NICKEL AND PALLADIUM CATALYZED ROUTES TO CARBOCYCLES AND HETEROCYCLES

by

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A dissertation submitted to the faculty of
The University of Utah
in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Department of Chemistry

The University of Utah

August 2015

The University of Utah Graduate School

STATEMENT OF DISSERTATION APPROVAL

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ABSTRACT

Transition metal-catalyzed synthesis of carbocycles and heterocycles is described. A Ni/NHC catalyst couples diynes to the C(α)−C(β) double bond of tropone, a type of reactions that is unprecedented for metal-catalyzed cycloadditions with aromatic tropone. Many different diynes were efficiently coupled to afford [5-6-7] fused tricyclic products, while [5-7-6] fused tricyclic compounds were obtained as minor byproducts in a few cases. The reaction has broad substrate scope and tolerates a wide range of functional groups, and excellent regioselectivity is found with unsymmetrical diynes. The mechanism of this interesting cycloaddition has been investigated using DFT calculations and it reveals an interesting 8π-insertion of tropone to afford [5-6-7] and [5-7-6] fused tricyclic products.

A unique and catalytic way to synthesize challenging eight-membered heterocycles is disclosed. The Ni/P(*p*-tol)$_3$ catalyst promoted the cycloaddition of a variety of 1,3-dienes with 3-azetidinones and 3-oxetanones to afford both monocyclic and bicyclic azocine and oxocine ring systems, respectively. Interestingly, the cycloaddition with 1,3-diene conjugated with a *p*-methoxylphenyl group led to a 3-piperidinone product instead of the azocine ring. The synthesis of the these interesting eight-membered heterocycles involved the challenging steps of C(sp^2)−C(sp^3) bond activation and C(sp^3)−C(sp^3) reductive elimination.

An efficient and convenient procedure that generates the active Ni(0) catalyst *in situ* from cheap, air stable Ni(II) precursors is developed for the [4+2]-cycloaddition of alkynes and 3-azetidinones. The reaction affords useful 3-dehydropiperidinones in comparable yields to the reported Ni(0) procedure. Additionally, the cycloaddition with 3-oxetanone afforded the 3-dehydropyranone product. The application of this methodology to the total synthesis of (+)-septicine is also described.

A protocol for the Suzuki-Miyaura coupling of heteroaryl boronic acids and vinyl chlorides that minimizes protodeboronation is disclosed. A combination of catalytic amounts of $Pd(OAc)_2$ and SPhos in conjunction with CsF in isopropanol effectively affords a variety of coupled products. Surprisingly, a dramatic temperature dependence in product selectivity was observed.

To my family

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LIST OF ABBREVIATIONS

BINAP – 2,2'-bis(diphenylphosphino)-1,1'-binaphthalene

Bnh – benzhydryl

Boc – *tert*-butoxycarbonyl

COD – cyclooctadiene

Cp – cyclopentadienyl

Cy – cyclohexyl

Cyp – cyclopentyl

$CyPPh_2$ – cyclohexyldiphenylphosphine

DCE – 1,2-dichloroethane

DCM – dichloromethane

DMAP – 4-dimethylaminopyridine

DMF - dimethylformamide

DPPB – 1,2-bis(diphenylphosphine)butane

DPPE – 1,2-bis(diphenylphosphino)ethane

DPPF – 1,1'-bis(diphenylphosphine)ferrocene

ESI – electron spray ionization

Et – ethyl

GC – gas chromatography

RT – room temperature

i-Pr – isopropyl

I*i*Pr – 1,3-diisopropyl-imidazol-2-ylidene

IMes – 1,3-bis-(2,4,6-trimethylphenyl)-imidazol-2-ylidene

IPr – 1,3-bis-(2,6-diisopropylphenyl)-imidazol-2-ylidene

m-CPBA – *meta*-chloroperbenzoic acid

$Ni(COD)_2$ – Bis(1,5-cyclooctadiene)nickel

nOe – nuclear Overhauser effect

NOESY-1D – one dimensional nuclear Overhauser spectroscopy

PCy_3 – tricyclohexylphosphine

PG – protecting group

PEt_3 – triethylphosphine

Ph – phenyl

P*n*Bu_3 – tri(n-butyl)phosphine

P(*o*-Tol)$_3$ – tri(o-tolyl)phosphine

PPh_3 – triphenylphosphine

SIPr – 1,3-bis(2,6-diisopropylphenyl)-imidazolin-2-ylidene

Skewphos - (2*S*,4*S*)-pentane-2,4-diylbis(diphenylphosphine)

Synphos – 6,6'-bis(diphenylphosphino)2,2',3,3'-tetrahydro-5,5'-bi-1,4-benzodioxin

t-Bu – tert-butyl

THF – tetrahydrofuran

TMS – trimethylsilyl

Tol- tolyl

Ts – tosyl

CHAPTER 1

TRANSITION METAL-CATALYZED CYCLOADDITION REACTIONS

Introduction

Carbocycles and heterocycles are ubiquitous in a variety of natural products, pharmaceuticals and agrochemicals. Cycloaddition reactions represent one of the most utilized approaches to construct these cyclic compounds, since they allow the formation of multiple bonds and rings to synthesize complex molecular architectures in an efficient manner. While numerous cycloaddition methodologies that are promoted by the use of heat, light or high pressure have been developed, the majority of these protocols are often limited to the use of activated substrates and/or harsh reaction conditions for their success.[1] Indeed, one of the most significant advancements in the field of cycloaddition chemistry came with the discovery of various transition metal catalysts that could not only promote the existing reactions under mild conditions but also allows for the discovery of new organic transformations that are otherwise not feasible using conventional methods.[2] Furthermore, the addition of ligands to metal complexes can enhance their reactivity and also provide opportunities to induce chemo-, regio- and stereoselectivity in these cycloaddition reactions.

This chapter will provide a brief background on the most commonly utilized transition metal catalyzed cycloaddition methodologies based on the ring size of cycloadduct that is formed in these reactions.

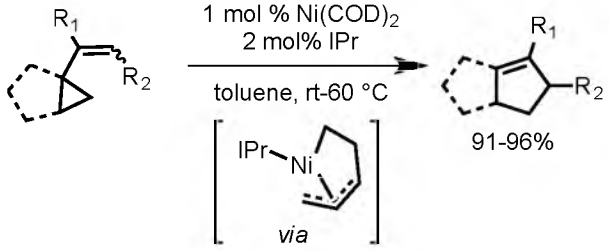
Synthesis of four-membered rings

The [2+2] cycloaddition between alkenes and/or alkynes is an important method to construct four-membered carbocycles. Since [2+2] cycloaddition is thermally forbidden according to Woodward-Hoffman rules, this process has been investigated photochemically[3a,b] and by Lewis-Acid acid catalyzed thermal cycloadditions.[3c,d] Additionally, transition metal catalysts can also render this cycloaddition under thermal conditions.[3e,f] Recently, Ogoshi and coworkers developed an efficient Ni/IPr-catalyzed intermolecular [2+2] cycloaddition of alkenes and conjugated enynes to form substituted cyclobutenes in moderate to high yields.[3g] This reaction proceeds through a chemoselective Ni-mediated oxidative coupling of alkene with the alkyne unit of enyne to form a Ni(II)-allyl complex that undergoes reductive elimination to afford the product (Figure 1.1).

The intramolecular [2+2] cycloaddition of ene-allenes has also been explored to form fused cyclobutane systems. Fürstner developed a highly enantioselective Au-catalyzed cycloaddition of a variety of ene-allenes to afford [5,4]-fused cyclobutanones in high yields (Figure 1.2).[3h] The proposed mechanism involves the activation of allene by gold to form a Au-allyl cationic intermediate that undergoes cyclization to afford a stabilized benzyl carbocation species. Subsequent intramolecular cyclization affords the fused bicyclic cyclobutane ring system.

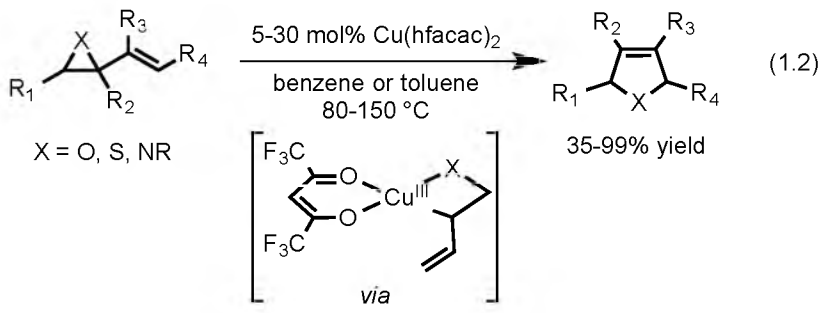
Synthesis of five-membered rings

One of the most utilized approaches to synthesize five-membered carbocycles is the vinylcyclopropane-cyclopentene (VCP-CP) rearrangement.[4a,b] A variety of transition metals (Rh, Pd, Ni, Cu, Cr, Mo, Fe) are known to promote this rearrangement; however, most of them either require stoichiometric metal complexes or are limited to the use of high catalyst loadings, high reaction temperature or activated VCPs.[4c] The introduction of electron rich and sterically bulky N-heterocyclic carbenes ligands in Ni-catalyzed VCP-CP rearrangement by Louie and coworkers successfully overcame these limitations by rearranging both activated as well as unactivated VCPs under mild conditions in excellent yields (eq 1.1).[4c]



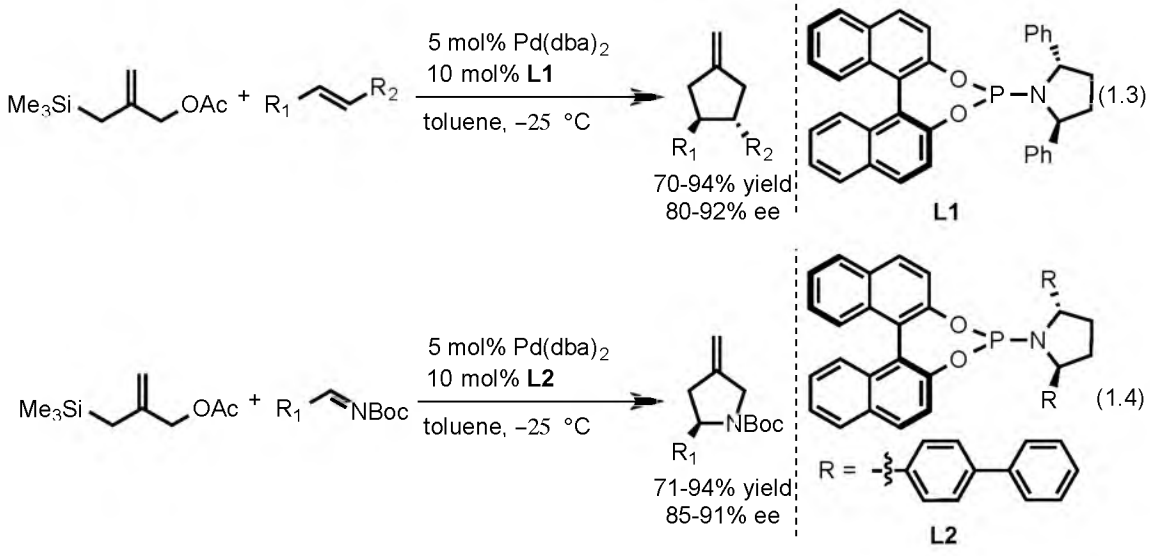
(1.1)

Njardarson advanced the heterocyclic variant of this rearrangement by developing a $Cu(hfacac)_2$ [hfacac = hexafluoroacetylacetonate] catalyst that could promote the ring expansion of vinyl oxiranes,[5a] vinyl thiiranes[5b] and vinyl aziridines[5c,d] to form 2,5-dihydrofurans, 2,5-dihydrothiphenes and 2,5-dihydropyrroles, respectively (eq 1.2).[5e] However, high reaction temperatures and variable catalyst loadings were required for the success of these reactions.



(1.2)

The Pd-catalyzed [3+2] cycloaddition of trimethylenemethane (TMM) with alkenes and imines is another important strategy to construct five-membered carbocycles and heterocycles.[6a] Trost and coworkers showed that the treatment of allyl acetate with Pd(0)/phosphine catalyst forms an intermediate Pd-π-allyl complex, which loses TMS group to generate the zwitterionic Pd-TMM complex. This Pd-TMM complex can undergo [3+2] cycloaddition with olefins and amines, to form the five-membered cycloadducts (Figure 1.3).[6b,c] In recent years, the use of chiral phosphoramidite ligands has allowed the development of the asymmetric versions of these [3+2] cycloadditions (eqs 1.3 and 1.4).[6d,e]



(1.3)

(1.4)

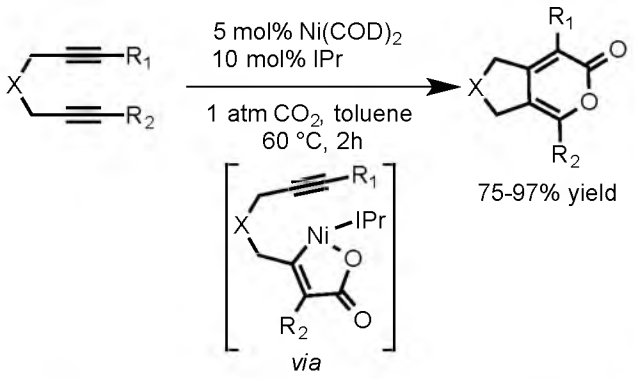
Synthesis of six-membered rings

The [4+2] cycloaddition or Diels Alder reaction is unarguably the most widely used method for the construction of six-membered rings.[2a,b] While tremendous progress has been made to utilize this cycloaddition for carbocycle synthesis, efforts are being devoted to develop new and efficient catalytic methods for synthesis of heterocycles.[2f,g] For example, Ogoshi developed the first general and catalytic dehydrogenative [4+2] cycloaddition of 1,3-butadienes and nitriles to form monocyclic pyridines.[7a] The Ni-promoted oxidative coupling of nitrile and terminal alkene forms the Ni-allyl complex, which on reductive elimination and subsequent dehydrogenation affords the substituted pyridine (Figure 1.4).

Alternatively, the [4+2] cycloaddition of azadienes and alkynes can also afford pyridines. Bergman and Ellman exploited the Rh-catalyzed C−H activation to promote the cycloaddition of azadienes and alkynes to form substituted dihydropyridines and pyridines in high yields (Figure 1.5).[7b] Their proposed mechanism involved Rh-promoted alkenyl C−H activation followed by alkyne insertion and reductive elimination to afford azatriene-intermediate. Subsequent 6π-electrocyclization of the azatriene afforded the dihydropyridine cycloadducts. These dihydropyridine products were easily converted to the corresponding pyridines under the Pd/C catalyzed debenzylation conditions.

In addition to extensively utilized [4+2] cycloaddition reactions, the transition metal catalyzed [2+2+2] cycloaddition is a highly versatile and atom efficient way to construct six-membered carbocycles and heterocycles.[8a-g] Since the first report on Ni-catalyzed cyclotrimerization of acetylene by Reppe in 1948,[8h] tremendous development has been made in the area of [2+2+2] cycloaddition reactions. A variety of Ni/NHC (NHC = *N*-

heterocyclic carbene) systems have been developed as versatile catalysts for the [2+2+2] cycloaddition of alkenes/alkynes with numerous coupling partners such as carbon dioxide, isocyanates, nitriles and carbonyl compounds in a highly efficient manner.[8g] The Louie group demonstrated the use of Ni/IPr and Ni/SIPr catalysts to promote the cycloaddition of diynes with CO_2 and pyridines, respectively, in high yields under mild conditions (eqs 1.5 and eq 1.6).[8i,j]



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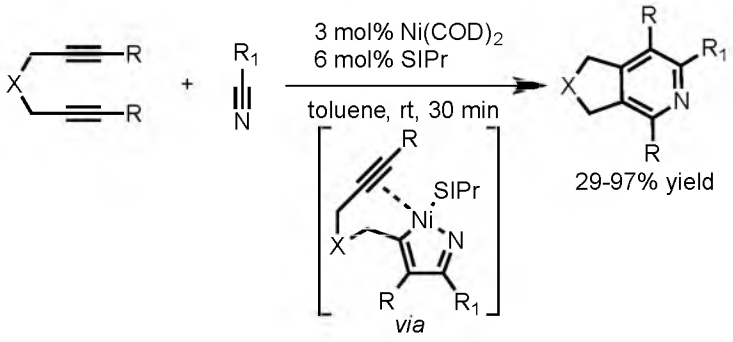
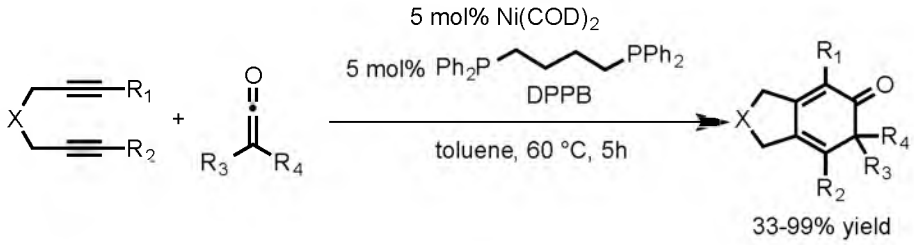


(1.6)

Recently, ketenes were also successfully incorporated for the first time in [2+2+2] cycloaddition with diynes by the use of the Ni/DPPB catalytic system. This catalytic system was found to be highly effective in eliminating the unfavorable decarbonylation pathway generally observed with the reaction of ketenes with metal complexes (eq 1.7).[8k]

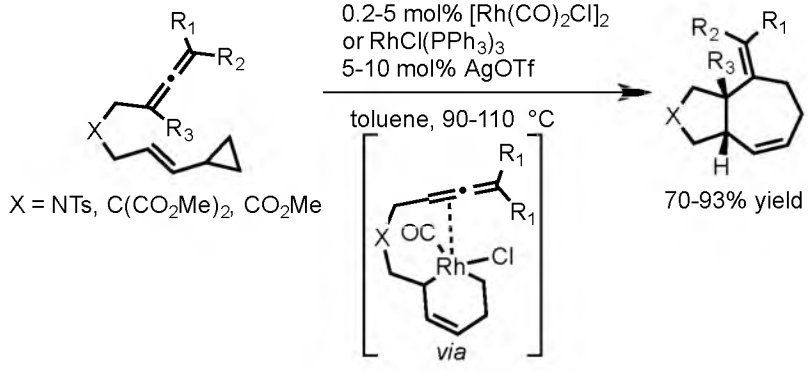


(1.7)

Besides these cycloaddition reactions, numerous other methodologies such as ring-closing olefin metathesis,[8l] [3+3] cycloaddition,[2] [3+2+1] cycloaddition,[2] etc., have also been explored to construct six-membered cycloadducts.

Synthesis of seven-membered rings

The synthesis of medium-sized rings (ring size seven or higher) is challenging due to unfavorable enthalpic and entropic factors.[8l] The ring expansion of more accessible smaller ring systems (ring size three to six) is the most common approach to synthesize these cyclic compounds. For example, transition metal [5+2] cycloadditions of vinylcyclopropanes (VCPs) with allenes and alkynes serve as a highly efficient protocol to construct carbocycles.[9a] Wender's group has done extensive work on developing versatile Rh-catalysts that can promote these [5+2] cycloadditions in both intramolecular and intermolecular fashions in high yields (eqs 1.8 and 1.9).[9b,c]



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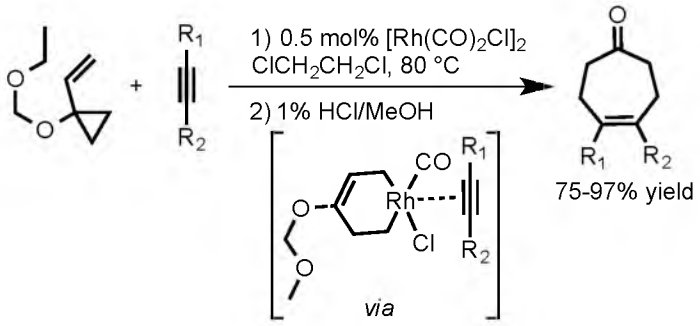
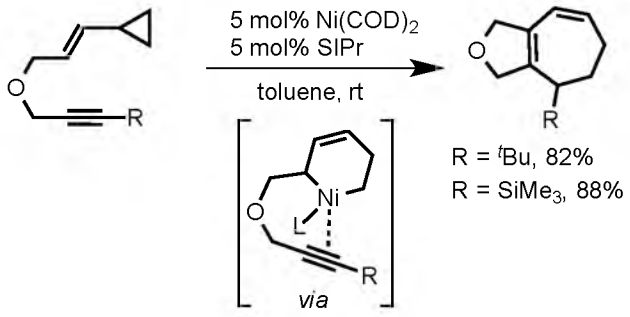


(1.9)

Ni-catalyzed intramolecular [5+2] cycloaddition of vinylcyclopropanes with alkynes has also been investigated. However, the reaction is limited to the use of bulky groups on alkyne to selectively form seven-membered rings (1.10).[10a]



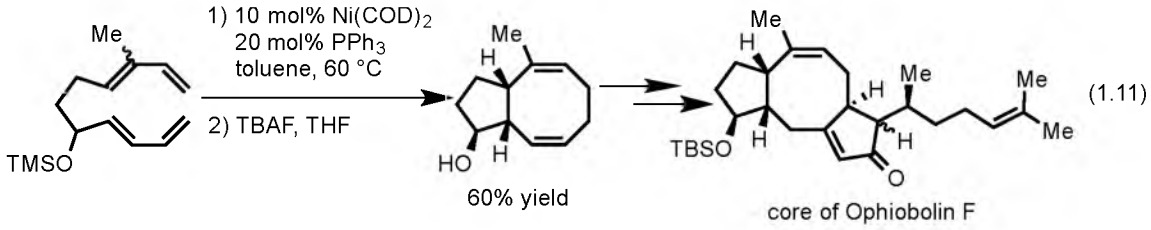
(1.10)

The [4+3] cycloaddition is another important strategy to construct seven-membered rings. Although the majority of these cycloadditions afford seven-membered carbocycles, new and efficient catalysts are being explored to synthesize seven-membered heterocycles. Recently, Toste and coworkers developed an interesting Au-catalyzed [4+3] cycloaddition of azadienes and propargyl esters to form substituted azepines (Figure 1.6).[10b] This cycloaddition proceeds via the generation of a gold carbenoid by 1,2-benzoyloxy migration followed by the nucleophilic attack of imine on the carbenoid to

form Au-allyl species. Subsequent intramolecular cyclization of this intermediate affords the azepine product.

Synthesis of eight-membered rings

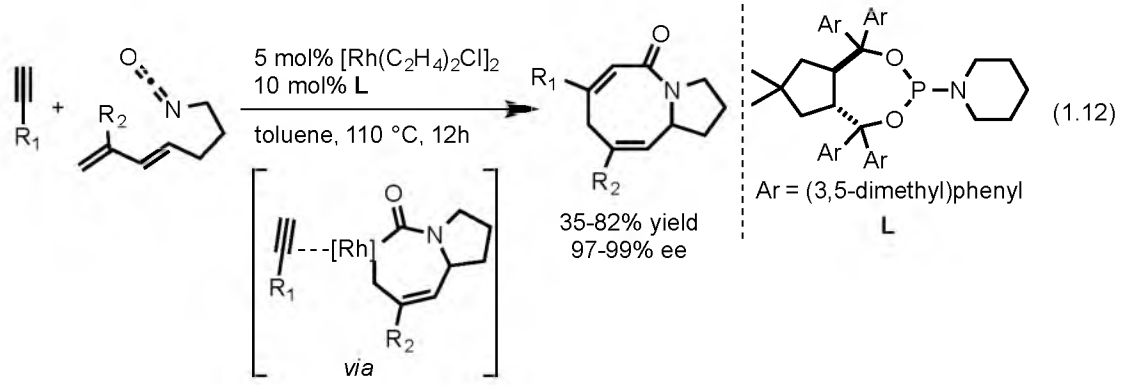
A variety of transition metal catalyzed cycloaddition reactions have been developed for the synthesis of eight-membered carbocycles.[11a] Since Reppe's first report on the Ni-catalyzed [2+2+2+2] cycloaddition/tetramerization of acetylene in 1948,[8h] various new methodologies such as [4+4], [4+2+2], [5+2+1] and [6+2] cycloadditions have been explored.[11a] Wender and coworkers reported an elegant Ni-catalyzed [4+4]-cycloaddition of bis-diene to form [5,8]-ring fused cycloadduct that was converted in a few steps to the core skeleton of the natural product, Ophiobolin F (eq 1.11).[11b]



(1.11)

Murakami and coworkers utilized the C–C σ-activation of cyclobutanones in cycloaddition with diynes to afford bicyclic eight-membered ketones in high yields (Figure 1.7).[11c] This interesting [4+2+2] cycloaddition involves the Ni-mediated oxidative coupling of the carbonyl group of cyclobutanone and alkyne to form a [5,4] spirocyclic intermediate that undergoes insertion of the pendant alkyne followed by β-carbon elimination to generate a nine-membered nickellacycle. Finally, reductive elimination affords the fused eight-membered carbocycle.

The transition metal catalyzed cycloaddition route to construct eight-membered heterocycles has been explored to a much lesser extent than their carbocyclic counterparts. Rovis reported an enantioselective [4+2+2]-cycloaddition of terminal alkynes and dienyl isocyanates to synthesize bicyclic azocine ring systems in good yields with excellent enantioselectivities (eq 1.12).[11d]



Conclusion

Transition metal catalyzed cycloaddition reactions have played a prominent role in the synthesis of carbocycles and heterocycles. A variety of transition metal catalysts have been developed for a diverse range of substrates to afford cycloadducts ranging from small rings to medium ring systems. However, this area of catalysis is still evolving and more mechanistic understanding as well as applications of these catalytic processes are required. The synthesis of medium sized carbocycles and heterocycles is still challenging and urges the need for efficient and selective catalytic systems. Additionally, a number of transition metal catalysts used in these processes are expensive and/or air and moisture sensitive, which further necessitates the need for cost-effective and convenient

procedures to perform these reactions. Finally, new concepts and new coupling partners are required to advance this interesting and useful field of catalysis.

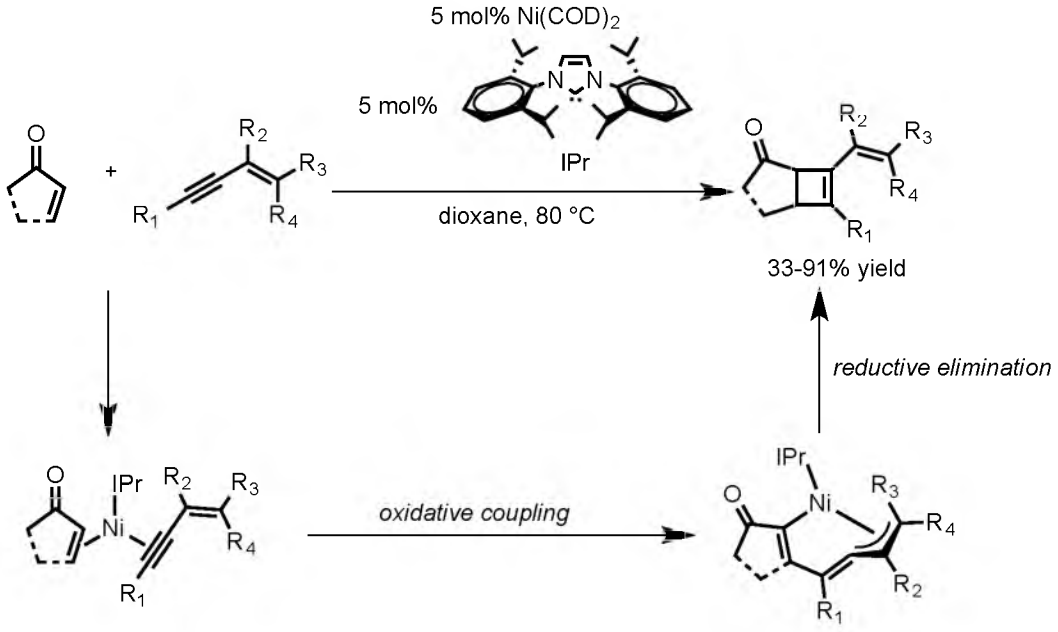


Figure 1.1. Ni/IPr catalyzed [2+2] cycloaddition of alkenes and 1,3-enynes.

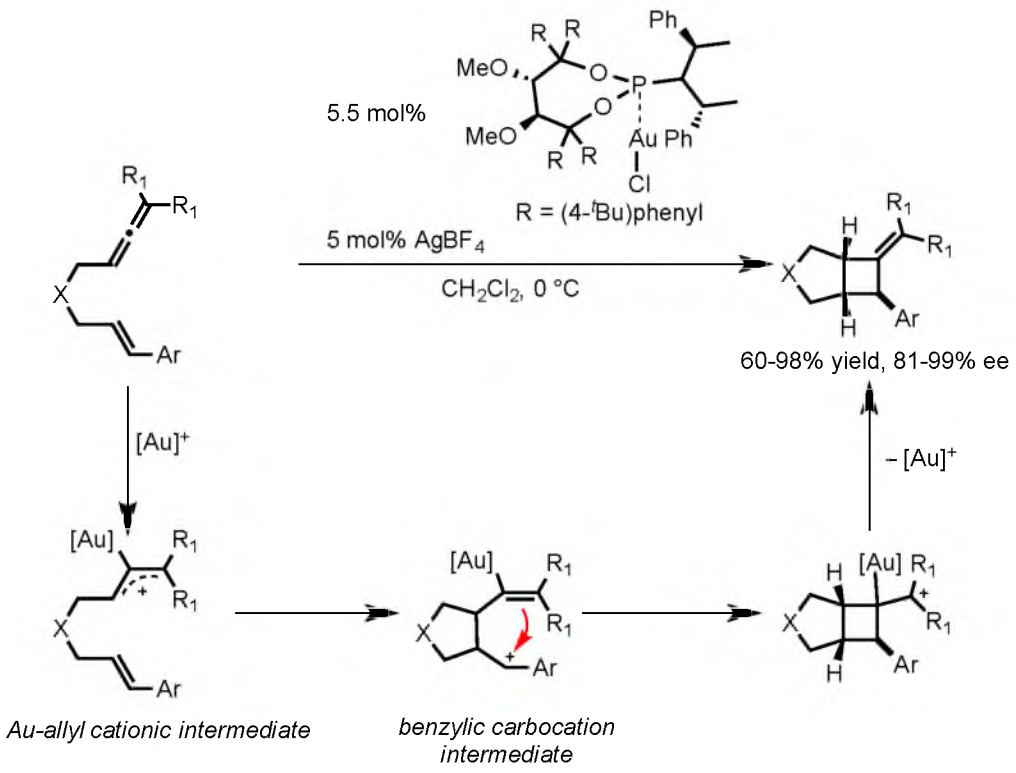


Figure 1.2. Au-catalyzed enantioselective [2+2] cycloaddition.

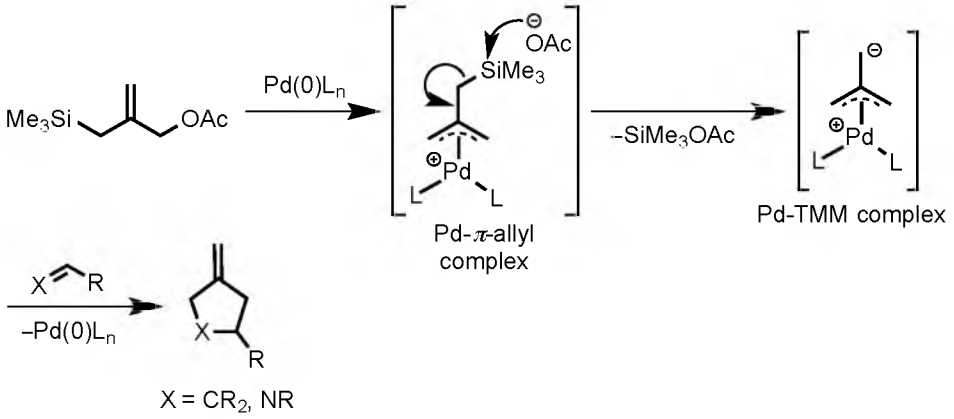


Figure 1.3. Pd(0)-catalyzed [3+2] cycloaddition of trimethylenemethane with alkenes and imines.

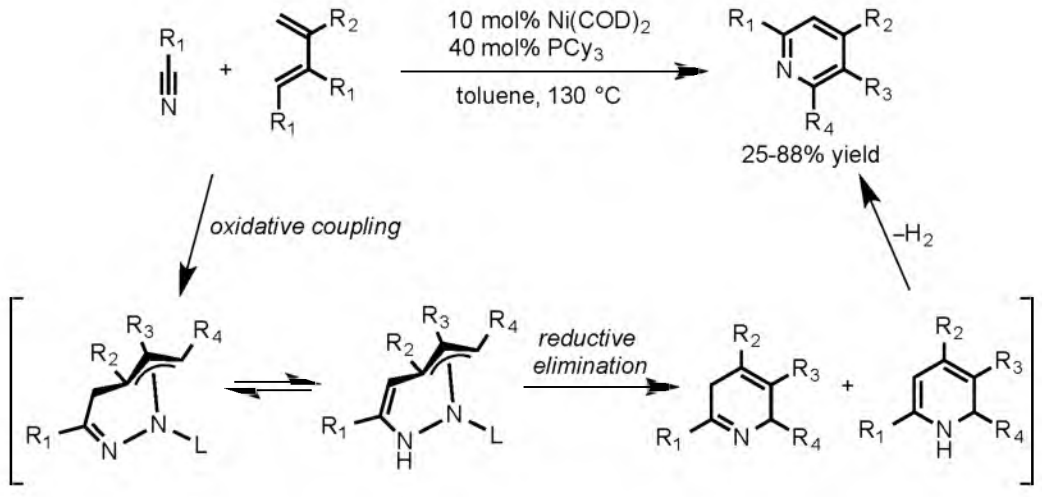


Figure 1.4. Ni-catalyzed dehydrogenative coupling of 1,3-butadienes and nitriles.

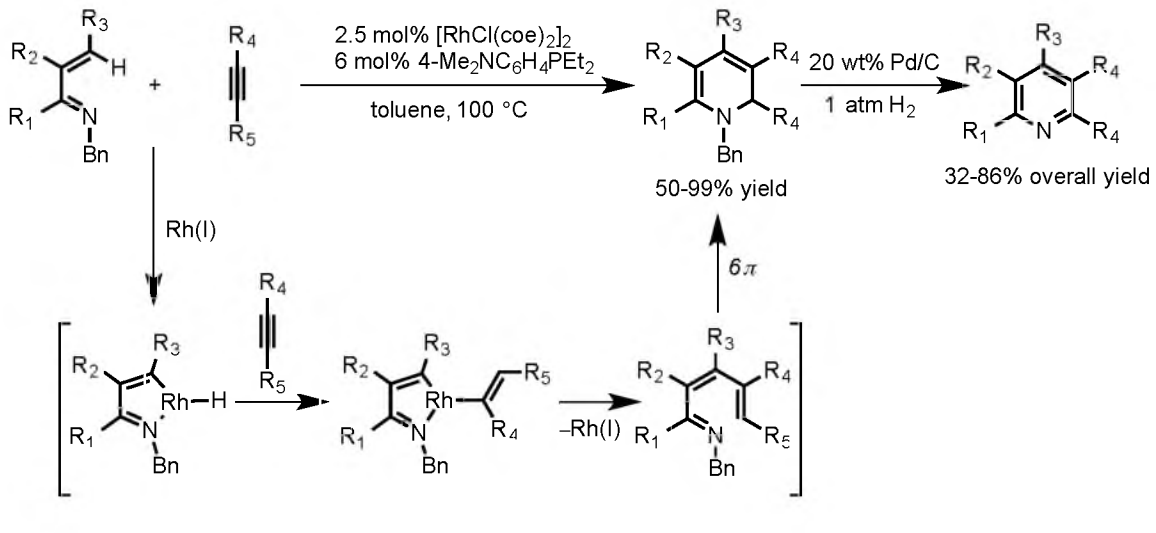


Figure 1.5. Rh-catalyzed cycloaddition of azadienes and alkynes via C–H activation.

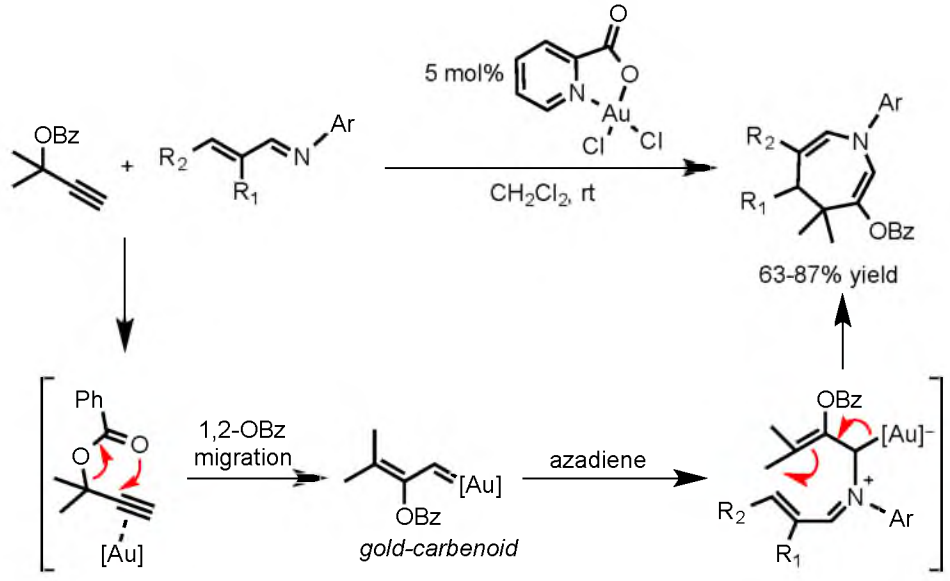


Figure 1.6. Au-catalyzed [4+3] cycloaddition.

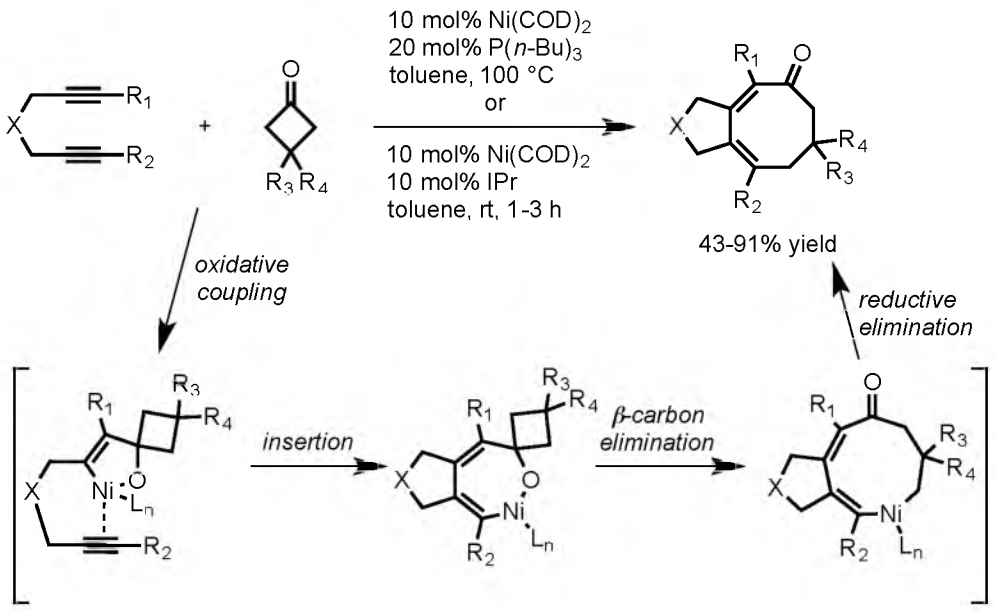


Figure 1.7. Ni-catalyzed [4+2+2] cycloaddition of diynes and cyclobutanones.

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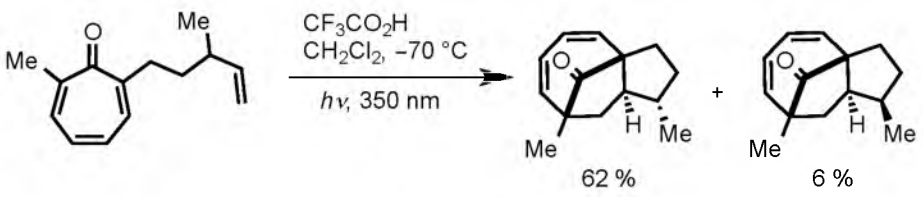
CHAPTER 2

NICKEL(NHC)-CATALYZED CYCLOADDITION OF DIYNES AND TROPONE: APPARENT ENONE CYCLOADDITION INVOLVING AN 8π INSERTION

Introduction

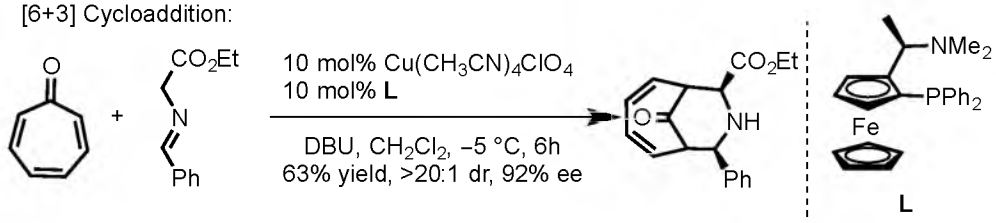
Tropone is a readily available seven-membered non-benzenoid aromatic compound that can undergo cycloadditions to afford complex bridged motifs of a variety of natural products and medicinally important compounds.[1-4] The tropone cycloaddition reactivity can be generally understood by its resonance contributor, tropylium oxide (Figure 2.1a). This resonance structure explains the dipolar nature of tropone[3a] and the large LUMO coefficients at the alpha-positions (Figure 2.1 b).[5] Therefore, tropone cycloaddition reactions usually lead to bond formations at the α-positions as in (6+2),[6] (6+3)[7] and (6+4)[8] cycloaddition reactions or in one α-position and the carbonyl oxygen atom as in (8+2)[9] and (8+3)[10] cycloaddition reactions.[11] Specifically, Feldman utilized tropone as a 6-membered synthon in photochemically induced intramolecular [6+2] cycloaddition with alkene to afford a diastereomeric mixture of bridged cycloadducts (eq 2.1).[6b] To exploit tropone for the formation of bicyclic heterocycles, Guo and coworkers recently reported an enantioselective Cu-catalyzed intermolecular [6+3] cycloaddition with azomethine ylides to form interesting piperidine-fused cycloadducts (eq 2.2).[7e]

[6+2] Cycloaddition:



(2.1)

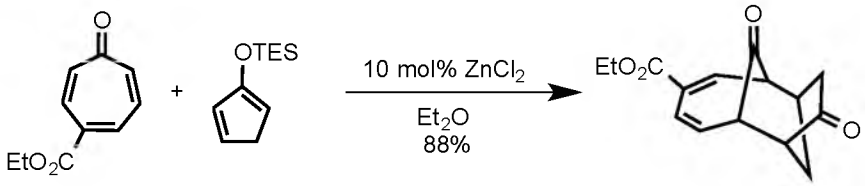
[6+3] Cycloaddition:



(2.2)

Gleason utilized tropone in Lewis-acid catalyzed [6+4] cycloaddition with substituted cyclopentadienes to form bicyclic ten-membered carbocycles (eq 2.3).

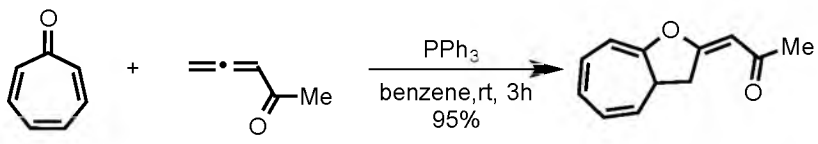
[6+4] Cycloaddition:



(2.3)

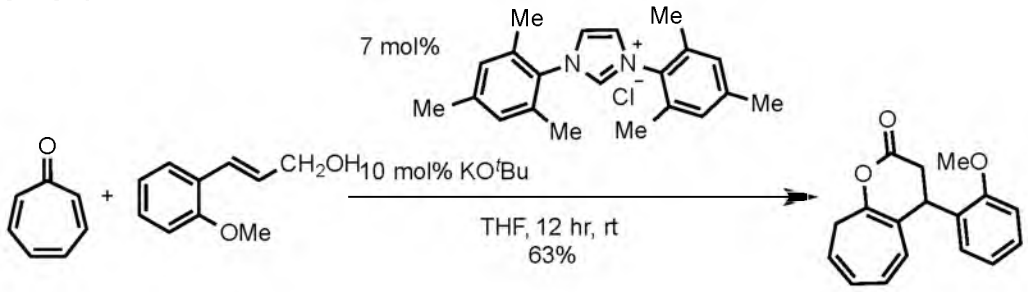
Additionally, tropones can also serve as eight-membered synthons to afford [8+2] and [8+3] cycloadducts. For instance, Ishar and coworkers disclosed the [8+2] cycloaddition of tropone and 1,3-dipoles that are generated by the reaction of allenyl-ketones and triphenylphosphine, to access [7,5] fused cycloadducts (eq 2.4). Nair utilized a NHC-catalyzed [8+3] annulation of tropone and enals to afford bicyclic lactones (eq 2.5).

[8+2] Cycloaddition:



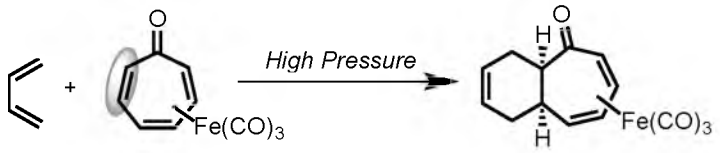
(2.4)

[8+3] Cycloaddition:



(2.5)

Despite its versatile reactivity, reactions involving tropone as an enone moiety are rare. The exception involves disrupting the conjugation of tropone by precomplexation with iron-carbonyl (eq 2.6).[12] Although this approach affords the desired non-bridged bicyclic products, such reactions require stoichiometric amounts of metal complexes as a protecting group for the other two double bonds.

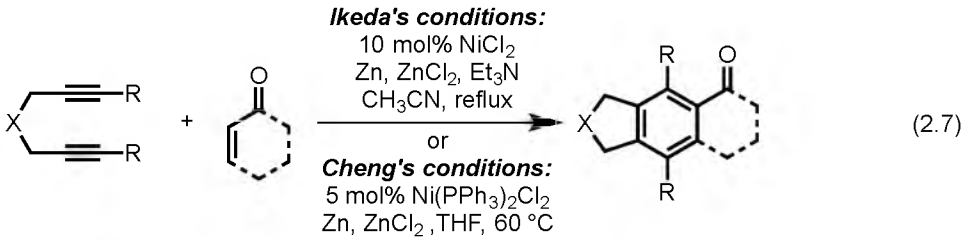


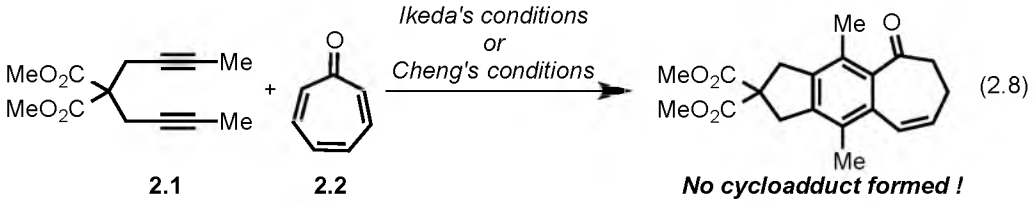
(2.6)

This inability to utilize tropones as enones is unfortunate, since selective activation of a single C−C π-bond in cycloaddition would greatly expand the synthetic utility of tropones, given the frequent occurrence of non-bridged seven-membered ring systems in biologically relevant compounds.[4] We describe a solution to the long-standing problem of utilizing tropone as an enone through the use of a highly effective nickel catalyst that couples diynes with a single double bond of a tropone selectively to form fused tricyclic frameworks (vs bridged frameworks) *without the need for precomplexation*.

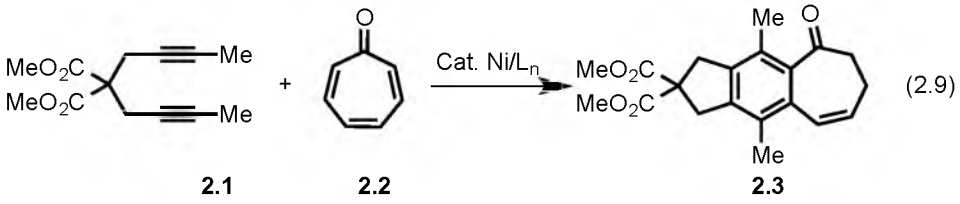
Results and discussion

Simple enones are known to undergo Ni-catalyzed cycloaddition with diynes to form tricyclic products (eq 2.7).[13] However, these conditions fail to provide any cycloadduct product with tropone as shown in (eq 2.8). Thus, we focused our investigation on discovering an alternative Ni-catalyzed cycloaddition protocol.





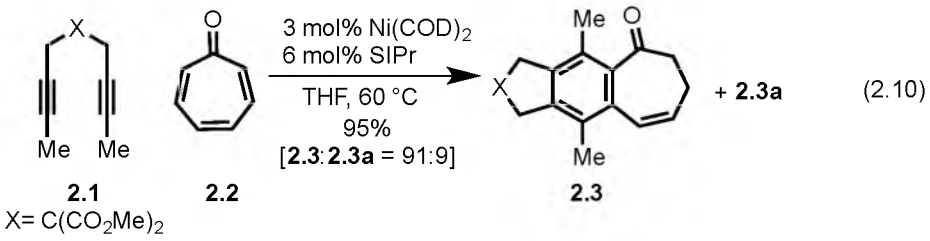
Diyne **2.1** and tropone **2.2** were used as model substrates and were subjected to a catalytic amount of Ni(0) and a variety of phosphine and *N*-heterocyclic carbene (NHCs) ligands (eq 2.9).



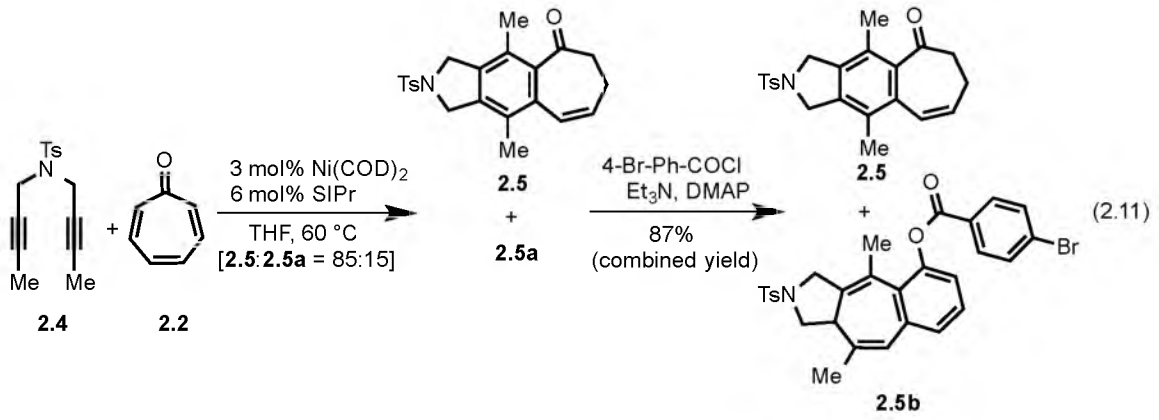
Reactions run with monodentate and bidentate phosphines mostly afforded dimerization of diyne along with traces or a low amount of the desired cycloadduct (Table 2.1, entry 1-10). However, reactions run with NHCs resulted in good to excellent

yields of cycloadduct **2.3**, which couples the diyne with a *single C-C double bond* of the tropone selectively (entries 11-15). I collaborated with Dr. Puneet Kumar for optimization as well as substrate scope studies related to this work. Ultimately, SIPr proved to be the best ligand. Further optimization led to our final reaction conditions: diyne (1 equiv), tropone (1.1 equiv), 3 mol% $Ni(COD)_2$, 6 mol% SIPr, THF, 60 °C and 5 h.

The model substrates afforded the desired product **2.3** along with another isomer **2.3a** in excellent yield and *>90% selectivity* for **2.3** (eq 2.10). The spectroscopic analysis of **2.3a** revealed the presence of a broad peak in ^{1}HNMR at 4.97 ppm, a broad band in IR at 3389 cm^{-1} and the absence of a carbonyl peak in ^{13}CNMR and IR. These observations along with deuterium exchange reactions indicated the presence of a –OH functionality in **2.3a**.



Similarly, cycloaddition of sulfonamide diyne **2.4** afforded a mixture of major and minor isomers, **2.5** and **2.5a**, respectively, which on subsequent treatment with *p*-bromo-benzoyl chloride/NEt_3/DMAP afforded major isomer **2.5** in 74% yield and *p*-bromo-benzoyl derivative of minor isomer (**2.5b**) in 13% yield (eq 2.11) as crystalline solids (Figure 2.2). Surprisingly, **2.5b** (and, therefore, **2.5a** as well) has [5-7-6] ring fusion compared to [5-6-7] in case of major isomer, **2.5**.[14]

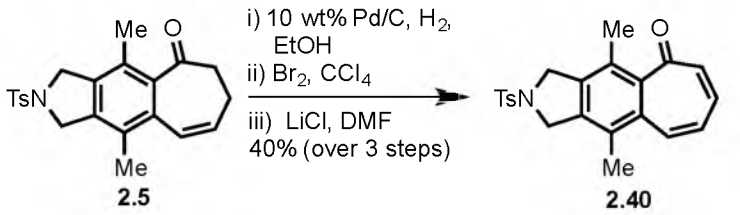


With optimized reaction conditions in hand, the substrate scope was explored (Table 2.2). The cycloaddition occurred smoothly with the diyne bearing a sulfone backbone to form **2.7** along with minor isomer **2.7a**. Notably, this diyne is completely unreactive in several reported Ni-catalyzed cycloadditions.[15] Although Ni catalysts have been reported to catalyze the cycloaddition of nitriles and diynes to form pyridines,[15b,d] diyne **2.8**, which has a nitrile group in the backbone, selectively reacted with tropone to afford the desired cycloadducts (**2.9** and **2.9a**) in excellent yield. Inspired by Carreira's work, we performed the cycloaddition reaction with **2.10**, a diyne with a metabolically stable backbone,[16] to give cycloadduct **2.11** in good yield along with minor isomer **2.11a**. Aryl substituted internal diynes are one of the most challenging substrates in Ni/NHC-catalyzed cycloaddition reactions.[15e,17] Nevertheless, the reaction of aryl substituted symmetrical diynes with tropone afforded **2.13** and **2.15** in good yields. Interestingly, no minor cycloadduct (**2.13a** or **2.15a**) was obtained in these cases. To investigate the effect of electronics on the regioselectivity, we subjected unsymmetrical diynes **2.16** and **2.18** to standard reaction conditions; remarkably, exclusive formation of one regioisomer was detected (**2.17** and **2.19**). The use of different aryl groups (i.e. 3,4-dimethoxyphenyl and naphthyl) on alkyne terminals is also possible (**2.21** and **2.23**). Due to recent interest in

indole bearing novel compounds,[18] diynes **2.24** and **2.26** were investigated. In the event, biaryl cycloadducts (**2.25** and **2.27**) were formed in very good yield and high regioselectivity. Interestingly, the regioselectivity was higher in the case of 3-substituted indole diyne than 5-substituted indole diyne (**2.25** vs **2.27**). Cycloaddition of phenyl-ethyl diyne **2.28** and phenyl-silyloxymethyl **2.30** afforded regioisomers **2.29** and **2.31**, where the carbonyl resides next to the phenyl ring, exclusively, while a diyne with covalently bound δ-tocopherol can also be easily clicked together with tropone to afford regioselective cycloadduct, **2.33**. An unsymmetrical diyne bearing an internal gem-dimethyl group reacted with tropone to afford an exclusive regioisomer **2.35**, which suggests that regioselectivity is highly dependent on the substituents on the alkyne units of a diyne rather than backbone.[19] The cycloaddition of unsymmetrical isopropyl-methyl diyne (**2.36**) afforded products **2.37** and **2.37a**, where the bulkier group is next to carbonyl of tropone. Cycloaddition of phenyl-isopropyl diyne **2.38** affords a product where the isopropyl group is away from the carbonyl group suggesting electronic factors override the steric factors (**2.39**). Unfortunately, terminal diynes did not afford any cycloaddition product with tropone due to their high propensity to oligomerize under our reaction conditions (Figure 2.3). 2-methoxy and 2-morpholine-susbtituted tropones did not participate in this cycloaddition and were either completely decomposed or recovered with partial decomposition under the reaction conditions (Figure 2.3).

The lack of general methods to access troponoids prompted our investigation on the ability of converting the cycloadduct to fully aromatized product. We found that compound **2.5** can be consistently converted to tropone, **2.40** by a three-step protocol.[20] The hydrogenation of alkene of **2.5** led to a saturated cycloheptanone that was then

subjected to dibromination. Finally, di-dehydrobromination afforded the desired tropone, **2.40** (eq 2.12).



(2.12)

Mechanism

We also undertook a mechanistic investigation of this reaction. We collaborated with Xin Hong and Dr. K. N. Houk of UCLA for computational studies related to the mechanism of this cycloaddition. Specifically, we studied the catalytic cycles for [Ni(IPr)$_2$]-catalyzed cycloaddition of nona-2,7-diyne and tropone with DFT calculations.[21] Homocoupling,[22] where two alkynes undergo initial oxidative coupling, and heterocoupling,[23] where an alkyne and the tropone undergo initial oxidative coupling, were both investigated.

The free energy changes for the homocoupling pathway are shown in Figure 2.4. From [Ni(IPr)$_2$] complex **2.41**, the coordination of diyne to form intermediate **2.42** is endergonic by 7.0 kcal/mol. Subsequent intramolecular oxidative cyclization via **TS 2.43** requires a 13.4 kcal/mol barrier with respect to **2.42**, generating the metallacyclopentadiene intermediate **2.44**. This intermediate undergoes a facile 8π insertion (instead of 2π-insertion, *vide infra*) of tropone via **TS 2.45**, with a barrier of only 9.8 kcal/mol. The 8π insertion produces the eight-membered ring intermediate **2.46** with the tropone oxygen coordinated to nickel. The tropone piece of complex **2.46** can coordinate to nickel in four different fashions, generating the complexes **2.46** to **2.49**.[24]

The four isomers have similar stabilities, and complex **2.49** undergoes the reductive elimination via **TS 2.50** to give the product-coordinated complex **2.51**. Product extrusion from **2.52** is exergonic by 2.8 kcal/mol to release the product and regenerate the nickel-diyne complex **2.42**. The tautomerization of intermediate complex **2.49** to **2.49-enol** is endergonic by 5.8 kcal/mol and subsequent reductive elimination from **2.49-enol** will form the 5-7-6 tricyclic product; however, the irreversible reductive elimination via **TS 2.50** suggests that the 5-7-6 tricyclic product arises from Ni-free tautomerization.

The calculations indicate that the resting state of the pathway A is [Ni(IPr)$_2$] complex **2.41**, and oxidative cyclization through **TS 2.43** is the rate-limiting step of the catalytic cycle. The overall reaction barrier is 20.4 kcal/mol, which is consistent with the experimental conditions (60 °C, 5h). In contrast, the heterocoupling pathway of [Ni(IPr)]-catalyzed cycloaddition between nona-2,7-diyne and tropone displays higher free energies (Figure 2.5). Specifically, from nickel-diyne complex **2.42**, the intermolecular oxidative cyclization between alkyne and tropone can occur via **TS 2.54**, with the carbonyl group of tropone distal to the forming C−C bond. This step requires a barrier of 42.5 kcal/mol with respect to the [Ni(IPr)$_2$] complex **2.41**, which is much less favorable as compared to the homocoupling pathway discussed above (Figure 2.5). Alternatively, the intermolecular cyclization can occur with the tropone carbonyl group proximal to the forming C−C bond, as in **TS 2.56**. **TS 2.56** is 31.6 kcal/mol higher in free energy than the resting state **2.41**, which is also less favorable than the productive homocoupling pathway. Therefore, unlike other Ni catalyzed couplings between alkynes and carbonyls,[15e,25] a heterocoupling mechanism is not operative in the [Ni(IPr)]-catalyzed cycloaddition between diyne and tropone.

Next, insertion of the tropone was investigated, and two probable pathways emerged- a traditional 2π insertion and a distinctive 8π insertion. The transition states of 8π (**TS 2.45**) and 2π insertion (**TS 2.57**) of tropone were both located, and their free energies and structures are shown in Figure 2.6.[26] Interestingly, the 8π insertion is found to be more favorable by 12.3 kcal/mol.

We studied the origins of this preference by employing the distortion/interaction model on **TS 2.45** and **TS 2.57**.[27] The distortion energy reflects the structural changes from nickel complex **2.44** or tropone to the corresponding geometries in the transition states, and the interaction energy is the energy of interactions between the distorted fragments, computed as the difference between the activation energy and the total distortion energy. The difference between the distortion energies of **TS 2.45** and **TS 2.57** is the major reason for the preference for 8π insertion. The distortion energy is 17.8 kcal/mol energy for **2.44** and 13.7 kcal/mol energy for tropone to achieve the distorted geometries in **TS 2.45**, while it requires much larger distortions (24.3 kcal/mol for **2.44** and 16.6 kcal/mol for tropone) in **TS 2.57**. Stronger steric repulsions are generated between the nickelacyclopentadiene moiety and tropone in **TS 2.57** as compared to those in **TS 2.45**. This difference between the steric repulsions eventually leads to the preference of the unconventional 8π insertion, and this is the highest order of poly-π insertion so far.[28]

The transition states for the 8π-insertion of tropone with unsymmetrical diynes were also studied. For the isopropyl-methyl diyne (Figure 2.7), the transition state **TS 2.58-C1** that contains the bulky isopropyl group on the diyne next to tropone is more stable than **TS 2.58-C2** by 0.7 kcal/mol to avoid steric repulsions between the isopropyl group and

IPr ligand. For phenyl-methyl diyne, the transition state **TS 2.59-C1** is 4.7 kcal/mol more stable than **TS 2.59-C2** mainly due to the steric repulsions between the phenyl group and the bulky NHC ligand in **TS 2.59-C1**. Also, for phenyl-isopropyl diyne, the phenyl group is more sterically demanding, and a 4.0 kcal/mol preference to the **TS 2.60-C1** is found.

Overall, our data suggest that Ni-catalyzed cycloaddition occurs via the mechanism shown in Figure 2.8. The homo-oxidative coupling of diyne on Ni(0) forms Ni(II)-cyclopentadiene intermediate I that undergoes 8π-insertion of tropone to afford seven-membered ring complex II. Intermediate II isomerizes from oxygen coordination to η^3-coordination resulting in intermediate III, which can subsequently isomerize to an η^3-coordinated-Ni(II) complex V through intermediates IV. Finally intermediate V reductive eliminates to give VI, which releases the tricyclic product, VII, and regenerates the Ni(0) catalyst. At this point, compound VII can preferentially aromatize via sigmatropic shifts to afford major product VIII. However, a minor pathway involves tautomerization of VII to cycloheptatrienol IX which undergoes further 6π electrocyclization to afford an interesting bis-(divinyl)-cyclopropane intermediate, X. Intermediate X can either revert to IX or irreversibly rearrange to [5-7-6] fused intermediate XI, which undergoes further sigmatropic shifts to yield the observed minor product, XII. This sigmatropic shift could be catalyzed by trace amount of water through the bridge of one or multiple molecules of water.[29] Due to the uncertainty of the catalyst, we did not perform computational studies on the isomerization of the tricyclic product VI.

Conclusion

In summary, we have discovered a nickel catalyst that can effectively and selectively incorporate a single C−C π-bond of tropone in the cycloaddition with diynes. We have also successfully converted the [5-6-7]-fused cycloadduct formed in this reaction to useful troponoid. The mechanism of this novel cycloaddition reaction has been investigated using DFT calculations. It involves a unique 8π-insertion of tropone to form the observed major and minor products. The mechanistic studies to further understand this unique reactivity of tropone and application of this chemistry are underway in our laboratories. Future efforts would also be focused on the development of a fully intermolecular cycloaddition of monoalkynes and tropones.

General experimental

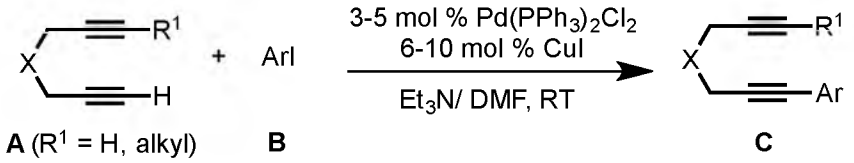
All reactions were conducted under an atmosphere of N_2 using standard Schlenk techniques or in a N_2-filled glove box unless otherwise noted. Toluene was dried over neutral alumina under N_2 using a Grubbs type solvent purification system. THF was freshly distilled from Na/benzophenone. $Ni(COD)_2$ was purchased from Strem and used without further purification. Sodium hydride was thoroughly washed with pentane and dried *in vacuo* prior to use. Tropone was purchased from Sigma-Aldrich and used as received. Diynes **2.1**,[17a] **2.4**,[15a] **2.6**,[30a] **2.8**,[30b] **2.10**,[16b] **2.12**,[30c] **2.16**[30d] and **2.18**[30e] were prepared according to reported literature procedure. All other reagents were purchased and used without further purification unless otherwise noted.

^1H and ^{13}C Nuclear Magnetic Resonance spectra of pure compounds were acquired at 400 and 100 MHz or 500 and 125 MHz, respectively, unless otherwise noted. All spectra

are referenced to a singlet at 7.27 ppm for ^{1}H and to the central line of a triplet at 77.23 ppm for ^{13}C. The abbreviations s, d, dd, dt, dq, t, td, tq, q, qt, quint, sept, septd, septt, m, brm, brd, brt, and brs stand for singlet, doublet, doublet of doublets, doublet of triplets, doublet of quartets, triplet, triplet of doublets, triplet of quartets, quartet, quartet of triplets, quintet, septet, septet of doublets, septet of triplets, multiplet, broad multiplet, broad doublet, broad triplet, and broad singlet, in that order. All ^{13}C NMR spectra were proton decoupled. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer.

Gas Chromatography was performed on an Agilent 6890 gas chomatograph with a 30 meter HP-5 column using the following conditions: initial oven temperature: 100 °C; temperature ramp rate 50 °C/min.; final temperature: 300 °C held for 7 min; detector temperature: 250 °C.

General procedure for the Sonogashira coupling in the syntheses of symmetrical and unsymmetrical diynes (**G1**)

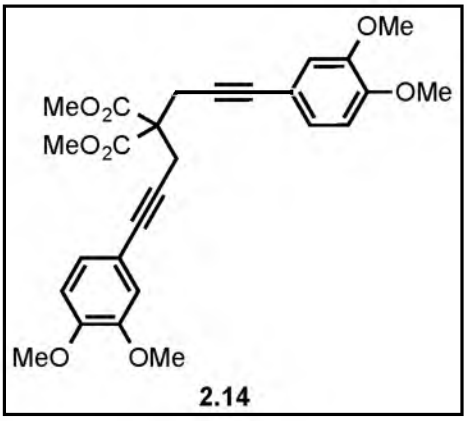


A (R^1 = H, alkyl) **B** **C**

In a nitrogen-filled glove box, a round bottomed flask (or a Schlenk tube under N_2) was charged with terminal diyne **A** (1.00 equiv), aryl iodide **B** (1.10-2.20 equiv), $Pd(PPh_3)_2Cl_2$ (0.03-0.05 equiv), and CuI (0.06-0.10 equiv.) in dry and degassed NEt_3 (2.4 ml/mmol of diyne) and dry dimethylformamide (1.2 ml/mmol of diyne), unless otherwise noted. The resulting reaction mixture was stirred at room temperature for an indicated

period of time. The solvent was evaporated *in vacuo* and satd. NH_4Cl was added to the reaction mixture. The aqueous layer was extracted three times with ethyl acetate and the combined organic extract was washed with brine. The organic phase was collected, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The remaining residue was purified by silica gel flash column chromatography to yield pure unsymmetrical diyne **C**.

Dimethyl-2,2-bis(3-(3,4-dimethoxyphenyl)prop-2-yn-1-yl) malonate (**2.14**)

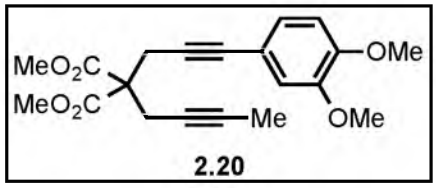


2.14

The general procedure **G1** was used with dimethyl-2,2-di(prop-2-yn-1-yl)malonate (333.00 mg, 1.60 mmol), 4-iodo-1,2-dimethoxybenzene[31] (929.50 mg, 3.52 mmol), $Pd(PPh_3)_2Cl_2$ (56.20 mg, 0.08 mmol) and CuI (30.5 mg, 0.16 mmol) in 3.7 ml of NEt_3 and 1.4 ml of DMF. The reaction mixture was stirred at room temperature for 16 h. The remaining residue was purified by silica gel flash column chromatography using 45% ethyl acetate in hexanes (R_f = 0.27) to afford the title compound **2.14** (693.00 mg, 1.44 mmol, mp: 132-134 °C) as an off-white solid in 90% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.99 (dd, J = 1.6, 8.0 Hz, 2H), 6.88 (d, J = 2.0 Hz, 2H), 6.78 (s, 1H), 6.76 (s, 1H), 3.87 (d, J = 3.2 Hz, 12H), 3.81 (s, 6H), 3.26 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 169.7, 149.6, 148.8, 125.2, 115.5, 114.6, 111.1, 83.9, 82.5, 57.5, 56.12, 56.10, 53.3, 24.1; IR (CH_2Cl_2, cm^{-1}): 3002, 2955, 2836, 1739, 1578, 1441, 1077, 763, 622; HRMS (ESI) calcd for $C_{27}H_{28}O_8Na$ $[M+Na]^+$ 503.1682, found 503.1685.

Dimethyl-2-(but-2-yn-1-yl)-2-(3-(3,4-dimethoxyphenyl)prop-2-yn--1-yl)malonate (**2.20**)

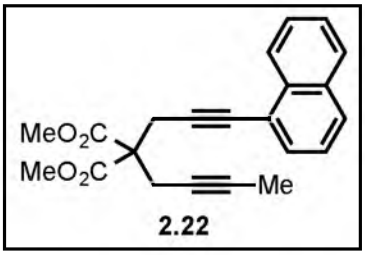


2.20

The general procedure **G1** was used with dimethyl-2-(but-2-yn-1-yl)-2-(prop-2-yn-1-yl)malonate (223.20 mg, 1.00 mmol), 4-iodo-1,2-dimethoxybenzene (292.00 mg, 1.11 mmol), $Pd(PPh_3)_2Cl_2$ (35.30 mg, 0.05 mmol) and CuI (19.10 mg, 0.1 mmol) in 2.4 ml of NEt_3 and 1.2 ml of DMF. The reaction mixture was stirred at room temperature for 16 h. The remaining residue was purified by silica gel flash column chromatography using 25% ethyl acetate in hexanes (R_f = 0.31) to afford the title compound **2.20** (338.40 mg, 0.14 mmol) as a yellow oil in 94% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.93 (dd, J = 1.6, 8.4 Hz, 1H), 6.83 (d, J = 1.6 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 3.83 (d, J = 2.0 Hz, 6H), 3.74 (s, 6H), 3.15 (s, 2H), 2.95 (bq, J = 2.4 Hz, 2H), 1.74 (t, J = 2.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 169.7, 149.4, 148.6, 125.0, 115.5, 114.5, 111.0, 83.6, 82.5, 79.3, 73.1, 57.3, 56.0, 55.9, 53.0, 23.7, 23.3, 3.6; IR (CH_2Cl_2, cm^{-1}): 3004, 2955, 2839, 2256, 1741, 1600, 1439, 1074, 763, 649; HRMS (ESI) calcd for $C_{20}H_{22}O_6Na$ $[M+Na]^+$ 381.1314, found 381.1323.

Dimethyl 2-(but-2-yn-1-yl)-2-(3-(naphthalen-1-yl)prop-2-yn-1-yl) malonate (**2.22**)



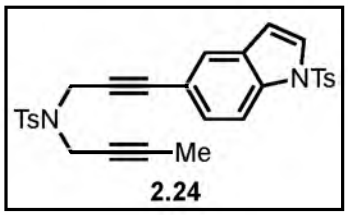
2.22

The general procedure **G1** was used with dimethyl-2-(but-2-yn-1-yl)-2-(prop-2-yn-1-yl)malonate (329.50 mg, 1.48 mmol), 1-iodo-naphthalene (414.40 mg, 1.63 mmol), $Pd(PPh_3)_2Cl_2$ (52.00 mg, 0.07 mmol) and CuI (28.30 mg,

0.15 mmol) in 3.6 ml of NEt_3 and 1.8 ml of DMF. The reaction mixture was stirred at room temperature for 16 h. The remaining residue was purified by silica gel flash column chromatography using 20% ethyl acetate in hexanes (R_f = 0.42) to afford the title compound **2.22** (355.70 mg, 1.02 mmol) as a yellow oil in 69% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.28 (d, J = 8.4Hz, 1H), 7.82 (dd, J = 8.4, 14.0 Hz, 2H), 7.63 (d, J = 6.4 Hz, 1H), 7.58 (td, J = 1.2, 6.4 Hz, 1H), 7.51 (td, J = 1.2, 8.4 Hz, 1H), 7.40 (dd, J = 7.2, 8.4 Hz, 1H), 3.82 (s, 6H), 3.38 (s, 2H), 3.10 (q, J = 2.4 Hz, 2H), 1.81 (t, J = 2.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 169.9, 113.6, 133.3, 130.7, 128.6, 128.4, 126.9, 126.5, 126.3, 125.3, 121.0, 89.2, 81.8, 79.6, 73.2, 57.4, 53.3, 24.3, 23.7, 3.8; IR (CH_2Cl_2, cm^{-1}): 3057, 3004, 2954, 2845, 2235, 1741, 1586, 1397, 1017, 776, 737; HRMS (ESI) calcd for $C_{22}H_{20}O_4Na$ $[M+Na]^+$ 371.1259, found 371.1253.

N-(but-2-yn-1-yl)-4-methyl-*N*-(3-(1-tosyl-1*H*-indol-5-yl)prop-2-yn-1-yl)benzenesulfonamide (**2.24**)

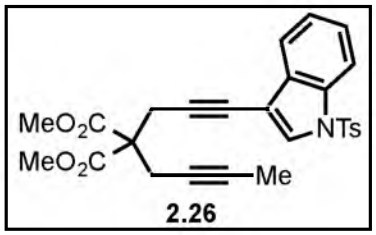


2.24

The general procedure **G1** was used with N-(but-2-yn-1-yl)-4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide (228.70 mg, 0.88 mmol), 5-iodo-1-tosyl-1-indole[32] (382.40 mg, 0.96 mmol), $Pd(PPh_3)_2Cl_2$ (31.00 mg, 0.04 mmol) and CuI (17.00 mg, 0.09 mmol) in 2.0 ml of NEt_3 and 1.0 ml of DMF. The reaction mixture was stirred at room temperature for 24 h. The remaining residue was purified via silica gel flash column chromatography using 55% ethyl acetate in hexanes (R_f = 0.31) to afford the title compound **2.24** (374.00 mg, 0.71 mmol, mp: 136-138 °C) as an off-white solid in 80% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.88 (d, J = 8.4 Hz, 1H), 7.76 (m, 4H), 7.58 (d, J = 3.2 Hz, 1H), 7.38 (s, 1H), 7.25 (m, 4H), 7.13 (d, J = 8.4 Hz, 1H), 6.59 (d, J = 3.2 Hz, 1H), 4.39 (s, 2H), 4.15 (s, 2H), 2.36 (s, 3H), 2.32 (s, 3H), 1.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 145.4, 143.7, 135.8, 135.3, 134.5, 130.7, 130.2, 129.6, 128.21, 128.16, 127.6, 127.0, 125.1, 117.5, 113.6, 108.8, 85.9, 82.1, 81.1, 71.8, 37.3, 37.2, 21.8, 21.6, 3.7; IR (CH_2Cl_2, cm^{-1}): 3142, 2980, 2922, 2236, 1734, 1597, 1455, 1371, 1045, 629, 572; HRMS (ESI) calcd for $C_{29}H_{26}N_2O_4NaS_2$ $[M+Na]^+$ 553.1232, found 553.1237.

Dimethyl-2-(but-2-yn-1-yl)-2-(3-(1-tosyl-1H-indol-3-yl)prop-2-yn-1-yl)malonate (**2.26**)



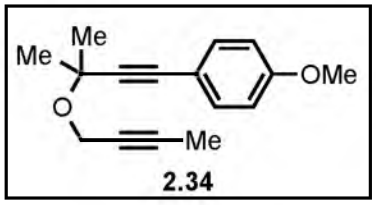
2.26

The general procedure **G1** was used with dimethyl-2-(but-2-yn-1-yl)-2-(prop-2-yn-1-yl)malonate (297.80 mg, 1.34 mmol), 3-iodo-1-tosyl-1-indole[33] (585.50 mg, 1.47 mmol), $Pd(PPh_3)_2Cl_2$ (47.00 mg, 0.07 mmol) and CuI (25.50 mg, 0.13 mmol) in 3.1 ml of NEt_3 and 1.5 ml of DMF. The reaction mixture was stirred at room temperature for 24 h. The remaining residue was purified by silica gel flash column chromatography using 25-35% ether in hexanes (R_f = 0.21) to afford the title compound **2.26** (478.10 mg, 0.98 mmol, mp: 46-48°C) as a yellow solid in 73% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.95 (d, J = 7.2 Hz, 1H), 7.76 (d, J = 6.8 Hz, 2H), 7.65 (s, 1H), 7.57 (d, J = 6.8, 1H), 7.21-7.33 (m, 4H), 3.78 (s, 6H), 3.26 (s, 2H), 3.01 (s, 2H), 2.33 (s, 3H), 1.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 169.7, 145.5, 135.2, 134.3, 131.2, 130.2, 128.8, 127.1, 125.6, 123.9, 120.6, 113.7, 105.2, 88.7, 79.6,

74.7, 73.1, 57.3, 53.2, 24.1, 23.5, 21.7, 3.7; IR (CH_2Cl_2, cm^{-1}): 3140, 3005, 2955, 2923, 2259, 1748, 1597, 1445, 1004, 730, 606, 572; HRMS (ESI) calcd for $C_{27}H_{25}NO_6NaS$ $[M+Na]^+$ 514.1300, found 365.1296.

1-(3-(but-2-yn-1-yloxy)-3-methylbut-1-yn-1-yl)-4-methoxy-benzene (**2.34**)

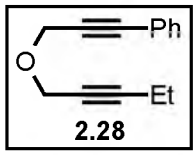


2.34

The general procedure **G1** was used with 3-(but-2-yn-1-yloxy)-3-methylbut-1-yne (243.00 mg, 1.78 mmol), 1-iodo-4-methoxybenzene (460.00 mg, 1.96 mmol), $Pd(PPh_3)_2Cl_2$ (37.60 mg, 0.05 mmol) and CuI (20.40 mg, 0.11 mmol) in 4.1 ml of NEt_3. The reaction mixture was stirred at room temperature for 24 h. The remaining residue was purified by silica gel flash column chromatography using 5-10% ether in hexanes (R_f = 0.27) to afford the title compound **2.34** (281.00 mg, 1.16 mmol) as a light yellow oil in 65% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.37 (bd, J = 8.8 Hz, 2H), 6.84 (bd, J = 8.8 Hz, 2H), 4.30 (q, J = 2.4 Hz, 2H), 3.82 (s, 3H), 1.86 (t, J = 2.4 Hz, 3H), 1.58 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 159.8, 133.4, 115.6, 114.1, 95.0, 89.2, 85.0, 81.9, 76.3, 71.5, 55.5, 53.2, 29.2, 4.0; IR (CH_2Cl_2, cm^{-1}): 2984, 2933, 2860, 2241, 1714, 1606, 1463, 1151, 1045, 891, 558; HRMS (ESI) calcd for $C_{16}H_{18}O_2Na$ $[M+Na]^+$ 265.1204, found 265.1205.

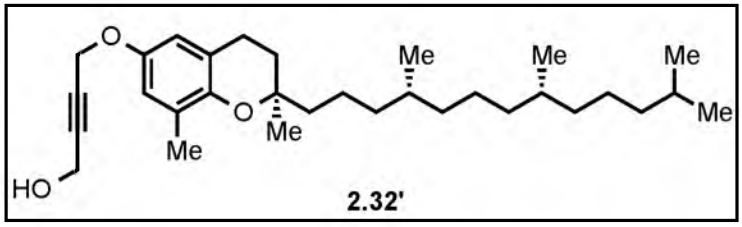
(3-(pent-2-yn-1-yloxy)prop-1-yn-1-yl)benzene (**2.28**)



2.28

To a suspension of pre-washed and dried NaH (98.00 mg, 4.10 mmol) in THF (8.5 ml) was added dropwise a solution of 3-phenylprop-2-yn-1-ol (472.00 mg, 3.60 mmol) at 0 °C. The resulting solution was stirred for 45 min and then 1-bromopent-2-yne (500.00 mg, 3.40 mmol) was added and stirred overnight. The reaction was quenched by the addition of satd. NH_4Cl and the aqueous phase was extracted three times with ether. The combined organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The remaining residue was purified by silica gel flash column chromatography using 2% ether in pentane (R_f = 0.5) to afford the title compound **2.28** (640.30 g, 3.23 mmol) as yellow oil in 95% yield. The spectral data was consistent with the reported literature.[34]

4-(((R)-2,8-dimethyl-2-((4R,8R)-4,8,12-trimethyltridecyl)chroman-6-yl)oxy)but-2-yn-1-ol (**2.32'**)



2.32'

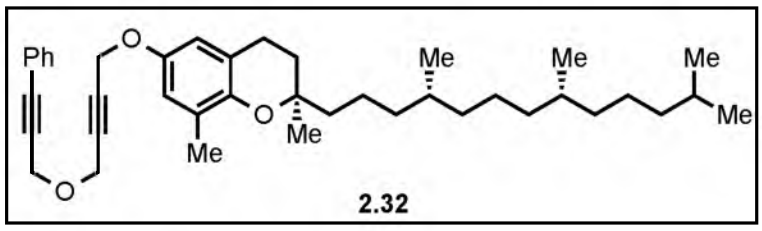
To a suspension of pre-washed and dried NaH (146.00 mg, 6.08 mmol) in THF (10 ml) was added dropwise a solution of δ-tocopherol (1.75 g, 4.35 mmol) in THF (4.5 ml) at 0 °C. The resulting yellow solution was stirred for 45 min and then ((4-bromobut-2-yn-1-yl)oxy)(tert-butyl)dimethylsilane[35] (1.26 g, 4.78 mmol) was added and stirred overnight. The reaction was quenched by the addition of satd. NH_4Cl and the aqueous phase was extracted three times with ether. The combined organic phase was dried over anhydrous

$MgSO_4$, filtered and concentrated *in vacuo*. The crude product obtained was dissolved in THF (10 ml) and tetra-*n*-butylammonium fluoride soln. (4.57 ml, 4.57 mmol, 1 M) was added dropwise at room temperature under nitrogen atmosphere. The resulting solution was stirred overnight at room temperature. The reaction was quenched by the addition of water and then satd. $NaHCO_3$ solution was added. The aqueous phase was extracted with ether, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The remaining residue was purified by silica gel flash column chromatography using 15-25% ether in hexanes (R_f = 0.18) to afford the title compound **2.32'** (1.21 g, 2.57 mmol) as a yellow oil in 59% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.64 (d, J = 2.0 Hz, 1H), 6.53 (d, J = 2.0 H, 1H), 4.64 (s, 2H), 4.30 (s, 2H), 2.74 (t, J = 5.2 Hz, 2H), 2.18 (s, 3H), 0.88-1.81 (m, 39H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 150.4, 147.1, 127.5, 121.2, 116.1, 112.7, 90.0, 85.2, 81.7, 75.9, 57.0, 51.5, 40.3, 39.6, 37.69, 37.66, 37.5, 33.0, 32.9, 31.5, 28.2, 25.0, 24.7, 24.4, 22.9, 22.8, 21.2, 20.0, 19.9, 16.4; IR (CH_2Cl_2, cm^{-1}): 3059, 2927, 2863, 1604, 1479, 1377, 1347, 1079, 755, 691, 585; HRMS (ESI) calcd for $C_{31}H_{50}O_3Na$ $[M+Na]^+$ 493.3658, found 493.3668.

(R)-2,8-dimethyl-6-((4-((3-phenylprop-2-yn-1-yl)oxy)but-2-yn-1-yl)oxy)-2-((4R,8R)-4,8,12-trimethyltridecyl)chroman (**2.32**)

To a stirring suspension of pre-washed and dried NaH (17.40 mg, 0.72 mmol) in THF (2.0 ml) was

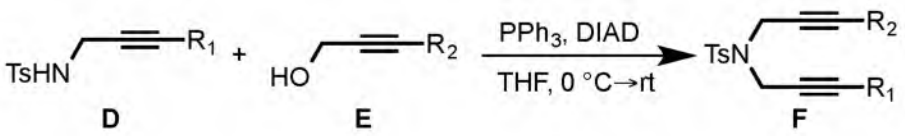


2.32

added dropwise a solution of **2.32'** (262.30 mg, 0.56 mmol) in THF (0.8 ml) at 0 °C. The resulting yellow solution was stirred for 45 min and then (3-bromoprop-1-yn-1-yl)benzene (113.00 mg, 0.59 mmol) was added and stirred overnight. The reaction was quenched by the addition of satd. NH_4Cl and the aqueous phase was extracted three times with ether. The combined organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The remaining residue was purified by silica gel flash column chromatography using 15-25% ether in hexanes (R_f = 0.18) to afford the title compound **2.32** (195.70 g, 0.34 mmol) as a yellow oil in 60% yield.

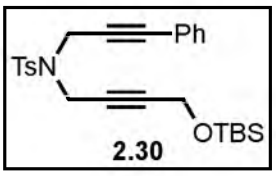
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.45 (m, 2H), 7.32 (m, 3H), 6.64 (d, J = 2.8 Hz, 1H), 6.53 (d, J = 2.8Hz, 1H), 4.66 (t, J = 2.0 Hz, 2H), 4.46 (s, 2H), 4.38 (t, J = 2.0 Hz, 2H), 2.73 (m, 2H), 2.15 (s, 3H), 0.84-1.83 (m, 38H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 150.4, 147.1, 132.0, 128.7, 128.5, 127.5, 122.7, 121.2, 116.2, 112.8, 87.0, 84.4, 82.8, 82.4, 75.9, 57.5, 57.1, 57.0, 40.3, 39.6, 37.7, 37.6, 37.5, 33.0, 32.9, 31.5, 28.2, 25.0, 24.7, 24.3, 22.94, 22.91, 22.8, 21.2, 20.0, 19.9, 16.4; IR (CH_2Cl_2, cm^{-1}): 2927, 2361, 1650, 1558, 1541, 1478, 1222, 757, 690; HRMS (ESI) calcd for $C_{40}H_{56}O_3Na$ $[M+Na]^+$ 607.4127, found 607.4131.

General Procedure for the Mitsunobu reaction for the syntheses of diynes **2.30** and **2.38 (G2)**



To a stirring solution of tosylamide **D** (1.00 equiv), PPh_3 (1.20 equiv), and propargyl alcohol **E** (1.10 equiv) in THF (4.6 ml/mmol of **D**) at 0 °C, was added dropwise DIAD (1.10 equiv.) in 20 min. The resulting solution was warmed to room temperature and continued stirring for 24 h at the same temperature. Silica gel was the added and the solvent was evaporated *in vacuo* and the remaining residue was directly purified by silica gel flash chromatography to yield pure diyne **F**.

N-(4-((tert-butyldimethylsilyl)oxy)but-2-yn-1-yl)-4-methyl-N-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (**2.30**)

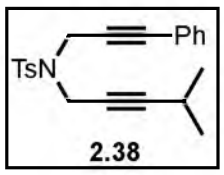


2.30

The general procedure **G2** was used with 4-methyl-N-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (403.50 mg, 1.41 mmol), PPh_3 (445.60 mg, 1.70 mmol), 4-((tert-butyldimethylsilyl)oxy)but-2-yn-1-ol[35] (312.00 mg, 1.56 mmol) and DIAD (314.40 mg, 1.56 mmol) in THF (6.5 ml). The resulting solution was warmed to room temperature and continued stirring for 24 h. The remaining residue was purified by silica gel flash column chromatography using 5-15% ether in hexanes (R_f = 0.30) to afford the title compound **2.30** (496.00 mg, 1.06 mmol, mp: 65-66 °C) as a colorless solid in 75 % yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.76 (d, J = 8.4 Hz, 2H), 7.24-7.30 (m, 5H), 7.17 (m, 2H), 4.40 (s, 2H), 4.23 (bt, J = 1.6 Hz, 2H), 4.21 (t, J = 1.6 Hz, 2H), 2.37 (s, 3H), 0.89 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 144.0, 135.6, 131.8, 129.7, 128.7, 128.4, 128.2, 122.4, 86.0, 84.7, 81.6, 51.8, 37.4, 37.1, 26.0, 21.7, 18.5, -5.0; IR (CH_2Cl_2, cm^{-1}): 3061, 2954, 2930, 2857, 2244, 1917, 1807, 1598, 1467, 1215, 1004, 779, 715; HRMS (ESI) calcd for $C_{26}H_{33}NO_3NaSSi$ $[M+Na]^+$ 490.1848, found 490.1853.

4-methyl-N-(4-methylpent-2-yn-1-yl)-N-(3-phenylprop-2-yn-1-yl) benzenesulfonamide (**2.38**)



2.38

The general procedure **G2** was used with 4-methyl-N-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (637.00 mg, 2.23 mmol), PPh_3 (703.60 mg, 2.68 mmol), 4-methylpent-2-yn-1-ol[36] (241.00 mg, 2.46 mmol) and DIAD (497.30 mg, 2.46 mmol) in THF (10.3 ml). The resulting solution was warmed to room temperature and stirred for 24 h. The remaining residue was purified by silica gel flash column chromatography using 10-20% ether in hexanes (R_f = 0.30) to afford the title compound **2.38** (571.00 mg, 1.56 mmol) as a colorless oil in 70 % yield.

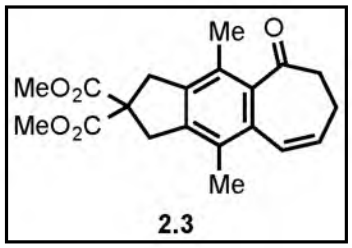
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.73 (d, J = 8.0 Hz, 1H), 7.21-7.26 (m, 5H), 7.17 (m, 2H), 4.36 (s, 2H), 4.16 (bd, J = 2.0 Hz, 2H), 2.39 (m, 1H), 2.33 (s, 3H), 1.01 (d, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 143.8, 135.7, 131.8, 129.7, 128.6, 128.3, 128.1, 122.5, 92.1, 85.6, 81.9, 71.7, 37.5, 37.18, 37.16, 22.8, 21.6, 20.5; IR (CH_2Cl_2, cm^{-1}): 3060, 2972, 2929, 2874, 2250, 1598, 1492, 1120, 950, 757, 575; HRMS (ESI) calcd for $C_{22}H_{23}NO_2NaS$ $[M+Na]^+$ 388.1347, found 388.1355.

General Procedure for Ni-Catalyzed Cycloaddition of Diynes and Tropone (**G3**)

In a nitrogen-filled glove box, 3 mol% catalyst solution (prepared from Ni $(cod)_2$ and SIPr in 1:2 ratio in THF) was added to solution of diyne (1.00 equiv, 0.1 M) and tropone (1.1 equiv) in THF at room temperature. The resulting reaction mixture was then brought out of the glove box, sealed and stirred for indicated period of time at rt or 60 °C (unless

otherwise noted). The reaction was opened to air, concentrated *in vacuo,* and purified by silica gel flash column chromatography.

Dimethyl-4,10-dimethyl-5-oxo-3,5,6,7-tetrahydrocyclohepta[*f*]ind-ene-2,2(1*H*)-dicarboxylate (**2.3**) and dimethyl-5-hydroxy-4,10-di-methyl-1,10a-dihydrobenzo[*f*]azulene-2,2(3*H*)-dicarboxylate (**2.3a**)

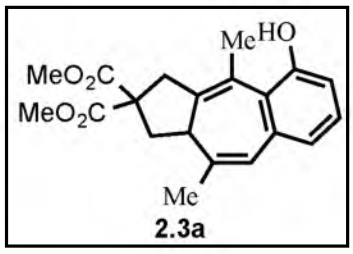


2.3

The general procedure **(G3)** was used with 43.20 mg (0.18 mmol) of diyne **2.1**, 21.30 mg (0.20 mmol) of tropone and 3 mol% of catalyst in THF. The reaction mixture was heated at 60 °C for 5 h. The remaining residue was purified by flash column chromatography using 20% ethyl acetate in hexanes (R_f = 0.25) to afford the title compound **2.3** (49.00 mg, 0.14 mmol) as a pale yellow oil and an inseparable mixture of **2.3** and minor isomer **2.3a** (10.60 mg, 0.03 mmol) as a light brown oil, in 95% yield.

[2.3]: ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.54 (d, J = 11.2 Hz, 1H), 6.20 (dt, J = 7.0, 11.2 Hz, 1H), 3.76 (s, 6H), 3.57 (s, 2H), 3.56 (s, 2H), 2.92 (t, J = 6.8 Hz, 2H), 2.34 (q, J = 6.8 Hz, 2H), 2.15 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 208.7, 172.2, 140.3, 139.6, 138.9, 132.5, 131.3, 129.4, 128.7, 127.7, 59.2, 53.2, 50.2, 40.4, 40.3, 23.0, 16.7, 15.9.; IR (CH_2Cl_2, cm^{-1}): 2954, 1737, 1688, 1436, 1254, 1165; HRMS (ESI) calcd for $C_{20}H_{23}O_3Na$ $[M+Na]^+$ 365.1365, found 365.1373.

[2.3a]: ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.08 (t, J = 7.6 Hz, 1H), 6.81 (d, J = 7.6 Hz, 1H), 6.68 (dd, J = 1.2, 8.0 Hz, 1H), 6.38 (s, 1H), 4.97 (brs, 1H), 3.80 (s, 3H), 3.74 (s,



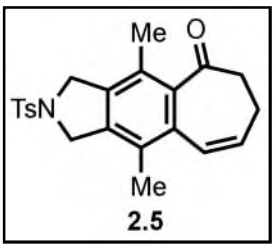
2.3a

3H), 3.10 (m, 2H), 2.77-2.67 (m, 2H), 2.64 (dd, J = 4.0, 11.2 Hz, 1H), 2.07 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 172.48, 172.46, 153.2, 145.4, 144.1, 138.2, 128.6, 126.5, 125.4, 121.8, 121.6, 113.2, 60.5, 53.2, 53.1, 42.3, 39.2, 35.4, 22.5. IR (CH_2Cl_2, cm^{-1}): 3389, 2924, 2853, 1736, 1457, 1264, 1071, 738. HRMS (ESI) calcd for $C_{20}H_{22}O_5Na$ $[M+Na]^+$ 365.1365, found 365.1383.

4,10-dimethyl-2-tosyl-2,3,6,7-tetrahydrocyclohepta[*f*]isoindol-5(1*H*)-one (**2.5**) and 4,10-dimethyl-2-tosyl-1,2,3,10a-tetrahydrobenzo[4,5] cyclohepta[1,2-*c*]pyrrol-5-yl4-bromo-benzoate (**2.5b**)

The general procedure **(G3)** was used with 103.00 mg (0.37 mmol) of diyne **2.4**, 43.70 mg (0.41 mmol) of tropone and 3 mol% of catalyst in THF. The reaction mixture was heated at 60 °C for 5 h. The resulting reaction mixture was filtered through a short pad of silica and washed with dichloromethane. The filtrate was collected and concentrated *in vacuo*. The remaining residue was dissolved in 1.9 ml of dichloromethane and stirred at 0 °C in an ice bath. To this solution was added 24.60 mg (0.11 mmol) of *p*-bromobenzoyl chloride, 1.40 mg of 4-dimethylaminopyridine followed by 15.20 mg of NEt_3 (0.15 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by addition of H_2O and aq. sat. NH_4Cl soln. and the aqueous phase was extracted three times with dichloromethane. The combined organic layers were collected, dried over $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by flash column chromatography using 30-45% ether in hexanes to afford the title compound **2.5b** (28.50

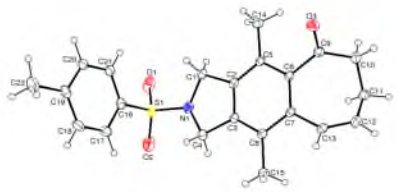
mg, 0.05 mmol, decomposition > 230 ºC, R_f = 0.33 in 35% ether/hexanes) as a light yellow solid and compound **2.5** (105.10 mg, 0.28 mmol, decomposition > 210 °C, R_f = 0.25 in 40% ether/hexanes) as an off-white solid, in 87% yield.



2.5

[2.5]: ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.79 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 6.51 (d, J = 10.8 Hz, 1H), 6.23 (dt, J = 6.8, 10.8 Hz, 1H), 4.61 (s, 2H), 4.60 (s, 2H), 2.92 (t, J = 6.8 Hz, 2H), 2.42 (s, 3H), 2.34 (q, J = 6.8 Hz, 2H), 2.09 (s, 6H); ^{13}C NMR (100 MHz , $CDCl_3$): δ (ppm) 207.9, 143.9, 140.3, 136.7, 135.3, 134.0, 133.3, 132.3, 130.1, 128.7, 127.8, 127.7, 127.0, 54.0, 50.0, 23.1, 21.7, 16.5, 15.8; IR (CH_2Cl_2, cm^{-1}): 2925, 1451, 1345, 1164, 1110, 667; HRMS (ESI) calcd for $C_{22}H_{23}NO_3NaS$ $[M+Na]^+$ 404.1296, found 404.1301.

The crystals suitable for crystallographic analysis were grown using THF and hexanes as solvents.

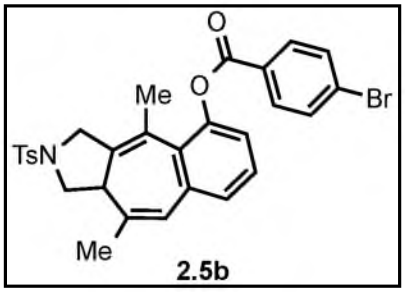


Crystal data and structure refinement for **2.5**

Empirical formula	$C_{22}H_{23}NO_3S$
Formula weight	381.47
Temperature	150(1) K
Wavelength	0.71073 Å

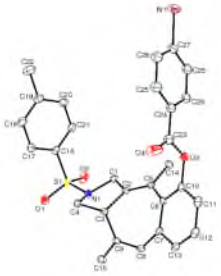
Crystal system	Monoclinic	
Space group	$P\,2_1/n$	
Unit cell dimensions	a = 8.16640(10) Å	α = 90°.
	b = 26.8552(4) Å	β = 105.3641(9)°.
	c = 8.76720(10) Å	γ = 90°.
Volume	1854.02(4) $Å^3$	
Z	4	
Density (calculated)	1.367 Mg/m^3	
Absorption coefficient	0.198 mm^{-1}	
F(000)	808	
Crystal size	0.25 x 0.23 x 0.13 mm^3	
Theta range for data collection	2.53 to 27.48°.	
Index ranges	-10<=h<=10, -34<=k<=34, -11<=l<=11	
Reflections collected	8416	
Independent reflections	4261 [R(int) = 0.0207]	
Completeness to theta = 27.48°	100.0 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.9748 and 0.9522	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4261 / 0 / 326	
Goodness-of-fit on F^2	1.021	
Final R indices [I>2sigma(I)]	R1 = 0.0423, wR2 = 0.1076	
R indices (all data)	R1 = 0.0630, wR2 = 0.1204	

Extinction coefficient	0.0127(15)
Largest diff. peak and hole	0.273 and -0.445 e.Å^{-3}



2.5b

[2.5b]: ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.01 (dd, *J* = 2.0, 6.5 Hz, 2H), 7.72 (d, *J* = 8.5 Hz, 2H), 7.63 (dt, *J* = 2.5, 8.0 Hz, 2H), 7.34 (d, *J* = 7.5 Hz, 2H), 7.24 (d, *J* = 7.0 Hz, 1H), 7.18 (dd, *J* = 1.0, 8.0 Hz, 1H), 6.97 (dd, *J* = 1.5, 8.0 Hz, 1H), 6.42 (s, 1H), 4.17 (d, *J* = 14.0 Hz, 1H), 3.97 (d, *J* = 10.0 Hz, 1H), 3.38 (d, 14.5 Hz, 1H), 2.89 (dd, *J* = 6.5, 9.5 Hz, 1H), 2.43 (bs, 4H), 2.13 (s, 3H), 1.83 (d, *J* = 1.0 Hz, 3H); ^{13}C NMR (125 MHz , $CDCl_3$): δ (ppm) 164.5, 148.3, 144.1, 144.0, 140.0, 138.2, 133.2, 132.3, 132.0, 131.9, 130.0, 129.2, 128.6, 128.3, 127.4, 126.6, 125.0, 121.2, 120.2, 50.4, 50.1, 42.0, 21.8, 19.8, 19.5; IR (CH_2Cl_2, cm^{-1}): 2927, 2287, 1553, 1737, 1591, 1553, 1224, 1012, 673, 549; HRMS (ESI) calcd for $C_{29}H_{26}NO_4NaSBr$ $[M+Na]^+$ 586.0664, found 586.0667.



The crystals suitable for crystallographic analysis were grown using dichloromethane and hexanes as solvents.

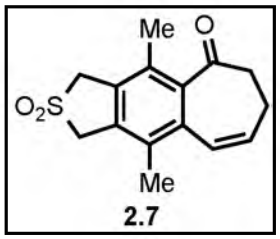
Crystal data and structure refinement for **2.5b**

Empirical formula	$C_{29}H_{26}BrNO_4S$
Formula weight	564.48
Temperature	150(1) K
Wavelength	0.71073 Å

Crystal system	Triclinic	
Space group	***P***	
Unit cell dimensions	a = 10.7009(1) Å	α = 95.2769(8)°.
	b = 11.9592(2) Å	β = 111.3317(10)°.
	c = 12.0410(2) Å	γ = 110.8436(9)°.
Volume	1297.32(3) $Å^3$	
Z	2	
Density (calculated)	1.445 Mg/m^3	
Absorption coefficient	1.701 mm^{-1}	
F(000)	580	
Crystal size	0.40 x 0.28 x 0.20 mm^3	
Theta range for data collection	2.23 to 27.53°.	
Index ranges	-13<=h<=13, -15<=k<=15, -15<=l<=15	
Reflections collected	11304	
Independent reflections	5941 [R(int) = 0.0191]	
Completeness to theta = 27.53°	99.4 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.7273 and 0.5495	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5941 / 0 / 328	
Goodness-of-fit on F^2	1.023	
Final R indices [I>2sigma(I)]	R1 = 0.0347, wR2 = 0.0854	
R indices (all data)	R1 = 0.0483, wR2 = 0.0920	

Largest diff. peak and hole 0.454 and -0.602 e.Å^{-3}

4,10-dimethyl-6,7-dihydro-1*H*-cyclohepta[4,5]benzo[1,2-*c*]thiophen-5(3*H*)-one-2,2-dioxide (**2.7**)



2.7

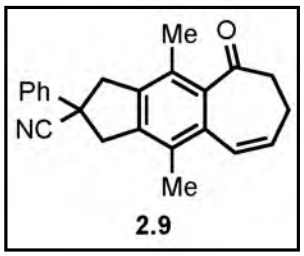
The general procedure **(G3)** was used with 30.90 mg (0.18 mmol) of diyne **2.6**, 21.20 mg (0.12 mmol) of tropone and 3 mol% of catalyst in THF. The reaction mixture was heated at 60 °C for 5 h. The remaining residue was purified by flash column chromatography using 70% ether in hexanes (R_f = 0.24) to afford the title compound **2.7** (27.60 mg, 0.10 mmol) as a colorless solid and an inseparable mixture of **2.7** and **2.7a** (6.00 mg, 0.02 mmol) as a yellow oil, in 67% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.56 (d, *J* = 10.8 Hz, 1H), 6.32 (dt, *J* = 6.8, 10.8 Hz, 1H), 4.36 (d, *J* = 4.4 Hz, 4H), 2.98 (t, *J* = 6.8 Hz, 2H), 2.39 (q, *J* = 6.8 Hz, 2H), 2.17 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (100 MHz , $CDCl_3$): δ (ppm) 207.5, 141.0, 133.9, 133.2, 132.0, 130.7, 130.3, 129.3, 128.8, 57.03, 57.0, 50.4, 22.9, 17.6, 16.8. IR (CH_2Cl_2, cm^{-1}): 2967, 2926, 1690, 1445, 1129, 829, 731, 605; HRMS (ESI) calcd for $C_{15}H_{17}O_3S$ $[M+H]^+$ 277.0898, found 277.0896.

4,10-dimethyl-5-oxo-2-phenyl-1,2,3,5,6,7-hexahydrocyclohepta[*f*]-indene-2-carbonitrile (**2.9**)

The general procedure **(G3)** was used with 41.90 mg (0.19 mmol) of diyne **2.8**, 22.10 mg (0.21 mmol) of tropone and 3 mol% of catalyst in THF. The reaction mixture was heated at 60 °C for 5 h. The remaining residue was purified by flash column

chromatography using 15% ethyl acetate in hexane (R_f = 0.25) to afford the title compound **2.9** (41.70 mg, 0.13) as a light yellow semi-solid and an inseparable mixture of **2.9** and **2.9a** (18.2 mg, 0.06 mmol) as a yellow oil, in 97% yield.

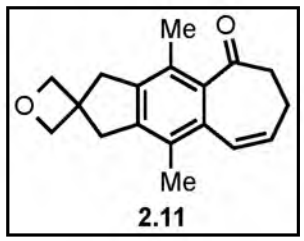


2.9

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.49 (m, 2H), 7.38 (m, 3H), 6.59 (d, J = 10.8 Hz, 1H), 6.26 (dt, J = 6.8, 10.8 Hz, 1H), 3.82 (dd, J = 6.8, 16.4 Hz, 2H), 3.51 (dd, J = 4.0, 16.4 Hz, 2H), 2.98 (t, J = 6.8 Hz, 2H), 2.41 (m, 2H), 2.18 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 208.6, 140.5, 140.3, 139.8, 138.4, 133.3, 131.9, 129.34, 129.26, 129.2, 128.4, 128.1, 125.8, 124.6, 50.3, 47.1, 47.0, 46.2, 23.1, 16.9, 16.1; IR (CH_2Cl_2, cm^{-1}): 2927, 2235, 1686, 1444, 1125, 738. HRMS (ESI) calcd for $C_{23}H_{21}NO_3Na$ $[M+Na]^+$ 350.1521, found 350.1529.

4,10-dimethyl-6,7-dihydro-1*H*-spiro[cyclohepta[*f*]indene-2,3'-oxetan]-5(3*H*)-one (**2.11**)

The general procedure **(G3)** was used with 28.10 mg (0.17 mmol) of diyne **2.10**, 20.20 mg (0.19 mmol) of tropone and 3 mol% of catalyst in THF. The reaction mixture was heated at 60 °C for 5 h. The remaining residue was purified by flash column chromatography using 40-70% ether in hexanes (R_f = 0.20) to afford the title compound **2.11** (23.70 mg, 0.09 mmol, mp: 152-154 °C) as an off-white solid and an inseparable mixture of **2.11** and **2.11a** (16.90 mg, 0.06 mmol) as a yellow oil, in 87% yield.

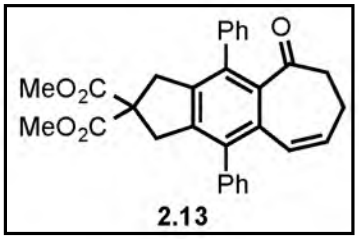


2.11

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.56 (d, J = 10.8 Hz, 1H), 6.20 (dt, J = 6.4, 10.8 Hz, 1H), 4.69 (s, 4H), 3.24 (d, J = 5.2 Hz, 4H), 2.94 (t, J = 6.8 Hz, 2H), 2.36 (q, J = 6.8

Hz, 2H), 2.17 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 208.9, 142.1, 140.7, 139.5, 132.3, 131.3, 129.5, 129.0, 128.0, 84.3, 50.3, 45.9, 44.0, 43.8, 23.1, 16.9, 16.0; IR (CH_2Cl_2, cm^{-1}): 3029, 2927, 2861, 1684, 1440, 1334, 1181, 1122, 834, 797, 737. HRMS (ESI) calcd for $C_{18}H_{21}O_2$ $[M+H]^+$ 269.1542, found 269.1540.

Dimethyl-5-oxo-4,10-diphenyl-3,5,6,7-tetrahydrocyclohepta[*f*]-indene-2,2(1*H*)-dicarboxylate (**2.13**)

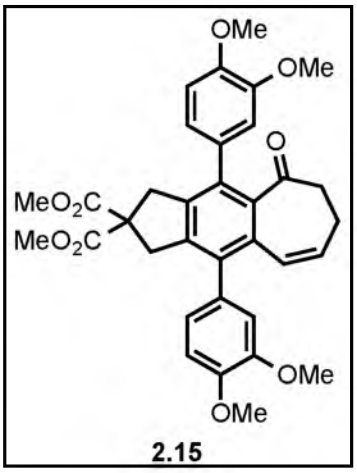


2.13

The general procedure **(G3)** was used with 55.30 mg (0.15 mmol) of diyne **2.12**, 17.90 mg (0.17 mmol) of tropone and 3 mol% of catalyst in THF. The reaction mixture was heated at 60 °C for 5 h. The remaining residue was purified by flash column chromatography using 15% ethyl acetate in hexanes (R_f = 0.25) to afford the title compound **2.13** (45.7 mg, 0.98 mmol, mp = 164-166 °C) as a colorless solid in 64% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.47-7.37 (m, 5H), 7.36-7.29 (m, 3H), 7.26-7.23 (m, 2H), 6.17 (d, J = 11.0 Hz, 1H), 6.03 (dt, J = 6.5, 11.0 Hz, 1H), 3.70 (s, 6H), 3.47 (s, 2H), 3.42 (s, 2H), 2.91 (t, J = 7.0 Hz, 2H), 2.54 (q, J = 7.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 207.3, 172.0, 140.6, 139.2, 138.8, 138.4, 136.4, 135.7, 132.0, 131.3, 130.1, 129.6, 128.9, 128.62, 128.56, 127.64, 127.57, 59.8, 53.2, 50.2, 40.9, 40.7, 23.7; IR (CH_2Cl_2, cm^{-1}): 2954, 1736, 1692, 1436, 1200, 1072, 732, 702. HRMS (ESI) calcd for $C_{30}H_{26}O_5Na$ $[M+Na]^+$ 489.1678, found 489.1685.

Dimethyl-4,10-bis(3,4-dimethoxyphenyl)-5-oxo-3,5,6,7-tetra-hydrocyclohepta[f]indene-2,2(1H)-dicarboxylate (**2.15**)

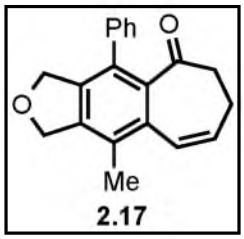


2.15

The general procedure **(G3)** was used with 57.60 mg (0.12 mmol) of diyne **2.14**, 14.00 mg (0.13 mmol) of tropone and 10 mol% of catalyst in THF. The reaction mixture was stirred at room temperature for 24 h. The remaining residue was purified by flash column chromatography using 60% ethyl acetate in hexanes (R_f = 0.25) to afford the title compound **2.15** (50.72 mg, 0.09 mmol) as a light yellow semi-solid in 72% yield.

^{1}H NMR (4 00 MHz, $CDCl_3$): δ (ppm) 6.95 (d, J = 8.0 Hz, 1H), 6.89 (d, J = 8.0 Hz, 1H), 6.79 (m, 4H), 6.23 (d, J = 10.8 Hz, 1H), 6.02 (dt, J = 6.4, 11.2 Hz, 1H), 3.94 (s, 3H), 3.90 (d, J = 4.0 Hz, 6H), 3.88 (s, 3H), 3.70 (s, 6H), 3.48 (s, 2H), 3.44 (s, 2H), 2.91 (t, J = 6.8 Hz, 2H), 2.54 (q, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 207.4, 172.0, 149.0, 148.9, 148.6, 140.8, 140.7, 139.1, 136.2, 135.2, 132.0, 131.7, 131.0, 130.9, 130.3, 122.0, 121.2, 113.0, 112.6, 111.4, 111.3, 59.9, 56.19, 56.15, 56.12, 56.02, 53.2, 50.0, 41.0, 40.8, 29.9, 23.8; IR (CH_2Cl_2, cm^{-1}): 3002, 2955, 2838, 2255, 1735, 1692, 1517, 1201, 1027, 915, 731, 690. HRMS (ESI) calcd for $C_{34}H_{34}O_9Na$ $[M+Na]^+$ 609.2101, found 609.2106.

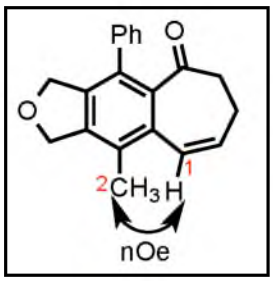
10-methyl-4-phenyl-6,7-dihydro-1*H*-cyclohepta[*f*]isobenzofuran-5(3*H*)-one (**2.17**)



2.17

The general procedure **(G3)** was used with 28.20 mg (0.15 mmol) of diyne **2.16**, 17.90 mg (0.17 mmol) of tropone and 3 mol% of catalyst in THF. The reaction mixture was heated at 60 °C for 5 h. The remaining residue was purified by flash column chromatography using 30% ether in pentane (R_f = 0.30) to afford the title compound **2.17** (35.90 mg, 0.12 mmol) as a light yellow semi-solid in 81% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.29-7.39 (m, 3H), 7.23 (m, 2H), 6.64 (d, J = 10.8 Hz, 1H), 6.31 (dt, J = 6.8, 10.8 Hz, 1H), 5.18 (t, J = 1.6 Hz, 2H), 4.98 (t, J = 1.6 Hz, 2H), 2.91 (t, J = 7.2 Hz, 2H), 2.50 (q, J = 7.2 Hz, 2H), 2.22 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 207.2, 140.6, 140.0, 138.9, 138.0, 133.1, 132.5, 131.8, 128.64, 128.60, 128.5, 128.1, 127.7, 74.4, 74.0, 51.0, 23.1, 16.2; IR (CH_2Cl_2, cm^{-1}): 3029, 2952, 2852, 1735, 1691, 1597, 1496, 1281, 1035, 754, 665. HRMS (ESI) calcd for $C_{20}H_{18}O_2Na$ $[M+Na]^+$ 313.1204, found 313.1210.

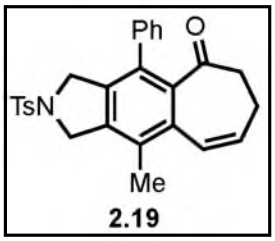


The regiochemistry was assigned on the basis of nOe of proton on C-1 with protons on C-2.

10-methyl-4-phenyl-2-tosyl-2,3,6,7-tetrahydrocyclohepta[f]iso-indol-5(1H)-one (**2.19**)

The general procedure **(G3)** was used with 45.60 mg (0.14 mmol) of diyne **2.18**, 15.80 mg (0.15 mmol) of tropone and 3 mol% of catalyst in THF. The reaction mixture

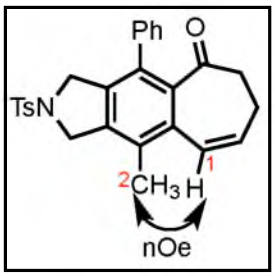
was heated at 60 °C for 5 h. The remaining residue was purified by flash column chromatography using 25% ethyl acetate in hexanes (R_f = 0.22) to afford the title compound **2.19** as an off-white solid (54.30 mg, 0.12 mmol, mp = 210-212 °C) in 91% yield.



2.19

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.74 (d, J = 8.4 Hz, 2H), 7.35 (m, 5H), 7.15 (m, 2H), 6.57 (d, J = 10.8 Hz, 1H), 6.28 (dt, J = 6.8, 10.8 Hz, 1H), 4.66 (s, 2H), 4.43 (s, 2H), 2.83 (t, J = 6.8 Hz, 2H), 2.43 (m, 5H), 2.17 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 206.7, 143.9, 140.9, 138.1, 136.9, 134.9, 133.8, 133.3, 133.0, 132.8, 130.1, 129.4, 128.7, 128.5, 127.9, 127.7, 54.1, 53.9, 50.9, 22.9, 21.7, 15.9; IR (CH_2Cl_2, cm^{-1}): 3031, 2956, 2859, 2255, 1697, 1597, 1347, 1068, 772, 667. HRMS (ESI) calcd for $C_{27}H_{25}NO_3NaS$ $[M+Na]^+$ 466.1453, found 466.1449.

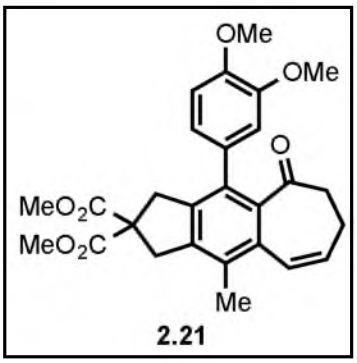
The regiochemistry was assigned on the basis of nOe of proton on C-1 with protons on C-2.



Dimethyl-4-(3,4-dimethoxyphenyl)-10-methyl-5-oxo-3,5,6,7-tetrahydrocyclohepta[f]indene-2,2(1H)-dicarboxylate

(2.21)

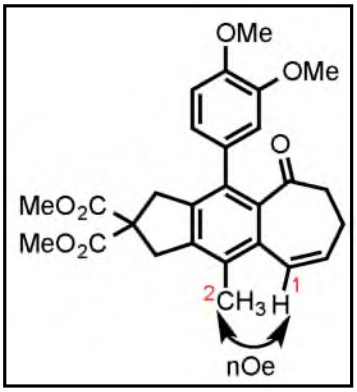
The general procedure **(G3)** was used with 34.90 mg (0.10 mmol) of diyne **2.20**, 11.40 mg (0.11 mmol) of tropone and 3 mol% of catalyst in THF. The reaction mixture was heated at 60 °C for 5 h. The remaining residue



2.21

was purified by flash column chromatography using 40% ethyl acetate in hexanes (R_f = 0.28) to afford the title compound **2.21** as a light yellow oil (40.4 mg, 0.087 mmol) in 89% yield.

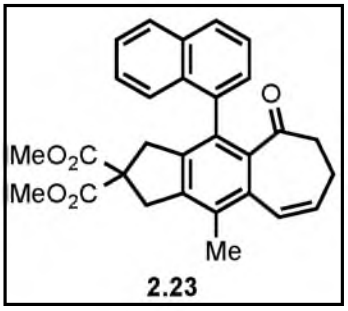
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.85 (d, J = 8.0 Hz, 1H), 6.79 (d, J = 1.6 Hz, 1H), 6.76 (d, J = 2.0, 8.0 Hz, 1H), 6.61 (d, J = 10.8 Hz, 1H), 6.24 (dt, J = 6.8, 10.8 Hz, 1H), 3.88 (d, J = 4.8 Hz, 6H), 3.74 (s, 6H), 3.64 (s, 2H), 2.44 (s, 2H), 2.86 (t, J = 6.4, 2H), 2.46 (q, J =6.8 Hz, 2H), 2.23 (s, 3H) . ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 207.6, 172.2, 148.8, 148.4, 140.5, 140.4, 138.8, 133.6, 132.5, 131.9, 131.8, 130.4, 129.2, 121.2, 112.7, 111.2, 59.6, 56.1, 56.0, 53.2, 51.2, 40.7, 40.5, 23.0, 16.1; IR (CH_2Cl_2, cm^{-1}): 2955, 1735, 1692, 1606, 1583, 1385, 1252, 1025, 761, 670. HRMS (ESI) calcd for $C_{27}H_{28}O_7Na$ $[M+Na]^+$ 487.1733, found 487.1729.



The regiochemistry was assigned on the basis of nOe of proton on C-1 with protons on C-2.

Dimethyl-10-methyl-4-(naphthalen-1-yl)-5-oxo-3,5,6,7-tetra-hydro-cyclohepta[f]indene-2,2(1H)-dicarboxylate (**2.23**)

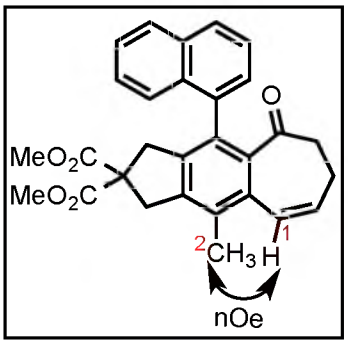
The general procedure **(G3)** was used with 38.70 mg (0.11 mmol) of diyne **2.22**, 13.00 mg (0.12 mmol) of tropone and 3 mol% of catalyst in THF. The reaction mixture was heated at 60 °C for 12 h. The remaining residue was purified by flash column chromatography using



2.23

20% ethyl acetate in hexanes (R_f = 0.23) to afford the title compound **2.23** as a colorless semi-solid (45.80 mg, 0.10 mmol) in 91% yield.

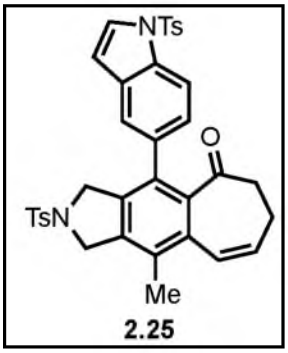
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.87 (m, 1H), 7.83 (d, *J* = 8.4, 1H), 7.54 dd, *J* = 0.8, 8.4 Hz, 1H), 7.48 (m, 2H), 7.43(m, 1H), 7.33 (dd, *J* = 1.2, 6.8 Hz, 1H), 6.67 (d, *J* = 10.8 Hz, 1H), 6.26 (dt, *J* = 6.8, 10.8 Hz, 1H), 3.76-3.62 (m, 8H), 3.28-3.05 (dd, *J* = 17.2, 73.2, 2H), 2.64 (m, 2H), 2.44 (m, 2H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 206.9, 172.1, 141.0, 140.6, 139.6, 136.6, 133.7, 132.5, 132.0, 131.8, 130.9, 129.8, 129.2, 128.5, 128.0, 127.9, 127.0, 126.1, 125.9, 125.8, 125.4, 59.5, 53.13, 53.06, 50.1, 40.5, 40.4, 23.0, 16.2; IR (CH_2Cl_2, cm^{-1}): 3036, 2954, 2361, 2339, 1736, 1692, 1436, 1251, 1164, 1072, 780, 718. HRMS (ESI) calcd for $C_{29}H_{26}O_5NaS$ $[M+Na]^+$ 477.1678, found 477.1685.



The regiochemistry was assigned on the basis of nOe of proton on C-1 with protons on C-2.

10-methyl-2-tosyl-4-(1-tosyl-1*H*-indol-5-yl)-2,3,6,7-tetrahydrocyclo-hepta[*f*]isoindol-5(1*H*)-one (**2.25**) and 4-methyl-2-tosyl-10-(1-tosyl-1H-indol-5-yl)-2,3,6,7-tetrahydrocyclohepta-[f]isoindol-5(1H)-one (**2.25'**)

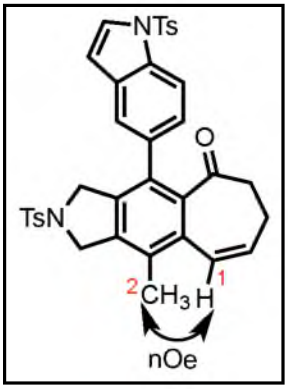
The general procedure **(G3)** was used with 68.60 mg (0.13 mmol) of diyne **2.24**, 15.10 mg (0.14 mmol) of tropone and 10 mol% of catalyst in THF. The reaction mixture was heated at 60 °C for 24 h. The remaining residue was purified by flash column



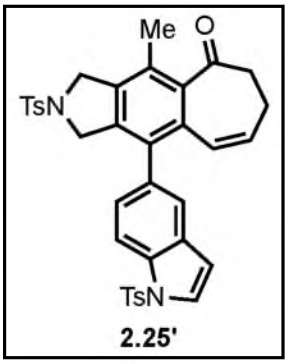
chromatography using 35-45% ethyl acetate in hexanes to afford the title compound **2.25** (52.80 mg, 0.08 mmol) as a yellow semi-solid in 64% yield and **2.25'** (11.5 mg, 0.018 mmol) as a yellow semi-solid in 14% yield, respectively.

[**2.25**]: ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.95 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 8.4 Hz, 2H), 7.71 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 3.6 Hz, 1H), 7.31 (m, 5H), 7.07 (d, J = 8.8 Hz, 1H), 6.63 (d, J = 6.8, 10.8 Hz, 1H), 6.57 (d, J = 10.8 Hz, 1H), 6.27 (dt, J = 6.8, 10.8 Hz, 1H), 4.64 (s, 2H), 4.37 (s, 2H), 2.80 (t, J = 6.8 Hz, 2H), 2.42 (m, 10 H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 206.7, 145.4, 144.0, 141.2, 136.9, 135.6, 135.3, 134.3, 133.9, 133.1, 132.8, 130.9, 130.3, 130.1, 129.4, 128.5, 127.7, 127.1, 127.0, 125.4, 125.1, 121.4, 113.6, 108.9, 54.2, 53.9, 51.0, 22.9, 21.8, 21.7, 15.9; IR (CH_2Cl_2, cm^{-1}): 3143, 3033, 2955, 2859, 2255, 1692, 1596, 1440, 1371, 1346, 1096, 730, 693. HRMS (ESI) calcd for $C_{36}H_{32}N_2O_5NaS_2$ $[M+Na]^+$ 659.1650, found 659.1670.

The regiochemistry was assigned on the basis of nOe of proton onC-1 with protons on C-2.

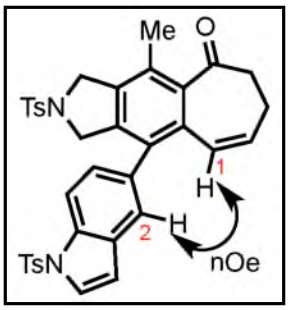


[**2.25'**]: ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.94 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 8.4 Hz, 2H), 7.70 (d, J = 8.0 Hz, 2H), 7.59 (d, J = 3.6 Hz, 1H), 7.31 (m, 5H), 7.22 (bs, 1H), 6.98 (dd, J = 1.6, 8.4 Hz, 1H), 6.62 (d, J = 4.0 Hz, 1H), 6.49 (dt, J = 4.4, 11.6 Hz, 1H), 6.99 (m, 1H), 4.65 (s, 2H), 4.32 (s,2H), 3.00 (t, J = 6.0



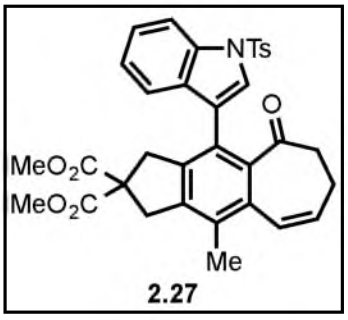
Hz, 2H), 2.40-2.50 (m, 10H), 2.34 (s,3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 149.5, 145.4, 143.92, 143.89, 137.6, 136.2, 135.7, 134.5, 134.2, 134.0, 133.3, 132.3, 130.9, 130.3, 130.1, 128.5, 127.7, 127.2, 126.9, 125.2, 121.3, 113.5, 109.0, 54.3, 29.8, 27.9, 21.9, 21.7, 15.9; IR (CH_2Cl_2, cm^{-1}): 3029, 2924, 2856, 2256, 1660, 1596, 1492, 1166, 1096, 703, 667. HRMS (ESI) calcd for $C_{36}H_{32}N_2O_5NaS_2$ $[M+Na]^+$ 659.1650, found 659.1654.

The regiochemistry was assigned on the basis of nOe of proton on C-1 with protons on C-2.



Dimethyl-10-methyl-5-oxo-4-(1-tosyl-1H-indol-3-yl)-3,5,6,7-tetrahydrocyclohepta[f]indene-2,2(1H)-dicarboxylate (**2.27**)

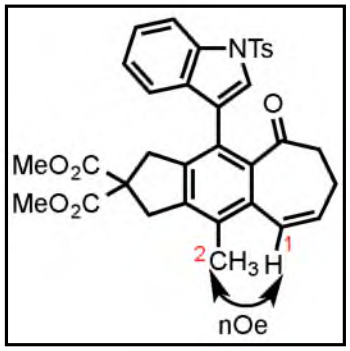
The general procedure **(G3)** was used with 45.00 mg (0.09 mmol) of diyne **2.25**, 10.70 mg (0.10 mmol) of tropone and 3 mol% of catalyst in THF. The reaction mixture was heated at 60 °C for 12 h. The remaining residue was purified via flash column chromatography using 55-60% ethyl acetate in hexanes to afford the title compound **2.27** (31.0 mg, 0.052 mmol) as a light yellow oil and an inseparable mixture of **2.27** and its other regioisomer **2.27'** (10.2 mg, 0.02 mmol) as a yellow oil, in 75% yield.



^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.97 (d, J = 8.0 Hz, 1H), 7.72 (d, J = 8.4 Hz, 2H), 7.49 (s, 1H), 7.19-7.33 (m, 5H), 6.63 (d, J = 10.8 Hz, 1H), 6.25 (dt, J = 6.8, 10.8 Hz, 1H),

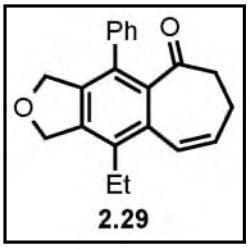
3.73 (d, J = 6.0 Hz, 6H), 3.65 (s, 2H), 3.27 (q, J = 17.2 Hz, 2H), 2.68 (m, 2H), 2.41(m, 2H), 2.35 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 206.5, 172.1, 171.9, 145.0, 141.5, 140.9, 140.1, 135.4, 135.1, 132.7, 132.1, 131.5, 130.8, 130.2, 130.0, 129.1, 126.9, 125.2, 125.0, 123.7, 123.4, 120.7, 120.5, 114.1, 59.5, 53.20, 53.16, 50.4, 40.6, 40.5, 23.0, 21.7, 16.2; IR (CH_2Cl_2, cm^{-1}): 3129, 3032, 2954, 2257, 1735, 1691, 1597, 1173, 1095, 730, 690. HRMS (ESI) calcd for $C_{34}H_{31}NO_7NaS$ $[M+Na]^+$ 620.1719, found 620.1729.

The regiochemistry was assigned on the basis of nOe of proton on C-1 with protons on C-2.



10-ethyl-4-phenyl-6,7-dihydro-1*H*-cyclohepta[*f*]isobenzofuran-5(3*H*)-one (**2.29**)

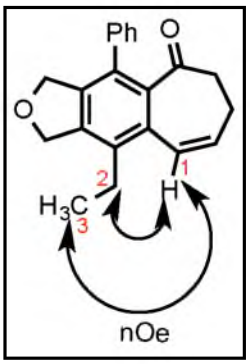
The general procedure (**G3**) was used with 32.30 mg (0.16 mmol) of diyne **2.28**, 19.00 mg (0.18 mmol) of tropone and 3 mol% of catalyst in THF. The reaction mixture was heated at 60 °C for 5 h. The remaining residue was purified by flash column chromatography using 25% ether in pentane (R_f = 0.28) to afford the title compound **2.29** (42.70 mg, 0.14 mmol) as light yellow oil in 86% yield.



^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.35 (m, 3H), 7.24 (m, 2H), 6.71 (d, J = 11.2 Hz, 1H), 6.32 (dt, J = 6.8, 11.2 Hz, 1H), 5.21 (t, J = 1.6 Hz, 2H), 4.97 (t, J = 1.6 Hz, 2H), 2.91 (t, J = 6.4 Hz, 2H), 2.60 (q, J = 7.6 Hz, 2H), 2.49 (q, J = 6.8 Hz, 2H), 1.17 (t, J = 7.6

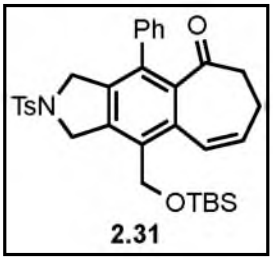
Hz, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 207.4, 140.9, 139.4, 138.9, 138.3, 134.4, 132.7, 132.5, 131.9, 128.6, 128.4, 128.3, 127.7, 74.2, 73.5, 51.2, 23.9, 23.0, 14.0; IR (CH_2Cl_2, cm^{-1}): 3030, 2965, 2873, 2249, 1697, 1600, 1496, 1332, 1229, 1092, 770, 732, 581. HRMS (ESI) calcd for $C_{21}H_{20}O_2Na$ $[M+Na]^+$ 327.1361, found 327.1351.

The regiochemistry was assigned on the basis of nOe of proton on C-1 with protons on C-2 and C-3.



10-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-phenyl-6,7-dihydro-1*H*-cyclohepta[*f*]isobenzo-furan-5(3*H*)-one (**2.31**)

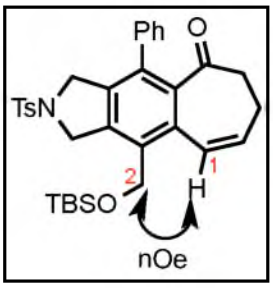
The general procedure **(G3)** was used with 38.10 mg (0.08 mmol) of diyne **2.30**, 9.50 mg (0.09 mmol) of tropone and 10 mol% of catalyst in THF. The reaction mixture was heated at 60 °C for 12 h. The remaining residue was purified via flash column chromatography starting from 10% to 40% ether in hexanes (R_f = 0.29) to afford the title compound **2.31** (37.10 mg, 0.07 mmol) as yellow semi-solid in 79% yield.



^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.72 (d, J = 8.4 Hz, 2H), 7.35 (m, 5H), 7.14 (dd, J = 2.0, 7.6 Hz, 2H), 6 .62 (d, J = 11.2 Hz, 1H), 6.30 (dt, J = 7.2, 10.8 Hz, 1H), 4.77 (s, 2H), 4.67 (s, 2H), 4.37 (s, 2H), 2.82 (t, J = 6.4 Hz, 2H), 2.42 (m, 5H), 0.943 (s, 9H), 0.13 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 206.4, 143.9, 141.0, 138.0, 137.0, 136.0, 134.6, 133.7, 133.4, 132.6, 131.7, 130.0, 128.8, 128.4, 128.1, 127.9, 127.8, 60.8, 54.1,

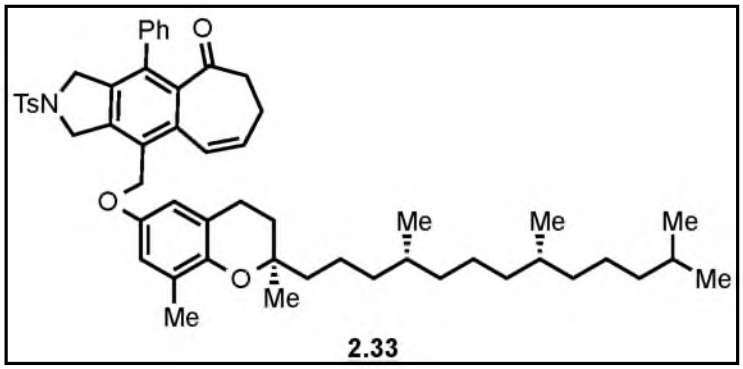
53.4, 51.2, 26.1, 22.6, 21.7, 18.5, 5.2; IR (CH_2Cl_2, cm^{-1}): 3032, 2954, 2930, 2857, 2256, 1696, 1598, 1096, 703, 666. HRMS (ESI) calcd for $C_{33}H_{39}NO_4NaSSi$ $[M+Na]^+$ 596.2267, found 596.2273.

The regiochemistry was assigned on the basis of nOe of proton on C-1 with protons on C-2.



10-((((*R*)-2,8-dimethyl-2-((4*R*,8*R*)-4,8,12-trimethyltridecyl)chroman-6-yl)oxy)methyl)-4-phenyl-6,7-dihydro-1*H*-cyclohepta[*f*]-isobenzo-furan-5(3*H*)-one (**2.33**)

The general procedure **(G3)** was used with 30.60 mg (0.05 mmol) of diyne **2.32**, 6.10 mg (0.06 mmol) of tropone and 3 mol% of catalyst in THF. The reaction mixture was heated at 60 °C for 24 h. The remaining residue was purified by flash column chromatography using 20% ether in hexanes (R_f = 0.18) to afford the title compound **2.33** (23.40 mg, 0.03 mmol) as yellow oil in 65% yield.

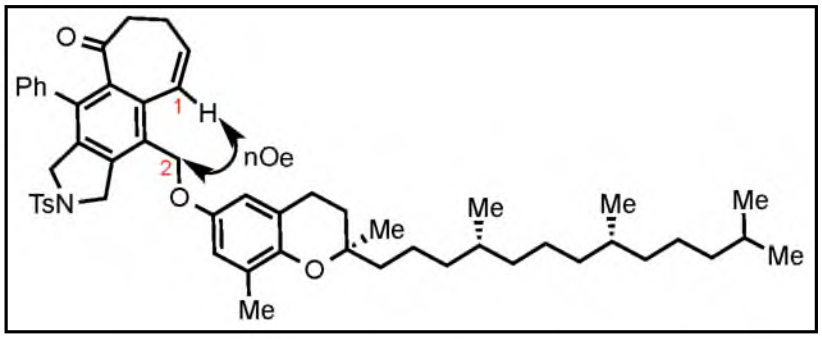


2.33

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.31-7.41 (m, 3H), 7.23-7.27 (m, 2H), 6.76 (d, *J* = 11.2 Hz, 1H), 6.64 (d, *J* = 2.8 Hz, 1H), 6.52 (d, *J* = 2.8 Hz, 1H), 6.36 (dt, *J* = 6.8, 11.2 Hz, 1H), 5.31 (s, 2H), 4.97 (s, 2H), 4.94 (s, 2H), 2.92 (t, *J* = 6.8 Hz, 2H), 2.74 (m, 2H),

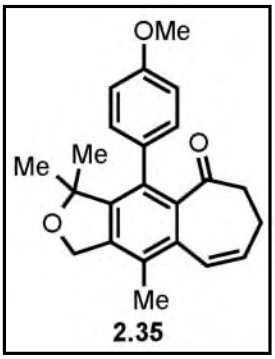
2.52 (q, J = 6.8 Hz, 2H), 2.17 (s, 3H), 0.88-1.85 (m, 38H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 206.7, 151.1, 146.9, 140.8, 140.7, 139.2, 138.6, 134.2, 133.6, 133.2, 128.7, 128.4, 128.0, 127.9, 127.6, 127.5, 121.3, 115.6, 112.2, 75.9, 74.0, 73.6, 66.0, 51.2, 40.3, 39.6, 37.7, 37.6, 37.5, 33.0, 32.9, 31.5, 28.2, 25.0, 24.7, 24.4, 22.9, 22.8, 21.2, 20.0, 19.9, 16.5; IR (CH_2Cl_2, cm^{-1}): 2927, 2863, 2361, 1695, 1605, 1478, 1121, 1182, 1066, 702. HRMS (ESI) calcd for $C_{47}H_{62}O_4Na$ $[M+Na]^+$ 713.4546, found 713.4539.

The regiochemistry was assigned on the basis of nOe of proton on C-1 with protons on C-2.



4-(4-methoxyphenyl)-3,3,10-trimethyl-6,7-dihydro-1H-cyclo-hepta-[f]isobenzofuran-5(3H)-one (**2.35**)

The general procedure **(G3)** was used with 45.60 mg (0.19 mmol) of diyne **2.34**, 22.00 mg (0.21 mmol) of tropone and 10 mol% of catalyst in THF. The reaction mixture was heated at 60 °C for 12 h. The remaining residue was purified via flash column chromatography starting from 25-30% ether in hexanes (R_f = 0.21) to afford the title compound **2.35** (45.9 mg, 0.13 mmol, mp = 148-150 °C) as a light yellow solid in 70% yield.

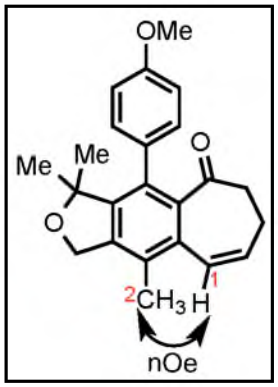


2.35

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.13 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 6.64 (d, J = 10.8 Hz, 1H), 6.25 (dt, J = 6.8, 10.8 Hz, 1H), 5.04 (s, 2H), 3.83 (s, 3H), 2.73

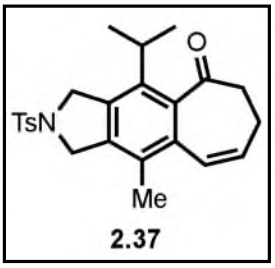
(t, J = 6.4 Hz, 2H), 2.41 (q, J = 6.8 Hz. 2H), 2.19 (s, 3H), 1.24 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 207.5, 159.1, 144.1, 142.2, 139.7, 132.4, 132.3, 131.6, 131.1, 129.2, 128.9, 128.0, 113.0, 87.9, 69.7, 53.3, 51.1, 28.4, 23.1, 15.7; IR (CH_2Cl_2, cm^{-1}): 3031, 2968, 2933, 2361, 1695, 1611, 1459, 1141, 872, 612, 541. HRMS (ESI) calcd for $C_{23}H_{24}O_3Na$ $[M+Na]^+$ 371.1623, found 371.1634.

The regiochemistry was assigned on the basis of nOe of proton on C-1 with protons on C-2.



10-isopropyl-4-phenyl-2-tosyl-2,3,6,7-tetrahydrocyclohepta[f]-isoindol-5(1H)-one (**2.37**)

The general procedure **(G3)** was used with 48.00 mg (0.16 mmol) of diyne **2.36**, 20.10 mg (0.19 mmol) of tropone and 3 mol% of catalyst in THF. The reaction mixture was heated at 60 °C for 12 h. The remaining residue was purified by flash column chromatography starting from 10% to 40% ether in hexanes (R_f = 0.23) to afford **2.37** (49.9 mg, 0.12 mmol) as a yellow semi-solid in 77% yield.

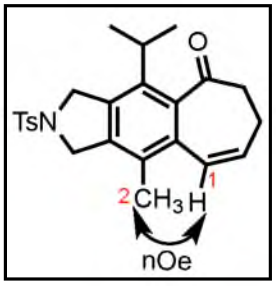


2.37

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.79 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 6 .50 (d, J = 10.8 Hz, 1H), 6.23 (dt, J = 6.8, 10.8 Hz, 1H), 4.74 (s, 2H), 4.53 (s, 2H), 2.98 (t, J = 6.8 Hz, 2H), 2.86 (septet, J = 7.2 Hz, 1H), 2.42 (s, 3H), 2.34 (q, J = 6.8 Hz, 2H),

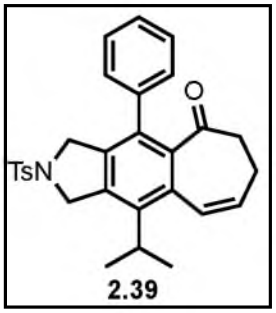
2.08 (s, 3H), 1.21 (d, J = 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 209.2, 144.0, 140.3, 137.6, 137.0, 133.8, 133.6, 133.1, 132.4, 130.1, 128.8, 127.9, 127.7, 54.0, 53.0, 51.3, 31.8, 22.9, 21.9, 21.7, 15.6.; IR (CH_2Cl_2, cm^{-1}): 2962, 1692, 1597, 1449, 1347, 1098, 730, 667. HRMS (ESI) calcd for $C_{24}H_{27}NO_3NaS$ $[M+Na]^+$ 432.1609, found 432.1617.

The regiochemistry was assigned on the basis of nOe of proton on C-1 with protons on C-2.



10-isopropyl-4-phenyl-2-tosyl-2,3,6,7-tetrahydrocyclohepta[f]-isoindol-5(1H)-one (**2.39**)

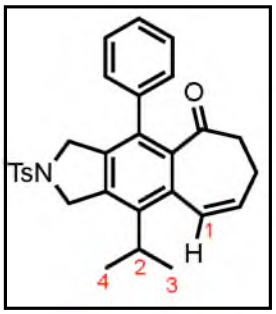
The general procedure **(G3)** was used with 30.60 mg (0.08 mmol) of diyne **2.38**, 9.80 mg (0.09 mmol) of tropone and 5 mol% of catalyst in THF. The reaction mixture was heated at 60 °C for 10 h. The remaining residue was purified by silica gel flash column chromatography starting from 10% to 40% ether in hexanes (R_f = 0.17) to afford the title compound **2.39** (30.0 mg, 0.06 mmol) as a yellow semi-solid in 76%.



^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.72 (d, J = 8.4 Hz, 2H), 7.35 (m, 5H), 7.13 (dd, J = 1.2, 7.6 Hz, 2H), 6 .70 (d, J = 10.8 Hz, 1H), 6.26 (dt, J = 7.2, 10.8 Hz, 1H), 4.77 (s, 2H), 4.32 (s, 2H), 3.22 (septet, J = 6.8 Hz, 1H), 2.78 (t, J = 6.8 Hz, 2H), 2.43 (s, 3H), 2.38 (q, J = 6.8 Hz, 2H), 1.26 (d, J = 7.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm)

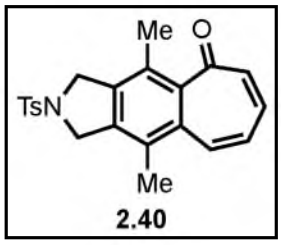
207.0, 144.0, 141.5, 139.5, 138.0, 136.3, 135.3, 133.8, 132.7, 132.6, 132.4, 130.1, 129.4, 128.7, 128.5, 128.0, 127.6, 54.0, 53.1, 51.8, 30.4, 22.2, 21.7, 21.2 ; IR (CH_2Cl_2, cm^{-1}): 3032, 2964, 2871, 2255, 1695, 1598, 1347, 1097, 704, 668, 548. HRMS (ESI) calcd for $C_{29}H_{29}NO_3NaS$ $[M+Na]^+$ 494.1766, found 494.1764.

The regiochemistry was assigned on the basis of nOe of proton on C-1 with protons on C-2, C-3 and C-4.



4,10-dimethyl-2-tosyl-2,3-dihydrocyclohepta[f]isoindol-5(1H)-one (**2.40**)

To a solution of 156.60 mg (0.41 mmol) of **2.5** in 4 ml of EtOH, was added 16.00 mg of 5 wt% of Pd/C. The reaction was stirred under atmospheric pressure of H_2 (balloon) at room temperature for overnight. The reaction mixture was filtered through a short pad of celite and the solvents were evaporated *in vacuo*. The product obtained was dissolved in 1.3 ml of dry CCl_4 and stirred under an atmosphere of nitrogen. Bromine (98.50 mg, 0.62 mmol) was dissolved in 0.4 ml of CCl_4 and dropwise added to the reaction mixture at room temperature. Upon completion of the addition, the mixture was stirred at room temperature for 30 min and then brought to reflux for 1 h. The solvent was removed *in vacuo* and the residue was dissolved in 3.7 ml of dry DMF followed by the addition of LiCl (50.00 mg, 1.17 mmol) under an atmosphere of nitrogen. The reaction mixture was refluxed for 2 h under and worked up by the addition of water and



2.40

extraction with CH_2Cl_2. The organic layers were washed with brine and then dried over anhydrous $MgSO_4$. The solvent was evaporated *in vacuo* and the crude product was purified by silica gel flash chromatography using 25-30% EtOAc in hexanes (R_f= 0.22) to obtain the title compound **2.40** (62.2 mg, 0.164 mmol, decomposition > 210 °C) in 40% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.81 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 12.0 Hz, 1H), 7.34 (d, J = 8.0 Hz, 2H), 6.82 (dd, J = 6.8, 11.6 Hz, 1H), 6.67 (m, 2H), 4.71 (d, J = 7.6 Hz, 4H), 2.42 (s, 3H), 2.38 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 194.1, 144.1, 140.4, 138.3, 137.8, 134.0, 133.0, 133.2, 131.7, 131.4, 130.2, 129.4, 128.1, 127.8, 126.4, 54.5, 54.4, 21.7, 17.5, 17.1; IR (CH_2Cl_2, cm^{-1}): 2925, 2854, 1731, 1598, 1557, 1268, 1100, 867, 781, 582. HRMS (ESI) calcd for $C_{22}H_{21}NO_3NaS$ $[M+Na]^+$ 402.1140, found 402.1157.

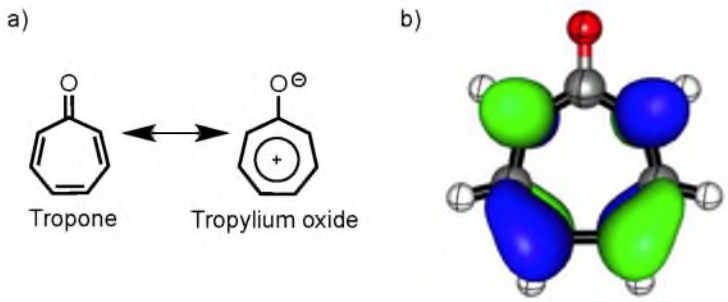


Figure 2.1. Structural features of tropone. a) Tropone-tropylium oxide resonance. b) LUMO of tropone computed by HF/6-311+G(d,p).

Table 2.1. Ni-catalyzed cycloaddition of diyne (**2.1**) with tropone (**2.2**)[a]

Entry	L_n	Ni:L_n	% Conv. of **2.1**[b]	% Yield of **2.3**[b]
1	PPh_3	1:2	>99	14
2	PCy_3	1:2	>99	29
3	$P(O^iPr)_3$	1:2	>99	14
4	PPh_2Me	1:2	>99	9
5	P(*o*-tolyl)$_3$	1:2	>99	3
6	DPPF	1:1	>99	4
7	BINAP	1:1	85	6
8	DPPB	1:1	>99	6
9	Xantphos	1:1	>99	-
10	^{t}Bu-Xantphos	1:1	>99	-
11	IMes	1:2	96	79
12	I^{t}Bu	1:2	98	71
13	IPr	1:2	>99	>99 (**92**)[c]
14	SIPr	1:2	>99	>99 (**92**)[c]
15	SIPr	1:2	>99	>99 (**95**)[c,d]

[a]Reaction Conditions: 10 mol% $Ni(COD)_2$, 20 mol% L_n, Diyne (1 equiv, 0.1M), Tropone (1.1 equiv), toluene, 60 °C, 5 h. [b] Determined by GC using naphathalene as an internal standard. [c] Isolated yield. [d] THF was used instead of toluene.

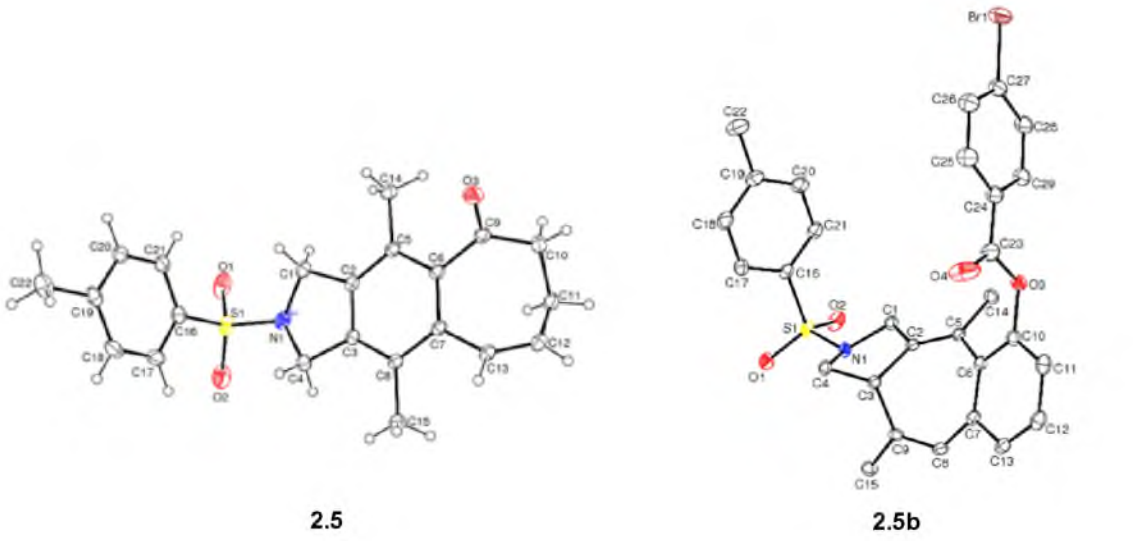


Figure 2.2. Ortep diagram of **2.5** and **2.5b**.

Table 2.2. Ni-catalyzed cycloaddition of diynes and tropone[a,b]

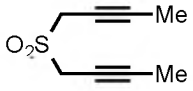
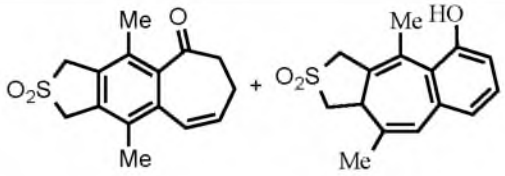
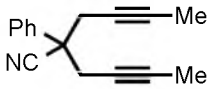
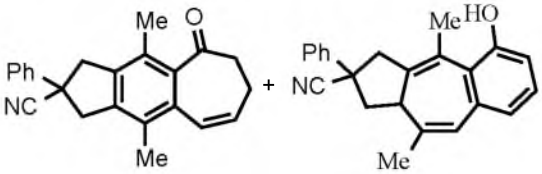
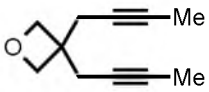
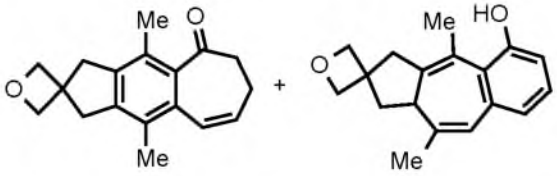
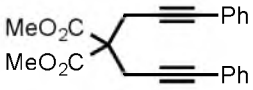
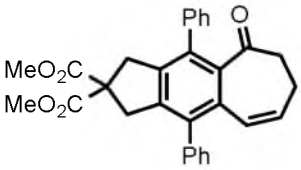
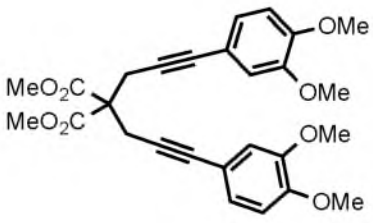
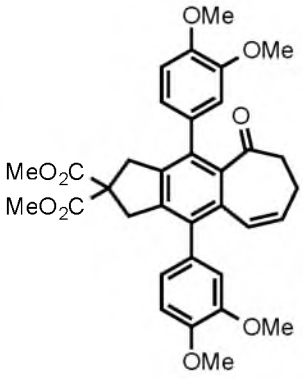
Entry	Diyne	Product(s), Yield(%), major:minor
1	 **2.6**	 **2.7** + **2.7a** 67% (combined yield) **2.7:2.7a** = 94:6[c]
2	 **2.8**	 **2.9** + **2.9a** 97% (combined yield) **2.9:2.9a** = 93:7[c]
3	 **2.10**	 **2.11** + **2.11a** 87% (combined yield) **2.11:2.11a** = 80:20[c]
4	 **2.12**	 **2.13**, 64%
5	 **2.14**	 **2.15**, 72%[d]

Table 2.2. Continued

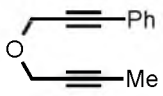
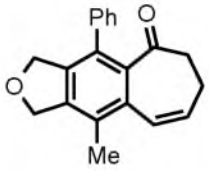
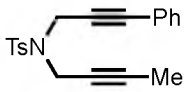
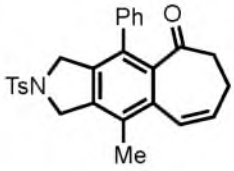
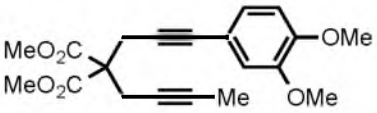
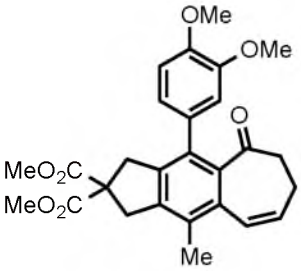
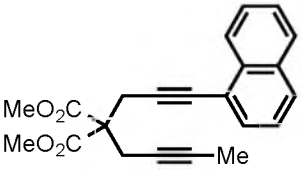
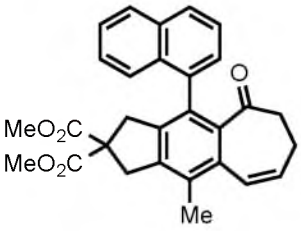
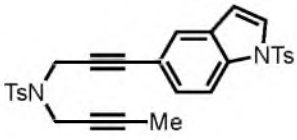
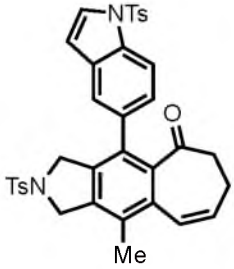
6	 **2.16**	 **2.17**, 81% *Regioselectivity >95:5[c]*
7	 **2.18**	 **2.19**, 91% *Regioselectivity >95:5[c]*
8	 **2.20**	 **2.21**, 89% *Regioselectivity >95:5[c]*
9	 **2.22**	 **2.23**, 91% *Regioselectivity >95:5[c]*
10	 **2.24**	 **2.25**, 78% *Regioselectivity = 82:18[c]*

Table 2.2. Continued

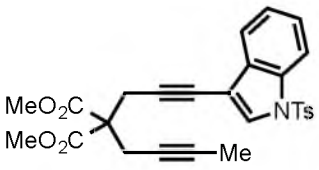
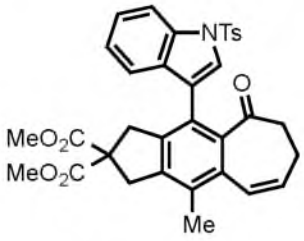
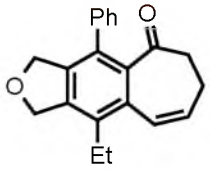
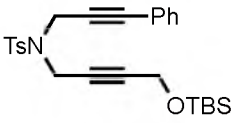
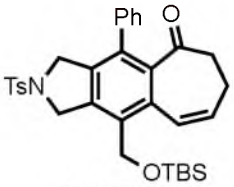
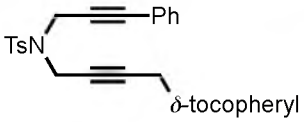
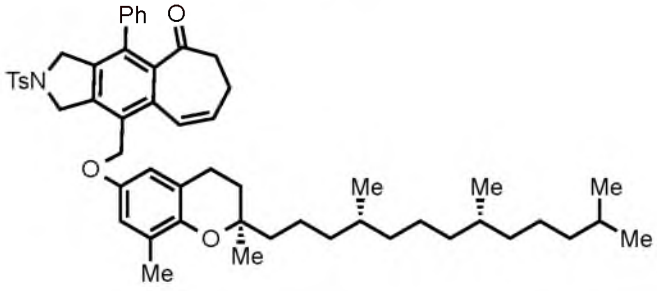
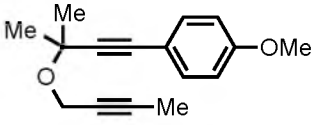
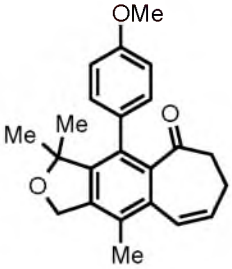
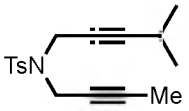
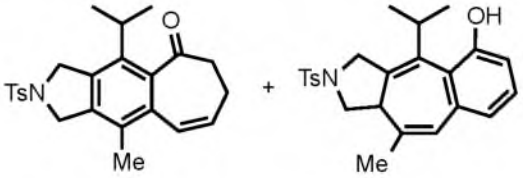
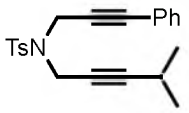
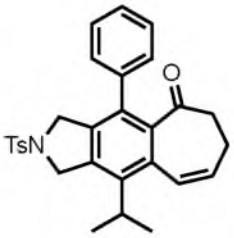
11	 **2.26**	 **2.27**, 75% *Regioselectivity = 93:7[c]*
12	 **2.28**	 **2.29**, 86% *Regioselectivity >95:5[c]*
13	 **2.30**	 **2.31**, 79% *Regioselectivity >95:5[c]*
14	 **2.32**	 **2.33**, 65% *Regioselectivity >95:5[c]*
15	 **2.34**	 **2.35**, 70% *Regioselectivity >95:5[c]*

Table 2.2. Continued

16			**2.37** + **2.37a** 77% (combined yield) **2.37:2.37a** = 93:7[c] *Regioselectivity >95:5*[c]
	2.36		
17			**2.39**, 76% *Regioselectivity >95:5*[c]
	2.38		

[a]Reaction conditions: diyne (1 equiv, 0.1 M), tropone (1.2 equiv), 3 mol% $Ni(COD)_2$, 6 mol% SIPr, THF, 60 °C, 5 h. [b]Isolated yields (in black), ratio of major and minor cycloadduct (in blue), ratio of major and minor regioisomers (in red). [c]The ratios were determined by ^1H NMR of crude reaction mixture. [d]The reaction was performed with 10 mol% catalyst loading at room temperature.

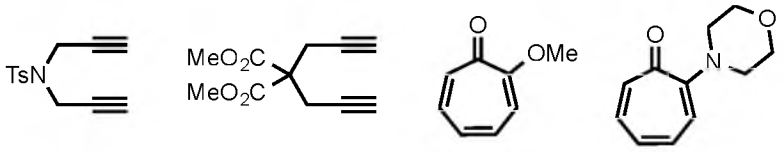


Figure 2.3. Attempted substrates in Ni-catalyzed cycloaddition.

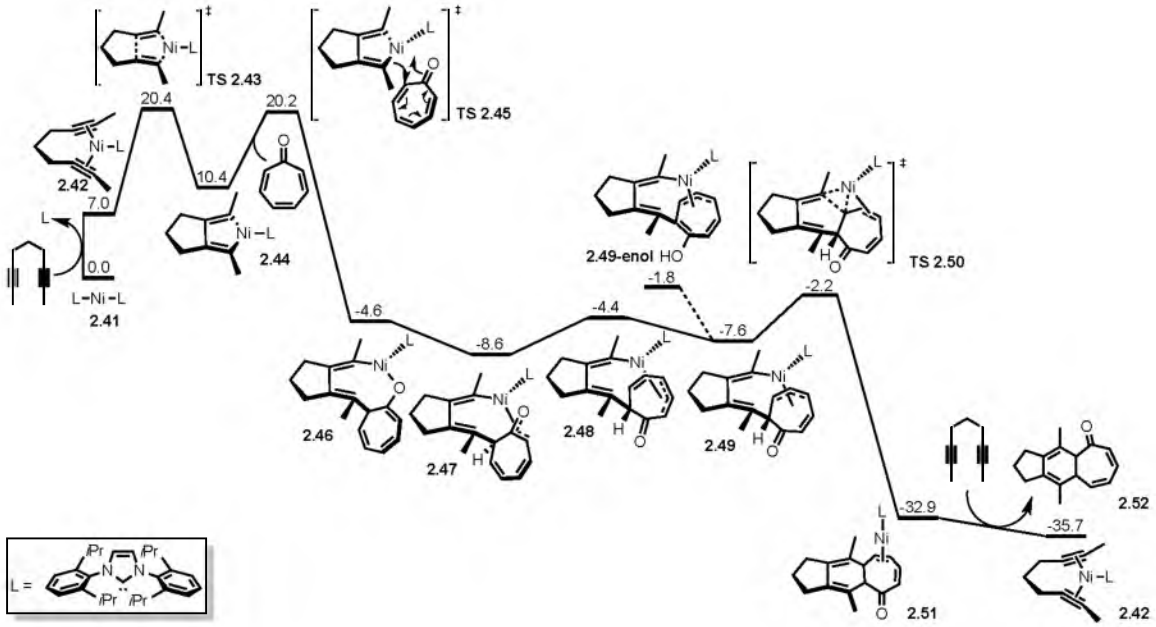


Figure 2.4. The homocoupling pathway A [Ni(IPr)]-catalyzed cycloaddition between nona-2, 7-diyne and tropone. Free energies (298K) with respect to **2.41** are shown in kcal/mol.

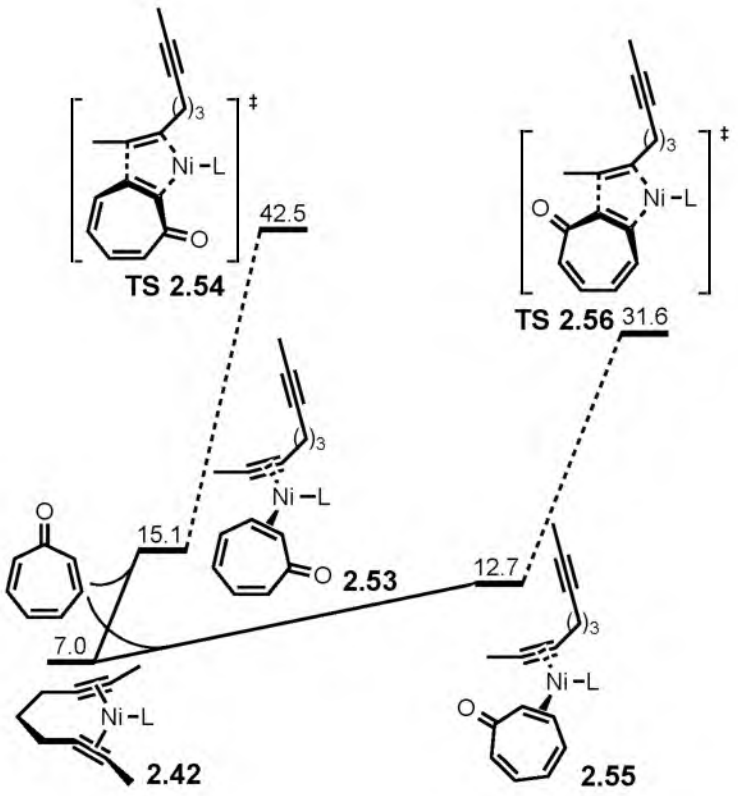


Figure 2.5. The heterocoupling pathway B of [Ni(IPr)]-catalyzed cycloaddition between nona-2,7-diyne and tropone. Free energies (298 K) with respect to **2.41** are shown in kcal/mol.

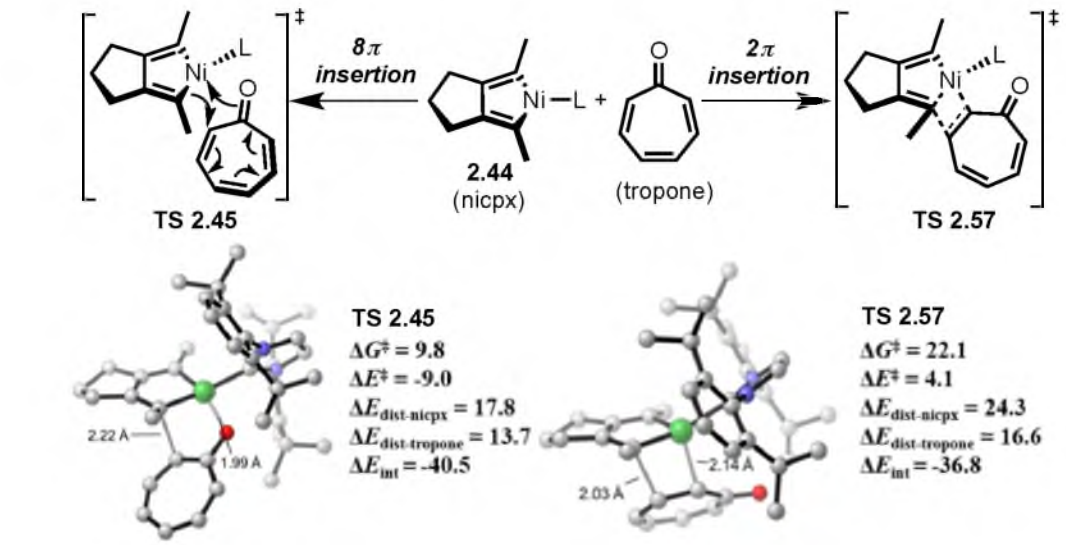


Figure 2.6. Optimized structures, Gibbs free energies and distortion and interaction energies of transition states of 8π insertion (**TS 2.45**) and 2π insertion (**TS 2.57**) of tropone. The Gibbs free energy changes (298 K) with respect to **2.44** are shown in kcal/mol.

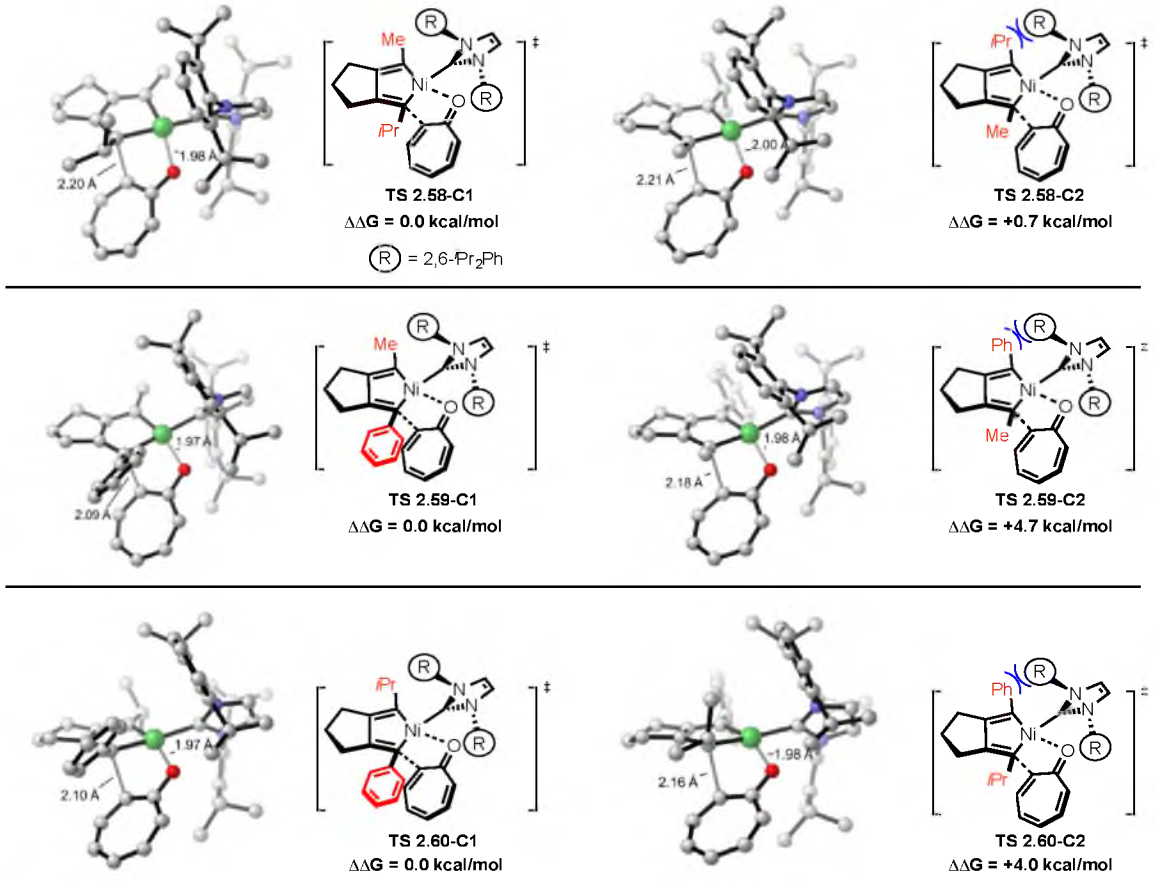


Figure 2.7. Transition states for the intermolecular insertion of tropone into Ni(IPr)-unsymmetrical diyne complex.

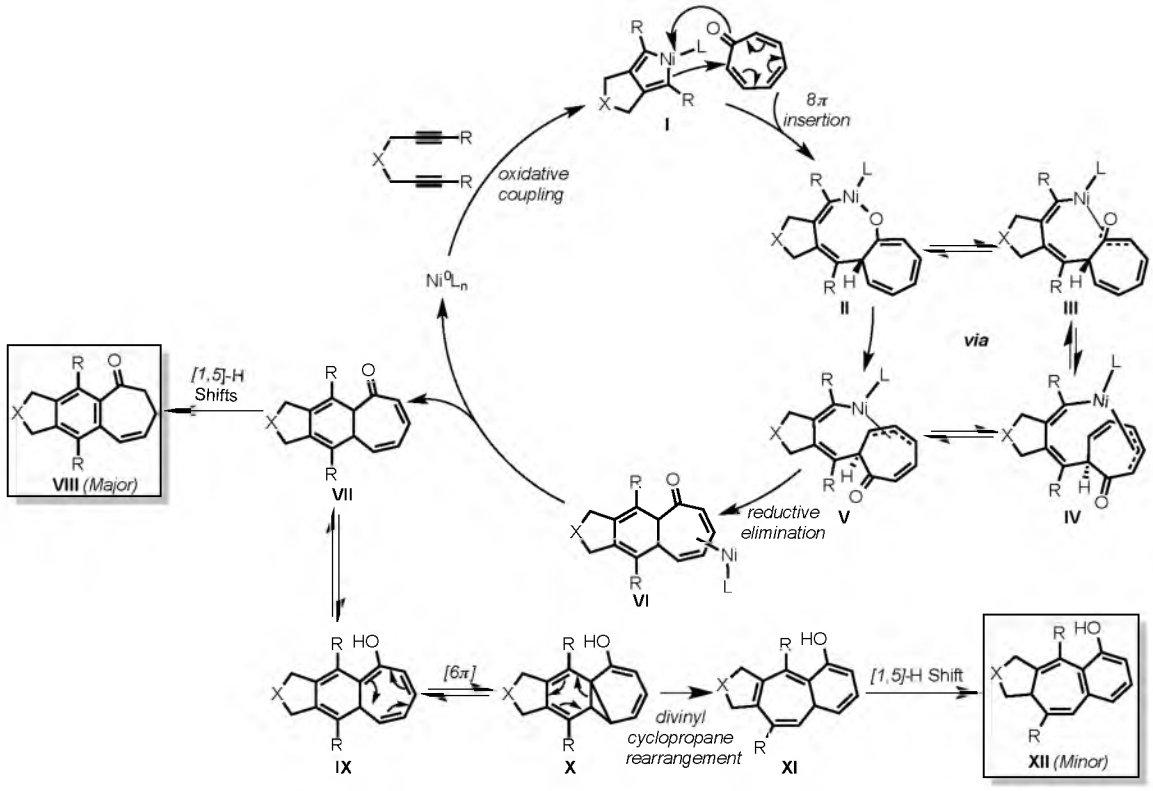


Figure 2.8. Proposed mechanism for the Ni-catalyzed cycloaddition of diynes and tropone.

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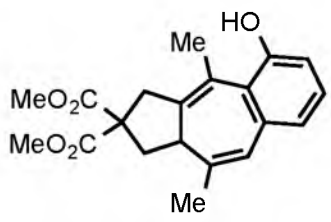
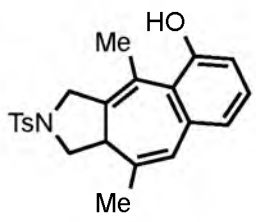


2.3a



2.5a

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(21) The optimization was carried out with B3LYP method, and the SDD basis set for nickel and the 6-31G(d) basis set for the other atoms. The single-point energies and solvent effects in THF were computed with M06 method, and the SDD basis set for nickel and the 6-311+G(2d,p) basis set for the other atoms. Solvation energies were evaluated using the CPCM model. Computational details are included in Supporting Information.

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CHAPTER 3

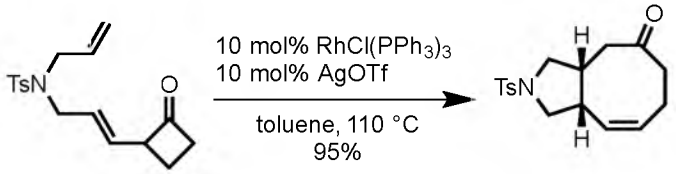
NICKEL-CATALYZED CYCLOADDITION OF 1,3-DIENES WITH 3-AZETIDINONES AND 3-OXETANONES

Introduction

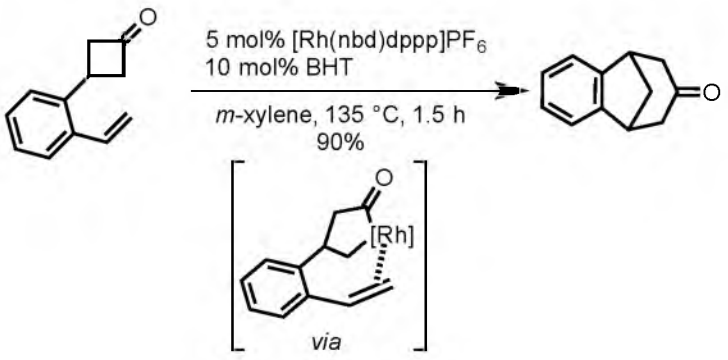
Both thermodynamic and kinetic forces make C−C bond activation one of the most difficult processes to facilitate.[1] Breaking the strong bond between two carbon-carbon atoms is further hampered by the increased steric congestion between C−C bonds relative to C−H and C−X bonds.[1a,b,2] Despite the difficulty associated with C−C bond activation, a handful of transition metal catalyzed methods have been developed to promote this process.[1] The C−C bond activation step in these systems is generally achieved by two important processes: i) oxidative addition of C−C bond to the transition metal, or ii) β-carbon elimination of the transition metal-alkyl complexes (Figure 3.1).[1a,j] Furthermore, the use of small cyclic systems such as cyclopropanes, cyclobutenes and cyclobutanes, wherein the release of inherent strain provides the necessary driving force for C−C bond cleavage, has been a central theme to C−C bond activation strategies.[1,3,4]

Ito and coworkers pioneered the use of cyclobutanone as substrates in transition-metal catalyzed reactions involving C−C bond activation.[5] They showed that stoichiometric amount of Wilkinson's catalyst promoted the decarbonylation of bicyclic cyclobutanone *via* oxidative addition of Rh into C−C bond of cyclobutanone (Figure 3.2).

Since then, a handful of processes involving insertion of unsaturated hydrocarbons into the C–C bond of cyclobutanones have been developed. For example, Murakami developed the Ni-catalyzed cycloaddition of alkynes and diynes with cyclobutanones to form six- and eight-membered carbocycles (Figure 3.3).[6a-d] Wender reported Rh-catalyzed intramolecular [6+2] cycloaddition of activated cyclobutanones (i.e. 2-vinylcyclobutanones) and olefins to construct eight-membered carbocycles (eq 3.1).[6e,f] Recently, Murakami demonstrated the use of Rh- and Ni-catalysts for the intramolecular olefin insertion into cyclobutanones to form a variety of carbocycles (eqs 3.2 and 3.3).[6g-k]



(3.1)



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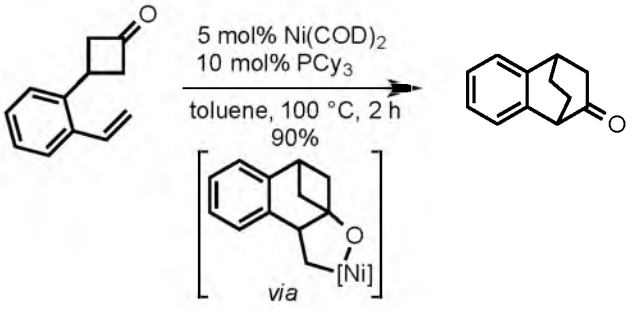
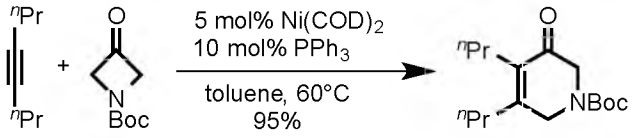


(3.3)

In addition, we and others independently disclosed the syntheses of substituted 3-piperidones by the Ni-catalyzed cycloaddition of alkynes and 3-aza-cyclobutanones (3-azetidinones, eq 3.4).[7] We successfully extended this concept to synthesize eight-membered heterocycles by Ni-catalyzed insertion of diynes into 3-azetidinones (eq 3.5).[8]



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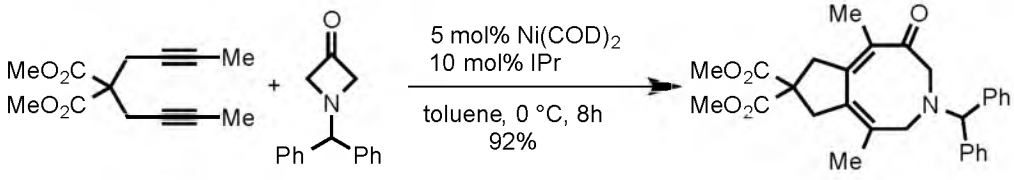
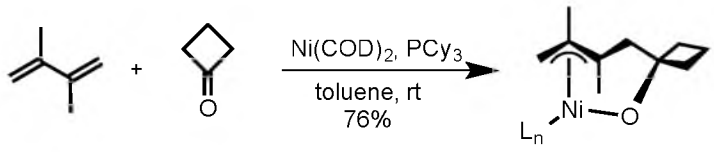


(3.5)

To further advance this interesting concept of C−C bond activation for the synthesis of heterocycles, we were interested in developing a Ni-catalyzed intermolecular cycloaddition of 1,3-dienes with heteroatom-substituted cyclobutanones. Despite these recent advances in transition-metal catalyzed C−C bond cleavage of cyclobutanones (Figure 3.2 and 3.3, eqs 3.1-3.5), the intermolecular insertion of 1,3-dienes remained a challenge. Interestingly, Ogoshi has shown that 1,3-dienes do indeed react with cyclobutanones in the presence of typical Ni catalysts.[9] The Ni(0) complex undergoes oxidative coupling between the diene and the carbonyl of the cyclobutanone as is seen in numerous reductive coupling methodologies of unsaturated hydrocarbons, carbonyls (i.e., aldehydes, ketones, carbon dioxide, isocyanates, etc.), and a reducing agent (eq 3.6).[10,11]

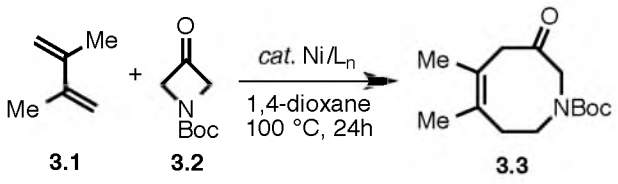


(3.6)

However, in the diene case, instead of turning over as would be necessary to complete a catalytic cycle, β-carbon elimination does not occur, resulting in a relatively stable catalyst sink, a η^3:η^1allylalkoxyNi(II) complex.[9] Thus, given the difficulties associated with catalyst turnover, we were delighted to discover effective conditions for the Ni-catalyzed cycloaddition of azetidinones and 1,3-dienes to afford eight-membered ring N-heterocycles.

Results and discussion

The Ni-catalyzed cycloaddition was investigated using the commercially available diene **3.1** and azetidinone **3.2** as model substrates (eq 3.7). Our recent success with the use of Ni/IPr-catalyst for the cycloaddition of diynes and enynes with carbonyl compounds[8,12] prompted us to explore these highly σ-donating *N*-heterocyclic carbenes (NHCs) to affect this reaction. Although good conversion of the azetidinone was observed, unfortunately, no desired product was detected (Table 3.1, Entries 1-3). 3-Azetidinone was significantly decomposed under the reaction conditions presumably due to the highly basic nature of these ligands in conjunction with the high temperature of the reaction.



3.1 **3.2** **3.3**

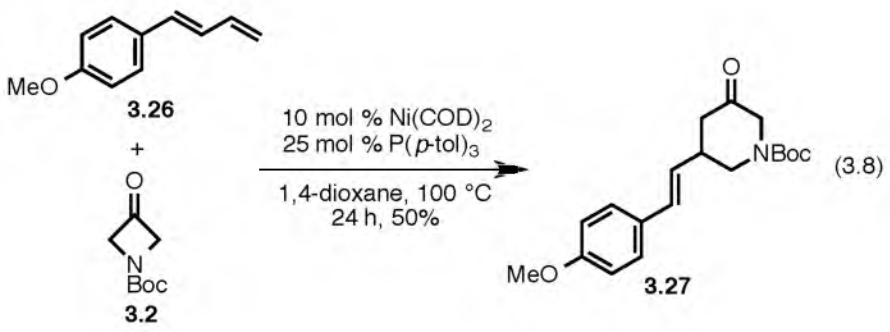
(3.7)

We then turned our focus toward less basic monodentate and bidentate phosphines. While DPPF and DPPP gave poor conversion of azetidinone (Table 3.1, Entry 4-5), the use of DPPB led to the quantitative conversion with 79% isolated yield of the product (Entry 6). With monodentate ligands, low conversion was obtained with PCy_3. However, the use of PPh_3, which has been recently reported to catalyze the coupling of alkynes and azetidinones, was also effective in this reaction and resulted in 75% isolated yield of the cycloadduct (Table 3.1, Entry 7 vs. 8). With the discovery of PPh_3 as a simple and effective ligand, we became interested in evaluating other PAr_3 ligands for this reaction (Table 3.1, Entries 8-11). To our delight, the use of P(*p*-tolyl)$_3$ *consistently* afforded high yield of the product.[13] Further optimizations led to these final reaction conditions: 10 mol % $Ni(COD)_2$, 25 mol % P(*p*-tolyl)$_3$, 1,4-dioxane, 100 °C, 24-48 h.

With the optimized reactions conditions in hand, the substrate scope of this methodology was explored. I collaborated with Megan E. Facer for the substrate scope studies related to this work (Table 3.2). The reaction of oxetanone **3.4** with volatile diene **3.1** afforded oxocine **3.5** in moderate yield. Dienes **3.6** and **3.9** bearing benzyl and homo-benzyl substituents also underwent cycloaddition with both azetidinone **3.2** and oxetanone **3.4**, respectively, to form eight-membered N- and O-containing heterocycles (**3.7**, **3.8**, **3.10**, **3.11**). The reaction of azetidinone **3.2** with dienes bearing primary and secondary alkyl substituents, **3.12** and **3.14**, respectively, was well tolerated in this cycloaddition to afford the azocine products (**3.13**, **3.15**) in good yield. We have recently reported the Ni-catalyzed cycloaddition of 1,6-diynes and 3-azetidinones to form 5-8-ring-fused azocine products.[8] The cycloaddition of cyclic diene **3.16** with 3-azetidinone **2a** afforded a similar [5,8]-ring fused cycloadduct (**3.17**) in good yield and, therefore,

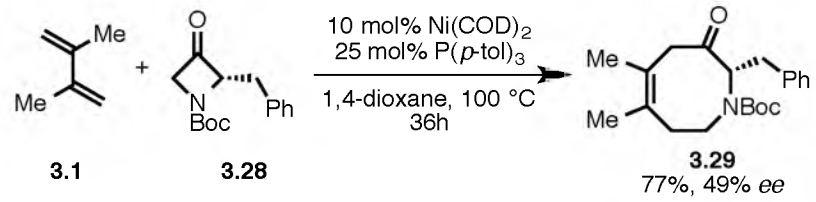
complements our diyne-azetidinone cycloaddition. Our prior attempts to synthesize [6,8]-ring-fused heterocycles by the cycloaddition of 1,7-diyne and 3-azetidinone afforded the spirocyclic pyran product.[8] Gratifyingly, [6,8]-ring-fused azocine **3.19** was obtained in high yield by the use of diene **3.18**. Due to the recent interest in macrocyclic heterocycles,[14] we synthesized macrocyclic dienes **3.20** and **3.23** and subjected them to cycloaddition reaction conditions with both azetidinone 3.**2** and oxetanone **3.4**. To our delight, fused macrocyclic azocines and oxocines (**3.21**, **3.22**, **3.24**, **3.25**) were obtained in high yields. The structure of **3.22** was unambiguously determined by single crystal X-ray crystallography (Figure 3.4).[15]

Interestingly, the reaction between unsymmetrical diene **3.26** and 3-azetidinone **3.2** afforded the six-membered substituted piperidinone **3.27** rather than the expected eight-membered azocine ring, in moderate yield (eq 3.8).



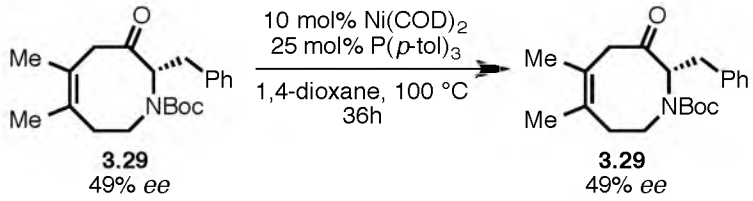
To address the question of regioselectivity in the ring-opening of 2-substituted azetidinone, we synthesized 2-benzyl-3-azetidinone (**3.28**) and treated it in cycloaddition with diene **3.1** (eq 3.9). Gratifyingly, only one regioisomer was obtained in high yield, which suggests that the preferential cleavage of the C−C σ-bond between the carbonyl

carbon and the unsubstituted α-carbon of the 3-azetidinone takes place to afford the heterocyclic product. However, the regioselective product **3.29** retained only 49% enantioselectivity. This outcome is in contrast to our previously reported cycloaddition of alkynes and 3-azetidinones where excellent enantioretention was observed in the case of enantiopure 2-substituted azetidinones.[7a]



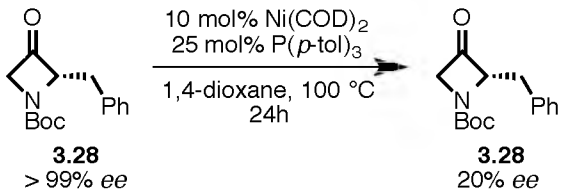
3.1 **3.28** **3.29** 77%, 49% *ee* (3.9)

To rule out the possibility of product racemization under our Ni-catalyzed reaction conditions, we subjected the chiral 8-membered azocine product **3.29** (49% *ee*) to our catalytic conditions (eq 3.10). No erosion of enantioselectivity was observed over the course of the reaction.



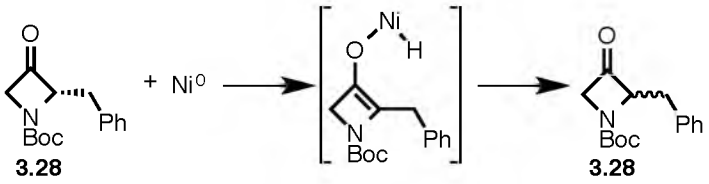
3.29 49% *ee* **3.29** 49% *ee* (3.10)

However, on treating our enantiopure 2-benzyl-3-azetidinone **3.28** to the Ni-catalyst in absence of diene, significant loss in enantioselectivity was observed within 24 hours of the reaction (eq 3.11).



(3.11)

This observation suggests that the chiral 3-azetidinone can undergo reversible α C−H activation by Ni(0) leading to the loss of enantioselectivity (eq 3.12). Additionally, Aïssa and coworkers also proposed the intermediacy of Ni(0)-catalyzed α C−H activation of 3-azetdinones to explain the formation of hydroalkynylation product observed in the cycloaddition of 3-azetidinone and diphenylacetylene.[7b]



(3.12)

Mechanism

The proposed mechanism for this cycloaddition reaction is shown in Figure 3.5. The oxidative coupling of 1,3-diene and the carbonyl group of the 3-azetdinone/3-oxetanone would result in the formation of η^3:η^1allylalkoxyNi(II) complex **Z₁**.[9] This complex would then undergo β-carbon elimination to afford the intermediate **Z₂**. For 2-substituted 3-azetidinones, β-carbon elimination would occur from the less hindered side of azetidinone, *i.e.* the cleavage of the C−C bond between the carbonyl carbon and the unsubstituted α-carbon of the 3-azetidinone. Complex **Z₂** would then isomerize to complex **Z₃**, which can undergo two different $C(sp^3)$–$C(sp^3)$ reductive elimination

pathways to either form piperidinone or 8-membered heterocyclic product. Subsequent C−C bond-forming reductive elimination of the η^3:η^1allylalkylNi(II) complex **Z3** generally yields the 8-membered heterocyclic product. However, the formation of the six-membered heterocycle **3.27** could be rationalized by reductive elimination at the C3 position of the η^3:η^1-benzylalkylnickel(II) complex **Z3** due to stabilization by the phenyl group.[17]

Conclusion

In summary, we have developed a Ni/P(*p*-tol)$_3$-catalyzed intermolecular cycloaddition of 1,3-dienes and 3-azetidinones/3-oxetanones. This synthetic method involves C−C activation of the strained four-membered heterocycle to form monocyclic and bicyclic eight-membered heterocyclic products, which are difficult to access by conventional methods. Interestingly, the use of a diene conjugated with a benzene ring led to the formation of a piperidinone rather than an eight-membered heterocycle. Future work would be focused on improving the scope of this reaction and also to develop an efficient and general catalytic system for the selective formation of piperidinones *via* the cycloaddition of dienes and 3-azetidinones.

General experimental

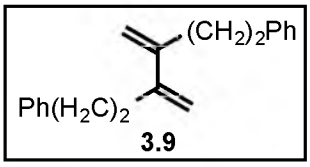
All reactions were conducted under an atmosphere of N_2 using standard Schlenk techniques or in a N_2 filled glove-box unless otherwise noted. Toluene was dried over neutral alumina under N_2 using a Grubbs type solvent purification system. THF was freshly distilled from Na/benzophenone. Ni(COD)$_2$ was purchased from Strem and used

without further purification. The dienes **3.1** and **3.6** were purchased from Sigma-Aldrich and used as such. The dienes **3.12**[18a], **3.14**[18a] **3.16**[18b], **3.18**[18c], **3.20**[18d], **3.26**[18e] and 2-benzyl-3-azetidinone **3.28**,[18f] were prepared according to literature procedure. All other reagents were purchased and used without further purification unless otherwise noted.

^{1}H and ^{13}C Nuclear Magnetic Resonance spectra of pure compounds were acquired at 500 and 125 MHz, respectively, unless otherwise noted. Proton resonances were reported relative to the deuterated solvent peak: 7.27 ppm for $CDCl_3$, 2.50 ppm (center line signal) for DMSO-d^6 and 2.09 ppm (center line signal) for toluene-d^8. Carbon resonances were reported relative to the deuterated solvent peak: 77.23 ppm (center line signal) for $CDCl_3$, 39.51 ppm (center line signal) for DMSO-d^6 and 20.40 (center line signal) for toluene- d^8. The abbreviations s, d, dd, dt, dq, t, td, tq, q, qt, quint, sept, septd, septt, m, brm, brd, brt, and brs stand for singlet, doublet, doublet of doublets, doublet of triplets, doublet of quartets, triplet, triplet of doublets, triplet of quartets, quartet, quartet of triplets, quintet, septet, septet of doublets, septet of triplets, multiplet, broad multiplet, broad doublet, broad triplet, and broad singlet, in that order. All ^{13}C NMR spectra were proton decoupled. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer.

Gas Chromatography was performed on an Agilent 6890 gas chomatograph with a 30 meter HP-5 column using the following conditions: initial oven temperature: 100 °C; temperature ramp rate 50 °C/min.; final temperature: 300 °C held for 7 min; detector temperature: 250 °C.

(3,4-dimethylenehexane-1,6-diyl)dibenzene (**3.9**)

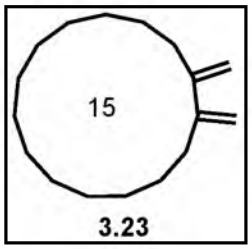


3.9

Diene **3.9**, was prepared according to the Butsugan's procedure.[18a] To a solution of phenethylmagnesium bromide, prepared in a conventional manner from Mg turnings (0.42 g, 17.34 mmol) and (2-bromoethyl)benzene (3.21 g, 17.34 mmol) in thf (23 ml), was added CuI (330 mg, 1.73 mmol) at 0 °C and the mixture is stirred for 10 min. A solution of but-2-yne-1,4-diyl-tetraethyl-bis(phosphate) (2.07 g, 5.78 mmol) in thf (12 ml) was then added dropwise and the mixture is stirred for 16 h at room temperature. The reaction is quenched by the addition of water and the aqueous layer is extracted 3 times with pentane. The organic extracts was collected, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The remaining residue was purified by silica gel flash column chromatography using 2% ether in pentane (R_f = 0.62 in 2% ether/pentane) to afford the title compound **3.9** (1.09 g, 4.15 mmol, 72%) as a semi-solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.34-7.40 (m, 4H), 7.24-7.30 (m, 6H), 5.27 (s, 2H), 5.09 (s, 2H), 2.86-2.91 (m, 4H), 2.65-2.69 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 147.0, 142.4, 128.6, 128.52, 128.47, 126.0, 125.9, 112.4, 36.4, 36.0, 35.4, 31.3; IR (CH_2Cl_2, cm^{-1}): 3086, 3063, 3027, 3003, 2936, 2959, 1630, 1596, 1496, 1178, 1074, 894, 842; HRMS (ESI) calcd for $C_{20}H_{22}Ag$ $[M+Ag]^+$ 369.0772, found 369.0764.

1,2-dimethylenecyclopentadecane (**3.23**)

Diene **3.23** was prepared according to Fokin and Schreiner's procedure.[18d] A 500 ml 2-neck round-bottomed flask fitted with a reflux condenser was charged with NaH (1.7g, 70.83 mmol) and 150 ml of diglyme. To the well-stirred suspension of NaH, was added



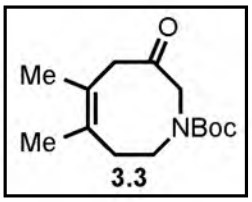
portionwise trimethylsulfoxonium iodide (9.4 g, 42.52 mmol) at room temperature. The reaction mixture was then gently heated to 130 °C and cyclopentadecanone (3.18 g, 14.17 mmol) was added to the reaction mixture in one portion. The reaction mixture was heated at 130 °C for 30 min and cooled down to room temperature. The reaction is then carefully quenched by the addition of water and the aqueous layer is extracted 3 times with pentane. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The remaining residue was purified by silica gel flash column chromatography using pure pentane (R_f = 0.3 in pentane) to afford the title compound **3.23** (0.85 g, 3.63 mmol, 26%) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 5.07 (s, 2H), 4.94 (s, 2H), 2.32 (brt, J = 6.4 Hz, 4H), 1.41-1.48 (m, 6H), 1.27-1.30 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 147.7, 112.4, 27.8, 27.64, 27.62, 26.8, 26.6; IR (CH_2Cl_2, cm^{-1}): 3089, 2929, 2857, 1629, 1593, 1460, 1385, 1350, 891.

General Procedure for Cycloaddition

In a nitrogen-filled glove box, 10 mol% catalyst solution (prepared from $Ni(COD)_2$ and Tri(*p*-tolyl)phosphine in 1:2.5 molar ratio in 1,4-dioxane) was added to solution of 3-azetidinone (1 equiv., 0.4 M) or 3-oxetanone (1 equiv., 0.2 M) and 1,3-diene (2 equiv.) in 1,4-dioxane at room temperature. The resulting reaction mixture was then stirred for indicated time at 100 °C, opened to air, concentrated *in vacuo,* and purified by silica gel flash column chromatography. This procedure was used for the cycloaddition reactions unless otherwise noted.

(Z)-tert-butyl 5,6-dimethyl-3-oxo-3,4,7,8-tetrahydroazocine-1-(2H)-carboxylate (**3.3**)

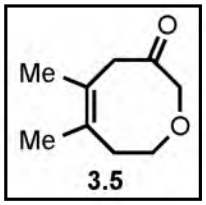


3.3

The general procedure was used with 66.0 mg (0.80 mmol) of diene **3.1**, 68.8 mg (0.40 mmol) of 1-boc-3-azetidinone **3.2** and 10 mol % of catalyst in 1,4-dioxane. The resulting reaction mixture was stirred at 100 °C for 24 h. The remaining residue was purified via flash column chromatography using 15-20% ether in pentane (R_f = 0.16 in 20% ether/pentane) to afford the title compound **3.3** (80.0 mg, 0.32 mmol, 79%) as colorless oil.

^{1}H NMR (500 MHz, DMSO-d^6, 89 °C): δ (ppm) 3.72 (s, 2H), 3.44-3.46 (m, 2H), 3.05 (brs, 2H), 2.34 (brt, J = 5.0 Hz, 2H), 1.76 (s, 3H), 1.61 (s, 3H), 1.41 (brs, 9H); ^{13}C NMR (125 MHz, DMSO-d^6, 89 °C): δ (ppm) 206.7, 153.9, 131.0, 122.0, 79.1, 56.3, 47.6, 46.9, 35.2, 27.5, 20.0, 18.2; IR (CH_2Cl_2, cm^{-1}): 2977, 2935, 1705, 1478, 1456, 1395, 1218, 1159, 973, 928, 916, 867, 830, 779.; HRMS (ESI) calcd for $C_{14}H_{23}NO_3Na$ $[M+Na]^+$ 276.1576, found 276.1566.

(*Z*)-5,6-dimethyl-7,8-dihydro-2*H*-oxocin-3(4*H*)-one (**3.5**)

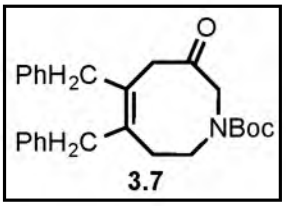


3.5

The general procedure was used with 51.0 mg (0.68 mmol) of diene **3.1**, 22.3 mg (0.31 mmol) of 3-oxetanone **3.4** and 10 mol % of catalyst in 1,4-dioxane. The resulting reaction mixture was stirred at 100 °C for 24 h. The remaining residue was purified via silica gel flash column chromatography using 10-20% ether in pentane (R_f = 0.30 in 20% ether/pentane) to afford the title compound **3.5** (19.2 mg, 0.12 mmol, 40%) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 4.00 (s, 2H), 3.81 (brd, J = 4.8Hz, 2H), 3.38 (s, 2H), 2.45 (brs, 2H), 1.78 (s, 3H), 1.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 211.2, 131.8, 123.5, 77.6, 74.9, 47.8, 38.9, 21.4, 19.2; IR (CH_2Cl_2, cm^{-1}): 2934, 2862, 1713, 1663, 1455, 1420, 1386, 1335, 1279, 1168, 1125, 995, 956, 860, 820; HRMS (ESI) calcd for $C_9H_{14}O_2Na$ $[M+Na]^+$ 177.0891, found 177.0896.

(*Z*)-*tert*-butyl 5,6-dibenzyl-3-oxo-3,4,7,8-tetrahydroazocine-1-(2*H*)-carboxylate (**3.7**)

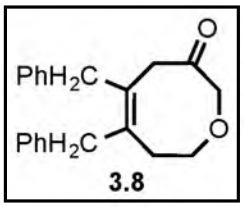


3.7

The general procedure was used with 123.2 mg (0.53 mmol) of diene **3.6**, 45.0 mg (0.26 mmol) of 1-boc-3-azetidinone **3.2** and 10 mol % of catalyst in 1,4-dioxane. The resulting reaction mixture was stirred at 100 °C for 36 h. The remaining residue was purified via flash column chromatography using 15-25% ether in pentane (R_f = 0.20 in 25% ether/pentane) to afford the title compound **3.7** (85.2 mg, 0.21 mmol, 80%) as colorless oil.

^{1}H NMR (500 MHz, Toluene-d^8, 80 °C): δ (ppm) 7.08-7.13 (m, 6H), 7.01-7.03 (m, 2H), 6.94-6.95 (m, 2H), 3.54 (brs, 2H), 3.47 (brs, 2H), 3.36 (s, 2H), 3.11 (s, 2H), 2.97 (brs, 2H), 2.29 (brs, 2H), 1.31 (s, 3H); ^{13}C NMR (125 MHz, Toluene-d^8, 80 °C): δ (ppm) 206.4, 154.9, 139.8, 139.6, 136.6, 129.5, 129.0, 128.92, 128.86, 128.8, 126.8, 126.6, 80.3, 57.5, 50.0, 44.9, 41.3, 38.3, 34.8, 28.5; IR (CH_2Cl_2, cm^{-1}): 2976, 2932, 2865, 1704, 1602, 1559, 1541, 1494, 1476, 1452, 1398, 1332, 1239, 1162, 1075, 962, 912; HRMS (ESI) calcd for $C_{26}H_{31}NO_3Na$ $[M+Na]^+$ 408.2202, found 408.2202.

(*Z*)-5,6-dibenzyl-7, 8-dihydro-2*H*-oxocin-3(4*H*)-one (**3.8**)

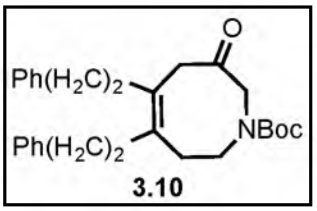


3.8

The general procedure was used with 159.4 mg (0.68 mmol) of diene **3.6**, 24.5 mg (0.34 mmol) of 3-oxetanone **3.4** and 10 mol % of catalyst in 1,4-dioxane. The resulting reaction mixture was stirred at 100 °C for 36 h. The remaining residue was purified via silica gel flash column chromatography using 20-30% ether in pentane (R_f = 0.34 in 30% ether/pentane) to afford the title compound **3.8** (62.5 mg, 0.20 mmol, 60%) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.23-7.27 (m, 4H), 7.15-7.19 (m, 4H), 7.09-7.11 (m, 2H), 3.90 (s, 2H), 3.59 (s, 4H), 3.40-3.44 (m, 2H), 3.34 (brs, 2H), 2.45 (brt, J = 4.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 211.2, 139.09, 139.06, 136.0, 129.1, 129.0, 128.8, 128.7, 128.3, 126.7, 126.5, 77.6, 75.2, 44.9, 41.1, 37.9, 37.0; IR (CH_2Cl_2, cm^{-1}): 2934, 2875, 1711, 1645, 1601, 1583, 1453, 1277, 1226, 1097, 1076, 971, 945, 836, 756; HRMS (ESI) calcd for $C_{21}H_{22}O_2Na$ $[M+Na]^+$ 329.1517, found 329.1530.

(*Z*)-*tert*-butyl-3-oxo-5,6-diphenethyl-3,4,7,8-tetrahydroazocine-1-(2*H*)-carboxylate (**3.10**)



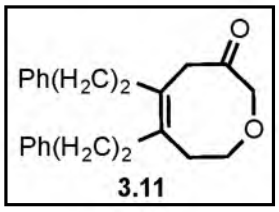
3.10

The general procedure was used with 133.0 mg (0.51 mmol) of diene **3.9**, 43.4 mg (0.25 mmol) of 1-boc-3-azetidinone **3.2** and 10 mol % of catalyst in 1,4-dioxane. The resulting reaction mixture was stirred at 100 °C for 36 h. The remaining residue was purified via silica gel flash column chromatography using 15-25% ether in pentane (R_f = 0.39 in 25% ether/pentane) to afford the title compound **3.10** (90.0 mg, 0.21 mmol, 82%) as colorless oil.

^{1}H NMR (500 MHz, DMSO-d^6, 89 °C): δ (ppm) 7.25-7.29 (m, 4H), 7.13-7.20 (m, 6H), 3.74 (s, 2H), 3.47 (brt, J = 4.0 Hz, 2H), 3.14 (s, 2H), 2.64 (t, J = 7.5 Hz, 2H), 2.56 (t, J = 7.5 Hz, 2H), 2.44 (brt, J = 4.0 Hz, 2H), 2.38 (t, J = 7.5 Hz, 2H), 2.26 (t, J = 7.5 Hz, 2H), 1.43 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d^6, 89 °C): δ (ppm) 207.5, 153.8, 141.3, 141.1, 135.9, 127.7, 127.64, 127.58, 127.5, 127.3, 125.2, 79.2, 56.4, 48.3, 44.8, 35.7, 33.9, 33.4, 33.3, 33.2 27.5; IR (CH_2Cl_2, cm^{-1}): 3026, 2974, 2934, 2863, 1703, 1603, 1496, 1477, 1454, 1419, 1394, 1367, 1238, 1162, 1102, 1030, 917, 860; HRMS (ESI) calcd for $C_{28}H_{35}NO_3Na$ $[M+Na]^+$ 456.2515, found 456.2528.

(*Z*)-5,6-diphenethyl-7,8-dihydro-2*H*-oxocin-3(4*H*)-one (**3.11**)

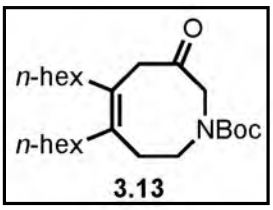
The general procedure was used with 178.4 mg (0.68 mmol) of diene **3.9**, 24.5 mg (0.34 mmol) of 3-oxetanone **3.4** and 10 mol % of catalyst in 1,4-dioxane. The resulting reaction mixture was stirred at 100 °C for 36 h. The remaining residue was purified via silica gel flash column chromatography using 15-25% ether in pentane (R_f = 0.36 in 25% ether/pentane) to afford the title compound **3.11** (71.7 mg, 0.21 mmol, 63%) as colorless oil.



3.11

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.30-7.35 (m, 4H), 7.17-7.26 (m, 6H), 4.03 (s, 2H), 3.86 (brd, J = 4.4 Hz, 2H), 3.48 (s, 2H), 2.60-2.67 (m, 4H), 2.55 (brt, J = 4.4 Hz, 2H), 2.37-2.40 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 211.6, 144.8, 141.7, 136.4, 128.63, 128.60, 128.5, 128.4, 126.2, 126.1, 77.6, 75.4, 45.6, 37.09, 37.06, 34.8, 34.6, 34.5; IR (CH_2Cl_2, cm^{-1}): 3084, 3061, 3026, 2933, 2862, 1711, 1649, 1496, 1454, 1277, 1176, 1125, 963, 843, 817; HRMS (ESI) calcd for $C_{23}H_{26}O_2Na$ $[M+Na]^+$ 357.1831, found 357.1833.

(*Z*)-*tert*-butyl 5,6-dihexyl-3-oxo-3,4,7,8-tetrahydroazocine-1(2*H*)-carboxylate (**3.13**)

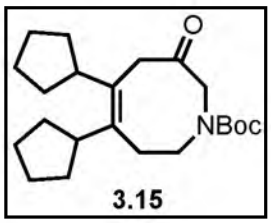


3.13

The general procedure was used with 105.8 mg (0.48 mmol) of diene **3.12**, 40.7 mg (0.24 mmol) of 1-boc-3-azetidinone **3.2** and 10 mol % of catalyst in 1,4-dioxane. The resulting reaction mixture was stirred at 100 °C for 36 h. The remaining residue was purified via silica gel flash column chromatography using 5-15% ether in pentane (R_f = 0.5 in 15% ether/pentane) to afford the title compound **3.13** (72.3 mg, 0.18 mmol, 77%) as colorless oil.

^{1}H NMR (500 MHz, DMSO-d^6, 89 °C): δ (ppm) 3.72 (s, 2H), 3.43-3.45 (m, 2H), 3.06 (s, 2H), 2.34-2.36 (m, 2H), 2.09 (brt, J = 7.5 Hz, 2H), 1.99 (brt, J = 7.5 Hz, 2H), 1.27-1.41 (m, 26 H), 0.86-0.90 (m, 5H); ^{13}C NMR (125 MHz, DMSO-d^6, 89 °C): δ (ppm) 207.4, 153.7, 135.8, 127.3, 79.2, 56.4, 48.6, 44.8, 33.6, 33.3, 31.7, 30.54, 30.47, 28.3, 28.2, 27.5, 27.3, 27.1, 21.4, 21.3, 13.08, 13.07; IR (CH_2Cl_2, cm^{-1}): 2957, 2928, 2859, 1708, 1455, 1419, 1394, 1367, 1239, 1166, 1110, 861, 778; HRMS (ESI) calcd for $C_{24}H_{43}NO_3Na$ $[M+Na]^+$ 416.3141, found 416.3143.

(*Z*)-*tert*-butyl-5,6-dicyclopentyl-3-oxo-3,4,7,8-tetrahydroazocine-1(2*H*)-carboxylate (**3.15**)



3.15

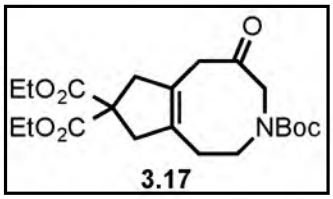
The general procedure was used with 99.4 mg (0.52 mmol) of diene **3.14**, 44.7 mg (0.26 mmol) of 1-boc-3-azetidinone **3.2** and 15 mol % of catalyst in 1,4-dioxane. The resulting reaction mixture was stirred at 100 °C for 48 h. The remaining residue was purified via silica gel

flash column chromatography using 10-15% ether in pentane (R_f = 0.26 in 15% ether/pentane) to afford the title compound **3.15** (51.7 mg, 0.14 mmol, 55%) as colorless semi-solid.

^{1}H NMR (500 MHz, DMSO-d^6, 89 °C): δ (ppm) 3.74 (s, 2H), 3.44-3.45 (m, 2H), 2.99-3.10 (m, 5H), 2.32-2.34 (m, 2H), 1.50-1.67 (m, 12H), 1.33-1.39 (m, 12H); ^{13}C NMR (125 MHz, DMSO-d^6, 89 °C): δ (ppm) 208.6, 153.6, 137.5, 129.9, 79.2, 56.8, 49.5, 42.0, 41.9, 41.8, 39.9, 39.8, 39.6, 30.24, 30.20, 29.2, 27.5, 24.5, 24.3 ; IR (CH_2Cl_2, cm^{-1}): 2962, 2869, 1705, 1477, 1453, 1419, 1396, 1366, 1213, 1162, 947, 860, 779; HRMS (ESI) calcd for $C_{22}H_{35}NO_3Na$ $[M+Na]^+$ 384.2515, found 384.2520.

3-*tert*-butyl-8,8-diethyl-5-oxo-5,6,7,9-tetrahydro-1*H*-cyclopenta-[*d*]azocine-3,8,8(2*H*,4*H*)-tricarboxylate (**3.17**)

The general procedure was used with 139.2 mg (0.58 mmol) of diene **3.16**, 50.0 mg (0.29 mmol) of 1-boc-3-azetidinone **3.2** and 10 mol % of catalyst in 1,4-dioxane. The resulting reaction mixture was stirred at 100 °C for 24 h. The remaining residue was purified via silica gel flash column chromatography using 35-45% ether in pentane (R_f = 0.30 in 45% ether/pentane) to afford the title compound **3.17** (80.2 mg, 0.20 mmol, 67%) as colorless oil.

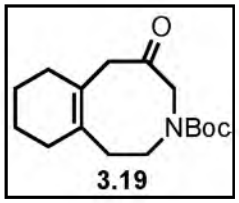


3.17

^{1}H NMR (500 MHz, DMSO-d^6, 89 °C): δ (ppm) 4.14 (q, J = 7.0 Hz, 4H), 3.72 (s, 2H), 3.38-3.40 (m, 2H), 3.04 (brs, 4H), 2.84 (brs, 2H), 2.30 (brt, J = 5.0 Hz, 2H), 1.43 (brs, 9H), 1.19 (t, J = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, DMSO-d^6, 89 °C): δ (ppm) 206.2, 170.6, 153.5, 134.8, 125.9, 79.4, 60.6, 56.8, 47.4, 44.6, 43.5, 40.6, 27.5, 27.2, 13.2; IR

(CH_2Cl_2, cm^{-1}): 2979, 2935, 2360, 1730, 1704, 1453, 1422, 1394, 1367, 1314, 1255, 1160, 1073, 1015, 893, 860, 779; HRMS (ESI) calcd for $C_{21}H_{31}NO_7Na$ $[M+Na]^+$ 432.1998, found 432.1993.

(*Z*)-*tert*-butyl 5-oxo-1,2,5,6,7,8,9,10-octahydrobenzo[*d*]azocine-3(4*H*)-carboxylate (**3.19**)

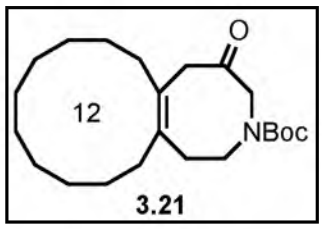


3.19

The general procedure was used with 60.3 mg (0.56 mmol) of diene **3.18**, 47.7 mg (0.28 mmol) of 1-boc-3-azetidinone **3.2** and 10 mol % of catalyst in 1,4-dioxane. The resulting reaction mixture was stirred at 100 °C for 24 h. The remaining residue was purified via silica gel flash column chromatography using 15-20% ether in pentane (R_f = 0.30 in 20% ether/pentane) to afford the title compound **3.19** (63.5 mg, 0.23 mmol, 81%) as colorless oil.

^{1}H NMR (500 MHz, DMSO-d^6, 89 °C): δ (ppm) 3.74 (s, 2H), 3.42-3.44 (m, 2H), 3.01 (brs, 2H), 2.27 (brt, J = 4.5 Hz, 2H), 2.06 (brs, 2H), 1.86 (brs, 2H), 1.55 (brt, J = 2.5 Hz, 4H), 1.42 (brs, 9H); ^{13}C NMR (125 MHz, DMSO-d^6, 89 °C): δ (ppm) 206.9, 153.8, 133.0, 124.2, 79.2, 56.4, 47.6, 45.9, 34.2, 30.7, 29.0, 27.5, 22.1, 21.9; IR (CH_2Cl_2, cm^{-1}): 2975, 2932, 2862, 2833, 1704, 1478, 1452, 1418, 1394, 1367, 1330, 1163, 1068, 1021, 912, 894, 836, 779; HRMS (ESI) calcd for $C_{16}H_{25}NO_3Na$ $[M+Na]^+$ 302.1732, found 302.1717.

(*Z*)-*tert*-butyl-5-oxo-1,2,5,6,7,8,9,10,11,12,13,14,15,16-tetradeca-hydrocyclodo-deca[*d*]azocine-3(4*H*)-carboxylate (**3.21**)

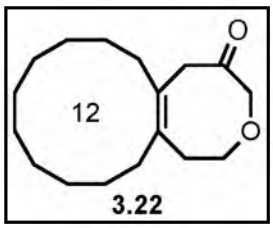


3.21

The general procedure was used with 126.5 mg (0.66 mmol) of diene **3.20**, 56.3 mg (0.33 mmol) of 1-boc-3-azetidinone **3.2** and 10 mol % of catalyst in 1,4-dioxane. The resulting reaction mixture was stirred at 100 °C for 24 h. The remaining residue was purified via silica gel flash column chromatography using 10-15% ether in pentane (R_f = 0.31 in 15% ether/pentane) to afford the title compound **3.21** (98.1 mg, 0.27 mmol, 82%, mp: 124-126°C) as a colorless solid.

^{1}H NMR (500 MHz, DMSO-d^6, 80 °C): δ (ppm) 3.72 (s, 2H), 3.44-3.46 (m, 2H), 3.10 (brs, 2H), 2.99 (brs, 2H), 2.36-2.38 (m, 2H), 2.17 (t, J = 7.0 Hz, 2H), 2.06 (t, J = 7.0 Hz, 2H), 1.27-1.54 (m, 23H); ^{13}C NMR (125 MHz, DMSO-d^6, 89 °C): δ (ppm) 207.4, 154.4, 136.1, 127.6, 79.2, 56.5, 48.2, 44.2, 32.6, 29.9, 28.3, 27.5, 24.9, 24.82, 24.80, 24.6, 24.4, 24.2, 22.1, 21.9; IR (CH_2Cl_2, cm^{-1}): 2929, 2860, 1705, 1455, 1418, 1395, 1367, 1331, 1238, 1159, 1106, 999, 928, 871, 779; HRMS (ESI) calcd for $C_{22}H_{37}NO_3Na$ $[M+Na]^+$ 386.2671, found 386.2672.

(*Z*)-4,6,7,8,9,10,11,12,13,14,15,16-dodecahydro-1*H*-cyclododeca-[*d*]-oxocin-5(2*H*)-one (**3.22**)

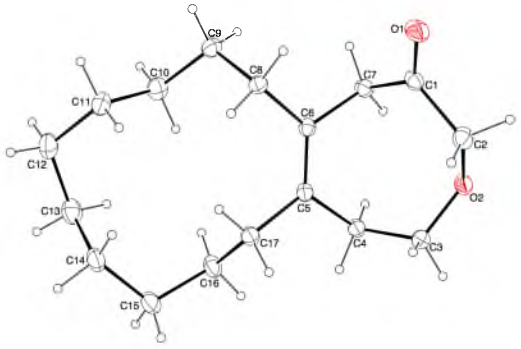


3.22

The general procedure was used with 107.3 mg (0.56 mmol) of diene **3.20**, 20.1 mg (0.28 mmol) of 3-oxetanone **3.4** and 10 mol % of catalyst in 1,4-dioxane. The resulting reaction mixture was stirred at 100 °C for 24 h. The remaining residue was purified

via silica gel flash column chromatography using 5-10% ether in pentane (R_f = 0.28 in 10% ether/pentane) to afford the title compound **3.22** (46.6 mg, 0.18 mmol, 63%, mp: 64-65 °C) as colorless solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 3.99 (s, 2H), 3.82 (brs, 2H), 3.40 (s, 2H), 2.45-2.47 (brm, 2H), 2.10-2.14 (m, 4H), 1.28-1.53 (m, 16H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 211.8, 136.8, 129.0, 77.7, 75.4, 44.9, 36.3, 30.8, 28.6, 25.7, 25.6, 25.5, 25.4, 25.1, 24.6, 22.9, 22.6; IR (CH_2Cl_2, cm^{-1}): 2928, 2858, 1712, 1643, 1469, 1447, 1384, 1345, 1277, 1243, 1193, 1125, 1091, 993, 947, 811; HRMS (ESI) calcd for $C_{17}H_{28}O_2Na$ $[M+Na]^+$ 287.1987, found 287.1983. The crystals suitable for crystallographic analysis were grown using chloroform as solvent.

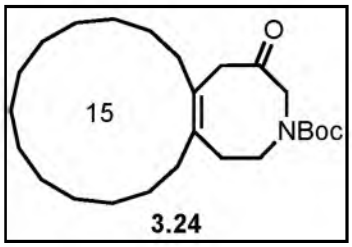


Crystal data and structure refinement for **3.22**

Empirical formula	$C_{17}H_{28}O_2$
Formula weight	264.39
Temperature	150(1) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	***P***

Unit cell dimensions	a = 5.9071(1) Å	α = 85.1334(9)°
	b = 7.7361(1) Å	β = 89.6057(10)°
	c = 17.5970(3) Å	γ = 70.2975(10)°
Volume	754.14(2) $Å^3$	
Z	2	
Density (calculated)	1.164 Mg/m^3	
Absorption coefficient	0.074 mm^{-1}	
F(000)	292	
Crystal size	0.30 x 0.28 x 0.25 mm^3	
Theta range for data collection	2.81 to 27.47°.	
Index ranges	-7<=h<=7, -10<=k<=10, -22<=l<=22	
Reflections collected	6622	
Independent reflections	3438 [R(int) = 0.0137]	
Completeness to theta = 27.47°	99.8 %	
Absorption correction	Mult-scan	
Max. and min. transmission	0.9818 and 0.9782	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3438 / 0 / 172	
Goodness-of-fit on F^2	1.033	
Final R indices [I>2sigma(I)]	R1 = 0.0387, wR2 = 0.0977	
R indices (all data)	R1 = 0.0482, wR2 = 0.1037	
Largest diff. peak and hole	0.230 and -0.178 e	

(*Z*)-*tert*-butyl-5-oxo-4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19-hexa-decahydro-1*H*-cyclopentadeca[*d*]azocine-3(2*H*)-carboxylate (**3.24**)

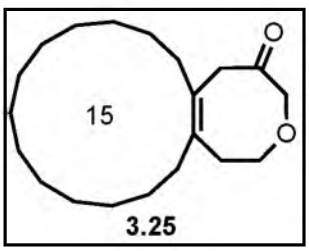


3.24

The general procedure was used with 144.9 mg (0.62 mmol) of diene **3.23**, 52.9 mg (0.31 mmol) of 1-boc-3-azetidinone **3.2** and 10 mol% of catalyst in 1,4-dioxane. The resulting reaction mixture was stirred at 100 °C for 24 h. The remaining residue was purified via silica gel flash column chromatography using 10-15% ether in pentane (R_f = 0.25 in 15% ether/pentane) to afford the title compound **3.24** (104.0 mg, 0.26 mmol, 83%) as colorless oil.

^{1}H NMR (500 MHz, DMSO-d^6, 89 °C): δ (ppm) 3.72 (s, 2H), 3.44-3.45 (m, 2H), 3.06 (brs, 2H), 2.98 (brs, 2H), 2.34-2.36 (m, 2H), 2.09 (brt, J = 7.0 Hz, 2H), 1.98 (brt, J = 7.5 Hz, 2H), 1.34-1.44 (m, 29H); ^{13}C NMR (125 MHz, DMSO-d^6, 89 °C): δ (ppm) 207.4, 153.8, 136.0, 127.3, 79.2, 56.4, 48.4, 45.0, 39.8, 33.5, 31.7, 27.5, 27.0, 26.9, 26.3, 26.21, 26.16, 26.0, 25.9, 25.72, 25.70, 25.4; IR (CH_2Cl_2, cm^{-1}): 2930, 2858, 1707, 1455, 1419, 1394, 1366, 1331, 1252, 1163, 1107, 958, 860, 779; HRMS (ESI) calcd for $C_{25}H_{43}NO_3Na$ $[M+Na]^+$ 428.3141, found 428.3140.

(*Z*)-1,2,6,7,8,9,10,11,12,13,14,15,16,17,18,19-hexadecahydrocyclo-pentadeca[*d*]oxocin-5(4*H*)-one (**3.25**)



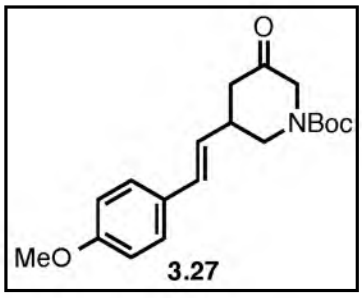
3.25

The general procedure was used with 156.2 mg (0.67 mmol) of diene **3.23**, 24.0 mg (0.33 mmol) of 3-oxetanone **3.4** and 10 mol% of catalyst in 1,4-dioxane. The resulting reaction

mixture was stirred at 100 °C for 24 h. The remaining residue was purified via silica gel flash column chromatography using 10-15% ether in pentane (R_f = 0.34 in 15% ether/pentane) to afford the title compound **3.25** (75.4 mg, 0.25 mmol, 74%) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.97 (d, *J* = 3.2 Hz, 2H), 3.80 (brs, 2H), 3.35 (brs, 2H), 2.42 (brs, 2H), 1.99-2.03 (m, 4H), 1.29-1.36 (m, 22 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 211.9, 136.8, 128.6, 77.6, 75.7, 45.9, 37.3, 34.9, 32.3, 27.7, 27.6, 27.2, 27.1, 27.0, 26.90, 26.87, 26.3, 26.2, 25.64, 25.60; IR (CH_2Cl_2, cm^{-1}): 2938, 2857, 1714, 1650, 1457, 1419, 1277, 1219, 1172, 1126, 958, 828; HRMS (ESI) calcd for $C_{20}H_{35}O_2$ $[M+H]^+$ 307.2637, found 207.2631.

tert-butyl-(*E*)-3-(4-methoxystyryl)-5-oxopiperidine-1-carboxylate (**3.27**)

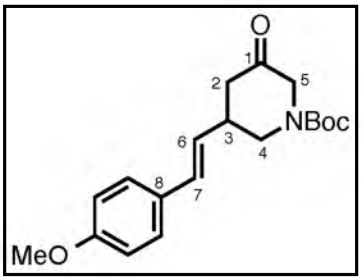


3.27

The general procedure was used with 140.6 mg (0.88 mmol) of diene **3.26**, 75.1 mg (0.44 mmol) of 1-boc-3-azetidinone **3.2** and 10 mol% of catalyst in 1,4-dioxane. The resulting reaction mixture was stirred at 100 °C for 24 h. The remaining residue was purified via silica gel flash column chromatography using 30-45% ether in pentane (R_f = 0.16 in 40% ether/pentane) to afford the title compound **3.27** (72.7 mg, 0.22 mmol, 50%) as light yellow oil.

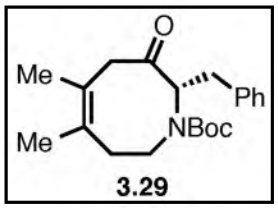
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.28 (brd, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 6.42 (d, *J* = 15.6 Hz, 1H), 5.96 (dd, *J* = 6.8, 15.6 Hz, 1H), 4.13 (d, *J* = 18 Hz, 1H), 3.82-3.97 (m, 2H), 3.80 (s, 3H), 3.25-3.30 (m, 1H), 2.84-2.95 (m, 1H), 2.68 (dd, *J* = 4.8,

16.4 Hz, 1H), 2.44 (dd, J = 10.0, 16.4 Hz, 1H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 205.1, 159.5, 154.6, 130.9, 129.5, 127.6, 126.7, 114.2, 80.8, 55.4, 54.5, 47.2, 44.7, 37.8, 28.5; IR (CH_2Cl_2, cm^{-1}): 2976, 2934, 2838, 1725, 1696, 1608, 1586, 1512, 1457, 1416, 1367, 1302, 1250, 1174, 1123, 1003, 968, 886, 808, 765; HRMS (ESI) calcd for $C_{19}H_{25}NO_4Na$ $[M+Na]^+$ 354.1681, found 354.1688.



g-HMBC summary: The following cross-peaks were observed: H(2) and C(1); H(2) and C(3); H(2) and C(6); H(2) and C(5); H(3) and C(2); H(3) and C(4); H(3) and C(6); H(3) and C(7); H(4) and C(3); H(4) and C(6); H(4) and C(2); H(5) and C(1); H(5) and C(2); H(6) and C(3); H(6) and C(7); H(6) and C(2); H(7) and C(6); H(7) and C(8); H(7) and C(3).

Tert-butyl-(*Z*)-2-benzyl-5,6-dimethyl-3-oxo-3,4,7,8-tetra-hydro-azocine-1(2*H*)-carboxylate (**3.29**)



The general procedure was used with 30.9 mg (0.38 mmol) of diene **3.1**, 49.2 mg (0.19 mmol) of azetidinone **3.28** and 10 mol % of catalyst in 1,4-dioxane. The resulting reaction mixture was stirred at 100 °C for 36 h. The remaining residue was purified via silica gel flash column chromatography using 5-10% ether in pentane (R_f = 0.25 in 10% ether/pentane) to afford the title compound **3.29** (50.0 mg, 0.15 mmol, 77%) as a colorless oil; $[\alpha]^{20}_D$ = –186.1° (c = 1.4, $CHCl_3$).

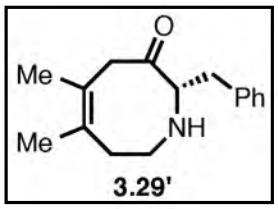
^{1}H NMR (500 MHz, DMSO-d^6, 89 °C): δ (ppm) 7.24-7.27 (m, 2H), 7.14-7.19 (m, 3H), 4.24-4.26 (brm, 1H), 3.32-3.58 (brm, 2H), 3.12 (dd, J = 5.0, 14.0 Hz, 1H), 2.92-2.99 (m,

2H), 2.83 (brs, 1H), 2.46 (brs, 1H), 2.13 (brs, 1H), 1.74 (s, 3H), 1.64 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d^6, 89 °C): δ (ppm) 206.5, 153.4, 138.3, 130.0, 128.2, 127.6, 125.4, 123.5, 79.4, 65.4, 47.8, 46.4, 34.6, 33.4, 27.5, 20.0, 18.8; IR (CH_2Cl_2, cm^{-1}): 3028, 2976, 2934, 1719, 1699, 1605, 1496, 1417, 1392, 1366, 1323, 1284, 1165, 1113, 1081, 934, 911, 856, 776. HRMS (ESI) calcd for $C_{21}H_{29}NO_3Na$ $[M+Na]^+$ 366.2045, found 366.2040.

The regiochemistry of **3.29** was determined by 2D-NMR-analysis of the Boc-deprotected derivative, **3.29'** shown below.

(*Z*)-2-benzyl-5,6-dimethyl-1,4,7,8-tetrahydroazocin-3(2*H*)-one (**3.29'**)

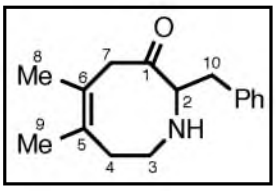
To a solution of racemic **3.29** (77.0 mg, 0.22 mmol, 0.1 M) in DCM (2.2 ml) at 0 °C, trifluoroacetic acid was added (511.2 mg, 4.5 mmol, 0.35 ml) dropwise. The reaction mixture was allowed to warm upto room temperature and stirred for 24 h. The solvent was removed under vacuum. The residue was diluted by dichloromethane and washed with saturated aqueous K_2CO_3 solution. The organic phase was dried by Na_2SO_4 and solvent was removed under vacuum to yield **3.29'** (50.2 mg, 0.21 mmol, 92%) as light yellow oil.



3.29'

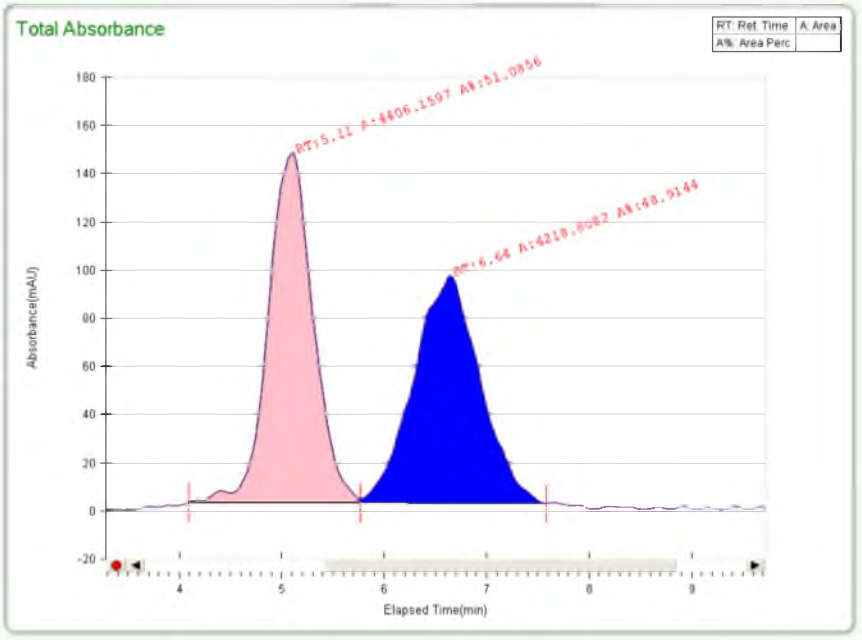
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.18-7.23 (m, 2H), 7.27-7.30 (m, 3H), 3.61 (d, J = 14.0 Hz, 1H), 3.41-3.44 (m, 1H), 3.07 (dd, J = 6.4, 13.6 Hz, 1H), 2.96-3.06 (m, 1H), 2.76 (d, J = 13.6, 1H), 2.66 (dd, J = 9.2, 13.6 Hz, 1H), 2.53-2.58 (m, 1H), 2.18 (brt, J = 4.0 Hz, 2H), 1.72 (brs, 1H), 1.70 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 214.1, 138.4, 129.6, 129.3, 128.7, 126.7, 124.8, 68.1, 48.9, 48.0, 39.1, 37.5, 20.6, 20.1; IR

(CH_2Cl_2, cm^{-1}): 3060, 3027, 2927, 2858, 1703, 1635, 1597, 1496, 1454, 1385, 1357, 1148, 1076, 1056, 1031, 936, 799; HRMS (ESI) calcd for $C_{16}H_{22}NO$ $[M+H]^+$ 244.1696, found 244.1696.

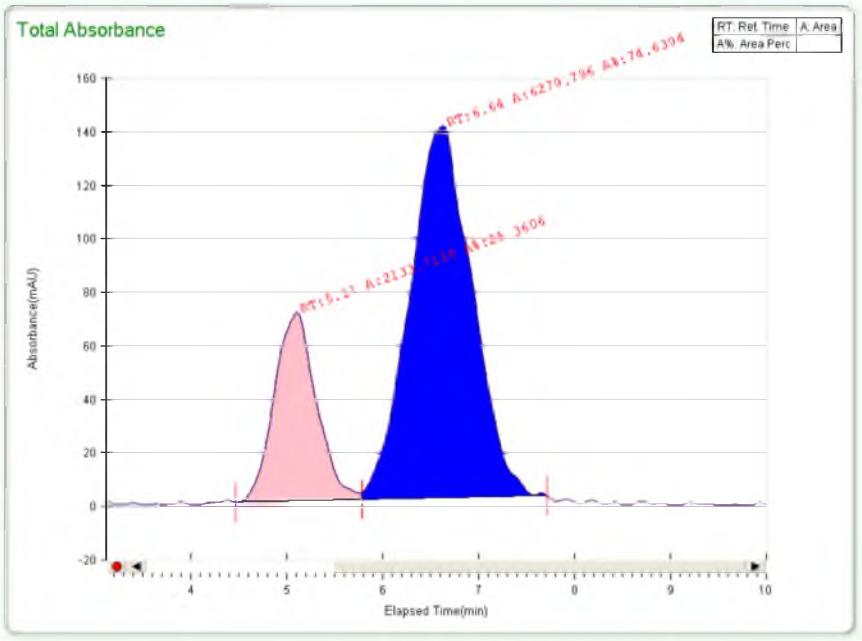


g-HMBC summary: The following cross-peaks were observed: H(7) and C(1); H(7) and C(6); H(7) and C(8); H(8) and C(6); H(9) and C(5); H(9) and C(6); H(9) and C(4); H(4) and C(3); H(3) and C(4); H(3) and C(2); H(2) and C(1); H(2) and C(10); H(2) and C(3); H(10) and C(1); H(10) and C(2).

Chromatogram of racemic *tert*-butyl-(*Z*)-2-benzyl-5,6-dimethyl-3-oxo-3,4,7,8-tetrahydroazocine-1(2*H*)-carboxylate (rac-**3ac**)



Chromatogram of chiral *tert*-butyl-(*Z*)-2-benzyl-5,6-dimethyl-3-oxo-3,4,7,8-tetrahydroazocine-1(2*H*)-carboxylate (**3ac**)



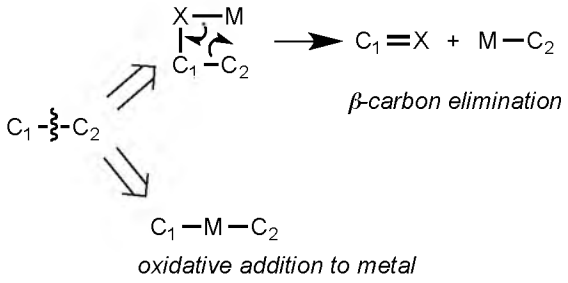


Figure 3.1. Metal mediated modes of C−C activation.

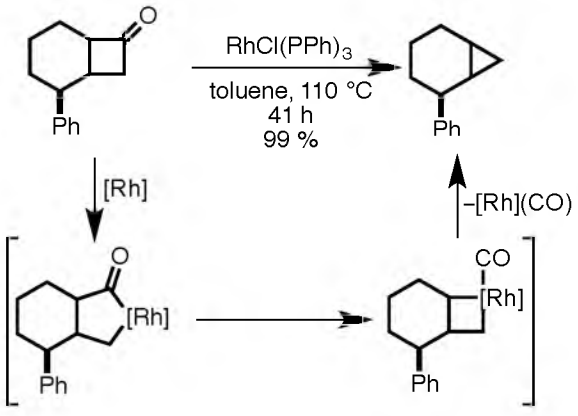


Figure 3.2. Rh-mediated decarbonylation of fused cyclobutanone.

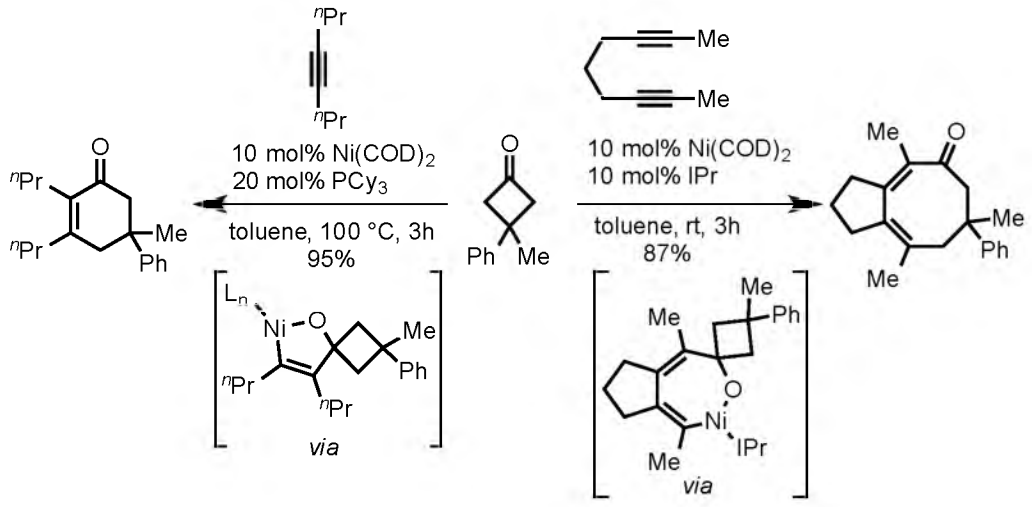


Figure 3.3. Ni-catalyzed cycloaddition of alkynes and diynes with cyclobutanones.

Table 3.1. Ligand screening for nickel catalyzed cycloaddition of diene **3.1** and azetidinone **3.2**[a]

Entry	Ligand	Conv.[%][b]	Yield [%][c]
1	IPr	83	-
2	SIPr	42	-
3	IMes	89	-
4	DPPF	34	n.d.
5	DPPP	-	-
6	DPPB	**>99**	**79**
7	PCy_3	25	n.d.
8	PPh_3	>99	75
9	P(*p*-CF_3Ph)$_3$	59	n.d.
10	P(*p*-OMePh)$_3$	70	n.d.
11	P(*p*-tol)$_3$	**>99**	**79**

[a]Diene **3.1** (2 equiv), Azetidinone **3.2** (1 equiv, 0.4 M), 10 mol % $Ni(COD)_2$, Ligand (20 mol% for entries 1-3; 12 mol% for entries 4-6 and 25 mol % for entries 7-11. [b]Conversion of **3.1** was determined by GC using naphthalene as an internal standard. [c]Isolated yield of **3.3**. n.d. = not determined.

Table 3.2. Nickel catalyzed cycloaddition of 1,3-dienes and azetidinone **3.2** and oxetanone **3.4**[a]

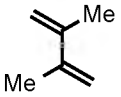
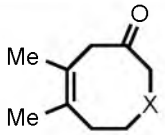
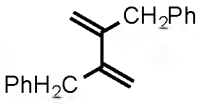
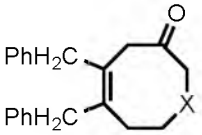
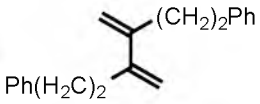
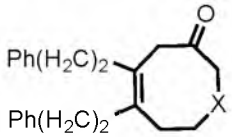
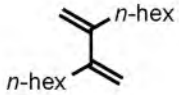
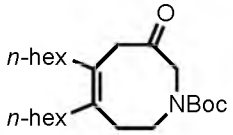
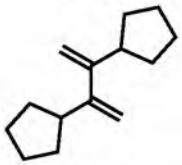
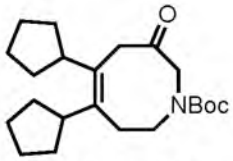
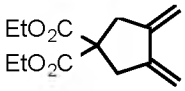
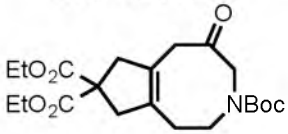
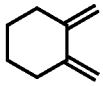
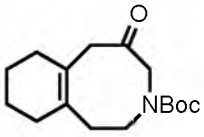
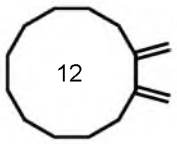
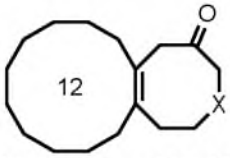
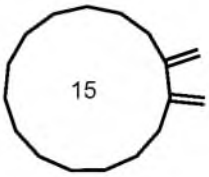
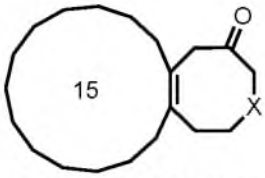
Entry	Diene	3-Azetidinone/3-Oxetanone	Product, reaction time, Yield [%][c]
1			
	3.1	**3.2**, X = NBoc	**3.3,** X = NBoc, 24h, 79%
2	**3.1**	**3.4**, X = O	**3.5**, X = O, 24h, 40%
3			
	3.6	**3.2**	**3.7**, X = NBoc, 36h, 80%
4	**3.6**	**3.4**	**3.8**, X = O, 36h, 60%
5			
	3.9	**3.2**	**3.10**, X = NBoc, 36h, 82%
6	**3.9**	**3.4**	**3.11**, X = O, 36h, 63%
7			
	3.12	**3.2**	**3.13**, 36h, 77%
8			
	3.14	**3.2**	**3.15**,[b] 48h, 55%
9			
	3.16	**3.2**	**3.17**, 24h, 67%
10			
	3.18	**3.2**	**3.19**, 24h, 81%

Table 3.2. Continued

11	 **3.20**	**3.2**	 **3.21**, X = NBoc, 24h, 82%
12	**3.20**	**3.4**	**3.22**, X = O, 24h, 63%
13	 **3.23**	**3.2**	 **3.24**, X = NBoc, 24h, 83%
14	**3.23**	**3.4**	**3.25**, X = O, 24h, 74%

[a]Diene (2 equiv), Azetidinone **3.2** (1 equiv, 0.4 M) or Oxetanone **3.4** (1 equiv, 0.2 M),10 mol % $Ni(cod)_2$, 25 mol % P(*p*-tol)$_3$, 1,4-dioxane, 100 °C.[b] 15 mol % catalyst loading was required.

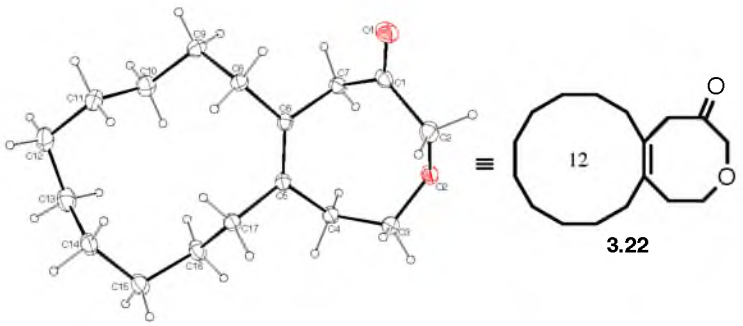


Figure 3.4. Ortep diagram of **3.22**

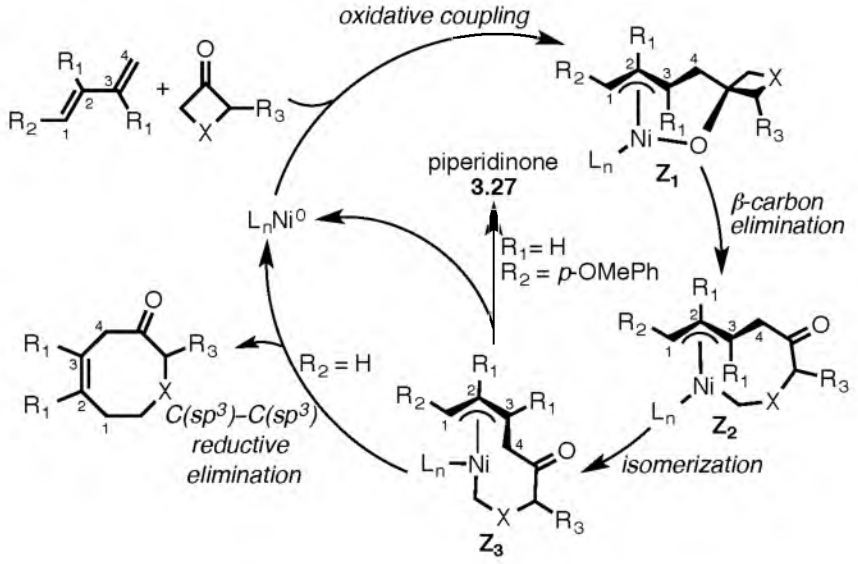


Figure 3.5. Proposed mechanism for the Ni-catalyzed cycloaddition reaction.

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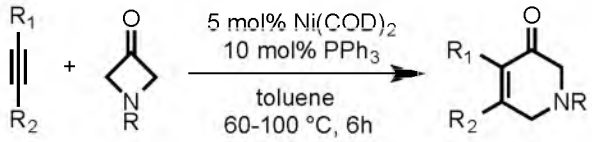
CHAPTER 4

AN *IN SITU* APPROACH TO NICKEL CATALYZED CYCLOADDITION OF ALKYNES AND 3-AZETIDINONES: EFFORTS TOWARDS SYNTHESES OF INDOLIZIDINE ALKALOIDS

Introduction

The prevalence of substituted piperidines in biologically active alkaloid natural products (Figure 4.1) and pharmaceuticals have attracted synthetic chemists to develop new and efficient methodologies to construct these cores in an efficient manner.[1,2] One of the most utilized strategies for the synthesis of piperidines involves the functionalization of substituted 2- and 4-dehydropiperidinones. Unfortunately, the 3-dehydropiperidinone scaffolds remain underexplored in this area due to the limited number of methods available for their synthesis. Typically, Aza-Achmatowicz oxidative rearrangement[3] and ring-closing metathesis[4] are employed to synthesize 3-dehydropiperidinones (Figure 4.2). However, both of these methodologies suffer from poor step economy as multiple steps are often required for the synthesis of functionalized precursors involved in these reactions. Thus, efficient protocols to access these important motifs are highly desirable.

To address this challenge, recently, we and others independently reported a unique and simple route to access 3-dehydropiperidinones via a Ni-catalyzed [4+2]-cycloaddition of 3-azetidinones and alkynes, (eq 4.1).[5]

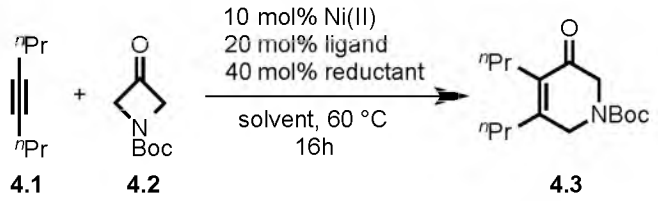


(4.1)

This interesting reaction provides a single-step access to synthetically important 3-piperidione cores via insertion of alkynes into the C−C bond of 3-azetdinones. Despite the use of relatively mild conditions in this methodology, one major drawback is the use of air-sensitive and expensive $Ni(COD)_2$ which necessitates the use of glove box or Schlenk techniques. In order to make this chemistry synthetically more convenient and applicable, we have discovered the use of air-stable, less expensive and readily available precursors that generate the active Ni/PPh_3 catalyst *in situ*.

Results and Discussion

The nickel-catalyzed cycloaddition was investigated using commercially available 4-octyne **4.1** and 1-Boc-3-azetidinone **4.2** as model substrates (eq 4.2).



4.1 **4.2** **4.3**

(4.2)

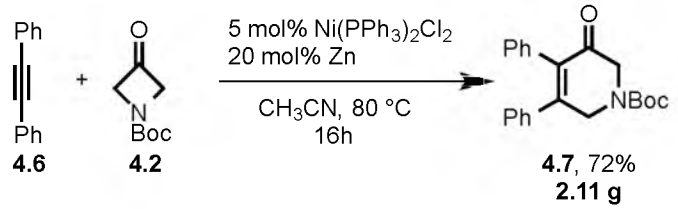
Gratifyingly, the use of $Ni(acac)_2$ (acac = acetylacetonate) as Ni(II) source with PPh_3 ligand and *n*-BuLi as reductant led to excellent conversion of 3-azetidinone to afford the

desired cycloadduct **4.3** in 92% isolated yield (Entry 1, Table 4.1). Substitution of *n*-BuLi by a milder reductant such as Zn, however, gave poor conversions of 3-azetidinone (Entry 2, Table 4.1). We also evaluated the commercially available bis(triphenylphosphine)Ni(II) salts in conjunction with Zn, to promote this cycloaddition. However, poor GC conversions were obtained when these salts were used in toluene presumably due to the insolubility of the Ni(II) salts in toluene (Entries 3-5, Table 4.1). Interestingly, the replacement of toluene with a polar solvent such as acetonitrile afforded excellent conversions and isolated yields of cycloadduct **4.3** (Entries 6-7, Table 4.1). Further optimizations led to these final conditions: 5 mol % $Ni(PPh_3)_2Cl_2$, 20 mol % Zn, acetonitrile, 60-80 °C, 16-24 h.

These optimized reactions were applied to the cycloaddition of 3-azetidinone with a variety of alkynes (Table 4.2). The yields obtained by our previously reported $Ni(COD)_2/PPh_3$ catalytic system are also shown in parentheses for comparison. The cycloaddition of 4-octyne **4.1** with 3-azetidinone **4.2** afforded the heterocyclic product **4.3** in 95% yield. Sterically biased terminal alkyne **4.4** was regioselectively coupled to form cycloadduct **4.5**, in which the bulky *t*-butyl group was placed at the *β*-position. The reaction also tolerates diaryl alkyne such as diphenylacetylene to form the substituted 3-dehydropiperidinone **4.7** in good yield. Interestingly, the use of mixed aryl-alkyl alkynes led to the regioselective formation of the cycloadducts (**4.9**, **4.11**), in which the alkyl group always stays next to the carbonyl group. Importantly, cycloadducts **4.9** and **4.11** were formed in better yields than our reported Ni(0) protocol. This methodology also tolerates stannyl-substituted alkyne to regioselectively form the heterocycle **4.13** suggesting that the aryl group and not the sterically bulky stannyl group govern the

regioselectivity. Aryl-silyl alkynes were also coupled to form 3-dehydropiperidinone products (**4.15-4.17**) in excellent regioselectivity and high yields. Interestingly, an aryl-silyl alkyne bearing electron-withdrawing group (-CF_3) on the phenyl ring afforded lower yield than the alkyne containing phenyl with an electron-donating group (-OMe) (**4.16** *vs* **4.17**). Importantly, the challenging heteroaryl-silyl alkynes were successfully coupled to form furanyl- and thiophenyl-substituted dehydropiperidinones **4.21** and **4.23**, in good yields. The growing interest in macrocyclic heterocycles[6] prompted us to investigate the macrocyclic alkyne **4.24** in this cycloaddition. Gratifyingly, the cycloaddition underwent smoothly to regioselectively afford the desired macrocyclic 3-dehydropiperidone **4.25** in good yield.

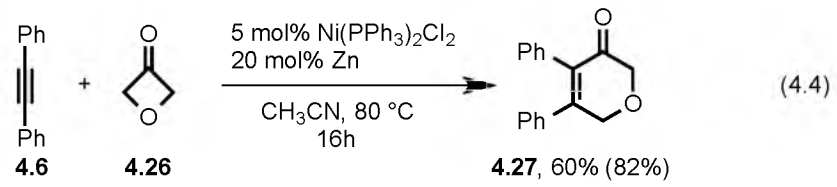
Importantly, this methodology is scalable and was successfully applied to gram-scale quantities of 3-azetdinone and diphenylacetylene to afford cycloadduct **4.7** in 72% yield (eq 4.3).



(4.3)

Unfortunately, terminal alkynes (e.g., phenylacetylene, 1-hexyne and 1-octyne) did not afford dehydropiperidinone product due to their rapid oligomerization under the reaction conditions. Alkynes bearing boron-functional groups (Figure 4.3) also failed to participate in this cycloaddition and were either completely decomposed or recovered with partial decomposition under the reaction conditions.

The cycloaddition of 3-oxtenaone **4.26** with diphenylacetylene afforded the substituted 3-dehyrdopyranone product **4.27**, albeit in lower yield than the reported Ni(0)-protocol (eq 4.4).



4.6 **4.26** **4.27**, 60% (82%) (4.4)

We next investigated the Ni-catalyzed cycloaddition of 2-substituted-3-azetdinones with alkynes (Table 4.3). The chiral 2-substituted azetidinones were synthesized from the corresponding amino acids using Seebach's procedure.[7] The yields and enantiomeric excess (ee) obtained by previously reported $Ni(COD)_2/PPh_3$ catalytic system are also shown in parentheses for comparison.[5a,c] The cycloaddition of alanine-derived azetidinone **4.28** with 4-octyne led to the regioselective formation of the cycloadduct **4.29**, which suggests the selective insertion of alkyne into the unsubstituted $C(sp^2)–C(sp^3)$ σ-bond of 3-azetidinone. The dehydropiperidinone product **4.29** retained 98% ee, which was slightly less than the reported Ni(0) method. Similarly, the Boc-protected azetidinone **4.30** and Cbz-protected azetidinone **4.32** afforded regioselective dehydropiperidinones **4.30** and **4.33** in high yields with 93% and 97% ee, respectively. Diaryl alkyne **4.34** was also coupled with azetidinones **4.32** and **4.36** to form regioselective cycloadducts **4.35** and **4.37** in high yields and high enantioretention.

Mechanism

Our proposed mechanism for regioselective formation of these 3-piperidinones is shown in Figure 4.4. The oxidative coupling of sterically biased unsymmetrical alkyne

and azetidinone would form nickellacycles **A** and **B**. However, the formation of nickellacycle **A** would be favored over **B**, to avoid the steric hindrance between bulky substituent R_L and the quaternary carbon present in **B**. β-Carbon elimination from **A** would form intermediate **C** that would reductively eliminate to afford the regioselective 3-dehydropiperidone product.

With partially polarized alkynes, such as mixed aryl-alkyl, silyl-aryl and stannyl-aryl alkynes, the high regioselectivity observed could be rationalized by the polarity-based preferential oxidative coupling of alkyne and azetidinone. As shown in Figure 4.5, the formation of nickellacycle **D** would be favored over **E**, since it involves the Ni-mediated nucleophilic attack of the partially negatively charged carbon of alkyne to the partially positively charged carbonyl, whereas the unmatched polarity would be required for the formation of **E**. Finally, β-carbon elimination from **D** and subsequent reductive elimination would afford the observed cycloadduct.

With this convenient route to 3-dehydropiperidinones, we next focused our attention towards the synthetic utility of this methodology. Specifically, we were interested in the synthesis of Tylophora alkaloids such as Septicine and Tylophorine due to their interesting biological profile[8] (Figure 4.1). Our retrosynthetic strategy for these natural products is outlined in Figure 4.6. We envisioned that the functionalized indolizidine core **F** in these molecules would be obtained from the late-stage reductions of ketone and amide moieties in intermediate **G**. Boc-deprotection followed by intramolecular cyclization in dehydropiperidine **H** would afford bicyclic intermediate **G**. Our *in situ* Ni-catalyzed cycloaddition of alkyne and 2-substituted chiral azetidinone **4.36** would form the dehydropiperidine product **H**.

Our forward synthesis began with the removal of the Boc-protecting group in **4.37** using trifluoroacetic acid, followed by 2-hydroxypyridine catalyzed intramolecular cyclization to afford compound **4.38** in high yield. The conversion of **4.38** to dihydroindolizidinone **4.39** was performed by a two-step procedure involving the $NaBH_4$ mediated reduction of ketone and subsequent triethylsilane/trifluoroacetic acid promoted deoxygenation of the resulting alcohol.[9] Finally, the reduction of the amide group in **4.39** using $LiAlH_4$ afforded the Tylophora Alkaloid Septicine, in excellent yield.[10] Currently we are determining the enantiomeric excess of our final natural product as well as some of the individual intermediate compounds.

Conclusion

In summary, we have discovered an efficient and convenient procedure that can generate the active Ni(0) catalyst *in situ* to catalyze the cycloaddition of alkynes and 3-azetidinones. The reaction affords useful 6-membered heterocycles in comparable yields to the reported Ni(0) procedures. The application of this methodology to the synthesis of (+)-Septicine is also shown. Further applications to the synthesis of Septicine as well as other Indolizidine alkaloids in more efficient and enantioselective fashion are under way in our laboratory.

General experimental

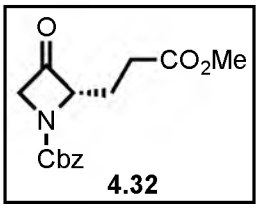
All reactions were conducted under an atmosphere of N_2. Toluene and acetonitrile was dried over neutral alumina under N_2 using a Grubbs type solvent purification system. $Ni(acac)_2$ and $Ni(PPh_3)_2X_2$ (X = Cl, Br, I) were purchased from Sigma-Aldrich and used

without further purification. 1-Boc-3-azetidinone was purchased from Sigma-Aldrich and used as received. The alkynes **4.24**,[11a] **4.34**[11b], *tert*-butyl (*S*)-2-methyl-3-oxoazetidine-1-carboxylate **4.28**[5c] and *tert*-butyl (*S*)-2-benzyl-3-oxoazetidine-1-carboxylate **4.30**,[5a] were prepared according to literature procedure. All other reagents were purchased from commercial suppliers and used without further purification unless otherwise noted.

^{1}H and ^{13}C Nuclear Magnetic Resonance spectra of pure compounds were acquired at 400 and 100 MHz or 500 and 125 MHz, respectively, unless otherwise noted. All spectra are referenced to a singlet at 7.27 ppm for ^{1}H and to the central line of a triplet at 77.23 ppm for ^{13}C. The abbreviations s, d, dd, dt, dq, t, td, tq, q, qt, quint, sext, sept, septd, septt, m, brm, brd, brt, and brs stand for singlet, doublet, doublet of doublets, doublet of triplets, doublet of quartets, triplet, triplet of doublets, triplet of quartets, quartet, quartet of triplets, quintet, sextet, septet, septet of doublets, septet of triplets, multiplet, broad multiplet, broad doublet, broad triplet, and broad singlet, in that order. All ^{13}C NMR spectra were proton decoupled. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer.

Gas Chromatography was performed on an Agilent 6890 gas chomatograph with a 30 meter HP-5 column using the following conditions: initial oven temperature: 100 °C; temperature ramp rate 50 °C/min.; final temperature: 300 °C held for 7 min; detector temperature: 250 °C. SFC (supercritical fluid chromatography) analysis was performed at 25–40 °C, using a Thar instrument fitted with a chiral stationary phase as indicated. Optical rotations were measured (Na D line) on a Perkin Elmer Model 343 Polarimeter fitted with a micro cell with a 1 dm path length; concentrations are reported in g/100 mL.

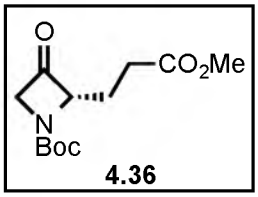
benzyl (*S*)-2-(3-methoxy-3-oxopropyl)-3-oxoazetidine-1-carboxylate (**4.32**)



4.32

Azetidinone **4.32** was also prepared according to Seebach's procedue.[7] To a solution of Cbz-Glu(OMe)-OH[12a] (2.73 g, 9.24 mmol) in THF (45 mL) under N_2 atmosphere, dry NEt_3 (1.35 mL, 9.71 mmol) and $ClCO_2Et$ (1.05 g, 9.71 mmol) were added at -15 °C. The suspension was allowed to warm to 0 °C. CH_2N_2 (23.10 mmol) in Et_2O was slowly added in portions over a period of 2 h, and allowed to warm to rt. The mixture was stirred for an additional 5 h. The reaction was quenched by the addition of water, extracted three times with EtOAc, washed with brine and dried over $MgSO_4$. Purification by flash chromatography on silica gel using 35-45% EtOAc/hexanes, afforded the pure diazo ketone (2.14 g, 6.7 mmol, 73%). Under N_2 atmosphere, the diazo ketone was dissolved in CH_2Cl_2 (33 mL) and dry NEt_3 (10 μL, 0.07 mmol) was added. After cooling to 0 °C, $Rh_2(OAc)_4$ (14.8 mg, 0.03 mmol, 0.5 mol %) was added, and the mixture was stirred for 14 h. After then, water was added, extracted with CH_2Cl_2, washed with water and brine dried over $MgSO_4$. The remaining residue was purified by silica gel flash column chromatography using 40-50% ether in hexanes (R_f = 0.29 in 50% ether/hexanes) to afford the title compound **4.32** (1.13 g, 3.88 mmol, 58%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.37 (m, 5H), 5.17 (s, 2H), 5.06 (m, 1H), 4.79 (d, J = 16.4 Hz, 1H), 4.61 (dd, J = 4.4, 16.4 Hz, 1H), 3.65 (s, 3H), 2.44-2.59 (m, 2H), 2.19 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 199.0, 172.9, 157.0, 136.1, 128.8, 128.6, 128.4, 82.4, 69.7, 67.9, 51.9, 29.5, 25.6. IR (CH_2Cl_2, cm^{-1}): 2953, 1822, 1733, 1711, 1437, 1403, 1344, 1253, 1119, 1123, 1059, 1026, 745, 699. HRMS (ESI) calcd for $C_{15}H_{17}NO_5Na$ $[M+Na]^+$ 314.1004, found 314.1006.

tert-butyl (*S*)-2-(3-methoxy-3-oxopropyl)-3-oxoazetidine-1-carboxylate (**4.36**)



4.36

Azetidinone **4.36** was prepared according to Seebach's procedue.[7] To a solution of Boc-Glu(OMe)-OH[12b] (2.10 g, 8.04 mmol) in THF (40 mL) under N_2 atmosphere, dry NEt_3 (1.2 mL, 8.44 mmol) and $ClCO_2Et$ (0.92 g, 8.44 mmol) were added at -15 °C. The suspension was allowed to warm to 0 °C. CH_2N_2 (21.10 mmol) in Et_2O was slowly added in portions over a period of 2 h, and allowed to warm to rt. The mixture was stirred for an additional 5 h. The reaction was quenched by the addition of water, extracted three times with EtOAc, washed with brine and dried over $MgSO_4$. Purification by flash chromatography on silica gel using 30-35% EtOAc/hexanes, afforded the pure diazo ketone (2.03 g, 7.1 mmol, 88%). Under N_2 atmosphere, the diazo ketone was dissolved in CH_2Cl_2 (35 mL) and dry NEt_3 (10 μL, 0.07 mmol) was added. After cooling to 0 °C, $Rh_2(OAc)_4$ (15.5 mg, 0.04 mmol, 0.5 mol%) was added, and the mixture was stirred for 14 h. After then, water was added, extracted with CH_2Cl_2, washed with water and brine dried over $MgSO_4$. The remaining residue was purified by silica gel flash column chromatography using 30-40% ether in hexanes (R_f = 0.32 in 40% ether/hexanes) to afford the title compound **4.36** (0.96 g, 3.73 mmol, 53%). ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 4.95 (td, J = 4.8, 6.8 Hz, 1H), 4.71 (d, J = 16.8 Hz, 1H), 4.52 (dd, J = 4.4, 16.8 Hz, 1H), 3.68 (s, 3H), 2.51 (qd, J = 8.0, 16.4, 2H), 2.15 (m, 2H), 1.48 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 200.0, 173.1, 156.6, 82.0, 81.3, 69.4, 51.9, 29.6, 28.4, 25.8. IR (CH_2Cl_2, cm^{-1}): 2978, 2932, 1822, 1738, 1704, 1437, 1367, 1176, 1132, 1060, 1021, 862, 776. HRMS (ESI) calcd for $C_{12}H_{19}NO_5Na$ $[M+Na]^+$ 280.1161, found 280.1167.

General procedure '**G1**' for cycloaddition

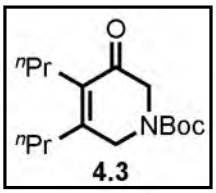
To an oven-dried Schlenk tube containing a stirring bar was added 5 mol% $Ni(PPh_3)_2Cl_2$, 20 mol% activated Zn powder, 3-azetdinone (1 equiv) and alkyne [(1.5 equiv), if solid at room temperature]. This Schlenk tube containing all the solid compounds was then evacuated followed by refilling with N_2 at room temperature (this process was repeated two times). Dry acetonitrile (0.2 M, based on 3-azetidinone) and alkyne [(1.5 equiv), if oil at room temperature] were added via syringe through the rubber septum, under a flow of nitrogen. The Schlenk tube was sealed, stirred at 60-80 °C for indicated period of time and then opened to air. The remaining residue was filtered through a short pad of celite, concentrated in vacuo, and purified by silica gel flash column chromatography.

General procedure '**G2**' for cycloaddition

To an oven-dried Schlenk tube containing a stirring bar was added 5 mol% $Ni(PPh_3)_2Cl_2$, 20 mol% activated Zn powder and alkyne [(1.5 equiv), if solid at room temperature]. This Schlenk tube containing all the solid compounds was then evacuated followed by refilling with N_2 at room temperature (this process was repeated two times). Dry acetonitrile (0.2 M, based on 3-azetidinone) and alkyne [(1.5 equiv), if oil at room temperature] were added via syringe through the rubber septum, under a flow of nitrogen. The reaction mixture was stirred under nitrogen for 20 min followed by the addition of 3-azetidinone (1 equiv, 0.2 M) or 3-oxetanone (1 equiv, 0.2 M) in dry acetonitrile. The Schlenk tube was sealed, stirred at 60-80 °C for indicated period of time and then opened

to air. The remaining residue was filtered through a short pad of celite, concentrated in vacuo, and purified by silica gel flash column chromatography.

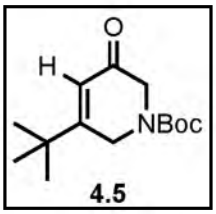
tert-butyl 3-oxo-4,5-dipropyl-3,6-dihydropyridine-1(2*H*)-carboxylate (**4.3**)



4.3

The general procedure **G1** was used with 118.7 mg (0.69 mmol, 0.2 M) of 3-azetidinone **4.2**, 114.6 mg (1.04 mmol) of 4-octyne **4.1**, 22.7 mg (0.04 mmol) of $Ni(PPh_3)_2Cl_2$ and 9.1 mg (0.14 mmol) of Zn powder in acetonitrile. The reaction mixture was heated at 60 °C for 16 h. The remaining residue was purified by silica gel flash column chromatography using 25% ether in hexanes (R_f = 0.24) to afford the title compound **4.3** (186.1 mg, 0.66 mmol, 95%) as colorless oil. ^1H NMR and ^{13}C NMR was consistent with reported data.[5a]

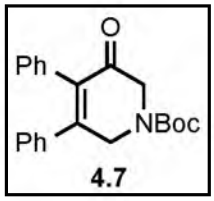
tert-butyl 5-(*tert*-butyl)-3-oxo-3,6-dihydropyridine-1(2*H*)-carboxylate (**4.5**)



4.5

The general procedure **G1** was used with 117.5 mg (0.69 mmol, 0.2 M) of 3-azetidinone **4.2**, 84.6 mg (1.03 mmol) of *t*-butylacteylene **4.4**, 22.6 mg (0.03 mmol) of $Ni(PPh_3)_2Cl_2$ and 9.0 mg (0.14 mmol) of Zn powder in acetonitrile. The reaction mixture was heated at 80 °C for 16 h. The remaining residue was purified by silica gel flash column chromatography using 15-25% ether in hexanes (R_f = 0.27 in 25% ether/hexanes) to afford the title compound **4.5** (104.5 mg, 0.41 mmol, 60%) as colorless oil. ^1H NMR and ^{13}C NMR was consistent with reported data.[5a]

tert-butyl 5-oxo-3,4-diphenyl-5,6-dihydropyridine-1(2H)-carboxylate (**4.7**)



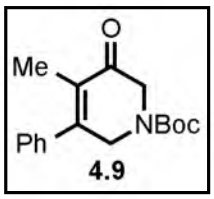
4.7

The general procedure **G1** was used with 130.3 mg (0.76 mmol, 0.2 M) of 3-azetidinone **4.2**, 203.4 mg (1.14 mmol) of diphenylacetylene **4.6**, 24.9 mg (0.04 mmol) of $Ni(PPh_3)_2Cl_2$ and 7.5 mg (0.12 mmol) of Zn powder in acetonitrile. The reaction mixture was heated at 80 °C for 20 h. The remaining residue was purified by silica gel flash column chromatography using 15-20% ethyl acetate in hexanes (R_f = 0.3 in 20% EtOAc/hexanes) to afford the title compound **4.7** (191.0 mg, 0.55 mmol, 72%) as pale oil. ^1H NMR and ^{13}C NMR was consistent with reported data.[5a]

Gram scale reaction

The general procedure **G1** was used with 1.43 g (8.35 mmol, 0.2 M) of 3-azetidinone **4.2**, 2.23 g (12.5 mmol) of diphenylacetylene **4.6**, 273.1 mg (0.42 mmol) of $Ni(PPh_3)_2Cl_2$ and 109.2 mg (1.67 mmol) of Zn powder in acetonitrile. The reaction mixture was heated at 80 °C for 20 h. The remaining residue was purified by silica gel flash column chromatography using 15-20% ethyl acetate in hexanes (R_f = 0.3 in 20% EtOAc/hexanes) to afford the title compound **4.7** (2.11 g, 6.0 mmol, 72%) as pale oil. ^1H NMR and ^{13}C NMR was consistent with reported data.[5a]

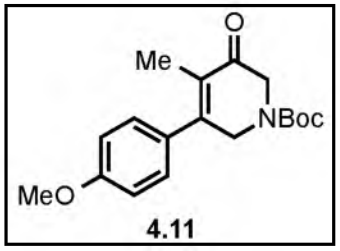
tert-butyl 4-methyl-5-oxo-3-phenyl-5,6-dihydropyridine-1(2H)-carboxylate (**4.9**)



4.9

The general procedure **G1** was used with 100.5 mg (0.59 mmol, 0.2 M) of 3-azetidinone **4.2**, 102.2 mg (0.88 mmol) of phenyl-methyl alkyne **4.8**, 19.3 mg (0.03 mmol) of $Ni(PPh_3)_2Cl_2$ and 7.7 mg (0.12 mmol) of Zn powder in acetonitrile. The reaction mixture was heated at 80 °C for 20 h. The remaining residue was purified by silica gel flash column chromatography using 25% ether in hexanes (R_f = 0.20) to afford the title compound **4.9** (147.0 mg, 0.51 mmol, 86%) as colorless oil. ^{1}H NMR and ^{13}C NMR was consistent with reported data.[5a]

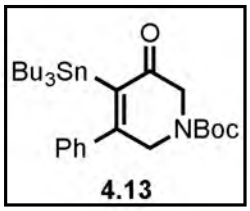
tert-butyl 3-(4-methoxyphenyl)-4-methyl-5-oxo-5,6-dihydro-pyridine-1(2H)-carboxylate (**4.11**)



4.11

The general procedure **G1** was used with 105.0 mg (0.61 mmol, 0.2 M) of 3-azetidinone **4.2**, 134.5 mg (0.92 mmol) of *p*-methoxyphenyl-methyl alkyne **4.10**, 20.1 mg (0.03 mmol) of $Ni(PPh_3)_2Cl_2$ and 8.0 mg (0.12 mmol) of Zn powder in acetonitrile. The reaction mixture was heated at 80 °C for 20 h. The remaining residue was purified by silica gel flash column chromatography using 30% ether in hexanes (R_f = 0.20) to afford the title compound **4.11** (170.0 mg, 0.54 mmol, 87%) as colorless oil. ^{1}H NMR and ^{13}C NMR was consistent with reported data.[5a]

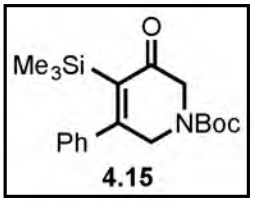
tert-butyl 5-oxo-4-phenyl-3-(tributylstannyl)-5,6-dihydro-pyridine-1(2H)-carboxylate (**4.13**)



4.13

The general procedure **G1** was used with 79.5 mg (0.46 mmol, 0.2 M) of 3-azetidinone **4.2**, 272.5 mg (0.70 mmol) of tributyltin-phenyl alkyne **4.12**, 15.3 mg (0.02 mmol) of $Ni(PPh_3)_2Cl_2$ and 6.1 mg (0.09 mmol) of Zn powder in acetonitrile. The reaction mixture was heated at 80 °C for 20 h. The remaining residue was purified by silica gel flash column chromatography using 15% ether in hexanes (R_f = 0.29) to afford the title compound **4.13** (190.0 mg, 0.34 mmol, 73%) as yellow oil. ^{1}H NMR and ^{13}C NMR was consistent with reported data.[5a]

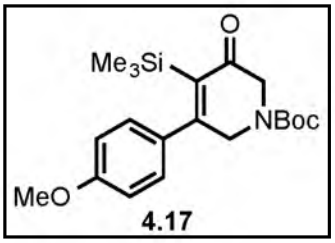
tert-butyl 5-oxo-3-phenyl-4-(trimethylsilyl)-5,6-dihydro-pyridine-1(2H)-carboxylate (**4.15**)



4.15

The general procedure **G1** was used with 121.6 mg (0.71 mmol, 0.2 M) of 3-azetidinone **4.2**, 185.7 mg (1.07 mmol) of phenyl-trimethylsilyl alkyne **4.14**, 23.2 mg (0.04 mmol) of $Ni(PPh_3)_2Cl_2$ and 9.3 mg (0.14 mmol) of Zn powder in acetonitrile. The reaction mixture was heated at 80 °C for 20 h. The remaining residue was purified by silica gel flash column chromatography using 15-20% ether in hexanes (R_f = 0.26 in 20% ether/hexanes) to afford the title compound **4.15** (184.8 mg, 0.53 mmol, 75%) as pale oil. ^{1}H NMR and ^{13}C NMR was consistent with reported data.[5a]

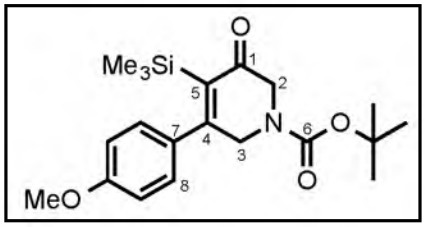
tert-butyl 5-(4-methoxyphenyl)-3-oxo-4-(trimethylsilyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (**4.17**)



4.17

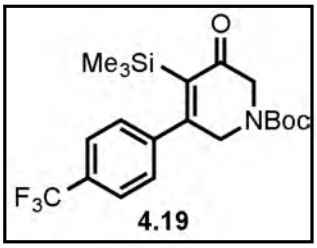
The general procedure **G1** was used with 99.0 mg (0.58 mmol, 0.2 M) of 3-azetidinone **4.2**, 177.3 mg (0.87 mmol) of (*p*-methoxy)phenyl-trimethylsilyl alkyne **4.16**, 19.0 mg (0.03 mmol) of $Ni(PPh_3)_2Cl_2$ and 7.6 mg (0.12 mmol) of Zn powder in acetonitrile. The reaction mixture was heated at 80 °C for 20 h. The remaining residue was purified by silica gel flash column chromatography using 25-30% ether in hexanes (R_f = 0.30 in 30% ether/hexanes) to afford the title compound **4.17** (161.1 mg, 0.43 mmol, 74%) as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.20 (d, J = 8.0 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 4.29 (s, 2H), 4.05 (s, 2H), 3.82 (s, 3H), 1.48 (s, 9H), 0.11 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 198.4, 161.0, 154.5, 131.74, 131.66, 129.8, 114.0, 113.9, 81.0, 55.5, 51.8, 49.0, 28.6, 0.7. IR (CH_2Cl_2, cm^{-1}): 2977, 1699, 1665, 1607, 1509, 1458, 1413, 1248, 1160, 1110, 1031, 843, 766, 736. HRMS (ESI) calcd for $C_{20}H_{29}NO_4SiNa$ $[M+Na]^+$ 398.1764, found 398.1760.



Key g-HMBC correlations: The following cross-peaks were observed: H(2) and C(1); H(2) and C(6); H(3) and C(6); H(3) and C(4); H(3) and C(5); H(3) and C(7); H(8) and C(7); H(8) and C(4).

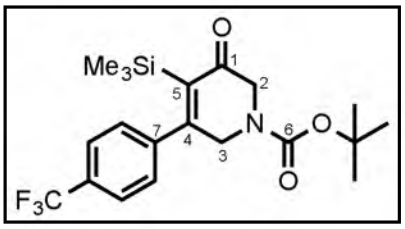
tert-butyl 3-oxo-5-(4-(trifluoromethyl)phenyl)-4-(trimethylsilyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (**4.19**)



4.19

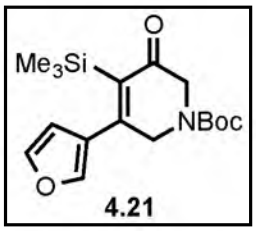
The general procedure **G1** was used with 122.0 mg (0.71 mmol, 0.2 M) of 3-azetidinone **4.2**, 259.0 mg (1.07 mmol) of (*p*-trifluoromethyl)phenyl-trimethylsilyl alkyne **4.18**, 23.3 mg (0.04 mmol) of $Ni(PPh_3)_2Cl_2$ and 9.3 mg (0.14 mmol) of Zn powder in acetonitrile. The reaction mixture was heated at 80 °C for 20 h. The remaining residue was purified by silica gel flash column chromatography using 20% ether in hexanes (R_f = 0.29) to afford the title compound **4.19** (151.0 mg, 0.36 mmol, 51%) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.67 (d, *J* =7.6 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 4.28 (s, 2H), 4.09 (s, 2H), 1.48 (s, 9H), 0.14 (s, 9H) ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 197.7, 154.4, 154.4, 143.1, 138.8, 132.1, 131.8, 131.5, 131.1, 128.5, 128.0, 125.70, 125.67, 125.6, 125.3, 122.6, 119.9, 81.3, 51.7, 49.0, 28.5, 0.5. IR (CH_2Cl_2, cm^{-1}): 2979, 1701 1670, 1588, 1405, 1368, 1324, 1248, 1164, 1128, 1109, 1069, 1016, 938, 843, 766. HRMS (ESI) calcd for $C_{20}H_{26}F_3NO_3SiNa$ $[M+Na]^+$ 436.1532, found 436.1540.



Key g-HMBC correlations: The following cross-peaks were observed: H(2) and C(1); H(2) and C(6); H(3) and C(6); H(3) and C(4); H(3) and C(5); H(3) and C(7); H(8) and C(7); H(8) and C(4).

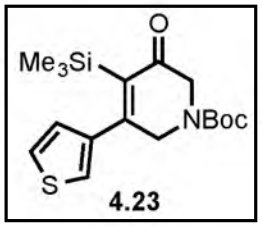
tert-butyl 3-(furan-3-yl)-5-oxo-4-(trimethylsilyl)-5,6-dihydro-pyridine-1(2H)-carboxylate (**4.21**)



4.21

The general procedure **G1** was used with 86.5 mg (0.51 mmol, 0.2 M) of 3-azetidinone **4.2**, 124.5 mg (0.76 mmol) of furanyl-trimethylsilyl alkyne **4.20**, 16.7 mg (0.03 mmol) of $Ni(PPh_3)_2Cl_2$ and 6.7 mg (0.10 mmol) of Zn powder in acetonitrile. The reaction mixture was heated at 80 °C for 24 h. The remaining residue was purified by silica gel flash column chromatography using 10-20% ether in hexanes (R_f = 0.27 in 20% ether/hexanes) to afford the title compound **4.21** (126.8 mg, 0.38 mmol, 75%) as yellow oil. ^1H NMR and ^{13}C NMR was consistent with reported data.[5a]

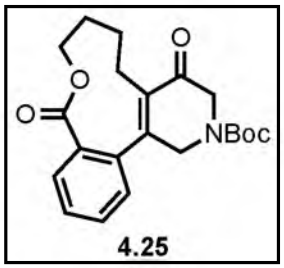
tert-butyl-5-oxo-3-(thiophen-3-yl)-4-(trimethylsilyl)-5,6-dihydro-pyridine-1(2H)-carboxylate (**4.23**)



4.23

The general procedure **G1** was used with 101.0 mg (0.59 mmol, 0.2 M) of 3-azetidinone **4.2**, 158.7 mg (0.88 mmol) of thiophenyl-trimethylsilyl alkyne **4.22**, 19.3 mg (0.03 mmol) of $Ni(PPh_3)_2Cl_2$ and 7.7 mg (0.12 mmol) of Zn powder in acetonitrile. The reaction mixture was heated at 80 °C for 24 h. The remaining residue was purified by silica gel flash column chromatography using 10-20% ether in hexanes (R_f = 0.27 in 20% ether/hexanes) to afford the title compound **4.23** (150.8 mg, 0.43 mmol, 73%) as pale oil. ^1H NMR and ^{13}C NMR was consistent with reported data.[5a]

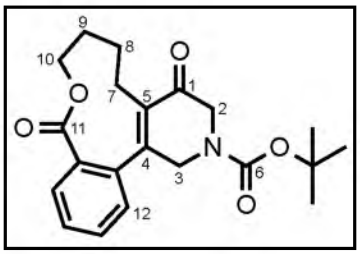
tert-butyl-4,10-dioxo-4,5,6,7,8,10-hexahydro-1*H*-benzo[3,4]-oxecino[5,6-*c*]pyridine-2(3*H*)-carboxylate (**4.25**)



4.25

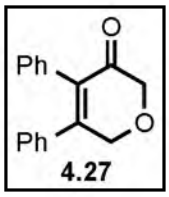
The general procedure **G1** was used with 55.0 mg (0.32 mmol, 0.2 M) of 3-azetidinone **4.2**, 96.5 mg (0.48 mmol) of macrocyclic alkyne **4.24**, 10.5 mg (0.02 mmol) of $Ni(PPh_3)_2Cl_2$ and 4.2 mg (0.06 mmol) of Zn powder in acetonitrile. The reaction mixture was heated at 80 °C for 20 h. The remaining residue was purified by silica gel flash column chromatography using 30-40% ether in hexanes (R_f = 0.28 in 40% ether/hexanes) to afford the title compound **4.25** (65.5 mg, 0.18 mmol, 55%) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.96 (d, *J* = 7.6 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.21 (brs, 1H), 4.68 (m, 1H), 4.36-4.50 (m, 3H), 4.19 (m, 1H), 4.00 (brm, 1H), 2.54 (m, 1H), 1.92-2.26 (m, 2H), 1.53-1.77 (m, 4H), 1.47 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 193.8, 167.9, 154.4, 136.9, 135.1, 132.0, 130.2, 129.8, 128.8, 128.2, 125.7, 81.2, 67.3, 52.3, 48.8, 31.8, 28.5, 25.8, 25.2. IR (CH_2Cl_2, cm^{-1}): 2973, 2917, 2849, 1700.96, 1676, 1626, 1597, 1439, 1417, 1368, 1290, 1246, 1165, 1129, 1089, 1047, 905, 764, 736. HRMS (ESI) calcd for $C_{21}H_{25}NO_5Na$ $[M+Na]^+$ 394.1630, found 394.1633.



Key g-HMBC correlations: The following cross-peaks were observed: H(2) and C(1); H(2) and C(6); H(3) and C(6); H(3) and C(4); H(3) and C(5); H(3) and C(7); H(7) and C(5); H(7) and C(1); H(8) and C(5); H(10) and C(11); H(12) and C(4).

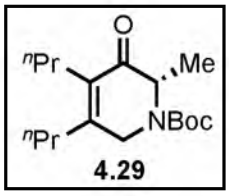
4,5-diphenyl-2*H*-pyran-3(6*H*)-one (**4.27**)



4.27

The general procedure **G2** was used with 63.4 mg (0.88 mmol, 0.1 M) of 3-oxetanone **4.26**, 235.3 mg (1.32 mmol) of diphenylacetylene **4.6**, 29.0 mg (0.04 mmol) of $Ni(PPh_3)_2Cl_2$ and 11.6 mg (0.18 mmol) of Zn powder in acetonitrile. The reaction mixture was heated at 80 °C for 16 h. The remaining residue was purified by silica gel flash column chromatography using 30% ether in hexanes (R_f = 0.23) to afford the title compound **4.27** (132.2 mg, 0.53 mmol, 60%) as colorless gel. ^{1}H NMR and ^{13}C NMR was consistent with reported data.[5b]

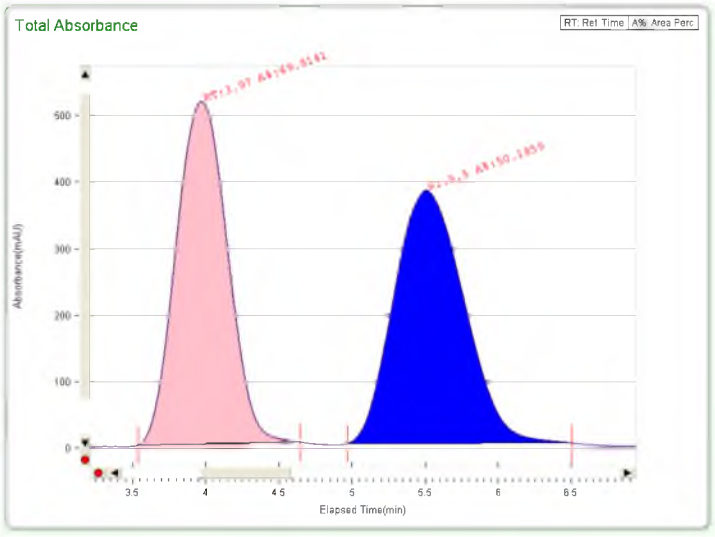
tert-butyl (*S*)-2-methyl-3-oxo-4,5-dipropyl-3,6-dihydropyridine-1(2*H*)-carboxylate (**4.29**)



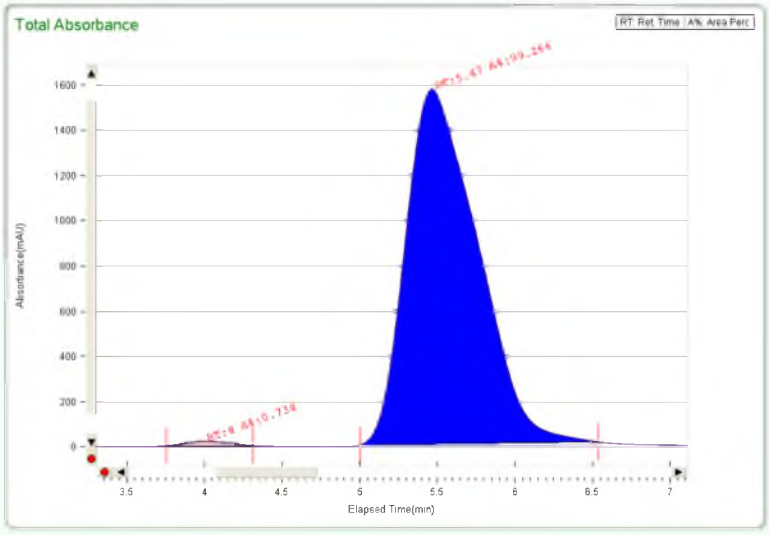
4.29

The general procedure **G2** was used with 63.2 mg (0.34 mmol, 0.2 M) of enantiopure 2-methyl-3-azetidinone **4.28**, 56.4 mg (0.51 mmol) of 4-octyne **4.1**, 11.2 mg (0.02 mmol) of $Ni(PPh_3)_2Cl_2$ and 4.5 mg (0.07 mmol) of Zn powder in acetonitrile. The reaction mixture was heated at 60 °C for 20 h. The remaining residue was purified by silica gel flash column chromatography using 15-20% ether in hexanes (R_f = 0.28 in 20% ether/hexanes) to afford the title compound **4.29** (100.8 mg, 0.30 mmol, 87%) as colorless oil. $[\alpha]_D^{20}$ = 25.2 (c = 1.0, $CHCl_3$); (Daicel Chiralpak OZ-H Column, 3% *i*-PrOH, 25 °C, flow rate = 2 mL/min, 160 bar), Retention time: *minor* = 4.00 min, *major* = 5.47 min, ee = 98%]. ^{1}H NMR and ^{13}C NMR was consistent with reported data.[5b]

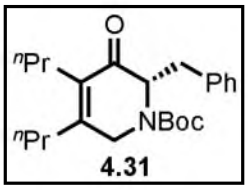
Chromatogram of racemic *tert*-butyl 2-methyl-3-oxo-4,5-dipropyl-3,6-dihydropyridine-1(2*H*)-carboxylate (rac-**4.29**)



Chromatogram of chiral *tert*-butyl (*S*)-2-methyl-3-oxo-4,5-dipropyl-3,6-dihydropyridine-1(2*H*)-carboxylate (**4.29**)



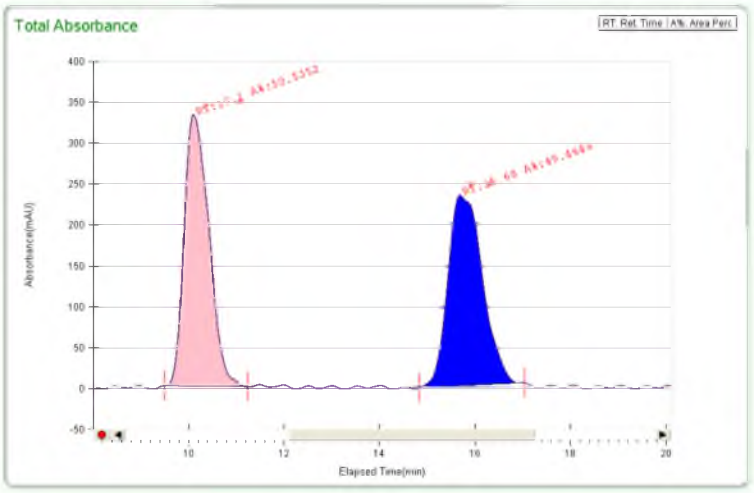
tert-butyl (*S*)-2-benzyl-3-oxo-4,5-dipropyl-3,6-dihydropyridine-1(2*H*)-carboxylate (**4.31**)



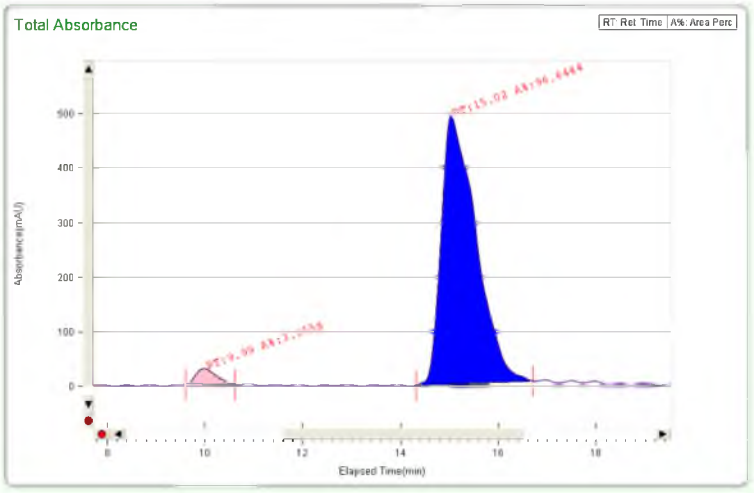
4.31

The general procedure **G2** was used with 42.3 mg (0.16 mmol, 0.2 M) of enantiopure 2-benzyl-3-azetidinone **4.30**, 26.8 mg (0.24 mmol) of 4-octyne **4.1**, 5.3 mg (0.01 mmol) of $Ni(PPh_3)_2Cl_2$ and 2.1 mg (0.03 mmol) of Zn powder in acetonitrile. The reaction mixture was heated at 60 °C for 20 h. The remaining residue was purified by silica gel flash column chromatography using 10-20% ether in hexanes (R_f = 0.41 in 20% ether/hexanes) to afford the title compound **4.31** (51.2 mg, 0.14 mmol, 85%) as colorless oil. $[\alpha]_D^{20}$ = -20.7 (c = 1.0, $CHCl_3$); (Daicel Chiralpak OZ-H Column, 3% *i*-PrOH, 40 °C, flow rate = 2 mL/min, 160 bar), Retention time: *mino*r = 9.99 min, *major* = 15.02 min, ee = 93%]. ^1H NMR and ^{13}C NMR was consistent with reported data.[5a,b]

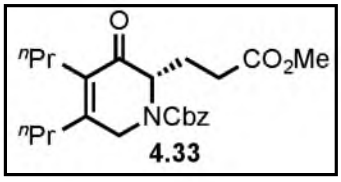
Chromatogram of racemic *tert*-butyl 2-benzyl-3-oxo-4,5-dipropyl-3,6-dihydropyridine-1(2*H*)-carboxylate (rac-**4.31**)



Chromatogram of chiral *tert*-butyl (*S*)-2-benzyl-3-oxo-4,5-dipropyl-3,6-dihydropyridine-1(2*H*)-carboxylate (**4.31**)



benzyl (*S*)-2-(3-methoxy-3-oxopropyl)-3-oxo-4,5-dipropyl-3,6-dihydropyridine-1(2*H*)-carboxylate (**4.33**)

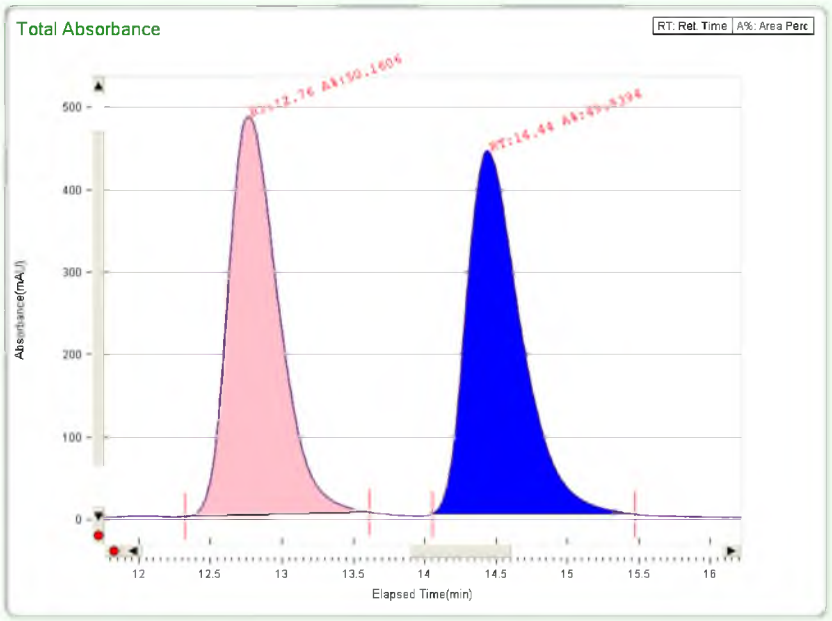


The general procedure **G2** was used with 53.3 mg (0.18 mmol, 0.2 M) of enantiopure 3-azetidinone **4.32**, 30.2 mg (0.27 mmol) of 4-octyne **4.1**, 6.0 mg (0.01 mmol) of $Ni(PPh_3)_2Cl_2$ and 2.4 mg (0.04 mmol) of Zn powder in acetonitrile. The reaction mixture was heated at 60 °C for 20 h. The remaining residue was purified by silica gel flash column chromatography using 10-20% EtOAc in hexanes (R_f = 0.25 in 20% EtOAc/hexanes) to afford the title compound **4.33** (63.4 mg, 0.16 mmol, 86%) as colorless oil. $[\alpha]_D^{20}$ = 13.2 (c = 1.0, $CHCl_3$); (Daicel Chiralpak AY-H Column, 5-15% *i*-PrOH, 25 °C, flow rate = 2 mL/min, 160 bar), Retention time: *major* = 12.76 min, *minor* = 14.68 min, ee = 97%].

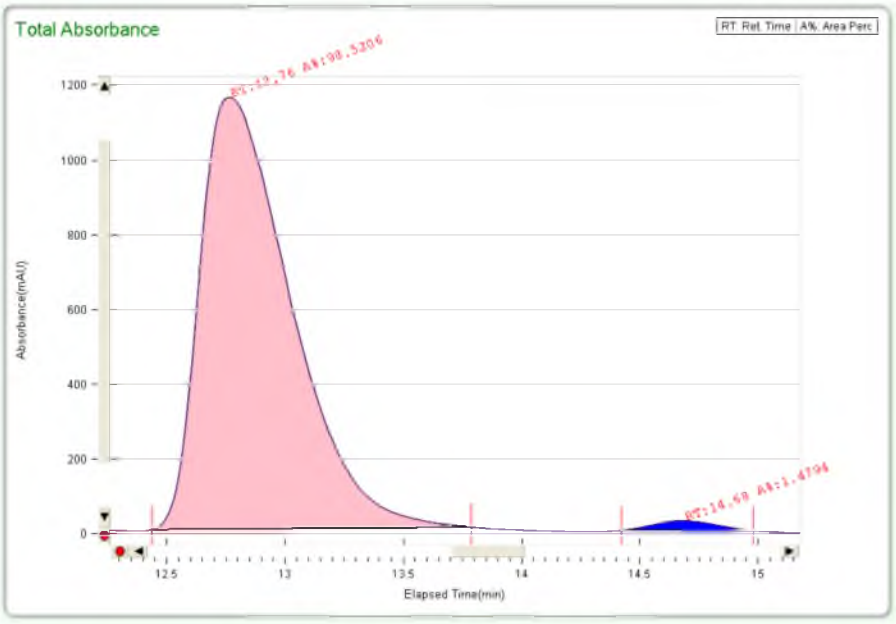
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.36 (brs, 5H), 5.13 (brs, 2H), 4.48-4.67 (m, 2H),

3.78-3.91 (m, 1H), 3.61 (s, 3H), 2.17-2.42 (m, 6H), 1.94 (m, 2H), 1.56 (m, 2H), 1.33 (sext, J = 7.6 Hz, 2H), 1.00 (m, 3H), 0.91 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 194.7, 173.2, 155.1, 153.8, 136.1, 133.0, 128.8, 128.5, 128.4, 68.0, 59.5, 51.9, 43.4, 34.2, 30.8, 26.9, 25.7, 22.7, 21.8, 14.5, 14.4. IR (CH_2Cl_2, cm^{-1}): 2959, 2872, 1734, 1700, 1668, 1635, 1559, 1498, 1424, 1384, 1230, 1176, 1157, 1108, 1015, 736, 697, 668. HRMS (ESI) calcd for $C_{23}H_{31}NO_5Na$ $[M+Na]^+$ 424.2100, found 424.2095.

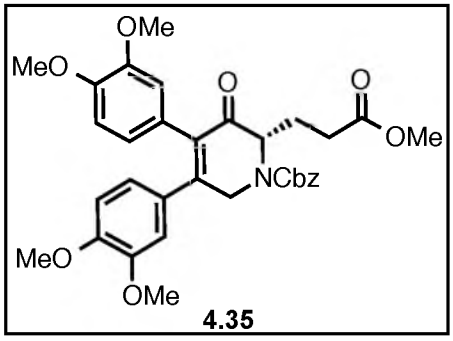
Chromatogram of racemic benzyl 2-(3-methoxy-3-oxopropyl)-3-oxo-4,5-dipropyl-3,6-dihydropyridine-1(2*H*)-carboxylate (rac-**4.33**)



Chromatogram of chiral benzyl-*(S)*-2-(3-methoxy-3-oxopropyl)-3-oxo-4,5-dipropyl-3,6-dihydropyridine-1(2*H*)-carboxylate (**4.33**)



benzyl-(*S*)-4,5-bis(3,4-dimethoxyphenyl)-2-(3-methoxy-3-oxo-propyl)-3-oxo-3,6-dihydropyridine-1(2*H*)-carboxylate (**4.35**)



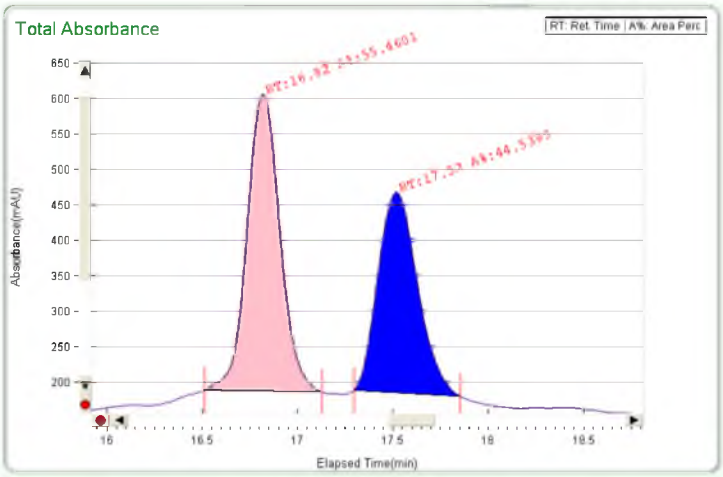
4.35

The general procedure **G2** was used with 52.7 mg (0.18 mmol, 0.2 M) of enantiopure 3-azetidinone **4.32**, 81.0 mg (0.27 mmol) of alkyne **4.34**, 5.9 mg (0.01 mmol) of $Ni(PPh_3)_2Cl_2$ and 2.4 mg (0.04 mmol) of Zn powder in acetonitrile. The reaction mixture was heated at 80 °C for 20 h. The remaining residue was purified by silica gel flash column chromatography using 45-55% EtOAc in hexanes (R_f = 0.25 in 55% EtOAc/hexanes) to afford the title compound **4.35** (89.1 mg, 0.15 mmol, 83%) as

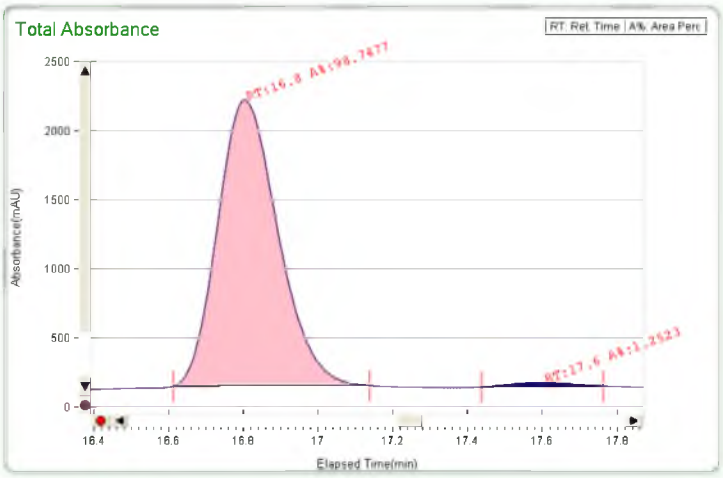
yellow oil. $[\alpha]_D^{20}$ = -106.6 (c = 1.0, $CHCl_3$); (Daicel Chiralpak OZ-H Column, 5-15-50% *i*-PrOH, 40 °C, flow rate = 30 mL/min, 200 bar), Retention time: *major* = 16.82 min, *minor* = 17.6 min, ee = 97%].

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.33-7.40 (m, 5H), 6.89 (brd, *J* =7.6 Hz, 1H), 6.72-6.75 (m, 2H), 6.57 (brd, *J* = 8.0 Hz, 1H), 6.49-6.51 (m, 2H), 5.31 (brd, *J* = 20.4 Hz, 1H), 5.21 (s, 2H), 4.81-4.91 (m, 1H), 4.11-4.16 (m, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.67 (s, 3H), 3.64 (s, 3H), 3.52 (brs, 3H), 2.40-2.55 (m, 2H), 2.20-2.27 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 194.1, 173.2, 155.4, 153.4, 149.9, 148.7, 148.5, 135.9, 133.3, 128.8, 128.6, 128.4, 126.9, 123.7, 121.7, 114.4, 112.7, 111.0, 110.7, 88.2, 68.2, 59.8, 56.0, 55.8, 52.0, 44.2, 30.8, 25.4. IR (CH_2Cl_2, cm^{-1}): 2916, 2849, 1734, 1700, 1684, 1653, 1559, 1539, 1463, 1456, 1251, 1171, 1144, 1027, 764, 681. HRMS (ESI) calcd for $C_{33}H_{35}NO_9Na$ $[M+Na]^+$ 612.2210, found 612.2206.

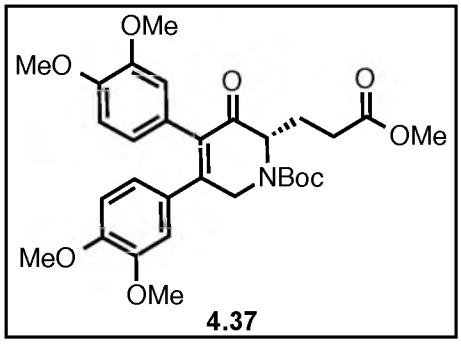
Chromatogram of racemic benzyl-(4,5-bis(3,4-dimethoxyphenyl)-2-(3-methoxy-3-oxopropyl)-3-oxo-3,6-dihydropyridine-1(2*H*)-carboxylate (rac-**4.35**)



Chromatogram of chiral benzyl-*(S)*-4,5-bis(3,4-dimethoxyphenyl)-2-(3-methoxy-3-oxopropyl)-3-oxo-3,6-dihydropyridine-1(2*H*)-carboxylate (**4.35**)



tert-butyl-(*S*)-4,5-bis(3,4-dimethoxyphenyl)-2-(3-methoxy-3-oxo-propyl)-3-oxo-3,6-dihydropyridine-1(2*H*)-carboxylate (**4.37**)



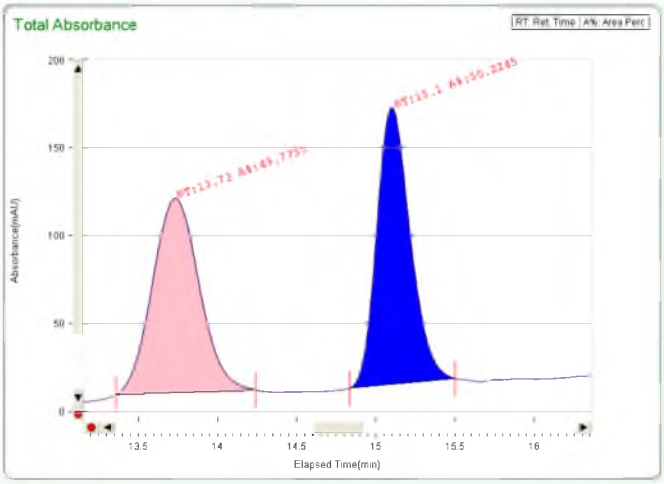
4.37

The general procedure **G2** was used with 55.2 mg (0.22 mmol, 0.2 M) of enantiopure 3-azetidinone **4.36**, 96.0 mg (0.32 mmol) of alkyne **4.34**, 7.0 mg (0.01 mmol) of $Ni(PPh_3)_2Cl_2$ and 2.8 mg (0.04 mmol) of Zn powder in acetonitrile. The reaction mixture was heated at 80 °C for 20 h. The remaining residue was purified by silica gel flash column chromatography using 40-50% ethylacetate in hexanes (R_f = 0.25 in 50% EtOAc/hexanes) to afford the title compound **4.37** (105.0 mg, 0.19 mmol, 88%) as yellow gel. $[\alpha]_D^{20}$ = -113.9 (c = 1.0, $CHCl_3$); (Daicel Chiralpak OZ-H Column, 5-15-

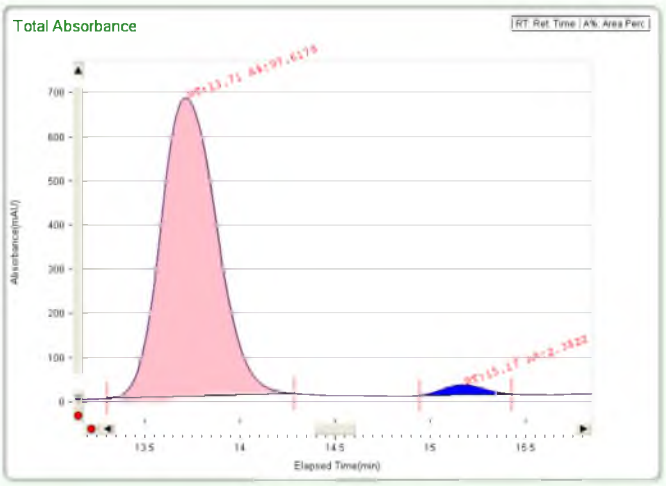
50% *i*-PrOH, 40 °C, flow rate = 30 mL/min, 200 bar), Retention time: *major* = 13.71 min, *minor* = 15.17 min, ee = 95%].

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.87 (brm, 1H), 6.74 (d, J = 8.0 Hz, 2H), 6.59 (d, J = 8.0 Hz, 1H), 6.50 (s, 2H), 5.28 (brd, J = 20.4 Hz, 1H), 4.74 (brs, 1H), 4.05 (brd, J = 20.0 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.70 (s, 3H), 3.67 (s, 3H), 3.53 (s, 3H), 2.50 (m, 2H), 2.18 (m, 2H), 1.52 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 194.7, 173.3, 154.5, 153.7, 149.9, 148.7, 148.5, 133.3, 129.0, 127.1, 123.8, 121.7, 114.5, 112.8, 111.0, 110.9, 110.7, 81.6, 59.9, 56.01, 56.00, 55.8, 52.0, 43.7, 39.1, 30.9, 28.6, 25.5. IR (CH_2Cl_2, cm^{-1}): 2917, 2848, 1736, 1695, 1600, 1594, 1463, 1411, 1366, 1320, 1254, 1205, 1161, 764. HRMS (ESI) calcd for $C_{30}H_{37}NO_9Na$ $[M+Na]^+$ 578.2366, found 578.2365.

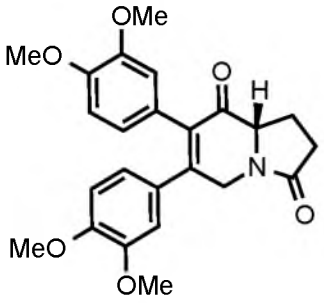
Chromatogram of racemic *tert*-butyl-4,5-bis(3,4-dimethoxyphenyl)-2-(3-methoxy-3-oxopropyl)-3-oxo-3,6-dihydropyridine-1(2*H*)-carboxylate (rac-**4.37**)



Chromatogram of chiral *tert*-butyl-*(S)*-4,5-bis(3,4-dimethoxyphenyl)-2-(3-methoxy-3-oxopropyl)-3-oxo-3,6-dihydropyridine-1(2*H*)-carboxylate (**4.37**)



(*S*)-6,7-bis(3,4-dimethoxyphenyl)-1,8a-dihydroindolizine-3,8(2*H*,5*H*)-dione (**4.38**)



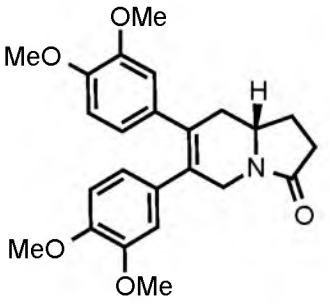
To a solution of **4.37** (72.2 mg, 0.13 mmol, 0.05 M) in CH_2Cl_2 (2.6 ml) at 0 °C under nitrogen atmosphere, was dropwise added trifluoroacetic acid (148.2 mg, 1.3 mmol, 0.10 ml) in 10 min. The reaction mixture was stirred for 3 h followed by the evaporation of solvent under vacuum. The remaining residue was diluted by dichloromethane and washed with saturated aqueous $NaHCO_3$ solution. The organic phase was extracted three times using dichloromethane, dried over Na_2SO_4 and concentrated under vacuum to afford yellow oil. This compound was dissolved in dry THF (1.3 ml) and transferred to a 2-neck 50 ml round-bottom flask

fitted with a water condenser under nitrogen atmosphere. 2-pyridone (2.5 mg, 0.03 mmol) was then added to this flask and the reaction mixture was heated at reflux for 2 h. The remaining residue was concentrated in vacuo and purified by silica gel flash column chromatography using 70-85% ethyl acetate in dichloromethane (R_f = 0.25 in 85% EtOAc/dichloromethane) to obtain **4.38** as yellow gel [50.6 mg, 0.12 mmol, 92%, $[\alpha]_D^{20}$ = + 8.0 (c = 0.24, $CHCl_3$)].

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.88 (dd, *J* = 2.0, 8.0 Hz, 1H), 6.74 (m, 2H), 6.56-6.61 (m, 1H), 6.51 (dd, *J* = 2.0, 8.8 Hz, 2H), 5.25 (d, *J* = 20.0 Hz, 1H), 4.34 (m, 1H), 4.04 (d, *J* = 20.0 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.66 (s, 3H), 3.52 (s, 3H), 2.50 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 194.2, 174.5, 153.2, 150.0, 148.8, 148.61, 148.59, 134.9, 128.9, 127.0, 123.8, 121.7, 114.4, 112.7, 111.0, 110.8, 60.6, 56.0, 55.8, 44.1, 30.1, 20.8, 14.4. IR (CH_2Cl_2, cm^{-1}): 2955, 2916, 2848, 1668, 1513, 1462, 1261, 1141, 1026, 862, 813, 764. HRMS (ESI) calcd for $C_{24}H_{25}NO_6Na$ $[M+Na]^+$ 446.1580, found 446.1587.

(*S*)-6,7-bis(3,4-dimethoxyphenyl)-1,5,8,8a-tetrahydroindolizin-3(2*H*)-one (**4.39**)

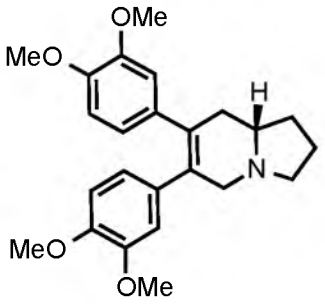
To a stirring solution of **4.38** (40.0 mg, 0.09 mmol) in CH_2Cl_2 (1.9 mL) at 0 °C, was added $NaBH_4$ (4.3 mg, 0.11 mmol). After the addition, the ice-bath was removed and the reaction was stirred for 1 h at room temperature. The solvent was evaporated under vacuum and the remaining residue was dissolved in ethyl acetate followed by washing with saturated aqueous NH_4Cl solution. The organic phase was extracted three times using ethyl acetate, dried over Na_2SO_4 and



concentrated under vacuum to afford white semi-solid. This compound was dissolved in CH_2Cl_2 (1.9 mL) and then transferred to a 2-neck 50 ml round-bottom flask fitted with a water condenser under nitrogen atmosphere. After cooling to 0 °C, triethylsilane (65.9 mg, 0.57 mmol) and trifluoroacetic acid (107.8 mg, 0.94 mmol) were added to the reaction. The cooling bath was removed and the reaction was allowed to come to room temperature. The reaction mixture was then heated at reflux for 10 h, cooled to room temperature and concentrated under vacuum. The remaining residue was diluted with ethyl acetate and washed with saturated aqueous $NaHCO_3$ solution. The organic phase was extracted three times using ethyl acetate, dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified using purified by silica gel flash column chromatography using 70-85% ethyl acetate in dichloromethane (R_f = 0.27 in 85% EtOAc/dichloromethane) to obtain **4.39** as off-white gel [27.2 mg, 0.07 mmol, 70%]. ^{1}H NMR and ^{13}C NMR was consistent with reported data.[10b]

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.61-6.71 (m, 4H), 6.50 (dd, *J* = 2, 18.0 Hz, 2H), 4.76 (dd, *J* = 2, 18.4 Hz, 1H), 3.91-3.94 (m, 1H), 3.82 (s, 6H), 3.76 (m, 1H), 3.61 (s, 3H), 3.60 (s, 3H), 2.75 (dd, *J* = 3.2, 16.4, 1H), 2.54-2.39 (m, 4H), 1.74-1.85 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 174.1, 148.6, 148.5, 148.1, 147.9, 134.7, 132.2, 132.0, 130.9, 121.4, 121.0, 113.0, 110.9, 56.03, 56.0, 55.91, 55.90, 53.6, 44.2, 39.0, 30.3, 25.1.

(*S*)-6,7-bis(3,4-dimethoxyphenyl)-1,2,3,5,8,8a-hexahydro-indolizine (**I**)



To a stirring solution of **4.39** (23.0 mg, 0.06 mmol) in thf (2.2 ml) at 0 °C, was added $LiAlH_4$ (2.0 M in thf, 0.08 mmol) in 10 min. After addition, the cooling bath was removed and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was carefully quenched by the addition of water at 0 °C and the solids were filtered through celite. The filtrate was extracted with ethyl acetate, washed with brine and dried over Na_2SO_4. The solvent was removed under vacuum and purified by silica gel flash column chromatography using 2-6% methanol in dichloromethane (R_f = 0.19 in 6% MeOH/CH_2Cl_2) to obtain **I** as off-white solid [21.0 mg, 0.053 mmol, 95%, $[\alpha]_D^{20}$ = + 95.6 (c = 0.5, MeOH)]. ^{1}H NMR and ^{13}C NMR was consistent with reported data.[10b]

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.64-6.70 (m, 4H), 6.53 (d, *J* = 8.4 Hz, 2H), 3.91 (d, *J* = 16.0 Hz, 1H), 3.81 (s, 6H), 3.60 (s, 3H), 3.58 (s, 3H), 3.45 (t, *J* = 8.8 Hz, 1H), 3.13 (d, *J* = 16.0 Hz, 1H), 2.76 (d, *J* =14.8 Hz, 1H), 2.39-2.43 (m, 2H), 2.27-2.36 (m, 1H), 2.09-2.17 (m, 1H), 2.04-1.93 (m, 1H), 1.81-1.91 (m, 1H), 1.55-1.65 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 148.5, 148.3, 147.7, 147.5, 133.2, 133.8, 133.1, 132.7, 121.1, 120.9, 113.2, 113.0, 110.7, 110.9, 110.8, 60.7, 57.6, 55.85, 55.80, 54.4, 38.5, 30.9, 29.9, 21.7.

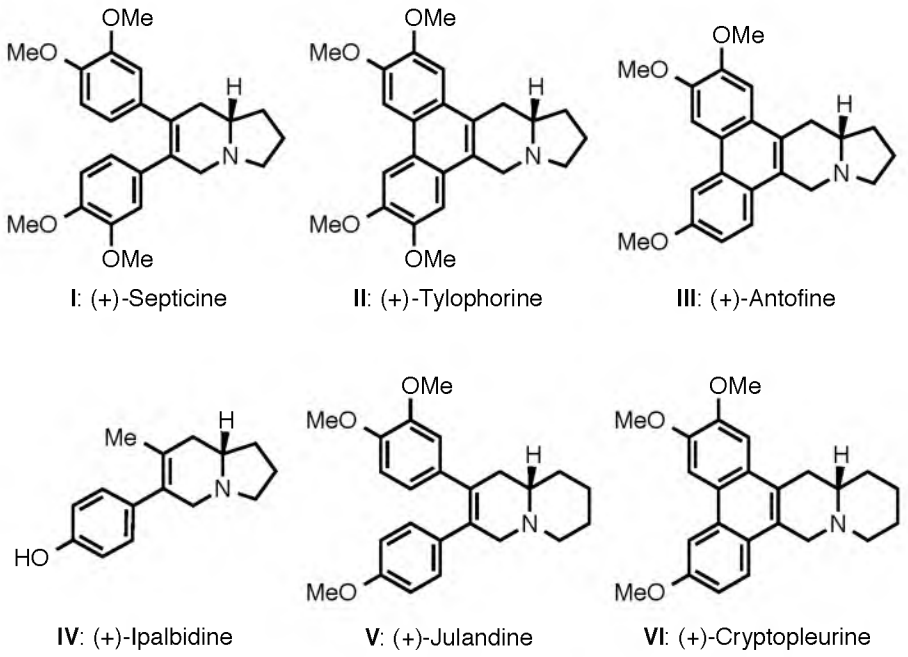


Figure 4.1. Biologically active indolizidine and quinazolidine alkaloids.

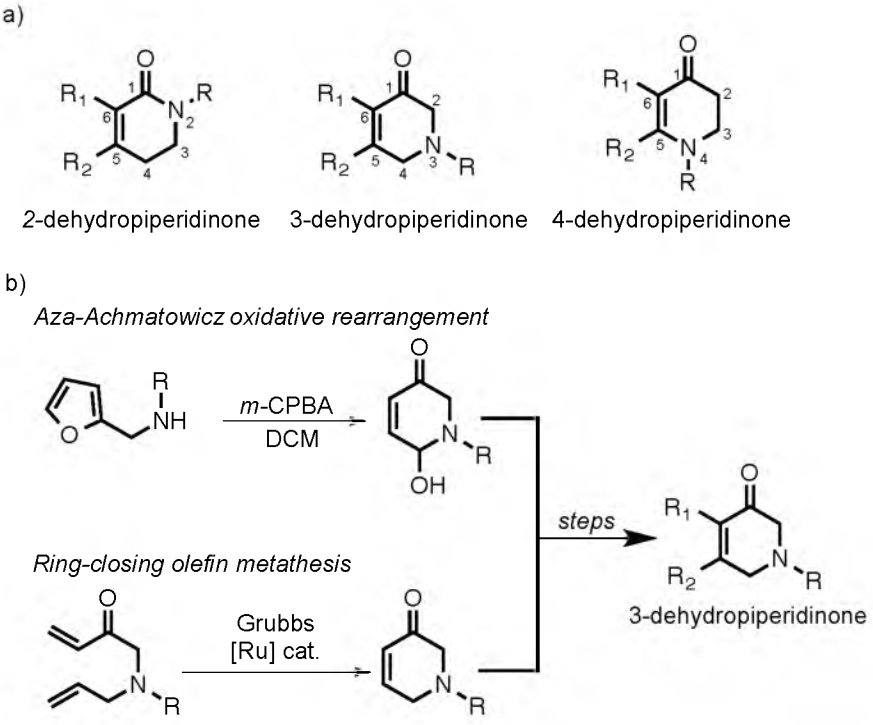


Figure 4.2. Substituted dehydropiperidinones and their synthesis. (a) Structures of substituted dehydropiperidinones. (b) Methods for the synthesis of substituted 3-dehydropiperidinones.

Table 4.1. *In situ* Ni-catalyzed cycloaddition of 4-octyne with 1-Boc-3-azetidinone[a]

Entry	Ni(II)	Ligand	Reductant	Solvent	Conv.[%][b]	Yield [%][c]
1	$Ni(acac)_2$	PPh_3	*n*-BuLi	toluene	>99	92
2	$Ni(acac)_2$	PPh_3	Zn	acetonitrile	37	-
3	$Ni(PPh_3)_2Cl_2$	-	Zn	toluene	6	trace
4	$Ni(PPh_3)_2Br_2$	-	Zn	toluene	62	n.d.[d]
5	$Ni(PPh_3)_2I_2$	-	Zn	toluene	16	trace
6	$Ni(PPh_3)_2Cl_2$	-	Zn	acetonitrile	>99	**95**
7	$Ni(PPh_3)_2Br_2$	-	Zn	acetonitrile	>99	**95**
8	$Ni(PPh_3)_2I_2$	-	Zn	acetonitrile	15	trace

[a]Reaction Conditions: 4-octyne **4.1** (1.5 equiv), 1-Boc-3-Azetidinone **4.2** (1 equiv, 0.4 M), 10 mol % Ni(II), 20 mol% Ligand, 40 mol% reductant, 60 °C, 16 h. [b] Determined by GC using naphathalene as an internal standard. [c]Isolated Yield. [d]n.d. = not determined.

Table 4.2. *In situ* Ni-catalyzed cycloaddition of alkynes and 3-azetidinone[a]

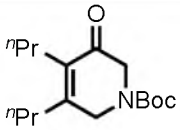
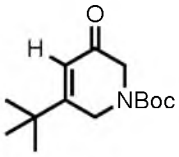
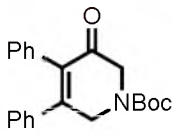
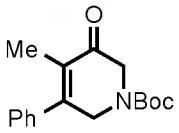
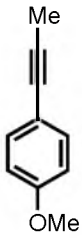
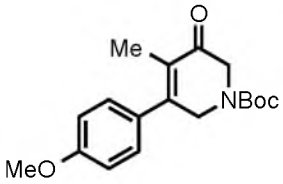
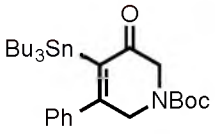
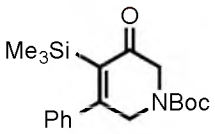
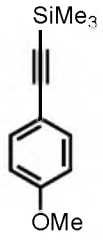
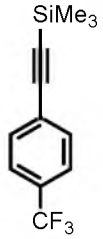
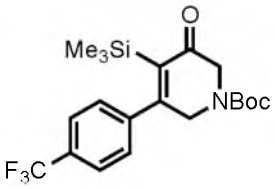
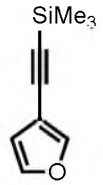
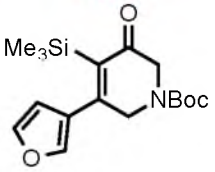
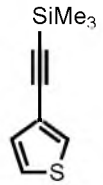
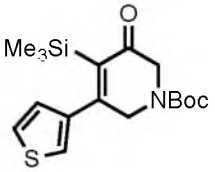
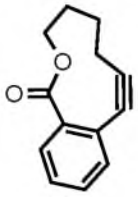
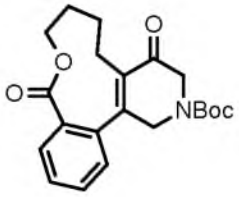
Entry	Alkyne	Product, Yield (%),[b] Regioselectivity[c]
1	 **4.1**	 **4.3**, 95% (97%)
2	 **4.4**	 **4.5**, 60% (71%) *> 95:5*
3	 **4.6**	 **4.7**, 72% (79%)
4	 **4.8**	 **4.9**, 86% (85%) *> 95:5*
5	 **4.10**	 **4.11**, 87% (74%) *> 95:5*
6	 **4.12**	 **4.13**, 73% (83%) *> 95:5*
7	 **4.14**	 **4.15**, 75% (75%) *> 95:5*

Table 4.2. Continued

8	 **4.16**	 **4.17**, 74% *> 95:5*
9	 **4.18**	 **4.19**, 51% *> 95:5*
10	 **4.20**	 **4.21**, 74% (82%) *> 95:5*
11	 **4.22**	 **4.23**, 73% (80%) *> 95:5*
12	 **4.24**	 **4.25**, 55% *> 95:5*

[a]Reaction conditions: 1-Boc-3-Azetdidinone (1.0 equiv, 0.2 M) alkyne (1.5 equiv), 5 mol% $Ni(PPh_3)_2Cl_2$, 20 mol% Zn, 60-80 °C, 16-24 h. [b]Isolated yield (in parentheses) obtained using reported Ni(0) procedure. [c]Regioselectivity was calculated by ^1H NMR of crude reaction mixture.

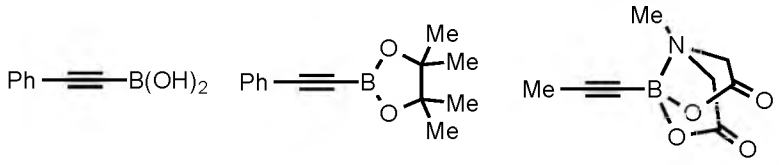
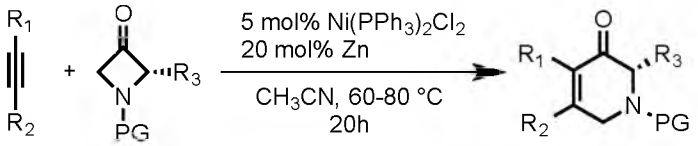


Figure 4.3. Attempted alkynes in Ni-catalyzed cycloaddition.

Table 4.3. *In situ* Ni-catalyzed cycloaddition of alkynes with 2-substituted-3-azetidinones[a]



> 99% ee

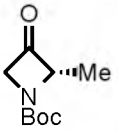
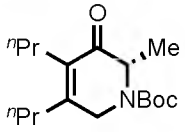
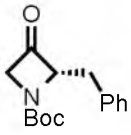
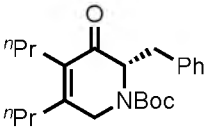
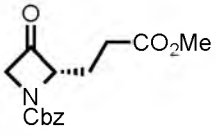
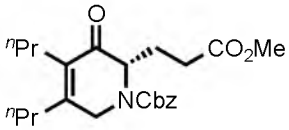
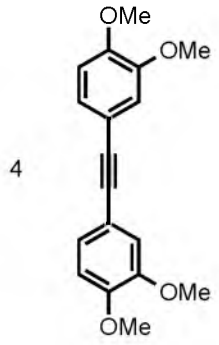
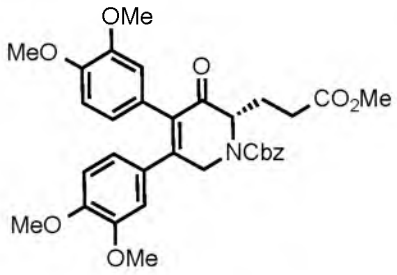
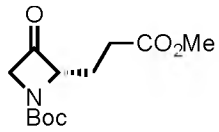
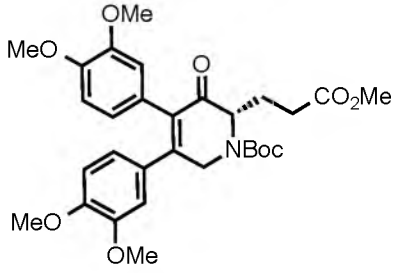
Entry	Alkyne	Azetidinone	Product Yield, ee[b,c]
1			
	4.1	**4.28**	**4.29**, 87%, 98% ee (73%, >99% ee)
2	**4.1**		
		4.30	**4.31**, 85%, 93% ee (84-88%,97->99% ee)
3	**4.1**		
		4.32	**4.33**, 86%, 97% ee

Table 4.3. Continued

4	 **4.34**	**4.32**		**4.35**, 83%, 97% ee
5	**4.34**	 **4.36**		**4.37**, 88%, 95% ee

[a]Reaction Conditions: Reaction conditions: Azetidinone (1.0 equiv, 0.1 M) alkyne (1.5 equiv), 5 mol% $Ni(PPh_3)_2Cl_2$, 20 mol% Zn, 60-80 °C, 16-24 h. [b]Isolated yield and enantiomeric excess of the product. [c]Isolated yield and enantiomeric excess (in parentheses) obtained using reported Ni(0) procedure.

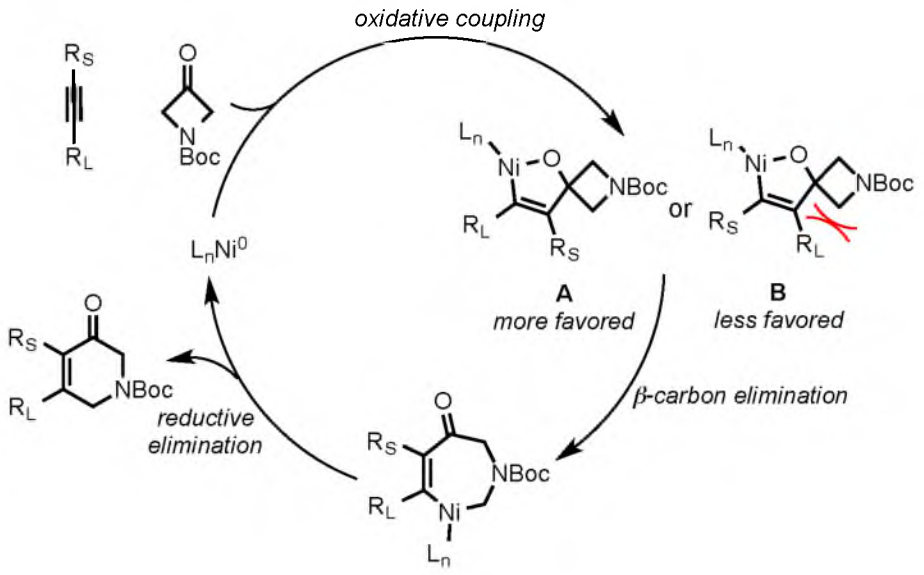


Figure 4.4. Proposed mechanism for the *in situ* Ni-catalyzed cycloaddition of sterically biased alkynes and 3-azetidinone.

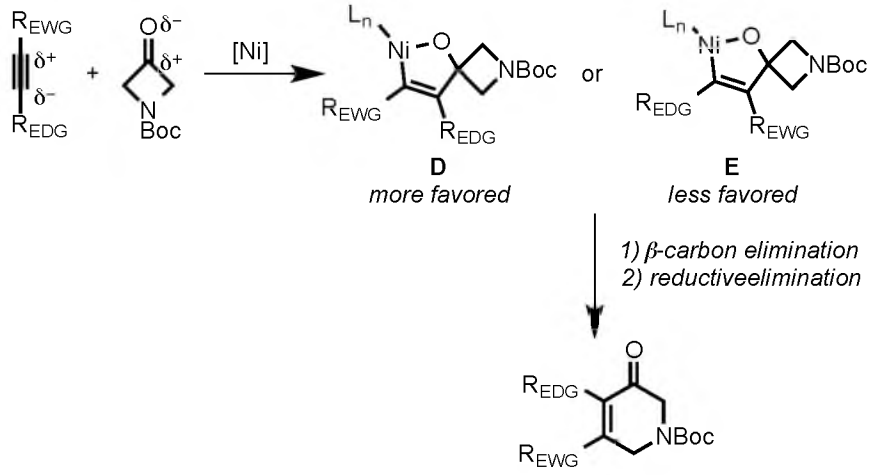


Figure 4.5. Proposed mechanism for the *in situ* Ni-catalyzed cycloaddition of partially polarized alkynes and 3-azetidinone.

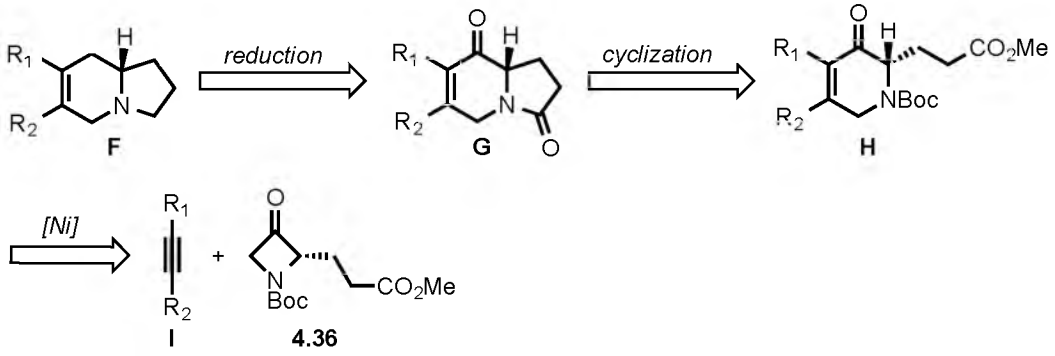


Figure 4.6. Retrosynthetic analysis of indolizidine alkaloids.

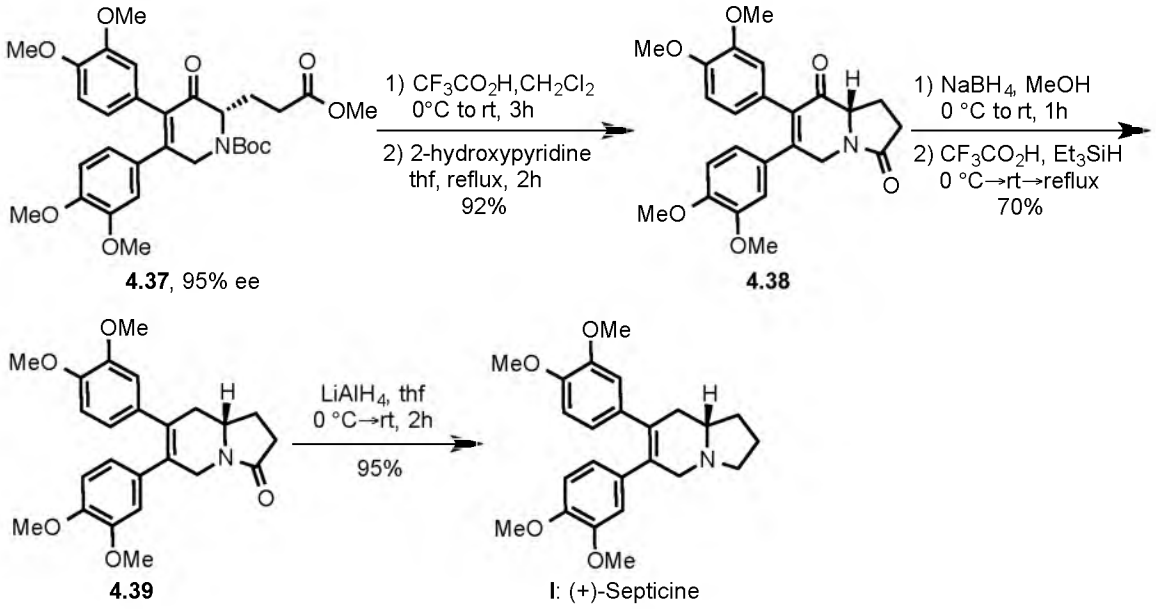


Figure 4.7. Synthesis of (+)-septicine.

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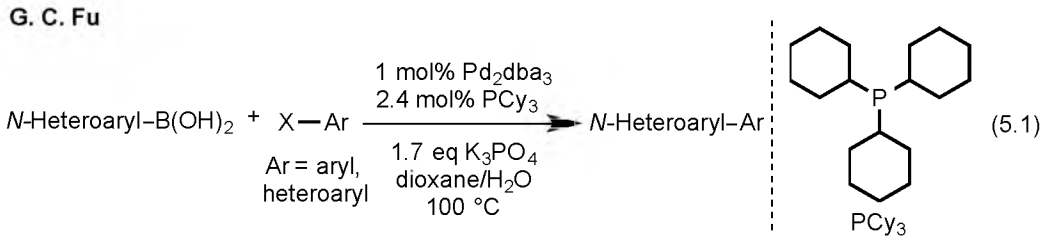
CHAPTER 5

SUZUKI-MIYAURA COUPLING OF HETEROARYL BORONIC ACIDS AND VINYL CHLORIDES

Introduction

Since the first report in 1979, the Suzuki-Miyaura coupling reaction has emerged as one of the most utilized C-C bond forming methods for the syntheses of natural products, pharmaceuticals and materials.[1,2] Low catalyst loadings, flexibility of compatible functional groups, commercial availability of organoboron reagents, relative ease of product separation and low toxicity of boron by-products have led to its prominence in both academic and industrial research.[2d-f]

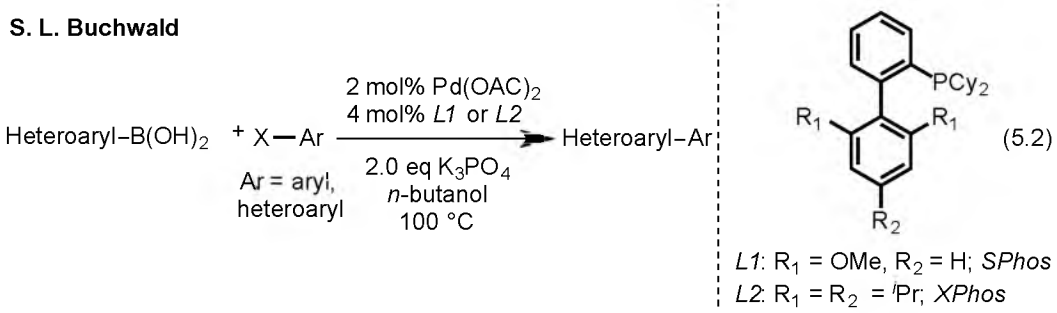
In recent years, significant progress has been made in the Suzuki-Miyaura coupling of heteroaryl boronic acids and aryl/heteroaryl halides. For example, Fu demonstrated the use of a Pd_2dba_3/PCy_3 catalytic system to couple *N*-heteroaryl boronic acids with aryl and *N*-heteroaryl chlorides in good to excellent yields (eq 5.1).[3]



(5.1)

Undoubtedly, the Buchwald group has made tremendous contributions to this field by designing sterically-hindered, electron-rich biarylmonodentate phosphine ligands such as SPhos and XPhos that, when combined with catalytic amounts of Pd(0), efficiently couple heteroaryl boronic acids with both aryl and heteroaryl chlorides (eq 5.2).[4]

S. L. Buchwald

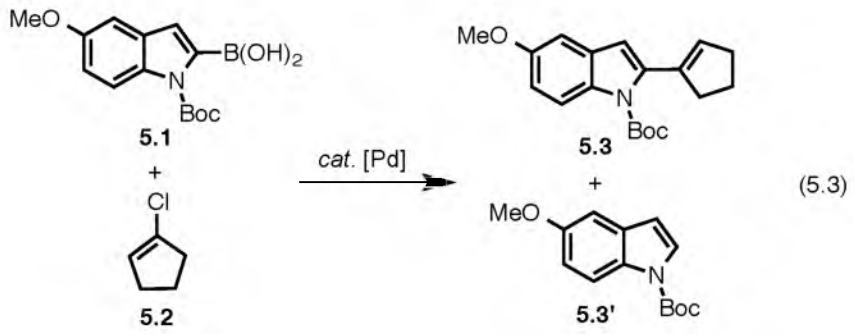


(5.2)

Despite these reports, the Suzuki-Miyaura coupling of heteroaryl boronic acids and vinyl chlorides is largely unexplored.[5] One of the challenges associated with heteroaryl boronic acids is their propensity to protodeboronate in the presence of base and polar protic solvents.[4a,7a-b] The instability of these boronic acids has led to the conventional approach of using excess amounts (>1.2 equiv) of these transmetallating reagents while using the other electrophilic coupling partner as the limiting reagent. Furthermore, the protodeboronation is enhanced by the slow oxidative addition of vinyl chlorides leading to low yields of desired coupling product. Molander has developed methods that utilize more stable potassium heteroaryltrifluoroborates in the coupling with the aryl/heteroaryl halides.[7b,7c] However, these potassium trifluoroborate salts are themselves prepared from boronic acids in moderate to good yields.[7b] In view of these challenges, we were delighted to discover a highly efficient Pd-catalyzed protocol to couple heteroaryl boronic acids and vinyl chlorides in good yields.

Results and discussions

We were interested in preparing diene **5.3** via a Suzuki-Miyaura coupling of *N*-Boc-indole-2-boronic acid **5.2** and 1-chlorocyclopentene **5.2** (eq 5.3). Dr. Kainan Zhang conducted the initial optimization studies for this reaction. Unfortunately, known protocols afforded either low yields or no desired product **5.3**.



(5.3)

Specifically, when **5.1** and **5.2** were subjected to Fu's Pd_2dba_3/PCy_3 catalytic system,[3] complete protodeboronation to free indole (**5.3'**) occurred exclusively. Gratifyingly, some product was obtained (46% yield by ^1H NMR spectroscopy) utilizing Buchwald's conditions (i.e., 2 mol% $Pd(OAc)_2$, 4 mol% SPhos, K_3PO_4, ^{n}butanol, 100 °C).[4d] However, the remaining boronic acid **5.1** was completely protodeboronated. Alternatively, the more stable potassium trifluoroborate salt of boronic acid **5.1** was synthesized and investigated under Molander's conditions (i.e., 2 mol% $Pd(OAc)_2$, 4 mol% RuPhos, 2 Na_2CO_3, EtOH, 85 °C).[7b] Unfortunately a 1:1 mixture of coupling product **5.3** and protodeboronated indole **5.3'** was obtained. Furthermore, attempts to isolate the coupling product **5.3** proved futile as it co-elutes with **5.3'** during

chromatographic separation. As such, we began to evaluate an unconventional approach of using the heteroaryl boronic acid as the limiting reagent.

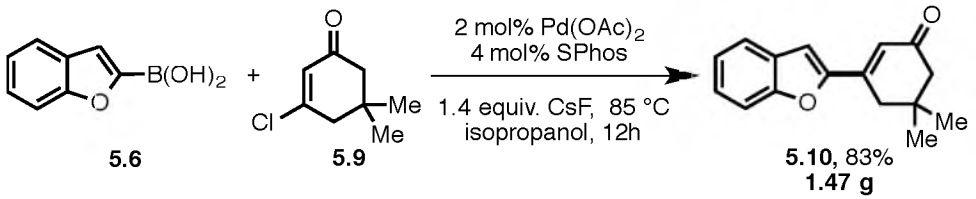
Using Buchwald's conditions as a guide, we evaluated whether a change in base, solvent or temperature would result in higher product yields (Table 5.1). Initially, when K_3PO_4 and *n*-butanol were substituted for Cs_2CO_3 and toluene, no change in the selectivity between **5.3** and **5.3'** was observed. Replacement of Cs_2CO_3 with CsF as the base led to a slight increase in the product ratio (i.e., 1.9:1, entry 2). Although switching from toluene to *tert*-butanol led to a decrease in selectivity (entry 3), the use of isopropanol as the solvent afforded a 3:1 ratio in favour of the desired **5.3** (entry 4). Surprisingly, lowering the reaction from 110 °C to 100 °C resulted in an, albeit slight, increase in selectivity (entry 5). Further investigation revealed a dramatic temperature dependence (entries 4-9) and excellent selectivity of the coupling product over protodeboronated product was obtained when the reaction was run at 85 °C (entry 7). An increase or decrease of the reaction temperature by as little as 5 °C led to lower selectivities (entries 6 and 8).[8] Further optimization led to these reactions conditions: 2 mol% $Pd(OAc)_2$, 4 mol% SPhos, 1.4 equiv. CsF, isopropanol (0.2 M), 3-10 h.

With optimized conditions in hand, the coupling of other heteroaryl boronic acids and vinyl chlorides was explored. A particularly challenging heteroaryl boronic acid that is known for fast protodeboronation, *N*-Boc-indole-2-boronic acid,[4a,7b] was successfully coupled with both unactivated cyclic and acyclic vinyl chlorides to yield vinyl indoles in high yields (**5.3**, **5.5**, Table 5.2). Similarly, benzofuran-2-boronic acid and benzothiophene-2- boronic acid afforded the desired products (**5.7**, **5.8**, **5.10**, **5.12**).

Notably boronic acid with *N*-heteroaromatics like pyrimidines, which can potentially bind [Pd] and kill its catalytic activity, worked efficiently in excellent yields (**5.14**, **5.16**, **5.17**, **5.19**). Additionally, both quinoline and isoquinoline boronic acids were also coupled in moderate to good yields (**5.21**, **5.23**, **5.25**). The coupling with (*Z*)-2-chloro-2-butene afforded the vinyl heteroaryl compounds with retention of stereochemistry (**5.23**, **5.25**). Five-membered heteroaryl boronic acids were also demonstrated to couple effectively in good to excellent yields (**5.27**, **5.29**).

Gratifyingly, this coupling is scalable and was successfully applied to gram scale quantities of benzofuran-2-boronic acid **5.6** and 3-chloro-5,5-dimethylcyclohex-2-en-1-one **5.9** to afford the desired product **5.10** in 83% yield (eq 5.4).

Gram Scale Reaction:



5.6 **5.9** **5.10**, 83% **1.47 g** (5.4)

Conclusion

In summary, we have developed an efficient catalytic system to couple challenging heteroaryl boronic acids and vinyl chlorides. This coupling takes the advantage of using heteroaryl boronic acids as the limiting reagent thereby minimizing protodeboronation. Future efforts will be focused to develop the challenging Suzuki-Miyaura coupling reaction of aryl/heteroaryl boron nucleophiles with alkyl halides.

General experimental

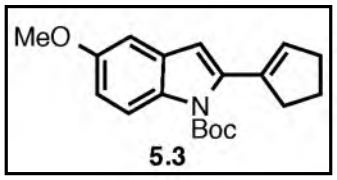
All reactions were conducted under an atmosphere of N_2 using standard Schlenk techniques or in a N_2-filled glove box unless otherwise noted. Toluene was dried over neutral alumina under N_2 using a Grubbs type solvent purification system. $Pd(OAc)_2$ and SPhos was purchased from Strem and used without further purification. *N*-Boc-5-methoxy-2-indolylboronic acid (**1**), 1-chlorocyclopentene (**a**) and CsF were purchased from Sigma-Aldrich and used without further purification. Isopropanol was distilled and degassed prior to use. All the other heteroaryl boronic acids were purchased from Frontier Scientific. The heteroaryl boronic acids were stored at -40 °C in the refrigerator within the glove box. The vinyl chlorides 1-Chloro-2-methylpropene and (*Z*)-2-chloro-2-butene were purchased from TCI America. 3-Chloro-5,5-dimethyl-2-cyclohexen-1-one was bought from Alfa Aesar. 4-chloro-1,2,5,6-tetrahydro-1-tosylpyridine[9] was prepared according to the literature procedure. All other reagents were purchased and used without further purification unless otherwise noted.

^1H and ^{13}C Nuclear Magnetic Resonance spectra of pure compounds were acquired at 400 and 100 MHz, respectively, unless otherwise noted. All spectra are referenced to a singlet at 7.27 ppm for ^1H and to the centerline of a triplet at 77.23 ppm for ^{13}C. The abbreviations s, d, dd, dt, dq, t, td, tq, q, qt, quint, sept, septd, septt, m, brm, brd, brt, and brs stand for singlet, doublet, doublet of doublets, doublet of triplets, doublet of quartets, triplet, triplet of doublets, triplet of quartets, quartet, quartet of triplets, quintet, septet, septet of doublets, septet of triplets, multiplet, broad multiplet, broad doublet, broad triplet, and broad singlet, in that order. All ^{13}C NMR spectra were proton decoupled. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer.

General procedure for Suzuki-Miyaura Coupling

In a nitrogen-filled glove box, a screw-cap vial was charged with 1 equiv heteroaryl boronic acid, 2-4 mol% $Pd(OAc)_2$, 4-8 mol% SPhos, 1.4 equiv CsF, 1.1-1.2 equiv of vinyl chloride and isopropanol (0.2 M). The vial was brought out of the box and heated at 85 °C in an oil bath for indicated period of time. The resulting reaction mixture was filtered though a short pad of silica gel and eluted with diethyl ether. The solvent was removed *in vacuo,* and the crude product was purified by silica gel flash column chromatography.

N-Boc-2-(cyclopenten-1-yl)-5-methoxyindole (**5.3**)



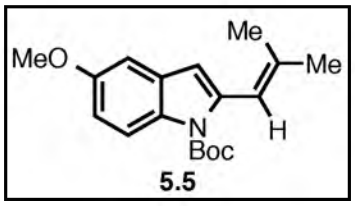
5.3

The general procedure was used with 202.8 mg (0.70 mmol) of *N*-Boc-5-methoxy-2-indolylboronic acid, 3.1 mg (0.01 mmol) of $Pd(OAc)_2$, 11.5 mg (0.03 mmol) of SPhos, 148.2 mg (0.98 mmol) of CsF and 54.2 mg of 1-chlorocyclopentene in isopropanol (3.5 ml, 0.2 M). The reaction mixture was heated at 85 °C for 3 h. The remaining residue was purified via flash column chromatography using 5% ether in pentane (R_f = 0.46) to afford the title compound **5.3** and the protodeboronated indole **5.3'**[10] as colorless oil in 88% global yield (192.6 mg, 0.62 mmol; **5.3:5.3'** = 96: 4 by ^{1}H-NMR).

5.3 : ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.0 (d, *J* = 9.2 Hz, 1 H), 6.99 (d, *J* = 2.8 Hz, 1H), 6.92 (dd, *J*= 2.4 Hz, 9.2 Hz, 1H), 6.40 (s, 1H), 5.93 (m, 1H), 3.90 (s, 3H), 2.71 (m, 2H), 2.57 (m, 2H), 2.07 (quint, *J*= 6.4 Hz, 2H), 1.7 (s, 9H); ^{13}C NMR (100 MHz , $CDCl_3$): δ (ppm) 156.0, 150.4, 139.3, 137.0, 132.0, 130.2, 129.8, 116.0, 112.6, 108.7, 102.9, 83.5, 55.7, 36.2, 33.2, 28.2, 23.8; IR (CH_2Cl_2, cm^{-1}): 2977, 2842 1731, 1615, 1474,

1126, 1034, 847, 734; HRMS (ESI) calcd for $C_{19}H_{23}NO_3Na$ $[M+Na]^+$ 336.1576, found 336.1579.

N-Boc-2-(2-methylpropen-1-yl)-5-methoxyindole (**5.5**)

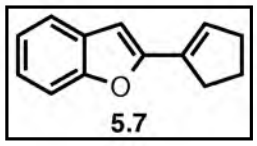


5.5

The general procedure was used with 145.1 mg (0.50 mmol) of *N*-Boc-5-methoxy-2-indolylboronic acid, 2.24 mg (0.01 mmol) of $Pd(OAc)_2$, 8.20 mg (0.02 mmol) of SPhos, 106 mg of CsF (0.70 mmol) and 54.2 mg (0.60 mmol) of 1-chloro-2-methylpropene in isopropanol (2.5 ml, 0.2 M). The reaction mixture was heated at 85 °C for 6 h. The remaining residue was purified via flash column chromatography using 5% ether in pentane (R_f = 0.57) to afford the title compound **5.5** and the protodeboronated indole **1a'**[10] as colorless oil in 80% global yield (121.1 mg, 0.40 mmol; **5.5:5.5'** = 95:5 by ^{1}H-NMR).

5.5: ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.04 (d, *J* = 9.2 Hz, 1H), 7.0 (d, *J* = 2.4 Hz, 1H), 6.90 (dd, *J* = 2.4 Hz, 8.0 Hz, 1H), 6.53 (s, 1H), 6.38 (brs, 1H), 3.87 (s, 3H), 1.99 (brs, 3H), 1.96 (brs, 3H), 1.69 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 156.0, 150.6, 138.5, 136.4, 130.7, 130.5, 118.2, 116.5, 112.4, 109.4, 102.7, 83.5, 55.7, 28.4, 26.7, 20.1; IR (CH_2Cl_2, cm^{-1}): 2978, 1729, 1615, 1477, 1365, 1315, 1165, 1123, 851, 800; HRMS (ESI) calcd for $C_{18}H_{23}NO_3Na$ $[M+Na]^+$ 324.1576, found 324.1577.

2-(cyclopenten-1-yl)benzofuran (**5.7**)



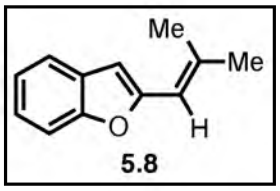
5.7

The general procedure was used with 165.1 mg (1.02 mmol) of benzofuran-2-boronic acid, 4.6 mg (0.02 mmol) of $Pd(OAc)_2$, 16.7

mg (0.04 mmol) of SPhos, 217 mg of CsF (1.43 mmol) and 125.5 mg (1.22 mmol) of 1-chlorocyclopentene in isopropanol (5 ml, 0.2 M). The reaction mixture was heated at 85 °C for 6 h. The remaining residue was purified via flash column chromatography using 2% ether in pentane (R_f = 0.4) to afford the title compound **5.7** as colorless solid (mp: 68-70 °C) in 82% yield (154.6 mg, 0.84 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.54 (m, 1H), 7.46 (dd, *J* = 0.8 Hz, 8.0 Hz, 1H), 7.26 (td, *J* = 1.6 Hz, 7.2 Hz, 1H), 7.20 (td, *J* = 1.2 Hz, 7.6 Hz, 1H), 6.52 (s, 1H), 6.43 (quint, *J* = 2.0 Hz, 1H), 2.73 (m, 2H), 2.61 (m, 2H), 2.07 (quint, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$); δ (ppm) 155.0, 154.4, 133.1, 129.3, 129.0, 124.2, 122.7, 120.9, 111.0, 102.5, 33.6, 32.5, 23.4; IR (CH_2Cl_2, cm^{-1}): 2952, 1448, 1252, 1003, 797, 746. HRMS (ESI) calcd for $C_{13}H_{13}O$ $[M+H]^+$ 185.0996, found 185.0971.

2-(2-methylpropen-1-yl)benzofuran (**5.8**)



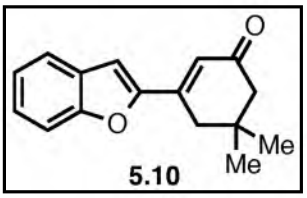
5.8

The general procedure was used with 154.2 mg (0.94 mmol) of benzofuran-2-boronic acid, 4.2 mg (0.02 mmol) of $Pd(OAc)_2$, 15.4 mg (0.04 mmol) of SPhos, 200 mg of CsF (1.32 mmol) and 102.2 mg (1.13 mmol) of 1-chloro-2-methylpropene in isopropanol (4.7 ml, 0.2 M). The reaction mixture was heated at 85 °C for 6 h. The remaining residue was purified via flash column chromatography using pure pentane (R_f = 0.5) to afford the title compound **5.8** as colorless solid (mp: 40-42 °C) in 83% yield (133.9 mg, 0.78 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.53 (dd, *J* = 1.0 Hz, 7.5 Hz, 1H), 7.44 (m, 1H), 7.22 (m, 2H), 6.53 (s, 1H), 6.21 (brs, 1H), 2.15 (brs, 3H), 2.02 (brs, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 155.9, 154.3, 139.8, 129.3, 123.8, 122.8, 120.6, 114.7, 111.0,

103.8, 27.6, 20.7; IR (CH_2Cl_2, cm^{-1}): 2912, 1658, 1453, 1256, 1195, 1055, 846, 790; HRMS (ESI) calcd for $C_{12}H_{13}O$ $[M+H]^+$ 173.0966, found 173.0968.

3-(benzofuran-2-yl)-5,5-dimethylcyclohex-2-en-1-one (**5.10**)

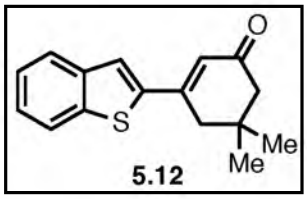


5.10

The general procedure was used with 132.1 mg (0.82 mmol) of benzofuran-2-boronic acid, 3.7 mg (0.02 mmol) of $Pd(OAc)_2$, 13.5 mg (0.03 mmol) of SPhos, 174.4 mg of CsF (1.15 mmol) and 155.3 mg (0.98 mmol) of 3-chloro-5,5-dimethyl-2-cyclohexen-1-one in isopropanol (4.1 ml, 0.2 M). The reaction mixture was heated at 85 °C for 10 h. The remaining residue was purified via flash column chromatography using 20% ether in pentane (R_f = 0.3) to afford the title compound **5.10** as light yellow solid (mp: 114-116 °C) in 87% yield (173.1 mg, 0.72 mmol).

^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.60 (d, J = 7.5 Hz, 1H), 7.50 (d, J = 8.5 Hz, 1H), 7.37 (m, 1H), 7.26 (m, 1H), 7.07 (s, 1H), 6.72 (brs, 1H), 2.62 (d, J = 1.5 Hz, 2H), 2.37 (s, 2H), 1.15 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 199.6, 155.7, 154.1, 145.1, 128.4, 126.7, 123.5, 122.5, 121.9, 111.7, 108.7, 51.5, 39.5, 33.8, 28.6; IR (CH_2Cl_2, cm^{-1}): 2958, 2872, 1660, 1608, 1382, 1300, 1113, 1014, 809, 751; HRMS (ESI) calcd for $C_{16}H_{16}O_2Na$ $[M+Na]^+$ 263.1048, found 263.1039.

3-(benzothiophen-2-yl)-5,5-dimethylcyclohex-2-en-1-one (**5.12**)



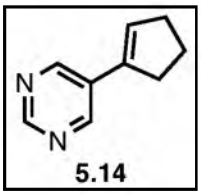
5.12

The general procedure was used with 179.9 mg (1.01 mmol) of benzothiophene-2-boronic acid, 9.1 mg (0.04 mmol) of $Pd(OAc)_2$, 33.2 mg (0.08 mmol) of SPhos, 214.8 mg of CsF

(1.41 mmol) and 176.3 mg (1.11 mmol) of 3-chloro-5,5-dimethyl-2-cyclohexen-1-one in isopropanol (5 ml, 0.2 M). The reaction mixture was heated at 85 °C for 10 h. The remaining residue was purified via flash column chromatography using 20% ether in pentane (R_f = 0.26) to afford the title compound **5.12** as light yellow solid (mp: 136-138 °C) in 81% yield (209.9 mg, 0.82 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.79 (m, 2H), 7.60 (s, 1H), 7.37 (m, 2H), 6.50 (brs, 1H), 2.72 (d, *J* = 1.2 Hz, 2H), 2.36 (s, 2H), 1.16 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 199.6, 150.4, 142.9, 140.3, 139.9, 126.4, 125.0, 124.9, 124.6, 124.0, 122.5, 51.2, 41.7, 33.8, 28.6; IR (CH_2Cl_2, cm^{-1}): 2962, 1652, 1596, 1366, 829, 728; HRMS (ESI) calcd for $C_{16}H_{16}ONaS$ $[M+Na]^+$ 279.0820, found 279.0813.

5-(cyclopenten-1-yl)pyrimidine (**5.14**)

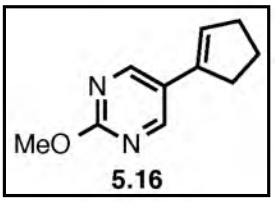


5.14

The general procedure was used with 143.5 mg (1.16 mmol) of pyrimidine-5-boronic acid, 5.2 mg (0.02 mmol) of $Pd(OAc)_2$, 19.1 mg (0.05 mmol) of SPhos, 246.7 mg of CsF (1.62 mmol) and 142.53 mg (1.39 mmol) of 1-chlorocyclopentene in isopropanol (5.8 ml, 0.2 M). The reaction mixture was heated at 85 °C for 6 h. The remaining residue was purified via flash column chromatography using 50% ether in pentane (R_f = 0.21) to afford the title compound **5.14** as off-white solid (mp: 48-50 °C) in 76% yield (128.4 mg, 0.88 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.97 (s, 1H), 8.69 (s, 2H), 6.31 (brs, 1H), 2.65 (m, 2H), 2.50 (t, *J* = 7.2 Hz, 2H), 1.99 (quint, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 156.9, 153.6, 136.5, 130.5, 130.2, 33.7, 32.6, 23.2; IR (CH_2Cl_2, cm^{-1}): 2956, 2899, 2846, 1555,

1439, 1411, 1325, 1181, 725, 630, 538; HRMS (ESI) calcd for $C_9H_{11}N_2$ $[M+H]^+$ 147.0922, found 147.0935.

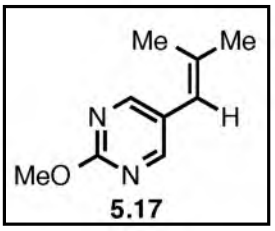
5-(cyclopenten-1-yl)-2-methoxypyrimidine (**5.16**)



5.16

The general procedure was used with 138.1 mg (0.90 mmol) of 2-methoxypyrimidine-5-boronic acid, 4.0 mg (0.02 mmol) of $Pd(OAc)_2$, 14.8 mg (0.036 mmol) of SPhos, 191 mg of CsF (1.26 mmol) and 110.6 mg (1.08 mmol) of 1-chlorocyclopentene in isopropanol (4.5 ml, 0.2 M). The reaction mixture was heated at 85 °C for 6 h. The remaining residue was purified via flash column chromatography using 40% ether in pentane (R_f = 0.35) to afford the title compound **5.16** as semi-solid in 80% yield (126.2 mg, 0.72 mmol): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.53 (s, 2H), 6.16 (m, 1H), 3.99 (s, 3H), 2.65 (m, 2H), 2.52 (m, 2H), 2.01 (quint, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 164.6, 156.1, 136.2, 127.1, 124.4, 55.0, 33.5, 32.9, 23.2; IR (CH_2Cl_2, cm^{-1}): 2957, 1607, 1592, 1556, 1479, 1031, 805; HRMS (ESI) calcd for $C_{10}H_{13}N_2O$ $[M+H]^+$ 177.1028, found 177.1034.

5-(2-methylpropen-1-yl)-2-methoxypyrimidine (**5.17**)



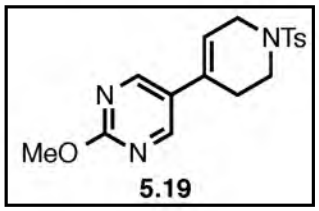
5.17

The general procedure was used with 139.1 mg (0.90 mmol) of 2-methoxypyrimidine-5-boronic acid, 4.1 mg (0.02 mmol) of $Pd(OAc)_2$, 14.9 mg (0.04 mmol) of SPhos, 192.2 mg of CsF (1.27 mmol) and 98.2 mg (1.08 mmol) of 1-chloro-2-methylpropene in isopropanol (5.8 ml, 0.2 M). The reaction mixture was heated at 85 °C for 6 h. The remaining residue was purified via flash column chromatography using 40% ether in

pentane (R_f = 0.49) to afford the title compound **5.17** as colorless oil in 82% yield (121.1 mg, 0.74 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.30 (s, 2H), 5.99 (brs, 1H), 3.93 (s, 3H), 1.84 (d, *J* = 0.8 Hz, 3H), 1.76 (brs, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 163.7, 158.7, 138.6, 125.9, 117.6, 54.8, 26.7, 19.4; IR (CH_2Cl_2, cm^{-1}) 2976, 1702, 1594, 1475, 1410, 1326, 1039, 804; HRMS (ESI) calcd for $C_9H_{13}N_2O$ $[M+H]^+$ 165.1028, found 165.1035.

4-(2-methoxypyrimidin-5-yl)-1,2,5,6-tetrahydro-1-tosyl-pyridine (**5.19**)

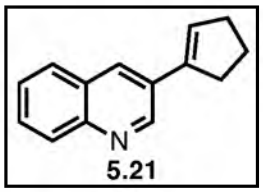


5.19

The general procedure was used with 51.3 mg (0.33 mmol) of 2-methoxypyrimidine-5-boronic acid, 1.5 mg (0.01 mmol) of $Pd(OAc)_2$, 5.5 mg (0.02 mmol) of SPhos, 69.6 mg of CsF (0.47 mmol) and 98.0 mg (0.36 mmol) of 4-chloro-1,2,5,6-tetrahydro-1-tosylpyridine in isopropanol (1.65 ml, 0.2 M) . The reaction mixture was heated at 85 °C for 6 h. The remaining residue was purified via flash column chromatography using 50% ether in pentane (R_f = 0.38) to afford the title compound **5.19** as colorless solid (178-180 °C) in 96% yield (110.7 mg, 0.32 mmol).

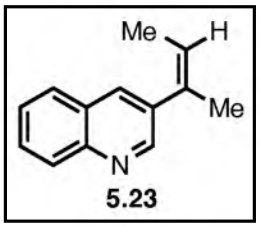
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.43 (s, 2H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8 Hz, 2H), 5.95 (brs, 1H), 3.99 (s, 3H), 3.76 (d, *J* = 2.8 Hz, 2H), 3.33 (t, *J* = 5.6 Hz), 2.55 (brs, 2H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 165.2, 155.9, 144.0, 133.3, 129.9, 127.9, 127.3, 120.4, 55.2, 45.3, 42.8, 27.3, 21.7; IR (CH_2Cl_2, cm^{-1}) 2927, 1593, 1547, 1474, 1335, 1163, 726, 549; HRMS (ESI) calcd for $C_{17}H_{20}N_3O_3S$ $[M+H]^+$ 346.1225, found 346.1218.

3-(cyclopenten-1-yl)quinoline (**5.21**)



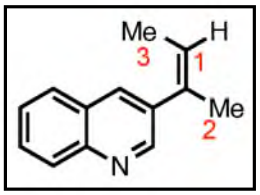
The general procedure was used with 138.4 mg (0.80 mmol) of quinoline-3-boronic acid, 3.6 mg (0.02 mmol) of $Pd(OAc)_2$, 13.1 mg (0.03 mmol) of SPhos, 170.1 mg of CsF (1.12 mmol) and 98.5 mg (0.36 mmol) of 1-chlorocyclopentene in isopropanol (4.0 ml, 0.2 M). The reaction mixture was heated at 85 °C for 10 h. The remaining residue was purified via flash column chromatography using 25% ether in pentane (R_f = 0.3) to afford the title compound **5.21** as colorless solid (mp: 52-54 °C) in 73% yield (113.6 mg, 0.582 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.14 (d, *J* = 2.0 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.94 (brs, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.65 (m, 1H), 7.51 (m, 1H), 6.45 (t, *J* = 2.0 Hz, 1H), 2.82 (m, 2H), 2.62 (m, 2H), 2.08 (quint, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 149.4, 147.1, 139.9, 131.0, 129.8, 129.3, 128.9, 128.7, 128.2, 128.0, 126.9, 33.9, 33.2, 23.2; IR (CH_2Cl_2, cm^{-1}): 2955, 2844, 1624, 1569, 1493, 786, 749, 542; HRMS (ESI) calcd for $C_{14}H_{14}N$ $[M+H]^+$ 196.1126, found 196.1128.

3-((*Z*)-buten-2-yl)quinoline (**5.23**)



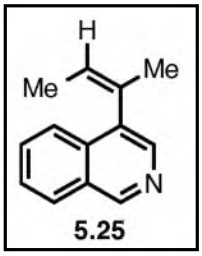
The general procedure was used with 143.3 mg (0.83 mmol) of quinoline-3-boronic acid, 3.7 mg (0.02 mmol) of $Pd(OAc)_2$, 13.6 mg (0.03 mmol) of SPhos, 176.5 mg of CsF (1.16 mmol) and 90.0 mg (0.36 mmol) of (*Z*)-2-chloro-2-butene in isopropanol (4.15 ml, 0.2 M). The reaction mixture was heated at 85 °C for 10 h. The remaining residue was purified via flash column chromatography using 25% ether in pentane (R_f = 0.35) to afford the title compound **5.23** as colorless oil in 67% yield (101.6 mg, 0.56 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.81 (d, J = 2.0 Hz, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.92 (brs, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.67 (t, J = 7.2, 1H), 7.52 (t, J = 7.6, 1H), 5.75 (m, 1H), 2.12 (s, 3H), 1.65 (dd, J = 1.2 Hz, 6.8 Hz, 3H), ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 151.2, 147.0, 134.8, 134.3, 133.5, 129.3, 129.1, 128.0, 127.8, 126.8, 124.3, 25.3, 15.1; IR (CH_2Cl_2, cm^{-1}): 2970, 2916, 1567, 1490, 1450, 1126, 1035, 787, 752, 570. HRMS (ESI) calcd for $C_{13}H_{14}N$ $[M+H]^+$ 184.1126, found 184.1133.



Stereochemistry was assigned on the basis of nOe of proton on C-1 with the protons on C-2 and C-3.

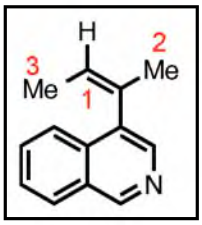
3-((*Z*)-buten-2-yl)isoquinoline (**5.25**)



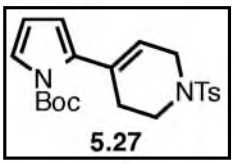
The general procedure was used with 149.6 mg (0.86 mmol) of isoquinoline-4-boronic acid, 3.9 mg (0.02 mmol) of $Pd(OAc)_2$, 14.2 mg (0.04 mmol) of SPhos, 184 mg of CsF (1.21 mmol) and 94.0 mg (1.04 mmol) of (*Z*)-2-chloro-2-butene in isopropanol (4.2 ml, 0.2 M) for 10 h. The remaining residue was purified via flash column chromatography using 30% ether in pentane (R_f = 0.3) to afford the title compound **5.25** as colorless oil in 51% yield (80.1 mg, 0.44 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.16 (s, 1H), 8.30 (s, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.80 (dd, J = 0.8 Hz, 8.4 Hz, 1H), 7.66 (m, 1H), 7.57 (m, 1H), 5.88 (m, 1H), 2.08 (quint, J = 1.6 Hz, 3H), 1.35 (dq, J = 1.2 Hz, 6.8 Hz, 3H), ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 151.4, 142.1, 133.9, 133.4, 132.4, 130.4, 128.6, 128.1, 127.1, 125.4, 124.6, 26.0, 15.0; IR (CH_2Cl_2, cm^{-1}): 2968, 2915, 1620, 1570, 789, 754, 606 HRMS (ESI) calcd for $C_{13}H_{14}N$ $[M+H]^+$ 184.1126, found 184.1127.

Stereochemistry was assigned on the basis of nOe of proton on C-1 with the protons on C-2 and C-3.



4-(*N*-Boc-pyrrol-2-yl)-1,2,5,6-tetrahydro-1-tosylpyridine (**5.27**)

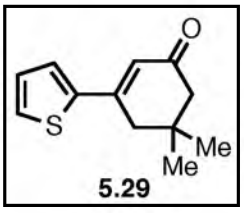


The general procedure was used with 47.6 mg (0.23 mmol) of *N*-Boc-2-pyrroleboronic acid, 1.0 mg (0.01 mmol) of $Pd(OAc)_2$, 3.7 mg (0.02 mmol) of SPhos, 48 mg of CsF (0.32 mmol) and 67.4 mg (0.25 mmol) of 4-chloro-1,2,5,6-tretrahydro-1-tosylpyridine in isopropanol (1.2 ml, 0.2 M). The reaction mixture was heated at 85 °C for 6 h. The remaining residue was purified via flash column chromatography using 25% ether in pentane (R_f = 0.38) to afford the title compound **5.27** as a light yellow oil in 95% yield (86.7 mg, 0.215 mmol): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.70 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.16 (m, 1H), 6.08 (td, *J* = 0.8 Hz, 3.2 Hz, 1H), 5.97 (m, 1H), 5.64 (brs, 1H), 3.71 (q, *J* = 2.4 Hz, 2H), 3.29 (t, 5.6, 2H), 2.44 (brs, 5H), 1.54 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 148.9, 143.7, 135.6, 133.4, 131.2, 129.8, 127.9, 127.8, 122.19, 122.16, 113.4, 110.5, 83.9, 45.2, 43.3, 29.7, 28.1, 21.7; IR (CH_2Cl_2, cm^{-1}): 2968, 2915, 1742, 1333, 1163, 1142, 719, 549; HRMS (ESI) calcd for $C_{21}H_{26}N_2O_4NaS$ $[M+Na]^+$ 425.1511, found 425.1504.

3-(thiophen-2-yl)-5,5-dimethyl-2-cyclohexen-1-one (**5.29**)

The general procedure was used with 112.8 mg (0.88 mmol) of thiophene-2-boronic acid, 7.9 mg (0.04 mmol) of $Pd(OAc)_2$, 29.0 mg (0.07 mmol) of SPhos, 187.6 mg of CsF

(1.24 mmol) and 153.8 mg (0.97 mmol) of 3-chloro-5,5-dimethyl-2-cyclohexen-1-one in isopropanol (4.4 ml, 0.2 M). The reaction mixture was heated at 85 °C for 10 h. The remaining residue was purified via flash column chromatography using 20% ether in pentane (R_f = 0.25) to afford the title compound **5.29** as yellow solid (mp: 62-64 °C) in 77% yield (139.4 mg, 0.68 mmol): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.41 (dd, *J* = 1.2 Hz, 2.8 Hz, 1H), 7.08 (dd, *J*= 1.2 Hz, 4.0 Hz, 1H), 6.40 (brs, 1H), 2.63 (d, *J* = 1.6 Hz, 2H), 2.30 (s, 2H), 1.11 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 199.6, 150.3, 143.1, 128.8, 128.4, 127.4, 121.7, 51.1, 42.1, 33.6, 28.5. IR (CH_2Cl_2, cm^{-1}): 2957, 1666, 1594, 1422, 1368, 829, 708; HRMS (ESI) calcd for $C_{12}H_{14}ONaS$ $[M+Na]^+$ 229.0663, found 229.0651.

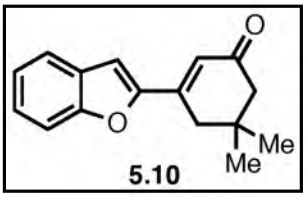


5.29

Gram scale reaction

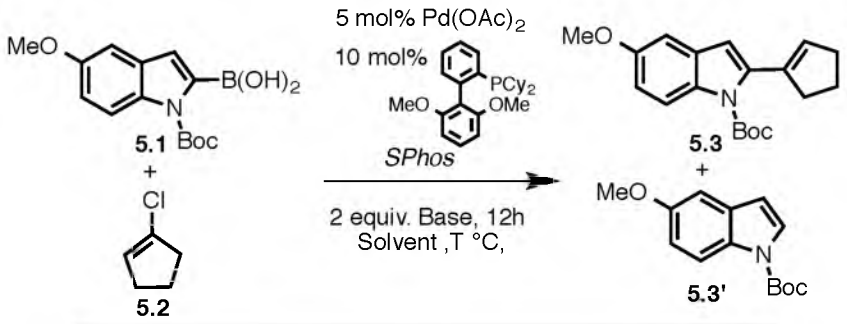
3-(benzofuran-2-yl)-5,5-dimethylcyclohex-2-en-1-one (**2c**)

The general procedure was used with 1.2 g (7.41 mmol) of benzofuran-2-boronic acid, 33.2 mg (0.15 mmol) of $Pd(OAc)_2$, 122.0 mg (0.30 mmol) of SPhos, 1.58 g of CsF (10.37 mmol) and 1.41g (8.89 mmol) of 3-chloro-5,5-dimethyl-2-cyclohexen-1-one in isopropanol (37 ml, 0.2 M). The reaction mixture was heated at 85 °C for 12 h. The remaining residue was purified via flash column chromatography using 20% ether in pentane (R_f = 0.3) to afford the title compound **2c** as a light yellow solid in 83% yield (1.47 g, 6.12 mmol). For spectroscopic data, see above.



5.10

Table 5.1. Various reaction parameters for the Suzuki-Miyaura coupling[a]



Entry	Base	Solvent	Temp. (°C)	Ratio[b] **5.3** : **5.3'**
1.	Cs_2CO_3	toluene	110	1.1:1
2.	CsF	toluene	110	1.9:1
3.	CsF	*t*butanol	110	1.5:1
4.	CsF	isopropanol	110	3:1
5.	CsF	isopropanol	100	3.3:1
6.	CsF	isopropanol	90	10:1
7.	**CsF**	**isopropanol**	85	**16.7:1**
8.	CsF	isopropanol	80	11.1:1
9.	CsF	isopropanol	75	6.7:1

[a]Reaction conditions: **5.1** (1 equiv, 0.2 M), **5.2** (1.2 equiv), 5 mol% $Pd(OAc)_2$, 10 mol% SPhos . [b]Ratio **5.3** : **5.3'** determined by ^{1}H NMR Spectroscopy.

Table 5.2. Suzuki-Miyaura couping of heteroaryl boronic acids and vinyl chlorides[a]

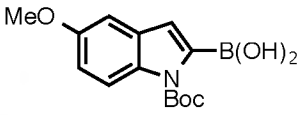
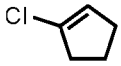
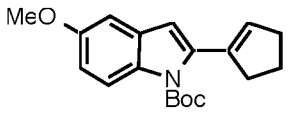
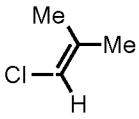
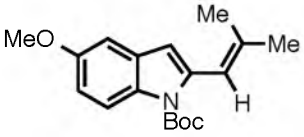
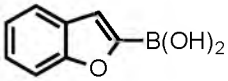
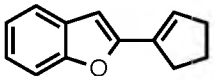
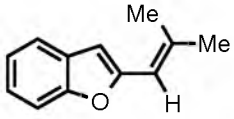
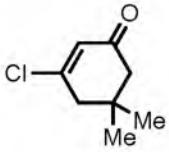
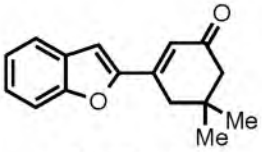
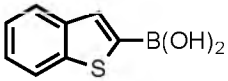
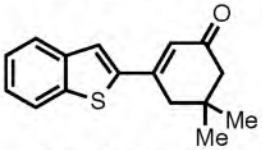
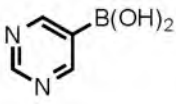
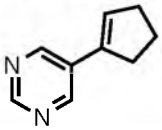
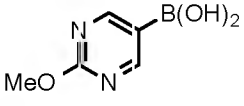
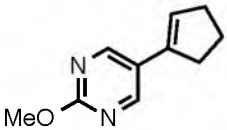
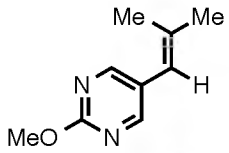
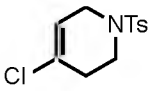
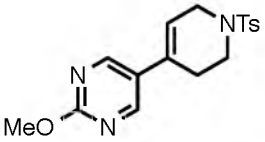
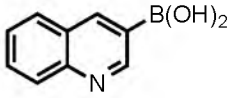
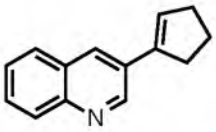
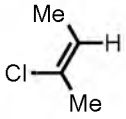
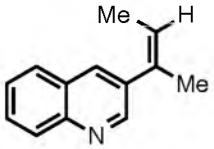
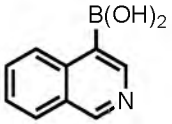
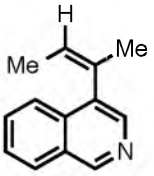
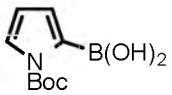
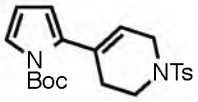
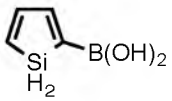
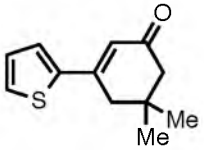
Entry	Boronic Acid	Vinyl Chloride	Product, Isolated Yield, Time
1	 **5.1**	 **5.2**	 **5.3**,[b] 88%, 3 h
2	**5.1**	 **5.4**	 **5.5**,[b] 80%, 6 h
3	 **5.6**	**5.2**	 **5.7**, 82%, 6 h
4	**5.6**	**5.4**	 **5.8**, 83%, 6 h
5	**5.6**	 **5.9**	 **5.10**, 87%, 10 h
6	 **5.11**	**5.9**	 **5.12**,[c,d] 81%, 10 h
7	 **5.13**	**5.2**	 **5.14**, 76%, 6 h
8	 **5.15**	**5.2**	 **5.16**, 80%, 6 h

Table 5.2. Continued

9	**5.15**	**5.4**	 **5.17**, 82%, 6 h
10	**5.15**	 **5.18**	 **5.19**,[d] 96%, 6 h
11	 **5.20**	**5.2**	 **5.21**, 73%, 10 h
12	**5.20**	 **5.22**	 **5.23**,[e] 67%, 10 h
13	 **5.24**	**5.22**	 **5.25**,[e] 51%, 6 h
14	 **5.26**	**5.18**	 **5.27**,[d] 95%, 6 h
15	 **5.28**	**5.9**	 **5.29**,[c,d] 77%, 10 h

[a]Reaction conditions: 1 equiv heteroaryl boronic acid (0.2M), 1.2 equiv vinyl chloride, 2 mol% $Pd(OAc)_2$, 4 mol% SPhos, isopropanol, 85 °C. [b]Product was contaminated with very low amounts of protodeboronated indole **5.3'**. [c]4 mol% $Pd(OAc)_2$/SPhos was used. [d]1.1 equiv of vinyl chloride was used. [e]Retention of stereochemistry was observed as determined by 1D NOESY spectroscopy.

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(8) We currently do not know the reason for the dramatic temperature effect on product yields. We found, not surprisingly, that proto-deboronation of **5.3** occurs within 30 min at 80 °C in the presence of only base. As such, the high yield of product **5.3** at 85 °C does not seem to be due to a simple correlation between the rate of cross coupling and the rate of protodeboronation.

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