Methods for Dearomatization

Any hydrocarbon or heterocycle with \(4n+2\) electrons in a fully conjugated cyclic \(\pi\) system is considered aromatic.

General characteristics of aromatic compounds:
- chemical behavior (electrophilic substitution vs addition, resistance to oxidation)
- structural characteristics (bond length equalization)
- energetic profile (resonance energy)
- magnetic properties (ring current effects-downfield shifts of peripheral protons)  

Why are aromatic compounds desirable building blocks?
- ubiquitous
- very stable (many are crystalline)
- easy to functionalize
- aromaticity can be view as masked functionality

Available methods for "controlled" dearomatization:
- Enzymatic
- Photochemical / Thermal (concerted)
- Radical
- Transition-metal mediated
- Nucleophilic
- Oxydative (polyvalent iodine mediated)
- Reductive (Birch reduction/reductive alkylation; cat hydrogenation)

Dearomatization under enzymatic conditions

Available methods for direct epoxidation of polycyclic aromatics:
- mCPBA  \textit{Angew. Chem. Int. Ed.}, 1977, 16, 171
- Mn(TDCCP)Cl, \(\text{H}_2\text{O}_2\)  \textit{Chem. Commun.}, 2004, 608
- NaOCl, \(\text{Na}_2\text{HPO}_4\)  \textit{J. Am. Chem. Soc.}, 1984, 106, 2463

The carcinogenicity of polyaromatic compounds might be due to reactive intermediates generated upon dearomatization. For polyaromatic hydrocarbons, oxidation occurs primarily in the K-region.

Among the oxidized products, epoxide-diols are particularly prone to nucleophilic ring-opening by DNA.

\textit{Acc. Chem. Res.}, 1981, 14, 218

\textit{Tet. Lett.}, 1990, 31, 6097
Methods for Dearomatization

Florina Voica

Baran lab GM
11/6/2010

O

CO₂Bu

HN

S

S

R = C₆H₄OMe-p

R = C₆H₄OBn

R = C₆H₄Cl

Triton-B

PhLi, THF

DMSO

+ 22% epimer

+ 22% epimer

45%


(5 steps from benzoic acid)

(3 steps from benzoic acid)

For an extensive list of substrates and applications in total synthesis (conduritols, inositols, carbohydrates, prostaglandins, some alkaloids) see Aldrichimica Acta, 1999, 32, 35; Synlett, 2009, 685

For more on biocatalysis, see Baran Lab GM Biocatalysis, Gulder, 2009

For an extensive review on cyclohexane epoxide natural products Chem. Rev., 2004, 104, 2857

Also, see Baran Lab GM Shikimic Acid, Ambhaikar, 2005.
Methods for Dearomatization

Dearomatization of benzenoids is certainly possible, although not as yet competitive with the biological process in terms of selectivity and efficiency. We hope that present and future generations of organic chemists are stimulated by the magnitude of this challenge and eventually succeed in the development of catalytic process that would rival the enzymatic transformation and allow for this reaction to be removed from the list of unsolved problems in organic chemistry.

Tomas Hudlicky, Synlett 2009, 685
Methods for Dearomatization

Photochemical methods

"The aromatic nucleus, known for its rigidity in the ground state, becomes an extremely flexible and extrovert acrobat when being doped with a light quantum"

[2+2] cycloadditions


[4+2]


[4+4]

J. Org. Chem. 1981, 46, 2405

Tetrahedron 1985, 41, 2405


Chem. Commun. 1979, 1038

For more examples of [2+2] with arenes:
J. Org. Chem. 1981, 46, 2405
Tetrahedron 1985, 41, 2405
"The problems originally posed by many synthetic targets have now been solved at a practical level. However, for the majority of synthetic problems, solutions either do not exist or are far from being practical. In general, few solutions approach the ideal, wherein a target is prepared from readily-available starting materials in one step that proceeds in 100% yield and is operationally safe, simple and ecologically acceptable. Obviously, this is a rather demanding but no unrealistic objective. While it is unlikely to be commonly achieved, efforts to reach this standard of sophistication are of great importance as they are likely to lead to the fundamentally new science that will clearly have a profound impact on the ways in which total synthesis will be done in the future."

Paul Wender, Pure & Appl. Chem. 1990, 62, 1597

[2+3] meta-photocycloaddition

Generalities:
- the nature of the reactive intermediates is not yet decided (biradical vs zwitterion)
- depending on the electronic nature of the arene substituents, the reaction is regioselective
- RDS - bonding between the arene and the alkene
- reaction proceeds via a concerted mechanism (alkene stereochemistry preserved)
- reaction can be performed neat or in an inert solvent
- it is temperature independent
- for intermolecular reaction, an excess of the arene is required

Chem. Rev. 1993, 93, 615

For a review of applications in total synthesis see Pure & Appl. Chem. 1990, 62, 1597

For a recent application in an asymmetric synthesis see J. Am. Chem. Soc. 2009, 131, 452

Org. Lett. 2008, 10, 1223
Methods for Dearomatization

Thermal cycloaddition

Radical methods for dearomatization

J. Am. Chem. Soc. 1968, 90, 215

Tetrahedron 2006, 62, 6830


Chem. Commun. 2002, 316

**Methods for Dearomatization**

**Pd-catalyzed dearomatization reactions**

- **J. Am. Chem. Soc. 2001, 123, 759**
  
  ![Reaction Scheme](image1)

- **Angew. Chem. Int. Ed. 2008, 47, 4366**
  
  ![Reaction Scheme](image2)

- **Tetrahedron 2010, 66, 6013**
  
  ![Reaction Scheme](image3)

- **J. Am. Chem. Soc. 2009, 131, 6676**
  
  ![Reaction Scheme](image4)

**Transition-metal mediated dearomatization methods**

- **Inorg. Synth. 1990, 28, 136**
  
  ![Cr(CO)₆](image5)

- **J. Org. Chem. 1992, 57, 6487**
  
  ![Cr(CO)₃L₃](image6)

- **J. Organomet. Chem. 1985, 286, 183**
  
  ![Cr(CO)₃L₃](image7)

**Reactivity of nucleophiles toward (PhH)Cr(CO)₃ in THF**

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>Reaction</th>
<th>Metalation</th>
</tr>
</thead>
<tbody>
<tr>
<td>LiCH₂CO₂R₂</td>
<td>successful</td>
<td>nBuLi</td>
</tr>
<tr>
<td>LiCH₂CN</td>
<td>successful</td>
<td>LiMe</td>
</tr>
<tr>
<td>KCH₂CO₂Bu</td>
<td>successful</td>
<td>sBuLi</td>
</tr>
<tr>
<td>LiCH₂(OR)</td>
<td>unreactive</td>
<td></td>
</tr>
<tr>
<td>LiCH₂CN</td>
<td>unreactive</td>
<td></td>
</tr>
<tr>
<td>LiCH₂SPh</td>
<td>unreactive</td>
<td></td>
</tr>
<tr>
<td>LiCH₂CH₂</td>
<td>unreactive</td>
<td></td>
</tr>
<tr>
<td>LiC=CR</td>
<td>unreactive</td>
<td></td>
</tr>
<tr>
<td>LiCH₂CH=CH₂</td>
<td>unreactive</td>
<td></td>
</tr>
</tbody>
</table>

**Regioselectivity of nucleophilic addition**

<table>
<thead>
<tr>
<th>R</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>OMe</td>
<td>meta</td>
</tr>
<tr>
<td>NMe₂</td>
<td>meta</td>
</tr>
<tr>
<td>Me, Et</td>
<td>meta/ortho</td>
</tr>
<tr>
<td>Cl</td>
<td>ortho/para</td>
</tr>
<tr>
<td>Hydrazonе</td>
<td>ortho</td>
</tr>
<tr>
<td>Imine</td>
<td>ortho</td>
</tr>
<tr>
<td>Oxazoline</td>
<td>ortho</td>
</tr>
<tr>
<td>SiMe₃</td>
<td>para</td>
</tr>
<tr>
<td>tBu</td>
<td>para</td>
</tr>
<tr>
<td>CF₃</td>
<td>para</td>
</tr>
</tbody>
</table>

**Chem. Rev. 2000, 100, 2917**
Methods for Dearomatization

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Baran lab GM
11/6/2010

NCy

Cr(CO)₃

MeLi then

MeI, CO, HMPA

THF

58% (2 steps)

NaH

Br

NHCy

Me

O

Me

Br

NaH

58% (2 steps)

O

Me

O


Me

O

J. Am. Chem. Soc. 2002, 125, 5642

Ph

Li,

THF,

-90 °C

then

TMS

Br

73%, >98% ee

Pure Appl. Chem. 1997, 69, 543

Cr(CO)₃

Me

OEt


R* = (-) menthyl

Mn(CO)₃⁺

(in situ from Mn(CO)₃Br and AgBF₄)

Synlett 1990, 565

Mn(CO)₃ClO₄

Mn(CO)₅(acetone)⁺


Mn(CO)₃Br, AlBr₃

(for arenes with sensitive functionality)

J. Am. Chem. Soc. 1957, 79, 5826

Mn(CO)₃ClO₄

Mn(CO)₅(acetone)⁺


Mn(CO)₃Br, AlBr₃

(for arenes with sensitive functionality)

J. Am. Chem. Soc. 1957, 79, 5826

Mn(CO)₃

LAH

H

H

O₂

88%

Cy

CN

Organometallics 1993, 12, 224

RuCp

CuBr₂

THF/H₂O, CO

55%

Angew. Chem Int. Ed. 2007, 46, 2887

Tetrahedron 2008, 64, 10123

For a review on organo-iron complexes see Tetrahedron 1983, 39, 4027
Methods for Dearomatization

- $\eta^2$-Os complexes are e-rich and prone to electrophilic substitution
- thermally stable complexes
- stable under inert atmosphere in solution
- decomplexation with Mg or Zn/Hg in DME or MeOH

$[\text{Os}^2+ (\text{NH}_3)_5] \rightarrow \text{C}_5 + [\text{Os}(\text{NH}_3)_2(OTf)](OTf)_2$ (1.5 - 20 eq) !!!

$\text{H}_2, \text{Pd/C}$ 89%

Other viable dienophiles:

$\text{Cu(OTf)}_2$ 2. Me$_3$N, aq Na$_2$CO$_3$

65% dr 1:1

1. Cu(OTf)$_2$
2. Me$_3$N, aq Na$_2$CO$_3$

65% dr 1:1

$\text{Tetrahedron, 2001, 57, 8203}$

$\text{J. Am. Chem. Soc. 1998, 120, 2218}$
Methods for Dearomatization

Nucleophilic methods for dearomatization

\[
\text{R'}^* \xrightarrow{\text{R'M}} \text{R'}^*
\]

\[\text{M} = \text{Li, Mg}\]

\[
\text{R}^* = \begin{array}{c}
\text{OR} \\
\text{NH}_2 \\
\text{X} \\
\text{NR} \\
\text{etc.}
\end{array}
\]

\text{Chem. Rev. 2007, 107, 1580}

\[\text{PhMgBr} \xrightarrow{\text{O}} \text{PhCPh}_3\]

\text{Ber. Dtsch. Chem. Ges. 1910, 43, 1145}

\text{J. Am. Chem. Soc. 1953, 75, 4604}

1,4-addition to aromatic ketones is favored in the case of hindered ketones or when a bulky LA is employed

\[\text{Mes} \xrightarrow{\text{O}} \text{Mes}\]

\text{J. Org. Chem. 1961, 26, 756}

\[\text{MeO} \xrightarrow{\text{Me}} \text{Me}\]

\text{J. Am. Chem. Soc. 1995, 117, 9091}

For the synthesis of isodomoic acid C by a similar strategy see \text{J. Am. Chem. Soc. 2005, 127, 2412}
Methods for Dearomatization

For an example of nucleophilic dearomatization of aryl phosphinamidines see J. Org. Chem. 2007, 72, 9704

Miscellaneous dearomatization methods

Angew. Chem. Int. Ed. 2003, 42, 2487

Org. Lett. 2009, 11, 3398