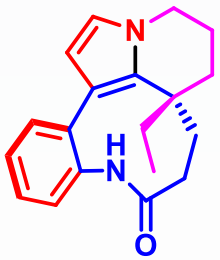
C-H Activation Rules -
Total Synthesis of Rhazinilam

Advisors: Prof. Yang
Prof. Li
Speaker: Tao Xu
Sep. 14th 2010

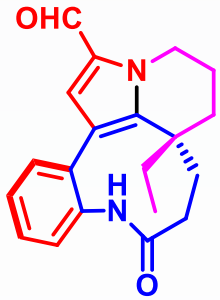
Contents

Introduction

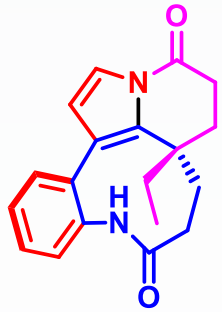
Kopsia singapurensis flowers



(-)-Rhazinilam (1)

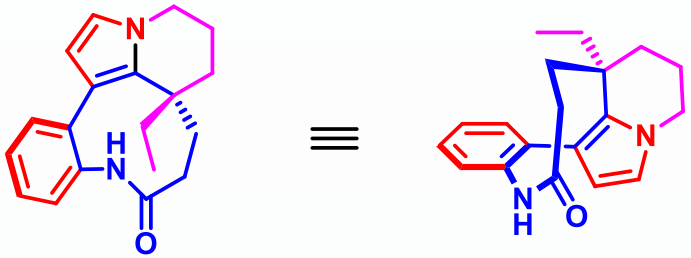


(-)-Rhazinal (2)



(-)-Rhazinicine (3)

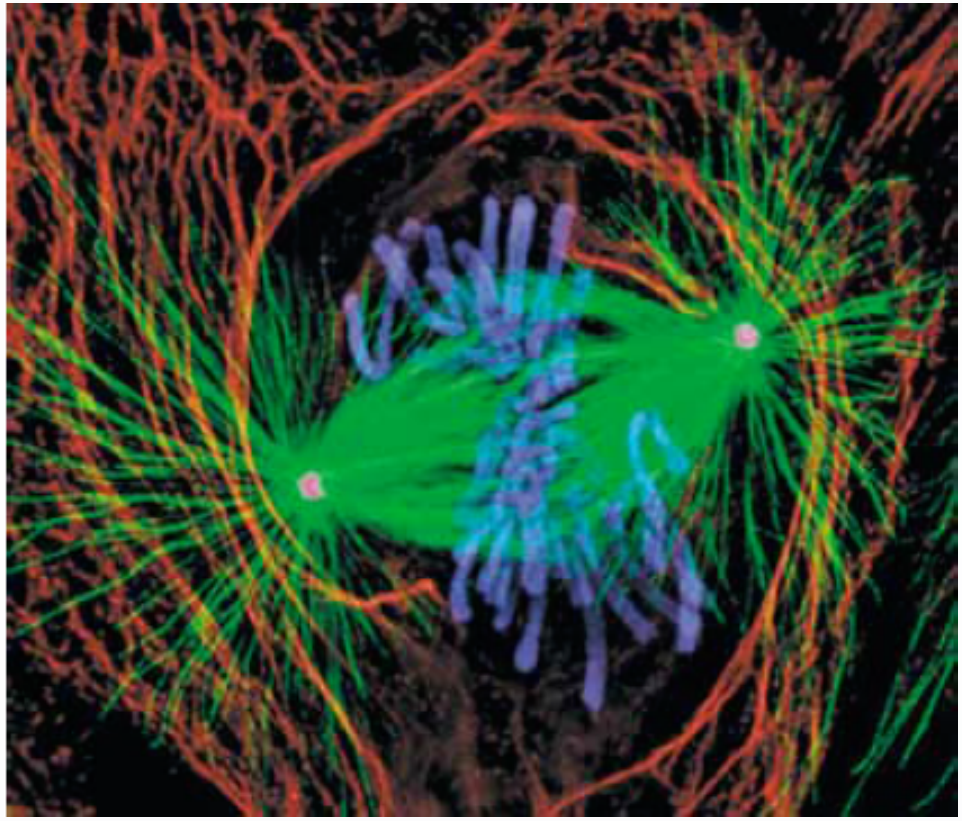
Kopsia singapurensis fruits



(-)-Rhazinilam (1)

(1) Banerji, A.; Majumder, P. L.; Chatterjee, A. G. Phytochemistry 1970, 9, 1491
(2) Kam, T. S.; Tee, Y. M.; Subramaniam, G. Nat. Prod. Lett. 1998, 12, 307
(3) Gerasimenko, I.; Sheludko, Y.; Stlckigt, J.; J. Nat. Prod. 2001, 64, 114

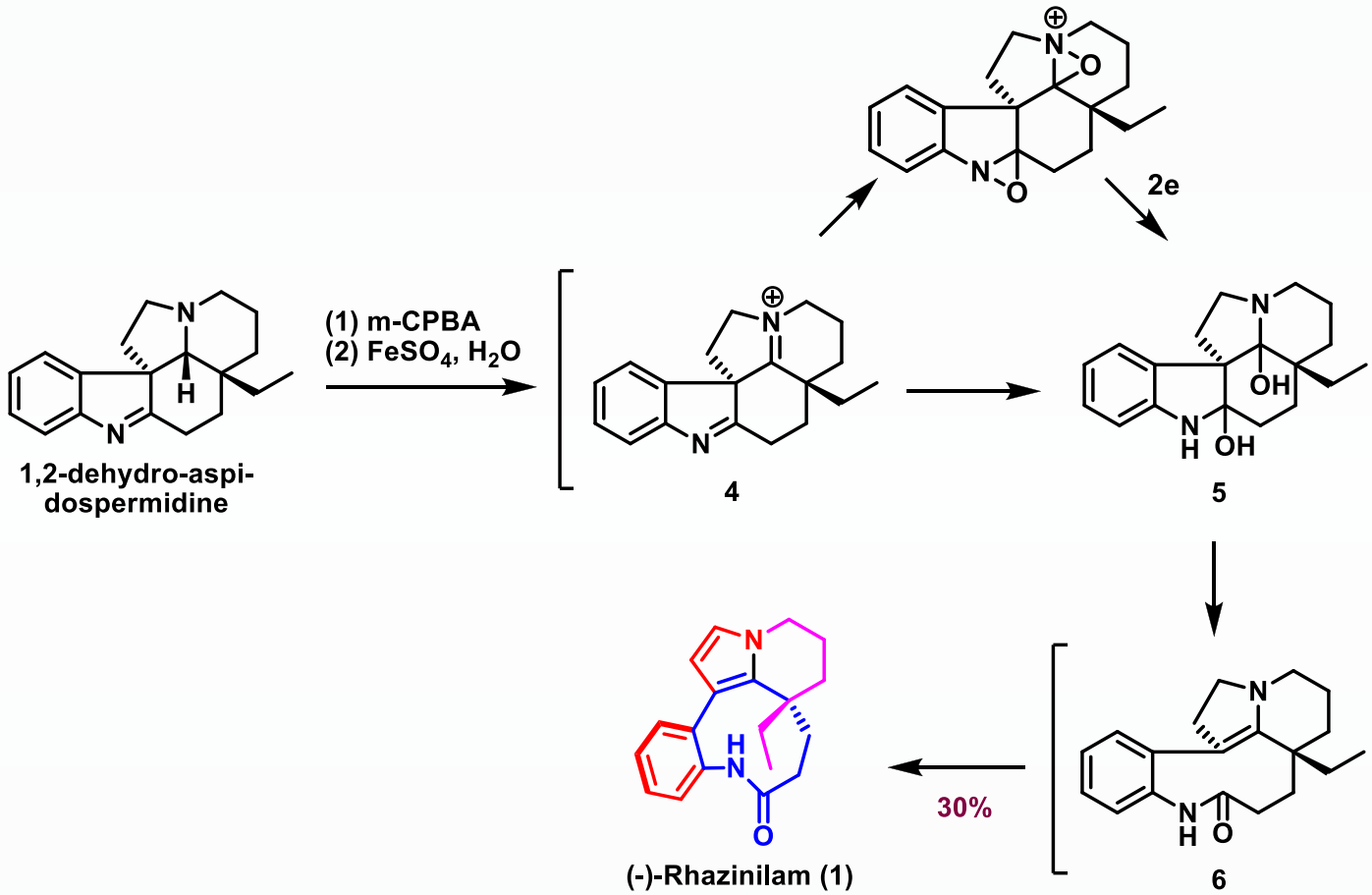
Biological Activity



Fluorescence microscopy image of the spindle apparatus of a cell during the process of mitosis in the metaphase. The microtubules are marked green and the chromosomes are colored blue.

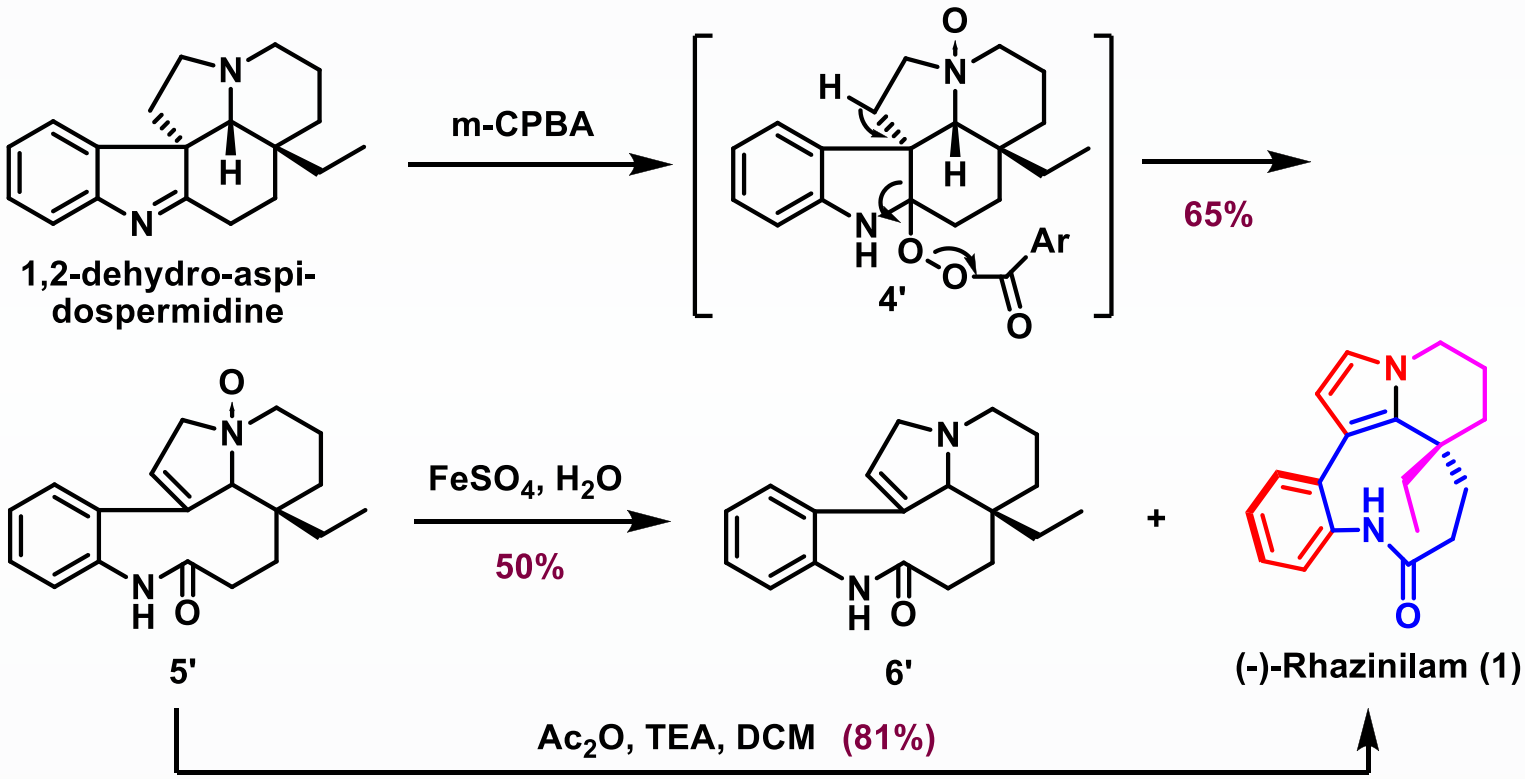
The cochicine binding α β–tubulin dimers if added to the terminus of a microtuble the latter won't proliferate any more. So the mitosis suspended.

Biomimetic Synthesis



Ratcliffe, A. H.; Smith, G. F.; Smith, G. N. *Tetrahedron Lett. 1973,14, 5179–5184.*

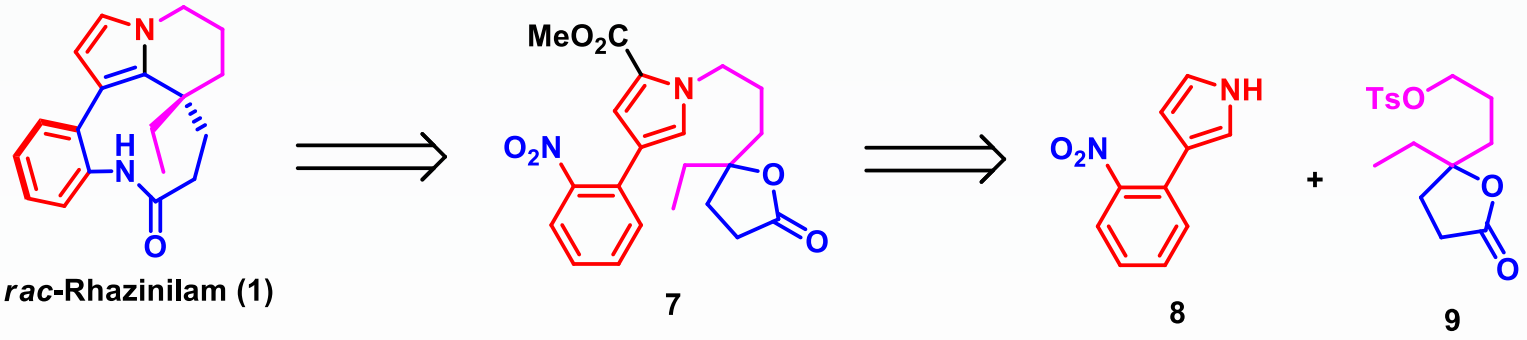
Biomimetic Synthesis

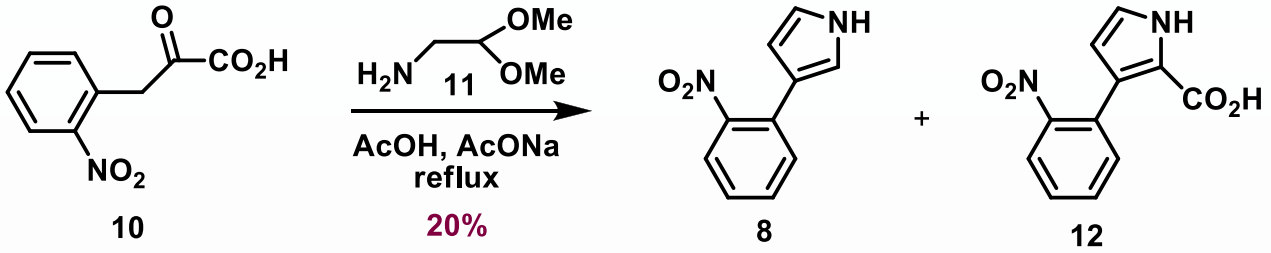


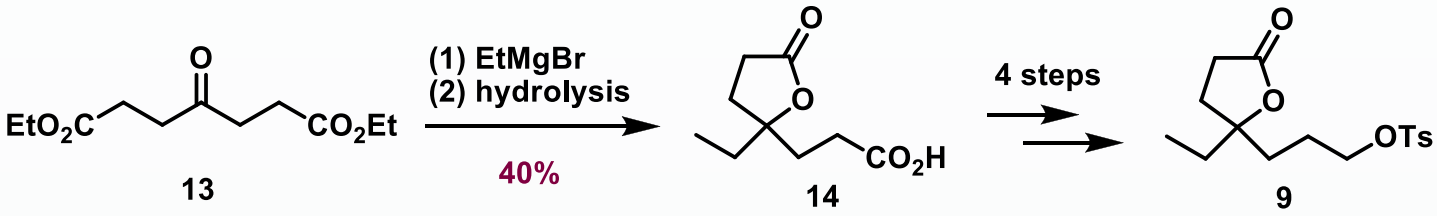
David, B.; Sevenet, T.; Thoison, O.; Awang, K.; Pais, M.; Wright, M.; Guenard, D. *Bioorg. Med. Chem. Lett. 1997, 7, 2155.*

Contents

First total synthesis of rac-rhazinilam







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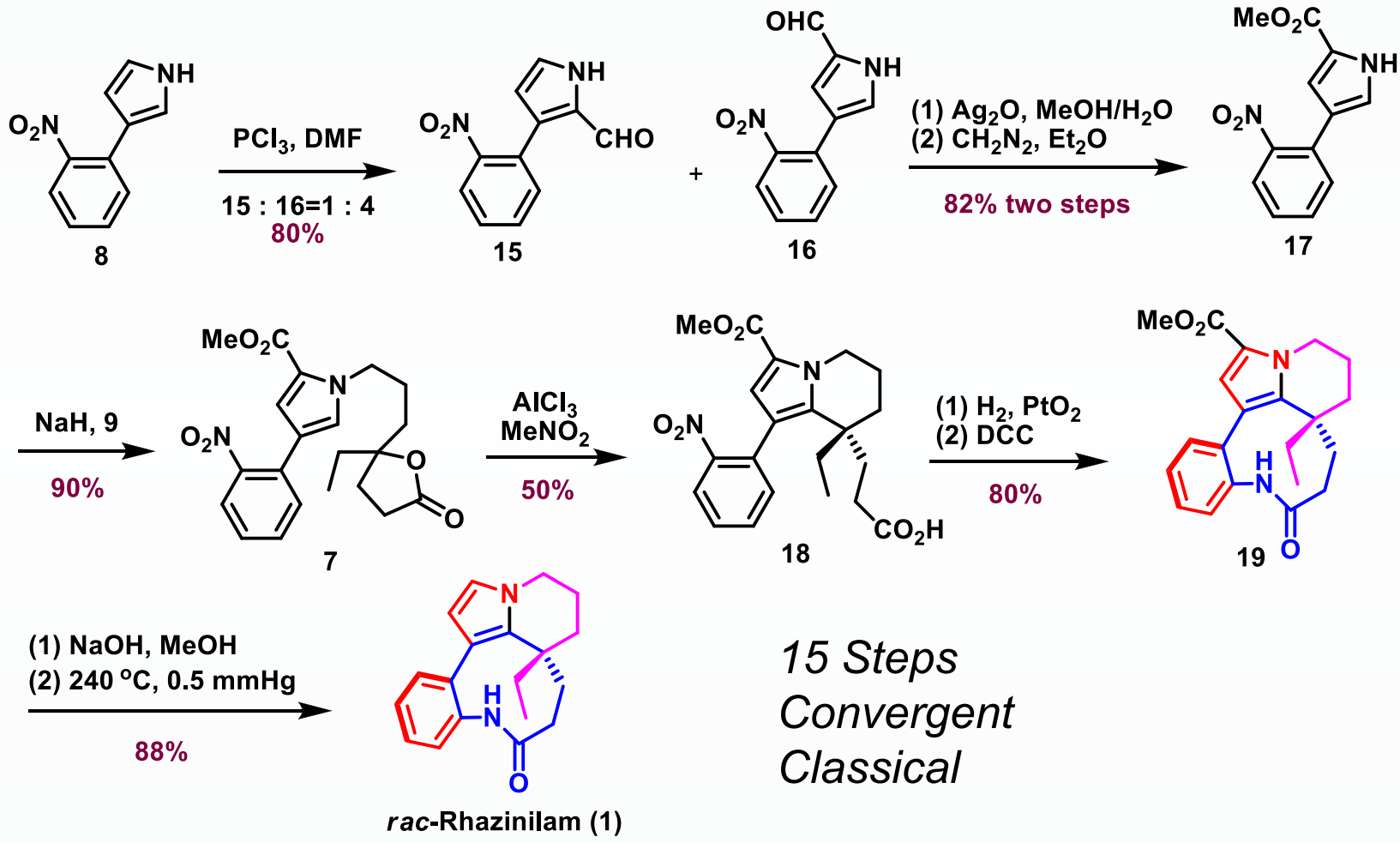
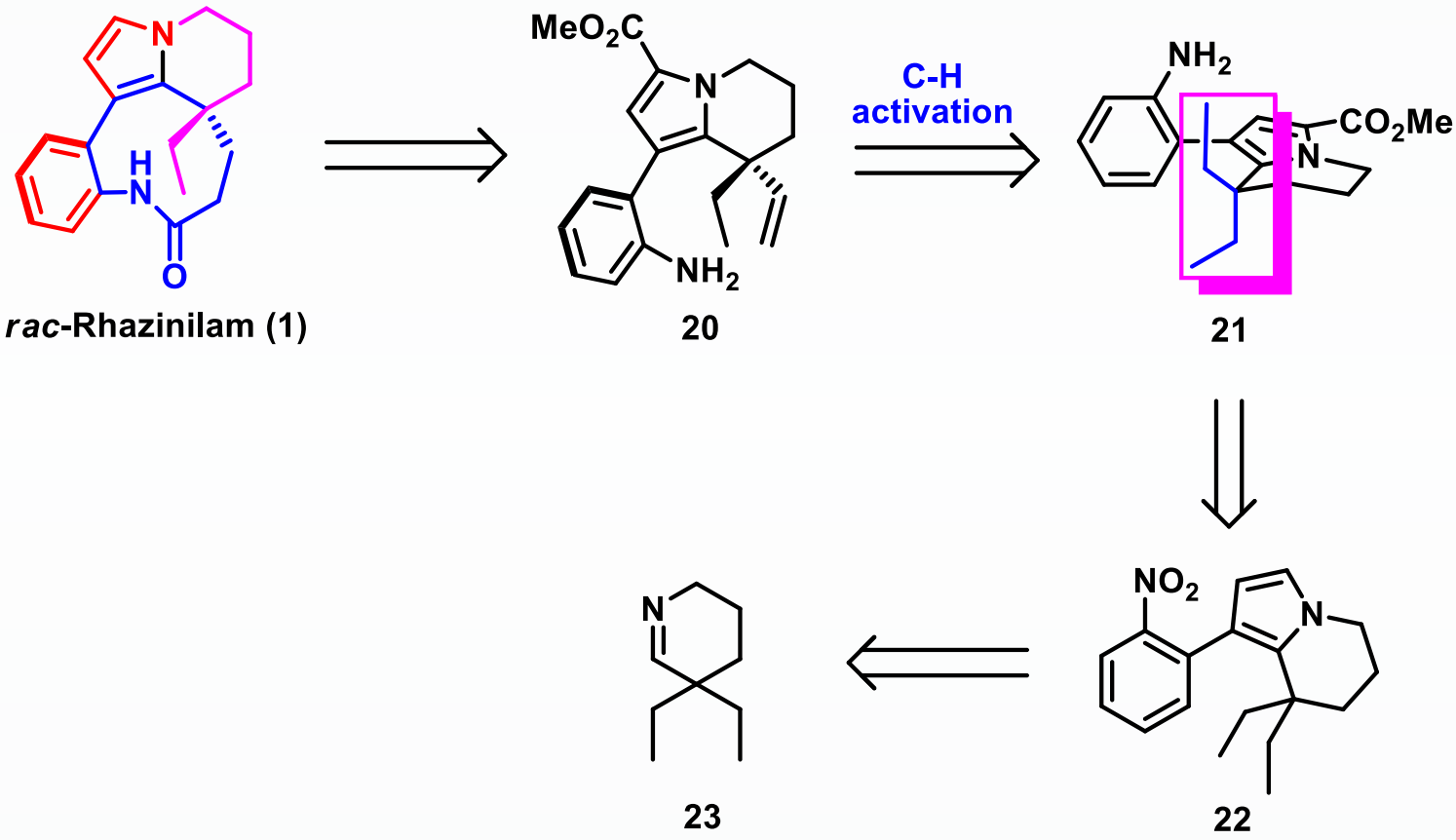
First total synthesis of rac-rhazinilam



15 Steps
Convergent
Classical

Ratcliffe, A. H.; Smith, G. F.; Smith, G. N. *Tetrahedron Lett. 1973,14, 5179–5184.*

Alkane C-H Functionalization



rac-Rhazinilam (1)

20

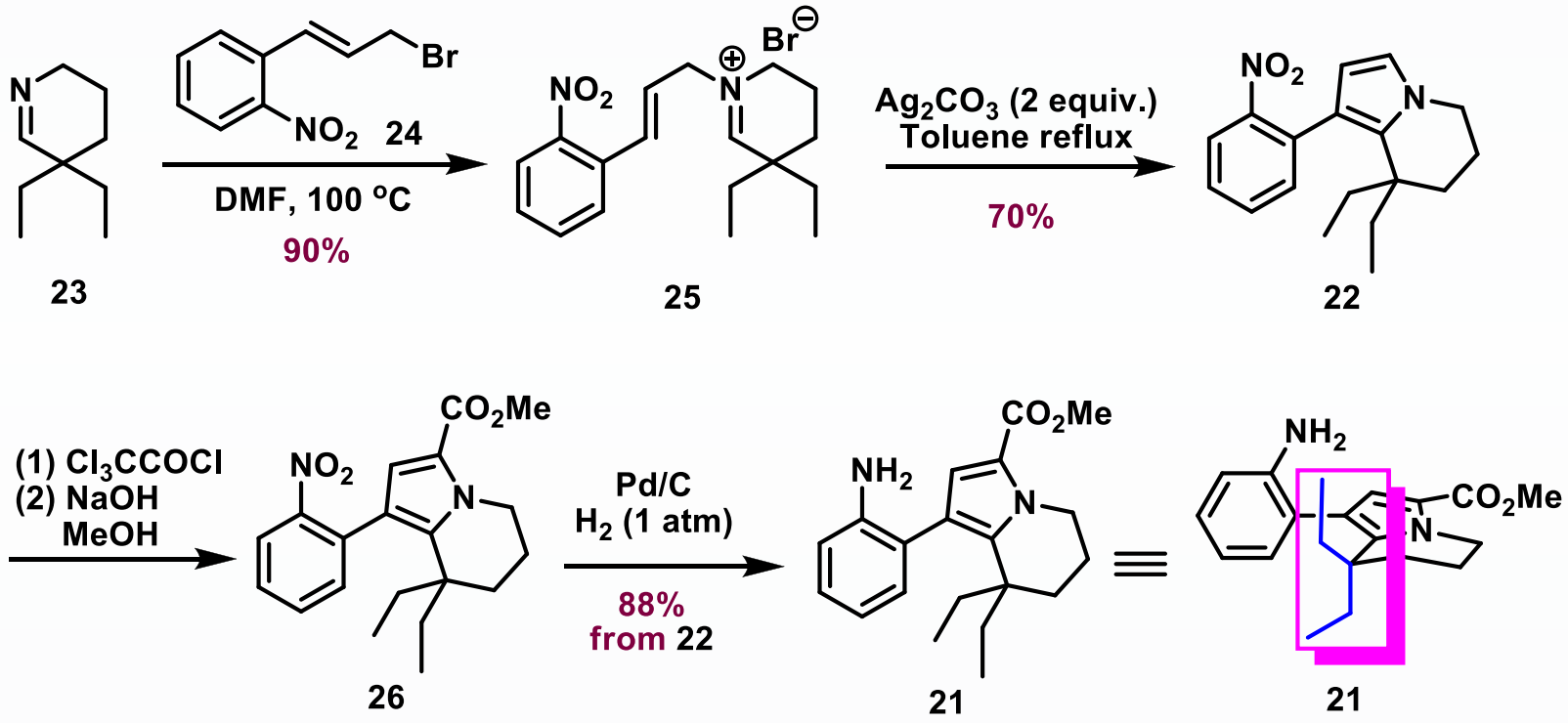
21

22

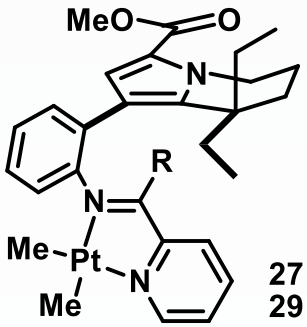
23

Johnson, J. A.; Sames, D. *J. Am. Chem. Soc. 2000, 122, 6321*–6322.

Synthesis of Precursor 21



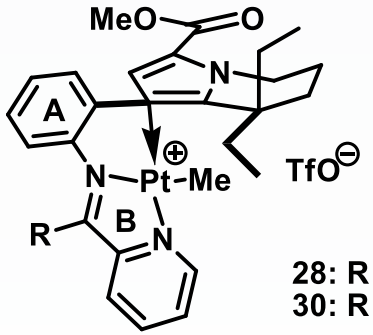
C-H functionalisation Using Pt(II)



27: R = H
29: R = Ph

TfOH, DCM

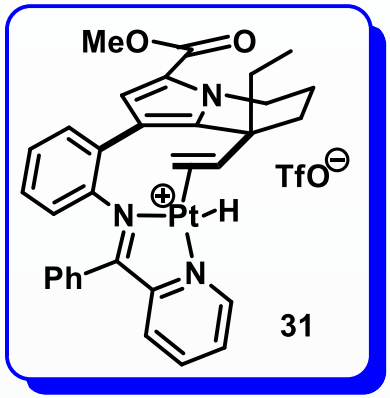
loss CH_4



28: R = H
30: R = Ph

R = H
CF_3CH_2OH
70 °C, 60 h

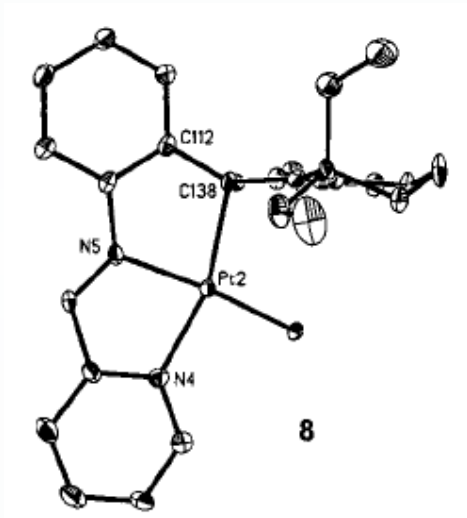
90%



31

R = H
CF_3CH_2OH
70 °C

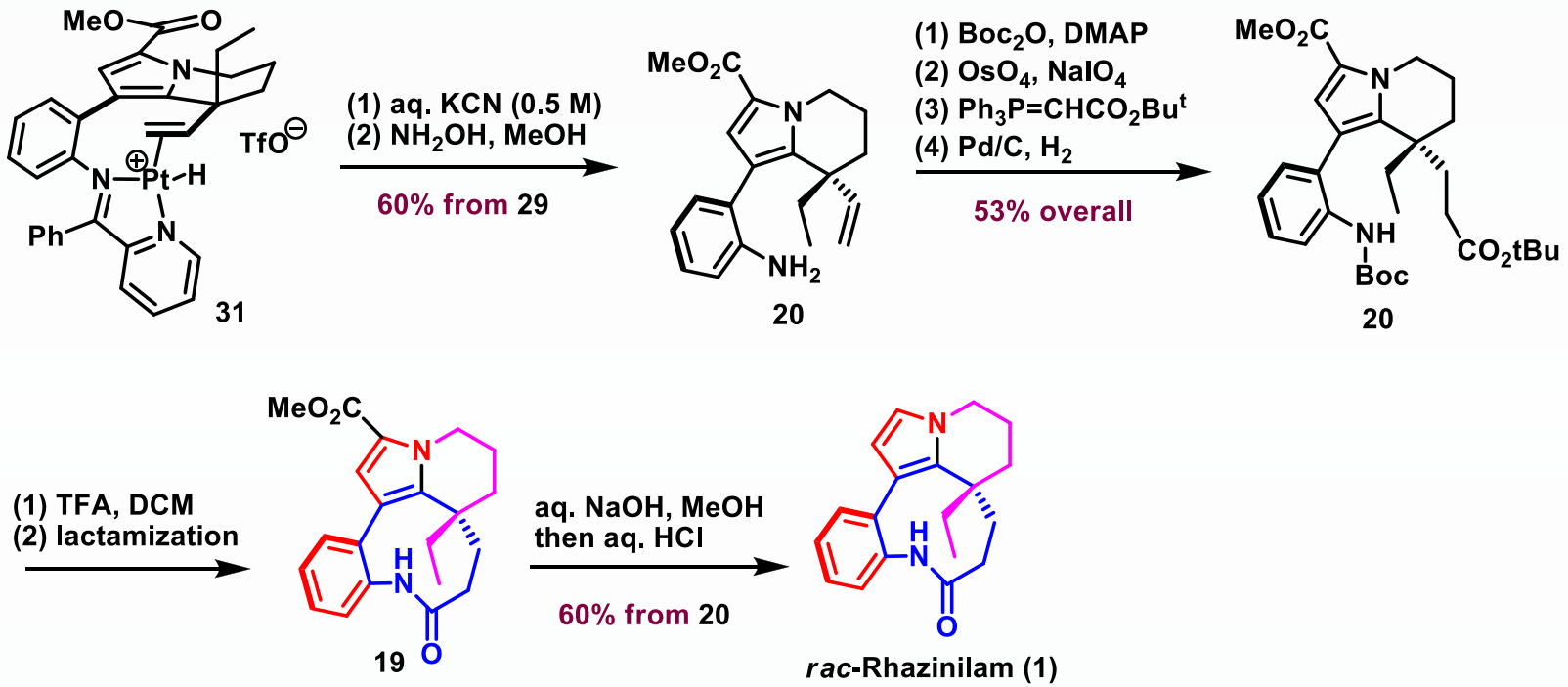
Decomposition



8

Johnson, J. A.; Sames, D. *J. Am. Chem. Soc. 2000, 122, 6321*–6322.
Johnson, J. A.; Li, N.; Sames, D. *J. Am. Chem. Soc. 2002, 124,* 6900–6903.

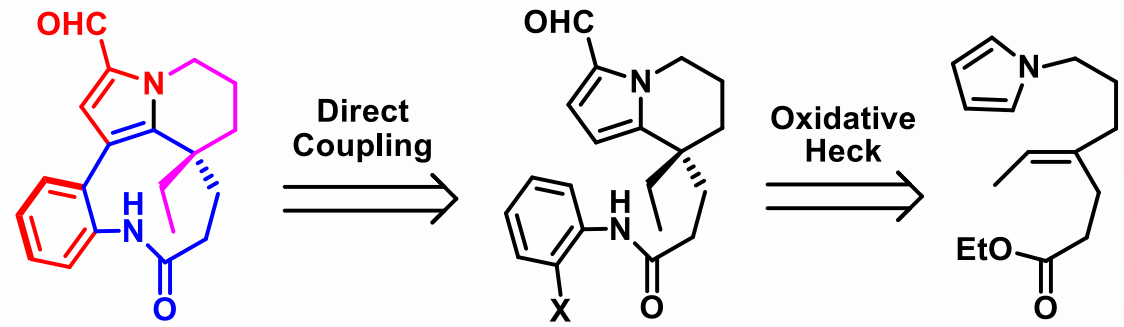
Total Synthesis Completion



Summary:

1) Selective alkane C-H bond was activated, tolerating functional groups and heterocycles.
2) C-H bond activation strategy was educatively implemented in this total synthesis work.
3) Enantioselective C-H activation was discribed in 2002 JACS article from this group.

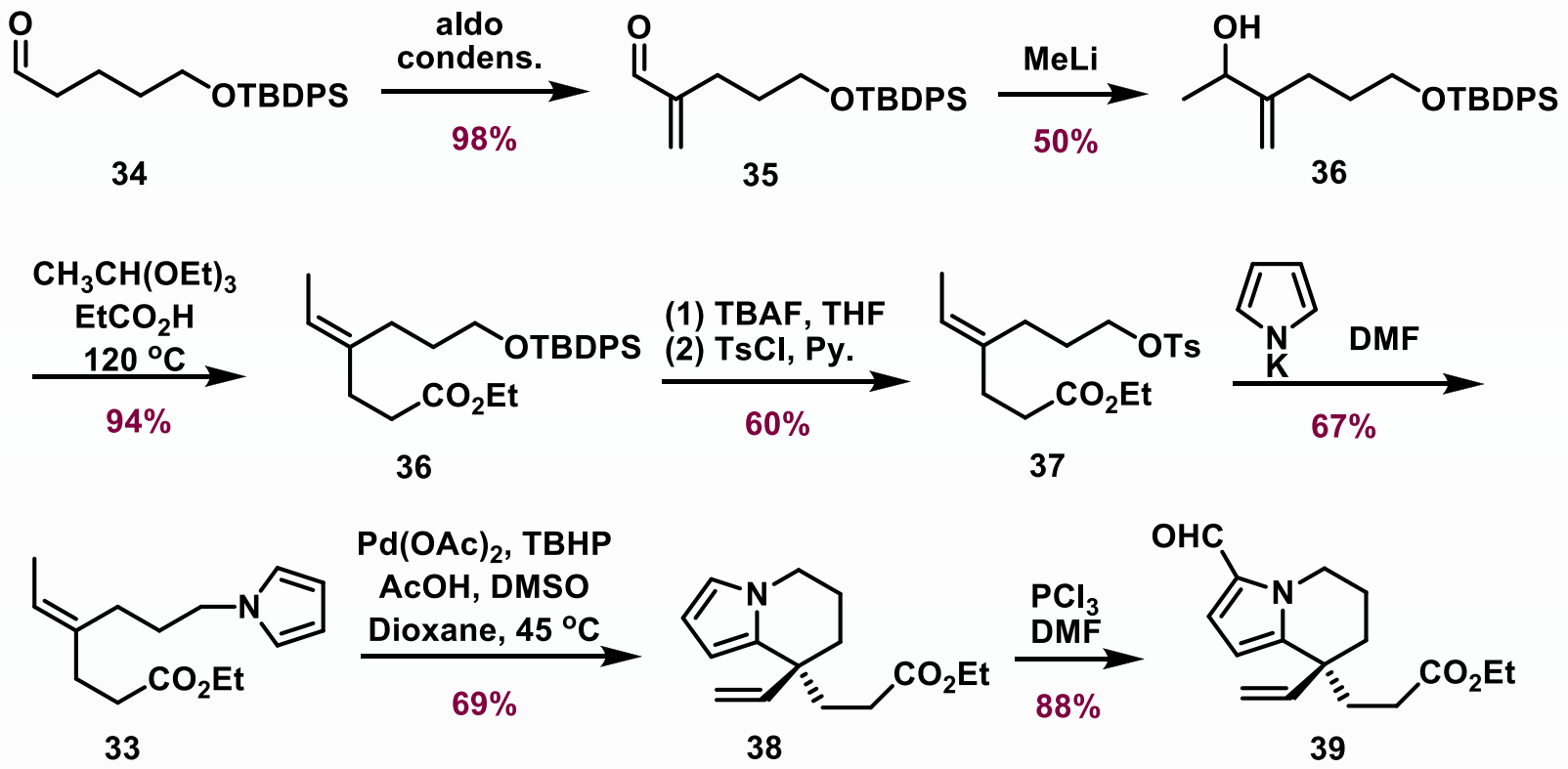
C-H Activation + Heck Coupling



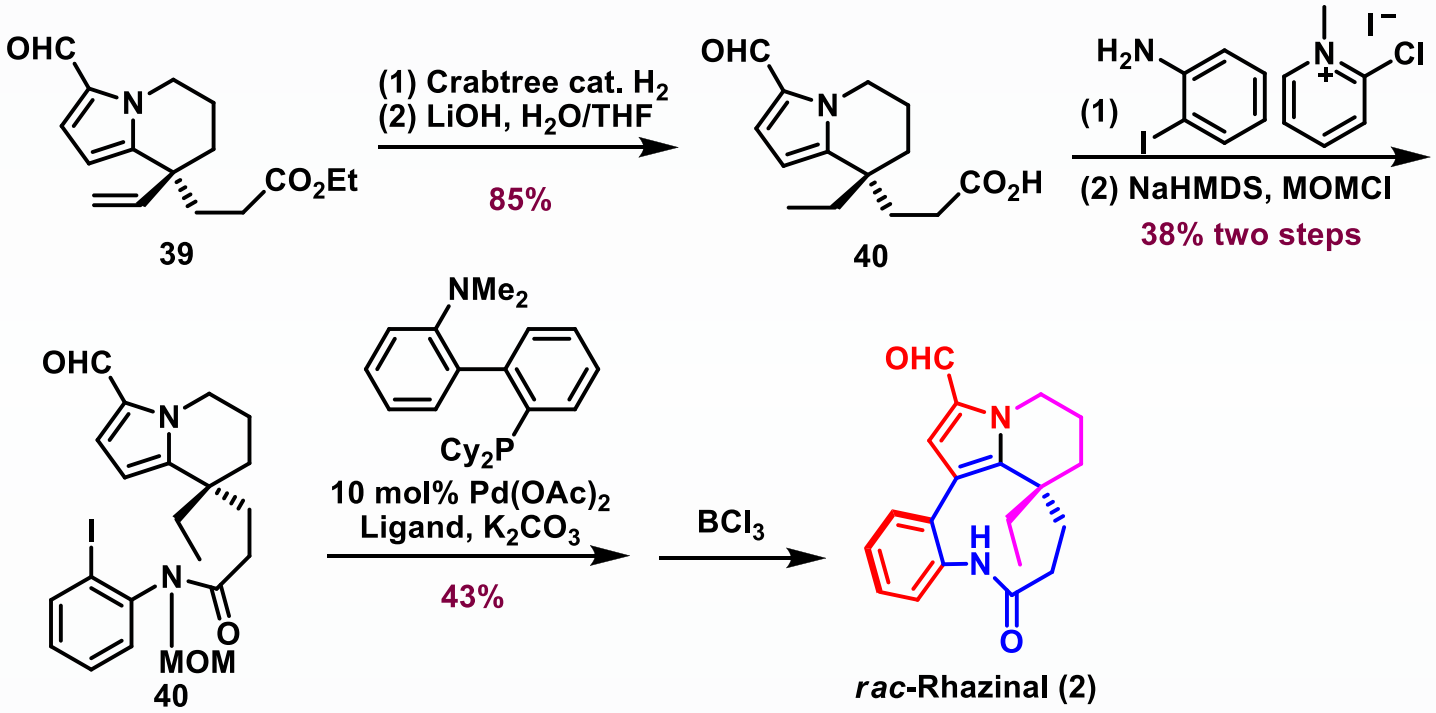
rac-Rhazinal (2) 32 33

Bowie, A. L.; Hughes, C. C.; Trauner, D. *Org. Lett. 2005, 7,* 5207–5209.
Bowie, A. L.; Trauner, D. *J. Org. Chem. 2009, 74, 1581*–1586.

Oxidative Heck Reaction



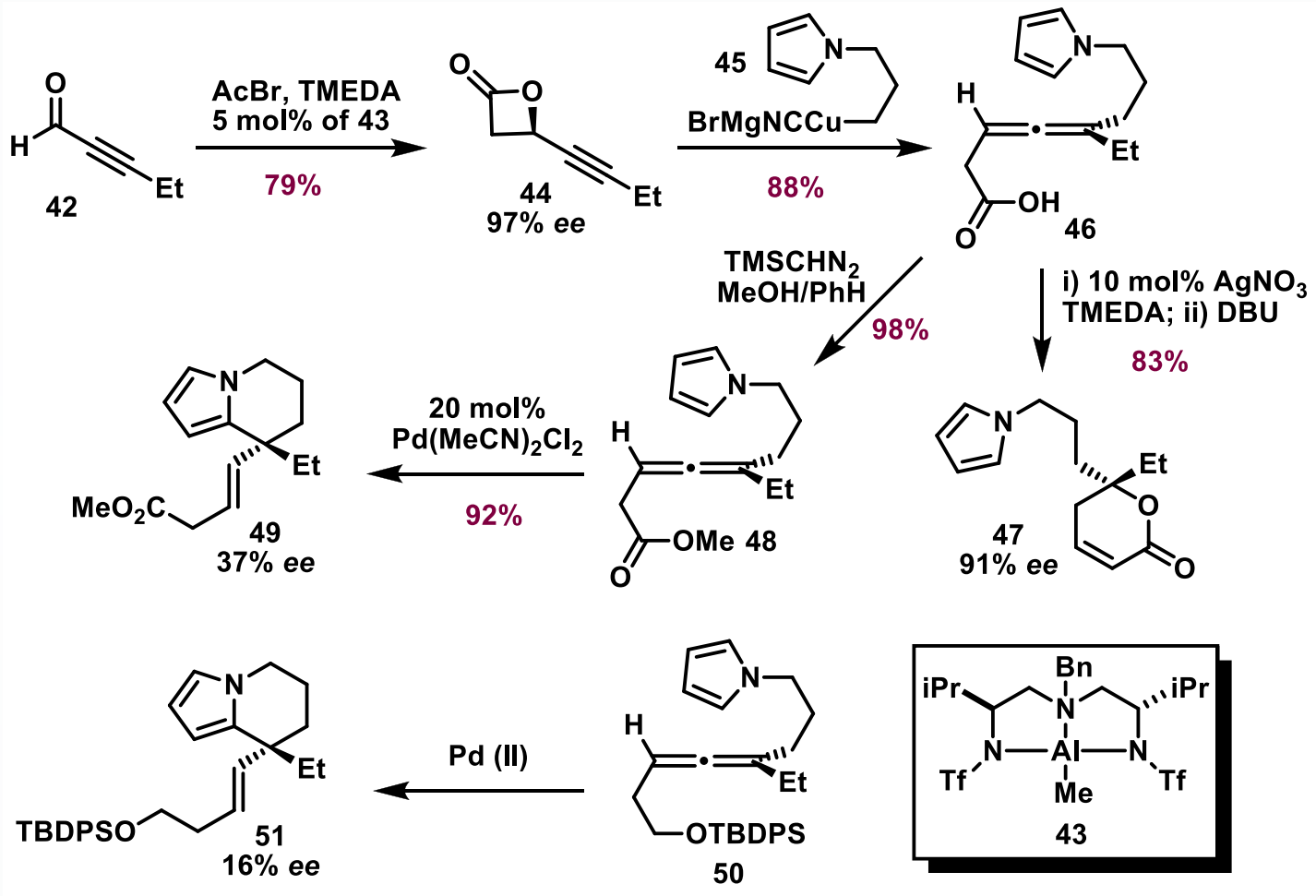
Direct Coupling



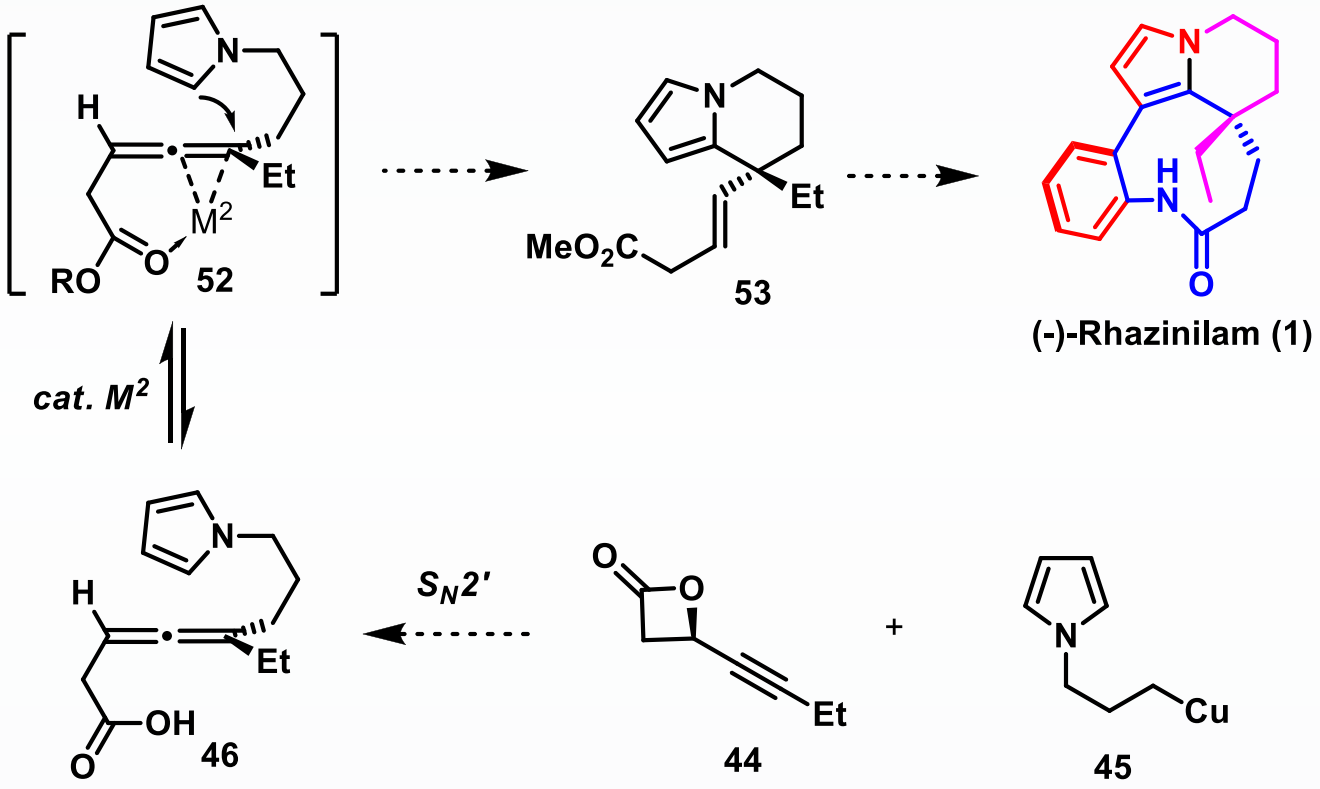
Summary:

(1) Pyrrole was selectively functionalized
(2) Iterative use of Heck reaction
(3) Total synthesis of rhazinal

Au Plays a Role

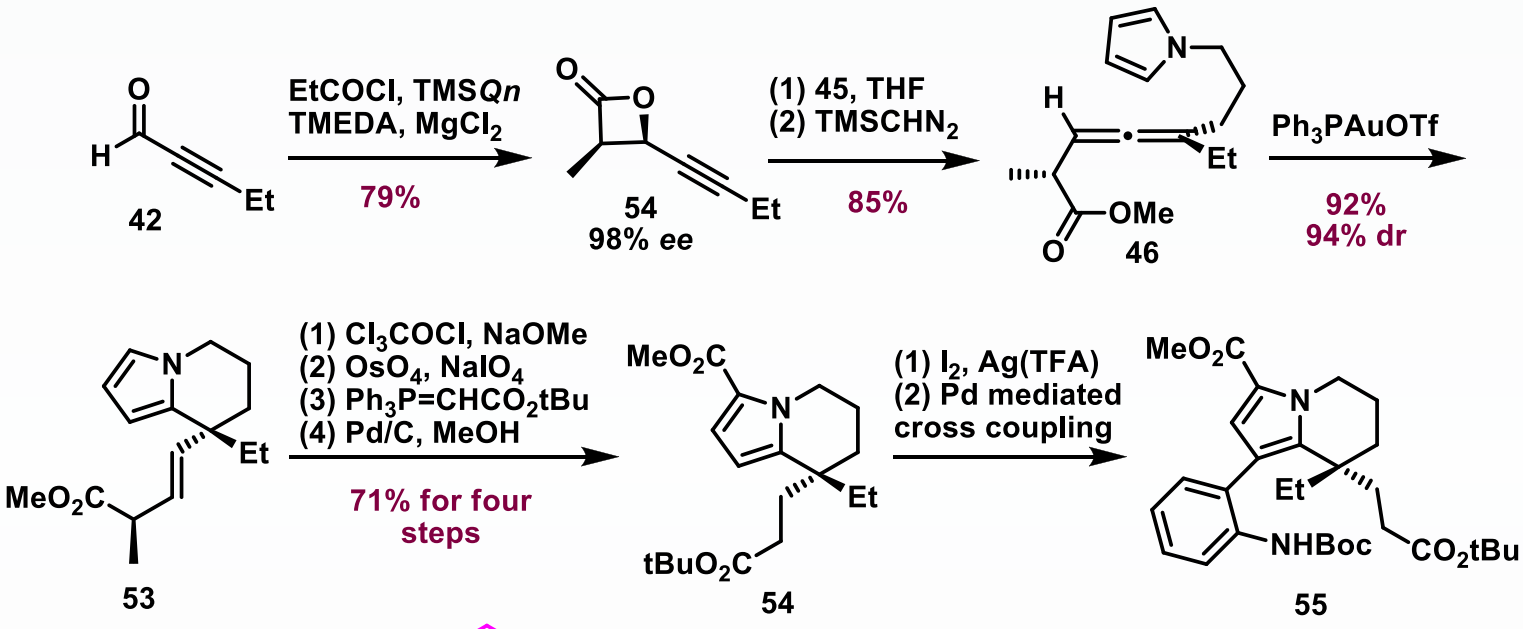


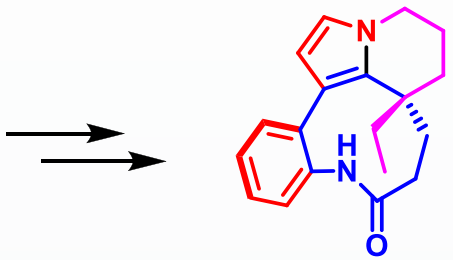
Strategy



Liu, Z.; Wasmuth, A. S.; Nelson, S. G. *J. Am. Chem. Soc. 2006, 128, 10352–10353.*

Completion of rhazinilam



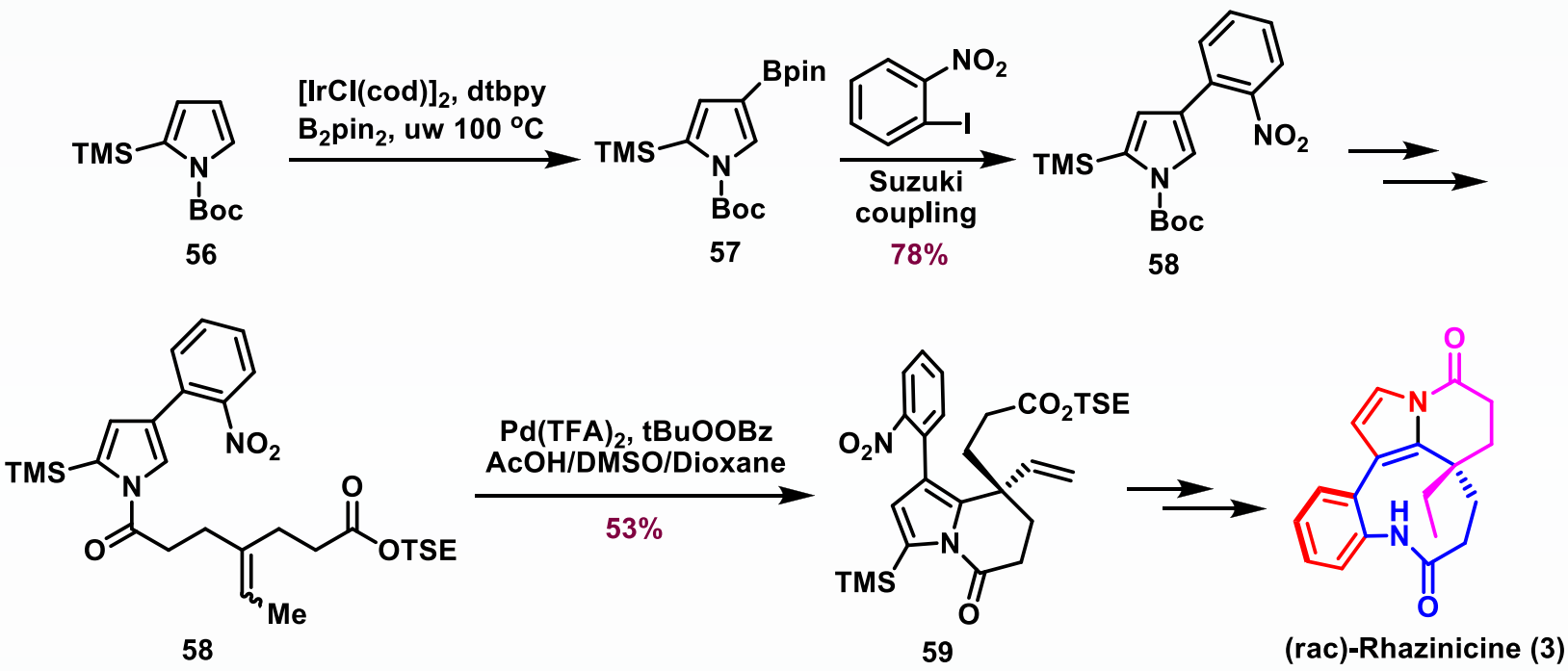


(-)-Rhazinilam (1)

Summary:

(1) Chiral transfer – axial to point
(2) Allenes is employed for heterocycle annulation
(3) Generating quaternary carbon center.
(4) Au (III) catalyzed asymmetric reaction..

A Collage of Metal Catalyzed Reactions



Summary:

(1) every efficient synthesis. 11 steps
(2) a collage of metal catalyzed reactions
(3) no innovation ideas

Beck, E. M.; Hatley, R.; Gaunt, M. J. *Angew. Chem., Int. Ed. 2008, 47, 3004–3007.*

Summary