



**Trip Report for**  
**“The 35<sup>th</sup> Northeast Regional Meeting**  
**of the American Chemical Society (NERM)”**  
**Burlington, VT**  
**June 29-July 2, 2008**

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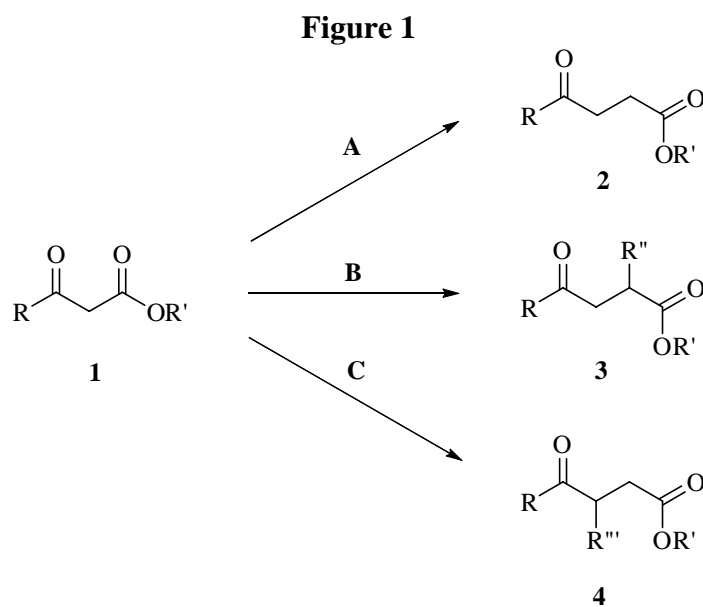
**Abstract:** *The 35<sup>th</sup> Northeast Regional Meeting of the American Chemical Society (NERM 2008) was held in Burlington, Vermont from June 29, 2008 through July 2, 2008. This report contains a sampling of summaries of oral and poster presentations given during the meeting.*

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## “Zinc carbenoid-mediated chain extension: formation of peptide isosteres”

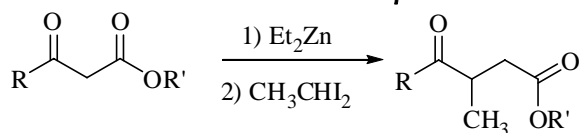
Charles K. Zercher, University of New Hampshire, Durham, NH

In this presentation, Professor Charles Zercher reported on the incorporation of a methylene functionality into the alpha position of  $\beta$ -keto esters **1** and  $\beta$ -keto amides by treatment with zinc carbenoids derived from 1,1-diiodoethane. The addition of phenyl groups at the alpha position has also successfully been achieved through treatment of substrates **1** with diiodotoluene (W. Lin, *et al.*, *Synthesis*, **2007**, *15*, 2404). Chain extension reaction of  $\beta$ -keto esters to  $\gamma$ -keto esters *via* donor-acceptor cyclopropanes has been reported by Reissig and workers (H. Reissig, *et al.*, *Top Curr. Chem.* **1988**, *144*, 73). The proposed mechanism suggests that after fragmenting of an intermediate cyclopropane, an organometallic intermediate exists which is quenched with a proton to provide compound **2**, in which a  $\text{CH}_2$  unit is effectively inserted between the carbonyl moieties (Route A, Figure 1).



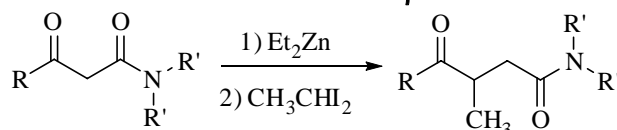
Others have trapped this intermediate with various electrophiles to give hydroxyl alkyl substituents, methyl groups and iodomethyl groups at the alpha position (Route B, Figure 1) to give compounds like **3**. Similarly, Zercher and coworkers have developed a one-pot zinc-mediated chain extension to convert  $\beta$ -keto esters into  $\gamma$ -keto esters with substitutions at the beta position (Route C, Figure 1) to give a variety of compounds **4**.

In the procedure described by Professor Zercher, diiodoethane and diiodotoluene were prepared in house from readily available reagents, and were used to prepare various  $\beta$ -substituted  $\gamma$ -keto esters **6a-f** in generally good yields (Table 1). The best reaction conditions involved pre-formation of the zinc enolate of substrates **5** followed by diiodoalkane addition. In an alternative protocol, the carbenoid was generated before adding the  $\beta$ -keto ester **5**, which commonly gave incomplete conversion of the starting material, but was readily pushed to completion by addition of a second equivalent of carbenoid.

**Table 1. Chain extensions of  $\beta$ -keto esters 5.**

	5a-f		6a-f	
Entry	R	R'	Product	Yield (%)
1	CH <sub>3</sub>	CH <sub>3</sub>	<b>6a</b>	76
2	CH <sub>3</sub>	<i>t</i> -Bu	<b>6b</b>	88
3	CH <sub>3</sub>	CH <sub>2</sub> CH=CH <sub>2</sub>	<b>6c</b>	74
4	CH <sub>3</sub>	Bn	<b>6d</b>	80
5	<i>t</i> -Bu	CH <sub>3</sub>	<b>6e</b>	82
6	Ph	CH <sub>2</sub> CH <sub>3</sub>	<b>6f</b>	84

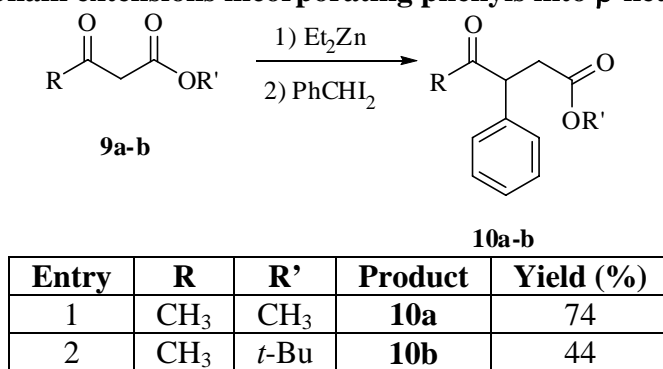
The same synthetic transformation was carried out on  $\beta$ -keto amides **7a-c** to give their corresponding  $\beta$ -substituted  $\gamma$ -keto amide products **8a-c** (Table 2.) The initial investigation used diiodomethane to chain-extend  $\beta$ -keto amides to  $\gamma$ -keto amides and this showed no difference in reactivity between the  $\beta$ -keto amides and the  $\beta$ -keto esters. However, when treated with diiodoethane to form the  $\beta$ -methyl compounds **8a-c**, the reaction rates slowed significantly. Less hindered substituents were well tolerated (entries 1-2, Table 2), however, increasing the steric bulk of substituents (entry 3, Table 2) hindered the formation of the initial carbon-carbon bond, allowing the decomposition of diiodoethane to become competitive with the desired reaction. All previous chain extension reactions (Table 1) were fast enough to negate the effects of the decomposition of diiodoethane on the overall reaction progress.

**Table 2. Chain extensions of  $\beta$ -keto amides 7.**

	7a-c		8a-c	
Entry	R	R'	Product	Yield (%)
1	CH <sub>3</sub>	CH <sub>3</sub>	<b>8a</b>	67
2	CH <sub>3</sub>	-(CH <sub>2</sub> ) <sub>4</sub> -	<b>8b</b>	74
3	<i>i</i> -Pr	CH <sub>3</sub>	<b>8c</b>	Incomplete conversion

Treatment of  $\beta$ -keto esters **9a-b** with diiodotoluene gave substituted  $\gamma$ -keto esters **10a-b** as shown in Table 3. Attempts were made to chain extend a  $\beta$ -keto amide substrate with the incorporation of a phenyl, but only resulted in the recovery of starting material.

**Table 3. Chain extensions incorporating phenyls into  $\beta$ -keto esters 9.**



Based on the results of this study, Professor Zercher's group has further investigated the ability to control the stereochemistry at the  $\beta$ -position, and tandem reactions involving the organometallic intermediate. The group has converted a variety of amino acid substrates to ketomethylene peptide isosteres and has also used this method to generate a mimic of the human CMV protease cleavage site. Further investigations are underway.

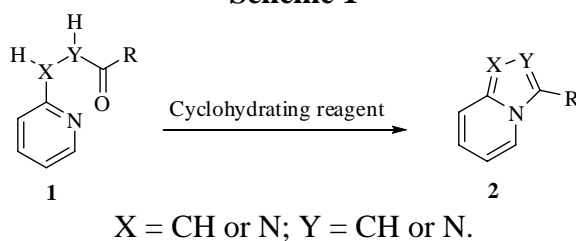
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**“A synthesis of *N*-bridged 5,6-bicyclic pyridines *via* a mild cyclodehydration using the Burgess reagent and discovery of a novel carbamylsulfonylation reaction”**

*Ashok K. Trehan, Bristol Myers Squibb Co., Wallingford, CT*

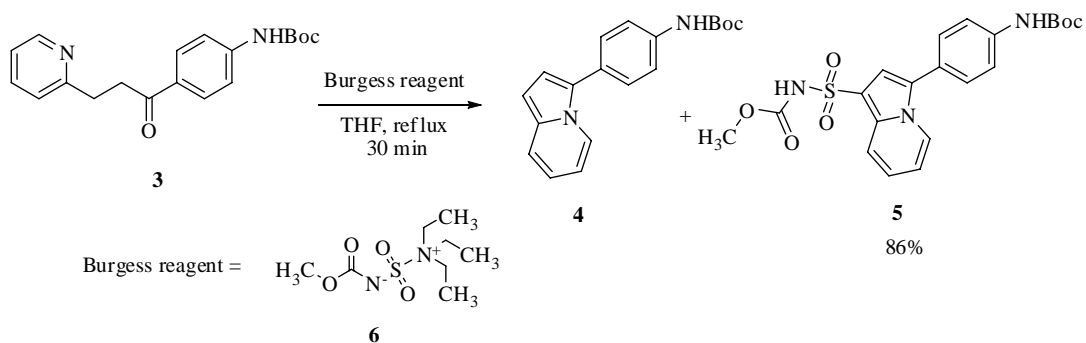
Ashok Trehan presented work on cyclohydration reactions under mild and neutral conditions using the Burgess reagent to give novel results in the synthesis of 5,6-bicyclic pyridines. These conditions were tolerant of acid sensitive functional groups. Previous work in this area to make bicyclic heterocycles (Scheme 1) involved the use of toxic, strongly acidic and/or corrosive reagents like POCl<sub>3</sub>, SOCl<sub>2</sub>, Ph<sub>3</sub>PCl<sub>2</sub> and P<sub>2</sub>O<sub>5</sub>. Recently, cyclohydrations using Lawesson's reagent and modified Mitsunobu conditions have been reported to prepare triazolopyridines and triazolopyrimidines (J.-J. Li, *et al.*, *Org. Lett.* **2008**, 10, 2897).

**Scheme 1**



Also observed in this study was the incorporation of a sulfonyl carbamate adduct acquired from the Burgess reagent to give a novel addition product **5** from the conditions required for the cyclohydration of **3**, where **4** was the expected product **4** (Scheme 2).

### Scheme 2



Various substrates were chosen to prepare pyrolopyridine, imidazopyridine and triazolopyridine products using the Burgess reagent method, and the results are shown in Table 4. Notable in this are entries 2-4 which show the retention of the sensitive Boc and OTBDPS protecting groups.

**Table 4. Cyclohydrations of various substrates using the Burgess reagent.**

Entry	Substrate	Product	Yield
1			75%
2			80%
3			57%
4			63%
5			54%

The unexpected results of this study are the novel sulfonyl carbamate adduct compounds shown in Table 5. The cyclohydration products were reactive enough to undergo an electrophilic substitution with the Burgess reagent. Attempts were made to stop the reaction at the cyclohydration product, but it seems the adduct formation was much faster than the cyclohydration and none of the non-substituted products from Table 5 were isolated. Also

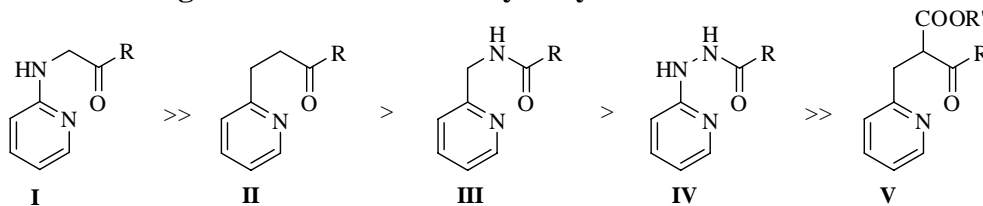
noteworthy is the inactivity of entry 5, in which no cyclohydration product was observed after 2 days at reflux. It is presumed that the electronic effects of the ester and the steric hindrance of the substrate led to the lack of reactivity.

**Table 5. Unexpected sulfonyl carbamate adducts.**

Entry	Substrate	Product	Yield
1			86%
2			67%
3			64%
4			56%
5		N/A	N/A

Based on these results, the reactivities of various substrates to give the pyrolopyridine, imidazopyridine and triazolopyridine cyclohydration products can be ranked as shown in Figure 2.

**Figure 2. Reactivities of cyclohydration substrates.**

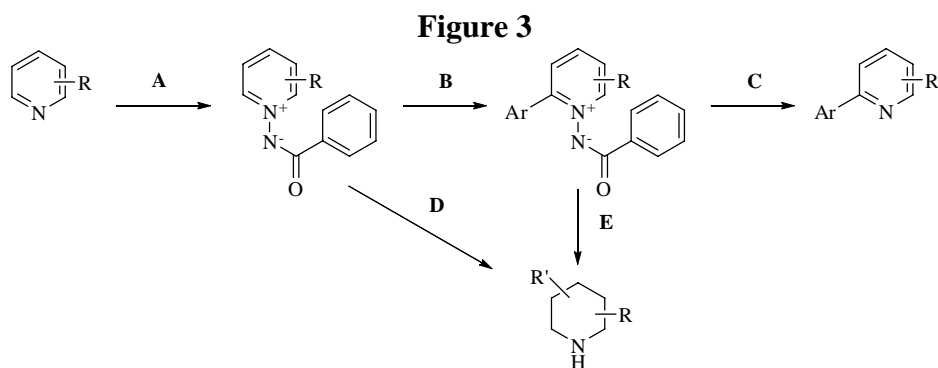


A mechanism has been proposed for the transformation of the cyclohydrations using the Burgess reagent, and the scope and limitations of this novel reaction are still under investigation.

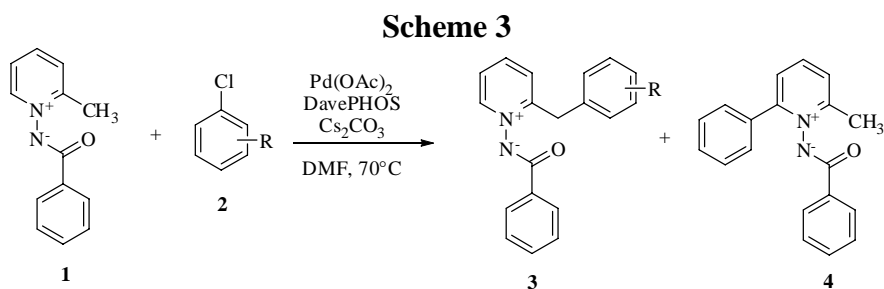
## “Palladium-catalyzed C-H insertion of *N*-iminopyridinium ylides”

James J. Mousseau, Université de Montréal, Montreal, QC, Canada

James Mosseau presented work on direct arylation of  $sp^3$  carbon atoms on methyl pyridine derivatives as an alternative to conventional cross-coupling methods. This method has very little precedent in the literature and is a greener alternative to the environmentally harmful organometallic reagents used in cross-couplings. Pyridine derivatives are of great interest to the medicinal chemistry community and synthetic organic chemists on the whole. Pyridines are readily converted to the pyridinium ylide *via* amination of pyridine (Route A, Figure 3), and then subjected to various reaction conditions including direct arylation (Route B, Figure 3), Grignard reagent addition and hydrogenation (Routes C-E, Figure 3) to give multi-substituted pyridine and piperidine products.

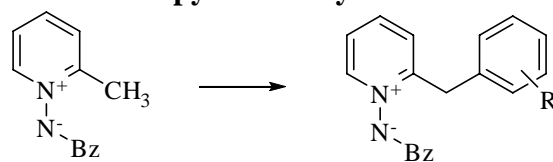


While working on the direct arylation of pyridinium ylides **1** it was discovered that a methyl group at the 2-position lead to very poor yields of expected products **4**, and instead gave **3** as the major product in an almost 3:1 ratio (Scheme 3). Upon optimization of the solvent, temperature and phosphine ligands, the products **4** derived from functionalization of the  $sp^2$  center was not observed by NMR, and products similar to compound **3** were isolated in good to excellent yield (J. Mousseau, *et al.*, *Org. Lett.* **2008**, *10*, 1641).



The scope of reactivity with ylide **1** is shown in Table 6. Aryl chlorides were found to be the best substrates, though aryl bromides and aryl iodides were investigated. Reactions with both electron poor (entries 6-11) and electron rich aryl chlorides (entries 2-5) were achievable under these conditions. Poorer yields are attributed to unreacted starting material rather than undesired products.

**Table 6. Arylation of *N*-iminopyridinium ylide 1 with various aryl chlorides.**



Entry	Ar-Cl	Ar Product	Yield*	Entry	Ar-Cl	Product	Yield*
1	PhCl	Ph	86%	7	1-Cl-4-CO <sub>2</sub> CH <sub>3</sub> -Ph	4-CO <sub>2</sub> CH <sub>3</sub> -Ph	72%
2	1-Cl-2-CH <sub>3</sub> -Ph	2-CH <sub>3</sub> -Ph	93%	8	1-Cl-4-COPh-Ph	4-COPh-Ph	71%
3	1-Cl-3-CH <sub>3</sub> -Ph	3-CH <sub>3</sub> -Ph	76%	9	1-Cl-4-F-Ph	4-F-Ph	94%
4	1-Cl-4-CH <sub>3</sub> -Ph	4-CH <sub>3</sub> -Ph	72%	10	1-Cl-4-NHBoc-Ph	4-NHBoc-Ph	48%
5	1-Cl-4-OCH <sub>3</sub> -Ph	4-OCH <sub>3</sub> -Ph	69%	11	1-Cl-4-CF <sub>3</sub> -Ph	4-CF <sub>3</sub> -Ph	64%
6	1-Cl-2-CO <sub>2</sub> CH <sub>3</sub> -Ph	2-CO <sub>2</sub> CH <sub>3</sub> -Ph	43%				

\*Reaction conditions: 1.1 equivalents ylide, 1.0 equivalents aryl chloride, 5 mol % Pd(OAc)<sub>2</sub>, 12 mol % DavePHOS, 3 equivalents Cs<sub>2</sub>CO<sub>3</sub>, DMF (0.8 M), 70 °C, 16 h. Yields are of isolated products.

Next the team studied the effect of the ylide on the overall reactivity as shown in Table 7. The high yield of entry 2 was unexpected because though electronically equivalent to the yield used in entry 1, it was expected that the extra steric encumbrance in entry 2 would give a poorer yield. Also, entries 3-6 led the researchers to believe that the arylation at the sp<sup>3</sup> center was not limited to only methyl groups, and further functionality could be introduced.

**Table 7.**

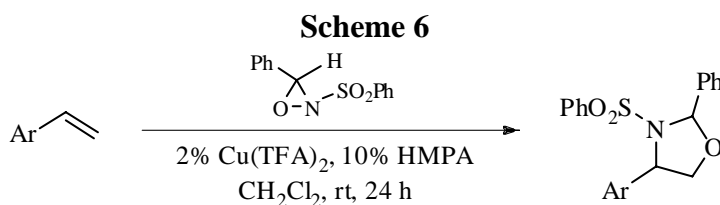
Entry	Ylide	Aryl Chloride	Product	Yield**
1		PhCl		43%
2		PhCl		92%
3		PhCl		86%
4		2-Cl-4-OCH <sub>3</sub> -Ph		79%
5		2-Cl-4-CO <sub>2</sub> CH <sub>3</sub> -Ph		53%
6		2-Cl-4-CF <sub>3</sub> -Ph		69%

\*\* Reaction conditions: 1.1 equivalents ylide, 1.0 equivalents aryl chloride, 5 mol % Pd(OAc)<sub>2</sub>, 12 mol % DavePHOS, 3 equivalents Cs<sub>2</sub>CO<sub>3</sub>, DMF (0.8 M), 70 °C, 16 h. Yields are of isolated products.

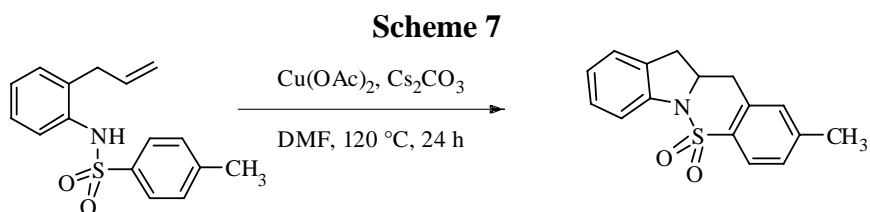


1207). For this reason, alternative catalysts for the method are still actively being explored. Furthermore, an intramolecular variant has yet to be reported.

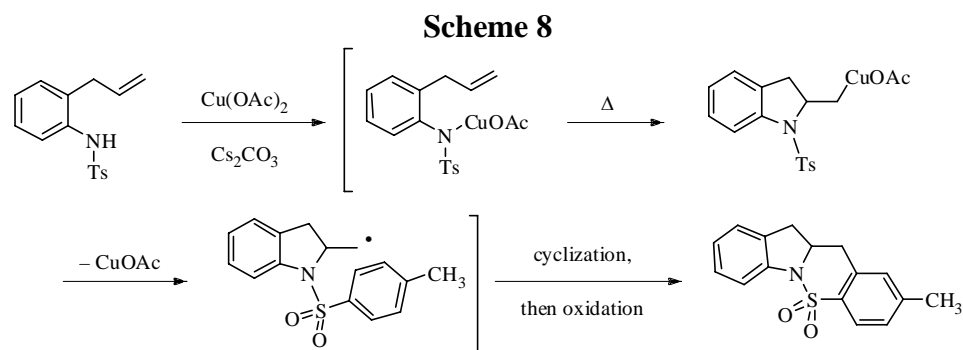
Recently research from the Chemler group has been reported in which a catalytic asymmetric intramolecular variant of the aminohydroxylation reaction was achieved using a copper(II) catalyst. This was followed by a similar report in 2007 by the Yoon research group (Michaelis, D. J.; Shaffer, C. J.; Yoon, T. P. *J. Am. Chem. Soc.* **2007**, 129, 1866), in which a copper (II) catalyzed aminohydroxylation of olefins was reported (Scheme 6).



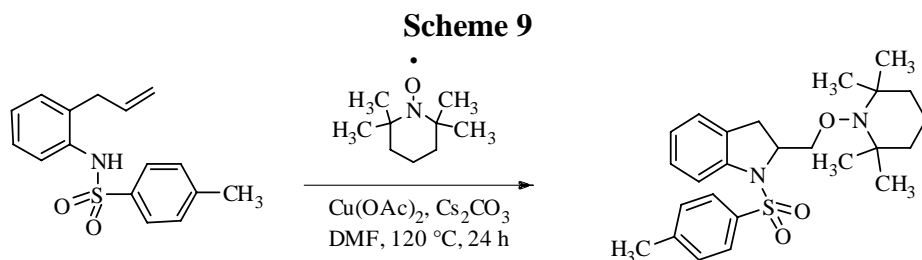
Previous work from Chemler and coworkers has successfully demonstrated an oxidative cyclization of arylsulfonyl-*o*-allylanilines using copper(II) acetate as the catalyst, as well as a copper(II)-catalyzed diamination reaction of unactivated olefins (see: (a) Sherman, E. S.; Chemler, S. R.; Tan, T. B.; Gerlits, O. *Org. Lett.* **2004**, 6, 1573. (b) Zabawa, T. P.; Kasi, D.; Chemler, S. R. *J. Am. Chem. Soc.* **2005**, 127, 11250). More recently the Chemler group reported the first copper(II) catalyzed intramolecular carboamination of olefins, which constituted a net addition of a nitrogen and a carbon across an alkene as shown in Scheme 7 (Sherman, E. S.; Fuller, P. H.; Kasi, D.; Chemler, S. R. *J. Org. Chem.* **2007**, 72, 3896. Whitesides, G. M.; Newirth, T. L. *J. Org. Chem.* **1975**, 40, 3448. Ganong, C.; Kiessling, A. J. *Abstract the 38<sup>th</sup> Middle Atlantic Regional Meeting*, June 4-7, **2006**).



This new chemistry was used to prepare a number of pyrrolidines and piperidines in good yields and with high enantioselectivities. A variety of 4- and 5-substituted allyl aniline derivatives and 4-pentenylamines were cyclized in 61-97% yields with ee's from 78-92%. Furthermore, evidence supports a mechanism where the N-C bond is formed by an intramolecular *syn* aminocupuration and the C-C bond is formed by an intramolecular addition of a primary carbon radical (Scheme 8).



When the same type of reactions were performed in the presence of the TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) radical, a known radical trapping agent, it was observed that TEMPO reacted faster than the formation of the intramolecular C–C bond (Scheme 9).



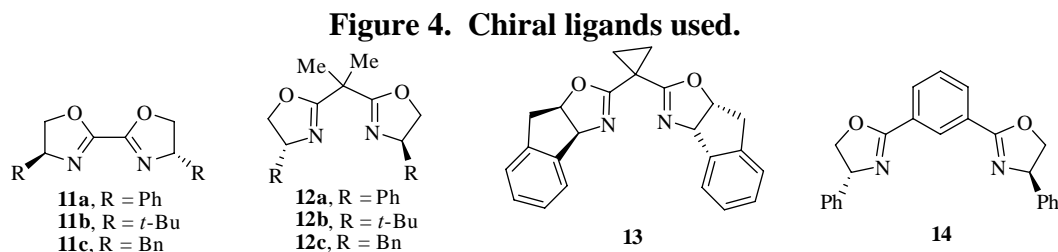
Initially, a number of oxidants ( $O_2$ ,  $PhI(OAc)_2$ , oxone,  $Me_3NO$ ,  $MnO_2$ ) were screened for copper turnover, with and without ligands in different solvents for the conversion of **1a** to **2a**. The highest conversions were obtained with  $MnO_2$  (3 equiv) as the oxidant in trifluorotoluene in the presence of ligands (Table 8). The use of 2,2'-bipyridine (**10**) as ligand (0.2 equiv) gave a better conversion versus *N,N*-diethyl-2-hydroxybenzamide (**9**) as a ligand when  $Cu(OTf)_2$  was used (Table 8; compare entries 6 to 8).

**Table 8. Dependence on solvent and ligand.**

Entry	R	Solvent	Ligand (equiv)	Yield of <b>2</b> (%)	Yield of <b>8</b> (%)
1	EH	PhCH <sub>3</sub>	--	< 5	Trace
2	EH	PhCF <sub>3</sub>	--	7	Trace
3	EH	PhCH <sub>3</sub>	<b>9</b> (0.2)	41	7
4	EH	PhCH <sub>3</sub>	<b>9</b> (0.8)	63	17
5	EH	PhCF <sub>3</sub>	<b>9</b> (0.8)	75	< 5
6	OTf	PhCF <sub>3</sub>	<b>9</b> (0.8)	29	12
7	OTf	PhCH <sub>3</sub>	<b>10</b> (0.2)	59	< 5
8	OTf	PhCF <sub>3</sub>	<b>10</b> (0.2)	60	< 5

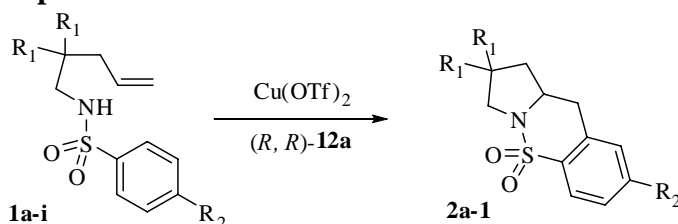
EH = 2-ethylhexanoate

Chiral ligands **11–14** (Figure 4) were screened and it was found that 2,2-bis[(4*R*)-4-phenyl-2-oxazolin-2-yl]propane (**12a**) gave the highest asymmetric induction, providing carboamination adduct **2a** in 85% isolated yield and in 92% ee.



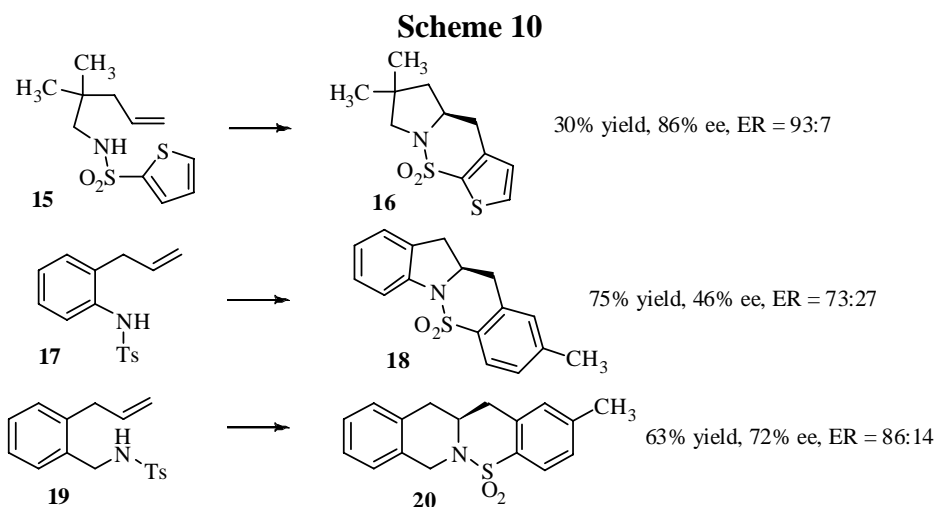
The generality of the reaction was examined as shown in Table 9.  $\gamma$ -Alkenyl arylsulfonamides **1** cyclized in 45–85% yield and 80–94% ee

**Table 9. Scope of the enantioselective carboamination with (*R,R*)-**12a**.**



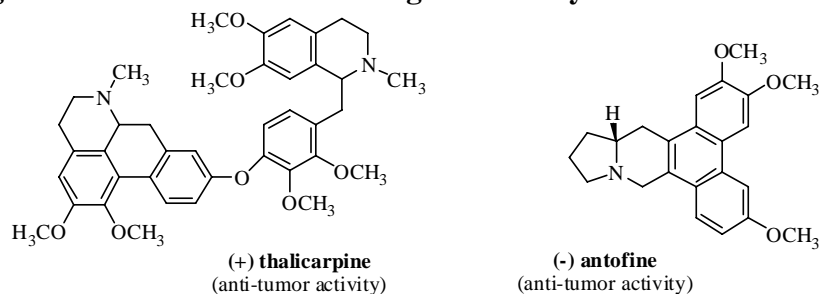
Entry	Substrate	Product	Yield	ee	ER
1	<b>1a</b> , R <sup>1</sup> = Me, R <sup>2</sup> = Me	<b>2a</b>	85%	92%	96:4
2	<b>1b</b> , R <sup>1</sup> = Me, R <sup>2</sup> = Me	<b>2b</b>	73%	92%	96:4
3	<b>1c</b> , R <sup>1</sup> = Me, R <sup>2</sup> = Me	<b>2c</b>	45%	92%	96:4
4	<b>1d</b> , R <sup>1</sup> = Me, R <sup>2</sup> = Me	<b>2d</b>	75%	94%	97:3
5	<b>1e</b> , R <sup>1</sup> = Me, R <sup>2</sup> = Me	<b>2e</b>	78%	94%	97:3
6	<b>1f</b> , R <sup>1</sup> = Me, R <sup>2</sup> = Me	<b>2f</b>	83%	92%	96:4
7	<b>1g</b> , R <sup>1</sup> = Me, R <sup>2</sup> = Me	<b>2g</b>	68%	92%	96:4
8	<b>1h</b> , R <sup>1</sup> = Me, R <sup>2</sup> = Me	<b>2h</b>	68%	80%	90:10
9	<b>1i</b> , R <sup>1</sup> = Me, R <sup>2</sup> = Me	<b>2i</b>	77%	82%	91:9

The 2-sulfamido thiophene substrate **15** reacted very sluggishly but with good enantioselectivity (Scheme 10). *N*-Tosyl-2-allylaniline **17** reacted efficiently, but with low (46%) enantioselectivity, and *N*-tosyl-2-allylbenzylamine **19** reacted sluggishly, and in moderate yield and enantioselectivity, to provide tetrahydroisoquinoline **20** (entry 12).



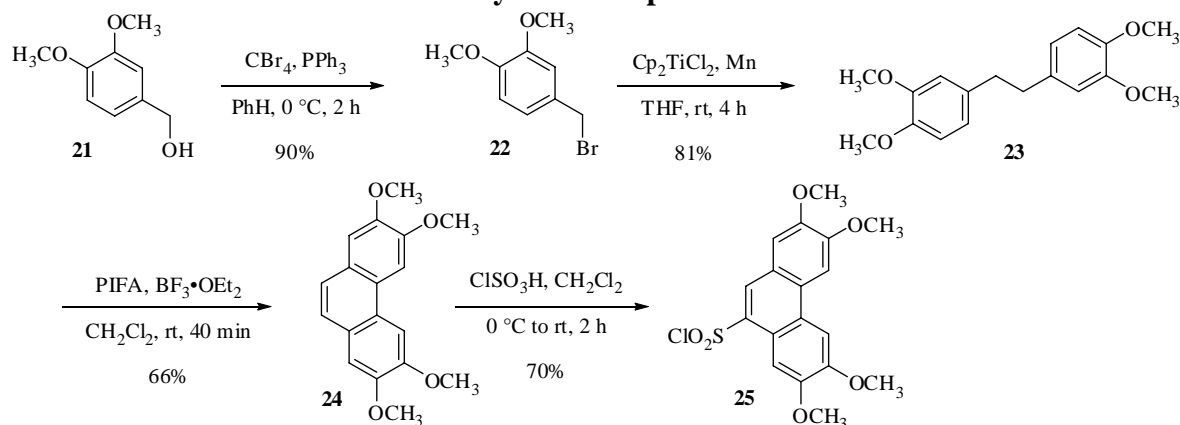
Nitrogen-containing heterocycles are prevalent in many biologically active small organic molecules and natural products. These heterocycles are often good leads into the discovery and development of small molecule drugs. The chemistry developed by Chemler and coworkers allows for the installation of two rings in a single step to prepare nitrogen heterocycles, specifically with pyrrolidine or piperidine moieties. The method can be advantageous for the preparation of a number of biologically active natural products, some of which are currently being pursued by Chemler group members (Figure 5).

**Figure 5. Natural Products Being Pursued by the Chemler Group.**



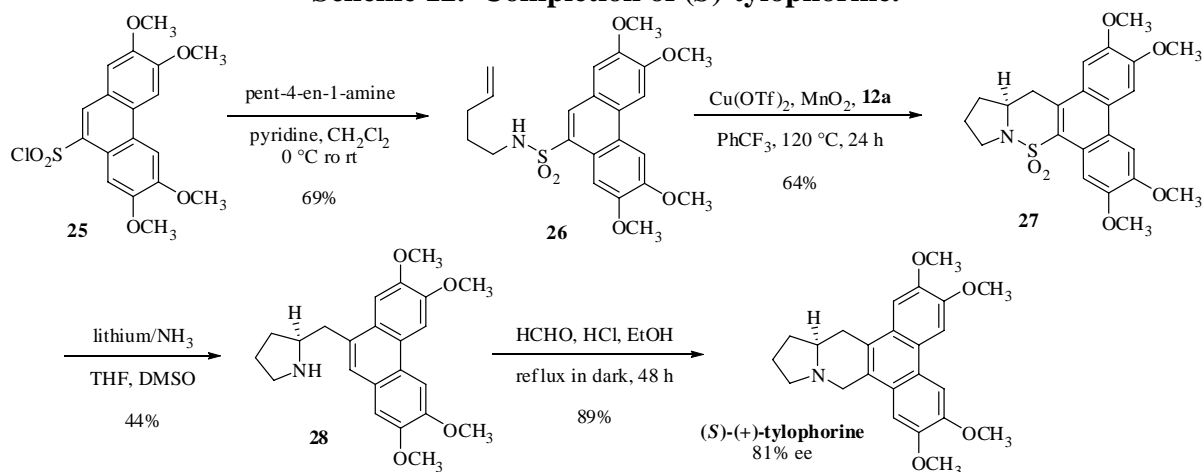
The method has been successfully applied to the synthesis of the biologically active natural product (*S*)-(+)-tylophorine. Since the isolation of (*R*)-tylophorine, in 1935 from *Tylophora indica*, over 60 compounds in this class have been isolated from the *Asclepiadaceae* and *Moraceae* plant families, found primarily in India and Japan. The biological properties of these alkaloids range from cancer cell growth inhibition (*in vitro* and *in vivo*) and anti-inflammatory activity to antiameobicidal and anti-viral activity. Although (*S*)-tylophorine is the unnatural enantiomer, it is a more potent inhibitor of cancer cell growth than (*R*)-tylophorine. The presentation outlined the synthesis of this compound utilizing this method. The synthesis started from commercially available compound **21**, which was converted to sulfonyl chloride compound **25** in four steps (Scheme 11).

### Scheme 11. Synthesis of phenanthrene 25.



Coupling of 3-pentenyl amine with arylsulfonyl chloride **25** provided the key intermediate sulfonamide **26** (Scheme 12) for the asymmetric carboamination. The obtained sultam **27** was converted to compound **28** under dissolving metal conditions. The final product **7** was realized by Pictet-Spengler reaction with formaldehyde to close the indolizidine ring.

### Scheme 12. Completion of (*S*)-tylophorine.



In summary, a novel asymmetric carboamination reaction was described. Different catalysts, solvents, chiral ligands and oxidants were screened. The method was successfully applied to the synthesis of the biologically active natural product (*S*)-(+)-tylophorine.

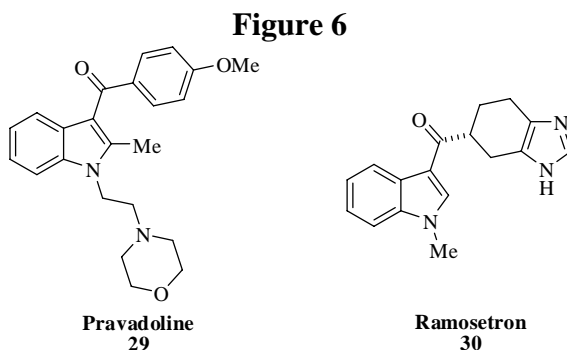
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### “Friedel-Crafts acylation of indoles and azaindoles in acidic imidazolium chloroaluminate ionic liquid at room temperature”

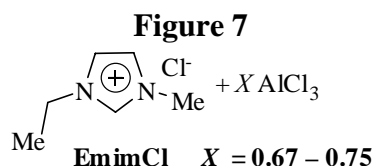
*K.-S. Yeung, M. E. Farkas, Z. Qiu, Z. Yang, Q. Xue, J. A. Bender, A. Regueiro-Ren, A. Good and J. F. Fadow, Bristol-Myers Squibb, Wallingford, CT*

The presentation outlined a practical and convenient protocol for the acidic 1-ethyl-3-methylimidazolium chloroaluminate ionic liquid-promoted Friedel-Crafts acylation of indoles and azaindoles at room temperature. Substituted indoles are drug fragments

commonly found in molecules of pharmaceutical interest in a variety of therapeutic areas. Examples include the analgesic pravodoline (**29**) and the antiemetic ramosetron (**30**) shown in Figure 6.

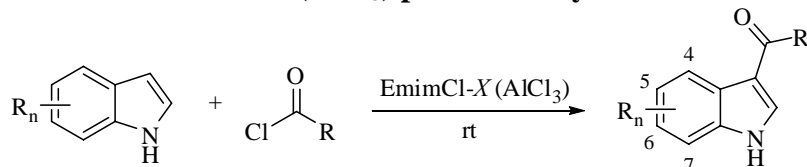


This group developed a practical and convenient method for acidic 1-ethyl-3-methylimidazolium chloroaluminate ionic liquid EmimCl-X( $\text{AlCl}_3$ ) and demonstrated its application in Friedel-Crafts acylation of indoles and azaindoles at room temperature. The ionic liquid was generated from 1-ethyl-3-methylimidazolium chloride (EmimCl) and aluminium chloride ( $\text{X}(\text{AlCl}_3)$ ) with mole fraction  $X = 0.67\text{-}0.75$  (Figure 7).



Representative examples of the acidic imidazolium chloroaluminate-promoted acylation reactions of substituted *N*-unprotected indoles with acid chlorides were explored. Good to high yields were obtained and no side products of over-acylation were observed as shown in Table 10. Useful and diverse functional groups (*e.g.*  $\text{R}_n = \text{halogens}$ , CN and  $\text{NO}_2$ ,  $\text{R} = \text{CH}_3$ , aryl,  $\text{CO}_2\text{H}$  and furan) were well-tolerated under these strongly acidic conditions.

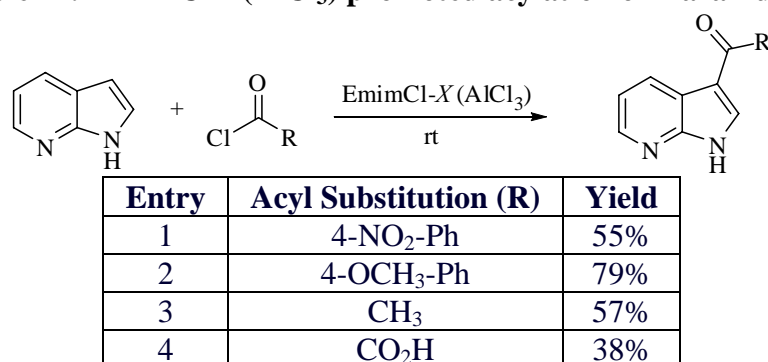
**Table 10. EmimCl-X( $\text{AlCl}_3$ ) promoted acylation of indoles.**



Entry	Aryl Substitution ( $\text{R}_n$ )	Acyl Substitution ( $\text{R}$ )	Yield
1	4- $\text{NO}_2$	$\text{CH}_3$	87%
2	4-Cl	Ph	71%
3	5-CN	3- $\text{OCH}_3$ -Ph	78%
4	5-CN	2-furanyl	75%
5	6-F	4- $\text{NO}_2$ -Ph	66%
6	6-F	4- $\text{NO}_2$ -Ph	59%

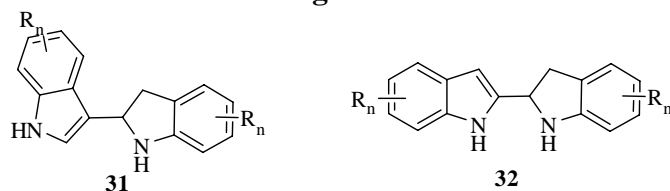
Moderate to good yields were also obtained for the acidic imidazolium chloroaluminate-promoted acylation reactions of substituted *N*-unprotected 7-azaindoles with acid chlorides (Table 11). Some of the highlights of this study as asserted by Yeung are that, entries 2 in Table 10 and 2 in Table 11 were yet to be published in any literature to their knowledge. In addition these conditions offer advantages over existing methods. For example, 3-acetyl-4-nitroindole (Table 10, entry 1), a useful intermediate of indole alkaloid natural product (M. Murase, *et al.*, *Chem. Pharm. Bull.* **1987**, 35, 2656) was previously synthesized only by a non-regioselective nitration of 3-acetylindole in poor yields (2-20%). As shown in Table 11 entry 3, this method avoids the use of poisonous CS<sub>2</sub> and excessive AlCl<sub>3</sub> used in the reported synthesis of 3-acetyl-7-azaindole (C. Galvez and P. Viladoms, *J. Heterocyclic Chem.* **1982**, 19, 665). In addition this procedure circumvents an aqueous workup for the very polar glyoxylic acid derivative (Table 11, entry 4) by using ethyl chlorooxoacetate as the acylating agent and directly isolating the acid from the reaction mixture by precipitation. In practice this can be useful if the subsequent ester hydrolysis is required for synthesis.

**Table 11. EmimCl-X(AlCl<sub>3</sub>) promoted acylation of 7-azaindoles.**



For reactions of less-reactive acid chlorides, *e.g.* pivaloyl chloride or electron-rich indoles, Mannich-type indole dimerization was the predominant reaction pathway that gave rise to a mixture of the dimeric isomers **31** and **32** in varying ratios (Figure 8).

**Figure 8**



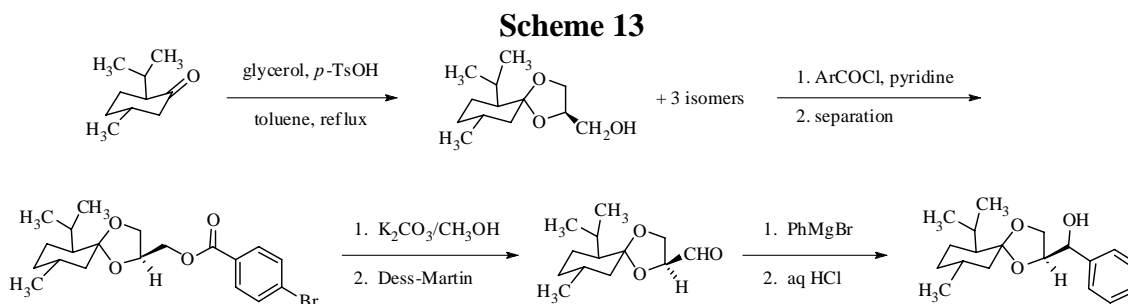
In summary, a practical and convenient protocol has been developed for the Friedel-Crafts type acylation of the C-3 position of indoles that is promoted by acidic imidazolium chloroaluminate ionic liquid at room temperature. This reaction appears to be general for less electron-rich indole ring systems. It can tolerate various functionalities (*e.g.* halogens, CN, NO<sub>2</sub>, anisole, aryl, CO<sub>2</sub>H and furan), which can lead to unlimited chemical diversity. For additional information see the published research: K. S. Yeung, *et al.*, *Tetrahedron Lett.* **2002**, 43, 5793.

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## “Preparation of derivatives of an isomer of glycerol menthonide”

*Amber McCloskey and Anthony J. Kiessling, Mansfield University, Mansfield, PA*

Glycerol menthonide was originally prepared as an additive to spearmint gum by the chemists at Wrigley’s Inc. The reaction to prepare glycerol menthonide involves the treatment of menthone and glycerol refluxed in toluene with *p*-toluenesulfonic acid (Scheme 13). However, this reaction can yield a total of six possible isomers when considering the ketal formed in the reaction can either be a 5- or a 6-membered ring, and each can exist as a set of stereoisomers. Kiessling and McCloskey have prepared glycerol menthonide using these reaction conditions, but have shown the product mixture to be a mixture of only four isomers in nearly equal portions. Although the mixture of isomers was inseparable by most methods, conversion of all components of the mixture to their 4-bromobenzoate derivatives allowed separation of isomers (Scheme 6). This allowed for further chemistry to be done on each single pure isomer to prepare other analogues of glycerol menthonide, although work on any of these single isomer glycerol menthonide species has not yet been reported.



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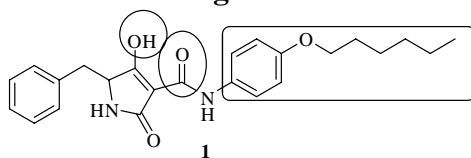
## “Tetramic acids and more: discovery of potent and selective leads inhibiting undecaprenyl pyrophosphate synthase (UPPS)”

*Stefan Peukert, Novartis, Cambridge, MA*

UPPS is an enzyme that catalyzes the formation of undecaprenylpyrophosphate, a lipid carrier for the precursors involved in the construction of cell wall structures, such as peptidoglycan that stabilizes bacterial membrane from rupture by forming a polymeric mesh. Antibiotics such as vancomycin and ramoplanin act by targeting the peptidoglycan biosynthesis pathway. This presentation by Stefan Peukert from Novartis focused on developing a small molecule inhibitor for UPPS as novel antibacterial agent.

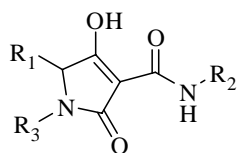
The compound **1** (Figure 9) was identified through high-throughput screening (HTS) and was found that it can be docked into the active site of UPPS occupied by the natural substrate farnesyl pyrophosphate (FPP). The binding mode analyses lead to the hypothesis that two hydrogen acceptor and hydrophobic groups serve as pharmacophoric anchor points.

**Figure 9**

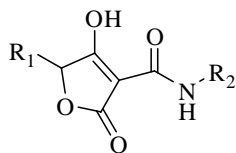


A series of novel inhibitors such as tetramic acids, tetrionic acids and dihydropyridones were synthesized (Fig 10). Structure-activity relationship (SAR) studies suggested that potency increases with the substitution of R<sub>2</sub> with 4-hexyloxyphenyl group with conformationally restricted cyclohexyl phenyl group (Figure 11). The SAR of tetrionic acids and dihydropyridones are similar in trend with tetramic acids. Hydrophobic groups at R<sub>1</sub> position found to be favorable and polar substitutions are less tolerated. The structures of selective UPPS inhibitor analogs are shown below (Figure 11).

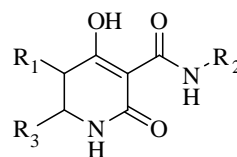
**Figure 10**



Tetramic acids

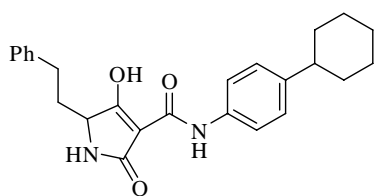


Tetrionic acids



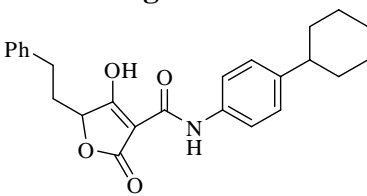
Dihydropyridin-2-one

**Figure 11**



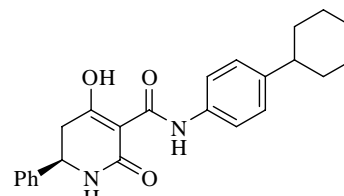
**2**

IC<sub>50</sub> = 0.16 uM



**3**

IC<sub>50</sub> = 0.50 uM



**4**

IC<sub>50</sub> = 0.07 uM

Compound **2** (tetramic acid) was found to have better antibacterial activity against gram positive bacteria. A reasonable correlation was found between UPPS inhibition and minimum inhibitory concentration (MIC) effectiveness in *streptococcus pneumoniae* among these classes of compounds. The more potent UPPS inhibitor **4** was a weak antibacterial agent and the difference was attributed to the physiochemical properties and cell permeability. For more information, see: (a) S. Walker, *et al.*, *Chem. Rev.* **2005**, *105*, 449. (b) K. C. Nicolau, *et al.*, *Angew. Chem. Int. Ed.* **1999**, *38*, 2096. (c) S. Peukert, *et al.*, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1840.

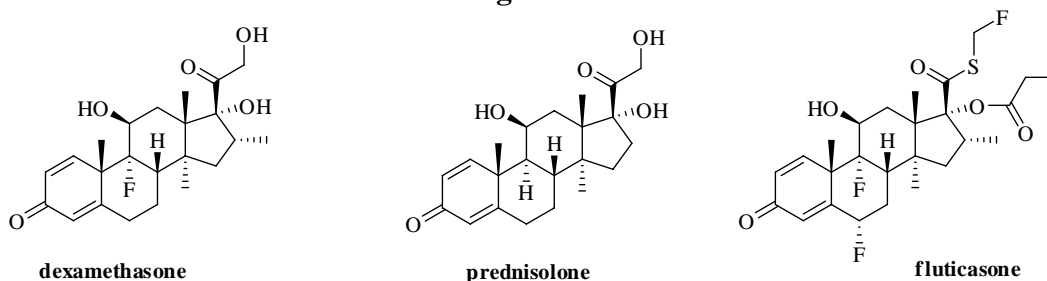
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**“Structure activity relationship of steroid D-ring mimetics in nonsteroidal dissociated glucocorticoid agonists”**

Pingrong Liu, Boehringer-Ingelheim Pharmaceuticals Inc, Ridgefield, CT

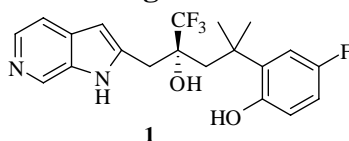
Pingrong Liu from Boehringer-Ingelheim presented a poster on his team's work to develop glucocorticoid agonists. Glucocorticoids are steroid hormones secreted by adrenal cortex in response to the adrenocorticotrophic hormone ACTH (R. M. Evans, *Science* **1988**, 240, 889; M. Beato, *et al.*, *Cell* **1995**, 83, 851). Glucocorticoids bound to the glucocorticoid receptor (GR) influence many physiological functions such as glucose metabolism, electrolyte and water balance, blood pressure maintenance and modulation of inflammatory processes. Synthetic glucocorticoids (dexamethasone and prednisolone) are effective against treatment of chronic inflammation disease (arthritis, asthma), however the uses of these synthetic agents are limited by their side effects (Figure 12).

**Figure 12**



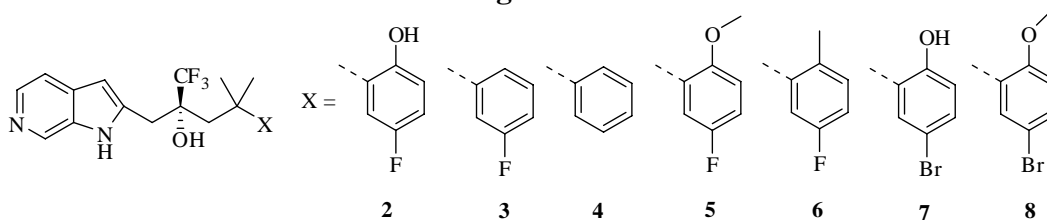
Previously this group reported that a compound **1** (Figure 13) exhibited a prednisolone-like anti-inflammatory profile *in vivo* in a collagen-induced arthritis (CIA) model, and displayed reduced side effects (D. Thomson, "Identification and optimization of non-steroidal glucocorticoid receptor agonists," ACS National Meeting, Spring 2007).

**Figure 13**



Analogues **2-8** with smaller substituents (Figure 14) were potent in a GR assay, but were not selective over the progesterone receptor (PR) or mineralocorticoid receptor (MR).

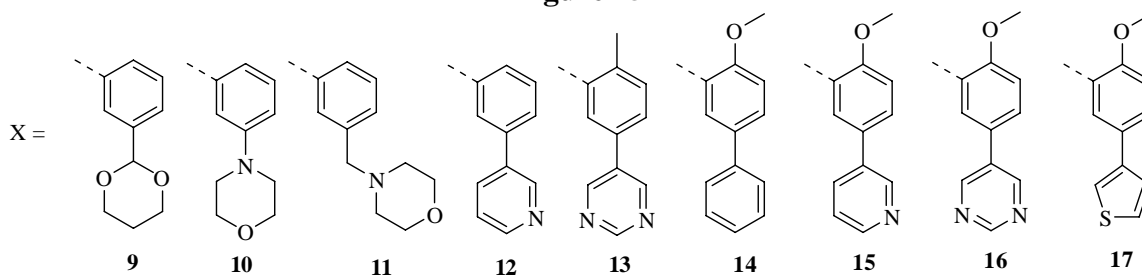
**Figure 14**



An X-ray crystal structure of fluticasone bound within the glucocorticoid receptor revealed an expanded binding pocket in the D-ring region not utilized in dexamethasone binding. As a result, a series of analogues **9-17** with larger substituents at the aryl *meta*-position were prepared and it was found that large mono-substitution resulted in great selectivity of GR over PR and MR (Figure 15). In particular, anisole substituent analogues with additional

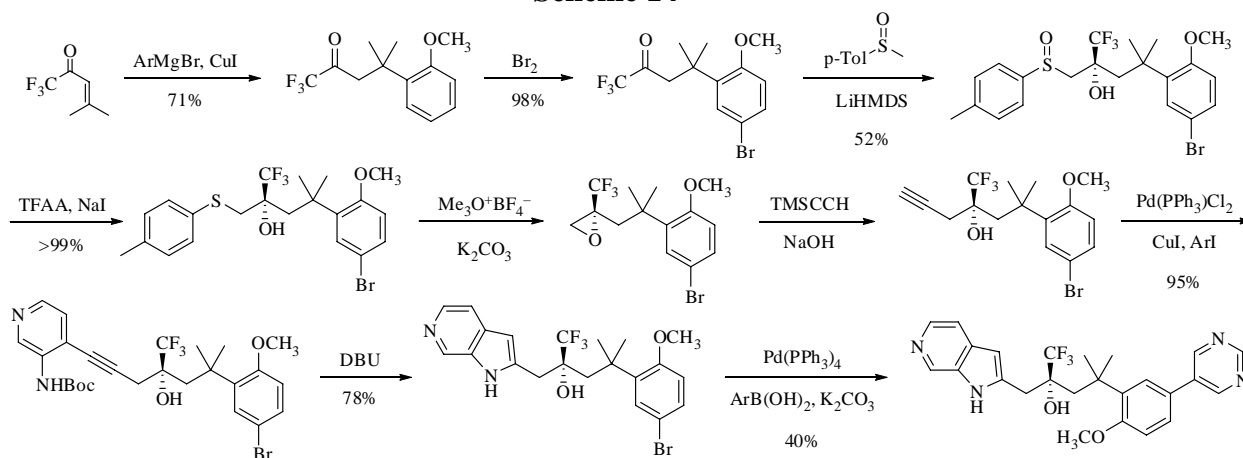
large substitution were explored (**14-17**) and it was found that the compound **16** was active against GR at 27 nM, and was selective over PR and MR (each >2000 nM). Phenolic compounds showed similar profiles as anisole series.

**Figure 15**



The active single enantiomer of **16** was synthesized in nine steps as shown in Scheme 14.

**Scheme 14**

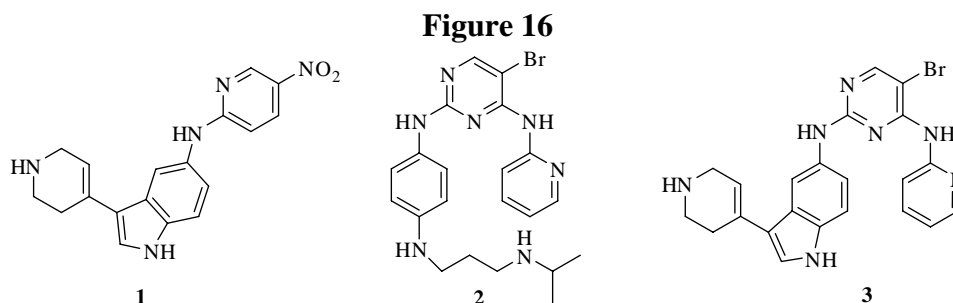


### “Design, synthesis and activity of inhibitors of focal adhesion kinase: Discovery of PF-562271 currently in clinical trials”

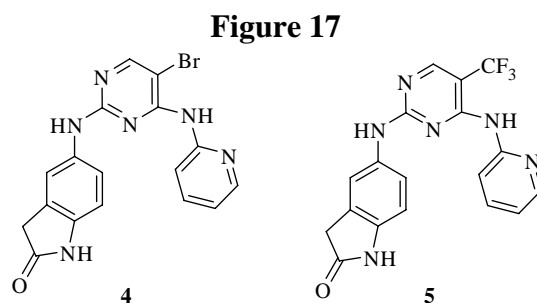
Michael J. Luzzio, *et al.*, Novartis Institutes for Biomedical Research, Cambridge, MA and Pfizer Central Research, Groton, CT

Cancer cells are characterized by their ability to proliferate regardless of adhesion to a substrate. Focal adhesion kinase (FAK), a non-receptor tyrosine kinase, plays important role in the ability of cells to grow in an adhesion-independent manner. FAK has been implicated in tumor progression and found at elevated levels in most human cancers, especially at the metastasis stage. The kinase Pyk2 is a member of the FAK family with 48% amino acid identity, but for which the role is not well established in tumorigenesis. FAK is expressed in most tissues and cell types, but Pyk2 has limited tissue distribution (H. Avraham, *et al.*, *Cell Signal* **2000**, *12*, 123).

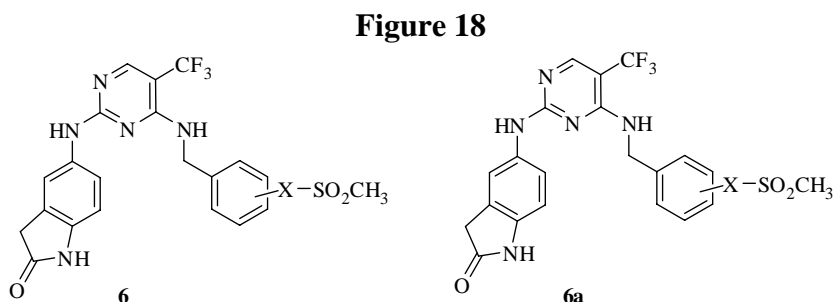
The talk presented by Michael Luzzio centered on Pfizer's FAK inhibitor candidate PF-562271 currently under clinical investigation. Compound **1** and **2** (Figure 16) were identified by initial high throughput screening (HTS). The important structural features of compounds **1** and **2** were incorporated into the compound **3**. Compound **1** was metabolically labile due to the nitro group present in the molecule.



Analogues of **3** were designed to address various factors such as the size of the molecule, lipophilicity and the number of hydrogen bond donors and acceptors (Figure 17). The left side of compound **3** was changed into a lactam in compound **4**. Replacing the bromine with a  $\text{CF}_3$  group in compound **5** increased potency.

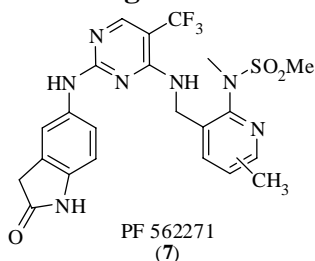


A series of methylsulfone analogues were prepared that showed good potency as FAK inhibitors and also exhibited FAK/Pyk selectivity (Figure 18). The FAK/Pyk selectivity based on aryl regiochemistry was in the order *para* > *meta* > *ortho* substitution.



The antitumor activity and pharmacology of FAK inhibitor PF-562271 (**7**, Figure 19) can be found in the recent publication from this research group (W. G. Roberts, *et al.*, *Cancer Res.* **2008**, *68*, 1935).

**Figure 19**



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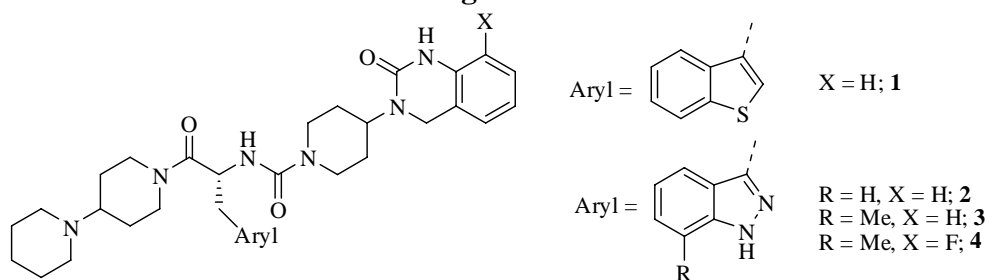
**“Discovery of potent calcitonin gene related peptide receptor antagonists for the treatment of migraine”**

*Prasad Chaturvedula, Bristol-Myers Squibb Pharmaceutical Company, Wallingford, CT*

Migraine headaches are associated with the dilation of cranial blood vessels. The current triptan series of drugs are non-selective vasoconstrictors and are associated with cardiovascular side effects. The plasma level of calcitonin gene related peptide (CGRP), a 37 amino acid peptide, was found to be elevated during the migraine attacks. Intravenous delivery of certain CGRP antagonists effectively treat migraine and cardiovascular side effects are not observed. This talk presented by Dr. Chaturvedula was focused on a BMS effort to develop a small molecule CGRP antagonist as an oral or intranasal spray. Nasal sprays can be effective quickly and also avoid nausea that limits the use of oral compounds in migraine patients.

Compound **1** (Figure 20) was found to be a CGRP antagonist (0.55 nM), but later also found to be an inhibitor of CYP3A4 (0.87 nM). Compound **2** with an indazole moiety showed improved potency (0.26 nM) and reduced CYP3A4 inhibition (>40 nM). The introduction of a C-7 methyl group on indazole lead to analogue **3** with greater potency (0.010 nM).

**Figure 20**



Compound **3** showed poor enough aqueous solubility to be discounted as a therapy by intranasal dosing. Further modification of **3** led to an analogue **4** with a fluorine on the C-8 position of the quinoline with improved aqueous solubility (> 500 mg/mL). Compound **4** showed a potency of (0.013 nM) against CGRP and reduced CYP3A4 inhibition (26 nM). It also exhibited a good intranasal pharmacokinetic profile and shows good migraine pain relief in an animal model (A. P. Degnan, *et al.*, *J. Med. Chem.* **2008**).

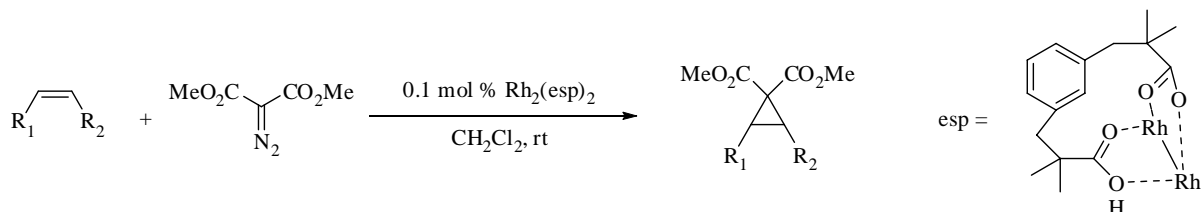
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## “Cyclopropanation of alkenes with diazomalonates using Rh<sub>2</sub>(esp)<sub>2</sub> as catalyst”

Sussane Kiau et al., Bristol-Myers Squibb Pharmaceutical Company, New Brunswick, NJ

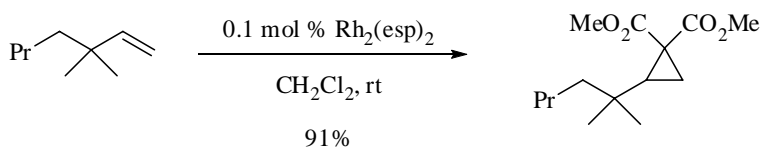
This poster presentation described the use of diazomalonates for cyclopropanation of alkenes in presence of a rhodium catalyst (Scheme 15). The earlier reports of rhodium catalyst-based cyclopropanation reactions suffered from low yields and stringent reaction conditions required. The advantage of this method are the stoichiometric amount of olefin used (not excess equivalents), low catalyst loading and slow addition of carbenoid is not required.

Scheme 15



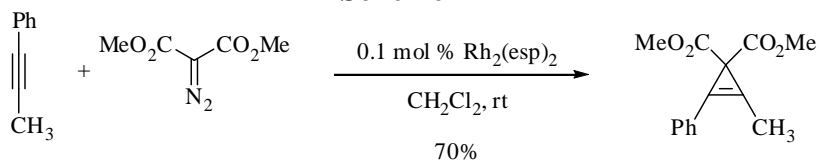
Interestingly, increasing the steric bulk on the allylic position did not affect the reaction efficiency (Scheme 16). The *cis* isomer of alkene afforded exclusive *cis* product while the *trans* olefin led to mixture of products.

Scheme 16



Internal alkynes react with diazomalonates to produce cyclopropenes in good yields (Scheme 17).

Scheme 17



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## “The path to a potent, selective and orally bioavailable C-Met inhibitor with antitumor activity”

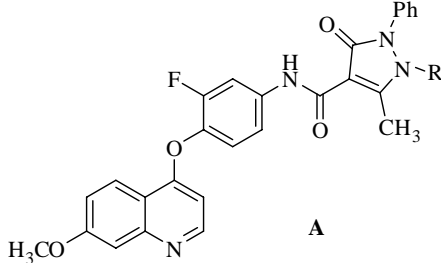
David Bauer, Amgen Inc., Cambridge, MA



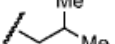
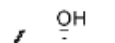
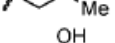

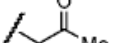
The hepatocyte growth factor receptor (HGFR, also known as c-Met) is a tyrosine-kinase transmembrane heterodimeric receptor that plays a role in cellular physiology when activated by its endogenous ligand hepatocyte growth factor (HGF), resulting in proliferation, survival, motility, branching morphogenesis, wound healing and angiogenesis. Cancer progression has been observed in cases of abnormal regulation of HGF, and as such provides a pathway

of treatment of this disease through the inhibition of HGF/c-Met pathway. (For leading references, see S. Giordano, *et al.*, *Nature* **1989**, 339, 155; C. Birchmeier, *et al.*, *Nature Reviews Mol. Cell Biol.* **2003**, 4, 915; P. G. Dharmawardana, *et al.*, *Curr. Mol. Med.* **2004**, 4, 855.)

This presenter discussed the work around a series of novel pyrazolones **A** that were identified as potent inhibitors of c-Met, culminating in the synthesis of compound **7** (Table 12, entry 7). This derivative showed enhanced selectivity over VEGFR-2 (vascular endothelial cell growth factor receptor) with the incorporation of a 2-hydroxypropyl group in the N-1 position of the pyrazolone ring of **A** (L. Longbin, *et al.*, *J. Med. Chem.* **2008**, 51, 3688).

**Table 12. N-Alkyl analogues 1-7 of pyrazolone A.**



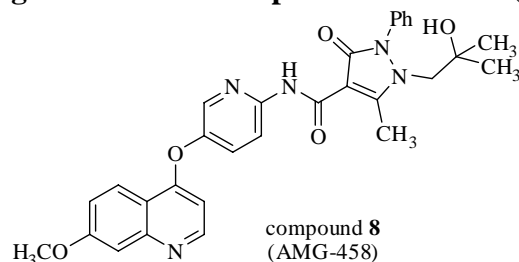
	R	c-Met Ki <sup>a</sup> (nM)	PC3 IC <sub>50</sub> <sup>b</sup> (nM)	VEGFR2 Ki <sup>a</sup> (nM)	Huvec IC <sub>50</sub> <sup>c</sup> (nM)
1		1.0	37	24	52
2		1.0	49	460	143
3		8.0	204	999	329
4		1.0	24	396	236
5		1.1	23	386	208
6		1.3	48	2	86
7		2.7	50	1160	921

<sup>a</sup>Inhibitory constant for kinase activities (gastrin as substrate). <sup>b</sup>IC<sub>50</sub> (ip) value for HGF-mediated c-Met phosphorylation in PC3 cells. <sup>c</sup>IC<sub>50</sub> (ip) value for VEGFR2-mediated survival of human umbilical vein endothelial cells.

As compound **1** was established as both a potent inhibitor of VEGFR2 and a strong inhibitor of c-Met, the presenter sought to improve the selectivity by structurally modifying the methyl group at the N-1 position. Replacement of methyl with a propyl group (compound **2**, Table 12) was successful, although branching of the n-propyl group to an isobutyl group (compound **3**) resulted in lower activity. On the other hand, secondary alcohol analogue isomers **4** and **5** both exhibited similar enzymatic and cellular activities versus **2**, and with better selectivity over VEGFR2. However the incubation of **4** and **5** in liver microsomes led

to the formation of a ketone (compound **6**), which was predominant in rat and mouse liver chromosomes although minor in dog, monkey and human liver slices. This variation in species made the determination of efficacy across species difficult. To prevent the formation of ketone **6** the presenter chose to replace the secondary alcohol with a tertiary alcohol (compound **7**) which exhibited lower cellular activity, but which was more selective against VEGFR2 versus **4** and **5** while inhibiting c-Met phosphorylation in PC3 cells. From previous SAR data, the presenter noted that replacing the fluorophenyl ring with a pyridyl ring could be advantageous, as the predicted physiochemical properties would result in a change of log D at Ph 6.5 from 4.4 to 3.0, significantly reducing the side effects associated with quinine-imine formation (S. D. Nelson, *et al.*, *J. Med. Chem.* **1982**, 25, 753). The combination of these SAR observations resulted in the synthesis of compound **8** (AMG-458, Figure 21), which showed potent inhibition of c-Met at the enzyme and at the cellular levels in vitro ( $K_i = 1.2$ ,  $IC_{50} = 60$  nM).

**Figure 21. Lead compound AMG-458 (8)**



Compound **8** also exhibited activity against several c-Met mutants that have been identified in cancer patients (W. Wang, *et al.*, *Proc. Natl. Acad. Sci. USA* **2006**, 103, 3563). Higher selectivity against VEGFR2 was observed in **8** compared to compared **7**, and when tested against a panel of 55 tyrosine and serine/threonine kinases, compound **8** was >100-fold selective over 98% and >1000-fold selective over 80% of the panel. Compound **8** was metabolically stable in liver chromosomes of mouse, dog, rat, monkey and humans with a low intrinsic clearance ( $Cl_{int} < 5, 62, 8, 8$  and  $18 \mu\text{L}/\text{min}/\text{mg}$ , respectively). Moreover, **8** significantly inhibited tumor growth when dosed orally in the TPR-Met and U-87 MG xenograft models with no adverse effects on body weight.

In conclusion, the presenter described medicinal chemistry efforts toward the discovery of compound **8** (AMG 458) through the modification chemistry of the lead compound **1**. AMG 458 has subsequently been shown to be a potent, selective and stable c-Met inhibitor and the favorable profile of this molecule has enabled it to be nominated as a preclinical candidate for the treatment of human cancers.