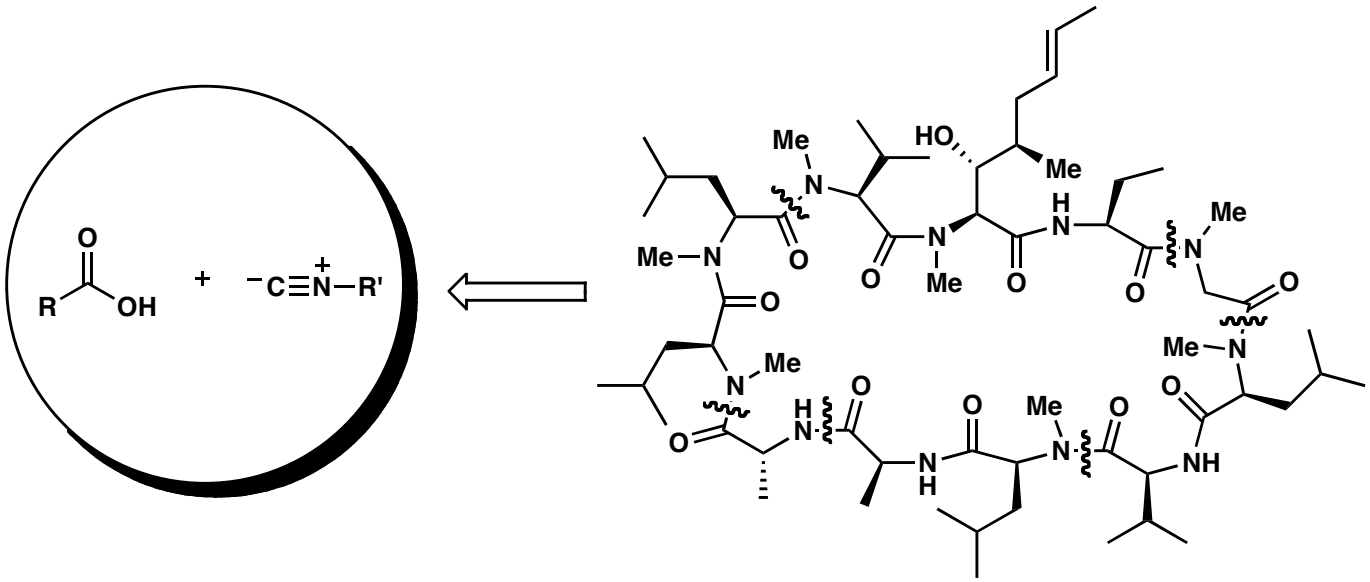
Total Synthesis of Cyclosporine: Access to *N*-Methylated Peptides via Isonitrile Coupling Reactions

Xiangyang Wu, Jennifer L. Stockdill, Ping Wang, Samuel J. Danishefsky*

J. Am. Chem. Soc. **2010**,*132*, 4098-4100



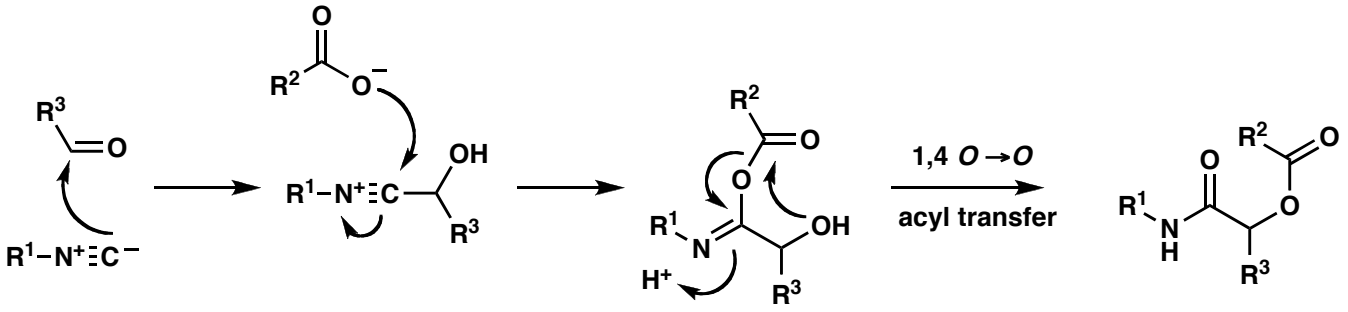
Adam T. Hoye

Current Literature

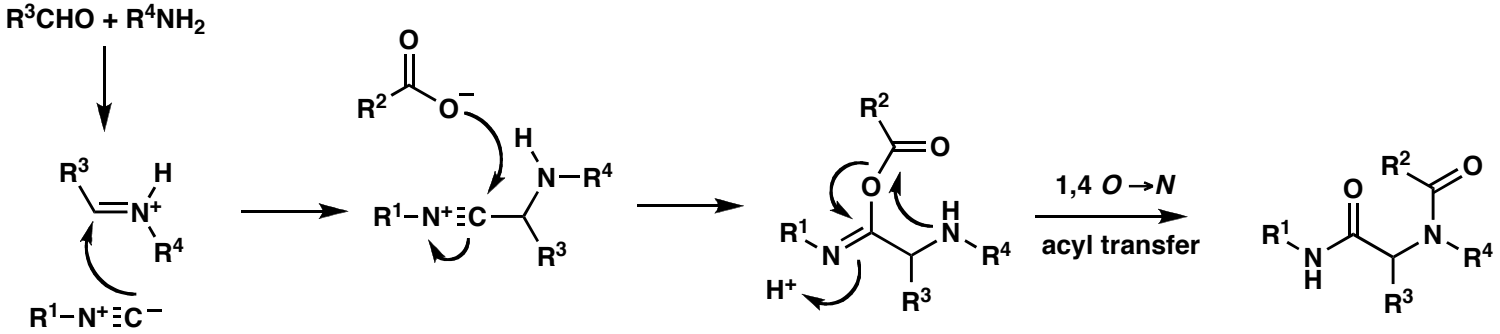
March 27, 2010

Historical perspective and hypothesis

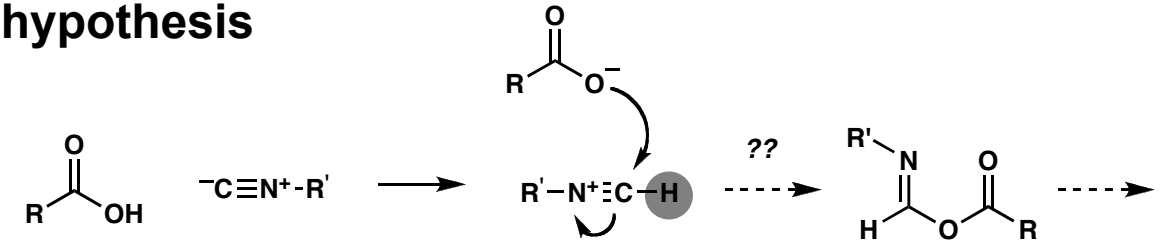
Passerini reaction



Ugi four-component coupling reaction

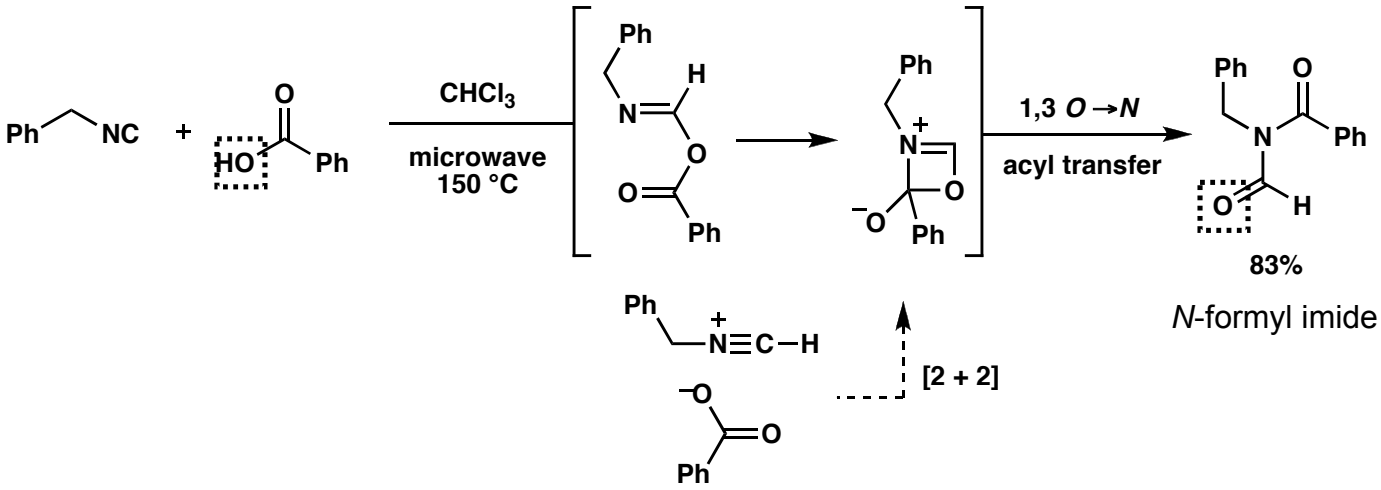


Current hypothesis

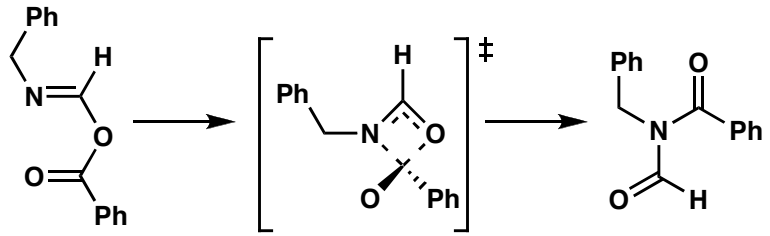


Li, X.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2008**, *130*, 5446-5448

Initial discovery



"concerted pseudopericyclic [1,3]-acyl rearrangement"

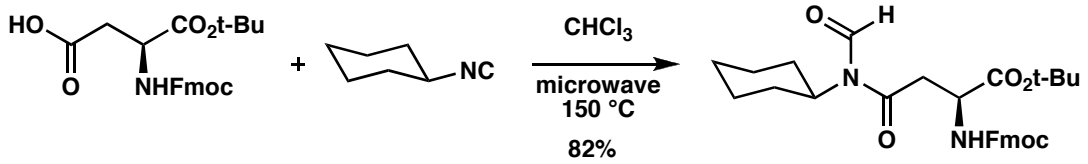


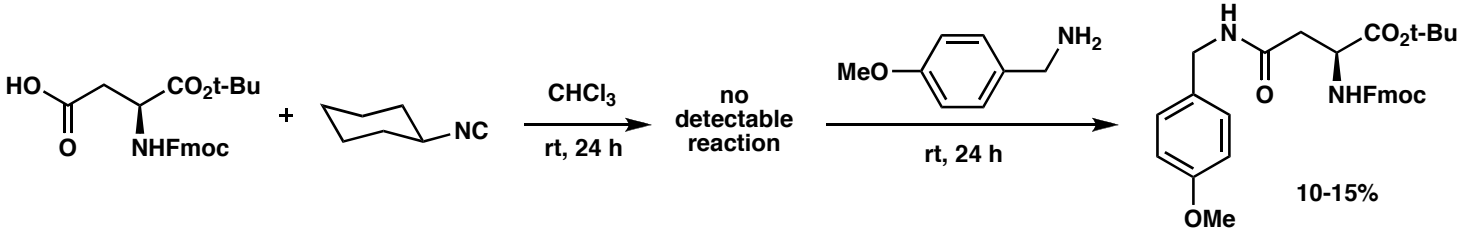
FCMA

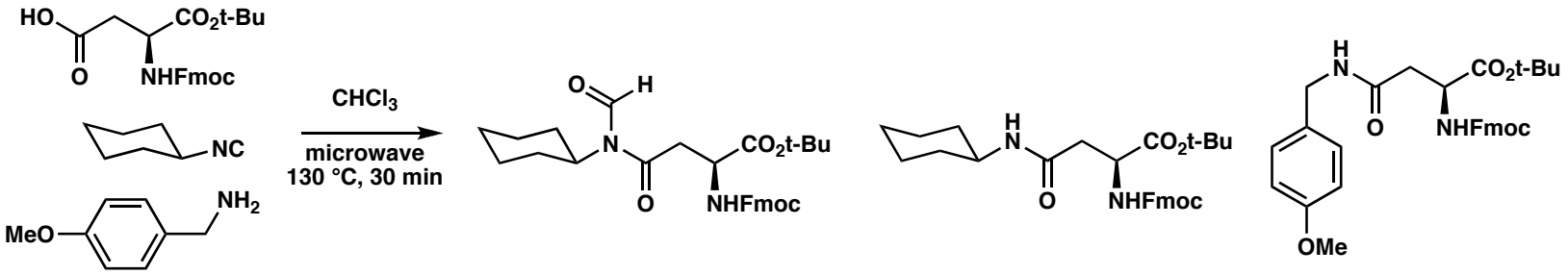
"Formamidine Carboxylate Mixed Anhydride"

Jones, G. O.; Li, X.; Hayden, A. E.; Houk, K., N.; Danishefsky, S. J. *Org. Lett.* **2008**, *10*, 4093-4096.

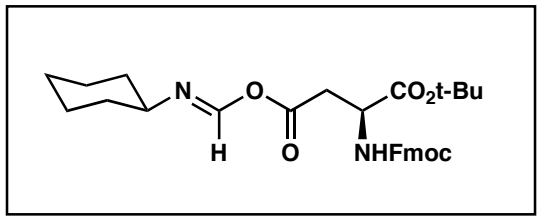
Probing reaction conditions







1.3 : 1.0 : 2.0

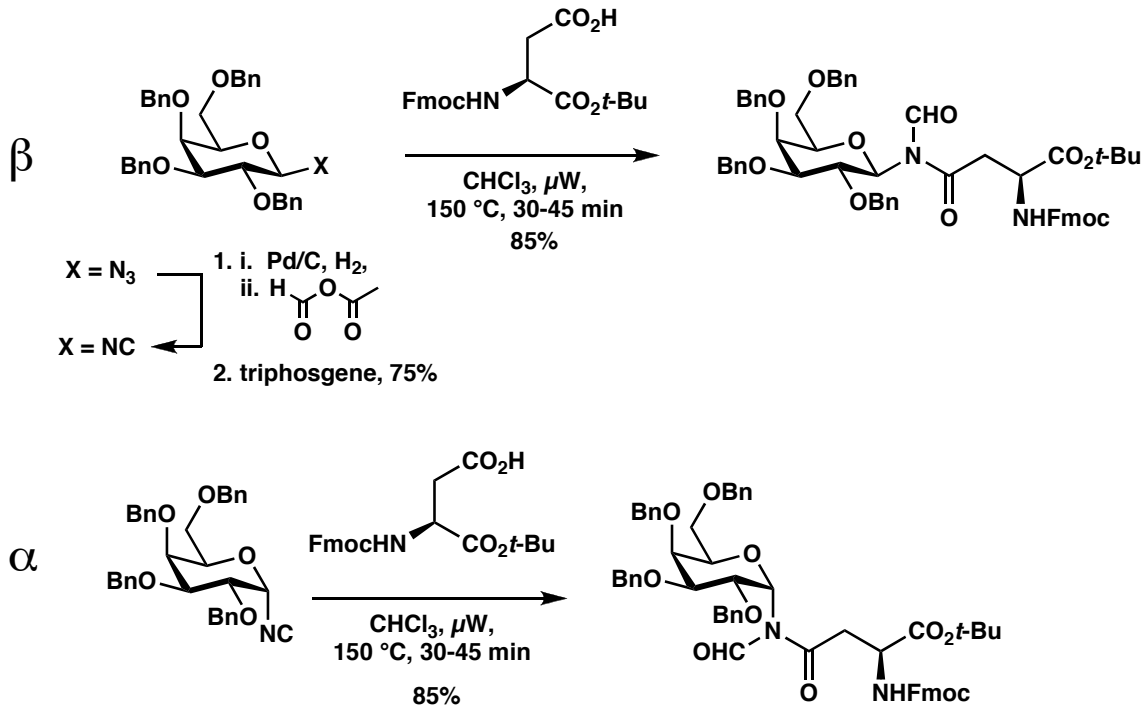


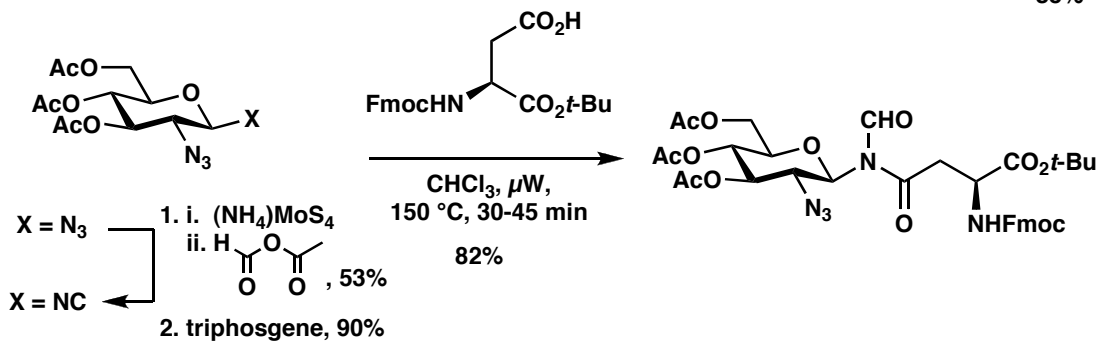
common intermediate

Li, X.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2008**, *130*, 5446-5448

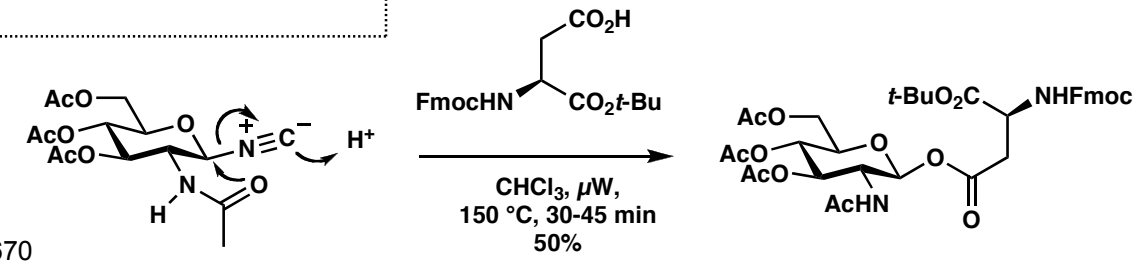
Application to asparagine-linked glycopeptides

Anomerically-specific glycosidic imidations





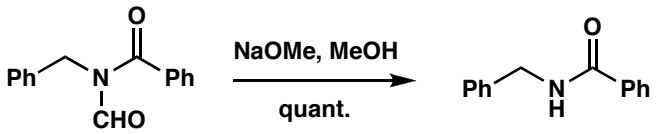
Glycosidic esterification

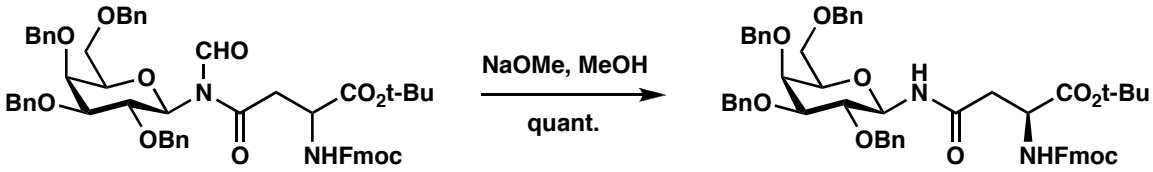


Also see: Li, X.; Danishefsky, S. J. *Nat. Protoc.* **2008**, *3*, 1666-1670

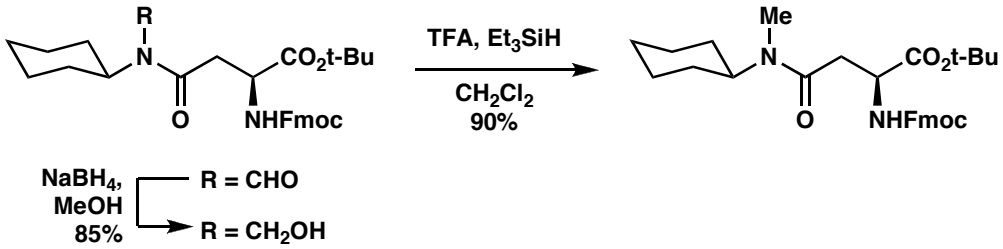
N-Formyl imide manipulations

Deformylation

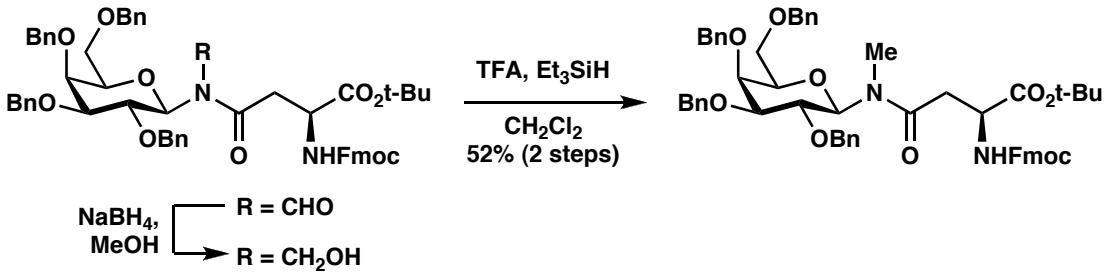




Reduction

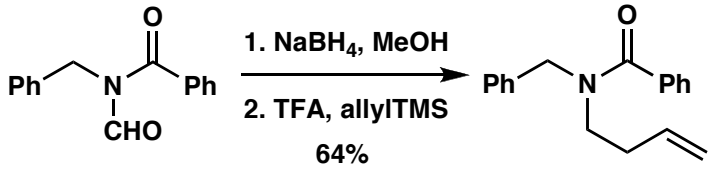


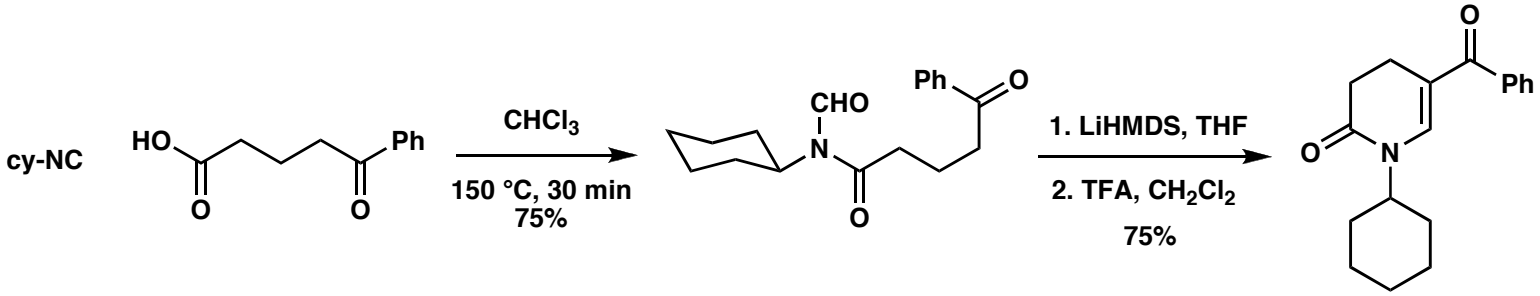
Tertiary *N*-Me amides!



N-Formyl imide manipulations

Further functionalization





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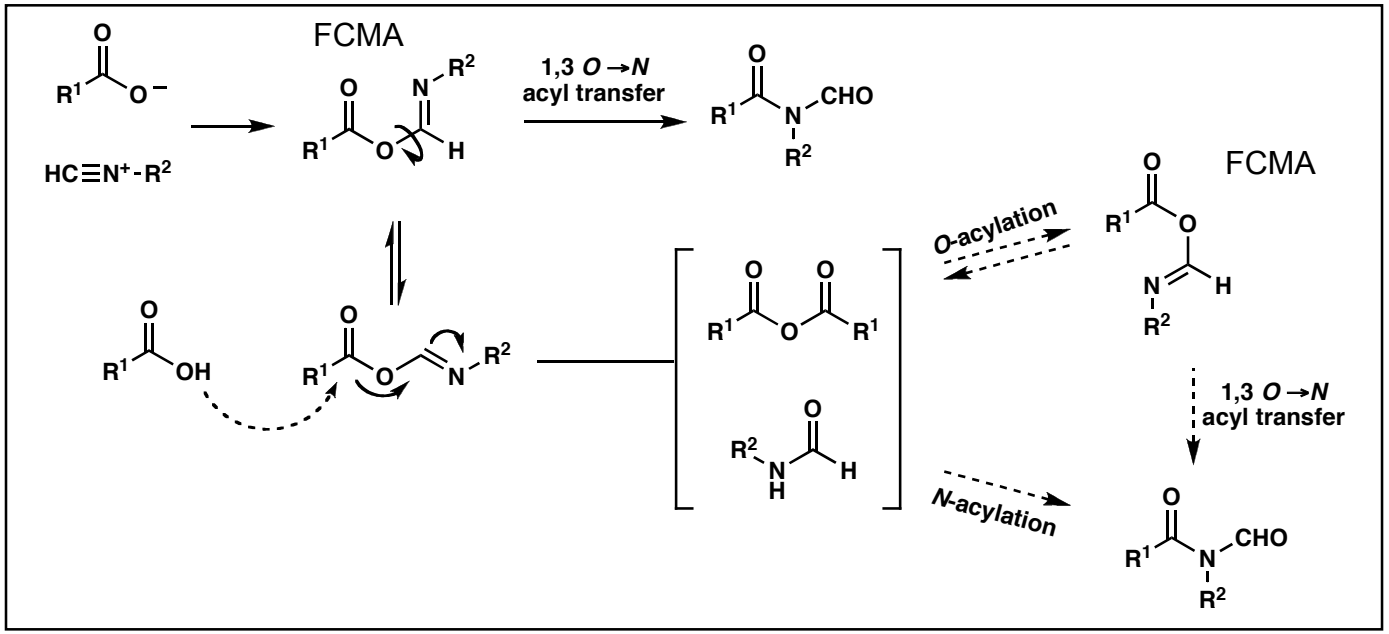
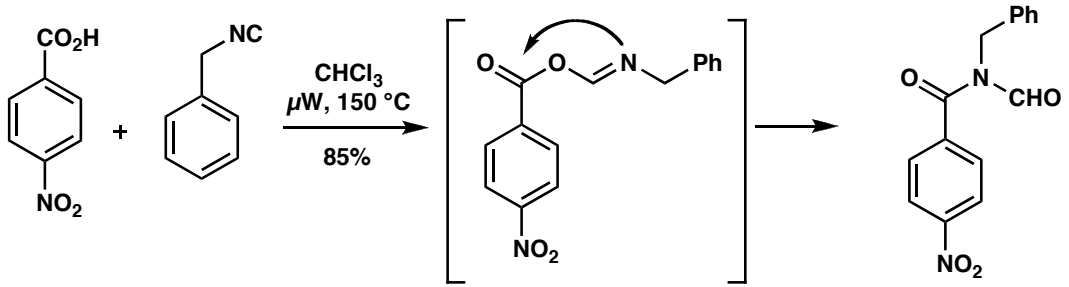
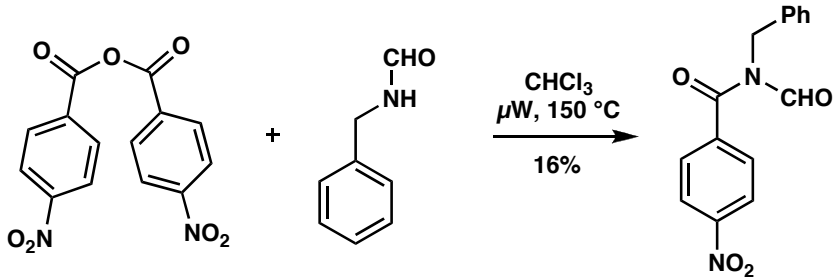
Mechanistic investigations





"Formamidine Carboxylate Mixed Anhydride"

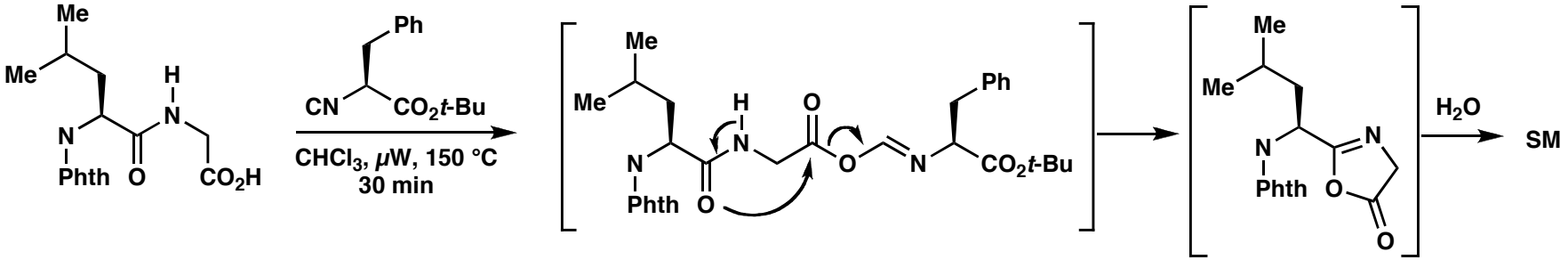


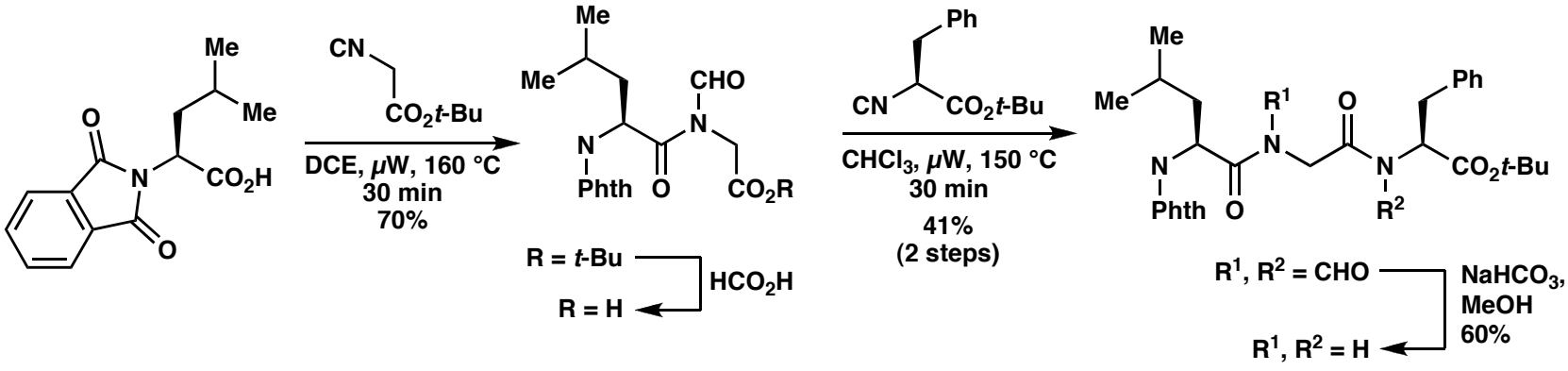
-Anhydride mechanism *could* be minor contributor to mechanism

-Possibility of anydride conversion to FCMA and acyl transfer

Li, X.; Yuan, Y.; Kan, C.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2008**, *130*, 13225-13227

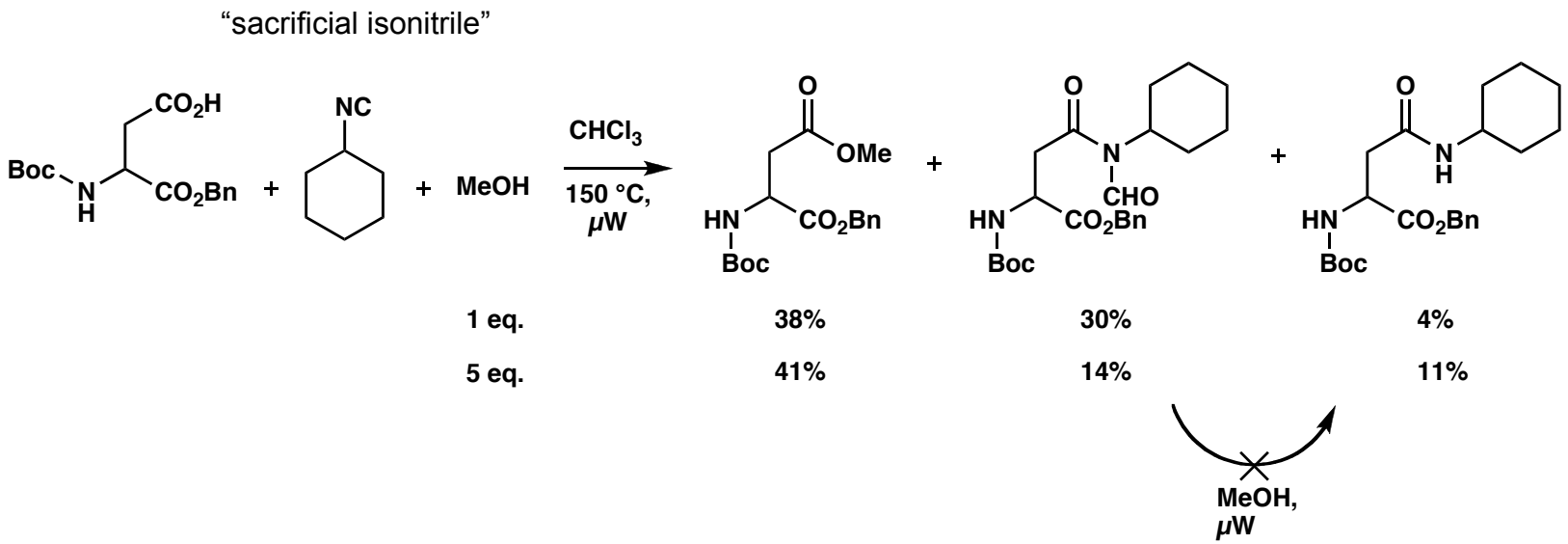
Iterative isonitrile couplings



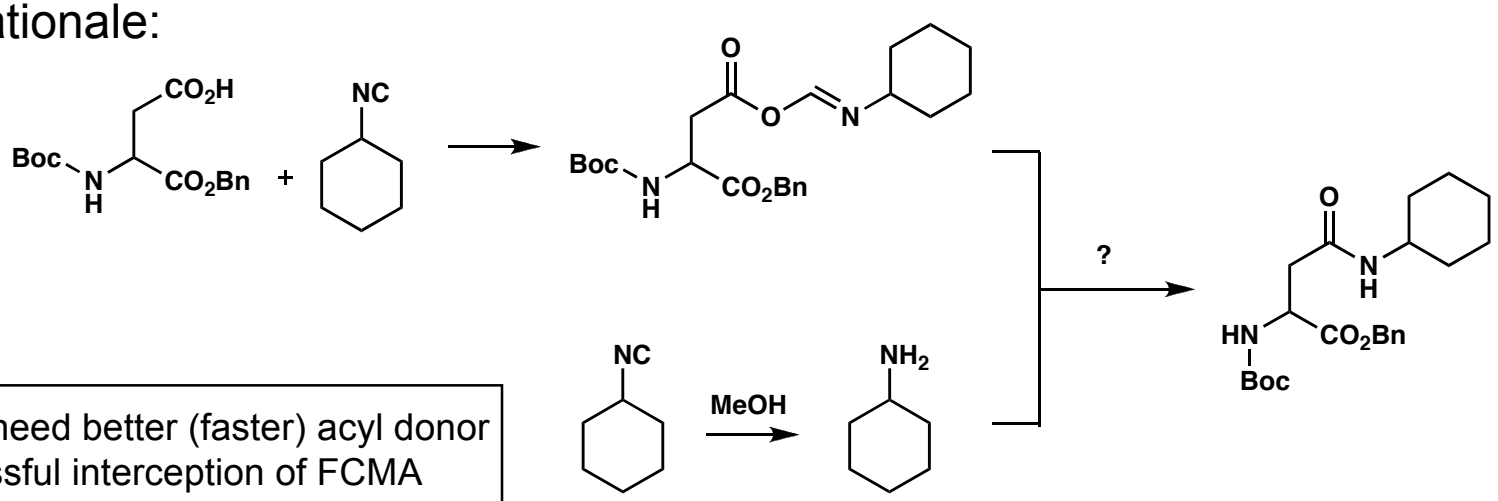


Li, X.; Yuan, Y.; Kan, C.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2008**, *130*, 13225-13227

Interception of FCMA



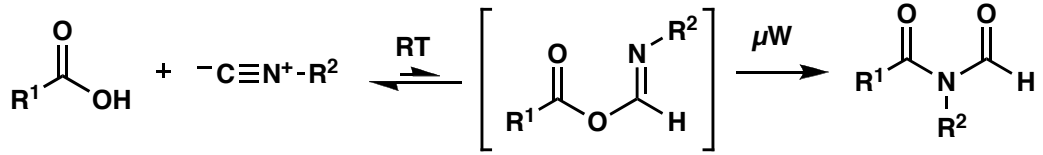
Rationale:



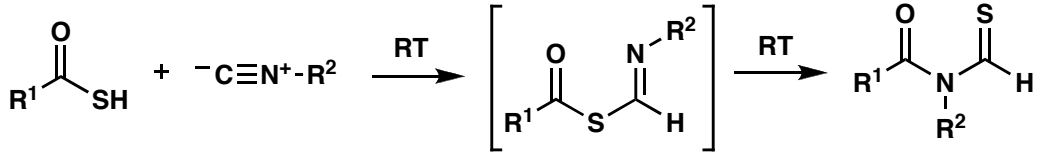
Solution: need better (faster) acyl donor for successful interception of FCMA intermediate

Sulfur effect

oxo-FCMA formation and rearrangement

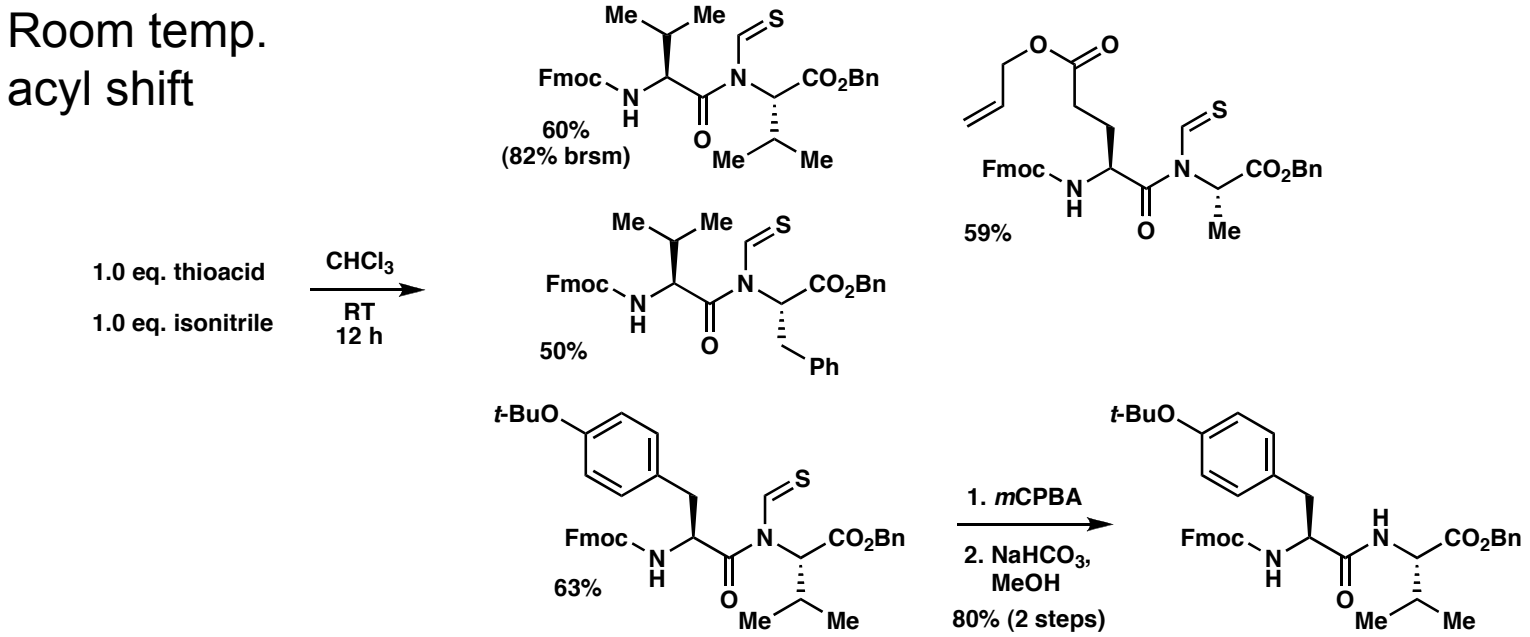


thio-FCMA formation and rearrangment



thio-FCMA

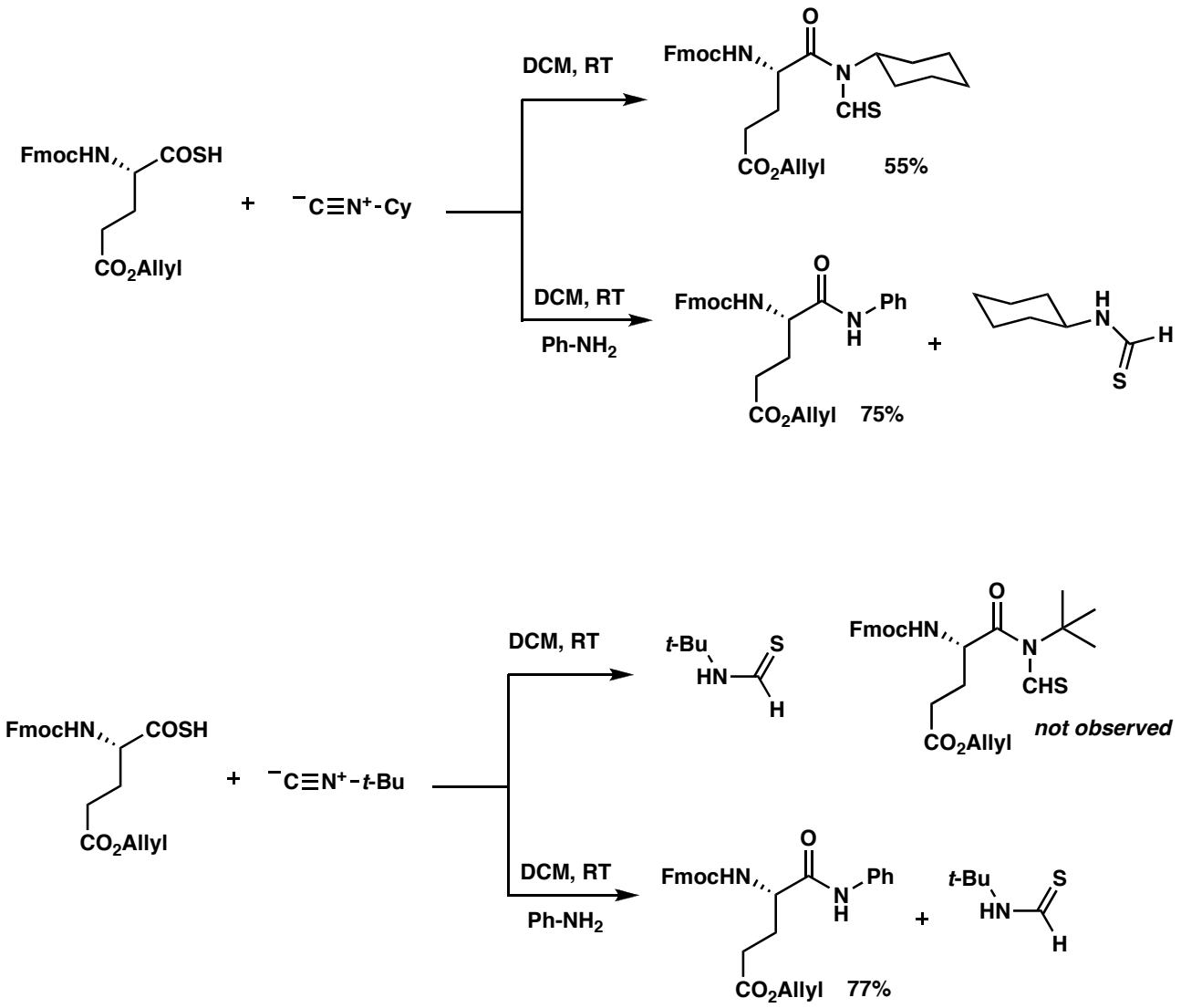
Room temp. acyl shift



Rao, Y.; Li, X.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2009**, *131*, 12924-12926
Yuan, Y.; Zhu, J.; Li, X.; Wu, X.; Danishefsky, S. J. *Tetrahedron Lett.* **2009**, *50*, 2329-2333

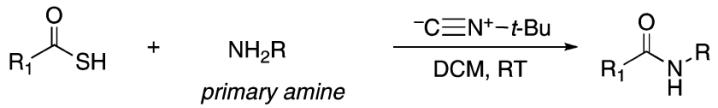
More reactive, but better acyl donors?

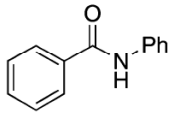
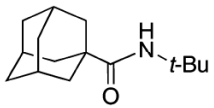
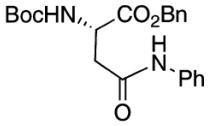
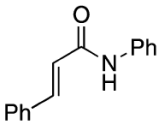
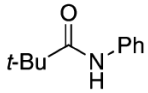
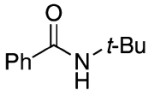
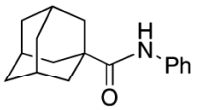
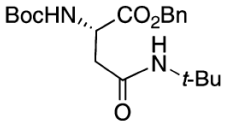
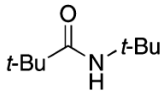
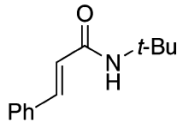
Sulfur effect



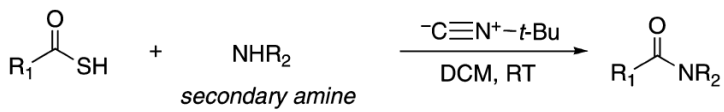
Substrate scope

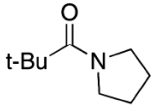
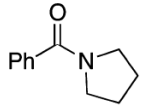
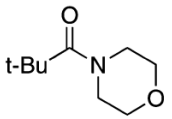
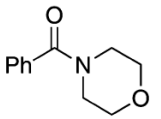
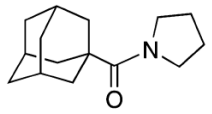
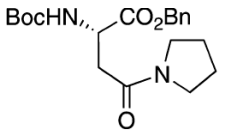
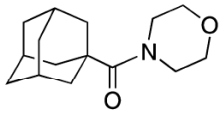
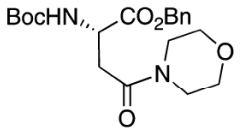
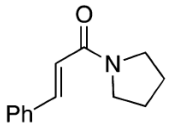
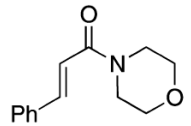
Secondary amides

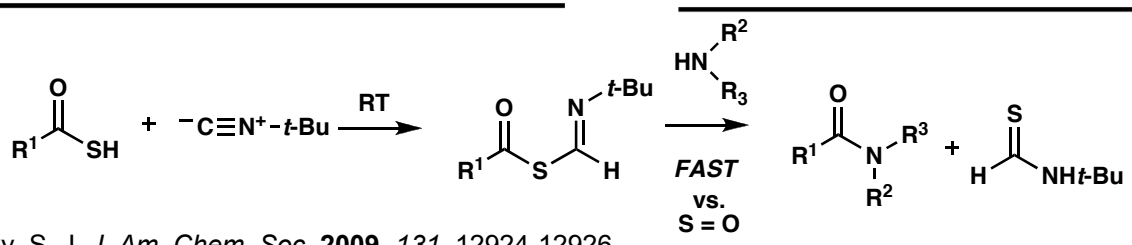


		Isolated Yield			Isolated Yield
	**18**	88%		**23**	72%
	**19**	86%		**24**	86%
	**20**	83%		**25**	80%
	**21**	85%		**26**	77%
	**22**	61%		**27**	81%

Tertiary amides



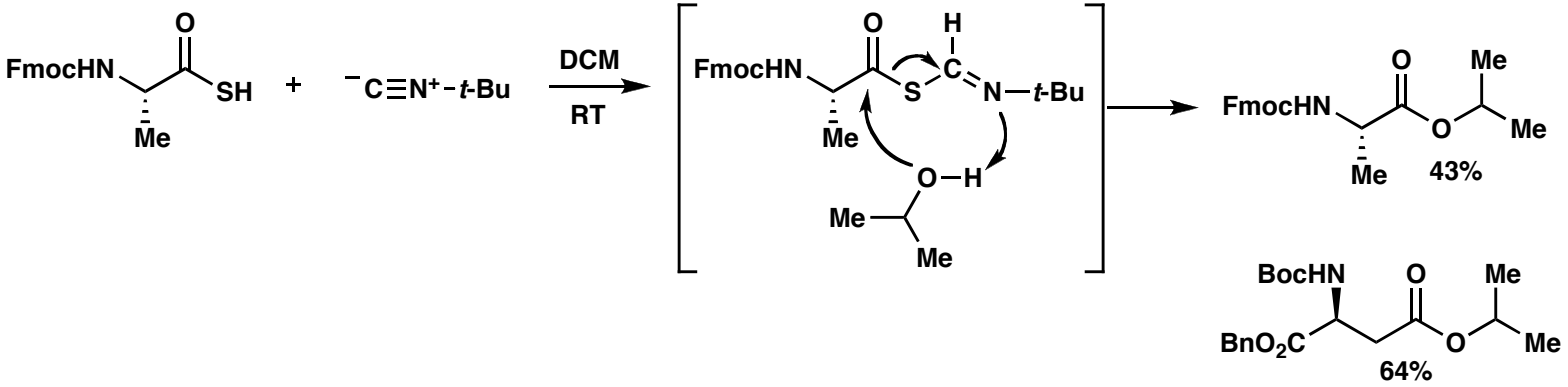
		Isolated Yield			Isolated Yield
	**28**	85%		**33**	88%
	**29**	79%		**34**	82%
	**30**	82%		**35**	85%
	**31**	80%		**36**	81%
	**32**	83%		**37**	86%



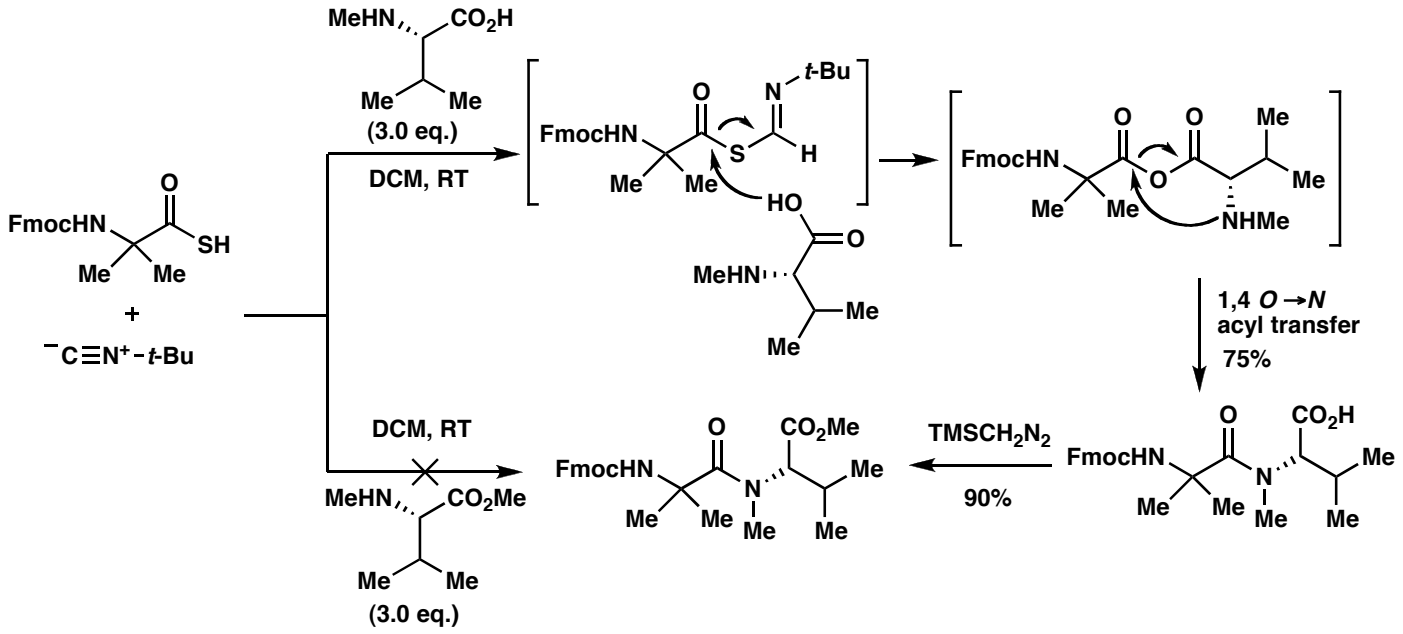
Rao, Y.; Li, X.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2009**, *131*, 12924-12926

Substrate scope

Esterification

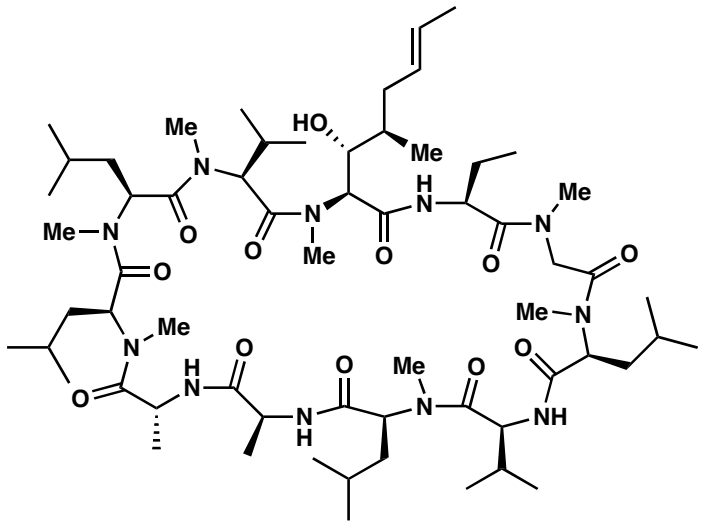


Tertiary amide formation



Cyclosporine A

· Fungal metabolite from *Tolypocladium inflatum gams*
· Initially isolated in early 1960s at Sandoz (later Novartis) in Basel, Switz.
· Narrow antibiotic activities, shelved until 1970s
· Crude fungal extract inhibited lymphocyte proliferation w/out affecting somatic cells
· Structure reported in 1976 (chem degradation, NMR, X-ray)
· Dr. Thomas E. Starzl (Univ. of Pittsburgh) established clinical utility of cyclosporine in liver transplants (preventing organ rejection) in 1982
    -landmarks around Pitt campus
· Acts by inhibiting cytokines (via calcineurin) that stimulate growth, differentiation, and survival of T-cells.



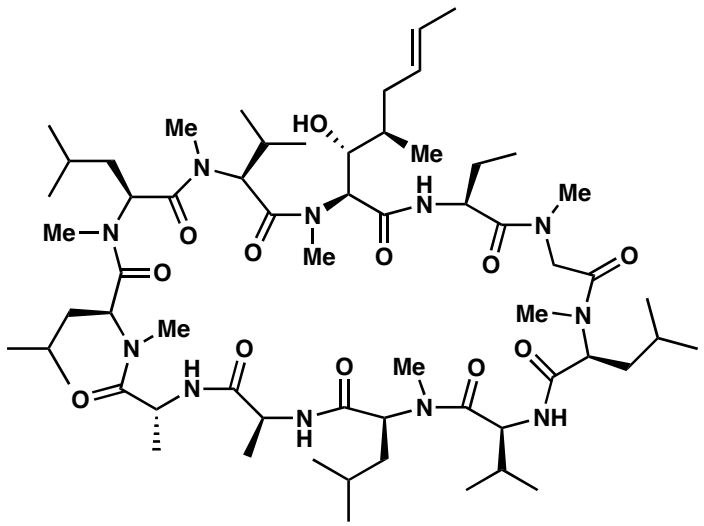
Corey, E. J.; Czakó, B.; Kürti, L. *Molecules and Medicine*; Wiley: Hoboken, NJ, 2007; p. 124

Previous syntheses of cyclosporine A

· Total synthesis reported by Wenger in 1984

· Unusual amino acid (MeBmt) critical to activity; considerable attention, synthetically

· Bioavailability (proteolysis) dependent on N-Me amide pattern in 7 of 11 amide bonds (SAR crucial) (Wenger, Rich, Galpin)



Synthesis: Wenger, R. M. *Helv. Chim. Acta*. **1984**, *67*, 502-525

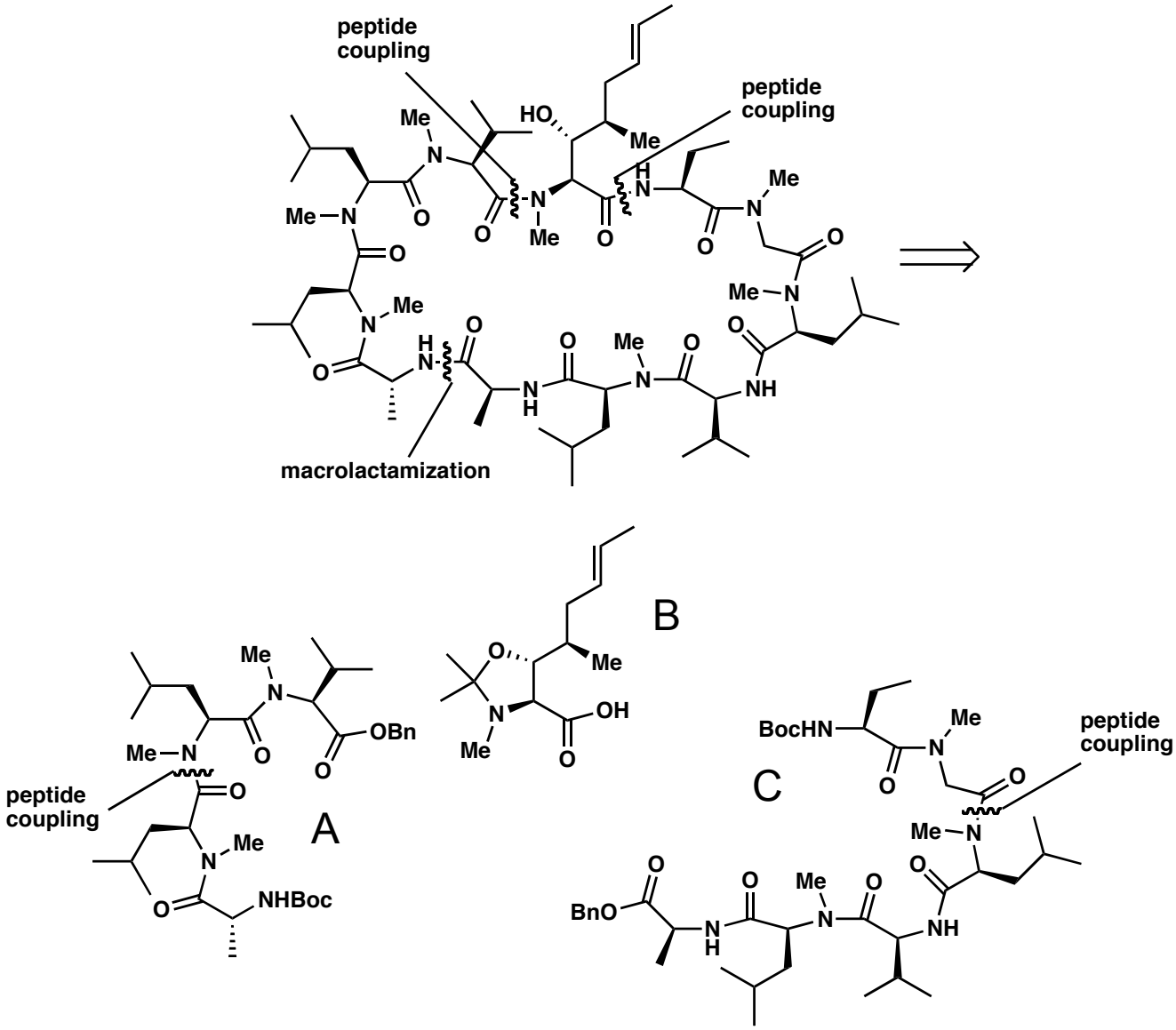
SAR studies: Wenger, R. M. *Angew. Chem. Ind. Ed. Engl.* **1985**, *24*, 77-138

Colucci, W. J.; Tung, R. D.; Petri, J. A., Rich, D. H. *J. Org. Chem.* **1990**, *55*, 2895-2903

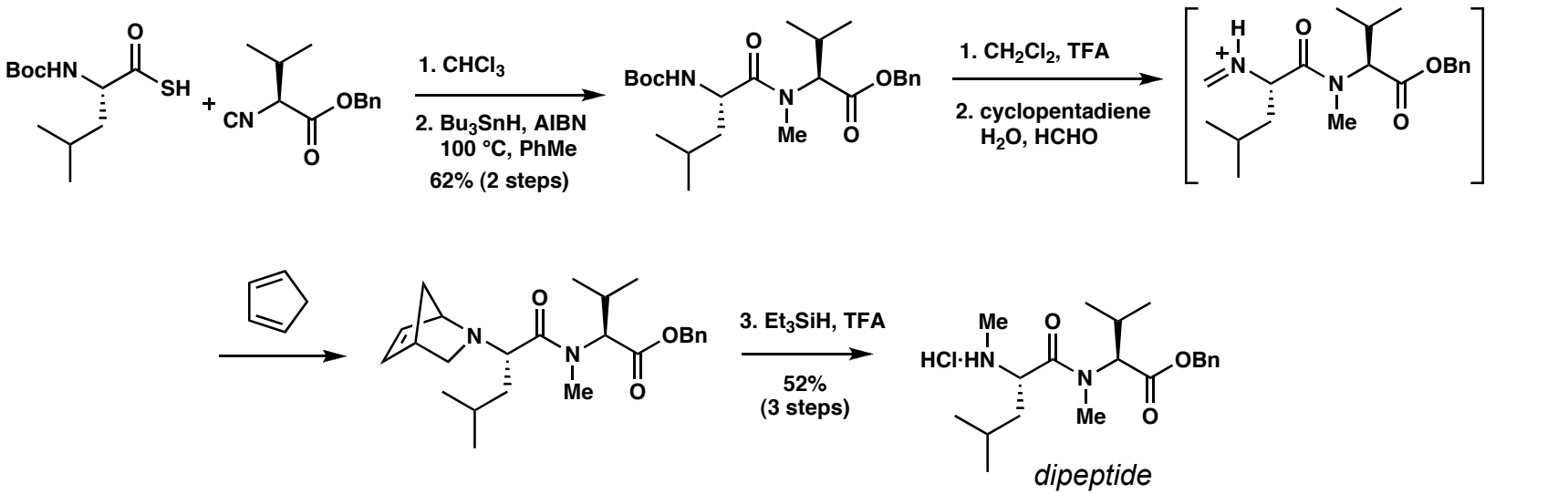
Rich, D. H.; Sun, C.-Q.; Guillaume, D.; Evans, D. A.; Weber, A. E. *J. Med. Chem.* **1989**, *32*, 1982-1987

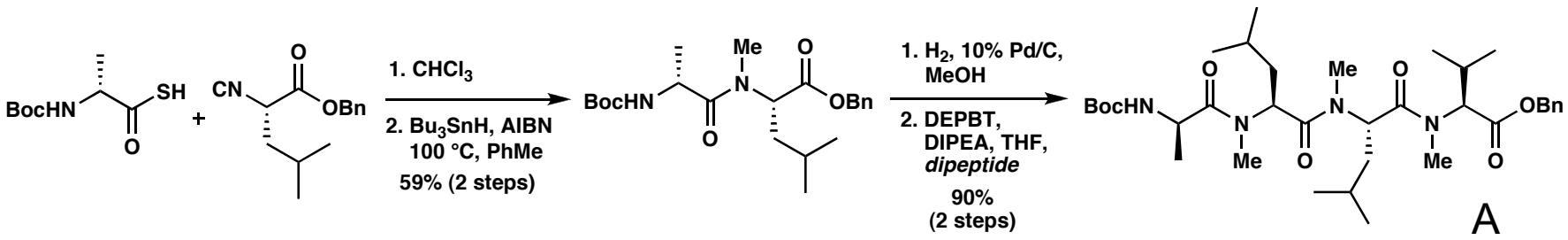
Galpin, I. J.; Mohammed, A. K. A.; Patel, A. *Tetrahedron* **1988**, *44*, 1783-1794

Retrosynthetic analysis



Fragment A

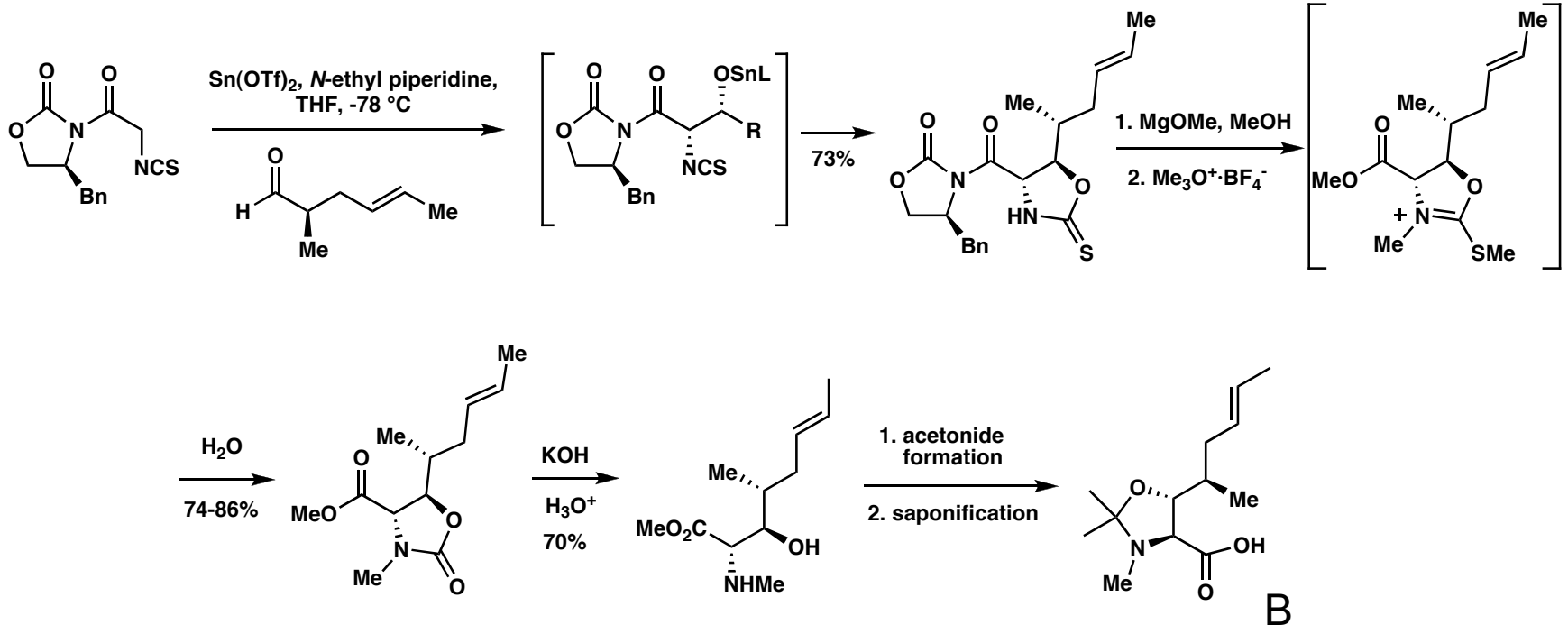




Grieco, P. A.; Bahsas, A. *J. Org. Chem.* **1987**, *52*, 5746-5749

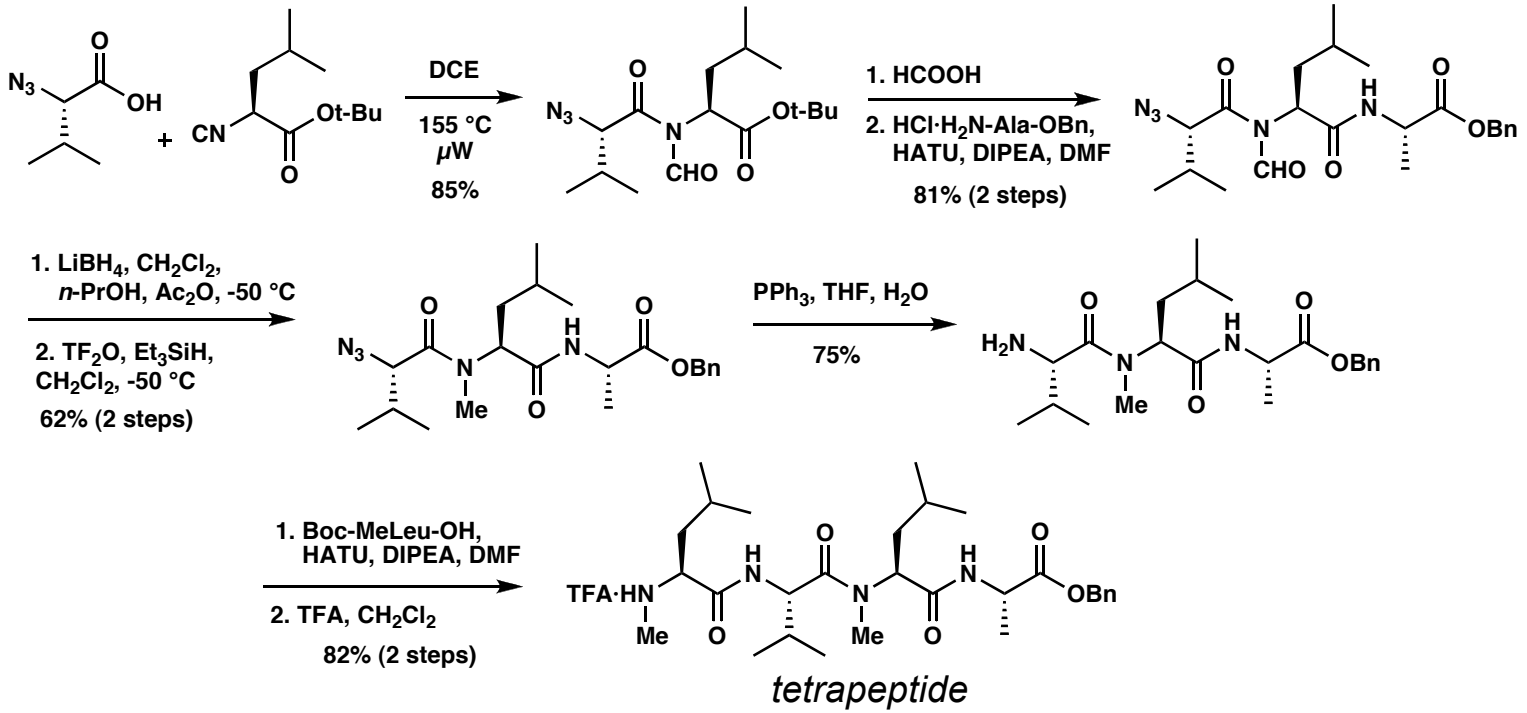
Fragment B

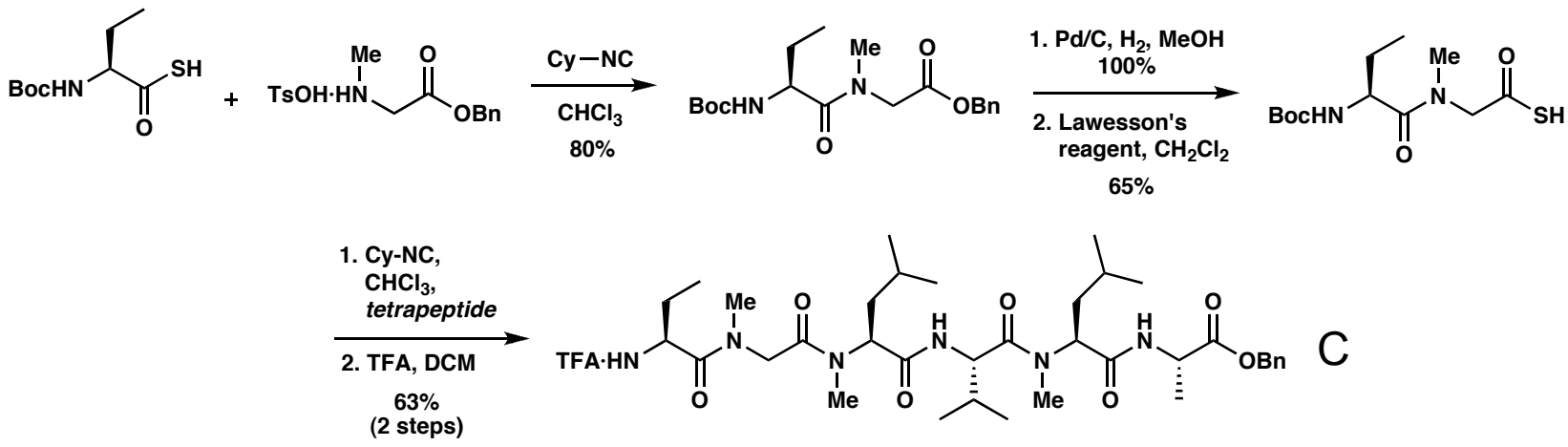
Route by Evans and Weber:



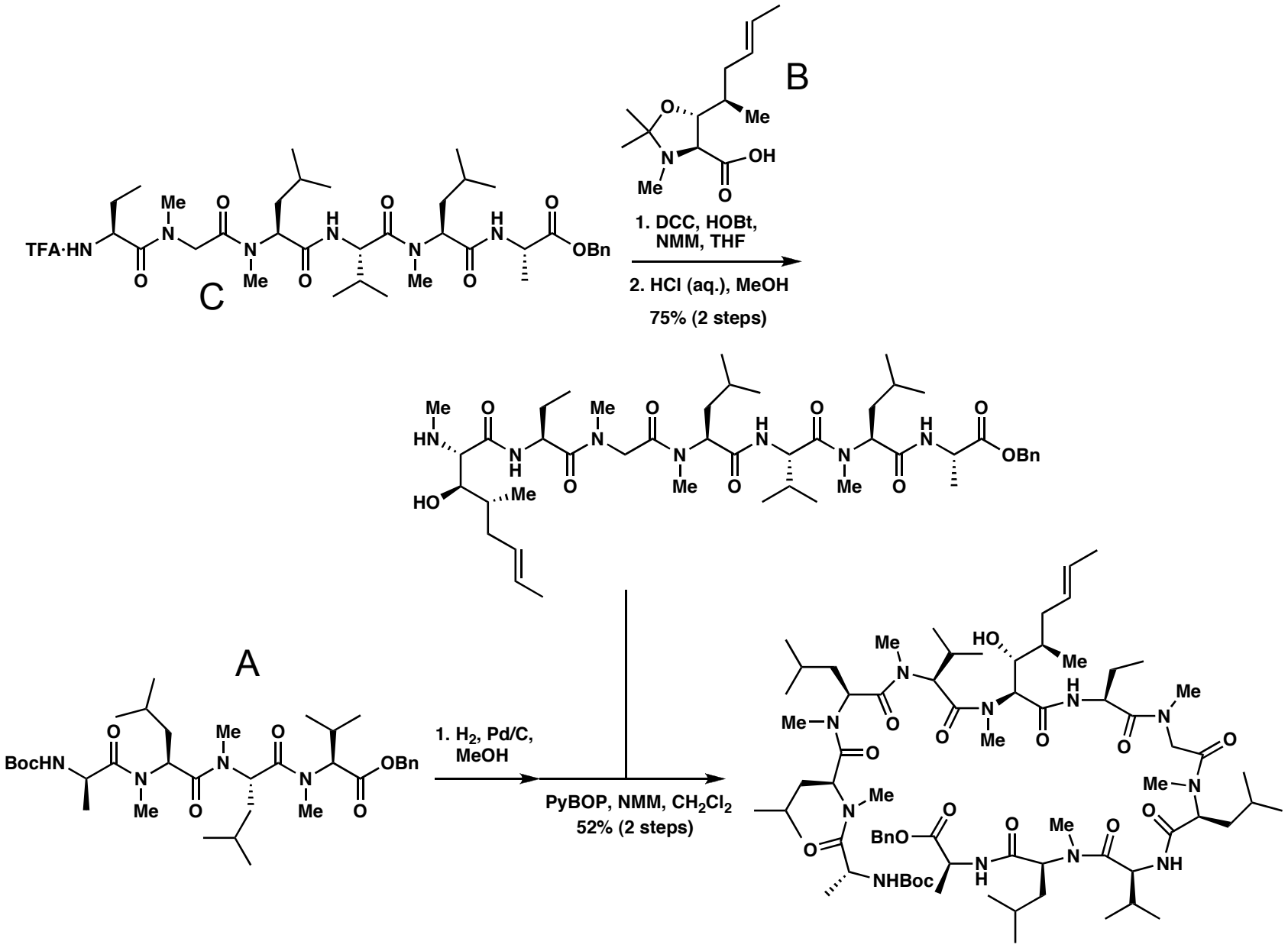
Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1986**, *108*, 6757-6761

Fragment C

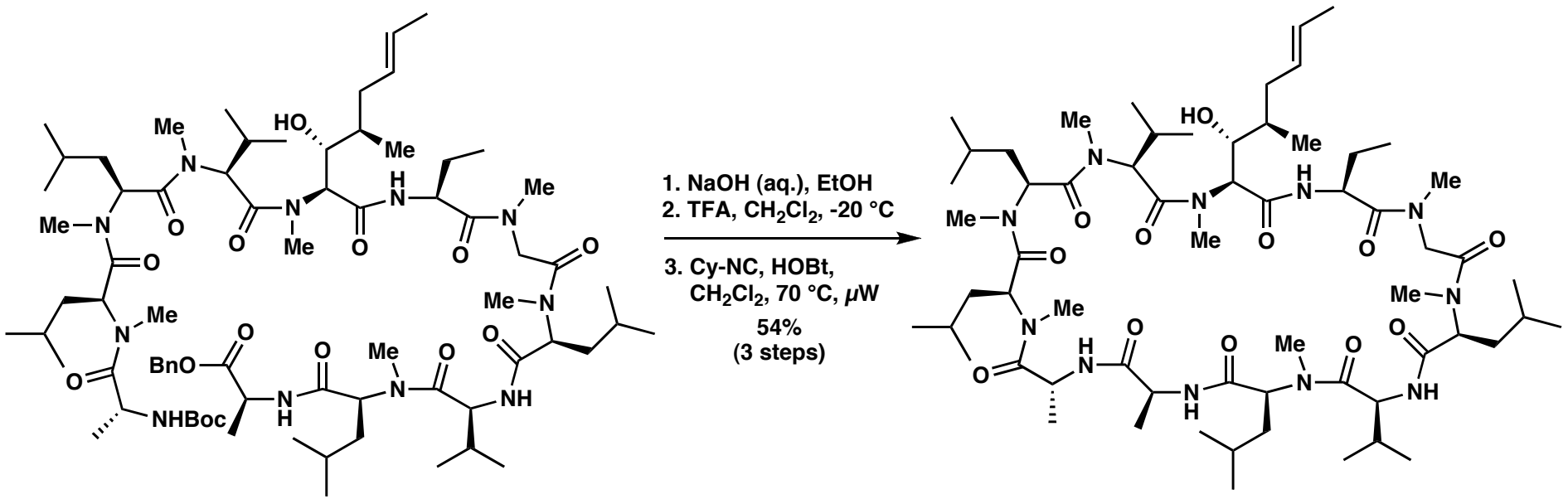

DCE
155 °C
μW
85%
1. HCOOH
2. HCl·H2N-Ala-OBn, HATU, DIPEA, DMF
81% (2 steps)
1. LiBH4, CH2Cl2, n-PrOH, Ac2O, -50 °C
2. TF2O, Et3SiH, CH2Cl2, -50 °C
62% (2 steps)
PPh3, THF, H2O
75%
1. Boc-MeLeu-OH, HATU, DIPEA, DMF
2. TFA, CH2Cl2
82% (2 steps)
tetrapeptide


Cy—NC
CHCl3
80%
1. Pd/C, H2, MeOH
100%
2. Lawesson's reagent, CH2Cl2
65%
1. Cy-NC, CHCl3, tetrapeptide
2. TFA, DCM
63% (2 steps)
C

Completion of cyclosporine



Completion of cyclosporine



19 steps (longest linear)
3.5%* overall yield

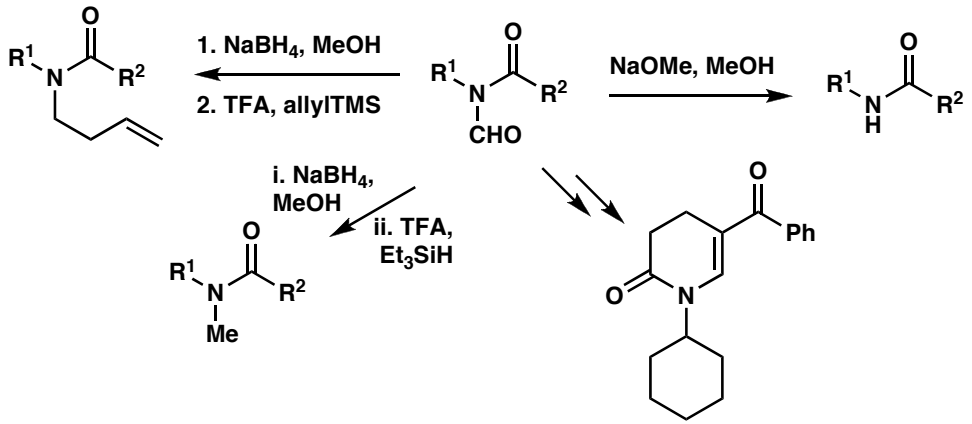
Conclusions

· Synthesis of cyclosporin in a fashion that allows for more detailed mapping of SAR

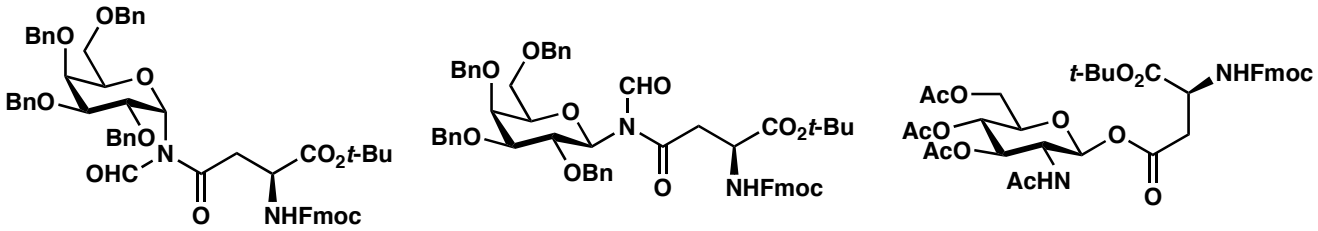
· Excellent showcase of methodology- power and diversity (*N*-formyl imide and acyl transfer chemistry)

· Thiol effect in mechanism (acyl donor capabilities)

· Diversity of *N*-formyl imide products



· Application to glycopeptides



Conclusions

"We note in passing that amines, isonitriles, and thioacids are very old functional groups which go back to the beginnings of organic chemistry. The amide forming construction described here could, in principle, have been conducted in 1909 without difficulty. It is not unlikely that careful mechanistically based revisitation of the foundations of organic chemistry might yield additional surprises of considerable value"

Rao, Y.; Li, X.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2009**, *131*, 12924-12926