

Albany Molecular Research, Inc.

Trip Report for

**“6th Annual Florida Heterocyclic Conference” Gainesville, Florida,
February 27–March 2, 2005**

**Jeremy A. Cody, Ph.D.; Matthew Isherwood, Ph. D.;
John W. Lippert, III, Ph.D.; John E. Manette, Ph.D.;
Scott V. Plummer, Ph.D.**

April 19, 2005

Albany Molecular Research, Inc.
Memorandum

TO: William G. Earley, Ph.D.; David J. Fairfax, Ph.D.; Michael A. Guaciaro, Ph.D.; Peter R. Guzzo, Ph.D.; Michael D. Ironside, Ph.D.; Richard King, Ph.D.; Douglas B. Kitchen, Ph.D.; Donald E. Kuhla, Ph.D.; David D. Manning, Ph.D.; Bruce F. Molino, Ph.D.; Bruce J. Sargent, Ph.D.; Eric Smart ; Michael P. Trova, Ph.D.; Paul F. Vogt, Ph.D.; Mark A. Wolf, Ph.D.; Jim Zhang, Ph.D.

FROM: Jeremy A. Cody, Ph.D.; Matthew Isherwood, Ph. D.; John W. Lippert, III, Ph.D.; John E. Manette, Ph.D.; Scott V. Plummer, Ph.D.

DATE: April 7, 2004

RE: “6th Annual Florida Heterocyclic Conference” Gainesville, Florida, February 27–March 2, 2005

Abstract: *The Sixth Annual Florida Heterocyclic Course and Conference was held over a three-day period from February 28th to March 2 at the University of Florida in Gainesville and was organized by ARKAT-USA with sponsorship from IUPAC. The two-part short course in heterocyclic chemistry was held in the afternoons and was presented by Drs. Alan Katritzky and Gordon Gribble. The conference contained lectures from world renowned heterocyclic chemists from both academia and industry. There was also a poster session ongoing throughout the event. This report highlights selected chemistry topics presented in both the short course and the lectures.*

All of the information presented below is referenced back to the speaker in question unless otherwise noted.

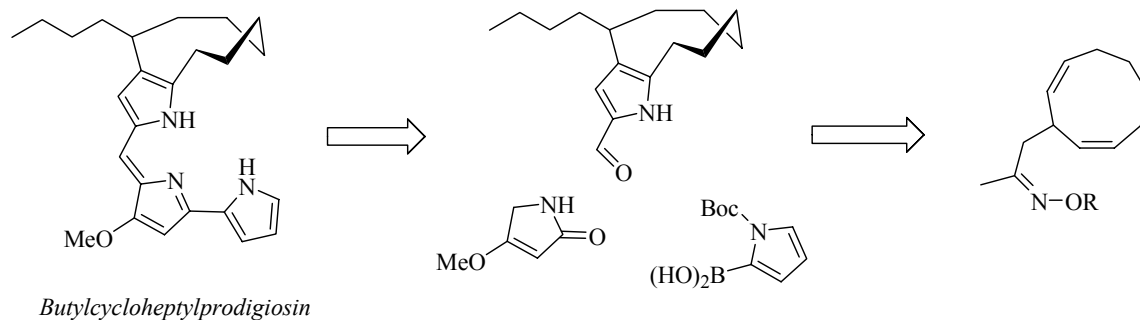
I. Plenary Lectures

“Transition Metal catalyzed Reactions for the Synthesis and Functionalization of Heterocycles” Professor Alois Fürstner, Max-Planck-Institute für Kohlenforschung

Professor Fürstner presented some of his group’s recent research efforts directed toward the synthesis of heterocyclic natural products. The prodigiosins are a class of conjugated pyrroles which display immunosuppressive properties and synergistic action with cyclosporin and FK506. A total synthesis of the structurally interesting butylcycloheptylprodigiosin was presented, the main strategy to which is outlined in the retro synthetic analysis in Scheme 1. The approach was to start with the nine-membered ring already in place early in the synthesis and utilize a novel palladium catalyzed

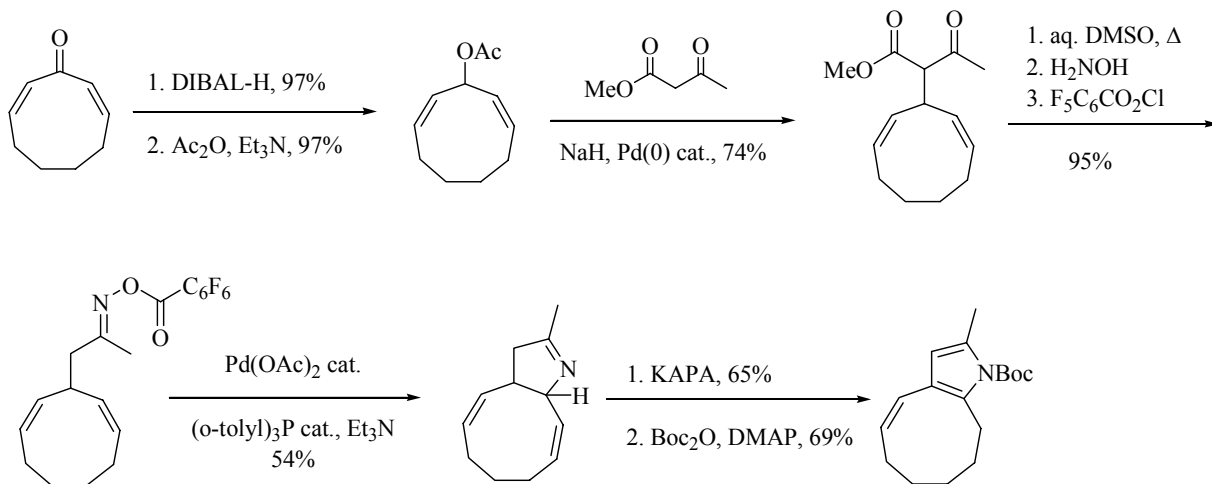
cyclization of a γ,δ -unsaturated *O*-pentafluorobenzoyloxime which was originally reported by Narasaka and coworkers. This reaction could be used to form the pyrrole ring which could then be appended sequentially with the other two pendant heterocycles.

Scheme 1



In the forward sense (Scheme 2), reduction of the cyclic α,β -unsaturated ketone and subsequent acylation afforded the diallyl acetate in high yield. Palladium catalyzed addition of methyl acetoacetate to the diallyl acetate produced the expected β -ketoester derivative in good yield. In situ hydrolysis and dicarboxylation of the β -ketoester afforded a methyl ketone which was converted to the oxime. *O*-Acylation of the oxime with pentafluorobenzoyl chloride afforded the cyclization precursor. The cyclization which proceeds via Pd-insertion between the *N*-*O* bond went in decent yield giving rise to a cyclic imine intermediate. The imine was aromatized to the 2-methylpyrrole using the strong base potassium diaminopyrrolamine and protected as the Boc-derivative.

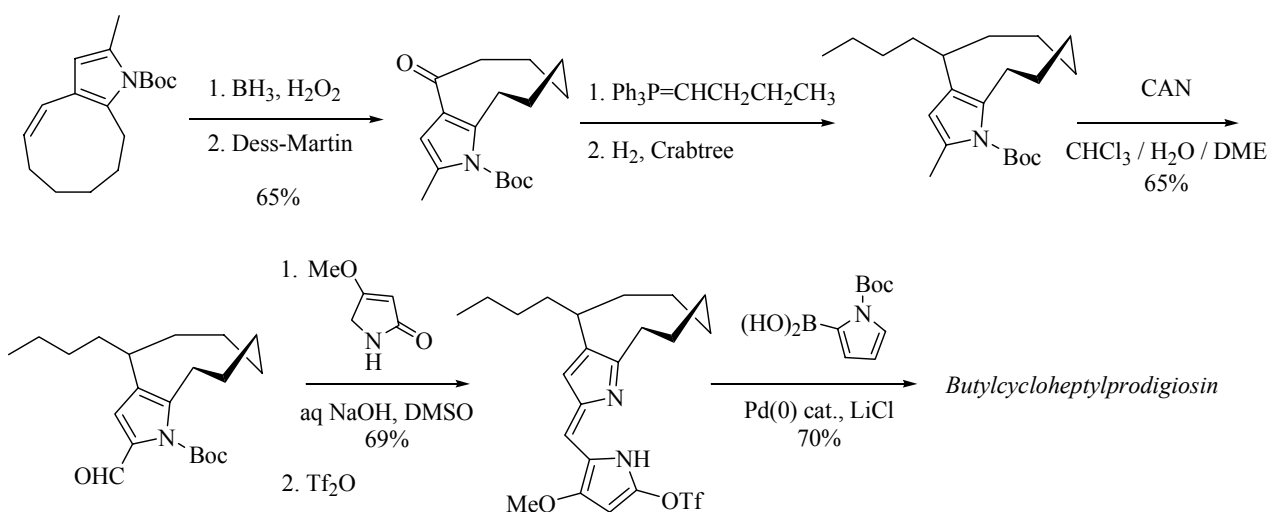
Scheme 2



The butyl side-chain was then incorporated in a series of four steps starting with regio-selective hydroboration of the endo-cyclic alkene (Scheme 3). The alcohol obtained after

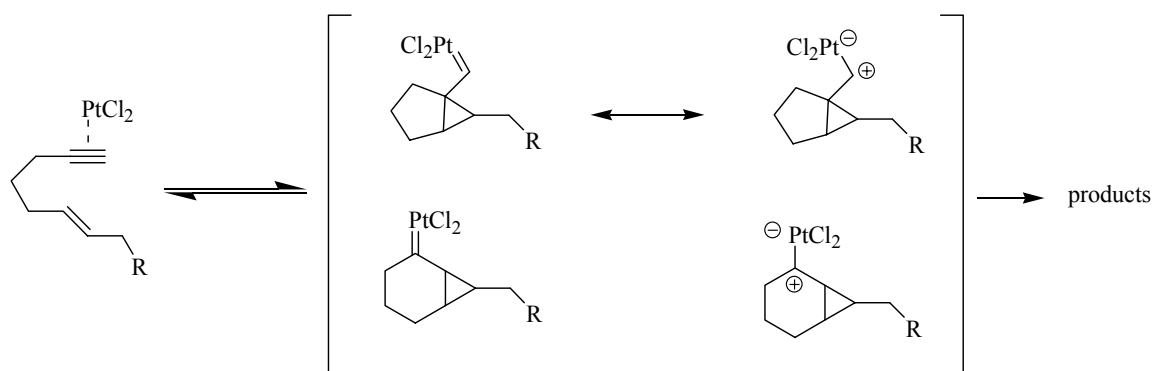
oxidative hydrolysis was converted to the ketone with the Dess-Martin periodinane. A standard Wittig reaction afforded an alkene which was subjected to a directed hydrogenolysis using Crabtree's catalyst. Critical to appending the remaining two heterocyclic rings was finding a method to functionalize the pyrrole methyl group. This was done by a ceric ammonium nitrate oxidation to the corresponding aldehyde. Biphasic solvent conditions ($\text{CHCl}_3/\text{H}_2\text{O}/\text{DME}$) were adopted as this was found to improve yields by limiting over oxidation. The aldehyde was then condensed with 4-methoxy-3-pyrrolin-2-one under basic conditions which also cleaved the Boc-protecting group. The resulting pyrrolin-2-one was converted to a pyrrole-2-triflate with a rearrangement of π -bonds in the neighboring ring. Finally, a Suzuki coupling was used to attach the terminal pyrrole and afford butylcycloheptylprodigiosin in good yield.

Scheme 3

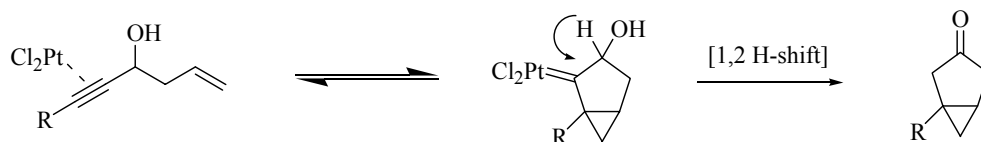


Professor Fürstner then moved on to discuss some new synthetic methodology developed in his group, namely platinum and gold catalyzed cycloisomerization reaction of alkenes. It has been shown by other groups that complexation of enynes to PtCl_2 engenders a host of selective cycloisomerization reactions which likely involve platinum carbenes as reactive intermediates (Scheme 4). These species are best viewed as latent cyclopropyl methyl cations that can evolve along different pathways. The cycloisomerization reactions result in a significant increase in structural complexity forming functionalized bicyclic cyclopropanes. The Fürstner group set out to extend the utility of the process for the synthesis of the bicyclo[3.1.0]hexanone skeleton, a structural motif which is present in a number of terpenes.

Scheme 4

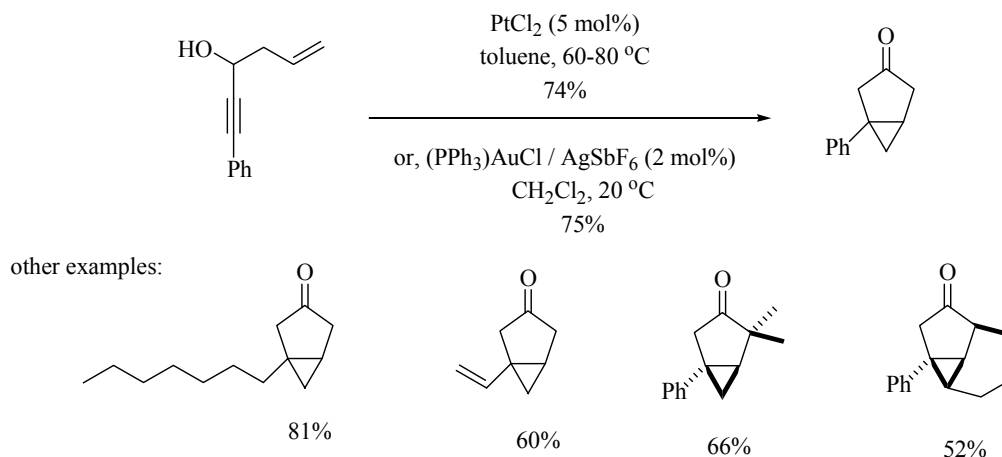


Mechanism and proposal



It was envisaged that incorporation of a hydroxyl group in the propargylic position might give access to an alternative transformation of synthetic utility. If the PtCl_2 induced cyclization occurred as predicted the intermediate carbene might be expected to undergo a 1,2-hydrogen shift. The theory proved successful and the expected product was obtained in a model reaction using catalytic PtCl_2 with toluene as solvent (Scheme 5). Four other examples also gave moderate to good yields. Evidence for the proposed 1,2-hydrogen shift reaction mechanism was gained by using a deuterium labeling technique. A propargyl alcohol incorporating a deuterium in the methine position was subjected to reaction conditions. On examination of the product it was found that the deuterium had migrated to the neighboring C-atom adjacent to the newly formed carbonyl group.

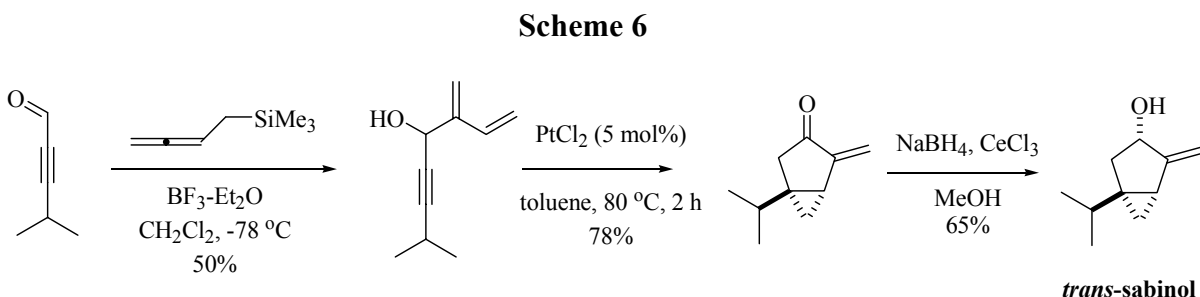
Scheme 5



It was also found that PtCl₂ could be replaced by (PPh₃)AuCl/AgSbF₆ as catalyst. The resulting cationic gold complex was particularly reactive and induced the cyclization at ambient temperature in CH₂Cl₂. Extending the practicality of the reaction further it was found that the procedure could be reduced to a one-pot process from precursor propargyl-aldehydes. Treatment of an aldehyde with allyl chlorodimethylsilane in the presence of PtCl₂ at 80 °C in CH₃CN enabled both an initial carbon-carbon forming reaction and the subsequent cycloisomerization.

The new methodology was used in the synthesis of the natural product *trans*-sabinol (Scheme 6).

A Lewis acid catalyzed addition of allenyl silane produced a 1,3-butadienyl derivative which underwent the cycloisomerization under the standard reaction conditions without incident. The ketone was reduced to give a 1:1 mixture of *cis*- and *trans*- alcohols which were separated by preparative GC.



References:

- (1) Narasaka, K. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1451
- (2) Fürstner et al. *Angew. Chem.* **2005**, in press. (prodigiosin synthesis)
- (3) Mamane, V.; Gress, T.; Krause, H.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654

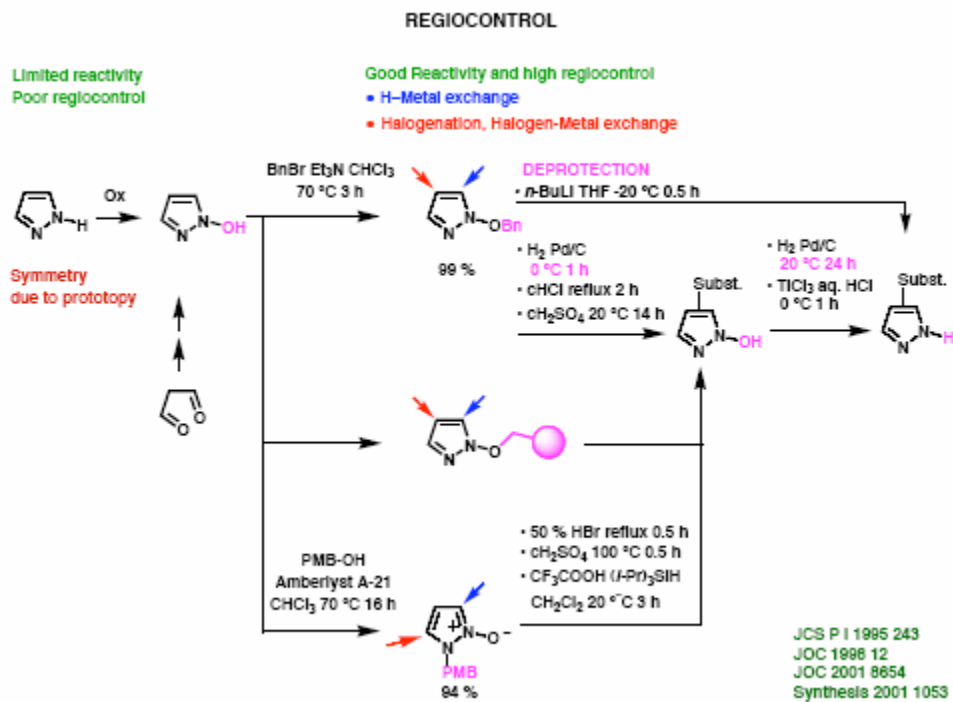
“Anion Based Strategies by Regiocontrolled Synthesis of Heterocycles” Mikael Begtrup, *Department of Medicinal Chemistry, The Danish University of Pharmaceutical Sciences.*

Dr. Begtrup gave a synthetically powerful presentation for the formation of a wide range of heterocyclic rings. The presentation was applicable for a wide-range of heterocyclic systems.

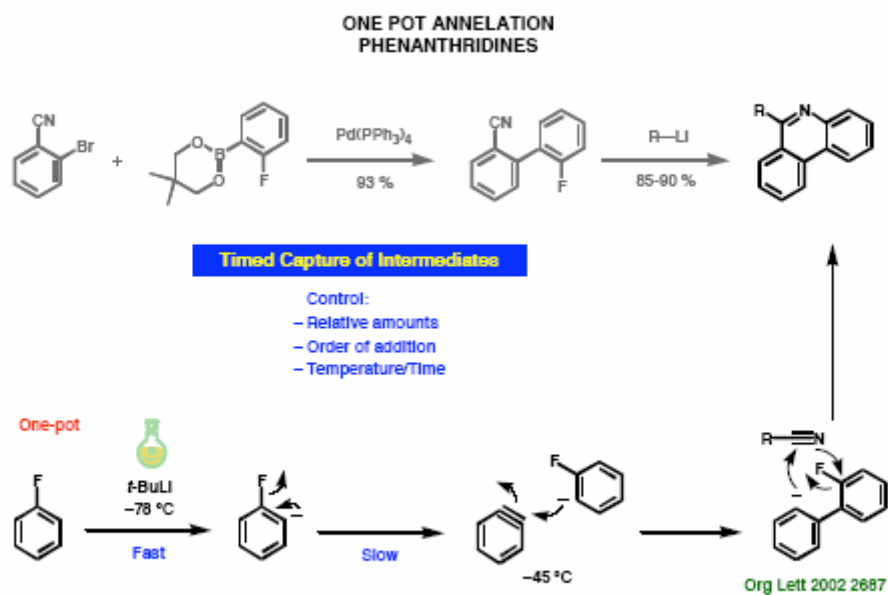
Schemes 7, 8, and 9 illustrate the regiocontrol one can have with a pyrazole system and two one pot synthetic schemes toward both phenanthridines and quinoxalines, respectively.

For further schemes and references I would recommend viewing his notes in full.

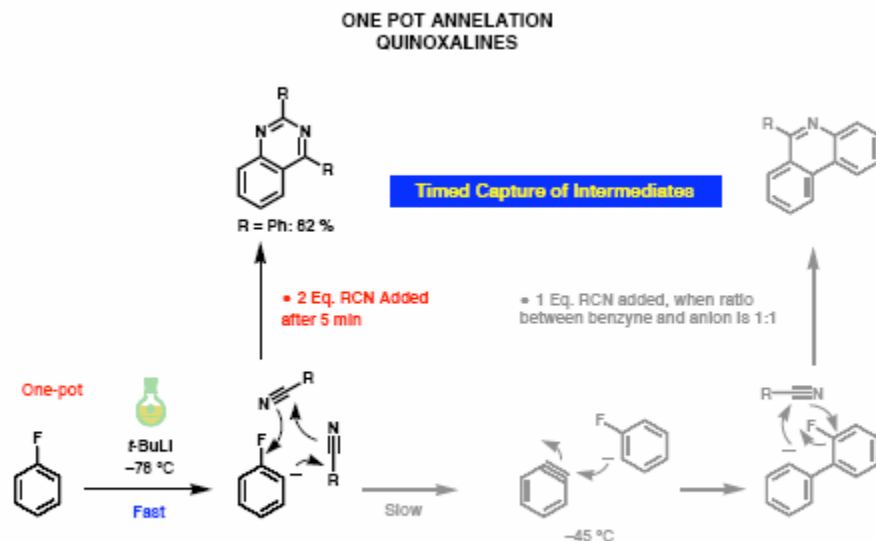
Scheme 7



Scheme 8



Scheme 9



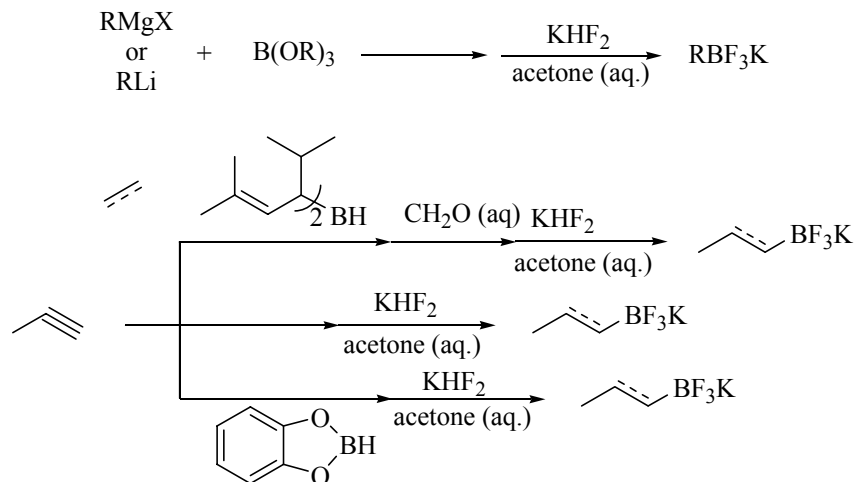
“Organotrifluoroborates in Selective Organic Synthesis”

Gary A. Molander, Department of Chemistry, University of Pennsylvania

One methodology project currently ongoing in the Molander group is the use of organotrifluoroborates in Suzuki-type cross coupling reactions. The organotrifluoroborates provide an alternative to tin (Stille coupling) and other boron derivatives (Suzuki-Miyaura coupling). Organotrifluoroborates have the same environmental advantages of other boron derivatives and are stable to air and moisture. The majority of the organotrifluoroborates are solids, easily accessed, atom efficient and compatible with many functional groups.

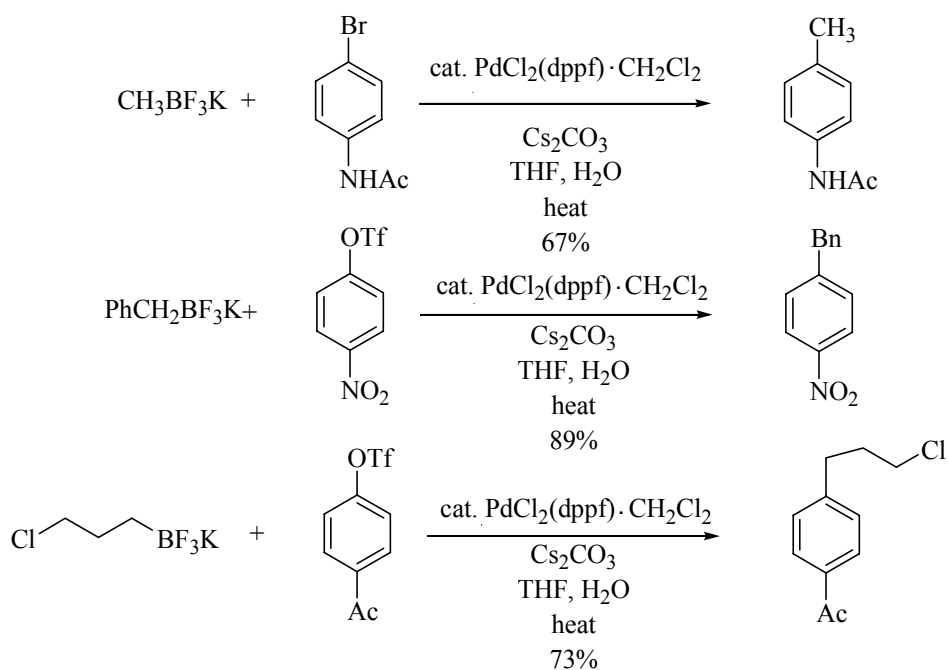
Organotrifluoroborates are prepared from other boron derivatives upon treatment with KHF_2 (Scheme 10).

Scheme 10
General Methods of Organotrifluoroborate Synthesis

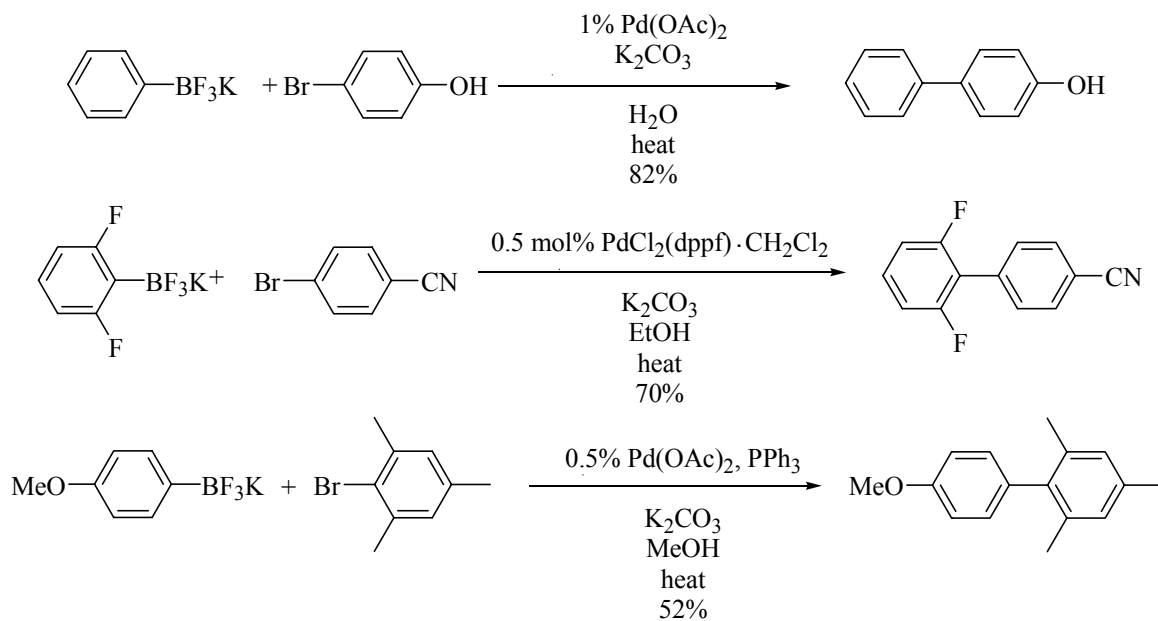


The Suzuki-Miyaura cross-coupling reactions of organotrifluoroborates provide good yields of coupled products with a wide range of tolerated functional groups. Some representative examples can be seen in Schemes 11-15. For further reading see Molander, G. A.; Bernardi, C. R. *J. Org. Chem.* **2002**, *67*, 8424-8429.

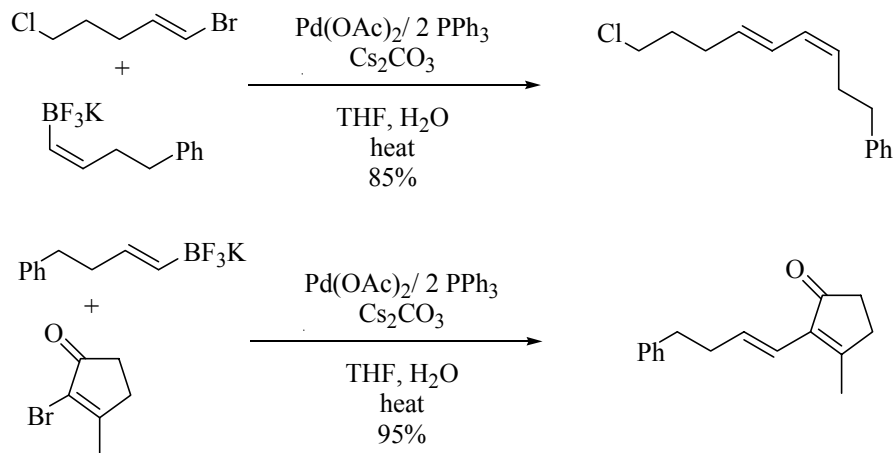
Scheme 11
Alkyl/Aryl Cross-Coupling



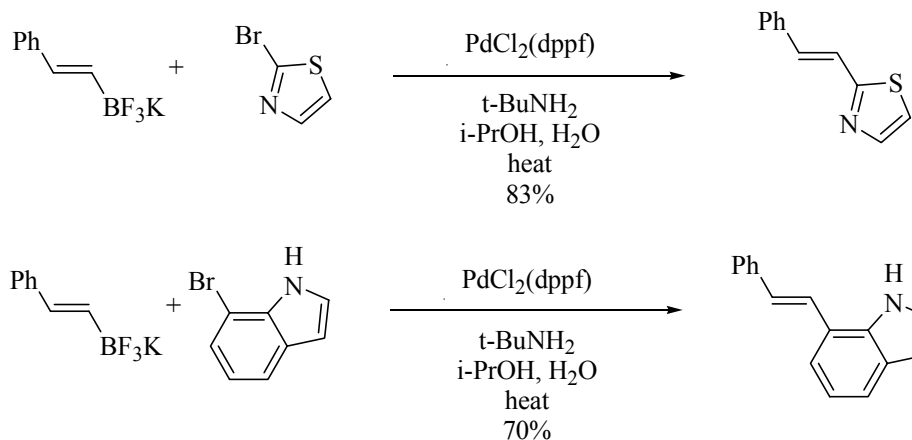
Scheme 12
Aryl/Aryl Cross-Coupling



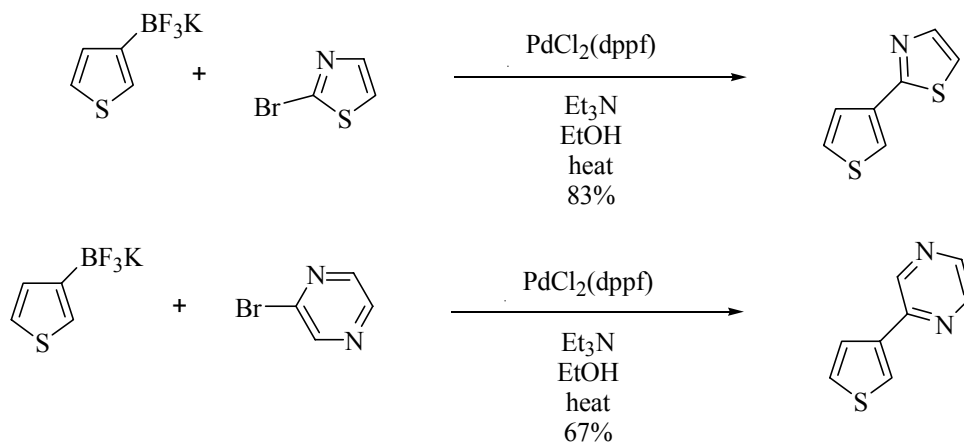
Scheme 13
Alkenyl/Alkenyl Cross-Coupling



Scheme 14 Alkenyl/Heteroaryl Cross-Coupling

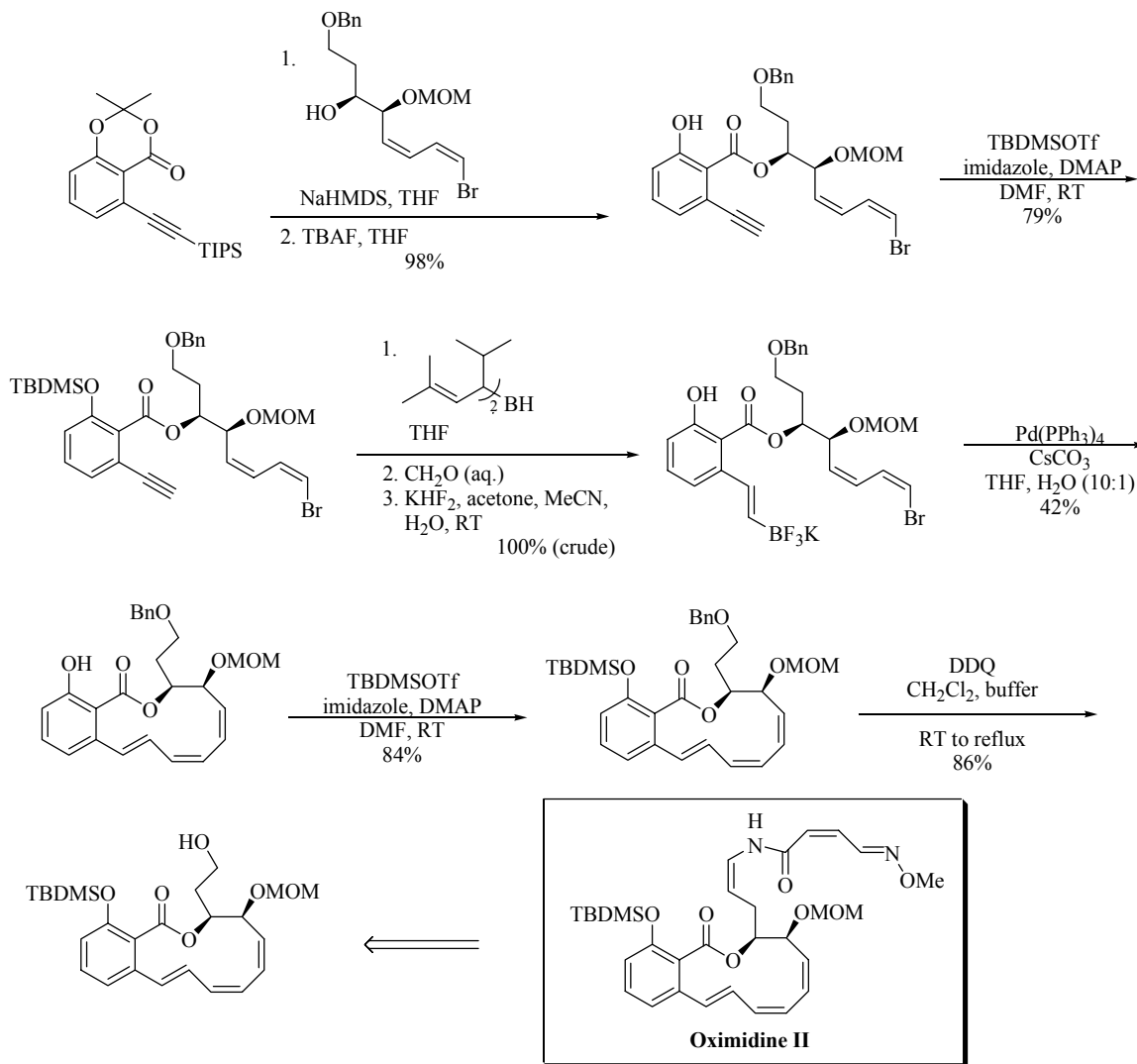


Scheme 15 Heteroaryl/Heteroaryl Cross-Coupling



To complete the talk and to validate the use of organotrifluoroborates in Suzuki-Miyaura cross-coupling reactions Gary Molander described work conducted in his lab for the formal total synthesis of Oximidine II (Scheme 16). Oximidine II is a salicylate enamide macrolide isolated from *Pseudomonas sp.* Q52002 with the observed biological activity to inhibit mammalian vacuolar-type H^+ ATPase. The Suzuki-type cross-coupling using potassium organotrifluoroborates was employed for the macrocyclization to provide the core of Oximidine II. The complete work is described in the reference: Molander, G. A.; Dehmel, F. *J. Am. Chem. Soc.* **2004**, *126*, 10313-10318.

Scheme 16
Molander's Formal Synthesis of Oximidine II

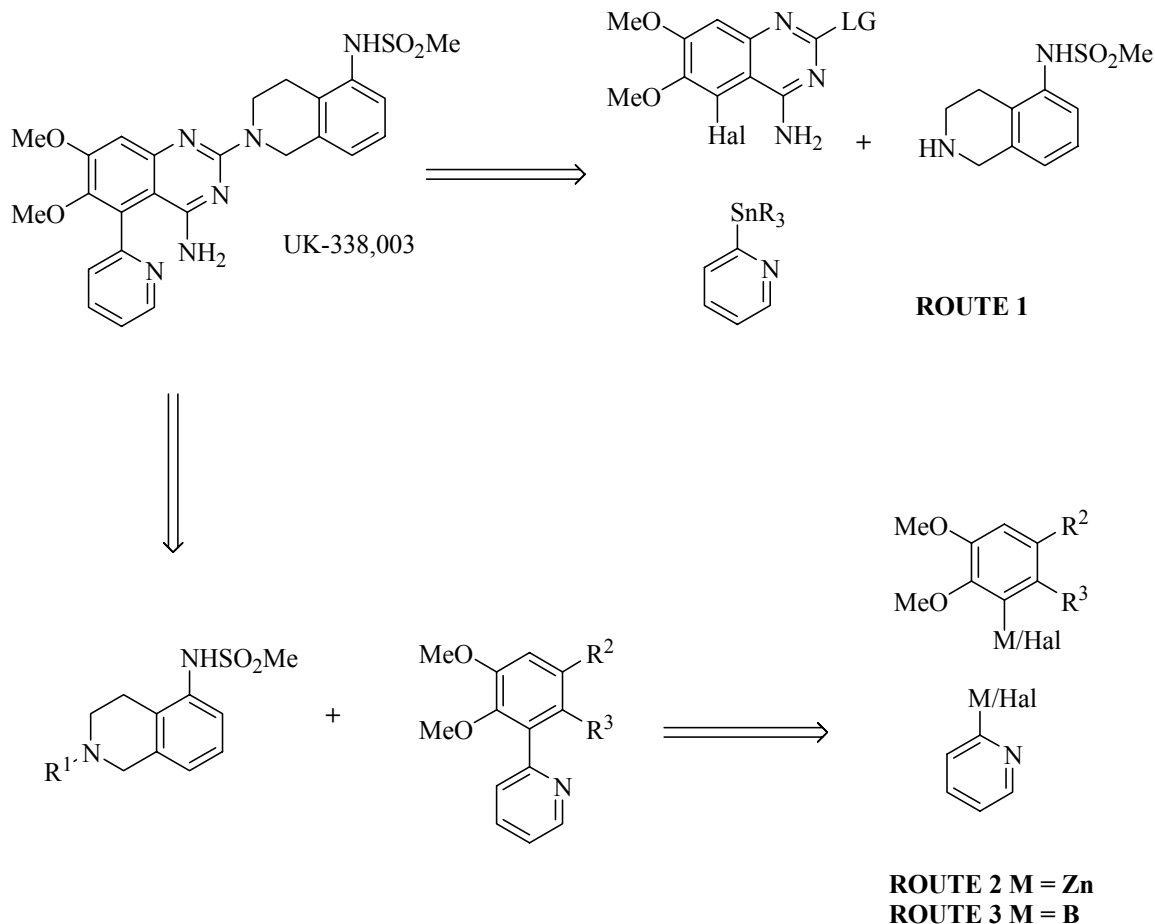


“Quinazolines, Pyridines and Isoquinolines-The Chemical Development of UK-338,003” Dr. Paul Hodgson, Pfizer, Ltd., Sandwich, UK

Dr. Paul Hodgson presented the process development work involved in the preparation of the compound UK-338,003. This quinazoline compound has been nominated for the treatment of benign prostatic hyperplasia. BPH is characterized by the enlargement of the prostate resulting in urethral constriction. The disease affects >50% of males over 60 in the US, and the probability of a 50 year old man requiring surgery for BPH during his lifetime is 25-30 percent. Scheme 17 below illustrates the retrosynthetic analysis for three basic routes described in the presentation. The two principal steps are the

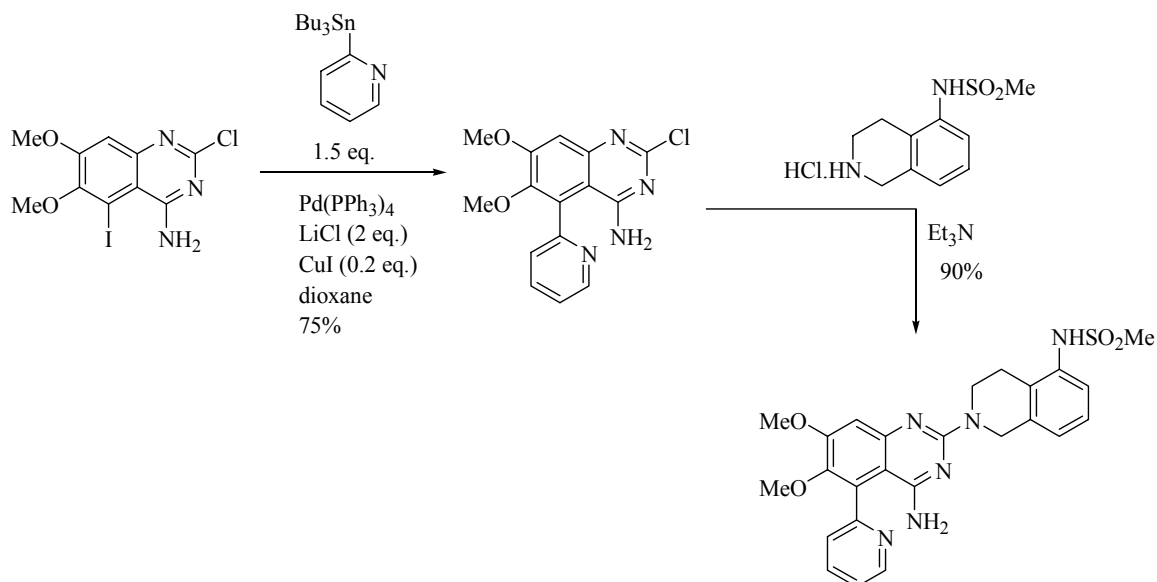
formation of the aryl-aryl bond (pyridine-quinazoline), as well as the incorporation of the isoquinoline moiety via annulation.

Scheme 17



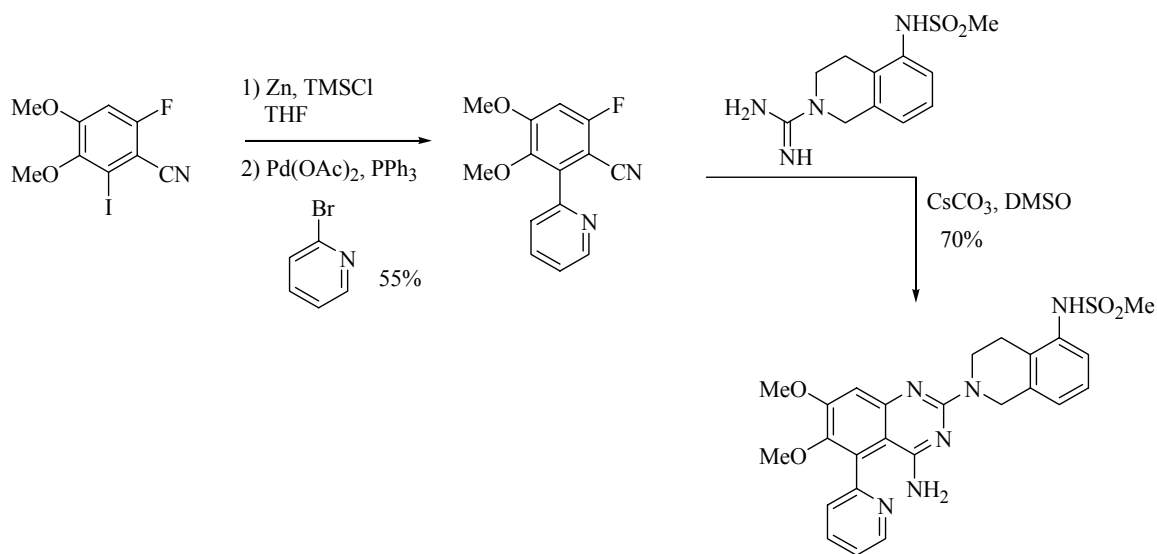
The bond-forming chemistry of Route 1 is shown in Scheme 18. The Stille coupling of the chloroquinazoline with the aryl stannane proceeded in acceptable yield; however pebble-like inorganic aggregates were formed in the reaction. The corresponding Suzuki reaction with 2-pyridine boronic acid was less successful. This procedure suffered from significant proto-dehalogenation. The condensation of the tetrahydroisoquinoline with the chloroquinazoline in the subsequent step, however, was successful.

Scheme 18



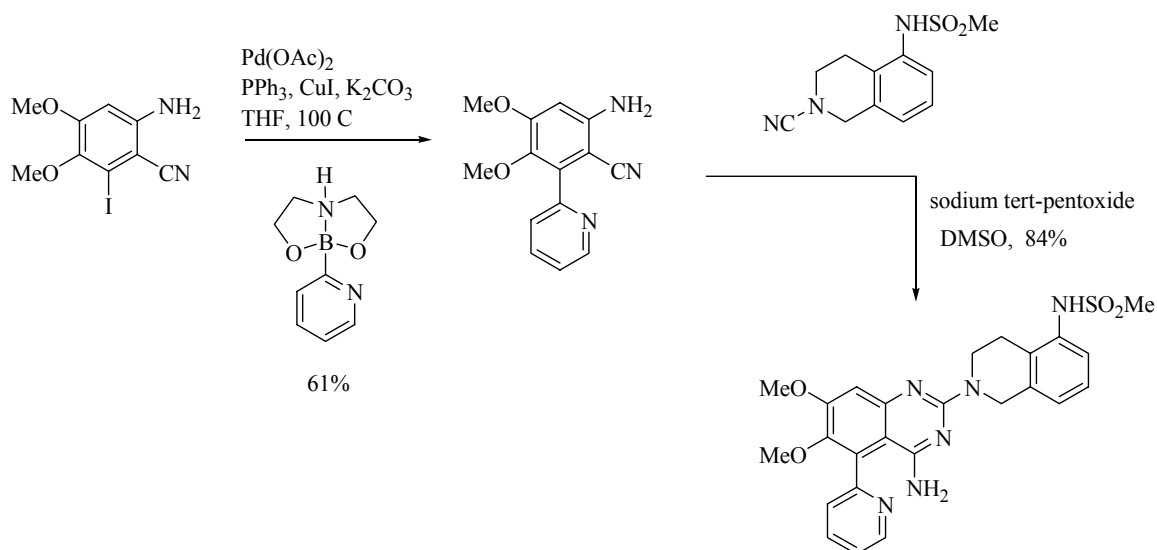
As the route described above was not commercializable due to scale-up problems with the Stille reaction, a second pathway was explored as shown below in Scheme 19. This route contained an initial aryl-aryl coupling of a zincate with 2-bromopyridine. In the kilo-lab a significant problem was encountered in two of the five runs. An in-process test of these runs indicated that the zincate was not formed to an appreciable extent. The zinc had to be filtered off, and the aryl iodide solution was resubmitted to the reaction conditions. The biaryl product was subsequently coupled to a tetrahydroisoquinoline-guanidine species in acceptable yields. Route 2 contained significant upgrades from Route 1. The waste generated from this process was estimated at 600 kg/kg, while that generated from Route 1 was 2720 kg/kg. The process was also quite convergent and displayed consistent performance upon scale-up.

Scheme 19



The difficulties encountered during the zincate coupling led to the development of a third route (Scheme 20) in which a Suzuki coupling was performed instead. This Suzuki coupling was achieved via the stable *N*-phenyldiethanolamine pyridyl boronate (Hodgson, Salingue *Tetrahedron Lett.* **2004**, *45*, 685). Very low levels of deiodinated by-product were encountered, and a 61% yield was achieved in the pilot plant. The annulation of the biaryl product with a tetrahydroquinoline-cyanamide species provided UK-388,003 in 84% yield in the pilot plant. This third route to the API was convergent and contained high yielding steps. The amount of waste was also reduced further to only 240 kg/kg.

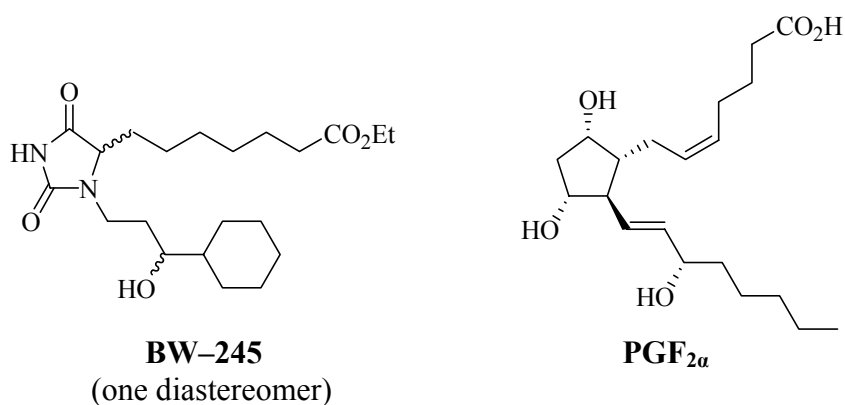
Scheme 20



“Heterocyclic Receptor Selective Prostaglandin Ligands” Mitchell A. deLong, *The Proctor & Gamble Co., Cincinnati, OH*

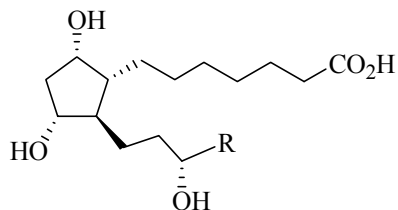
Early research into prostaglandin pharmacology revealed a possible role in bone growth acceleration in infants and in fracture healing. However, chemical instability, severe side effect profiles, and lack of reproducible activity across species slowed progress on active compounds.


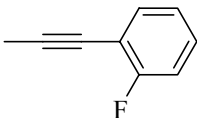
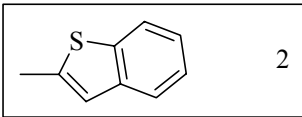
In the mid-1990's the prostaglandin receptors were cloned, allowing more accurate initial testing. This prompted Proctor & Gamble to reestablish a research program aimed at developing an anabolic agent for the treatment of osteoporosis. Initial efforts at evaluating many known prostaglandin receptor ligands identified BW-245 (see below for a structural comparison versus a natural prostaglandin, PGF_{2α}) as a potent agonist of the DP prostanoid receptor with a K_i of 0.3 nM in the hDP binding assay. Unfortunately,



chemists working with the compound suffered facial flushing, headache and nausea, similar to the severe side effects attributed to activity at the EP prostanoid receptors.

Subsequent work focused on PGF_{2α} which had good activity at the FP receptor (hFP IC₅₀ of 5 nM). Preparation of tetrahydro analogs produced some highly active compounds. The benzothiophene analog, with an hFP IC₅₀ of 2 nM and >10,000 nM at most other PG receptors, was chosen for development. Bone density studies and cross section analyses clearly demonstrated bone regeneration in rats and dogs comparable to that induced by parathyroid hormone (PTH) injections.



R	hFP IC ₅₀ (nM)
(CH ₂) ₄ CH ₃	450
CH ₂ OPh	10
CH ₂ O(<i>m</i> -ClPh)	2
CH ₂ SPh	2.5
CH ₂ S- 	5.5
CH ₂ S(<i>o</i> -ClPh)	25
	12
	2

Further testing, though, revealed cardiac necrosis in baboons at high dose levels. As a result, other lead compounds are being evaluated, while testing continues on the benzothiophene analog for glaucoma and skin care, indications with much lower dose levels.

References:

- (1) Kiriya, M.; Ushikubi, F.; Kobayashi, T.; Hirata, M.; Sugimoto, Y.; Narumiya, S. *Br. J. Pharmacol.* **1997**, *122*, 217.
- (2) deLong, M. A.; Wos, J. A.; De, B.; Ebetino, F. H. US 6,372,730.
- (3) deLong, M. A.; Soper, D. L.; Wos, J. A.; De, B. US 6,586,463.
- (5) Wos, J. A.; deLong, M. A.; Amburgey, Jr., J. S.; De, B.; Dai, H. G.; Wang, Y. US 5,977,173.

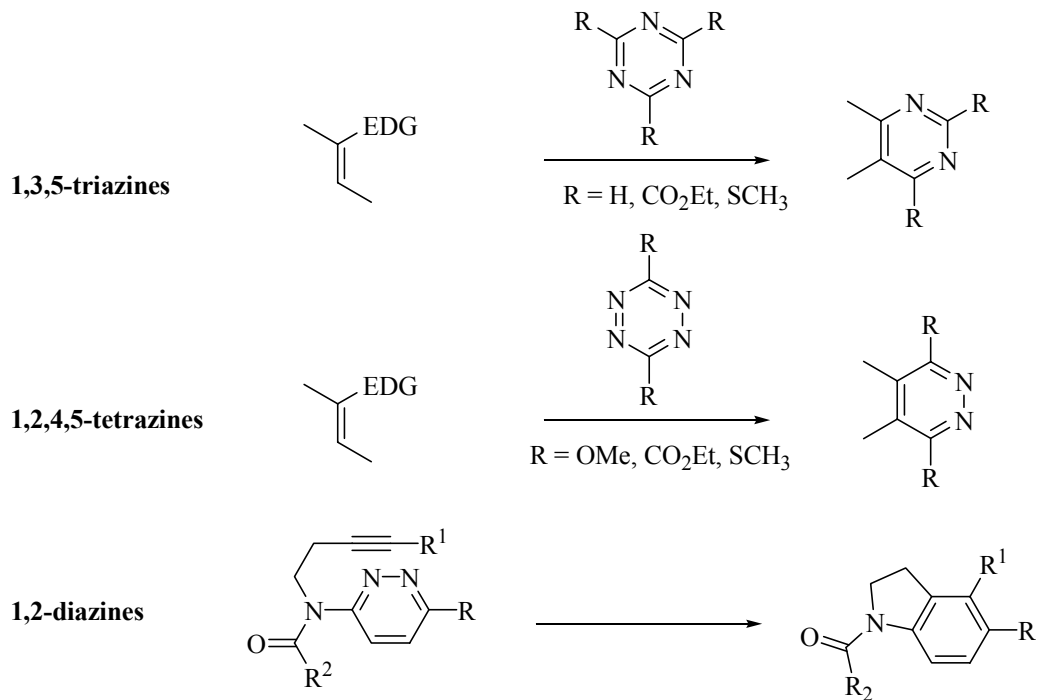
“Heterocyclic Azadiene Diels-Alder Reactions: Scope and Applications”

Dale Boger, Scripps Research Institute, La Jolla, CA, USA

Dr. Boger initially presented an overview of heteroaromatic azadiene Diels-Alder reactions used to prepare a wide range of heterocycles such as those shown in Scheme 21. The triazines, diazines, and tetrazines shown react with a wide variety of dienophiles and heterodienophiles. Electron-rich dienophiles usually participate in an inverse electron demand Diels-Alder reaction at room temperature. Neutral and electron-

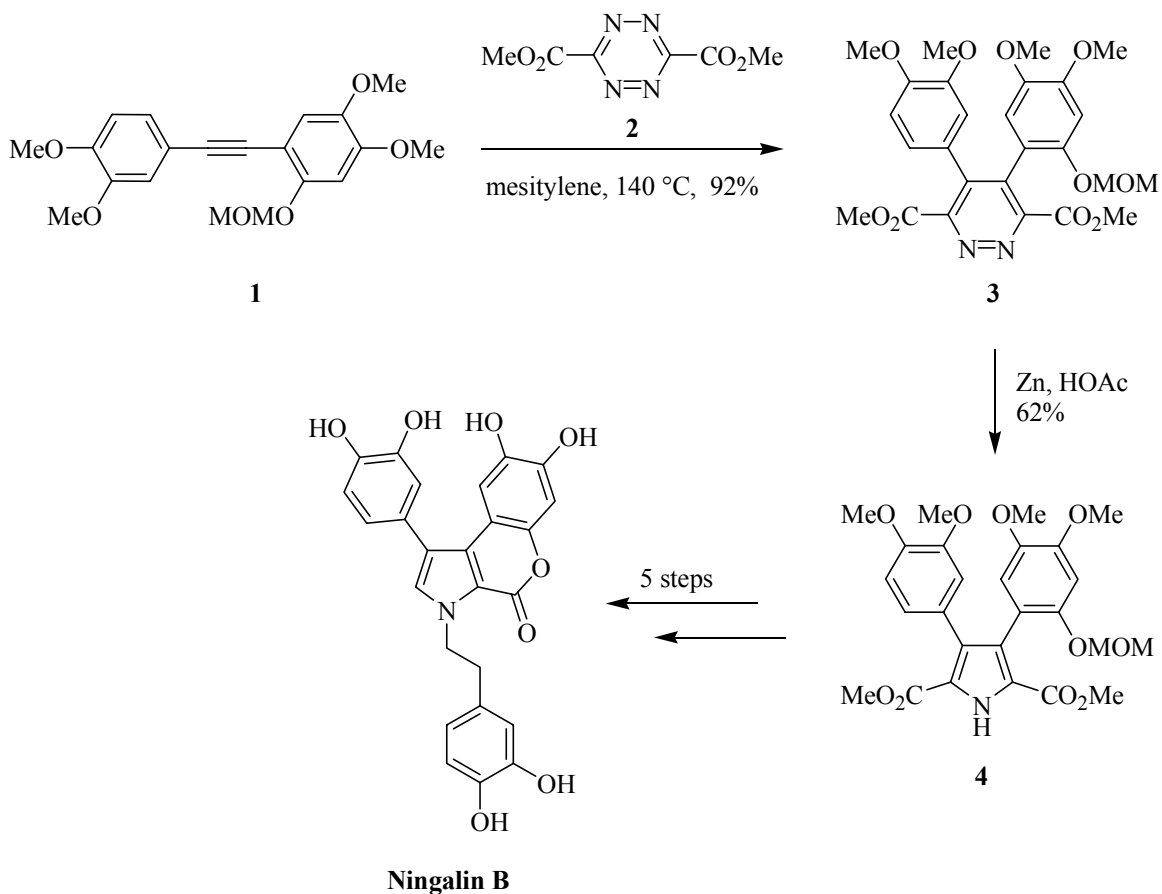
deficient dienophiles require higher reaction temperatures. The heterocycles prepared via this process are valuable intermediates for the preparation of natural products.

Scheme 21



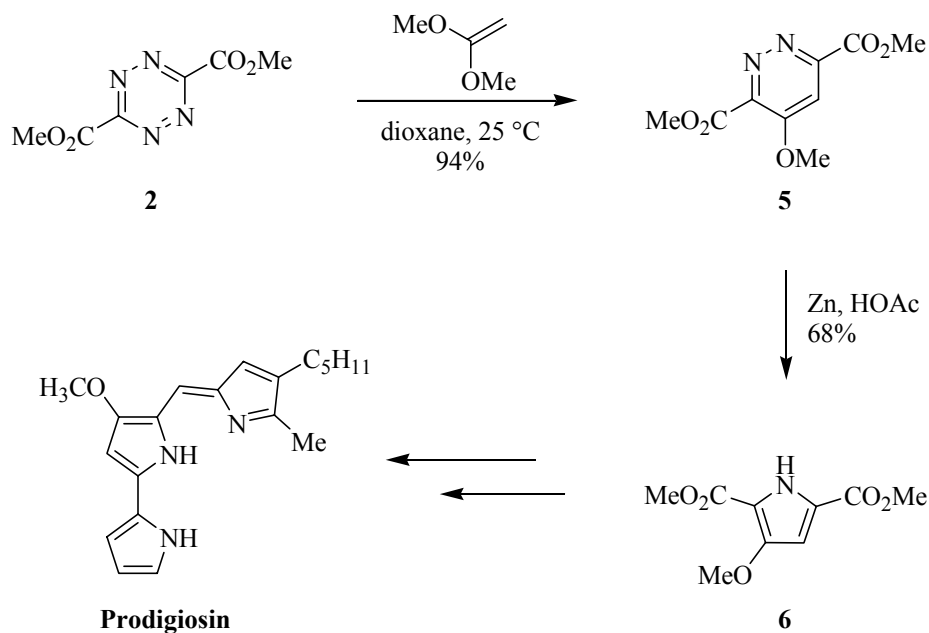
The utility of this Azadiene Diels-Alder reaction was exemplified via the synthesis of the marine natural product Ningalin B. The reaction of the readily prepared electron-rich diphenylacetylene **1** with the electron-deficient tetrazine **2** proceeded to give the desired 1,2-diazine **3** in excellent yield (Scheme 22). Subsequent reductive ring contraction (Zn, HOAc, 62%) provided the core pyrrole found in the natural product. Extensive biological testing was undertaken on this material, as well as analogs prepared in a similar manner. Several analogs of Ningalin B were found to possess moderate cytotoxic activity (IC_{50} 10-125 μ m), and these materials were also found to be potent multi-drug resistance reversing agents.

Scheme 22



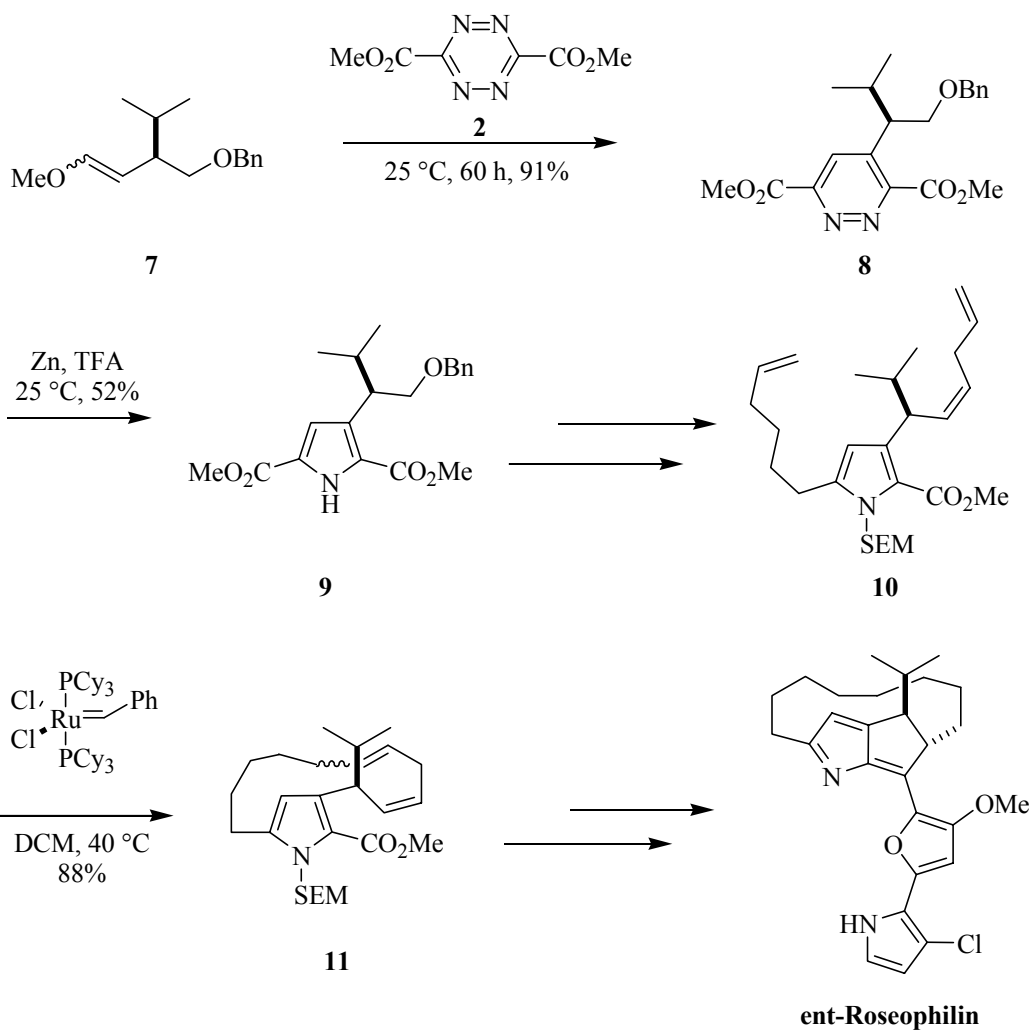
The method also plays a crucial role in the synthesis of Prodigiosin. This heterocyclic natural product displays potent antitumor, antibiotic, and antifungal activity. The reaction of tetrazine **2** with 1,1-dimethoxyethylene provided the inverse electron demand Diels-Alder product **5** (Scheme 23). Notably, this reaction proceeded at 25 °C. Reductive ring contraction of this electron-deficient diazine provided dimethyl 3-methoxypyrrole-2,5-dicarboxylate in an acceptable yield. This short 2-step procedure provided the B ring of Prodigiosin.

Scheme 23



Lastly, the synthesis of Roseophilin was described (Scheme 24). This pentacyclic natural product, isolated from *Streptomyces griseoviridis*, has demonstrated significant cytotoxic activity against several human epidermoid and leukemia cell lines. The heterocyclic azadiene inverse electron demand Diels-Alder was once again used for the construction of the pyrrole ring present in the azafulvene core of this natural product. The reaction of tetrazine **2** with the optically active electron-rich enol ether **7** at room temperature provided the 1,2-diazine **8**. Reductive ring contraction by treatment with Zn-TFA gave the pyrrole **9**. Unlike the previously described zinc reductions, this reduction was less effective when using acetic acid. The pyrrole **9** was converted to triol **10** in 14 steps. Ring closing metathesis of **10** with Grubb's catalyst gave **11** as a 1:1 mixture of E and Z olefin isomers in high yield. With the completion of the ansa-bridged macrocycle, the intermediate **10** was converted to Roseophilin. The optical rotation of the prepared product was identical, but of opposite sign to the natural product. This indicates that the enantiomer of the naturally occurring Roseophilin was synthesized.

Scheme 24



References:

- Review: Boger, D.L. *Chem. Rev.* **1986**, *86*, 781.
 Ningalin B: Boger, D.L.; Soenen, D.R.; Boyce, C.W.; Hendrick, M.P.; Jin, Q. *J. Org. Chem.* **2000**, *65*, 2479.
 Prodigiosin: Boger, D.L.; Patel, M. *J. Org. Chem.* **1988**, *53*, 1405.
Ent-(-)-Roseophilin: Boger, D.L.; Hong, J. *J. Am. Chem. Soc.* **2001**, *123*, 8515.

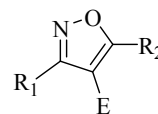
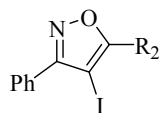
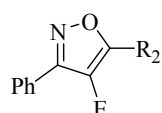
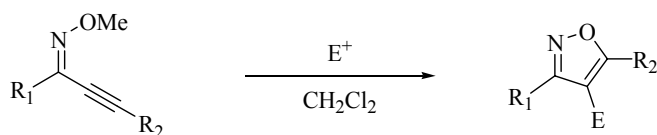
“Synthesis of Heterocycles via Iodine- and Palladium- Promoted Cyclization and Annulation” *Richard C. Larock, Department of Chemistry, Iowa State University.*

Professor Larock broke his talk down into three parts: (1) the synthesis of various heterocyclic ring systems containing an iodine, (2) the application of these iodo heterocyclic compounds in cross-coupling reactions, and (3) cyclization and annulation chemistry associated with heterocyclic systems. The schemes outlined below represent only a small fraction of the heterocyclic chemistry presented.

In part one, he discussed the synthesis of 3-iodobenzofurans, benzothiophenes, 3-iodobenzo[b]selenophenes, 3-iodoindoles, isoxazoles, furans, isochromenes, naphthalenes, isocoumarins, pyrones, isoindolin-1-ones, quinolines, spirodienones, naphthalenes, and naphthols. An example is shown in Scheme 25. [unpublished results]

Scheme 25

ISOXAZOLES



R_2	E	%
	ICl	86
	Br ₂	75
	PhSeBr	91
	ICl	78
	PhSeBr	88

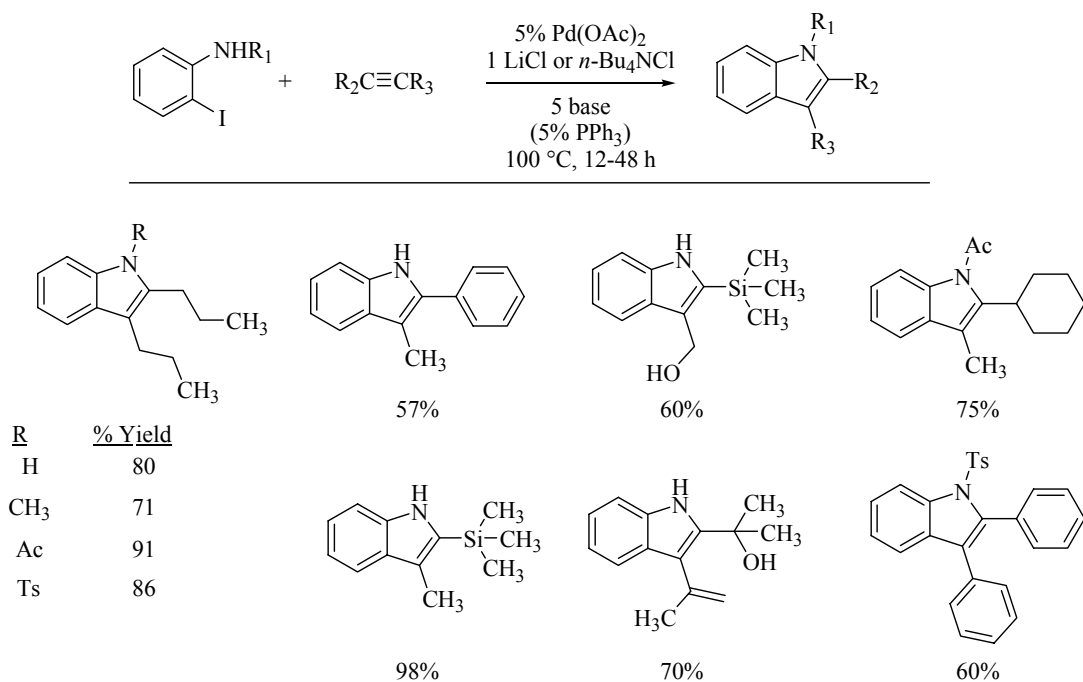
R_2	%
	82
	89
	80
<i>n</i> -Bu	72
<i>t</i> -Bu	80
TIPS	78

R_2	%
	55
	68
<i>i</i> -Pr	84
<i>t</i> -Bu	100

Professor Larock then discussed the application of organopalladium chemistry on the above iodo substrates. Most notably he discussed the reaction of the iodo compounds with an alkyne in order to synthesize a desired heterocycle or conjugated ring system. An example is illustrated in Scheme 26. [JACS, **1991**, *113*, 6689; JOC, **1998**, *63*, 7652].

Scheme 26

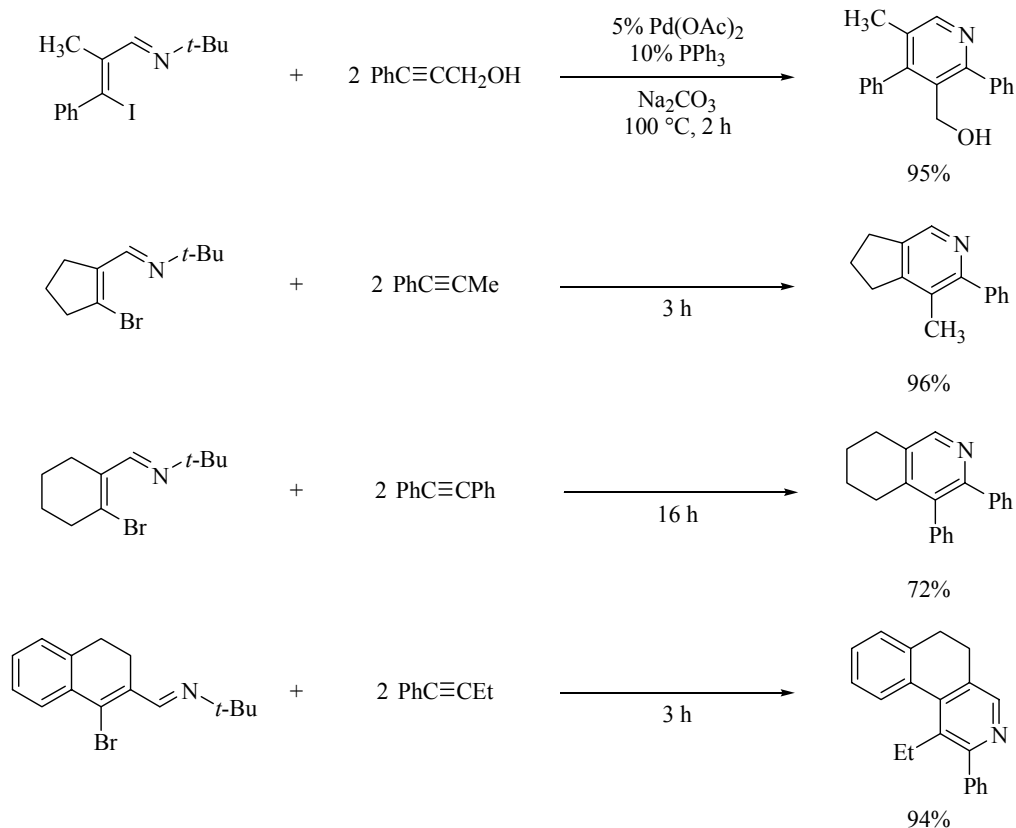
INDOLES



Finally, Scheme 27 illustrates the last topic discussed regarding annulation. One example was presented which afforded pyridine systems [JOC, **2001**, *66*, 8042].

Scheme 27

PYRIDINES

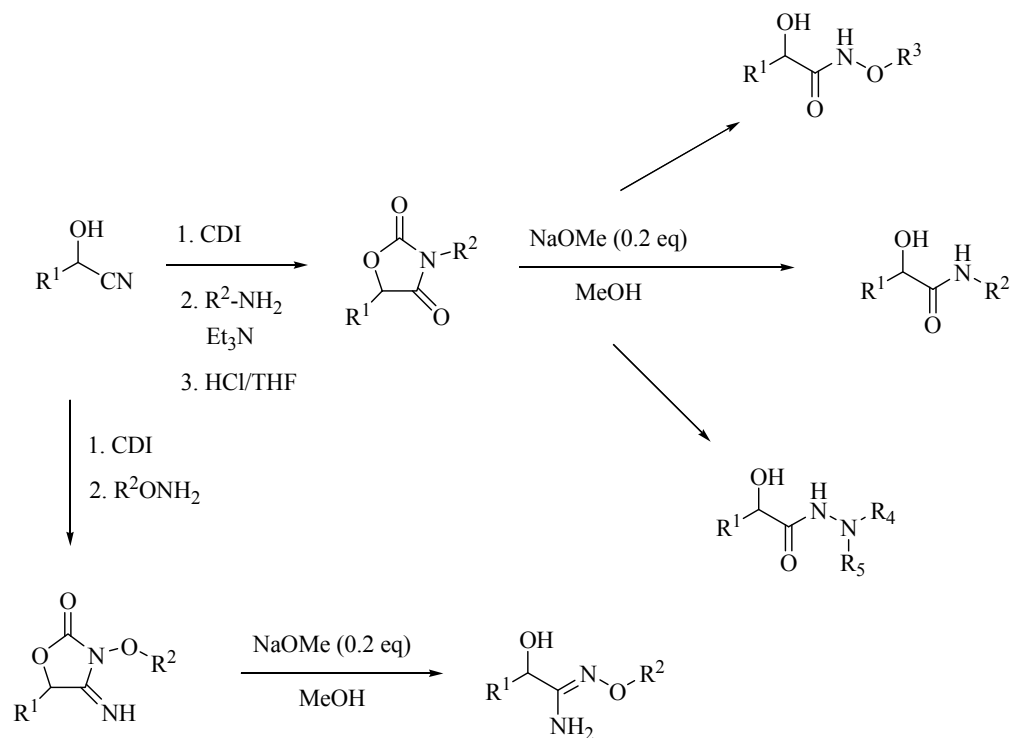


II. Short Talks

“Synthesis and Reactivity of 4-Functionalized Oxazolidin-2-ones” Dr. Thomas Kurz,
Institute of Pharmacy, University of Hamburg, Germany

An operationally simple method for the efficient synthesis of α -hydroxycarboxylic acid derivatives was presented (see Scheme 28). Readily available cyanohydrins can be easily converted to 4-functionalized oxazolidin-2-ones in a three step one-pot process. Reaction of the cyanohydrins with carbonyldiimidazole gives an activated intermediate which can undergo addition and cyclization with a variety of primary amines. The resulting *N*-substituted 4-imino oxazolidin-2-ones are then hydrolyzed to the corresponding oxazolidin-2,4-diones. On treatment with a catalytic amount of sodium methoxide the oxazolidin-2,4-diones undergo ring opening to furnish α -hydroxyamides. The reaction was extended to incorporated *O*-alkyl hydroxylamines and dialkylhydrazines as the amine components.

Scheme 28



Additionally, by leaving out the hydrolysis step the intermediate *N*-substituted 4-imino oxazolidin-2-ones could be used for a variety of transformations. For example, in a case where an *O*-alkyl-hydroxylamine was used as the primary amine component, cleavage of the ring with catalytic sodium methoxide gave a straightforward access to *O*-substituted α -hydroxyamidoximes.

References:

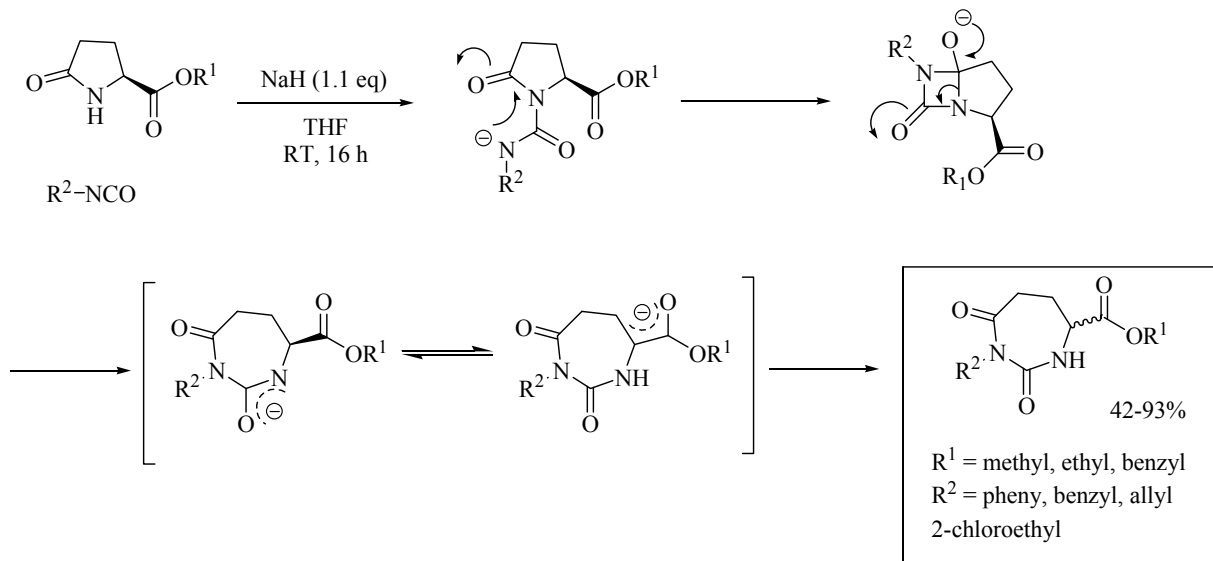
- (1) Kurz, T.; Widyan, K. *Org. Biomol. Chem.* **2004**, *2*, 2023.
- (2) Kurz, T.; Widyan, K. *Org. Lett.* **2004**, *6*, 4403.

“Straightforward Ring Expansion of Pyroglutamates to Perhydro-1,3-diazepine-2,4-diones” Christian Stevens, Nicolai Dieltiens and Diederica Claeys, *Research group SynBioC, Department of Organic Chemistry, Ghent University*

While trying to prepare 1-carbamoyl-2-pyrrolidinones, the authors discovered a new and convenient method for preparation perhydro-1,3-diazepine-2,4-diones. In initial experiments, treatment of a pyroglutamate with an isocyanate produced a complex mixture of products resulting from reaction at both the N-atom and the C2-atom. Performing the reaction with NaH as a base in Et₂O improved the selectivity and the sodium salt of the expected urea was precipitated cleanly. However, when the reaction

was performed in THF, the now soluble intermediate sodium salt unexpectedly underwent an anionic rearrangement as proposed in Scheme 29.

Scheme 29



Cyclization onto the adjacent carbonyl group affords a strained intermediate which ring opens to the seven-membered cyclic product. Despite utilizing optically active pyroglutamates as starting materials, the final products obtained after rearrangement were racemic. This can be rationalized by equilibration between conjugated anions. Moderate to high yields of the corresponding 1,3-diazepine-2,4-diones were obtained after purification by chromatography or recrystallization.

Reference:

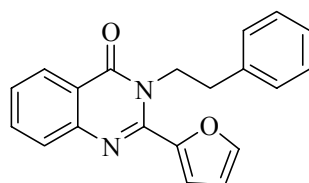
(1) Stevens, C. V.; Dieltiens, N.; Claeys, D. D.; *Org. Lett.* **2005**, *7*, 1117.

“Design and Novel Synthesis of Substituted Quinazolin- and Pyrimidin-4-ones as New Calcilytic Templates”

Irina Shcherbakova, NPS Pharmaceuticals, Inc., Salt Lake City, UT.

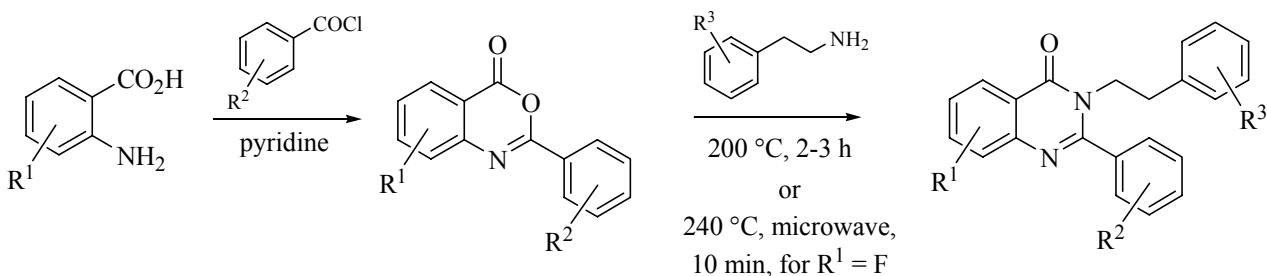
As an alternative approach for treating osteoporosis, scientists at NPS have been searching for a way to indirectly and transiently increase levels of PTH, a natural bone growth promoter, through antagonism of the calcium receptor (CaR), a known PTH regulator.

Following the identification of quinazolinone **NPS 53574** as a lead compound via high-throughput screening, analog preparation was carried out using the synthesis shown in Scheme 30.

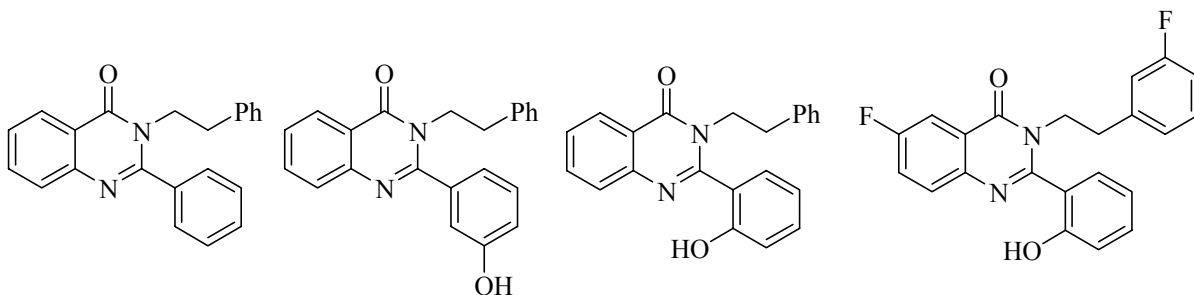


NPS 53574 ($IC_{50} = 3.5 \mu M$)

Scheme 30



In vitro testing on more than twenty compounds indicated a clear preference for $R^2 = o\text{-OH}$ (attributed to increased permeability associated with intramolecular hydrogen bonding) and an optimized structure with $R^1 = 6\text{-F}$ and $R^3 = 3\text{-F}$.



IC_{50} (μM): 14

2.8

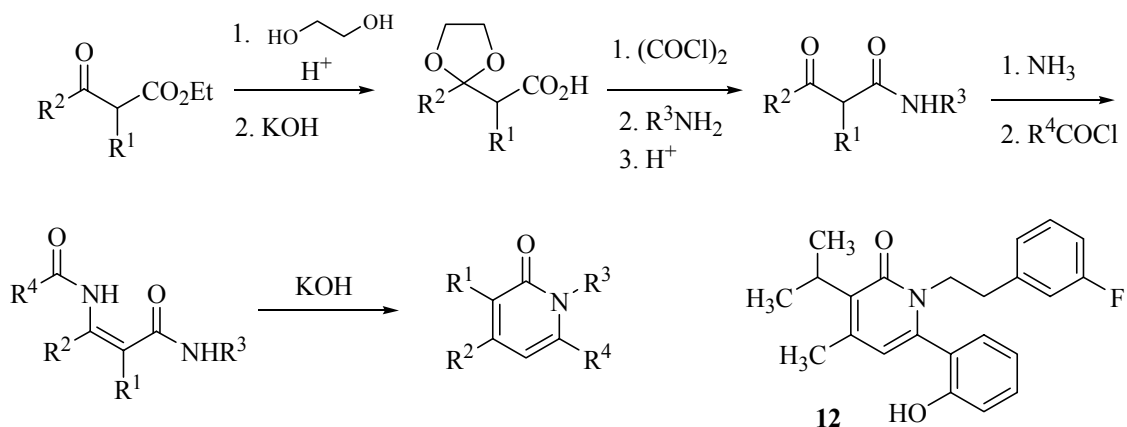
0.3

0.19

In vivo testing of analogs with IC_{50} values less than $0.5 \mu M$ showed rapid, dose-related increases in plasma PTH levels in rats, but also a quick return (within 10 minutes) to the preinjection status. The duration of the effect was not long enough to alter the plasma calcium ion levels.

More recent work has shown that the pyrimidinone compounds, prepared as in Scheme 31, were more potent and had improved pharmacological properties. Compound **12** was the best reported in the series with an $IC_{50} = 80 \text{ nM}$ for the calcium receptor.

Scheme 31



References:

- (1) Shcherbakova, I.; Balandrin, M. F.; Fox, J.; Ghatak, A.; Heaton, W. L.; Conklin, R. L. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1557.
- (2) Shcherbakova, I.; Balandrin, M. F.; Huang, G.; Geoffroy, O.; Fox, J.; Nair, S. K. WO 2004/092121 A2.

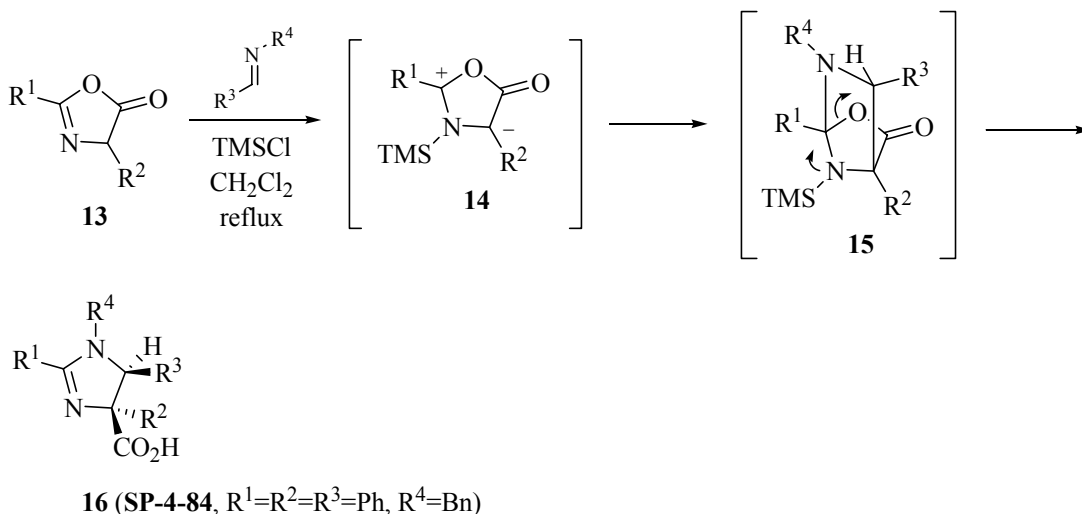
“Synthesis of Biologically Active Heterocycles: Exploring the Effects of NF-κB Regulation”

Jetze J. Tepe, Michigan State University, East Lansing, MI.

In an effort to improve the efficacy of chemotherapeutic agents, the Tepe group has focused on developing and evaluating imidazolines as inhibitors of NF-κB mediated gene transcription. Activation of NF-κB by TNF-α is suspected to protect cancer cells by preventing programmed cell death. This same activation is also thought to be initiated by some chemotherapy drugs. Standard chemotherapy in conjunction with a second agent to block NF-κB activation is proposed to inhibit cancer cell protection, and thus sensitize the cells to standard drugs.

To generate the imidazolines, a route was developed that allowed for differentiation at four sites on the heterocyclic ring with essentially complete stereochemical control. Treatment of azalactones **13** (prepared by EDCI dehydration of *N*-acyl α amino acids), with trimethylsilylchloride and a preformed imine generated a 1,3-dipolar cycloaddition product through the proposed *N*-silylated intermediate **14** (see Scheme 32). Loss of the carboxylate giving the free acid and hydrolysis of the trimethylsilyl group produced the final imidazoline **16**. Acetyl chloride was the only other reagent to promote the reaction; ten other Lewis acids failed. Yields of **16** ranged from 60–90%, and in almost all cases, only the *trans* diastereoisomer was obtained (NOE experiments and X-ray crystallography). The selectivity was rationalized by steric repulsion between R³ of the imine and the trimethylsilyl group on the ring nitrogen.

Scheme 32



In testing for biological activity, the imidazolines, alone, were found to be inactive against leukemia T cells. However, they significantly improved the sensitivity of the cancer cells to chemotherapeutic agents. Imidazoline SP-4-84 gave the best results with an efficacy enhancement of 75-fold for camptothecin and 6-fold for cisplatin. More detailed evaluation showed that the imidazoline acted by preventing nuclear translocation of NF- κ B.

References:

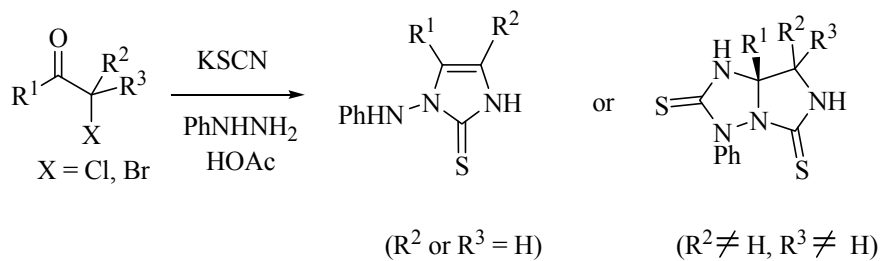
- (1) Wang, C.-Y.; Mayo, M. W.; Baldwin Jr., A. S. *Science* **1996**, 274, 784.
- (2) Peddibhotla, S.; Jayakumar, S.; Tepe, J. J. *Org. Lett.* **2002**, 4, 3533.
- (3) Peddibhotla, S.; Tepe, J. J. *Synthesis* **2003**, 1433.
- (4) Peddibhotla, S.; Tepe, J. J. *J. Am. Chem. Soc.* **2004**, 126, 12776.
- (5) Sharma, V.; Lansdell, T. A.; Peddibhotla, S.; Tepe, J. J. *Chem. Biol.* **2004**, 11, 1689.

“Unexpected Reactions of α,α -Dihalo Carbonyl Compounds with Potassium Thiocyanate and Arylhydrazines”

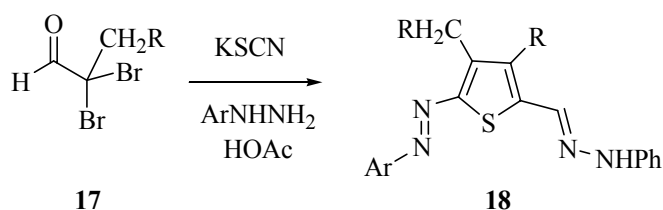
Joachim G. Schantl, University of Innsbruck, Innsbruck, Austria.

As a follow-up to previously reported work on the reaction of α -halo ketones with potassium thiocyanate and phenylhydrazine in acetic acid to generate interesting [3 + 2] cycloaddition products (see Scheme 33), the speaker described the reaction of α,α -dihalo ketones under the same conditions.

Scheme 33



Aldehyde **17** produced **18**, identified by X-ray crystallography, which is a 2:1:2 adduct of aldehyde:KSCN:hydrazine.



The proposed reaction path involves hydrazone formation and displacement of one or both bromine atoms by thiocyanate (see Scheme 34). Elimination of HBr or HSCN would give diazodiene **20**, a Michael acceptor, and its tautomer **21**, a nucleophilic species.

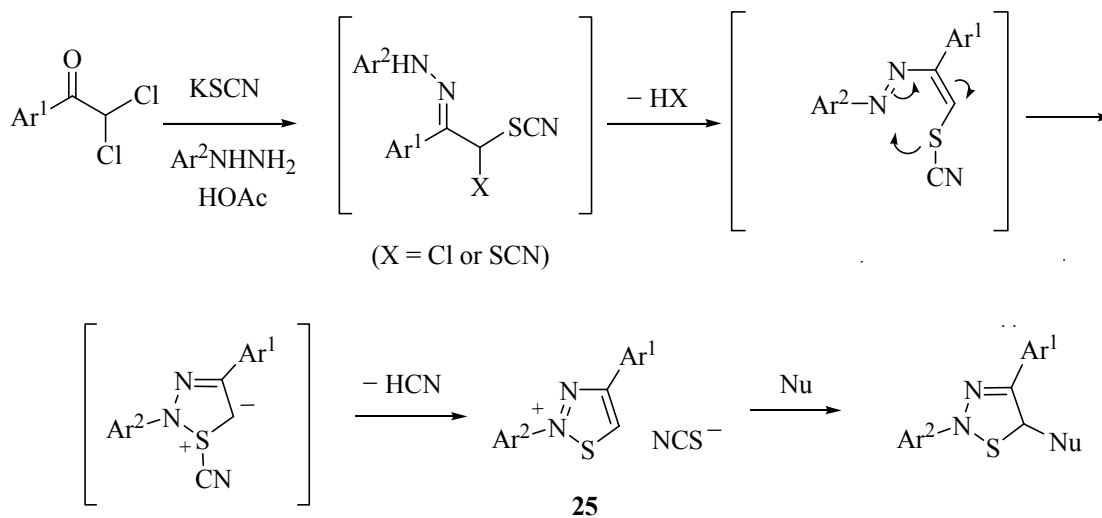
Scheme 34



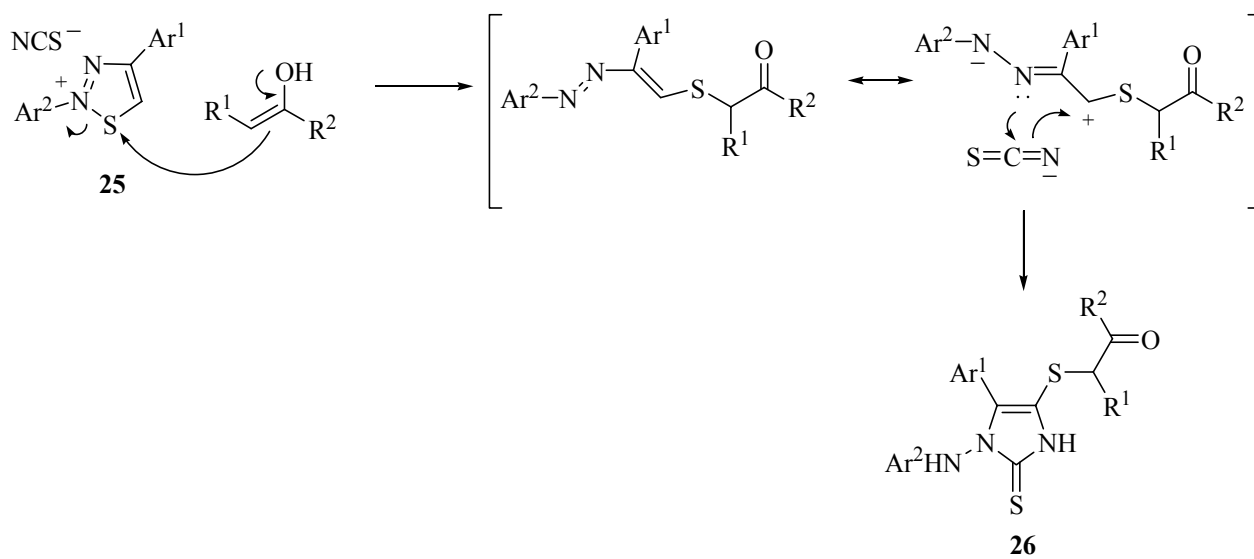
Dimerization to give **22** is followed by loss of thiocyanic acid and tautomerization to **23**. [1,5] Electrocyclic ring closure, loss of hydrogen cyanide and tautomerization gives **18**.

When α,α -dichloroacetophenones were used as the starting material, thiadiazolium thiocyanate salts **25**, resulting from electrocyclic ring closure, were isolated (see Scheme 35). As reported in the literature, they react with nitrogen and oxygen nucleophiles at the 5-position to form 2,5-dihydro[1,2,3]thiadiazoles. Unexpectedly, though, aliphatic ketones reacted with **25**, presumably through the enol tautomer, to open the ring by attack at sulfur (see Scheme 36). The product **26** could then be rationalized with a [3 + 2] cycloaddition with thiocyanate followed by tautomerization and protonation.

Scheme 35



Scheme 36



Reference:

(1) Schantl, J. G.; Nadenik, P. *Synlett* **1998**, 786.

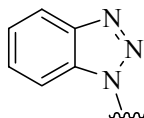
III. Short Course, Part 1 – “Benzotriazole Synthetic Methodology”

Alan R. Katritzky, University of Florida, Gainesville, FL .

The Katritzky section of the short course covered the powerful applications of benzotriazole (Bt) in synthetic methodology. The course outline from day one, part one, included Bt-mediated synthetic methodology, Bt-mediated acylation, imidoylation, thioacylation and sulfonation.

Bt (**1**) is intrinsically unreactive, stable, and inexpensive (Figure 1). Bt is easily inserted and can behave as a leaving group and as a proton activator. An attached Bt group is also an ambient anion-directing group; it can stabilize cations, and it can act as a radical or carbanion precursor.

Figure 1



A. Bt-Mediated Acylation

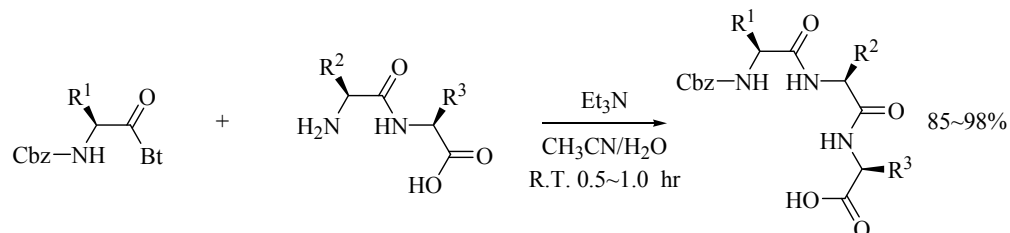
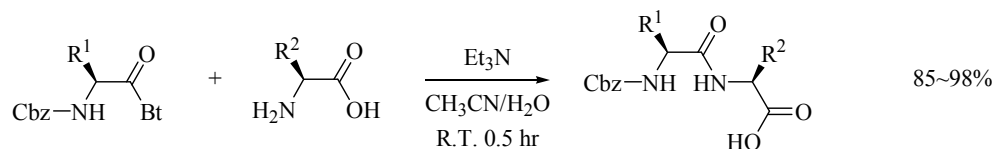
The use of *N*-acylazoles as acylating agents is not new. Most particularly the work of H. A. Staab in the 1960's showed the advantages of the use of acylimidazoles and other acylazoles as acylating agents.

N-Acylbenzotriazoles can be prepared classically from the acid chloride or directly from the carboxylic acid. [JOC, **2000**, 8210; Tetrahedron, **1992**, 7817; Synthesis, **2003**, 2795.]

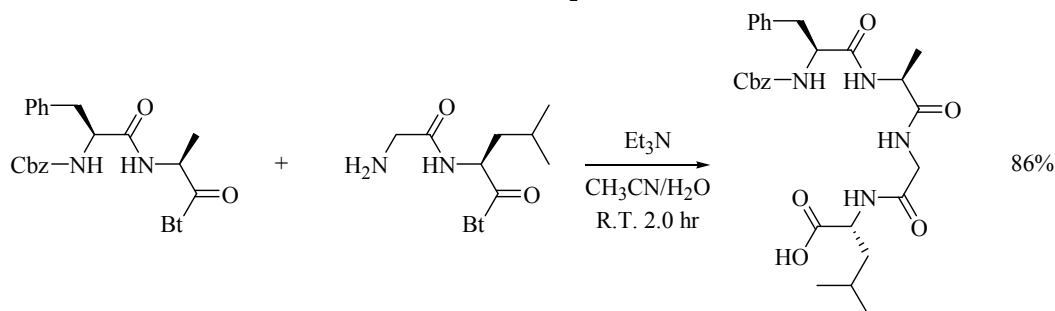
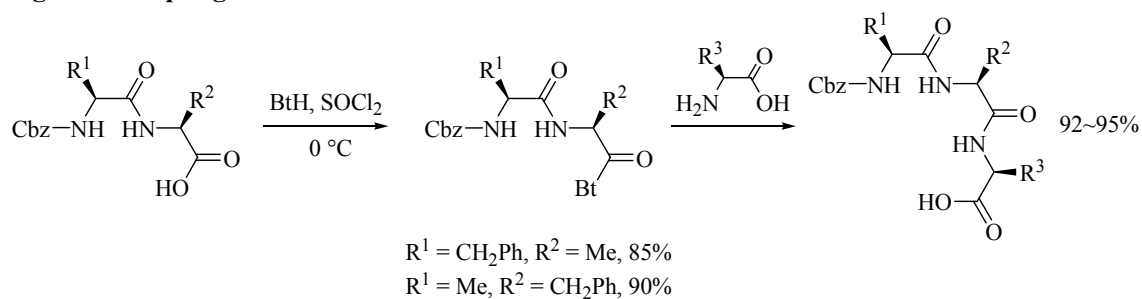
Peptide chain extension can be carried out on unprotected amino acids with minimal racemization (<5%) via stepwise or fragment coupling (Scheme 37). [Unpublished Results]

Scheme 37

Stepwise Coupling:



Fragment Coupling:

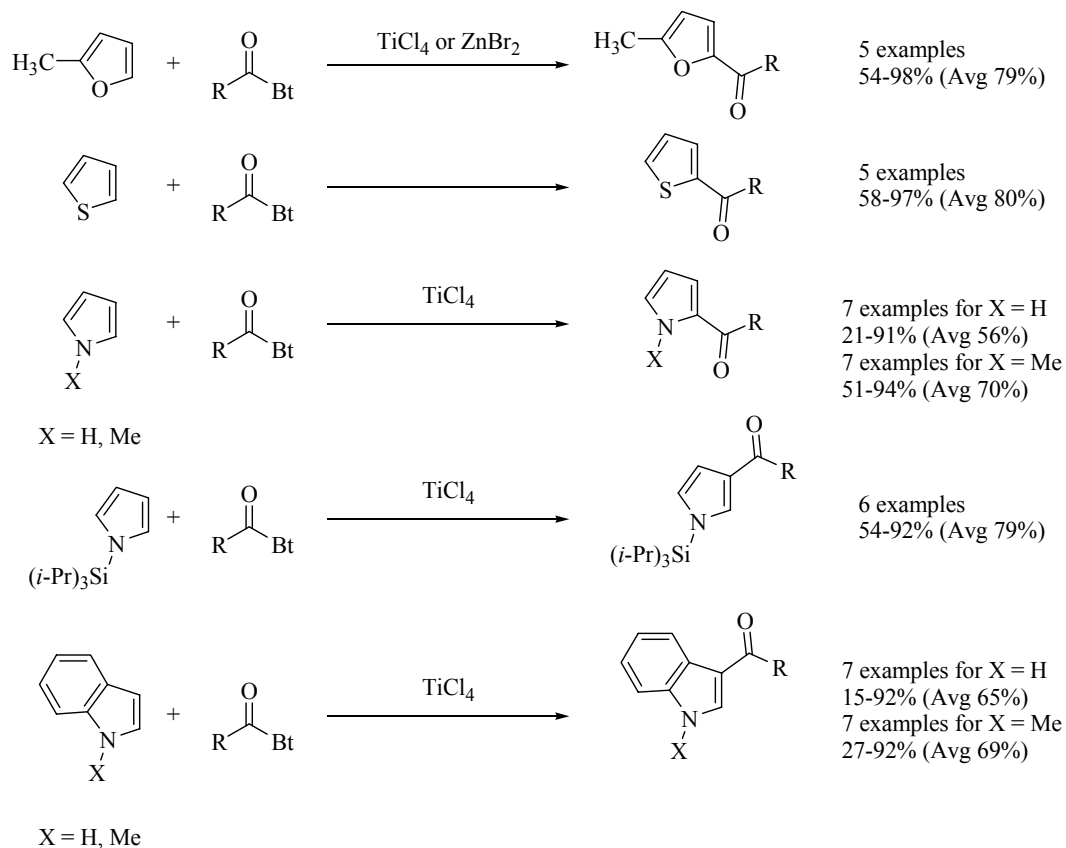


B. C-Acylation of Heterocycles

C-Acylation of *N*-acylbenzotriazoles with furan, thiophene, pyrrole, and indole under Friedel-Crafts type conditions usually provides high yields (Scheme 38). *C*-Acylation reactions of furan and thiophene were carried out in the presence of TiCl_4 (at R.T.) and/or ZnBr_2 (at $110\text{ }^\circ\text{C}$), and these conditions gave comparable yields of the 2-acylated products. *C*-Acylation of pyrroles and indoles produced regioselective products in the presence of TiCl_4 . [JOC, **2003**, 5720.]

Scheme 38

Regiospecific C-Acylation of Furan, Thiophene, and Indole

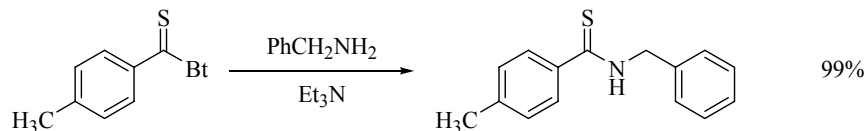


C. Thioacylation and Sulfonylation

Thioamides have been made classically by three major routes in which are formed a C-C bond, and C=S double bond, or a C-N bond. The crystalline odorless thioacylbenzotriazoles and the easily prepared bis-benzotriazolymethanethione, which are stable to storage, have many advantages for the preparation of thioamides (Scheme 39).

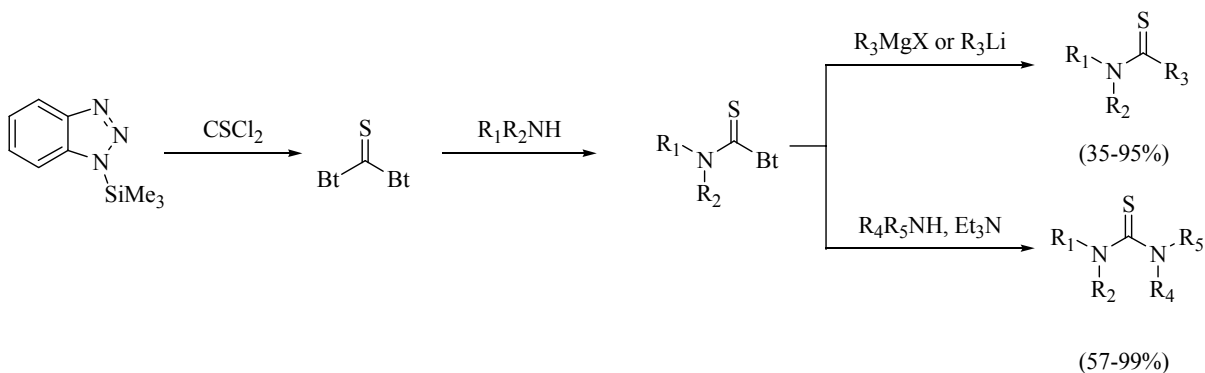
Scheme 39

Synthesis of Thioamides from Thioacylbenzotriazoles



- Aryl substituted thioacylbenzotriazoles have been prepared.
- Use of hazardous and unstable thioacyl chlorides are avoided.
- Thioacylbenzotriazoles react fast and readily with primary and secondary amines

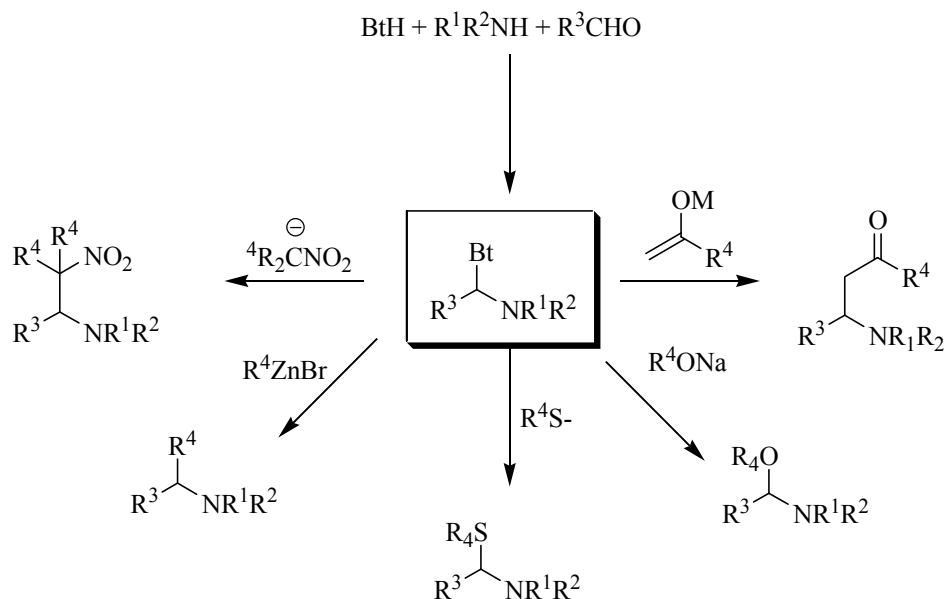
Synthesis of Thiocarbonyl Compounds Using Thiocarbonyl-bisbenzotriazole



D. Aminoalkylation

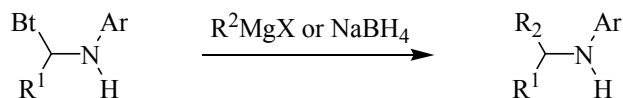
In the second part of the benzotriazole short course, Professor Katritzky outlined the heteroalkylation methodology which had been extensively studied in his laboratories. The first method described involved the aminoalkylation of benzotriazole intermediates. The condensation of benzotriazole, a complex amine, and an aldehyde provided a Mannich-like product as shown in Scheme 40. Professor Katritzky emphasized that the classical Mannich reaction is limited mostly to the use of formaldehyde, while the benzotriazole mediated reaction is quite versatile in the identity of the aldehyde. The benzotriazole moiety can then be displaced with a variety of nucleophiles to provide a wide range of substrates.

Scheme 40

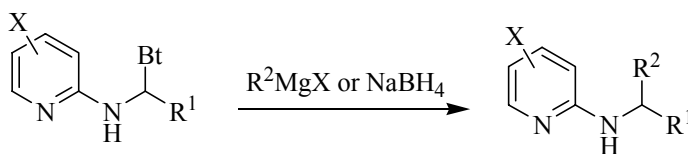


Aromatic amines can be selectively monoalkylated conveniently using benzotriazole methodology as shown in Scheme 41. The benzotriazole moiety (Bt) can be smoothly reduced to amines by sodium borohydride or the Bt moiety can be replaced by an alkyl group using Grignard reagents. This method is particularly advantageous with respect to the N-alkylation of heteroaromatic amines.

Scheme 41



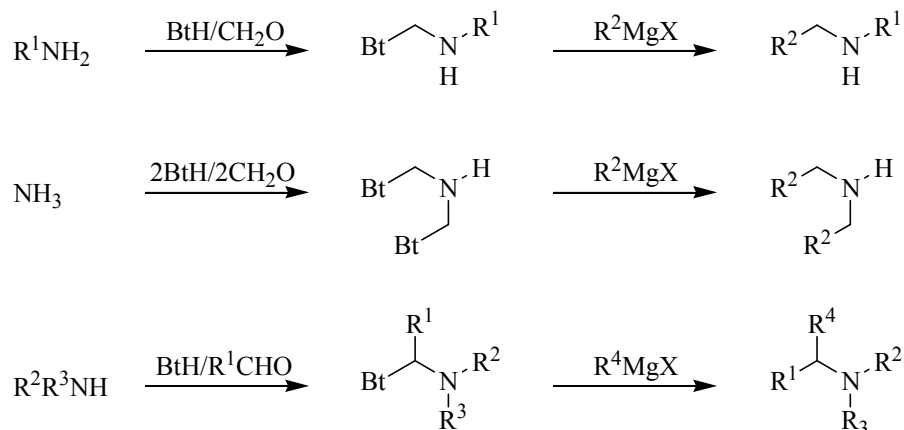
Ar = 4-ClPh, 2-pyridyl, etc.; R¹ = H, Pr, etc.; R² = Me, allyl, Bn, H, etc.



X = H, Me, Cl, Br, NO₂; R¹ = H, Pr, *t*Bu; R² = Me, allyl, Bn, H

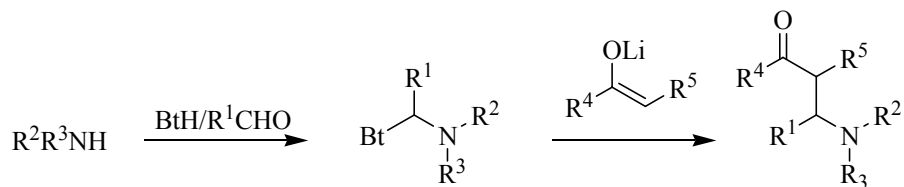
The conversion of primary aliphatic amines into unsymmetrical secondary amines can also be achieved by Grignard reactions of 1-[(alkylamino)methyl]-benzotriazoles as shown in Scheme 42. The preparation of symmetrical secondary amines, as well as unsymmetrical tertiary amines, can also be undertaken in this manner.

Scheme 42

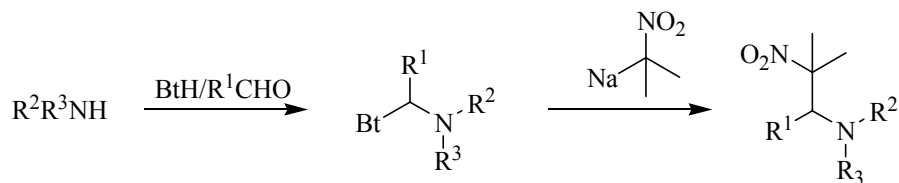


A wide variety of β -amino ketones have been prepared in good yields by the reaction of enolates of ketones with the readily available adducts from an aldehyde, an amine and benzotriazole as shown in Scheme 43. Similarly, aminoalkylation of nitro compounds can also be achieved via the reaction of benzotriazole adducts with alkylnitronate anions.

Scheme 43



$\text{R}^1 = \text{H, Me, Ph, Pr}$; $\text{R}^2 = \text{H}$; $\text{R}^3 = \text{Ph}$; $\text{R}^2\text{R}^3 = \text{-(CH}_2\text{)}_5\text{-, -(CH}_2\text{)}_2\text{O(CH}_2\text{)}_2\text{-}$; $\text{R}^4\text{R}^5 = \text{-(CH}_2\text{)}_4\text{-}$

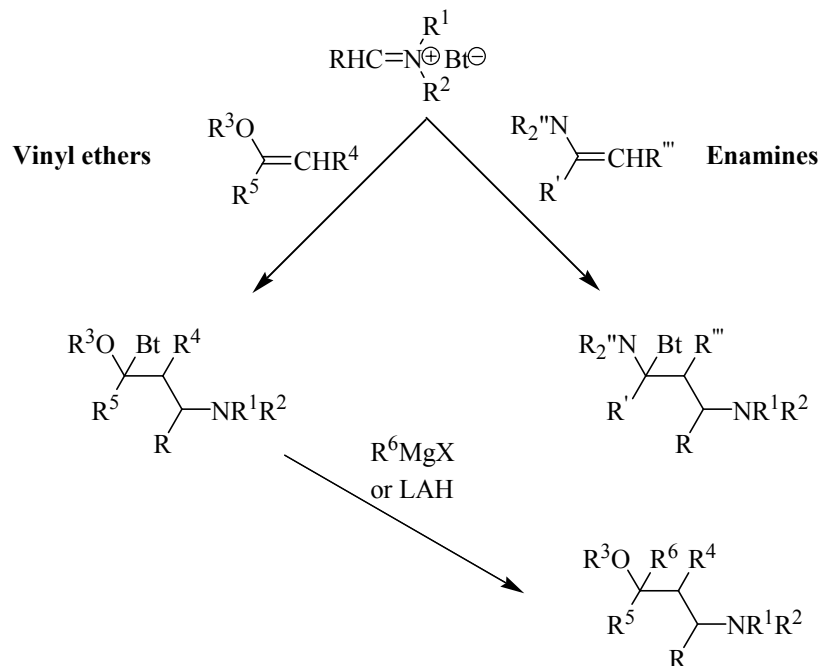


$\text{R}^1 = \text{H, Me, 2-pyridyl}$; $\text{R}^2 = \text{H}$; $\text{R}^3 = \text{Ph, c-C}_6\text{H}_{11}$; $\text{R}^2\text{R}^3 = \text{-(CH}_2\text{)}_5\text{-, -(CH}_2\text{)}_4\text{-, -(CH}_2\text{)}_2\text{O(CH}_2\text{)}_2\text{-}$

1-(α -Aminoalkyl)benzotriazoles in solution undergo partial ionization to the corresponding iminium cation as shown in scheme 44. This moiety can be trapped by enamines and vinyl ethers to give the corresponding *N*-(1-dialkylamino-3-aminoalkyl)benzotriazoles and *N*-(1-alkoxy-3-aminoalkyl)benzotriazoles. These species

can further react with Grignard reagents or LAH to give 1,3-diamines and 1,3-aminoethers.

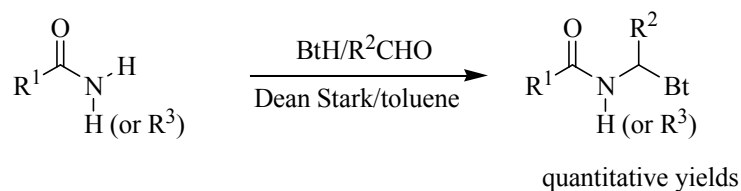
Scheme 44



E. Amidoalkylation

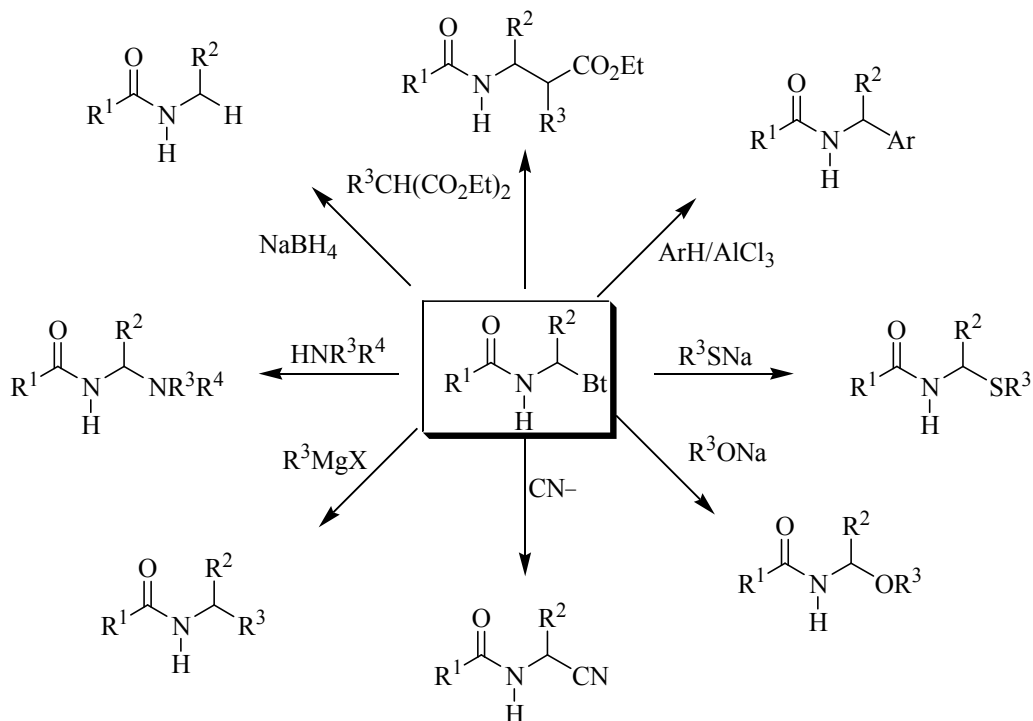
The amidoalkylating reagent derived from the condensation of a primary (or secondary) amide with benzotriazole and an aldehyde as shown in Scheme 45 has been extensively studied by the Katritzky group.

Scheme 45



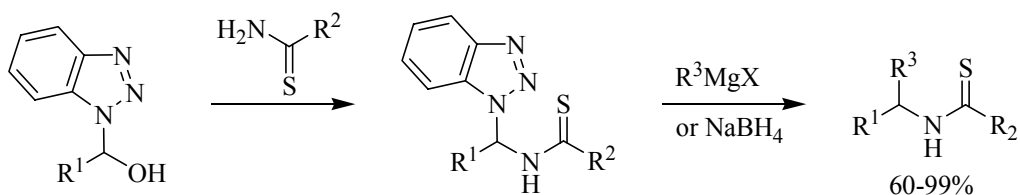
A summary of amidoalkylation reactions is shown below in Scheme 46.

Scheme 46

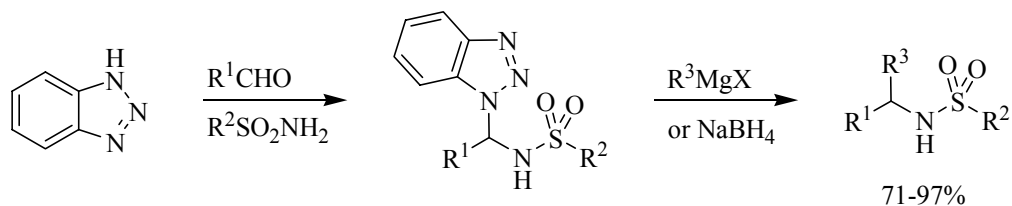


Several related processes were also discussed. Both thioamidoalkylation and sulfonamidoalkylation can be undertaken using this methodology. An example of each process is shown below in Scheme 47. Once again the benzotriazole moiety can be displaced with either a Grignard reagent or sodium borohydride.

Scheme 47



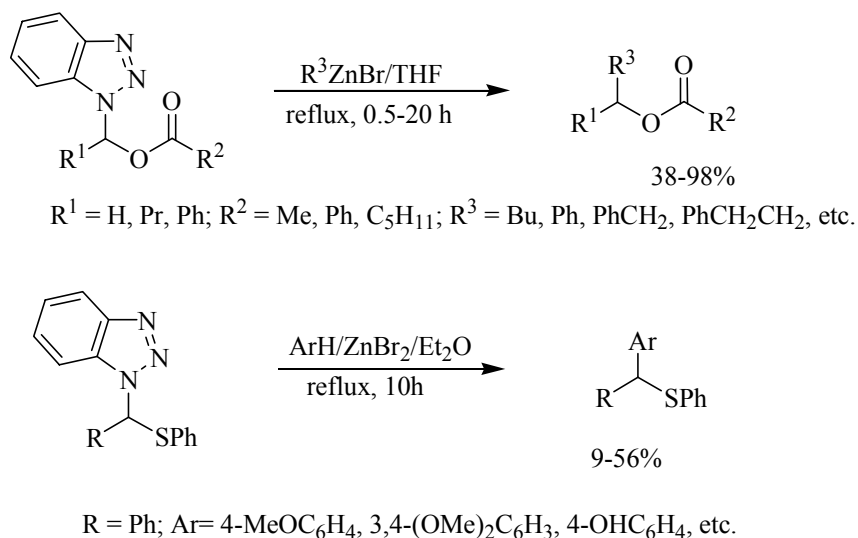
$R^1 = \text{H, Pr, C}_5\text{H}_{11}, \text{C}_7\text{H}_{15}, \text{C}_{11}\text{H}_{23}$; $R^2 = \text{Ph, NH}_2$; $R^3 = \text{PhCH}_2, \text{Bu, Ph}$



$R^1 = \text{H, } i\text{Pr-2-pyridyl, Ph}$; $R^2 = \text{Ph}$; $R^3 = \text{H, Ph}$

Lastly, acyloxyalkylation and thioalkylation reactions are also feasible using the benzotriazole method as shown in Scheme 48. Acyloxyalkylation is best achieved utilizing organozinc reagents, and various alkyl or aryl groups can be introduced at the alkoxy part of the ester.

Scheme 48



Comprehensive Review: Katritzky et. al. *Chem. Rev.* **1998**, 409.

IV. Short Course, Part 2 – “Applications of Lithium and Palladium in Heterocycle Synthesis”

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

Course Outline

1. Lithium
 - 1.1 Generation of Heteroaryllithiums
 - 1.2 Applications in Synthesis
 - 1.3 Heterocyclic Ring Synthesis Using Lithium
2. Palladium
 - 2.1 Palladium-Catalyzed Cross Coupling
 - 2.2 Oxidative Coupling/Cyclization
 - 2.3 Applications in Synthesis
 - 2.4 Ring Construction

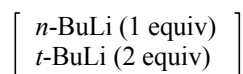
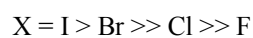
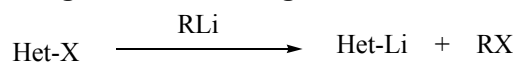
1. Lithium

1.1 Generation of Heteroaryllithiums

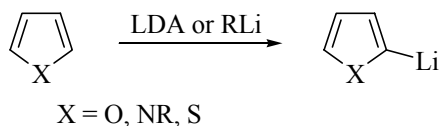
Heteroaryllithiums can be synthesized by halogen-lithium exchange, direct deprotonation, and directed-lithiation (Scheme 49).

Scheme 49 Generation of Heteroaryllithiums

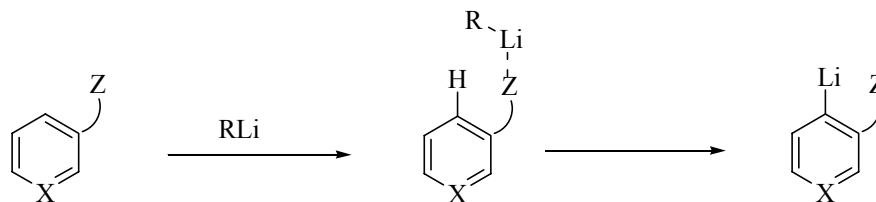
Halogen-Lithium Exchange



Direct Deprotonation



Directed-Lithiation

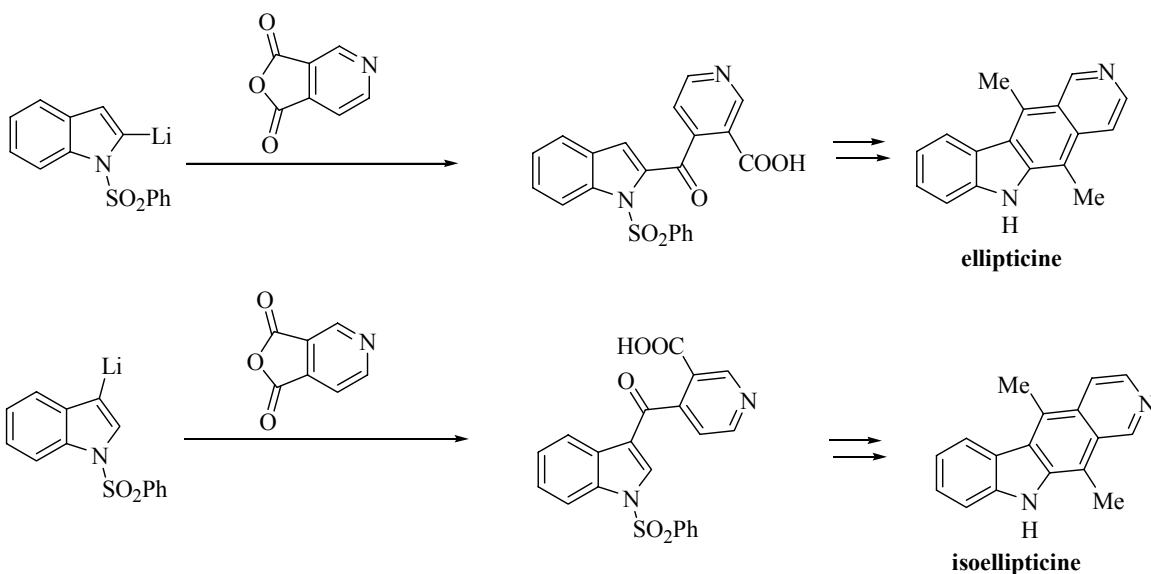


$\text{Z} = \text{amides, carbamates, alkoxy, amines, halogens, etc.}$

1.2 Applications in Synthesis

As one can imagine the use heteroaryllithiums in synthesis is extensive. Two examples presented by Gribble were his synthesis of ellipticine and isoellipticine (Scheme 50). This example stood out among the others because of the selective addition into the anhydride.

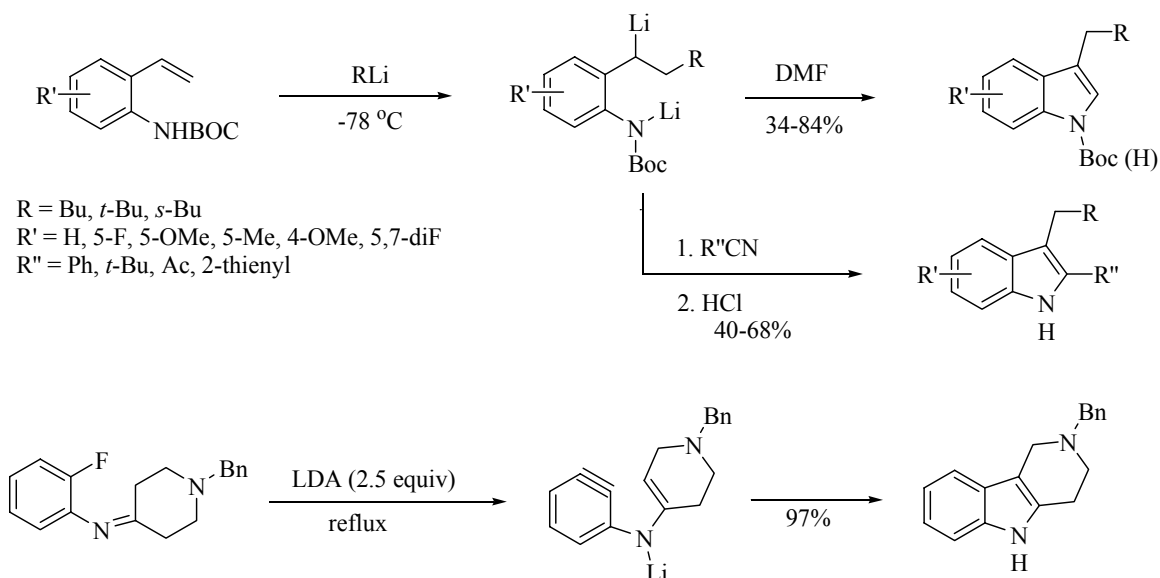
Scheme 50
Applications of Lithiated Indoles in Synthesis



1.3 Heterocyclic Ring Synthesis Using Lithium

The majority of the syntheses of heterocyclic ring systems discussed were indole forming reactions. A comparison of two lithiation methods to synthesize indoles can be seen in Scheme 51.

Scheme 51
Indole Ring Synthesis *via* Lithiation



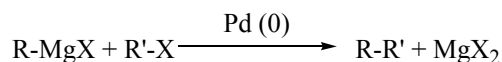
2 Palladium

2.1 Palladium Catalyzed Cross-Coupling

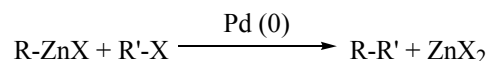
Gribble provided us with a complete list of the popular palladium cross-coupling reactions and examples of each. The complete list and generic reaction schemes can be seen in Scheme 52.

Scheme 52 Common Palladium Catalyzed Cross-Coupling Reactions

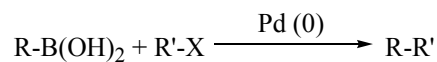
Kumada Coupling



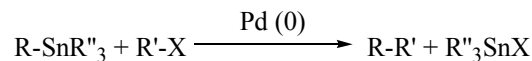
Negishi Coupling



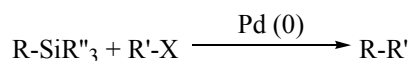
Suzuki Coupling



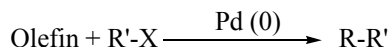
Stille Coupling



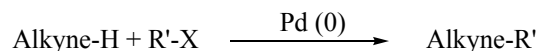
Hiyama Coupling



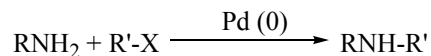
Heck Reaction



Sonogashira Coupling



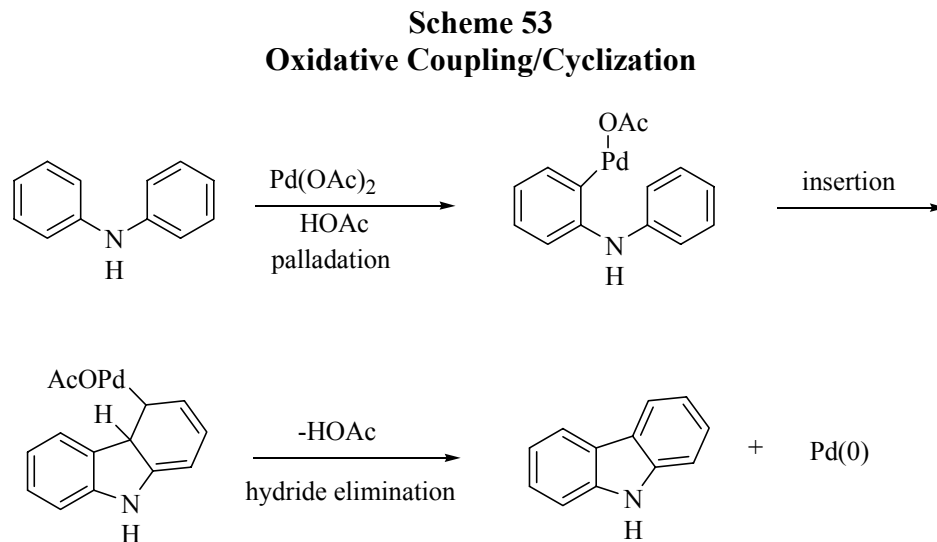
Buchwald-Hartwig Amination



Some miscellaneous palladium coupling reactions discussed were phosphination, cyanation, thiolation, methylation, and reduction. Another coupling described was the carbonylation reactions in which carbon monoxide is inserted into the activated bond and then the acylpalladium species is trapped by a nucleophile.

2.2 Oxidative Coupling/Cyclization

The oxidative coupling/cyclization reactions begin with an insertion into a C-H bond to form the organopalladium species. An example of this chemistry can be seen in Scheme 53.



2.3 Applications in Synthesis

The applications of palladium cross-coupling chemistry in synthesis of natural products is extensive as the literature abounds with examples.

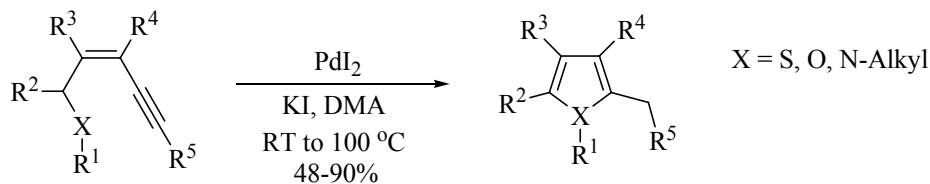
2.4 Ring Construction

Gribble starts the discussion of heterocyclic ring synthesis by providing a list of recent reviews. Some of the general literature reviews are:

- J. J. Li and G. W. Gribble, "Palladium in Heterocyclic Chemistry", Pergamon, NY, 2000.
- B. Gabriele *et al.*, "PdI₂-Catalyzed Synthesis of Heterocycles", *Synlett*, **2004**, 2468.
- R. C. Larock *et al.*, "Synthesis of Heterocycles *via* Palladium pi-Olefin and pi-Alkyne Chemistry", *Chem. Rev.* **2004**, *104*, 2285.
- G. Kirsch *et al.*, "Synthesis of Five- and Six-Membered Heterocycles Through Palladium-Catalyzed Reactions", *Curr. Org. Syn.* **2004**, *1*, 47.
- D.J. Hiasta *et al.*, "Current Methods for the Synthesis of 2-Substituted Azoles", *Tetrahedron* **2004**, *60*, 8991.
- Y. Yamamoto *et al.*, "Transition-Metal-Catalyzed Reactions in Heterocyclic Synthesis", *Chem. Rev.* **2004**, *104*, 2127.

The majority of the examples of heterocyclic ring synthesis provided by Gribble were published recently (2004). Pyrroles, furans, and thiophenes can be assembled from vinylogous propargyl equivalents (Scheme 54).

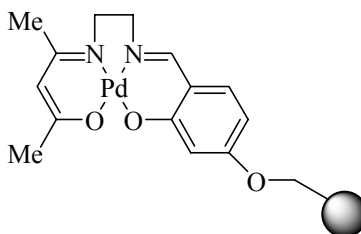
Scheme 54



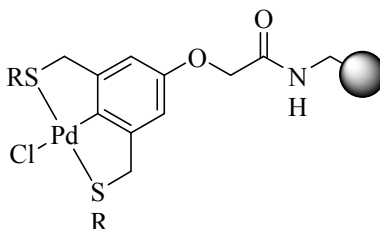
As one can imagine, fused ring systems can also be assembled using the same chemistry in Scheme 15 and several examples are discussed.

Gribble closed his short course with descriptions of novel palladium catalysts and phosphine ligands presented in the literature in the last three years. The most intriguing palladium catalysts are the ones linked to beads (Scheme 55). The bead-bound palladium catalyst could relieve the pharmaceutical chemist of the inherent problem of removing palladium in the final steps of a drug production.

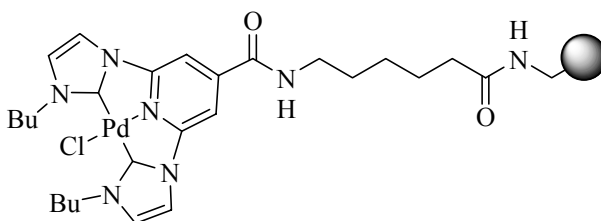
Scheme 55



P. Styring *et al.*, *Tetrahedron Lett.* **2004**, 45, 7915.



M. Bradley *et al.*, *Tetrahedron Lett.* **2004**, 45, 8239.



P. G. Steel *et al.*, *Tetrahedron Lett.* **2004**, 45, 8977.