



**Trip Report:  
230<sup>th</sup> ACS National Meeting  
Washington, D.C.  
August 29 – September 1, 2005**

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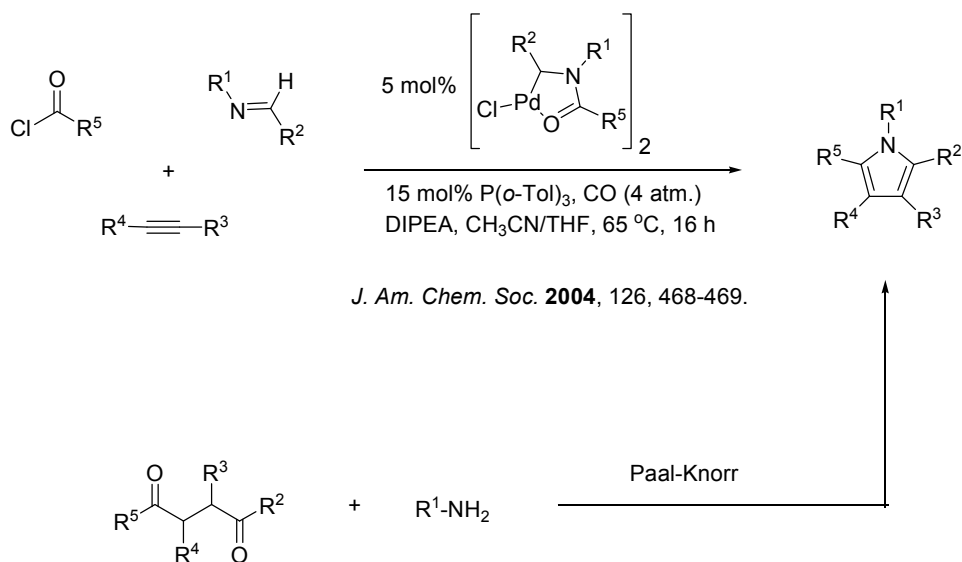
***Abstract:** “230<sup>th</sup> ACS National Meeting was held in Washington, D.C., August 29<sup>th</sup>-September 1, 2005. A summary of selected lectures and posters from the Organic Chemistry sections of the meeting are presented dealing with heterocycle synthesis, new protecting groups and general synthetic methodology.*

**“Efficient and modular synthesis of pyrroles in one pot from imines, acid chlorides and alkynes”**

Daniel J. St.Cyr, Rajiv Dhawan and Bruce A. Arndtsen, Department of Chemistry, McGill University.

Further development of a recently revealed modular pyrrole synthesis was presented. The broad utility of pyrroles in medicinal chemistry and materials science has made them important synthetic targets. Traditional methods of assembly, such as the Paal-Knorr synthesis require the construction of complex intermediates to introduce diversity (Scheme 1). Several alternative routes have been developed lately including a multi-component coupling of imine, acid chloride, and alkyne (Scheme 1).

**Scheme 1**



A new metal-free variation on this methodology eliminates the need to separately synthesize a palladium catalyst and thus allows independent variation of all five substituents (R1-R5) by modulation of the three constituent substrates. The need for pressured reaction vessels is also eliminated by the replacement of carbon monoxide with isocyanides (Table 1).

**Table 1**

isocyanide	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	Yield
tBu	Bn	Tol	CO <sub>2</sub> Et	CO <sub>2</sub> Et	Tol	86%
Chx	Bn	Tol	CO <sub>2</sub> Et	CO <sub>2</sub> Et	Tol	54%
Bn	Bn	Tol	CO <sub>2</sub> Et	CO <sub>2</sub> Et	Tol	43%
o-Tol	Bn	Tol	CO <sub>2</sub> Et	CO <sub>2</sub> Et	Tol	0%
tBu	Bn	iPr	CO <sub>2</sub> Et	CO <sub>2</sub> Et	p-C <sub>6</sub> H <sub>4</sub> OMe	50%
tBu	Bn	Tol	CO <sub>2</sub> Et	CO <sub>2</sub> Et	p-C <sub>6</sub> H <sub>4</sub> OMe	86%
tBu	Et	Tol	CO <sub>2</sub> Et	CO <sub>2</sub> Et	tBu	48%

<i>t</i> Bu	<i>Bn</i>	<i>Tol</i>	<i>CO</i> <sub>2</sub> <i>Et</i>	<i>H</i>	<i>Tol</i>	42%
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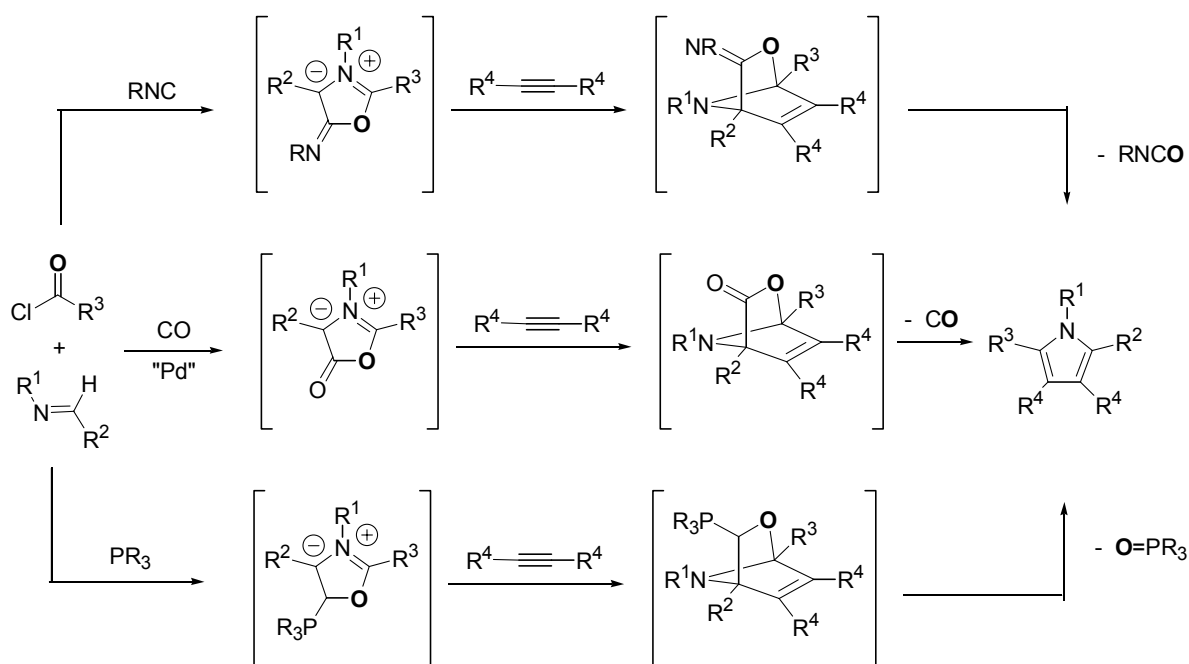
It was also demonstrated that phosphorous compounds could be used in place of isocyanides or carbon monoxide in the process (Table 2). The best results were obtained with 2-phenyl-benzo [1,3,2] dioxaphosphole although triphenyl phosphite or phenylphosphorous acid diphenyl ester gave similar results in most cases.

Table 2

<b>R<sup>1</sup></b>	<b>R<sup>2</sup></b>	<b>R<sup>3</sup></b>	<b>R<sup>4</sup></b>	<b>R<sup>5</sup></b>	<b>Yield</b>
<b>Bn</b>	<b>Tol</b>	<b>CO<sub>2</sub>Et</b>	<b>CO<sub>2</sub>Et</b>	<b>Tol</b>	<b>86%</b>
<b>Bn</b>	<b>Tol</b>	<b>CN</b>	<b>H</b>	<b>Tol</b>	<b>54%</b>
<b>Bn</b>	<b>Tol</b>	<b>H</b>	<b>H</b>	<b>Tol</b>	<b>43%</b>

The proposed reaction mechanisms illustrate how isocyanides, phosphines and carbon dioxide can all serve to remove an oxygen atom by elimination from bicyclic intermediates to give pyroles (Figure 1).

Figure 1

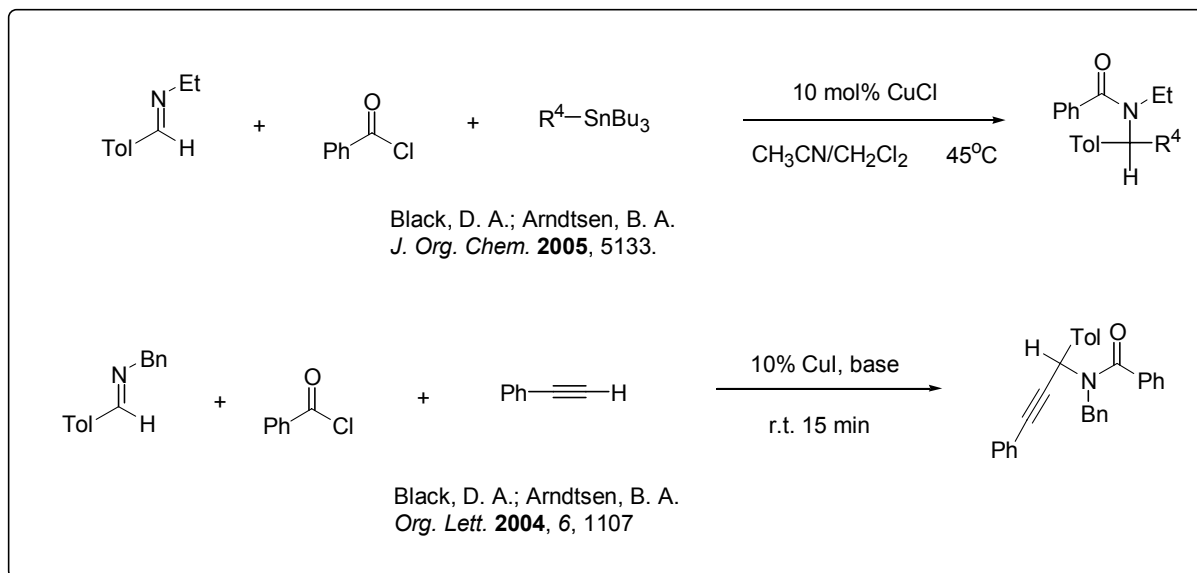
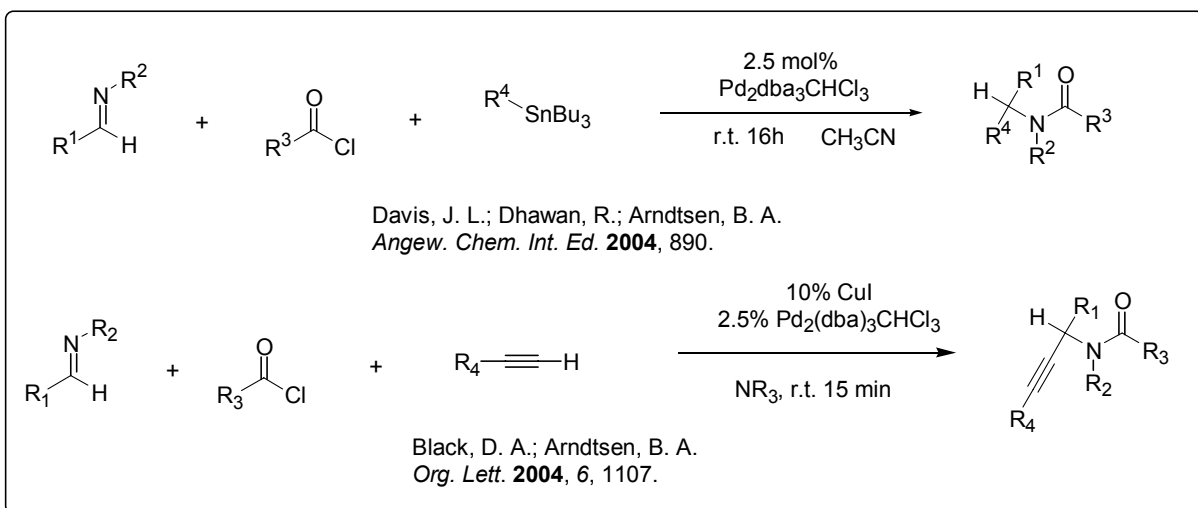


### “Copper Catalyzed Coupling of Alkynes, Pyridine, and Acid Chlorides”

Ramsay E. Beveridge, Daniel A. Black, and Bruce A. Arndtsen, Department of Chemistry, McGill University.

A mild, regioselective coupling of pyridines, acid chlorides and alkynes was shown to be possible in the presence of catalytic copper. Recent developments have demonstrated the ability of iminium salts to participate in both palladium and copper catalyzed cross-couplings (Scheme 2).

Scheme 2



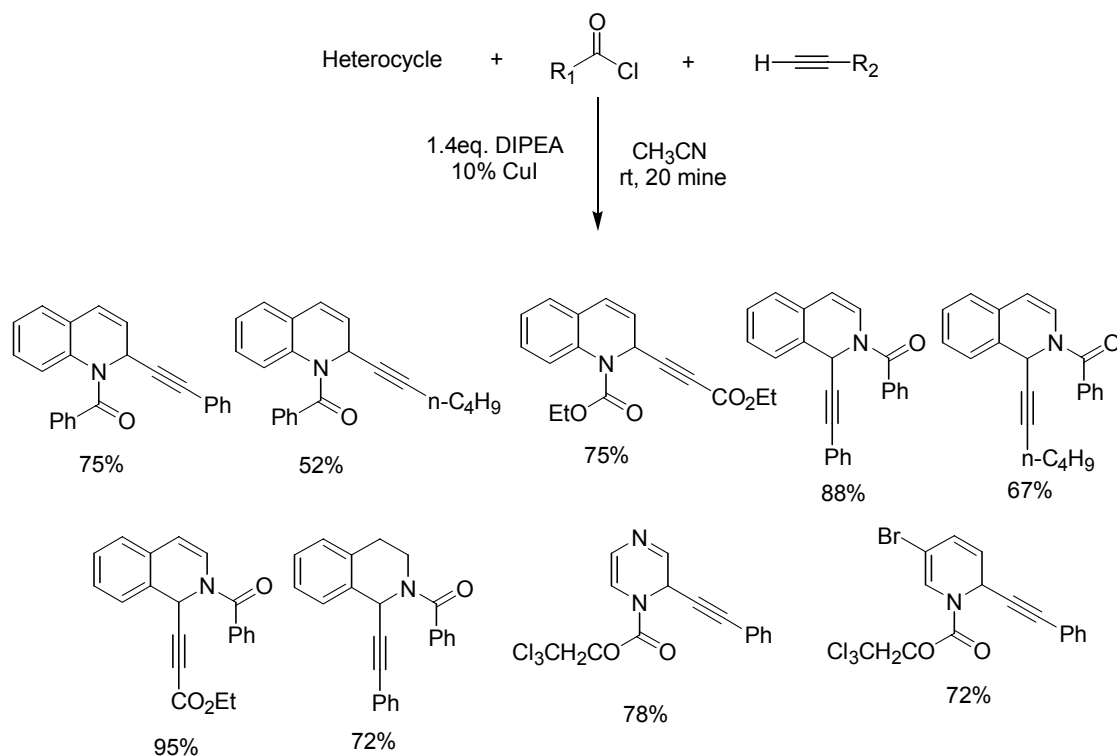
Since pyridines contain an “imine-like” component and can form pyridinium salts it was expected that pyridines might exhibit similar reactivity. Pyridinium salts, in fact, can participate in copper catalyzed alkynylations (Table 3).

Table 3

<i>R</i> <sup>1</sup>	<i>R</i> <sup>2</sup>	<i>Yield</i>
<i>Ph</i>	<i>Ph</i>	73%
<i>EtOCO</i>	<i>Ph</i>	82%
<i>EtOCO</i>	<i>TMS</i>	57%
<i>EtOCO</i>	<i>CH<sub>2</sub>Cl</i>	52%
<i>EtOCO</i>	<i>n-Bu</i>	53%
<i>EtOCO</i>	<i>CO<sub>2</sub>Et</i>	64%

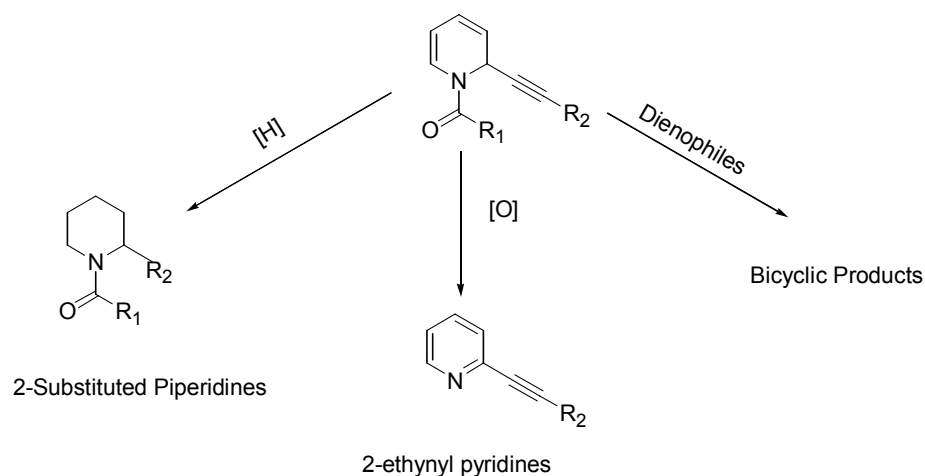
The copper catalyzed alkynylation conditions are also successful with a number of pyridine related heterocycles (Scheme 3).

Scheme 3



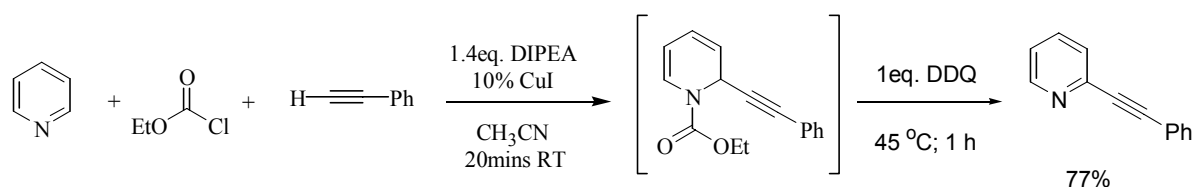
The alpha alkynylated pyridines and heterocycles generated by the copper catalyzed process are useful synthetic intermediates for 2-substituted piperidines, 2-ethynyl pyridines, and other heterocycles (Scheme 4).

Scheme 4



Conveniently, substituted pyridines can be directly synthesized via a one-pot sequence of copper catalyzed coupling followed by oxidation (Scheme 5).

**Scheme 5**

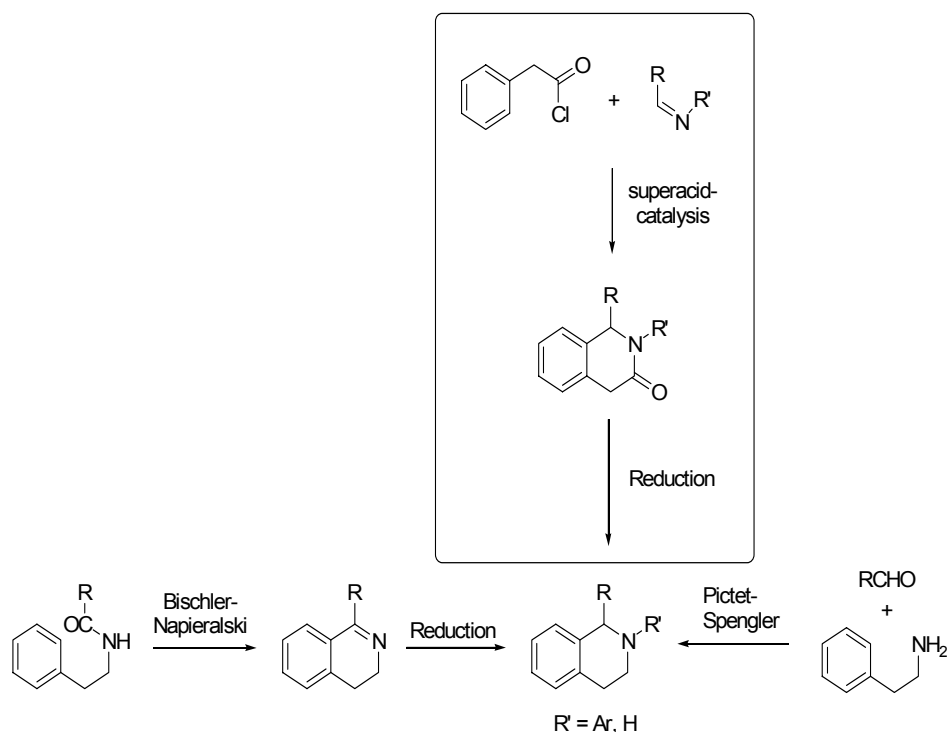


**“Superacid-Catalyzed Reactions of N-Acylimines: A Convenient Route to Tetrahydroisoquinolines and the Role of Superelectrophiles”**

*Yiliang Zhang, Patrick J. Kindelin, Douglas A. Klumpp, Department of Chemistry, Northern Illinois University.*

Superacid-catalyzed reactions of N-acyliminium salts were revealed as an expedient route to 2-aryl-tetrahydroisoquinolines via 1,4-dihydro-2H-isoquinolin-3-ones. Tetrahydroisoquinolines are found widely in naturally occurring and synthetic bioactive molecules. These structures are commonly synthesized from  $\alpha$ -phenethylamines through the Pictet-Spengler reaction or from N-acylated  $\alpha$ -phenethylamines by reduction of 3,4-dihydroisoquinolines formed by the Bischler-Napieralski synthesis. Cyclization of N-acyliminium ions are well known, however these methods usually involve very high temperatures, long reaction times and have not been utilized to directly create isoquinoline cores from imines and phenylacetyl chlorides (Scheme 6).

**Scheme 6**

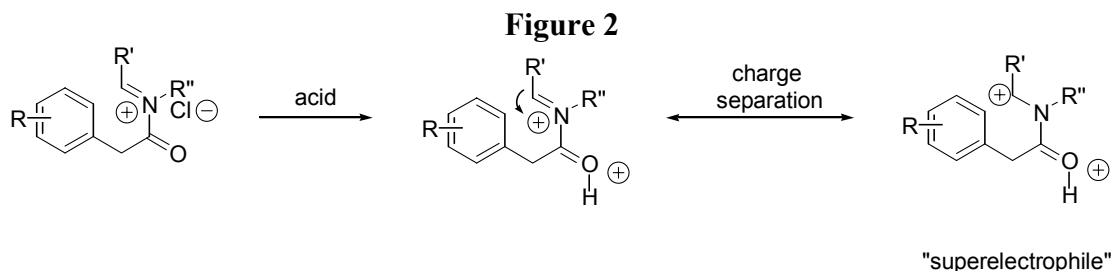


In practice, N-acyliminium salts formed *in-situ* from a variety of phenylacetyl chloride and imines yielded 1,4-dihydro-2H-isoquinolin-3-ones in good to excellent yield when treated with appropriate superacids at room temperature (Table 4).

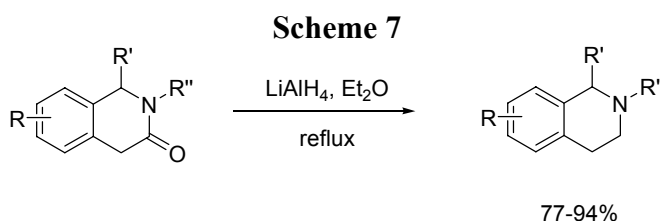
**Table 4**

Entry	R	R'	R''	Acid	Yield
1	H	Ph	Ph	CF <sub>3</sub> SO <sub>3</sub> H	97%
2	H	Ph	Ph	H <sub>2</sub> SO <sub>4</sub>	97%
3	H	Ph	Ph	CF <sub>3</sub> CO <sub>2</sub> H	<5%
4	H	Ph	H	"	60%
5	H	Ph	Bn	"	69%
6	H	Ph	Me	"	95%
7	H	C <sub>6</sub> F <sub>5</sub>	Ph	"	55%
8	H	<i>p</i> -C <sub>6</sub> H <sub>4</sub> F	Ph	"	92%
9	H	<i>p</i> -C <sub>6</sub> H <sub>4</sub> F	<i>p</i> -C <sub>6</sub> H <sub>4</sub> F	"	91%
10	<i>p</i> -F	Ph	Ph	"	95%
11	H	Ph	Nap	"	86%
12	2,5-di-OMe	Ph	Ph	"	65%
13	2,5-di-OMe	Ph	Me	"	90%
14	2,5-di-OMe	gem di-Ph	H	"	90%

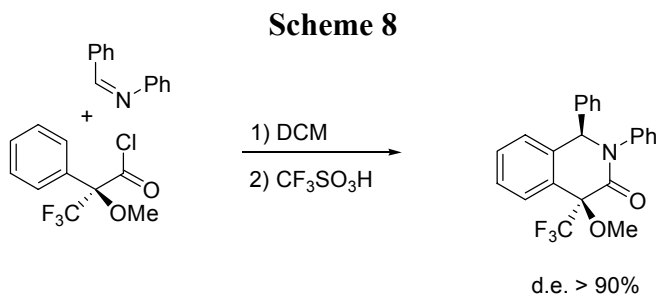
It was proposed that the high reactivity of N-acyliminium ions in superacid media with even poor nucleophiles such as deactivated arenes is due to the formation of doubly charged "superelectrophile" (Figure 2).



All 1,4-dihydro-2H-isoquinolin-3-ones synthesized were also easily converted to tetrahydroisoquinolines in good to excellent yield with lithium aluminum hydride (Scheme 7).



Another interesting aspect of this chemistry is the high stereoselectivity exhibited when a chiral acid chloride was used (Scheme 8).

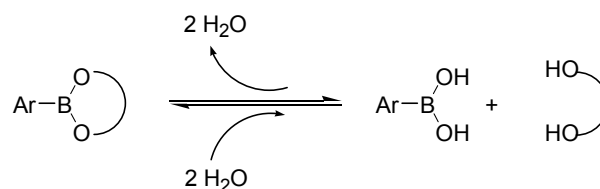


### "A New Redox-Sensitive Protecting Group for Boronic Acids"

*Jun Yan, Shan Jin, Binge Wang, Department of Chemistry and Center for Biotechnology and Drug Design, Georgia State University.*

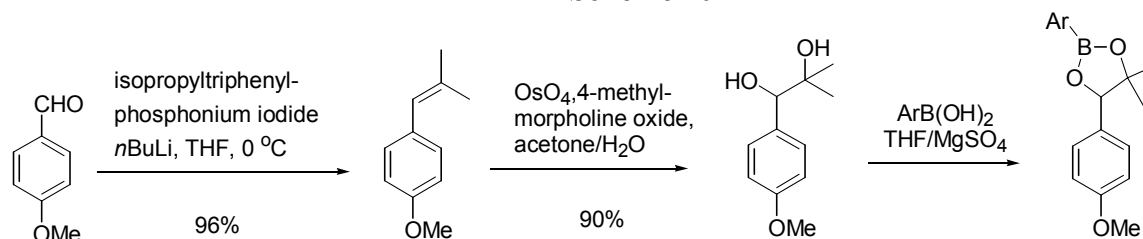
A new protecting group for aryl boronic acids was introduced. Although boronic acids are utilized extensively in modern organic chemistry, reliable methods for protection/deprotection are still lacking. Pinacol and neopentylglycol boranate esters are commonly used but are often times difficult to deprotect and isolate because the deprotection involves equilibrium (Scheme 9). Reagents such as NaIO<sub>4</sub> and BCl<sub>3</sub> have been used to try and perturb the equilibrium by trapping or destroying the pinacol with only limited success (TL 1994, 35, 5109, JACS 1980, 102, 7590).

### Scheme 9



Thus, there still exists the need for development of effective protection/deprotection methods for boronic acids. 1-(4-methoxy-phenyl)-2-methyl-propane-1,2-diol was envisioned as group that could form stable boronate esters and be cleaved under conditions which prevent reformation of the ester. The diol can be synthesized in three steps from inexpensive starting material and is easily coupled with boronic acids (Scheme 10).

Scheme 10



The new boronate ester is readily cleaved under mild oxidative conditions that also convert the liberated diol to a ketone thus preventing reformation of the ester. Either electron deficient or electron rich aryl boronic acids are obtained in good yields after silica gel chromatography (Table 5).

Table 5

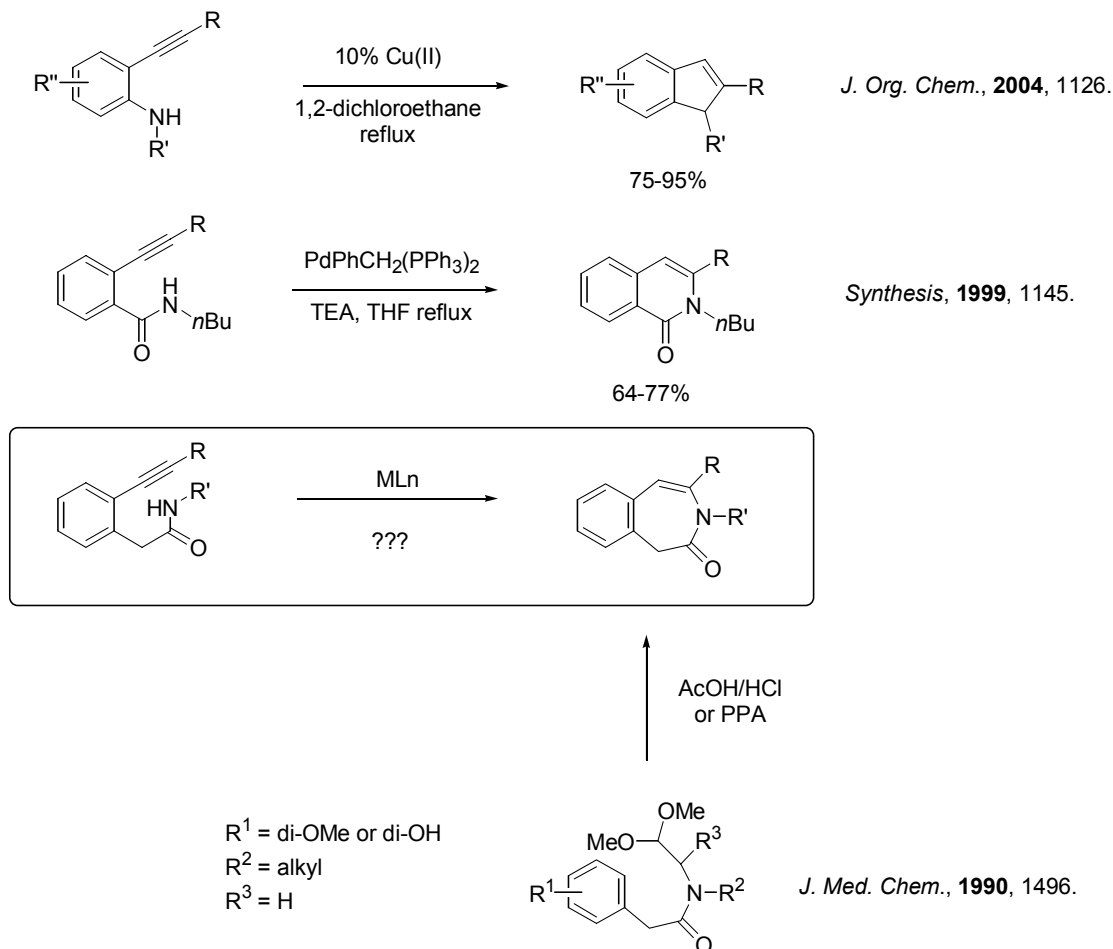
<i>Boronic Acid</i>	<b>Reaction Time (h)</b>	<b>Reaction Temperature (°C)</b>	<b>Isolated Yield</b>
Phenyl	8	rt	81%
3-Nitrophenyl	24	50	65%
4-Methoxyphenyl	24	rt	80%
3-N-Boc-aminomethylphenyl	24	rt	77%
3-Methoxycarbonyl-phenyl	6	rt	85%

### “Benzoazepinone Synthesis: Seven-Membered Ring Formation Via Palladium-Catalyzed Cyclization of Alkynyl Benzeneacetamides”

Ying Yu and David Mitchell, *Chemical Product R&D, Eli Lilly.*

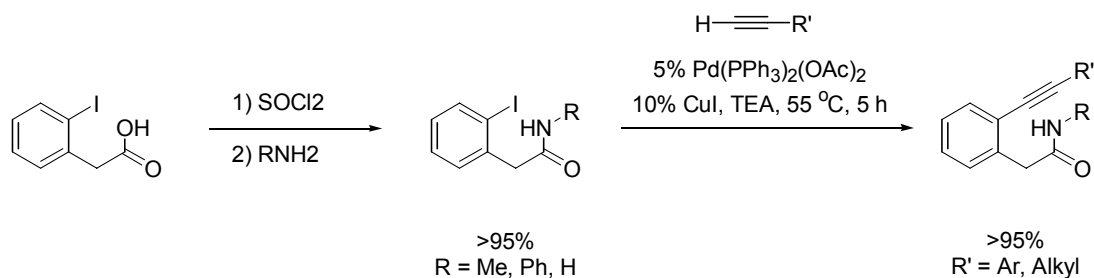
A novel palladium catalyzed synthesis of benzo[d]azepin-2-ones from alkynyl benzeneacetamides was presented. These benzo-fused seven-member heterocycle rings, and the corresponding benzoazepines are interesting structural motifs for medicinal chemistry and often have useful biological activity. Previous synthetic methods have relied on methods such as the acid catalyzed cyclization of pendant acetals which is only successful with very electron-rich aryl rings (Scheme 11). While literature examples for the formation of 5 and 6 member rings from transition metal-catalyzed cyclization of alkynes exist, no previous examples of 7 member rings are known. Consequently, benzo[d]azepin-2-ones formed from alkynyl benzeneacetamides would provide a unique and useful method for establishing benzoazepine rings (Scheme 11).

Scheme 11



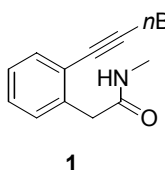
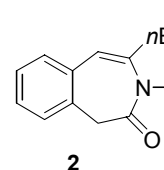
The alkynyl benzeneacetamide starting materials were readily prepared via a two step amidation/Sonogashira sequence (Scheme 12).

Scheme 12



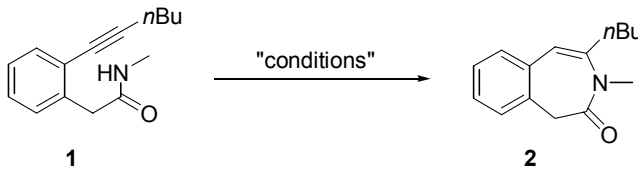
A wide range of cyclization conditions was initially scanned for proof of concept (Table 6).

**Table 6**

 <b>1</b>	"conditions"		 <b>2</b>
<b>Conditions</b>	<b>1</b>	<b>2</b>	<b>Observations</b>
10% Cu(OTf) <sub>2</sub> , ClCH <sub>2</sub> CH <sub>2</sub> Cl, o.n. reflux	100 %	0	-
10% Cu(OAc) <sub>2</sub> , ClCH <sub>2</sub> CH <sub>2</sub> Cl, o.n. reflux	>95 %	0	Trace of by-products
10% Cu(OAc) <sub>2</sub> , K <sub>2</sub> CO <sub>3</sub> , THF, 55 °C, 6 h	100 %	0	-
1 equiv. LiN(TMS) <sub>2</sub> , DMF, 55 °C, 6 h	-	0	Complex mixture
30% LiN(TMS) <sub>2</sub> , 10% Cu(OTf) <sub>2</sub> , PhMe, 55 °C, 6 h	100 %	0	-
30% LiN(TMS) <sub>2</sub> , 10% AgOTf, PhMe, 55 °C, 6 h	100 %	0	-
1.2 equiv. NaOEt, EtOH, reflux, 6h	100 %	0	-
1.5 equiv. NaOEt, THF, reflux, 5h	100 %	0	-
1.0 equiv. KO(t-Bu), t-BuOH, 55 °C, 7 h	>90 %	trace	-
1.2 equiv. KO(t-Bu), THF, 55 °C, 5 h	0	~50%	One major by-product
5% Pd(OAc) <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> , 1.0 equiv. KO(t-Bu), THF, 55 °C, 5 h	0	~65%	One major by-product

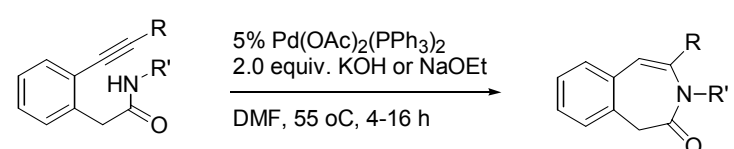
Gratifyingly, both strong base and strong base in the presence of palladium produced the desired cyclized product in good yield. Further exploration based on these results gave optimized conditions which yielded benzodiazepinone in greater than 80% yield (Table 7).

Table 7

			
Conditions	1	2	Observations
1.5 equiv. NaH, DMF, 60 °C, 2 h	0	~50%	Multiple by-products
2.0 equiv. NaOH, DMF, 55 °C, 24 h	~80 %	~20%	-
2.0 equiv. KOH, DMF, 55 °C, 24 h	~60 %	~35%	-
5% Pd(OAc) <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> , 2.0 equiv. KOH, DMF, 55 °C, 16 h	trace	82%	Trace by-products
5% Pd(OAc) <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> , 2.0 equiv. NaOEt, DMF, 55 °C, 3 h	0	80%	Trace by-products
5% Pd(OAc) <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> , TEA, DMF, 55 °C, 16 h	100 %	0%	-
5% Pd(OAc) <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> , DBU, DMF, 55 °C, 16 h	100 %	0%	-
5% Pd(OAc) <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> , K <sub>2</sub> CO <sub>3</sub> , DMF, 60 °C, 16 h	100 %	0%	-
5% Pd(OAc) <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> , Cs <sub>2</sub> CO <sub>3</sub> , DMF, 60 °C, 16 h	100 %	0%	-
5% Pd(dba) <sub>2</sub> , 20% dppf, Cs <sub>2</sub> CO <sub>3</sub> , THF, 60 °C, 16 h	100 %	0%	-
5% Pd(dba) <sub>2</sub> , 20% P(o-tolyl), Cs <sub>2</sub> CO <sub>3</sub> , PhMe, 60 °C, 16 h	100 %	0%	-
10% Pd(Ph <sub>3</sub> ) <sub>4</sub> , Bu <sub>4</sub> NCl, K <sub>2</sub> CO <sub>3</sub> , CH <sub>3</sub> CN, reflux, 6 h	100 %	0%	-

The optimized reaction conditions were also successful for other various alkynyl benzeneacetamides (Table 8). However, a mixture of products including unstable 6-membered rings was obtained for phenylethynyl benzeneacetamides. These results were rationalized by considering the relative lack of polarization in the bis-aryl-alkynyl bond.

Table 8

		
R	R'	Yield
<i>i</i> Pr	Me	78%
<i>n</i> Bu	Ph	61%
<i>n</i> Bu	H	55%

CH <sub>2</sub> OMe	Me	42%
-(CH <sub>2</sub> ) <sub>3</sub> CO <sub>2</sub> Me	Me	71%
Ph	Me	Multiple products

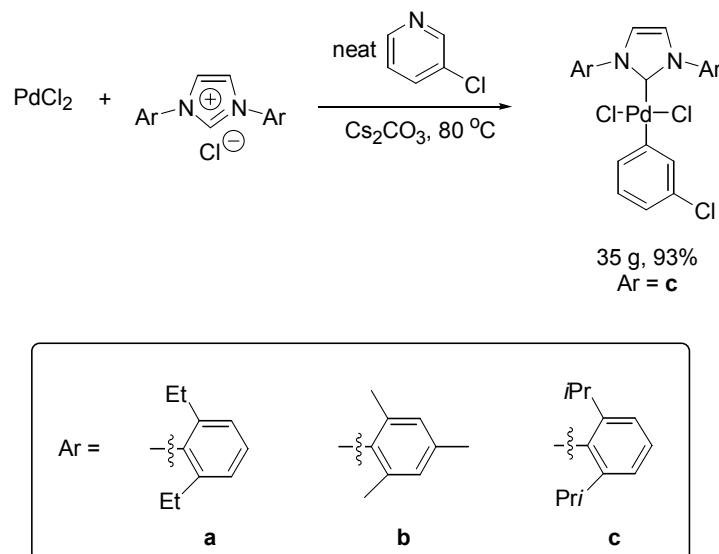
**“User-friendly palladium-N-heterocyclic carbene (NHC) complexes for coupling reactions: Employing a throw away ligand approach”**

*Christopher J. O'Brien, Niloufar Hadei, Eric Assen B. Kantchev, and Michael G. Organ, Department of Chemistry, York University.*

The synthesis and application of an air and moisture stable palladium N-heterocyclic carbene (NHC) pre-catalyst was described. Palladium catalyzed reactions such as the Suzuki, Negishi, and Sonogashira couplings have transformed the practice of organic synthesis in recent decades. However, most protocols still involve in-situ formation of the catalyst since active palladium (0) complexes are unstable and/or difficult to isolate.

Thus, the development of a stable, easily prepared pre-catalyst that could be used in a variety of palladium-catalyzed procedures would be of significant utility. NHC ligands are becoming increasingly popular for transition metal catalysis and a variety are now commercially available. Air and moisture stable Pd-NHC complexes are easily prepared in large scale from NHC salts in pyridine solvent (Scheme 13).

**Scheme 13**



These Pd(II) pre-catalysts generate monoligated NHC-Pd(0) complexes in solution and are thus convenient reagents for performing Suzuki, Negishi, and Buchwald-Hartwing reactions (Tables 9-11).



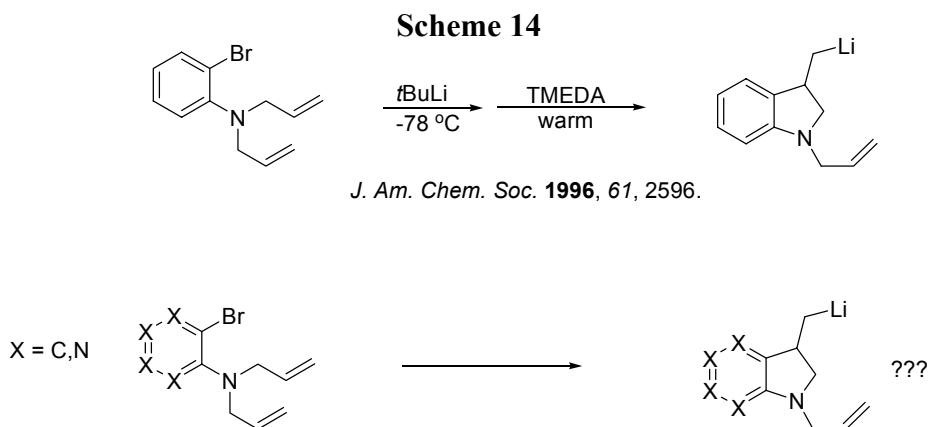
Table 11

$R^1-X + NHR^2R^3 \xrightarrow[50\text{ }^\circ\text{C, 2-24 h}]{1\text{ Mol \% Pd-NHC complex}} R^1-NR^2R^3$		X = Cl, Br
$R^1$	$R^2$	Yield
		86%
		95%
		84%
		70%

### “Preparation of 3-Substituted 4-, 5-, 6- and 7-azaindoles via Anionic Cyclization”

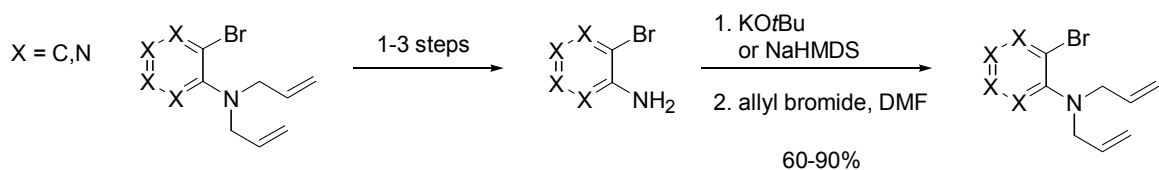
*Paresh D. Salgaonkar, Vijayata Sharma, Jason D. Brubaker, and William F. Bailey Department of Chemistry, University of Connecticut.*

A three-step, one-pot synthesis of 3-substituted azaindoles via a novel anionic cyclization of readily available bromo-N-allylaminopyridines was presented. Azaindoles, also known as dihydropyrollopyridines, are present in numerous biologically active compounds such as CNS stimulants, anti-ulcer agents and 3H-flunitrazepam binding inhibitors. Azaindoles are commonly accessed by five main methods: 1) Diels-Alder/ retro Diels-Alder reactions; 2) Nucleophilic substitution of an appropriately installed leaving group; 3) Intramolecular Chichibabin reaction; 4) Radical mediated ring closure; 5) Reduction of azaindoles. Previous work had demonstrated that 3-substituted indolines could also be readily produced by anionic cyclization of 2-bromo-N,N-diallylanilines. Thus it was expected that a general method for all isomeric azaindoles could also be developed using the same chemistry (Scheme 14).



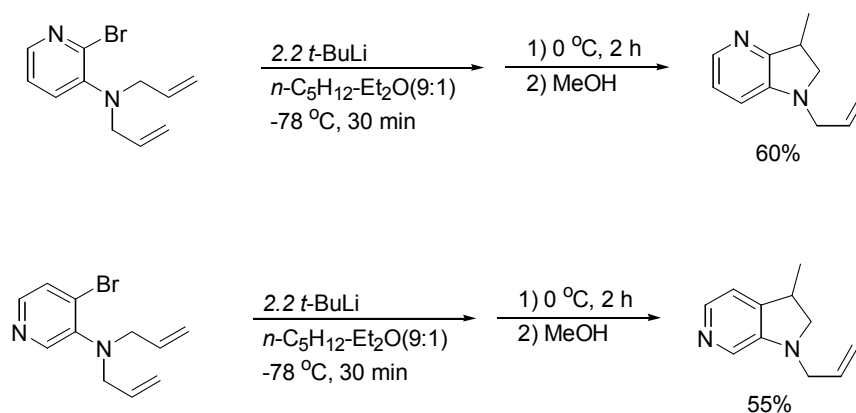
The necessary bromo-N,N-diallylaminopyridines were easily prepared from aminopyridines in 3-5 steps (Scheme 15).

## Scheme 15



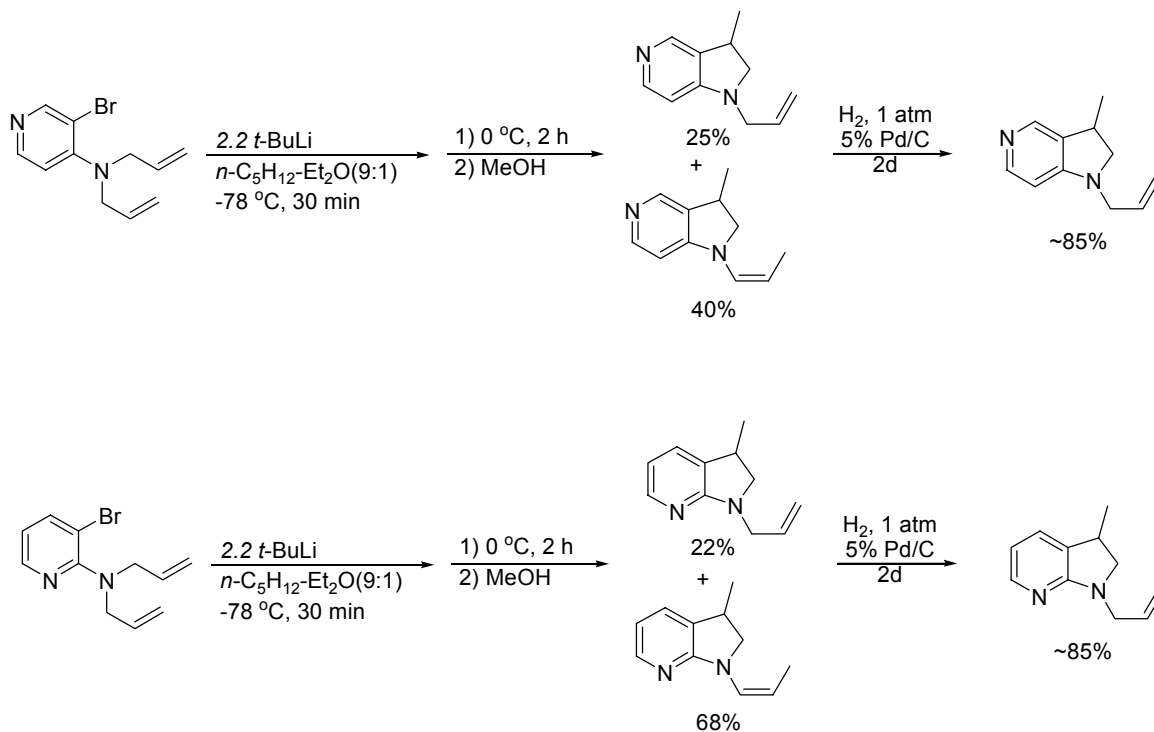
Formation of the 4 and 6-azaindolines proceeded smoothly with good yields and the formation of only isomer (Scheme 16).

## Scheme 16



In the case of the 5 and 7-azaindoles an enamine isomer was also formed as major product or by-product. Quenching the reaction at lower temperatures and/or the addition of a ligand such as TMEDA resulted in only minor changes in product distribution. However, the isomeric mixtures could easily be reduced to a single product in very good yields (Scheme 17).

## Scheme 17



These results were rationalized by proposing that the pyridine nitrogen was affecting the acidity of the allyl group by a resonance structure in which the pyridine nitrogen carries a negative charge while the amine nitrogen carries a positive charge (Figure 3). However, the amino nitrogen at the C-3 position of pyridine cannot sustain a positive charge since the resulting negative charge cannot be distributed to the pyridine nitrogen and isomerization would not be expected with formation of the 4- and 6-azaindolines.

Figure 3

