Greener Chemistry via the Application of Novel Oxidation Technology

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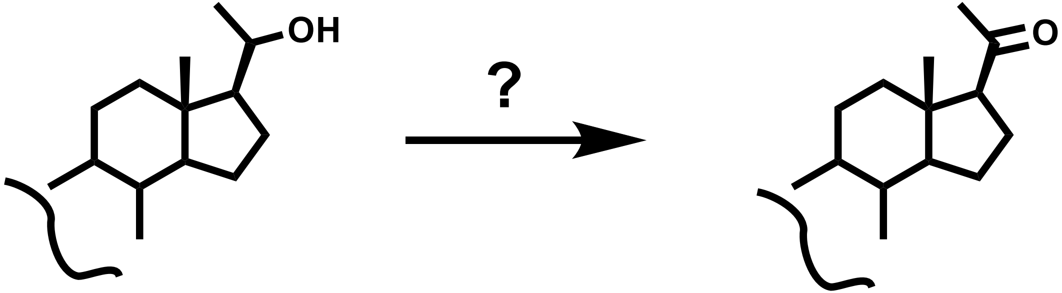
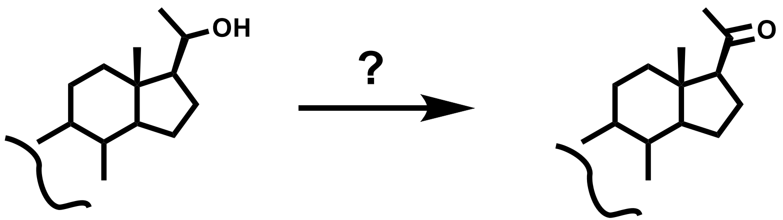
Late Stage API Intermediate



- The goal of this project was to selectively oxidize a hindered secondary alcohol
  - Reaction needed to go to completion
  - Without forming any impurities (making API)
  - Without adding significant cost.
- This API is also the starting material for other API's
  - If the cost goal was met it would reduce their costs also

Must not produce significant impurities

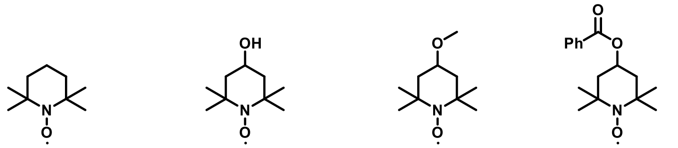
Search for Alternative Oxidations



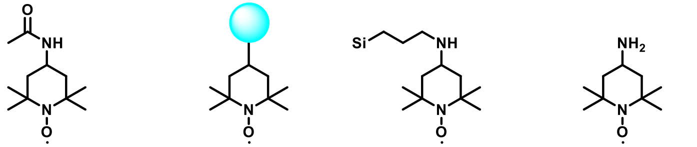
- Numerous methods to oxidize 2^o alcohols to ketones
- Most do not fit the needs of the project
  - Heavy Metals (Cr, Mn, Rh, Ru, Pt, Pd, etc.) which can be toxic (disposal issues) or expensive (require recycle)
  - Dangerous oxidants – peroxides, hypervalent iodide, etc. – can be explosive
  - Hazardous reaction conditions (O_2 / air atmosphere) – fires / explosions
  - Harsh conditions which lead to impurities and low yields
- It is very challenging to develop a "Clean", "Safe", and "Inexpensive" commercial oxidation process
- Three methods were explored in the laboratory
  - Chromium (IV) oxidation – toxic metal and requires significant waste disposal
  - STP oxidation (variation of the Swern) – odor issues and chemistry was dirty (thioacetal)
  - TEMPO / Bleach oxidation – incomplete reactions despite high catalyst loading
    - Most promising

No success with known reagents

TEMPO Catalyst Derivatives



TEMPO CAS# 2564-83-2 | 4-OH-TEMPO CAS# 2226-96-2 | 4-MeO-TEMPO CAS# 14691-88-4 | 4-OBz-TEMPO CAS# 2226-96-2

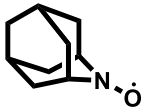


4-acetamido-TEMPO CAS# 14691-89-5 | TEMPO polymer bond | TEMPO on silica gel | 4-amino-TEMPO CAS# 14691-88-4

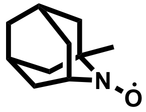
- Screened 8 TEMPO derivatives but none were adequate (grossly incomplete rxns LT 20% product)
  - Remote functionality at the 4 position has no effect
- Why doesn’t the TEMPO/Bleach oxidation work on our substrate?
  - Catalyst instability is not the likely cause since these catalysts perform well with other less hindered substrates
  - Even rxns with high catalyst loadings failed (0.5eq)
- Hypothesis: TEMPO-catalysts are too sterically hindered to react with the bulky alcohol
- Hypothesis Testing: Use a less sterically crowded nitroxyl radical catalyst (if one exists)
  - Tetramethylpiperidine functionality is essential for the stability of the nitroxyl radical, and thus the active catalyst, since there are no α-H for abstraction, but it imparts significant steric bulk

Tetramethylpiperidine (Tempo) type catalysts will not work

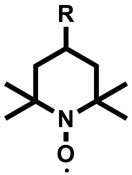
Nitroxyl Radical Catalysts (AZADO)



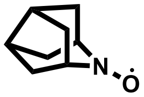
AZADO



1-Me-AZADO

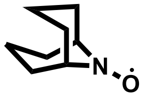


TEMPO



Nor-AZADO

not commercially available

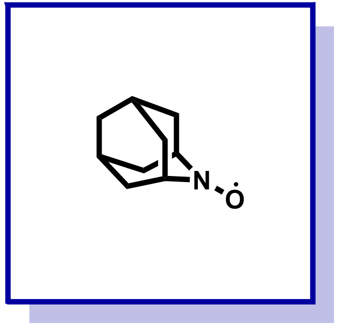


ABNO

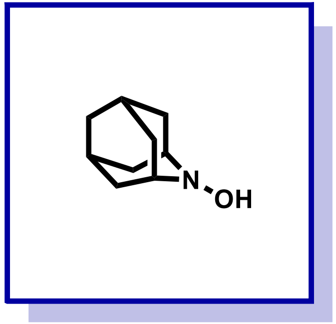
not commercially available

- A structure-based literature search identified several obscure nitroxyl radical catalysts
- AZADO (2-azaadamantane-*N*-oxyl) originally synthesized in 1975 for ESR spectroscopy exps
- AZADO was 1st reported in the literature in 2006 as an oxidation catalyst
- Only ADADO and 1-Me-AZADO, were commercially available (mg quantities from Aldrich)

Highly Active Catalyst AZADOL®



AZADO

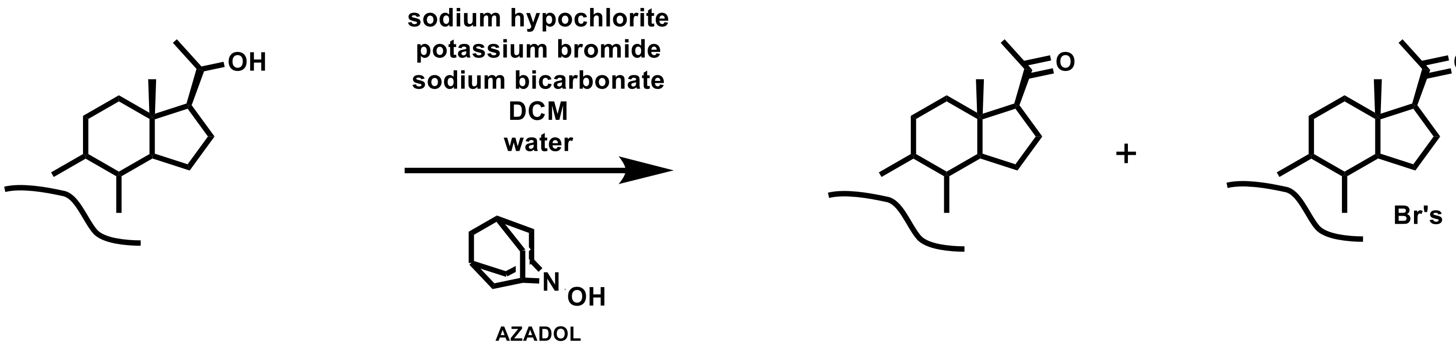


AZADOL

- Found these two compound were currently available
    - Only from Nissan Chemical Industries, Ltd. (Japan) – initially limited quantities
- No cmp patents, but two process patents for the preparation of AZADOL® (2-Azaadamantan-2-ol)
- AZADOL® is a more stable catalyst for storage and has the same catalytic activity as AZADO
    - AZADOL® is a white crystalline solid that is stable at room temperature
    - AZADO is a bright red crystal that requires freezer storage
- AZADOL® costs $35,000-45,000/Kg

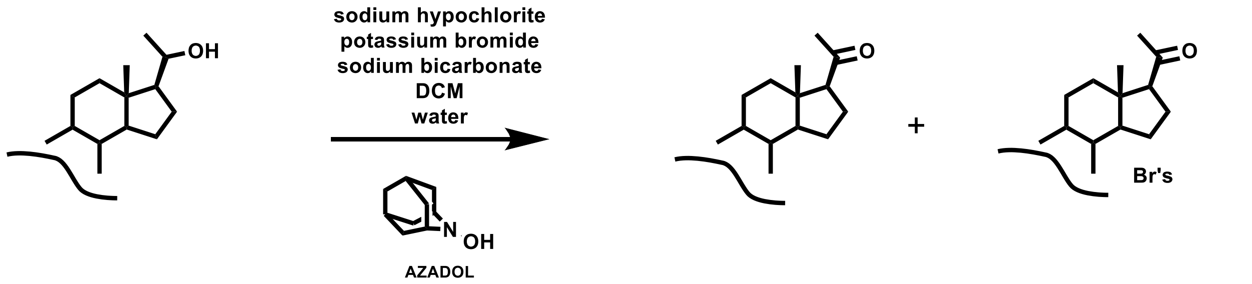
Very expensive

AZADOL® Oxidation Process



- AZADOL® worked astonishingly well in the first laboratory use-test! It was far superior to all TEMPO derivatives!
    - Reactions went to completion (99% conversion of starting material)
    - Reactions were relatively clean with the exception of brominated impurities (1-9 area%)
- Successful lab demonstration of the proof of concept (POC) of this new technology

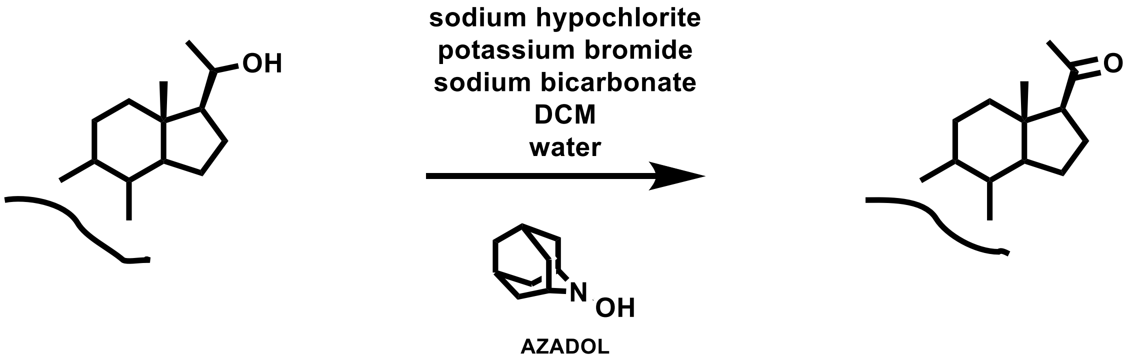
AZADOL® Oxidation Process



- Process optimized through Design of Experiments (DOE)
  - Minimized total imps. (reduced from 1-9% to LT 0.3 area%)
  - Maximized reaction concentration– increase throughput for lower COGs
  - Optimized reaction temperature
  - Amounts of reagents (KBr, $NaHCO_3$and NaOCl)
  - Minimized AZADOL® loading
- Nissan had not produced significant quantities AZADOL®

Highly efficient

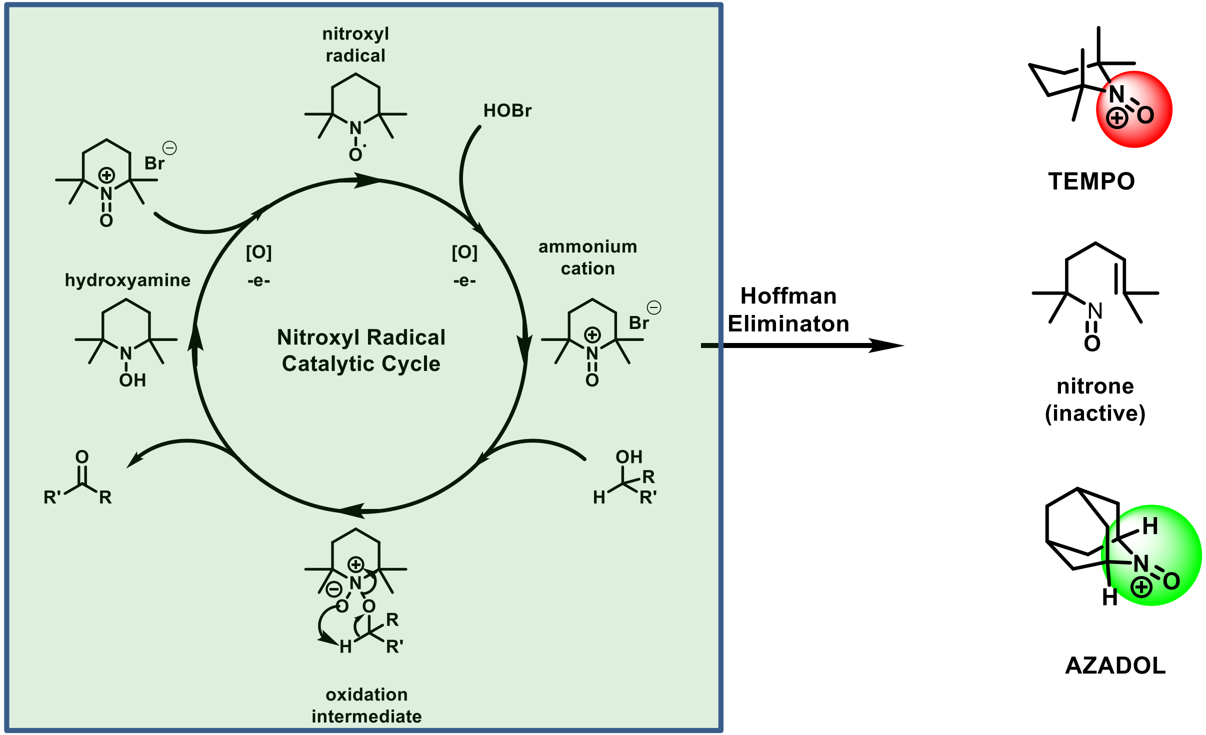
AZADOL®Oxidation Process



- Demonstration in Pilot Plant in July 2013
  - Ran 6 successful batches (high conversion, yields and purity)
  - 45 – 90 Kg
- 1st large-scale application of this new technology!
- The success of the campaign established the foundation for this oxidation technology platform

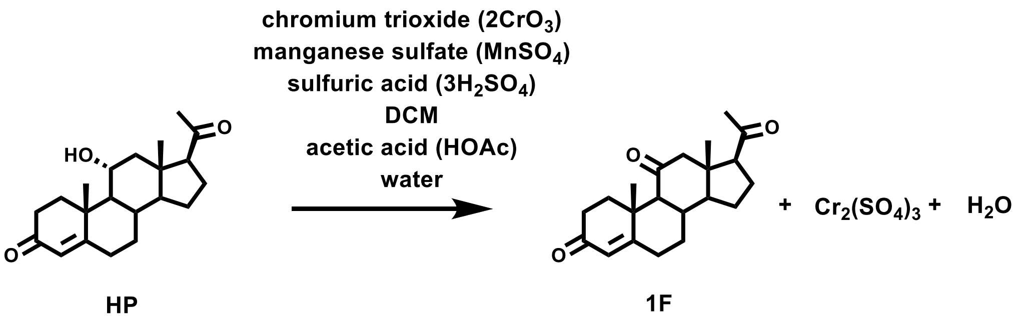
API produced that meets all specifications

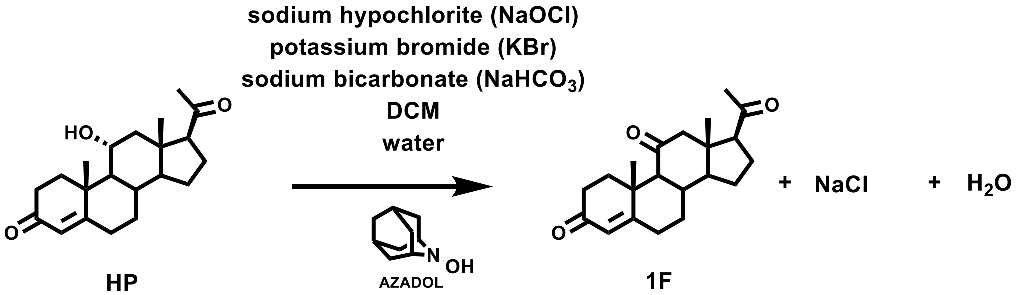
Catalytic Cycle



- Steric hindrance about ammonium cation precludes rxn with bulky 2º alcohols
- The cage-like structure of AZADOL® is more stable and less likely to eliminate (cannot become anti-periplanar because of rigid ring structure) than TEMPO derivatives resulting in high turnover numbers

1F/2F Process

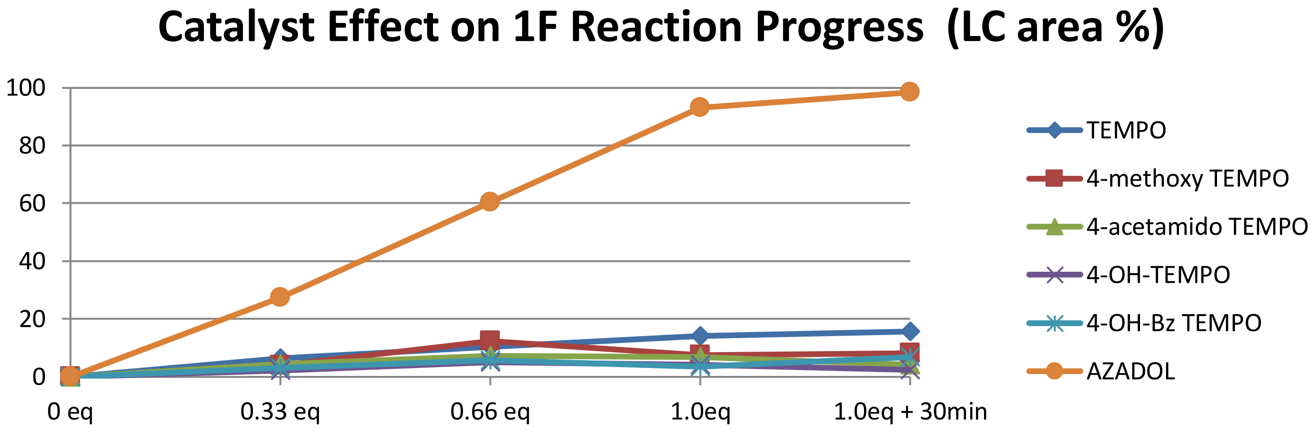




- Can AZADOL/TEMPO chemistry replace the CrO_3 used in the current 1F step?

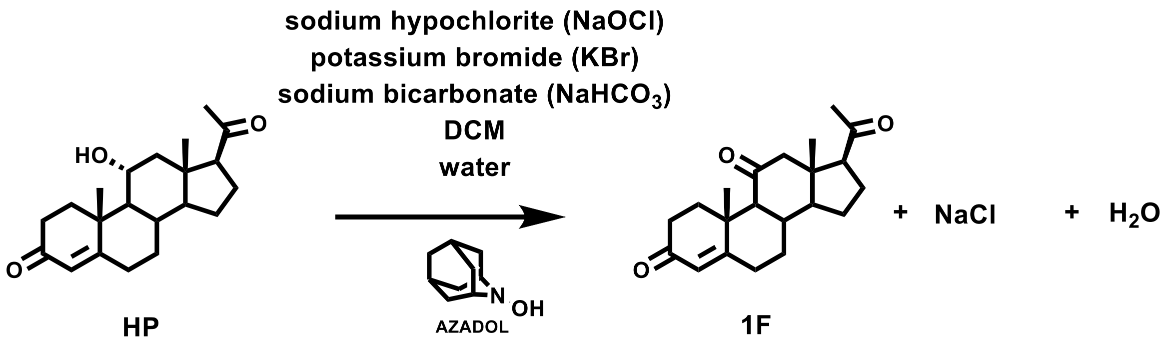
53 grams/460 kg of HP

Catalytic Efficiency



- AZADOL is the only competent catalyst
- All TEMPO derivatives perform very poorly (LT 20% conversion) despite 30X loading
- Catalyst loading: AZADOL® 0.03 mole% vs. TEMPO (derivatives) 1.0 mole%

1F/2F Process



- We developed a new 1F process (1FA) to oxidize HP to 1F in the lab (DOE)
- We successfully demonstrated this process (2FA) in a three lot PT
  - 2F Process is a telescoped process
- No impurities were present above historical (mean + 3SD)
- No new impurities were detected by LC at or above 0.10%
- Potencies were equivalent to historical 2F
- 2FA Yields were comparable or higher than historical (81-82%wt)
- Process cycle times were comparable or faster than typical (18hrs)
- 10's of grams of AZADOL® ($2100) was used to catalyze the oxidation of 100's of Kg of HP!

10's of grams of AZADOL catalyzes the oxidation of 100's of Kg of HP!

New 2FA Process

Environment	➢ Eliminates use 52MT/yr of CrO_3 solution or 21MT/yr of CrO_3 solids ➢ Eliminates 1,000,000 L /yr of waste disposal (5700L/lot) ❖ This would fill 8 DOT tanker cars/yr or 1 Olympic-sized swimming pool every 2.5yrs ➢ 80% reduction in chromium usage and waste disposal
Health	➢ Eliminates potential operator exposure to CrO_3 which is a known human carcinogen
Safety	➢ Eliminates the potential for fires/explosions (CrO_3 is a strong oxidizer and possible ignition source of organic compounds!) ➢ Eliminates CrO_3 drum handling (~180 drums/yr)
Cost of Goods	➢ Small ~2% yield increase ➢ Slightly lower COGs
Implementation	➢ Commercial batches since 2015 ➢ Other potential CrO_3 oxidations (1DEB, 2PE) that may be potential candidates for AZADOL® oxidations

Remove the use of 52 MT of Chromium trioxide each year

Acknowledgements

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Rod Mason
B91 Operators

B149 API Production
David Stagray
B149 Operators

EHS
Adam Muir

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Thank you


EXIT
Greener Chemistry via the Application of
Novel Oxidation Technology
PGS-Kalamazoo


EXIT