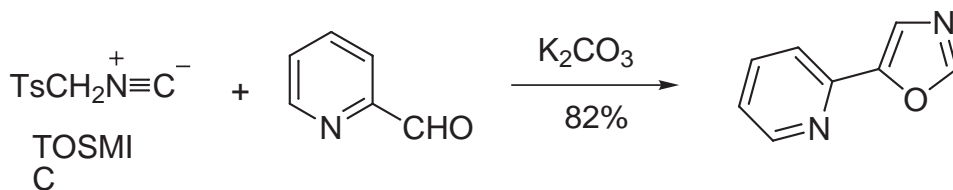


The Tosmic Reagent and Its Use in Heterocyclic Synthesis

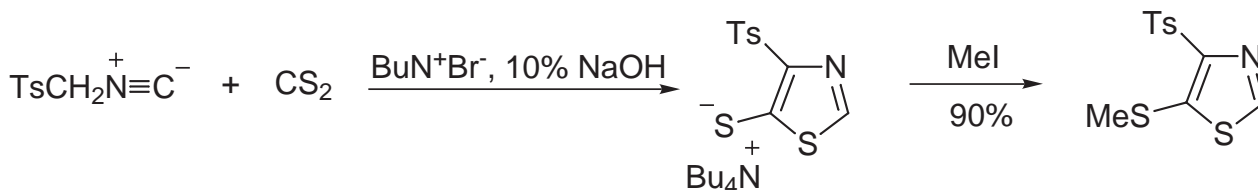
1. Reaction with Aldehydes to Form Oxazoles



Saikachi, H.; Kitagawa, T.; Sasaki, H.; van Leusen, A.M. *Chem. Pharm. Bull.* **1979**, 27, 793.

To a mixture of 2-pyridinecarboxaldehyde (0.01 mol) and tosylmethyl isocyanide (1.9 g, 0.01 mol) in 30 mL of MeOH was added K_2CO_3 (1.4 g, 0.01 mol). The solution was refluxed for 2 h and the solvent was removed under reduced pressure. The residue was poured into ice water and extracted with ether. The organic layer was washed with 2% HCl and water and dried over Na_2SO_4 . After filtration and evaporation of the solvent, the crude residue was distilled (95-98°C/0.15 torr) to give an 82% yield of the desired oxazole.

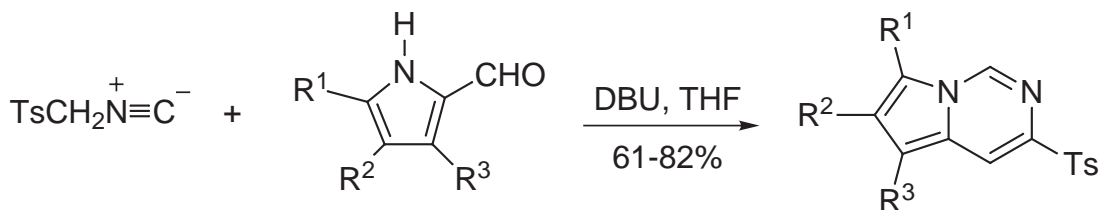
2. Reaction with Carbon Disulfide to Form Thiazoles



van Leusen, A.M.; Wildeman, J. *Synthesis* **1979**, 501.

To a solution of tosylmethyl isocyanide (1.9 g, 10 mmol), carbon disulfide (5 mL) and chloroform (10 mL) was added tetrabutylammonium bromide (3.5 g, 11 mmol) and 10% NaOH (10 mL). The mixture was stirred for 1.5 h at rt and the layers were separated. The aqueous layer was extracted with chloroform and the combined organic layers were washed with water and dried over MgSO_4 . After filtration and removal of the solvent, the crude residue was taken up in chloroform (20 mL), methyl iodide (2.8 g, 20 mmol) was added, and the mixture was stirred for 3 h at rt. The solvent was removed and the crude solid was washed with methanol, ether, and dried. Recrystallization from chloroform/methanol gave 2.6 g (90%) of the desired thiazole.

3. Formation of Pyrrolo[1,2-c]pyrimidines

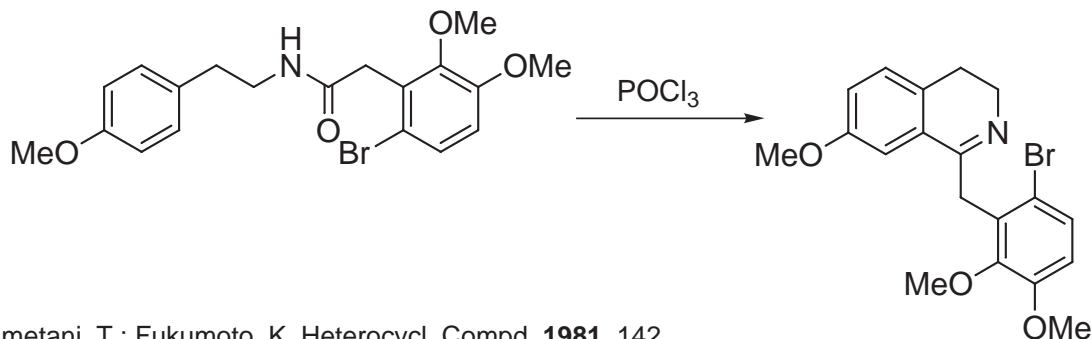


Minguez, J.M.; Vaquero, J.J.; Garcia-Navio, J.L.; Alvarez-Builla, J. *Tetrahedron Lett.* **1996**, 37, 4263.

To a mixture of 214 mg (1.1 mmol) of tosylmethyl isocyanide and 167 mg (1.1 mmol) of DBU in 2 mL of THF was added 95 mg (1 mmol) of pyrrole-2-carboxaldehyde in 2 mL of THF. The mixture was stirred at rt for 2 h and then neutralized with acetic acid. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel and recrystallized from CH_3CN to give the desired product in 82% yield.

Five Top Methods to Synthesize Isoquinolines

1. The Bischler-Napieralski Method



Kametani, T.; Fukumoto, K. *Heterocycl. Compd.* **1981**, 142.

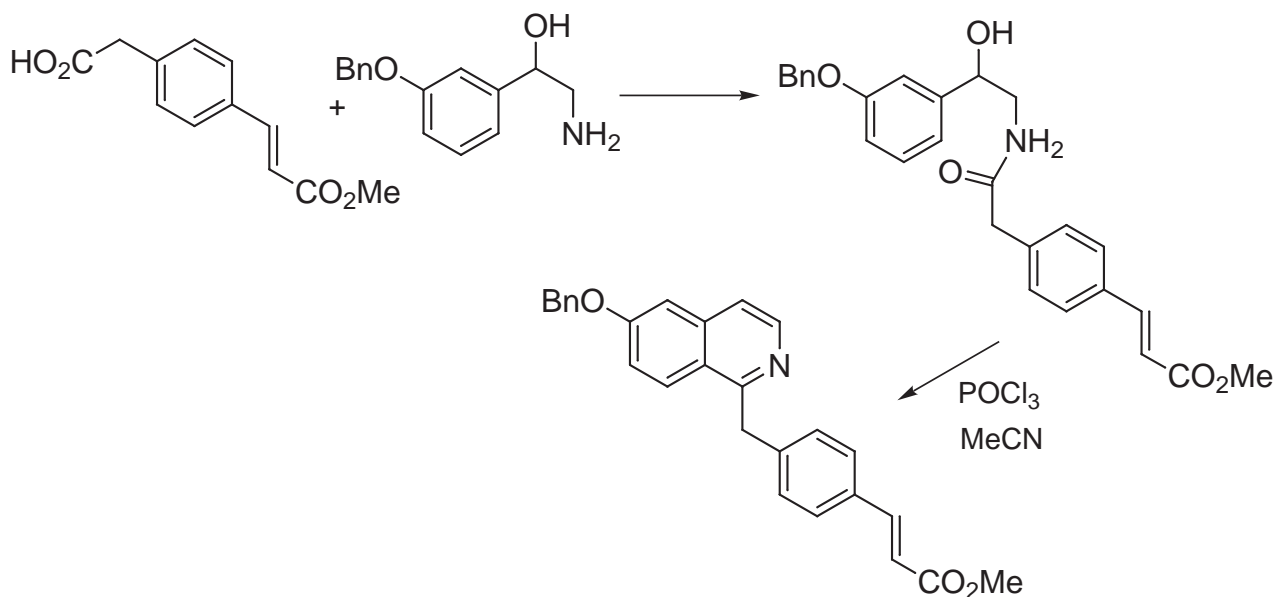
Jones, G. *Compr. Heterocycl. Chem. II*, **1996**, 179, 182.

Zhou, D. -M.; Yue, B. -Z.; Cui, J. -Q.; Cai, M. -S.; Zhang, L. -H. *Heterocycles* 45, 3, **1997**, 439.

Cerri, A.; Mauri, P.; Mauro, M.; Melloni, P. *J. Heterocycl. Chem.* 30,6, **1993**, 1581.

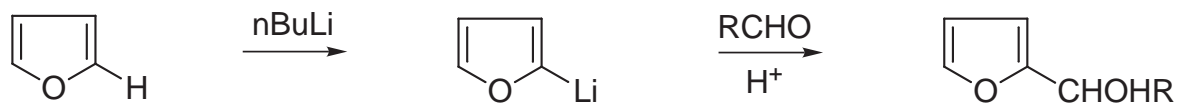
A solution of the amide (1.2 mmol) and phosphorus oxychloride (1.3 g, 8.5 mmol) in dry acetonitrile (20 mL) was refluxed for 2-5 h. The excess reagent and solvent were removed under vacuum and the residue was poured into 5% sodium hydroxide and then extracted with CH_2Cl_2 . The extracts were dried over magnesium sulfate and evaporated to give a white solid in 91% yield. The solution was dissolved in CH_2Cl_2 and HCl gas was bubbled through to give the hydrochloride salt.

Pictet-Gams Modification of the Bischler-Napieralski



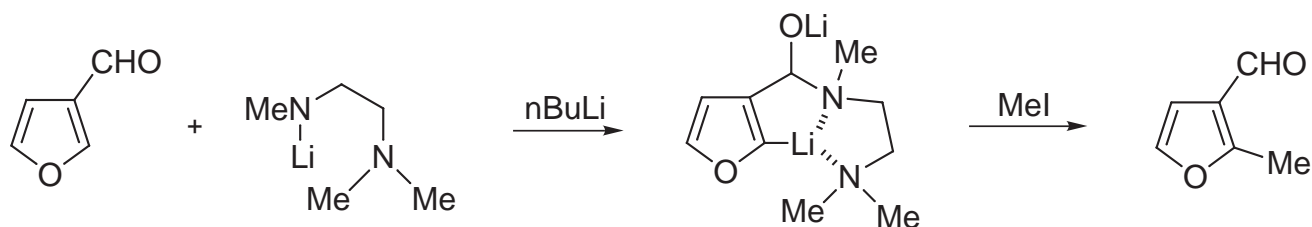
A solution of 2.2 g (10 mmol) of the acid and 1.5 mL (20 mmol) of thionyl chloride in 20 mL of benzene was heated at reflux for 1.5 h. After cooling, the solution was evaporated. The residue contained 2.4 g (100%) of the corresponding acetyl chloride as an orange solid which was used in the next reaction without any further purification. To a solution of 2.4 g (10 mmol) of the amino alcohol in 11 mL of 1 N (11 mmol) sodium hydroxide and 20 mL of dioxane was added a solution of 2.4 g of the acid chloride in 15 mL of ether and 3 mL of dioxane. After stirring for 1.5 h, the mixture was filtered, the solid was washed with water and dried to give 3.6 g (80%) of the amide as a white solid. To a stirred and boiling solution of 2.7 g (6 mmol) of the amide in 50 mL of acetonitrile was added dropwise 5.6 mL (60 mmol) of phosphorus oxychloride. After 1.5 h at reflux, the solution was cooled and aqueous 5% sodium hydrogen carbonate was added carefully until pH 8.0 was reached. The mixture was extracted with ethyl acetate. The organic phase was dried and the solvent evaporated. The residue was purified by silica gel chromatography to give 2.1 g (85%) of the isoquinoline as a white solid.

Alpha-metalation of furans



Gschwend, H. W.; Rodriguez, H. R. *Organic Reactions* **1979**, 26, 1

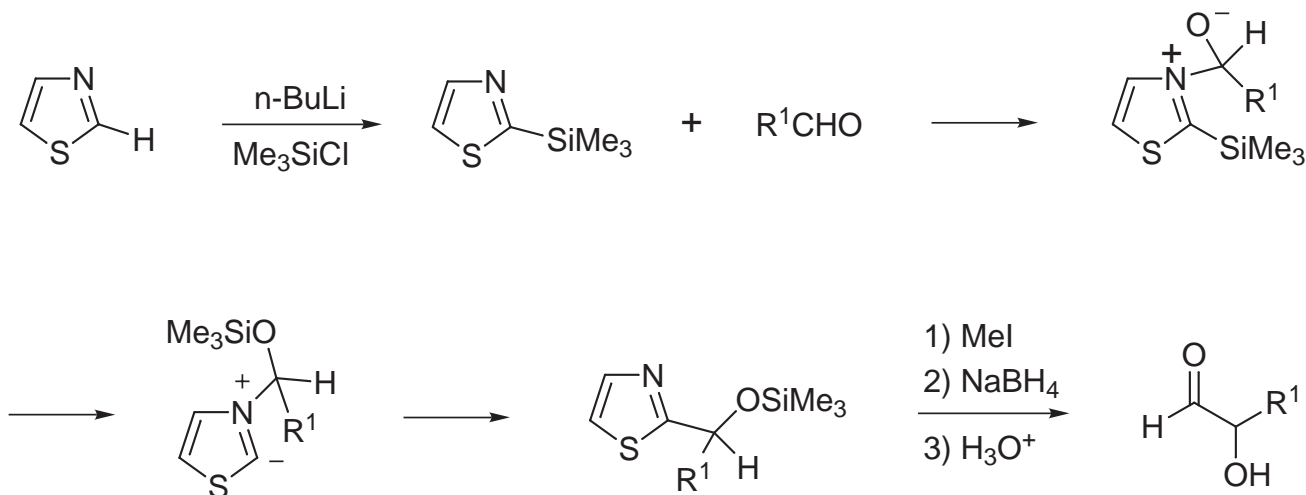
5-Substituted 3-furaldehydes



Lee, G. C. M.; Holmes, J. M.; Harcourt, D. A.; Garst, M. E. *J. Org. Chem.* **1992**, 57, 3126

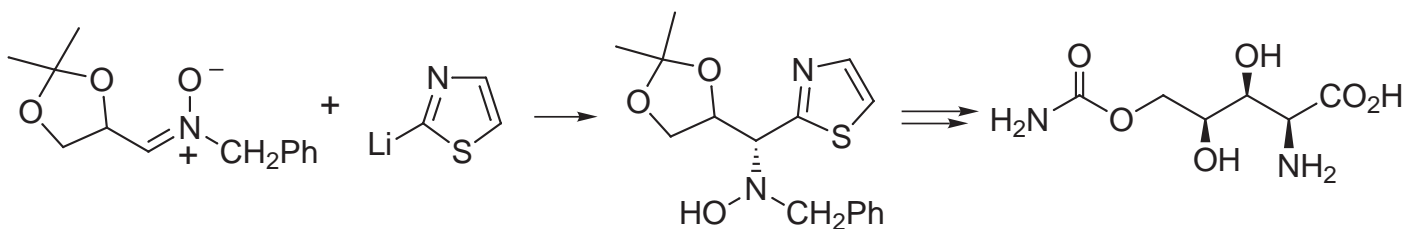
2-(Trimethylsilyl)thiazole as an effective source of formyl anion synthon

For some leading references, see: Dondoni, A.; Fautin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *J. Org. Chem.* **1988**, 53, 1748. Dondoni, A.; Fautin, G.; Fogagnolo, M.; Pedrini, P. *J. Org. Chem.* **1990**, 55, 1439



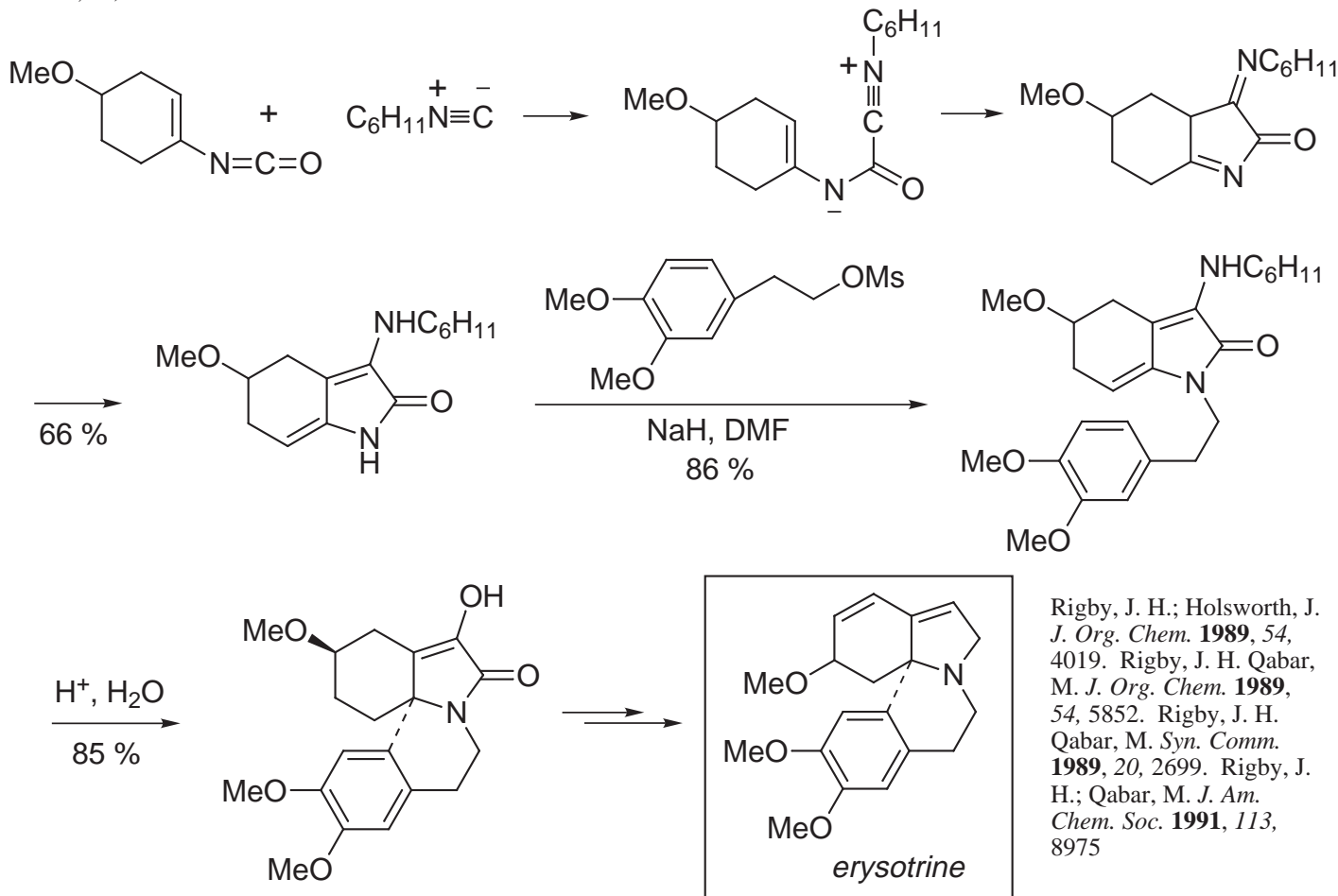
Synthesis of carbamoylpolyoxamic acid using 2-lithiothiazole addition to nitrones

Dondoni, A.; Franco, S.; Merchan, F. L.; Merino, P.; Tejero, T. *Tetrahedron Lett.* **1993**, 34, 5479

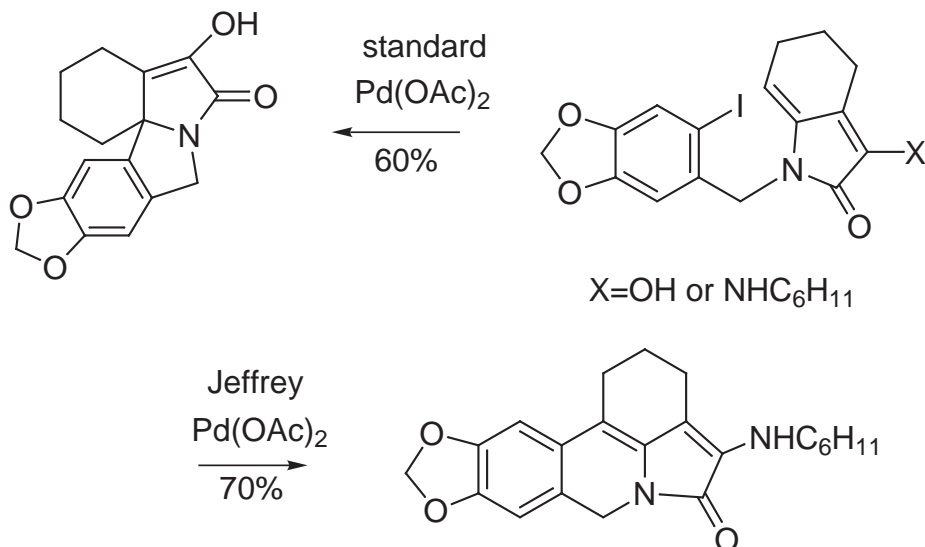


*[4+1]-Cycloaddition of vinyl isocyanates with alkyl isocyanides**Isocyanide as a 1,1-dipole*

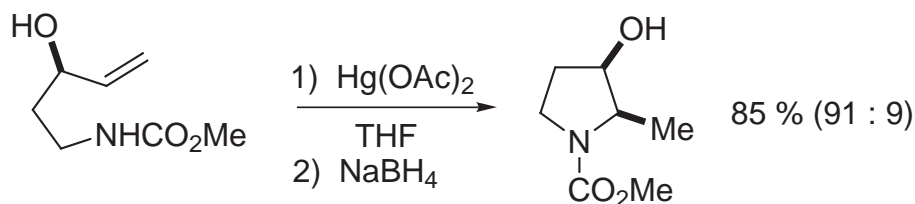
Rigby, J. H.; Hughes, R. C.; Heeg, M. J. *J. Am. Chem. Soc.* 1995, *117*, 7834. Rigby, J. H.; Balasubramanian, N. *J. Org. Chem.* **1984**, *49*, 4569. Rigby, J. H. Burkhardt, F. J. *J. Org. Chem.* **1986**, *51*, 1374. Rigby, J. H. Balasubramanian, N. *J. Org. Chem.* **1989**, *54*, 224.

*Subsequent Palladium Induced Cyclization*

Rigby, J. H.; Hughes, R. C.; Heeg, M. J. *J. Am. Chem. Soc.* 1995, *117*, 7834. Rigby, J. H.; Balasubramanian, N. *J. Org. Chem.* **1984**, *49*, 4569. Rigby, J. H. Burkhardt, F. J. *J. Org. Chem.* **1986**, *51*, 1374. Rigby, J. H. Balasubramanian, N. *J. Org. Chem.* **1989**, *54*, 224. Rigby, J. H.; Holsworth, J. *J. Org. Chem.* **1989**, *54*, 4019. Rigby, J. H. Qabar, M. *J. Org. Chem.* **1989**, *54*, 5852. Rigby, J. H. Qabar, M. *Syn. Comm.* **1989**, *20*, 2699. Rigby, J. H.; Qabar, M. *J. Am. Chem. Soc.* **1991**, *113*, 8975

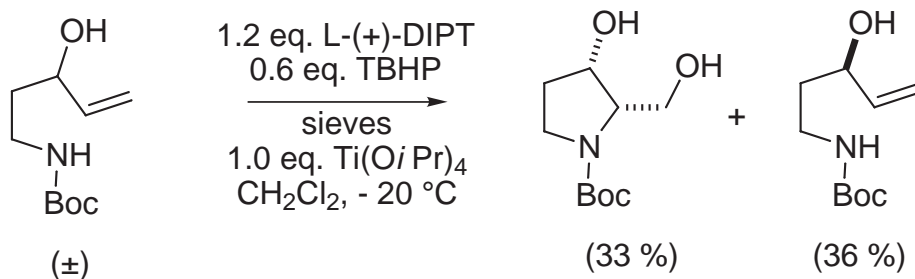


*Stereoselective amidomercuration of allylic alcohols
(Chamberlin Model-*vide supra*)*

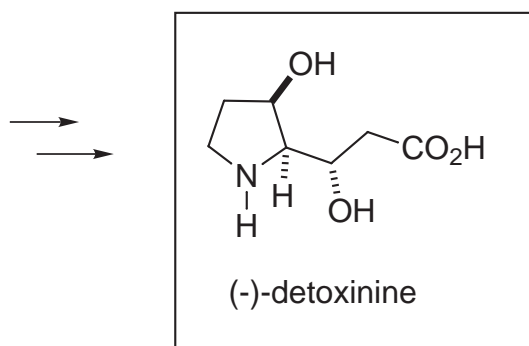
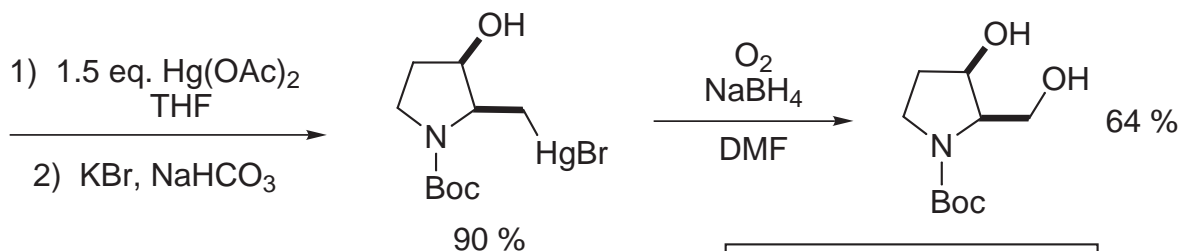


Tamaru, Y.; Hojo, M.; Yoshida, Z. *J. Org. Chem.* **1988**, *53*, 5731-5741.

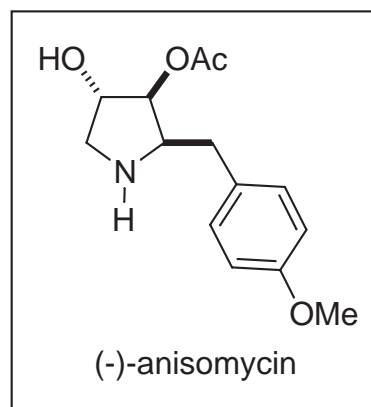
Chamberlin, A. R.; Dezube, M.; Dussault, P.; McMills, M. *J. Am. Chem. Soc.* **1983**, *105*, 5819. Labelle, M.; Guindon, Y. *J. Am. Chem. Soc.* **1989**, *111*, 2204-2210. Chamberlin, A. R.; Mulholland, R. L., Jr.; Kahn, S. E.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 672. Reitz, A. B.; Nortey, S. O.; Maryanoff, B. E.; Liotta, D.; Monahan, R., III *J. Org. Chem.* **1987**, *52*, 4191-4202. Houk, K. N.; Moses, S. R.; Wy, Y.-D.; Rondan, N. G.; Jager, V.; Schoehe, R.; Fronczek, F. R. *J. Am. Chem. Soc.* **1984**, *106*, 3880.



Takahata, H.; Banba, Y.; Tajima, M.; Momose, T. *J. Org. Chem.* **1991**, *56*, 240-245.

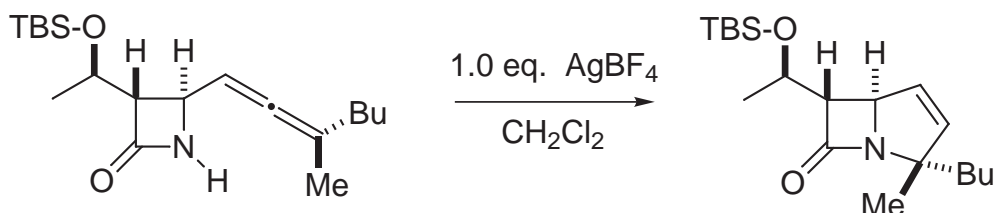


and



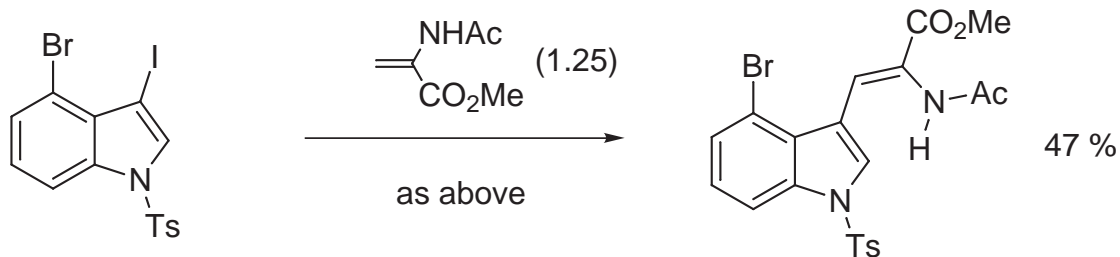
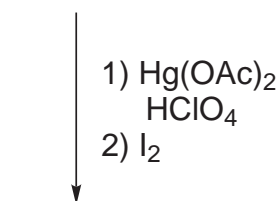
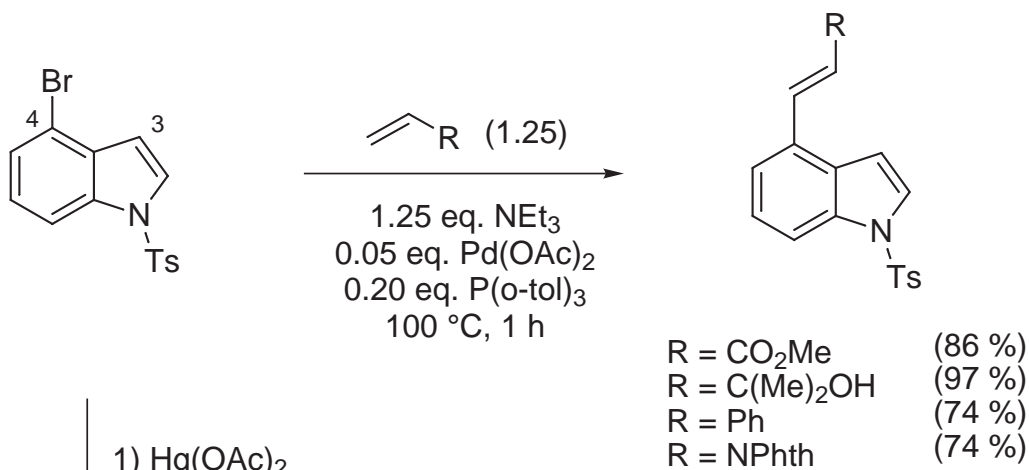
Silver Induced Cycloamidation of Alkenes

Prasad, J. S.; Liebeskind, L. S. *Tetrahedron Lett.* **1988**, *29*, 4253-4256.

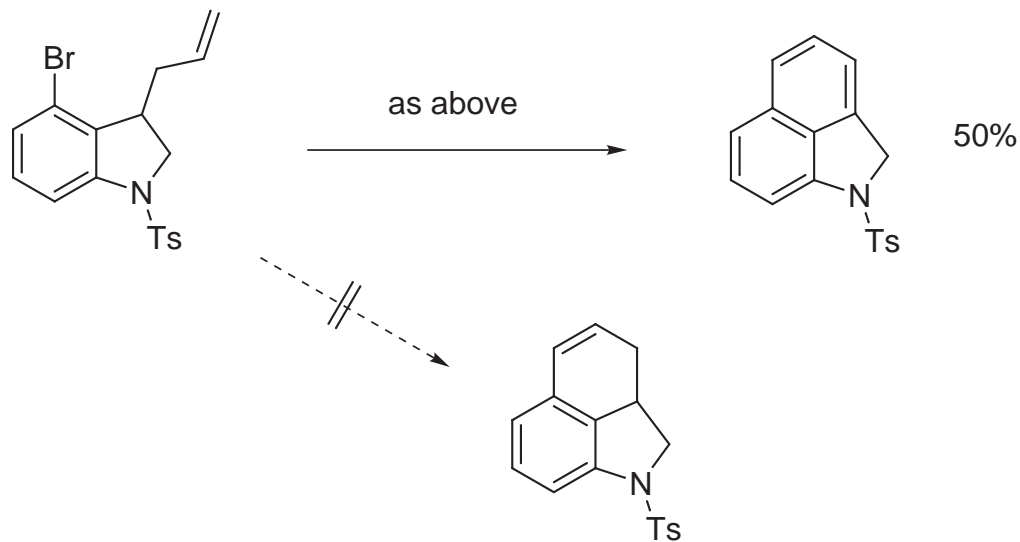


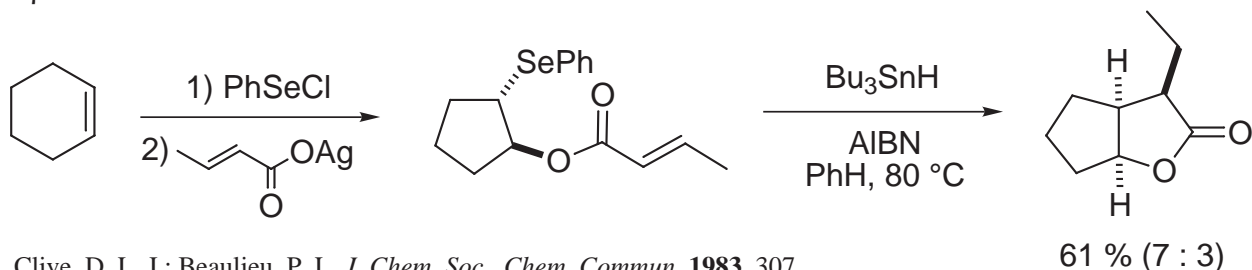
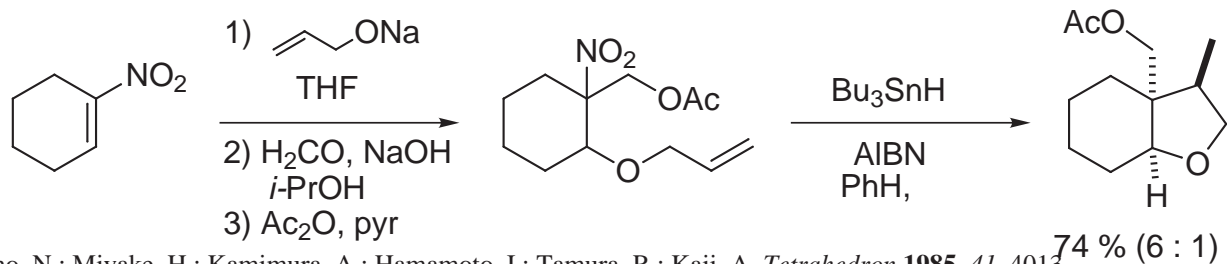
Examples of intermolecular Heck-reactions for heterocycle modification

Modification of indoles at C-4 and C-3

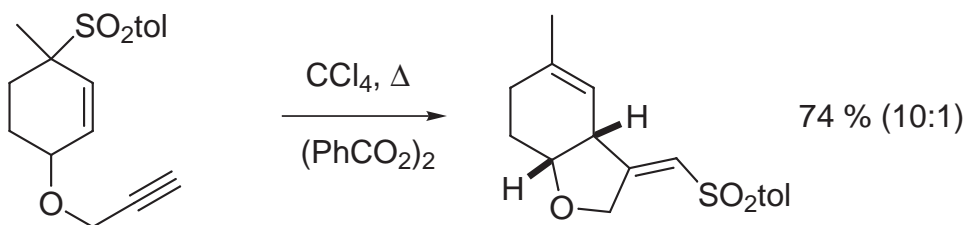


Harrington, P. J.; Hegedus, L. S. *J. Org. Chem.* **1984**, *49*, 2657-2662.

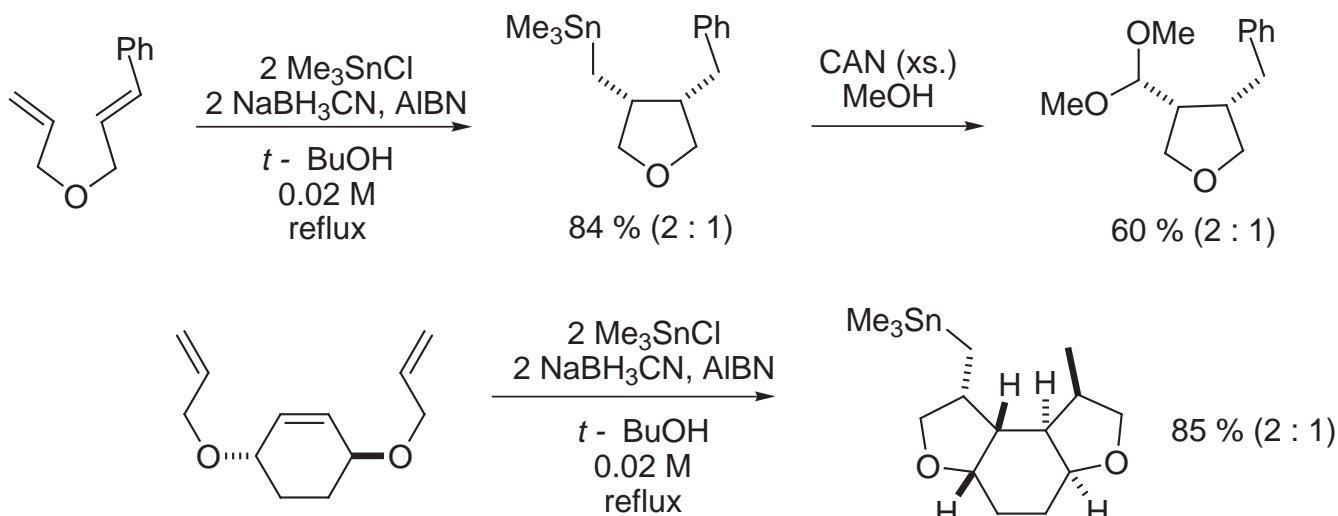


β -Selenoethers β -Nitroethers

Cleavage of allylic sulfones



Stannyl radical addition



(Oxidation: 54%)