



**University  
of Victoria**

Graduate Studies

# **PROGRAMME**

The Final Oral Examination for the Degree of

**DOCTOR OF PHILOSOPHY**  
(Department of Chemistry)

**Natasha Felicia O'Rourke**

2008

St. Francis Xavier University  
(Chemistry and Biology)

B.Sc.

**"Mechanistic Studies of Orthogonal Transformations  
of Bis-Vinyl Ethers: Modular Access to Complex  
Small Molecules"**

**Monday, October 27th, 2014  
2:30 PM  
ECS 128**

**Supervisory Committee:**

Dr. Jeremy Wulff, Department of Chemistry, UVic (Supervisor)  
Dr. Tom Fyles, Department of Chemistry, UVic (Member)  
Dr. Fraser Hof, Department of Chemistry, UVic (Member)  
Dr. Perry Howard, Department of Biochemistry and Microbiology,  
UVic (Outside Member)

**External Examiner:**

Dr. Michel Gravel, Department of Chemistry,  
University of Saskatchewan

**Chair of Oral Examination:**

Dr. Stan Dosso, School of Earth and Ocean Sciences, UVic

## **Abstract**

Efficient access to molecular complexity and diversity is important for the development of small-molecule libraries designed to identify highly specific modulators of disease-relevant macromolecular targets. We envisioned the use of iteratively synthesized bis-vinyl ether substrates (BVEs) for cascade-type transformations to gain rapid access to several different classes of stereochemically rich scaffolds. To evaluate the utility of BVEs in this context, mechanistic investigations were undertaken to understand the chemical reactivity of these substrates in radical cyclization reactions and [3,3]-sigmatropic rearrangements.

BVEs were found to undergo Claisen rearrangement at low temperatures. To better understand the substituent effects governing the rate of rearrangement, a quantitative structure-reactivity relationship was investigated to characterize the transition-state structure. BVEs were found to undergo rearrangement through a polar, dissociative-type mechanism. An asymmetric, palladium-mediated Claisen rearrangement was also investigated. Preliminary results yielded a moderate degree of stereoinduction, provided the chiral directing element was proximal to the pericyclic framework.

Lastly, a cascading radical cyclization across BVE/alkyne conjugates to afford hexahydro-2*H*-furo[3,4-*b*]pyrans was investigated and found to occur through a 5-*exo-trig*/3-*exo-trig*/retro-3-*exo-trig*/5-*exo-trig* cyclization pathway, rather than the apparent 6-*endo-trig*/5-*exo-trig* pathway assumed previously.

## **Awards, Scholarships, Fellowships**

2013 Excellence in Graduate Student Teaching Award  
2011 VIVA NMR Symposium, Best Lecture  
2010 NSERC PGS-D3 (3 years)  
2010 University of Victoria President's Award (3 years)  
2009 NSERC CGS-M (1 year)  
2009 University of Victoria President's Award (1 year)  
2009 CIC/E.G. Young Award Best Graduate Student Poster  
2008 Pacific Century Award, University of Victoria  
2008 University of Victoria Graduate Student Award  
2008 NSERC Innovation Award Best Undergraduate Lecture  
2002 Duke of Edinburgh Gold Award (H.R.H. Prince Edward)

## **Selected Presentations**

1. "Cascading Radical Cyclization of Bis-Vinyl Ethers: A Mechanistic Investigation." 97<sup>th</sup> Annual CIC Canadian Society for Chemistry Conference and Exhibition, Vancouver, BC on June 5, 2014. (Oral) *Honourable Mention in General Organic Symposium.*
2. "Studies Toward the Development of the First Small Molecule Inhibitors of Programmed Death 1/Programmed Death Ligand 1 in Metastatic Cancer." 2014 Volcano Conference in Chemical Biology, Seattle, WA on March 2, 2014. (Oral)
3. † "Investigation of Quantitative Structure-Reactivity Relationships in the Aliphatic Claisen Rearrangement of Bis-Vinyl Ethers." 7<sup>th</sup> Annual VIVA NMR Symposium, Victoria, BC on June 21, 2013. (Oral)
4. "An Iterative Approach to Molecular Complexity: Synthesis of Biologically Relevant Building Blocks from Polyvinyl Ether Substrates." 2011 Banff Symposium in Organic Chemistry, Banff, AB, on November 11, 2011. (Oral)
5. † "Synthesis of Diruthenium (II, III) Tetracarboxylate Complexes Containing Biologically Relevant Ligands." 2008 CIC-Atlantic Provinces Council on the Sciences, Halifax, NS, on May 9, 2008. (Oral)

† Indicates presentations that have received an award.

## **Publications**

1. M. P. Thomson, N. F. O'Rourke, R. Wang, M. A. S. Aquino. "Crystal structure of tetrakis( $\mu$ -*n*-butyrato- $\kappa^2$ O:O')bis [chloridorhenium(III)](Re-Re)," Acta Crystallographica, **2014**, E70, m349-m350.
2. R. L. Stoddard, J. Luo, N. van der Wal, N. F. O'Rourke, J. E. Wulff, J. S. McIndoe. "A Multi-Pronged Mechanistic Study of the Phosphine-Mediated Conjugate Addition of an Alcohol to an Acetylenic Ester," New Journal of Chemistry, **2014**, 38, 5382-5390.
3. N. F. O'Rourke, J. E. Wulff. "Investigation of Quantitative Structure-Reactivity Relationships in the Aliphatic Claisen Rearrangement of Bis-Vinyl Ethers Reveals a Dipolar, Dissociative Mechanism," Organic and Biomolecular Chemistry, **2014**, 12, 1292-1308.
4. N. F. O'Rourke, M. Ronaldson, T. S. Cameron, R. Wang, M. A. S. Aquino. "Equatorial  $\pi$ -Stacking Interactions in Diruthenium (II, III) Tetracarboxylate Complexes Containing Extended  $\pi$ -Systems," Journal of Molecular Structure, **2013**, 1052, 17-23.
5. N. F. O'Rourke, K. A. Davies, J. E. Wulff. "Cascading Radical Cyclization of Bis-Vinyl Ethers: Mechanistic Investigation Reveals a 5-*exo* / 3-*exo* / retro-3-*exo* / 5-*exo* Pathway," **2012**, Journal of Organic Chemistry, 77, 8634-8647.