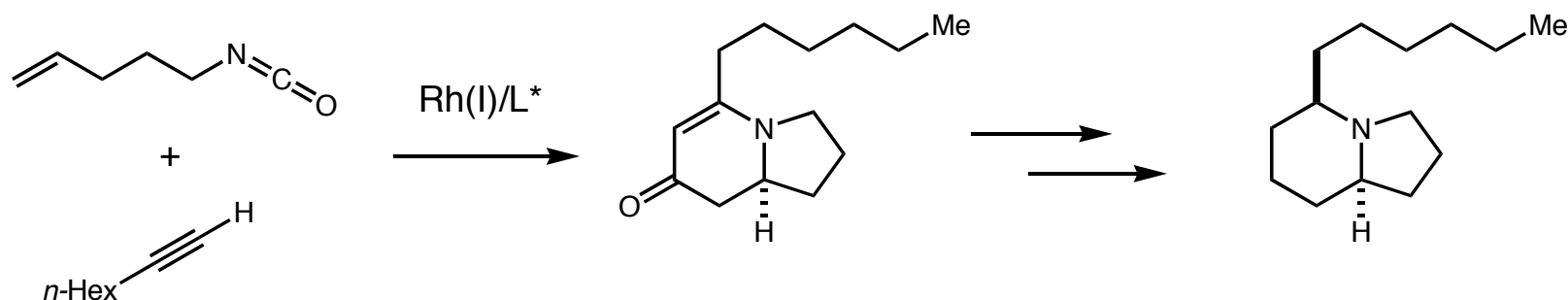


Total Synthesis of Indolizidine Alkaloid (–)-209D: Overriding Substrate Bias in the Asymmetric Rhodium-Catalyzed [2+2+2] Cycloaddition

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

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

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

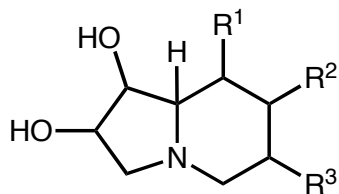


Robert B. Lettan II
April 11, 2009

Wipf Group Saturday Morning Meeting
Current Literature Abstracts & Reports

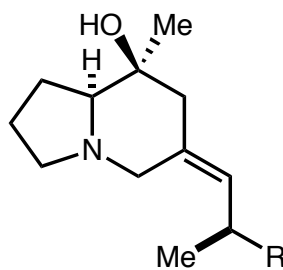
Indolizidine Alkaloids

hydroxylated indolizidines

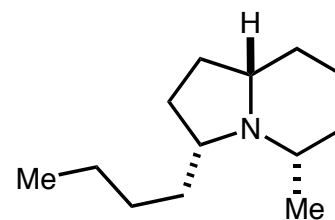


$R^1, R^2, R^3 = H$: lentiginosine
 $R^1 = OH; R^2, R^3 = H$: swainsonine
 $R^1, R^2 = OH; R^3 = H$: castanospermine
 $R^1, R^2, R^3 = OH$: uniflorine

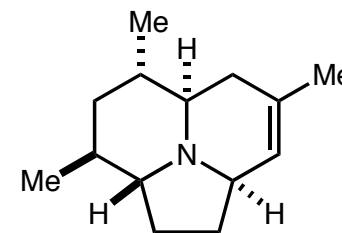
Alkaloids from ants and amphibians



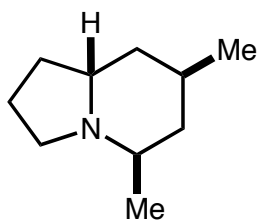
(+)-pumiliotoxin



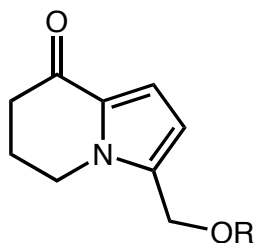
(+)-monomorine



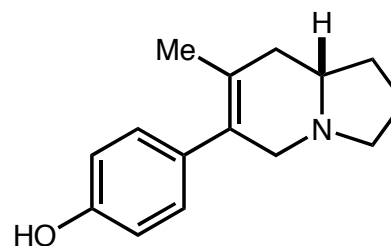
(-)-alkaloid 205B



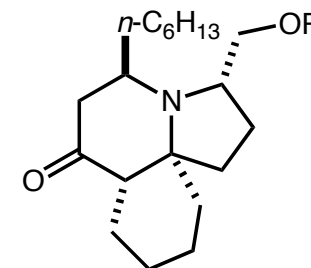
(-)-dendroprimine



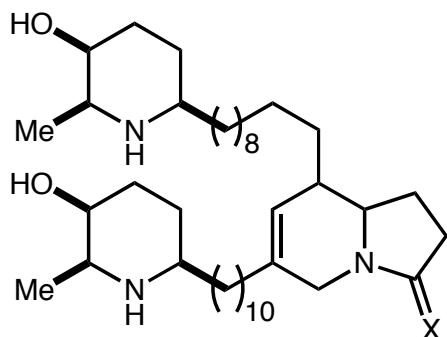
polygonatum alkaloids



(+)-ipalbidine

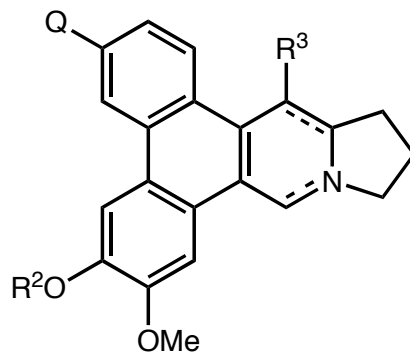


(+)-cylindricines

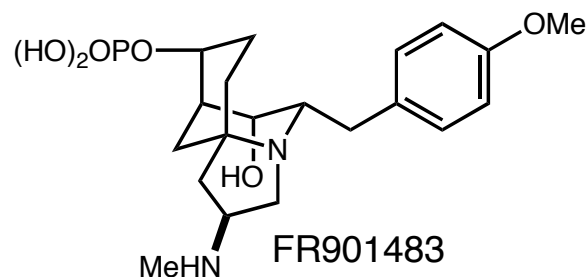


prosopis alkaloids

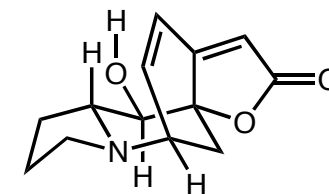
$X = O, H_2$



tylophoridicines



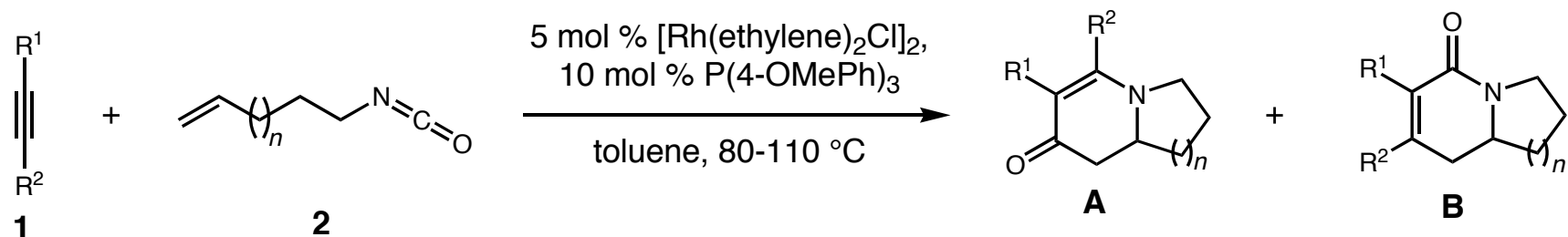
FR901483



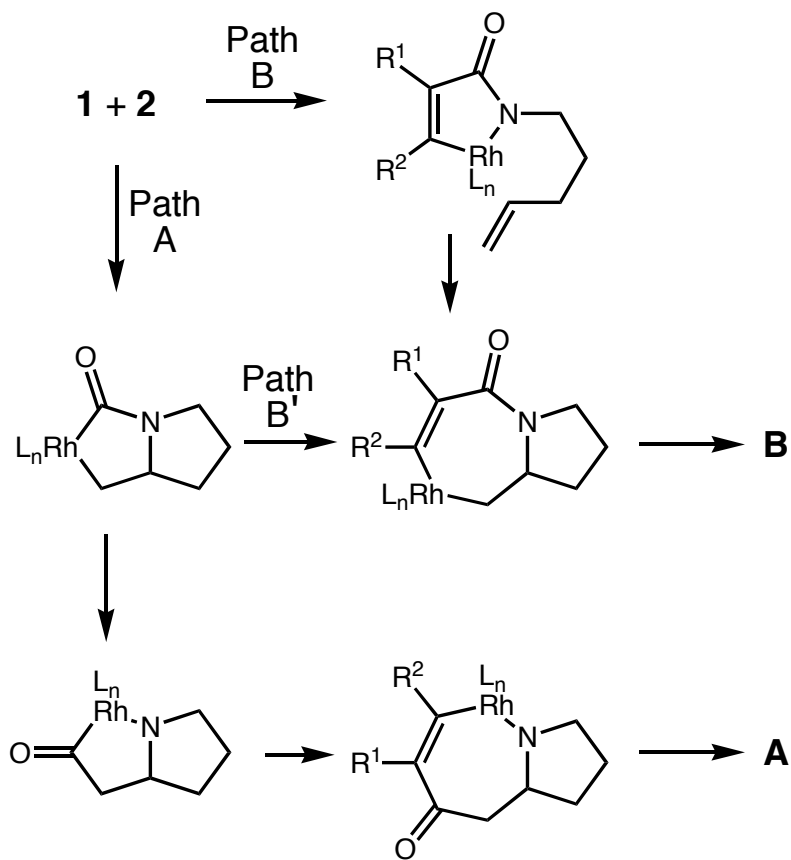
(-)-secu'amamine A

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

Rovis' Initial Approach towards Indolizidines



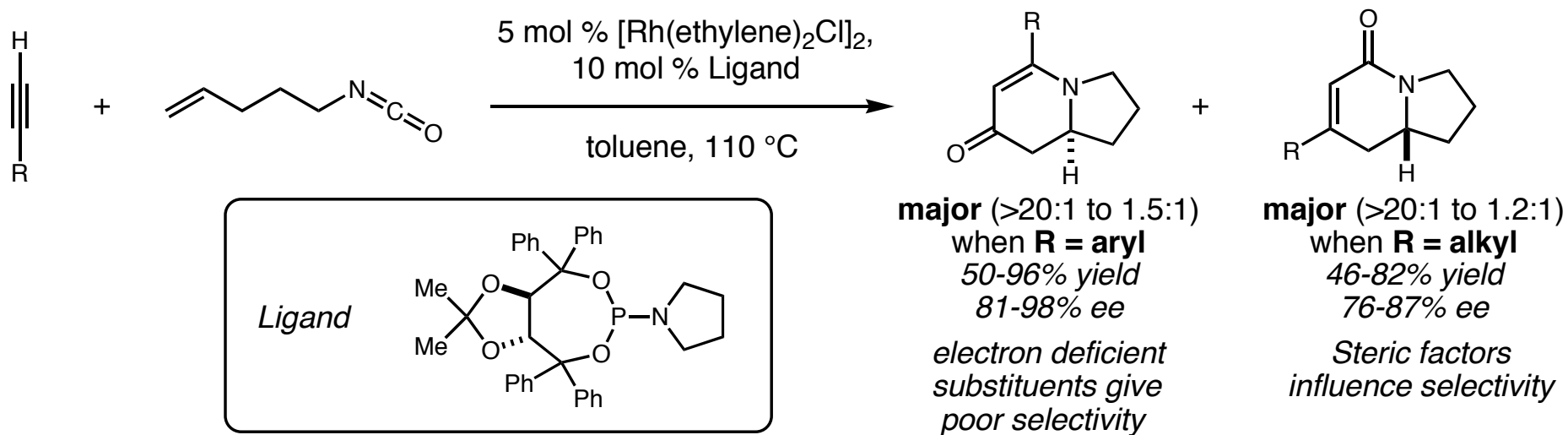
Proposed Mechanism



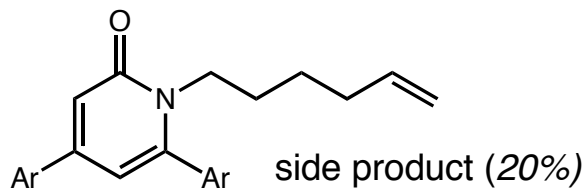
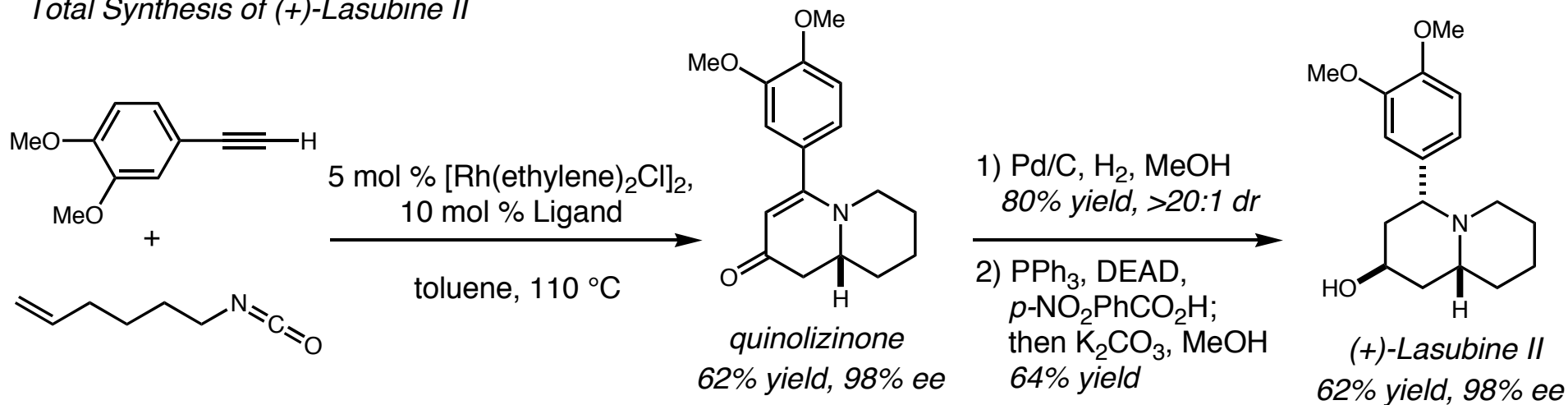
R ¹ /R ²	n	Yield (%)	Selectivity (A:B)
substituted phenyl	1	60-72	>20:1
1-cyclohexene	1	75	>20:1
1-cyclopentene	1	50	>20:1
3-furyl	1	66	1.1 : 1
2-thiophene	1	72	1.3 : 1
<i>n</i> -propyl	1	60	>1:20
<i>n</i> -butyl	1	70	1:6
(CH ₂) ₂ OTBS	1	56	>1:20
<i>n</i> -butyl	2	62	1:3.5
(CH ₂) ₂ OTBS	2	56	>20:1
R 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



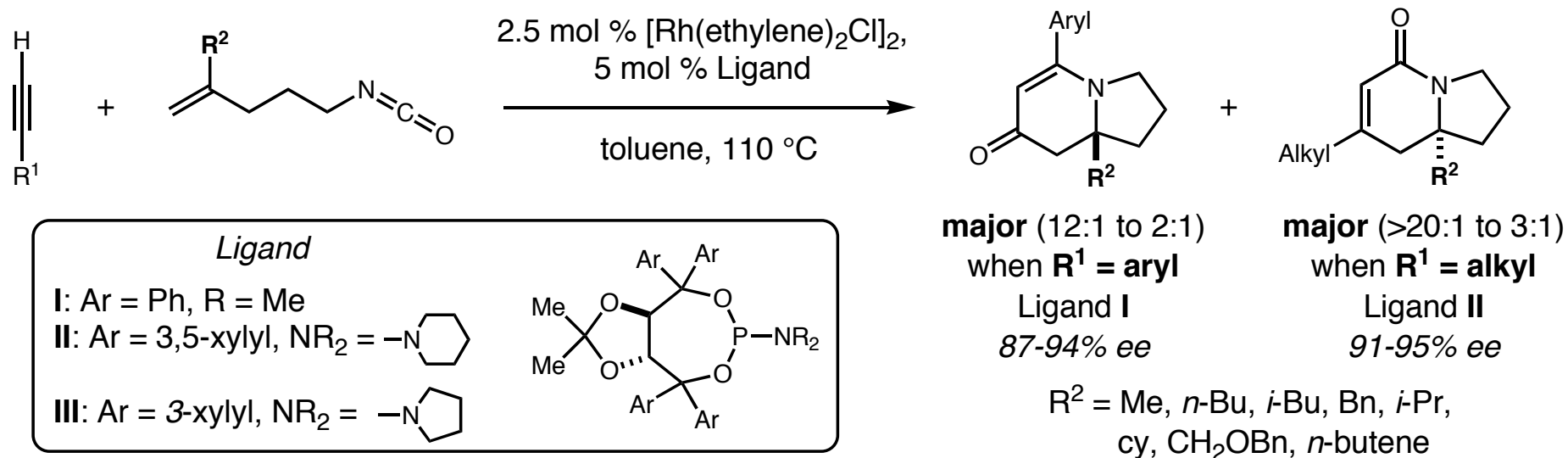
Total Synthesis of (+)-Lasubine II



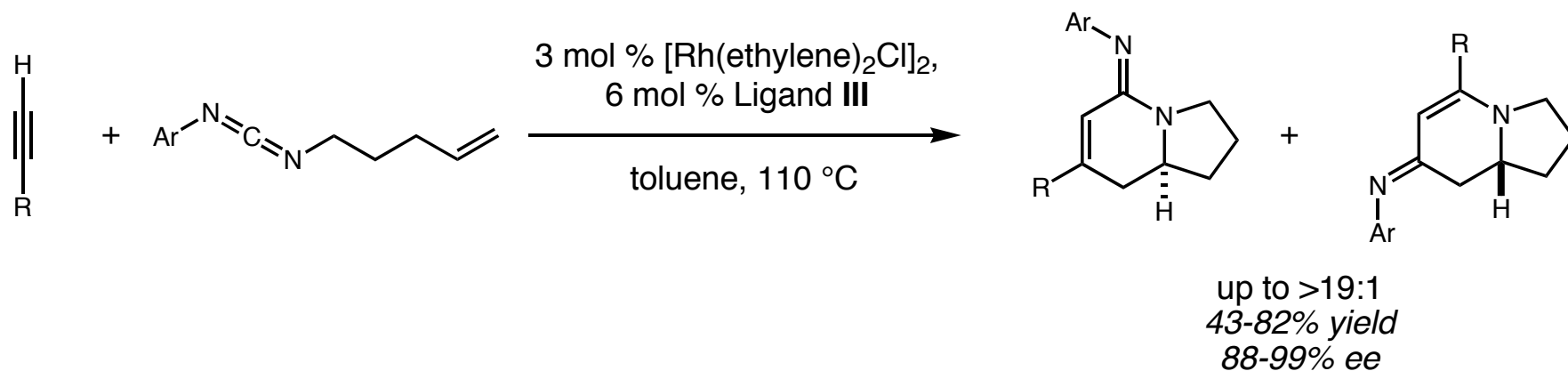
Yu, R. T.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 12370.

Additional Applications

Formation of Quaternary Stereocenters

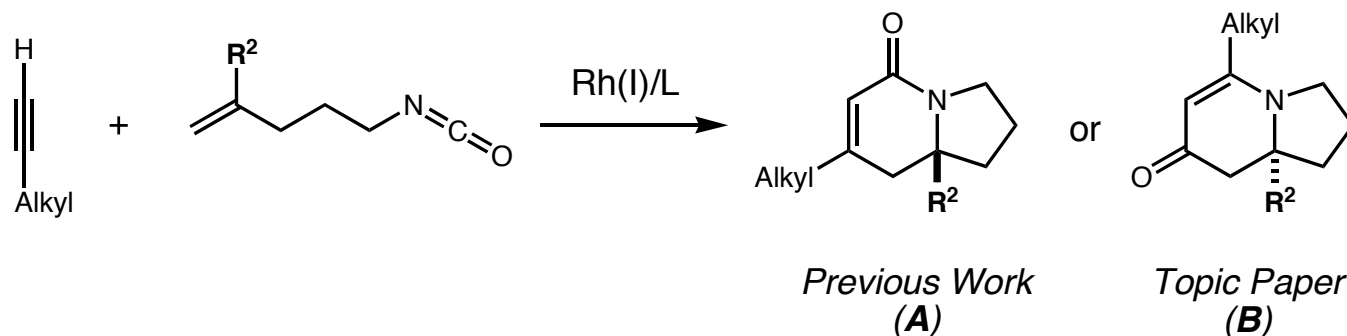


Synthesis of Bicyclic Amidines



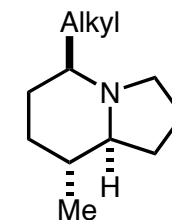
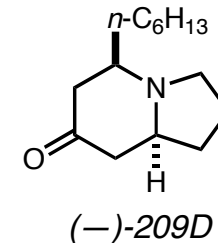
Lee, E. E.; Rovis, T. *Org. Lett.* **2008**, *10*, 1231.
 Yu, R. T.; Rovis, T. *J. Am. Chem. Soc.* **2008**, *130*, 3262.

Overriding Substrate Bias

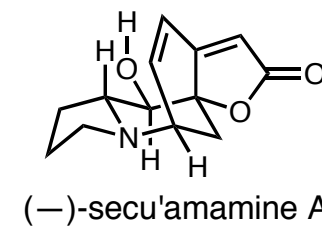
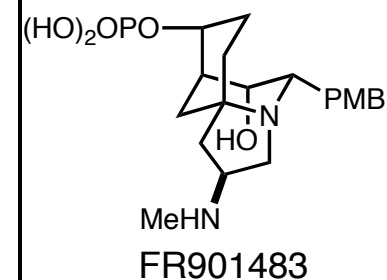
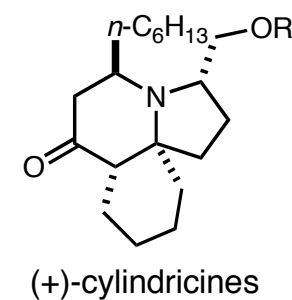


Ligand Screening (alkyl = *n*-Hex; R² = H)

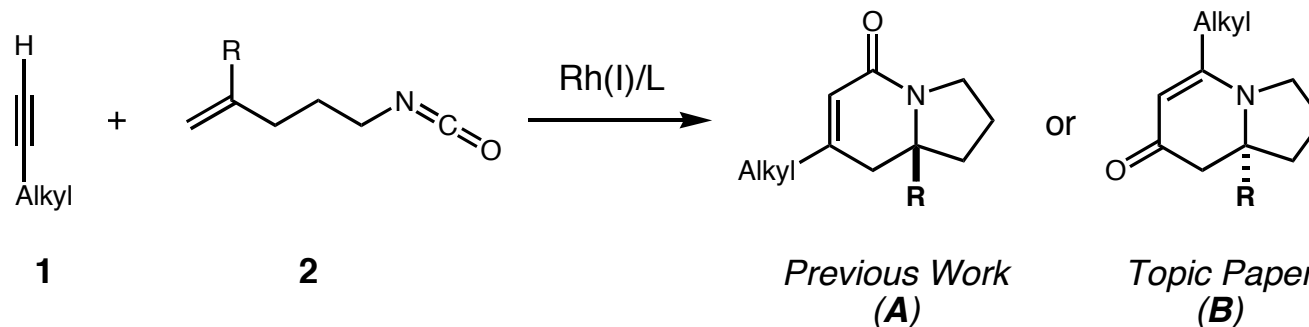
Ligand	A:B	Yield of B (%)	ee of B (%)
	3.2 : 1	20	73
	1 : 2.2	22	72
	1 : 3.8	60	96
	R = SiMe ₃ 1 : 3.5	50	94
	R = <i>t</i> -Bu 1 : 6.2	75	91



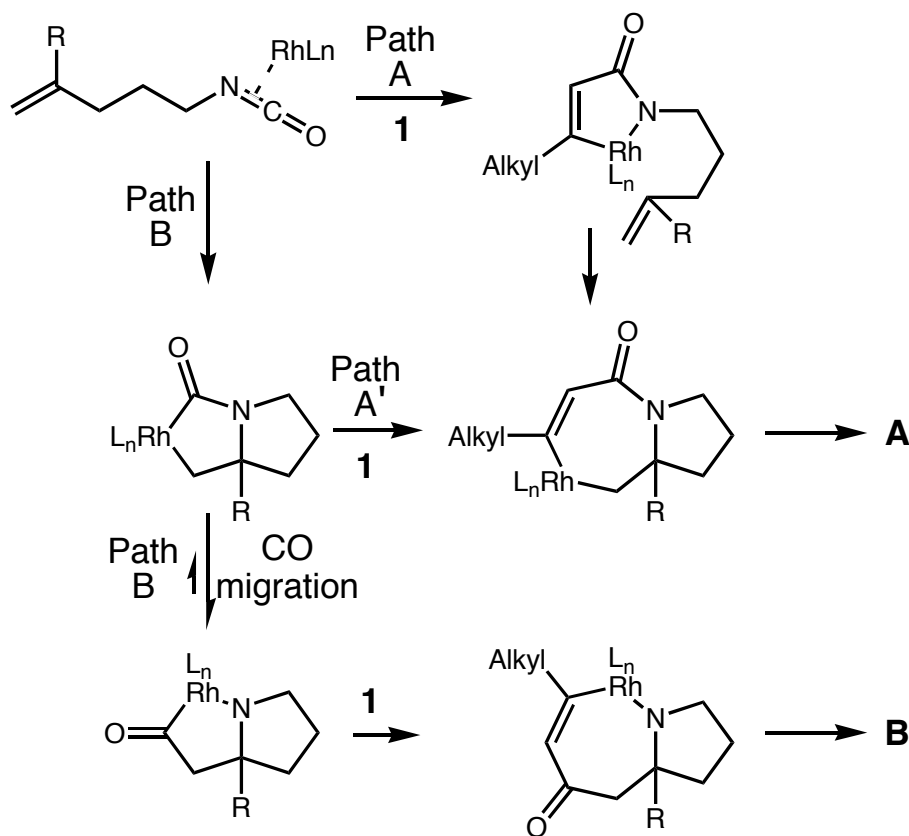
dialkylated indolizidines



Revisiting the Mechanism



Proposed Mechanism



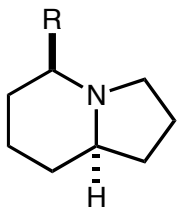
Previously, Path A is favored, presumably due to relatively low steric interactions between the alkyl side chain of the alkyne and the taddol-derived ligand on the Rhodium catalyst. Product **A** is generated.

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' substituted 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



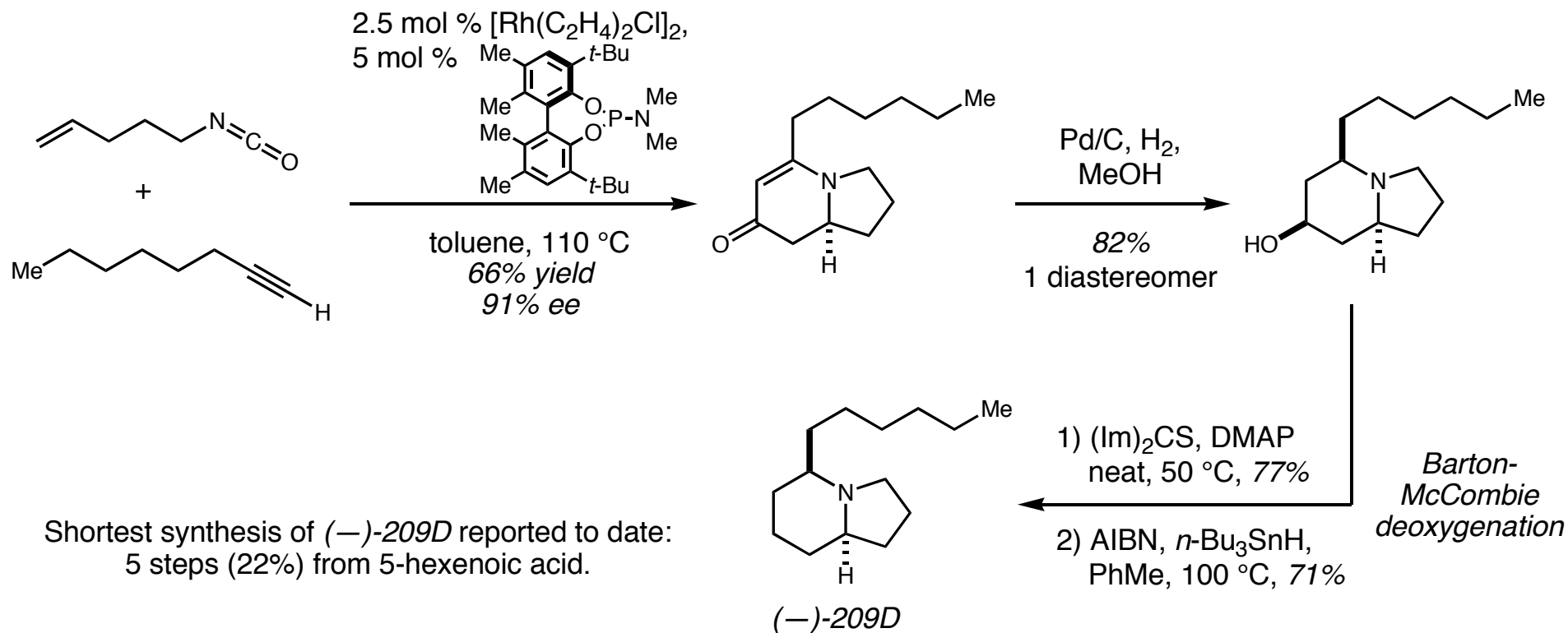
R = *n*-hexyl, (–)-209D
R = *n*-propyl, (–)-167B

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

Isolated from the skin secretions of neotropical frogs.

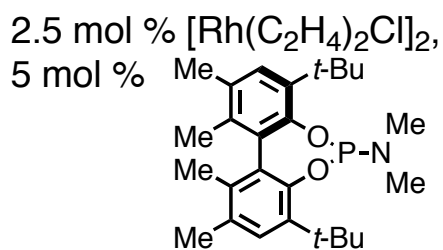
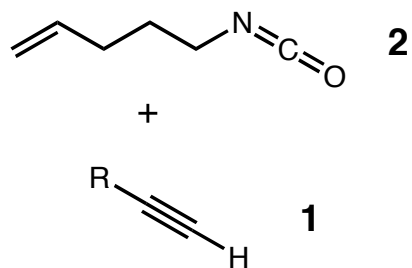
These 2 alkaloids have only been isolated in minute quantities.

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

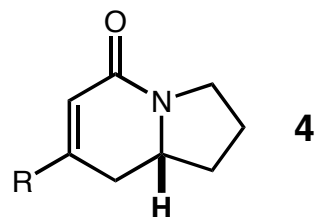
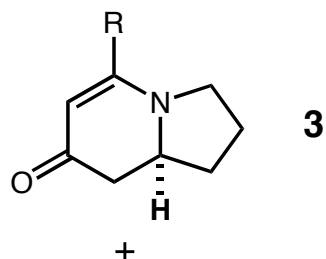


Synthesis of 5-Alkyl Indolizinones

Acetylene Scope



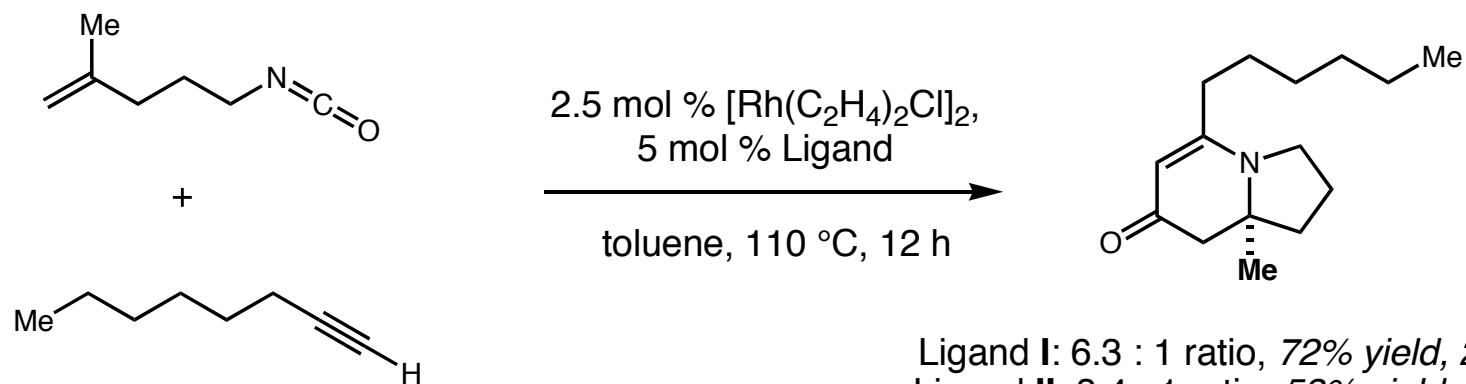
toluene, 110 °C



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]	1 a (<i>n</i> Hex)		6:1 66, 91	9	1 i (-CH ₂ OTIPS)		1.6:1 44, 87
2	1 b (-(-CH ₂) ₄ CO ₂ CH ₃)		5:1 66, 90	10	1 j (CH ₂ Cy)		8:1 72, 91
3	1 c (-(-CH ₂) ₄ Cl)		5:1 57, 94	11	1 k (Cy)		14:1 86, 91
4	1 d (-(-CH ₂) ₄ OTBS)		5:1 62, 90	12	1 l (<i>c</i> Pent)		14:1 87, 89
5	1 e (-(-CH ₂) ₃ CON(OCH ₃)(CH ₃))		5:1 54, 90	13	1 m ()		> 20:1 60, 81
6	1 f (-(-CH ₂) ₅ C≡CH)		5:1 55, 91	14	1 n (<i>t</i> Bu)		10:1 67, 79
7	1 g (-(-CH ₂) ₂ Ph)		5:1 56, 91	15 ^[f]	1 n (<i>t</i> Bu)		6:1 66, 88
8	1 h (Bn)		3:1 52, 90				

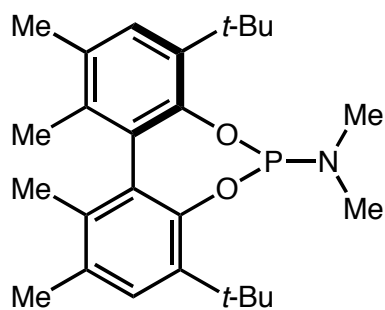
[a]–[d] See Table 1. [e] 1.4 mmol scale (**2**) at 100 °C. [f] guiphos ((*R*)-**L3**) used as the ligand. TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl, Cy = cyclohexyl, MOM = methoxymethyl.

Application to Disubstituted Isocyanate

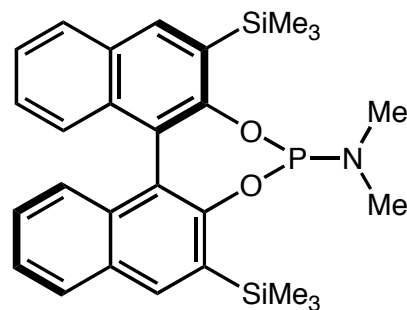


Ligand I: 6.3 : 1 ratio, 72% yield, 27% ee
Ligand II: 3.4 : 1 ratio, 53% yield, 72% ee

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 envisioned 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.