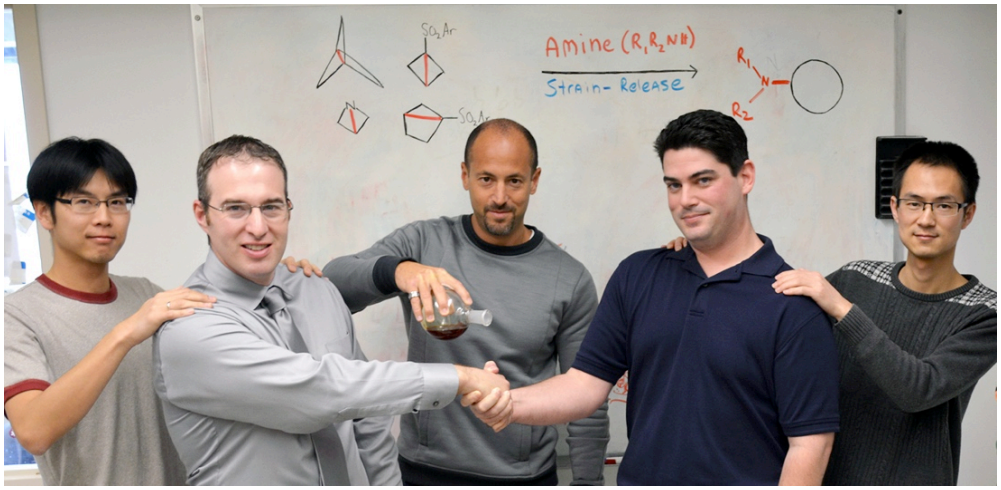
Strain-release amination



Gianatassio, R.; Lopchuk, J. M.; Wang, J.; Pan, C-M.; Malins, L. R.; Prieto, L.; Brandt, T. A.; Collins, M. R.; Gallego, G. M.; Sach, N. W.; Spangler, J. E.; Zhu, H.; Zhu, J.; Baran, P. S.

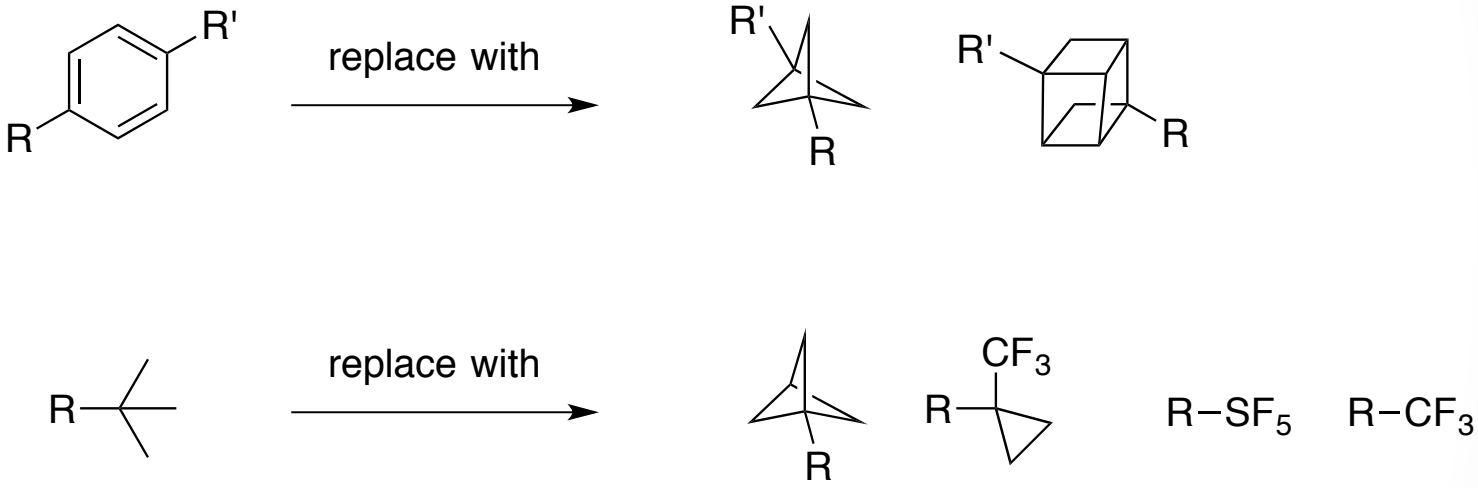
Science **2016**, *351*, 241-246

John Milligan

Current Literature

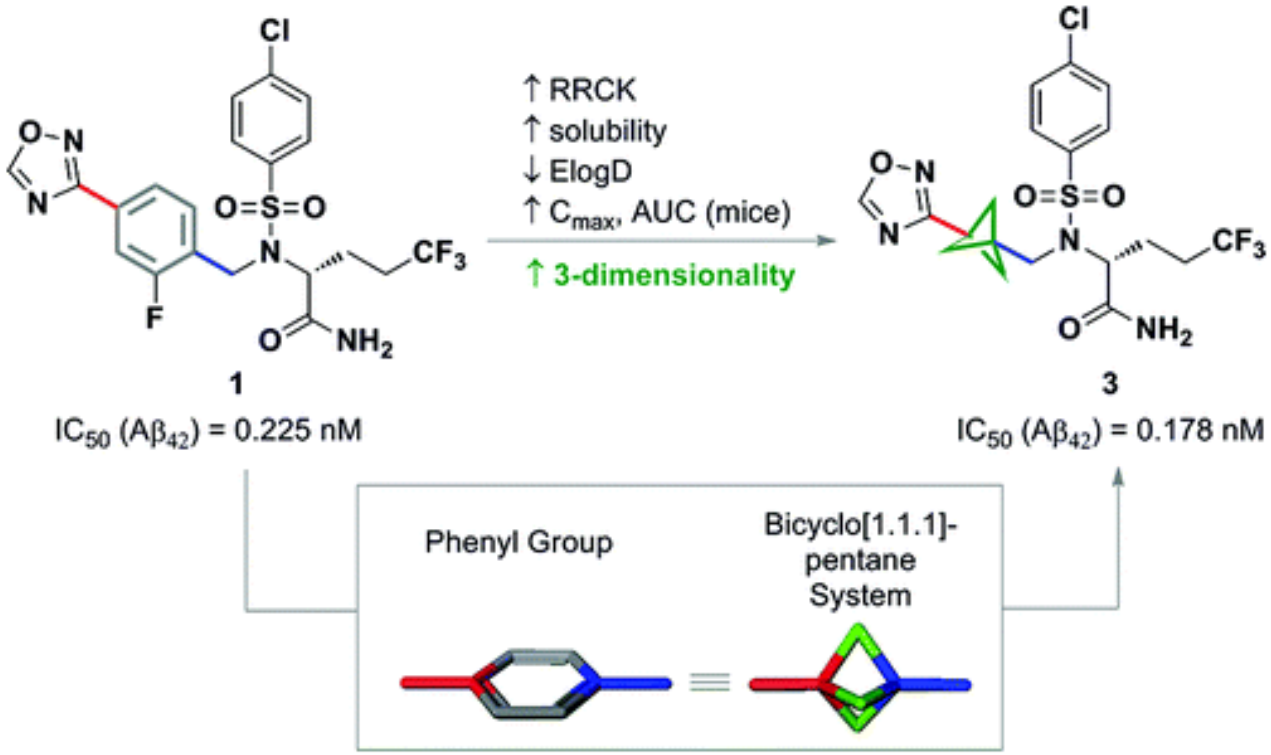
Wipf Group Meeting- February 13, 2016

Bioisosteres of *t*-butyl or phenyl



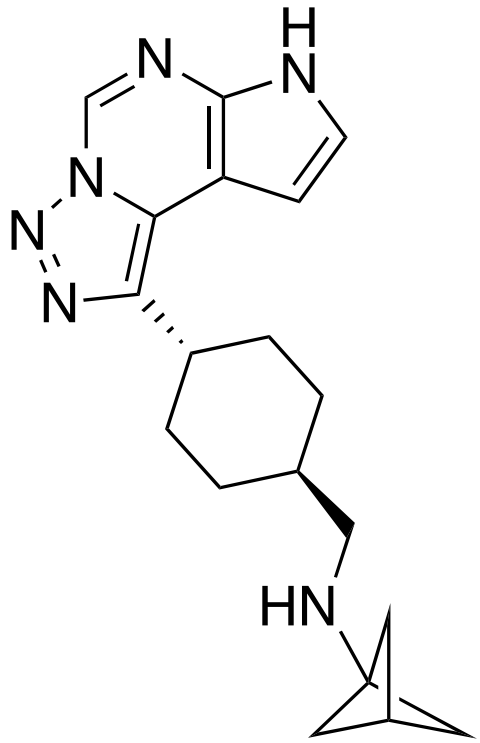
Meanwell, N. A. *J. Med. Chem.* **2011**, *54*, 2529-2591
Westphal, M. V.; Wolfstädter, B. T.; Plancher, J-M.; Gatfield, J.; Carreira, E. M. *ChemMedChem* **2015**, *10*, 461-469

Bicyclo[1.1.1] pentane as a Ph Bioisostere



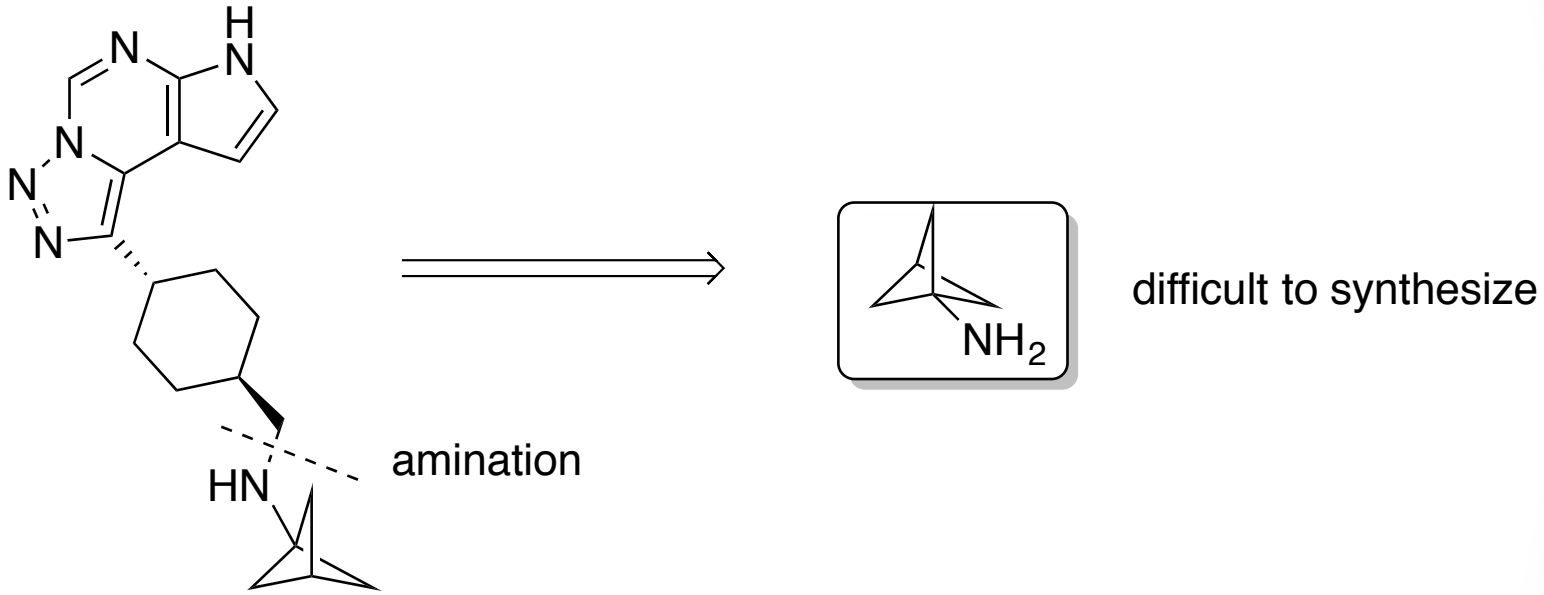
Stephan, A. F.; et al. *J. Med. Chem.* **2012**, *55*, 3414-3424

JAK inhibitor (Pfizer)

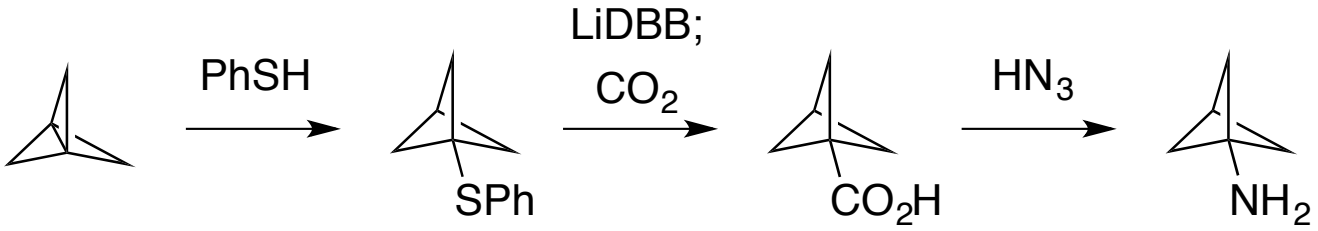


Hayashi, K. et al. PCT Int. Appl. WO2013024895 (**2013**)

JAK inhibitor (Pfizer)



Original synthesis of amine



Weiberg, K. B.; Waddell, S. T. *J. Am. Chem. Soc.* **1990**, *112,* 2194-2216

Other approaches

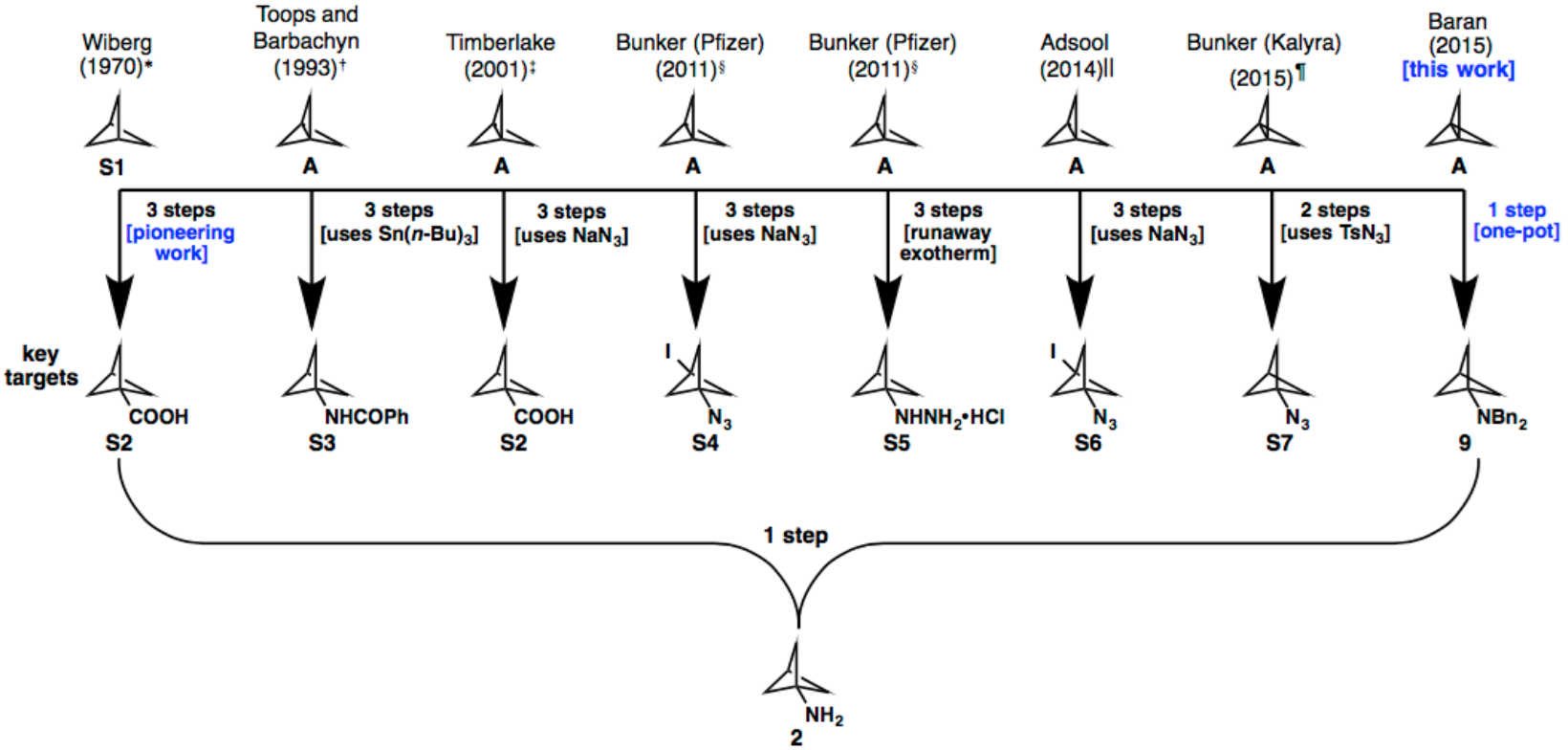
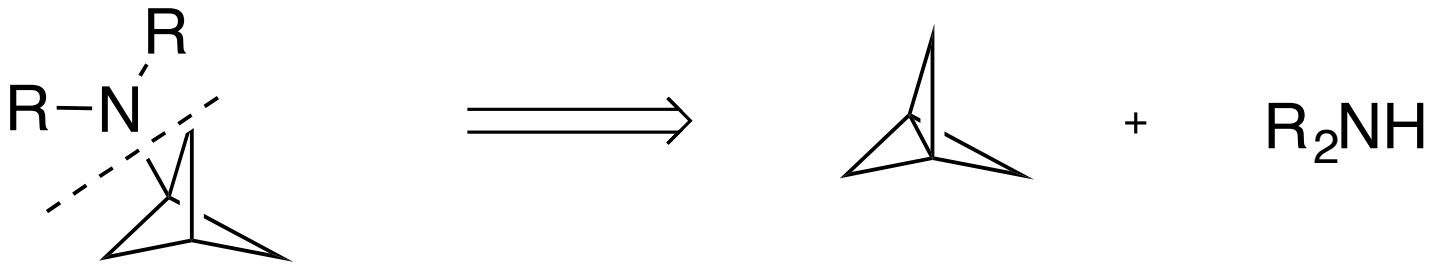


Fig. S1. Timeline of the synthetic approaches toward bicyclo[1.1.1]pentan-1-amine **(2)**. *See reference *(7)*. †See reference *(39)*. ‡See reference *(40)*. §See reference *(10)*. §See reference *(10)*. ||See reference *(41)*. ¶See reference *(42)*.

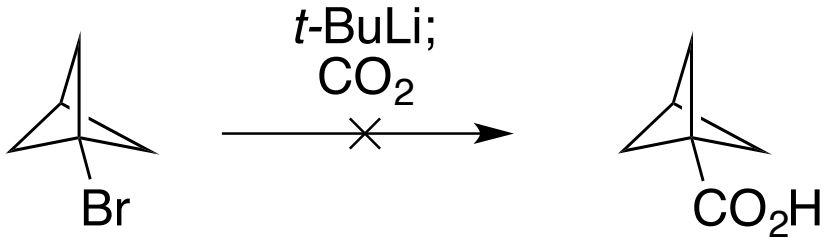
Baran et al.'s proposal



"strain release amination"

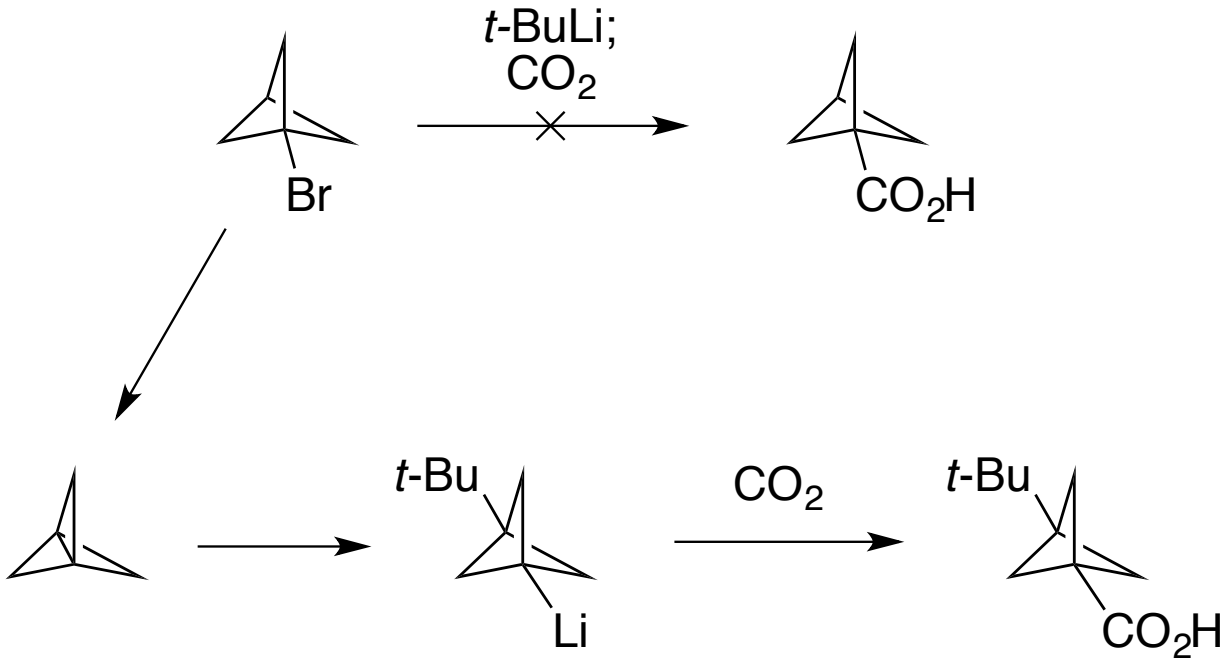
general method for installing this motif!

Precedence for propellane opening



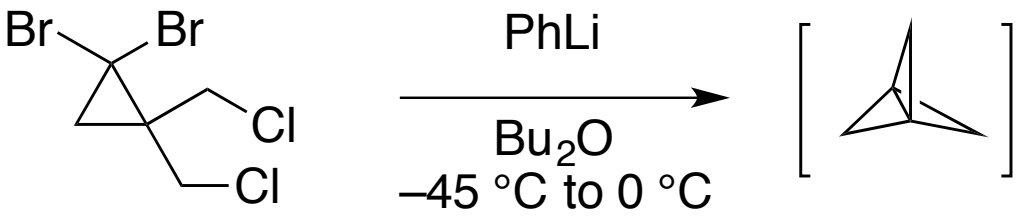
Della, E. W.; Taylor, D. K.; Tsanakisidis, J. *Tetrahedron Lett.* **1990**, *31,* 5219-5220

Precedence for propellane opening



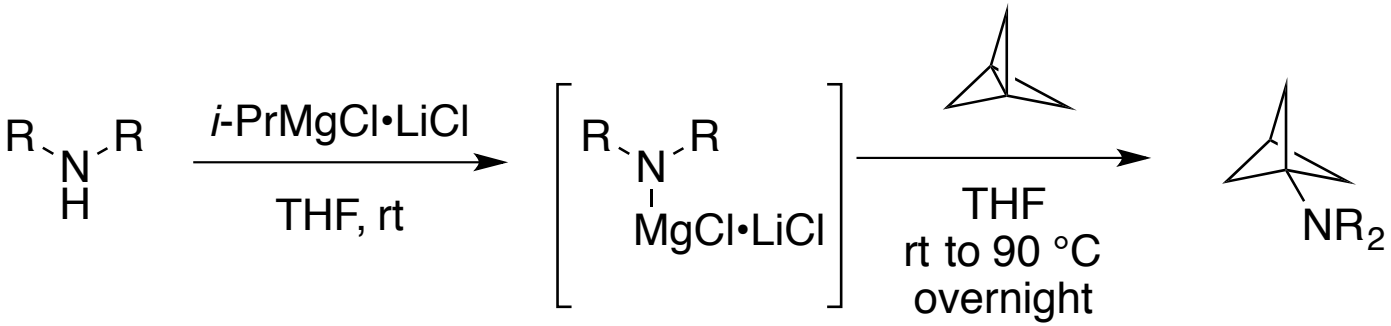
Della, E. W.; Taylor, D. K.; Tsanakisidis, J. *Tetrahedron Lett.* **1990**, *31,* 5219-5220

Preparation of propellane

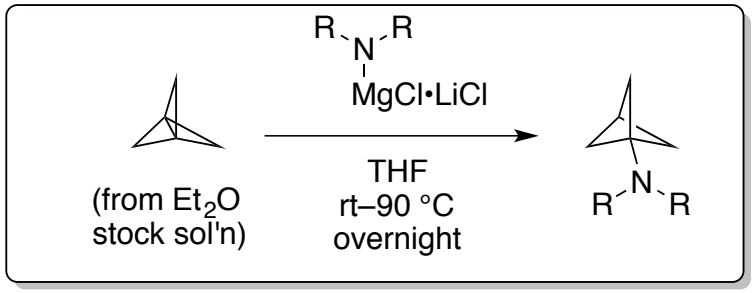


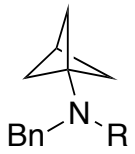
can be stored as a stock solution

Amine addition

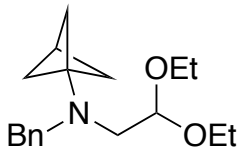


Results





R = Bn, 62%
R = Me, 48%
R = Et, 64%
R = *i*-Bu, 72%



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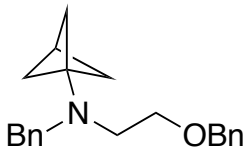

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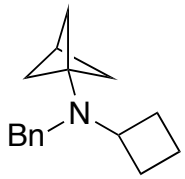

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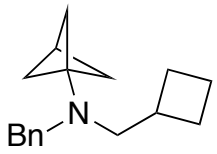

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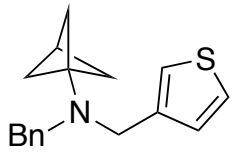
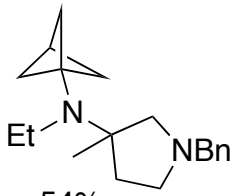


74%



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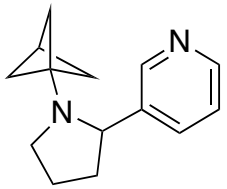

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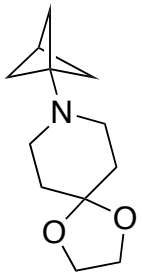

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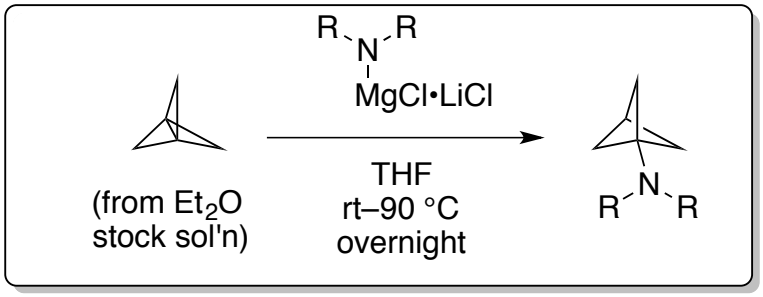
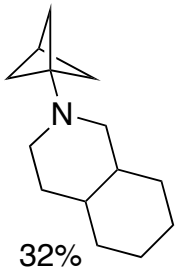
Results





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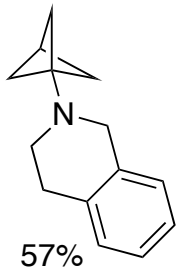

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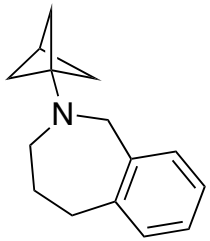

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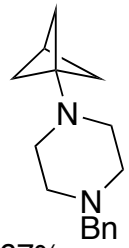

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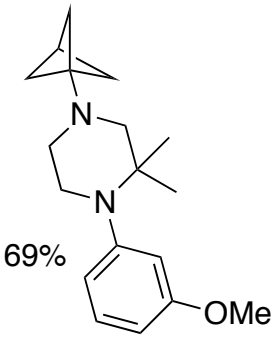

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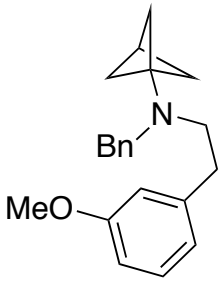

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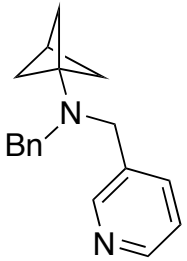

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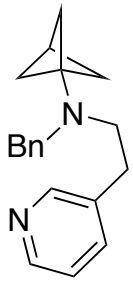

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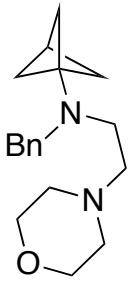

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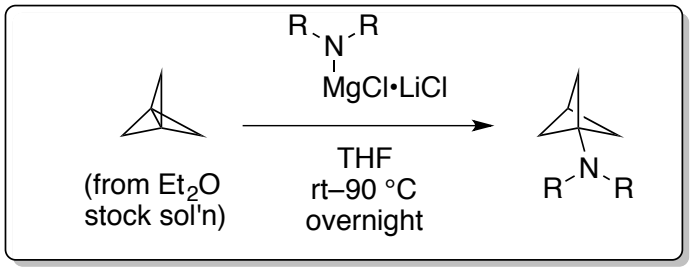
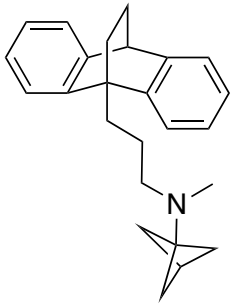
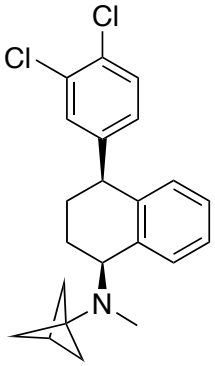
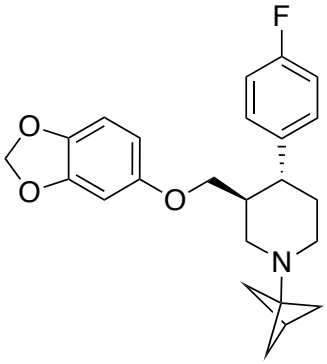




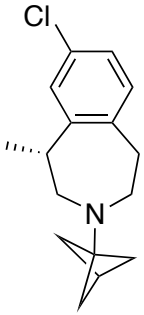
"propellerized"
maprotilline
80%



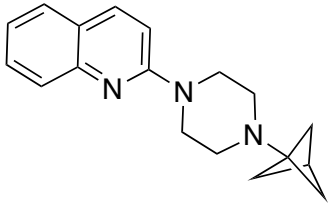
"propellerized"
sertraline
62%



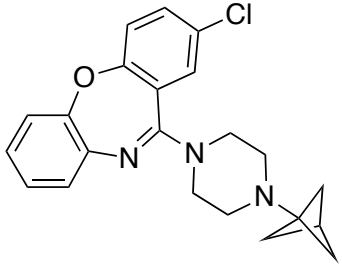
"propellerized"
maprotilline
67%



"propellerized"
lorcaserin
84%

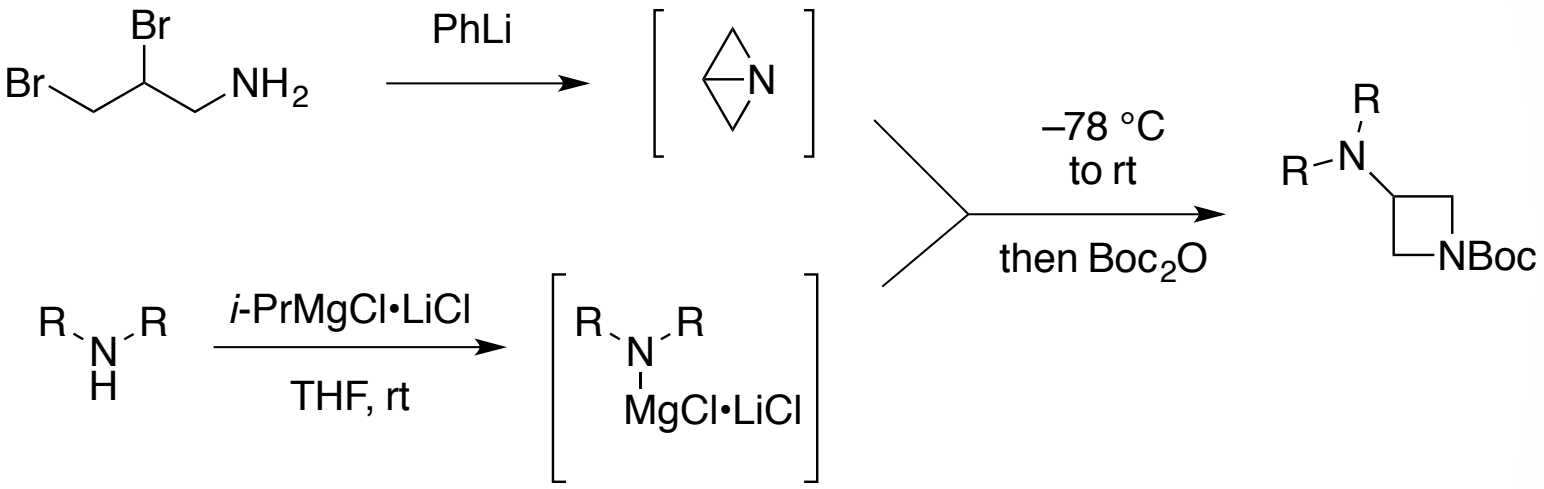


"propellerized"
quipazine
81%

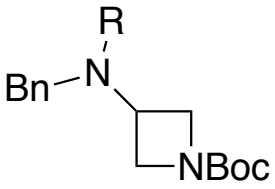


"propellerized"
amoxapine
31%

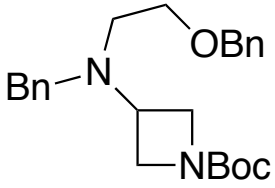
Azetidine formation



Azetidine formation: results



R = Me, 46%
R = Et, 44%
R = *i*Bu, 42%



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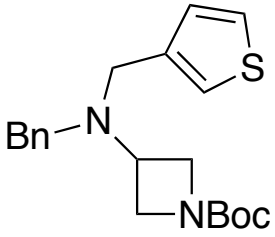

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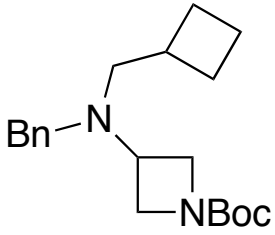
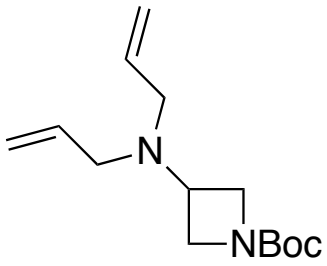


50%



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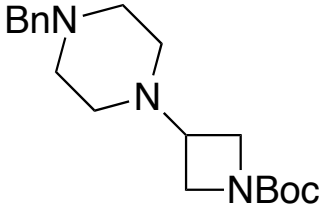

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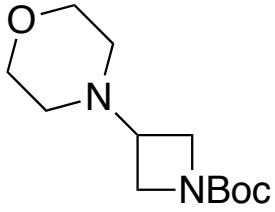
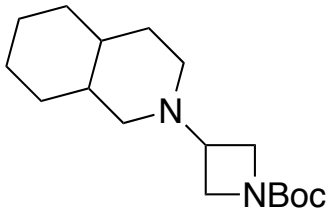


58%

Azetidine formation: results



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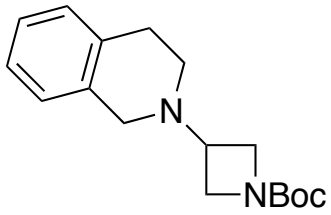
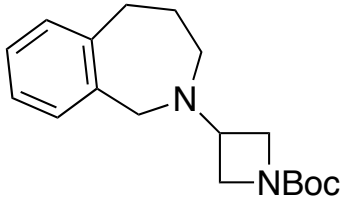


55%



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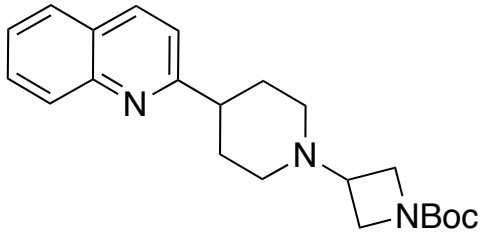
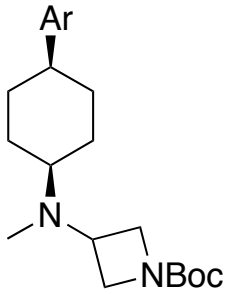
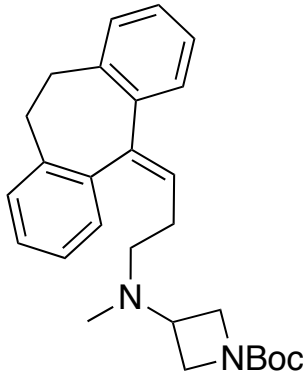


"azetidinylated"
quipazine
51%



"azetidinylated"
sertraline
45%



"azetidinylated"
nortriptyline
45%

Bicyclobutane formation

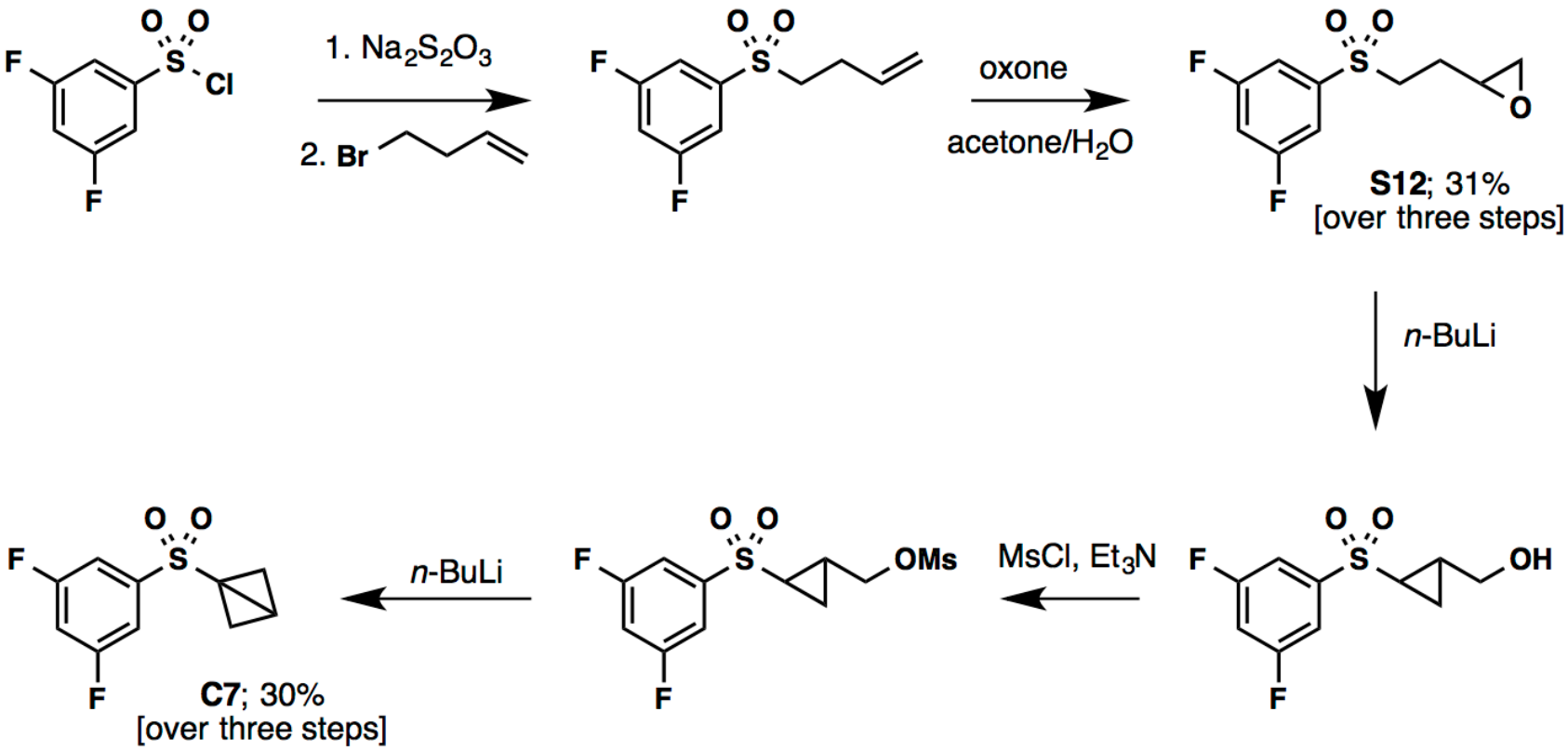
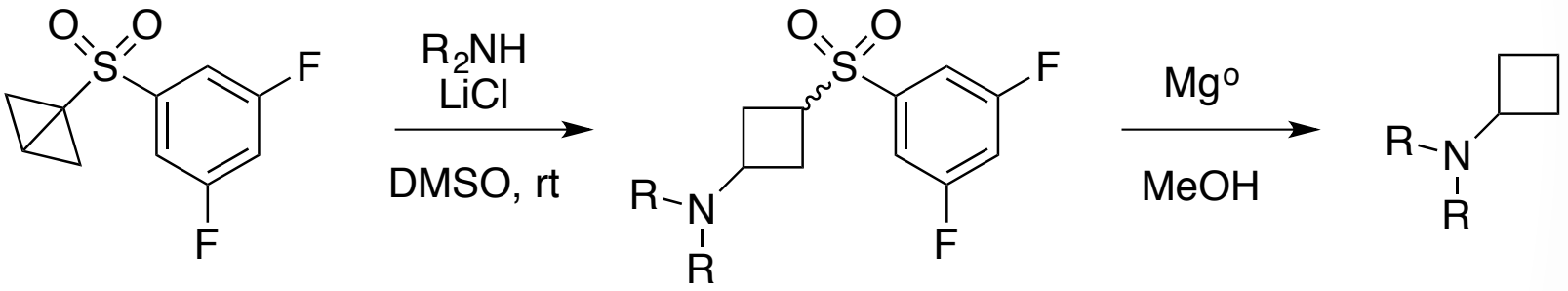


Fig. S27. Overall scheme for the synthesis of **C7**

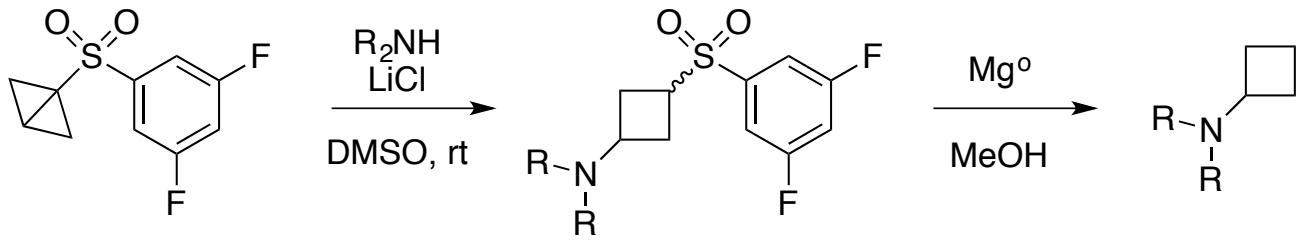
Bicyclobutane addition

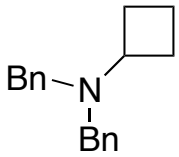
One pot process:



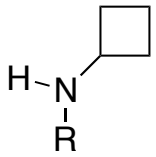
Cyclobutane Results

One pot process:

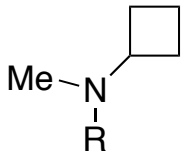




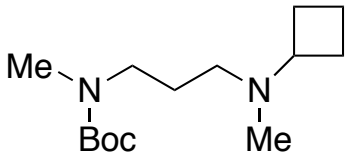
97%



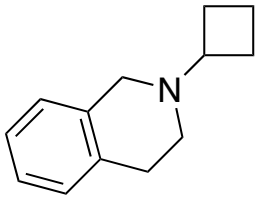
R = Ph, 61%
R = Bn, 40%



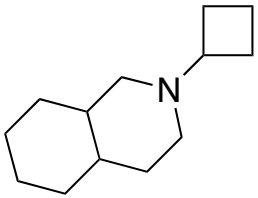
R = Ph, 73%
R = Bn, 93%



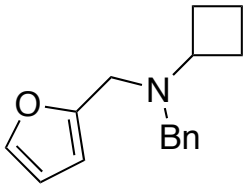
95%



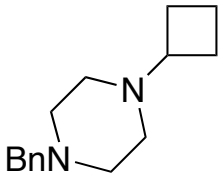
68%



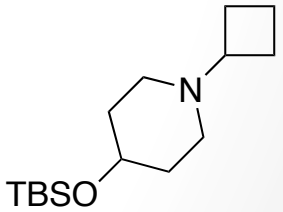
71%



60%



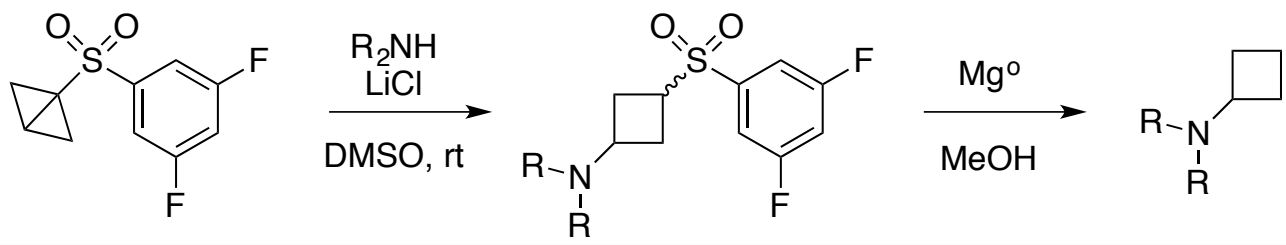
76%

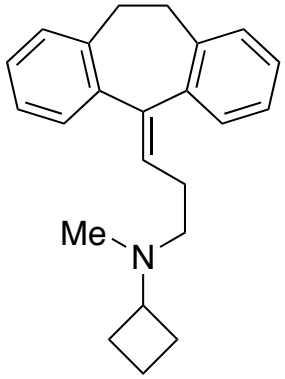


75%

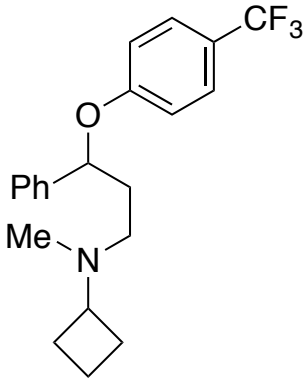
Cyclobutane Results

One pot process:

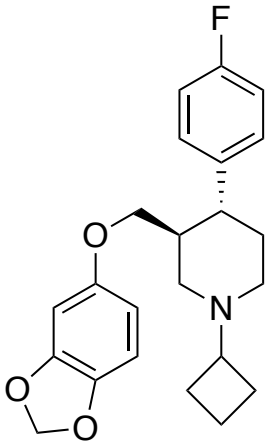




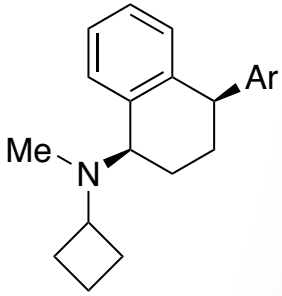
"cyclobutylated"
nortriptyline
83%



"cyclobutylated"
fluoxetine
61%

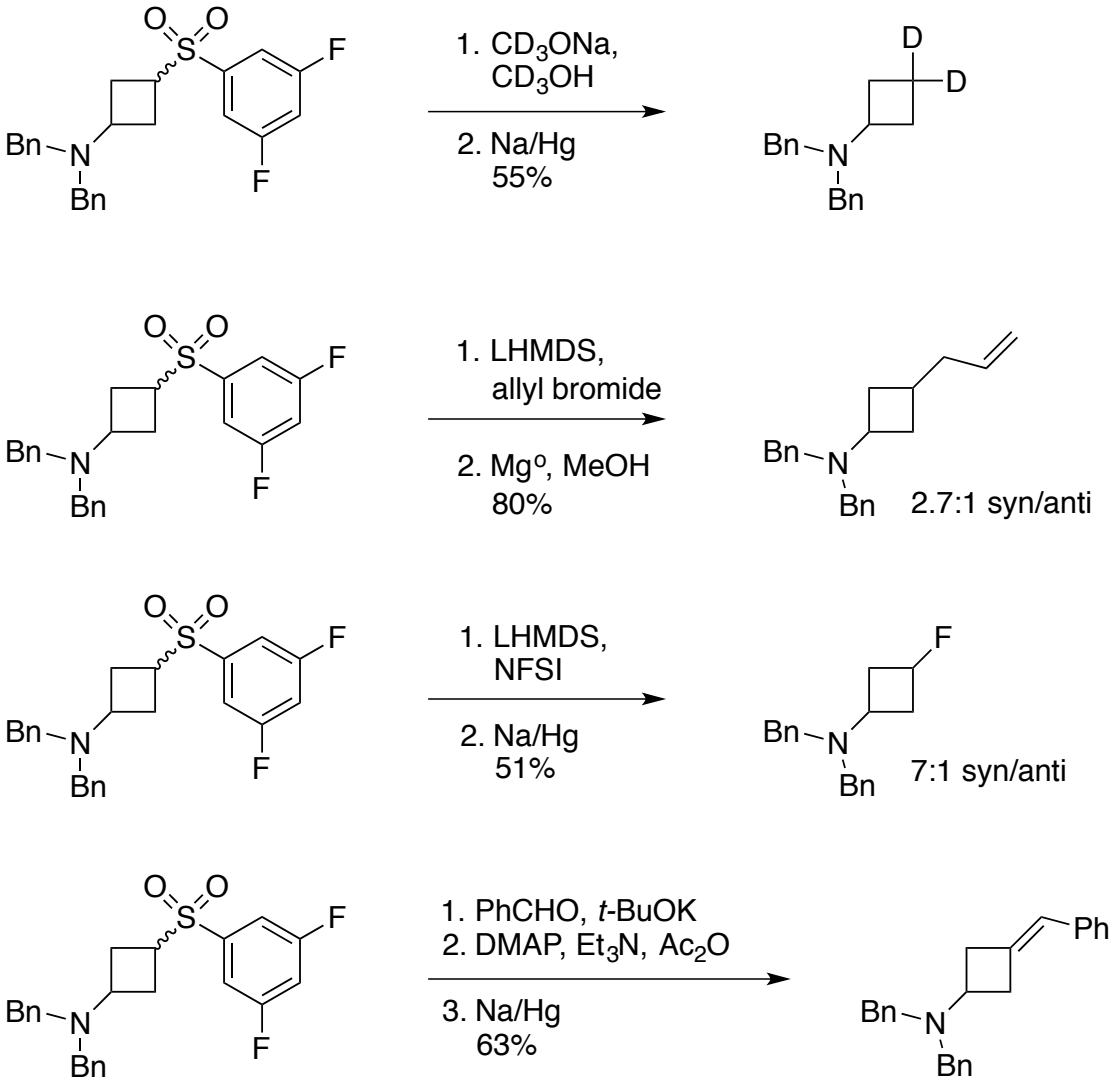


"cyclobutylated"
paroxetine
70%

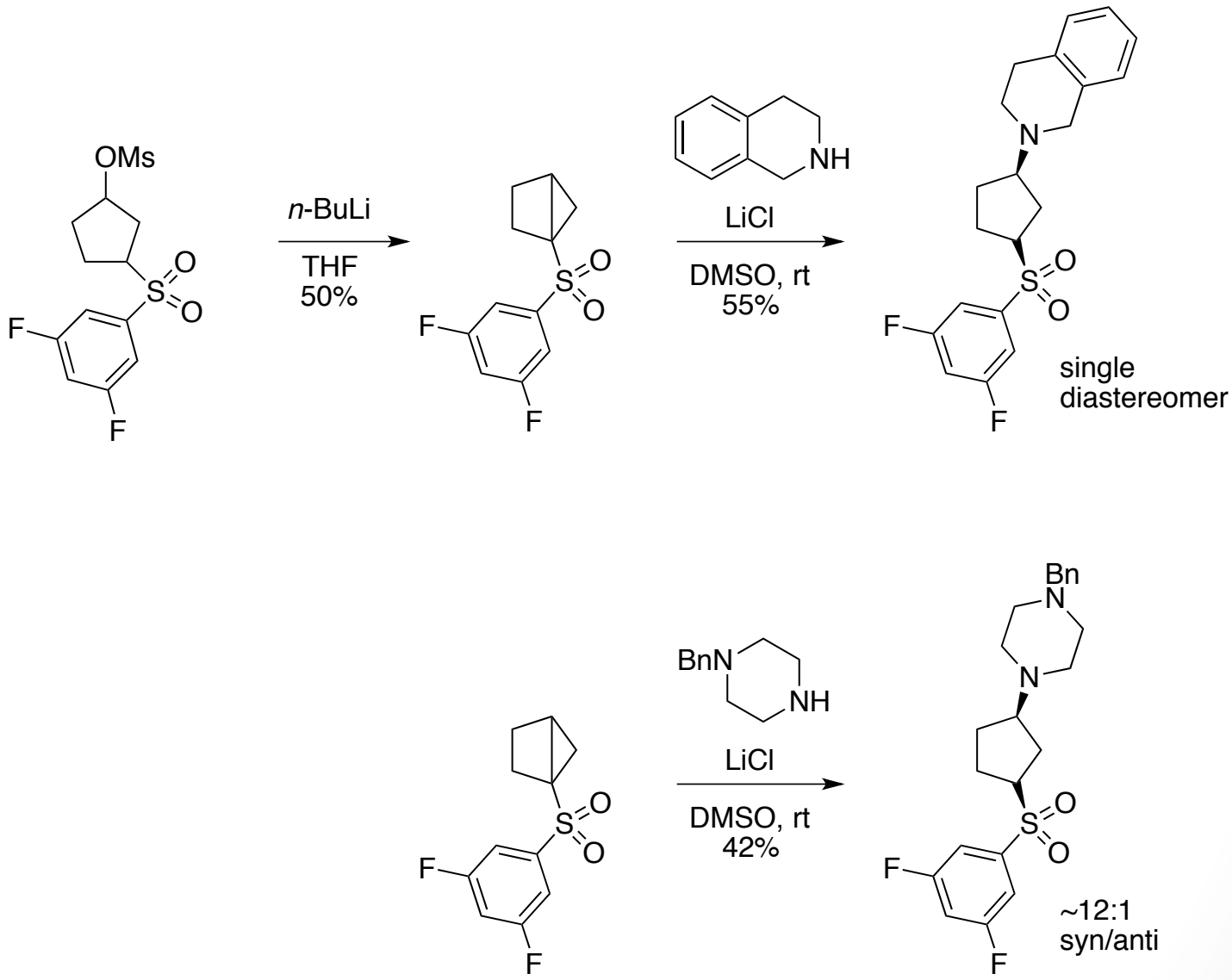


"cyclobutylated"
sertraline
67%

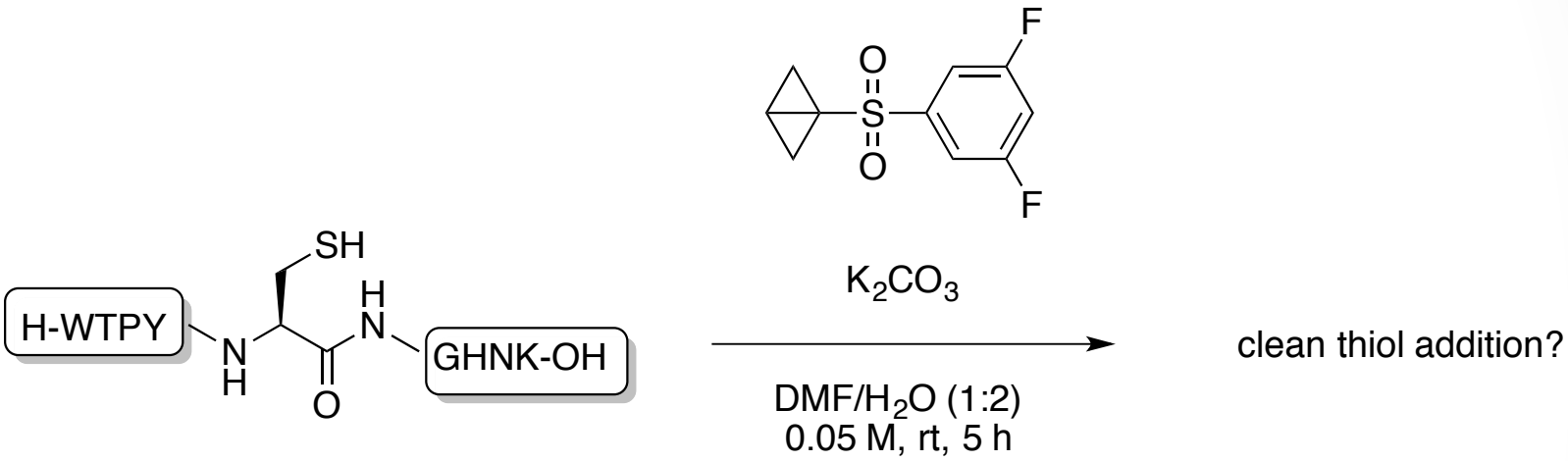
Sulfone utility



Cyclopentanes

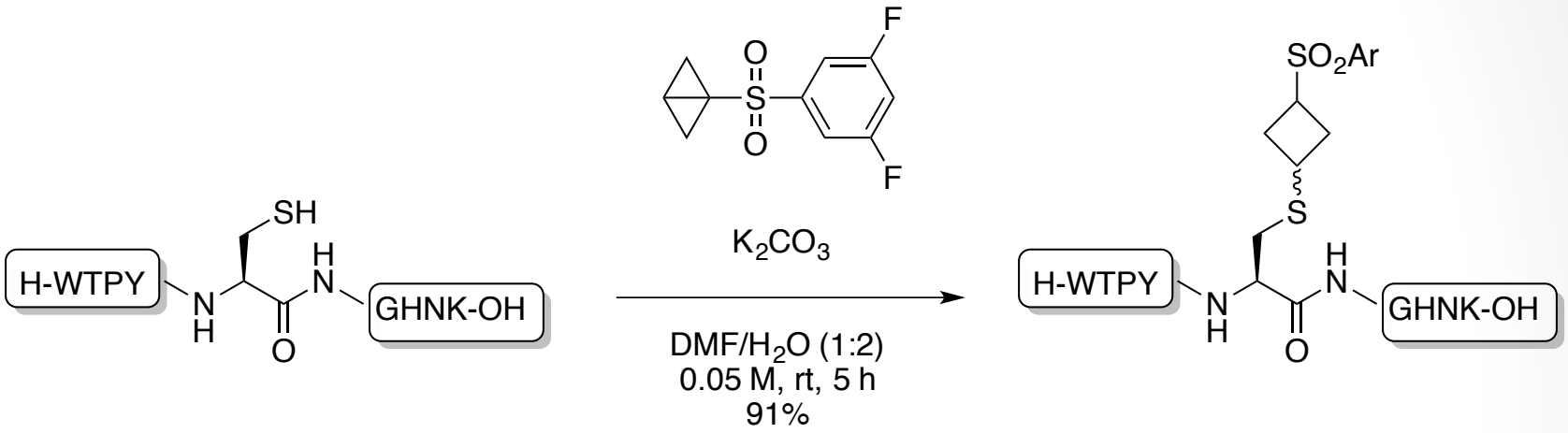


Peptide labeling



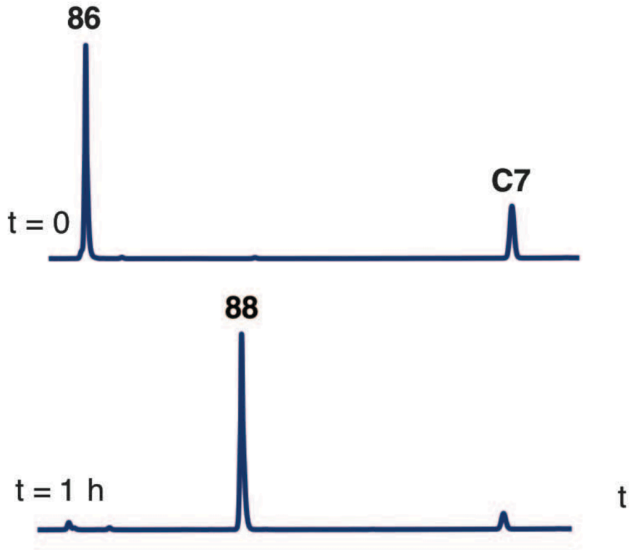
side chains include:
imidizole (H)
amine (K)
phenol (Y)
indole NH (W)

Peptide labeling

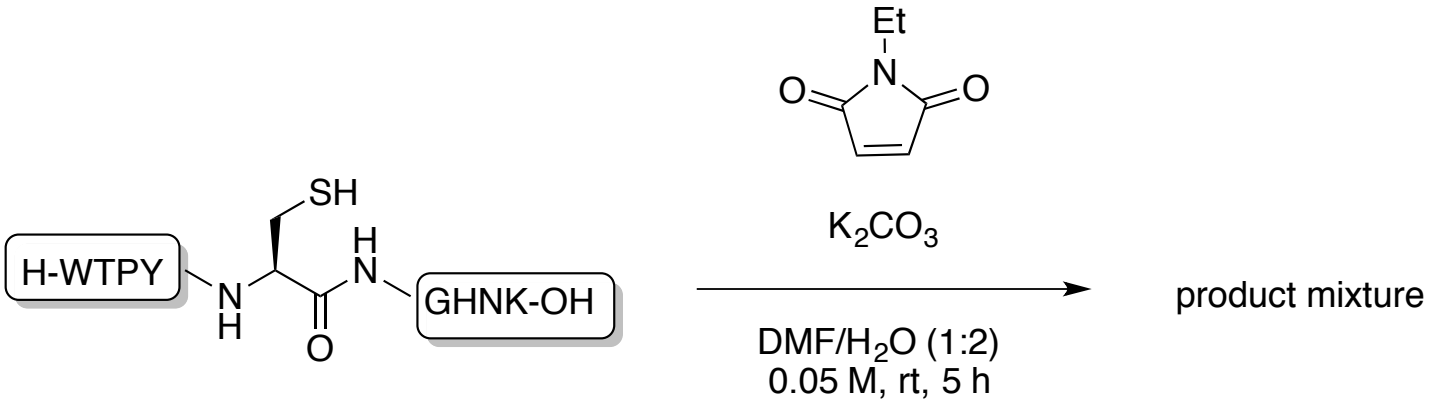


side chains include:
imidizole (H)
amine (K)
phenol (Y)
indole NH (W)

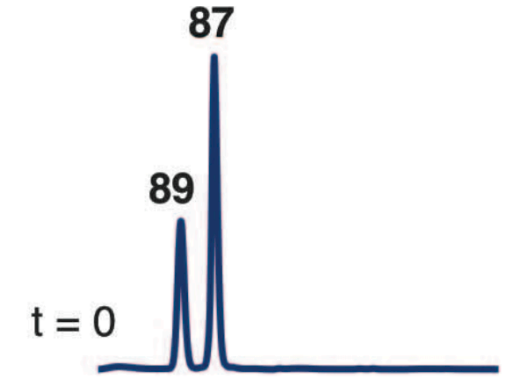
HPLC trace:

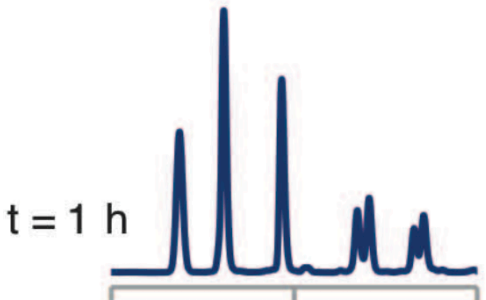


Peptide labeling

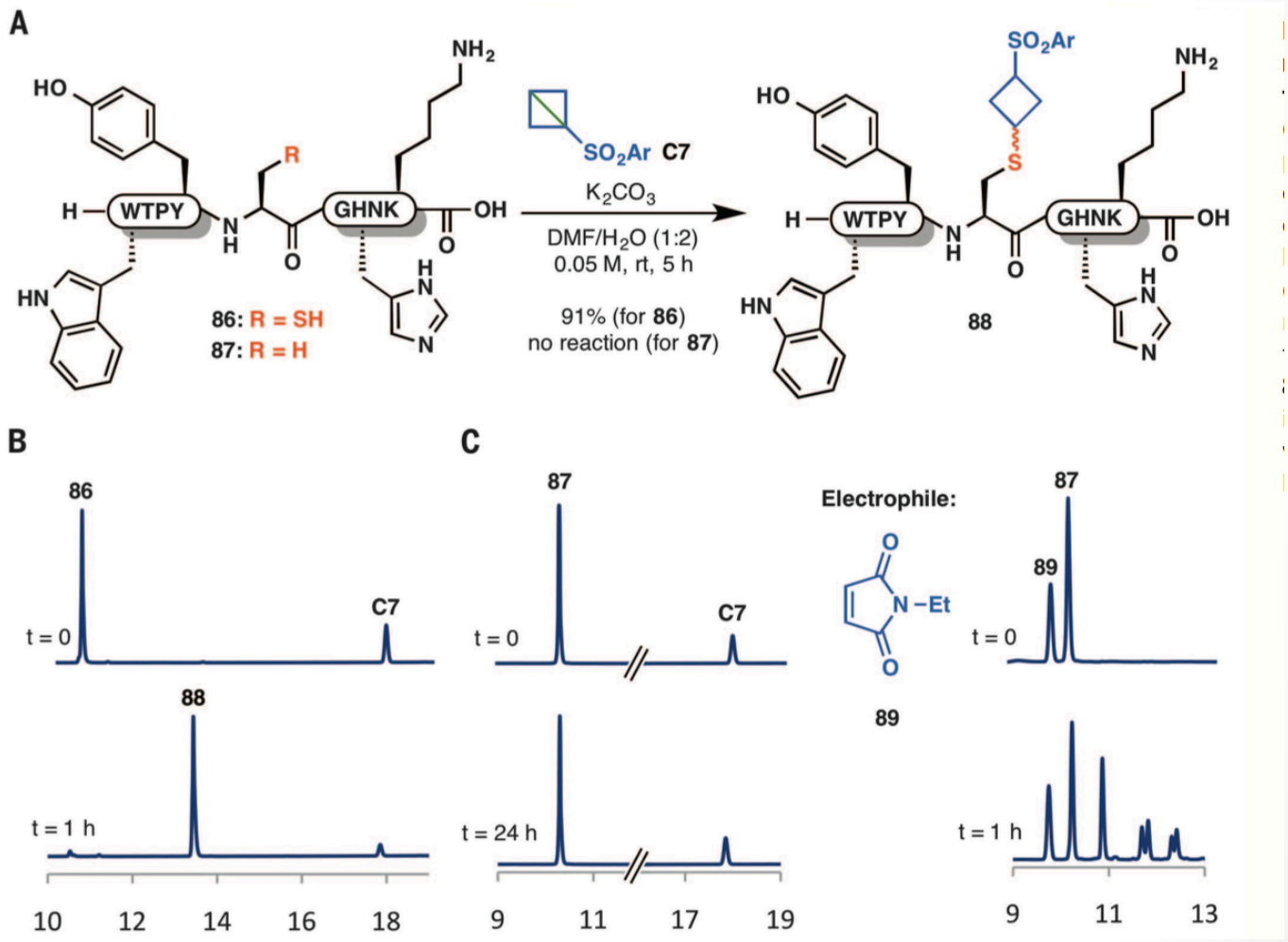


HPLC trace:

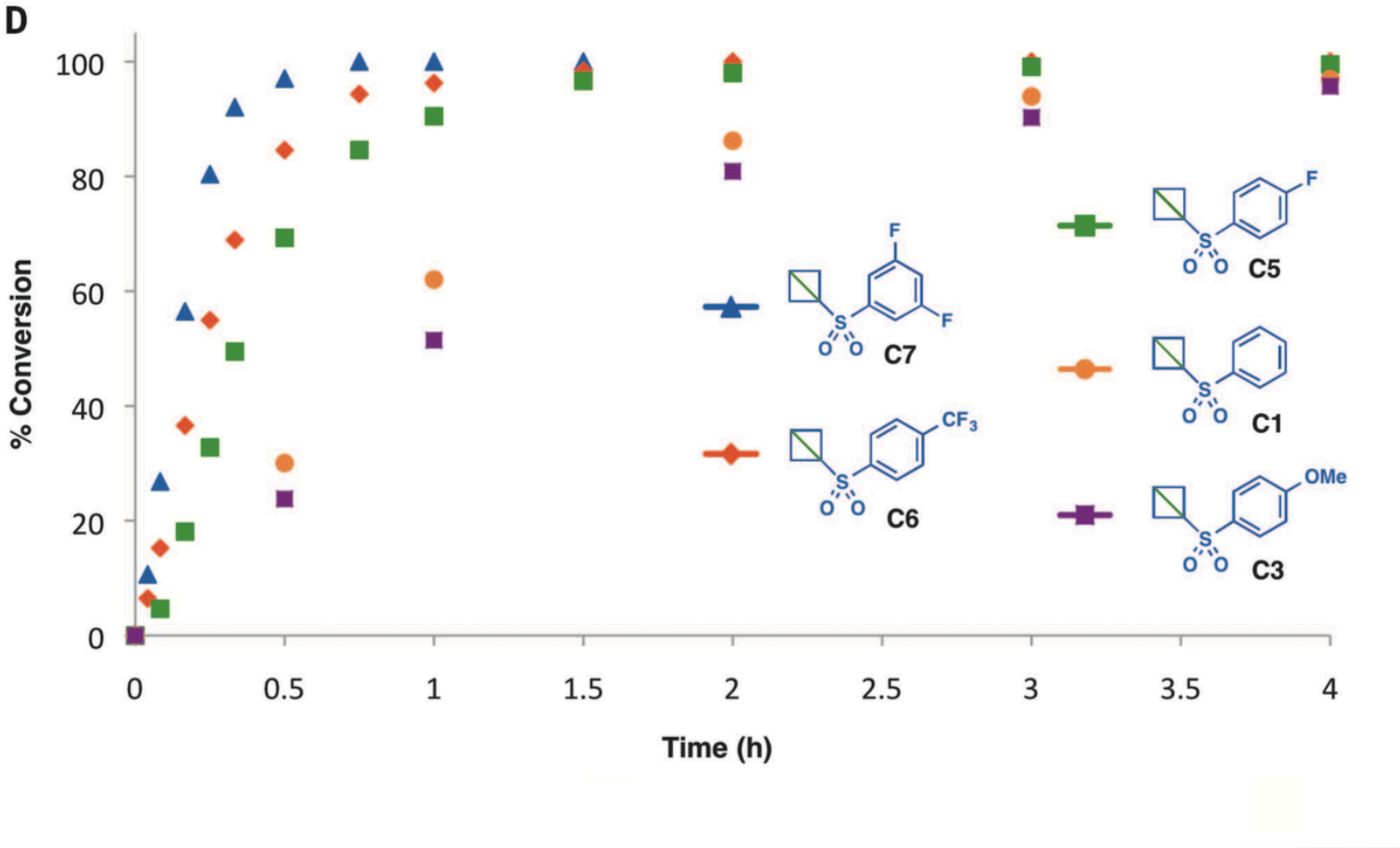




Peptide labeling



Kinetic studies



Conclusion

- A new, efficient method to produce the bicyclo[1.1.1] amine function via addition to propellane was developed
- By its nature, this method is general to any secondary amine
- The method was extended to bicyclobutanes and azabicyclobutanes
- These reagents may be of use in bioconjugation, peptide labeling, and stapled peptides