

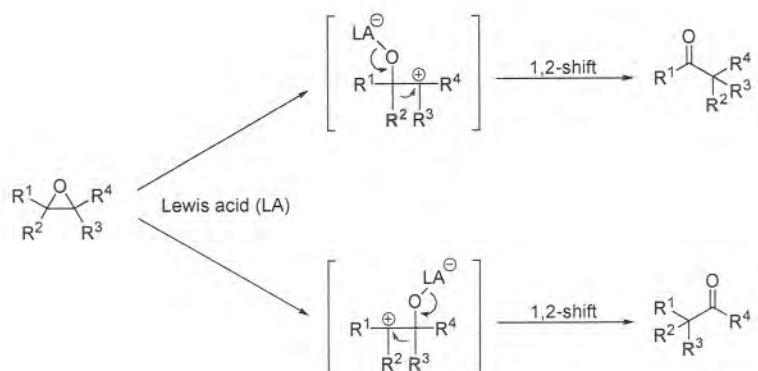


Metal Promoted Ring Forming and Ring Cleaving Reactions: New Methods and Applications

Mark Lautens
University of Toronto

IASOC 2004
September 22, 2004.

Lewis Acid Catalyzed Rearrangement of Epoxides

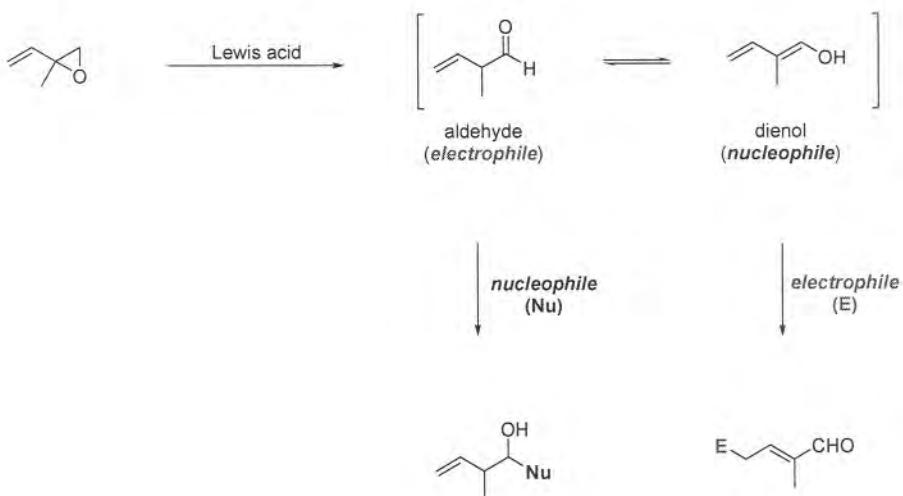


Reviews:

- (1) Rickborn, B. In *Comprehensive Organic Synthesis*, Trost, B.M., Ed.; Pergamon: Oxford, 1991; Vol 3; 733.
- (2) Parker, E.E.; Isaacs, N.S. *Chem. Rev.* 1959, 59, 737.
- (3) Fujioka, H.; Yoshida, Y.; Kita, Y. *Yuki Gosei Kagaku Kyokaishi* 2003, 61, 133.



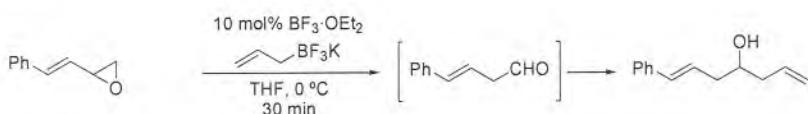
Rearrangement of Vinyloxiranes



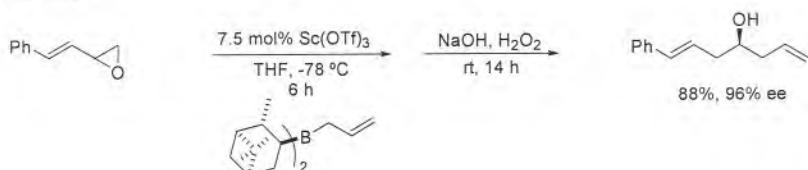
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Addition of Allyl Boron Reagents to *in situ* Generated β,γ -Unsaturated Aldehydes

Racemic version



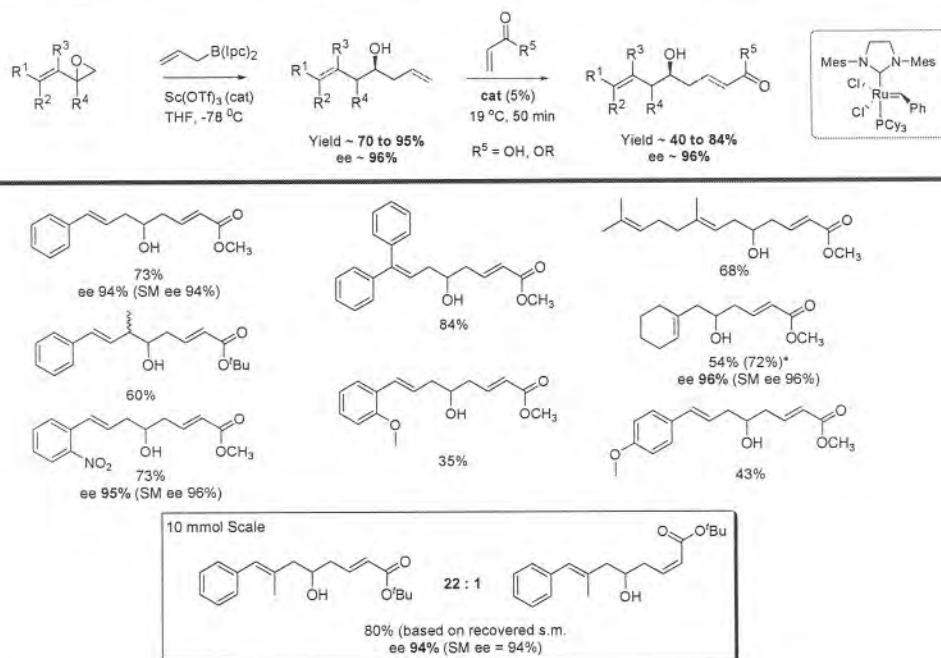
Asymmetric version



Lautens, M.; Ouellet, S.G.; Raeppe, S. *Angew. Chem. Int. Ed.* **2000**, *39*, 4079.
Lautens, M.; Maddess, M.L.; Sauer, E.L.O.; Ouellet, S.G. *Org. Lett.* **2002**, *4*, 83.

University of Toronto

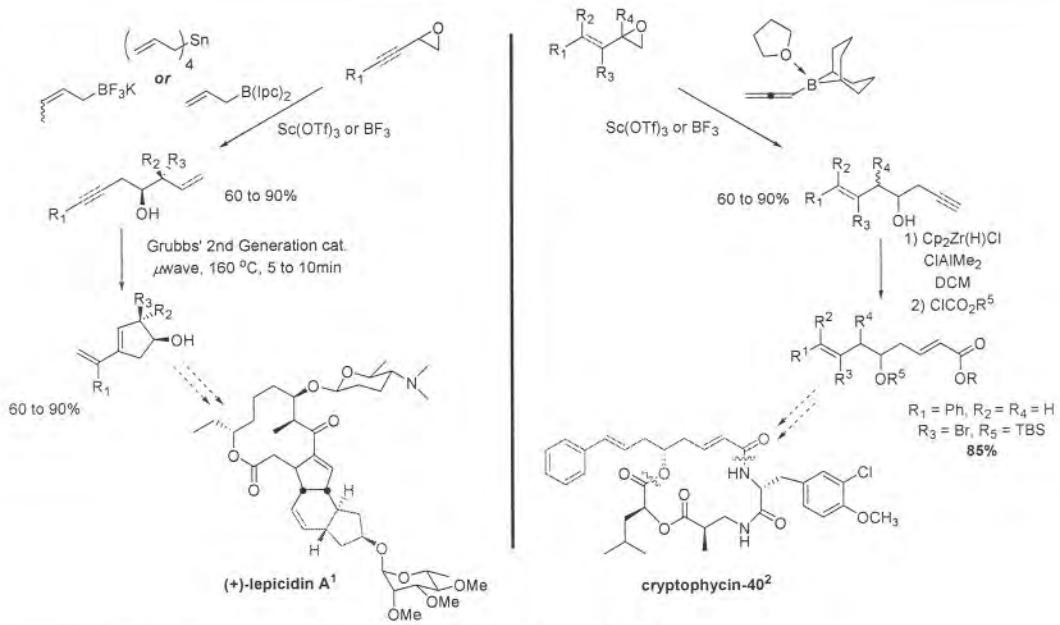
Chemosselective Cross Metathesis of Bishomoallylic Alcohols



Lautens, M.; Maddess, M.L. *Org. Lett.* **2004**, *6*, 1883.

University of Toronto

Preparation of Differentiated π - Systems



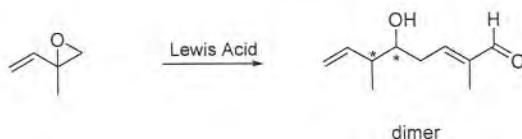
1) Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497.

2) Lautens, M.; Maddess, M. L. *Org. Lett.* **2004**, *6*, 1883.

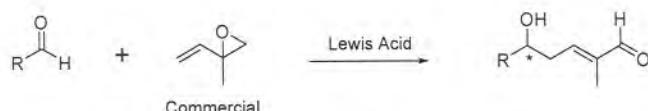
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Vinylogous Mukaiyama-Aldol Reaction

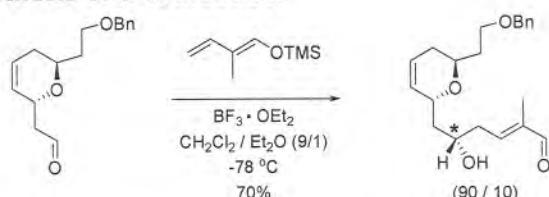
Initial observation



Cross-Aldol?



Key Step in the Total Synthesis of Swinholide A

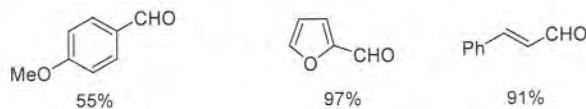
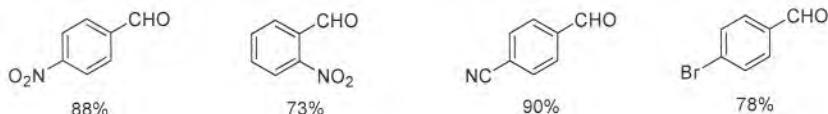
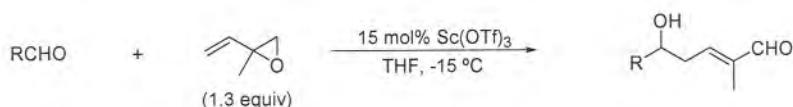


Paterson, I.; Smith, J.D.; Ward, R.A. *Tetrahedron*. **1995**, *51*, 9413.

Saito, S.; Shiozawa, M.; Ito, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1998**, *120*, 813.

University of Toronto

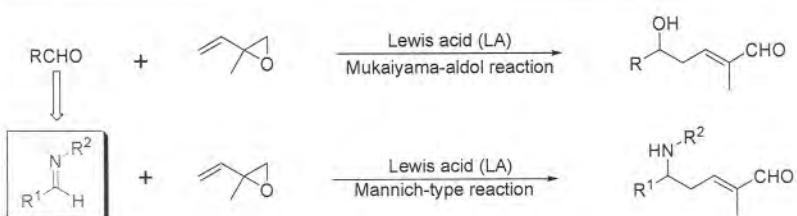
Vinylogous Mukaiyama-Aldol Reactions via Lewis Acid Catalyzed Rearrangement of Vinyloxiranes



Lautens, M.; Ouellet, S.G.; Raeppe, S. *Angew. Chem. Int. Ed.* **2000**, *39*, 4079.

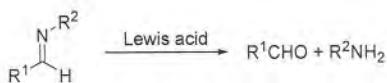
University of Toronto

Next Approach : Vinylogous Mannich-Type Reaction



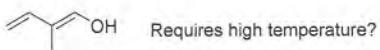
Problems

1) Acid sensitive

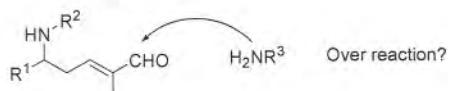


2) Reduced reactivity of dienol

Which types of imine will yield good results?

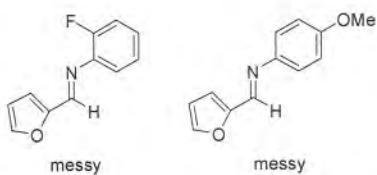
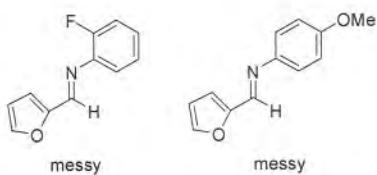
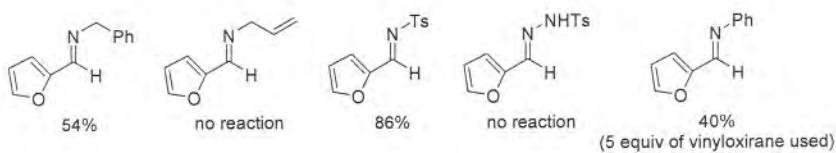
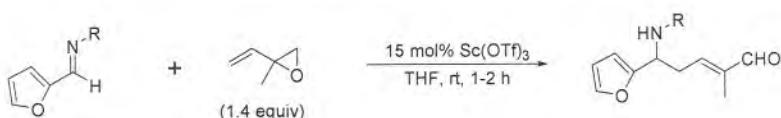


3) Product instability



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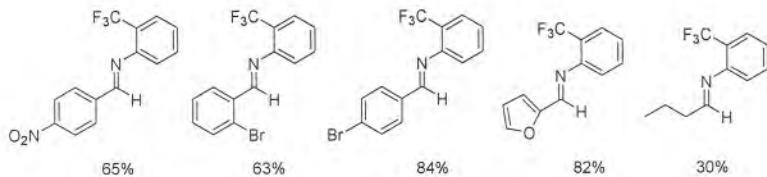
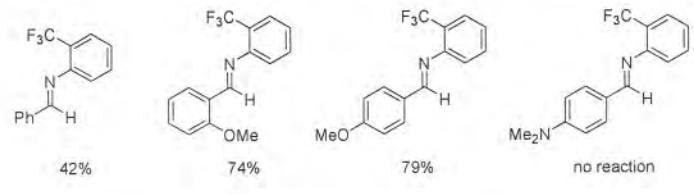
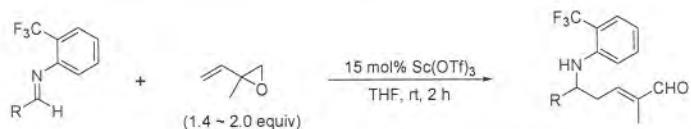
Effect of the Substituent on the Imine Nitrogen in the Vinylogous Mannich-Type Reaction



Lautens, M.; Tayama, E.; Nguyen, D. *Org. Lett.* **2004**, 6, 345.

University of Toronto

Generality of Benzylidene (2-CF₃-Phenyl)Amine

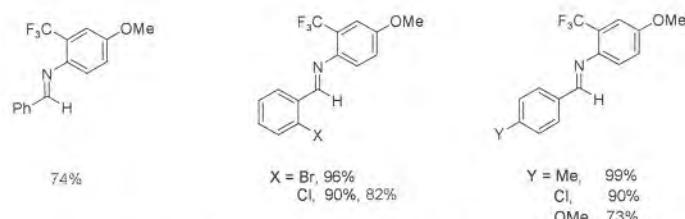
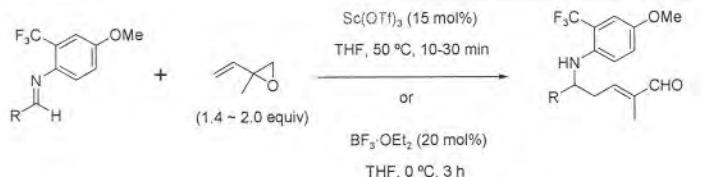
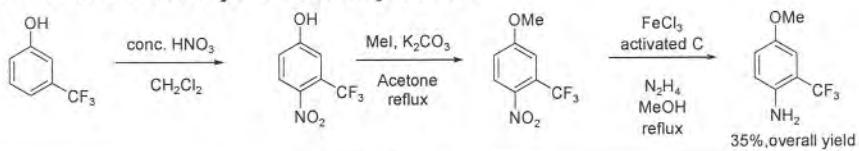


Lautens, M.; Tayama, E.; Nguyen, D. *Org. Lett.* **2004**, 6, 345.

University of Toronto

Reactivity of the Deprotectable Benzylidene (4-MeO-2-CF₃-Phenyl)Amine

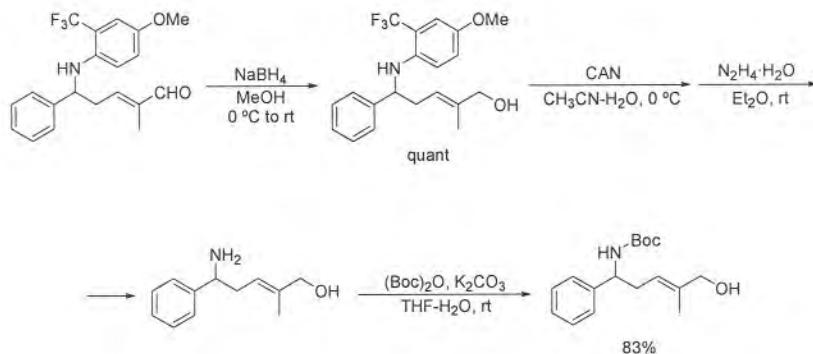
Preparation of 2-Trifluoromethyl-4-Methoxyaniline



Lautens, M.; Tayama, E.; Nguyen, D. *Tetrahedron Lett.* **2004**, 45, 5131.

University of Toronto

Deprotection of 4-MeO-2-CF₃-Phenyl Group

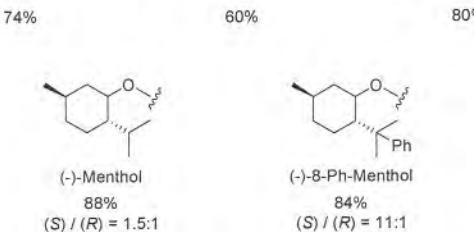
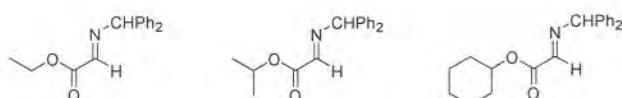
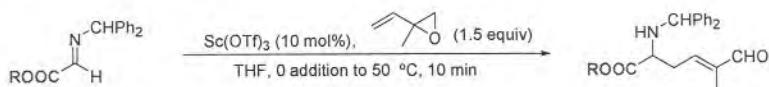


Deprotection: Ohkura, H.; Handa, M.; Katagiri, T.; Uneyama, K. *J. Org. Chem.* **2002**, 67, 2692.

University of Toronto

Lewis Acid Catalyzed Direct Vinylogous Mannich-Type Reaction with an *in situ* Generated β,δ -Unsaturated Aldehyde

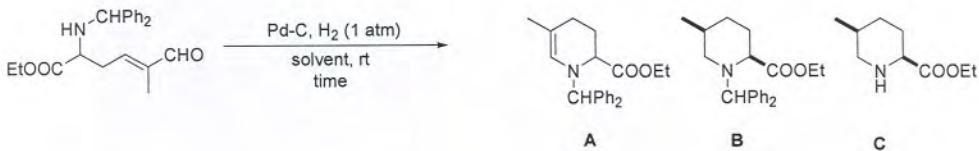
α -Imino ester as an electrophile



Lautens, M.; Tayama, E.; Nguyen, D. *Org. Lett.* **2004**, 6, 345.

University of Toronto

Transformation to Cyclic Unnatural Amino Acid Ester Under Hydrogenation Conditions

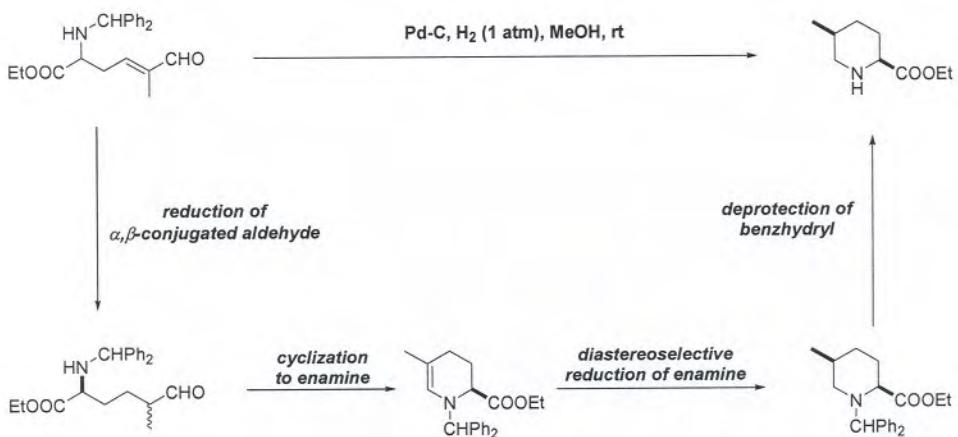


solvent & reaction time	A	B	C
Benzene, 1 h	53%	trace	0%
Benzene, 24 h	5%	77% (cis/trans = >20:1)	trace
MeOH, 4 h	0%	0%	84% (cis/trans = >20:1)

Lautens, M.; Tayama, E.; Nguyen, D. *Org. Lett.* **2004**, 6, 345.

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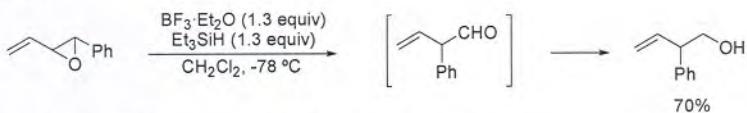
Expected Cyclization



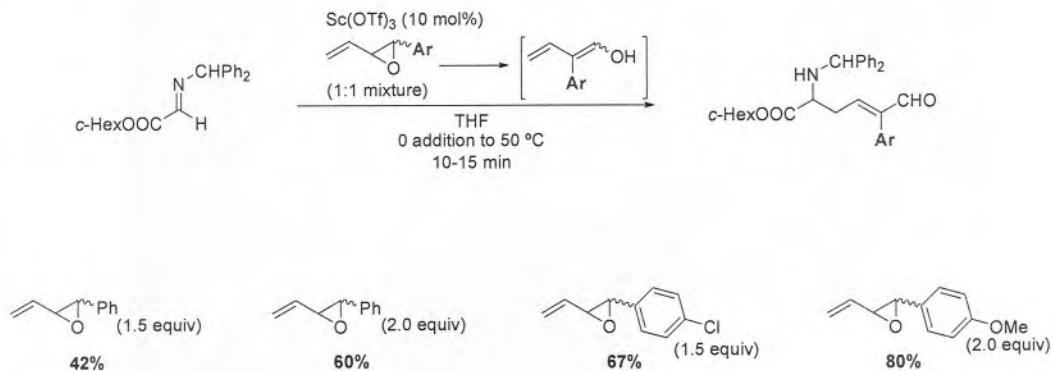
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Direct Vinylogous Mannich-Type Reaction with *in situ* Generated α -Aryl- β,δ -Unsaturated Aldehydes

One recent example:

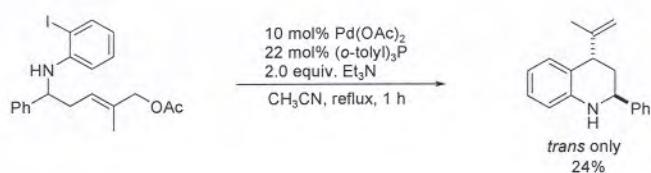
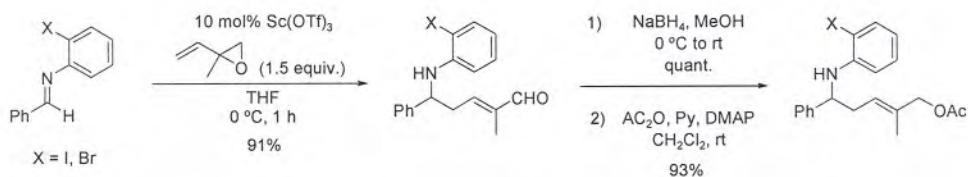


Jung, M. E.; Anderson, K. L. *Tetrahedron Lett.* **1997**, *38*, 2605.



University of Toronto

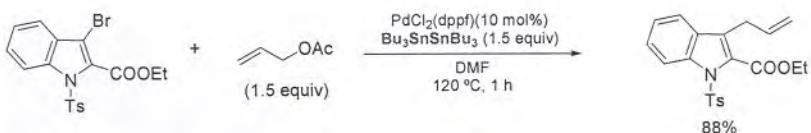
Approach to Heterocycles : Intramolecular Cross-Coupling Reaction to an Allyl Acetate



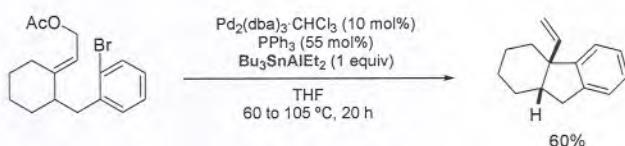
Eiji Tayama – Unpublished results

University of Toronto

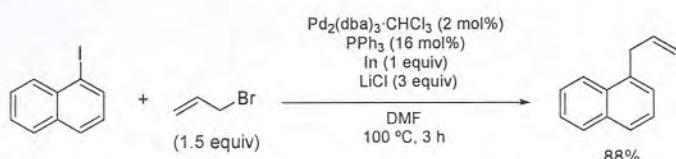
Previous Examples of Cross-Coupling Reactions Between an Aryl Halide and Allyl Acetate/Halide



Yokoyama, Y.; Ito, S.; Takahashi, Y.; Murakami, Y. *Tetrahedron Lett.* **1985**, *26*, 6457.



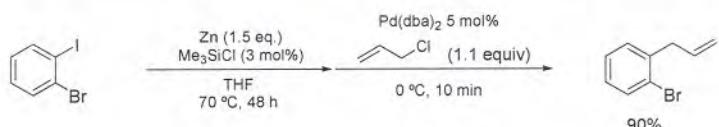
Trost, B.M.; Walchli, R. *J. Am. Chem. Soc.* **1987**, *109*, 3487.



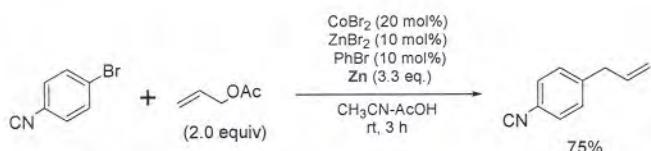
Lee, P. H.; Sung, S-Y.; Lee, K. *Org. Lett.* **2001**, *3*, 3201.

University of Toronto

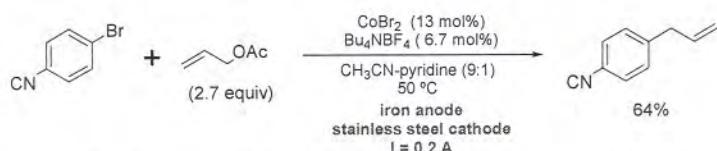
Recent Examples of Cross-Coupling Reactions Between an Aryl Halide and Allyl Acetate/Halide



Ikegami, R.; Koresawa, A.; Shibata, T.; Takagi, K. *J. Org. Chem.* **2003**, *68*, 2195.



Gomes, P.; Gosmini, C.; Perichon, J. *Org. Lett.* **2003**, *5*, 1043.

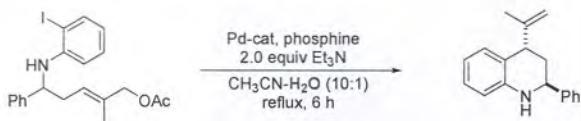


Gomes, P.; Gosmini, C.; Perichon, J. *J. Org. Chem.* **2003**, *68*, 1142.

University of Toronto

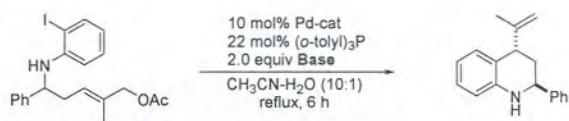
Optimization of Reaction Conditions

Effect of H_2O



catalyst system (mol%)	without H_2O	with H_2O
$Pd(OAc)_2 + (o\text{-tolyl})_3P$ (10) (22)	24% (recov 64%)	66%
$Pd_2(dbu)_3 + (o\text{-tolyl})_3P$ (5) (22)	34% (recov 60%)	73%
$PdCl_2[(o\text{-tolyl})_3P]_2$ (10)	30%	65%

Effect of base



Pd-cat						
$Pd(OAc)_2$	69%		66%	46%		4%
$Pd_2(dbu)_3$	76%	68%			17%	

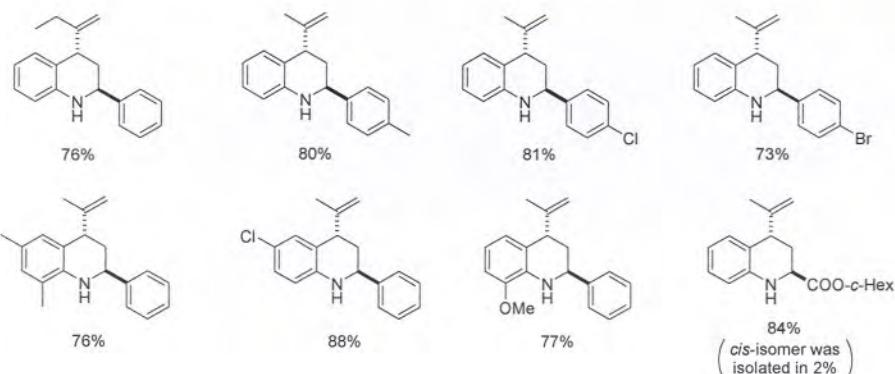
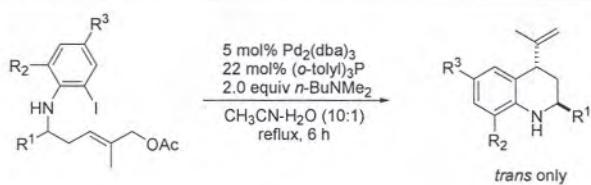
● Inorganic bases
 $Pd(OAc)_2$ as a catalyst
 K_2CO_3 (3.0 equiv), 10%
 $NaOH$ (2.5 equiv), 8%

Eiji Tayama – Unpublished results



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Palladium Catalyzed Intramolecular Cross-Coupling Reactions Between an Aryl Iodide and Allyl Acetate

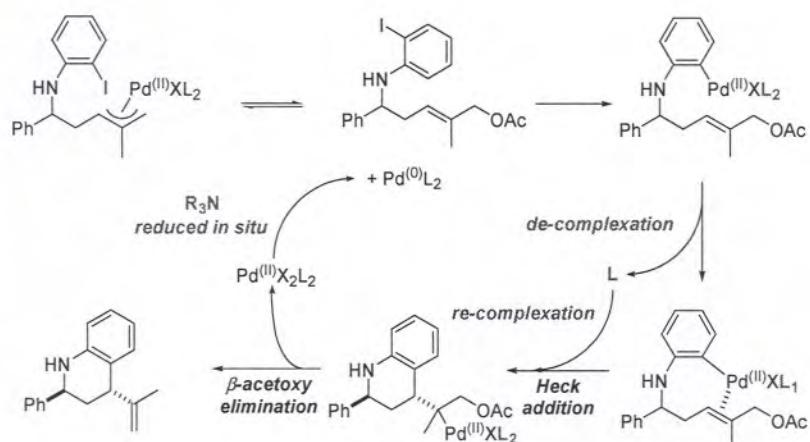


Eiji Tayama – Unpublished results



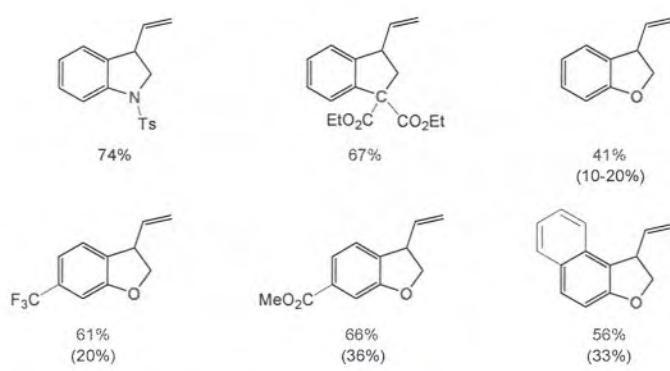
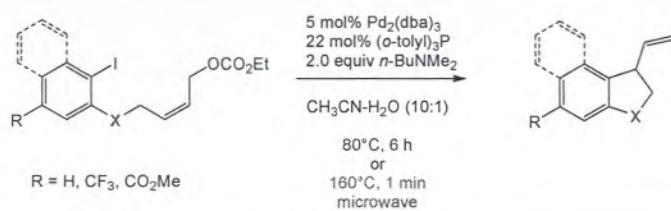
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Proposed Mechanism of Palladium Catalyzed Direct Intramolecular Cyclization



University of Toronto

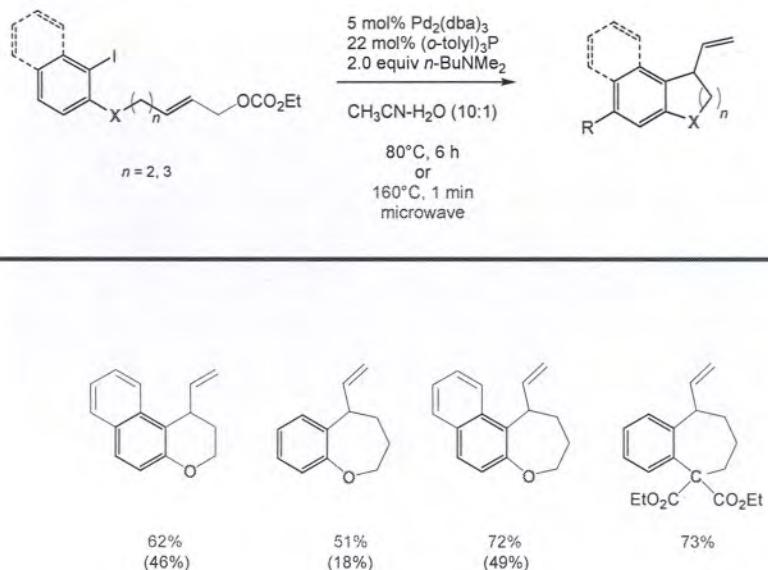
Scope for 5-Membered Ring Systems



Christelle Herse – Unpublished results

University of Toronto

Scope for 6 and 7-Membered Ring Systems

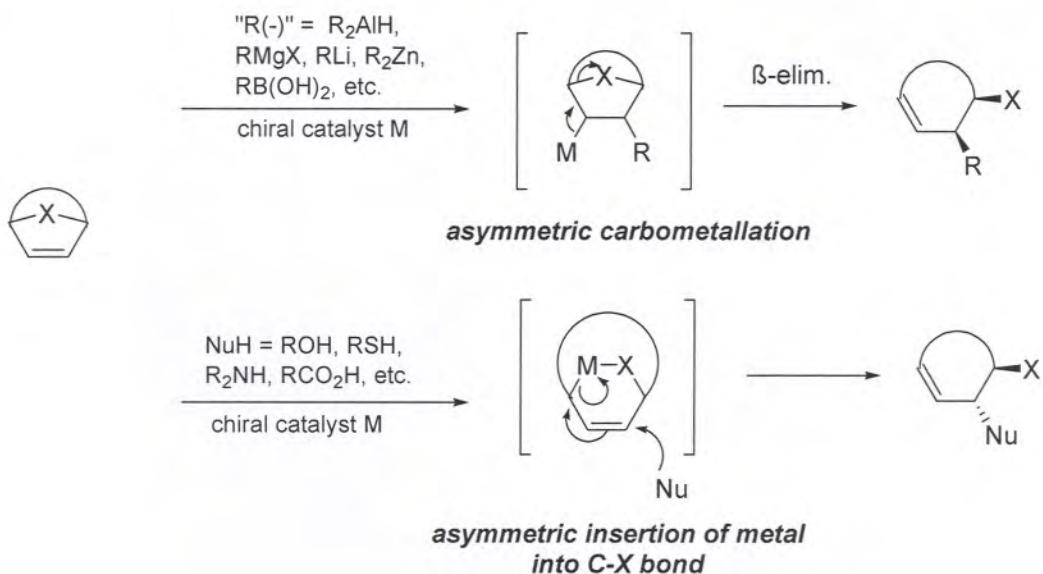


Christelle Herse – Unpublished results



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Ring-Opening Reactions: General Scheme

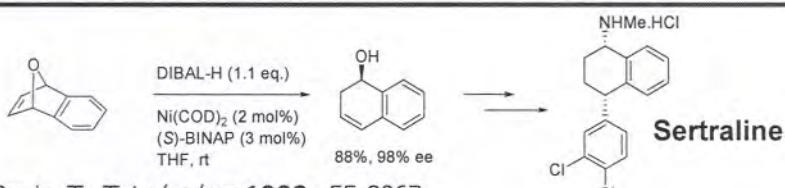


Lautens, M.; Fagnou, K.; Hiebert, S. *Acc. Chem. Res.* **2003**, *36*, 48-58

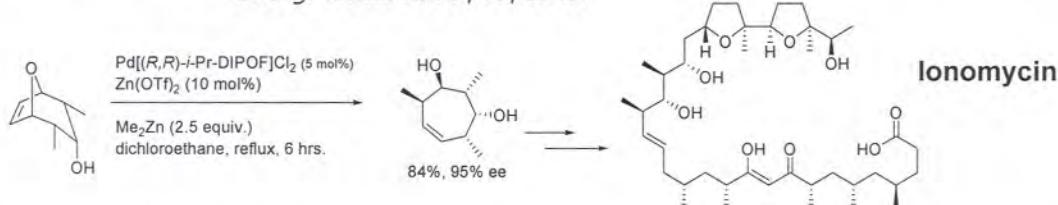


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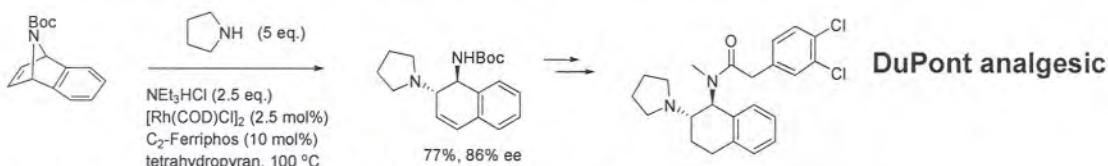
Efficient Syntheses of Pharmaceutical Agents and Natural Products by ARO



Lautens, M.; Rovis, T. *Tetrahedron* **1999**, *55*, 8967.
J. Org. Chem. **1997**, *62*, 5246.



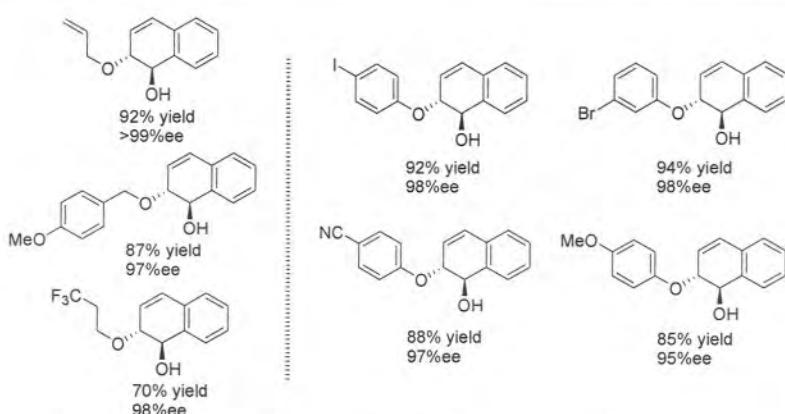
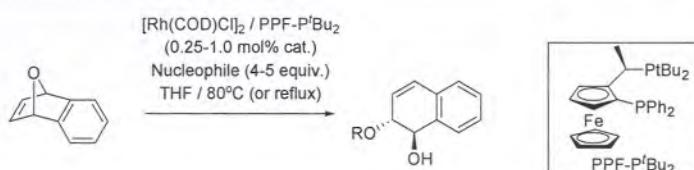
Lautens, M.; Colucci, J.T.; Hiebert, S.; Smith, N.D.; Bouchain, G. *Org. Lett.* **2002**, *4*, 1879.



Lautens, M.; Fagnou, K.; Zunic, V. *Org. Lett.* **2002**, *4*, 3465.

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Rh-Catalyzed ARO: Preliminary Results

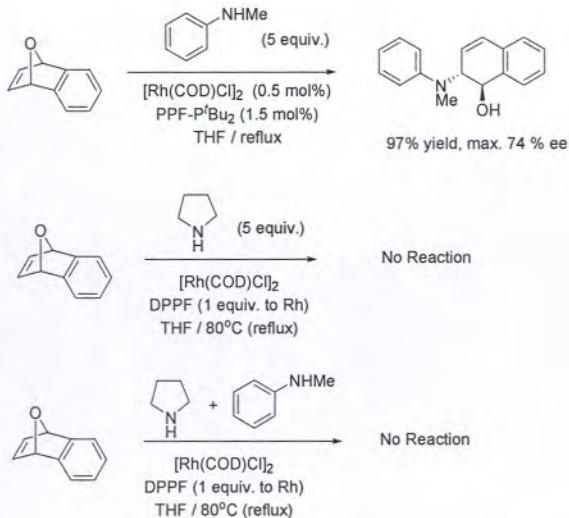


Lautens, M.; Fagnou, K.; Rovis, T. *J. Am. Chem. Soc.* **2000**, *122*, 5650.

Lautens, M.; Fagnou, K.; Taylor, M. *Org. Lett.* **2000**, *2*, 1677.

University of Toronto

Rh-Catalyzed ARO: Disappointments

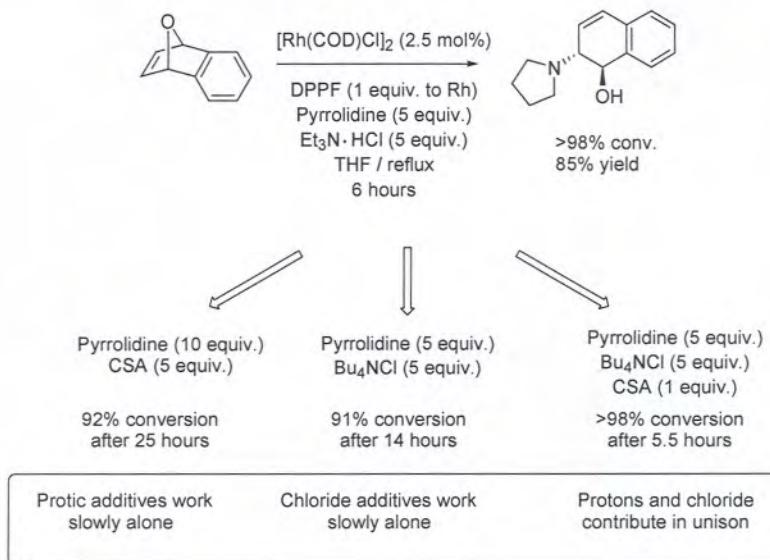


- Dialkyl amines poison the catalyst

Lautens, M.; Fagnou, K. *J. Am. Chem. Soc.* **2001**, 123, 7170.

University of Toronto

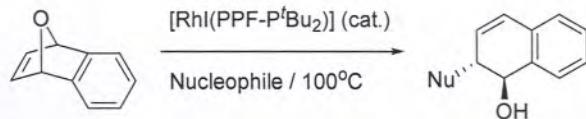
Amine Poisoning and Amine Hydrochloride Additives



Review of halide effects in catalysis: Lautens, M.; Fagnou, K. *Angew. Chem. Int. Ed.* **2002**, 41, 26.

University of Toronto

Combination of these Discoveries Results in a Highly Efficient, Atom Economical Process



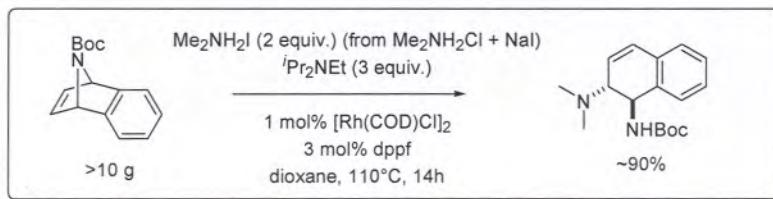
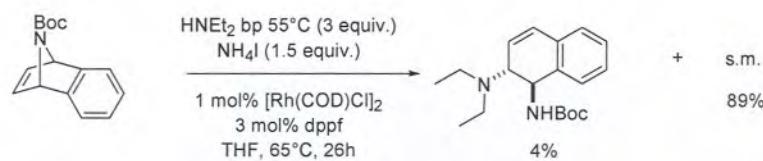
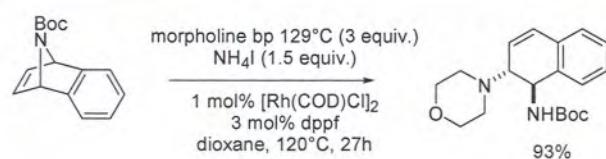
Mol% Catalyst	s:c	Nucleophile (equiv.)	Reaction Time	Yield (%)	ee (%)
0.01	10000:1	PhOH (1.5)	3hr	90	94
0.01	10000:1	PhNHMe (1.5)	8hr	87	93
0.01	10000:1	Indole (1.5)	1.5hr	94	99

Fagnou, K.; Lautens, M. Patent#: WO 2001030734



University of Toronto

ARO using Volatile Amines

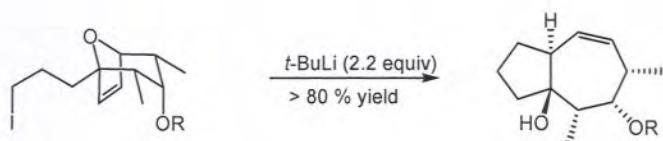
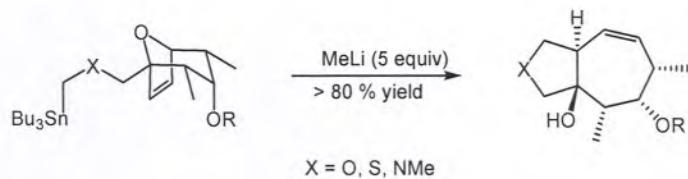


Hisanori Senboku – *Unpublished results*



University of Toronto

Intramolecular Ring Closing/ Ring Opening



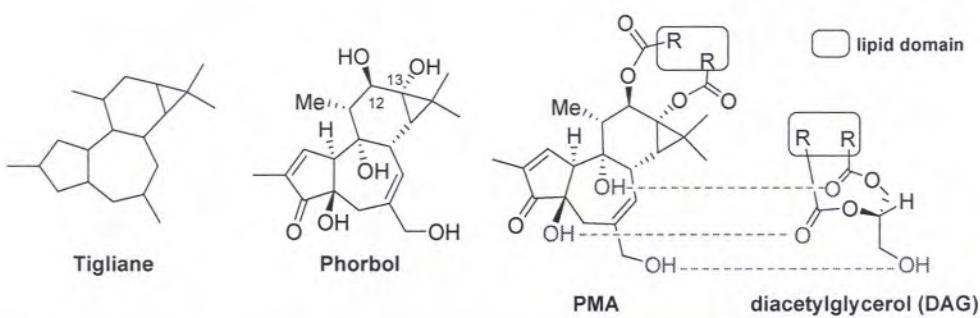
Lautens, M.; Kumanovic, S. *J. Am. Chem. Soc.* **1997**, *117*, 1954.



University of Toronto

Phorbol: Background

• Pharmacophore model



- First isolated as a hydrolysis product of Croton tiglium oil in 1935 (Bohm *et al.*)

- PMA tumour promoters, inflammatory agents.

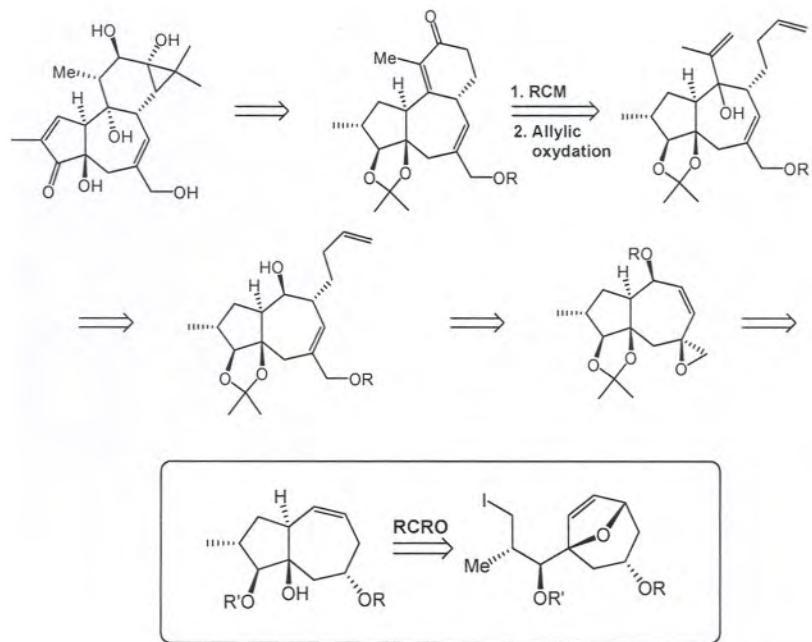
- Total synthesis:

- Wender, P.A.; Rice, K.D.; Schnute, M.E. *J. Am. Chem. Soc.* **1997**, *119*, 7897.
- Kwangho, L.; Cha, J.K. *J. Am. Chem. Soc.* **2001**, *123*, 5590.



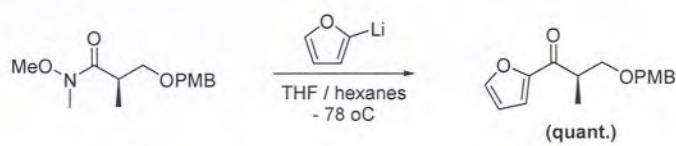
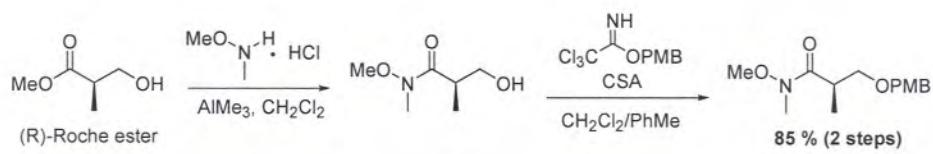
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Phorbol: Retrosynthesis



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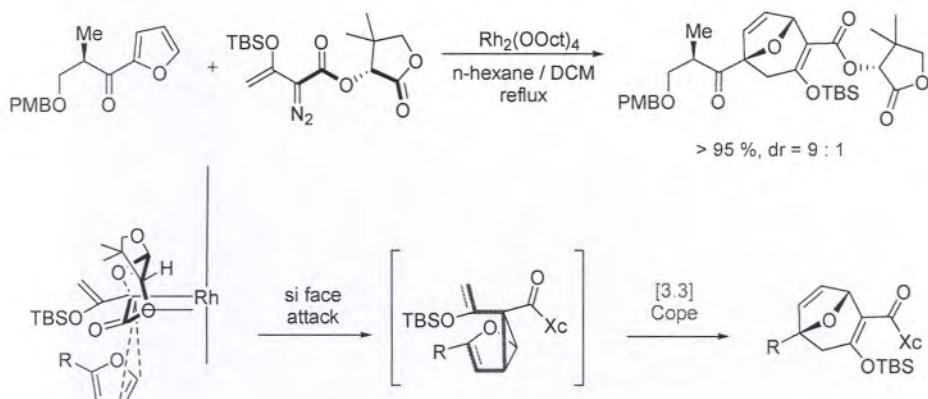
Synthesis of AB Ring System



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Synthesis of AB Ring System

Tandem cyclopropanation / Cope rearrangement by H.M.L. Davies

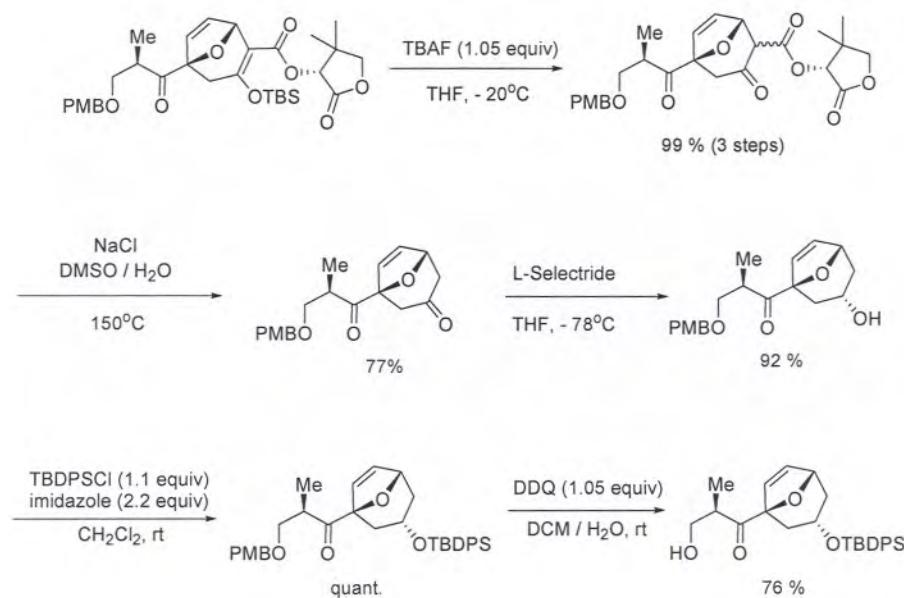


- low catalyst loading, < 0.5 mol%
- reaction viable for larger scale (160 mmol, 100 g)

Davies, H.M.L.; Ahmed, G.; Churchill, M.R. *J. Am. Chem. Soc.* **1996**, *118*, 10774.

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Synthesis of AB Ring System



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Synthesis of AB Ring System

Chelation-Controlled reduction

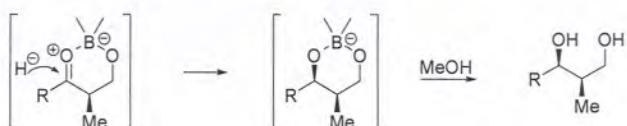


Nataka, T.; Oishi, T.
Acc. Chem. Res. **1984**, 17, 338.

$\xrightarrow[\text{Et}_2\text{O}, -40^\circ\text{C}]{\text{Zn}(\text{BH}_4)_2}$ 60%, d.r. = 6 : 4

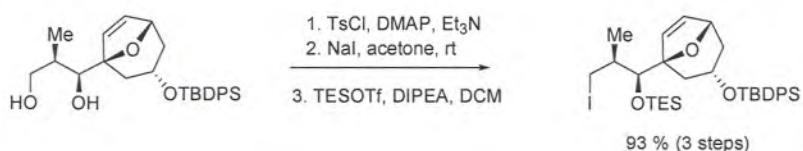
Prasad, K. et al.
Tetrahedron Lett. **1987**, 28, 155.

$\xrightarrow[1. \text{Et}_2\text{BOMe} (1.1 \text{ equiv})]{2. \text{NaBH}_4 (1.1 \text{ equiv})}$ 90 - 95%, d.r. = 44 : 1
isomers separable (89:2:9)

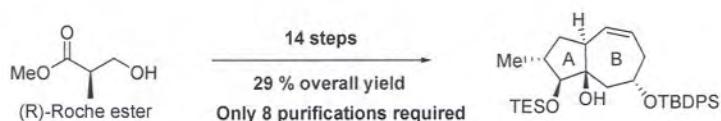
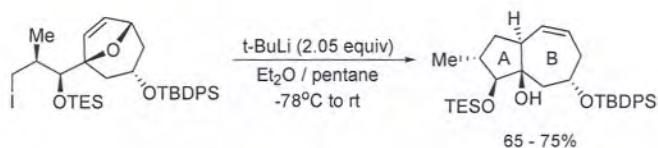


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Synthesis of AB Ring System

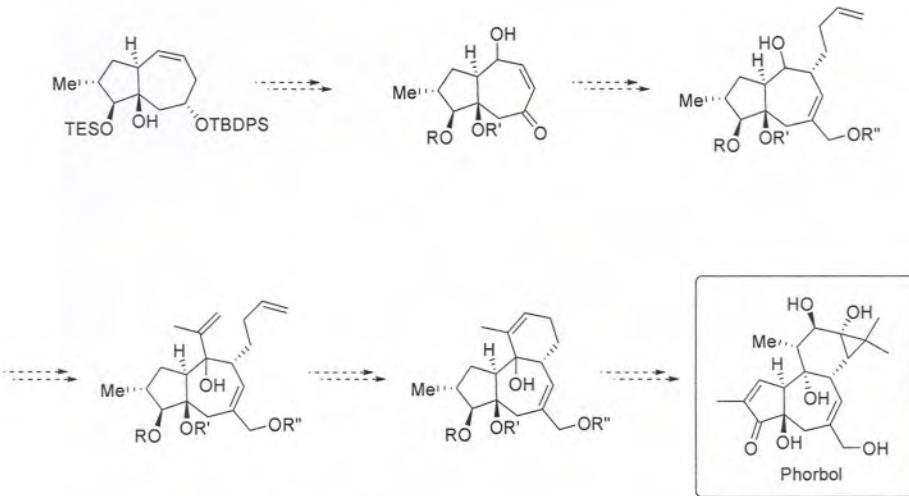


Anionic Ring-Closing Ring-Opening Reaction



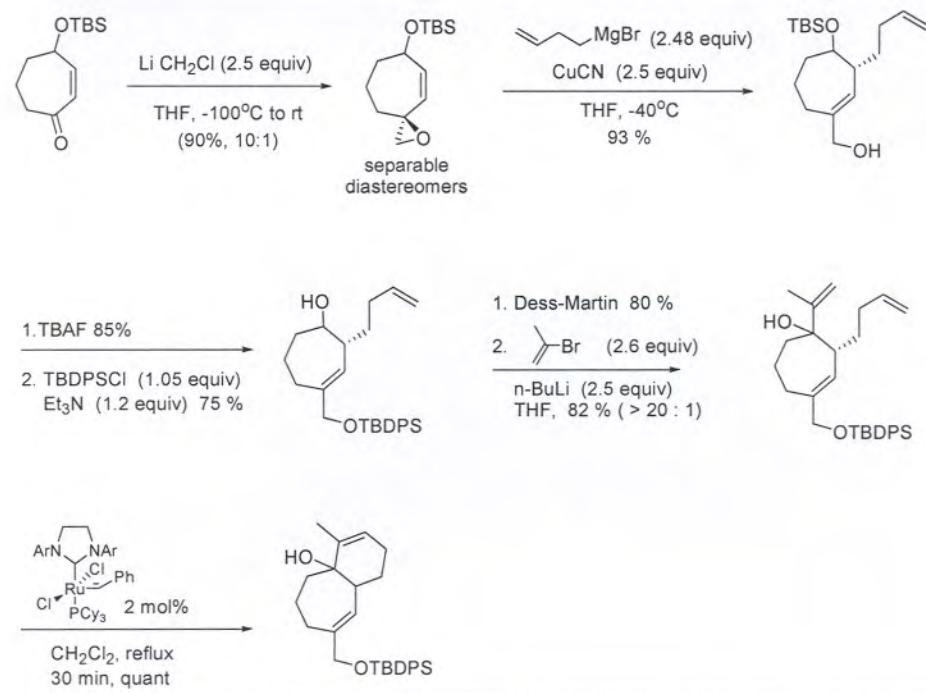
University of Toronto

Introduction of Ring C: Synthetic Plan



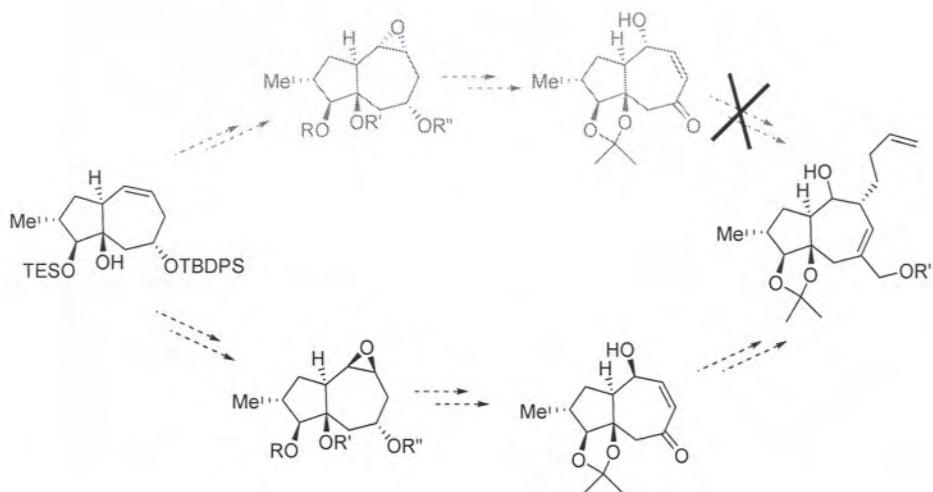
University of Toronto

Introduction of Ring C: Model Study



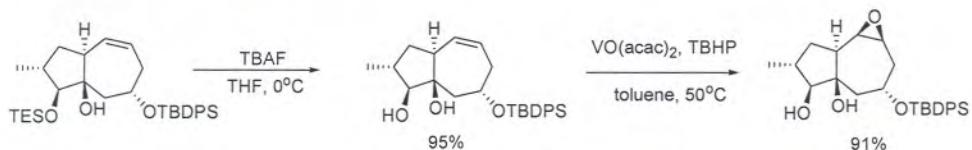
University of Toronto

Introduction of Ring C: Synthetic Plan

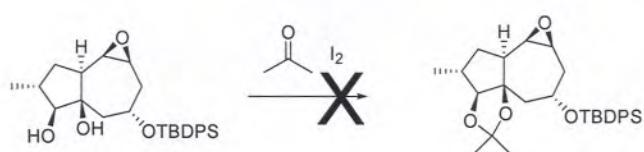


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Protecting Group Strategies



Dimethyl acetonide formation:



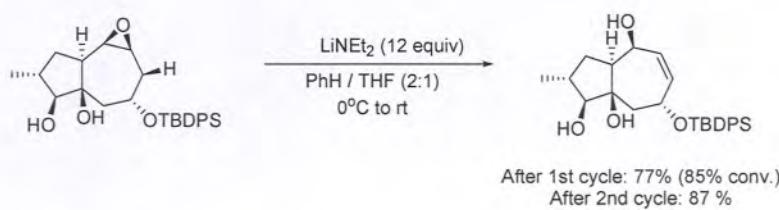
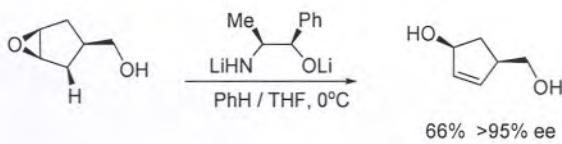
For acetonide formation see: Kartha, K.P.R. *Tetrahedron Lett.* **1986**, 27, 3415.



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Protecting Group Strategies

Base-induced epoxide ring opening



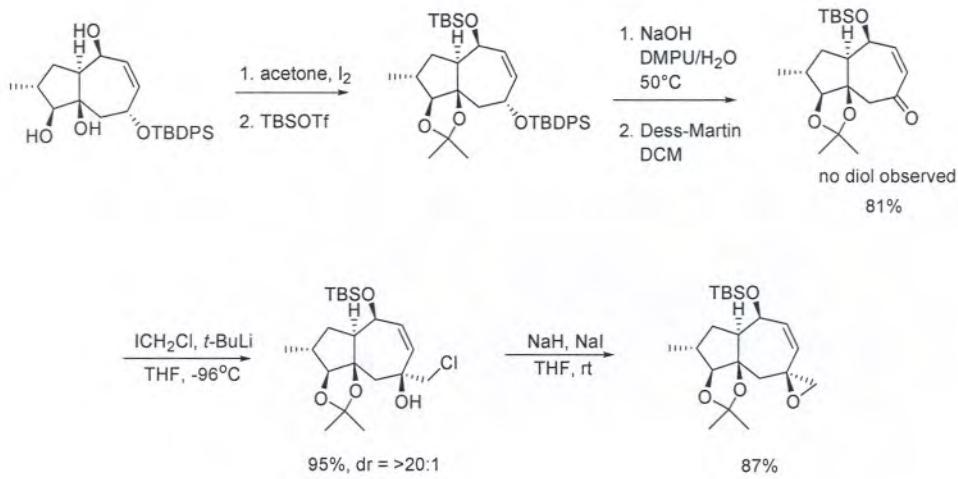
Crandall, J.K.; Apparu, M. *Org. React.* **1983**, 29, 345.

Hodgson, D.M.; Gibbs, A.R. *Synlett.* **1997**, 657.



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Introduction of Ring C



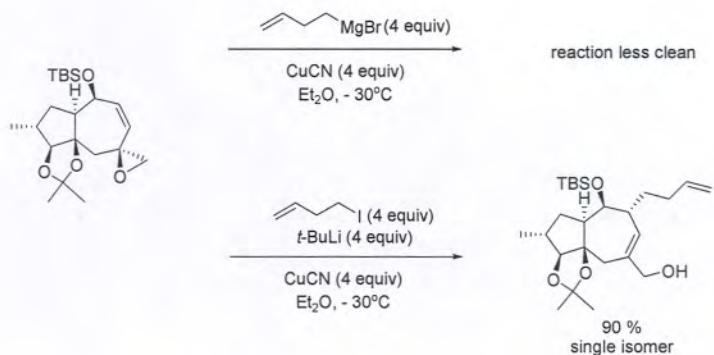
Selective deprot. with NaOH : Hatakeyama, S. et al. *Tetrahedron* **1994**, 50, 13369.



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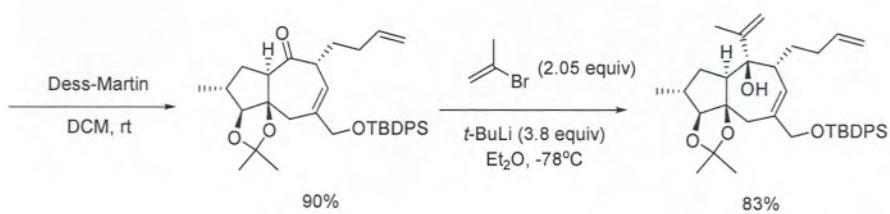
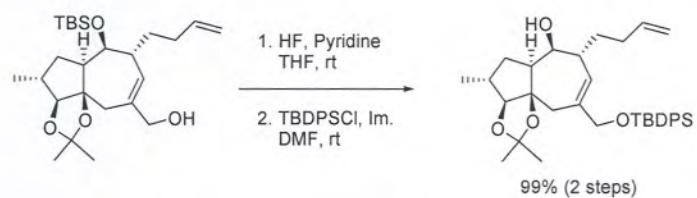
Introduction of Ring C

S_N2' addition of cuprate nucleophiles



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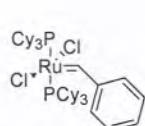
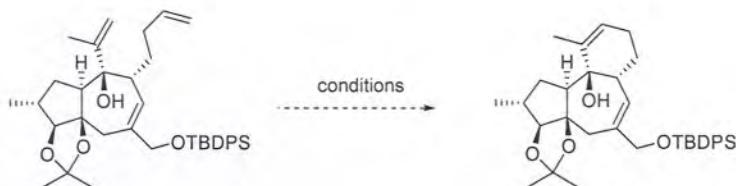
Introduction of Ring C



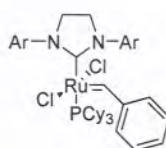
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Formation of Ring C: RCM

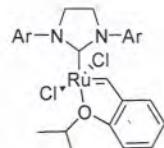
Ring Closing Metathesis (RCM) studies



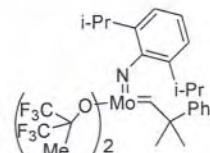
Grubbs' 1st



Grubbs' 2nd



Hoveyda



Schrock

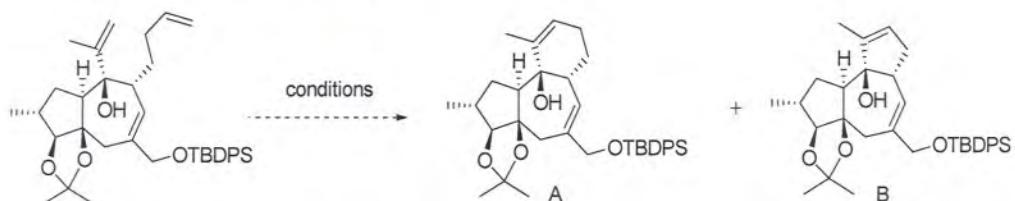
Catalyst loading, solvents, temperature, concentration and atmosphere



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Formation of Ring C: RCM

Ring Closing Metathesis (RCM) studies



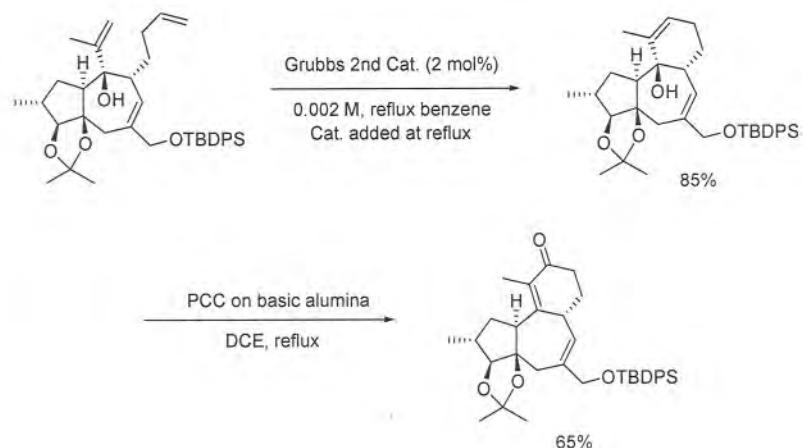
- Catalyst: **Grubbs 2nd generation**
- Solvent and temperature: **benzene, reflux**
- Low temperature favors dimerization
- Higher temperature favors the formation of **B**
- Ethylene atmosphere favors the formation of **B**
- Higher concentration favors the formation of **B** (**for A, 0.002M is optimal**)
- Catalyst loading: **2 - 10 mol%**
- **Catalyst loaded at reflux, otherwise slow and messy reaction**



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Formation of Ring C: RCM

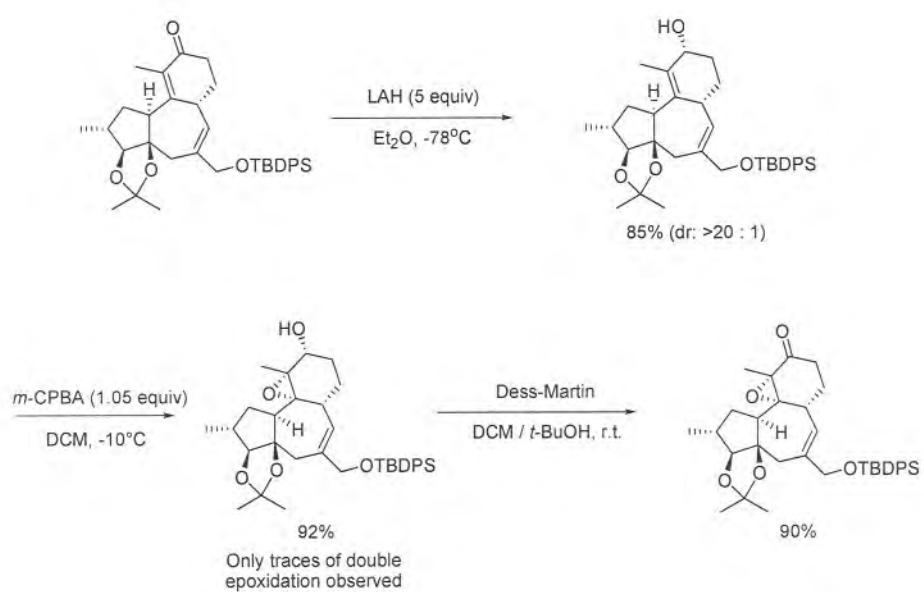
RCM / Allylic oxidation sequence



Other conditions such as PCC on silica gel, PCC gave similar results

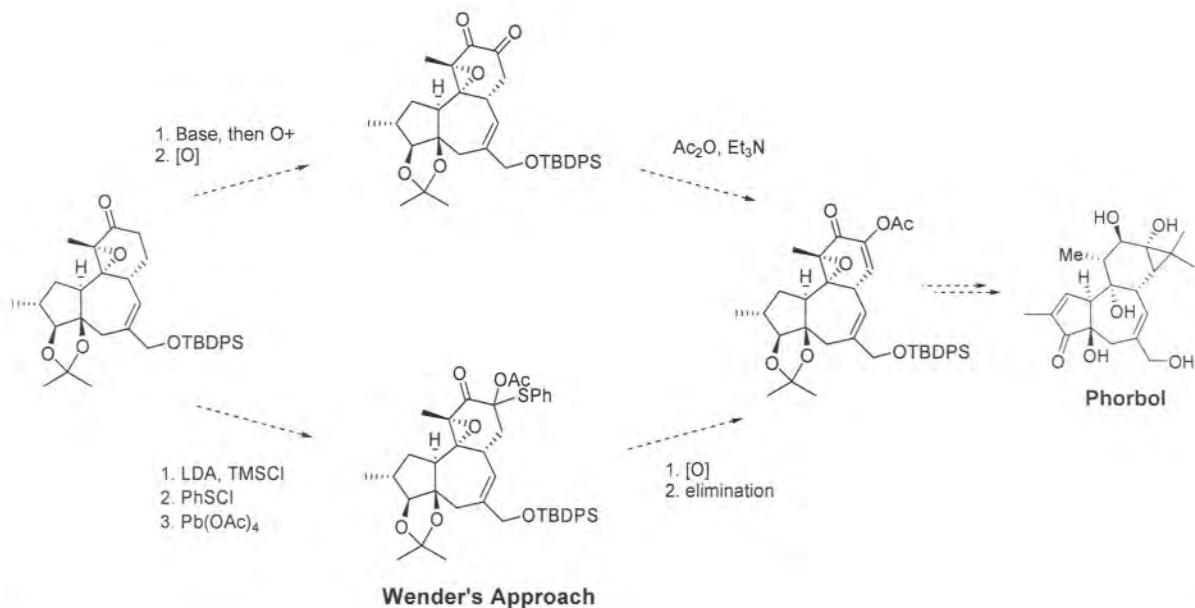
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Functionalization of Ring C



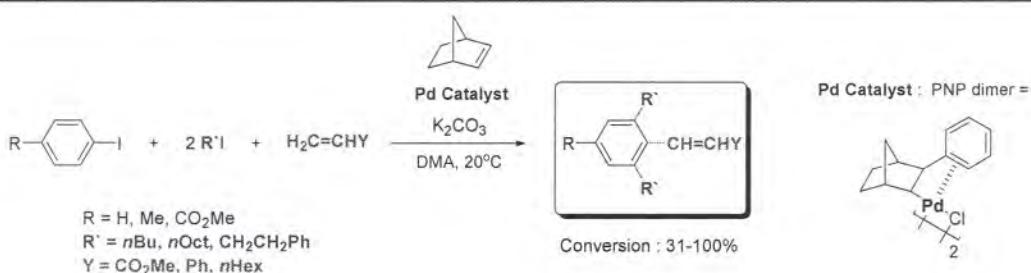
University of Toronto

Introduction of Ring D: Synthetic Plans

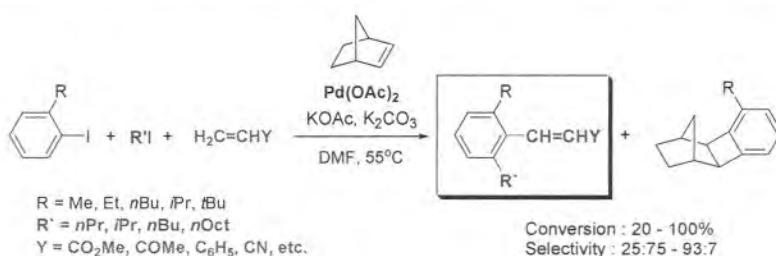


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Palladium-Catalyzed *Ortho* Alkylation: The Catellani Reaction



Catellani, M., Frignani, F., Rangoni, A., *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 119

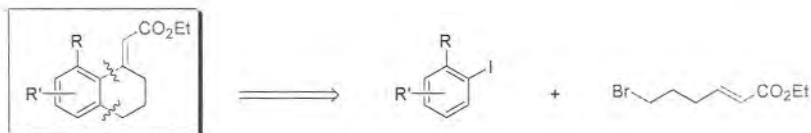


Catellani, M., Cugini, F., *Tetrahedron* **1999**, *55*, 6595

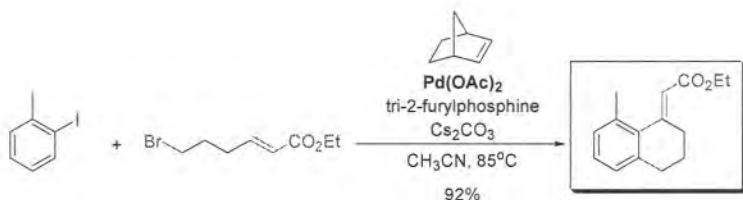


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Proposal



Preliminary Result

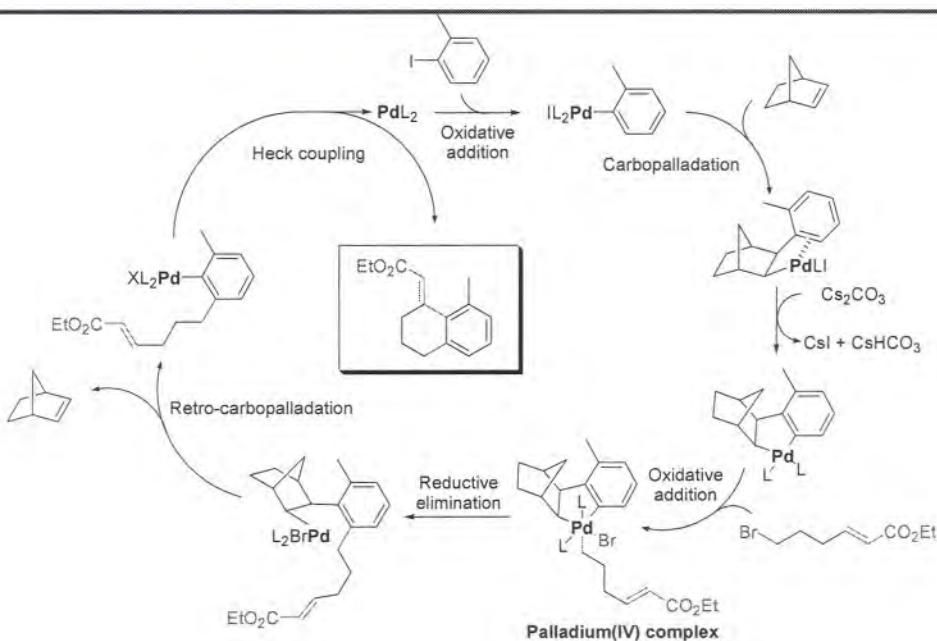


Lautens, M.; Piguel, S. *Angew. Chem. Int. Ed.* **2000**, *39*, 1045



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Proposed Mechanism



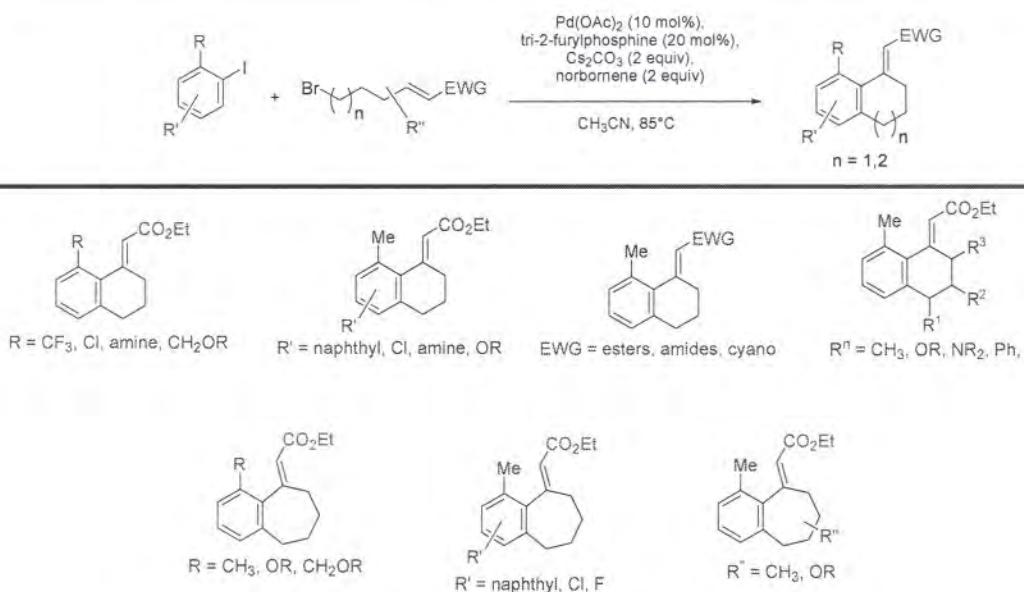
Catellani, M. et al. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 119; *J. Am. Chem. Soc.* **2002**, *124*, 4336.

For a review on palladium(IV) chemistry see: Carty, A. *Acc. Chem. Res.* **1992**, *25*, 83.



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Functionalized Carbocycles



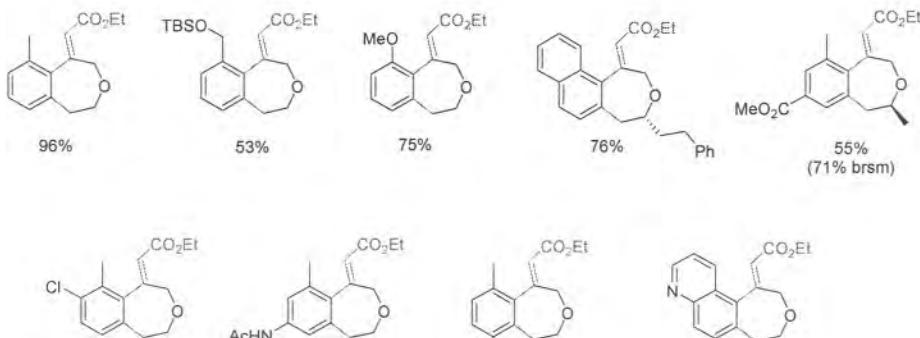
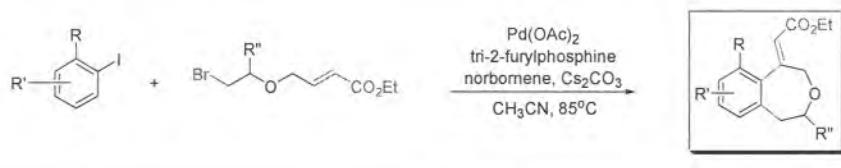
Lautens, M.; Piguel, S. *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 1045.

Lautens, M.; Paquin, J.-F.; Piguel, S.; Dahlmann, M. *J. Org. Chem.* **2001**, *66*, 8127.



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4-Benzoxepines

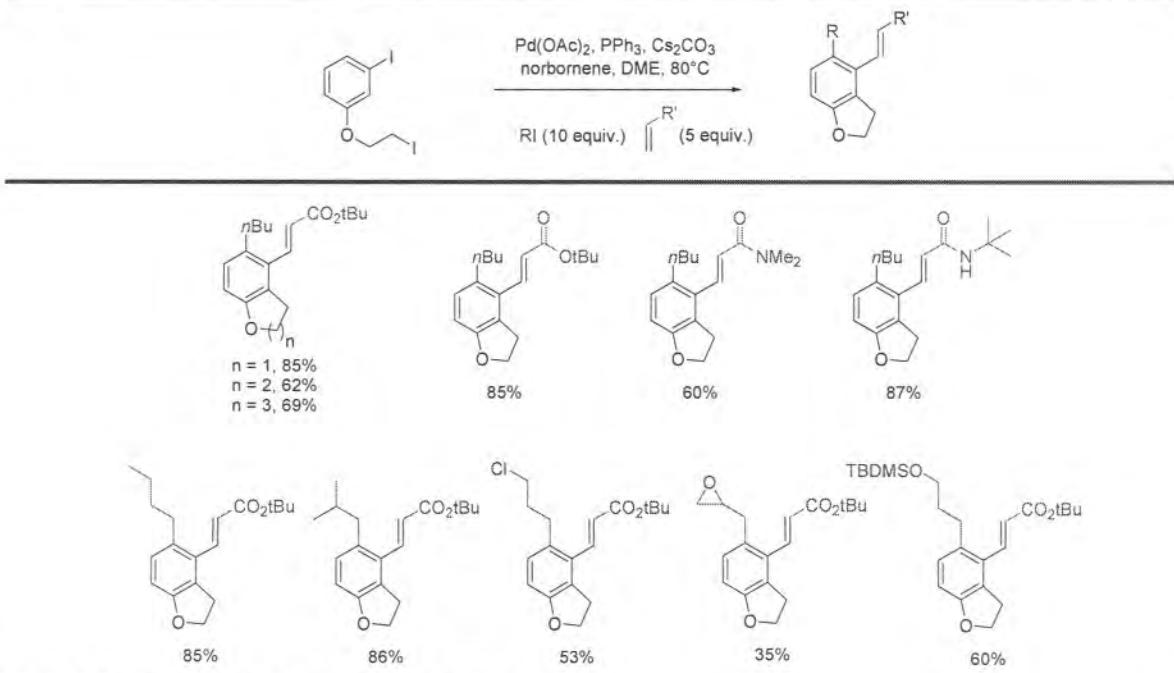


Lautens, M.; Paquin, J.-F.; Piguel, S. *J. Org. Chem.* **2002**, *67*, 3972



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New Concept: 3-Component Coupling

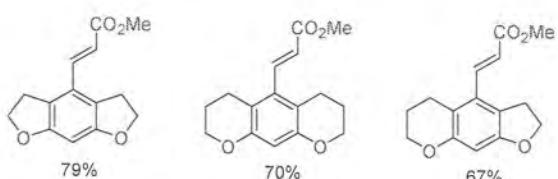
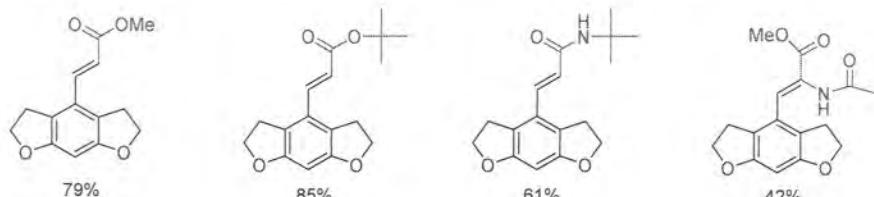
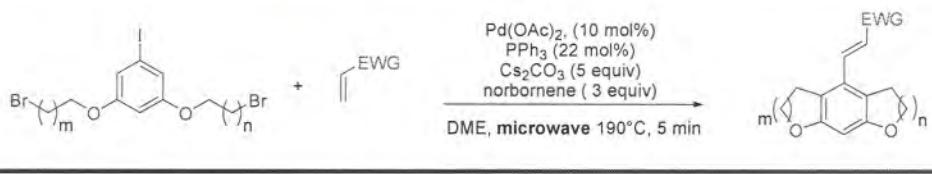


Pache, S.; Lautens, M. *Org. Lett.* **2003**, 5, 4827.



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Two Intramolecular Alkyl Halides / External Heck Acceptor – Preliminary Results

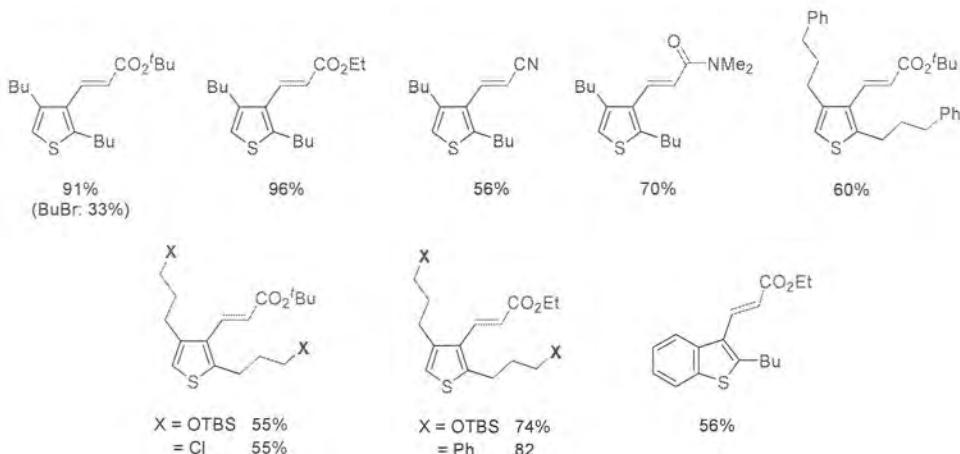
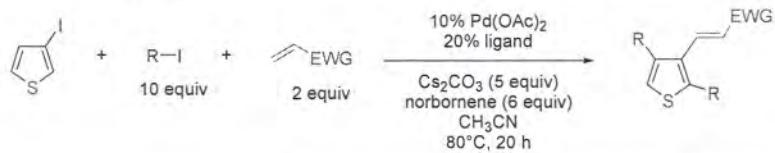


Dino Alberico – *Unpublished results*



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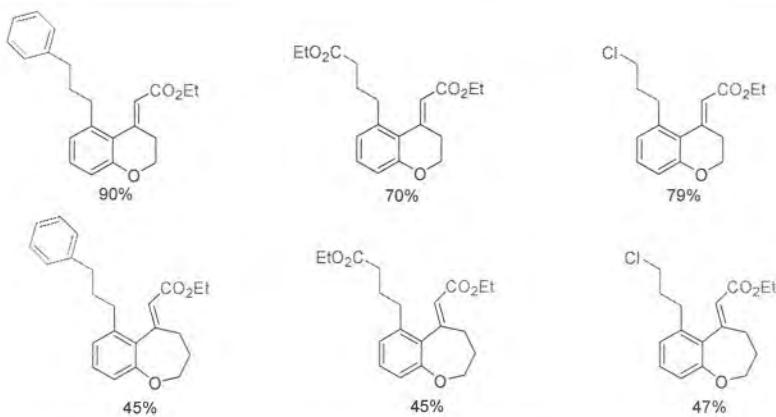
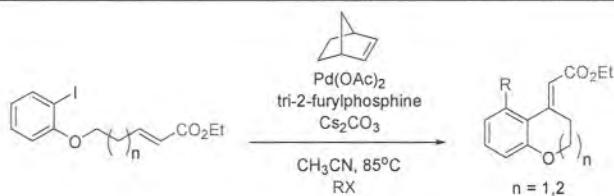
Reaction of Heterocyclic Iodides



 Koichi Mitsudo – *Unpublished results*

University of Toronto

External Alkyl Halides / Intramolecular Heck Acceptor – Preliminary Results



 Andrew Martins, Udo Marquardt, Neema Kasravi – *Unpublished results*

University of Toronto

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Pd-catalyzed annulation

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Phorbol

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University of Toronto

The Lautens Group at the Merck Frosst/NSERC Industrial Chair Ceremony



University of Toronto





The Lautens Group at the Summer BBQ



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