



**Trip Report:
International Chemical Congress of Pacific Basin Societies,
Pacifichem 2005
Honolulu, Hawaii
December 15 – 20, 2005**

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***Abstract:** Pacifichem 2005 was held in Honolulu, Hawaii on December 15 – 20, 2005. Founded in 1984, Pacifichem Conferences have been held in Honolulu, Hawaii around every five years. This international conference, which was co-sponsored by chemical societies in the United States, Japan, Canada, Korea, New Zealand, and Australia attracted more than 11,000 attendees from 70 countries this year. The objective of this conference is to bring together scientists from Pacific Rim countries to promote collaborations and share recent research contributions. This week-long symposium covered topics in all areas of chemical sciences including biological, medicinal and organic chemistry. This report highlights select material from the talks presented in the conference.*

“SAR Studies on 8-Quinolylpiperazines as Dual SSRI/5-HT_{1A} Antagonists for the Treatment of Depression,”

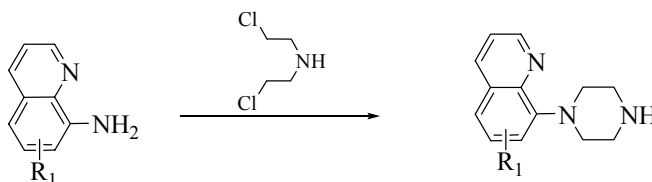
M. Asselin, T. Andree, K.L. Meagher, T. Coleman, D.A. Evrard, J. Kodah, R.E. Mewshaw, R. Scerni, L. Schechter, U.S. Shah, D. Smith, D. Zhou (Wyeth Research), Princeton, New Jersey, USA.

Scientists from Wyeth Research disclosed a new class of molecules, 8-quinolylpiperazines, that possess both SSRI and 5-HT_{1A} antagonist activities. Currently prescribed selective serotonin receptor inhibitors (SSRIs), such as Fluoxetine, Paroxetine and Citalopram, require several weeks before full therapeutic effect is observed. The delayed induction may be due to the involvement of the 5-HT_{1A} autoreceptors which suppress the firing of 5-HT neurons. Selective antagonists for 5-HT_{1A} receptor have been postulated to be useful in the treatment of CNS disorders such as anxiety depression. In the case of depression, the 5-HT_{1A} antagonists could facilitate the onset of action of SSRIs by blocking 5-HT_{1A} autoreceptors. Thus, an agent with both SSRI and 5-HT_{1A} antagonism activities would be a significant improvement on currently approved therapeutic effect.

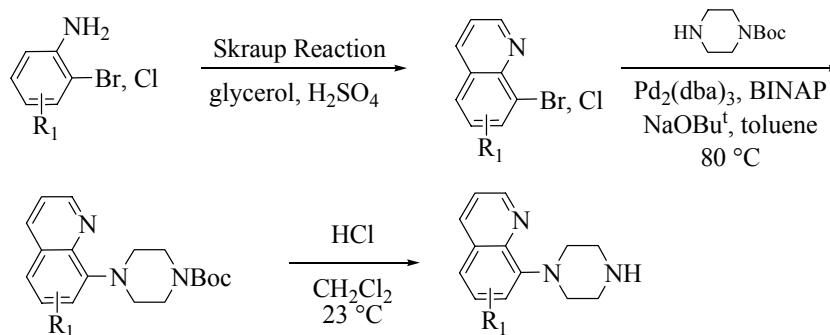
The design and synthesis of 8-quinolylpiperazine target compounds were presented. The synthesis of quinolylpiperazine is delineated in Scheme 1. Some of the quinoline core structure was constructed by Skraup reaction. The piperazine ring was incorporated either by cyclization or Buchwald coupling.

Scheme 1 Synthesis of 8-Quinolylpiperazines

Route 1

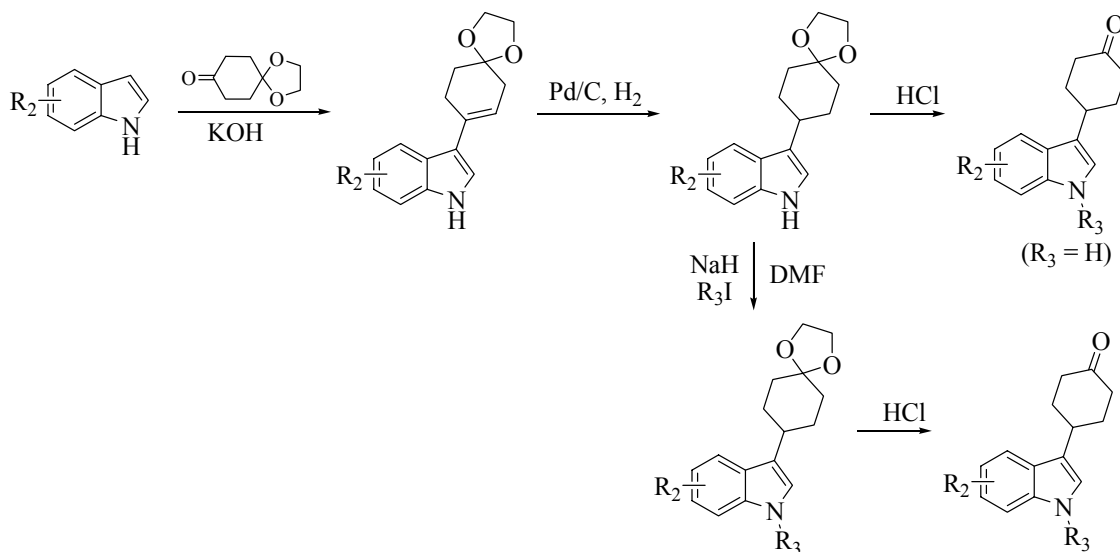


Route 2



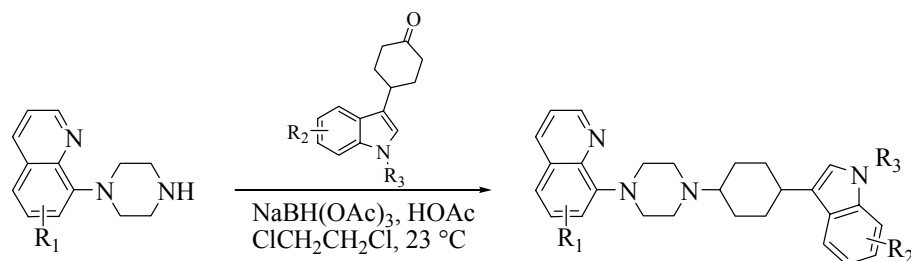
The synthesis of 4-(indol-3-yl) cyclohexanone is described in Scheme 2. Condensation of indole with partially protected 1,4-cyclohexanedione and hydrogenation followed by *N*-alkylation and deprotection completed the synthesis.

Scheme 2
Synthesis of 4-(Indol-3-yl)cyclohexanone



The final target molecules were synthesized by reductive amination as delineated in Scheme 3.

Scheme 3
Preparation of Targets by Reductive amination



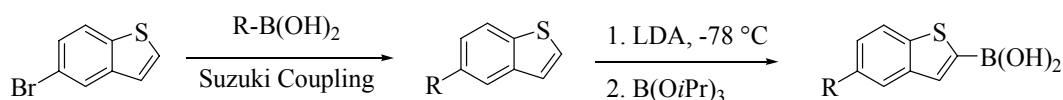
A systematic study of SAR by varying the substitution on quinoline (R_1), indole (R_2), and indole nitrogen (R_3) was presented. The stereochemistry across the cyclohexyl ring (cis or trans) can affect affinities at 5-HT transporter and 5-HT_{1A}. In general cis-isomer is more active than trans-isomer. *N*-Methylation on indole is optimal for dual affinities. The position and the nature of R_1 and R_2 can also affect affinities at 5-HT transporter and 5-HT_{1A}.

“Synthesis of 2,5-Disubstituted Benzothiophene Boronic Acids,”

D.R. Cefalo, J.I. Henderson (Frontier Scientific, Inc.), Logan, Utah, USA.

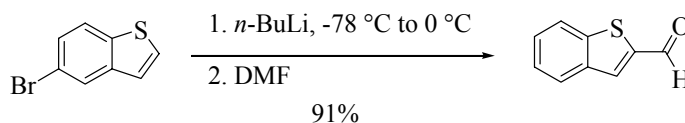
Benzothiophene ring system has been within many different therapeutically important compounds such as our CNS lead compounds, ALB 109737 and ALB 109780. Another example was the use of benzo[*b*]thiophene-2-boronic acid as an AmpC β -lactamase inhibitor in treating infections with β -lactamase resistant bacteria. Benzo[*b*]thiophene-2-boronic acid was found to be a potent inhibitor and exhibited a K_i (*E. coli* AmpC) of 27 nM. In order to optimize the biological activity, scientists at Frontier Scientific have developed the method for the preparation of 2,5-disubstituted benzothiophene boronic acids. The 5-bromobenzothiophene was coupled with various boronic acids using standard Suzuki coupling reaction conditions. Selective lithiation followed by addition of trialkylborate created the boronic acid functionality. This boronic acid intermediate could then be converted into a series of 2,5-disubstituted benzothiophenes.

Scheme 4
Synthesis of 5-Substituted Benzo[*b*]thiophene-2-boronic Acids



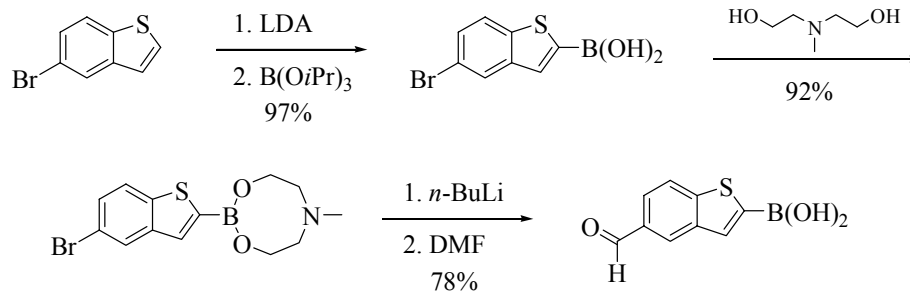
Lithium-halogen exchange of 5-bromobenzothiophene, followed by addition of DMF yielded a mixture of 2-formylbenzo[*b*]thiophene and 5-formylbenzo[*b*]thiophene. The reaction could be forced to form the 2-formylbenzo[*b*]thiophene by simply allowing the reaction mixture to warm to 0 °C before addition of DMF. However, none of the condition they examined allowed the selective formation of 5-formylbenzo[*b*]thiophene.

Scheme 5
Formylation of 5-Bromobenzothiophene



In order to prepare 5-formylbenzo[*b*]thiophene, the 5-bromobenzothiophene was selectively deprotonated using LDA followed by the formation of boronic acid. The resulting boronic acid was then protected using *N*-methyldiethanolamine. The ester formed is stable to exposure of *n*-BuLi, allowing for the lithium-halogen exchange to occur selectively. Subsequent treatment of the lithiate with DMF, followed by acid hydrolysis of the protecting group afforded the desired product in high yield and purity.

Scheme 6
Synthesis of 5-Formyibenzothiophene-2-boronic Acid



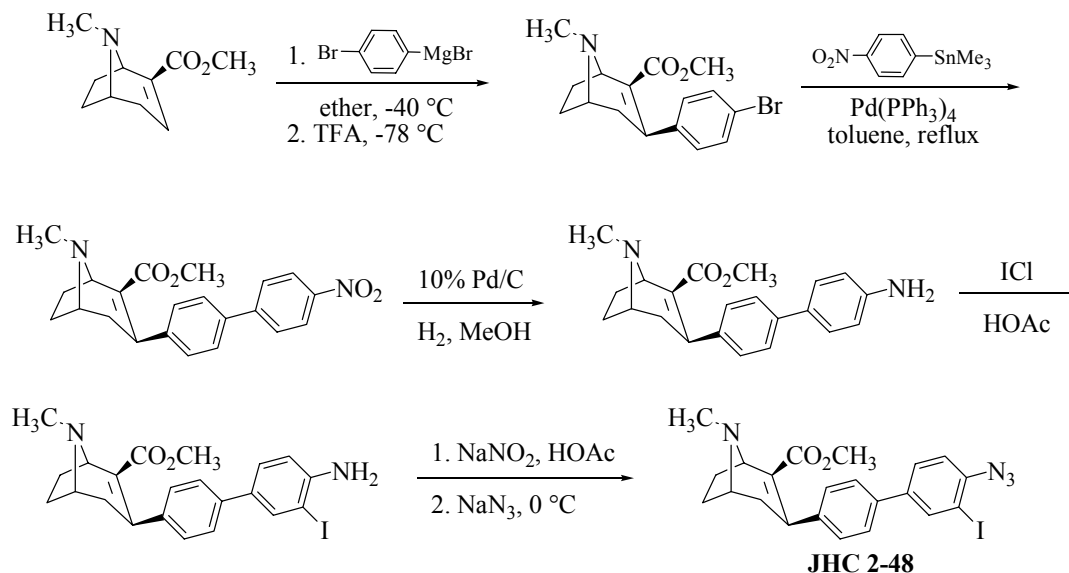
The ability to selectively incorporate specific functional groups at selected positions of the benzothiophene ring system allows for the preparation of numerous diversified analogs. The same methodology could be used to provide 2,4-, 2,6- and 2,7- disubstituted benzo[*b*]thiophenes.

“Design and Synthesis of a Novel DAT Photoaffinity Ligand Based on 2β-Carbomethoxy-3β-Biphenyltropane,”

J. Cao, J.H. Cha, T. Kopajtic, R. Vaughan, J. Lever, J.L. Katz, A.H. Newman (NIDA-IRP, NIH, DHHS), Baltimore, Maryland, USA.

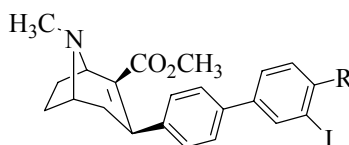
The inhibition of dopamine uptake via the dopamine transporter (DAT) has been established as the primary mechanism underlying the reinforcing actions leading to abuse and addiction of cocaine and has been a primary target for medication development. Site-directed mutagenesis and structure-activity relationship (SAR) studies suggest that structurally divergent DAT inhibitors bind to different sites or binding domains on the DAT. Scientists at NIH have pursued the development of molecular probes that include irreversible (N₃, NCS) and radiolabeled (³H, ¹²⁵I) ligands to provide important molecular tools with which to identify binding sites of DAT inhibitors at a molecular level. Photoaffinity ligands, based on tropane-based dopamine uptake inhibitors, have been designed to covalently bind to discrete points of attachment on the DAT. They have demonstrated that depending on the position of azide substitution on the tropane ring system, covalent attachment can occur in different transmembrane (TM) regions. This has suggested that not all tropane-based DAT inhibitors bind to the same recognition site on DAT and depending on the position of azide attachment, different TM domains are labeled. They hypothesized that appending azido groups at various positions on two tropane-based DAT inhibitors, cocaine and bupropion, would provide the opportunity to identify points of attachment on DAT, elucidate 3D-arrangement of the TM domains, and direct future drug design. To further explore SAR and improve the binding affinity, a 3'-iodo-4'-azido-3β-biphenyl analog was synthesized from cocaine via the route as delineated in Scheme 7.

Scheme 7
Synthesis of Novel Photoaffinity Ligand JHC 2-48



A novel photoaffinity ligand, **JHC 2-48**, and its precursors have been synthesized (Scheme 7) and evaluated for binding to DAT and SERT (Table 1).

Table 1
DAT and SERT Binding Results for JHC 2-48 and Precursors

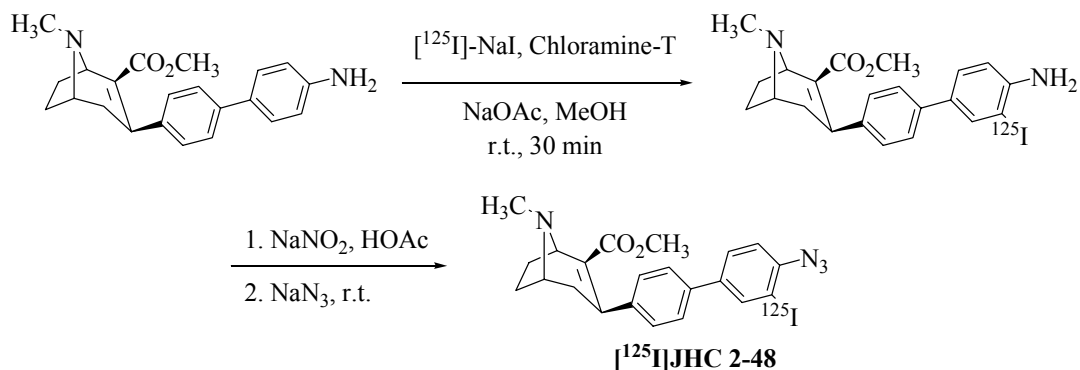


Compound	R	DAT K _i (nM)	DAT K _i (nM)
JHC 2-43	Br	0.42	4.1
JHC 2-45	4'-NO ₂ -Ph	5.03	51
JHC 2-46	4'-NH ₂ -Ph	12.9	1070
JHC 2-47	3'-I-4'-NH ₂ -Ph	8.82	134
JHC 2-48	3'-I-4'-N ₃ -Ph	15.1	109

The photoaffinity ligand **JHC 2-48** demonstrated the highest DAT binding affinity of any DAT photoaffinity ligand they have prepared so far. This compound also had reasonably high affinity at SERT.

In order to further characterize the binding domains of tropane based dopamine uptake inhibitors at DAT and SERT and irreversibly labeled these proteins, the ¹²⁵I labeled **JHC 2-48** was prepared as shown in Scheme 8.

Scheme 8
Radiosynthesis of [¹²⁵I]JHC 2-48



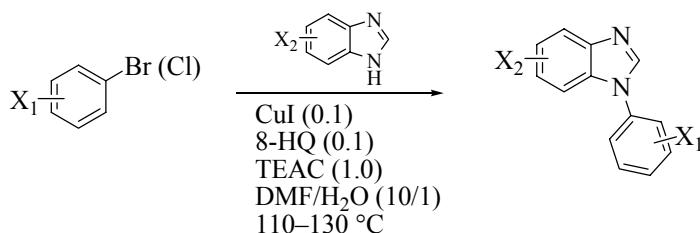
The [¹²⁵I]JHC 2-48 is the first high affinity photo label for both DAT and SERT in which the azido group is placed in the 3β-position of the tropane ring and will be used as an important irreversible ligand with which to characterize the 3D-structure and function of these proteins.

“Near-Homogeneous Cu-Catalyzed *N*-Arylation of Imidazoles with Aryl Bromide,”

L. Liu, M. Frohn, N. Xi, C. Dominguez (Amgen), Thousand Oaks, California, USA.

N-Aryl imidazoles constitute a class of compounds of medicinal importance. However there are limited synthetic methods that allow for efficient coupling between imidazoles and non-activated aryl halides, especially aryl bromides and chlorides. The existing protocols (such as Buchwald and Cristau coupling) involved the use of a large excess of insoluble inorganic bases in nonpolar solvents and works mainly for aryl iodides. Scientists at Amgen have developed a system that utilizes one equivalent of soluble base (tetraethylammonium carbonate, TEAC) and a new Cu-ligand (8-hydroxyquinoline, 8-HQ) system that is more efficient and is suitable for couplings between imidazoles and aryl bromides and even chlorides. The new reaction condition (Scheme 9) is near homogeneous, making it more convenient for scaling up operations and mechanistic studies.

Scheme 9
Cu-Catalyzed *N*-Arylation of Imidazoles with Aryl Bromides

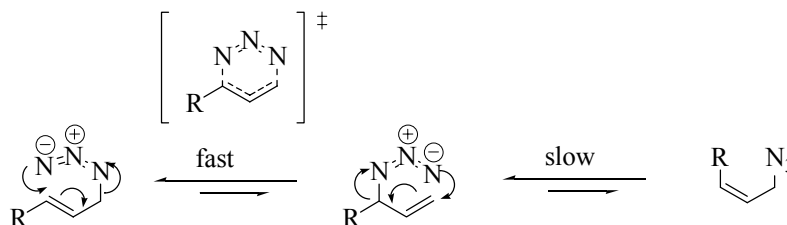


“Allylic Azide Rearrangement: Achieving Selectivity in the Dynamic [3,3] Process,”

A.K. Feldman, B. Colasson, V.V. Fokin, K.B. Sharpless (The Scripps Research Institute), La Jolla, California, USA.

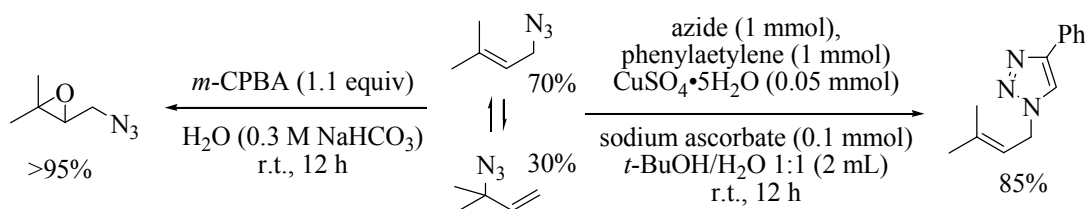
Allylic azides exist in a state of equilibrium of different isomers, a direct consequence of a dynamic [3.3] sigmatropic rearrangement involving a postulated 6-membered transition state (Scheme 10).

Scheme 10 Rearrangement of Allylic Azides



The rearrangement results in mixtures of products of isomeric allylic azides and, thus, it has been traditionally perceived as a synthetic limitation. Scientists at Scripps Research Institute have devised chemical methods for selective capture of one of the isomer. They used two model reactions: *m*-CPBA epoxidation of olefins and Cu(I)-catalyzed azide-alkyne cycloadditions to tackle either the alkene or the azide functionality, respectively. Several classes of allylic azides were submitted to these reactions. In general good to excellent selectivity was achieved as shown in Scheme 11.

Scheme 11 Achieving Selectivity by the "Fixing" Chemical Reaction



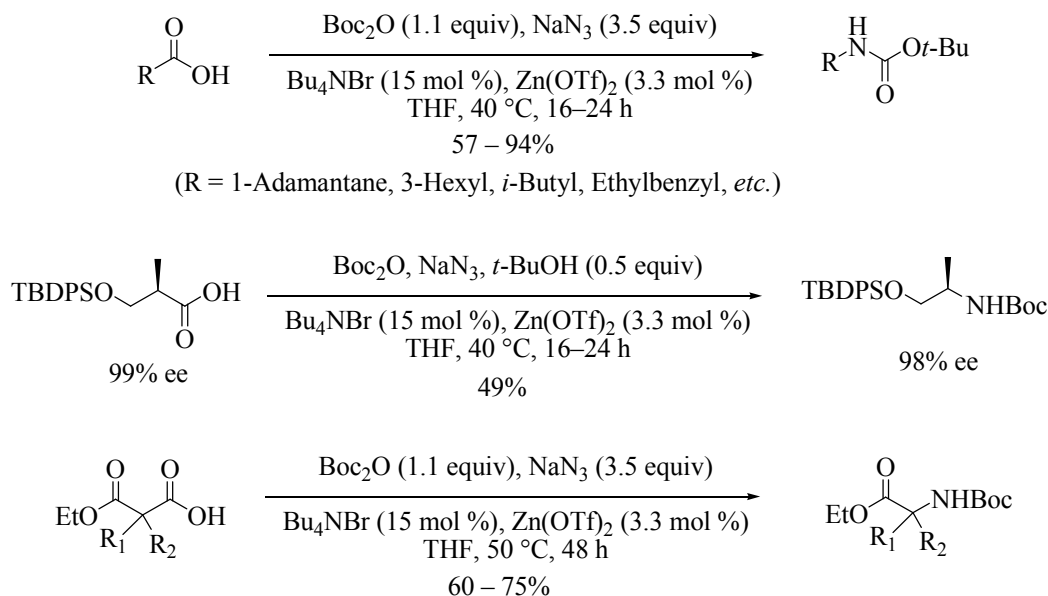
By use of an appropriate capture trick, a given [3.3]-sigmatropic rearrangement mixture of allylic isomers is uniquely "siphoned off" through the isomer preferred by the "fixing" reaction. The rearrangement process was terminated by reactions selective for azide functionality and for olefin functionality, respectively.

“Novel Zinc-Catalyzed Curtius Rearrangement,”

H. Lebel, O. Leogane (University of Montreal), Montreal, Québec, Canada.

Carbamates are compounds of great interest, especially as protected forms of amine functionality. They are also found in a variety of natural products, including pesticides and medicinal drugs. Scientists at the University of Montreal reported a simple and efficient zinc-catalyzed rearrangement of carboxylic acids into carbamates, via acyl azide intermediates. The activation of carboxylic acids with *t*-butoxycarbonyl anhydride and sodium azide in the presence of a phase transfer catalyst and zinc(II) triflate in THF, allows the formation of the acyl azide intermediate, which then undergoes the rearrangement to form the corresponding isocyanate. The addition of *t*-butanol resulting from the degradation of *t*-butoxycarbonyl anhydride affords the desired *t*-butoxy carbamates in high yields at low temperature (Scheme 12). These reaction conditions are compatible with a variety of substrates, including malonate derivatives, which provide access to protected amino acids. The rearrangement proceeded with retention of configuration as shown in the example of chiral α -substituted carboxylic acid.

Scheme 12 Zinc-Catalyzed Curtius Rearrangement

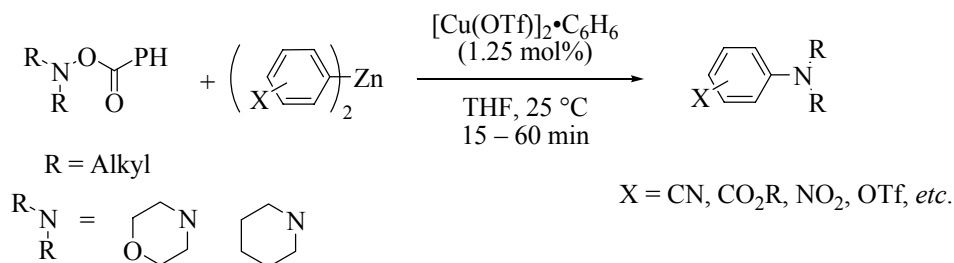


“Metal-Catalyzed Electrophilic Amination,”

J. Johnson, A. Berman (University of North Carolina), Chapel Hill, North Carolina, USA.

Arylamines are attractive targets, owing to the prominence of this structural motif in drug related molecules, and many methods have been developed for the preparation of such compounds. Scientists at University of North Carolina reported a copper-catalyzed electrophilic amination of diorganozinc reagents with *O*-acyl hydroxylamines, allowing for the preparation of tertiary amines in high yields under mild conditions (Scheme 13). The functionalized diarylzinc reagents were prepared via an iodine/magnesium exchange of the corresponding aryl iodide followed by transmetalation of the resultant Grignard species with zinc chloride.

Scheme 13
Copper-Catalyzed Electrophilic Amination of Diarylzinc Reagents



Diheteroarylzinc and dialkylzinc reagents work as well. The use of other copper salts is also feasible. Compatible results are obtained when CuCl_2 is substituted for CuOTf under the standard reaction conditions.