



**Trip Report for**  
**“10<sup>th</sup> Annual Florida Heterocycle and Synthetic Conference”**  
**Gainesville, FL**  
**March 8-11, 2009**

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**Medicinal Chemistry Department**

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**Abstract:** *The 10th Annual Florida Heterocycle Conference was held March 8-11, 2009 in Gainesville, Florida. The roughly 170 attendees were evenly split between industrial and academic chemists and a strong international contingent was present. The conference consisted of eleven plenary lectures by well-known speakers, five short courses which broadly covered topics relevant to the synthesis and reactivity of heterocycles, and forty invited lectures on an array of topics. This report summarizes a selection of these presentations.*

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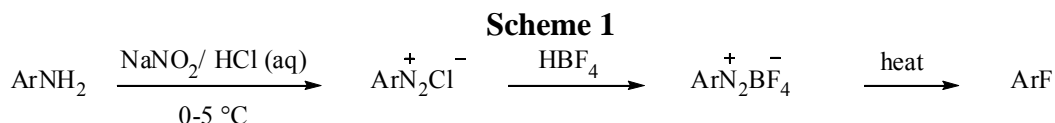
## “Overview of Fluorinated Aromatic and Heteroaromatic Compounds”

Short Course by William R. Dolbier, University of Florida, Gainesville, FL, USA

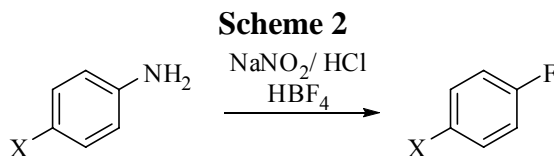
There are three classic ways to put fluorine substituents onto an aromatic ring system: The diazotization method; nucleophilic halogen/fluorine exchange; direct fluorination.

### The Diazotization Method

There are two diazotization methods for fluorinating aromatic ring systems. The first is the Balz-Schiemann method (Scheme 1). An aniline type amine is converted to the diazonium salt with nitrous acid (*via* sodium nitrite and aqueous hydrochloric acid). Treatment with fluoroboric acid gives a water insoluble salt, which precipitates from the aqueous solution and decomposes with heat to give nitrogen gas,  $\text{BF}_3$ , and an aryl fluoride.



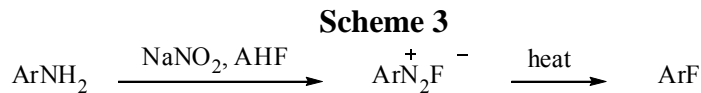
The Balz-Schiemann method works especially well with electron-donating groups on the ring system (Scheme 2). However, groups such as OH and  $\text{CO}_2\text{H}$  that increase water solubility are detrimental under Balz-Schiemann conditions.



X	Yield
Br	81%
OCH <sub>3</sub>	67%
NO <sub>2</sub>	40%
CO <sub>2</sub> H	19%

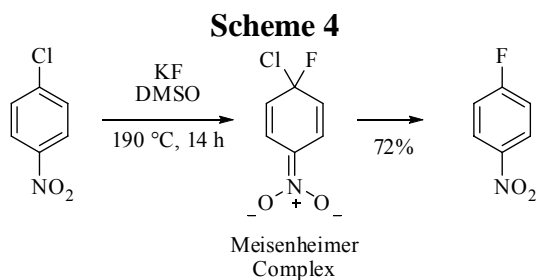
Reference: *J. Org. Chem.* **1961**, 26, 5149

The other diazotization method utilizes anhydrous hydrofluoric acid (AHF) (Scheme 3). Similarly to the Balz-Schiemann method, an aniline type amine is converted to a diazonium salt but with AHF. This salt can be directly decomposed with heat to give nitrogen gas and an aryl fluoride without ever isolating the diazonium salt. However, there are limitations because the HF mixture boils at roughly 40 °C and this can be too low for many decompositions. Just as with the Balz-Schiemann method, electron-donating substituents promote fluorination.



### Nucleophilic halogen/fluorine exchange

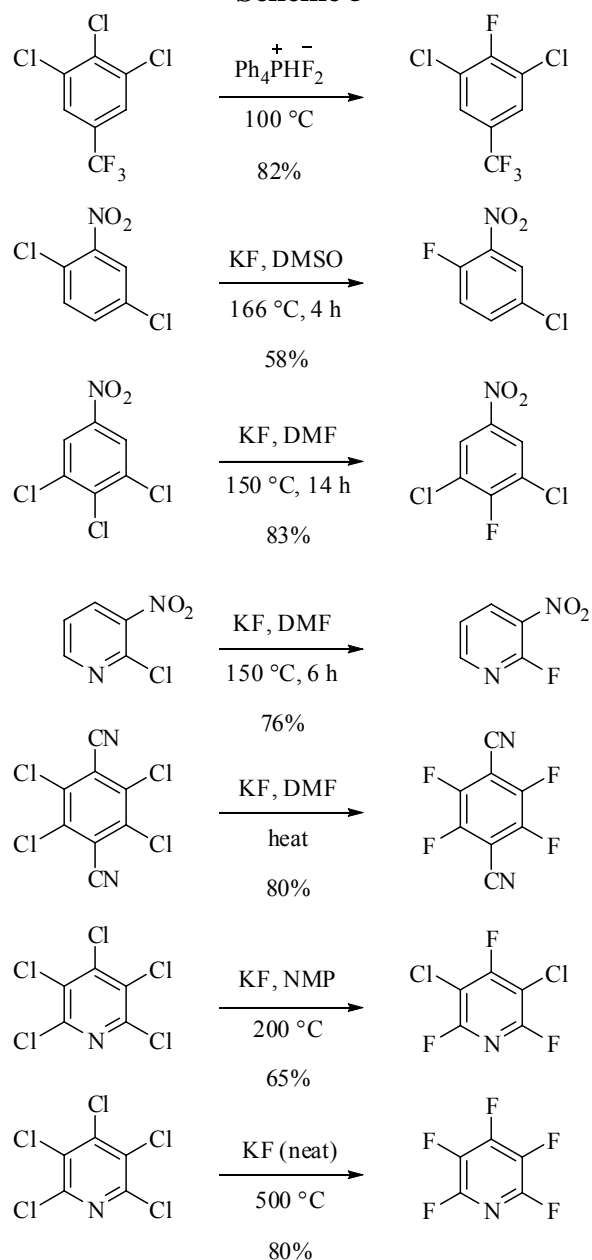
The halogen exchange method (Halex) converts an existing aryl halide into an aryl fluoride. A typical example is the conversion of *p*-chloro nitrobenzene to *p*-fluoro nitrobenzene (Scheme 4). Activating groups such as NO<sub>2</sub>, CN, COF, and SO<sub>2</sub>F (electron withdrawing) promote nucleophilic attack of F<sup>-</sup> on the chloro carbon (S<sub>N</sub>Ar) to give a Meisenheimer intermediate, which re-aromatizes to give *p*-fluoro nitrobenzene.



*J. Am. Chem. Soc.* **1956**, 78, 6034

Halex fluorinations, like most S<sub>N</sub>Ar reactions, work best with smaller halogens. Thus, the most commonly reported in the literature is the displacement of an aryl chloride. Electron withdrawing groups can promote selective chlorine displacement, (for examples see Scheme 5). Electron withdrawing groups effectively direct *para* displacement, as well as *ortho* displacement.

### Scheme 5

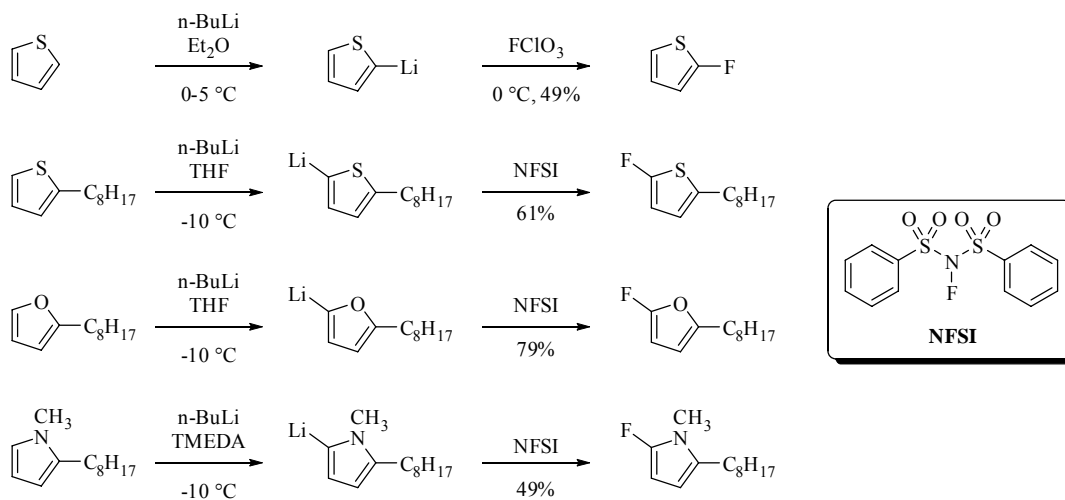


*J. Fluorine Chem.* **1989**, *44*, 291; *J. Am. Chem. Soc.* **1959**, *81*, 2674; *U.S.P.* **1977**, 3975424; *J. Chem. Soc.* **1965**, 594

### Direct Fluorination

There are many “direct” ways to incorporate a fluorine onto a heterocycle without a diazo or chloro intermediate. A popular method utilizes heterocyclic lithiation (Scheme 6). Treating a HetLi species with a source of fluorine gives a fluorinated heterocycle. A popular fluorine source is *N*-fluorodibenzenesulfonimide (NFSI).

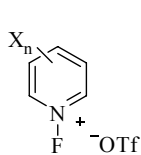
### Scheme 6



*J. Org. Chem.* **1971**, *36*, 2188; *J. Fluorine Chem.* **2003**, *124*, 159

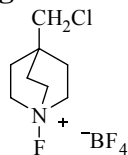
*N*-fluorinated compounds are often used because they are a good, stable source of electrophilic fluorine. Other popular *N*-fluorinated compounds are shown below (Figure 1).

Figure 1



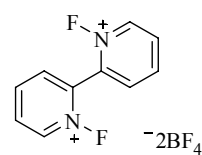
*J. Am. Chem. Soc.* **1990**, *112*, 8563

*J. Org. Chem.* **1991**, *56*, 5962



*J. Org. Chem.* **1993**, *58*, 2791

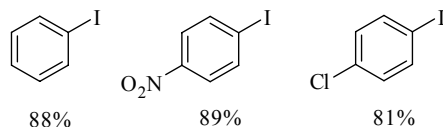
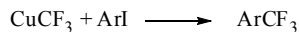
*Angew. Chem. Int. Ed.* **2005**, *44*, 192



*J. Org. Chem.* **1998**, *63*, 3379

Especially important to the field of medicinal chemistry is the incorporation of a trifluoromethyl group to an aromatic ring or aromatic heterocycle. There are many methods that make use of a nucleophilic  $\text{CF}_3$  source, but the most useful conditions, developed by Chen, use  $\text{CuCF}_3$  (Scheme 7).

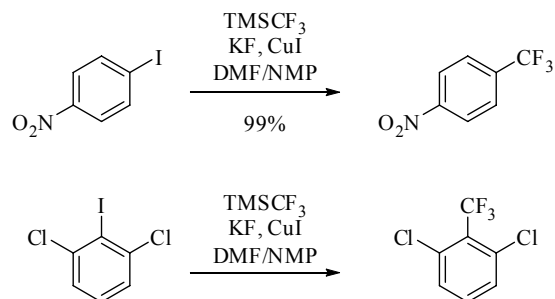
### Scheme 7



*Tetrahedron Lett.* **1991**, *32*, 7689

Another source of nucleophilic  $\text{CF}_3$  is  $\text{TMSCF}_3$  (Scheme 8). As seen in the literature  $\text{TMSCF}_3$  can be used to displace  $\text{ArI}$  compounds.

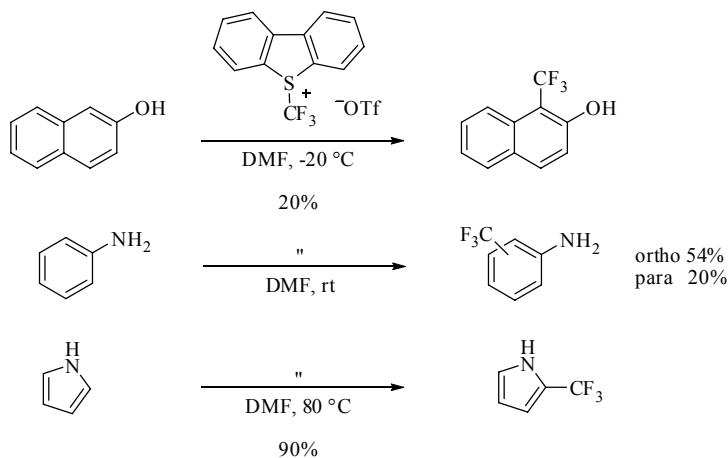
### Scheme 8



*Tetrahedron Lett.* **1991**, 32, 91; *Angew. Chem. Int. Ed.* **2006**, 45, 5432

Additionally, a CF<sub>3</sub> group can be introduced from an electrophilic source of CF<sub>3</sub>. One common example shown below is often used for enol ethers, but can also apply to aromatic systems (Scheme 9).

### Scheme 9



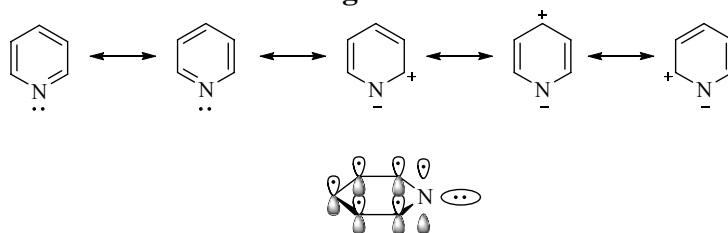
*Chem. Rev.* **1996**, 96, 1757

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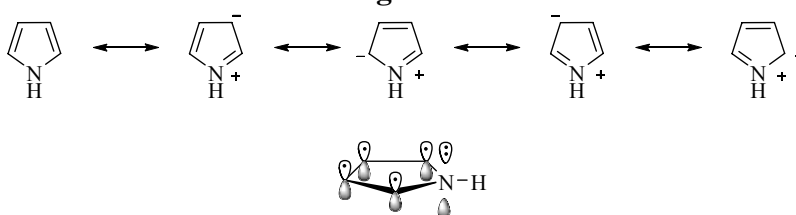
## “The Azoles – Reactions and Ring Synthesis”

*Short Course by John A. Joule, University of Manchester, Manchester, UK*

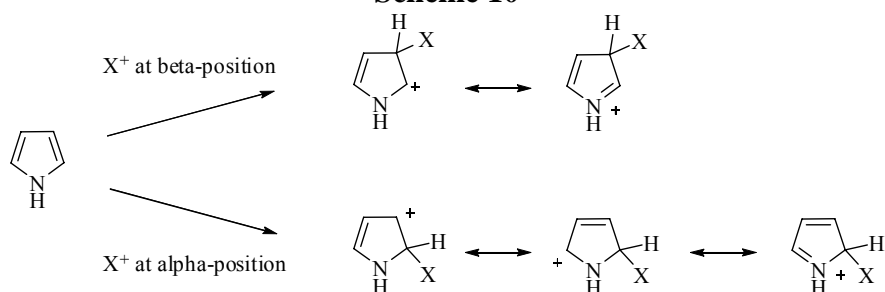
The course covered the reactivity and synthesis of pyrroles (including furan and thiophene analogs), and indoles. Although the reactivity and synthesis of pyridine was not covered, it was mentioned for comparison (Figure 2). Pyridine is an aromatic compound whose nitrogen is sp<sup>2</sup> hybridized and has a non-aromatic lone pair. Pyridine is both basic and nucleophilic at nitrogen.

**Figure 2**

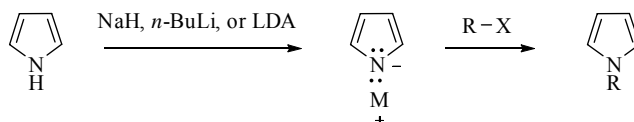
Pyrrole on the other hand is not basic and is not nucleophilic at nitrogen, but rather at the alpha and beta carbons. The pyrrole nitrogen is  $sp^2$  hybridized and does have a lone pair, but unlike pyridine it is a part of the aromatic sextet (Figure 3).

**Figure 3**

Since the alpha and beta sites are electron rich and hence nucleophilic, electrophilic substitution is facile. Although both sites are nucleophilic, substitution at the alpha site is roughly ten times faster than substitution at the beta site (Scheme 10).

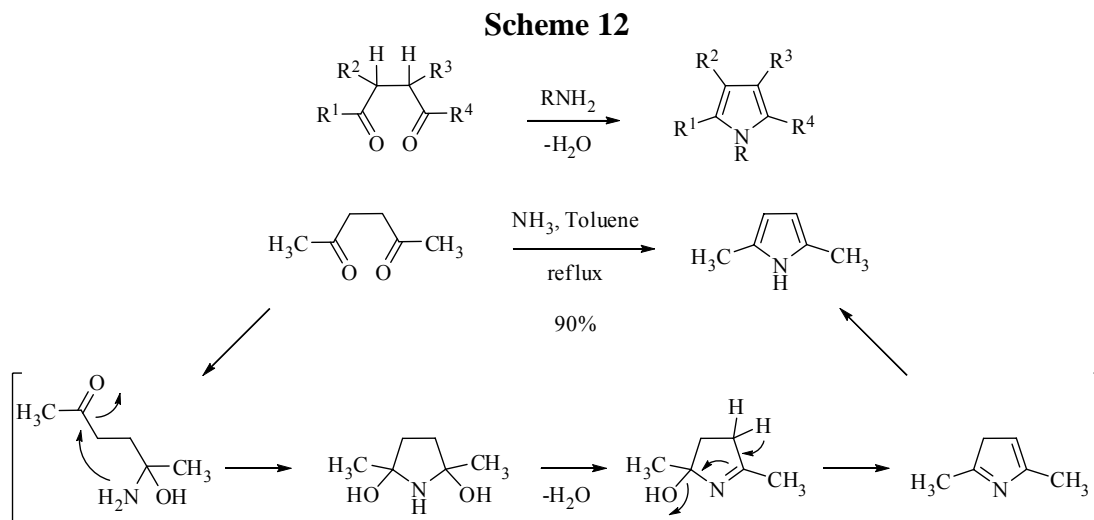
**Scheme 10**

If substitution at nitrogen is desired, then a strong base such as NaH, *n*-BuLi, or LDA is required to deprotonate the *N*-proton. The pyrrol anion is nucleophilic and will attack electrophilic sites (Scheme 11).

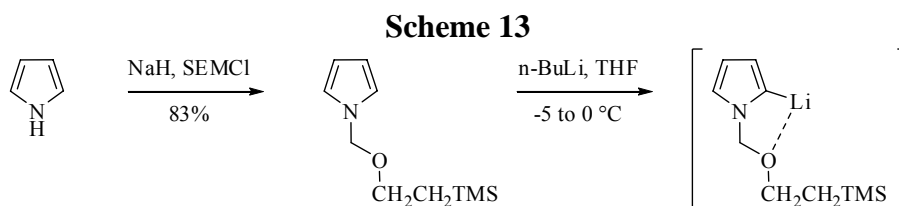
**Scheme 11**

Pyrroles can be made in a variety of ways, but the simplest comes from 1,4-diketones as in the Paal-Knorr synthesis (Scheme 12). In the first step an amine attacks one of the ketones to give a hemiaminal. The hemiaminal nitrogen attacks the second ketone in an

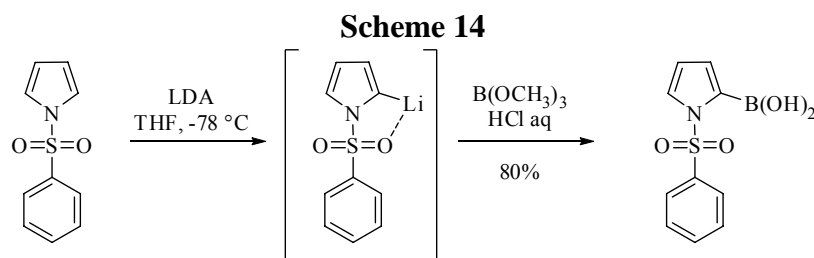
intramolecular fashion to give a pyrrolidine. The loss of two water molecules generates aromaticity, and a tautomerization yields the *N*-H pyrrole.



Pyrroles can be lithiated selectively at the alpha carbon under the correct conditions (Scheme 13). Alkylating the pyrrol anion with SEM-Cl incorporates an ether that can coordinate and direct lithium metal to the alpha carbon for subsequent chemistry. The alpha carbon also happens to be more acidic than the beta carbon, so both properties favor alpha-lithiation.

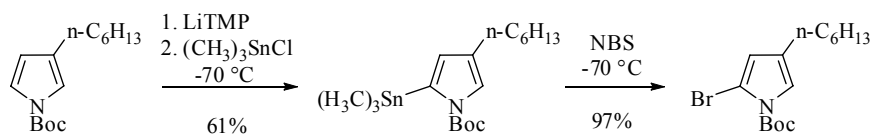


The same properties can be utilized to incorporate an alpha boronic acid (Scheme 14). The example shown uses a sulfonamide to direct lithiation however, instead of a SEM group.



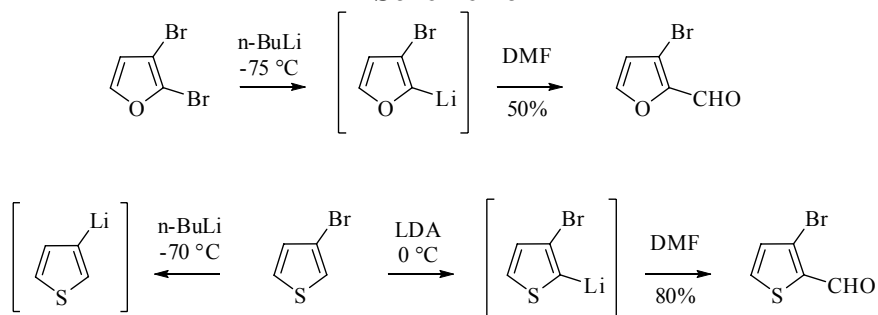
Alpha bromination can also be achieved by deprotonating the alpha carbon of the boc pyrrole with LiTMP. The lithiated pyrrole can be converted to the stannane, and then reacted further with NBS to yield the alpha brominated species (Scheme 15).

### Scheme 15



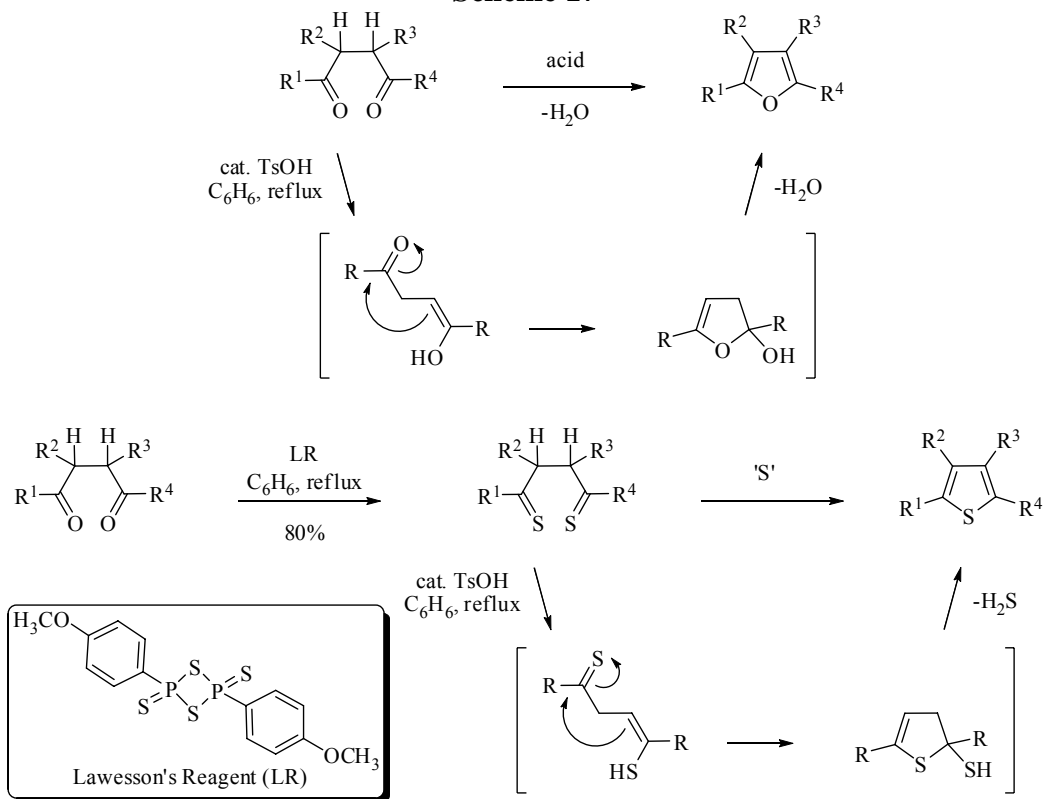
Furans and thiophenes are the oxygen and sulfur analogs of pyrrole. All three are aromatic, furan being the least aromatic and thiophene being the most aromatic because it is the most similar to benzene. Like pyrrole, furan and thiophene are nucleophilic at their alpha carbons (most electron density). These same properties can be utilized to alpha-lithiate, just as with pyrrole (Scheme 16). Even with a dibrominated furan, alpha-lithiation is favored. 3-Bromothiophene can undergo a lithium/halogen exchange at  $-70\text{ }^\circ\text{C}$ , or can undergo alpha-lithiation at  $0\text{ }^\circ\text{C}$ , leaving the beta-bromo intact.

### Scheme 16



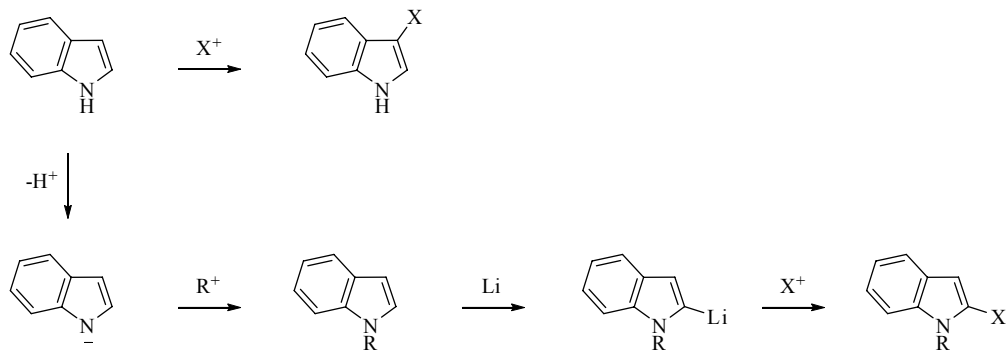
Similarly to pyrroles, furans and thiophenes come from 1,4-diketones (Scheme 17). Upon treatment with acid, 1,4-diketones enolize and condense in an intramolecular fashion to give a hemiacetal. Dehydration of the hemiacetal yields a furan. If the same 1,4-diketone is treated with Lawesson's reagent, a 1,4-dithiocarbonyl is given which can undergo the same cyclization described for furans.

### Scheme 17

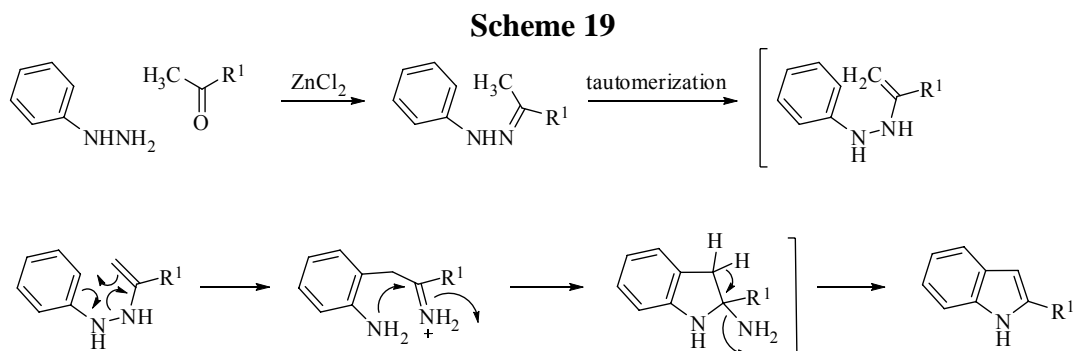


Indoles, like pyrroles, are neither basic nor nucleophilic at nitrogen. The nitrogen is sp<sup>2</sup> hybridized and has a lone pair in a 10 π-electron system. Because an indole is a pyrrole fused to a benzene ring, the beta carbon is more electron rich, and thus more nucleophilic. Treatment of indole with an electrophile will result in beta substitution. If alpha substitution is desired however, the indole must first be treated with a base to give the indolyl anion. Treatment with an electrophile will result in *N*-substitution. With the absence of an indole *N*-H, lithiation occurs at the alpha carbon (most acidic proton). Treatment of the lithiated species with an electrophile yields an alpha substituted indole (Scheme 18).

### Scheme 18



The most common way to make an indole would be the Fischer synthesis (Scheme 19). Beginning with aryl hydrazones, a tautomerization and rearrangement forms a new carbon-carbon bond between the ortho position of the aryl ring and the alpha position of former ketone. Aromatization occurs to form an aminal, followed by loss of ammonia to yield an indole. Choosing the appropriate ketone will dictate both alpha and beta substitution on the final indole.




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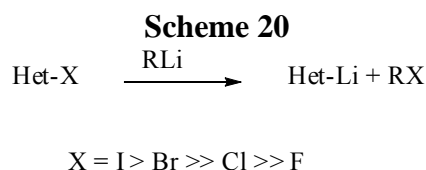
### “Applications of Lithium, Palladium, Magnesium, Gold, and Copper in Heterocyclic Chemistry”

*Short Course by Gordon Gribble, Dartmouth College, Hanover, NH, USA*

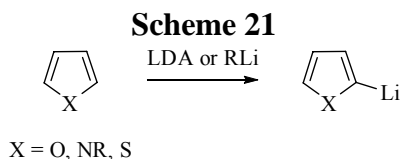
This course covered the generation and reactions of heteryllithiums, briefly covered some magnesium, gold, and copper chemistry, and finally palladium cross coupling reactions.

Heteryllithiums are generated three ways: Halogen-lithium exchange, direct deprotonation and directed-lithiations.

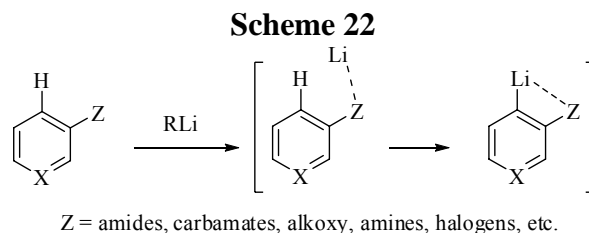
Halogen–lithium exchange occurs when a hetero-halide is treated with an organolithium reagent to give the corresponding hetero-lithium species, plus an organo-halide by-product. The reaction is not typically reversible because the lithium is often stabilized by the electron rich aryl compound. Typically lithium exchanges most readily with iodine and then bromine, but much more slowly with chlorine and fluorine atoms (Scheme 20).



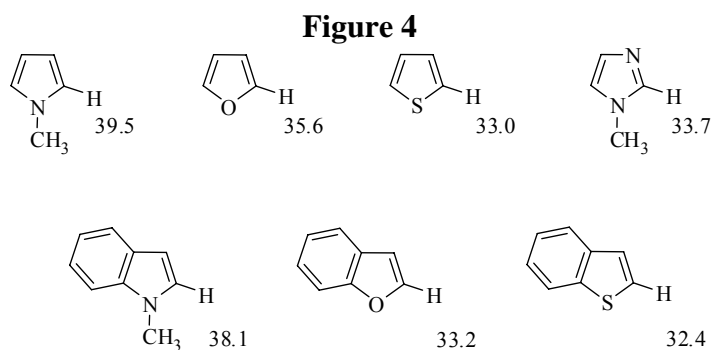
Direct deprotonation occurs when a lithium source is exposed to a hetaryl compound with a sufficiently acidic proton (Scheme 21). Again, the lithiated ring will often be more stable than the original organo-lithium species and will not reverse.



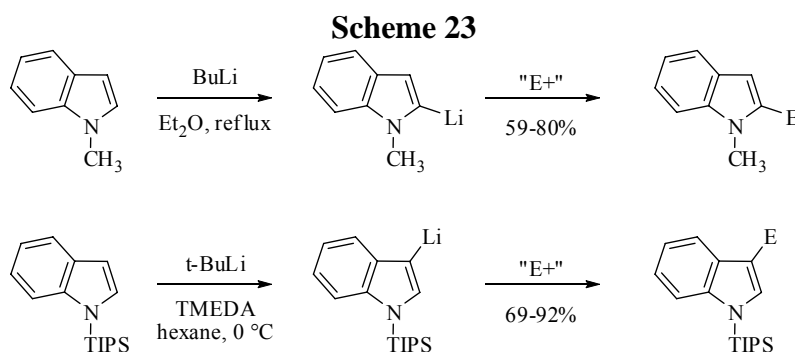
Directed lithiations are still direct deprotonations, but the deprotonation is directed by another substituent on the ring. Substituents with unbound lone pairs can complex to a lithium reagent and then direct the deprotonation to the nearest site on the ring (Scheme 22).



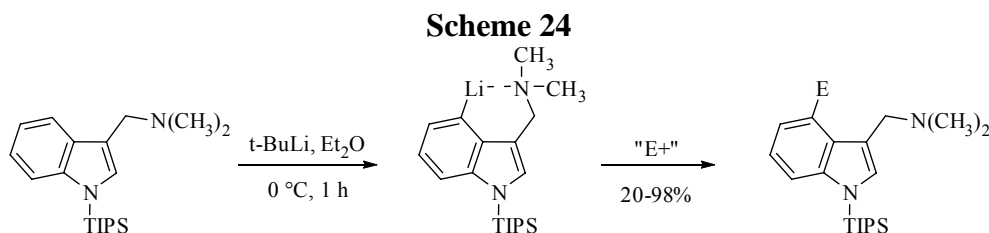
Listed below are the  $pK_a$ s of the most acidic protons of heterocycles most discussed in the short courses (Figure 4). These are significant protons for direct lithiation.



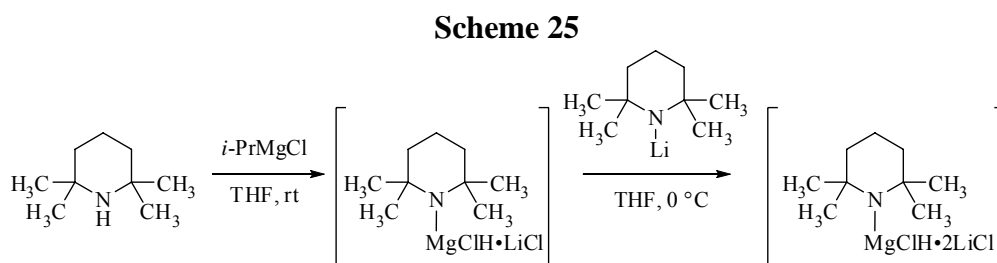
Indole for instance is most easily lithiated at the alpha carbon. However, beta lithiation can be achieved if a large enough protecting group is on the nitrogen (Scheme 23). A trisopropylsilyl group is sufficiently large to block alpha deprotonation, and hence lithiation.



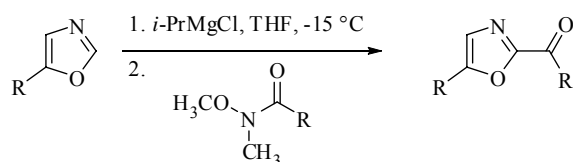
Substitution can also be directed to the 4 position of an indole with a dimethylamino directing group (Scheme 24). A triisopropylsilyl group on the indole nitrogen will still prohibit alpha deprotonation, and the dimethylamino side chain will block substitution at the beta position. The nitrogen of the side chain will complex with lithium and direct metalation to the only available position in reach, the C-4 carbon.



Similarly to lithium, magnesium can be used to metalate nitrogens or carbons with acidic protons. A popular magnesiumation reagent is  $\text{TMPMgCl}\cdot\text{LiCl}$  (Scheme 25). Such a reagent is remarkably basic, but unlike alkyl lithium reagents and lithium amides  $\text{TMPMgCl}\cdot\text{LiCl}$  is not nucleophilic and is very stable in THF. Magnesium amides also don't require low temperatures, which is convenient for larger scale reactions. A common magnesium source is *i*-PrMgCl. The function of lithium chloride is to break up aggregates of magnesium amides.



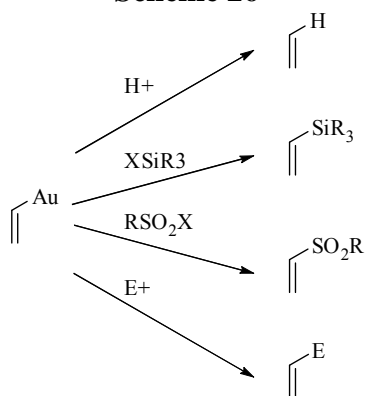
*Org. Lett.* **2007**, *9*, 5525; *Angew. Chem. Int. Ed.* **2006**, *45*, 2958



*J. Org. Chem.* **2007**, *72*, 5828

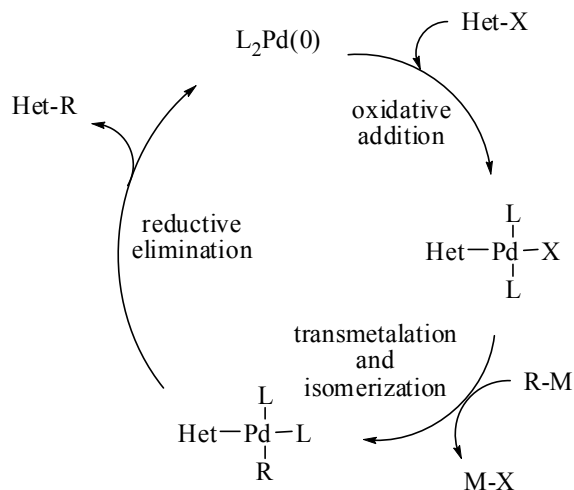
Gold catalysts are also becoming very popular for coupling chemistry. Gold is less expensive than Pd, Pt, Rh, and Ir catalysts, but is relatively new to the field (50% of all published work on gold-catalyzed organic reactions has appeared since 2004). Gold species can be quenched with acids or electrophiles, and they can also be silylated or sulfonated (Scheme 26).

### Scheme 26



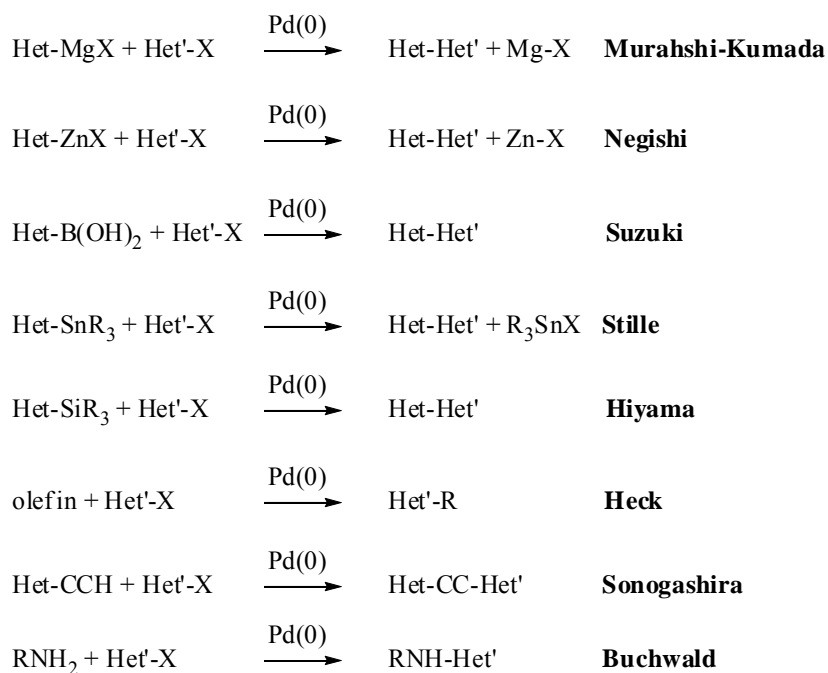
The most common coupling reagents used in heterocyclic chemistry are, of course, palladium based. Palladium-catalyzed cross coupling reactions (Scheme 27) begin with a halogenated heterocycle (Het-X). A palladium species inserts itself between the heterocycle and the halogen in a process known as oxidative addition. A metalated species (R-M) is introduced and the palladium complex undergoes transmetalation and isomerization to give a metal-halogen species (M-X) and a Het-Pd-R species. Reductive elimination occurs to regenerate the palladium catalyst and the newly coupled product (Het-R).

### Scheme 27



Palladium (0) catalysts are used to couple halogenated species with magnesium species (Murahashi-Kumada), zinc species (Negishi), boron species (Suzuki), tin species (Stille), silicon species (Hiyama), olefin species (Heck), alkynes (Sonogashira), and nitrogen species (Buchwald) (Scheme 28).

### Scheme 28



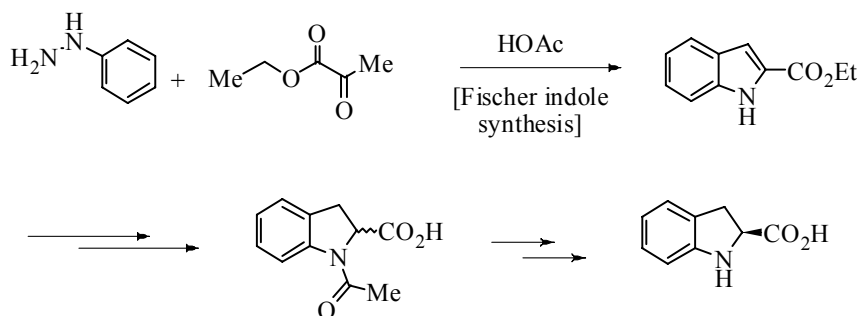

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### “Keep Taking the Metal Away: An Industrial Case Study”

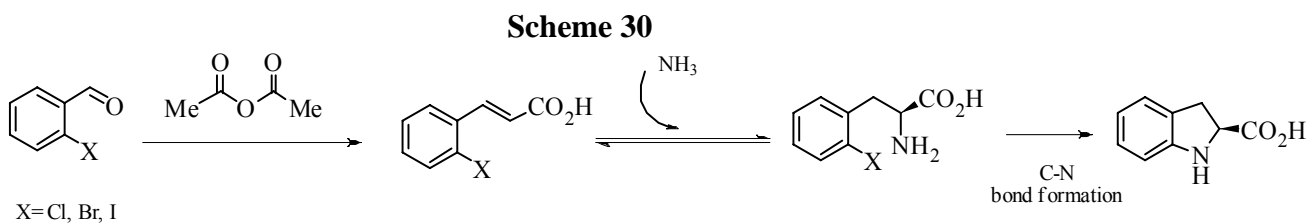
David Ager (DSM Pharma Chemicals), Raleigh, North Carolina, USA

The research described by Dr. Ager focused on the asymmetric reductions with MonoPhos type ligands. Specifically dealing with (*S*)-2,3-dihydro-1*H*-indole-2-carboxylic acid (INDAC), he demonstrated progress on work being done to improve the chemical process. A previous method involving a Fischer indole synthesis followed by classical resolution, shown in scheme 29, was thought to be more expensive and time consuming.

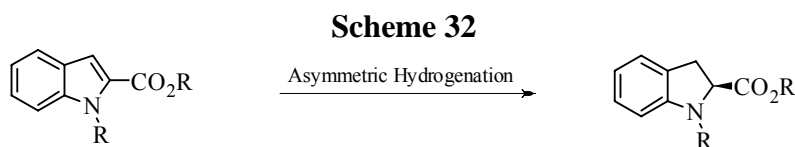
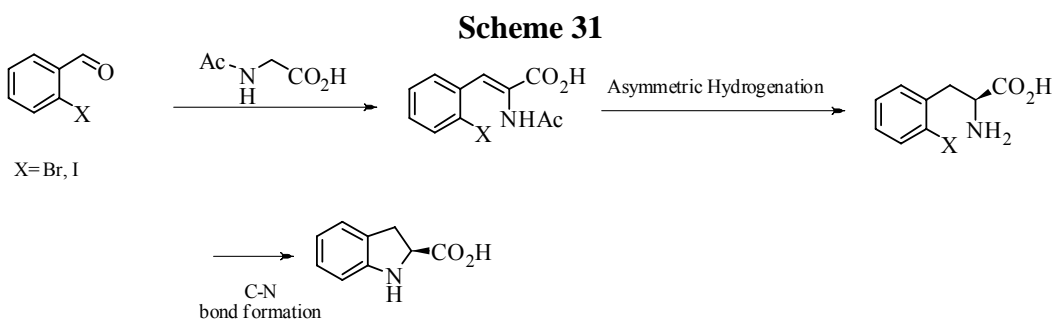
### Scheme 29



The group considered and explored a few other routes to this material. One route involved an enzyme assisted addition of ammonia followed by a C-N bond formation as shown in Scheme 30.



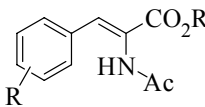
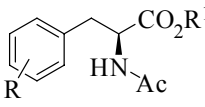
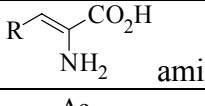
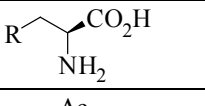
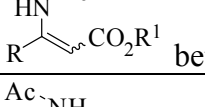
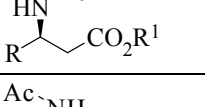
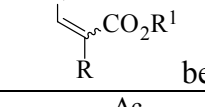
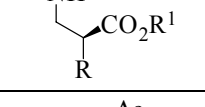
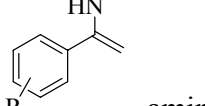
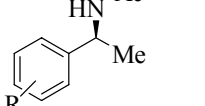
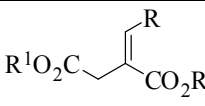
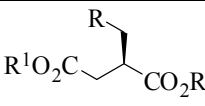
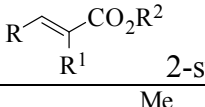
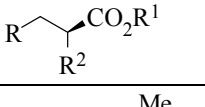
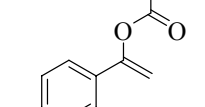
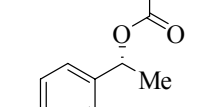
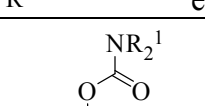
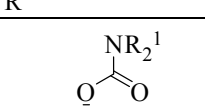
Two other routes involved an asymmetric hydrogenation in either an intermediate stage or to provide the target molecule. This group chose to explore these routes, shown in Schemes 31 and 32, and focus on the optimization of the asymmetric hydrogenation.



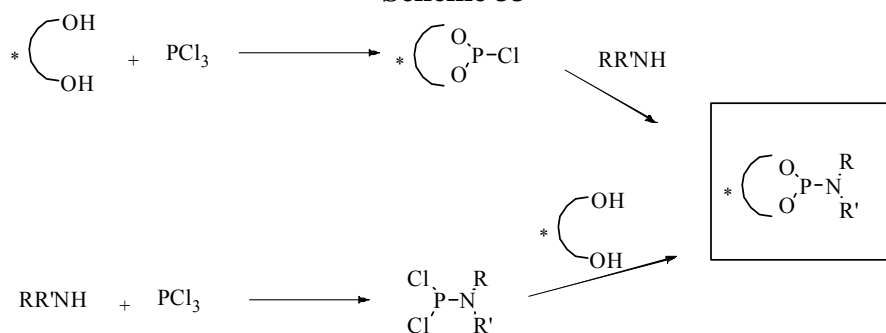
The group was able to perform a mass screening of a large number of catalysts based on MonoPhos ligands. Ease of synthesis, cost and a large library led to the exploration of MonoPhos ligands for catalytic asymmetric hydrogenations. DSM was able to use a 96 well, high-throughput reactor to prepare a large number of compounds and then use high speed analysis to find active catalyst compounds. The ligands were prepared in one day and then tested the following day. Scheme 33 shows the synthesis of the phosphoramidite ligands while Scheme 34 shows the application of asymmetric hydrogenation toward the preparation of INDAC.

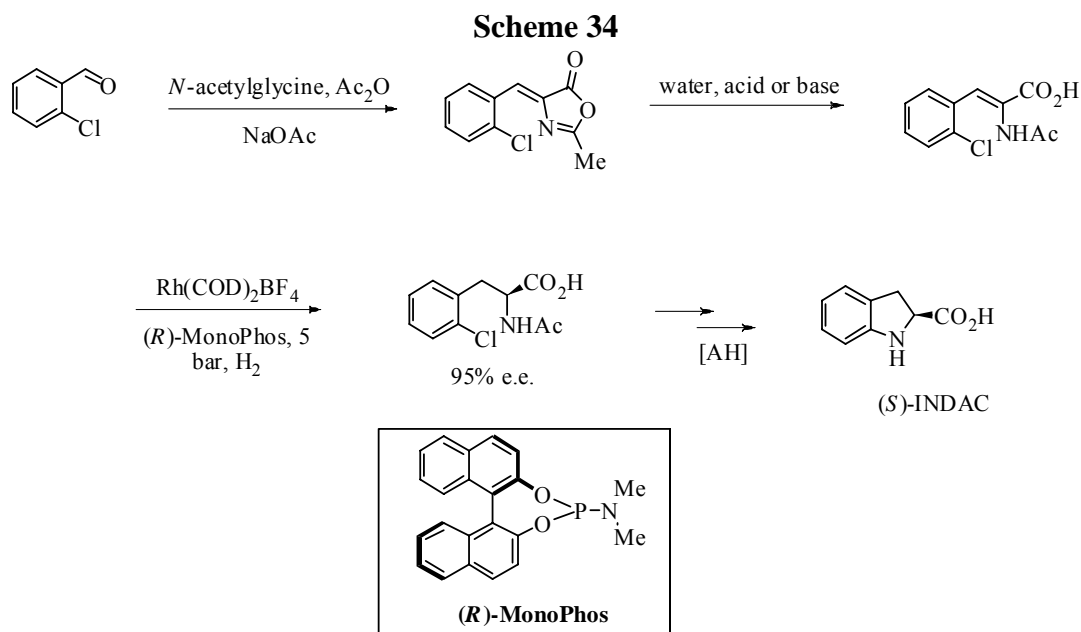
Table 1 shows a few reactions that were performed using MonoPhos type ligands.

**Table 1**

	Starting olefin/ Rh-MonoPhos	Product
1	 amino acid derivatives	
2	 amino acid derivatives	
3	 beta amino acids	
4	 beta amino acids	
5	 amines and amides	
6	 succinic acid derivatives	
7	 2-substituted carboxylic acids	
8	 esters (chiral alcohols)	
9	 carbamates (chiral alcohols)	

**Scheme 33**





Dr. Ager was able to use high throughput screening to find active catalyst for asymmetric hydrogenation. This method provided INDAC in high yield and high enantiomeric excess.

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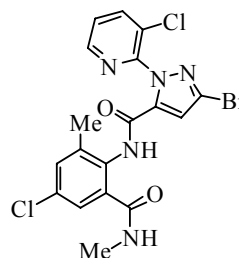
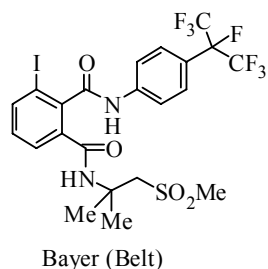
### “Insecticidal Quinoline Bisamides”

*Andrew J.F. Edmunds (Syngenta), Basel, Switzerland*

Dr. Andrew Edmunds gave an interesting lecture detailing research toward the development of insecticides. Insecticides aimed at agricultural pests specifically chewing pests, have grown to almost 25% of the global market. The requirements for a modern insecticide are low environmental impact and a long half-life, requiring a compound to be used very seldom. The compounds must not damage the crop and must be non-toxic to animals and beneficial insects. It must be environmentally sound in that there should be no leaching into ground water and it must be degradable, leaving no detectable residues in the soil. Finally, the product must have low production costs.

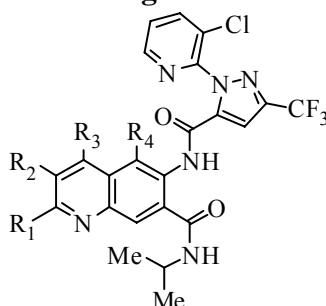
Syngenta took leads from Bayer and Du Pont (Figure 5) and focused on bisamide compounds.

**Figure 5**



Syngenta's compounds were further developed to include a quinoline moiety as well as the bisamide function shown in Figure 6.

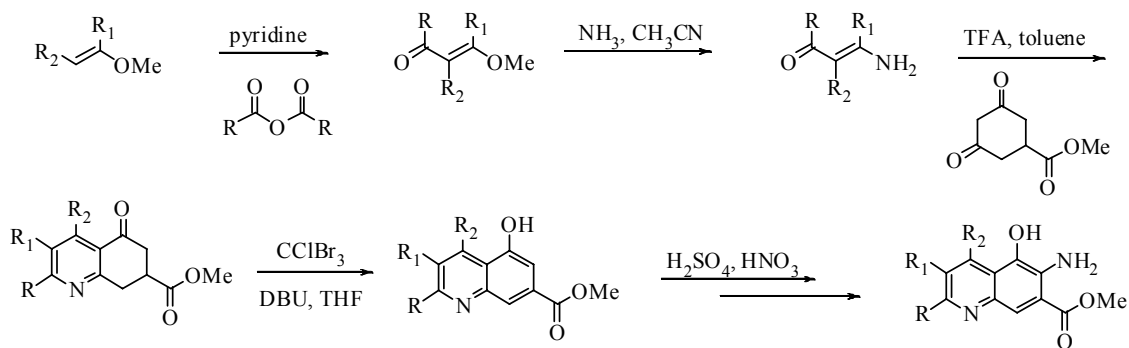
**Figure 6**



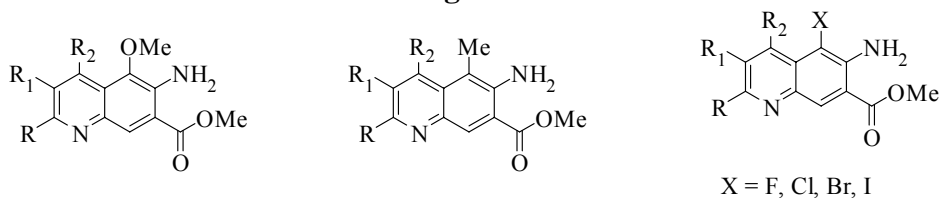
Target quinolines

The synthesis of the target quinolines is illustrated in Scheme 35. The appropriate enol ether was treated with an anhydride to provide alpha-beta unsaturated ketone. Treatment with ammonia in acetonitrile led to the amine which was further transformed to the pyridyl compound. Aromatization followed by nitration and reduction to the corresponding amine led to a key intermediate that could be further elaborated to final analogues.

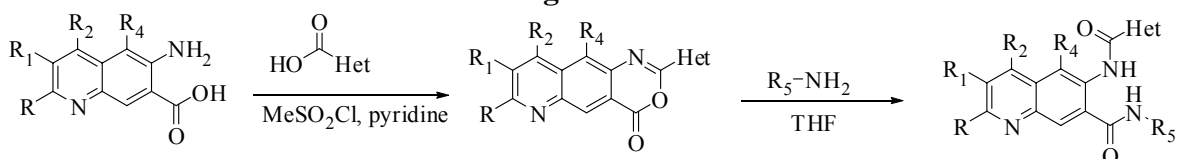
**Scheme 35**



The phenol handle was used to convert the intermediate to the methoxy, methyl and halide as shown in Figure 7.

**Figure 7**

The formation of the bisamide final targets was accomplished by the method shown in Scheme 36. The amino quinoline was treated with the heterocyclic acid in pyridine and methane sulfonyl chloride. The intermediate was then treated with the appropriate amine to open the lactone resulting in the bisamide final target.

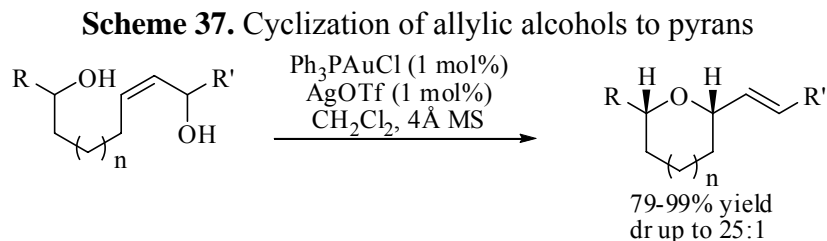
**Figure 36**

Dr. Edmunds finished his lecture by summarizing Syngeta's overall accomplishments of this project. They developed a selective approach to the synthesis of multi-substituted quinolines. They then used these quinolines in the preparation of bisamide insecticides. Those compounds had activity which was comparable to Rynaxypyr and better than Flubendiamide (Bayer-Belt). This synthetic approach provided various handles on the molecules for further elaboration.

### “The Development of New Au-catalyzed Transformations of Unsaturated Alcohols”

Aaron Aponick (University of Florida), Gainesville, FL, USA

Professor Aponick described his group's use of Au(I) and Au(III) as air and water stable catalysts which are tolerant of a wide array of functional groups. The Aponick group has studied the transformation of mono-allylic alcohols to pyrans using a combination of Au and Ag catalysis as shown in Scheme 37 (A. Aponick, *et al.*, *Org. Lett.* **2008**, *10*, 669-671). Under these conditions, the reactions are very fast, requiring only minutes at room temperature. Greater selectivity can be achieved by running the reaction at  $-50\text{ }^{\circ}\text{C}$  for several hours.



Both the gold and silver catalysts are necessary for the reaction to proceed quickly and cleanly. The reaction will proceed with under triflic acid catalysis but the reaction is significantly slower and more decomposition is observed. The reactions have been scaled up multi-gram scale without complications and required only 20 mg of the gold catalyst to afford over two grams of desired product (Aponick, A.; Biannic, B; *Synthesis* **2008**, 3356-3359). In theory, the gold could be recovered and recycled if the reactions were performed on an industrial scale but it is generally not feasible on lab scale reactions due to the low catalyst loading (0.1-1%). The lower catalyst loading gives only slightly lower yields and longer reaction times.

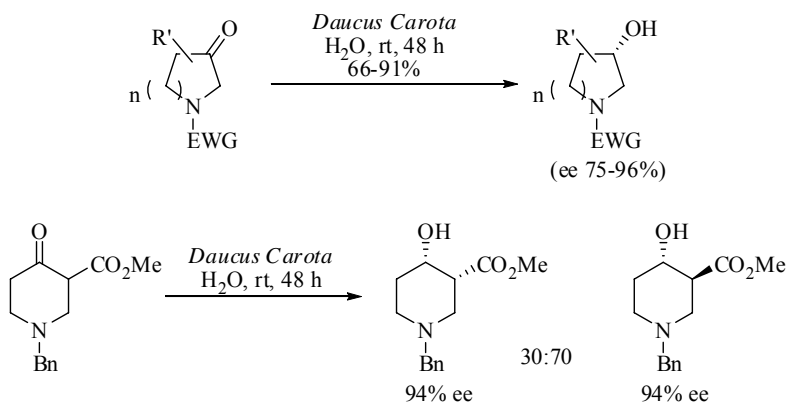
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### “Synthesis of Substituted Piperidines and Pyrrolizines: Selective Methodologies and Applications to the Synthesis of Biologically Active Compounds”

Janine Cossy (CNRS), Paris, France

Professor Cossy described the development of several new methodologies which were invented to overcome problems encountered in the synthesis of natural products or biologically interesting molecules. One of the more striking examples she detailed was the use of carrots to effect the stereospecific reduction of a cyclic ketone as shown in Scheme 38 (R. Lachertz, *et al.*, *Org. Lett.* **2009**, *11*, 1245-1248). In working on the synthesis of capromorelin, the reduction of the ketone with baker’s yeast gave racemic material so an alternative procedure was required. The group stumbled onto the use of carrots, which, because of the sugars contained in them, do not require any other reagents to effect the desired reduction. In a typical experiment, 2 mmol of substrate was reduced by 140 g of carrots in 600 mL of water in 2 days. The best results are obtained with electron withdrawing groups on the nitrogen. The reaction proceeds with the unprotected nitrogen but isolation of the final product from the aqueous solution can be problematic. Non-electron withdrawing protecting groups such as benzyl gave significantly lower yields and enantiomeric excesses.

**Scheme 38.** Ketone reduction with carrots

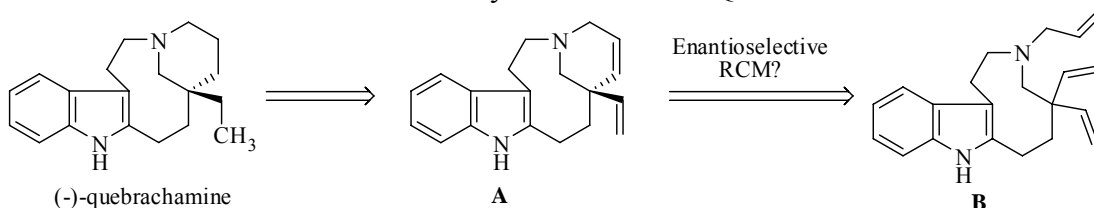


## “A New Class of Fluxional Chiral Catalysts for Olefin Metathesis: Inspired by Total Synthesis, Identified through Theory”

Amir H. Hoveyda (Boston College), Boston, MA

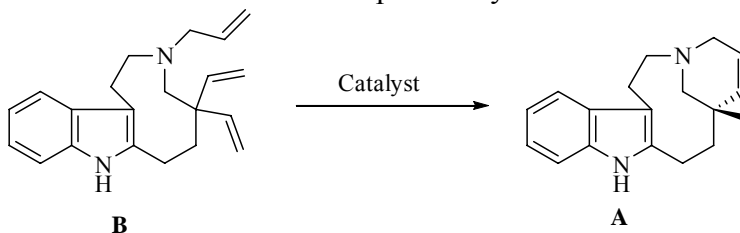
Professor Hoveyda described work on new chiral catalysts for olefin metathesis in which the metal is an asymmetric center. The Hoveyda group chose to work on the total synthesis of the alkaloid quebrachamine (Scheme 39), knowing that the successful synthesis would require the development of improved olefin metathesis technology (E. S., Sattley, *et al.*, *J. Am. Chem. Soc.* **2009**, *131*, 943-953).

**Scheme 39.** Retrosynthetic Plan for Quebrachamine



In their initial work on the synthesis, using traditional Schrock and Grubbs catalysts, the olefin metathesis of **B** to **A** (Scheme 40) proceeded in low yields or low conversion depending upon the catalyst loading. Attempts to employ over 80 known chiral catalysts resulted in no product formation in all attempts. The lack of reactivity by the chiral catalysts was explained by the fact that their more rigid nature prevents them from obtaining the high energy conformations necessary for the reaction to proceed. At this point, the group realized that a more novel approach would be necessary to effect the transformation.

**Scheme 40.** Initial attempts at Key RCM reaction

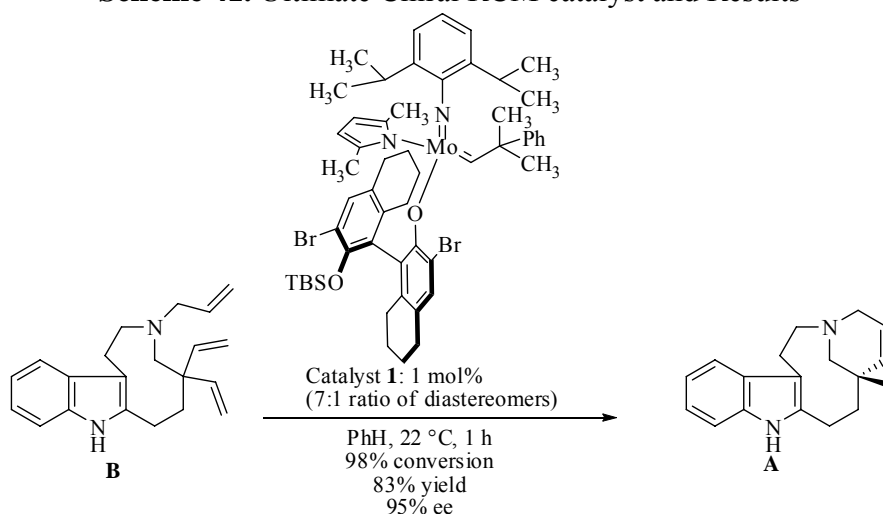


30% Schrock Mo catalyst: 98% conversion, 58% yield  
5% Grubbs G1 Ru catalyst: 30% conversion  
>80 known chiral RCM catalysts: 0% yield

In many metal-containing chiral catalysts, the metal is simply part of the scaffold and is not itself an asymmetric center. The challenges of making the metal center chiral include generating asymmetry at the metal centers as well as the fact that the metal center would invert in the course of catalyzing a reaction, resulting in an erosion of selectivity. In the case of olefin metathesis, however, a complete reaction cycle involves two metathesis reactions which invert the metal center, resulting in net retention of configuration.

In developing the new chiral RCM catalysts, the Hoyveda group focused on modifications of the molybdenum catalysts as they appeared to be more active than the ruthenium ones. After significant thought and experimentation, the group was able to develop catalyst **1** (Scheme 41). The synthesis of the catalyst afforded a 7:1 mixture of diastereomeric catalysts which, when applied to the synthesis of quebrachamine, afforded a product of 95% ee. Recrystallization of the catalyst to afford enantiopure material resulted in a nearly identical ee of the product **A**. NMR studies revealed that the minor isomer of the catalyst is much more difficult to initiate and, when the initiation does occur, that the barrier of inversion is lower than the reaction activation energy for the RCM reaction so the minor isomer, once initiated, inverts to the major isomer to give the desired enantiomer of product **A**.

**Scheme 41.** Ultimate Chiral RCM catalyst and Results



The Hoyveda group has found that much of what they learned in their work on the enantioselective RCM catalysts can be applied to work on non-chiral RCM reactions. This is seen in Scheme 42 in which the achiral catalyst affords the racemic product quickly and in good yields. The group found that much greater catalyst activity results from the presence of 1 donor and 1 acceptor group on the metal. In this case, based upon the X-ray crystal data, the pyrrole is acting as the donor group while the ether moiety is the electron acceptor group.

### Scheme 42. Highly active Achiral Catalyst

