



Trip Report for

“9th Annual Florida Heterocyclic and Synthetic Conference”

Gainesville, FL

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Abstract: *The 9th Annual Florida Heterocyclic and Synthetic Conference (FloHet) was organized by ARKAT-USA. The conference featured 12 plenary lectures, 6 short courses and 40 invited lecturers. This report highlights some of the chemistry presented during this conference.*

“Overview of Organic Fluorine Chemistry”

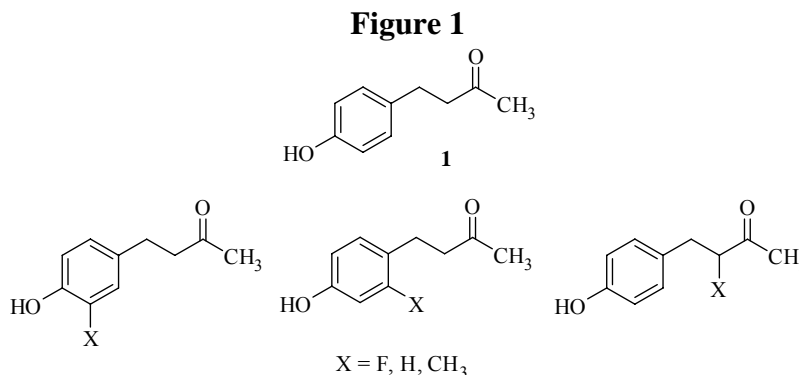
William Dolbier, University of Florida

The first part of the short course presented a background on the effects of fluorine as a substituents. Fluorine has a unique character as a substituent, which is derived from its electronegativity, its three non-bonded electron pairs, the excellent match between fluorine’s 2p orbitals and the corresponding s and p orbitals, and the π bonding orbitals of carbon and its small size. The bond lengths of F and OH are effectively the same. Also, looking at the I-value for the two different substituents shows that F = 4.6 and OH = 6.5. Therefore, F and OH are essentially isosteres.

Bond lengths for CH₃-X (in angstroms):

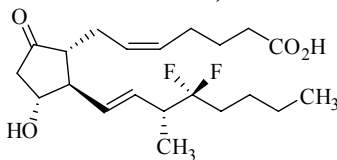
H: 1.09; **F:** 1.38; **OH:** 1.43; **Cl:** 1.78; **Br:** 1.94; **I:** 2.13

Next, Dolbier looked at the physiological size of the fluorine substituent (Figure 1). Structure **1** is a raspberry flavor compound. By replacing the H on the structure with F, the smell of the compound was unaffected, but the compound was vastly altered when the H was replaced with a methyl group. This can be justified because a fluorine atom is small in size, as is a hydrogen atom. This reinforces the aspect that fluorine is very similar to hydrogen and can sometimes be used as a replacement with little effect on pharmaco/physical properties.



In other circumstances a fluorine substituent can have a very pronounced effect on the characteristics of a drug molecule. It can help to increase the activity or stabilize a molecule (Figure 2). In 16,16-difluoro PGE₁, the presence of the fluorines help to inhibit metabolic oxidation of the neighboring OH group and enhance the anti-fertility activity of the drug.

Figure 2. Structure of 16,16-difluoro PGE₁.



Another important aspect to consider when working with fluorine is the effect it has on the acidity (pK_a values) and the basicity (pK_b values) of a compound. Some pK_a values

for various fluorinated acids are shown in Figure 3. Installing a fluorine atom as a substituent on various systems makes the molecule more acidic. For instance, TFA is four pKa units more acidic than acetic acid. Likewise, pentafluorophenol is five pKa units more acidic than phenol. However, fluorine does not have as much of an effect on the basicity. Shown in figure 4 are pK_b values for various fluorinated amines. Basicity is only attenuated to great extent when multiple fluorines are substituted.

Figure 3. pKa Values for various fluorinated acids.

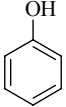
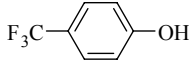







<u>Alcohols</u>		<u>Phenols</u>			
CH ₃ CH ₂ OH	15.9		10		
CF ₃ CH ₂ OH	12.4		8.7		
(CF ₃) ₂ CHOH	9.3				
<u>Aliphatic Carboxylic Acids</u>		<u>Benzoic Acids</u>			
CH ₃ CO ₂ H	4.8		4.3		4.0
CH ₂ FCO ₂ H	2.6		4.3		3.6
CF ₃ CO ₂ H	0.2				

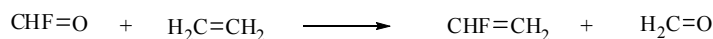
Figure 4. pK_b Values for various fluorinated amines.

<u>Aliphatic Amines</u>		<u>Aromatic Amines</u>			
CH ₃ CH ₂ NH ₂	3.3		9.4		10.8
CF ₃ CH ₂ NH ₂	8.3		11.5		
(CF ₃) ₃ N	behaves like a perfluorocarbon				

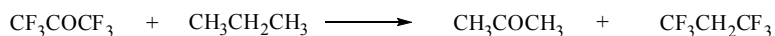
Fluorine also has very different effects on carbonyl groups depending on whether the fluorine atom is directly substituted or adjacent (Figure 5). When the fluorine atom is directly substituted the $\Delta H = + 18.3$ kcal/mol, and is stabilizing. However, when the fluorine atom is adjacent, the $\Delta H = - 28.2$ kcal/mol, and is destabilizing.

Figure 5

Stabilizing when directly substituted:

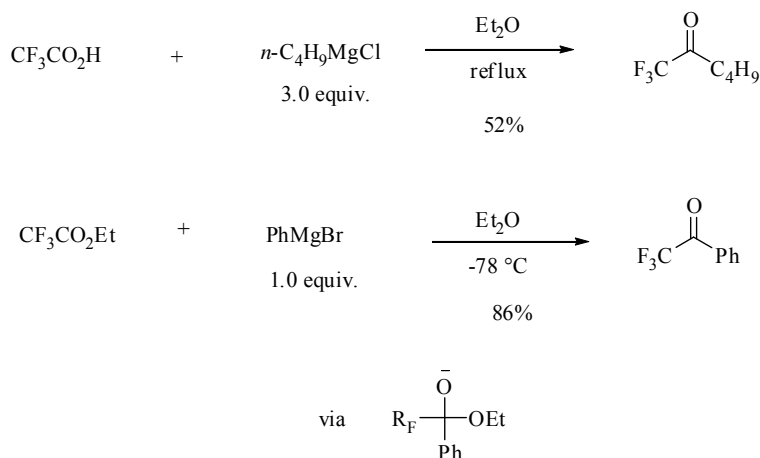


Destabilizing when adjacent:



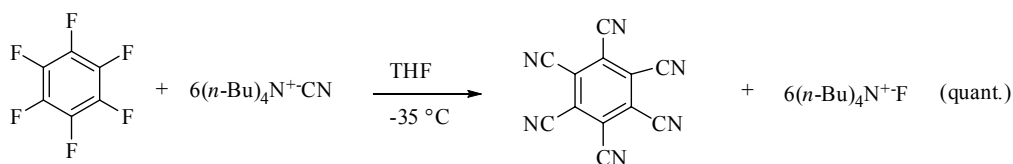
The destabilization of the carbonyl group by CF₃ allows the use of Grignard chemistry of carboxylic acids and esters that would not be useful for nonfluorinated systems (Scheme 1).

Scheme 1



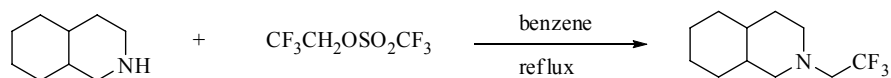
Fluoride is known to be a good in electrophilic reactions, but often performs poorly in nucleophilic reactions. There are a few exceptions however for when having a fluorinated molecule in a nucleophilic reaction can be beneficial (Figure 6).

Figure 6



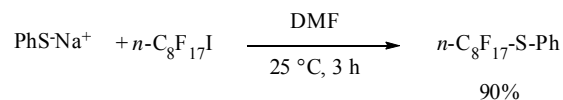
A fluorinated group can drastically affect the reactivity of a nearby site of nucleophilic attack. For example an $\text{R}_\text{F}\text{I}$ compound is almost totally unreactive towards $\text{S}_{\text{N}}2$ reactions with hard nucleophiles, such as CN^- . $\text{R}_\text{F}-\text{CH}_2-\text{I}$ compounds have low reactivity with $\text{S}_{\text{N}}2$ reactions. However, $\text{R}_\text{F}-\text{CH}_2-\text{CH}_2-\text{I}$ compounds have normal reactivity towards $\text{S}_{\text{N}}2$ chemistry (Scheme 2).

Scheme 2



Perfluoroalkyl halides can undergo clean substitution via an electron-transfer mechanism known as the $\text{S}_{\text{RN}}1$ mechanism (Scheme 3).

Scheme 3

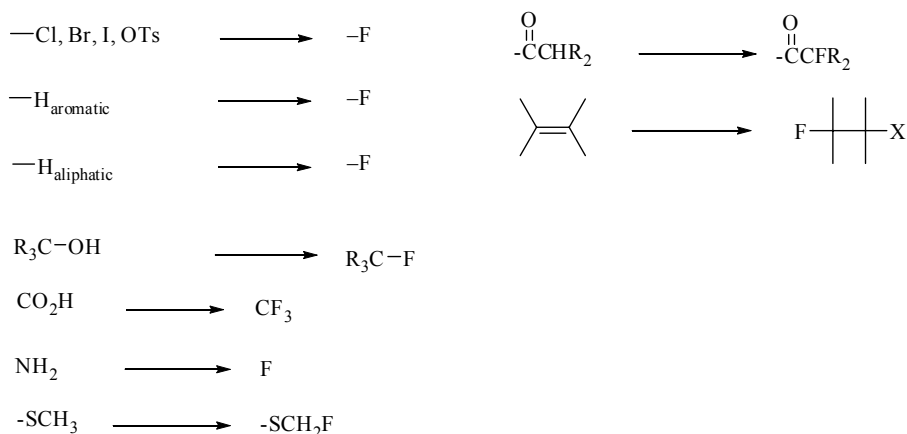


Fluorine can have a very large influence on the physical and chemical properties of compounds and it is essential to understand the properties and nature of a fluorine atom before being able to effectively design new fluorine-containing bioactive compounds.

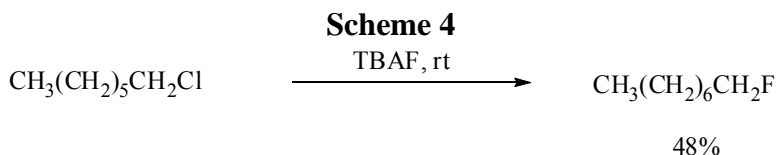
The second half of Dolbier's talk discussed an overview of synthetic methodology in organofluorine chemistry.

Installing fluorine into a compound must be timed perfectly because often the fluorine reagent is expensive and sometimes the fluorine can be difficult to install. Therefore, when installing a fluoride substituent, it is usually done at the last step possible in a synthesis. There are various functionalities that can be transformed into fluorines (Figure 7). Also there are a variety of radical and electrophilic fluorinating agents such as; F_2 , XeF_2 , ClO_3F , CsSO_4F and RCO_2F , and a variety of nucleophilic fluoride-transfer agents such as; KF , SbF_3 , AHF , SF_4 , and BrF .

Figure 7

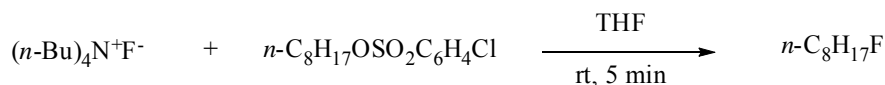


One of the most commonly used fluoride reagents in the industrial setting is TBAF (Scheme 4).



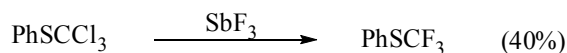
However, more recently anhydrous TBAF has been used in nucleophilic reactions, which result in quantitative yield (Scheme 5). The only downside is that anhydrous TBAF has a very short lifetime above 0 °C.

Scheme 5



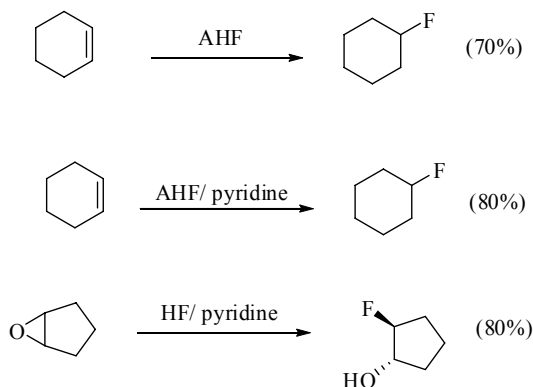
Most of the chemistry that is performed involving fluoride substituents is electrophilic halogen exchange. This was first performed by Swartz and Henne after World War II. The most common and efficient catalyst used in this synthesis is SbF_3 (Scheme 6). Antimony is used because of its stability over the other metalloids or transition metals.

Scheme 6



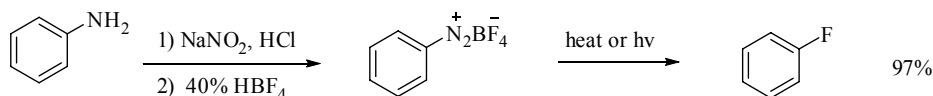
One of the simplest ways to add fluorine to a compound is by using HF. It is commonly used as a last resort in industry however because it is dangerous, acidic and often the reaction needs to be performed in an autoclave. The yields however are high for most of the reactions that have been performed using HF or AHF (anhydrous HF). The reactions seem to work slightly better when they are in the presence of a Lewis base such as pyridine (Scheme 7).

Scheme 7

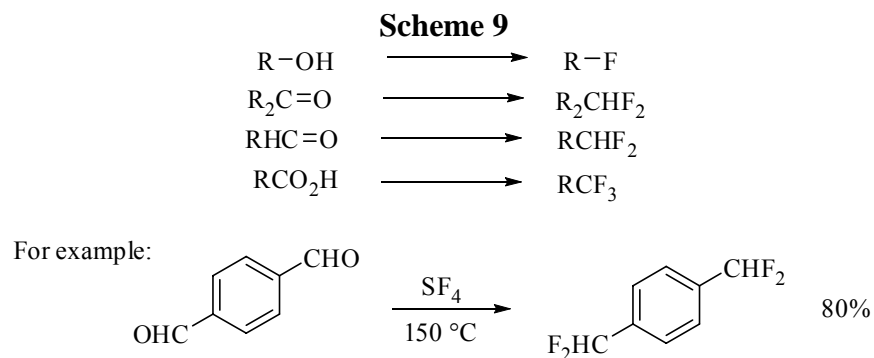


Another commonly used reaction to install a fluoride substituent is the Balz-Schiemann reaction. This reaction converts aryl amines to aryl fluorides via diazotization followed by thermal decomposition of the derived tetrafluoroborates or hexafluorophosphates (Scheme 8).

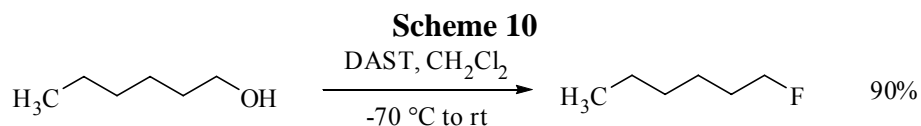
Scheme 8



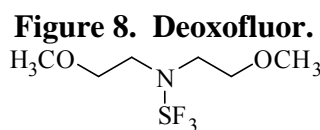
SF₄, which is an epoxic gas (forms polymers), can also be utilized to add fluorine to a compound. SF₄ is not commonly used because it is quite expensive, but it is useful in deoxyfluorination reactions. The most common SF₄ reactions are shown in Scheme 9. The yields for reactions utilizing SF₄ are relatively good, ranging from 60-100% (for examples, see W. Hasek & D. Coffman, *J. Am. Chem. Soc.* **1960**, 82, 543-551).



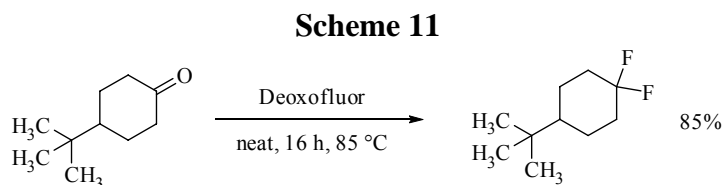
4-Dimethylamino-*N*-methyl-4-stilbazolium tosylate (DAST) is a good alternative to SF₄, however it is dangerous to synthesize and therefore if large scale chemistry is needed, this alternative is not a viable option. DAST works similar to SF₄ (Scheme 10) and it affords similar yields as well (W. Middleton, *J. Org. Chem.* **1975**, 40, 574-578).



There is however a more thermally stable analog of DAST that is commercially available (Air Products), bis(2-methoxyethyl)aminosulfur trifluoride or “deoxofluor” reagent (Figure 8).

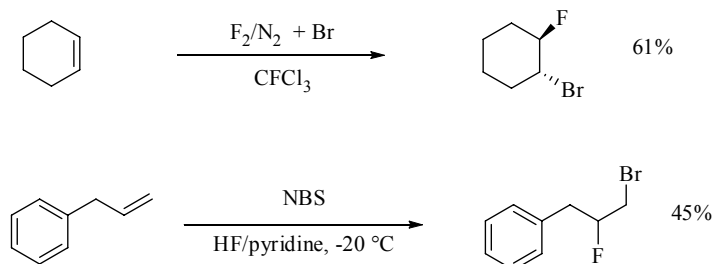


This provides yet another way to install a fluorine molecule into an organic compound, as shown in Scheme 11 (G. Lal & H. Cheng, *J. Org. Chem.* **1999**, 64, 7048-7054).



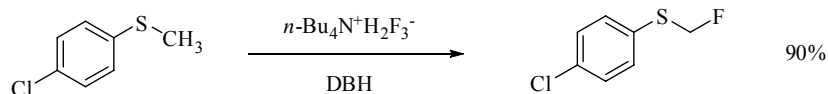
Halogen fluorides are often very useful to carry out further reactions in a synthesis and they can be made very easily (Scheme 12).

Scheme 12



The Fluoro-Pummerer reaction provides an efficient method to fluorinate sulfur analogs in decent yield as shown in Scheme 13 (S. Hiranuma & C. H. Wong, *Tetrahedron Lett.* **1995**, 36, 8243-8246). The reagent BrF_3 can also be utilized to perform similar chemistry. This method will also work on thioamides, sulfoxides, xanthates and thiocarbonates.

Scheme 13



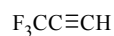
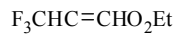
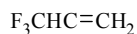
Being able to efficiently and selectively incorporate a fluorine atom into a compound can require difficult measures. Often times, a method that works for chlorine or bromine will not work for fluorine. Because there are challenges in this area, it is constantly growing and there is a need to further efforts to make installing a fluorine substituent into a compound simpler.

Fluorine chemistry can be utilized in Diels Alder chemistry since it can make good dienophiles, in cycloaddition chemistry, fluoro ylide chemistry, and in modified Julia olefinations where it has relatively decent stereoselectivity (Scheme 14).

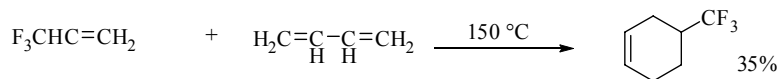
Scheme 14

-Diels Alder chemistry

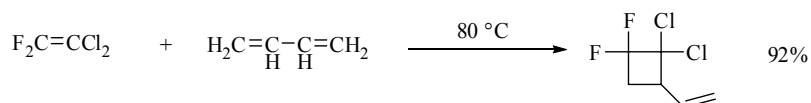
Dienophiles:



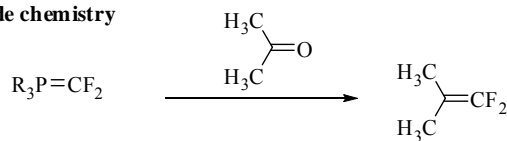
Example:



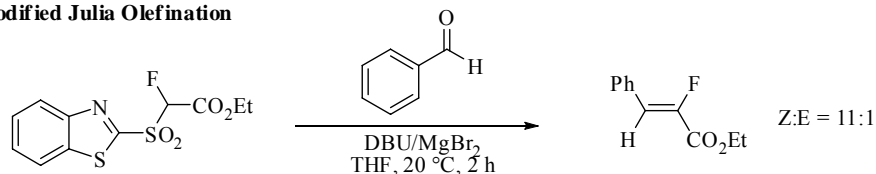
-Cycloaddition chemistry [2+2]



-Fluoro Ylide chemistry

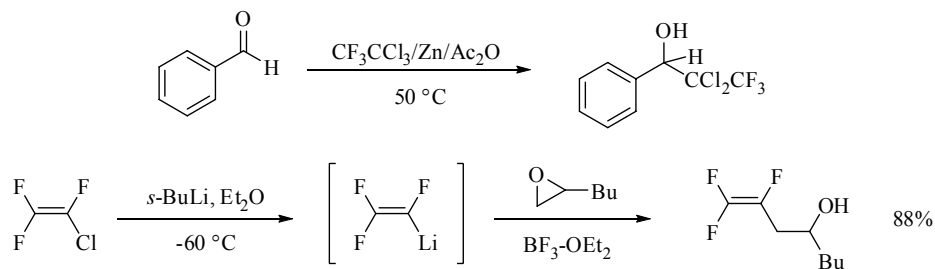


-Modified Julia Olefination

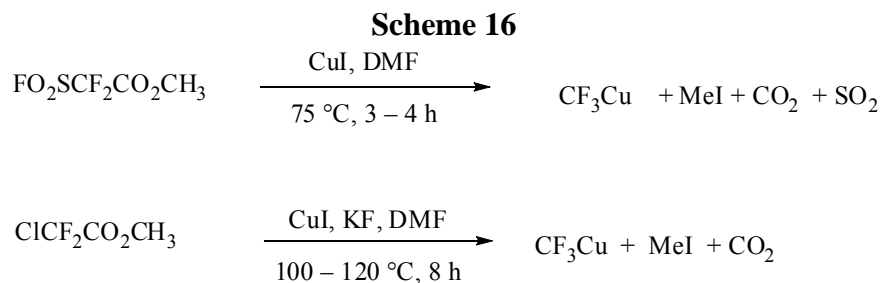


There is sometimes a need for a fluorinated Grignard or alkyl lithium reagents. These reagents however are very unstable above room temperature. Because of the problems with using these reagents, they are instead made by exchange of halides by RLi or RMgX reagents as shown in Scheme 15 (D. White & K. J. Raymond, *J. Med. Chem.* **1988**, 11-18).

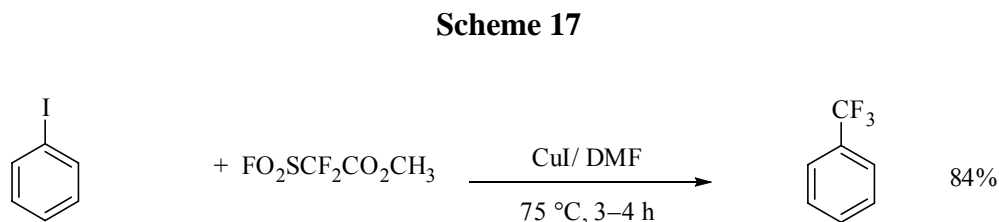
Scheme 15



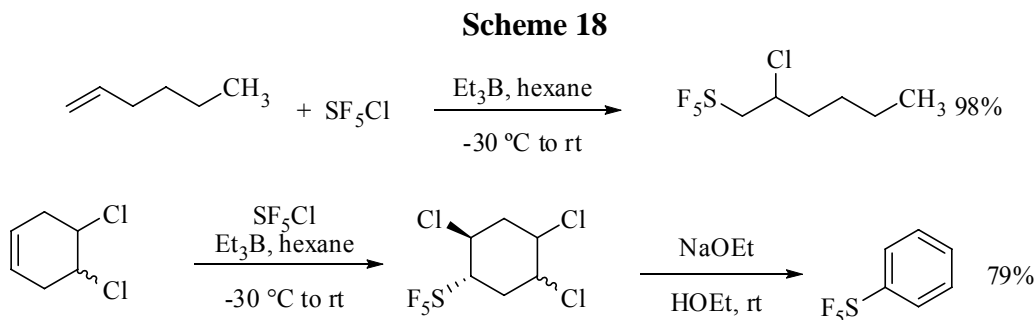
One of the last things examined by Dolbier is the use of trifluoromethyl copper reagents in chemistry. The two best methods for making these have been developed by Chen (Scheme 16).



Trifluoromethyl copper reagent can be easily used to install trifluoromethyl substituents in place of a halogen, such as iodine (Scheme 17).



The last topic discussed has been of recent interest to the pharmaceutical companies because of its unique nature. The SF₅ group can be incorporated into aliphatic and aromatic structures by free radical chemistry (Scheme 18). The SF₅ group has a greater lipophilicity, polarity and hydrolytic stability than a CF₃ molecule. The SF₅ group also is thermally stable which makes performing chemistry after it has been installed much simpler. SF₅ is not available commercially as a gas, but it is sold (Air Products) as organic reagents and chemical intermediates (T. Sergeeva & W. Dolbier, *Org. Lett.* **2004**, *14*, 2417-2419).



Overall, fluorine chemistry can be complex, and the results can be unpredictable. Having knowledge of traditional organic synthesis methodology can get you started and the more

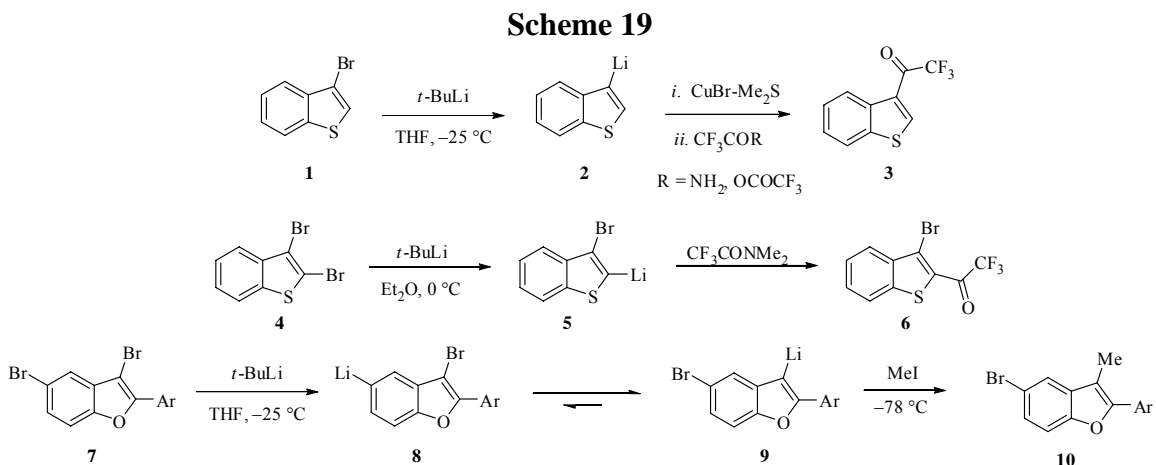
experience you, get in the sub-field of organofluorine chemistry, the easier it will be to predict the outcome of a fluorine reaction.

“Applications of Lithium, Palladium and (to a lesser extent) Magnesium, Copper and Gold in Heterocyclic Chemistry”

Dr. Gordon W. Gribble, Department of Chemistry, Dartmouth College

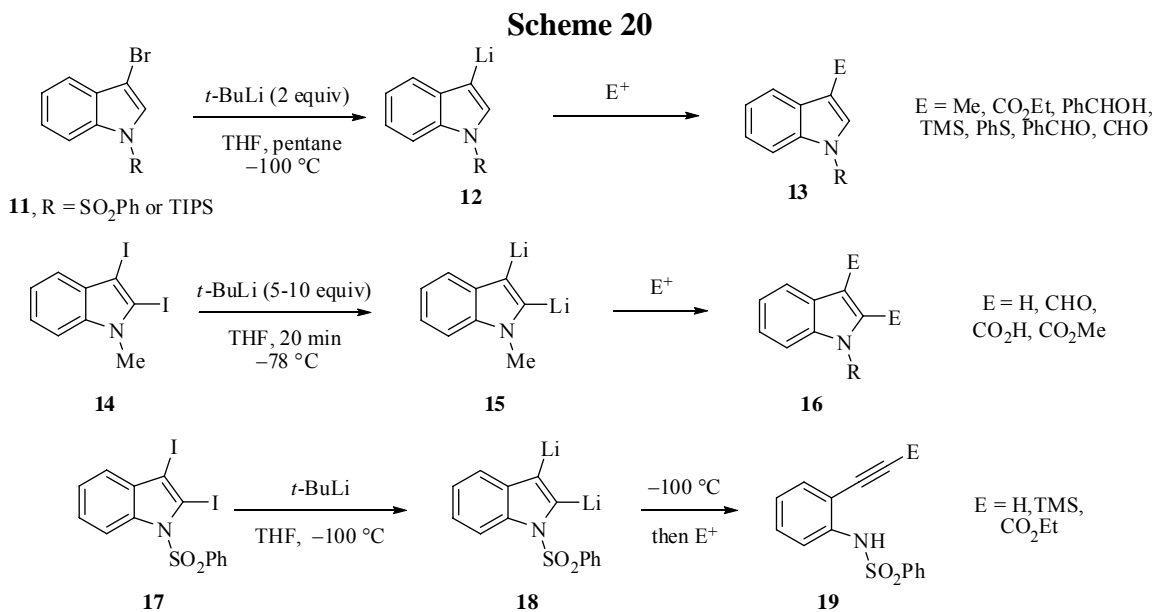
The short course presented by Professor Gribble focused on the utility of lithium, palladium, magnesium, copper, and gold in heterocyclic chemistry. Due to the vast extent of information presented during this short course, this report will only focus on the lithium chemistry that was discussed.

Scheme 19 highlights some of the lithiation chemistry that can be performed on benzothiophenes and benzofurans. Compound **1** can undergo metal-halogen exchange followed by quenching with an electrophile to afford the trifluoromethylketone **3**. This ketone can be easily converted to the corresponding acid if desired (F. A. J. Kerdesky, *et al.*, *Tetrahedron Lett.* **1991**, 32, 2003). The 2,3-dibromo benzothiophene can undergo selective metal halogen exchange at the 2-position, followed by quenching with the appropriate electrophile to afford the trifluoromethylketone **6** (W. S. DiMenna, *Tetrahedron Lett.*, **1980**, 21, 2129). Finally, the 3,5-dibromo benzofuran can undergo a single metal halogen exchange followed by rearrangement of the anion to afford 3-substituted benzofurans such as **10** (T. Bach. *et al.*, *Synthesis* **2003**, 925).

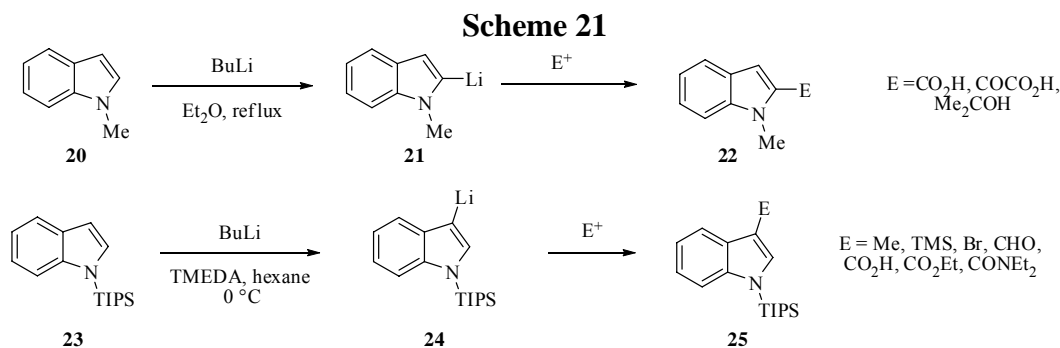


As shown in Scheme 20, 3-bromo indoles can undergo metal halogen exchange followed by quenching with a variety of electrophiles to afford 3-substituted indoles such as **13** (G. W. Gribble, *et al.*, *J. Org. Chem.* **1982**, 47, 757; G. W. Gribble, *et al.*, *J. Org. Chem.* **1985**, 50, 5900; G. W. Gribble, *et al.*, *Heterocycles* **1990**, 30, 627; J. Bosch, *et al.*, *Heterocycles* **1996**, 43, 1713; J. Bosch, *et al.*, *J. Org. Chem.* **1994**, 59, 10). The 2,3-diiido indole can form the 2,3-dilithio species that can be quenched with an electrophile to synthesize 2,3-disubstituted indoles in one pot (G. W. Gribble, *et al.*, *Tetrahedron Lett.* **2001**, 42, 2949). Finally, the 2,3-diiido indole **17** can be converted to the 2,3-dilithio

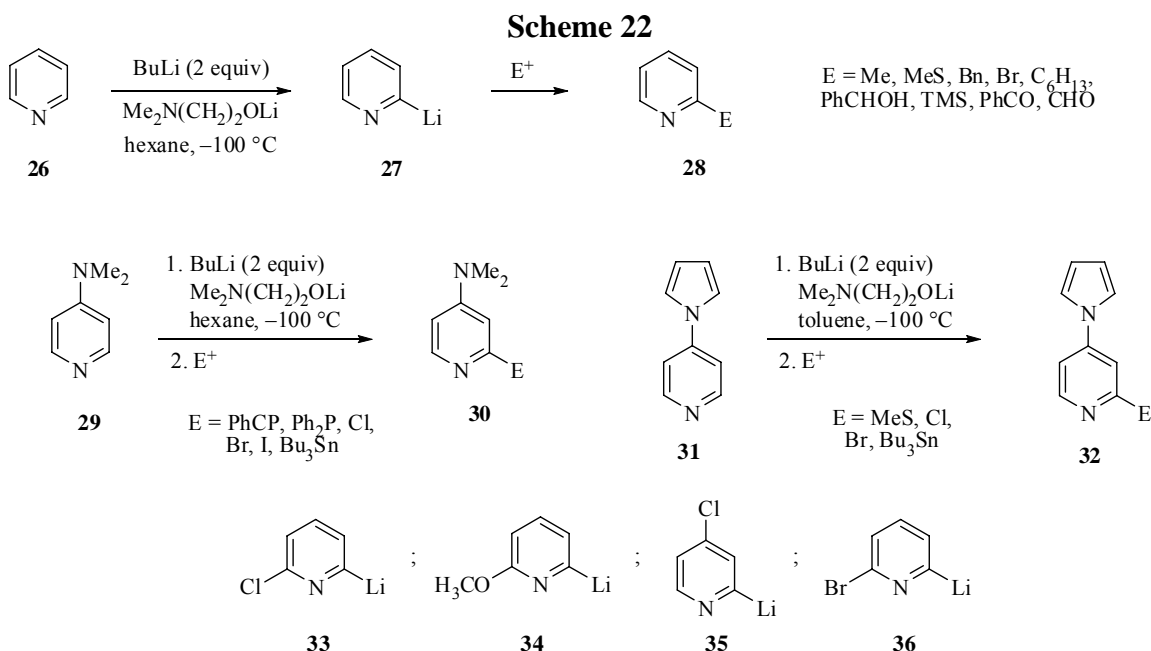
species but due to the electron withdrawing nature of the sulfonamide, the ring fragments to form the alkyne **19** (G. W. Gribble, *et al.*, *J. Org. Chem.* **1983**, *48*, 607).



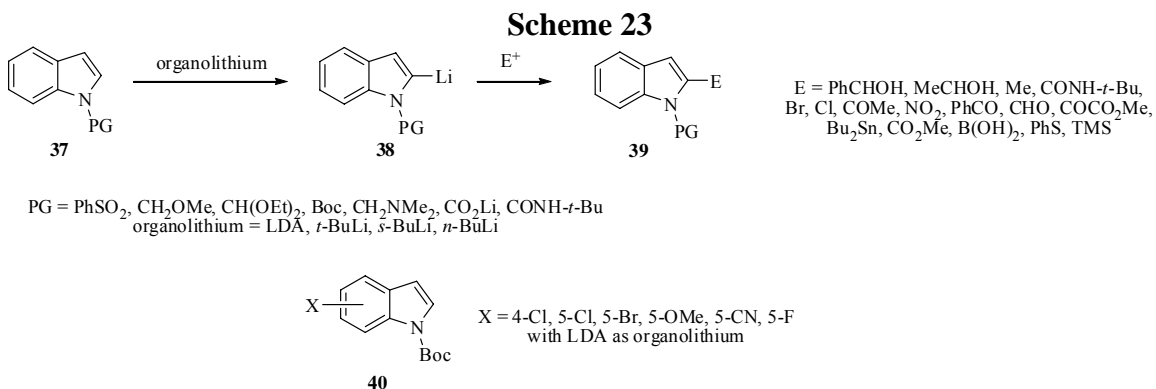
In Scheme 21, the direct deprotonation of indole **20** at the 2-position followed by quenching of the lithium anion by a variety of electrophiles can afford 2-substituted indoles (D. A. Shirley, *et al.*, *J. Am. Chem. Soc.* **1953**, *75*, 375). In the case of indole **23**, the bulky group on the indole nitrogen forces the anion formation at the 3-position when a bulky organolithium is used. This allows for the synthesis of a variety of 3-substituted indoles (M. Iwao, *et al.*, *Tetrahedron Lett.* **2001**, *42*, 7621; R. J. Sundberg, *et al.*, *J. Org. Chem.* **1973**, *38*, 3324).



In Scheme 22, the direct de-protonation of different pyridine-containing ring systems is highlighted. Pyridine itself can be de-protonated to form the lithium anion at the 2-position. This anion can be reacted with a variety of electrophiles to form the 2-substituted pyridines **28**. Dimethylaminopyridine **29** and 4-pyrrolopyridine **31** can both be lithiated at the 2-position and then quenched with different electrophiles. The lithiated pyridines **33-36** are known in the literature and can be used to react with different electrophiles.



In Scheme 23, there are some more examples of the lithiation of unsubstituted indole **37** using a combination of different protecting groups, organolithium reagents and electrophiles. In the case of certain substituted indoles **40**, lithiation and reaction with electrophiles can be accomplished using LDA as the base. For leading references, see: D. W. Knight, *et al.*, *Synlett* **1991**, 315; E. Vazquez, *et al.*, *J. Org. Chem.* **2002**, 67, 7551; R. J. Sundburg, *et al.*, *J. Org. Chem.* **1973**, 38, 3324; R. J. Sundberg, *et al.*, *J. Heterocyclic Chem.* **1981**, 18, 807; R. J. Sundburg, *et al.*, *J. Org. Chem.* **1980**, 45, 3382; M. G. Saulnier, *et al.*, *J. Org. Chem.* **1982**, 47, 757; G. W. Gribble, *et al.*, *Tetrahedron* **1988**, 44, 3195; D. M. Ketcha, *et al.*, *J. Org. Chem.* **1989**, 54, 4350; G. W. Gribble, *et al.*, *Org. Prep. Proced. Int.* **1992**, 24, 649; G. W. Gribble, *et al.*, *Synth. Commun.* **2002**, 32, 2035; G. W. Gribble, *et al.*, *Tetrahedron Lett.* **2002**, 43, 4115; P. Molina, *et al.*, *Tetrahedron Lett.* **1993**, 34, 4701; J. Kraxner, *et al.*, *Synthesis* **2000**, 1081; Hasan, *et al.*, *J. Org. Chem.* **1981**, 46, 157; P. Beak, *et al.*, *J. Org. Chem.* **1993**, 58, 1109; S. Coulton, *et al.*, *Tetrahedron* **1997**, 53, 791; A. R. Katritzky, *et al.*, *J. Org. Chem.* **1990**, 55, 3688; A. R. Katritzky, *et al.*, *Tetrahedron Lett.* **1985**, 26, 5935; T. Fukuda, *et al.*, *Tetrahedron* **2001**, 57, 975; V. Snieckus, *et al.*, *Synthesis* **1991**, 1079.

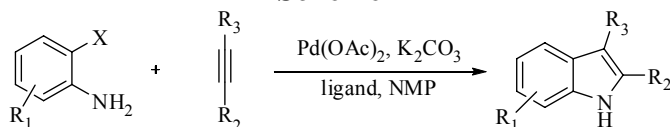


“Practical Regioselective Approaches to Complex 2,3-Disubstituted Indoles”

Vittorio Farina, Johnson and Johnson Pharmaceutical Research & Development

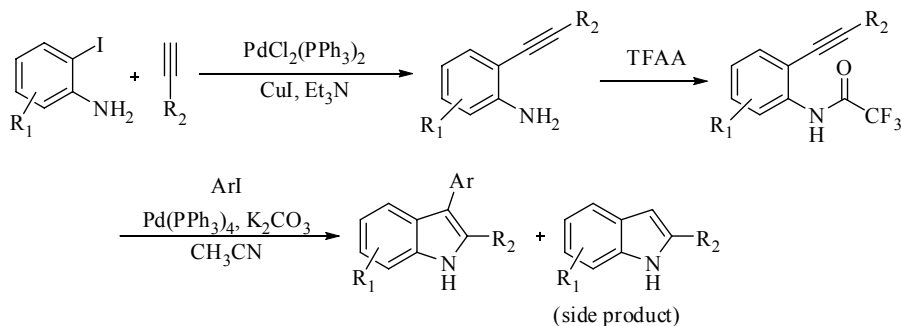
Vittorio Farina was one of the plenary lecturers and his talk was based on the desire to have an effective and scalable approach to 2-heteroaryl substituted indoles. The work eventually led to the preparation of 2,3-disubstituted indoles in a regioselective manner. As shown in Scheme 24, Farina and coworkers have recently developed a novel Pd-catalyzed regioselective indolization of 2-bromo or 2-chloroanilines with alkynes based on Larock's chemistry (R. C. Larock & E. K. Yum, *J. Am. Chem. Soc.* **1991**, *113*, 6689; R. C. Larock, E. K. Yum, M. D. Refvik, *J. Org. Chem.* **1998**, *63*, 7652.).

Scheme 24



This method had the common problem of difficult removal of the minor regioisomer, which led them to investigate the Cacchi reaction as shown in Scheme 25 (A. Arcadi, S. Cacchi, F. Marinelli, *Tetrahedron Lett.* **1992**, *33*, 3915).

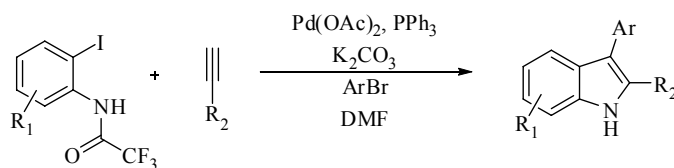
Scheme 25



This reaction involves the Sonogashira coupling, acylation with trifluoroacetic anhydride and the cyclization by aminopalladation and reductive elimination. The drawback of this method is the stepwise fashion and use of a lot of expensive Pd catalyst. It was the practical one pot process for the preparation of 2,3-disubstituted indoles using Cacchi's protocol that Farina based most of his lecture on.

After evaluating the effects of different bases, solvents, and catalysts it was determined that the best conditions for the one pot synthesis were the following: (a) use of trifluoroacetyl as a nitrogen protecting group, (b) K₂CO₃ as base and DMF as solvent, (c) use of Pd(OAc)₂ and Ph₃P and (d) a reaction temperature of 60 °C (Scheme 26).

Scheme 26



This Pd-catalyzed indolization procedure allows for the rapid and high yielding synthesis of a variety of 2,3-disubstituted indoles regioselectively under mild conditions (Table 1).

Table 1

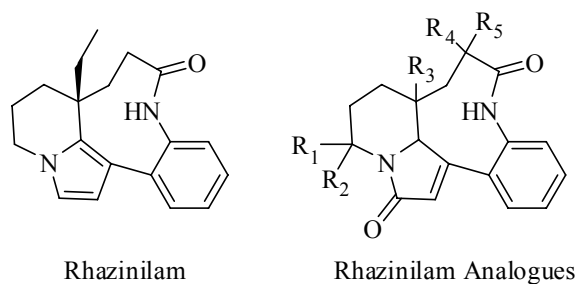
entry	reaction time	product	yield (%)
1	0.5 h		91
2	1.0 h		60
3	5.0 h		86
4	3.8 h		94

“The Use of Mukaiyama Aldol Reaction in the Synthesis of Rhazinilam Analogues”

Ana-Maria Buciumas, Olivier Vallat and Reinhard Neier, University of Neuchatel, Neuchatel, Switzerland

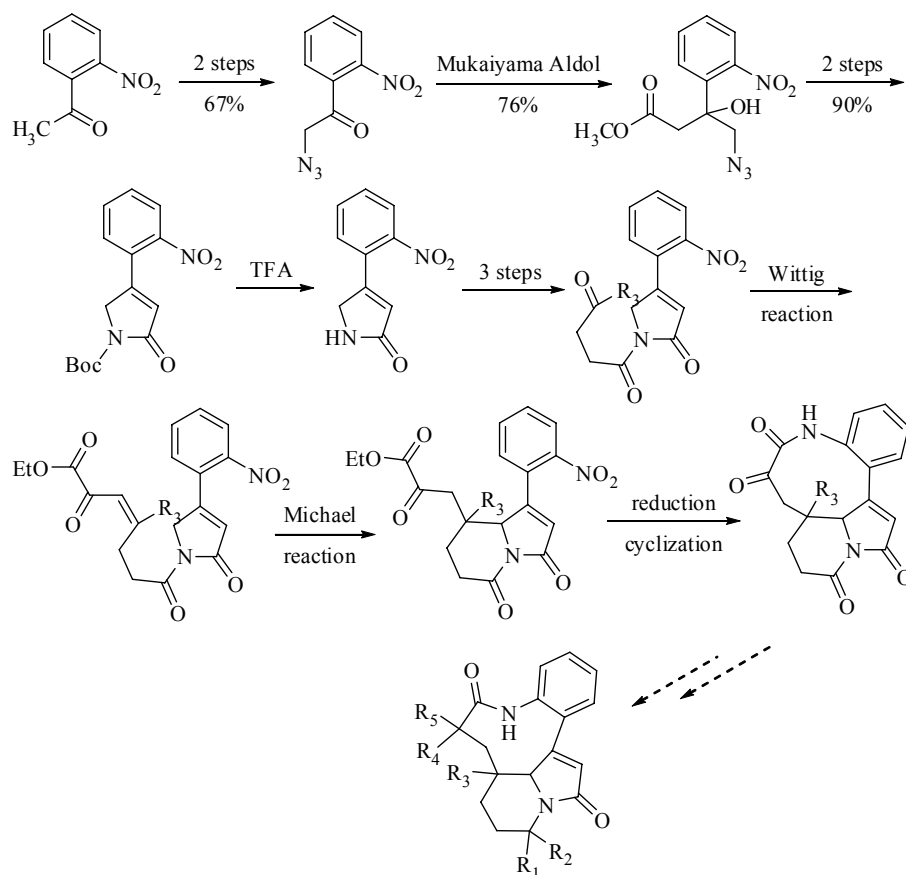
This poster was presented to show the proposed synthesis used by this group in order to make analogues of Rhazinilam (Figure 19).

Figure 9



Rhazinilam is a potent in-vitro anti-tumor agent. It interacts with microtubules formed during cell division and prevents them from depolymerising into tubulin. This disrupts the cell mitosis by blocking anaphase. Although not complete, the synthetic pathway that the group intends to use can be seen in Scheme 27. The group was able to get what they considered their key reaction, the Mukaiyama Aldol, to work in 76% yield.

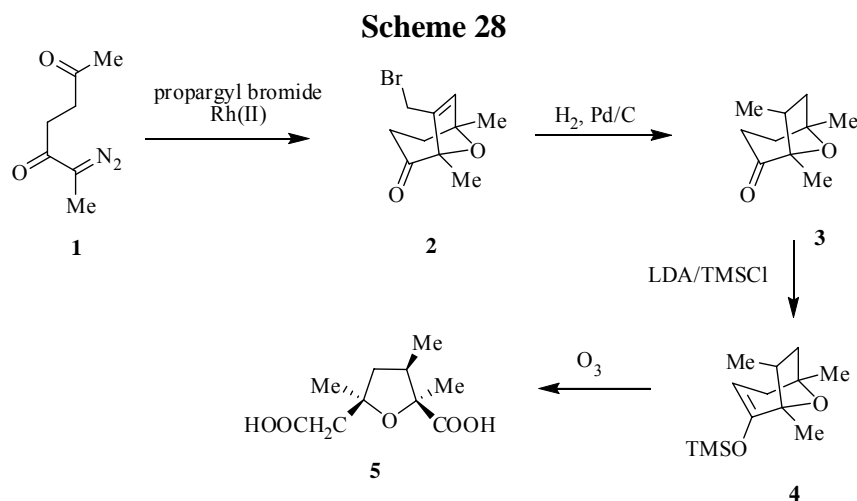
Scheme 27



“The Synthesis of Heterocycles Using Cascade Chemistry”

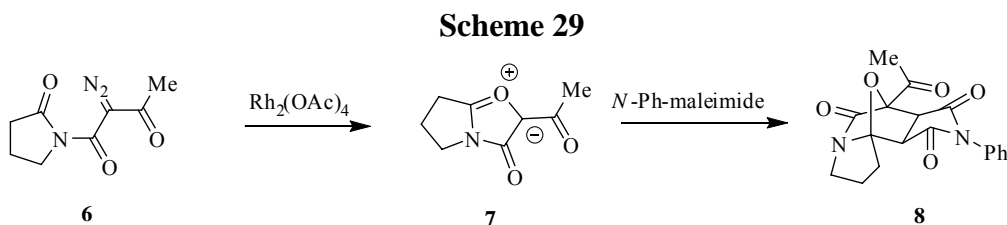
Albert Padwa, Emory University

A major challenge in organic synthesis today is to devise reactions that can form several carbon-carbon bonds in one operation leading to the construction of polycyclic structures with proper regio- and stereochemical control. Tandem or cascade processes occupy a central role in molecular construction, and new methods which lead to synthetically versatile arrays are particularly valuable. In recent years the research efforts of the Prof. Albert Padwa group have been concerned with application of the metallo carbenoids to the selective formation of polycyclic systems. Several distinct synthetic methodologies based of this strategy were presented on the conference. One of the early examples included synthesis of *cis*-nemorensic acid depicted on Scheme 28.

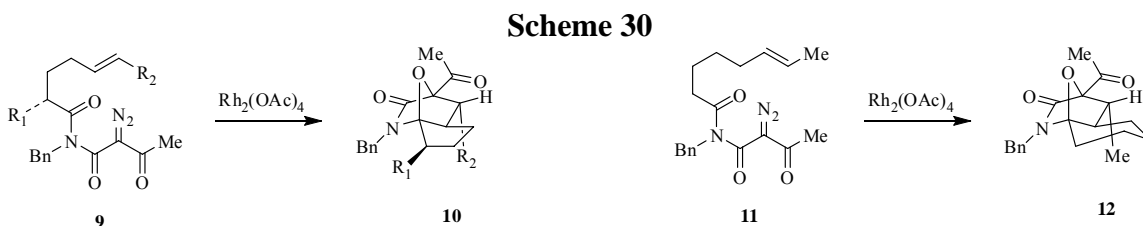


Diazodione **1** (readily available from levulinic acid and diazoethane) undergoes Rh₂(OAc)₄-catalyzed tandem carbonyl ylide formation-cycloaddition with propargyl bromide to give cycloadduct **2**. Its reaction with H₂-Pd/C in MeOH effected both hydrogenolysis of the C-Br bond and *exo* selective alkene hydrogenation to give a single saturated ketone **3** (92%), with the correct relative stereochemistry at all three stereocenters for *cis*-nemorensic acid synthesis. Formation of the silyl enol ether **4** (90%) under standard conditions was followed by oxidative cleavage to give *cis*-nemorensic acid **5**. This latter step was efficiently carried out (97% from silyl enol ether **4**) by ozonolysis and reaction of the crude ozonide with aqueous formic acid and hydrogen peroxide.

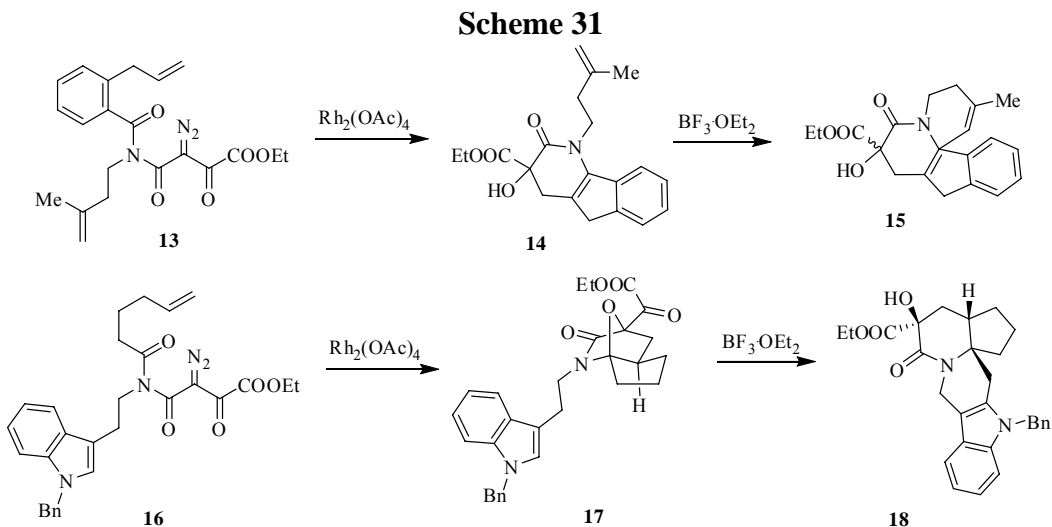
Treatment of diazo lactam **6** with rhodium catalyst leads to the formation of the intermediate isomünchnone **7** which undergoes further cycloaddition with *N*-phenylmaleimide to afford polycyclic compound **8** (Scheme 29).



Other examples included intramolecular cycloadditions of the unsaturated isomünchnones **9**, and **11** to yield complex polycyclic lactams **10** and **12**, respectively (Scheme 30).

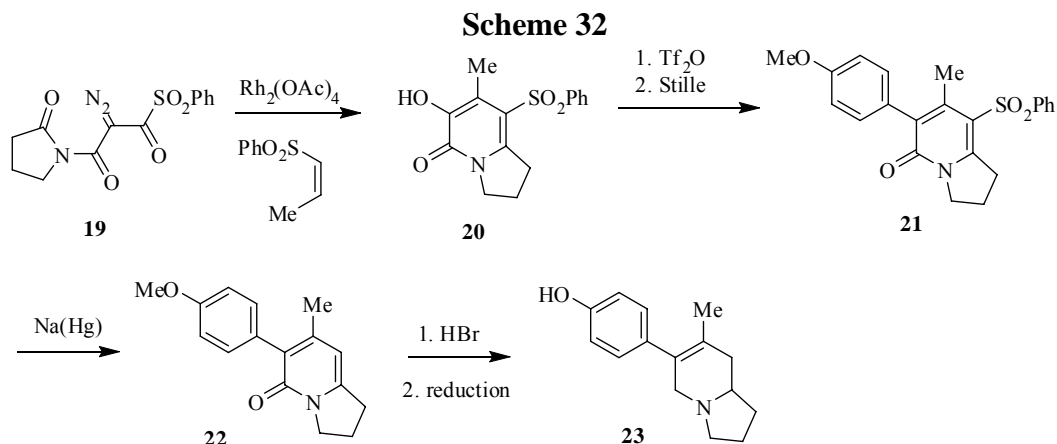


This methodology was further extended to tandem cyclization-cycloaddition-cationic cyclization sequence. In this case the intramolecular cycloaddition of isomünchnone dipoles containing alkenyl π -bonds produces oxabicyclic amides. These cycloadducts can be further employed as masked *N*-acyliminium ions for cationic π -cyclizations as exemplified by synthesis of compounds **15** and **18** as an approach to B-ring homologues of erythrinane alkaloids (Scheme 31).

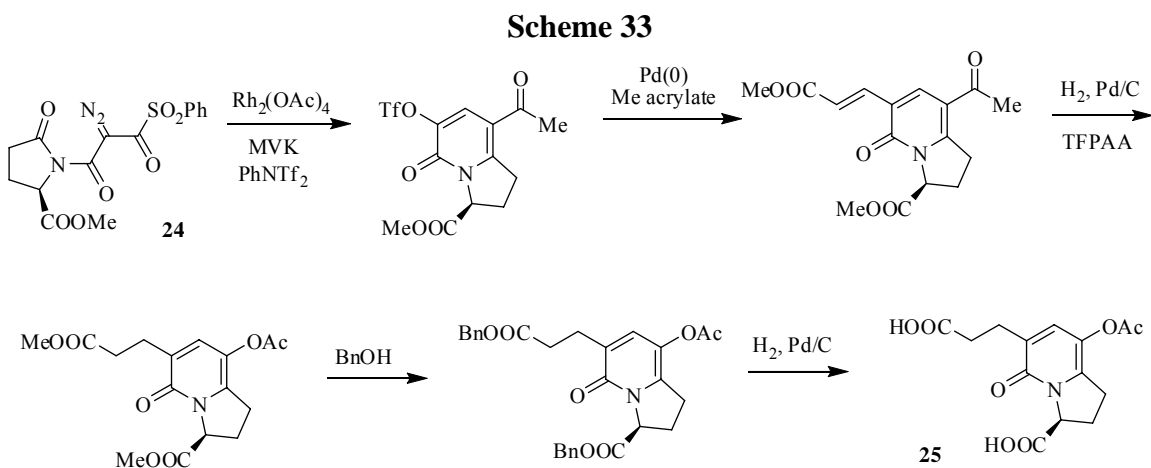


Synthetic scope of the method can be further demonstrated by synthesis of pyridone based bicyclic systems. Reaction of *R*-diazouimide **19** with *cis*-1-(phenylsulfonyl)-1-propene and a catalytic quantity of Rh(II) acetate provides the expected 3-hydroxy-2(1*H*)-pyridone **20** in 51% isolated yield (Scheme 32). Conversion of **20** to the corresponding vinyl triflate (86%), followed by Stille coupling with tributyl(4-

methoxyphenyl)tin, gives the aryl-substituted 2-pyridone **21** in 72% yield. Desulfonation of **21** can be performed using Raney nickel to give 2-pyridone **22** in 90% yield. Heating with 48% HBr followed by reduction (LiAlH_4 , AlCl_3) gives (\pm)-ipalbidine **23** in eight steps in 17% overall yield.



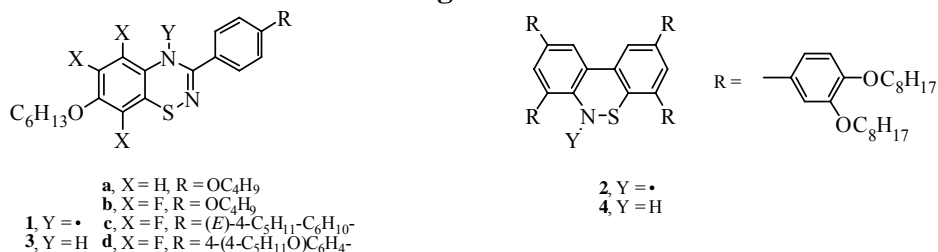
Synthetic sequence started from the similar cyclization of diazoimide **24** results in potent ACE inhibitor A58365A **25**, as depicted in Scheme 33.



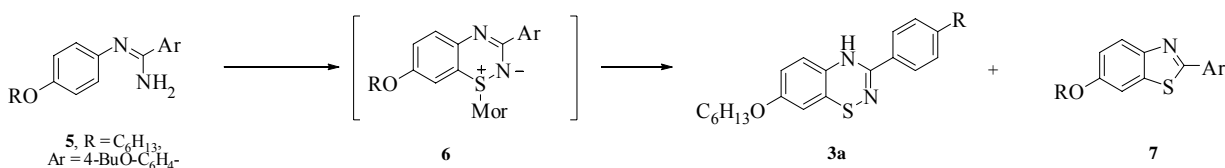
“Heteroaromatic Radicals as Components of Molecular Materials. Synthesis of Heterocyclic Liquid Crystals and Generation of Persistent Radicals”

Piotr Kaszynski, Vanderbilt University

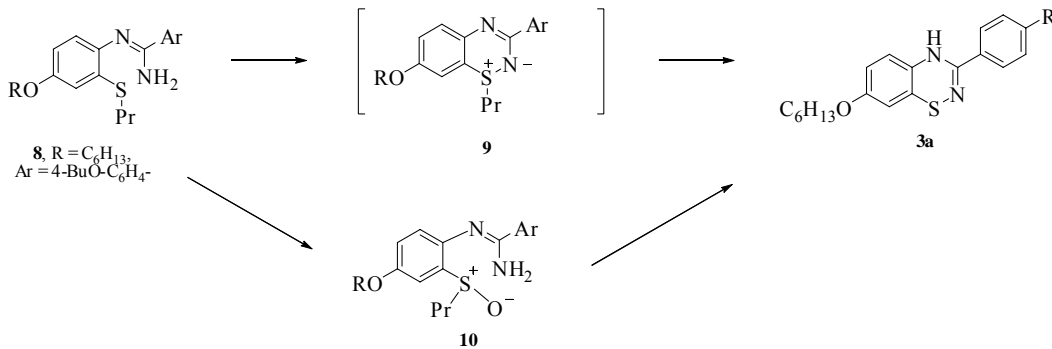
The research described by professor Kaszynski focused on the synthesis of 4H-benzo[1,2,4]thiadiazines (Figure 10) with three of the five compounds exhibiting liquid crystalline properties. Oxidation of these compounds led to the corresponding persistent radicals.

Figure 10

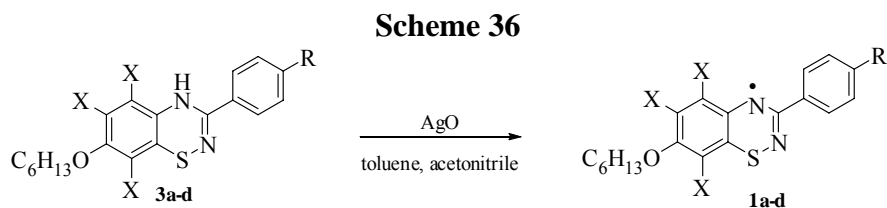
The initial synthesis of compound **3a** (Scheme 34) led to poor yields of an impure product. Amidine **5** was treated with a bis(4-morpholinyl)chlorosulfonium compound led to the ylide **6**. This compound was decomposed to provide **3a** in less than 5% yield. Professor Kaszynski also reported difficulty with the separation of **3a** from the by-product **7**.

Scheme 34

The synthesis was improved by using the synthetic route shown in Scheme 35. Attempts were first made to prepare the intermediate **9**, however difficulty was encountered with characterization of this compound. Compound **3a**, was then successfully prepared by going through the sulfoxide **10**. Compound **8** was oxidized with sodium periodate providing **10** in good yield. Thermolysis of **10** in toluene led to the desired compound, **3a**, in 12% yield. Preparation of the fluoro compounds **3b-3d** went better, 30-46% yield.

Scheme 35

Compounds **3a-3d**, were then used to generate radicals by treatment with AgO in a solution of acetonitrile and toluene (Scheme 36).

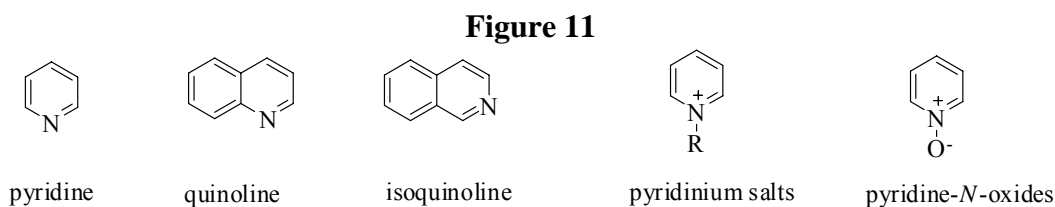


The radicals which were generated were measured by ESR and were shown to persist in solution for a few hours.

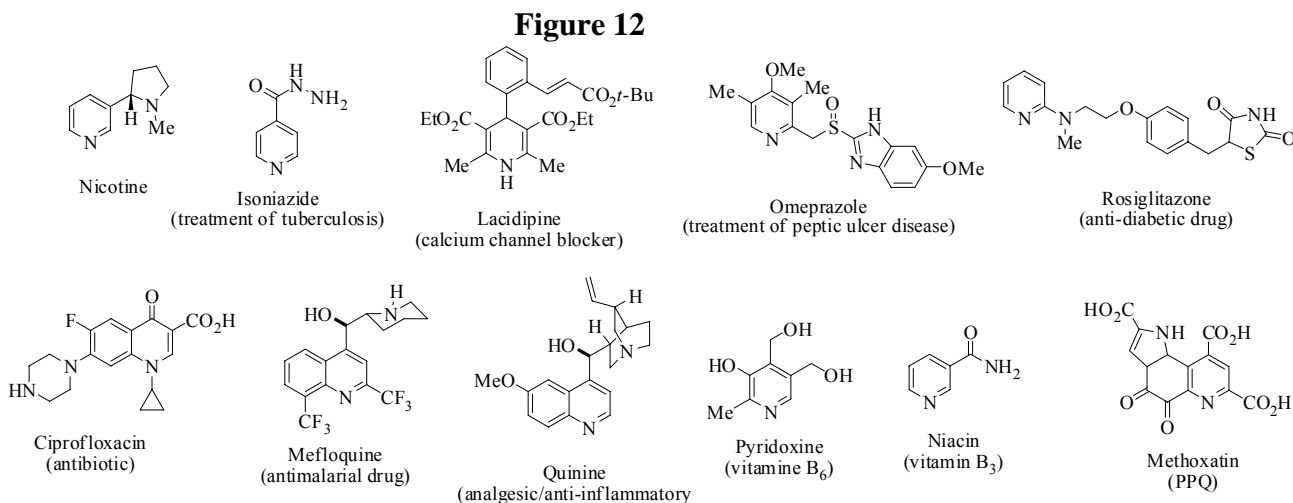
“The Azines-Chemistry and Ring Synthesis”

Professor John Joule, University of Manchester, UK.

Professor Joule presented a two hour short course on the synthesis, chemical and biological properties of azine compounds. On focus were pyridine, quinoline and isoquinoline. The course followed a brief review of the Huckel rule of aromaticity ($4n+2$) and covered the aromatic character of nitrogen containing aromatics (Figure 11).

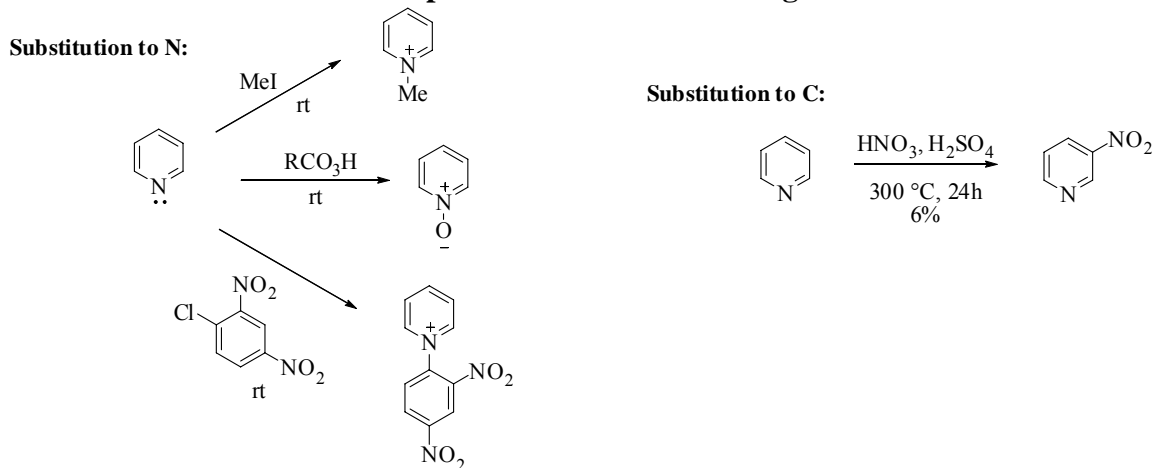


Pyridine makes up the nucleus of some important biological molecules. Some of these compounds, both natural and unnatural, can possess harmful or beneficial characteristics (Figure 12).



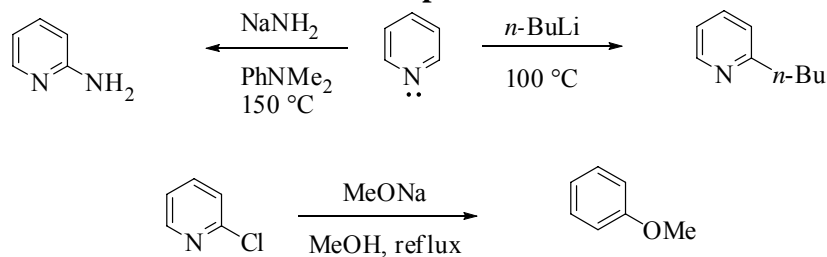
Pyridine Chemistry. In comparison to carbocyclic compounds such as benzene, substitutions to the ring may be difficult. While electrophilic substitution is undergone easily to the nitrogen in the ring, electrophilic substitution to the carbon can be quite difficult, especially with no activating groups present. Transformations which are carried out on benzene rings, such as the Friedel-Crafts reaction, are extremely rare (Scheme 37).

Scheme 37. Electrophilic substitution to nitrogen and carbon.



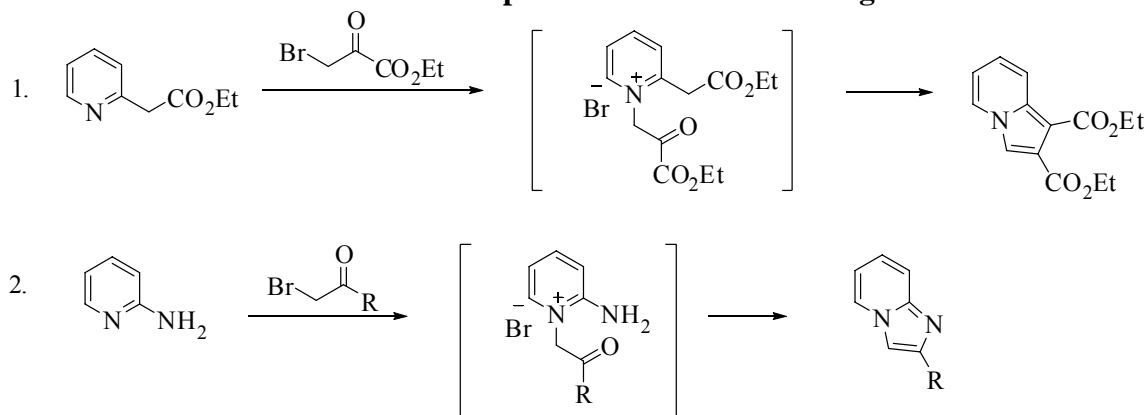
Pyridines can undergo nucleophilic substitution at the alpha position with strong nucleophiles and high temperatures. Substitution at the alpha or gamma positions if a leaving group is present. In these cases, elevated temperatures are usually required and yields may be low (Scheme 38).

Scheme 38. Nucleophilic substitution.



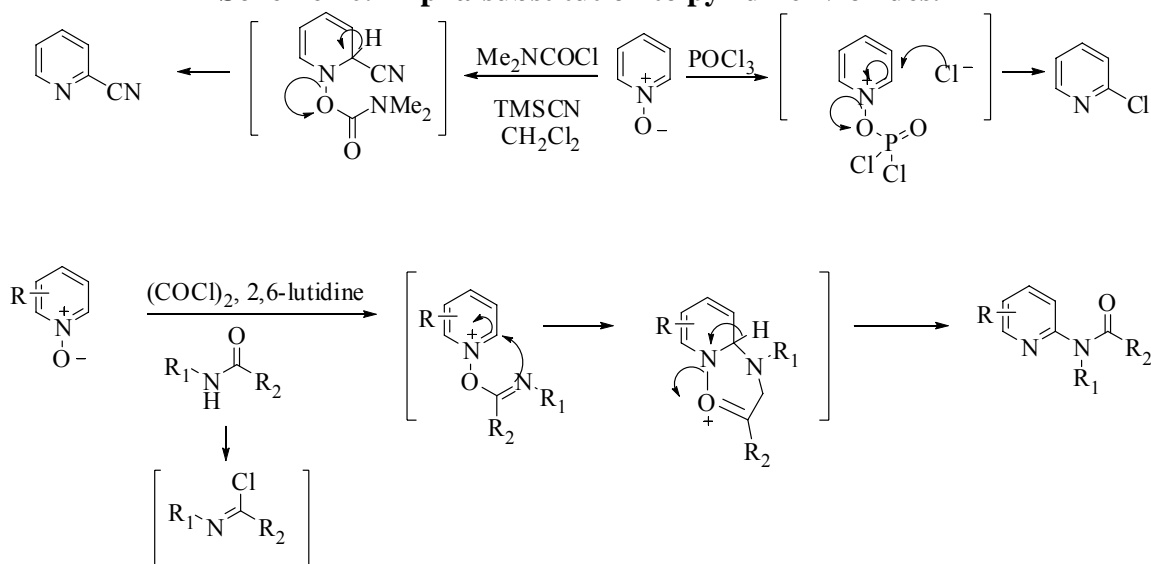
Although electrophilic substitution to the pyridine ring is difficult, electrophilic substitution at the nitrogen, by way of pyridinium salts occurs quite readily. Many additions have led to interesting heterocyclic compounds (Scheme 39).

Scheme 39. Electrophilic substitution at nitrogen.



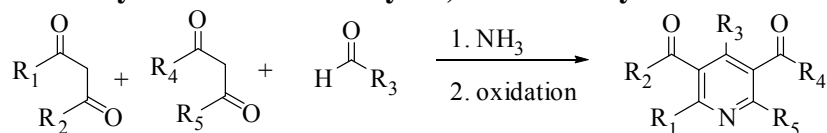
The introduction of alpha substituents can be accomplished by conversion of the pyridine to the *N*-oxide. This allows for the initial substitution at the *N*-oxide oxygen followed by rearrangement to alpha-substituted products (Scheme 40).

Scheme 40. Alpha-substitution to pyridine-*N*-oxides.



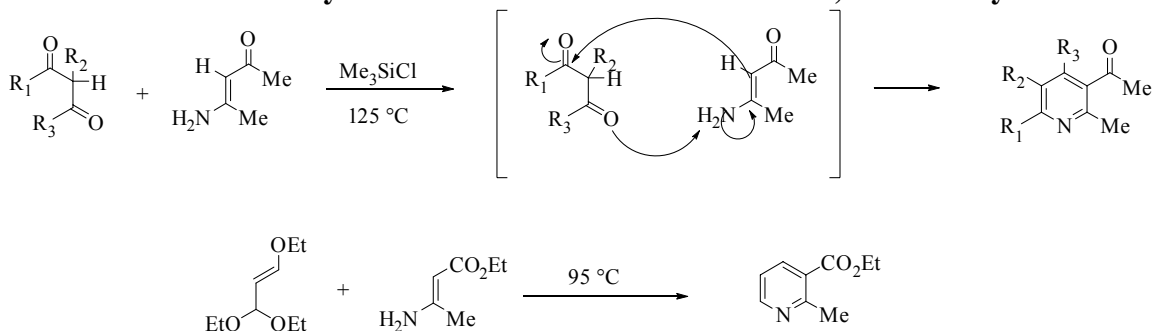
Ring Synthesis of Pyridines and Quinolines. The rings of pyridines and quinolines have been constructed in various ways to provide useful substituted compounds. The following schemes show a few synthetic approaches to these ring systems. Scheme 41 shows a synthesis of pyridine from aldehydes, active methylenes and ammonia.

Scheme 41. Pyridines from aldehydes, active methylenes and ammonia.



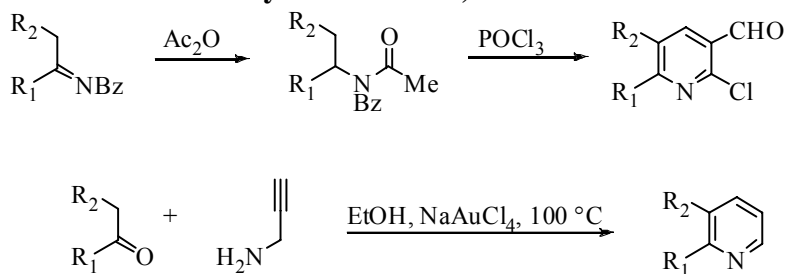
Scheme 42 shows a pyridine synthesis from a beta-amino-enone and a 1,3 dicarbonyl compound to provide a highly substituted pyridine compound.

Scheme 42. Pyridine from beta-amino-enone and 1,3-dicarbonyl.



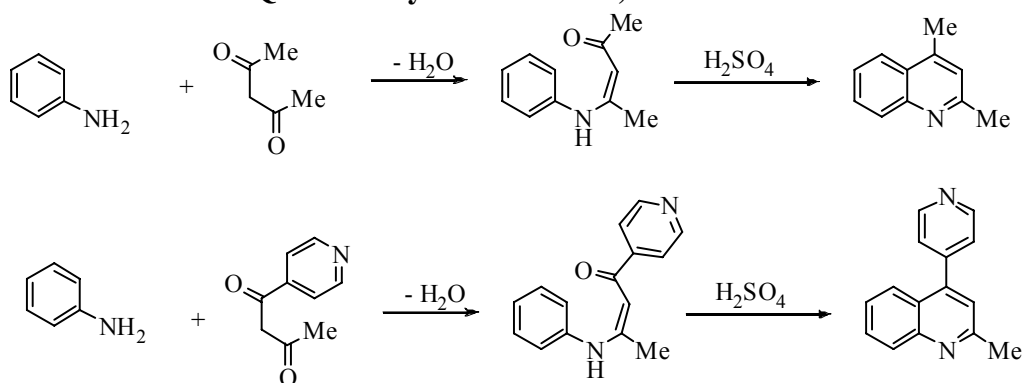
Pyridines have also been constructed by forming the 3,4 bond as shown in Scheme 43.

Scheme 43. Pyridine from 3,4-bond formation.



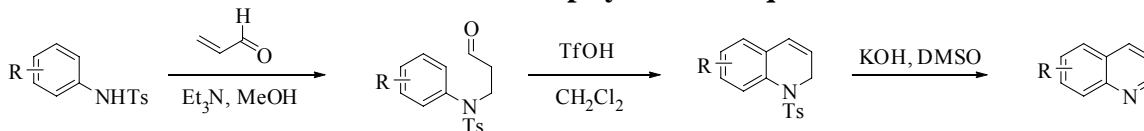
Quinolines can be constructed in a similar fashion to pyridines. Scheme 44 shows a quinoline synthesis from a 1,3-diketone and aniline. Similar to the pyridine synthesis, and early connection is followed by ring closure and aromatization.

Scheme 44. Quinoline synthesis from 1,3-diketones and aniline.



Quinolines can be prepared by using the Skraup reaction. In this case, enals or enones are reacted with anilines to provide the desired quinoline compound as shown in Scheme 45.

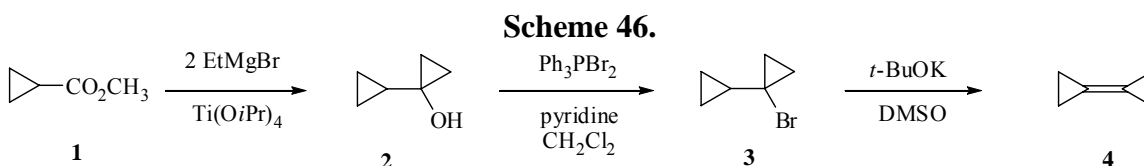
Scheme 45. The Skraup synthesis of quinolines.



“New Routes to Versatile Heterocycles from Small Ring Compounds”

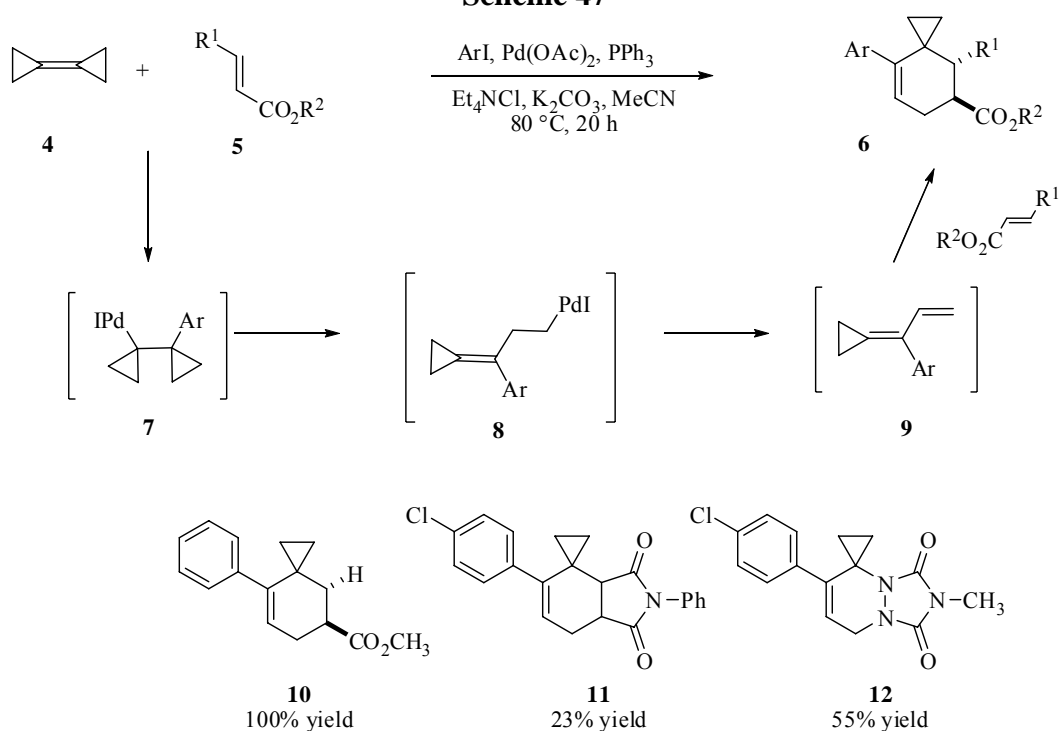
Armin de Meijere, University of Gottingen, Germany

This seminar focused on compounds containing small rings and their use as building blocks for larger systems. Incorporation of a cyclopropyl group into the building blocks was a major aspect of this research. Scheme 46 shows the preparation of bicyclopropylidene from cyclopropyl methyl ester **1** (A. de Meijere, *et al.*, *J. Org. Chem.* **1993**, 58, 502). This three-step process includes addition of ethylmagnesium bromide in the presence of titanium isopropoxide, followed by bromination to give intermediate **3**. Elimination of HBr using potassium *t*-butoxide provides bicyclopropylidene **4**. All steps were in good yield.



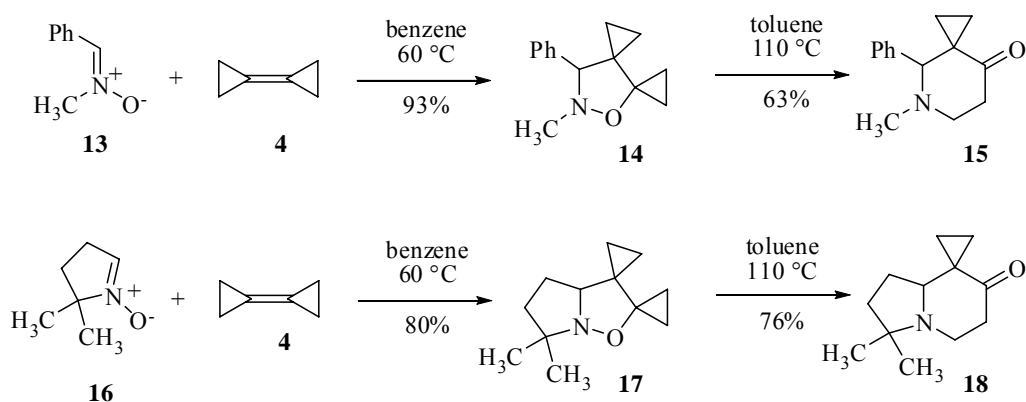
Scheme 47 shows how bicyclopropylidene **4** was used to make larger cyclopropyl-containing compounds **6** using an aryl iodide and substituted olefins **5** with palladium catalysis (H. Nuske, *et al.*, *Chem. Eur. J.* **2002**, 8, 2350). This procedure, described as a “domino Heck-Diels-Alder reaction”, presumably involves insertion of palladium and addition of the aryl group to give intermediate **7**, followed by rearrangement and elimination to the diene **9**, and finally a Diels-Alder type reaction with olefin (dienophile) **5**. In the initial trials, the aryl group was substituted phenyl or pyridyl and R¹ was H or methyl ester, such as product **10**. In these cases, the yields for the reaction varied from 60-100%. The procedure was expanded to include dienophiles containing nitrogen, with some success (compounds such as **11** and **12** were prepared in lower yields).

Scheme 47



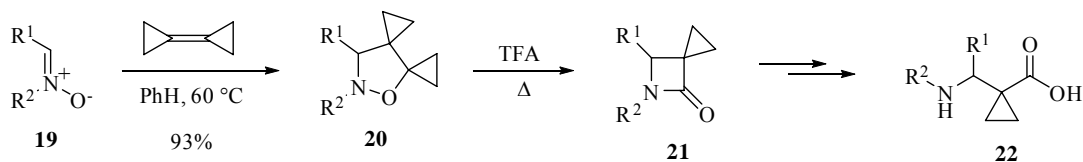
Dipolar cycloaddition of nitrones such as **13** and **16** with bicyclopropylidene afforded isoxazolidines **14** and **17**, as shown in Scheme 48. Heating the isoxazolidenes caused rearrangement to occur to give piperidinones **15** and **18**.

Scheme 48



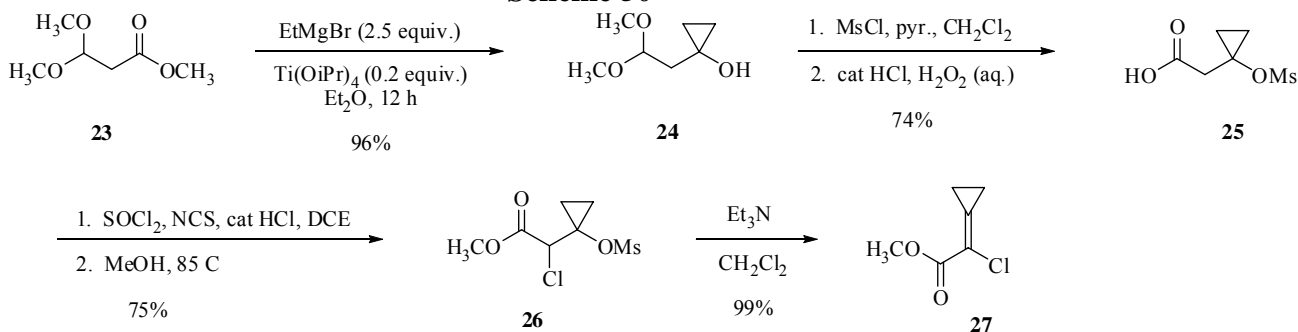
Additional use of the isoxazolidenes generated by cycloaddition is shown in Scheme 49 (F. M. Cordero, *et al.*, *J. Am. Chem. Soc.* **2000**, *122*, 8075). Heating compound **20** in acid afforded lactam **21** which was elaborated to amino acid **22**.

Scheme 49



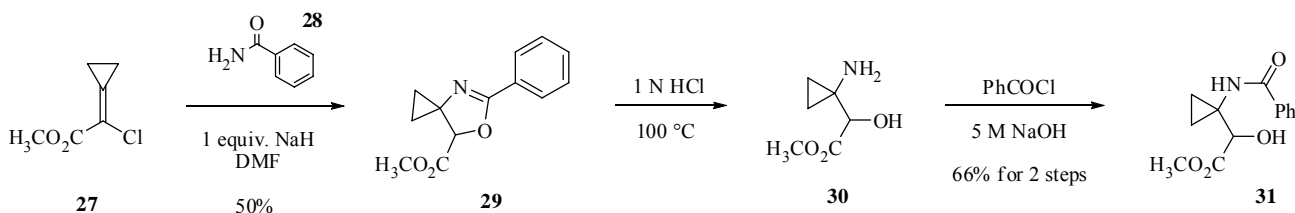
Synthesis of a cyclopropylidene acetate is shown in Scheme 50. The first step in this procedure is similar to that described in Scheme 1, and involves addition of ethylmagnesium bromide to ester **23** in the presence of titanium isopropoxide. The resulting tertiary hydroxyl is transformed into a leaving group. After installation of a chloro group and ester formation, treatment with base affords elimination to the cyclopropylidene acetate **27** (M. Limbach, *et al.*, *Adv. Synth. Catal.* **2004**, 346, 760).

Scheme 50



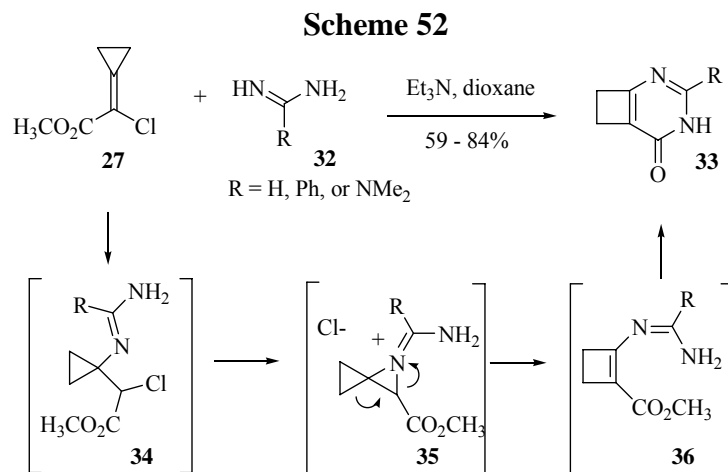
2-Chlorocyclopropylidene acetate (**27**) is also a versatile starting material as shown in Scheme 51) The addition of compound **27** to aryl amides afforded highly substituted and reactive oxazoles **29**. Treatment of the oxazole **29** with acid afforded ring-opening and cleavage of the benzaldehyde group to give compound **31** (M. W. Notzel, *et al.*, *J. Org. Chem.* **2000**, 65, 3850).

Scheme 51



2-Chlorocyclopropylidene acetate (**27**) was also reacted with amidines under basic conditions to give cyclobutene-annelated pyrimidones **33** as shown in Scheme 52 (M. W. Notzel, *et al.*, *Org. Lett.* **2002**, 4, 839). The postulated mechanism involves addition of the amidine to compound **27** in a Michael-type fashion, followed by attack of the nitrogen at the neighboring electrophilic center and displacing the chloride, to give

intermediate **35**. Rearrangement gives intermediate **36**, the attack of the nitrogen onto the ester gives bicycle **33**.



Addition of amines to 2-chlorocyclopropylidene acetate (**27**), followed by acylation of the amine provided intermediate **37** (Scheme 53). The first step in this procedure is similar to the first step in the mechanism of Scheme 52, in which compound **34** is the presumed reactive intermediate. Addition of a second amine to compound **37** gave cyclopropyl piperazinones **38**. Yields for this procedure ranged from 62-99%.

