

REPORT DOCUMENTATION PAGE			Form Approved OMB NO. 0704-0188		
The public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington VA, 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.					
1. REPORT DATE (DD-MM-YYYY) 02-05-2011		2. REPORT TYPE Final Report		3. DATES COVERED (From - To) 1-Feb-2005 - 14-Jun-2010	
4. TITLE AND SUBTITLE Final Report			5a. CONTRACT NUMBER		
			5b. GRANT NUMBER W911NF-04-D-0004		
			5c. PROGRAM ELEMENT NUMBER 611102		
6. AUTHORS Stephen J Lee, Michel R Gagne			5d. PROJECT NUMBER		
			5e. TASK NUMBER		
			5f. WORK UNIT NUMBER		
7. PERFORMING ORGANIZATION NAMES AND ADDRESSES University of North Carolina - Chapel Hill Office of Sponsored Research The University of North Carolina at Chapel Hill Chapel Hill, NC 27599 -1350			8. PERFORMING ORGANIZATION REPORT NUMBER		
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Research Office P.O. Box 12211 Research Triangle Park, NC 27709-2211			10. SPONSOR/MONITOR'S ACRONYM(S) ARO		
			11. SPONSOR/MONITOR'S REPORT NUMBER(S) 47516-CH-SR.1		
12. DISTRIBUTION AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision, unless so designated by other documentation.					
14. ABSTRACT The use of dynamic Combinatorial Chemistry to discover, new synthetic receptors is fledgling and its rules remain to be established. This work has articulated how important molecular recognition elements such as h-bonding, aromatic interactions, and especially C-H pi interactions can control how both small molecules and large molecules interact in a recognition scenario.					
15. SUBJECT TERMS molecular recognition					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT UU	15. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON Stephen Lee
a. REPORT UU	b. ABSTRACT UU	c. THIS PAGE UU			19b. TELEPHONE NUMBER 919-549-4365

Report Title

Final Report

ABSTRACT

The use of dynamic Combinatorial Chemistry to discover, new synthetic receptors is fledgling and its rules remain to be established. This work has articulated how important molecular recognition elements such as h-bonding, aromatic interactions, and especially C-H pi interactions can control how both small molecules and large molecules interact in a recognition scenario.

List of papers submitted or published that acknowledge ARO support during this reporting period. List the papers, including journal references, in the following categories:

(a) Papers published in peer-reviewed journals (N/A for none)

“Constitutional, Diastereo- and Enantioselective Amplification of 84-Membered Macrocyclic Hosts for (–)-Cytidine” M. K. Chung, K. Severin, S. J. Lee, M. L. Waters, M. R. Gagné, Chem. Science 2011, 2, 744-747.

“Dynamic Cyclic Thiodipeptide Libraries From Thiol-Thioester Exchange” S. Ghosh, L. A. Ingeman, A. Frye, S. J. Lee, M. R. Gagné, M. L. Waters, Org. Lett. 2010, 12, 1860-1863.

“Synthesis of interlocked 56-membered rings by dynamic self-templating” M. K. Chung, P. S. White, S. J. Lee, M. R. Gagné, Angew. Chem. Int. Ed. 2009, 48, 8683-8686.

“Gold(I)-Catalyzed Cascade Cyclization of Allenyl Epoxides” M. A. Tarselli, J. L. Zuccarello, S. J. Lee, M. R. Gagné, Org. Lett. 2009, 11, 3490-3492.

“Sn-Free Ni-Catalyzed Reductive Coupling of Glycosyl Bromides with Activated Alkenes” H. Gong, R. S. Andrews, J. L. Zucarello, S. J. Lee, M. R. Gagné, Org. Lett. 2009, 11, 879-882.

“The Effect of Gas-Phase Reactions on the Quantitation of Cyclic Hydrazone Libraries by Electrospray Ionization (ESI) Mass Spec” H. Schiltz, M.-K. Chung, S. J. Leeb and M. R. Gagné, Org. Biomol. Chem., 2008, 6, 3597-3600.

“Deracemization of a Racemic Dynamic Combinatorial Library Induced by (–)-Cytidine and (–)-2-Thiocytidine” M.-K. Chung, C. M. Hebling, J. W. Jorgenson, K. Severin, S. J. Lee, M. R. Gagné J. Am. Chem. Soc. 2008, 130, 11819-11827.

“Gold(I)-Catalyzed Asymmetric Cycloisomerization of Ene-Allenenes into Vinyl-cyclohexenes” M. A. Tarselli, A. R. Chianese, S. J. Lee, M. R. Gagné, Angew. Chem. Int. Ed. 2007, 46, 6670-6673.

“Electrophilic Activation of Alkenes by Pt(II): So Much More Than a Slow Version of Pd(II)” A. R. Chianese, S. J. Lee, M. R. Gagné, Angew. Chem. Int. Ed. 2007, 46, 4042-4059.

“The Discovery of an Enantioselective Receptor for (–)-adenosine from a Racemic Dynamic Combinatorial Library” S. M. Voshell, S. J. Lee, M. R. Gagné, J. Am. Chem. Soc. 2006, 128, 12422-12423.

“Modulating the Activity and Selectivity of an Immobilized Ru-Porphyrin Catalyst using a Fluorous Solvent” E. Burri, S. M. Leeder, K. Severin, M. R. Gagné, Adv. Synth. & Cat. 2006, 348, 1640-1644.

Number of Papers published in peer-reviewed journals: 11.00

(b) Papers published in non-peer-reviewed journals or in conference proceedings (N/A for none)

Number of Papers published in non peer-reviewed journals: 0.00

(c) Presentations

each year at the DTRA S&T Conference

Number of Presentations: 4.00

Non Peer-Reviewed Conference Proceeding publications (other than abstracts):

Number of Non Peer-Reviewed Conference Proceeding publications (other than abstracts): 0

Peer-Reviewed Conference Proceeding publications (other than abstracts):

Number of Peer-Reviewed Conference Proceeding publications (other than abstracts): 0

(d) Manuscripts

Number of Manuscripts: 0.00

Patents Submitted

Patents Awarded

Awards

Graduate Students

<u>NAME</u>	<u>PERCENT SUPPORTED</u>
Shannon Leeder	1.00
Sharon Voshell	1.00
Steve Andrews	0.25
FTE Equivalent:	2.25
Total Number:	3

Names of Post Doctorates

<u>NAME</u>	<u>PERCENT SUPPORTED</u>
Mee-Kyung Chung	0.25
Anthony Chianese	1.00
Luke Zucarello	1.00
FTE Equivalent:	2.25
Total Number:	3

Names of Faculty Supported

<u>NAME</u>	<u>PERCENT SUPPORTED</u>	National Academy Member
Michel Gagne	0.00	No
FTE Equivalent:	0.00	
Total Number:	1	

Names of Under Graduate students supported

NAME

PERCENT SUPPORTED

FTE Equivalent:

Total Number:

Student Metrics

This section only applies to graduating undergraduates supported by this agreement in this reporting period

The number of undergraduates funded by this agreement who graduated during this period: 1.00

The number of undergraduates funded by this agreement who graduated during this period with a degree in
science, mathematics, engineering, or technology fields:..... 0.00

The number of undergraduates funded by your agreement who graduated during this period and will continue
to pursue a graduate or Ph.D. degree in science, mathematics, engineering, or technology fields:..... 1.00

Number of graduating undergraduates who achieved a 3.5 GPA to 4.0 (4.0 max scale):..... 1.00

Number of graduating undergraduates funded by a DoD funded Center of Excellence grant for
Education, Research and Engineering:..... 0.00

The number of undergraduates funded by your agreement who graduated during this period and intend to
work for the Department of Defense 0.00

The number of undergraduates funded by your agreement who graduated during this period and will receive
scholarships or fellowships for further studies in science, mathematics, engineering or technology fields: 0.00

Names of Personnel receiving masters degrees

NAME

Holly Schiltz

Total Number:

1

Names of personnel receiving PHDs

NAME

Shannon Leeder

Sharon Voshell

Total Number:

2

Names of other research staff

NAME

PERCENT SUPPORTED

FTE Equivalent:

Total Number:

Sub Contractors (DD882)

Inventions (DD882)

Scientific Progress

see attached

Technology Transfer

Final Report

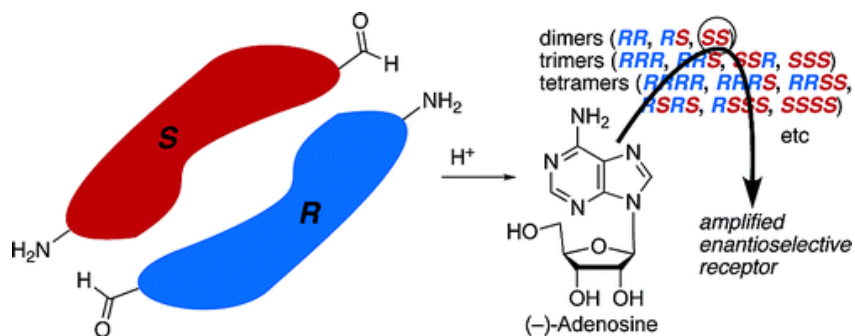
Dr. Stephen J. Lee

W911NF-04-D-0004

Dynamic Combinatorial Chemistry (DCC) is emerging as a new approach to discover synthetic receptors for a broad array of guests. One important reason for its applicability is the fact that the assay is carried out under competitive selection conditions, which causes only the most competent host to be amplified over its competitors. Research efforts have been primarily been focused on articulating the “rules” which describe how this phenomenon presents itself and also utilizes the known methodologies for molecular recognition. When non-obvious strategies are discovered, these situations were examined in more detail. Outlined below are our contributions to the discovery and selection of new molecular receptors for binding and catalysis.

“The Discovery of an Enantioselective Receptor for (–)-Adenosine from a Racemic Dynamic Combinatorial Library” Sharon M. Voshell, Stephen J. Lee, and Michel R. Gagné *J. Am. Chem. Soc.*, **2006**, 128, 12422–12423.

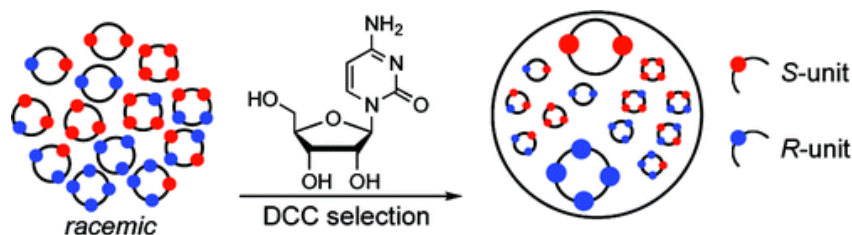
The use of laser polarimetry detection coupled with HPLC is demonstrated to enable the discovery of enantioselective receptors from racemic dynamic combinatorial libraries. Templating with an enantiopure analyte, such as (–)-adenosine, leads to amplification of one enantiomer of the cyclic dimer. A result confirmed with a pseudo-racemic library wherein one of the enantiomers was d-labeled for mass spec analysis. The resulting dimer is thus an enantioselective receptor for (–)-adenosine.



“Deracemization of a Dynamic Combinatorial Library Induced by (–)-Cytidine and (–)-2-Thiocytidine” Mee-Kyung Chung, Christine M. Hebling, James W. Jorgenson, Kay Severin, Stephen J. Lee and Michel R. Gagné *J. Am. Chem. Soc.*, **2008**, 130, 11819–11827.

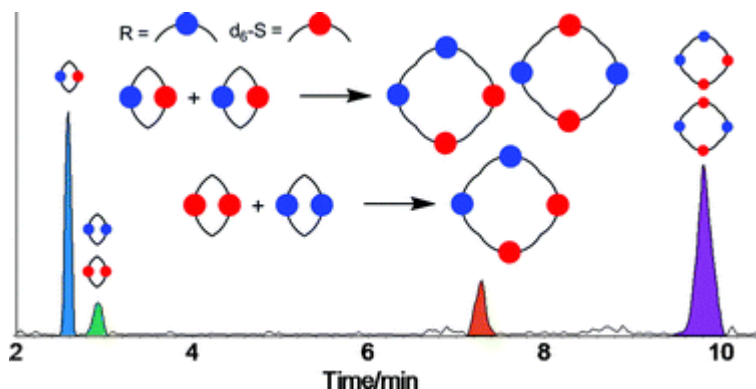
A dynamic combinatorial library composed of racemic hydrazone-based dipeptides becomes deracemized on binding to the chiral analytes (–)-cytidine and (–)-2-thiocytidine through the amplification of two receptors, (SS)-dimer and (RRRR)-tetramer. The deracemization phenomenon was investigated by laser polarimetry, mass-tagged pseudo-enantiomers in

conjunction with electrospray ionization mass spectrometry, HPLC/UV-MS, UPLC/UV-MS, rapid-resolution LC-MS, collision-induced dissociation MS/MS, and numerical simulations. These data were consistent with a phenomenon where (*SS*)-dimer and (*RRRR*)-tetramer selectively bind the chiral analyte in preference to their enantiomeric counterparts, which ultimately causes them to be amplified and the library to become deracemized.



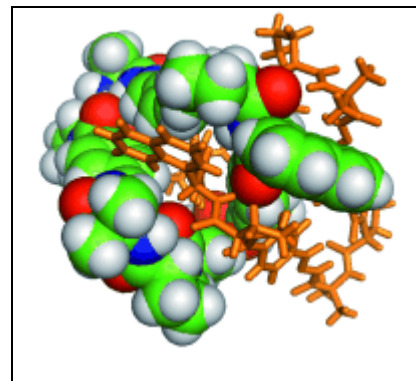
“The effect of gas-phase reactions on the quantitation of cyclic hydrazone libraries by electrospray ionization (ESI) mass spectrometry” Holly Schiltz, Mee-Kyung Chung, Stephen J. Lee and Michel R. Gagné *Org. Biomol. Chem.*, **2008**, 6, 3597-3600.

Using mass spectrometry coupled with LC analysis we report evidence of diastereomer dependent fragmentation and oligomerization reactions in the ionization of acyl-hydrazone-based libraries of cyclic oligomers. These effects can significantly affect the accuracy of MS-based quantitations, but also provide a venue for examining ionization effects in dynamic combinatorial libraries (DCLs).



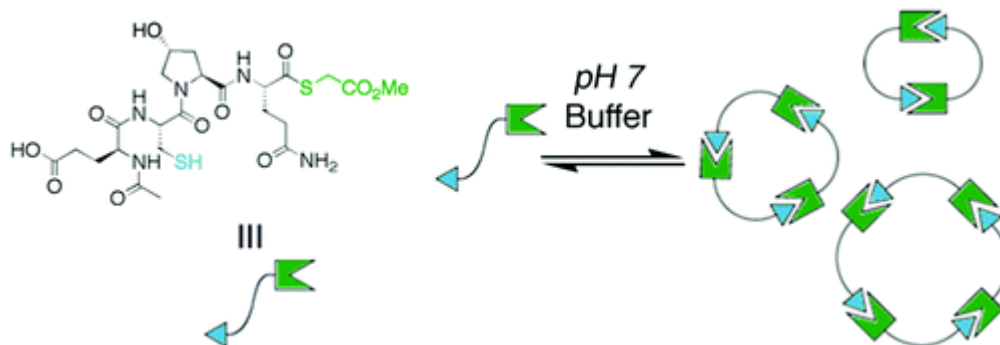
“Synthesis of Interlocked 56-Membered Rings by Dynamic Self-Templating” Mee-Kyung Chung, Peter S. White, Stephen J. Lee, and Michel R. Gagné* *Angew. Chem. Int. Ed.* **2009**, 48, 8683-8686.

A love of self: Narcissistic macrocyclic rings self-assemble into highly ordered, chiral [2]-catenanes displaying high component diastereoselectivity. The picture shows one such structure. One ring is shown in a space-filling representation, while the other is shown as orange sticks.



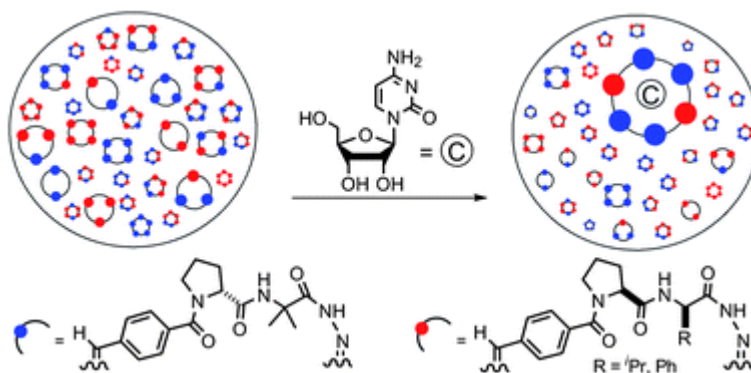
“Dynamic Cyclic Thiopeptide Libraries From Thiol-Thioester Exchange” Soumyadip Ghosh, Lindsey A. Ingeman, Aaron G. Frye, Stephen J. Lee, Michel R. Gagné and Marcey L. Waters *Org. Lett.*, **2010**, 12, 1860–1863.

Thiol–thioester exchange was found to readily generate libraries of cyclic thiopeptides under thermodynamic control, which will enable their use in a variety of dynamic combinatorial chemistry assays. The kinetic determinants of macrocycle formation and the role of amino acid structure on the reaction dynamics are discussed.



“Constitutionally selective amplification of multicomponent 84-membered macrocyclic hosts for (–)-cytidine•H⁺” Mee-Kyung Chung, Kay Severin, Stephen J. Lee, Marcey L. Waters and Michel R. Gagné* *Chem. Sci.*, **2011**, 2, 744-747.

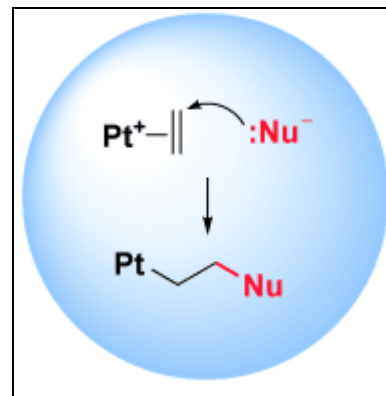
Mixtures of dipeptide monomers create stereochemically and constitutionally complex dynamic libraries of potential receptors. When (–)-cytidine was utilized as guest an 84-membered cyclic host was amplified (70–175 fold) from a nearly undetectable initial concentration. Only the specified diastereomeric combination of the two chiral building blocks yielded a dynamic library from which the macrocyclic receptor could be amplified.



Catalysis

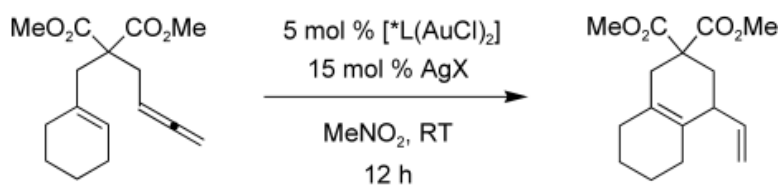
“Electrophilic Activation of Alkenes by Platinum(II): So Much More Than a Slow Version of Palladium(II)” Anthony R. Chianese, Stephen J. Lee, Michel R. Gagné *Angew. Chem. Int. Ed.* **2007**, 46, 4042-4059.

The electrophilic activation of alkenes by transition-metal catalysts is a fundamental step in a rapidly growing number of catalytic processes. Although palladium is the best known metal for this purpose, the special properties of its third-row cousin platinum (strong metal–ligand bonds and slow substitution kinetics) have enabled the development of transformations that are initiated by addition to the C=C bonds by protic carbon, nitrogen, oxygen, and phosphorus nucleophiles, as well as alkene or arene nucleophiles. Additionally, reactivity profiles, which are often unique to platinum, provide wholly new reaction products. This Review concerns platinum-catalyzed electrophilic alkene activation reactions, with a special emphasis on the mechanistic properties of known systems, on the differences between platinum and palladium catalysts, and on the prospects for the development of new systems.



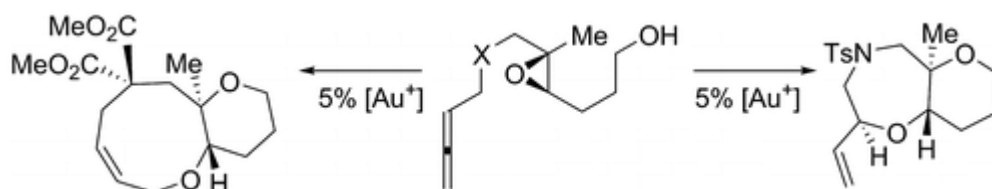
“Gold(I)-Catalyzed Asymmetric Cycloisomerization of Eneallenes into Vinylcyclohexene” Michael A. Tarselli, Anthon R. Chianese, Stephen J. Lee, Michel R. Gagné* *Angew. Chem. Int. Ed.* **2007**, 46, 6670-6673.

Cycloisomerization of eneallenes by cationic gold(I) catalysts produces vinylcyclohexene derivatives in up to 77 % ee, using [3,5-xylyl-binap(AuCl)₂] and AgOTf additive (see scheme; 3,5-xylyl-binap=2,2'-bis(di(3,5-xylyl)phosphino)-1,1'-binaphthyl). The procedure is amenable to the synthesis of mono- and bicyclic products and is tolerant of ester, alcohol, and amide groups.



“Gold(I)-Catalyzed Cascade Cyclization of Allenyl Epoxides” Michael A. Tarselli, J. Lucas Zuccarello, Stephen J. Lee and Michel R. Gagné *Org. Lett.*, **2009**, *11*, 3490–3492.

Cationic gold(I) phosphite catalysts activate allenes for epoxide cascade reactions. The system is tolerant of numerous functional groups (sulfones, esters, ethers, sulfonamides) and proceeds at room temperature in dichloromethane. The cyclization pathway is sensitive to the substitution pattern of the epoxide and the backbone structure of the A-ring. It is capable of producing medium-ring ethers, fused 6-5 bicyclic, and linked pyran-furan structures. The resulting cycloisomers are reminiscent of structures found in numerous polyether natural products.



“Sn-Free Ni-Catalyzed Reductive Coupling of Glycosyl Bromides with Activated Alkenes” Hegui Gong, R. Stephen Andrews, Joseph L. Zuccarello, Stephen J. Lee and Michel R. Gagné* *Org. Lett.*, **2009**, *11*, 879–882.

A mild, stereoselective method for the Ni-catalyzed synthesis of α -C-alkylglycosides is reported. This approach entails the reductive coupling of glycosyl bromides with activated alkenes at room temperature, with low alkene loading as an important feature. Diastereoselective coupling with 2-substituted acrylate derivatives was made possible through the use of 2,4-dimethyl-3-pentanol as a proton source.

