Direct Stereospecific Synthesis of Unprotected N-H and N-Me Aziridines from Olefins

Jat, J. L.; Paudyal, M. P.; Gao, H.; Xu, Q.-L.; Yousufuddin, M.; Devarajan, D.; Ess, D. H.; Kürti, L.; Falck, J. R.

Science, **2014**, *343*, 61

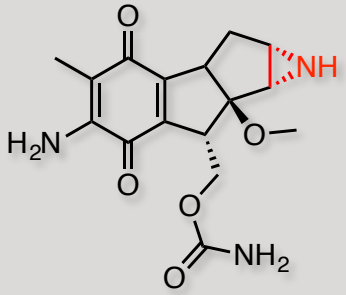
Joshua Sacher

Current Lit

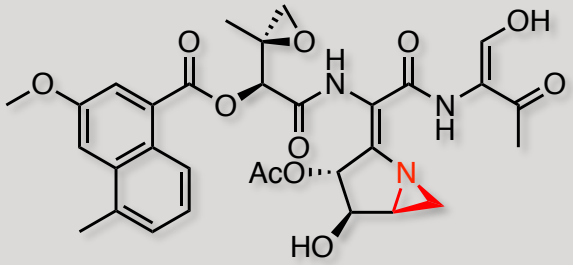
18 Jan 2014

The Importance of Aziridines

Natural products



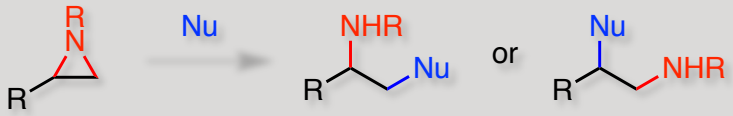
mitomycin C



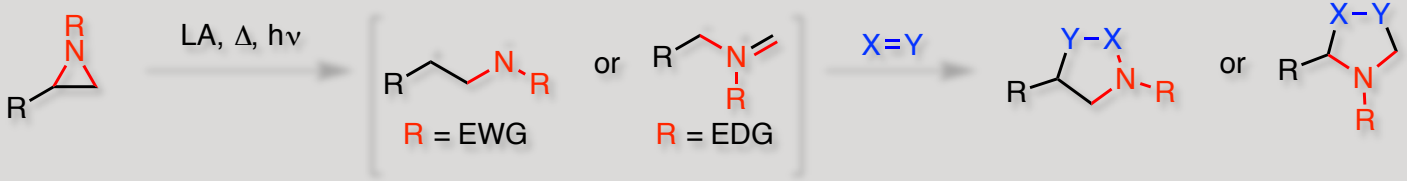
azinomycin B

Reactive functional group

electrophile



[3+2] reactions

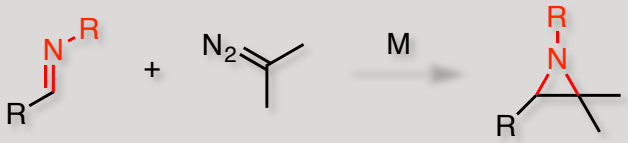


Padwa, A.; Murphree, S. S. *ARKIVOC*, **2006**, *iii*, 6

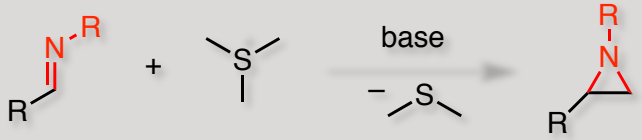
Aziridine Synthesis

Nitrene

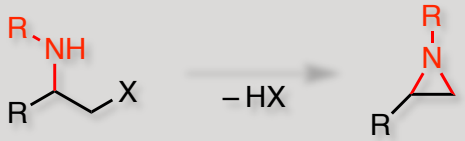
Carbene



Sulfur ylide

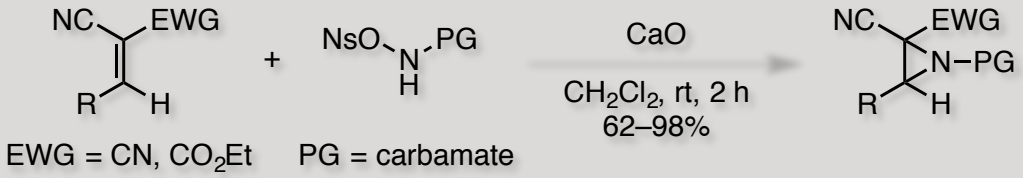


Nucleophilic cyclization



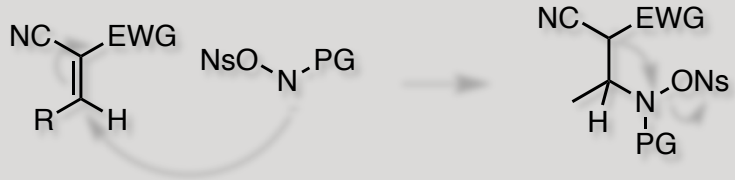
Padwa, A.; Murphree, S. S. *ARKIVOC*, **2006**, *iii*, 6

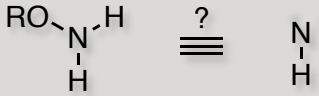
Hydroxylamines in Aziridination



EWG = CN, CO_2Et PG = carbamate

via



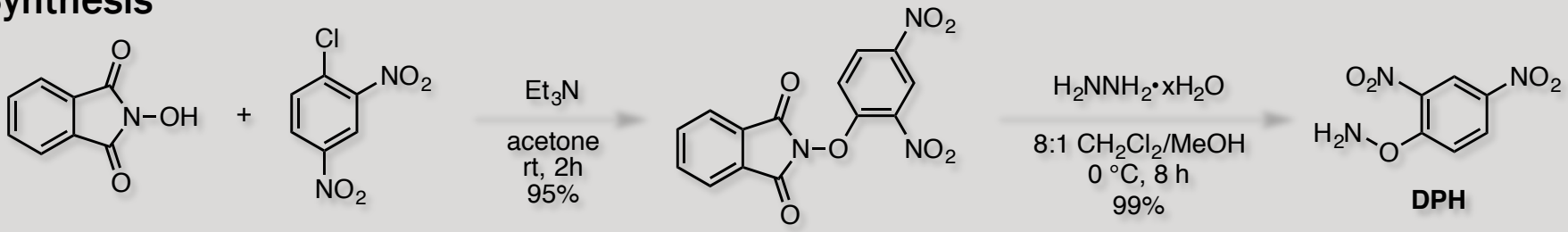


Possibility of using O-(EWG) hydroxylamine as nitrene?

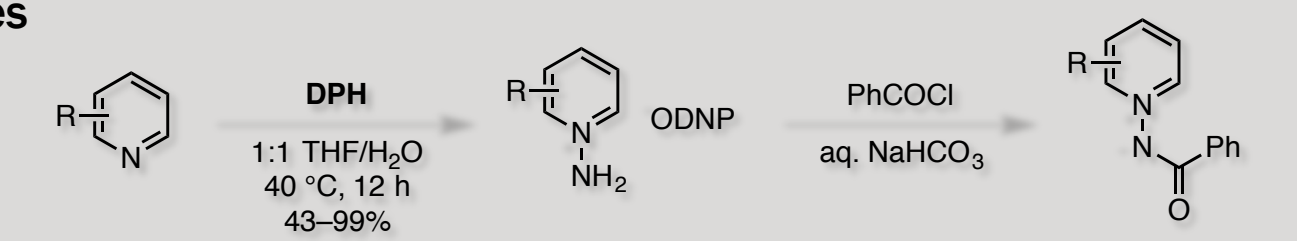
Fiorvanti, S.; Morreale, A.; Pellacani, L.; Tardella, P. A. *Synlett*, **2004**, 1083

O-(2,4-Dinitrophenyl)hydroxylamine

Synthesis



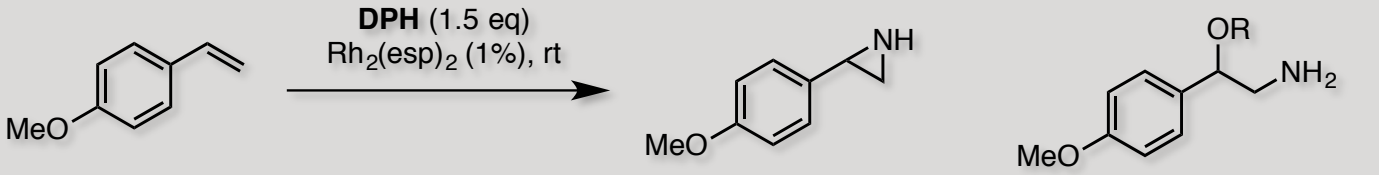
Previous uses



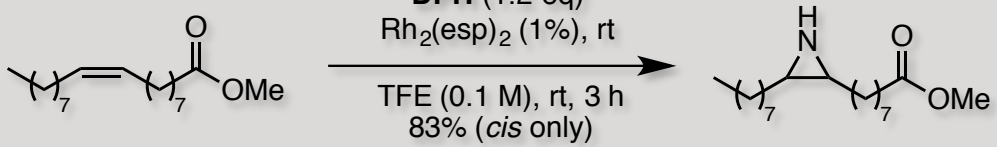
Legault, C.; Charette, A. B. *J. Org. Chem.* **2003**, *68*, 7119

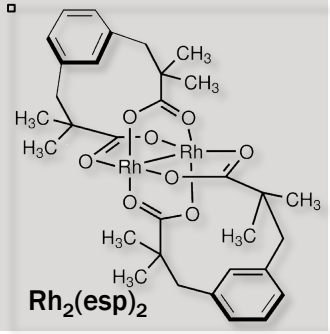
Zhu, C.; Li, G.; Ess, D. H.; Falck, J. R.; Kürti, L. *J. Am. Chem. Soc.* **2012**, *134*, 18253

Initial Studies

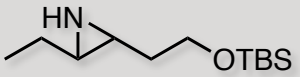


Solvent		
MeCN	0%	75% (R = DNP)
MeOH	0%	56% (R = Me) + 22% (R = DNP)
CF_3CH_2OH	0%	66% (R = DNP)

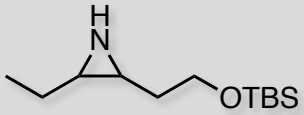




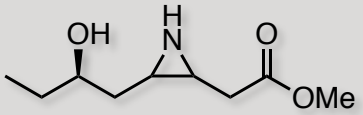
Substrate Scope: Aliphatic



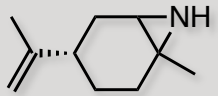
1% cat., 4 h, 72%



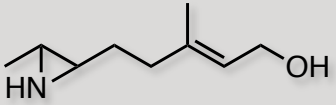
2 x 1% cat., 29 h, 55%



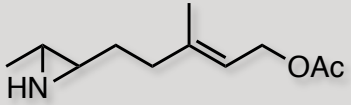
3 x 1% cat., 6 h, 82% (1:1 dr)



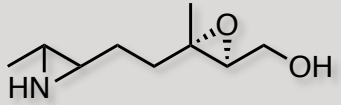
1% cat., 12 h, 72%
(1:1 dr, 9:1 regio)



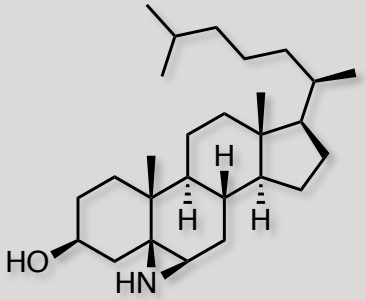
1% cat., 3 h, 71%
(5:1 regio)



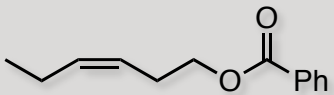
1% cat., 5 h, 81%
(14:1 regio)

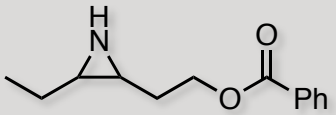


1% cat., 0 °C, 5 h
81% (1:1 dr)

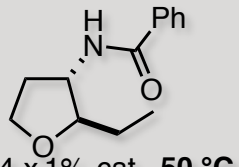


2.2 eq. DPH, 2 x 1% cat.
1:1 THF/TFE, 48 h, 71%



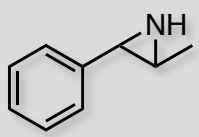


5% cat., **rt**, 2 h, 69%

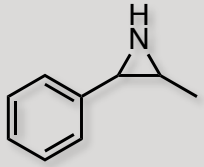


4 x 1% cat., **50 °C**
96 h, 84%

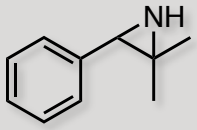
Substrate Scope: Aromatic, N-Me



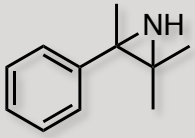
1% cat. -10 °C
14 h, 53%



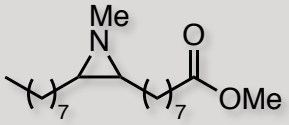
3 x 1% cat. -10 °C
68 h, 76%



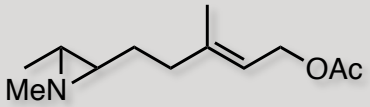
1% cat., 3h, 92%



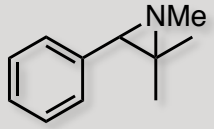
1% cat, 1.5 h, 70%



2% cat., 6 h, 80%

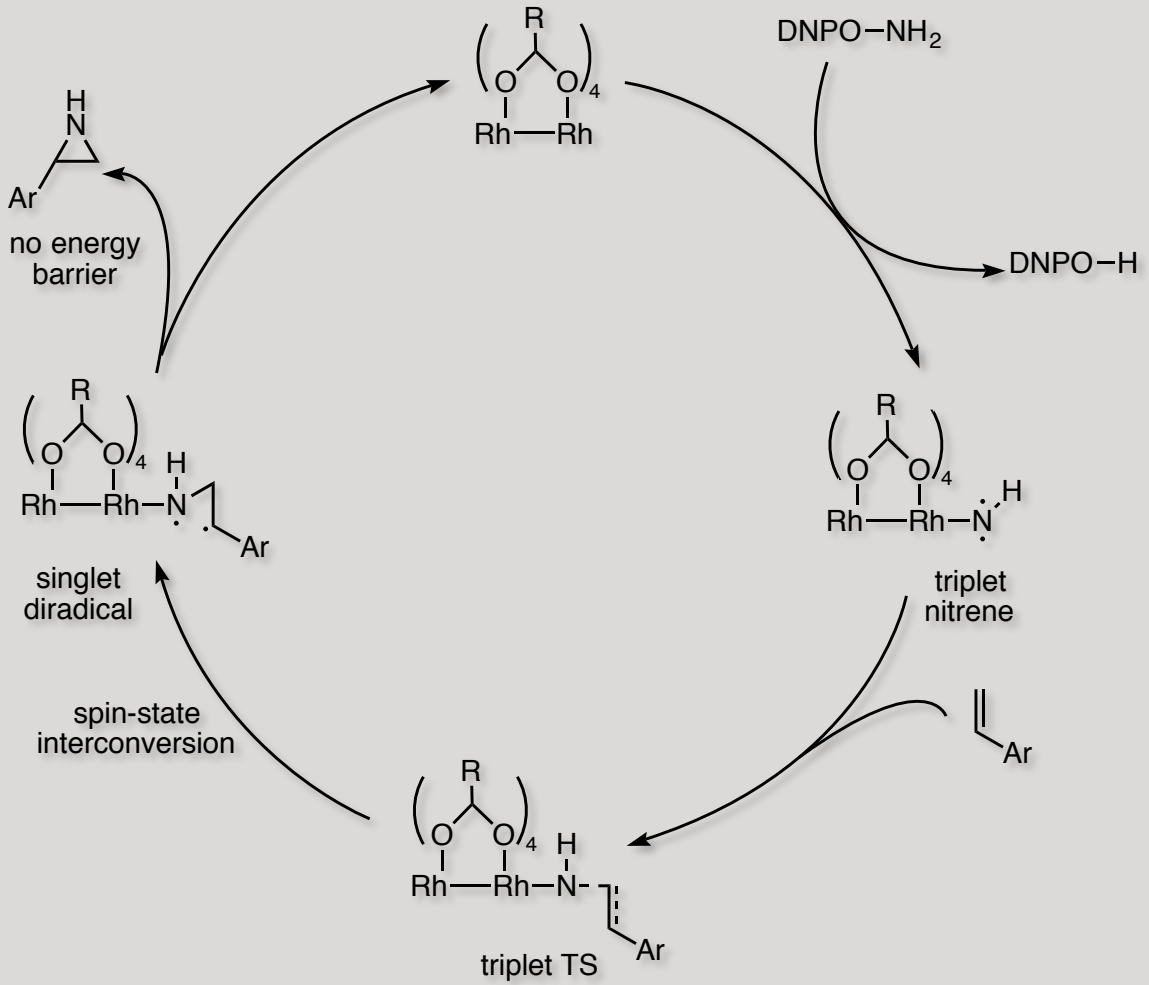


1.25% cat., 4 h
83% (>30:1 regio)



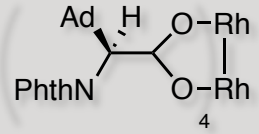
1.25% cat., 4 h, 81%

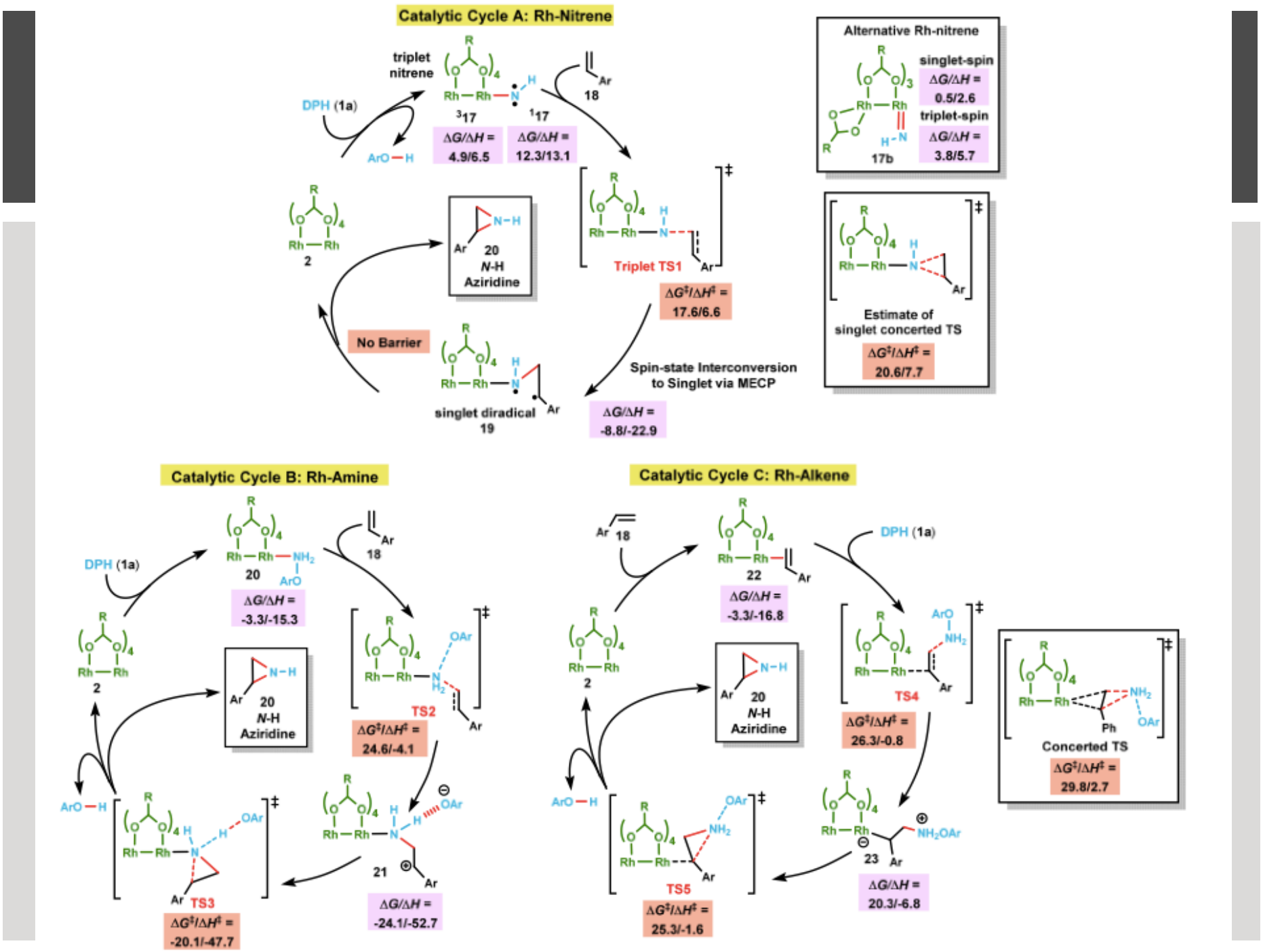
Proposed Mechanism



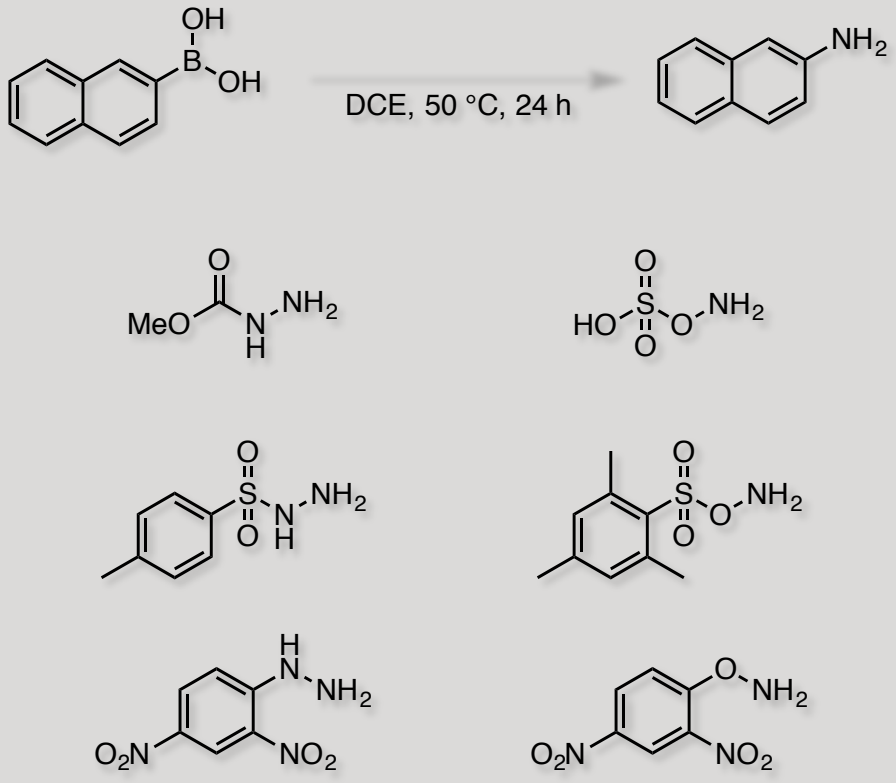
SUMMARY

- New method for the direct formation of unprotected/methyl aziridines
  - Easily synthesized DPH as nitrogen source
  - Retention of alkene geometry
  - Mild conditions, low catalyst loading
- Behind the scenes:
  - Large catalyst screen (Mn, Fe, Co, Ni, Cu, Ru, Rh, Pd, Ir, Au)
  - No competing C–H amination (cyclohexene)
  - Attempt at asymmetric reaction using Rh_2-(*S*)-PTAD
- For the future
  - Successful asymmetric reaction?
  - Expand scope of aryl compounds
  - Alkynes → azirines?
  - Application in complex synthesis




Catalytic Cycle A: Rh-Nitrene
triplet nitrene
DPH (1a)
ArO—H
^{3}17
^{1}17
ΔG/ΔH = 4.9/6.5
ΔG/ΔH = 12.3/13.1
18
2
20 N-H Aziridine
No Barrier
singlet diradical 19
Triplet TS1
ΔG‡/ΔH‡ = 17.6/6.6
Spin-state Interconversion to Singlet via MECP
ΔG/ΔH = -8.8/-22.9
Alternative Rh-nitrene
17b
singlet-spin ΔG/ΔH = 0.5/2.6
triplet-spin ΔG/ΔH = 3.8/5.7
Estimate of singlet concerted TS
ΔG‡/ΔH‡ = 20.6/7.7
Catalytic Cycle B: Rh-Amine
DPH (1a)
20
ΔG/ΔH = -3.3/-15.3
18
2
20 N-H Aziridine
TS2
ΔG‡/ΔH‡ = 24.6/-4.1
ArO—H
TS3
ΔG‡/ΔH‡ = -20.1/-47.7
21
ΔG/ΔH = -24.1/-52.7
Catalytic Cycle C: Rh-Alkene
18
22
ΔG/ΔH = -3.3/-16.8
DPH (1a)
2
20 N-H Aziridine
TS4
ΔG‡/ΔH‡ = 26.3/-0.8
Concerted TS
ΔG‡/ΔH‡ = 29.8/2.7
ArO—H
TS5
ΔG‡/ΔH‡ = 25.3/-1.6
23
ΔG/ΔH = 20.3/-6.8

Aminating Agents



Zhu, C.; Li, G.; Ess, D. H.; Falck, J. R.; Kürti, L. *J. Am. Chem. Soc.* **2012**, *134*, 18253

Title

References