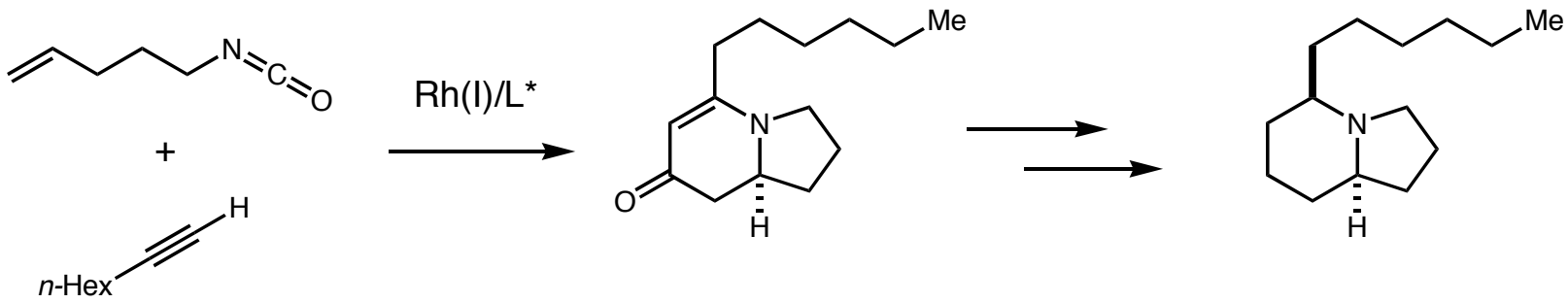
# *Total Synthesis of Indolizidine Alkaloid (—)-209D: Overriding Substrate Bias in the Asymmetric Rhodium-Catalyzed [2+2+2] Cycloaddition*

Robert T. Yu, Ernest E. Lee, Guillaume Malik, Tomisav Rovis*

Department of Chemistry, Colorado State University, Fort Collins, CO

*Angewandte Chemie International Addition,* **2009**, *48*, 2379-2382.

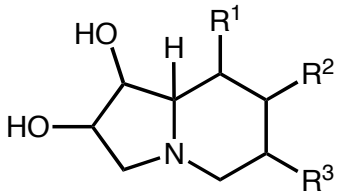



*Robert B. Lettan II*
*April 11, 2009*

*Wipf Group Saturday Morning Meeting*
*Current Literature Abstracts & Reports*

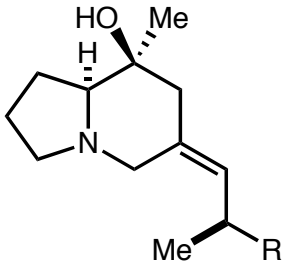
# *Indolizidine Alkaloids*

*hydroxylated indolizidines*

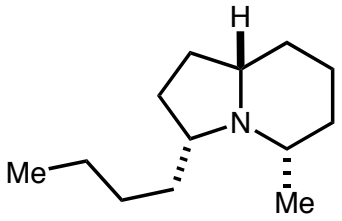



$R^1,R^2,R^3$ = H: lentiginonsine
$R^1$ = OH; $R^2,R^3$ = H: swainsonine
$R^1,R^2$ = OH; $R^3$ = H: castanospermine
$R^1,R^2,R^3$ = OH: uniflorine

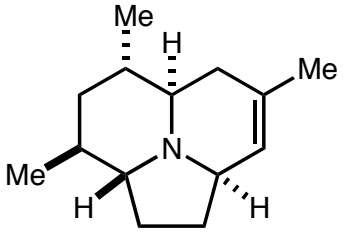
*Alkaloids from ants and amphibians*



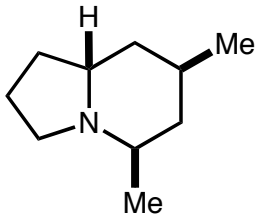

(+)-pumiliotoxin



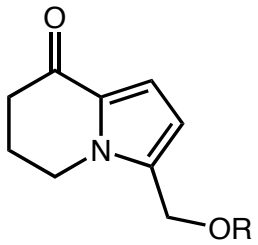

(+)-monomorine



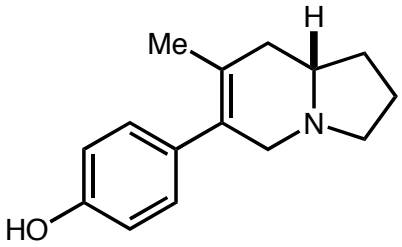

(—)-alkaloid 205B



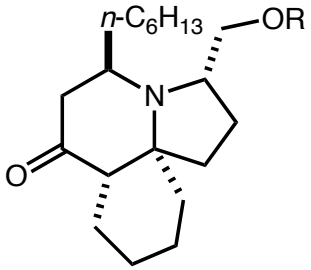

(—)-dendroprimine



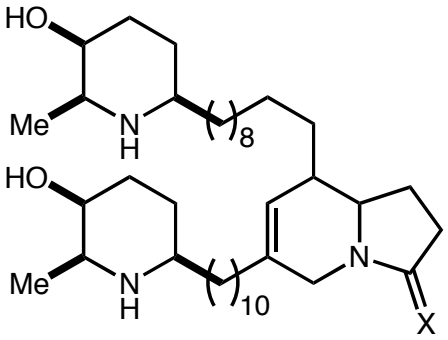

*polygonatum* alkaloids



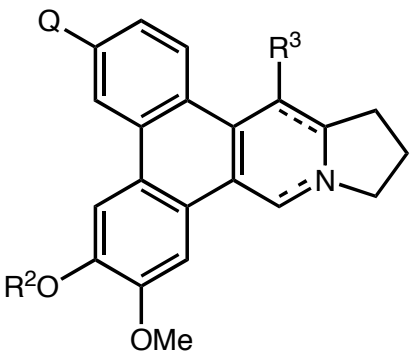

(+)-ipalbidine



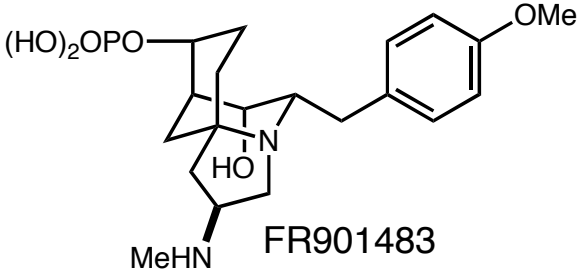

(+)-cylindricines



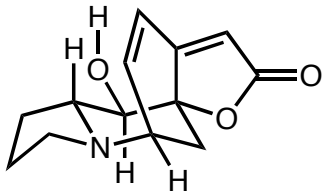

*prosopis* alkaloids
X = O, $H_2$




tylophoridicines



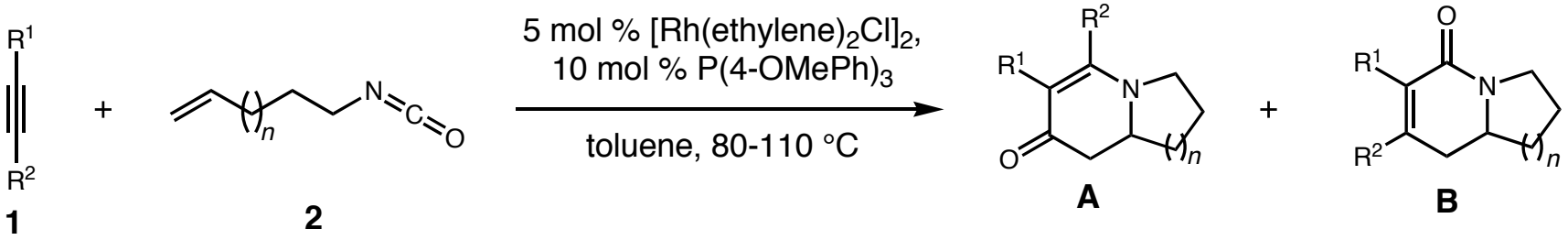

FR901483



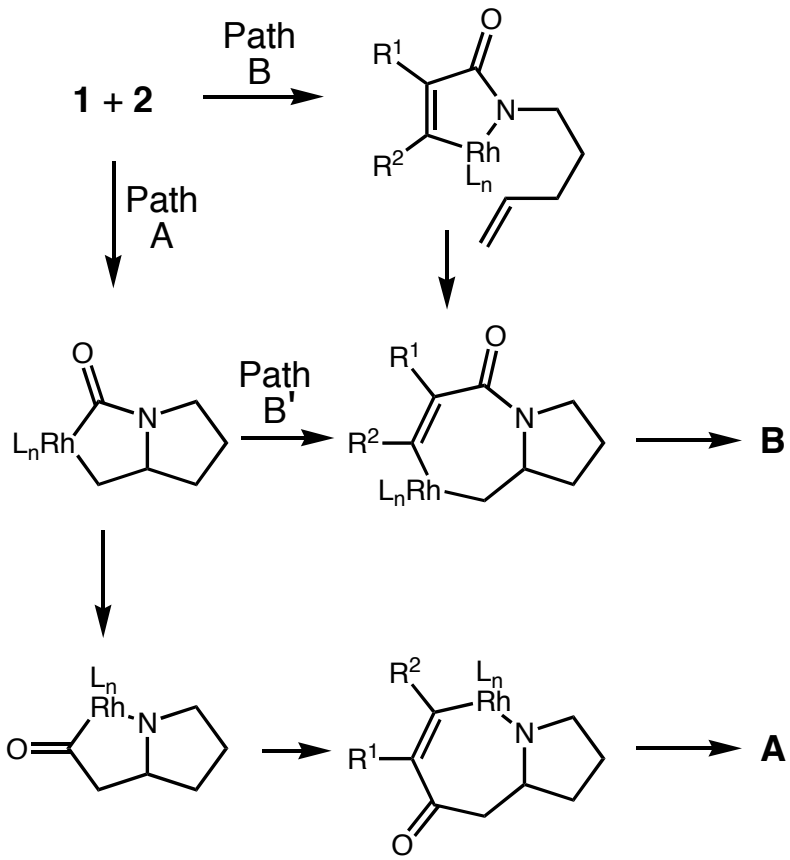

(—)-secu'amamine A

Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139-165.

# *Rovis' Initial Approach towards Indolizidines*



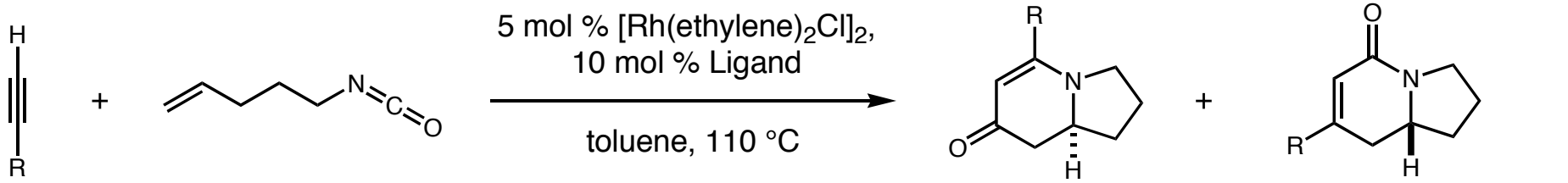

*Proposed Mechanism*



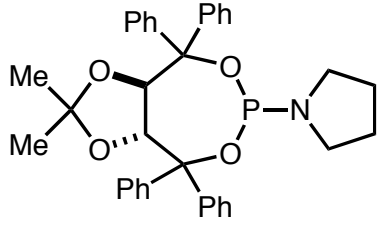

| $R^1/R^2$ | n | Yield (%) | Selectivity (**A**:**B**) |
|---|---|---|---|
| substituted phenyl | 1 | 60-72 | >20:1 |
| 1-cyclohexene | 1 | 75 | >20:1 |
| 1-cylopentene | 1 | 50 | >20:1 |
| 3-furyl | 1 | 66 | 1.1 : 1 |
| 2-thiophene | 1 | 72 | 1.3 : 1 |
| *n*-propyl | 1 | 60 | >1:20 |
| *n*-butyl | 1 | 70 | 1:6 |
| $(CH_2)_2OTBS$ | 1 | 56 | >1:20 |
| *n*-butyl | 2 | 62 | 1:3.5 |
| $(CH_2)_2OTBS$ | 2 | 56 | >20:1 |
| $R^1$ = Me, $R^2$ = Ph | 1 | 60 | 60 |
| $R^1$ = Et, $R^2$ = Ph | 1 | 63 | 63 |

Yu, R. T.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 2782.

# *Application to Terminal Alkynes with Chiral Ligands*




*Ligand*



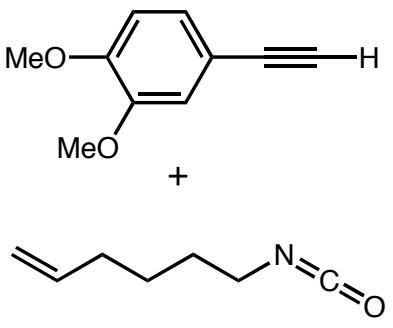
**major** (>20:1 to 1.5:1)
when **R = aryl**
*50-96% yield*
*81-98% ee*

*electron deficient substituents give poor selectivity*

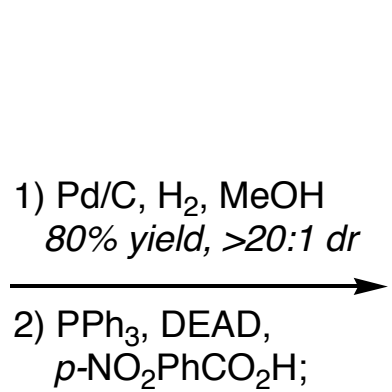
**major** (>20:1 to 1.2:1)
when **R = alkyl**
*46-82% yield*
*76-87% ee*

*Steric factors influence selectivity*

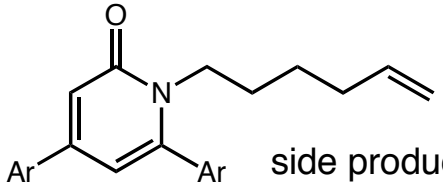
*Total Synthesis of (+)-Lasubine II*




*quinolizinone*
*62% yield, 98% ee*




*(+)-Lasubine II*
*62% yield, 98% ee*

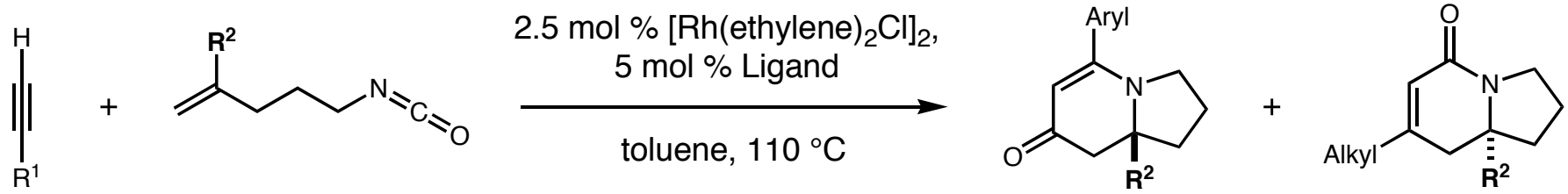


side product (*20%*)

Yu, R. T.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 12370.

# *Additional Applications*

*Formation of Quaternary Stereocenters*

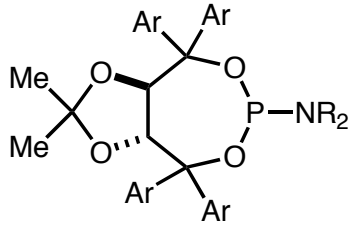



**major** (12:1 to 2:1)
when **$R^1$ = aryl**
Ligand **I**
*87-94% ee*

**major** (>20:1 to 3:1)
when **$R^1$ = alkyl**
Ligand **II**
*91-95% ee*

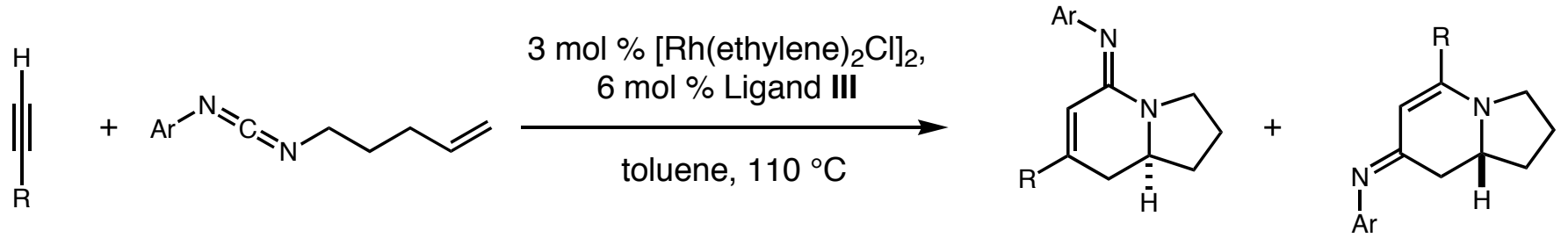
*Ligand*

**I**: Ar = Ph, R = Me
**II**: Ar = 3,5-xylyl, $NR_2$ = –N
**III**: Ar = *3*-xylyl, $NR_2$ = –N




$R^2$ = Me, *n*-Bu, *i*-Bu, Bn, *i*-Pr,
cy, $CH_2OBn$, *n*-butene

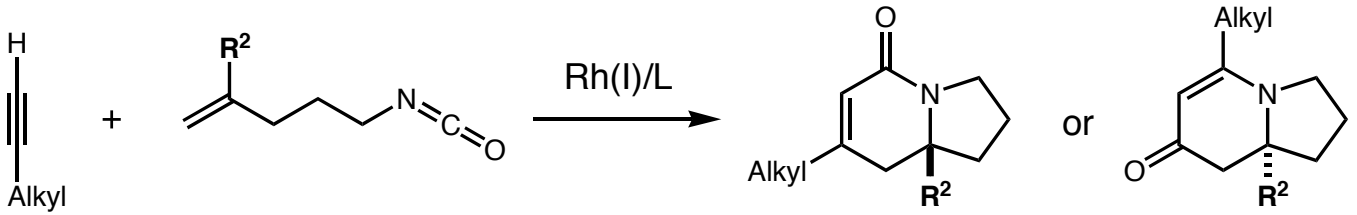
*Synthesis of Bicyclic Amidines*




up to >19:1
*43-82% yield*
*88-99% ee*

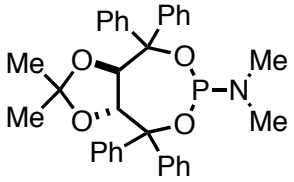
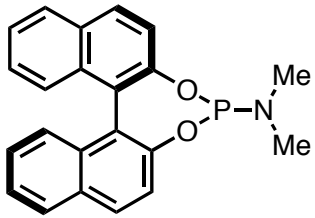
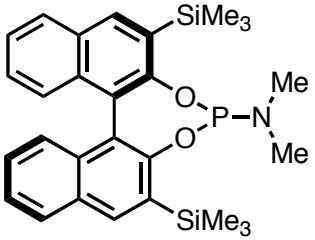
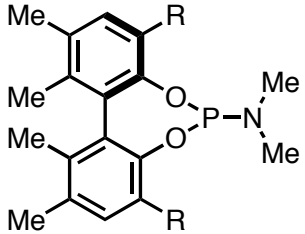

Lee, E. E..; Rovis, T. *Org. Lett.* **2008**, *10*, 1231.
Yu, R. T.; Rovis, T. *J. Am. Chem. Soc.* **2008**, *130*, 3262.

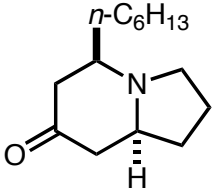
# Overriding Substrate Bias



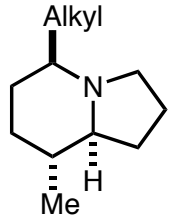

*Previous Work* (***A***) *Topic Paper* (***B***)

***Ligand Screening (alkyl = n-Hex; $R^2$ = H)***

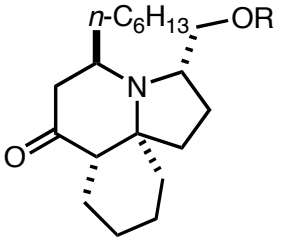
| Ligand | | **A:B** | Yield of **B** (%) | *ee* of **B** (%) |
|---|---|---|---|---|
|  | | 3.2 : 1 | 20 | 73 |
|  | | 1 : 2.2 | 22 | 72 |
|  | | 1 : 3.8 | 60 | 96 |
|  | R = $SiMe_3$ | 1 : 3.5 | 50 | 94 |
| | R = *t*-Bu | 1 : 6.2 | 75 | 91 |



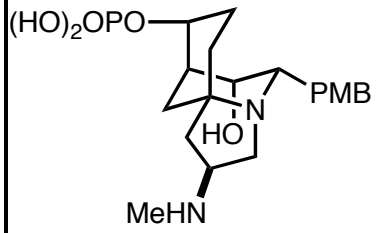

*(−)-209D*



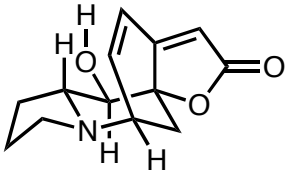

*dialkylated indolizidines*




(+)-cylindricines

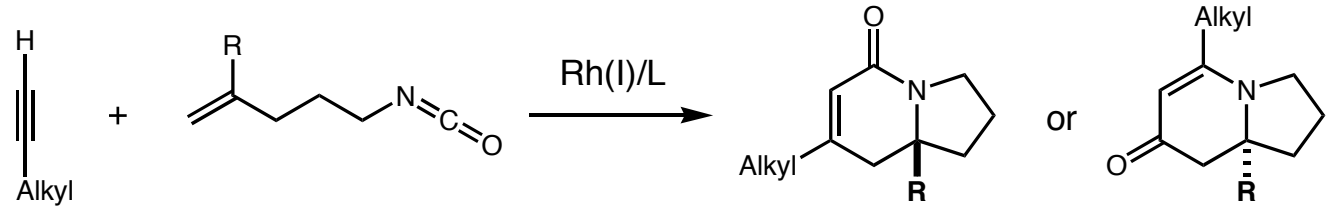



FR901483




(−)-secu'amamine A

# *Revisiting the Mechanism*

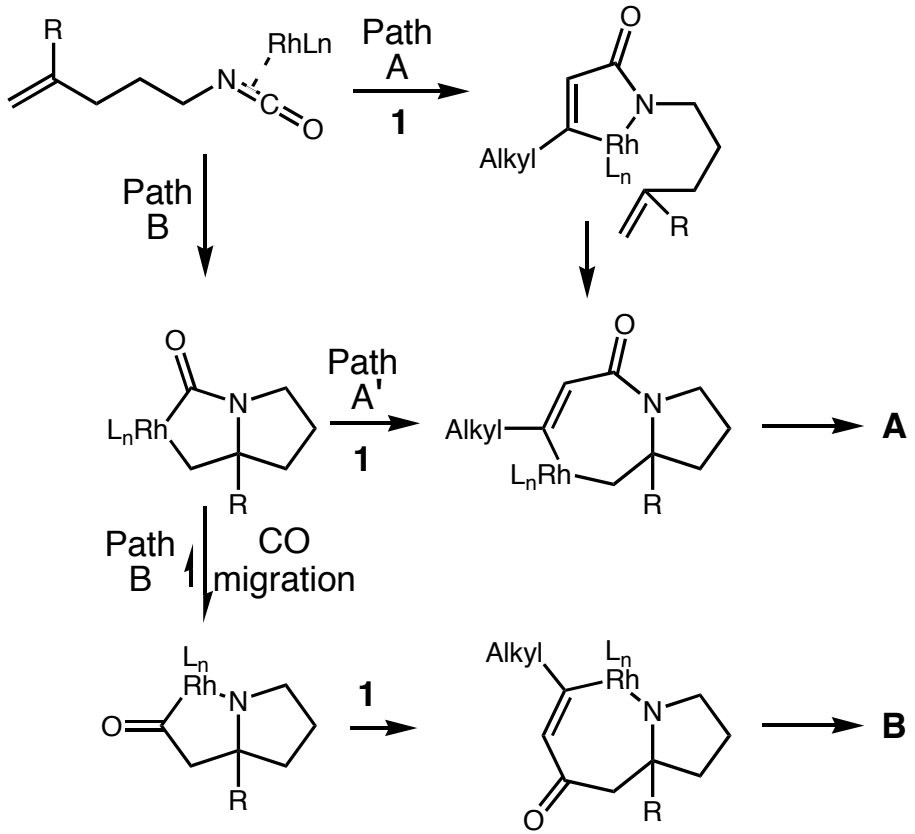



**1** **2**

*Previous Work* (***A***)

*Topic Paper* (***B***)

*Proposed Mechanism*



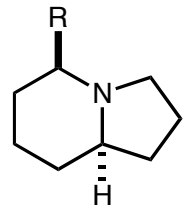

Previously, Path A is favored, presumably due to relatively low steric interactions between the alkyl side chain of the alkyne and the taddol-derived ligand on the Rhodium catalyst. Product **A** is generated.

Previously, when the steric interaction is increased (aryl or branched alkyl acetylenes) Path B becomes more favorable, leading to product **B**.

When the catalyst is modified to the binol-derived phosphoramidites (especially the 3/3' subsituted variants) the increase in steric interactions due to the catalyst overrides the substrate bias, leading to Path B and the formation of product **B**.

Additional substitution on the olefin (R) does not appear to play a part in the mechanistic pathway.

# *Synthesis of Indolizidine Alkaloid (—)-209D*



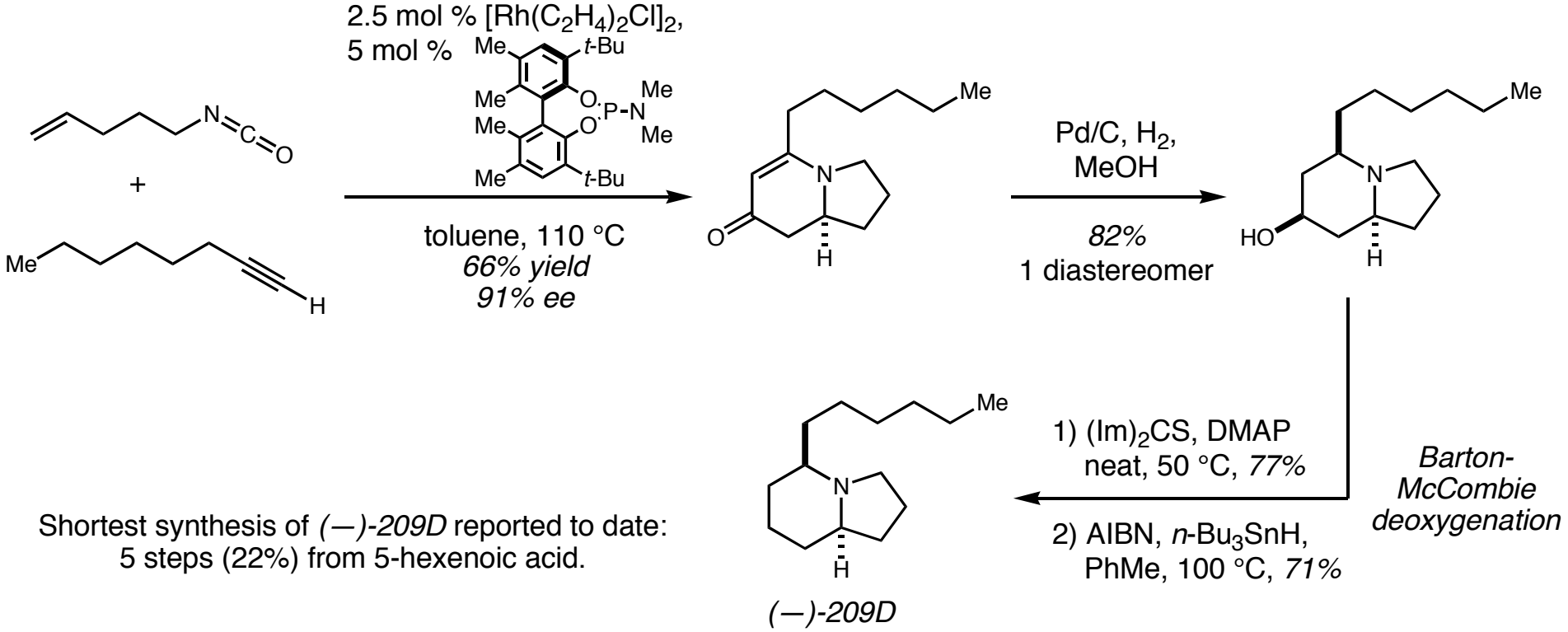
R = *n*-hexyl, (—)-209D
R = *n*-propyl, (—)-167B

Part of a family of 22 natural products referred to as the gephyrotoxins.

Isolated from the skin secretions of neotropical frogs.

These 2 alkaloids have only been isolated in minute quantities.

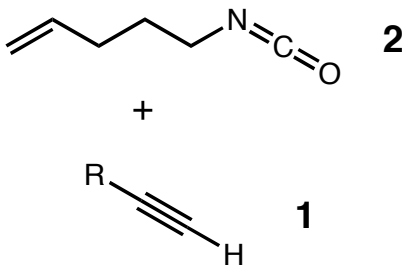
Multiple syntheses (>12) in literature aimed to both prepare in greater quantities and to validate methodologies.




Shortest synthesis of *(—)-209D* reported to date:
5 steps (22%) from 5-hexenoic acid.

*Acetylene Scope*

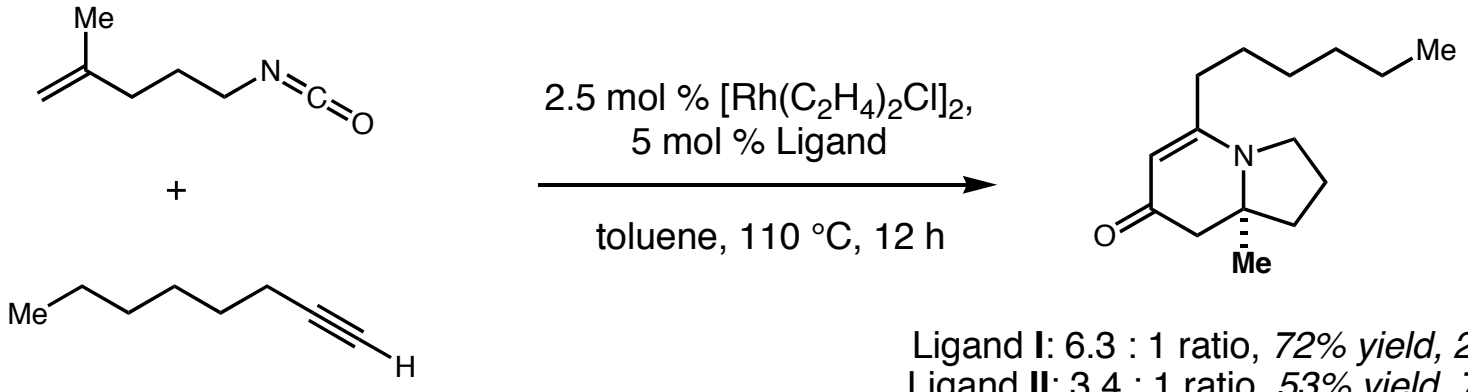
# Synthesis of 5-Alkyl Indolizinones




| Entry | 1 (R) | Major product | 3:4 ratio[b] yield [%][c] and *ee* [%][d] of 3 | Entry | 1 (R) | Major product | 3:4 ratio[b] yield [%][c] and *ee* [%][d] of 3 |
|---|---|---|---|---|---|---|---|
| 1[e] | **1a** (*n*Hex) | **3a** | 6:1<br>66, 91 | 9 | **1i** (-$CH_2$OTIPS) | **3i** | 1.6:1<br>44, 87 |
| 2 | **1b** (-$(CH_2)_4CO_2CH_3$) | **3b** | 5:1<br>66, 90 | 10 | **1j** ($CH_2$Cy) | **3j** | 8:1<br>72, 91 |
| 3 | **1c** (-$(CH_2)_4$Cl) | **3c** | 5:1<br>57, 94 | 11 | **1k** (Cy) | **3k** | 14:1<br>86, 91 |
| 4 | **1d** (-$(CH_2)_4$OTBS) | **3d** | 5:1<br>62, 90 | 12 | **1l** (*c*Pent) | **3l** | 14:1<br>87, 89 |
| 5 | **1e** (-$(CH_2)_3$CON(OMe)(Me)) | **3e** | 5:1<br>54, 90 | 13 | **1m** (MOMO) | **3m** | >20:1<br>60, 81 |
| 6 | **1f** (-$(CH_2)_5$C≡CH) | **3f** | 5:1<br>55, 91 | 14 | **1n** (*t*Bu) | **3n** | 10:1<br>67, 79 |
| 7 | **1g** (-$(CH_2)_2$Ph) | **3g** | 5:1<br>56, 91 | 15[f] | **1n** (*t*Bu) | **3n** | 6:1<br>66, 88 |
| 8 | **1h** (Bn) | **3h** | 3:1<br>52, 90 | | | | |

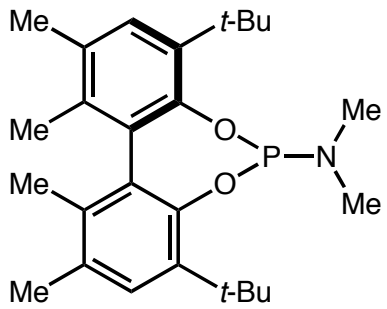
[a]–[d] See Table 1. [e] 1.4 mmol scale (**2**) at 100 °C. [f] guiphos ((*R*)-**L3**) used as the ligand. TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl, Cy = cyclohexyl, MOM = methoxymethyl.

# *Application to Disubstituted Isocyanate*

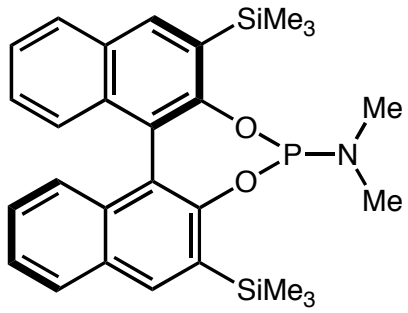



Ligand **I**: 6.3 : 1 ratio, *72% yield, 27% ee*
Ligand **II**: 3.4 : 1 ratio, *53% yield, 72% ee*

*Ligands*




**I**




**II**

# ***Summary***

Utilizing a Rhodium (I) catalyzed process in the presence of chiral ligands the Rovis group has developed a method for the product selective and enantioselective process for the synthesis of Indolizidine alkaloids.

This methodology has been applied to the synthesis of the efficient enantioselective synthesis natural products (+)-lasubine II and alkaloid (—)-209D.

This route can be enivisioned to access other more-complex 5-substituted indolizidine alkaloids, including FR901483, the cylindricines, and derivatives of these compounds.

An improvement on the selective synthesis of corresponding quinolzinones is still necessary.