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## Creativity Exercise OSMUM-FREE DIHYDROXYLATION OF OLEFINS

#### Situation

 As grimly forewarned by Dennis Sherwood, the Republic of Osmikistan has succumbed to civil unrest, yet another stage in what has become known as the "Transitionmetal Spring". Supplies of Os join the other transition metals in their scarcity. Chemists everywhere are in a state of panic over their potential inability to dihydroxylate olefins. Luckily a brave band of researchers in the TJD group are preparing to tackle this synthetic problem head on...

#### Os-mediated dihydroxylation

1925 – Milas dihydroxylation



1976 – Upjohn dihydroxylation

Tet. Lett., 1976, 36, 1973



#### Sharpless AD

- Utilises K<sub>2</sub>OsO<sub>2</sub>(OH)<sub>4</sub>, ligand, base, and a stoichiometric reoxidant (NMO, K<sub>3</sub>Fe(CN)<sub>6</sub>, etc.).
- "Ligand-accelerated catalysis" reaction is faster in presence of amine base than in absence (originally noticed by Criegee with pyridine).
- Chiral *Cinchona* alkaloid-based catalysts for AD.



 Applicable to most olefin classes, although limited somewhat with tetrasubstituted and *cis*-disubstituted olefins

For a comprehensive review see: Chem. Rev., 1994, 2483

#### Sharpless AD (cont)





#### Sharpless AD (cont)

 Some debate over whether addition of Os is via a [3+2] or [2+2] with migration to form osmium glycolate species. Most evidence seems to support [3+2] mechanism



Acc. Chem. Res., 2003, 36, 645

## Os-free dihydroxylation

#### Ru-catalysed dihydroxylation



Angew. Chem. Int. Ed. Engl., **1994**, 33, 2312

#### Ru-catalysed AD

• Not many examples of Ru AD, but there are examples of combined CM-AD using a chiral sultam-derived enamide chiral auxiliary:



For an excellent review see Chem. Soc. Rev., 2011, 114

Mn-catalysed dihydroxylation



For catalytic KMnO<sub>4</sub> dihydroxylations see: a) Angew. Chem. Int. Ed. Engl., **1999**, 38, 980. b) Chem. Comm., **2010**, 46, 1640. c) Tet. Lett., **2002**, 43, 2619. d) JACS, **2005**, 127, 7990.

#### Mn-catalysed AD

Asymmetric phase-transfer catalysed dihydroxylation:



Prévost trans-dihydroxylation



*C. R. Hebd. Seances Acad. Sci.*, **1933**, 1129 *e.g: JOC*, **1999**, 74, 1902

Woodward cis-dihydroxylation



JACS, 1958, 80, 209

Catalytic Woodward dihydroxylation



Org. Lett., 2005, 7, 5071

Asymmetric Prévost/Woodward reaction



Hypervalent iodine(III) dihydroxylation



Tet. Lett., 2006, 3659

Hydroxamic acid aerobic dioxygenation



DLP = dilauroyl peroxide

Diphenyldiselenide dihydroxylation



R<sub>1</sub> = Me, R<sub>2</sub>,R<sub>3</sub> = -(CH<sub>2</sub>)<sub>4</sub>-, yield = 95%, syn:anti = 97:3 R<sub>1</sub>,R<sub>3</sub> = *n*Pr, R<sub>2</sub> = H, yield = 50%, syn:anti = 0:100

#### Diphenyldiselenide AD





Adv. Synth. Cat., 2008, 2881

#### Os-free dihydroxylation (cont) Rh-catalysed diboration/oxidation B<sub>2</sub>cat<sub>2</sub> (nbd)Rh(acac) (5 mol%) (S)-Quinap (5 mol%) ΟН JOC, 2005, 9538 THF **PMP** then H<sub>2</sub>O<sub>2</sub>, NaOH 71%, >98% ee Pt-catalysed diboration/oxidation $Pt(dba)_3$ (3 mol%) 3 (6 mol%) B<sub>2</sub>Pin<sub>2</sub> JACS, 2009, 13210 Ph-ОН then H<sub>2</sub>O<sub>2</sub>, NaOH 87%, 94% ee Pt/Pd-catalysed hydrosilylation/oxidation i) [PtCl<sub>2</sub>(C<sub>2</sub>H<sub>4</sub>)]<sub>2</sub> (0.005 mol%) HSiCI<sub>3</sub> JACS, 2002, 1584 **OH** ii) [PdCl(C<sub>3</sub>H<sub>5</sub>)]<sub>2</sub> (0.15 mol%) x (0.6 mol%) Ar iii) KF, K<sub>2</sub>CO<sub>3</sub>, MeOH, H<sub>2</sub>O<sub>2</sub> up to 95% ee 12

Operation Pd(II)-catalysed diacetoxylation



Org. Lett., 2010, 2450

Resin-supported epoxidation/hydrolysis



#### Strained peroxide dihydroxylation

Originally reported by Green using phthaloyl peroxide:



• Strained-malonyl peroxides:



*JACS*, **2010**, *132*, 14409 *JOC*, **2012**, *77*, 921

#### Strained peroxide dihydroxylation (cont)

Ostulated mechanism:



#### Strained peroxide dihydroxylation

Entry	Substrate	Product	Yield (%)	syn/anti
1	Ph	Ph Ph OH	78	28:1
2	Ph	Ph OH OH	80	4:1
3	PMP		77	6:1
4	Ph Ph	HO Ph OH	78	3:1
5		ОН	67	>50:1

Poor *syn*-selectivities observed for sterically less demanding substrates (Entries 2 and 3), as well as for cis-olefins which are not conformationally constrained (Entry 4 vs Entry 5), presumably due to free rotation in the postulated cationic intermediate A.

#### **Creativity Exercise!**

- Write down everything you know about oxidation of organic molecules
  - What are the current classes of oxidants?
  - What are the mechanisms of action of these classes?
  - Describe any catalytic oxidizing systems and how they work.
- Brainstorm the different ways to achieve dihydroxylation.
- List possible options for developing a novel dihydroxylation methodology.

# Thinking Hats!

