), 6.35 (dd, *J* = 17.6 Hz, 10.8 Hz, 1H), 6.23 (t, *J* = 6.4 Hz, 1H), 4.97-4.88 (m, 3 H), 4.64-4.60 (m, 3H), 4.04 (dd, *J* = 16.0 Hz, 6.0 Hz, 1H), 3.97 (d, *J* = 14.4 Hz, 1H), 3.89 (d, *J* = 13.6 Hz, 1H), 3.39 (d, *J* = 15.6 Hz, 1H), 3.34 (dd, *J* = 16.0 Hz, 7.6 Hz, 1H), 2.61 (d, *J* = 14.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.0, 147.4, 139.9, 139.4, 137.7, 137.6, 136.3, 132.2, 131.9, 130.3, 128.8, 128.3, 127.8, 126.8. 126.6, 112.4, 111.1, 55.6, 50.2, 46.7, 34.5, 31.3; FTIR (neat, cm^{-1}): 3061, 2920, 1689, 1659, 1438, 1253, 1169, 1079, 906, 735; HRMS (EI) calcd for $C_{24}H_{24}NO$ *m/z* 342.1858 $[M+H]^+$, found 342.1839.



***N*-benzyl-1-phenyl-*N*-(prop-2-yn-1-yl)-3-vinylcyclopent-3-ene-1-carboxamide (1.85)**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.27 (m, 5H), 6.96 (s, 1H), 6.61–6.47 (br m, 1H), 5.66 (s, 1H), 5.19–4.92 (m, 3H), 4.86–4.70 (m, 1H), 4.18 (s, 1H), 4.09 (s, 1H), 3.66–3.43 (m, 3H), 2.93–2.74 (m, 2H), 2.20 (s, 1H).

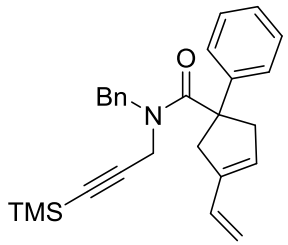


***N*-benzyl-1-phenyl-*N*-(3-(trimethylsilyl)prop-2-yn-1-yl)-2,2-divinylcyclopropane-1-carboxamide (1.86)**: General procedure A was applied to *N*-benzyl-1-phenyl-*N*-(3-(trimethylsilyl)prop-2-yn-1-yl)amine (41 mg, 0.19 mmol) to give the title compound (30 mg, 78%) as a clear oil: ^{1}H NMR ($CDCl_3$, 400 MHz) (2:1 mixture of rotamers) δ 7.49-7.40 (m, 2H), 7.36-7.07 (m, 8H), 6.74 (d, *J* = 6.3 Hz, 1H), 6.16 (dd, *J* = 17.1 Hz, 10.5 Hz, 1H), 5.62-5.42 (m, 1H), 5.22-5.09 (m, 1H), 5.04-5.93 (m, 2H), 4.79-4.67 (m, 1H), 4.45-4.30 (1.5H), 4.06-3.83 (m, 1.5H), 2.15-1.94 (m, 1H), 1.83-1.77 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) (2:1 mixture of rotamers) δ 169.9, 169.4, 138.4, 138.2, 137.5, 137.3, 136.7, 136.2, 135.8, 135.6, 129.6, 129.5, 128.8, 128.7, 128.4, 128.3, 128.3, 127.4, 127.2, 127.2, 127.1, 127.1, 125.6, 116.0, 115.7, 114.8, 100.2, 99.9, 89.9, 88.4, 49.9, 47.6, 42.8, 42.7, 37.7, 37.6, 37.6, 34.3, 33.8, 29.6, 22.0, 21.3, -0.2, -0.3; FTIR (neat, cm^{-1}) 3084, 3062, 3029, 2960, 2922, 2177, 1648, 14951449, 1411, 1249, 1000, 912, 846; HRMS (ESI) calcd for $C_{27}H_{32}NOSi$ *m/z* 414.2253 $[M+H]^+$, found 414.2238.

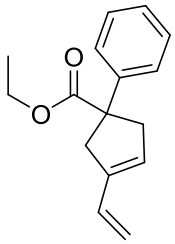


(Z)-1'-benzyl-4'-((trimethylsilyl)methylene)-7-vinyl-6,9-dihydrospiro[benzo[7]annulene-5,3'-pyrrolidin]-2'-one (**1.87**): General procedure B was

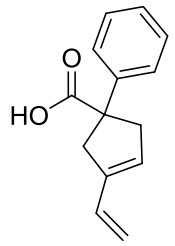
applied to divinylcyclopropane **1.86** (28 mg, 0.07 mmol), H NMR of the crude residue shows the title compound with a minor compound, assigned as the product of the VCP-CP reaction, in a 4.5:1 ratio. Flash chromatography (15% EtOAc in hexanes) provided the title compound (14.8 mg, 53%) as a clear oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.66-7.46 (m, 5H), 7.35-7.28 (m, 3H), 7.00-6.95 (m, 1H), 6.97 (d, *J* = 8.6 Hz, 1H), 6.54 (dd, *J* = 17.4 Hz, 10.8 Hz, 1H), 6.45 (t, *J* = 6.7 Hz, 1H), 5.30 (t, *J* = 2.2 Hz, 1H), 5.13 (d, *J* = 18.2 Hz, 1H), 5.10 (d, *J* = 11.3 Hz, 1H), 4.92 (d, *J* = 14.7 Hz, 1H), 4.83 (d, *J* = 14.6 Hz, 1H), 4.32 (dd, *J* = 15.6 Hz, 5.7 Hz, 1H), 4.22 (app dd, *J* = 14.1 Hz, 2.6 Hz, 1H), 4.16 (app dd, *J* = 14.1 Hz, 1.9 Hz, 1H), 3.62 (dd, *J* = 14.4 Hz, 1.0 Hz, 1H), 3.50 (dd, *J* = 15.7 Hz, 7.9 Hz, 1H), 2.81 (d, *J* = 14.3 Hz, 1H), 0.15 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ177.2, 124.6, 140.1, 139.3, 137.9, 137.6, 136.3, 132.5, 132.2, 130.2, 128.8, 128.1, 127.8, 127.0, 126.6, 111.1, 57.2, 50.4, 46.6, 34.5, 31.6, -0.8; FTIR (neat, cm^{-1}) 3028, 2952, 1694, 1635, 1493, 1422, 1247, 863, 841, 735; HRMS (EI) calcd for $C_{27}H_{32}NOSi$ *m/z* 414.2253 $[M+H]^+$, found 414.2262.



N-benzyl-1-phenyl-N-(3-(trimethylsilyl)prop-2-yn-1-yl)-3-vinylcyclopent-3-ene-1-carboxamide (1.88): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.27 (m, 5H), 7.00 (s, 1H), 6.61–6.47 (br m, 1H), 5.60 (s, 1H), 5.18–4.91 (m, 3H), 4.86–4.70 (m, 1H), 4.21–4.05 (m, 2H), 4.09 (s, 1H), 3.73–3.41 (m, 3H), 2.99–2.70 (m, 2H), 0.12–0.12 (m, 9H).

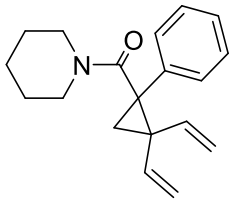


Ethyl 1-phenyl-3-vinylcyclopent-3-ene-1-carboxylate (**1.89)**: General procedure B was applied to ester **1.73** (15 mg, 0.015 mmol) to give the title compound (13 mg, 87%) as a clear oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32-7.20 (m, 5H), 6.52 (dd, *J* = 17.2 Hz, 10.0 Hz, 1H), 5.71 (s, 1H), 5.18 (d, *J* = 17.2 Hz), 5.11 (d, *J* = 10.0 Hz, 1H), 4.11 (q, *J* = 7.2 Hz, 2 H), 3.53-3.48 (m, 2H), 3.53-3.48 (m, 2H), 1.16 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.9, 143.9, 141.3, 133.0, 128.4, 128.2, 126.7, 126.3, 114.6, 61.2, 58.0, 43.2, 41.1, 14.0; FTIR (neat, cm^{-1}) 3054, 2985, 1722, 1640, 597, 1495, 1446, 1265, 1226, 1166, 1051, 909, 738; HRMS (EI) calcd for $C_{16}H_{19}O$ *m/z* 243.1385 $[M+H]^+$, found 243.1361.

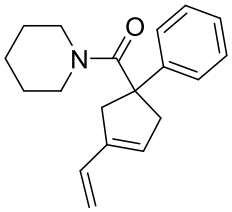


1-Phenyl-3-vinylcyclopent-3-ene-1-carboxylic acid (**1.90)**: General procedure B was applied to acid **1.74** (10 mg, 0.05 mmol) to give the title compound (8.6 mg, 86%) as a white crystalline solid, mp 86–88 °C: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.88 (br s, 1H), 7.36 (d, *J* = 7.4 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.24 (t, *J* = 7.0 Hz, 1H), 6.50 (dd, *J* = 17.4 Hz, 10.6 Hz, 1H), 5.70 (s, 1H), 5.17 (d, *J* = 17.5 Hz, 1H), 5.11 (d, *J* = 10.6 Hz, 1H), 3.52 (app t *J* = 15.8 Hz, 2H), 2.84 (app d, *J* = 15.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.3, 142.7, 141.4, 132.8, 128.5, 128.1, 127.1, 126.8, 114.8, 58.1, 42.7, 40.7 ; FTIR (neat, cm^{-1}) : 3441, 3054, 2917, 1695, 1641,

14, 1446, 1282, 1227, 1193, 985, 903; HRMS (EI) calcd for $C_{14}H_{15}O_2$ *m/z* 215.1072 $[M+H]^+$, found 215.1072.

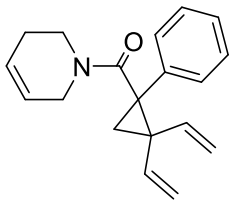


(1-Phenyl-2,2-divinylcyclopropyl)-(piperidin-1-yl)methanone (1.91): General procedure A was applied to piperidine (13 µL, 0.14 mmol) to give the title compound (17 mg, 84%) as a clear oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.43 (d, J=7.8 Hz, 2H), 7.28 (t, J=8.3 Hz, 2H), 7.21 (t, J=7.3 Hz, 1H), 6.10 (dd, J=17.1 Hz, 10.5, 1H), 5.54 (dd, J=17.2 Hz, 10.60 Hz, 1H), 5.14 (d, J=10.45 Hz, 1H), 5.09 (d, J=17.2 Hz, 1H), 5.00 (d, J=17.9 Hz, 1H), 4.99 (d, J=9.8 Hz, 1H), 3.68-3.61 (m, 1H), 3.54-3.46 (m, 1H), 3.46-3.33 (m, 2H), 1.84 (d, J=5.4 Hz, 1H), 1.76 (d, J=5.4 Hz, 1H), 1.60-1.27 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.5, 138.8, 137.6, 136.8, 129.5, 128.1, 126.8, 115.7, 114.3, 46.8, 43.1, 42.9, 37.4, 25.9, 25.4, 24.4, 22.3; FTIR (neat, cm^{-1}) 3150, 2927, 2853, 1623, 1447, 1430, 1384, 1239, 1095, 912, 738, 651; HRMS (ESI) calcd for $C_{19}H_{24}NO$ *m/z* 282.1858 $[M+H]^+$, found 282.1858.

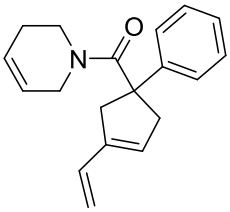


(1-Phenyl-3-vinylcyclopent-3-en-1-yl)(piperidin-1-yl)methanone (1.92): General procedure B was applied to amide **1.91** (20 mg, 0.07 mmol) to give the title compound (18 mg, 90%) as a clear oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.30 (t, *J* = 7.6 Hz, 2H), 7.23-7.12 (m, 3H),

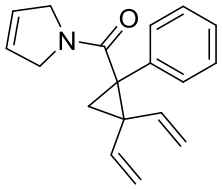
6.53 (dd, *J* = 17.4 Hz, 10.7 Hz, 1H), 5.65 (s, 1H), 5.09 (d, *J* = 17.5 Hz, 1H), 5.07 (d, *J* = 10.5 Hz, 1H), 3.72-3.51 (br s, 2H), 3.50 (app d, *J* = 18.5 Hz, 1H), 2.96 (br s, 2H), 2.83 (app d, *J* = 16.1 Hz, 1H), 2.77 (app d, *J* = 16.1 Hz, 1H), 2.77 (app d, *J* = 18.2 Hz, 1), 1.49 (br m, 4H) 1.09 (br s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.6, 146.6, 139.9, 132.9, 128.7, 127.5, 126.2, 124.4, 114.2, 57.4, 47.4, 45.7, 43.4, 29.7, 25.5, 25.3, 24.4; FTIR (neat, cm^{-1}) 3003, 2943, 1632, 1445, 1376, 1039, 919; HRMS (ESI) calcd for $C_{19}H_{24}NO$ *m/z* 282.1858 $[M+H]^+$, found 282.1864.



(3,6-dihydropyridin-1(2*i*)-yl)(1-phenyl-2,2-divinylcyclopropyl)methanone (1.93): General procedure A was applied to 1,2,3,6-tetrahydropyridine (21 µL, 0.23 mmol) to give the title compound (50 mg, 77%) as a clear oil: ^{1}H NMR ($CDCl_3$, 500 MHz) (1:1 rotamers) δ 7.45-7.18 (m, 5H), 6.11-6.00 (m, 1H), 5.81-5.66 (m, 1H), 5.63-5.54 (m, 1H), 5.34-5.21 (m, 1H), 5.14-4.90 (m 4H), 4.24-4.74 (m, 2.5H), 3.48-3.26 (m, 1H), 3.19-2.78 (m, 0.5H), 2.78-1.66 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) (1:1 rotamers) δ 174.6, 169.2, 168.8, 138.4, 137.8, 137.7, 137.6, 137.4, 136.5, 136.4, 136.2, 135.8, 134.8, 131.5, 130.1, 129.7, 129.5, 128.6, 128.4, 128.2, 128.1, 127.8, 127.3, 126.9, 126.3, 125.6, 124.5, 124.3, 123.5, 118.0, 115.9, 115.8, 115.7, 114.9, 114.6, 45.7, 43.3, 42.8, 42.8, 42.5, 42.4, 39.2, 39.0, 37.5, 37.4, 29.6, 25.2, 24.8, 22.6, 22.4, 22.2; FTIR (neat, cm^{-1}) 3150, 2927, 2853, 1623, 1447, 1430, 1384, 1239, 1095, 912, 738, 651; HRMS (EI) calcd for $C_{19}H_{22}NO$ *m/z* 280.1701 $[M+H]^+$, found 280.1689.

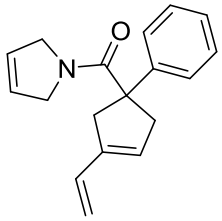


(3,6-Dihydropyridin-1(2*H*)-yl)(1-phenyl-3-vinylcyclopent-3-en-1-yl)methanone (1.94): General procedure B was applied to amide **1.93** (24 mg, 0.09 mmol) to give the title compound (22 mg, 91%) as a clear oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30 (t, *J* = 7.3 Hz, 2H), 7.22-7.15 (m, 3H), 6.54 (dd, *J* = 17.3 Hz, 10.8 Hz, 1H), 5.81-5.53 (br m, 3H), 5.09 (d, *J* = 18.5 Hz, 1H), 5.08 (d, *J* = 9.8 Hz, 1H), 4.11 (br s, 1.3H), 3.75 (br s, 0.7H) 3.51 (br m, 3H), 3.09 (br s, 1.3 H), 2.81 (br m, 2H), 2.17 (br s, 0.7H), 1.68 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.4, 146.5, 134.0, 132.9, 128.9, 128.8, 127.5, 126.3, 124.6, 124.4, 114.4, 57.4, 45.6, 43.4, 29.7, 24.8, 22.7; FTIR (neat, cm^{-1}) 3150, 2927, 2853, 2253, 1794, 1623, 1447, 1430, 1384, 1239, 1095, 912, 738, 650; HRMS (ESI) calcd for $C_{19}H_{22}NO$ *m/z* 280.1701 $[M+H]^+$, found 280.1710.

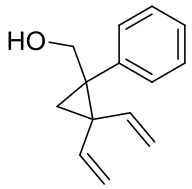


(2,5-Dihydro-1*H*-pyrrol-1-yl)-(1-phenyl-2,2-divinylcyclopropyl)methanone (1.95): General procedure A was applied to 2,5-dihydro-1H-pyrrole (35 µL, 0.47 mmol) to give the title compound (55 mg, 89%) as a thick clear oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.44 (d, J = 7.5, 2H), 7.28 (1, *J* = 7.7 Hz, 3H), 7.23 (d, *J* = 7.2 Hz, 1H), 6.12 (dd, *J* = 17.1 Hz, 10.4 Hz), 5.77 (d, J=6.4 Hz, 1 H) 5.70 (d, J=6.5 Hz, 1 H), 5.53 (dd, J=17,2 Hz, 10.6 Hz, 1 H), 5.15 (d, J=10.5 Hz, 1 H), 5.11 (d, J=17.0 Hz, 1 H), 4.99 (d, J=19.0 Hz, 1 H), 4.98 (d, J=10.1 Hz, 1 H), 4.34-4.08 (m, 4H), 1.87 (d, J=5.45 Hz, 1 H), 1.76 (d, J=5.45 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.2, 138.8,

137.5, 135.6, 131.5, 129.9, 128.2, 127.8, 127.1, 125.8, 125.1, 115.9, 114.7, 53.7, 53.0, 43.9, 37.5, 21.7; FTIR (neat, cm^{-1}) 3054, 2986, 1708, 1640, 1603, 1420, 1265, 896, 739; HRMS (EI) calcd for $C_{18}H_{20}NO$ *m/z* 266.1545 $[M+H]^+$, found 266.1534.

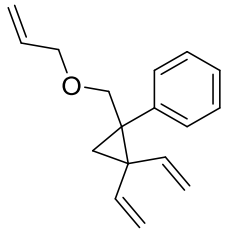


(2,5-Dihydro-1*H*-pyrrol-1-yl)(1-phenyl-3-vinylcyclopent-3-en-1-yl)methanone (1.96): General procedure B was applied to amide **1.95** (15 mg, 0.06 mmol) to give the title compound (12 mg, 80%) as a clear oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.30-7.18 (m, 5H), 6.54, (dd, *J* = 10.5 Hz, 17.5 Hz, 1H), 5.79-5.77 (m, 1H), 5.67 (s, 1H), 5.56-5.55 (m, 1H), 5.11 (d, *J* = 17.0 Hz, 1H), 5.08 (d, *J* = 10.0 Hz, 1H), 4.35 (s, 2H), 3.70 (d, *J* = 14.8 Hz, 1H), 3.62 (d, *J* = 14.7 Hz, 1H), 3.51 (d, *J* = 17.9 Hz, 1H), 3.41 (d, *J* = 16.0 Hz, 1H), 2.90 (d, *J* = 16.0 Hz, 1H), 2.81 (d, *J* = 17.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.7, 145.1, 140.0, 133.0, 128.8, 127.5, 126.4, 125.3, 125.2, 125.1, 114.4, 57.7, 55.0, 53.0, 44.6, 42.2; FTIR (neat, cm^{-1}) 3054, 2986, 1708, 1640, 1603, 1420, 1265, 739; HRMS (EI) calcd for $C_{18}H_{20}O$ *m/z* 266.1545 $[M+H]^+$, found 266.1575.



(1-Phenyl-2,2-divinylcyclopropyl)methanol (1.104): LAH (0.12 mL, 1M in hexanes, 0.12 mmol) was added dropwise to solution of ester **1.73** (27 mg, 0.12 mmol) in THF (2 mL) at —78 °C, the mixture was allowed to slowly warm to room temperature. The mixture was poured

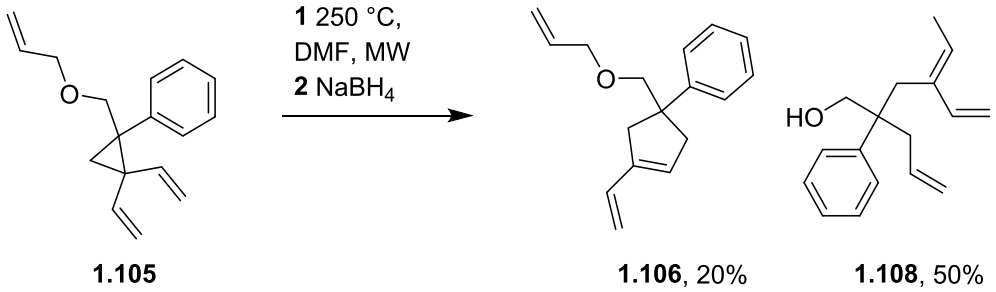
into saturated aqueous Rochelle's salt (5 mL) mixture at 0 °C, the mixture was stirred 14 h. The aqueous phase was extracted, the combined organic phase was washed with brine, dried over $MgSO_4$ and volatile compounds are removed under vacuum. Flash chromatography (15% EtOAc in hexanes) gave the title compound (23 mg, 97%) as a clear oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35-7.24 (m, 5H), 6.26 (dd, *J* = 17.2 Hz, 10.4 Hz, 1H), 5.37 (d, *J* = 10.4 Hz, 1H), 5.24 (d, *J* = 17.2 Hz, 1H), 5.15 (dd, *J* = 17.2 Hz, 10.4 Hz, 1H), 4.94 (d, *J* = 17.2 Hz, 1H), 4.82 (d, *J* = 10.4 Hz, 1H), 3.79 (d, *J* = 12.0 Hz, 1H), 3.66 (d, *J* = 12.0 Hz, 1H), 1.52 (d, *J* = 5.2 Hz, 1H), 1.35 (d, *J* = 5.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 141.1, 139.7, 136.2, 130.5, 128.4, 126.9, 118.1, 112.9, 68.2, 40.6, 35.9, 21.2; FTIR (neat, cm^{-1}) 3595, 3054, 2981, 2875, 1494, 1423, 1266, 1025, 915; HRMS (EI) calcd for $C_{14}H_{14}$ *m/z* 182.1096 $[M-H_2O]^+$, found 182.1122.



(1-((Allyloxy)methyl)-2,2-divinylcyclopropyl)benzene (**1.105)**: NaH (6 mg, 0.12 mmol) was added in one portion to alcohol **1.104** (24 mg, 0.12 mmol) in DMF (1 mL) at 0 °C. After stirring at this temperature for 30 min, allyl bromide (31 µL, 0.36 mmol) was added; the mixture was allowed to warm to room temperature then stirred 4 h. The mixture was quenched with aq. NH_4Cl, the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and then volatile compounds were removed under vacuum. Flash chromatography (5-10% EtOAc in hexanes) gave the title compound (24 mg, 67%) as a clear oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34-7.18 (m, 5H), 6.25 (dd, J = 17.2, 10.3 Hz, 1H), 5.75 (app dtd, *J* = 21.3 Hz, 10.6 Hz, 5.4 Hz, 1H), 5.22-5.03 (m, 4H), 4.93 (dd, *J* = 17.3 Hz, 1.6 Hz, 1H),

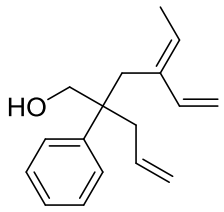
4.79 (dd, *J* = 10.5 Hz, 1.6 Hz, 1H), 3.85-3.74 (m, 2H), 3.59-3.51 (m, 2H), 1.48 (d, *J* = 5.2 Hz, 1H), 1.39 (d, *J* = 5.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 141.2, 140.8, 136.7, 135.0, 130.5, 127.9, 126.4, 117.4, 116.2, 112.8, 75.3, 71.7, 38.4, 36.0, 21.2; FTIR (neat, cm^{-1}): 3081, 2923, 2852, 1727, 1642, 1628, 1496, 1447, 1264, 1133, 1092, 994, 919, 702; HRMS (ESI) calcd for $C_{14}H_{15}$ *m/z* 241.1287 $[M+H]^+$, found 241.1593

General Procedure C: The starting cyclopropane in DMF (1 mL) was heated in a microwave reactor to 250 °C for 5 min. The solvent was removed under vacuum; the residue was analyzed by ^{1}H NMR before flash chromatography was performed.

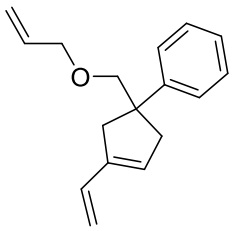


1.105 **1.106**, 20% **1.108**, 50%

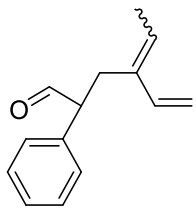
Microwave thermolysis of ether 1.105: General procedure C was applied to vinylcyclopropane **1.105** (10 mg, 0.04 mmol). Inspection of the residue after evaporation by ^{1}H NMR showed a mixture of two products in 2.5:1, which were inseparable by flash chromatography. The reaction mixture was dissolved in EtOH (1 mL) and cooled to 0 °C. Then $NaBH_4$ (3 mg, 0.08 mmol) was added in one portion, the mixture was stirred at this temperature for 1 h. The mixture was quenched by addition of aqueous NH_4Cl. The aqueous layer was extracted with EtOAc, the combined organic layer was washed with brine, dried over $MgSO_4$ then evaporates. Flash chromatography provided alcohol **1.108** (5 mg, 50%) and allyl ether **1.06** (2 mg, 20%):



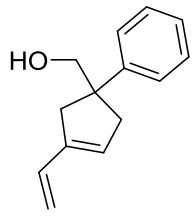
(E)-2-Allyl-2-phenyl-4-vinylhex-4-en-1-ol (1.108): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37–7.27 (m, 4H), 7.23–7.17 (m, 1H), 6.22 (dd, *J* = 17.5 Hz, 10.9 Hz, 1H), 5.77 (dddd, *J* = 17.1 Hz, 10.1 Hz, 8.5 Hz, 5.8 Hz, 1H), 5.65 (q, *J* = 7.15 Hz, 1H), 5.16 (dd, *J* = 17.0 Hz, 1.0 Hz, 1H), 5.06–4.98 (m, 2H), 4.77 (d, *J* = 10.9 Hz, 1H), 3.98-3.88 (m, 2H), 2.78 (app dd, *J* = 14.4 Hz, 5.7 Hz, 1H), 2.63 (app dd, *J* = 14.4 Hz, 8.6 Hz, 1H), 2.54 (app q, *J* = 13.47 Hz), 1.54 (t, J = 6.6 Hz, 1H), 1.18 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.5, 142.1, 135.6, 135.4, 130.5, 128.2, 127.3, 126.1, 117.6, 110.3, 66.3, 47.3, 40.7, 35.5, 14.0; FTIR (neat, cm^{-1}): 3444, 3060, 2921, 2852, 1635, 1499, 1445, 1028, 994, 913; HRMS (ESI) calcd for $C_{17}H_{23}O$ *m/z* 243.1740 $[M+H]^+$, found 243.1737.



(1-((Allyloxy)methyl)-3-vinylcyclopent-3-en-1-yl)benzene (1.106): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38-7.23 (m, 5H), 6.56 (dd, *J* = 17.5 Hz, 10.7 Hz, 1H), 5.75 (app ddt, *J* = 17.3 Hz, 10.6 Hz, 5.4 Hz, 2H), 5.22-5.03 (m, 4H), 5.15 (d, *J* = 17.5 Hz, 1H), 5.09 (d, *J* = 10.6 Hz, 1H), 3.57 (app d, *J* = 6.8 Hz, 2H), 3.59-3.51 (m, 2H), 2.90-2.75 (m, 4H); FTIR (neat, cm^{-1}) 3081, 2920, 2858, 1727, 1639, 1496, 1264, 1092, 919; HRMS (ESI) calcd for $C_{14}H_{15}$ *m/z* 241.1287 $[M+H]^+$, found 241.1590



2-Phenyl-4-vinylhex-4-enal (1.111): General procedure C was applied to alcohol **1.104** (15 mg, 0.07 mmol) to give a mixture of aldehyde **1.111** (9 mg, 6:1 E:Z, 59%) and cyclopentene **1.110** (3 mg, 21%). ^{1}H NMR ($CDCl_3$, 400 MHz) (major) δ 9.77 (d, *J* = 1.3 Hz, 1H), 6.25 (dd, *J* = 17.6 Hz, 10.9 Hz, 1H), 5.58 (q, *J* = 7.1 Hz, 1H), 5.04 (d, *J* = 17.6 Hz, 1H), 4.94 (d, *J* = 10.9 Hz, 1H), 3.70 (td, *J* = 7.2 Hz, 1.9 Hz, 1H), 2.57 (dd, *J* = 13.9 Hz, 8.3 Hz, 1H), 1.37 (d, *J* = 7.0 Hz, 3H); (minor) δ 9.69 (d, *J* = 2.0 Hz, 1H), 6.66 (dd, *J* = 17.6 Hz, 11.1 Hz, 1H) 5.34 (q, 6.9 Hz, 1H), 5.21 (d, *J* = 17.6 Hz, 1H), 5.14 (d, *J* = 11.1 Hz, 1H), 3.76 (td, *J* = 7.1 Hz, 1.9 Hz, 1H), 2.50 (dd, *J* = 14.4 Hz, 7.1 Hz, 1H), 1.64 (d, *J* = 7.0 Hz, 3H); (overlapping resonances) δ 7.38-7.25 (m, 3H), 7.18-7.14 (m, 2H), 3.09 (dd, *J* = 13.9 Hz, 5.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 200.5, 139.8, 136.5, 135.5, 133.5, 132.0, 130.1, 129.1, 128.9, 128.8, 128.7, 127.5, 110.5, 57.6, 26.7, 12.7; FTIR (neat, cm^{-1}) 2917, 1721, 1602, 1493, 1453, 993, 898, 757, 700; HRMS (EI) calcd for $C_{14}H_{17}O$ $[M+H]^+$ *m/z* 201.1279 $[M+H]^+$, found 201.1279.



(1-Phenyl-3-vinylcyclopent-3-en-1-yl)methanol (1.110): Isolated as a clear oil (3, mg, 21%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38-7.23 (m, 5H), 6.56 (dd, *J* = 17.5 Hz, 10.7 Hz, 1H), 5.74 (s, 1H), 5.15 (d, *J* = 17.5 Hz, 1H), 5.09 (d, *J* = 10.6 Hz, 1H), 3.57 (app d, *J* = 6.8 Hz, 2H), 2.90-2.75 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.5, 141.5, 133.5, 128.8, 128.5, 127.1,

126.3, 114.2, 71.5, 552.1, 41.6, 39.6; FTIR (neat, cm^{-1}) 3391, 3085, 2919, 2848, 1496, 1445, 1069, 1034, 987, 899, 758, 700; HRMS (EI) calcd for $C_{14}H_{16}O$ *m/z* 200.1201 $[M]^+$, found 200.1218.

2.0 RADICAL CYCLIZATIONS INVOLVING β-ELIMINATION OF SULFONYL RADICALS

2.1 INTRODUCTION

2.1.1 Chemistry of β-sulfonyl radicals

The prototypical reaction of a β-sulfonyl radical is fragmentation to form a sulfonyl radical and a multiple bond.[92-94] The β-sulfonyl radical can be based on nitrogen or carbon and fragmentation can form carbon-carbon double bonds or carbon-nitrogen double bonds. Figure 2-1 shows three general types of fragmentation: **1)** alkene formation from a β-sulfonyl carbon radical, **2)** imine formation from a β-sulfonyl nitrogen radical and **3)** imine formation from a β-sulfonyl carbon radical.

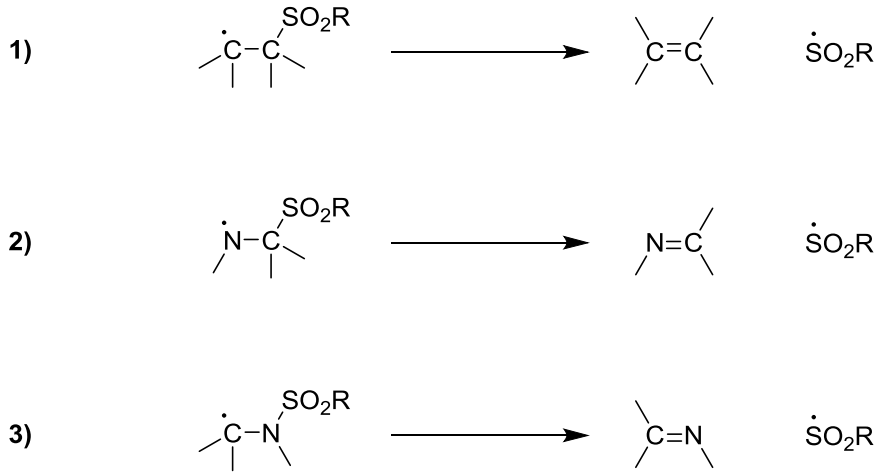
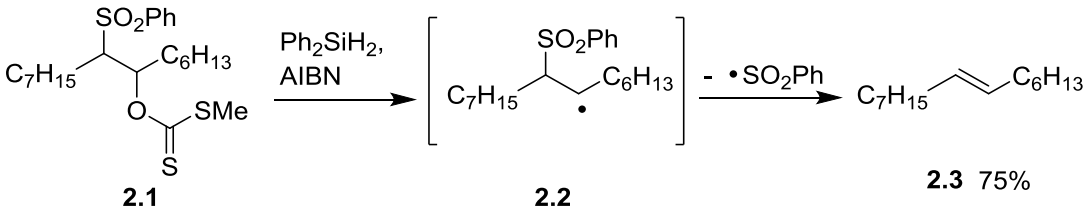


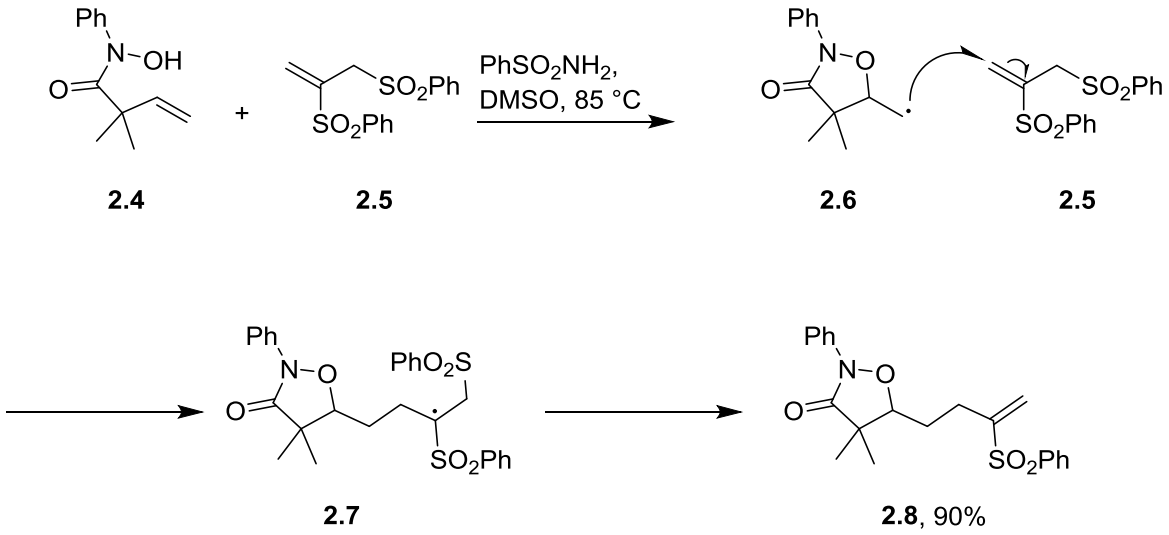
Figure 2-1 Three classes of β-sulfonyl radicals that undergo fragmentation to give sulfonyl radicals and C=C or C=N bonds

The first class of fragmentations shown in Figure 2-1 represents a common alkene forming strategy. In the simplest systems, a radical precursor generates a β-sulfonyl carbon radical that fragments to give an alkene and a sulfonyl radical. Common precursors have been used for radical generation and include halides,[95-96] xanthates,[97] nitro compounds,[98] and boranes.[99] A typical example is shown in Scheme 2-1; treatment of xanthate **2.1** with Ph_2SiH_2 and AIBN generated radical **2.2** followed by radical fragmentation to produce alkene **2.3** in 75% yield in a radical variation of the Julia olefination.[97]



Scheme 2-1 Radical sulfonyl elimination of an β-sulfonyl xanthate

β-Sulfonyl radicals can also be generated in more complex reactions. In an example of a cascade reaction involving sulfonyl addition-fragmentation, Alexanian showed that hydroxamic acids and allyl sulfones can be coupled to form functionalized isoxazolidinones.[100] Scheme 2-2 shows that heating hydroxamic acid **2.4** with allyl sulfone **2.5** at 85 °C in the presence of phenylsulfonamide provided isoxazolidinone **2.8** in 90% yield. The reaction proceeds by generation of radical **2.6** followed by intermolecular addition to vinylsulfone **2.5** to give β-sulfonyl radical **2.7**. Fragmentation of **2.7** gives isoxazolidinone **2.8** and phenylsulfonyl radical. Phenylsulfonamide was not necessary for the reaction to occur but raised the reaction rate and overall yield of **2.8**. The role of $PhSO_2NH_2$ is not well understood, but was proposed to involve hydrogen bond activation of hydroxamic acid **2.4**.



Scheme 2-2 Cascade cyclization addition elimination reaction of hydroxamic acid 2.4

Alkene synthesis by radical sulfonyl fragmentation has also been coupled to additional inter- and intra-molecular bond formation in cascade chain reactions. Whitham has described a series of intermolecular bond forming reactions that proceed by sulfonyl addition-elimination to carbon-carbon double and triple bonds.[101-103] Figure 2-2 shows the benzoyl peroxide promoted intermolecular radical addition-fragmentation rearrangement between acrylonitrile and allyl tosylate **2.9** to give acrylate **2.10** in 42%. The key bond forming steps of the reaction are addition or sulfonyl radical to acrylonitrile to give radical **2.11**, which adds to allyl tosylate **2.9** to provide the radical intermediate **2.12**. Sulfonyl radical β-elimination generates the product **2.10** and regenerates toluenesulfonyl radical, thus transferring the radical chain.

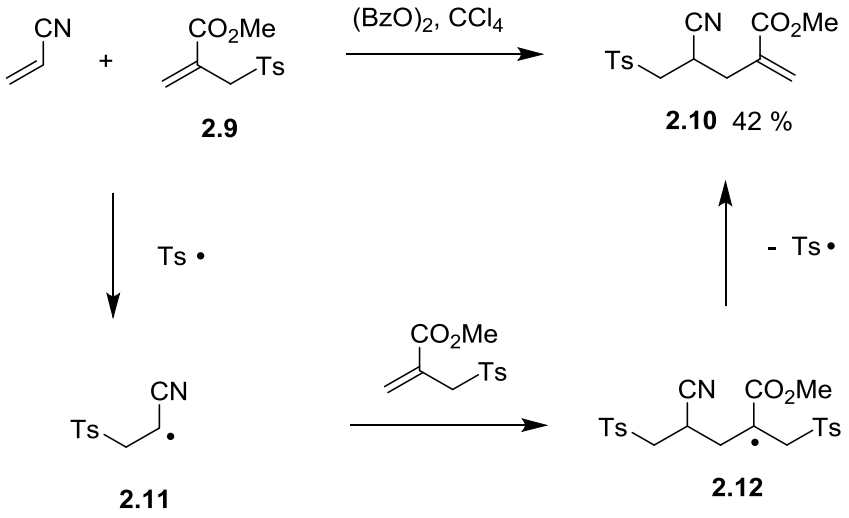
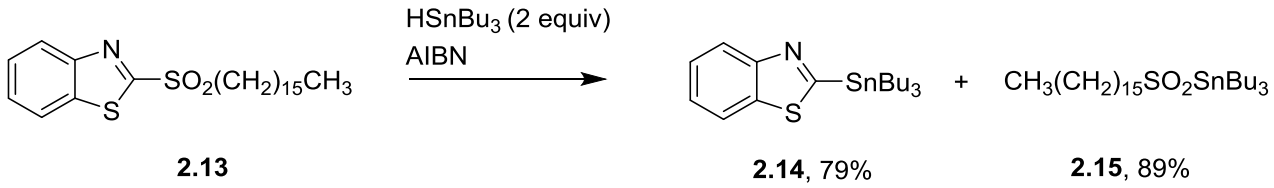


Figure 2-2 Addition-elimination reaction of sulfonyl radicals

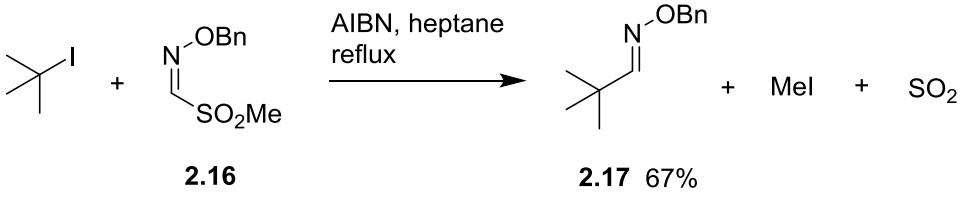
The second class of reactions in Figure 2-1 consists of β-sulfonyl nitrogen radicals that fragment to give a sulfonyl radical and a C═N bond, and represents a useful method to make assorted imines, hydrazones and oximes. Scheme 2-3 shows 2-(phenylsulfonyl)benzothiazole **2.13** was treated with 2 equiv tributyltin hydride and catalytic AIBN to give the corresponding aryl stannane **2.14** in 79% yield along with stannyl sulfinate **2.15** in 89%.[104]



Scheme 2-3 Radical substitution of a sulfone by a stannane

Kim disclosed a second example of C═N products using a radical addition-elimination strategy.[105] Scheme 2-4 shows treatment of *tert*-butyl iodide and oxime ether **2.16** with AIBN results in a chain reaction to produce oxime **2.17** in 67% with methyl iodide and SO_2 as

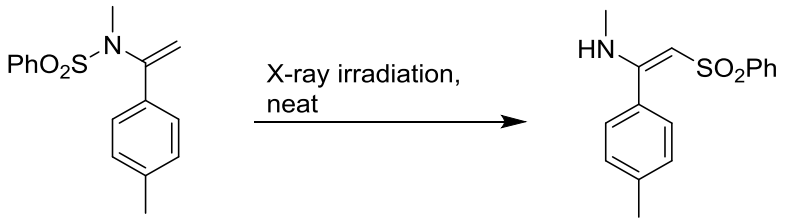
byproducts. This was proposed to occur by addition of a *tert*-butyl radical to the oxime carbon, then elimination of methyl sulfonyl radical. The sulfonyl radical dissociates to SO_2 and a methyl radical which abstracts iodine from *tert*-butyl iodide, thus propagating the chain reaction.



2.16 **2.17** 67%

Scheme 2-4 Radical reaction of an alkyl halide to form an α-sulfonyl oxime ether

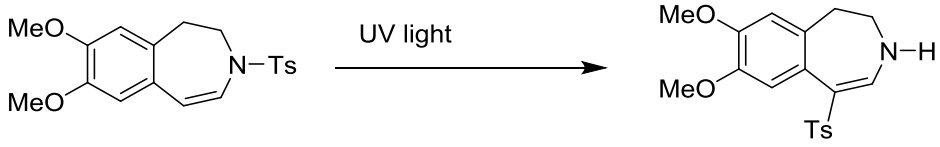
While many examples of sulfonyl radical transformations from β-sulfonyl carbon radicals and β-sulfonyl nitrogen radicals have been reported; only few examples of the third class of reactions represented in Figure 2-1 have been reported. In 1959 Stacey reported that X-ray irradiation of crystalline ene-sulfonamide **2.18** results in a transformation to sulfonyl enamine **2.19**, shown in Scheme 2-5[106] The product structure was confirmed by elemental analysis, IR, UV, and ^{1}H NMR spectroscopy. By measuring the number of molecules transformed per dose of radiation received, the authors propose that the rearrangement involves a radical chain process. The rearrangement proved to have limited scope, removal of the α-aromatic group in particular proved detrimental to yields, which were generally between 1–20%, with ene-sulfonamide **2.19** as one of few species that rearranged in greater than 40% yield. This example represents a mild method for N–S bond cleavage of the stable sulfonamide group.



2.18 **2.19** 72%

Scheme 2-5 X-Ray induced rearrangement of ene-sulfonamide 2.18

Direct X-ray irradiation may not represent a practical synthetic methodology. However, examples of rearrangements of ene-sulfonamides to β-sulfonyl enamines have also been reported to occur by UV irradiation and by thermal and photo-initiated solid state reactions.[107] Scheme 2-6 shows the UV irradiation of ene-sulfonamide **2.20** in wet ether produced β-sulfonyl enamine **2.21** in 40%.[108] Again, this may be a light initiated radical chain reaction.



2.20 **2.21**, 40%

Scheme 2-6 UV induced rearrangement of ene-sulfonamide 2.20

The reactions shown in Scheme 2-5 and Scheme 2-6 generally have low yield and limited scope. A more synthetically useful reaction was disclosed by Zard in 2002; xanthate **2.22** and ene-sulfonamide **2.23** were treated with AIBN to give pyrrole **2.26** in 50% isolated yield, shown in Figure 2-3.[109] The reaction proceeds by generation of cyclohexyl radical **2.24** which adds to alkene **2.23**. Elimination of ethanesulfonyl radical gives imine **2.25** as the primary product of sulfonyl fragmentation. In the reaction mixture imine **2.25** condensed to form water and pyrrole

2.26 as a secondary product. Other pyrroles in the Zard report were synthesized in modest yields of 36–67%.

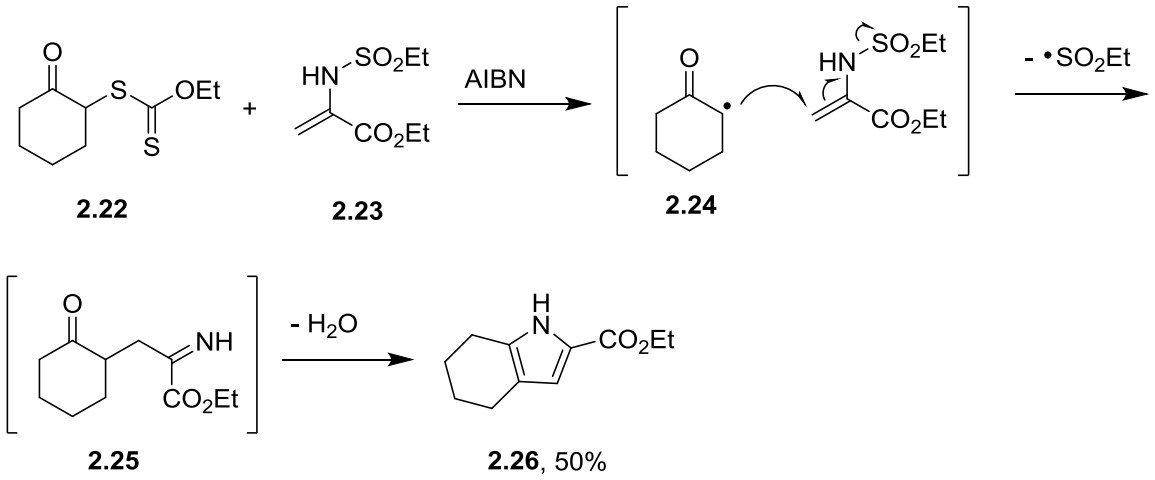
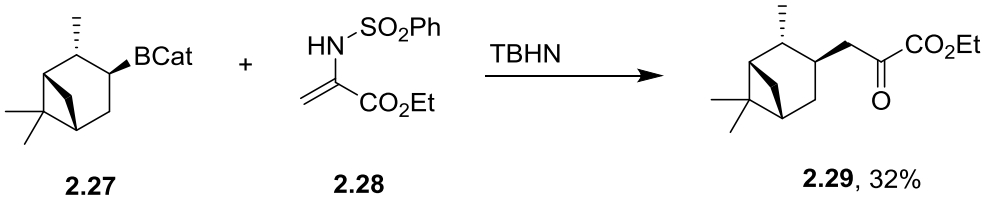


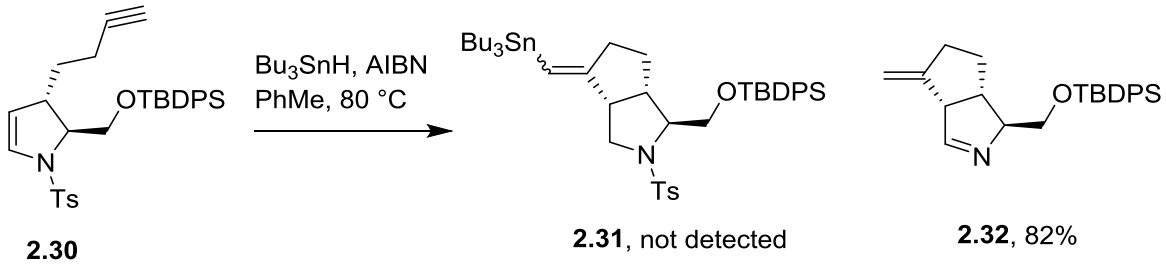
Figure 2-3 Pyrrole 2.26 synthesis by radical sulfonyl elimination

In 2005 Renaud reported another process which presumably involved imine primary products.[110] Treatment of catechol-borane **2.27** with *tert*-butyl hyponitrite (TBHN) and ene-sulfonamide **2.28** gave rise to acyl ester **2.29** in 32% yield, shown in Scheme 2-7. It was proposed that an alkyl radical, generated from the borane by TBHN, added to ene **2.28** followed by radical sulfonyl elimination to give an imine primary product. Imine hydrolysis provided the acyl-ester **2.29** as the secondary product. Reactions of few borane substrates were reported, with modest yields of 20–32% of the α-keto ester.



Scheme 2-7 Radical synthesis of α-keto-ester 2.29

In 1999 during the synthesis of α-kainic acid, the Cossy group reported the isolation of an imine from the reaction of an ene-sulfonamide. Ene-sulfonamide **2.30** was treated with tin hydride and AIBN, expecting to isolate tosylamine **2.31**. However cyclic imine **2.32** was isolated in 82% yield, as indicated in Scheme 2-8.[111] This result represents the first reported isolation of an imine from radical cyclization of an ene-sulfonamide.



2.30 **2.31**, not detected **2.32**, 82%

Scheme 2-8 Radical cyclization of ene-sulfonamide 2.30 gives imine 2.32

2.1.2 Classical imine forming reactions

Cossy's synthesis of a bicyclic imine from an ene-sulfonamide represents a non-classical route to carbon nitrogen double bonds. This is important considering the powerful role imines and iminium ions play reactions such as the Mannich reaction,[112] Ugi multicomponent reaction,[113] aza-Baylis-Hillman reaction,[114] Pictet-Spengler reaction,[115] and the Strecker reaction.[116]

The classical way to form an imine is the condensation of an amine with a ketone or aldehyde, shown in Figure 1.3. This condensation is often performed in the presence of an acid and may involve removal of water from the reaction mixture.[117-118]

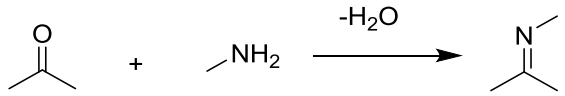


Figure 2-4 Imine formation through condensation

Additional imine forming reactions include direct reagent or enzyme-controlled amine oxidation[119-121] or a two step oxidative halogenation-elimination process,[122-123] shown in Figure 2-6. Another route is the reaction of an iminophosphorane and a ketone to form an imine and a phosphine oxide, as in the aza-Wittig reaction also shown in Figure 2-6.[124] The forward and reverse aza-Cope rearrangement forms or consumes imine or iminium species, respectively, in a [3,3]-sigmatropic rearrangement.[125]

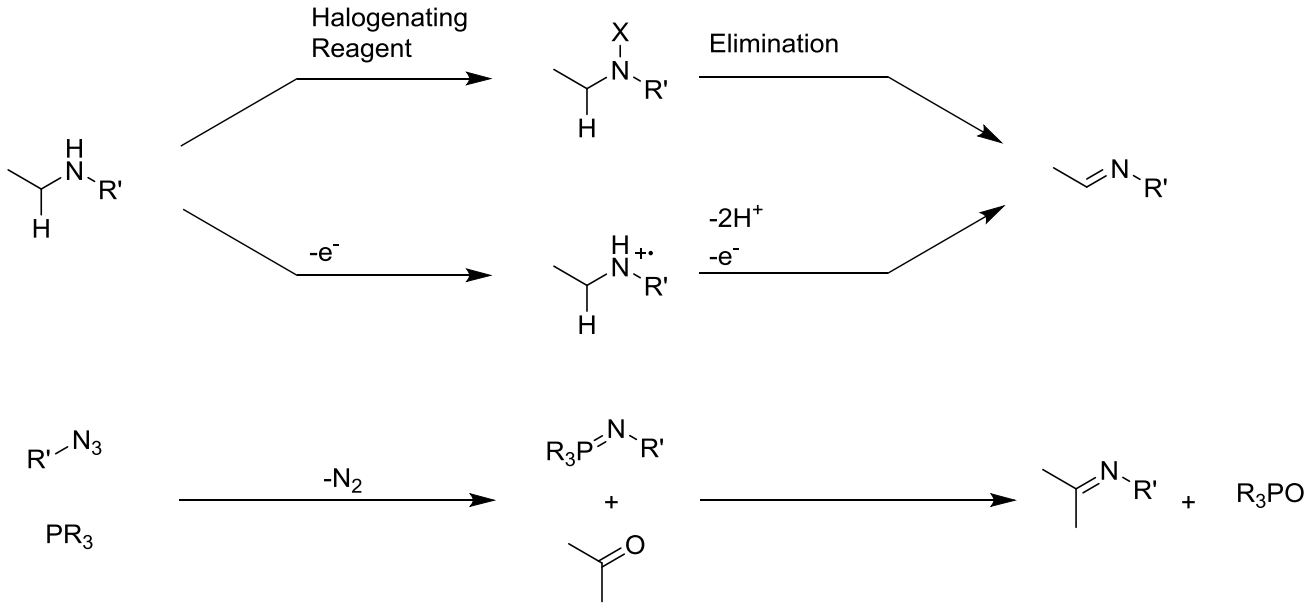
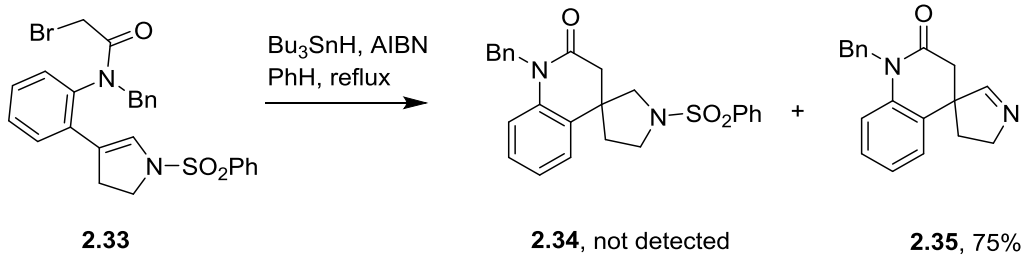


Figure 2-5 Oxidative imine formation

Preliminary work in the Curran group has suggested that radical cyclizations of ene-sulfonamides might provide an unrecognized path to imines.

2.1.3 Discovery of imine forming reaction and preliminary studies

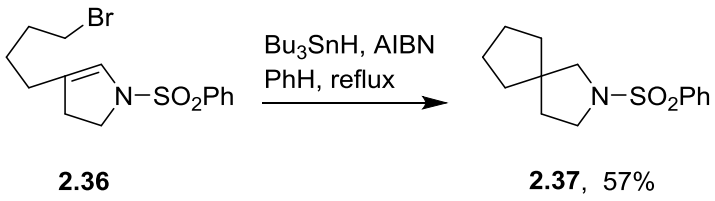
During methodology work for the synthesis of meloscine, Dr. H. Zhang found that treatment of anilide **2.33** with tributyltin hydride and AIBN did not give the expected sulfonamide **2.34** but rather spirocyclic imine **2.35**, isolated in 75% as shown in Scheme 2-9.[80]



2.33 **2.34**, not detected **2.35**, 75%

Scheme 2-9 Radical reaction of anilide 2.23

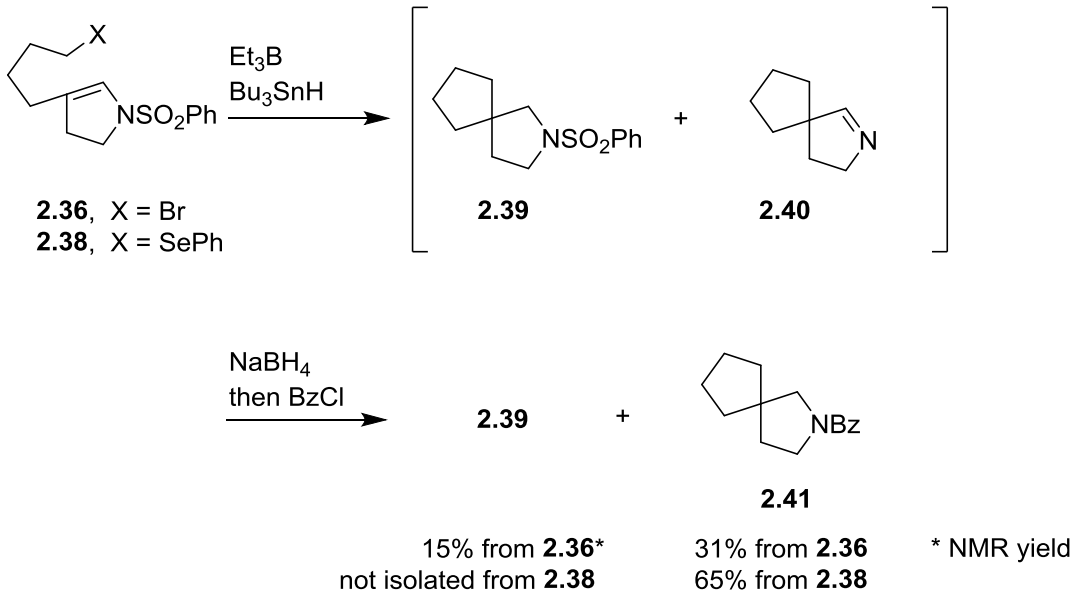
The example in Scheme 2-9 contrasts with a report by Somfai given in 1994.[126] The report stated that slow addition of Bu_3SnH and AIBN into a dilute mixture of bromide **2.36** in refluxing benzene produced spirocyclic sulfonamide **2.37** in 57% yield, as shown in Scheme 2-10. The proposed mechanism was a standard radical mediated reductive cyclization which presumably involved a β-sulfonyl carbon radical which abstracted hydrogen from tin hydride.



2.36 **2.37**, 57%

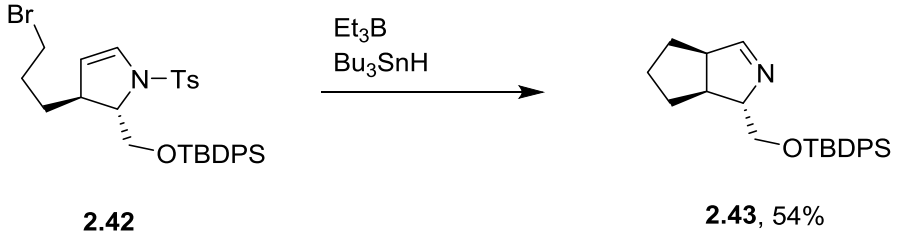
Scheme 2-10 Cyclization of ene-sulfonamide 2.36

To test whether the different results of the Zhang and Somfai reactions was due to a difference in mechanism, the reactions depicted in Scheme 2.11 were conducted by Zhang. The initial reaction of bromide **2.36** produced a mixture of spiro-sulfonamide **2.39** and spiro-imine **2.40**, which was unstable to isolation. To avoid isolation of unstable **2.40**, bromide **2.36** and phenylselenide **2.38** were separately treated with Bu_3SnH and Et_3B in benzene, followed by reduction with $NaBH_4$ and benzoylation with benzoyl chloride in ethanol as shown in Scheme 2-11. Spiro amide **2.41** was isolated in 31% yield in two steps from **2.36** and in 65% in two steps from **2.38**. Bromides undergo radical abstraction as well as S_N2 displacement, while phenyl selenides only undergo radical abstraction; these results suggest that bromide **2.36** cyclizes in competing ionic and radical pathways, while phenyl selenide **2.38** cyclizes exclusively by a radical pathway to give imine **2.40** as the primary product.



Scheme 2-11 Tin hydride reductions of ene-sulfonamides 2.36 and 2.38

Returning to the example of Cossy, the observation of imine **2.32** but not stannyl imine **2.31** prompted the question of whether ene-sulfonamides act as radical precursors or radical acceptors. The reaction in Scheme 2-12 shows bromide **2.42** was treated with Bu_3SnH and Et_3B to give imine **2.43** in 54% isolated yield. Because bromine can be a radical precursor, but does not a radical acceptor; **2.42** should only give the imine product via the β-elimination mechanism. This confirmed that sulfonyl radical β-elimination, rather than sulfonyl abstraction, gave rise to imines **2.32**, **2.35** and **2.43**.



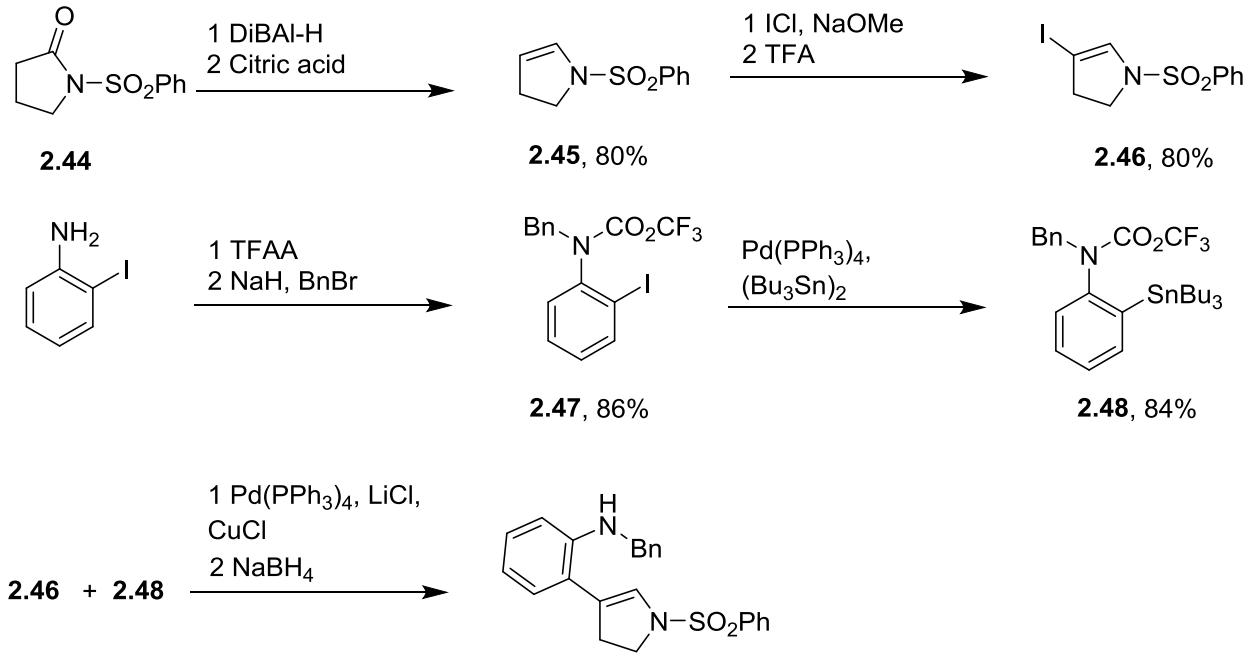
Scheme 2-12 Evidence for sulfonyl radical β-elimination

Building on these mechanistic studies, we are interested in exploring imine formation in different ene-sulfonamide ring systems.

2.2 RESULTS AND DISCUSSION

2.2.1 Radical cyclizations of ene-sulfonamides

To investigate synthesis of analogs of imine **2.35**, we first set out to make additional quantities of aniline **2.49**. The original route to **2.49** is shown in Scheme 2-13 and shows the DIBAL-H reduction of sulfonamide **2.44** in THF, followed by dehydration with citric acid in refluxing toluene to give the ene-sulfonamide **2.45** in 80% over 2 steps. The ene-sulfonamide **2.45** was treated with ICl and NaOMe in MeOH followed by treatment with TFA in refluxing toluene to afford vinyl-iodide **2.46** in 80% over two steps. Treatment of 2-iodoaniline with TFAA in THF, followed by deprotonation with NaH and benzylation with benzyl bromide provided protected anilide **2.47** in 86% over two steps. Aryl bromide **2.47** was treated with $(Bu_3Sn)_2$ and $Pd(PPh_3)_4$ in toluene to give arylstannane **2.48** in 84% yield. Coupling stannane **2.48** and vinyl-iodide **2.46** with $Pd(PPh_3)_4$, CuCl, and LiCl in DMSO, followed by removal of the trifluoroacetyl group with $NaBH_4$ in EtOH gave aniline **2.49** in 67% over two steps.



2.44

2.45, 80%

2.46, 80%

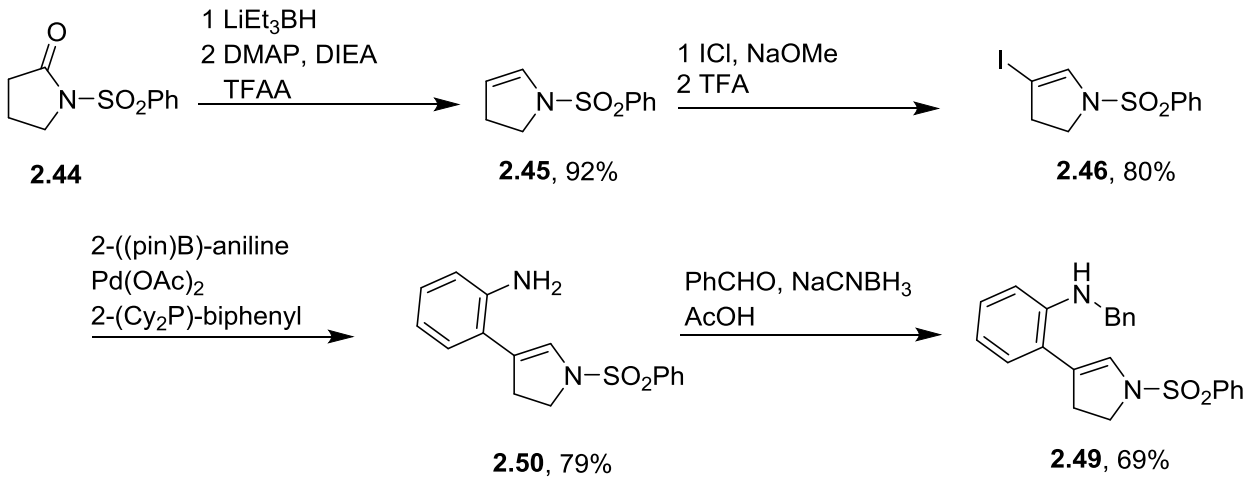
2.47, 86%

2.48, 84%

2.49, 67%

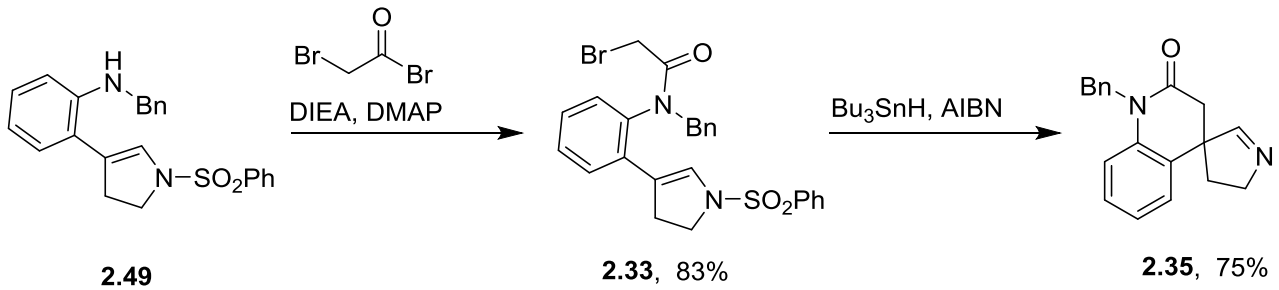
Scheme 2-13 First-generation synthesis of *o*-coupled aniline 2.49

A second-generation synthesis of the coupled aniline **2.49** was later used, as shown in Scheme 2-14. The reduction and dehydration of sulfonamide **2.44** was carried out as a two-step, one-pot reaction with lithium triethylborohydride and TFAA in toluene to provide ene-sulfonamide **2.45** in 92% yield.[127] Coupling of vinyl-iodide **2.46** and commercially available 2-(pinacolboronate)aniline with $Pd(OAc)_2$ and 2-(dicyclohexylphosphino)biphenyl gave the coupled aniline **2.50** in 79% yield. The coupled aniline **2.50** was benzylated under reductive amination conditions with benzaldehyde and $NaBH_3CN$ to give aniline **2.49** in 69% yield. The second-generation synthesis was used because 1) it has fewer steps: Suzuki route has 5 transformations while the original Stille route has 8 transformations; 2) the aryl boronate is commercially available while the aryl stannane **2.48** is not; and 3) separations are easier without tin byproducts.



Scheme 2-14 Second-generation synthesis of *o*-coupled aniline 2.49

Scheme 2-15 shows the final steps of imine **2.35** synthesis. Acylation of aniline **2.49** with bromoacetyl bromide, DIEA and DMAP in CH_2Cl_2 gave anilide **2.33** in 83% yield. A refluxing solution of anilide **2.33** in benzene (0.01 M) was treated by slow addition of Bu_3SnH (3.0 equiv) and AIBN (0.1 equiv) by syringe pump over 2 h. After the volatile compounds were removed under vacuum, the residue was partitioned between acetonitrile and hexanes to remove the non-polar tin byproducts. The acetonitrile layer was separated and evaporated; flash chromatography of the residue provided the polar imine **2.35** in 75% yield.



Scheme 2-15 Synthesis of imine 2.35

The propagation steps of the proposed mechanism of imine formation are shown in Figure 2-6. After standard tin radical generation,[128] the tributyltin radical abstracts bromine from the anilide **2.33** provides radical intermediate **2.51**. Radical **2.51** undergoes 6-*exo*-trig closure to form β-sulfonyl radical **2.52**, followed by benzenesulfonyl radical elimination to form imine **2.35** and phenylsulfonyl radical. Benzenesulfonyl radical then abstracts hydrogen from tributyltin hydride to regenerate the tributyltin radical. The fate of the resultant phenylsulfinic acid is not known, but the requirement of excess Bu_3SnH suggests that $PhSO_2H$ and Bu_3SnH undergo an acid-base reaction to generate H_2 and $PhSO_2SnBu_3$.

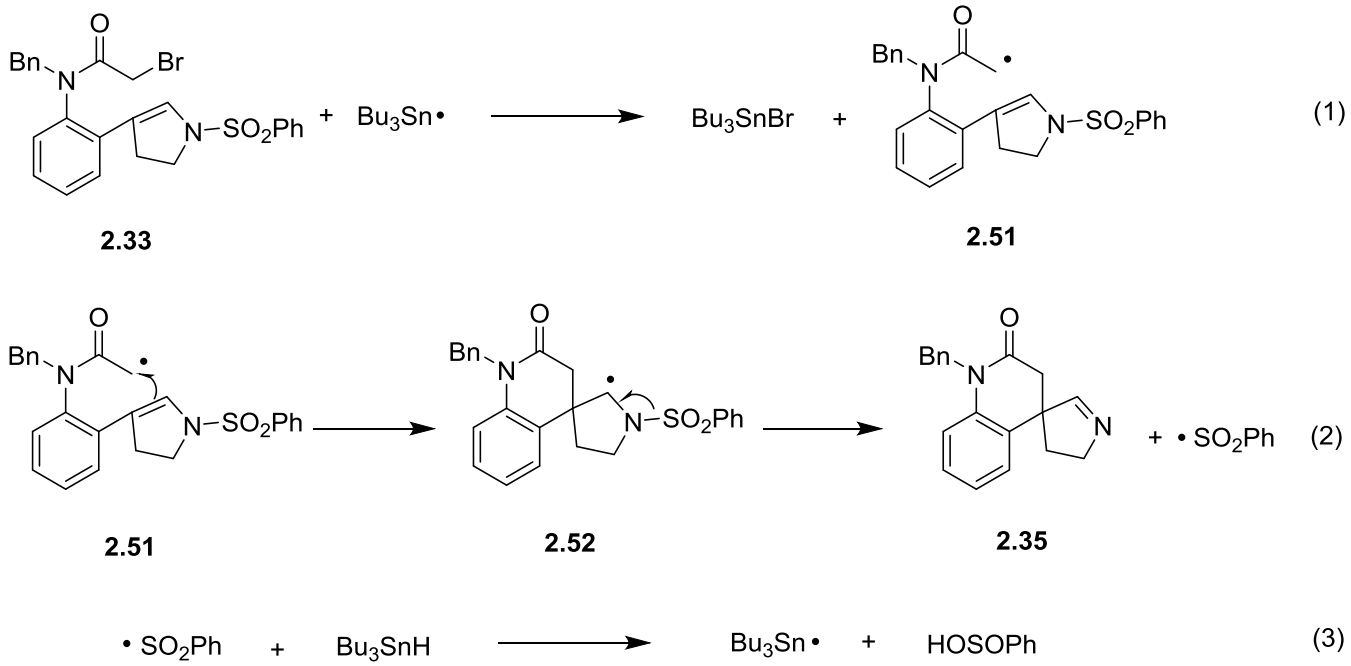
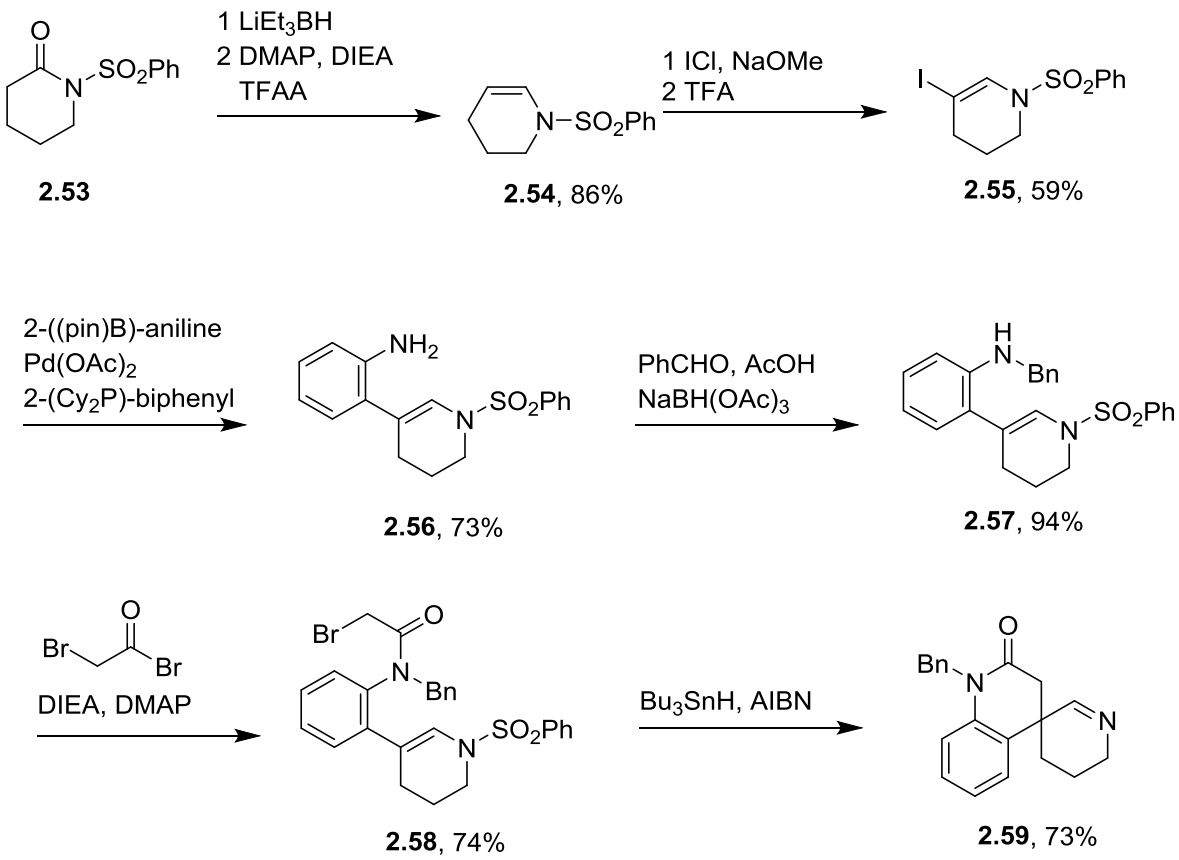


Figure 2-6 Proposed mechanism for imine 2.35 formation

We next targeted 6-membered imine **2.59**, shown in Scheme 2-16. Sulfonamide **2.53** was treated with $LiEt_3BH$, followed by DMAP, DIEA and TFAA in toluene to provide ene-sulfonamide **2.54** in 86% yield. **2.54** was treated with ICl and NaOMe in MeOH followed by

TFA in refluxing toluene which provided vinyl-iodide **2.55** in 73% yield over two steps. Coupling **2.55** and 2-(pinacolboronate)aniline with $Pd(OAc)_2$ gave the coupled aniline **2.6** in73% yield. **2.56** was benzylated under reductive amination conditions with benzaldehyde and $NaBH(OAc)_3$ to give benzaniline **2.57** in 94% yield. Acylation of **2.57** with bromoacetyl bromide provided amide **2.58** in 74% yield. Slow addition of Bu_3SnH (3.0 equiv) and AIBN (0.1 equiv) in refluxing benzene provided 6,6-spiro-imine **2.59** in 73% yield. The structure of imine **2.59** was easily deduced from the spectral similarities to imine **2.35**: 10 aromatic proton signals including the imine signal at δ 7.65 ppm, 6 diastereotopic signals for the benzylic, α-acyl and α-azo protons, and additional signals for four alkyl protons. The ^{13}C NMR of **2.59** also contained signals similar to **2.35**: two carbonyl resonances at δ 167.8 and 163.6 ppm, 10 additional aromatic signals and 6 alkyl signals, compared to 5 alkyl signals for imine **2.35**.

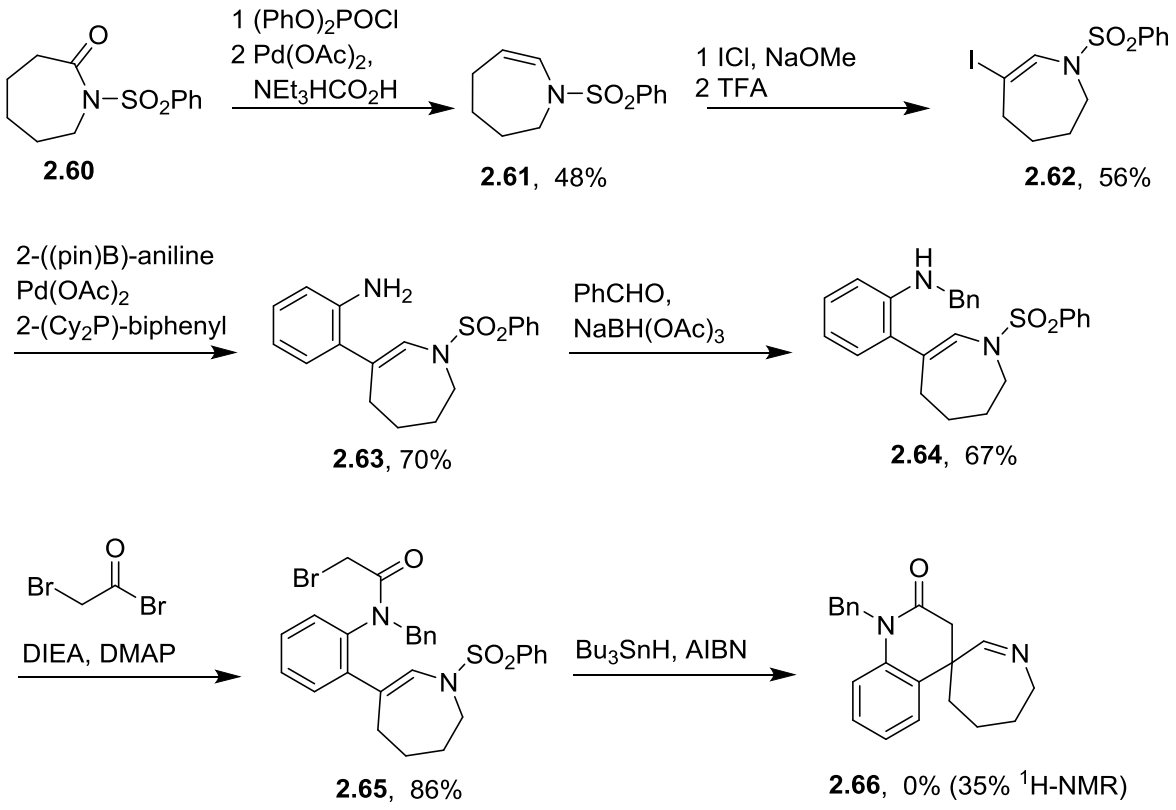


Scheme 2-16 Synthesis of spiro-imine 2.59

To test whether 7-membered spirocyclic imines could be formed, the reactions shown in Scheme 2-17 were performed. Two-step reduction-elimination protocols used to access ene-sulfonamides **2.45** and **2.54** resulted in low yields of ene-sulfonamide **2.61**; presumably due to instability of a strained 7-membered aminal intermediate. To avoid a strained aminal intermediate, a two step protocol developed by Dauban was used.[129] *N*-Sulfonylcaprolactam was treated with NaHMDS and diphenyl chlorophosphate followed by palladium catalyzed phosphate reduction with ammonium formate to give ene-sulfonamide **2.61** in 48% over two steps. Treatment of **2.61** with ICl and NaOMe in MeOH followed by heating with TFA in toluene provided vinyl iodide **2.62** in 65% yield. Suzuki coupling of vinyl iodide **2.62** and 2-(pinacolboronate)aniline with $Pd(OAc)_2$ provided the coupled aniline **2.63** in 70% yield. Aniline

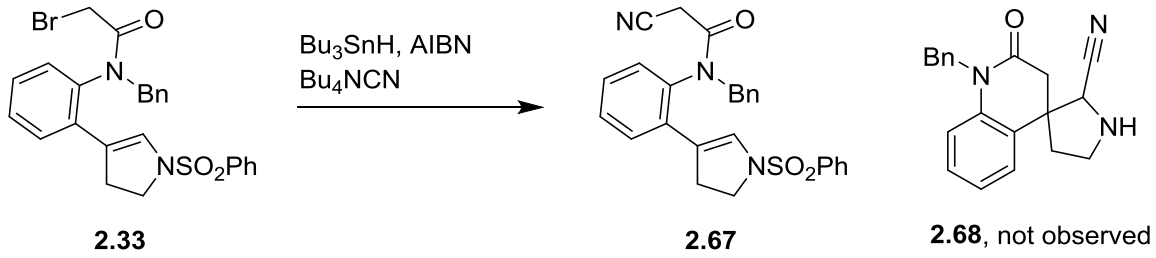
2.63 was treated with benzaldehyde and $NaBH(OAc)_3$ to afford aniline **2.64** in 67%. Acylation with bromoacetyl bromide and DMAP provided anilide **2.65** in 86% yield.

Treatment of anilide **2.65** with tributylstannane (3.0 equiv) and AIBN (0.1 equiv) in refluxing benzene followed by chromatography did not produce the expected imine **2.66**. To directly observe the reaction products, the reaction was also performed in C_6D_6 and followed by ^1H NMR using an internal standard. Imine **2.66** was formed in 35% yield, it was identified by comparison to the spectra of pure imine compounds **2.35** and **2.59**. The ^1H NMR signals proposed to correspond to imine **2.66** are a partially obscured singlet at δ 7.80 ppm, benzylic signals at δ 5.42 and 4.97 ppm, a partially obscured α-azo proton signal at δ 3.89 ppm and two diastereotopic α-acyl proton signals at δ 2.97 and 2.90 ppm. Other spectral signals were obscured by aromatic or tin byproduct resonances. Addition of silica gel to the reaction mixture resulted in rapid disappearance of ^1H NMR signals corresponding to imine **2.66**.



Scheme 2-17 Synthesis of 6,7-spiro-imine 2.66

Imine **2.66** was observed in solution but was not stable to silica gel chromatography; trapping of unstable imines with a nucleophile may provide isolable compounds. Because the addition of HCN is a quintessential reaction of imines,[130] we designed the reaction shown in Scheme 2-18. In preparation for slow addition of Bu_3SnH and AIBN, a solution of anilide **2.33** and Bu_4NCN in benzene was brought to reflux. A rapid change in color from clear to purple occurred and a new species appeared by TLC as the starting material disappeared. No further change was observed by TLC during Bu_3SnH and AIBN addition. ^1H NMR analysis of the crude reaction showed a clear shift in the resonances assigned to the protons geminal to the bromide from δ 3.46 and 3.42 ppm to δ 4.33 and 4.08 ppm, suggesting ionic displacement of bromide to give nitrile **2.67**.



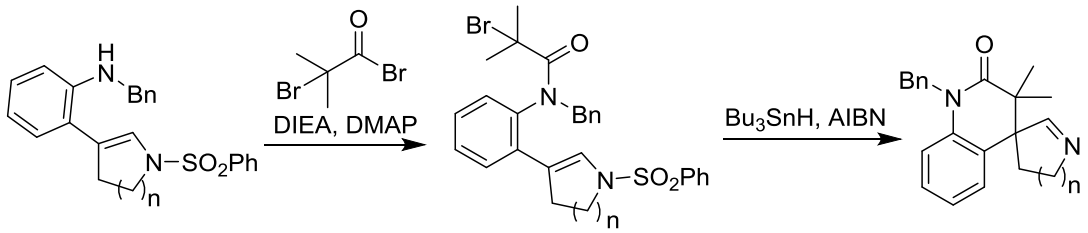
2.33 **2.67** **2.68**, not observed

Scheme 2-18 Failed *in situ* imine cyanation

Because increasing steric hindrance greatly slows the nucleophilic displacement of primary bromides, a series of tertiary bromides was targeted. In preparation for imine trapping reactions, a family of 2-bromo-2-methyl propionamides was synthesized, shown in Table 2-1. Aniline **2.49** was treated with 2-bromo-2-methylpropionyl bromide in the presence of DIEA and DMAP to produce anilide **2.69** with 90% yield. The six-membered ene-sulfonamide **2.71** was produced by an analogous procedure from aniline **2.57** in 58% yield. The seven-membered ene-sulfonamide **2.73** was produced from aniline **2.64** in 49% yield.

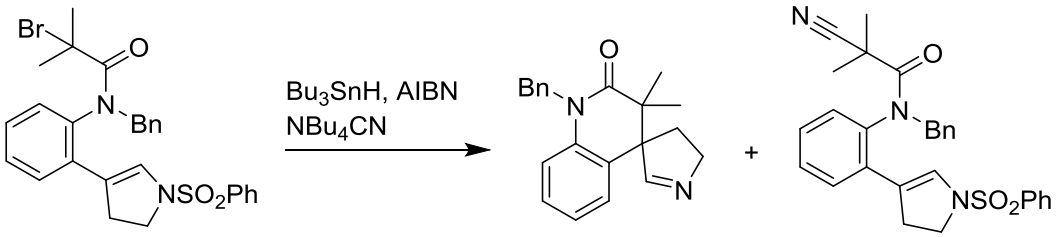
When treated with Bu_3SnH (3.0 equiv) and AIBN (0.1 equiv) in refluxing benzene, 5-membered ene-sulfonamide **2.69** cleanly produced imine **2.70** in 81% isolated yield after chromatography. Treatment of 6-membered propionamide **2.71** with tributylstannane and AIBN led to recovery of 6-membered imine **2.72** in 50% yield after flash chromatography. Treatment of 7-membered ene-sulfonamide **2.73** with tributylstannane and AIBN led to recovery of stable 7-membered imine **2.74** in 40% yield after flash chromatography. This time, the steric hindrance provided by the two methyl groups rendered the primary imine product stable to chromatography.

Table 2-1 Synthesis of spiro-imines 2.70, 2.72 and 2.74



entry	aniline	yield	yield
1	**2.49**, n=1	**2.69**, 90%	**2.70**, 81%
2	**2.57**, n=2	**2.71**, 58%	**2.72**, 50%
3	**2.64**, n=3	**2.73**, 49%	**2.74**, 40%

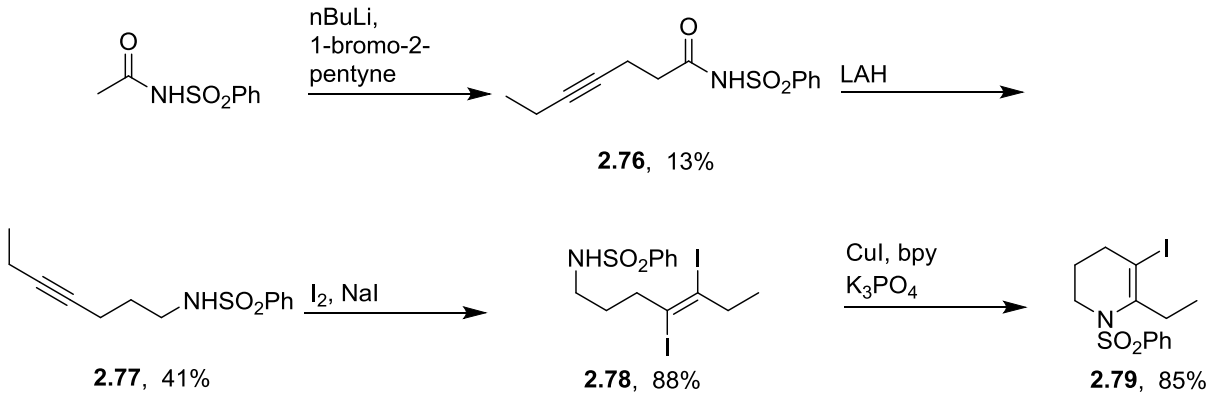
To test whether imines can be trapped *in situ* by cyanide the reaction shown in Scheme 2-19 was performed. To test whether bromide **2.69** was susceptible to S_N2 displacement by cyanide, **2.69** was refluxed in benzene with tetrabutylammonium cyanide for 1 h; no change was observed by TLC. Bu_3SnH and AIBN were then added by syringe pump. Flash chromatography provided imine **2.70** in 40% yield and nitrile **2.75** in 5% yield, shown in Scheme 2-19. Apparently, the methyl groups provide more stability to spirocyclic imine products than to their bromide precursors. In essence, cyanide trapping is not necessary.



2.69 **2.70** 40% **2.75** 5%

Scheme 2-19 Radical reaction of anilide 2.69 in the presence of cyanide

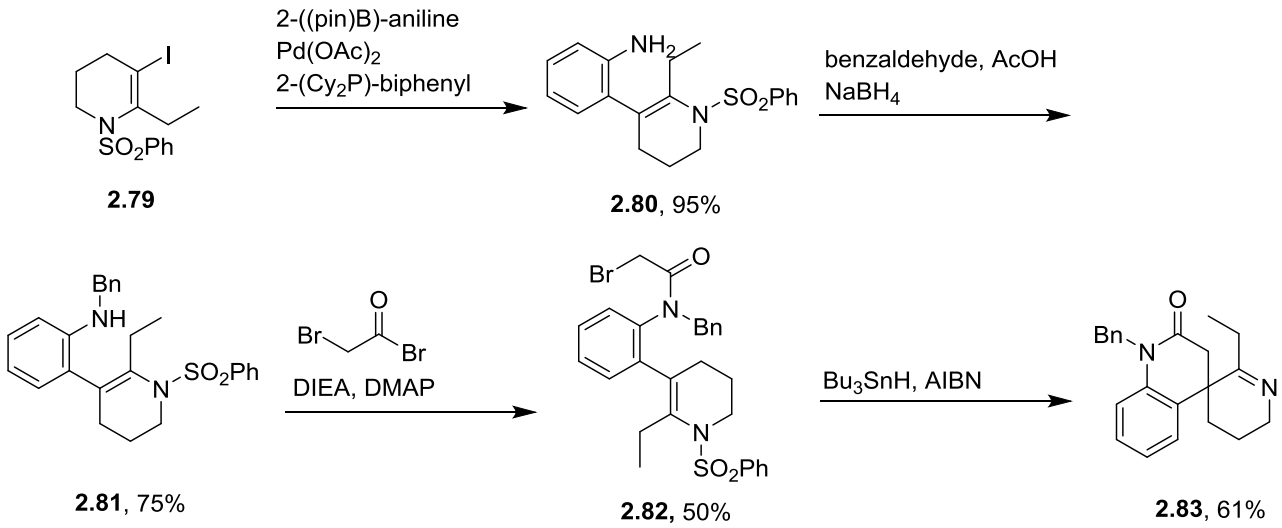
Moving away from the trapping experiments, bromide **2.82** was designed to study ketimine formation, shown in Scheme 2.20 and Scheme 2.21. Alkylation of *N*-acetylsulfonamide with 1-bromo-2-pentyne in THF-HMPA provided alkyne **2.76** in 13% yield.[131] Despite the low yield of **2.76**, we produced enough material to carry forward the synthesis. LAH reduction of **2.76** in provided sulfonamide **2.77** in 41% yield. Treatment with I_2 and NaI provided diiodide **2.78** in 88% yield.[132] A copper mediated cyclization of **2.78** with CuI, 2,2′-bipyridine, and K_3PO_4 in toluene provided vinyl iodide **2.79** in 85% yield.[132]



Scheme 2-20 Synthesis of vinyl-iodide 2.79

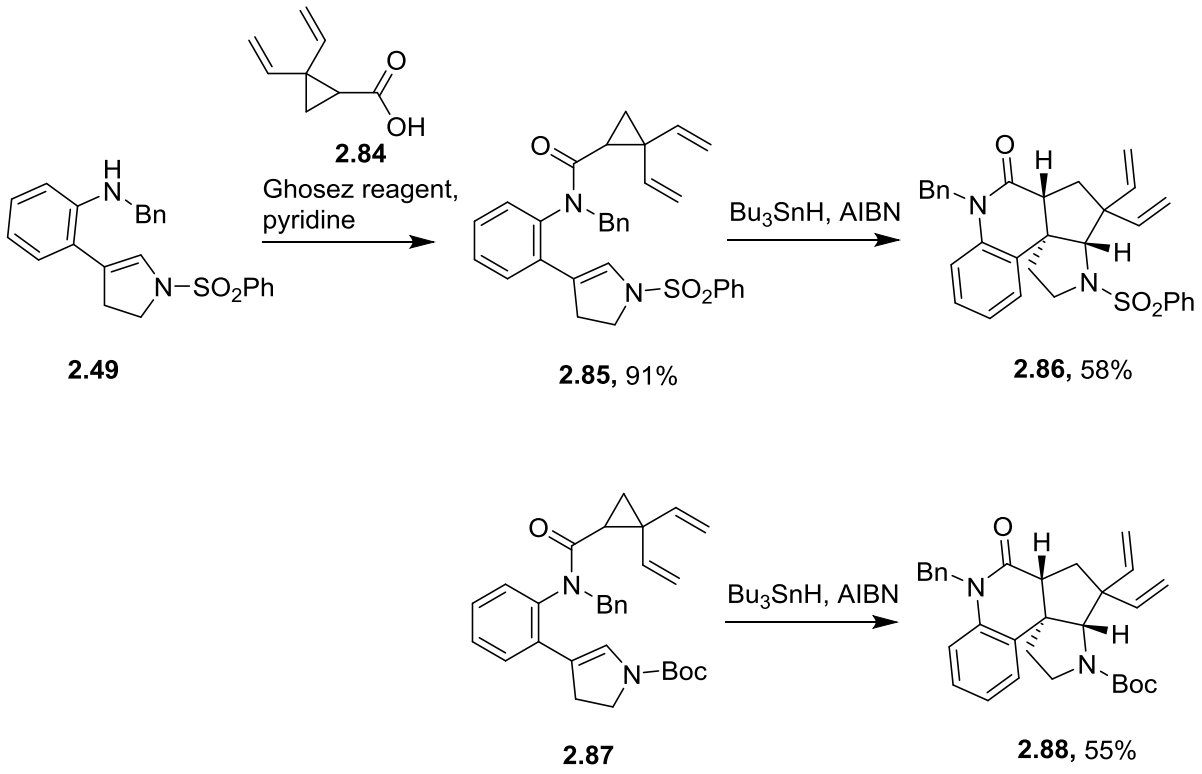
Suzuki coupling of vinyl iodide **2.79** and 2-(pinacolboronate)aniline with $Pd(OAc)_2$, and 2-(Cy_2P)biphenyl provided coupled aniline **2.80** in 95% yield, shown in Scheme 2-21. Benzylation of **2.80** with benzaldehyde and $NaBH_4$ provided aniline **2.81** in 75% yield. Acylation of **2.81** with bromoacetyl bromide provided anilide **2.82** in 50% yield. Slow addition of Bu_3SnH and AIBN to anilide **2.82** in refluxing benzene gave ketimine **2.83** in 61% yield. The 61% yield of ketimine **2.83** is close to the 73% yield of aldimine **2.59**, indicating that radical

cyclization of an ene-sulfonamide represents a useful route to both spirocyclic ketimines and aldimines.



Scheme 2-21 Synthesis of ketimine 2.83

To learn whether the sulfonyl radical elimination competes with 5-*exo*-trig ring closure the reactions in Scheme 2-22 were performed. The coupling of aniline **2.49** and cyclopropyl acid **2.84**[55] with Ghosez reagent and pyridine gave anilide **2.85** in 91% yield. Slow addition of Bu_3SnH (2.0 equiv) and AIBN (0.1 equiv) to a refluxing solution of divinylcyclopropane **2.85** in benzene followed by silica gel chromatography provided bis-cyclized compound **2.86** in 58% yield. For comparison, Zhang reported the cyclization of cyclopropyl amide **2.87** with Bu_3SnH and AIBN to give tetracycle **2.88** in 55% yield.[55]



Scheme 2-22 Radical cascade cyclization of anilide 2.85

Figure 2-7 shows possible reaction pathways of the transformation in Scheme 2-22. The addition of a tin radical intermediate to the terminal end of one of the double bonds of anilide **2.85** followed by opening of the cyclopropyl ring gives intermediate **2.80**. Addition to the double bond forms a 6-membered ring and gives β-sulfonyl radical intermediate **2.90** which may proceed through one of two reaction pathways. If sulfonyl elimination is relatively slow, then 5-*exo* closure occurs followed by radical tin elimination to give bis-cyclized sulfonamide **2.86**. If sulfonyl elimination is relatively fast, then intermediate imine **2.91** forms. Bis-cyclized sulfonamide **2.86** was recovered in 58% yield, suggesting that the second cyclization event is much faster than sulfonyl elimination.

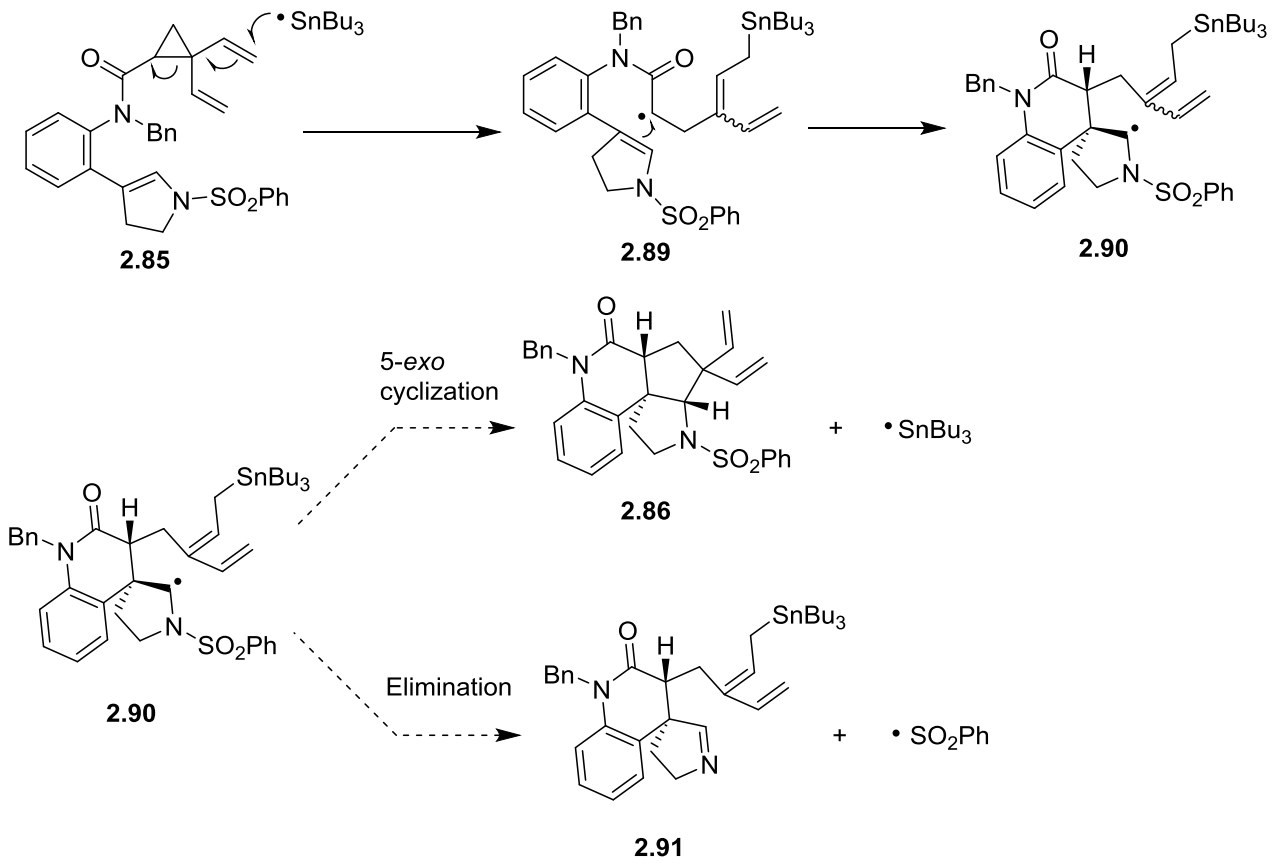
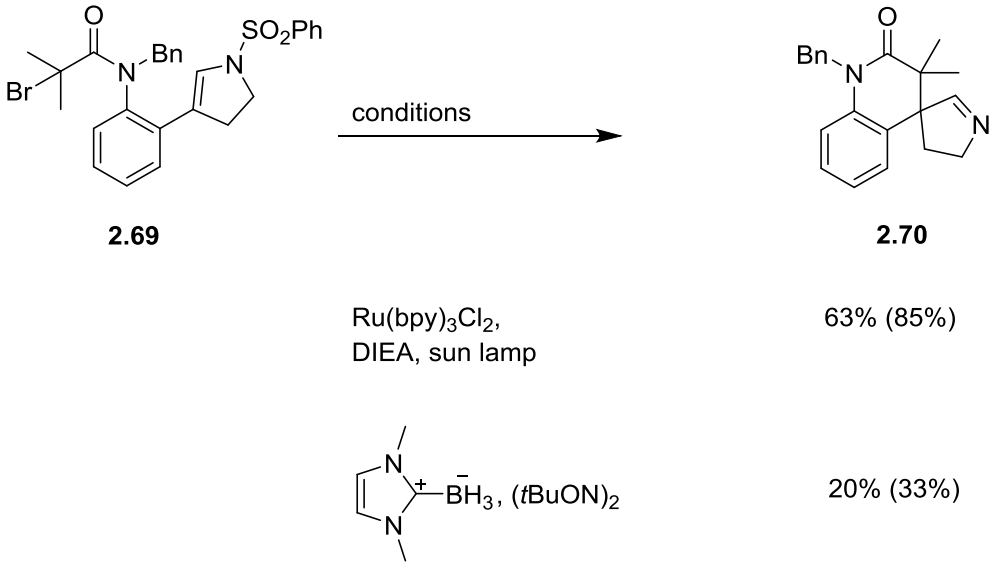


Figure 2-7 Possible reaction pathways for anilide 2.85

Reactions involving organo-tin species often produce toxic tin byproducts which can complicate product isolation. To avoid these problems, cyclization of ene-sulfonamides was also attempted with alternatives to tributyltin hydride, shown in Scheme 2-23. Substrate **2.69** was chosen because it gave a high yield of imine **2.70** under the standard tin hydride conditions. Photo-redox catalysts have been used to generate radicals from activated alkyl halides.[133] Amide **2.69**, $Ru(bpy)_3Cl_2$ and Hunig's base in degassed DMF were exposed to light from a sunlamp to give imine **2.70** in 63% recovery, 85% based on recovered starting material. *N*-Heterocyclic carbene boranes (NHC-boranes) have also been shown to act as radical mediators in atom abstraction radical chemistry.[134] Exposure of amide **2.69** to (1,3-dimethyl-1*H*-imidazol-3-ium-2-

yl)trihydroborate and di-*tert*-butylhyponitrite in refluxing benzene afforded imine **2.70** in 20%, 33% based on recovered starting material. The use of $Ru(bpy)_3Cl_2$ provided a slightly lower yield than the standard tin hydride method; however, the transformation was clean with no detectable byproducts and product isolation was easy without the byproducts associated with tin hydride.



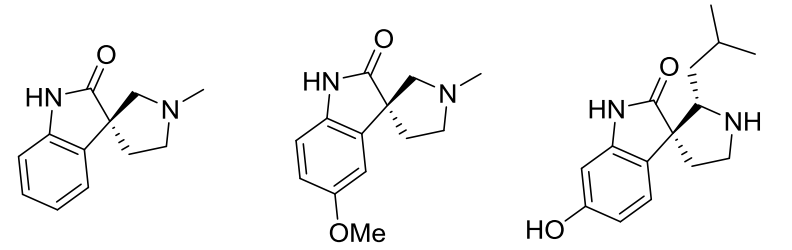
Scheme 2-23 Tin-free radical reactions of amide 2.69

In summary, we have shown that radical sulfonyl elimination may be used to synthesize a variety of α-spiro-imines under standard tin hydride conditions as well as tin-free conditions.

2.2.2 Oxindole synthesis by ene-sulfonamide cyclization

The spiro[pyrrolidin-3,3′-oxindole] ring system is a widely distributed structural framework present in a number of cytostatic alkaloids. The simplest members of this family of products are coerulescine **2.92**, horsfiline **2.93** and elacomine **2.94**, shown in Figure 2-8.

Coerulescine was isolated by Colegate in 1998 from the blue canary grass, *Phalaris coerulescens*.[135] Horsfiline was first isolated in 1991 by Bodo from a Malaysian medical plant, *Horsfieldia superb.*[136] An alkaloid isolated from *Eleagnus commutata* was first reported in 1969,[137] and was named elacomine when it was synthesized and the absolute configuration of the (+) isomer was established in 1996 by Pellegrini.[138]



Coerulescine **2.92** Horsfiline **2.93** Elacomine **2.94**

Figure 2-8 Structures of oxindole natural products

Because horsfiline and coerulescine are simple representatives of a class of natural products, their syntheses have been reported by several groups to showcase new methodologies. Key steps in the syntheses of horsfiline and coerulescine include oxidative indole rearrangements,[139] intramolecular Mannich reaction,[140] radical cyclization,[141-142] [3+2] cyclizations,[143-145] and transition metal catalyzed cyclizations.[146-148] The four syntheses of elacomine reported to date involve oxidative rearrangement,[138] intramolecular Mannich reaction,[149] photocyclization,[150] and Heck cyclization.[151]

The synthetic plan based on radical cyclization of an ene-sulfonamide for horsfiline is outlined in Figure 2-9. Amide coupling of aniline fragment **2.95** with carboxylic acid fragment **2.96** will provide anilide **2.97**. The oxindole ring would be formed during the key radical cyclization step while simultaneously removing the sulfonyl group to give imine **2.98**. The

resulting imine would then undergo simple hydride reduction, *N*-methylation, and removal of the amide protecting group to give horsfiline **2.93**.

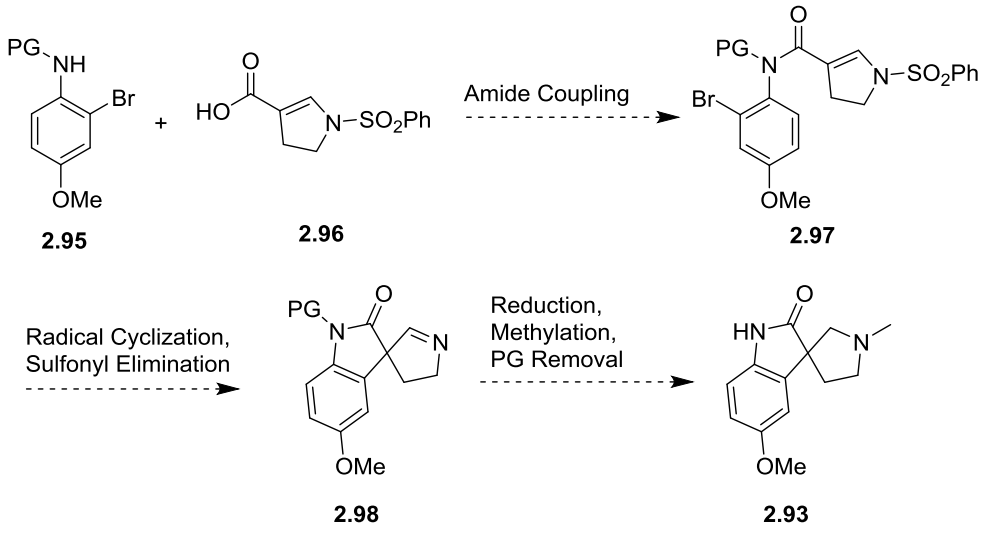
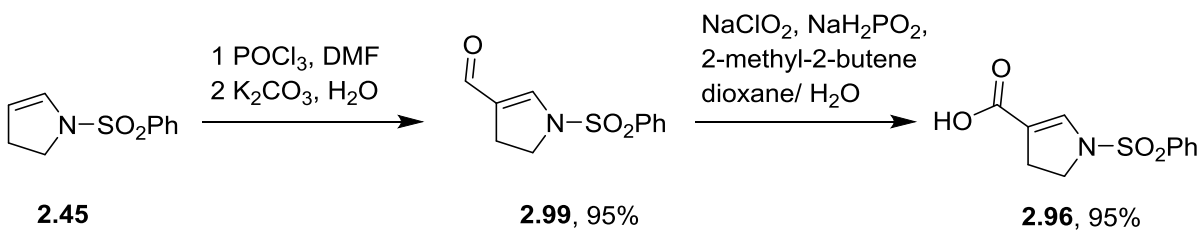


Figure 2-9 Synthetic plan for horsfiline 2.93

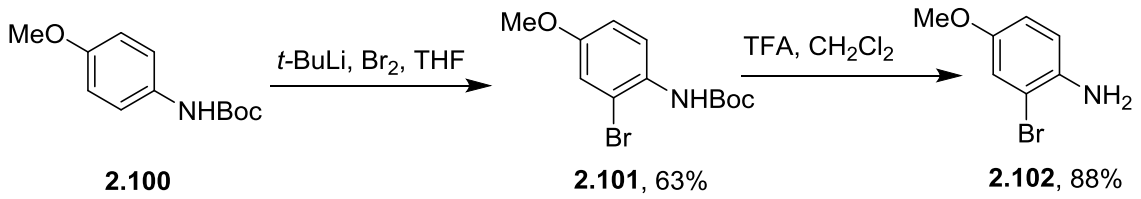
2.2.3 Studies towards synthesis of horsfiline, coerulescine and elacomine

The synthesis of acid component **2.96** started with Vilsmeier-Haak formylation of ene-sulfonamide **2.45**. Phosphorous oxychloride was combined with DMF, to which was added **2.45**, followed by aqueous carbonate to produce aldehyde **2.99** cleanly in 95% yield. Oxidation of **2.99** with $NaClO_2$ produced carboxylic acid **2.96** in 95% yield.



Scheme 2-24 Synthesis of carboxylic acid 2.96

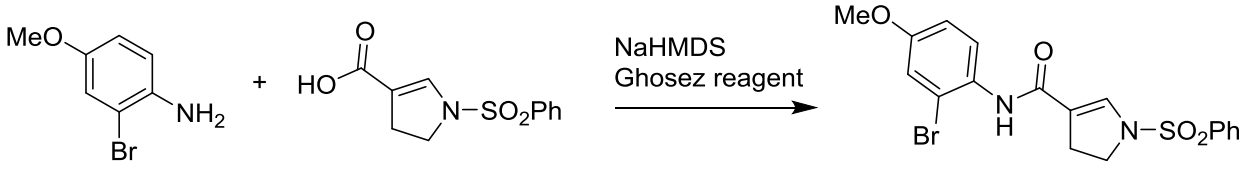
The synthesis of aniline component **2.102** started from commercially available Boc-protected anisidine **2.100**. Treatment of **2.100** with 2 equiv of *tert*-BuLi at –20 °C followed by addition of bromine at –78 °C provided bromoaniline **2.101** in 63% yield. Removal of the Boc group with TFA in CH_2Cl_2 gave aniline **2.102** in 88% yield.



2.100 **2.101**, 63% **2.102**, 88%

Scheme 2-25 Synthesis of aniline 93

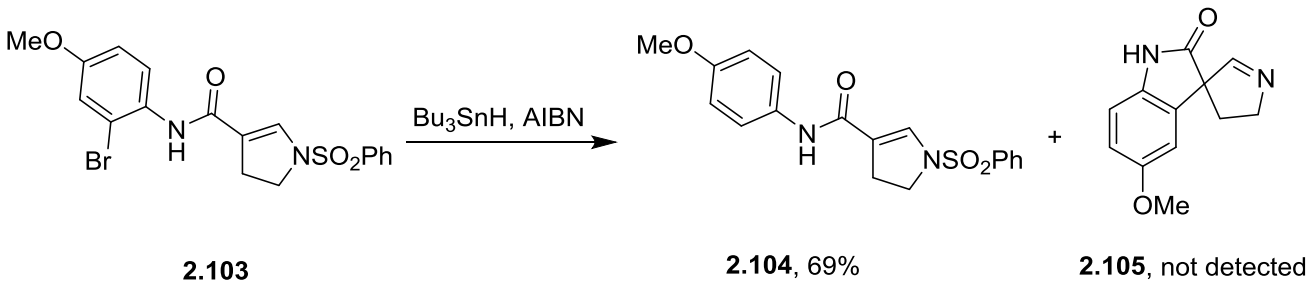
The coupling of acid **2.96** and aniline **2.102** proved to be challenging. Treatment of **1.96** and **2.102** with standard amide coupling reagents DCC, EDCI,[152-153] BOP[154] and HATU[155] failed to produce amide **2.103**. To increase amine nucleophilicity, aniline **2.102** was treated with a strong base and added slowly to acid chloride generated from treatment of carboxylic acid **2.96** to with the Ghosez reagent, 1-chloro-*N*,*N*-2-trimethyl-1-propenylamine, as shown in Scheme 2-26.[76] Aniline **2.96** was treated with NaHMDS in THF then added via cannula to a solution of acid **1.201** in toluene treated with Ghosez reagent to produce bromoanilide **2.103** in 65% yield.



2.102 **2.96** **2.103**, 65%

Scheme 2-26 Synthesis of bromoanilide 2.103

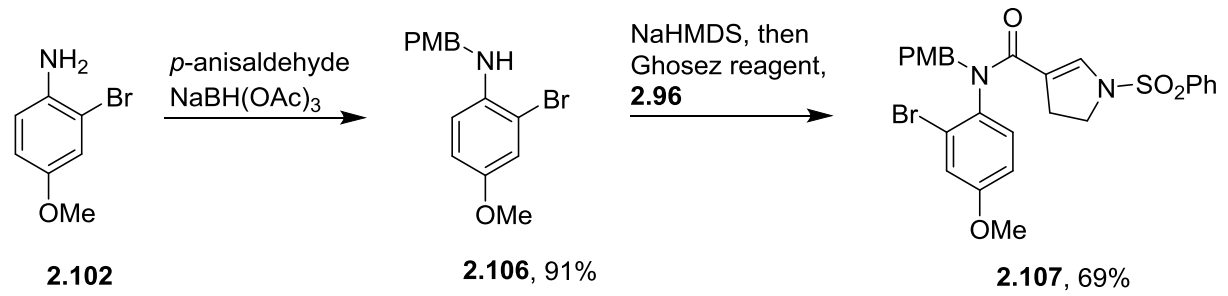
Addition of Bu_3SnH and AIBN via syringe pump to bromoanilide **2.103** in refluxing benzene produced the directly reduced anilide **2.104** in 69% yield. The amide is likely in the Z-conformation, a rotamer not disposed to cyclization.[156] Radical cyclizations of primary amides are more efficient at higher temperature due to increased amide bond rotation.[157-158] Bu_3SnH and *tert*-butylperoxide were added to anilide **2.103** in refluxing *tert*-butylbenzene at 169 °C. ^1H NMR analysis of the crude reaction showed resonances corresponding to the reduced anilide **2.103**, but no resonances corresponding to imine **2.105**.



2.103 **2.104**, 69% **2.105**, not detected

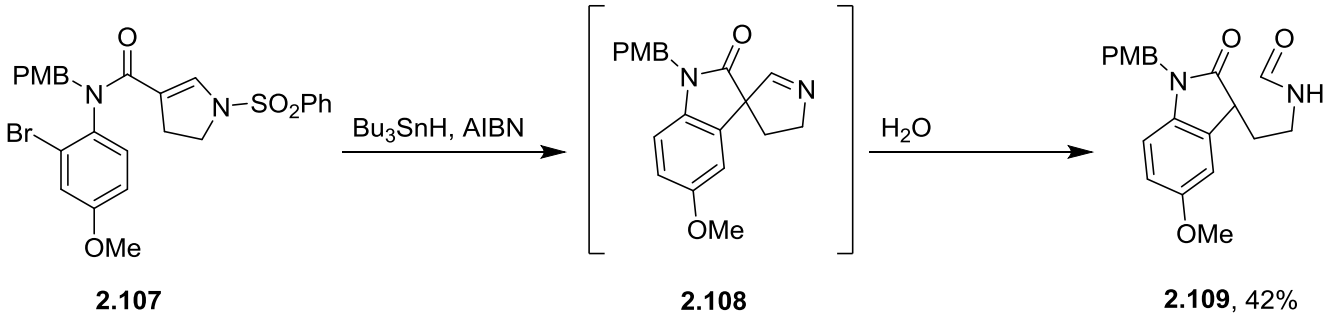
Scheme 2-27 Attempted cyclization of unprotected bromoanilide 2.103

N-Alkylanilides generally adopt the E-rotamer, which is more disposed to cyclization.[55, 156] We chose to protect the amide nitrogen with the *p*-methoxybenzyl (PMB) group because hydrogenation of structurally related *N*-benzylamides proved to be problematic during the synthesis of meloscine[55-56] and because the PMB group may be removed under acidic or oxidative conditions.[159] Anilide **2.107** was thus chosen as our target, shown in Scheme 2-28. Reductive amination of aniline **2.102** with anisaldehyde and $NaBH(OAc)_3$ gave aniline **2.106** in 91% yield. Coupling with acid **2.96** under Ghosez conditions gave the cyclization precursor **2.107** in 69% yield.



Scheme 2-28 Synthesis of protected amide 2.107

In Scheme 2-29, syringe pump addition of Bu_3SnH and AIBN to amide **2.107** in refluxing benzene gave formamide **2.109** in 42% isolated yield after flash chromatography. The crude reaction mixture did not contain the starting material **2.107**, the directly reduced product or the expected imine **2.108** as judged by ^{1}H NMR analysis. Key resonances in the ^{1}H NMR spectrum of **2.109** include a singlet at δ 8.15 ppm, 2 distinct signals corresponding to the PMB aromatic protons, 3 additional aromatic signals, 1 signal corresponding to the *N*-benzyl protons and 5 total alkyl signals. The ^{13}C and HMQC spectra along with IR and high resolution mass spectrometry are fully consistent with the structure of formamide **2.109**.



Scheme 2-29 Unexpected reactivity of bromoaniline 2.107

Formamide **2.109** could form on acidic silica gel during chromatography by addition of H_2O to the imine followed by a retro Dieckmann reaction. Or, it could perhaps form during the radical reaction due to the presence of adventitious water. To learn whether formamide **2.109** was a primary reaction product, we performed the reaction shown in Scheme 2-29 in d_6-benzene with ^{1}H NMR monitoring. Figure 2-11 shows key resonances of the starting anilide **2.107**, the isolated formamide **2.109**, and the reaction mixture in d_6-benzene. Resonances at δ 7.52 (d), 7.39 (d), 4.05 (d) and 3.05 (ddd) disappear with heating, while resonances at δ 7.79 (s), 4.61 (d), 4.52 (d), 3.41 (m), and 3.01 (t) appear in the isolated product and the crude reaction after heating.

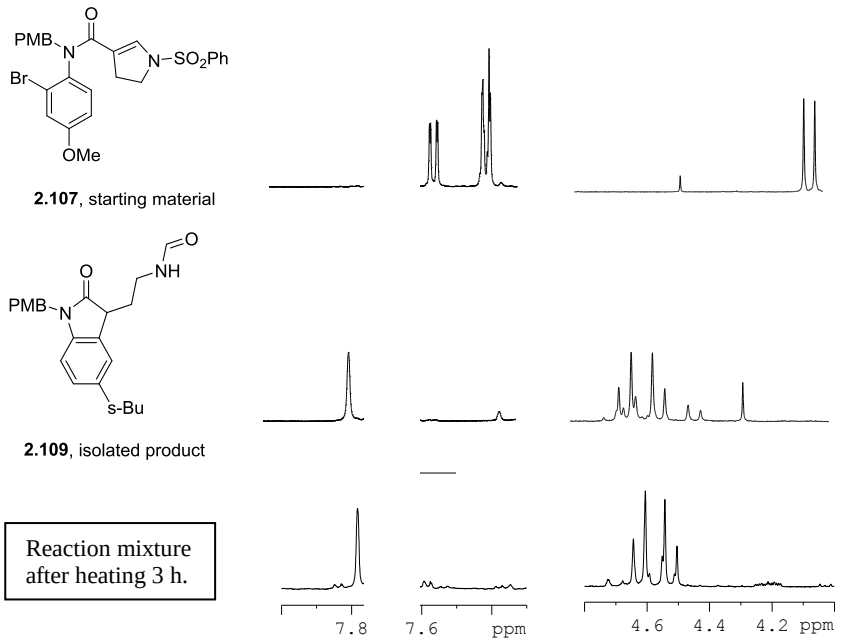
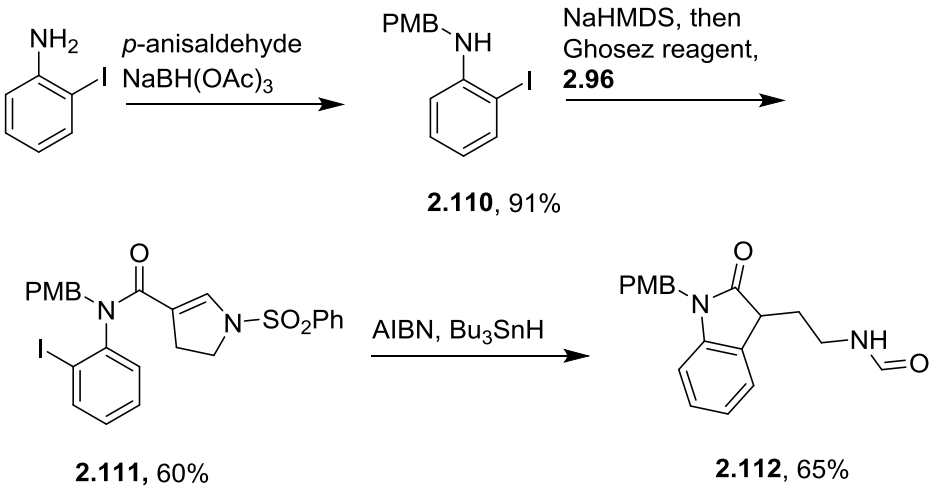


Figure 2-10 Key resonances of anilide 2.109 with Bu_3SnH heated in d_6-benzene

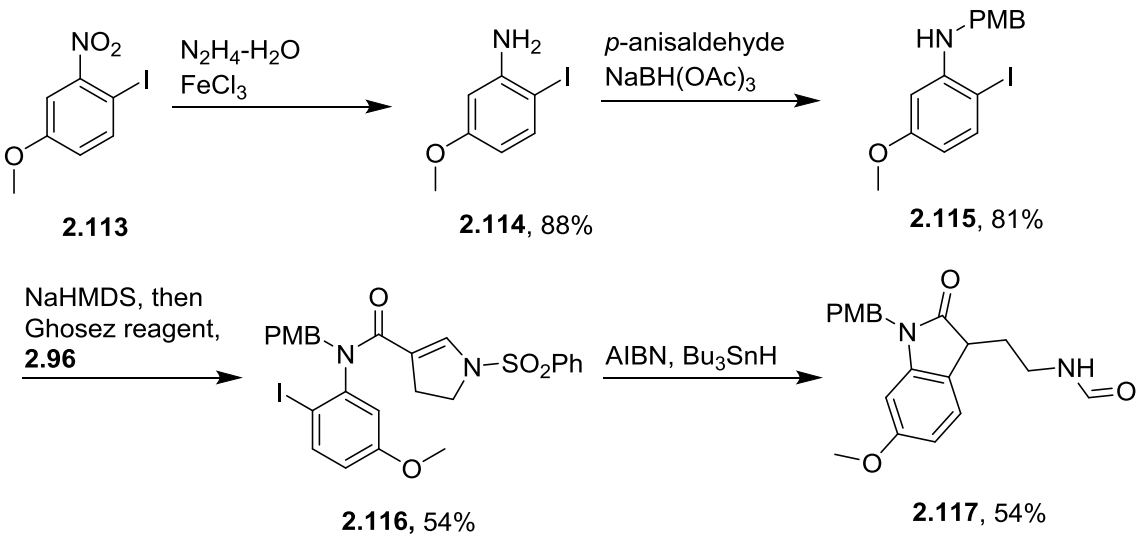
Iodoanlides **2.111** and **2.116** were originally designed as precursors for coerulescine **2.92** and elacomine **2.94** respectively, but we redirected them to study the generality of the formamide forming reaction shown in Scheme 2-29. Reductive amination of commercially available 2-iodoaniline with $NaBH(OAc)_3$ and *p*-anisaldehyde gave the aniline **2.110** in 91% yield. Aniline

2.110 was treated with NaHMDS and added to acid **2.96** treated with the Ghosez reagent to give the anilide **2.111** in 60% yield. Syringe pump addition of Bu_3SnH and AIBN to refluxing solution of iodoaniline **2.111** in refluxing benzene gave formamide **2.112** in 65% yield.



Scheme 2-30 Synthesis of formamide 2.112

The reduction of nitroanisole **2.113** was accomplished with hydrazine hydrate and catalytic $FeCl_3$ to give aniline **2.114** in 88% yield. Reductive amination of this unstable compound with *p*-anisaldehyde and $NaBH(OAc)_3$ provided aniline **2.115** in 81% yield. Deprotonation with NaHMDS in THF followed by addition of the acid chloride formed from acid **2.96** and Ghosez reagent in toluene gave coupled anilide **2.116** in 54% yield. Standard syringe pump addition of Bu_3SnH and AIBN to refluxing solution of iodoanilide **2.116** in refluxing benzene gave formamide **2.117** in 54% yield. Formamide **2.117** also yielded a crystal structure, shown in Figure 2-11.



Scheme 2-31 Synthesis of formamide 2.117

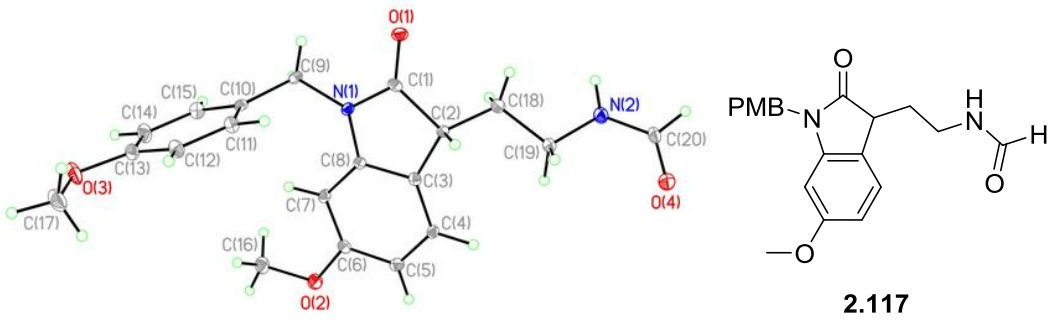
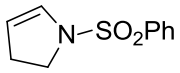


Figure 2-11 Crystal structure of formamide 2.117

In conclusion, we have synthesized a family of 5-, 6-, and 7-membered spirocyclic imines by a radical cyclization-sulfonyl elimination strategy. We have also discovered a novel radical cyclization-retro-Dieckmann ring opening process which allows access to substituted oxindole species from *ortho*-halogenated anilides.

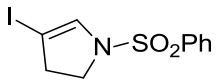
2.3 EXPERIMENTAL



1-(Phenylsulfonyl)-2,3-dihydro-1H-pyrrole (2.45):[160] DIBAL-H citric acid preparation: A DIBAL-H solution (1 M in hexane, 39 mL) was added dropwise to a solution of sulfonamide **2.44**[161] (5.8 g, 26 mmol) in THF (250 mL) at −78 °C. After 1 h, the reaction mixture was diluted with Et_2O (200 mL) and a saturated aqueous potassium-sodium tartrate solution (400 mL) was added. After 12 h of stirring, the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and volatile compounds were removed under vacuum. The crude hemiaminal product was dissolved in toluene (150 mL). Citric acid (5.4 g, 26 mmol) was added and the reaction mixture was stirred at 80 °C for 4 h. The reaction mixture was cooled to room temperature and a saturated aqueous $NaHCO_3$ solution was carefully added. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine, dried over $MgSO_4$, and volatile compounds were removed under vacuum. The crude residue was purified by flash chromatography (15% EtOAc in hexanes) to provide the title compound (4.3 g, 80%) as a white solid: mp 114–115 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.8 Hz, 2H), 7.61–7.50 (m, 3H), 6.38 (td, *J* = 4.2 Hz, 2.1 Hz, 1H), 5.12 (td, *J* = 4.2 Hz, 2.7 Hz, 1H), 3.50 (t, *J* = 9.0 Hz, 2H), 2.48 (tt, *J* = 9.0 Hz, 2.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.8, 133.0, 130.5, 129.0, 127.6, 111.5, 47.2, 29.0; HRMS (EI) *m/z* calcd for $C_{10}H_{11}NO_2S$ $[M]^+$ 209.0510, found 209.0510.

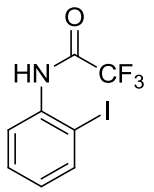
$LiEt_3BH$-TFAA preparation: Sulfonamide **2.44** (1.00 g, 4.44 mmol) is added to a flame dried 100 mL, three necked, round bottom flask. Anhydrous toluene (44 mL) is added, the flask is cooled to –78 °C and a solution of lithium triethylborohydride (4.88 mL, 1.0 M) is added

dropwise. After addition, the reaction mixture is stirred for one additional h at –78. Solid DMAP (4 mg, 0.05 mmol) is added in one portion, followed by dropwise addition of *N*,*N*–diisopropylethylamine (4.4 mL, 25.3 mmol) and trifluoroacetic anhydride (0.74 mL, 5.33 mmol). The mixture is allowed to warm to r.t. then stirred for two h. The reaction mixture is cooled to 0 °C then is quenched by dropwise addition of water (15 mL). The mixture is transferred to a 0.25-L separatory funnel where the phases are separated. The organic phase is washed twice with water (15 mL each) and then is dried over anhydrous $MgSO_4$. The solution is filtered and volatile compounds are removed under vacuum. The residue is purified by flash chromatography (15% EtOAc in hexanes) to afford the title compound (0.85 g, 92%) as a white crystalline solid.

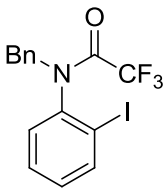


4-Iodo-1-(phenylsulfonyl)-2,3-dihydro-1*H*-pyrrole (2.46):[160] ICl (3.1 mL, 1M in CH_2Cl_2) was added dropwise to a solution of ene-sulfonamide **2.45** (650 mg, 3.1 mmol) and $NaOCH_3$ (169 mg, 3.1 mmol) in methanol (15 mL). The resulting yellow suspension was stirred for 30 min, then a 10% aqueous solution of $Na_2S_2O_3$ (5 mL) was added and stirring continued for 30 min. The mixture was extracted with EtOAc (3 x 10 mL). The combined organic layer was washed with brine, dried over $MgSO_4$ and the volatile compounds were removed under vacuum. The residue was suspended in toluene (15 mL). Trifluoroacetic acid (20 µL, 0.2 mmol) was added at room temperature. The reaction flask was fitted with a condenser and submersed into an oil bath preheated to 140 °C. The mixture was stirred for 5 min then cooled to room temperature. Triethylamine (60 µL, 0.3 mmol) was added, volatile compounds were removed under vacuum. The residue is purified by flash chromatography (15% EtOAc in hexanes) to give the title compound (835 mg, 80%) as a white crystalline solid, mp 104–105 °C. ^{1}H NMR (300

MHz, $CDCl_3$) δ 7.79 (dd, *J* = 7.8 Hz, 1.8 Hz, 2H), 7.63–7.53 (m, 3H), 6.57 (t, *J* = 2.1 Hz, 1H), 3.55 (t, *J* = 9.0 Hz, 2H), 2.70 (dt, *J* = 9.0 Hz, 2.1 Hz, 2H); 13C NMR (300 MHz, CDCl3) δ 135.7, 135.5, 133.3, 129.31, 127.7, 70.5, 48.2, 39.6; FTIR (thin film, CH2Cl2, cm-1) 3105, 3062, 2857, 1607, 1474, 1445, 1351, 1166, 1099;HRMS (TOF ES) *m/z* calcd for $C_{10}H_{10}NO_2NaSI$ $[M+Na]^+$ 357.9375, found 357.9355.

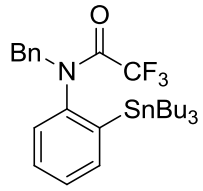


2,2,2-Trifluoro-*N*-(2-iodophenyl)acetamide (S1):[162] Et_3N (3.6 mL, 25.6 mmol) was added to a solution of 2-iodoaniline (5.1 g, 23.3 mmol) in THF (30 mL) at 0 °C, followed by dropwise addition of trifluoroacetic anhydride (3.5 mL, 25.6 mmol). The reaction mixture was stirred at 0 °C for 30 min and then at room temperature for 2 h. The reaction was quenched with water and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and volatile compounds were removed under vacuum. The residue was passed through a pad of silica gel (10% EtOAc in hexanes) to provide the title compound (14.0 g, 95%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (s, 1H), 8.23 (dd, *J* = 8.1 Hz, 1.2 Hz, 1H), 7.85 (dd, *J* = 8.1, *J* = 1.2 Hz, 1H), 7.42 (dt, *J* = 7.8 Hz, 1.2 Hz, 1H), 6.98 (dt, *J* = 7.8 Hz, 1.2 Hz, 1H).



***N*-Benzyl-2,2,2-trifluoro-*N*-(2-iodophenyl)acetamide (2.47)**:[160] A solution of acetamide **S1** (3.0 g, 9.52 mmol) in THF (10 mL) was added dropwise to a suspension of NaH (274 mg,

11.43 mmol) in THF (25 mL) at 0 °C. After 30 min, a solution of benzyl bromide (1.36 mL, 11.43 mmol) in THF (10 mL) was added dropwise at 0 °C. The reaction mixture was warmed to room temperature and stirred for 12 h. The reaction was quenched with a saturated aqueous NH_4Cl solution and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and volatile compounds were removed under vacuum. The crude residue was purified by flash chromatography (2% Et_2O in hexanes) to provide the title compound (3.5 g, 91%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 7.8 Hz, 1.5 Hz, 1H), 7.33–7.17 (m, 6H), 7.09 (dt, *J* = 7.8 Hz, 1.5 Hz, 1H), 6.70 (d, *J* = 7.8 Hz, 1H), 5.74 (d, *J* = 14.1 Hz, 1H), 4.04 (d, *J* = 14.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9 (q, J_{CF} = 35.2 Hz), 140.1, 134.8, 131.4, 131.3, 130.7, 129.7, 128.7, 128.6, 128.3, 116.1 (q, J_{CF} = 287 Hz), 99.4, 53.8; HRMS (TOF ES) *m/z* calcd for $C_{15}H_{11}NOF_3NaI$ $[M+Na]^+$ 427.9735, found 427.9705.



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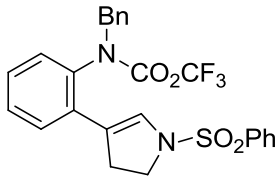
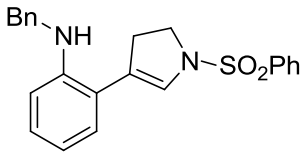
***N*-Benzyl-2,2,2-trifluoro-*N*-(2-(tributylstannyl)phenyl)acetamide (2.48)**:[160] $Pd(PPh_3)_4$ (143 mg, 0.12 mmol) and hexabutylditin (3.7 mL, 7.4 mmol) were added to a solution of aryl iodide **2.47** (1.0 g, 2.5 mmol) in toluene (20 mL), the mixture heated to reflux for 24 h. The solvent was evaporated and the crude residue was purified by flash chromatography (2% Et_2O in hexanes) to provide the title compound (1.2 g, 84%) as a light yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H), 7.33–7.27 (m, 4H), 7.15–7.10 (m, 3H), 6.51 (d, *J* = 7.5 Hz, 1H), 5.75 (d, *J* = 13.5 Hz, 1H), 3.83 (d, *J* = 13.5 Hz, 1H), 1.59–1.47 (m, 6H), 1.34 (m,

6H), 1.10 (m, 6H), 0.90 (t, J = 7.2 Hz, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9 (q, J_{CF} = 14.1 Hz), 144.4, 142.5, 138.1, 135.0, 130.1, 129.7, 128.5, 128.3, 128.2, 128.1, 116.5 (q, J_{CF} = 118.7 Hz), , 55.4, 29.0, 27.3, 13.5, 10.3; HRMS (EI) *m/z* calcd for $C_{23}H_{29}NOF_3Sn$ $[M-C_4H_9]^+$ 508.1219, found: 508.1229.

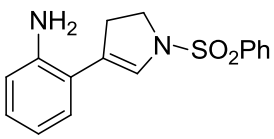


***N*-Benzyl-2,2,2-trifluoro-*N*-(2-(1-(phenylsulfonyl)-4,5-dihydro-1*H*-pyrrol-3-yl)phenyl)acetamide (S2)**:[160] A Schlenck tube (100 mL) was charged with LiCl (1.14 g, 26.8 mmol) and flame dried under vacuum. Upon cooling, CuCl (2.22 g, 22.34 mmol) and $Pd(PPh_3)_4$ (0.518 g, 0.448 mmol) were added and the mixture was degassed under vacuum with an Ar purge. Anhydrous DMSO (15 mL) was introduced, followed by a solution of aryl stannane **2.48** (3.05 g, 5.37 mmol) in anhydrous DMSO (5 mL), and finally vinyl iodide **2.46** (1.5 g, 4.48 mmol). The resulting mixture was degassed three times through freeze-pump-thaw processes, and stirred at room temperature for 30 min and then heated to 60 °C for 1.5 h. The reaction mixture was cooled, diluted with Et_2O, and washed with a 5% aqueous NH_4OH solution (30 mL) and brine (150 mL). The aqueous layer was extracted with Et_2O, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash chromatography (25% EtOAc in hexanes) to provide the title compound (1.90 g, 87%) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (dd, J = 7.8 Hz, 1.5 Hz, 2H), 7.59–7.54 (m, 3H), 7.29 (t, J = 6.3 Hz, 3H), 7.24 (dt, J = 6.3 Hz, 1.5 Hz, 2H), 7.10 (dd, J = 7.8 Hz, 1.5 Hz, 2H), 7.46 (dt, J = 7.8 Hz, 1.5 Hz, 1H), 6.68 (t, J = 1.5 Hz, 1H), 6.57 (d, J = 7.8 Hz, 1H), 5.53 (d, J = 13.5 Hz, 1H), 3.79–3.70 (m, 2H), 3.56 (app q, J = 9.3 Hz, 1H), 2.85 (t, J = 9.3

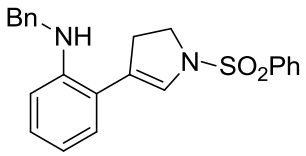
Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.10 (q, J_{CF} = 35.2 Hz), 135.4, 134.6, 133.3, 132.0, 131.0, 129.6, 129.5, 129.4, 129.1, 128.6, 128.3, 128.3, 127.6, 127.0, 120.4, 116.2 (q, J_{CF} = 287.2 Hz) 53.4, 47.1, 32.0; FTIR (thin film, CH_2Cl_2, cm^{-1}) 3417, 3064, 2918, 2849, 1504, 1446, 1349, 1166; HRMS (TOF ES) *m/z* calcd for $C_{25}H_{21}N_2O_3F_3NaS$ $[M+Na]^+$: 509.1123, found: 509.1147.



***N*-Benzyl-2-(1-(phenylsulfonyl)-4,5-dihydro-1*H*-pyrrol-3-yl)aniline (2.49)**:[160] **First-Generation Synthesis:** $NaBH_4$ (16 mg, 0.432 mmol) was added in two portions to a solution of trifluoroacetamide **S2** (30 mg, 0.062 mmol) in EtOH (1 mL). The reaction mixture was stirred at room temperature for 3 h. After the solvent was evaporated, the residue was purified by flash chromatography (25% EtOAc in hexanes) to provide the title compound (23 mg, 96%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61–7.58 (m, 2H), 7.53–7.29 (m, 8H), 7.13 (dt, *J* = 7.8 Hz, 1.5 Hz, 1H), 7.24 (dt, *J* = 6.3 Hz, 1.5 Hz, 2H), 7.10 (dd, *J* = 7.8 Hz, 1.5 Hz, 2H), 7.46 (dt, *J* = 7.5 Hz, 1.5 Hz, 1H), 6.96 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H), 6.83 (t, *J* = 1.8 Hz, 1H), 6.72 (dt, *J* = 7.5 Hz, 1.2 Hz, 1H), 6.69 (d, *J* = 7.8 Hz, 1H), 4.30 (s, 2H), 4.07 (br s, 1H), 3.58 (t, J = 9 Hz, 1H), 2.84 (dt, *J* = 9 Hz, 1.5, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.3, 139.0, 135.1, 133.0, 129.1, 128.9, 128.4, 127.7, 127.7, 127.5, 127.4, 127.1, 122.7, 119.9, 117.6, 111.2, 46.9, 46.8, 32.9; FTIR (thin film, CH_2Cl_2, cm^{-1}) 3340, 3031, 2923, 2853, 1596, 1500, 1448, 1349, 1164, 1090, 1043, 749, 704; HRMS (EI) m/z calcd for $C_{23}H_{22}N_2O_2S$ $[M]^+$: 390.1402, found: 390.1408.

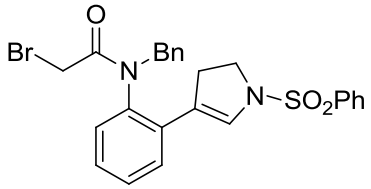


2-(1-(Phenylsulfonyl)-4,5-dihydro-1H-pyrrol-3-yl)aniline (2.50):[160] A dried Schlenk tube was charged under Ar with dioxane (15 mL), vinyl iodide **2.46** (960 mg, 2.74 mmol), $Pd(OAc)_2$ (31 mg, 0.14 mmol), 2-(dicyclohexylphosphino)biphenyl (192 mg, 0.53 mmol), $Ba(OH)_2$-$(H_2O)_8$ (2.59 g, 8.22 mmol) and 2-(pinacolboronate)aniline (600 mg, 2.74 mmol). The mixture was heated to 70 °C for 1 h. After cooling to room temperature, water and EtOAc were added, the phases were separated, and the aqueous phase was extracted with more EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and the volatile compounds were removed under vacuum. The residue was subjected to column chromatography (25% EtOAc in hexanes) to give the title compound (650 mg, 79%) as a white solid: mp 125–126 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.2 Hz, 2H), 7.62 (t, *J* = 7.2 Hz, 1H), 7.55 (t, *J* 7.2 Hz, 2H), 7.04 (t, *J* = 7.6 Hz, 1H), 6.94 (d, *J* = 7.6 Hz, 1H), 6.85 (s, 1H), 6.75–6.70 (m, 2H), 3.75 (br s, 2H), 3.63 (t, *J* = 8.8 Hz, 2H), 2.87 (t, *J* = 8.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.9, 135.6, 133.1, 129.2, 127.9, 127.5, 127.4, 126.7, 122.7, 119.8, 118.7, 116.4, 47.0, 32.5; FTIR (thin film, CH_2Cl_2, cm^{-1}) 3417, 3064, 2918, 2849, 1504, 1446, 1349, 1166; HRMS (TOF ES) *m/z* calcd for $C_{16}H_{16}N_2O_2SNa$ $[M+Na]^+$ 323.0830, found 323.0844.



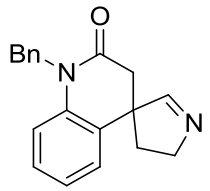
***N*-Benzyl-2-(1-(phenylsulfonyl)-4,5-dihydro-1*H*-pyrrol-3-yl)aniline (2.49): Second-Generation Synthesis:** Benzaldehyde (0.75 mL, 2.49 mmol) was added to a solution of substituted aniline **39** (650 mg, 2.16 mmol) and AcOH (0.19 mL, 3.25 mmol) in anhydrous MeOH (22 mL) over 4Å molecular sieves. The solution was heated to 40 °C and allowed to stir at room temperature for 1 h. $NaCNBH_3$ (177 mg, 2.81 mmol) was added in one portion. The

mixture was stirred 16 h. CH_2Cl_2 was added, the mixture was filtered, then volatile compounds were removed under vacuum. The residue was subjected to flash chromatography (25% EtOAc in hexanes) to give the title compound (580 mg, 69 %) as a colorless oil.



***N*-Benzyl-2-bromo-*N*-(2-(1-(phenylsulfonyl)-4,5-dihydro-1*H*-pyrrol-3-yl)phenyl)acetamide (2.33)**:[160] Pyridine (10 μL, 0.128 mmol) and bromoacetyl bromide (7 μL, 0.077 mmol) were added to a solution of aniline **2.49** (25 mg, 0.064 mmol) in CH_2Cl_2 (1 mL). After 10 min, the reaction was quenched with a saturated aqueous NH_4Cl solution. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over $MgSO_4$, and volatile compounds were removed under vacuum. The crude residue was purified by flash chromatography (30% EtOAc in hexanes) to provide the title compound (27 mg, 83%) as a viscous, colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86–7.83 (m, 2H), 7.61–7.54 (m, 3H), 7.31–7.19 (m, 5H), 7.15–7.11 (m, 2H), 7.06 (td, *J* = 7.8 Hz, 1.5 Hz, 1H), 6.71 (s, 1H), 6.67 (dd, *J* = 7.8 Hz, 0.9 Hz, 1H), 5.55 (d, *J* = 13.8 Hz, 1H), 3.73 (d, *J* = 13.8 Hz, 1H), 3.75–3.68 (m, 1H), 3.52 (app q, *J* = 9.3 Hz, 1H), 3.46 (d, *J* = 16.8 Hz, 1H), 3.42 (d, *J* = 16.8 Hz, 1H), 2.83 (t, *J* = 9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 137.2, 136.1, 135.5, 133.4, 131.8, 130.6, 129.5, 129.4, 129.3, 129.2, 128.5, 128.4, 127.9, 127.7, 120.0, 52.0, 47.1, 32.0, 27.5; FTIR (thin film, CH_2Cl_2, cm^{-1}) 3062, 1662, 1356, 1167; HRMS (TOF ES) *m/z* calcd for $C_{25}H_{23}N_2O_3NaSBr$ $[M+Na]^+$ 533.0510, found: 533.0506.

General Procedure A: Tin Hydride Radical Cyclization: Bu_3SnH (2.2 equiv) and AIBN (0.1 equiv) in benzene (0.1 M) were added by syringe pump over 2 h to a refluxing mixture of radical precursor (1.0 equiv) in refluxing benzene (0.01 M). The mixture was heated at reflux an additional 1 h. The solvent was evaporated and the residue was partitioned between hexane (approx. equal volume as in reaction mixture) and acetonitrile (approx. equal volume). The acetonitrile layer was diluted with CH_2Cl_2, dried over $MgSO_4$, and volatile compounds were removed under vacuum. The residue was applied to a silica column, which was washed with hexanes (approx 2 column volumes) before flash chromatography.



1'-Benzyl-4,5-dihydro-1'*H*-spiro[pyrrole-3,4'-quinolin]-2'(3'*H*)-one (2.35):[160]

General Procedure A was applied to bromoacetamide **2.33** (12 mg, 0.023 mmol) to provide the title compound (5 mg, 75%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.34–7.15 (m, 6H), 7.04–6.95 (m, 3H), 5.35 (d, *J* = 16.2 Hz, 1H), 5.10 (d, *J* = 16.2 Hz, 1H), 4.08 (m, 2H), 2.97 (d, *J* = 15.6 Hz, 1H), 2.67 (d, *J* = 15.4 Hz, 1H), 2.22 (dt, *J* = 13.2 Hz, 6.6 Hz, 1H), 1.89 (dt, *J* = 13.2 Hz, 6.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 168.7, 167.8, 138.7, 136.6, 129.4, 128.8, 128.4, 127.3, 26.5, 125.0, 123.6, 116.4, 61.1, 54.8, 46.1, 39.5, 35.9; FTIR (thin film, CH_2Cl_2, cm^{-1}) 3033, 2960, 2867, 1676, 1625, 1600, 1495, 1455, 1379, 1324, 1284, 1223, 1192; HRMS (EI) *m/z* calcd for $C_{19}H_{18}N_2O$ $[M]^+$ 290.1419, found: 290.1414.

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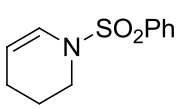
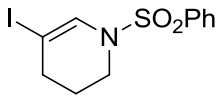
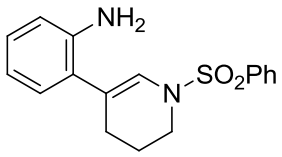


1-(Phenylsulfonyl)-1,2,3,4-tetrahydropyridine (2.54):[163] A solution of lithium triethylborohydride (9.19 mL, 1.0 M) is added dropwise to a solution of sulfonamide **2.53**[164] (2.00 g, 8.36 mmol) in toluene (84 mL) at –78 °C. After addition, the reaction mixture is stirred for an additional 1 h at –78 °C. Solid DMAP (10 mg, 0.08 mmol) is added in one portion, followed by dropwise addition of *N*,*N*-diisopropylethylamine (8.29 mL, 47.6 mmol) and trifluoroacetic anhydride (1.51 mL, 10.0 mmol). The mixture is allowed to warm to room temperature then stirred for 2 h. The reaction is cooled to 0 °C then is quenched by addition of water (20 mL). The mixture is transferred to a 0.5-L separatory funnel where the phases are separated. The organic phase is washed twice with water (15 mL each) and once with brine, then dried over $MgSO_4$. Volatile compounds were removed under vacuum. The residue was subjected to flash chromatography (5–10% EtOAc in hexanes) to give the title compound (1.60 g, 86%) as a white crystalline solid, mp 80–81 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.2 Hz, 2H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 2H), 6.64 (dt, *J* = 8.4 Hz, 1.8 Hz, 1H), 4.98 (dt, *J* = 8.4 Hz, 3.9 Hz, 1H), 3.40–3.36 (m, 2H), 1.94–1.88 (m, 2H), 1.65 (p, *J* = 6.0 Hz, 2H).



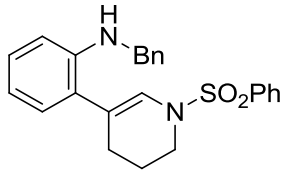
5-Iodo-1-(phenylsulfonyl)-1,2,3,4-tetrahydropyridine (2.55):[160] A solution of ICl in dichloromethane (1.48 mL, 1.0 M) was added dropwise to a mixture of ene-sulfonamide **2.54** (300 mg, 1.34 mmol) and $NaOCH_3$ (145 mg, 2.69 mmol) in methanol (5 mL). The resulting yellow suspension was stirred for 30 min, then a 10% aqueous solution of $Na_2S_2O_3$ (2 mL) was added, stirring continued for 30 min. The aqueous phase was extracted with EtOAc. The combined organic extract was washed with brine, dried over $MgSO_4$ and volatile compounds were removed under vacuum. The crude residue was dissolved in toluene (5 mL), trifluoroacetic

acid (18 μL, 0.2 mmol) was added at room temperature. The reaction flask was fitted with a condenser and submersed into an oil bath preheated to 140 °C. The reaction mixture was stirred for 5 min, and then cooled to room temperature. Triethylamine (54 μL, 0.3 mmol) was added, and then volatile compounds were removed under vacuum. The residue was subjected to flash chromatography (5–10% EtOAc in hexanes) to give the title compound (306 mg, 59%) as a white crystalline solid, mp 64–66 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.5 Hz, 2H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 2H), 7.14 (t, *J* = 1.5 Hz, 1H), 3.41 (dd, *J* = 5.5 Hz, 2H), 2.33 (td, *J* = 6.5 Hz, 1.5 Hz, 2H), 1.72 (p, *J* = 6.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.5, 133.1, 130.1, 129.3, 126.9, 73.9, 42.4, 34.0, 23.0; FTIR (thin film, CH_2Cl_2, cm^{-1}) 3105, 3062, 2931, 1605, 1474, 1445, 1355, 1159, 1099; HRMS (TOF ES) *m/z* calcd for $C_{11}H_{12}NO_2SI$ $[M]^+$ 348.9634, found 348.9624.



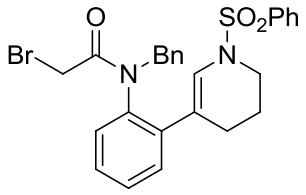
2-(1-(Phenylsulfonyl)-1,4,5,6-tetrahydropyridin-3-yl)aniline (2.56):[160] A dried Schlenk tube was charged under Ar with dioxane (3 mL), vinyl iodide **2.55** (150mg, 0.43mmol), $Pd(OAc)_2$ (5 mg, 0.02 mmol), 2-(dicyclohexylphosphino)biphenyl (30 mg, 0.09 mmol), $Ba(OH)_2$-$(H_2O)_8$ (407 mg, 1.29 mmol) and 2-(pinacolboronate)aniline (94mg, 0.43mmol). The mixture was heated at 70°C for 1 h. After cooling the mixture to room temperature, water and EtOAc were added, the phases were separated. The aqueous phase was extracted with more EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and the volatile compounds were removed under vacuum. The residue was subjected to flash chromatography (10% EtOAc in hexanes) to give the title compound (98 mg, 73%) as a colorless oil. ^{1}H NMR

(400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.5 Hz, 2H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 2H), 7.07 (td, *J* = 7.5 Hz, 1.5 Hz, 1H), 7.38 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H), 6.81 (s, 1H), 7.25 (t, *J* = 7.5 Hz, 1H), 6.71 (d, *J* = 7.6 Hz), 3.65 (s, 2H), 3.48 (at, *J* = 4.5Hz, 2H), 2.19 (t, *J* = 6.0 Hz, 2H), 1.82 (p, *J* = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7, 137.8, 132.9, 129.4, 129.2, 128.1, 127.0, 126.4, 123.8, 118.8, 118.4, 115.5, 43.5, 25.5, 21.2; FTIR (thin film, CH_2Cl_2, cm^{-1}) 3446, 2929, 1614, 1446, 1341, 1170, 966; HRMS *m/z* calcd for $C_{19}H_{23}N_2O_2S$ $[M+H]^+$ 343.1480, found 343.1474.

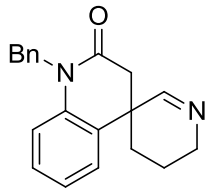


***N*-Benzyl-2-(1-(phenylsulfonyl)-1,4,5,6-tetrahydropyridin-3-yl)aniline (2.57)**:[160]

$NaBH(OAc)_3$ (1.17 g, 5.53 mmol) was added in one portion to a solution of aniline **2.56** (580 mg, 1.84 mmol), benzaldehyde (0.22 mL, 2.21 mmol), and AcOH (0.11 mL, 1.84 mmol) in anhydrous 1,2-DCE (50 mL). The mixture was stirred 14 h, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography (20% EtOAc in hexanes) to give the title compound (705 mg, 94%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.2 Hz, 2H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.42 (t, J = 8.0 Hz, 2H), 7.37–7.26 (m, 5H), 7.13 (td, *J* = 7.5 Hz, 1.5 Hz, 1H), 6.96 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H), 6.84 (s, 1H), 6.73 (t, *J* = 7.5 Hz, 1H), 6.61 (d, *J* = 7.8 Hz, 1H), 4.32 (s, 2H), 3.47 (dd, *J* = 6.0 Hz, 5.7 Hz, 2H), 2.19 (t, *J* = 6.6 Hz, 2H), 1.76 (p, *J* = 6.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.1, 139.4, 137.7, 132.8, 129.3, 129.1, 128.7, 128.4, 127.2, 127.1, 126.9, 126.5, 124.2, 118.9, 117.1, 110.7, 48.2, 43.5, 25.7, 21.1; FTIR (thin film, CH_2Cl, cm^{-1}) 3428, 3063, 2931, 2859, 1599, 1505, 1447, 1340, 1175, 1095; HRMS (TOF ES) *m/z* calcd for $C_{24}H_{25}N_2O_2S$ $[M+H]^+$ 405.1673, found 405.1623.

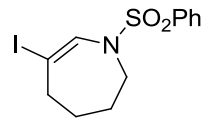


***N*-Benzyl-2-bromo-N-(2-(1-(phenylsulfonyl)-1,4,5,6-tetrahydropyridin-3-yl)phenyl)acetamide (2.58)**:[160] Bromoacetyl bromide (25µL, 0.29mmol) was added to a solution of aniline **2.57** (78 mg, 0.19 mmol) and triethylamine (54 µL, 0.39 mmol) in dry CH_2Cl_2 (2 mL) at 0 °C, the mixture was stirred for 1 h. The reaction was quenched with aqueous $KHCO_3$. The aqueous layer was extracted with EtOAc, the combined organic layer was washed with brine, dried over $MgSO_4$, and volatile compounds were removed under vacuum. The residue was subjected to flash chromatography (10% EtOAc in hexanes) to give the title compound (75mg, 74%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.0 Hz, 2H), 7.59 (t, *J* = 7.0 Hz, 1H), 7.52 (m, 3H), 7.33 (td, *J* = 7.0 Hz, 1.0 Hz, 1H), 7.29 (dd, *J* = 7.5 Hz, 2.0 Hz, 1H), 7.25 (d, *J* = 3.5 Hz, 2H), 7.14 (dd, 7.5 Hz, 2.0 Hz, 1H), 7.12–7.10 (m, 2H), 6.86 (s, 1H), 6.74 (dd, *J* = 7.5 Hz, 2.0 Hz, 1H), 5.46 (d, *J* = 14.1 Hz, 1H), 3.73 (d, *J* = 14.1 Hz, 1H), 3.61 (d, *J* = 11.5 Hz, 1H), 3.69 (d, *J* = 11.5 Hz, 2H), 3.50 (ddd, *J* = 11.5 Hz, 6.5 Hz, 4.0 Hz, 1H), 3.40 (ddd, *J* = 11.5 Hz, 6.5 Hz, 4.0 Hz, 1H), 2.20 (dt, *J* = 15.5 Hz, 6.5 Hz, 1H), 2.07 (td, *J* = 15.5 Hz, 6.5 Hz, 1H), 1.84–1.80 (m, 2H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 138.6, 138.4, 137.4, 136.3, 133.2, 130.6, 129.8, 129.4, 129.0, 128.5, 128.1, 127.8, 127.0, 125.4, 118.2, 110.0, 52.1, 43.3, 27.4, 25.3, 21.1; FTIR (thin film, CH_2Cl_2, cm^{-1}) 2957, 2928, 1724, 1461, 1275, 1125, 1074; HRMS (TOF ES) *m/z* calcd for $C_{26}H_{26}BrN_2O_3S$ $[M+H]^+$ 525.0848, found 525.0894.



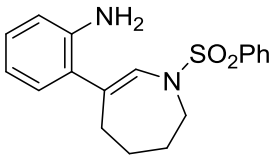
1'-Benzyl-5,6-dihydro-1'*H*,4*H*-spiro[pyridine-3,4'-quinolin]-2'(3'*H*)-one (2.59):[160]

General Procedure A was applied to bromoacetamide **2.58** (76 mg, 0.145 mmol) to provide the title compound (32 mg, 73%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.27–7.20 (m, 3H), 7.18 (dt, *J* = 6.5 Hz, 2Hz, 1H), 7.05 (dt, *J* = 7.5 Hz, 2 Hz, 2H), 6.97 (d, *J* = 8.0 Hz, 1H), 5.42 (d, *J* = 16.0 Hz, 1H), 4.98 (d, *J* = 16.0 Hz, 1H), 3.80–3.76 (m, 1H), 3.67–3.63 (m, 1H), 2.93 (d, *J* = 15.0 Hz, 1H), 2.71 (d, *J* = 15.0 Hz, 1H), 1.84–1.81 (m, 2H), 1.64–1.55 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 163.3, 138.6, 136.7, 128.8, 128.7, 128.4, 127.3, 126.5, 123.2, 116.3, 49.5, 46.2, 40.9, 40.4, 30.3, 18.0; HRMS (TOF ES) *m/z* calcd for $C_{20}H_{20}N_2O$ $[M]^+$: 304.1576, found 304.1561



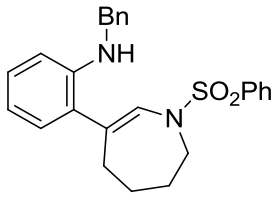
6-Iodo-1-(phenylsulfonyl)-2,3,4,5-tetrahydro-1*H*-azepine (2.62):[160] ICl (3.16 mL, 1M in CH_2Cl_2) was added dropwise to a solution of ene-sulfonamide **2.61**[129] (680 mg, 2.87 mmol) and $NaOCH_3$ (310 mg, 5.73 mmol) in methanol (14 mL). The resulting yellow suspension was stirred for 30 min, then a 10% aqueous solution of $Na_2S_2O_3$ was added and stirring continued for 30 min. The mixture was extracted with EtOAc. The combined organic extract was washed with brine, dried over $MgSO_4$ and concentrated to give a yellow oil. The oil was suspended in toluene (14 mL), TFA (10 µL, 0.1 mmol) was added. The reaction flask was fitted with a condenser then

submersed into an oil bath preheated to 140 °C. The solution was stirred for 5 min then cooled to room temperature. DIEA (30 µL, 0.2 mmol) was added, then volatile compounds removed under vacuum. A short silica column (20% EtOAc in hexanes provided an impure material (840 mg, with 30% de-iodinated compound, 56%) as a clear oil which was quickly used for the coupling step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.0 Hz, 2H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 2H), 6.93 (s, 1H), 3.57 (dd, *J* = 6.0 Hz, 5.2 Hz, 2H), 2.66–2.63 (m, 2H), 1.71 (p, *J* = 6.0 Hz, 2H), 1.48–1.42 (m, 2H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 135.0, 133.0, 127.4, 126.8, 49.5, 41.5, 27.9, 24.9; FTIR (thin film, CH_2Cl_2, cm^{-1}) 3064, 2932, 1446, 1344, 1240, 1163, 1096, 959; HRMS (TOF ES) *m/z* calcd for $C_{12}H_{15}NIO_2S$ $[M+H]^+$ 363.9868, found 363.9858.



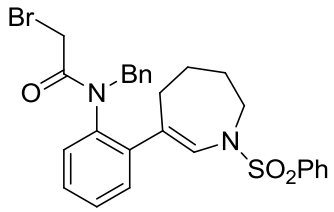
2-(1-(Phenylsulfonyl)-1,4,5,6-tetrahydropyridin-3-yl)aniline (2.63):[160] A dried Schlenk tube was charged under Ar with dry dioxane (10 mL), vinyl iodide **2.62** (500 mg, 1.38 mmol), $Pd(OAc)_2$ (15 mg, 0.05 mmol), 2-(dicyclohexylphosphino)biphenyl (72 mg, 0.20 mmol), $Ba(OH)_2$-$(H_2O)_8$ (1.30 g, 4.13 mmol) and 2-(pinacolboronate)aniline (302 mg, 1.38 mmol). The mixture was heated at 70 °C for 1 h. After cooling the mixture to room temperature, water and EtOAc were added, the phases were separated, and the aqueous phase was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and the volatile compounds were removed under vacuum. The residue was subjected to flash chromatography (20% EtOAc in hexanes) to give the title compound (315 mg, 70%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 7.5 Hz, 2H), 7.59 (t, *J* = 7.3 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 2Hz, 7.06 (td, *J* = 7.7 Hz, 1.5 Hz, H), 6.93 (dd, *J* = 7.5 Hz, 1.3 Hz, 1H), 6.72–6.67 (m, 2H), 6.47 (s,

1H), 3.59 (t, *J* = 5.7 Hz, 2H) 3.5 (br s, 2H), 2.41 (t, *J* = 5.5 Hz, 2H), 1.87 (p, *J* = 5.9 Hz, 2H), 1.63 (br p, *J* = 5.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 139.3, 132.8, 131.6, 129.4, 129.2, 128.7, 128.3, 128.0, 126.9, 118.2, 115.5, 49.7, 31.8, 29.6, 24.6; FTIR (thin film, CH_2Cl_2, cm^{-1}) 3454, 3380, 3055, 2936, 2253, 1731, 1615, 1447, 1345, 1162, 909; HRMS (TOF APCI) *m/z* calcd for $C_{18}H_{21}N_2O_2S$ [M+H]+ 329.1324, found 329.1324.

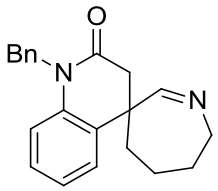


***N*-Benzyl-2-(1-(phenylsulfonyl)-1,4,5,6-tetrahydropyridin-3-yl)aniline (2.64)**:[160]

$NaBH(OAc)_3$ (1.17 g, 5.53 mmol) was added in one portion to a solution of aniline **2.63** (125 mg, 0.38 mmol), benzaldehyde (0.05 mL, 0.55 mmol), and AcOH (0.03 mL, 0.38 mmol) in anhydrous 1,2-DCE (12 mL). The mixture was stirred 14 h, filtered and concentrated under reduced pressure. The residue was subjected to flash chromatography (20% EtOAc in hexanes) to give the title compound (107 mg, 67%) as a thick yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.2 Hz, 2H), 7.52, (t, *J* = 7.2 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.37–7.29 (m, 5H), 7.14 (td, *J* = 7.6 Hz, 1.2 Hz, 1H), 6.97 (dd, *J* = 7.6 Hz, 1.2 Hz, 1H), 6.69 (td, *J* = 7.6, 0.4 Hz, 1H), 6.62 (d, *J* = 8.0 Hz, 1H), 6.51 (s, 1H), 4.36 (d, *J* = 3.0 Hz, 2H), 4.13 (s, 1H), 3.63 (at, *J* = 5.6Hz, 2H), 2.39 (at, *J* = 5.6 Hz, 2H), 1.84 (p, *J* = 6.0 Hz, 2H), 1.55 (p, *J* = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6, 139.3, 139.2, 132.7, 131.7, 129.2, 129.0, 128.9, 128.6, 128,5, 128.1, 127.2, 127.1, 126.8, 116.9, 110.6, 49.6, 48.6, 31.7, 29.3, 24.5; FTIR (thin film, CH_2Cl_2, cm^{-1}) 3454, 3380, 3055, 2936, 2253, 1731, 1615, 1447, 1345, 1162, 909; HRMS (TOF APCI) *m/z* calcd for $C_{25}H_{27}N_2O_2S$ $[M+H]^+$ 419.1793, found 419.1805.

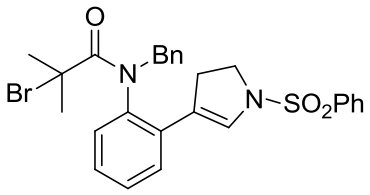


***N*-Benzyl-2-bromo-*N*-(2-(1-(phenylsulfonyl)-4,5,6,7-tetrahydro-1*H*-azepin-3-yl)phenyl)acetamide (2.65)**:[160] Bromoacetyl bromide (15 µL, 0.17 mmol) was added to a stirring solution of aniline **2.64** (60 mg, 0.14 mmol) and DIEA (45 µL, 0.29 mmol), and the mixture was stirred for one h. The reaction was quenched with aqueous NH_4Cl, the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and evaporated under vacuum. The residue was subjected to flash chromatography (15–20% EtOAc in hexanes) to give the title compound (65mg, 86%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.5 Hz, 2H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.56 (t, *J* = 7.5 Hz, 2H), 7.37–7.30 (m, 5H), 7.20–7.17 (m, 3H), 7.79 (d, *J* = 8.0 Hz, 1H), 6.59 (s, 1H), 5.66 (d, *J* = 14 Hz, 1H), 3.86 (d, *J* = 14 Hz, 1H), 3.87–3.65 (m, 2H), 3.64 (d, *J* = 2.0 Hz, 2H), 2.45–2.37 (m, 2H), 1.87 (br m, 2H), 1.68 (br m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 140.6, 139.3, 138.5, 136.4, 133.0, 130.7, 130.2, 129.6, 129.3, 139.1, 129.0, 128.9, 128.4, 128.3, 127.7, 126.8, 52.3, 49.3, 31.7, 28.8, 17.5, 24.4; HRMS (TOF ES) *m/z* calcd for $C_{27}H_{27}BrN_2O_3NaS$ $[M+Na]^+$ 561.0823, found 561.0878.



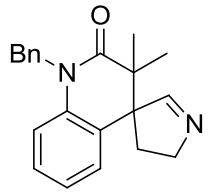
1'-Benzyl-4,5,6,7-tetrahydro-1'*H*-spiro[azepine-3,4'-quinolin]-2'(3'*H*)-one (2.66): Bromoacetamide **2.65** (28 mg, 0.05 mmol), Bu_3SnH (38 µL, 0.16 mmol) and AIBN (4 mg, 0.02

mmol) were dissolved in C_6H_6 (2.4 mL). The mixture was degassed by argon sparge then brought to reflux and stirred for 2 h. A solution containing 0.33 equiv 1,3,5-trimethoxybenzene (35 μL, 0.50 M in $CDCl_3$) was added and then the mixture was evaporated. The ^{1}H NMR showed full conversion of **2.65** and 34% yield of proposed imine **2.66** by integrating the benzyl peaks at δ 5.42 (d, *J* = 16.4 Hz, 0.36H) and 4.97 (d *J* = 16.1 Hz, 0.34H) ppm compared to internal standard at δ 6.09 (s, 1H) ppm. A silica column was prepared by pre-eluting with 1%TEA in hexanes, no material was recovered with spectral agreement to observed reaction mixture.

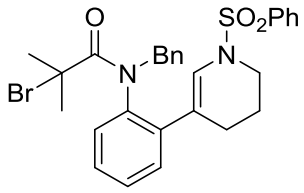


***N*-Benzyl-2-bromo-2-methyl-*N*-(2-(1-(phenylsulfonyl)-4,5-dihydro-1*H*-pyrrol-3-yl)phenyl)propanamide (2.69)**:[160] DMAP (3.6mg, 0.029 mmol) and 2-bromo-2-methylpropionyl bromide (109 μL, 0.883 mmol) were added to a solution of aniline **2.49** (230 mg, 0.589 mmol) in THF (5 mL). After 10 min, the reaction mixture was quenched with a saturated aqueous $KHCO_3$ solution, and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and volatile compounds were removed under vacuum. The residue was subjected to flash chromatography (20% EtOAc in hexanes) to provide the title compound (285 mg, 90%) as a viscous, colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (m, 2H), 7.60–7.53 (m, 3H), 7.26–7.24 (m, 4H), 7.17–7.12 (m, 3H), 7.03 (t, *J* = 8.0 Hz, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 6.79 (s, 1H), 5.72 (d, *J* = 13.2 Hz, 1H), 3.68 (t, *J* = 9.2, 2H), 3.49 (d, *J* = 13.2 Hz, 1H), 2.95 (br, 2H), 1.91 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 138.1, 136.3, 135.9, 133.3, 131.9, 131.8, 129.3, 129.2, 128.8, 128.3, 127.7,

127.6, 126.8, 120.3, 58.5, 54.1, 46.9, 34.4, 32.0, 30.9; FTIR (thin film, CH_2Cl_2, cm^{-1}) 3062, 2925, 1738, 1640, 1446, 1367, 1167, 1094, 969; HRMS (TOF ES) *m/z* calcd for $C_{27}H_{27}N_2O_3NaSBr$ $[M+Na]^+$ 561.0823, found 561.0823.

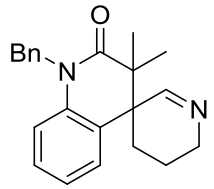


1'-Benzyl-3',3'-dimethyl-4,5-dihydro-1'*H*-spiro[pyrrole-3,4'-quinolin]-2'(3'*H*)-one (2.70):[160] General Procedure B was applied to bromoacetamide **2.69** (50 mg, 0.093 mmol), then flash chromatography (50% EtOAc in hexanes) was performed to provide the title compound (24 mg, 81%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, 50°C) δ 7.65 (s, 1H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.29– 7.24 (m, 3H), 7.20 (t, *J* = 8.0 Hz, 1H), 7.03 (t, *J* = 7.6 Hz, 1H), 7.10–6.98 (m, 2H), 5.35 (d, *J* = 16.0 Hz, 1H), 5.106 (d, *J* = 16.0 Hz), 4.06 (br m, 2H), 2.33 (p, *J* = 7.2Hz, 1H), 1.80 (br m, 1H), 1.29 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 166.7, 137.9, 137.1, 128.7, 128.0, 127.1, 126.3, 125.1, 123.5, 115.7, 62.9, 62.1, 46.6, 43.5, 21.7, 19.7, 13.5; FTIR (thin film, CH_2Cl_2, cm^{-1}) 2937, 2855, 1672, 1598, 1455, 1324, 1284, 1192; HRMS (TOF ES) *m/z* calcd for $C_{21}H_{23}N_2O$ $[M]^+$: 319.1810, found: 319.1825.



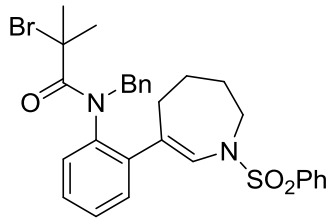
***N*-Benzyl-2-bromo-2-methyl-*N*-(2-(1-(phenylsulfonyl)-1,4,5,6-tetrahydropyridin-3-yl)-phenyl)-propanamide (2.71)**:[160] 2-Bromo-2-methyl-priopionyl bromide (9 µL, 0.07 mmol)

was added to a solution of aniline **2.57** (25 mg, 0.06 mmol), triethylamine (16 µL, 0.12 mmol) in dry DCM (1 mL), the mixture was stirred for 1 h. The reaction was quenched with aqueous $KHCO_3$. The aqueous layer was extracted with EtOAc, the combined organic layer was washed with brine, dried over $MgSO_4$, and volatile compounds were removed under vacuum. The residue was subjected to flash chromatography (15% EtOAc in hexanes) to give the title compound (20 mg, 58%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) rotamers: δ 7.82 (d, *J* = 7.4 Hz, 2H), 7.57 (t, *J* = 7.2 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 2H), 7.31-7.19 (m , 5H), 7.15–7.02 (m, 4H), 7.01–6.88 (br m, 1H) 5.52 (d, *J* = 14.2 Hz, 1H), 3.62 (d, *J* = 12.2 Hz, 1H), 3.53–3.44(br m, 2H), 2.44–2.29 (br m, 1H), 2.23–2.13 (br m, 1H), 1.96 (s, 6H), 1.86-1.77 (br m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 139.1, 137.7, 133.1, 130.9, 129.9, 129.3, 129.0, 128.8, 128.3, 127.6, 127.0, 125.6,, 125.3, 125.0, 117.8, 55.1, 43.3, 32.5, 30.6, 29.7, 25.2; FTIR (thin film, CH_2Cl_2, cm^{-1}) 3063, 2925, 1738, 1640, 1446, 1367, 1167, 1094, 969; HRMS (TOF ES) *m/z* calcd for $C_{28}H_{30}BrN_2O_3S$ $[M+H]^+$ 553.1161, found 553.1167.



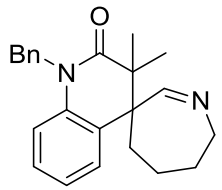
1'-Benzyl-3',3'-dimethyl-5,6-dihydro-1'*H*,4*H*-spiro[pyridine-3,4'-quinolin]-2'(3'*H*)-one (2.72):[160] General Procedure B was applied to bromoacetamide **2.71** (20 mg, 0.145 mmol) then flash chromatography was performed (50% EtOAc in hexanes) to provide the title compound (6 mg, 50%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.36–7.32 (m, 2H), 7.27–7.25 (m, 3H), 7.22–7.18 (m, 1H), 7.06–7.03 (m, 2H), 6.98 (d, *J* = 8.2 Hz, 1H), 5.52 (d, *J* = 15.3 Hz, 1H), 4.80 (d, *J* = 15.3 Hz, 1H), 3.88 (d, *J* = 16.5 Hz, 1H), 3.44 (d, *J* = 15.0 Hz, 1H), 1.97 (td, *J* = 13.5 Hz, 3.9 Hz, 1H), 1.67–1.45 (m, 3H), 1.35–1.27 (br m, 6H); ^{13}C NMR

(125 MHz, $CDCl_3$) δ 173.8, 161.8, 138.2, 137.3, 129.5, 128.8, 128.1, 128.0, 127.2, 126.4, 122.9, 115.8, 49.8, 46.9, 43.4, 29.7, 29.2, 26.4, 20.6, 19.7; FTIR (thin film, CH_2Cl_2, cm^{-1}) 2937, 2855, 1672, 1598, 1455, 1183; HRMS (TOF ES) *m/z* calcd for $C_{22}H_{25}N_2O$ $[M+H]^+$: 333.1967, found 333.1964

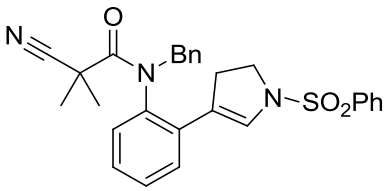


***N*-Benzyl-2-bromo-2-methyl-*N*-(2-(1-(phenylsulfonyl)-4,5,6,7-tetrahydro-1*H*-azepin-3-yl)phenyl)propanamide (2.73)**:[160] 2-Bromo-2-methylpropionyl bromide (72 μL, 0.72mmol) was added to a solution of aniline **2.64** (300 mg, 0.95 mmol) and DIEA (250 μL, 1.43 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C, the mixture was stirred for 1 h. The reaction was quenched with aqueous $KHCO_3$. The aqueous layer was extracted with EtOAc, the combined organic layer was washed with brine, dried over $MgSO_4$, and volatile compounds were removed under vacuum. The residue was subjected to flash chromatography (15–20% EtOAc in hexanes) to give the title compound (198 mg, 49%) as a white foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.4 Hz, 2H), 7.59 (t, *J* = 7.3 Hz, 1H), 7.52 (t, *J* = 7.4 Hz, 2H), 7.24–7.13 (m, 5H), 7.11–6.76 (m, 3H), 6.70–6.25 (br m, 1H), 5.66 (d, *J* = 13.6 Hz, 1H), 3.87–3.85 (br m, 3H), 2.56–2.46 (m, 1H), 2.24–1.90 (br m, 4H), 1.86 (s, 3H), 1.74–1.58 (br m, 2H), 1.55 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) Contains broad and overlapping resonances δ 170.3, 139.4 (overlapping), 136.5 (br), 132.8, 130.9 (br), 130.4, 130.1 (br), 129.2, 128.8 (br, overlapping), 128.2, 127.5, 127.3, 126.9, 59.5 (br), 57.9 (br), 54.7, 49.3 (br), 34.6 (br), 32.7 (br), 32.2 (br), 31.2 (br), 29.6 (br), 29.3 (br), 28.5

(br), 24.4; FTIR (thin film, CH_2Cl_2, cm^{-1}) 2933, 2861, 1642, 1446, 1348, 1164, 934; HRMS (TOF ES) *m/z* calcd for $C_{29}H_{32}BrN_2O_3S$ $[M+H]^+$ 567.1317, found 567.1370.

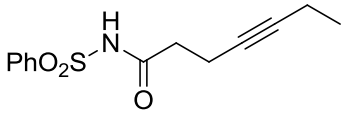


1'-Benzyl-3',3'-dimethyl-4,5,6,7-tetrahydro-1'*H*-spiro[azepine-3,4'-quinolin]-2'(3'*H*)-one (2.74):[160] General Procedure B was applied to bromoacetamide **2.73** (98 mg, 0.17 mmol) then flash chromatography was performed (50–70% EtOAc in hexanes) to provide the title compound (24 mg, 40%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.34–7.27 (m, 2H), 7.25–7.16 (m, 4H), 7.13 (d, *J* = 7.2 Hz, 1H), 7.05 (t, *J* = 7.4 Hz, 1H), 7.10 (d, *J* = 8.0 Hz, 1H), 5.51 (d, *J* = 16.1 Hz, 1H), 4.80 (d, *J* = 16.0 Hz, 1H), 3.93–3.83 (m, 2H), 2.30–2.20 (m, 1H), 2.01–1.89 (m, 1H), 1.77–1.68 (m, 1H), 1.58–1.49 (m, 1H), 1.45 (s, 3H), 1.39–1.26 (m, 2H), 1.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ174.0, 164.2, 1238.0, 137.2, 128.9, 128.8, 128.2, 128.0, 127.2, 126.4, 122.9, 116.0, 56.2, 47.9, 46.8, 45.5, 27.5, 25.1, 21.4, 20.0, 19.8; FTIR (thin film, CH_2Cl_2, cm^{-1}) 2391, 2856, 1672, 1599, 1495, 1454, 1388, 1319, 1278, 1186; HRMS (TOF ES) *m/z* calcd for $C_{23}H_{27}N_2O$ $[M+H]^+$ 347.2123, found 347.2112.

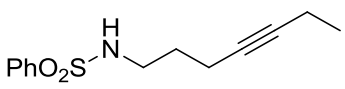


***N*-Benzyl-2-cyano-2-methyl-*N*-(2-(1-(phenylsulfonyl)-4,5-dihydro-1*H*-pyrrol-3-yl)phenyl)propanamide (2.75)**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 7.6 Hz, 1.2 Hz,

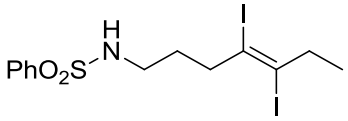
2H), 7.61–7.54 (m, 3H), 7.24–7.22 (m, 5H), 7.10–7.08 (m, 2H), 7.03 (td, *J* = 7.4 Hz, 2.0 Hz, 1H), 6.70 (s, 1H), 6.58 (dd, *J* = 8.0 Hz, 1.2 Hz, 1H), 5.56 (d, *J* = 14.0 Hz, 1H), 3.66 (t, *J* = 8.8 Hz, 2H), 3.58 (d, *J* = 14.0 Hz, 1H), 2.92–2.75 (m, 2H), 0.99 (d, *J* = 6.4 Hz, 3H), 0.85 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2, 138.4, 137.2, 135.9, 133.2, 132.1, 130.5, 129.4, 129.3, 129.2, 129.1, 128.4 128.3, 128.2, 127.7, 127.4, 120.5, 51.0, 47.2, 32.0, 31.5, 20.2, 19.2, 13.6;



***N*-(Phenylsulfonyl)hept-4-ynamide (2.76)**: Adapted from a known procedure.[131] Under an Ar atmosphere n-BuLi (4.3 mL, 1.6 M in hexane) was added to a solution of *N*-benzenesulfonylacetamide (500 mg, 2.5 mmol) and HMPA (0.44 mL, 2.5 mmol) at –78 °C, the mixture was stirred for 30 minutes. Then 1-bromo-2-pentyne was added, the mixture was stirred for 2 h, and then allowed to warm to 0 °C. The reaction was quenched with aqueous NH_4Cl, the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$ and volatile compounds were removed under vacuum, The residue was subjected to flash chromatography (20% EtOAc in hexanes) to give the title compound (88 mg, 13%) as a white crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (s, 1H), 8.07 (d, *J* = 9.0 Hz, 2H), 7.66 (t, *J* = 9.0 Hz, 1H), 7.55 (t, *J* = 9.0 Hz, 2H), 2.47–2.38 (m, 4H), 2.13 (qt, *J* = 8.0 Hz, 2.0Hz, 2H), 1.10 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 138.5, 134.0, 129.0, 128.3, 84.4, 35.9, 14.2, 13.9, 12.3.

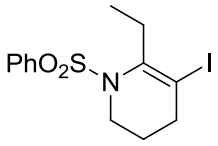


***N*-(Hept-4-yn-1-yl)benzenesulfonamide (2.77)**: Adapted from a known procedure.[165] $LiAlH_4$ (0.66 mL, 1.0 M in hexanes) was added to a stirring solution of sulfonamide **2.76** (80 mg, 0.3 mmol) in THF (3 mL) at –78 °C, the mixture was allowed to warm to room temperature. The reaction was quenched with aqueous potassium sodium tartrate, the mixture stirred for 14 h. The aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and volatile compounds were removed under vacuum. The residue was subjected to flash chromatography (20% EtOAc in hexanes) to give the title compound (31 mg, 41%) as a light oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.5 Hz, 2H), 7.58 (t, *J* = 8.5 Hz, 1H), 7.50 (t, *J* = 8.5 Hz, 2H), 4.84 (t, *J* = 5.6 Hz, 1H), 3.08 (q, *J* = 6.4 Hz), 2.19–2.08 (m, 4H), 1.63 (p, *J* = 6.8 Hz, 2H), 1.07 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.9, 132.6, 129.1, 127.0, 83.2, 77.7, 42.5, 28.4, 16.1, 14.1, 12.3.

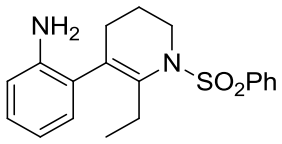


(E)-*N*-(4,5-Diiodohept-4-en-1-yl)benzenesulfonamide (2.78): Procedure was adapted from a known procedure.[132] A solution of sulfonamide **2.77** in CH_2Cl_2 (2 mL) was added under Ar to a flask charged with anhydrous NaI (55 mg, 0.37 mmol) and iodine (38 mg, 0.15 mmol), the mixture was stirred for 24 h under dark. The reaction was quenched with 10% aqueous Na_2SO_3 (10 mL), the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and evaporated under vacuum. The residue was purified by flash chromatography (15% EtOAc in hexanes) to give the title compound (55 mg, 88%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.5 Hz, 2H), 7.6 (t, *J* = 8.5 Hz, 1H), 7. (t, *J* = 8.5 Hz, 2H), 4.61 (t, *J* = 10Hz, 1H), 3.00 (q, *J* = 6.4 Hz, 2H), 2.70–2.64 (m, 4H), 1.72, (p,

J = 6.8 Hz, 2H), 1.00 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.8, 132.7, 129.2, 127.1, 104.8, 98.8, 47.9, 45.2, 41.7, 28.1, 12.6.

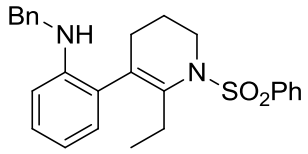


6-Ethyl-5-iodo-3,4-dihydropyridin-1(2*H*)-yl benzenesulfinate (2.79): Adapted from a known procedure.[132] A Schlenk flask was charged with diiodide **2.78** (55 mg, 0.11 mmol), 2,2'-bipyridyl (10 mg, 0.06 mmol), K_3PO_4 (46 mg, 0.22 mmol), CuI (4 mg, 0.02 mmol) and toluene (3.6 mL, 0.04 M). The reaction mixture was stirred at 40 °C for 15 min, H_2O (3.00 µl, 0.168 mmol) was then added. The mixture was stirred for 21 h at 40 °C, then cooled to 0 °C, filtered over silica gel and washed with EtOAc (15 mL). The volatile compounds were removed under vacuum, then the residue was purified by flash chromatography (20% EtOAc in hexanes) on silica gel to afford the title compound (35mg, 85%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 9.0 Hz, 2H), 7.62 (t, *J* = 9.0 Hz, 1H), 7.50 (t, *J* = 9.0 Hz, 2H), 3.66 (t, *J* = 7.2 Hz, 2H), 2.85 (q, *J* = 7.2 Hz, 2H), 2.13 (t, *J* = 7.6 Hz, 2H), 1.26 (p, *J* = 7.2 Hz, 2H), 1.16 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 138.5, 133.3, 129.2, 127.6, 107.7, 52.1, 36.2, 34.3, 21.0, 15.6.



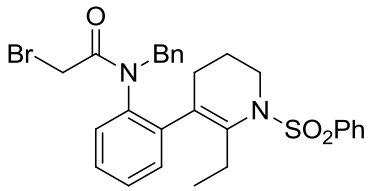
5-(2-Aminophenyl)-6-ethyl-3,4-dihydropyridin-1(2*H*)-yl benzenesulfinate (2.80): A dried Schlenk tube was charged under Ar with dry dioxane (3 mL), vinyl iodide **2.79** (81 mg, 0.21 mmol), $Pd(OAc)_2$ (2 mg, 0.01 mmol), 2-(dicyclohexylphosphino)biphenyl (19 mg, 0.05

mmol), $Ba(OH)_2$-$(H_2O)_8$ (260 mg, 0.83 mmol) and 2-(pinacolboronate)aniline (35 mg, 0.21 mmol). The mixture was heated at 70 °C for 1 h. After cooling the mixture to room temperature, water and EtOAc were added, the phases were separated, and the aqueous phase was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and the volatile compounds were removed under vacuum. The residue was subjected to flash chromatography (25% EtOAc in hexanes) to give the title compound (89 mg, 79% purity, 95% yield) as a colorless oil with inseparable aniline impurity. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, 7.2 Hz, 2H), 7.60 (t, *J* = 7.2 Hz, 1H), 7.52 (t, *J* = 7.2 Hz, 2H), 7.19 (td, *J* = 7.6 Hz, 1.6 Hz, 1H), 7.13 (dd, *J* = 7.6 Hz, 1.6 Hz, 1H), 7.08 (td, *J* = 7.6 Hz, 1.6 Hz, 1H), 6.90 (dd, *J* = 7.2 Hz, 1.2 Hz), 6.84 (td, *J* = 7.6 Hz, 1.2 Hz, 1H), 6.79 (dd, 8.0 Hz, 0.8 Hz, 1H), 6.75–6.71 (m, 2H), 3.72 (s, 2H), 3.82 (s, 2H), 3.67 (dt, *J* = 12 Hz, 7.6 Hz, 1H), 3.46 (dt, *J* = 12 Hz, 7.6 Hz, 1H), 2.72 (q, *J* = 7.6 Hz, 2H), 1.83–1.79 (m, 2H), 1.48–1.39 (m, 1H), 1.31–1.24 (m, 1H), 0.97 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 138.9, 136.2, 133.2, 133.0, 130.1, 129.1, 128.8, 128.0, 127.7, 126.0, 124.6, 118.8, 115.5, 50.3, 28.0, 27.3, 21.3, 11.0.



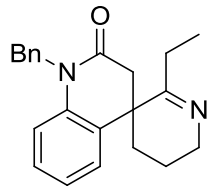
5-(2-(Benzylamino)phenyl)-6-ethyl-3,4-dihydropyridin-1(2*H*)-yl benzenesulfinate (2.81): AcOH (23 µL) was added to a solution of aniline **2.80** (100 mg, 0.26 mmol) and benzaldehyde (31 µL, 0.31 mmol) in dry CH_2Cl_2 (3 mL), the mixture was stirred for 1 h. $NaBH_4$ (39 mg, 1.02 mmol) was added in one portion, the mixture was stirred 14 h. Aqueous $KHCO_3$ was added slowly. The aqueous layer was extracted with EtOAc, the combined organic layer was washed with brine and dried over $MgSO_4$. The volatile compounds were removed under vacuum.

The residue was subjected to flash chromatography (25% EtOAc in hexanes) to give the title compound (85 mg, 75%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.6 Hz, 2H), 7.53 (t, *J* = 7.2 Hz, 1H), 7.39–7.31 (m, 6H), 7.25 (t, *J* = 6.8 Hz, 1H), 7.12 (t, *J* = 8.0 Hz, 1H), 6.89 (d, *J* = 7.2 Hz, 1H), 6.69 (t, *J* = 7.2 Hz, 1H), 6.62 (d, *J* = 8.0 Hz, 1H), 4.60 (s, 1H), 4.41 (dd, *J* = 6.0 Hz, 3.2 Hz, 2H), 3.64 (ddd, *J* = 16.2 Hz, 8.2 Hz, 4.2 Hz, 1H), 3.44 (dt, *J* = 12.4 Hz, 8.0 Hz, 1H), 2.73 (q, *J* = 6.8 Hz, 2H), 1.87–1.71 (m, 2H), 1.47–1.37 (m, 1H), 1.23–1.14 (m, 1H), 1.00 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4, 139.7, 128.7, 136.6, 133.2, 132.9, 129.0, 128.7, 128.3, 128.2, 127.7, 127.2, 127.1, 126.0, 116.7, 110.5, 50.2, 48.2, 28.0, 27.4, 21.2, 12.1; LCMS *m/z* calcd for $C_{26}H_{28}N_2O_2S$ 432, found 432.

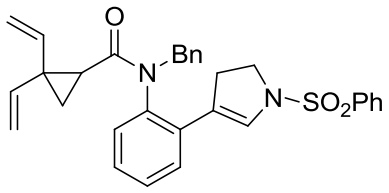


5-(2-(*N*-Benzyl-2-bromoacetamido)phenyl)-6-ethyl-3,4-dihydropyridin-1(2*H*)-yl benzenesulfinate (2.82):[160] Bromoacetyl bromide (2.5µL, 0.03 mmol) was added to a solution of aniline **2.81** (8 mg, 0.019 mmol) and triethylamine (6 µL, 0.04 mmol) in dry CH_2Cl_2 (1 mL) at 0 °C, the mixture was stirred for 1 h. The reaction was quenched with aqueous $KHCO_3$. The aqueous layer was extracted with EtOAc, the combined organic layer was washed with brine, dried over $MgSO_4$, and volatile compounds were removed under vacuum. The residue was subjected to flash chromatography (20% EtOAc in hexanes) to give the title compound (5mg, 50%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.5 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.59-7.54 (m, 2H), 7.48 (t, *J* = 8.0 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.24-7.22 (m, 2H), 7.18-7.15 (m, 2H), 7.11-7.08 (m, 2H), 6.92 (d, *J* = 6.5 Hz, 1H), 6.81 (d, *J* = 7.5 Hz, 1H), 5.69 (d, *J* = 14.0 Hz, 1H), 3.58-3.50 (m, 2H), 2.93 (q, *J* = 7.0 Hz, 2H), 2.71-2.67 (m, 4H), 1.75-1.72 (m,

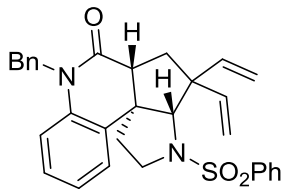
2H), 1.61-1.56 (m, 2H), 1.22 (t, *J* = 7.0 Hz, 3H); LCMS *m/z* calcd for $C_{28}H_{30}BrN_2O_3S$ $[M+H]^+$ 553, found 553.



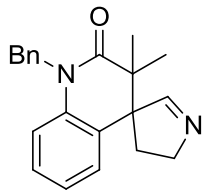
1'-Benzyl-2-ethyl-5,6-dihydro-1'*H*,4*H*-spiro[pyridine-3,4'-quinolin]-2'(3'*H*)-one (2.83):[160] **General Procedure A** was applied to bromoacetamide **2.82** (11 mg, 0.02 mmol) then flash chromatography (60% EtOAc in hexanes) was performed to provide the title compound (4 mg, 61%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 7.6 Hz, 1H), 7.24 (d, *J* = 7.5 Hz, 2H), 7.19 (d, *J* = 7.5 Hz, 1H), 7.18–7.12 (m, 3H), 7.02 (t, *J* = 7.6 Hz, 1H), 6.92 (d, *J* = 7.6 Hz, 1H), 5.47 (d, *J* = 16.4 Hz, 1H), 4.92 (d, *J* = 16.4 Hz, 1H), 3.92–3.79 (m, 2H), 3.28 (d, *J* = 15.6 Hz, 1H), 2.63 (d, *J*= 15.6 Hz, 1H), 2.39 (pt, *J* = 6.5 Hz, 2.0 Hz, 1H), 2.17 (hex, *J* = 7.5 Hz, 1H), 2.09 (pt, *J* = 6.5 Hz, 2.0 Hz), 1.95 (hex, *J* = 7.5 Hz, 1H), 1.85–1.76 (m, 1H), 1.72–1.64 (m, 1H), 0.95 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.8, 169.7, 139.4, 137.1, 128.6, 128.5, 128.0, 127.0, 126.9, 125.9, 122.9, 116.1, 61.1, 45.0, 44.9, 38.9, 33.5, 29.7, 28.2, 22.9; FTIR (thin film, CH_2Cl_2, cm^{-1}) 2957, 2928, 1649, 1597, 1506, 1457, 1409, 1252, 1086; HRMS (TOF ES) *m/z* calcd for $C_{22}H_{25}N_2O$ $[M+H]^+$ 333.1967, found 333.1946.



***N*-Benzyl-*N*-(2-(1-(phenylsulfonyl)-4,5-dihydro-1*H*-pyrrol-3-yl)phenyl)-2,2-divinylcyclopropanecarboxamide (2.85)**:[56] Ghosez reagent (41 µL, 0.31 mmol) was added to stirring cyclopropyl acid **2.84**[55] in CH_2Cl_2 (2 mL) at 0 °C, the mixture was stirred for 1 h. This mixture was cannulated to a stirring mixture of aniline **2.49** (80 mg, 0.20 mmol) and pyridine (25 µL, 0.31 mmol) in CH_2Cl_2 (2 mL), this mixture was stirred for 2 h. Aqueous $KHCO_3$ was added, the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and volatile compounds were removed under vacuum. The residue was subjected to flash chromatography (20% EtOAc in hexanes) to give the title compound (95 mg, 91%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ major rotamer: 7.87 (d, *J* = 7.5 Hz, 2H), 7.01 (td, *J* = 7.5 Hz, 2.0 Hz, 1H), 6.80 (s, 1H), 6.52 (d, *J* = 7.0 Hz, 1H), 6.86 (dd, *J* = 17.5 Hz, 11.0 Hz, 1H), 5.62 (dd, *J* = 17.5 Hz, 11.0 Hz, 1H), 5.46 (d, *J* = 14.0 Hz, 1H), 5.13 (dd, *J* = 11.0 Hz, 1.0 Hz, 1H), 5.08 (dd, *J* = 17.0 Hz, 1.0 Hz, 1H), 4.74 (dd, *J* = 9.0 Hz, 1.0 Hz, 1H), 4.40 (dd, *J* = 17.0 Hz, 1.0 Hz, 1H), 1.79 (dd, 7.0 Hz, 5.0 Hz, 1H), 1.51 (dd, *J* = 7.5 Hz, 5.5 Hz, 1H), 1.06 (dd, *J* = 8.0 Hz, 5.0 Hz, 1H); minor rotamer: 7.13 (dd, *J* = 7.5 Hz, 2.0 Hz, 1H), 6.71 (s, 1H), 6.66 (d, *J* = 8.0 Hz, 1H), 6.01 (dd, *J* = 17.5 Hz, 10.5 Hz, 1H), 5.72 (dd, *J* = 17.0 Hz, 10.0 Hz, 1H), 5.54 (d, *J* = 14.0 Hz, 1H), 5.07 (dd, *J* = 10.5 Hz, 1.0 Hz, 1H), 5.02 (dd, *J* = 17.5 Hz, 1.0 Hz, 1H), 4.79 (dd, *J* = 10.5 Hz, 1.0 Hz, 1H), 4.43 (dd, *J* 17.0 Hz, 1.0 Hz, 1H), 1.68 (dd, *J* = 7.0 Hz, 4.5 Hz, 1H), 1.12 (dd, *J* = 8.0 Hz, 4.5 Hz, 1H); overlapping peaks: 7.62–7.54 (m, 4H), 7.27–7.22 (m, 2H), 7.21–7.19 (m, 4H), 7.08–7.07 (m, 2H), 3.70–3.51 (m, 4H), 3.00–2.90 (m, 1H), 2.82–2.75 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) (rotamers) δ 169.6, 169.1, 138.6, 138.3, 137.8, 137.7, 137.1, 136.9, 136.8, 136.2, 135.5, 133.1, 132.7, 131.9, 131.6, 131.2, 129.2, 129.1, 129.0, 129.0, 128.8, 128.4, 128.3, 128.2, 128.1, 128.0, 127.6, 127.5, 127.4, 127.3, 127.2, 126.8, 126.7, 120.9, 120.5, 115.7, 114.4, 114.3, 51.2, 50.8, 47.2, 35.3, 33.9, 31.9, 31.8, 29.7, 27.6, 20.5, 18.9; LRMS (LC–MS) *m/z* calcd for $C_{31}H_{31}N_2O_3S$ $[M+H]^+$ 511, found 511.



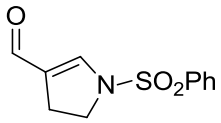
7-Benzyl-3-(phenylsulfonyl)-4,4-divinyl-2,3,3a,4,5,5a-hexahydro-1*H*-pyrrolo[3',2':2,3]cyclopenta[1,2-c]quinolin-6(7*H*)-one (2.86):[56] **General Procedure A** was applied to anilide **2.85** (50 mg, 0.10 mmol) to produce the title compound (29 mg, 58%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.5 Hz, 2H), 7.78 (t, *J* = 7.5 Hz, 1H), 7.68 (t, *J* = Hz, 2H), 7.33–7.31 (m, 3H), 7.27 (d, *J* = 7.5 Hz, 1H), 7.24 (d, *J* = 7.0 Hz, 2H), 7.07 (t, *J* = 8.0 Hz, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 6.51 (t, *J* = 7.5 Hz, 1H), 6.42 (dd, *J* = 17.0 Hz, 11.5 Hz, 1H), 6.10 (dd, *J* = 17.0 Hz, 11.5 Hz, 1H), 5.75 (d, *J* = 7.5 Hz, 1H), 5.29 (d, *J* = 16.0 Hz, 1H), 5.24–5.16 (m, 4H), 5.03 (d, *J* = 16.0 Hz, 1H), 4.32 (s, 1H), 3.54 (t, *J* = 8.5 Hz, 1H), 3.14 (ddd, *J* = 15.5 Hz, 9.5 Hz, 6.5 Hz, 1H), 2.97 (dd, *J* = 13.0 Hz, 6.5 Hz, 1H), 2.44 (t, *J* = 15.0 Hz, 1H), 2.33 (dd, *J* = 13.5 Hz, 6.0 Hz, 1H), 2.23 (td, *J* = 12.0 Hz, 7.5 Hz, 1H), 1.46 (dd, *J* = 12.5 Hz, 6.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 143.6, 141.5, 138.8, 138.0, 136.9, 134.3, 133.0, 129.4, 128.7, 127.9 127.6, 127.3, 126.9, 122.9, 122.6, 116.7, 113.2, 112.4, 72.9, 55.1, 54.2, 47.5, 46.0, 45.6, 31.6, 30.5; LRMS (LC-MS) *m/z* calcd for $C_{31}H_{31}N_2O_3S$ $[M+H]^+$ 511, found 511.



1'-Benzyl-3',3'-dimethyl-4,5-dihydro-1'*H*-spiro[pyrrole-3,4'-quinolin]-2'(3'*H*)-one (2.70): **Cyclization of anilide 2.69 under NHC-Borane mediated conditions**: NHC-borane[134] (19 mg, 0.17 mmol) and *tert*-butylhyponitrite (5 mg) in benzene (0.5 mL) were added by syringe

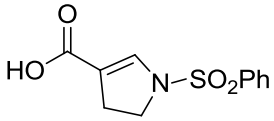
pump over 2 h to a mixture of bromoacetamide **2.69** (30 mg, 0.056 mmol) in degassed benzene (5 mL), the mixture was refluxed an additional 1 h. The solvent was evaporated under vacuum. The crude residue was purified by flash chromatography (50% EtOAc in hexanes) to provide the title compound (3.5 mg, 20%, 35% BRSM) as a colorless oil.

Cyclization of anilide 2.69 under photo-redox conditions: A flame dried 5 mL round bottom flask was equipped with a rubber septum and magnetic stir bar and was charged with tris(2,2´-bipyridyl)ruthenium(II) chloride hexahydrate (3.8 mg, 0.005 mmol), anilide **2.69** (27 mg, 0.05 mmol), DIEA (17 µL, 0.10 mmol) and DMF (1.0 mL). The mixture was degassed by the freeze-pump-thaw procedure, and placed 10 cm from a 15 W compact fluorescent lamp. After stirring for 12 h, the mixture was poured into a separatory funnel containing 10 mL of EtOAc and 10 mL of H_2O. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by flash chromatography to give title compound (10.0 mg, 63%, 85% BRSM) as a colorless oil.

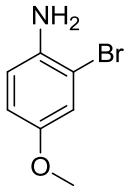


1-(Phenylsulfonyl)-4,5-dihydro-1*H*-pyrrole-3-carbaldehyde (2.99): Phosphorous oxychloride (1.21 mL, 12.9mmol) was added to a solution of DMF (8.4 mL, 10.8 mmol) in CH_2Cl_2 (8.4 mL) at 0 °C. The solution as stirred at 0 °C for 10 min, then ene-sulfonamide **2.45** (2.50 g, 10.8mmol) in CH_2Cl_2 (10 mL) was added. After 10 min, the solution was poured into saturated aqueous K_2CO_3 (100 mL) and the mixture was stirred vigorously for 1 h. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined extracts

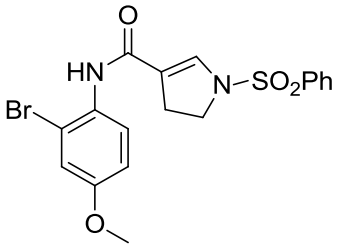
were dried over $MgSO_4$ and concentrated. The residue was purification by flash chromatography (20% EtOAc in hexanes) to give the title compound (2.40 g, 94%) as a crystalline solid: mp 76–79 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.55 (s, 1H), 7.82 (d, *J* = 7.5 Hz, 2H), 7.66 (t, *J* = 7.0 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 2H), 7.39 (s, 1H), 3.73 (t, *J* = 9.5 Hz, 2H), 2.78 (t, *J* = 9.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.4, 147.1, 136.1, 133.9, 129.6, 127.2, 125.8, 48.6, 25.9; HRMS (APCI) *m/z* calcd for $C_{11}H_{12}NO_3S$ $[M+H]^+$ 238.0538, found 238.0552.



1-(Phenylsulfonyl)-4,5-dihydro-1*H*-pyrrole-3-carboxylic acid (2.96): $NaClO_2$ (0.97 g, 8.60 mmol) was added in one portion to a mixture of aldehyde **2.99** (1.70 g, 7.16 mmol), 2-methyl-2-butene (17.9 mL, 2M in THF), and NaH_2PO_4 (4.30 g, 35.8 mmol) in 3:1 1,4-dioxane:H_2O (35 mL). The reaction mixture was stirred for 1 h at room temperature. A saturated $NaHCO_3$ solution (50 mL) was added with precaution to the solution and the final mixture was stirred vigorously for 30 min. The mixture was concentrated and the residue was dissolved in EtOAc. The organic mixture was washed with 10% HCl and H_2O, then evaporated under vacuum. The residue was purified by flash chromatography (50% EtOAc in hexanes) to give the title compound (1.3 g, 72%) as a white crystalline solid: mp 145–147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.0 Hz, 2H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 2H), 7.46 (s, 1H), 3.72 (t, *J* = 9.6 Hz, 2H), 2.79 (t, *J* = 9.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 142.7, 136.2, 133.8, 129.5, 127.4, 113.5, 48.7, 27.8; HRMS (APCI) *m/z* calcd for $C_{11}H_{12}NO_4S$ $[M+H]^+$ 254.0487, found 254.0510.

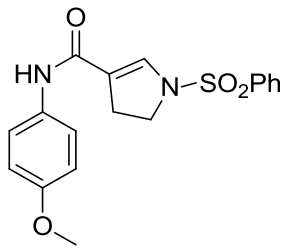


2-Bromo-4-methoxyaniline (2.102): Trifluoroacetic acid (2.5 mL, 33 mmol) was added to a stirring solution of carbamate **2.101**[166] (1.0 g, 3.3 mmol) in CH_2Cl_2 (3 mL), the mixture was stirred for 1 h. The volatile compounds were removed under vacuum, residue was subjected to flash chromatography (10% EtOAc in hexanes) to give the title compound (0.74 g, 90%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 1.4 Hz, 1H), 6.77 (dd, *J* = 8.8 Hz, 1.4 Hz, 1H), 6.69 (d, *J* = 8.8 Hz, 1H), 3.80 (s, 2H), 3.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 140.8, 123.4, 116.1, 115.3, 84.2, 55.9.

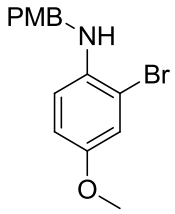


N-(2-Bromo-4-methoxyphenyl)-1-(phenylsulfonyl)-4,5-dihydro-1*H*-pyrrole-3-carboxamide (2.103): Ghosez reagent (111 µL, 0.85 mmol) was added to a suspension of carboxylic acid **2.96** (187 mg, 0.85 mmol) in toluene (6.0 mL), the mixture was stirred for 1 h. NaHMDS (0.59 mL, 1M in THF) was added to a solution of aniline **2.102** (120 mg, 0.59 mmol) at –78 °C in THF (6.0 mL). The mixture was stirred 30 minutes, then cannulated into the stirring acid chloride solution, the mixture was stirred to r.t. for 3 h. The reaction was quenched with $KHCO_3$, the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, volatile compounds were removed under vacuum. Flash chromatography (20% EtOAc in hexanes) give the title compound (167 mg, 65%). ^{1}H NMR

(500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 2.8 Hz, 1H), 7.83 (d, *J* = 7.2 Hz, 2H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.60–7.55 (m, 3H), 7.44 (s, 1H), 7.40 (s, 1H), 6.46 (dd, *J* = 7.2 Hz, 3.0 Hz, 1H), 3.81–3.76 (m, 5H), 2.94 (t, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 160.6, 138.6, 138.4, 138.2, 133.7, 129.5, 127.4, 118.0, 113.0, 106.5, 77.8, 55.4, 48.6, 28.4, 27.8;

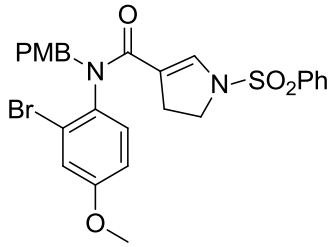


***N*-(4-Methoxyphenyl)-1-(phenylsulfonyl)-4,5-dihydro-1*H*-pyrrole-3-carboxamide (2.104): General Procedure A** was applied to anilide **2.103** (23 mg, 0.05 mmol) to give the title compound (13 mg, 69%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.6 Hz, 2H), 7.65 (t, *J* = 7.2 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 2H), 7.41 (d, *J* = 8.8 Hz, 2H), 7.30 (s, 1H), 7.18 (br s, 1H), 6.83 (d, *J* = 8.8 Hz, 2H), 3.78, (s, 3H), 3.72 (t, *J* = 8.8 Hz, 2H), 2.86 (t, *J* = 8.4 Hz, 2H)



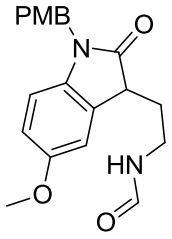
2-Bromo-4-methoxy-*N*-(4-methoxybenzyl)aniline (2.106): $NaBH(OAc)_3$ (5.10 g, 24.1 mmol) was added to a solution of p-anisaldehyde (0.41 mL, 6.63 mmol), aniline **2.102** (1.5 g, 6.02 mmol) and AcOH (0.11 mL, 1.91 mmol) in 1,2-DCE (30 mL). The mixture was stirred 24 h, then saturated aqueous $KHCO_3$ (15 mL) was slowly added while stirring vigorously. The

aqueous layer was extracted with EtOAc, the combined organic layer was washed with brine, dried over $MgSO_4$, and volatile compounds were removed under vacuum. The residue was subjected to flash chromatography (20% EtOAc in hexanes) to give the title compound (2.14 g, 91%) as a white solid: mp 63–64 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 6.8 Hz, 2H), 7.08 (d, *J* = 2.4 Hz, 1H), 6.89 (d, *J* = 6.8 Hz 2H), 6.77 (dd, *J* = 7.2 Hz, 2.4 Hz, 1H), 6.58 (d, *J* = 7.2 Hz, 1H), 4.33 (s, 1H), 4.28 (s, 2H), 3.81 (s, 3H), 3.73 (s, 3H).

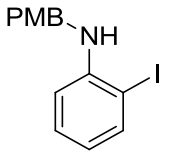


***N*-(2-Bromo-4-methoxyphenyl)-*N*-(4-methoxybenzyl)-1-(phenylsulfonyl)-4,5-dihydro-1*H*-pyrrole-3-carboxamide (2.107):** Ghosez reagent (75 µL, 0.57 mmol) was added to a suspension of carboxylic acid **2.96** (144 mg, 0.57 mmol) in toluene (5.7 mL), the mixture was stirred for 1 h. NaHMDS (0.38 mL, 1M in THF) was added to a solution of protected aniline **2.106** (140 mg, 0.38 mmol) at –78 °C. The mixture was stirred 30 minutes, then cannulated into the stirring acid chloride solution, the mixture was stirred to r.t. for 3 h. The reaction was quenched with $KHCO_3$, the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, volatile compounds were removed under vacuum. Flash chromatography (20% EtOAc in hexanes) gave the title compound (158 mg, 69%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (tt, *J* = 7.0 Hz, 1.8 Hz, 1H) 7.54–7.48 (m, 4H) 7.19 (d, *J* = 3.0 Hz, 1H), 7.10 (d, *J* = 8.5 Hz, 2H), 6.77 (d, *J* = 8.5 Hz, 2 H), 6.74 (dd, *J* = 9.0 Hz, 3.0 Hz, 1H), 6.66 (d, *J* = 9.0 Hz, 1H), 6.02 (s, 1H), 5.47 (d, *J* = 14.0 Hz, 1H), 4.02 (d, *J* = 14.0 Hz, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 3.38 (ddd, *J* = 50.0 Hz, 10.0 Hz, 7.5 Hz, 2H), 2.67–2.48 (m, 2H); ^{13}C

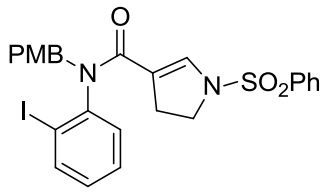
NMR (125 MHz, $CDCl_3$) δ 164.7, 159.8, 159.0, 136.7, 135.9, 133.6, 133.3, 132.0, 130.8, 129.2, 129.0, 127.3, 124.6, 119.0, 118.2, 113.8, 113.7, 55.9, 55.2, 47.3, 30.7; HRMS (ESI) *m/z* calcd for $C_{26}H_{25}BrNaN_2O_5S$ $[M+Na]^+$ 579.0565, found 579.0604.



***N*-(2-(5-Methoxy-1-(4-methoxybenzyl)-2-oxoindolin-3-yl)ethyl)formamide (2.109):** A solution of Bu_3SnH (0.24 mL, 0.83 mmol) and AIBN (14 mg, 0.014 mmol) in degassed benzene (4 mL) were added via syringe pump to a refluxing solution of iodoaniline (100 mg, 0.17 mmol) in degassed benzene (8 mL). After 2 h, the mixture was cooled to r.t. and volatile compounds were removed under vacuum. Flash chromatography (0–5 % MeOH in CH_2Cl_2) gives the title compound (25 mg, 42%) as a white solid, mp >220 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.21 (dt, *J* = 10.0 Hz, 2.5 Hz, 2H), 6.91 (dd, *J* = 2.5 Hz, 0.9 Hz, 1H), 6.84 (dt, *J* = 10.0 Hz, 2.5 Hz, 2H), 6.71 (dd, *J* = 8.0 Hz, 2.5 Hz, 1H), 6.66 (d, *J* = 8.5 Hz, 1H), 4.82 (s, 2H), 3.77 (s, 3H), 3.76 (S, 3H), 3.58–3.53 (m, 2H), 2.31 (dq, *J* = 15.0 Hz, 6.0 Hz, 1H), 2.06–1.98 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.6, 161.3, 159.1, 156.2, 136.4, 129.7, 128.6, 127.7, 114.2, 112.6, 111.2, 109.6, 55.7, 55.2, 44.4, 43.3, 35.9, 30.1; HRMS (ESI) *m/z* calcd for $C_{20}H_{21}N_2O_3$ $[M+H]^+$ 337.1552, found 337.1558.

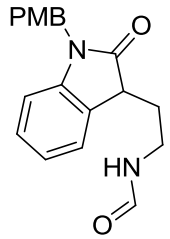


2-Iodo-*N*-(4-methoxylbenzyl)aniline (2.110): $NaBH(OAc)_3$ (9.67 g, 45.6 mmol) was added to a solution of p-anisaldehyde (1.53 mL, 12.6 mmol), 2-iodoaniline (2.5 g, 11.4 mmol) and AcOH (0.11 mL, 0.11 mmol) in 1,2-DCE (60 mL). The mixture was stirred 24 h, then saturated aqueous $KHCO_3$ (30 mL) was slowly added while stirring vigorously. The aqueous layer was extracted with EtOAc, the combined organic layer was washed with brine, dried over $MgSO_4$, and volatile compounds were removed under vacuum. The residue was subjected to flash chromatography (20% EtOAc in hexanes) to give the title compound (3.53 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 8.0 Hz, 1.2. Hz, 1H), 7.29 (d, *J* = 8.8 Hz, 2H), 7.17 (td, *J* = 8.0 Hz, 1.2 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.56 (dd, *J* = 8.4 Hz, 1.2 Hz, 1H), 6.45 (td, *J* = 8.0 Hz, 1.2 Hz, 1H), 4.54 (s, 1H), 4.33 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 147.1, 139.0, 130.5, 129.4, 128.8, 118.7, 114.1, 110.1, 85.3, 55.3, 47.8; HRMS (APCI) *m/z* calcd for $C_{14}H_{13}INO$ $[M–H]^+$ 338.0084, found 338.0070.

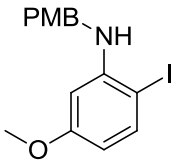


***N*-(2-Iodophenyl)-*N*-(4-methoxybenzyl)-1-(phenylsulfonyl)-4,5-dihydro-1*H*-pyrrole-3-carboxamide (2.111):** Ghosez reagent (0.15 mL, 1.25 mmol) was added to a suspension of carboxylic acid **2.96** (317 mg, 1.25 mmol) in toluene (12.5 mL), the mixture was stirred for 1 h. NaHMDS (0.93 mL, 1M in THF) was added to a solution of aniline **2.110** (315 mg, 0.93 mmol) in THF (9 mL) at –78 °C. The mixture was stirred 30 minutes then cannulated into the stirring acid chloride solution. The mixture was stirred to rt for 3 h. The reaction was quenched with aqueous $KHCO_3$, the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, volatile compounds were removed under vacuum. The

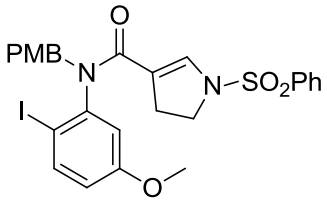
residue was subjected to flash chromatography (20% EtOAc in hexanes) to give the title compound (320 mg, 60%) as a colorless solid: mp 53–56 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 8.0 Hz, 1.5 Hz, 1H), 7.60–7.57 (m, 1H), 7.49–7.48 (m, 4H), 7.28 (td, *J* = 8.0 Hz, 1.5 Hz, 1H), 7.18–7.09 (m, 2H), 6.79–6.76 (m, 3H), 5.83 (s, 1H), 5.49 (d, *J* = 14.0 Hz, 1H), 4.02 (d, *J* = 14.0 Hz, 1H), 3.75 (s, 3H), 3.45–3.41 (m, 1H), 3.29–3.29 (m, 1H), 2.65 (m, 1H), 2.55 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.0, 159.0, 144.1, 140.2, 136.7, 135.7, 133.2, 131.1, 130.8, 128.0, 129.3, 129.2, 128.6, 118.1, 113.6, 101.0, 55.1, 52.0, 47.0, 30.8; HRMS (ESI) *m/z* calcd for $C_{25}H_{25}IN_2O_4S$ $[M+H]^+$ 575.2502, found 575.0508.



***N*-(2-(1-(4-Methoxybenzyl)-2-oxoindolin-3-yl)ethyl)formamide (2.112): General Procedure A** was applied to iodoaniline **2.111** (98 mg, 0.17 mmol to afford the title compound (34 mg, 65%) as a colorless solid: mp >220 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.28 (d, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 7.2 Hz, 2H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.05 (t, *J* = 7.6 Hz, 1H), 6.84 (D, *j* = 7.6 Hz, 2H), 6.78 (d, *J* = 7.6 Hz, 1H), 6.52 (s, 1H), 4.84 (s, 2H), 3.77 (s, 3H), 3.59–3.54 (m, 3H), 2.32 (dq, *J* = 14.0 Hz, 6.0 Hz, 1H), 2.03 (hex, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0, 161.3, 159.1, 143.0, 128.7, 128.6, 128.4, 128.2, 127.7, 123.9, 122.9, 114.2, 109.2, 55.3, 44.1, 43.3, 36.0, 30.1; HRMS (TOF ES) *m/z* calcd for $C_{19}H_{21}N_2O_3$ $[M+H]^+$ 325.1552, found 325.1562.

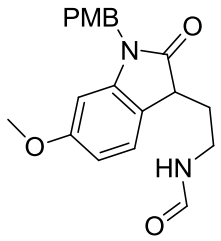


2-Iodo-5-methoxy-*N*-(4-methoxybenzyl)aniline (2.115): $NaBH(OAc)_3$ (5.10 g, 24.1 mmol) was added to a solution of p-anisaldehyde (0.41 mL, 6.63 mmol), 2-iodo-5-methoxyaniline **2.114**[167] (1.5 g, 6.02 mmol) and AcOH (0.11 mL, 0.11 mmol) in 1,2-DCE (30 mL). The mixture was stirred 24 h, then saturated aq. $KHCO_3$ (15 mL) was slowly added while stirring vigorously. The aqueous layer was extracted with EtOAc, the combined organic layer was washed with brine, dried over $MgSO_4$, and volatile compounds were removed under vacuum. The residue was subjected to flash chromatography (20% EtOAc in hexanes) to give the title compound (1.80 g, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.6 Hz, 1H), 7.26 (d, *J*= 8.6 Hz, 2H), 6.87 (d, *J*= 8.6 Hz, 2H), 6.14 (d, *J* = 2.8 Hz, 1H), 6.07 (dd, *J* = 8.6 Hz, 2.8 Hz, 1H), 4.49 (s, 1H), 4.27 (s, 1H), 4.26 (s, 1H), 3.78 (s, 3H), 3.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 158.8, 147.9, 138.9, 130.3, 128.5, 114.0, 104.0, 97.9, 74.5, 55.2, 47.8.



***N*-(2-Iodo-5-methoxyphenyl)-*N*-(4-methoxybenzyl)-1-(phenylsulfonyl)-4,5-dihydro-1*H*-pyrrole-3-carboxamide (2.116):** Ghosez reagent (0.12 mL, 0.93 mmol) was added to a suspension of carboxylic acid **2.96** (236 mg, 0.93 mmol) in toluene (7 mL), the mixture was stirred for 1 h. NaHMDS (0.72 mL, 1M in THF) was added to a solution of aniline **2.115** (265 mg, 0.72 mmol) in THF (7 mL) at –78 °C. The mixture was stirred 30 minutes, then added by cannula into the stirring acid chloride solution, the mixture was warmed to room temperature and

stirred for 3 h. The reaction was quenched with $KHCO_3$, the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, volatile compounds were removed under vacuum. The residue was purified by flash chromatography (20% EtOAc in hexanes) to give the title compound (235 mg, 54%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 9.0 Hz, 1H), 7.61 (tt, *J* = 6.5 Hz, 2.0 Hz, 1H), 7.53–7.50 (m, 3H), 7.13 (d, *J* = 8.5 Hz, 2H), 6.78 (d, *J* = 8.5 Hz, 2H), 6.74 (dd, *J* = 9.0 Hz, 3.0 Hz, 1H), 6.29 (d, *J* = 3.0 Hz, 1H), 5.92 (s, 1H), 5.52 (d, *J* = 14.5 Hz, 1H), 3.98 (d, *J* = 14.5 Hz, 1H), 3.77 (s, 3H), 3.61 (s, 3H), 3.42 (td, *J* = 10.0 Hz, 7.5 Hz, 1H), 3.34 (td, *J* = 10.0 Hz, 7.5 Hz, 1H), 2.72–2.58 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.9, 160.5, 159.1, 144.9, 140.2, 136.9, 135.3, 133.3, 130.9, 129.3, 128.9, 127.3, 118.1, 117.0, 116.6, 113.7, 89.0, 55.6, 55.2, 52.0, 57.1, 30.9; HRMS (ESI) *m/z* calcd for $C_{26}H_{26}IN_2O_5S$ $[M+H]^+$ 605.0607, found 605.0616.



***N*-(2-(6-Methoxy-1-(4-methoxybenzyl)-2-oxoindolin-3-yl)ethyl)formamide (2.117): General Procedure A** was applied to iodoanilide **2.116** (20 mg, 0.03 mmol) in degassed benzene (1.5 mL). After heating an additional 2 h, the mixture was cooled to room temperature and volatile compounds were removed under vacuum. The residue was purified by flash chromatography (5% MeOH in CH_2Cl_2) to give the title compound (6 mg, 54%) as a white solid: mp >220 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.22 (dt, *J* = 10.0 Hz, 2.5 Hz, 2H), 7.17 (d, *J* = 8.5 Hz, 1H), 6.84 (dt, *J* = 10.0 Hz, 2.5 Hz, 2H), 6.54 (dd, *J* = 8.0 Hz, 2.5 Hz, 1H), 6.37 (d, *J* = 2.5 Hz, 1H), 4.81 (s, 2H), 3.77 (s, 3H), 3.75 (S, 3H), 3.56–3.49 (m, 2H), 2.26 (dq, *J* = 14.5 Hz, 6.0

Hz, 1H), 2.04–1.97 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.7, 161.3, 160.1, 159.2, 144.2, 128.7, 127.7, 124.4, 120.2, 114.3, 106.4, 97.6, 55.5, 55.3, 43.5, 43.3, 36.0, 30.3; HRMS (ESI) *m/z* calcd for $C_{20}H_{21}N_2O_3$ $[M+H]^+$ 337.1552, found 337.1558.

APPENDIX A

CONTENT OF THE SUPPORTING USB DRIVE

1. An electronic copy of this dissertation
2. Two papers with Supporting Information where results of this dissertation work were published:
    a. Zhang, H.; Hay, E. B.; Geib, S. J.; Curran, D. P., Radical cyclizations of cyclic ene sulfonamides occur with beta-elimination of sulfonyl radicals to form polycyclic imines. *J Am Chem Soc* **2013,** *135* (44), 16610-7.
    b. Zhang, H.; Jeon, K. O.; Hay, E. B.; Geib, S. J.; Curran, D. P.; Laporte, M. G., Radical [3 + 2]-annulation of divinylcyclopropanes: rapid synthesis of complex meloscine analogs. *Org Lett* **2014,** *16* (1), 94-7.
3. Copies of NMR spectra for all unpublished compounds
4. Cif file for X-ray structure of **2.117**

3.0 BIBLIOGRAPHY

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