



**Trip Report for**  
**“40<sup>th</sup> National Organic Chemistry Symposium”**  
**Duke University, Durham, North Carolina**  
**June 3-7, 2007**

**Zhongping Huang, Ph.D.; Xiao-wu (May) Jiang, Ph.D.;**  
**Lisa Peterson; Andrew J. Zych, Ph.D.**

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**Abstract:** *The 40<sup>th</sup> National Organic Chemistry Symposium was held at Duke University in Durham, North Carolina, from June 3-7, 2007. This symposium included fourteen presentations and 358 posters from academic laboratories and pharmaceutical companies. This report highlights select material from presentations disclosed at the symposium.*

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## “Natural Products as a Driving Force for Discovery in Organic Chemistry”

Professor Brian M. Stoltz, Department of Chemistry and Chemical Engineering, California Institute of Technology.

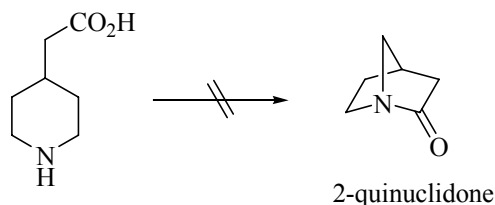
The presentation given by Professor Stoltz is summarized in three parts.

### Part One: Synthesis and structural analysis of 2-quinuclidonium tetrafluoroborate

2-Quinuclidone belongs to the group of bicyclic bridgehead lactams. Unlike acyclic amides which are planar in structure, the amide groups of bicyclic bridgehead lactams are highly twisted. As a result, this distortion from planarity can dramatically affect the stability and reactivity of these special-case amides. The twisted nature also decreases the delocalization effect, increasing the basicity of the nitrogen so that it often behaves more like an amine than as a typical planar amide. As a result, the structures and reactivity profiles of these ‘anti-Bredt’ amides differ significantly from those of planar amides.

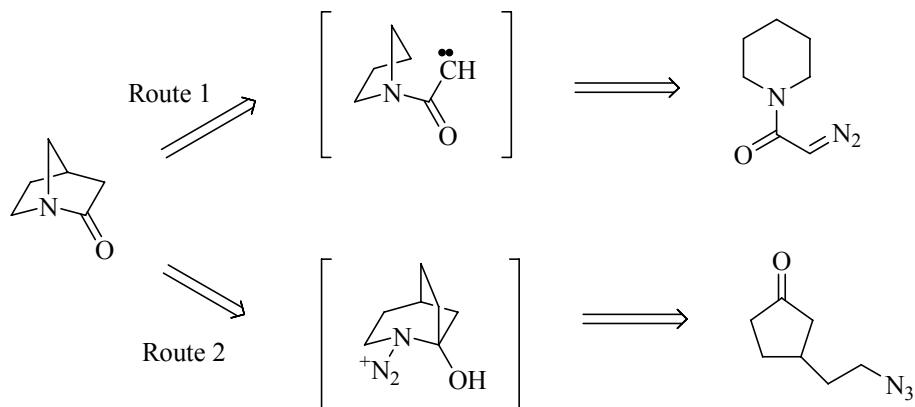
Following the initial description of 2-quinuclidone by Lukes and coworkers, Woodward became interested in the properties of 2-quinuclidone as it related to the structure of quinine and how syntheses might be carried out using a quinuclidone base unit. He later examined quinuclidone in the context of the structural assignment of penicillin and the predicted increase in the general chemical reactivity of bridgehead amides due to non-planarity arguments. Woodward connected the difficulty in preparing this bicyclic lactam from the corresponding amino acid to the unstable and unusual nature of the twisted amide (Scheme 1).

#### **Scheme 1. 2-Quinuclidone cannot be made from the cyclic amino acid.**



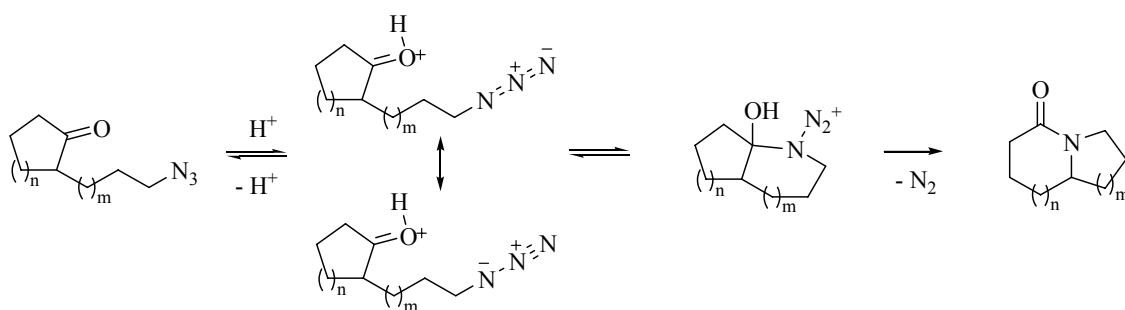
To solve this synthesis problem, the Stoltz group sought to utilize reaction strategies involving nitrogen release as a driving force for the construction of the strained bicyclic core. This approach would potentially obviate aqueous work-up conditions in the final step. Initially, two distinct synthetic plans were devised to construct the molecule. In Route 1, a C-C bond formation via C-H insertion of an acylcarbene species was envisioned that could be catalysed by Rh(II) de-diazotization of the known acyldiazo derivative. In Route 2, a C-N bond formation was proposed through an intramolecular Schmidt-Aube reaction of a cyclopentanone azide. The initial attempts toward the synthesis of 2-quinuclidone focused on the C-H insertion of a rhodium-stabilized acylcarbene generated from a diazocarbonyl derivative. Reaction conditions investigated for this strategy led to complex mixtures and was therefore the route was abandoned.

### Scheme 2. Two approaches to 2-quinuclidone.



In 1991, Professor Aube's group reported the intramolecular Schmidt reaction of alkyl azides. They showed that an intramolecular reaction of alkyl azides tethered to ketones accomplished ring-expansion cyclizations in high yields and under remarkably mild and straightforward reaction conditions (Scheme 3).

### Scheme 3. The Schmidt-Aube ring-expansion reaction.



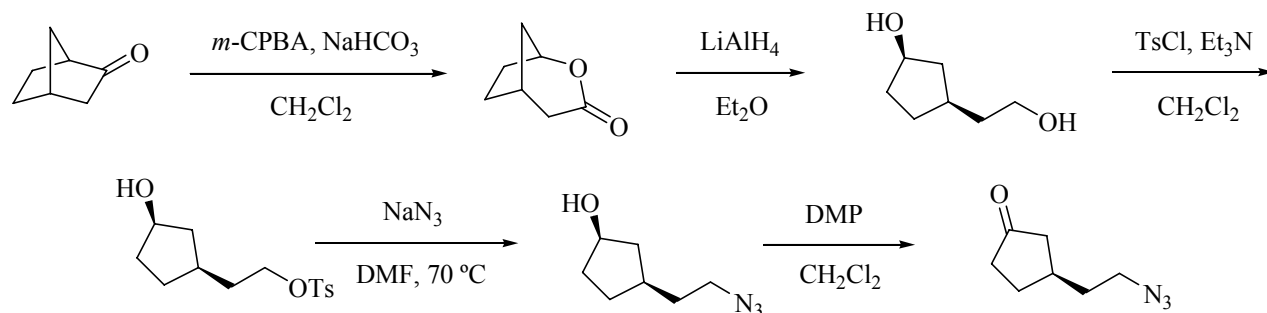
Some examples of these intramolecular Schmidt reactions are shown in Table 1. Most reactions were carried out in neat TFA, although those that failed under the TFA conditions generally could be carried out by catalysis with  $\text{TiCl}_4$  in methylene chloride.

**Table 1. Intramolecular Schmidt reactions of ketone-tethered alkyl azides.**

entry	compounds	conditions	yield
1	<b>a</b> R = H	TFA, 40 min	83%
2	<b>b</b> R = CO <sub>2</sub> Me	TFA, 16 h	66%
3	<b>b</b>	TiCl <sub>4</sub> , CH <sub>2</sub> Cl <sub>2</sub> , 20 min	70%
4	<b>a</b> R <sub>1</sub> = H, R <sub>2</sub> = H, n = 1	TFA, 10 min	90%
5	<b>b</b> R <sub>1</sub> = CO <sub>2</sub> Me, R <sub>2</sub> = H, n = 1	TFA, 1 h	93%
6	<b>c</b> R <sub>1</sub> = H, R <sub>2</sub> = H, n = 2	TFA, 24 h	(no reaction)
7	<b>c</b>	TiCl <sub>4</sub> , CH <sub>2</sub> Cl <sub>2</sub> , 16 h	90%
8	<b>d</b> R <sub>1</sub> = H, R <sub>2</sub> = CH <sub>3</sub> , n = 1	TFA, 20 min	74%
9	<b>a</b> R = H	TFA, 20 min	91%
10	<b>b</b> R = CH <sub>3</sub>	TFA, 20 min	91%
11	<b>a</b> R = H, n = 1	TFA or TiCl <sub>4</sub> /CH <sub>2</sub> Cl <sub>2</sub>	(no reaction)
12	<b>b</b> R = CO <sub>2</sub> Me, n = 2	TFA, 12 h	66%
13	<b>b</b>	TiCl <sub>4</sub> /CH <sub>2</sub> Cl <sub>2</sub> , 15 min	64%

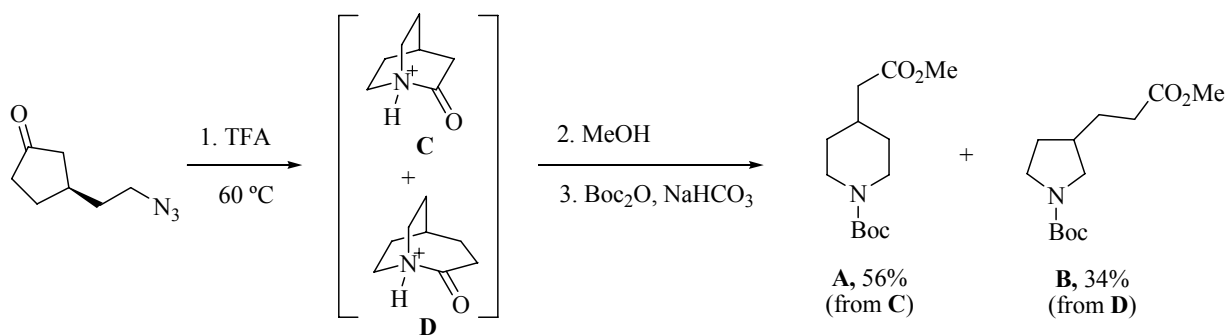
The Stoltz group successfully applied the intramolecular Schmidt-Aube reaction conditions to the synthesis of 2-quinuclidone. The ketoazide precursor was prepared as shown in Scheme 4.

#### Scheme 4. Preparation of azide-tethered cyclopentanone.



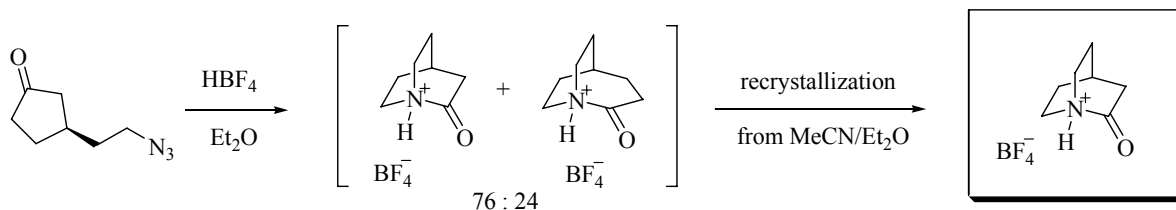
The ketoazide was then subjected to the typical intramolecular Schmidt-Aube reaction conditions of neat TFA at 60 °C. Since the liability of the amide bond was expected to be unstable, the crude reaction mixture was treated with methanol to induce the bond cleavage. Subsequent Boc-protection of the amine and purification afforded derivatives **A** and **B** in 56% and 34% yields, respectively. It was deduced that the production of **A** and **B** strongly suggested the initial formation of a 2-quinuclidonium intermediate **C**, along with an undesired isomer arising from the regioisomeric intermediate **D** (Scheme 5).

#### Scheme 5. Schmidt-Aube reaction produces the 2-quinuclidone intermediate.



To improve the regioselectivity of the rearrangement, the team screened various acid and solvent combinations. It was found that when the rearrangement reaction was carried out with HBF<sub>4</sub> as the acidic component, a precipitate was formed upon cooling the reaction mixture. Recrystallization of this crude mixture of regioisomers from an acetonitrile/diethyl ether combination produced the pure 2-quinuclidonium tetrafluoroborate isomer as colorless crystals (Scheme 6). The chemical structure was unambiguously confirmed by spectroscopic analyses.

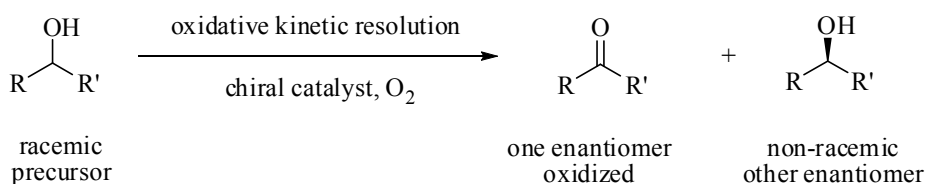
**Scheme 6. Schmidt-Aube reaction produces the 2-quinuclidonium BF<sub>4</sub> salt.**



**Part Two: Palladium-catalyzed oxidative kinetic resolution of secondary alcohols with molecular oxygen.**

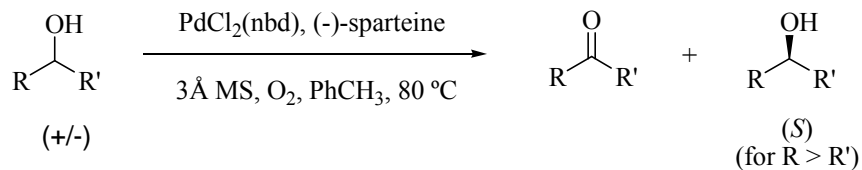
Professor Stoltz presented his group's work toward the catalytic oxidative kinetic resolution of secondary alcohols using molecular oxygen as the terminal oxidant (Scheme 7).

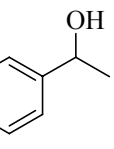
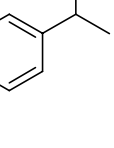
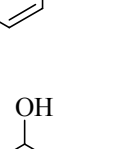
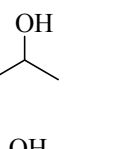
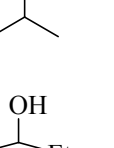
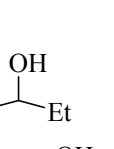
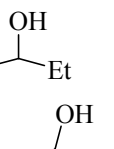
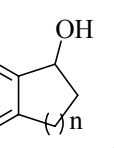
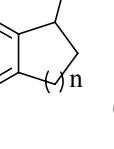
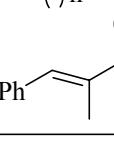
**Scheme 7. Oxidative kinetic resolutions of secondary alcohols.**



From exploratory studies to determine general reaction conditions, the team found that the most promising conditions were able to use molecular oxygen as a stoichiometric oxidant with (-)-sparteine as a chiral ligand and PdCl<sub>2</sub>(nbd) as a catalyst. With an optimized system in hand, the reaction's scope was investigated, which was shown in Table 2.

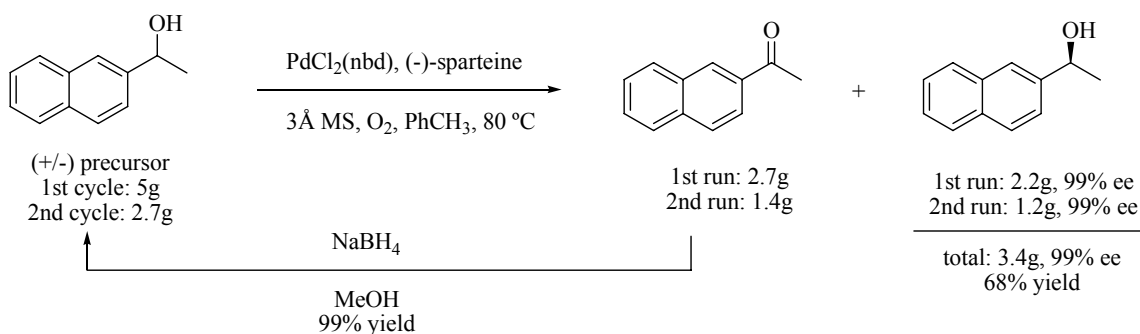
**Table 2. The oxidative kinetic resolution of secondary alcohols.**



entry	racemic alcohol	time	conversion	(S)-ROH yield	(S)-ROH ee
1	 R = H	96 h	59.9%	37%	98.7%
2	 R = OMe	96 h	66.6%	32%	98.1%
3	 R = F	54 h	63.3%	32%	97.4%
4	 R = 1-naphthyl	192 h	55.9%	43%	78.4%
5	 R = 2-naphthyl	112 h	55.2%	44%	99.0%
6	 R = o-tolyl	144 h	48.4%	49%	68.7%
7	 R = Ph	192 h	59.3%	40%	93.1%
8	 n = 1	54 h	67.5%	30%	93.4%
9	 n = 2	40 h	68.6%	31%	99.8%
10		120 h	70.4%	29%	91.8%

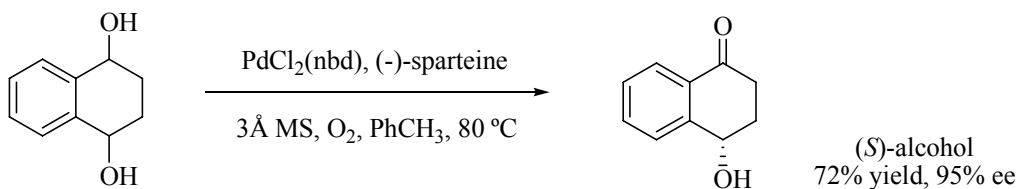
It is noteworthy that the oxidative kinetic resolution performs well on multigram scales, usually with good recovery of the optically enriched alcohols. In the case of (+/-)-2-naphthylethanol, the (S)-alcohol was recovered in 44% yield and in 99% ee. Quantitative reduction of ketone byproduct provided the chiral alcohol in >50% overall yield from a racemic mixture after multiple oxidative kinetic resolution cycles (Scheme 8).

**Scheme 8. Kinetic oxidative resolution of racemic 2-naphthylethanol.**



The scope of the reaction was further extended to include the oxidative desymmetrization of meso diol precursors (Scheme 9).

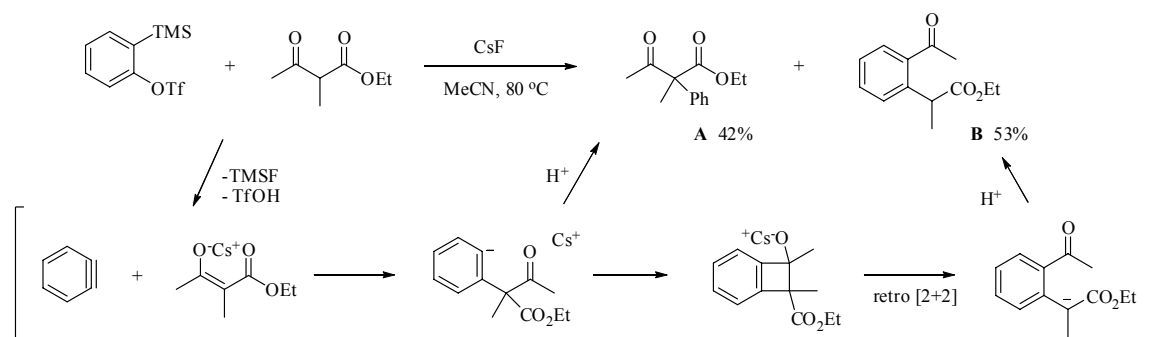
**Scheme 9. Kinetic oxidative desymmetrization of a meso diol.**



### Part Three: Direct acyl-alkylation of arynes

In 1983, Kobayashi and coworkers described a mild method for the in situ preparation of benzyne at moderate temperatures through a fluoride-induced elimination of *ortho*-silyl aryl triflates. In the presence of ethyl 2-methyl-3-oxobutanoate, the in-situ generated benzyne reacted with the  $\beta$ -ketoester enolate to produce the anticipated  $\alpha$ -phenyl product **A** in moderate yield (Scheme 10). Surprisingly, the *ortho*-substituted adduct **B** was also isolated in comparable yield. This acyl-alkylation product **B** was the net result of benzyne insertion into the C-C bond of the  $\beta$ -ketoester, presumably by attack of the aryl anion onto the ketone carbonyl, followed by a retro-[2 + 2] fragmentation.

**Scheme 10. Acyl-alkylation products from in-situ generated benzyne.**



Upon further investigation it was found that reaction with  $\beta$ -ketoesters lacking  $\alpha$ -substitution led to even greater yields of the acyl-alkylation products **B**, presumably because the formation of the putative benzocyclobutene intermediate is formed more readily, thus diverting the protonation of the aryl anion intermediate. As shown in Table 3, the method tolerates substitution at the  $\gamma$ -position (entries 2-6), including aliphatic and aromatic groups. The ester moiety can also be varied while maintaining the efficiency of the reaction (entries 7 and 8).

**Table 3. Acyl-alkylation of benzyne with  $\beta$ -ketoesters.**

Entry	Substrate	Product	Yield
1			90%
2			78%
3			84%
4			85%
5			53%
6			99%
7			72%
8			75%

It was further envisioned that a cyclic  $\beta$ -ketoester should undergo ring expansion to furnish medium-sized carbocycles, a motif that prevails in natural products and drug substances. These results are shown in Table 4. When the optimized conditions were applied to a series of  $\beta$ -carboxyalkyl cyclopentanones, seven-membered benzannulated structures were obtained in

synthetically useful yields (entries 1-3). Somewhat less efficient was the reaction with the six-membered ring substrate (entry 4), while the expansion of a seven-membered ring furnished a nine-membered carbocycle in 69% yield (entry 5).

**Table 4. Ring expansion of cyclic  $\beta$ -ketoesters.**

Entry	Substrate	Product	Yield
1			50%
2			61%
3			65%
4			45%
5			69%

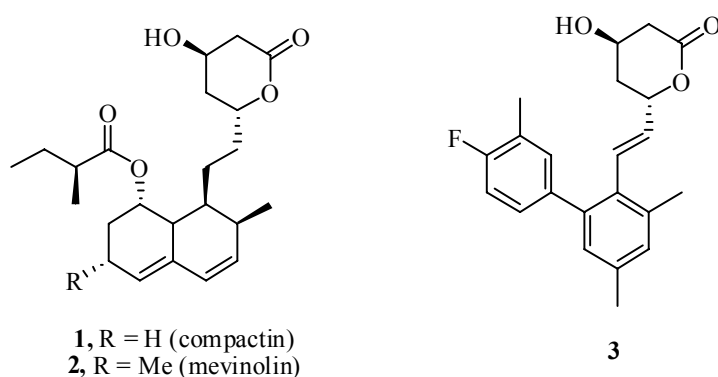
**“The Discovery and Development of Lipitor™ (Atorvastin Calcium)”**

*Bruce D. Roth, Ann Arbor Laboratories, Pfizer Global Research and Development, USA*

Dr. Roth presented the development of Lipitor from bench to market, including the SAR leading up to atorvastin calcium and the total synthesis of Lipitor.

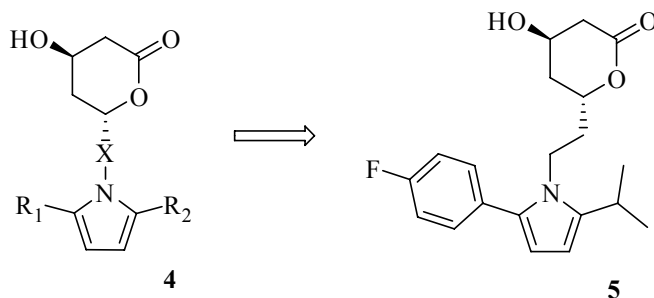
Compactin (**1**), mevinolin (**2**) and synthetic compound **3** (Scheme 11) are potent inhibitors of the enzyme HMG-CoA reductase (HMGR). Roth and coworkers compared structures of these known inhibitors and proposed the hypothesis that the *ortho* phenyl substituent of **3** occupies the same receptor space as the isobutyric ester moiety of compactin and mevinolin. It is thought that this aryl portion of **3** might fit into a lipophilic pocket in the active site of HMGR, a space normally occupied by coenzyme A. As the lactone moiety is a key functionality for inhibitors, the remainder of the structure may simply be a template or anchor connecting the two functional groups. Based on this idea, a pyrrole ring was selected by Roth's team as the anchor with various connecting groups.

**Scheme 11. Potent natural and synthetic inhibitors of HMG-CoA reductase.**



Several analogues were prepared with the pyrrole scaffold **4** (Scheme 12). By measuring the inhibition of HMGR *in vitro*, the linker length between the lactone and pyrrole ring was optimized, as was the substitution at the pyrrole C-2 and C-5 positions. It was found that a two-carbon bridge between the lactone and the pyrrole ring was superior to either a three-methylene length or an aryl spacer. Through systematic alteration of the C-2 C-5 substituents, the maximal potency was obtained with the 2-(4-fluorophenyl)-5-isopropyl derivative **5**, which possessed 30% of the *in vitro* potency of compactin.

**Scheme 12. The first generation pyrrole-based inhibitors.**

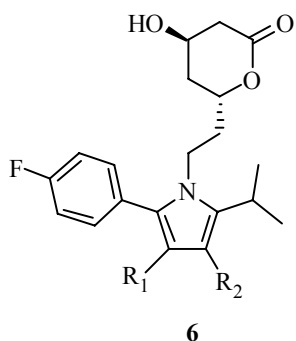


The subsequent introduction of lipophilic electron-withdrawing groups onto the pyrrole C-3 and C-4 positions of **5** resulted in the significant improvement of HMGR inhibition *in vitro* (Table 5). Compounds disubstituted with either chlorine (**6d**) or bromine (**6e**) displayed potency equivalent to compactin, although the compounds were not chosen as preclinical candidates due to their associated toxicities. The electron-withdrawing effect did not hold, however, for groups such as

esters (**6b,c**) or ketone **6f**. Another improvement in potency was achieved when the phenyl group at C-3 was replaced with a 2-pyridyl moiety (**6i**).

**Table 5. Second-generation pyrrole inhibitor partial SAR.**

No.	R <sub>1</sub>	R <sub>2</sub>	IC <sub>50</sub> (μM)
<b>6a</b>	Me	Me	0.140
<b>6b</b>	CO <sub>2</sub> Me	CO <sub>2</sub> Me	0.180
<b>6c</b>	CO <sub>2</sub> Et	CO <sub>2</sub> Et	0.350
<b>6d</b>	Cl	Cl	0.028
<b>6e</b>	Br	Br	0.028
<b>6f</b>	COCF <sub>3</sub>	H	0.800
<b>6g</b>	Ph	H	0.347
<b>6h</b>	H	Ph	0.120
<b>6i</b>	2-pyridyl	H	0.046
<b>6j</b>	3-pyridyl	H	0.071
<b>6k</b>	4-pyridyl	H	0.310



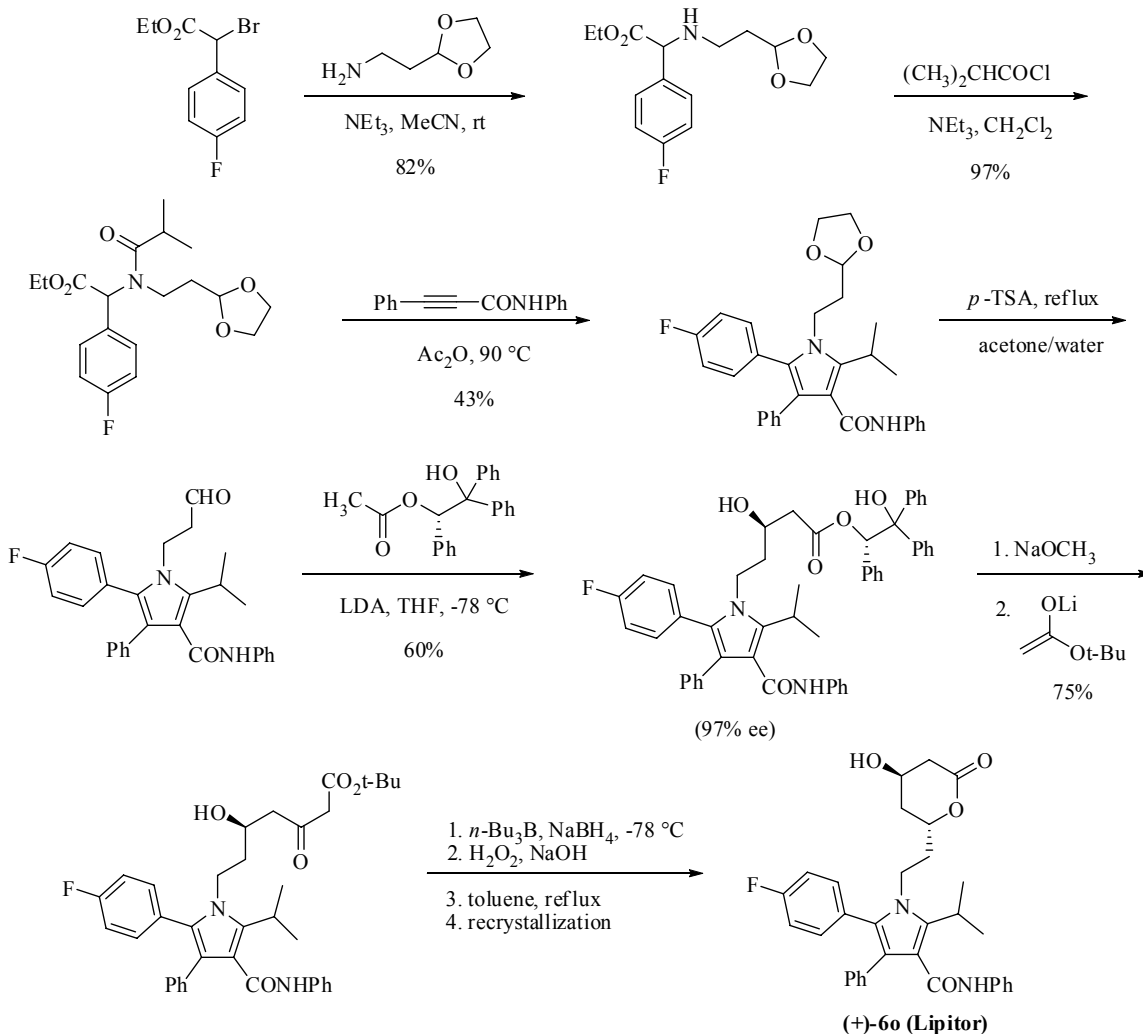
Roth and his team continued to explore the SAR around substitution of the pyrrole C-3 phenyl group and found that activity was improved significantly by increasing the size of the substituents on the *para* position (Table 6). The 3-phenyl-4-phenylcarbonyl analogue **6o** displayed potency equivalent to compactin. Moreover, the *in vitro* activity of the compound **6o** was found to come from its dextrorotatory stereoisomer (+)-**6o**, which displayed excellent activity (7 nM) *in vitro*. This enantiopure compound was chosen for clinical trials and has been commercialized as Lipitor.

**Table 6. Partial SAR for third-generation pyrrole inhibitors.**

No.	R <sub>1</sub>	R <sub>2</sub>	IC <sub>50</sub> (μM)
<b>6m</b>	Ph	CO <sub>2</sub> Et	0.200
<b>6n</b>	Ph	CO <sub>2</sub> CH <sub>2</sub> Ph	0.040
<b>6o</b>	Ph	CONHPh	0.025
<b>6p</b>	4-CN-Ph	CO <sub>2</sub> Et	0.280
<b>6q</b>	CO <sub>2</sub> Et	Ph	0.050
(+)- <b>6o</b>	Ph	CONHPh	0.007
(-)- <b>6o</b>	Ph	CONHPh	0.440

Dr. Roth also presented the total synthesis of Lipitor (Scheme 13).

### Scheme 13. The total synthesis of Lipitor.



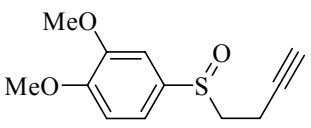
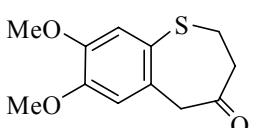
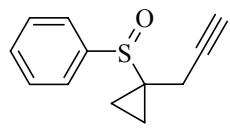
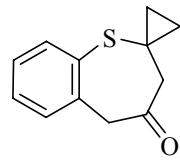
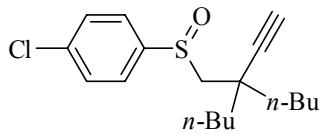
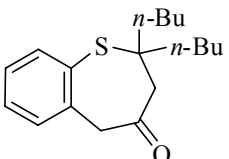
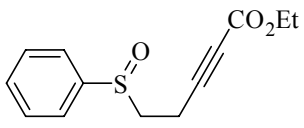
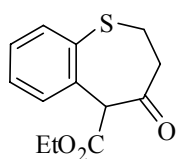
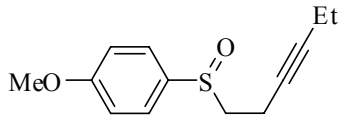
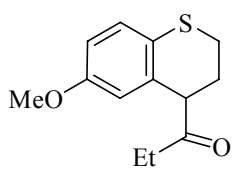
### “Gold(I) Catalysts for Organic Synthesis: Development, Applications and Asymmetric Catalysis”

F. Dean Toste, Department of Chemistry, University of California, Berkeley, USA

Professor Toste presented the use of cationic phosphine gold(I) complexes as catalysts for cycloisomerization, rearrangement, ring expansion and addition reactions.

Through the use of the catalyst IMesAuCl/AgSbF<sub>6</sub> (5 mol %) in CH<sub>2</sub>Cl<sub>2</sub>, a wide range of homopropargyl arylsulfoxides were shown to undergo a gold-catalyzed rearrangement to benzothiepinones (Table 7). The triphenylphosphinegold(I)-catalyzed reaction of an alkyl-substituted alkyne afforded a benzothiepine.

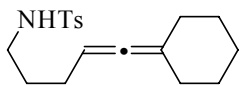
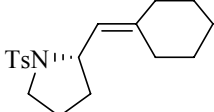
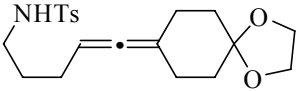
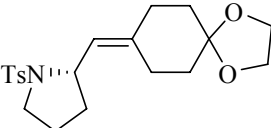
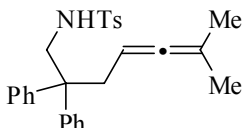
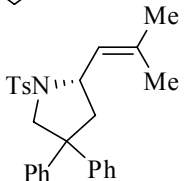
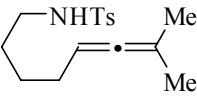
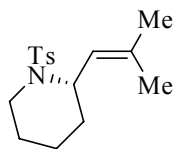
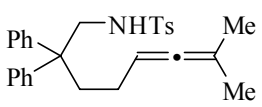
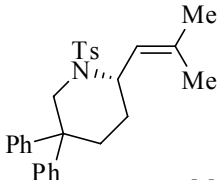
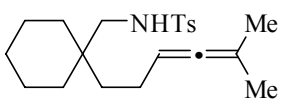
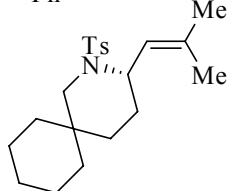
**Table 7. Gold(I)-catalyzed rearrangement of homopropargyl sulfoxides.**

Sulfoxide	Conditions	Product	Yield
	A		87%
	A		71%
	A		75%
	A		61%
	B		50%

Conditions. Method A: sulfoxide (0.2 M in CH<sub>2</sub>Cl<sub>2</sub>), 5% IMesAuCl, 5% AgSbF<sub>6</sub>, rt;  
 Method B: sulfoxide (0.2 M in CH<sub>2</sub>Cl<sub>2</sub>) 5% Ph<sub>3</sub>PAuCl, 5% AgSbF<sub>6</sub>, rt.

Phosphinegold(I)-bis-*p*-nitrobenzoate complexes were used as catalysts for enantioselective formation of vinyl-substituted pyrrolidines and piperidines (Table 8). (*R*)-Xylyl-BINAP(AuOPNB)<sub>2</sub> was used as the general catalyst for both cyclic and linear alkanes, yielding the corresponding pyrrolidines in good yield and in excellent enantiomeric excesses. Moreover, the chiral piperidine was obtained with good enantioselectivity by simply switching the catalyst to (*R*)-ClMeOBIPHEP(AuOPNB)<sub>2</sub>.

**Table 8. Au(I)-catalyzed enantioselective intramolecular hydroamination of allenes.**

Sulfoxide	Conditions	Product	Yield	ee
	A		80%	98%
	A		79%	98%
	A		99%	87%
	B		88%	81%
	B		70%	88%
	B		66%	97%

Conditions. Method A: 3% (*R*)-xylyl-BINAP-(AuOPNB)<sub>2</sub>, 0.3 M in DCE, rt;  
Method B: 5% (*R*)-ClMeOBiPHEP(AuOPNB) 0.3 M in MeNO<sub>2</sub>, 50 °C; OPNB = *p*-nitrobenzoate.

### “Selective N-1 Arylation of 3-Substituted-pyrazole-5-carboxylates by Boronic Acids in the Presence of Copper(II) Acetate.”

Carol L. Ensinger, Torsten Haaack, William C. Patt, Yu Mi Ahn, Lakshminarayana Vogeti, Michael D. Kaufman, Daniel L. Flynn, Deciphera Pharmaceuticals, LLC, KS.

A selective N-1 arylation of 3-substituted-pyrazole-5-carboxylates with boronic acids in the presence of Cu(OAc)<sub>2</sub> was presented. The method provided an alternative strategy for the preparation of N-1 aryl pyrazoles that were not readily available through traditional methods. Under these reaction conditions, *N*-arylation (and *N*-heteroarylation) was well tolerated by pyrazoles containing substitution at C-3 (Table 9). It was found that the larger the size of the pyrazole C-3 substituent, the greater the selectivity for arylation at pyrazole N-1. It was also found to be essential to protect any basic functionality on the boronic acid coupling partner.

**Table 9. Cu(OAc)<sub>2</sub>-catalyzed *N*-arylation of 3-dubstituted pyrazole-5-carboxylates.**

Substrate	R <sub>3</sub>	Yield	N-1 arylation
		75%	>90%
		70%	85%
		43%	65%
		73%	>90%
		88%	>90%
		NR	NR
		62%	>90%

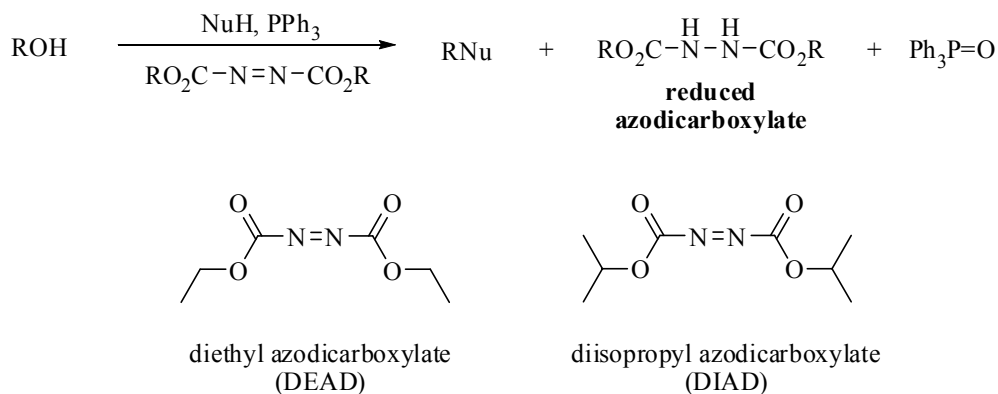
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## “Simplification of the Mitsunobu Reaction. Di-*p*-chlorobenzyl Azodicarboxylate: A New Azodicarboxylate”

Bruce H. Lipshutz, David W. Chung, Brian Rich, and Ricardo Corral, Department of Chemistry and Biochemistry, University of California, Santa Barbara

The ubiquitous Mitsunobu reaction is a popular method for the replacement of primary and secondary alcohols with a variety of acidic nucleophiles. Triphenylphosphine is typically combined with an azodicarboxylate such as DEAD or DIAD to convert the alcohol into an efficient leaving group that is then displaced by a deprotonated nucleophile (Scheme 14).

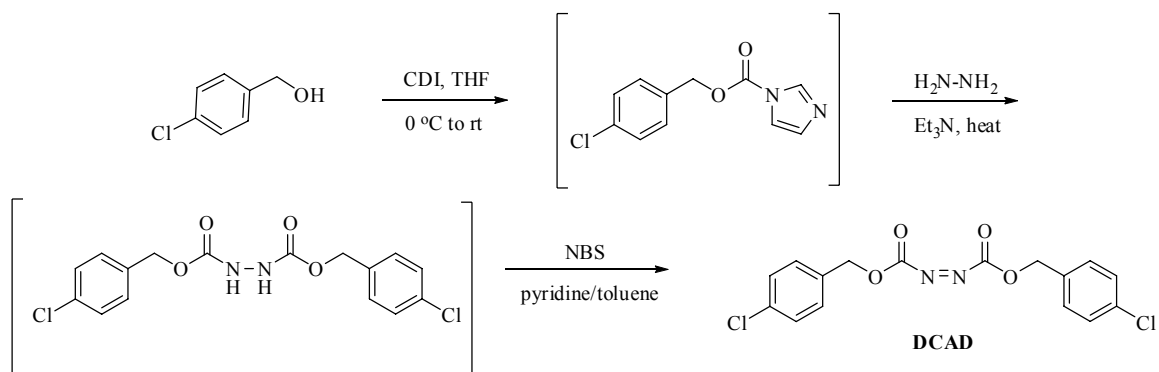
### Scheme 14. The Mitsunobu reaction.



The reaction has been developed to successfully utilize many oxygen, nitrogen and stabilized carbon nucleophiles. However, one issue that remains is that of product separation from the reaction byproducts, which include Triphenylphosphine oxide and the reduced azodicarboxylate. A number of strategies for easier byproduct removal have been reported recently, including fluorine-tagged and solid-supported reagents. Although these technologies all have utility, a new inexpensive solution phase reagent was sought after that would allow easy separation products, with recycling of the hydrazine byproduct.

The Lipshutz group has found that di-*p*-chlorobenzyl azodicarboxylate (DCAD) is an excellent alternative to DEAD and DIAD. It is fully soluble in dichloromethane while the reduced form is only sparingly soluble, allowing for greater than 80% recovery of the hydrazine byproduct through a simple filtration procedure. Additionally, any residual DCAD-derived hydrazine remaining in the crude product mixture is generally easier to remove through flash chromatography than the corresponding DEAD and DIAD byproducts, due to the greater polarity and UV-activity of reduced DCAD. It is also notable that DCAD is a very stable, easily handled, crystalline solid that can be stored at room temperature, unlike DEAD and DIAD. DCAD can be synthesized in a simple two-pot procedure from *p*-chlorobenzyl alcohol (Scheme 15) and is also commercially available from Aldrich.

**Scheme 15. Preparation of di-*p*-chlorobenzyl azodicarboxylate (DCAD).**



The performance of DCAD was evaluated versus DEAD for a variety of Mitsunobu reactions and found to be quite comparable in all cases (Table 10). This work was also published as *Organic Letters* **2006**, 8(22), 5069.

**Table 10. Comparison of DCAD versus DEAD.**

$\text{ROH} \xrightarrow[\text{PPh}_3, \text{NuH}, \text{CH}_2\text{Cl}_2, \text{rt}]{\text{RO}_2\text{C}-\text{N}=\text{N}-\text{CO}_2\text{R}} \text{RNu}$				
NuH	ROH	RNu	DEAD Yield	DCAD Yield
			94%	92%
			98%	88%
			97%	98%
			83%	77%
-			86%	90%
			76%	80%
---			92%	88%

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## “A Convenient Procedure for the Esterification of Benzoic Acids with Phenols: A New Application for the Mitsunobu Reaction”

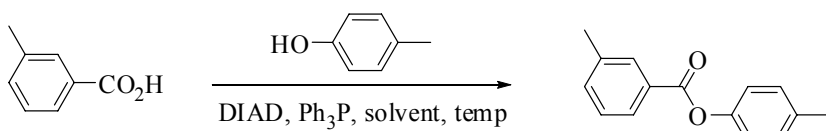
Victor Fitzjarrald and Rongson Pongdee, Department of Chemistry and Biochemistry, Colorado College, Colorado Springs

As mentioned above, the synthetic methodology of the Mitsunobu reaction is well developed for the replacement of alcohols with many types of acidic nucleophiles. It has also been successfully applied to the coupling of alkyl alcohols with aryl and alkyl carboxylic acids to produce carboxylic esters. Interestingly, it has never been examined in the context of a dehydrative coupling reaction between benzoic acids and phenols.

In the midst of a natural product synthesis, numerous esterification conditions (including the use of carbodiimides, acid chlorides and mixed anhydrides) were found to be unsatisfactory for the production of a particular benzoic phenolic ester. The authors thus became interested in the possibility of developing the Mitsunobu reaction conditions for this application as an alternative to standard esterification procedures.

For their initial optimization experiments, they chose the coupling of *o*-toluic acid with *p*-cresol in various solvents at a range of temperatures. The use of THF as a solvent at refluxing temperature proved to be the best general combination (Table 11).

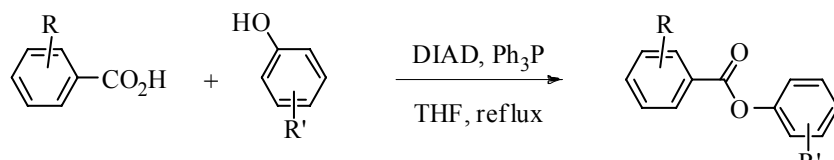
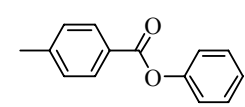
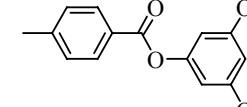
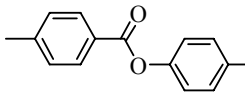
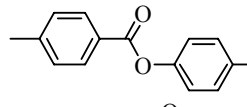
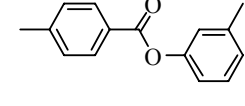
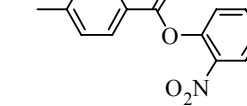
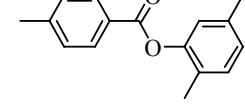
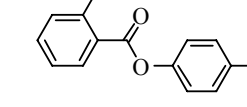
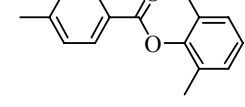
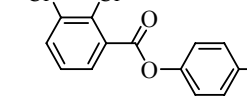
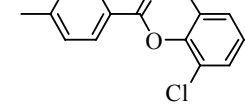
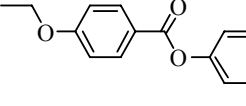
**Table 11. Optimization of the Mitsunobu condensation reaction.**



Solvent	Temperature	Yield
CH <sub>2</sub> Cl <sub>2</sub>	25 °C	20%
benzene	25 °C	17%
DMF	25 °C	29%
THF	25 °C	60%
THF	65 °C (reflux)	99%

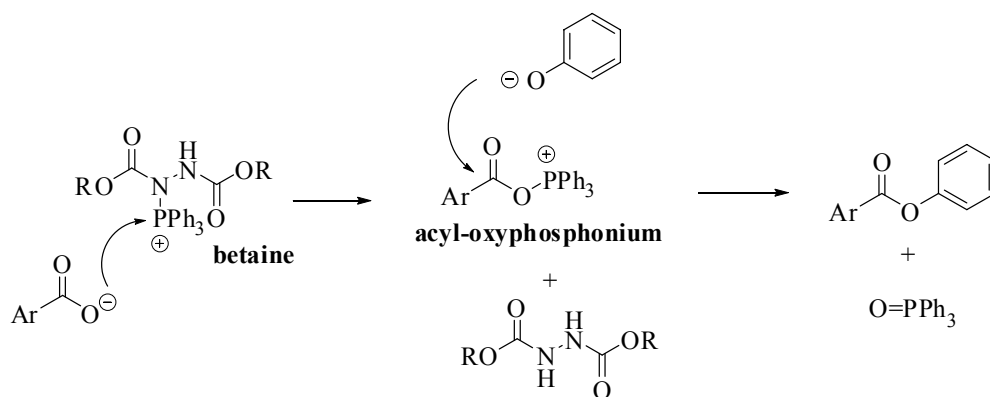
With these optimal conditions in hand, the scope of the reaction was then examined. Overall, the reaction proved quite robust at accepting a variety of electron-donating and electron-withdrawing groups on either coupling partner (Table 12). Electron-rich phenols provided the best results while *ortho* substitution of any kind led to reduced yields.

**Table 12. The Mitsunobu condensation reaction.**

			
Product	Yield	Product	Yield
	89%		81%
	99%		69%
	74%		42%
	67%		92%
	50%		71%
	45%		82%

The authors proposed that these reactions proceed through an acyl-oxyphosphonium species, which originates from the cationic Mitsunobu betaine intermediate reacting with the benzoate anion (Scheme 16). This is in contrast with the “normal” Mitsunobu mechanism where the alcohol is thought to react with the betaine. This work has also been published as *Tetrahedron Letters* **2007**, 48, 3553.

**Scheme 16. Proposed mechanistic pathway.**



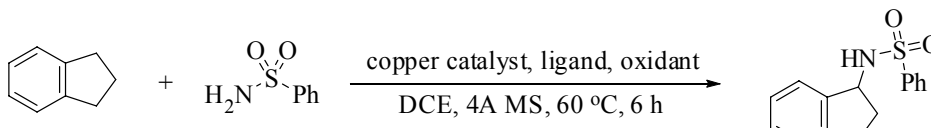
## “Copper-Catalyzed Amidation of Allylic and Benzylic C-H Bonds”

David A. Powell and Guillaume Pelletier, Department of Medicinal Chemistry, Merck Frosst Centre for Therapeutic Research, Montreal, Canada

The development of mild, selective transition metal-catalyzed methods for the functionalization of C-H bonds has been a very active field of organic chemistry in recent years. Much this work has focused on the transformation of C-H bonds into C-C bonds, while metal catalyzed C-H activation/oxidation reactions that allow the installation of carbon-heteroatom bonds are still less developed. With this in mind, the authors set out to develop an improved, more general method for the metal-catalyzed amidation of various hydrocarbon species.

Initial investigations focused on the coupling of indane and benzenesulfonamide. The choice of copper catalyst and oxidant was shown to be critical for reaction efficiency, with copper(II) triflate and *tert*-butyl peroxyacetate observed to be the best combination (Table 13).

**Table 13. Copper(II)-catalyzed sulfonamidation of indane.**

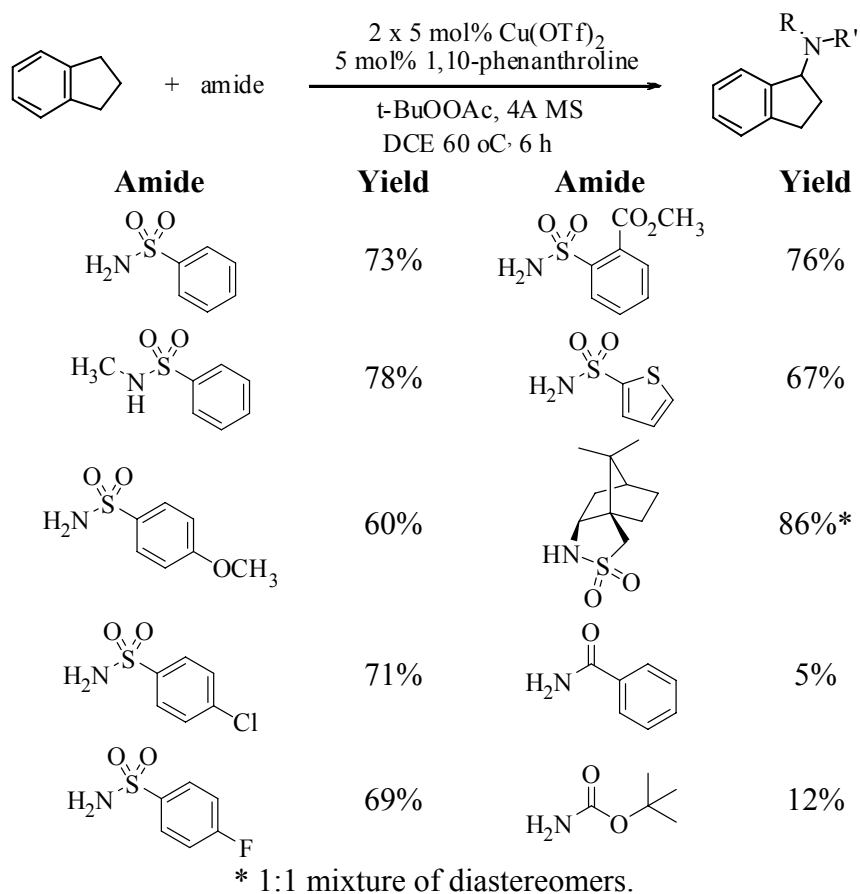


Catalyst	1,10-Phenanthroline	Oxidant	Yield
none	5 mol%	<i>t</i> -BuOOAc	0
Cu(OAc) <sub>2</sub> [10 mol%]	10 mol%	<i>t</i> -BuOOAc	8%
Cu(OTf) <sub>2</sub> [10 mol%]	10 mol%	<i>t</i> -BuOOH	20%
Cu(OTf) <sub>2</sub> [10 mol%]	10 mol%	<i>t</i> -BuOOBz	48%
Cu(OTf) <sub>2</sub> [10 mol%]	10 mol%	<i>t</i> -BuOOAc	49%
Cu(OTf) <sub>2</sub> [10 mol%]	10 mol%	<i>t</i> -BuOOAc**	63%
Cu(OTf) <sub>2</sub> [10mol%]*	5 mol%	<i>t</i> -BuOOAc**	73%

\* Two additions of 5 mol%; \*\* Slow addition over 6 h.

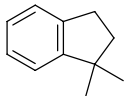
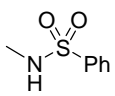
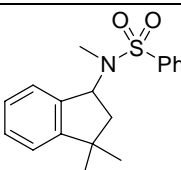
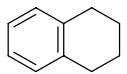
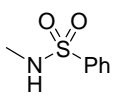
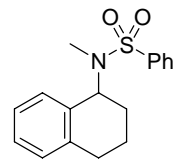

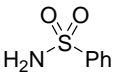
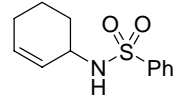

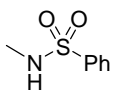
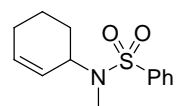

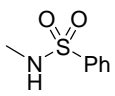
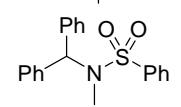
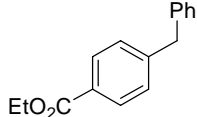
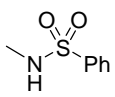
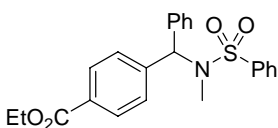

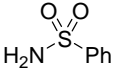
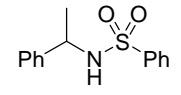
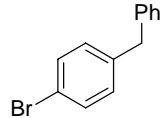
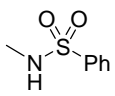
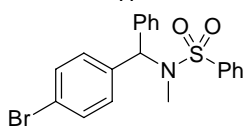
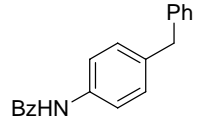
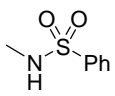
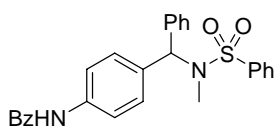

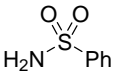
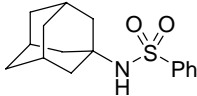
The scope of amide coupling partner was then examined using these optimized conditions. Significantly, both primary and secondary sulfonamides reacted successfully with indane using this copper-catalyzed procedure. Previously developed methods, such as those based on metal nitrenes, can only utilize primary amides. Carboxamides and carbamates give only poor results with the current procedure (Table 14).

**Table 14. Copper(II)-catalyzed sulfonamidation and amidation of indane.**



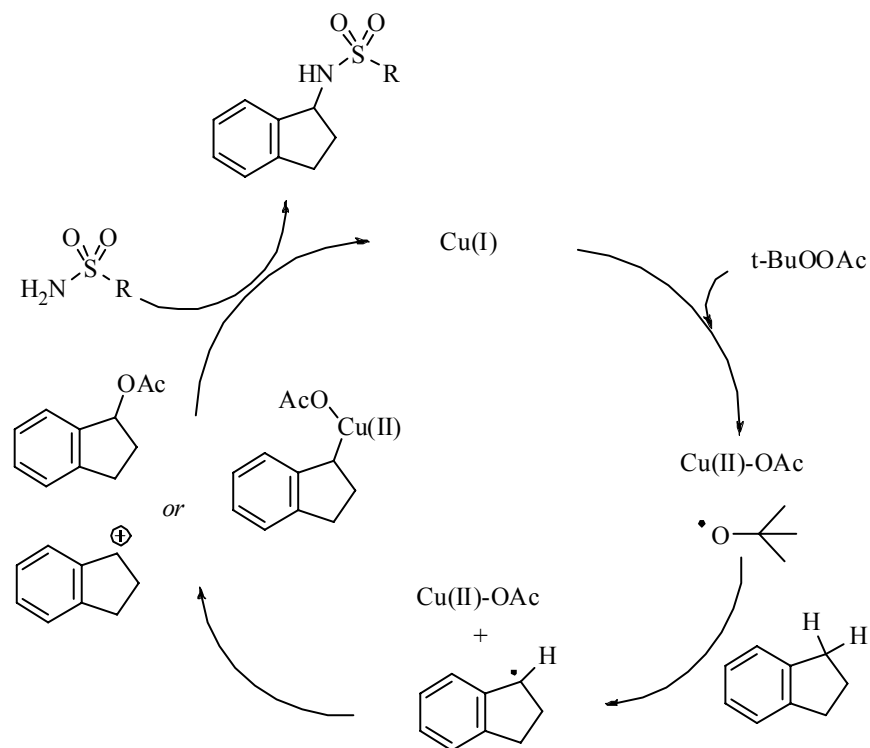
The range of suitable hydrocarbon substrates was also examined. Notably, allylic C-H bonds (cyclohexene specifically) could be cleanly amidated using this procedure (Table 15). Most metal nitrene methods give aziridines as the main product in the corresponding transformation.

**Table 15. Copper(II)-catalyzed sulfonamidation of alkanes.**

Hydrocarbon	Sulfonamide	Product	Yield
$\text{RH} + \text{R}'\text{-N}(\text{H})\text{S}(\text{O})_2\text{Ph} \xrightarrow[\text{DCE } 60^\circ\text{C, 6 h}]{\text{2 x 5 mol\% Cu(OTf)}_2, \text{5 mol\% 1,10-phenanthroline, t-BuOOAc, 4A MS}} \text{R}'\text{-N}(\text{R})\text{S}(\text{O})_2\text{Ph} \quad \text{R}' = \text{CH}_3, \text{H}$			
			63%
			54%
			75%
			61%
			50%
			47%
			60%
			49%
			64%
			56%

Benzylic acetates are observed in minor quantities during these reactions, suggesting that these species might be intermediates (Scheme 17). This initial hypothesis is also supported by experiments demonstrating that benzylic acetates can be coupled with sulfonamides using the standard copper conditions or with acid catalysis.

**Scheme 17. Proposed catalytic cycle and reaction pathway.**

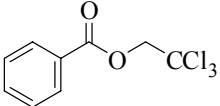
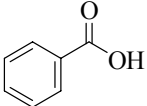
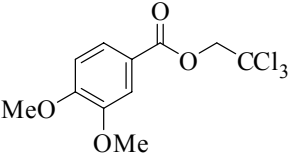
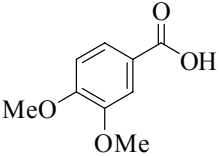
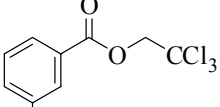
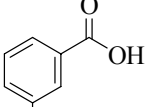
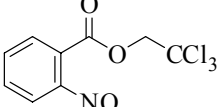
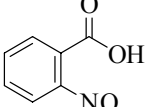
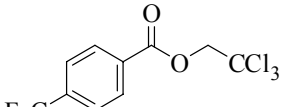
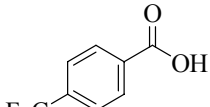
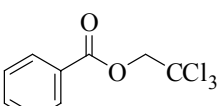
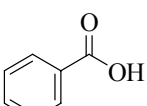
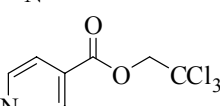
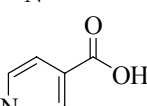
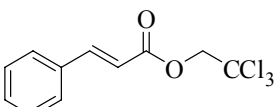
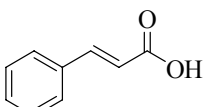
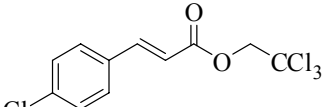
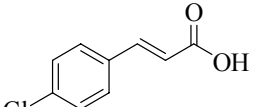
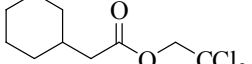
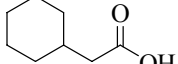
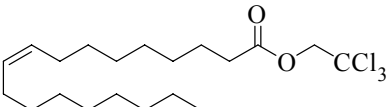
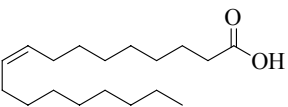


**“Indium-mediated Chemoselective Deprotection of 2,2,2-trichloroethyl Esters”**

*Tomoko Mineo, Hisao Kanui, and Takehisa Kunieda. Laboratory of Organic Chemistry, Faculty of Pharmaceutical Sciences, Sojo University, Kumamoto, Japan*

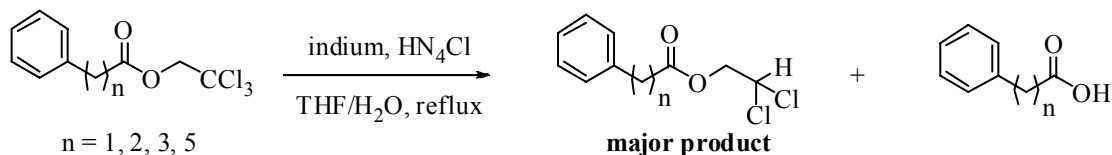
The 2,2,2-trichloroethyl (TCE) group is a useful blocking group for carboxylic acids that can be removed under a variety of mild conditions. Indium metal has already been demonstrated as useful reagent for the removal of TCE from alcohols and amines, and is now shown to be an effective reagent for the cleavage of TCE esters under mild conditions (Table 16).

**Table 16. Indium-catalyzed deprotection of TCE esters.**

$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{O}-\text{CH}_2-\text{CCl}_3 \xrightarrow[\text{THF}/\text{H}_2\text{O, reflux}]{\text{indium, HN}_4\text{Cl}} \text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{OH}$			
Amide	Product	Time	Yield
		7 h	92%
		11 h	75%
		4 h	74%
		3.5 h	93%
		7 h	73%
		11 h	95%
		12 h	62%
		15 h	76%
		1.5 h	94%
		3 h	80%
		48 h	88%

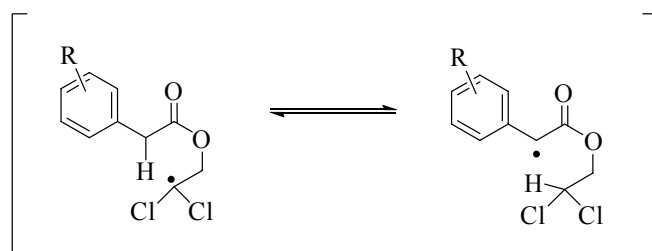
The reaction works well for electron-rich or electron-poor benzoates, nicotines, cinnamates and aliphatic carboxylates. However, TCE esters containing a benzylic methylene moiety such as phenylacetate give 2,2-dichloroethyl esters as their major product using the indium mediated conditions (Scheme 18).

**Scheme 18. Byproducts formed from the deprotection of benzylic substrates.**



This curious result was rationalized as an intramolecular transfer of the initially-generated radical to form the more stable benzyl radical (Scheme 19). Further study is required to support this hypothesis. Some of this work has been reported as *Tetrahedron Letters* **2007**, 48, 5027.

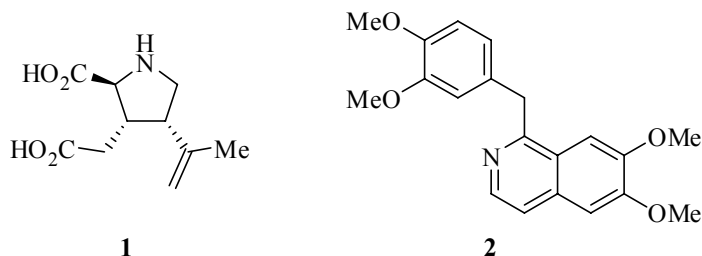
**Scheme 19. Proposed radical-transfer intermediates.**



### “Synthesis of Heterocycles via Palladium Catalysis”

*Paul Stoker, Julian G. Knight, Simon J. Harwood and Ken Lawrie, School of Natural Sciences, Bedson Building, Newcastle University, Newcastle, UK and GlaxoSmithKline, Medicines Research Centre, Stevenage, UK*

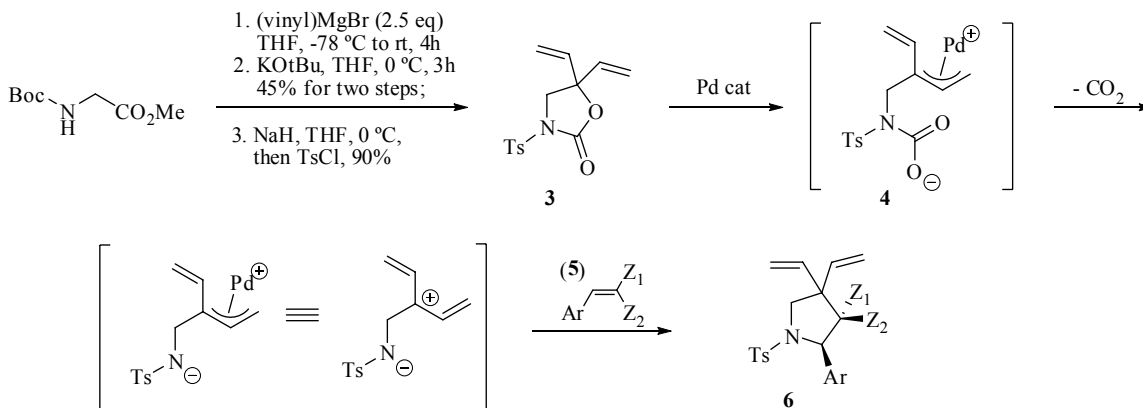
This poster provided an overview of palladium-catalyzed syntheses of pyrrolidines and isoquinolines. Pyrrolidines, such as the neuroexcitatory compound kainic acid (**1**), and isoquinolines, such as the muscle relaxant papaverine (**2**), are important classes of compounds that exhibit a wide range of biological activities. Stoker and colleagues have developed approaches to these nitrogen heterocycles using palladium-catalyzed decarboxylative cyclizations of 5-vinyloxazolidonone precursors.



## Part One: Pyrrolidine Syntheses

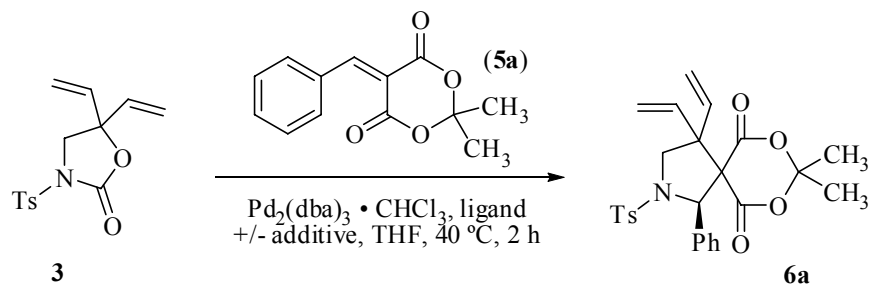
The achiral 5,5-divinylloxazolidinone **3** was synthesized in good yield from *N*-Boc glycine methyl ester. Stoker envisaged that the formation of a  $\pi$ -allylpalladium intermediate **4** would spontaneously lose CO<sub>2</sub> to produce an intermediate analogous to a 1,3-dipole. This species would in turn undergo cycloaddition across an activated alkene **5** to form a pyrrolidine **6** (Scheme 20).

**Scheme 20. Proposed mechanism for the palladium-catalyzed cycloaddition.**



Stoker and colleagues initially found that the reaction would work when the carbamate **3** was reacted with 2,2-dimethyl-5-(phenylmethylene)-1,3-dioxane-4,6-dione (**5a**), albeit in moderate yield for the first attempt (Table 17, entry 1). Further investigations found that use of a chelating diphosphine ligand gave no reaction (entries 4-5), while the bulky electron rich phosphines gave a slight increase in yield (entry 6). They also found that iodide and (to a lesser extent) bromide additives gave a dramatic increase in yield (entries 11-12).

**Table 17. Ligand and additive effects on the [3 + 2] cycloaddition of 3 with olefin 5a.**

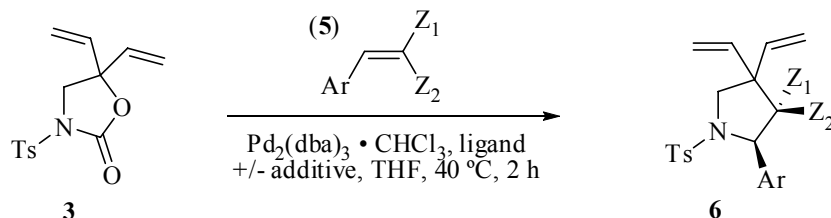


Entry <sup>a</sup>	Phosphine	Additive	Yield <sup>b</sup>
1	PPh <sub>3</sub>	-	23%
2	PBu <sub>3</sub>	-	(no reaction)
3	TMPP	-	35%
4	dppb	-	(no reaction)
5	dppf	-	(no reaction)
6	(o-biphenyl)PCy <sub>2</sub>	-	36%
7	(o-biphenyl)P( <i>t</i> Bu) <sub>2</sub>	-	11%
8	PPh <sub>3</sub>	Bu <sub>4</sub> NOAc	42%
9	PPh <sub>3</sub>	Bu <sub>4</sub> NF	(no reaction)
10	PPh <sub>3</sub>	Bu <sub>4</sub> NCl	(no reaction)
11	PPh <sub>3</sub>	Bu <sub>4</sub> NBr	67%
12	PPh <sub>3</sub>	Bu <sub>4</sub> NI	77%

<sup>a</sup>Conditions: 5 mol% Pd<sub>2</sub>(dba)<sub>3</sub> · CHCl<sub>3</sub>, 40 mol % phosphine, 1.5 equiv. Michael acceptor **5a**, 2 equiv. additive, THF, 40 °C, 2 h. <sup>b</sup>NMR yield.

The Stoker group was able to synthesize a series of pyrrolidines in good to excellent yield using the optimized method (Table 18). It was also found that tetrabutylammonium iodide had a detrimental effect on the yield when highly electrophilic malononitriles were used (entries 4-6 and 9).

**Table 18. Palladium-catalyzed cycloaddition of 3 with Michael acceptors 5.<sup>a</sup>**



Entry	Michael Acceptor: Ar, Z <sup>1</sup> , Z <sup>2</sup>	P/Pd <sup>b</sup> ratio	Product	Yield <sup>d</sup> (no additive)	Yield <sup>d</sup> (with additive) <sup>c</sup>
1	<b>5a</b>	1:1	<b>6a</b>	23% <sup>c</sup>	-
2	<b>5a</b>	2:1	<b>6a</b>	21% <sup>c</sup>	-
3	<b>5a</b>	4:1	<b>6a</b>	24% <sup>c</sup>	77%
4	<b>5b</b> : Ar = Ph, Z <sup>1</sup> , Z <sup>2</sup> = CN	1:1	<b>6b</b>	95%	33%
5	<b>5c</b> : Ar = 4-MeOPh, Z <sup>1</sup> , Z <sup>2</sup> = CN	1:1	<b>6c</b>	97%	53%
6	<b>5d</b> : Ar = 2-furyl, Z <sup>1</sup> , Z <sup>2</sup> = CN	1:1	<b>6d</b>	82%	43%
7	<b>5e</b> : Ar = Ph, Z <sup>1</sup> = CN, Z <sup>2</sup> = CO <sub>2</sub> Et	1:1	<b>6e</b>	65%	73%
8	<b>5f</b>	1:1	<b>6f</b>	38%	78%
9	<b>5g</b>	1:1	<b>6g</b>	61%	0%

<sup>a</sup>Conditions: 5 mol% Pd<sub>2</sub>(dba)<sub>3</sub> • CHCl<sub>3</sub>, 10-40 mol % Ph<sub>3</sub>P, 1.5 equiv. Michael acceptor **5**, THF, 40 °C, 2 h.

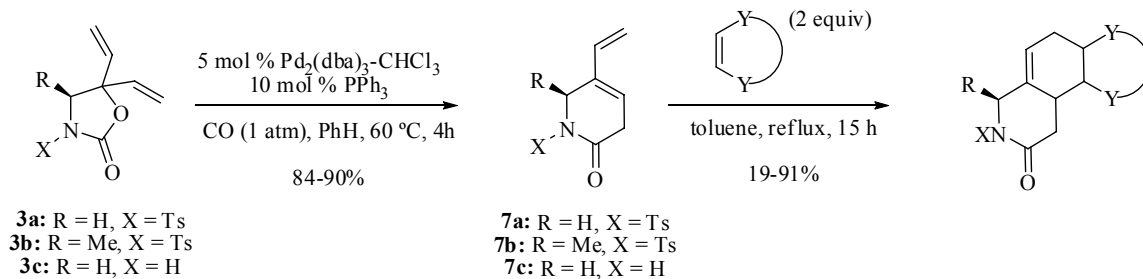
<sup>b</sup>phosphine/palladium ratio. <sup>c</sup>NMR yield. <sup>d</sup>Isolated yield. <sup>e</sup>Conditions: 5 mol% Pd<sub>2</sub>(dba)<sub>3</sub> • CHCl<sub>3</sub>, 40 mol % Ph<sub>3</sub>P, 1.5 equiv. Michael acceptor **5**, 2 equiv. nBu<sub>4</sub>NI, THF, 40 °C, 2 h

### Part Two: Isoquinoline Synthesis

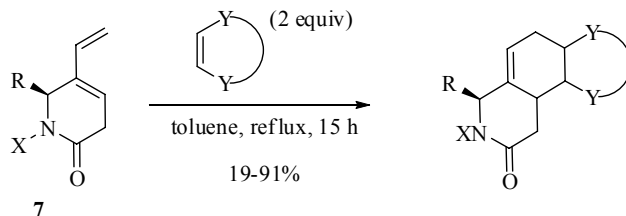
This method was next applied to the synthesis of isoquinolines. Palladium-catalysed decarboxylative carbonylation of the *N*-tosyl-5,5-divinylloxazolidinones **3a** (R = H) and **3b** (R = Me) and the non-tosylated oxazolidinone **3c** gave the corresponding dienes **7a-c**, which were in turn subjected to Diels-Alder cycloaddition reactions to provide hexahydro-2*H*-isoquinolin-3-ones (Scheme 21, Table 19). Stoker and colleagues synthesized a number of isoquinolines with

good endo:exo selectivity and found that poor yields were obtained using the non-tosylated lactam **7b** (entries 3-4).

**Scheme 21. Application to the synthesis of isoquinolin-3-ones.**



**Table 19. Diels-Alder Cycloadditions of dienes 7 with dienophiles.<sup>a</sup>**



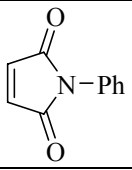
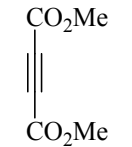
<sup>a</sup>Conditions: diene (0.07M in solvent), 2.0 equiv. of dienophile, toluene, reflux, 15 h. <sup>b</sup>anti-endo/syn-endo/anti-

Entry	Diene	Dienophile	Product	Yield (%)
1				91
2				54
3				19
4				23
5				42 9:6:3:1 <sup>b</sup>
6				43 1:1 <sup>c</sup>

exo/syn-exo ratio. <sup>c</sup>Mixture of diastereomers.

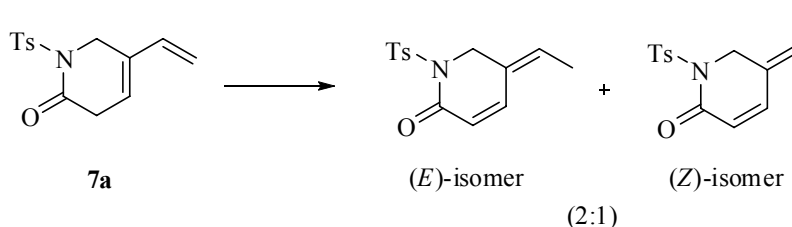
A solvent study was also performed by Stoker's group for the Diels-Alder cycloadditions in a microwave reactor. It was found that reaction times were reduced to just 5 minutes under microwave heating in a range of solvents (Table 20).

**Table 20. Solvent study for Diels-alder cycloadditions of 7a in a microwave reactor.**

Entry	Dienophile	Toluene	DMSO	H <sub>2</sub> O	H <sub>2</sub> O / Dioxane <sup>b</sup>	1,2-DCE	DMF
<b>Conditions<sup>a</sup></b>		150 °C/ 5 min	200 °C/ 5 min	170 °C/ 5 min	170 °C/ 5 min	200 °C/ 5 min	200 °C/ 5 min
1		60%	59%	52%	58%	42%	55%
2		69%	(trace)	(trace)	(trace)	66%	40 % Isomerized SM <sup>c</sup>

<sup>a</sup>Conditions: diene (0.07 M in solvent), 2.0 equiv. of dienophile. <sup>b</sup>1:1 ratio. <sup>c</sup>Recovered the starting material (7a) as a 2:1 mixture of isomerized dienes as (*E*) and (*Z*) regioisomers, as shown in Scheme 22.

**Scheme 22. Isomerisation of diene 7a.**



In conclusion Stoker and colleagues have extended the versatility of palladium catalysis to initiate decarboxylative cyclization reactions as a pathway to the formation of pyrrolidines and isoquinolines. For further information, see the following literature references: (a) Mitchinson, A.; Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2862-2892; (b) Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev.* **2004**, *104*, 3341-3370; (c) Knight, J. G.; Tchabanenko, K.; Stoker, P. A.; Harwood, S. J. *Tetrahedron Lett.* **2005**, 6261-6264.

### “Palladium-Catalyzed Coupling Reactions of Pyrazoles”

Gytė Vilkauskaitė,<sup>a</sup> Eglė Nedzelskytė,<sup>a</sup> Gernot A. Eller,<sup>b</sup> Wolfgang Holzer<sup>b</sup> and Algirdas Šačkus,<sup>a</sup>

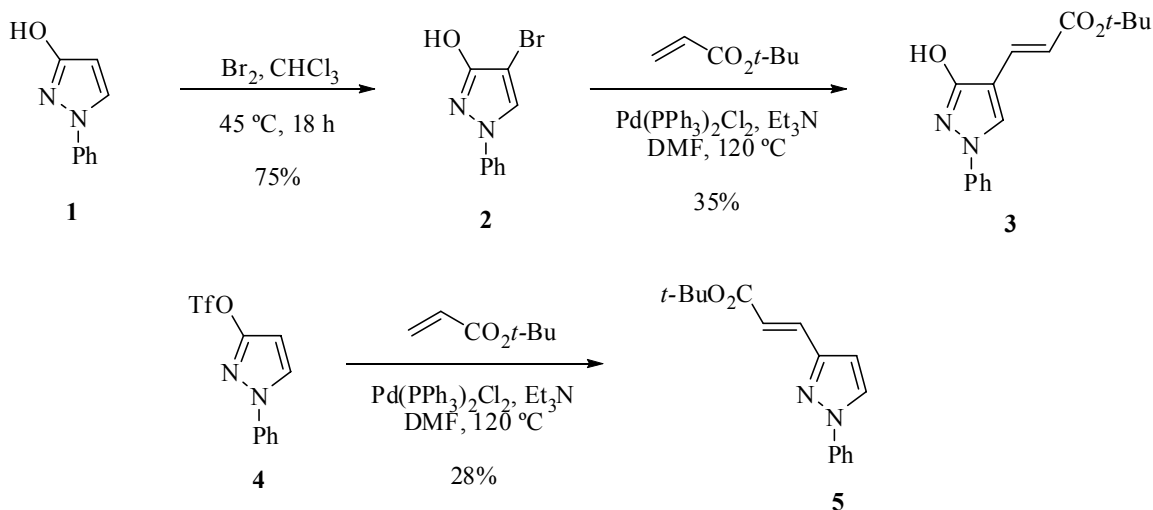
<sup>a</sup>Kaunas University of Technology, Institute of Synthetic Chemistry, Kaunas, Lithuania and

<sup>b</sup>University of Vienna, Faculty of Life Sciences, Department of Drug and Natural Product Synthesis, Vienna, Austria.

This poster provided an overview of palladium-catalyzed coupling reactions of 3-bromo and/or pyrazole-3-triflate substrates. Pyrazole-containing derivatives are found in many pharmaceuticals, dyes and complexing compounds. Palladium-catalyzed reactions represent a versatile tool for C-C bond formation. In this work Vilkauskaitė and colleagues demonstrated the use of Heck, Stille, Sonogashira and Suzuki reactions to prepare new pyrazole derivatives.

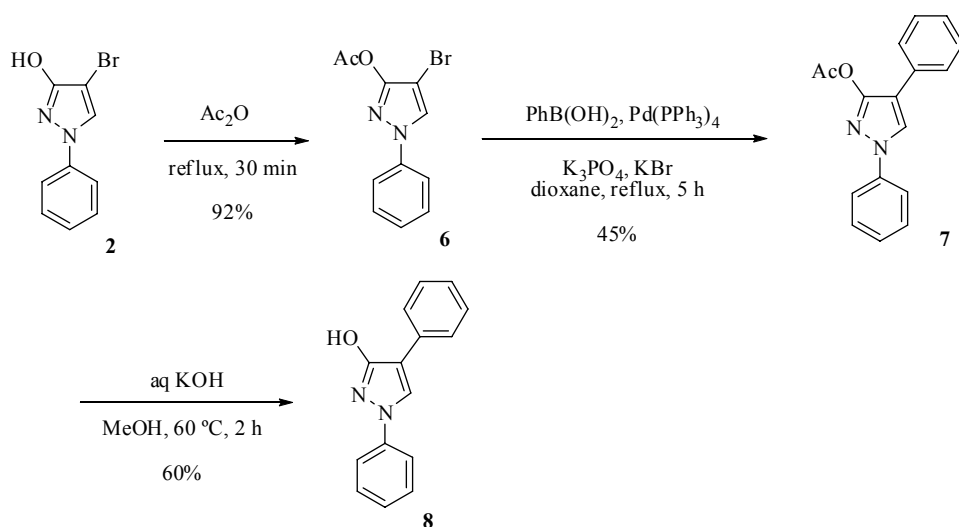
Bromination of 1-phenyl-1*H*-pyrazol-3-ol (**1**) and subsequent treatment with *tert*-butyl acrylate under Heck reaction conditions afforded the vinyl pyrazole product **3** in a 35% yield (Scheme 23). Treatment of 1-phenyl-1*H*-pyrazol-3-yl triflate (**4**) with *tert*-butyl acrylate under the same reaction conditions gave the vinyl pyrazole **5** in a 28% yield.

**Scheme 23. Heck coupling reactions of pyrazole substrates.**



The reaction of 4-bromo-1-phenyl-1*H*-pyrazol-3-ol (**2**) with acetic anhydride afforded the corresponding *O*-acetylated product (**6**) in a 92% yield (Scheme 24). The reaction of **6** with phenylboronic acid under Suzuki reaction conditions gave 4-aryl-1-phenyl-1*H*-pyrazol-3-ol ester **7** in 45% yield, which was then hydrolyzed to the final hydroxypyrazole product **8** in 60% yield.

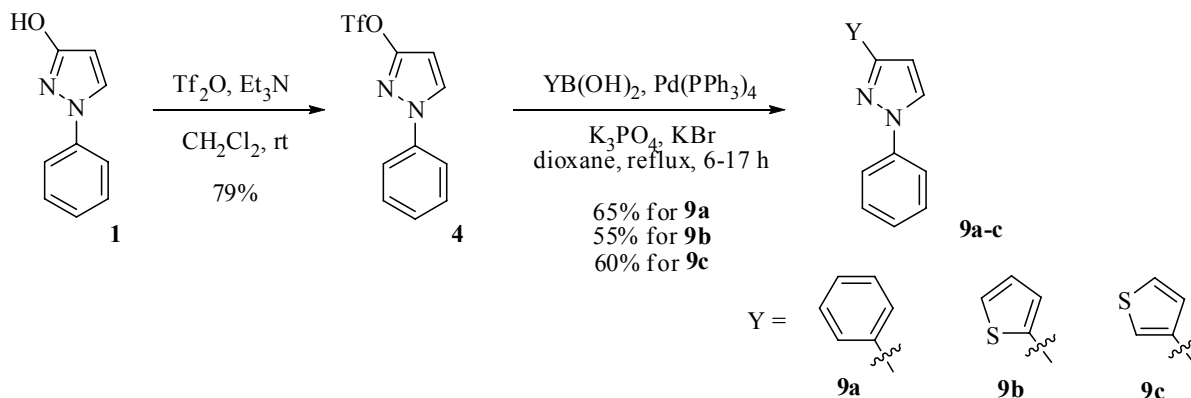
**Scheme 24. Suzuki coupling reactions of a 3-bromo pyrazole substrate.**



Vilkauskaitė and colleagues also reported the reaction of 1-phenyl-1*H*-pyrazol-3-ol (**1**) with triflic anhydride which gave 1-phenyl-1*H*-pyrazol-3-yl triflate (**4**) in a 79% yield (Scheme 25).

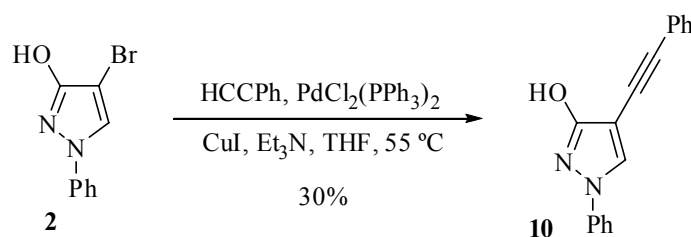
The reaction of **4** with arylboronic acids under Suzuki reaction conditions gave 3-aryl-1-phenyl-1*H*-pyrazol-3-ols (**9a-c**) in yields ranging from 55–65%.

**Scheme 25. Suzuki coupling reactions of a pyrazole-3-triflate substrate.**



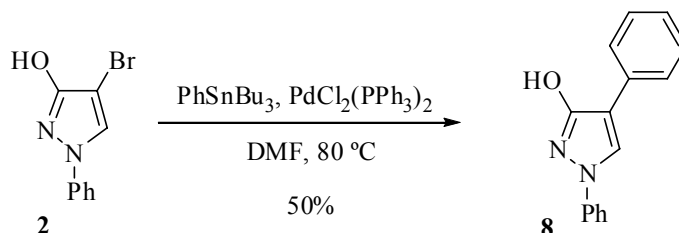
The Vilkauskaitė group also reported the coupling of 4-bromo-1-phenyl-1*H*-pyrazol-3-ol (**2**) with phenylacetylene under Sonogashira reaction conditions (Scheme 26). This reaction afforded 1-phenyl-4-(2-phenylethynyl)-1*H*-pyrazol-3-ol (**10**) in 30% yield.

**Scheme 26. Sonogashira coupling reactions of a 3-bromo pyrazole substrate.**



The coupling reaction of 4-bromo-1-phenyl-1*H*-pyrazol-3-ol (**2**) with tributylphenyltin under Stille reaction conditions afforded 1,4-diphenyl-1*H*-pyrazol-3-ol (**8**) in a 50% yield (Scheme 27).

**Scheme 27. Stille coupling reactions of a 3-bromo pyrazole substrate.**



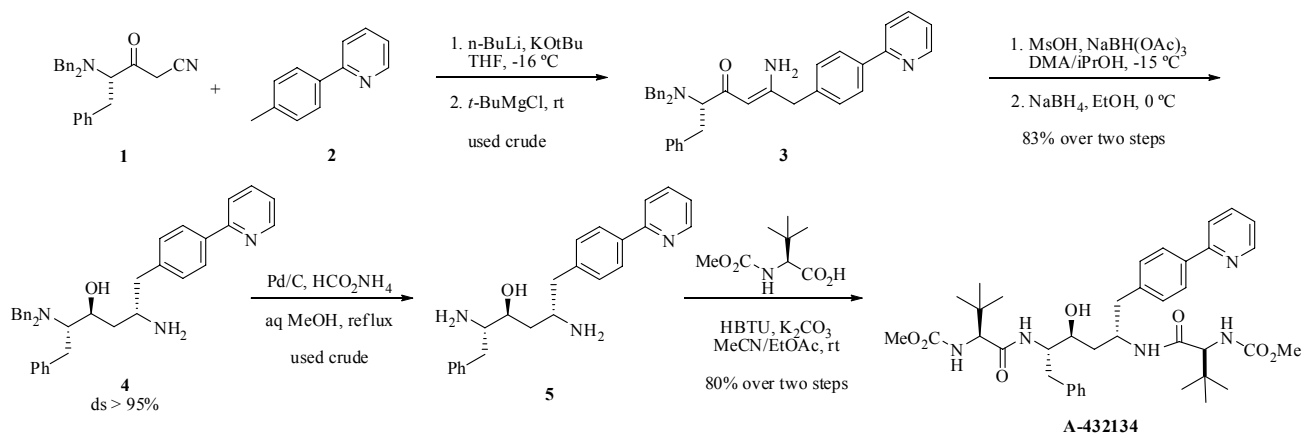
In conclusion, the Vilkauskaitė group reported the use of palladium-catalyzed methods to synthesize new 3-substituted pyrazole compounds. For further information, see the following literature references: (a) Auterhoff, H.; Knabe, J.; Hölting, H.-D. in *Lehrbuch der Pharmazeutischen Chemie*, Stuttgart, 1999, p. 358; (b) Tsuji, J. in *Palladium Reagents and Catalysts – New Perspectives for the 21st Century*, New York, 2004, p. 1.

## “A Short and Highly Efficient Synthesis of HIV Protease Inhibitor A-432134 via Site-Selective Metalation-Alkylation and Stereoselective Reduction”

Xiu. C. Wang, Su Yu, Zhenping Tian and Casey Zhou, Department of Process Chemistry, Global Pharmaceutical R&D, Abbott Laboratories, 1401 Sheridan Rd., North Chicago, IL 60064

This poster provided by Wang and colleagues reported a highly efficient, stereocontrolled synthesis of the hydroxyethylene dipeptide isostere protease inhibitor **A-432134** (Scheme 28). Starting with the readily available  $\beta$ -ketonitrile **1** and 2-*p*-tolyl-pyridine (**2**), the keto-enamine intermediate **3** was prepared in high yield *via* a site-selective metalation-alkylation approach. With modified reduction conditions, the core compound **4** was prepared with high diastereoselectivity and 83% yield in only two steps. Deprotection of **4** and double-coupling with a protected *tert*-leucine afforded **A-432134** in an overall four-step synthesis with a marked improvement over their previously-reported process.

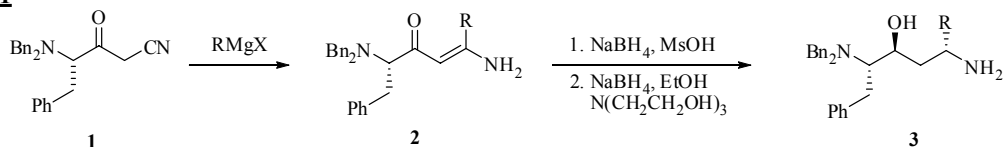
Scheme 28. A New Synthesis of A-432134.



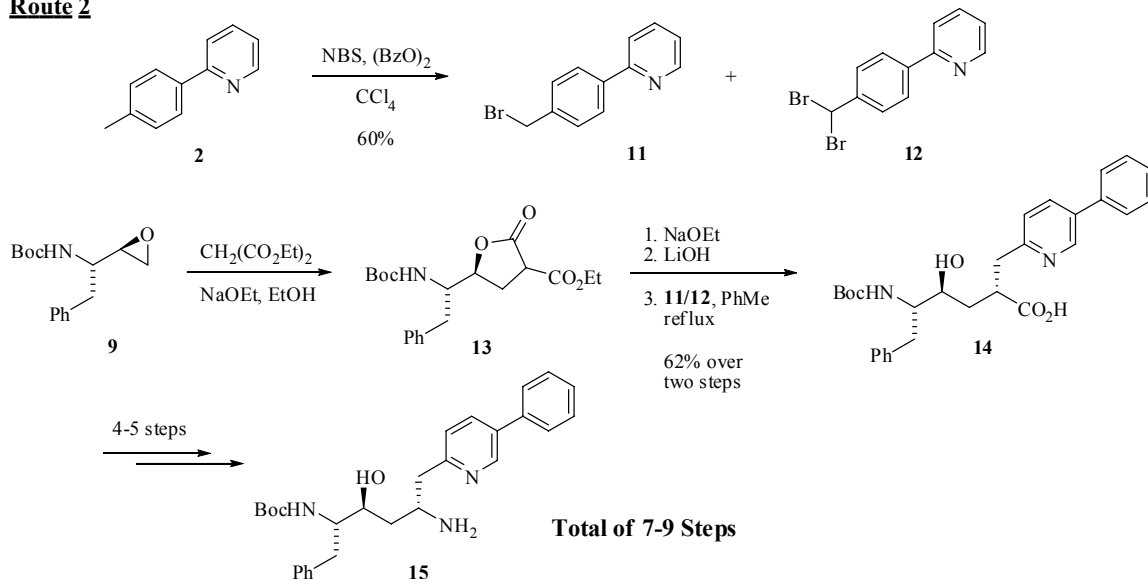
Hydroxyethylene dipeptide isosteres are found in several successful HIV protease inhibitors. Two commonly used synthetic approaches for the core compounds of these molecules have been reported (*i.e.*, Scheme 29). Route 1 focuses on the coupling of the readily available and inexpensive ketonitrile **1** and a Grignard reagent, followed by a stereoselective reduction of the ketoenamine **2** to prepare the diamino alcohol **3**. Route 2 to prepare the core compound **15** is typically accomplished through a coupling reaction of a benzylic bromide **11** with the enolate **13**, followed by several manipulations to **15**.

## Scheme 29. Previous syntheses of core compounds.

### Route 1

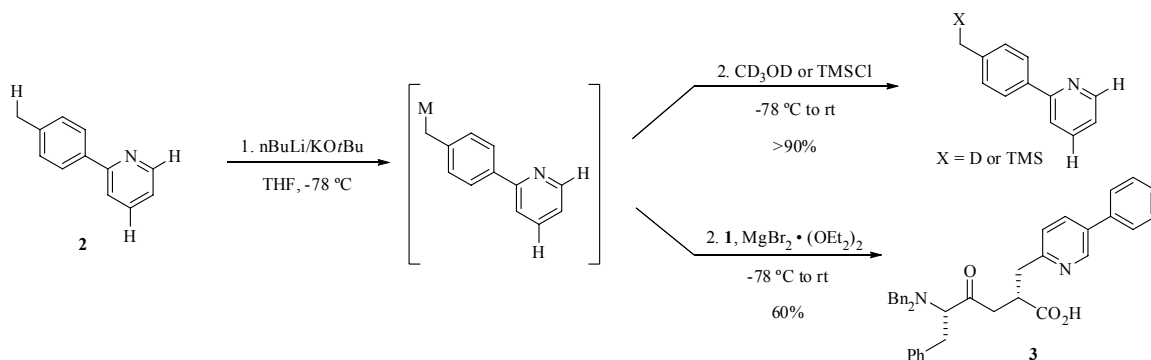


### Route 2



Wang and colleagues found that the use of Schlosser's super base ( $n\text{-BuLi}/\text{KO}t\text{Bu}$ ) afforded selective benzylic metalation over nuclear deprotonation (Scheme 30). Alkylation of ketonitrile **1** with the benzylic anion of **2**, generated under the same conditions, afforded the desired product **3** in a much-improved yield.

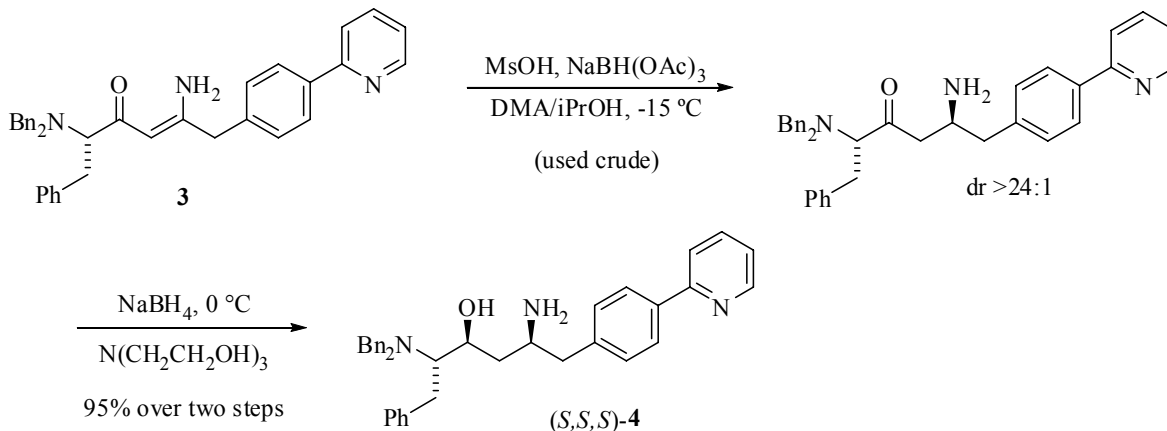
## Scheme 30. Improved yield through the use of Schlosser's base.



More controlled experiments were carried out to optimize the conditions for metalation at the benzylic position (Table 21). Conditions were systematically varied (only some shown here) to study the effect on the regioselectivity of the metalation.



**Scheme 32. Double reduction to the (*S,S,S*)-amino alcohol 4.**

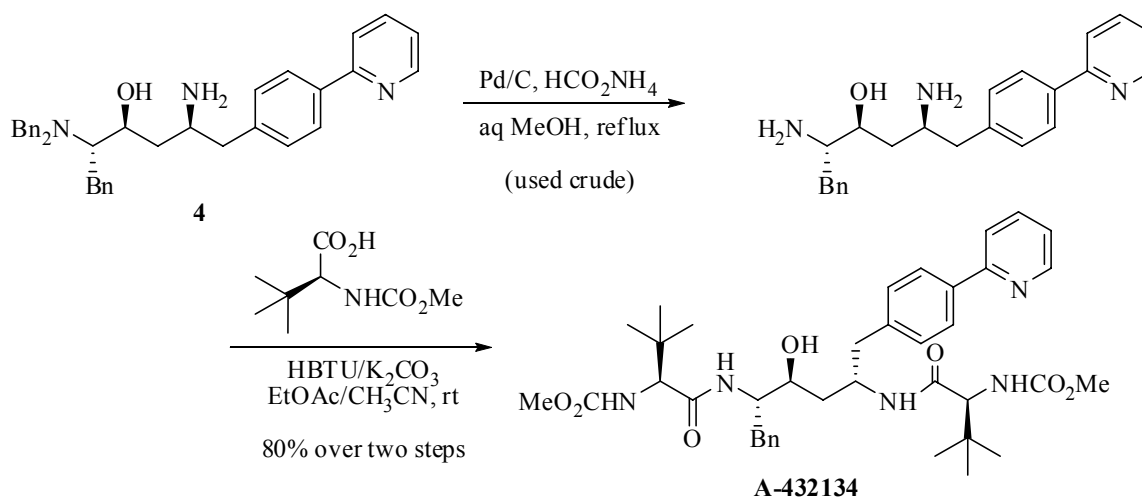


**Table 22. Solvent optimization for the first reduction of enamine 3.**

Solvent	Reducing Agent	Yield of ( <i>S,S,S</i> )-4
DME-IPA	NaBH <sub>4</sub>	88%
<b>DMA-IPA</b>	<b>NaBH(OAc)<sub>3</sub></b>	<b>95%</b>
CH <sub>2</sub> Cl <sub>2</sub>	NaBH <sub>4</sub>	57%

Deprotection and a peptide coupling were carried out without significant modification to complete the high-efficiency synthetic route to **A-432134** (Scheme 33).

**Scheme 33. Final manipulations to A-432134.**



In conclusion Wang and colleagues at Abbott Laboratories have established the 2-step synthesis of the core compound **4** in 83% yield with high diastereoselectivity. With these modifications they have significantly improved upon their previously-established synthesis.

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