Form Approved Through 09/30/2011 OMB No. 0925-0002

Department of Health and Human Services
Public Health Service

DEC 1

12150871

onal Research Service
owship Application

Follow instructions carefully.
Do not exceed character length restrictions indicated.

PI: OLSON, ANGELA C
1 F31 GM089137-01
Dual:
IRG: ZRG1 CB-N(29) L

Council: 05/2009
Received: 12/16/2008

1. TITLE OF RESEARCH TRAINING PROPOSAL (Do not exceed 81 char [illegible])
Catalytic Asymmetric Synthesis of Vinyl Chromans Using Palladium(II) Catalysts

2. LEVEL OF FELLOWSHIP
Predoctoral

3. RESPONSE TO SPECIFIC REQUEST FOR APPLICATIONS OR PROGRAM ANNOUNCEMENT (If "Yes," state number and title) ☐ NO ☒ YES
Number: PA-07-106 Title: Ruth L. Kirschstein National Research Service Awards for Individual Predoctoral Fellowships (F31) to Promote Diversity in Health-Related Research

4a. NAME OF APPLICANT (Last, First, Middle)
Olson, Angela, Christine

4b. ERA COMMONS USER NAME

4c. HIGHEST DEGREE(S)
B.S.

4d. PRESENT MAILING ADDRESS (Street, City, State, Zip Code)

4e. PERMANENT MAILING ADDRESS (Street, City, State, Zip Code)

4f. E-MAIL ADDRESS: [redacted]

TELEPHONES AND FAX (Area code, number and extension)

4g. OFFICE
949-824-9017

4h. HOME

4i. PERMANENT

4j. FAX NUMBER
949-824-3866

4k

5. TRAINING UNDER PROPOSED AWARD (See Fields of Training)
Discipline No.: 1770
Subcategory Name: Synthetic Chemistry

6. PRIOR AND/OR CURRENT NRSA SUPPORT (Individual or Institutional)
☒ NO ☐ YES (If "Yes," refer to item 22, Form Page 5)

7a. DATES OF PROPOSED AWARD
From (MM/DD/YY): 07/01/09
Through (MM/DD/YY): 06/30/12

7b. PROPOSED AWARD DURATION (in months): 36

8. DEGREE SOUGHT DURING PROPOSED AWARD
Degree: Ph.D.
Expected Completion Date: 06/2012

9. HUMAN SUBJECTS RESEARCH
☒ No ☐ Yes
☐ Indefinite

9b. Federalwide Assurance No.
N/A

9c. Clinical Trial ☒ No ☐ Yes

9d. NIH-defined Phase III Clinical Trial ☒ No ☐ Yes

10. VERTEBRATE ANIMALS ☒ No ☐ Yes

10a. Animal Welfare Assurance No.
N/A

9a. Research Exempt ☒ No ☐ Yes
If "Yes," Exemption No. N/A

11. SPONSORING INSTITUTION
Name: Regents, University of California
Address: Sponsored Projects Administration
University of California, Irvine
300 University Tower
Irvine, CA 92697-7600

12a. ENTITY IDENTIFICATION NO.
1-95-2226406-A1

12b. DUNS NO.
04-670-5849

13. OFFICIAL SIGNING FOR SPONSORING INSTITUTION
Name: Judith Aguirre
Title: Contract and Grant Officer
Address: Sponsored Projects Administration
University of California, Irvine
300 University Tower
Irvine, CA 92697-7600
Tel: (949) 824-0446 Fax: (949) 824-2094
E-Mail: judith.aguirre@uci.edu

14. APPLICANT ORGANIZATION CERTIFICATION AND ACCEPTANCE: I certify that the statements herein are true, complete, and accurate to the best of my knowledge, and I agree to comply with the terms and conditions of award if an award is issued as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. Angela C. Olson 1/6/08

SIGNATURE OF OFFICIAL NAMED IN 13. (In ink. "Per" signature not acceptable.)

DATE 1-7-09

Judith Aguirre
Contract & Grant Officer

Kirschstein–NRSA Individual Fellowship Application *(To be completed by applicant – follow PHS 416-1 instructions)*	NAME OF APPLICANT *(Last, first, middle initial)* Olson, Angela, C.

SPONSOR and Co-Sponsor Information

15. NAME OF SPONSOR	16. NAME OF Co-SPONSOR *(When applicable)*
15a. NAME AND DEGREE(S) Professor Larry E. Overman, Ph.D.	16a. NAME AND DEGREE(S) N/A
15b. ERA COMMONS USER NAME [redacted]	16b. ERA COMMONS USER NAME
15c. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT Chemistry	16c. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT
15d. MAJOR SUBDIVISION Physical Sciences	16d. MAJOR SUBDIVISION
15e. Address: University of California, Irvine Chemistry Department 1102 Natural Sciences 2 Irvine, CA 92697-2025 Telephone: [redacted] Fax: [redacted] E-Mail: [redacted]	16e. Address: Telephone: Fax: E-Mail:

RESEARCH PROPOSAL

17. DESCRIPTION: See instructions. State the application's broad, long-term objectives and specific aims, making reference to the health relatedness of the project (i.e., relevance to the **mission of the agency**). Describe concisely the research design and methods for achieving these goals. Describe the rationale and techniques you will use to pursue these goals.

In addition, in two or three sentences, describe in plain, lay language the relevance of this research to public health. If the application is funded, this description, as is, will become public information. Therefore, do not include proprietary/confidential information. **DO NOT EXCEED THE SPACE PROVIDED.**

The proposal describes the development of a mild and efficient method for the catalytic asymmetric synthesis of vinyl chromans. The chroman motif is present in numerous small molecules of biological importance and the current methods available to access these substrates are limited.

The SN2' allylic substitution chemistry of trichloroacetimidates using a tethered phenol nucleophile will be examined using chiral cobalt oxazoline palladium(II) catalysts. An efficient and convergent method to access a variety of key cyclization substrates will be developed. The scope of functional groups and substitution patterns compatible with this system will be explored. A variety of heterocycles with important biological activity may also be synthesized using this chemistry. This methodology will allow easy access to a broader range of biologically active small molecules and their analogues.

This proposal describes the development of a general method to access biologically important small molecules in a selective manner. This methodology will be beneficial to the synthetic community because a vast number of small molecules and their analogues will be readily available and their biological activity can be explored.

18. GOALS FOR KIRSCHSTEIN-NRSA FELLOWSHIP TRAINING AND CAREER

My main interest in research is the development of novel methodology and its application in organic synthesis. Currently, my specific area of research focuses on intramolecular reactions of allylic trichloroacetimidates. I hope to expand upon the cobalt oxazoline palladacycle-catalyzed SN2' allylic substitution reactions that have been developed in our group. By studying these new reactions, I hope to gain new insight into these types of transformations and develop new tools for the synthetic community.

During my graduate studies, I would like to further develop my research skills by learning new techniques and improving my ability to approach, analyze, and solve problems in organic chemistry. I am interested in applications of organic chemistry in a government laboratory setting. I would like to contribute to the well-being and health of our society through research and development.

19. ACTIVITIES PLANNED UNDER THIS AWARD: Approximate percentage of proposed award time in activities identified below. *(See instructions.)*

Year	Research	Course Work	Teaching	Clinical
First	100%			
Second	100%			
Third	100%			
PREDOCTORAL FELLOWSHIPS ONLY				
Fourth				
Fifth				
MD/PhD FELLOWSHIPS ONLY				
Sixth				

Briefly explain activities other than research and relate them to the proposed research training.
N/A

20. TRAINING SITE(S) *Is the Primary Training Site the same as the Sponsoring Institution?* ☒ Yes ☐ No

If No, provide detailed information below for the Primary Training Site Location

Organizational Name:

DUNS:

Street 1: Street 2:

City: County: State:

Province: Country: Zip/Postal Code:

Project/Performance Site Congressional Districts:

21. HUMAN EMBRYONIC STEM CELLS ☒ No ☐ Yes

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list:
http://stemcells.nih.gov/research/registry/eligibilityCriteria.asp. *Use continuation pages as needed.*

If a specific line cannot be referenced at this time, include a statement that one from the Registry will be used.

Cell Line

Name of Applicant (Last, first, middle): Olson, Angela, Christine

APPLICANT/FELLOW BIOGRAPHICAL SKETCH

USE ONLY FOR INDIVIDUAL PREDOCTORAL and POSTDOCTORAL FELLOWSHIPS. DO NOT EXCEED FOUR PAGES.

NAME OF APPLICANT/FELLOW	POSITION TITLE
Angela Christine Olson	Graduate Student Researcher
eRA COMMONS USER NAME (credential, e.g., agency login)	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Northern State University-Aberdeen, South Dakota	B.S.	2001-2006	Chemistry, Biology
University of California Irvine-Irvine, California	Ph.D.	Anticipated completion 2012	Organic Chemistry

Please refer to the application instructions in order to complete sections A, B, and C of the Biographical Sketch.

A. Positions and Honors

ACTIVITY/OCCUPATION	BEGINNING DATE (mm/yy)	ENDING DATE (mm/yy)	FIELD	INSTITUTION/COMPANY	SUPERVISOR/ EMPLOYER
Teaching Assistant	04/07	07/07	General Chemistry	UC Irvine	

Academic and Professional Honors

Fellowships

-University of California Irvine Faculty Mentor Program Fellowship, 2008-2009 ($37,802)
-Graduate Assistance in Areas of National Need (GAANN) Fellowship, 2006-2007 ($29,000)
-National Science Foundation Alliances for Graduate Education and the Professoriate (AGEP) Fellowship, Summer 2006 ($3,000)
[redacted]
-University of North Dakota Research Experience for Undergraduates (REU) Program, Summer 2004 ($3,000)

Scholarships

-Northern State University James and Jeanette Anderson Arts & Sciences Scholarship, 2005 ($500)
-Northern State University Sueltz-Jensen Award in Chemistry, 2004-2005 ($5,226)
-American Colloid Company Paul Bechtner Memorial Scholarship, 2001-2005 ($12,000)
-Northern State University-University College Scholarship, 2005 ($125)
-Northern State University Mary L. Koczon Memorial Endowment in Chemistry, 2003 ($500)
[redacted]
-Northern State University Dean's Scholarship, 2001-2003 ($2,000)
-Northern State University Hatterscheidt Foundation Educational Scholarship, 2001-2002 ($1,400)
-Knights of Columbus Ed Eixenberger Memorial Scholarship, 2002 ($250)
-St. Paul's Catholic Church Scholarship, 2002 ($300)
-Doug Shaw Memorial Scholarship, 2001 ($150)
-Bill Husband Memorial Scholarship, 2001 ($500)
-Belle Fourche Optimist Club Scholarship, 2001 ($250)
-Northern Black Hills Association of Realtors Scholarship, 2001 ($500)
-P.E.O. Scholarship, 2001 ($300)
-Women's Club Scholarship, 2001 ($100)

Academic Honors

-Northern State University Women's Honor Student-Athlete Award, 2004-2005
-National Student Athlete Award, 2005

-Northern State University Honors Program, 2001-2005
-Academic All-Northern Sun Intercollegiate Conference Spring and Fall Sports Teams, 2001-2006

Memberships
-American Association for the Advancement of Science, 2008
-Iota Sigma Pi National Honor Society for Women in Chemistry, 2006-2008
-Kappa Mu Epsilon National Mathematics Honor Society, 2006-2008

B. Publications

C. Scholastic Performance

SCIENCE			OTHER		
YEAR	COURSE TITLE	GRADE	YEAR	COURSE TITLE	GRADE
	Northern State University Courses			Northern State University Courses	
2002	General Biology I/Lab		2001	Literature and Culture	
2002	General Chemistry I/Lab		2001	Composition I	
2003	General Biology II/Lab		2001	Unites States History II	
2003	General Chemistry II/Lab		2001	First Aid and CPR	
2003	Microbiology/Lab		2001	Honors Seminar I	
2003	Organic Chemistry I/Lab		2001	Principles of Sociology	
2003	Introduction to Physics I/Lab		2002	History of Western Civilization I	
2004	Organic Chemistry II/Lab		2002	Trigonometry	
2004	Analytical Chemistry/Lab		2002	Introduction to Computers	
2004	Introduction to Physics II/Lab		2002	Exploring Music	
2004	Human Anatomy/Lab		2002	Principles of Wellness/Lab	
2004	Medical Terminology		2002	Statistics	
2004	Advanced Laboratory Techniques		2002	World Geography	
2005	Physiology/Lab		2002	Electronic Networking	
2005	Cell and Molecular Biology/Lab		2003	The Process of Criminal Law	
2005	Ornithology/Lab		2003	Honors Composition II	
2005	Inorganic Chemistry		2003	Criminal Law	
2005	Instrumental Analysis		2003	Tutor/Mentor Training	
2005	Environmental Biology		2004	Human Relations	
2005	Plant Systematics/Lab		2004	Fundamentals of Speech	
2005	Physical Chemistry I		2004	Calculus I	
2006	Environmental Biology		2005	Calculus II	
2006	Biochemistry		2005	Intermediate Spanish I	
			2006	Calculus III	
	University of California Irvine Courses				
2006	Organic Reaction Mechanisms I				
2006	Organometallic Chemistry				
2006	Chemical Biology				
2007	Organic Spectroscopy				
2007	Organic Synthesis I				
2007	Organic Reaction Mechanisms II				
2007	Organic Synthesis II				

Kirschstein–NRSA Individual Fellowship Application

Previous Research Experience

(To be completed by applicant – follow PHS 416-1 instructions.)

NAME OF APPLICANT (Last, first, middle initial)
Olson, Angela, C.

22. PRIOR AND CURRENT KIRSCHSTEIN–NRSA SUPPORT. List type (individual and/or institutional), level (predoctoral or postdoctoral), dates, and grant or award numbers.

None

23. APPLICATION(S) FOR CONCURRENT SUPPORT

☒ NO ☐ YES Using format below, list all support (training, research, supplies, travel, etc.) applied for that would run concurrently with the period covered by this application. Include the type, dates, source, and amount.

Type:	Dates:
Source:	Amount:
Type:	Dates:
Source:	Amount:
Type:	Dates:
Source:	Amount:

24a. TITLE(S) OF THESIS/DISSERTATION(S) (Predoctoral and Senior Fellowships omit this section.)
N/A

24b. NAME OF DISSERTATION ADVISOR OR CHIEF OF SERVICE *(If reference report not included, explain why not.)*	TITLE, DEPARTMENT, AND INSTITUTION
N/A	N/A

25. DOCTORAL DISSERTATION AND OTHER RESEARCH EXPERIENCE
(See Instructions – particularly Predoctoral and Senior Fellowships should follow special instructions for this section. Use continuation pages. Do not exceed two pages.)

University of North Dakota (Summer 2004)
Research Advisor: Professor Anamitro Banerjee

As an undergraduate research fellow, my work focused on the synthesis of ethylaminediaminetetraacetic acid (EDTA) analogs with phenylene, diethynyl phenyl, and aromatic spacers. The goal of the project was to form polymers in the presence of metal cations such as As3+, Cd2+, and Cs+. The EDTA analogs would be useful in the detection and extraction of toxic metals. A viable synthetic route to access one of the EDTA analogs was developed.

California Institute of Technology (Summer 2005)
Research Advisor: Professor David MacMillan

As a [ ] Undergraduate Research Fellow, I worked on the synthesis of the natural product, Cylindrocyclophane A. The cylindrocyclophane family displays a toxic effect against the KB and LoVo tumor cell lines. The focus of my project was the development of suitable synthetic route for a trifluoroborate salt and a trialkylanilinium salt utilizing enantioselective organocatalytic methods developed within the MacMillan group. These substrates were to be tested in a nickel-catalyzed Suzuki coupling reaction. During my ten weeks working on this project, I successfully prepared precursors for each of these substrates on a large multi-gram scale.

Research Training Proposal

Specific Aims

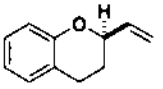
The specific aims of the proposed project are:

- To expand the scope of S_N2' allylic substitution reactions catalyzed by cobalt oxazoline palladacycles (COP) to include intramolecular reactions
- To synthesize biologically active compounds from the products of COP-catalyzed intramolecular cyclization reactions
- To develop a general synthetic route to access key cyclization substrates
- To explore the compatibility of various functional groups and substitution patterns in the intramolecular cyclization reaction catalyzed by COP

Introduction

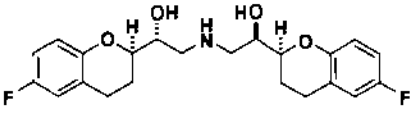
Chiral chromans **1** *are a class of small molecules that possess important biological properties (Figure 1).* For example, Nebivolol **(2)** is an important anti-hypertensive agent,[1] while Daurichromenic acid **(3)** shows potent anti-HIV activity.[2] Vitamin E **(4)**[3] and its analog trolox **(5)**[4] are active lipophilic antioxidants (Figure 2). Enantioenriched vinyl chroman **1** is a common intermediate in the synthesis of numerous biologically active small molecules.

Figure 1. Chiral vinyl chroman

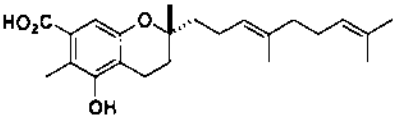


1

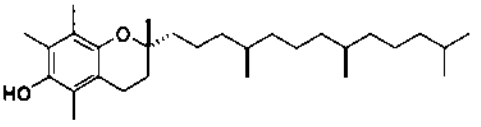
Figure 2. Biologically active natural products that contain the chroman motif



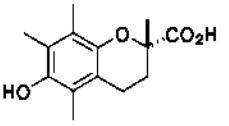
2
Nebivolol



3
Daurichromenic acid



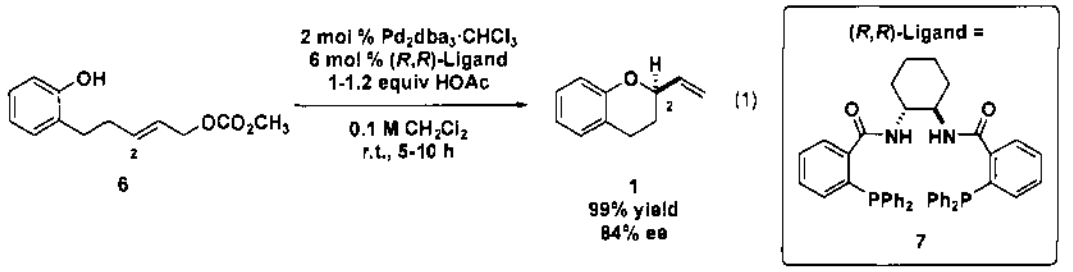
4
vitamin E



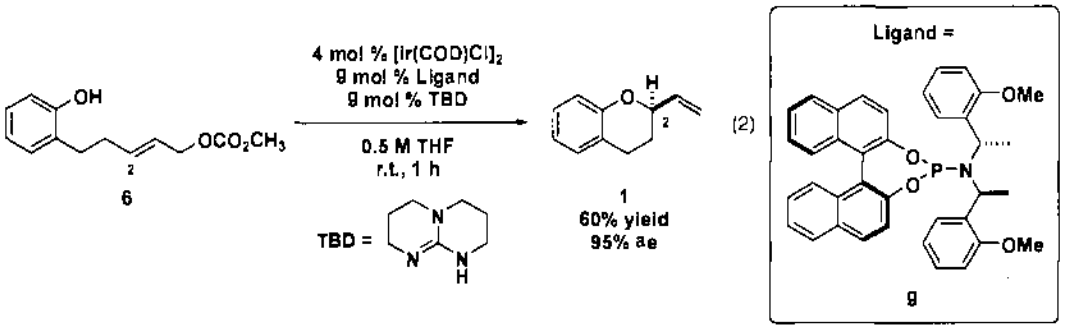
5
trolox

Currently, the methods used to access these synthetically important enantioenriched chroman intermediates are limited. These methods typically employ palladium(0) or iridium(I) catalysts in the presence of chiral ligands. Commonly in these transformations, competitive formation of linear substitution products is observed. These methods are also limited in reaction scope dependent on substitution patterns.

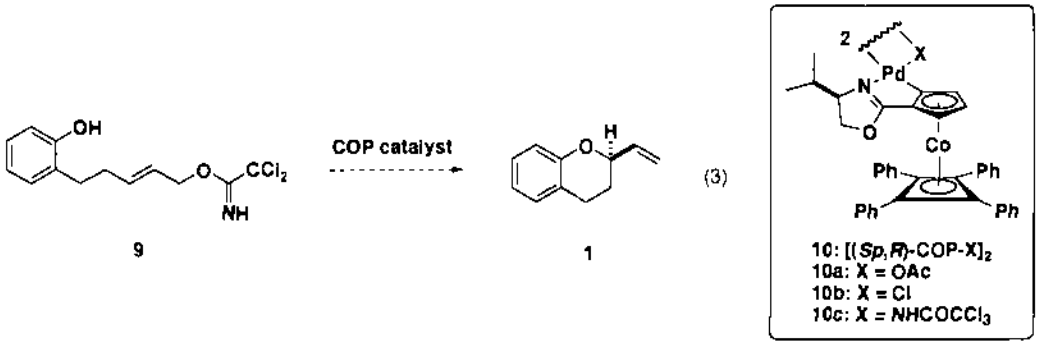
Trost and coworkers have shown that allyl carbonate **6** undergoes intramolecular asymmetric allylic alkylation using a Pd(0)/**7**-based catalyst system (eq 1).[10] However, this reaction requires the use of an acid additive in order to achieve high enantioselectivity. Further, when unsubstituted at C2, moderate enantioselectivities are observed.



Iridium(I) in the presence of chiral phosphoramidite ligand **8** have been used by the Helmchen group to access the vinyl chroman motif from allylic carbonate **6** (eq 2).[11]. Moderate yields are achieved when substrates are unsubstituted at C2 and basic reaction conditions are required in order to activate the iridium catalyst.

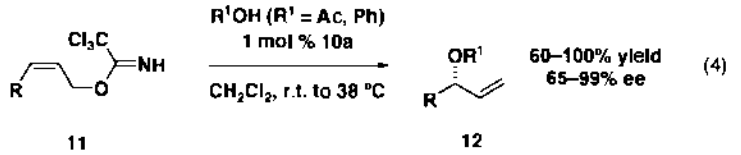


The development of a new and efficient method would be beneficial to access other biologically active small molecules and their analogues derived from vinyl chromans. We envision that enantioenriched chroman heterocycles could be accessed by a cobalt oxazoline palladium(II) (COP) **10**-catalyzed intramolecular substitution reaction of trichloroacetimidate **9** with a tethered phenol nucleophile (eq 3).



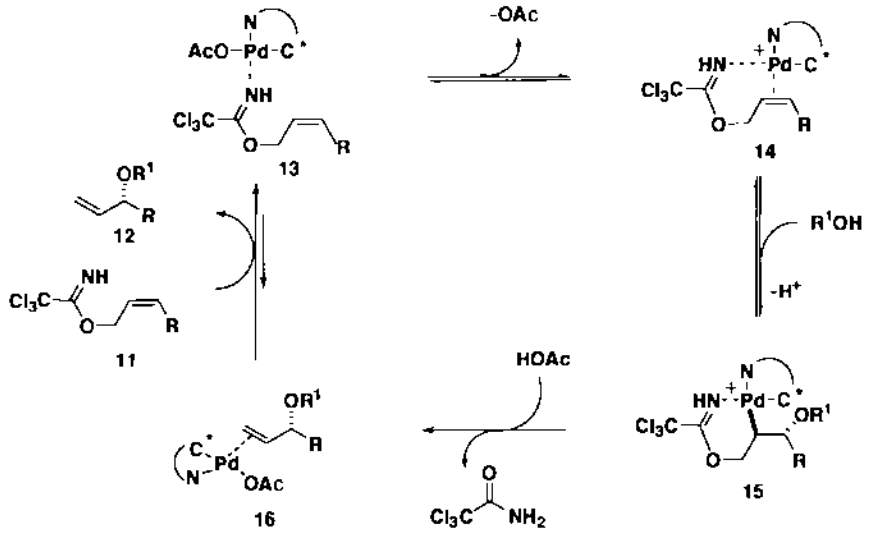
Background

Numerous methods exist for the catalytic asymmetric functionalization of alkenes. These methods typically involve suprafacial addition over a single face of an olefin (e.g. epoxidation, dihydroxylation, hydrogenation). The Overman lab has developed methods that involve catalytic asymmetric antarafacial addition to alkenes. Prochiral (*Z*)-allylic trichloroacetimidates **11** have been shown to undergo enantioselective intermolecular S_N2' allylic substitution reactions in the presence of oxygen nucleophiles and a catalytic amount of COP catalyst **10a** (eq 1). These substitution reactions proceed in good to excellent enantioselectivity and yield, tolerate catalyst loading as low as 1 mol % and proceed under mild conditions. The neutral conditions employed allow for a wider scope of functional groups to be tolerated than the previously mentioned catalyst systems, which require acidic or basic conditions. Another distinguishing characteristic of the COP-catalyzed allylic substitution reactions is the exceptional level of regioselectivity that is achieved, typically branched to linear ratios being >800:1.[7,a]



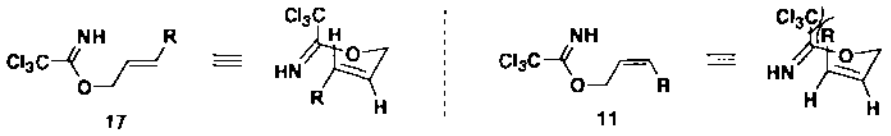
A plausible mechanism for the allylic substitution reaction is illustrated in Figure 2. The nitrogen atom of trichloroacetimidate **11** reversibly coordinates to palladium to form olefin complex **13**. The catalyst loses an acetate ligand, which frees a coordination site for olefin activation and produces complex **14**. Preliminary mechanistic studies suggest that the catalyst likely binds to a single face of the olefin and nucleophilic attack occurs antarafacially in an S_N2' fashion to afford carbopalladated species **15**. Deoxypalladation affords complex **16** and enantioenriched allylic product **12** is formed.

Figure 3. Proposed mechanism of COP-catalyzed allylic substitution reaction

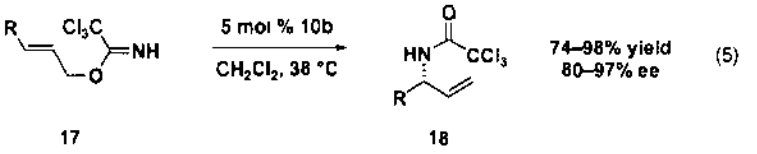


Until recently, a limitation of the COP-catalyzed S_N2' allylic substitution reaction was its compatibility with only the *Z* isomer of allylic trichloroacetimidates. This restriction is due to the propensity of the more easily accessible *E* isomer **17** to undergo competitive [3,3]-sigmatropic rearrangement in the presence of **10a** to form branched trichloroacetamides **18**.[8] The aza-Claisen rearrangement of trichloroacetimidates to branched trichloroacetamides has been found to occur more rapidly with the *E* isomer of allylic trichloroacetimidate substrates (Figure 4).[9] This phenomenon likely results from unfavorable steric interaction between the CCl_3 and R groups in the *Z* substrates which are not present for the [3,3]-sigmatropic rearrangement of *E* substrates.

Figure 4. Steric interactions in the [3,3]-sigmatropic rearrangement

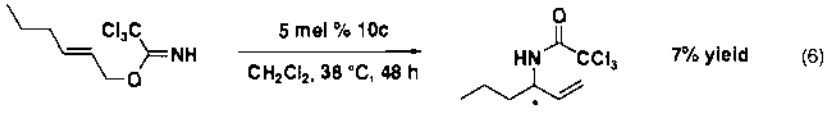


The allylic trichloroacetimidate rearrangement has become the preferred method for transforming allylic alcohols to branched allylic amines. An enantioselective [3,3]-sigmatropic rearrangement of (*E*)-trichloroacetimidates to form allylic trichloroacetamides **18** is catalyzed by another member of the COP family, chloride-bridged dimer **10b**, also developed in the Overman group (eq 5).[10]



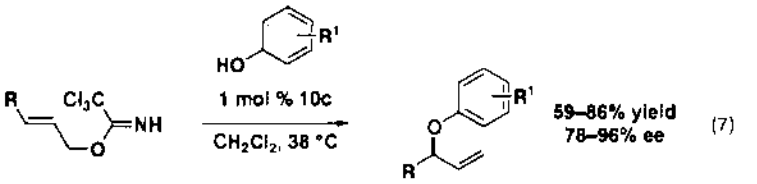
17 18

During recent studies in the Overman group, the trichloroacetamide-bridged COP catalyst **10c** was prepared and studied as a catalyst in the [3,3]-sigmatropic rearrangement. Initial results showed that **10c** was not a viable catalyst for [3,3]-sigmatropic rearrangement of (*E*)-allylic trichloroacetimidate **19** (eq 6).



19 20

In light of this discovery, I studied the intermolecular allylic substitution reaction using (*E*)-allylic trichloroacetimidates using enantioselective catalyst **10c**. The reaction of prochiral imidates **17** and phenolic nucleophiles provided branched allylic aryl ethers **21** in high enantioselectivities and moderate yields (eq 7).[11] The scope of this reaction was explored and various functional groups were tolerated, such as base-labile acetoxy groups, aldehydes, silyl ethers, and protected amines. The development of this method to obtain enantioenriched branched allylic ethers from the more easily accessible (*E*)-trichloroacetimidates is complimentary to chemistry previously reported in the Overman group and serves as the first example of (*E*)-trichloroacetimidates undergoing an intermolecular S_N2' allylic substitution reaction faster than a [3,3]-sigmatropic rearrangement.

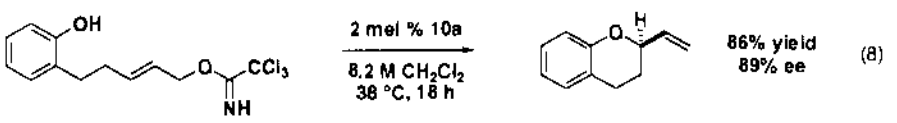


17 21

Recent work in the Overman lab has focused on expanding the synthetic utility of this transformation. It was envisioned that trichloroacetimidate **9** would undergo a COP-catalyzed intramolecular cyclization to provide vinyl chroman **1** (eq 3). By studying COP-catalyzed S_N2' intramolecular allylic substitution reactions of (*E*)-allylic trichloroacetimidates and the formation of enantioenriched vinyl chroman intermediates an improved method could become available for use in organic synthesis. With the ability to form chiral vinyl chromans under neutral conditions with a variety of substitution patterns, a number of biologically active small molecules and their derivatives would be quickly and easily accessible.

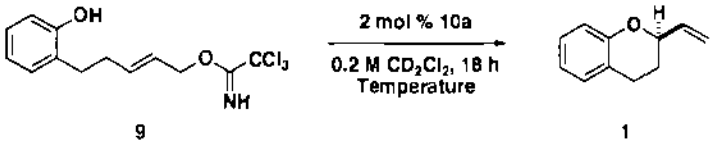
Preliminary Studies

Initial results obtained while studying the COP-catalyzed vinyl chroman formation are promising. Trichloroacetimidate **9** underwent intramolecular cyclization under neutral conditions using a catalytic amount of **10a** to obtain enantioenriched product **1** in high enantioselectivity and high yield (eq 8). Also, a slight increase in enantioselectivity is observed as the reaction temperature is decreased, and cyclization occurs at temperatures as low as –78 °C (Table 1).



6 7

Table 1. Temperature effects of COP-catalyzed intramolecular cyclization

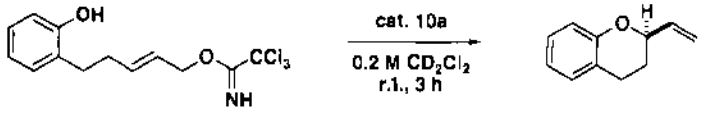


9 1

Temperature	NMR Yield	ee
38 °C	>95%	89%
r.t.	>95%	90%
0 °C	>95%	90%
-25 °C	>95%	92%
-78 °C	>95%	94%

Further studies established that catalyst loading as low as 0.5 mol % is tolerated with no significant effect on reaction times or the level of enantioselectivity observed (Table 2). Importantly, vinyl chroman **1** is the only product observed in the ^{1}H NMR of the crude reaction mixture. Preliminary studies have demonstrated that the COP-catalyzed intramolecular allylic substitution reaction proceeds under neutral reaction conditions, and high enantioselectivity can be achieved when unsubstituted at the C2 position.

Table 2. Catalyst loading effects of COP-catalyzed intramolecular cyclization



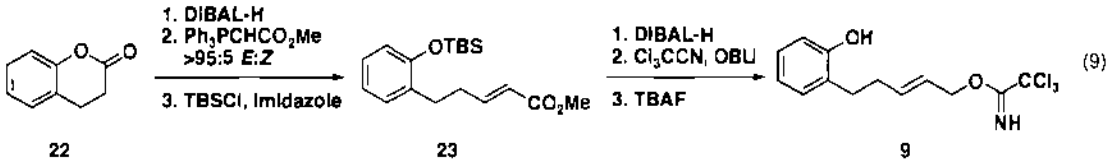
9 1

Catalyst Laading	Conversion (observed by NMR)	ee
2 mol %	>95%	92%
1 mol %	87%	92%
0.5 mal %	75%	94%

Research Design and Methods

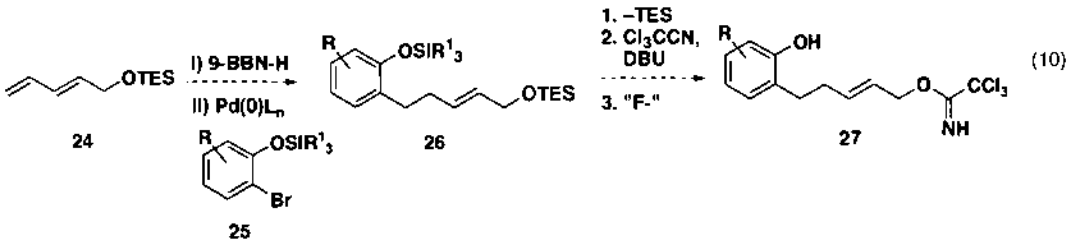
SUBSTRATE SYNTHESIS

In order to increase the synthetic utility of the COP-catalyzed cyclization reaction, an efficient synthesis of the key cyclization substrates is necessary. The first-generation synthesis of (*E*)-trichloroacetimidate **9** involved DIBAL reduction of dihydrocoumarin **22** to the corresponding lactol followed by Wittig olefination to provide the α,β-unsaturated methyl ester with >95:5 *E*:*Z* selectivity (eq 9). TBS protection of the phenol yielded intermediate **23**. Hydride reduction of the ester provided the allylic alcohol which was subsequently converted to the trichloroacetimidate. TBAF deprotection of the phenol afforded the key cyclization substrate **9** in 23% overall yield from lactone **22**. While this synthetic strategy provided access to the key cyclization substrate, the synthesis is not convergent and variation of functional groups or substitution patterns on the aromatic ring and/or tether is difficult.



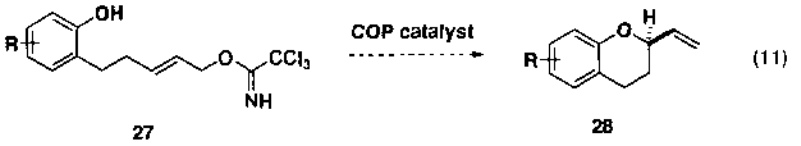
22 23 9

Studies will commence with the investigation of a second-generation synthetic route to access a variety of substituted cyclization substrates **27** in a more convergent fashion (eq 10). Conjugated diene **24** undergoes selective hydroboration of the terminal olefin with 9-BBN.[12] Palladium-catalyzed *B*-alkyl Suzuki-Miyaura coupling of the resulting alkylborane[13] should occur with a variety of functionalized aryl bromides **25** to yield **26**. Selective deprotection of the triethylsilyl group, followed by trichloroacetimidate formation and subsequent deprotection of the phenol should yield **27** in a highly convergent manner.



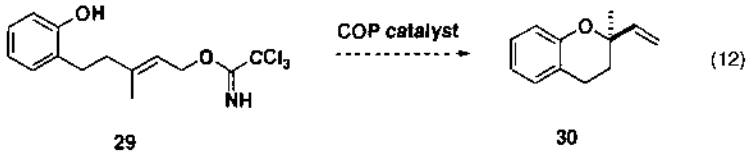
FUNCTIONAL GROUP TOLERANCE ON PHENOL

Once a viable synthetic route is established, the functional group compatibility will be explored. Electronic and substituent effects will be examined to determine their effects on the S_N2' intramolecular allylic substitution chemistry in the presence of COP catalysts (eq 11). A vast number of functionalized 2-bromophenol derivatives **25** (R = F, Cl, Me, OMe, CHO, CN, NO_2) are commercially available, and after protection and cross-coupling with **24**, should provide numerous cyclization precursors **27** of interest.



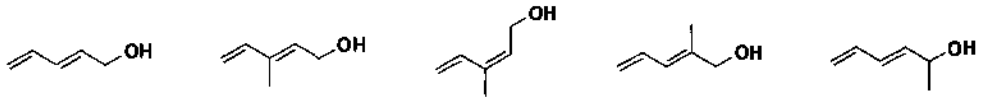
SUBSTITUTION PATTERN COMPATIBILITY OF ALLYLIC CHAIN

Another important aspect of the COP-catalyzed intramolecular allylic substitution to be explored is the formation of tetrasubstituted stereocenters by attack of the phenol on a trisubstituted olefin **29** (eq 12). This type of reaction has been a limitation in the intermolecular S_N2' allylic substitution reaction catalyzed by **10a**. However, when the nucleophile is tethered and the substitution event takes place in an intramolecular fashion, this type of reactivity may be feasible to access chroman **30**.



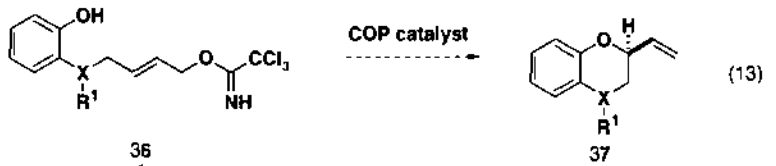
To fully explore substitution patterns of the sidechain, other conjugated dienes will be required for the *B*-alkyl Suzuki-Miyaura cross-coupling reaction. Allylic alcohols with various substitution patterns are known compounds and are readily available from simple starting materials (Figure 4).

Figure 4. Allylic alcohols reported in the literature



HETEROCYCLE SYNTHESIS

In addition to synthesizing a variety of vinyl chroman intermediates, the proposed methodology should also be useful for accessing various enantioenriched *O*-, *N*-, and *S*- heterocycles containing a pendent vinyl group (**37**) (eq 13). Many small molecules that contain these motifs are important therapeutic agents and display unique biological activity.[14,15,16]

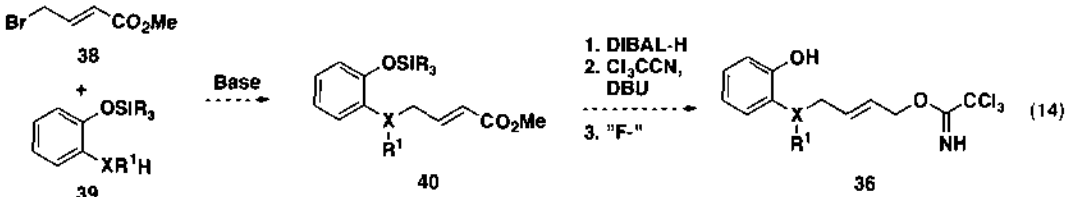


(13)

36
36a: XR^1 = NBn
36b: XR^1 = O
36c: XR^1 = S

37
37a: XR^1 = NBn
37b: XR^1 = O
37c: XR^1 = S

Cyclization precursors for the *O*-, *N*-, and *S*-heterocycles can be accessed from commercially available allyl bromide **38** and silyl-protected phenol, aniline, or thiol derivatives **39** (eq 14). In the presence of mild base, XR^1 will displace the bromide to afford **40**. Reduction of the ester, followed by imidate formation and deprotection of the phenol should yield **36**, which can then be studied in the COP-catalyzed allylic substitution reaction.



(14)

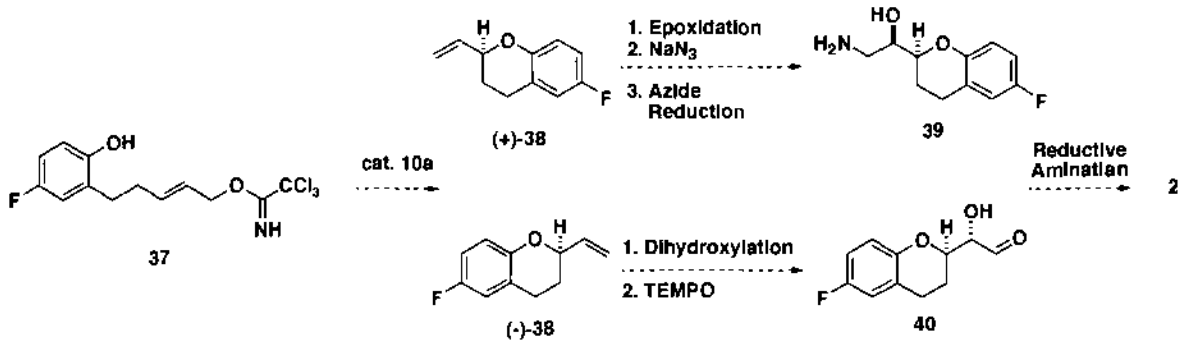
39a: XR^1 = NBn
39b: XR^1 = O
39c: XR^1 = S

36a: XR^1 = NBn
36b: XR^1 = O
36c: XR^1 = S

APPLICATION IN TOTAL SYNTHESIS

As a measure of the utility of this new methodology, the synthesis of a biologically important small molecule Nebivolol (**2**) will be pursued (Figure 5). Nebivolol is an active and selective antihypertensive agent that acts as a β_1-adrenergic blocker.[1] It is used to treat heart conditions and is marketed in over 50 countries. This small molecule is of particular interest because access to synthetic intermediates lacking substitution at the C2 position was previously limited using other technologies. It is envisioned that the newly developed methodology will provide access to both enantiomers of chroman **38** from trichloroacetimidate **37** by using opposite enantiomers of chiral catalyst **10a**. Amine **39** can be accessed from **(+)-38** *via* epoxidation of the olefin, followed by attack of an azide at the terminus of the epoxide[17] and reduction of the azide moiety. Aldehyde **40** can be accessed from dihydroxylation of **(-)-38** followed by selective oxidation of the primary alcohol using TEMPO.[18] The epoxidation and dihydroxylation steps will be investigated first using substrate-directing methods. If needed, catalyst-controlled methods may also be invoked. Reductive amination of primary amine **39** with aldehyde **40** would provide Nebivolol (**2**) in five linear steps from prochiral (*E*)-allylic trichloroacetimidate **37**.

Figure 5. Synthetic plan toward Nebivolol



Conclusion

The COP-catalyzed S_N2' allylic substitution chemistry of prochiral trichloroacetimidates demonstrates great synthetic potential for the formation of enantioenriched vinyl chromans, which can be elaborated into biologically active small molecules in few synthetic transformations. Further examination is required to explore and define the scope of functional groups and substitution patterns that are compatible in the catalytic system. This methodology is not limited to the formation of vinyl chromans and may be used to access other enantioenriched *O*-, *N*-, and *S*-heterocycles. Currently, the methods used to access enantioenriched vinyl chroman species and their analogues are limited and the development of a highly selective and efficient method would be beneficial to the synthetic community.

Literature Citations

[1] De Cree, J; Geukens, H.; Leempoels, J.; Verhaegen, H. "Haemodynamic Effects in Man During Exercise of a Single Oral Dose of Narbivolol (R 67555), a New Beta-1-Adrenoceptor Blocking Agent: A Comparitive Study with Atenolol, Pindolol, and Propranolol" *Drug Dev. Res.* **1986**, *8*, 109–117.

[2] Dashiwada, Y.; Yamazaki, K.; Ikeshiro, Y.; Yamagishi, T.; Fujioka, T.; Mihashi, K.; Mizuki, K.; Cosentino, L. M.; Fowke, K.; Morris-Natschke, S. L.; Lee, K. H. "Isolation of Rhododaurichromanic Acid B and the Anti-HIV Principles Rhododaurichromanic Acid A and Rhododaurichromenic Acid from *Rhododendron dauricum*" *Tetrahedron* **2001**, *57*, 1559–1563.

[3] *Vitamin E*; Machlin, L. J., Ed.; Marcel Dekker: New York, 1980.

[4] Terao, K.; Niki, E. "Damage to Biological Tissues Induced by Radical Initiator 2,2'-Azobis(2-amidinopropane) Dihydrochloride and its Inhibition by Chain-Breaking Antioxidants" *J. Free Rad. Biol. Med.* **1986**, *2*, 193–201.

[5] Trost, B. M.; Shen, H. C.; Dong, L.; Surivet, J. P.; Sylvain, C. "Synthesis of Chiral Chromans by the Pd-Catalyzed Asymmetric Allylic Alkylation (AAA): Scope, Mechanism, and Applications" *J. Am. Chem. Soc.* **2004**, *126*, 11966–11983.

[6] Welter, C.; Dahnz, A.; Brunner, B.; Streiff, S.; Dubon, P.; Helmchen, G. "Highly Enantioselective Synthesis of Heterocycles via Intramolecular Ir-Catalyzed Allylic Amination and Etherification" *Org. Lett.* **2005**, *7*, 1239–1242.

[7] Kirsch, S. F.; Overman, L. E. "Catalytic Asymmetric Synthesis of Chiral Allylic Esters" *J. Am. Chem. Soc.* **2005**, *127*, 2866–2867.

[8] Kirsch, S. F.; Overman, L. E.; White, N. S. "Catalytic Asymmetric Synthesis of Allylic Aryl Ethers" *Org. Lett.* **2007**, *9*, 911–913.

[9] Overman, L. E.; Carpenter, N. E. *Organic Reactions*; John Wiley & Sons, Inc.: Hoboken, NJ, **2005**, Vol. 66, pp 3–97.

[10] Anderson, C. E.; Overman, L. E. "Catalytic Asymmetric Rearrangement of Allylic Trichloroacetimidates. A Practical Method for Preparing Allylic Amines and Congeners of High Enantiomeric Purity" *J. Am. Chem. Soc.* **2003**, *125*, 12412–12413.

[12] Lange, H.; Frohlich, R.; Hoppe, D. "Cu(I)-Catalyzed Stereospecific Coupling Reactions of Enantioenriched α-Stannylated Benzyl Carbamates and Their Application" *Tetrahedron*, **2008**, *64*, 9123–9135.

[13] Chemler, S. R.; Trauner, D.; Danishefsky, S. J. "The *B*-Alkyl Suzuki–Miyaura Cross-Coupling Reaction: Development, Mechanistic Study, and Applications in Natural Product Synthesis" *Angew. Chem., Int. Ed.*, **2001**, *40*, 4544–4568.

[14] Stillings, M. R.; Chapleo, C. B.; Butler, R. C. M.; Davis, J. A.; England, C. D.; Myers, M.; Myers, P. L.; Tweddle, N.; Welbourn, J. C.; Doxey, J. C.; Smith, C. F. C. "α-Adrenoreceptor Reagents. Synthesis of Some 2-Substituted 1,4-Benzodioxans as Selective Presynaptic α_2-Adrenoreceptor Antagonists" *J. Med. Chem.* **1985**, *28*, 1054–1062.

[15] Hibert, M. F.; Gittos, M. W.; Middlemiss, D. N.; Mir, A. K.; Fozard, J. R. "Graphics Computer-Aided Receptor Mapping as a Predictive Tool for Drug Design: Development of Potent, Selective, and Stereospecific Ligands for the 5-HT_{1A} Receptor" *J. Med. Chem.* **1988**, *31*, 1087–1093.

[16] Fagan, G. P.; Chapleo, C. B.; Lane, A. C.; Myers, M.; Roach, A. G.; Smith, C. F. C.; Stillings, M. R.; Welbourn, A. P. "Indoline Analogs of Idazoxan: Potent α_2-Antagonists and α_1-Antagonists" *J. Med. Chem.* **1988**, *31*, 944–948.

[17] Yokoyama, J.; Kobayashi, H.; Miyazawa, M.; Yamaguchi, S.; Hirai, Y. "Palladium(II)-Catalyzed Cyclization of Urethanes and its Application to a Total Synthesis of 1-Deoxynojirimycin" *Heterocycles* **2007**, *74*, 283–292.

[18] De Luca, L.; Giacomelli, G.; Porcheddu, A. "A Very Mild and Chemoselective Oxidation of Alcohols to Carbonyl Compounds" *Org. Lett.* **2001**, *3*, 3041–3043.

Respective Contributions

I was responsible for the development and preparation of the attached research training plan. Professor Overman approved the proposal before submission of the application packet.

Selection of Sponsor and Institution

I chose to attend the University of California, Irvine because of the prestige of the chemistry department as well as the broad range of research opportunities available. The department is well-equipped to support quality research and the facilities are of top quality. I chose to work with Professor Overman because of my interest in the synthesis of organic molecules that have interesting and important biological activities. His research program allows me to explore new methods in organic synthesis in a highly established and well-respected laboratory.

Responsible Conduct of Research

Students entering Professor Overman's group are provided written guidelines on standard experimental protocols, laboratory notebooks and characterization data, ethical conduct in research, ethical guidelines to the publication of chemical research, misconduct in research, conduct in science and scientists, and on the integrity of research. Professor Overman holds individual meetings with each incoming student to discuss these issues. In addition, the Department of Chemistry at the University of California, Irvine currently offers a course entitled "Responsible Conduct of Research". This course is offered annually as a one quarter course and is taught by regular rank faculty.

Section II—Sponsor and Co-Sponsor Information

Current support: My laboratory is supported by four major federal grants and smaller unrestricted grants from several pharmaceutical companies:
NIH-NS 12389 "New Methods for the Synthesis of Neurological Agents" (06/01/05–05/31/09) $1,513,111 (TC)
PHS-HL 25854 "Practical Chemical Synthesis of Complex Alkaloids" (12/01/04–11/30/09) $1,823,887 (TC)
NSF-CHE-0616201 "New Methods for the Asymmetric Synthesis of Valuable Chemicals" (7/01/06–6/30/09) $645,840 (TC)
NIH-GM 30859 "General Methods for Synthesis of Bioactive Materials" (04/01/08–01/31/12) $1,441,503 (TC).

Sponsor's Previous Fellows/Trainees

I have supervised more than 50 NIH Postdoctoral Fellows. Representative recent fellows are:
Dr. Jose Madalengoitia, Professor, Department of Chemistry, University of Vermont
Dr. John Wolfe, Associate Professor, Department Chemistry, University of Michigan
Dr. Neil Garg, Assistant Professor, Department Chemistry and Biochemistry, UCLA (K99/R00 award)
Dr. Jason Katz, Senior Research Scientist, [redacted]
Dr. Aaron Wrobleski, Research Scientist, [redacted]

I have a long-standing involvement in mentoring scientists from [redacted]. Past undergraduate mentees include Vy Dong (Assistant Professor, Department of Chemistry, [redacted] and Brian Leon and Alex Cortez (current Ph.D. students CSU and Boston College); former graduate mentees include Alex Romero (research scientist, [redacted] and Ramón Pineda (Coro Fellow in Public Affairs); former postdoctoral mentees who have gone on (or will go) to tenure-track academic posts in the U.S. include Jose Madalengoitia (Professor of Chemistry, University of Vermont), Mary Cloninger (Professor of Chemistry, Montana State University, UC Presidents Fellow 1997–1999), and Javier Read de Alaniz (Colorado State University, UC Presidents Fellow 2006–2008).

Training Plan, Environment, Research Facilities

To increase selectivity and safety, new pharmaceuticals introduced into clinical practice are increasingly complex chiral molecules marketed as single enantiomers. Chiral drug sales are greater than $200 billion today and are estimated to increase significantly in coming years. Angela Olson's proposed program of research should lead to new methods for preparing complex heterocyclic molecules as single enantiomers, initially chiral chromans, thus providing the pharmaceutical industry with new tools for the synthesis and discovery of single enantiomer drugs. The importance of gaining skills in organic synthesis was recently highlighted by Dr. Elias A. Zerhouni, Director of NIH (July 3, 2006 cover story in *Chemical and Engineering News*): "One interesting result of the NIH Roadmap development process came when we surveyed scientists to find out what the stumbling blocks for biological sciences were. The number one stumbling block turned out to be synthetic organic chemistry. I was shocked because I thought the limiting factor was computational biology. So the NIH Roadmap really changed my view of the importance of chemistry and chemical engineering."

My research group is interested in the development of new reactions and strategies that allow complex molecules to be assembled efficiently with high stereo- and enantiocontrol. We are particularly interested in the formation of complex polycyclic networks and in inventing/developing transformations for preparing molecules having a large number of heteroatoms. Current studies in the area of reaction engineering focus on a broad range of transformations: cascade cyclization processes initiated by iminium, oxonium and sulfenium cations, construction of quaternary carbon centers from the union of prostereogenic nucleophiles with chiral electrophiles, cycloaddition reactions of *N*-amidinyliminium ions, asymmetric transformations catalyzed by novel palladacyclic Pd(II) complexes, and new cascade sequences in which absolute chirality is established by asymmetric Heck reactions. We have active total synthesis programs underway that target a dozen natural products; these targets are structurally diverse and include guanidinium alkaloids, polypyrrolidinoindoline alkaloids, epipolythiodioxopiperazine toxins, diterpenoid polycyclic ethers, and other structurally novel molecules such as daphinipaxinin and kapakahine A. Many of these target molecules display biological activities of potential importance in medicine. Natural products synthesized in my laboratory during the past three years (all for the first time), include: (±)-actinophyllic acid, (–)-sarain A, (+)-nankakurines A and B, (+)-gliocladin C, (+)-guanacastepene N, (+)-minfiensine, (–)-crambidine, (–)-crambescidin 359, and (–)-

Section II—Sponsor and Co-Sponsor Information

dehydrobatzelladine C. In all cases, these syntheses featured new synthetic transformations developed in our laboratories.

Ms. Angela Olson will work on the topic of her application, developing catalytic asymmetric syntheses of chiral chromans. I would stress that many other chiral heterocycles, nitrogen as well as oxygen, should be available by related methods. I see her broadening her research objectives towards other heterocycles during the latter stages of her Ph.D. training.

Ms. Olson will also receive training in the general area of reaction and synthesis design and medicinal chemistry by participation in our weekly research group meetings (once a month these focus on complex molecule synthesis design – molecule of the month) and from auditing special topics courses in the synthesis and medicinal chemistry areas. Her training in the area of medicinal chemistry will also revolve around our weekly research group meetings. A number of these meetings focus on contemporary topics in bioorganic and medicinal chemistry. Ms. Olson will also benefit from Irvine's excellent organic chemistry seminar program. Because of support from [redacted] this program is particularly strong in the area of synthetic organic and medicinal chemistry.

The training environment at Irvine in the area of synthetic organic chemistry is outstanding. Twelve faculty members have active programs in this area - S. Blum, A. R. Chamberlin, S. Hanessian, Z. Guan, E. Jarvo, J. Nowick, L. E. Overman, K. S. Shea, S. Rychnovsky, D. Van Vranken, C. Vanderwal, and K. Woerpel. The instrumentation to support research in this area is among the best in the country. The Chemistry Department at the University of California, Irvine maintains shared analytical instrumentation facilities to support the research effort. Major equipment and facilities pertinent to the research described in this proposal include: *UCI Biomolecular NMR Facility:* This facility is operated by Dr. Evgeny Fadeev and is equipped with an 800 MHz spectrometer. *UCI Chemistry NMR Facility:* This facility, staffed by Ph.D. NMR spectroscopist Dr. Philip Dennison, provides routine access to a range of 400, 500 and 600 MHz NMR spectrometers. *Department Mass Spectrometry Facility:* Dr. John Greaves and one full-time technician operate this facility. The facility has walk-in access to three instruments: a Micromass LCT API-TOF that supports APCI and ESI, and two Finnigan Trace Quad-GCMS's (CI and EI). The facility has two magnetic sector instruments: a Micromass Autospec that supports EI, CI, Static and dynamic LSIMS/FAB, Field Desorption Ionization and Field Ionization and a Micromass 7070 medium resolution magnetic sector. For polymers and proteins the facility has a Perseptive DESTR MALDI-TOF. For sequencing peptides it has a tandem Quad-TOF instrument. *UCI Chemistry Department X-Ray Facility:* This facility, supervised by Dr. Joseph Ziller, has 2 diffractometers, both with low temperature capability, 1 with CCD. *UCI Chemistry Department Spectroscopy Facility:* This facility, headed by Dr. Wytze van der Veer, provides primarily laser spectroscopy support and CD instrument for the use of the organic and bioorganic groups. *UCI Parallel Synthesis Facility and Organic Compound Archive.* The Department of Chemistry at UC-Irvine is building a state-of-the-art, Parallel Synthesis Facility and Organic Compound Archive. The Organic Compound Archive, which currently consists of approximately 15,000 small molecules collected from the synthetic chemistry research groups at UC Irvine, will be arrayed into bar-coded 96-well microtiter plates to be available to UCI researchers for screening.

Number of Fellows/Trainees to be Supervised During the Fellowship

During Ms. Olson's tenure, my laboratory will likely number ~15–20 (~30% grad students/~70% postdoctorals). I anticipate that several postdoctorals will be NRSA fellows.

Applicant's Qualifications and Potential for a Research Career

Ms. Olson has compiled a record of academic excellence at both her baccalaureate institution, Northern State University, and in the UCI Ph.D. program, where she compiled a strong [redacted] coursework average. Angela gave a strong performance on her oral advancement to candidacy Ph.D. examination last spring. Angela has already recorded a significant research success by showing that our catalytic asymmetric synthesis of branched allylic phenols can be accomplished with a new chiral Pd(II) complex (COP-TCA) and utilize imidate derivatives of readily available (E)-allylic alcohols; [redacted] Angela has a charming personality and excellent communication skills. That she is a most-promising young [redacted] scientist is apparent in the impressive collection of awards and fellowships she has received. She is certainly well qualified to undertake the research proposed in this application. After completing her Ph.D. in my laboratory, Ms. Olson should be extremely well qualified to pursue a career in the health sciences.