



Trip Report for
“The 234th American Chemical Society National Meeting & Exposition”

Boston, Massachusetts

August 19-23, 2007

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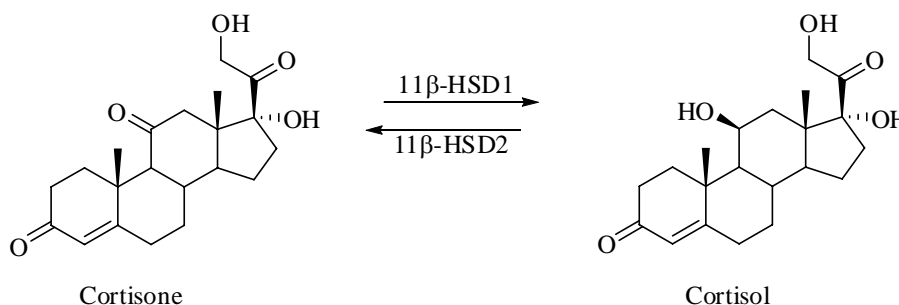
Abstract: *The 234th American Chemical Society National Meeting & Exposition was held in Boston, Massachusetts from August 19- 23, 2007. The overall theme for this year’s National Meeting was “Material Innovations: From Nanotech to Biotech and Beyond”. This National Meeting was well attended by people from academia and industry. Many interesting papers in the area of medicinal chemistry and organic chemistry were presented. This report highlights select material from the talks and posters presented at the Conference.*

“Discovery and SAR of novel derivatives as 11 β -hydroxysteroid dehydrogenase type 1 inhibitors,”

Claire M. Lankin, Craig D. Boyle, Samuel Chackalamannil, Unmesh Shah, Hana Baker, Timothy Kowalski, Lili Zhang, Giuseppe Terracina, (Schering-Plough Research Institute).

11 β -hydroxysteroid dehydrogenase type 1 (11 β HSD1) is an enzyme that converts cortisone (inactive) to cortisol (active) as depicted in Figure 1. This conversion is found in several tissues throughout the body including in liver and fat, where the conversion results in increased local concentrations of glucocorticoid. Existing data suggests that local glucocorticoid may be involved in the development of metabolic syndrome and abdominal obesity. Given this data, inhibitors of 11 β HSD1 could produce a potential treatment for diabetes and metabolic syndrome.¹

Figure 1
Interconversion of Cortisone to Cortisol



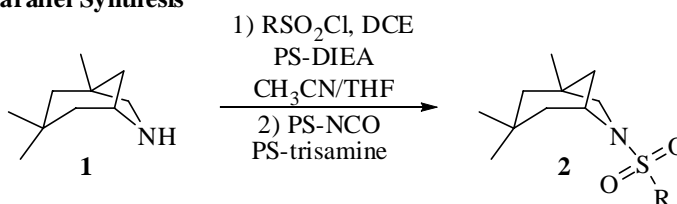
Based on high throughput screening, a series of azabicyclooctanes were identified as potential inhibitors of 11 β HSD1. In particular, N-sulfonyl compounds showed the most activity. A medicinal chemistry effort was undertaken to further explore these hits. A parallel synthesis approach was first employed to rapidly identify the key structural components necessary for good inhibition. A synthetic scheme describing this action is shown in Figure 2.

Figure 2
Parallel Synthesis Approach to Azabicyclooctanes

Traditional Synthesis

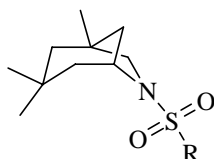


Parallel Synthesis



Selected results from the SAR developed from the parallel synthesis are shown in Table 1. The general trend observed was the para-substituted aryl sulfonamides showed the best inhibition of 11 β HSD1. While several substituents were tolerated, a para-methyl or methyl ether group displayed the most promising results with IC₅₀'s less than 1 micromolar.

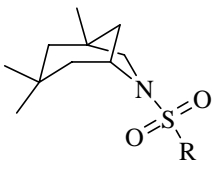
Table 1

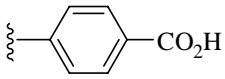
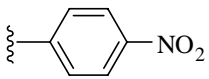
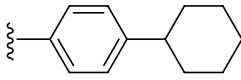
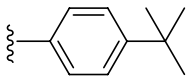
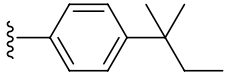
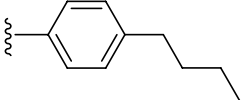


Compound	R	11 β -HSD1 h IC ₅₀ (nM)	11 β -HSD1 m IC ₅₀ (nM)
1		2509	3167
2		268	686
3		1415	28195
4		407	2483
5		3006	18247
6		247	670

The results from the parallel synthesis study were followed upon by a series of compounds prepared containing para-substitution. A selection of these compounds with their associated data is shown in Table 2. The SAR developed indicated that branched alkyl groups at the para-position showed the best inhibitory activity, with IC₅₀ values under 100 nM. In particular, compounds **10** and **11** showed promise both in *in vitro*, as well as *in vivo* studies, with 26-30% inhibition in a mouse cortisone challenge assay at 30 mpk.

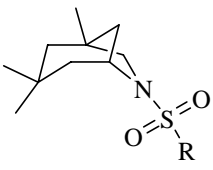
Table 2



Compound	R	11 β -HSD1 h IC ₅₀ (nM)	11 β -HSD1 m IC ₅₀ (nM)	Mouse cort. challenge % I @ 30 mpk
7		5714	11136	
8		126	5937	
9		415	165	
10		31	71	30
11		28	19	26
12		372	950	

Additional derivatives were prepared based on the success of the branched alkyl compounds **10** and **11**. These new analogues incorporated alcohols or ethers into the branching at the para-position. Selected results are shown in Table 3. These compounds displayed excellent *in vitro* data with IC₅₀ values as low as 7 nM for compound **16**. Additionally, several compounds showed improved *in vivo* efficacy including compounds **14** and **19**. Interestingly, while the *in vitro* data is similar between analogous alcohol/ether combinations, the ether compounds were found to have superior *in vivo* data. The synthesis of these compounds is shown in Figure 3.

Table 3



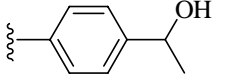
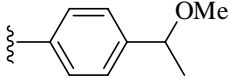
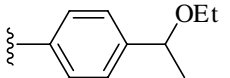
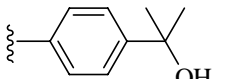
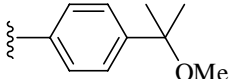
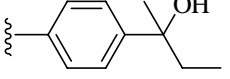
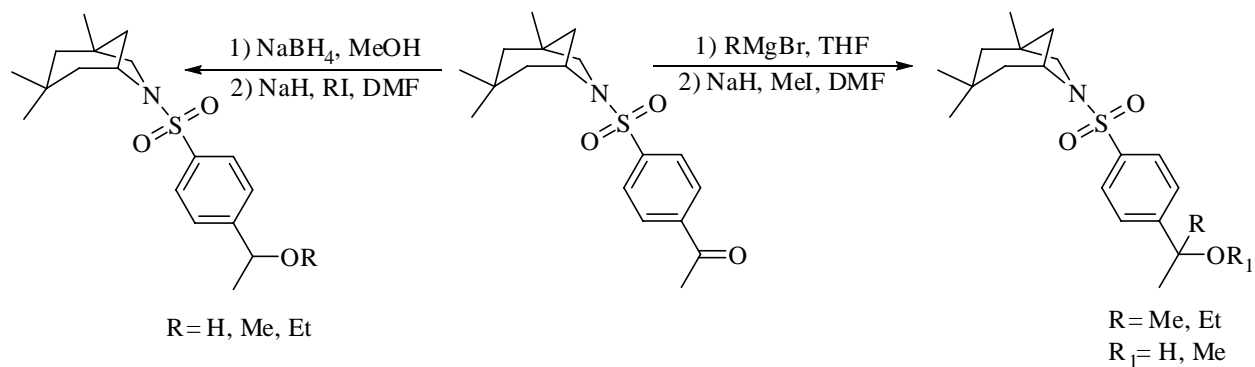
Compound	R	11 β -HSD1 h IC ₅₀ (nM)	11 β -HSD1 m IC ₅₀ (nM)	Mouse cort. challenge % I @ 30 mpk
13		16	67	63
14		19	27	16
15		10	87	
16		7	43	43
17		23	11	19
18		30	68	

Figure 3
Synthesis of Branched Alcohols and Ethers



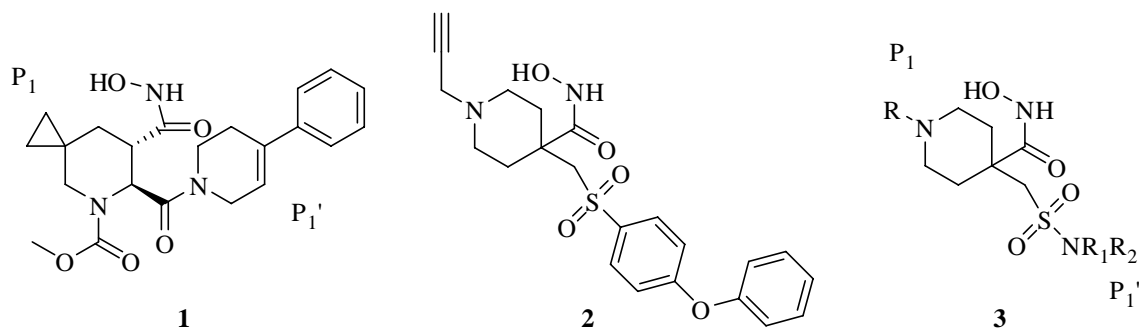
- For a recent review see: C.D. Boyle; T.J. Kowalski; and L. Zhang, *Annu. Rep. Med. Chem.*, **2006**, *41*, 127-140, and references cited therein.

“Discovery of β -sulfonamide piperidine hydroxamates as potent and selective HER-2 sheddase inhibitors,”

David M Burns, Chunhong He, Yanlong Li, Peggy Scherle, Maryanne B. Covington, Max Pan, Richard Wynn, Sharon Turner, Jordan S. Fridman, Brian Metcalf, Wenqing Yao, (Incyte Corporation).

The human epidermal growth factor receptor-2 (HER-2 or ErB-2) is a tyrosine kinase receptor that becomes activated when homo- or heterodimerization occurs with another member of the HER family. Activation can also occur via proteolytic cleavage (shedding) of the extracellular domain (ECD).¹ The activation of HER-2 initiates intracellular signaling that mediates a range of cellular activities such as cell differentiation, proliferation, adhesion, motility, as well as survival.² However, the over expression of the oncogene HER-2/*neu* has been linked to aggressive pathogenesis, poor prognosis, and decreased responsiveness towards conventional chemotherapeutic treatments for several non-small cell lung, ovarian, and breast cancer patients. Additionally, elevated plasma levels of HER-2 ECD have been associated with an increase in metastatic potential and a decrease in disease-free, as well as overall survival in patients with breast cancer.³ Given this information, it is believed that an inhibitor of the protease responsible for HER-2 ECD shedding may provide a desirable therapy for cancer patients that overexpress HER-2.

Figure 1



Previous studies towards this end at Incyte led to the discovery of compound **1** in Figure 1, a potent and selective inhibitor of HER-2 sheddase.⁴ This compound was identified to possess excellent pharmacodynamic and pharmacokinetic properties in addition to decreased cleaved HER-2 ECD plasma levels, tumor size, and diminish the effects of the humanized anti-HER-2 monoclonal antibody *in vivo* in a HER-2 overexpressing cancer model. However, an alternative scaffold was desired due to the complexity in the synthesis of analogues of compound **1**. Compound **2**, a MMP-2, -9, and -13 inhibitor was identified as a possible lead replacement, despite the desire for the new inhibitors to be selective against the MMP's.⁵ It was hypothesized that through development at the P₁' site of compound **3**, potent and selective inhibitors could be developed.

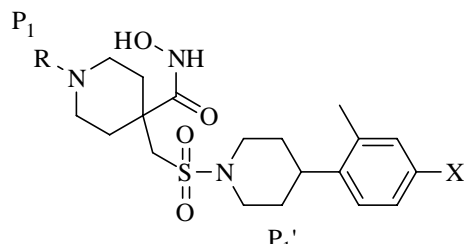
Selected SAR that was developed around the P₁' site is displayed in Table 1. A number of aryl-substituted piperidine derivatives were prepared containing a tetrahydrofuranyl carbamate at the P₁ site. As can be seen in the data below, both the potency, and especially the selectivity of the compounds was highly sensitive to the nature of substitution around the aromatic ring. It was found that compounds containing a methyl group in the ortho-position gave rise to very selective

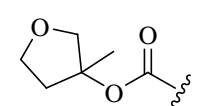
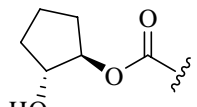
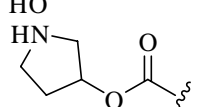
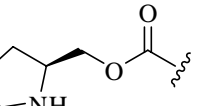
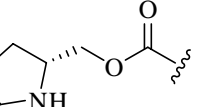
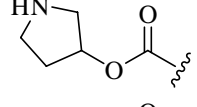
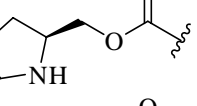
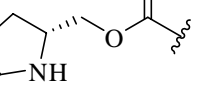
inhibitors. Furthermore, it was observed that both potency and selectivity were improved when a fully saturated piperidine sulfonamide was employed relative to the unsaturated derivative.

Table 1

Cmpd	P ₁ '	IC ₅₀ (nM) HER-2	Enzymatic Binding IC ₅₀ (nM)			
			ADAM-10	MMP-1	MMP-2	MMP-3
4		7.1	10	259	4	237
5		22	28	753	18	266
6		76	60	---	135	---
7		41	5	>5000	>2000	>5000
8		141	92	---	>2000	---
9		14	13	>5000	1999	>5000
10		45	107	---	1563	---
11		833	286	>5000	315	2157

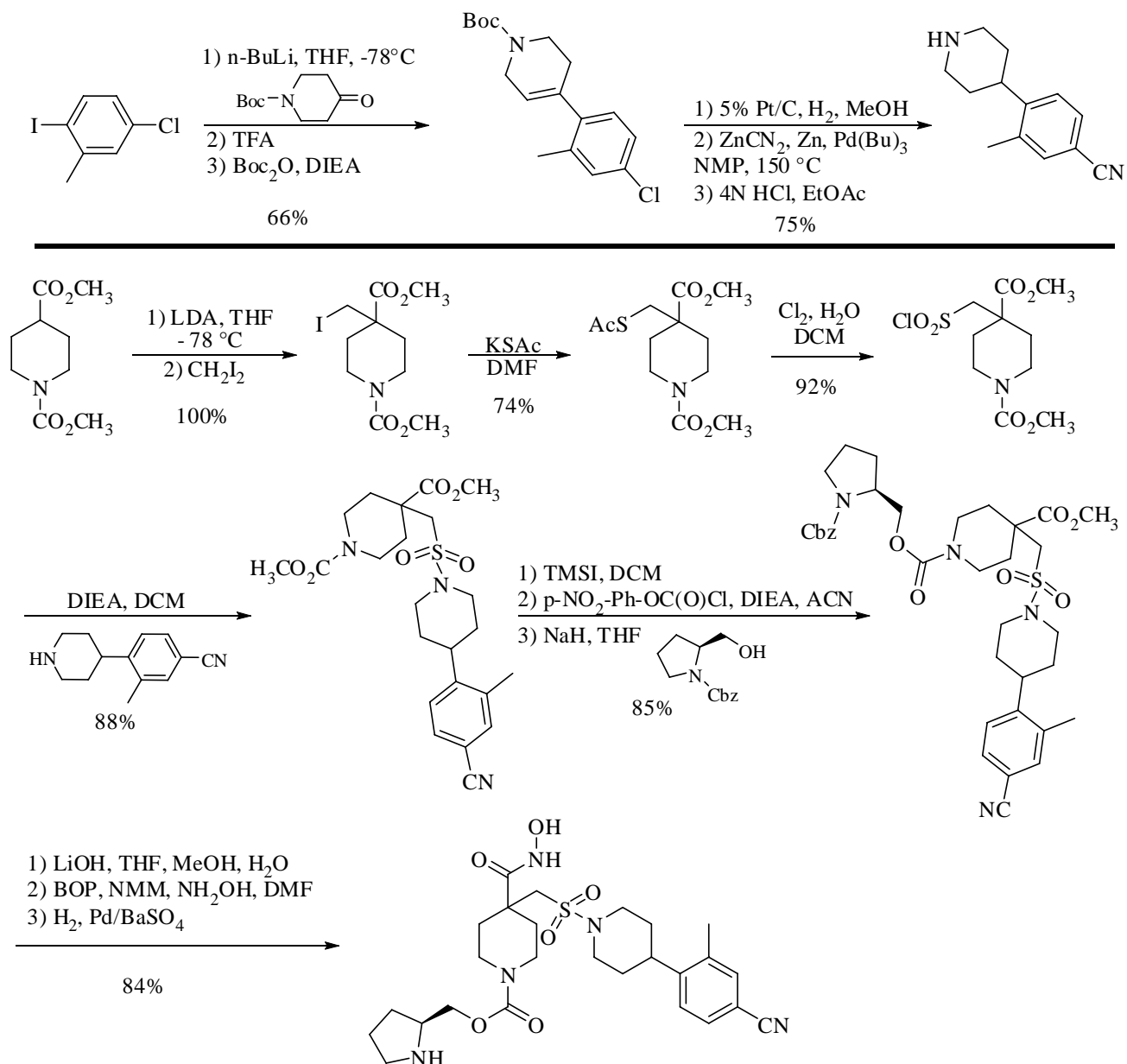
Although very potent and selective inhibitors were prepared such as compounds **7** and **9**, the projected human clearance for these compounds was high, giving rise to low projected bioavailability. Metabolic studies were undertaken and evidence was presented that the carbamate moiety was being cleaved. Chemists addressed this problem from two angles: the first was to increase the steric bulk around the carbamate to decrease the likelihood of cleavage; the second was to introduce a polar group that could reduce the binding affinity to cytochrome P450 and thus decrease the clearance. Selected compounds from this study are shown in Table 2.

Table 2


Cmpd	R	X	IC ₅₀ (nM) HER-2	Enzymatic Binding IC ₅₀ (nM)			Projected h-Clr L/h/kg (% free)
				ADAM-10	MMP-1	MMP-2	
12		H	36	11	>5000	564	1.1 (15%)
13		H	6.2	16	4999	537	1 (20%)
14		H	16	18	>5000	546	<0.5 (>60%)
15		H	23	34	>5000	>2000	1.1 (14%)
16		H	30	19	>5000	>2000	0.7 (42%)
17		CN	13	7.8	>5000	>2000	---
18		CN	6.5	9.1	>5000	1272	0.6 (49%)
19		CN	23	11	>5000	1380	<0.5 (>60%)

Initial attempts at lowering clearance by introduction of steric bulk around the carbamate, such as in compound **12** proved unsuccessful. However, the incorporation of a polar group (via the methanol pyrrolidine carbamate) gave rise to compounds **16** and **19** which displayed low projected clearance and high bioavailability which maintaining potency and selectivity. The synthesis of these compounds is shown in Figure 2. A particularly interesting transformation is the conversion of the aryl chloride to the aryl nitrile in good yield employing palladium catalysis at elevated temperatures.

Figure 2



1. Mass, R. D. *Int. J. Radiation Oncology Biol. Phys.* **2004**, *58*, 932-940.
2. Marmor, M. D.; Skaria, K.B.; Yarden, Y. *Int. J. Radiation Oncology Biol. Phys.* **2004**, *58*, 903-913.
3. Molina, M. A.; Saez, R.; Ramsey, E. E.; Garcia-Barchino, M. -J.; Rojo, F.; Evans, A. J.; Albanell, J.; Keenan, E. J.; Lluch, A.; Garcia-Conde, J.; Baselga, J.; Clinton, G. M. *Clinical Cancer Research*, **2002**, *8*, 347-353.
4. Wenqing, Y.; Zhuo, J.; Burns, D. M.; Xu, M.; Zhang, C.; Li, Y. -L.; Qian, D. -Q.; He, C.; Weng, L.; Shi, E.; Lin, Q.; Agrios, C.; Burn, T. C.; Caulder, E.; Covington, M. B.; Fridman, J. S.; Friedman, S.; Katiyar, K.; Hollis, G.; Li, Y.; Liu, C.; Liu, X.; Marando, C. A.; Newton, R.; Pan, M.; Scherle, P.; Taylor, N.; Vaddi, K.; Wasserman, Z. R.; Wynn, R.; Yeleswaram, S.; Jalluri, R.; Bower, M.; Metcalf, B. *J. Med. Chem.* **2007**, *50*, 603-606.

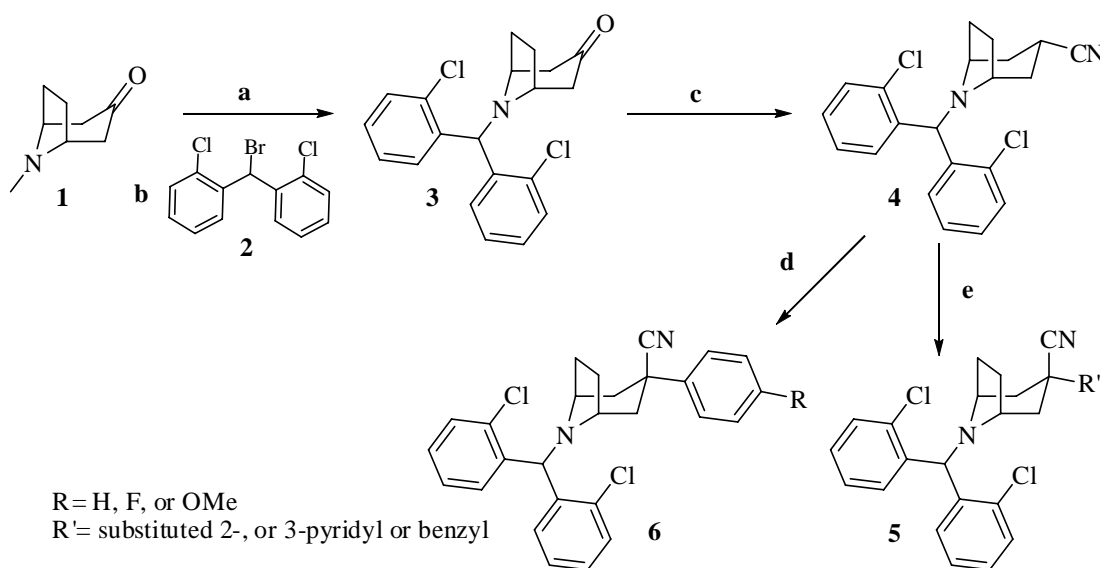
5. Becker, D. P.; Villamil, C. I.; Barta, T. E.; Bedell, L. J.; Boehm, T. L.; DeCrescenzo, G. A.; Freskos, J. N.; Getman, D. P.; Hockerman, S.; Heintz, R.; Howard, S. C.; Li, M. H.; McDonald, J. J.; Carron, C. P.; Funckes-Shippy, C. L.; Mehta, P. P.; Munie, G. E.; Swearingen, C. A. *J. Med. Chem.* **2005**, *48*, 6713.

“Synthesis and SAR relationships of 3-substituted 8-benzhydryl-nortropine analogs as nociceptin receptor ligands,”

Shu-Wei Yang, Deen Tulshian, Ginny Ho, William J. Greenlee, Stephen Eckel, John Anthes, (Schering-Plough Research Institute).

The nociceptin receptor (NOP, ORL-1), an orphan opioid receptor discovered in 1994, has high sequence homology to the rest of the opioid receptor family, however does not bind classical endogenous opioid receptor ligands.^{1,2} Nociceptin (a 17 amino acid peptide), which is an endogenous NOP ligand, has been shown to mediate several physiological processes including cough, pain, anxiety, urinary incontinence, and cognition.³⁻⁷ It is believed that selective NOP agonists could have clinical potential for the treatment of the related diseases without the traditional side effects associated with other opioid receptors. Shown below are a series of small molecule ligands derived from nortropine that show modest to excellent selectivity against MOP (a representative of the opioid receptor family, typically associated with codeine-like side effects including respiratory depression, sedation, constipation, and addictive liabilities).

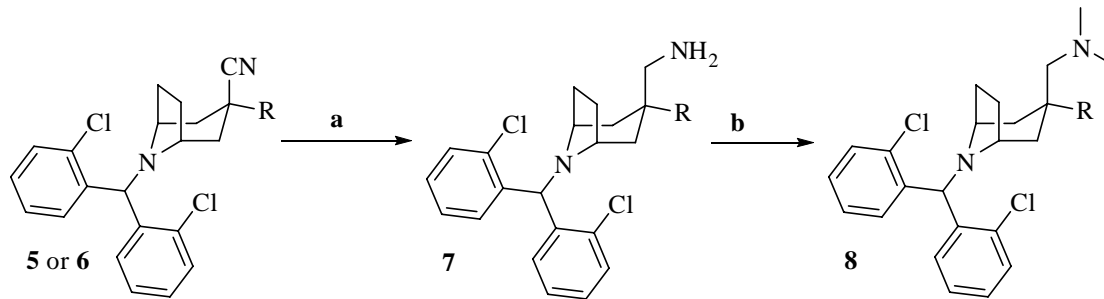
Figure 1



a) α -chloromethyl chloroformate, DCE, reflux; b) **2**, K_2CO_3 , CH_3CN , reflux; c) KOTBu, tosylmethyl isocyanide, DME, -40 °C to rt; d) RPhF, KHMDs, microwave, 100 °C; e) NaHMDS, R'X, THF, -78 °C to rt.

The synthesis of the various 3-cyano-nortropine intermediates is shown in Figure 1. These compounds were readily prepared in three steps from commercial starting materials. The cyano-containing compound could then be converted to the corresponding amines as shown in Figure 2. The resulting primary amines could then be further functionalized to afford the final compounds as shown in Figures 2,3.

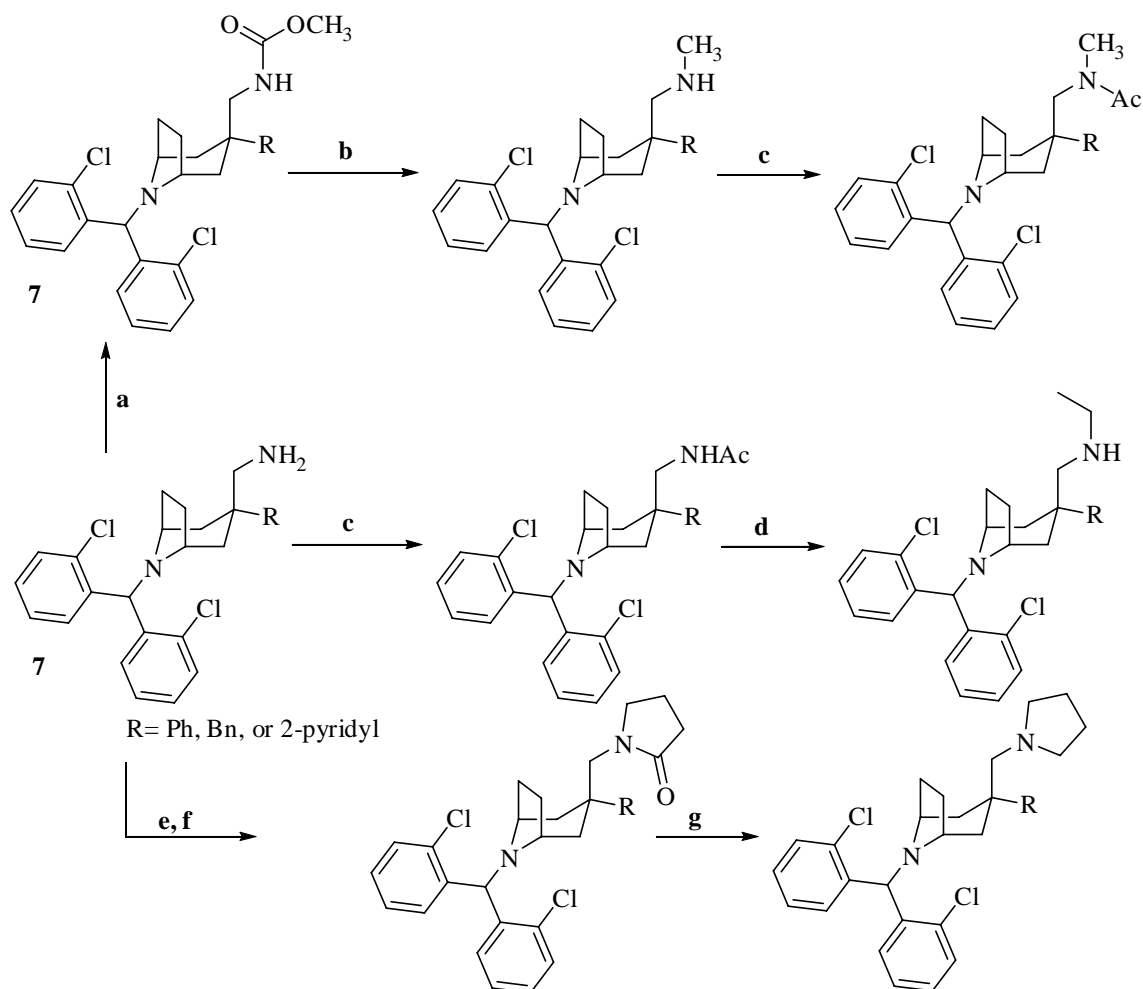
Figure 2



R = Ph, Bn, or 2-pyridyl

a) LAH, ether, rt; b) HCHO, HCO₂H, 100 °C, (R = Ph) or HCHO, AcOH, NaBCNH₃, MeOH, rt

Figure 3



R = Ph, Bn, or 2-pyridyl

a) ClCO₂Me, aq. K₂CO₃, DCM, rt; b) LAH, THF, reflux; c) Ac₂O, Pyr, 0 °C; d) DIBAL, THF, -78 °C to rt; e) Cl(CH₂)₃COCl, Et₃N, DCM, rt; f) KOtBu, THF, rt; LAH, THF, reflux.

The researchers began by exploring the SAR around the C-3 phenyl analogs, the results of which are displayed in Table 1 (the K_i values were determined from dose-response curves against radiolabeled nociceptin). The unsubstituted aminomethyl compound **8** showed excellent potency

against NOP, and importantly also displayed over 100-fold selectivity against MOP. Alkylation or acylation of the aminomethyl moiety lead to even less potency against MOP, however the potencies against NOP also fell, although in some cases reasonable selectivities were maintained, as in compounds **10** and **16**.

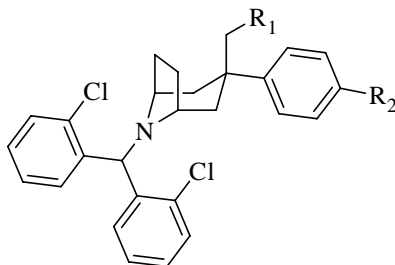


Table 1

Compounds	R ₁	R ₂	NOP	MOP	selectivity
8	NH ₂	H	6	674	118
9	NHCH ₃	H	10	566	57
10	N(CH ₃) ₂	H	17	1486	89
11	NHAc	H	20	777	38
12	NHCO ₂ CH ₃	H	20	905	45
13	N(CH ₃)(Ac)	H	210	2620	13
14		H	70	4169	60
15		H	68	Nd	Nd
16	NHAc	4-F	31	2106	68
17	NHAc	4-OMe	118	2407	20

A similar study was undertaken in the C-3 benzyl series of compounds. As was observed in the C-3 phenyl series, the unsubstituted aminomethyl derivative **18** showed excellent potency against NOP and again over 100-fold selectivity with respect to MOP. However, potency quickly dropped when the aminomethyl group was alkylated or acylated. When the benzyl group was changed to the 4-fluoro benzyl analog, a slight decrease in potency was observed. However, the combination of the fluoro benzyl group, with the pyrrolidinomethyl group at C-3 lead to an extremely selective ligand with good potency at NOP.

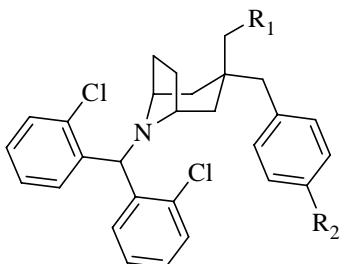



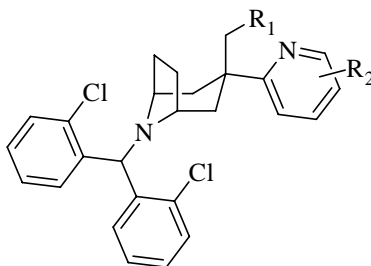


Table 2

Compounds	R ₁	R ₂	NOP	MOP	selectivity
18	NH ₂	H	11	1336	121
19	NHAc	H	12	458	36
20	NHEt	H	39	nd	nd
21	N(CH ₃) ₂	H	55	nd	nd
22		H	116	nd	nd
23		H	336	nd	nd
24	NH ₂	4-F	34	1414	42
25	NHAc	4-F	15	782	53
26		4-F	58	>10,000	>172

Finally, studies were undertaken to explore the effects of substituted pyridines in the C-3 position on potency and selectivity, the results of which are shown in Table 3. Several compounds (**27-30**, **35**) showed excellent potency against NOP. Unlike in the previous two series, alkylation of the aminomethyl group with an unsubstituted pyridine gave both selective and potent compounds (**29** and **30**). Unfortunately, any substitution on the pyridine ring examined led to reduced NOP binding activity and subsequent loss in selectivity.

**Table 3**

Compounds	R ₁	R ₂	NOP	MOP	selectivity
27	NH ₂	H	7	617	88
28	NHAc	H	5	374	75
29	NHEt	H	6	743	124
30	N(CH ₃) ₂	H	7	785	116
31	NH ₂	6-F	29	nd	nd
32	NHAc	6-F	24	1284	54
33	N(CH ₃) ₂	6-F	104	3976	38
34	NH ₂	6-OCH ₃	11	123	11
35	NHAc	6-OCH ₃	4	251	63
36	NHEt	6-OCH ₃	20	442	22
37	NH ₂	3-CH ₃	50	nd	nd
38	NHAc	3-CH ₃	173	nd	nd
39	NH ₂	3-piperidiny-	245	nd	nd

		methyl			
40	NHAc	3-piperidinyl-methyl	670	758	1
41	NHAc	5-OCH ₃	62	3447	56
42	NHAc	5-Br	27	752	27
43	NHAc	5-piperidinyl	99	nd	nd

- 1) Mollereau, C.; Parmentier, M.; Mailleux, P.; Butour, J.; Moisand, P.; Chalon, D.; Caput, D.; Vassart, G.; Meunier, J. C. *FEBS* **1994**, *341*, 33-38.
- 2) Meunier, J. C.; Mollereau, C.; Toll, L. *Nature*, **1995**, *377*, 532-535.
- 3) Bolser, D. C.; McLeod, R. L.; Tulshian, D. B.; Hey, J. A. *Eur. J. Pharmacol.* **2001**, *430*, 107-111.
- 4) McLeod, R. L.; Parra, L. E.; Mutter, J. C.; Erickson, C. H.; Carey, G. J.; Tulshian, D. B.; Fawzi, A. B.; Smith-Tohan, A.; Egan, R. W.; Cuss, F. M.; Hey, J. A. *Br. J. Pharmacol.* **2001**, *13*, 1175-1178.
- 5) Sajdyk, T. J.; Zink, C.; Gackenheimer, S. –L. Abstract # 396.5, 32nd Ann. Meeting of the Soc. For Neuroscience, Orlando, FL, USA, Nov. 2-7, 2002.
- 6) Lecci, A.; Giuliani, S.; Meini, S. *Peptides* **2000**, *21*, 1007-1021.
- 7) Lazzeri, M.; Calo, G.; Spinelli, M. *J. Of Urology* **2001**, *166*, 2237-2240.

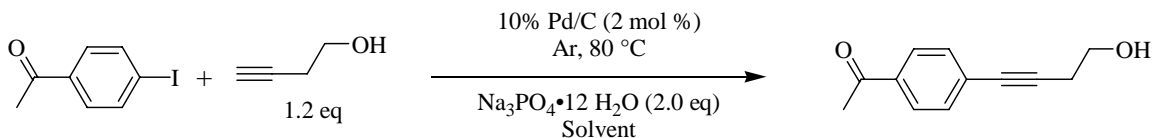
“A practical and efficient Pd/C-catalyzed copper-, ligand- and amine-free Sonogashira coupling reaction,”

Satoka Aoyagi, Shigeki Mori, Takayoshi Yanase, Yasunari Monguchi, Tomohiro Maegawa, Hironao Sajiki, (Gifu Pharmaceutical University).

Researchers at Gifu Pharmaceutical University are working on developing better conditions to effect the Sonogashira Coupling reaction. Traditional reactions employ homogeneous catalysis conditions that make removal of the catalyst more difficult. Heterogeneous catalysts are easy to remove but are not as active, which leads to longer reaction times. The standard use of copper iodide also has the draw back of inducing alkyne dimerization. They set out to optimize the choice of solvent, base, temperature and catalyst loading. Their results are shown in the tables that follow.

Table 1

Solvent

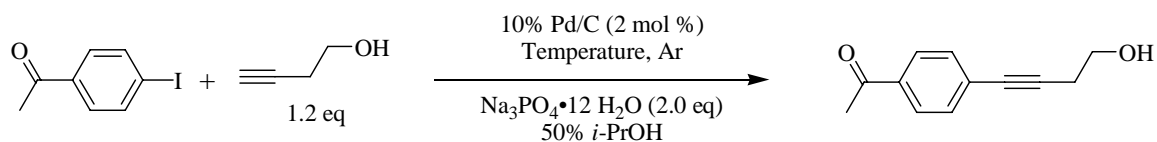


Entry	Solvent	Time (h)	Isolated yield (%)
1	Toluene	24	7
2	MeCN	24	19
3	1,4-dioxane	24	22
4	THF	24	24

5	DMF	5	30
6	Water	6	34
7	MeOH	0.5	78
8	<i>i</i> -PrOH	2	48
9	50% <i>i</i>-PrOH	0.5	79

Table 2

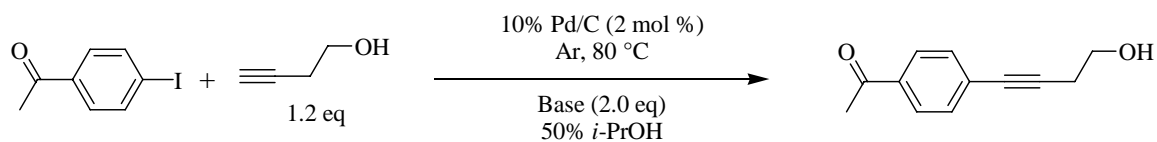
Temperature



Entry	Temperature (°C)	Time (h)	Isolated yield (%)
1	rt	24	34
2	40	6	72
3	60	3	57
4	80	0.5	79
5	100	3	78

Table 3

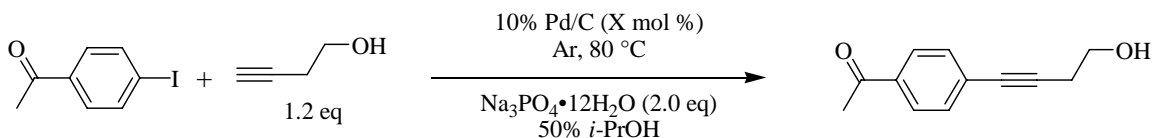
Base



Entry	Base	Time (h)	Isolated yield (%)
1	None	24	0
2	NaOAc	1.5	5
3	Na_2HPO_4	1.5	11
4	NaHCO_3	3	20
5	K_2CO_3	6	36
6	$\text{Na}_3\text{PO}_4 \cdot 12 \text{H}_2\text{O}$	0.5	79
7 ^a	$\text{Na}_3\text{PO}_4 \cdot 12 \text{H}_2\text{O}$	0.5	68
8 ^b	$\text{Na}_3\text{PO}_4 \cdot 12 \text{H}_2\text{O}$	0.5	77

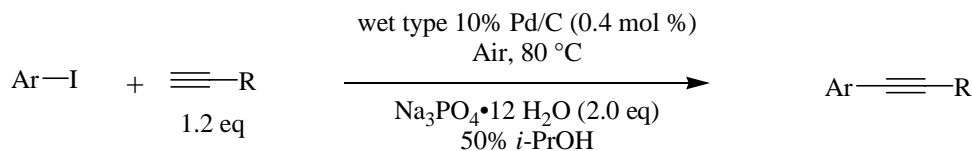
^a1.5 eq of $\text{Na}_3\text{PO}_4 \cdot 12 \text{H}_2\text{O}$ was used in this reaction

^b2.5 eq of $\text{Na}_3\text{PO}_4 \cdot 12 \text{H}_2\text{O}$ was used in this reaction

Table 4**Catalyst Loading**

Entry	X (mol %)	Time (h)	Isolated yield (%)
1	2	0.5	79
2	1	0.5	79
3	0.8	0.5	82
4	0.6	0.5	80
5	0.4	1	85
6	1.5	1.5	78

The researchers then went on to show that since the reaction was being run in 50% water, one could use wet catalyst in place of dry catalyst with minimal if any change in overall isolated yield. Furthermore, since there is no copper in the reaction, one does not have to rigorously exclude oxygen so the reaction does not have to be run under argon. In summary, the best conditions for the copper and amine free Sonogashira coupling are shown in Scheme 1.

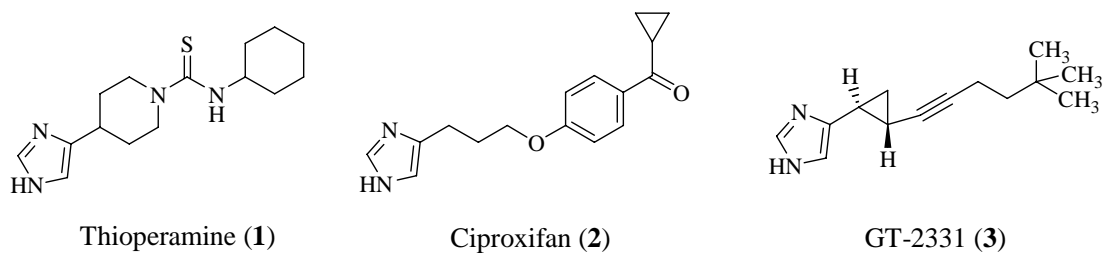
Scheme 1

“Design, Synthesis and SAR of Potent Substituted Benzothiazole-cyclobutane Histamine H₃ Receptor Antagonists,”

Chen Zhao, Minghue Sun, Thomas R. Miller, Timothy A. Esbenshade, Jill M. Wetter, Kennan C. Marsh, Jorge D. Brioni, Marlon D. Cowart, (Abbott Laboratories)

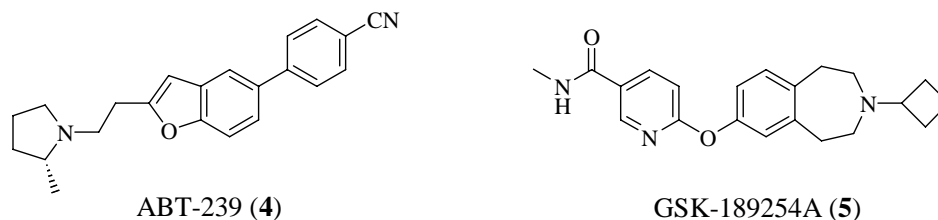
Researchers at Abbott have prepared a new series of H₃ antagonists based on benzothiazole-cyclobutanes. H₃ Antagonists have been proven to stimulate the release of neurotransmitters and therefore offer a promising approach for the treatment of several CNS disorders such as ADHD, sleep disorder, epilepsy, schizophrenia and obesity. Earlier generations of H₃ antagonists were based on structures containing an imidazole moiety as shown in Figure 1.

Figure 1



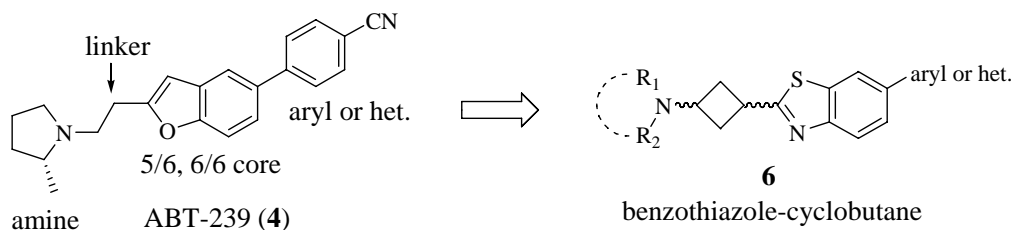
Recently, a non-imidazole containing class of compounds (Figure 2) has been developed by several research groups. It was found that a tertiary amine could replace the imidazole moiety.

Figure 2



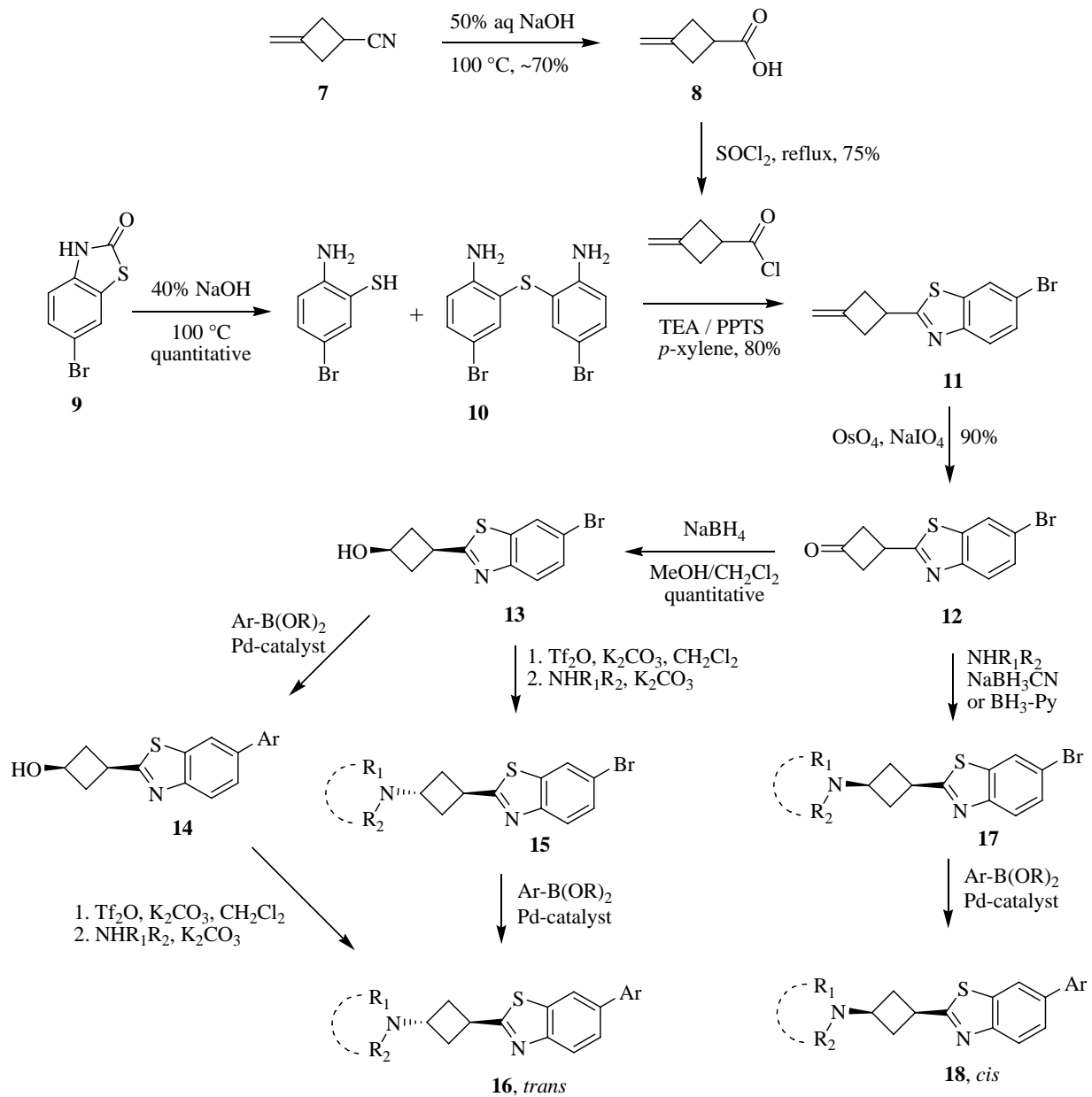
To further extend the structural diversity of H₃ antagonists, the researchers at Abbott designed a series of benzothiazole-cyclobutanes as shown in Figure 3. The benzothiazole core displays high H₃ binding potency and is relatively straight forward to make.

Figure 3



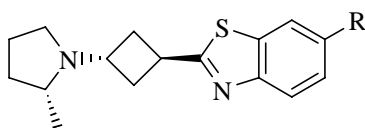
The synthesis of this class of compounds is shown in Scheme 1. The key intermediate ketone **12** can be made in three steps in about a 70% yield. Performing a reductive amination on **12** provides the *cis* compound **18** while reduction of **12** followed by activation of the alcohol and displacement by an amine provides the *trans* compound **16**.

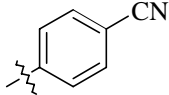
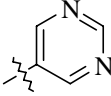
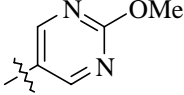
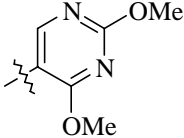
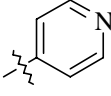
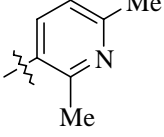
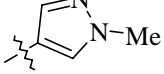
Scheme 1



A variety of different heterocycles were incorporated as shown in Table 1.

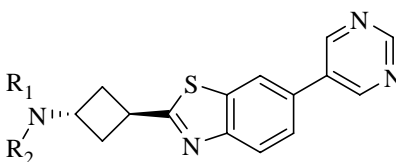
Table 1
Survey of Heterocycles

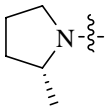

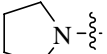
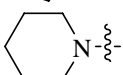
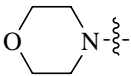


	R	hH ₃ Ki (nM)	rH ₃ Ki (nM)
19		0.14	0.28
20		0.06	0.08
21		0.06	0.06
22		0.07	0.13
23		0.17	0.24
24		0.08	0.10
25		0.05	0.09

Employing the heterocycle from compound **20**, they then moved on to optimize the amine portion of the molecule as shown in Table 2.

Table 2
Survey of Secondary Amines

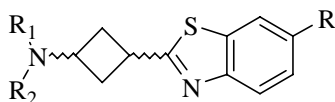


	NR ₁ R ₂	hH ₃ Ki (nM)	rH ₃ Ki (nM)
26		0.06	0.08
27		0.68	2.95
28		0.06	0.18
29		0.05	0.07
30		0.22	1.10

31		0.11	0.22
32		0.09	0.13
33		0.08	0.13
34		0.06	0.18
35		0.07	0.35

A few examples of *cis* vs. *trans* stereochemistry around the cyclobutane ring are shown in Table 3.

Table 3
cis vs. *trans* stereochemistry



	R	NR ₁ R ₂	<i>trans</i>		<i>cis</i>	
			hH ₃ Ki (nM)	rH ₃ Ki (nM)	hH ₃ Ki (nM)	rH ₃ Ki (nM)
36/37			0.09	0.13	1.00	2.00
38/39			0.05	0.09	1.41	2.95
40/41			0.11	0.21	4.07	45.6

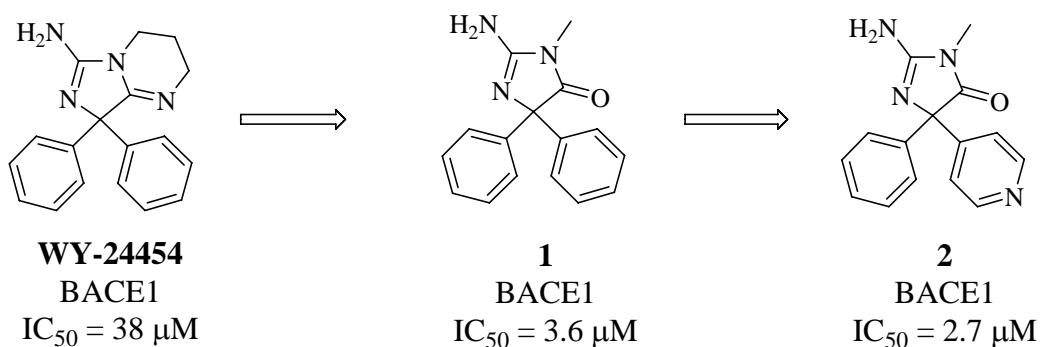
In conclusion, benzothiazole-cyclobutane compounds are novel and potent H₃ antagonists. The *trans* isomers are generally 10-200x more potent than their *cis* counterparts in vitro and most compounds in this series exhibited good to excellent PK profiles.

“Pyridinylaminohydantoin as small molecule BACE1 Inhibitors: Exploration of the S3 Pocket,”

Ping Zhou, Jonathan Bard, Rajiv Chopra, Kristi Y. Fan, Yun Hu, Yanfang Li, Ronald L. Magolda, Michael Malamas, Menelas Pangalos, Peter Reinhart, Jim Turner, Zheng Wang, Albert J. Robichaud, (Wyeth Research)

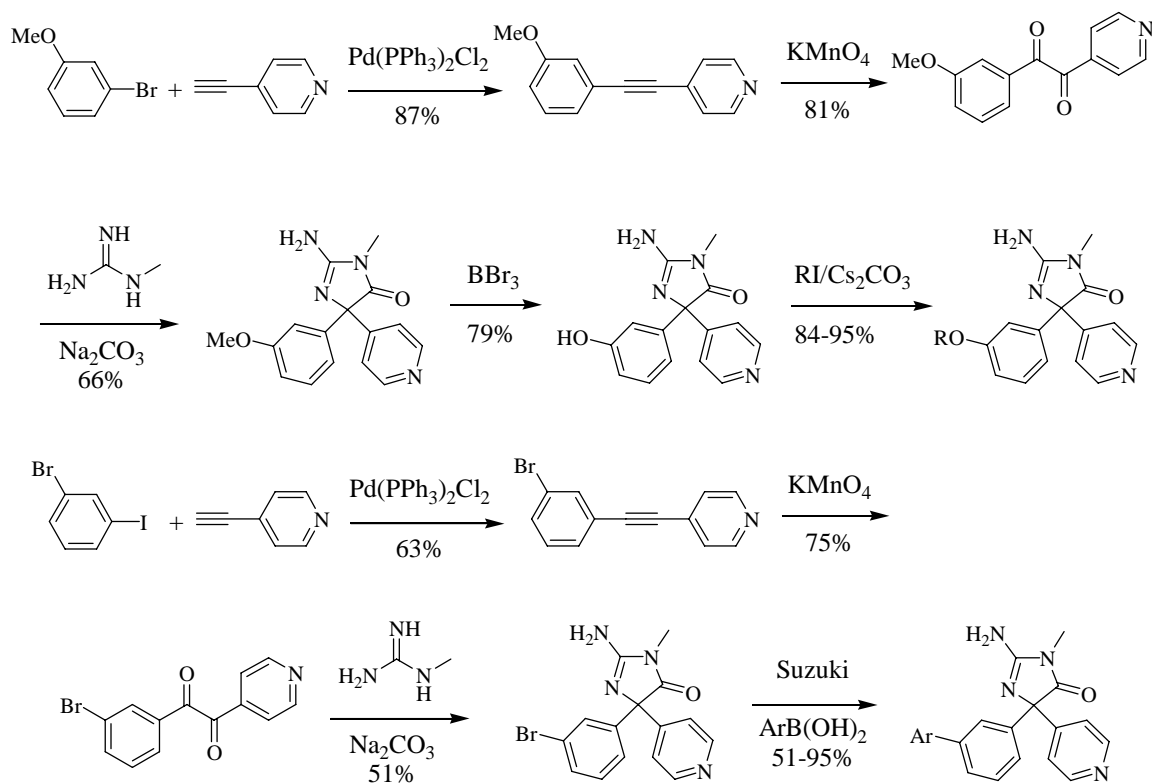
Researchers at Wyeth have been searching for novel compounds that inhibit BACE1 as a potential treatment for Alzheimer's disease. A high throughput screen identified WY-24454 as a potential starting point for optimization (Figure 1). Removal of the tetrahydropyrimidine ring gave hydantoin **1** which resulted in a ten-fold improvement in potency against BACE1. Replacement of one phenyl group in **1** with a pyridine gave compound **2** which showed even further improvement. Modeling studies suggested that functionalization of the phenyl group in **2** could further increase the potency by increasing the interaction with the S3 pocket.

Figure 1



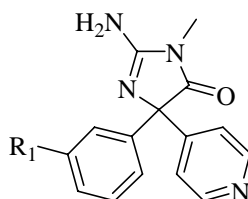
The general synthetic route is shown in Scheme 1. To generate a variety of alkoxy substituents, the phenol was alkylated as shown in the top of the scheme. To create a variety of biphenyl substituents, a Suzuki coupling was performed with an arylbromide as shown in the lower half of the scheme.

Scheme 1



The activity of the 3-alkoxy phenyl compounds is presented in Table 1. As can be seen, there was not much improvement in this series.

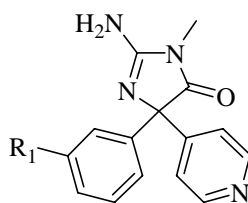
Table 1
3-Alkoxyphenyl pyridinyl aminohydantoin

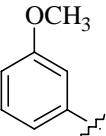
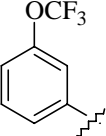
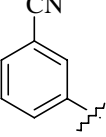
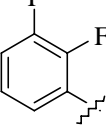
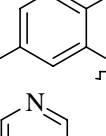
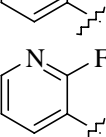
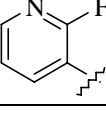


Compound	R ₁	IC ₅₀ (μM)
2	H	2.7
3	OH	3.4
4	OMe	3.1
5		0.2
6		0.1

In the biphenyl series (Table 2), there was more improvement observed. Many of the compounds were at least 50 times more potent than the parent compound.

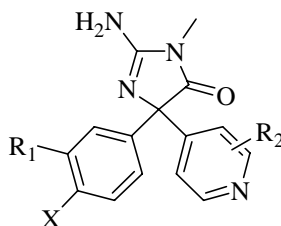
Table 2
Biphenyl and 3-Heteroarylphenyl pyridinyl aminohydantoins



Compound	R ₁	IC ₅₀ (μM)
7	Br	1.6
8	Ph	0.1
9		0.03
10		0.3
11		0.04
12		0.04
13		0.04
14		0.05
15		0.03

In an effort to further improve the affinity, a number of substituted pyridinyl compounds were prepared as shown in Table 3. These substitutions were also well tolerated and gave improvements in the binding affinity.

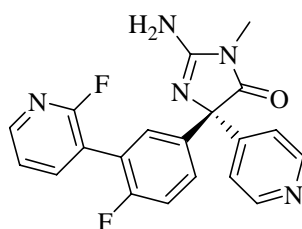
Table 3
Substituted-pyridinyl aminohydantoins



Compound	R ₁	R ₂	X	IC ₅₀ (μM)
2	H	H	H	2.7
8	Ph	H	H	0.1
16	Ph	2-Me	H	0.2
17		2- <i>i</i> Pr	H	0.2
18		2,6-di-Et	H	0.04
19		3-F	H	0.06
20		H	F	0.03

Several racemic compounds were separated into their corresponding enantiomerically pure forms. The (*S*)-enantiomers uniformly showed higher affinity and one example is shown in Figure 2.

Figure 2

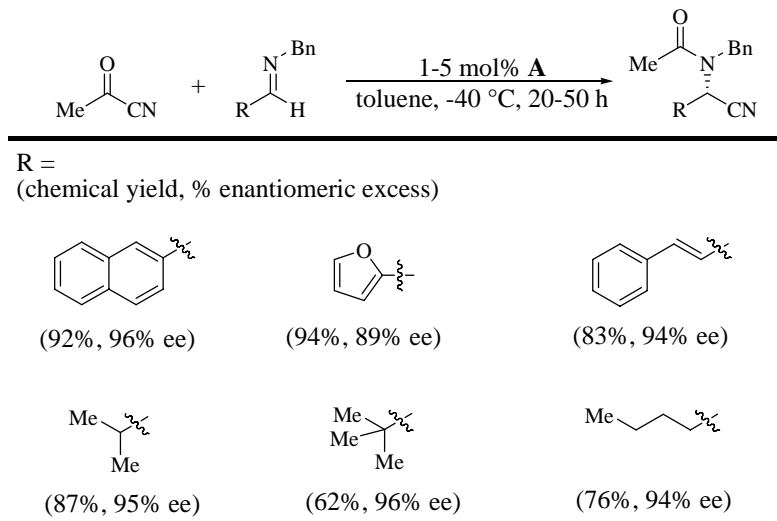


(*S*)-**20**: IC₅₀ = 7 nM

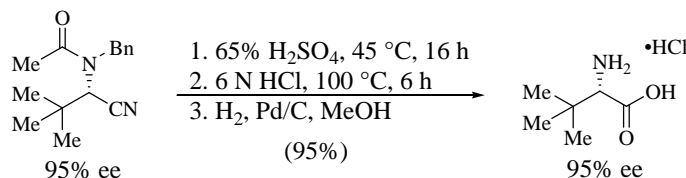
“Catalytic Asymmetric Acylcyanation of Imines,”

Subhas Chandra Pan, Jian Zhou and Benjamin List (Max-Planck-Institut für Kohlenforschung).

Researchers in Germany report on an interesting variation of a Strecker like reaction. Their efforts focused on the reaction of aldehyde imines with acyl cyanide (a less toxic cyanide source

Table 2

One of the primary uses of the Strecker reaction is the preparation of α -amino acids and thus nitrile hydrolysis and *N*-deprotection were demonstrated. In the example shown, an excellent yield of the α -amino acid was obtained while maintaining the integrity of the chiral center. The conditions outlined however may not be suitable for all of the analogues as the strongly acidic conditions as well as the hydrogenation step are expected to be incompatible with some functional groups.

Scheme 1

The reported methodology appears to be quite versatile. One area that was not discussed is whether or not both enantiomers of a product could be obtained by utilizing a different catalyst. An area for additional research may be to evaluate the applicability of the methodology with ketone imines as this could provide access to chiral quaternary centers.

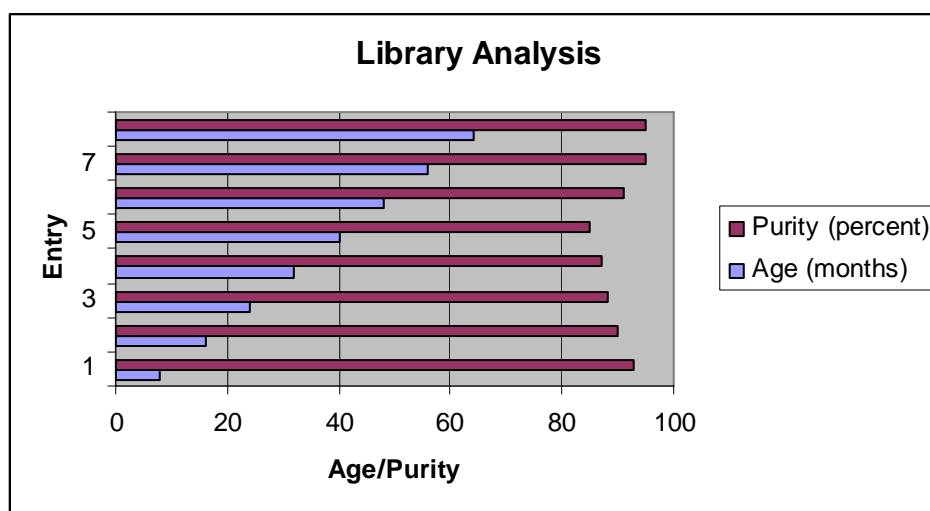
“Analysis of Sample Purity and Integrity Data Using Structural Fragments: Patterns in the Stability of Compounds Stored as Solutions,”

L. Greenblatt, D. Mobilio, R. Nilakantan, (Wyeth Research Chemical & Screening Sciences).

Corporate sample libraries have become a customary source of chemical leads for pharmaceutical programs thus the purity/quality of these libraries is a critical concern. These sample libraries are frequently available to screening programs as solutions in DMSO, having regularly been stored at low temperature for extended periods. Researchers at Wyeth set out to evaluate the integrity of a library and if possible identify common functional groups that may be more prone to degradation.

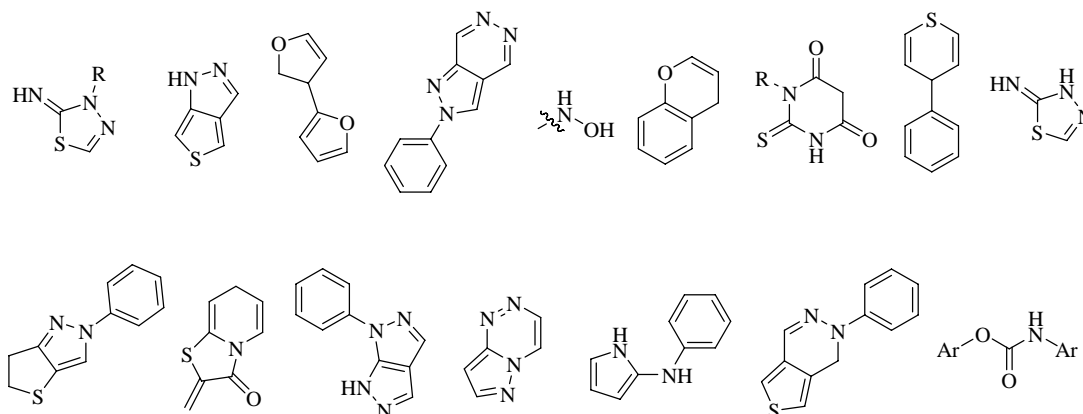
About 37,000 compounds that had been stored as DMSO solutions for variable periods of time were analyzed by LC/UV/MS. The sample age ranged from 0 to 63 months. Following analysis, it was discovered that the average purity of the samples remained relatively constant over time with an average purity of 86%. While the median age of samples was 37 months, 75% of the samples were found to be >88% pure and 59% of the samples were found to be >99% pure.

Figure 1



The Wyeth team subsequently analyzed the samples with a purity level of <80% for common functionality. A majority of the common fragments were present in less than 40 structures thus a detailed analysis was conducted for common fragments that were present in more than 40 structures. Figure 2 contains some common fragments (functionality) that were found in structures with failure rates of >70%.

Figure 2



Many of the structures with high failure rates contained functionality, such as a divalent sulfur, that was susceptible to oxidation. These findings suggest that improved methods for the storage of samples in the absence of oxygen may be beneficial. The results of this study validate the strategy of analyzing corporate libraries of samples stored in DMSO as the overall integrity of

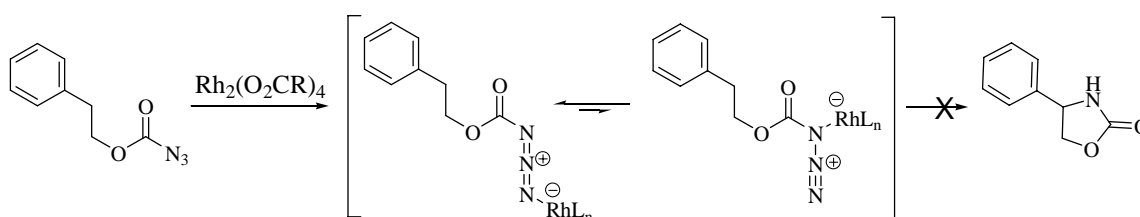
the library was very good however caution should be used when screening structures that may be more susceptible to oxidation.

“Rhodium-Catalyzed C-H Insertion of Nitrene Intermediates,”

Kim Huard, H  l  ne Lebel, (Universit   de Montr  al).

The preparation of organic amine derivatives is valuable to both large scale industrial processes and small scale research. Researchers from Montreal report on the chemistry of metal nitrenes which they first envisioned could be derived from the activation of azides with a rhodium complex. However, upon treatment of an azidoformate with a rhodium complex no nitrene formation was observed.

Scheme 1

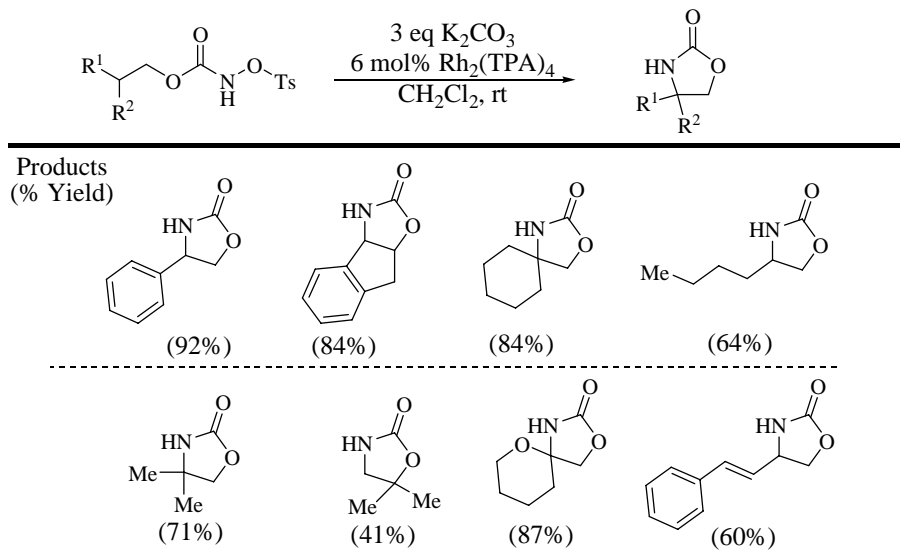


It was postulated that rhodium complexation was occurring on the terminal nitrogen thus preventing the expulsion of nitrogen toward the formation of a metal nitrene. This research group set out to explore the possibility of achieving the desired transformation by preparing a less coordinating leaving group. A series of *N*-oxycarbamates were treated with a rhodium catalyst and the yield of nitrene insertion products (a cyclic carbamate) obtained. Excellent yields of cyclic carbamate were obtained when using a *N*-tosyloxycarbamate (tosylate leaving group).

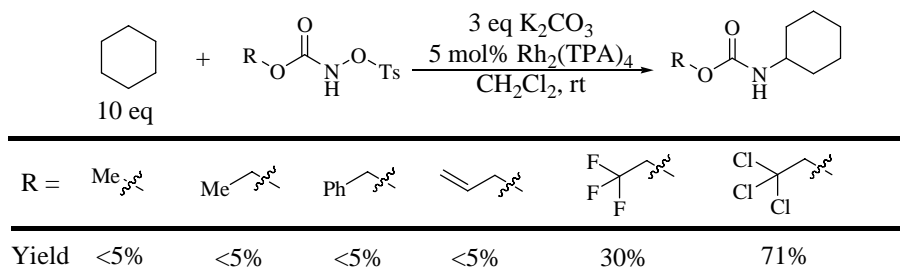
Table 1

R =	
Yield =	<5% <5% <5% 15% >95%

The intramolecular *N*-tosyloxycarbamate approach was subsequently applied to a diverse set of scaffolds. Yields of the nitrene insertion products were generally very good thus it is envisioned that this methodology could prove of value in discovery programs if applied to novel scaffolds. Formation of the C-N bond is reported to be stereospecific (not shown) and the reaction is dependent on the presence of water (not shown).

Table 2

Intermolecular nitrene insertion into C-H bonds was also explored. A series of *N*-tosylloxycarbamates were evaluated and trichloroethyl *N*-tosylloxycarbamate was found to give excellent yields of a Troc protected amine.

Table 3

Several symmetrical aliphatic materials were derivatized to give Troc protected aliphatic amines in good yields. If possible insertion at a tertiary carbon took precedent over insertion at a secondary carbon. Benzylic insertions were also reported and in the case of readily available starting materials, the yield of Troc protected products could be increased by increasing the number of equivalents of substrate used.

Table 4

Cond A: 5 eq
 Cond B: 15 eq

Products

Yield Conditions A				
	68%	78%	61%	52%
Yield Conditions B				
	75%	87%	71%	65%

Diphenyl substrates were also suitable for derivatization (note it is not clear if an additional solvent was used in these experiments). This has the potential to be very useful as it demonstrates that unsymmetrical diphenylmethyl amines can be prepared. It should be noted that a diphenyl methane analogue where one phenyl was substituted with methyl did lead to two products and in fact insertion on the doubly benzylic center (25%) was less than on the tolyl methyl group (32%). Despite the selectivity issue when more than one benzylic center is present, this methodology should find applications in research programs particularly if it proves viable for derivatization of analogues containing additional functional groups. It may also prove of value to the cost effective large scale manufacturing of amines. For the future it would be interesting to modify the approach to provide access to enantiomerically enriched chiral compounds.

Table 5

5 eq
 1 eq

Products

Yield =	60%	61%	37%
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