The synthetic challenges of accessing design space

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SCI exploring Chemical Space
23rd March 2011

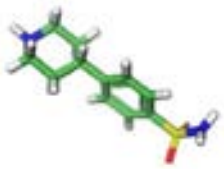
Outline of Talk

- Introduction
- Accessing chemical space by evolving existing methodology.
- Expanding chemical space by innovative synthesis of ideal medicinal chemistry fragments
- Conclusion

Pfizer

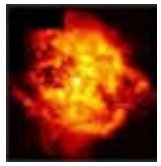
Chemical space – the numbers

- ca 600-1000 drugable targets
- 2500 therapeutically relevant genes



- 10^{63} possible stable structures with less than 30 non-hydrogen atoms (C, N, O, P, S, F, Cl and Br), with a molecular weight of less than 500 dalton
- $10^{20\text{-}24}$ possible structures from currently known synthetic methods.

- winning the lottery 10^{7} to 1 chance



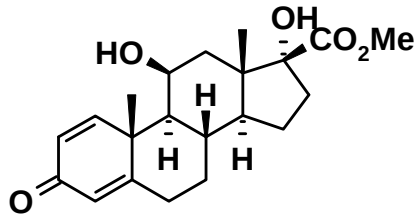
- 10^{17} number of seconds since the Big Bang (15 billion years)

Nature Drug Disc. Rev. (2002), 1 (9), 727-730

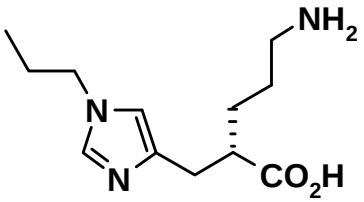
Nature Drug Disc. Rev. (2003), 2,38-51

Chemical Space – A synthetic chemist's definition!

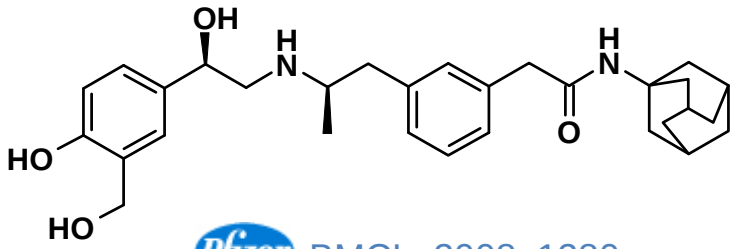
What our molecules really look like:



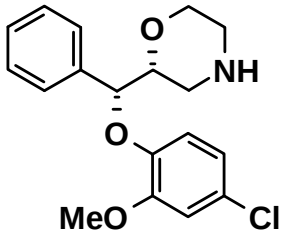
Steroids, 2008, 274



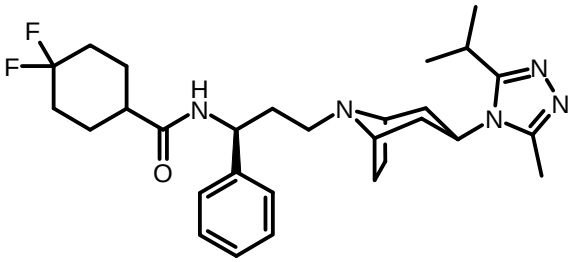
J Med Chem, 2007, 6095



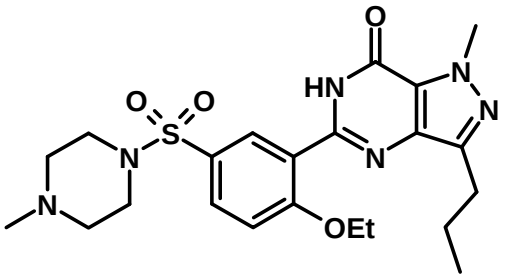
BMCL, 2008, 1280



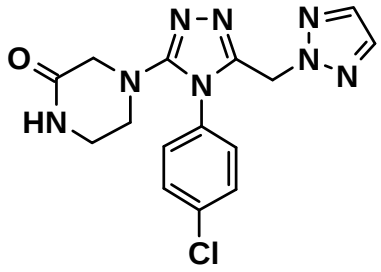
Tet Lett, 2009, 389



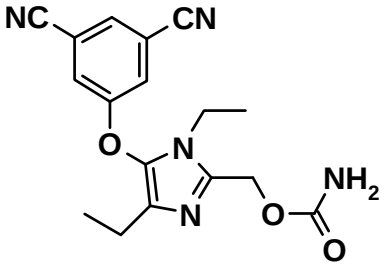
Tet Lett, 2005, 5005



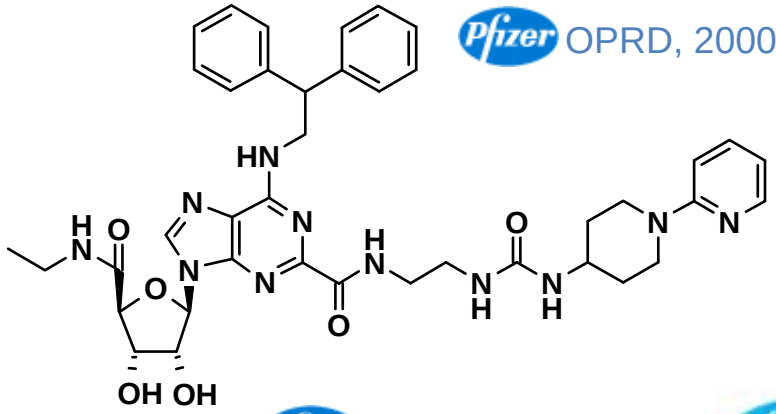
OPRD, 2000, 17



Synlett, 2008, 2421



Org Lett, 2006, 1725

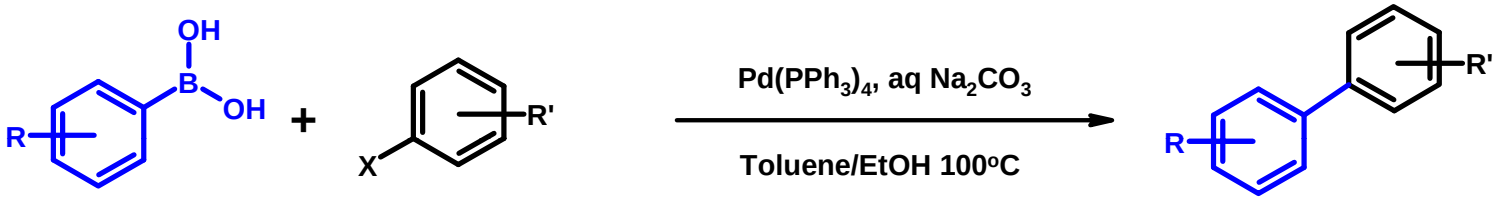


OPRD, 2008, 575

Accessing chemical space (I) Methodology evolution

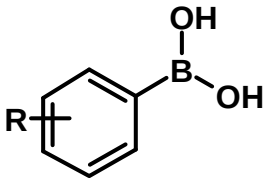
1) Suzuki Coupling

- Improving the methodology of a Nobel prize winner??
- Our “bread and butter” for SP2-SP2 couplings in the pharma industry :



- Yet how much are we biasing/restricting our chemical space by starting with boronic acids?

- Commercially available in Scifinder:



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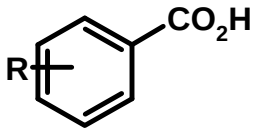
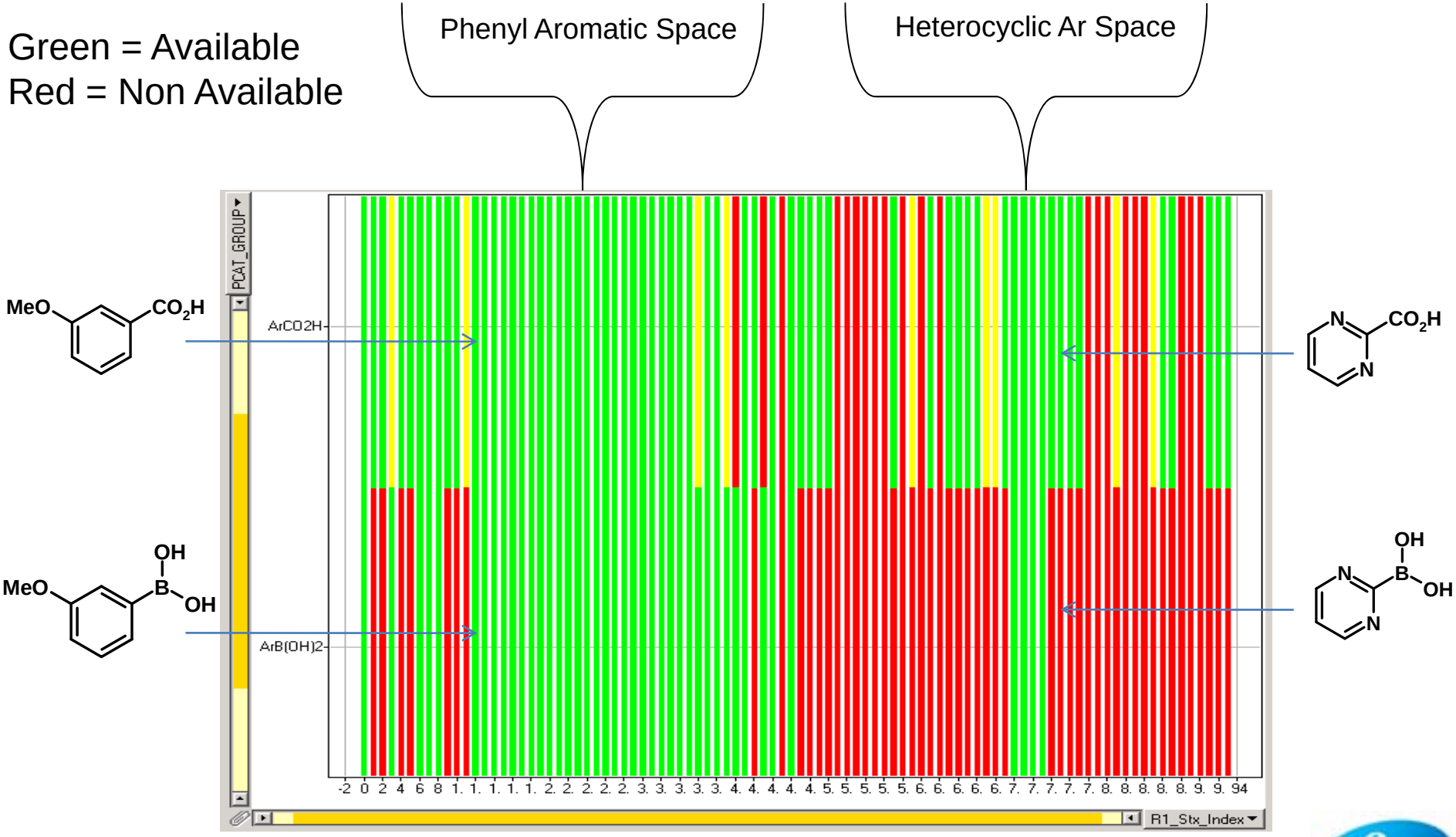


250701

- It’s more than just the numbers…….

Carboxylic Acid Vs. Boronic Acid: Chemical Space Comparison

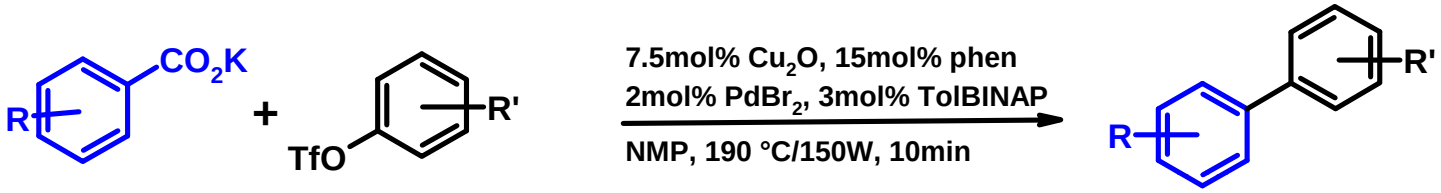
Green = Available
Red = Non Available



Carboxylic acids open up more heterocyclic design space!

Expanded space…..

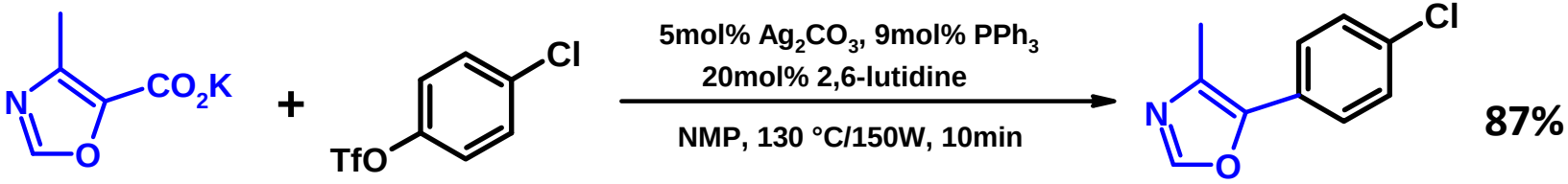
• Goossen decarboxylative coupling protocol enables carboxylic acid to be used as starting material



48 examples, 40-99% yield
o-, m-, p-substituted acids

Chem. Eur. J . **2009**, *15*, 9336-9349

• Several examples of heterocyclic acids

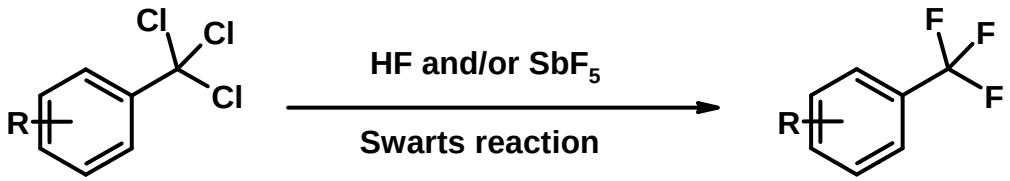


87%

Chem. Eur. J . **2010**, *16*, 3906-3909

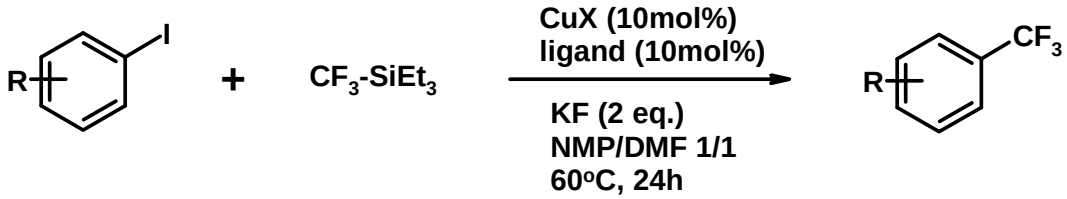
2) Aromatic trifluoromethylation

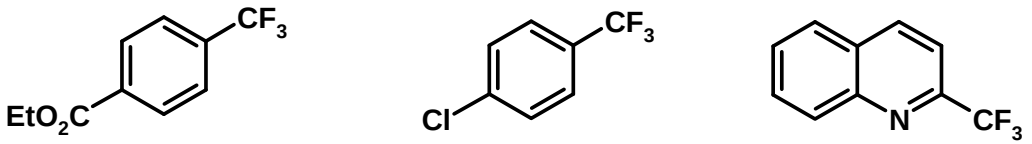
- CF_3 group loved by medicinal chemists but its introduction used to be a "holy grail" for synthesis.
- Typically involved chloride exchange with fluoride under harsh conditions



Bull. Soc. Chim. Belg. **1892**, *24*, 309

- **Fantastic** progress made in academia over the last 3 years:
  - Amii – 2008. First aromatic halide to CF_3 catalytic in copper:

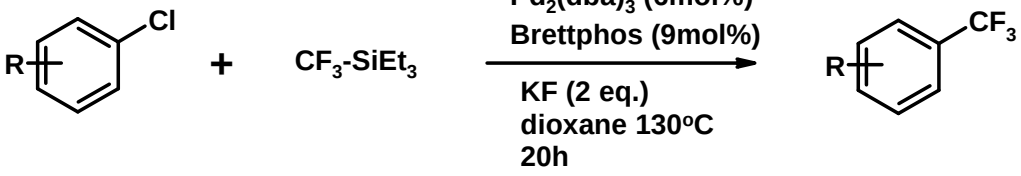


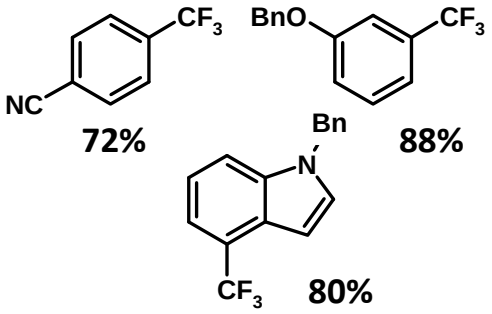


Chem. Comm. **2009**, *14*, 1909-1911

Aromatic trifluoromethylation

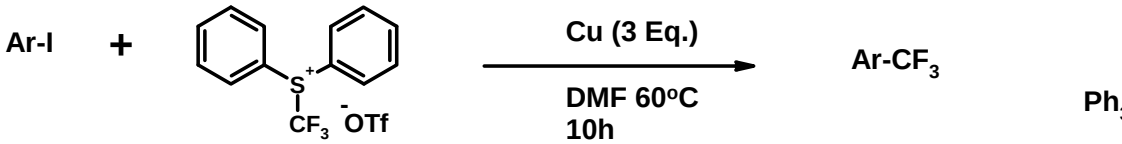
- **Buchwald 2010**: Trifluoromethylation of aryl **chlorides!**

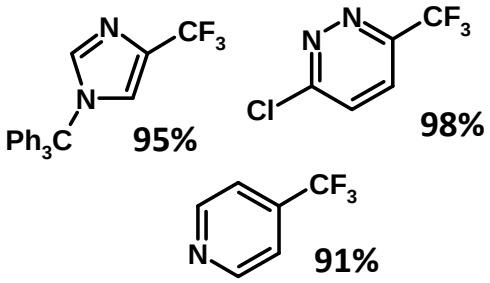




Science. **2010**, *328*, 1679-1681

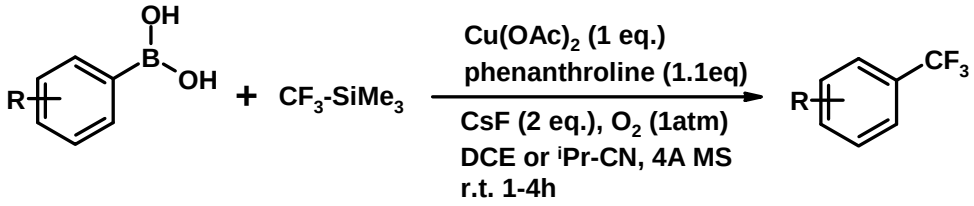
- **Xiao 2011**: excellent range of 5 and 6 membered heteroaromatic substrates

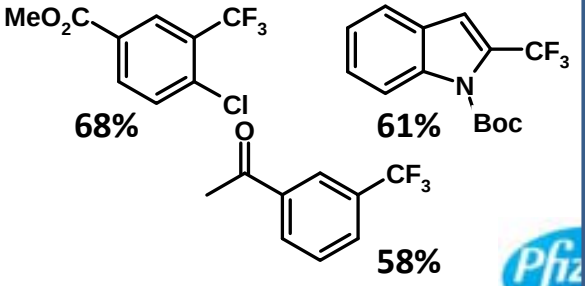




Angew. Chem. Int. Ed. **2011**, *50*, 1896-1900

- **Buchwald 2011**: Oxidative trifluoromethylation of boronic acids at r.t.!

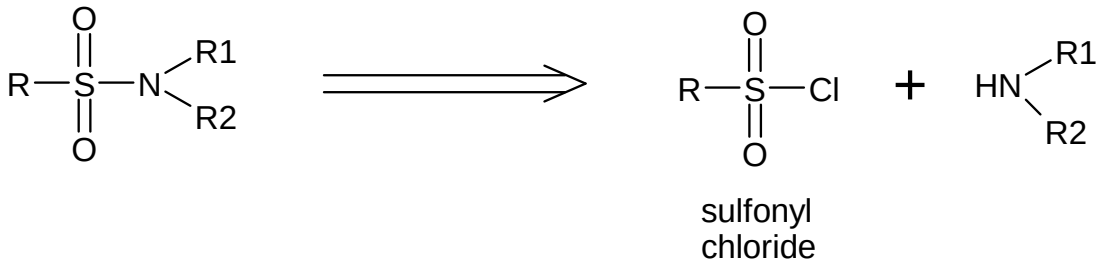




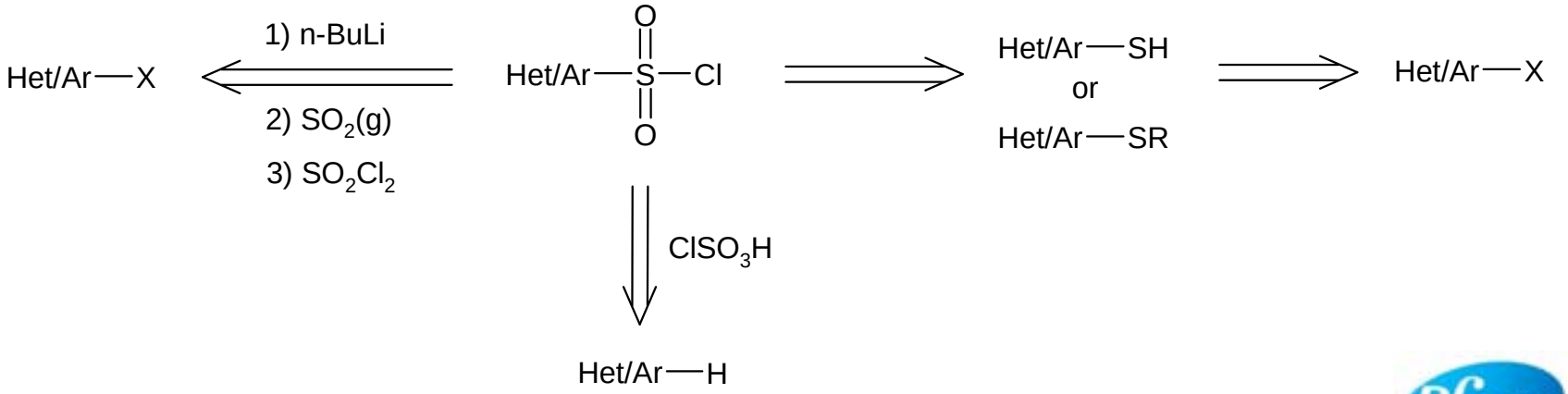
J. Org. Chem. **2011**, *76*, 1174-1176

An in house example

•Sulfonamide is another group loved in drug design but substituent scope is generally limited to commercial availability (or “synthesisability”)of sulfonyl chlorides:

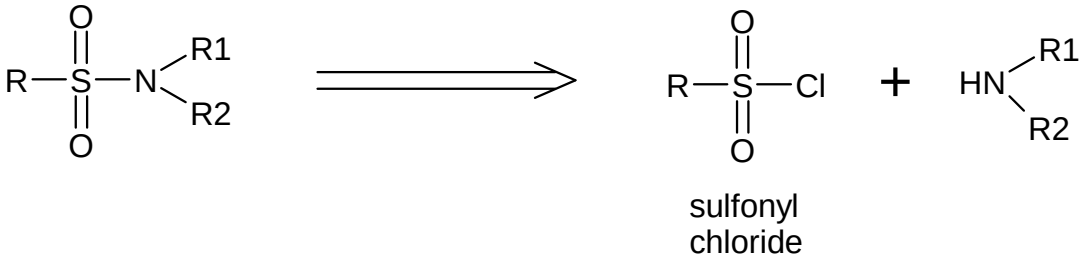


•Common methods to synthesise sulphonyl chlorides:



An in house example

•Sulfonamide is another group loved in drug design but substituent scope is generally limited to commercial availability (or “synthesisability”)of sulfonyl chlorides:



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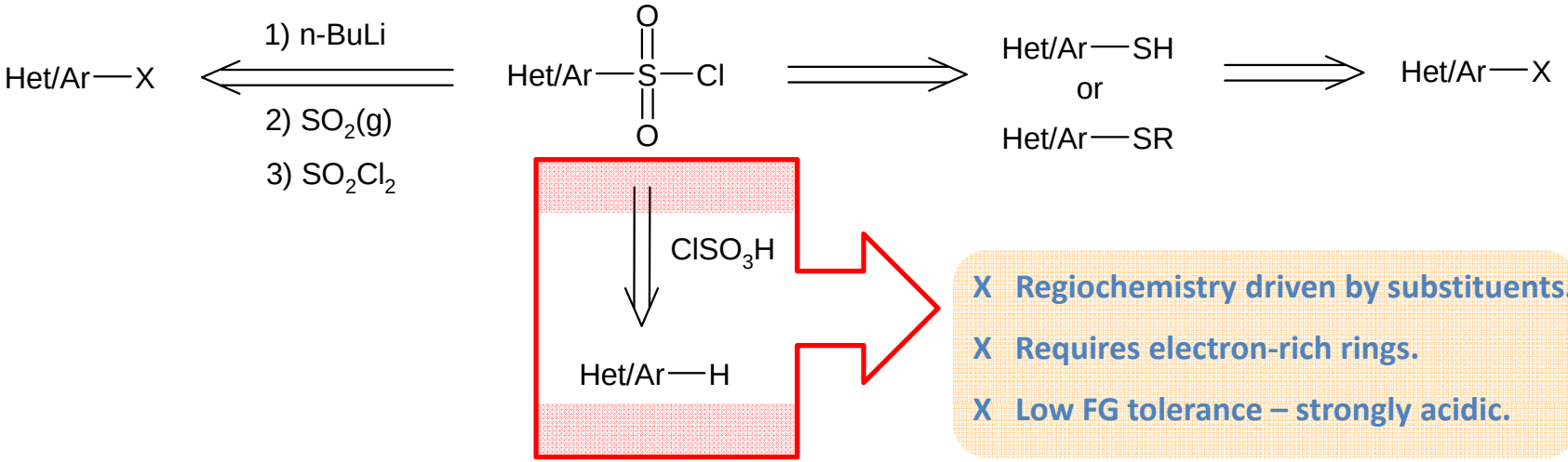
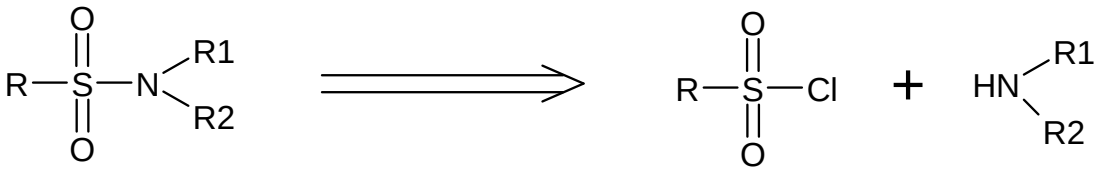


- X Regiochemistry driven by substituents.
- X Requires electron-rich rings.
- X Low FG tolerance – strongly acidic.

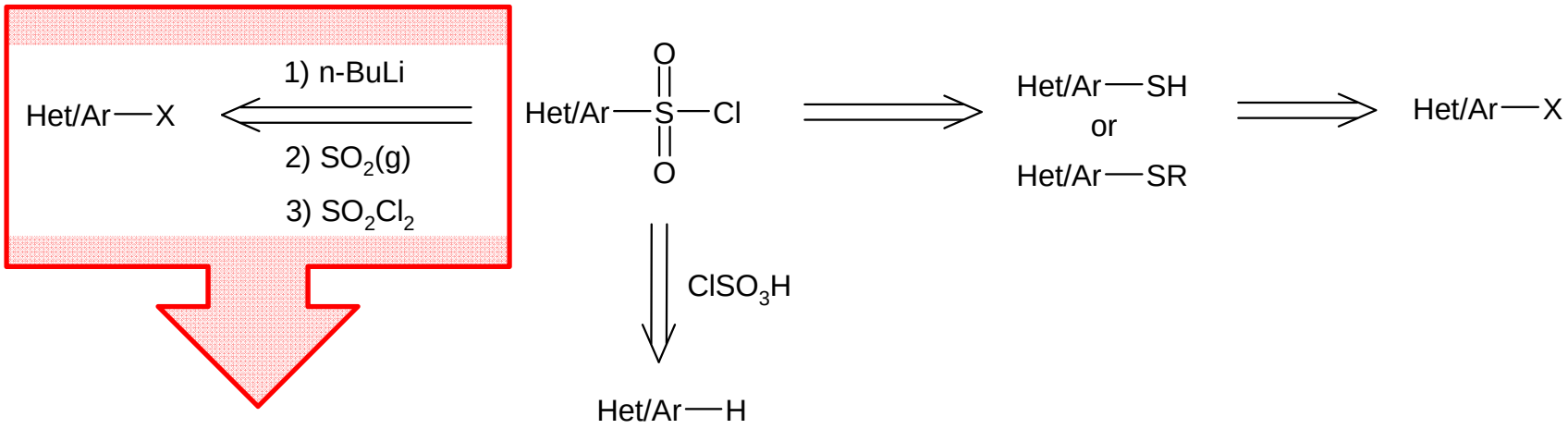
An in house example

•Sulfonamide is another group loved in drug design but substituent scope is generally limited to commercial availability (or “synthesisability”)of sulfonyl chlorides:



sulfonyl chloride

•Common methods to synthesise sulphonyl chlorides:

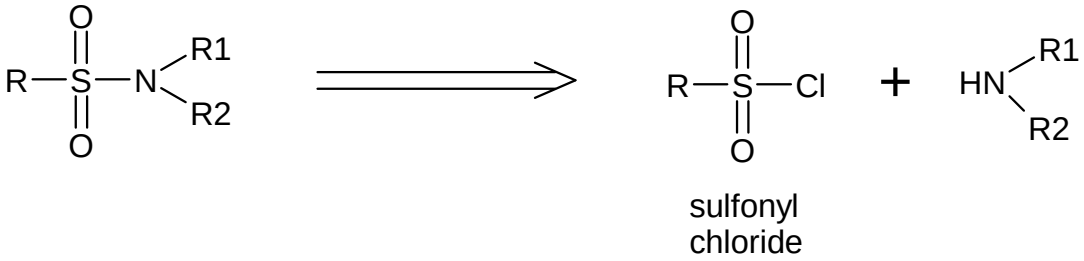


X Organometallics – air-sensitive, difficult to handle, low FG tolerance.

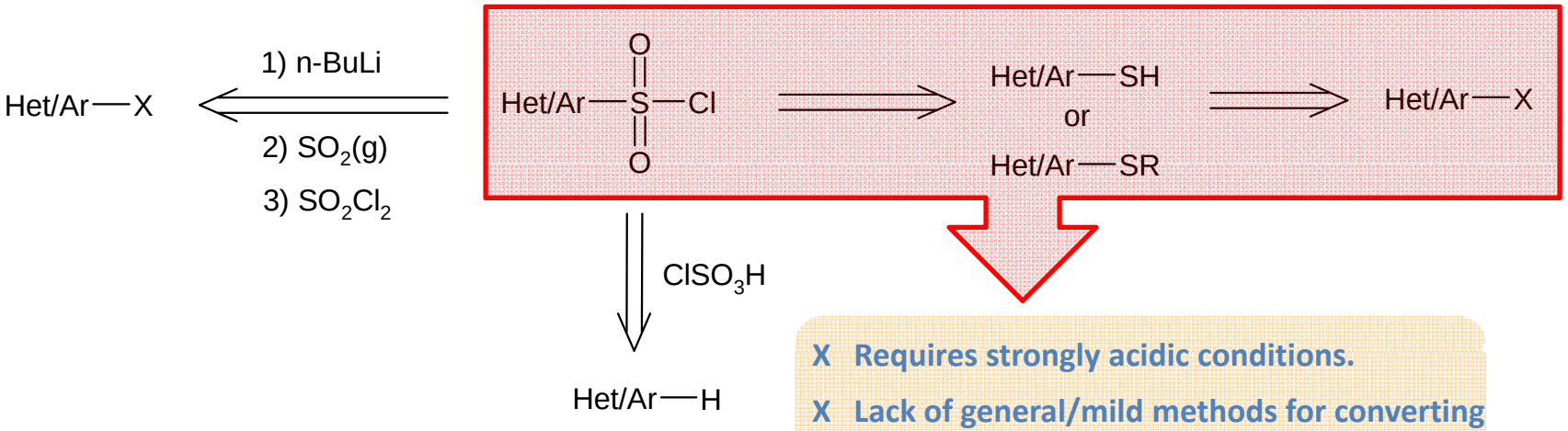
X SO_2 gas- hazardous.

An in house example

•Sulfonamide is another group loved in drug design but substituent scope is generally limited to commercial availability (or “synthesisability”)of sulfonyl chlorides:



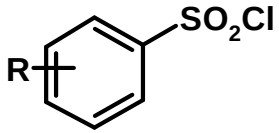
•Common methods to synthesise sulphonyl chlorides:



X Requires strongly acidic conditions.

X Lack of general/mild methods for converting Het/Ar-X to Het/Ar-SH(or R).

• Aryl/heteroaryl halide definitely a better starting point than sulphonyl chloride to maximise chemical space accessed by sulfonamide synthesis. Commercially available in Scifinder:



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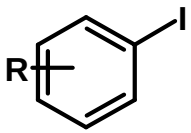
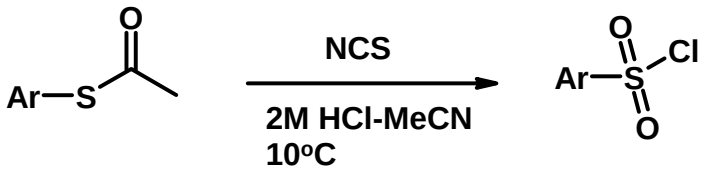


108253

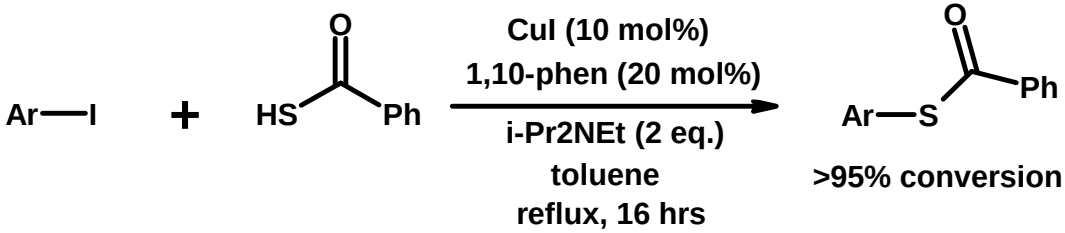
• Oxidation of thioacetates to sulfonyl chlorides well established……



Synthesis. **2006**, 1896-1900

• …but their formation from aryl halides not well precedented.

• However formation of **thiobenzoates** from aryl iodides **is** well precedented….



>95% conversion (HPLC)

Itoh, T. et. al., Tet. Lett., 2006, 6595

• **So how about oxidation of thiobenzoates to sulphonyl chlorides???**

Optimisation Studies

Chlorinating agent	Additives	pH	Result
TCCA (1 eq)[1]	$BnMe_3NCl$ (3 eq), H_2O	2 to 0	90%
TCCA (1 eq)	$BnMe_3NCl$ (3 eq), H_2O, NEt_3 (1 eq)	9-11	No reaction
TCCA (1 eq)	**$BnMe_3NCl$ (3 eq), H_2O, Na_2CO_3 (1 eq)**	**6 to 5**	**87%**
TCCA (1 eq)	$BnMe_3NCl$ (3 eq), H_2O, K_2CO_3 (1 eq)	~4	100%*
TCCA (1 eq)	$BnMe_3NCl$ (3 eq), H_2O, NaOAc (1 eq)	~1	100%*
HOCl (~3eq)	None	1-2	Little reaction
HOCl (~3eq)	NaOAc (2 eq)	8	Little reaction

* Crude Yield

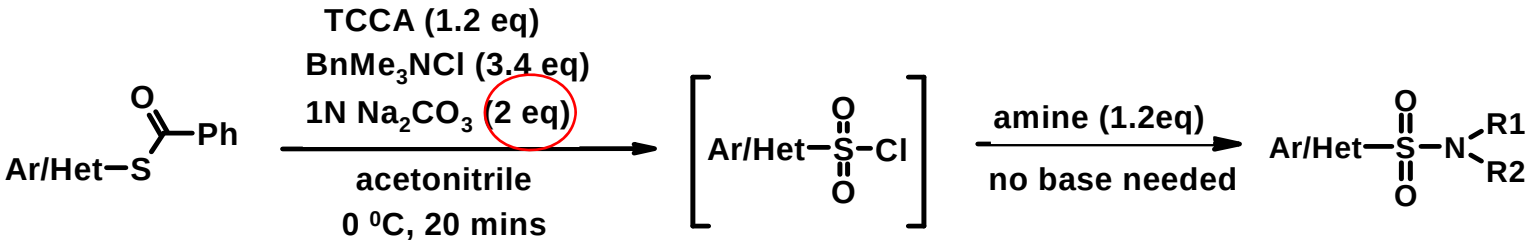
[1] Bonk, J. et. al., *Syn. Comm.*, **2007**, 2039

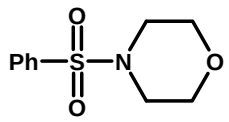
Tet. Lett **2011**, *52*, 820-823

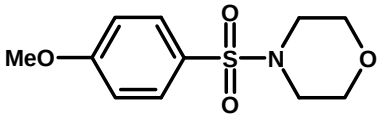
• Developed buffered conditions to carry out required oxidation and also allow toleration of acid labile groups – improved functional group compatibility:

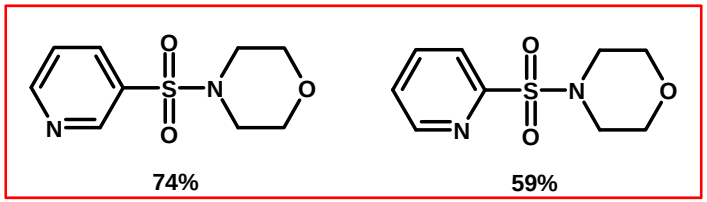
One-pot oxidation/sulfonamide formation

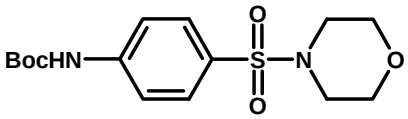
- A second equivalent of base added at the start allows sulfonamides to be formed in one pot, upon addition of appropriate amine. Good for unstable SO_2Cl!




81%


70%


74% 59%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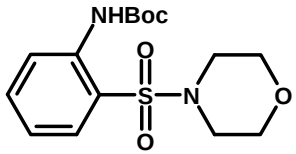
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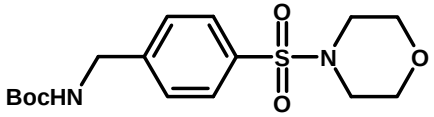
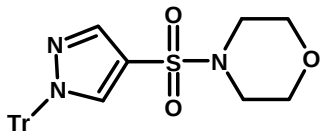

85%

Pfizer *Tet. Lett* **2011**, *52*, 820-823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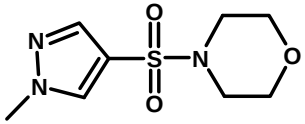
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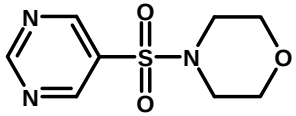
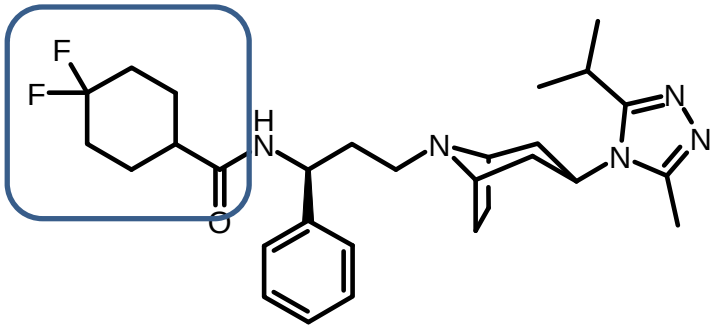

0%

- **Overall 2 step protocol: aryl/heteroaryl halide to sulfonamide– chemical space expansion!**

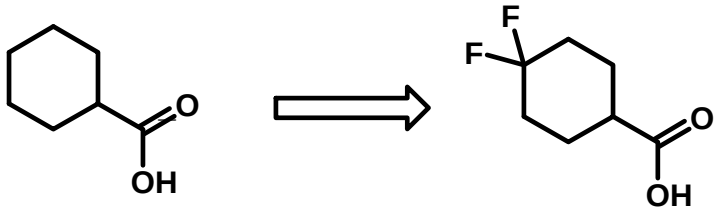
Accessing chemical space (II) Ideal medicinal chemistry fragments

Maraviroc



CCR5 inhibitor for HIV
Discovered in Sandwich

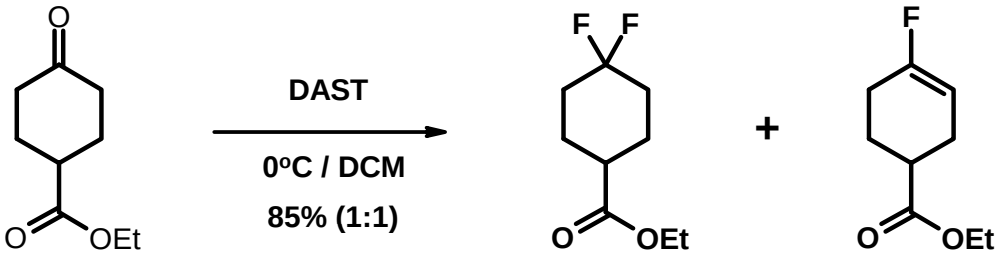
- Difluorocyclohexane carboxylic acid – a simple molecule but…



- Improved metabolic profile and reduced lipophilicity
- Drastically reduced hERG liability due to dipole of gem difluoro

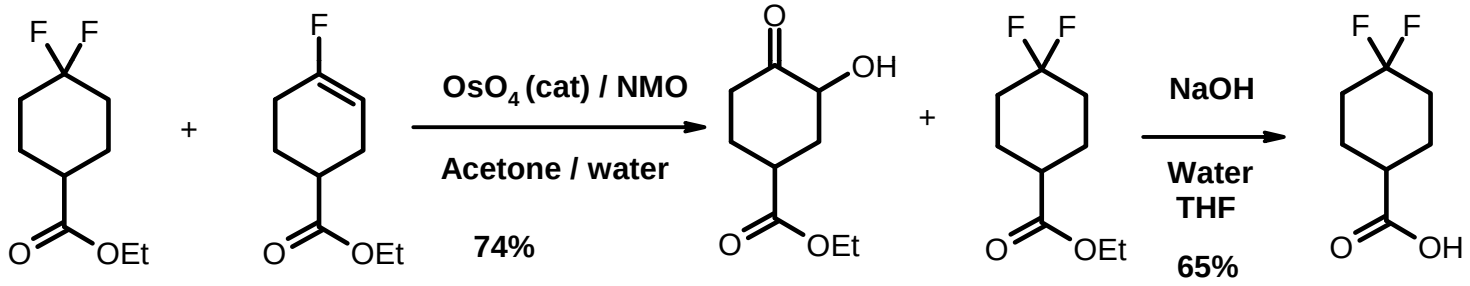
Biorg. Med. Chem. Lett. **2006**, *16*, 4633-4637

Synthesis

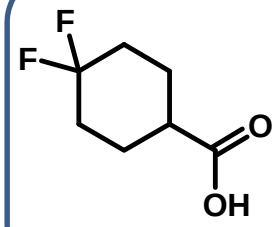


Tet. Lett. (2005), 5005

- Fluorination of ketone gave an inseparable mixture of difluoro and vinyl fluoride..

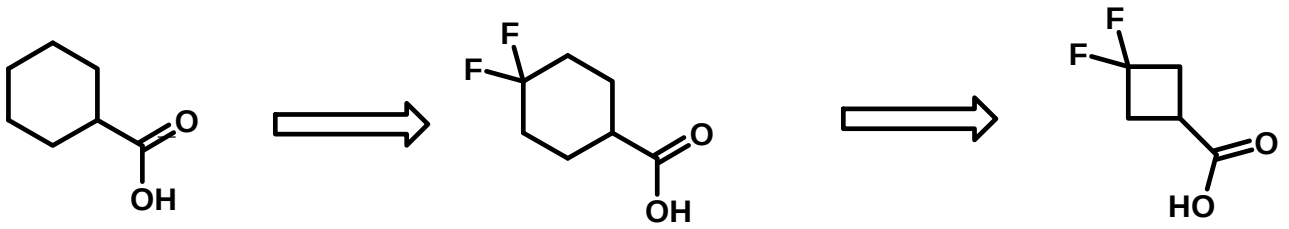


- Separate difluoro-ester by silica chromatography
- Straightforward chemistry but accesses a nice fragment with better physicochemical properties
- Others agree!

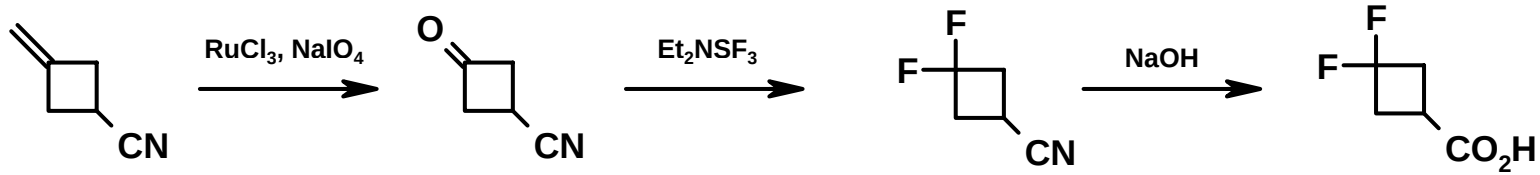


	Scifinder hits:
Before Maraviroc	2
Since Maraviroc	74

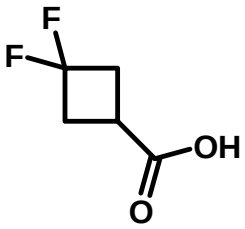
Further reducing lipophilicity



- Existing difluorocyclobutane synthesis impractical – toxic reagents/solvents
- Improved synthesis:



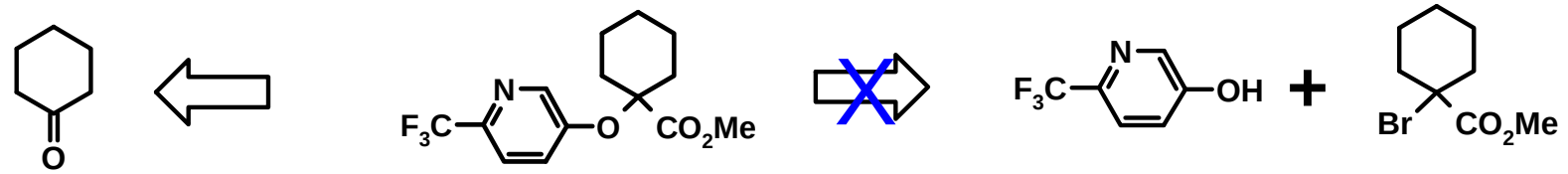
Synlett, **(2005),** 657



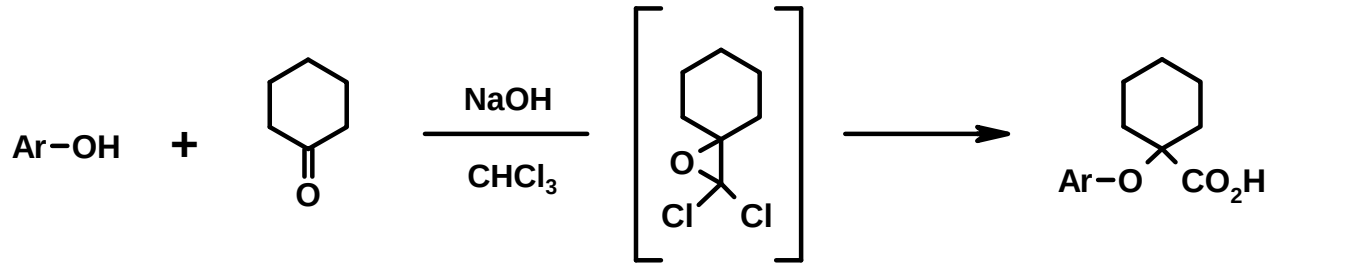
	Scifinder hits:
Before Synlett	2
Since Synlett	34

Synthetic innovation drives chemical space expansion

- Hindered ether target



- Ancient literature holds the key:



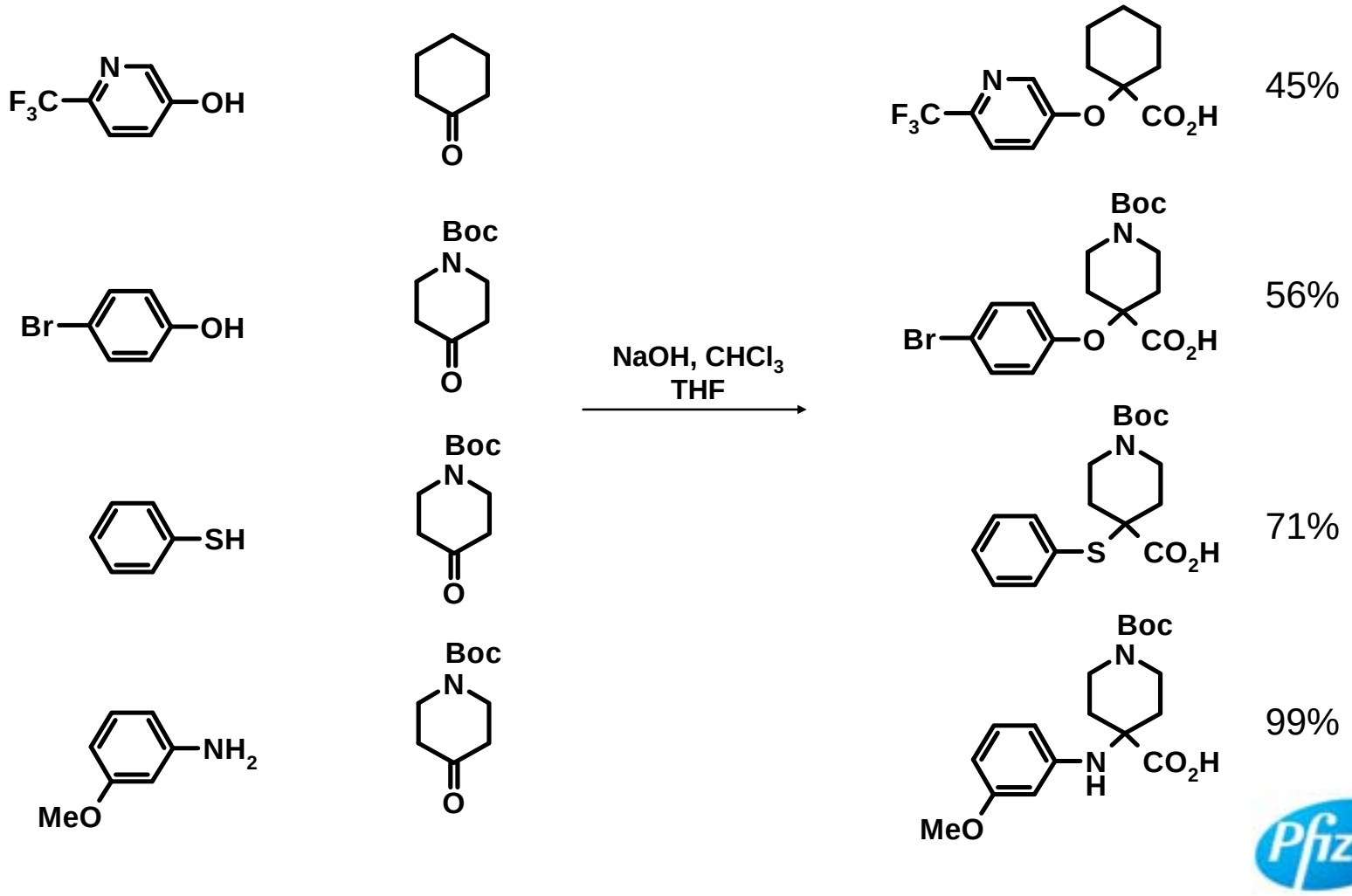
Bargellini reaction (1906)

- Reaction generates dichlorocarbene, which adds across ketone

- **Now comes the innovation; what else can we use in this reaction??**

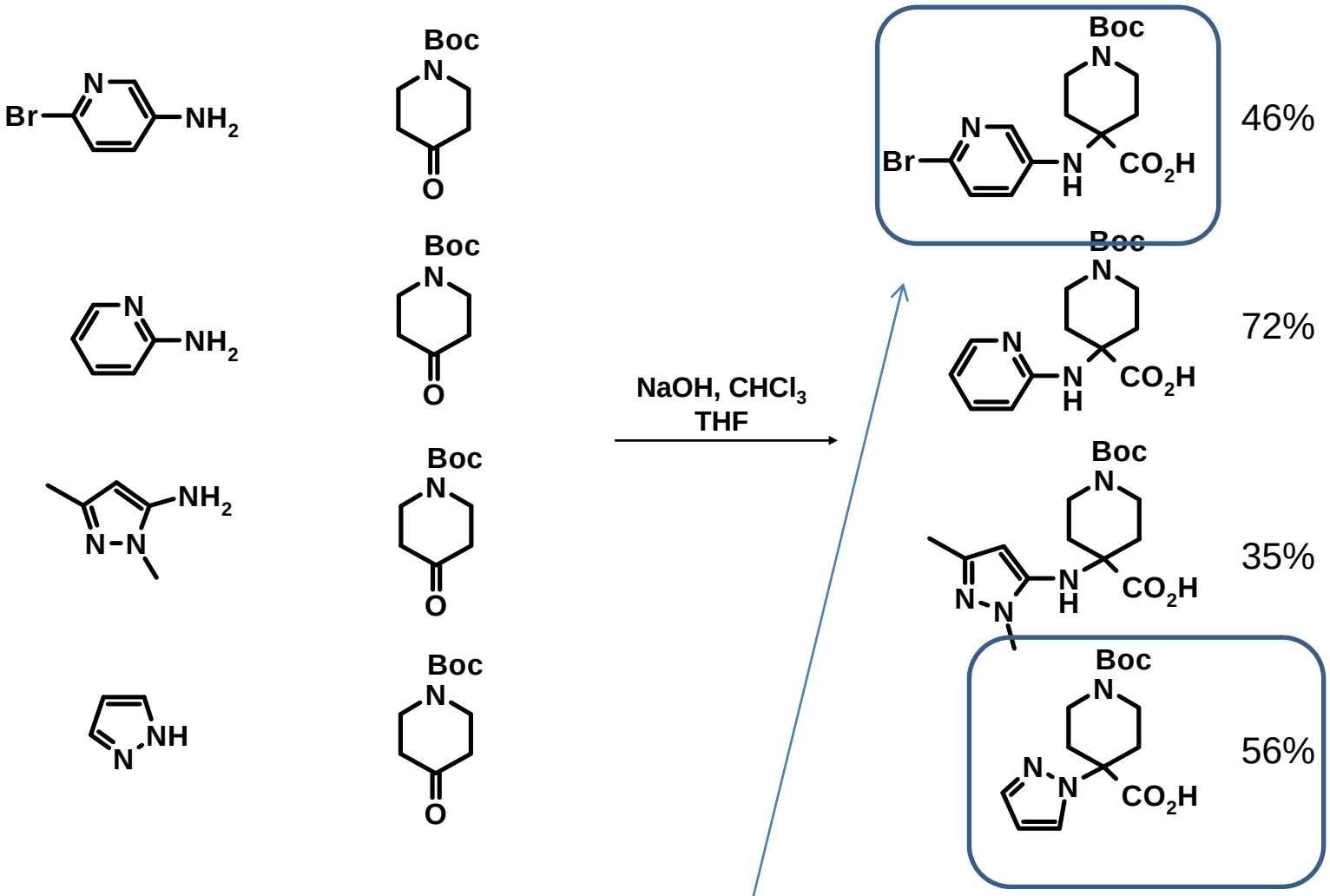
Different nucleophiles and ketones?

Original Bargellini reaction used phenols only.



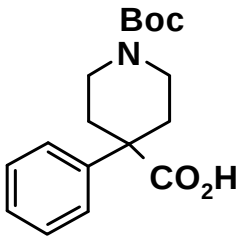
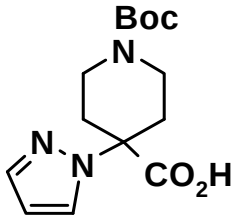
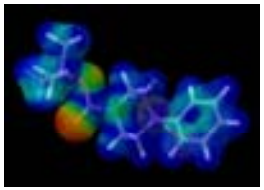
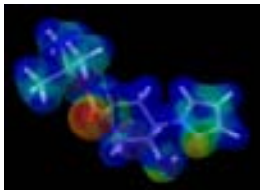
Pfizer

"Perfect" medchem fragments……



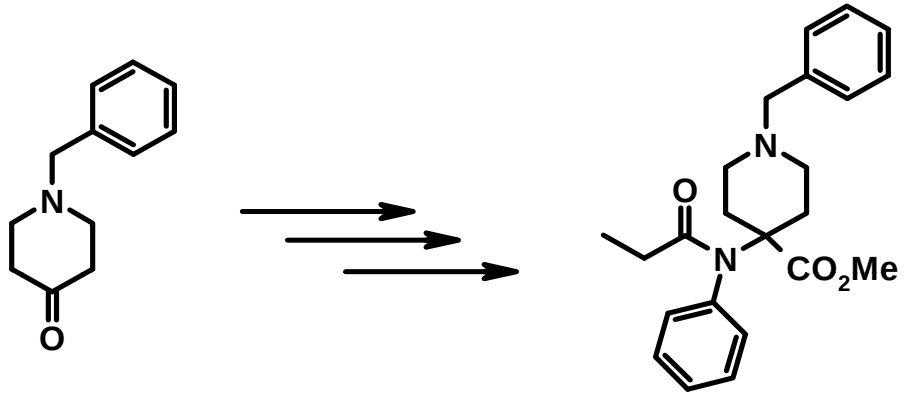
4 points of synthetic diversity!!

Compare and contrast…….

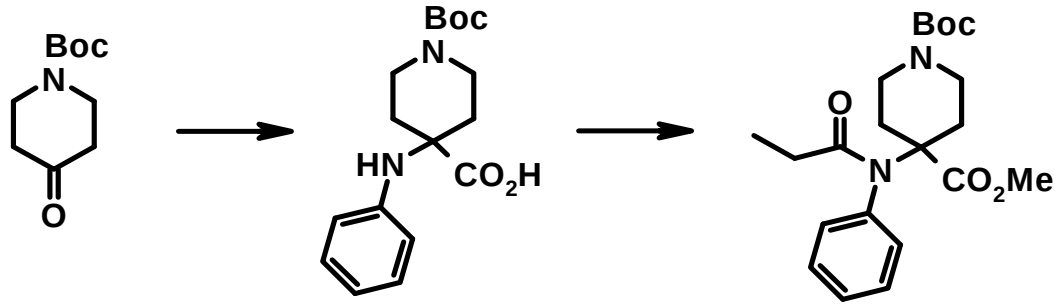
		
SciFinder Hits	>>10,000	1
δ pKa (-2)	4.1	2.1
δ cLogP (-1.6)	2.9	1.3
δ TPSA (+18)	67	85
δ MWt (-10)	305	295
Dipole		
Availability	Aldrich	Now 4 suppliers!

Improved synthesis of a Carfentanil intermediate

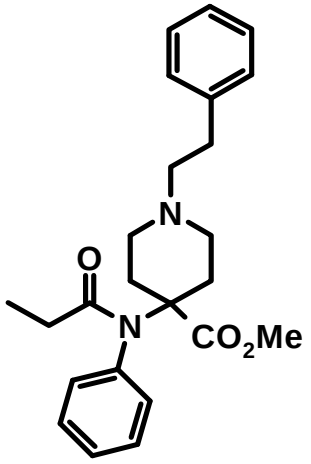
Original synthesis



Strecker, CH_3I, 3 day amide formation



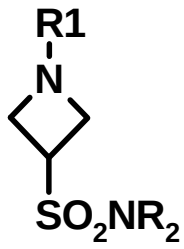
i. Aniline, NaOH, $CHCl_3$, THF, 70%,
ii. Propionic anhydride, Et_3N iii. MeOH



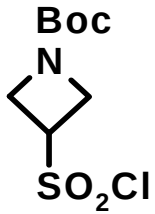
Carfentanil

Tet. Lett. 2009, 2497

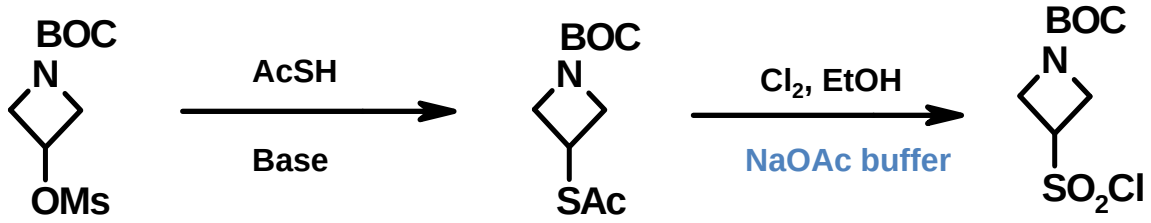
Another great fragment



- How many ‘hits’ in SciFinder for this substructure?
- <10 - makes it novel design space
- Polar, bifunctional, unusual vectors, pKa



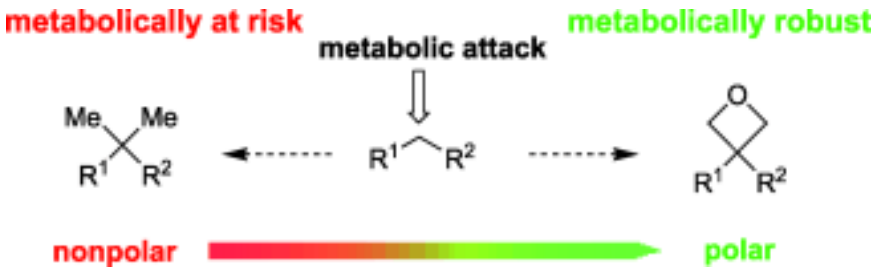
- This would be the perfect intermediate – but has never been reported!
- Generally sulfonyl chloride synthesis requires harsh conditions. New synthetic methodology solves the problem.



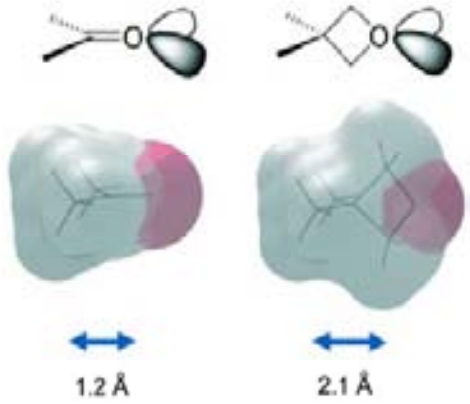
Pfizer

Innovation from the literature

- Oxetanes very much in vogue in medicinal chemistry recently

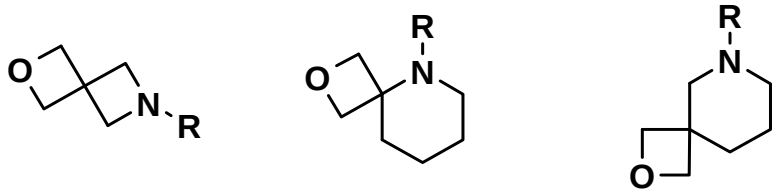


As metabolic blocking groups…



…or as carbonyl isosteres

- Seminal paper from Carreira synthesised some very useful spirocyclic oxetanes:

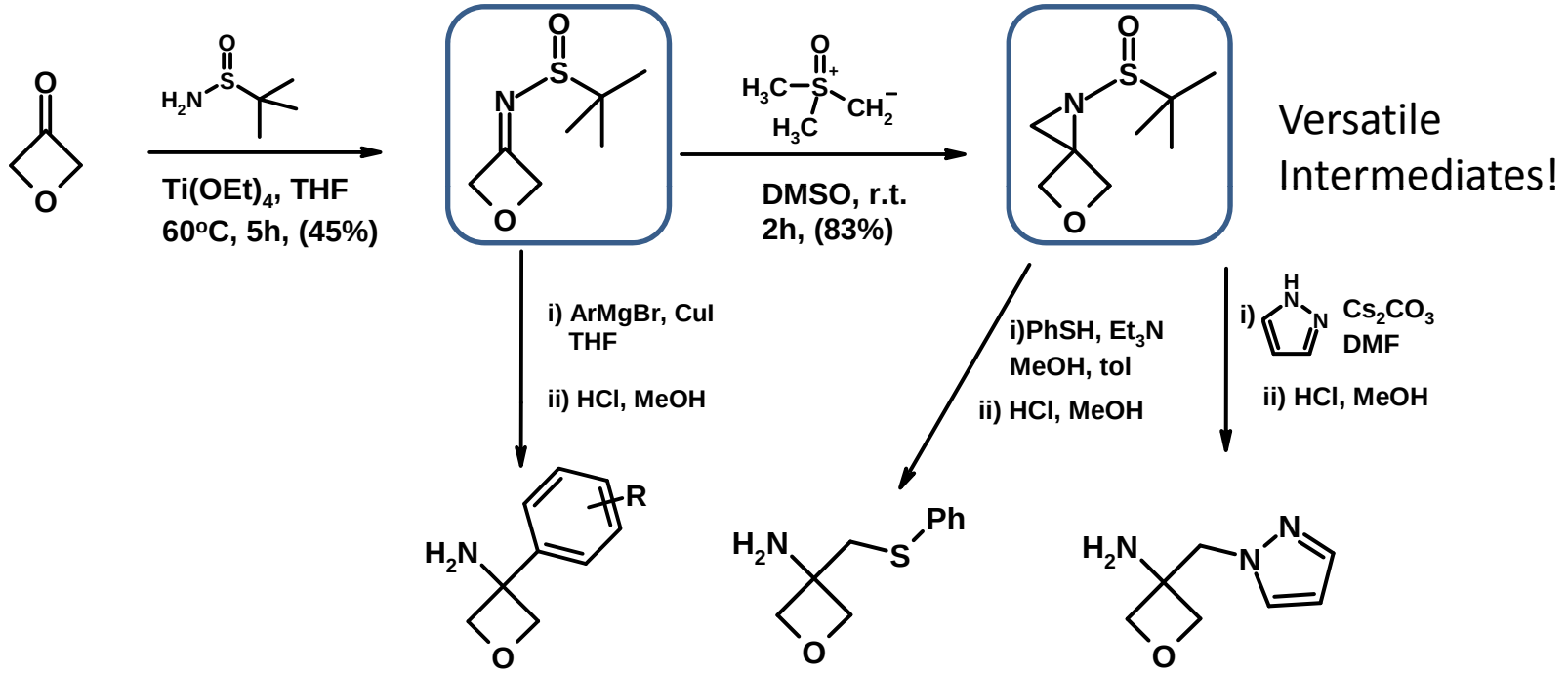


Angew. Chem. Int. Ed. **2008**, *47*, 4512-4515

Pfizer

Oxetane diversity

- Great paper from Merck
- Amino oxetanes – modulated pKa, possible amide isostere?



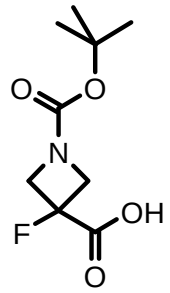
Org. Lett. **2010**, *12*, 1116-1119

Conclusions

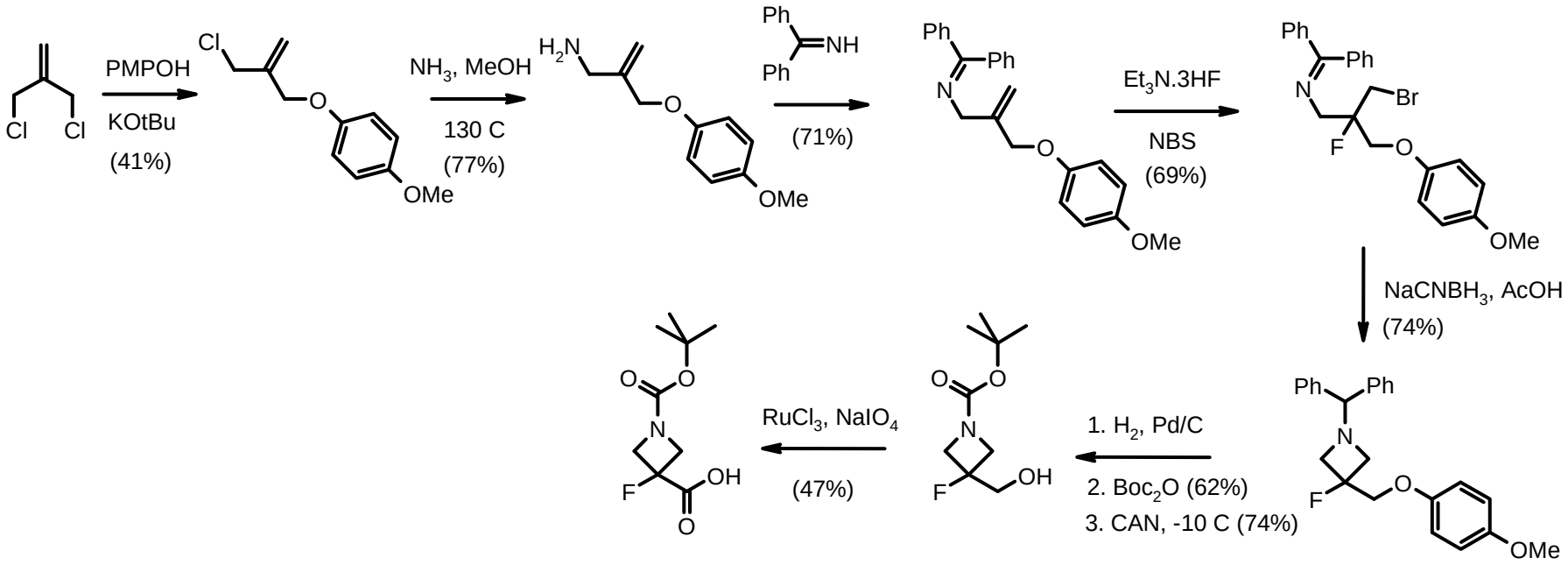
• Innovative synthesis is the cornerstone of chemical space exploration and expansion

• New takes on ubiquitous reactions utilising more commonly available substrates to increase substituent scope are clearly desirable.

• Population of chemical space with small expressions of polarity and lipophilicity containing 1 or 2 points of diversity, is highly desirable but…….



Not if it's a 9 step route…….



JOC, 2009, **74**, 2250-2253

Conclusions

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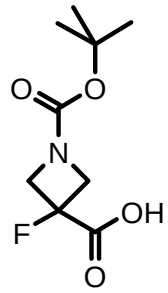


• **Must be accessible in a relatively small number of steps**

• **Synthetic Innovation can come from anywhere. Communication and collaboration between the pharmaceutical industry and academia is key.**

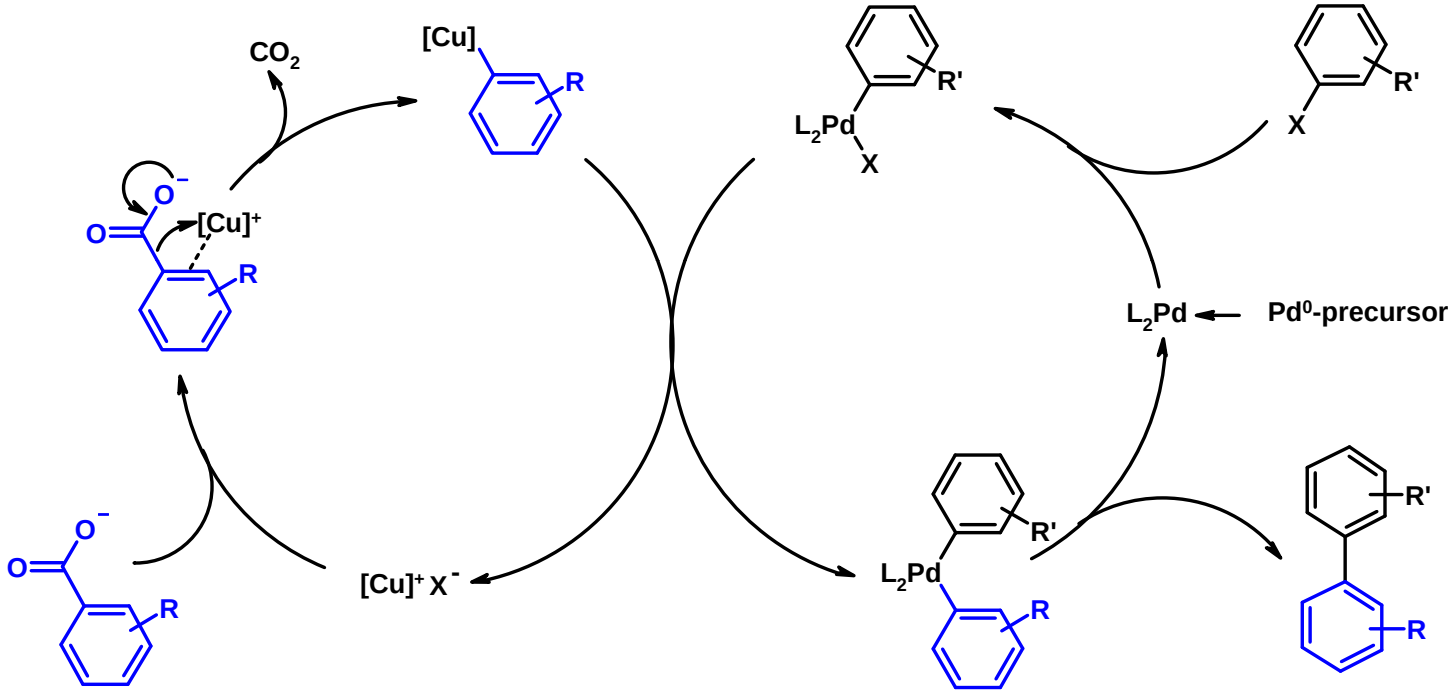
Acknowledgements

Dafydd Owen
David Blakemore
Danny Ho
Lily Chan
Ken Butcher
Pete Wilson
Matt Selby
Jonathan Fray
Andrew Cronin
Nunzio Sciammetta
All other synthetic chemists at Sandwich

Backups

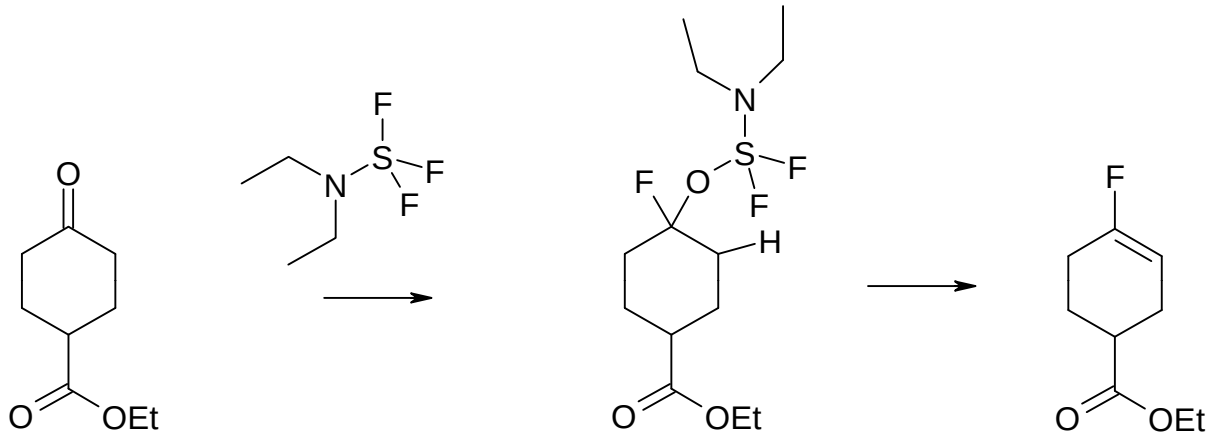
Goossen Mech

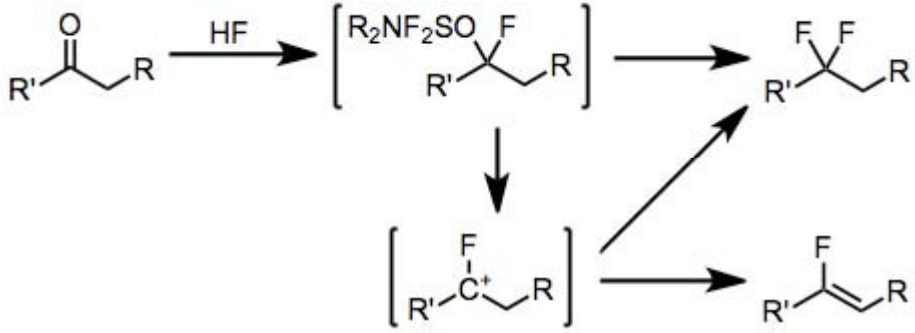
- Combination of a decarboxylation with a Pd-catalyzed cross-coupling



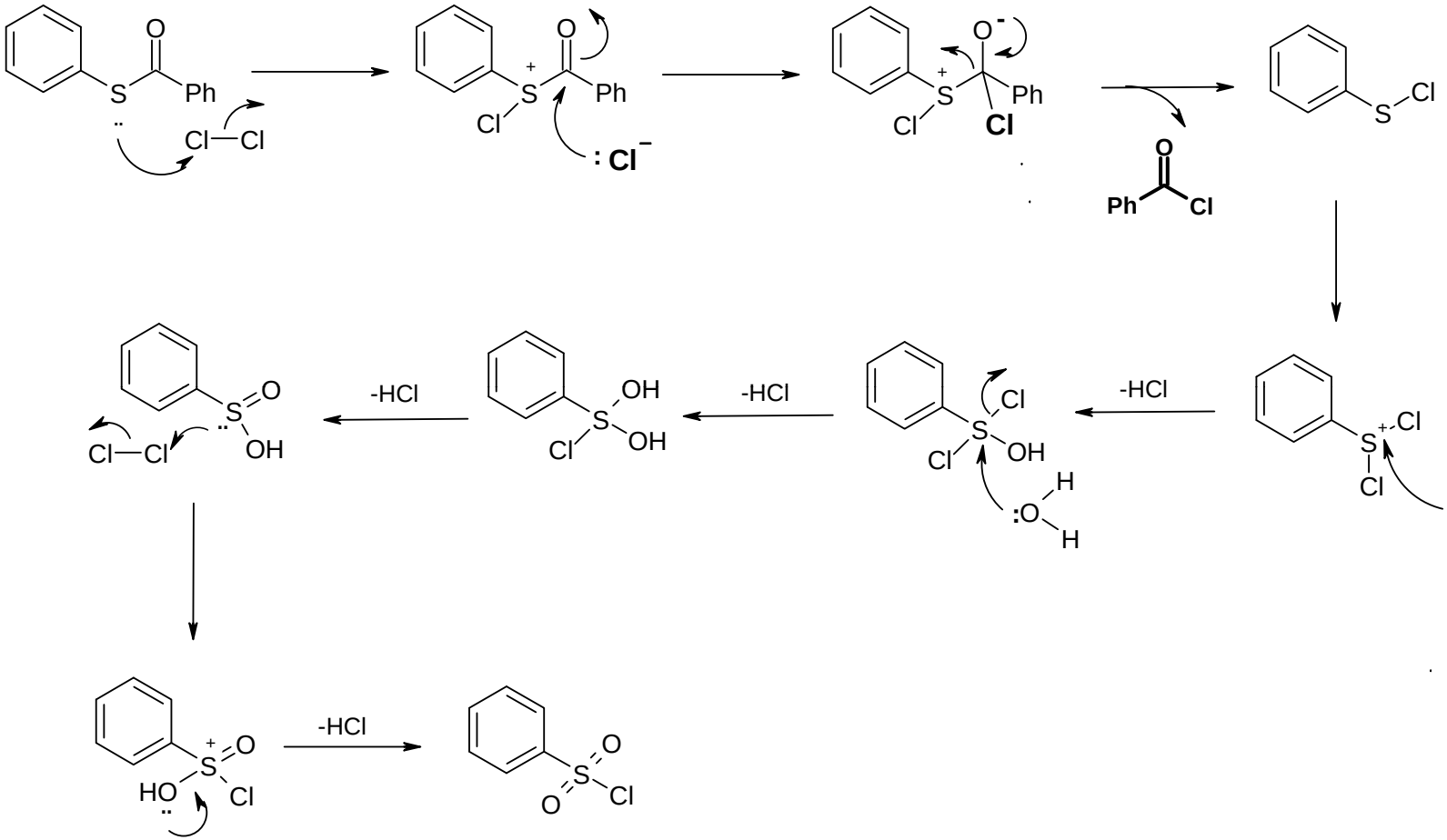
  - In principle, only a catalytic amount of copper is required
  - Ligand exchange between potassium carboxylate and copper halide closes a second catalytic cycle

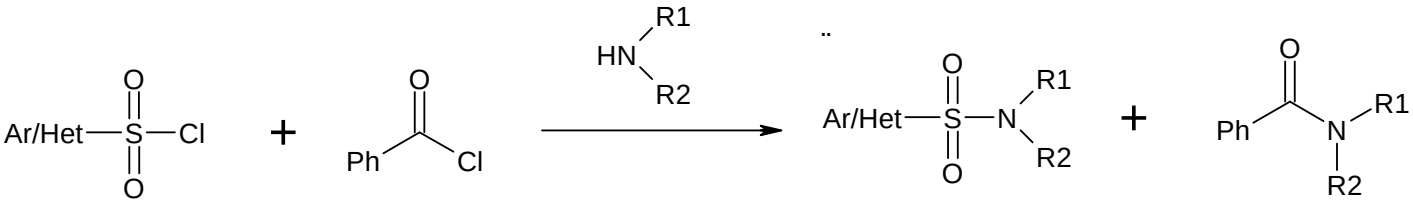
Origin of vinyl fluoride



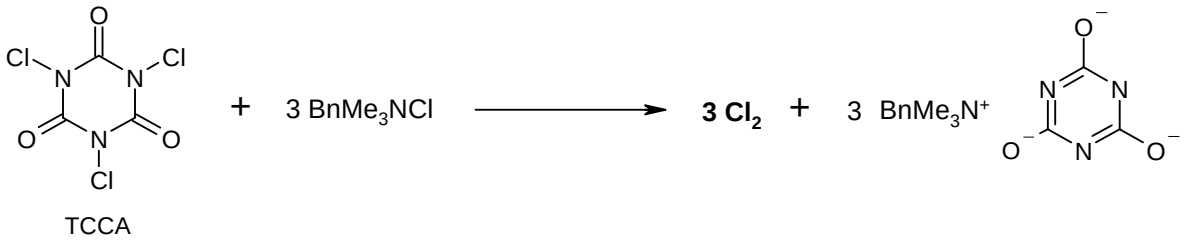


Thiobenzoate Oxidation mechanism





- It is believed that Cl_2 is generated in-situ, so Cl_2 is the actual oxidant.



Practical observation:

- Need to premix TCCA and R_4NCl.
- Solution goes green upon mixing.