1,3-Dipolar and 1,3,6-Tripolar Reactivity of 3-hydroxy- and 3-amino-1-*N*-arylazopropenes for Heterocycle Formation

By

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Dedication

The hardest part about working towards a goal that requires most of your time and energy, is not being able to spend time with the people you want most to share that success with. I would like to dedication this thesis to Jan and Limbo, who passed a few months before this defense. I am grateful for the time we spent together.

Acknowledgements

I would like to appreciate my advisor, Dr. Don Coltart, for his novel ideas that have assisted in my development. I would also like to thank my committee for their helpful feedback, exceptionally Dr. Jeremy May for assisting me in finishing my degree.

I have had the pleasure to work with colleagues at the University of Houston who I have developed close friendships. I would like to thank my previous lab mates Uyen, Nasir, Thien, Sabrina and Kyle for their encouragement, and Ngoc, Ettore and Maulen for the amazing collaborations. Special thanks to Dr. James Korp, for the months of work he put in solving complex crystals on a dying machine. The May group has been very supportive in this time of transition, and I greatly appreciated them.

Thanks to my family, although they never understand why, have all been supportive in their own way for my thirst of knowledge. Thank you for your personal sacrifices, your unconditional love, support, and food.

Abstract

3-Alkoxy-1-*N*-aryl azopropene structural motifs in the Eschenmoser-Tanabe Fragmentation pathway have been known for almost 50 years, yet one unexploited feature of these intermediates is their putative 1,3-dipole. Described here is a transformation leveraging this reactivity to synthesize an important class of oxygen heterocycles, β,γ-fused bicyclic γ-lactones, by the simple combination of an ester or acyl pyrrole, an α-epoxy-2-nitrophenyl hydrazone, and a base. The products of this reaction, including those containing quaternary centers, are generated with high (up to >25:1) diastereoselectivity. Conveniently, both *syn*- and *anti*-fused bicyclic systems can be generated stereoselectively by simply changing the counter-ion of the base, LiHMDS and KHMDS, respectively.

This dissertation also describes the development of a new functional group, 3-amino-1-azopropene, and its use in novel annulation strategies leading to *N*-heterocycles, which are important structures found in drugs and biologically active natural products. The 3-amino-1-azopropene functional group possesses multiple nucleophilic sites and, as such, is expected to inspire the development of a wide range of new synthetic methods and/or find applications in the development of new drugs and materials.

Lastly, as part of the continuing effects to develop new reactions for the formation of saturated heterocycles, the conjugated π systems of azoalkenes in 3-hydroxy-azopropenes and 3-amino-1-azopropene were utilized in a [4+2] cyclization reaction in order to achieve ring closure. Compounds were prepared

in high (up to >25:1) diastereoselectivity from a cascading Tsuji-Trost [4+2] cycloaddition, producing a wide array of fused tetrahydrofuran- and pyrrolidine-tetrahydropyridazine derivatives.

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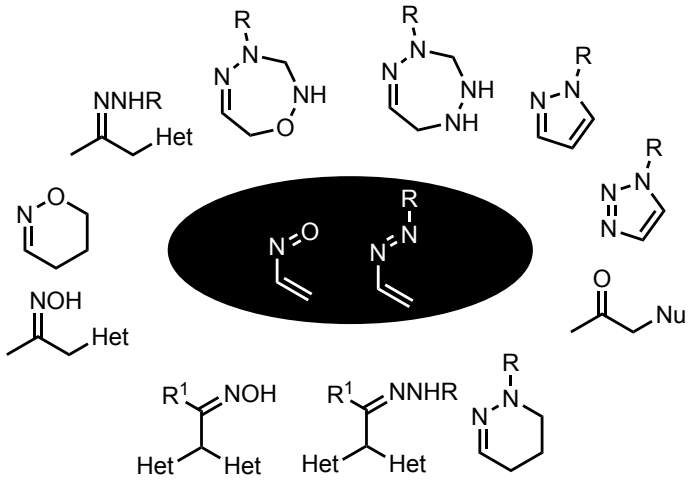
List of Abbreviations

AAP = 1-amino-3-azopropene
Ac = acetyl
ACC = N-aminocyclic carbamate
AK = azoalkene
All = allyl
aq = aqueous
Bn = benzyl
t-Bu = tert-butyl
CN = nitrile
Cy = cyclohexyl
DMAP = 4-(dimethylamino)pyridine
dr = diastereomeric ratio
EDCI = 1-ethyl[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
ee = enantiomeric excess
equiv = equivalents
er = enantiomeric ratio
Et = ethyl
EWD = electron-donating group
EWG electron-withdrawing group
HAP = 1-hydroxy-3-azopropene
HOBt = hydroxybenzotriazole
KHMDS = potassium bis(trimethylsilyl)amide
LDA = lithium diisopropylamide
LiHMDS = lithium bis(trimethylsilyl)amide
MeCN = acetonitrile
Me = methyl
NA = nitrosoalkene
NaHMDS = sodium bis(trimethylsilyl)amide
nOe = nuclear overhauser effect
Ph = phenyl
PPTS = pyridinium p-toluenesulfonate
PIDA = (Diacetoxyiodo)benzene
TBAF = tetrabutyl ammonium fluoride
TBS = tert-butyldimethylsilyl
TCIC = trichloroisocyanuric acid
TEMPO = 2,2,6,6-tetramethylpiperidin-1-yl)oxyl
THF = tetrahydrofuran
TMS tetramethylsilane
Ts = tosyl (para-toluenesulfonyl)

1.1 Introduction and background

1.1.1 Azoalkenes and nitrosoalkenes



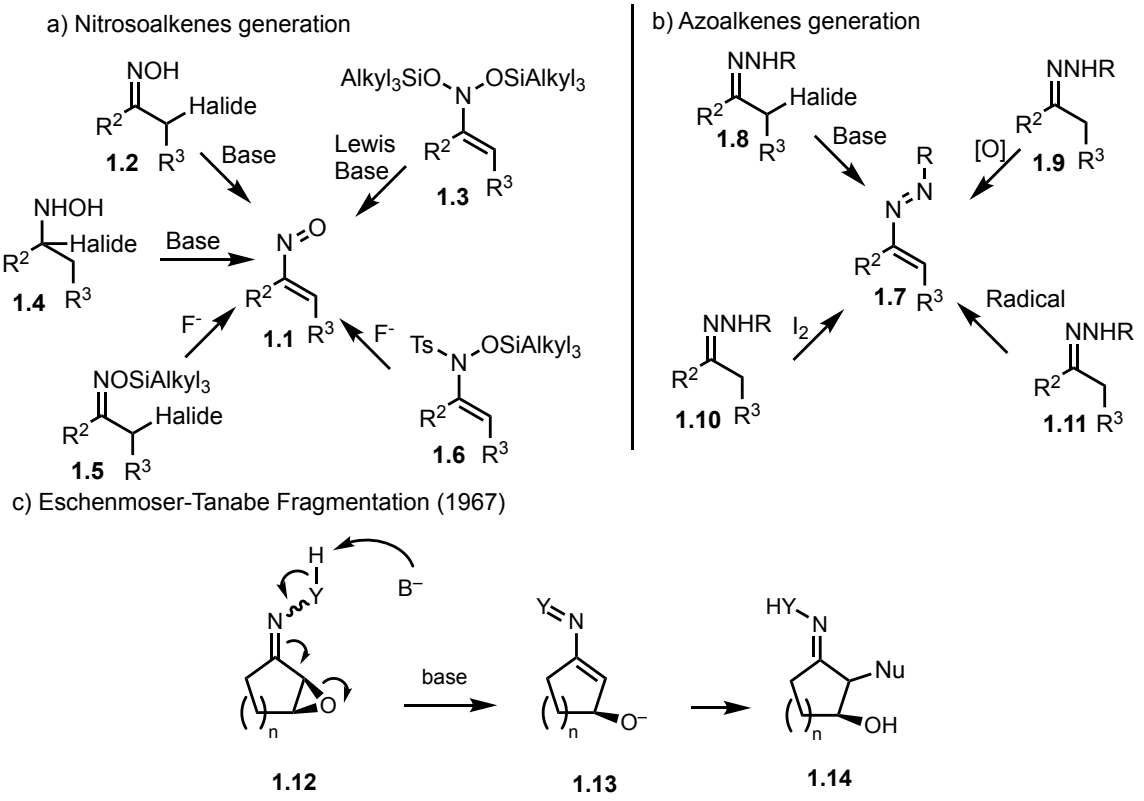
Scheme 1. The reaction web of conjugated nitrosoalkenes and azoalkenes.

Conjugated nitrosoalkenes (NA) and azoalkenes (AK) have been successfully explored as a valuable intermediates in organic synthesis, especially for the production of heterocycles, a prevalent structural motif present in the majority of pharmaceutical compounds **(Scheme 1)**.[1,2,3,4,5,6,7] NA and AK are mainly used as electron-deficient heterodienes in hetero-Diels–Alder reactions with electron-rich heterocycles, nucleophilic olefins, as well as other types of cycloaddition reactions, namely [4+3], [4+1], and [3+2] cycloadditions.[8,9,10,11,12,13,14,15] NA and AK are also Michael-type acceptors in 1,4-addition conjugate addition reactions, and subsequent hydrolysis provides an Umpolung approach to α-functionalization of ketones.[16,17,18,19,20]

1.1.2 Generation and stability of azoalkenes and nitrosoalkenes

NA and AK have attracted significant attention as useful intermediates and have consolidated their importance in organic chemistry for the synthesis of heterocyclic systems.[21,22,23,24] This is due to the simple and reliable methods for their generation from readily available precursors, usually through base-mediated dehydrohalogenation of α-halooximes or α-halohydrazones **(Scheme 2a)**.[25,26] Many factors such as temperature, concentration and solvent affect coupling of NA, but the nature of the its precursor is especially important, so other methods have been developed to broaden its application. For instance, α-halooxime silyl ethers, *N,N*-bis(silyloxy)enamines, and *N*-siloxysulfonamides have all been employed for NA production.[27,28,29,30,31,32] AK can be generated through the oxidation of hydrazones with 2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), I_2, HgO, or through the pyrolysis of 1,2,3-thiadiazole dioxides, oxadiazinones, or 3-hydroxy-2-arylhydrazonoalkanoic acid derivatives **(Scheme 2b)**.[33,34,35,36,37] The electrophilic character of a heterodiene is crucial for efficient cycloaddition, therefore, NA having electron-withdrawing substituents at R^2- and/or R^3-positions such as aryl, trifluoromethyl, acyl, alkoxycarbonyl, phosphorus, tetrazolyl, and triazolyl groups have been used in the target-oriented synthesis of naturally occurring and biologically active molecules.[38,39,40] Once formed, the highly reactive NA differs from AK, because AK's physical properties and stabilities can also be altered by electron-withdrawing groups (EWG) on the distal nitrogen, AKs unsubstituted at the R^3-position are unstable and are typically generated *in situ*, whereas heavily substituted AKs are stable enough to be isolated and characterized, allowing for their study and use in the formation of AK cycloaddition products with pharmacological properties.[41,42,20] NA and

AK have also been prepared through the deprotonation of α,β-epoxyoximes or α,β-epoxyhydrazones followed by ring opening of an epoxide. These intermediates are typically intercepted by a nucleophile, but isolation of 1-hydroxy-3-azopropenes (HAP) have been reported, more on this in Section 1.1.5 **(Scheme 2c)**.[43]

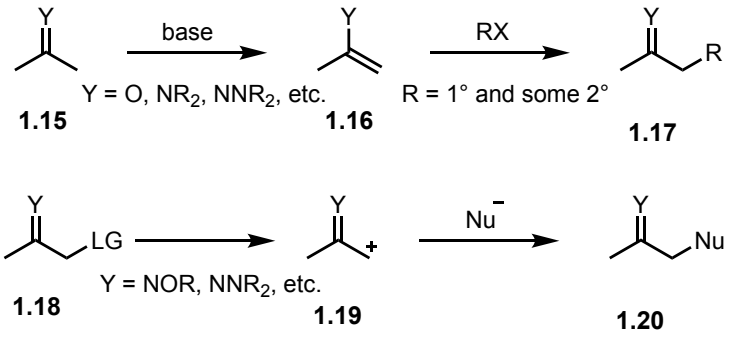


Scheme 2. Routes to nitrosoalkenes and azoalkenes

1.1.3 Conjugate addition to azoalkenes and nitrosoalkenes

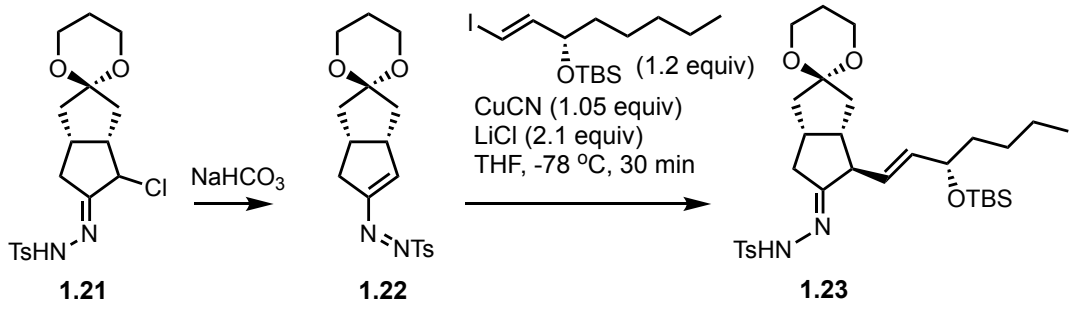
While traditional enolate chemistry has been instrumental to synthetic organic chemistry for the assembly of carbon-carbon bonds in complex molecular architectures, the transformation is inherently limited due to its mechanistic requirements of enolate attack to an electrophile through a S_N2 reaction.[44,45,46,47,48,49] Consequently, this S_N2 requirement restricts the incorporation of substituents whose parent electrophile is incapable of undergoing an S_N2 reaction. Azo- or nitroso- substituents impart strong

electrophilic character on the terminal carbon in AK and NA systems, which activates and makes them susceptible to nucleophilic attack.[50,51,52] Thus, nitrosoalkenes and AKs are enolium synthetic equivalents, and their reactivity toward nucleophiles opens the way to Umpolung α-functionalization of ketones (**Scheme 3**).



Scheme 3. Enolate chemistry vs umpolung-based approach

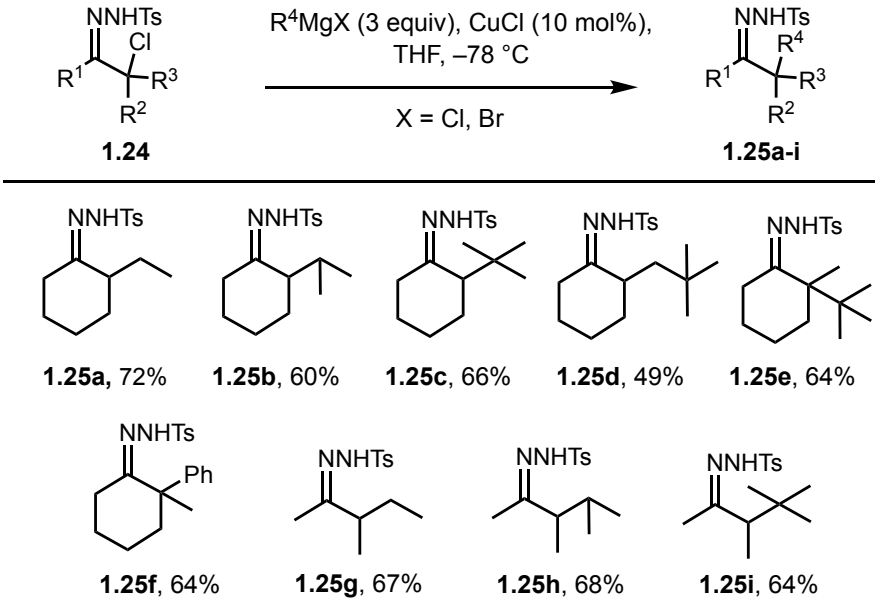
Gais and co-workers[53] reported a conjugate addition of alkenyl copper to a bicyclic AK as a key step in the synthesis of 3-oxacarbacyclin (**Scheme 4**). The AK **1.21**, prepared from dehydrohalogenation of α-haloketone **1.22**, underwent the stereocontrolled reaction with an alkenyl iodide in the present of CuCN/LiCl to produce the alkenylated product **1.23** in 73% yield.



Scheme 4. Addition of a phenyl cuprate to azoalkene 1.22

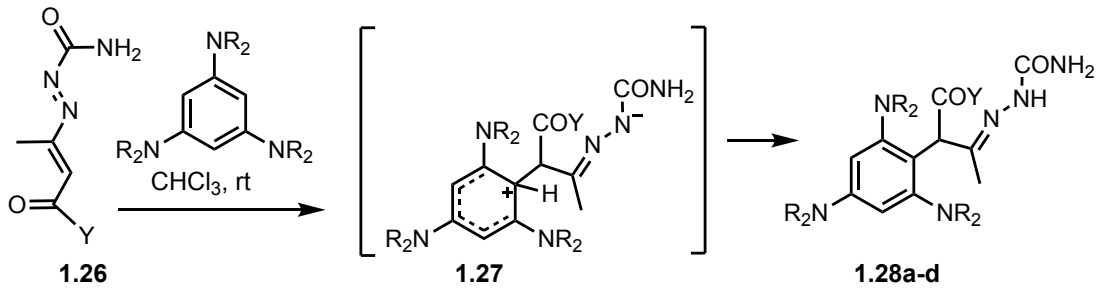
In 2010, the Coltart group reported a method for α-alkylation of hydrazones via *in situ*-generated AKs with commercial Gignard reagents using a catalytic amount of CuI (**Scheme 5**).[54] The AKs, derived from α-chloro *N*-sulfonylhydrazones, react with

primary alkyl, secondary alkyl, tertiary alkyl, and phenyl reagents to form the alkylated products. This method also allows the formation of regiocontrolled α,α-bisalkylated products from the α,α-dichloro-*N*-sulfonylhydrazones.



Scheme 5. Cu(I)-catalyzed Grignard addition to *in situ* generated azoalkenes

In 2008 Zanna *et al*. reported an unusual addition of 1,3,5-trianilines to AKs to form α-arylated hydrazones (**Scheme 6**).[55] The reactions proceeded via the formation of σ-complexes **1.27**, which are well-known intermediates in the context of electrophilic substitution of aromatic rings. In the present of sodium methoxide, these products undergo cyclizations to afford pyrazalone derivatives or cinnoline derivatives depending on the solvent of the reaction.

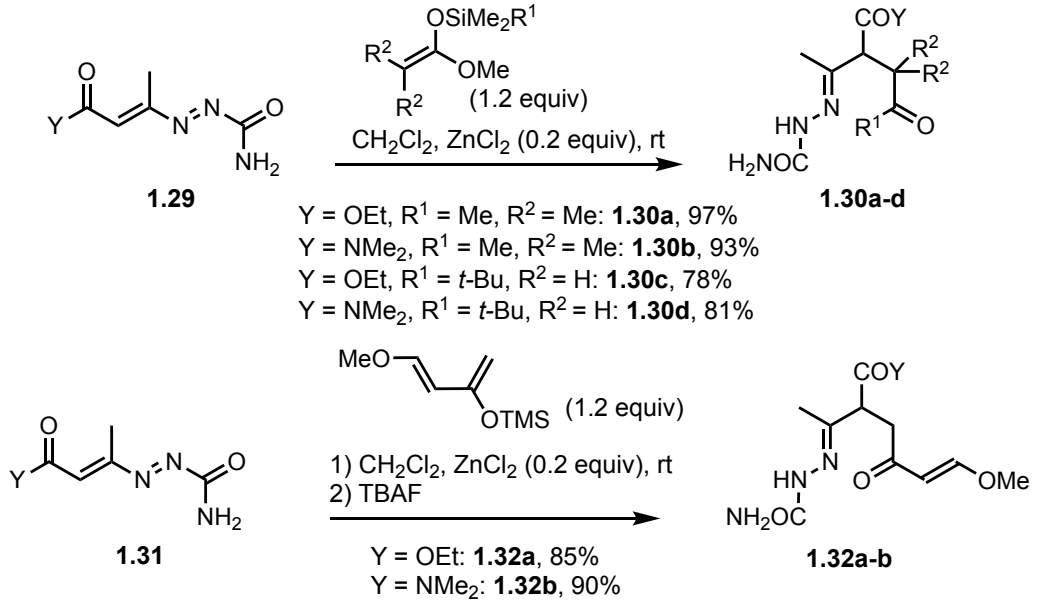


1.26 **1.27** **1.28a-d**

1.28a NR_2 = Piperidinyl, Y = OEt: 77%
1.28b NR_2 = Piperidinyl, Y = NMe_2: 96%
1.28c NR_2 = Morpholinyl, Y = OMe: 83%
1.28d NR_2 = Morpholinyl, Y = NMe_2: 93%

Scheme 6. Nucleophilic addition of aromatic compounds to azoalkenes

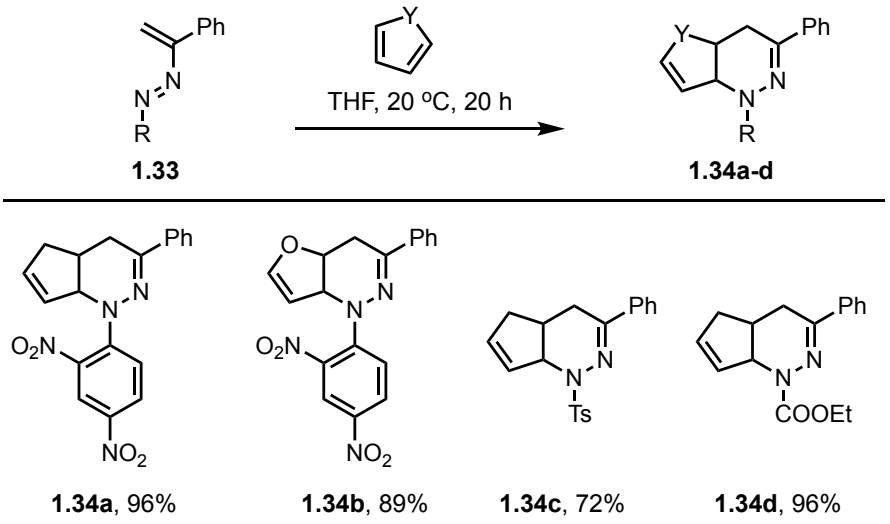
AKs also react with silyl enol ethers in the Mukaiyama-Michael-type addition. In 2007, Filippone *et al*. reported the addition of various silyl enol ethers to AKs at room temperature in the present of $ZnCl_2$ (**Scheme 7**).[56] The coordination of $ZnCl_2$ with the silyl enol ethers promoted the nucleophilic addition to AKs and generates the products. In 2008, the same group reported a similar transformation of AKs **1.31** with Danishefsky's diene **1.32**.[57]



Scheme 7. Nucleophilic addition of silyl enol ethers to azoalkenes

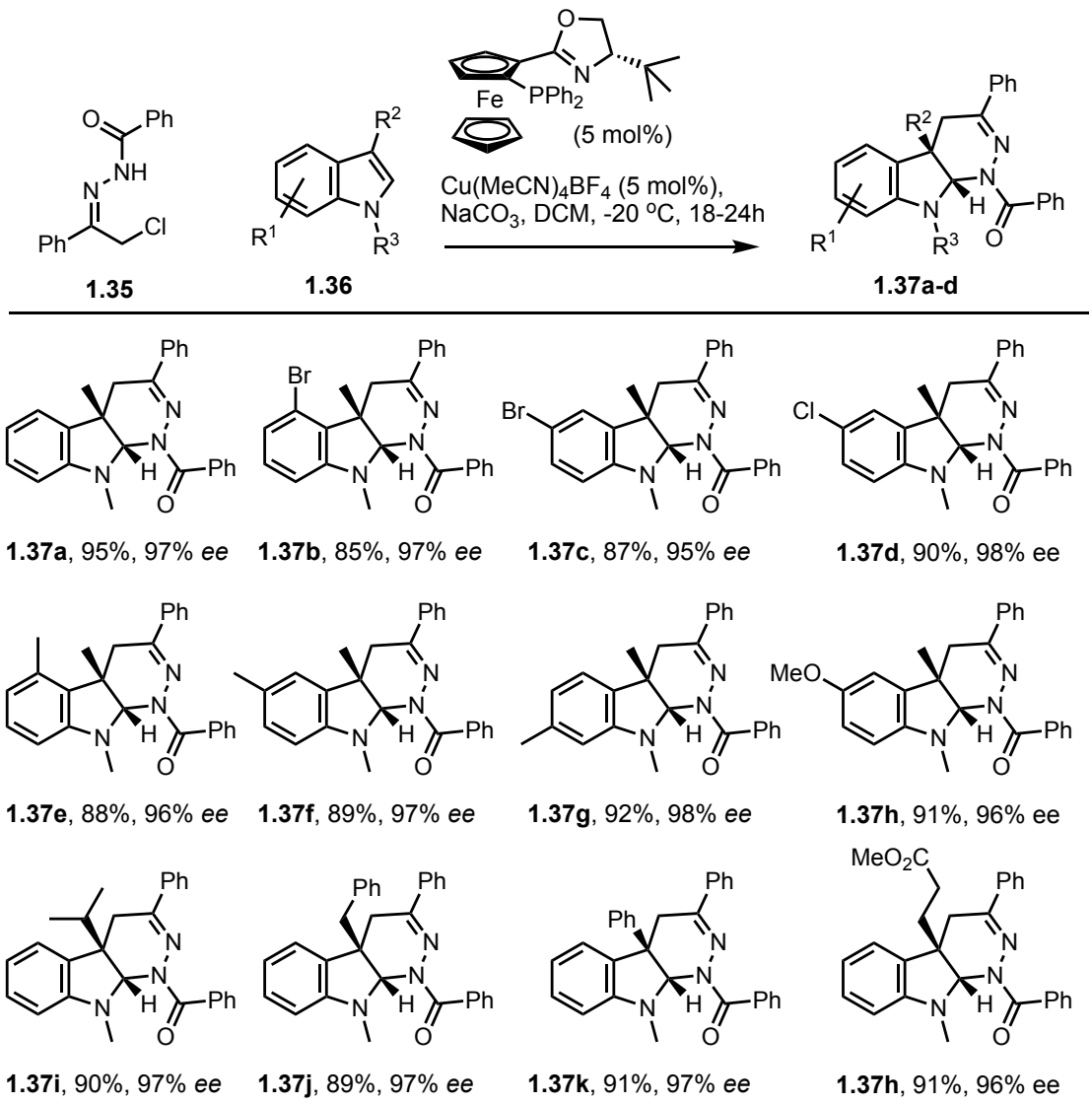
1.1.4 Cycloadditions of azoalkenes and nitrosoalkenes

In 1979, Gilchrist *et al*. reported another cycloadditon of AK species **1.33**, generated *in situ* from α-chloroacetophenone hydrazones, with cyclopentadiene and furan (**Scheme 8**).[58] AKs bearing an electron-withdrawing group on the azo group or electron-rich dienes facilitated the cycloaddition and generated the pyridazine derivatives **1.34** in good yields.



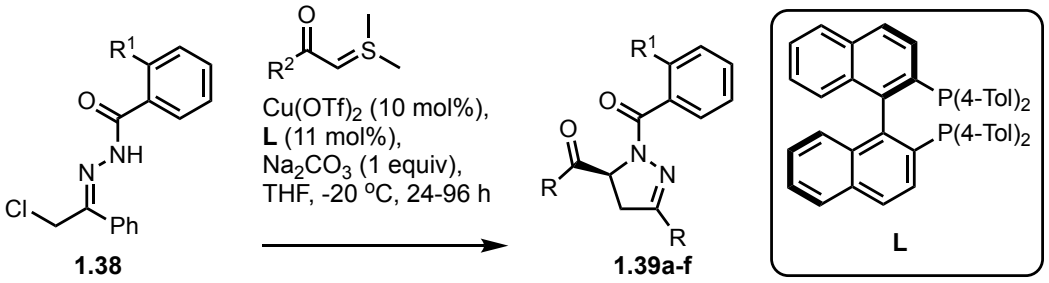
Scheme 8. [4+2] cycloaddition of electron-deficient azoalkenes and electron-rich alkenes

In 2014, Wang *et al*. reported the copper-catalyzed asymmetric aza-Diels-Alder reactions of *in situ* generated AK **1.35** and indoles **1.36** to generate tetrahydropyridazine derivatives **1.37** (**Scheme 9**).[59] Using a chiral nonracemic ligand and copper (I) as a chelating metal to the AK, the cycloaddtion of this AK with indoles generated adducts with excellent yields and high levels of enantioselectivity.



Scheme 9. Catalytic asymmetric aza-Diels-Alder reactions of an azoalkene with indoles

The copper-catalyzed asymmetric [4+1] cycloaddition of *in situ* generated AKs with sulfur ylides to produce dihydropyrazole derivatives was reported in 2012 by Bolm *et al.* (**Scheme 10**).[60] In the presence of base (Na_2CO_3), α-halo hydrazones **1.38** underwent a dehydrohalogenation to form AKs, which was presumably activated by $Cu(OTf)_2$ complexed to the chiral nonracemic Tol-BINAP ligand **L**. The cycloaddition of the activated AKs with ylides produced synthetically and biologically important dihydropyrazoles **1.39** in good yields with high enantioselectivitives (up to 97:3 *er*).



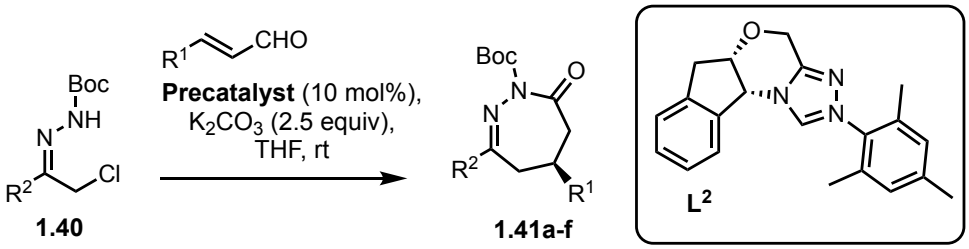
1.38 → **1.39a-f**

L

R^1 = H, R^2 = Ph: **1.39a**, 89%, 91:9 *er*
R^1 = H, R^2 = 4-ClC_6H_4: **1.39b**, 85%, 90:10 *er*
R^1 = H, R^2 = 4-$OMeC_6H_4$: **1.39c**, 95%, 90:10 *er*
R^1 = OMe, R^2 = Ph: **1.39d**, 84%, 97:3 *er*
R^1 = OMe, R^2 = 4-ClC_6H_4: **1.39e**, 93%, 96:4 *er*
R^1 = OMe, R^2 = 4-$OMeC_6H_4$: **1.39f**, 95%, 92:8 *er*

Scheme 10. Asymmetric [4+1] cycloaddition of *in situ*-derived azoalkenes with sulfur ylides

The enantioselective [4+3] annulation reactions between enals and *in situ* formed AKs was reported in 2014 by Glorius *et al* (**Scheme 11**).[61] This organocatalysis process, catalyzed by an *N*-heterocyclic carbene generated from $\mathbf{L^2}$, produced a diverse set of 1,2-diazepine derivatives **1.41** in good yields with excellent enantioselectivities.



1.40 → **1.41a-f**

$\mathbf{L^2}$

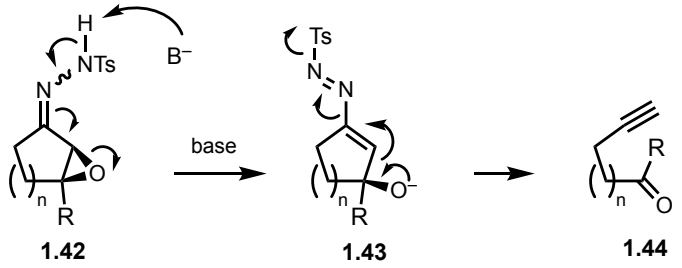
R^1 = Ph, R^2 = H: **1.41a**, 70%, 99% *ee*
R^1 = Ph, R^2 = F: **1.41b**, 60%, 99% *ee*
R^1 = Ph, R^2 = Me: **1.41c**, 63%, 99% *ee*
R^1 = 4-$OMeC_6H_4$, R^2 = Ph: **1.41d**, 68%, 99% *ee*
R^1 = 4-FC_6H_4, R^2 = Ph: **1.41e**, 58%, 98% *ee*
R^1 = 4-$CF_3C_6H_4$, R^2 = Ph: **1.41f**, 61%, 99% *ee*

Scheme 11. Asymmetric [4+3] cycloaddition of *in situ*-derived azoalkenes with enals

1.1.5 Ring expansion for azoalkenes and nitrosoalkenes formation

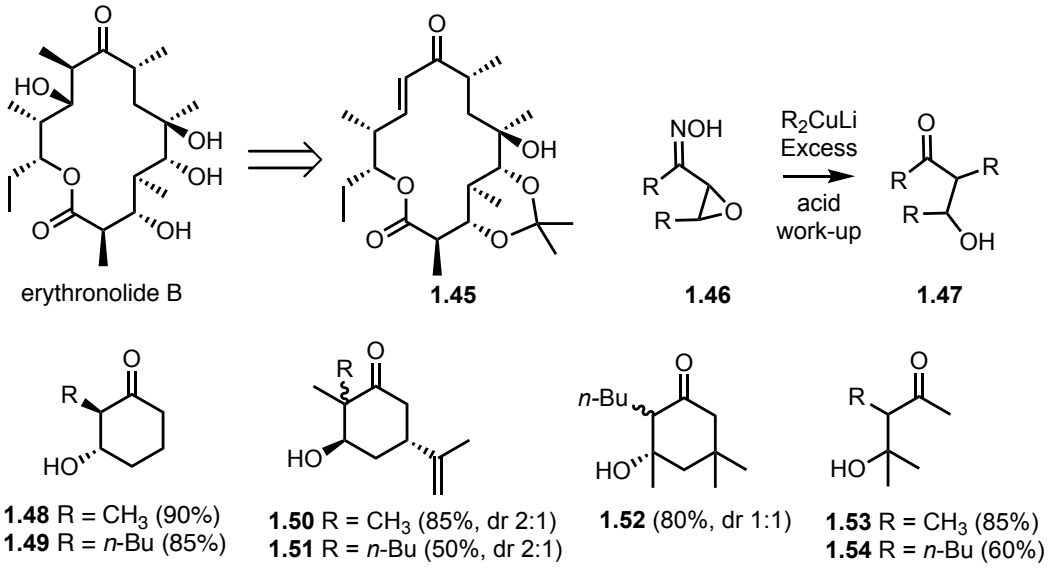
Almost 50 years ago, 3-alkoxy-*N*-toluenesulfonyl azopropene **1.43** was introduced as an intermediate in the Eschenmoser-Tanabe fragmentation of α,β-epoxy-*p*-toluenesulfonylhydrazones **1.42** to yield the alkynyl ketone or aldehyde **1.44** (**Scheme**

12).[62,63] This method has been widely applied to fused rings to form internal acetylenes, as well as the synthesis of many natural products.[64,65]



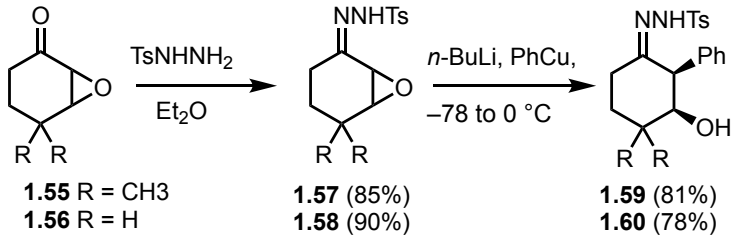
Scheme 12. Eschenmoser-Tanabe Fragmentation and known 3-hydroxy-1-*N*-aryl or *N*-alkyl azopropenes.

In 1975, during the total synthesis of erythronolide B from intermediate **1.45**, Corey and co-workers employed the ring opening of α,β-epoxy oximes with Gilman's reagents to generate a 1-hydroxy-3-nitrosopropene and introduce a methyl group at the C-10 position (**Scheme 13**).[66] Interestingly, with cyclohexenone oxime excellent stereoselectivity was observed (exclusively *trans* isomers were formed), yet substituted cyclohexenone oxime derivatives such as α,β-epoxycarvone and epoxyisophorone oximes produced diastereomeric mixtures of products.



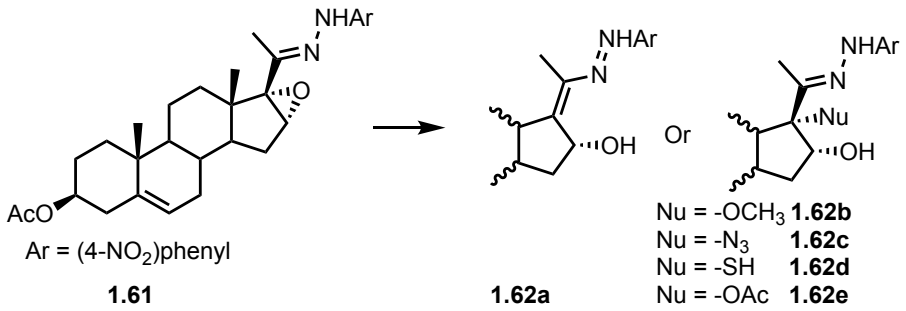
Scheme 13. Corey and co-workers employed the ring opening of α,β-epoxy oximes

In 1976, Fuchs reported a new methodology for the α-arylation of α,β-unsaturated ketones (**Scheme 14**).[67] Fuchs recognized that a nucleophile should be primed to intercept the 3-alkoxy-1-*N*-toluenesulfonyl azopropene intermediate at the α-position. Thus, the 3-alkoxy-1-*N*-toluenesulfonyl azopropene moiety was formed by the addition of *n*-BuLi at –78 °C to α-epoxy hydrazone (**1.57** or **1.58)** and Gilman's reagents in good yield. Fuchs then progressed the α-phenyl-β-hydroxy hydrazone to the α-arylation-α,β-unsaturated ketones by dehydration and hydrolysis of the hydrazone. While it was not the initial goal of Fuchs, this reaction provided a fundamentally new approach to the synthesis of α-aryl-β-hydroxy ketones.



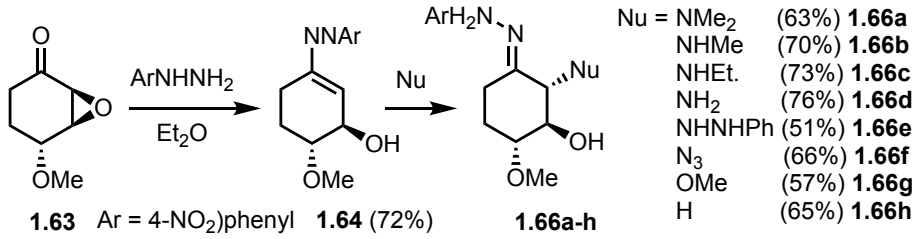
Scheme 14. Interception of the 3-alkoxy-1-*N*-toluenesulfonyl azopropene intermediate with phenyl copper.

From the early 70s into the 80s, Kamernitskii and Akhram employed α,β-epoxy-hydrazones several times to directly modify steroids **1.61** (**Scheme 15**).[68] They were able to demonstrate a variety of hetero nucleophiles that could be added to the α-position in diastereoselective manor. They also isolated a steroidal HAP **1.62a** during one of their investigations but never utilized it further.[69]



Scheme 15. Kamernitskii and Akhram modified steroids

In 1982, Hajivarnava and co-workers showed that reacting anhydro-glycopyranosiduloses **1.63** with p-nitrophenyl-hydrazine yielded isolatable HAPs **1.64**.[70] Subsequent, they reacted HAP **1.64** with a range of nucleophiles yielding the *anti*-α-substituted phenylhydrazones by 1,4-addition (**Scheme 16**).

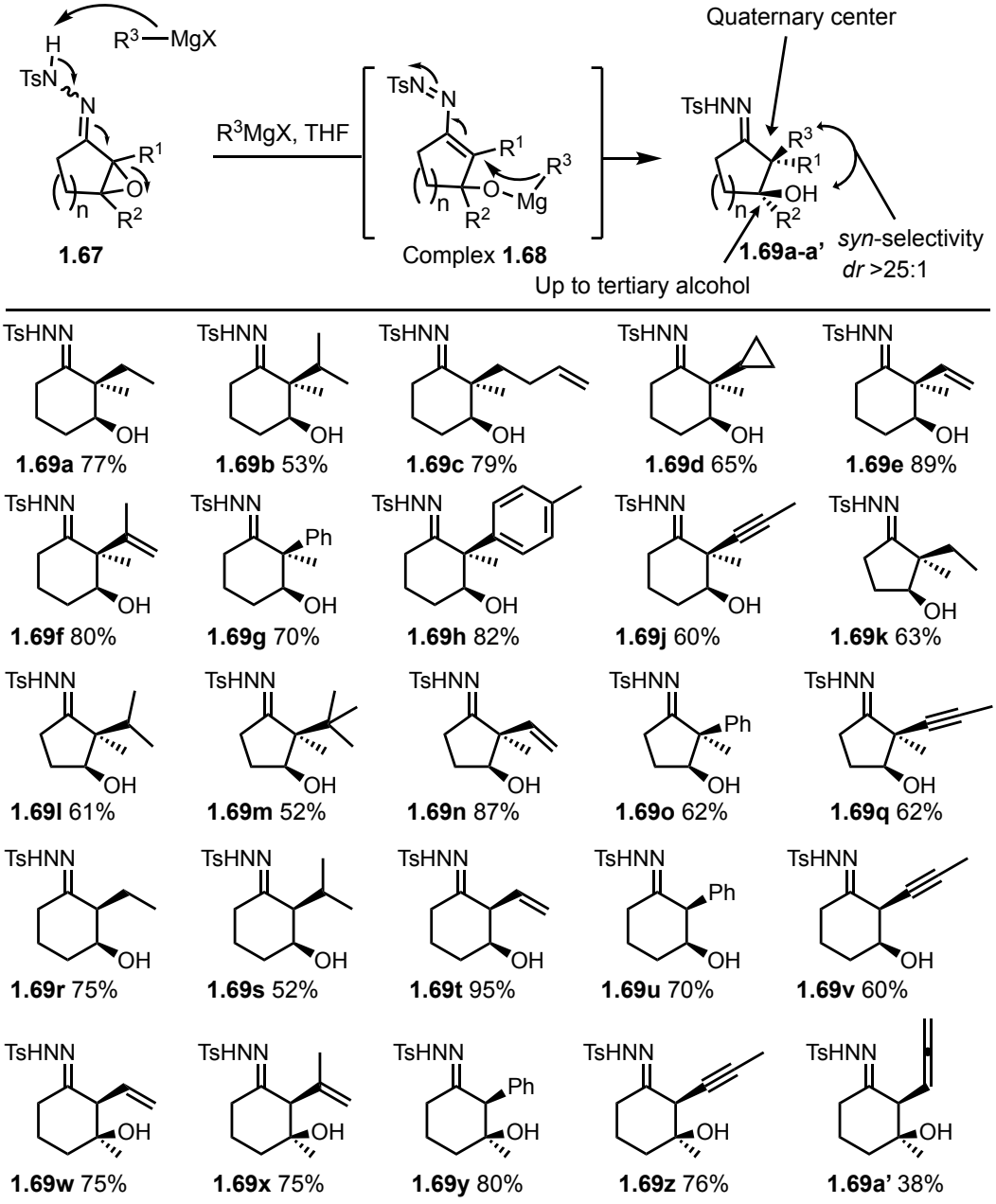


Scheme 16. Reactions of isolatable HAP

The Coltart group has been studying the conjugate addition of various nucleophiles to AKs and nitrosoalkene for *umpolung* α-functionalization of ketones.[71] As an extension of that work and the previously reported results discussed in this section, the Coltart group recently utilized Grignard reagents to serve as the organometallic species for conjugate addition to 3-alkoxy-1-*N*-toluensesulfonyl azopropenes. To prevent the intermediate from undergoing fragmentation, Grignard reagents were used in excess at –78 °C to intercepted it (**Scheme 17**). One equiv of the Grignard reagent deprotonated the hydrazone. This triggered ring opening of the epoxide and led to the desired 3-alkoxy-1-*N*-sulfony-l-azopropene intermediate. The second equiv of the Grignard species

underwent 1,4-addition to the AK, and ultimately produced the α-alkyl-β-hydroxy *N*-sulfonyl hydrazone on acidic workup. Such a process provided diastereoselective addition of various Grignard reagents to 3-alkoxy-1-*N*-toluensesulfonyl azopropenes, as well as gave access to synthetically challenging α-quaternary centers. The products, α-alkyl-β-hydroxy-*N*-sulfonyl hydrazones, were formed in up to > 25:1 *syn*:*anti* ratio.

While that work proved successful for the conjugate addition of Grignard reagents to *in situ* generated HAPs, it had yet to be proven that this substrate could be utilized in new transformations. Specifically, in the context of generating saturated heterocycles.



Scheme 17. Grignard addtion to 3-alkoxy-1-N-tolenesulfonyl azopropenes.

1.1.6 Saturated heterocycles

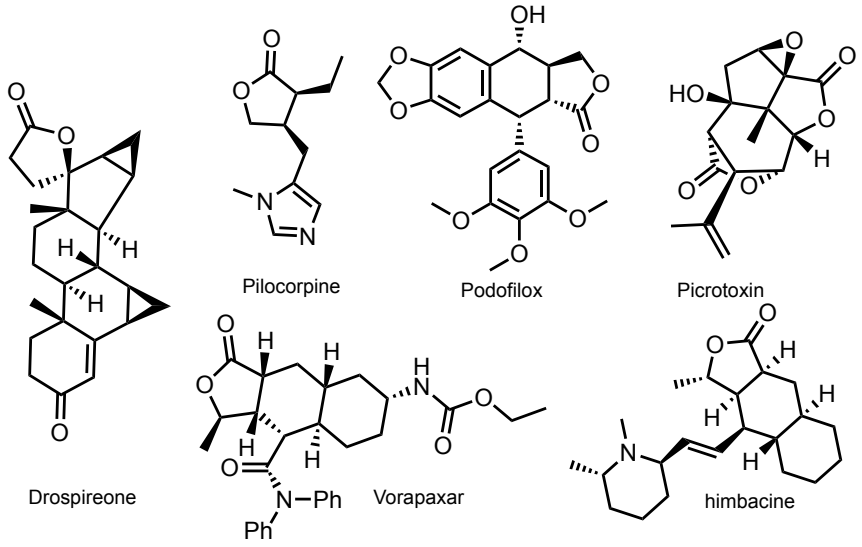
O- and *N*-heterocycles are among the most prevalent structural motifs present in pharmaceutical compounds. Depending on the hybridization state (sp^2 or sp^3) of their ring atoms, heterocycles may be classified as: 1) unsaturated (only sp^2 hybridized ring atoms), 2) partially saturated (sp^2 and sp^3 hybridized ring atoms), or 3) saturated (only sp^3

hybridized ring atoms). Interestingly, while *N*- and *O*-heterocycles of all degrees of saturation are widely represented among natural products, the unsaturated forms are by far the most common in pharmaceuticals.[72,73,74,75,76,77,78,79,80] The underrepresentation of saturated and partially saturated heterocycles among drugs is surprising given the potential benefits that they offer in comparison to their unsaturated counterparts. Deficiencies in the synthesis of these species are largely to a lack of simple, effective, and broadly applicable methods for their synthesis. It has been shown that saturation levels impact the clinical success of drug candidates by effecting their bioavailability and target promiscuity, which are the leading causes of attrition in the drug development process.[81] In general, the higher the sp^3 content of a compound, the greater its bioavailability and target specificity will be, thereby increasing its likelihood to succeed as a drug. It is also the case that lower molecular weight drug candidates tend to be more successful; the mean MW of compounds at the drug discovery stage is 442, but this drops to 360 for those compounds that become drugs. Increasing structural complexity by increasing levels of saturation allows a vastly greater portion of chemical space to be explored, with a minor increase in molecular weight. Clearly, there is a critical need to develop simple, effective, and broadly applicable methods for the synthesis of saturated and partially saturated *N*- and *O*-heterocycles. Such methods will not only find application in the asymmetric total synthesis of natural products, but will also be of great value by providing opportunities to investigate hitherto non- or underexplored areas of structure space in the search for new drugs. What follows describes the development of a simple, effective, and broadly applicable method for the synthesis of saturated and partially saturated *O*-and *N*-heterocycles.

1.2 Synthesis of β,γ-fused bicyclic γ-lactones[82,83]

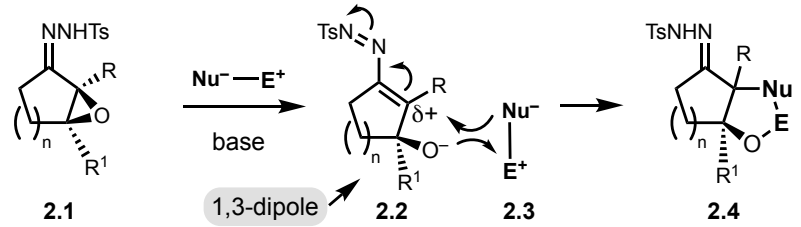
1.2.1 γ-lactones

γ-lactones appear in 10 U.S. FDA approved pharmaceuticals, all of which are polycyclic, and only one contains unsaturation and lacks a stereocenter (**Scheme 18**).[73] Substitution in γ-lactones plays a critical role in its bioactivity; for instance, spirolactone steroids are critical for mineralocorticoid receptor antagonist activity that helps to increase sodium excretion and potassium retention, whereas sentacyclic cores containing γ-lactones are thrombin receptor antagonist, and disubstituted γ-lactones are used to treat glaucoma, xerostomia and to help prevent transplant rejection.[84,85,86,87]



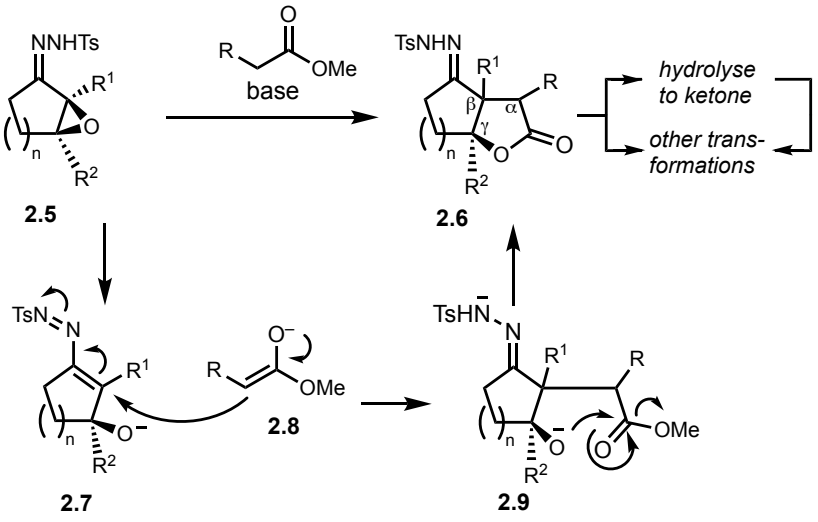
Scheme 18. Examples of lactones in drugs and natural products

1.2.3 Multicomponent ring expansion cascade



Scheme 19. Suspected 1,3-dipole of 3-alkoxy-*N*- *p*-toluenesulfonyl azopropene

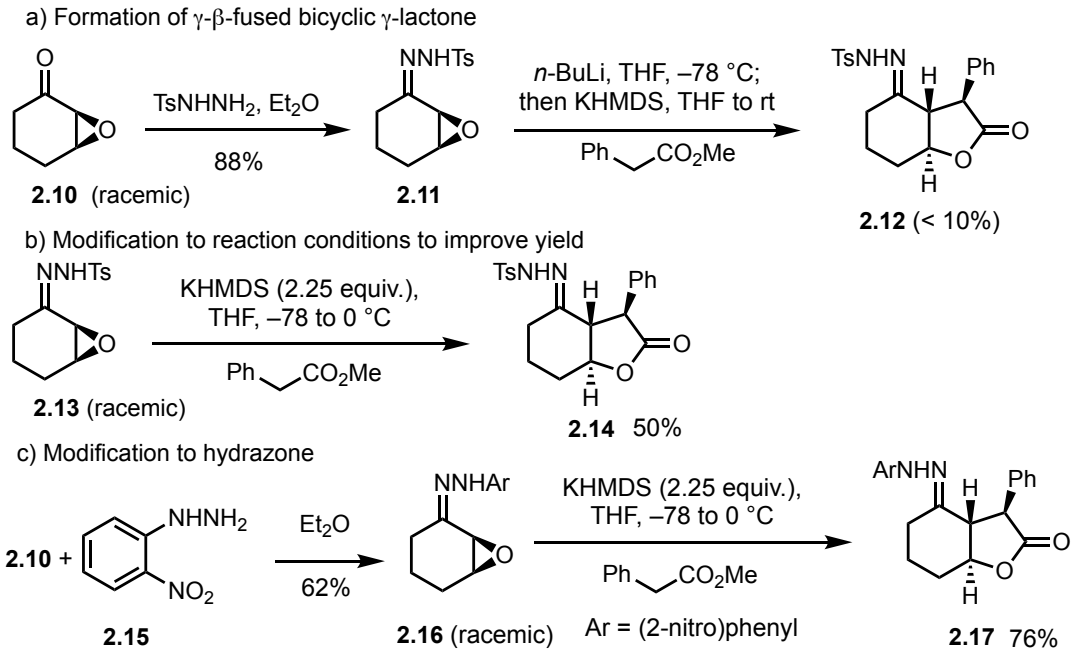
While the previously mentioned examples utilizing HAP moieties for non-Eschenmoser-Tanabe fragmentations are impressive, little has been reported on the alkoxide being used as a nucleophile or the development of these intermediate in the context of a 1,3-dipole (**Scheme 19**).[68] Therefore, these intermediates were engaged with suitable dipoles to investigate their potential reactivity. While a range of dipoles can be envisioned, for our initial investigation the use an enolate derived from an ester was most practical. The product of such a novel cascade reaction would be an β-γ-fused bicyclic γ-lactone (**2.6**). Mechanistically, this would require 2 equiv of enolate. The first equiv would deprotonate the α,β-epoxy-*p*-toluenesulfonylhydrazones initiating a reopening of the epoxide to generate the 3-alkoxy-*N*-*p*-toluenesulfonyl azopropene (**2.7**), then the second equiv of enolate would engage in nucleophilic addition to the AK (**2.9**). Finally, the alkoxide induced transesterification to give the desired β-γ-fused bicyclic γ-lactone (**2.6**) (**Scheme 20**).



Scheme 20. Proposed mechanism for α-β-fused bicyclic γ-lactone

To investigate the proposed ring expansion cascade, α-epoxy tosyl hydrazone **2.11** was treated with *n*-BuLi in THF at –78 °C to generate the putative 3-alkoxy-*N*-

toluenesulfonyl azopropene (**Scheme 21a**). To this reaction mixture was added an enolate derived from methyl phenylacetate and KHMDS. The desired β-γ-fused bicyclic γ-lactone **2.12** was produced, but the low yield is mostly due to the Eschenmoser-Tanabe Fragmentation. To simplify the procedure, 2.25 equiv of enolate was added to **2.11**, with one equiv of the enolate acting as a sacrificial base to deprotonate the α-epoxy tosyl hydrazone to form the HAP. This modified procedure reduced the fragmentation reaction by generating the reactive HAP while in the presence of the nucleophile. By implementing this modified procedure, the desired β-γ-fused bicyclic γ-lactone **2.14** was formed in 50% yield (**Scheme 21b**). Unfortunately, no additional experimentation with the reaction conditions led to an increase in yield, so the hydrazone was then modified to avoid the unwanted fragmentation reaction pathway.



Scheme 21. Initial reaction conditions for the multicomponent ring expansion cascade

To circumvent the unwanted Eschenmoser-Tanabe fragmentation reaction, hydrazones lacking a leaving group on the distal nitrogen were investigated. Also, to

maintain the electrophilicity of the AK component an EWG would be incorporated. *o*-NO_2 phenyl hydrazine was selected as our substrate because the nitro group at the *ortho* positioned was suspected to be sufficiently electron withdrawing to maintain electrophilicity, and the *o*-nitro group could also provide higher reactivity in the AK by a through-space electronic interaction between oxygen and nitrogen lone pair. α-epoxy-*N*-(2-nitro)phenyl hydrazone **2.16** was then prepared by condensing (2-nitro)phenyl hydrazide (**2.15**) on to **2.10** (**Scheme 21c**). **2.16** was then added to a solution of phenyl methylacetate and KHMDS in THF at –78 ºC, followed by warming to 0 ºC, which resulted in the formation of the desired product **2.17** in very good yield as a single diastereomer. The relative stereochemistry of **2.17** was established via 1D and 2D NMR studies, including nOe experiments, and was later confirmed by X-ray crystal analysis of the ketone obtained from hydrolysis.

1.2.4 Synthesis of β,γ-anti-β,γ-fused bicyclic γ-lactones

After establishing the ring expansion cascade with respect to **2.11a,** other aryl groups and a heteroaryl group were tested with α-epoxy hydrazone **2.16**, and all were found to give good yields and excellent diastereoselectivities (**Table 1**). All transformations involving the 5-membered α-epoxy hydrazone failed to give an adequate amount of desired product, but the corresponding 7-membered α-epoxy hydrazone successfully underwent the ring expansion cascade, providing the desired α-β-fused bicyclic γ-lactones as single diastereomers and good yield (**2.29, 2.30, and 2.31**).

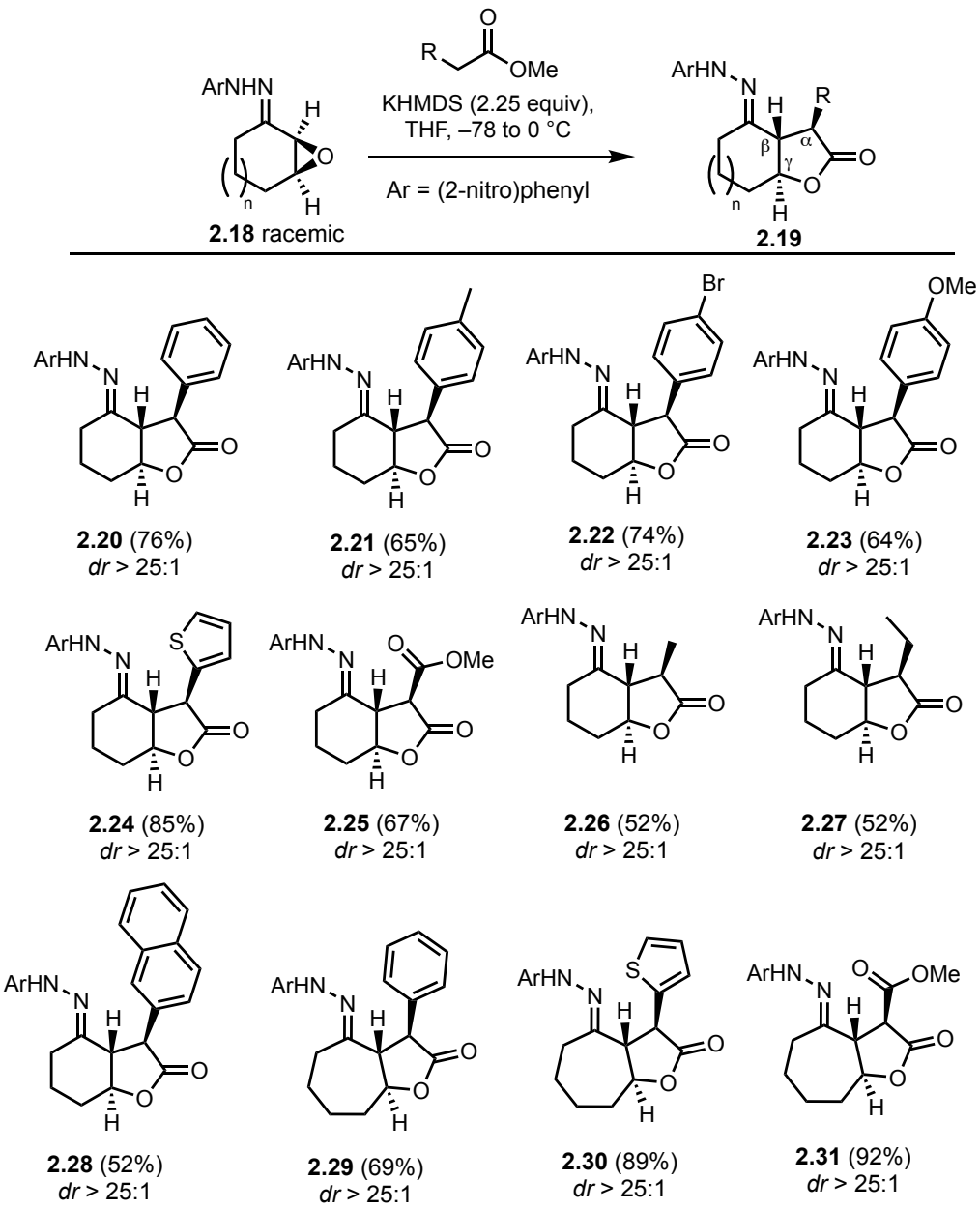
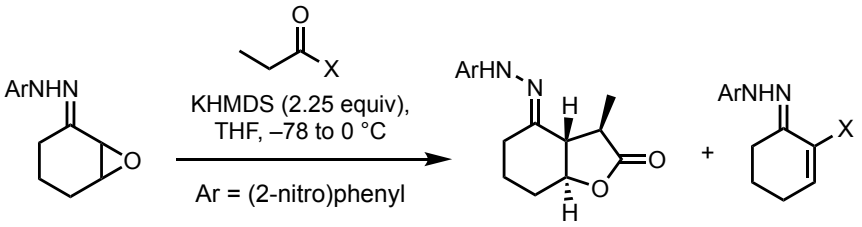


Table 1. **Synthesis of β,γ-*anti*-β,γ-fused bicyclic γ-lactones**

Incorporating alkyl groups into the α-position of the lactone ring using methyl propionate under the same reaction conditions as before failed, as the enolate precursor gave a complex mixture with no visible formation of the desired product (**Table 2**). The utilization of 2-oxazolidinone and pyrrole (**Table 2, entries 2 and 3**) gave the desired γ-lactone in low yield, but with further experimentation using pyrrole propionoate systems

the β,γ-fused bicyclic γ-lactone was eventually produced in 52% yield. This was done by diluting the reaction concentration from 0.06 M to 0.03 M, increasing the amount of KHMDS used to 2.55 equiv, and working up the reaction using CH_2Cl_2 rather than EtOAc. The dilution of the reaction conditions proved pivotal in reducing the amount of Claisen-condensation byproduct.



2.16 racemic **2.32** **2.33**

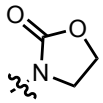
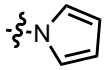
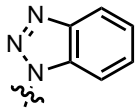
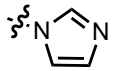
entry	x	Yield of **2.32:2.33**(%)
1	-OMe	complex mixture
2		8:0
3		28:0
4	-SEt	11:78
5		complex mixture
6		complex mixture

Table 2. **Incorporating alkyl groups**

1.2.5 Formation of α-and β-quaternary centers and α-tertiary esters

Our next interest was to explore the ring expansion cascade for the production of heavily substituted γ-lactones. Being slower to form, it was ultimately found that after the addition of the hydrazone to the preformed enolate at –78 °C, warming the reaction to –40 °C for 20 h, and then subsequently warming the reaction to 0 °C the desired γ-lactones

were provided in 51% yield and 8:1 dr at the Cβ-Cγ ring fusion, while maintaining excellent stereoselectivity at the Cα-Cβ bond (>25:1 dr) (**Table 3**).

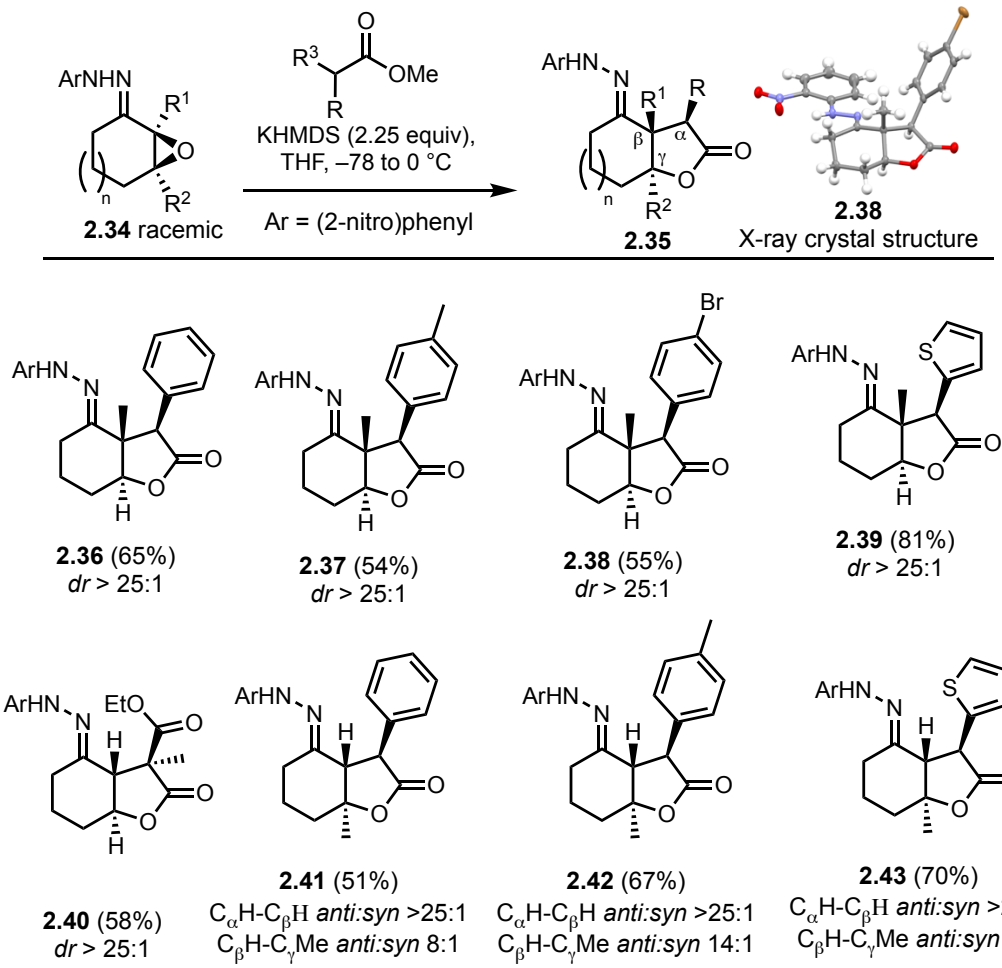
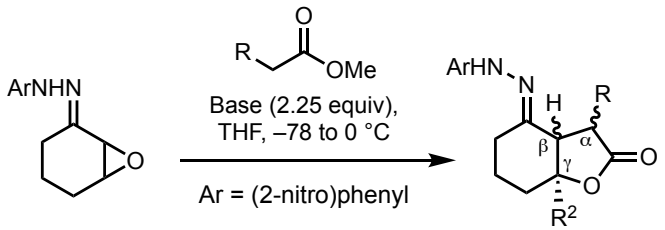


Table 3. **Synthesis of β,γ-fused bicyclic γ-lactones containing α- and β-quaternary center**

1.2.6 Synthesis of β,γ-syn-β,γ-fused bicyclic γ-lactones

While the cascading ring expansion reaction proved successful using KHMDS, other bases were tested (**Table 4**). With the exception of KO*t*-Bu, the desired product was obtained, but the diastereoselectivity varied. Interestingly, the stereochemistry at the ring fusion was altered to favor the *syn*-product with the use of LiHMDS, with the best selectivity being obtained by increasing the reaction temperature and time (**Table 4,**

entry 5). Conditions providing access to *syn*-β,γ-fused bicyclic γ-lactones were further explored using **2.16** and several different aryl methyl esters. Once again, the selectivity outcome of these reactions favored the *syn*-ring fused products, thereby establishing the stereodivergent nature of the ring expansion process.



2.16 racemic **2.44**

entry	base	time (h)	temp (ºC)	CαH-CβH *anti:syn*	CβH-CγH *anti:syn*
1	KHMDS	1	–78 to 0	>25:1	>25:1
2	NaHMDS	1	–78 to 0	>25:1	5:1
3	LDA	1	–78 to 0	>25:1	1:2
4	LiHMDS	1	–78 to 0	>25:1	1:5.5
5	LiHMDS	5	–78 to rt	>25:1	1:6.5
6	KO*t*-Bu	1	–78 to 0	complex mixture obtained	

Table 4. **Effect of the base on the reaction outcome**

Due to the pronounced effect of the base, the procedure was reevaluated with respect to the 5-membered α-epoxy hydrazone, which had previously been unable to cyclize. Thus, a α-epoxy-methyl (2-nitro)phenyl hydrazone was combined with the Li-enolate of phenyl methyl acetate in THF to produce **2.47** as a single diastereomer, but this time the reaction was selective for the *syn*-fused product (**Table 5**). The transformation was tried with different aryl acetic methyl esters and consistently produced only the *syn*-fused diastereomer (**2.47-2.55**).

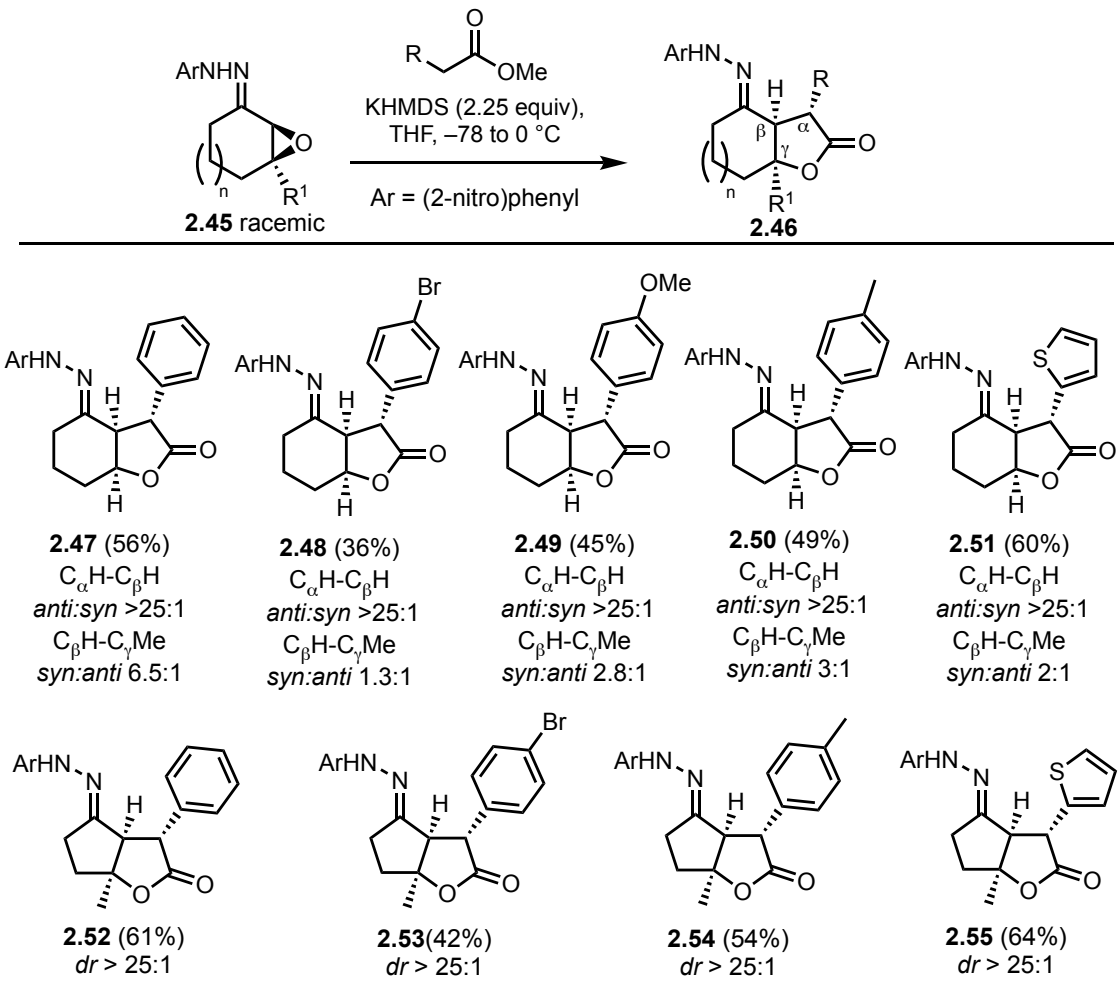


Table 5. **Synthesis of β,γ-*syn*-β,γ-fused bicyclic γ-lactones**

1.2.7 Hydrolysis conditions

Using conditions previously established by the Coltart group to hydrolyze ACC-hydrazones into their corresponding ketones, the β,γ-fused bicyclic γ-lactone hydrazones were hydrolyzed with *p*-TsOH·H_2O in acetone:H_2O (4:1 v/v) at rt.[88] All substrates underwent efficient hydrolysis in good to excellent yield, with no indication of epimerization at any of the stereogenic centers (**Table 6**).

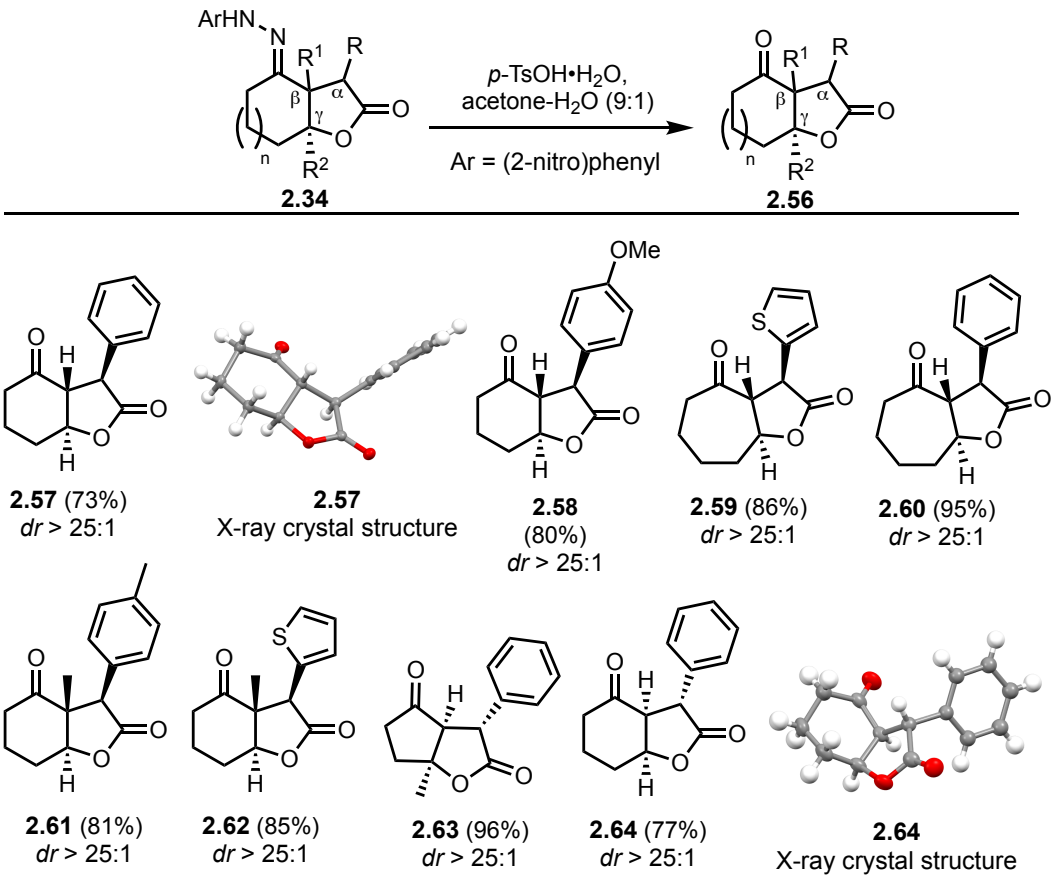
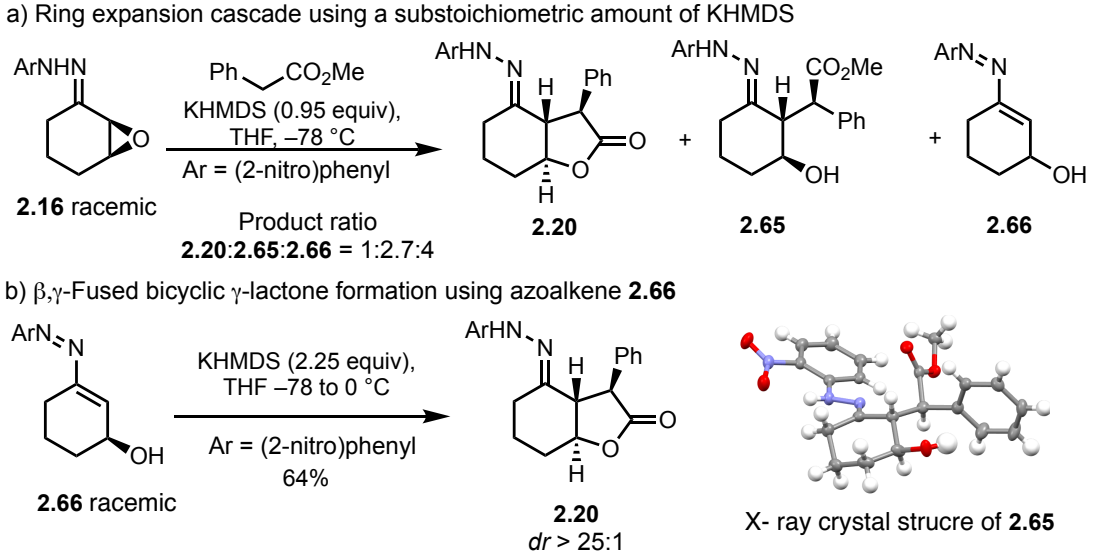


Table 6. **(2-nitro)phenyl hydrazone hydrolysis**

1.2.8 Mechanistic studies

Investigations into the mechanism of the reaction were undertaken. It was suspected that the transformation was proceeding via a 3-alkoxy-1-*N*-(2-nitro)phenyl azopropene intermediate, because the *syn*-fused products form fromed α-methyl-α-epoxy hydrazones would be unlikely to undergo an S_N2 reaction. However, the possibility that the transformation was simply an S_N2 epoxide ring opening[89,90] by the enolate can not be completely ruled out. Nonetheless, to test for the existence of the 3-alkoxy-1-*N*-(2-nitro)phenyl azopropene intermediate, the transformation between **2.16** and enolate was carried out, but this time using only 0.95 equivalents of KHMDS and immediately quenching the reaction following addition of the α-epoxy hydrazone to the enolate

solution (**Scheme 22a**). If the 3-alkoxy-1-*N*-(2-nitro)phenyl azopropene intermediate was being formed in the reaction mixture, then these conditions should lead to its formation without leaving a sufficient amount of the enolate species to fully consume it, thereby allowing the alkoxy azoalkene to be trapped upon rapid quenching. This experiment gave a mixture of **2.20**, **2.65**, and **2.66** in a 1:2.7:4 ratio. The presence of **2.66** in the reaction mixture is a strong indication of the involvement of the 3-alkoxy-1-*N*-(2-nitro)phenyl azopropene in the above reactions. To obtain further evidence for the existence of this intermediate, compound **2.16** was treatment with NaOH. Alcohol **2.66** could be isolated and purified, and it was then added to a solution of the enolate under the standard reaction conditions established above (**Scheme 22b**). This resulted in the exclusive formation of **2.20**, further supporting the intermediacy of the 3-alkoxy-1-*N*-(2-nitro)phenyl azopropene in the ring expansion method.



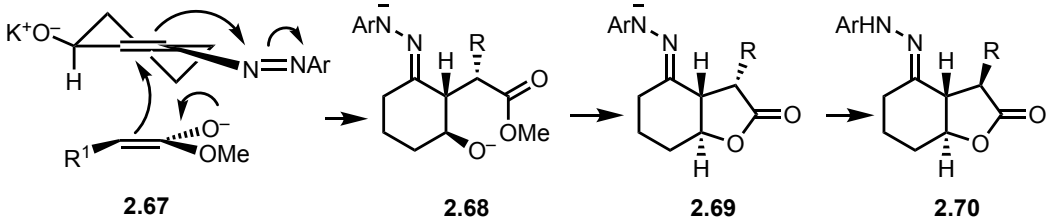
Scheme 22. Mechanistic studies of the ring expansion cascade

With regard to the formation of the *anti*-ring fusion product giving a single diastereomer of the uncyclized product **2.65**, it seems likely that an enolate of a single

geometry adds in a stereoselective manner to the alkoxy azopropene intermediate. This could conceivably occur through the stereoselective kinetic deprotonation to give *E(O)*- or *Z(O)*-enolate, which would then add to the AK in a diastereoselective manner to produce **2.65**.

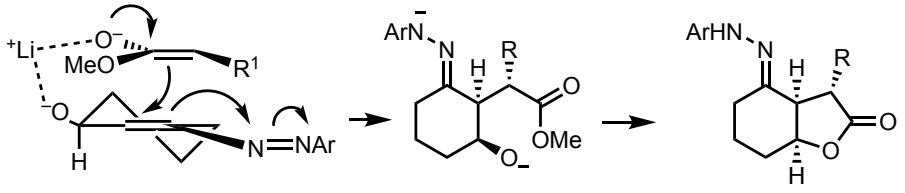
The production of the *anti*-ring fusion suggests opposite face addition would be favored based on the relatively low affinity of the potassium (versus lithium) and oxygen ions – which diminishes the likelihood of a closed transition state – coupled with the relatively large atomic radius of potassium (versus lithium), which would sterically bias the addition (**Scheme 23a**). Dianion **2.68** would then undergo protonation by residual ester and intramolecular *O→O* acyl transfer to produce γ-lactone **2.69**, which would be followed by epimerization at the lactone α-carbon to produce **2.70**, the thermodynamically more stable product.[91]

a) Proposed stereochemical rational for the formation of the *anti*-ring-fused products.



2.67 **2.68** **2.69** **2.70**

b) Proposed stereochemical rational for the formation of the *syn*-ring-fused products.



2.71 **2.72** **2.73**

Scheme 23. Preliminary stereochemical models

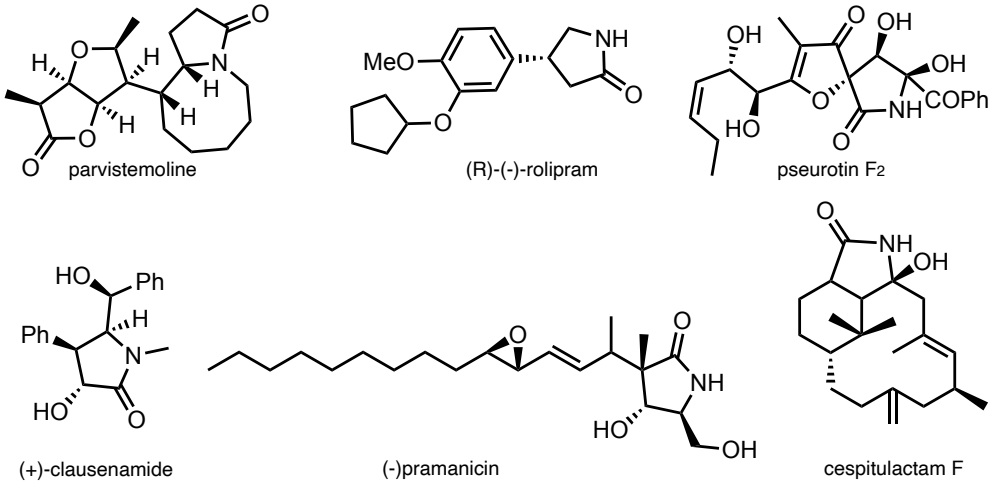
Formation of the *syn*-fused product when LiHMDS is used can be rationalized by a closed transition state in which both the alkoxy function and the enolate

oxygen are coordinated via a lithium ion (**Scheme 23b**). This would be expected to lead preferentially to addition of enolate to the AK from the same face as the alkoxy group, establishing the *syn* relative configuration at what becomes the ring fusion position of the final product (**2.72**), as well as the stereochemistry at what becomes the β-lactone position. Nitrogen protonation and intramolecular $O \rightarrow O$ acyl transfer would then produce γ-lactone **2.73**, directly providing the thermodynamically more stable lactone.[91]

1.3 Synthesis of α,β-fused bicyclic γ-lactams[92]

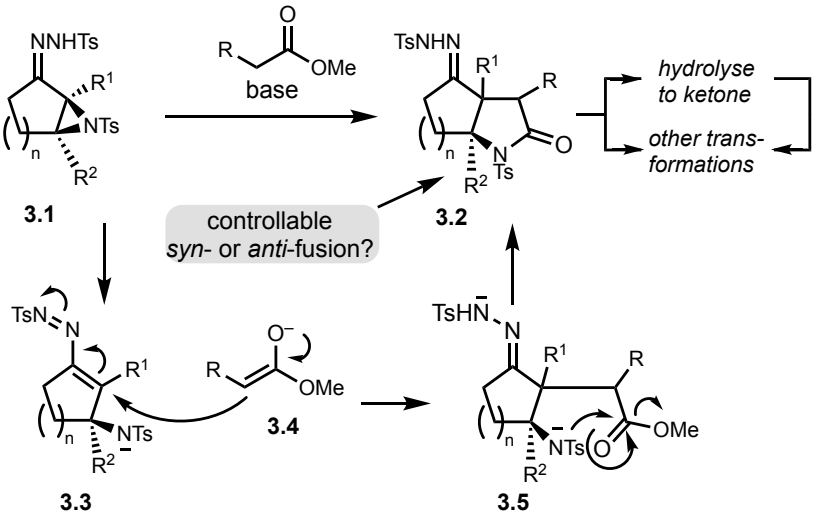
1.3.1 γ-lactams

Nitrogen containing heterocycles makeup 59% of U.S. FDA approved drugs (**Scheme 24**).[72] This has spurred the development of numerous methods to prepare achiral *N*-heterocycles; however, few approaches are available to access more synthetically challenging chiral *N*-heterocycles.[93,94,95,96] In fact, it has been argued that the lack of straightforward and reliable approaches to chiral *N*-heterocycles has led to an undersaturation of heterocyclic drugs. As such, the potential of chiral variants in drug development has yet to be fully developed.



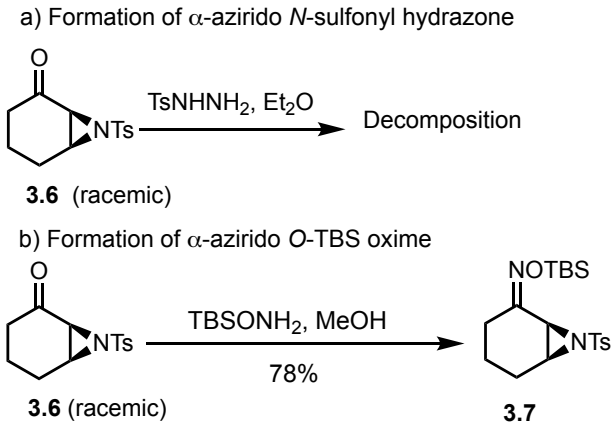
Scheme 24. Examples of lactams in drugs and natural products

1.3.2 Synthesis of α-alkyl-β-amino oximes



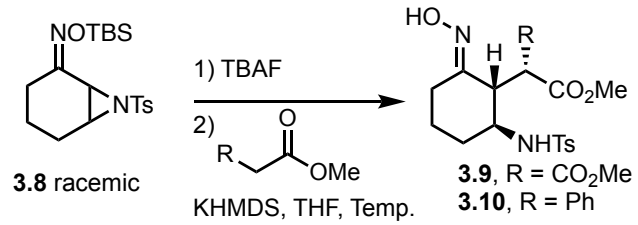
Scheme 25. Proposed mechanism for α-β-fused bicyclic γ-lactam

In an effort to expand on α-epoxy N-sulfonyl hydrazone chemistry, a modification was proposed, in which an aziridine would replaced the epoxide functional group to give α,β-aziridino-*p*-toluenesulfonylhydrazones **3.1** (**Scheme 25**).[83] Considering the previous success with the formation of α-β-fused bicyclic γ-lactones using HAP, this would potentially give us access to both *syn*- and *anti*-α-β-fused bicyclic γ-lactams moiety **3.2**. Similar ring opening would produce a new functional group, not previous reported in literature, in the form of 1-amino-3-azopropene **3.3** (AAP). Nucleophilic addition to AAP with an enolate ester, followed by intramolecular *N→O* acyl transfer would produce a γ-lactam.



Scheme 26. Substrate for multicomponent ring expansion cascade

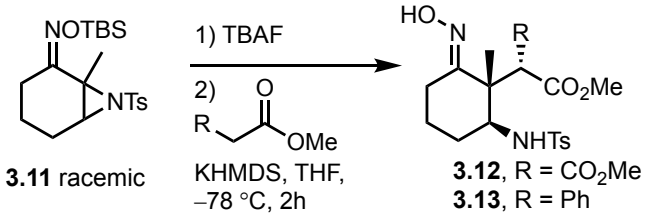
Unable to synthesize an α,β-aziridino-*p*-toluenesulfonylhydrazones **3.1**, as all conditions tried led to decomposition of starting material with no desired product formed. E.J. Corey's use of α,β-epoxyoxime then inspired the combination of α,β-aziridino ketone **3.6** and $TBSONH_2$ in MeOH, for the successful preparation of α,β-aziridino O-silyloxime **3.7** (**Scheme 26**). After surveying reaction conditions, it was found that a solution of **3.7** could be treated with TBAF and enolate at −78 °C. However, no desired γ-lactams was detected by ^1H NMR of the crude material, and only the uncyclized amine was isolated. When methyl phenyl acetate was changed to methyl malonate ester, having two possible sites for intramolecular *N→O* acyl transfer to occur, cyclized was still not observed. Regardless, the α-alkyl-β-amino oxime are still synthetically useful, so further experimentation was conducted. Increasing the equivalence of enolate and maintaining low temperatures throughout the reaction lead to high yield and diastereoselectivity (**Table 7, entry 5**).



entry	R	equiv	temp. (°C)	dr.	yield (%)
1	Ph	2	–78 °C	2:1	82
2	CO_2Me	1.2	–78 °C to 0 °C	>25:1	23
3	CO_2Me	1.2	–78 °C to –40 °C	>25:1	26
4	CO_2Me	1.2	–78 °C	>25:1	53
5	CO_2Me	2	–78 °C	>25:1	77

Table 7. **Synthesis of α-alkyl-β-amino oximes**

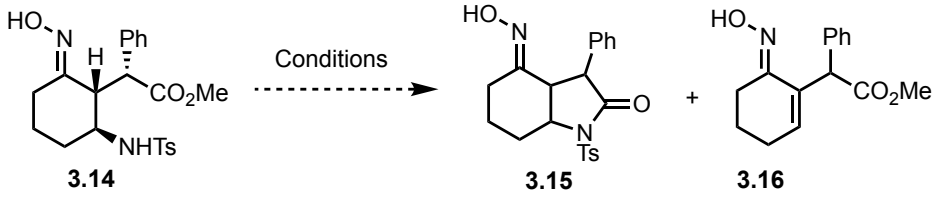
Our methodology is also Conducive for the formation of all carbon α-quaternary center (**Table 8**). After testing several reactions conditions, it was found that the desired product could be made in good yield and diastereoselectivity.



entry	R	conc.	dr.	yield (%)
1	CO_2Me	0.2	>25:1	35
2	CO_2Me	0.7	>25:1	69
3	Ph	0.6	2:1	54

Table 8. **Synthesis of α-alkyl-β-amino oxime containing α-quaternary centers**

After establishing enolate addition, attempts to induce cyclization by modification of **3.14** were carried out. Despite trying numerous reaction conditions for transesterification, amidation, and deprotection of the tosyl groups, the formation of a fused bicyclic γ-lactam from β-amido oximes was unsuccessful. (**Table 9**).

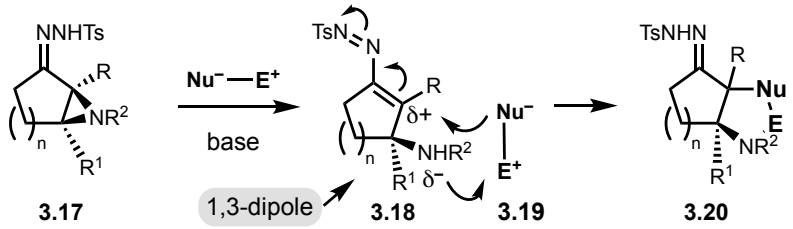


3.14 3.15 3.16

entry	conditions	result
1	NaOMe	Starting material
2	Naphthalene, Li, THF, –78 °C to rt	Decomposition
3	NaOH, 90 °C	**3.16**

Table 9. **Examples of further attempts at cyclization**

1.3.3 Synthesis of β,γ-fused bicyclic γ-lactams

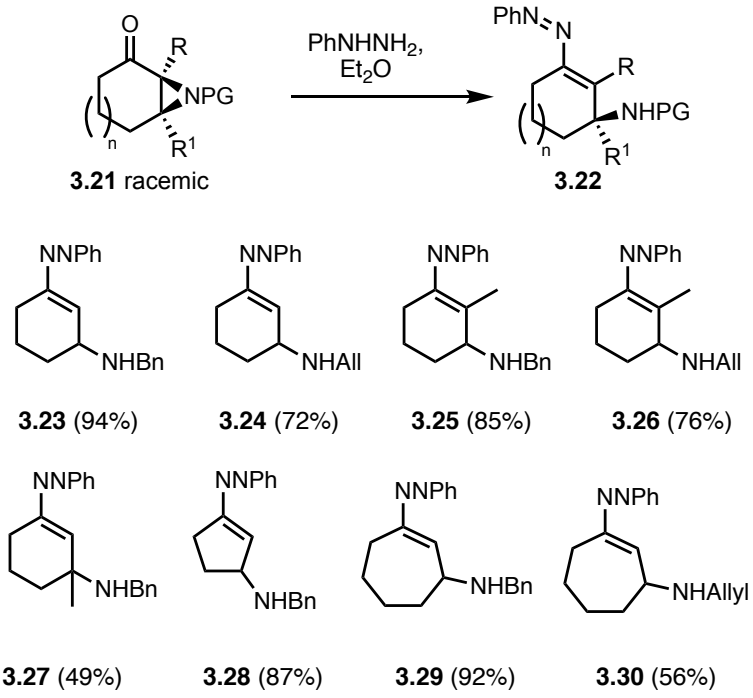


3.17 3.18 3.19 3.20

Scheme 27. New functional group: 3-amino-1-azopropene

With the above knowledge, the AAP substrate were redesigned to have a less electron withdrawing protecting group on the amine, to give it move nucleophilicity upon ring opening of the aziridine (**Scheme 27**). From the mechanistic studies on the synthesis of α-β-fused bicyclic γ-lactones, a HAP was isolated, hinting at the possibility of preparing AAPs and using them for the synthesis of *N*-heterocycles. In fact, it found that the condensation of an α-aziridino ketone with a phenyl hydrazine in Et_2O directly generated AAP without the need for base (**Table 10**). As it was with HAPs, this compound was stable to silica gel chromatography, atmosphere, moisture and it could be heated to reflux in toluene and recovered unaltered. It was also dissolved in a solution with *n*-BuLi followed by an acidic work-up in saturated ammonium chloride, AAP was recovered without decomposition. Both allyl and benzyl protected AAPs of

varying ring sizes and substitution were prepared. All products were stable to silica gel chromatography and gave good yield.



3.21 racemic **3.22**

3.23 (94%) **3.24** (72%) **3.25** (85%) **3.26** (76%)

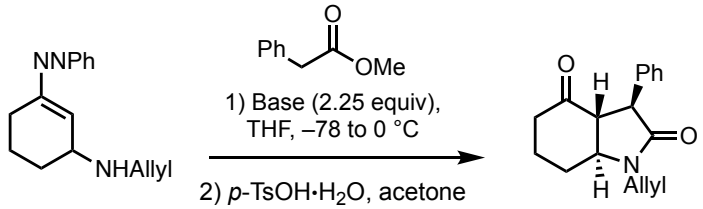
3.27 (49%) **3.28** (87%) **3.29** (92%) **3.30** (56%)

Table 10. **Synthesis of 3-amino-1-azopropene**

1.3.4 Synthesis of β,γ-anti-β,γ-fused bicyclic γ-lactam

For the use of AAP in cyclization KHMDS was first tested in THF –78 °C and gradually warmed to 0 °C over 2 hours. In this case, sterics controlled the stereochemical outcome of the addition of enolate to the face opposite of the amino group as it had for β,γ-*anti*-β,γ-fused bicyclic γ-lactones. A solution of methyl phenyl acetate and KHMDS in THF was added to AAP and the intended β,γ-*anti*-β,γ-fused bicyclic γ-lactam was indeed generated in good yield and with very high diastereoselectivity. Unfortunately, the γ-lactam hydrazones produced were unstable to silica gel purification, in fact, Bozzini has shown that some phenyl hydrazones are unstable and undergo radical based autoxidation process with molecular oxygen.[97,98] Fortunately, immediately hydrolyzing the cyclized

product was possible by using *p*-TsOH in wet acetone to give the corresponding keto β,γ-*anti*-β,γ-fused bicyclic γ-lactams after silica gel purification in good yield and excellent diastereoselectivity (**Table 11, entry 1**). A brief survey of related reaction conditions did not increase yield and the use of lithium bases decreased the diastereoselectivity but did not produce β,γ-*syn*-β,γ-fused bicyclic γ-lactam as the major stereoismer (**Table 11, entries 2-4**).



3.31 **3.32**

entry	base	dr.	yield (%)
1	KHMDS	>25:1	68
2	NaHMDS	>3:1	14
3	LiHMDS	>3:1	16
4	LDA	>3:1	20

Table 11. **Survey reaction conditions for cyclization**

With an approach for β,γ-*anti*-β,γ-fused bicyclic γ-lactams the scope was tested with AAPs of different ring sizes and substitutions. High yields are reported for for most β,γ-*anti*-β,γ-fused bicyclic γ-lactams (**Table 12**). The stereochemistry was established via nOe experiments, and was confirmed in the case of compound **3.35** with an X-ray crystal structure.

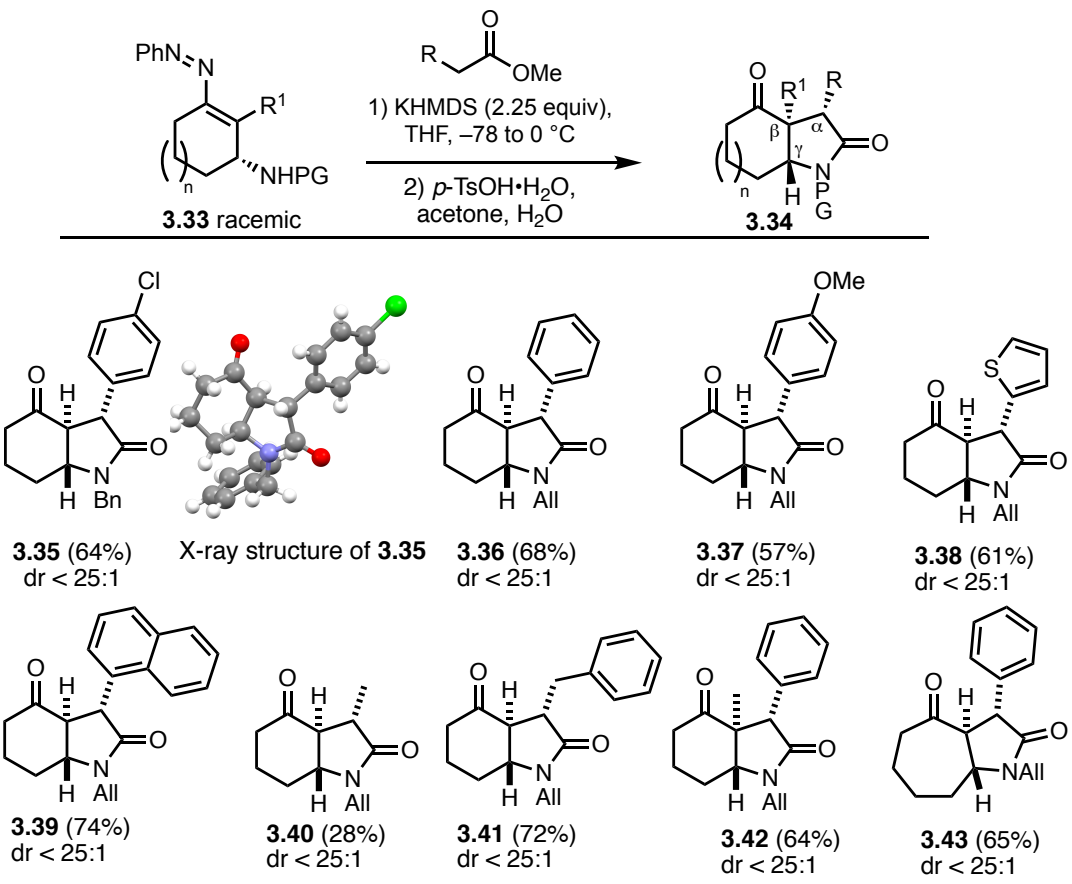


Table 12. **Synthesis of β,γ-*Anti*-β,γ-fused bicyclic γ-lactams**

Having developed a successful approach to β,γ-*anti*-β,γ-fused bicyclic γ-lactams via the intermolecular enolate addition to AAP, and the failure of lithium bases to reverse the stereo outcome of this reaction. To access the corresponding β,γ-*syn*-β,γ-fused bicyclic γ-lactams the order of connectivity was reversed, by forming the amide bond first then using base to induce an intramolecular cyclization reaction.

1.3.5 Synthesis of β,γ-syn-β,γ-fused bicyclic γ-lactam

With AAPs already prepared, reaction parameters for amidation were tested next. It was found that cross coupling could be effectively achieved using a combination of EDCI, HOBt, and Et_3N in CH_2Cl_2 (**Table 13**). Using these conditions

amidoazopropenes **3.45-3.53** were prepared in very good to excellent yield after purified by silica gel chromatography.

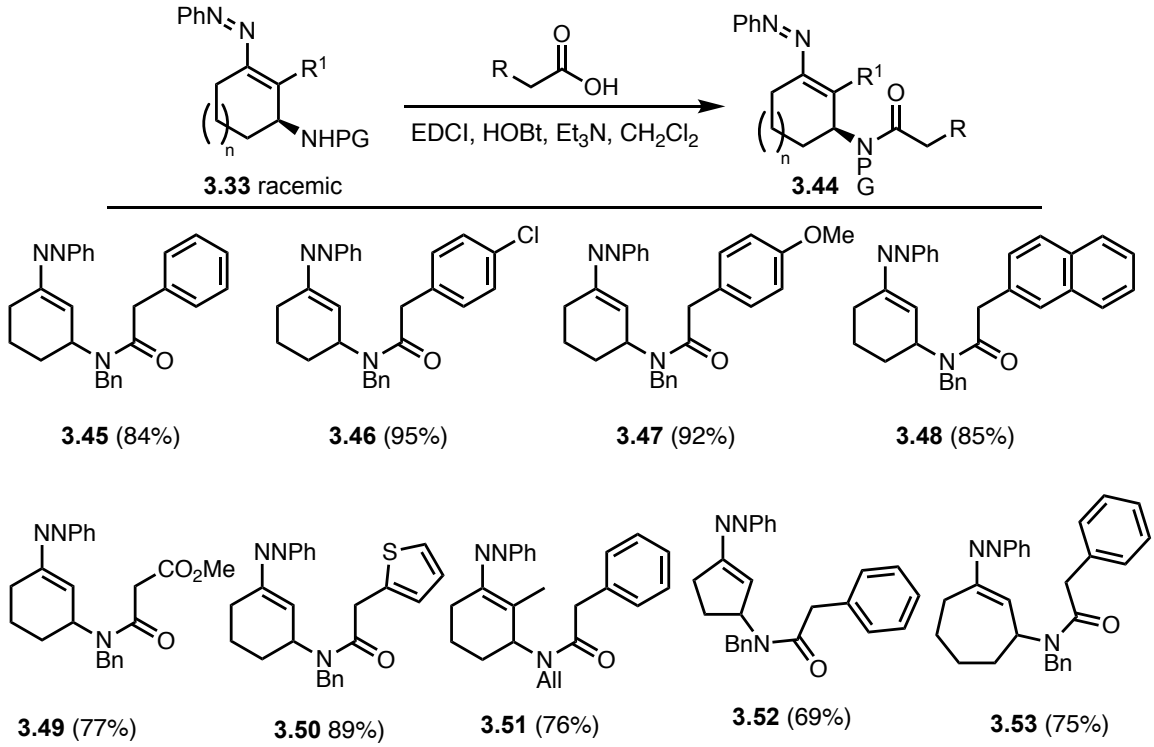
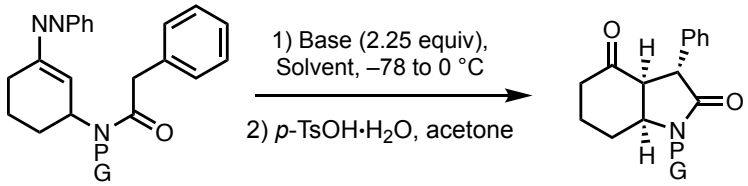


Table 13. **Amidation of 3-amino-1-azopropene**

To test the theory that a stereodivergence synthesis of bicyclic γ-lactams was possible, KHMDS was added to **3.45** in THF at –78 °C, followed by hydrolysis to give the intended β,γ-*anti*-β,γ-fused bicyclic γ-lactam in good yield and with very high diastereoselectivity. A survey of reaction conditions saw no increase in yield (**Table 14**).



3.45 racemic **3.54**

entry	base	solvent	temp. (^{o}C)	dr.	yield (%)
1	KHMDS	THF	–78 ^{o}C – 0 ^{o}C	>25:1	79
2	NaHMDS	THF	–78 ^{o}C – 0 ^{o}C	>25:1	25
3	LiHMDS	THF	–78 ^{o}C – 0 ^{o}C	>25:1	13
4	LDA	THF	–78 ^{o}C – 0 ^{o}C	>25:1	20
5	KHMDS	Et_2O	–78 ^{o}C – 0 ^{o}C	>25:1	10

Table 14. **Survey reaction conditions for cyclization**

All amidoazopropenes reacted to give the desired β,γ-*syn*-β,γ-fused bicyclic γ-lactams in good yield and diastereoselectivity (**Table 15**). The reaction worked with different ring sizes and was able to form quaternary centers. The stereochemistry was established via nOe experiments, and was confirmed in the case of compound **3.60** with an X-ray crystal structure.

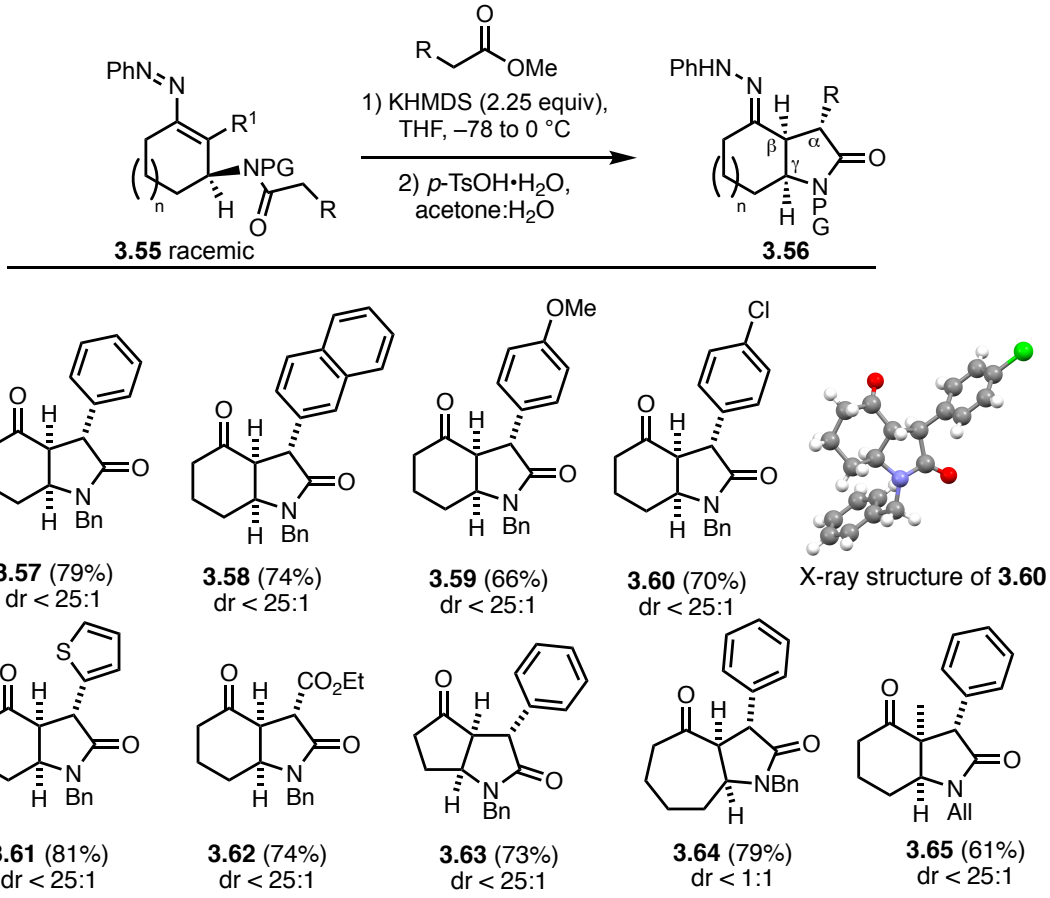


Table 15. **Synthesis of β,γ-*syn*-β,γ-fused bicyclic γ-lactams**

By simply changing the mode of addition of enolates from inter to intramolecular addition a stereodivergent strategy was established for both *syn*- and *anti*-β,γ-fused bicyclic γ-lactams.

1.3.6 Substrate scope of hydroxy- and amino-azopropenes

AK's physical properties and stabilities can also be altered by EWG or EDG on the distal nitrogen. The formation of HAPs and AAPs was then studied in relationship to the EWGs and EDGs in their aromatic ring. Several cyclic HAPs and AAPs were prepared with moderate to good yields (**Table 16**). In the case of HAP **3.69**, the hydrazone form was was preffered over the AK. Excitingly for HAP **3.71** and AAP **3.82** X-ray crystal structures were obtained.

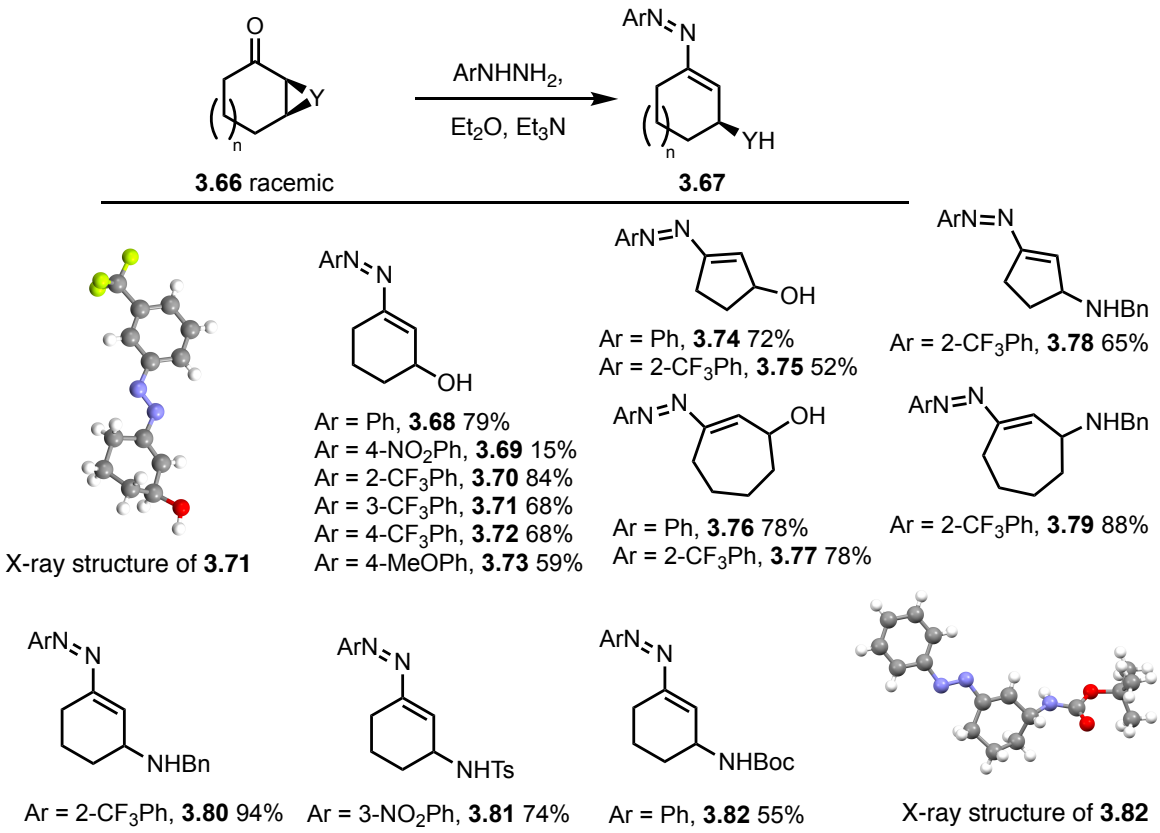


Table 16. **Scope of hydroxy- and amino-azopropenes**

Next acyclic HAPs and AAPs were prepared, but yields were obstructed by the formation of pyrazole **3.85**, which was preferred in some cases (**Table 17**). No pyrazole was observed with **3.95** or **3.97** and in cases where R = Ph, no acycle HAP or AAP was detected in the NMR of the crude material, only pyrazole was formed. Attempts to crystallize acycle HAPs and AAPs have been unsuccessful.

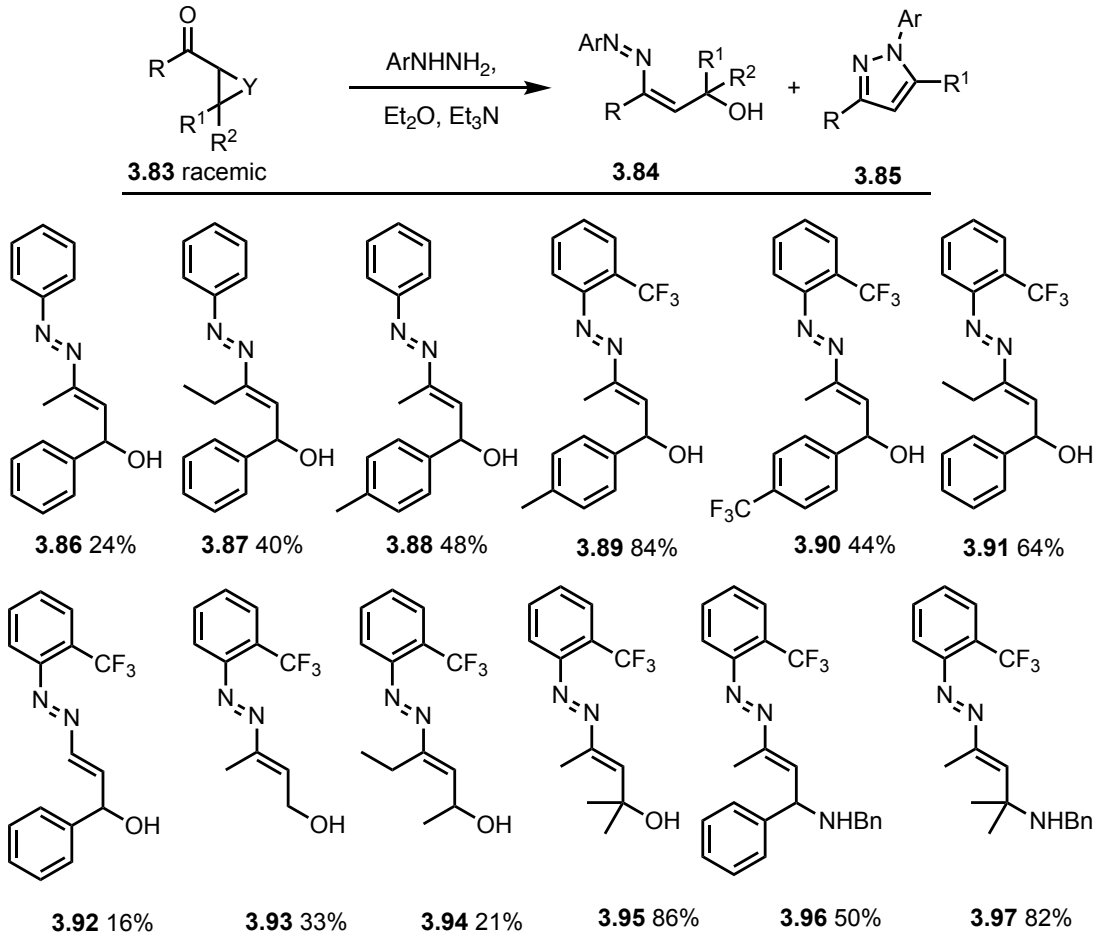
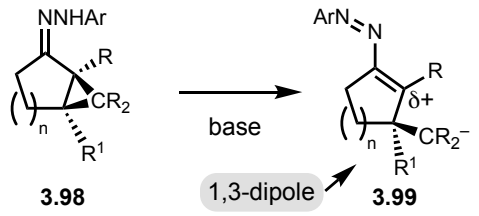


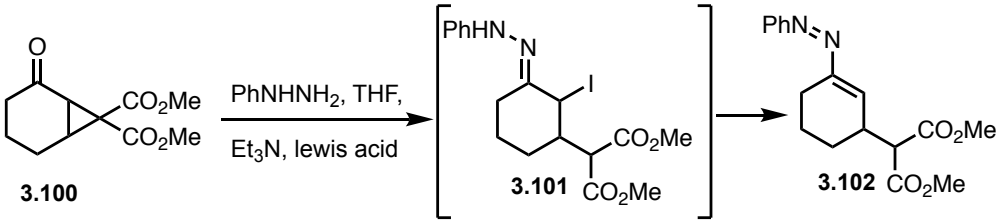
Table 17. **Scope of acyclic hydroxy- and amino-azopropenes**

The synthetic equivalent of 1,3-carbodipoles still remains a challenging problem in organic synthesis (**Scheme 28**).[99] In general donor–acceptor cyclopropanes can fill this role with defined reactivity in [3+n] cycloadditions to form various saturated compounds.[100] This system provides one of the most rational and straightforward synthetic routes to cyclopentane, an ubiquitous core scaffolds in numerous bioactive compounds including drugs, via a [3+2] cycloaddition with a C–C double or triple bonds.[101,102,103] This reactivity also provides possibilities for the development of a general strategy for the synthesis of diverse heterocycles. This approach has been successfully utilized to preparing five-, six-, and seven- membered rings.[104,105,106]



Scheme 28. 3-carbo-1-azopropenes

Our chemistry allows for the formation of 3-carbo-1-azopropenes (CAP). However, the simple combinations of base, substrate, hydrazine and lewis acid were unable to form CAPs cleanly. Moderate success has only been achieved using a combination of base and a lewis acid that also contains a nucleophilic halide (**Table 18**).[107] It's purpose that the formation of CAP progresses through intermediate **3.101.** Currently, studies are underway to use CAPs as a 1,3 dipole in cyclization reaction.



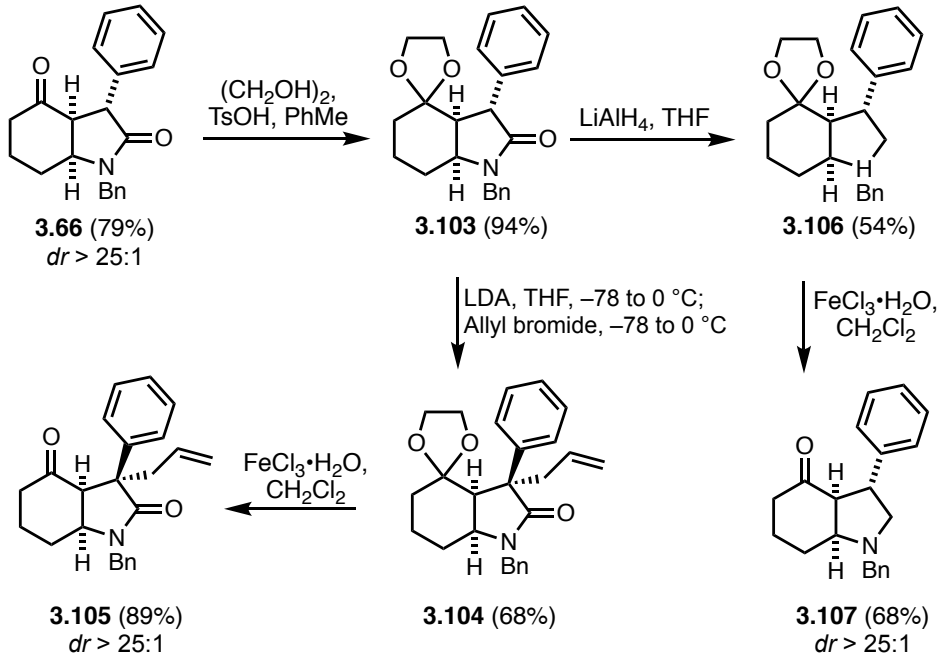
entry	lewis acid	yield (%)
1	MgI_2	71
2	$Cu(OTf)_2$	42
3	$AlCl_3$	26
4	$BF_3{\cdot}Et_2O$	21

Table 18. **Survey reaction conditions for 3-carbo-1-azopropenes.**

1.3.7 Synthetic utility and other reactions

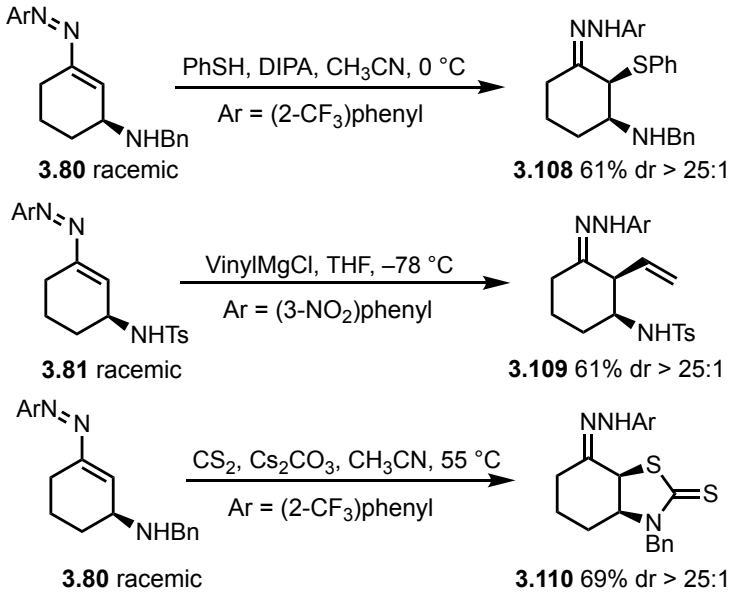
As a preliminary demonstration of further synthetic utility, the keto lactams **3.66** was converted into its corresponding acetal upon treatment with ethylene glycol (**Scheme 29**). **3.103** was then allylated With LDA and allyl bromide to give **3.104**, or in another intense **3.66** was reduced using $LiAlH_4$ in THF to give a pyrrolidine **3.106**,

another biologically relevant core. Both products were followed by deprotection with $FeCl_3$ hydrate in CH_2Cl_2.



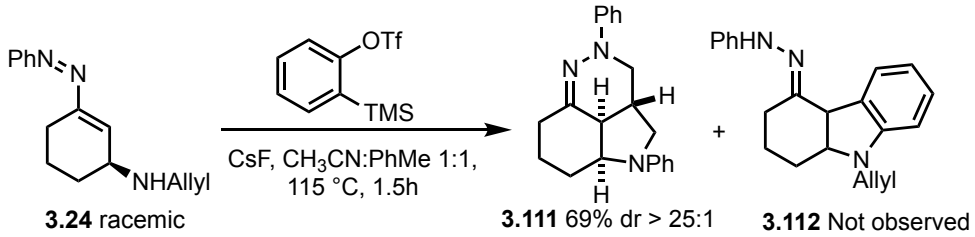
Scheme 29. Synthetic utility of keto lactams

Next AAPs were tested with benzenethiolate to give **2.108**, vinyl Grignard to produce **2.109**, and carbon disulfide for the cyclized product **2.110**, all with high diastereoselectivity and good yields, further demonstrating the synthetic potential of AAPs (**Scheme 30**).



Scheme 30. Reactivity of 3-amino-1-azopropenes

Serendipitously, while reacting AAP with an *in situ* formed benzyne, nucleophilic addition was not preceded by the proposed cascade cyclization to form **3.112**, but instead an inverse electron-demand aza-Diels–Alder reaction with the allylic protecting group proceeded to give **3.111** (**Scheme 31**). This inspired a novel annulation strategy of utilizing the 4 π system of the AK for the formation of saturated *O*- and *N*-heterocycles (see next section).

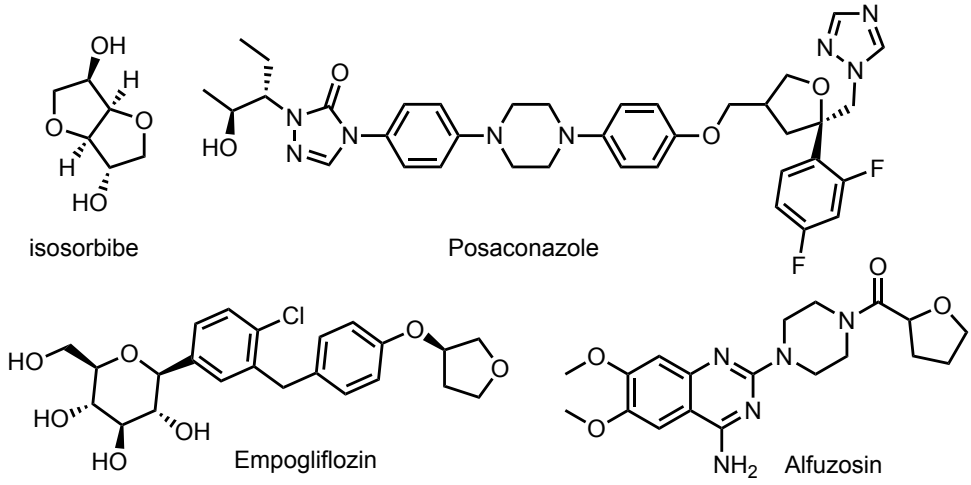


Scheme 31. [4+2] Cyclization of amino-azopropene

1.4 The stereocontrolled synthesis of tetrahydrofurans and pyrrolidines[108]

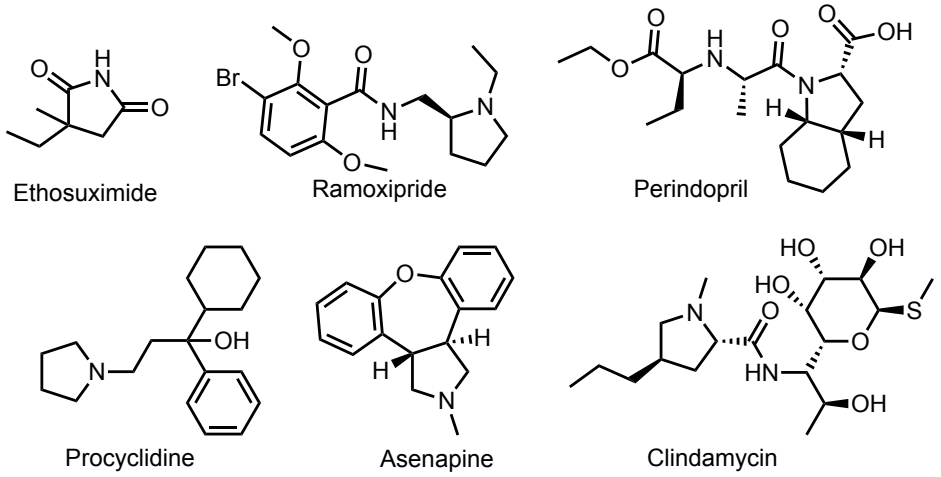
1.4.1 Tetrahydrofurans and pyrrolidines

O-heterocycles are the second most common type of heterocycles that appear in approved pharmaceuticals.[74] Tetrahydrofuran-containing drugs are prescribed as treatments for various diseases including cardiovascular, cancer, antifungal, diabetes, urinary, and HIV infections.[109,110,111,112] Only 13 tetrahydrofuran-containing drugs are currently on the market, all contain at least one stereocenter. A number of synthetic approaches to substituted THFs have been reported, along with their application to natural product targets containing these structures.[113] However, the majority of these strategies concern the construction of di- and trisubstituted furans with relatively few focused on the synthesis of tetrasubstituted tetrahydrofurans.[114] Tetrasubstituted tetrahydrofurans, often with multiple stereogenic centers, are commonly encountered as structural core units in various natural products displaying a broad spectrum of biological activities.[115]



Scheme 32. Examples of tetrahydrofurans in drugs

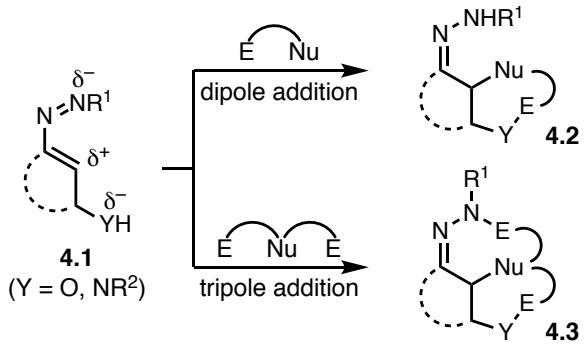
Conversely, pyrrolidines are the most represented nonaromatic *N*-heterocyclic core, with 37 drugs currently in market.[73] Tetrasubstituted-pyrrolidines are underrepresented, with disubstitution being the most dominant pattern observed. The natural proline core is a commonly employed pyrrolidine structural fragment.[116,117,118,119] Efficient methods for the synthesis of tetrasubstituted heterocycles would go a long way to breaking our dependency on chiral pools.



Scheme 33. Examples of pyrrolidines in drugs

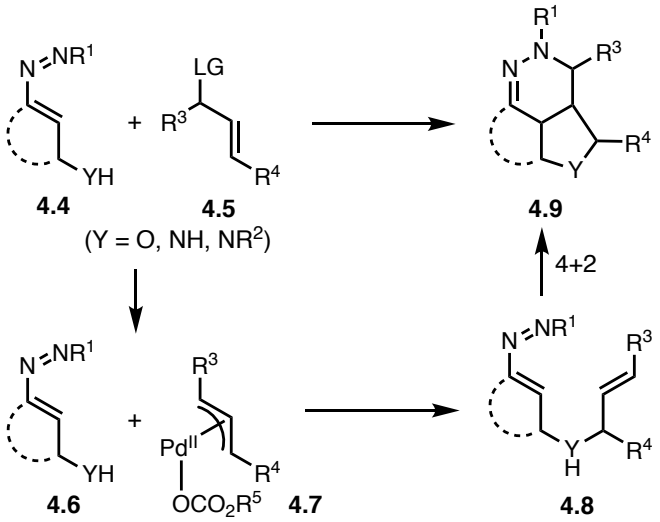
1.4.2 Tsuji-Trost allylation [4+2] cycloaddition

As mentioned above, AKs are heterodienes capable of various [4+1], [4+2], and [4+3] reactions to generate *N*-heterocycles. As part of our continuing efforts to develop new reactions for the formation of saturated heterocycles, the conjugated π systems of AK in HAPs and AAPs was utilized in a [4+2] cyclization reaction in order to achieve ring closure (**Scheme 34**). The introduction of the dienophile could be achieved through a simple S_N2 allylation, where the nucleophile is the hydroxyl group of the HAP or the amino group of the AAP. The products of the following [4+2] cycloaddition reaction would be a fused furan-tetrahydropyridazine derivative, or pyrrolidine-tetrahydropyridazine derivative for AAP systems, both biologically relevant cores.



Scheme 34. 1,3-dipolar and 1,3,6-tripolar reactivity

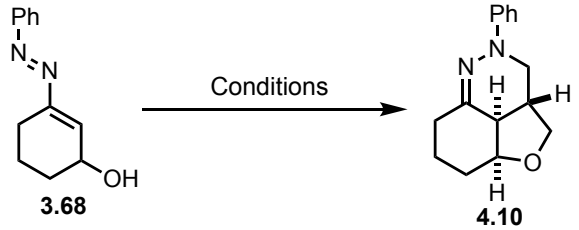
Initial attempts to perform a S_N2 displacement on an allyl bromide were unsuccessful. Fortunately, the Tsuji-Trost could also grant access to these highly functionalized tetrahydrofurans and pyrrolidines (**Scheme 35**).[120] In this transformation, again, the hydroxyl group of the HAP or amino group of the AAP would serve as the nucleophile in a Tsuji-Trost reaction, giving rise to an allyl ether or allyl amine, respectively, *in situ* that would then undergo a [4+2] addition with the AK moiety.[121,122,123124,125,126,127,128,129,130,131] The use of cyclic HAPs/AAPs would produce tricyclic tetrahydrofurans/pyrrolidines, whereas the use of acyclic ones would give rise to the corresponding bicyclic products. Interestingly, as mentioned above, not only are the tetrahydrofuran and pyrrolidine motifs in these multicyclic products highly valuable, but the six-membered cyclic hydrazones that are generated are also important, as they are widely represented among biologically active compounds.[132,133,134,135,136,137]



Scheme 35. Mechanism for the Tsuji-Trost allylation [4+2] cycloaddition

1.4.3 Synthesis of tetrahydrofurans

Initial studies using HAP **3.68** and diallyl carbonate, in combination with $Pd_2(dba)_3$ (5 mol%) and Xantphos (10 mol%) in toluene at 100 ºC found the predicted product **4.10** as a single diastereomer (**Table 19, entry 1**). The stereochemistry of **4.10** was established using standard 1D and 2D NMR techniques, and correlated to crystal structures from a previous transformation (**Scheme 28**). The stereochemistry is consistent with the alkene component of allyl alcohol intermediated undergoing a [4+2] addition to the AK from the same face of the cyclohexene ring as the oxygen atom. A survey of the reactions conditions was conducted to improve on the initial result (**Table 18, entries 2-14**). Best results have been achieved use $Pd(OAc)_2$ (2.5 mol%) and racemic (±)-BINAP (5 mol%) in toluene to give **4.10** as a single diastereomer in 86% yield.



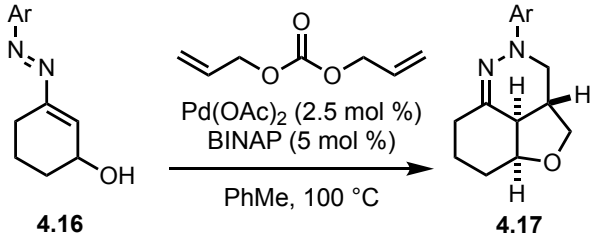
3.68 **4.10**

entry	HAP	HAP:diallyl carbonate	Pd species (mol %)	ligand (mol %)	solvent	product	isolated yield (%)
1	**3.68**	1 : 2.2	$Pd_2(dba)_3$	Xantphos (10)	PhMe	**4.10**	55
2	**3.68**	1 : 2.2	$Pd_2(dba)_3$ (5)	dppf (10)	PhMe	**4.10**	41
3	**3.68**	1 : 2.2	$Pd_2(dba)_3$ (5)	(±)-BINAP	PhMe	**4.10**	67
4	**3.68**	1 : 2.2	$Pd_2(dba)_3$ (5)	dppcy (10)	PhMe	**4.10**	52
5	**3.68**	1 : 2.2	$Pd_2(dba)_3$ (5)	Xphos (10)	PhMe	**4.10**	45
6	**3.68**	1 : 2.2	$Pd_2(dba)_3$ (5)	dppe (10)	PhMe	**4.10**	47
7	**3.68**	1 : 2.2	$Pd_2(dba)_3$ (5)	PCy_3 (10)	PhMe	n.a.†	n.r. ‡
8	**3.68**	1 : 2.2	$Pd_2(dba)_3$ (5)	PPh_3 (10)	PhMe	**4.10**	55
9	**3.68**	1 : 2.2	$Pd(OAc)_2$	(±)-BINAP	PhMe	**4.10**	74
10	**3.68**	1 : 1.7	$Pd(OAc)_2$	(±)-BINAP	PhMe	**4.10**	88
11	**3.68**	1 : 1.7	$Pd(OAc)_2$	(±)-BINAP (5)	PhMe	**4.10**	86
12	**3.68**	1 : 1.7	$Pd(OAc)_2$	(±)-BINAP(5)	dioxane	**4.10**	47
13	**3.68**	1 : 1.7	$Pd(OAc)_2$	(±)-BINAP (5)	1,2-	n.a.†	n.r. ‡
14	**3.68**	1 : 1.7	None	None	PhMe	n.a.†	n.r. ‡

* = 1,2-dichloroethane; † n.a. = not applicable; ‡ n.r. = no reaction

Table 19. **Screening conditions for the cascading Tsuji-Trost allylation [4+2] cycloaddition**

These conditions were also tried using different HAPs **3.69-3.73** (**Table 20**). In all cases the desired product was observed by ^{1}H NMR of the crude material, however, attempts to isolate **4.11**, **4.14**, and **4.15** by silica gel chromatography were unsuccessful and caused the desired products to decompose. Again, this may have been due to radical-based auto oxidation with molecular oxygen, although this has not been confirmed.[97,98]



4.16 **4.17**

entry	HAP	Ar	product	yield (%)
1	**3.68**	Ph	**4.11**	55
2	**3.69**	(4-NO_2)C_6H_4	**4.12**	dec.
3	**3.70**	(2-CF_3)C_6H_4	**4.13**	78
4	**3.71**	(3-CF_3)C_6H_4	**4.14**	dec.
5	**3.72**	(4-CF_3)C_6H_4	**4.15**	dec.
6	**3.73**	(4-OMe)C_6H_4	**4.18**	71

Table 20. **Screening hydroxy azoalkenes for the cascading Tsuji-Trost allylation [4+2] cycloaddition**

With suitable conditions established the scope of HAPs with varying ring sizes and different substituted allylic carbonates were tested (Table). The products from the substituted allylic carbonates have greater structurally complexity, so for the remainder of our studies HAP **3.70** was used because they would provide the option of conducting ^{19}F NMR should it be needed in determining diastereomer ratios. Many aryl allyl *t*-butyl carbonates, including heteroaryls, underwent the Tsuji-Trost allylation [4+2], and in all cases the four contiguous stereogenic centers where obtain in high diastereoselectivity. The relative stereochemistry of the products was determined by 1D and 2D nOe NMR, and confirmed by X-ray crystal structure obtained for compound **4.26**. In each case, the stereochemical outcome of the reaction was consistent with the Tsuji-Trost allylation reaction producing an *E*-olefin that then underwent the [4+2] addition to the AK from the same face as the oxygen atom.

1.4.4 Scope of tetrahydrofurans and pyrrolidines

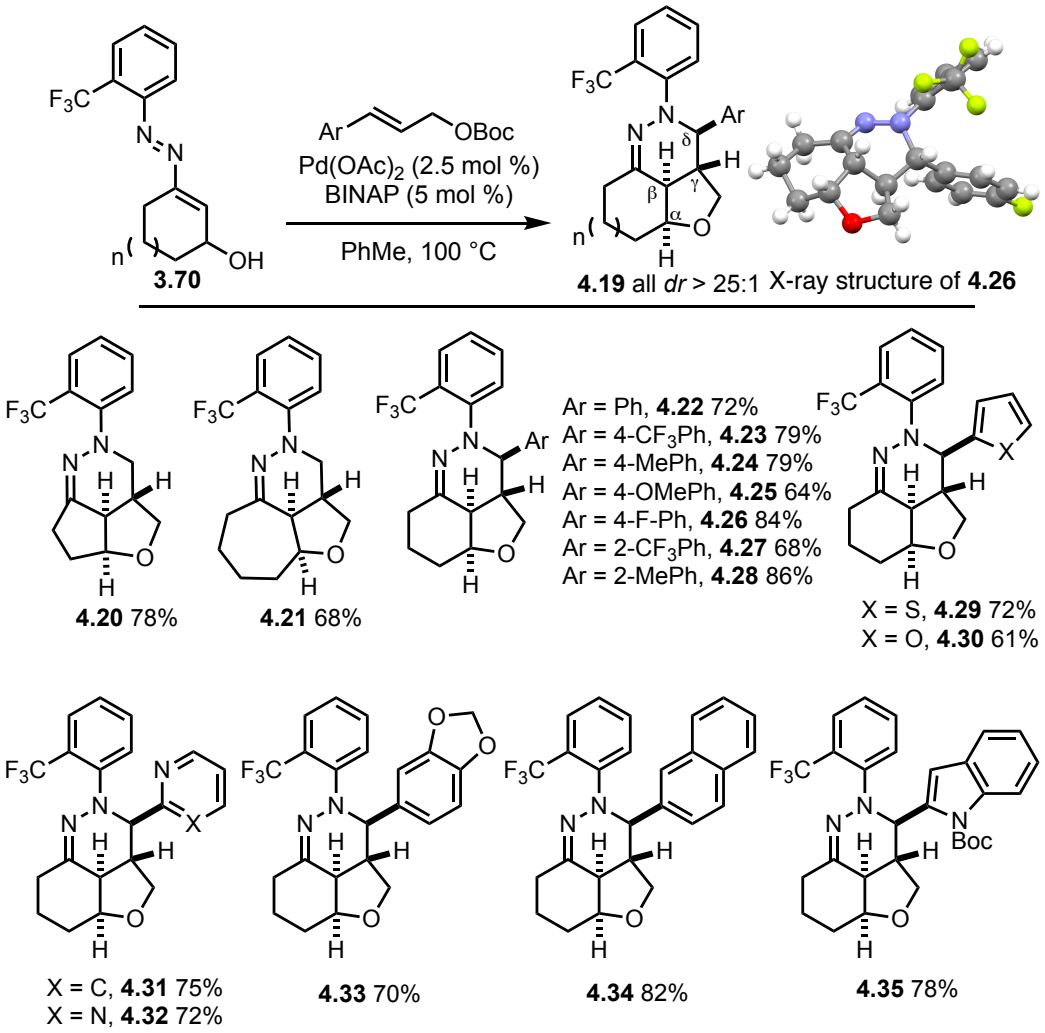
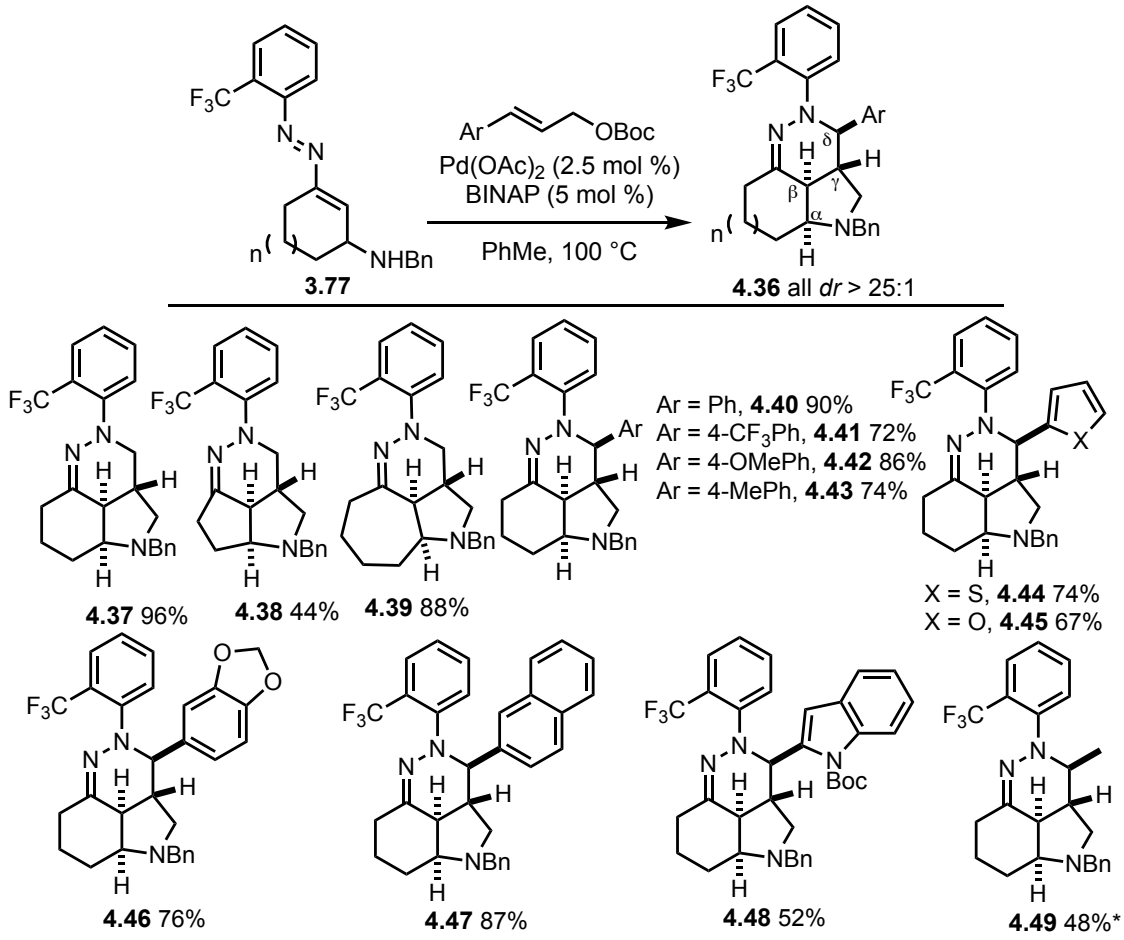


Table 21. **Scope of hydroxy azoalkene in Tsuji-Trost [4+2] cycloaddition**

The corresponding benzyl protected AAPs were examined under the same reaction conditions and it was found that it produced **4.36** in moderate to excellent yield and in all case as a single diastereomer. The incorporation of electron rich, electron deficient phenyl groups and heteroaryl where tolerated. To introduce a methyl group, conditions where screened and $[Pd(allyl)Cl]_2$ (2.5 mol%) and (±)-BINAP (5 mol%) in THF at 65 °C was found to be affective.



* $[Pd(allyl)Cl]_2$ (2.5 mol %), BINAP (5 mol %), THF, 65 °C

Table 22. **Scope of amino azoalkene in Tsuji-Trost [4+2] cycloaddition**

1.4.5 Tsuji-Trost allylation [4+2] cycloaddition of acyclic hydroxy and amino azopropenes

Acyclic HAP and AAP systems also underwent the cascading [4+2] cycloaddition with moderate yield and as a single diastereomer. The stereochemical outcome was determined using 1D and 2D nOe NMR techniques, and confirmed by X-ray crystal structure obtained for compound **4.55**.

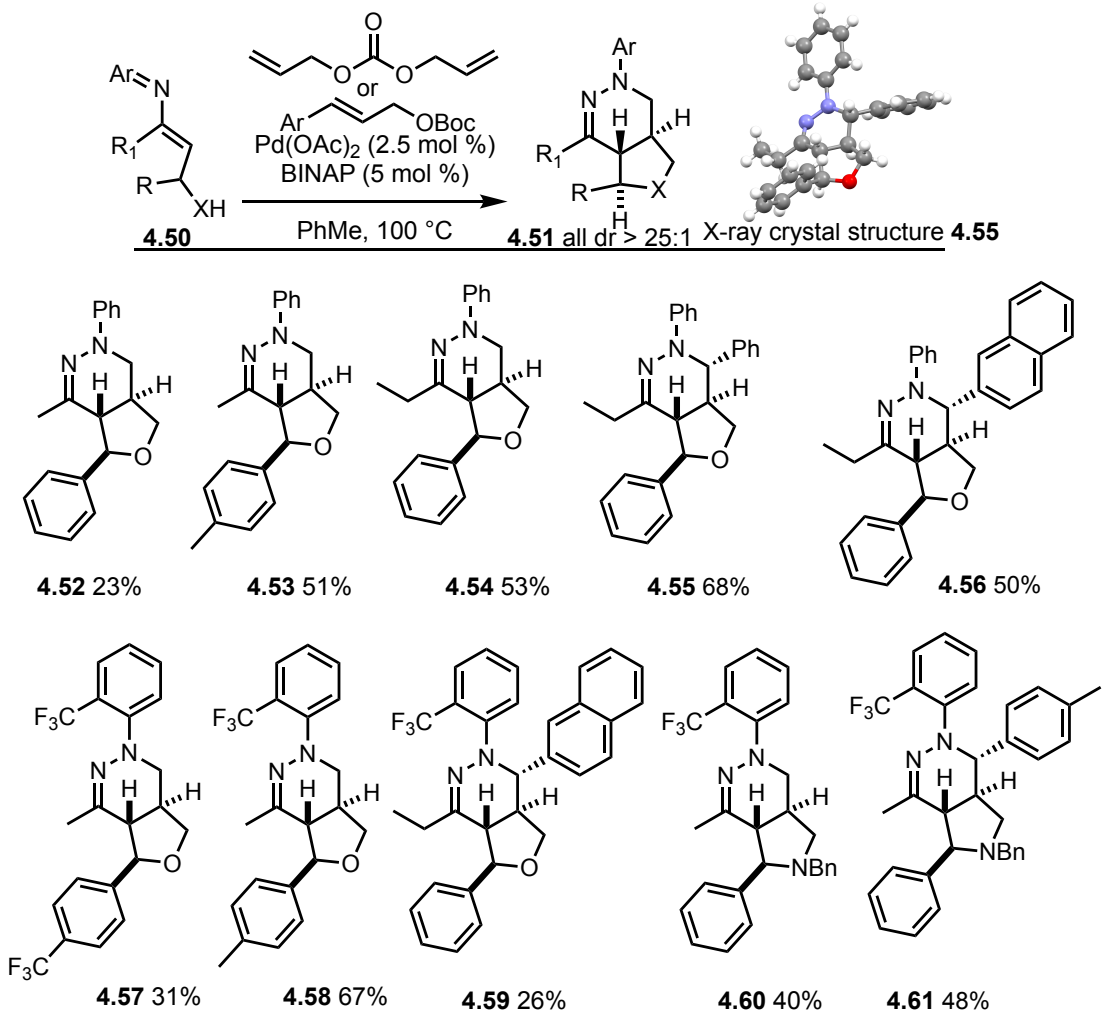
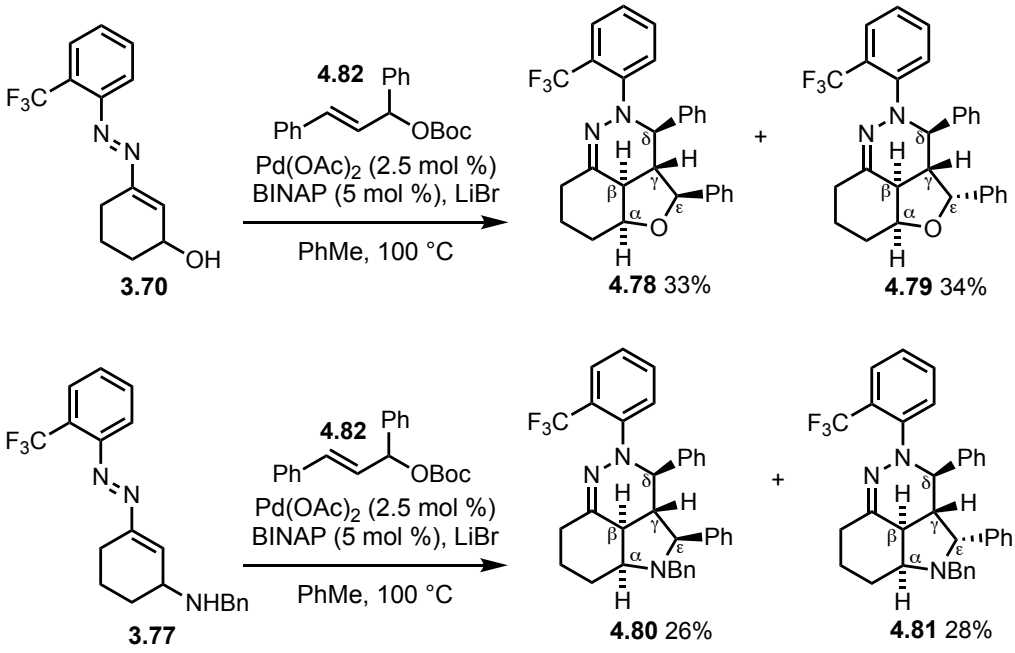


Table 23. **Scope of acyclic systems in Tsuji-Trost [4+2] cycloaddition**

1.4.6 Synthetic utility and other reactions

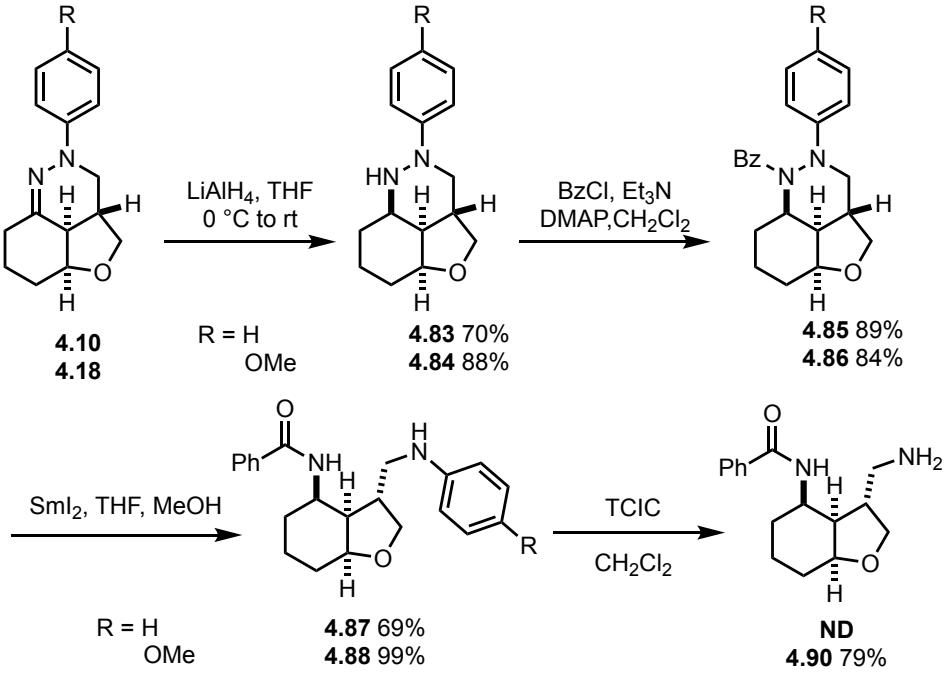
A Tsuji-Trost allylation [4+2] cycloaddition reaction was attempted using an allyl *t*-butyl carbonate having two phenyl substituents. Initial conditions did not work, but the trivial modification of adding LiBr gave the desired product in 1:1 mixture of diastereomers. The formation of three new bonds and four new stereogenic centers during this reaction surpasses the venerable Diels-Alder reaction, in which two new bonds and up to four new stereogenic centers can be formed.[138] The stereochemistry of the products were

established via 1D and 2D NMR techniques. While the stereochemistry at C-ε position has yet to be control, the use a chiral nonracemic ligand could facilitate better selectivity.



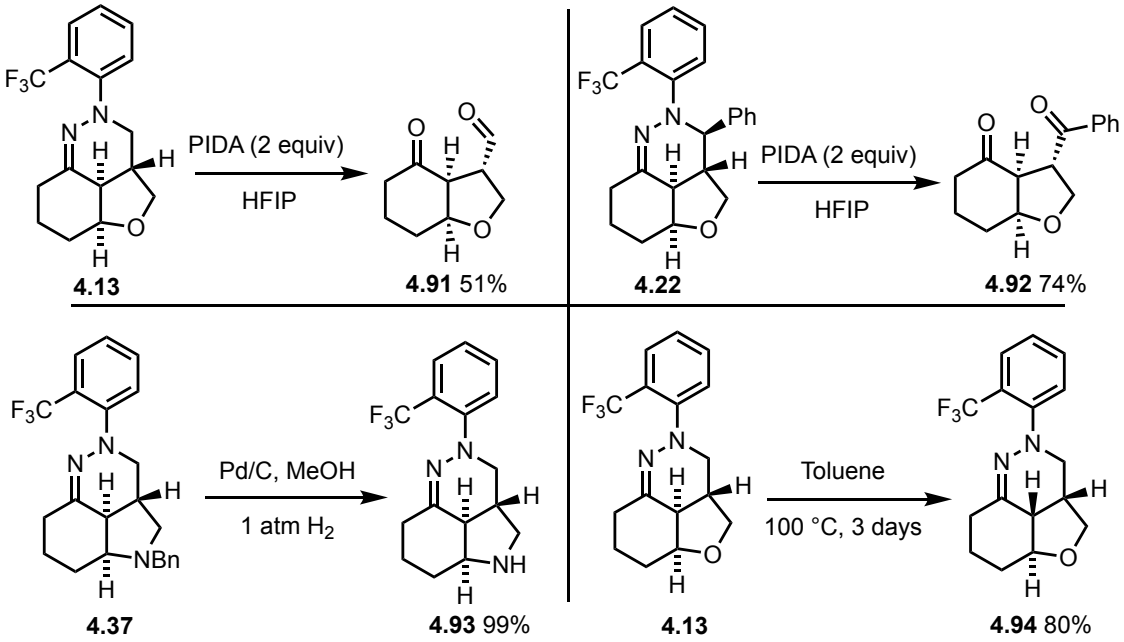
Scheme 36. Synthetic utility of keto lactams

To exhibit the synthetic utility of the Tsuji-Trost allylation [4+2] cycloaddition products, the nitrogen–nitrogen bond of the cyclic hydrazone was cleaved. This was achieved by treating **4.10** or **4.18** with $LiAlH_4$ to give the corresponding diamine, which was then benzoylated to produce **4.85** or **4.86** (respectfully) as a single diastereomer. The nitrogen–nitrogen bond then cleaved using SmI_2 to give **4.87** or **4.88** (respectfully). **4.88**, substituted with 4-OMe-phenyl could then be oxidative cleaved by treatment with trichloroisocyanuric acid (TCICA) into **4.90**, a primary amine and an amide, with the orthogonally differentiated amines poised for further reaction.[139]



Scheme 37. Synthetic utility of keto lactams

The oxidation of cyclic hydrazone was made possible by treatment of **4.13** with (diacetoxyiodo)benzene in hexafluoroisopropanol (HFIP) to produce the keto-aldehyde **4.91** in 51% yield.[140] In a similar fashion reaction of **4.22** gave diketone **4.92** in 74% yield. Hydrogenolysis of **4.37** was carried out in essentially quantitative yield to give secondary amine **4.93**. Lastly, it was found that epimerize the center α-to the hydrazone of **4.94** was possible by simply heating it at 100 ºC in toluene, providing a simple modification for stereodivergence.

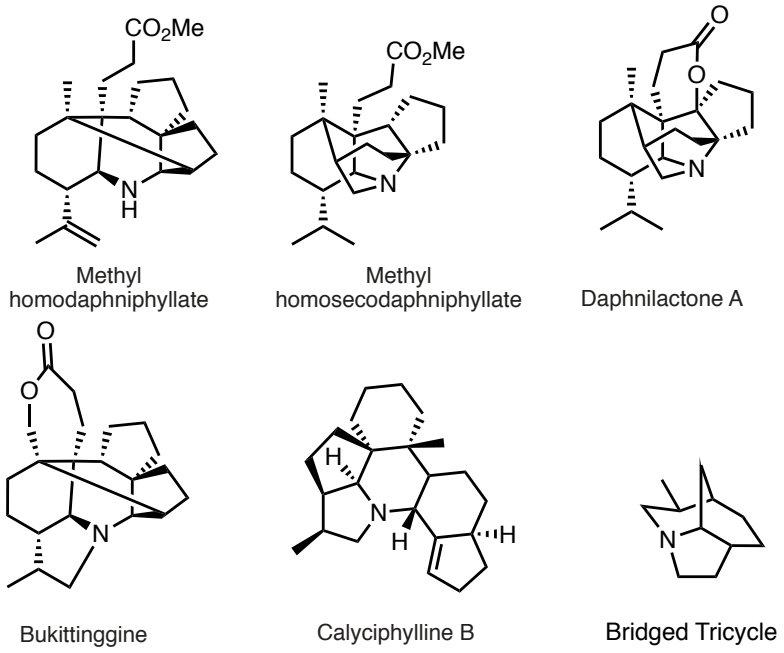


Scheme 38. Synthetic utility of keto lactams

1.5 A ring expansion cascade for the formation of tricycles

1.5.1 Daphniphyllum alkoloids

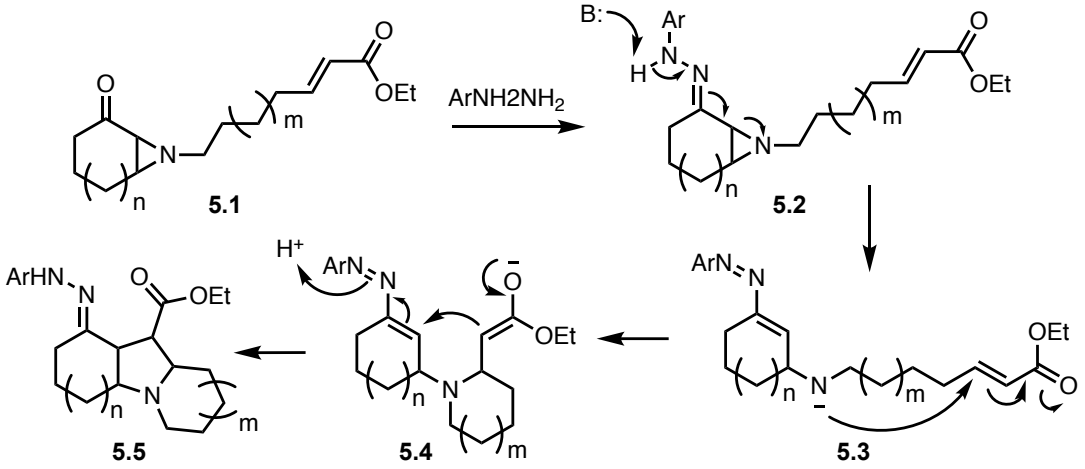
Since their isolation from the bark of *Daphniphyllum* macropodum Miquel (Euphorbiaceae) in 1909 by Yugi and later characterization by Hirata, the azapolycyclic cagelike architecture of *Daphniphyllum* alkaloids have proven to be some of the most structurally complex and synthetically challenging targets for total synthesis (**Scheme 39**).[141,142,143,144,145] Their unique rigid and compact tetracyclic cores, often containing one or more quaternary stereogenic center at a ring junctions and a single tertiary nitrogen at another ring junction, make them challenging to retrosynthetically deconstruct.[146,147] Heathcock's seminal contributions have been toward the biomimetic total synthesis of several *Daphniphyllum* alkaloids.[148,149] Since then over 300 other *Daphniphyllum* alkaloids have been isolated and characterized, some of which possess unprecedented ring systems that still resist the efforts of synthetic chemists.[150,151] New synthetic methodologies to construct azapolycyclic with quaternary stereogenic carbon centers at ring junctions would be an extraordinary step in the direction of an efficient total or partial synthesis of these cores. With potent anticancer, antioxidant, vasorelaxant, and anti-HIV properties of these alkaloids further efforts toward their synthesis and of their chemically modified congeners are warranted.[152,153,154,155]



Scheme 39. Daphniphyllum alkaloids

1.5.2 Cascading reaction for azapolycycles

Amines, like those in the AAP motifs, are versatile in their ability to perform multiple nucleophilic attacks on separate electrophiles.[156] This has inspired a reaction involving an α-aziridino ketone, which upon the addition of phenylhydrazine, would initiating a ring opening release of an amino nucleophile (**5.1** to **5.3**) with a tethered electron-deficient double bond (**5.3** to **5.4**). The following aldol addition to the azoalkene would then produce a tricycle **5.5** (**Scheme 40**). The proposed structural motifs generated by this reaction appears in the structural class of natural products called the *Daphniphyllum* alkaloids, which display a remarkable range of biological activities.[157] Due to the scarcity of *Daphniphyllum* alkaloids from natural sources, an expedient synthesis of its core structure would allow for further exploration of its bioactivity.



Scheme 40. Proposed mechanism for tricyclic core

To start our investigation, a variety of different ring sizes and tethered chain lengths were synthesized by mixing iodoenone, Cs_2CO_3, 1,10-phenanthroline, and alkene-amine **5.7** in CH_2Cl_2. This aziridination method gave **5.8** in good to moderate yield (**Table 22**).

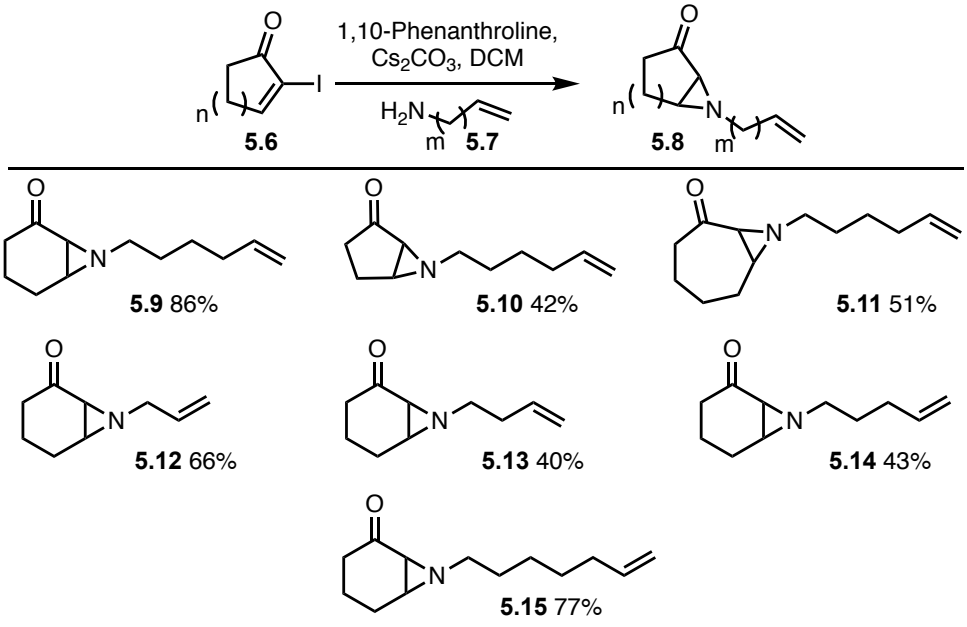
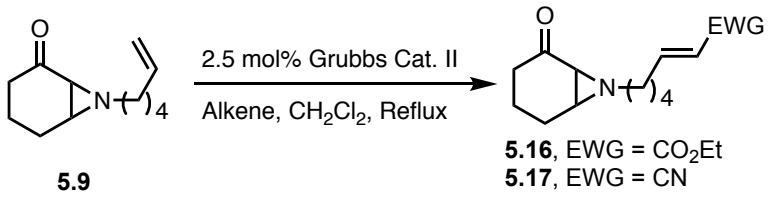


Table 24. **Scope for aziridination**

Transalkylidenation of **5.9** was carried with a variety of electron deficient alkenes using Hoveyda-Grubbs Catalyst$^{(TM)}$ 2nd Generation in CH_2Cl_2 (**Table 25**). However only ethyl ester and cyano electron withdrawing groups were successfully installed.



5.9

5.16, EWG = CO_2Et
5.17, EWG = CN

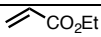
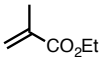
entry	product	yield (%)
1		83
2		32
3		Start material
4		Start material
5		Start material
6		Dimerized aziridine

Table 25. **Screening of cross metathesis**

The remaining substrate were installed with ethyl ester as mixture of E to Z alkenes, the major E isomer was isolated after column chromatography to good yield (**Table 26**).

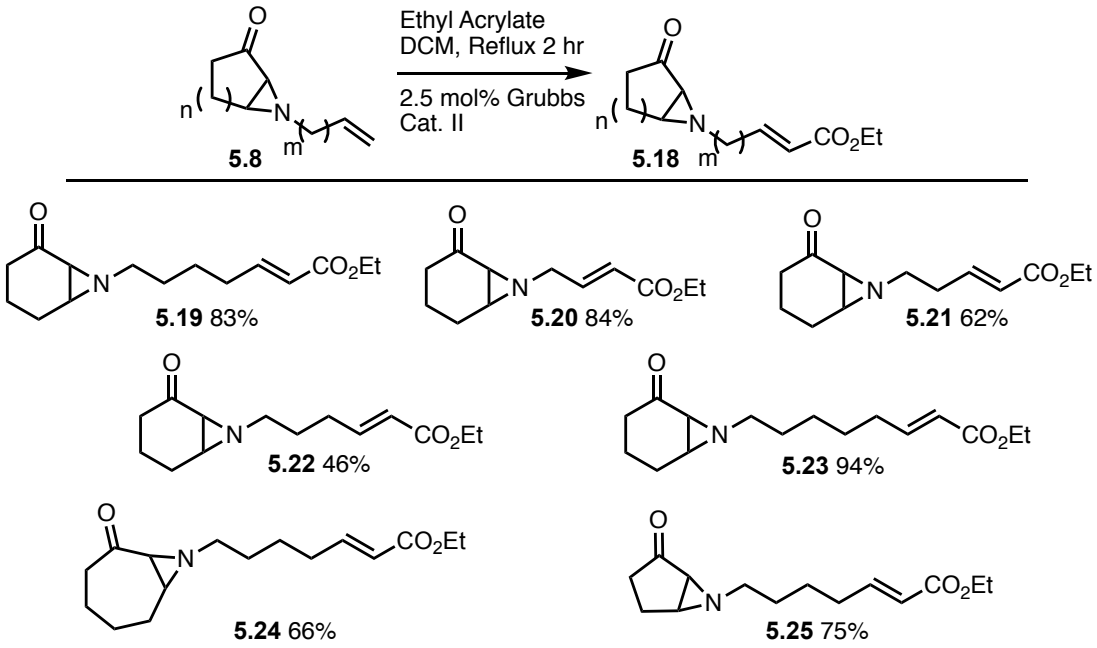


Table 26. **Scope for cross metathesis**

The cascade reaction was attempted using a thio-urea organic catalyst designed to enhance the electrophilic character of conjugated esters, to moderate success (**Table 27**). The relative stereochemistry of **5.27** was established via 1D and 2D nOe NMR experiments, and later confirmed by X-ray crystal analysis of compound **5.27**.

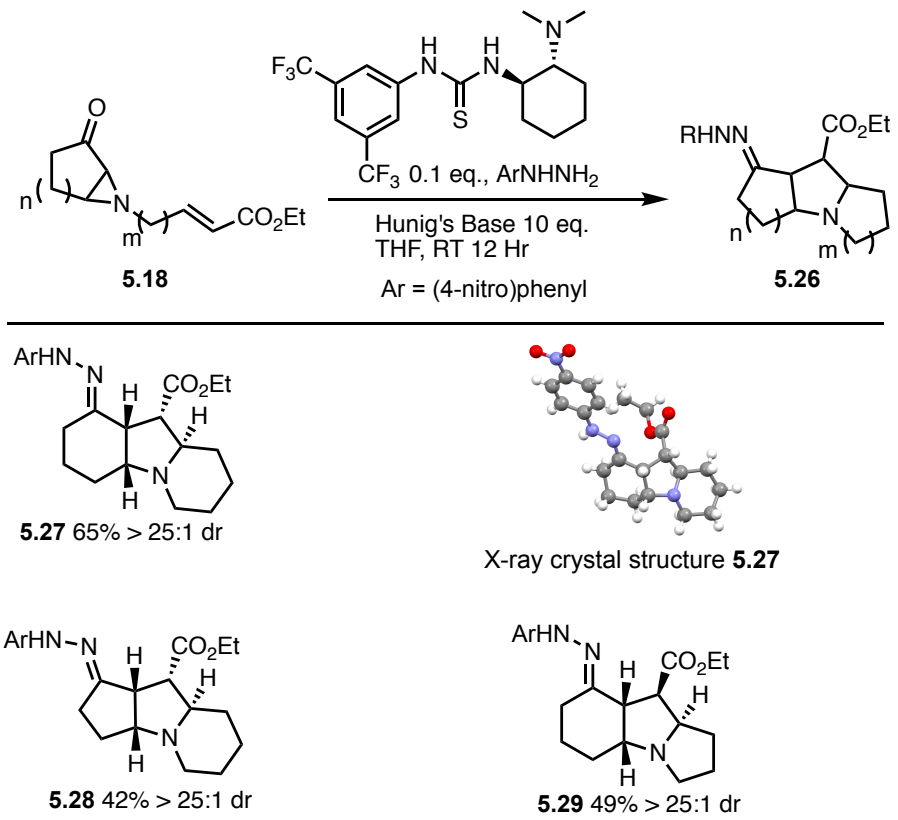
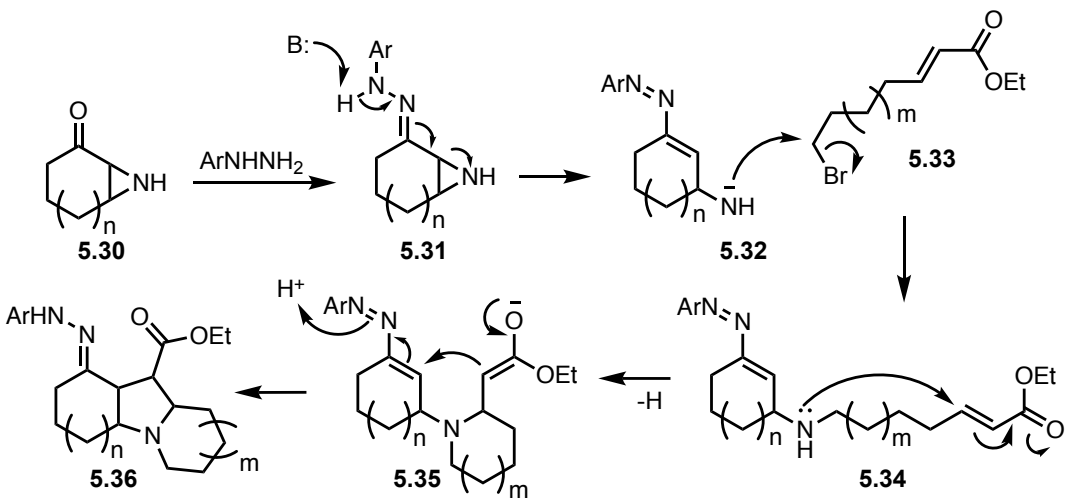


Table 27. **Ring expansion cascade for the formation of tricycles**

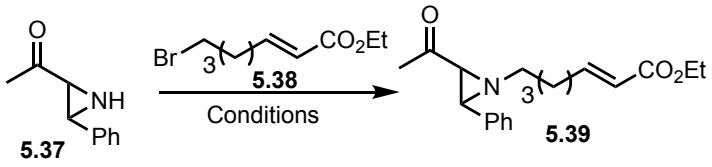
1.5.3 Convergent cascading reaction for azapolycycles

The products of these reactions are exciting, but the utility of AAPs could be advanced further. Convergent synthesis of these substrates was invisioned (**Scheme 41**). This would require the amino of the AAP to carryout two nucleophilic attacks. The unprotected α-aziridino ketone upon addition of phenylhydrazine would initiate a ring opening release of an amino nucleophile. This amine would attack, in an intermolecular fashion, a dielectrophilic substrate. An intramolecular attack to the tethered electron-deficient double bond would then follow as before. Lastly, the enolate addition to the azoalkene would produce a *N*-heterocycle.



Scheme 41. Proposed convergent mechanism for tricyclic core

Unprotected α-aziridino ketone are prone to dimerization, so substrate **5.37** was chosen as it could be stored for weeks at a time and was readily produce from commercially available starting materials.[158,159] Unfortunately, all attempts have failed to produce the desired cyclized product, even attempts at first alkylating the α-aziridino ketone are insolvent (**Table 28**). This reaction still warrants further investigation as it addresses gaps in current mythologies for the synthesis of unsaturated *N*-heterocycles.

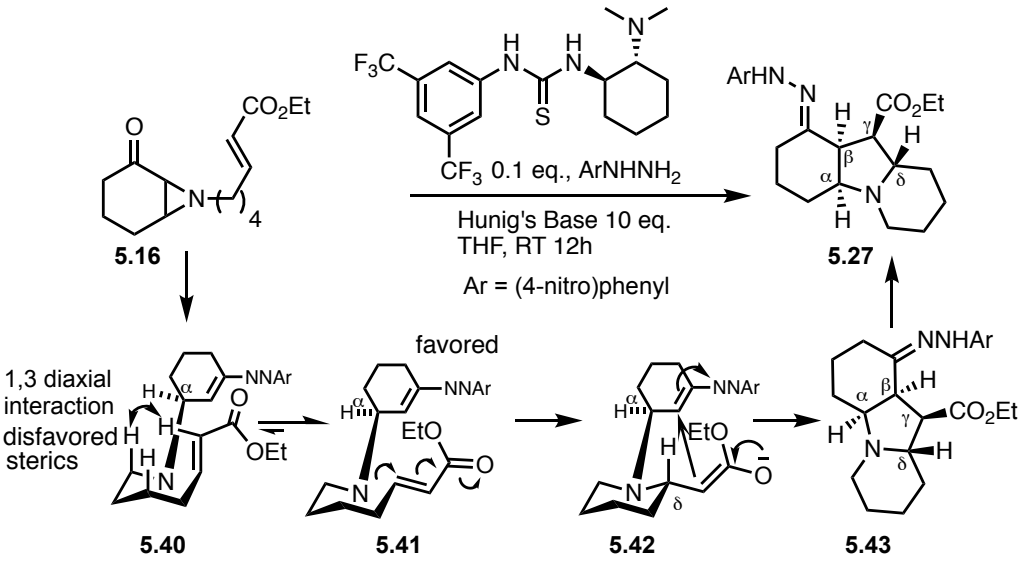


entry	conditions	yield (%)
1	K_2CO_3, DMF at 75 °C 16h	Start material
2	NaOH, TBAS, CH_2Cl_2 rt 2h	Decomposition
3	*n*-BuLi at –78 °C; **5.38** to 0 °C	Decomposition
4	Cs_2CO_3, $Pd(OAc)_2$, BINAP, tolune reflux, 2h	Start material
5	18-crown-6, K_2CO_3 THF, 96h	Start material

Table 28. **Attempts at alkylating aziridine 5.37**

1.5.4 Mechanism

The formation of a single diastereomer of tricycle **5.16** is explained based on the preference for conformer **5.41** over **5.40** during conjugate addition (**Scheme 42**). This would lead to coordinated intramolecular addition of enolate to the azoalkene from the same face as the amino group, establishing the *syn* relative configuration at what becomes the α,β ring fusion position of the final product **5.27**.



Scheme 42. Proposed mechanism for diastereoselectivity

1.6 Conclusion

In conclusion, we have discovered a new synthetically rich landscape, with inspiring chemistry and we have built a chemical library incorporating straightforward approaches for unlocking the chemical space of heterocycles from readily available HAPs and AAPs. In this dissertation we covered;

The stereodivergent synthesis of β,γ-fused bicyclic γ-lactones—an important class of *O*-heterocycles—including those with quaternary centers. The combination of a substrate, ester and a commercially available base, KHMDS or LiHMDS, giving the *anti*- or *syn*-fused bicyclic systems, respectively, with high (up to >25:1) diastereoselectivity.

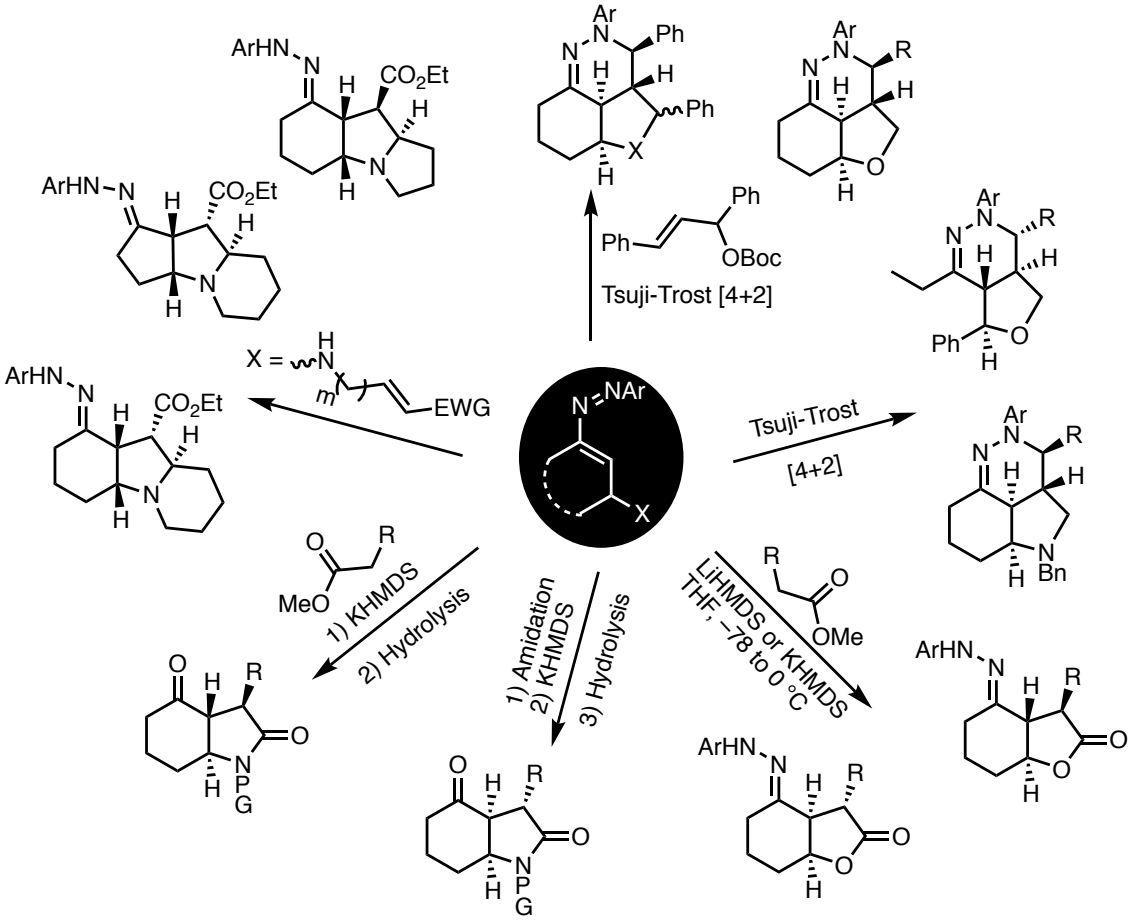
The synthesis of β,γ-fused bicyclic γ-lactams—an important class of *N*-heterocycles—including those with quaternary centers, using a new functional group in the form of AAPs. Selectivity for the *anti*-β,γ-fused bicyclic γ-lactams was preferred with intramolecular addition of enolate, even when Li bases were used. The *syn*-β,γ-fused bicyclic γ-lactams excessed by first using forming an amidoazopropene, by coupling with EDCI HOBt, then forming the enolate with KHMDS. Both *syn* and *anti*-β,γ-fused bicyclic γ-lactams were form with high (up to >25:1) diastereoselectivity.

A variety of stable HAPs, AAPs and a CAP have been prepared. Acyclic HAPs and AAPs have also been formed.

The synthesis of fused tetrahydrofuran- and Pyrrolidine-tetrahydropyridazines—both important classes of heterocycles—including heavily substituted systems. Utilizing the conjugated π systems of AKs in HAPs and AAPs in a cascading Tsuji-Trost [4+2]

cyclization reaction to give tetrahydrofuran- and Pyrrolidine-tetrahydropyridazines, respectively, with high (up to >25:1) diastereoselectivity.

Lastly, the synthesis of azapolycycles—a core structure in many important *N*-heterocycles—through an impressive cascading ring expansion. A variety of different azapolycycles where prepared with high (up to >25:1) diastereoselectivity.



Scheme 43. The reaction web of 3-hydroxy- and 3-amino-1-azoalkenes.

It is our sincere hope that these will be the tools to escape flatland, on saturated heterocycles of our own design.

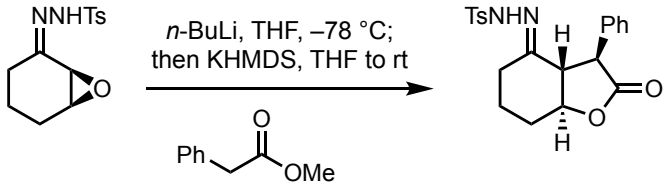
"I come, to proclaim that there is a land of Three Dimensions."

— Edwin A. Abbott, Flatland: A Romance of Many Dimensions

1.7 Experimental

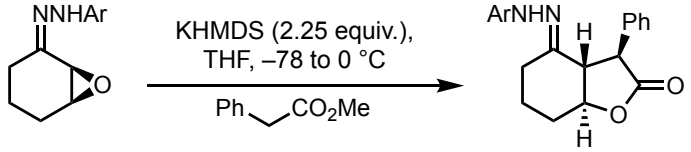
General Considerations. Unless stated to the contrary, where applicable, the following considerations apply: Reactions were carried out using dried solvents (see below) and under a slight static pressure of Ar (pre-purified quality) that had been passed through a column (5 x 20 cm) of Drierite. Glassware was dried in an oven at 120 °C for at least 12 h prior to use and then either cooled in a desiccator cabinet over Drierite or assembled quickly while hot, sealed with rubber septa, and allowed to cool under a stream of Ar. Reactions were stirred magnetically using Teflon-coated magnetic stirring bars. Teflon-coated magnetic stirring bars and syringe needles were dried in an oven at 120 °C for at least 12 h prior to use then cooled in a desiccator cabinet over Drierite. Hamilton microsyringes were dried in an oven at 60 °C for at least 24 h prior to use and cooled in the same manner. Commercially available Norm-Jet disposable syringes were used. Dry THF and PhMe was obtained using an Innovative Technologies solvent purification system. All other dry solvents were of anhydrous quality purchased from Aldrich. Commercial grade solvents were used for routine purposes without further purification. Flash column chromatography was performed on silica gel 60 (230-400 mesh). ^{1}H and ^{13}**C NMR** spectra were recorded on a JEOL ECA-500 or ECX-400P spectrometer at ambient temperature. All ^{1}H and ^{13}C chemical shifts are reported in ppm (δ) using residual solvent as an internal reference ($CDCl_3$: 7.25 ppm for ^{1}H NMR and 77.1 ppm for ^{13}**C NMR**). HRMS analyses were performed at the Univ. of Texas-Austin mass spectrometry facility using an Agilent Technologies 6530 Accurate Mass Q-ToF LC/MS. All commercially available materials were purchased from Aldrich.

1.7.1 Synthesis of lactones



(*E*)-4-methyl-*N*'-2-oxo-3-phenylhexahydrobenzofuran-4(2*H*)-ylidene)benzenesulfonohydrazide (**2.12**). To a stirred solution of phenyl methyl acetate (0.062 g, 0.416 mmol) in THF (0.5 mL) was added KHMDS (0.42 mL, 0.416 mmol, 1.0 M soln. in THF) at –78 °C. The mixture was stirred for 30 min. Separately, N'(7-oxabiocyclo[4.1.0]heptane-2-ylidene)-4-methylbenzenesulfonohydrazide[71] (**2.11**) (0.053 g, 0.189 mmol) was dissolved in THF (1.0 mL) and cooled to –78 °C. This solution was added dropwise over a period ca. 1 min to the preformed enolate solution followed by the addition of a THF wash (0.5 mL). The resulting solution was stirred 5 min at –78 °C and subsequently warmed to 0 °C (ice-bath) and stirred 1 h. The reaction was quenched with aq. 10% NH_4OH saturated with NH_4Cl (5 mL). The biphasic solution was partitioned between EtOAc and H_2O, and the aq. phase extracted with EtOAc (3 X 15 mL). The combined organic extracts were washed with sat. aq. NaCl, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash chromatography over silica gel (60:40 EtOAc-Hexanes) gave an off-white solid (0.038 g, 50%). mp 160-162 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.96 (brs, 1 H), 7.60 (d, *J* = 8.24 Hz, 2 H), 7.28-7.23 (m, 3 H), 7.19-7.16 (m, 2 H), 7.12 (d, *J* = 8.24 Hz, 2 H), 4.06 (d, *J* = 12.36 Hz, 1 H), 3.93 (dt, *J* = 11.45 Hz, 3.66 Hz, 1 H), 2.84 (t, *J* = 11.91 Hz, 1 H), 2.70 (dq, *J* = 15.11 Hz, 2.29 Hz, 1 H), 2.41-2.39 (m, 4 H with an apparent singlet at 2.39 ppm), 2.08-2.03 (m, 1 H), 1.82-1.71 (m, 2 H), 1.61-1.53 (m, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 176.1, 154.3, 144.2, 135.1, 134.8, 129.6, 128.9,

128.6, 127.9, 127.5, 81.0, 56.8, 48.2, 29.3, 26.0, 22.2, 21.7; **HRMS-ESI:** *m/z* calcd. for $C_{21}H_{22}N_2O_4S$ $[M+Na]^+$: 421.1192, found 421.1196.



(*E*)-4-(2-(2-nitrophenyl)hydrazono)-3-phenylhexahydrobenzofuran-2(3*H*)-one (**2.12**). To a stirred solution of phenyl methyl acetate (0.066 g, 0.444 mmol) in THF (0.5 mL) was added KHMDS (0.45 mL, 0.454 mmol, 1.0 M soln. in THF) at –78 °C. The mixture was stirred for 30 min. Separately, α-epoxy 2-nitrophenylhydrazone (**2.16**) (0.050g, 0.202 mmol) was dissolved in THF (1.0 mL) and cooled to –78 °C. This solution was added dropwise over a period ca. 1 min to the preformed enolate solution followed by the addition of a THF wash (0.5 mL). The resulting deep purple solution was stirred 5 min at –78 °C and subsequently warmed to 0 °C (ice-bath) and stirred 1 h. The reaction was quenched with aq. 10% NH_4OH saturated with NH_4Cl (5 mL). The orange biphasic solution was partitioned between EtOAc and H_2O, and the aq. phase extracted with EtOAc (3 X 15 mL). The combined organic extracts were washed with sat. aq. NaCl, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash chromatography over silica gel (30:70 EtOAc-Hexanes) gave an orange solid (0.056 g, 76%). mp 158-160 ºC; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 10.84 (s, 1 H), 8.13 (dd, *J* = 8.59 Hz, 1.15 Hz, 1 H), 7.66 (dd, *J* = 8.59 Hz, 1.15 Hz, 1 H), 7.51 (td, *J* = 6.87 Hz, 1.15 Hz, 1H), 7.41-7.36 (m, 4 H), 7.32-7.28 (m, 1 H), 6.81 (td, *J* = 8.02 Hz, 1.15 Hz, 1 H), 4.20 (d, *J* =12.60 Hz, 1 H), 4.06 (td, *J* = 11.46, 4.01 Hz, 1 H), 3.06 (t, *J* = 11.46 Hz, 1 H), 2.91 (dq, *J* = 14.89 Hz, 2.29 Hz, 1 H), 2.53-2.48 (m , 1 H), 2.27-2.22 (m, 1 H), 2.08-2.02 (m, 1 H), 1.91 (qd, *J* = 11.74 Hz, 4.01 Hz, 1 H), 1.76 -1.67 (m , 1 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 176.2,

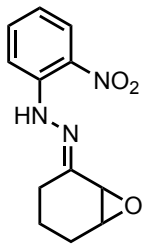
148.7, 142.2, 136.3, 135.5, 131.1, 128.9, 128.7, 127.9, 126.0, 118.3, 115.6, 81.3, 57.4, 49.0, 29.5, 25.7, 22.3; **HRMS-ESI:** *m/z* calcd. for $C_{20}H_{19}N_3O_4$ $[M+H]^+$: 366.1448, found 366.1451.

*General procedure **A**: Formation of α-epoxy (2-nitro)phenylhydrazones from α-epoxy ketones*

To a stirred solution of α-epoxy ketone (1.0 equiv) in Et_2O (1.0 M) was added 2-nitrophenylhydrazine (1.0 equiv) at rt. The reaction was stirred 14 h and concentrated *in vacuo*. Flash chromatography over silica gel gave the desired α-epoxy 2-nitrophenylhydrazones.

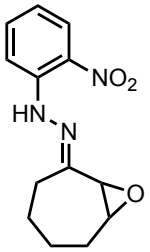
*General procedure **B**: Formation of α-epoxy (2-nitro)phenylhydrazones from α-epoxy ketones*

To a stirred solution of α-epoxy ketone (1.0 equiv) in Et_2O (1.0 M) was added 2-nitrophenylhydrazine (1.0 equiv) at rt. The reaction was 14 h. The reaction was cooled to 0 °C (ice bath), and subsequently filtered and rinsed with cold Et_2O. The resulting solid was dried under vacuum overnight.



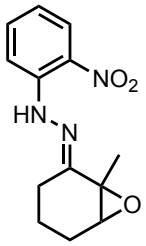
(*E*/*Z*)-1-(7-oxabicyclo[4.1.0]heptan-2-ylidene)-2-(2-nitrophenyl)hydrazine (**2.16**). α-epoxy ketone[160] **2.10** (0.470 g, 4.19 mmol) was treated following general procedure **A**. Flash chromatography (10:90 EtOAc-Hexanes) gave an orange solid (0.642 g, 62%, 3:1 E:Z). mp 83-85 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 11.34 (s, 1 H) major, 10.82 (s, 1 H) minor, 8.17-8.15 (m, 1 H), 7.95 (dd, J = 8.70 Hz, 1.37 Hz, 1

H) minor, dd (7.83 , J = 8.70 Hz, 1.14 Hz, 1 H) major, 7.56-7.47 (m, 1 H), 6.87-6.80 (m, 1 H), 3.74 (d, J = 3.66 Hz, 1 H) major, 3.70 (d, J = 4.12 Hz, 1 H) minor, 3.60-3.58 (m, 1 H) minor, 3.55-3.53 (m, 1 H) major, 2.61-2.50 (m, 1 H), 2.28-2.25 (m, 1 H), 2.20-2.12 (m, 1 H) major, 2.09-2.00 (m, 1 H) minor, 1.94-1.76 (m, 1 H), 1.72-1.52 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): major: δ 149.0, 142.3, 136.2, 131.2, 126.0, 118.2, 115.9, 53.3, 45.1, 30.6, 24.2, 17.8, minor: δ 147.7, 141.7, 136.3, 125.9, 118.6, 116.0, 54.7, 53.6, 23.5, 23.4, 14.6; **HRMS-ESI:** *m/z* calcd. for $C_{12}H_{13}N_3O_3$ $[M+H]^+$: 248.1030, found 248.1033.

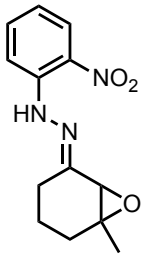


(*E/Z*)-1-(8-oxabicyclo[5.1.0]octan-2-ylidene)-2-(2-nitrophenyl)hydrazine (**SI1**). α-epoxy ketone[161] (0.225 g, 1.78 mmol) was treated following general procedure **A**. Flash chromatography (7:93 EtOAc-Hexanes) gave a red solid (0.291 g, 62%, 1.7:1 E/Z). mp 69-70 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 11.23 (s, 1 H) major, 10.03 (s, 1 H) minor, 8.11 (d, J = 8.59 Hz, 1 H), 7.85 (d, J = 8.59 Hz, 1 H) minor, 7.79 (d, J = 8.59 Hz, 1 H) major, 7. 51-7.45 (m, 1 H), 6.80-6.75 (m, 1 H), 3.79 (d, J = 4.01 Hz, 1 H) major, 3.74 (d, J = 4.58 Hz, 1 H) minor, 3.50-3.48 (m, 1 H), 3.39-3.33 (m, 1 H), 2.70 (dd, J = 13.75 Hz, 5.15 Hz, 1 H) minor, 2.50-2.38 (m, 2 H), 2.36-2.27 (m, 1 H) minor, 2.14 (td, J = 13.17 Hz, 2.86 Hz, 1 H) minor, 2.01-1.50 (m, 8 H), 1.39-1.32 (m, 1 H) major, 1.26-1.21 (m, 1 H), 1.08-0.97 (m, 1 H) minor; **^{13}C NMR** (125 MHz, $CDCl_3$): Major: δ 1153.0, 142.4, 136.1, 131.2, 125.9, 117.9, 115.7, 55.3, 52.1, 34.0, 28.7, 28.6, 22.6,

Minor: δ 153.8, 142.1, 136.3, 125.9, 118.2, 115.8, 58.7, 56.0, 27.4, 25.2, 24.0, 23.6; **HRMS-ESI:** *m/z* calcd. for $C_{13}H_{15}N_3O_3$ $[M+H]^+$: 262.1186, found 262.1193.

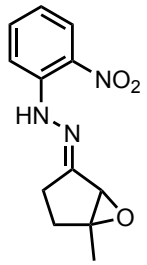


(*E*)-1-(1-methyl-7-oxabicyclo[4.1.0]heptan-2-ylidene)-2-(2-nitrophenyl)hydrazine (**SI2**). α-epoxy ketone[162] (0.654 g, 5.18 mmol) was treated following general procedure **L.** Filtration gave an orange solid (0.920 g, 68%). mp 87-88 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 10.81 (s, 1 H), 8.16 (dd, *J* = 8.59 Hz, 1.15 Hz, 1 H), 7.92 (d, *J* = 8.02 Hz, 1 H), 7.54 (t, *J* = 8.02 Hz, 1 H), 3.36 (d, *J* = 3.44 Hz, 1 H), 2.58-2.54 (m, 1 H), 2.33-2.19 (m, 1 H), 2.08-2.01 (m, 1 H), 1.94-1.81 (m, 2 H), 1.69-1.63 (m, 4 H, apparent s at 1.63), **^{13}C NMR** (125 MHz, $CDCl_3$): δ 146.6, 142.1, 136.3, 131.3, 125.9, 118.4, 116.0, 61.0, 58.7, 23.6, 23.5, 19.1, 15.6; **HRMS-ESI:** *m/z* calcd. for $C_{13}H_{15}N_3O_3$ $[M+H]^+$: 262.1186, found 262.1187.



(*E/Z*)-1-(6-methyl-7-oxabicyclo[4.1.0]heptan-2-ylidene)-2-(2-nitrophenyl)hydrazine (**SI3**). α-epoxy ketone[163] (0.115 g, 0.911 mmol) was treated following general procedure **A**. Flash chromatography (10:90 EtOAc-Hexanes) gave an orange solid (0.167 g, 70%, 1.8:1 E/Z). mp 80-81 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 11.2 (s, 1 H) major, 10.76 (s, 1 H) minor, 8.12 (d, *J* = 8.70 Hz, 1 H), 7.90 (d, *J* = 8.70 Hz,

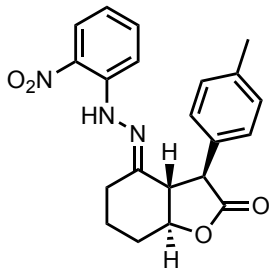
1 H) minor, 7.79 (d, J = 8.70 Hz, 1H) major, 7.53-7.45 (m, 1 H), 6.83-6.76 (m, 1 H), 3.51 (s, 1 H), 2.54-2.47 (m, 1 H), 2.16-1.93 (m, 2 H), 1.86-1.74 (m, 1 H), 1.72-1.50 (m, 2 H), 1.46 (s, 3 H) major, 1.45 (s, 3 H) minor; **^{13}C NMR** (100 MHz, $CDCl_3$): Major: δ 149.7, 142.3, 136.2, 131.1, 125.9, 118.1, 115.8, 59.4, 51.8, 30.5, 29.6, 22.9, 18.6, Minor: δ 148.6, 141.7, 136.3, 131.2, 125.9, 118.5, 115.9, 61.5, 59.5, 28.9, 23.2, 22.2, 15.9; **HRMS-ESI:** *m/z* calcd. for $C_{13}H_{15}N_3O_3$ $[M+H]^+$: 262.1186, found 262.1187.



(*E/Z*)-1-(5-methyl-6-oxabicyclo[3.1.0]hexan-2-ylidene)-2-(2-nitrophenyl)hydrazine (**SI4**). α-epoxy ketone[164] (0.281 g, 2.50 mmol) was treated following general procedure **A**. Flash chromatography (10:90 EtOAc-Hexanes) gave an orange solid (0.346 g, 62%, 3.5:1 E/Z). mp 112-114 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 11.12 (s, 1 H) minor, 10.56 (s, 1 H) major, 8.15 (dd, J = 8.70 Hz, 1.37 Hz, 1 H), 7.85 (dd, J = 8.70 Hz, 0.92 Hz, 1 H) major, 7.77 (d, J = 8.70 Hz, 1 H) minor, 7.55-7.47 (m, 1 H), 6.85-6.77 (m, 1 H), 3.81 (s, 1 H) minor, 3.70 (s, 1 H) major, 2.69-2.56 (m, 1 H), 2.48-1.86 (m, 3 H), 1.59 (s, 3 H) minor, 1.60 (s, 3 H) major; **^{13}C NMR** (125 MHz, $CDCl_3$): Major: δ 156.2, 141.9, 136.3, 131.1, 125.9, 118.3, 115.8, 63.7, 55.2, 29.8, 23.4, 17.9, Minor: δ 157.3, 142.4, 136.3, 130.8, 126.0, 118.0, 115.5, 67.7, 66.2, 29.0, 28.3, 18.3; **HRMS-ESI:** *m/z* calcd. for $C_{12}H_{13}N_3O_3$ $[M+H]^+$: 248.1030, found 248.1040.

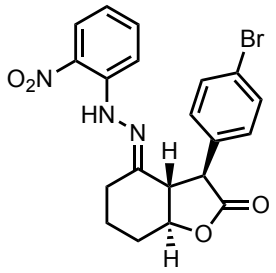
General procedure ***C****: Anti-selective formation of* β,γ*-fused bicyclic* γ*-lactone hydrazones from 6 or 7-membered-α-epoxy-(2-nitro)phenyl hydrazones and 6-membered-α-epoxy-α-methyl-(2- nitro)phenyl hydrazones*

To a stirred solution of the aryl acetic methyl ester (2.20 equiv) in THF (0.5 mL) was added KHMDS (2.25 equiv, 1.0 M soln. in THF) at –78 °C. The mixture was stirred for 30 min. Separately, the appropriate α-epoxy (2-nitro)phenylhydrazone (1.0 equiv) was dissolved in THF (1.0 mL) and cooled to –78 °C. This solution was added dropwise over a period ca. 1 min to the preformed enolate solution followed by the addition of a THF wash (0.5 mL). The resulting deep purple solution was stirred 5 min at –78 °C and subsequently warmed to 0 °C (ice-bath) and stirred 1 h. The reaction was quenched with aq. 10% NH_4OH saturated with NH_4Cl (5 mL). The orange biphasic solution was partitioned between EtOAc and H_2O, and the aq. phase extracted with EtOAc (3 X 15 mL). The combined organic extracts were washed with sat. aq. NaCl, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash chromatography over silica gel provided the desired β,γ-fused bicyclic γ-lactone hydrazones.

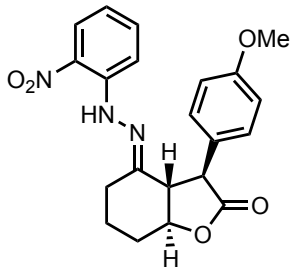


(*E*)-4-(2-(2-nitrophenyl)hydrazono)-3-(*p*-tolyl)-hexahydrobenzofuran-2(3*H*)-one (**2.37**). Hydrazone (**2.16**) (0.044 g, 0.177 mmol) was treated following general procedure **M.** Flash chromatography (30:70 EtOAc-Hexanes) gave an orange solid (0.044 g, 65%). mp 175-177 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.83 (s, 1 H), 8.13 (dd, *J* =

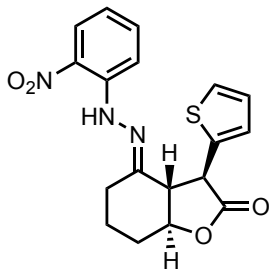
8.70 Hz, 1.37 Hz, 1 H), 7.70 (d, *J* = 8.70 Hz, 1 H), 7.52 (td, *J* = 7.79 Hz, 0.92 Hz, 1 H), 7.28 (d, *J* = 7.79 Hz, 2 H), 7.19 (d, *J* = 7.79 Hz, 2 H), 6.81 (td, *J* = 8.01 Hz, 1.37 Hz, 1 H), 4.17 (d, *J* = 12.36 Hz, 1 H), 4.04 (td, *J* = 11.22 Hz, 4.12 Hz, 1 H), 3.03 (t, *J* = 11.45 Hz, 1 H), 2.90 (dq, *J* = 15.34 Hz, 2.29 Hz, 1 H), 2.52-2.47 (m, 1 H), 2.32 (s, 3 H), 2.26-2.22 (m, 1 H), 2.08-1.99 (m, 1 H), 1.90 (qd, *J* = 11.91 Hz, 4.58 Hz, 1 H), 1.76-1.65 (m, 1 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 176.4, 148.8, 142.3, 137.6, 136.3, 132.6, 131.1, 129.5, 128.8, 126.0, 118.2, 115.6, 81.3, 57.6, 48.7, 29.5, 25.7, 22.4, 21.2; **HRMS-ESI:** *m/z* calcd. for $C_{21}H_{21}N_3O_4$ $[M+Na]^+$: 402.1424, found 402.1426.



(*E*)-3-(4-bromophenyl)-4-(2-(2-nitrophenyl)hydrazono)-hexahydrobenzofuran-2(3*H*)-one (**2.22**). Hydrazone (**2.16**) (0.058 g, 0.235 mmol) was treated following general procedure **M.** Flash chromatography (30:70 EtOAc-Hexanes) gave an orange solid (0.077 g, 74%). mp 198-199 °C; **^{1}H NMR** (400 MHz, d_6-DMSO): δ 10.49 (s, 1 H), 8.04 (dd, *J* = 8.47 Hz, 1.37 Hz, 1 H), 7.62-7.54 (m, 4 H), 7.37 (d, *J* = 8.70 Hz, 2 H), 6.86-6.82 (m, 1 H), 4.35 (d, *J* = 12.82 Hz, 1 H), 4.15 (td, *J* = 11.22 Hz, 4.12 Hz, 1 H), 3.38 (t, *J* = 11.91 Hz, 1 H), 2.75-2.71 (m, 1 H), 2.28-2.24 (m, 1 H), 2.15-2.06 (m, 2 H), 1.88 (qd, *J* = 11.91 Hz, 3.66 Hz, 1 H), 1.67-1.60 (m, 1 H); **^{13}C NMR** (150 MHz, d_6-DMSO): δ 176.4, 151.9, 142.3, 137.0, 136.5, 131.9, 131.6, 131.1, 126.2, 120.9, 118.6, 115.8, 81.2, 55.3, 49.1, 28.8, 25.6, 22.1; **HRMS-ESI:** *m/z* calcd. for $C_{20}H_{18}BrN_3O_4$ $[M+Na]^+$: 466.0370, found 466.0371.

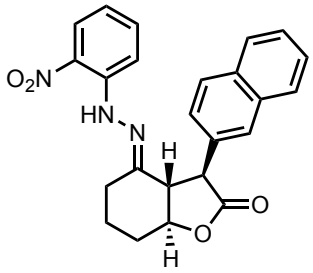


(*E*)-3-(4-methoxyphenyl)-4-(2-(2-nitrophenyl)hydrazono)-hexahydrobenzofuran-2(3*H*)-one (**2.23**). Hydrazone (**2.16**) (0.054 g, 0.218 mmol) was treated following general procedure **M.** Flash chromatography (35:65 EtOAc-Hexanes) gave an orange solid (0.055 g, 64%). mp 100-102 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.84 (s, 1 H), 8.12 (d, *J* =8.70 Hz, 1 H), 7.68 (d, *J* = 8.70 Hz, 1 H), 7.51 (t, *J* = 7.33 Hz, 1 H), 7.33-7.29 (m , 2 H), 6.93-6.89 (m, 2 H), 6.81 (td, *J* = 6.64 Hz, 1.37 Hz, 1 H), 4.15 (d, *J* = 12.36 Hz, 1 H), 4.04 (td, *J* = 11.22 Hz, 4.12 Hz, 1 H), 3.78 (s, 3 H), 3.00 (t, *J* = 11.45 Hz, 1H), 2.90 (dq, *J* = 15.11 Hz, 2.29 Hz, 1 H), 2.51-2.46 (m, 1 H), 2.25-2.22 (m, 1 H), 2.09-2.00 (m, 1 H), 1.90 (qd, *J* = 11.91 Hz, 4.58 Hz, 1 H), 1.76-1.67 (m, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 176.6, 159.1, 148.9, 142.3, 136.3, 131.1, 130.0, 127.6, 126.0, 118.2, 115.6, 114.2, 81.3, 57.5, 55.3, 48.2, 29.5, 25.7, 22.4; **HRMS-ESI:** *m/z* calcd. for $C_{21}H_{21}N_3O_5$ $[M+Na]^+$: 418.1373, found 418.1377.



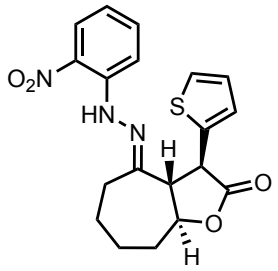
(*E*)-4-(2-(2-nitrophenyl)hydrazono)-3-(thiophen-2-yl)hexahydrobenzofuran-2(3*H*)-one (**2.24**). Hydrazone (**2.16**) (0.052 g, 0.210 mmol) was treated following general procedure **M.** Flash chromatography (30:70 EtOAc-Hexanes) gave an orange solid (0.067

g, 85%). mp 142-144 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.92 (s, 1 H), 8.14 (d, *J* = 8.70 Hz, 1 H), 7.81 (d, *J* = 8.70 Hz 1 H), 7.52 (t, *J* = 7.33 Hz, 1 H), 7.25-7.24 (m, 1 H), 7.19 (d, 3.66 Hz, 1 H), 7.01-6.99 (m, 1 H), 6.84 (t, *J* = 7.33 Hz, 1 H), 4.49 (d, *J* = 12.36 Hz, 1 H), 4.04 (td, *J* = 11.22 Hz, 4.12 Hz, 1 H), 3.05 (t, *J* = 11.91 Hz, 1 H), 2.95 (dq, *J* = 15.11 Hz, 2.29 Hz, 1 H), 2.51-2.46 (m, 1 H), 2.27-2.23 (m, 1 H), 2.14-2.04 (m, 1 H), 1.89 (qd, *J* = 11.91 Hz, 4.58 Hz, 1 H), 1.77-1.65 (m, 1 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 174.7, 148.1, 142.2, 137.1, 136.5, 131.1, 126.9, 126.5, 126.0, 125.2, 118.4, 115.7, 81.3, 57.9, 43.5, 29.5, 25.7, 22.4; **HRMS-ESI:** *m/z* calcd. for $C_{18}H_{17}N_3O_4S$ $[M+Na]^+$: 394.0832, found 394.0832.

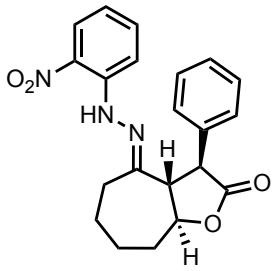


(*E*)-3-(napthalen-2-yl)-4-(2-(2-nitrophenyl)hydrazono)hexahydrobenzofuran-2(3*H*)-one (2.28). Hydrazone (**2.16**) (0.056 g, 0.226 mmol) was treated following general procedure **M.** Flash chromatography (40:50:10 EtOAc-Hexanes-CH_2Cl_2) gave an orange solid (0.049 g, 52%). mp 190-192 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 10.82 (s, 1 H), 8.11 (dd, *J* = 8.59 Hz, 1.72 Hz, 1 H), 7.90-7.81 (m, 4 H), 7.69 (dd, *J* = 8.59 Hz, 1.15 Hz, 1 H), 7.50-7.44 (m, 4 H), 6.80 (td, *J* = 8.59 Hz, 1.72 Hz, 1 H), 4.37 (d, *J* = 12.03 Hz, 1 H), 4.13 (td, *J* = 11.88 Hz, 4.01 Hz, 1 H), 3.16 (t, *J* = 10.88 Hz, 1 H), 2.92 (dq, *J* = 14.03 Hz, 2.86 Hz, 1 H), 2.55-2.52 (m, 1 H), 2.28-2.25 (m, 1 H), 2.10-2.04 (m, 1 H), 1.96 (qd, *J* = 11.74 Hz, 4.01 Hz, 1 H), 1.78-1.70 (m, 1 H); **^{13}C NMR** (125

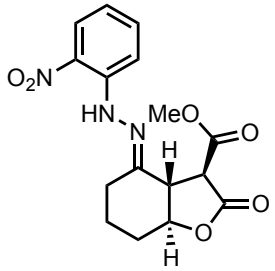
MHz, $CDCl_3$): δ 176.2, 148.6, 142.2, 136.3, 134.4, 133.3, 132.9, 131.1, 128.6, 127.8, 127.7, 126.4, 126.3, 126.2, 126.0, 122.3, 118.3, 115.6, 81.1, 57.4, 49.3, 29.5, 25.6, 22.3; **HRMS-ESI:** *m/z* calcd. for $C_{24}H_{21}N_3O_4$ $[M+Na]^+$: 438.1424, found 438.1431.



(*E*)-4-(2-(2-nitrophenyl)hydrazono)-3-(thiophen-2-yl)octahydro-*2H*-cyclohepta[*b*]furan-2-one (**2.30**). Hydrazone (**SI1**) (0.0425 g, 0.162 mmol) was treated following general procedure **M.** Flash chromatography (30:70 EtOAc-Hexanes) gave an orange solid (0.0553 g, 89%). mp 193-194 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.78 (s, 1 H), 8.16 (d, *J* = 8.70 Hz, 1 H), 7.88 (d, *J* = 8.70 Hz, 1 H), 7.54 (t, *J* = 7.33 Hz, 1 H), 7.20-7.19 (m, 1 H), 7.15-7.14 (m, 1 H), 6.99-6.94 (m, 1 H), 6.86 (t, *J* = 7.33 Hz, 1 H), 4.98 (d, *J* = 11.45 Hz, 1 H), 4.13 (td, *J* = 10.76 Hz, 3.66 Hz, 1 H), 3.50 (t, *J* = 10.53 Hz, 1 H), 2.77-2.72 (m, 1 H), 2.53-2.39 (m, 2 H), 2.19-2.14 (m, 2 H), 1.80-1.69 (m, 2 H), 1.37-1.27 (m, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 174.7, 148.2, 142.0, 137.9, 136.5, 131.5, 126.9, 126.3, 126.0, 125.0, 118.7, 115.9, 81.8, 57.2, 43.6, 35.0, 31.0, 24.8, 23.1; **HRMS-ESI:** *m/z* calcd. for $C_{19}H_{19}N_3O_4S$ $[M+Na]^+$: 408.0988, found 408.0992.

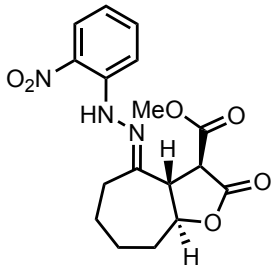


(*E*)-4-(2-(2-nitrophenyl)hydrazono)-3-phenyloctahydro-*2H*-cyclohepta[*b*]furan-2-one (2.29). Hydrazone (**SI1**) (0.065 g, 0.248 mmol) was treated following general procedure **M.** Flash chromatography (20:80 EtOAc-Hexanes) gave an orange solid (0.0647 g, 69%). mp 220-222 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.70 (s, 1 H), 8.16 (d, *J* = 8.24 Hz, 1 H), 7.82 (d, *J* = 8.70 Hz, 1 H), 7.57 (t, *J* = 8.70 Hz, 1 H), 7.39-7.33 (m, 4 H), 7.30-7.26 (m, 1 H), 6.86 (t, *J* = 6.87 Hz, 1 H), 4.72 (d, *J* = 11.91 Hz, 1 H), 4.16 (td, *J* = 10.53 Hz, 3.66 Hz, 1 H), 3.54 (t, *J* = 10.53 Hz, 1 H), 2.70-2.65 (m, 1 H), 2.57-2.53 (m, 1 H), 2.45-2.53 (m, 1 H), 2.21-2.10 (m, 2 H), 1.82-1.69 (m, 2 H), 1.38-1.24 (m, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 176.3, 148.8, 142.1, 136.5, 136.4, 131.4, 128.9, 128.8, 127.8, 126.1, 118.6, 115.7, 81.9, 56.6, 48.8, 35.2, 31.1, 24.9, 23.1; **HRMS-ESI:** *m/z* calcd. for $C_{21}H_{21}N_3O_4$ $[M+H]^+$: 380.1605, found 380.1604.

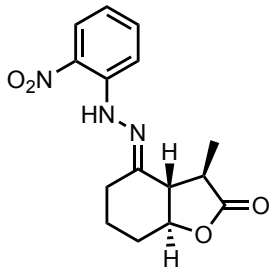


(*E*)-methyl 4-(2-(2-nitrophenyl)hydrazono)-2-oxooactahydrobenzofuran-3-carboxylate (2.25). Hydrazone (**2.16**) (0.051 g, 0.206 mmol) was treated following general procedure **M.** Dimethyl malonate was used in place of aryl acetic acid methyl ester. Flash chromatography (40:60 EtOAc- Hexanes) gave a yellow solid (0.047 g, 67%). mp 161-163 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.84 (s, 1 H), 8.13 (d, *J* = 8.24 Hz, 1 H), 7.69 (d, *J* = 8.70 Hz, 1 H), 7.51 (t, *J* = 7.79 Hz, 1 H), 6.82 (t, *J* = 8.70 Hz, 1 H), 3.98 (td, *J* = 11.45 Hz, 3.66 Hz, 1 H), 3.93 (d, *J* = 12.82 Hz, 1 H), 3.85 (s, 3 H), 3.38 (m, 1 H), 2.91-2.86 (m, 1 H), 2.47-2.43 (m, 1 H), 2.27-2.23 (m, 1 H), 2.17-2.10 (m, 1 H),

1.89 (qd, *J* - 11.91 Hz, 4.12 Hz, 1 H), 1.71-1.63 (m, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 170.8, 167.5, 147.3, 142.1, 136.4, 131.2, 126.0, 118.5, 115.4, 81.4, 53.25, 53.22, 49.1, 29.1, 25.0, 22.0; **HRMS-ESI:** *m/z* calcd. for $C_{16}H_{17}N_3O_6$ $[M+Na]^+$: 370.1010, found 370.1015.

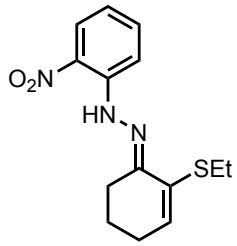


(*E*)-methyl-4-(2-(2-nitrophenyl)hydrazono)-2-oxooctahydro-*2H*-cyclohepta[*b*]furan-3- carboxylate (**2.31**). Hydrazone (**SI1**) (0.055 g, 0.463 mmol) was treated following general procedure **M.** Dimethyl malonate was used in place of aryl acetic acid methyl ester. Flash chromatography (45:55 EtOAc-Hexanes) gave an orange solid (0.0699 g, 92%). mp 220-222 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.69 (s, 1 H), 8.15 (d, *J* = 8.70 Hz, 1 H), 7.75 (d, *J* = 8.70 Hz, 1 H), 7.53 (t, *J* = 7.79 Hz, 1 H), 6.85 (t, *J* = 7.79 Hz, 1 H), 4.38 (d, *J* = 11.91 Hz, 1 H), 4.11 (td, *J* = 10.99 Hz, 3.20 Hz, 1 H), 3.88 (t, *J* = 10.99 Hz, 1 H), 3.85 (s, 3 H), 2.82-2.77 (m, 1 H), 2.51-2.47 (m, 1 H), 2.38-2.30 (m, 1 H), 2.21-2.13 (m, 2 H), 1.84-1.71 (m, 2 H), 1.35-1.27 (m, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 170.5, 167.7, 148.0, 141.9, 136.5, 131.5, 126.0, 118.8, 115.6, 82.1, 53.2, 52.6, 50.1, 34.7, 30.7, 24.9, 23.2; **HRMS-ESI:** *m/z* calcd. for $C_{17}H_{19}N_3O_6$ $[M+H]^+$: 362.1347, found 362.1350.



(*E*)-3-methyl-4-(2-(2-nitrophenyl)hydrazono)hexahydrobenzofuran-2(3*H*)-one (**2.26**). To a cooled (–78 °C) solution of KHMDS (0.59 mL, 0.596 mmol, 1.0 M soln in THF) in THF (5 mL) was added drop-wise over a period of ca. 5 min a solution of 1-(1*H*-pyrrol-1-yl)propan-1-one[193] (0.067 g, 0.586 mmol) in THF (1 mL). The reaction mixture was stirred at –78 °C for 10 min, warmed to 0 °C (ice-bath) for 30 min, and cooled back down to –78 °C for 10 min. A solution of hydrazone **2.16** (0.054 g, 0.218 mmol) in THF (1 mL) was cooled to –78 °C and added dropwise over a period ca. 5 min to the preformed enolate solution followed by the addition of a THF wash (0.5 mL). The resulting deep purple solution was stirred 5 min at –78 °C and subsequently warmed to 0 °C (ice-bath) and stirred 1 h. The reaction was quenched with aq. 10% NH_4OH saturated with NH_4Cl (5 mL). The orange biphasic solution was partitioned between CH_2Cl_2 and H_2O, and the aq. phase extracted with CH_2Cl_2 (3 X 15 mL). The combined organic extracts were washed with sat. aq. NaCl, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash chromatography (20:80 EtOAc-Hexanes) over silica gel gave an orange solid (0.032 g, 48%). mp 213-215 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.89 (s, 1 H), 8.16 (dd, *J* = 8.70 Hz, 1.37 Hz, 1 H), 7.78 (dd, *J* = 8.70 Hz, 0.92 Hz, 1 H), 7.58-7.51 (m, 1 H), 6.85-6.81 (m, 1 H), 3.88 (td, *J* = 11.22 Hz, 4.12 Hz, 1 H), 3.01-2.89 (m, 2 H), 2.48 (t, *J* = 11.45 Hz, 1 H), 2.44-2.39 (m, 1 H), 2.24-2.18 (m, 1 H), 2.12-2.03 (m, 1 H), 1.79 (qd, *J* = 11.91 Hz, 4.12 Hz, 1 H), 1.72-1.63 (m, 1 H), 1.42 (d, *J* = 6.87, 3 H); **^{13}C NMR**

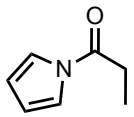
(125 MHz, $CDCl_3$): δ 178.5, 149.2, 142.3, 136.4, 131.1, 126.1, 118.3, 115.4, 81.2, 56.4, 37.8, 29.3, 25.5, 22.3, 13.5; **HRMS-ESI:** *m/z* calcd. for $C_{15}H_{17}N_3O_4$ $[M+Na]^+$: 326.1111, found 326.1116.



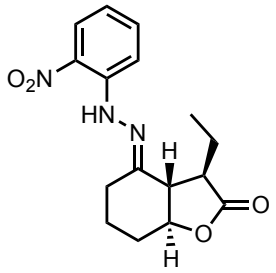
(*E*)-1-(2-ethylthio)cyclohex-2-en-1-ylidene)-2-(2-nitrophenyl)hydrazine

(**2.33**). To a cooled (– 78 °C) solution of KHMDS (0.46 mL, 0.463 mmol, 1.0 M soln in THF) in THF (1 mL) was added drop-wise over a period of ca. 5 min a solution of *S*-ethyl propanethioate (0.054 g, 0.453 mmol) in THF (1 mL). The reaction mixture was stirred at –78 °C for 10 min, warmed to 0 °C (ice-bath) for 30 min, and cooled back down to –78 °C for 10 min. A solution of hydrazone **2.16** (0.051 g, 0.206 mmol) in THF (1 mL) was cooled to –78 °C and added dropwise over a period ca. 5 min to the preformed enolate solution followed by the addition of a THF wash (0.5 mL). The resulting deep purple solution was stirred 5 min at –78 °C and subsequently warmed to 0 °C (ice- bath) and stirred 1 h. The reaction was quenched with aq. 10% NH_4OH saturated with NH_4Cl (5 mL). The orange biphasic solution was partitioned between EtOAc and H_2O, and the aq. phase extracted with EtOAc (3 X 15 mL). The combined organic extracts were washed with sat. aq. NaCl, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash chromatography (20:80 EtOAc-Hexanes) over silica gel gave an red solid (0.047 g, 78%). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 10.93 (s, 1 H), 8.14 (d, *J* = 8.59, 1 H), 7.96 (d, *J* = 8.59 Hz, 1 H), 7.54 (t, *J* = 6.87, 1 H), 6.83-6.80 (m, 1 H), 6.10 (t, *J* = 4.58 Hz, 1 H), 7.45 (q, *J* = 7.45 Hz, 2 H), 2.61 (t, *J* = 6.30, 2 H), 2.35 (q, *J* = 5.15 Hz, 2 H), 1.92 (quin., *J* = 6.87

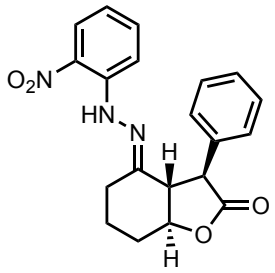
Hz, 2 H), 1.34 (t, J = 7.45 Hz, 3 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 147.2, 142.2, 136.4, 133.1, 131.3, 129.5, 125.8, 118.3, 116.4, 26.1, 24.8, 24.6, 21.1, 13.6; **MS-EI:** *m/z* calcd. for $C_{14}H_{17}N_3O_2S$ $[M]^+$: 291.10, found 291.20.



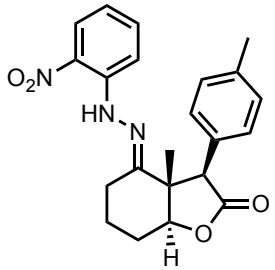
1-(1*H*-pyrrol-1-yl)butan-1-one (**SI5**). To a solution of freshly distilled pyrrole (1.4 mL, 20.21 mmol) in THF (20 mL) at 0 °C was added *n*-BuLi (7.70 mL, 19.25 mmol, 2.5 M hexanes). This solution was stirred 20 min at 0 °C and cooled to –78 °M. Butyryl chloride was added as a solution in THF (10 mL) via cannula, and the reaction was stirred at –78 °C for 30 min then warmed to rt. After 4 h, the reaction was poured into a separatory funnel containing Et_2O (20 mL) and H_2O (20 mL). The aqueous phase was extracted with Et_2O (3 X 20 mL). The combined organic extracts were washed with sat. aq. NaCl (20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by fractional distillation (102-105 °C, 30 mm Hg) to provide a colorless liquid (1.8 g, 69 %). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.31 (brs, 2 H), 6.28 (t J = 2.29 Hz, 2 H), 2.80 (t, J = 7.33 Hz, 2 H), 1.81 (sext, J = 7.79 Hz, 2 H), 1.03 (t, J = 7.33 Hz, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 170.6, 119.6, 113.0, 36.4, 18.1, 13.8; **HRMS-CI:** *m/z* calcd. for $C_8H_{11}NO$ $[M]^+$: 137.0841, found 137.0839.



(*E*)-3-ethyl-4-(2-(2-nitrophenyl)hydrazono)hexahydrobenzofuran-2(3*H*)-one (**2.27**). To a cooled (–78 °C) solution of KHMDS (0.52 mL, 0.525 mmol, 1.0 M soln in THF) in THF (5 mL) was added drop-wise over a period of ca. 5 min a solution of 1-(1*H*-pyrrol-1-yl)butan-1-one (**SI5**) (0.070 g, 0.515 mmol) in THF (1 mL). The reaction mixture was stirred at –78 °C for 10 min, warmed to 0 °C (ice-bath) for 30 min, and cooled back down to –78 °C for 10 min. A solution of hydrazone **2.16** (0.051 g, 0.206 mmol) in THF (1 mL) was cooled to –78 °C and added dropwise over a period ca. 5 min to the preformed enolate solution followed by the addition of a THF wash (0.5 mL). The resulting deep purple solution was stirred 5 min at –78 °C and subsequently warmed to 0 °C (ice-bath) and stirred 1 h. The reaction was quenched with aq. 10% NH_4OH saturated with NH_4Cl (5 mL). The orange biphasic solution was partitioned between CH_2Cl_2 and H_2O, and the aq. phase extracted with CH_2Cl_2 (3 X 15 mL). The combined organic extracts were washed with sat. aq. NaCl, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash chromatography (20:80 EtOAc-Hexanes) over silica gel gave an orange solid (0.035 g, 54%). mp 152-154 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.90 (s, 1 H), 8.15 (d, *J* = 8.24 Hz, 1 H), 7.77 (d, *J* = 7.77 Hz, 1 H), 7.55 (t, *J* = 7.79 Hz, 1 H), 6.86-6.80 (m, 1 H), 3.86 (td, *J* = 10.99 Hz, 3.66 Hz, 1 H), 2.99 (dt, *J* = 12.36 Hz, 5.50 Hz, 1 H), 2.92 (dq, *J* = 15.11 Hz, 3.66 Hz, 1 H), 2.61 (t, *J* = 11.45 Hz, 1 H), 2.41 (dq, *J* = 11.68 Hz, 3.66 Hz, 1 H), 2.25-2.19 (m, 1 H), 2.11-2.04 (m, 1 H), 2.00-1.75 (m, 3 H), 1.72-1.63 (m, 1 H), 1.06 (t, *J* = 7.33 Hz, 3 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 177.8, 149.5, 142.3, 136.4, 131.0, 126.1, 118.2, 115.4, 81.1, 53.4, 43.2, 29.4, 25.7, 22.3, 21.2, 11.2; **HRMS-ESI:** *m/z* calcd. for $C_{16}H_{19}N_3O_4$ $[M+Na]^+$: 340.1268, found 340.1276.

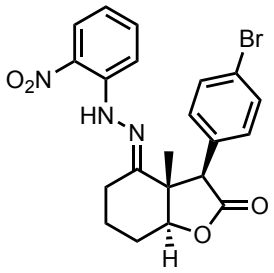


(*E*)-3a-methyl-4-(2-(2-nitrophenyl)hydrazono)-3-phenylhexahydrobenzofuran-2(3*H*)-one (**2.36**). Hydrazone (**SI2**) (0.0506 g, 0.193 mmol) was treated following general procedure **M.** Flash chromatography (30:70 EtOAc-Hexanes) gave an orange solid (0.048 g, 65%). mp 77-79 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 10.82 (s, 1 H), 8.16 (d, J = 8.59 Hz, 1H), 7.82 (d, J = 8.59 Hz, 1 H), 7.59-7.54 (m, 3 H), 7.39-7.36 (m, 2 H), 7.35-7.30 (m, 1 H), 6.85 (t, J = 8.02 Hz, 1 H), 4.47 (s, 1 H), 4.15 (dd, J = 12.60 Hz, 4.01 Hz, 1 H), 2.84-2.79 (m, 1 H), 2.33-2.19 (m, 3 H), 2.06 (qd, J = 12.60 Hz, 5.15 Hz, 1 H), 1.79-1.70 (m, 1 H), 1.16 (s, 3 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 176.2, 154.7, 142.4, 136.3, 133.1, 131.5, 131.3, 128.0, 127.8, 126.2, 118.3, 115.9, 83.1, 55.9, 53.1, 22.7, 22.0, 21.3, 15.0; **HRMS-ESI:** *m/z* calcd. for $C_{21}H_{21}N_3O_4$ $[M+Na]^+$: 402.1424, found 402.1428.

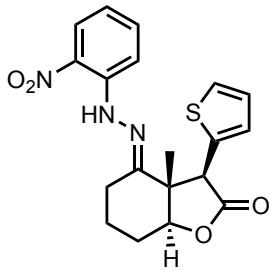


(*E*)-3a-methyl-4-(2-(2-nitrophenyl)hydrazono)-3-(*p*-tolyl)hexahydrobenzofuran-2(3*H*)-one (**2.37**). Hydrazone (**SI2**) (0.0608 g, 0.232 mmol) was treated following general procedure **M.** Flash chromatography (25:75 EtOAc-Hexanes) gave a yellow solid (0.049 g, 54%). mp 216-218 °C; **^{1}H NMR** (500

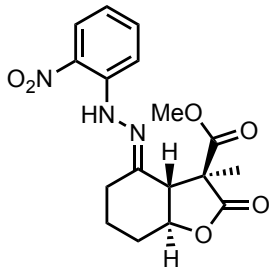
MHz, $CDCl_3$): δ 10.81 (s, 1 H), 8.16 (d, *J* = 8.59 Hz, 1H), 7.84 (d, *J* = 8.59 Hz, 1 H), 7.58 (t, *J* = 6.87 Hz, 1 H), 7.43 (d, *J* =8.59 Hz, 2 H), 7.18 (d, *J* = 8.02 Hz, 2 H), 6.85 (t, *J* = 6.87 Hz, 1 H), 4.43 (s, 1 H), 4.13 (dd, *J* = 12.60 Hz, 4.01 Hz, 1 H), 2.83-2.79 (m, 1 H), 2.34 (s, 3 H), 2.32-2.18 (m, 3 H), 2.05 (qd, *J* = 11.74 Hz, 5.15 Hz, 1 H), 1.77-1.69 (m, 1 H), 1.15 (s, 3 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 176.4, 154.8, 142.4, 137.5, 136.3, 131.4, 131.2, 130.0, 128.7, 126.1, 118.3, 116.0, 83.0, 55.7, 53.1, 22.7, 22.0, 21.3, 21.2, 15.0; **HRMS-ESI:** *m/z* calcd. for $C_{22}H_{23}N_3O_4$ $[M+Na]^+$: 416.1581, found 416.1584.



(*E*)-3-(4-bromophenyl)-3a-methyl-4-(2-(2-nitrophenyl)hydrazono)hexahydro-benzofuran-2(3*H*)- one (**2.38**). Hydrazone (**SI2**) (0.060 g, 0.229 mmol) was treated following general procedure **M.** Flash chromatography (20:80 EtOAc-Hexanes) gave an orange solid (0.057 g, 55%). mp 225- 227 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.81 (s, 1 H), 8.17 (dd, *J* = 8.70 Hz, 1.37 Hz, 1 H), 7.73 (dd, *J* = 8.70 Hz, 0.92 Hz, 1 H), 7.58 (td, *J* = 7.33 Hz, 1.37 Hz, 1 H), 7.51-7.43 (m, 4 H), 6.88- 6.84 (m, 1 H), 4.43 (s, 1 H), 4.14 (dd, *J* = 12.36 Hz, 4.12 Hz, 1 H), 2.82 (ddd, 15.8 Hz, 6.64 Hz, 0.92 Hz, 1 H), 2.33-2.17 (m, 3 H), 2.05 (dq, *J* 13.05 Hz, 4.35 Hz, 1 H), 1.79-1.67 (m, 1 H), 1.12 (s, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 175.7, 154.6, 142.2, 136.3, 133.1, 132.2, 131.4, 131.1, 126.2, 122.0, 118.5, 115.7, 83.1, 55.3, 53.1, 22.7, 22.1, 21.3, 14.9; **HRMS-ESI:** *m/z* calcd. for $C_{21}H_{20}BrN_3O_4$ $[M+Na]^+$: 480.0529, found 480.0570.



(*E*)-3a-methyl-4-(2-(2-nitrophenyl)hydrazono)-3-(thiophen-2-yl)hexahydro-benzofuran-2(3*H*)- one (**2.39**). Hydrazone (**SI2**) (0.062 g, 0.237 mmol) was treated following general procedure M. Flash chromatography (30:70 EtOAc-Hexanes) gave an orange solid (0.074 g, 81%). mp 155- 156 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 10.93 (s, 1 H), 8.17 (d, *J* = 8.59 Hz, 1H), 8.05 (d, *J* = 8.02 Hz, 1 H), 7.58 (t, *J* = 8.02 Hz, 1 H), 7.34 (d, *J* =3.44 Hz, 1 H), 7.27-7.25 (m, 1 H), 7.01 (dd, *J* = 5.15 Hz, 3.44 Hz, 1 H), 6.85 (t, *J* = 8.02 Hz, 1 H), 4.73 (s, 1 H), 4.07 (dd, *J* = 12.60 Hz, 4.01 Hz, 1 H), 2.85 (dd, *J* = 14.89 Hz, 5.73 Hz, 1 H), 2.34-2.19 (m, 3 H), 2.06 (qd, *J* = 12.03 Hz, 5.15 Hz, 1 H), 1.75-1.65 (m, 1 H), 1.09 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 174.8, 153.5, 142.2, 36.5, 134.5, 131.2, 128.5,126.6, 126.1, 125.7, 118.4, 116.1, 83.2, 53.4, 50.4, 22.9, 22.0, 21.8, 14.1; **HRMS-ESI:** *m/z* calcd. for $C_{19}H_{19}N_3O_4S$ $[M+Na]^+$: 408.0988, found 408.0990.

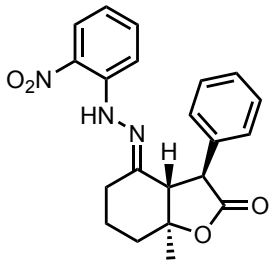


(*E*)-ethyl 3-methyl-4-(2-(2-nitrophenyl)hydrazono)-2-oxooactahydro-benzofuran-3-carboxylate (**2.40**). Hydrazone (**2.16**) (0.086 g, 0.347 mmol) was treated following general procedure **M.** Diethyl methylmalonate was used in place of aryl acetic acid methyl ester. Flash chromatography (30:70 EtOAc-Hexanes) gave an orange solid

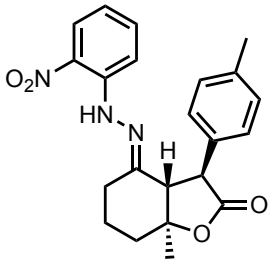
(0.0762 g, 58%). mp 144-146 °C; **^{1}H NMR** (400 MHz, CD_2Cl_2): δ 10.78 (s, 1 H), 8.10 (dd, *J* = 8.47 Hz, 1.37 Hz, 1 H), 7.69 (dd, *J* = 8.70 Hz, 0.92 Hz, 1 H), 7.56-7.52 (m, 1 H), 6.83-6.79 (m, 1 H), 4.70 (td, *J* = 11.45 Hz, 4.12 Hz, 1 H), 4.29-4.07 (m, 2 H), 2.85 (ddd, *J* = 15.68 Hz, 5.04 Hz, 2.75 Hz, 1 H), 2.79 (d, *J* = 11.45 Hz, 1 H), 2.47-2.42 (m, 1 H), 2.21-2.15 (m, 1 H), 2.12-2.03 (m, 1 H), 1.75-1.65 (m, 2 H), 1.57 (s, 3 H), 1.16 (t, *J* = 7.33 Hz, 3 H); **^{13}C NMR** (100 MHz, CD_2Cl_2): δ 174.7, 168.3, 146.9, 142.3, 136.4, 131.0, 125.7, 118.2, 115.7, 80.1, 61.9, 60.0, 51.6, 29.7, 25.0, 21.6, 20.0, 13.9; **HRMS-ESI:** *m/z* calcd. for $C_{18}H_{21}N_3O_6$ $[M+Na]^+$: 398.1323, found 398.1332.

*General procedure **D**: Anti-selective formation of* β,γ*-fused bicyclic* γ*-lactone hydrazones from 6- membered- α-epoxy-β-methyl-(2-nitro)phenyl hydrazones*

To a stirred solution of the aryl acetic methyl ester (2.20 equiv) in THF (0.5 mL) was added KHMDS (2.25 equiv, 1.0 M soln. in THF) at –78 °C. The mixture was stirred for 30 min. Separately, the α-epoxy-β-methyl (2-nitro)phenylhydrazone (**SI3**) (1.0 equiv) was dissolved in THF (1.0 mL) and cooled to –78 °C. This solution was added dropwise over a period ca. 1 min to the preformed enolate solution followed by the addition of a THF wash (0.5 mL). The resulting deep purple solution was stirred 5 min at –78 °C, warmed to –40 °C and stirred for 20 h, and subsequently warmed to 0 °C (ice-bath) and stirred 1 h. The reaction was quenched with aq. 10% NH_4OH saturated with NH_4Cl (5 mL). The orange biphasic solution was partitioned between EtOAc and H_2O, and the aq. phase extracted with EtOAc (3 X 15 mL). The combined organic extracts were washed with sat. aq. NaCl, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash chromatography over silica gel provided the desired β,γ-fused bicyclic γ-lactone hydrazones.

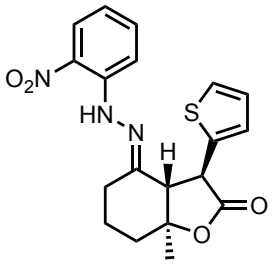


(*E*)-7a-methyl-4-(2-(2-nitrophenyl)hydrazono)-3-phenylhexahydrobenzofuran-2(3*H*)-one (**2.41**). Hydrazone (**SI3**) (0.053 g, 0.202 mmol) was treated following general procedure **D**. Flash chromatography (20:80 EtOAc-Hexanes) gave an orange solid (0.039 g, 51%, 8:1 *dr*). Major diastereomer [**^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.83 (s, 1 H), 8.14 (dd, *J* = 8.70 Hz, 1.37 Hz, 1 H), 7.74 (dd, *J* = 8.24 Hz, 0.92 Hz, 1 H), 7.54 (t, *J* = 7.33 Hz, 1 H), 7.41-7.26 (m, 5 H), 6.84-6.80 (m, 1 H), 4.28 (d, *J* = 12.82 Hz, 1 H), 3.19 (d, *J* = 12.82 Hz, 1 H), 2.85 (ddd, *J* = 14.31 Hz, 6.87 Hz, 2.75 Hz, 1 H), 2.29-2.07 (m, 4 H), 1.93-1.79 (m, 1 H), 1.32 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 176.3, 148.4, 142.3, 136.3, 136.0, 130.6, 129.0, 128.7, 127.8, 126.0, 118.2, 115.6, 83.9, 59.9, 46.8, 36.1, 25.3, 21.3, 20.1]; **HRMS-ESI:** *m/z* calcd. for $C_{21}H_{21}N_3O_4$ $[M+Na]^+$: 402.1424, found 402.1427.



(*E*)-7a-methyl-4-(2-(2-nitrophenyl)hydrazono)-3-(*p*-tolyl)hexahydrobenzofuran-2(3*H*)-one (**2.42**). Hydrazone (**SI3**) (0.0492 g, 0.188 mmol) was treated following general procedure **D**. Flash chromatography (30:70 EtOAc-Hexanes) gave an orange solid (0.0496 g, 67%, 13.5:1 *dr*). Major diastereomer

[**^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.82 (s, 1 H), 8.13 (dd, *J* = 8.70 Hz, 1.37 Hz, 1H), 7.76 (dd, *J* = 8.70 Hz, 1.37 Hz, 1 H), 7.55 (t, *J* = 7.79 Hz, 1 H), 7.27 (d, *J* =8.24 Hz, 2 H), 7.17 (d, *J* = 8.24 Hz, 2 H), 6.84-6.80 (m, 1 H), 4.24 (d, *J* = 12.82 Hz, 1 H), 3.17 (d, *J* = 12.82 Hz, 1 H), 2.84 (ddd, *J* = 15.46 Hz, 6.18 Hz, 2.75 Hz, 1 H), 2.31 (s, 3 H), 2.28-2.01 (m, 4 H), 1.88-1.77 (m, 1 H), 1.33 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 176.6, 148.5, 142.3, 137.6, 136.4, 133.0, 131.0, 129.5, 128.8, 126.0, 118.2, 115.6, 83.8, 60.0, 46.5, 36.1, 25.3, 21.3, 21.2, 20.0]; **HRMS-ESI:** *m/z* calcd. for $C_{22}H_{23}N_3O_4$ $[M+H]^+$: 394.1761, found 394.1765.

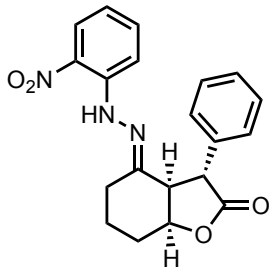


(*E*)-7a-methyl-4-(2-(2-nitrophenyl)hydrazono)-3-(thiophen-2-yl)hexahydrobenzo-furan-2(3*H*)- one (**2.43**). Hydrazone (**SI3**) (0.0604 g, 0.231 mmol) was treated following general procedure **C**. Flash chromatography (30:70 EtOAc-Hexanes) gave an orange foam (0.063 g, 70%, 3:1 *dr*). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 10.90 (s, 1 H) major, 10.87 (s, 1 H) minor, 8.14 (d, *J* = 7.45 Hz, 1 H) major, 8.13 (d, *J* = 8.02 Hz, 1H) minor, 7.84 (dd, *J* = 8.59 Hz, 1.15 Hz, 1 H) major, 7.75 (dd, *J* = 8.59 Hz, 1.15 Hz, 1 H) minor, 7.55-7.48 (m, 1 H), 7.27 (dd, *J* = 5.15 Hz, 1.15 Hz, 1 H) minor, 7.23 (dd, *J* = 5.15 Hz, 1.15 Hz, 1 H) major, 7.17-7.16 (m, 1 H) major, 7.13-7.12 (m, 1 H) minor, 6.99-6.97 (m, 1 H), 6.82 (t, *J* =7.45 Hz, 1 H), 4.55 (d, *J* = 12.03 Hz, 1 H) major, 4.32 (d, *J* = 10.88 Hz, 1 H) minor, 3.46 (d, *J* = 10.88 Hz, 1 H) minor, 3.19 (d, *J* = 12.60 Hz, 1 H) major, 2.92-2.86 (m, 1 H) major, 2.77 (dt, *J* = 16.61 Hz, 5.15 Hz, 1 H) minor,

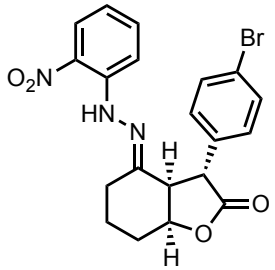
2.41-2.35 (m, 1 H) minor, 2.26-2.15 (m, 2 H), 2.10-1.92 (m, 1 H), 1.87-1.80 (m, 1 H) major, 1.72-1.69 (m, 1 H) minor, 1.59 (s, 3 H) minor, 1.31 (s, 3 H) major; **^{13}C NMR** (125 MHz, $CDCl_3$): major δ 174.8, 147.8, 142.2, 137.5, 136.4, 131.1, 126.9, 126.5, 126.0, 125.1, 118.3, 115.8, 83.9, 60.1, 41.6, 36.0, 25.3, 21.3, 20.0; minor δ 173.6, 148.5, 141.9, 137.1, 136.4, 131.2, 126.9, 126.4, 125.9, 125.6, 118.5, 115.9,84.5, 57.4, 46.9, 35.2, 26.8, 23.2, 19.4; **HRMS-ESI:** *m/z* calcd. for $C_{19}H_{19}N_3O_4S$ $[M+Na]^+$: 408.0988, found 408.0989.

*General procedure **E**: Syn-selective formation of* β,γ*-fused bicyclic* γ*-lactone hydrazones from 6- membered-α-epoxy-(2-nitro)phenyl hydrazones*

To a stirred solution of the aryl acetic methyl ester (2.20 equiv) in THF (0.5 mL) was added LiHMDS (2.25 equiv, 1.0 M soln. in THF) at –78 °C. The mixture was stirred for 30 min. Separately, α-epoxy (2-nitro)phenylhydrazone **2.16** (1.0 equiv) was dissolved in THF (1.0 mL) and cooled to –78 °C. This solution was added dropwise over a period ca. 1 min to the preformed enolate solution followed by the addition of a THF wash (0.5 mL). The resulting deep purple solution was stirred 3 h at –78 °C and subsequently warmed to rt and stirred 2 h. The reaction was quenched with aq. 10% NH_4OH saturated with NH_4Cl (5 mL). The orange biphasic solution was partitioned between EtOAc and H_2O, and the aq. phase extracted with EtOAc (3 X 15 mL). The combined organic extracts were washed with sat. aq. NaCl, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash chromatography over silica gel provided the desired β,γ-fused bicyclic γ-lactone hydrazones.

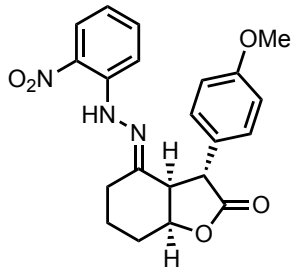


(*E*)-4-(2-(2-nitrophenyl)hydrazono)-3-phenylhexahydrobenzofuran-2(3*H*)-one (**2.47**). Hydrazone (**2.16**) (0.064 g, 0.258 mmol) was treated following general procedure **E**. Flash chromatography (30:70 EtOAc-Hexanes) gave an orange foam (0.053 g, 56%, 6.5:1 dr). **^{1}H NMR** (500 MHz, $CDCl_3$): δ major diastereomer 10.86 (s, 1 H), 8.14 (dd, *J* = 8.59 Hz, 1.15 Hz, 1 H), 7.61 (dd, *J* = 8.59 Hz, 1.15 Hz, 1 H), 7.48-7.45 (m, 1 H), 7.39-7.36 (m, 2 H), 7.32-7.28 (m, 3 H), 6.83-6.80 (m, 1 H), 4.97 (ddd, *J* = 6.30 Hz, 6.30 Hz, 6.87 Hz, 1 H), 4.40 (d, *J* = 6.87 Hz, 1 H), 3.55 (t, *J* = 6.87 Hz, 1 H), 2.64-2.58 (m, 1 H), 2.55-2.49 (m, 1 H), 2.16-2.10 (m, 1 H), 2.07-1.90 (m, 2 H), 1.79-1.69 (m, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ major diastereomer 176.1, 149.0, 142.0, 136.4, 135.8, 131.2, 129.1, 128.2, 127.8, 125.9, 118.5, 115.8, 77.3, 50.0, 49.8, 28.2, 24.7, 18.2; **HRMS-ESI:** *m/z* calcd. for $C_{20}H_{19}N_3O_4$ $[M+Na]^+$: 388.1268, found 388.1282.



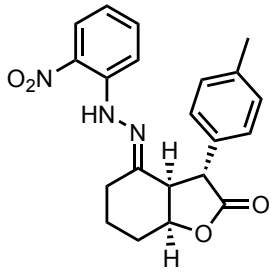
(*E*)-3-(4-bromophenyl)-4-(2-(2-nitrophenyl)hydrazono)-hexahydrobenzofuran-2(3*H*)-one (**2.48**). Hydrazone (**2.16**) (0.062 g, 0.250 mmol) was treated following general procedure **E**. Flash chromatography (30:70 EtOAc-Hexanes) gave an orange foam (0.0401 g, 36%, 1.3:1 dr). **^{1}H NMR** (500 MHz, d_6-DMSO): δ

major diastereomer 10.49 (s, 1 H), 8.03-8.01 (m, 1 H), 7.61-7.46 (m, 4 H), 7.37 (d, *J* = 8.59 Hz, 1 H), 7.29-7.26 (m, 1 H), 6.84-6.80 (m, 1 H), 4.94 (ddd, *J* = 8.16 Hz, 8.02 Hz, 6.30 Hz, 1 H), 4.43 (d, *J* = 11.46 Hz, 1 H), 3.68 (dd, *J* = 11.17 Hz, 8.02 Hz, 1 H), 2.61 (td, *J* = 16.61 Hz, 4.58 Hz, 1 H), 2.51-2.48 (m, 1 H), 2.15-2.01 (m, 1 H), 1.92-1.86 (m, 1 H), 1.83-1.74 (m, 1 H), 1.59-1.48 (m, 1 H); **^{13}C NMR** (125 MHz, d_6-DMSO): δ major diastereomer 175.8, 152.5, 142.0, 136.9, 136.1, 131.8, 131.7, 131.1, 126.1, 121.1, 118.7, 115.7, 77.5, 49.8, 48.5, 28.3, 23.8, 18.7; **HRMS-ESI:** *m/z* calcd. for $C_{20}H_{18}BrN_3O_4$ $[M+Na]^+$: 466.0373, found 466.0377.

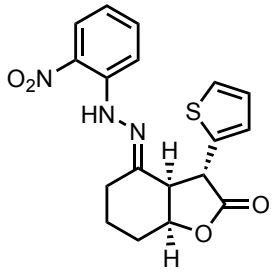


(*E*)-3-(4-methoxyphenyl)-4-(2-(2-nitrophenyl)hydrazono)-hexahydrobenzofuran-2(3*H*)-one (**2.49**). Hydrazone (**2.16**) (0.058 g, 0.234 mmol) was treated following general procedure **E**. Flash chromatography (30:60 EtOAc-Hexanes) gave an orange foam (0.042 g, 45%, 2.8:1 dr). **^{1}H NMR** (400 MHz, $CDCl_3$): δ major diastereomer 10.85 (s, 1 H), 8.14 (dd, *J* = 8.70 Hz, 1.37 Hz, 1 H), 7.62 (dd, *J* = 8.70 Hz, 1.37 Hz, 1 H), 7.49-7.44 (m, 1 H), 7.21 (d, *J* = 8.70 Hz, 2 H), 6.89 (d, *J* = 8.70 Hz, 2 H), 6.83-6.79 (m, 1 H), 4.95 (ddd, *J* = 6.18 Hz, 6.41 Hz, 6.87 Hz, 1 H), 4.30 (d, *J* = 7.33 Hz, 1 H), 3.79 (s, 3 H), 3.52 (t, *J* = 7.33 Hz, 1 H), 2.58-2.54 (m, 2 H), 2.16-2.10 (m, 1 H), 2.03-1.89 (m, 2 H), 1.78-1.68 (m, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 176.6, 159.1, 149.1, 142.0, 136.4, 130.0, 129.3, 127.6, 125.9, 118.5, 115.9, 114.4, 77.2, 55.4, 50.1,

49.0, 28.3, 24.6, 18.3; **HRMS-ESI:** *m/z* calcd. for $C_{21}H_{21}N_3O_5$ $[M+Na]^+$: 418.1373, found 418.1384.



(*E*)-4-(2-(2-nitrophenyl)hydrazono)-3-(*p*-tolyl)-hexahydrobenzofuran-2(3*H*)-one (**2.50**). Hydrazone (**2.16**) (0.065 g, 0.265 mmol) was treated following general procedure **E**. Flash chromatography (30:70 EtOAc-Hexanes) gave an orange foam (0.0486 g, 49%, 3:1 dr). **^{1}H NMR** (400 MHz, $CDCl_3$): δ major diastereomer 10.85 (s, 1 H), 8.14 (dd, *J* = 8.70 Hz, 1.37 Hz, 1 H), 7.63 (dd, *J* = 8.01 Hz, 1.37 Hz, 1 H), 7.49-7.45 (m, 1 H), 7.18 (m, 4 H), 6.84-6.79 (m, 1 H), 4.96 (ddd, *J* = 5.95 Hz, 6.29 Hz, 6.64 Hz, 1 H), 4.36 (d, *J* = 6.87 Hz, 1 H), 3.52 (t, *J* = 6.87 Hz, 1 H), 2.63-2.47 (m, 2 H), 2.34 (s, 3 H), 2.13-2.09 (m, 1 H), 2.01-1.89 (m, 2 H), 1.77-1.72 (m, 1 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ major diastereomer 176.3, 149.2, 142.0, 137.5, 136.3, 132.7, 131.2, 129.7, 128.0, 125.9, 118.4, 115.9, 77.3, 50.0, 49.4, 28.2, 24.7, 21.2, 18.2; **HRMS-ESI:** *m/z* calcd. for $C_{21}H_{21}N_3O_4$ $[M+Na]^+$: 402.1424, found 402.1432.



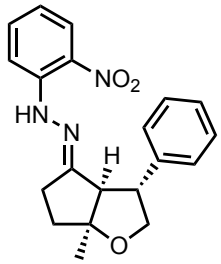
(*E*)-4-(2-(2-nitrophenyl)hydrazono)-3-(thiophen-2-yl)hexahydrobenzofuran-2(3*H*)-one (**2.51**). Hydrazone (**2.16**) (0.0495 g, 0.200 mmol) was treated following

general procedure **E**. Flash chromatography (30:70 EtOAc-Hexanes) gave an orange foam (0.044 g, 60%, 2:1 dr). **^{1}H NMR** (400 MHz, $CDCl_3$): δ major diastereomer 10.89 (s, 1 H), 8.14 (d, *J* = 8.70 Hz, 1 H), 7.75 (d, *J* = 7.33 Hz, 1 H), 7.53-7.49 (m, 1 H), 7.28 (dd, *J* = 5.04 Hz, 0.92 Hz, 1 H), 7.10-7.09 (m, 1 H), 7.02-6.99 (m, 1 H), 6.86-6.80 (m, 1 H), 5.01 (ddd, *J* = 6.53 Hz, 6.18 Hz, 5.50 Hz, 1 H), 4.64 (d, *J* = 6.87 Hz, 1 H), 3.65 (t, *J* = 6.41 Hz, 1 H), 2.66-2.58 (m, 1 H), 2.53-2.47 (m, 1 H), 2.14-2.08 (m, 1 H), 2.00-1.90 (m, 2 H), 1.83-1.72 (m, 1 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ major diastereomer 174.7, 148.4, 142.0, 137.2, 136.5, 131.3, 127.2, 126.3, 125.9, 125.5, 118.6, 115.8, 77.7, 50.0, 45.0, 28.2, 24.8, 18.4; **HRMS-ESI:** *m/z* calcd. for $C_{18}H_{17}N_3O_4S$ $[M+Na]^+$: 394.0832, found 394.0841.

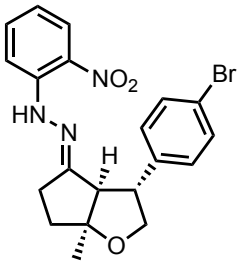
*General procedure **F**: Syn-selective formation of* β,γ*-fused bicyclic* γ*-lactone hydrazones from 5- membered-α-epoxy-β-methyl-(2-nitro)phenyl hydrazone*

To a stirred solution of the aryl acetic methyl ester (2.20 equiv) in THF (0.5 mL) was added LiHMDS (2.25 equiv, 1.0 M soln. in THF) at –78 °C. The mixture was stirred for 30 min. Separately, α-epoxy-β-methyl (2-nitrophenyl)hydrazone (**SI4**) (1.0 equiv) was dissolved in THF (1.0 mL) and cooled to –78 °C. This solution was added dropwise over a period ca. 1 min to the preformed enolate solution followed by the addition of a THF wash (0.5 mL). The resulting deep purple solution was stirred 4 h at –78 °C and subsequently warmed to 0 °C (ice-bath) and stirred 1 h. The reaction was quenched with aq. 10% NH_4OH saturated with NH_4Cl (5 mL). The orange biphasic solution was partitioned between EtOAc and H_2O, and the aq. phase extracted with EtOAc (3 X 15 mL). The combined organic extracts were washed with sat. aq. NaCl, dried over $MgSO_4$,

filtered, and concentrated *in vacuo*. Flash chromatography over silica gel provided the desired β,γ-fused bicyclic γ-lactone hydrazones.

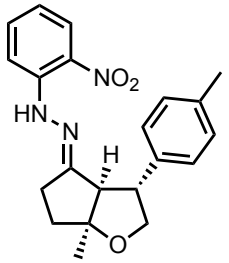


(*E*)-6a-methyl-4-(2-(2-nitrophenyl)hydrazono)-3-phenylhexahydro-*2H*-cyclopenta[*b*]furan-2-one (**SI4**). Hydrazone (**2.52**) (0.065 g, 0.262 mmol) was treated following general procedure **N.** Flash chromatography (20:80 EtOAc-Hexanes) gave an orange solid (0.059 g, 61%). mp 166-167 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.60 (s, 1 H), 8.17 (dd, *J* = 8.70 Hz, 1.37 Hz, 1H), 7.79 (dd, *J* = 8.24 Hz, 0.92 Hz, 1 H), 7.52 (t, *J* = 7.56 Hz, 1 H), 7.45-7.36 (m, 4 H), 7.36-7.31 (m, 1 H), 6.87-6.82 (m, 1 H), 4.25 (d, *J* = 2.75 Hz, 1 H), 3.42 (t, *J* = 2.29 Hz, 1 H), 2.79-2.63 (m, 2 H), 2.55-2.48 (m, 1 H), 2.12 (dt, *J* = 14.32 Hz, 9.16 Hz, 1 H), 1.52 (s, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 175.6, 158.7, 141.9, 136.3, 131.2, 129.1, 127.7, 127.6, 126.0, 118.5, 115.7, 91.2, 57.1, 54.4, 35.8, 26.0, 25.6; **HRMS-ESI:** *m/z* calcd. for $C_{20}H_{19}N_3O_4$ $[M+Na]^+$: 388.1268, found 388.1274.



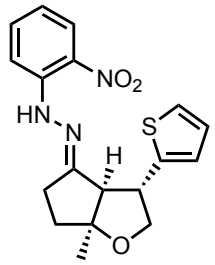
(*E*)-3-(4-bromophenyl)-6a-methyl-4-(2-(2-nitrophenyl)hydrazono)-hexahydro-*2H*- cyclopenta[*b*]furan-2-one (**SI4**). Hydrazone (**2.53**) (0.0474 g, 0.191

mmol) was treated following general procedure **N.** Flash chromatography (20:80 EtOAc-Hexanes) gave a yellow solid (0.036 g, 42%). mp 174-176 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 10.60 (s, 1 H), 8.16 (dd, *J* = 8.59 Hz, 1.72 Hz, 1 H), 7.76 (dd, *J* = 9.00 Hz, 1.15 Hz, 1 H), 7.55-7.51 (m, 3 H), 7.32 (d, *J* = 8.51 Hz, 2 H), 6.84 (m, 1 H), 4.26 (d, *J* = 3.34 Hz, 1 H), 3.37-3.36 (m, 1 H), 2.76-2.65 (m, 2 H), 2.53-2.47 (m, 1 H), 2.14 (dt, *J* = 14.32 Hz, 9.16 Hz, 1 H), 1.51 (s, 3 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 175.1, 158.2, 141.8, 136.4, 135.2, 132.2, 131.2, 129.3, 126.0, 121.8, 118.6, 115.6, 91.1, 57.1, 53.7, 35.8, 26.0, 25.6; **HRMS-ESI:** *m/z* calcd. for $C_{20}H_{18}BrN_3O_4$ $[M+Na]^+$: 466.0373, found 466.0375.



(*E*)-6a-methyl-4-(2-(2-nitrophenyl)hydrazono)-3-(*p*-tolyl)hexahydro-*2H*-cyclo-penta[*b*]furan-2- one (**SI4**). Hydrazone (**2.54**) (0.0543 g, 0.219 mmol) was treated following general procedure **N.** Flash chromatography (20:80 EtOAc-Hexanes) gave a yellow solid (0.045 g, 54%). mp 177- 179 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.59 (s, 1 H), 8.16 (d, *J* = 8.70 Hz, 1 H), 7.79 (d, *J* = 8.70 Hz, 1 H), 7.52 (t, *J* = 7.52 Hz, 1 H), 7.31 (d, *J* = 8.24 Hz, 2 H), 7.21 (d, *J* = 7.79 Hz, 2 H), 6.84 (t, *J* = 7.79 Hz, 1 H), 4.24 (d, *J* = 2.75 Hz, 1 H), 3.40 (t, *J* = 2.29 Hz, 1 H), 2.78-2.63 (m, 2 H), 2.54-2.47 (m, 1 H), 2.36 (s, 3 H), 2.10 (dt, *J* = 14.20 Hz, 9.16 Hz, 1 H), 1.51 (s, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 175.9, 158.9, 141.9, 137.4, 136.3, 133.2, 131.1, 129.8, 127.4, 126.0, 118.5, 115.7, 91.2,

57.2, 54.1, 35.8, 25.9, 25.6, 21.1; **HRMS-ESI:** *m/z* calcd. for $C_{21}H_{21}N_3O_4$ $[M+Na]^+$: 402.1424, found 402.1432.

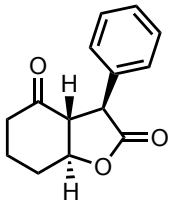


(*E*)-6a-methyl-4-(2-(2-nitrophenyl)hydrazono)-3-(thiophen-2-yl)hexahydro-*2H*-cyclopenta[*b*]- furan-2-one (**SI4**). Hydrazone (**2.55**) (0.049 g, 0.198 mmol) was treated following general procedure **N.** Flash chromatography (20:80 EtOAc-Hexanes) gave an orange solid (0.047 g, 64%). mp 168-169 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.60 (s, 1 H), 8.17 (dd, *J* = 8.70 Hz, 1.37 Hz, 1 H), 7.80 (d, *J* = 8.70 Hz, 1 H), 7.54-7.50 (m, 1 H), 7.30 (d, *J* = 4.58 Hz,1 H), 7.14-7.13 (m, 1 H), 7.02 (dd, *J* = 5.04 Hz, 3.66 Hz, 1 H), 6.87-6.83 (m, 1 H), 4.41 (d, *J* = 1.37 Hz, 1 H), 3.53 (t, *J* = 2.29 Hz, 1 H) 2.78-2.62 (m, 2 H), 2.55-2.48 (m, 1 H), 2.14 (dt, *J* = 14.20 Hz, 9.62 Hz, 1 H), 1.56 (s, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 174.5, 157.8, 141.8, 138.1, 136.4, 131.2, 127.3, 126.0, 125.6, 125.5, 118.6, 115.7, 91.8, 57.3, 49.9, 35.6, 25.9, 25.4; **HRMS-ESI:** *m/z* calcd. for $C_{18}H_{17}N_3O_4S$ $[M+Na]^+$: 394.0832, found 394.0837.

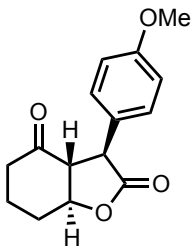
*General procedure **G**: Hydrolysis of* β,γ*-fused bicyclic* γ*-lactone hydrazones.*

To a stirred solution of the β,γ-fused bicyclic γ-lactone hydrazone (1.0 equiv) in acetone/H_2O (9:1, 0.1 M) at rt was added *p*-TsOH·H_2O (3.0 equiv). The reaction was monitored by TLC, typically taking 24-72 h. Upon completion, the reaction was diluted with CH_2Cl_2 (10 mL) and washed sequentially with sat. aq. $NaHCO_3$ (5 mL) and sat. aq.

NaCl (5 mL). The organic phase was then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash chromatography over silica gel gave the desired ketones.

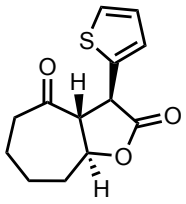


3-phenylhexahydrobenzofuran-2,4-dione (**2.57**). Hydrazone (**2.36**) (0.0151 g, 0.041 mmol) was treated following general procedure **P.** Flash chromatography (30:70 EtOAc-Hexanes) gave a white solid (0.007 g, 73%). mp 149-151 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.37-7.27 (m, 5 H), 4.08 (d, *J* = 12.03 Hz, 1 H), 4.06 (td, *J* = 11.74 Hz, 4.01 Hz, 1 H), 3.21 (t, *J* = 12.03 Hz, 1 H), 2.56-2.51 (m, 1 H), 2.44-2.35 (m, 2 H), 2.28-2.22 (m, 1 H), 1.99 (qd *J* = 12.03 Hz, 4.58 Hz, 1 H), 1.80-1.70 (m, 1 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 203.2, 175.0, 134.8, 128.9, 1286.6, 127.9, 80.1, 63.5, 47.0, 40.4, 29.6, 22.0; **HRMS-ESI:** *m/z* calcd. for $C_{14}H_{14}O_3$ $[M+Na]^+$: 253.0835, found 253.0844.

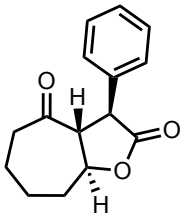


3-(4-methoxyphenyl)hexahydrobenzofuran-2,4-dione (**2.58**). Hydrazone (**2.23**) (0.046 g, 0.118 mmol) was treated following general procedure **P.** Flash chromatography (40:60 EtOAc- Hexanes) gave a white solid (0.024 g, 80%). mp 145-147 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.25-7.21 (m, 2 H), 6.89-6.86 (m , 2 H), 4.02 (m, 2 H with app. d, *J* = 11.91 Hz), 3.78 (s, 3 H), 3.16 (t, *J* = 11.91 Hz, 1 H), 2.52-2.39 (m, 1 H), 2.41-2.36 (m, 2 H), 2.26-2.22 (m, 1 H), 1.97 (qd *J* = 12.36 Hz, 4.12 Hz, 1 H), 1.80-1.69 (m, 1 H); **^{13}C**

NMR (100 MHz, $CDCl_3$): δ 203.4, 175.4, 159.2, 129.7, 126.8, 114.3, 80.0, 63.5, 55.4, 46.4, 40.4, 29.6, 22.0; **HRMS-ESI:** *m/z* calcd. For $C_{15}H_{16}O_4$ $[M+Na]^+$: 283.0941, found 283.0946.

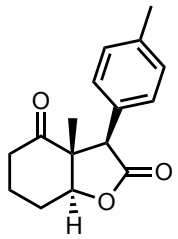


3-(thiophen-2-yl)hexahydro-*2H*-cyclohepta[*b*]furan-2,4(*5H*)-dione (**2.59**). Hydrazone (**2.30**) (0.0312 g, 0.083 mmol) was treated following general procedure **G** (after stirring at rt for 72 h, the reaction was heated to 50 °C for 6 h for consumption of the starting material). Flash chromatography (30:70 EtOAc-Hexanes) gave a yellow solid (0.0174 g, 86%). mp 95-97 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.23 (dd, *J* = 5.27 Hz, 1.37 Hz, 1 H), 7.02 (d, *J* = 3.66 Hz, 1 H), 6.96 (dd, *J* = 5.04 Hz, 3.66 Hz, 1 H), 4.66 (d, *J* = 11.45 Hz, 1 H), 4.09 (td, *J* = 10.76 Hz, 3.66 Hz, 1 H), 3.67 (t, *J* = 11.45 Hz, 1 H), 2.72-2.64 (m, 1 H), 2.54 (dq, *J* = 13.28 Hz, 3.66 Hz, 1 H), 2.46-2.37 (m, 1 H), 2.20-2.10 (m, 1 H), 2.08-1.97 (m, 1 H), 1.88-1.77 (m, 2 H), 1.37 (qdd, *J* = 13.05 Hz, 3.21 Hz, 1.37 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 205.9, 174.1, 137.0, 127.1, 126.7, 125.4, 78.4, 63.4, 43.1, 42.8, 35.3, 24.6, 22.5; **HRMS-ESI:** *m/z* calcd. for $C_{13}H_{14}O_3S$ $[M+Na]^+$: 273.0556, found 273.0563.

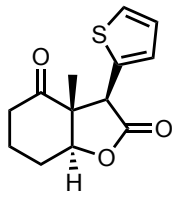


3-phenylhexahydro-*2H*-cyclohepta[*b*]furan-2,4(*5H*)-dione (**2.60**). Hydrazone (**3.29**) (0.030 g, 0.079 mmol) was treated following general procedure **G** (after stirring at

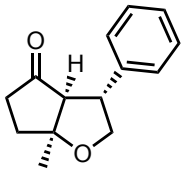
rt for 72 h, the reaction was heated to 50 °C for 6 h for consumption of the starting material). Flash chromatography (30:70 EtOAc-Hexanes) gave a yellow foam (0.0184 g, 95%). mp 75-76 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.36-7.32 (m, 2 H), 7.29-7.26 (m, 3 H), 4.41 (d, *J* = 11.91 Hz, 1 H), 4.10 (td, *J* = 10.99 Hz, 3.66 Hz, 1 H), 3.63 (t, *J* = 11.45 Hz, 1 H), 2.63-2.53 (m, 2 H), 2.37 (ddd, *J* = 19.42 Hz, 12.72 Hz, 4.12 Hz, 1 H), 2.20-2.12 (m, 1 H), 2.00-1.93 (m, 1 H), 1.89-1.73 (m, 2 H), 1.37 (qdd, *J* = 13.28 Hz, 3.21 Hz, 1.37 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 206.1, 175.6, 135.9, 128.9, 128.8, 127.9, 78.4, 63.6, 47.8, 43.1, 35.5, 24.7, 22.5; **HRMS-ESI:** *m/z* calcd. for $C_{15}H_{16}O_3$ $[M+Na]^+$: 267.0992, found 267.0999.



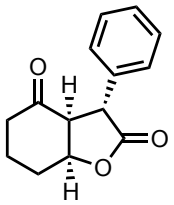
3a-methyl-3-(*p*-tolyl)hexahydrobenzofuran-2,4-dione (**2.61**). Hydrazone (**2.37**) (0.0256 g, 0.065 mmol) was treated following general procedure **P.** Flash chromatography (30:70 EtOAc- Hexanes) gave a white solid (0.0136 g, 81%). mp 166-168 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.35 (d, *J* = 8.24 Hz, 2 H), 7.14 (d, *J* = 8.24 Hz, 2 H), 4.30 (s, 1 H), 4.05 (dd, *J* = 12.59 Hz, 3.66 Hz, 1 H), 2.66-2.60 (m, 1 H), 2.32-2.25 (m, 5 H, apparent singlet at 2.32), 2.20-2.05 (m, 2 H), 1.79-1.71 (1 H), 3.19 (s, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 208.2, 175.0, 137.5, 130.5, 129.1, 128.9, 81.7, 59.4, 53.0, 36.5, 22.6, 21.2, 13.7; **HRMS-ESI:** *m/z* calcd. for $C_{16}H_{18}O_3$ $[M+Na]^+$: 281.1148, found 281.1155.



3a-methyl-3-(thiophen-2-yl)hexahydrobenzofuran-2,4-dione (**2.62**). Hydrazone (**2.39**) (0.0515 g, 0.133 mmol) was treated following general procedure **P.** Flash chromatography (30:70 EtOAc- Hexanes) gave a white solid (0.028 g, 85%). mp 134-136 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.27-7.24 (m, 2 H), 7.00-6.97 (m, 1 H), 4.51 (s, 1 H), 4.06 (dd, *J* = 12.59 Hz, 3.66 Hz, 1 H), 2.68-2.63 (m, 1 H), 2.36-2.05 (m, 4 H), 1.80-1.69 (m, 1 H), 1.09 (s, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 207.8, 173.8, 133.5, 128.5, 126.7, 125.8, 81.7, 59.7, 48.7, 36.4, 22.5, 21.1, 13.3; **HRMS-ESI:** *m/z* calcd. for $C_{13}H_{14}O_3S$ $[M+Na]^+$: 273.0556, found 273.0564.

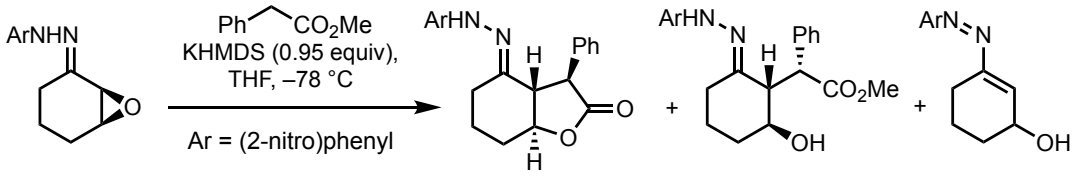


6a-methyl-3-phenyltetrahydro-*2H*-cyclopenta[*b*]furan-2,4 (*5H*)-dione (**2.63**). Hydrazone (**SI4**) (0.046 g, 0.125 mmol) was treated following general procedure **P.** Flash chromatography (30:70 EtOAc-Hexanes) gave a white solid (0.028 g, 96%). mp 58-59 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.38-7.28 (m, 5 H), 4.10 (d, *J* = 2. 86 Hz, 1 H), 2.86 (d, *J* = 2.86 Hz, 1 H), 2.56-2.47 (m, 3 H), 2.16-2.08 (m, 1 H), 1.54 (s, 3 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 215.8, 174.9, 136.0, 129.2, 127.8, 127.4, 89.8, 60.2, 51.0, 36.5, 33.8, 26.3; **HRMS-ESI:** *m/z* calcd. for $C_{14}H_{14}O_3$ $[M+Na]^+$: 253.0835, found 253.0846.



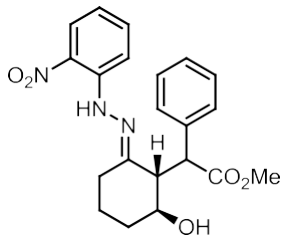
3-phenylhexahydrobenzofuran-2,4-dione (**2.64**). Hydrazone (**2.47**) (0.050 g, 0.136 mmol) was treated following general procedure **P.** Flash chromatography (30:70 EtOAc-Hexanes) gave a white solid (0.024 g, 77%). mp 96-98 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.37-7.34 (m, 2 H), 7.31-7.28 (m, 1 H), 7.25-7.23 (m, 2 H), 5.10 (ddd, *J* = 6.30 Hz, 5.15 Hz, 4.01 Hz, 1 H), 4.55 (d, *J* = 2.86 Hz, 1 H), 3.11 (dd, *J* = 6.30 Hz, 3.44 Hz, 1 H), 2.62-2.58 (dt, *J* = 15.46 Hz, 4.58 Hz, 1 H), 2.44-2.38 (m, 1 H), 2.26-2.22 (m, 1 H), 2.11-1.92 (m, 3 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 206.4, 175.7, 135.4, 129.2, 127.9, 127.5, 78.8, 56.2, 48.1, 40.0, 27.5, 19.3; **HRMS-ESI:** *m/z* calcd. for $C_{14}H_{14}O_3$ $[M+Na]^+$: 253.0835, found 253.0842.

Mechanistic Studies



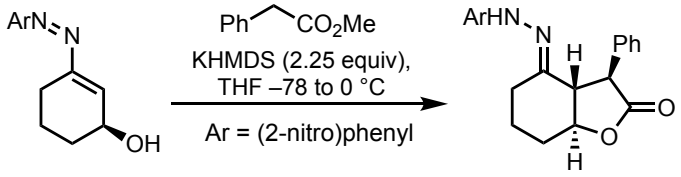
To a stirred solution of phenyl methyl acetate (0.033 g, 0.218 mmol) in THF (0.5 mL) was added KHMDS (0.20 mL, 0.207 mmol, 1.0 M soln. in THF) at –78 °C. The mixture was stirred for 30 min. Separately, hydrazone **2.16** (0.054 g, 0.218 mmol) was dissolved in THF (1.0 mL) and cooled to –78 °C. This solution was added in one portion to the preformed enolate solution, and the resulting deep purple solution was quenched immediately with aq. 10% NH_4OH saturated with NH_4Cl (5 mL). The orange biphasic

solution was partitioned between EtOAc and H_2O, and the aq. phase extracted with EtOAc (3 X 15 mL). The combined organic extracts were washed with sat. aq. NaCl, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. ^{1}H NMR of the crude reaction mixture displayed a 4:2.7:1 mixture of azoalkene **2.66**, uncyclized product **2.65**, and β,γ-fused bicyclic γ-lactone **2.20**, respectively. The ^{1}H NMR signals of the crude reaction material were compared to authentic samples of **2.66**, **2.65**, and **2.22**.



Methyl 2-((1,2,*E*)-2-hydroxy-6-(2-(2-nitrophenyl)hydrazono)cyclohexyl-2-phenyl-acetate (**2.65**). To a stirred solution of phenyl methyl acetate (0.036 g, 0.242 mmol) in THF (0.75 mL) at –78 °C was added KHMDS (0.25 mL, 0.252 mmol, 1.0 M soln. in THF). The mixture was stirred for 45 min. Separately, *n*-BuLi (0.084 mL, 0.212 mmol, 2.5 M soln. in hexanes) was added to a stirred solution of α-epoxy (2-nitro)phenylhydrazone (**2.16**) (1.0 equiv) in THF (1.0 mL) at –78 °C and stirred 10 min. The preformed enolate was then added to the preformed azoalkene dropwise over a period ca. 1 min. The reaction was stirred at –78 °C for 45 min and quenched with aq. 10% NH_4OH saturated with NH_4Cl (5 mL). The orange biphasic solution was partitioned between Et_2O and H_2O, and the aq. phase extracted with Et_2O (3 X 15 mL). The combined organic extracts were washed with sat. aq. NaCl, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash chromatography over silica gel (40:60 EtOAc-Hexanes) gave an orange solid (0.032 g, 40%). mp 156-158 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.90 (s, 1 H), 8.15 (dd, J = 8.24 Hz, 1.37 Hz, 1 H), 7.90 (dd, J = 8.24 Hz, 0.92 Hz, 1 H),

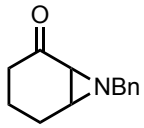
7.54-7.48 (m, 3 H), 7.41-7.32 (m, 3 H), 6.82-6.78 (m, 1 H), 4.14 (d, *J* = 10.53 Hz, 1 H), 3.78-3.79 (m, 1 H), 3.57 (s, 3 H), 3.32 (dd, *J* = 10.53 Hz, 6.87 Hz, 1 H), 2.70-2.63 (m, 1 H), 2.37-2.30 (m, 1 H), 2.04-1.96 (m, 1 H), 1.88-1.82 (m, 1 H), 1.68-1.57 (m, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 173.6, 153.5, 142.5, 136.6, 136.3, 130.9, 129.4, 128.8, 128.4, 126.0, 117.9, 115.7, 71.9, 54.5, 52.9, 52.1, 32.3, 26.1, 20.0; **HRMS-ESI**: *m/z* calcd for $C_{21}H_{23}N_3O_5$ $[M+H]^+$: 398.1710, found 398.1711.



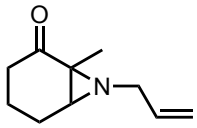
Following general procedure **C** using azoalkene **2.66** (0.0316 g, 0.127 mmol) in place of hydrazone **2.16**, **2.20** was isolated after flash chromatography (30:70::EtOAc:Hexanes) as an orange solid (0.0291 g, 63%).

1.7.2 Synthesis of lactams mechanism

The following procedures are representative of the preparation of α-aziridino ketones

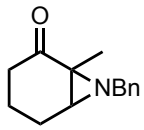


7-phenethyl-7-azabicyclo[4.1.0]heptan-2-one (S5). A mixture of -iodocyclohex-2-en-1-one (4.51 mmol), anhydrous Cs_2CO_3 (4.96 mmol), 1,10-phenanthroline (4.51 mmol), and benzylamine (6.77 mmol) in CH_2Cl_2 (34 mL) was stirred at rt for 4 h. The reaction was partitioned between CH_2Cl_2 and H_2O.[165] The aqueous layer was extracted with CH_2Cl_2 (3 x 10mL). The combined organic phase was washed with H_2O (2 x 10 mL), dried over $MgSO_4$ and evaporated. Flash chromatography over silica gel, using 1:3 EtOAc-hexane gave 7-phenethyl-7-azabicyclo[4.1.0]heptan-2-one as a pale yellow oil (0.6366 g; 70%). Spectroscopic data was identical to that previously reported.[165]



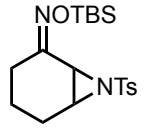
7-allyl-1-methyl-7-azabicyclo[4.1.0]heptan-2-one (S6). To a stirred solution of 1-methyl-7-azabicyclo[4.1.0]heptan-2-one (300.0 mg, 2.397 mmol) in CH_3CN (3 ml) added allyl bromide (869.9 mg, 7.190 mmol), followed by addition of K_2CO_3 (662.5 mg, 4.793 mmol).[166] The mixture was stirred for 5 h at 65 ^oC. Solvent was evaporated under reduced pressure to give brown oil. Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave **S1** as light yellow oil (262.6 mg, 66%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 5.94-5.86 (m, 1 H), 5.22-5.17 (m, 1 H), 5.10-5.06 (m, 1 H), 3.22-3.17(m, 1 H),

3.06-3.00 (m, 1 H), 2.55-2.50 (m, 1 H), 2.03-1.97 (m, 4 H), 1.82-1.77 (m, 1 H), 1.60-1.50 (s, 3 H), 1.29 (s, 3 H); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 209.7,136.7, 115.6, 54.7, 49.5, 45.8, 36.8, 23.7, 20.3, 10.0; **HRMS-ESI:** *m*/*z* calcd. for $C_{10}H_{15}NO$ $[M+H]^+$:166.1226, found: 166.1228.



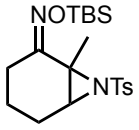
7-benzyl-1-methyl-7-azabicyclo[4.1.0]heptan-2-one (S7). Yield: 48% Procedure is same as **S6**, benzyl bromide was used instead. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.32-7.22 (m, 4 H), 3.85 (d, 1 H, *J* = 14.20 Hz), 3.59 (d, 1 H, *J* = 14.65 Hz), 2.15-2.14 (t, 1 H, *J* = 1.83 Hz), 2.06-1.95 (m, 3 H), 1.84-1.79 (m, 1 H), 1.65-1.58 (m, 1 H), 1.36 (s, 3 H); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ209.7, 139.6, 128.4, 127.3, 126.9, 56.0, 50.0, 46.0, 36.9, 23.7, 20.3, 10.3; **HRMS-ESI:** *m*/*z* calcd. for $C_{14}H_{17}NO$ $[M+H]^+$: 216.1383, found: 216.1386.

The following procedures are representative of the preparation of α-aziridino TBS-oxime



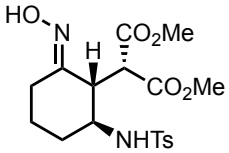
(E)-7-tosyl-7-azabicyclo[4.1.0]heptan-2-one O-(tert-butyldimethylsilyl) oxime (**3.7**). The solution of α-aziridino ketone (449.1 mg, 1.693 mmol) in MeOH (5 ml) was cooled in ice-bath. Followed by addition of TBSONH2 (249.3 mg, 1.693 mmol). The reaction mixture was continued to stir at room temperature for 90 min. The solvent was evaporated under reduced pressure to give colorless gel. Flash chromatography over silica gel using 1:4 EtOAc-hexanes gave 2.40, E/Z mixture (520.9 mg, 78%) as a

colorless gel. **^{1}H NMR** (CDCl3, 400 MHz): δ 7.74 (m, 2H), 7.40 (m, 2H), 2.34 (s, 3H), 1.62 (m, 1H), 1.60 (m, 1H), 1.56-1.18 (m, 6H), 0.98 (s, 9H), 0.21 (s, 6H); **^{13}C NMR** (CDCl3, 100 MHz): δ 149.4, 137.6, 136.7, 129.3, 129.2, 128.3, 128.2, 43.8, 30.6, 30.8, 28.2, 27.1, 25.6, 25.5, 25.4, 21.3, 18.8, -4.7, -4.6; LCMS m/z calcd. for $C_{19}H_{30}N_2O_3SSi$ $[M+H]^+$: 395.175, found: 395.170.



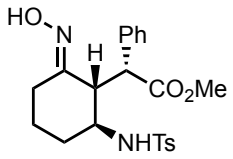
(E)-1-methyl-7-tosyl-7-azabicyclo[4.1.0]heptan-2-one-O-(tert-butyldimethylsilyl) oxime (**3.11**). Colorless solid. Yield is 72%. ^{1}H NMR (CDCl3, 400 MHz): δ 7.74 (m, 2H), 7.40 (m, 2H), 2.34 (m, 3H), 1.6 (m, 1H), 1.50-1.18 (6H), 1.36 (s, 3H), 0.98 (s, 9H), 0.21 (s, 6H); **^{13}C NMR** (CDCl3, 100 MHz): δ 162.0, 137.6, 136.7, 129.3, 129.2, 128.3, 128.2, 45.9, 37.5, 28.3, 28.2, 26.6, 25.5, 25.4, 24.6, 21.3, 20.0, 19.1, 0.21, .22; LCMS m/z calcd. for $C_{20}H_{32}N_2O_3SSi$ $[M+H]^+$: 409.190, found: 409.183

The following procedures are representative of the preparation of α-alkylated TBS-oxime

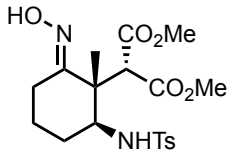


dimethyl-2-((1S,6S,E)-2-(hydroxyimino)-6-(4-methylphenylsulfonamido)cyclohexyl)malonate (**3.9**). The solution of dimethyl malonate (33.5 mg, 0.253 mmol) in THF (2 ml) was cooled to –78 °C followed by dropwise addition of KHMDS (1.0 M, 0.25 ml, 0.253 mmol). The reaction mixture continued to stir at – 78 oC for 45 min. At this time the solution of 2.40 (50 mg, 0.127 mmol) in THF (2 ml) was added all at once followed by dropwise addition of TBAF (1.0

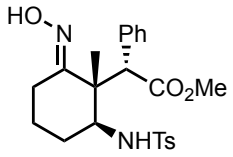
M, 0.25 ml, 0.253 mmol). Reaction mixture was continued to stir at –78 °C for another 2 hours. At this time sat. NH4Cl was added to quench the reaction. After warming up the reaction mixture to room temperature, it was extracted with EtOAc (3 x 10 mL), combined organic extracts were washed with saturated aqueous NaCl, dried (MgSO4), and evaporated under reduced pressure to give colorless oil. Flash chromatography over silica gel using 50:50 EtOAc-hexanes gave 2.41 (40.0 mg, 77%) as a colorless solid and singe diastereomer. ^{1}H NMR (CDCl3, 400 MHz): δ 7.74 (m, 3H), 7.40 (m, 2H), 3.68 (s, 6H), 3.10 (m, 1H), 2.68 (m, 1H), 2.60 (m, 1H)1.64-1.18 (6H); ^{13}**C NMR** (CDCl3, 100 MHz): δ 169.0, 169.1, 162.6, 141.5, 137.6, 129.3, 129.4, 128.3, 128.4, 51.9, 51.8, 45.4, 43.6, 34.9, 28.3, 24.8, 19.1; LCMS m/z calcd. for $C_{18}H_{24}N_2O_7S$ $[M+H]^+$: 413.130, found: 413.120



methyl-2-((1S,6S,E)-2-(hydroxyimino)-6-(4-methylphenylsulfonamido)cyclohexyl)-2-phenylacetate (**3.10**). Colorless solid. Yield is 82%, dr 2:1. 1H NMR (CDCl3, 400 MHz): δ 7.74 (s, 3H), 7.40 (m, 4H), 7.29 (m, 2H), 7.27 (m 1H), 3.68 (s, 3H), 3.6 (m, 1H), 2.6 (m, 1H), 2.43 (m, 1H), 2.34 (s, 3H), 1.64-1.18 (m, 6H); 13**C NMR** (CDCl3, 100 MHz): δ 172.1, 162.6, 137.6, 129.3, 129.4, 128.5, 128.6, 128.1, 128.2, 128.3, 128.4, 125.9, 141.4, 134.5, 43.8, 41.9, 25.1, 19.1, 28.6, 52.2 ; LCMS m/z calcd. for $C_{22}H_{26}N_2O_5S$ [M+H]+: 431.156, found: 431.150



dimethyl-2-((1S,6S,E)-2-(hydroxyimino)-1-methyl-6-(4-methylphenylsulfonamido)cyclohexyl)malonate (**3.12**) Colorless solid. Yield is 82%, dr >25:1. 1H NMR (CDCl3, 400 MHz): δ 7.74 (m, 3H), 7.40 (m, 2H), 3.68 (s, 6H), 4.03 (m, 1H), 2.6 (m 1H), 2.34 (s, 3H), 1.64-1.18 (m, 6H), 1.28 (s, 3H); 13**C NMR** (CDCl3, 100 MHz): δ 169.9, 169.8, 162.4, 141.5, 129.3, 129.4, 128.3, 128.4, 51.9, 51.8, 51.5, 38.0, 36.2, 25.8, 19.4, 12.2; LCMS m/z calcd. for $C_{19}H_{26}N_2O_7S$ [M+H]+: 427.146, found: 427.144



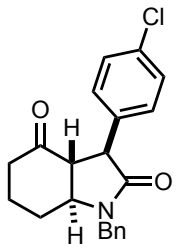
methyl-2-((1S,6S,E)-2-(hydroxyimino)-1-methyl-6-(4-methylphenylsulfonamido)cyclohexyl)-2-phenylacetate (**3.13**). Colorless solid. Yield is 82%, dr 2:1. 1H NMR (CDCl3, 400 MHz): δ7,74 (m, 3H), 7.40 (m, 4H), 7.29 (m, 2H), 3.68 (s, 3H), 3.60 (s, 1H), 2.60 (m, 1H), 1.64-1.18 (6H), 1.28 (s, 3H); 13**C NMR** (CDCl3, 100 MHz): δ; LCMS m/z calcd. for $C_{23}H_{28}N_2O_5S$ [M+H]+: 445.171, found: 445.168.

The following is representative for the synthesis of amides

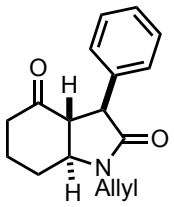
*General procedure **H**: Anti-selective formation of* β,γ*-fused bicyclic* γ*-lactam hydrazones and hydrolysis to anti-*β,γ*-fused bicyclic* γ*-lactam ketone from 3-amino-1-azopropenes*

To a stirred solution of methyl ester acetate (53.2 mg, 0.288 mmol) in THF (0.6 mL) at – 78 ^{o}C was added 1.0 M KHMDS (0.29 ml, 0.288 mmol), stirred for 40 min at – 78 ^{o}C, then a solution of **3.23** (40.0 mg, 0.137 mmol) in THF (0.8 mL) was added dropwise continued to stir in ice-bath for 1.5 hour. At this time saturated aqueous

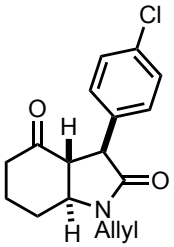
NH_4Cl/10% NH_4OH (2 mL) was added and the mixture was warmed to room temperature. The aqueous layer was extracted with EtOAc (3 x 20 mL), and the combined organic extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$), and evaporated under reduced pressure to give brown oil. The resulting dark yellow oil was dissolved in acetone/water 7:1 (1.4 mL) at room temperature and added TsOH H_2O (78.3 mg, 0.412 mmol). Reaction was monitored by TLC (usually done within 24 hours). At this time reaction mixture was diluted with EtOAc (20 ml) and washed with saturated aqueous $NaHCO_3$, saturated aqueous NaCl, dried over ($MgSO_4$), and solvent was evaporated under reduced pressure. Following flash chromatography over silica gel to give *anti*-β,γ-fused bicyclic γ-lactam.



(3S,3aR,7aS)-1-benzyl-3-(4-chlorophenyl)hexahydro-1H-indole-2,4-dione (3.35). AAP (**2.23**) (0.050 g, 0.136 mmol) was treated following general procedure **H**. Flash chromatography (20:80 EtOAc-Hexanes) gave a brown oil (0.024 g, 64%).**^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.35-7.25 (m, 9 H), 4.82 (d, 1 H, *J* = 14.89 Hz), 4.34 (d, 1 H, *J* = 14.89 Hz), 3.85 (d, 1 H, *J* = 11.46 Hz), 3.23-3.18 (m, 1 H), 2.88 (t, 1 H, *J* = 11.46 Hz), 2.33-2.12 (m, 4 H), 1.66-1.59 (m, 1 H); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 205.3, 174.5, 136.5, 135.7, 133.3, 130.3, 128.9, 128.8, 128.0, 127.9, 61.2, 60.9, 47.3, 45.5, 40.8, 29.3, 24.0; **HRMS-ESI:** calcd. for $C_{21}H_{20}ClNO_2$ $[M+Na]^+$: 376.1075, found: 376.1075.

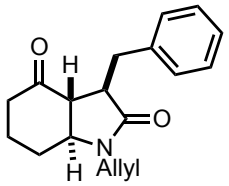


(3S,3aR,7aS)-1-allyl-3-phenylhexahydro-1H-indole-2,4-dione (3.36). AAP (**2.23**) (0.050 g, 0.136 mmol) was treated following general procedure **H**. Flash chromatography (20:80 EtOAc-Hexanes) gave a brown oil (0.024 g, 68%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.32-7.22 (m, 5 H), 5.79-5.75 (m, 1 H), 5.26-5.20 (m, 2 H), 4.22-4.18 (m, 1 H), 3.86-3.81 (m, 2 H), 3.35-3.30 (m, 1 H), 2.91 (t, 1 H, *J* = 11.46 Hz), 2.38-2.32 (m, 3 H), 2.23-2.20 (1 H), 1.76-1.68 (m, 2 H); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 205.5, 174.7, 137.4, 132.8, 128.9, 128.7, 127.3, 118.2, 61.4, 61.3, 47.8, 44.3, 40.9, 29.3, 24.2; **HRMS-ESI:** calcd. for $C_{17}H_{19}NO_2$ $[M+H]^+$: 270.1489, found: 270.1493.

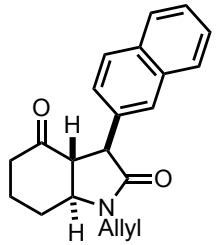


(3S,3aR,7aS)-1-allyl-3-(4-chlorophenyl)hexahydro-1H-indole-2,4-dione (3.37). AAP (**2.23**) (0.050 g, 0.136 mmol) was treated following general procedure **H**. Flash chromatography (20:80 EtOAc-Hexanes) gave a brown oil (0.024 g, 57%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.29-7.23 (m, 4 H), 5.76-5.75 (m, 1 H), 5.25-5.20 (m, 2 H), 4.20 (dd, 1 H, *J* = 5.15 Hz, *J* = 10.31 Hz), 3.83-3.79 (m, 2 H), 3.32 (td, 1 H, *J* = 2.86 Hz, *J* = 8.59 Hz), 2.85 (t, 1 H, *J* = 11.46 Hz), 2.38-2.31 (m, 3 H), 2.24-2.20 (m, 1 H), 1.72-1.67 (m, 2 H); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 205.4, 174.1, 135.8, 133.2, 132.6, 130.3,

128.8, 118.4, 61.3, 61.2, 47.2, 44.3, 40.8, 29.3, 24.1; **HRMS-ESI:** calcd. for $C_{17}H_{18}ClNO_2$ $[M+Na]^+$: 326.0918, found: 326.0922.

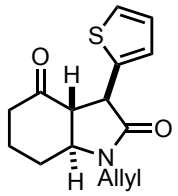


(3R,3aR,7aS)-1-allyl-3-benzylhexahydro-1H-indole-2,4-dione (3.41). AAP (**2.23**) (0.050 g, 0.136 mmol) was treated following general procedure **H**. Flash chromatography (20:80 EtOAc-Hexanes) gave a brown oil (0.024 g, 72%). dr. 5:1 as judged by ^{1}H NMR of the crude material, isolated single diastereomer. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.26-7.11 (m, 5 H), 5.72-5.63 (m, 1 H), 5.13-5.06 (m, 2 H), 4.09-4.04 (m, 1 H), 3.73-3.67 (m, 1 H), 3.24-3.16 (m, 2 H), 3.02-2.87 (m, 2 H), 2.33-2.10 (m, 5 H), 1.70-1.63 (m, 1 H), 1.45-1.41 (m, 1 H); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 206.2, 175.3, 138.2, 132.7, 129.8, 128.5, 126.5, 117.7, 61.1, 55.9, 43.9, 42.9, 40.6, 33.3, 28.9, 24.0; **HRMS-ESI:** calcd. for $C_{18}H_{21}NO_2$ $[M+Na]^+$: 306.1465, found: 306.1469.

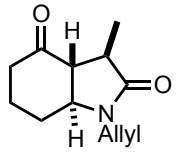


(3S,3aR,7aS)-1-allyl-3-(naphthalen-1-yl)hexahydro-1H-indole-2,4-dione (3.39). AAP (**2.23**) (0.050 g, 0.136 mmol) was treated following general procedure **H**. Flash chromatography (20:80 EtOAc-Hexanes) gave a brown oil (0.024 g, 74%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.81-7.78 (m, 4 H), 7.44-7.41 (m, 3 H), 5.84-5.79 (m, 1 H), 5.29-5.22 (m, 2 H), 4.27-4.23 (m, 1 H), 4.04 (d, 1 H, J = 12.03 Hz), 3.89-3.84 (m, 1 H), 3.38 (td, 1 H, J = 2.86 Hz, J = 11.46 Hz), 3.01 (t, 1 H, J = 11.46 Hz), 2.42-2.32 (m, 3 H),

2.26-2.22 (m, 1 H), 1.83-1.71 (m, 2 H); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 205.5, 174.7, 134.8, 133.5, 132.8, 132.7, 128.5, 128.0, 127.9, 127.7, 126.6, 126.1, 125.9, 118.3, 61.5, 61.4, 47.9, 44.4, 40.9, 29.4, 24.2; **HRMS-ESI:** calcd. for $C_{21}H_{21}NO_2$ $[M+H]^+$: 320.1645, found: 320.1654.

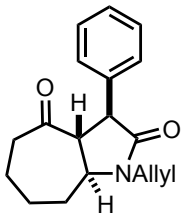


(3R,3aR,7aS)-1-allyl-3-(thiophen-2-yl)hexahydro-1H-indole-2,4-dione (3.28). AAP (**2.23**) (0.050 g, 0.136 mmol) was treated following general procedure **H**. Flash chromatography (20:80 EtOAc-Hexanes) gave a brown oil (0.024 g, 61%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.21-7.19 (m, 1 H), 7.02-7.01 (m, 1 H), 7.01-6.93 (m, 1 H), 5.80-5.70 (m, 1 H), 5.24-5.18 (m, 2 H), 4.22-4.17 (m, 1 H), 4.08 (d, 1 H, *J* = 11.91 Hz), 3.82-3.76 (m, 1 H), 3.33 (td, 1 H, *J* = 3.21 Hz, *J* = 8.24 Hz), 2.98 (t, 1 H, *J* = 11.91 Hz), 2.46-2.42 (m, 2 H), 2.34-2.22 (m, 2 H), 1.80-1.67 (m, 2 H); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 205.3, 173.2, 138.8, 132.5, 126.8, 126.2, 124.9, 118.4, 61.15, 61.12, 44.3, 42.6, 40.9, 29.2, 24.1; **HRMS-ESI:** calcd. for $C_{15}H_{17}NO_2S$ $[M+H]^+$: 276.1053, found: 276.1055.



(3R,3aR,7aS)-1-allyl-3-methylhexahydro-1H-indole-2,4-dione (3.40). AAP (**2.23**) (0.050 g, 0.136 mmol) was treated following general procedure **H**. Flash chromatography (20:80 EtOAc-Hexanes) gave a brown oil (0.024 g, 28%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 5.76-5.66 (m, 1 H), 5.20-5.14 (m, 2 H), 4.16-4.10 (m, 1 H), 3.74-3.69 (m, 1 H), 3.21 (td, 1 H, *J* = 3.21 Hz, *J* = 8.24 Hz), 2.59-2.53 (m, 1 H), 2.42-2.40 (m,

2 H), 2.28-2.19 (m, 2 H), 1.77-1.57 (m, 4 H), 1.21 (d, 3 H, *J* = 6.87 Hz); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 206.5, 176.9, 132.8, 117.9, 61.2, 60.5, 43.8, 40.7, 36.6, 29.1, 24.0, 14.2; **HRMS-ESI:** calcd. for $C_{25}H_{23}NO_2$ $[M+H]^+$: 208.1332, found: 208.1329.

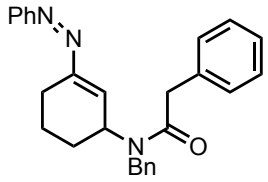


(3S,3aR,8aS)-1-allyl-3-phenyloctahydrocyclohepta[b]pyrrole-2,4-dione (3.43). AAP (**2.23**) (0.050 g, 0.136 mmol) was treated following general procedure **H**. Flash chromatography (20:80 EtOAc-Hexanes) gave a brown oil (0.024 g, 65%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.32-7.23 (m, 5 H), 5.72-5.67 (m, 1 H), 5.22-5.19 (m, 2 H), 4.37-4.25 (m, 2 H), 3.74-3.68 (m, 1 H), 3.32-3.27 (m, 2 H), 2.60-2.38 (m, 3 H), 2.16-2.12 (m, 1 H), 1.92-1.90 (m, 1 H), 1.77-1.73 (m, 1 H), 1.51-1.47 (m, 1 H), 1.39-1.32 (m, 1 H); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 208.4, 174.1, 138.9, 132.5, 128.9, 128.8, 127.3, 118.3, 61.0, 58.2, 48.1, 43.7, 43.2, 35.0, 26.4, 22.8; **HRMS-ESI:** calcd. for $C_{18}H_{21}NO_2$ $[M+H]^+$: 270.1489, found: 270.1493.

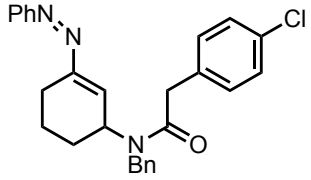
*General procedure **I**: Formation of 3-amido-1-azopropenes from 3-amino-1-azopropenes*

To a stirred solution of **3.33** (50.0 mg, 0.171 mmol) in CH_2Cl_2 (1.5 mL) at room temperature was added phenylacetic acid (28.3 mg, 0189 mmol), EDCI (31.9 mg, 0.206 mmol), HOBt (27.8 mg, 0.206 mmol) and Et_3N (0.06 ml, 0.429 mmol). The mixture stirred for 16 hours at room temperature. At this time DI water (3 mL) was added. The aqueous layer was extracted with EtOAc (3 x 20 mL), and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (10 ml) followed by washing with

saturated aqueous NaCl, dried ($MgSO_4$), and solvent was evaporated under reduced pressure to give dark red-brown oil. Flash chromatography over silica gel using 20:80 EtOAc-hexanes gave 3-amido-1-azopropenes.

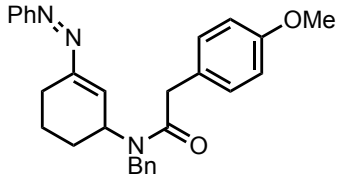


N-benzyl-2-phenyl-N-(3-(phenyldiazenyl)cyclohex-2-en-1-yl)acetamide (3.45). 3.23 (0.050 g, 0.136 mmol) was treated following general procedure **I**. Flash chromatography (20:80 EtOAc-Hexanes) gave a brown oil (59.0 mg, 84%) consisting of mixture of rotamers. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.73-7.69 (m, 2 H), 7.45-7.18 (m, 13 H), 6..68 (br. s, 1 H), 5.75 (br. s, 1 H), 4.60 (d, 1 H, *J* = 17.76 Hz), 4.44 (d, 1 H, *J* = 17.76 Hz), 3.62 (d, 1 H, *J* = 2.86 Hz), 2.60-2.56 (m, 1 H), 2.21-2.08 (m, 2 H), 1.99-1.92 (m, 1 H), 1.74-1.64 (m, 1 H), 1.53-1.46 (m, 1 H); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 172.3, 157.6, 152.6, 140.6, 138.4, 134.9, 130.6, 129.08, 129.05, 128.8, 128.7, 127.5, 127.0, 125.8, 122.5, 53.1, 48.3, 41.5, 27.6, 22.3, 20.9; **HRMS-ESI:** *m*/*z* calcd. for $C_{27}H_{27}N_3O$ $[M+H]^+$: 410.2227, found: 410.2235.

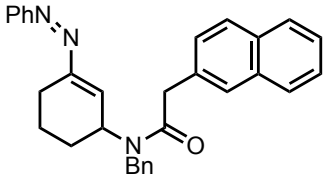


N-benzyl-2-(4-chlorophenyl)-N-(3-(phenyldiazenyl)cyclohex-2-en-1-yl)acetamide (3.46). 3.23 (0.050 g, 0.136 mmol) was treated following general procedure **I**. Flash chromatography (20:80 EtOAc-Hexanes) gave a brown oil (59.0 mg, 95%) major rotomer: **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.74-7.70 (m, 2 H), 7.44-7.37 (m, 4 H), 7.32-7.24 (m, 6 H), 7.11-7.09 (m, 2 H), 6.68 (br. s, 1 H), 5.74 (br. s, 1 H), 4.60 (d, 1 H, *J* =

17.76 Hz), 4.46 (d, 1 H, *J* = 17.76 Hz), 3.56 (s, 2 H), 2.61-2.57 (m, 1 H), 2.21-1.97 (m, 2 H), 1.74-1.48 (m, 3 H); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 171.9, 157.7, 152.6, 140.3, 138.3, 133.4, 130,6, 130.3, 129.1, 129.0, 128,8, 127.6, 127.3, 125.8, 122.5, 53.2, 48.4, 40.6, 27.7, 22.3, 20.9; **HRMS-ESI:** calcd. for $C_{27}H_{26}ClN_3O$ $[M+H]^+$: 444.1837, found: 444.1842.

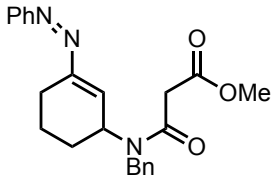


N-benzyl-2-(4-methoxyphenyl)-N-(3-(phenyldiazenyl)cyclohex-2-en-1-yl)acetamide (3.47). 3.23 (0.050 g, 0.136 mmol) was treated following general procedure **I**. Flash chromatography (20:80 EtOAc-Hexanes) gave a brown oil (59.0 mg, 92%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.75-7.69 (m, 2 H), 7.45-7.37 (m, 4 H), 7.32-7.22 (m, 4 H), 7.12-7.10 (m, 2 H), 6.91-6.84 (m, 2 H), 6.68 (br. s, 1 H), 5.76-5.73 (m, 1 H), 4.60 (d, 1 H, *J* = 18.32 Hz), 4.43 (d, 1 H, *J* = 18.32 Hz), 3.80 (s, 3 H), 3.54 (s, 2 H), 2.60-2.55 (m, 1 H), 2.20-1.96 (m, 3 H), 1.73-1.69 (m, 1 H), 1.53-1.47 (m, 1 H); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 172.7, 158.6, 157.6, 152.6, 140.7, 138.5, 130.6, 129.8, 129.1, 129.0, 127.5, 125.8, 122.5, 114.2, 55.4, 53.1, 48.3, 40.6, 27.6, 22.3, 20.9; **HRMS-ESI:** *m*/*z* calcd. for $C_{28}H_{29}N_3O_2$ $[M+H]^+$: 440.2333, found: 440.2342.

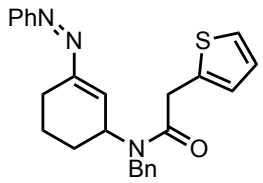


N-benzyl-2-(naphthalen-2-yl)-N-(3-(phenyldiazenyl)cyclohex-2-en-1-yl)acetamide (3.48). 3.23 (0.050 g, 0.136 mmol) was treated following general procedure **I**. Flash chromatography (20:80 EtOAc-Hexanes) gave a brown oil (59.0 mg, 85%). **^{1}H**

NMR ($CDCl_3$, 400 MHz): δ 7.85-7.76 (m, 3 H), 7.70-7.68 (m, 2 H), 7.58 (br. s, 1 H), 7.47-7.24 (m, 11 H), 6.69 (s, 1 H), 5.78 (br. s, 1 H), 4.63 (d, 1 H, *J* = 17.76 Hz), 4.46 (d, 1 H, *J* = 18.33 Hz), 4.10 (s, 1 H), 3.78 (d, 2 H, *J* = 1.15 Hz), 2.59-2.53 (m, 1 H), 2.18-2.10 (m, 2 H), 1.99-1.97 (m, 1 H), 1.75-1.71 (m, 1 H), 1.53-1.46 (m, 1 H); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 172.3, 157.6, 152.6, 140.5, 132.5, 130.6, 129.09, 129.06, 128.5, 127.7, 127.5, 127.3, 127.1, 126.2, 125.9, 125.8, 122.6, 53.2, 48.4, 41.727.7, 22.3, 20.9; **HRMS-ESI:** *m*/*z* calcd. for $C_{31}H_{29}N_3O$ $[M+H]^+$: 460.2392, found: 460.2383.

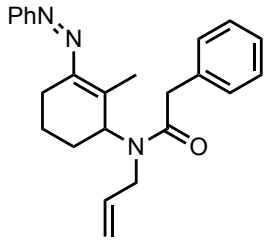


Methyl 3-(benzyl(3-(phenyldiazenyl)cyclohex-2-en-1-yl)amino)-3-oxopropanoate (3.49). 3.23 (0.050 g, 0.136 mmol) was treated following general procedure **I**. Flash chromatography (20:80 EtOAc-Hexanes) gave a brown oil (59.0 mg, 77%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.76-7.70 (m, 2 H), 7.44-7.35 (m, 4 H), 7.29-7.23 (m, 4 H), 6.74 (br. s, 1 H), 5.73-5.70 (m, 1 H), 4.64 (d, 1 H, *J* = 17.86 Hz), 4.52 (d, 1 H, *J* = 18.32 Hz), 3.73 (s, 3 H), 3.40-3.31 (m, 2 H), 2.62-2.56 (m, 1 H), 2.23-1.99 (m, 3 H), 1.71-1.51 (m, 2 H); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 186.1, 167.6, 157.8, 152.6, 152.5, 139.9, 137.6, 130.6, 129.1, 129.0, 125.8, 122.6, 53.3, 52.6, 48.7, 41.7, 27.6, 22.3, 20.8; **HRMS-ESI:** *m*/*z* calcd. for $C_{23}H_{25}N_3O_3$ $[M+H]^+$: 392.1964, found: 392.69.

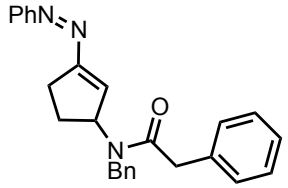


N-benzyl-N-(3-(phenyldiazenyl)cyclohex-2-en-1-yl)-2-(thiophen-2-yl)acetamide (3.50). 3.23 (0.050 g, 0.136 mmol) was treated following general procedure

I. Flash chromatography (20:80 EtOAc-Hexanes) gave a brown oil (59.0 mg, 89%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.72-7.70 (m, 2 H), 7.45-7.37 (m, 5 H), 7.26-7.21 (m, 5 H), 6.95-6.93 (m, 1 H), 6.80-6.79 (m, 1 H), 6.70 (br. s, 1 H), 5.76 (br. s, 1 H), 4.66 (d, 1 H, *J* = 17.76 Hz), 4.51 (d, 1 H, *J* = 17.76 Hz), 3.78 (s, 2 H), 2.61-2.57 (m, 1 H), 2.20-2.09 (m, 2 H), 1.98-1.97 (m, 1 H), 1.80-1.45 (m, 2 H); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 171.3, 157.7, 152.6, 140.2, 138.2, 136.4, 130.6, 129.1, 129.0, 127.5, 126.8, 126.0, 125.8, 125.1, 122.6, 53.2, 48.4, 35.9, 27.6, 22.3, 20.9; **HRMS-ESI:** *m*/*z* calcd. for $C_{25}H_{25}N_3OS$ $[M+H]^+$: 416.1791, found: 416.1798.

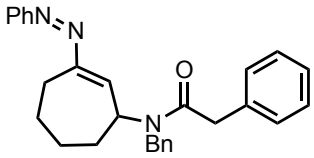


N-allyl-N-(2-methyl-3-(phenyldiazenyl)cyclohex-2-en-1-yl)-2-phenylacetamide (3.51). 3.26 (0.050 g, 0.136 mmol) was treated following general procedure **I**. Flash chromatography (20:80 EtOAc-Hexanes) gave a brown oil (59.0 mg, 76%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.76-7.72 (m, 2 H), 7.47-7.24 (m, 8 H), 5.90-5.85 (m, 1 H), 5.30-5.25 (m, 2 H), 4.00-3.88 (m, 1 H), 3.77 (s, 2 H), 3.59-3.55 (m, 1 H), 2.61-2.58 (m, 1 H), 2.22-2.18 (m, 1 H), 2.06-1.98 (m, 5 H), 1.65-1.61 (m, 3H); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 172.4, 153.2, 145.8, 135.3, 135.1, 130.4, 130.2, 129.1, 129.0, 128.7, 127.0, 122.6, 116.8, 60.6, 42.3, 41.4, 27.9, 23.3, 20.8, 14.3; **HRMS-ESI:** *m*/*z* calcd. for $C_{24}H_{27}N_3O$ $[M+H]^+$: 374.2228, found: 374.2227.



N-benzyl-2-phenyl-N-(3-(phenyldiazenyl)cyclopent-2-en-1-yl)acetamide

(3.52). 3.28 (0.050 g, 0.136 mmol) was treated following general procedure **I**. Flash chromatography (20:80 EtOAc-Hexanes) gave a brown oil (59.0 mg, 69%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.78-7.76 (m, 1 H), 7.63-7.57 (m, 2 H), 7.50-7.46 (m, 1 H), 7.41-7.33 (m, 4 H), 7.29-7.27 (m, 1 H), 7.11 (d, 1 H, *J* = 0.92), 4.03-3.99 (d, 2 H, *J* = 4.58), 3.67-3.63 (m, 1 H), 2.51-2.46 (m, 1 H), 2.36-2.34 (m, 1 H), 2.09-1.94 (m, 2 H), 1.07-1.53 (m, 2 H); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 172.2, 171.3, 161.7, 160.9, 152.9, 152.8, 138.8, 131.1, 129.2, 129.1, 129.0, 128.9, 128.8, 128.5, 127.6, 127.4, 127.0, 125.8, 122.9, 122.8, 63.3, 60.2, 47.9, 46.2, 42.0, 41.4, 28.5, 28.2, 27.0, 26.9; **HRMS** *m*/*z* calcd. for $C_{26}H_{25}N_3O$ $[M+H]^+$: 396.2070, found: 396.2065.



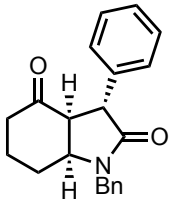
N-benzyl-2-phenyl-N-(3-(phenyldiazenyl)cyclohept-2-en-1-yl)acetamide

(5.53). 3.30 (0.050 g, 0.136 mmol) was treated following general procedure **I**. Flash chromatography (20:80 EtOAc-Hexanes) gave a brown oil (59.0 mg, 75%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.73-7.69 (m, 3 H), 7.47-7.20 (m, 12 H), 6.87 (d, 2 H, *J* = 3.44 Hz), 5.53 (br. s, 1 H), 4.63 (dd, 2 H, *J* = 17.76 Hz, *J* = 38.95 Hz), 3.65 (s, 2 H), 3.21-3.16 (m, 1 H), 2.30-2.25 (m, 1 H), 1.89-1.82 (m, 3 H), 1.77-1.71 (m, 2 H), 1.39-1.24 (m, 2 H); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 171.8, 159.3, 146.9, 134.9, 130.3, 129.1, 129.0, 128.9,

128.86, 128.81, 128.5, 127.5, 127.0, 126.1, 122.6, 49.4, 42.4, 41.5, 32.6, 28.5, 24.9, 23.8; **HRMS-ESI:** calcd. for $C_{28}H_{29}N_3O$ $[M+H]^+$: 424.2383, found: 424.2388.

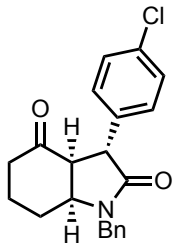
*General procedure **J**: Syn-selective formation of β,γ-fused bicyclic γ-lactam hydrazones and hydrolysis to syn-β,γ-fused bicyclic γ-lactam ketone from 3-amido-1-azopropenes*

To a stirred solution of **3.44** (59 mg, 0.144 mmol) in THF (1.4 mL) at – 78 ^{o} C was added 1.0 M KHMDS (0.16 ml, 0.158 mmol), stirred for 30 min at – 78 ^{o}C, then continued to stir in ice-bath for 1.5 hour. At this time saturated aqueous NH_4Cl/10% NH_4OH (3 mL) was added and the mixture was warmed to room temperature. The aqueous layer was extracted with EtOAc (3 x 20 mL), and the combined organic extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$), and evaporated under reduced pressure to give brown oil. The resulting brown oil was dissolved in acetone/water 7:1 (1.4 mL) at room temperature and added TsOH H_2O (82.2 mg, 0.432 mmol). Reaction completion was monitored by TLC (usually done within 24 hours). At this time reaction mixture was diluted with EtOAc (20 ml) and washed with saturated aqueous $NaHCO_3$, saturated aqueous NaCl, dried over ($MgSO_4$), and solvent was evaporated under reduced pressure to give brown oil. Flash chromatography over silica gel using 20:80 EtOAc-hexanes gave syn-β,γ-fused bicyclic γ-lactam ketone.



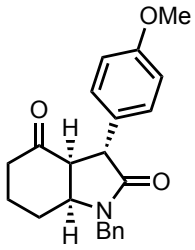
(3S,3aS,7aS)-1-benzyl-3-phenylhexahydro-1H-indole-2,4-dione (3.57). 3.45 (0.050 g, 0.136 mmol) was treated following general procedure **J**. Flash chromatography

(20:80 EtOAc-Hexanes) gave a a yellow oil (36.4 mg, 79%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.34-7.16 (m, 10 H), 5.05 (d, 1 H, *J* = 14.89 Hz), 4.20 (d, 1 H, *J* = 6.30 Hz), 4.04-3.96 (m, 2 H), 2.97 (t, 1 H, *J* = 7.45 Hz), 2.47-2.45 (m, 1 H), 2.40-2.38 (m, 1 H), 2.06-2.03 (m, 1 H), 1.83-1.79 (m, 1 H), 1.70-1.66 (m, 2 H); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 207.9, 173.7, 138.0, 136.2, 128.98, 128.95, 128.3, 128.1, 127.9, 127.5, 56.6, 53.9, 49.1, 44.7, 39.2, 26.9, 19.4; **HRMS-ESI:** calcd. for $C_{21}H_{21}NO_2$ $[M+H]^+$: 320.1654, found: 320.1651.

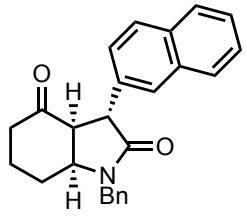


(3R,3aS,7aS)-1-benzyl-3-(4-chlorophenyl)hexahydro-1H-indole-2,4-dione

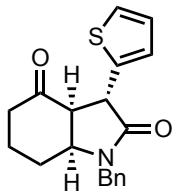
(3.60). 3.46 (0.050 g, 0.136 mmol) was treated following general procedure **J**. Flash chromatography (20:80 EtOAc-Hexanes) gave a a yellow oil (36.4 mg, 70%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.36-7.25 (m, 7 H), 7.12-7.11 (m, 2 H), 5.06 (d, 1 H, *J* = 14.89 Hz), 4.14 (d, 1 H, *J* = 6.87 Hz), 4.03 (d, 1 H, *J* = 14.89 Hz), 3.96-3.94 (m, 1 H), 2.95 (t, 1 H, *J* = 7.45 Hz), 2.48-2.42 (m, 2 H), 2.11-2.05 (m, 1 H), 1.90-1.84 (m, 1 H), 1.70-1.62 (m, 2 H); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 207.8, 173.1, 136.5, 136.1, 133.4, 129.6, 129.1, 129.0, 128.3, 128.1, 56.6, 53.7, 48.6, 44.8, 39.1, 27.0, 19.4; **HRMS-ESI:** calcd. for $C_{21}H_{20}ClNO_2$ $[M+Na]^+$: 376.1075, found: 376.1075.



(3R,3aS,7aS)-1-benzyl-3-(4-methoxyphenyl)hexahydro-1H-indole-2,4-dione (3.59). 3.47 (0.050 g, 0.136 mmol) was treated following general procedure **J**. Flash chromatography (20:80 EtOAc-Hexanes) gave a a yellow oil (36.4 mg, 66%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.36-7.25 (m, 5 H), 7.10-7.08 (m, 2 H), 6.86-6.84 (m, 2 H), 5.07 (d, 1 H, *J* = 14.89 Hz), 4.10 (d, 1 H, *J* = 6.87 Hz), 4.03 (d, 1 H, *J* = 14.89 Hz), 3.95-3.93 (m, 1 H), 3.78 (s, 3 H), 2.96 (t, 1 H, *J* = 7.45 Hz), 2.49-2.41 (m, 2 H), 2.07-2.02 (m, 1 H), 1.87- 1.83 (m, 1 H), 1.70-1.66 (m, 1 H); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 208.1, 173.8, 158.9, 136.3, 129.9, 129.2, 128.9, 128.3, 128.0, 114.4, 56.5, 55.4, 54.2, 48.6, 44.8, 39.1, 27.0, 19.5; **HRMS-ESI:** calcd. for $C_{22}H_{23}NO_3$ $[M+Na]^+$: 372.1570, found: 372.1574.

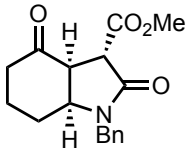


(3R,3aS,7aS)-1-benzyl-3-(naphthalen-2-yl)hexahydro-1H-indole-2,4-dione (3.58). 3.48 (0.050 g, 0.136 mmol) was treated following general procedure **J**. Flash chromatography (20:80 EtOAc-Hexanes) gave a a yellow oil (36.4 mg, 74%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.81-7.78 (m, 2 H), 7.72-7.71 (m, 1 H), 7.59 (s, 1 H), 7.45-7.43 (m, 2 H), 7.43-7.28 (m, 6 H), 5.13 (d, 1 H, *J* = 14.89 Hz), 4.39 (d, 1 H, *J* = 6.30 Hz), 4.06-4.04 (m, 2 H), 3.05 (t, 1 H, *J* = 6.87 Hz), 2.56-2.50 (m, 1 H), 2.43-2.38 (m, 1 H), 2.08-2.04 (m, 1 H), 1.87-1.75 (m, 3 H); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 207.9, 173.9, 136.3, 135.5, 133.5, 132.7, 129.0, 128.9, 128.5, 128.0, 127.9, 127.7, 126.9, 126.3, 126.0, 56.6, 53.9, 49.5, 44.7, 39.4; **HRMS-ESI:** calcd. for $C_{25}H_{23}NO_2$ $[M+H]^+$: 370.1802, found: 370.1830.



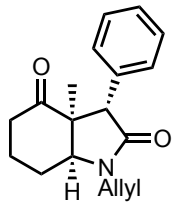
(3S,3aS,7aS)-1-benzyl-3-(thiophen-2-yl)hexahydro-1H-indole-2,4-dione

(3.61). 3.50 (0.050 g, 0.136 mmol) was treated following general procedure **J**. Flash chromatography (20:80 EtOAc-Hexanes) gave a a yellow oil (36.4 mg, 81%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.34-7.28 (m, 3 H), 7.24-7.22 (m, 3 H), 6.98-6.94 (m, 2 H), 5.07-5.03 (d, 1 H, *J* = 15.11), 4.54-4.53 (d, 1 H, *J* = 5.04), 4.08-4.06 (q, 1 H, J = 5.50), 4.00-3.96 (d, 1 H, *J* = 15.11), 3.08-3.05 (t, 1 H, J = 6.41), 2.55-2.49 (m, 1 H), 2.45-2.37 (m, 3 H), 2.06-1.98 (m, 1 H), 1.82-1.76 (m, 3 H); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 207.4, 173.0, 139.7, 135.9, 128.9, 128.2, 128.0, 127.0, 125.9, 125.0, 56.7, 53.8, 51.3, 44.6, 44.4, 39.6, 26.6, 19.5; **HRMS-ESI:** calcd. for $C_{19}H_{19}NO_2S$ $[M+Na]^+$: 348.1029, found: 348.1029.



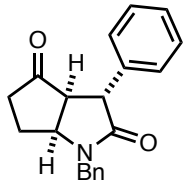
(3S,3aS,7aS)-methyl 1-benzyl-2,4-dioxooctahydro-1H-indole-3-carboxylate

(3.62). 3.49 (0.050 g, 0.136 mmol) was treated following general procedure **J**. Flash chromatography (20:80 EtOAc-Hexanes) gave a a yellow oil (36.4 mg, 74%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.33-7.27 (m, 3 H), 7.21-7.20 (m, 2 H), 4.97 (d, 1 H, *J* = 14.89 Hz), 4.14-4.10 (m, 2 H), 3.97 (d, 1 H), 3.79 (s, 3 H), 3.28-3.26 (m, 1 H), 2.47-2.39 (m, 2 H), 1.97-1.96 (m, 1 H), 1.80-1.77 (m, 1 H), 1.72-1.66 (m, 2 H); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 207.0, 169.7, 169.4, 135.5, 128.9, 128.0, 127.9, 57.1, 53.1, 49.2, 48.6, 44.7, 39.6, 26.4, 19.0; **HRMS-ESI:** calcd. for $C_{17}H_{19}NO_4$ $[M+Na]^+$: 324.1206, found: 324.1208.



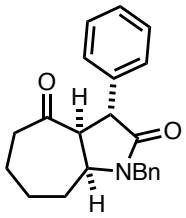
(3S,3aS,7aS)-1-allyl-3a-methyl-3-phenylhexahydro-1H-indole-2,4-dione

(3.65). 3.51 (0.050 g, 0.136 mmol) was treated following general procedure **J**. Flash chromatography (20:80 EtOAc-Hexanes) gave a a yellow oil (36.4 mg, 61%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.29-7.24 (m, 3 H), 7.04-7.02 (m, 2 H), 5.86-5.82 (m, 1 H), 5.35-5.5.28 (m, 2 H), 4.60-4.56 (m, 1 H), 4.32 (s, 1 H), 3.77 (t, 1 H, *J* = 4.58 Hz), 3.49-3.45 (m, 1 H), 2.54 (t, 2 H, *J* = 5.73 Hz), 2.05-2.00 (m, 2 H), 1.86-1.82 (m, 2 H), 0.82 (s, 3 H); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 210.9, 174.6, 135.0, 132.4, 129.6, 128.6, 127.5, 119.4, 62.9, 53.7, 53.2, 43.4, 38.1, 24.4, 19.8, 19.2; **HRMS-ESI:** calcd. for $C_{18}H_{21}NO_2$ $[M+H]^+$: 284.1689, found: 284.1678.

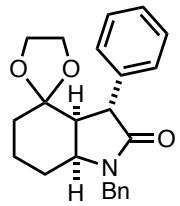


(3R,3aS,6aS)-1-benzyl-3-phenylhexahydrocyclopenta[b]pyrrole-2,4-dione

(3.63). 3.52 (0.050 g, 0.136 mmol) was treated following general procedure **J**. Flash chromatography (20:80 EtOAc-Hexanes) gave a a yellow oil (36.4 mg, 73%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.37-7.23 (m, 8 H), 7.18-7.16 (m, 2 H), 5.00-4.97 (d, 1 H), 4.36-4.33 (t, 1 H), 4.21-4.18 (d, 1 H), 3.88-3.86 (m, 1 H), 2.82-2.80 (m, 1 H), 2.39-2.17 (m, 3 H), 2.04-1.94 (m, 1 H); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 217.0, 174.2, 138.9, 136.1, 129.1, 129.0, 128.4, 128.1, 127.5, 127.4, 59.0, 53.3, 51.3, 44.8, 34.4, 24.1; **HRMS-ESI:** calcd. for $C_{20}H_{19}NO_2$ $[M+H]^+$:328.1308, found: 328.1307.

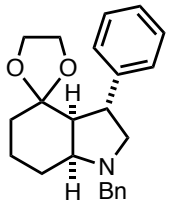


(3R,3aS,8aS)-1-benzyl-3-phenyloctahydrocyclohepta[b]pyrrole-2,4-dione (3.64). 3.53 (0.050 g, 0.136 mmol) was treated following general procedure **J**. Flash chromatography (20:80 EtOAc-Hexanes) gave a a yellow oil (36.4 mg, 79%). dr. 1:1 **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.39-7.24 (m, 10 H), 5.20 (d, 1 H, *J* = 14.89 Hz), 4.33-4.22 (m, 2 H), 3.80-3.76 (m, 1 H), 3.47 (t, 1 H, *J* = 9.16 Hz), 2.55-2.42 (m, 2 H), 2.13-2.09 (m, 1 H), 1.90-1.86 (m, 2 H), 1.53-1.19 (m, 3 H). **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 208.4, 174.5, 139.6, 136.4, 129.1, 128.9, 128.8, 128.2, 127.7, 127.3, 60.9, 57.9, 48.3, 44.8, 43.2, 35.1, 26.6, 22.7; **HRMS-ESI:** calcd. for $C_{22}H_{23}NO_2$ $[M+Na]^+$: 356.1621, found: 356.1628.

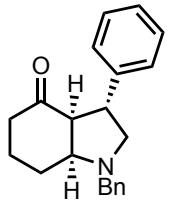


(3'R,3a'S,7a'S)-1'-benzyl-3'-phenylhexahydrospiro[[1,3]dioxolane-2,4'-indol]-2'(1'H)-one (3.101). To a stirred solution of **3.66** (87.8 mg, 0.275 mmol) in Toluene (4 mL) at room temperature was added ethylene glycol (0.15 ml, 2.749 mmol) and TsOH H_2O (156.9 mg, 0.825 mmol). The mixture was stirred for 24 hours. At this time reaction mixture was diluted with EtOAc (20 ml) and washed with saturated aqueous $NaHCO_3$, saturated aqueous NaCl, dried over $MgSO_4$, and evaporated under reduced pressure to give yellow oil. Flash chromatography over silica gel using 40:60 EtOAc-hexanes gave **3.101** as off-white solid (93.9 mg, 94%) consisting of >25:1 dr. **^{1}H NMR** ($CDCl_3$, 400

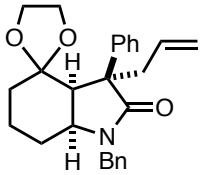
MHz): δ 7.37-7.21 (m, 10 H), 5.07 (d, 1 H, *J* = 15.11 Hz), 4.01 (d, 1 H, *J* = 14.65 Hz), 3.80 (m, 2 H), 3.69-3.57 (m, 3 H), 3.17 (q, 1 H, *J* = 6.87 Hz, *J* = 7.79 Hz), 2.62-2.58 (m, 1 H), 2.01-1.95 (m, 1 H), 1.85-1.78 (m, 1 H), 1.70-1.57 (m, 2 H), 1.51-1.42 (m, 1 H), 1.37-1.24 (m, 1 H); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 174.5, 139.7, 136.8, 128.9, 128.8, 128.5, 128.3, 127.7, 126.8, 109.3, 64.6, 64.2, 54.9, 50.2, 49.3, 44.8, 32.1, 27.2, 19.1; **HRMS-ESI:** calcd. for C23H25NO3 $[M+H]^+$: 364.1907, found: 364.1915.



(3'R,3a'S,7a'S)-1'-benzyl-3'-phenyloctahydrospiro[[1,3]dioxolane-2,4'-indole] (3.104). To a stirred solution of **3.101** (33.5 mg, 0.092 mmol) in THF (2 mL) in ice-bath was added LAH (3.5 mg, 0.246 mmol) in small portions. The mixture continued to stir in ice-bath for 5 min then heat to reflux for 80 min. At this time saturated aqueous NH_4Cl (3 mL) was added and the mixture was warmed to room temperature. The aqueous layer was extracted with EtOAc (3 x 20 mL), and the combined organic extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$), and evaporated under reduced pressure to give brown oil. Flash chromatography over silica gel using 40:60 EtOAc-hexanes gave **3.104** as off-white solid (17.5 mg, 54%) consisting of >25:1 dr. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.39-7.32 (m, 2 H), 7.32-7.21 (m, 7 H), 7.15-7.13 (m, 1 H), 3.81-3.63 (m, 5 H), 3.27-3.15 (m, 4 H), 2.72-2.69 (m, 1 H), 2.62-2.59 (m, 1 H), 1.90-1.67 (m, 3 H), 1.58-1.46 (m, 3 H); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 146.9, 139.6, 128.7, 128.3, 128.2, 127.9, 126.8, 125.7, 110.9, 64.3, 64.1, 62.6, 60.5, 56.1, 54.5, 44.9, 31.6, 21.7, 19.7; **HRMS-ESI:** calcd. for C23H27NO2 $[M+H]^+$: 350.2119, found: 350.2115.

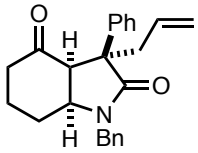


(3R,3aS,7aS)-1-benzyl-3-phenylhexahydro-1H-indol-4(2H)-one (3.105). To a stirred solution of **3.104** (30.2 mg, 0.086 mmol) in CH_2Cl_2 (1.5 mL) at room temperature was added $FeCl_3$ $6H_2O$ (81.7 mg, 0.302 mmol). The mixture refluxed for 1 hour. At this time mixture was warmed to room temperature and DI water (3 mL) was added. The aqueous layer was extracted with EtOAc (3 x 20 mL), and the combined organic extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$), and evaporated under reduced pressure to give yellow oil. Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave **3.105** as a colorless oil (17.9 mg, 68%) consisting of >25:1 dr. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.30-7.15 (m, 10 H), 4.05 (d, 1 H, *J* = 12.82 Hz), 3.88-3,83 (m, 1 H), 3.29 (t, 1 H, *J* = 8.70 Hz), 3.23-3.17 (m, 2 H), 2.80-2.78 (m, 1 H), 2.54-2.47 (m, 1 H), 2.38-2.30 (m, 1 H), 2.25 (t, 1 H, *J* = 9.16 Hz), 2.11-1.94 (m, 3 H), 1.84-1.80 (m, 1 H); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 211.2, 144.2, 138.9, 128.7, 128.6, 128.3, 127.7, 127.1, 126.4, 65.4, 61.1, 59.5, 57.4, 41.9, 40.8, 26.5, 20.2; **HRMS-ESI:** calcd. for C21H23NO $[M+H]^+$: 306.1858, found: 306.1852.



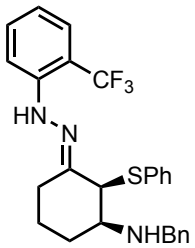
(3'S,3a'S,7a'S)-3'-allyl-1'-benzyl-3'-phenylhexahydrospiro[[1,3]dioxolane-2,4'-indol]-2'(1'H)-one (3.102). *n*-BuLi (2.5 M, 0.099 mmol) was added to a solution of *i*-Pr_2NH (0.015 ml, 0.107 mmol) in THF (0.3 ml) at – 78 ^{o}C. Stirred at – 78 ^{o}C for 5 min

then at 0 °C for 30 min. At this time cooled back to – 78 °C and solution of **3.101** (30 mg, 0.082 mmol) in THF (0.6 ml) was added dropwise over 2 min. Reaction mixture was stirred for 10 min at – 78 °C, then at 0 °C for 30 min. At this time cooled back to – 78 °C and solution of allyl bromide (0.021 ml, 0.248 mmol) in THF (0.3 ml) was added dropwise. Reaction mixture was stirred at – 78 °C for 1 h then at 0 °C for 1 hour. At this time reaction mixture was quenched with sat. NH_4Cl (2 ml), diluted with EtOAc (20 ml) and washed saturated aqueous NaCl, dried over $MgSO_4$, and evaporated under reduced pressure to give yellow oil. Flash chromatography over silica gel using 30:70 EtOAc-hexanes gave **3.102** as off-white solid (22.7 mg, 68%) consisting of >18:1 dr. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.52-7.51 (m, 2 H), 7.36-7.20 (M, 8 H), 5.86-5.81 (m, 1 H), 5.25-5.16 (m, 3 H), 4.12 (d, 1 H, *J* = 14.89 Hz), 4.09-4.06 (m, 1 H), 3.97-3.94 (m, 1 H), 3.86-3.84 (m, 1 H), 3.83-3.75 (m, 1 H), 3.43-3.39 (m, 1 H), 3.05-3.00 (m, 1 H), 2.91-2.87 (m, 1 H), 2.66-2.64 (m, 1 H), 1.79-1.72 (m, 1 H), 1.33-1.12 (m, 5 H); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 175.5, 141.5, 136.8, 135.8, 129.9, 128.8, 128.3, 127.8, 127.7, 126.9, 119.1, 110.3, 65.5, 63.6, 55.8, 55.5, 48.3, 44.8, 43.1, 32.0, 26.9, 19.9; **HRMS-ESI:** calcd. for $C_{26}H_{29}NO_3$ $[M+Na]^+$: 426.2040, found: 426.2043.



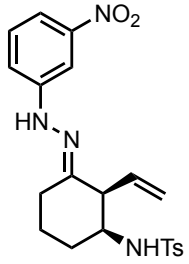
(3S,3aS,7aS)-3-allyl-1-benzyl-3-phenylhexahydro-1H-indole-2,4-dione (3.103). The procedure is the same as for compound **3.105.** Flash chromatography over silica gel using 20:80 EtOAc-hexanes gave **3.103** as colorless oil. (Yield: 89%) consisting of >25:1 dr. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.36-7.16 (m, 10 H), 5.87-5.81 (m, 1 H), 5.37-5.26 (m, 3 H), 4.15 (d, 1 H, *J* = 15.11 Hz), 3.57-3.50 (m, 1 H), 3.23 (d, 1 H, *J* = 8.70

Hz), 2.96-2.86 (m, 2 H), 2.09-2.00 (m, 2 H), 1.65-1.61 (m, 1 H), 1.32-1.22 (m, 2 H), 0.92-0.84 (m, 1 H); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 210.3, 173.8, 140.1, 136.2, 133.9, 128.9, 128.7, 128.2, 127.9, 127.5, 121.2, 56.9, 56.5, 52.3, 44.9, 41.9, 41.1, 27.4, 19.8; **HRMS-ESI:** calcd. for $C_{24}H_{25}NO_2$ $[M+H]^+$: 360.1958, found: 360.1962.

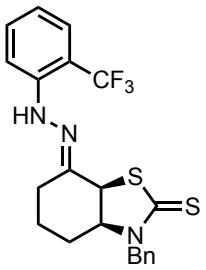


rel-(1*S*,2*S*,*E*)-*N*-benzyl-2-(phenylthio)-3-(2-(2-(trifluoromethyl)phenyl)hydrazono) cyclohexanamine (3.108). To a stirred solution of **3.80** (35 mg, 0.0974 mmol) in CH_2Cl_2 (1.5 ml) was added PhSH (0.022 ml, 0.2142 mmol). Reaction mixture was cooled in ice-bath followed by a dropwise addition of diisopropyl amine (0.027 ml, 0.1948 mmol). Reaction mixture was stitrred for 1 h. At this time saturated aqueous NH_4Cl/10% NH_4OH (2 mL) was added and the mixture was warmed to room temperature. After 3 min, the aqueous layer was extracted with EtOAc (3 x 20 mL), and the combined organic extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$), and evaporated under reduced pressure to give brown oil. Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave **3.108** as yellow solid (27.7 mg, 61%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.64 (br. s, 1 H), 7.52-7.50 (m, 2 H), 7.44-7.19 (m, 10 H), 6.86-6.83 (m, 1 H), 4.43 (d, 1 H, *J* = 4.12), 3.92 (d, 1 H, *J* = 12.82), 3.74 (d, 1 H, *J* = 12.82), 3.11-3.07 (m, 1 H), 2.48-2.44 (m, 2 H), 2.02-1.97 (m, 1 H), 1.91-1.87 (m, 1 H), 1.78-1.68 (m, 1 H), 1.52-1.44 (m, 1 H); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 149.4, 142.7, 139.9, 134.7, 133.1, 132.5, 128.9, 128.5, 128.3, 127.2, 127.1, 126.1, 126.0,

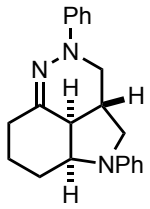
118.7, 114.6, 58.7, 58.5, 50.3, 29.0, 22.6, 21.3; **HRMS** *m*/*z* calcd. for $C_{26}H_{26}F_3N_3S$ $[M+Na]^+$: 492.1692, found: 492.1694.



4-methyl-*N*-((1S,2S,E)-3-(2-(3-nitrophenyl)hydrazono)-2-vinylcyclohexyl) benzenesulfonamide (3.109). To a stirred solution of **3.81** (50.0 mg, 0.12 mmol) in THF (1.2 mL) at –78 °C was added vinylMgCl (0.23 mL of a 1.6 M solution in THF, 0.37 mmol). The resulting mixture was stirred for 2 h at –78 °C. At this time saturated aqueous NH_4Cl/10% NH_4OH (2 mL) was added and the mixture was warmed (rt water bath). After 3 min, the aqueous layer was extracted with EtOAc (3 x 20 mL), and the combined organic extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$), and evaporated under reduced pressure to give brown solid. Flash chromatography over silica gel using 40:60 EtOAc-hexanes gave **3.109** as a yellow solid (84.9 mg, 61%) consisting of a >25:1 mixture of *syn* and *anti* diastereomers. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.80 (s, 1 H), 7.75-7.73 (m, 2 H), 7.62-7.76 (m, 2 H), 7.42 (br. s, 1 H), 7.33-7.30 (m, 3 H), 7.23-7.21 (m, 1 H), 5.93-5.86 (m, 1 H), 5.14-5.12 (d, 1 H, *J* = 10.31), 5.00-4.97 (d, 1 H, *J* = 17.18), 4.76-4.75 (d, 1 H, *J* = 8.02), 3.54-3.50 (m, 1 H), 3.04-3.02 (m, 1 H), 2.44 (s, 3 H), 2.42-2.36 (m, 1 H), 2.18-2.13 (m, 1 H), 1.89-1.77 (m, 2 H), 1.70-1.65 (m, 1 H), 1.51-1.49 (m, 1 H); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 149.4, 149.0, 146.4, 143.8, 137.7, 132.5, 129.9, 129.8, 127.1, 120.2, 118.6, 114.3, 107.4, 55.2, 53.3, 29.8, 22.6, 22.0, 21.6; **HRMS** *m*/*z* calcd. for $C_{21}H_{24}N_4O_4S$ $[M+H]^+$: 429.1518, found: 429.1514.



rel-(3a*S*,7a*S*,*E*)-3-benzyl-7-(2-(2-(trifluoromethyl)phenyl)hydrazono)hexahydrobenzo[d]thiazole-2(3H)-thione (3.110). To a stirred solution of **3.80** (35 mg, 0.0974 mmol) in CH_2Cl_2 (1.5 ml) was added PhSH (0.022 ml, 0.2142 mmol). Reaction mixture was cooled in ice-bath followed by a dropwise addition of diisopropyl amine (0.027 ml, 0.1948 mmol). Reaction mixture was stirred for 1 h. At this time saturated aqueous NH_4Cl/10% NH_4OH (2 mL) was added and the mixture was warmed to room temperature. After 2 min, the aqueous layer was extracted with EtOAc (3 x 20 mL), and the combined organic extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$), and evaporated under reduced pressure to give brown oil. Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave **3.110** as yellow solid (27.7 mg, 61%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.80 (br. s, 1 H), 7.60-7.57 (m, 1 H), 7.46-7.33 (m, 7 H), 6.92-6.88 (m, 1 H), 5.81 (d, 1 H, *J* = 15.11), 4.90 (d, 1 H, *J* = 7.79), 4.24 (d, 1 H, *J* = 14.65), 4.18-4.14 (m, 1 H), 2.59-2.53 (m, 1 H), 2.34-2.26 (m, 1 H), 2.08-1.88 (s, 3 H), 1.45-1.39 (m, 1 H); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 196.3, 141.8, 141.4, 135.5, 133.3, 129.1, 128.4, 128.0, 126.2, 126.1, 119.6, 114.5, 112.7, 65.9, 50.9, 50.7, 24.8, 22.1, 19.4; **HRMS** *m*/*z* calcd. for $C_{21}H_{20}F_3N_3S_2$ $[M+H]^+$: 436.1124, found: 436.1135.



2,5-diphenyl-2,3,3a,3a1,4,5,5a,6,7,8-decahydropyrrolo[4,3,2-de]cinnoline

(**3.111**). To a scintillated vial added 2.52 (63.0 mg, 0.261 mmol), benzyne precursor (116.8 mg, 0.392 mmol) and CH_3CN/Toluene (0.6ml, 1:1). After quick addition of CsF (237.9 mg, 1.566 mmol) all at once, the vial was capped and stirred for 1.5 h at 115 oC. At this time reaction was stopped and solvent was removed under the vacuum. Flash chromatography over silica gel using 0:100 to 5:95 EtOAc-hexanes gave 2.94 as a off yellow solid (82.9 mg, 70%). 1H NMR (CDCl3, 400 MHz): δ 7.31-7.26 (m, 4 H), 7.21-7.19 (m, 2 H), 6.87-6.84 (m, 1 H), 6.77-6.74 (m, 1 H), 6.69-6.68 (m, 1 H), 3.84-3.81 (m, 3 H), 3.68-3.63 (m, 1 H), 3.00-2.97 (m, 1 H), 2.72-2.68 (m, 1 H), 2.60-2.34 (m, 3 H), 1.99-1.97 (m, 1 H), 1.74-1.69 (m, 1 H), 1.18-1.14 (m, 1 H); 13**C NMR** (CDCl3, 100 MHz): δ 151.2, 148.2, 148.0, 129.5, 129.1, 119.1, 116.7, 112.6, 112.0, 58.6, 52.1, 50.0, 42.8, 36.5, 28.5, 27.5, 20.0; HRMS m/z calcd. for $C_{21}H_{23}N_3$ $[M+H]^+$: 318.1868, found: 318.1965.

1.7.3 Synthesis of hydroxy azoalkenes

*General procedure **K**: Formation of HAP from α-epoxy ketones*

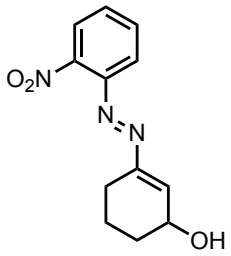
To a stirred solution of α-epoxy ketone (1.2 equiv) in Et_2O (1.0 M) at rt was added phenyl hydrazine (1.0 equiv). The reaction was stirred 14 h and concentrated *in vacuo*. Flash chromatography over silica gel gave the desired HAPs.

*General procedure **L**: Formation of HAP from α-epoxy ketones*

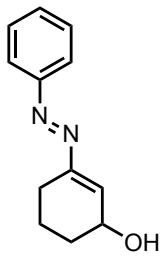
To a stirred solution of α-epoxy ketone (1.2 equiv) in THF (1.0 M) at rt was added aryl hydrazine (1.2 equiv), followed by *i*-Pr_2NEt (1.2 equiv). The reaction was stirred 14 h and poured into a separatory funnel. The reaction was then partitioned between EtOAc (20 mL) and H_2O (5 mL). The organic phase was washed with sat. NaCl (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography over silica gel gave the desired HAPs.

*General procedure **M**: Formation of HAP from α-epoxy ketones*

To a stirred solution of α-epoxy ketone (1.2 equiv) in THF (1.0 M) at rt was added aryl hydrazine (1.2 equiv). The reaction was stirred 14 h and cooled to 0 °C (ice-bath). 1 M NaOH (7 mL, 1.5 equiv) was added, and the reaction was stirred 10 min. The reaction was then poured into a separatory funnel and partitioned between Et_2O (20 mL) and H_2O (5 mL). The organic phase was washed with sat. NaCl (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography over silica gel gave the desired HAPs.

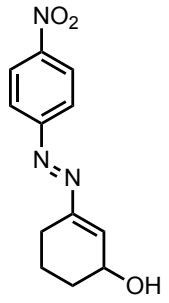


***(E)*-3-((2-nitrophenyl)diazenyl)cyclohex-2-enol** (**2.66**). To a solution of hydrazone **2.16** (0.045 g, 0.182 mmol) in THF (2 mL) at 0 °C was added 1 M aq. NaOH (0.54 mL, 0.546 mmol). The reaction was stirred 10 min and then partitioned between Et_2O and H_2O. The aqueous phase was then extracted with Et_2O (3 X 10 mL), and the combined organic extracts were washed with sat. aq. NaCl, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide an orange solid in quantitative yield. mp 75-77 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.83 (dd, J = 7.33 Hz, 0.92 Hz, 1 H), 7.63-7.59 (m, 1 H), 7.52-7.46 (m, 2 H), 7.01 (d, 0.92 Hz, 1 H), 4.65 (brs, 1 H), 2.40-2.26 (m, 2 H), 2.12-2.02 (m, 1 H), 1.97-1.82 (m, 2 H), 1.76-1.60 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 156.7, 147.3, 145.6, 144.2, 135.1, 130.1, 124.0, 118.3, 66.9, 31.9, 22.4, 18.7; **HRMS-ESI**: *m/z* calcd for $C_{12}H_{13}N_3O_3$ $[M+H]^+$: 248.1030, found 248.1039.

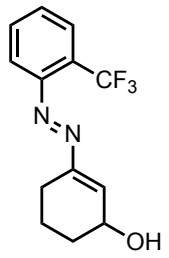


(*E*)-3-(phenyldiazenyl)cyclohex-2-enol (3.68). 7-oxabicyclo[4.1.0]heptan-2-one (0.998 g, 8.90 mmol) was treated following general procedure **(K).** Flash chromatography (20:80 EtOAc-Hexanes) gave an orange solid (1.42 g, 79%). mp 59-61 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.77-7.74 (m, 2 H), 7.48-7.39 (m, 3 H), 6.90-6.89 (m,

1 H), 4.64 (brs, 1 H), 2.44-2.39 (m, 2 H), 2.10-2.01 (m, 1 H), 1.98-1.90 (m, 1 H), 1.76-1.66 (m, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 156.0, 152.6, 140.6, 130.6, 129.0, 122.5, 68.8, 32.1, 22.6, 18.8; **IR (neat)**: 3311, 2944, 1638, 1463, 1135, 1058, 1032, 764, 687 cm^{-1}. **HRMS-CI**: *m/z* calcd. for $C_{12}H_{14}N_2O$ $[M]^+$: 202.1106, found 202.1101.

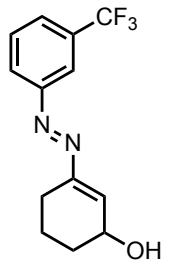


(*E*)-3-((4-nitrophenyl)diazenyl)cyclohex-2-enol (3.69). 7-oxabicyclo[4.1.0]heptan-2-one (0.250 g, 2.23 mmol) was treated following general procedure **L.** Flash chromatography (35:65 EtOAc-Hexanes) gave a red solid (0.082 g, 15%). mp 125-127 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.31 (d, *J* = 8.59 Hz, 2 H), 7.85 (d, *J* = 8.59 Hz, 2 H), 7.05-7.04 (m, 1 H), 4.68 (brs, 1 H), 2.41-2.37 (m, 2 H), 2.11-2.06 (m, 1 H), 2.00-1.82 (m, 2 H), 1.76-1.60 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 15.64, 155.8, 148.8, 144.7, 124.7, 123.2, 66.9, 31.9, 22.5, 18.8; **HRMS-ESI**: *m/z* calcd. for $C_{12}H_{13}N_3O_3$ $[M+H]^+$: 248.1030, found 248.1024.

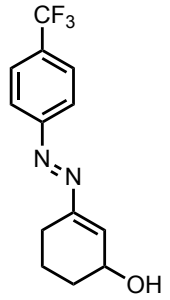


(*E*)-3-((2-(trifluoromethyl)phenyl)diazenyl)cyclohex-2-enol (3.70). 7-oxabicyclo[4.1.0]heptan-2-one (0.544 g, 4.85 mmol) was treated following general procedure **C**. Flash chromatography (20:80 EtOAc-Hexanes) gave a orange solid (1.10 g,

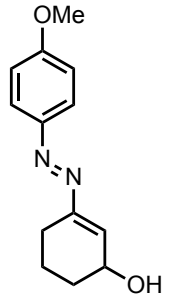
84%). mp 99-100 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.77 (d, J = 7.79 Hz, 1 H), 7.64-7.57 (m, 2 H), 7.50 (t, J = 7.33 Hz, 1 H), 7.00-6.99 (m, 1 H), 4.68-4.64 (m, 1 H), 2.42-2.39 (m, 2 H), 2.10-2.04 (m, 1 H), 1.99-1.91 (m, 1 H), 1.77-1.63 (m, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 156.8, 149.5, 142.9, 132.6, 130.0, 128.2 (q, J_{C-F} = 31 Hz), 126.5 (q, J_{C-F} = 5 Hz) 124.0 (q, J_{C-F} = 273 Hz), 116.0, 67.0, 32.0, 22.4, 18.8; **^{19}F NMR** (376 MHz, $CDCl_3$): δ –58.0 (s, 3 F); **HRMS-ESI**: *m/z* calcd. for $C_{13}H_{13}F_3N_2O$ $[M+H]^+$: 271.1053, found 271.1049.



(*E*)-3-((3-(trifluoromethyl)phenyl)diazenyl)cyclohex-2-enol (3.71). 7-oxabicyclo[4.1.0]heptan-2-one (0.220 g, 1.96 mmol) was treated following general procedure **L.** Flash chromatography (20:80 EtOAc-Hexanes) gave a orange solid (0.360 g, 68%). mp 52-54 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.02 (s, 1 H), 7.93 (d, J = 8.02 Hz, 1 H), 7.67 (d, J = 7.45 Hz, 1 H), 7.58 (t, J = 8.02 Hz, 1 H), 6.98-6.97 (m, 1 H), 4.68-4.66 (m, 1 H), 2.41-2.38 (m, 2 H), 2.09-2.04 (m, 1 H), 1.99-1.93 (m, 1 H), 1.76-1.65 (m, 3 H with apparent doublet at 1.73 ppm (J = 6.87 Hz)); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 155.9, 152.5, 142.6, 131.6 (q, J_{C-F} = 32 Hz), 129.6, 126.8 (q, J_{C-F} = 4 Hz), 125.7, 123.9 (q, J_{C-F} = 272 Hz), 119.5 (q, J_{C-F} = 4 Hz), 66.8, 32.0, 22.5, 18.8; **^{19}F NMR** (376 MHz, $CDCl_3$): δ –62.5 (s, 3 F); **HRMS-ESI**: *m/z* calcd. for $C_{13}H_{13}F_3N_2O$ $[M+H]^+$: 271.1053, found 271.1063.

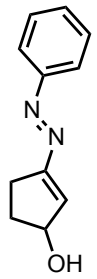


(*E*)-3-((4-(trifluoromethyl)phenyl)diazenyl)cyclohex-2-enol (3.72). 7-oxabicyclo[4.1.0]heptan-2-one (0.398 g, 3.55 mmol) was treated following general procedure **L.** Flash chromatography (20:80 EtOAc-Hexanes) gave a orange solid (0.652 g, 68%). mp 81-83 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.83, 7.72 (ABq, J_{AB} 8.59 Hz, 4 H), 6.98-6.98 (m, 1 H), 4.71-4.65 (m, 1 H), 2.41-2.39 (m, 2 H), 2.10-2.04 (m, 1 H), 1.99-1.93 (m, 1 H), 1.76-1.65 (m, 3 H with apparent doublet at 1.73 ppm (J = 6.30 Hz)); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 156.1, 154.4, 143.0, 131.8 (q, $J_{C\text{-}F}$ = 32 Hz), 126.2 (q, $J_{C\text{-}F}$ = 3 Hz), 124.0 (q, $J_{C\text{-}F}$ = 272 Hz), 122.7, 66.9, 32.0, 22.5, 18.8; **^{19}F NMR** (376 MHz, $CDCl_3$): δ –62.3 (s, 3 F); **HRMS-ESI**: *m/z* calcd. for $C_{13}H_{13}F_3N_2O$ $[M+H]^+$: 271.1053, found 271.1050.

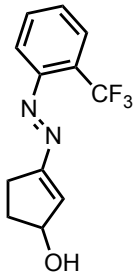


(*E*)-3-((4-methoxyphenyl)diazenyl)cyclohex-2-enol (3.73). To a stirred solution of 7-oxabicyclo[4.1.0]heptan-2-one (0.416 g, 4.07 mmol) in Et_2O (1.0 M) at rt was added 4-methoxyphenylhydrazine (0.512 g, 3.70 mmol). The reaction was stirred 14 h and concentrated *in vacuo*. Flash chromatography (1:4 EtOAc-Hexanes) gave an orange solid

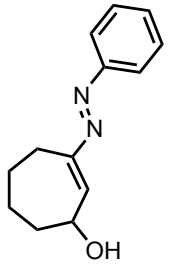
(0.510 g, 59%). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.6 Hz, 2 H), 6.95 (d, *J* = 8.7 Hz, 2 H), 6.79 (s, 1 H), 4.61 (s, 1 H), 3.84 (s, 3 H), 2.37 (m, 2H), 2.20 (s, 1H), 2.02 (m, 11.5 Hz, 1H), 1.91 (m, 6.3 Hz, 1H), 1.75-1.60 (m, 2H) ; **^{13}C NMR** (125 MHz, $CDCl_3$): δ 161.7, 155.7, 146.9, 139.0, 124.4, 114.2, 66.8, 55.6, 32.1, 22.6, 18.9; **HRMS-CI:** *m/z* calcd. for $C_{13}H_{16}N_2O_2$ $[M]^+$: 232.165, found 232.168.



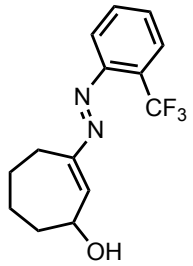
(*E*)-3-(phenyldiazenyl)cyclopent-2-enol (3.74). 6-oxabicyclo[3.1.0]hexan-2-one (0.332 g, 3.38 mmol) was treated following general procedure **A**. Flash chromatography (35:65 EtOAc-Hexanes) gave a orange solid (0.457 g, 72%). mp 91-93 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.79-7.76 (m, 2 H), 7.49-7.42 (m, 3 H), 6.85-6.84 (m, 1 H), 5.13-5.09 (m, 1 H), 2.86-2.80 (m, 1 H), 2.60-2.48 (m, 2 H), 1.93-1.87 (m, 1 H), 1.73 (d, *J* = 7.45 Hz, 1 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 161.1, 152.9, 140.3, 131.1, 129.1, 122.8, 75.9, 32.8, 26.6; **HRMS-ESI**: *m/z* calcd. for $C_{11}H_{12}N_2O$ $[M+H]^+$: 189.1022, found 189.1017.



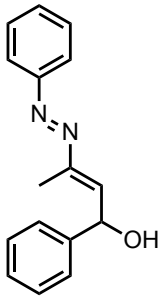
(*E*)-3-((2-(trifluoromethyl)phenyl)diazenyl)cyclopent-2-enol (3.75). 6-oxabicyclo[3.1.0]hexan-2-one (0.257 g, 2.57 mmol) was treated following general procedure **C**. Flash chromatography (20:80 EtOAc-Hexanes) gave a bright orange solid (0.343 g, 52%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.78 (d, *J* = 7.56 Hz, 1 H), 7.64 (d, *J* = 7.56 Hz, 1 H), 7.60 (t, *J* = 6.87 Hz, 1 H), 7.51 (t, *J* = 7.56 Hz, 1 H), 6.94 (s, 1 H), 5.15-5.11 (m, 1 H), 2.85-2.81 (m, 1H), 2.60-2.50 (m, 2 H), 1,91-1.88 (m, 1 H), 1.72 (d, *J* = 7.56 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 161.1, 149.7, 142.2, 132.5 130.5, 128.7, 128.5, 126.6 (q, J_{C-F} = 5 Hz), 125.0, 122.8, 115.9, 76.0, 32.7, 26.6; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –57.9 (s, 3 F); **HRMS-ESI:** *m/z* calcd. for C12H11F3N2O $[M+Na]^+$: 279.0716, found 279.0725.



(*E*)-3-(phenyldiazenyl)cyclohept-2-enol (3.76). 8-oxabicyclo[5.1.0]octan-2-one[10] (0.325 g, 2.57 mmol) was treated following general procedure **(K)**. Flash chromatography (20:80 EtOAc-Hexanes) gave a orange solid (0.434 g, 78%). mp 92-94 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.76-7.73 (m, 2 H), 7.47-7.38 (m, 3 H), 6.97-6.96 (m, 1 H), 4.80-4.77 (m, 1 H), 3.27 (dd, *J* = 15.80 Hz, 5.95 Hz, 1 H), 2.19-2.12 (m, 1 H), 2.04-1.99 (m, 2 H), 1.83-1.69 (m, 4 H), 1.38-1.28 (m, 1 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 157.3, 152.3, 149.9, 130.3, 129.0, 122.5, 71.5, 36.4, 27.5, 25.1, 23.8; **HRMS-ESI**: *m/z* calcd. for $C_{13}H_{16}N_2O$ $[M+H]^+$: 217.1335, found 217.1339.

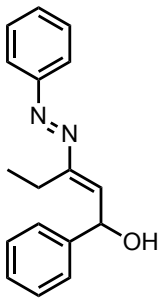


(*E*)-3-((2-(trifluoromethyl)phenyl)diazenyl)cyclohept-2-enol (3.77). 8-oxabicyclo[5.1.0]octan-2-one (0.578 g, 4.60 mmol) was treated following general procedure **C**. Flash chromatography (20:80 EtOAc-Hexanes) gave a bright orange solid (1.302 g, 78%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 7.8 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 2H), 7.07 (d, *J* = 2.4 Hz, 1H), 4.81 (d, *J* = 9.5 Hz, 1H), 3.26 (dd, *J* = 15.6, 6.8 Hz, 1H), 2.24-2.10 (m, 1H), 2.07-1.91 (m, 3H), 1.91-1.68 (m, 3H), 1.41-1.22 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 158.2, 152.3, 149.3, 132.6, 129.7, 126.5, 126.4, 116.3, 71.6, 36.5, 27.4, 24.9, 24.0; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –58.0 (s, 3 F); **HRMS-ESI:** *m/z* calcd. for $C_{14}H_{15}F_3N_2O$ $[M+Na]^+$: 307.1034, found 307.1031.

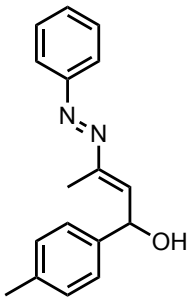


(*E*)-1-phenyl-3-((*E*)-phenyldiazenyl)but-2-en-1ol (**3.86**). 1-(3-phenyloxiran-2-yl)ethanone (0.354 g, 2.18 mmol) was treated following general procedure **(K)**. Flash chromatography (15:85 EtOAc-Hexanes) gave a red oil (0.131 g, 24%). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.76 (d, *J* = 7.56 Hz, 2 H), 7.47-7.44 (m, 4 H), 7.42-7.36 (m, 3 H), 7.32-7.29 (m, 1 H), 6.93 (d, *J* = 9.62 Hz, 1 H), 5.78 (d, *J* = 8.94 Hz, 1 H), 2.63-2.56 (brs, 1 H),

2.07 (S, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 152.9, 152.4, 144.0, 142.5, 130.6, 129.1, 128.9, 128.2, 126.4, 122.6, 71.0, 11.1; **HRMS-ESI:** *m/z* calcd. for $C_{16}H_{16}N_2O$ $[M+H]^+$: 253.1335, found 253.1339.

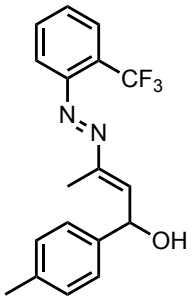


(*E*)-1-phenyl-3-((*E*)-phenyldiazenyl)pent-2-en-1ol (3.87). 1-(3-phenyloxiran-2-yl)propan-1-one (0.118 g, 0.669 mmol) was treated following general procedure **(K)**. Flash chromatography (15:85 EtOAc-Hexanes) gave a red oil (0.071 g, 40%). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.70-7.74 (m, 2 H), 7.51-7.50 (m, 2 H), 7.47-7.44 (m, 2 H), 7.42-7.38 (m, 3 H), 7.33-7.30 (m, 1 H), 6.83 (d, *J* = 9.16 Hz, 1 H), 5.80 (dd, *J* = 9.16 Hz, 3.44 Hz, 1 H), 2.72-2.63 (m, 2 H), 2.10 (d, *J* = 4.10 Hz, 1 H), 1.02 (t, *J* = 7.45 Hz, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 158.2, 152.5, 142.6, 130.6, 129.0, 128.9, 128.2, 126.5, 122.6, 70.9, 18.2, 12.9; **HRMS-CI:** *m/z* calcd. for $C_{17}H_{18}N_2O$ $[M]^+$: 266.1419, found 266.1415.

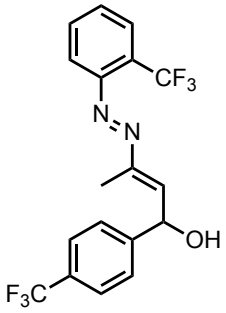


(*E*)-3-((*E*)-phenyldiazenyl)-1-(*p*-tolyl)but-2-en-1ol (3.88). 1-(3-(*p*-tolyl)oxiran-2-yl)ethanone (0.127 g, 0.720 mmol) was treated following general procedure **(K)**. Flash

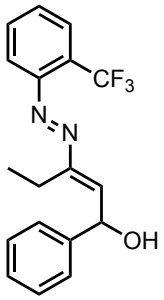
chromatography (10:90 EtOAc-Hexanes) gave a red oil (0.92 g, 48%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.70 Hz, 2 H), 7.48-7.36 (m, 5 H), 7.20 (d, *J* = 7.79 Hz, 2 H), 6.95 (d, *J* = 9.16 Hz, 1 H), 5.77 (dd, *J* = 8.93 Hz, 3.21 Hz, 1 H), 2.51-2.35 (m, 4 H with apparent singlet at 2.35 ppm), 2.07 (s, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 158.8, 152.5, 144.2, 139.6, 138.0, 130.5, 129.6, 129.1, 126.3, 122.6, 71.0, 21.3, 11.1; **HRMS-ESI:** *m/z* calcd. for $C_{17}H_{18}N_2O$ $[M+H]^+$: 267.1492, found 267.1488.



(*E*)-1-(*p*-tolyl)-3-((*E*)-(2-(trifluoromethyl)phenyl)diazenyl)but-2-en-1-ol (3.89). 1-(3-(*p*-tolyl)oxiran-2-yl)ethanone (0.140 g, 0.794 mmol) was treated following general procedure **(K)**. Flash chromatography (10:90 EtOAc-Hexanes) gave a orange oil (0.223 g, 84%). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.78 (d, *J* = 7.68 Hz, 1 H), 7.68-7.53 (m, 2 H), 7.48 (t, *J* = 7.48 Hz, 1 H), 7.37 (d, *J* = 8.03 Hz, 2 H), 7.20 (d, *J* = 7.92 Hz, 2 H), 7.05 (d, *J* = 9.15 Hz, 1 H), 5.77 (dd, *J* = 3.25 Hz, 8.89 Hz, 1 H), 2.77 (d, *J* = 3.47 Hz, 1 H), 2.35 (s, 3 H), 2.06 (s, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 153.5, 149.3, 146.4, 139.3, 138.1, 132.5, 130.0, 129.6, 126.5, 125.4, 122.7, 116.0, 70.9, 21.2, 14.2, 11.0; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –58.0 (s, 3 F); **HRMS-ESI:** *m/z* calcd. for $C_{18}H_{17}F_3N_2O$ $[M+H]^+$: 335.1371, found 335.1369.

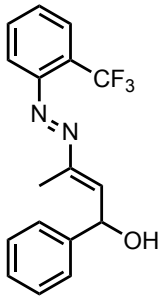


(*E*)-1-(4-(trifluoromethyl)phenyl)-3-((*E*)-(2-(trifluoromethyl)phenyl)diazenyl)but-2-en-1-ol (3.90). 1-(3-(4-(trifluoromethyl)phenyl)oxiran-2-yl)ethanone (0.306 g, 1.30 mmol) was treated following general procedure **C**. Flash chromatography (10:90 EtOAc-Hexanes) gave a orange oil (0.229 g, 44%). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.78 (d, *J* = 7.69 Hz, 1 H), 7.68-7.53 (m, 6 H), 7.50 (t, *J* = 7.47 Hz, 1 H), 6.94 (d, *J* = 9.17 Hz, 1 H), 5.86 (dd, *J* = 8.8 Hz, 1.28 Hz, 1 H), 3.04 (d, *J* = 2.69 Hz, 1 H), 2.10 (s, 3 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 154.2, 149.1, 146.0, 144.7, 132.6, 130.4, 130.3, 126.6, 126.5, 125.8, 115.9, 70.3, 11.1; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –57.9 and -62.4 (two s, 6 F); **HRMS-ESI:** *m/z* calcd. for $C_{18}H_{14}F_6N_2O$ $[M+H]^+$: 389.1088, found 389.1090.



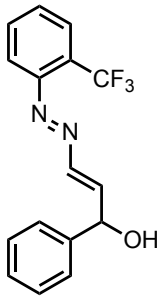
(*E*)-1-phenyl-3-((*E*)-(2-trifluoromethyl)phenyldiazenyl)pent-2-en-1ol (3.91). 1-(3-phenyloxiran-2-yl)propan-1-one[12] (0.447 g, 2.53 mmol) was treated following general procedure **C**. Flash chromatography (10:90 EtOAc-Hexanes) gave a red oil (0.543 g, 64%). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.78 (d, *J* = 8.02 Hz, 1 H), 7.65 (d, *J* =

8.02 Hz, 1 H), 7.58 (t, J = 7.45, 1 H), 7.51-7.48 (m, 3 H), 7.42-7.38 (m, 2 H), 7.34-7.32 (m, 1 H), 6.95 (d, J = 9.16 Hz, 1 H), 5.81 (dd, J = 9.16 Hz, 3.44 Hz, 1 H), 2.71-2.58 (m, 2 H), 2.23 (d, J = 3.44 Hz, 1 H), 1.01 (t, J = 7.45 Hz, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 159.0, 149.2, 145.2, 142.4, 132.5, 130.1, 129.0, 128.4 (q, J_{C-F} = 30 Hz), 128.2, 126.6 (q, J_{C-F} = 5 Hz), 126.5, 124.0 (q, J_{C-F} = 274 Hz), 115.9, 71.0, 18.4, 12.4; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –57.9 (s, 3 F); **HRMS-X**: *m/z* calcd. for $C_{18}H_{17}F_3N_2O$ $[M+Na]^+$: 357.1191, found 357.1190.

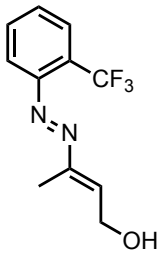


(*E*)-1-phenyl-3-((*E*)-(2-(trifluoromethyl)phenyl)diazenyl)but-2-en-1-ol

(3.86a). 1-(3-phenyloxiran-2-yl)ethanone. (0.414 g, 2.56 mmol) was treated following general procedure **C**. Flash chromatography (15:85 EtOAc-Hexanes) gave an orange oil (0.177 g, 42%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.79 (d, J = 7.7 Hz, 1 H), 7.65 (d, J = 8.0 Hz, 1 H), 7.56 (t, J = 7.4 Hz, 1 H), 7.52-7.43 (m, 3 H), 7.43 -7.28 (m, 3 H), 7.06 (dd, J = 9.1, 0.7 Hz, 1 H), 5.78 (dd, J = 9.0, 3.5 Hz, 1 H), 3.33 (d, J = 3.6 Hz, 1 H), 2.08 (S, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 153.7, 149.2, 146.2, 142.3, 132.6, 130.1, 129.0, 128.5, 128.2, 126.4, 125.5, 122.8, 116.0, 71.0, 11.0; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –57.8 (s, 3 F); **HRMS-ESI:** *m/z* calcd. for $C_{17}H_{15}F_3N_2O$ $[M+Na]^+$: 343.1034, found 343.1029.

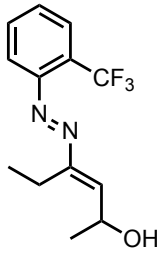


(E)-1-phenyl-3-((E)-(2-(trifluoromethyl)phenyl)diazenyl)prop-2-en-1-ol (3.92). 3-phenyloxirane-2-carbaldehyde (0.250 g, 1.69 mmol) was treated following general procedure **(K)**. Flash chromatography (10:90 EtOAc-Hexanes) gave an orange oil (0.0851 g, 16%). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.79 (d, *J* = 7.7 Hz, 1 H), 7.68-7.53 (m, 2 H), 7.53-7.32 (m, 7 H), 7.17 (dd, *J* = 13.5, 6.1 Hz, 1 H), 5.60 (m, 1 H), 2.76 (d, *J* = 3.6 Hz, 1 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 149.7, 147.9, 147.4, 141.4, 132.5, 130.3, 129.0, 128.5, 126.7, 126.5, 125.0, 122.9, 116.4, 73.0; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –57.5 (s, 3 F); **ESI:** *m/z* calcd. for $C_{16}H_{13}F_3N_2O$ $[M+H]^+$: 307.1058, found 307.1055.

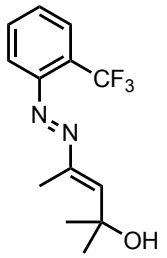


(E)-3-((E)-(2-(trifluoromethyl)phenyl)diazenyl)but-2-en-1-ol (3.93). 1-(oxiran-2-yl)ethanone (0.0831 g, 0.944 mmol) was treated following general procedure **(K)**. Flash chromatography (15:85 EtOAc-Hexanes) gave an orange oil (0.075 g, 33%). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.76 (d, *J* = 7.8 Hz, 1 H), 7.65-7.52 (m, 2 H), 7.47 (t, 1 H), 4.61 (t, *J* = 6.1 Hz, 2 H), 2.33 (t, *J* = 5.6 Hz, 1 H), 1.95 (s, 3 H) ; **^{13}C NMR** (125 MHz, $CDCl_3$): δ 154.2, 149.4, 143.5, 132.5, 129.9, 126.5, 126.4, 125.1, 122.9, 116.0, 59.6,

10.7; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –58.0 (s, 3 F); **HRMS-ESI:** *m/z* calcd. For $C_{11}H_{11}F_3N_2O$ $[M+H]^+$: 245.0901, found 245.0901.



(E)-4-((E)-(2-(trifluoromethyl)phenyl)diazenyl)hex-3-en-2-ol (3.94). 1-(3-methyloxiran-2-yl)propan-1-one (0.182 g, 1.60 mmol) was treated following general procedure **C**. Flash chromatography (15:85 EtOAc-Hexanes) gave an orange oil (0.090 g, 21%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 7.7 Hz, 1 H), 7.71-7.55 (m, 2 H), 7.50 (t, *J* = 7.5 Hz, 1 H), 6.72 (d, *J* = 9.0 Hz, 1 H), 4.95 (m, 1 H), 2.62-2.45 (m, 2 H), 1.74 (d, *J* = 3.7 Hz, 1 H), 1.47 (d, *J* = 6.3 Hz, 3 H), 1.03 (t, *J* = 7.5 Hz, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 158.5, 149.2, 147.5, 132.5, 130.0, 125.4, 122.7, 115.9, 64.8, 23.5, 18.3, 12.8; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –57.9 (s, 3 F); **HRMS-ESI:** *m/z* calcd. for $C_{13}H_{15}F_3N_2O$ $[M+H]^+$: 273.1214, found 273.1219.



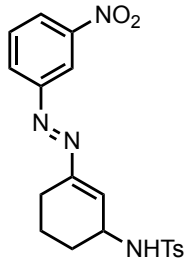
(E)-2-methyl-4-((E)-(2-(trifluoromethyl)phenyl)diazenyl)pent-3-en-2-ol (3.95). 1-(3,3-dimethyloxiran-2-yl)ethanone (0.543 g, 4.76 mmol) was treated following general procedure **C**. Flash chromatography (10:90 EtOAc-Hexanes) gave an orange oil (0.205 g, 16%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ7.77 (d, *J* = 7.8 Hz, 1H), 7.63 – 7.55 (m,

2H), 7.48 (t, J = 7.1 Hz, 1H), 6.94 (s, 1H), 2.19 (s, 3H), 1.70 (s, 1H), 1.58 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 154.3, 153.0, 149.5, 132.5, 129.6, 125.2, 123.0, 116.1, 71.0, 30.7, 11.1; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –58.0 (s, 3 F);**HRMS-ESI:** *m/z* calcd. for $C_{13}H_{15}F_3N_2O$ $[M+H]^+$: 273.1214, found 273.1215.

1.7.5 Synthesis of amino azoalkenes

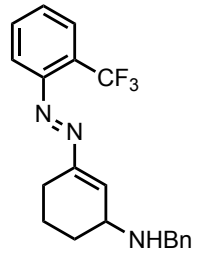
General procedure for the formation of AAP from α-aziridino ketones

To a stirred solution of α-aziridino ketone (1.2 equiv) in Et_2O (1.0 M) at rt was added aryl hydrazine (1.0 equiv). The reaction was stirred 14 h and concentrated *in vacuo*. 1 M NaOH (7 mL, 1.5 equiv) was added, and the reaction was stirred 10 min. The reaction was then poured into a separatory funnel and partitioned between Et_2O (20 mL) and H_2O (5 mL). The organic phase was washed with sat. NaCl (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography over silica gel gave the desired HAPs.

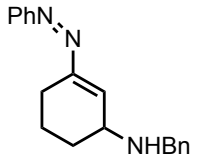


(*E*)-4-methyl-*N*-(3-((3-nitrophenyl)diazenyl)cyclohex-2-en-1-yl)benzenesulfonamide (3.81). $ArNHNH_2$ HCl (153.3 mg, 0.8088 mmol) was added to a stirred solution of 7-tosyl-7-azabicyclo [4.1.0] heptan-2-one (195.1 mg, 07353 mmol) in THF (4 mL), followed by addition of N,N-Diisopropylethylamine (0.25 ml, 1.4706 mmol). The mixture was stirred for 12 h. Solvent was evaporated under reduced pressure to give orange solid. Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave **2.51** as orange solid (218.2 mg, 74 %). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.49-8.51 (m, 1 H), 8.24-8.26 (m, 1 H), 8.03-8.06 (m, 1 H), 7.83-7.85 (m, 2 H), 7.60-7.64 (m, 1 H), 7.33-7.35 (m, 2 H), 6.68-6.69 (m, 1 H), 5.06-5.08 (d, 1 H, *J* = 9.16), 4.25-4.26 (m, 1 H) 2.44 (s, 3 H), 2.30-2.33 (m, 2 H), 1.83-1.95 (m, 2 H), 1.57-1.69 (m, 3 H); **^{13}C NMR**

($CDCl_3$, 100 MHz): δ 156.6, 152.8, 148.9, 143.8, 141.3, 137.9, 130.05, 130.01, 129.1, 127.2, 124.8, 116.9, 50.3, 30.4, 22.1, 21.7, 19.3; **HRMS** *m/z* calcd. for $C_{19}H_{20}N_4O_4S$ $[M+H]^+$: 401.1205, found: 401.1200.

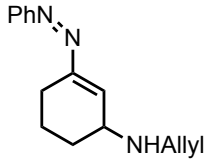


(E)-N-benzyl-3-((2-(trifluoromethyl)phenyl)diazenyl)cyclohex-2-enamine (3.80). $ArNHNH_2$ (192.5 mg, 1.0928 mmol) was added to a stirred solution of 7-benzyl-7-azabicyclo [4.1.0]heptan-2-one (200 mg, 0.9935 mmol) in Et_2O (2 mL). The mixture was stirred for 12 h. Solvent was evaporated under reduced pressure to give orange oil. Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave **3.80** as dark red oil (178.5 mg, 50 %). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.78-7.76 (m, 1 H), 7.63-7.57 (m, 2 H), 7.50-7.46 (m, 1 H), 7.41-7.33 (m, 4 H), 7.29-7.27 (m, 1 H), 7.11 (d, 1 H, *J* = 0.92), 4.03-3.99 (d, 2 H, *J* = 4.58), 3.67-3.63 (m, 1 H), 2.51-2.46 (m, 1 H), 2.36-2.34 (m, 1 H), 2.09-1.94 (m, 2 H), 1.07-1.53 (m, 2 H); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 156.6, 149.8, 144.4, 140.3, 132.5, 129.7, 128.6, 128.3, 128.1, 127.2, 126.5, 126.4, 116.0, 53.7, 51.2, 29.8, 22.8, 19.9; **HRMS** *m/z* calcd. for $C_{20}H_{20}N_3F_3$ $[M+H]^+$: 360.1687, found: 360.1690

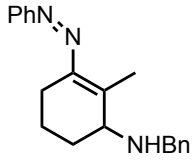


N-benzyl-3-(phenyldiazenyl)cyclohex-2-enamine (3.24). $PhNHNH_2$ (475.5 mg, 4.398 mmol) was added to a stirred solution of 7-benzyl-7-azabicyclo[4.1.0]heptan-2-

one[2] (737.7 g, 3.665 mmol) in Et_2O (10 mL). The mixture was stirred for 16 h. Solvent was evaporated under reduced pressure to give orange oil. Flash chromatography over silica gel using 20:80 EtOAc-hexanes gave **13** as dark red oil (1.00 g, 94%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.76-7.72 (m, 2 H), 7.46-7.25 (m, 8 H), 7.01 (d, 1 H, *J* = 1.09), 4.03-3.95 (m, 2 H), 3.65-3.62 (m, 1 H), 2.51-2.45 (m, 1 H), 2.38-2.31 (m, 1 H), 2.08-1.94 (m, 2 H), 1.70-1.64 (m, 1 H), 1.59-1.48 (m, 1 H); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 155.6, 152.8, 142.2, 140.4, 130.3, 129.0, 128.5, 128.2, 127.1, 122.5, 122.4, 53.6, 51.1, 29.9, 22.9, 20.1; **HRMS-ESI:** *m*/*z* calcd. for $C_{19}H_{21}N_3$ $[M+H]^+$: 292.1808, found: 292.1812.

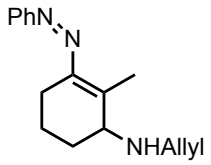


N-allyl-3-(phenyldiazenyl)cyclohex-2-enamine (15). Yield: 72% **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.75-7.72 (m, 2 H), 7.47-7.39 (m, 3 H), 6.96 (br s, , 1 H), 6.00-5.92 (m, 1 H), 5.27-5.22 (m, 1 H), 5.14-5.12 (m, 1 H), 3.63-3.60 (m, 1 H), 3.49-3.3.42 (m, 1 H), 2.51-2.45 (m, 1 H), 2.35-2.32 (m, 1H), 2.05-2.02 (m, 1H), 1.95-1.93 (m, 1 H), 1.69-1.66 (m, 1 H), 1.52-1.48 (m, 1 H); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 155.6, 152.8, 142.1, 136.9, 130.3, 129.0, 122.5, 122.4, 122.2, 53.6, 49.8, 30.0, 22.9, 20.0; **HRMS-ESI:** *m*/*z* calcd. for $C_{15}H_{19}N_3$ $[M+H]^+$: 242.1652, found:242.1654.

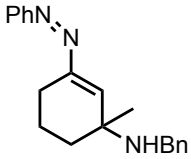


N-benzyl-2-methyl-3-(phenyldiazenyl)cyclohex-2-enamine (3.25). Yield: 85% **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.76-7.74 (m, 2 H), 7.46-7.7.32 (m, 7 H), 7.28-7.24 (m, 1 H), 3.97 (d, 1 H, *J* = 12.82 Hz), 3.84 (d, 1 H, *J* = 13.28 Hz), 3.38 (t, 1 H, *J* = 4.03 Hz),

2.49-2.47 (m, 1 H), 2.43 (s, 3 H), 2.33-2.29 (m, 1 H), 1.88-1.68 (m, 4 H); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 153.4, 149.9, 148.2, 140.8, 129.8, 129.0, 128.5, 128.3, 127.0, 122.557.5, 51.5, 27.4, 23.5, 18.4, 16.1; **HRMS-ESI:** *m/z* calcd. for $C_{20}H_{23}N_3$ $[M+H]^+$: 306.1965, found: 306.1966.

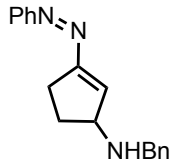


N-allyl-2-methyl-3-(phenyldiazenyl)cyclohex-2-enamine (3.26). Yield: 76% **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.76-7.73 (m, 1 H), 7.46-7.42 (m, 2 H), 7.39-7.35 (m, 1 H), 6.01-5.91 (m, 1 H), 5.27-5.21 (m, 1 H), 5.13-5.10 (m, 1 H), 3.44-3.28 (m, 3 H), 2.47-2.46 (m, 1 H), 2.43 (s, 3 H), 2.33-2.29 (m, 1 H), 1.83-1.65 (m, 4 H); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 153.4, 149.8, 148.1, 137.4, 129.9, 129.0, 122.5, 116.0, 57.4, 50.2, 27.6, 23.5, 18.4, 16.1; **HRMS-ESI:** *m/z* calcd. for $C_{16}H_{21}N_3$ $[M+H]^+$: 256.1808, found: 256.1813.

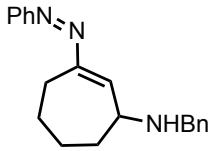


N-benzyl-1-methyl-3-(phenyldiazenyl)cyclohex-2-enamine (3.27). $PhNHNH_2$ (0.45 ml, 4.5 mmol) and $BnNH_2$ (0.50 ml, 4.5 mmol) were added to a stirring suspension of K_2CO_3 (2.2539 g, 16.3 mmol) and 2-Iodo-3-methyl-2-cyclohexen-1-one (962.6 mg, 4.1 mmol) in THF (24 mL) at RT under Ar. The mixture was stirred for 3 days. Solvent was evaporated under reduced pressure to give dark red past. Product was diluted with EtOAc and washed with DI H_2O, the organic phase was dried over $MgSO_4$ and concentrated. Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave **18** as dark red oil (98 %). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.77-7.75 (m, 2 H), 7.47-7.26 (m,

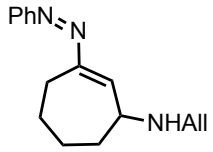
8 H), 6.89 (s, 1 H), 3.91-3.88 (d, 1 H, *J* = 13.28), 3.83-3.80 (d, 1 H, *J* = 13.74), 2.55-2.48 (m, 1 H), 2.38-2.30 (m, 1 H), 1.98-1.91 (m, 2 H), 1.84-1.68 (m, 2 H), 1.42 (s, 3 H); **^{13}C NMR (**$CDCl_3$, 400 MHz): δ 155.1, 152.8, 147.3, 141.0, 130.4, 129.1, 128.6, 128.4, 127.1, 122.5, 54.4, 47.3, 34.8, 27.3, 22.7, 19.5; **HRMS-ESI:** *m*/*z* calcd. for $C_{20}H_{23}N_3$ $[M]^+$: 305.1892, found: 305.1898.



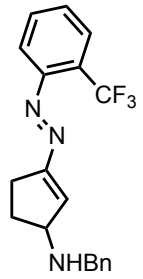
(E)-N-benzyl-3-(phenyldiazenyl)cyclopent-2-enamine (3.28). Yield: 87% **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.78-7.76 (m, 2 H), 7.49-7.32 (m, 7 H), 7.29-7.24 (m, 1 H), 6.97-6.95 (m, 1 H), 4.17-4.13 (m, 1 H), 3.93 (s, 2 H), 2.83-2.75 (m, 1 H), 2.61-2.42 (m, 2 H), 1.86-1.77 (m, 1 H); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 160.5, 153.1, 141.8, 140.3, 130.8, 129.1, 129.0, 128.6, 128.4, 128.2, 127.2, 62.7, 52.0, 30.7, 26.9; **HRMS-ESI:** *m*/*z* calcd. for $C_{18}H_{19}N_3$ $[M+H]^+$: 278.1652, found: 278.1648.



(E)-N-benzyl-3-(phenyldiazenyl)cyclohept-2-enamine (3.29). Yield: 92% **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.78-7.76 (m, 2 H), 7.48-7.45 (m, 2 H), 7.41-7.24 (m, 6 H), 7.03 (d, 1 H, *J* = 4.12 Hz), 3.99 (d, 1 H, *J* = 13.28 Hz), 3.88 (d, 1 H, *J* = 13.28 Hz), 3.79-3.76 (m, 1 H), 3.35-3.30 (m, 1 H), 2.22-2.15 (m, 1 H), 2.05-2.03 (m, 1 H), 1.94-1.91 (m, 1 H), 1.81-1.67 (m, 3 H), 1.31-1.29 (m, 1 H) ; **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 159.0, 152.5, 150.4, 140.2, 130.1, 129.0, 128.6, 128.3, 127.1, 122.5, 57.9, 51.8, 33.9, 29.2, 25.2, 23.6; **HRMS-ESI:** *m*/*z* calcd. for $C_{20}H_{23}N_3$ $[M+H]^+$: 306.1965, found: 306.1971.

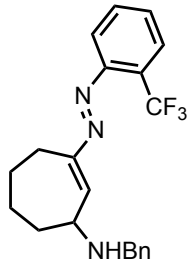


(E)-N-benzyl-3-(phenyldiazenyl)cyclohept-2-enamine (3.30). Yield: 56% **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.76-7.73 (m, 2 H), 7.46-7.43 (m, 2 H), 7.40-7.37 (m, 1 H), 6.93-6.92 (m, 1 H), 6.00-5.92 (m, 1 H), 5.25-5.24 (m, 1 H), 5.15-5.12 (m, 1 H), 3.77-3.73 (m, 1 H), 3.46-3.42 (m, 1 H), 3.37-3.29 (m, 2 H), 2.22-2.21 (m, 1 H), 2.05-2.01 (m, 1 H), 1.91-1.88 (m, 1 H), 1.80-1.63 (m, 3 H), 1.30-1.24 (m, 1 H); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 158.9, 152.5, 150.3, 136.6, 130.1, 129.1, 122.5, 116.3, 57.9, 50.3, 33.9, 29.2, 25.2, 23.6; **HRMS-ESI:** *m*/*z* calcd. for $C_{16}H_{21}N_3$ $[M+H]^+$: 256.1808, found: 256.1807.

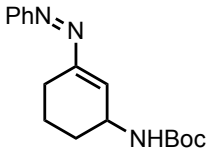


(*E*)-*N*-benzyl-3-((2-(trifluoromethyl)phenyl)diazenyl)cyclopent-2-enamine (3.28a). 6-benzyl-6-azabicyclo[3.1.0]hexan-2-one (0.101 g, 0.54 mmol) was treated following general procedure **D**. Flash chromatography over silica gel using (20:80 EtOAc-hexanes) gave a dark red oil (0.122 g, 65%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.78 (d, J = 7.79 Hz, 1 H), 7.64-7.57 (m, 2 H), 7.51 (t, J = 7.33 Hz, 1 H), 7.39-7.25 (m, 4 H), 7.05 (s, 1 H), 4.17-4.15 (m, 1 H), 3.93 (s, 2 H), 2.83-2.77 (m, 1 H), 2.62-2.54 (m, 1 H), 2.51-2.43 (m, 1 H), 1.85-1.78 (m, 1 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 161.2, 149.9, 143.8, 140.2, 132.5, 130.2, 128.6, 128.3, 128.2, 127.2, 126.5 (q, J_{C-F} = 5 Hz), 115.9, 62.8,

52.0 30.5, 26.9; **^{19}F NMR** (564 MHz, $CDCl_3$): δ –57.7 (s, 3 F); **HRMS-ESI:** *m/z* calcd. for C19H18F3N3 $[M+H]^+$: 346.1526, found 346.1532.

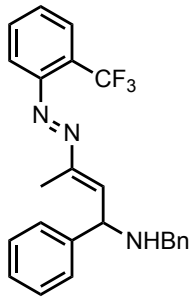


(*E*)-N-benzyl-3-((2-(trifluoromethyl)phenyl)diazenyl)cyclohept-2-enamine (3.29a). 8-benzyl-8-azabicyclo[5.1.0]octan-2-one (0.104 g, 0.48 mmol) was treated following general procedure **D**. Flash chromatography over silica gel using (20:80 EtOAc-hexanes) gave a dark red oil (0.148 g, 81%). **^{1}H NMR** (500 MHz, $CDCl_3$): δ7.78 (d, *J* = 7.7 Hz, 1H), 7.68 (d, *J* = 7.9 Hz, 1H), 7.60 (t, *J* = 7.7 Hz, 1H), 7.48 (t, *J* = 7.4 Hz, 1H), 7.38 (m, 4H), 7.32-7.27 (m, 1H), 7.22 (m, 1H), 7.15 (d, *J* = 4.0 Hz, 1H), 3.95 (dd, *J* = 51.5, 13.1 Hz, 2H), 3.82 (m, 1H), 3.33 (dd, *J* = 15.4, 6.9 Hz, 1H), 2.27-2.17 (m, 1H), 2.03 (m, 1H), 1.95 (m, 1H), 1.86-1.66 (m, 3H), 1.29 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ159.9, 152.9, 149.6, 140.1, 132.6, 129.5, 128.6, 128.3, 127.7, 127.2, 126.5, 117.4, 58.0, 51.8, 33.9, 29.1, 25.0, 23.8; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –58.0 (s, 3 F); **HRMS-ESI:** *m/z* calcd. for $C_{14}H_{15}F_3N_2O$ $[M+H]^+$: 374.1844, found 374.1833.

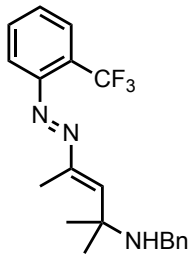


(*E*)-tert-butyl-(3-(phenyldiazenyl)cyclohex-2-en-1-yl)carbamate (3.82). 2-oxo-7-aza-bicyclo[4.1.0]heptane-7-carboxylic acid tert-butyl ester[14] (0.398 g, 1.32 mmol) was treated following general procedure **D**. Flash chromatography (20:80 EtOAc-Hexanes) gave an orange solid (0.331 g, 58%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 6.87

Hz, 2 H), 7.47-7.38 (m, 3 H), 6.80 (s, 1 H), 4.75-4.57 (m, 2 H), 2.49-2.30 (m, 2 H), 2.10-2.01 (m, 1 H), 1.93-1.82 (m, 1 H), 1.81-1.69 (m, 1 H), 1.60-1.45 (m, 10 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 156.1, 155.3, 152.6, 140.0, 130.5, 129.1, 122.5, 79.7, 47.2, 29.9, 28.5, 22.4, 19.7; **HRMS-CI**: *m/z* calcd. for C17H23N3O2 $[M+Na]^+$: 324.1682, found 324.1682.

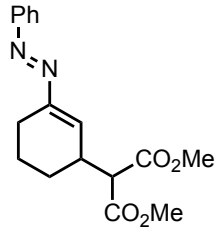


(*E*)-N-benzyl-1-phenyl-3-((*E*)-(2-(trifluoromethyl)phenyl)diazenyl)but-2-en-1-amine (3.96). 1-(1-benzyl-3-phenylaziridin-2-yl)ethanone[15] (0.125 g, 0.50 mmol) was treated following general procedure **D**. Flash chromatography (10:90 EtOAc-Hexanes) gave an orange oil (0.147, 71%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.78 (d, *J* = 7.8 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.57 (m, 2H), 7.55-7.44 (m, 4H), 7.44-7.19 (m, 11H), 7.02 (d, *J* = 9.6 Hz, 1H), 4.87 (d, *J* = 9.6 Hz, 1H), 3.86 (q, *J* = 13.3 Hz, 2H), 2.03 (s, 3H), 1.88 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 152.4, 147.5,146.4, 140.2, 138.2, 130.7, 128.0, 127.1, 126.9, 126.7, 126.4, 126.0, 125.7, 125.4, 124.8, 124.6, 114.2, 58.1, 49.7, 9.3; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –58.1; **HRMS-ESI:** *m/z* calcd. for C24H22F3N3 $[M+Na]^+$: 432.1658, found 432.1670.



(E)-N-benzyl-2-methyl-4-((E)-(2-(trifluoromethyl)phenyl)diazenyl)pent-3-en-2-amine (3.97). 1-(1-benzyl-3,3-dimethylaziridin-2-yl)ethanone (0.270 g, 1.33 mmol) was treated following general procedure **L.** Flash chromatography (10:90 EtOAc-Hexanes) gave an orange oil (0.059 g, 12%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.80 (d, *J* = 7.7 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.39 (d, *J* = 7.2 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.30 – 7.25 (m, 1H), 6.96 (s, 1H), 3.80 (s, 2H), 2.27 (s, 3H), 1.54 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 153.2, 152.6, 147.7, 139.2, 130.7, 127.7, 126.7, 126.5, 126.3, 125.2, 124.7, 124.6, 114.3, 52.8, 46.3, 27.4, 9.4; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –58.0; **HRMS-ESI:** *m/z* calcd. for $C_{20}H_{22}F_3N_3$ $[M+H]^+$: 253.1335, found 253.1339.

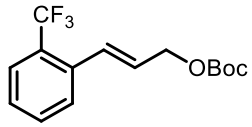
1.7.6 Synthesis of carbono azoalkenes



(*E*)-dimethyl 2-(3-(phenyldiazenyl)cyclohex-2-enyl)malonate (3.102). Cyclopropane (0.22 mmol) and phenylhydrazine (0.23 mmol) were dissolved in THF (1.0 mL). The reaction mixture was stirred at room temperature for 2 h. Then Et_3N was added with MgI_2. Solution turns an orange color, after 2 h solvent was then removed by rotavap. Flash chromatography (hexane:EtOAc = 1:10) was performed to isolate the product **3.41** as an orange solid (0.516 g, 71%). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.74-7.72 (m, 2 H), 7.46-7.37 (m, 3 H), 6.83 (s, 1 H), 3.78 (d, *J* = 4.12 Hz, 6 H), 3.48 (d, *J* = 9.62 Hz, 1 H), 3.39-3.32 (m, 1 H), 2.57-2.52 (m, 1 H), 2.33-2.23 (m, 1 H), 1.99-1.87 (m, 2 H), 1.74-1.64 (m, 1 H), 1.52-1.40 (m, 1 H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 168.7, 168.6, 150.5, 137.4, 135.0 129.3, 129.2, 124.7, 122.2, 122.1, 54.9, 52.1 52.0, 38.5. 28.3, 25.4, 19.3. **HRMS-ESI**: *m/z* calcd. for $C_{17}H_{20}N_2O_4$ $[M + H]^+$: 316.14

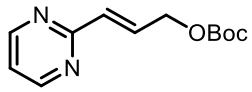
1.7.7 Synthesis of fused tetrahydrofuran- or pyrrolidine-tetrahydropyridazine

Synthesis of allylic *t*-butyl carbonates



(*E*)-*tert*-butyl (3-(2-trifluoromethyl)phenyl)allyl) carbonate (S8). To a –78 °C solution of (*E*)-ethyl 3-(2-trifluoromethyl)phenyl)acrylate[7] (1.20 g, 4.91 mmol) in PhMe (50 mL) was added DIBAL (14.7 mL, 14.73 mmol, 1.0 M soln. in PhMe). The reaction was stirred at –78 °C for 30 min, warmed to rt, and stirred 2 additional hours. The reaction was cooled to 0 °C (ice-bath), diluted with Et_2O (50 mL) and added sequentially H_2O (0.5 mL), 15% aq. NaOH (0.5 mL), and H_2O (1.4 mL). The reaction was warmed to rt, $MgSO_4$ was added and stirred 20 min. The reaction was filtered and concentrated *in vacuo*. The crude allylic alcohol (0.750 g, 3.70 mmol), used without purification, was dissolved in THF (30 mL) and cooled to 0 °C (ice-bath). *n*-BuLi (1.42 mL, 3.55 mmol, 2.5 M soln. in hexane) was added dropwise, and the reaction was stirred for 20 min. A solution of Boc_2O (0.842 g, 3.85 mmol) in THF (5 mL) was added to the reaction (2 mL THF wash). The reaction was allowed to warm to rt and stirred 12 h. The reaction was quenched by the addition of sat. NH_4Cl (5 mL) and partitioned between H_2O and EtOAc. The aqueous phase was extracted with EtOAc (3 X 15 mL), and the combined organic phases were washed with sat. NaCl (20 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Flash chromatography (8:92 EtOAc-Hexanes) gave a colorless oil (0.942 g, 63% over 2 steps). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.61 (t, *J* = 7.45 Hz, 2 H), 7.49 (t, *J* = 7.45 Hz, 1 H), 7.35 (t, *J* = 7.45 Hz, 1 H), 7.02 (dd, *J* = 15.75 Hz, 1.72 Hz, 1 H), 6.26 (dt, *J* = 15.46 Hz, 6.30 Hz, 1 H), 4.74 (dd, *J* = 6.30 Hz, 1.72 Hz, 2 H), 1.50 (s, 9 H); **^{13}C NMR**

(125 MHz, $CDCl_3$): δ 153.3, 135.3, 131.9, 129.9, 127.8, 127.7,127.5 (q, J_{C-F} = 29 Hz), 127.4, 125.8 (q, J_{C-F} = 5 Hz), 124.2 (q, J_{C-F} = 273 Hz), 82.5, 67.1, 27.8; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –59.3 (s, 3 F); **HRMS-ESI**: *m/z* calcd. for $C_{15}H_{17}F_3O_3$ $[M + Na]^+$: 325.1028, found 325.1022.



(*E*)-*tert*-butyl (3-pyrimidin-2-yl)allyl) carbonate (S9). To a –78 °C solution of (*E*)-ethyl 3-(pyrimidin-2-yl)acrylate[167] (0.604 g, 3.39 mmol) in THF (25 mL) was added DIBAL (7.8 mL, 7.80 mmol, 1.0 M soln. in PhMe). The reaction was stirred at –78 °C for 30 min, warmed to rt, and stirred 2 additional hours. The reaction was quenched by the addition of sat. aq. sodium potassium tartrate (15 mL) and stirred 1 h. 2 M NaOH (7.8 mL) was added, and the reaction was stirred 15 min. The mixture was poured into a separatory funnel and partitioned between H_2O and THF. The aqueous phase was extracted with Et_2O (3 X 15 mL), and the combined organic phases were washed with sat. NaCl (20 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude allylic alcohol (0.347 g, 2.55 mmol), used without purification, was dissolved in CH_2Cl_2 (6 mL). Bu_4NHSO_4 (0.026 g, 0.076 mmol) was added followed by 30% NaOH (1.2 mL, 8.92 mmol) and the reaction was stirred 15 min. A solution of Boc_2O (0.667 g, 3.06 mmol) in CH_2Cl_2 (1 mL) was added to the reaction (1 mL CH_2Cl_2 wash). The reaction was allowed to warm to rt and stirred 12 h. The reaction was diluted with CH_2Cl_2 (10 mL) and partitioned between H_2O and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 (3 X 10 mL), and the combined organic phases were washed with sat. NaCl (20 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Flash chromatography (40:60 EtOAc-Hexanes) gave a colorless oil (0.449 g, 56% over 2 steps). (**^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.67 (d,

J = 4.87 Hz, 2 H), 7.16 (dt, *J* = 15.75 Hz, 5.44 Hz, 1 H), 7.10 (t, *J* = 4.87 Hz, 1 H), 6.79 (d, *J* = 15.75 Hz, 1 H), 4.82 (d, *J* = 5.15 Hz, 2 H), 1.49 (s, 9 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 163.9, 157.1, 153.3, 133.7, 131.6, 119.1, 82.5, 66.1, 27.8; **HRMS-APPI**: *m/z* calcd. for $C_{12}H_{16}N_2O_3$ $[M+H]^+$: 237.1234, found 237.1239.

*General procedure **N***: Cascading Tsuji-Trost [4+2] cycloaddition

To a flame dried 1 dram vial with stir bar was added $Pd(OAc)_2$ (2.5 mol %) and BINAP (5.0 mol %), and the vial was placed under an Ar atmosphere. PhMe (1.5 mL) was added, and the solution was stirred at rt for 20 min. Diallyl carbonate (1.7 equiv) or aryl substituted allylic carbonate (1.7 equiv) in PhMe (0.5 mL) was then added to the vial, followed by addition of the HAP or AAP (1.0 equiv). For solid HAPs, the addition is done in one portion. For oil HAPs, the addition is executed as a solution in PhMe (0.5 mL). The vial is then capped, placed in a pre-heated oil-bath (100 °C), and stirred for 2 h. After 2 h, the reaction is cooled to rt, diluted with EtOAc (10 mL), and washed with sat. NaCl (5 mL). The organic phase is then dried over $MgSO_4$, filtered, and concentrated i*n vacuo*. Flash chromatography over silica gel provided the desired fused furan- or pyrrolidine-tetrahydropyridazine derivatives.

*General procedure **O***: Cascading Tsuji-Trost [4+2] cycloaddition

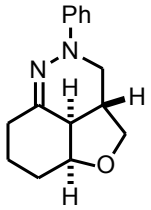
To a flame dried 1 dram vial with stir bar was added $Pd(OAc)_2$ (2.5 mol %) and BINAP (5.0 mol %), and the vial was placed under an Ar atmosphere. PhMe (1.5 mL) was added, and the solution was stirred at rt for 20 min. LiBr (1 equiv) was added followed by diaryl substituted allylic carbonate (1.7 equiv) in PhMe (0.5 mL) was then added to the vial, followed by addition of the HAP or AAP (1.0 equiv), the addition is

executed as a solution in PhMe (0.5 mL). The vial is then capped, placed in a pre-heated oil-bath (100 °C), and stirred for 2 h. After 2 h, the reaction is cooled to rt, diluted with EtOAc (10 mL), and washed with sat. NaCl (5 mL). The organic phase is then dried over $MgSO_4$, filtered, and concentrated i*n vacuo*. Flash chromatography over silica gel provided the desired fused furan- or pyrrolidine-tetrahydropyridazine derivatives.

General procedure ***P***: Cascading Tsuji-Trost [4+2] cycloaddition

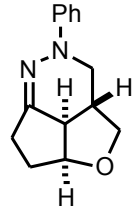
To a flame dried 1 dram vial with stir bar was added $Pd(allyl)_2$ (2.5 mol %) and BINAP (5.0 mol %), and the vial was placed under an Ar atmosphere. THF (1.5 mL) was added, and the solution was stirred at rt for 20 min. allyl carbonate (1.01 equiv) or aryl substituted allylic carbonate (1.7 equiv) in PhMe (0.5 mL) was then added to the vial, followed by addition of the HAP or AAP (1.0 equiv), the addition is executed as a solution in THF (0.5 mL). The vial is then capped, placed in a pre-heated oil-bath (65 °C), and stirred for 8 h. The reaction is cooled to rt, diluted with EtOAc (10 mL), and washed with sat. NaCl (5 mL). The organic phase is then dried over $MgSO_4$, filtered, and concentrated i*n vacuo*. Flash chromatography over silica gel provided the desired fused furan- or pyrrolidine-tetrahydropyridazine derivatives.

Furan-tetrahydropyridazine derivatives

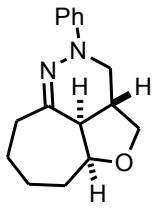


2-phenyl-3,3a,3a^1,4,5a,6,7,8-octahydro-2*H*-furo[4,3,2-*de*]cinnoline (4.10). HAP **(3.68)** (0.035 g, 0.173 mmol) was treated following general procedure **N.** Flash chromatography (25:75 EtOAc-Hexanes) gave a tan solid (0.036 g, 86%). Scaled up

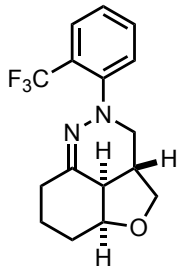
reaction (0.700 g, 3.46 mmol) was treated following general procedure **E**, gave (0.658 g, 78%). mp: 130-131 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.29-7.26 (m, 2 H), 7.16-7.15 (m, 2 H), 6.84 (t, *J* = 7.45 Hz, 1 H), 4.26 (ddd, *J* = 10.31 Hz, 9.16 Hz, 5.43 Hz, 1 H), 4.21 (dd, *J* = 7.45 Hz, 6.30 Hz, 1 H), 3.69-3.59 (m, 2 H), 3.49 (dd, *J* = 10.88 Hz, 7.45 Hz, 1 H), 2.64-2.59 (m, 1 H), 2.52-2.44 (m, 2 H), 2.12-2.04 (m, 2 H), 1.91-1.85 (m, 1 H), 1.52-1.46 (m, 1 H), 1.14 (qd, *J* = 10.88 Hz, 2.86 Hz, 1 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 151.8, 148.2, 129.0, 119.1, 112.6, 75.2, 70.7, 49.2, 44.0, 39.4, 30.1, 27.3, 19.1; **HRMS-ESI:** *m/z* calcd. for $C_{15}H_{18}N_2O$ $[M+H]^+$: 243.1492, found 243.1492.



6-phenyl-1,2,2a,2a^1,4,4a,5,6-octahydro-3-oxa-6,7-diazacyclopenta[*cd*]indene (4.20a). HAP **(3.74)** (0.040 g, 0.212 mmol) was treated following general procedure **N.** Flash chromatography (20:80 EtOAc-Hexanes) gave a tan solid (0.034 g, 71%). mp 107-109 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.30-7.25 (m, 2 H), 7.20-7.18 (m, 2 H), 6.88 (t, *J* = 7.33 Hz, 1 H), 4.57 (td, *J* = 5.50 Hz, 1.37 Hz, 1 H), 3.91 (t, *J* = 8.24 Hz, 1 H), 3.70-3.65 (m, 1 H), 3.59 (dd, *J* = 8.70 Hz, 6.41 Hz, 1 H), 3.18-3.10 (m, 2 H), 2.76-2.75 (m, 1 H), 2.71-2.66 (m, 2 H), 2.21-2.12 (m, 1 H), 1.98-1.90 (m, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 155.5, 148.6, 129.0, 120.0, 114.3, 83.4, 71.1, 43.9, 42.6, 36.6, 31.0, 28.7; **HRMS-ESI:** *m/z* calcd. for $C_{14}H_{16}N_2O$ $[M+H]^+$: 229.1335, found 229.1333.

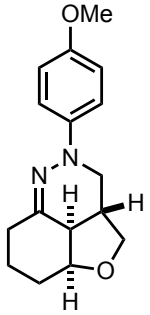


4-phenyl-2,2a,2a^1,3,4,6,7,8,9,9a-decahydro-1-oxa-4,5-diazabenzo[*cd*]azulene (4.21a). HAP **(3.76)** (0.040 g, 0.212 mmol) was treated following general procedure **N.** Flash chromatography (20:80 EtOAc-Hexanes) gave a tan solid (0.034 g, 71%, 9:1 dr). Major diastereomer: mp: 129-130 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.29-7.25 (m, 2 H), 7.20-7.18 (m, 2 H), 6.83 (t, *J* = 7.33 Hz, 1 H), 4.35-4.30 (m, 1 H), 4.24-4.20 (m, 1 H), 3.97-3.93 (m, 1 H), 3.50-3.40 (m, 2 H), 2.67 (dd, *J* = 13.74 Hz, 5.95 Hz, 1 H), 2.58-2.40 (m, 2 H), 2.20 (t, *J* = 11.91 Hz, 1 H), 1.96-1.82 (m, 3 H), 1.44-1.31 (m, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 147.5, 144.5, 129.0, 119.1, 112.6, 79.9, 70.3, 48.1, 45.7, 38.0, 35.5, 35.2, 29.8, 25.9; **HRMS-ESI:** *m/z* calcd. for $C_{16}H_{20}N_2O$ $[M+H]^+$: 257.1648, found 257.1646.

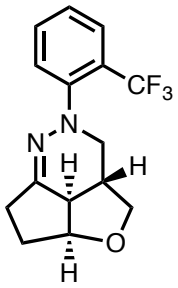


2-(2-(trifluoromethyl)phenyl)-3,3a,3a1,4,5a,6,7,8-octahydro-2*H*-furo[4,3,2-*de*]cinnoline (4.13). HAP **(3.70)** (0.045 g, 0.160 mmol) was treated following general procedure **N.** Flash chromatography (20:80 EtOAc-Hexanes) gave a yellow foam (0.040 g, 78%). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.62 (d, *J* = 7.79, 1 H), 7.55 (t, *J* = 7.79, 1 H) 7.47 (d, *J* = 7.79 Hz, 1 H), 7.24 (t, *J* = 7.79 Hz, 1 H), 4.32-4.25 (m, 1 H), 4.13 (dd, *J* = 7.79 Hz, 5.95 Hz, 1 H), 3.66 (dd, *J* = 11.68 Hz, 10.07 Hz, 1 H), 3.48 (dd, *J* = 10.99 Hz, 7.79 Hz, 1 H), 3.31 (t, *J* = 8.24 Hz, 1 H), 2.60-2.53 (m, 2 H), 2.47-2.37 (m, 1 H), 2.10-1.84 (m, 3 H), 1.55-1.45 (m, 1 H), 1.16 (dq, *J* = 2.75 Hz, 13.05 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 154.2, 150.2, 133.2, 126.9 (q, J_{C-F} = 6 Hz), 125.4 125.1, 75.0, 70.8, 54.5,

43.7, 39.7, 30.1, 27.1, 19.2; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –59.5 (s, 3 F); **HRMS-ESI:** *m/z* calcd. for C16H17F3N2O $[M+H]^+$: 311.1366, found 311.1368.

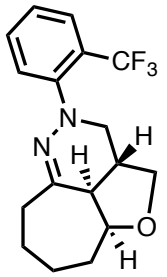


2-(4-methoxyphenyl)-3,3a,3a1,4,5a,6,7,8-octahydro-2H-furo[4,3,2-de]cinnoline (4.18). HAP **(3.73)** (0.060 g, 0.258 mmol) was treated following general procedure **N.** Flash chromatography (1:2:7 EtOAc-Hexanes- CH_2Cl_2) gave an off-white solid (0.050 g, 71%) **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.08 (d, *J* = 9.1 Hz, 2H), 6.84 (d, *J* = 9.1 Hz, 2H), 4.28-4.19 (m, 1H), 4.17 (dd, *J* = 7.5, 6.2 Hz, 1H), 3.75 (s, 3H), 3.56 (d, *J* = 9.7 Hz, 2H), 3.45 (dd, *J* = 10.8, 7.8 Hz, 1H), 2.58 (dd, *J* = 18.5, 5.9 Hz, 1H), 2.50-2.36 (m, 2H), 2.11-1.94 (m, 2H), 1.85 (ddd, *J* = 9.5, 7.2, 4.5 Hz, 1H), 1.56-1.38 (m, 1H), 1.12 (qd, *J* = 13.1, 2.7 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 153.1, 151.1, 143.0, 114.5, 113.9, 75.2, 70.8, 55.7, 49.5, 43.9, 39.4, 30.1, 27.2, 19.2.; **HRMS-CI:** *m/z* calcd. for $C_{16}H_{20}N_2O_2$ $[M+Na]^+$: 295.1417, found 295.1427.

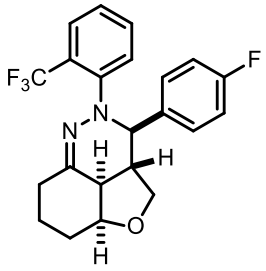


6-(2-(trifluoromethyl)phenyl)-1,2,2a,2a1,4,4a,5,6-octahydro-3-oxa-6,7-diazacyclopenta[*cd*]indene (4.20). HAP **(3.75)** (0.057 g, 0.222 mmol) was treated

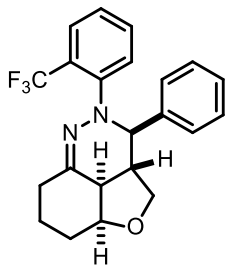
following general procedure **N.** Flash chromatography (20:80 EtOAc-Hexanes) gave a yellow foam (0.051 g, 78%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.61 (dd, *J* = 3.44 Hz, 8.02 Hz, 2 H), 7.56 (t, *J* = 7.45 Hz, 1 H), 7.26 (t, *J* = 8.02 Hz, 1 H), 4.44 (dd, *J* = 4.58 Hz, 6.30 Hz, 1 H), 3.79-3.76 (m, 1 H), 3.42 (dd, *J* = 8.53 Hz, 10.91 Hz, 1 H), 3.32-3.24 (m, 1 H), 2.76-2.67 (m, 1 H), 2.27-2.20 (m, 1 H), 2.01 (p, *J* = 8.02 Hz, 1 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 166.6, 150.6, 133.0, 126.7 (q, $J_{C\text{-}F}$ = 6 Hz), 125.8, 125.5, 125.4, 125.3, 83.8, 72.9, 58.2, 43.0, 40.6, 30.7, 27.8; **^{19}F NMR** (564 MHz, $CDCl_3$): δ –59.3 (s, 3 F); **HRMS-ESI:** *m/z* calcd. for C15H15F3N2O $[M+Na]^+$: 319.1029, found 319.1042.



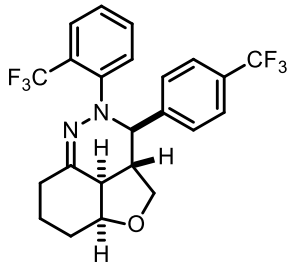
4-(2-(trifluoromethyl)phenyl)-2,2a,2a1,3,4,6,7,8,9,9a-decahydro-1-oxa-4,5-diazabenzo[*cd*]azulene (4.21). HAP **(3.77)** (0.058 g, 0.205 mmol) was treated following general procedure **N.** Flash chromatography (20:80 EtOAc-Hexanes) gave a yellow foam (0.045 g, 68%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.62 (d, *J* = 5.73 Hz, 1 H), 7.48 (t, *J* = 7.45 Hz, 1 H), 7.29 (d, *J* = 8.02 Hz, 1 H), 7.17 (t, *J* = 8.02 Hz, 1 H), 4.34-3.29 (m, 1 H), 4.13 (t, *J* = 7.45 Hz, 1 H), 3.70 (dd, *J* = 5.15 Hz, 10.60 Hz, 1 H), 3.62 (t, *J* = 10.88 Hz, 1 H), 3.41 (dd, *J* = 8.02 Hz, 10.31 Hz, 1 H), 2.67-2.48 (m, 3 H), 2.17 (t, *J* = 12.13 Hz, 1 H), 1.94-1.82 (m, 3 H), 1.44-1.26 (m, 3 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 148.6, 146.2, 132.6, 127.7 (q, $J_{C\text{-}F}$ = 5 Hz), 125.2, 124.1, 79.7, 69.9, 53.3, 45.8, 37.6, 35.5, 34.9, 29.8, 25.9; **^{19}F NMR** (564 MHz, $CDCl_3$): δ –59.1 (s, 3 F); **HRMS-ESI:** *m/z* calcd. for C17H19F3N2O $[M+H]^+$: 325.1522, found 325.1536.



4-(4-fluorophenyl)-2-(2-trifluoromethyl)phenyl-3,3a,3a[1],4,5a,6,7,8-octahydro-2*H*-furo[4,3,2-*de*]cinnoline (2.26). HAP **(3.70)** (0.094 g, 0.35 mmol) was treated following general procedure **N.** Flash chromatography (25:75 EtOAc-Hexanes) gave a yellow foam (0.118 g, 84%). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.45 (d, J = 7.45 Hz, 1 H), 7.22-7.15 (m, 2 H), 7.00-6.97 (3 H), 6.82 (t, J = 8.59 Hz, 2 H), 4.95 (d, J = 10.88 Hz, 1 H), 4.35 (ddd, J = 10.31 Hz, 9.16 Hz, 5.73 Hz, 1 H), 3.86 (dd, J = 7.73 Hz, 5.73 Hz, 1 H), 6.57 (dd, J = 10.88 Hz, 8.02 Hz, 1 H), 2.92 (t, J = 10.88 Hz, 1 H), 2.65-2.60 (m, 1 H), 2.55-2.47 (m, 1 H), 2.29 (qd, J = 11.74 Hz, 5.73 Hz, 1H), 2.13-2.11 (m, 1 H), 1.94-1.87 (m, 1 H), 1.58-1.49 (m, 1 H), 1.27-1.20 (m, 1 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 162.1 (d, $J_{C\text{-}F}$ = 247 Hz), 156.1, 145.9, 135.8 (d, $J_{C\text{-}F}$ = 2 Hz), 132.0, 129.5, 129.4 (d, $J_{C\text{-}F}$ = 9 Hz), 126.8 (q, $J_{C\text{-}F}$ = 6 Hz), 125.1 (q, $J_{C\text{-}F}$ = 28 Hz), 124.4, 124.3 (q, $J_{C\text{-}F}$ = 272 Hz), 115.3 (d, $J_{C\text{-}F}$ = 21 Hz), 75.1, 70.6, 67.2, 50.0, 43.7, 30.3, 27.2, 19.3; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –59.5 (s, 3 F), -114.0 (m, 1 F); **HRMS-ESI:** *m/z* calcd. for $C_{22}H_{20}F_4N_2O$ $[M+H]^+$: 405.1585, found 405.1589.

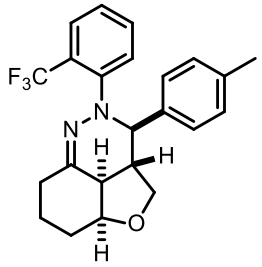


4-phenyl-2-(2-trifluoromethyl)phenyl)-3,3a,3a^1,4,5a,6,7,8-octahydro-2*H*-furo[4,3,2-*de*]cinnoline (4.22). HAP (3.70) (0.050 g, 0.185 mmol) was treated following general procedure **N.** Flash chromatography (20:80 EtOAc-Hexanes) gave a yellow foam (0.062 g, 72%). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.44 (d, *J* = 7.56, 1 H), 7.16 (d, *J* = 4.12, 2 H) 7.14-7.08 (m, 3 H), 7.00 (d, *J* = 6.87 Hz, 2 H), 6.97-6.94 (m, 1 H), 4.94 (d, *J* = 10.31 Hz, 1 H), 4.33 (td, *J* = 9.62 Hz, 5.50 Hz, 1 H), 3.86 (t, *J* = 6.19 Hz, 1 H), 3.57 (dd, *J* = 10.65 Hz, 7.90 Hz, 1 H), 2.93 (t, *J* = 11.00 Hz, 1 H), 2.65-2.61 (m, 1 H), 2.55-2.48 (m, 1 H), 2.33 (qd, *J* = 11.34 Hz, 5.50 Hz, 1 H), 2.12-2.10 (m, 1 H), 1.92-1.88 (m, 1 H), 1.57-1.49 (m, 1 H), 1.23 (dq, *J* = 10.31 Hz, 2.75 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 156.1, 146.0, 140.1, 131.9, 129.4, 128.4, 127.8, 127.7, 126.7 (q, $J_{C\text{-}F}$ = 5 Hz), 125.0 (q, $J_{C\text{-}F}$ = 30 Hz), 124.3 (q, $J_{C\text{-}F}$ = 272 Hz), 124.2, 75.2, 70.7, 68.0, 50.0, 43.7, 30.4, 27.2, 19.3; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –59.4 (s, 3 F); **HRMS-ESI:** *m/z* calcd. for $C_{22}H_{21}F_3N_2O$ $[M+H]^+$: 387.1679, found 387.16800.



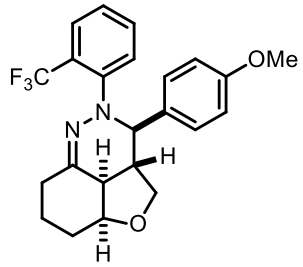
2-(2-trifluoromethyl)phenyl)-4-(4-(trifluoromethyl)phenyl)-3,3a,3a^1,4,5a,6,7,8-octahydro-2*H*-furo[4,3,2-*de*]cinnoline (4.23). HAP **(3.70)** (0.040 g, 0.148 mmol) was treated following general procedure **N.** Flash chromatography (20:80 EtOAc-Hexanes) gave a yellow foam (0.053 g, 79%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.46 (d, *J* = 7.33, 1 H), 7.40 (d, *J* = 8.24, 2 H) 7.21 (d, *J* = 4.21 Hz, 2 H), 7.14 (d, *J* = 7.79 Hz, 2 H), 7.01-6.97 (m, 1 H), 5.04 (d, *J* = 10.53 Hz, 1 H), 4.36 (td, *J* = 9.16 Hz, 5.95

Hz, 1 H), 3.85 (dd, J = 10.76 Hz, 5.95 Hz, 1 H), 3.59 (dd, J = 10.53 Hz, 7.79 Hz, 1 H), 2.94 (t, J = 10.99 Hz, 1 H), 2.68-2.62 (m, 1 H), 2.57-2.48 (m, 1 H), 2.27 (qd, J = 11.33 Hz, 5.95 Hz, 1 H), 2.16-2.11 (m, 1 H), 1.95-1.88 (m, 1 H), 1.60-1.48 (m, 1 H), 1.22 (dq, J = 10.53 Hz, 2.75 Hz, 1 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 156.6, 145.6, 144.5, 132.1, 129.9 (q, $J_{C\text{-}F}$ = 33 Hz), 128.9, 128.0, 127.0 (q, $J_{C\text{-}F}$ = 5 Hz), 125.4 (q, $J_{C\text{-}F}$ = 4 Hz), 124.6 (q, $J_{C\text{-}F}$ = 30 Hz), 124.4, 124.3 (q, $J_{C\text{-}F}$ = 273 Hz), 123.9 (q, $J_{C\text{-}F}$ = 272 Hz), 75.1, 70.4, 67.4, 50.3, 43.6, 30.3, 27.2, 19.2; **^{19}F NMR** (564 MHz, $CDCl_3$): δ –59.5 (s, 3 F), –62.5 (s, 3 F); **HRMS-ESI:** *m/z* calcd. for $C_{23}H_{20}F_6N_2O$ $[M+H]^+$: 455.1553, found 455.1557.

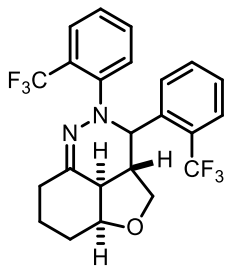


4-(*p*-tolyl)-2-(2-trifluoromethyl)phenyl-3,3a,3a^1,4,5a,6,7,8-octahydro-2*H*-furo[4,3,2-*de*]cinnoline (4.24). HAP **(3.70)** (0.045 g, 0.166 mmol) was treated following general procedure **N.** Flash chromatography (20:80 EtOAc-Hexanes) gave a yellow foam (0.053 g, 79%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.45 (d, J = 7.79 Hz, 1 H), 7.21-7.15 (m, 2 H), 6.98-6.88 (m, 5 H), 4.92 (d, J = 10.99 Hz, 1 H), 4.33 (td, J = 9.85 Hz, 5.26 Hz, 1 H), 3.86 (dd, J = 7.79 Hz, 5.95 Hz, 1 H), 3.56 (dd, J = 10.76 Hz, 8.01 Hz, 1 H, 2.92 (t, J = 10.99 Hz, 1 H), 2.64-2.60 (m, 1 H), 2.56-2.27 (m, 2 H), 2.21 (s, 3 H), 2.12-2.09 (m, 1 H), 1.94-1.87 (m, 1 H), 1.59-1.47 (m, 1 H), 1.28-1.88 (m, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 155.7, 146.1, 137.3, 137.1, 131.9, 129.4, 129.0, 127.6, 126.7 (q, $J_{C\text{-}F}$ = 5 Hz), 125.0 (q, $J_{C\text{-}F}$ = 29 Hz), 124.3 (q, $J_{C\text{-}F}$ = 272 Hz), 124.1, 75.2, 70.7, 67.7, 50.0, 43.7, 30.3,

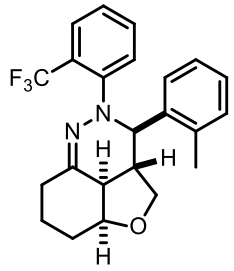
27.1, 21.1, 19.3; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –59.4 (s, 3 F); **HRMS-ESI:** *m/z* calcd. for $C_{23}H_{23}F_3N_2O$ $[M+H]^+$: 401.1835, found 401.1836.



4-(4-methoxyphenyl)-2-(2-trifluoromethyl)phenyl)-3,3a,3a^1,4,5a,6,7,8-octahydro-2*H*-furo[4,3,2-*de*]cinnoline (4.25). HAP **(3.70)** (0.045 g, 0.166 mmol) was treated following general procedure **N.** Flash chromatography (25:75 EtOAc-Hexanes) gave a yellow foam (0.044 g, 64%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.45 (d, *J* = 7.79 Hz, 1 H), 7.197.3 (m, 2 H), 6.97 (t, *J* = 7.33 Hz, 1 H), 6.92 (d, *J* = 8.70, 2 H), 6.65 (d, *J* = 8.70 Hz, 2 H), 4.90 (d, *J* = 10.99 Hz, 1 H), 4.33 (td, *J* = 9.62 Hz, 5.50 Hz, 1 H), 3.89-3.84 (m, 1 H), 3.69 (s, 3 H), 3.56 (dd, *J* = 10.53 Hz, 7.79 Hz, 1 H), 2.92 (t, *J* = 10.99 Hz, 1 H), 2.68-2.60 (m, 1 H), 2.55-2.46 (m, 1 H), 2.32 (qd, *J* = 11.45 Hz, 5.95 Hz, 1 H), 2.13-2.10 (m, 1 H), 1.94-1.88 (m, 1 H), 1.56-1.51 (m, 1 H), 1.29-1.25 (m, 1 H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 158.9, 155.6, 146.1, 132.0, 131.9, 129.7, 128.9, 126.6 (q, J_{C-F} = 5 Hz), 125.2 (q, J_{C-F} = 29 Hz), 124.3 (q, J_{C-F} = 270 Hz), 124.2, 113.6, 75.2, 70.8, 67.5, 55.2, 49.8, 43.7, 30.4, 27.2, 19.3; **^{19}F NMR** (376 MHz, $CDCl_3$): δ –59.5 (s, 3 F); **HRMS-ESI:** *m/z* calcd. for $C_{23}H_{23}F_3N_2O_2$ $[M+H]^+$: 417.1784, found 417.1772.

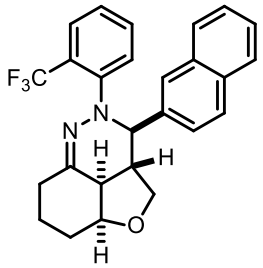


2,4-bis(2-trifluoromethyl)phenyl-3,3a,3a^1,4,5a,6,7,8-octahydro-2*H*-furo[4,3,2-*de*]cinnoline (4.27). HAP **(3.70)** (0.045 g, 0.166 mmol) was treated following general procedure **N.** Flash chromatography (20:80 EtOAc-Hexanes) gave a yellow foam (0.051 g, 68%). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.61-7.60 (m, 1 H), 7.55-7.52 (m, 2 H), 7.44 (d, J = 7.45 Hz, 1 H), 7.28 (t, J = 7.45 Hz, 1 H), 7.17-7.13 (m, 1 H), 7.08-7.03 (m, 2 H), 5.36 (d, J = 9.74 Hz, 1 H), 4.33 (ddd, J = 10.45 Hz, 9.16 Hz, 5.73 Hz, 1 H), 3.88 (dd, J = 8.02 Hz, 5.73 Hz, 1 H), 3.65 (dd, J = 10.60 Hz, 8.02 Hz, 1 H), 3.06 (t, J = 10.31 Hz, 1 H), 2.72-2.67 (m, 1 H), 2.58-2.50 (m, 1 H), 2.25 (qd, J = 12.31 Hz, 6.30 Hz, 1 H), 2.14-2.11 (m, 1 H), 1.94-1.88 (m, 1 H), 1.60-1.50 (m, 1 H), 1.25-1.79 (m, 1 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 159.7, 145.3, 141.3, 132.1, 131.8, 129.6, 128.5, 128.2 ($J_{C\text{-}F}$ = 30 Hz), 127.6, 127.2 (q, $J_{C\text{-}F}$ = 6 Hz), 126.7 ($J_{C\text{-}F}$ = 29 Hz), 125.5, ($J_{C\text{-}F}$ = 6 Hz), 125.0, 124.1 ($J_{C\text{-}F}$ = 271 Hz), 123.9 ($J_{C\text{-}F}$ = 274 Hz), 74.5, 70.1, 62.4, 53.2, 43.9, 30.4, 27.2, 19.3; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –57.9 (s, 3 F), –58.7 (s, 3 F); **HRMS-ESI:** *m/z* calcd. for $C_{23}H_{20}F_6N_2O$ $[M+H]^+$: 455.1553, found 455.1544.



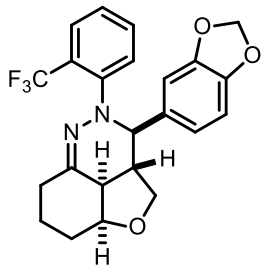
4-(*o*-tolyl-2-(2-trifluoromethyl)phenyl-3,3a,3a^1,4,5a,6,7,8-octahydro-2*H*-furo[4,3,2-*de*]cinnoline (4.28). HAP **(3.70)** (0.045 g, 0.166 mmol) was treated following general procedure **N.** Flash chromatography (20:80 EtOAc-Hexanes) gave a off-white foam (0.058 g, 86%). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.51 (d, J = 8.02 Hz, 1 H), 7.26-7.25 (m, 1 H), 7.19-7.12 (m, 2 H), 7.06-6.99 (m, 3 H), 6.91 (d, J = 7.45 Hz, 1 H), 5.27 (d,

J = 10.31 Hz, 1 H), 4.33 (ddd, *J* = 10.31 Hz, 9.16 Hz, 5.73 Hz, 1 H), 3.94 (dd, *J* = 7.45 Hz, 6.30 Hz, 1 H), 3.66 (dd, *J* = 10.88 Hz, 7.45 Hz, 1 H), 3.00 (t, *J* = 10.31 Hz, 1 H), 2.69-2.65 (m, 1 H), 2.57-2.50 (m, 1 H), 2.33-2.29 (m, 1 H), 2.12-2.10 (m, 1 H), 2.01 (s, 3 H), 1.93-1.88 (m, 1 H), 1.56-1.52 (m, 1 H), 1.26-1.21 (m, 1 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 158.2, 145.8, 139.1, 135.6, 131.8, 130.4, 128.5, 127.3, 127.1 (q, J_{C-F} = 5Hz), 126.4, 125.2 (J_{C-F} = 29 Hz), 124.4 (J_{C-F} = 271 Hz), 124.2, 74.8, 70.4, 62.7, 52.0, 43.9, 30.4, 27.1, 19.4, 19.0; **^{19}F NMR** (376 MHz, $CDCl_3$): δ –58.4 (s, 3 F); **HRMS-ESI:** *m/z* calcd. for $C_{23}H_{23}F_3N_2O$ $[M+H]^+$: 401.1835, found 401.1840.

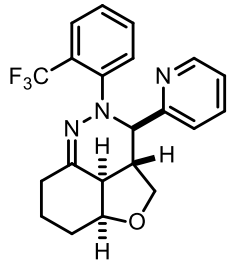


4-(napthalen-2-yl)-2-(2-trifluoromethyl)phenyl)-3,3a,3a^1,4,5a,6,7,8-octahydro-2*H*-furo[4,3,2-*de*]cinnoline (4.34). HAP **(3.70)** (0.045 g, 0.166 mmol) was treated following general procedure **N.** Flash chromatography (20:80 EtOAc-Hexanes) gave a yellow foam (0.059 g, 82%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.73-7.71 (m, 1 H), 7.68-7.65 (m, 2 H), 7.43-7.38 (m, 4 H), 7.28-7.22 (m, 2 H), 7.10 (t, *J* = 7.79 Hz, 1 H), 6.85 (t, *J* = 7.33 Hz, 1 H), 5.14 (d, *J* = 10.99 Hz, 1 H), 4.36 (td, *J* = 9.62 Hz, 5.50 Hz, 1 H), 3.83 (dd, *J* = 7.56 Hz, 5.59 Hz, 1 H), 3.61 (dd, *J* = 10.76 Hz, 7.79 Hz, 1 H), 2.98 (t, *J* = 10.99 Hz, 1 H), 2.70-2.64 (m, 1 H), 2.61-2.52 (m, 1 H), 2.42 (qd, *J* = 11.45 Hz, 5.95 Hz, 1 H), 2.14-2.11 (m, 1 H), 1.97-1.89 (m, 1 H), 1.62-1.50 (m, 1 H), 1.31-1.21 (m, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 156.0, 145.9, 137.7, 133.0, 132.8, 132.0, 129.2, 128.3, 127.8, 127.6, 127.1, 126.8 (q, J_{C-F} = 5 Hz), 126.2, 126.1, 125.0,124.9 (q, J_{C-F} = 29 Hz),

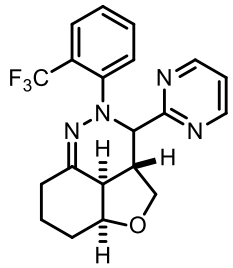
124.4 (q, $J_{C\text{-}F}$ = 272 Hz), 124.2, 75.2, 70.7, 68.1, 50.1, 43.7, 30.4, 27.2, 19.3; **^{19}F NMR** (376 MHz, $CDCl_3$): δ –59.4 (s, 3 F); **HRMS-ESI:** *m/z* calcd. for $C_{26}H_{23}F_3N_2O_2$ $[M+H]^+$: 437.1835, found 437.1834.



4-(benzo[*d*][1,3]dioxol-5-yl)-2-(2-trifluoromethyl)phenyl)-3,3a,3a^1,4,5a,6,7,8-octahydro-2*H*-furo[4,3,2-*de*]cinnoline (4.33). HAP **(3.70)** (0.045 g, 0.166 mmol) was treated following general procedure **N.** Flash chromatography (20:80 EtOAc-Hexanes) gave a yellow foam (0.050 g, 70%, isolated with a trace amount unidentifiable material). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.47 (d, *J* = 7.86 Hz, 1 H), 7.27-7.21 (m, 2 H), 7.01 (t, *J* = 6.87 Hz, 1 H), 6.56-6.52 (m, 2 H), 6.44 (dd, *J* = 8.01 Hz, 1.37 Hz, 1 H), 5.86 (dd, *J* = 8.70 Hz, 1.37 Hz, 2 H), 4.87 (d, *J* = 10.99 Hz, 1 H), 4.33 (td, *J* = 9.85 Hz, 5.95 Hz, 1 H), 3.87 (dd, *J* = 7.56 Hz, 5.95 Hz, 1 H), 3.55 (dd, *J* = 10.99 Hz, 7.79 Hz, 1 H), 2.90 (t, *J* = 10.53 Hz, 1 H), 2.65-2.59 (m, 1 H), 2.54-2.45 (m, 1 H), 2.27 (qd, *J* = 11.91 Hz, 5.95 Hz, 1 H), 2.12-2.09 (m, 1 H), 1.93-1.87 (m, 1 H), 1.58-1.49 (m, 1 H), 1.28-1.18 (m, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 156.0, 147.7, 147.0, 146.0, 134.0, 132.0, 129.4, 126.8 (q, $J_{C\text{-}F}$ = 5 Hz), 125.1 (q, $J_{C\text{-}F}$ = 29 Hz),124.4 (q, $J_{C\text{-}F}$ = 272 Hz), 124.3, 121.5, 107.9, 107.6, 101.1, 75.2, 70.7, 67.7, 50.0, 43.6, 30.3, 27.1, 19.3; **^{19}F NMR** (376 MHz, $CDCl_3$): δ –59.5 (s, 3 F); **HRMS-ESI:** *m/z* calcd. for $C_{23}H_{21}F_3N_2O_3$ $[M+H]^+$: 431.1577, found 431.1576.

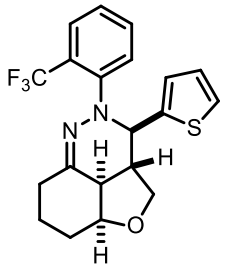


4-(pyridin-2-yl)-2-(2-trifluoromethyl)phenyl)-3,3a,3a^1,4,5a,6,7,8-octahydro-2*H*-furo[4,3,2-*de*]cinnoline (4.31). HAP **(3.70)** (0.045 g, 0.166 mmol) was treated following general procedure **N.** Flash chromatography (60:40 EtOAc-Hexanes) gave an off-white foam (0.048 g, 75%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.50 (d, J = 4.58 Hz, 1 H), 7.45 (d, J = 6.87 Hz, 1 H), 7.35 (td, J = 7.45 Hz, 1.72 Hz, 1 H), 7.15-7.09 (m, 2 H), 7.02-6.95 (m, 2 H), 6.83 (d, J = 8.02 Hz, 1 H), 5.04 (d, J = 10.88 Hz, 1 H), 4.34 (td, J = 9.74 Hz, 4.58 Hz, 1 H), 3.87 (dd, J = 7.73 Hz, 6.30 Hz, 1 H), 3.60 (dd, J = 10.88 Hz, 8.02 Hz, 1 H), 2.90 (t, J = 12.03 Hz, 1 H), 2.76-2.68 (m, 1 H), 2.64-2.53 (m, 2 H), 2.12-2.08 (m, 1 H), 1.94-1.87 (m, 1 H), 1.57-1.47 (m, 1 H), 1.33-1.24 (m, 1 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 159.0, 155.7, 149.5, 146.3, 136.3, 132.0, 129.9, 126.4 (q, $J_{C\text{-}F}$ = 5 Hz), 125.4 (q, $J_{C\text{-}F}$ = 29 Hz), 124.4, 124.3 (q, $J_{C\text{-}F}$ = 273 Hz), 123.5, 122.6, 75.2, 70.5, 68.8, 47.3, 43.4, 30.2, 27.1, 19.3; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –59.4 (s, 3 F); **HRMS-ESI:** *m/z* calcd. for $C_{21}H_{20}F_3N_3O$ $[M+H]^+$: 388.1631, found 388.1631.



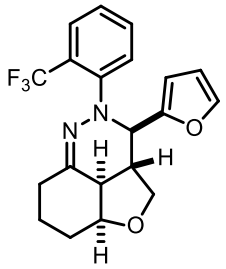
4-(pyrimidin-2-yl)-2-(2-trifluoromethyl)phenyl)-3,3a,3a^1,4,5a,6,7,8-octahydro-2*H*-furo[4,3,2-*de*]cinnoline (4.32). HAP **(3.70)** (0.081 g, 0.30 mmol) was

treated following general procedure **N.** Flash chromatography (80:20 EtOAc-Hexanes) gave an off-white foam (0.084 g, 72%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.53 (d, *J* = 4.58 Hz, 2 H), 7.48 (d, *J* = 8.24 Hz, 1 H), 7.17-7.14 (m, 2 H), 7.05-7.00 (m, 2 H), 5.18 (d, *J* = 10.53 Hz, 1 H), 4.36 (td, *J* = 10.07 Hz, 5.95 Hz, 1 H), 3.92 (dd, *J* = 7.79 Hz, 6.41 Hz, 1 H), 3.67 (dd, *J* = 10.99 Hz, 7.79 Hz, 1 H), 2.94 (t, *J* = 11.91 Hz, 1 H), 2.74-2.60 (m, 3 H), 2.16-2.10 (m, 1 H), 1.94-1.89 (m, 1 H), 1.59-1.48 (m, 1 H), 1.35-1.25 (m, 1 H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 168.3, 156.5, 156.3, 145.7, 131.3, 129.8, 125.9 (q, $J_{C\text{-}F}$ = 4 Hz), 125.8 (q, $J_{C\text{-}F}$ = 29 Hz), 124.4, 123.4 (q, $J_{C\text{-}F}$ = 273 Hz), 118.9, 74.2, 69.8, 69.3, 47.1, 42.7, 29.7, 26.5, 18.7; **^{19}F NMR** (376 MHz, $CDCl_3$): δ –59.7 (s, 3 F); **HRMS-ESI:** *m/z* calcd. for $C_{20}H_{19}F_3N_4O$ $[M+H]^+$: 389.1584, found 389.1587.

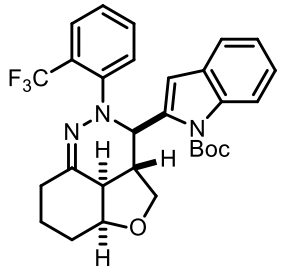


4-(thiophen-2-yl)-2-(2-trifluoromethyl)phenyl)-3,3a,3a^1,4,5a,6,7,8-octahydro-2*H*-furo[4,3,2-*de*]cinnoline (4.29). HAP **(3.70)** (0.045 g, 0.166 mmol) was treated following general procedure **N.** Flash chromatography (15:85 EtOAc-Hexanes) gave a yellow foam (0.047 g, 72%). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.51 (d, *J* = 8.02 Hz, 1 H), 7.21 (t, *J* = 8.02 Hz, 1 H), 7.12 (d, *J* = 8.02 Hz, 1 H), 7.09-7.06 (m, 2 H), 6.67 (dd, *J* = 5.15 Hz, 3.44 Hz, 1 H), 6.51 (d, *J* = 3.44 Hz, 1 H), 5.19 (d, *J* = 11.46 Hz, 1 H), 4.36 (td, *J* = 9.74 Hz, 5.73 Hz, 1 H), 4.02 (dd, *J* = 7.73 Hz, 6.30 Hz, 1 H), 3.59 (dd, *J* = 10.88 Hz, 8.02 Hz, 1 H), 2.92 (t, *J* = 10.31 Hz, 1 H), 2.64-2.60 (m, 1 H), 2.57-2.50 (m, 1 H), 2.33

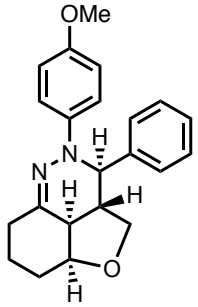
(qd, J = 11.74 Hz, 6.30 Hz, 1 H), 2.16-2.13 (m, 1 H), 1.94-1.88 (m, 1 H), 1.58-1.49 (m, 1 H), 1.33-1.24 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 157.3, 146.1, 143.0, 132.2, 130.5, 127.7, 126.5, 125.3 (q, $J_{C\text{-}F}$ = 29 Hz), 126.1 (q, $J_{C\text{-}F}$ = 5 Hz), 125.2, 124.1, 124.3 (q, $J_{C\text{-}F}$ = 273 Hz), 75.0, 70.8, 62.7, 50.5, 44.0, 30.4, 27.2, 19.3; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –59.7 (s, 3 F); **HRMS-ESI:** *m/z* calcd. for $C_{20}H_{19}F_3N_2OS$ $[M+H]^+$: 393.1243, found 393.1234.



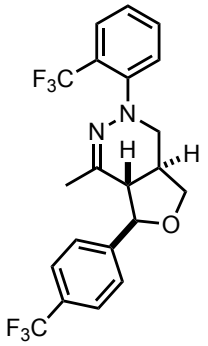
4-(furan-2-yl)-2-(2-trifluoromethyl)phenyl)-3,3a,3a^1,4,5a,6,7,8-octahydro-2*H*-furo[4,3,2-*de*]cinnoline (4.30). HAP **(3.70)** (0.045 g, 0.166 mmol) was treated following general procedure **N.** Flash chromatography (25:75 EtOAc-Hexanes) gave a yellow foam (0.038 g, 61%). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.52-7.50 (m, 1 H), 7.29-7.25 (m, 1 H), 7.19 (d, J = 1.72 Hz, 1 H), 7.13-7.10 (m, 2 H), 6.02 (dd, J = 3.15 Hz, 1.72 Hz, 1 H), 5.84 (d, J = 2.86 Hz, 1 H), 4.90 (d, J = 10.88 Hz, 1 H), 4.35 (td, J = 8.88 Hz, 6.30 Hz, 1 H), 3.98 (dd, J = 7.73 Hz, 6.30 Hz, 1 H), 3.54 (dd, J = 10.88 Hz, 8.02 Hz, 1 H), 2.85 (t, J = 10.88 Hz, 1 H), 2.64-2.58 (m, 1 H), 2.57-2.46 (m, 2 H), 2.16-2.11 (m, 1 H), 1.93-1.87 (m, 1 H), 1.57-1.48 (m, 1 H), 1.32-1.23 (m, 1 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 156.6, 151.6, 146.9, 142.2, 132.4, 130.4, 126.7 (q, $J_{C\text{-}F}$ = 29 Hz), 125.9 (q, $J_{C\text{-}F}$ = 4 Hz), 125.5, 124.2 (q, $J_{C\text{-}F}$ = 273 Hz), 110.1, 110.0, 75.0, 70.8, 61.1, 45.1, 43.6, 30.4, 27.2, 19.3; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –60.0 (s, 3 F); **HRMS-ESI:** *m/z* calcd. for $C_{20}H_{19}F_3N_2O_2$ $[M+H]^+$: 377.1471, found 377.1464.



***tert*-butyl 3-2-(2-trifluoromethyl)phenyl-3,3a,3a^1,4,5a,6,7,8-octahydro-2*H*-furo[4,3,2-*de*]cinnolin-4-yl)-1*H*-indole-1-carboxylate (4.35).** HAP **(3.70)** (0.045 g, 0.166 mmol) was treated following general procedure **N.** Flash chromatography (20:80 EtOAc-Hexanes) gave a off-white foam (0.68 g, 78%). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.01 (brs, 1 H), 7.47 (dd, *J* = 7.73 Hz, 1.72 Hz, 1 H), 7.43 (dd, *J* = 7.45 Hz, 1 H), 7.28-7.19 (m, 4 H), 7.02 (t, *J* = 7.45 Hz, 1 H), 6.96 (t, *J* = 7.45 Hz, 1 H), 5.14 (d, *J* = 10.88 Hz, 1 H), 4.37 (td, *J* = 9.74 Hz, 5.73 Hz, 1 H), 3.88 (dd, *J* = 8.02 Hz, 6.30 Hz, 1 H), 3.58 (dd, *J* = 10.31 Hz, 8.02 Hz, 1 H), 2.98 (t, *J* = 10.88 Hz, 1 H), 2.75-2.56 (m, 3 H), 2.15-2.12 (m, 1 H), 1.97-1.92 (m, 1 H), 1.64-1.53 (m, 10 H with an apparent s at 1.61 ppm), 1.29-1.22 (m, 1 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 157.2, 149.4, 146.2, 135.7, 132.2, 129.5, 128.3, 126.4 (q, $J_{C\text{-}F}$ = 5 Hz), 125.6 (q, $J_{C\text{-}F}$ = 30 Hz), 124.9, 124.5, 124.4 (q, $J_{C\text{-}F}$ = 274 Hz), 122.7, 120.0, 119.8, 115.4, 84.1, 75.0, 71.2, 60.4, 46.8, 43.8, 30.5, 28.2, 27.4, 19.4; **^{19}F NMR** (376 MHz, $CDCl_3$): δ –59.7 (s, 3 F); **HRMS-ESI:** *m/z* calcd. for $C_{29}H_{30}F_3N_3O_3$ $[M+H]^+$: 526.2312, found 526.2322.

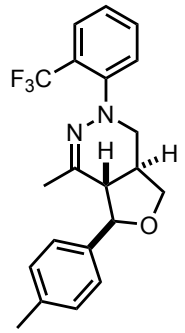


2-(4-methoxyphenyl)-3-phenyl-3,3a,3a1,4,5a,6,7,8-octahydro-2*H*-furo[4,3,2-*de*]cinnoline (4.18a). HAP **(3.73)** (0.046 g, 0.20 mmol) was treated following general procedure **N.** Flash chromatography (1:2:7 EtOAc-Hexanes- CH_2Cl_2) gave a yellow oil (0.049 g, 71%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.25-7.22 (m, 3 H), 7.16 (t, *J* = 7.21, 1 H), 7.05 (d, *J* = 6.87, 2 H), 6.88 (d, *J* = 9.16, 2 H), 6.66 (d, *J* = 9.36, 2 H), 5.04 (d, *J* = 10.88 Hz, 1 H), 4.33-4.26 (m, 1 H), 3.98 (t, *J* = 7.45 Hz, 1 H), 3.69-3.65 (m, 4 H), 2.77-2.70 (m, 2 H), 2.59-2.51 (m, 1 H), 2.13-2.06 (m, 2 H), 1.92-1.86 (m, 1 H), 1.53-1.44 (m, 1 H), 1.13 (dq, *J* = 2.29 Hz, 12.03 Hz, 1 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 157.2, 152.4, 142.5, 140.5, 129.0, 127.2, 125.7, 115.3, 114.0, 75.2, 70.6, 64.8, 55.5, 52.6, 43.4, 30.3, 27.2, 19.2; **HRMS-ESI:** *m/z* calcd. for C22H24N2O2 $[M+H]^+$: 349.1911, found 349.1921.

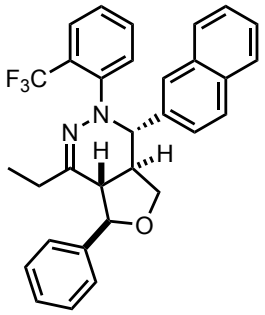


4-methyl-2-(2-(trifluoromethyl)phenyl)-5-(4-(trifluoromethyl)phenyl)-1,2,4a,5,7,7a-hexahydrofuro[3,4-*d*]pyridazine (4.57). HAP **(3.90)** (0.084 g, 0.222 mmol) was treated following general procedure **N.** Flash chromatography (20:80 EtOAc-Hexanes) gave a yellow foam (0.029 g, 31%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.64 (t, *J* = 9.16 Hz, 3 H), 7.56 (d, *J* = 8.24 Hz, 2 H), 7.52 (t, *J* = 7.33 Hz, 1 H), 7.34 (d, *J* = 7.79 Hz, 2 H), 7.21 (t, *J* = 7.79 Hz, 1 H), 4.88 (d, *J* = 9.62 Hz, 1 H), 4.31 (t, *J* = 7.33 Hz, 1 H), 3.83 (dd, *J* = 7.79 Hz, 10.07 Hz, 1 H), 3.73-3.61 (m, 2 H), 2.73-2.56 (m, 2 H), 1.80 (s, 3

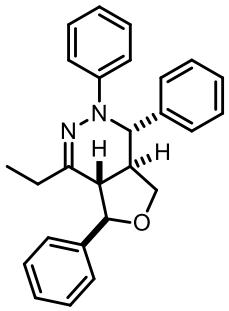
H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 148.8, 145.0, 142.5, 132.9, 130.7 (q, *J* = 33 Hz), 128.1, 127.8, 127.5 (q, *J* = 5 Hz), 126.0, 125.7 (q, *J* = 3 Hz), 125.1, 124.8, 124.3 (q, *J* = 31 Hz), 123.0, 81.0, 70.8, 53.7, 50.8, 39.5, 21.3; **^{19}F NMR** (564 MHz, $CDCl_3$): δ –59.3 (s, 3 F), –62.4 (s, 3 F); **HRMS-ESI:** *m/z* calcd. for C21H18F6N2O $[M+H]^+$: 429.1396, found 429.1391.



(4a*S*,5*R*,7a*S*)-4-methyl-5-(*p*-tolyl)-2-(2-(trifluoromethyl)phenyl)-1,2,4a,5,7,7a-hexahydrofuro[3,4-*d*]pyridazine (4.58). HAP **(3.89)** (0.074 g, 0.222 mmol) was treated following general procedure **N.** Flash chromatography (20:80 EtOAc-Hexanes) gave a yellow foam (0.055 g, 67%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.02 Hz, 1 H), 7.51 (t, *J* = 7.45 Hz, 1 H), 7.34 (d, *J* = 8.02 Hz, 1 H), 7.32 (d, *J* = 8.02 Hz, 2 H), 7.22-7.18 (m, 3 H), 4.80 (d, *J* = 9.74 Hz, 1 H), 4.26 (t, *J* = 7.45 Hz, 1 H), 3.79 (dd, *J* = 8.02 Hz, 10.02 Hz, 1 H), 3.69 (t, *J* = 10.88 Hz, 1 H), 3.63-3.60 (m, 1 H), 2.65-2.58 (m, 2 H), 2.36 (s, 3 H) 1.78 (s, 3 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ149.0, 143.7, 138.3, 137.6, 132.8, 129.4, 127.6, 127.5, 127.5, 127.4, 125.9, 125.2, 124.6, 124.2, 124.0, 123.0, 81.6, 70.5, 53.9, 50.1, 39.3, 21.3, 21.2; **^{19}F NMR** (564 MHz, $CDCl_3$): δ –59.2 (s, 3 F); **HRMS-ESI:** *m/z* calcd. for C21H21F3N2O $[M+H]^+$: 375.1679, found 375.1676.

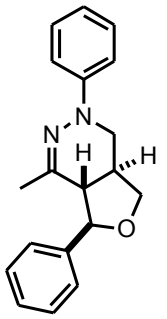


(4aS,5R,7R,7aS)-4-ethyl-7-(naphthalen-2-yl)-5-phenyl-2-(2-(trifluoromethyl)phenyl)-1,2,4a,5,7,7a-hexahydrofuro[3,4-d]pyridazine (4.56). HAP **(3.87)** (0.042 g, 0.125 mmol) was treated following general procedure **N.** Flash chromatography (10:90 EtOAc-Hexanes) gave a pale yellow oil (0.0382 g, 29%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.79-7.68 (m, 1H), 7.65 (s, 1H), 7.55-7.32 (m, 3H), 7.10 (t, *J* = 7.3 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 6.90 (t, *J* = 7.5 Hz, 1H), 5.22 (d, *J* = 10.4 Hz, 1H), 4.89 (d, *J* = 9.9 Hz, 1H), 3.88 (dd, *J* = 10.5, 7.9 Hz, 1H), 3.79 (t, *J* = 7.4 Hz, 1H), 3.16-2.94 (m, 2H), 2.19 (dq, *J* = 15.0, 7.4 Hz, 1H), 2.08-1.94 (m, 1H), 0.88 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 150.8; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –58.0; **HRMS-ESI:** *m/z* calcd. for $C_{31}H_{27}F_3N_2O$ $[M+Na]^+$: 523.1968, found 523.1982.

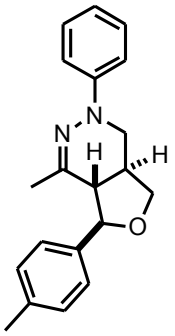


4-ethyl-2,5,7-triphenyl-1,2,4a,5,7,7a-hexahydrofuro[3,4-*d*]pyridazine (4.55). HAP **(3.87)** (0.047 g, 0.176 mmol) was treated following general procedure **N.** Flash chromatography (10:90 EtOAc-Hexanes) gave a colorless foam (0.046 g, 68%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.45-7.25 (m, 7 H), 7.21-7.16 (m, 3 H), 7.10-7.06 (m, 2 H), 7.03-

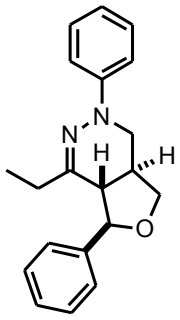
7.01 (m, 2 H), 6.69 (t, *J* = 7.33 Hz, 1 H), 5.05 (d, *J* = 10.53 Hz, 1 H), 4.89 (d, *J* = 10.07 Hz, 1 H), 4.09-4.01 (m, 2 H), 2.83 (dd, *J* = 11.68 Hz, 10.53 Hz, 1 H), 2.67-2.57 (m, 1 H), 2.44-2.35 (m, 1 H), 2.21-2.12 (m, 1 H), 1.06 (t, *J* = 7.33 Hz, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 150.7, 146.2, 142.2, 140.5, 129.1, 128.8, 128.6, 128.4, 127.4, 125.5, 118.8, 115.1, 81.7, 71.4, 64.7, 51.6, 49.8, 27.5, 10.2; **HRMS-ESI:** *m/z* calcd. for $C_{26}H_{26}N_2O$ $[M+H]^+$: 383.2118, found 383.2119.



4-methyl-2,5-diphenyl-1,2,4a,5,7,7a-hexahydrofuro[3,4-*d*]pyridazine (4.52). HAP **(3.86)** (0.029 g, 0.115 mmol) was treated following general procedure **N.** Flash chromatography (10:90 EtOAc-Hexanes) gave a yellow foam (0.008 g, 23%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.44-7.31 (m, 5 H), 7.30-7.25 (m, 2 H), 7.19-7.19 (m, 2 H), 6.84 (t, *J* = 7.33 Hz, 1 H), 4.85 (d, *J* = 10.07 Hz, 1 H), 4.37 (t, *J* = 7.33 Hz, 1 H), 3.94-3.86 (m, 2 H), 3.60 (t, *J* = 10.99 Hz, 1 H), 2.70-2.57 (m, 2 H), 1.87 (s, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 147.6, 141.3, 140.6, 129.1, 128.7, 128.6, 127.4, 119.2, 112.7, 81.9, 71.1, 50.4, 48.5, 39.4, 21.3; **HRMS-ESI:** *m/z* calcd. for $C_{19}H_{20}N_2O$ $[M+H]^+$: 293.1648, found 293.1652.

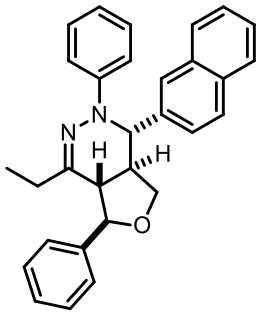


4-methyl-2-phenyl-5-(*p*-tolyl)-1,2,4a,5,7,7a-hexahydrofuro[3,4-*d*]pyridazine (4.53). HAP **(3.88)** (0.031 g, 0.116 mmol) was treated following general procedure **N.** Flash chromatography (10:90 EtOAc-Hexanes) gave a colorless solid (0.018 g, 51%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.32-7.25 (m, 4 H), 7.19-7.17 (m, 4 H), 6.84 (t, *J* = 7.73 Hz, 1 H), 4.81 (d, *J* = 9.62 Hz, 1 H), 4.35 (t, *J* = 6.87 Hz, 1 H), 3.98-3.84 (m, 2 H), 3.59 (t, *J* = 10.53 Hz, 1 H), 2.68-2.55 (m, 2 H), 2.36 (s, 3 H), 1.86 (s, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 147.6, 141.5, 138.3, 137.5, 129.4, 129.0, 127.3, 119.2, 112.6, 81.7, 70.9, 50.1, 48.5, 39.4, 21.3; **HRMS-ESI:** *m/z* calcd. for $C_{20}H_{22}N_2O$ $[M+H]^+$: 307.1805, found 307.1809.



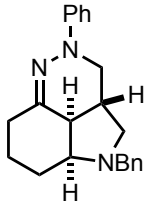
4-ethyl-2,5-diphenyl-1,2,4a,5,7,7a-hexahydrofuro[3,4-*d*]pyridazine (4.54). HAP **(3.87)** (0.030 g, 0.113 mmol) was treated following general procedure **N.** Flash chromatography (10:90 EtOAc-Hexanes) gave a yellow foam (0.018 g, 53%). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.44-7.42 (m, 2 H), 7.40-7.37 (m, 2 H), 7.35-7.32 (m, 1 H), 7.29-7.26 (m, 2 H), 7.21-7.19 (m, 2 H), 6.84 (t, *J* = 7.45 Hz, 1 H), 4.85 (d, *J* = 9.74 Hz, 1 H),

4.37-4.34 (m, 1 H), 3.96-3.93 (m, 1 H), 3.85 (dd, *J* = 9.74 Hz, 8.02 Hz, 1 H), 3.59 (t, *J* = 11.46 Hz, 1 H), 2.68-2.60 (m, 2 H), 2.29-2.21 (m, 1 H), 2.67-1.99 (m, 1 H), 0.94 (t, *J* = 7.45 Hz, 3 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 147.8, 144.7, 140.7, 129.0, 128.7, 128.6, 127.5, 119.1, 112.6, 81.8, 70.9, 49.9, 48.5, 39.6, 28.0, 10.2; **HRMS-ESI:** *m/z* calcd. for $C_{20}H_{22}N_2O$ $[M+H]^+$: 307.1805, found 307.1803.

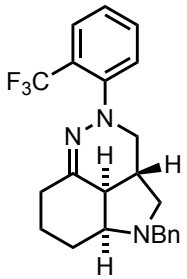


4-ethyl-7-(napthalen-2-yl)-2,5-diphenyl-1,2,4a,5,7,7a-hexahydrofuro-[3,4-*d*]pyridazine (4.59). HAP **(3.87)** (0.036 g, 0.135 mmol) was treated following general procedure **N.** Flash chromatography (10:90 EtOAc-Hexanes) gave a colorless foam (0.029 g, 50%). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.76 (t, *J* = 9.16 Hz, 3 H), 7.67 (s, 1 H), 7.48-7.28 (m, 7 H), 7.25 (dd, *J* = 8.59 Hz, 1.72 Hz, 1 H), 7.09-7.02 (m, 4 H), 6.65 (tt, *J* = 7.45 Hz, 1.72 Hz, 1 H), 5.22 (d, *J* = 10.88 Hz, 1 H), 4.90 (d, *J* = 10.31 Hz, 1 H), 4.11-4.03 (m, 2 H), 2.88 (t, *J* = 12.03 Hz, 1 H), 2.75-2.66 (m, 1 H), 2.45-2.38 (m, 1 H), 2.23-2.17 (m, 1 H), 1.08 (t, *J* = 7.45 Hz, 3 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 150.8, 146.2, 140.5, 139.8, 133.6, 132.9, 129.3, 128.8, 128.6, 128.5, 127.9, 127.8, 127.4, 126.3, 125.9, 124.5, 123.4, 118.9, 115.2, 81.8, 71.4, 65.0, 51.6, 49.9, 27.6, 10.3; **HRMS-ESI:** *m/z* calcd. for $C_{30}H_{28}N_2O$ $[M+H]^+$: 433.2274, found 433.2276.

1.7.8 Pyrrolidine-tetrahydropyridazine derivatives

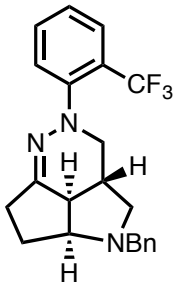


5-benzyl-2-phenyl-2,3,3a,3a^1,4,5,5a,6,7,8-decahydropyrrolo[4,3,2-*de*]-cinnoline (4.37a). HAP **(3.23)** (0.047 g, 0.161 mmol) was treated following general procedure **N.** Flash chromatography (40:60 EtOAc-Hexanes) gave a yellow foam (0.049 g, 92%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.36-7.30 (m, 4 H), 7.25-7.23 (m, 3 H), 7.15-7.12 (m, 2 H), 6.81 (t, *J* = 8.24 Hz, 1 H), 3.85 (q, *J* = 12.82 Hz, 2 H), 3.65-3.61 (m, 1 H), 3.57-3.51 (m, 1 H), 3.22 (dd, *J* = 8.01 Hz, 4.81 Hz, 1 H), 2.96 (td, *J* = 9.85 Hz, 5.27 Hz, 1 H), 2.59-2.53 (m, 1 H), 2.49-2.28 (m, 3 H), 2.17-2.08 (m, 1 H), 1.81-1.70 (m, 2 H), 1.48-1.38 (m, 1 H), 1.16-1.06 (m, 1 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 152.9, 148.3, 139.6, 129.1, 129.0, 128.3, 127.1, 118.6, 112.3, 60.4, 59.7, 57.4, 50.3, 42.8, 37.6, 30.8, 28.2, 20.4; **HRMS-ESI:** *m/z* calcd. for $C_{22}H_{25}N_3$ $[M+H]^+$: 332.2121, found 332.2124.

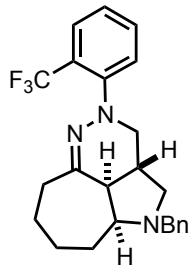


5-benzyl-2-(2-(trifluoromethyl)phenyl)-2,3,3a,3a1,4,5,5a,6,7,8-decahydropyrrolo[4,3,2-*de*]cinnoline (4.37). HAP **(3.77)** (0.040 g, 0.111 mmol) was treated following general procedure **N.** Flash chromatography (20:80 EtOAc-Hexanes) gave a yellow foam (0.042 g, 96%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.61 (d, *J* = 7.45 Hz, 1 H), 7.52 (t, *J* = 8.02 Hz, 1 H), 7.44 (d, *J* = 8.02 Hz, 1 H), 7.36-7.30 (m, 3 H), 7.25 (t, *J*

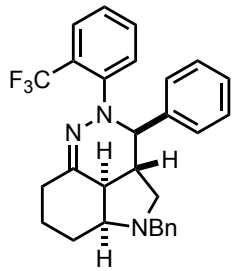
= 7.45 Hz, 1 H), 7.20 (t, *J* = 7.45 Hz, 1 H), 3.93 (d, *J* = 13.17 Hz, 1 H), 3.78 (d, *J* = 12.60 Hz, 1 H), 3.61 (t, *J* = 10.31 Hz, 1 H), 3.29 (t, *J* = 7.45 Hz, 1 H), 3.13 (dd, *J* = 5.15 Hz, 8.02 Hz, 1 H), 2.99 (d, *J* = 5.15 Hz, 1 H), 2.53-2.36 (m, 3 H), 2.29 (dd, *J* = 8.59 Hz, 10.31 Hz, 1 H), 2.04-1.98 (m, 1 H), 1.76-1.73 (m, 2 H) 1.49-1.40 (m, 1 H) 1.17-1.09 (m, 1 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 153.1, 148.7, 137.2, 131.2, 127.3, 126.5, 125.3, 125.2 (q, $J_{C\text{-}F}$ = 6 Hz), 125.1, 123.7, 123.2, 122.8, 121.0, 58.5, 57.9, 55.5, 53.7, 40.5, 35.9, 28.9, 26.1, 18.6; **^{19}F NMR** (564 MHz, $CDCl_3$): δ –59.3 (s, 3 F); **HRMS-ESI:** *m/z* calcd. for C23H24F3N3 $[M+Na]^+$: 422.1815, found 422.1822.



3-benzyl-6-(2-(trifluoromethyl)phenyl)-2,2a,2a1,3,4,4a,5,6-octahydro-1*H*-3,6,7-triazacyclopenta[*cd*]indene (4.38). AAP **(3.78)** (0.076 g, 0.222 mmol) was treated following general procedure **N.** Flash chromatography (20:80 EtOAc-Hexanes) gave a yellow foam (0.037 g, 44%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 7.79 Hz, 1 H), 7.60 (d, *J* = 7.79 Hz, 1 H), 7.55 (t, *J* = 7.79 Hz, 1 H), 7.31-7.21 (m, 6 H), 3.98 (d, *J* = 13.74 Hz, 1 H), 3.30 (t, *J* = 8.70 Hz, 1 H), 3.21 (t, *J* = 13.28 Hz, 1 H), 3.10-3.01 (m, 2 H), 2.77-2.70 (m, 2 H), 2.66-2.61 (m, 2 H) 2.28 (dd, *J* = 7.79 Hz, 9.62 Hz, 1 H), 2.13 (t, *J* = 10.99 Hz, 1 H), 2.06-1.90 (m, 2 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 169.3, 151.2, 139.0, 132.9, 128.5, 128.2, 126.9, 126.6 (q, $J_{C\text{-}F}$ = 5 Hz), 125.7, 125.1, 67.8, 59.8, 58.1, 56.7, 43.0, 37.3, 30.2, 25.6; **^{19}F NMR** (564 MHz, $CDCl_3$): δ –59.2 (s, 3 F); **HRMS-ESI:** *m/z* calcd. for C22H22F3N3 $[M+Na]^+$: 408.1658, found 408.1672.

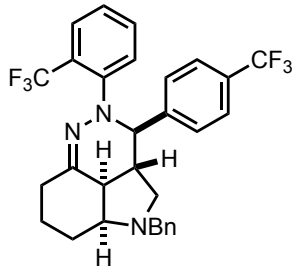


1-benzyl-4-(2-(trifluoromethyl)phenyl)-2,2a,2a1,3,4,6,7,8,9,9a-decahydro-1*H*-1,4,5-triazabenzo[*cd*]azulene (4.39). AAP **(3.79)** (0.073 g, 0.197 mmol) was treated following general procedure **N.** Flash chromatography (20:80 EtOAc-Hexanes) gave a yellow foam (0.071 g, 88%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.60 (d, *J* = 7.79 Hz, 1 H), 7.45 (t, *J* = 7.79 Hz, 1 H), 7.35-7.30 (m, 4 H), 7.25-7.21 (m, 2 H), 7.13 (t, *J* = 7.33 Hz, 1 H), 3.94 (d, *J* = 12.82 Hz, 1 H), 3.76 (d, *J* = 12.82 Hz, 1 H), 3.67 (d *J* = 10.53 Hz, 1 H), 3.44 (t, *J* = 10.07 Hz, 1 H), 3.12-3.03 (m, 2 H), 2.53-2.45 (m, 3 H), 2.20-2.10 (m, 2 H) 1.88 (d, 10.99 Hz, 1 H), 1.79-1.60 (m, 3 H), 1.40-1.17 (m, 3 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 146.7, 146.4, 137.6, 130.5, 127.1, 126.4, 125.8 (q, $J_{C\text{-}F}$ = 5 Hz), 125.2, 123.6, 122.8, 121.7, 121.4 (q, $J_{C\text{-}F}$ = 30 Hz), 63.2, 58.3, 54.2, 52.0, 43.6, 35.7, 34.2, 32.0, 27.9, 25.7; **^{19}F NMR** (564 MHz, $CDCl_3$): δ –58.9 (s, 3 F); **HRMS-ESI:** *m/z* calcd. for C24H26F3N3 $[M+Na]^+$: 436.1971, found 436.1987.



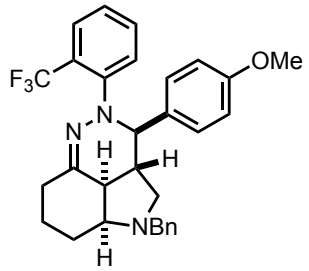
5-benzyl-3-phenyl-2-(2-(trifluoromethyl)phenyl)-2,3,3a,3a^{1},4,5,5a,6,7,8-decahydropyrrolo[4,3,2-*de*]cinnoline (4.40). AAP **(3.77)** (0.055 g, 0.139 mmol) was treated following general procedure **N.** Flash chromatography (20:80 EtOAc-Hexanes)

gave a yellow foam (0.065 g, 90%). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.44 (d, *J* = 7.79, 1 H), 7.29-6.93 (m, 12 H), 4.90 (d, *J* = 10.07 Hz, 1 H), 3.93 (d, *J* = 12.82 Hz, 1 H), 3.75 (d, *J* = 12.82 Hz, 1 H), 3.07-3.04 (m, 1 H), 2.87-2.77 (m, 2 H), 2.59-2.32 (m, 4 H), 1.80-1.79 (m, 2 H), 1.53-1.44 (m, 1 H), 1.27-1.17 (m, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 157.0, 146.4, 140.6, 139.6, 131.8, 129.1 (q, J_{C-F} = 5 Hz), 129.0, 128.3, 128.2, 127.9, 127.4, 127.0, 126.8, 126.7. 123.7, 69.0, 60.3, 59.8, 57.3, 48.5, 42.4, 31.1, 28.1, 20.5; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –59.4 (s, 3 F); **HRMS-ESI:** *m/z* calcd. for C29H28F3N3 $[M+H]^+$: 476.2308, found 476.2319.

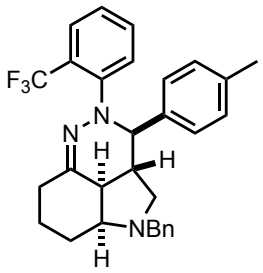


5-benzyl-2-(2-(trifluoromethyl)phenyl)-3-(4-(trifluoromethyl)phenyl)-2,3,3a,3a^1,4,5,5a,6,7,8-decahydropyrrolo[4,3,2-*de*]cinnoline (4.41). AAP **(3.77)** (0.045 g, 0.125 mmol) was treated following general procedure **N.** Flash chromatography (20:80 EtOAc-Hexanes) gave a yellow foam (0.050 g, 72%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.46 (d, *J* = 7.79, 1 H), 7.37 (d, *J* = 8.24, 2 H), 7.30-7.17 (m, 7 H), 7.13 (d, *J* = 8.24 Hz, 2 H), 6.99-6.93 (m, 1 H), 5.00 (d, *J* = 10.53 Hz, 1 H), 3.94 (d, *J* = 13.28 Hz, 1 H), 3.75 (d, *J* = 12.82 Hz, 1 H), 3.13-2.99 (m, 1 H), 2.84-2.78 (m, 2 H), 2.60-2.39 (m, 3 H), 2.34-2.17 (m, 1 H), 1.83-1.79 (m, 1 H), 1.55-1.42 (m, 1 H), 1.34-1.15 (m, 1 H), 0.97-0.83 (m, 1 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 158.2, 148.8, 139.6, 132.1, 129.4, 129.0, 128.3 (q, J_{C-F} = 4 Hz), 127.0, 126.1, 124.8, 124.5 (q, J_{C-F} = 5 Hz), 124.3, 122.5, 120.3, 115.3, 61.4, 60.2, 59.8, 57.9, 42.5, 34.7, 31.2, 28.4, 28.2, 20.7; **^{19}F NMR** (564 MHz, $CDCl_3$): δ –59.4 (s, 3

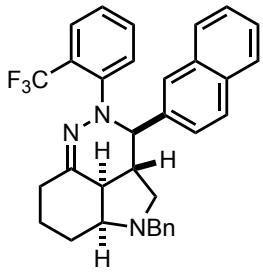
F), –62.4 (s, 3 F); **HRMS-ESI:** *m/z* calcd. for C30H27F6N3 $[M+H]^+$: 544.2182, found 544.2193.



5-benzyl-3-(4-methoxyphenyl)-2-(2-(trifluoromethyl)phenyl)-2,3,3a,3a^1,4,5,5a,6,7,8-decahydropyrrolo[4,3,2-*de*]cinnoline (4.42). AAP (3.77) (0.044 g, 0.124 mmol) was treated following general procedure **N.** Flash chromatography (20:80 EtOAc-Hexanes) gave a yellow foam (0.054 g, 86%). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.45 (d, *J* = 7.79, 1 H), 7.33-7.12 (m, 6 H), 6.96-6.89 (m, 3 H), 6.63 (d, *J* = 8.70, 1 H), 4.86 (d, *J* = 10.53 Hz, 1 H), 3.93 (d, *J* = 12.82 Hz, 1 H), 3.77-3.74 (m, 1 H), 3.67 (s, 3 H), 3.04-2.97 (m, 1 H), 2.87-2.76 (m, 2 H), 2.58-2.31 (m, 3 H), 1.80-1.79 (m, 2 H), 1.53-1.42 (m, 1 H), 1.34-1.17 (m, 2 H), 0.97-0.83 (m, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 158.7, 156.5, 147.9 146.5 139.8, 131.9, 129.4, 129.1, 128.3, 127.0, 126.7 (q, J_{C-F} = 5 Hz), 124.9, 123.8, 113.5, 77.3, 68.5, 60.4, 59.8, 57.4, 55.1, 48.2, 42.4, 31.0, 28.1, 20.5; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –59.3 (s, 3 F); **HRMS-ESI:** *m/z* calcd. for C30H30F3N3O $[M+H]^+$: 506.2414, found 506.2413.

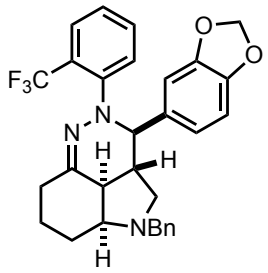


5-benzyl-2-phenyl-3-(*p*-tolyl)-2,3,3a,3a1,4,5,5a,6,7,8-decahydropyrrolo[4,3,2-*de*]cinnoline (4.43). AAP **(3.77)** (0.071 g, 0.199 mmol) was treated following general procedure **N.** Flash chromatography (20:80 EtOAc-Hexanes) gave a yellow foam (0.072 g, 74%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.24 Hz, 1 H), 7.32-7.15 (m, 8 H), 6.94-6.88 (m, 5 H), 4.86 (d, *J* = 10.07 Hz, 1 H), 3.91 (d, *J* = 13.28 Hz, 1 H), 3.72 (d, *J* = 12.82 Hz, 1 H), 3.06-3.00 (m, 1 H), 2.99-2.84 (m, 1 H), 2.77 (t, *J* = 10.99 Hz, 1 H), 2.60-2.43 (m, 2 H) 2.39-2.29 (m, 1 H), 2.17 (s, 3 H), 1.83-1.74 (m, 1 H), 1.53-1.42 (m, 1 H), 1.29-1.17 (m, 1 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 156.3, 146.3, 137.0, 131.8, 129.8, 129.2, 129.1, 128.9, 128.8, 128.4, 128.2, 127.9, 127.8, 127.4, 126.7, (q, $J_{C\text{-}F}$ = 6 Hz), 125.5, 123.8, 68.7, 60.8, 59.7, 57.4, 48.3, 42.3, 30.8, 28.0, 21.1, 20.5; **^{19}F NMR** (564 MHz, $CDCl_3$): δ –60.5 (s, 3 F); **HRMS-ESI:** *m/z* calcd. for C30H30F3N3 $[M+Na]^+$: 512.2284, found 512.2294.



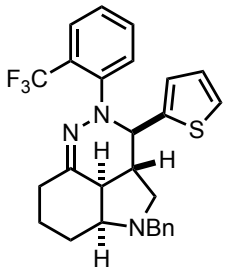
5-benzyl-3-(naphthalen-2-yl)-2-(2-(trifluoromethyl)phenyl)-2,3,3a,3a^{1},4,5,5a,6,7,8-decahydropyrrolo[4,3,2-*de*]cinnoline (4.47). AAP **(3.77)** (0.044 g, 0.124 mmol) was treated following general procedure **N.** Flash chromatography (20:80

EtOAc-Hexanes) gave a yellow foam (0.057 g, 87%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.70-7.63 (m, 3 H), 7.42-7.36 (m, 4 H), 7.28-7.19 (m, 7 H), 7.08 (t, *J* = 7.79, 1 H), 6.85 (t, *J* = 7.33, 1 H), 5.11 (d, *J* = 8.24 Hz, 1 H), 3.94 (d, *J* = 13.28 Hz, 1 H), 3.75 (d, *J* = 12.82 Hz, 1 H), 3.15-2.99 (m, 1 H), 2.88-2.78 (m, 2 H), 2.64-2.43 (m, 4 H), 1.90-1.75 (m, 2 H), 1.57-1.43 (m, 1 H), 1.33-1.12 (m, 1 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 156.8, 146.3, 139.6, 138.4, 133.0, 132.7, 131.9, 129.0, 128.8, 128.3, 128.1, 127.8, 127.6, 127.0, 126.9, 126.8 (q, $J_{C\text{-}F}$ = 5 Hz), 126.0, 125.8, 125.4, 123.8, 77.3, 69.1, 60.4, 59.8, 57.3, 48.6, 42.4, 31.0, 28.1, 20.5; **^{19}F NMR** (564 MHz, $CDCl_3$): δ –59.1 (s, 3 F); **HRMS-ESI:** *m/z* calcd. for C33H30F3N3 $[M+H]^+$: 526.2465, found 526.2472.

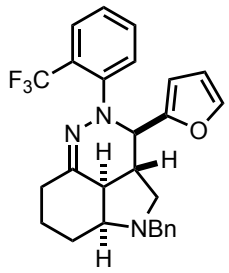


2-(2-trifluoromethyl)phenyl)-4-(4-(trifluoromethyl)phenyl)-3,3a,3a^1,4,5a,6,7,8-octahydro-2*H*-furo[4,3,2-*de*]cinnoline (4.46). AAP **(3.77)** (0.044 g, 0.124 mmol) was treated following general procedure **N.** Flash chromatography (20:80 EtOAc-Hexanes) gave a yellow foam (0.047 g, 76%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.45 (d, *J* = 8.04, 1 H), 7.33-7.17 (m, 7 H), 6.97 (t, *J* = 6.87, 1 H), 6.54 (s, 1 H), 6.49 (d, *J* = 8.02 Hz, 1 H), 6.42 (d, *J* = 8.02 Hz, 1 H), 5.83 (d, *J* = 11.46 Hz, 2 H), 4.83 (d, *J* = 10.88 Hz, 1 H), 3.92 (d, *J* = 13.17 Hz, 1 H), 3.72 (d, *J* = 12.60 Hz, 1 H), 3.05-3.00 (m, 1 H), 2.88-2.85 (m, 1 H), 2.76 (t, 11.46 Hz, 1 H), 2.56-2.43 (m, 2 H), 2.35 (t, 10.31 Hz, 1 H) 2.27-2.22 (m, 1 H), 1.81-1.78 (m, 2 H), 1.52-1.42 (m, 1 H), 1.27-1.18 (m, 1 H); **^{13}C**

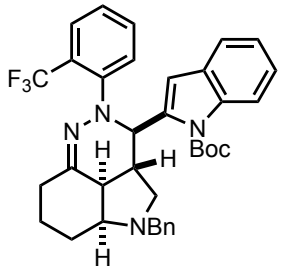
NMR (125 MHz, $CDCl_3$): δ 155.3, 145.7, 145.0, 144.4, 130.2, 127.4, 127.3, 126.6, 126.5, 125.5, 125.0, 124.9 (q, J_{C-F} = 5 Hz), 123.9, 123.2, 122.2, 119.8, 106.0, 99.2, 66.9, 58.9, 57.9, 55.5, 46.4, 40.4, 28,9, 26.1, 18.7; **^{19}F NMR** (564 MHz, $CDCl_3$): δ –59.6 (s, 3 F); **HRMS-ESI:** *m/z* calcd. for C30H28F3N3O2 $[M+H]^+$: 520.2206, found 520.2217.



5-benzyl-3-(thiophen-2-yl)-2-(2-(trifluoromethyl)phenyl)-2,3,3a,3a^1,4,5,5a,6,7,8-decahydropyrrolo[4,3,2-*de*]cinnoline (4.44). AAP **(3.77)** (0.043 g, 0.124 mmol) was treated following general procedure **N.** Flash chromatography (20:80 EtOAc-Hexanes) gave a yellow oil (0.043 g, 74%) **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.51 (d, *J* = 7.79, 1 H), 7.34-7.18 (m, 7 H), 7.13 (d, *J* = 7.79 Hz, 1 H), 7.07-7.02 (m, 2 H), 6.64 (dd, *J* = 5.04 Hz, 3.21 Hz, 1 H), 6.50 (d, *J* = 2.75, 1 H), 5.16 (d, *J* = 10.53 Hz, 1 H), 3.96 (d, *J* = 12.82 Hz, 1 H), 3.76 (d, *J* = 12.82 Hz, 1 H), 3.10-3.02 (m, 2 H), 2.82 (t, *J* = 10.53 Hz, 1 H), 2.59-2.28 (m, 4 H), 1.90-1.76 (m, 2 H), 1.55-1.43 (m, 1 H), 1.35-1.22 (m, 1 H), 0.97-0.83 (m, 1 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 156.3, 144.6, 141.6, 130.3, 128.7, 127.4, 126.6, 125.6, 125.4, 124.5, 124.3 (q, J_{C-F} = 5 Hz), 124.2, 123.8, 123.1, 121.1, 61.9, 58.3, 57.9, 55.7, 47.1, 40.8, 28.9, 26.3, 18.7; **^{19}F NMR** (564 MHz, $CDCl_3$): δ –59.6 (s, 3 F); **HRMS-ESI:** *m/z* calcd. for C27H26F3N3S $[M+H]^+$: 482.1881, found 482.1872.

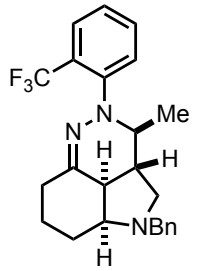


5-benzyl-3-(furan-2-yl)-2-(2-(trifluoromethyl)phenyl)-2,3,3a,3a^1,4,5,5a,6,7,8-decahydropyrrolo[4,3,2-*de*]cinnoline (4.45). AAP **(3.77)** (0.044 g, 0.124 mmol) was treated following general procedure **N.** Flash chromatography (20:80 EtOAc-Hexanes) gave a yellow foam (0.039 g, 67%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.50-7.46 (m, 1 H), 7.38-7.21 (m, 7 H), 7.14-7.07 (m, 3 H), 5.98 (dd, *J* = 2.00 Hz, 2.86 Hz, 1 H), 5.80 (d, *J* = 2.86, 1 H), 4.86 (d, *J* = 11.46 Hz, 1 H), 3.95 (d, *J* = 12.60 Hz, 1 H), 3.74 (d, *J* = 12.60 Hz, 1 H), 3.07-3.02 (m, 1 H), 2.92 (dd, *J* = 7.45 Hz, *J* = 8.02 Hz, 1 H), 2.74 (t, *J* = 10.88 Hz, 1 H), 2.54-2.45 (m, 3 H), 2.37 (dd, *J* = 10.31 Hz, *J* = 8.02 Hz, 1 H), 1.87-1.75 (m, 2 H), 1.53-1.42 (m, 2 H), 1.31-1.22 (m, 2 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 157.7, 152.3, 147.3, 141.9, 139.6, 132.3, 130.5, 129.0, 128.3. 128.1, 127.1, 125.8 (q, J_{C-F} = 5 Hz),125.2, 119.9, 109.9, 109.6, 62.2, 60.0, 59.8, 57.4, 43.8, 42.3, 31.1, 28.2, 20.6; **^{19}F NMR** (564 MHz, $CDCl_3$): δ –59.8 (s, 3 F); **HRMS-ESI:** *m/z* calcd. for C27H26F3N3O $[M+H]^+$: 466.2101, found 466.2105.



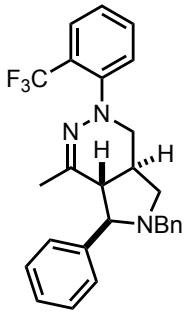
***tert*-butyl-3-5-benzyl-2-(2-(trifluoromethyl)phenyl)-2,3,3a,3a^1,4,5,5a,6,7,8-decahydropyrrolo[4,3,2-*de*]cinnolin-3-yl)-1*H*-indole-1-carboxylate (4.48).** AAP **(3.77)**

(0.045 g, 0.125 mmol) was treated following general procedure **N.** Flash chromatography (20:80 EtOAc-Hexanes) gave a yellow foam (0.039 g, 52%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.46 (d, *J* = 7.79, 2 H), 7.32-7.15 (m, 10 H), 7.02 (t, *J* = 7.33 Hz, 1 H), 6.95 (t, *J* = 7.79 Hz, 1 H), 5.09 (d, *J* = 10.53 Hz, 1 H), 3.94 (d, *J* = 12.82 Hz, 1 H), 3.73 (d, *J* = 12.82 Hz, 1 H), 3.10-3.04 (m, 1 H), 2.88-2.81 (m, 2 H), 2.64-2.49 (m, 3 H), 2.37 (dd, *J* = 8.24 Hz, 10.30 Hz, 1 H), 1.86-1.79 (m, 2 H), 1.59 (s, 9 H), 1.52-1.43 (m, 1 H), 1.30-1.19 (m, 3 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 158.2, 149.5, 148.8, 139.6, 132.1, 129.4, 129.0, 128.3, 127.0, 126.3, 124.5, (q, J_{C-F} = 4 Hz), 124.3, 122.5, 120.3, 115.3, 83.8, 61.4, 60.2, 59.8, 57.9, 42.5, 34.7, 31.2, 28.4, 28.2, 20.7; **^{19}F NMR** (564 MHz, $CDCl_3$): δ –59.6 (s, 3 F); **HRMS-ESI:** *m/z* calcd. for C36H37F3N4O2 $[M+H]^+$: 615.2941, found 615.2951.

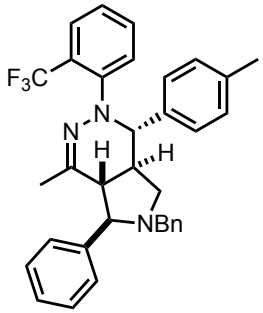


5-benzyl-3-methyl-2-(2-(trifluoromethyl)phenyl)-2,3,3a,3a1,4,5,5a,6,7,8-decahydropyrrolo[4,3,2-*de*]cinnoline (4.49). AAP (**3.77**) (0.088 g, 0.244 mmol) was treated following general procedure **P.** Flash chromatography (20:80 EtOAc-Hexanes) gave a yellow foam (0.048 g, 48%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.58 (d, *J* = 8.02 Hz, 1 H), 7.53-7.48 (m, 2 H), 7.35-7.30 (m, 4 H), 7.27-7.24 (m, 1 H), 7.18 (t, *J* = 7.45 Hz, 1 H), 4.00-3.94 (m, 1 H), 3.92 (d, *J* = 13.17 Hz, 1 H), 3.75 (d, *J* = 12.60 Hz, 1 H), 3.07 (dd, *J* = 4.58 Hz, 7.73 Hz, 1 H), 3.00-2.95 (m, 1 H), 2.58 (t, 11.17 Hz, 1 H), 2.49-2.43 (m, 1 H), 2.39-2.33 (m, 1 H) 2.30 (dd, *J* = 8.02 Hz, 10.88 Hz, 1 H),, 1.78-1.70 (m, 3 H), 1.46-

1.38 (m, 1 H), 1.14 (dd, J = 10.88 Hz, 22.05 Hz, 1 H), 0.84 (d, J = 6.30 Hz, 3 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 153.8, 146.7, 132.3, 130.3, 129.1, 129.0, 128.6, 128.3, 128.1, 127.2, 126.8 (q, $J_{C\text{-}F}$ = 6 Hz), 126.1, 125.9, 125.7, 125.3, 124.6, 123.1, 65.9, 60.7, 59.8, 59.0, 57.4, 46.8, 42.4, 30.8, 27.9, 20.5, 20.1, 15.3; **^{19}F NMR** (564 MHz, $CDCl_3$): δ –60.5 (s, 3 F); **HRMS-ESI:** *m/z* calcd. for C24H26F3N3 $[M+Na]^+$: 436.1971, found 436.1982.

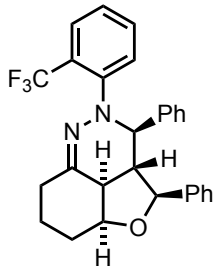


6-benzyl-4-methyl-5-phenyl-2-(2-(trifluoromethyl)phenyl)-2,4a,5,6,7,7a-hexahydro-1*H*-pyrrolo[3,4-*d*]pyridazine (4.60). AAP **(3.96)** (0.061 g, 0.148 mmol) was treated following general procedure **N.** Flash chromatography (20:80 EtOAc-Hexanes) gave a yellow foam (0.027 g, 40%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.59 (d, J = 8.02 Hz, 1 H), 7.53 (d, J = 7.45 Hz, 2 H), 7.47 (d, J = 7.75 Hz, 1 H), 7.38 (t, J = 7.45 Hz, 2 H), 7.31 (d, J = 8.02 Hz, 2 H), 7.27-7.14 (m, 4 H), 3.82 (d, J = 13.75 Hz, 1 H), 3.75 (d, J = 10.31 Hz, 1 H), 3.60 (t, J = 10.88 Hz, 1 H), 3.51 (dd, J = 5.73 Hz, 10.60 Hz, 1 H), 3.43 (d, J = 13.75 Hz, 1 H), 2.98 (t, J = 9.74 Hz, 1 H), 2.83 (t, J = 9.16 Hz, 1 H), 2.64 (d, J = 11.46 Hz, 1 H), 2.47-2.39 (m, 1 H), 1.65 (s, 3 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 149.2, 145.9, 141.9, 139.9, 132.7, 128.9, 128.5, 128.4, 128.2, 127.9, 127.4 (q, J = 5 Hz), 126.8, 125.5, 124.1, 124.2, 69.7, 57.3, 55.6, 53.5, 50.2, 36.5, 21.4; **^{19}F NMR** (564 MHz, $CDCl_3$): δ –59.2 (s, 3 F); **HRMS-ESI:** *m/z* calcd. for $C_{27}H_{26}F_3N_3$ $[M+H]^+$: 450.2152, found 450.2149.

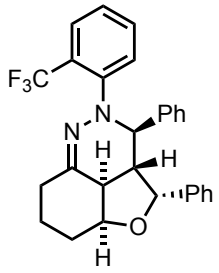


6-benzyl-4-methyl-5-phenyl-1-(*p*-tolyl)-2-(2-(trifluoromethyl)phenyl)-2,4a,5,6,7,7a-hexahydro-1*H*-pyrrolo[3,4-*d*]pyridazine (4.61). AAP **(3.96)** (0.030 g, 0.074 mmol) was treated following general procedure **N.** Flash chromatography (20:80 EtOAc-Hexanes) gave a yellow foam (0.027 g, 67%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.54 (d, *J* = 7.45 Hz, 1 H), 7.49-7.44 (m, 1 H), 7.38 (t, *J* = 7.45 Hz, 2 H), 7.30 (t, *J* = 7.45 Hz, 1 H), 7.23-7.12 (m, 6 H), 7.03 (d, *J* = 8.02 Hz, 2 H), 6.94-6.90 (m, 4 H), 4.90 (d, *J* = 10.31 Hz, 1 H), 3.79-3.76 (m, 2 H), 3.34 (d, *J* = 13.75 Hz, 1 H), 3.00 (t, *J* = 9.74 Hz, 1 H), 2.91 (t, *J* = 11.17 Hz, 1 H), 2.72 (p, *J* = 9.74 Hz, 1 H), 2.43-2.40 (m, 1 H), 2.19 (s, 3 H), 1.65 (s, 3 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 144.0, 139.9, 137.2, 136.8, 131.3, 129.4, 129.2, 129.1, 128.8, 128.7, 128.5, 128.3 (q, $J_{C\text{-}F}$ = 5 Hz), 128.2, 128.1, 127.9, 127.3, 126.7, 125.4, 123.1, 70.4, 67.1, 57.2, 53.5, 50.3, 45.5, 21.2, 21.1; **^{19}F NMR** (564 MHz, $CDCl_3$): δ –60.5 (s, 3 F); **HRMS-ESI:** *m/z* calcd. for C34H32F3N3 $[M+H]^+$: 540.2621, found 540.2634.

Highly substituted fused furans- and pyrrolidines-tetrahydropyridazine derivatives

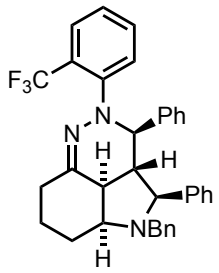


***Syn*-3,4-diphenyl-2-(2-(trifluoromethyl)phenyl)-3,3a,3a1,4,5a,6,7,8-octahydro-2*H*-furo[4,3,2-*de*]cinnoline (4.78).** HAP **(3.70)** (0.054 g, 0.199 mmol) was treated following general procedure **N.** Flash chromatography (10:90 EtOAc-Hexanes) gave seperable diastereomers: yellow oil (0.030 g, 33%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.44 (t, *J* = 7.79, 1 H), 7.12-7.08 (m, 2 H), 6.98-6.93 (m, 6 H), 6.83-6.80 (m, 3 H), 6.71-6.69 (m, 2 H), 5.00 (d, *J* = 10.53 Hz, 1 H), 4.80 (d, *J* = 10.07 Hz, 1 H), 4.53-4.46 (m, 1 H), 3.25 (t, *J* = 10.99 Hz, 1 H), 2.73-2.67 (m, 1 H), 2.63-2.51 (m, 1 H), 2.35-2.26 (m, 1 H), 2.04-1.95 (m, 1 H), 1.67-1.56 (m, 1 H), 1.54-1.42 (m, 1 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 157.0, 145.8, 138.9, 138.8 131.9, 130.1, 128.7, 128.0, 127.9, 127.8, 127.7, 127.2, 126.6 (q, J_{C-F} = 5 Hz), 126.3, 124.5, 84.6, 74.5, 68.3, 56.2, 44.8, 30.7, 27.3, 19.3; **^{19}F NMR** (564 MHz, $CDCl_3$): δ –59.2 (s, 3 F); **HRMS-ESI:** *m/z* calcd. for C28H25F3N2O $[M+H]^+$: 463.1992, found 463.1987.



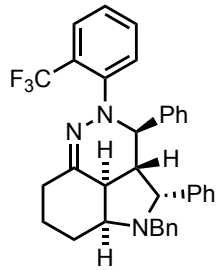
***Anti*-3,4-diphenyl-2-(2-(trifluoromethyl)phenyl)-3,3a,3a1,4,5a,6,7,8-octahydro-2*H*-furo[4,3,2-*de*]cinnoline (4.79).** Yellow oil (0.031 g, 34%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.40 (t, *J* = 7.45, 2 H), 7.34 (t, *J* = 6.30, 2 H), 7.18-7.14 (m, 3 H),

7.09-7.01 (m, 4 H), 6.94-6.91 (m, 3 H), 5.11 (d, *J* = 7.45 Hz, 1 H), 4.79-4.73 (m, 1 H), 4.29 (d, *J* = 10.31 Hz, 1 H), 3.17-3.13 (m, 1 H), 2.79-2.71 (m, 2 H), 2.63-2.56 (m, 1 H), 2.30-2.28 (m, 1 H), 2.04-1.96 (m, 1 H), 1.72-1.62 (m, 1 H), 1.41-1.36 (m, 1 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 158.5, 145.7, 139.8, 131.8 130.0, 128.4, 127.9, 127.9, 126.4, 126.4, 126.3 (q, $J_{C\text{-}F}$ = 5 Hz),126.0, 124.6, 81.0, 76.4, 66.3, 53.3, 40.7, 30.6, 27.1, 19.1; **^{19}F NMR** (564 MHz, $CDCl_3$): δ –60.2 (s, 3 F); **HRMS-ESI:** *m/z* calcd. for C28H25F3N2O $[M+Na]^+$: 485.1811, found 485.1820.



***Syn*-5-benzyl-3,4-diphenyl-2-(2-(trifluoromethyl)phenyl)-2,3,3a,3a1,4,5,5a,6,7,8-decahydropyrrolo[4,3,2-*de*]cinnoline (4.80).** AAP **(3.77)** (0.074 g, 0.207 mmol) was treated following general procedure **N.** Flash chromatography (10:90 EtOAc-Hexanes) gave seperable diastereomers: Yellow oil (0.029 g, 26%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.42 (d, *J* = 7.79, 1 H), 7.26-7.21 (m, 5 H), 7.15 (d, *J* = 6.87, 2 H), 7.10-7.05 (m, 2 H), 7.00-6.89 (m, 4 H), 6.77-6.76 (m, 3 H), 6.62-6.61 (m, 2 H), 4.88 (d, *J* = 10.07 Hz, 1 H), 3.84 (d, *J* = 13.28 Hz, 1 H), 3.78 (d, *J* = 9.16 Hz, 1 H), 3.47 (d, *J* = 12.82 Hz, 1 H), 3.21-3.14 (m, 1 H), 2.97 (t, *J* = 11.28 Hz, 1 H), 2.62-2.57 (m, 2 H), 2.49-2.40 (m, 1 H), 2.33-2.25 (dd, *J* = 10.07 Hz, 21.98 Hz, 1 H), 1.73-1.69 (m, 1 H), 1.42-1.38 (m, 1 H), 1.21-1.13 (m, 1 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 158.5, 140.1, 139.9, 139.8, 131.8 129.5, 129.2, 128.1, 127.9, 127.7, 127.4, 127.2, 126.9, 126.7, 126.6, (q, $J_{C\text{-}F}$ = 5 Hz), 123.9, 73.9, 68.9, 59.9, 57.1, 55.9, 42.1, 32.2, 28.0, 20.6; **^{19}F NMR** (564 MHz,

$CDCl_3$): δ –59.2 (s, 3 F); **HRMS-ESI:** *m/z* calcd. for C35H32F3N3 $[M+Na]^+$: 574.2441, found 574.2460.



***Anti*-5-benzyl-3,4-diphenyl-2-(2-(trifluoromethyl)phenyl)-2,3,3a,3a1,4,5,5a,6,7,8-decahydropyrrolo[4,3,2-*de*]cinnoline (4.81).** Yellow oil (0.032 g, 28%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.44-7.29 (m, 3 H), 7.20-7.15 (m, 2 H), 7.11-7.08 (m, 6 H), 6.99 (m, 1 H), 6.87-6.82 (m, 2 H), 4.16 (d, J = 10.53 Hz, 1 H), 4.03 (d, J = 6.41 Hz, 1 H), 3.93 (d, J = 13.74 Hz, 1 H), 3.98 (d, J = 14.20 Hz, 1 H), 3.68-3.62 (m, 1 H), 3.29 (t, J = 12.06 Hz, 1 H), 2.74-2.65 (m, 2 H), 2.59-2.51 (m, 1 H), 2.10-2.04 (m, 1 H), 1.92-1.86 (m, 1 H), 1.60-1.50 (m, 1 H), 1.31-1.20 (m, 1 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 157.6, 138.9, 138.8, 137.3 129.7, 127.4, 126.8 126.6, 126.5, 126.4, 126.2, 125.5, 125.4, 124.7, 124.5 (q, $J_{C\text{-}F}$ = 6 Hz), 121.9, 75.4, 65.1, 64.7, 58.5, 51.4, 51.3, 38.1, 29.8, 26.2, 18.3; **^{19}F NMR** (564 MHz, $CDCl_3$): δ –60.1 (s, 3 F); **HRMS-ESI:** *m/z* calcd. for C35H32F3N3 $[M+H]^+$: 552.2621, found 552.2612.

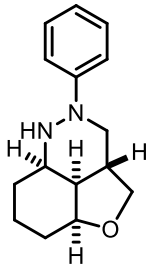
Transformation of fused furans- and pyrrolidines-tetrahydropyridazine derivatives

Hydrazone reduction, and Bz protection

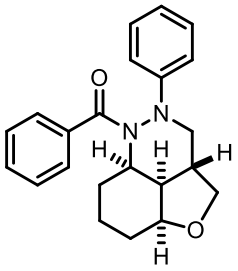
To a 0 °C (ice-bath) solution of hydrazone (1 equiv) in THF (0.1 M) was added $LiAlH_4$ (2 equiv). The reaction was allowed to warm to rt and stirred for 14 h. The reaction was cooled to 0 °C (ice-bath), diluted with Et_2O (10 mL) and added sequentially

H_2O (1.2 mL), 15% aq. NaOH (1.2 mL), and H_2O (3.6 mL). The reaction was warmed to rt, $MgSO_4$ was added and stirred 20 min. The reaction was filtered and concentrated *in vacuo* and purifed by flash chromatography.

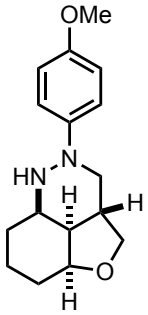
To a solution the above amine (1 equiv) in CH_2Cl_2 (0.1 M) was added DMAP (5 mol%), followed by Et_3N (1.5 equiv) and BzCl (1.2 equiv). The reaction was stirred for 14 h, diluted with CH_2Cl_2 (10 mL), and partitioned between H_2O and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 (3 X 10 mL), and the combined organic phases were washed with sat. NaCl (20 mL), dried over $MgSO_4$, and concentrated *in vacuo* and purifed by flash chromatography.



phenyl((3a,3a^1,5a,8a)2-phenyldecahydro-1*H*-furo[4,3,2-*de*]cinnolin-1-yl-methanone (4.83). Hydrazone **(4.10)** (0.179 g, 0.738 mmol). Flash chromatography (40:60 EtOAc-Hexanes) gave a colorless oil (0.126 g, 70%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.24-7.19 (m, 2 H), 7.11-7.08 (m, 2 H), 6.78-6.74 (m, 1 H), 4.20-4.06 (m, 3 H), 3.47 (dd, *J* = 10.6 Hz, 7.79 Hz, 1 H), 3.36 (ddd, *J* = 5.95 Hz, 5.95 Hz, 5.95 Hz, 1 H), 3.29 (brs, 1 H), 2.66 (t, *J* = 10.99 Hz, 1 H), 2.62-2.51 (m, 1 H), 1.95 (quin. *J* = 5.95 Hz, 1 H), 1.85-1.74 (m, 2 H), 1.72-1.66 (m, 1 H), 1.57-1.46 (m, 1 H), 1.18-1.12 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 151.1, 128.9, 118.5, 114.2, 76.5, 69.7, 55.5, 51.7, 46.5, 35.2, 29.8, 25.5, 21.8; **HRMS-ESI:** *m/z* calcd. for $C_{15}H_{20}N_2O$ $[M+H]^+$: 245.1648, found 245.1655.

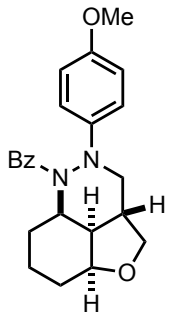


Amine (0.184 g, 0.753 mmol). Flash chromatography (45:55 EtOAc-Hexanes) gave an off-white foam **(4.85)** (0.234 g, 89%). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.52 (d, *J* = 7.45 Hz, 2 H), 7.31-7.19 (m, 5 H), 6.85-6.81 (m, 3 H), 5.37-5.35 (m, 1 H), 4.24-4.16 (m, 2 H), 4.12 (t, *J* = 7.45 Hz, 1 H), 3.44 (dd, *J* = 11.17 Hz, 8.02 Hz, 1 H), 2.94 (t, *J* = 12.03 Hz, 1 H), 2.60-2.47 (m, 1 H), 2.23-2.21 (m, 1 H), 1.81-1.78 (m, 2 H), 1.62-1.59 (m, 1 H), 1.30-1.01 (m, 3 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 174.0, 148.4, 135.6, 130.0, 129.3, 127.7, 126.8, 119.8, 113.4, 76.3, 69.0, 53.4, 50.3, 46.2, 32.2, 29.6, 26.0, 21.7; **HRMS-ESI:** *m/z* calcd. for $C_{22}H_{24}N_2O_2$ $[M+H]^+$: 349.1911, found 349.1912.



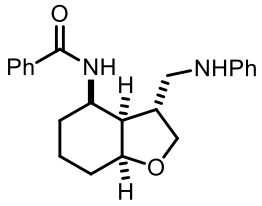
(2-(4-methoxyphenyl)decahydro-1H-furo[4,3,2-de]cinnolin-1-yl)(phenyl)methanone (4.84). Hydrazone **(4.18)** (0.043 g, 0.158 mmol). Concentrated in vacuo to give off-white solid (0.038 g, 88%). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.05 (d, *J* = 8.7 Hz, 2H), 6.80 (d, *J* = 8.7 Hz, 2H), 4.21-4.13 (m, 1H), 4.10 (t, *J* = 7.2 Hz, 1H), 3.94 (dd, *J* = 10.8, 2.9 Hz, 1H), 3.75 (s, 3H), 3.47 (dd, *J* = 10.8, 7.6 Hz, 1H), 3.39-3.29 (m, 1H), 2.63 (m, 1H), 2.54 (t, *J* = 10.8 Hz, 1H), 1.91 (dt, *J* = 12.5, 6.4 Hz, 1H), 1.82 (d, *J* =

6.4 Hz, 1H), 1.79-1.69 (m, 2H), 1.64 (dd, *J* = 24.9, 12.4 Hz, 1H), 1.23-1.10 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 153.2, 145.5, 116.6, 114.2, 69.7, 55.7, 55.5, 53.3, 46.6, 35.6, 29.6, 25.3, 21.9.; **HRMS-CI:** *m/z* calcd. for $C_{16}H_{22}N_2O_2$ $[M+H]^+$: 275.1754, found 275.1761.



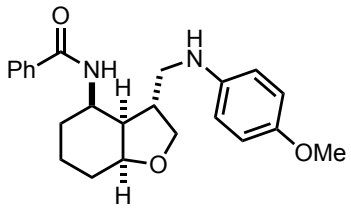
White foam **(4.86)** (0.044 g, 84%). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.54 (d, *J* = 7.2 Hz, 2H), 7.30 (m, 1H), 7.25 (d, *J* = 7.8 Hz, 2H), 6.77 (m, 4H), 5.31 (m, 1H), 4.26-4.05 (m, 3H), 3.73 (s, 3H), 3.43 (dd, *J* = 10.8, 7.9 Hz, 1H), 2.95 (t, *J* = 12.4 Hz, 1H), 2.54 (m, 1H), 2.29-2.14 (m, 1H), 1.76 (m, 2H), 1.59 (d, *J* = 13.0 Hz, 1H), 1.35-0.96 (m, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 174.0, 153.3, 142.3, 135.8, 130.0, 127.7, 126.9, 114.6, 114.6, 76.4, 69.1, 55.6, 53.2, 50.6, 46.3, 31.7, 29.7, 26.1, 21.8.; **HRMS-CI:** *m/z* calcd. for $C_{23}H_{26}N_2O_3$ $[M+H]^+$: 379.2019, found 379.2027.

N–N bond cleavage



***N*-3-((phenylamino)methyl)octahydrobenzofuran-4-yl)benzamide (4.87).** Following an adapted procedure,[16] Amide **(4.85)** (0.0746 g, 0.214 mmol) was dissolved in MeOH-THF (2 mL-0.5 mL, respectively) and degassed using the freeze-pump-thaw

method. SmI_2 (12.8 mL, 1.28 mmol, 0.1 M soln. in THF) was added, and the reaction was stirred at rt for 12 h. The reaction was poured onto sat. $NaHCO_3$ and partitioned between H_2O and EtOAc. The aqueous phase was extracted with EtOAc (3 X 10 mL), and the combined organic phases were washed with sat. NaCl (10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Flash chromatography (60:40 EtOAc-Hexanes) gave an white foam (0.052 g, 69%). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.73 (dd, *J* = 8.02 Hz, 1.15 Hz, 2 H), 7.48-7.43 (m, 2 H), 7.33 (t, *J* = 8.02 Hz, 2 H), 7.17 (dd, *J* = 8.59 Hz, 7.45 Hz, 2 H), 6.75 (t, *J* = 6.87 Hz, 1 H), 6.61 (d, *J* = 8.02 Hz, 2 H), 4.51-4.47 (m, 1 H), 4.17 (t, *J* = 8.59 Hz, 1 H), 4.01 (q, *J* = 4.01 Hz, 1 H), 3.71 (brs, 1 H), 3.52 (dd, *J* = 9.45 Hz, 6.30 Hz, 1 H), 3.18 (dd, *J* = 11.50 Hz, 8.59 Hz, 1 H), 3.05 (dd, *J* = 11.50 Hz, 6.30 Hz, 1 H), 2.54-2.48 (m, 1 H), 2.26 (q, *J* = 4.01 Hz, 1 H), 1.98-1.94 (m, 1 H), 1.78-1.60 (m, 4 H), 1.52-1.47 (m, 1 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 166.7, 148.0, 134.4, 131.4, 129.4, 128.6, 126.9, 118.5, 113.4, 77.4, 71.6, 47.9, 46.9, 45.7, 41.7, 28.9, 26.8, 16.4; **HRMS-ESI:** *m/z* calcd. for $C_{22}H_{26}N_2O_2$ $[M+H]^+$: 351.2067, found 351.2067.

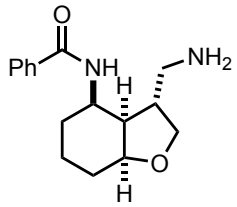


N-(3-(((4-methoxyphenyl)amino)methyl)octahydrobenzofuran-4-yl)benzamide (4.88). white foam **(4.86)** (0.042 g, 99%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.85 (d, *J* = 8.8 Hz, 1H), 7.70 (d, *J* = 7.6 Hz, 2H), 7.41 (t, *J* = 7.3 Hz, 1H), 7.27 (t, *J* = 7.7 Hz, 2H), 6.77 (d, *J* = 8.6 Hz, 2H), 6.58 (d, *J* = 8.7 Hz, 2H), 4.44 (m, 1H), 4.17 (t, *J* = 8.8 Hz, 1H), 4.04 (m, 1H), 3.74 (s, 3H), 3.54-3.50 (m, 1H), 3.45 (s, 1H), 3.17-2.97 (m, 2H), 2.49 (m, 1H), 2.27 (m, 1H), 1.82 (m, 1H), 1.78-1.61 (m, 4H), 1.47 (s, 1H); **^{13}C NMR**

(100 MHz, $CDCl_3$): δ 165.3, 151.5, 140.5, 132.9, 129.8, 127.0, 125.4, 113.6, 113.4, 76.4, 70.0, 54.3, 47.5, 45.4, 45.1, 39.7, 27.1, 25.5, 15.8.; **HRMS-CI:** *m/z* calcd. for $C_{23}H_{28}N_2O_3$ $[M+Na]^+$: 403.1992, found 403.2007.

Oxidative cleavage of the 4-OMe-phenyl

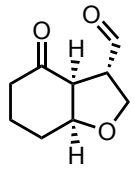
To a solution of amine in MeCN:H_2O (1:1) was added TCICA (finely ground). After 16 hr the reaction was washed with CH_2Cl_2 (3 X). To the resulting aqueous phase was added KOH (0.5 M) until pH ≈ 10.5. The aqueous phase was then extracted with EtOAc (4 X), and the combined organic extracts dried over $MgSO_4$, concentrated under vacuum to give the product.



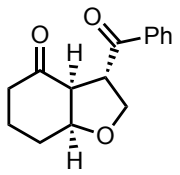
N-(3-(aminomethyl)octahydrobenzofuran-4-yl)benzamide (4.90). of amide **(4.88)** (0.0204 g, 0.053 mmol) gave brown solid (0.0114 g, 79%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.66 (s, 1H), 7.83 (d, *J* = 7.2 Hz, 2H), 7.45 (t, *J* = 7.2 Hz, 1H), 7.39 (t, *J* = 7.4 Hz, 2H), 4.36 (dt, *J* = 8.7, 4.6 Hz, 1H), 4.13 (m, 2H), 3.50-3.43 (m, 1H), 3.00 (dd, *J* = 12.2, 3.6 Hz, 1H), 2.55 (dd, *J* = 12.1, 9.9 Hz, 1H), 2.42-2.33 (m, 1H), 2.23 (dd, *J* = 13.1, 5.4 Hz, 1H), 1.91-1.81 (m, 1H), 1.80-1.66 (m, 2H), 1.65-1.48 (m, 3H), 1.48-1.36 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 165.3, 133.5, 129.1, 126.4, 125.4, 77.7, 69.2, 46.9, 45.3, 42.8, 39.9, 26.0, 25.7, 17.8.; **HRMS-CI:** *m/z* calcd. for $C_{16}H_{22}N_2O_2$ $[M+H]^+$: 275.1754, found 275.1763.

Synthesis of dicarbonyls

To a solution of furan-tetrahydropyridazine (1 equiv) in HFIP solvent (0.5 mL) under Ar atmosphere was added PIDA (2 equiv) and heated at 65 °C for 8 h. The reaction mixture was quenched with saturated $NaHCO_3$ (2 mL) solution and extracted twice with CH_2Cl_2 (2 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated and purified by column chromatography (10:90 EtOAc-Hexanes) to afford the oxidation product.

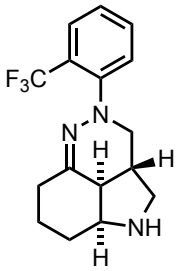


4-oxooctahydrobenzofuran-3-carbaldehyde (4.91). Furan-tetrahydropyridazine **(4.13)** (0.075 g, 0.24 mmol) was treated following general procedure **H**. Flash chromatography (10:90 EtOAc-Hexanes) gave a yellow oil (0.021 g, 51%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.74 (s, 1 H), 4.16-4.11 (m, 1 H), 4.02 (d, *J* = 6.87 Hz, 2 H), 3.95 (dt, *J* = 1.30 Hz, 6.80 Hz, 1 H), 3.17 (d, *J* = 4.03 Hz, 1 H), 2.53-2.49 (m, 1 H), 2.41-2.35 (m, 1 H), 2.10-2.08 (m, 1 H), 1.98-1.91 (m, 3 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 208.1, 200.4, 79.8, 65.3, 52.2, 52.1, 41.2, 27.3, 21.0; **HRMS-ESI:** *m/z* calcd. for C9H12O3 $[M+Na]^+$: 191.0679, found 191.0672.



3-benzoylhexahydrobenzofuran-4(2*H*)-one (4.92). Furan-tetrahydropyridazine **(4.22)** (0.135 g, 0.35 mmol) was treated following general procedure **H**. Flash chromatography (10:90 EtOAc-Hexanes) gave a tanned solid (0.064 g, 74%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.99 (d, *J* = 7.45 Hz, 2 H), 7.57 (t, *J* = 6.87 Hz, 1 H), 7.47 (d, *J* = 8.45 Hz, 2 H), 4.85 (ddd, *J* = 1.72 Hz, 5.73 Hz, 9.27 Hz, 1 H), 4.27-4.26 (m, 1 H), 4.19 (t, *J* = 8.54 Hz, 1 H), 3.92 (dd, *J* = 5.15 Hz, 8.88 Hz, 1 H), 3.19 (d, *J* = 5.15 Hz, 1 H), 2.54-2.51 (m, 1 H), 2.41-2.35 (m, 1 H), 2.16-2.11 (m, 1 H), 2.01-1.92 (m, 3 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 209.1, 199.0, 135.7, 133.6, 128.9, 128.8, 80.1, 68.4, 55.0, 46.8, 41.5, 27.2, 21.2; **HRMS-ESI:** *m/z* calcd. for C15H16O3 $[M+Na]^+$: 267.0992, found 267.1002.

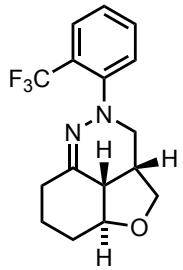
Debenzylation



2-(2-(trifluoromethyl)phenyl)-2,3,3a,3a1,4,5,5a,6,7,8-decahydropyrrolo[4,3,2-*de*]cinnoline (4.93). To a suspension of hydrogenated methanol and 0.04 g of 10% Pd/C charcoal was added Proline-tetrahydropyridazine **(4.37)** (0.052 g, 0.13 mmol). Under a H_2 balloon (1 atm) at 45° C the reaction ran for 30 mins. The catalyst is filtered, rinsed with methanol and the eluent vacuum evaporated. Flash chromatography (1:99 to 10:90

MeOH:CH_2Cl_2) to give a yellow oil (0.040 g, 99%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.61 (d, *J* = 7.45 Hz, 1 H), 7.53 (t, *J* = 7.45 Hz, 1 H), 7.45 (d, *J* = 8.02 Hz, 1 H), 7.21 (t, *J* = 8.02 Hz, 1 H), 3.62 (t, *J* = 10.31 Hz, 1 H), 3.49 (bs, 1 H), 3.35 (dd, *J* = 7.45 Hz, 9.74 Hz, 1 H), 3.23 (dd, *J* = 5.15 Hz, 9.16 Hz, 1 H), 2.68 (t, *J* = 9.16 Hz, 1 H), 2.58 (d, *J* = 7.45 Hz, 1 H), 2.54 (d, *J* = 6.87 Hz, 1 H), 2.45-2.37 (m, 2 H), 1.97-1.95 (m, 1 H), 1.90-1.81 (m, 2 H), 1.59-1.50 (m, 1 H), 1.06 (dq, *J* = 2.86 Hz, 11.74 Hz, 1 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 182.8, 154.7, 150.4, 133.0, 127.0 (q, J_{C-F} = 6 Hz), 126.8, 124.7, 55.6, 54.0, 50.2, 43.3, 38.8, 31.9, 27.5, 20.5; **^{19}F NMR** (564 MHz, $CDCl_3$): δ –59.3 (s, 3 F); **HRMS-ESI:** *m/z* calcd. for C16H18F3N3 $[M+H]^+$: 310..1526, found 310.1516.

Transformation of cis ring fusion to trans ring fusion



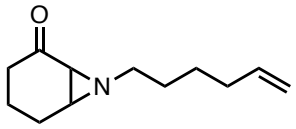
2-(2-(trifluoromethyl)phenyl)-3,3a,3a1,4,5a,6,7,8-octahydro-2*H*-furo[4,3,2-*de*]cinnoline (4.94). Furan-tetrahydropyridazine **(4.13)** (0.030 g, 0.10 mmol) in an over dried 1 dram vial under Ar atmosphere was heat to 100 °C in toluene for 3 days. Flash chromatography (20:80 EtOAc-Hexanes) gave a yellow foam (0.024 g, 80%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.02 Hz, 1 H), 7.55 (t, *J* = 8.02 Hz, 1 H), 7.48 (d, *J* = 8.02 Hz, 1 H), 7.26 (t, *J* = 8.02 Hz, 1 H), 4.31 (dd, *J* = 7.45 Hz, 9.45 Hz, 1 H), 3.48 (dd, *J* = 4.01 Hz, 9.74 Hz, 1 H), 3.35 (dd, *J* = 5.73 Hz, 11.74 Hz, 1 H), 3.26 (dt, *J* = 2.86 Hz, 10.88 Hz, 1 H), 3.01-2.93 (m, 1 H), 2.57 (t, *J* = 13.17 Hz, 1 H), 3.23 (ddd, *J* = 1.72 Hz,

5.15 Hz, 13.89 Hz, 1 H), 2.32-2.24 (m, 2 H), 2.13-2.09 (m, 1H), 2.00 (dd, J = 8.59 Hz, 10.88 Hz, 1 H), 1.71 (dt, J = 4.58 Hz, 7.45 Hz, 1 H), 1.64-1.54 (m, 1 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 154.9, 150.3, 133.0, 126.9 (q, J_{C-F} = 5 Hz), 126.3, 125.6, 125.2, 125.0, 122.9, 83.3, 71.4, 54.6, 44.9, 33.2, 32.7, 30.3, 24.7; **^{19}F NMR** (564 MHz, $CDCl_3$): δ –59.3 (s, 3 F); **HRMS-ESI:** *m/z* calcd. for C16H17F3N2O $[M+Na]^+$: 333.1185, found 333.1198.

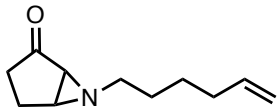
1.7.8 Synthesis of azapolycycles

Synthesis of aziridino ketos

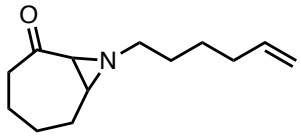
A mixture of iodocyclohex-2-en-1-one (4.51 mmol), anhydrous Cs_2CO_3 (4.96 mmol), 1,10-phenanthroline (4.51 mmol), and amino-terminal-alkene (6.77 mmol) in CH_2Cl_2 (34 mL) was stirred at rt for 4 h. The reaction was partitioned between CH_2Cl_2 and H_2O. The aqueous layer was extracted with CH_2Cl_2 (3 x 10mL). The combined organic phase was washed with H_2O (2 x 10 mL), dried over $MgSO_4$ and evaporated. Flash chromatography over silica gel.



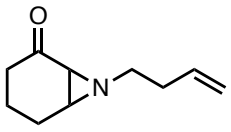
7-(hex-5-enyl)-7-azabicyclo[4.1.0]heptan-2-one (5.9). Flash chromatography (5:95 EtOAc-Hexanes) gave a yellow oil (0.6315 g, 86%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 5.68-5.62 (m, 1 H), 4.41-4.39 (m, 2 H), 5.26-5.20 (m, 2 H), 2.84 (t, 1 H, J = 2.72 Hz), 2.38-2.32 (m, 3 H), 2.23-2.20 (1 H), 1.76-1.68 (m, 2 H); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 203.8, 138.5, 115.3, 51.4, 42.9, 41.9, 36.8, 33.5, 27.1, 26.3, 22.6, 17.2; **HRMS-ESI:** calcd. for $C_{17}H_{19}NO_2$ $[M+H]^+$: 194.1539, found: 194.1539.



6-(hex-5-enyl)-6-azabicyclo[3.1.0]hexan-2-one (5.10). Flash chromatography (5:95 EtOAc-Hexanes) gave a yellow oil (0.2310 g, 42%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 5.67-5.55 (m, 1 H), 4.83-4.77 (m, 2 H), 2.96 (d, 1 H, *J* = 8.12 Hz), 2.84 (t, 2 H, *J* = 2.71 Hz), 2.69 (dt, 1 H, *J* = 8.12, 1.72 Hz), 2.51 (t, 1 H, *J* = 7.84 Hz), 2.14-1.98 (m, 4 H), 1.51-1.58 (m, 4 H); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 194.4, 138.5, 115.3, 51.4, 41.1, 41.0, 36.9, 33.5, 30.5, 27.1, 26.3; **HRMS-ESI:** calcd. for $C_{17}H_{19}NO_2$ $[M+H]^+$: 208.1696, found: 208.1697.

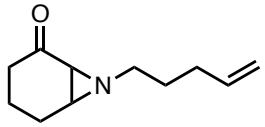


8-(hex-5-enyl)-8-azabicyclo[5.1.0]octan-2-one (5.11). Flash chromatography (5:95 EtOAc-Hexanes) gave a yellow oil (0.2310 g, 66%). Yield: 51% **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 5.68-5.56 (m, 1 H), 4.84-4.74 (m, 2 H), 2.95 (d, 1 H, *J* = 8.1 Hz), 2.80 (t, 2 H, *J* = 2.7 Hz), 2.65-2.37 (m, 3 H), 2.10-1.73 (m, 6 H), 1.62-1.44 (m, 6 H); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 203.8, 138.5, 115.3, 51.4, 42.9, 42.1, 38.7, 33.5, 27.8, 27.1, 26.3, 26.0, 25.2; **HRMS-ESI:** calcd. for $C_{17}H_{19}NO_2$ $[M+H]^+$: 270.1489, found: 270.1493.

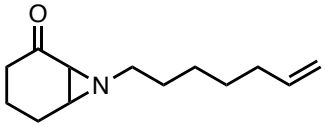


7-(but-3-enyl)-7-azabicyclo[4.1.0]heptan-2-one (5.13). Flash chromatography (5:95 EtOAc-Hexanes) gave a yellow oil (0.2310 g, 40%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 5.57-5.50 (m, 1 H), 4.86-4.80 (m, 2 H), 3.40 (t, 2 H, *J* = 2.7 Hz), 2.69 (d, 1 H, *J* = 8.1 Hz), 2.50-2.27 (m, 5 H), 2.00-1.73 (m, 4 H); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 203.8,

133.3, 117.5, 49.2, 42.9, 41.9, 36.8, 22.6, 17.2; **HRMS-ESI:** calcd. for $C_{17}H_{19}NO_2$ $[M+H]^+$: 166.1226, found: 166.1230.



7-(pent-4-enyl)-7-azabicyclo[4.1.0]heptan-2-one (5.14). Flash chromatography (5:95 EtOAc-Hexanes) gave a yellow oil (0.2310 g, 49%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 5.69-5.58 (m, 1 H), 4.85-4.76 (m, 2 H), 2.91 (t, 2 H, *J* = 2.7 Hz), 2.72 (d, 1 H, *J* = 8.1 Hz), 2.49-2.32 (m, 3 H), 2.03-1.71 (m, 8 H); **^{13}C NMR (**$CDCl_3$, 100 MHz): δδ (ppm) 203.8, 135.0, 117.1, 53.4, 42.9, 41.9, 36.8, 26.3, 22.6, 17.2; **HRMS-ESI:** calcd. for $C_{17}H_{19}NO_2$ $[M+H]^+$: 180.1383, found: 180.1378.

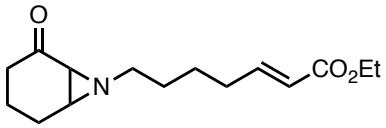


7-(hept-6-enyl)-7-azabicyclo[4.1.0]heptan-2-one (5.15). Flash chromatography (5:95 EtOAc-Hexanes) gave a yellow oil (0.1585 g, 77%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 5.67-5.56 (m, 1 H), 4.83-4.77 (m, 2 H), 2.74 (t, 2 H, *J* = 2.7 Hz), 2.59 (d, 1 H, *J* = 8.1 Hz), 2.54-2.37 (m, 3 H), 2.05-1.73 (m, 6 H), 1.63-1.57 (m, 2 H), 1.49-1.30 (m, 4 H); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 203.8, 138.5, 115.3, 51.4, 42.9, 41.9, 36.8, 34.0, 33.7, 26.7, 26.3, 22.6, 17.2; **HRMS-ESI:** calcd. for $C_{17}H_{19}NO_2$ $[M+H]^+$: 208.1696, found: 208.1695.

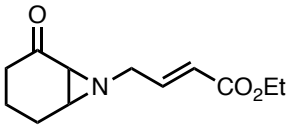
Cross metathesis using Grubbs Cat.

To a solution of Aziridino keto (4.51 mmol) and ethyl acrylate (15 mmol) in 5 ml of CH_2Cl_2 was added 1 mol% Hoveyda-Grubbs Catalyst$^{(TM)}$ 2nd Generation. Solution was refluxed for 2 h. The reaction was then ran through a short bed of celite, and washed with

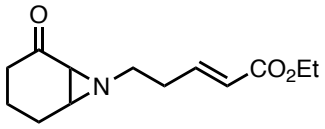
CH_2Cl_2. Solvent was evaporated under reduced pressure. Flash chromatography over silica gel gave the Aziridino keto ester.



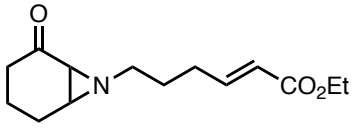
(*E*)-ethyl 7-(2-oxo-7-azabicyclo[4.1.0]heptan-7-yl)hept-2-enoate (5.19). Flash chromatography (5:95 EtOAc-Hexanes) gave a yellow oil (0.6932 g, 83%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.23 (dt, 1 H, *J* = 15.8, 6.8 Hz), 6.08 (d, 1 H, *J* = 15.8 Hz), 4.21 (q, 2 H, *J* = 7.1 Hz), 2.78 (t, 2 H, *J* = 2.7 Hz), 2.59 (d, 2 H, *J* = 8.1 Hz), 2.53-2.37 (m, 3 H), 2.24 (dd, 2 H, *J* = 8.1, 8.0 Hz), 2.07-1.77 (m, 4 H), 1.63-1.43 (m, 4 H), 1.25 (t, 3 H, *J* = 7.1 Hz); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 203.8, 166.1, 148.4, 122.2, 60.1, 51.4, 42.9, 41.9, 36.8, 29.8, 27.1, 26.3, 22.6, 17.2, 14.1; **HRMS-ESI:** calcd. for $C_{15}H_{23}NO_3$ $[M+Na]^+$: 288.1570, found: 288.1571.



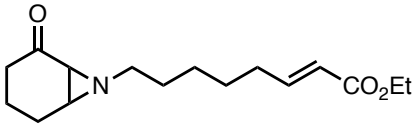
(3S,3aR,7aS)-1-allyl-3-phenylhexahydro-1H-indole-2,4-dione (5.20). Flash chromatography (5:95 EtOAc-Hexanes) gave a yellow oil (0.1122 g, 62%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.30 (dt, 1 H, *J* = 15.8, 6.8 Hz), 6.14 (d, 1 H, *J* = 15.8 Hz), 4.11 (q, 2 H, *J* = 7.1 Hz), 3.48 (d, 2 H, *J* = 8.1 Hz), 2.67 (d, 1 H, *J* = 8.1 Hz), 2.55-2.29 (m, 3 H), 2.10-1.81 (m, 4 H), 1.18 (t, 3 H, *J* = 7.1 Hz); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 203.6, 166.5, 126.1, 120.8, 60.1, 49.2, 42.9, 41.9, 36.8, 22.6, 17.2, 14.4; **HRMS-ESI:** calcd. for $C_{17}H_{19}NO_2$ $[M+H]^+$: 224.1281, found: 224.1285.



(*E*)-ethyl 4-(2-oxo-7-azabicyclo[4.1.0]heptan-7-yl)but-2-enoate (5.21). Flash chromatography (5:95 EtOAc-Hexanes) gave a yellow oil (0.0451 g, 84%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.19 (dt, 1 H, *J* = 15.8, 6.8 Hz), 6.10 (d, 1 H, *J* = 15.8 Hz), 4.22 (q, 2 H, *J* = 7.1 Hz), 3.05 (t, 2 H, *J* = 2.7 Hz), 2.70 (d, 1 H, *J* = 8.1 Hz), 2.54-2.38 (m, 5 H), 2.03-1.68 (m, 4 H), 1.17 (t, 3 H, *J* = 7.1 Hz); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 203.7, 166.1, 131.0, 122.2, 60.1, 53.4, 42.9, 41.9, 36.8, 26.3, 22.2, 17.4, 14.3; **HRMS-ESI:** calcd. for $C_{17}H_{19}NO_2$ $[M+H]^+$: 238.1438, found: 238.1437.

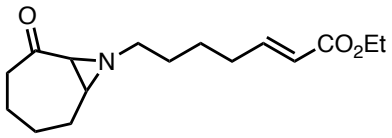


(*E*)-ethyl 6-(2-oxo-7-azabicyclo[4.1.0]heptan-7-yl)hex-2-enoate (5.22). Flash chromatography (5:95 EtOAc-Hexanes) gave a yellow oil (0.0389 g, 46%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.24 (dt, 1 H, *J* = 15.8, 6.8 Hz), 6.12 (d, 1 H, *J* = 15.8 Hz), 4.18 (q, 2 H, *J* = 7.1 Hz), 2.81 (t, 2 H, *J* = 2.7 Hz), 2.69 (d, 1 H, *J* = 8.1 Hz), 2.51-2.38 (m, 3 H), 2.13-1.98 (m, 2 H), 2.01-1.72 (m, 6 H), 1.28 (t, 3 H, *J* = 7.1 Hz);; **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 203.9, 166.1, 149.0, 122.2, 60.1, 51.4, 42.9, 41.9, 36.8, 27.1, 26.3, 22.6, 17.4, 14.2; **HRMS-ESI:** calcd. for $C_{17}H_{19}NO_2$ $[M+H]^+$: 252.1594, found: 252.1594.

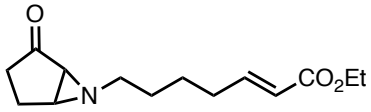


(*E*)-ethyl 8-(2-oxo-7-azabicyclo[4.1.0]heptan-7-yl)oct-2-enoate (5.23). Flash chromatography (5:95 EtOAc-Hexanes) gave a yellow oil (0.0296 g, 94%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.23 (dt, 1 H, *J* = 15.8, 6.8 Hz), 6.09 (d, 1 H, *J* = 15.8 Hz), 4.22 (q,

2 H, *J* = 7.1 Hz), 2.84 (t, 1 H, *J* = 2.7 Hz), 2.69 (d, 2 H, *J* = 8.1 Hz), 2.51-2.38 (m, 3 H), 2.22 (dd, 2 H, *J* = 8.1, 8.0 Hz), 2.05-1.73 (m, 4 H), 1.63-1.58 (m, 2 H), 1.52-1.32 (m, 4 H), 1.20 (t, 3 H, *J* = 7.1 Hz); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 203.8, 166.1, 148.4, 122.2, 60.1, 51.4, 42.9, 41.9, 36.8, 34.0, 33.1, 26.7, 26.3, 22.6, 17.2, 14.1; **HRMS-ESI:** calcd. for $C_{17}H_{19}NO_2$ $[M+H]^+$: 280.1907, found: 280.1902.



(*E*)-ethyl 7-(2-oxo-8-azabicyclo[5.1.0]octan-8-yl)hept-2-enoate (5.24). Flash chromatography (5:95 EtOAc-Hexanes) gave a yellow oil (0.0594 g, 66%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.24 (dt, 1 H, *J* = 15.8, 6.8 Hz), 6.12 (d, 1 H, *J* = 15.8 Hz), 4.24 (q, 2 H, *J* = 7.1 Hz), 2.95 (d, 1 H, *J* = 8.1 Hz), 2.80 (t, 2 H, *J* = 2.7 Hz), 2.64-2.55 (m, 2 H), 2.45-2.39 (m, 1 H), 2.25-2.07 (m, 3 H), 1.94-1.72 (m, 3 H), 1.62-1.44 (m, 6 H), 1.19 (t, 3 H, *J* = 7.1 Hz); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 204.8, 166.1, 148.4, 122.2, 60.1, 51.4, 42.9, 41.5, 38.1, 29.5, 27.7, 27.1, 26.2, 26.3, 25.6, 14.3; **HRMS-ESI:** calcd. for $C_{17}H_{19}NO_2$ $[M+H]^+$: 280.1907, found: 280.1907.

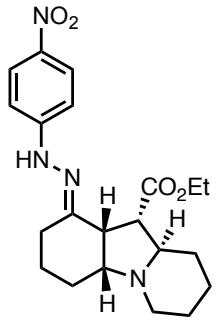


(*E*)-ethyl 7-(2-oxo-6-azabicyclo[3.1.0]hexan-6-yl)hept-2-enoate (5.25). Flash chromatography (5:95 EtOAc-Hexanes) gave a yellow oil (0.0852 g, 75%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.23 (dt, 1 H, *J* = 15.8, 6.8 Hz), 6.09 (d, 1 H, *J* = 15.8 Hz), 4.20 (q, 2 H, *J* = 7.1 Hz), 2.96 (d, 1 H, *J* = 8.1 Hz), 2.84 (t, 2 H, *J* = 2.7 Hz), 2.67-2.61 (m, 1 H), 2.53-2.48 (m, 2 H), 2.34-2.10 (m, 4 H), 1.66-1.44 (m, 4 H), 1.18 (t, 3 H, *J* = 7.1 Hz); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 194.4, 166.5, 148.2, 122.2, 60.3, 51.4, 41.8, 41.6, 36.7, 30.1,

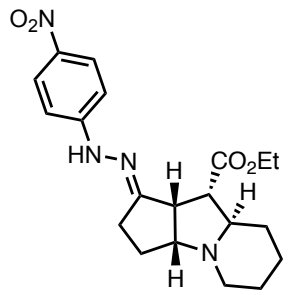
29.9, 27.1, 26.2, 14.7; **HRMS-ESI:** calcd. for $C_{17}H_{19}NO_2$ $[M+H]^+$: 270.1489, found: 270.1493.

Cyclization

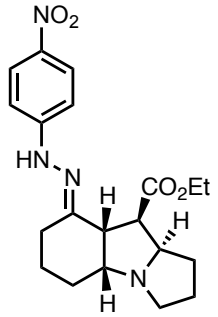
1-[3,5-bis(trifluoromethyl)phenyl]-3-[(1R,2R)-(-)-2-(dimethylamino)cyclohexyl]thiourea (.001 mmol) was added to a solution of 4-nitorphenylhydrazine (.10 mmol), aziridino keto ester (.10 mmol), and Hunig's base (1.0 mmol) in THF at room temperature. Solution was stirred for 12 h, and then solvent was evaporated under reduced pressure. Flash chromatography over silica gel gave the azapolycycle.



(4a*R*,9a*R*,10*S*,10a*R*,*E*)-ethyl 1-(2-(4-nitrophenyl)hydrazono)dodecahydropyrido[1,2-*a*]indole-10-carboxylate (5.27). Ester **5.19** (0.0302 g, 0.08 mmol) was treated following general procedure **x**. Flash chromatography (15:85 EtOAc-Hexanes) gave an orange semisolid (0.0296 g, 65%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.12 (d, 2 H, *J* = 8.4 Hz), 6.90 (d, 2 H, *J* = 8.4 Hz), 4.17 (q, 2 H, *J* = 7.2 Hz), 3.25-3.17 (m, 1 H), 3.06-2.88 (m, 2 H), 2.87-2.70 (m, 2 H), 2.64-2.51 (m, 1 H), 2.36-2.33 (m, 1 H), 2.07-1.40 (m, 10 H), 1.22 (t, 3 H, *J* = 7.2 Hz); **^{13}C NMR** (**(**$CDCl_3$, 100 MHz): δ 172.3, 164.0, 145.6, 140.4, 118.9, 118.8, 117.9, 117.2, 66.6, 66.4, 61.2, 52.7, 41.9, 40.9, 31.0, 28.3, 26.9, 26.6, 26.3, 24.3, 14.8; **HRMS-ESI:** calcd. for $C_{21}H_{28}N_4O_4$ $[M+H]^+$: 401.2183, found: 401.2189.



(3a*R*,8a*R*,9*S*,9a*R*,*E*)-ethyl 1-(2-(4-nitrophenyl)hydrazono)decahydro-1*H*-cyclopenta[*b*]indolizine-9-carboxylate (5.28). Ester **5.25** (0.0302 g, 0.08 mmol) was treated following general procedure **x**. Flash chromatography (15:85 EtOAc-Hexanes) gave an orange semisolid (0.0296 g, 42%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.13 (d, 2 H, *J* = 8.4 Hz), 6.87 (d, 2 H, *J* = 8.4 Hz), 4.15 (q, 2 H, *J* = 7.1 Hz), 3.24-3.12 (m, 1 H), 3.22-3.13 (m, 2 H), 3.04-2.98 (m, 1 H), 2.87-2.78 (m, 2 H), 2.61-2.56 (m, 2 H), 2.04-1.85 (m, 4 H), 1.76-1.40 (m, 4 H), 1.24 (t, 3 H, *J* = 7.1 Hz); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 172.5, 153.8, 145.4, 140.4, 119.3, 118.9, 117.9, 117.2, 67.1, 66.4, 61.2, 52.7, 41.9, 40.9, 32.0, 31.3, 27.6, 26.6, 24.2, 14.1; **HRMS-ESI:** calcd. for $C_{17}H_{19}NO_2$ $[M+H]^+$: 387.3632, found: 387.3633.



(4a*R*,8a*R*,9*R*,9a*R*,*E*)-ethyl 8-(2-(4-nitrophenyl)hydrazono)decahydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylate (5.29). Ester (**5.22**) (0.0294 g, 0.12 mmol) was treated following general procedure **x**. Flash chromatography (15:85 EtOAc-Hexanes) gave an orange semisolid (0.0223 g, 49%). **^{1}H NMR** ($CDCl_3$, 400 MHz): 8.13 (d, 2 H, *J*

= 8.4 Hz), 6.89 (d, 2 H, *J* = 8.4 Hz), 4.13 (q, 2 H, *J* = 7.1 Hz), 3.50-3.43 (m, 1 H), 3.25-3.03 (m, 3 H), 2.99-2.89 (m, 2 H), 2.37-1.51 (m, 8 H), 1.24 (t, 3 H, *J* = 7.1 Hz); **^{13}C NMR (**$CDCl_3$, 100 MHz): δ 172.0, 164.2, 145.4, 140.4, 118.9, 118.2, 117.3, 117.1, 66.4, 66.3, 61.2, 49.9, 41.9, 40.9, 33.7, 28.3, 26.9, 26.5, 23.4, 14.2; **HRMS-ESI:** calcd. for $C_{17}H_{19}NO_2$ $[M+H]^+$: 387.3632, found: 387.3633.

1.7.9 Single crystal x-ray diffraction data

Data Collection: All measurements were made with a Bruker DUO platform diffractometer equipped with a 4K CCD APEX II detector and an Incoatec 30 Watt Cu microsource with compact multilayer optics. A hemisphere of data (2713 frames at 4 cm detector distance) was collected using a narrow-frame algorithm with scan widths of 0.50\% in omega and an exposure time of 30 s/frame. The data were integrated using the Bruker-Nonius SAINT program, with the intensities corrected for Lorentz factor, polarization, air absorption, and absorption due to variation in the path length through the detector faceplate. The data were scaled, and an absorption correction was applied using SADABS. Redundant reflections were averaged.

Figure 1. **Crystal structure of 2.38**

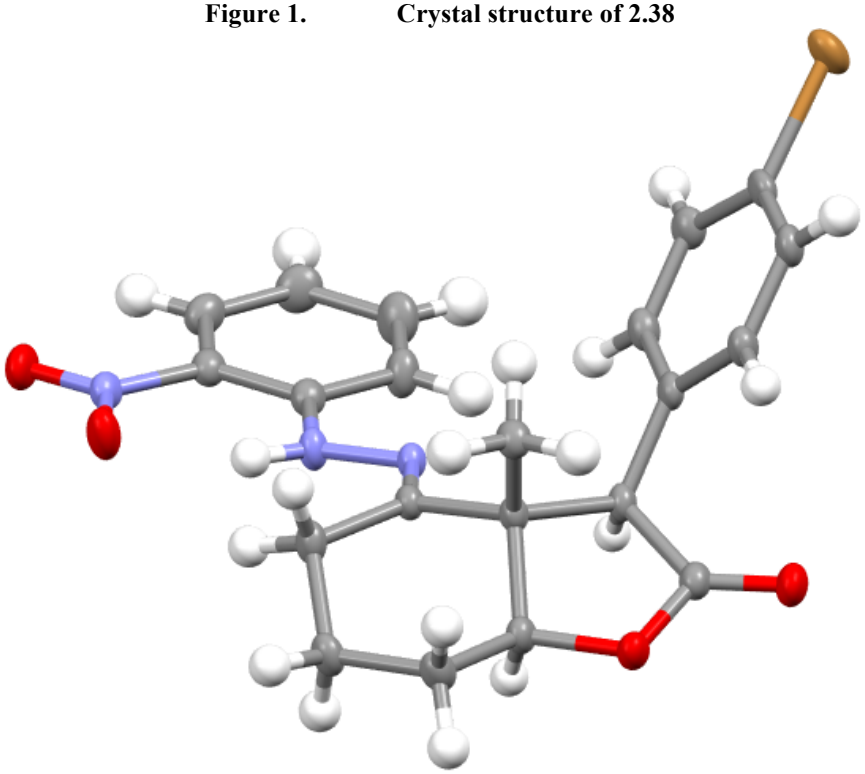


Table 29. **Crystal data and structure refinement for 2.38**

Empirical formula	$C_{21}H_{20}BrN_3O_4$
Formula weight	458.31
Temperature	123(2) K
Wavelength	1.54178 Å
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 9.844(2) Å α = 102.742(8)°
	b = 10.223(2)Å β = 94.719(10)°
	c = 10.396(2)Å γ = 107.032(7)°
Volume	963.5(3) A^3
Z, Calculated density	2, 1.580 Mg/m^3
Absorption coefficient	3.204 mm^{-1}
F(000)	468
Crystal color and shape	Orange thin plate
Crystal size	0.40 x 0.30 x 0.08 mm
Theta range for data collection	4.42 to 66.60°
Limiting indices	-11<=h<=11, -12<=k<=11, 0<=l<=12
Reflections collected / unique	6534 / 3163 [R(int) = 0.0310]
Completeness to theta = 66.60°	92.8 %
Absorption correction	Empirical
Max. and min. transmission	0.7528 and 0.5154
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3044 / 1 / 266
Goodness-of-fit on F^2	1.057
Final R indices [I>4sigma(I)]	R1 = 0.0359, wR2 = 0.0950
R indices (all data)	R1 = 0.0367, wR2 = 0.0972
Largest diff. peak and hole	0.956 and -0.471 $e.A^{-3}$

Figure 2. Crystal structure of 2.57

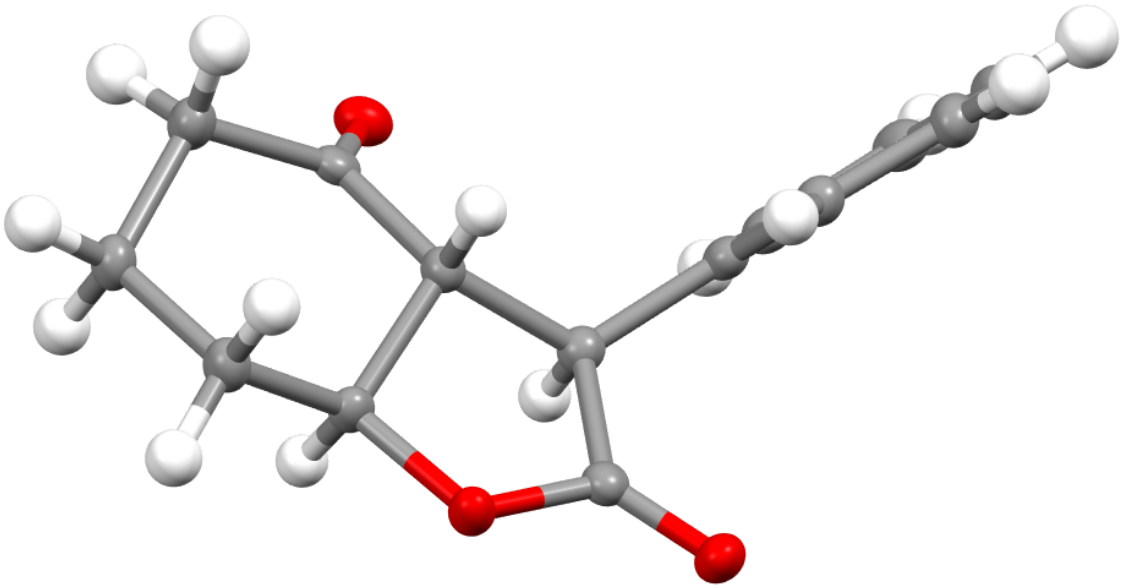


Table 30. **Crystal data and structure refinement for 2.57**

Empirical formula	$C_{14}H_{14}O_3$
Formula weight	230.25
Temperature	123(2) K
Wavelength	1.54178 Å
Crystal system, space group	Orthorhombic, P2(1)2(1)2(1)
Unit cell dimensions	a = 6.0024(1) Å α = 90°
	b = 9.6666(2) Å β = 90°
	c = 19.4769(4) Å γ = 90°
Volume	1130.10(4) A^3
Z, Calculated density	4, 1.353 Mg/m^3
Absorption coefficient	0.772 mm^{-1}
F(000)	488
Crystal color and shape	Orange thick plate
Crystal size	0.40 x 0.30 x 0.15 mm
Theta range for data collection	5.11 to 66.58 °
Limiting indices	-7<=h<=7, 0<=k<=10, 0<=l<=22
Reflections collected / unique	7707 / 1939 [R(int) = 0.0220
Completeness to theta = 66.58°	97.0 %
Absorption correction	Empirical
Max. and min. transmission	0.7528 and 0.6668
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1913 / 0 / 156
Goodness-of-fit on F^2	1.065
Final R indices [I>4sigma(I)]	R1 = 0.0231, wR2 = 0.0599
R indices (all data)	R1 = 0.0232, wR2 = 0.0602
Absolute structure parameter	0.52(16)
Extinction coefficient	0.0069(7)
Largest diff. peak and hole	0.172 and -0.136 $e.A^{-3}$

Figure 3. Crystal structure of 2.64

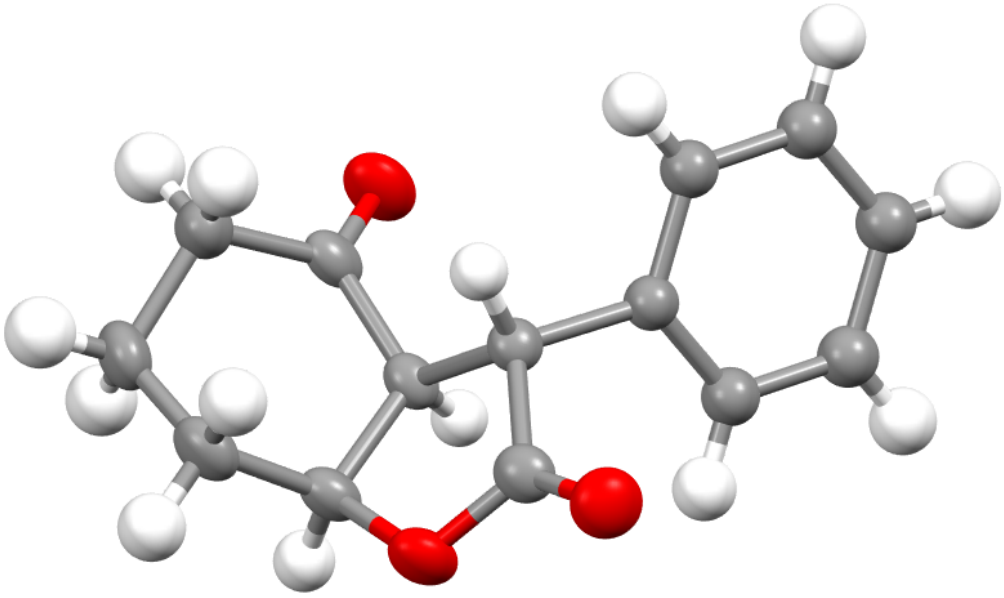


Table 31. **Crystal data and structure refinement for 2.64**

Empirical formula	$C_{14}H_{14}O_3$
Formula weight	230.25
Temperature	173(2) K
Wavelength	1.54178 Å
Crystal system, space group	Monoclinic, P2(1)
Unit cell dimensions	a = 6.3178(4) Å α = 90°
	b = 9.6038(5) Å β = 100.034(3)°
	c = 9.8028(5) Å γ = 90°
Volume	585.69(6) A^3
Z, Calculated density	2, 1.306 Mg/m^3
Absorption coefficient	0.744 mm^{-1}
F(000)	244
Crystal color and shape	Colorless plate
Crystal size	0.35 x 0.35 x 0.05 mm
Theta range for data collection	6.50 to 66.53°
Limiting indices	-7<=h<=7, -11<=k<=11, -11<=l<=11
Reflections collected / unique	3856 / 2052 [R(int) = 0.0289]
Completeness to theta = 66.53°	99.2 %
Absorption correction	Empirical
Max. and min. transmission	0.7528 and 0.6456
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1984 / 1 / 126
Goodness-of-fit on F^2	1.055
Final R indices [I>4sigma(I)]	R1 = 0.0365, wR2 = 0.1007
R indices (all data)	R1 = 0.0391, wR2 = 0.1025
Absolute structure parameter	0.2(2)
Extinction coefficient	0.010(2)
Largest diff. peak and hole	0.166 and -0.190 $e.A^{-3}$

Figure 4. Crystal structure of 2.65

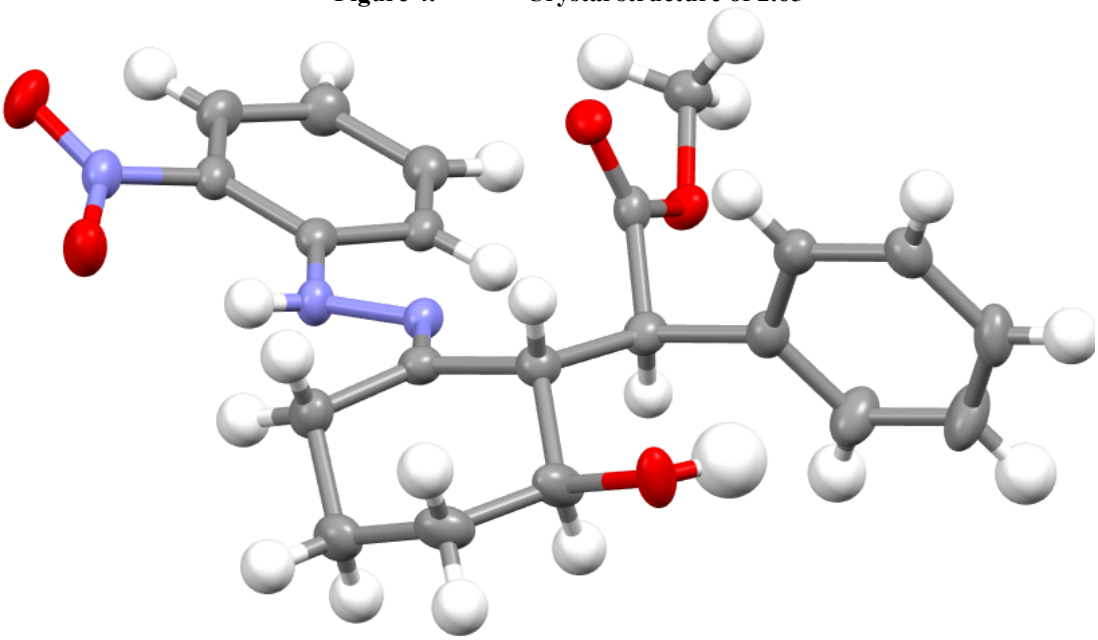


Table 32. **Crystal data and structure refinement for 2.65**

Empirical formula	$C_{21}H_{23}N_3O_5$
Formula weight	397.42
Temperature	123(2) K
Wavelength	1.54178 Å
Crystal system, space group	Monoclinic, I2/a
Unit cell dimensions	a = 22.6932(5) Å α = 90°
	b = 5.4053(1) Å β = 91.734(1)°
	c = 30.8647(9) Å γ = 90°
Volume	3784.24(16) $Å^3$
Z, Calculated density	8, 1.395 Mg/m^3
Absorption coefficient	0.833 mm^{-1}
F(000)	1680
Crystal color and shape	Orange flat column
Crystal size	0.40 x 0.06 x 0.03 mm
Theta range for data collection	2.86 to 66.66°
Limiting indices	-26<=h<=26, 0<=k<=6, 0<=l<=36
Reflections collected / unique	12937 / 3633 [R(int) = 0.0288]
Completeness to theta = 66.66°	97.1 %
Absorption correction	Empirical
Max. and min. transmission	0.7528 and 0.6211
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2863 / 4 / 291
Goodness-of-fit on F2	1.068
Final R indices [I>4sigma(I)]	R1 = 0.0340, wR2 = 0.0924
R indices (all data)	R1 = 0.0385, wR2 = 0.0978
Largest diff. peak and hole	0.199 and -0.250 e. $Å^{-3}$

Figure 5. **Crystal structure of 3.60**

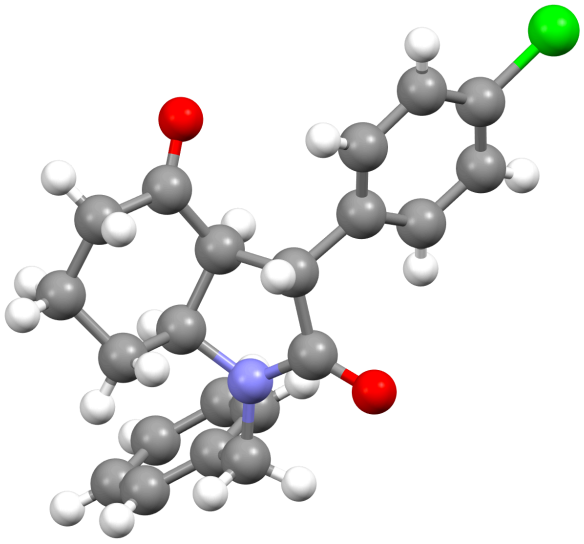


Table 33. **Crystal data structure and refinement for 3.60**

Empirical formula	$C_{21}H_{20}ClNO_2$
Formula weight	353.83
Temperature	123(2) K
Wavelength	1.54178 Å
Crystal system, space group	Monoclinic, P2(1)/c
Unit cell dimensions	a = 13.6557(4) Å α = 90°
	b = 8.6833(2) Å β = 113.237(1)°
	c = 16.1745(41) Å γ = 90°
Volume	1762.34(8) $Å^3$
Z, Calculated density	4, 1.334 Mg/m^3
Absorption coefficient	2.025 mm^{-1}
F (000)	744
Crystal color and shape	Pale orange thick plate
Crystal size	0.40 x 0.20 x 0.15 mm
Theta range for data collection	3.52 to 66.67°
Limiting indices	-16<=h<=15, -10<=k<=10, -14<=l<=18
Reflections collected /unique	11938 / 3055 [R (int) = 0.0228]
Completeness to theta = 66.50	98.0 %
Absorption correction	Empirical
Max. and min. transmission	0.7528 and 0.5384
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2974 / 0 / 227
Goodness-of-fit on F^2	1.057
Final R indices [I>4sigma(I)]	R1 = 0.0300, wR2 = 0.0781
R indices (all data)	R1 = 0.0306, wR2 = 0.0786
Largest diff. peak and hole	0.273 and -0.222 $e.Å^{-3}$

Figure 6. **Crystal structure of 3.35**

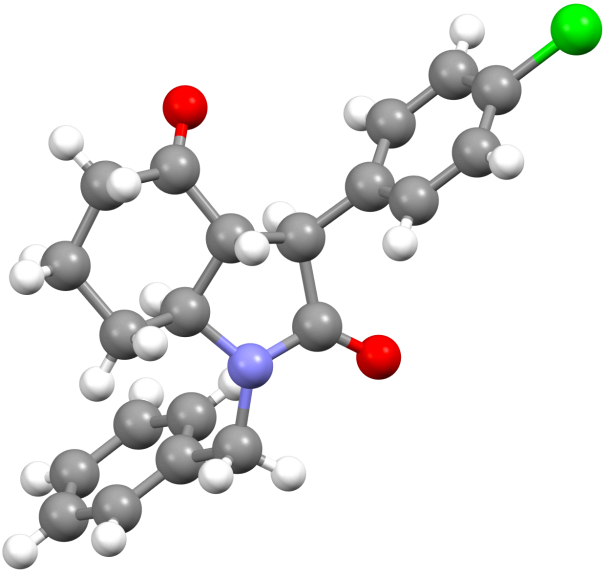


Table 34. **Crystal data structure and refinement for 3.35**

Empirical formula	$C_{21}H_{20}ClNO_2$
Formula weight	353.83
Temperature	123(2) K
Wavelength	1.54178 Å
Crystal system, space group	Monoclinic, P2(1)/c
Unit cell dimensions	a = 5.5366(1) Å α = 90°
	b = 13.5954(3) Å β = 91.751(1)°
	c = 22.9565(6) Å γ = 90°
Volume	1727.18(7) $Å^3$
Z, Calculated density	4, 1.361 Mg/m^3
Absorption coefficient	2.066 mm^{-1}
F (000)	744
Crystal color and shape	Yellow rectangular column
Crystal size	0.40 x 0.30 x 0.20 mm
Theta range for data collection	3.78 to 66.62°
Limiting indices	-6<=h<=6, 0<=k<=16, 0<=l<=27
Reflections collected /unique	11557 / 3077 [R (int) = 0.0238]
Completeness to theta = 66.50	96.7 %
Absorption correction	Empirical
Max. and min. transmission	0.7528 and 0.5748
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2974 / 0 / 227
Goodness-of-fit on F^2	1.084
Final R indices [I>4sigma(I)]	R1 = 0.0292, wR2 = 0.0747
R indices (all data)	R1 = 0.0295, wR2 = 0.0751
Largest diff. peak and hole	0.246 and -0.237 e. $Å^{-3}$

Figure 7. **Crystal structure of 3.101**

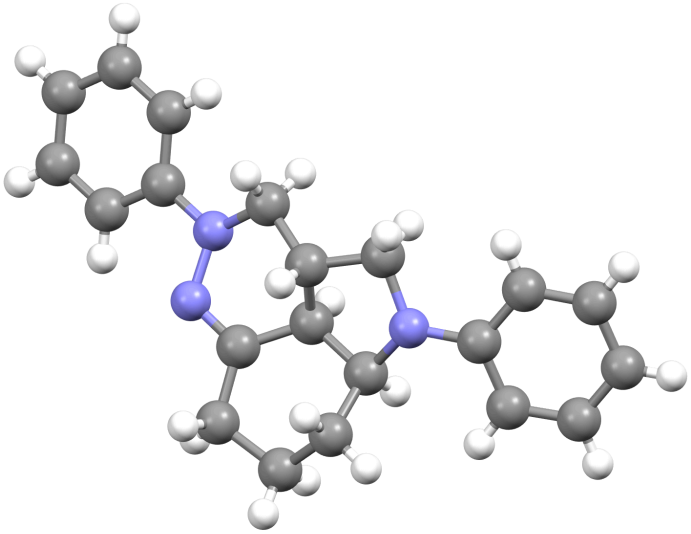


Table 35. **Crystal data structure and refinement for 3.101**

Empirical formula	$C_{21}H_{23}N_3$
Formula weight	317.42
Temperature	123(2) K
Wavelength	1.54178 Å
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 7.4425(3) Å α = 105.123(1)°
	b = 8.0451(3) Å β = 91.538(2)°
	c = 14.3142(5) Å γ = 92.074(2)°
Volume	826.26(5) $Å^3$
Z, Calculated density	2, 1.276 Mg/m^3
Absorption coefficient	0.586 mm^{-1}
F (000)	340
Crystal color and shape	Colorless block
Crystal size	0.35 x 0.30 x 0.20 mm
Theta range for data collection	3.20 to 66.62°
Limiting indices	-8<=h<=8, -9<=k<=9, 0<=l<=17
Reflections collected /unique	5540 / 2695 [R(int) = 0.0162]
Completeness to theta = 66.62	92.3 %
Absorption correction	Empirical
Max. and min. transmission	0.7528 and 0.6671
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2591 / 0 / 218
Goodness-of-fit on F^2	1.055
Final R indices [I>4sigma(I)]	R1 = 0.0348, wR2 = 0.0881
R indices (all data)	R1 = 0.0358, wR2 = 0.0893
Largest diff. peak and hole	0.239 and -0.182 e. $Å^{-3}$

Figure 8. Crystal structure of 4.26

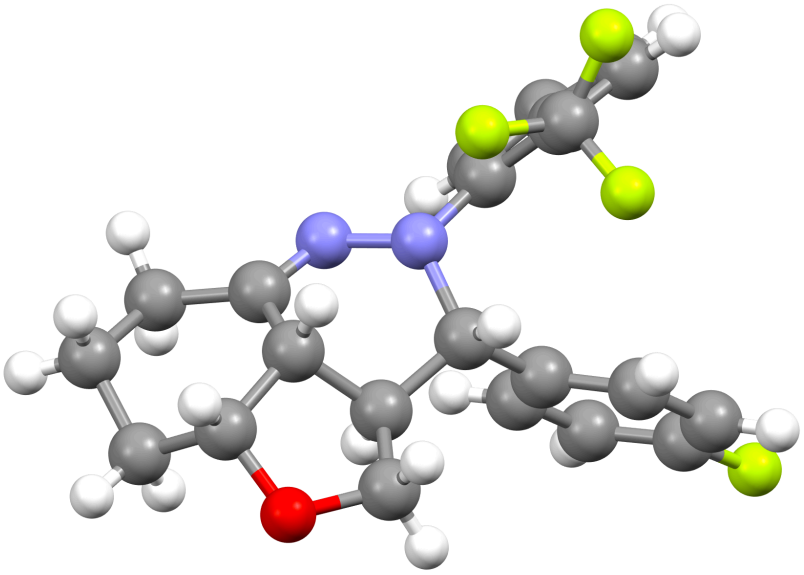


Table 36. **Crystal data and structure refinement for 4.26.**

Empirical formula	$C_{22}H_{20}F_4N_2O$
Formula weight	404.40
Temperature	123(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, P2(1)/c
Unit cell dimensions	a = 15.431(3) Å α = 90°
	b = 8.136(1) Å β = 91.829(2)°
	c = 15.105(2) Å γ = 90°
Volume	1895.4(5) $Å^3$
Z, Calculated density	4, 1.417 Mg/m^3
Absorption coefficient	0.115 mm^{-1}
F(000)	840
Crystal color and shape	Colorless thick plate
Crystal size	0.35 x 0.25 x 0.10 mm
Theta range for data collection	1.32 to 25.02°
Limiting indices	-18<=h<=15, -9<=k<=7, -17<=l<=17
Reflections collected / unique	11409 / 3336 [R(int) = 0.0117]
Completeness to theta = 25.02°	99.6 %
Absorption correction	Empirical
Max. and min. transmission	0.7452 and 0.6816
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2992 / 0 / 263
Goodness-of-fit on F2	1.036
Final R indices [I>4sigma(I)]	R1 = 0.0350, wR2 = 0.0837
R indices (all data)	R1 = 0.0389, wR2 = 0.0871
Largest diff. peak and hole	0.514 and -0.340 e. $Å^{-3}$

Figure 9. Crystal structure of 4.55

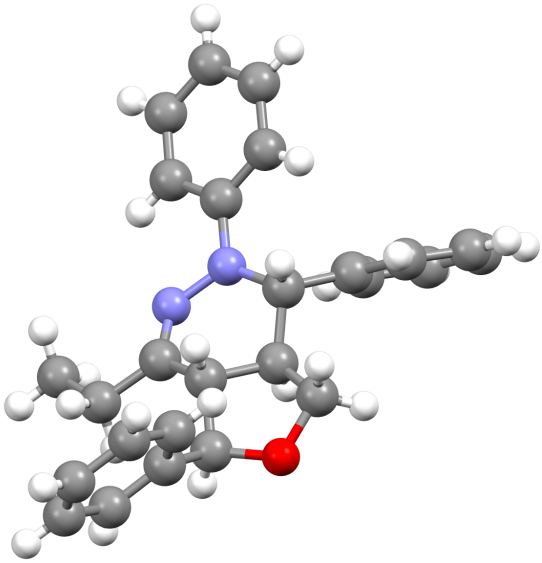


Table 37. **Crystal data and structure refinement for 4.55.**

Empirical formula	$C_{26}H_{26}N_2O$
Formula weight	382.49
Temperature	123(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, P2(1)/n
Unit cell dimensions	a = 16.586(2) Å α = 90°
	b = 14.730(2) Å β = 96.016(2)°
	c = 16.995(2) Å γ = 90°
Volume	4129.2(9) $Å^3$
Z, Calculated density	8, 1.231 Mg/m^3
Absorption coefficient	0.075 mm^{-1}
F(000)	1632
Crystal color and shape	Colorless thick plate
Crystal size	0.35 x 0.20 x 0.15 mm
Theta range for data collection	1.83 to 27.48°
Limiting indices	-21<=h<=21, 0<=k<=19, 0<=l<=22
Reflections collected / unique	30232 / 9783 [R(int) = 0.0132]
Completeness to theta = 27.48°	99.5 %
Absorption correction	Empirical
Max. and min. transmission	0.7456 and 0.7062
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7687 / 0 / 525
Goodness-of-fit on F2	1.010
Final R indices [I>4sigma(I)]	R1 = 0.0338, wR2 = 0.0865
R indices (all data)	R1 = 0.0428, wR2 = 0.0951
Largest diff. peak and hole	0.285 and -0.179 e. $Å^{-3}$

Figure 10. Crystal structure of 3.71

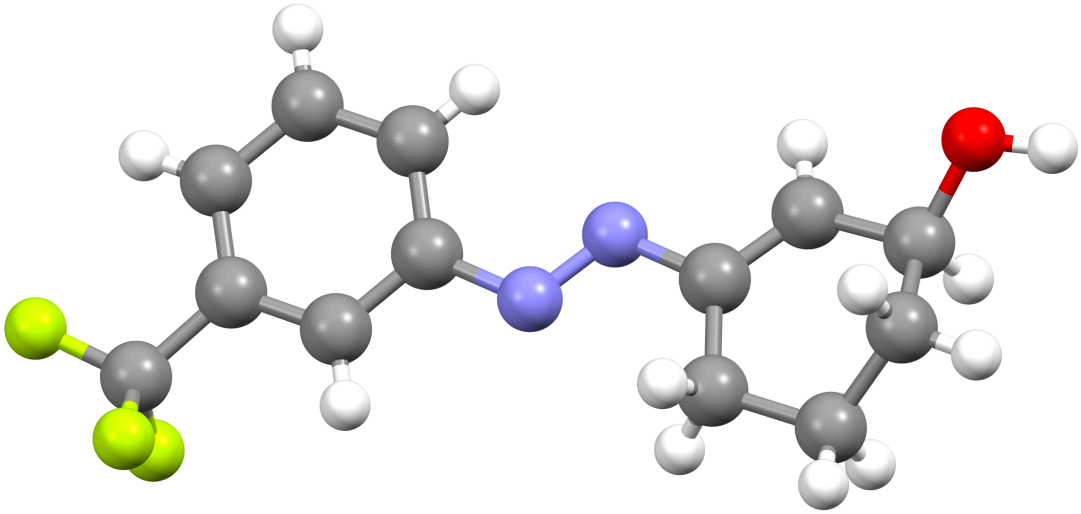


Table 38. **Crystal data and structure refinement for 3.71.**

Empirical formula	$C_{13}H_{13}F_3N_2O$
Formula weight	270.25
Temperature	123(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, P2(1)/c
Unit cell dimensions	a = 12.260(2) Å α = 90°
	b = 4.964(1) Å β = 90.954(2)°
	c = 20.129(3) Å γ = 90°
Volume	1224.9(4) $Å^3$
Z, Calculated density	4, 1.466 Mg/m^3
Absorption coefficient	0.125 mm^{-1}
F(000)	560
Crystal color and shape	Red-orange thick plate
Crystal size	0.25 x 0.25 x 0.10 mm
Theta range for data collection	2.02 to 27.48°
Limiting indices	-15<=h<=15, -6<=k<=6, -26<=l<=24
Reflections collected / unique	8818 / 2800 [R(int) = 0.0107]
Completeness to theta = 27.48°	99.3 %
Absorption correction	Empirical
Max. and min. transmission	0.7456 and 0.6900
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2446 / 2 / 178
Goodness-of-fit on F^2	1.045
Final R indices [I>4sigma(I)]	R1 = 0.0345, wR2 = 0.0943
R indices (all data)	R1 = 0.0388, wR2 = 0.0993
Largest diff. peak and hole	0.361 and -0.262 e. $Å^{-3}$

Figure 11. Crystal structure of 3.82

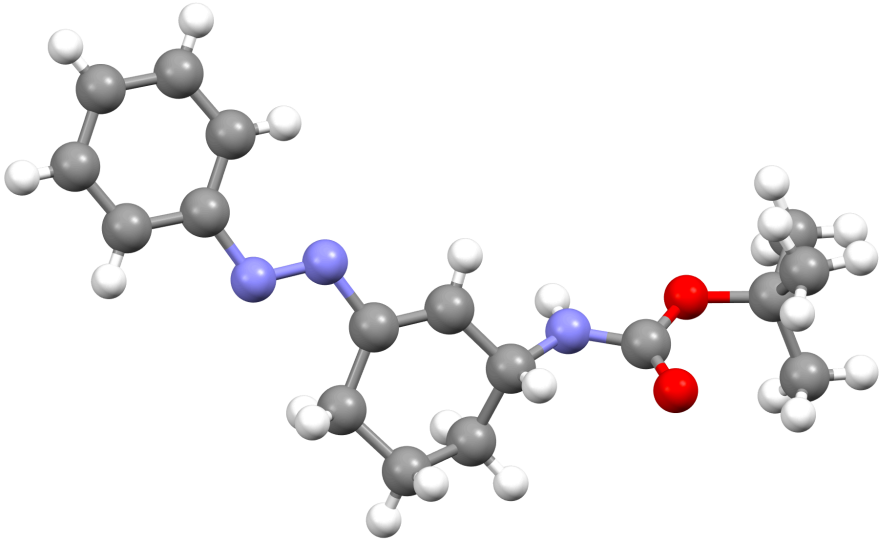


Table 39. **Crystal data and structure refinement for 3.82.**

Empirical formula	$C_{17}H_{23}N_3O_2$
Formula weight	301.38
Temperature	123(2) K
Wavelength	1.54178 Å
Crystal system, space group	Orthorhombic, P2(1)2(1)2(1)
Unit cell dimensions	a = 5.0768(2) Å α = 90°
	b = 10.5829(4) Å β = 90°
	c = 30.0958(12) Å γ = 90°
Volume	1616.97(11) $Å^3$
Z, Calculated density	4, 1.238 Mg/m^3
Absorption coefficient	0.661 mm^{-1}
F(000)	648
Crystal color and shape	Orange diamond column
Crystal size	0.30 x 0.15 x 0.15 mm
Theta range for data collection	4.43 to 66.60°
Limiting indices	-5<=h<=5, -12<=k<=12, -35<=l<=33
Reflections collected / unique	11085 / 2782 [R(int) = 0.0227]
Completeness to theta = 66.60°	98.7 %
Absorption correction	Empirical
Max. and min. transmission	0.7528 and 0.6362
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2766 / 0 / 206
Goodness-of-fit on F^2	1.089
Final R indices [I>4sigma(I)]	R1 = 0.0229, wR2 = 0.0574
R indices (all data)	R1 = 0.0231, wR2 = 0.0576
Absolute structure parameter	0.01(16)
Extinction coefficient	0.0073(4)
Largest diff. peak and hole	0.149 d -0.123 e. $Å^{-3}$

Figure 12. Crystal structure of 5.27

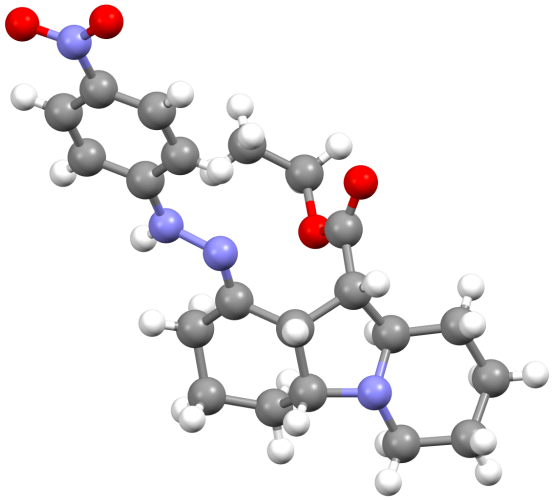


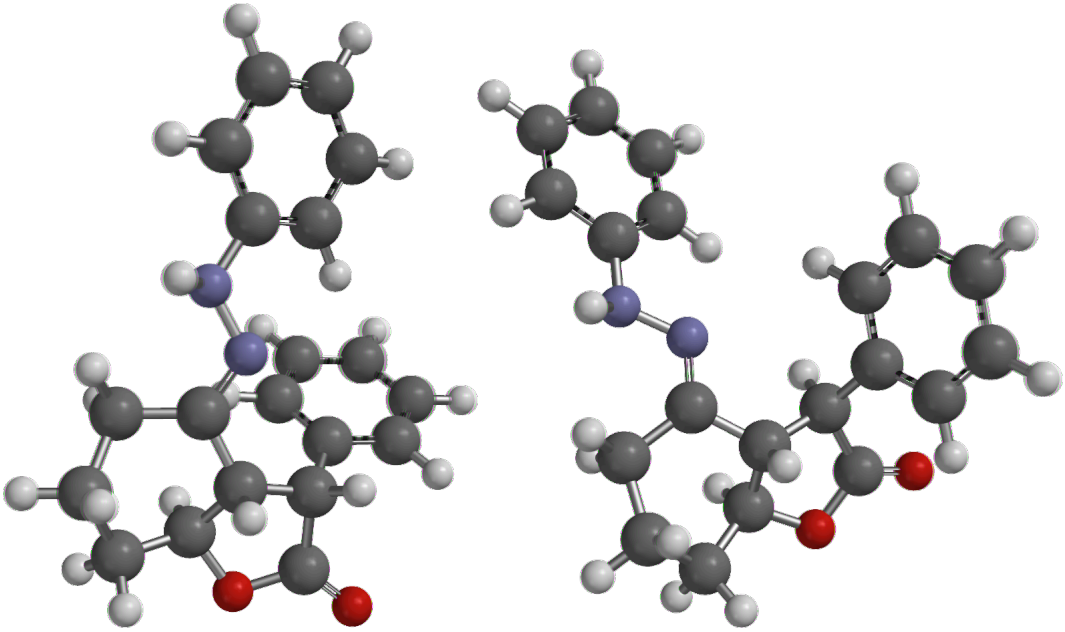
Table 40. **Crystal data and structure refinement for 5.27.**

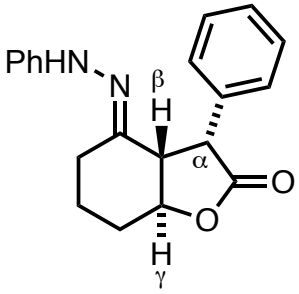
Empirical formula	$C_{21}H_{28}N_4O_4$
Formula weight	400.47
Temperature	123(2) K
Wavelength	1.54178 Å
Crystal system, space group	Monoclinic, C2/c
Unit cell dimensions	a = 16.6224(3) Å α = 90°
	b = 10.7563(2) Å β = 110.4145(7)°
	c = 23.6690(5) Å γ = 90°
Volume	3966.12(13) $Å^3$
Z, Calculated density	8, 1.341 Mg/m^3
Absorption coefficient	0.769 mm^{-1}
F(000)	1712
Crystal color and shape	Orange thin plate
Crystal size	0.40 x 0.20 x 0.08 mm
Theta range for data collection	3.99 to 66.67°
Limiting indices	-19<=h<=18, 0<=k<=11, 0<=l<=27
Reflections collected / unique	13658 / 3567 [R(int) = 0.0244]
Completeness to theta = 66.67	96.3 %
Absorption correction	Empirical
Max. and min. transmission	0.7528 and 0.5328
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3149 / 0 / 266
Goodness-of-fit on F^2	1.052
Final R indices [I>4sigma(I)]	R1 = 0.0314, wR2 = 0.0812
R indices (all data)	R1 = 0.0332, wR2 = 0.0835
Largest diff. peak and hole	0.205 and -0.175 e. $Å^{-3}$

1.7.10 Calculated relative energies mechanism

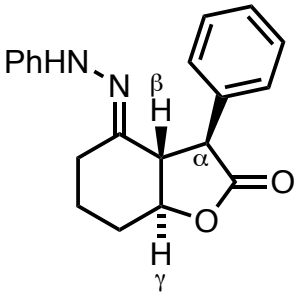
All relative energies were calculated using Semi-Empirical PM3 on Spartan Student version 6.1.9, Wavefunction, Inc.

The phenyl hydrazone CαH-CβH-*anti*-CβH-CγH-*anti* and CαH-CβH-*anti*-CβH-CγH-*syn* diastereomers of compound **2.20** showed a relative energy difference of 25.78 kcal/mol.





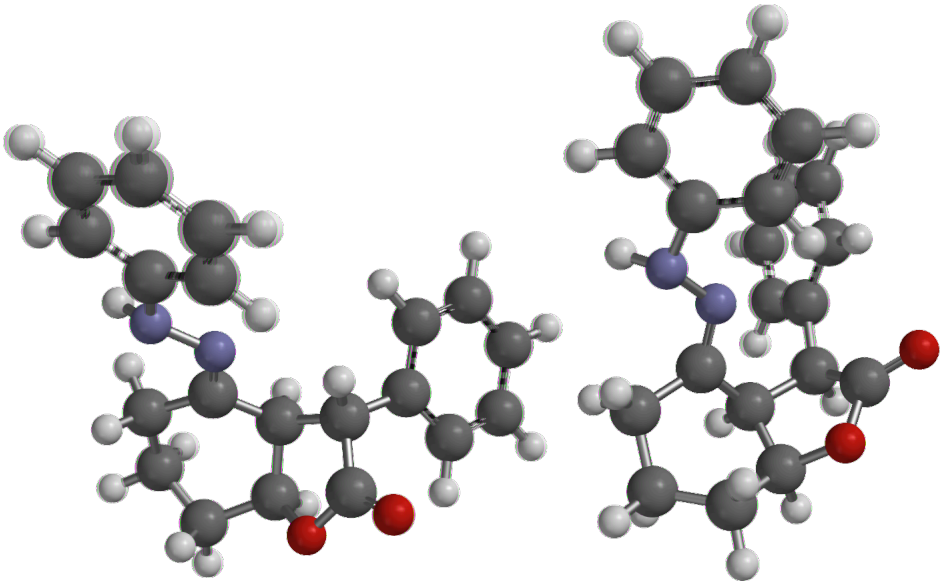
CαH-CβH-*anti*-CβH-CγH-*anti*
305.41 kcal/mol

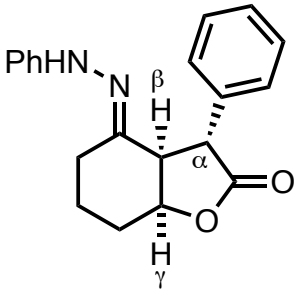


CαH-CβH-*anti*-CβH-CγH-*syn*
279.63 kcal/mol

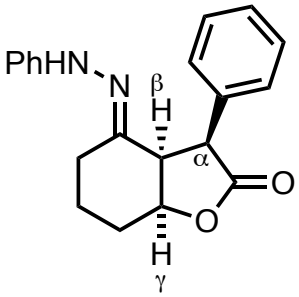
Figure 13. Calculated relative energies between the CαH-CβH-*anti*-CβH-CγH-*anti* and CαH-CβH-*anti*-CβH-CγH-*syn* diastereomers of the phenyl hydrazone of compound 2.20.

The phenyl hydrazone CαH-CβH-*syn*-CβH-CγH-*syn* and CαH-CβH-*syn*-CβH-CγH-*anti* diastereomers of compound **2.47** showed a relative energy difference of 29.94 kcal/mol.





CαH-CβH-*syn*-CβH-CγH-*syn*
266.24 kcal/mol



CαH-CβH-*syn*-CβH-CγH-*anti*
296.18 kcal/mol

Figure 14. Calculated relative energies between the CαH-CβH-*syn*-CβH-CγH-*syn* and CαH-CβH-*syn*-CβH-CγH-*anti* diastereomers of the phenyl hydrazone of compound 2.47.

The CαH-CβH-*syn*-CβH-CγH-*anti* and CαH-CβH-*anti*-CβH-CγH-diastereomers of compound **2.57** showed a relative energy difference of 31.34 kcal/mol.

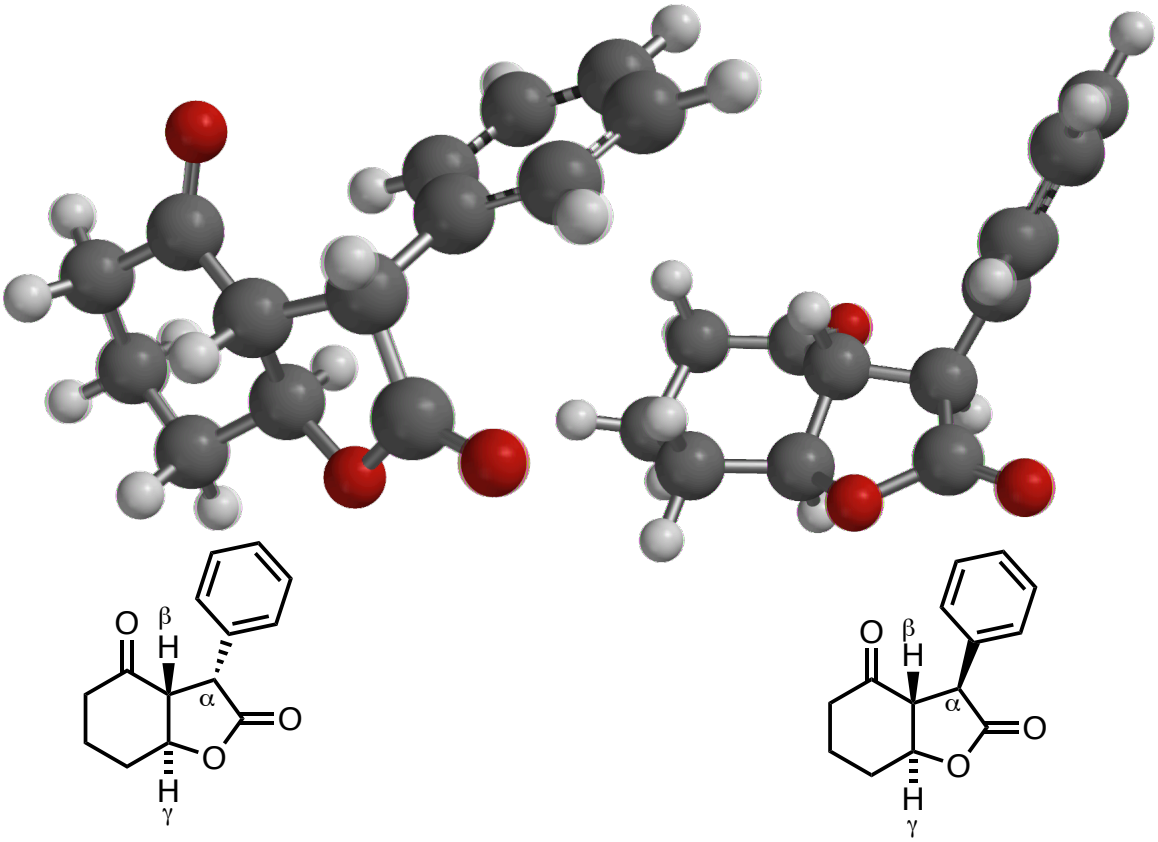


Figure 15. Calculated relative energies between the CαH-CβH-*syn*-CβH-CγH-*anti* and CαH-CβH-*anti*-CβH-CγH-*anti* diastereomers of compound 2.57.

The CαH-CβH-*anti*-CβH-CγH-*syn* and CαH-CβH-*syn*-CβH-CγH-*syn* diastereomers of compound **2.64** showed a relative energy difference of 31.75 kcal/mol.

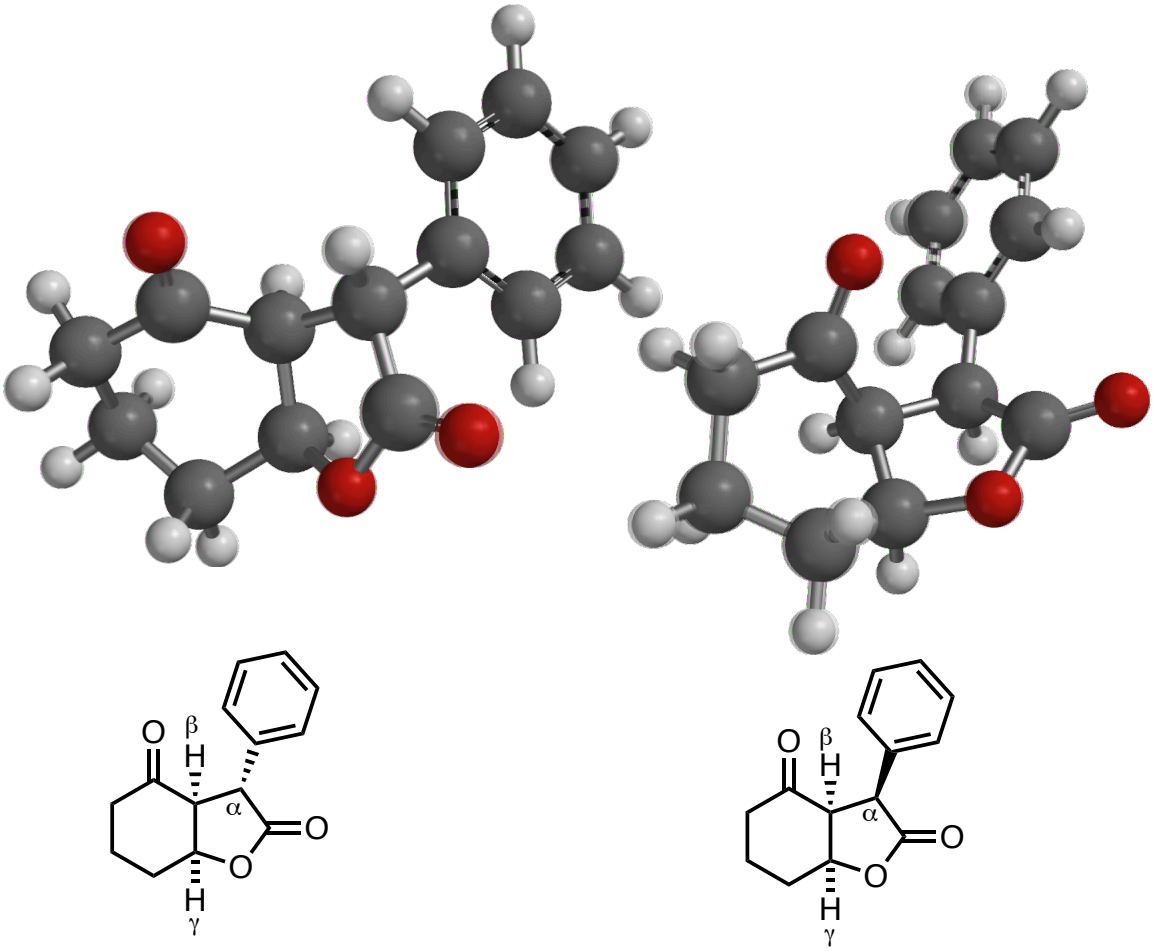
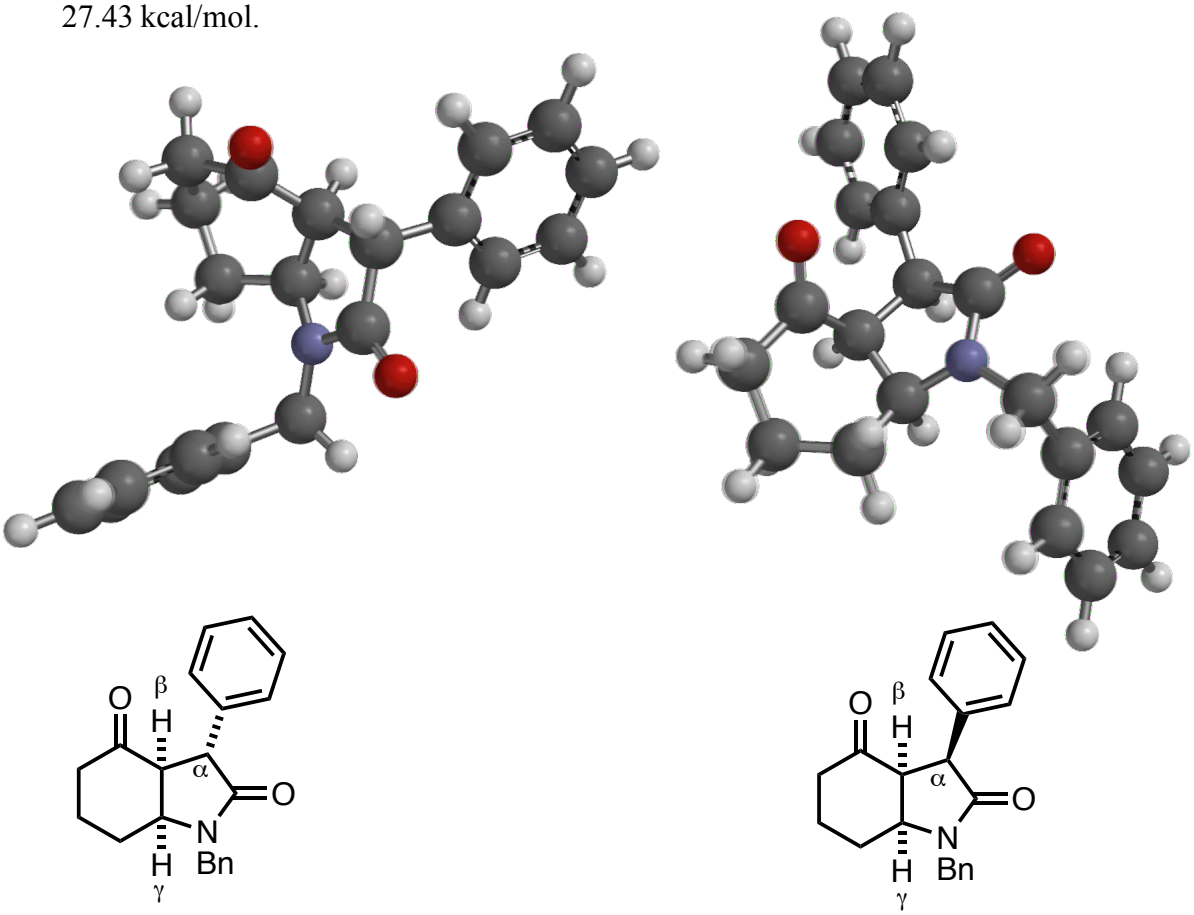


Figure 16. Calculated relative energies between CαH-CβH-*anti*-CβH-CγH-*syn* and CαH-CβH-*syn*-CβH-CγH-*syn* diastereomers of compound 2.64.

The CαH-CβH-*anti*-CβH-CγH-*syn* and CαH-CβH-*syn*-CβH-CγH-*syn* diastereomers of compound **3.57** showed a relative energy difference of 27.43 kcal/mol.

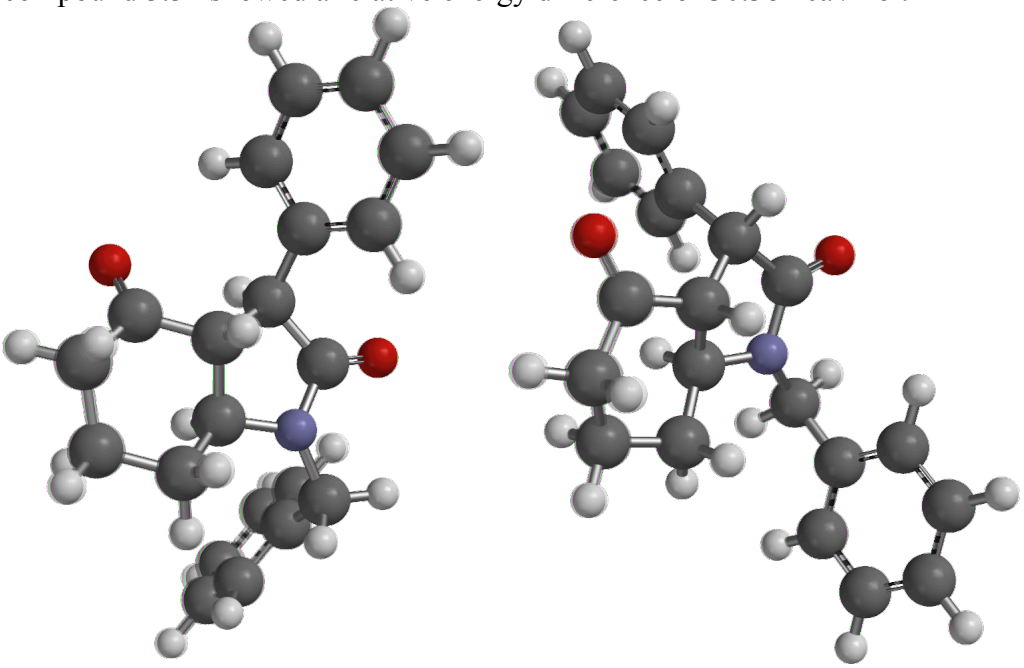


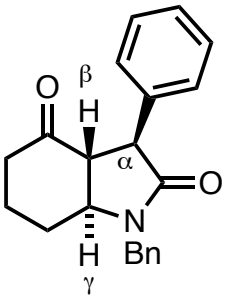
CαH-CβH-*syn*-CβH-CγH-*syn*
137.20 kcal/mol

CαH-CβH-*anti*-CβH-CγH-*syn*
164.63 kcal/mol

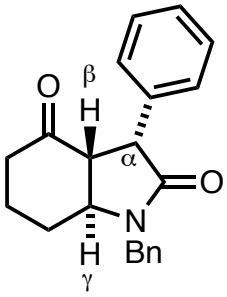
Figure 17. Calculated relative energies between CαH-CβH-*anti*-CβH-CγH-*syn* and CαH-CβH-*syn*-CβH-CγH-*syn* diastereomers of compound 3.57.

The CαH-CβH-*syn*-CβH-CγH-*anti* and CαH-CβH-*anti*-CβH-CγH-diastereomers of compound **3.32** showed a relative energy difference of 30.38 kcal/mol.





CαH-CβH-*anti*-CβH-CγH-*syn*
131.60 kcal/mol



CαH-CβH-*syn*-CβH-CγH-*syn*
161.98 kcal/mol

Figure 18. Calculated relative energies between the CαH-CβH-*syn*-CβH-CγH-*anti* and CαH-CβH-*anti*-CβH-CγH-*anti* diastereomers of compound 3.32.

The CαH-CβH-*syn*-CβH-CγH-*anti* and CαH-CβH-*anti*-CβH-CγH-diastereomers of compound **4.11** showed a relative energy difference of 13.06 kcal/mol.

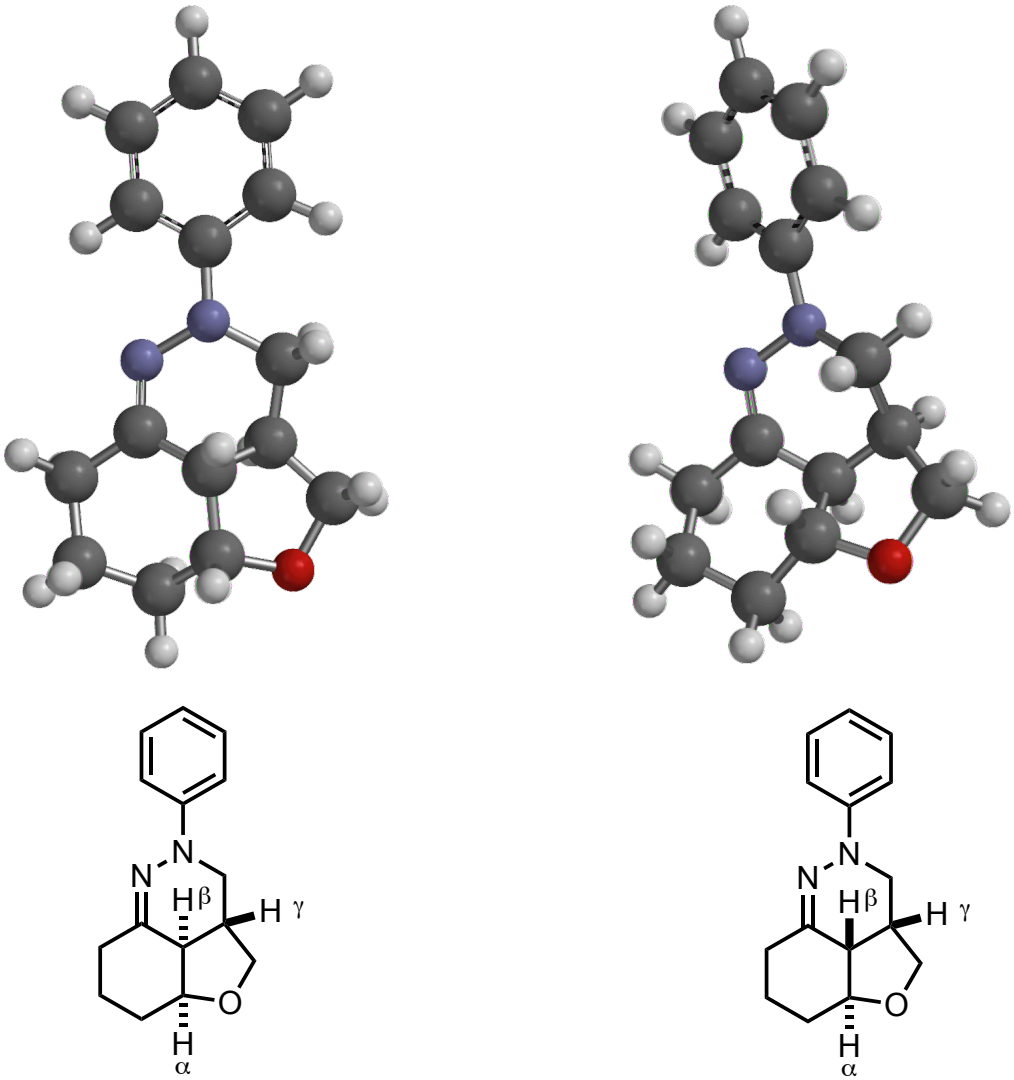
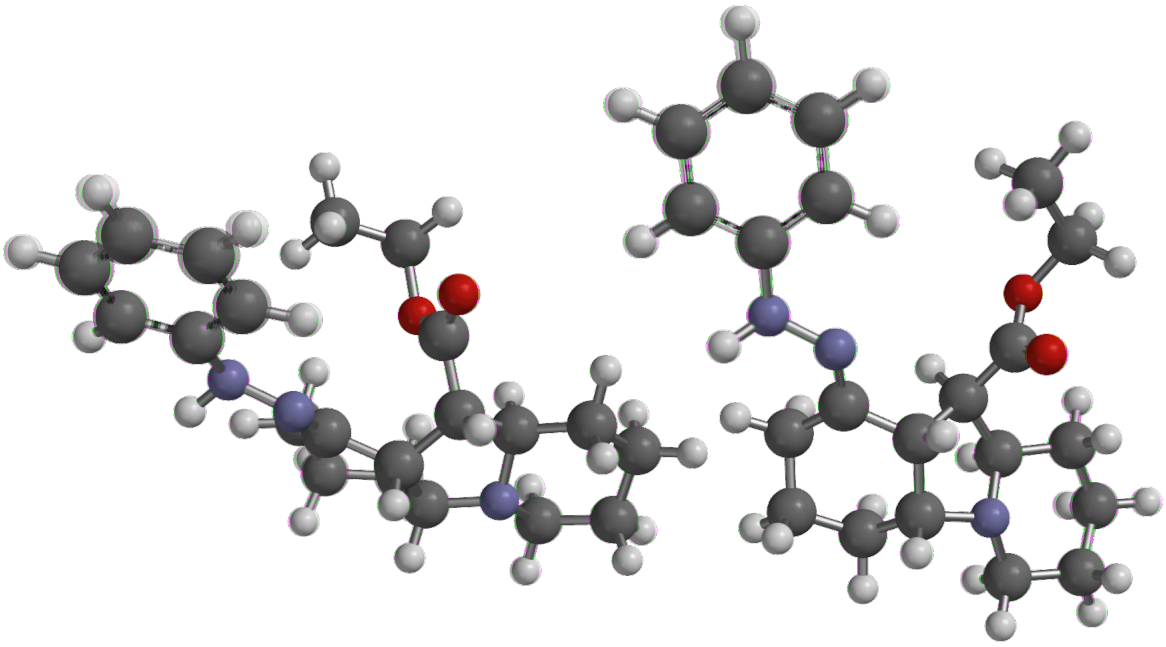
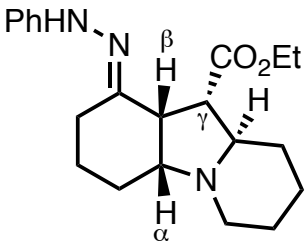


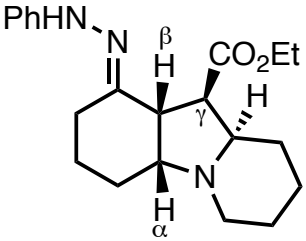
Figure 19. Calculated relative energies between the CαH-CβH-*syn*-CβH-CγH-*anti* compound 4.11 and CαH-CβH-*anti*-CβH-CγH-*syn* compound 4.94.

The CαH-CβH-*syn*-CβH-CγH-*anti* and CαH-CβH-*anti*-CβH-CγH-diastereomers of compound **5.27** showed a relative energy difference of 9.29 kcal/mol.





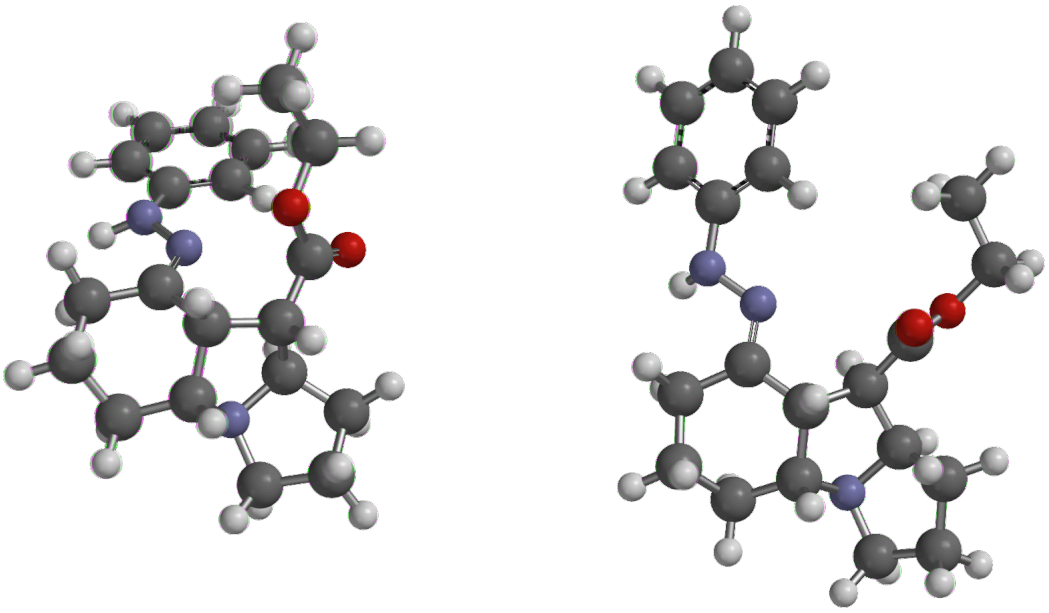
CαH-CβH-*syn*-CβH-CγH-*anti*
138.09 kcal/mol

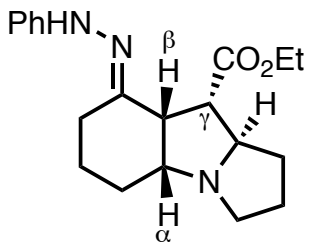


CαH-CβH-*syn*-CβH-CγH-*syn*
147.38 kcal/mol

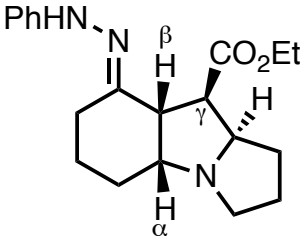
Figure 20. Calculated relative energies between the CαH-CβH-*syn*-CβH-CγH-*anti* and CαH-CβH-*syn*-CβH-CγH-*syn* diastereomers of compound 5.27.

The CαH-CβH-*syn*-CβH-CγH-*anti* and CαH-CβH-*anti*-CβH-CγH-diastereomers of compound **5.29** showed a relative energy difference of 6.94 kcal/mol.





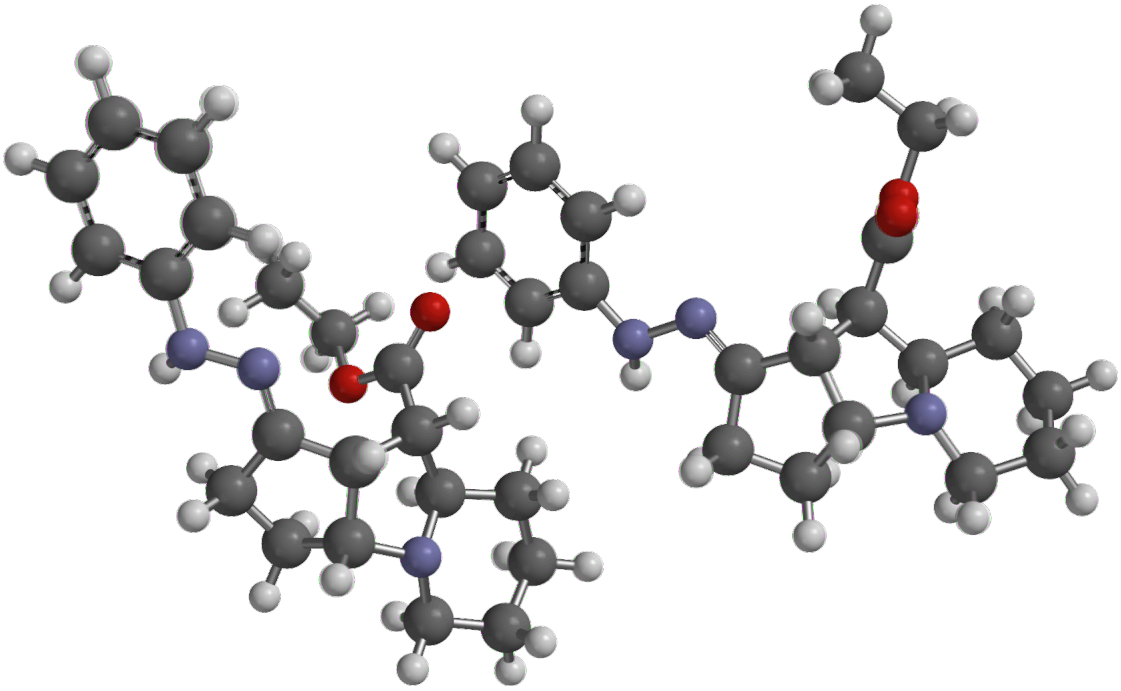
CαH-CβH-*syn*-CβH-CγH-*anti*
166.89 kcal/mol

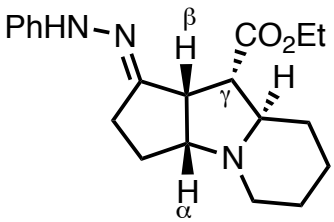


CαH-CβH-*syn*-CβH-CγH-*syn*
159.95 kcal/mol

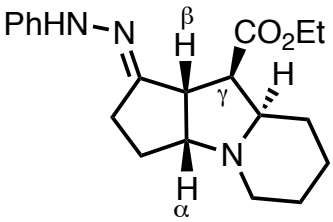
Figure 21. Calculated relative energies between the CαH-CβH-*syn*-CβH-CγH-*anti* and CαH-CβH-*syn*-CβH-CγH-*syn* diastereomers of compound 5.29.

The CαH-CβH-*syn*-CβH-CγH-*anti* and CαH-CβH-*anti*-CβH-CγH-diastereomers of compound **5.28** showed a relative energy difference of 7.66 kcal/mol.





CαH-CβH-*syn*-CβH-CγH-*anti*
130.09 kcal/mol



CαH-CβH-*syn*-CβH-CγH-*syn*
137.75 kcal/mol

Figure 22. Calculated relative energies between the CαH-CβH-*syn*-CβH-CγH-*anti* and CαH-CβH-*syn*-CβH-CγH-*syn* diastereomers of compound 5.28.

The CαH-CβH-*syn*-CβH-CγH-*anti* and CαH-CβH-*anti*-CβH-CγH-diastereomers of compound **5.27** intermediate showed a relative energy difference of 2.91 kcal/mol.

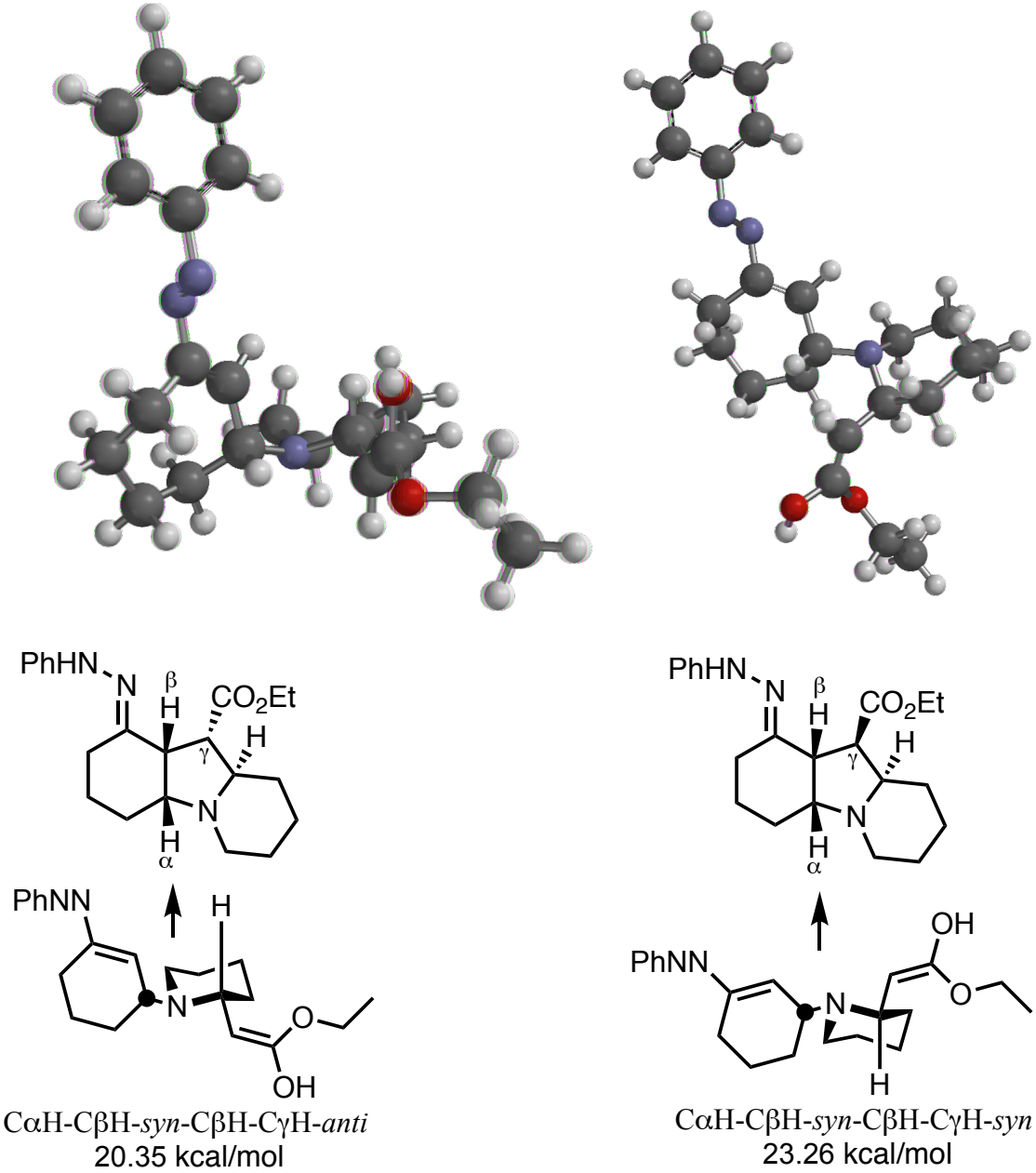


Figure 23. Calculated relative energies between the CαH-CβH-*syn*-CβH-CγH-*anti* and CαH-CβH-*syn*-CβH-CγH-*syn* intermediate diastereomers of compound 5.27.

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