C-H Methylation of Heteroarenes inspired by radical SAM Transferase

Gui, J.; Zhou, Q.; Pan, C-M.; Yabe, Y.; Burns, A. C.; Collins, M. R.; Ornelas, M. A.; Ishihara, Y.; Baran, P. S.

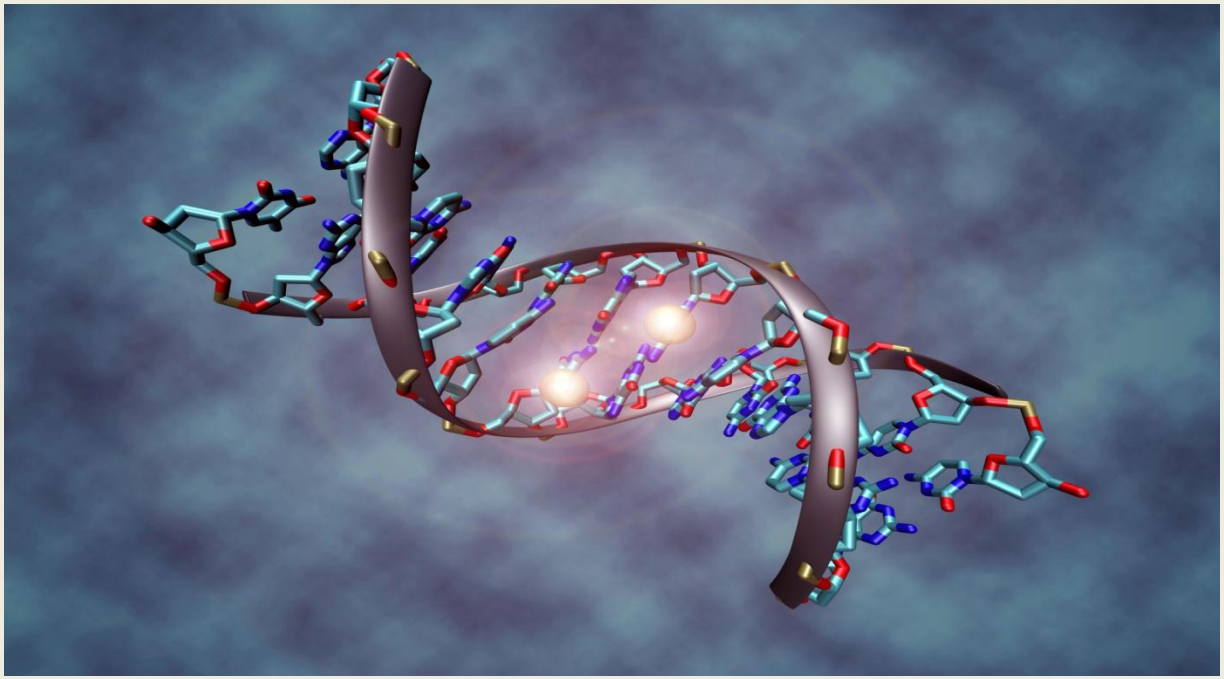
J. Am. Chem. Soc. **2014**, DOI: 10.1021/ja5007838

Wipf Group Current Literature 4/12/14

John Milligan

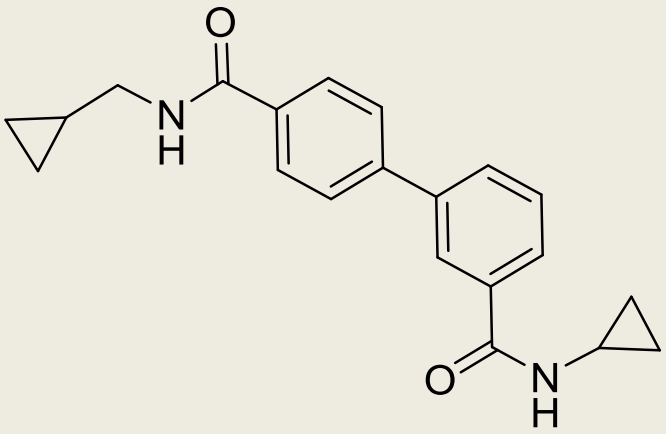
Methylation: Biological Implications

- DNA and protein methylation significant for expression, development, regulation, etc.

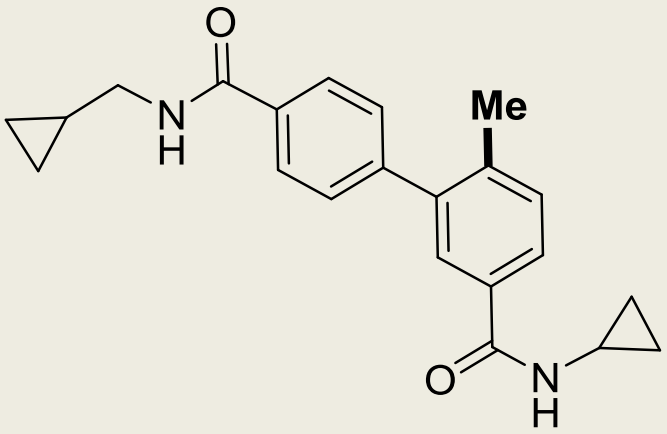


http://upload.wikimedia.org/wikipedia/commons/8/80/DNA_methylation.jpg

“The Magic Methyl Effect”



p38α IC_{50}: >2500 nM



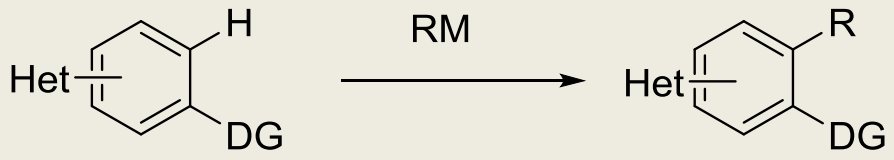
p38α IC_{50}: 12 nM

- A tolerant, late stage methylation methodology could enhance library diversity and enable chemical biology

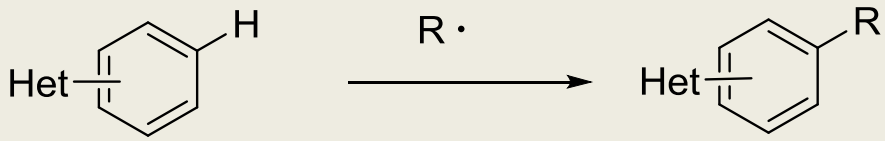
Review: Cernak, T.; Schonherr, H. *Angew. Chem. Int. Ed.* **2013**, *52*, 12256-12267

Expanding chemical space with innate reactivity

"Programmed Reactivity"



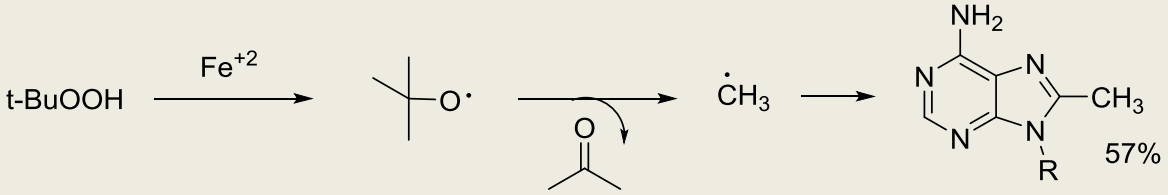
"Innate Reactivity"



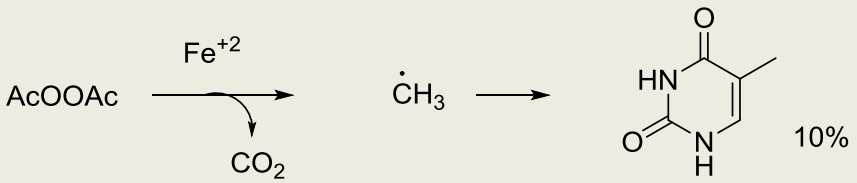
regiochemistry directed by heterocycle electronics

Previous work on Radical Methylation

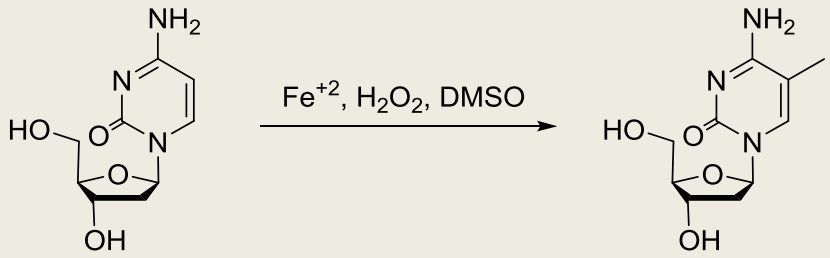
- Drawbacks: high temp, difficult separation



Maeda, M.; Nushi, K.; Kawazoe, Y. *Tetrahedron* **1974**, *30*, 2682

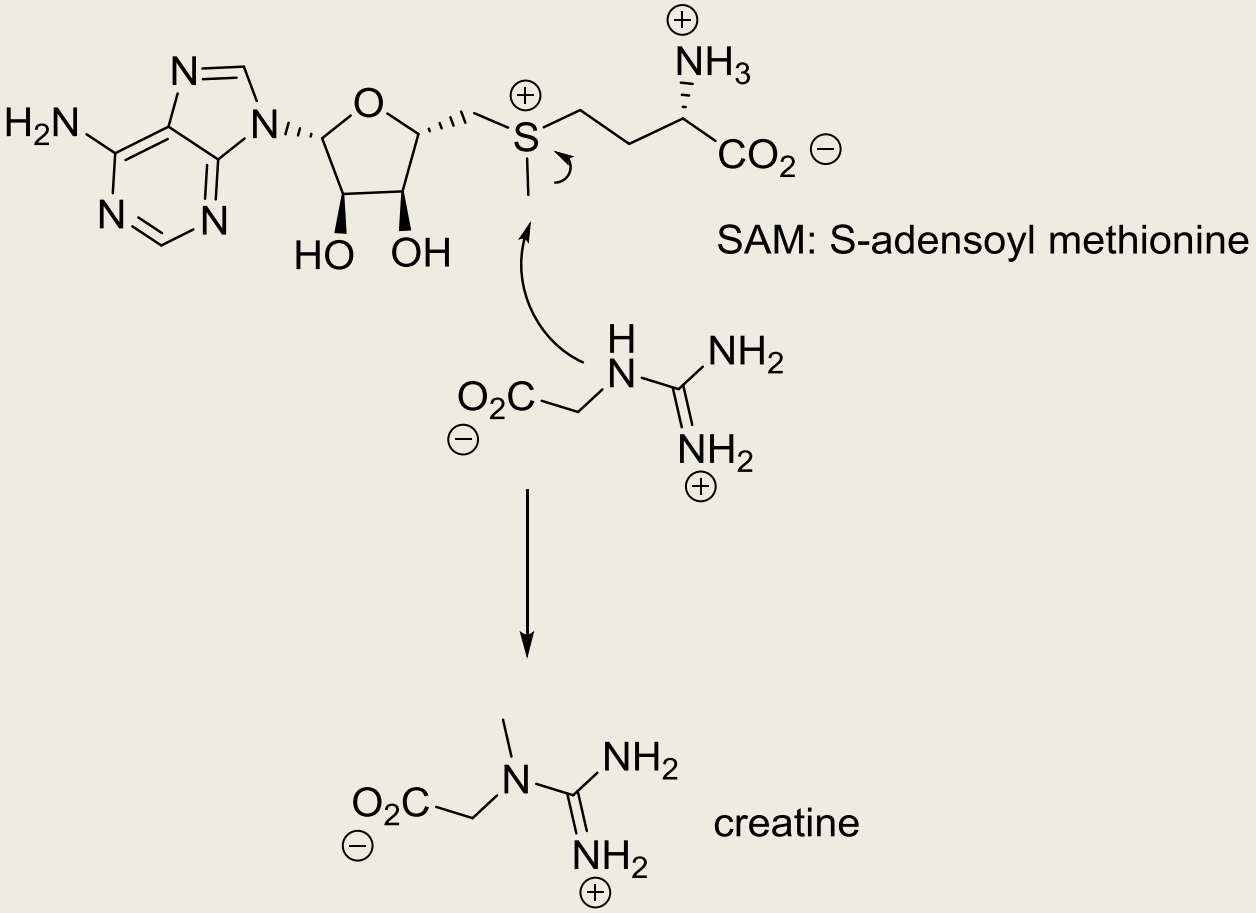


Araki, M.; Maeda, M.; Kawazoe, Y. *Tetrahedron* **1976**, *32*, 377

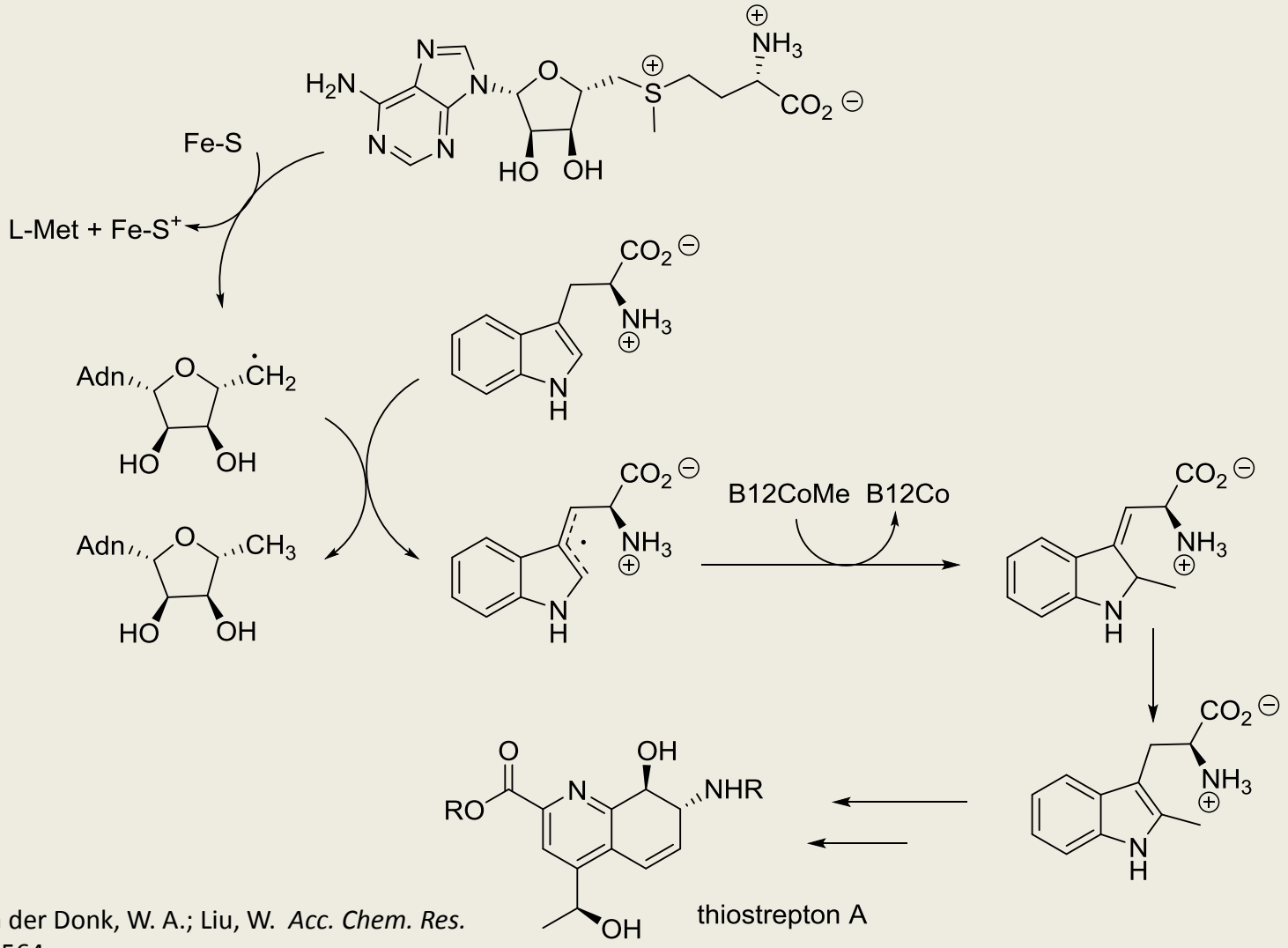


Kawai, K.; Li, Y-S.; Song, M-F.; Kasai, H. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 260

SAM: A Bioinspiration

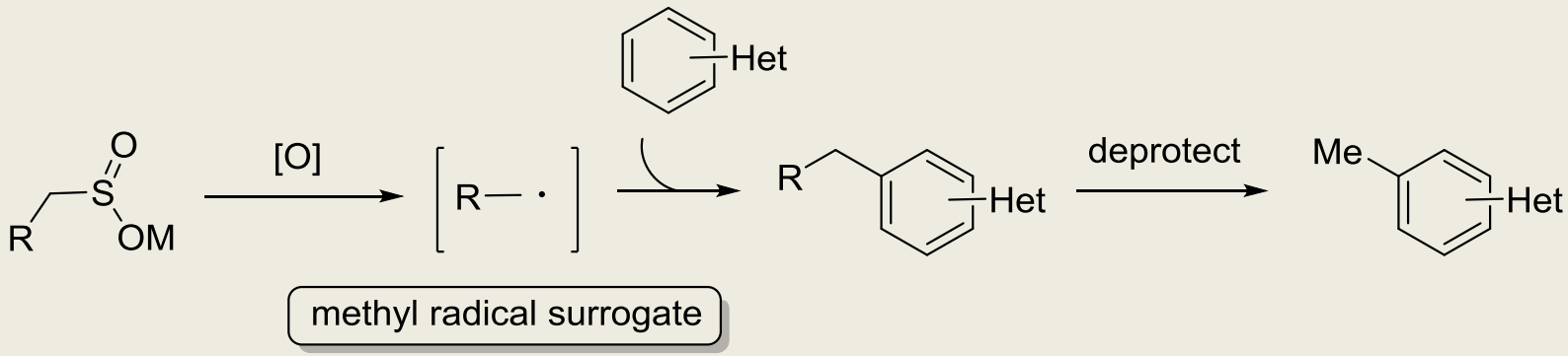


SAM: A Bioinspiration

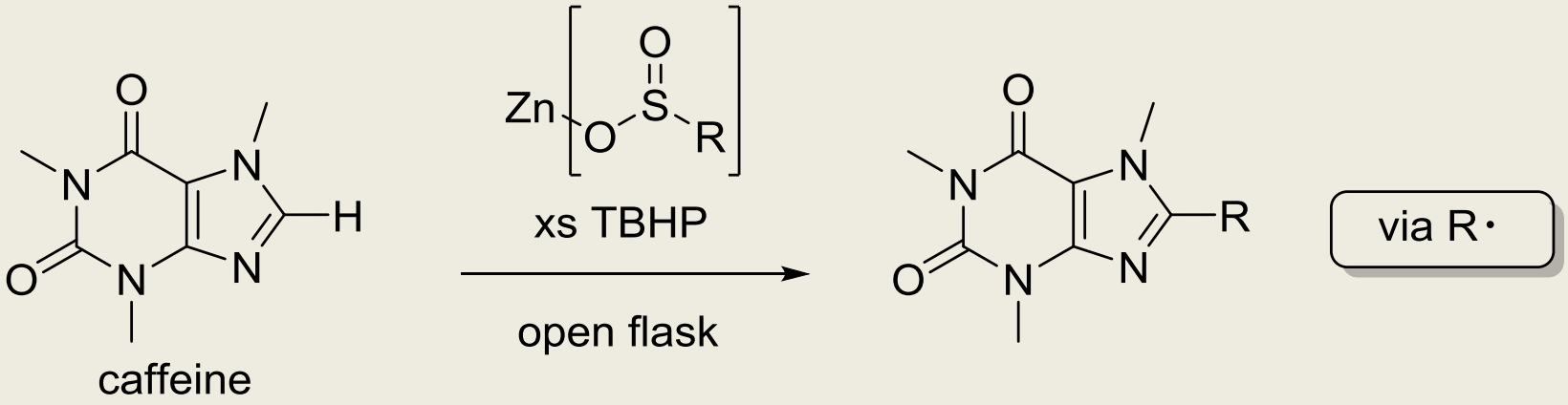


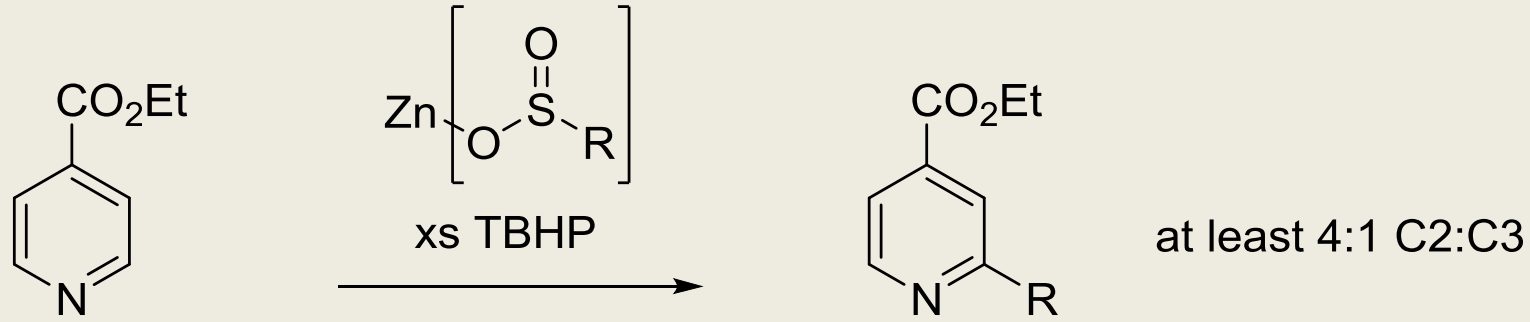
Zhang, Q.; Van der Donk, W. A.; Liu, W. *Acc. Chem. Res.* **2012**, *45*, 555-564.

Sulfinate salts as methyl surrogates



Previous Baran Work

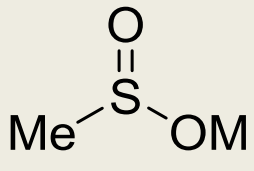




Fujiwara, Y.; Dixon, J. A.; O'Hara, F. O.; Funder, E. D.; Dixon, D. D.; Rodriguez, R. A.; Baxter, R. D.; Herle, B.; Sach, N.; Collins, M. R.; Ishihara, Y.; Baran, P. S. *Nature* **2012**, *492*, 95.

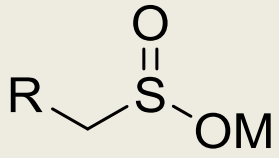
Problems with Attempted Methylation Reagents

low yeilding:



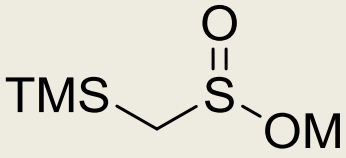
M= Na, Zn, Fe

difficult to prepare:



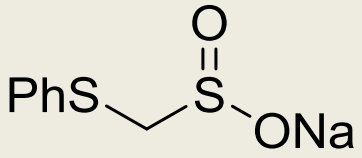
R= $B(OR)_2$, PPh_2

unreactive:



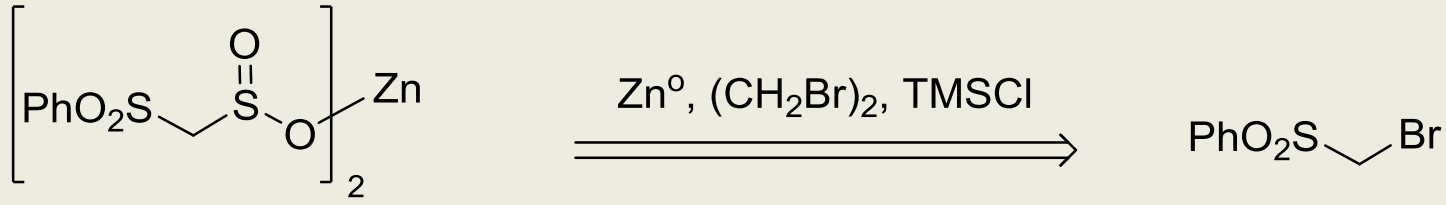
M= Li, Mg

poor scope:



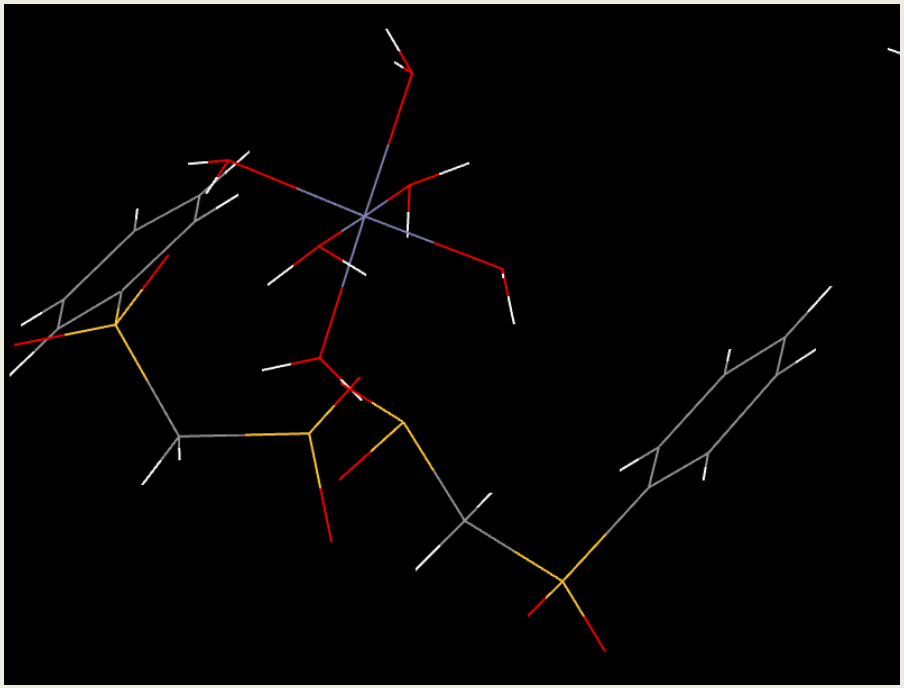
M= Li, Mg

PSMS



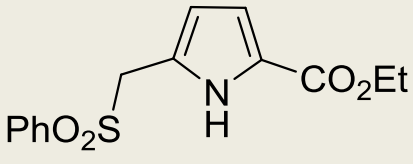
zinc bis(phenylsulfonylmethanesulfinate)

crystallized as hexahydrate dimer:

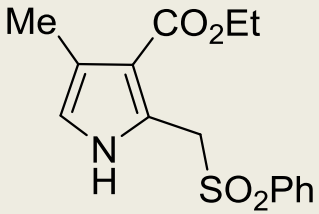


PSMS (6) is a free-flowing, bench-stable, white powder:

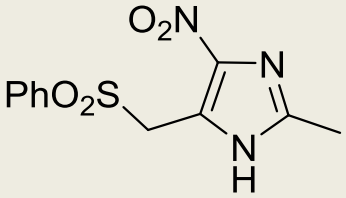
Representative Substrate Scope



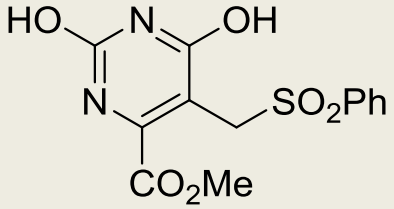
99%



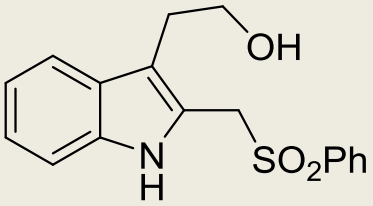
48%, 3:2 C2:C5



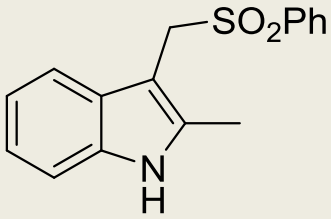
88%



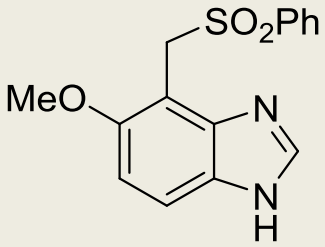
51%



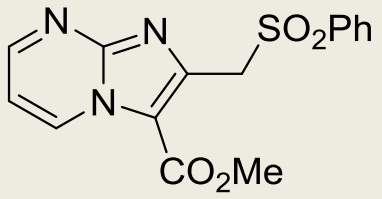
68%



62%



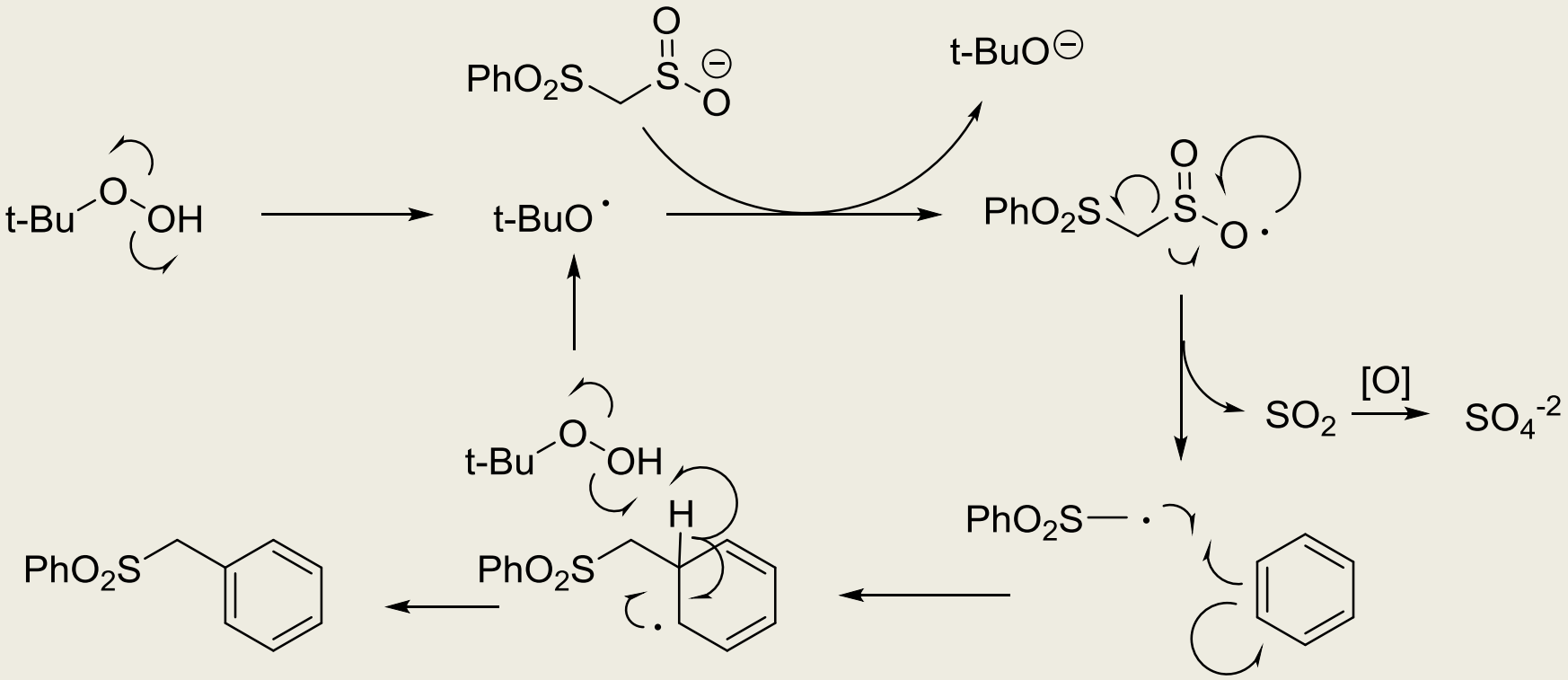
50%



80%

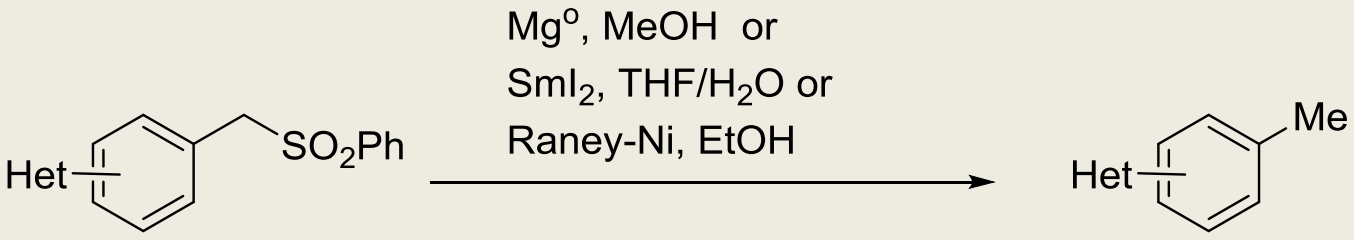
pyridines: no rxn

Plausible Mechanism

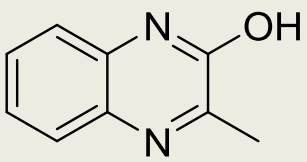


Analogous to $-CF_3$ addition: Ji, Y.; Brueckl, T.; Baxter, R. D.; Fujiwara, Y.; Seiple, I. B.; Su, S.; Blackmond, D. G.; Baran, P. S. *Proc. Nat. Acad. Sci.* **2011,** *108*, 14411.

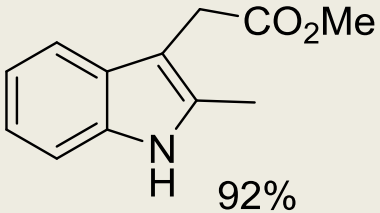
Reductive Desulfonylation



Mg°, MeOH

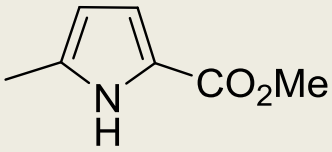


75%

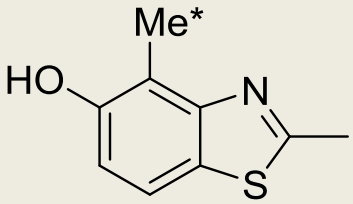


92%

SmI_2, THF/H_2O

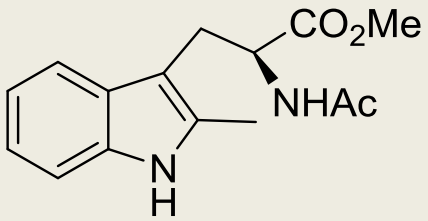


84%

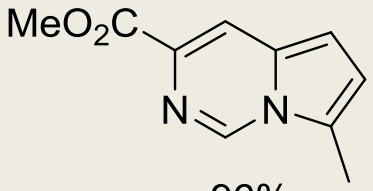


96%

Raney-Ni, EtOH

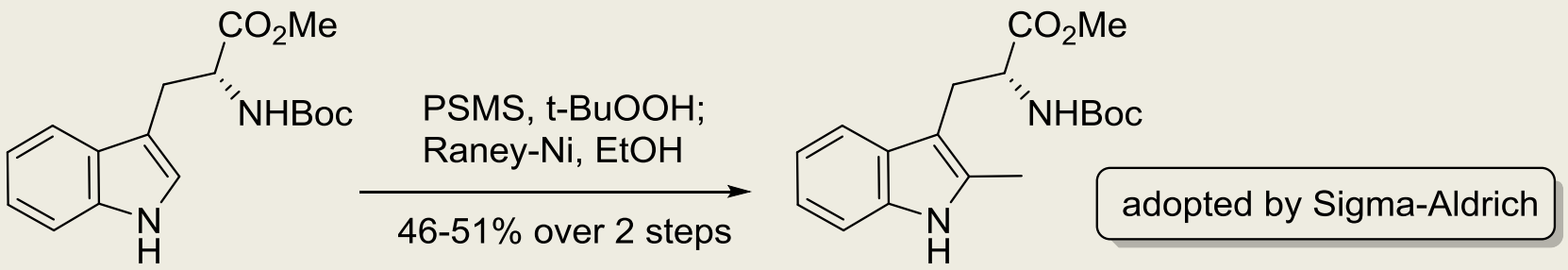


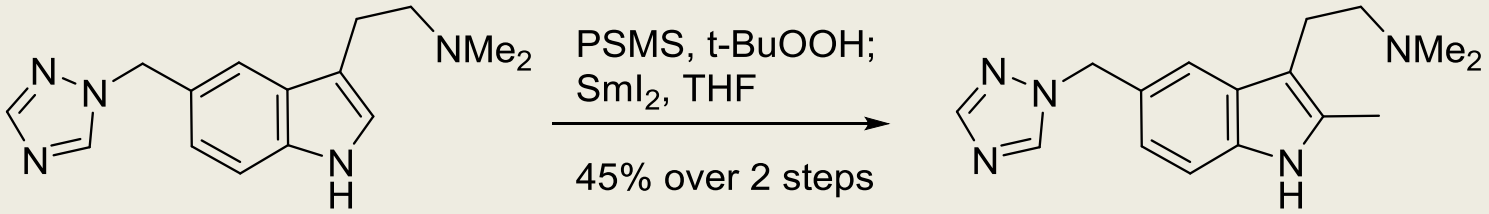
94%



96%

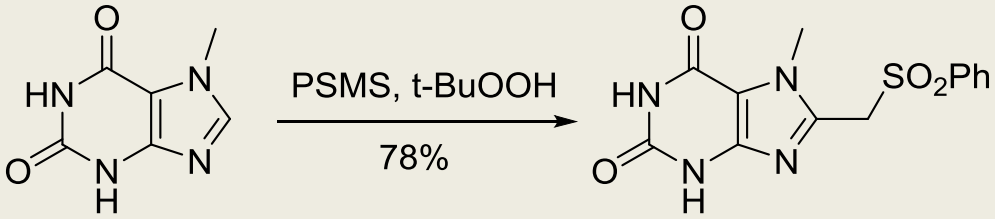
Useful Products





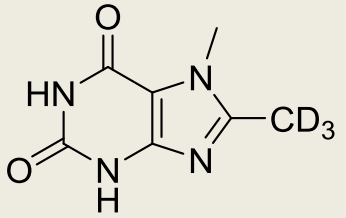
Maxalt (Merck drug for migranes)

Alternatives to methylation

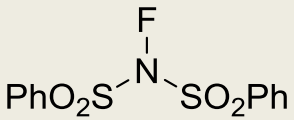


conditions → product

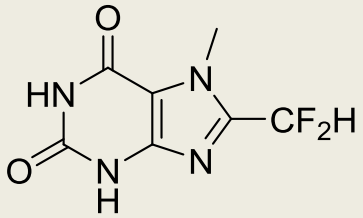
Mg, MeOD/ SmI_2, D_2O
70%, 91% D



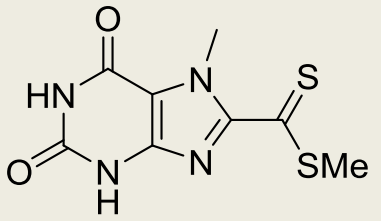
NFSI:



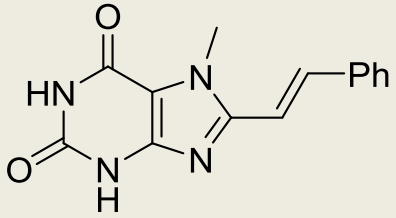
NaH, NFSI; Mg, AcOH
69%



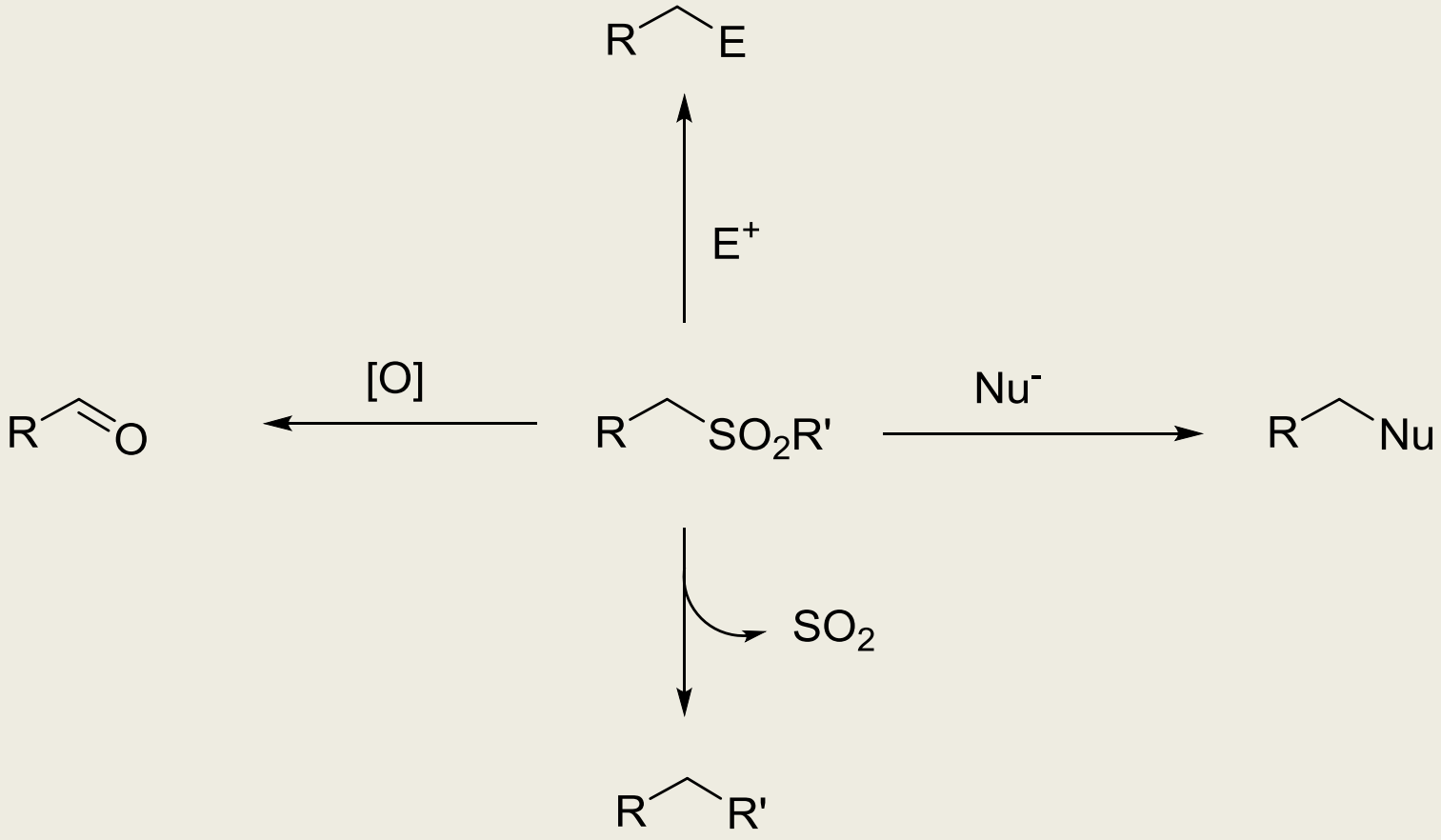
KOt-Bu, S_8; MeI
quant.



NaH, PhCHO; SmI_2
32%



Other opportunities?



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Conclusion

- This methodology provides a mild, substrate directed radical sulfonylation of electron rich heterocycles
- The sulfonyl group can be reductively cleaved in good yield or further elaborated
- The methodology bodes well for applications in chemical biology, library development, and instillation of other functionalized methylenes using zinc sulfinates