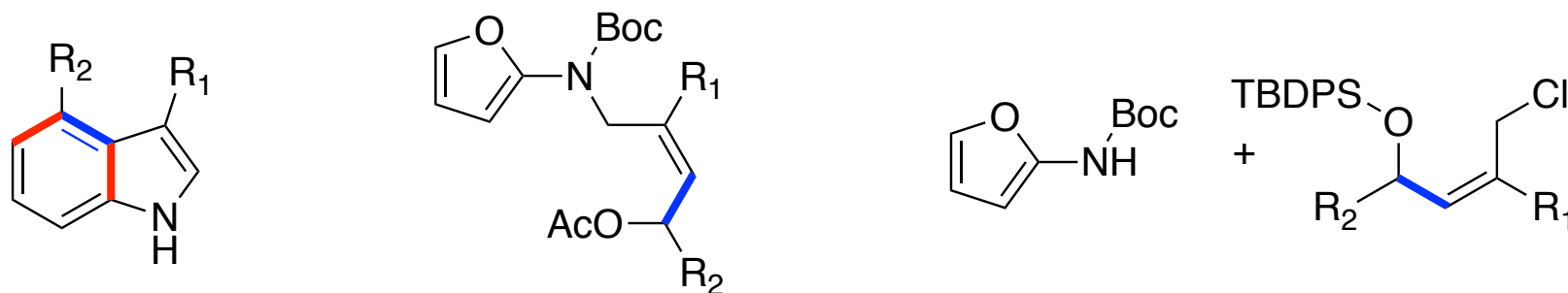
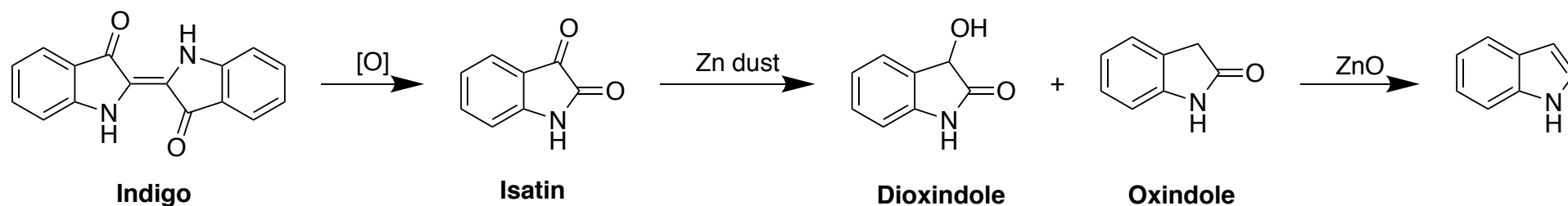


Transition metal-catalyzed IMDAF for the synthesis of 3,4-substituted indole



Dishit Jhaveri
Wipf Group

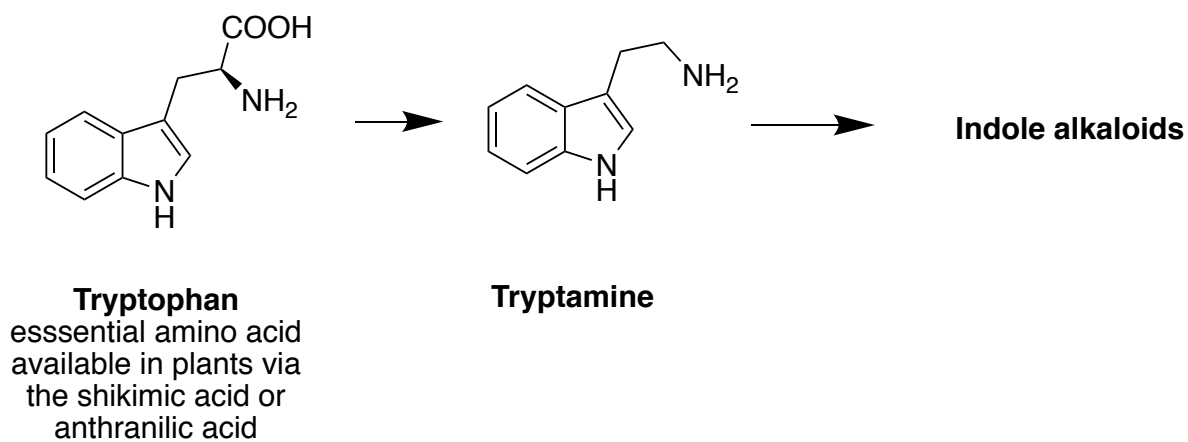
Introduction



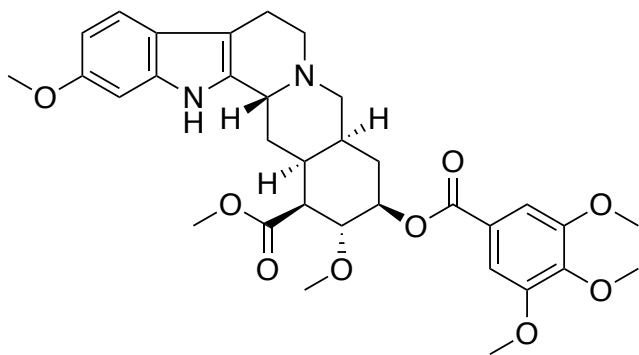
1868 – Adolf von Bayer prepared it from indigo

1869 – Bayer first proposed the currently accepted structure of indole

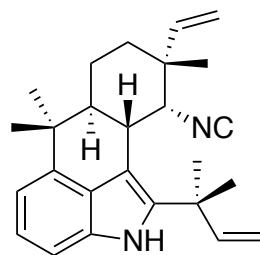
1883 – Fischer Indole Synthesis



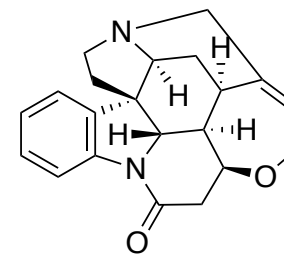
Indole alkaloids



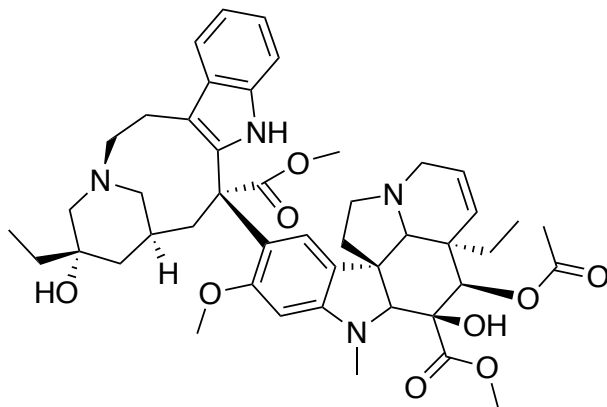
Reserpine



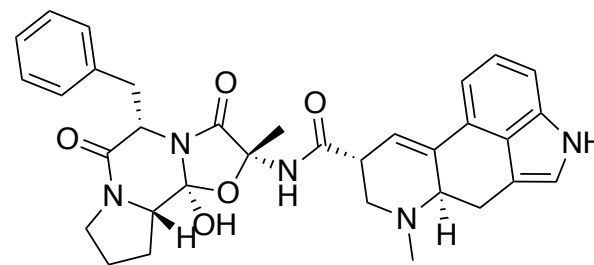
Ambiguine H



Strychnine

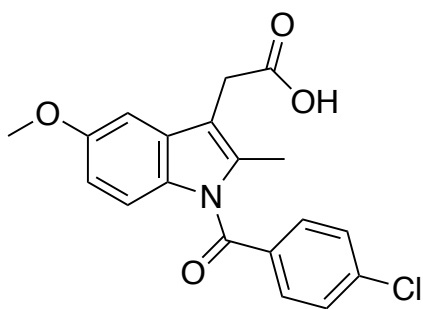


Vinblastine

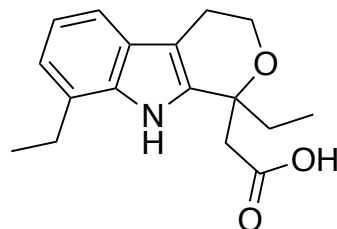


Ergotamine

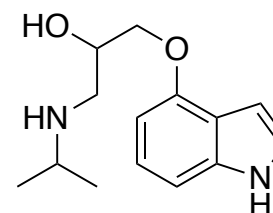
Indole containing drugs



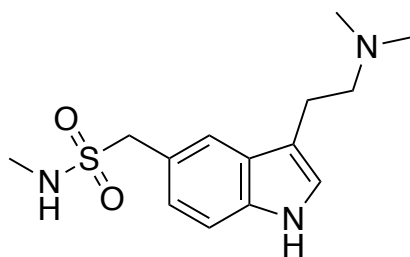
Indometacin
antiinflammatory and analgesic



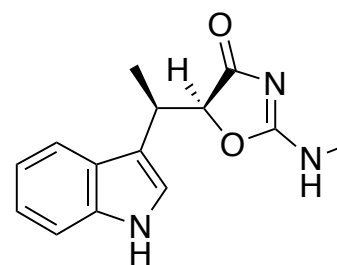
Etodolac
antiarthritis



Pindolol
anti-hypertensive

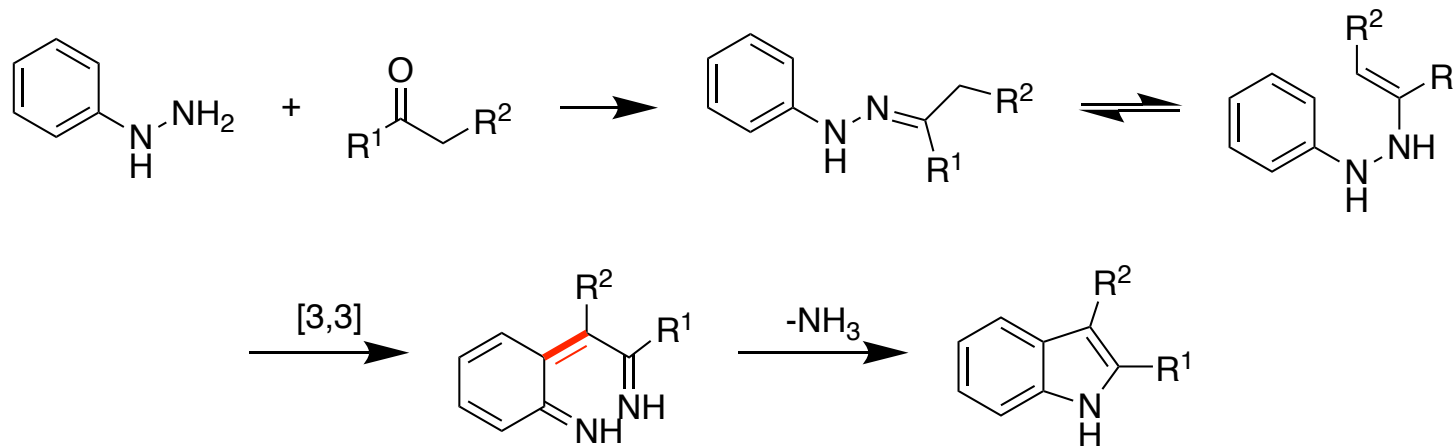
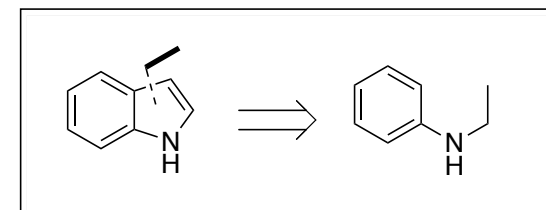


Sumatriptan
antimigraine



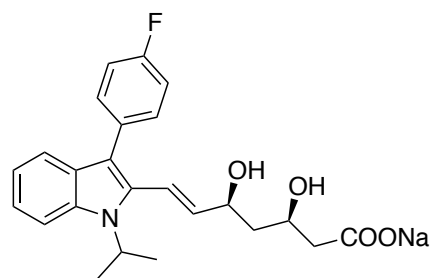
Indolmycin
antibiotic

Fischer Indole Synthesis

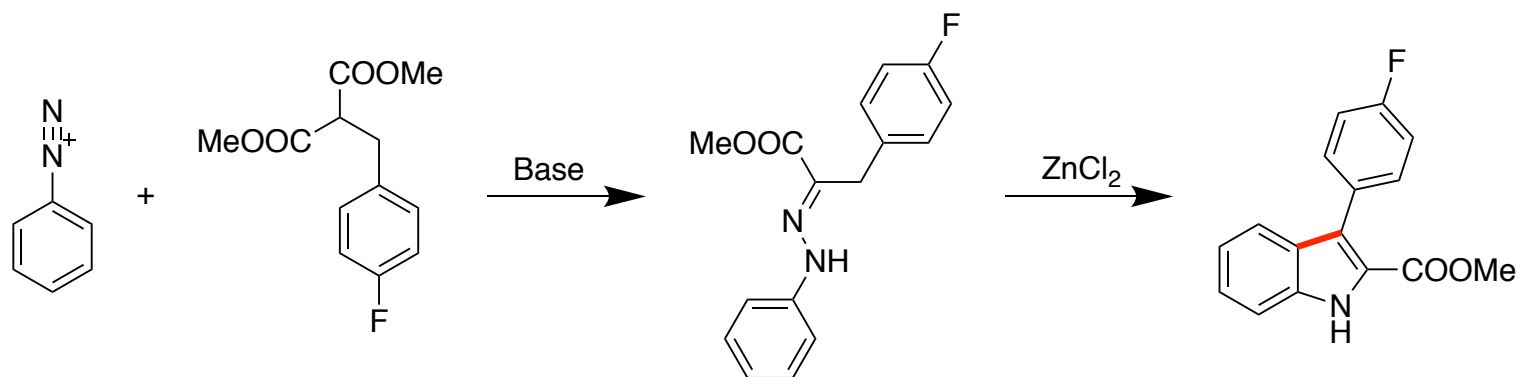
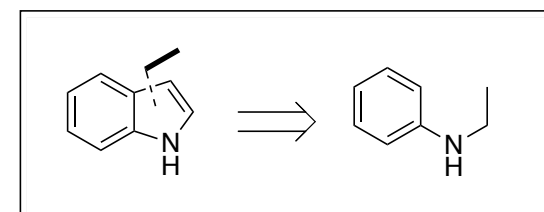


E. Fischer and F. Jourdan, *Berichte der Deutschen Chemischen Gesellschaft*, 1883, **16**, 2241–2245

Japp-Klingemann modification

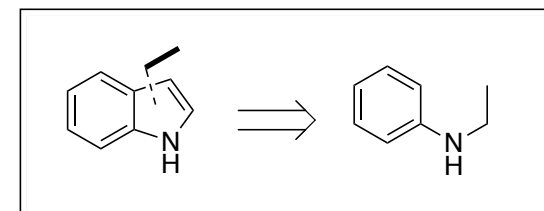
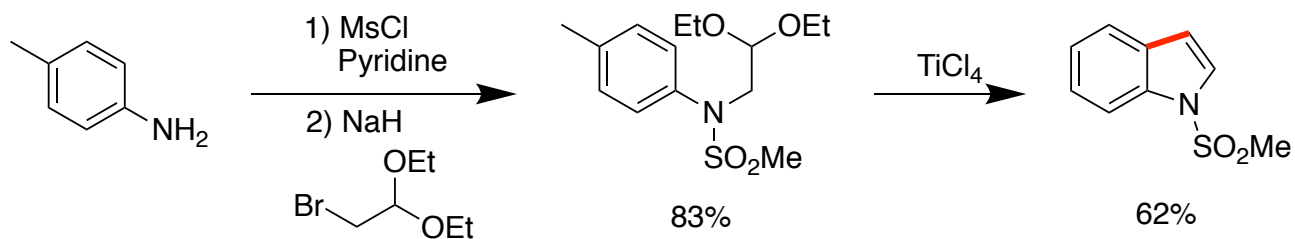


Fluvastatin

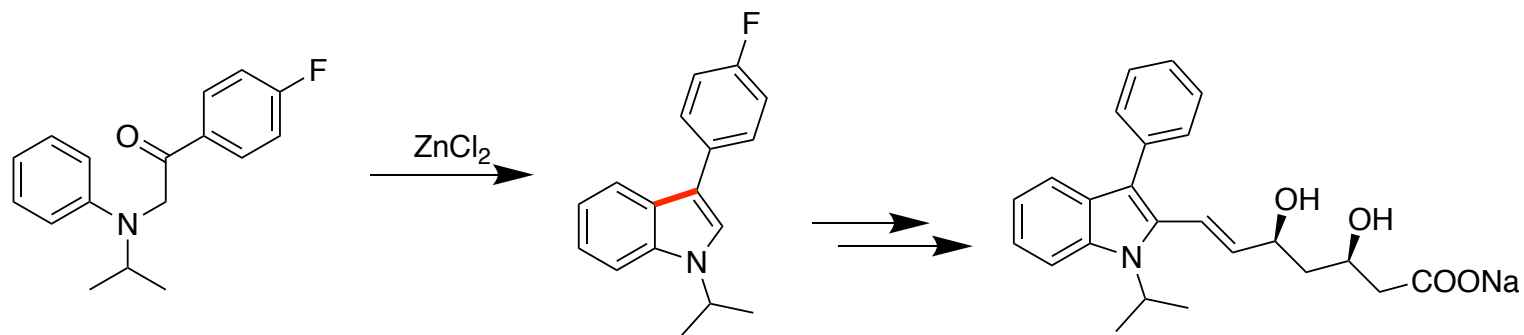


O. Repic, K. Prasad, and G. T. Lee, *Org. Process Res. Dev.* 2001, **5**, 519–527

Friedel-Craft reaction

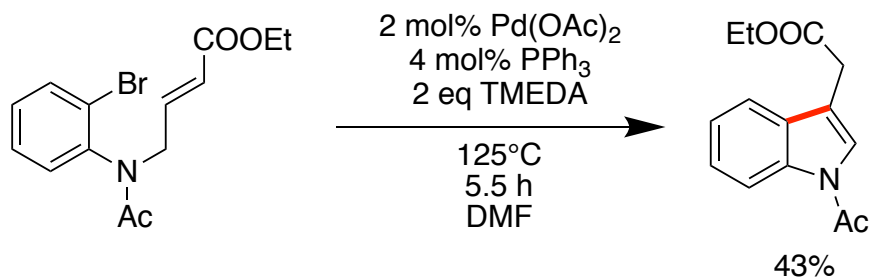


R. Sundberg and J. Laurino *J. Org. Chem.*, 1984, **49**, 249–254.

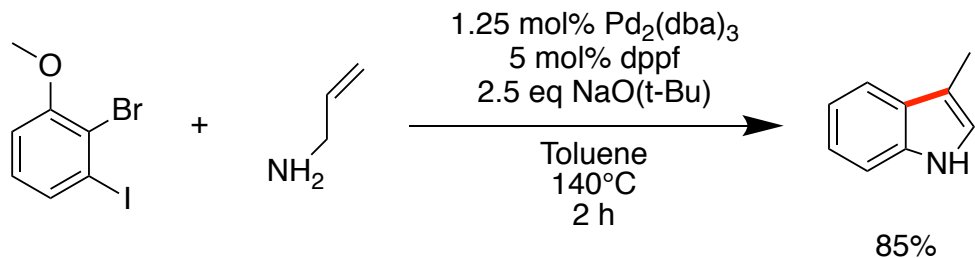


O. Repic, K. Prasad, and G. T. Lee, *Org. Process Res. Dev.* 2001, **5**, 519–527.

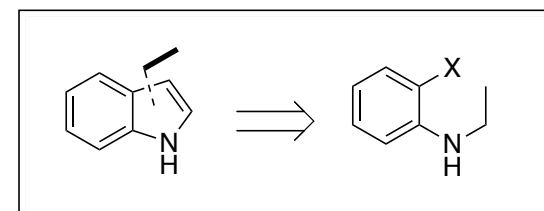
Intramolecular Heck reaction



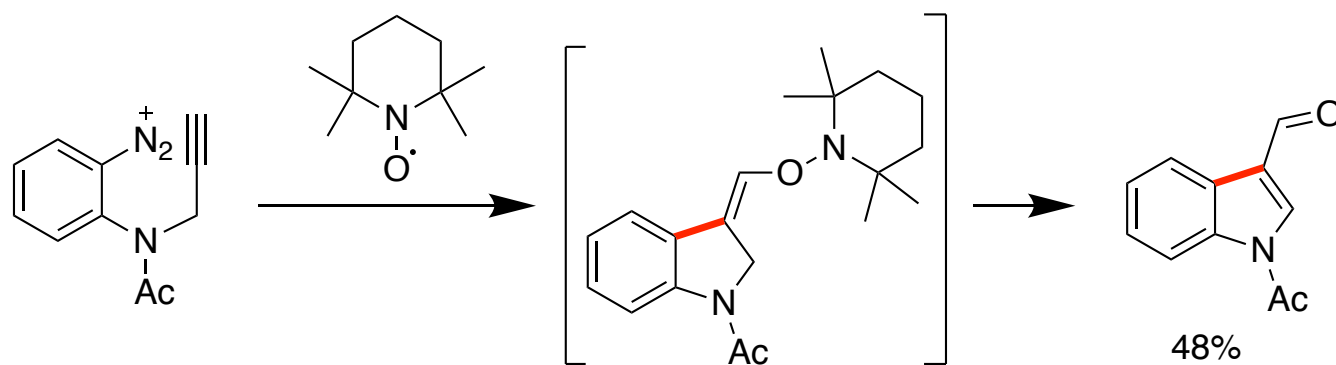
M. Mori et. al. *Tetrahedron Lett.* 1977, **18**, 1037



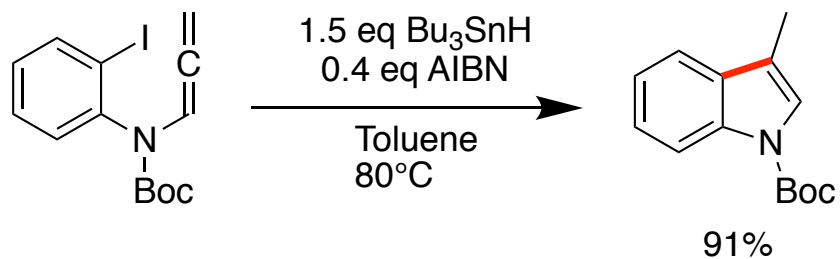
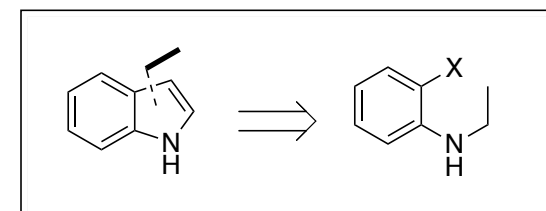
M. Jorgensen et al, *Angew. Chem. Int. Ed.* 2008, **47**, 888



Radical method

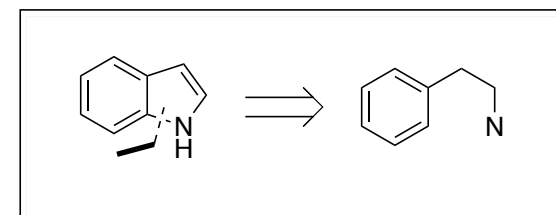
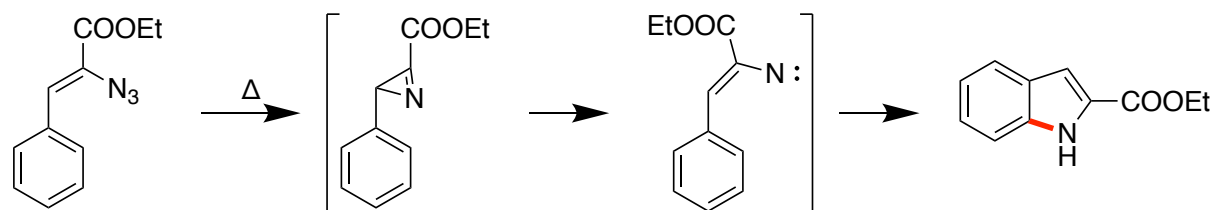


A. L. Beckwith et al, *J. Chem Soc. Chem Commun.* 1981, 595.

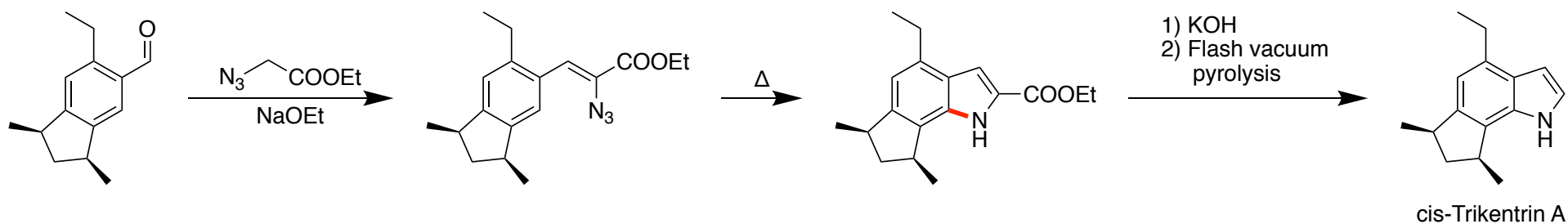


L. Shun and R. P. Hsung, *Org Lett*, 2005, **7**, 775.

Hemetsberger Indole Synthesis



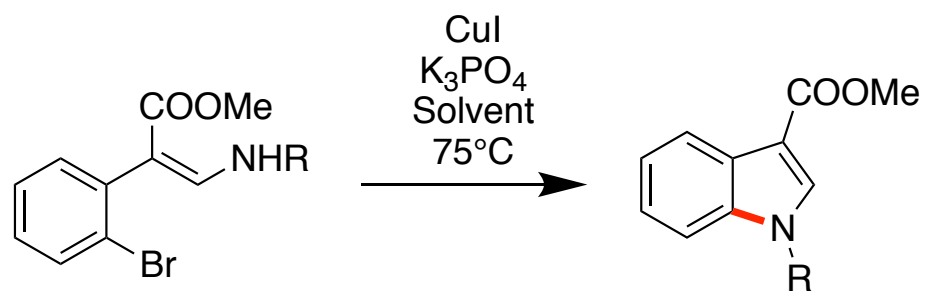
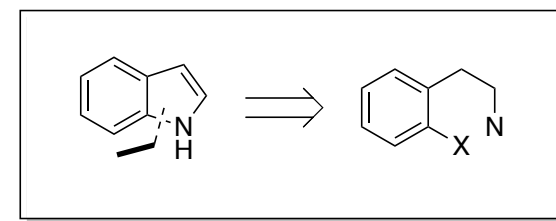
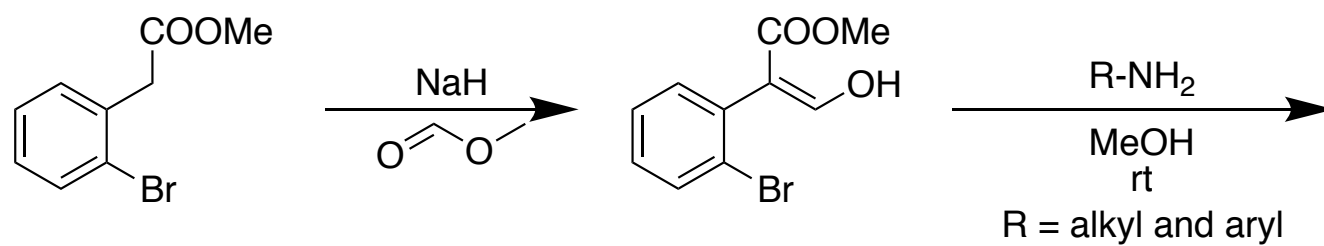
Hemetsberger, *Monatshefte für Chemie*, 1970, **101**, 161.



L. Monahan and J.K. MacLeod, *Tetrahedron Lett.* 1988, **29**, 391

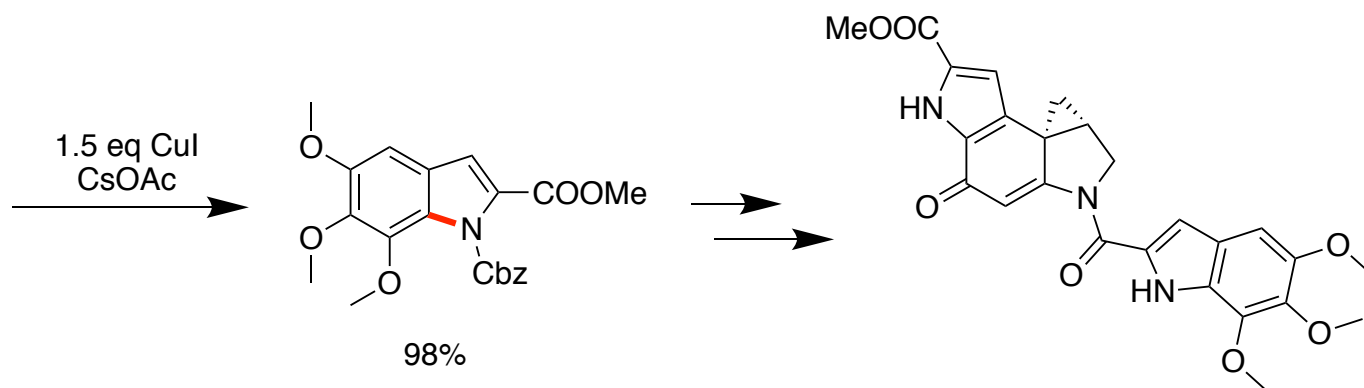
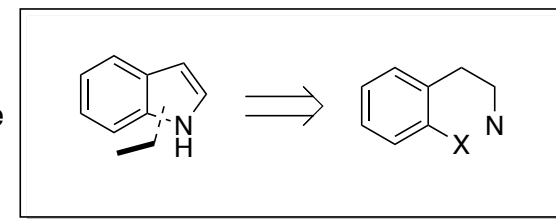
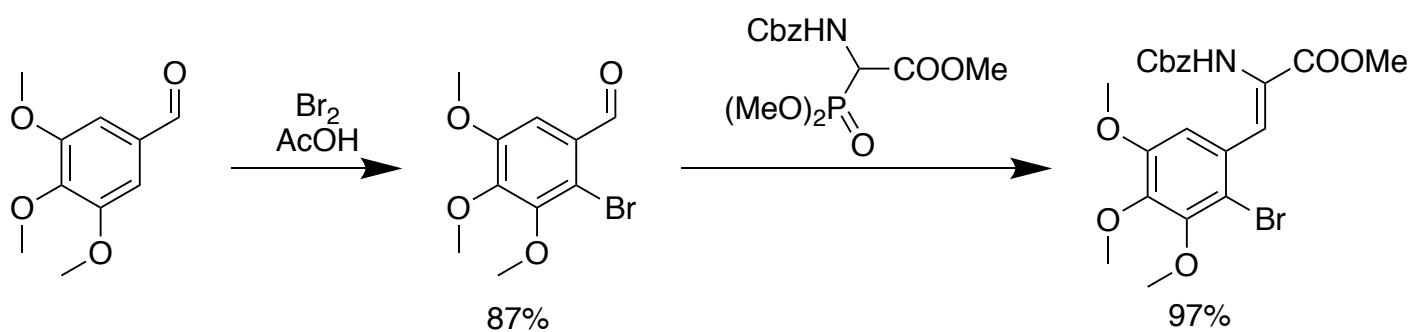
10

Ullmann Coupling



Moderate to high yields

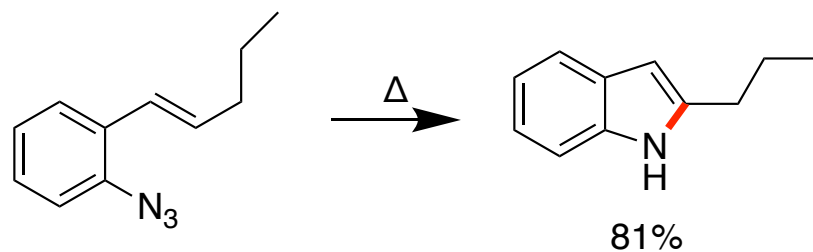
R. Sundberg and J. Laurino *J. Org. Chem.* 1984, **49**, 249-254.



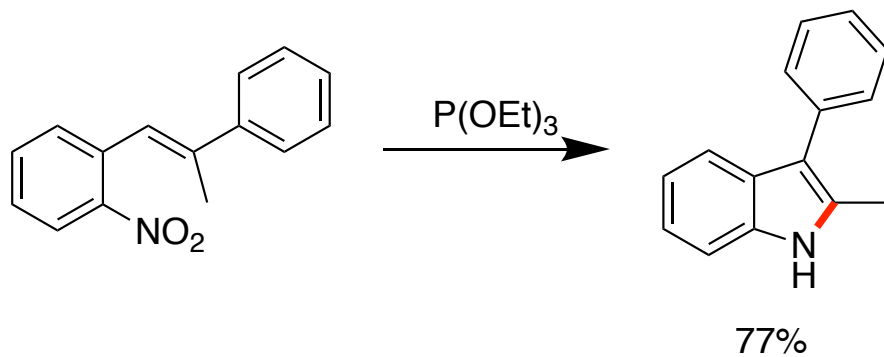
(+) Duocarmysin SA

T. Fukuyama et al., *J. Am. Chem. Soc.* **2003**, 125, 6630-6631

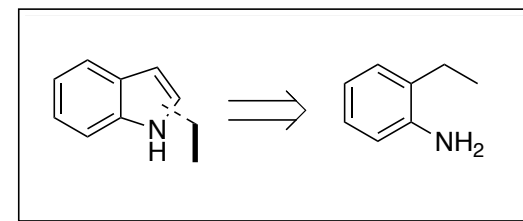
Sundberg synthesis

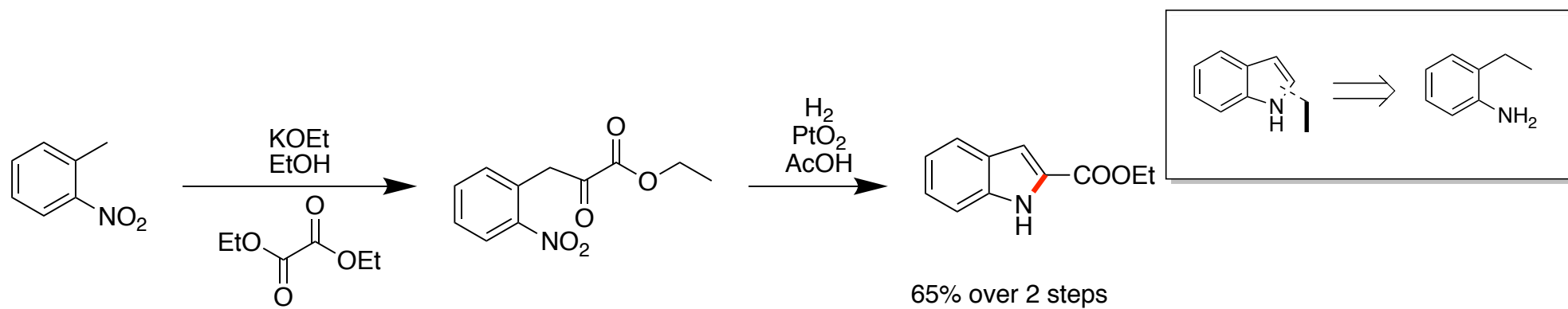


R. Sundberg et al., *J. Heterocycl. Chem.* 1969, **6**, 441.

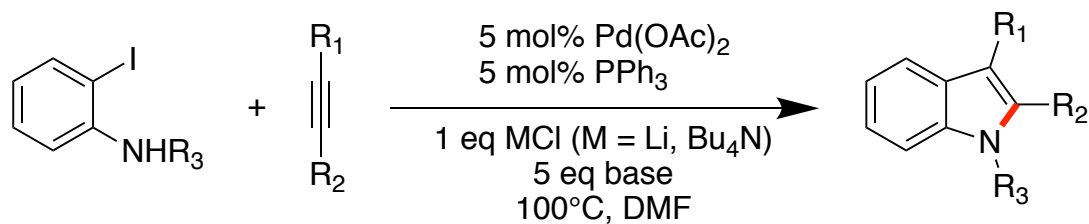


R. Sundberg and T. Yamazaki, *J. Org. Chem.*, 1967, **32**, 290.



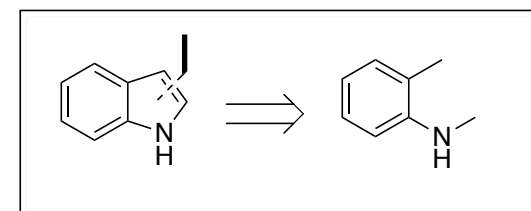
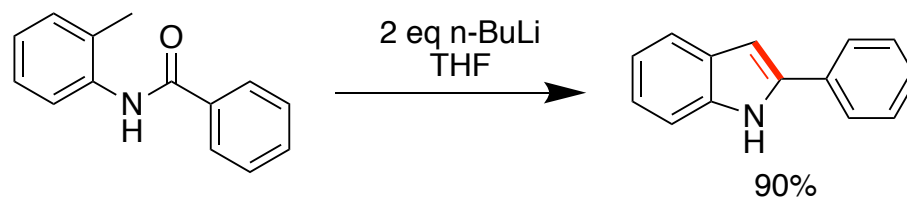
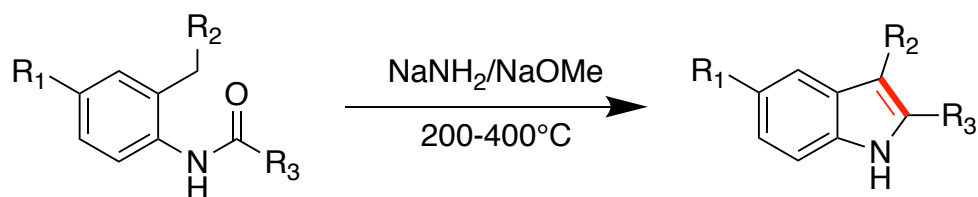


A. Reisert and H. Heller, *Chem. Ber.* 1904, **37**, 4364.

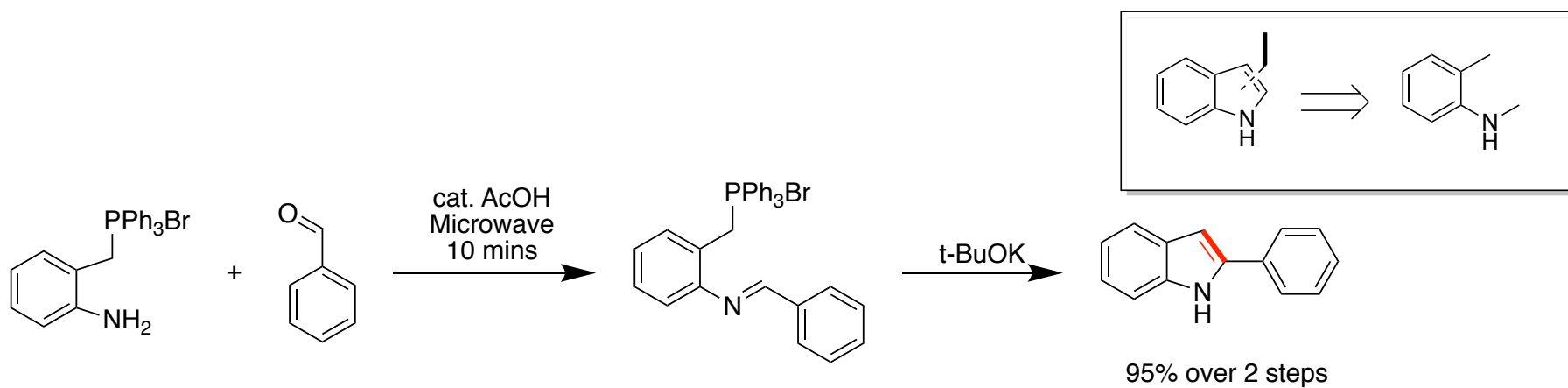


R. Larock and E. K. Yum *J. Am. Chem. Soc.* 1991, **113**, 6689-6690

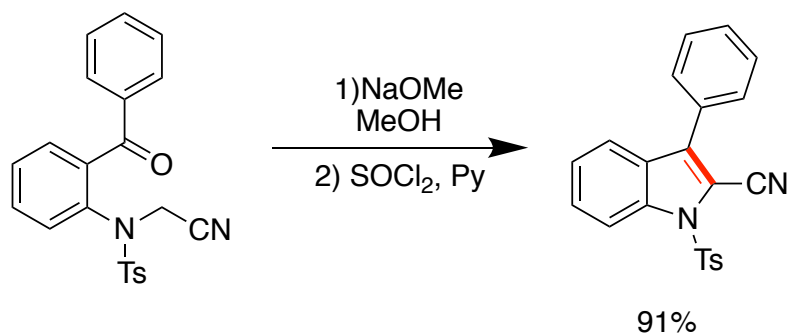
Madelung synthesis



W. J. Houlihan et al., *J. Org. Chem.*, 1981, **46**, 4511.

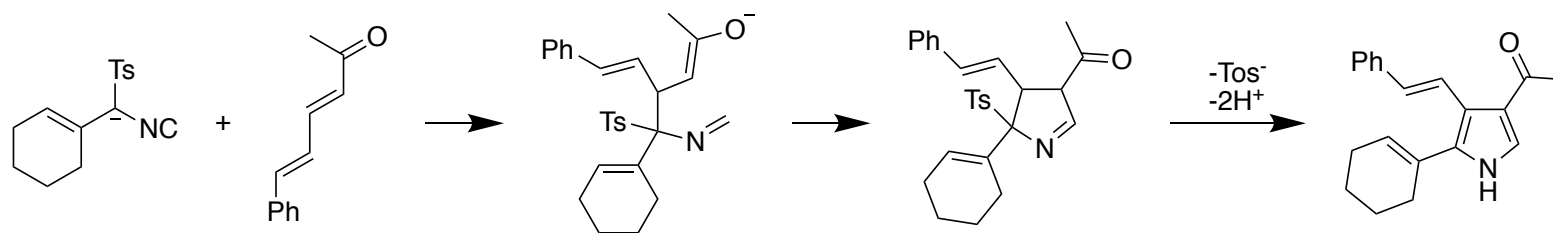
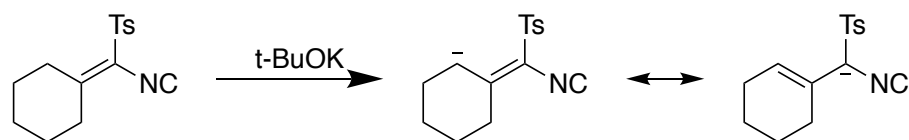
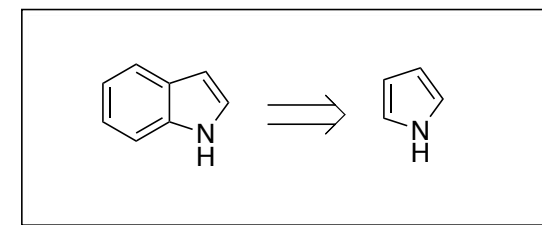
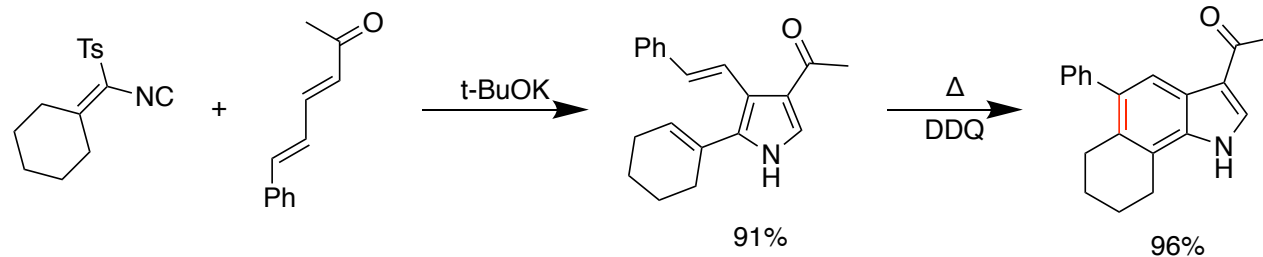


G. A. Kraus and H. Guo, *Org. Lett.*, 2008, **10**, 3061-3063

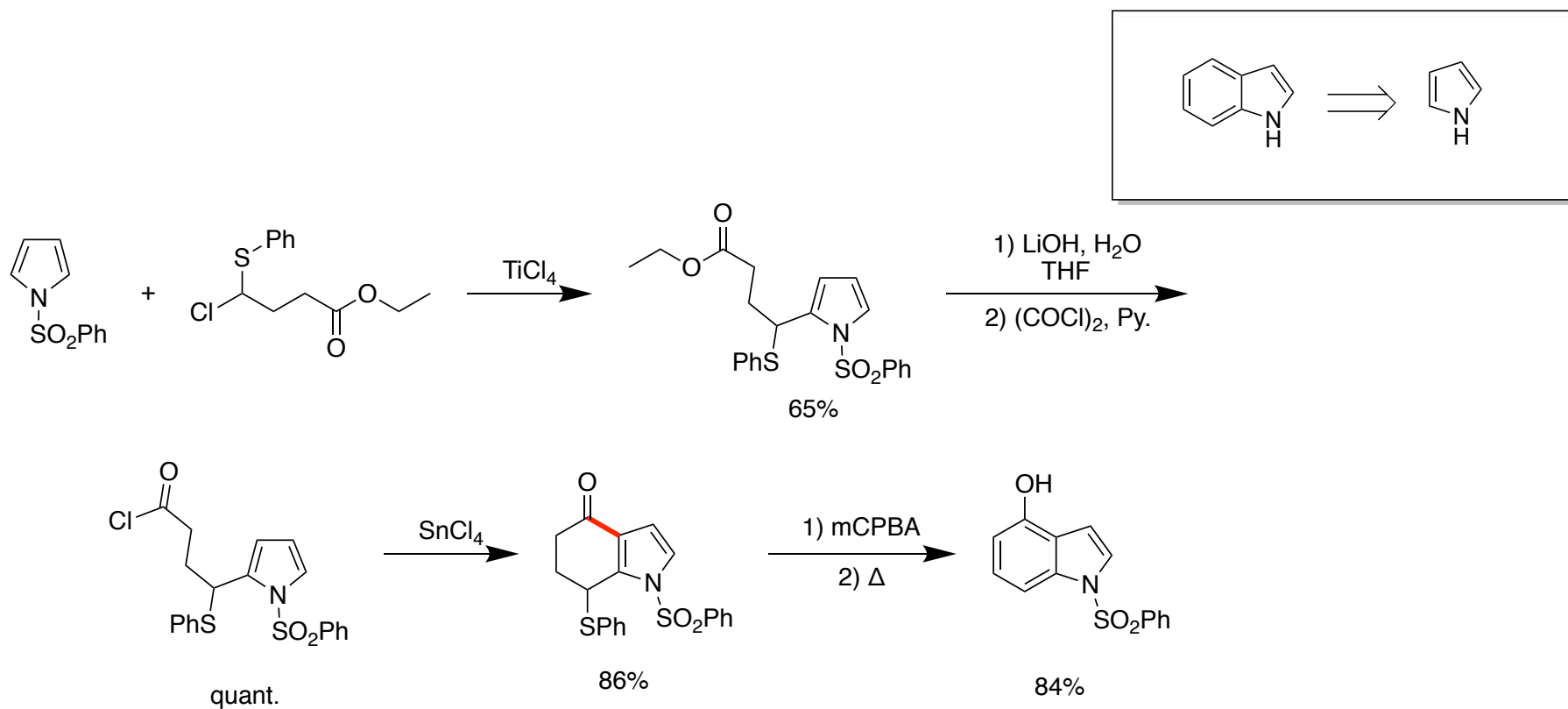


C. Jones, *J. Org. Chem.* 1972, **37**, 3624-3625

van Leusen synthesis

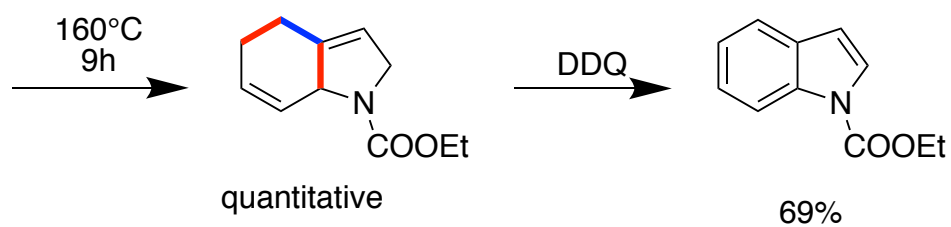
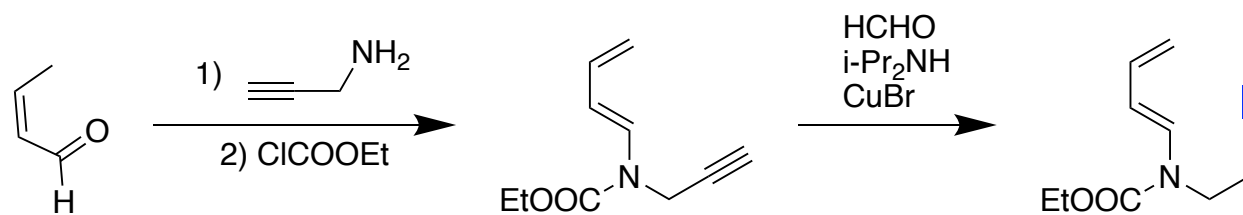
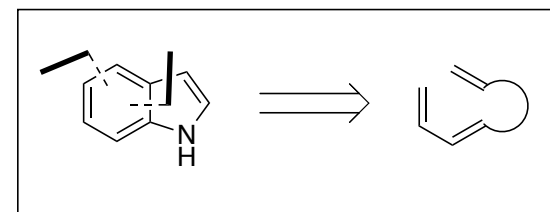
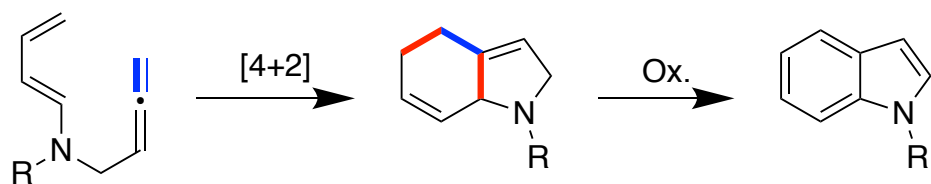


J. Moskal and A. van Leusen, *J. Org Chem*, 1986, 51, 4131-4139



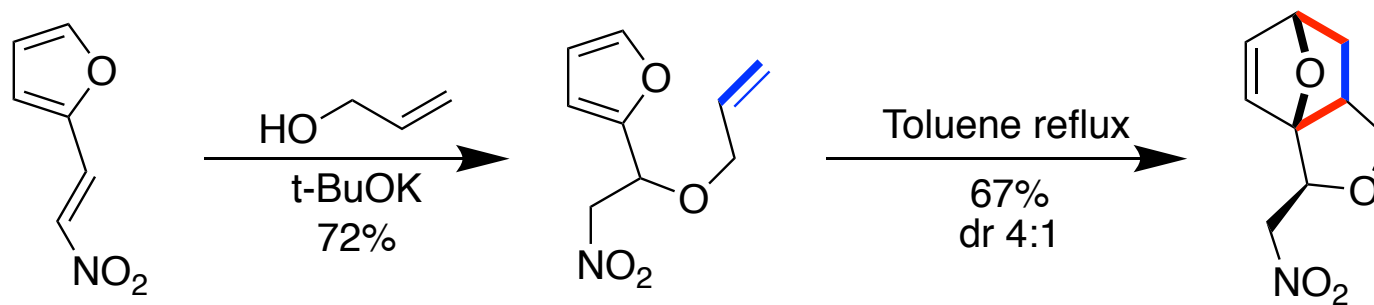
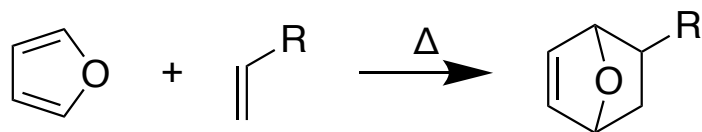
H. Ishibashi et al., *Tetrahedron Lett.*, 1993, **34**, 489.

Kanematsu synthesis



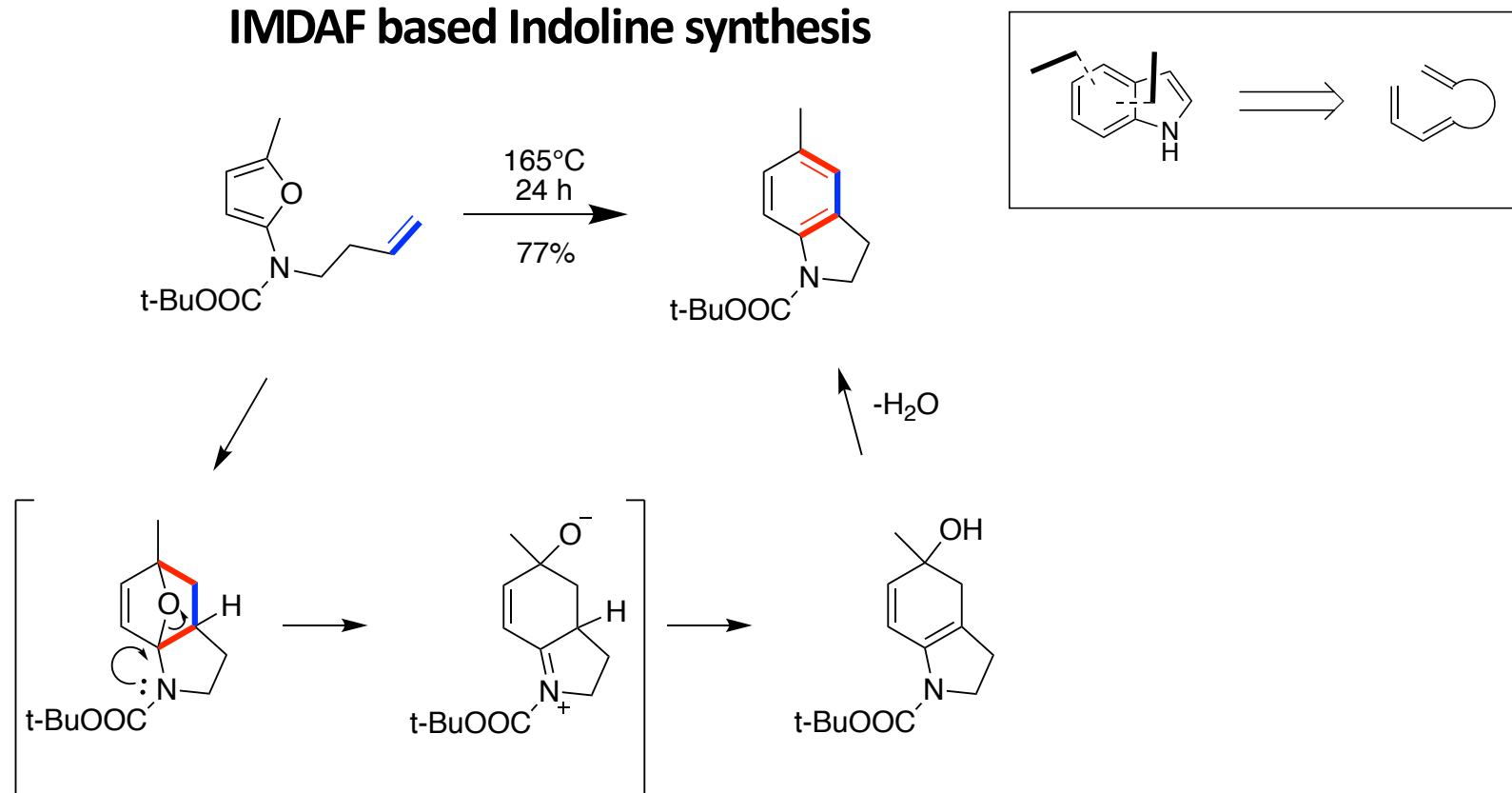
K. Kanematsu et. al., Tetrahedron Lett., 1986, 27, 1837-1840

IMDAF



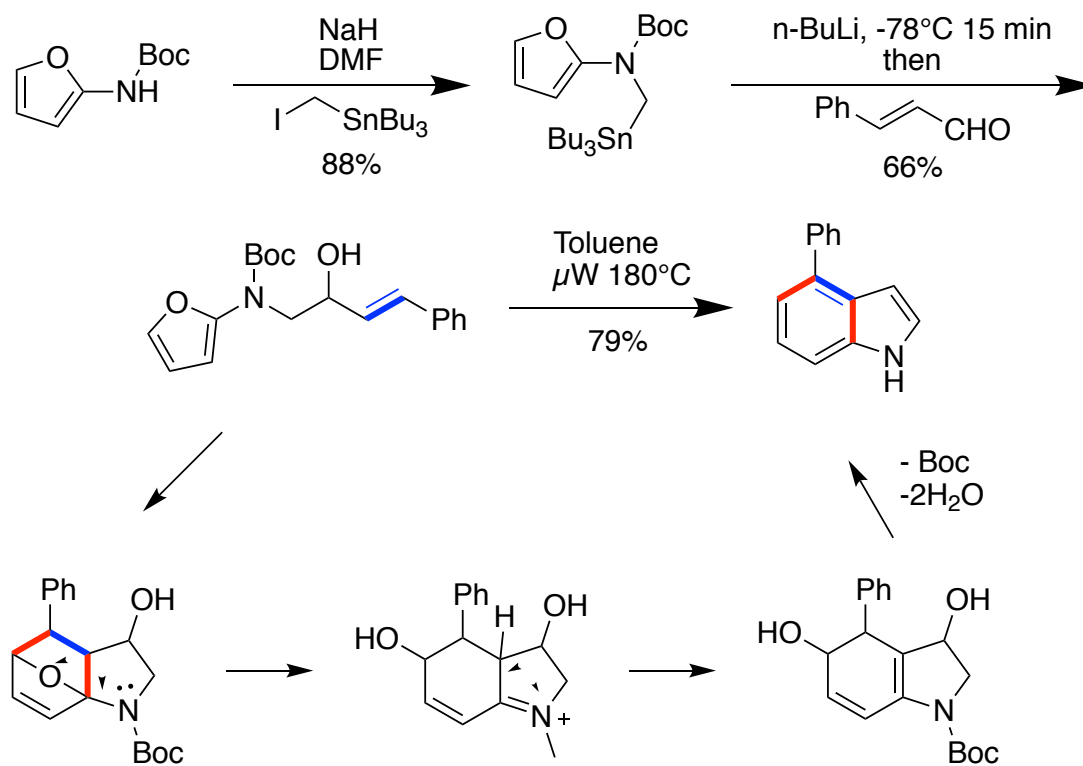
I. Namboothiri et. al., *J. Org. Chem.*, 2005, **70**, 2235-2243.

IMDAF based Indoline synthesis



A. Padwa et al., J. Org. Chem., 1999, 64, 3595-3607

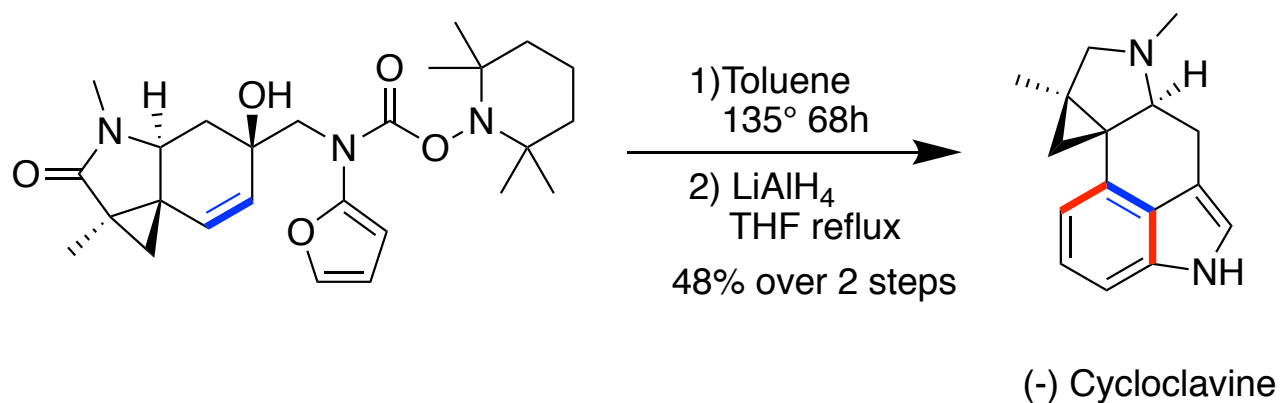
Microwave assisted IMDAF indole synthesis



F. Petronijevic, C. Timmons, A. Cuzzuppe and P. Wipf, *Chem. Commun.*, 2009, 104-106

22

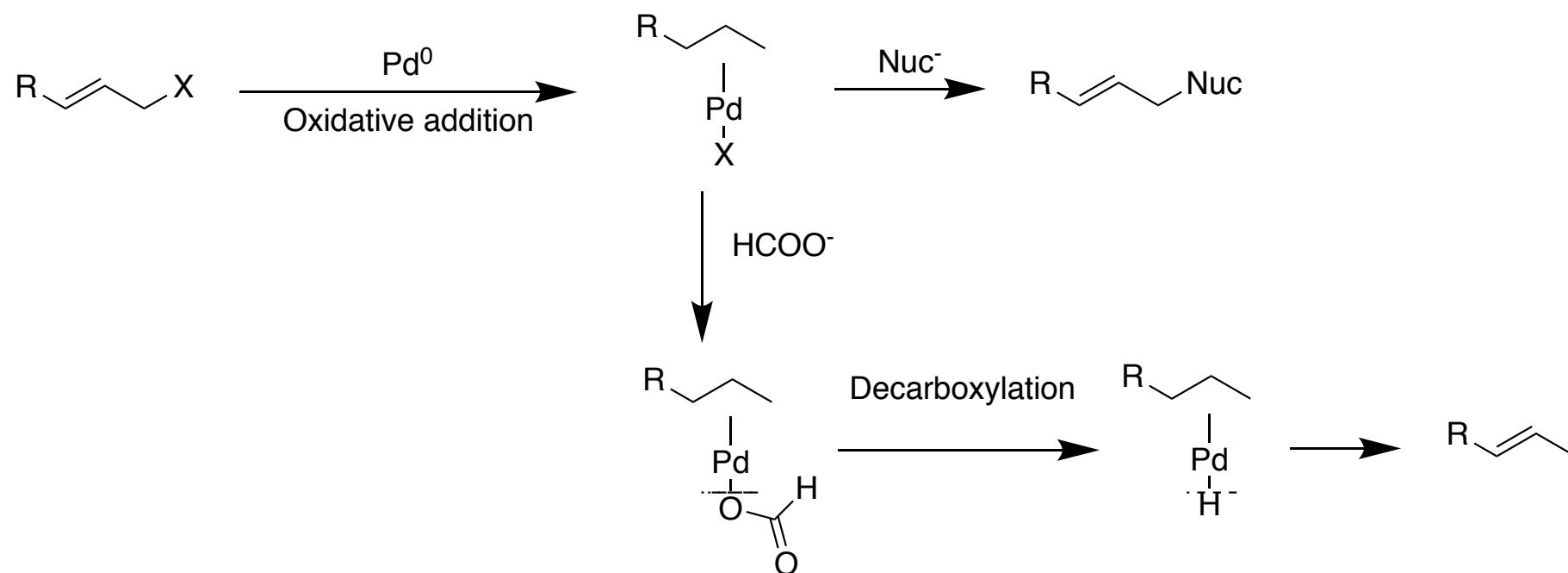
Application in total synthesis



F. Petronijevic and P. Wipf, *J. Am. Chem. Soc.*, 2011, **133**, 7704–7707.

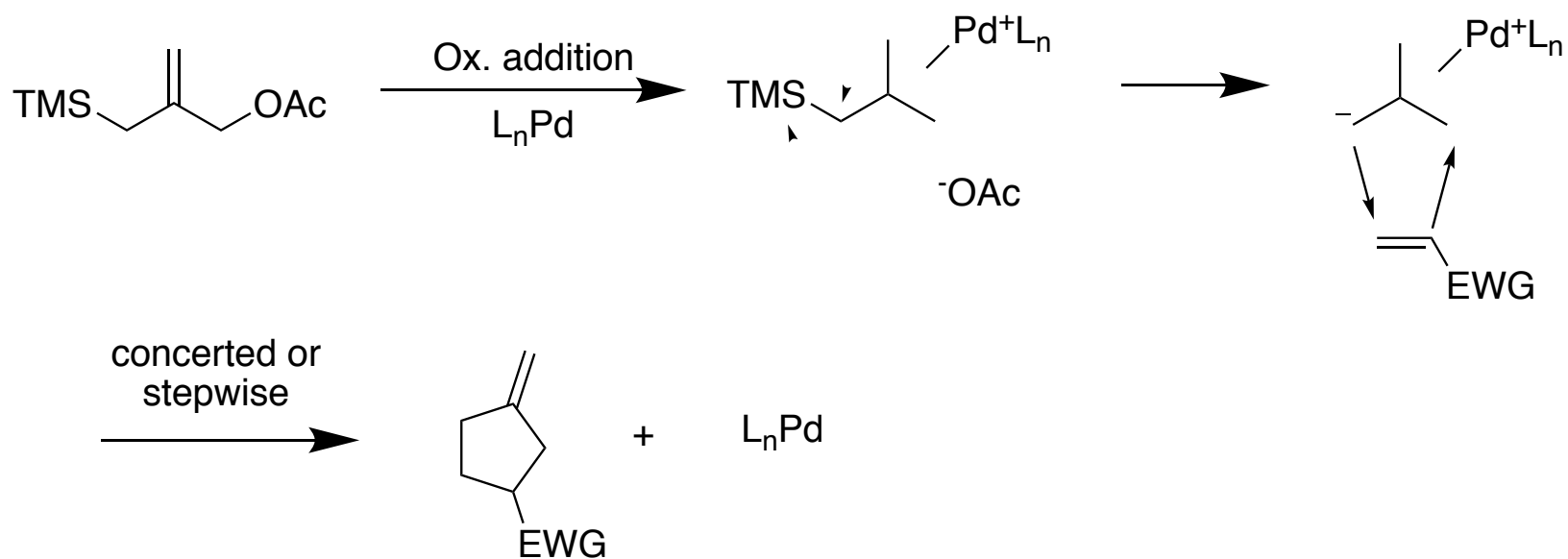
S. R. McCabe and P. Wipf, *Angew. Chem. Int. Ed.* 2017, **56**, 324-327.

π -allyl metal complexes



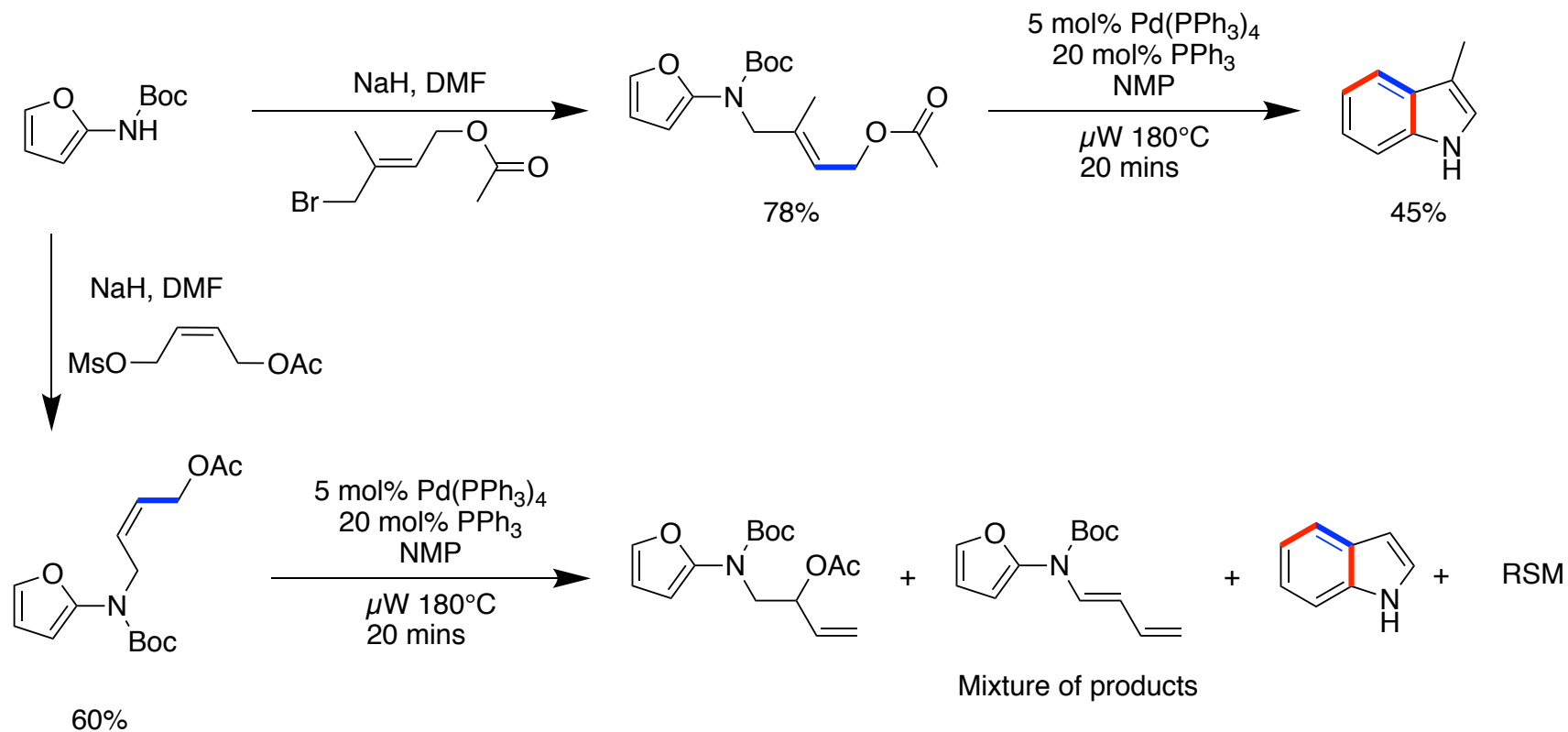
24

3+2 cyclization



B. Trost, *Angew. Chem. Int. Ed.*, 1986, **25**, 1-114

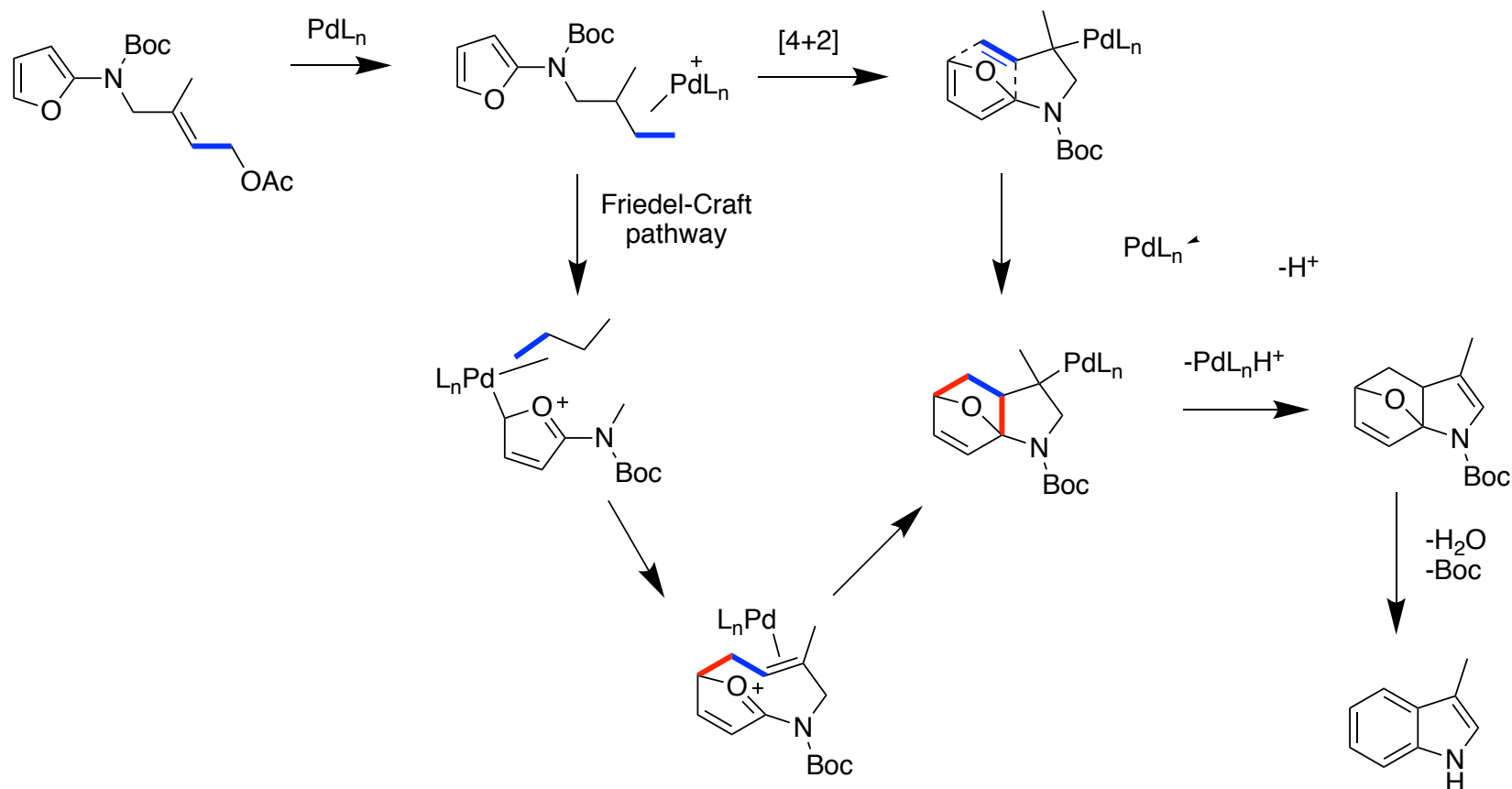
Pd-catalyzed IMDAF indole synthesis



J. Xu and P. Wipf, *Org. and Biomol. Chem.*, 2017, **15**, 7093.

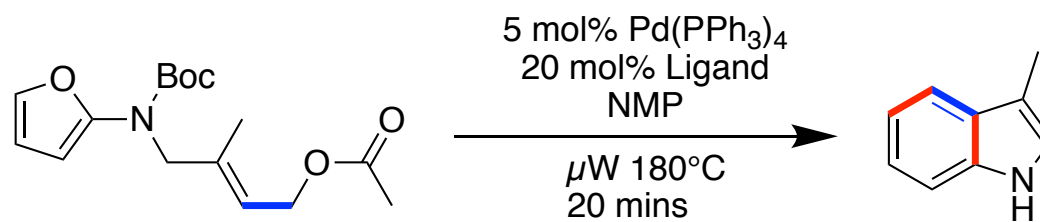
26

Pd-catalyzed IMDAF indole synthesis



J. Xu and P. Wipf, *Org. and Biomol. Chem.*, 2017, **15**, 7093.

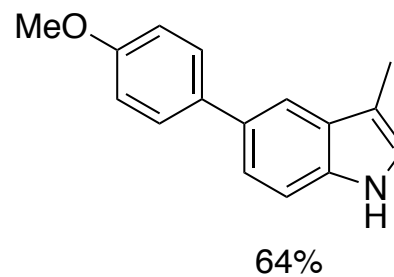
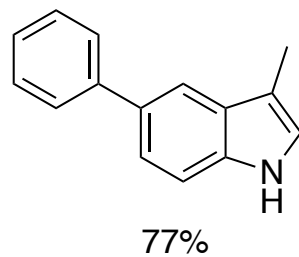
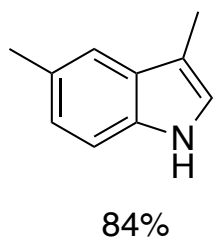
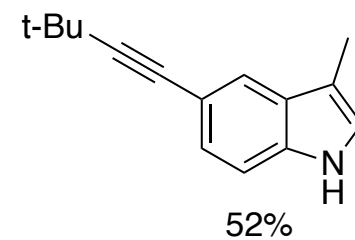
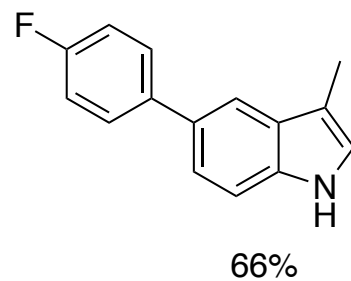
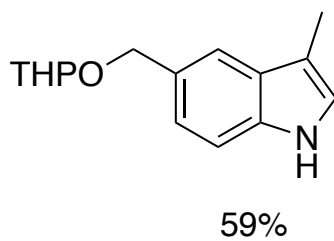
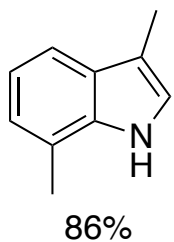
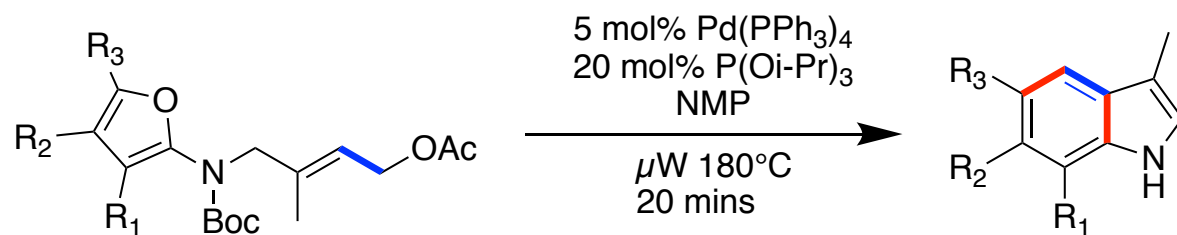
27



Entry	Ligand	Yield	Entry	Ligand	Yield
1	PPh ₃	45%	6	dppp	40%
2	PBn ₃	74%	7	dppb	59%
3	P(n-Bu) ₃	25%	8	P(OEt) ₃	71%
4	P(t-Bu) ₃	0%	9	P(Oi-Pr) ₃	83%
5	dppe	48%	10	P(OPh) ₃	27%

J. Xu and P. Wipf, *Org. and Biomol. Chem.*, 2017, **15**, 7093.

28



J. Xu and P. Wipf, *Org. and Biomol. Chem.*, 2017, **15**, 7093.

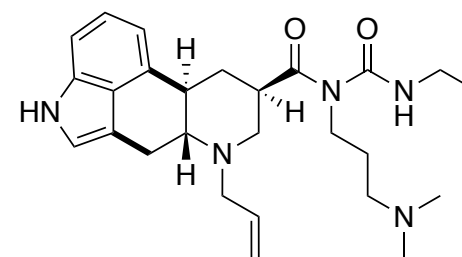
29

3,4-Substituted Indoles

Substitution pattern common in several alkaloids
(Ergot and Ambiguine)

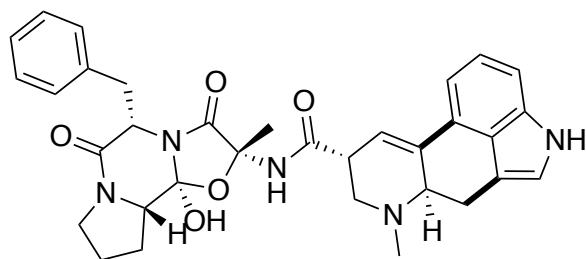
Few routes available to make them.

Several approved pharmaceuticals contain the
3,4-substituted indole motif.

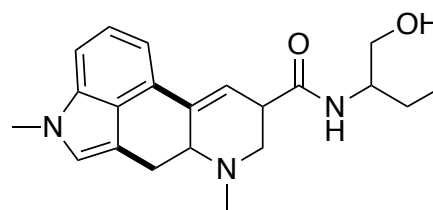


Cabergoline

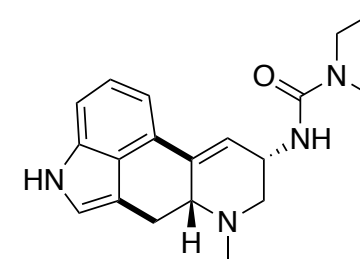
dopamine agonist



Ergotamine
antimigraine

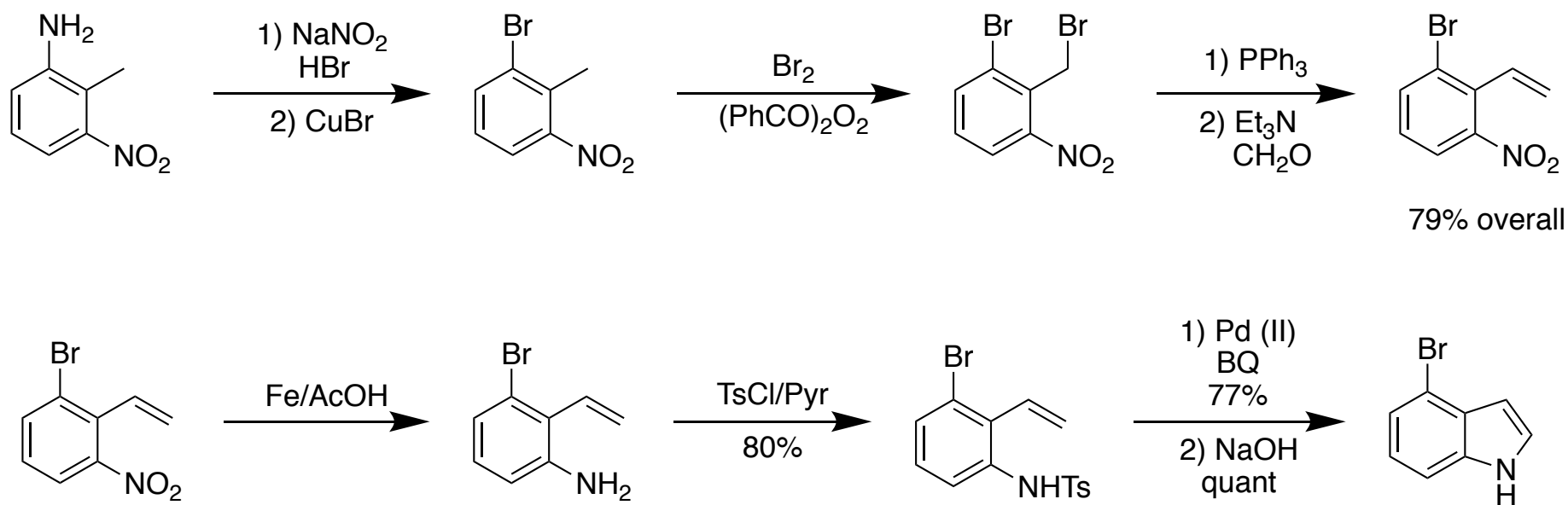


Methysergide
antimigraine



Lisuride
anti-Parkinson's

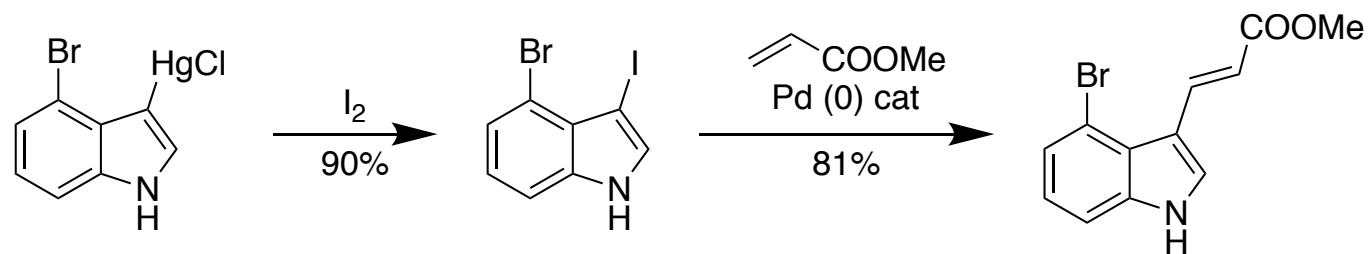
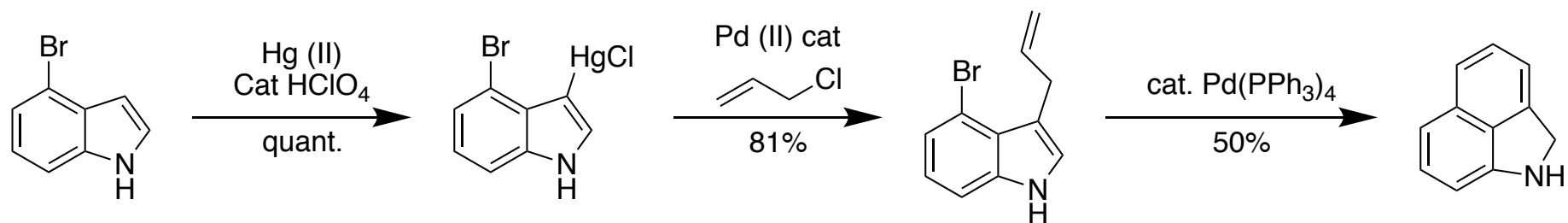
Synthesis of 3,4-substituted indoles



P. Harrington and L. Hegedus, *J. Org. Chem.*, 1984, 49, 2657-2662

31

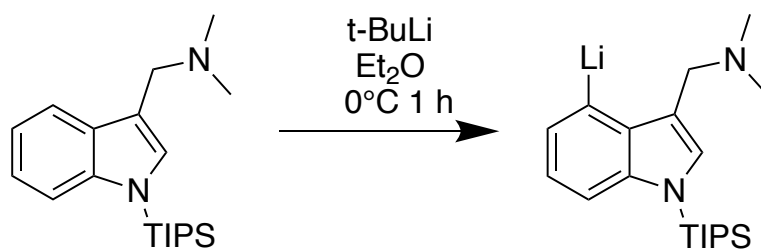
Synthesis of 3,4-substituted indoles



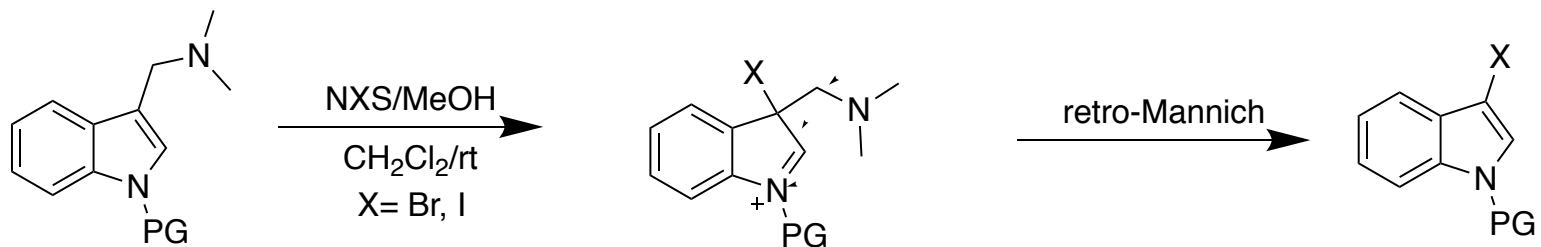
P. Harrington and L. Hegedus, *J. Org. Chem.*, 1984, 49, 2657-2662

32

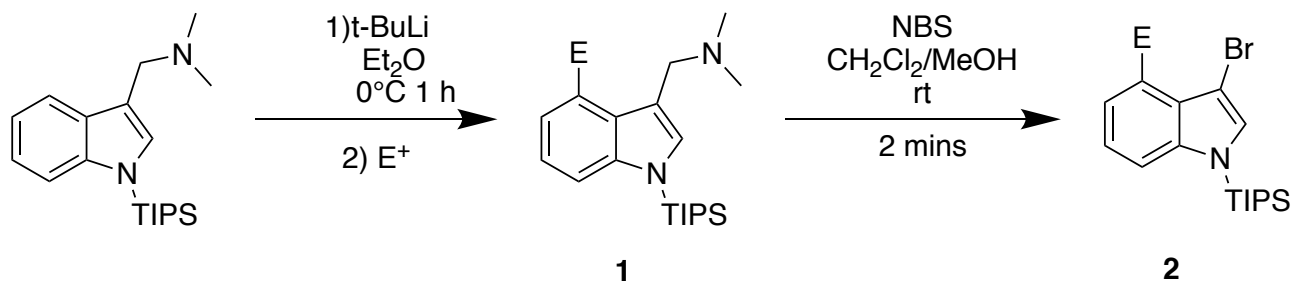
Synthesis of 3,4-substituted indoles



M. Iwao, *Heterocycles*, 1993, **36**, 29.



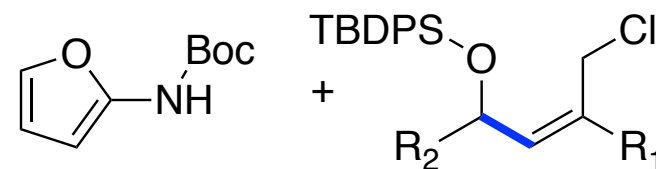
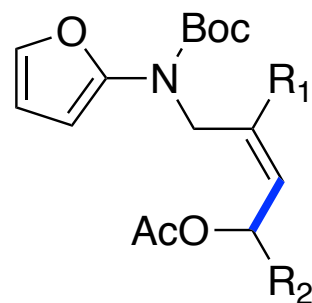
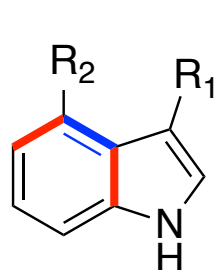
V. Snieckus et al., *Org. Lett.*, 2002, **4**, 815-817.



Entry	1	E ⁺	E	Yield (%) 1	Yield (%) 2
1	1a	Cl ₃ C-CCl ₃	Cl	64	80
2	1b	BrCH ₂ CH ₂ Br	Br	56	84
3	1c	DMF	CHO	51	79
4	1d	TMSCl	TMS	62	83

V. Snieckus et al., *Org. Lett.*, 2002, **4**, 815-817.

Synthesis of 3,4-substituted indoles via transition metal catalyzed IMDAF reaction



Acknowledgement

Dr. Wipf
Wipf group members - past and present

