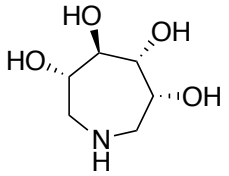
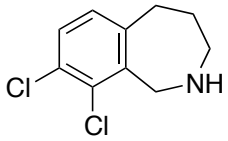
SnAP Reagents for the One-Step Synthesis of Medium-Ring Saturated N-Heterocycles from Aldehydes

Cam-Van T. Vo, Michael Luescher, and Jeffrey W. Bode
Nature Chemistry. doi:10.1038/nchem.1878
Current Lit 3-15-14
James Johnson

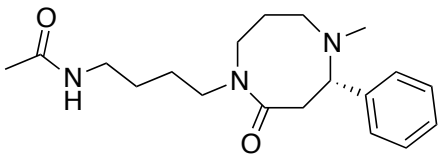
Medium-ring saturated N-heterocycles



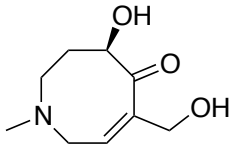
Iminocyclitols



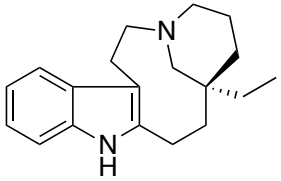
PNMT inhibitor



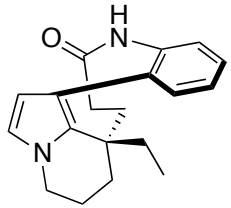
dovyalicin B



Otonocine



(+)-Quebrachamine

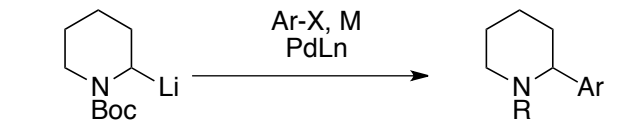


(+)-Rhazinilam

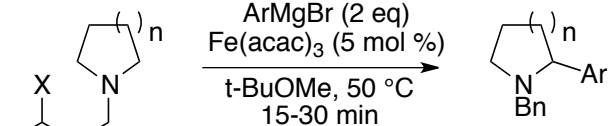
Saturated N-heterocycles as drugs

J. Am. Chem. Soc. **1996**, *118*, 7647- 7652; *J. Med. Chem*. **1996**, *39*, 3539-3546.
Org. Lett. 2**003,** 5, 2793-2796; *J. Am. Chem. Soc*. **1998**, *120*, 3613-3622
Nat. Chem. ***2012,*** **4**, 130–133

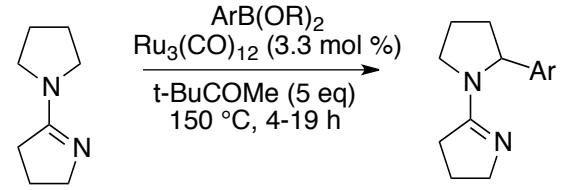
α-Arylation of cyclic amines



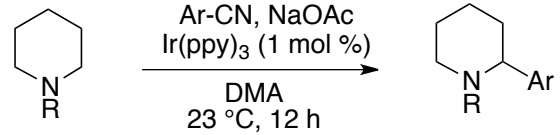
Dieter CuCN LiCl $Pd(PPh_3)_4$, (chiral Li)
Campos $ZnCl_2$, $Pd(OAc)_2$, $P(t\text{-}Bu)_3$ - HBF_4 (chiral Li)
Knochel $ZnCl_2$, Pd_2dba_3, RuPhos



Nakamura



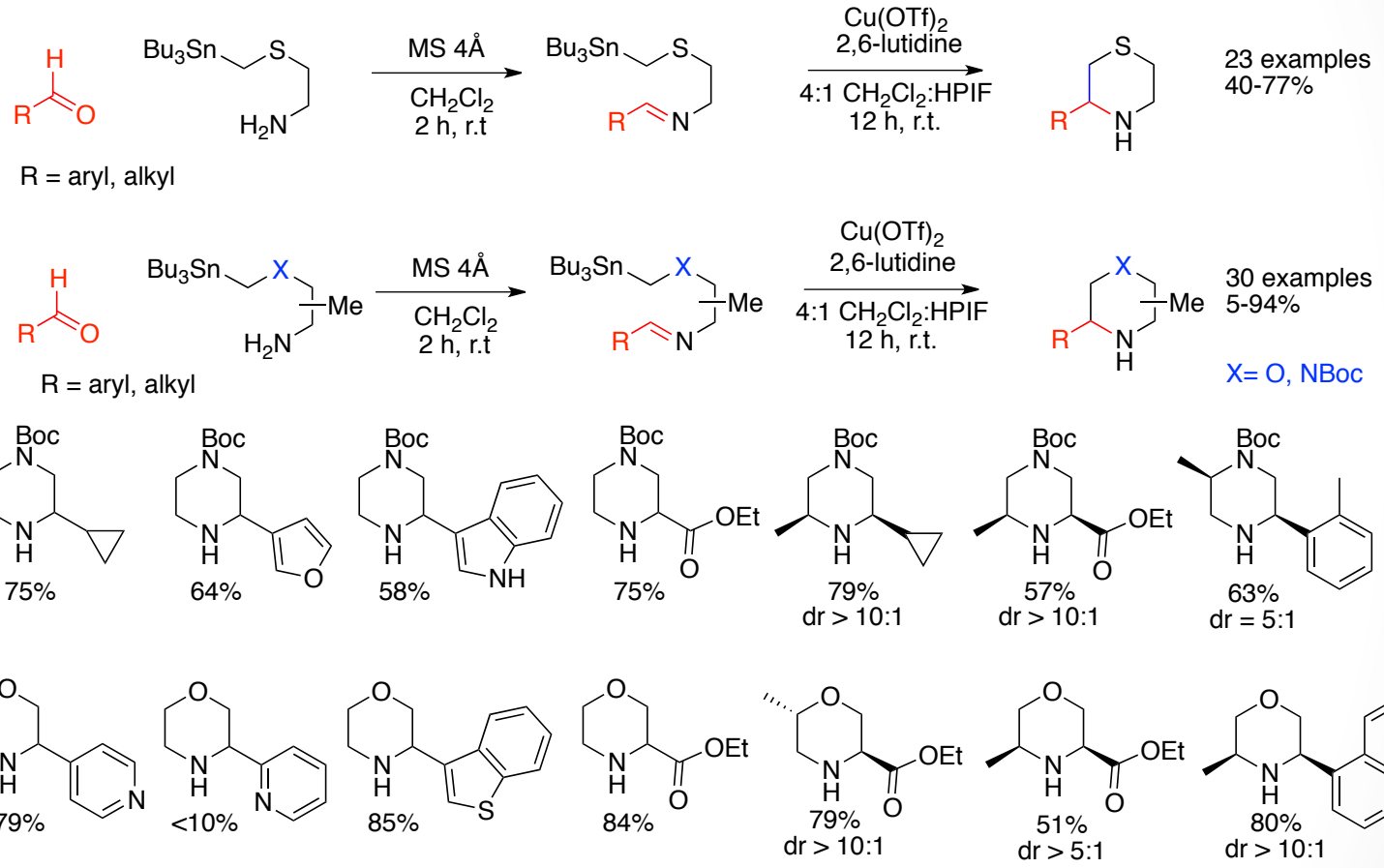
Sames



MacMillan

JACS **2001**, 123, 5132 – 5133; JACS **2006**, 128, 3538–3539; JACS **2011**, 133, 4774 – 4777;
JACS **2010**, 132, 5568 – 5569; JACS **2006**, 128, 14220 – 14221; Science **2011**, 334, 1114 – 1117.

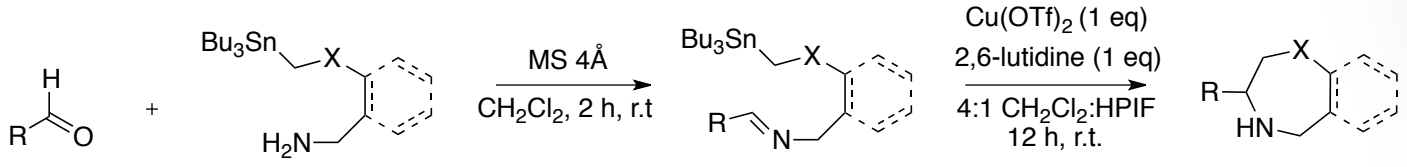
Previous work



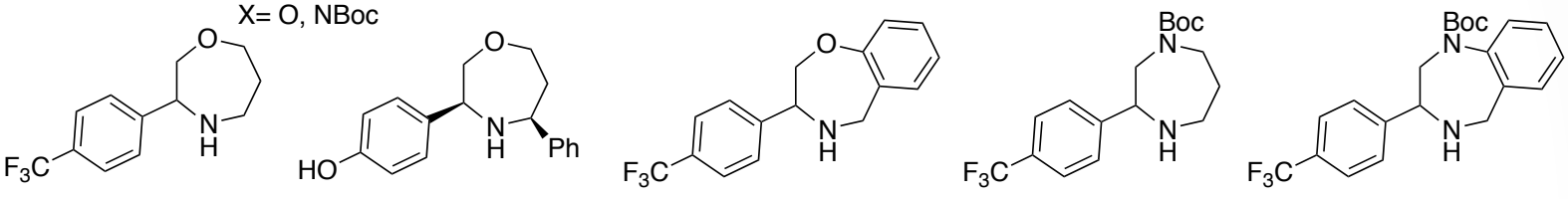
Vo, C.V.T., Mikutis, G., Bode, J.W., Angew. Chem. Int. Ed. **2013**, 52, 1705 –1708

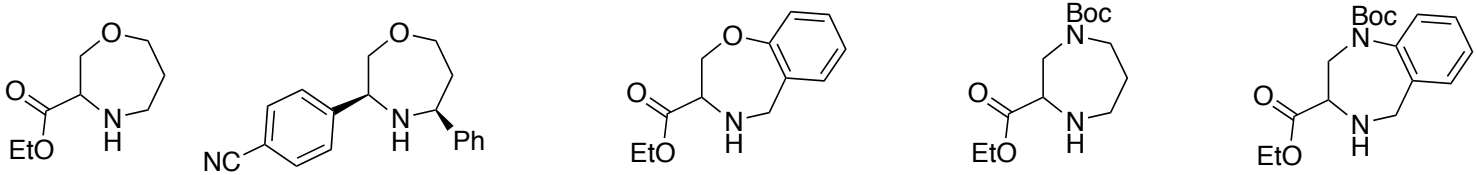
Luescher, M.U., Vo, C.V.T, Bode, J.W., Org. Lett. **2014, 16**, 1236-1239

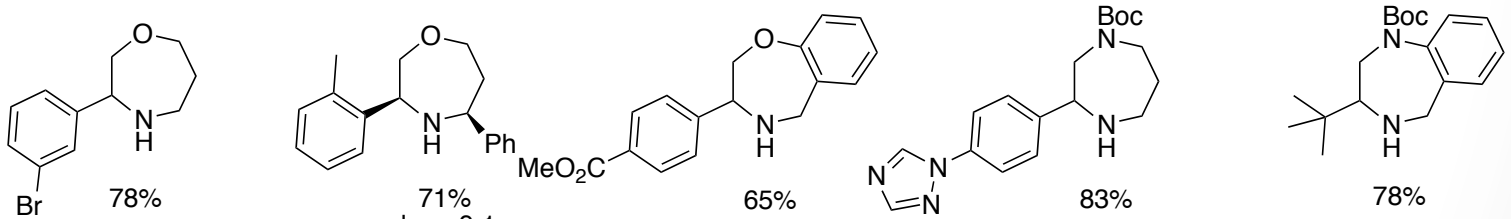
Seven-membered rings

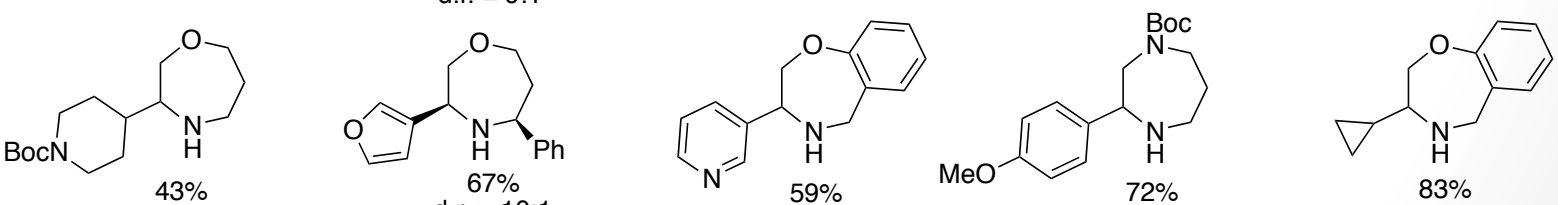


X= O, NBoc



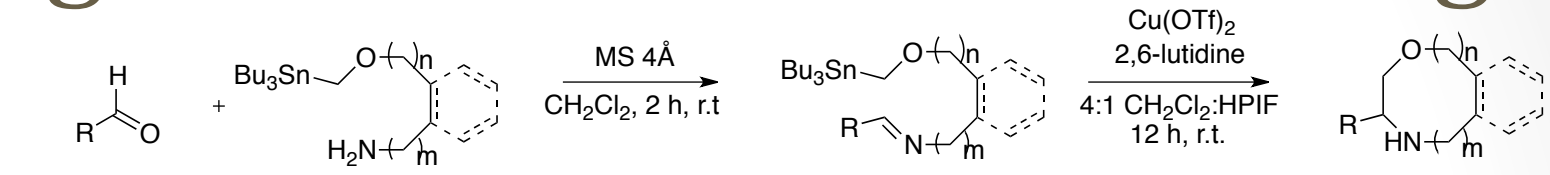




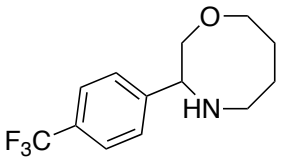


Nature Chemistry. doi:10.1038/nchem.1878

Eight and Nine-membered rings



X = O, NBoc
n = 0, 1; m = 1, 3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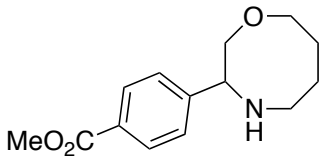
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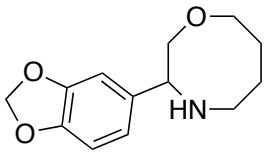
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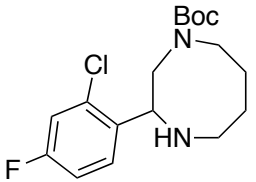
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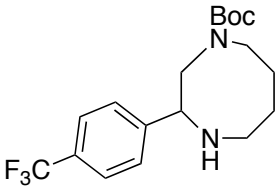
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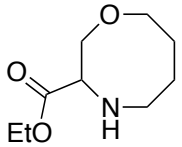
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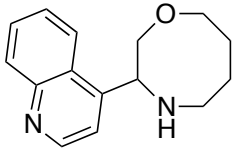
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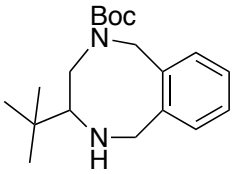
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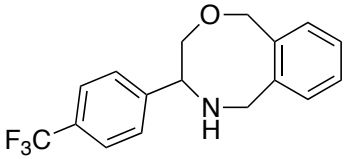
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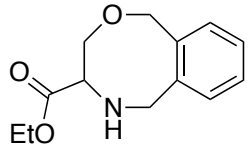
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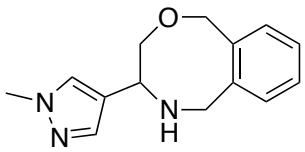
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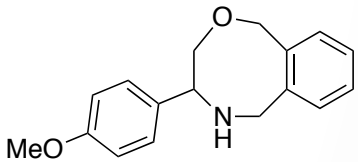
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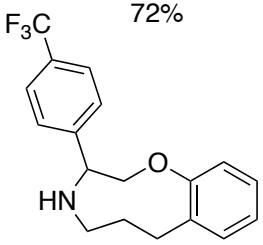
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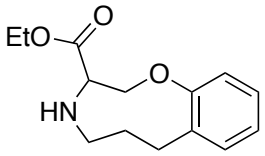
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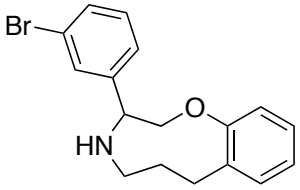
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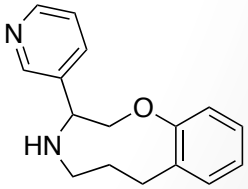
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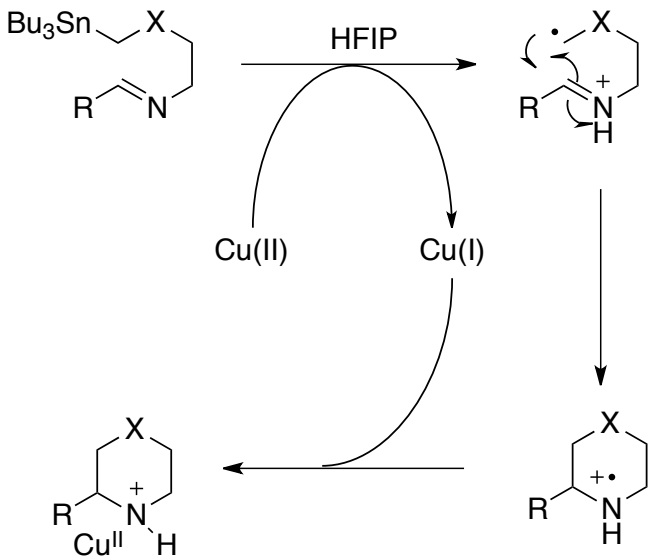
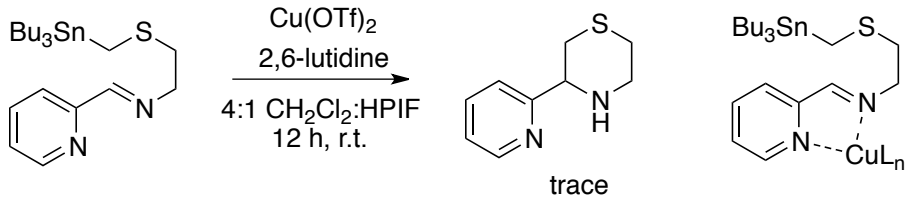
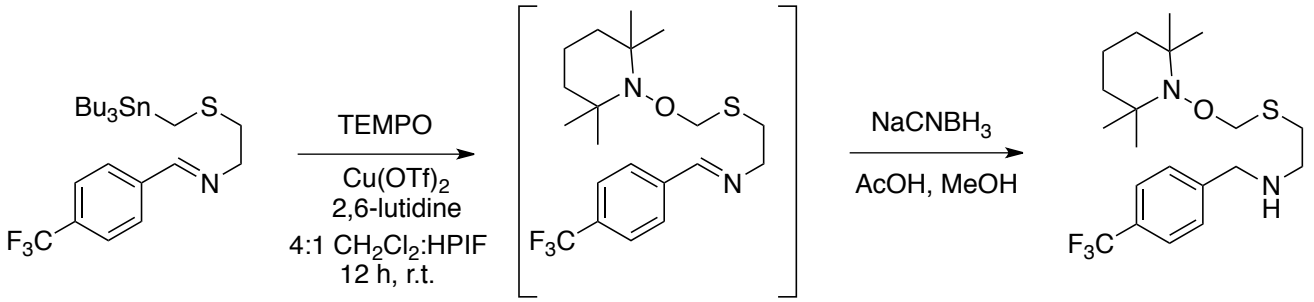
Mechanism



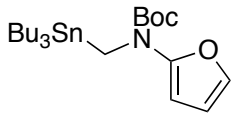
Mechanistic Studies

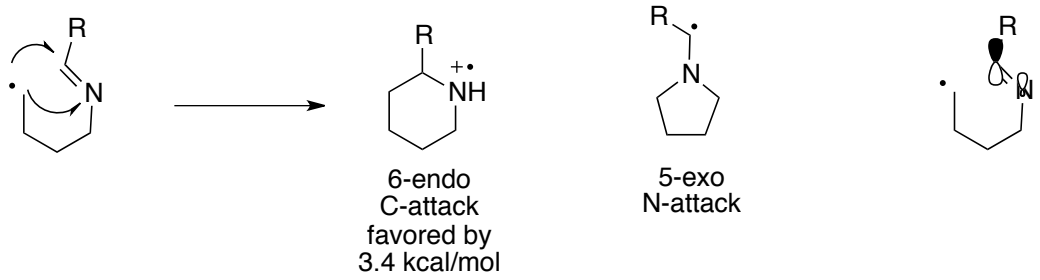




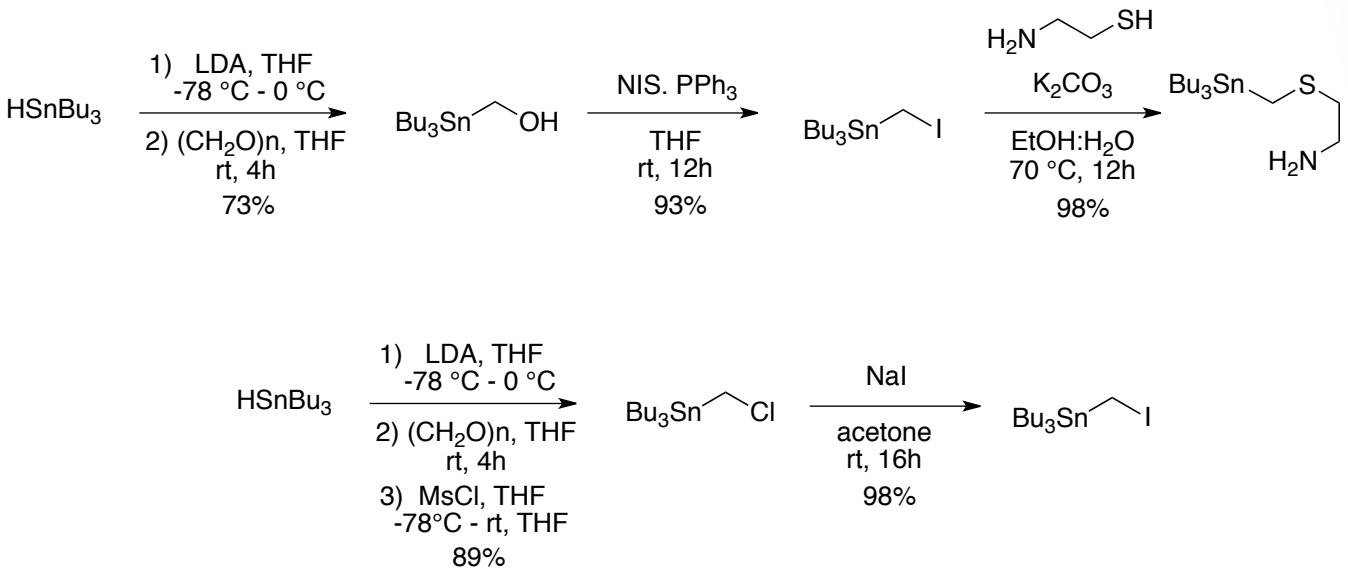
Conclusions

- SnAP provides an alternative method for the synthesis of medium-sized N-heterocycles.
- Uses mild reaction conditions.
- SnAP reagents air and moisture stable.
- Stoichiometric in Cu and Sn
- Future
  - Intermolecular variant



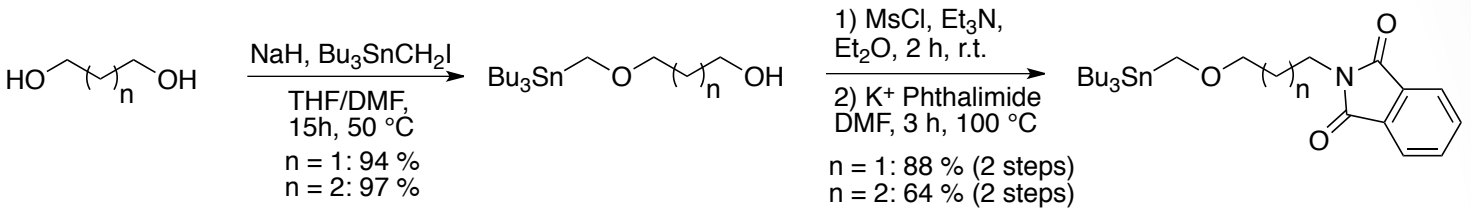

R
N
R
NH
6-endo
C-attack
favored by
3.4 kcal/mol
R
N
5-exo
N-attack
R
N
6-endo
5-exo
1:50

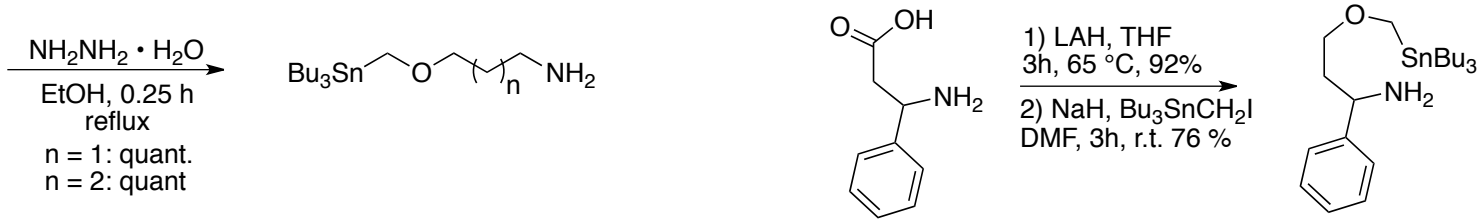
Synthesis of SnAP Reagents:

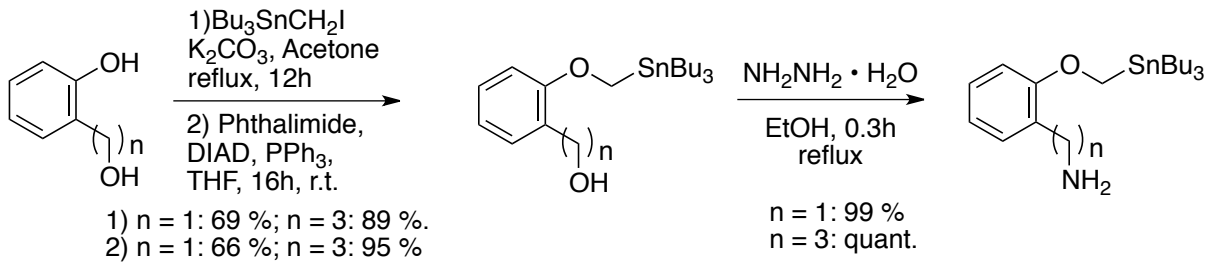


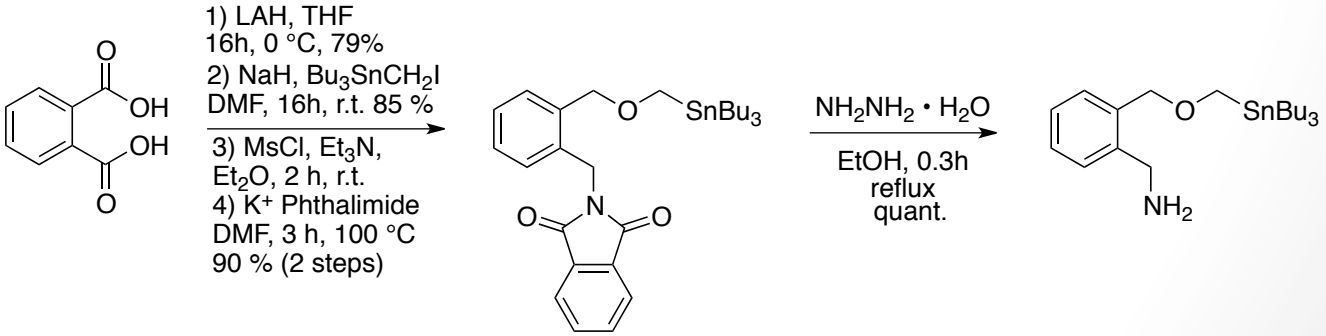
Angew. Chem. Int. Ed. 2013, 52, 1705 –1708

Synthesis of SnAP Reagents

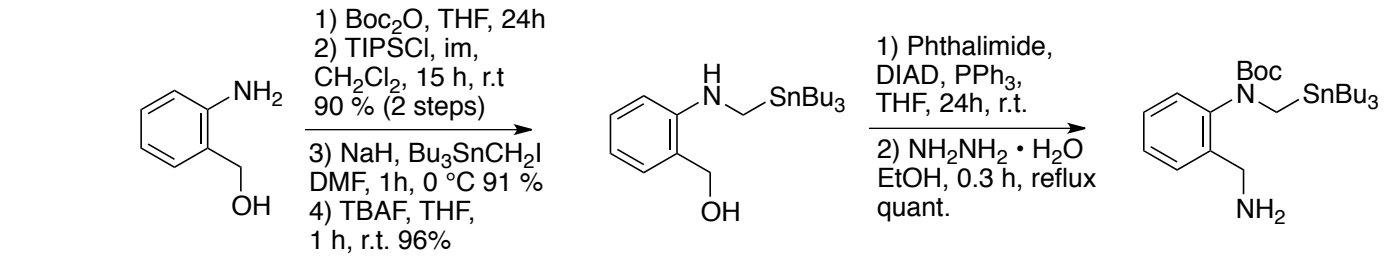


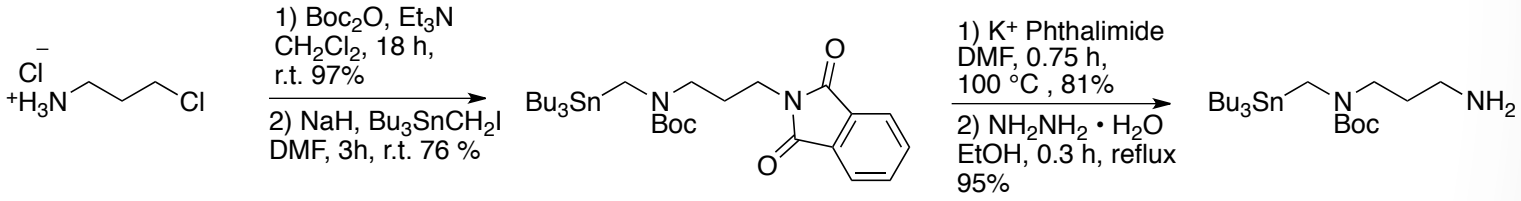




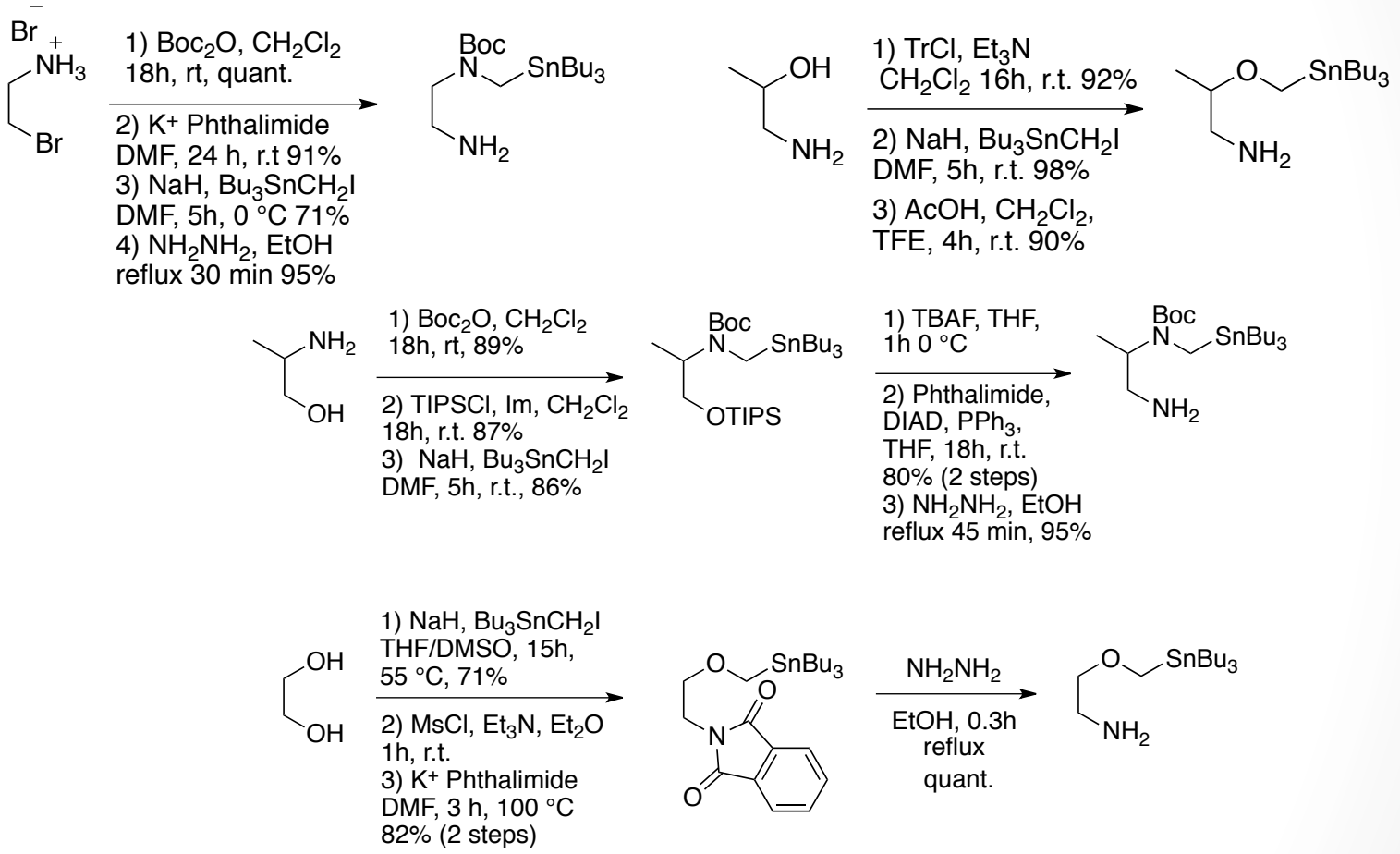


Synthesis of SnAP reagents





SnAP for Substituted Piperazines/ Morpholines



	3 Het + 0 Car	2 Het + 1 Car	1 Het + 2 Car	0 Het + 3 Car
Mol Wt	392	387	415	459
Solubility (uM)	242	184	128	83
Daylight clogP	2.5	3.25	4.19	5.14
CHI logD7.4	1.59	2.21	2.81	3.27
HSA (% binding)	87	92	94.7	95.7
AGP (% binding)	75.4	80.6	85.2	88.5
CyP 3A4 (pIC50)	4.71	4.8	4.91	4.98
CyP 2C9 (pIC50)	4.7	4.95	5.18	5.4
CyP 2C19 (pIC50)	4.55	4.72	4.87	5.1
CyP 2D6 (pIC50)	4.71	4.74	4.78	4.91
CyP 1A2 (pIC50)	4.51	4.6	4.56	4.39
hERG (pIC50)	5.04	5.17	5.35	5.48