



**Trip Report:
230th ACS National Meeting
Washington, DC
August 28 – September 1, 2005**

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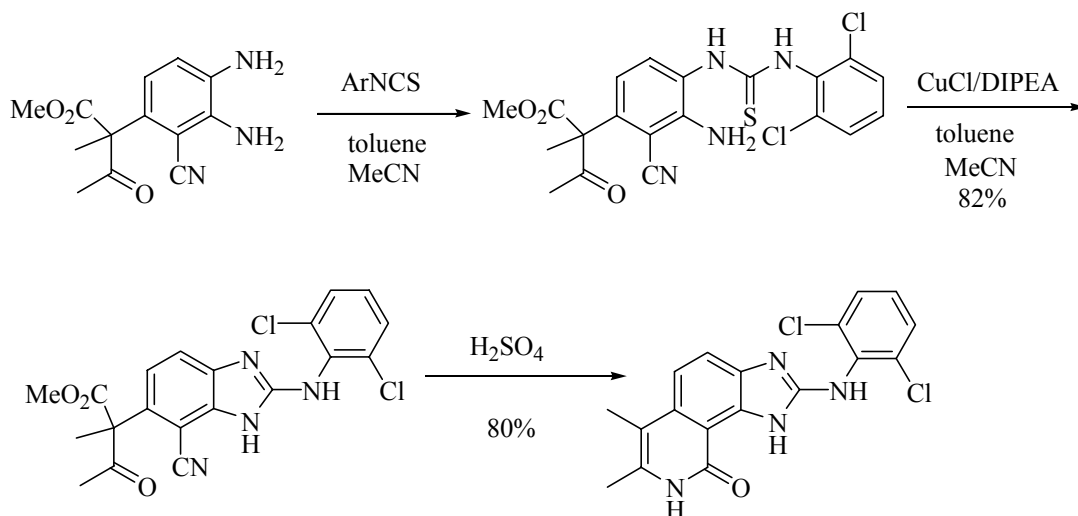
Abstract: The 230th ACS National Meeting was held in Washington, DC on August 28-September 1, 2005. The following lectures and posters were presented.

“Practical Synthesis of 2-(N-Substituted)-aminobenzimidazoles and Highly Functionalized Bicyclic Guanidines via CuCl-promoted Intramolecular Cyclization”

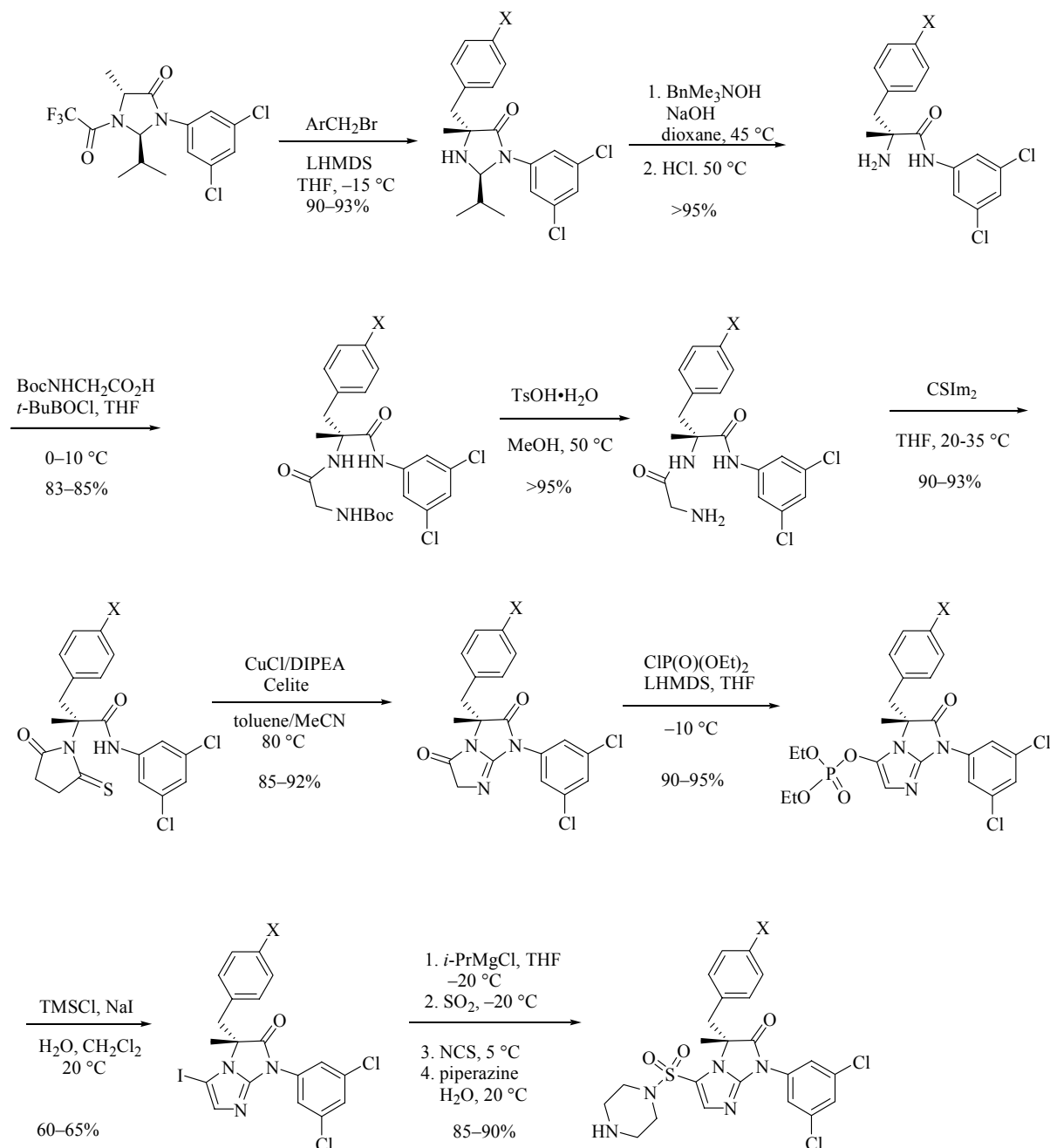
Li Zhang, *Chemical Development Department, Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Rd., PO Box 368, Ridgefield, CT 06877-0368.*

A chromatography free and general methodology to prepare 2-(*N*-substituted)-aminobenzimidazoles via CuCl/DIPEA mediated thiourea cyclization was developed.¹ The methodology was applied in the synthesis of an lck inhibitor (see Scheme 1) and extended to the synthesis of highly functionalized bicyclic guanidines. Furthermore, the methodology was applied successfully in the synthesis of a new class of LFA-1 inhibitor in multikilogram quantities (see Scheme 2).

Scheme 1



Scheme 2



X = Br or CN throughout to give two final products

“Synthesis of a Pre-operative Anesthetic Midazolam: Scale-up Issues and Challenges”

Madhup K. Dhaon, *Process and Analytical R&D, GPRD, Abbott, North Chicago, IL 60064.*

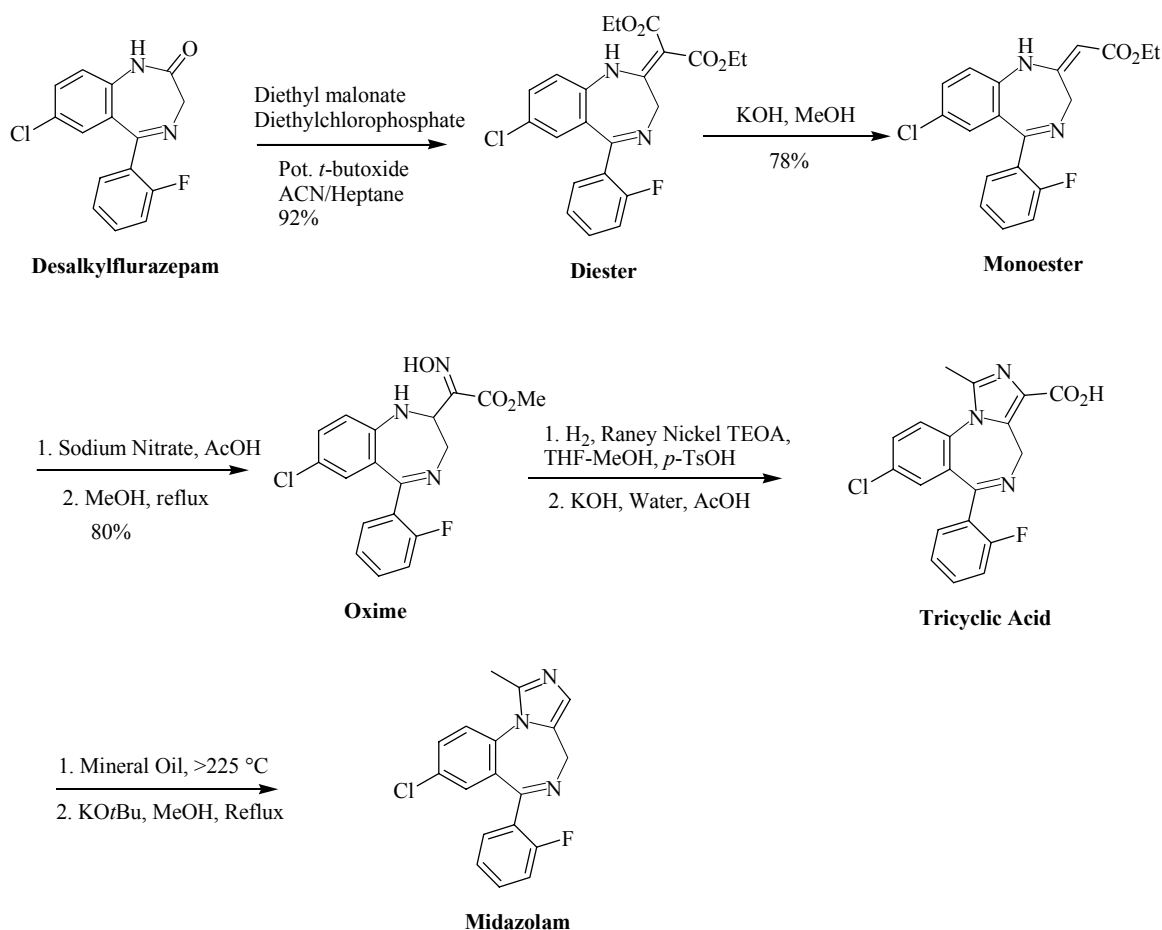
Midazolam is a Scheduled IV controlled drug used as a pre-operative anesthetic originally marketed by Roche as Versed. It was FDA approved in October 1999 and had early worldwide sales of \$600M.

A three-step-isolation process from Desalkylflurazepam was developed as described below:

- Step 1: three-step single isolation procedure to convert Desalkylflurazepam to an Oxime.
- Step 2: One-pot-three-step process (Reduction/Cyclization/Hydrolysis) to produce Tricyclic Acid.
- Step 3: Decarboxylation step performed at >225 °C in Mineral Oil as solvent.

The initial Step 3 yield was increased from 15–20% to 55–60% by employing a KO_tBu isomerization process. The R&D, scale-up, process justification, and validation was completed in 3.5 years. The DMF was filed in November 1997 and FDA approval was completed by October 1999. The process outlined in Scheme 3 was scaled-up to manufacturing in multi-Kg levels. The product was launched as a generic candidate June 2000.

Scheme 3



The formation of an Acetonitrile polymer (C₄H₅NO)_n during the conversion of the Desalkylflurazepam to the Diester initially resulted in a slow filtration and 4–5% of the polymer being carried through. This was overcome by altering the order of the reagent additions, cooling the batch, and changing the final phase isolation protocol for the Diester.

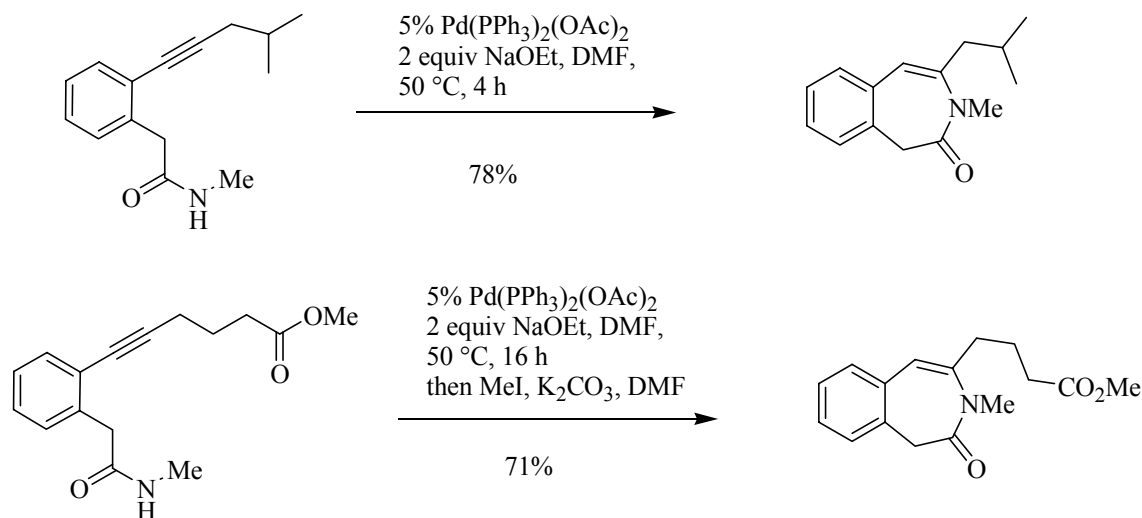
The level of Isomidazolam was significantly reduced by heating in MeOH in the presence of KO^tBu , thus cutting back on the need for several sequential recrystallizations. The optimized final step gave a 40–45% yield.

“Benzoazepinone Synthesis: Seven-membered Ring Formation via Palladium-catalyzed Cyclization of Alkynyl Benzeneacetamides”

Ying Yu, *Chemical Product R&D, Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285.*

The synthesis of benzo[d]azepin-2-one compounds by a Pd-catalyzed intramolecular cyclization of *o*-alkynyl benzeneacetamides was investigated. Benzeneacetamides with various acetylenic and *N*-substitutions were prepared. It was found that the 7-*endo* addition of nucleophilic amides to alkynes occurred in the presence of Pd catalysts and bases. The desired seven-membered ring benzoazepinones were obtained in good yields² (see Scheme 4 below for two examples of this work).

Scheme 4



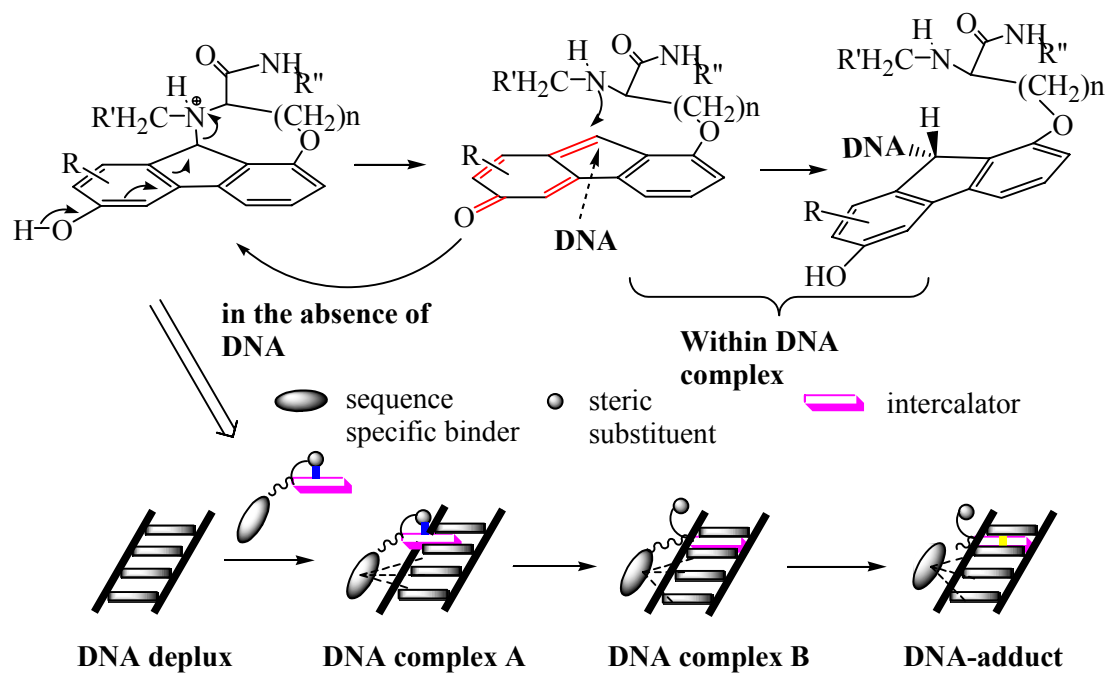
“Synthesis of a Cooperative DNA Alkylating Agent”

Jifeng Dai, *Department of Chemistry, Virginia Commonwealth University, Richmond, VA 23284.*

The goal of this research was to develop a DNA intercalating/alkylating agent in which high affinity DNA modification binding interacts cooperatively through sequence recognition.

The proposed target-promoted DNA alkylating agent contains a sequence-specific binding moiety which is linked through an amide as an “R” group. The reversible Quinone Methide (QM) precursor is incorporated as a bulky quaternary ammonium at the bridgehead of biphenyl ring (see Schemes 5–6 below).³

Scheme 5



Scheme 6

“Process Development of AAE421: A Somatostatin SST1 Receptor Antagonist”

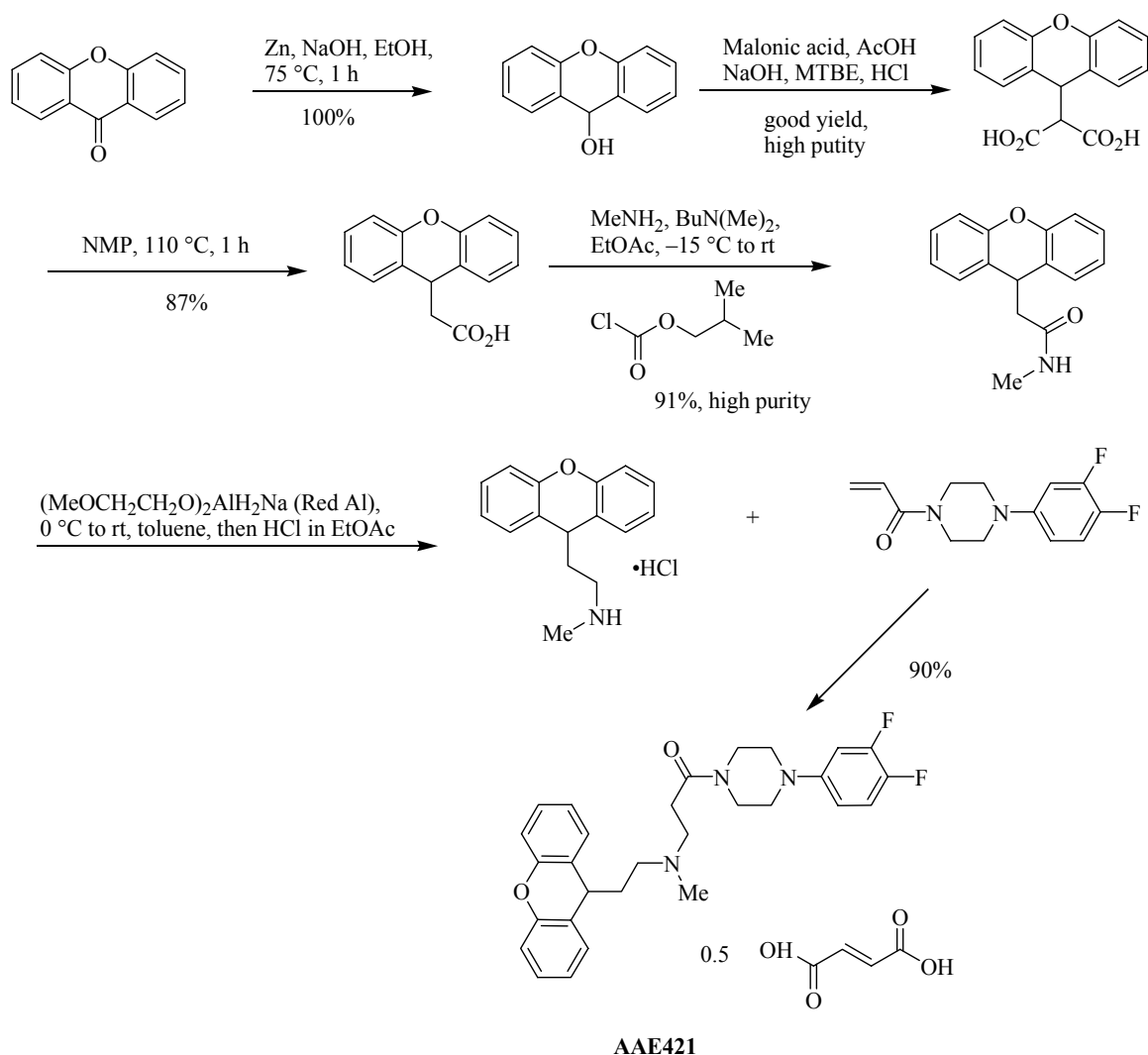
Y. Lu, *Process Research and Development, Novartis Institute for Biomedical Research, One Health Plaza, East Hanover, NJ 07936. (Technical Achievement in Organic Chemistry Awardee)*

The process development and the cGMP synthesis of AAE421 phase 1 material were presented (see Scheme 7). The medicinal chemistry route was developed; the process improvements included the elimination of the following:

- Use of pyridine.
- Use of EDCl.
- A chloroform/LAH reduction.
- Use of CH₂Cl₂.
- Chromatography.
- Final recrystallization from diethyl ether in MeOH.

For the cGMP campaign the final salt was recrystallized from EtOH/heptane to afford 938 g of AAE421 with 99.5% (AUC) purity.

Scheme 7



“A Practical Synthesis for the Core Structure of a Family of Selective Prostaglandin D2 Receptor Antagonists”⁴

Kevin Campos, *Department of Process Research, Merck & Co. Inc., PO Box 2000, Rahway, New Jersey 07065.*

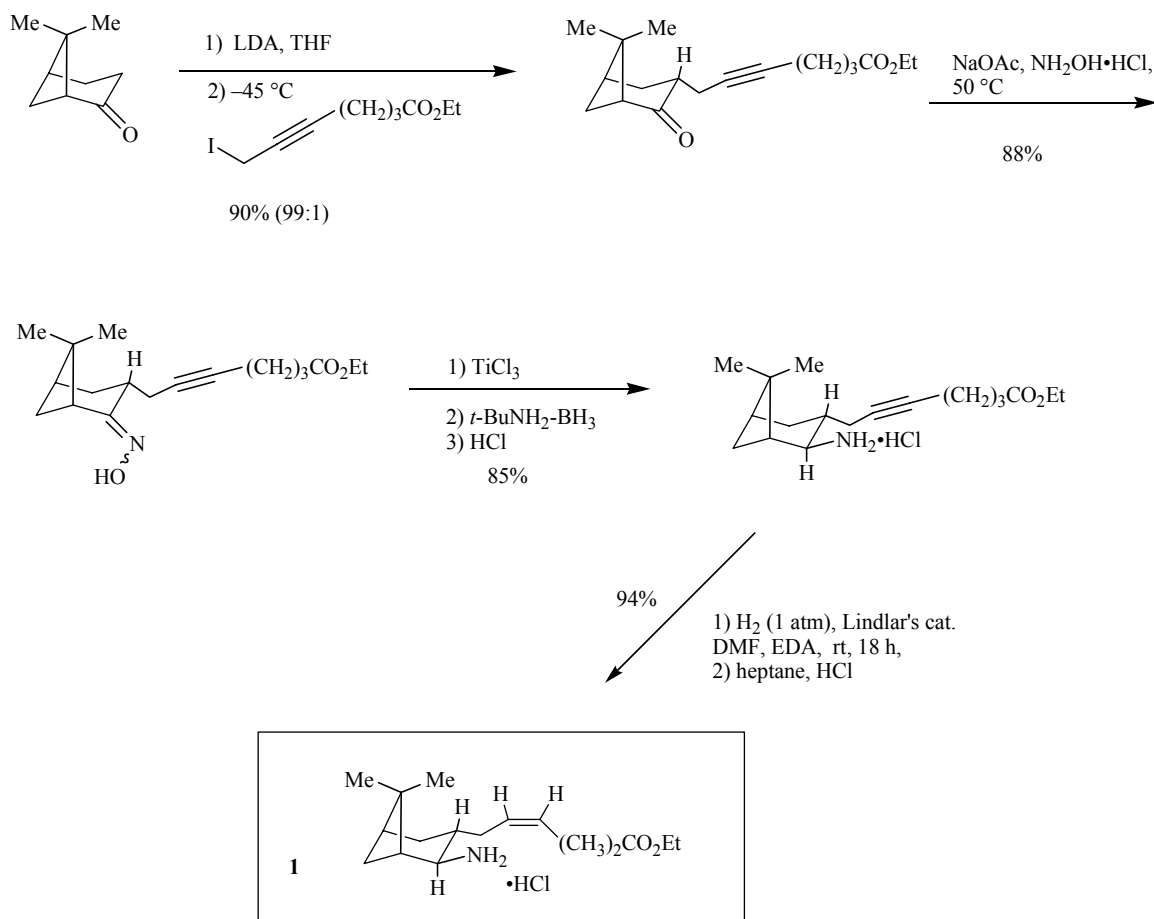
The original synthesis was ten liner steps, afforded **1** in 16% overall yield, and allowed for the production of 14 kg of material (no chromatography). Some of the cons of the synthesis included using Claisen conditions, ozonolysis, Na metal reduction, and an oxidation state “flip/flop.”

The development of a highly convergent, efficient synthesis of **1** was presented. It was found that the alkylation of the enolate of (+)-Nopinone with propargyl iodide afforded the alkylated adduct in 90% yield and 99:1 diastereoselectivity when the reaction was quenched with TFA at -45°C . These conditions avoided the epimerization to the thermodynamically favored product (kinetic alkylations favored the desired isomer).

Attempts at the one-step reductive amination were unsuccessful and the two-step approach (oxime formation, reduction) was considered a reasonable alternative. Initial attempts at reducing the methyl oxime were not selective enough to proceed, so efforts focused on the chemoselective reduction of the oxime. Conditions were found that employed TiCl_3 , $t\text{-BuNH}_2\text{-BH}_3$ (stable), aqueous EtOH in a one-pot procedure to give the aminoalkyne HCl salt in 85% yield after isolation; with good diastereoselectivity (98:2) and no reduction of the alkyne.

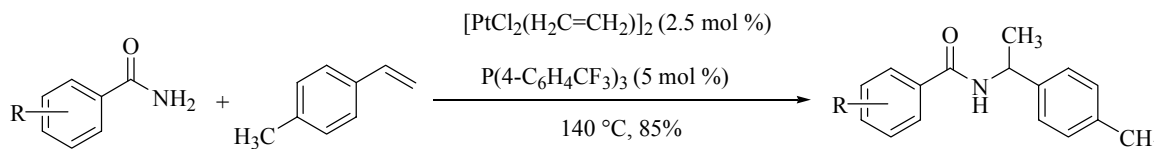
A process for the well controlled hydrogenation of the aminoalkyne was next sought. It was found that using ethylenediamine (EDA) as a catalyst poison afforded the least overreduction and Z/E isomerization, providing the desired *cis* amino-alkene in >97% yield with only 2% isomerization to the *trans* isomer, and 0.4% overreduction. The free base was readily recrystallized from pure heptane as the HCl salt to afford material that was >98% (AUC) pure. The ee of the crystallized material had been upgraded from 92% (technical grade β -pinene) to 99% (see Scheme 8 below for synthetic scheme). This improved chemistry was five linear steps with 50% overall yield.

Scheme 8

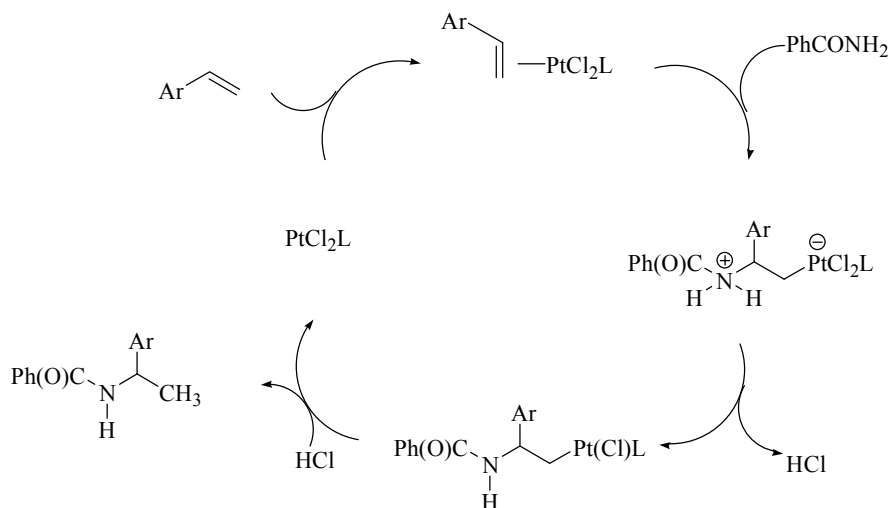


“Platinum-catalyzed Intermolecular Hydroamination of Vinyl Arenes with Carboxamide”Hua Qian, P.M. Gross *Chemical Laboratory, Duke University, Durham, North Carolina 27708.*

The speaker described the development of an effective protocol for the Markovnikov hydroamination of vinyl arenes with carboxamides and related derivatives to form *N*-(1-arylethyl)amide derivatives in good yield with high regioselectivity (see Scheme 9).

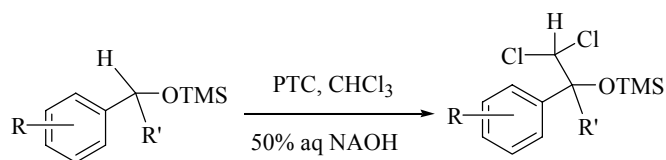
Scheme 9

The reaction conditions were optimized and a 1:2 mixture of [PtCl₂(H₂C=CH₂)₂]/P(4-C₆H₄CF₃)₃ in mesitylene were found to be ideal for optimum yield. Electron-rich, electron-poor, and hindered vinyl arenes underwent platinum-catalyzed hydroamination with a range of aryl carboxamides. The new protocol tolerated a number of polar functional groups, including aryl halides (R = *p*-Br), carboxylic esters (R = *p*-CO₂Me), acetals, and silyl ethers (R = OTBDMS). The speaker also offered a proposed mechanism for this catalytic reaction (see Scheme 10).

Scheme 10**“Tertiary Alcohols via Carbene Insertion Reaction”**Chun Li, *Merck Frosst Center for Therapeutic Research, P.O. Box 1005, Quebec, Canada, H9R 4P8.*

The poster described the synthesis of chiral tertiary dichloromethylcarbinols by stereospecific insertion of dichlorocarbene, generated under phase transfer catalyst conditions into protected secondary alcohols (see Scheme 11).

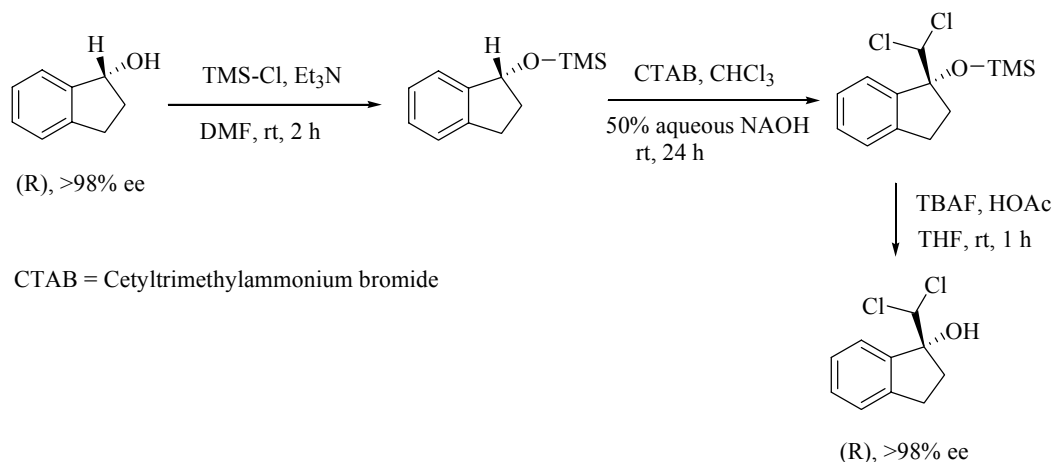
Scheme 11



Reaction conditions were optimized and the following observations were made:

- Cleaner reaction with higher carbene insertion is achieved at room temperature.
- TMS is the preferred protecting group.
- Electron-donating substituents (R) promote insertion reaction.
- Bulky substituents (R') impede carbene insertion.
- Heterocycles containing N and S are not compatible.
- 0.3 mol % catalyst loading is optimum. Higher catalyst loading leads to dimerization instead of insertion.
- No loss of chiral integrity is observed (see Scheme 12)

Scheme 12

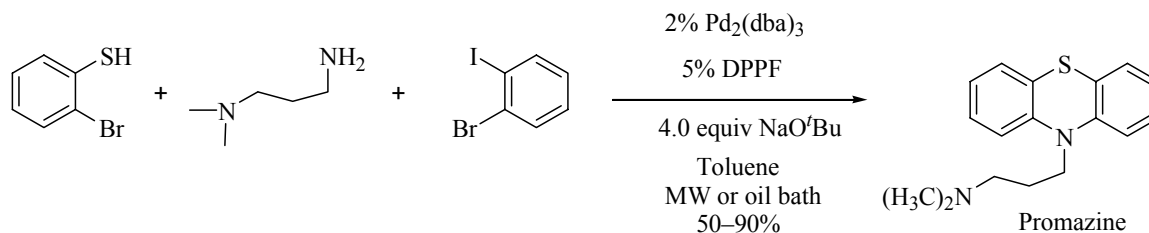


“Palladium-catalyzed Three-component Coupling Reaction Leading to Formation of One S and Two C-N bonds”

Morten Jorgensen, *Department of Chemistry, University of Southern Denmark.*

The speaker described conditions developed in their laboratory that allow for the formation of C-S bonds from thiophenols and aryl iodides as well as for the formation of C-N bonds from amines and aryl bromides using the same catalyst in a one-pot operation. This discovery was applied to the synthesis of the promazine family of antipsychotics and related compounds (see Scheme 13).

Scheme 13



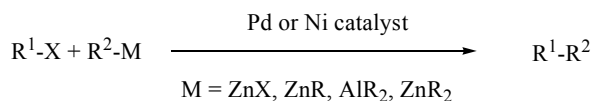
The reaction scope includes both aliphatic amines and anilines. This novel three component reaction works well for the promazine series with isolated yields ranging from 50 to 80%. The transformation can be carried out using either conventional oil-bath or microwave conditions.

“Room Temperature Alkyl-alkyl Negishi Cross-coupling Reaction Utilizing a Pd-NHC Catalyst”

Niloufar Hadei, *Department of Chemistry, York University, 4700 Keele Street, Toronto, ON Canada M3J 1P3.*

The Negishi cross-coupling reaction is represented in Scheme 14.

Scheme 14



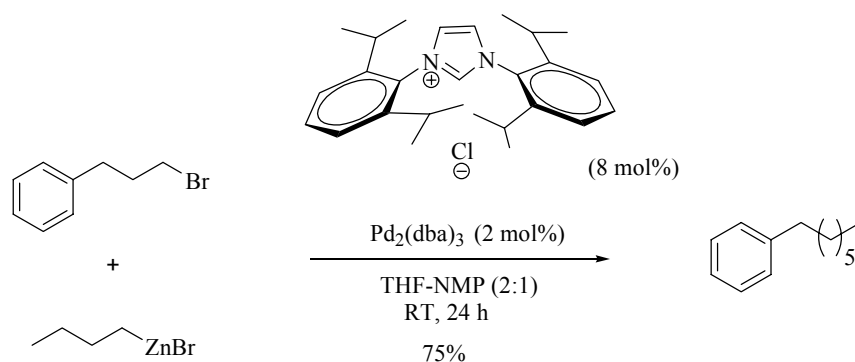
The ligands for Pd used in the above cross-coupling reactions are tertiary phosphines. Unfortunately, phosphines are air sensitive and some even pyrophoric. The poster describes the use of Pd-NHC catalytic system that achieves room temperature Negishi couplings of un-activated primary bromides and organozinc reagents with a variety of functionality.

Advantages of *N*-heterocyclic carbenes (NHC):

- High thermal stability.
- Tight coordination to the metal centre.
- Possibility to tune the steric and electronic properties of the ligand independently.

Scheme 15 shows an example of alkyl-alkyl Negishi cross-coupling reaction utilizing a Pd-NHC catalyst:

Scheme 15



- The carbene ligand is easy to make/commercially available.
- First high yielding Negishi cross-coupling utilizing Pd-NHC ligand.
- First palladium catalyzed Negishi alkyl-alkyl cross-coupling at room temperature.

References:

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- 1b. Wang, X.-j.; Zhang, L.; Xu, Y.; Krishnamurthy, D.; Varsolona, R.; Nummy, L.; Shen, S.; Frutos, R.; Byrne, D.; Chung, J. C.; Farina, V.; Senanayake, C. *Tetrahedron Lett.* **2005**, *46*, 273–276.
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