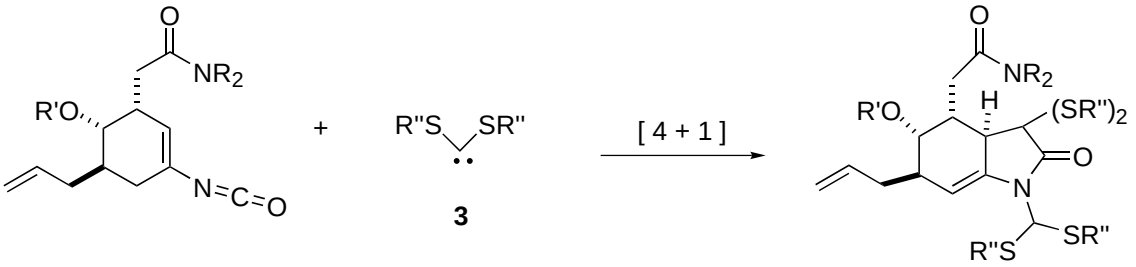
Studies Toward the Total Synthesis of Stenine

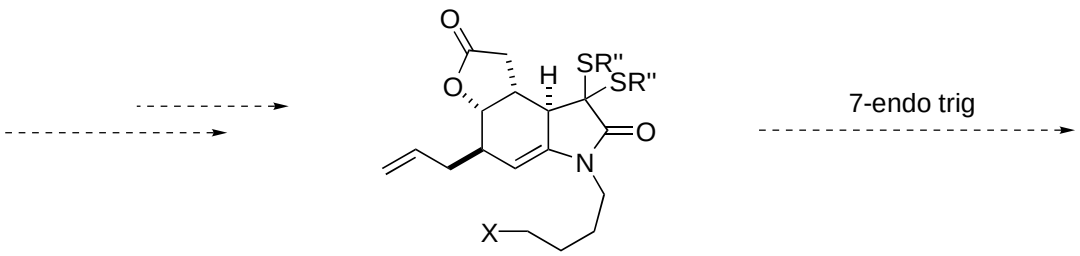
Current researcher: Weidong Zhang

Nucleophilic carbenes have recently emerged as powerful 1,1-dipole equivalents for the construction of functionalized hydroindolone derivatives via a novel [4+1] cycloaddition with vinyl isocyanates in our laboratory. This methodology has been successfully used in the total synthesis of several alkaloids, such as tazettine and mesembrine.

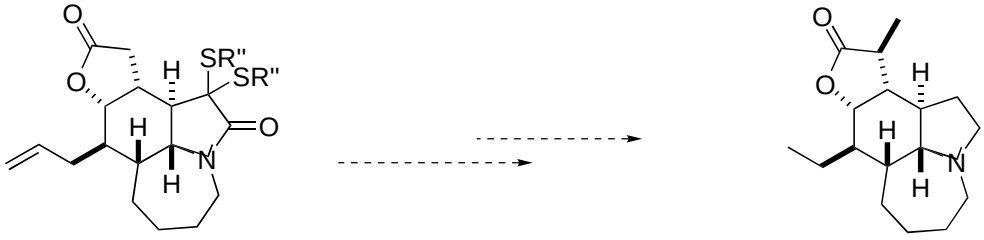
Currently, we are investigating the total synthesis of stenine (**1**), a member of *Stemona* alkaloids which are isolated from the root extracts of *Stemona* species of plants. Our synthetic strategy involves the assembly of hydroindolone **4** by using [4+1] cycloaddition of vinyl isocyanate **2** and bis(alkylthio)carbene **3**. Another key transformation of our approach is to install the 7-membered ring moiety of the azepinoindole on highly functionalized hydroindolone via a 7-endo trig radical cyclization (**5→6**). Current efforts are directed toward preparing advanced intermediate **5** and further elaborating it to stenine (**1**).



2 **3** **4**



5



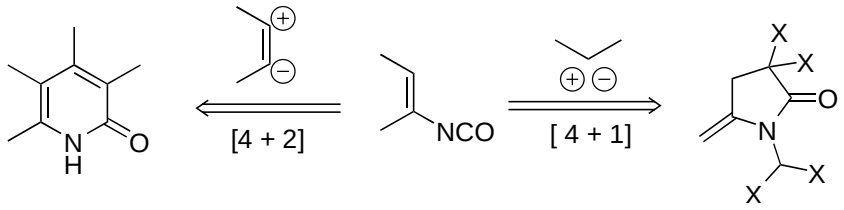
6 **Stenine (1)**

Novel Reactions of Nucleophilic Carbenes with Vinyl Isocyanates and Vinyl Ketenes

Current researcher: Zhengqiang Wang

My research in Professor Rigby's Group has been focused on the chemistry of vinyl isocyanates. As 1,4-dipole equivalents, these adducts have a high propensity to cyclize with a variety of electron rich 1,2- or 1,1-dipoles to afford different core structures for many alkaloids families (Scheme 1).

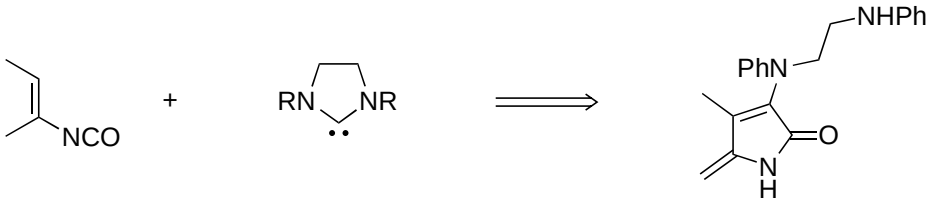
Scheme 1



Reactions between Vinyl Isocyanates and Nucleophilic Diaminocarbenes

An interesting feature about this new [4+1] cycloaddition reaction is that, although two equivalents of carbene precursor was employed, only one equivalent of carbene was found to be incorporated in the final product (Scheme 2). No N-H insertion was observed, which is in sharp contrast to the case of dialkoxy or dithio carbenes reactions. A hydantion compound obtained in some cases, which was derived from an intermolecular attack of the initially formed zwitterionic intermediate on the second molecule of vinyl isocyanate.

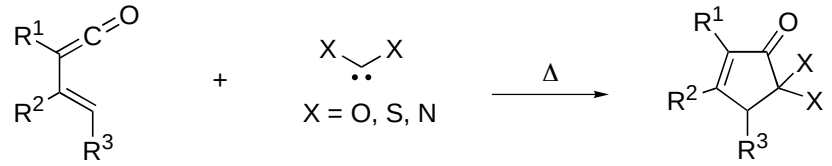
Scheme 2



Reactions between Vinyl Ketenes and Nucleophilic Carbenes

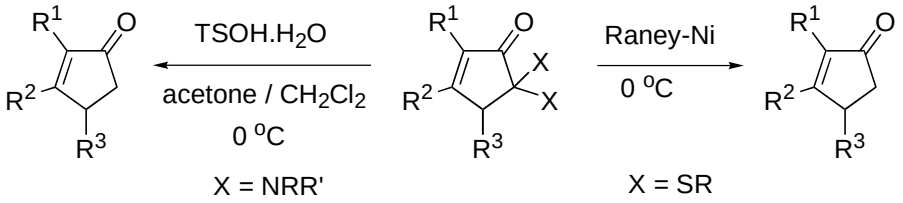
With the success of vinyl isocyanates as powerful building blocks in alkaloids synthesis, we became interested in looking into other possible 1,4-dipole equivalents for an efficient [4+1] cycloaddition reaction. Vinyl ketenes, which are structurally reminiscent to vinyl isocyanates, seem to be good candidates in this context. The chemistry of silyl-stabilized vinyl ketenes has been well established by Danheiser.

Scheme 3



The reaction was found to proceed with excellent yields. As depicted in Scheme 3, this new transformation provides an effective entry into functionalized five-membered carbocycles. Simple post-cyclization manipulations turned out to be valid in producing cyclopentenone ring structures (Scheme 4), which may find applications in the synthesis of various natural products.

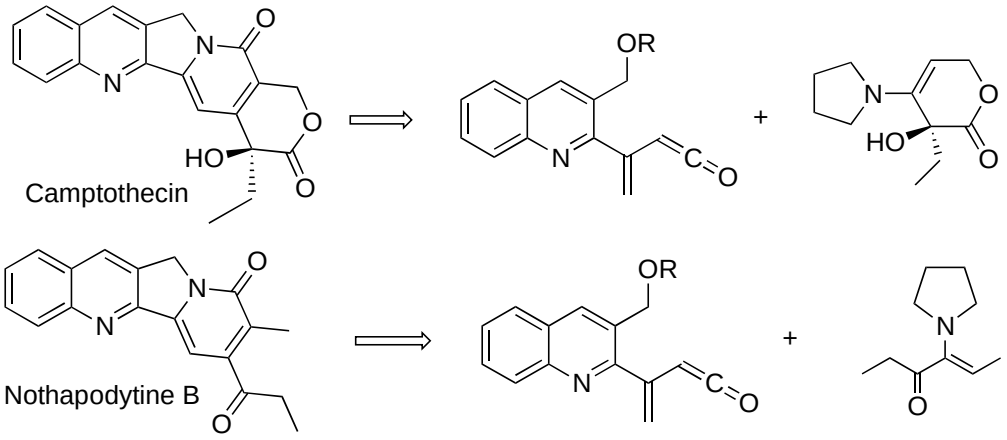
Scheme 4



Studies towards the Total Synthesis of Camptothecin and Nothapodytine B

Due to their interesting biological activities, Camptothecin and natural products of its family have drawn tremendous amount of interest in synthetic community. Many total syntheses of camptothecin and a few of Nothapodytine B have been reported. Based on the chemistry of our group, a [4+2] cycloadition reaction between a vinyl isocyanate and an enamine quickly constructs a highly substituted pyridone system. Hence, our strategy towards the total synthesis of Camptothecin and Nothapodytine B is straightforward as shown in Scheme 5.

Scheme 5

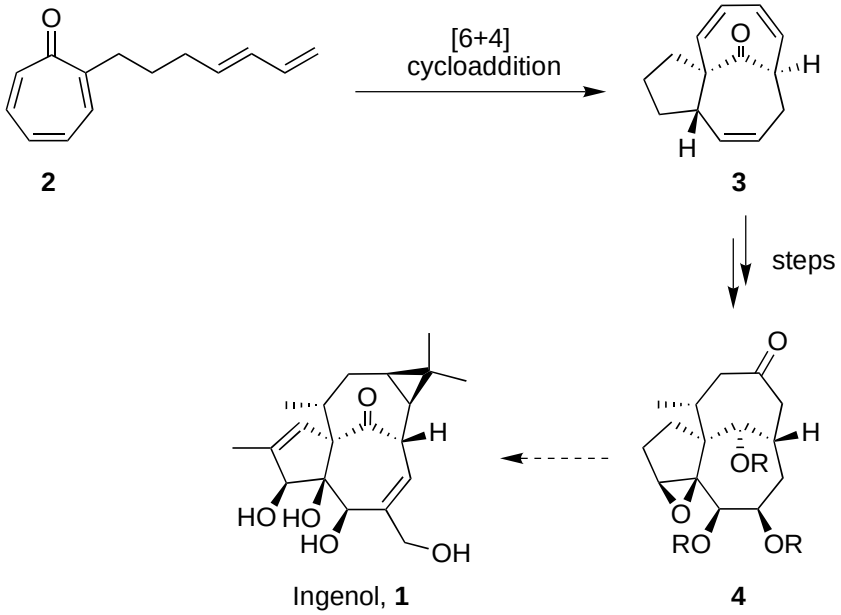


Research is currently underway towards the total synthesis of these two molecules.

Studies Toward the Total Synthesis of Ingenol

Current Researchers: Dr. Olivier Mirguet, Hoon Bae

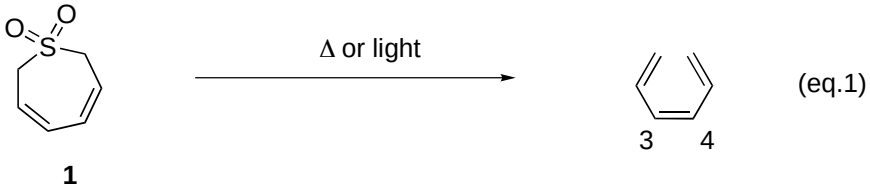
Ingenol (**1**), the ester of which is a known tumor promoter isolated from the genus Euphorbia in 1968, still remains a formidable challenge to the synthetic organic community. We are currently investigating the total synthesis of this interesting diterpene. Our plan entails the use of an intramolecular [6+4] cycloaddition of diene-tropone **2** to construct the A, B and C rings of **1**. This cycloaddition strategy not only forms two key C-C bonds, but also establishes three new stereocenters. Thus far, we have prepared tricycle **3** and elaborated it to the advanced intermediate **4** using novel reactions developed in our labs. Further studies have been initiated on an asymmetric version of the [6+4] cycloaddition reaction. Thus, an optically enriched tricycle **3** has been obtained. Intensive efforts are now being directed to elaborate intermediate **4** to ingenol (**1**).



Synthetic Application of 1,1-dioxo-2,7-dihydrothiepin: Studies Toward Total Synthesis of Leukotrienes

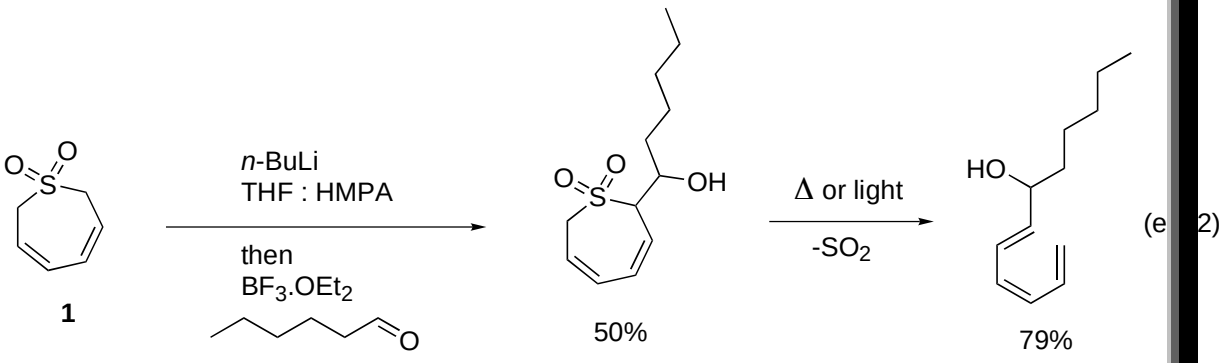
Current researcher: Bryan Forrest

Extrusion of sulfur dioxide from 1,1-dioxo-2,7-dihydrothiepin **1** gives 1,3,5-hexatriene with a geometrically defined (*Z)* double bond about carbons three and four (eq. 1).



1 (eq.1)

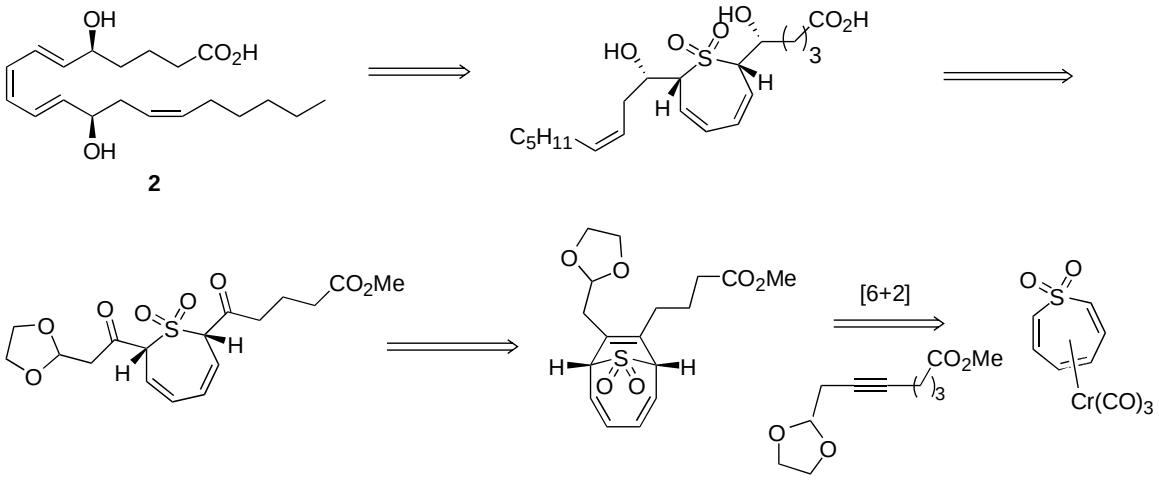
Alkylation of **1** alpha to the sulfone with aldehydes, primary alkyl triflates and acid chlorides followed by chelotropic extrusion provides various 1-substituted *E,Z,E* trienes (eq. 2).



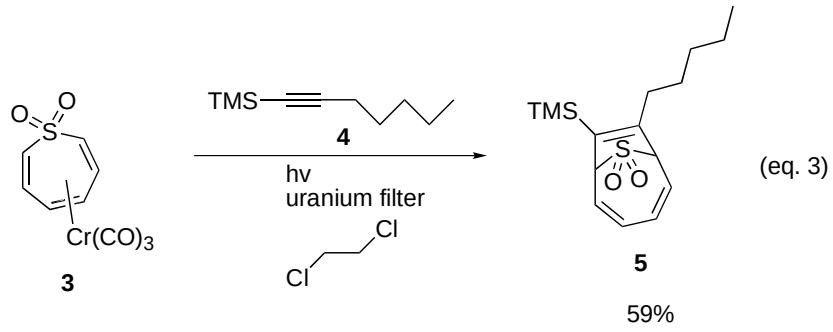
1 50% 79% (eq. 2)

The *E,Z,E* triene function is present in a number of important natural products, included are the leukotrienes. Some members of the leukotriene family are potent mediators of immediate hypersensitivity reactions and inflammation. A retrosynthetic scheme for total synthesis of (5*S,* 12*R*)-dihydroxy-6,8,10,14-eicosatetraeneoic acid **2** a member of the leukotriene family is outlined in Scheme 1. The synthesis utilizes **1** as a template for synthesis of the triene portion of the molecule and a metal-mediated [6+2] cycloaddition to establish the necessary carbon-carbon bonds at the two and seven positions of **1**. Key to the success of this synthesis will be the feasibility of a regioselective ozonolysis of the tetrasubstituted double bond in the cycloadduct.

Scheme 1



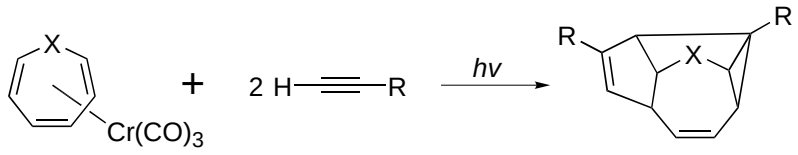
In a model study chromium complex **3** and alkyne **4** were irradiated for 7hrs and cycloadduct **5** was isolated in 59% yield (eq. 3).



Cr (0)-Mediated Multi-Component Higher Order Cycloaddition Reactions

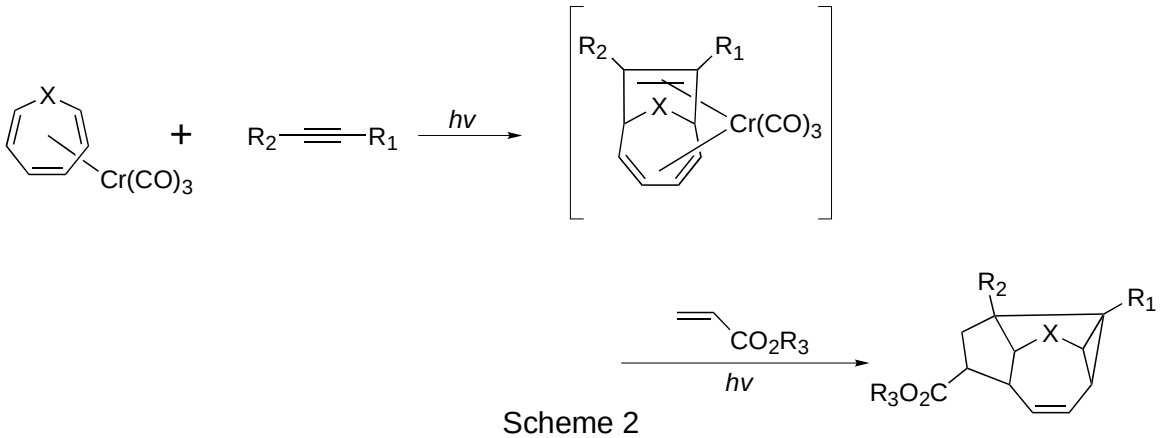
Current researcher: Zeeshan Kamal

A few years ago Cr (0)-mediated three-component triene/alkyne cycloaddition reaction was discovered and reported by the Rigby group. This reaction creates 5 new C-C bonds and 6 stereocenters from readily available starting materials (Scheme 1).



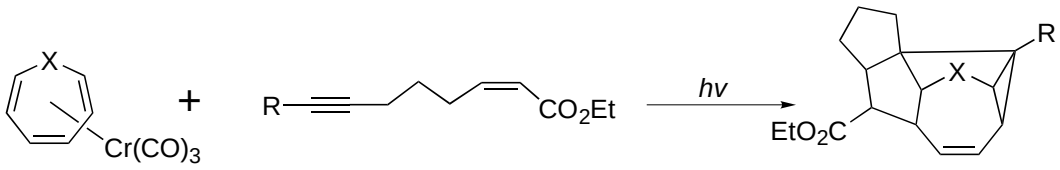
Scheme 1

My job in the Rigby's group is to widen the scope of this reaction by accomplishing tandem (6+2+2) cycoaddition with an alkyne and an alkene respectively (Scheme 2). This method will generate 5 new C-C bonds and 8 stereocenters.



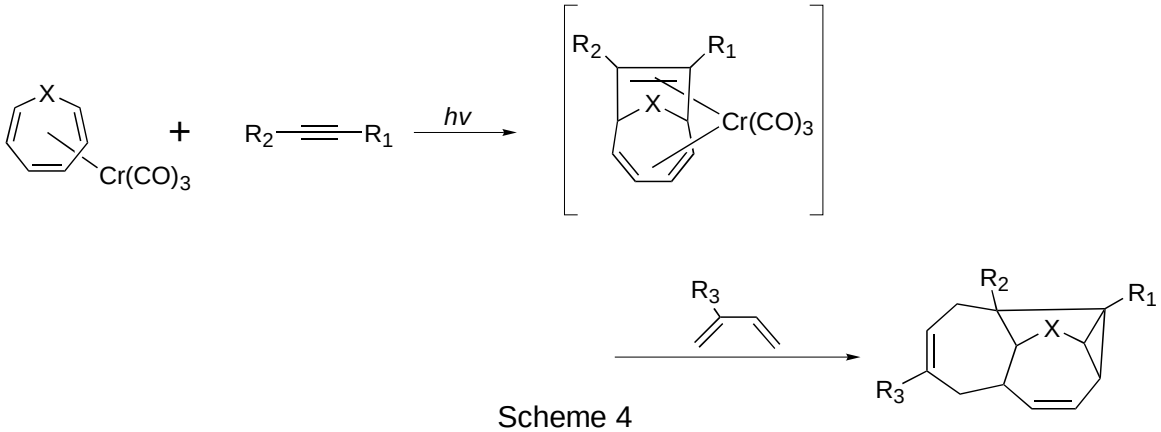
Scheme 2

The use of enynes as trieneophiles will further increase the flexibility and utility of this reaction by forming 5 carbocyclic rings, further functional group and structural manipulations will lead towards the total synthesis of *triquinane* type natural products (Scheme 3).



Scheme 3

One of a very interesting part of my research is to establish and explore the scope and utility of (6+2), *homo* (6+4) cycloaddition of triene with alkyne and a diene respectively (Scheme 4). This would prove to be a very powerful tool for the total synthesis of a*zulene* type natural products.



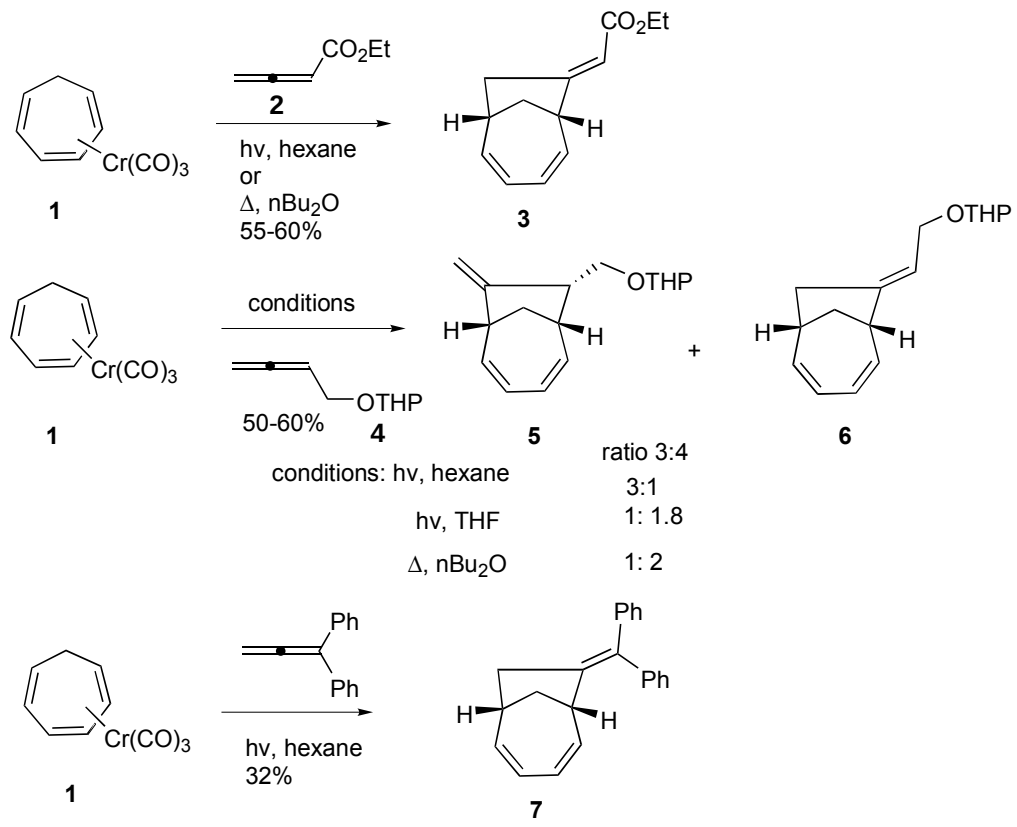
Scheme 4

[6+2] Cycloaddition of allenes with (cycloheptatriene)$Cr(CO)_3$ complex

Current researcher: Dr. Laxmisha, M.S.

Chromium(0)-mediated higher-order cycloaddition reaction has emerged as an important means for assembling complex ring systems that are often difficult or impossible to make in other ways. As part of our ongoing interest on the [6+2] cycloaddition of new trienophiles with (cycloheptatriene)$Cr(CO)_3$ complexes, we recently initiated a project on the [6+2]cycloaddition of allenes with (cycloheptatriene)$Cr(CO)_3$ complex. Since suitably substituted allenes can be chiral, this methodology can be employed to obtain chiral [6+2] cycloadducts.

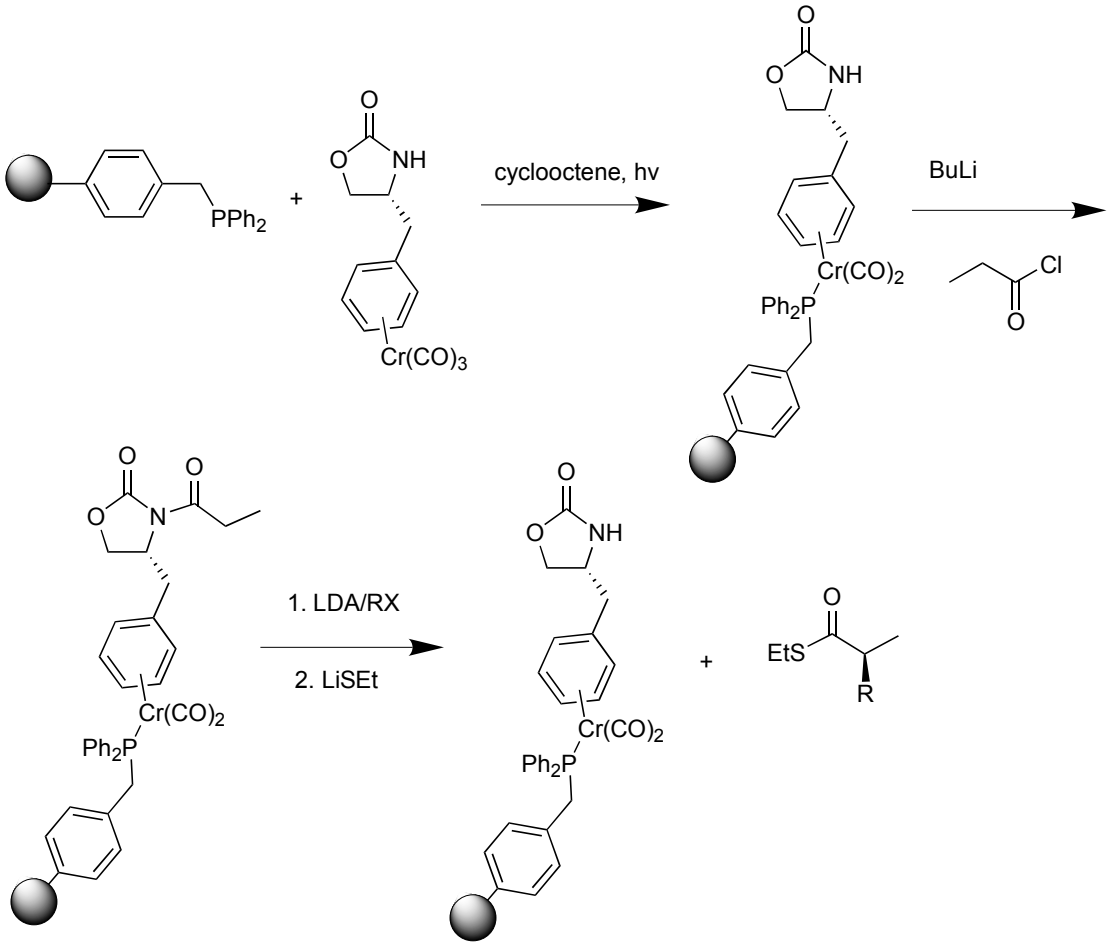
Some early results from this study are shown below. Irradiation of the chromium complex **1** with the allenic ester **2** furnished the cycloadduct **3** in 55-60% yield. Identical results were obtained for this cycloaddition when the reaction was carried out under thermal conditions. The allene **4** however gave a mixture of cycloadducts **5** and **6**, and the ratio depended on the reaction conditions used. Reaction of diphenylallene with the chromium complex **1** gave the cycloadduct **7** as a single regioisomer albeit in poor yield. Extension of this methodology employing axially chiral allenes, to obtain chiral cycloadducts is currently underway.



Evan's Oxazolidinone Asymmetric Chemistry on Solid-support

Current researcher: Dr. Laxmisha, M.S.

Over the past decade polymer supported reactions have been the subject of considerable study as a result of the increasing significance of combinatorial chemistry and multiple parallel synthesis. The design of new linkers has been important to the success of this endeavor since linker diversity allows a broader scope of substrates and reagents to participate in solid-phase chemistry. In this context, the use of π-(arene)Cr(CO)3 complexes for loading substrates onto solid supports offers attractive opportunities, because arene-chromium moiety is compatible with most functional groups. Described below is the projected use of arene-chromium linkers for carrying out Evan's oxazolidinone chemistry

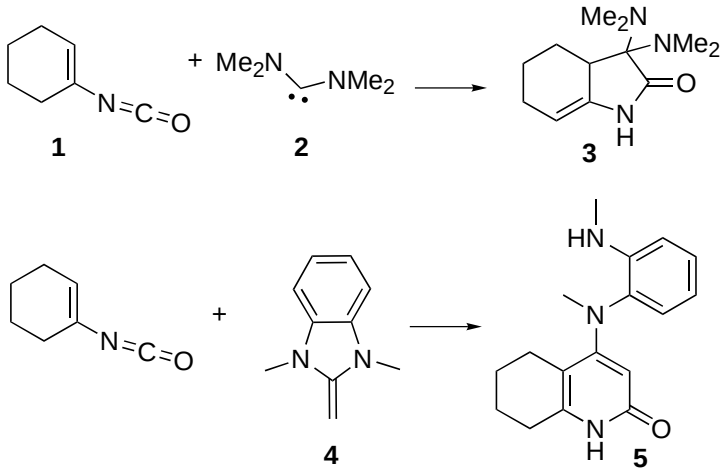


A rapid construction of 4-aminopyridones via a [4+2] cycloaddition of *N,N*-keteneacetal and vinyl isocyanates.

Current researcher: Dr. Chee-Seng, Lee

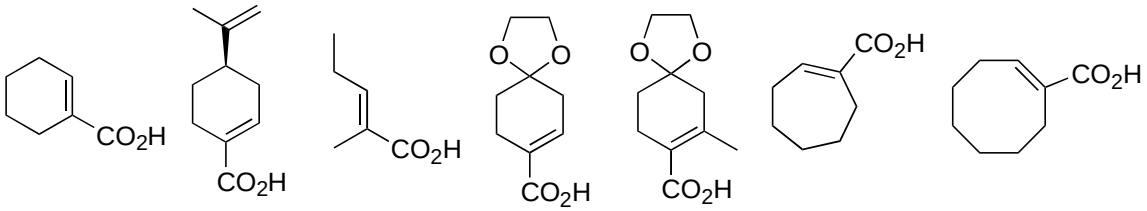
Many biological active natural products and other compounds of medicinal interest possess the pyridone moiety. It's our interest to explore new strategies for rapid construction of this important class of compounds.Reaction of vinylisocyanate **1** and nucleophilic carbene **2** allows one carbon unit addition to the vinylisocyanate to construct the 5-membered heterocycle **3**. Here we disclose the rapid construction of 6-membered 2-amino pyridones **5** via a [4+2] cycloaddition between 2-methylene imidazoline **4** and vinylisocyanate (Scheme 1).

Scheme 1



1 **2** **3** **4** **5**

A variety of substituted and functionalized vinyl isocyanates were used in this study to probe the utility of this process. We sought to test not only the scope of the reaction but also the versatility of the reaction in the presence of various functional groups. Acid **6-12** were obtained commercially or through synthesis via literature preparation. (Figure 1).



6 **7** **8** **9** **10** **11** **12**

Figure 1. Various vinylacids

All the isocyanates were synthesized directly from the corresponding acids and diphenylphosphoryl azide. The resulting azide was then refluxed in acetonitrile or benzene to give the isocyanate, which was either used without purification or quickly purified through column chromatography. Exposure of vinyl isocyanate to 2-methylene

imidazoline in either benzene or acetonitrile at 0 ºC followed by refluxing for 2 hours afforded the desired 2-amino pyridone either through column chromatography or simple filtration (Figure 2). The 6, 7, and 8-fused pyridones **6a**, **11a**, **12a**, were obtained in 65-75% yield. The ketal functional group survived through the process. The corresponding pyridone **9a** was obtained in 50% yield. The pyridone **7a** derived from perillic acid was obtained in 60% yield. In contrast to the cyclic vinylisocyanates, the acyclic 2-methylpent-1-ene vinylisocyanates gave the corresponding pyridone **8a** in only 32% yield. Most interestingly, we were able to construct pyridone **10a** which posseses a quaternary center at the ring fusion.

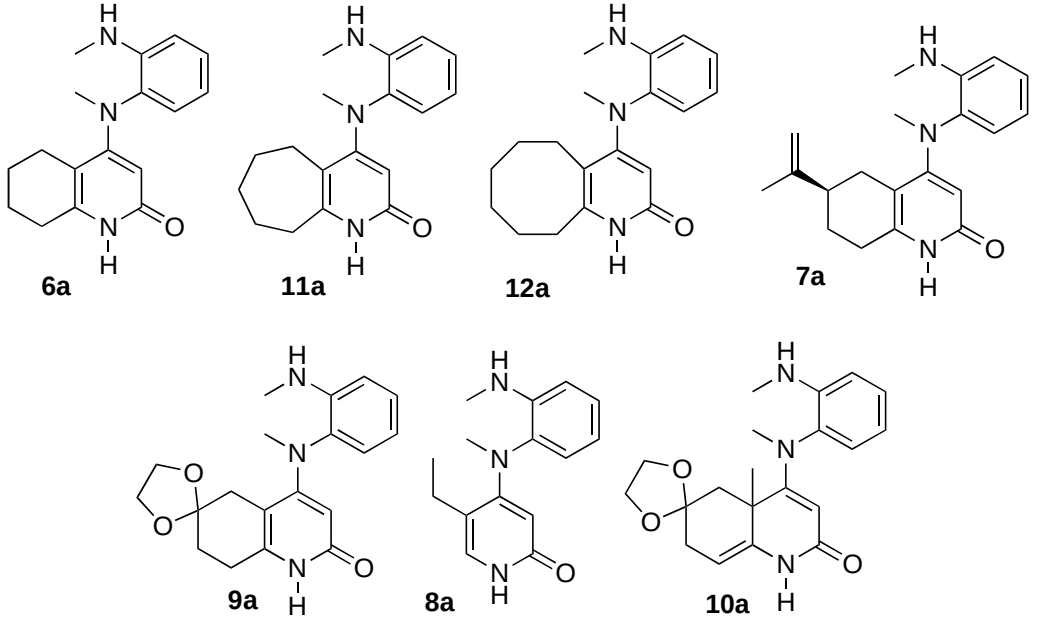
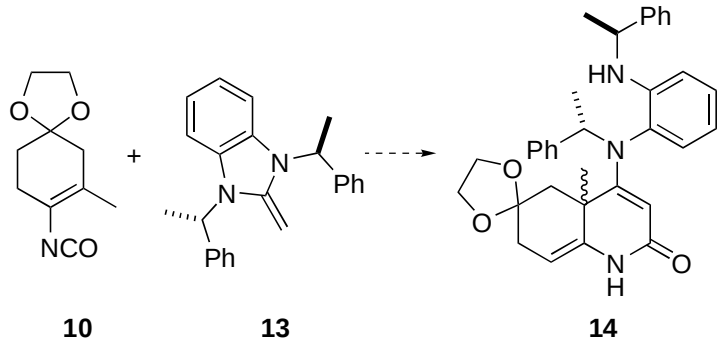


Figure 2. Pyridones obtained

The generation of this ring fusion quaternary center encouraged us to explore the possibility of chiral synthesis of this group of pyridones (Scheme 2). Chiral synthesis of various imidazolines and its application in this [4+2] cycloaddition with vinylisocyanates is currently under investigation. In conclusion, our results have illustrated the experimental ease and quick assembly of highly substituted pyridones as potential templates of several biological active compounds.

Scheme 2



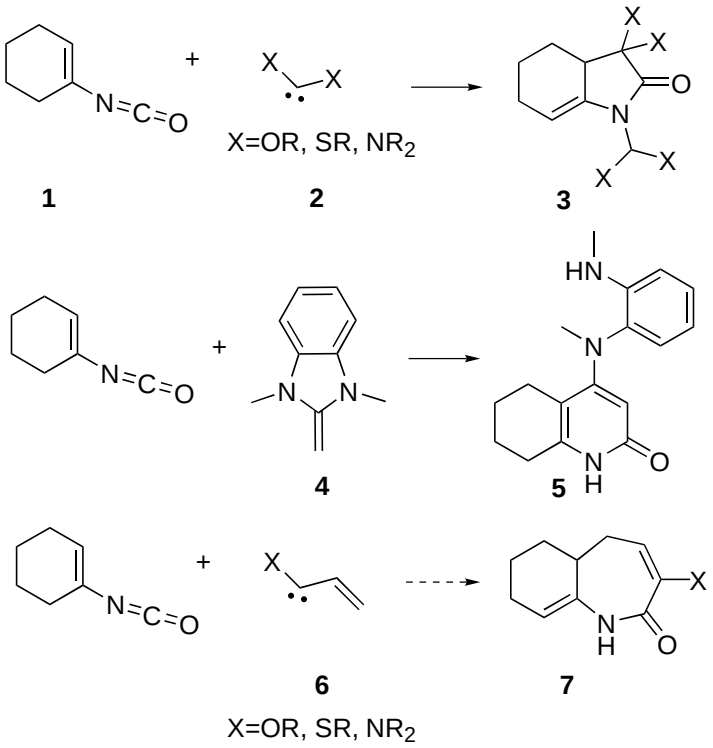
Studies in Synthesis of Vinyl Carbenes and Their Potential Application in Organic Synthesis

Current researcher: Dr. Chee-Seng Lee, Aarron Proffitt

Syntheses of indoline, pyridone and azepine moieties have attracted many synthetic interests. In our laboratory, we have successfully demonstrated facile approaches toward the indoline and pyridone unit. However, Many biological significant natural products and synthetically interesting molecules possess the azepine moiety. An efficient and easy synthesis of the azepine unit is required. Herein, we disclose our preliminary studies toward synthesis of azepines.

Nucleophilic carbenes **2**, such as dithiocarbene, dimethoxycarbene and diaminocarbene react with vinylisocyanate to give the corresponding 5-membered nitrogen heterocycle **3** while 2-methylene imidazoline **4** successfully adds to the vinylisocyanate to give the desired 6-membered pyridone **5**. Here, we set out to investigate the synthesis of vinylcarbenes **6** and their potential use in constructing azepines **7** (Scheme1).

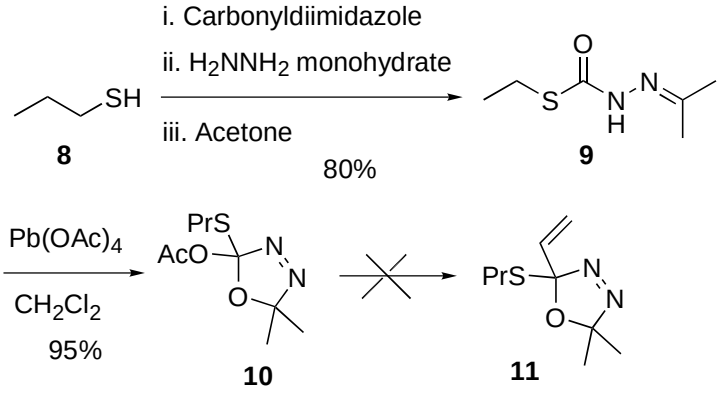
Scheme 1



Our approach toward the precursor of vinylcarbene **11** began with the synthesis of the required hydrazone **9** in 80% yield over 3 steps (Scheme 3). It was then oxidized to the cyclic oxadiazoline **10**. Exhausted attempt to convert the corresponding thioacetyloxadiazoline **10** to the vinyloxadiazoline **11** gave no fruitful result. Treatment of the thioacetyl-oxadiazoline **10** with various Lewis acids such as BF_3•Et_2O, TMSOTf,

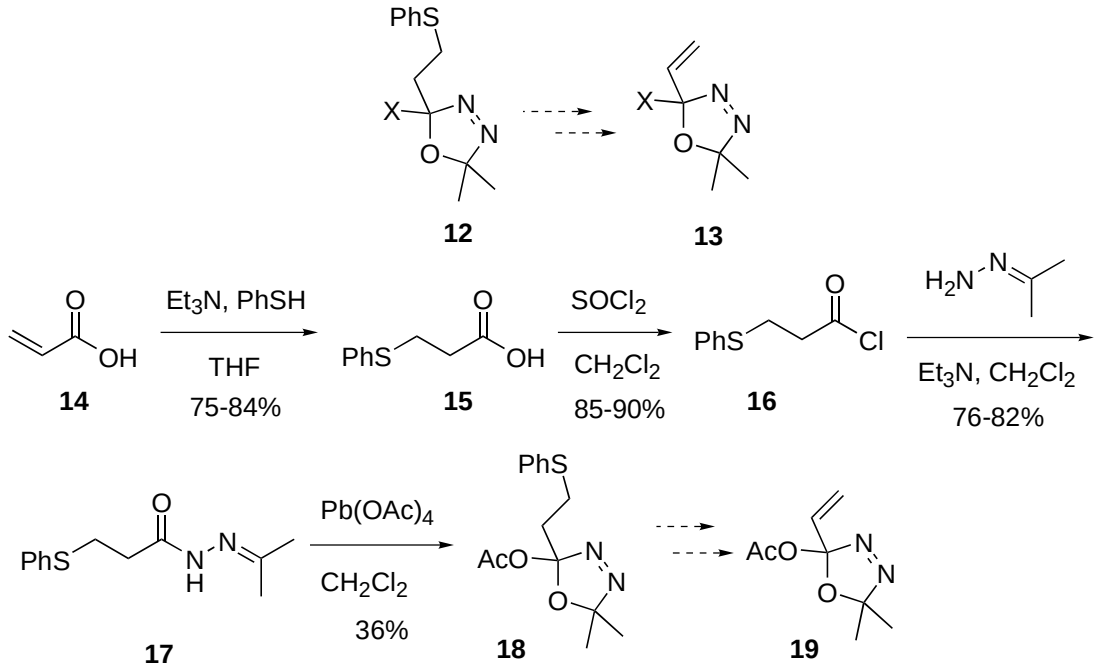
and organic acids such as p-TsOH and TFA in the presence of excess equivalent of various nucleophiles such as vinyl, allyl and propagylsilanes failed to produce any desired product. In most cases, complex mixtures or product decomposition was observed.

Scheme 3



We then turned our attention toward construction of the vinyl equivalent of the corresponding oxadiazoline (Scheme 4). Synthesis of the masking acetylvinyloxadiazoline **12** began with treatment of acrylic acid with PhSH to give the resulting Michael addition adduct **15** in excellent yield. Acid chloride formation followed by acylation gave the corresponding hydrazone **17** in good yield. Oxidation of the hydrazone using $Pb(OAc)_4$ gave the desired oxadiazoline **18** in 36% yield. However, attempts at conversion of sulphide **18** to the vinylcarbene precursor **19** were not successful. Currently, other approaches toward the vinylcarbene precursor are under vigorous exploration.

Scheme 4

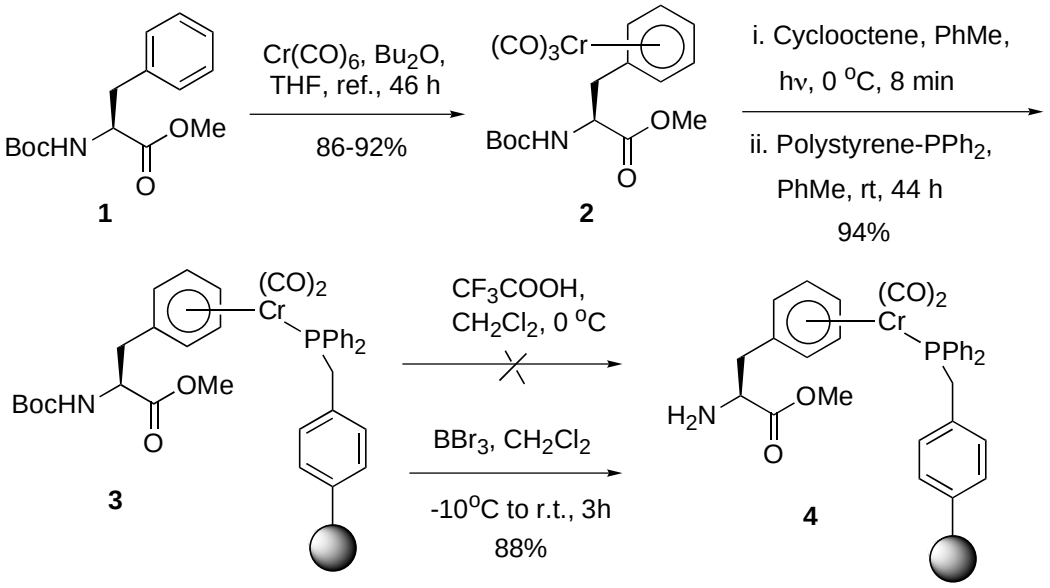


Studies on the Solid-Phase-Synthesis of Cyclic Peptides Using π-Arene Chromium "Traceless Linkers"

Solid-phase synthesis has become increasingly important in the past few years. Its ease in purification has attracted many interests especially the pharmaceutical industry. Recently, our laboratory has developed a convenient and efficient protocol for construction of π-arene-chromium linker and its usefulness in solid phase synthesis of small molecules.[1]

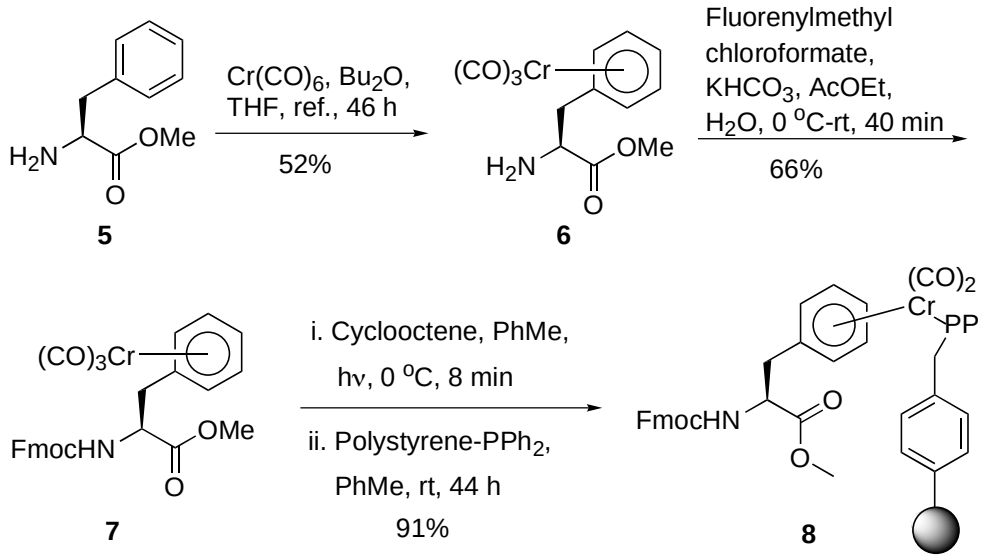
Many cyclic peptides possess significant biological activity and are drugs of choice for treatment of many diseases. The presence of aromatic amino acids in many of these peptides prompted us to employ our newly developed π-arene-chromium linker in the synthesis of complex cyclic peptides. Herein, we disclose our studies in the synthesis of a cyclic tetrapeptides. Boc-L-phenylalanine methyl ester chromium complex **2** was prepared from the corresponding Boc-protected amino acid **1** and $Cr(CO)_6$ in 92% yield. It was then tethered to the polystyrene-based resin to give the polymer-bound compound **3** in 94% yield. Attempt deprotection of the Boc-group using TFA was not successful. However, upon treatment of the compound **3** with BBr_3, the desired amine **4** was obtained in 88% yield (Scheme 1).

Scheme 1



Simultaneously, it was also found that Fmoc reaction conditions are compatible with the π-arene chromium bond. The $Cr(CO)_3$ precursor **7** was obtained in two steps starting from the L-phenylalanine methyl ester **5** bearing unprotected N-terminus. It was then tethered to the resin to give the polymer-bound compound **8** in 91% yield (Scheme 2).

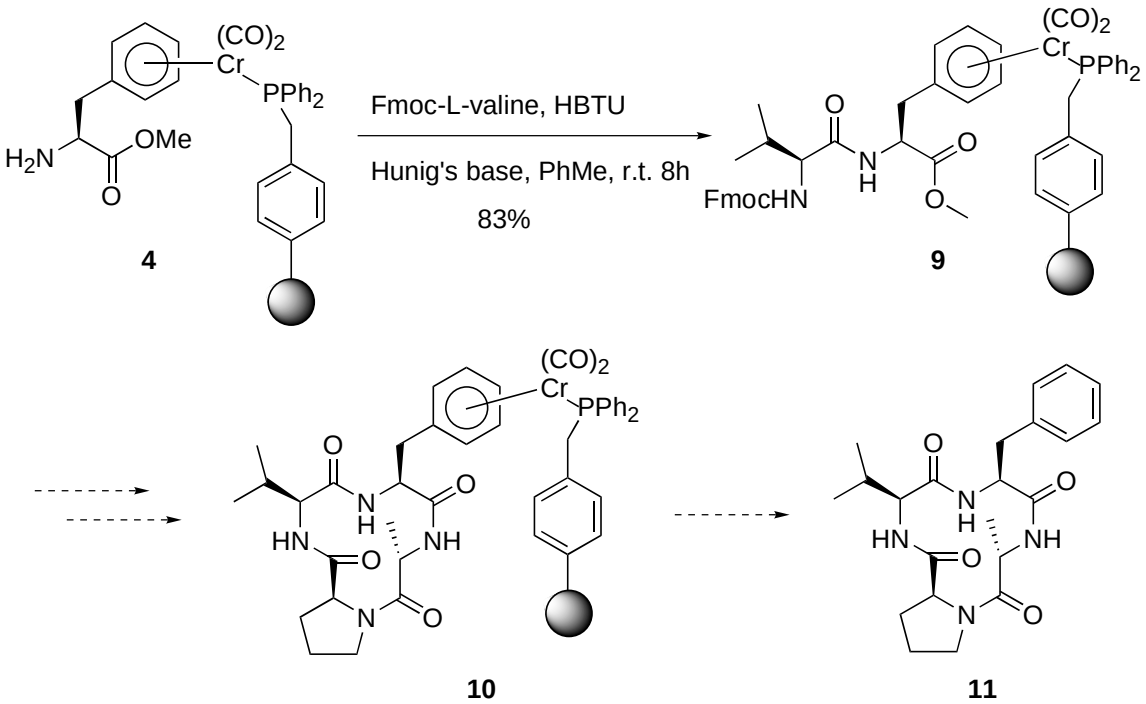
Scheme 2



5 **6** **7** **8**

The 'traceless' solid-phase synthesis of a cyclic tetrapeptide using π-arene-chromium began in the *N* to *C* direction. Compound **4** was coupled with Fmoc-L-valine to give the peptide **9**. Synthesis toward the polymer-bound cyclic tetrapeptide **11** is currently under vigorous investigation (Scheme 2).

Scheme 3



4 **9** **10** **11**