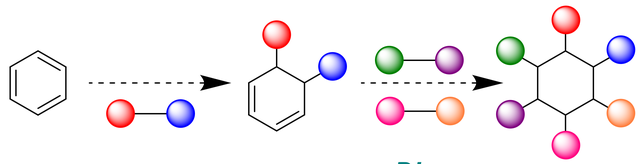
Harnessing the Dearomatization of *O*-Aryl Hydroxylamines to Synthesize Highly Functionalized Cyclic Molecules

Michael C. Eng, Robert E. Wiley, Prof. Jeffrey S. Johnson
Department of Chemistry, University of North Carolina at Chapel Hill

Background

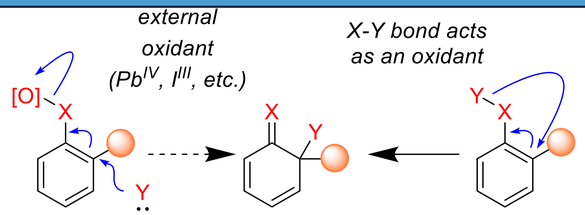
- Small organic molecules play a pivotal role in modern life
  - Defined as carbon-containing molecules under 1,000 Daltons
  - Frequently bioactive (binding ability to biomacromolecules)
  - Ubiquitous in pharmaceuticals, agrochemicals, and other fine chemicals[1]
- Increasing molecular complexity correlates with improved bioactivity
  - Increased saturation in a molecule helps improve bioactivity[2]
    - Density of sp^3 atoms in the molecule
    - More saturated molecules are more 3D (*i.e.* less planar)
  - Molecules containing rings are also more bioactive[3]
    - More defined shape because of their conformational lock



- Dearomatization is a powerful strategy for the synthesis of these highly desirable saturated, cyclic molecules

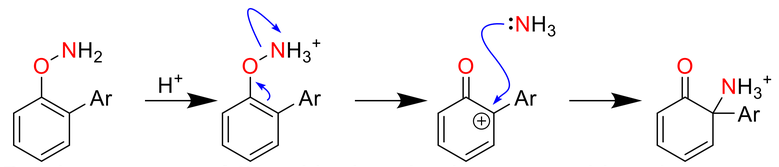
(1) *Med. Drug Discov.* **2021**, *9*, 100075 (2) *J. Med. Chem.* **2009**, *52* (21), 6752–6756 (3) *Chem. Biol. Drug Des.* **2014**, *83* (4), 450–46

Introduction



Weak Bond Cleavage Can Drive Dearomatizations

- Dearomatization requires a driving, exergonic reaction[4,5]
  - Oxidation is a popular way of generating this driving force
  - External oxidants (*i.e.*, hypervalent iodine or lead reagents) can be toxic, generating dangerous byproducts
  - Internal oxidants can avoid such drawbacks
    - Weak bonds between two heteroatoms can be broken in exchange for stronger bonds
    - Typically use a promoter to initiate the reaction



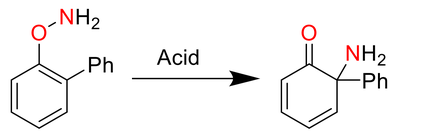
- Previous reports of O-aryl hydroxylamines use acid as the promoter[6,7]
  - Heterolysis forms an intimate ion-molecule pair
  - Ammonia adds back into the arenium ion at the *ortho* position
  - Substitution blocks tautomerization, preventing rearomatization

(4) *Angew. Chem. Int. Ed.* **2011**, *50* (18), 4068–4093 (5) *J. Am. Chem. Soc.* **2011**, *133* (16), 6449–6457
(6) *Tetrahedron Lett.* **1992**, *33* (23), 3339–3342. (7) *J. Am. Chem. Soc.* **1992**, *114* (25), 9795–9806

Results and Discussion

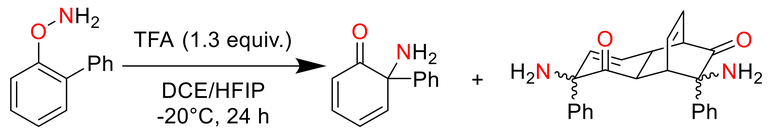
- Began with broad condition screening of the dearomative rearrangement to search for milder conditions
  - Initial reports require 10 equiv of trifluoroacetic acid (TFA)

Solvent	Yield
DCM	46%
$CHCl_3$	32%
THF	21%
MeOH	0%



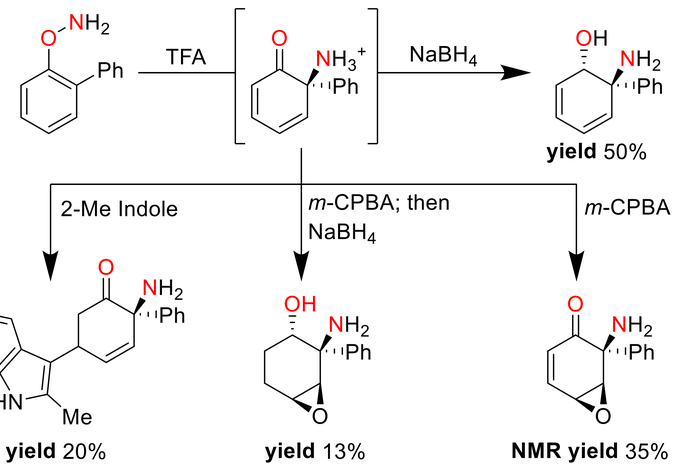
Acid (Equiv.)	Yield
TFA (1)	0%
TFA (5)	50%
TsOH (5)	0%
AcOH (5)	0%
BF_3 (5)	16%

- Initial optimization studies showed the limitations of the reaction
  - Chlorinated solvents performed best
  - Excess strong Bronsted acid was required



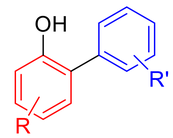
47% (also as Diels Alder adduct)

- TFA equiv could be decreased if a mixture of dichloroethane (DCE) and hexafluoroisopropanol (HFIP) was used as the solvent
  - HFIP is highly polar and can stabilize cationic intermediates
- Decreasing temperature lowered the reaction rate but improved selectivity
  - Even under optimized conditions, yields never exceeded ~50%
  - Several aromatic side products are observed

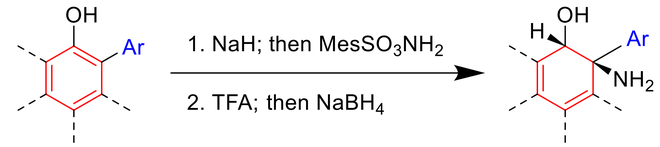


- With a promising dearomative transformation in hand, *in situ* transformations were explored for rapid complexity generation
- Instead of immediately working up the rearrangement, more reactions could be telescoped together
  - The amine acts as a directing group, promoting syn reductions and oxidations to produce diastereopure products (>20:1 dr)

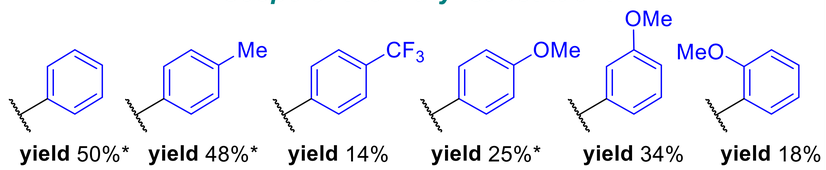
Phenol core can be diversified through electrophilic aromatic substitution

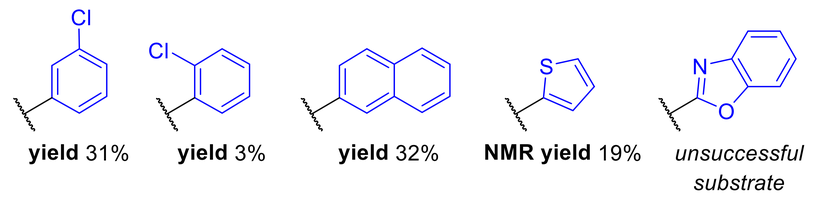


Aryl substituent can be diversified through cross coupling reactions

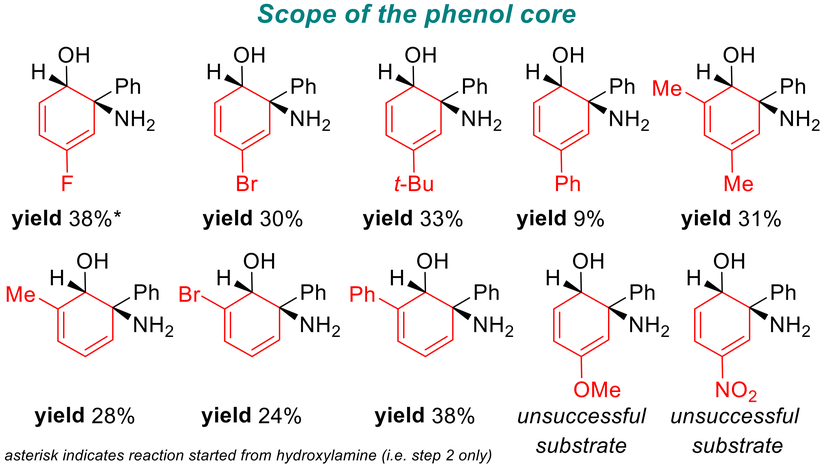


Scope of the 2-aryl substituent





Scope of the phenol core



asterisk indicates reaction started from hydroxylamine (i.e. step 2 only)

- Scope of the rearrangement with the reductive quench was established
  - Electron neutral substituents generally performed best
  - *Ortho* substitution on the 2-aryl decreased performance
  - Basic functionality completely prevents rearrangement

Conclusions and Future Directions

- An oxidative dearomatization was achieved by cleaving a weak, internal O-N bond
- *In situ* functionalizations of the cyclohexadienone core enable efficient access to several structurally interesting products
- Future Directions:
  - Continuing to expand the substrate scope
  - Studying additional synthetic applications of the products
  - Researching new weak bond promoted rearrangements