



**Trip Report:  
228<sup>th</sup> ACS National Meeting  
Philadelphia, Pennsylvania  
April 22– 26, 2005**

**Andrew Zych, Ph.D.**

Medicinal Chemistry Department  
Albany Molecular Research, Inc.  
21 Corporate Circle  
Albany, NY 12212

**Abstract.** *The 228th ACS National Meeting was held August 22–26, 2005 in Philadelphia, Pennsylvania. A summary of selected lectures and posters that were attended at the Organic Chemistry sections of this meeting are listed.*

### “Deprotection of silyl groups by Pd/C/H<sub>2</sub>: A simple and selective method”

Sheila Marie H. Jacobo, Seongjin Kim, Chih Tsung Chang, Sophie Bellone, and Joshua Rokach.  
 Claude Pepper Institute and Department of Chemistry,  
 Florida Institute of Technology, William S. Powell,  
 Meakins-Christie Laboratories and Department of Medicine, McGill University.

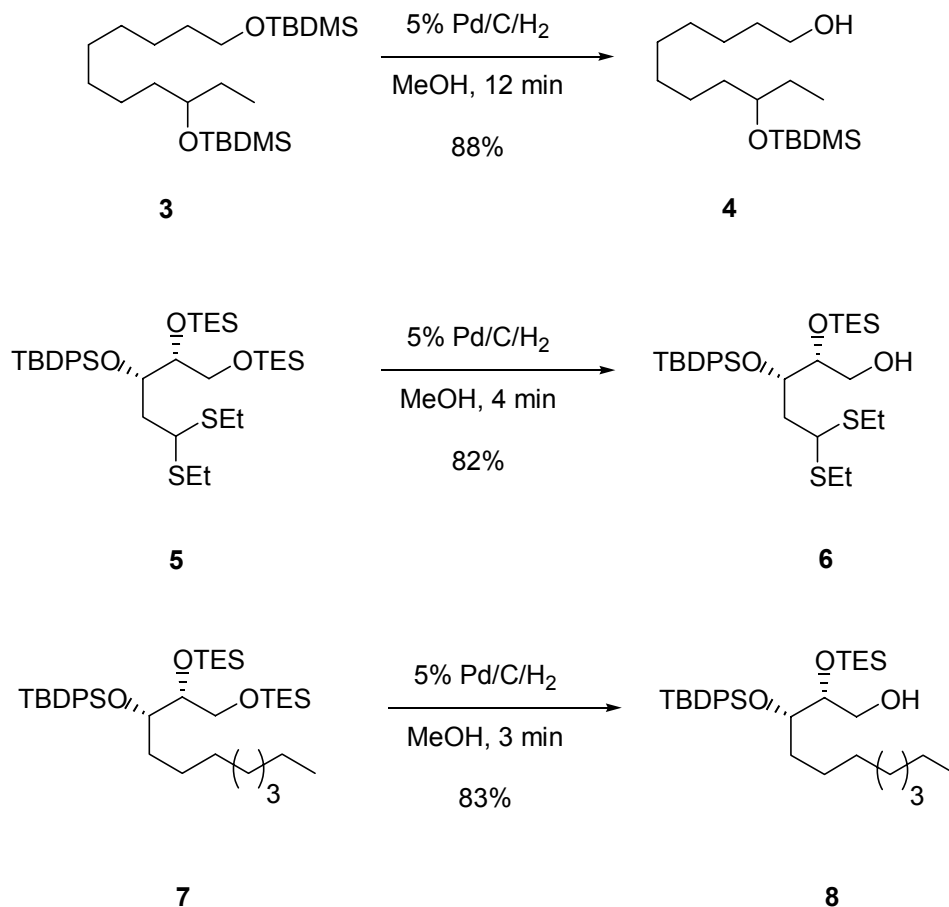
A simple and selective method for the deprotection of silyl groups using 5 % Pd/C/H<sub>2</sub> in methanol was presented. The reactivity of various silyl groups was found to be TES > TPS > TBS >> TBDMS > TIPS > TBDPS. This translates into a reaction time of 1-2 minutes for TES while TIPS and TBDPS generally require many hours. Importantly, this enables selective removal of varying groups based on reaction time (Table 1).

**Table 1**

<b>Entry</b>	<b>Substrate (1)</b>			
	<b>R<sup>1</sup></b>	<b>R<sup>2</sup></b>	<b>Reaction Time (min)</b>	<b>(2) Isolated Yield (%)</b>
<i>a</i>	TES	TBDMS	1	>99
<i>b</i>	TPS	TBDMS	2	98
<i>c</i>	TBS	TBDMS	5	97
<i>d</i>	TBDMS	TIPS	10	97
<i>e</i>	TBDMS	TBDPS	30	98

It was also observed that steric factors can influence the rate of desilylation and that this could be exploited for selective deprotection. For example, primary silyl groups could be cleaved in the presence of secondary groups in good yield (Scheme 1).

## Scheme 1



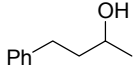
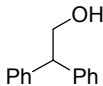
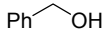
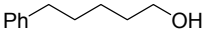
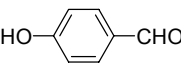
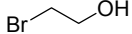
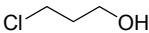
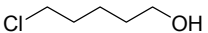
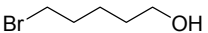
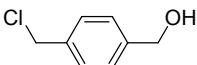
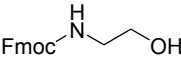
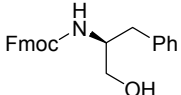
Reference: *Tetrahedron Letters* **2004**, 45, 1973-1976.

### “Versatile Silver Triflate-Assisted Method for Trityl Protection of Alcohols in Solution and on Solid Phase”

Joseph T. Lundquist, IV, and Andrew D. Satterfield,  
Department of Chemical and Screening Sciences, Wyeth.

A milder alternative to standard tritylation conditions based on silver triflate was revealed. Treatment of trityl chloride with silver triflate rapidly generates trityl cation which is then quenched with alcohols to produce ethers, often in less than one hour. This method gives yields comparable or better than known literature methods and was compatible with the base-labile Fmoc protecting group (Table 2, entries j and k). The conditions could also be adapted to electrophilic substrates, such as halo alcohols, that could compete for silver triflate by adding the substrate after allowing sufficient time for cation formation (Table 2, entries f – j). Tertiary alcohols failed to give trityl ethers in all cases presumably due to steric hinderance.

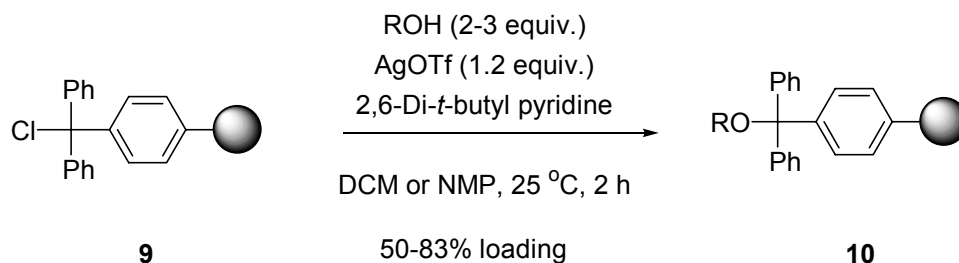
**Table 2**

$\text{R-OH} \xrightarrow{1, 2, \text{ or } 3} \text{R-O} \begin{array}{c} \text{Ph} \\   \\ \text{Ph} \end{array}$		1: pyridine, 100 °C, 1 h 2: DMAP, TEA, DCM, 25 °C, 12 h 3: AgOTf (1.2 equiv.), 2,6-Di- <i>t</i> -butyl pyridine (1.5 equiv.), DCM, 0 °C, 1 h		
Entry	Substrate	Yield (%)		
		1	2	3
a		49	59	56 68 <sup>a</sup>
b		84	-	80
c		82	59	47 81 <sup>b</sup>
d		88	-	76
e		28	-	15 53 <sup>b</sup>
f		9	60	73 <sup>c</sup>
g		57	-	22 63 <sup>c</sup>
h		74	50	73
i		26	50	0 67 <sup>c</sup>
j		14	36	21 68 <sup>b,c</sup>
k		2	0	10 60 <sup>b</sup>
l		60	-	76

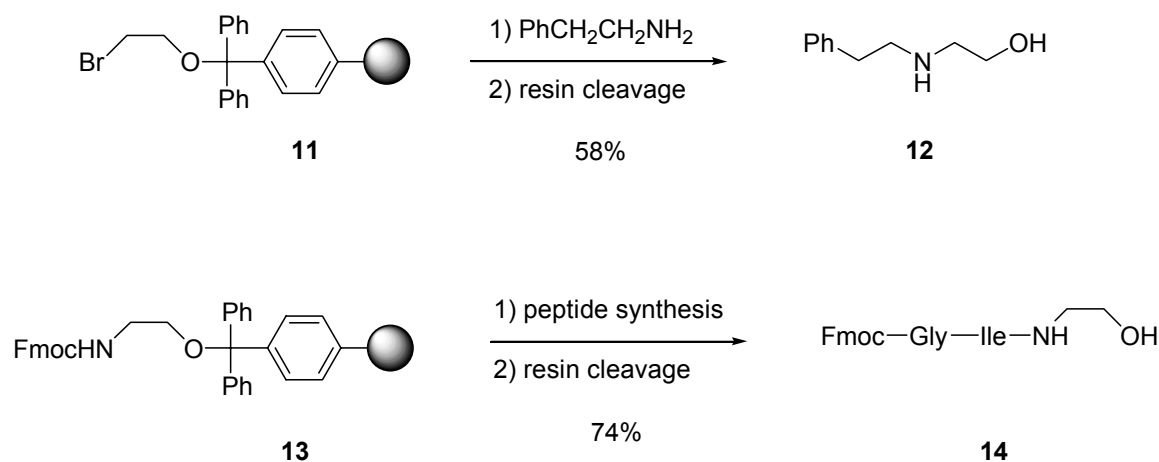
<sup>a</sup> 2 equiv. of alcohol, <sup>b</sup> NMP used in place of DCM, <sup>c</sup> ROH added 5 minutes after addition of AgOTf.

The silver triflate mediated tritylation procedure was also effectively adapted to solid phase. A number of Fmoc protected amino alcohols and halo-containing alcohols were successfully loaded onto trityl resin (Scheme 2) demonstrating the potential utility for synthesis of secondary amino alcohols and C-terminal peptide alcohols (Scheme 3).

### Scheme 2



### Scheme 3



### “Solid/Solution Phase Annulation (SPAN<sup>TM</sup>) Technology: Single-Step Derivatization of Primary Amines to Piperazines on Solid Phase”

*Calum MacLeod, Blanca Martinez-Teipel and Roland E. Dolle,  
 Department of Chemistry, Adolor Corporation.*

Single step amine annulation chemistry was developed to facilitate rapid synthesis of diverse cyclic amine derivatives. Solid phase reagents **17** and **18** (Scheme 4) undergo microwave assisted cyclization with primary amines, followed by resin cleavage to yield piperazines **19** and **20** (Table 3). A Wang resin based reagent (Scheme 4, R = H) was initially investigated but gave piperazine products contaminated with linker containing by-products during acidic cleavage. It was anticipated that reagents designed to have enhanced acid lability, **17** and **18**, would produce fewer cleavage by-products. Gratifyingly, reagent **17** yielded piperazines **19** in good purity without purification, while reagent **18** produced products **20** with some unreacted diol that was easily removed by prep HPLC, but with no linker by-products.

## Scheme 4

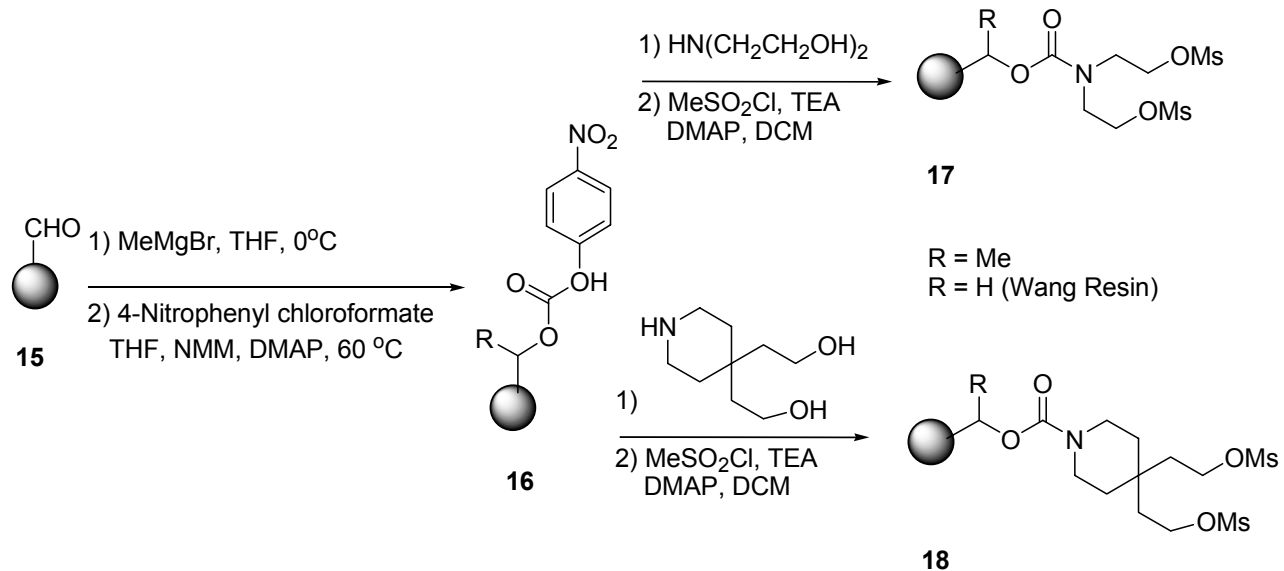
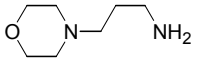
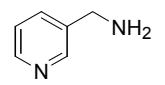
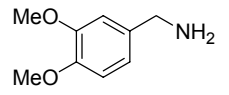
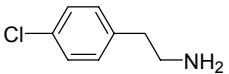
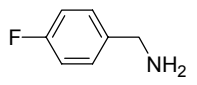
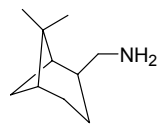
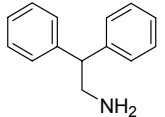
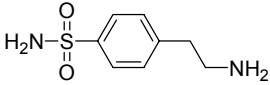
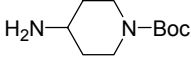
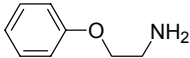
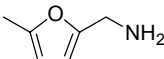
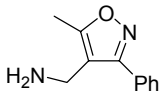
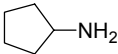
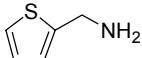
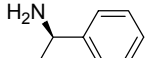
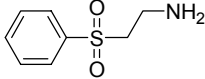
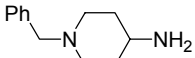
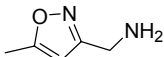
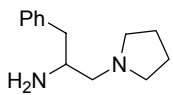


Table 3

<p> <math>\mathbf{17}</math> <math>\xrightarrow[2) \text{ TFA/DCM}]{1) \text{ RNH}_2, \text{ NMP, DIEA, MW } 160 \text{ }^\circ\text{C, } 0.5 \text{ h}}</math> <math>\mathbf{19}</math> </p> <p> <math>\mathbf{18}</math> <math>\xrightarrow[2) \text{ TFA/DCM}]{1) \text{ RNH}_2, \text{ NMP, DIEA, MW } 160 \text{ }^\circ\text{C, } 0.5 \text{ h}}</math> <math>\mathbf{20}</math> </p>		
RNH <sub>2</sub>	Crude <b>19</b> , Area % by ELSD*	HPCL purified <b>20</b> , Area % by ELSD*
	86	97
	90	87
	92	100
	92	100
	90	100
	90	100
	91	100

	95	100
	88	n.a.
	94	99
	98	99
	83	100
	92	100
	91	100
	85	100
	92	100
	92	94
	89	100

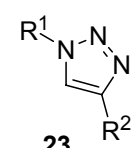
	75	n.a.
* Yields not given.		

### “Cu(I)-catalyzed Proline Promoted One-Pot Reaction of Aryl Halides, NaN<sub>3</sub>, and Terminal Alkynes”

Alina K. Feldman, Benoit Colasson, Valery V. Fokin, and K. Barry Sharpless,  
Department of Chemistry, The Scripps Research Institute.

The Cu(I)-catalyzed reaction of terminal alkynes and organic azides to produce 1,2,3-triazoles benefits from mild reaction conditions, wide scope of substrate, and generally high yields. A high yielding one-pot procedure to aryl triazoles from a variety of aryl halides was presented (Table 4). This method thus eliminates the time-consuming need to isolate the intermediate azides that, in some cases, can be unstable. Note that the greater reactivity of iodides versus bromides allows for the preparation of triazoles ready for further elaboration (Table 4, entry h)

**Table 4**

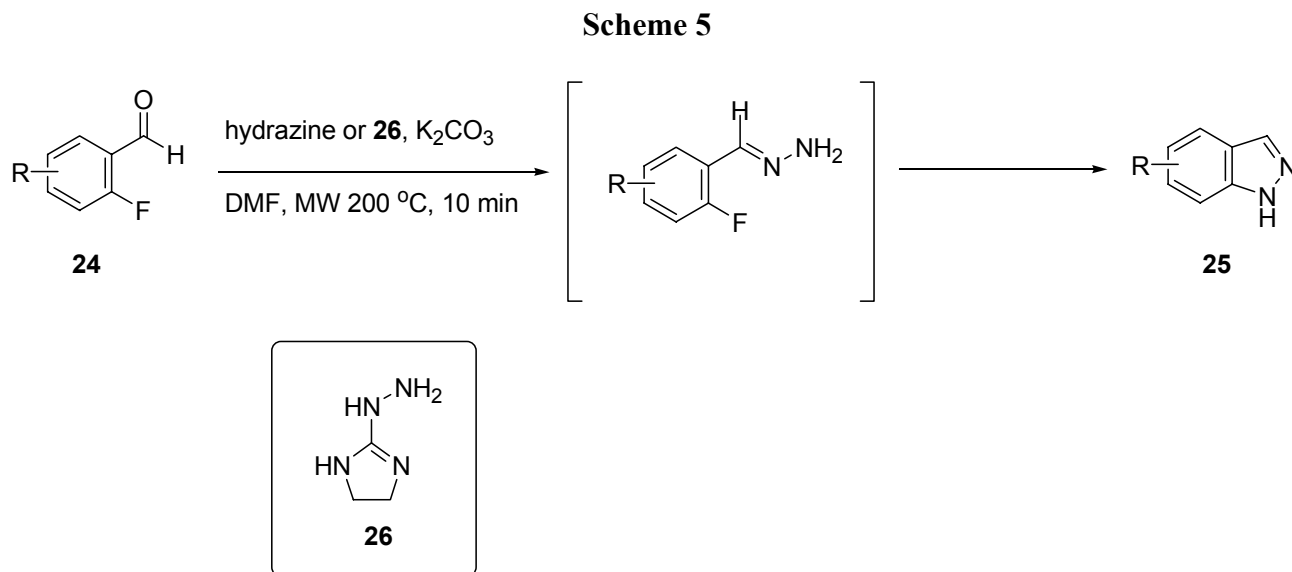
$R^1-I$ + $\equiv R^2$		$\xrightarrow[\text{DMSO:H}_2\text{O 9:1, 60 }^\circ\text{C}]{\begin{array}{l} \text{NaN}_3 \text{ (1.2 equiv.)} \\ \text{CuSO}_4 \cdot 5\text{H}_2\text{O (5-10 mol\%)} \\ \text{Na ascorbate (10-20 mol\%)} \\ \text{L-Pro (20 mol\%)} \\ \text{Na}_2\text{CO}_3 \text{ (20 mol\%)} \end{array}}$	
<b>21</b>	<b>22</b>		<b>23</b>
Entry	R <sup>1</sup>	R <sup>2</sup>	Isolated Yield <b>23</b> (%)
a	Ph	Phenyl	84
b	Ph	1-Cyclohexene	74
c	Ph	CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> OH	98
d	Ph	CH <sub>2</sub> NEt <sub>2</sub>	90
e	Ph	3-H <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	74
f	Ph	CH <sub>2</sub> C(NH <sub>2</sub> )CO <sub>2</sub> H	52
g	3-Pyridyl	CH <sub>2</sub> NEt <sub>2</sub>	94
h	<i>p</i> BrPh	CH <sub>2</sub> NEt <sub>2</sub>	78

Reference: *Organic Letters* **2004**, 22(6), 3897-3899.

### “Microwave-assisted Synthesis of Indazoles”

Anna R. Hazlewood, Yahua Liu, Sabine S. Hadida, Liming Huang, Benjamin J. Petzoldt, Dewey Fanning, Timothy D. Neubert,  
Discovery Chemistry, Vertex Pharmaceuticals,  
Dean M. Wilson. Drug Discovery Vertex Pharmaceuticals.

A one-pot procedure for the rapid synthesis of indazoles utilizing commercially available *o*-fluorobenzaldehydes was presented (Scheme 5). Literature routes to these compounds involve multistep syntheses not well suited for parallel synthesis, while the new route employing microwave heating produced the desired heterocycles in good yields in only 10 minutes.



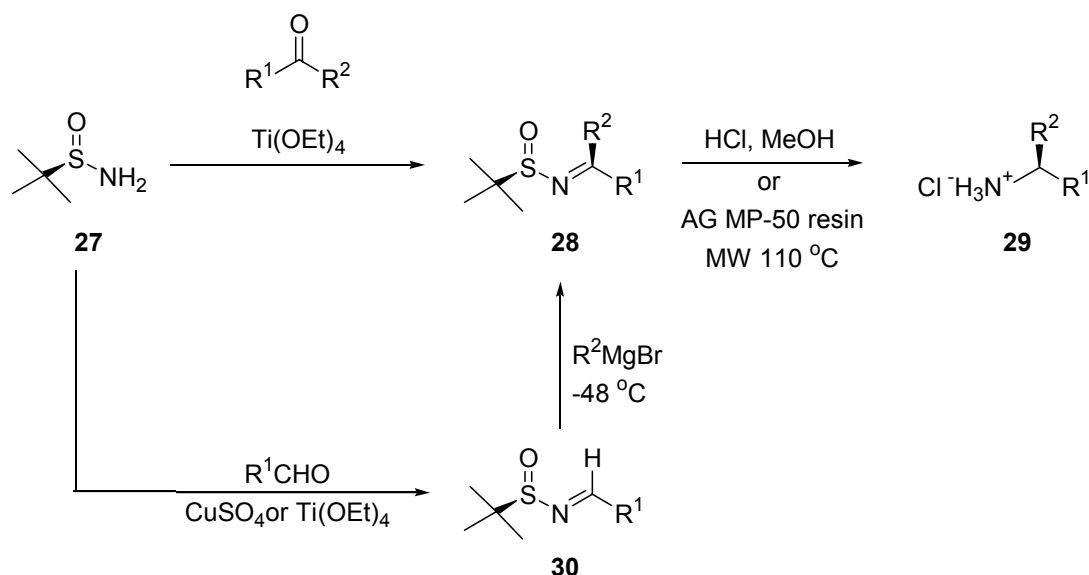
The ring forming intramolecular  $S_NAr$  reaction of the initially formed intermediates favored electronically deficient substrates, although electron-rich substrates gave acceptable results when excess hydrazine was used. However, the use of excess hydrazine in reaction mixture caused very high residual pressure in the sealed microwave vessels. This problem was circumvented by the use of 2-hydrazino-2-imidazoline (**26**) as novel hydrazine surrogate which gave comparable yields with greatly reduced pressures.

### “Microwave-assisted Asymmetric Amine Synthesis and C-H Activation Methods”

*Jonathan A. Ellman, Department of Chemistry,  
University of California at Berkeley.*

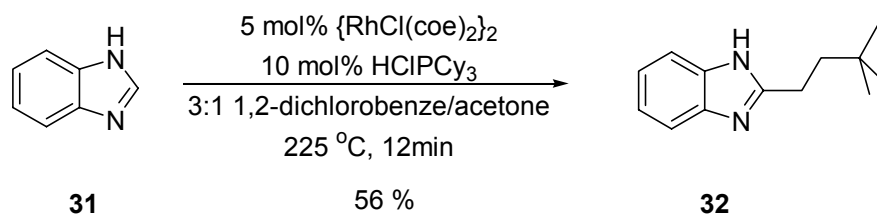
Two recently developed methods for carbon-carbon bond formation and their microwave-enhanced versions were presented. The first method makes use of the readily available enantiomerically pure *tert*-butanesulfinamide (**27**) for the efficient asymmetric synthesis of amines (Scheme 6), and the second method utilizes Rhodium catalyzed C-H bond functionalization to accomplish intra- and intermolecular coupling reactions with unactivated alkenes (Schemes 7, Table 5).

## Scheme 6



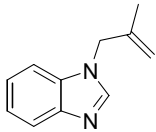
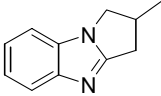
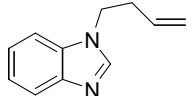
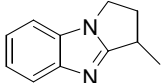
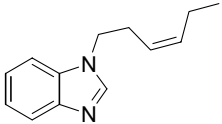
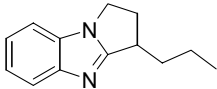
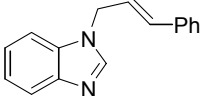
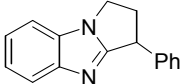
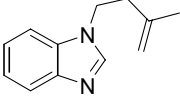
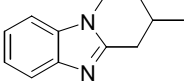
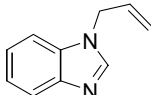
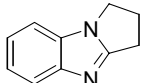
A general parallel method for the asymmetric synthesis of  $\alpha$ -branched amines utilizing microwave heating and resin capture of the final products was developed. Impressively, the final amines (**29**) were obtained in good yields (72-84%) with high enantio (80-97% ee) and chemical purities without chromatography or crystallization. Imine (**30**) formation between (**27**), 1-naphthylaldehyde, and  $\text{Ti(OEt)}_4$  in DCM could be accomplished in only ten minutes at 90-100  $^\circ\text{C}$  in a microwave reactor. Isolation of pure products was possible after treatment with diatomaceous earth and filtration. Addition of Grignard reagents to the imine (**30**) was carried out as usual to give (**28**). Finally, a rapid, efficient cleavage of the sulfinyl group utilizing microwave heating (110  $^\circ\text{C}$ , 10 minutes), AG MP-50 resin, and catalytic ammonium chloride in methanol gave the final amine products.

## Scheme 7



The functionalization of various azole heterocycles with unactivated alkenes had been previously demonstrated. However, the air-sensitivity of the catalyst, high temperatures, and lengthy reactions times required made this method cumbersome to apply. After screening various solvent, catalyst, and additive combinations, a very rapid and operationally simple procedure was obtained (Scheme 7). The method is also applicable to the synthesis of benzimidazole tricycles via pendant alkenes (Table 5).

## Table 5

Substrate	Product	Yield (%)
		64
		55
		64
		42
		59
		59

References: *Journal of Combinatorial Chemistry* **2003**, 5, 590-596; *Organic Letters* **2003**, 5(12), 2131-2134.