



**Trip Report for**  
**“8<sup>th</sup> Annual Florida Heterocyclic Conference”**  
**Gainesville, Florida**  
**March 11-14, 2007**

**Peter R. Guzzo, Ph.D., Jun-Ho Maeng, Ph.D.,  
Sang Lam, David M. Jenkins**

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**Abstract:** *This conference was an IUPAC-sponsored event that included plenary and invited lecturers, poster sessions, and short courses on heterocyclic chemistry given by leading experts in the field. Nearly 200 participants attended the relatively rigorous 3-day event filled with a plethora of synthetic heterocyclic chemistry, reflecting the justifiable interest in the subject due to its prevalence in industry, particularly the pharmaceutical community. Highlights from various speakers and short courses will be presented.*

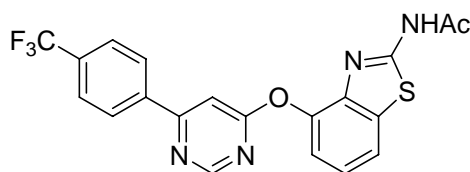
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## Plenary Speakers:

### “Synthesis and Development of VR1 Antagonists”

Dr. Robert Larsen (Amgen Inc.)

The VR1 receptor (also known as transient receptor potential vanilloid 1 or simply the vanilloid receptor 1) is a ligand-gated ion channel expressed on somatic and autonomic primary afferent neurons. The VR1 ion channels are one of the best known mediators of pain signaling and work by regulating the flow of ions (calcium and sodium) between the inside and outside of neurons. VR1 receptors are upregulated after nerve damage and inflammation. Once activated by low pH, heat or natural ligands (e.g. capsaicin), the VR1 receptor is involved in the transmission of pain signals. Many companies are pursuing VR1 receptor antagonists with the hypothesis that antagonism of the receptor would interrupt the pain signal and provide effective non-narcotic analgesia. In preclinical studies, VR1 antagonists have demonstrated an ability to block capsaicin and inflammation-induced pain (e.g. carrageenan- and complete Freund's adjuvant (CFA)-induced thermal hyperalgesia) and neuropathic pain (e.g. Chung model). AMG 517 is currently in phase I clinical trials for the treatment of pain.



**AMG 517**

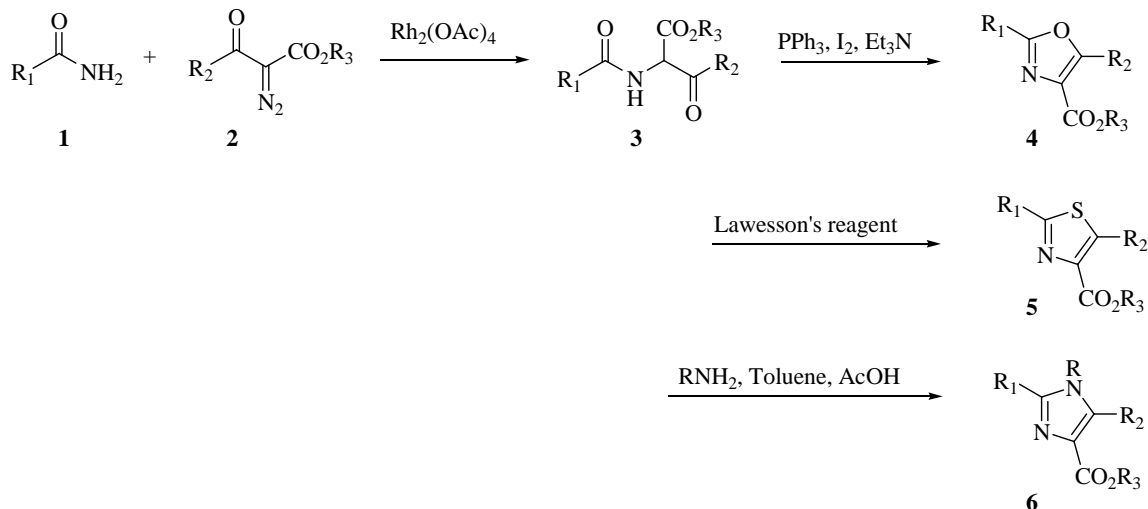
The solubility of AMG 517 was 0.003 mg/mL and all salts disproportionated in water. Through formulation studies, it was found that a co-crystal with sorbic acid improved solubility. Sorbic acid does not form a true salt but does form a hydrogen bond network that is believed to be the cause of the improved solubility.

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### “Synthesis of Heterocyclic Peptides”

Christopher Moody (University of Nottingham)

Professor Moody described an interesting reaction between amides (**1**) and diazocarbonyl compounds (**2**) catalyzed by dirhodium tetraacetate to give versatile 1,4-dicarbonyl compounds (**3**). 1,4-dicarbonyl compounds can be efficiently cyclized to a variety of 5-membered heterocycles, including oxazole, thiazole, and imidazole ( Davies, J. R.; Kane, P. D.; Moody, C. J. *Tetrahedron* **2004**, *60*, 3967). This methodology was applied to the synthesis of several complicated heterocyclic peptides.

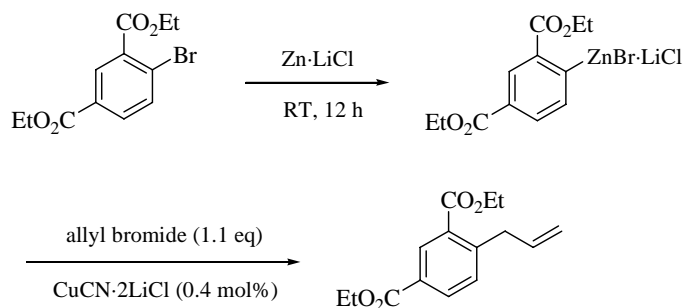


### “Functionalized Mg and Zn reagents for the synthesis of Polyfunctional Heterocycles”

Paul Knochel (Ludwig Maximilians-University of Munich, Germany)

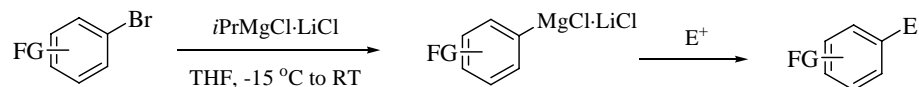
Professor Knochel presented the recent work on a new protocol for the preparation of functionalized aryl- and alkylzinc compounds by the direct insertion of commercially available Zn powder in the presence of LiCl in THF. The insertion of Zn into a C-Br bond is also possible in the case of activated aryl- and heteroaryl compounds. Thus, in the presence of LiCl, the functionalized zinc reagent was formed at room temperature in 91% yield starting from the bromodiester. Quenching with allyl bromide leads to the allylated diester in 90% yield (Scheme 1).

Scheme 1



Prof. Knochel also presented the preparation of functionalized arylmagnesium compounds using the new reagent  $i\text{PrMgCl}\cdot\text{LiCl}$ , which was made by adding  $i\text{PrCl}$  to Mg turnings and LiCl in THF. Alternatively, the reagent can be prepared by addition of a solution of  $i\text{PrMgCl}$  in THF to LiCl. This reagent was used for the preparation of a range of aryl- and heteroarylmagnesium derivatives starting from the corresponding bromides. After the reaction with electrophiles, the expected products were isolated in good to excellent yields (Scheme 2).

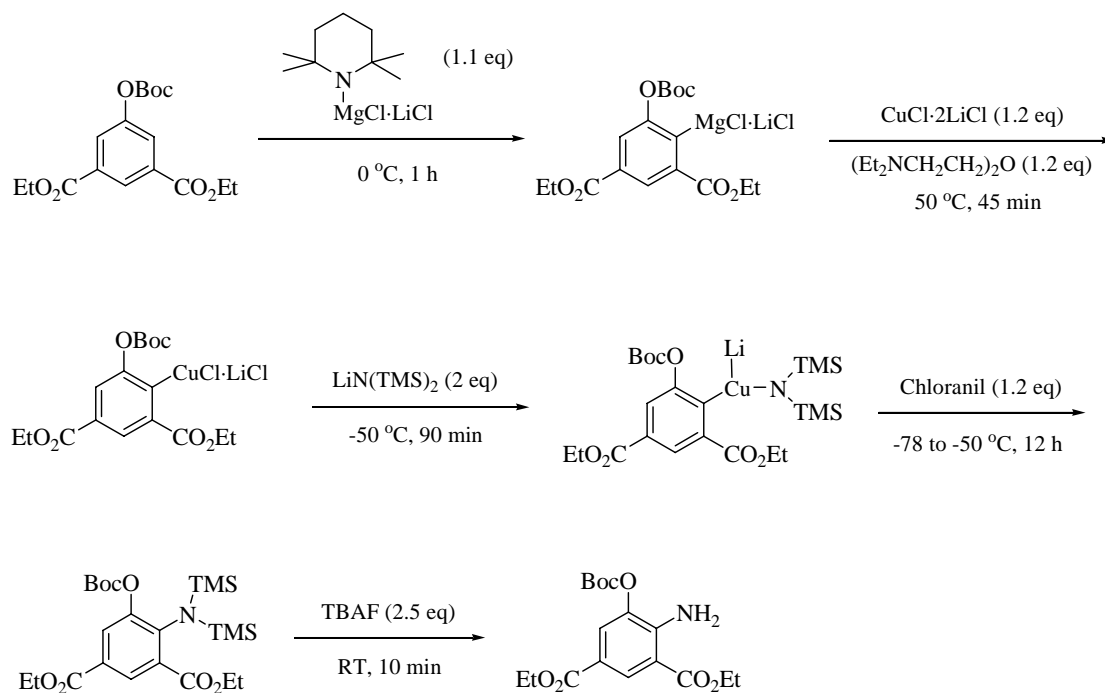
### Scheme 2



FG = F, Cl, Br, CN, CO<sub>2</sub>R, OMe

He also presented the preparation of primary amines through an oxidative amination with a magnesiated polyfunctional aryl derivatives and LiHMDS using 2,3,5,6-tetrachloro-1,4-benzoquinone (chloranil) as shown in Scheme 3. His research group extended and adapted this procedure to the preparation of various primary, secondary and tertiary amines.

### Scheme 3

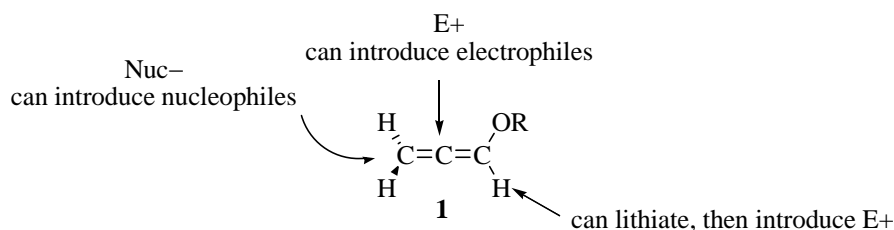


## “Heterocycles from Alkoxyallenes”

Professor Hans-Ulrich Reissig, Freie Universitat, Berlin, Germany

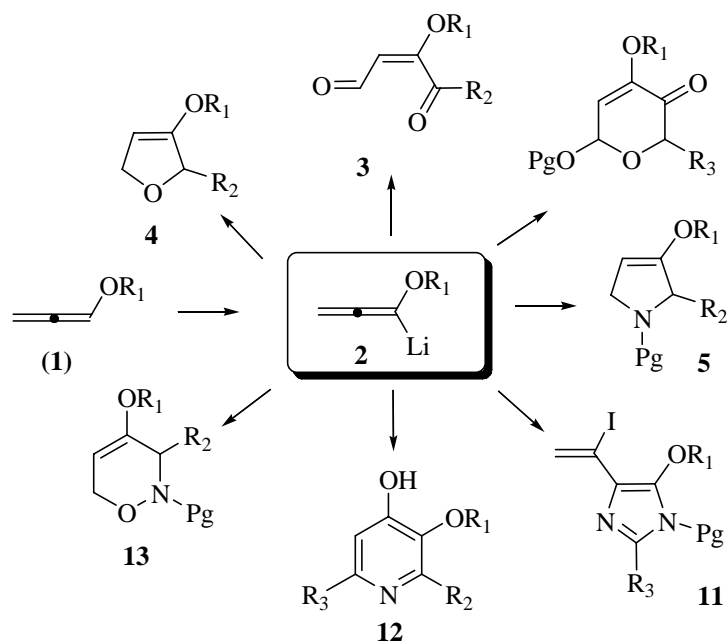
Professor Reissig delivered an informative seminar on the formation of various heterocycles from a common lithiated alkoxyallene intermediate. Alkoxyallenes (**1**), generated by lithiation of the corresponding alkynes and quenching with methanol, are reactive species that can undergo nucleophilic attack or can easily be lithiated by treatment with *n*-butyllithium. These lithio alkoxyallene intermediates are able to smoothly react with a variety of electrophiles (Figure 1).

Figure 1



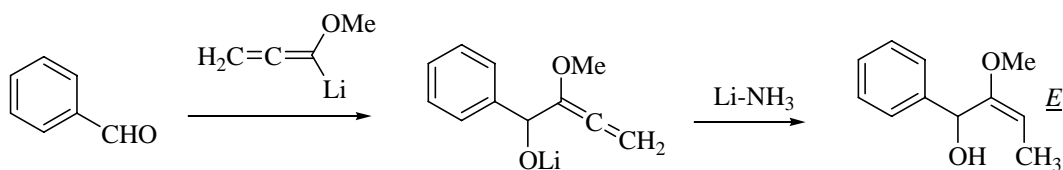
From this lithiated alkoxyallene intermediate **2**, a host of heterocyclic derivatives can be synthesized (Figure 2). An oxidative cleavage converts **2** into an  $\alpha,\beta$ -unsaturated  $\gamma$ -ketoaldehyde (**3**), a versatile precursor for the preparations of various heterocycles such as pyrans or pyridazines. In addition, **2** can react with nitriles to form pyridines (**12**) or with aldonitriles to furnish functionalized 2*H*-1,2-oxazines (**13**) by a highly stereoselective [3 + 3] cyclization. Alternatively, allenyl amines ( $-\text{NR}_2$  in place of  $-\text{OR}$ ) can undergo a three-component reaction with iodine and nitriles to afford iodovinyl-substituted imidazole derivatives (**11**).

Figure 2



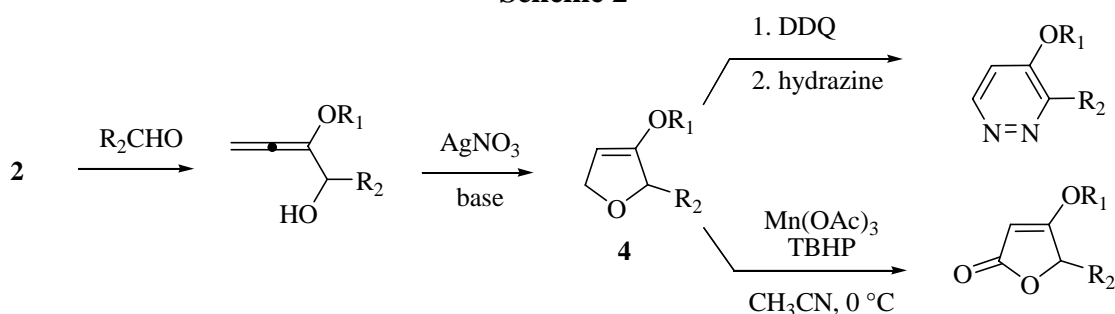
Note that in **3** the alkene geometry is exclusively *E*, which is supported by the early works of Weiberth and Hall using 1-lithio-1-methoxyallene to alkylate benzaldehyde followed by a lithium-ammonia reduction to exclusively furnish the (*E*)-1-hydroxymethyl methyl propenyl ether (Scheme 1).<sup>1</sup>

**Scheme 1**



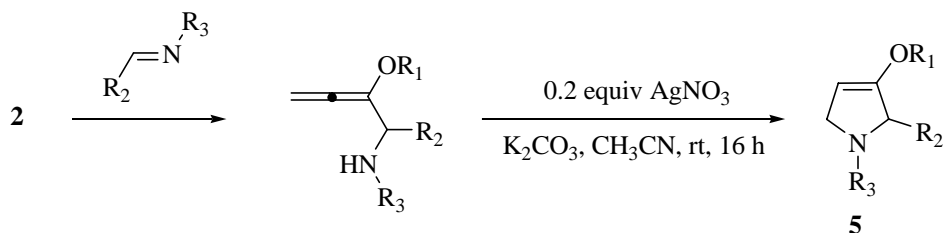
To form 2-substituted-3-methoxy-2,5-dihydrofurans (**4**), **2** is reacted with an aldehyde followed by cyclization with a base in the presence of catalytic silver nitrate (Scheme 2). Compound **4** can then be converted to furanones, pyridazines, and even pyrans (if R<sub>2</sub> = CH<sub>2</sub>(OPg)CH<sub>3</sub>).<sup>2</sup>

**Scheme 2**



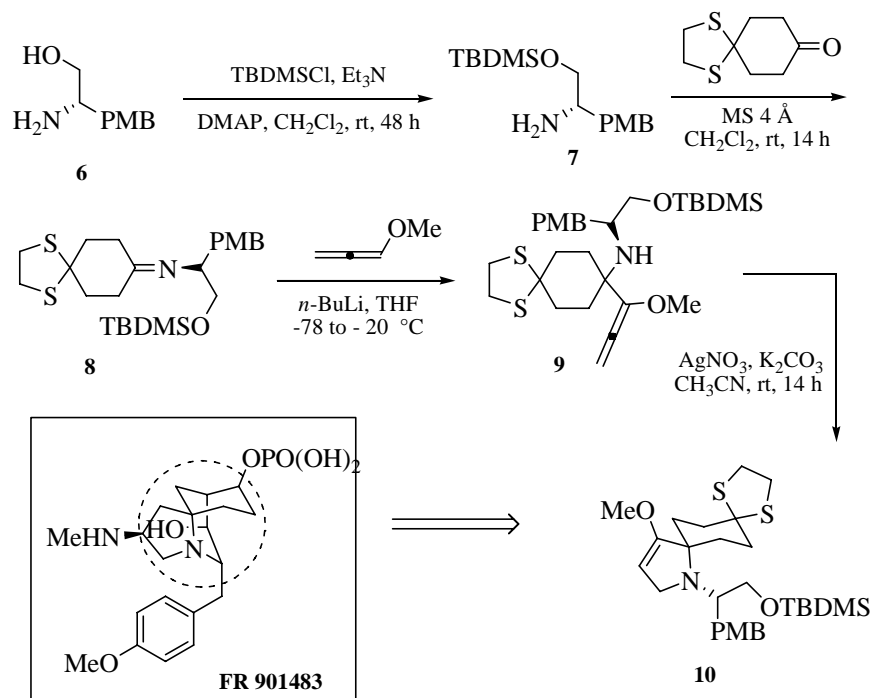
To form 2-substituted-3-methoxy-2,5-dihydropyrroles<sup>3,4</sup> (**5**), **2** is reacted with an imine followed by cyclization using K<sub>2</sub>CO<sub>3</sub> in the presence of catalytic silver nitrate (Scheme 3).

**Scheme 3**



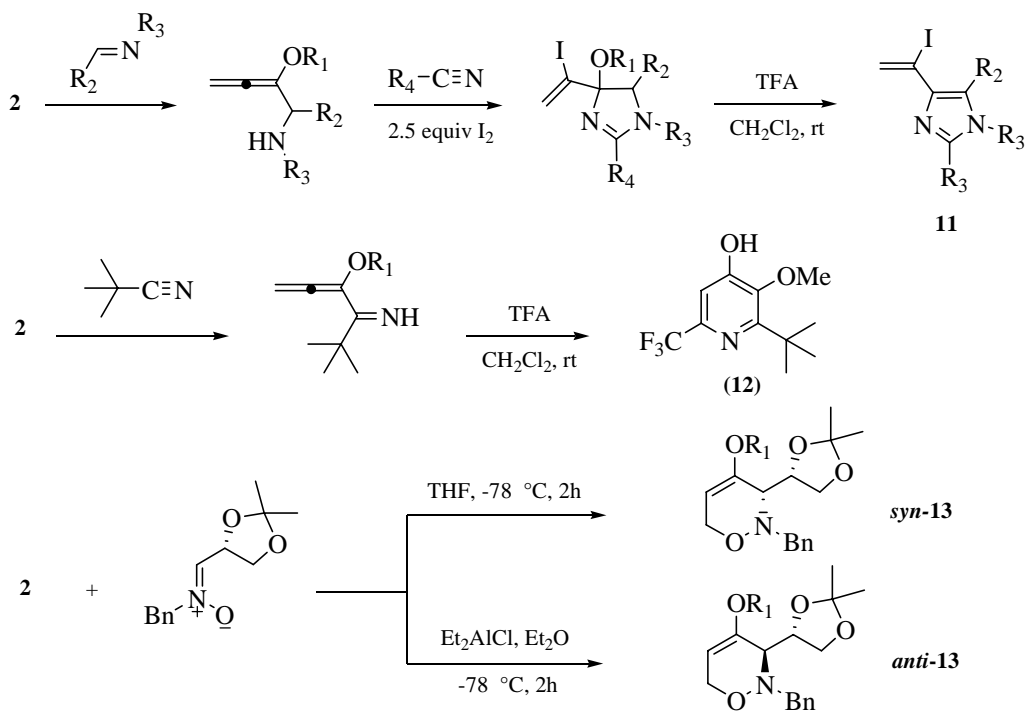
The dihydropyrrole method was applied recently to the azaspirane core of the natural product FR 901483, an inhibitor of purine nucleotide biosynthesis (Scheme 4).<sup>5</sup> The amino alcohol **6**, prepared from L-tyrosine, was protected as a silyl ether to give the primary amine **7** in excellent yield. The thioketal was condensed with **7** to afford the ketimine **8**, which was used crude due to its inherent instability towards chromatographic purification. The allenylamine **9** was also unstable to purification, thus the crude was cyclized to give **10** in 79% overall yield.

### Scheme 4



Highly substituted imidazoles (**11**),<sup>6</sup> pyridines (**12**), and 1,2-oxazines (**13**),<sup>7</sup> can also be easily synthesized using the alkoxyallene chemistry with nitriles and aldonitrone as precursors (Scheme 5).

### Scheme 5



## References

1. Weiberth, F. J.; Hall, S. S. *J. Org. Chem.* **1985**, *50*, 5308-5314.
2. Brasholz, M.; Reissig, H.-U. *Angew. Chem. Int. Ed.* **2007**, *46*, 1634-1637.
3. Flogel, O.; Reissig, H.-U. *Synlett* **2004**, *5*, 895-897.
4. Chowdhury, M. A.; Reissig, H.-U. *Synlett* **2006**, *15*, 2383-2386.
5. Kaden, S.; Reissig, H.-U. *Org. Lett.* **2006**, *8*, 4763-4766.
6. Gwiazda, M.; Reissig, H.-U. *Synlett* **2006**, *11*, 1683-1686.
7. Al-Harrasi, A.; Reissig, H.-U. *Angew. Chem. Int. Ed.* **2005**, *44*, 6227-6231.

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### “Controlled Template-Directed Synthesis”

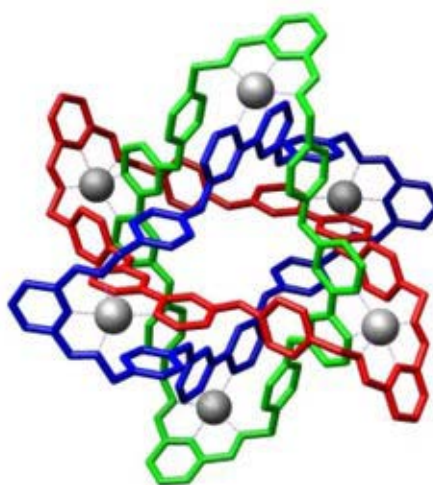
*Professor J. Fraser Stoddart, University of California, Los Angeles, USA*

Professor Stoddart gave a phenomenal seminar that incorporated not only science, but taught the audience art, history, technology, and mathematics which ultimately led to the subtle take home message that life is filled with struggles and serendipity. His favorite quote by Noel Coward was reiterated on more than a few occasions throughout his lecture that “there can be no success without failure.” The most memorable part of the talk was when he told the audience that he and his students had synthesized what he thought was a molecular version of the Borromean rings, (Figure 1), and that the night he received the X-ray crystallographic confirmation was the same night he found out his wife had passed away of cancer. A heart-felt silence just fell over the entire auditorium as one could not help but be moved by the simultaneous synthetic triumph and devastating personal tragedy.

**Figure 1**



**Artistic Representation**

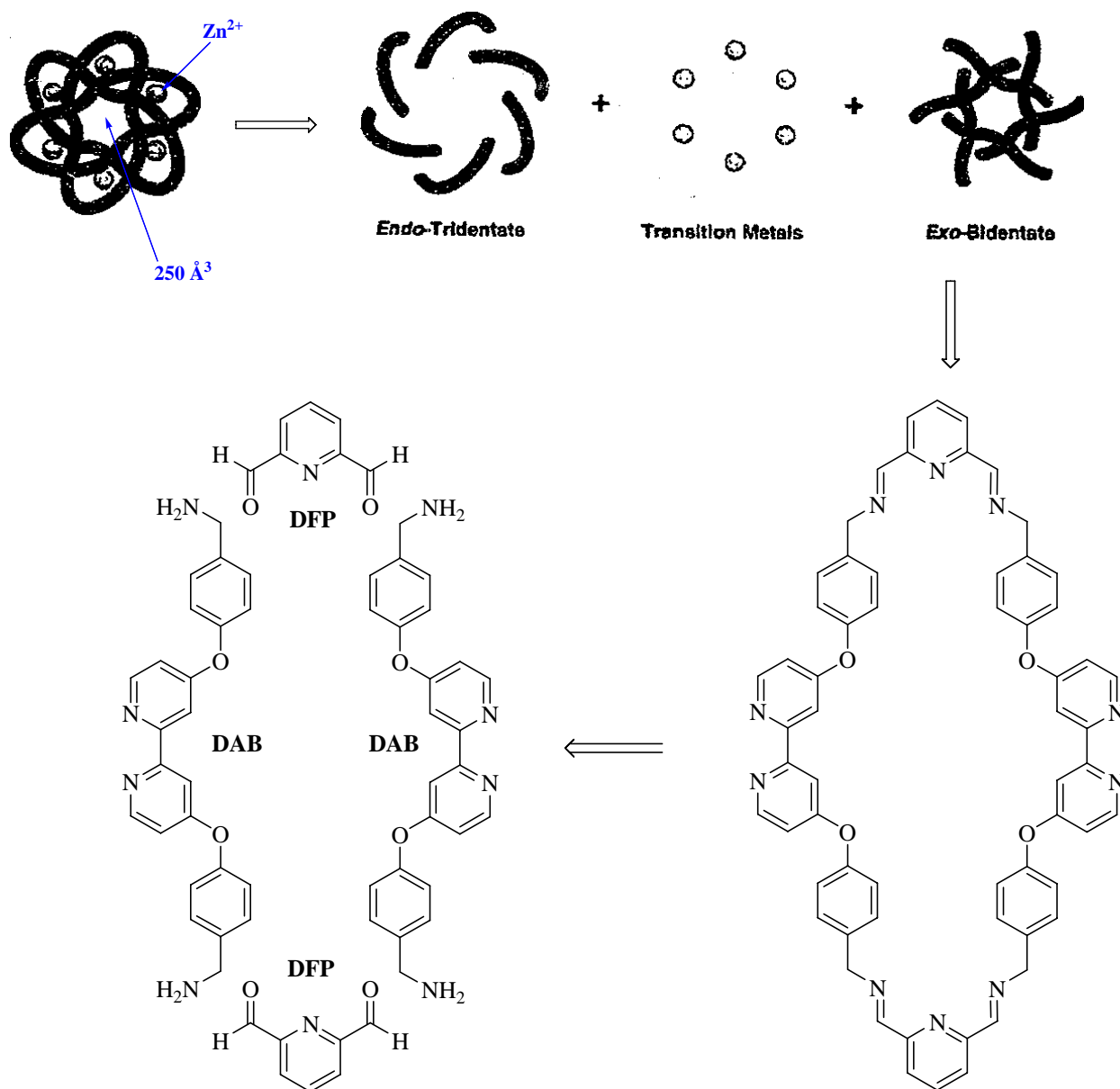


**Chemical Representation**

The Borromean rings (BRs) are an object of much interest in knot theory with its symbolism tracing back to early Christian iconography and Norse mythology.<sup>1</sup> Its use proliferated on the crests and statues of the Borromeo family in 15th century Tuscany.<sup>1</sup> The rings are interlocked with each other in the same manner: over-under-over-under. The scission of any one ring will lead to the falling apart of the entire interlocking system. The last century has witnessed the

emergence of the use of BRs in particle physics, magnetism, nanoclusters in the material sciences, medical imaging, and, of course, the formidable challenge it presents to organic chemists.<sup>1</sup> Such a synthetic task relies on the idea of cooperative self-assembly processes whereby the desired outcome spontaneously occurs if the molecular building blocks are positioned in a manner that will facilitate the reactions to proceed. To aid in the task, Professor Stoddart and his students utilized molecular modeling to optimize the cooperativity between the  $\pi$ - $\pi$  interactions and coordination geometries of the Zn(II) ions, two essential ingredients in the promotion of self-assembly processes.<sup>1</sup> The BR synthesis is somewhat of an orchestration of Zn(II) ions, which preferentially binds one *exo*-bipyridyl and one *endo*-diiminopyridyl ligand, in concert with the dynamic imine bond formations between 2,6-diformylpyridine (DFP) and diamine (DAB), which then culminates in a [2 + 2] macrocyclization to form the final BR structure, whose synthetic optimization has progressed to the point that undergraduates can now produce BRs on a gram scale (Scheme 1).<sup>1,2</sup>

Scheme 1



Professor Stoddart and co-workers have recently applied the principles from the BRs construction to the synthesis of another iconic symbol of knot theory, the Solomon links.<sup>2</sup> That synthesis, however, will not be covered in this report.

Among the ground-breaking synthetic accomplishments of the BRs and Solomon links that he presented were the equally impressive molecular switches<sup>3</sup> and the very fascinating electrochemical color-switchable pixel<sup>4</sup>, topics that also will not be covered in this report but the reader is urged to explore.

## References

1. Chichak, K. S.; Cantrill, S. J.; Pease, A. R.; Chiu, S.-H.; Cave, G. W. V.; Atwood, J. L.; Stoddart, J. F. *Science* **2004**, *304*, 1308-1312.
  2. Pentecost, C. D.; Chichak, K. S.; Peters, A. J.; Cave, G. W. V.; Cantrill, S. J.; Stoddart, J. F. *Angew. Chem. Int. Ed.* **2007**, *46*, 218-222.
  3. Flood, A. H.; Stoddart, J. F.; Steurman, D. W.; Heath, J. R. *Science* **2004**, *306*, 2055-2056.
  4. Deng, W.-Q.; Flood, A. H.; Stoddart, J. F.; Goddard III, W. A. *J. Am. Chem. Soc.* **2005**, *127*, 15994-15995.
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## Invited Lectures:

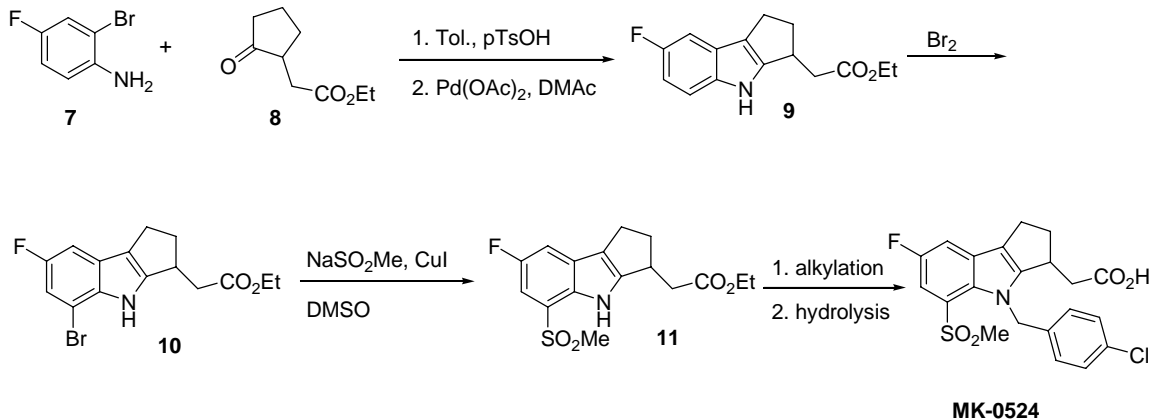
### **“The Search for the Ultimate Process for the Production of MK-0524 a Prostaglandin D2 Receptor Antagonist. An Unprecedented Asymmetric Hydrogenation of an Indole Exo-Cyclic Trisubstituted $\alpha,\beta$ -Unsaturated Acid”**

*Michel Journet (Merck & Co., Inc.)*

Prostaglandin D2 is the major metabolite of arachadonic acid produced by mast cells in response to an antigen challenge. The excess production of prostaglandin D2 is believed to cause inflammation in diseases such as asthma and allergic rhinitis. Therefore, antagonists of the prostaglandin D2 receptor are envisioned to be beneficial for the treatment of a variety of allergic responses. Dr. Journet described the synthesis and process development to prepare Merck's prostaglandin D2 receptor antagonist MK-0524.

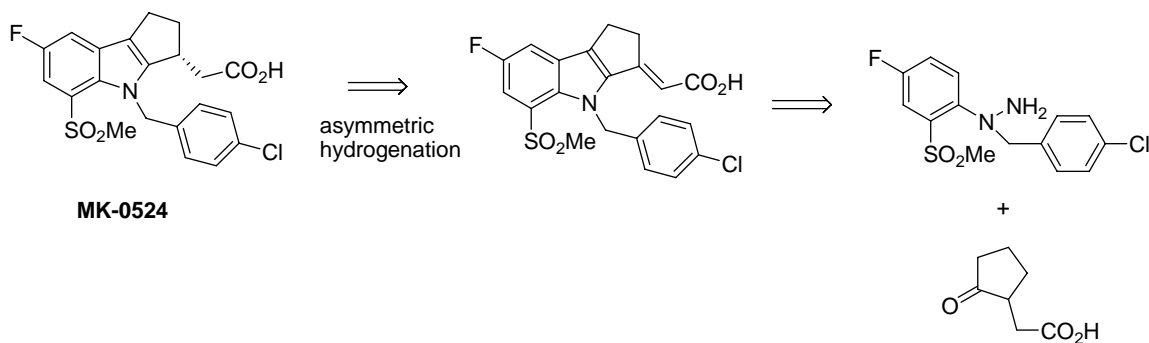
An early synthesis is shown in Scheme 1. In the key step to build the framework, amine **7** was condensed with ketone **8** to form an imine intermediate which was subjected to an intramolecular Heck cyclization catalyzed by palladium acetate to furnish **9**. Bromination of **9** provided **10** which was subjected to a copper catalyzed installation of the sulfone moiety to give **11**. Finally, alkylation and hydrolysis provided MK-0524.

### Scheme 1



A second more efficient process was described. A retrosynthetic analysis is shown in Scheme 2. The key bond forming reaction step was via a Fischer Indole reaction. The key step to induce the asymmetry was accomplished through asymmetric hydrogenation. A variety of ruthenium and rhodium catalysts with chiral phosphine ligands were explored and gave good levels of asymmetric induction (85-92% ee). More details on this asymmetric hydrogenation has been published (David M. Tellers, J. Christopher McWilliams, Guy Humphrey, Michel Journet, Lisa DiMichele, Joseph Hinksmon, Arlene E. McKeown, Thorsten Rosner, Yongkui Sun, and Richard D. Tillyer *J. Am. Chem. Soc.* **2006** *128*, 17063 – 17073).

### Scheme 2



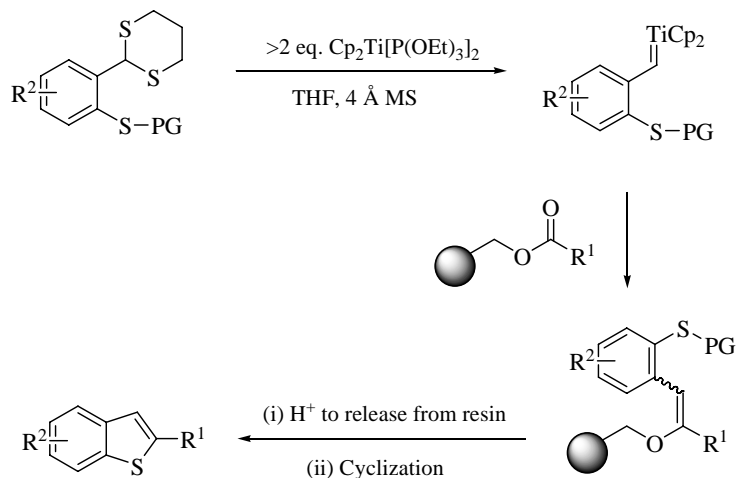
## “Diversity Oriented Synthesis of Privileged Heterocycles using Organotitanium Chemistry”

*Dr. Richard C. Hartley (University of Glasgow, UK)*

Dr. Hartley described how new titanium alkylidene reagents can be used to convert resin-bound esters into a range of such privileged structures: indoles, benzofurans, benzothiophenes, quinolines, piperidines and cyclic imines. Titanium(IV) benzylidenes (Schrock carbenes) bearing a masked sulfur nucleophile in the ortho position were generated from thioacetals with use of low-valent titanocene complex  $\text{Cp}_2\text{Ti}[\text{P}(\text{OEt})_3]_2$  and alkylidenated Merifield resin-bound esters to give enol ethers. Treatment of the resin-bound enol ethers with a 5:5:90 mixtures of TFA, TFAA and dichloromethane led to cleavage from resin, removal of the *tert*-

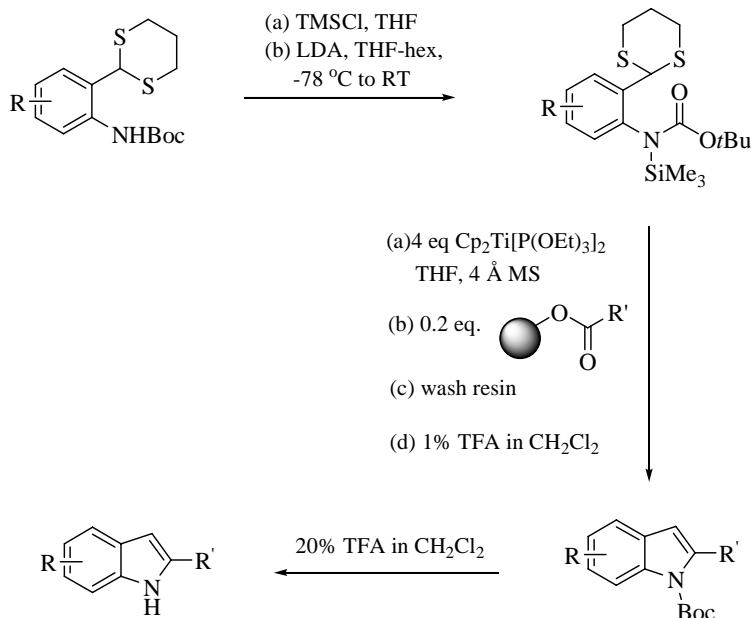
butyldimethylsilyl protecting group and concomitant cyclization to complete the traceless solid-phase synthesis of benzothiophenes (Scheme 1).

**Scheme 1**



In addition, the group has synthesized *N*-Boc indoles by employing of an unusual nitrogen protecting group, *N*-silylated *tert*-butyl carbamate. The *N*-silylated carbamates were added to 4 equiv of  $\text{Cp}_2\text{Ti}[\text{P}(\text{OEt})_3]_2$  in THF, and the resulting reagents were used to bezyldenate esters. The resin was washed and dried and treated with 1% TFA to give the *N*-Boc indoles in good yields and high purities after removal of solvent (Scheme 2).

**Scheme 2**

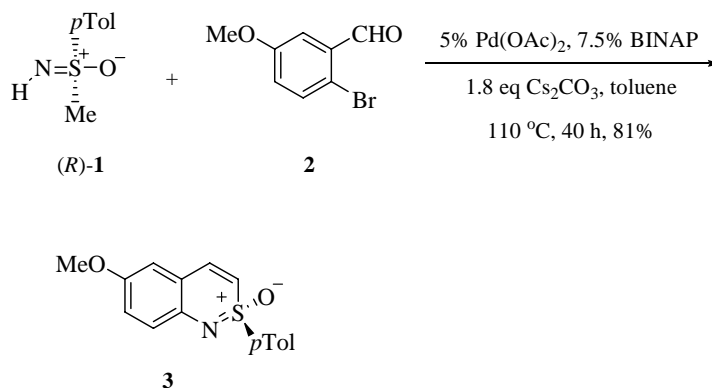


## “Benzothiazines in Organic Synthesis”

Michael Harmata (Dept. of Chemistry, University of Missouri-Columbia)

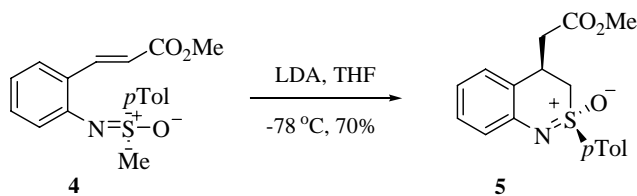
Professor Harmata showed the one-pot synthesis of enantiomerically pure benzothiazines via the reaction of enantiomerically pure N-H sulfoximines and *ortho*-bromobenzaldehydes (Scheme 1). This process involves the Buchwald-Hartwig reaction followed by an intramolecular condensation.

Scheme 1

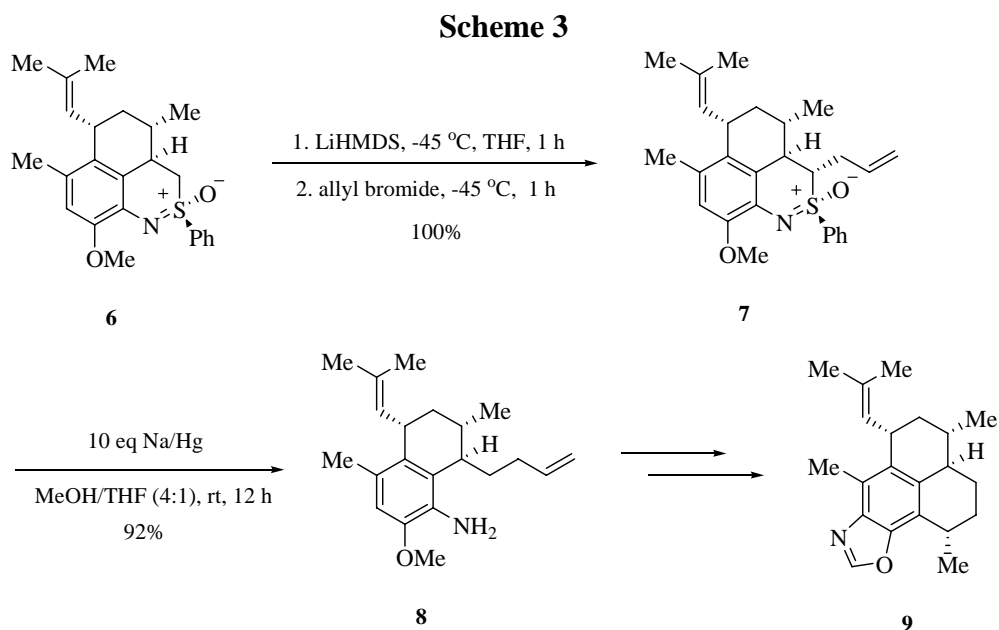


The Harmata group also demonstrated a single example of a reaction involving an intramolecular addition of a sulfoximine carbanion to an  $\alpha,\beta$ -unsaturated ester (Scheme 2). This reaction was completely stereoselective.

Scheme 2



This methodology was also used to synthesize a naturally occurring antitubercular agent pseudopteroxazole **9**. The enantioselective total synthesis of pseudopteroxazole was organized around the use of a stereoselective intramolecular addition of a sulfoximine carbanion to an  $\alpha,\beta$ -unsaturated ester to form an enantiomerically pure benzothiazine (Scheme 3).

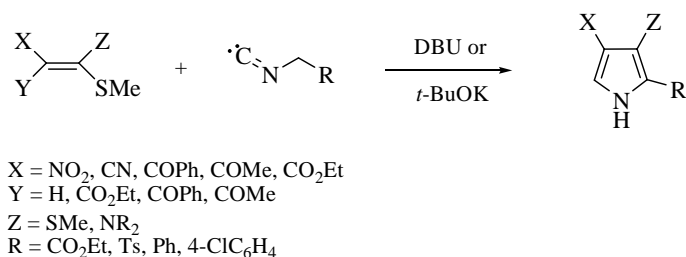


**“Polarized Ketene *S,S*- *N,S*- and *N,N*-acetals: Versatile Building Blocks for Synthesis of Biologically Active Heterocycles”**

*H. Ila (Indian Institute of Technology, Kanpur, India)*

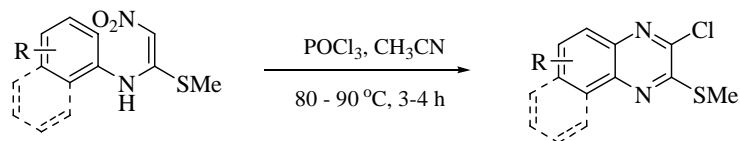
Professor Ila's group has developed an efficient route for regioselective synthesis of 2,3,4-substituted pyrroles allowing precise control over the introduction of a number of substituents and functionalities (tosyl, carbalkoxy, aryl, cyano, nitro, acetyl, benzoyl, cyclic amines, etc.) at the three positions of the pyrrole ring via 1,3-dipolar cycloaddition of readily accessible polarized ketene *S,S*- and *N,S*-acetals with carbanions derived from activated methylene isocyanides (Scheme 1).

**Scheme 1**



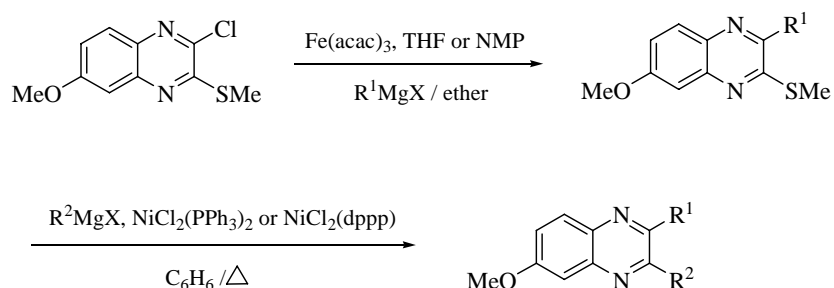
Professor Ila also presented a novel regioselective route for the synthesis of substituted and fused 3-chloro-2-(methylthio)quinoxalines through POCl<sub>3</sub>-mediated heteroannulation of a range of  $\alpha$ -nitroketene *N,S*-anilinoacetals (Scheme 2).

### Scheme 2



The 3-chloro and 2-methylthio groups in quinoxaline could be displaced by alkyl or aryl groups by sequential iron- and nickel-catalyzed cross-coupling reactions with the appropriate Grignard reagents as shown in Scheme 3.

### Scheme 3



### Poster:

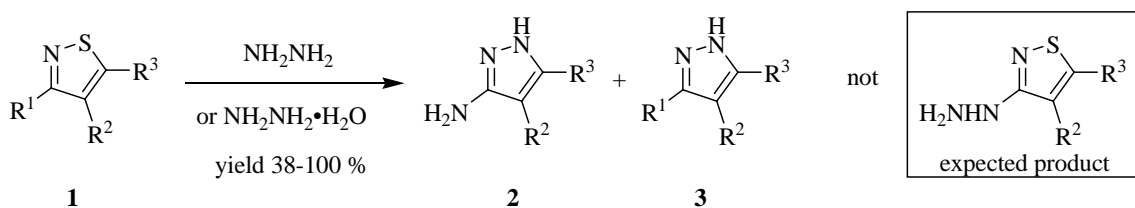
#### “The Conversion of Isothiazole into Pyrazole with Hydrazine”

*Herakilidia A. Ioannidou and Panayiotis A. Koutentis, University of Cyprus*

The investigation of a serendipitous conversion of 3-chloro-5-phenylisothiazole-4-carbonitrile into 3-amino-5-phenyl-1H-pyrazole-4-carbonitrile upon treatment with hydrazine has led to a simple and efficient method of obtaining substituted pyrazoles.

In the primary reaction a substituted isothiazole (**1**) is reacted in neat hydrazine hydrate or anhydrous hydrazine to give the unexpected pyrazole product (Scheme 1). Using a variety of substituents it was found that if R<sup>1</sup> is a good leaving group then 3-aminopyrazoles (**2**) are formed, however, if R<sup>1</sup> is a poor leaving group then 3(R<sup>1</sup>-substituted)pyrazoles (**3**) are obtained.

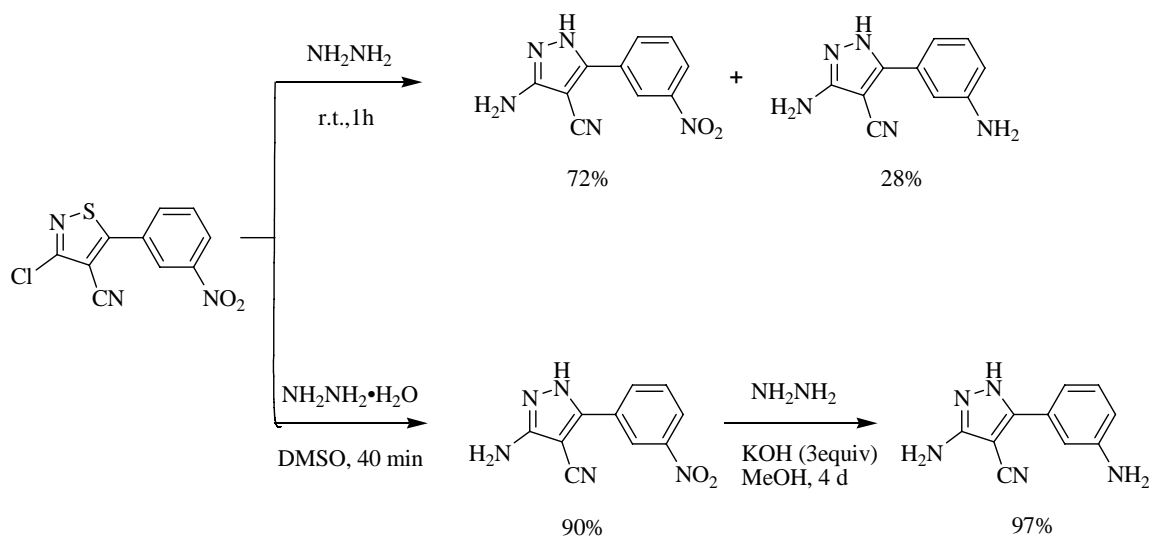
### Scheme 1



$\text{R}^1 = \text{Cl}, \text{NH}_2, \text{BnNH}, \text{morpholine}, \text{MeO}$   
 $\text{R}^2 = \text{CN}$   
 $\text{R}^3 = \text{Ph}, \text{various substituted phenyl groups}$

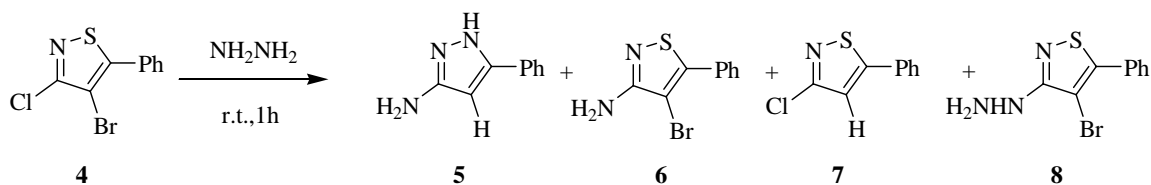
In the case of 3-Cl-5-(3-nitrophenyl)-isothiazole-4-carbonitrile reaction with hydrazine afforded a second product. Analysis of the product revealed it to be 3-amino-5-(3-aminophenyl)-pyrazole-4-carbonitrile. The reduction of the nitro group was prevented by using hydrazine monohydrate in DMSO. The nitro product can then be converted exclusively to the aniline by treatment with hydrazine in methanol. (Scheme 2)

### Scheme 2



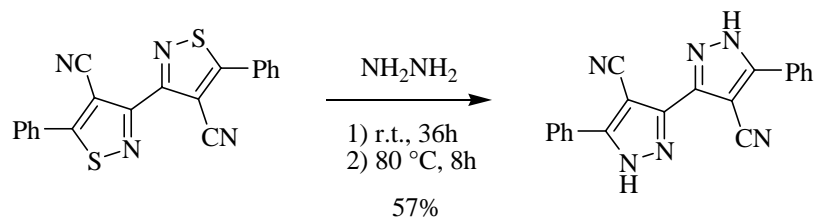
The presence of a bromo substituent on the isothiazole ring led to a complex mixture of products (5, 6, 7, and 8). Although changes in time, temperature, and reaction solvents were explored the mixture always afforded the 3-hydrazino-isothiazole target (8) as the major product. (Scheme 3)

### Scheme 3



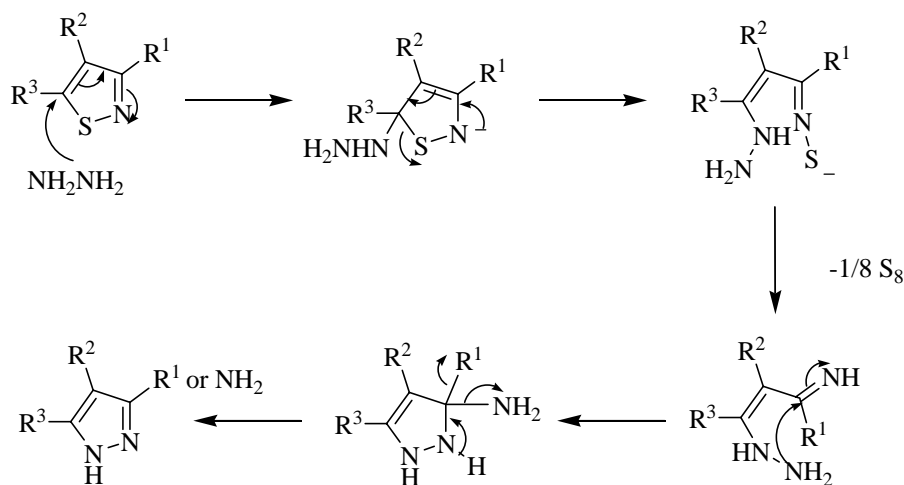
The conversion shown in scheme 3 was successfully extended to the more complex isothiazole dimer as seen in Scheme 4.

**Scheme 4**



A possible mechanism was also provided for the conversion. The hydrazine first attacks the ring carbon adjacent to the sulfur atom, pushing a negative charge onto the ring nitrogen. The extra electrons on the nitrogen reforms the double bond with the carbon and breaks the sulfur-carbon bond. The sulfur is expelled as elemental sulfur (S<sub>8</sub>). Finally the lone pairs on the hydrazine nitrogen then react with the ring carbon kicking out either the amino group or R<sub>1</sub>. (Scheme 5)

**Scheme 5**



Although the mechanism has to be studied further a reliable and effective route to substituted pyrazoles was developed.

## References

I.C. Christoforou, P. A. Koutentis, *Org. Biomol. Chem.*, **2004**, 4, 3681

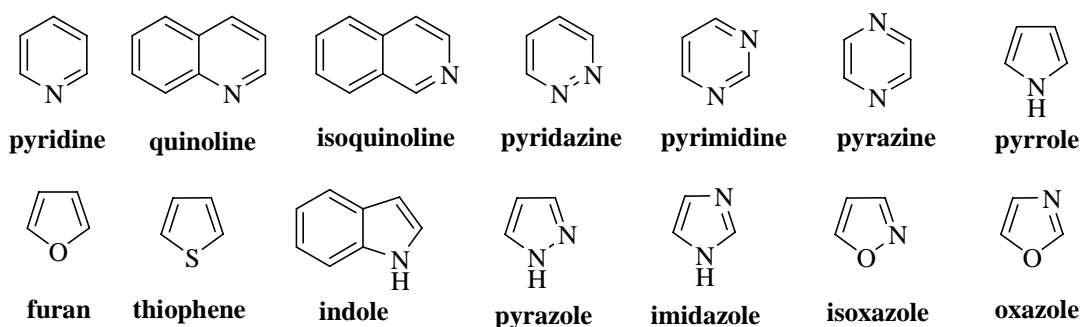
## Short Courses:

### “The Construction of Heterocycles from Non-Heterocyclic Precursors – Heterocyclic Ring Synthesis”

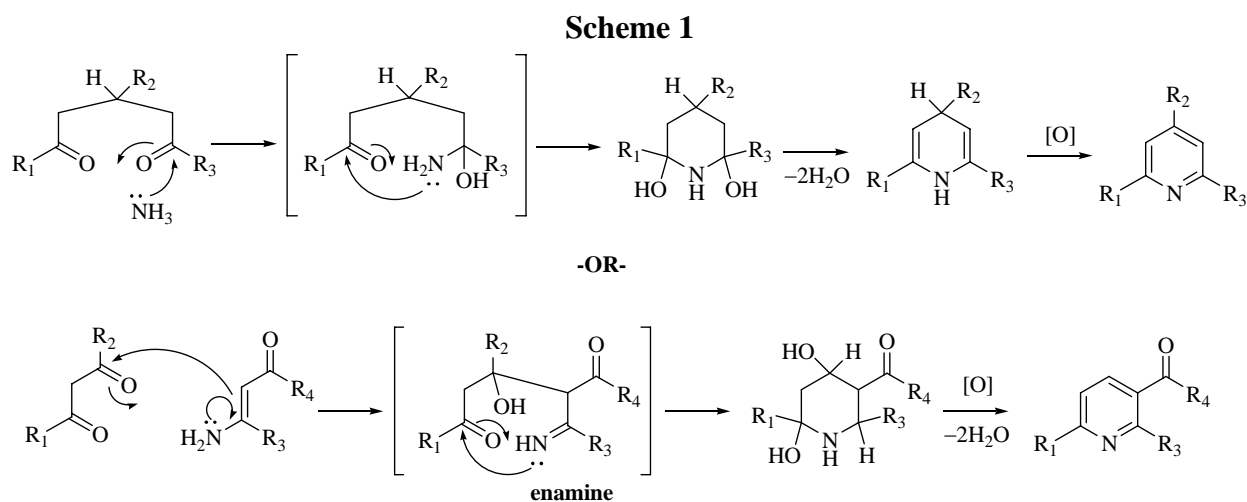
Professor John A. Joule, University of Manchester, UK

In a very comedic and dynamic pedagogical style, Professor Joule presented a course focused on the important routes to pyridines, quinolines, isoquinolines, pyridazines, pyrimidines, pyrazines, pyrroles, furans, thiophenes, indoles, pyrazoles, imidazoles, isoxazoles, and oxazoles (Figure 1). For the purpose of this report, only one representative example will be given for each of the mentioned heterocycles.

Figure 1

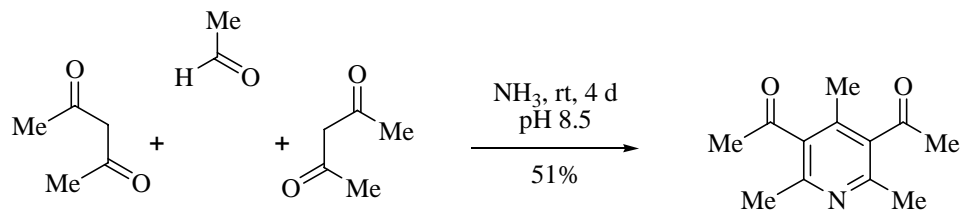


For most of the nitrogenous heterocycles, there are two general mechanisms (Scheme 1). The first mechanism is condensation of ammonia with a dicarbonyl derivative followed by a facile oxidation step. The second mechanism is the same as the first mechanism except that condensation occurs with an enamine instead of ammonia. Both mechanisms are shown for the preparation of substituted pyridines.



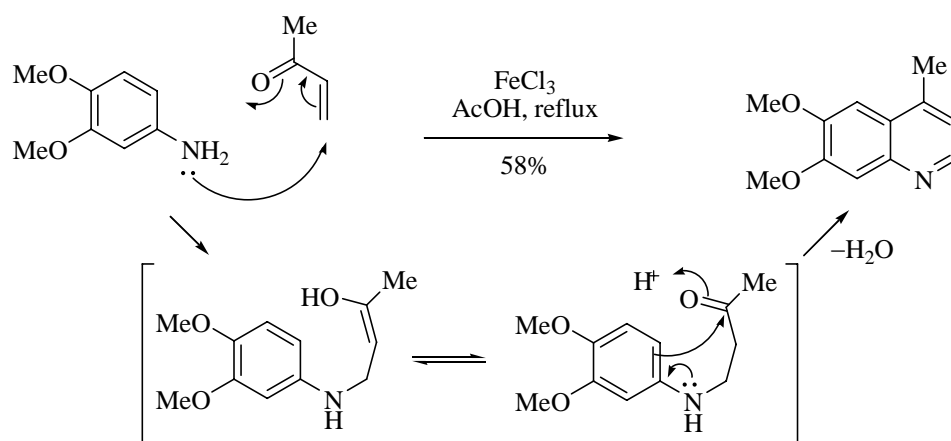
Another route to pyridines is the multi-component Hantzsch synthesis (Scheme 2).

### Scheme 2



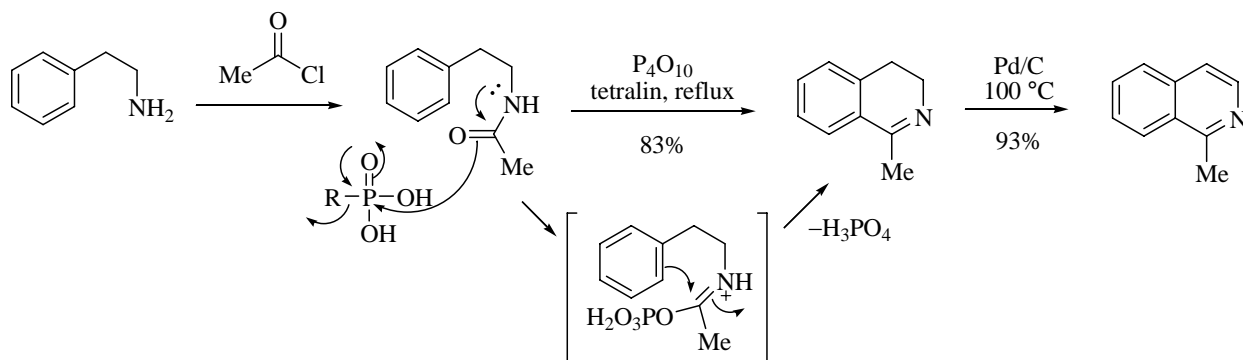
Typically, quinolines are accessed by condensing anilines with dicarbonyls as in the Combes and the Friedlander syntheses. In the traditional Skraup synthesis, the classical method for making quinolines, the aniline undergoes an aza-Michael addition with an  $\alpha$ ,  $\beta$ -unsaturated ketone followed by an intramolecular electrophilic substitution to yield the desired substituted quinoline (Scheme 3).

### Scheme 3



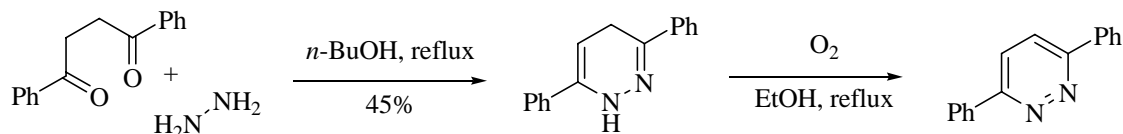
Isoquinolines are made by reacting aromatic aldehydes with aminoacetals as in the Pomeranz-Fritsch synthesis. In the Bischler-Napieralski synthesis, 2-arylethanamines are used to synthesize isoquinolines (Scheme 4).

### Scheme 4



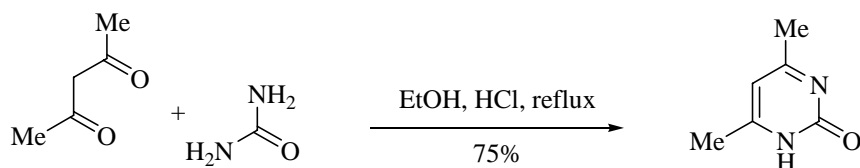
Condensations of 1,4-dicarbonyl compounds with hydrazines give rise to pyridazines (Scheme 5).

**Scheme 5**



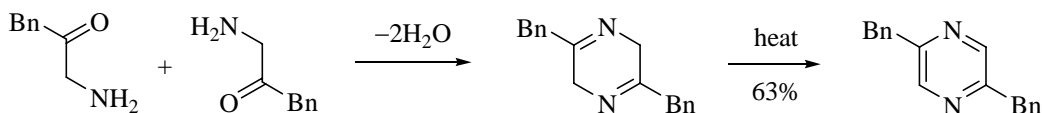
Condensations of 1,3-dicarbonyl compounds with amidines, guanidines, or ureas produce pyrimidines (Scheme 6).

**Scheme 6**



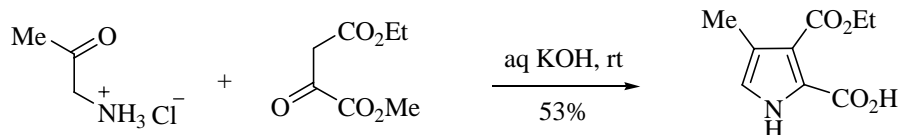
Pyrazines are synthesized by the condensations of 1,2-dicarbonyl compounds with 1,2-diamines or condensations of two equivalents of  $\alpha$ -amino ketones, which is shown below (Scheme 7).

**Scheme 7**



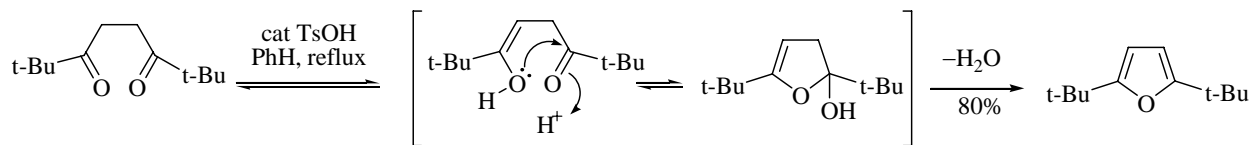
Pyrroles are typically obtained by the condensations of 1,4-dicarbonyl compounds with ammonia, also known as the Paal-Knorr synthesis. Similarly, the condensations of  $\alpha$ -amino-carbonyl compounds with activated ketones, also known as the Knorr synthesis, can also lead to pyrroles (Scheme 8). The salt is necessary to avoid self-condensation and must be liberated *in situ* or generated *in situ*.

**Scheme 8**



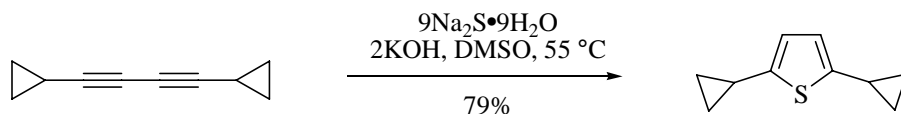
Condensations of 1,4-dicarbonyl compounds in the presence of catalytic amounts of toluenesulfonic acid yield furans (Scheme 9).

### Scheme 9



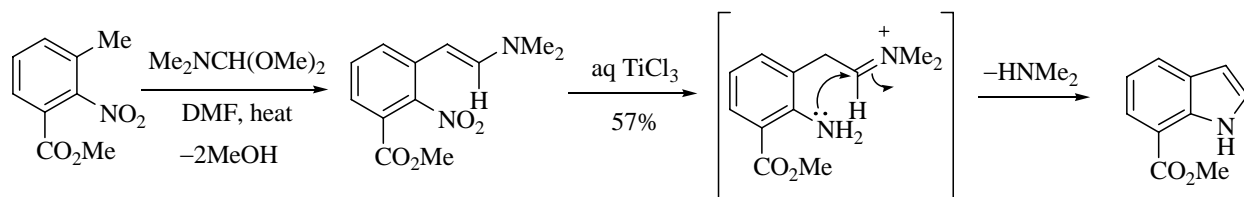
Thiophenes can be obtained in a manner similar to Scheme 9. Refluxing 1,4-dicarbonyl compounds in the presence of Lawesson's reagent (in effect replacing both oxygen atoms with sulfur atoms) in toluene will give the corresponding thiophenes in good yields. In addition, thiophenes can also be synthesized from diynes, serving as 1,4-dicarbonyl synthons, in the presence of sodium sulfide and potassium hydroxide (Scheme 10).

### Scheme 10



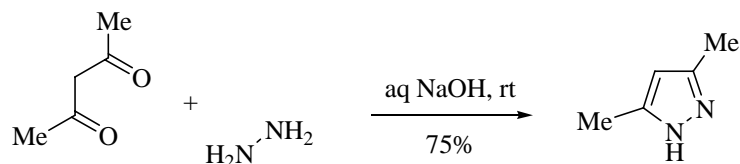
The classical approach to synthesize indoles is the Fischer indole synthesis utilizing arylhydrazones. Another method is the Leimgruber-Batcho synthesis (Scheme 11), which utilizes dimethylformamide dimethoxyacetal.

### Scheme 11



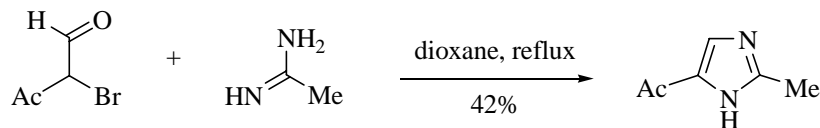
Condensations of 1,3-dicarbonyl compounds with hydrazines produce pyrazoles (Scheme 12).

### Scheme 12



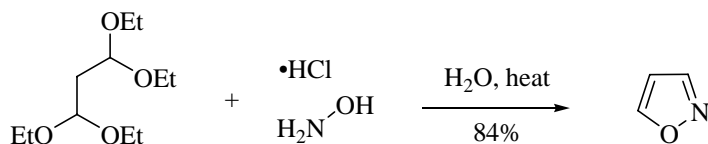
Condensations of  $\alpha$ -halo-ketones with amidines give imidazoles (Scheme 13).

### Scheme 13



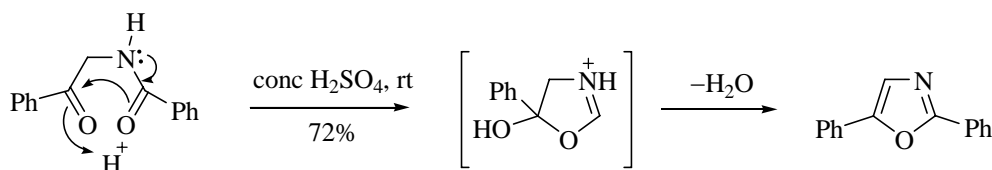
Similar to the synthesis of pyrazoles, isoxazoles are formed from a tetraethoxy moiety, i.e. a 1,3-dicarbonyl synthon, and hydroxylamine salt (Scheme 14).

### Scheme 14



Finally, condensations of 1,4-dicarbonyl compounds with a nitrogen atom in the starting chain in the presence of acid give rise to oxazoles (Scheme 15).

### Scheme 15



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## “Applications of Lithium and Palladium in Heterocyclic Chemistry”:

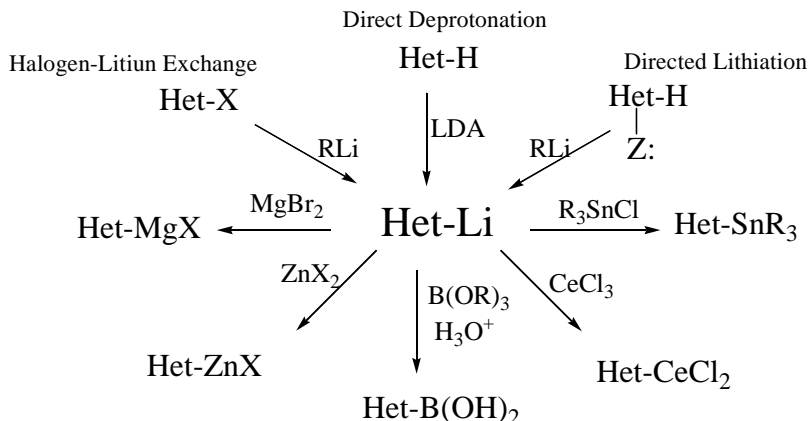
*Gordon W. Gribble, Dartmouth College*

### Part 1: Lithium in Heterocyclic Chemistry

Lithiation of heterocycles is generally performed by three methods. The first is halogen lithium exchange where a halogen on the heterocycle is replaced with a lithium atom. The second is direct deprotonation where the lithium atom directly replaces a hydrogen atom on the ring via an acid-base reaction. The third is directed lithiation where a substituent on the heterocycle directs the lithium atom to a position on the heterocycle via a hydrogen bonded intermediate.

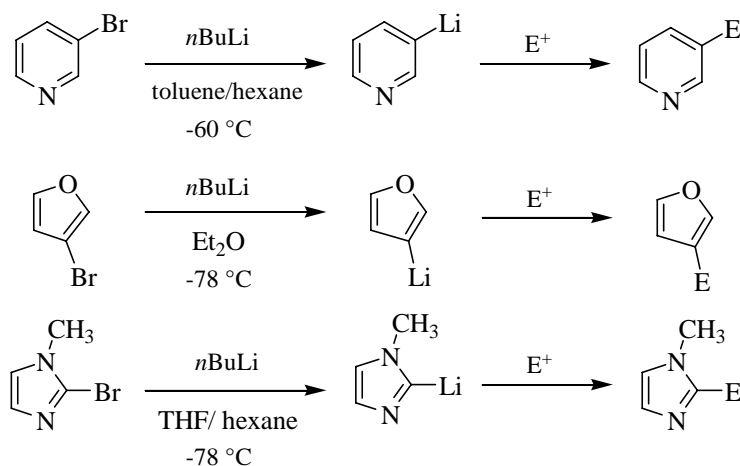
A lithiated heterocycle has several useful functions. Not only can it be used in reactions itself but it can be converted into other intermediates that can be used in various other reactions as shown in Scheme 1.

### Scheme 1



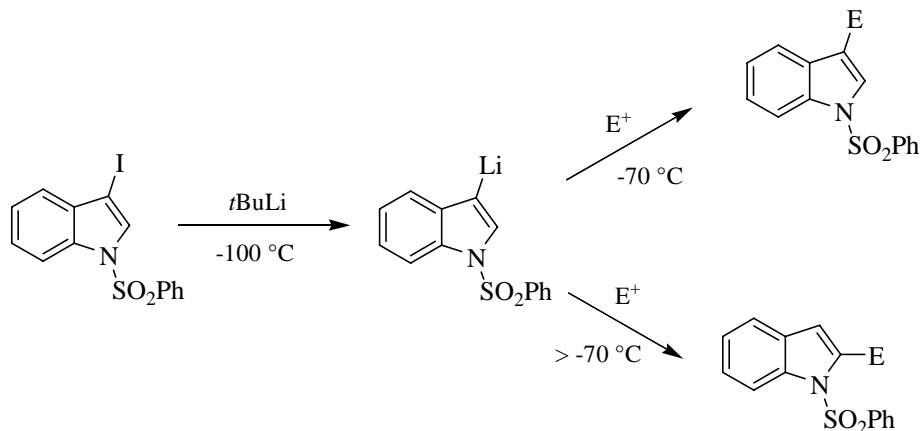
Halogen lithium exchange is directed in most cases by the position of the halogen on the heterocycle as seen in Scheme 2. These compounds are then usually treated with a variety of electrophiles.

### Scheme 2



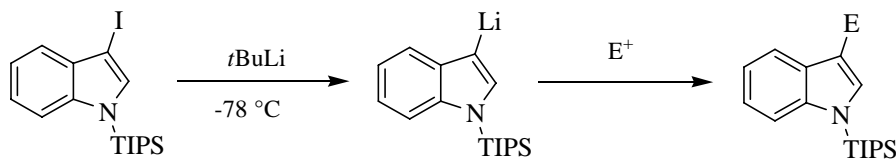
Lithium halogen exchanges are not always as straight forward as they may seem. The lithiation of a protected 3-iodoindole proceeds as expected until the reaction warms above  $-70^\circ\text{C}$  when a rearrangement of the lithium anion is seen from the 3-position to the 2-position giving an unexpected product (Scheme 3).

### Scheme 3



The addition of a TIPS protecting group on the nitrogen prevents this rearrangement presumably due to steric hindrance. (Scheme 4)

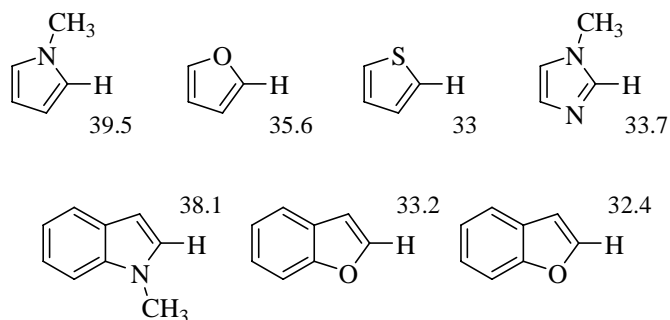
### Scheme 4



J. Bosch et al. *J. Org. Chem.*, **1994**, 59, 10

Lithiation by direct deprotonation is mediated by an acid-base reaction and therefore depends on the  $\text{pK}_{\text{a}}$ s of the heterocycle's protons. Below is a list of some common heterocycles and the  $\text{pK}_{\text{a}}$ s of their most acidic protons. (Scheme 5)

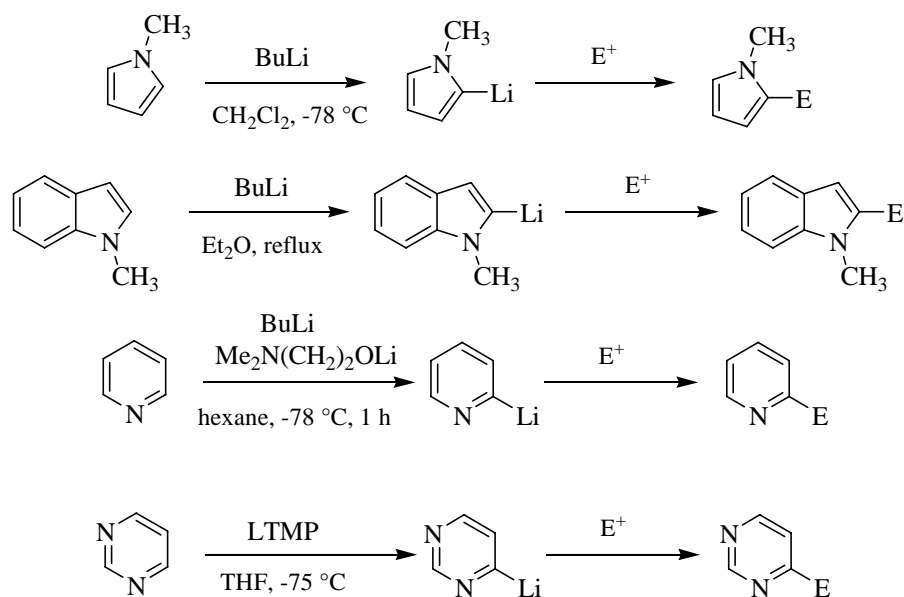
### Scheme 5



Fraser et al., *Can J. Chem.* **1985**, 63, 3505

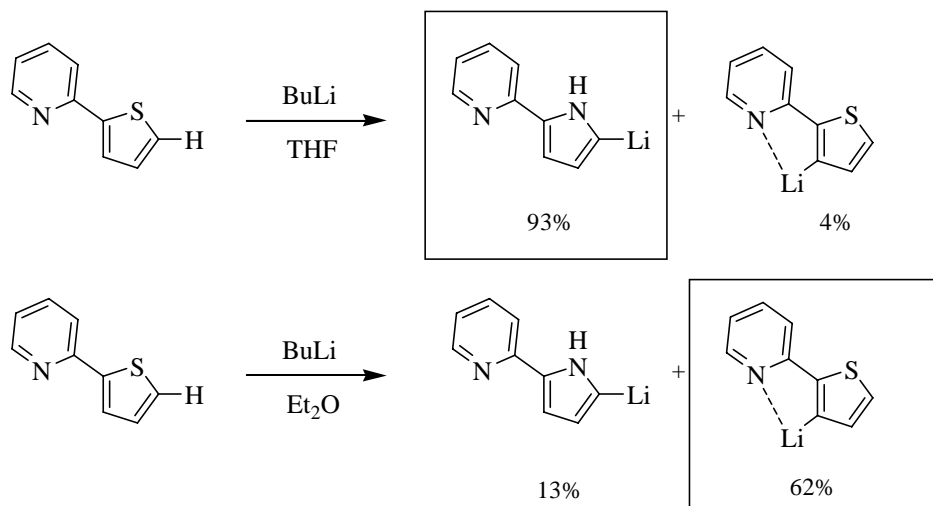
These reactions tend to be straight forward where the most acidic proton is replaced by the lithium atom and then reacted with the target electrophile. (Scheme 6)

### Scheme 6



Directed lithiation uses the directing groups to complex with the available alkyllithium and directs the lithium to an adjacent position via a Lewis acid mediated mechanism. Compare the following reactions using the same substrates, a simple solvent change can affect the reaction rates and outcome. (Scheme 7)

### Scheme 7

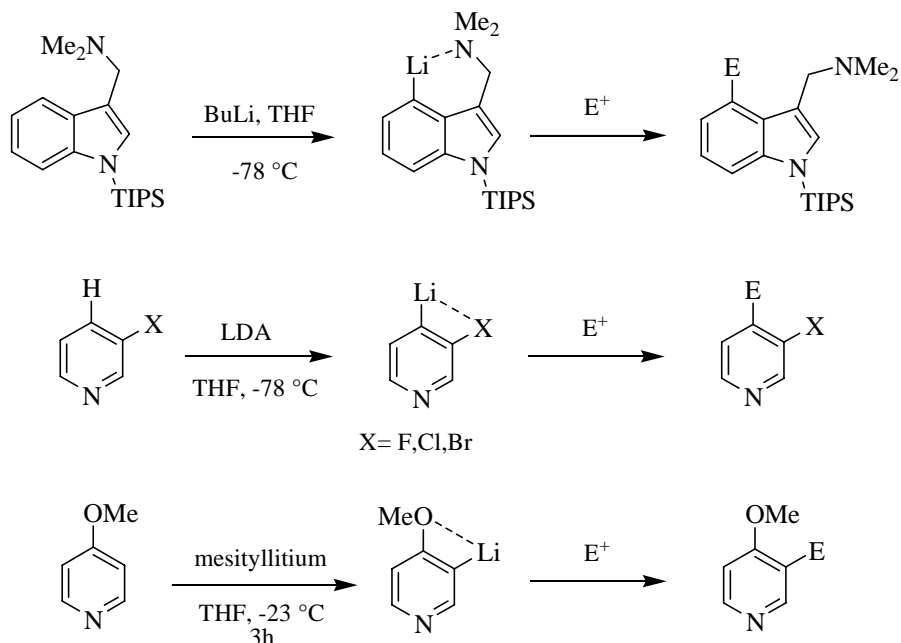


T. Gilchrist *et al.*, *Tetrahedron* **1990**, *46*, 2623

In the THF reaction the *n*-BuLi is dimeric and highly basic therefore it reacts through the direct deprotonation pathway. In the diethyl ether reaction the *n*-BuLi is tetrameric and acts like a Lewis acid favoring the directed metalation pathway.

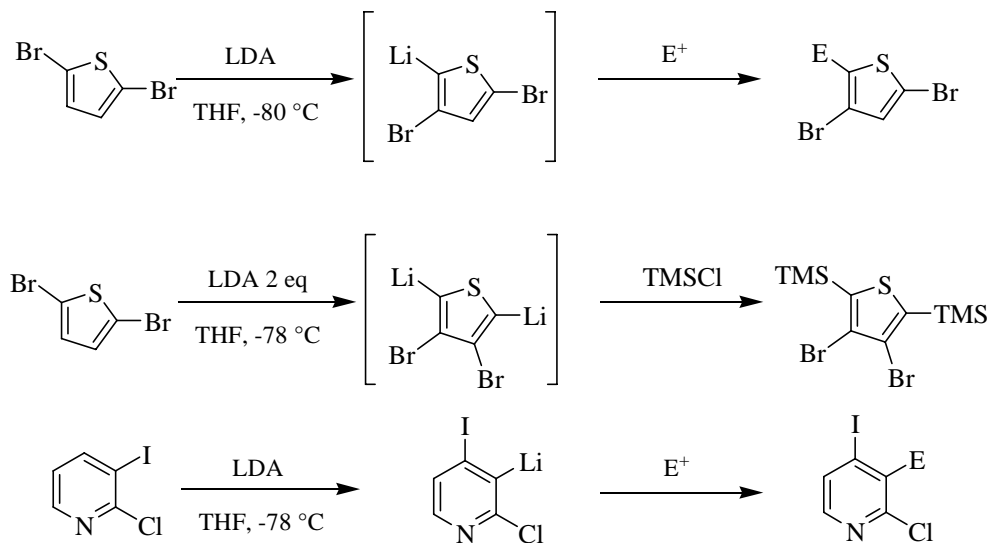
Some examples of other directed lithiations are shown in Scheme 8.

### Scheme 8



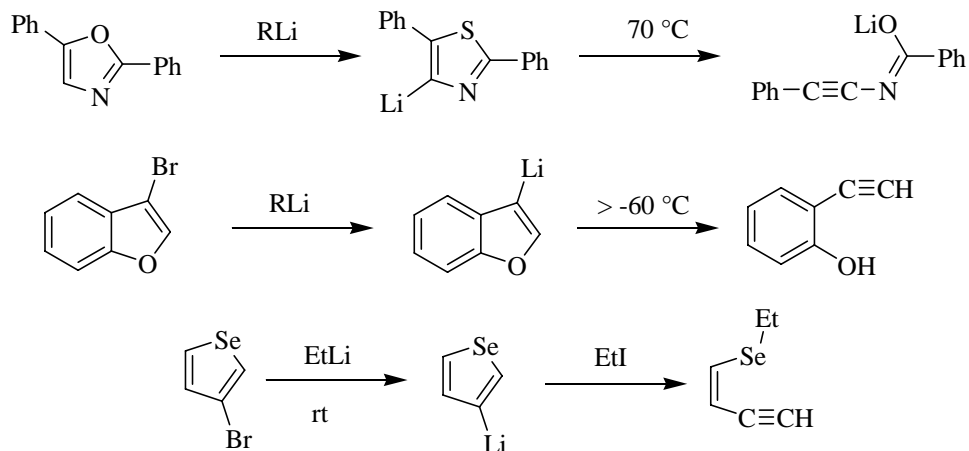
Lithium heterocycles are also known for the “Halogen-Dance” rearrangements, where the halogen atom “dances” to a position alpha to the lithium atom after the exchange. This is most likely due to the formation of an aryl carbanion affording a 1,2-rearrangement of the halogen. A few examples are shown in Scheme 9.

### Scheme 9



Lithiated heterocycles can also undergo ring opening reactions usually leading to the formation of a useful acetylene group. (Scheme 10)

**Scheme 10**



T. Gilcrist, *Adv. Heterocycl. Chem.*, **1987**, 41, 41.

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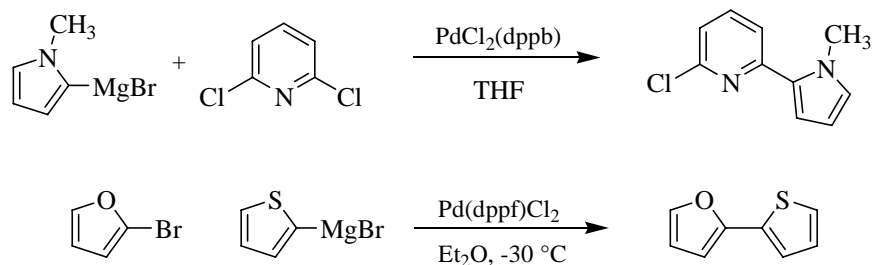
## Part II: Palladium reactions involving heterocycles.

Palladium is often an effective catalyst in initiating cross coupling reactions between aryls and heteroaryls. A great deal of work has been done in this area over the past several years. This report will simply touch on some of the more commonly used synthetic procedures listed below.

- 1) Murahashi-Kumada
- 2) Negishi
- 3) Suzuki-Miyaura
- 4) Stille
- 5) Hiyama
- 6) Heck
- 7) Sonogashira
- 8) Buchwald-Hartwig Amination
- 9) Buchwald Oxygenation

1.) The Kumada coupling successfully uses organolithium reagents in the presence of aryl or vinyl halogenides or triflates and a palladium catalyst. (Scheme 12) Murahashi has shown that these couplings can be performed with organolithium compounds in place of the aryl-Grignards. (Scheme 12)

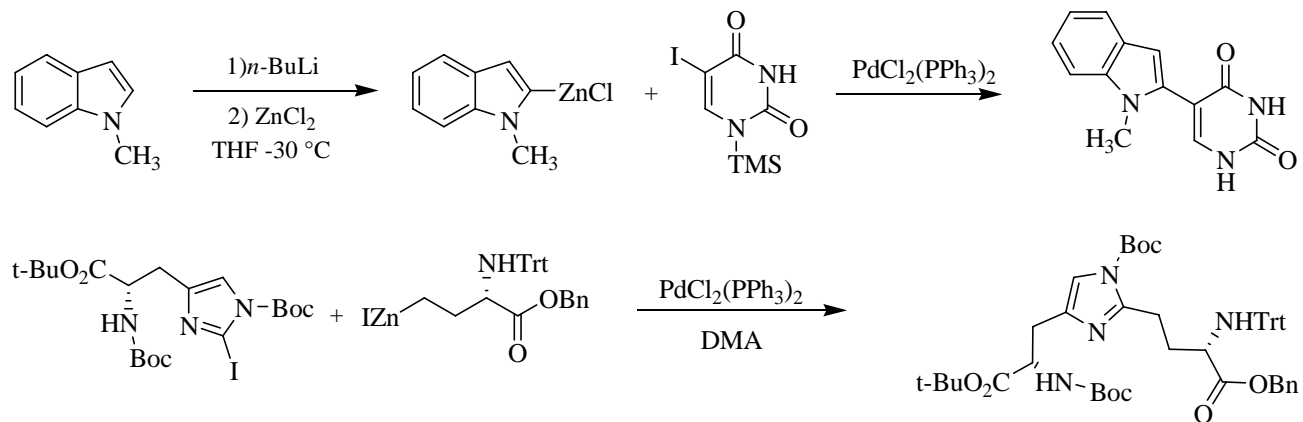
**Scheme 12**



M. Kumada *et al.*, *Tetrahedron Lett.* **1979**, 20, 1871

2) The Negishi coupling involves the reaction of an organozinc compound with a aryl or alkyl halide. Either one or both coupling reagents can be heterocyclic. (Scheme 13)

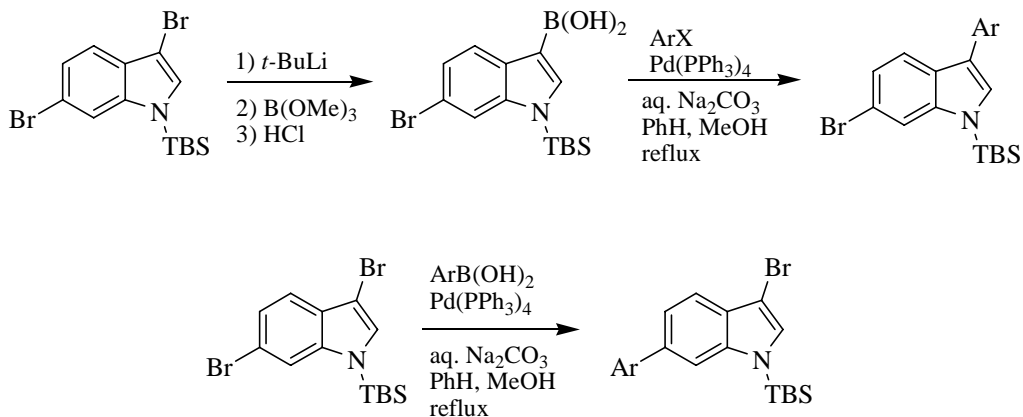
**Scheme 13**



P. Knochel *et al.*, *Chem Rev.*, **1993**, 93, 2117

3) With an aromatic boronic acid or boronate ester and an aryl halide a Suzuki-Miyaura coupling can be performed. (Scheme 14)

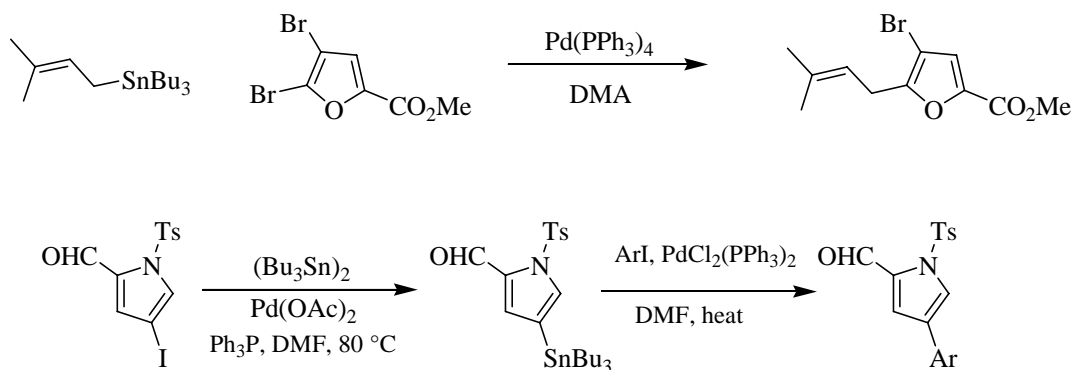
### Scheme 14



N. Miyaura, A. Suzuki *et al.*, *Chem. Rev.* **1995**, 95, 2457

4) A Stille coupling occurs when an aryl halide is reacted with an alkyl or aryl stannane reagent. (Scheme 15)

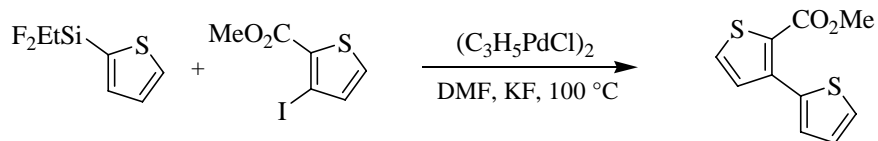
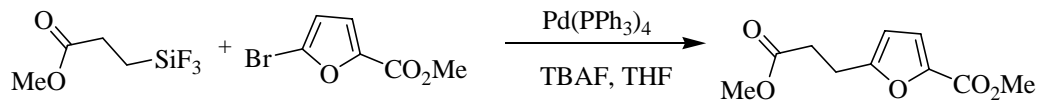
### Scheme 15



V. Farina *et al.*, "The Stille Reaction", Wiley New York, **1998**

5) A Hiyama coupling is a palladium-catalyzed cross-coupling reaction of organosilanes with organic halides or triflates. (Scheme 16)

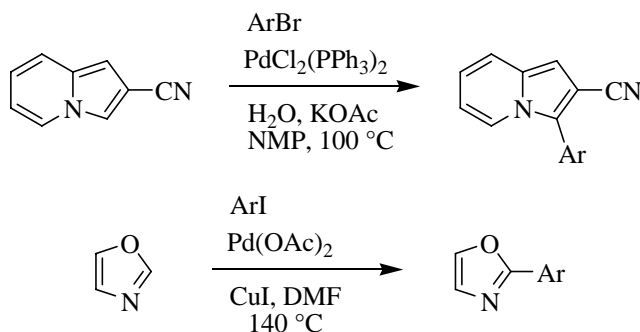
### Scheme 16



S. E. Denmark *et al.*, *Chem. Pharm. Bull.*, **2002**, 50, 1531

6) The Heck reaction couples an aryl, benzyl, or vinyl halide or triflate with an alkene in basic solution in the presence of a palladium catalyst. (Scheme 17)

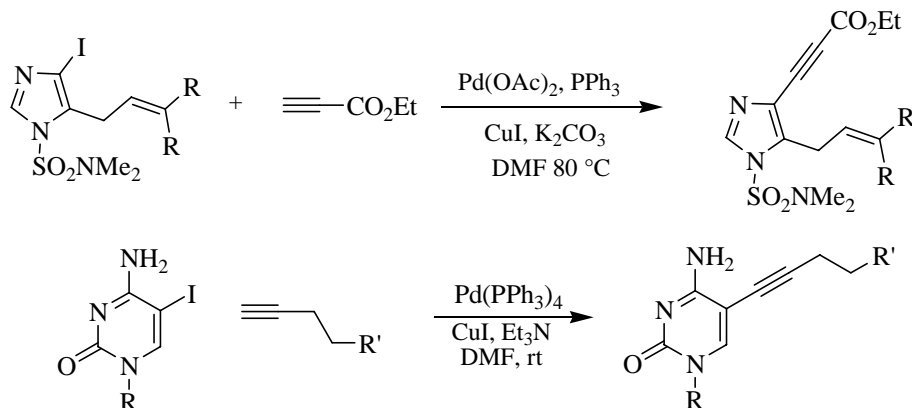
### Scheme 17



A. M. Echavarren *et al.*, *J. Am. Chem. Soc.*, **2006**, 128, 1066

7) Sonogashira couplings are reactions of terminal alkynes with aryl or vinyl halides in the presence of a palladium catalyst. (Scheme 18)

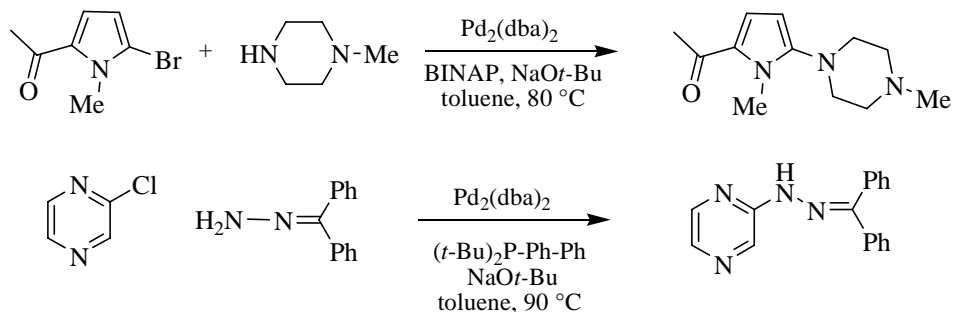
### Scheme 18



G. W. Gribble *et al.*, *Synth. Commun.*, **1992**, 22, 2129

8) A palladium-catalyzed synthesis of aryl amines, Buchwald-Hartwig aminations, use aryl halides or pseudohalides (for example triflates) and primary or secondary amines in cross coupling reactions. (Scheme 19)

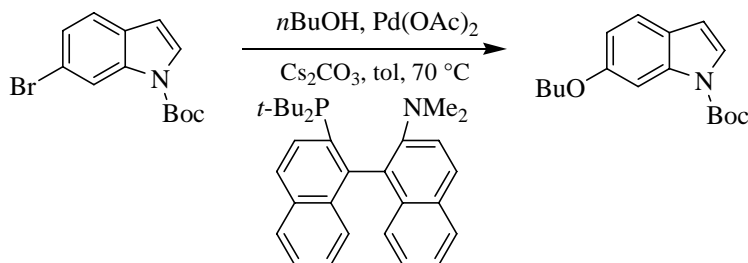
### Scheme 19



J. F. Hartwig, *Angew. Chem. Int. Ed. Engl.*, **1998**, 37, 2046

9) The Buchwald oxygenation is much like the above amination in that aryl halides are reacted with alcohols in the presence of a palladium catalyst to create aryl ethers. (Scheme 20)

### Scheme 20



S. L. Buchwald *et al.*, *J. Am. Chem. Soc.* **2001**, 123, 10770

Both palladium and lithium compounds are very useful in heterocyclic chemistry and what has been covered here is only a small representation of their overall efficacy. For more examples and information please find one of the many review articles published on these subjects or feel free to review the slides from the short course. Please contact Sang Lam, David Jenkins, Jun-Ho Maeng, or Peter Guzzo if interested in reviewing the slides.