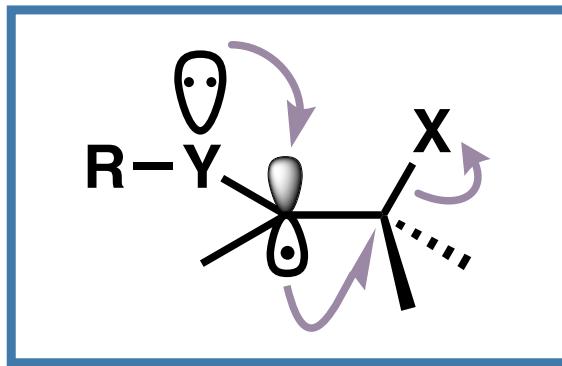


Spin-Center Shift: From Biology to Synthesis



Nicholas A. Falcone
Literature Group Meeting
June 16th, 2023

Reactions of Radical Intermediates

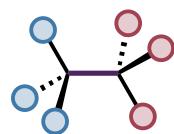


Reactions of Radical Intermediates

Destroying Radical Character

Preserving Radical Character

recombination

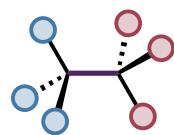


Reactions of Radical Intermediates

Destroying Radical Character

Preserving Radical Character

recombination



Additional examples:
disproportionations,
redox processes, etc.

Reactions of Radical Intermediates

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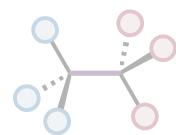
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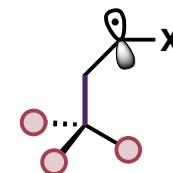
Destroying Radical Character

Preserving Radical Character

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addition



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Reactions of Radical Intermediates

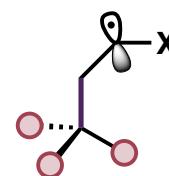
Destroying Radical Character

Preserving Radical Character

recombination



addition



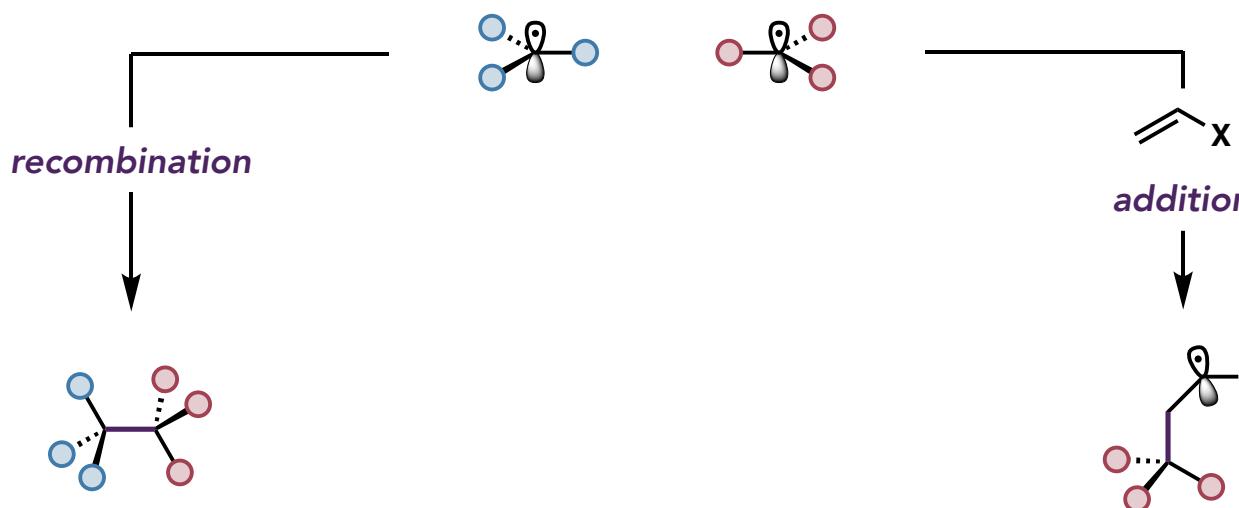
Additional examples:
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Additional examples:
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Reactions of Radical Intermediates

Destroying Radical Character

Preserving Radical Character



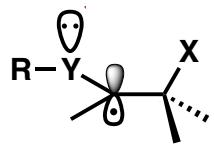
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Transition metals and metal cations can facilitate several of these processes

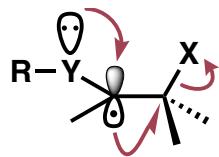
Spin-Center Shift (SCS)

Traditional SCS Processes



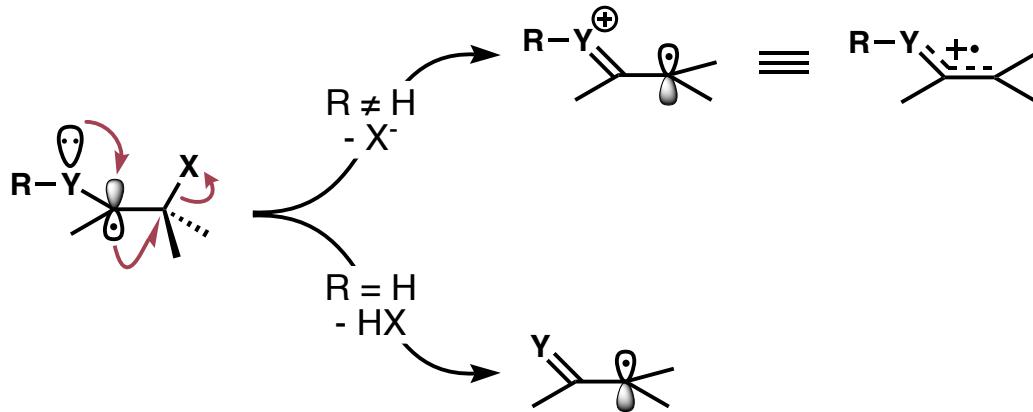
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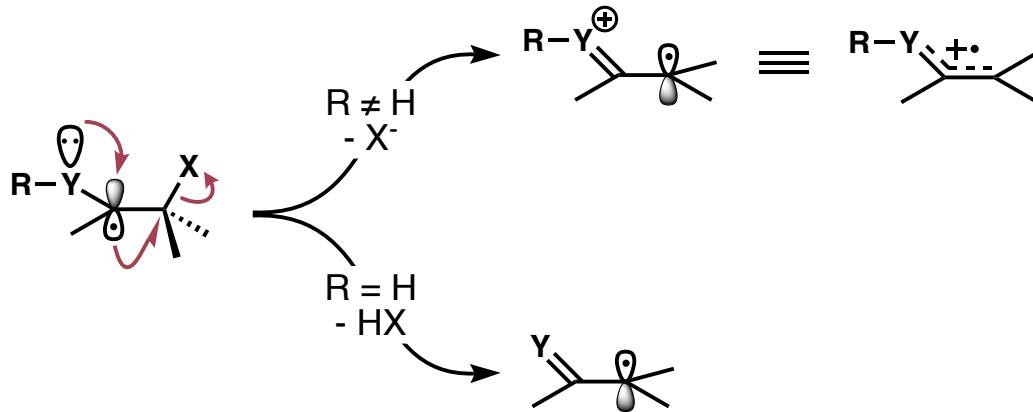
Traditional SCS Processes



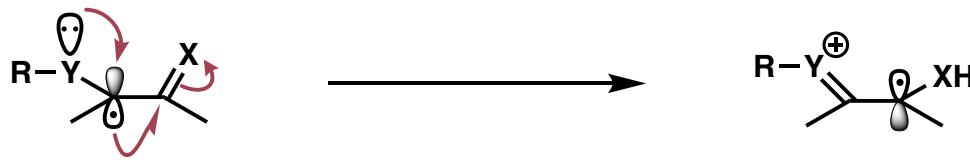
Extended SCS Processes

Spin-Center Shift (SCS)

Traditional SCS Processes



Extended SCS Processes



Spin-Center Shift (SCS)

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'radical-ionic fragmentations of C–O bonds'

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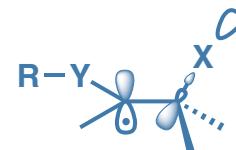
Crich, D. et al. In *Radicals in Synthesis I*, **2006**, 1–38.

'the 1,2-radical shift accompanied by the elimination of an adjacent leaving group'

Wessig, P.; Muehling, O. *Chem. Eur. J.* **2007**, 2219.

Spin-Center Shift (SCS)

adjacent electron-donating substituent/atom
stabilizes generated radical cation

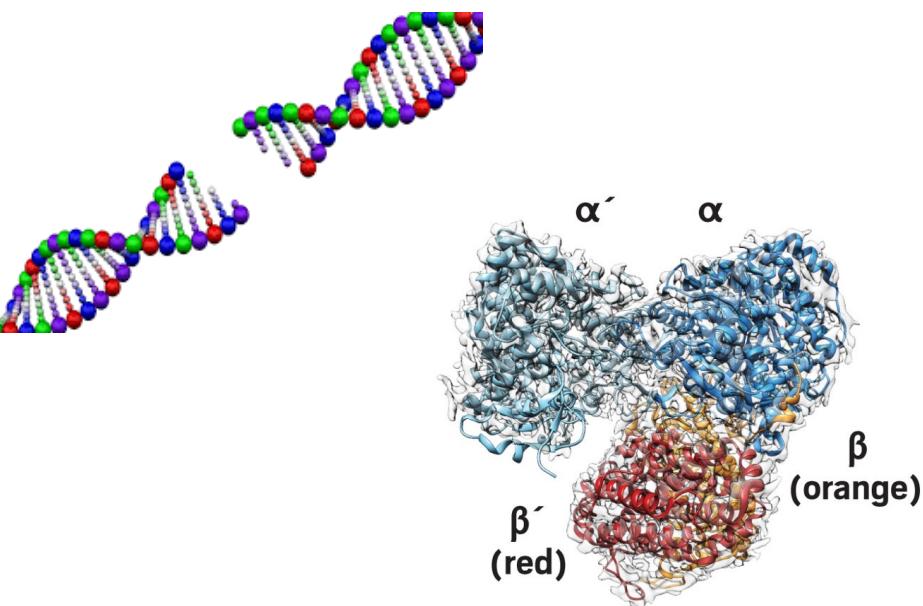


sufficient overlap between
SOMO & C-X σ^*

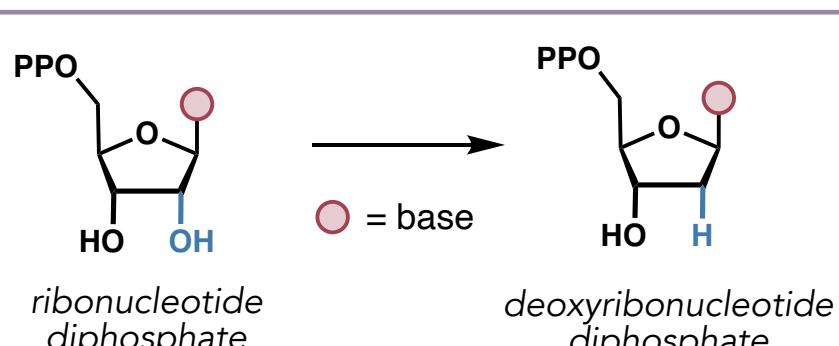
suitable leaving group or
additive to facilitate elimination

Spin-Center Shift (SCS)

Biochemical Processes

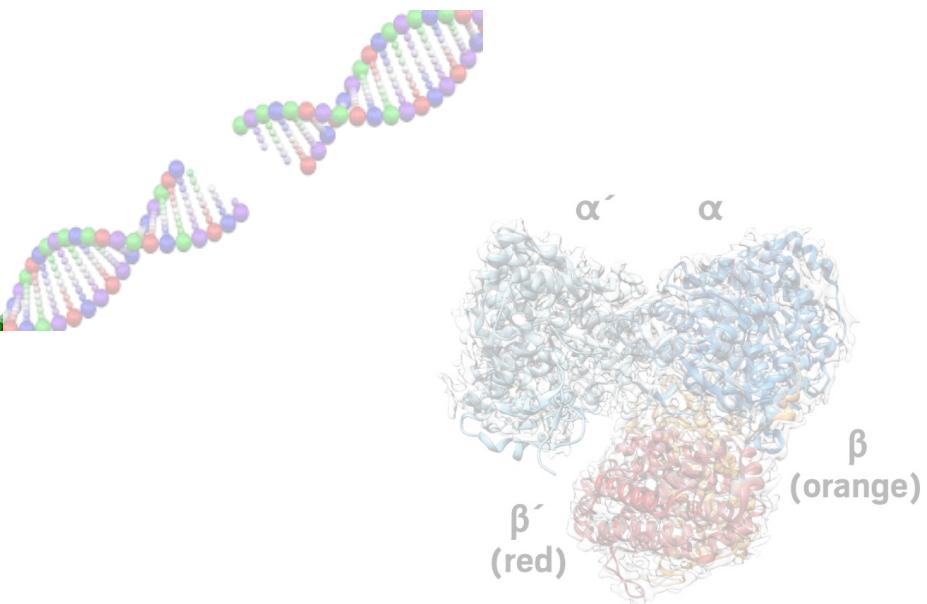


Synthetic Applications

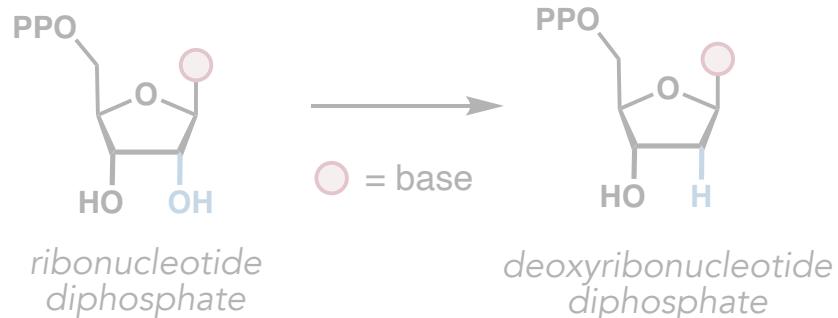
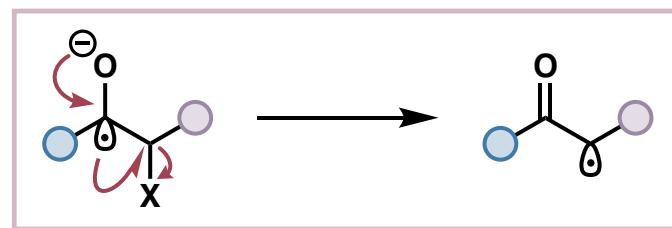


Spin-Center Shift (SCS)

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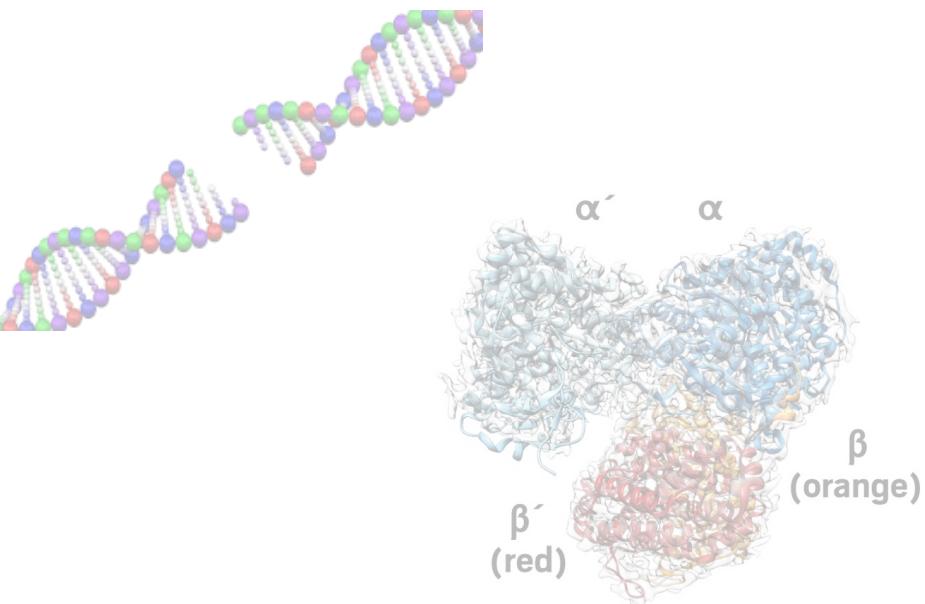


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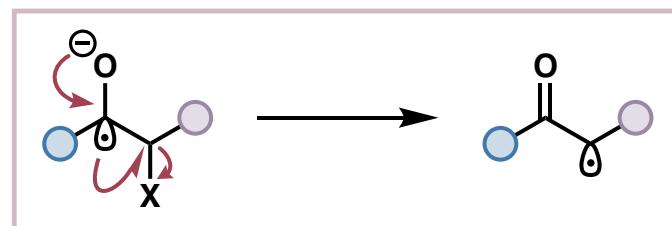


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Biochemical Processes



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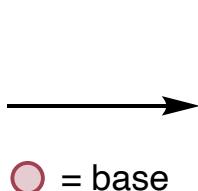
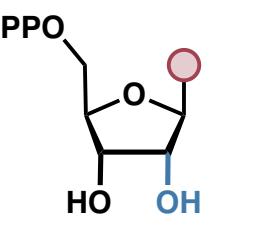
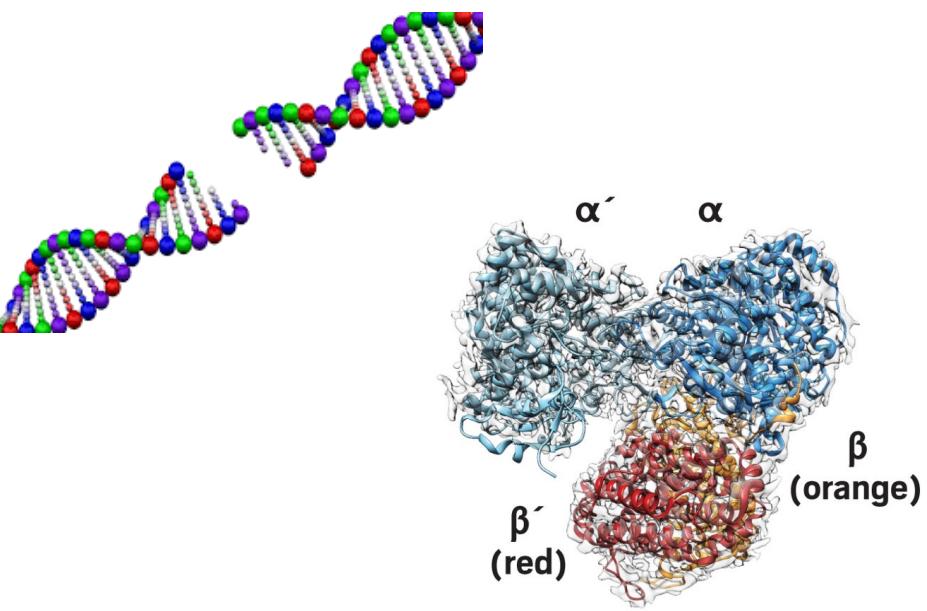


C-X bond
activation

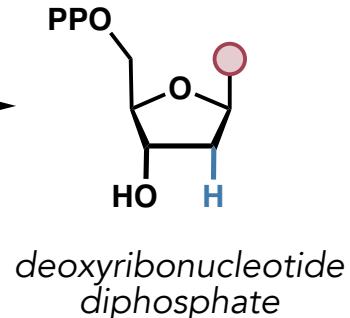


Spin-Center Shift (SCS)

Biochemical Processes



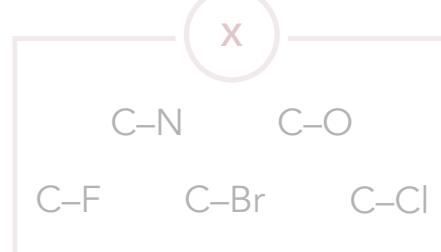
ribonucleotide diphosphate



Synthetic Applications

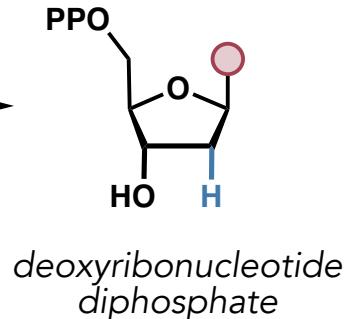
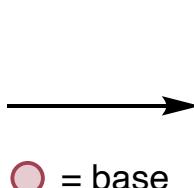
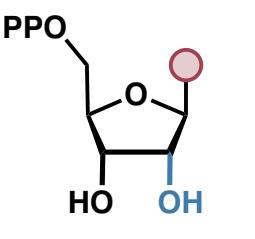
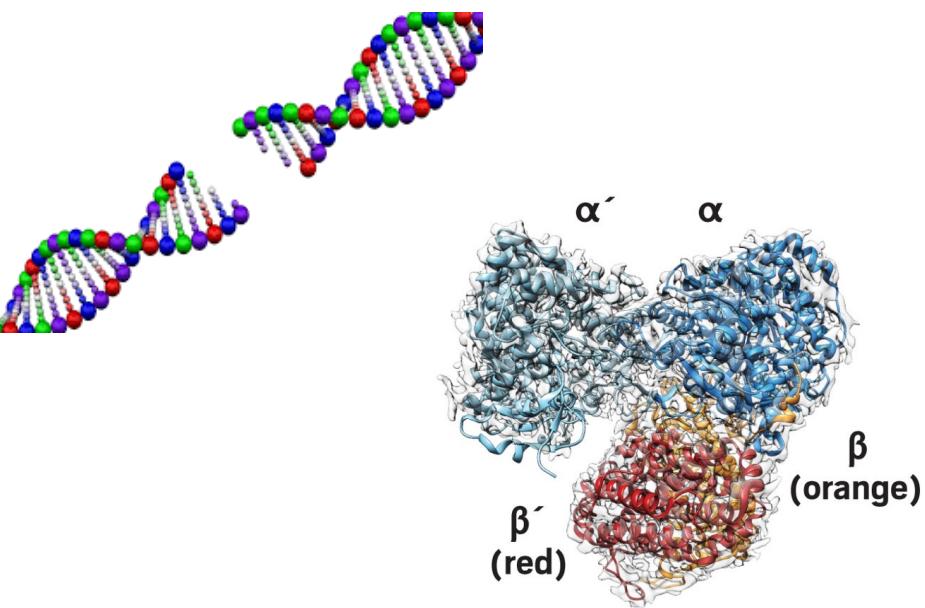


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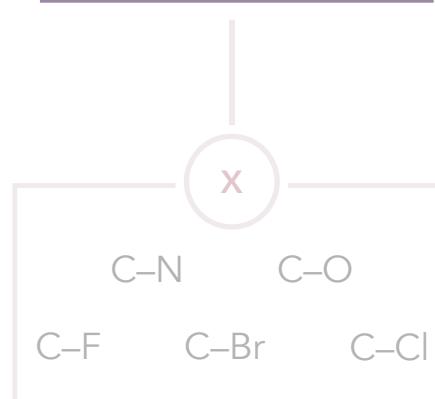
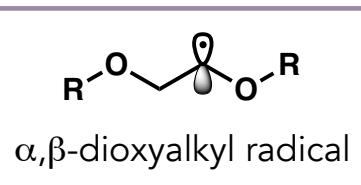
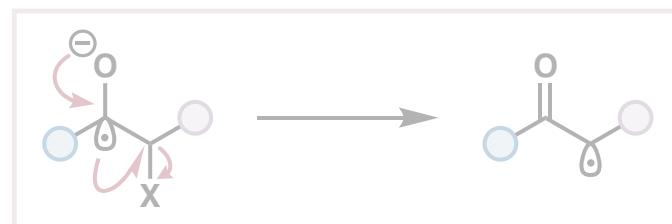


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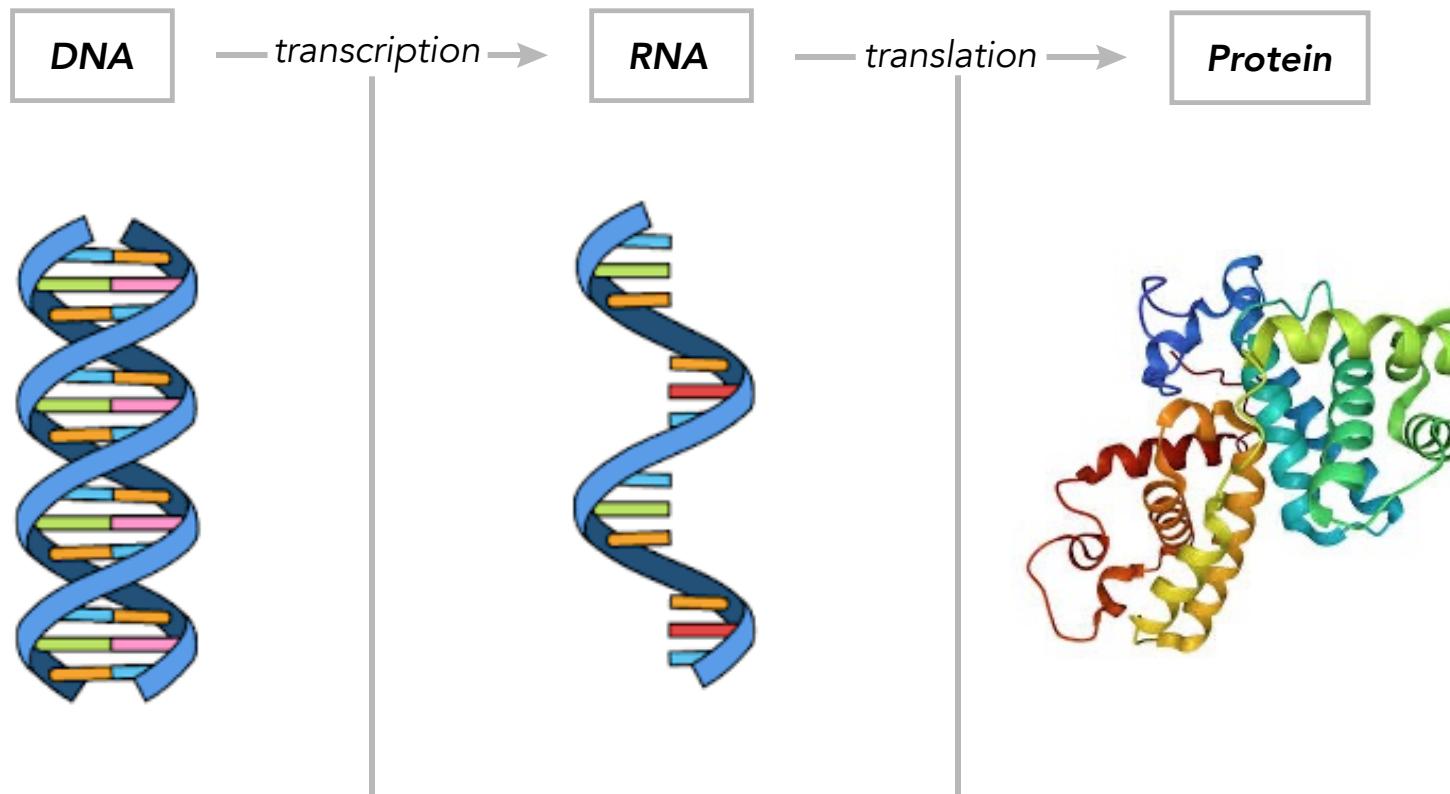
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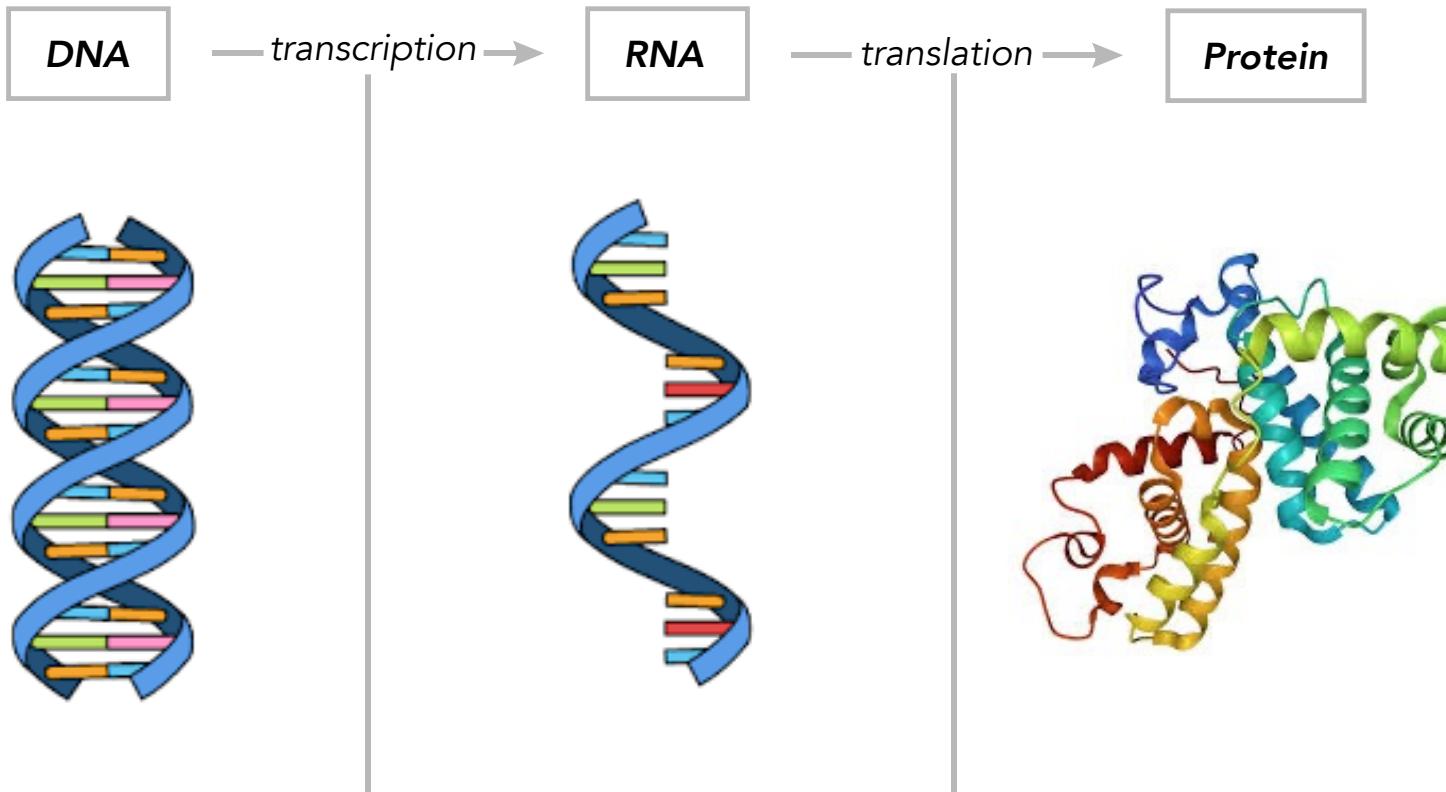
Synthetic Applications



DNA Structure Review

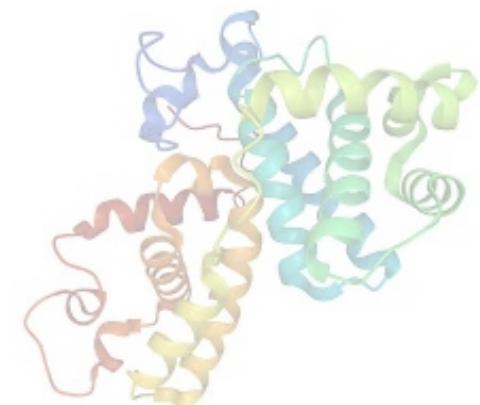


DNA Structure Review



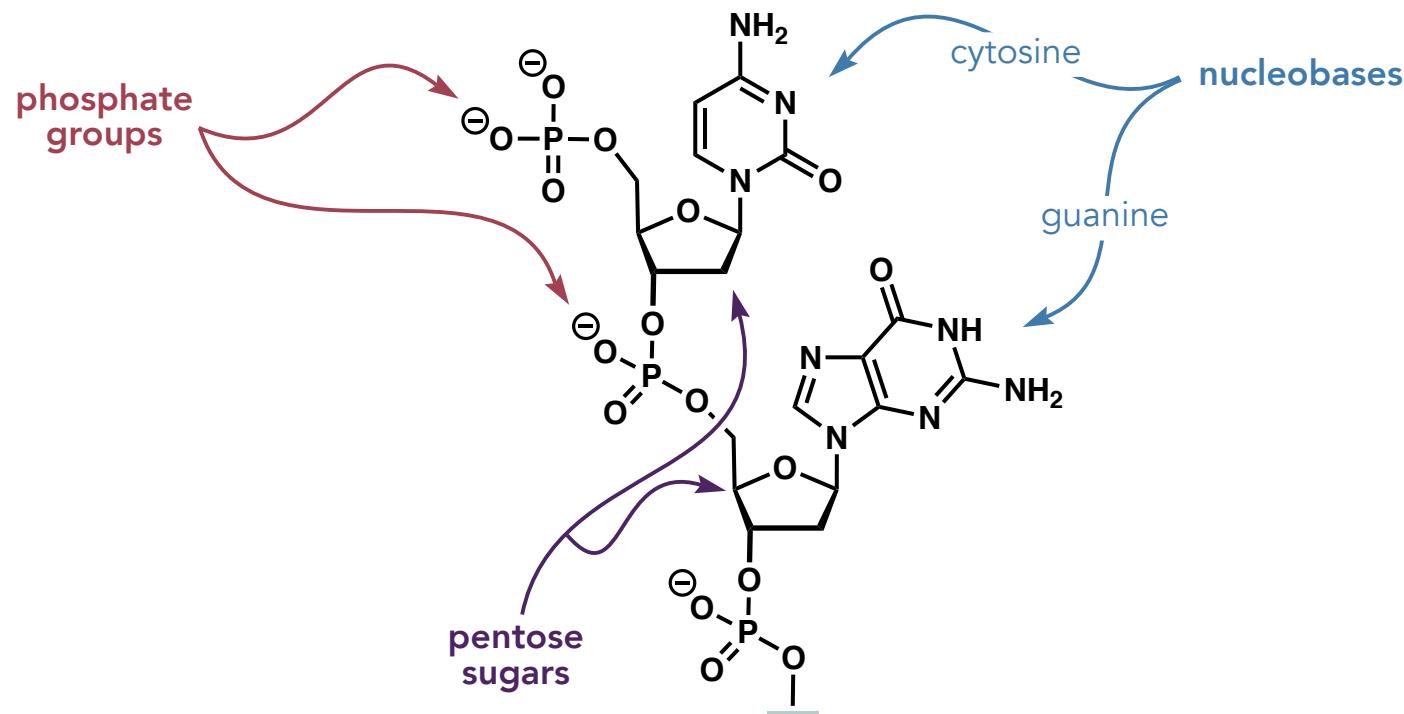
The central dogma of biology

DNA Structure Review



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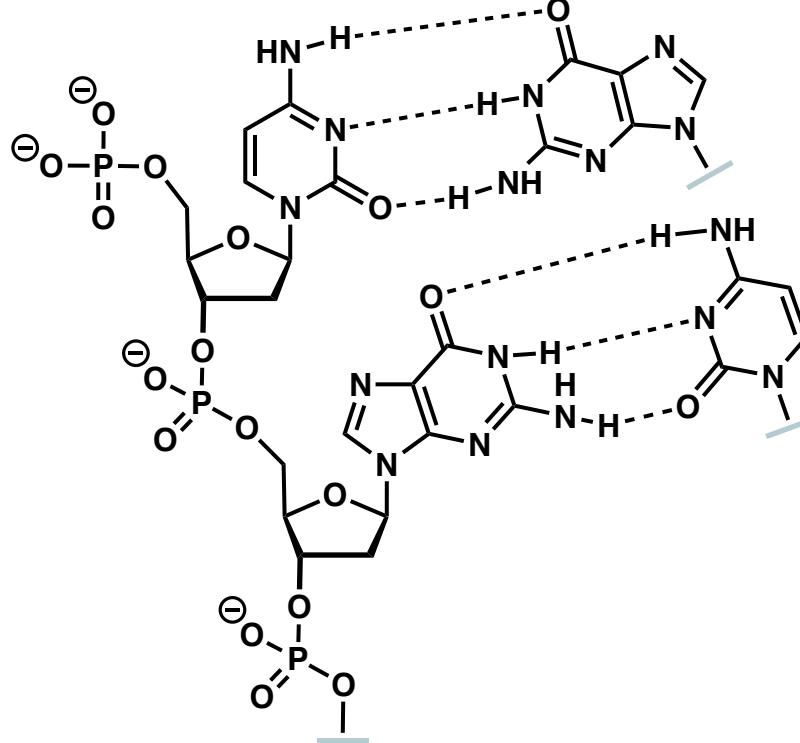


DNA Structure Review

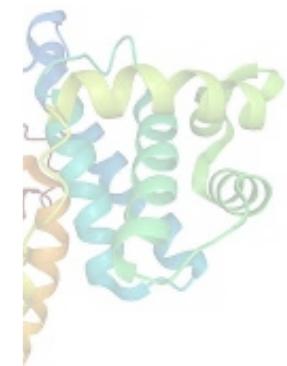
DNA



—transc

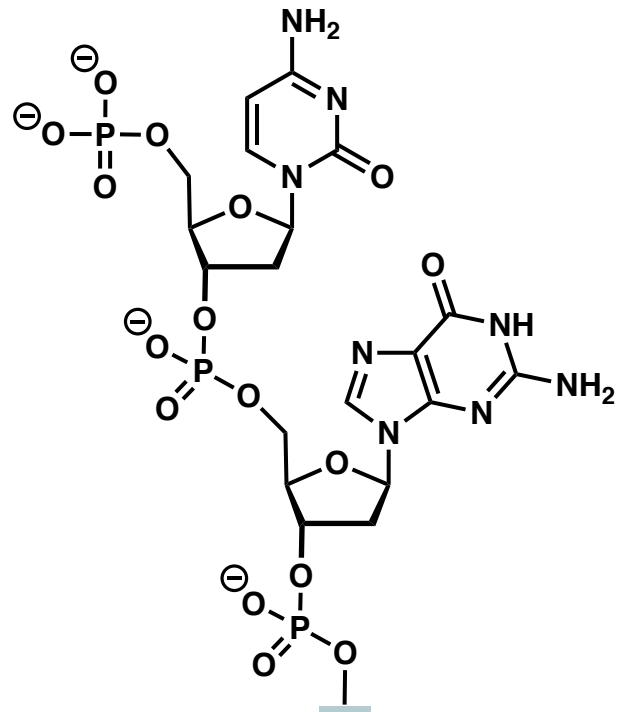


protein

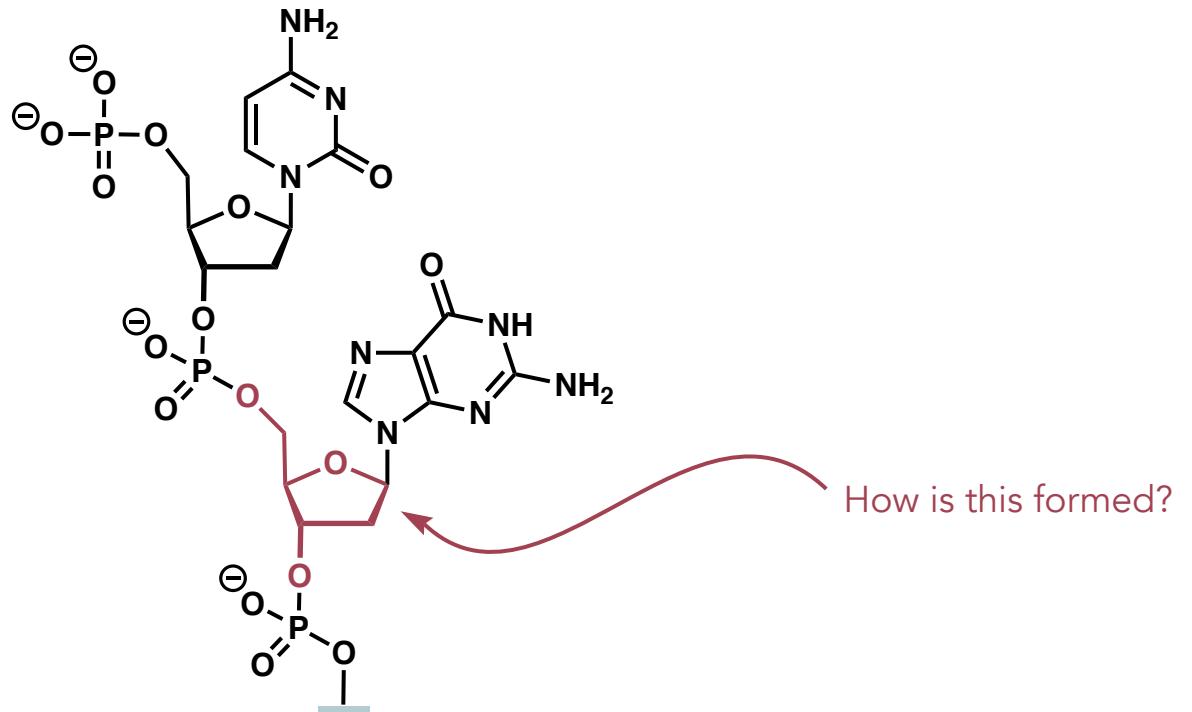


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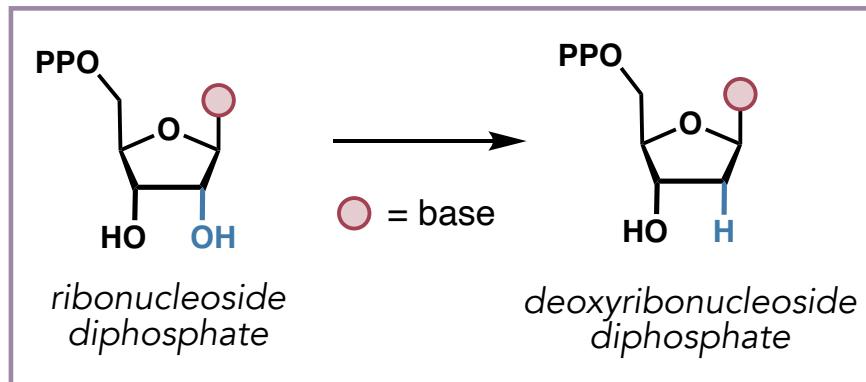
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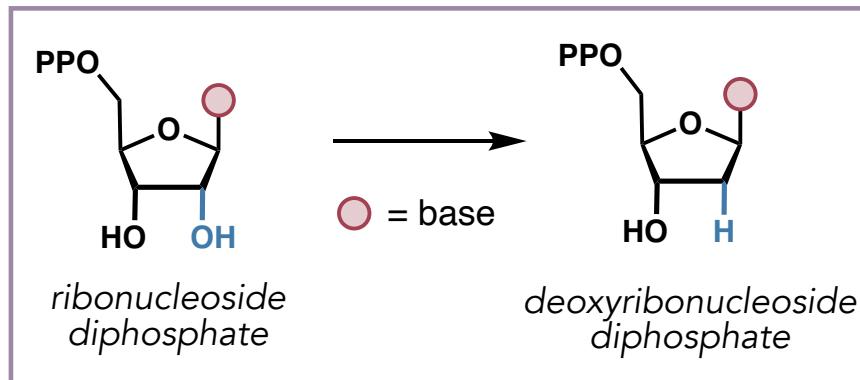
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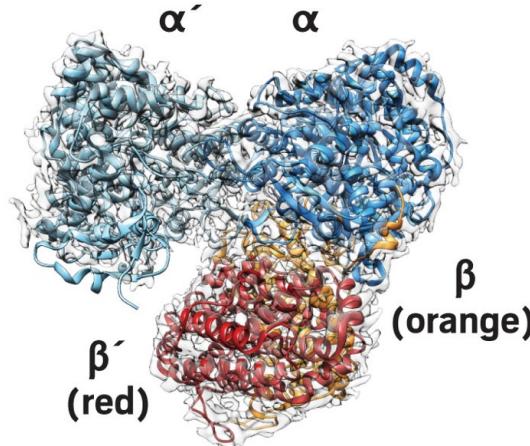
Synthesis of DNA: Deoxygenation of Ribonucleotides



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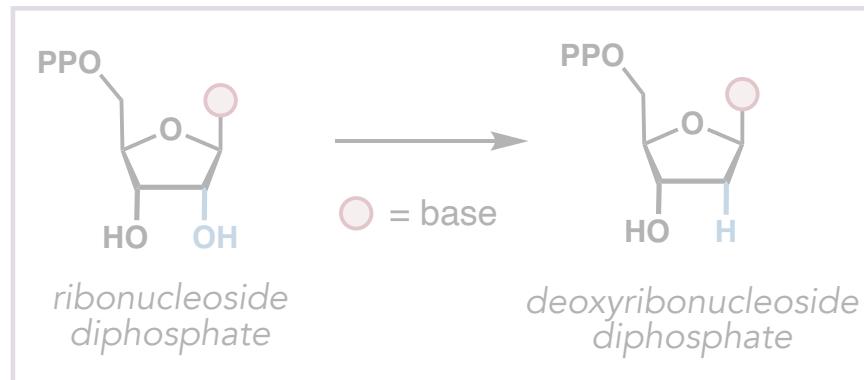
Dr. Peter Reichard
Karolinska Institute



ribonucleotide reductase (RNR)

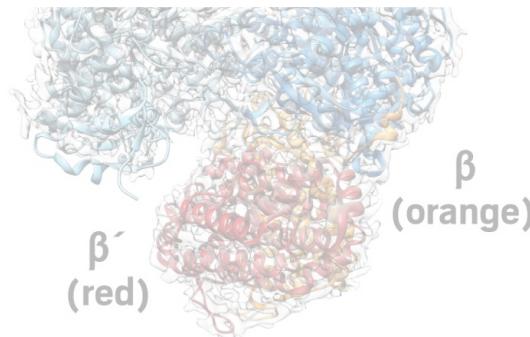
- Discovered in *E. coli*
- Catalyze the RLS in production of dNDPs

Synthesis of DNA: Deoxygenation of Ribonucleotides



Reviews on RNR:

Jordan, A.; Reichard, P. *Annu. Rev. Biochem.* **1998**, *67*, 71.
Eklund, H. et al. *Prog. Biophys. Mol. Biol.* **2001**, *77*, 177.



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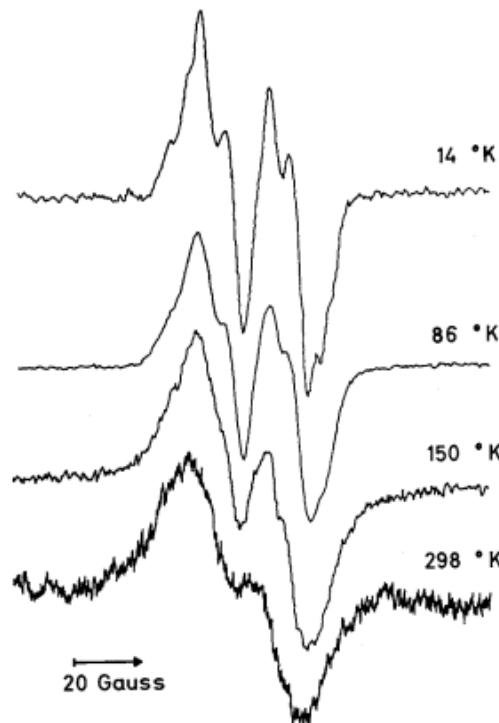
Synthesis of DNA: Deoxygenation of Ribonucleotides

Electron Spin Resonance of the Iron-containing Protein B2 from Ribonucleotide Reductase*

(Received for publication, December 2, 1971)

ANDERS EHRENBERG AND PETER REICHARD

From the Department of Biophysics, University of Stockholm, and the Department of Biochemistry, Medical Nobel Institute, Karolinska Institutet, Stockholm, Sweden



Synthesis of DNA: Deoxygenation of Ribonucleotides

Ribonucleotide Reductase— A Radical Enzyme

Peter Reichard and Anders Ehrenberg

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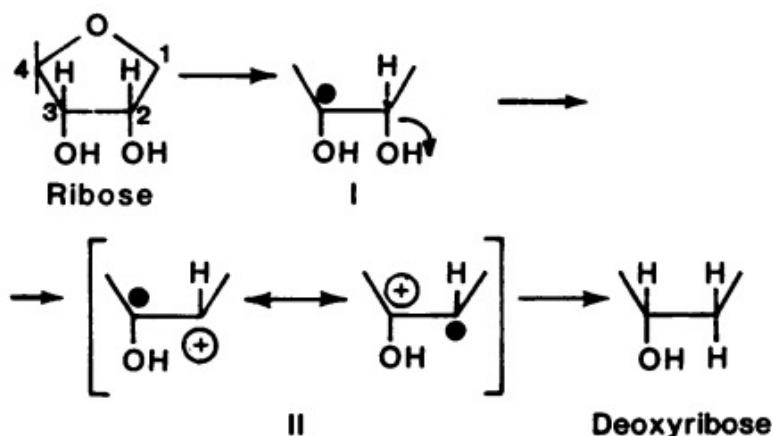
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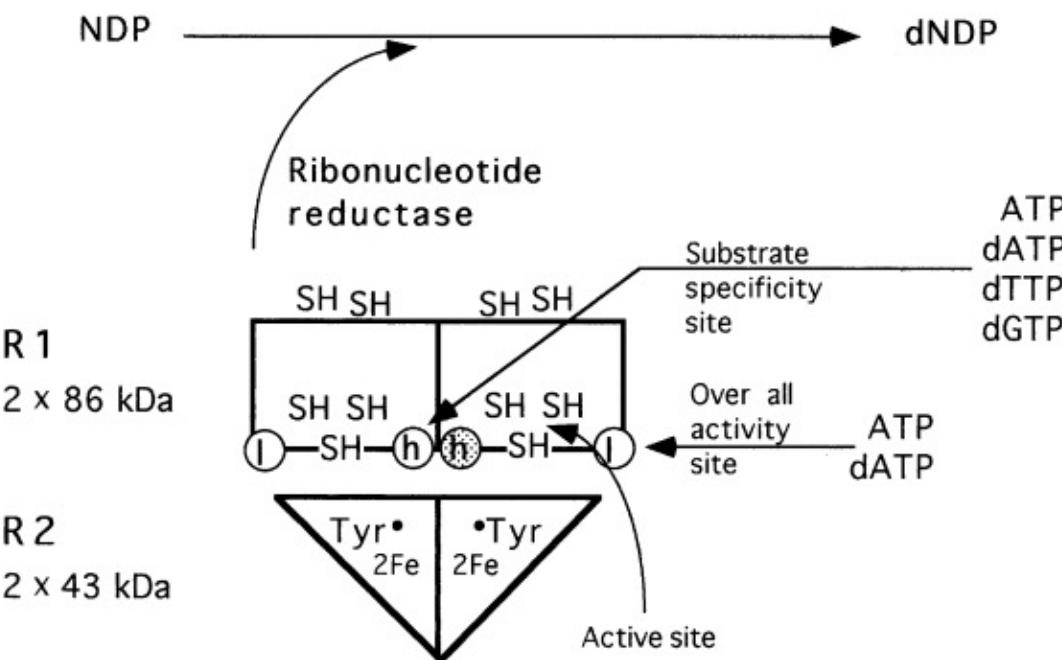
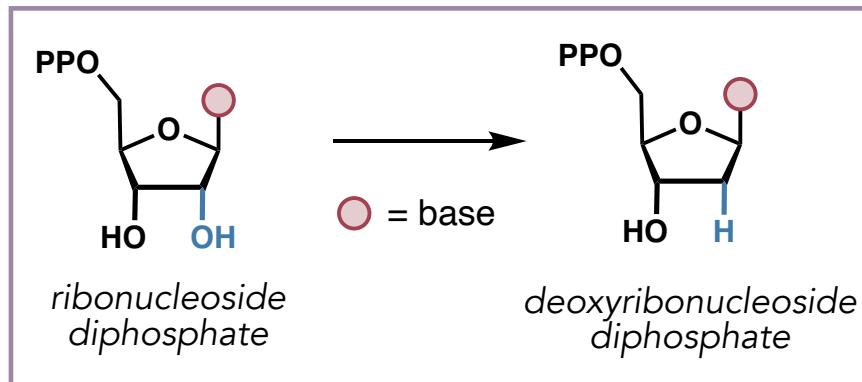
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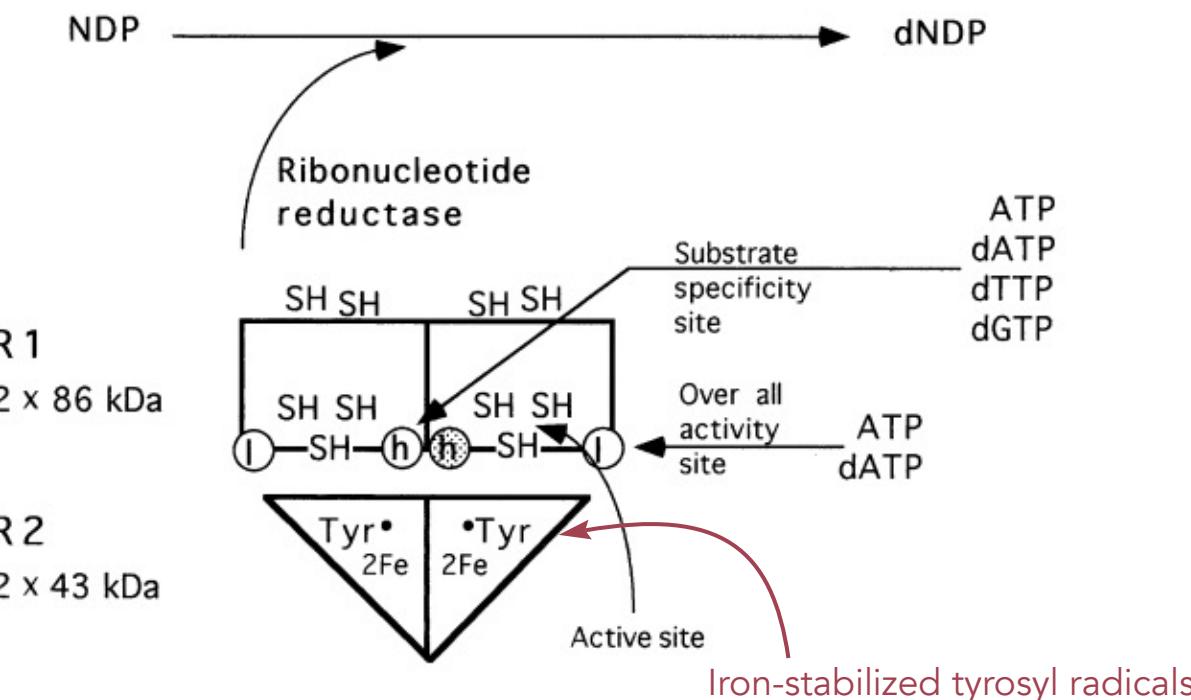
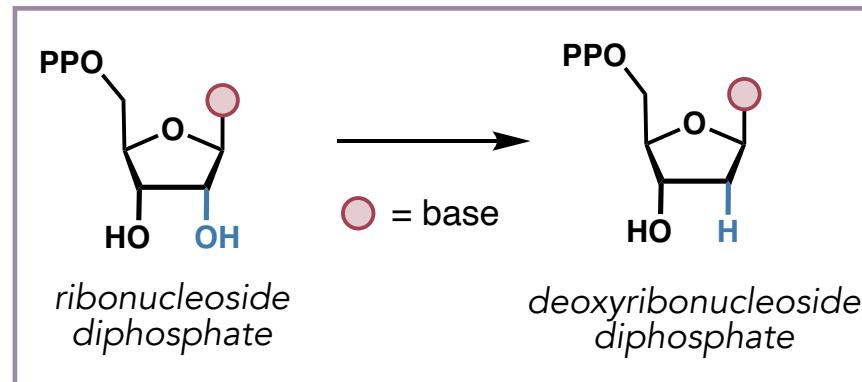


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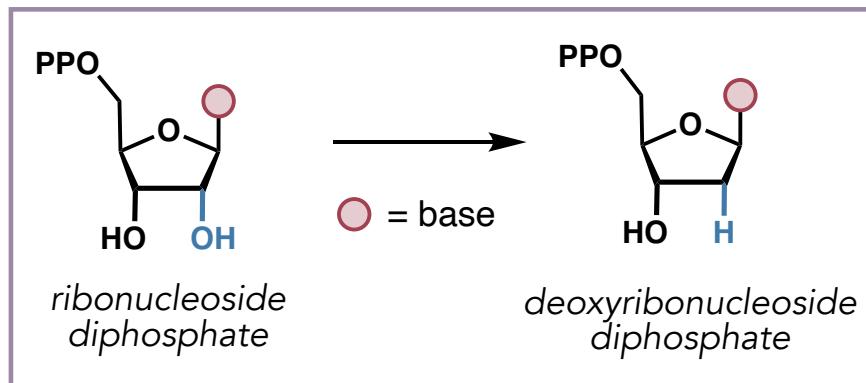
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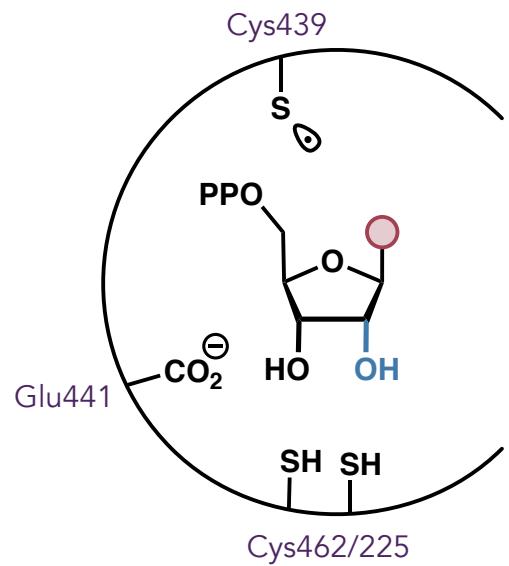
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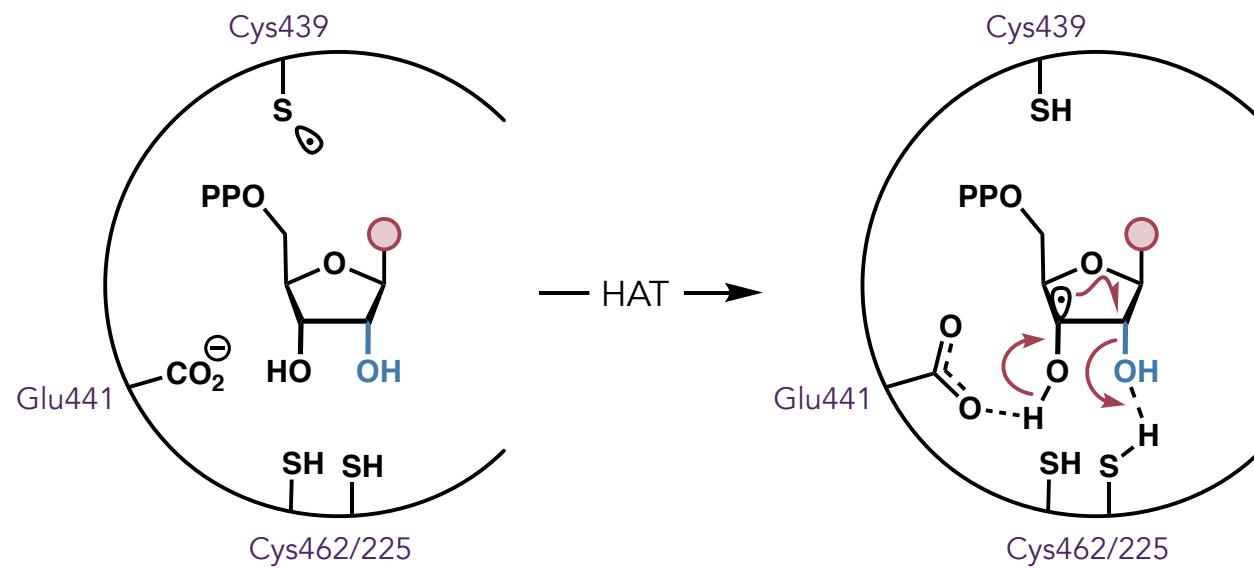
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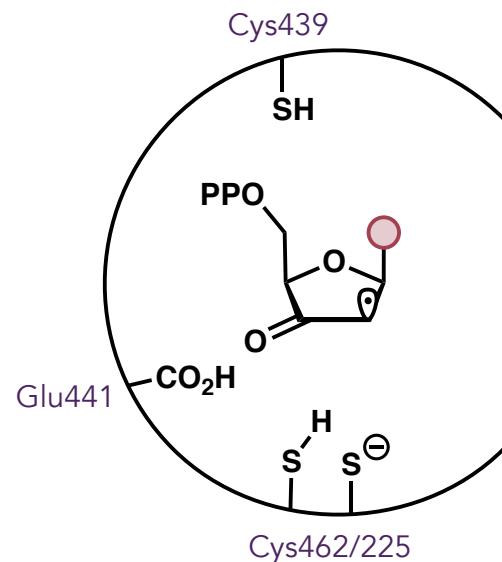
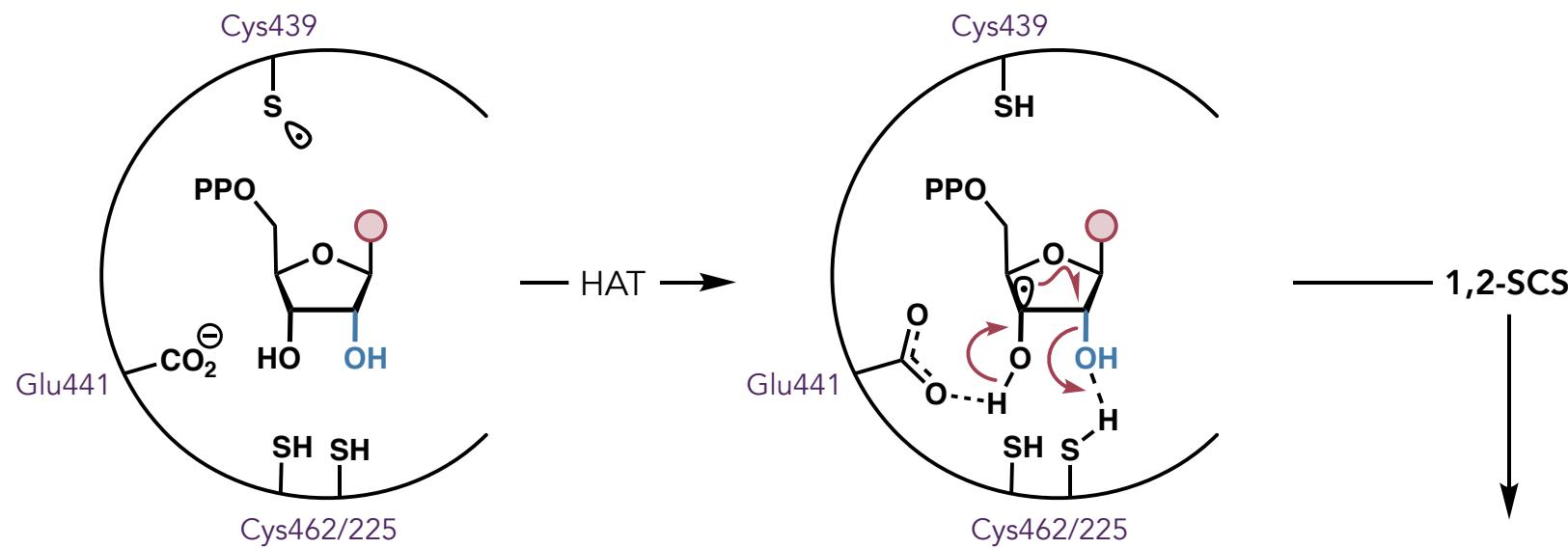
RNR Mechanism



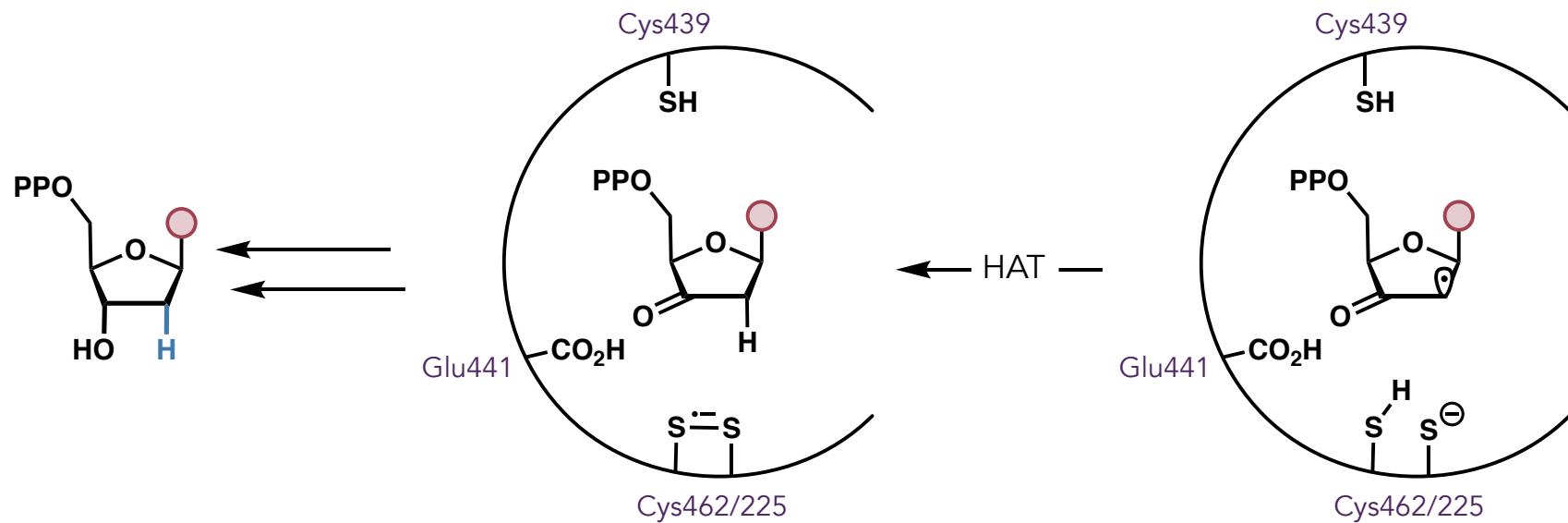
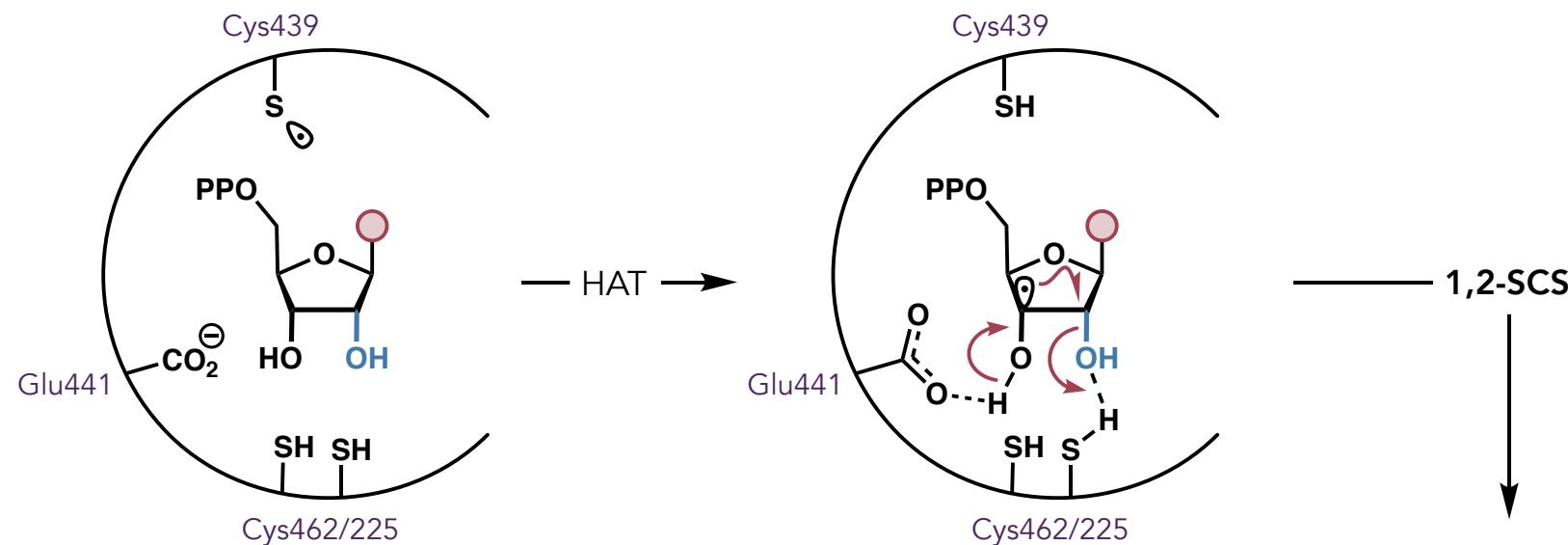
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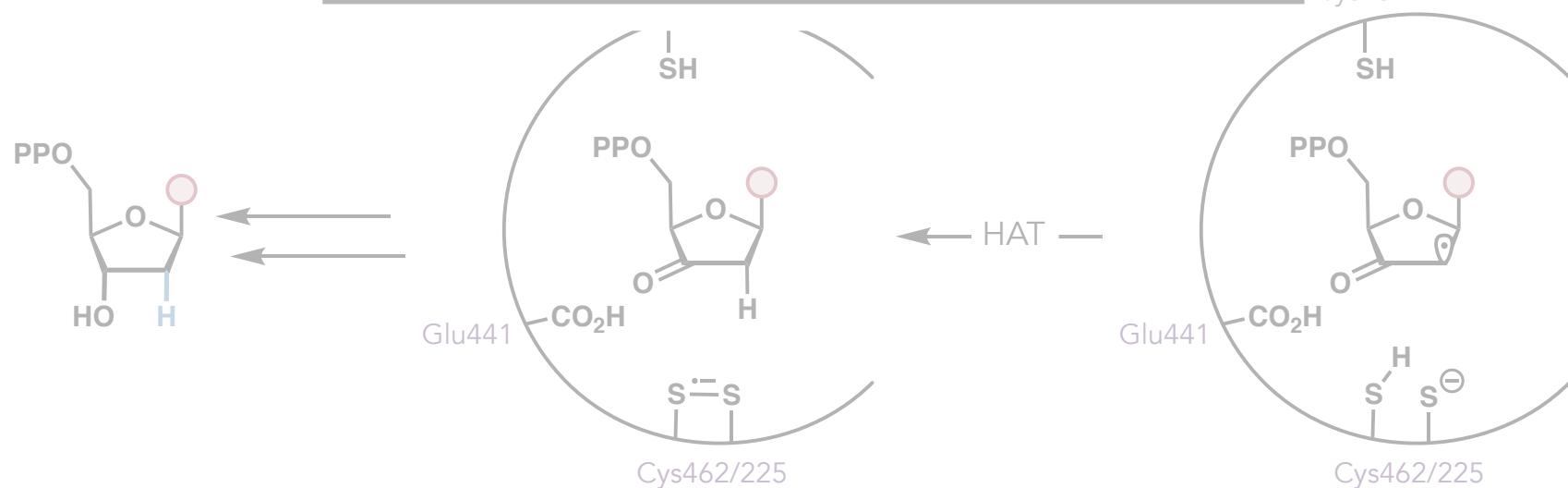
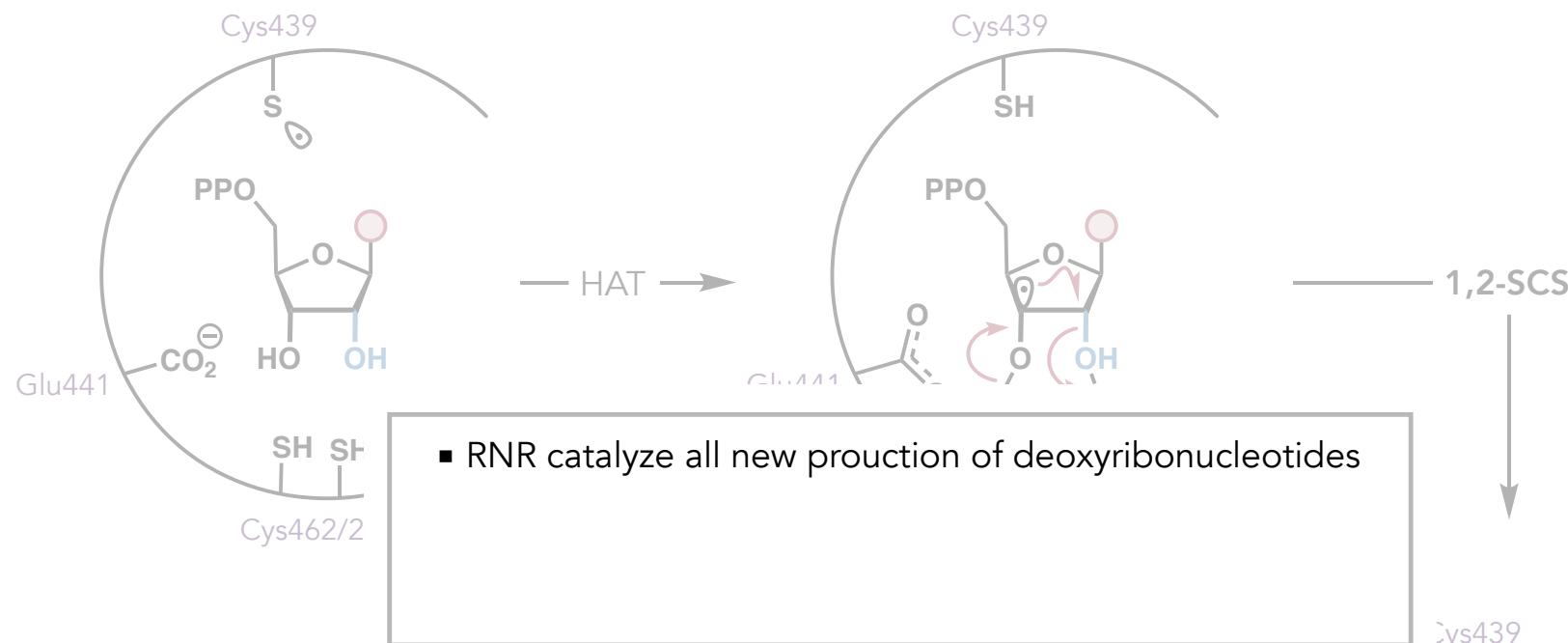
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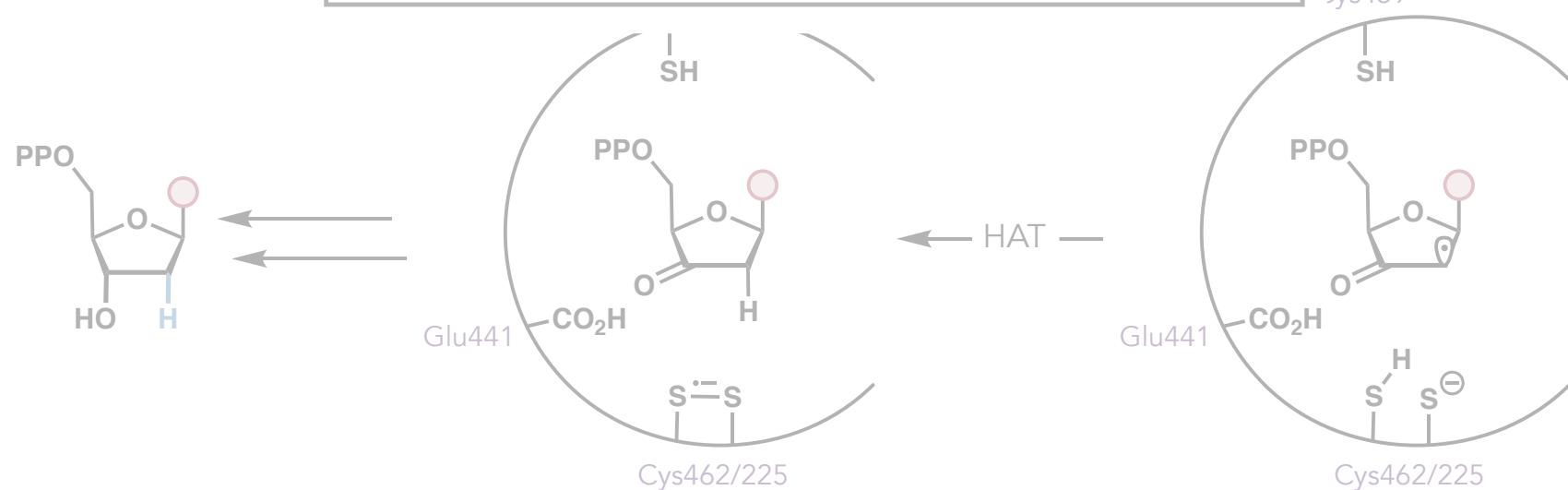
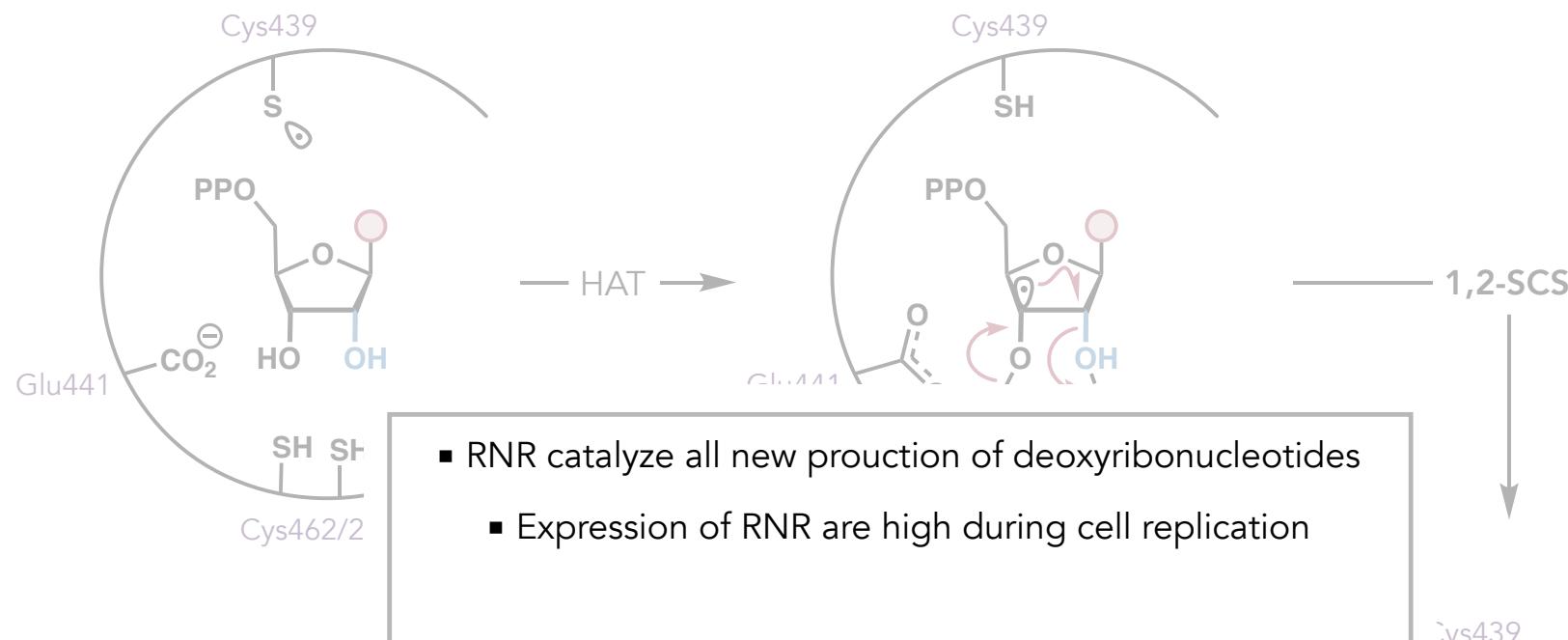
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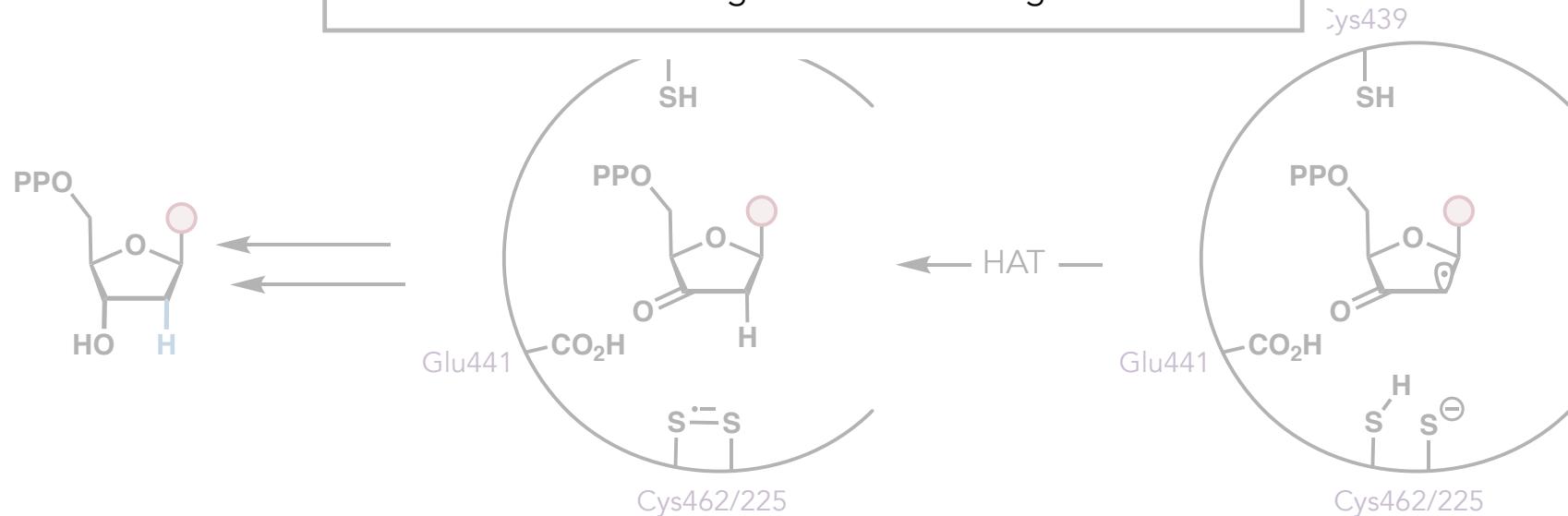
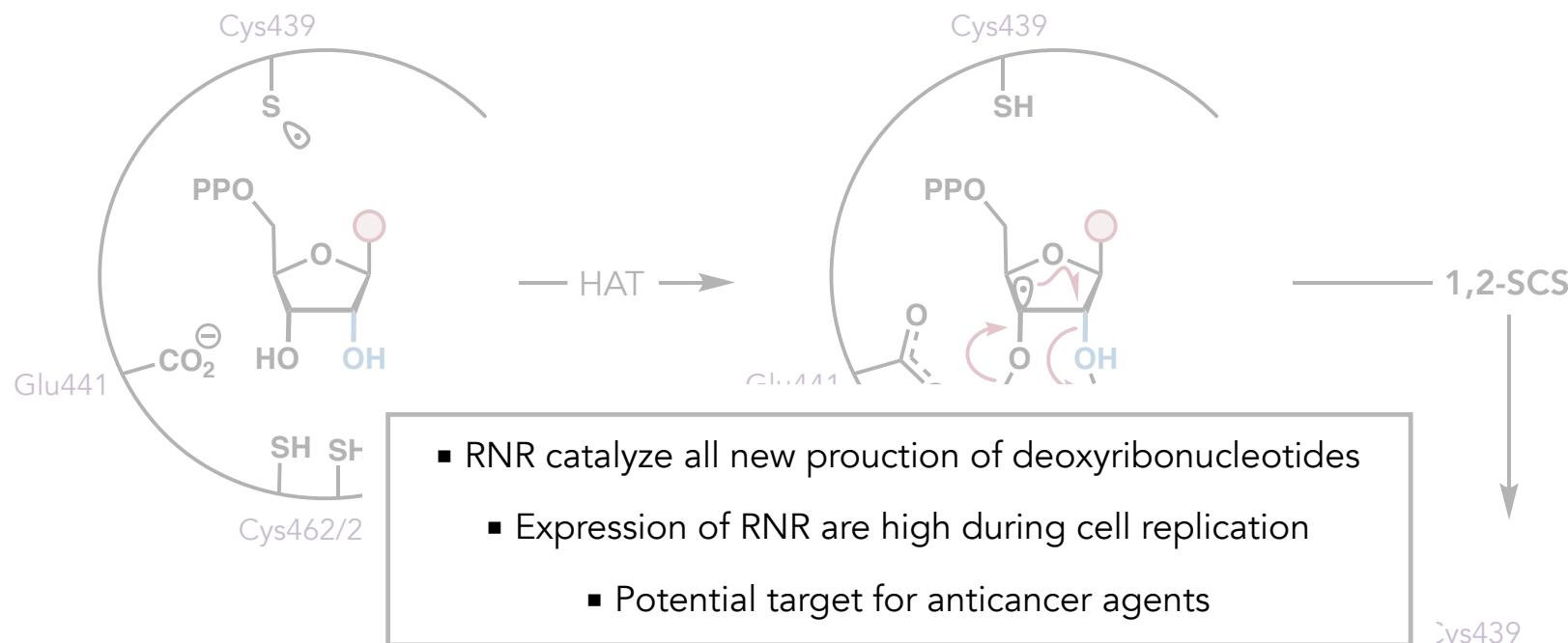
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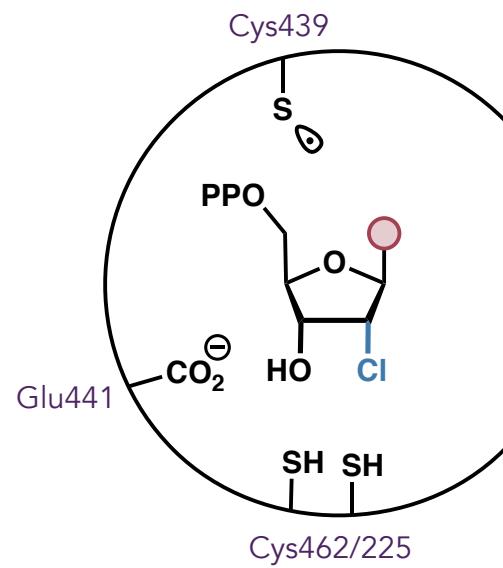
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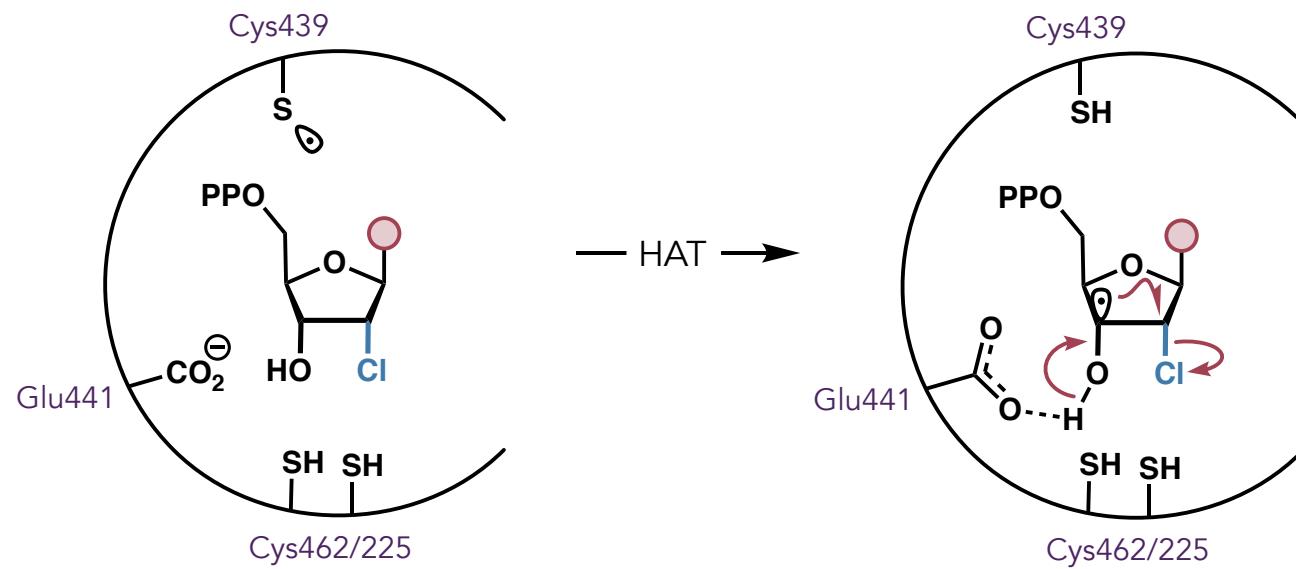
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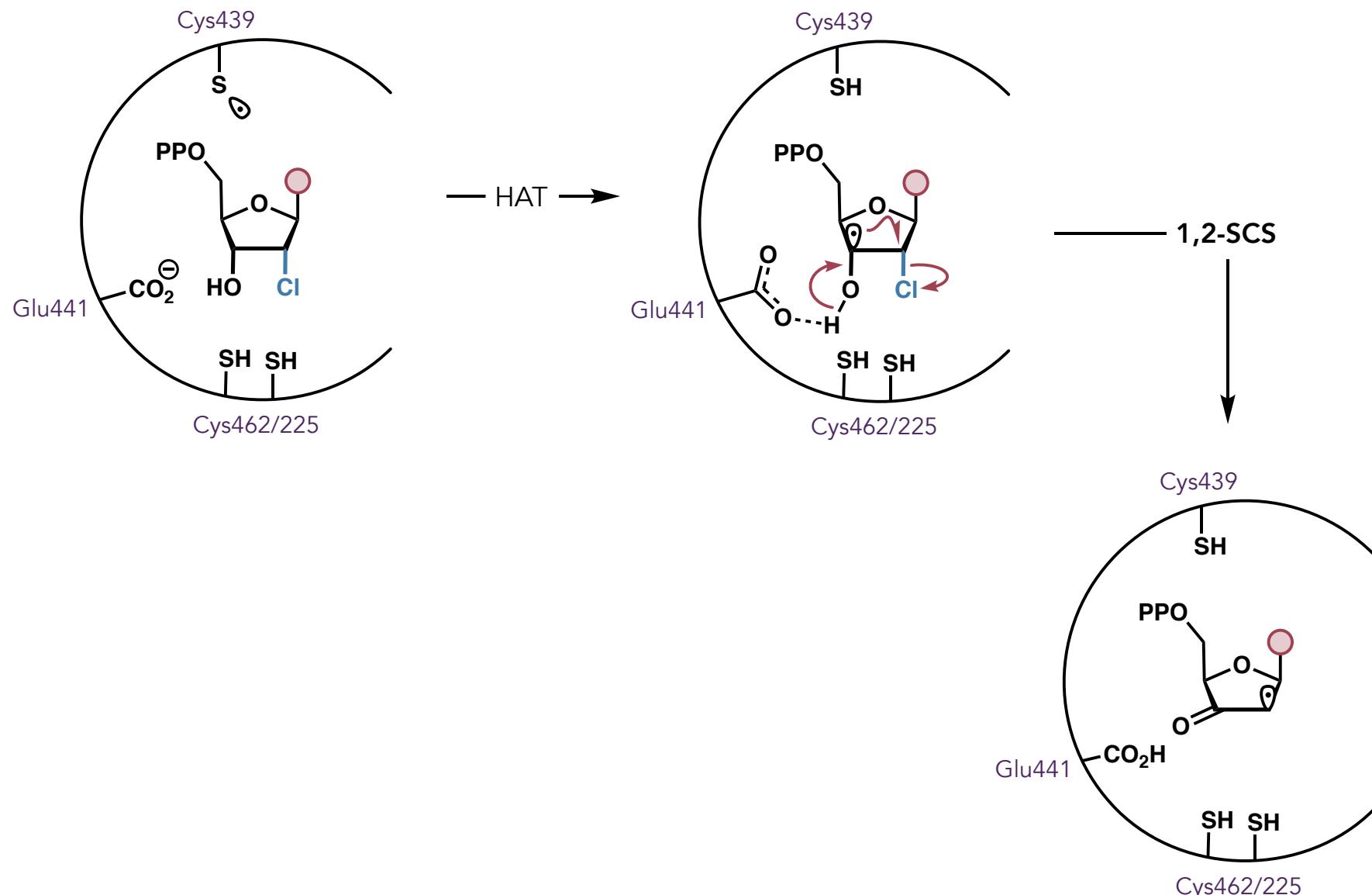
Ribonucleotide Reductase Inhibition



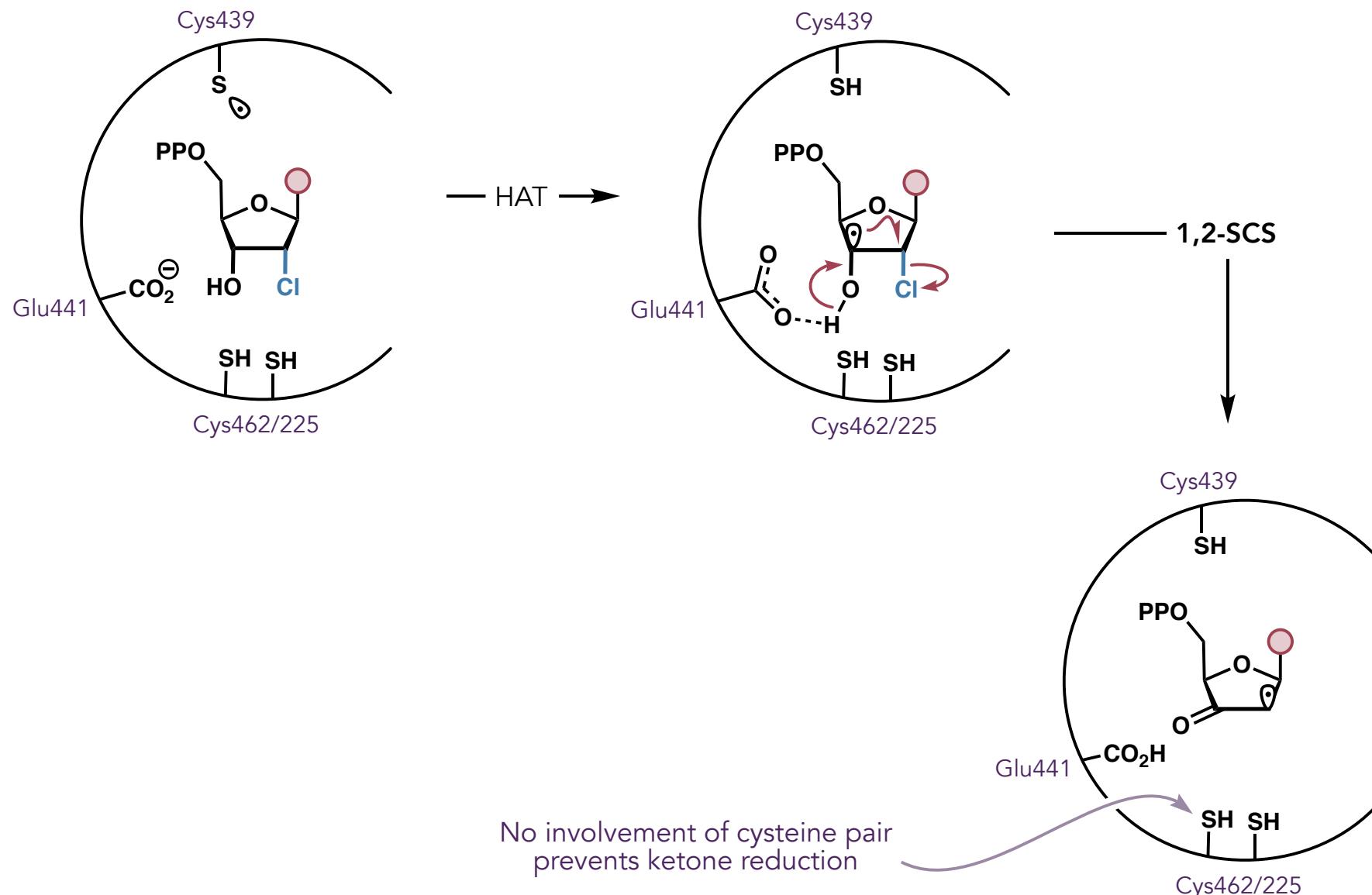
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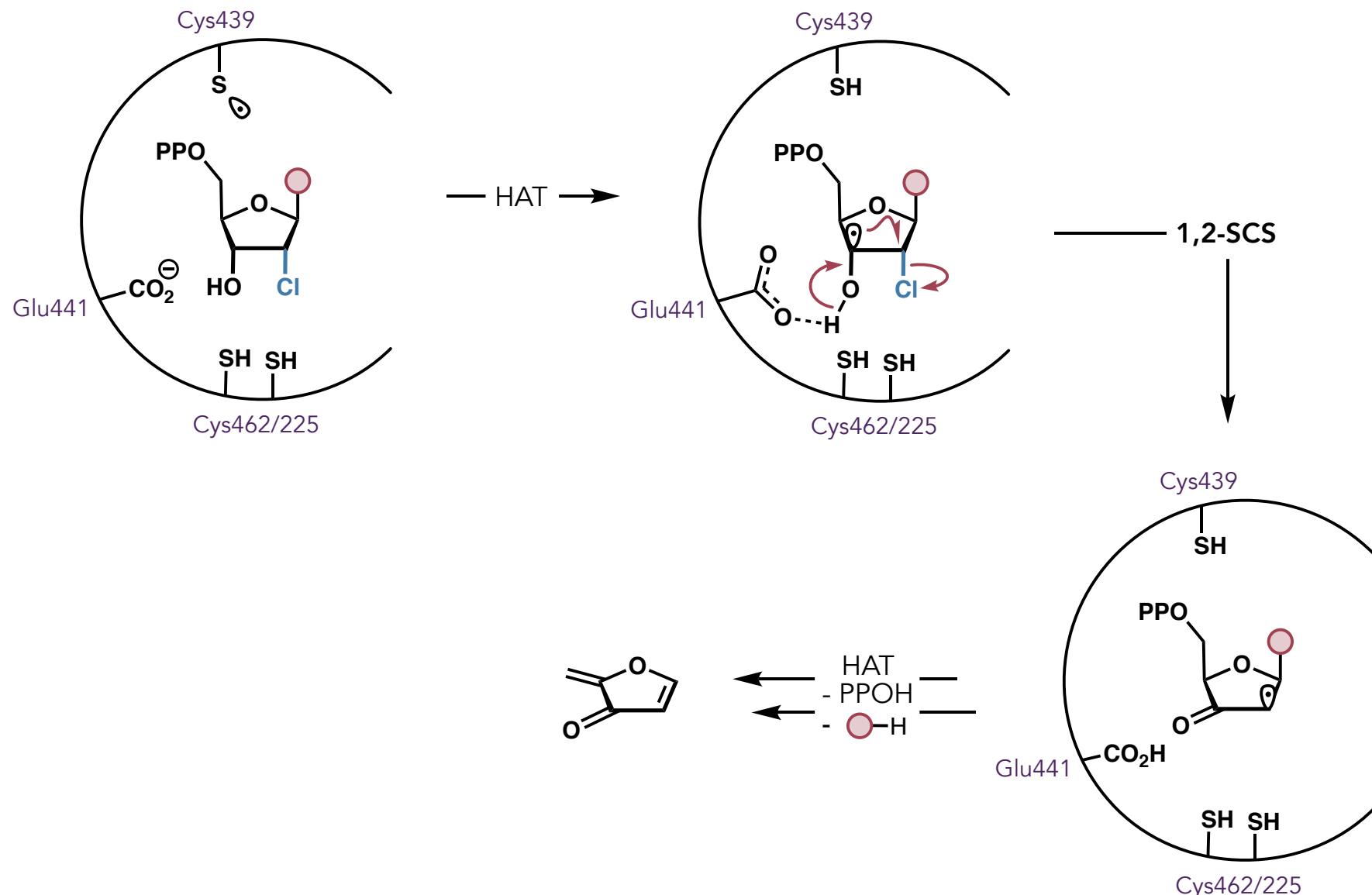
Ribonucleotide Reductase Inhibition



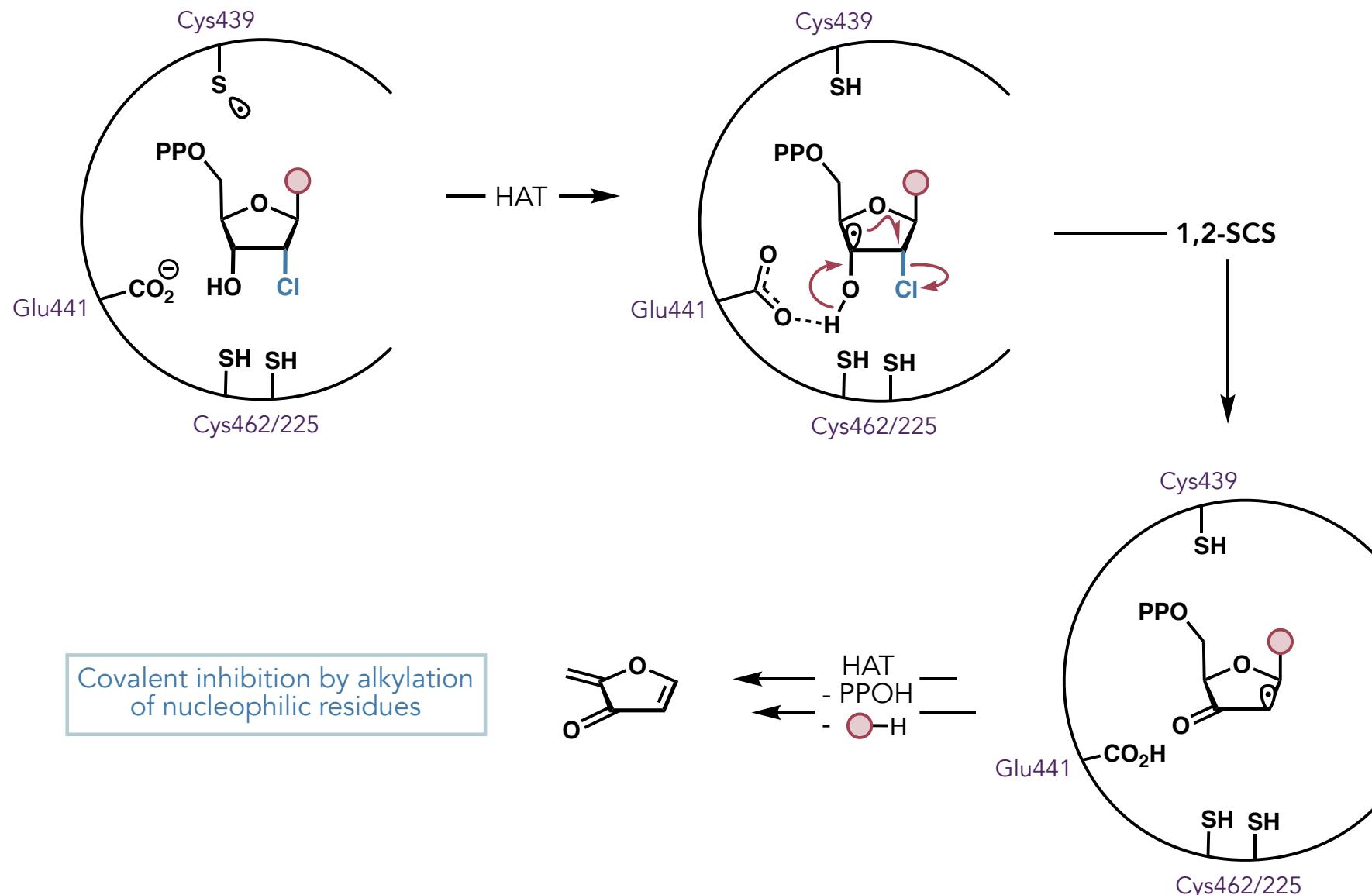
Ribonucleotide Reductase Inhibition



Ribonucleotide Reductase Inhibition



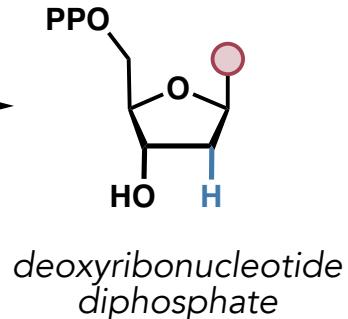
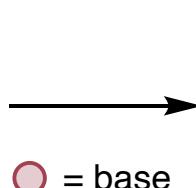
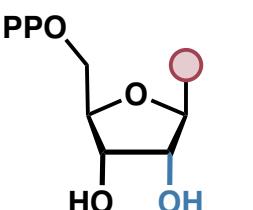
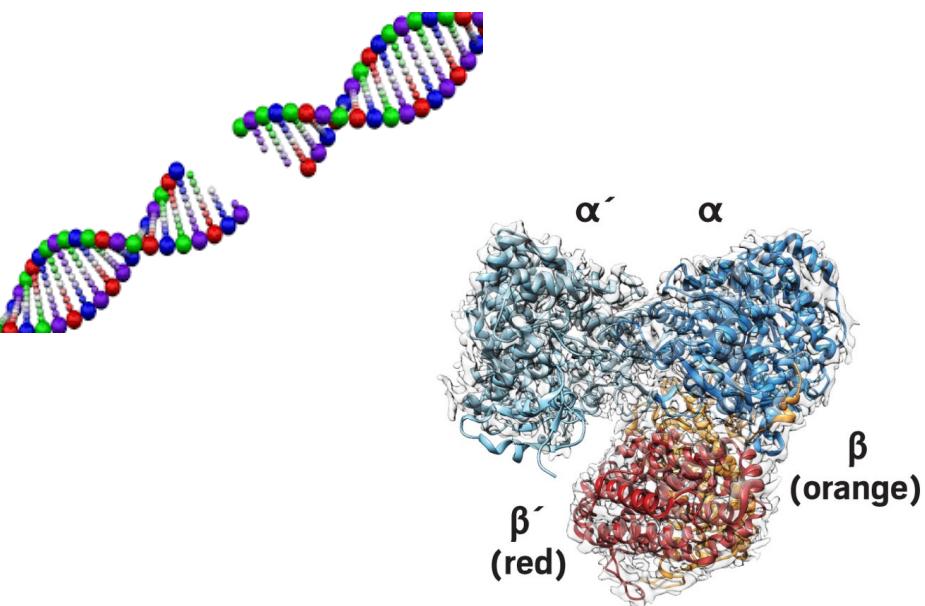
Ribonucleotide Reductase Inhibition



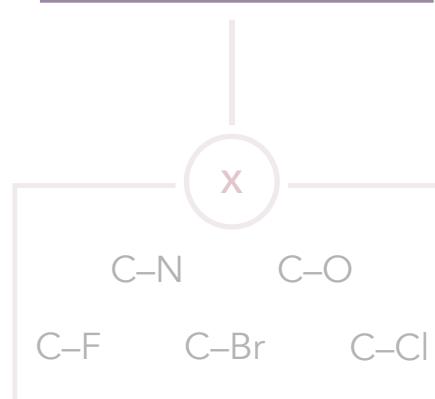
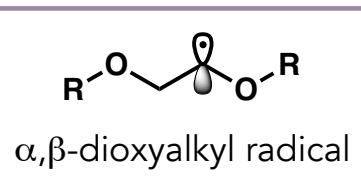
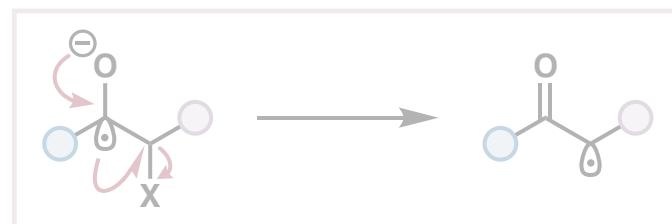
Stubbe, J.; van der Donk, W. *Chem. Biol.* **1995**, 2, 793.
Robbins, M. J. *Nucleotides Nucleosides Nucleic Acids* **2003**, 22, 519.

Spin-Center Shift (SCS)

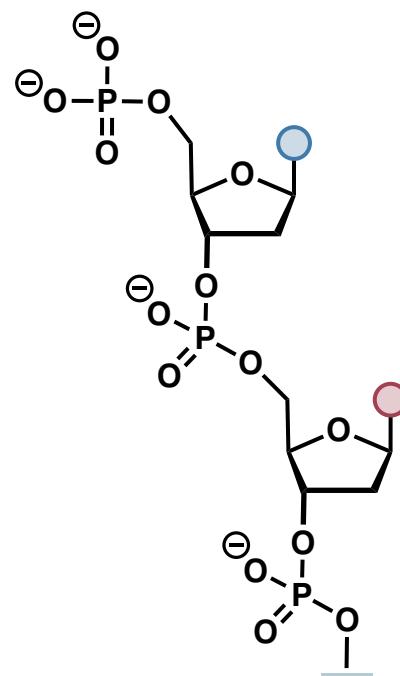
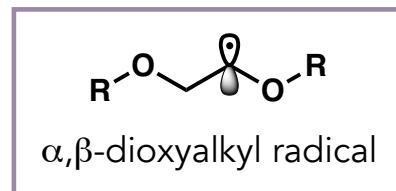
Biochemical Processes



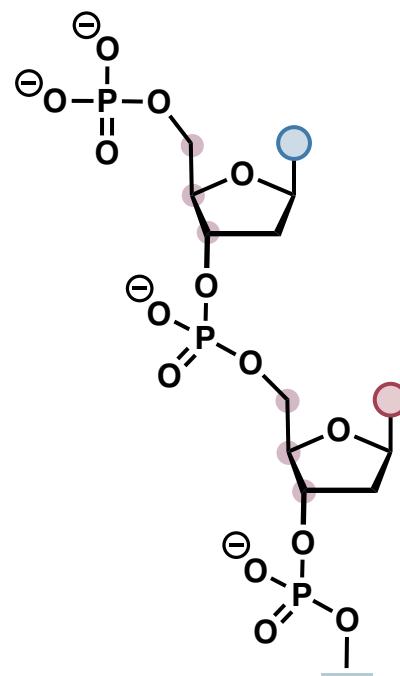
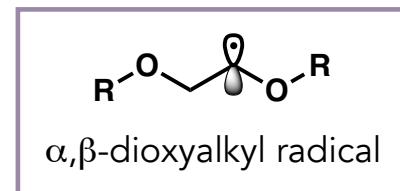
Synthetic Applications



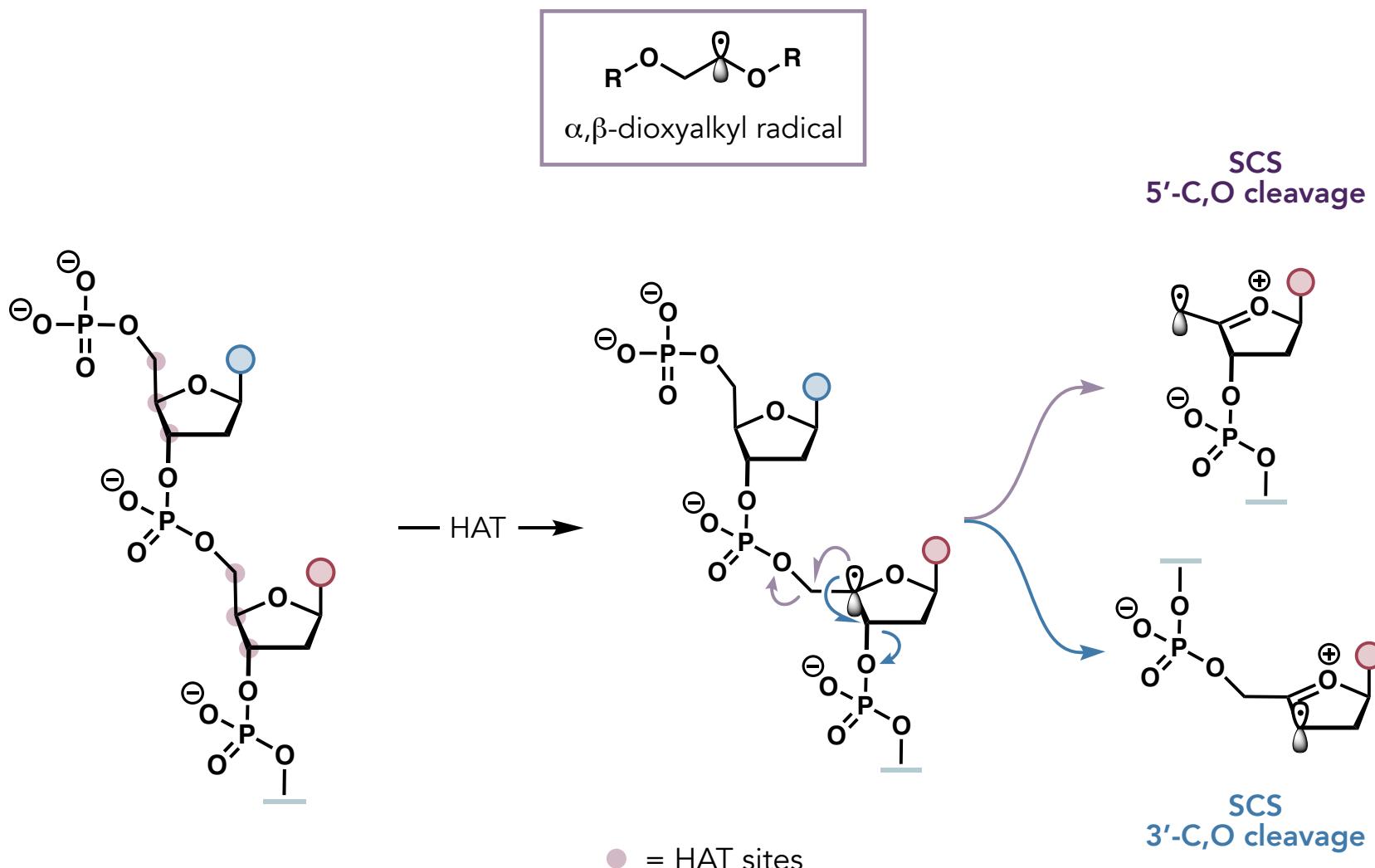
DNA Damage by Oxidative Stress



DNA Damage by Oxidative Stress

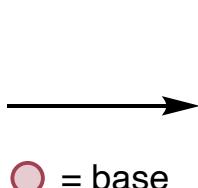
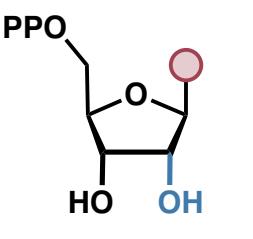
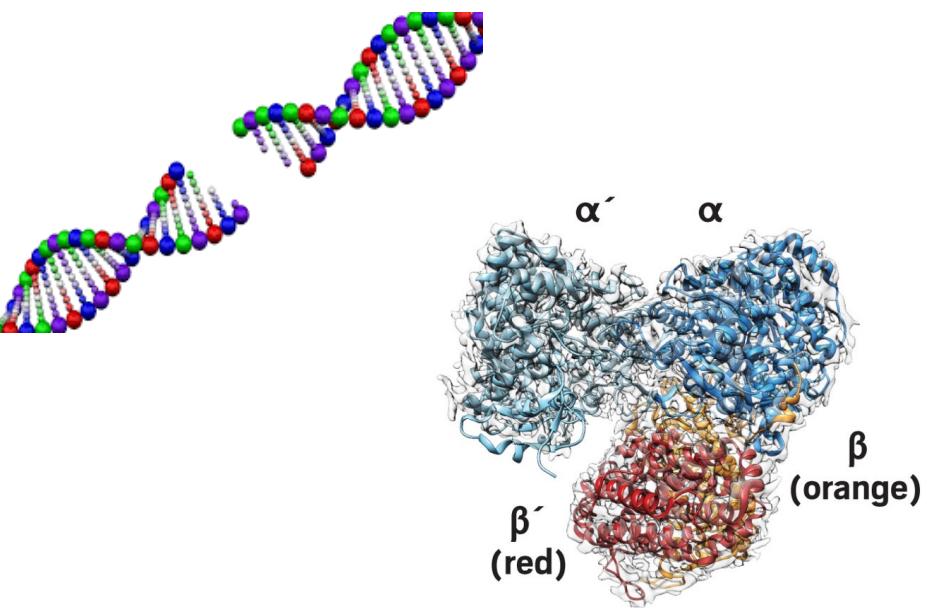


DNA Damage by Oxidative Stress

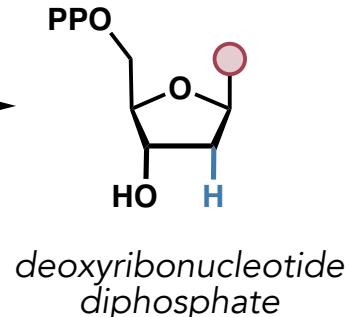


Spin-Center Shift (SCS)

Biochemical Processes



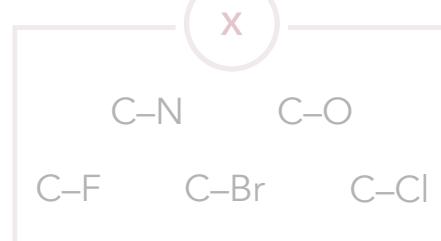
ribonucleotide diphosphate



Synthetic Applications

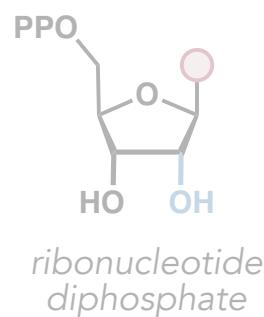
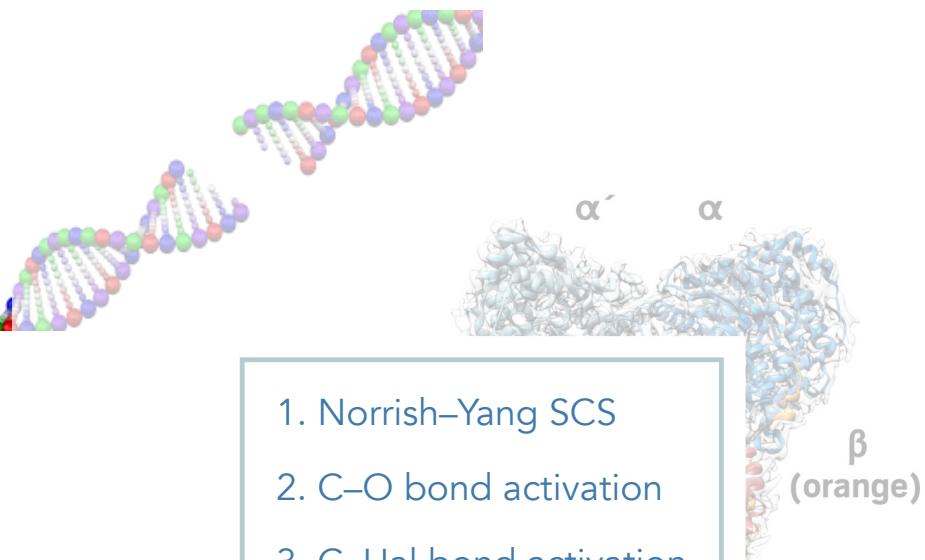


C-X bond activation

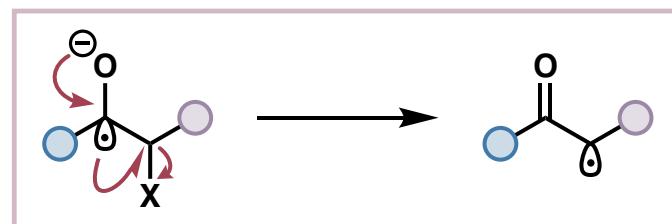


Spin-Center Shift (SCS)

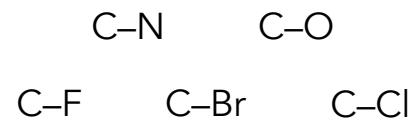
Biochemical Processes



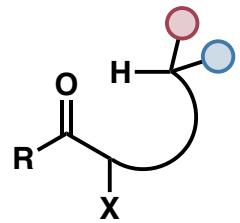
Synthetic Applications



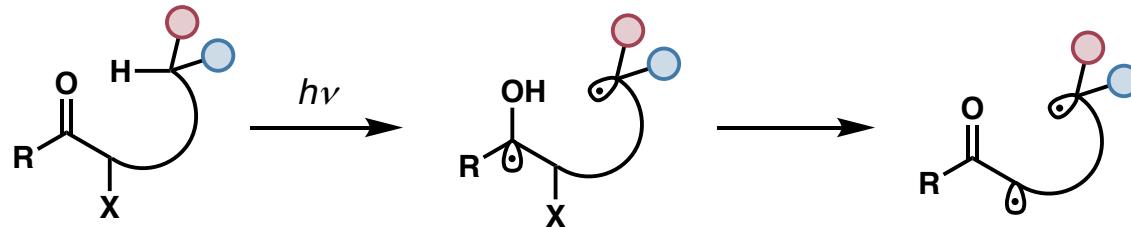
C–X bond activation



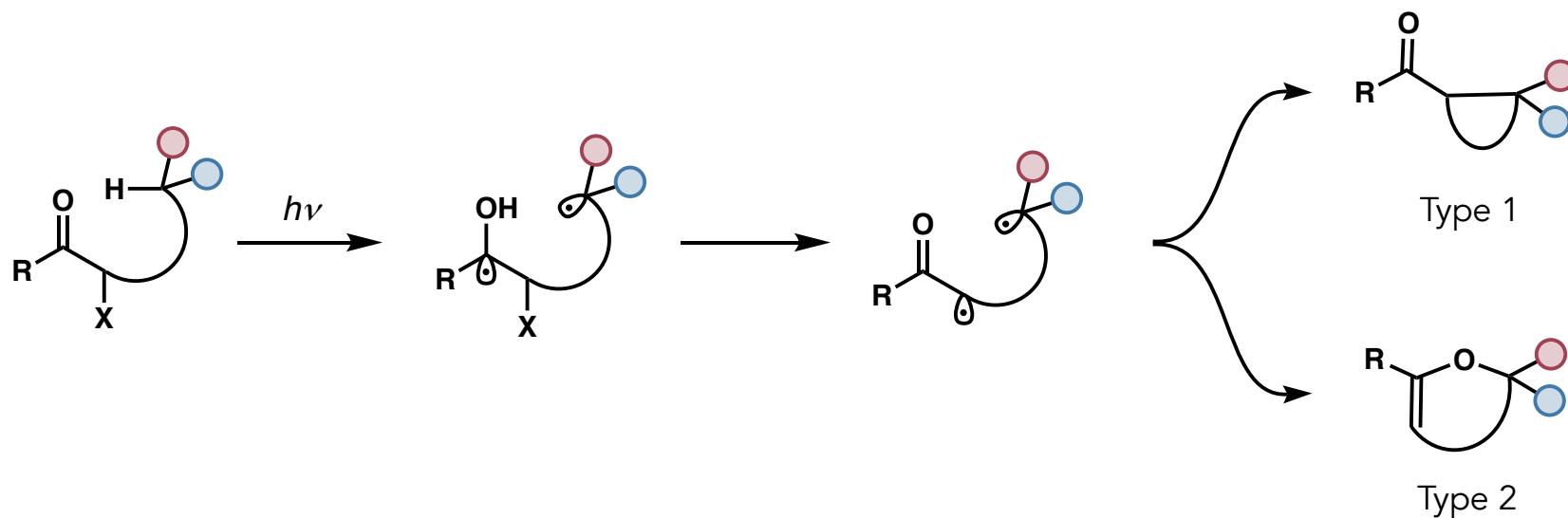
SCS Norrish–Yang Reactions



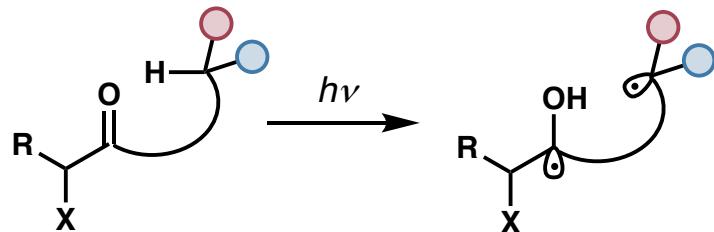
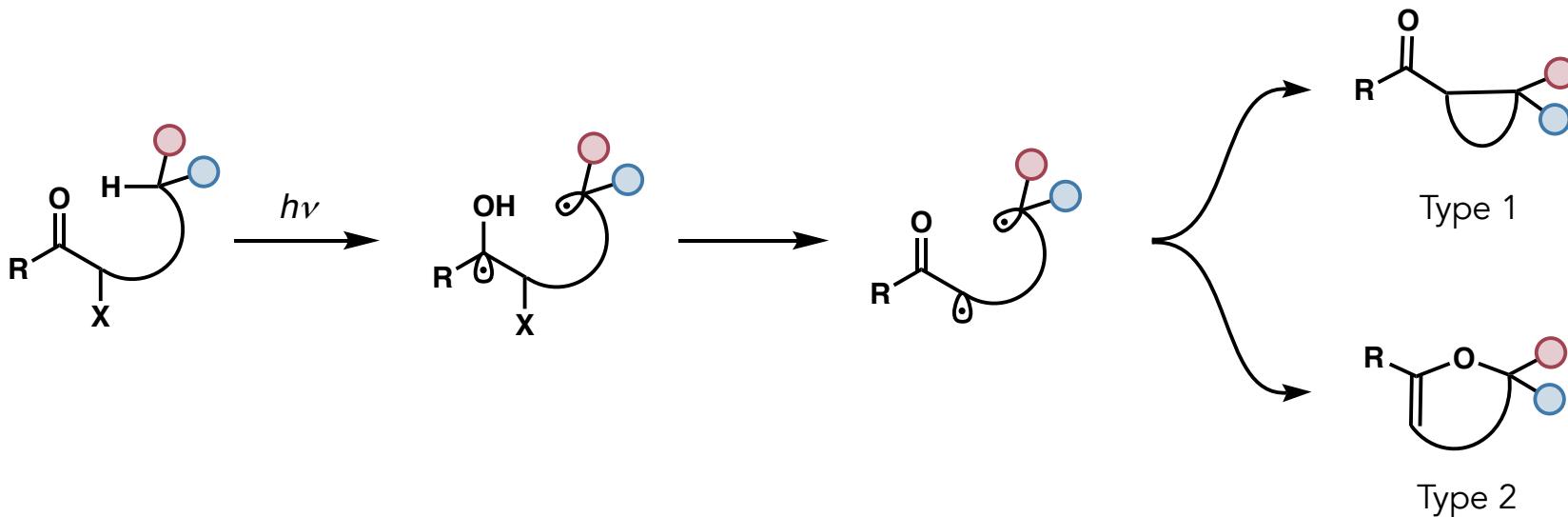
SCS Norrish–Yang Reactions



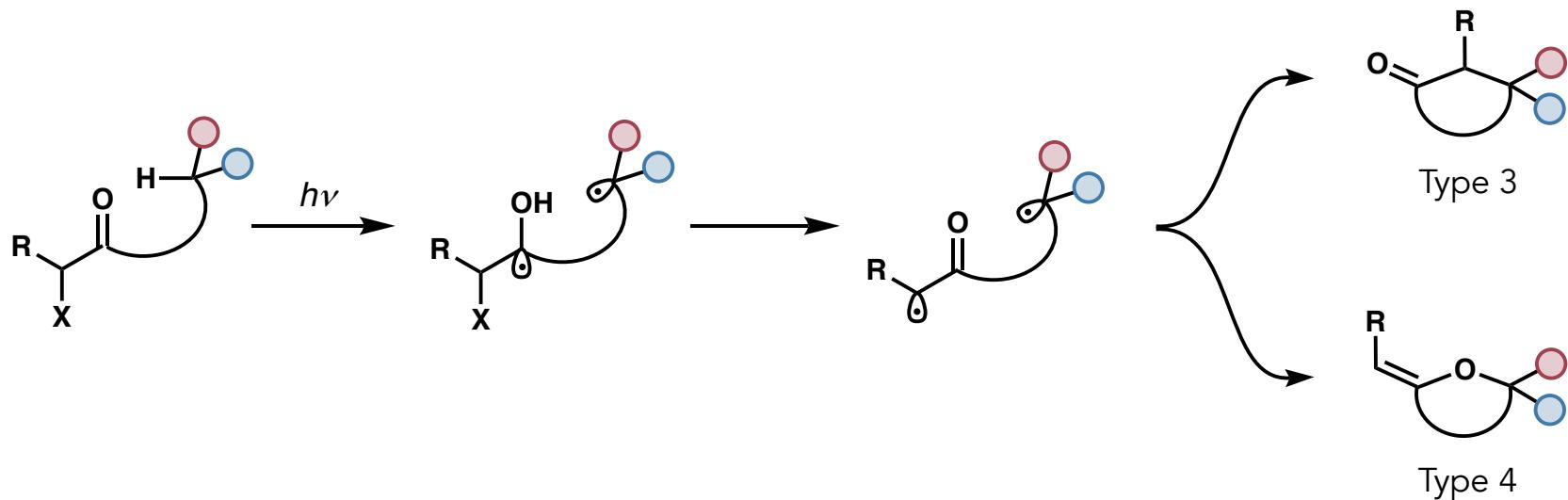
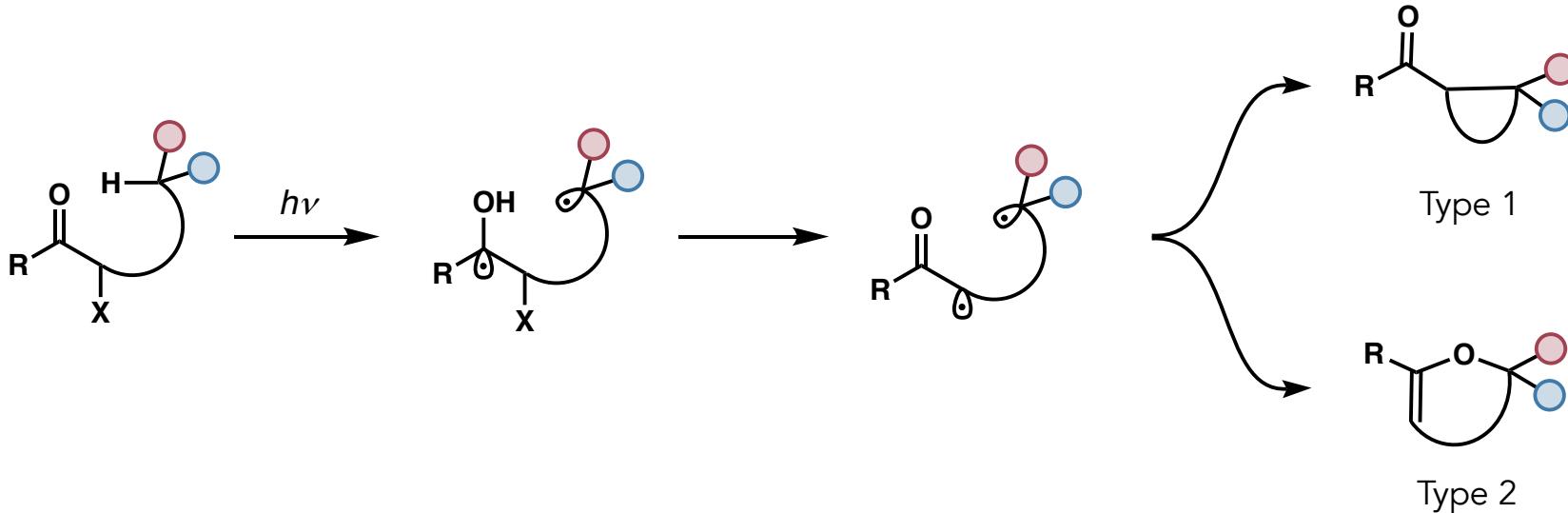
SCS Norrish–Yang Reactions



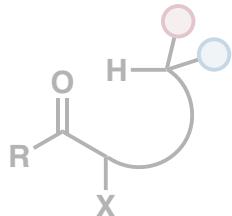
SCS Norrish–Yang Reactions



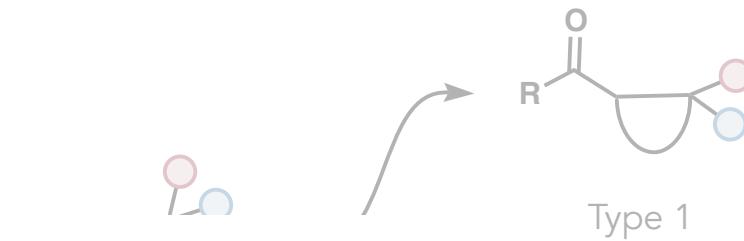
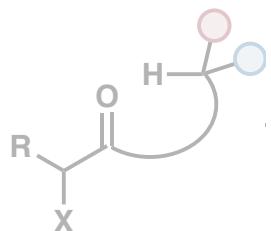
SCS Norrish–Yang Reactions



SCS Norrish–Yang Reactions



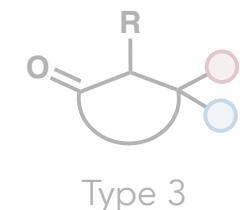
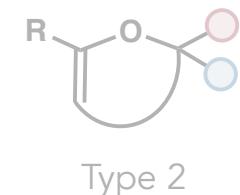
Prof. Pablo Wessig
University of Potsdam



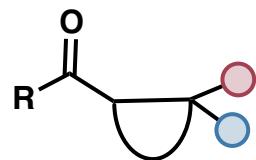
Universität



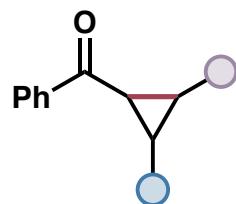
Potsdam



SCS Norrish–Yang Reactions



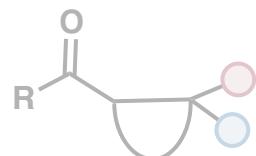
Type 1



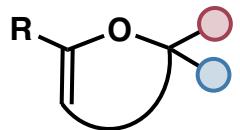
Wessig & Muehling

Angew. Chem. Int. Ed. **2001**, *40*, 1064.

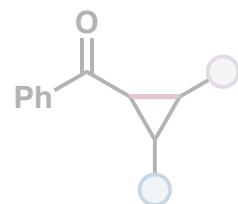
SCS Norrish–Yang Reactions



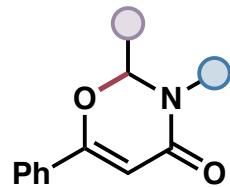
Type 1



Type 2

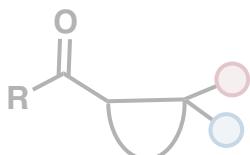


Wessig & Muehling
Angew. Chem. Int. Ed. **2001**, *40*, 1064.



Wessig & coworkers
Synthesis **2001**, 1258.

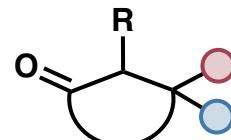
SCS Norrish–Yang Reactions



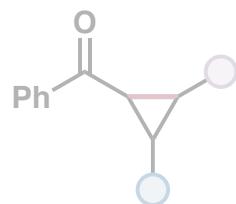
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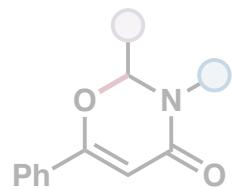
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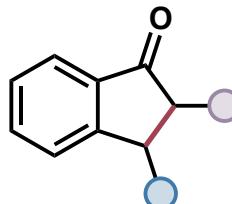
Type 3



Wessig & Muehling
Angew. Chem. Int. Ed. **2001**, *40*, 1064.

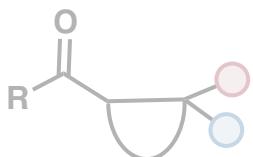


Wessig & coworkers
Synthesis **2001**, 1258.



Wessig & coworkers
JOC **2004**, *69*, 7582.

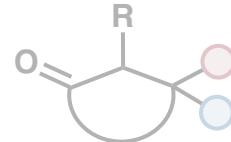
SCS Norrish–Yang Reactions



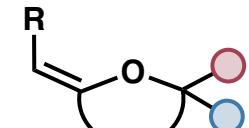
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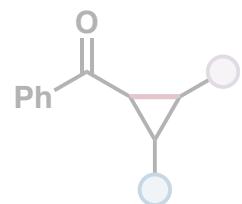
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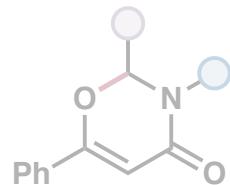
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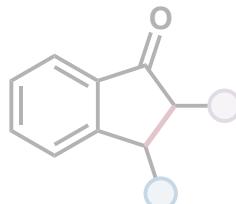
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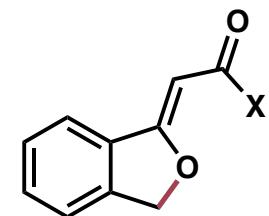
Wessig & Muehling
Angew. Chem. Int. Ed. **2001**, *40*, 1064.



Wessig & coworkers
Synthesis **2001**, 1258.

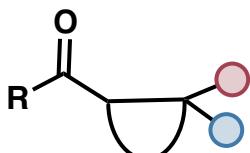


Wessig & coworkers
JOC **2004**, *69*, 7582.

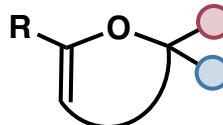


Wessig & coworkers
JOC **2004**, *69*, 7582.

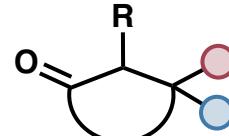
SCS Norrish–Yang Reactions



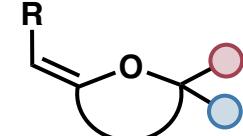
Type 1



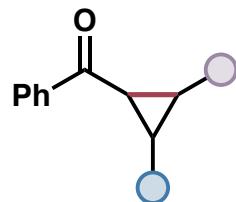
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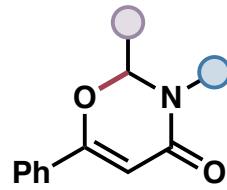
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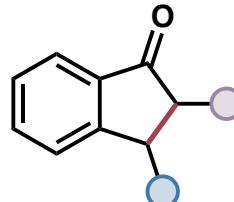
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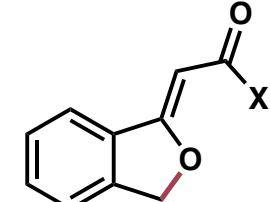
Wessig & Muehling
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Wessig & coworkers
Synthesis **2001**, 1258.



Wessig & coworkers
JOC **2004**, *69*, 7582.



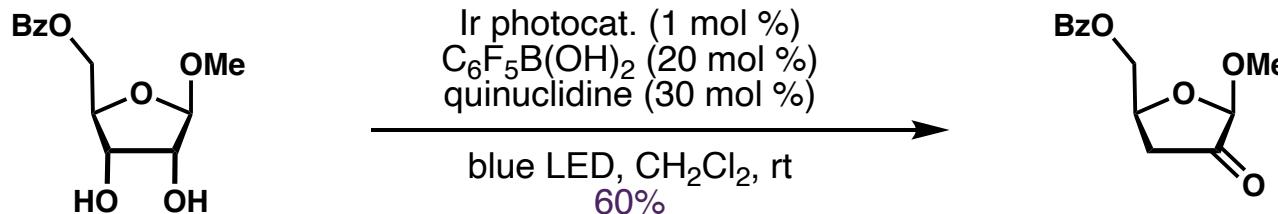
Wessig & coworkers
JOC **2004**, *69*, 7582.

Types 2 & 4 (C–O bond formation) are preferred over Types 1 & 3 (C–C bond formation) when an additional electron-withdrawing group is present

C–O Bond Activation

Dehydration Reactions

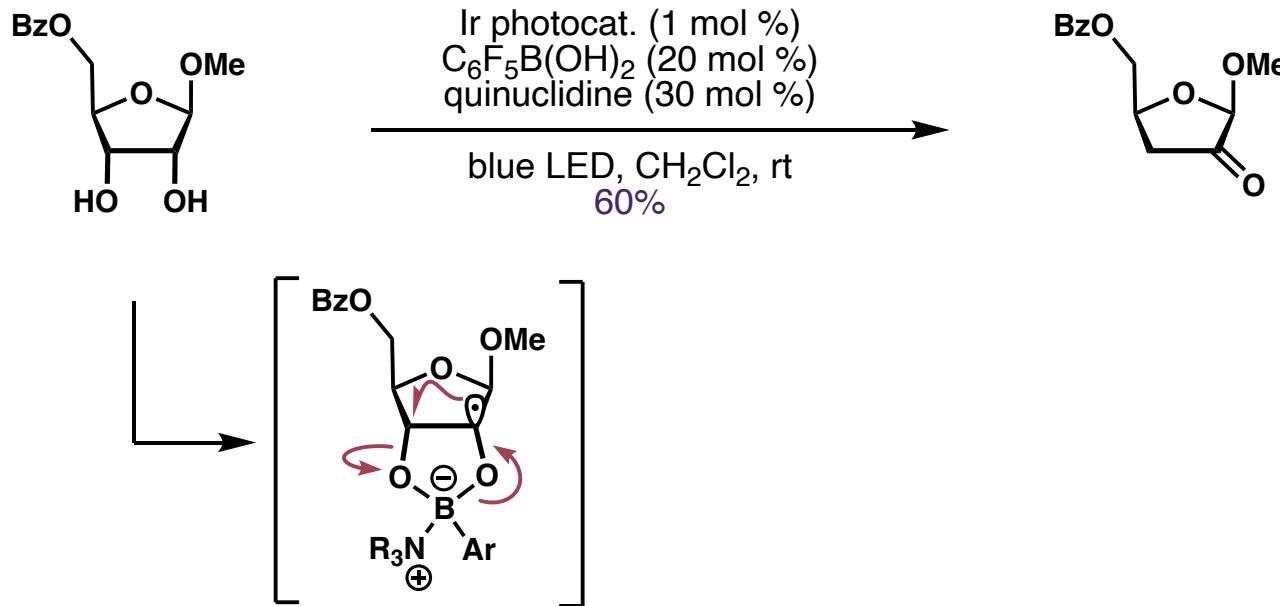
Taylor & coworkers:



C–O Bond Activation

Dehydration Reactions

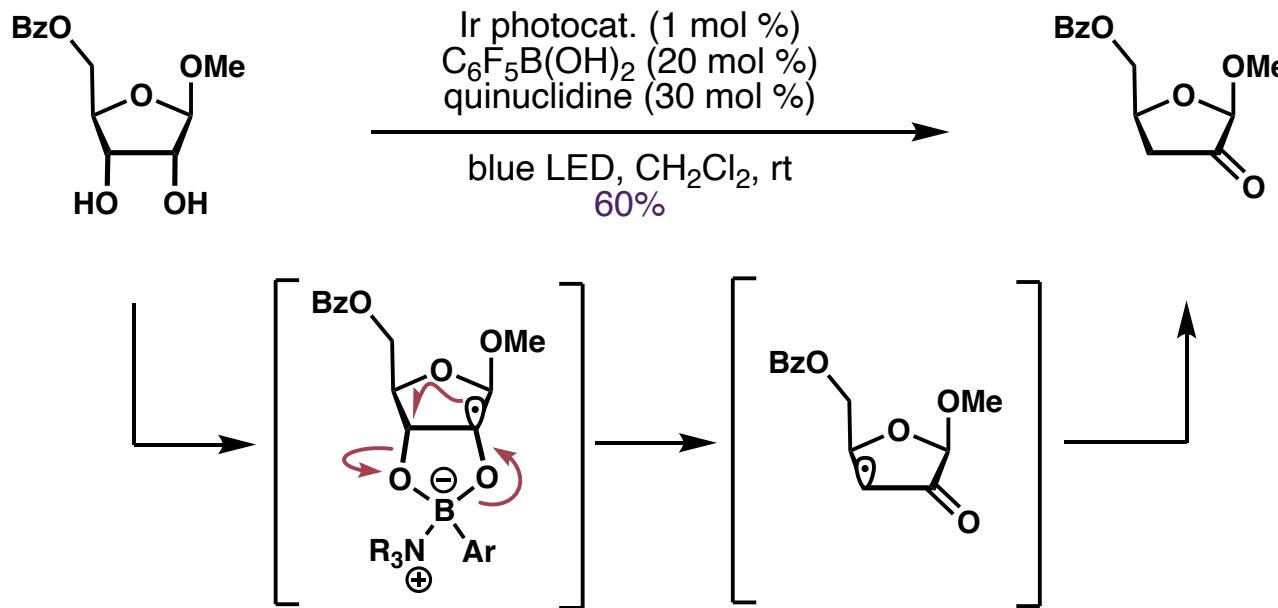
Taylor & coworkers:



C–O Bond Activation

Dehydration Reactions

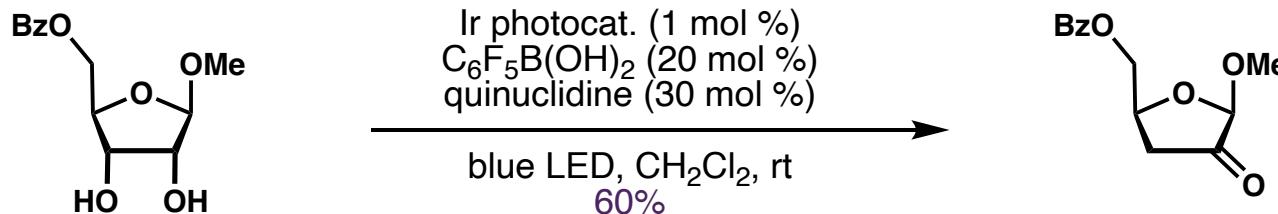
Taylor & coworkers:



C–O Bond Activation

Dehydration Reactions

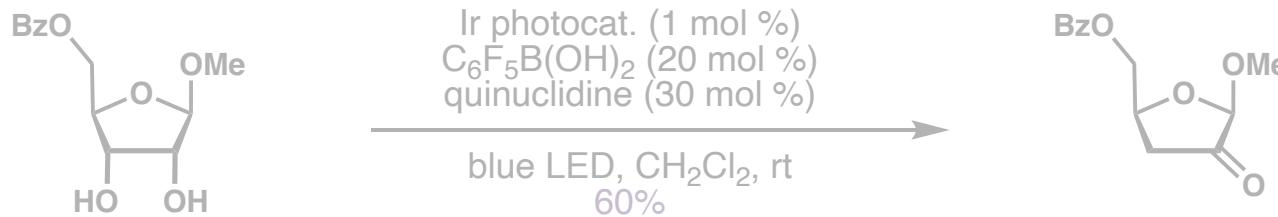
Taylor & coworkers:



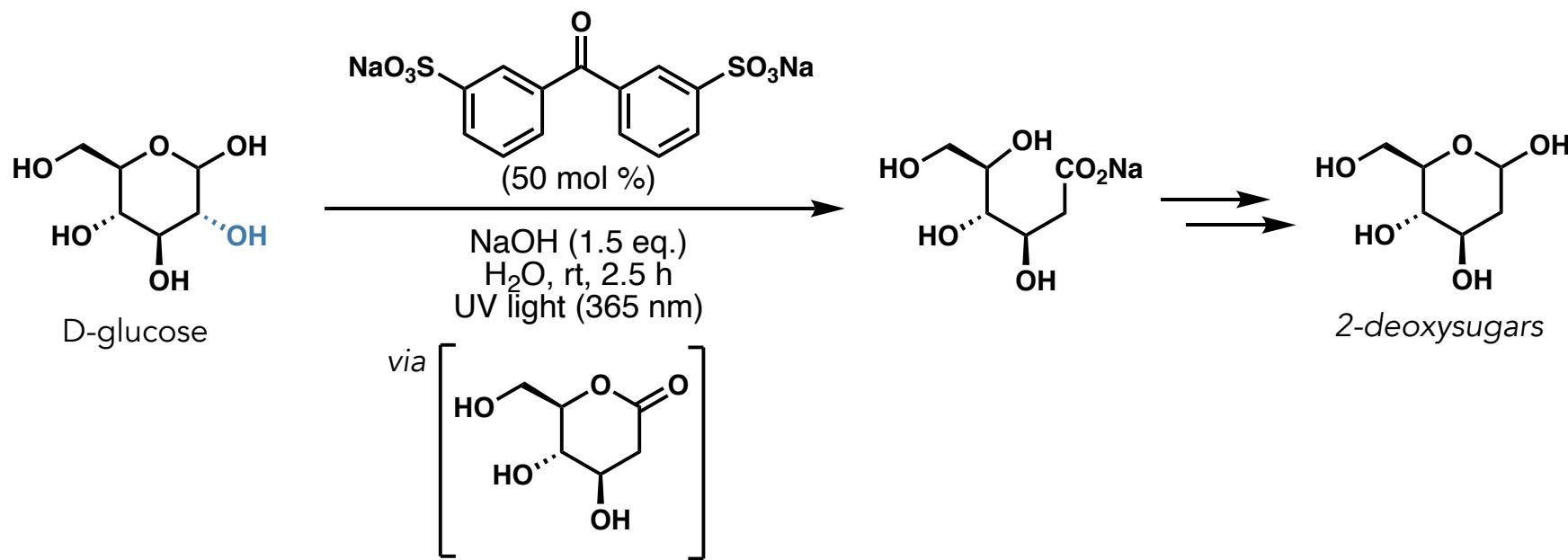
C–O Bond Activation

Dehydration Reactions

Taylor & coworkers:



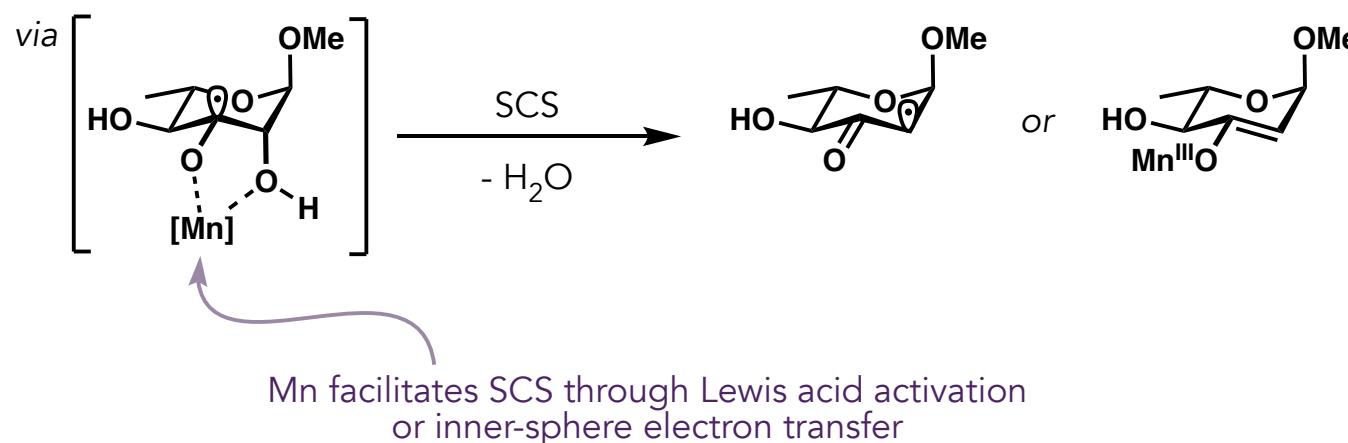
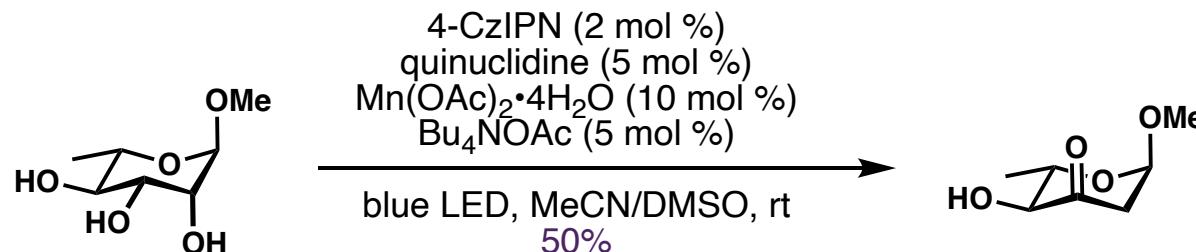
Murakami & coworkers:



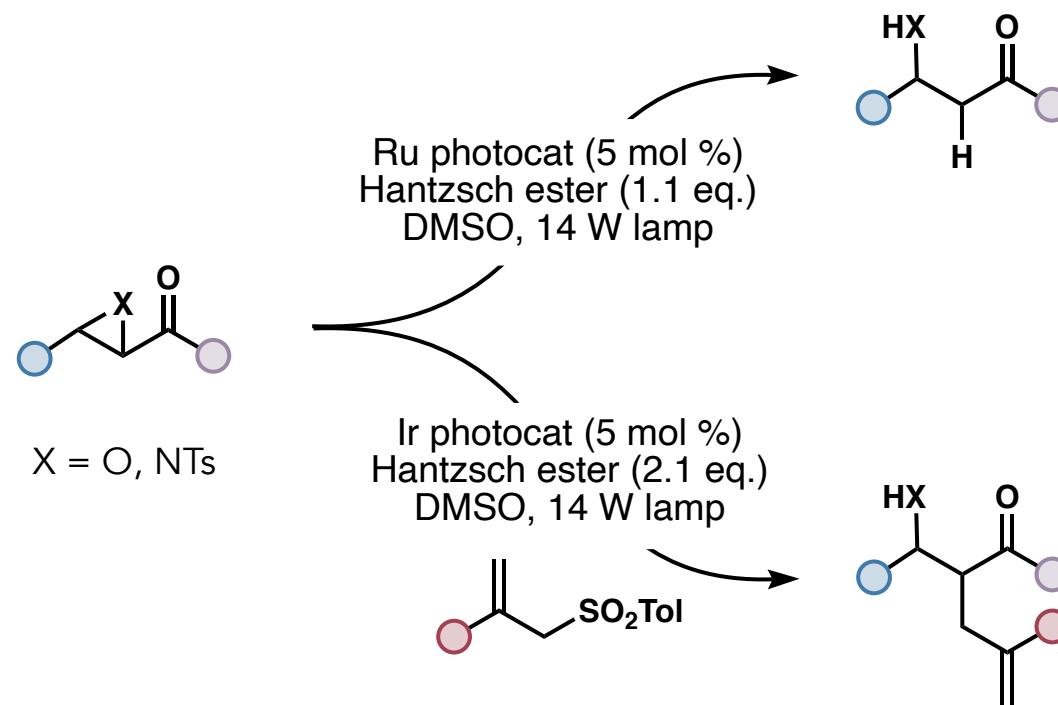
C–O Bond Activation

Dehydration Reactions

Wendlandt & coworkers:



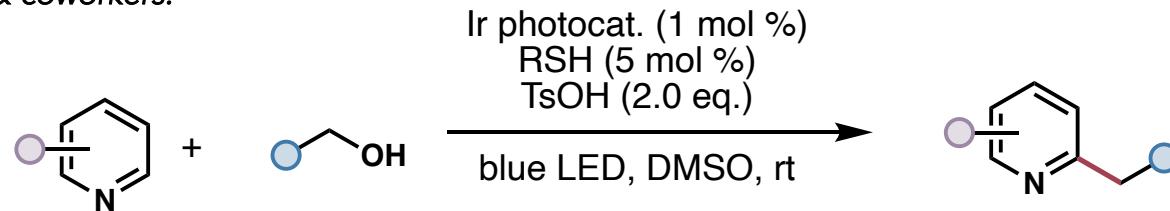
Reductive Functionalization of Ketoepoxides & Ketoaziridines



Alkylation Reactions

Alkylation of heteroarenes

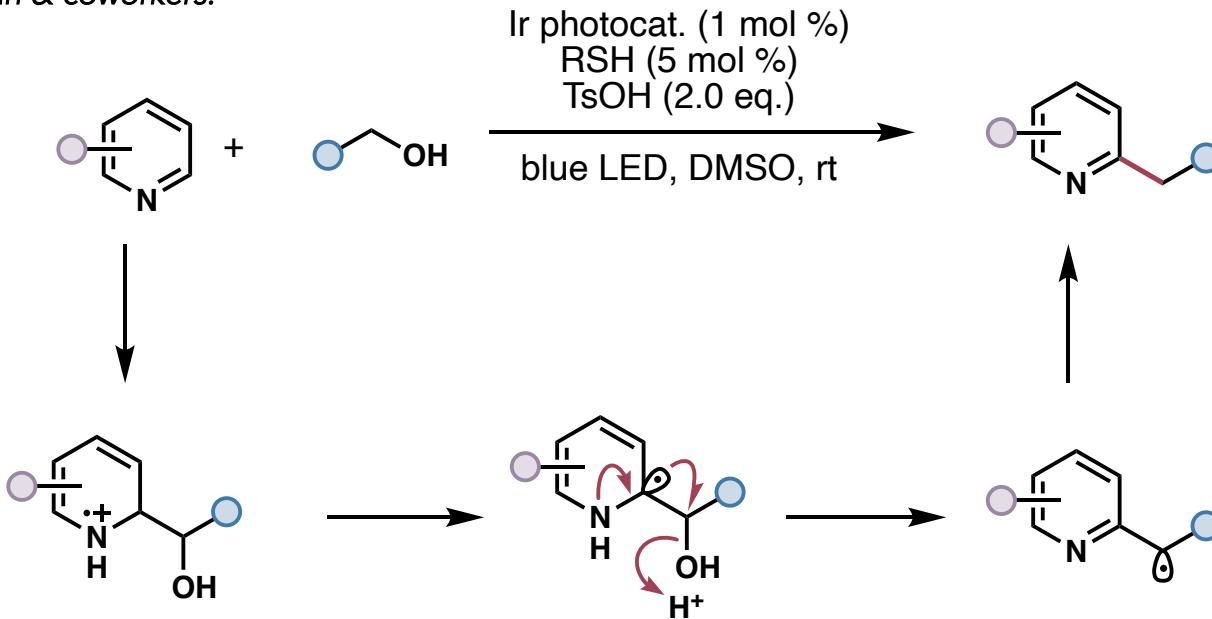
MacMillan & coworkers:



Alkylation Reactions

Alkylation of heteroarenes

MacMillan & coworkers:



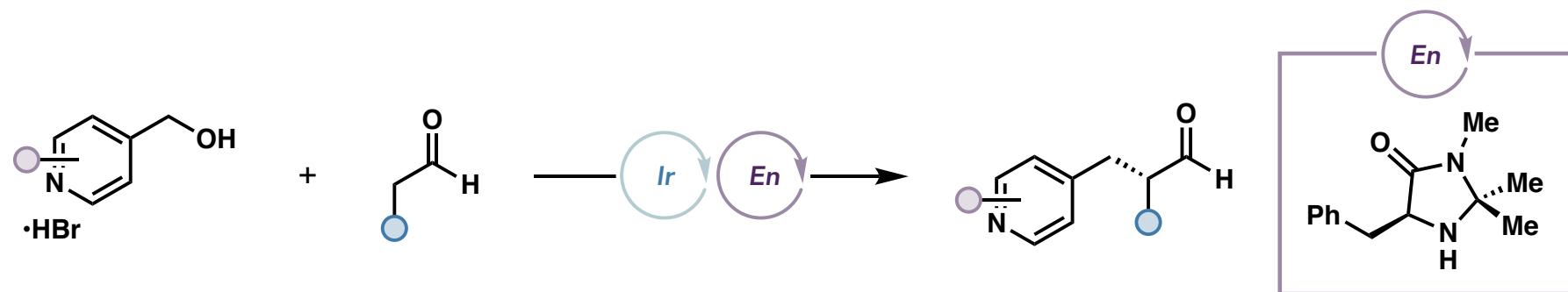
For a related transformation using LiBr as an HAT mediator, see:

Wang, Z.; Ji, X.; Han, T.; Deng, G.-J.; Huang, H. *Adv. Synth. Catal.* 2019, 361, 5643.

Alkylation Reactions

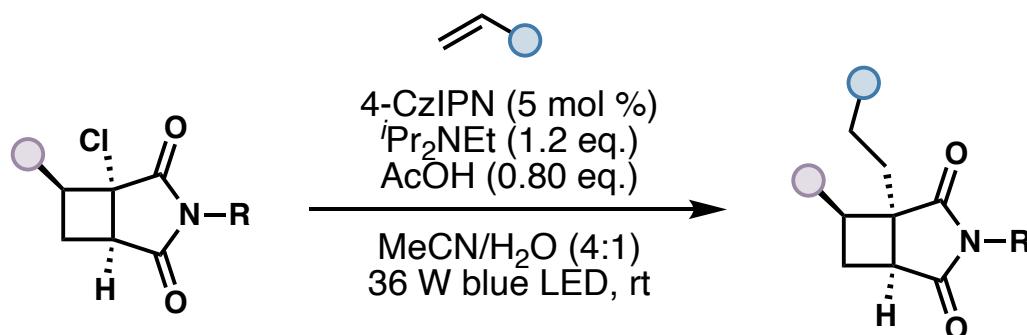
Alkylation of heteroarenes

MacMillan & coworkers:



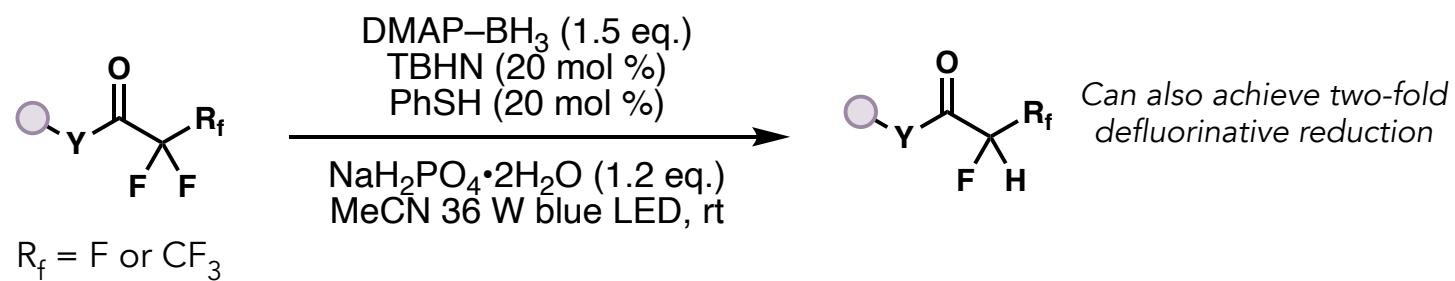
C–X Bond Activation

Noble, Booker-Millburn, & Aggarwal:



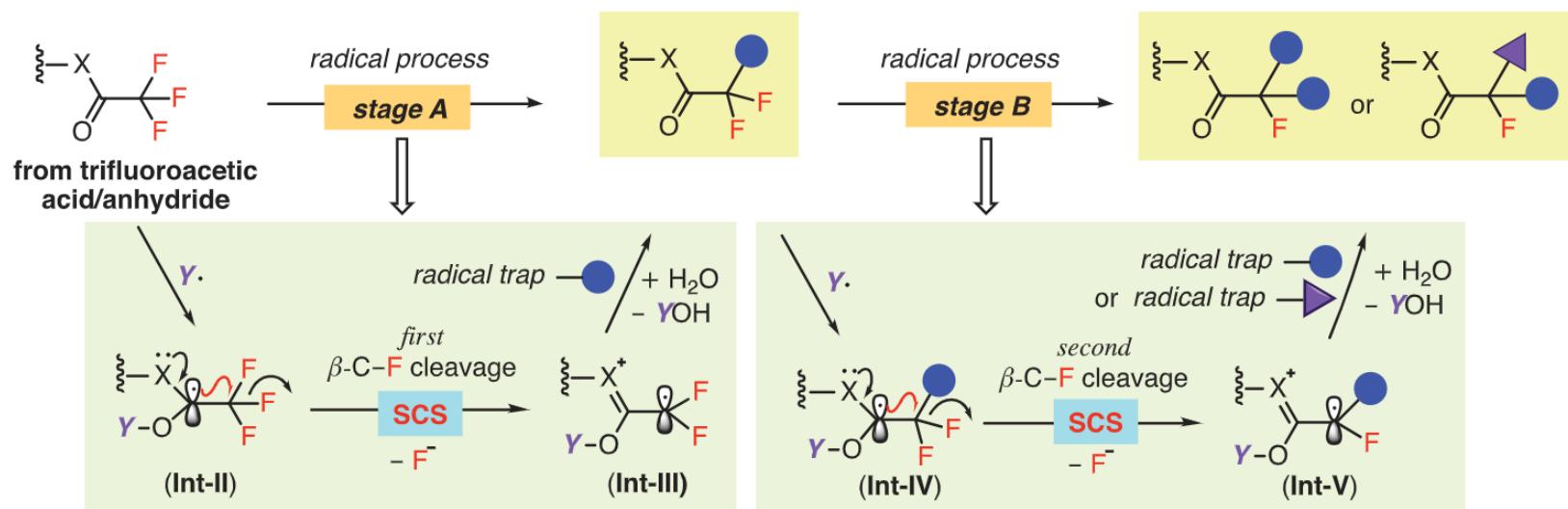
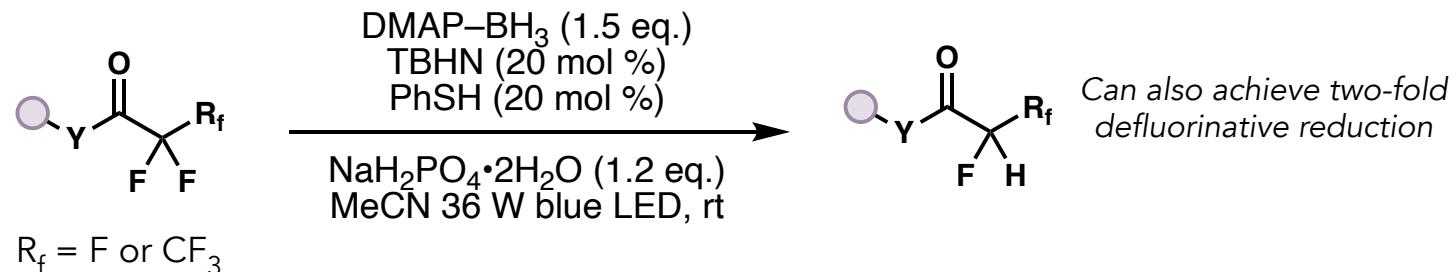
C–X Bond Activation

Houk & Wang's C–F activation:



C–X Bond Activation

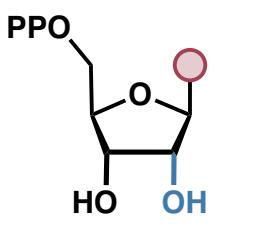
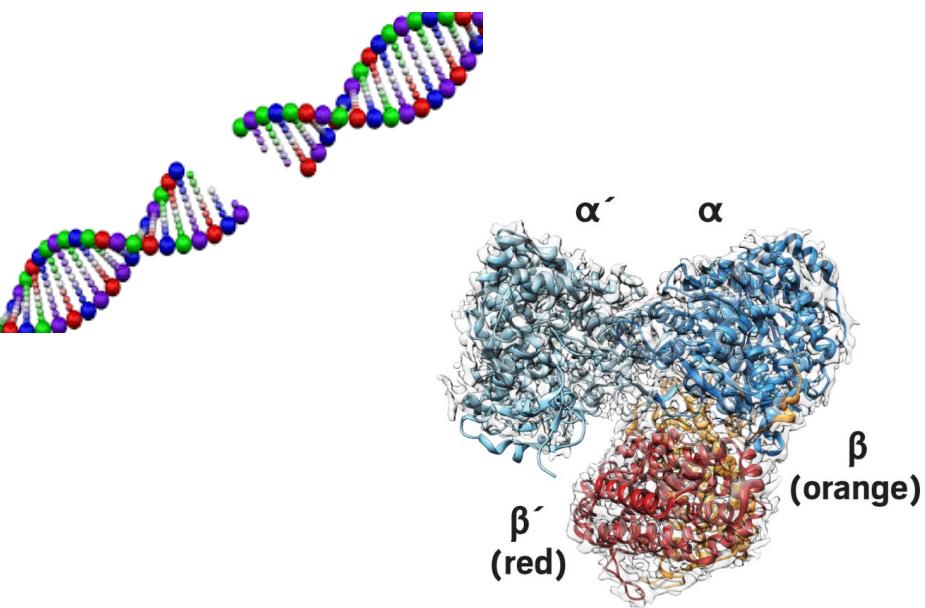
Houk & Wang's C–F activation:



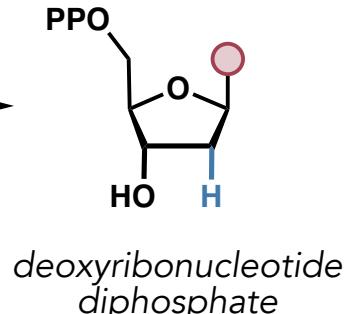
C–F bond reduction and alkylation

Spin-Center Shift (SCS)

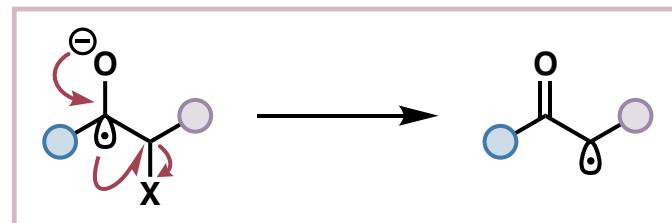
Biochemical Processes



ribonucleotide diphosphate



Synthetic Applications



C-X bond activation

