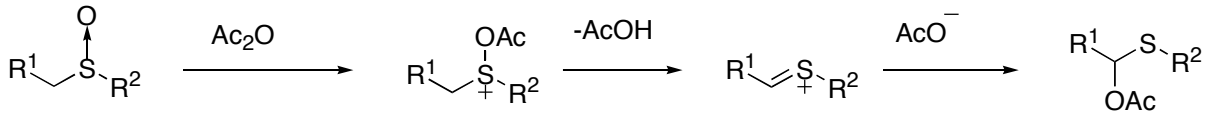
A Fluorous-Phase Pummerer Cyclative-Capture Strategy for the Synthesis of Nitrogen Heterocycles

D. J. Procter et al

Angew. Chem. Int. Ed. **2005**, *44*, 452-455.

Claire Coleman Current Lit Jan 15 2005

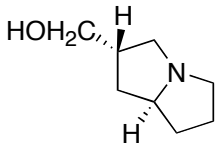
The Pummerer Reaction



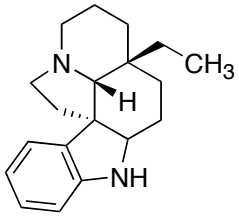
- Thionium ion intermediates are useful electrophiles
- Inter- and intramolecular reaction examples are widespread
- Heteroatom and carbon nucleophiles have been used
- Natural products and heterocycles

Pummerer, R. *Chem. Ber*. **1909**, *42*, 2282.

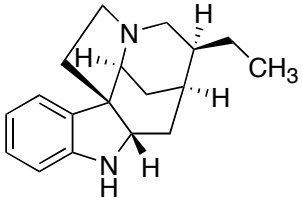
The Pummerer Reaction has been used to make Nitrogen Containing Molecules



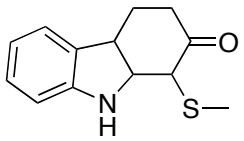
Trachelanthamidine

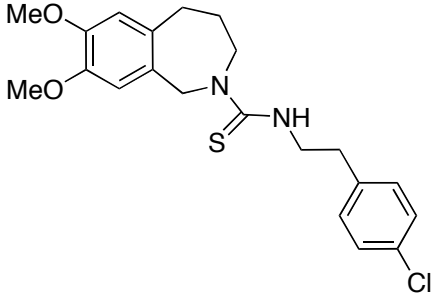


dl-Aspidospermidine

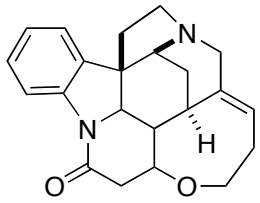


Tubifolidine



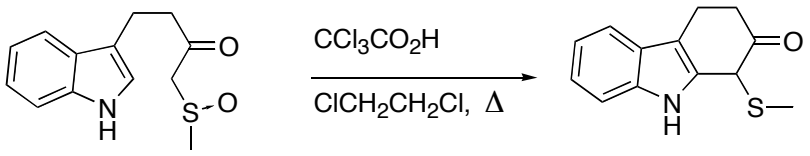


Capsazepine

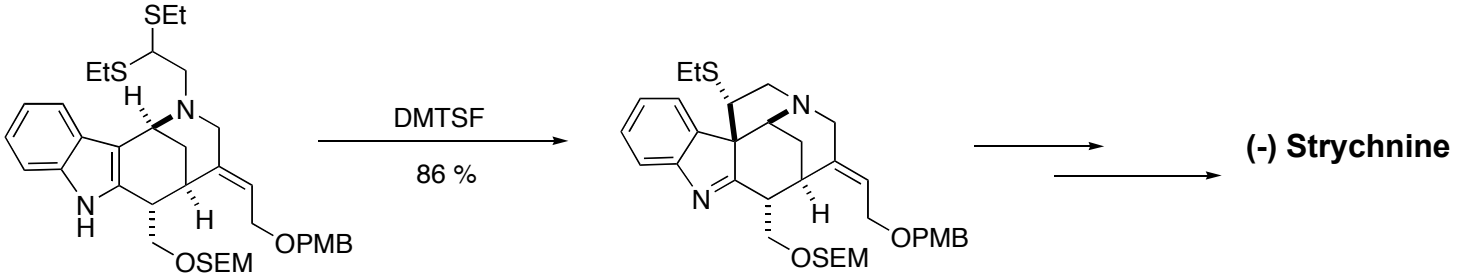


(-)-Strychnine

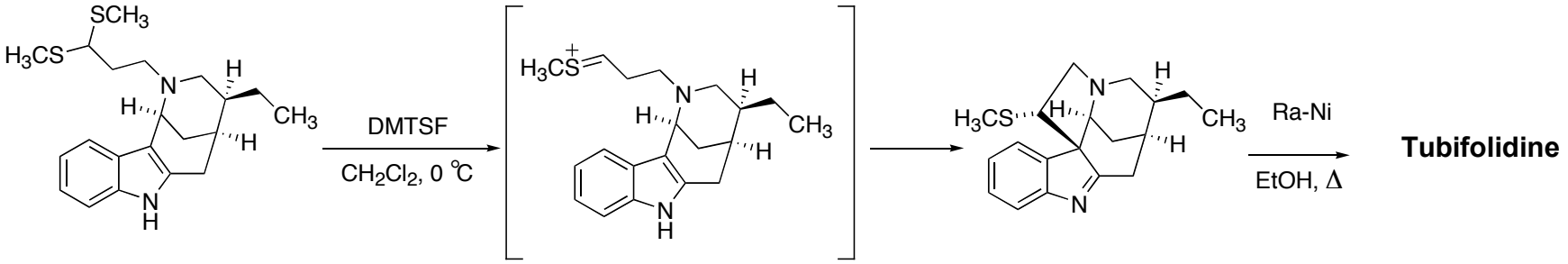
The Pummerer Reaction has been used to make Nitrogen Containing Molecules contd.



• Refunctionalisation of existing heterocyclic rings: *J. Org. Chem*. **1976**, *41*, 1118.

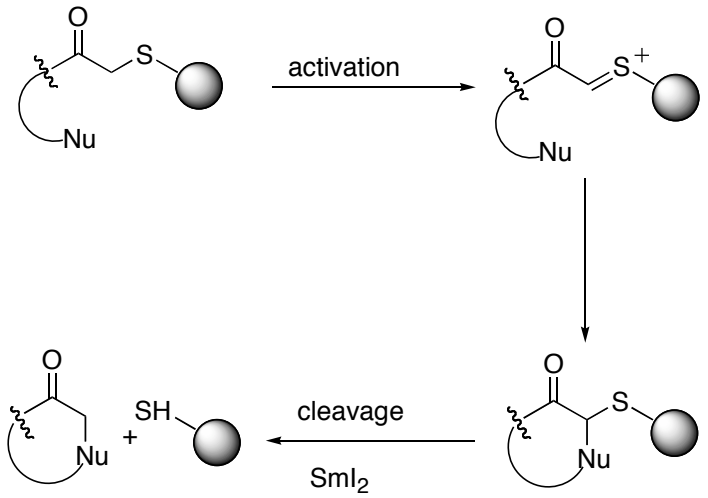


•Shibasaki employed a variation on the Magnus approach to form the pyrrolidine ring. *JACS*, **2002**, *124*, 14546.



• Bosch and co-workers; *J. Org. Chem*, **1990**, *55*, 6299. *J. Org. Chem*, **1992**, *57*, 5792.

Procters' Solid Phase Approach to Oxindoles (First Pummerer Cyclisations on Solid Phase)

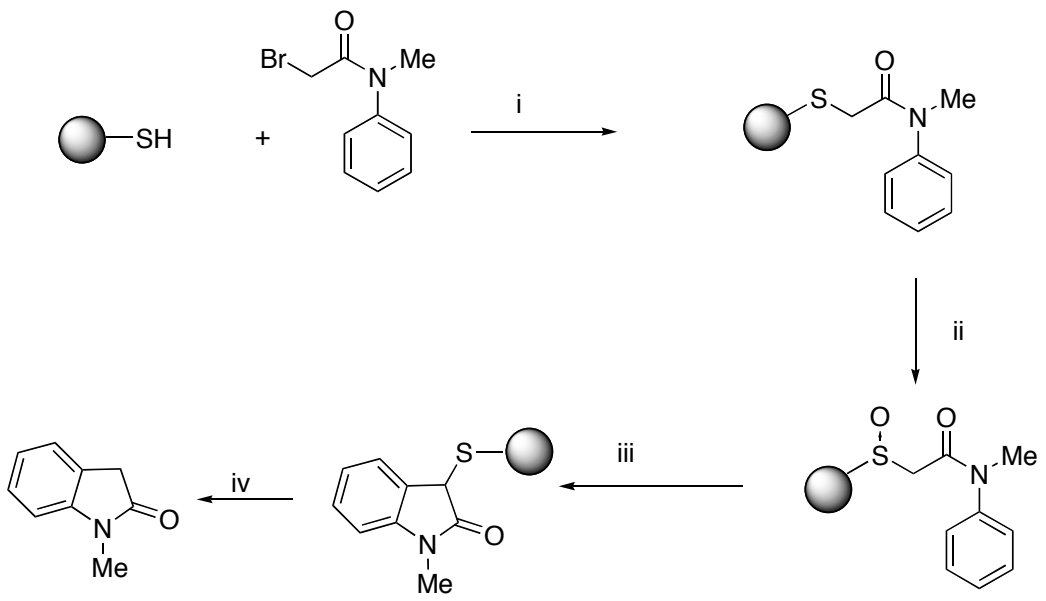


•α-Sulfanyl carbonyl compounds bearing tethered nucleophilic groups undergo cyclisation *via* the formation of reactive sulfonium ions

•**Aim** : Oxidation of sulfur in α sulfanyl *N*-aryl acetamides, attached to resin *via* the sulfur atom, followed by sulfonium ion formation to trigger cyclisation

Procter *et al*., *Chem*. *Comm*. **2003**, 2380.

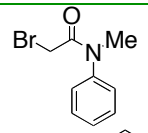
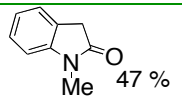
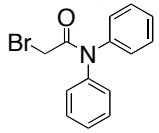
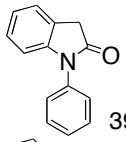
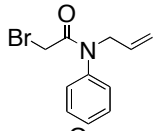
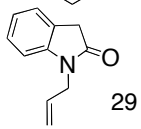
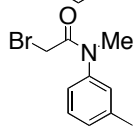
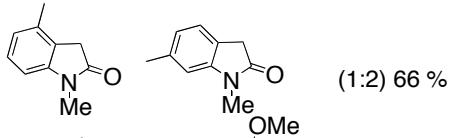
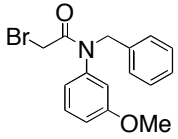
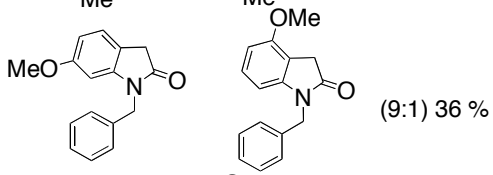
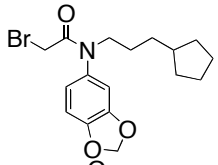
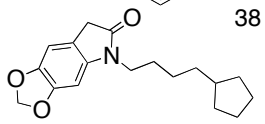
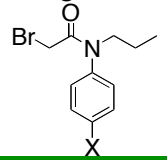
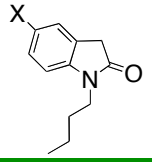
Procters' Solid Phase Approach to Oxindoles



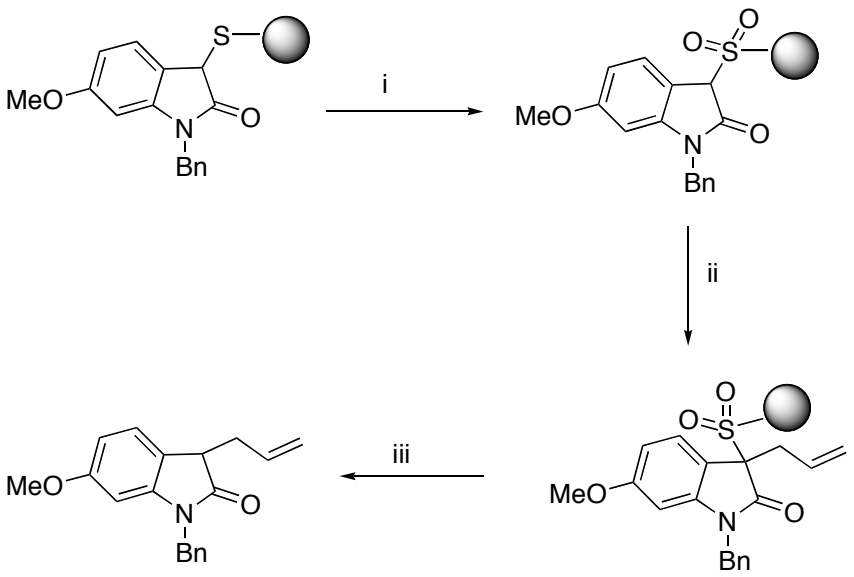
Reagents and conditions: i, NEt_3, DMF, rt; ii, HFIP–CH_2Cl_2(2 : 1), H_2O_2, rt; iii, TFAA, $BF_3{\cdot}OEt_2$, 1,2-dichloroethane, rt; iv, SmI_2, DMPU, THF, rt, 47% isolated yield after four steps on resin

cleavage conditions: Procter *et al*., *Chem. Comm*., **2002**, 584.

By Varying the α-Bromoamide used, a range of Oxindoles were prepared

Entry	Amide	Oxindole
1		 47 %
2		 39%
3		 29 %
4		 (1:2) 66 %
5		 (9:1) 36 %
6		 38 %
7		 X = I , 22 % X = Cl, 41%

As the Sulfur link remains intact after the Pummerer Cyclisation, further synthetic steps on resin allow access to more functionalised oxindoles



Reagents and conditions: i, oxone, DMF–H_2O (4 : 1), rt; ii, K_2CO_3, KI, allyl bromide, DMF, 60 °C; iii, SmI_2, DMPU, THF, rt, 30% overall yield for six steps on resin.

Advantages and Disadvantages of the Solid Phase Approach

Advantages

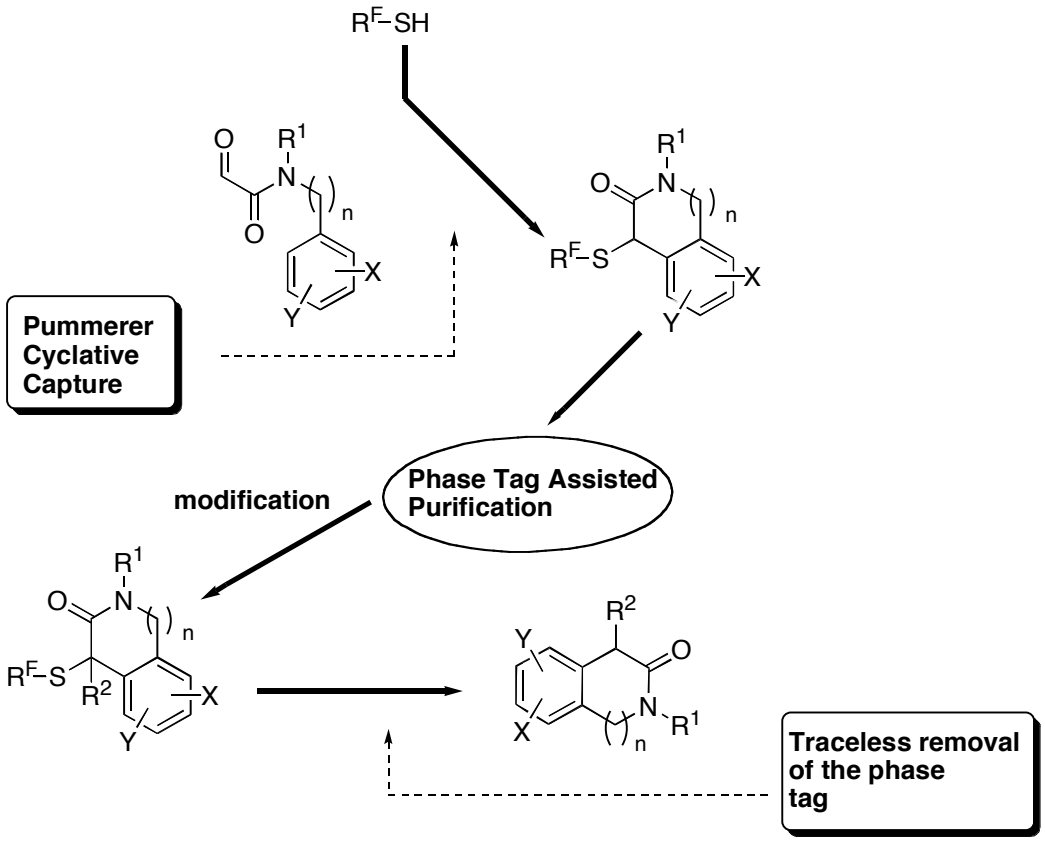
- As sulfur link remains intact after the Pummerer cyclisation
  -further elaboration of oxindole is possible
- Possible automation for library synthesis
  - Traceless cleavage

Disadvantages

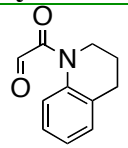
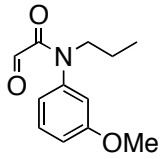
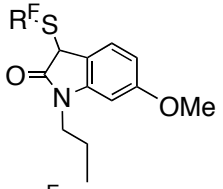
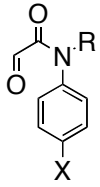
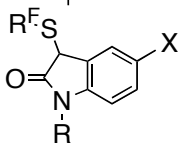
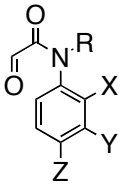
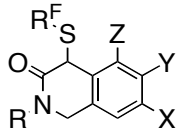
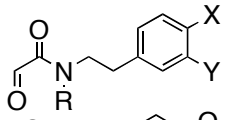
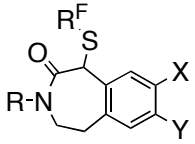
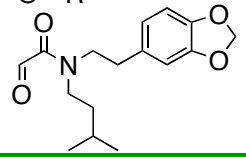
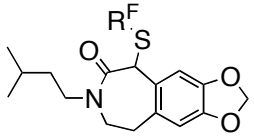
- Reaction optimization time
- Reaction monitoring
- Attachment/removal of linker

Procters' Fluorous –Phase Pummerer Cyclative-Capture Approach to *N*-Heterocycles

R^F-SH = $C_8F_{17}CH_2CH_2SH$



Advantages: • Easy to monitor
• Phase tag purification at each step (excess reagents can be used)
• Traceless cleavage using mild electron transfer conditions

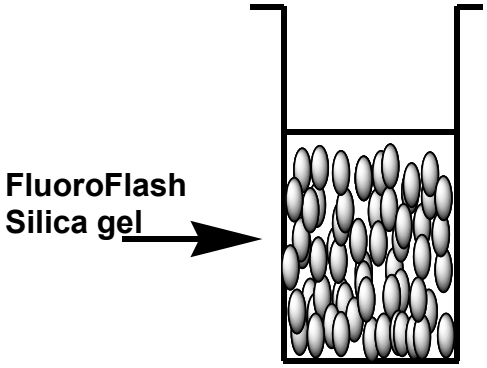
Entry	Glyoxamide	Tagged Heterocycle	Yield
1			65
2			75 (isomer ratio 5:1)
3 X = Cl, R = Me **4** X = Br, R = *n*Pr **5** X = F, R = Me			79 85 80
6 X,Y,Z = H, R = Me **7** X = OMe, Y,Z = H, R = *n*Pr **8** X, Y, Z = OMe, R = *n*-pentyl			45 51 (isomer ratio ~1:1) 60
9 X = H, Y = OMe, R = *n*Pr **10** X = Y= OMe, R = *n*-pentyl			76 (isomer ratio ~2:1) 98
11			82

Conditions: $C_8F_{17}CH_2CH_2SH$, CH_2Cl_2, 18 h, then trifluoroacetic acetic anhydride, 1 h, then $BF_3 \bullet OEt_2$, 1h. FSPE

Fluorous Solid Phase Extraction

*Fluoro*flash silica gel has a bonded phase of Si-$(CH_3)_2CH_2CH_2$ C_8F_{17}

Fluorous molecules such as R-C_8F_{17} can be easily separated from nonfluorous molecules by FSPE

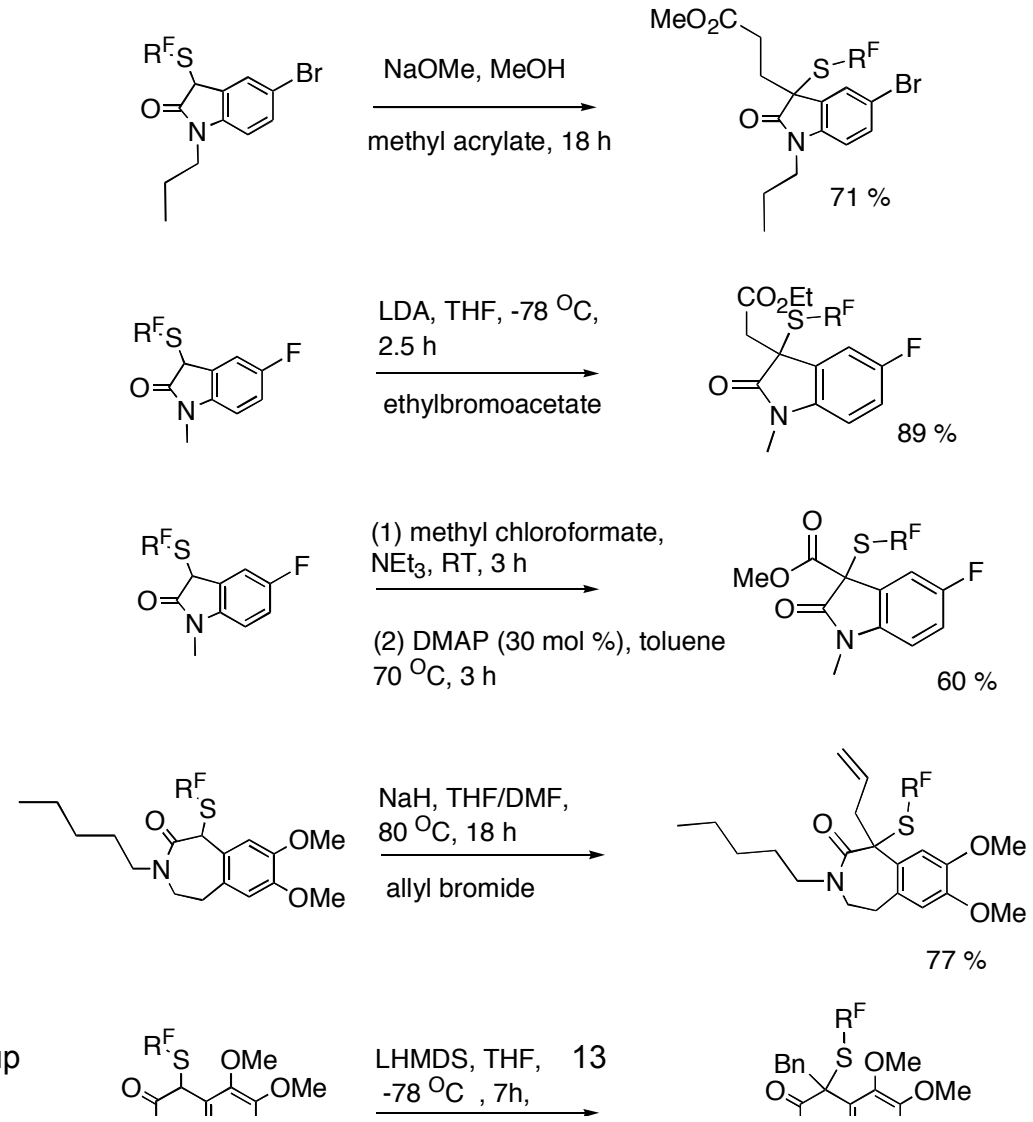


A crude reaction mixture is loaded onto the SPE cartridge with a minimum amount of organic solvent

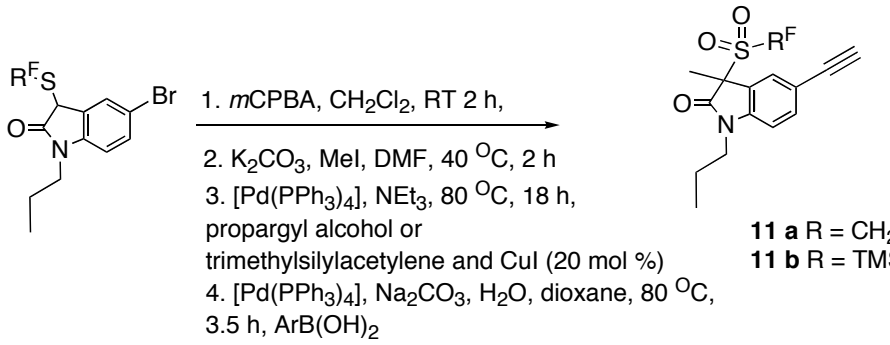
The cartridge is then eluted with a fluorophobic solvent such as 80:20 MeOH/H_2O for the nonfluorous compounds followed by a more fluorophilic solvent such as MeOH, acetone, acetonitrile or THF for fluorous compounds

The cartridge can be reused

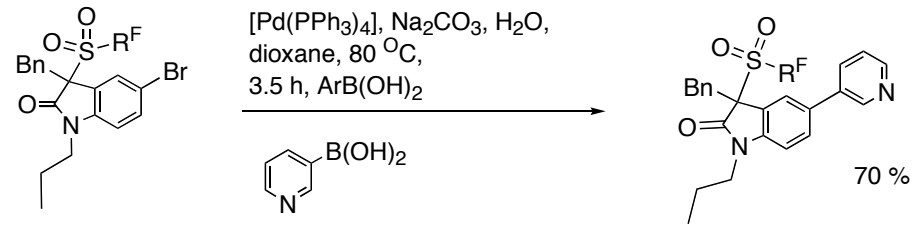
Manipulation of Fluorous Tagged Heterocycles-Modifications α □□ S□□□□□

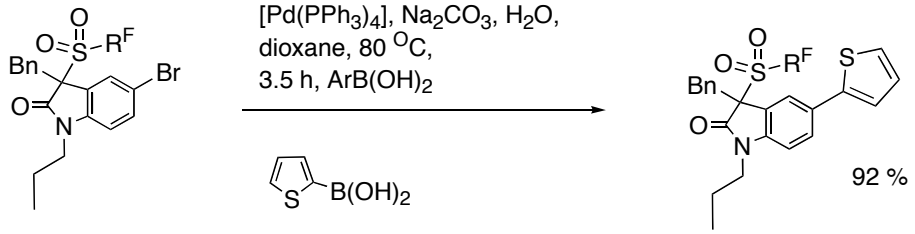


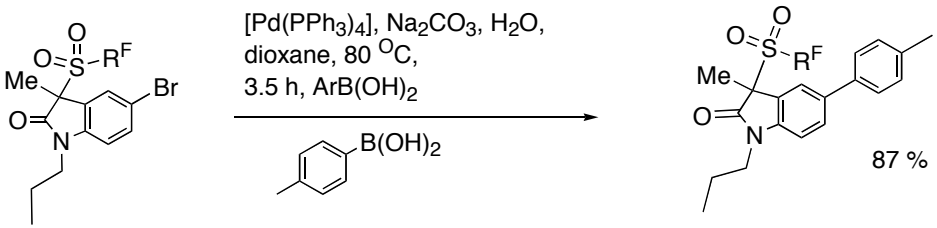
Manipulations of Fluorous-tagged Heterocycles-Pd-catalysed Modifications



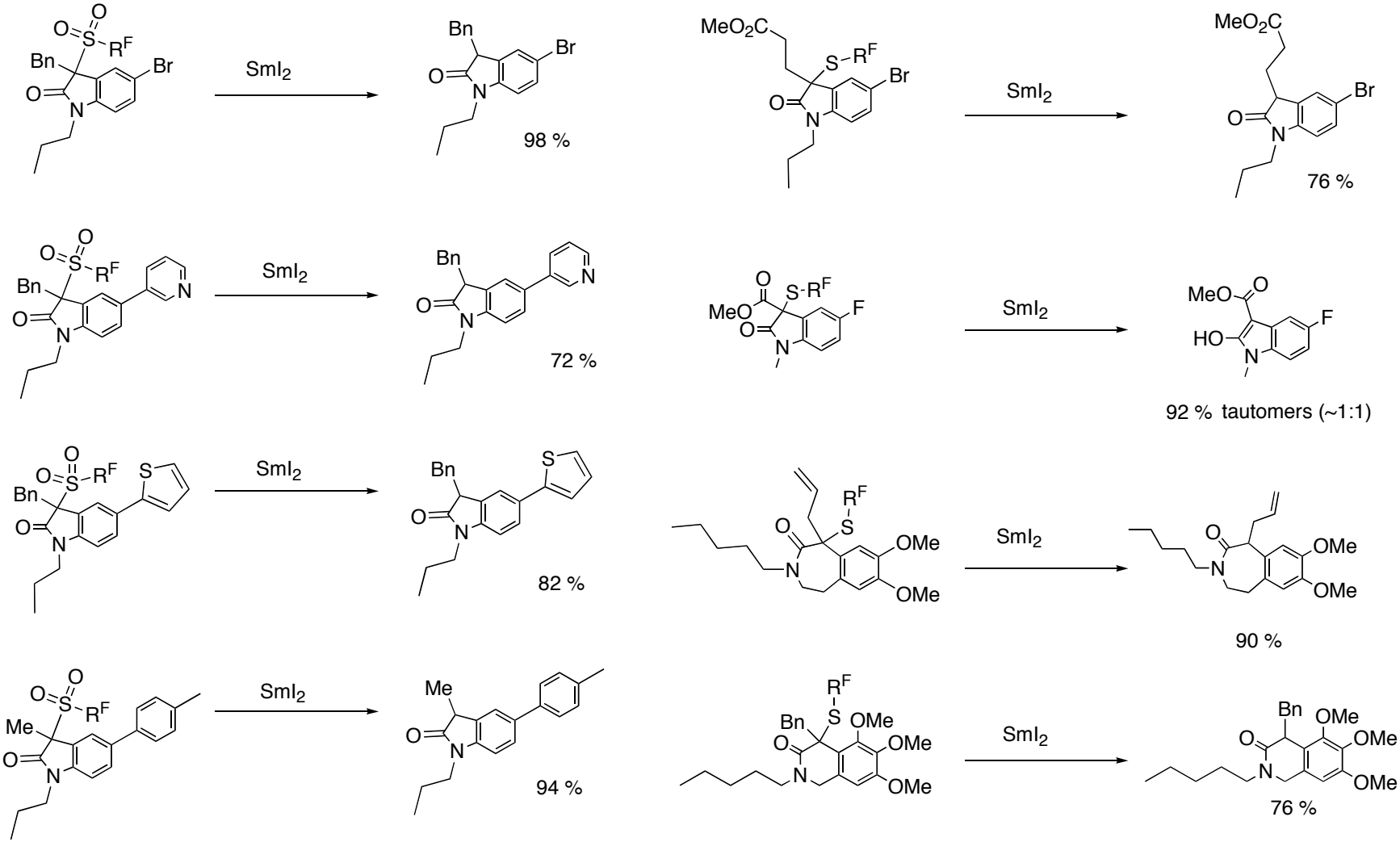
11 a R = CH_2OH, 44 % overall yield
11 b R = TMS, 60 % overall yield







Products of Reductive, Traceless Cleavage of the Fluorous Tag



Conclusions

Development of a new strategy for the fluorous phase synthesis of *N*-Heterocycles

First example of a fluorous-phase cyclative capture

Modification of the scaffold including Pd catalysed cross coupling reactions

Traceless reductive removal of the fluorous phase tag

Further Work

Solution phase Combinatorial Libraries

Further elaboration of the scaffold

For reviews on use of the Pummerer reaction in heterocyclic synthesis:

Chem. Rev. **2004**, *104*, 2401-2432.
Current Organic Chemistry, **2000**, *4*, 175-203.
Synthesis, **1997**, 1353.