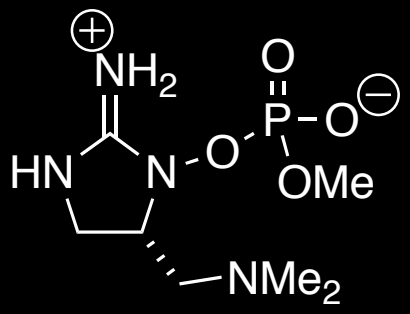
Towards a Total Synthesis of Anatoxin-a(s)



Eric E. Buck
Research Topic Seminar
September 19, 2009

Background

- Anatoxin-a(s) is a neurotoxin produced by the blue-green alga *Anabaena flos-aquae (picture right)* and *A. lemmermannii*

- A potent anticholinesterase with LD_{50} 20 - 40 μg/ Kg in mice

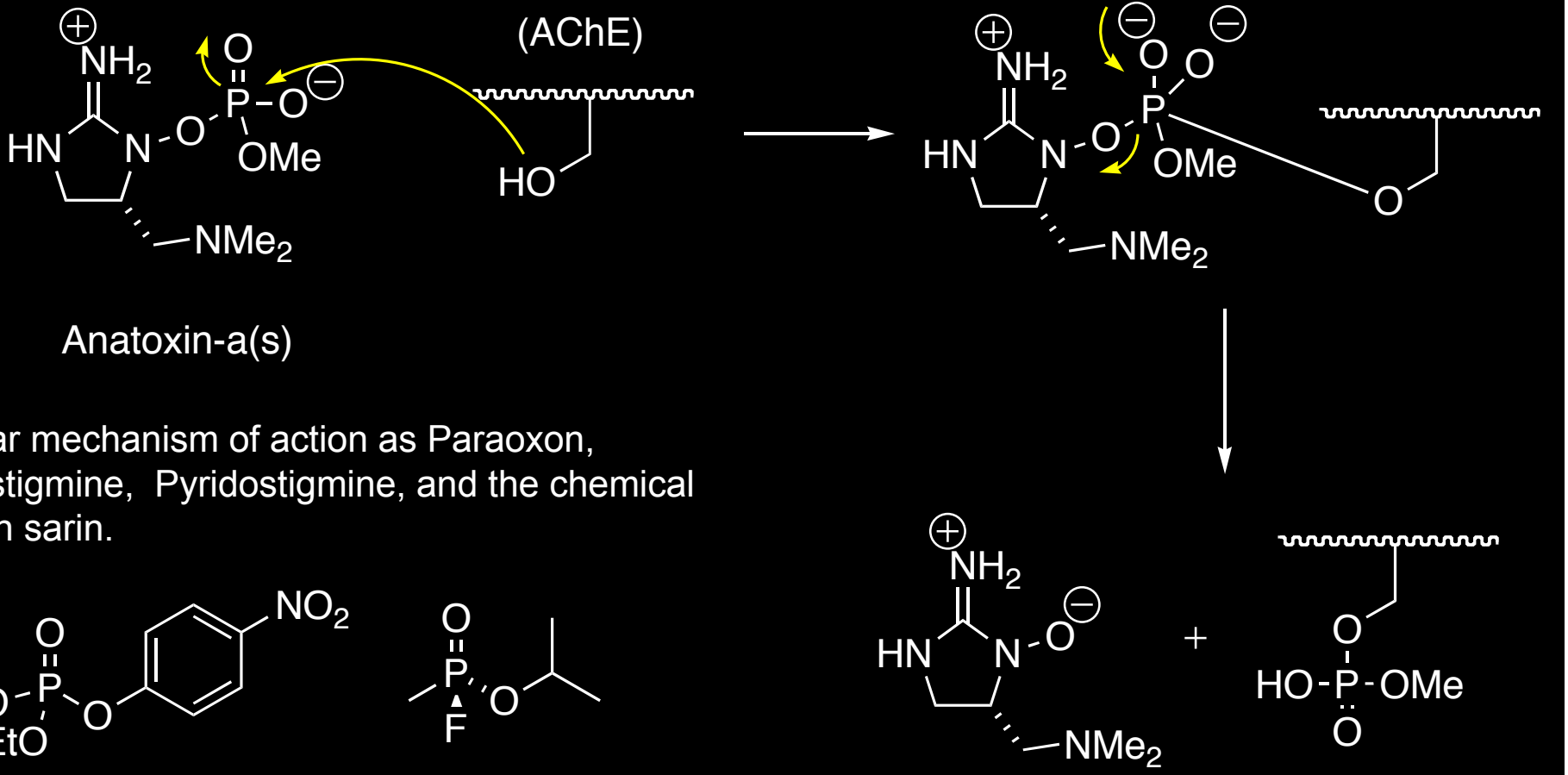
- Inhibits AChE in the peripheral nervous system which leads to the build up of acetylcholine in the synaptic cleft

- Symptoms included muscle weakness, respiratory distress, and convulsions leading to death

- Responsible for the death of dogs, pigs, and ducks in the USA and Canada and water fowl in Denmark

Aráoz, R., et al., Toxicon. 2009i, article in press.
Matsunaga, S.; Moore, R. E.; Niemezura, W. P. *J. Am. Chem. Soc.* **1989**, 111, 8021-8023

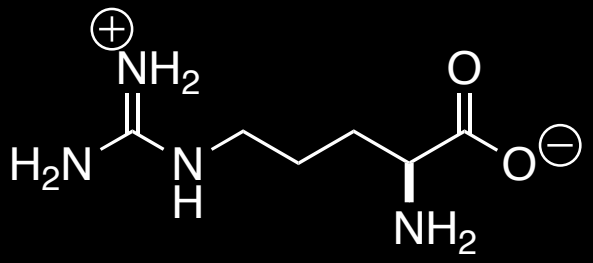
Mechanism of Action



• Similar mechanism of action as Paraoxon, Physostigmine, Pyridostigmine, and the chemical weapon sarin.

Aráoz, R., et al., Toxicon. 2009i, article in press.
Apeldoorn, M. E.; Egmond, H. P.; Speijers, G. J. A.; Bakker, G. J. I. *Mol. Nutr. Food Res.* **2007**, 51, 7 - 603

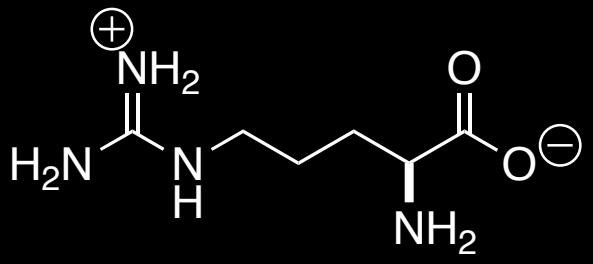
Biosynthesis



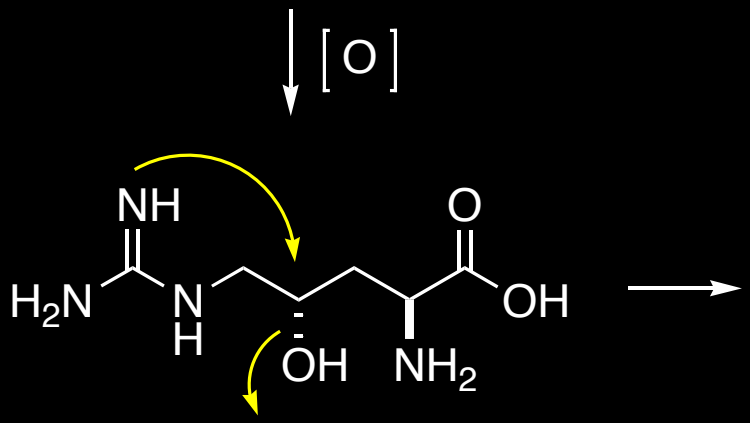
Arginine

Moore, B. S. *Nat. Prod. Rep.,* **1999**, 16, 653 - 674
Moore, B. S.; Ohtani, I.; de Koning, C. B.; Moore, R. E. *Tetrahedron Lett.* **1992**, 33, 6595 - 6598

Biosynthesis



Arginine



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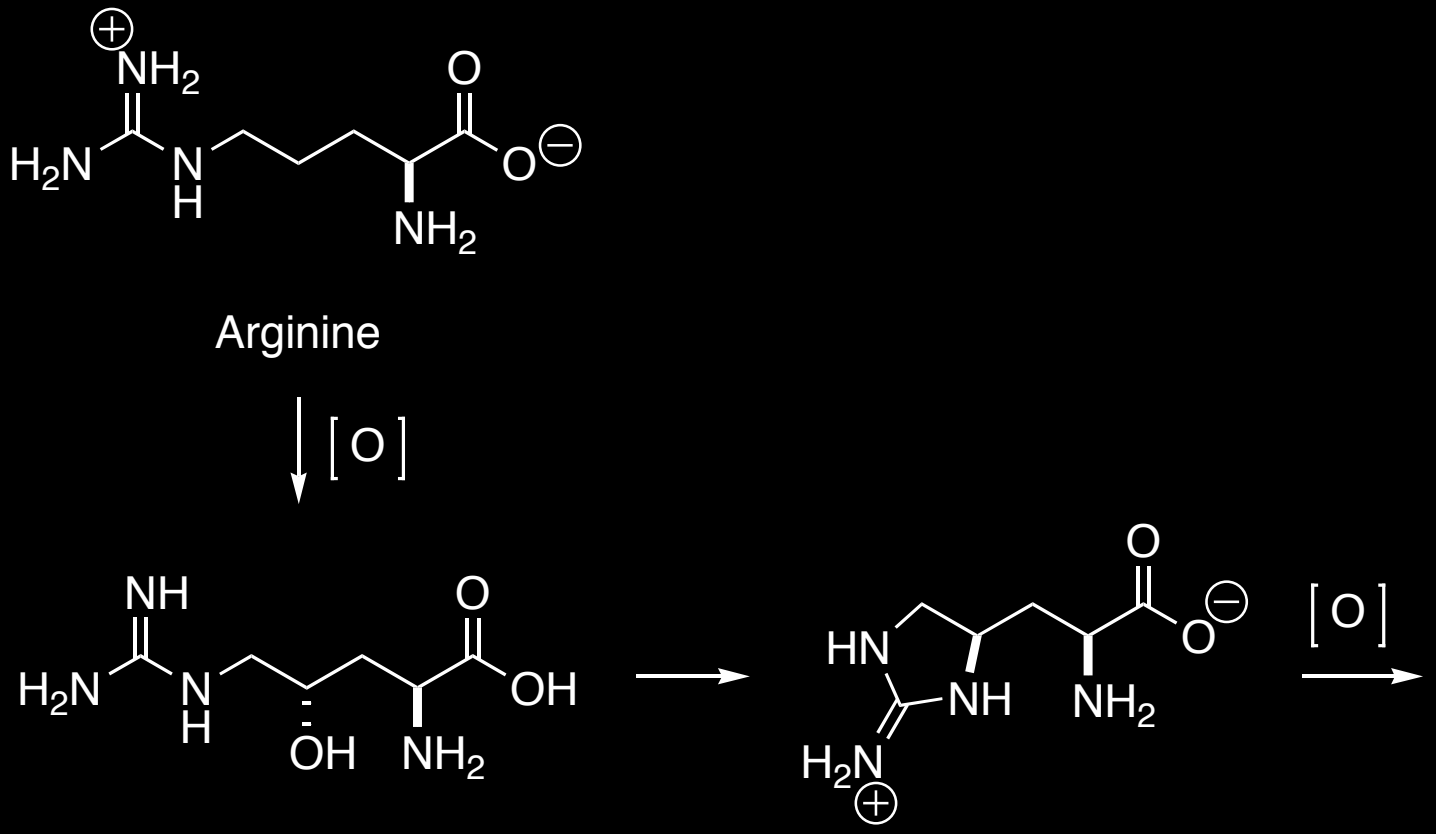

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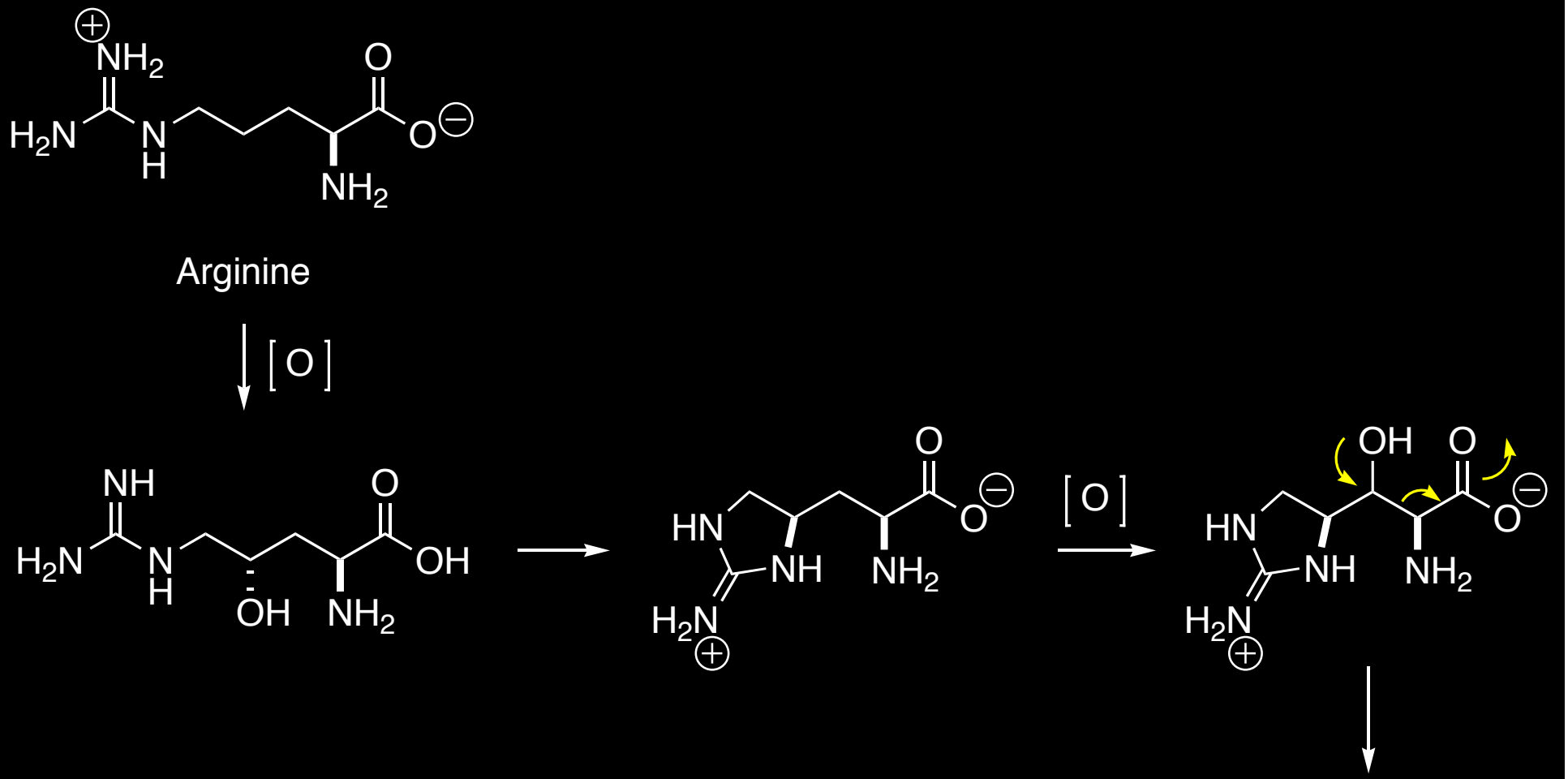

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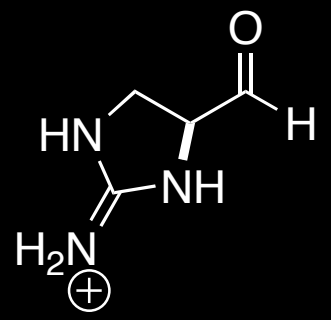

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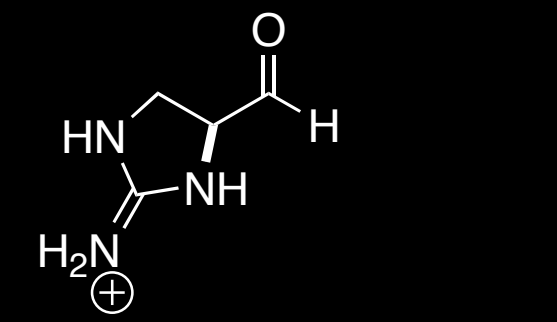

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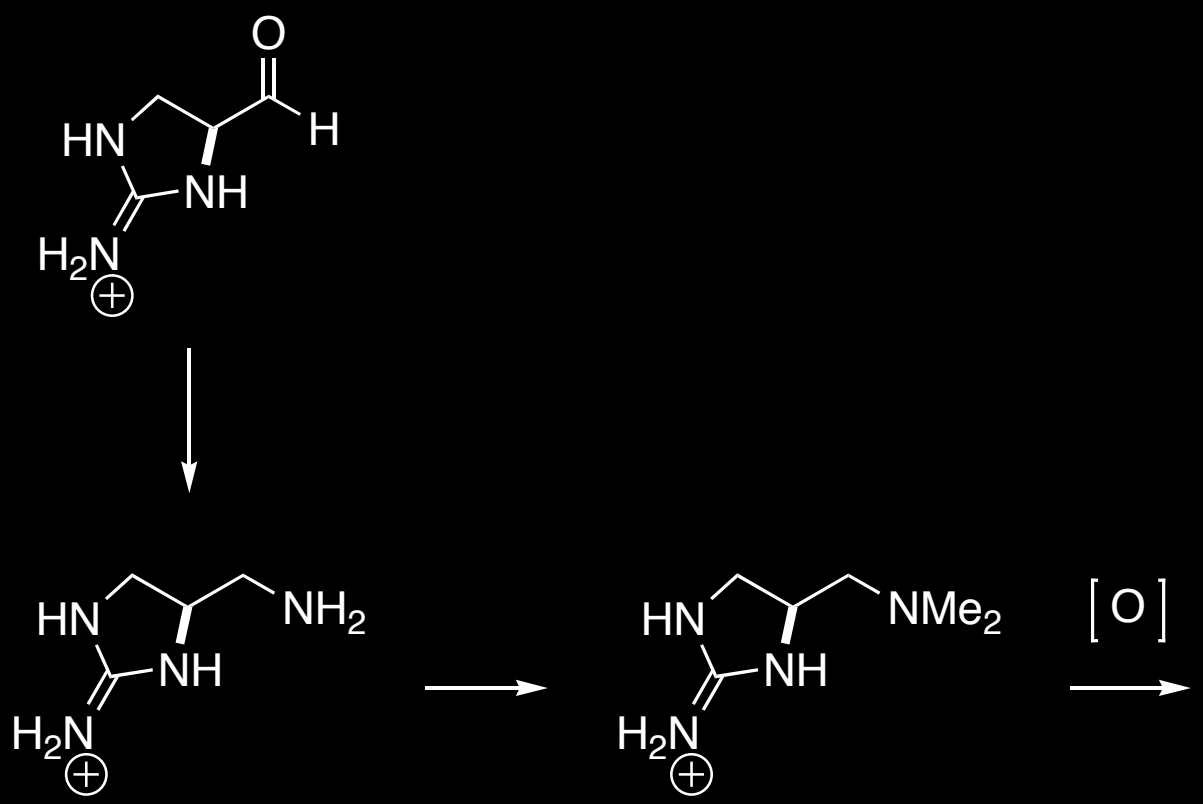

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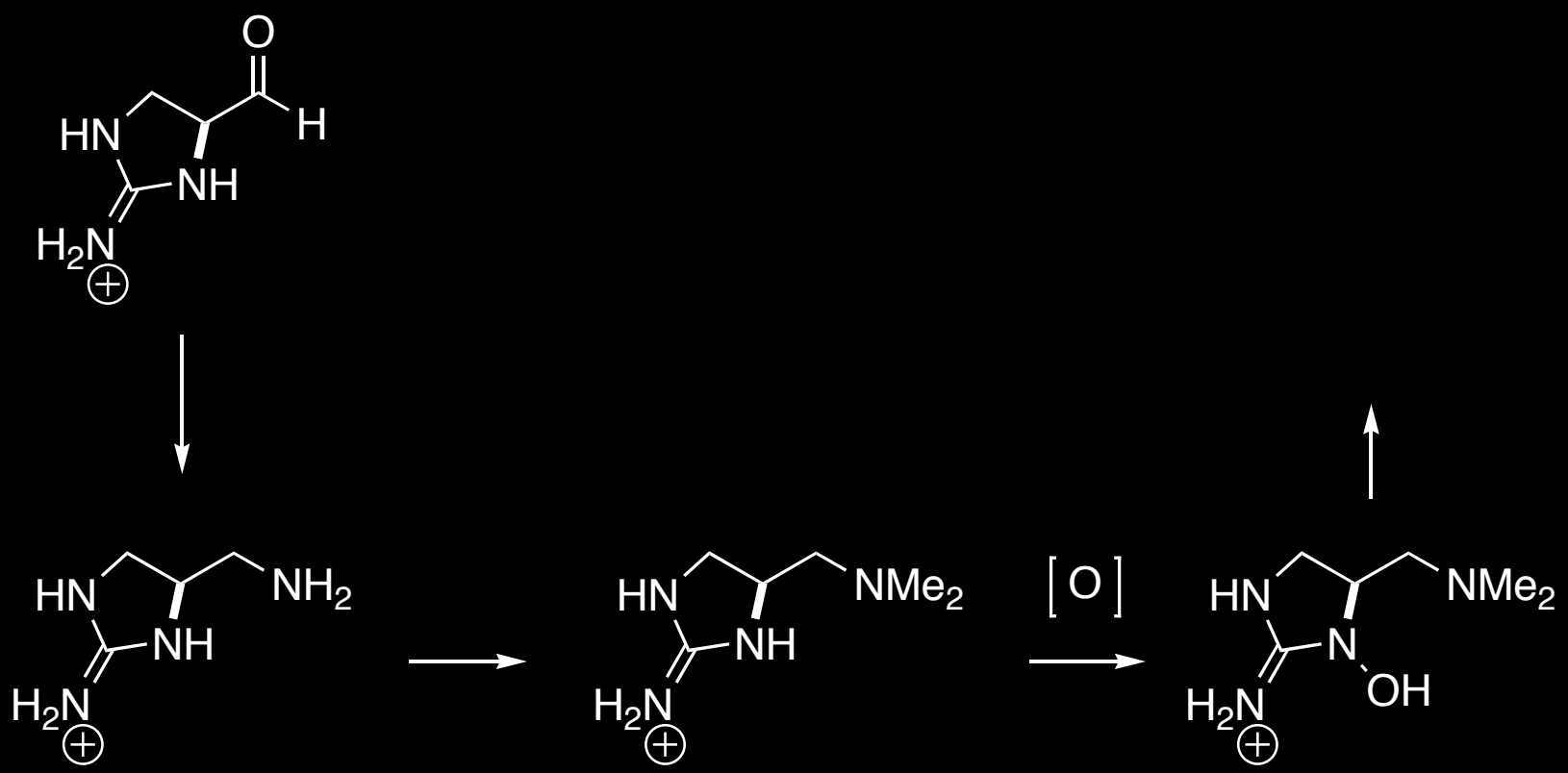

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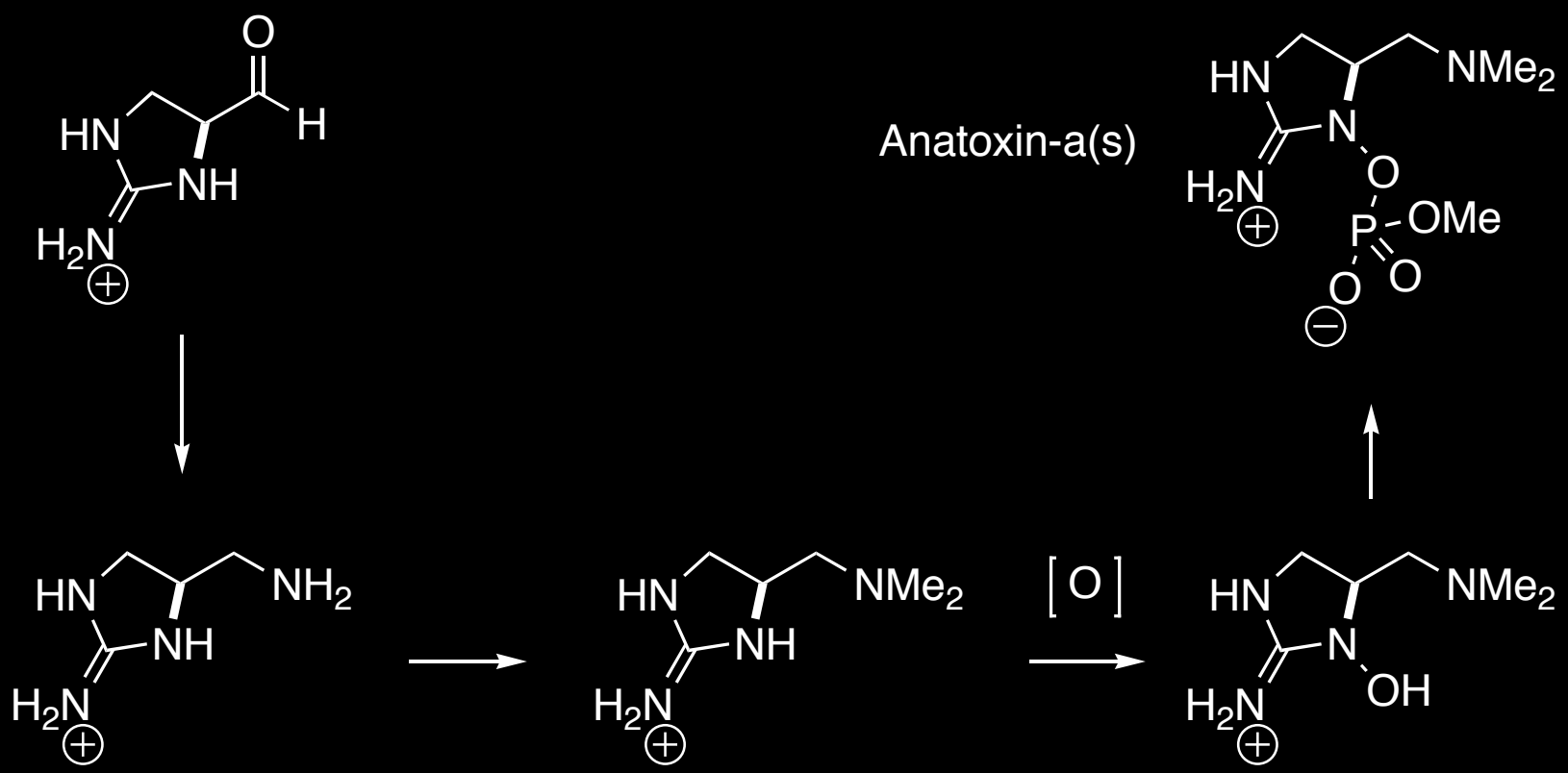

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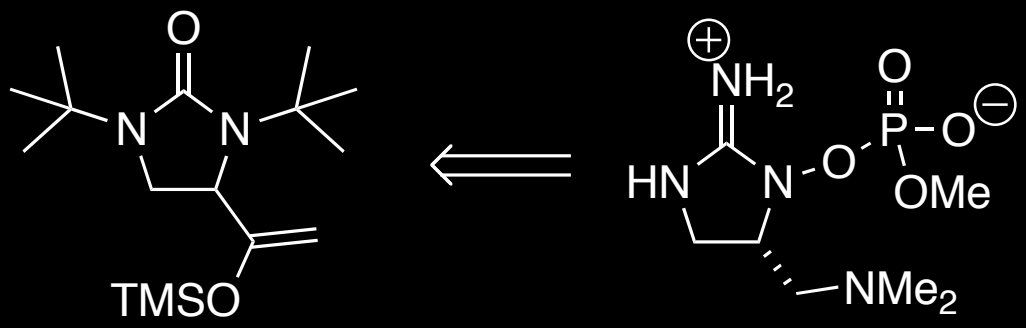
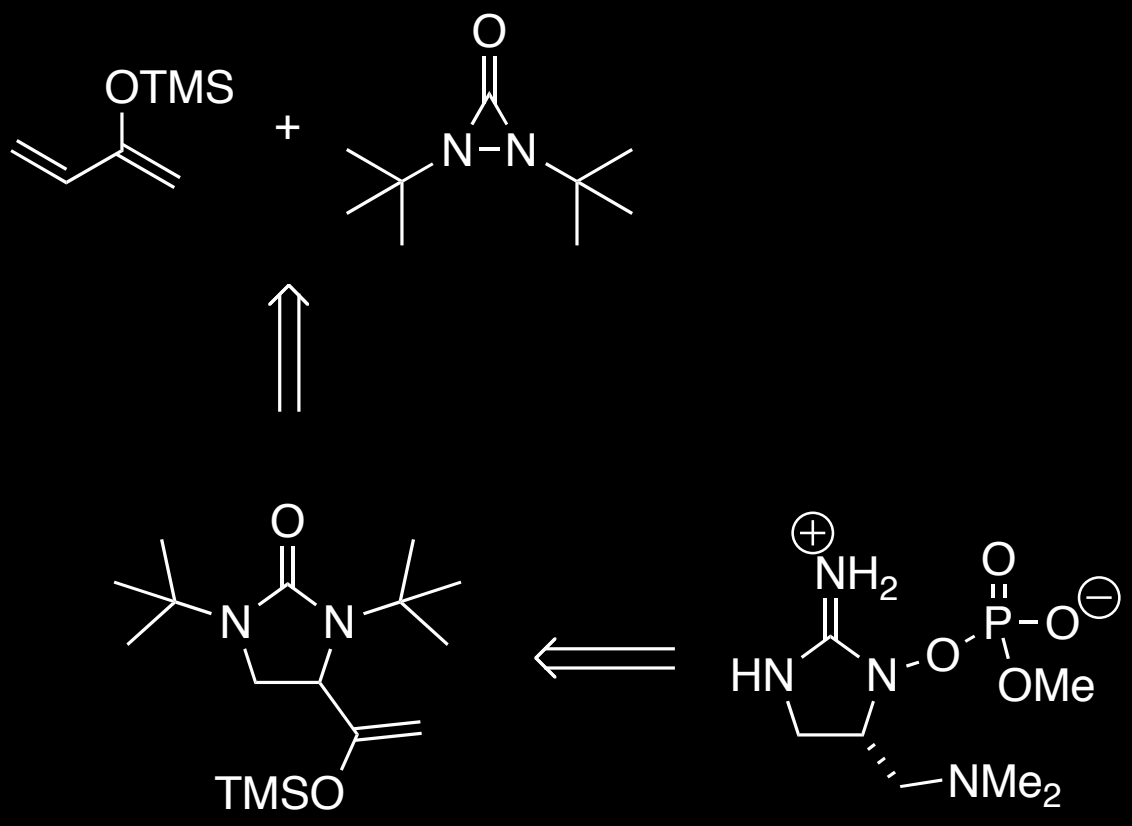
Retro-synthesis



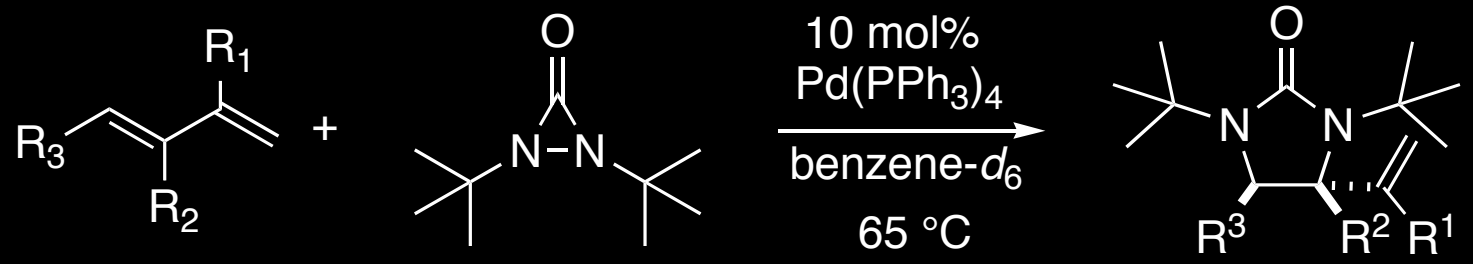
Anatoxin-a(s)

Retro-synthesis



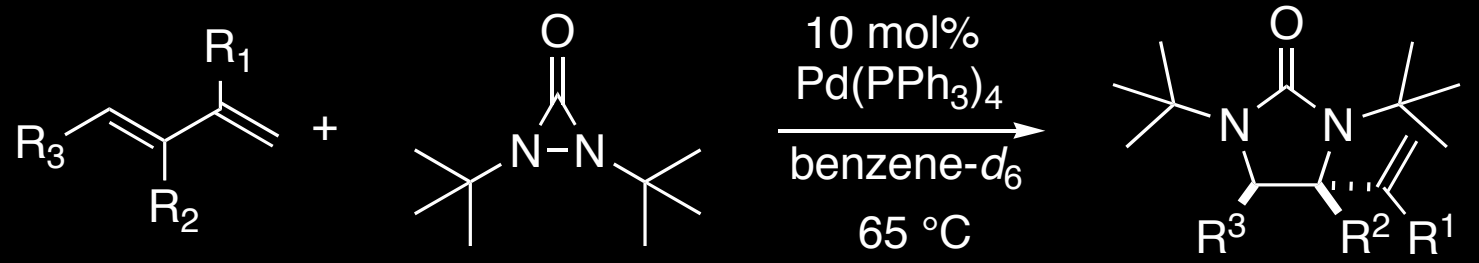
Anatoxin-a(s)

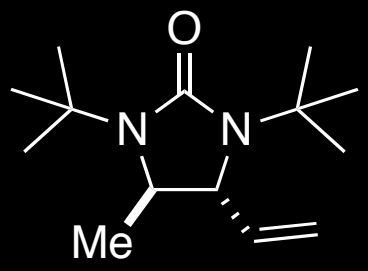
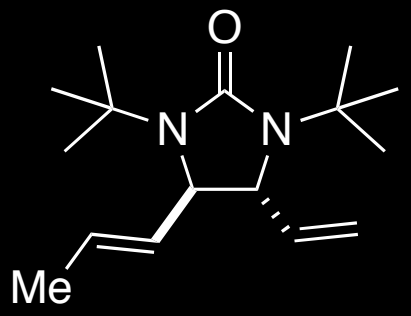
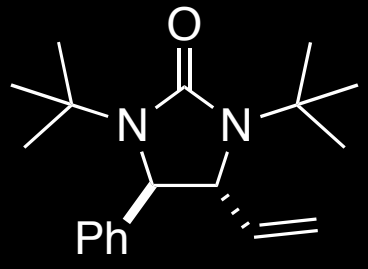
Shi's work on the diamination of olefins



Du, H.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.,* **2007**, 129, 762 - 763

Shi's work on the diamination of olefins



substrate	product	substrate	product
	 (94%)		 (86%
	 (90%)		

Du, H.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.,* **2007**, 129, 762 - 763

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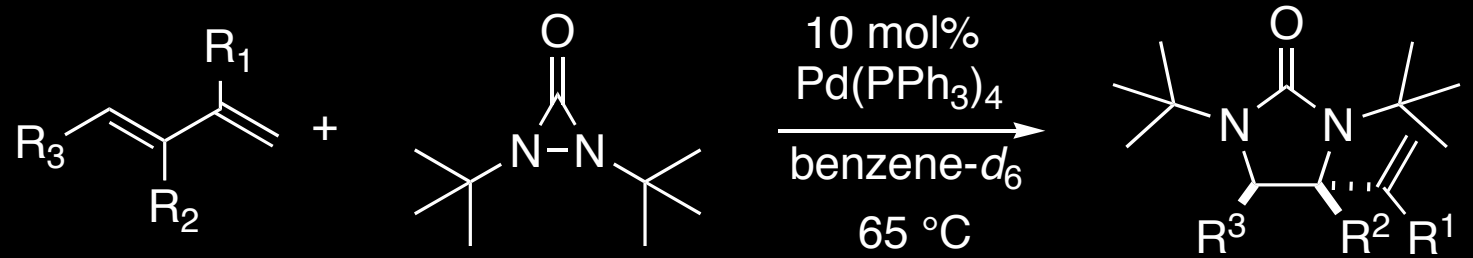
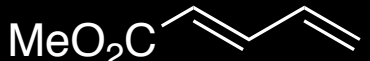
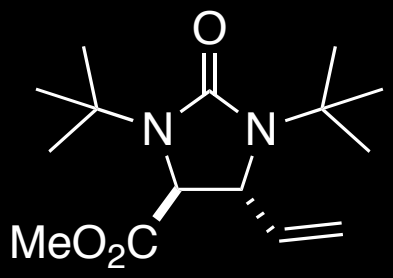
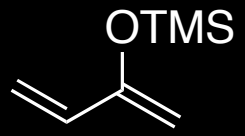
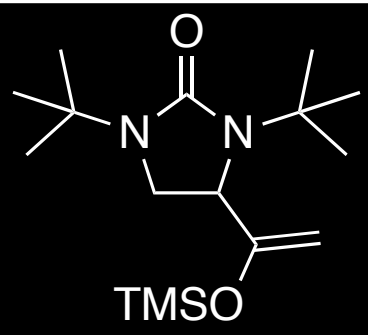


substrate	product	substrate	product
	 (60%)		 (90%)

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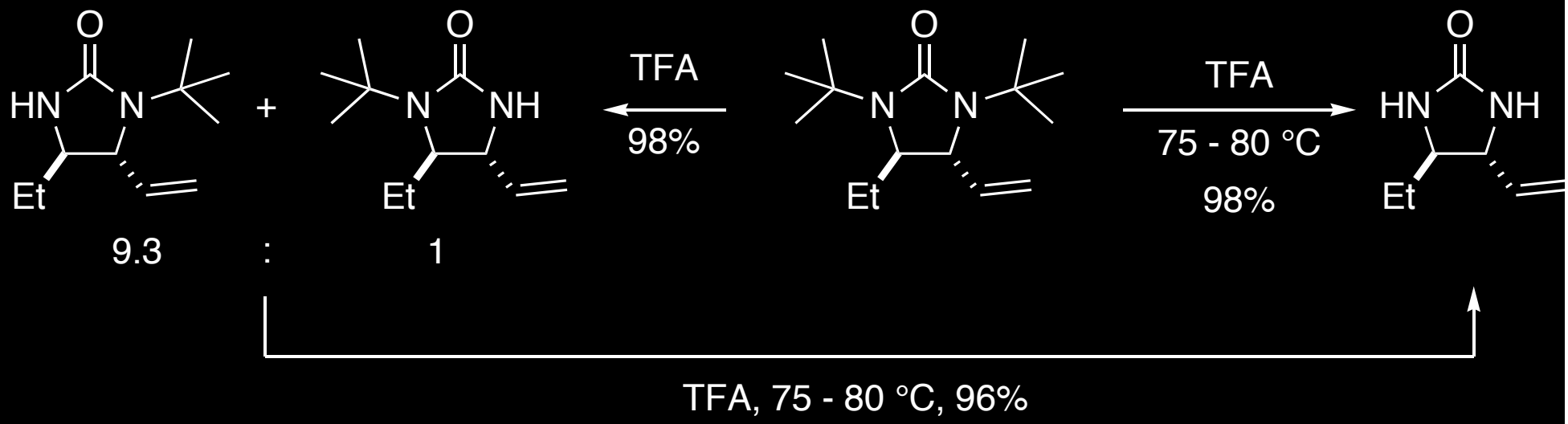

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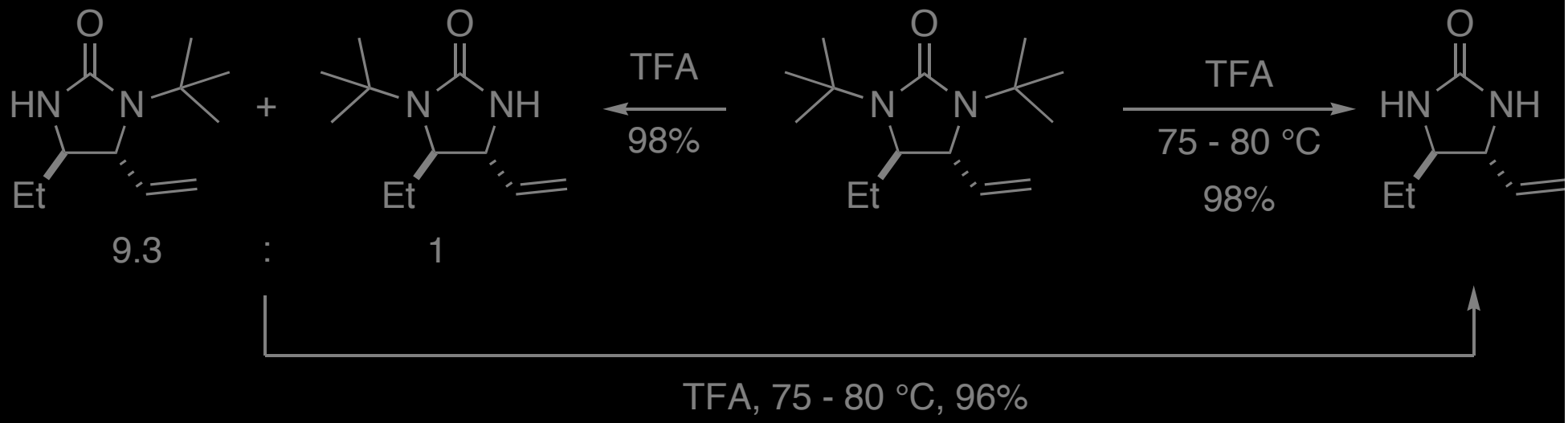

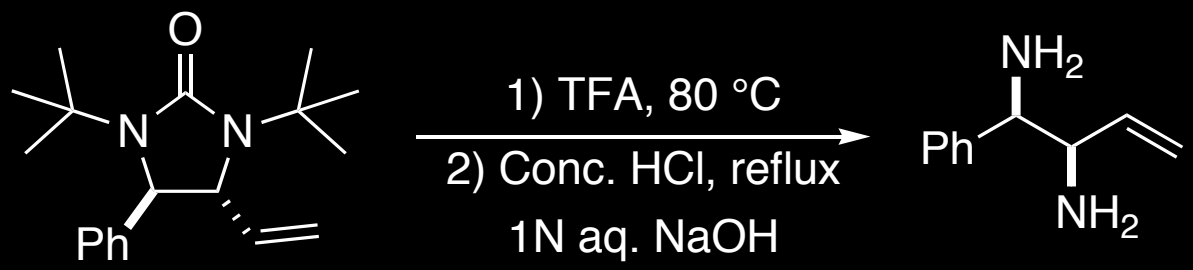

84%

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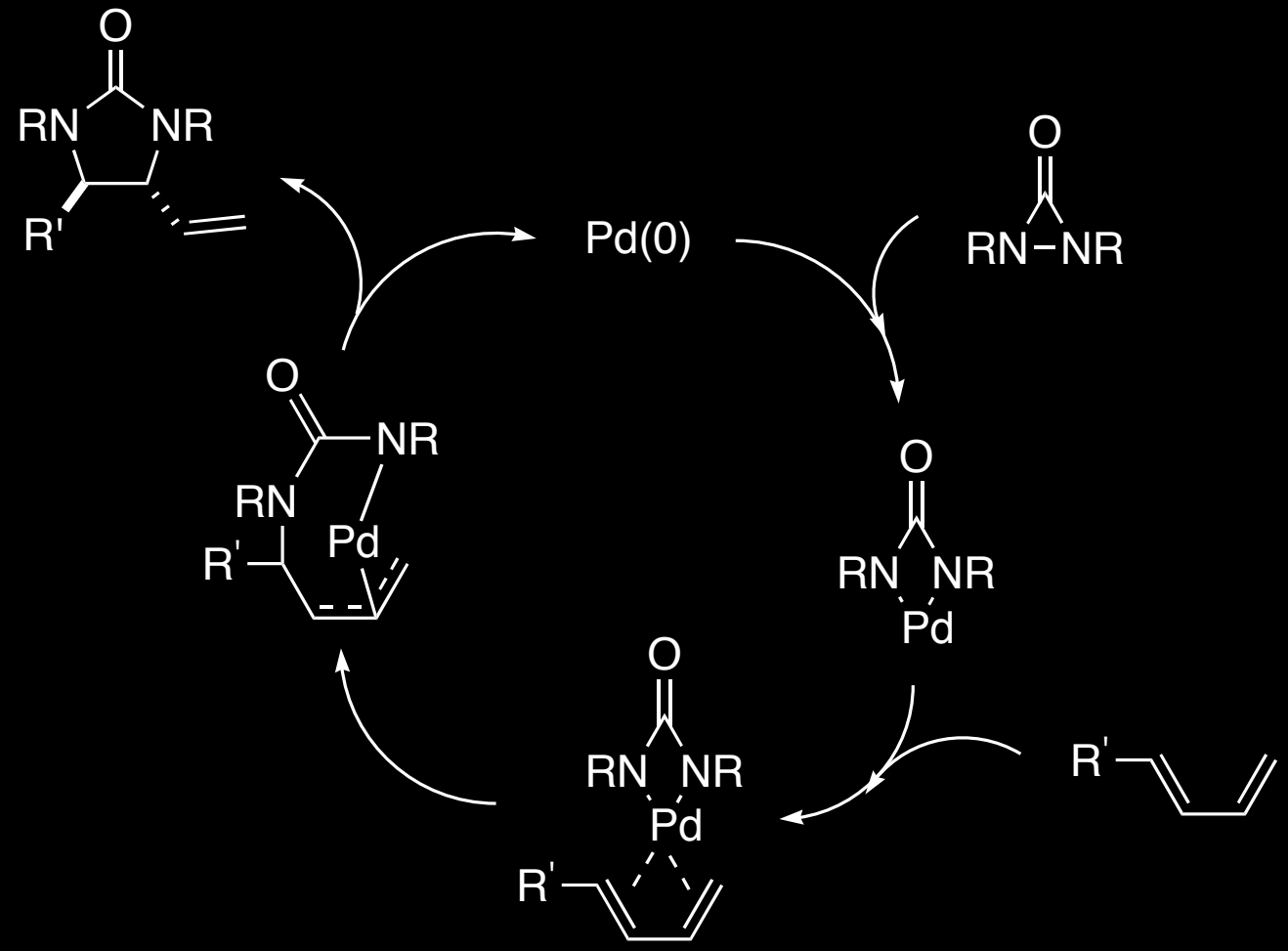

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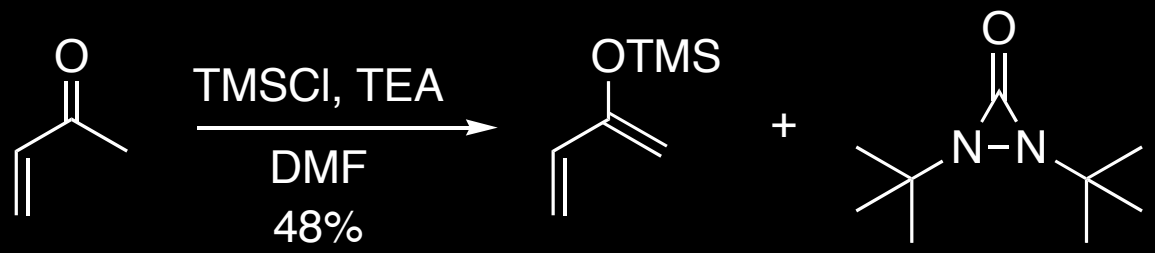
Route 1: diaminaiton of butadiene derivatives



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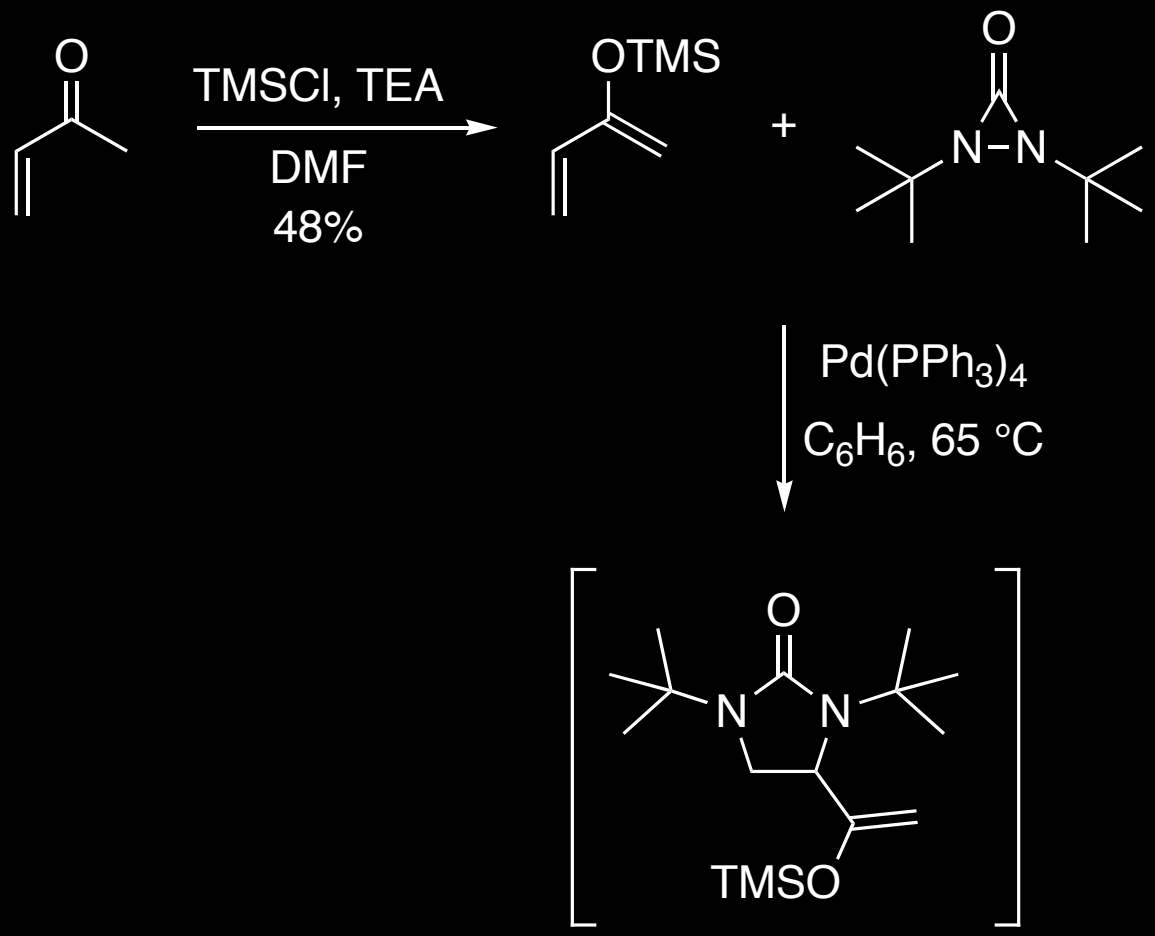

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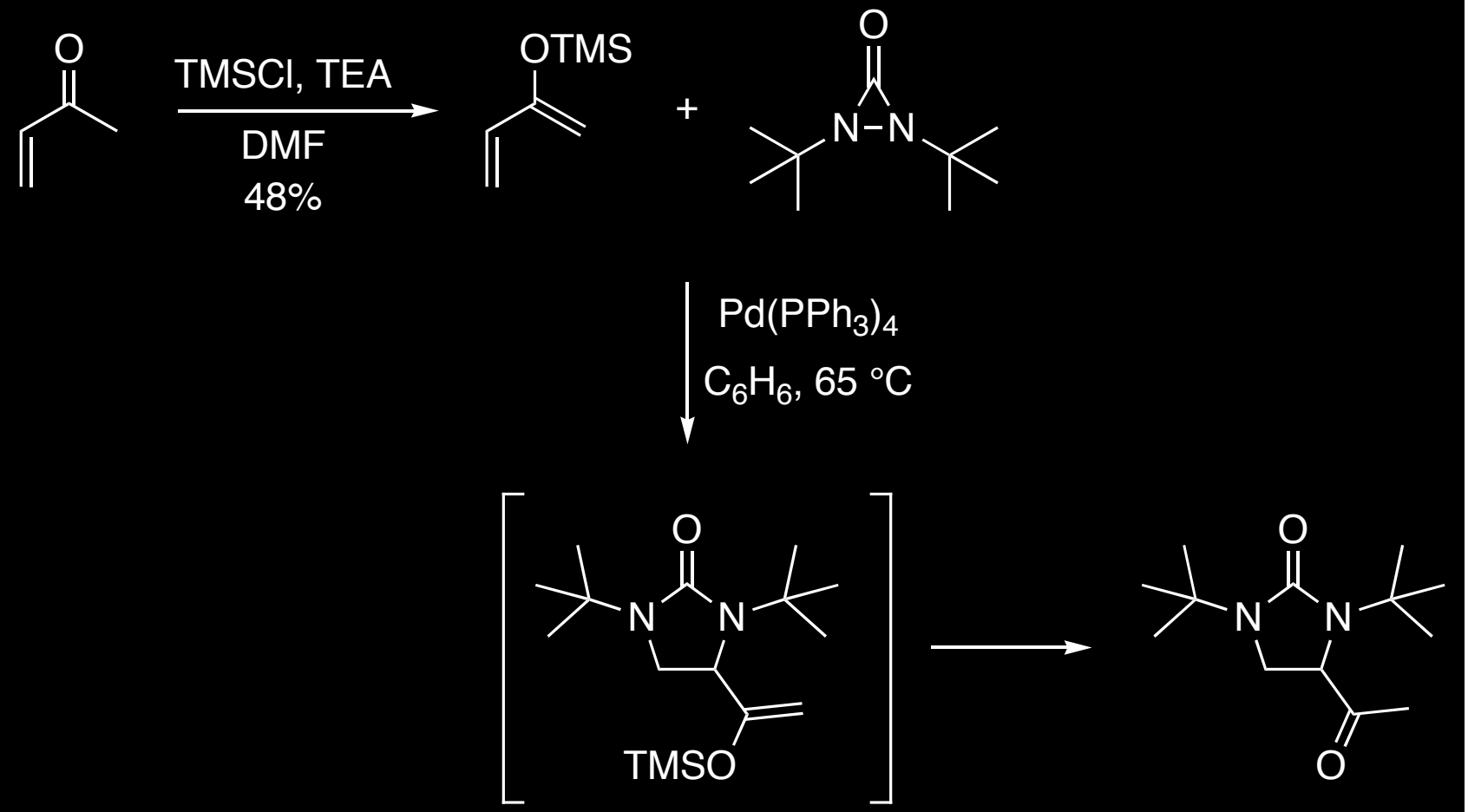

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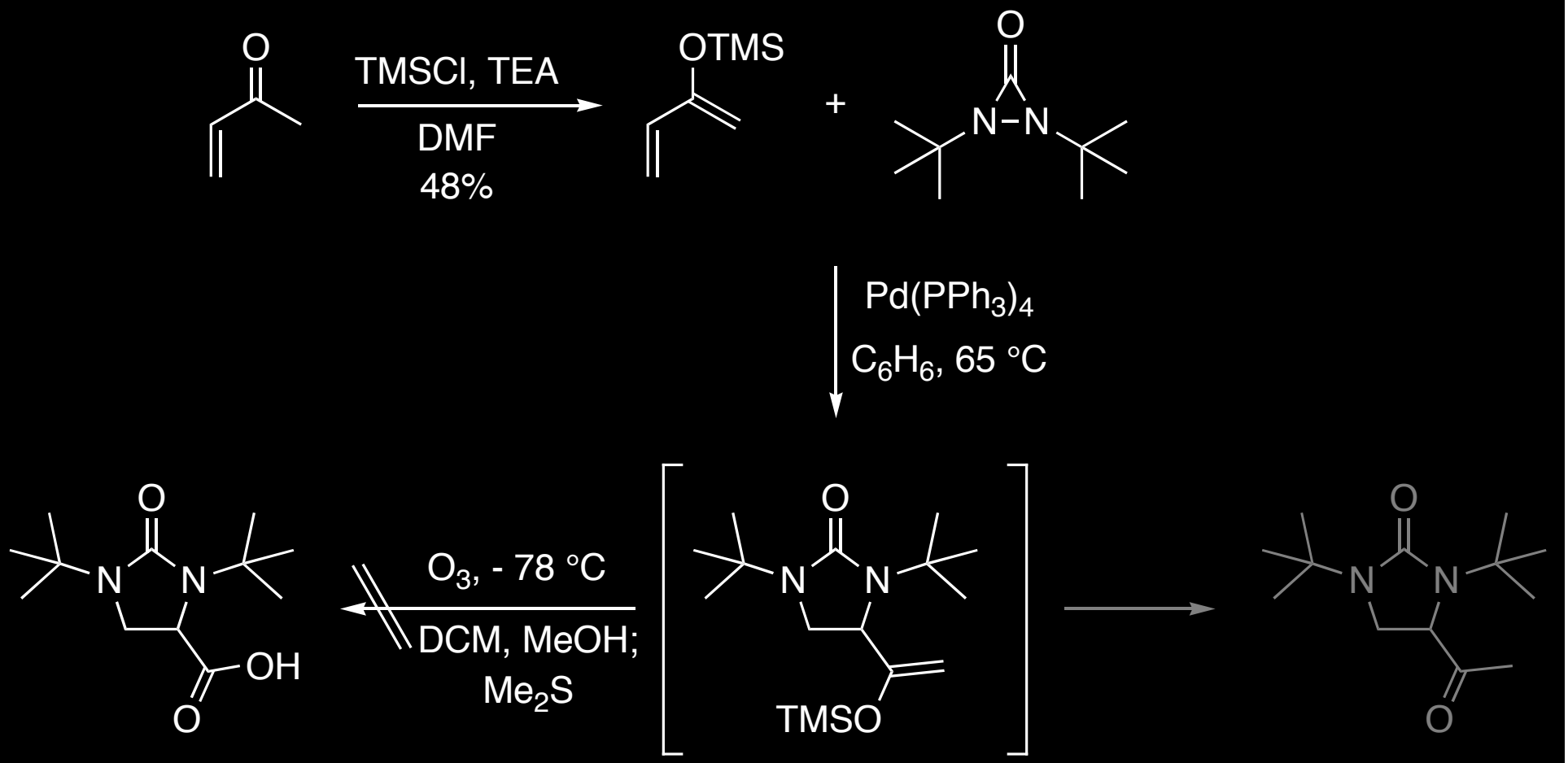

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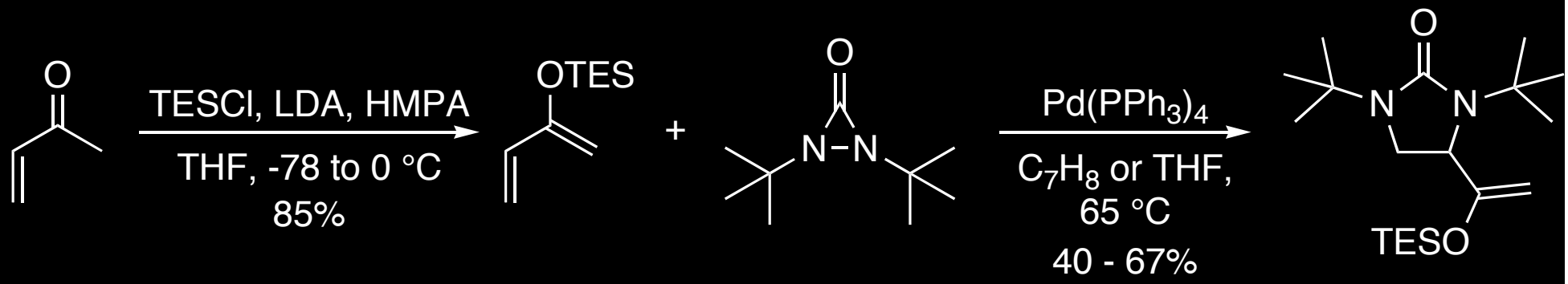

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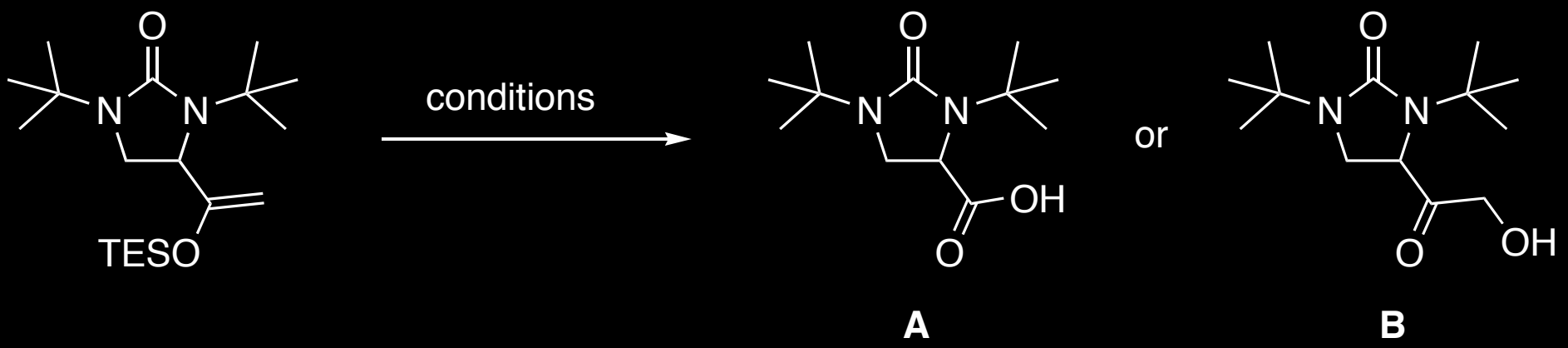

entry	conditions	yield
1	O_3, DCM, MeOH, -78 °C; Me_2S	**A**: ---
2	OsO_4, $NaIO_4$, THF, H_2O	**A**: ---
3	mCPBA, 5% $NaHCO_3$ (aq), DCM; 1.5 M HCl, MeOH	**B**: 5%[a]
4	OsO_4, NMO, THF, H_2O	**B**: ---

[a] Yield after isolation

Conclusion

- Route 1: diaminaiton of butadiene derivatives
- Route 2: ongoing
- Route 3: ongoing
- Screening conditions to close the ring asymmetrically
- Finish the synthesis