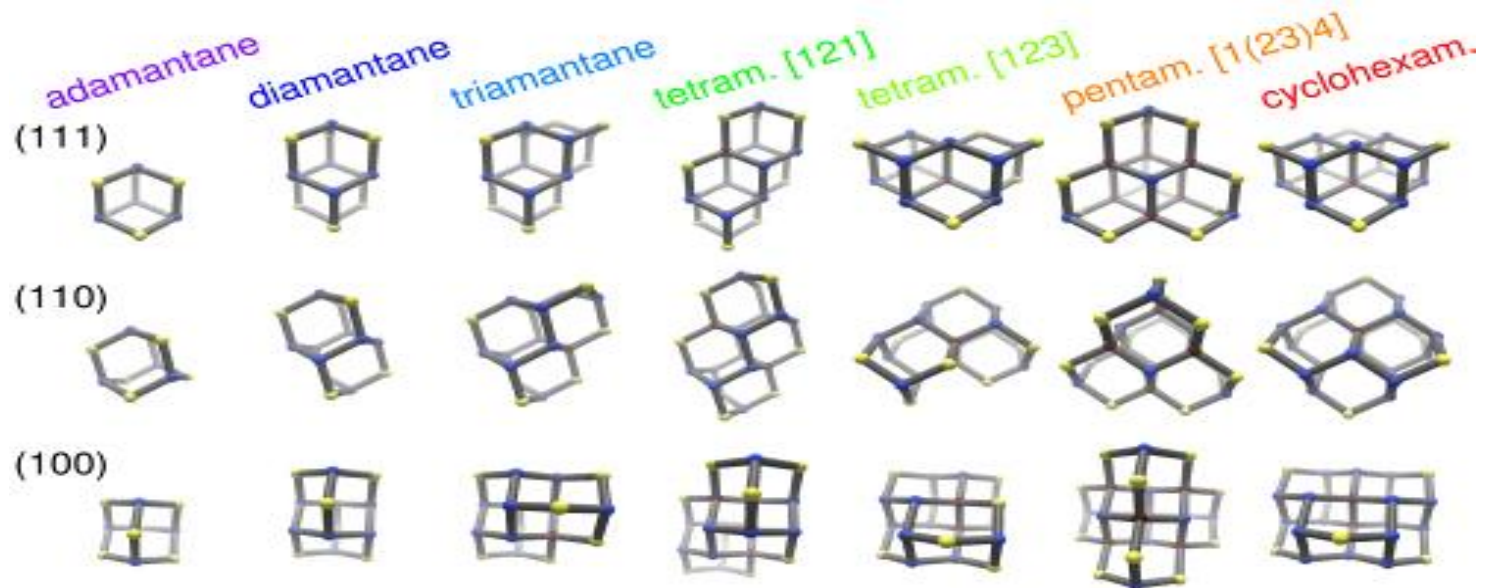

C–H functionalization: Synthesis of amino acids with adamantane group

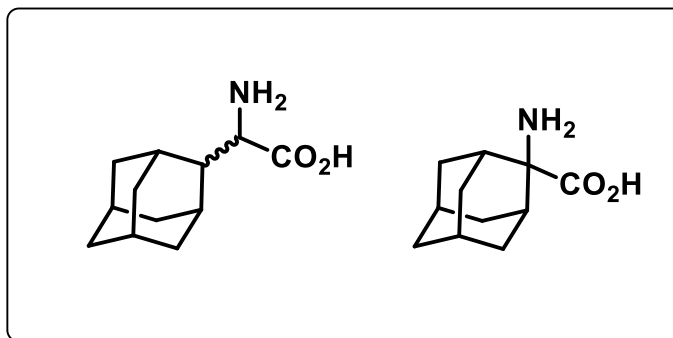
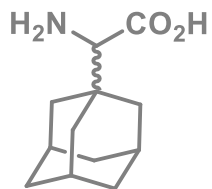
Mark O'Loughlin

Introduction to diamondoids



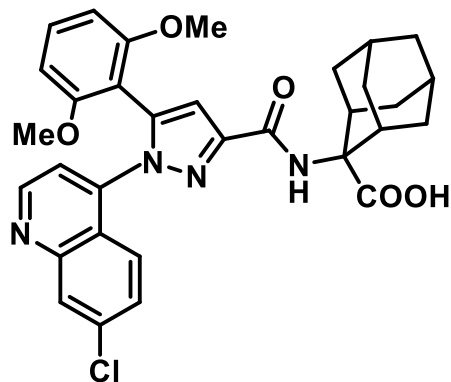
- Hydrogen-terminated diamond-like molecules consisting of fused adamantane cages
- Origin: synthesis ; higher analogs isolated from petroleum
- Optical and electronic properties
- Adamantane scaffold can tune catalyst properties

Project Aim: Amino acid synthesis

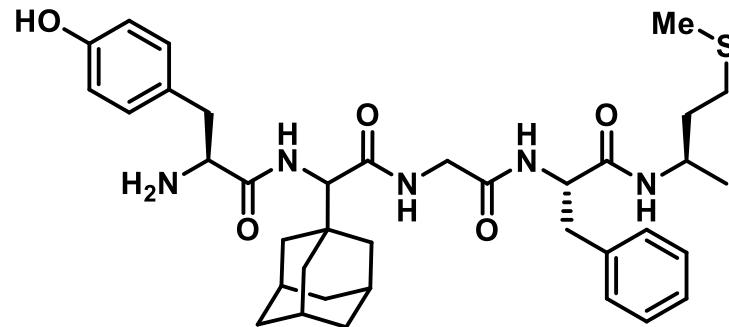


C–H activation: Formation of C–C and C–O bonds

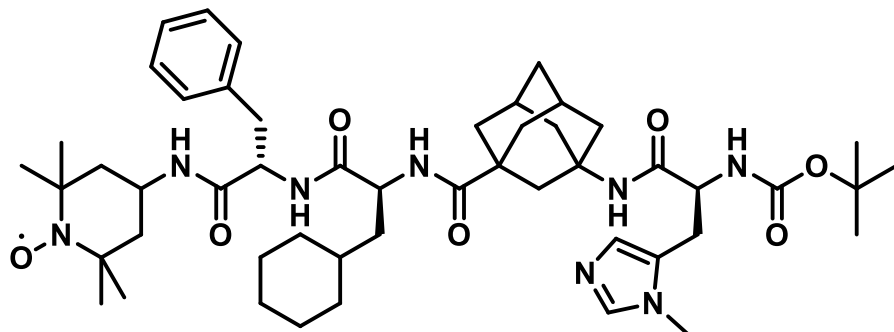
Applications of adamantane amino acids



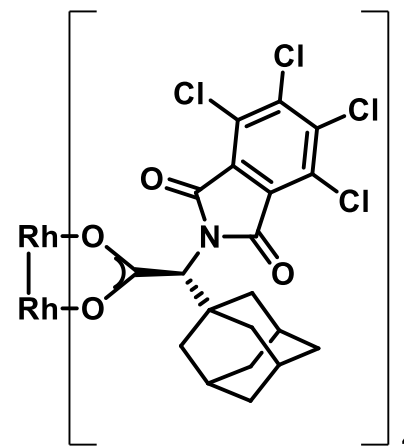
1



2



3

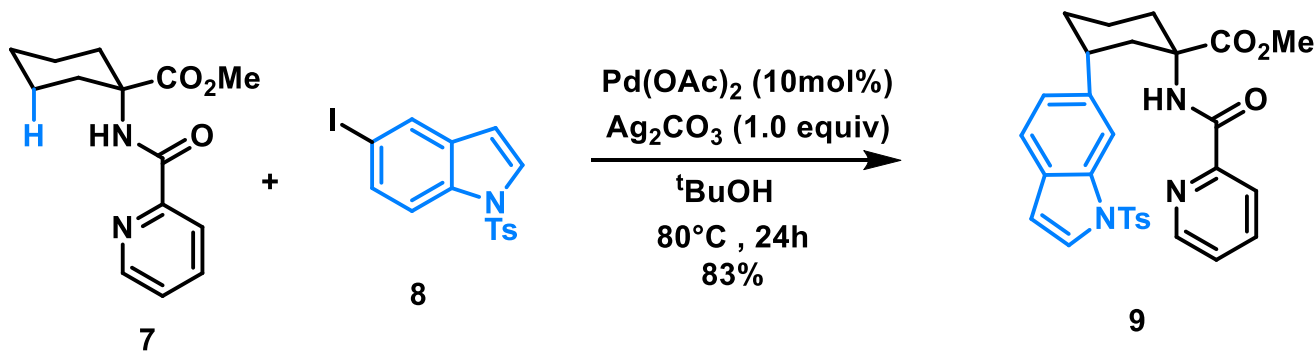
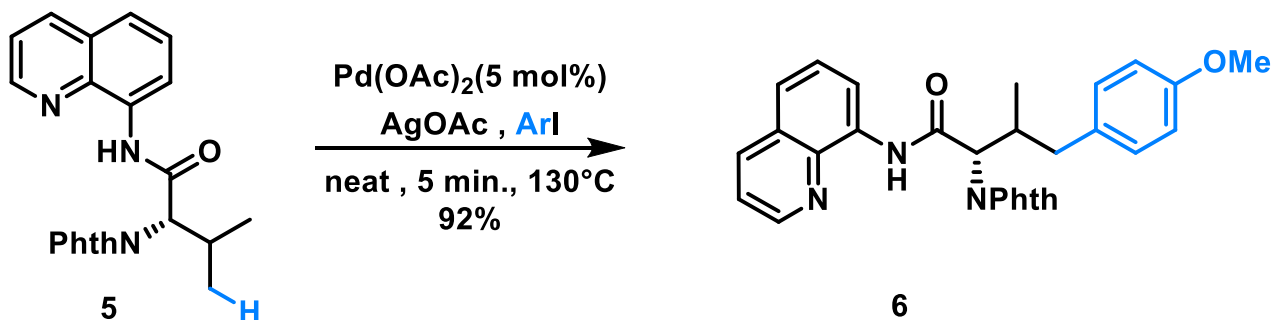


$\text{Rh}_2(\text{S-TCPTAD})_4$

4

J. Liu, D. Obando, V. Liao, T. Lifa, R. Codd *Eur. J. Med. Chem.* **2011**, 46, 1949-1963; S. Horvat et al. *J. Med. Chem.* **2006**, 49, 3136-3142; C. Hofmann, J. M. Schumann, P. R. Schreiner *J. Org. Chem.* **2015**, 80, 1972-1978; K. A. Agnew-Francis, C. M. Williams *Adv. Synth. Catal.* **2016**, 358, 675-700.

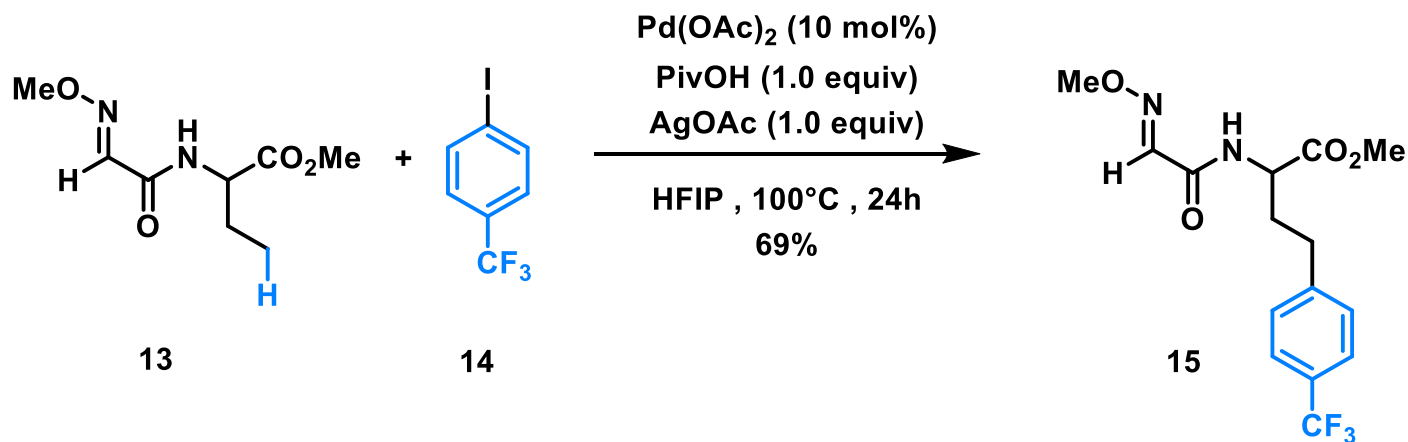
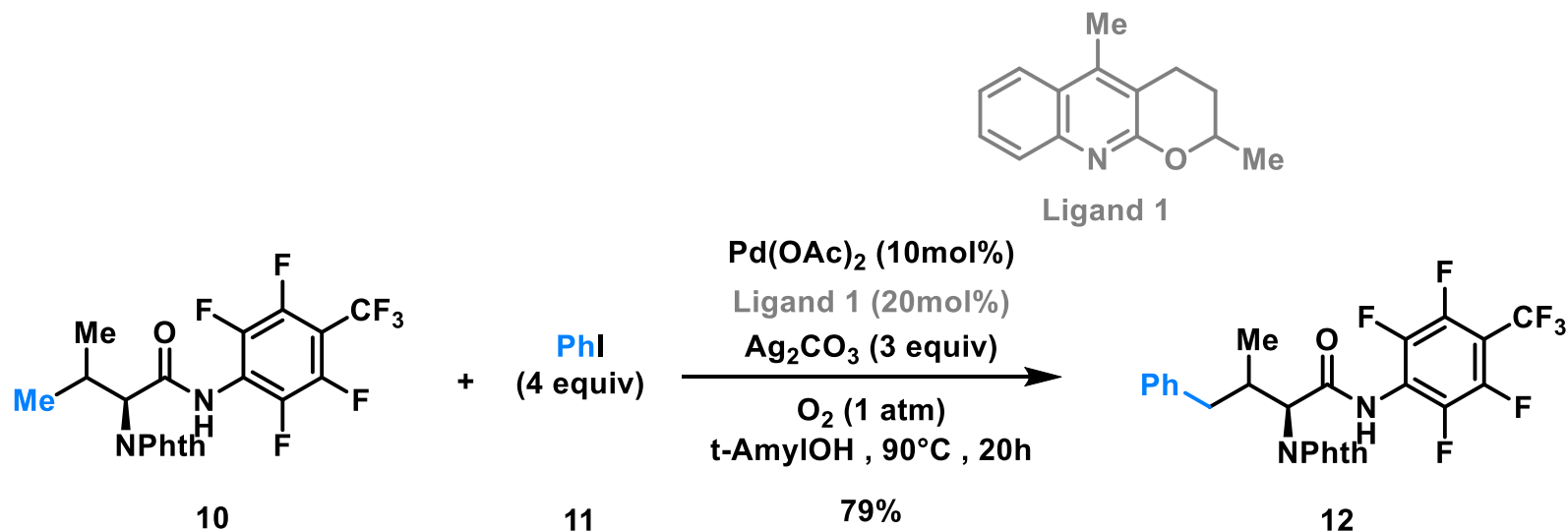
C–H activation of amino acids



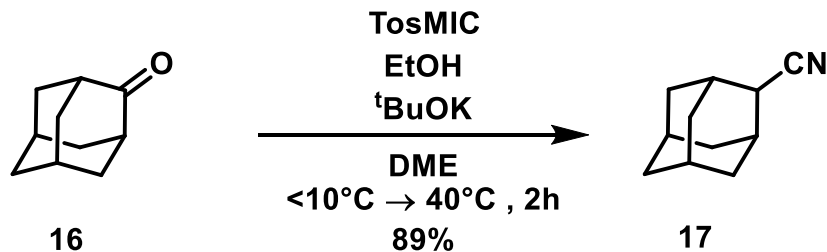
B. V. S. Reddy, L. R. Reddy, E. J. Corey *Org. Lett.* **2006**, 8, 3391-3394.

G. He, B. Wang, W. A. Nack, G. Chen *Acc. Chem. Res.* **2016**, 49, 635-645.

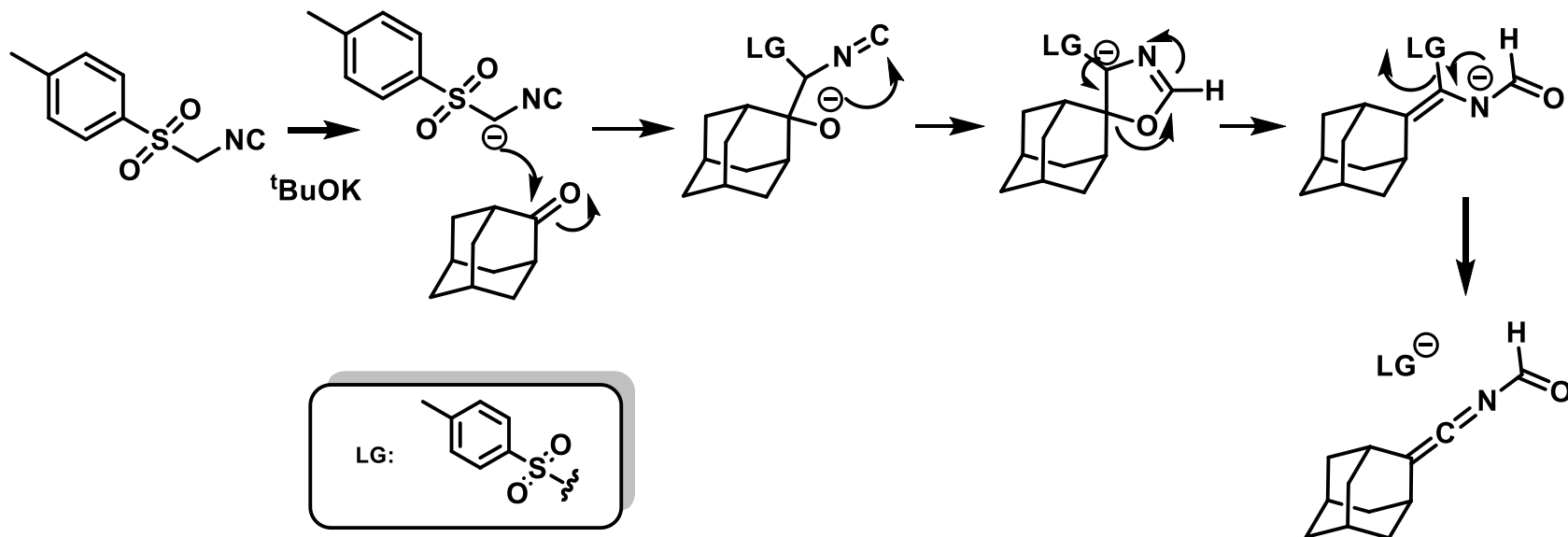
C–H activation of amino acids



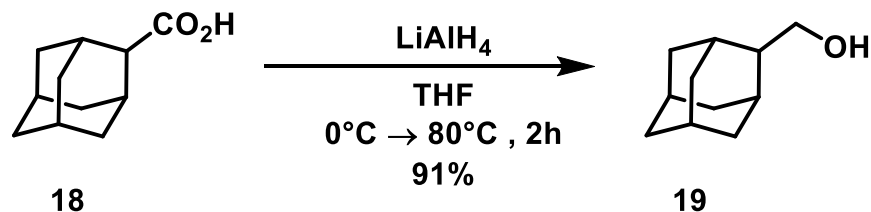
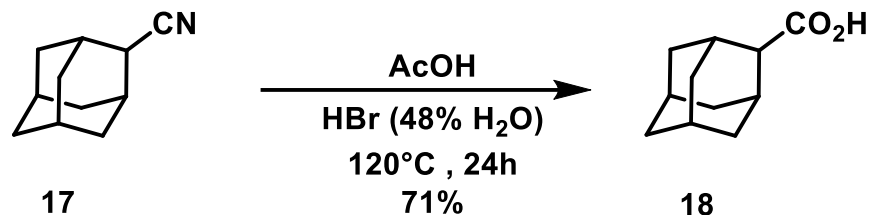
Synthesis of adamantane amino acids



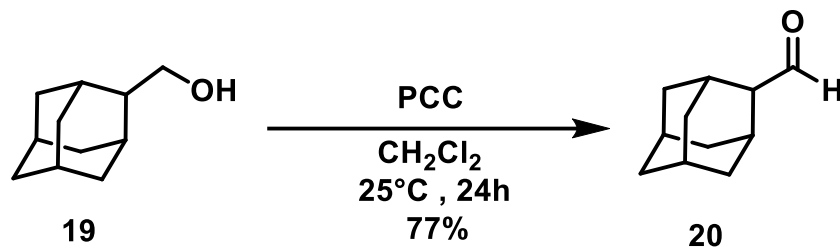
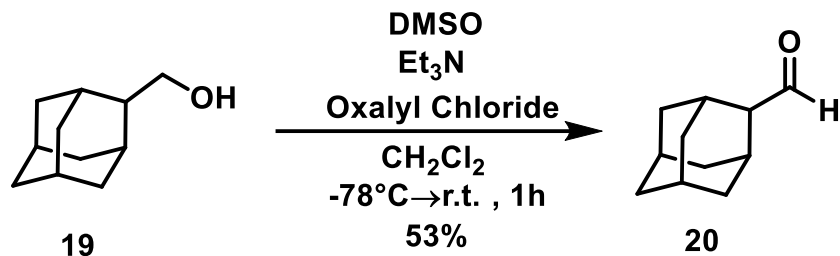
TosMIC Mechanism



Synthesis of adamantane amino acids

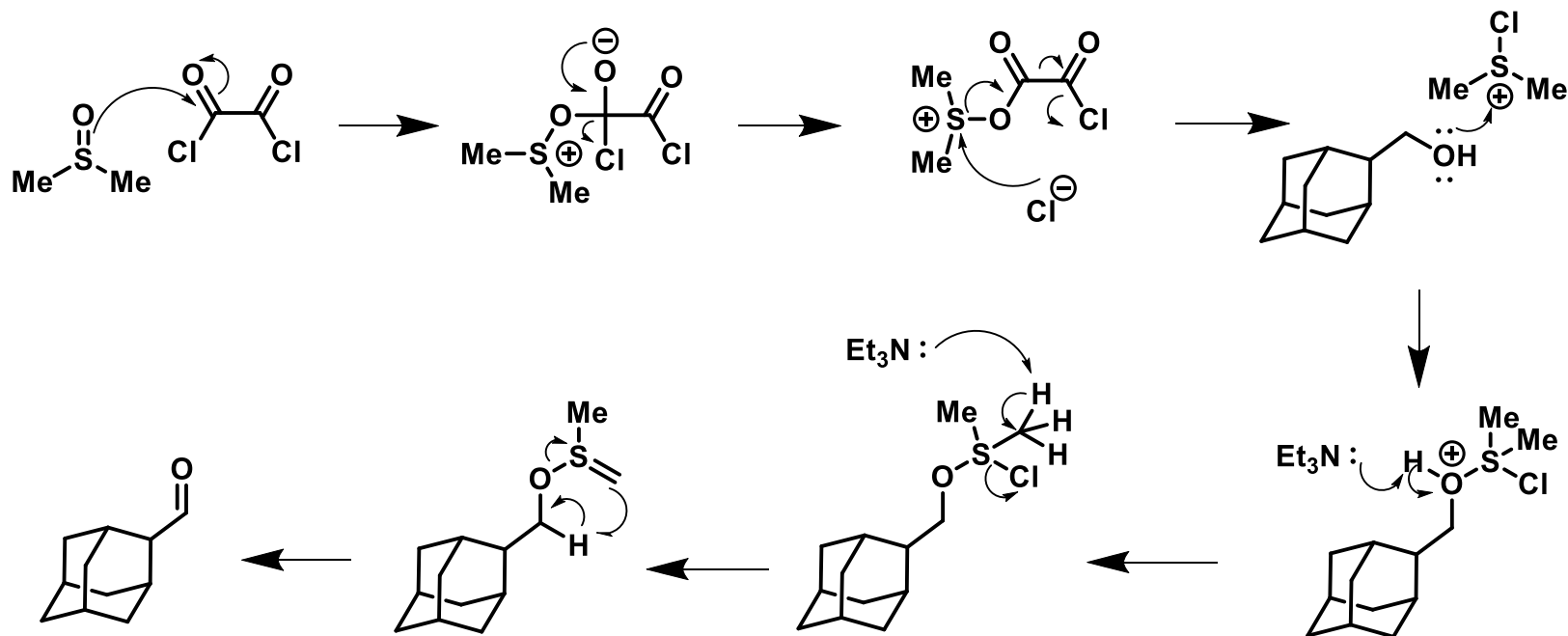


Synthesis of adamantane amino acids

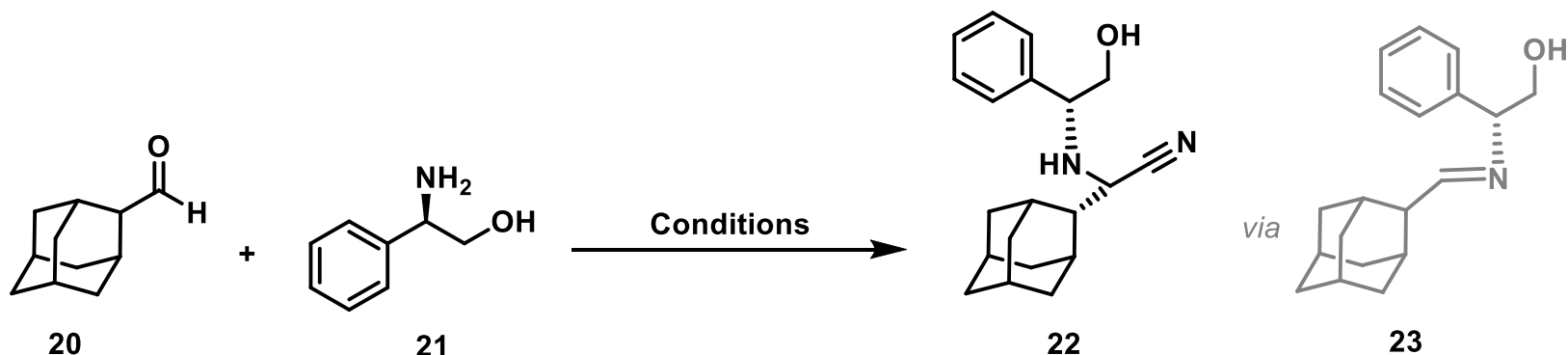


Synthesis of adamantane amino acids

Swern Mechanism:

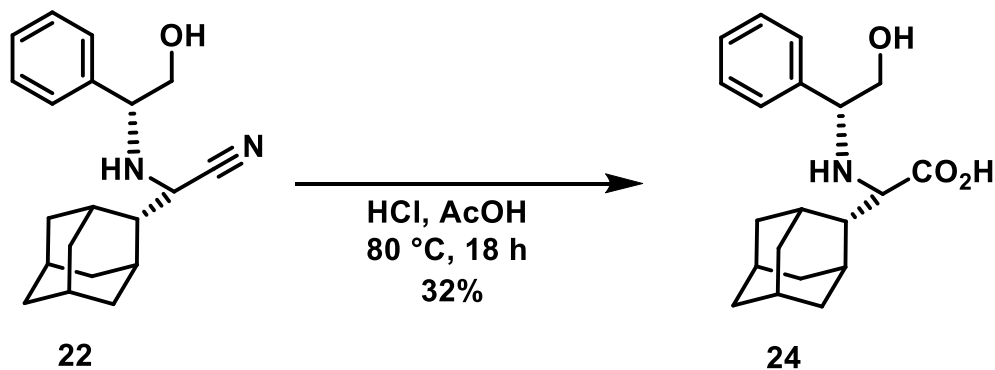


Synthesis of adamantane amino acids

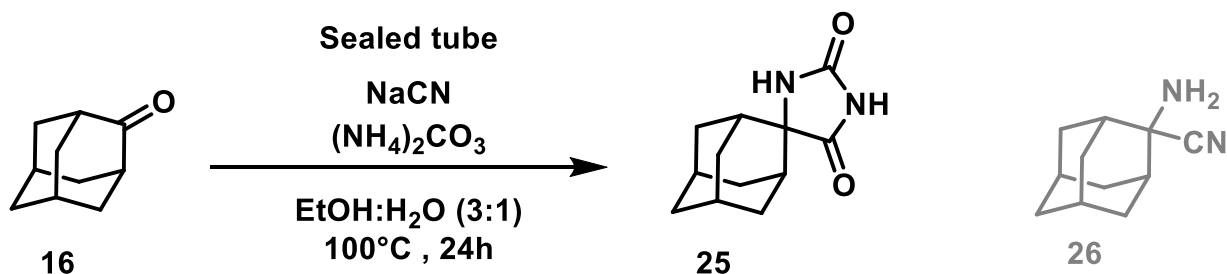
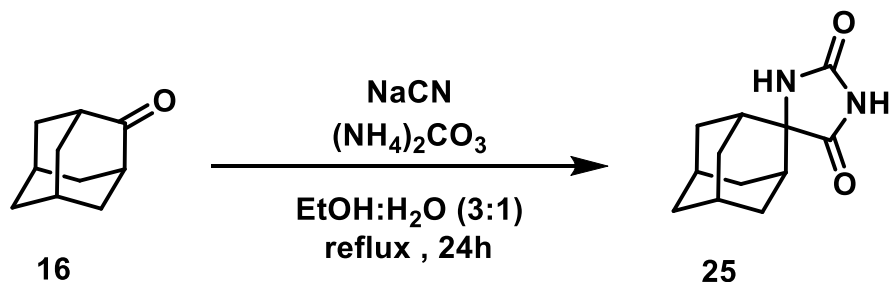


Entry	Conditions	Yield
1	Na ₂ S ₂ O ₅ (0.6 equiv), KCN (1.3 equiv) CH ₂ Cl ₂ , H ₂ O, MeOH, r.t. → 85 °C, 36 h	55%
2	TMSCN (1.8 equiv) CH ₂ Cl ₂ , -10 °C → r.t., 24 h	19%
3	TMSCN (1.3 equiv), Yb(OTf) ₃ (8 mol%) DMF, MeOH, r.t., 18 h	48%

Synthesis of adamantane amino acids



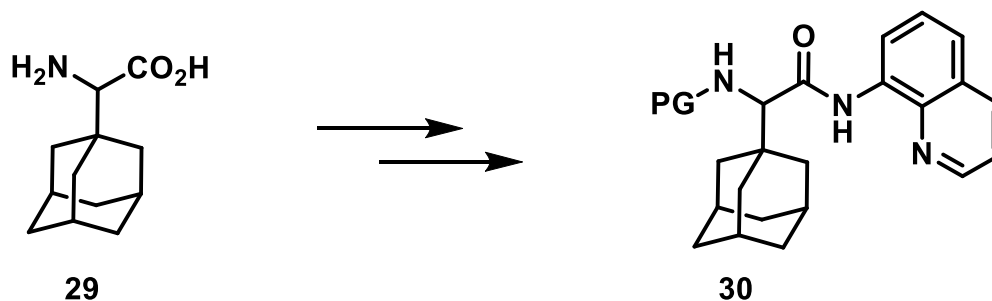
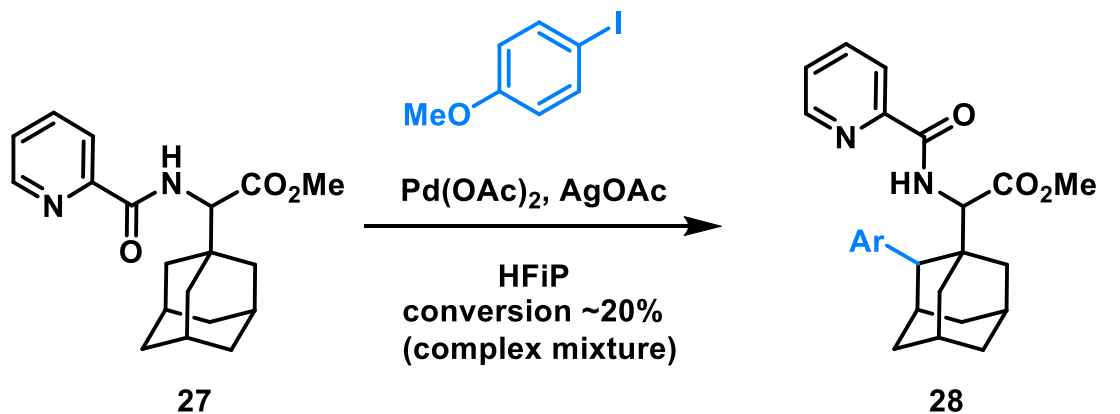
Synthesis of adamantane amino acids



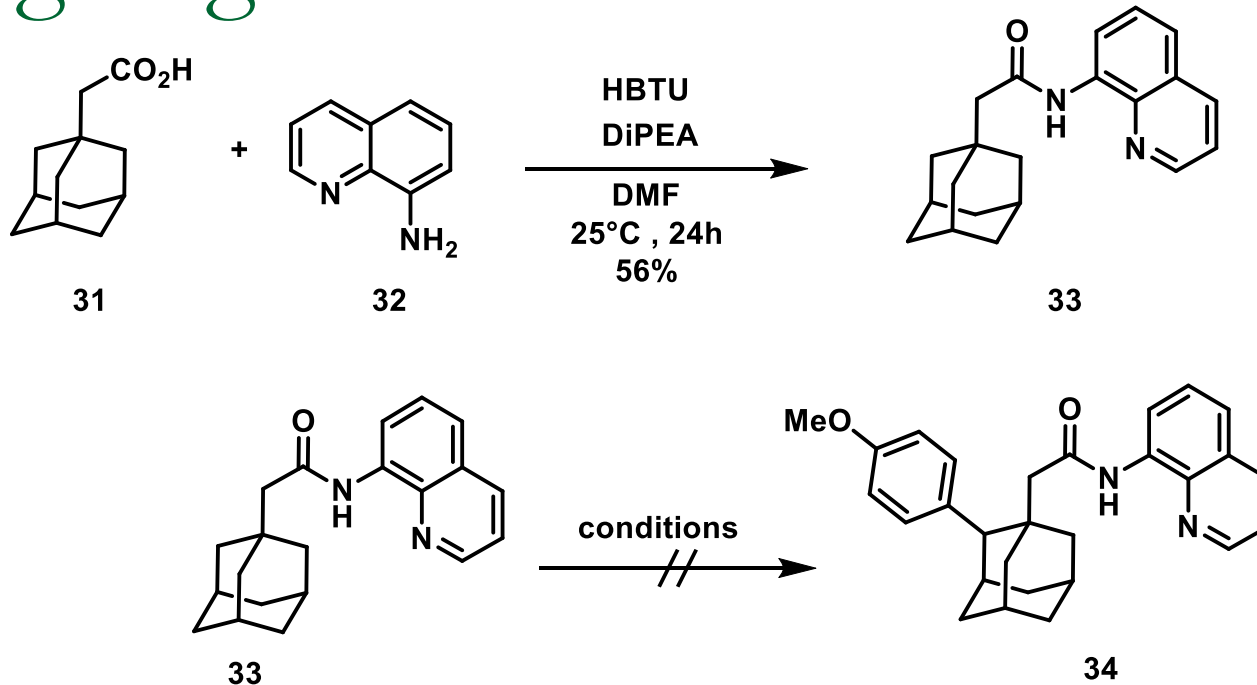
C. Battilocchio, I. R. Baxendale, M. Biava, M. O. Kitching, S. V. Ley *Org. Process Res. Dev.* **2012**, 16, 798-810.

I. R. Baxendale, S. Cheung, M. O. Kitching, S. V. Ley, J. W. Shearman *Bioorg. Med. Chem.* **2013**, 21, 4378-4387.

Assigning a DG



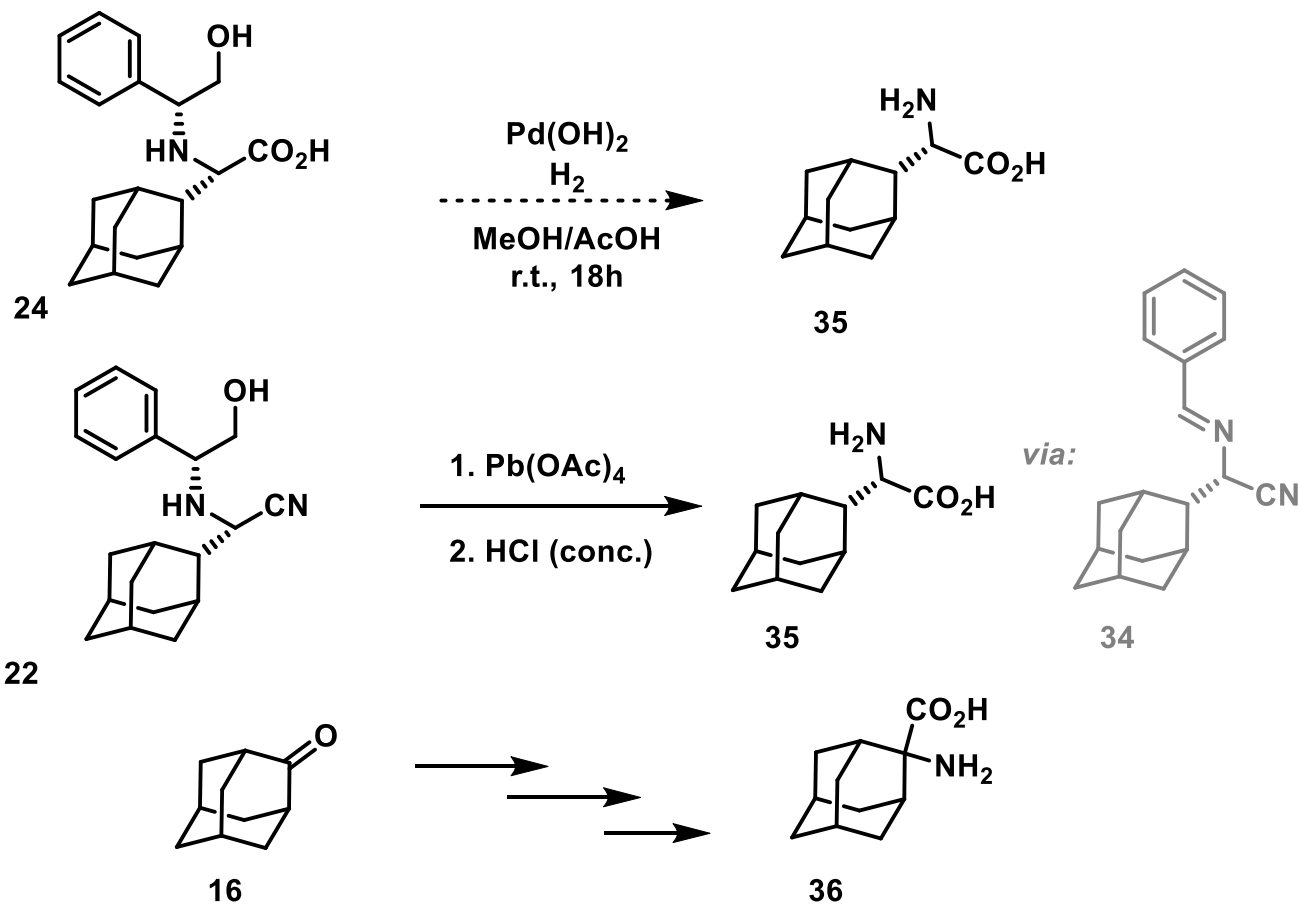
Assigning a DG



Entry	Conditions
1	Pd(OAc) ₂ (15 mol%), AgOAc (1.4 equiv), ArI (1.7 equiv) HFiP, 110 °C, 18h
2	Pd(OAc) ₂ (20 mol%), AgOAc (1.7 equiv), ArI (4.1 equiv) Neat, 110 °C, 18h
3	Pd(OAc) ₂ (20 mol%), PivOH (1.0 equiv) AgOAc (2.2 equiv), ArI (3.3 equiv) Toluene, 110 °C, 18h

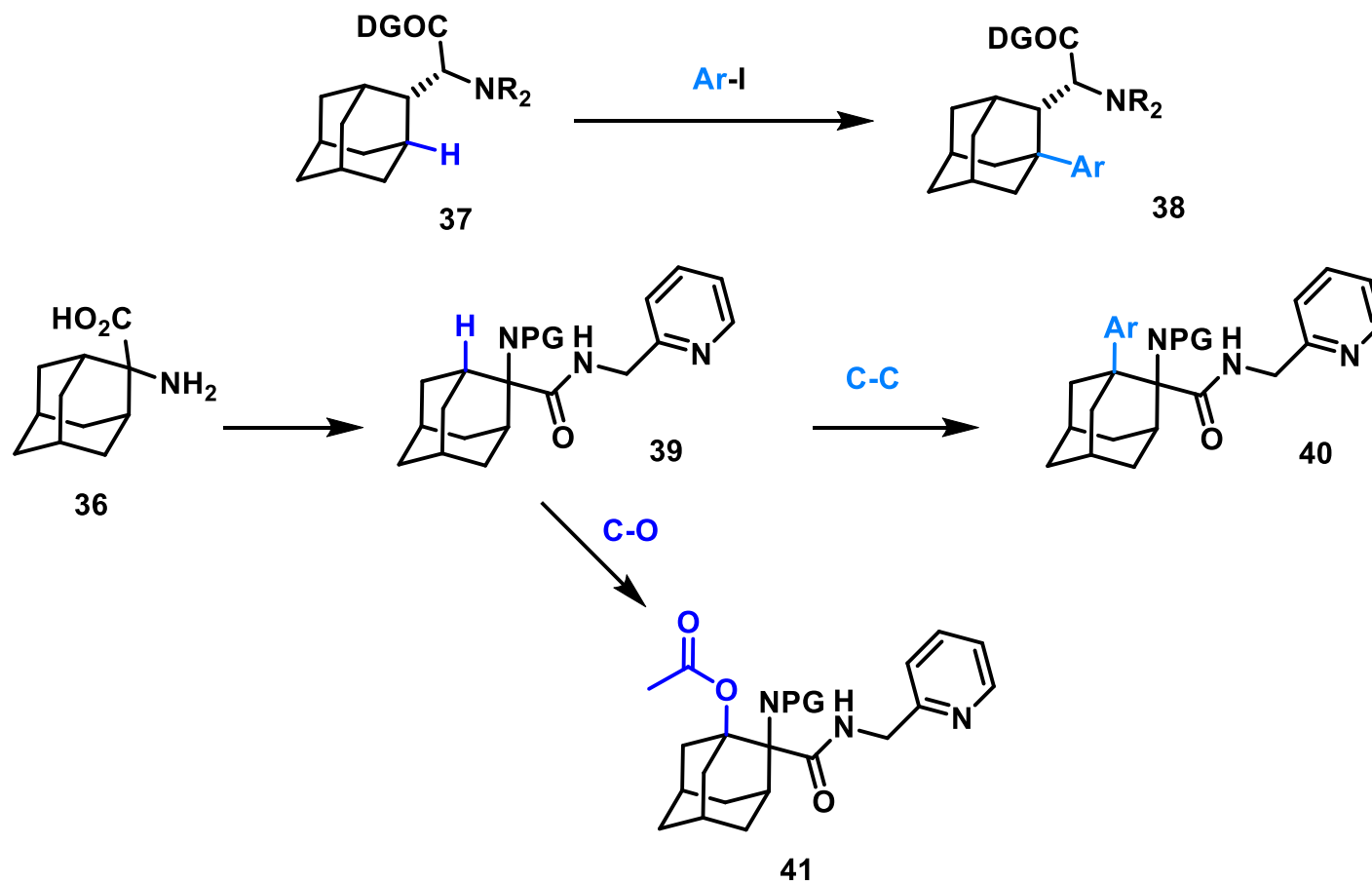
Outlook

■ Final synthetic steps:



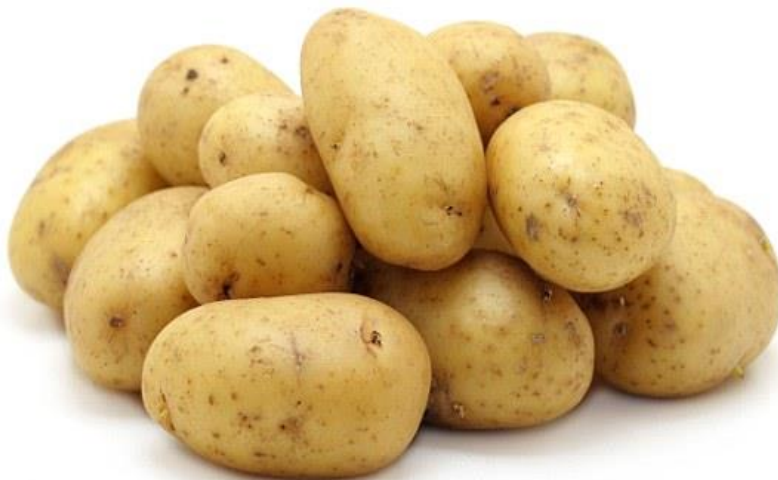
Outlook

■ C-H Activation

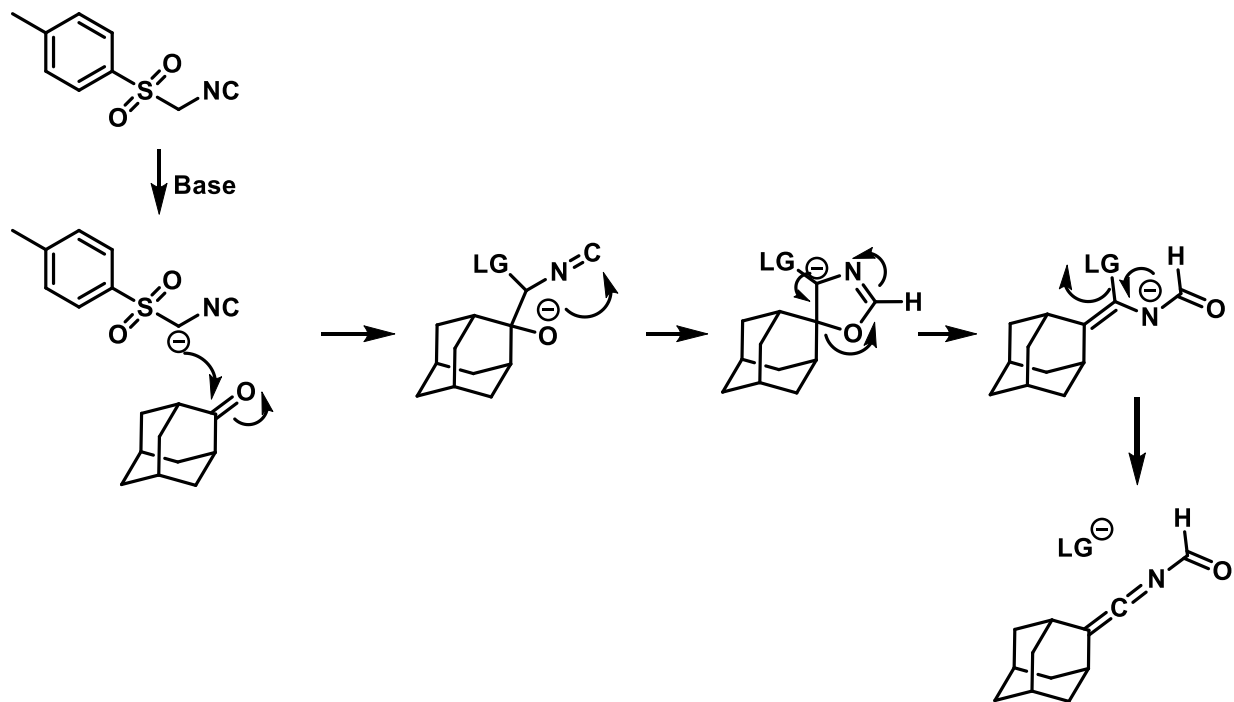


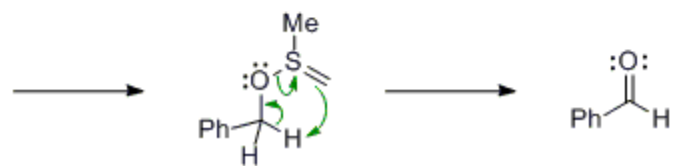
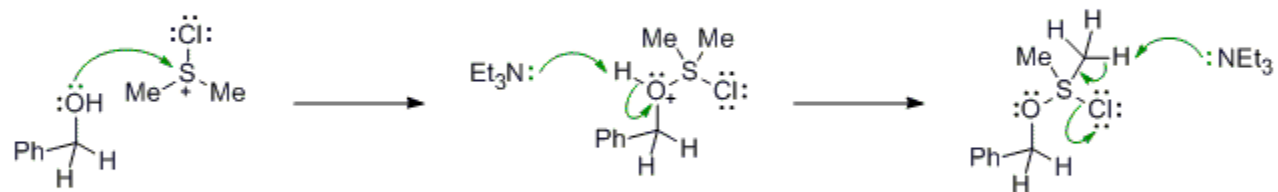
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 - AG Schreiner (Alex, Cesare, Eschi, Dominik, Jan)
-

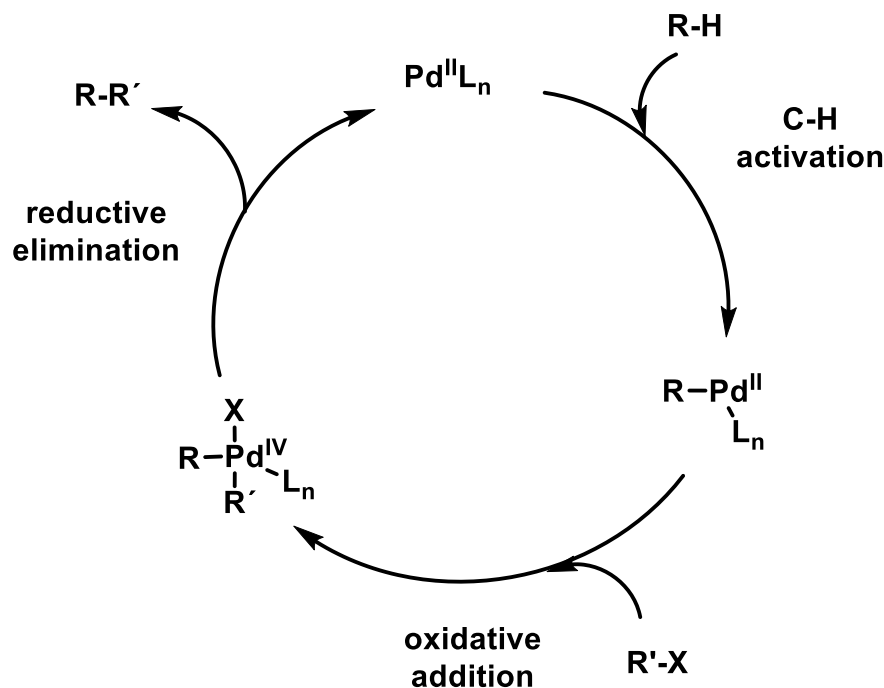


TosMIC mechanism:





Proposed mechanism Pd(II)/Pd(IV) pathway



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S-Y. Zhang, Q. Li, G. He, W. A. Nack, G. Chem *J. Am. Chem. Soc.* **2013**, 135, 12135-12141.

M. Anand, R. B. Sunoj, H. F. Schaefer *J. Am. Chem. Soc.* **2014**, 136, 5535-5538.

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Bucherer-Bergs reaction

