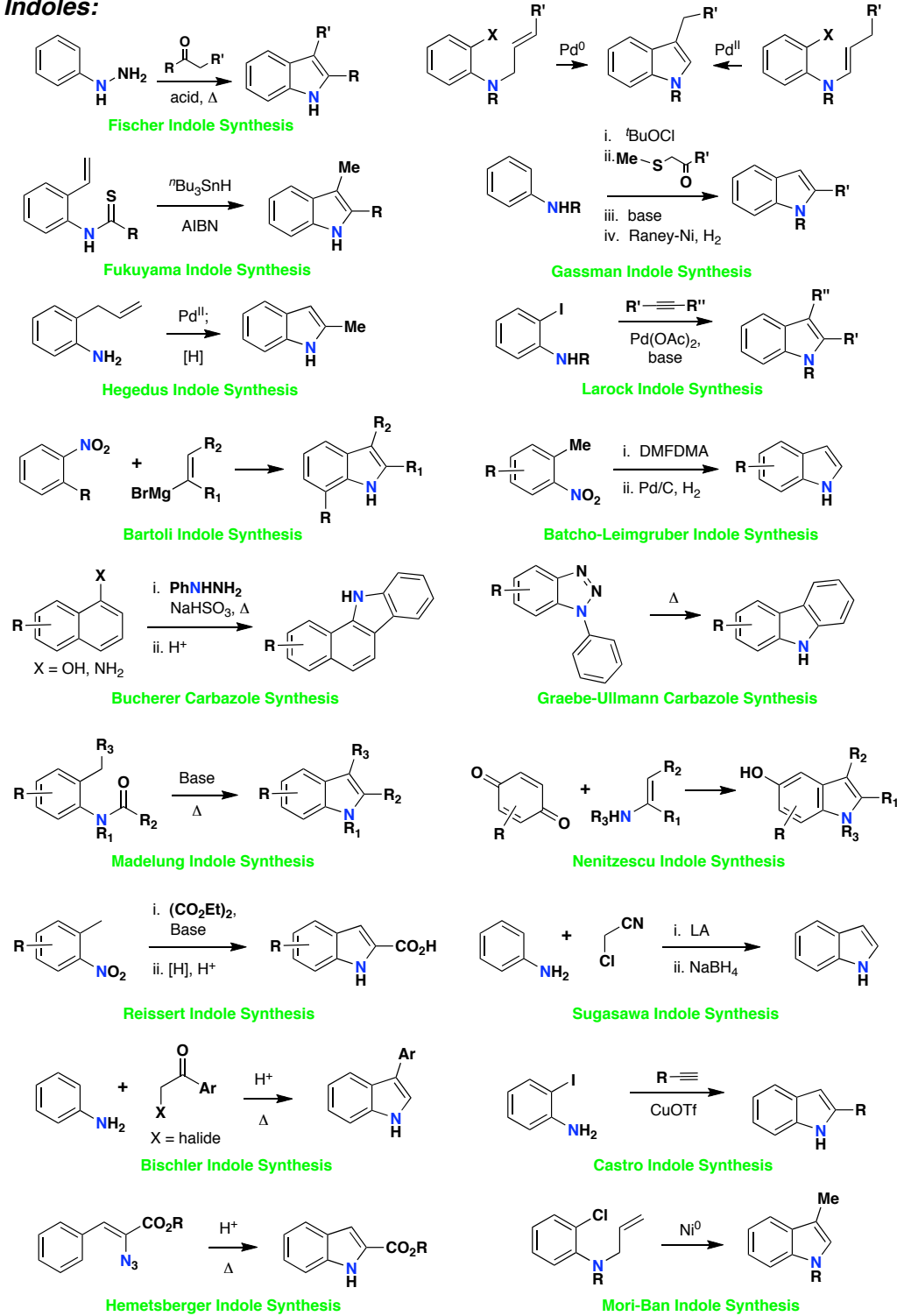
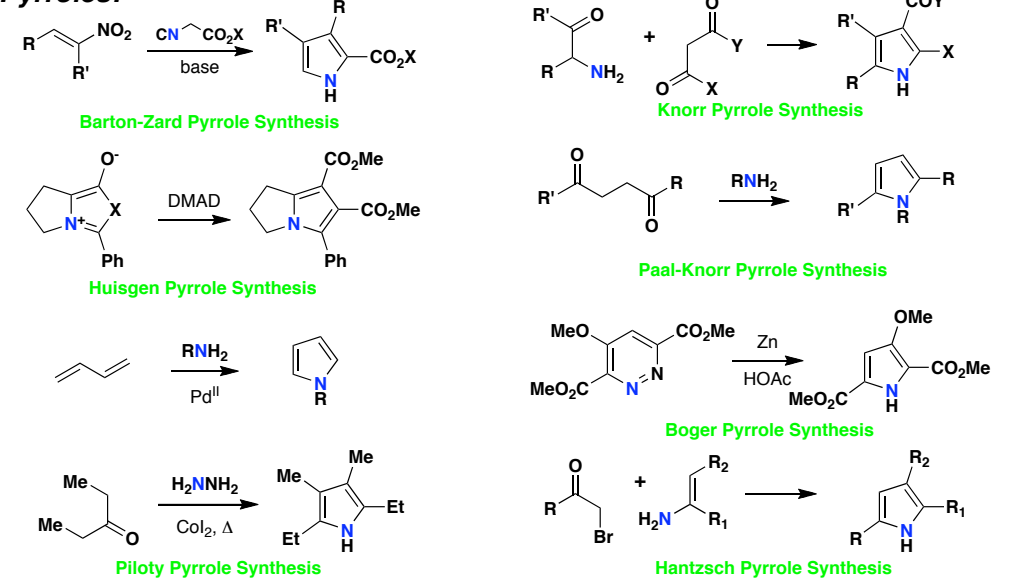


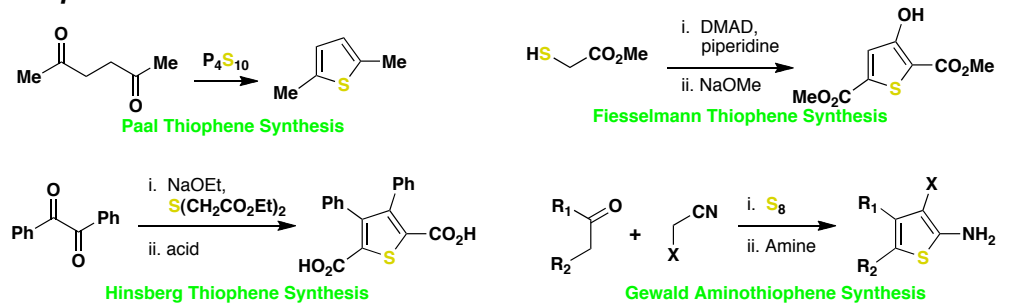
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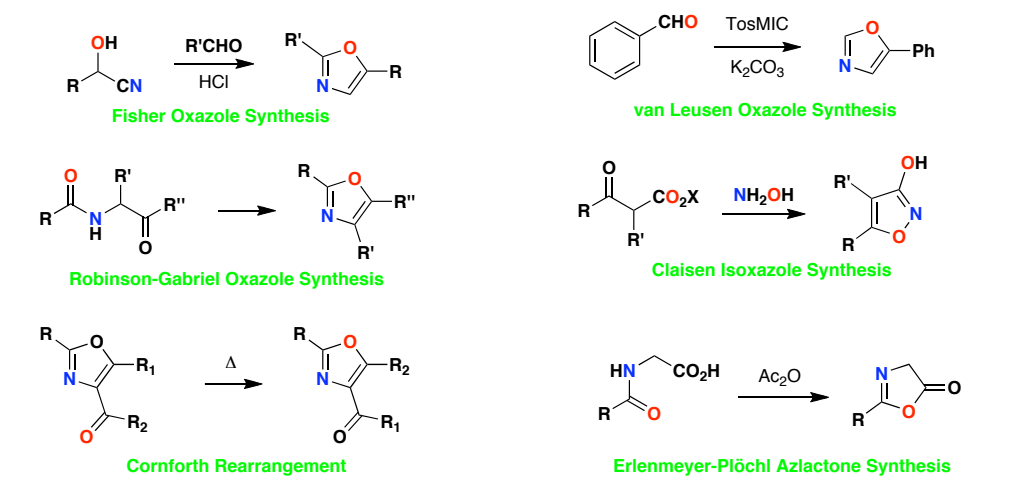
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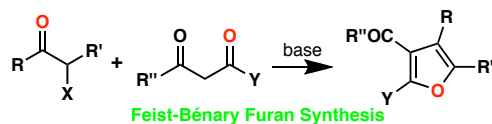
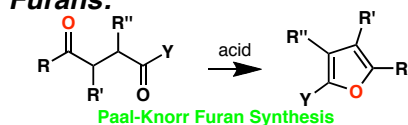
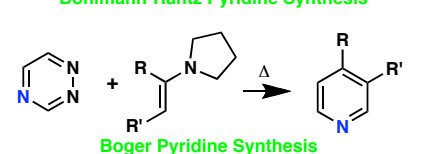
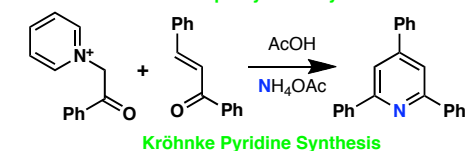
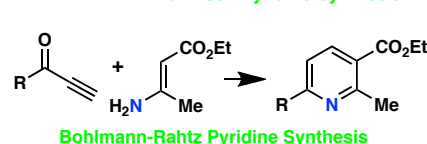
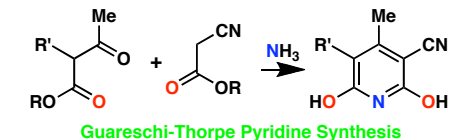
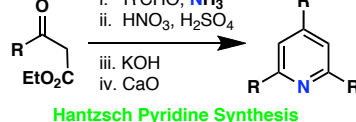
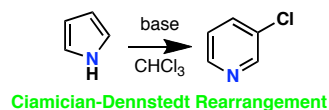
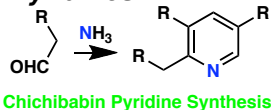
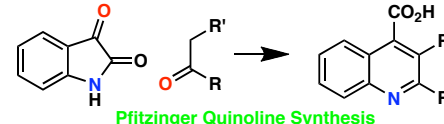
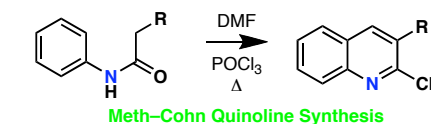
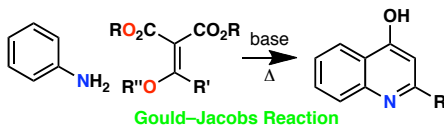
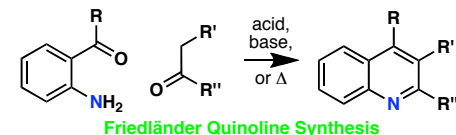
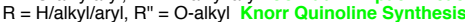
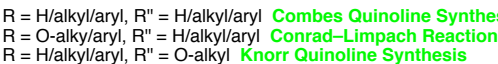
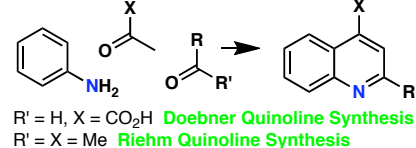
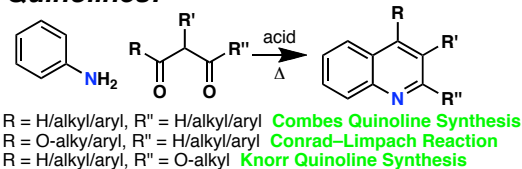
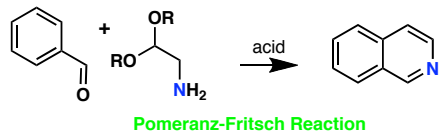
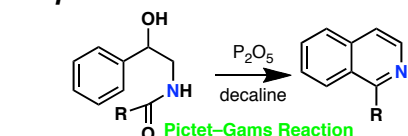
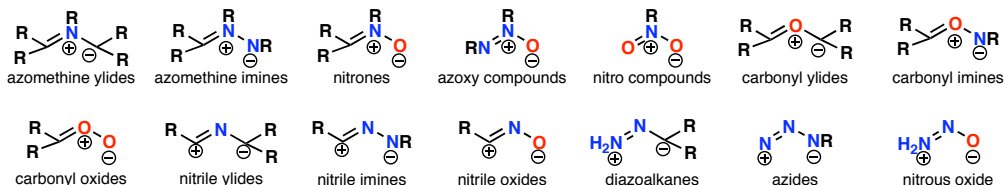
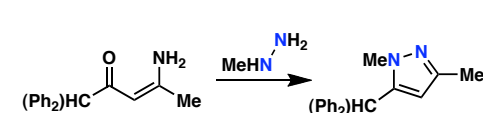
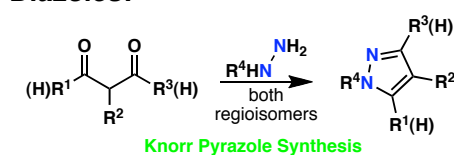
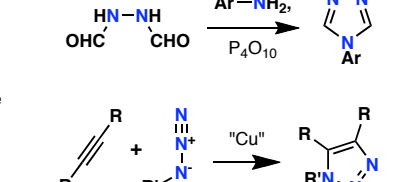
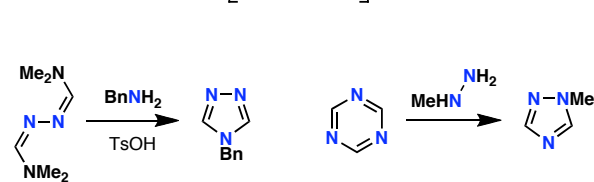
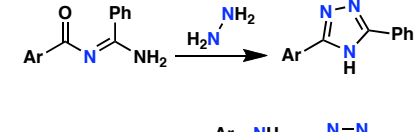
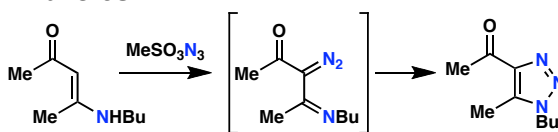
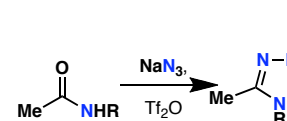
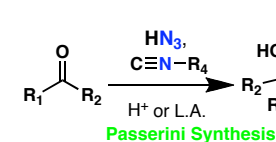
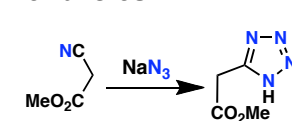
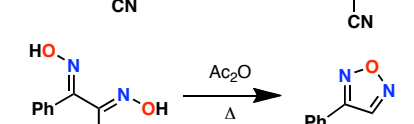
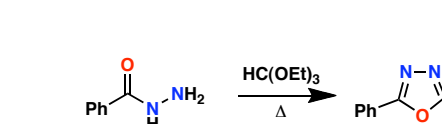
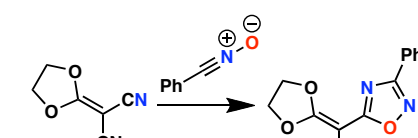
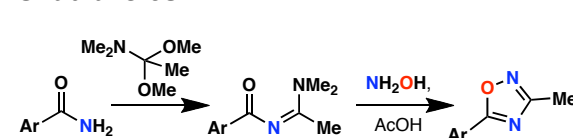
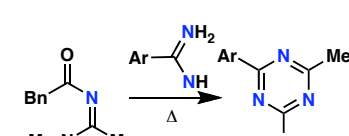
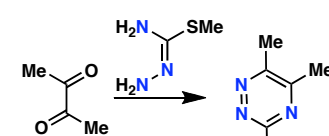
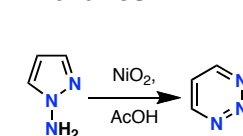
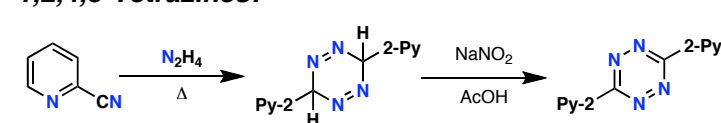


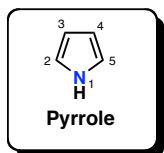
Thiophenes:



Oxazoles and Isoxazoles:



Furans:**Pyridines:****Quinolines:****Isoquinolines:****Useful 1,3-dipoles:****Diazoles:****Triazoles:****Tetrazoles:****Oxadiazoles:****Triazanes:****1,2,4,5-Tetrazines:**

**NMR Spectral Parameters****¹H (CDCl₃) ppm**

H-3, H-4: 6.22

H-2, H-5: 6.68

¹³C (CDCl₃)

C-3, C-4: 109.2

C-2, C-5: 117.3

H-H Coupling Constants (Hz) $J_{2,3}$ 2.660 $J_{3,4}$ 3.359 $J_{2,4}$ 1.491 $J_{1,2}$ 2.579 $J_{2,5}$ 1.845 $J_{1,3}$ 2.458**C-H Coupling Constants (Hz)** J_{C2-H} 183.28 J_{C3-H} 168.80**Structural Properties**

(Determined by microwave spectra)

Bond Lengths (Å)

N-C2: 1.370 NH: 0.996

C2-C3: 1.382 C2-H: 1.076

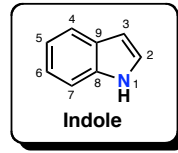
C3-C4: 1.417 C3-H: 1.077

Bond Angles

C2-N-C5: 109.8 N-C2-H2: 121.5

N-C2-C3: 107.7 C2-C3-C4: 125.5

C2-C3-C4: 107.4

**NMR Spectral Parameters****¹H (CDCl₃) ppm**

H-1: 7.74 H-4: 7.64 H-7: 7.24

H-2: 7.00 H-5: 7.12

H-3: 6.51 H-6: 7.18

¹³C (CDCl₃)

C-2: 124.2 C-4: 120.7 C-7: 111.1

C-3: 102.4 C-5: 119.8 C-8: 135.7

C-9: 127.8 C-6: 121.9

H-H Coupling Constants (Hz) $J_{1,2}$ 2.5 $J_{2,3}$ 3.1 $J_{4,6}$ 1.2 $J_{5,7}$ 1.3 $J_{1,3}$ 2.0 $J_{3,7}$ 0.7 $J_{4,7}$ 0.9 $J_{6,7}$ 8.1 $J_{1,4}$ 2.8 $J_{4,5}$ 7.8 $J_{5,6}$ 7.1**Structural Properties**

(x-ray of 1,3,5-trinitrobenzene complex of 3-methylindole)

Bond Lengths (Å)

N1-C2: 1.4 C4-C5: 1.37 C7-C8: 1.40

C2-C3: 1.34 C5-C6: 1.42 C8-N1: 1.38

C3-C8: 1.49 C6-C7: 1.39 C8-C9: 1.39

C8-C4: 1.37

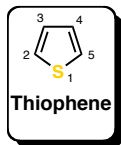
Bond Angles

C8-N1-C2: 108 C8-C9-C4: 123 C6-C7-C8: 115

N1-C2-C3: 111 C9-C4-C5: 116 C7-C8-C9: 122

C2-C3-C9: 106 C4-C5-C6: 122 C9-C8-N1: 109

C3-C9-C8: 106 C5-C6-C7: 121

**NMR Spectral Parameters****¹H (C₆D₁₂) ppm**

H-3, H-4: 6.96

H-2, H-5: 7.20

¹³C (acetone-*d*₆)

C-3, C-4: 127.3

C-2, C-5: 125.6

H-H Coupling Constants (Hz) $J_{2,3}$ 4.9-5.8 $J_{3,4}$ 3.45-4.35 $J_{2,4}$ 1.25-1.7 $J_{2,5}$ 3.2-3.65**C-H Coupling Constants (Hz)** J_{C2-H} 185 J_{C3-H} 168**Structural Properties**

(Determined by gas-phase microwave spectra)

Bond Lengths (Å)

S-C2: 1.714

C2-C3: 1.369

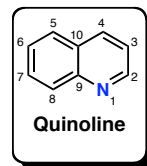
C3-C4: 1.423

Bond Angles

C2-S-C5: 92

S-C2-C3: 111

C2-C3-C4: 112

**NMR Spectral Parameters****¹H (CCl₄) ppm**

H-2: 8.82 H-5: 7.73 H-8: 8.05

H-3: 7.31 H-6: 7.46

H-4: 8.05 H-7: 7.65

¹³C (CDCl₃) ppm

C-2: 150.32 C-10: 128.32 C-7: 129.40

C-3: 121.01 C-5: 127.72 C-8: 129.40

C-4: 135.93 C-6: 126.46 C-9: 148.34

H-H Coupling Constants (Hz) $J_{2,3}$ 4.18 $J_{4,8}$ 0.75 $J_{5,8}$ 0.69 $J_{7,8}$ 8.57 $J_{2,4}$ 1.76 $J_{5,6}$ 8.24 $J_{6,7}$ 6.88 $J_{3,4}$ 8.19 $J_{5,7}$ 1.47 $J_{6,8}$ 1.25**C-H Coupling Constants (Hz)**

C-2: 178 C-4: 162 C-6: 161 C-8: 161

C-3: 165 C-5: 160 C-7: 162

Structural Properties(x-ray of NiS₂PEt₂ complex with quinoline)**Bond Lengths (Å)**

N1-C2: 1.33 C10-5: 1.45 C8-C9: 1.39

C2-C3: 1.44 C5-C6: 1.35 C9-N1: 1.38

C3-C4: 1.38 C6-C7: 1.41 C9-C10: 1.43

C4-C10: 1.39 C7-C8: 1.36

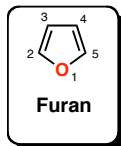
Bond Angles

C9-N1-C2: 119.1 C10-C5-C6: 120.5 C10-C7-N1: 120.5

N1-C2-C3: 121.1 C5-C6-C7: 120.1 C10-C9-C8: 119.7

C2-C3-C4: 120.4 C6-C7-C8: 120.9 C4-C10-C9: 119.1

C3-C4-C10: 119.6 C7-C8-C9: 121.0 C5-C10-C9: 117.7

**NMR Spectral Parameters****¹H (CDCl₃) ppm**

H-3, H-4: 6.24

H-2, H-5: 7.29

¹³C (acetone-*d*₆)

C-3, C-4: 110.4

C-2, C-5: 143.6

H-H Coupling Constants (Hz) $J_{2,3}$ 1.75 $J_{3,4}$ 3.3 $J_{2,4}$ 0.85 $J_{2,5}$ 1.4**C-H Coupling Constants (Hz)** J_{C2-H} 201 J_{C3-H} 175**Structural Properties**

(Determined by microwave spectra)

Bond Lengths (Å)

O-C2: 1.362

C2-C3: 1.361

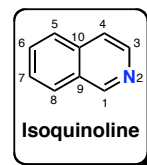
C3-C4: 1.430

Bond Angles

C2-O-C5: 106.50 O-C2-H2 115.93

O-C2-C3: 110.65 C2-C3-H3 127.83

C2-C3-C4: 106.07

**NMR Spectral Parameters****¹H (CCl₄) ppm**

H-1: 9.11 H-5: 7.70 H-8: 7.85

H-3: 8.45 H-6: 7.56

H-4: 7.50 H-7: 7.58

¹³C (CDCl₃) ppm

C-1: 152.6 C-5: 126.4 C-8: 127.5

C-3: 143.1 C-6: 130.2 C-9: 128.7

C-4: 120.4 C-7: 127.2 C-10: 135.7

H-H Coupling Constants (Hz) $J_{1,4}$ 1.0 $J_{4,5}$ -0.36 $J_{5,8}$ 0.80 $J_{7,8}$ 8.27 $J_{3,4}$ 5.75 $J_{5,6}$ 8.29 $J_{6,7}$ 6.92 $J_{3,7}$ 0.3 $J_{5,7}$ 1.17 $J_{6,8}$ 1.21**C-H Coupling Constants (Hz)**

C-1: 178 C-4: 161 C-6: 161 C-8: 161

C-3: 178 C-5: 161 C-7: 163

Structural Properties

(x-ray of C1-hydroxymethylphenyl derivative of isoquinoline)

Bond Lengths (Å)

C1-N2: 1.318 C10-5: 1.417 C8-C9: 1.414

N2-C3: 1.373 C5-C6: 1.360 C9-C1: 1.426

C3-C4: 1.349 C6-C7: 1.399 C9-C10: 1.416

C4-C10: 1.414 C7-C8: 1.364

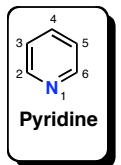
Bond Angles

C9-C1-N2: 123.2 C4-C10-C9: 117.8

C1-N2-C3: 117.8 C4-C9-C1: 117.8

N2-C3-C4: 123.9

C3-C4-C10: 119.5

**NMR Spectral Parameters****¹H (CDCl₃) ppm**

H-3: 7.25

H-4: 7.64

H-2: 8.60

¹³C (CDCl₃)

C-3: 123.46

C-4: 135.58

C-2: 149.59

H-H Coupling Constants (Hz) $J_{2,3}$ 4.93 $J_{2,6}$ -0.03 $J_{2,4}$ 1.80 $J_{3,5}$ 1.44 $J_{2,5}$ 1.00 $J_{3,4}$ 7.66**C-H Coupling Constants (Hz)** J_{C2-H} 179 J_{C3-H} 163 J_{C4-H} 152**Structural Properties**

(Determined by microwave and electron diffraction spectra)

Bond Lengths (Å)

N-C2: 1.338

C2-C3: 1.394

C3-C4: 1.392

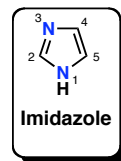
Bond Angles

C6-N-C5: 116.9

N-C2-C3: 123.8

C2-C3-C4: 118.5

C3-C4-C5: 118.4

**NMR Spectral Parameters****¹H (D₂O) ppm**

H-4, H-5: 7.14

H-2: 7.73

¹³C (D₂O) ppm

C-4, C-5: 122.3

C-2: 136.2

H-H Coupling Constants (Hz)**C-H Coupling Constants (Hz)****Structural Properties**

(Determined by X-Ray)

Bond Lengths (Å)

N1-C2: 1.349

C2-N3: 1.326

N3-C4: 1.378

C4-C5: 1.358

C5-N1: 1.369

Bond Angles

C2-N1-C5: 107.2

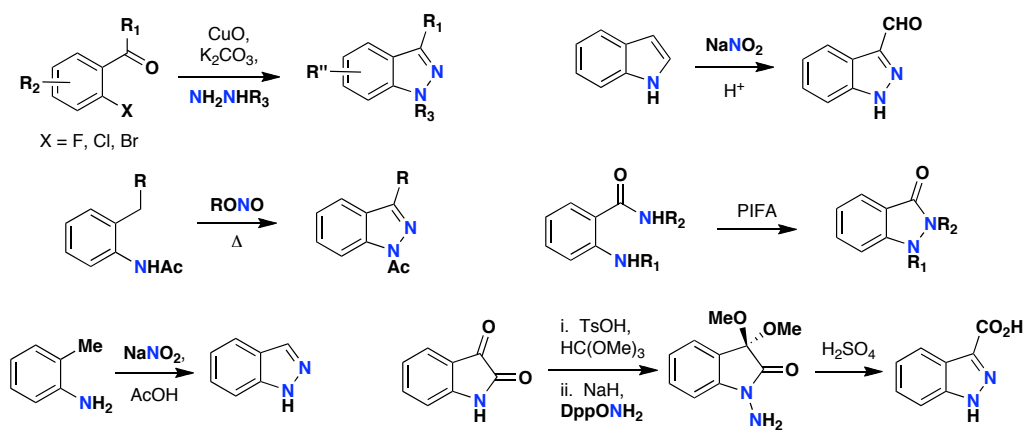
N1-C2-N3: 111.3

C2-N3-C4: 105.4

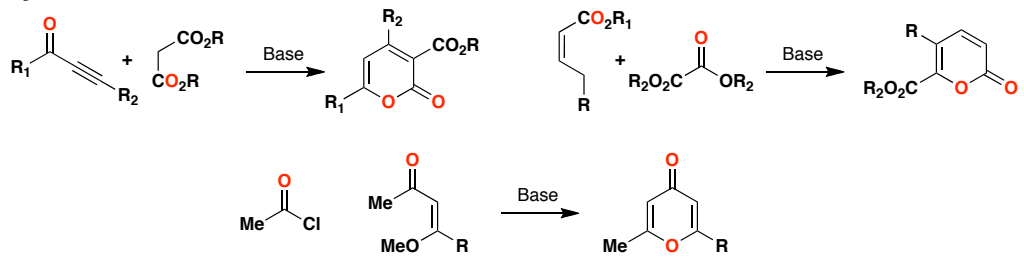
N3-C4-C5: 109.8

C4-C5-N1: 106.3

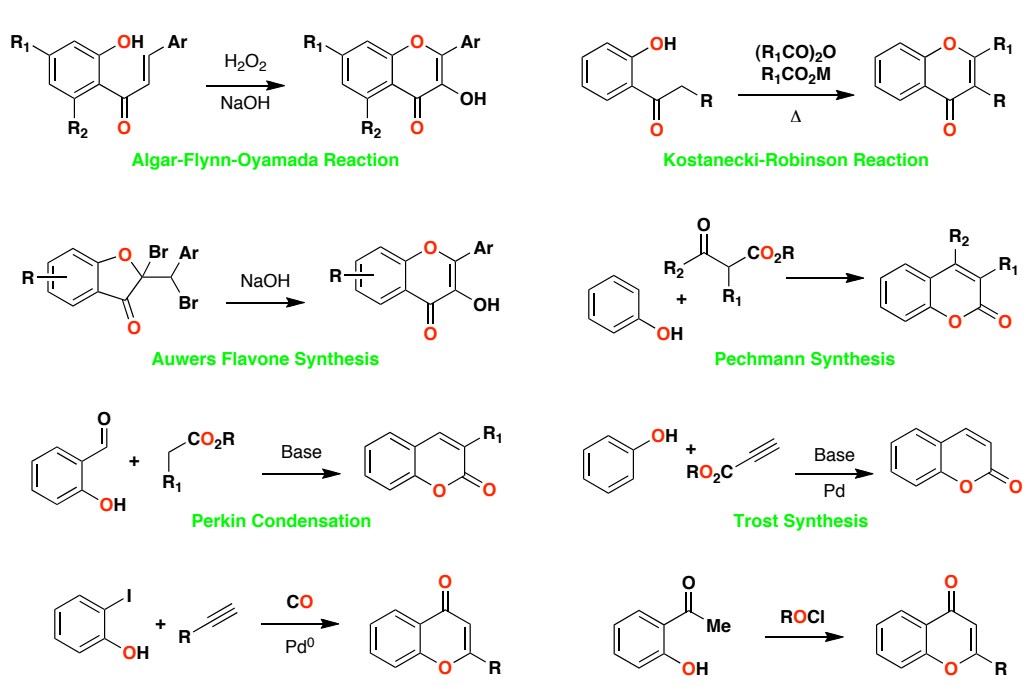
Indazoles:



Pyrones:



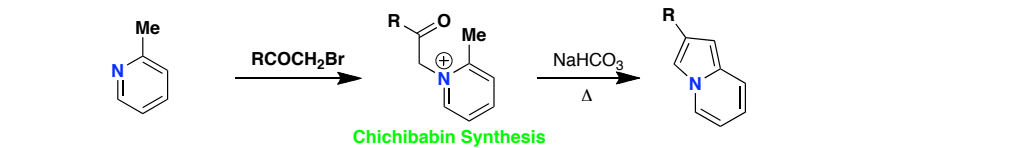
Chromanones and Coumarins:



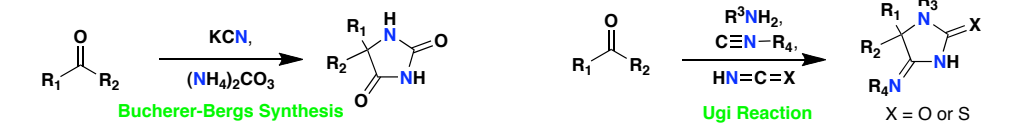
Purines:



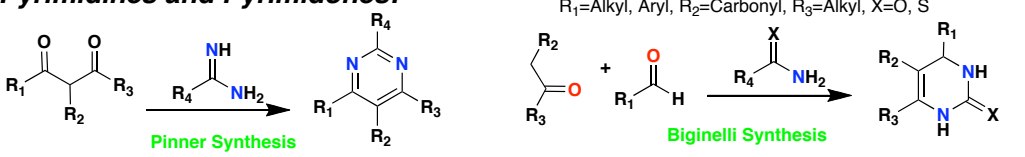
Indolizidines:



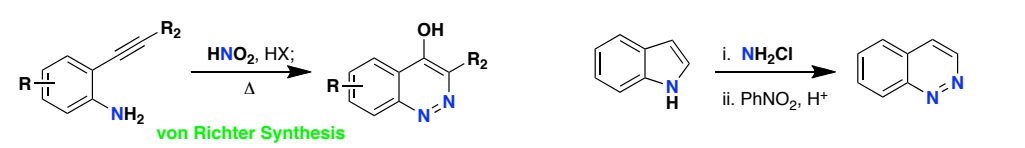
Hydantoins:



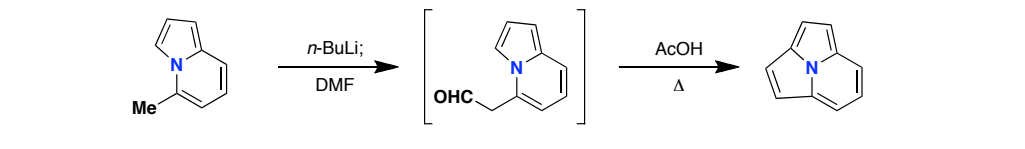
Pyrimidines and Pyrimidones:



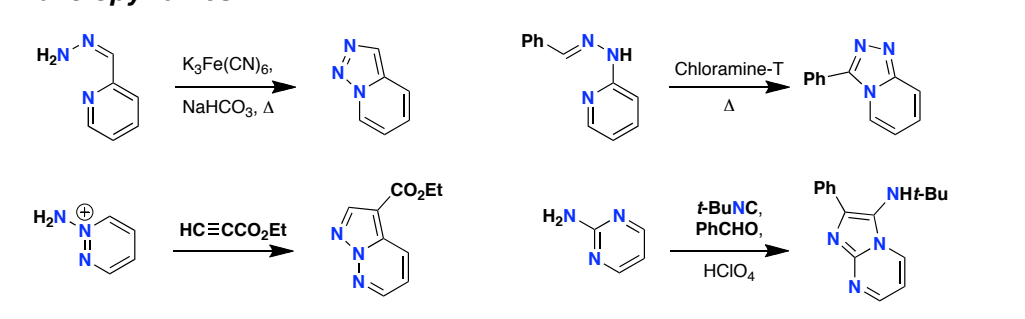
Cinnolines:



Cyclazines:



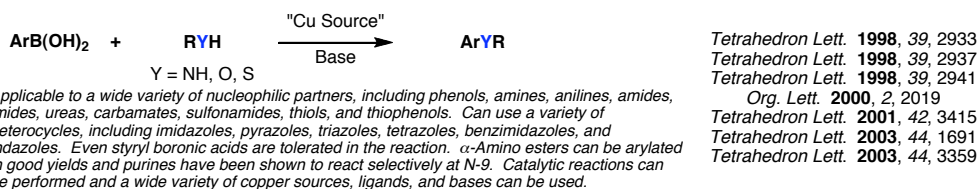
Triazolopyridines:



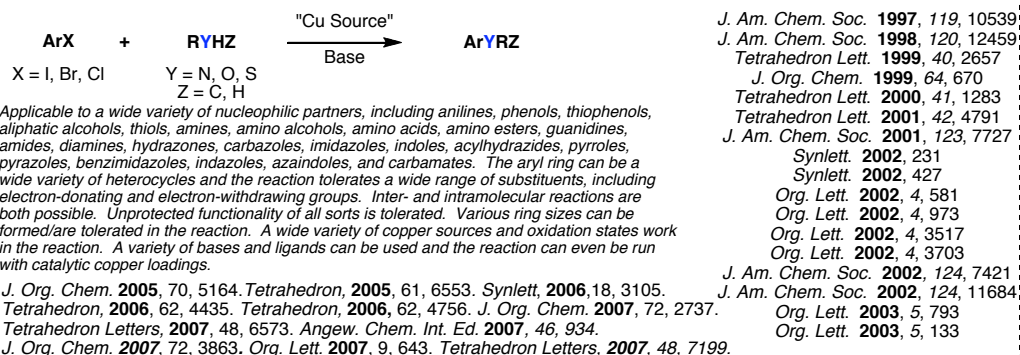
Useful Methods of Forming Aryl C–N and C–O Bonds:



Electron-donating and electron-withdrawing functional groups are tolerated on both coupling partners.



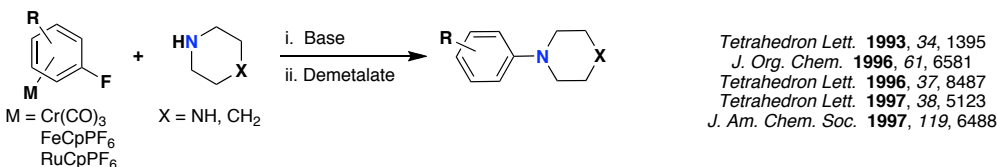
A wide variety of boronic acids are tolerated and hydrazinolysis reveals the O-arylhydroxylamine. Requires two equivalents of the boronic acid.



Applicable to a wide variety of aryl stannanes. Nucleophilic partners include amines, anilines, indazoles, benzimidazolones, pyridones, and aryl amides.



Various nucleophilic partners can be used, specifically alkoxides, silyloxides, anilines, and amines. A variety of electron-withdrawing and electron-donating groups are tolerated on the aromatic ring.

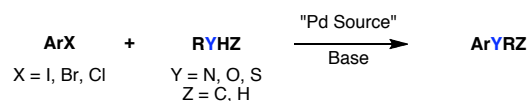


For chromium: will tolerate electron-donating groups on the aromatic ring and a variety (lack of) protecting groups on the piperazine. For iron: a range of amine nucleophiles can be used and some substitution on the aromatic ring is tolerable.



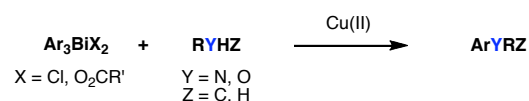
Ammonia, primary, and secondary amines can be used. Gives regioisomeric product mixtures if unsymmetrical.

Useful Methods of Forming Aryl C–N and C–O Bonds:



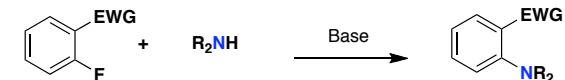
Applicable to a wide variety of nucleophilic partners, including amines, amides, silyloxides, sulfonamides, anilines, carbamates, ureas, alkoxides, vinylogous amides, phenoxides, cyclopropylamines, tert-butylcarbamates, sulfoximes, hydrazines, hydrazones, and imines. Various heterocycles can be N-arylated including indole, pyrrole, imidazole, carbazole, benzotriazole, and phenoxazole. A variety of aryl donors are tolerated, including electron-rich, electron-poor, hindered, unhindered, and heterocyclic. A tropone has even been aminated using this procedure. Five and six (not seven) membered heterocycles can routinely be formed via intramolecular cyclizations.

Tetrahedron Lett. **1995**, 36, 3609
Angew. Chem. Int. Ed. **1995**, 34, 1348
J. Org. Chem. **1996**, 61, 1133
J. Am. Chem. Soc. **1996**, 118, 7215, 7217
J. Org. Chem. **1996**, 61, 7240
Tetrahedron **1996**, 52, 7525
J. Org. Chem. **1997**, 62, 1264, 1268
J. Am. Chem. Soc. **1997**, 119, 3395
J. Org. Chem. **1997**, 62, 5413
Tetrahedron Lett. **1997**, 38, 6367
J. Am. Chem. Soc. **1998**, 120, 827
Tetrahedron Lett. **1998**, 39, 5731
J. Am. Chem. Soc. **1998**, 120, 9722
J. Am. Chem. Soc. **1999**, 121, 3224
Tetrahedron Lett. **1999**, 40, 3543
J. Org. Chem. **1999**, 64, 5575
Org. Lett. **2000**, 2, 219
Tetrahedron, **2001**, 57, 2953
Tetrahedron Lett. **2001**, 42, 4381
Org. Lett. **2000**, 2, 1109



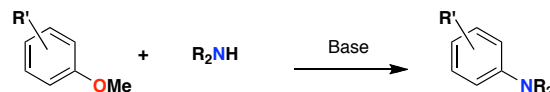
Can use with various substituted aryl groups, however phenyl is the most common. The nucleophilic partner can be an amide, aniline, alcohol, phenol, amine, or hydrazone.

Tetrahedron Lett. **1986**, 27, 3615
Synthesis **1994**, 775
Tetrahedron, **1997**, 53, 4137
Tetrahedron, **1999**, 55, 1341



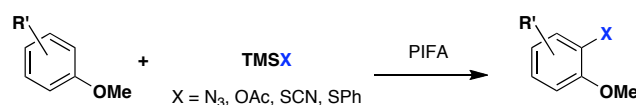
Various amines and electron-withdrawing groups can be used.

Tetrahedron Lett. **1996**, 37, 7343
J. Chem. Soc. Perkin Trans. 1. **1997**, 2229
J. Org. Chem. **1997**, 62, 3874



J. Org. Chem. **1993**, 58, 5101

A variety of amines can undergo the displacement. Electron-withdrawing groups are not required on the aromatic ring.



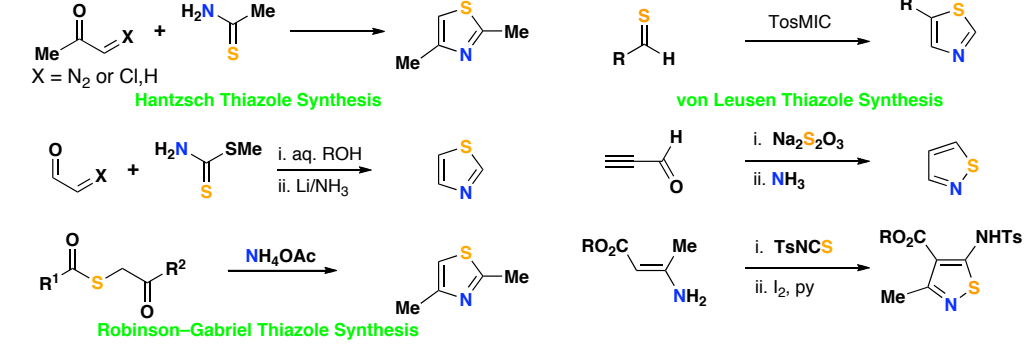
A variety of substitution can be tolerated on the aromatic ring. R can be either alkyl or methoxy. The reaction has even been performed in the absence of methoxy group.

Tetrahedron Lett. **1991**, 32, 4321
J. Am. Chem. Soc. **1994**, 116, 3684
Synlett **1995**, 211
J. Org. Chem. **1995**, 60, 7144
Pure Appl. Chem. **1996**, 68, 627

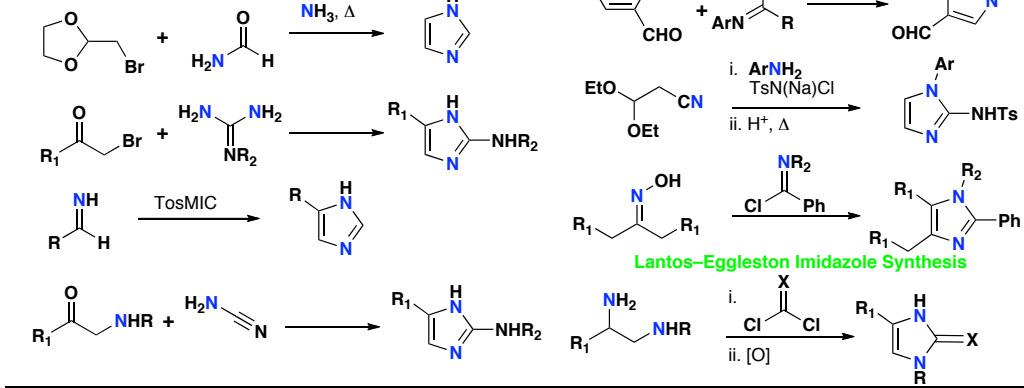
For Reviews on the Subject See:

- Ley, S. V.; Thomas, A. W. "Modern Synthetic Methods for Copper-Mediated C(aryl)–O, C(aryl)–N, and C(aryl)–S Bond Formation" *Angew. Chem. Int. Ed.* **2003**, 42, 5400 – 5449.
- Koser, G. F. "C-Heteroatom-Bond Forming Reactions" *Top. Curr. Chem.* **2003**, 224, 137 – 172.
- Muci, A. R.; Buchwald, S. L. "Practical Palladium Catalysts for C–N and C–O Bond Formation" *Top. Curr. Chem.* **2002**, 219, 131 – 209.
- Hartwig, J. F. "Palladium-Catalyzed Amination of Aryl Halides: Mechanism and Rational Catalyst Design" *Synlett* **1997**, 329 – 340.
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- Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. "Rational Development of Practical Catalysts for Aromatic Carbon–Nitrogen Bond Formation" *Acc. Chem. Res.* **1998**, 31, 805 – 818.
- Hartwig, J. F. "Carbon–Heteroatom Bond-Forming Reductive Eliminations of Amines, Ethers, and Sulfides" *Acc. Chem. Res.* **1998**, 31, 852 – 860.
- Frost, C. G.; Mendonça, P. "Recent developments in aromatic heteroatom coupling reactions" *J. Chem. Soc. Perkin Trans. 1.* **1998**, 2615 – 2623.
- Yang, B. H.; Buchwald, S. L. "Palladium-catalyzed amination of aryl halides and sulfonates" *J. Organometallic Chem.* **1999**, 576, 125 – 146.
- Belfield, A. J.; Brown, G. R.; Foubister, A. J. "Recent Synthetic Advances in the Nucleophilic Amination of Benzenes" *Tetrahedron* **1999**, 55, 11399 – 11428.
- Hartwig, J. F. "Approaches to catalyst discovery. New carbon-heteroatom and carbon-carbon bond formation" *Pure Appl. Chem.* **1999**, 71, 1417 – 1423.
- Prim, D.; Campagnaw, J.-M.; Joseph, D.; Andrioletti, B. "Palladium-catalysed reactions of aryl halides with soft, non-organometallic nucleophiles" *Tetrahedron* **2002**, 58, 2041 – 2075.

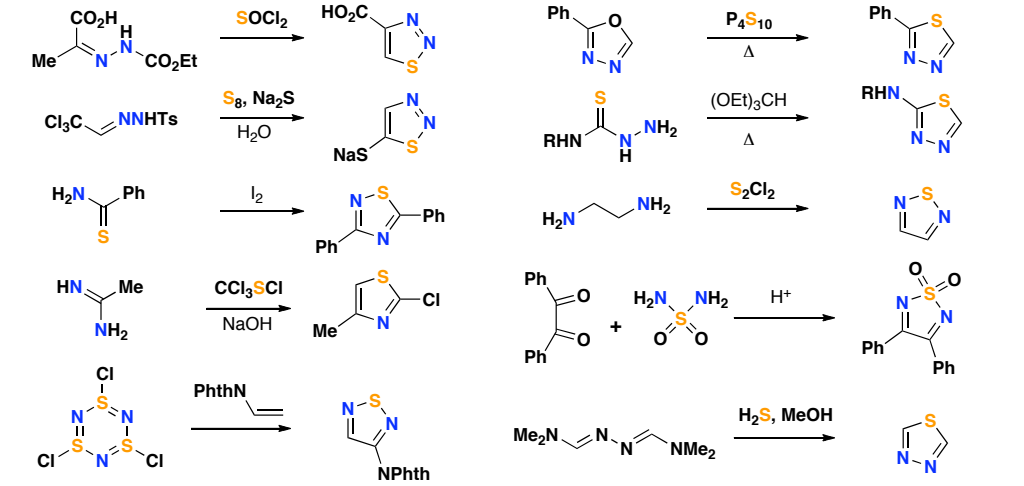
Thiazoles and Isothiazoles:



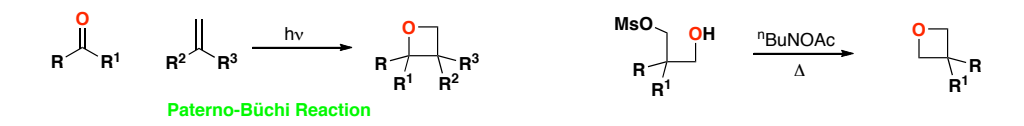
Imidazoles:



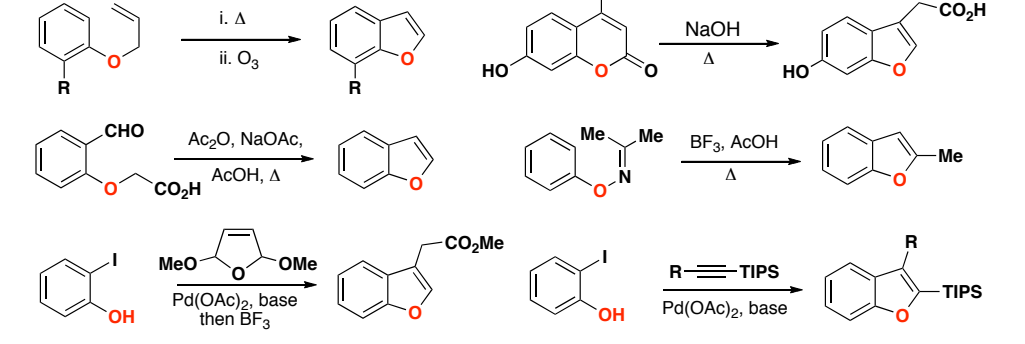
Thiadiazoles:



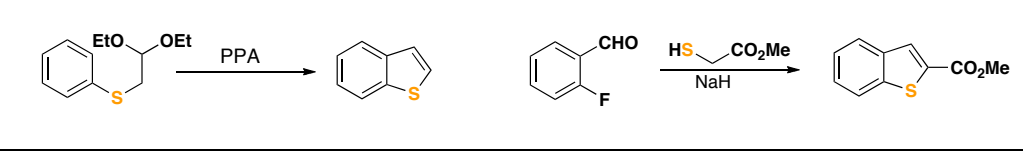
Oxetanes:



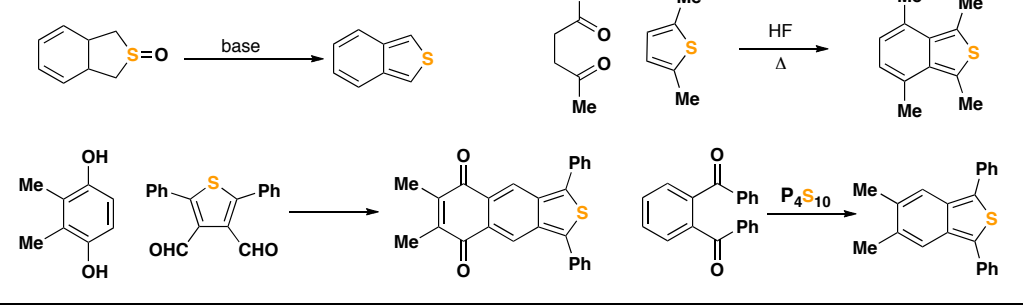
Benzofurans:



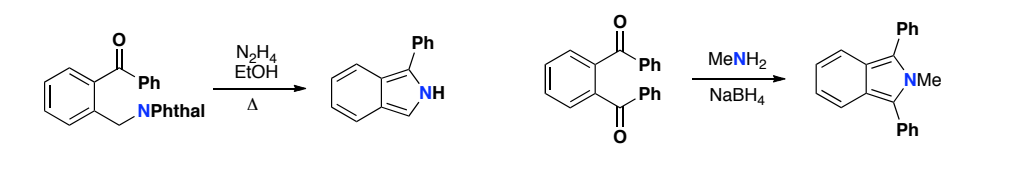
Benzothiophenes:



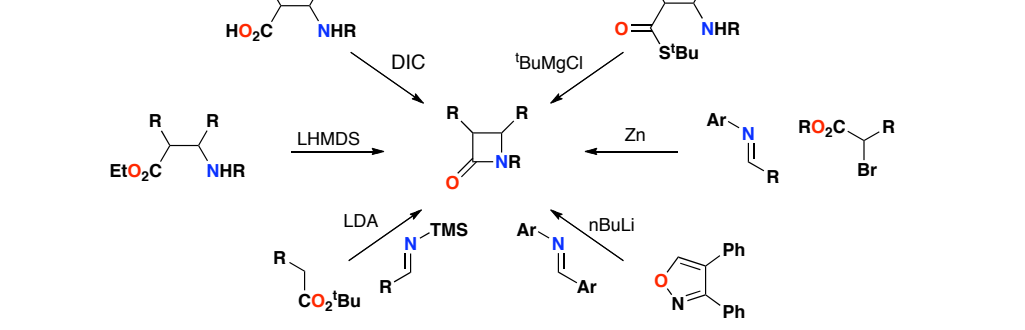
Benzo[c]thiophenes:



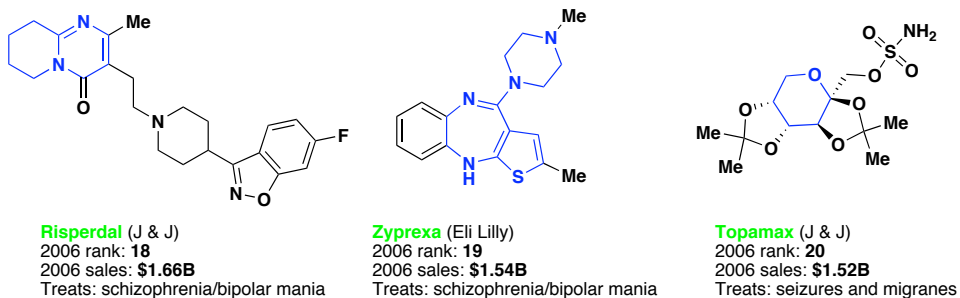
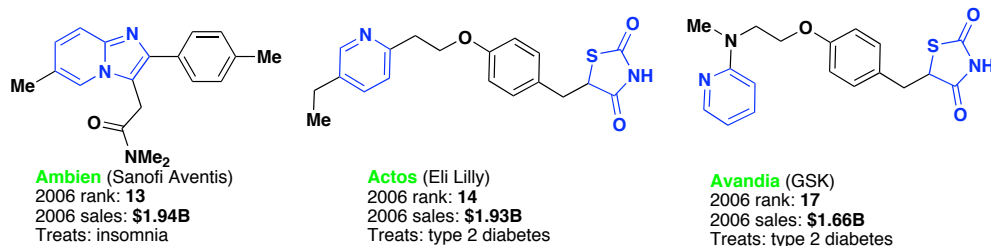
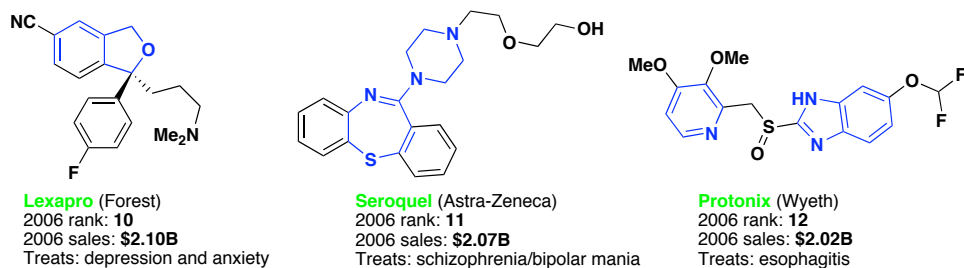
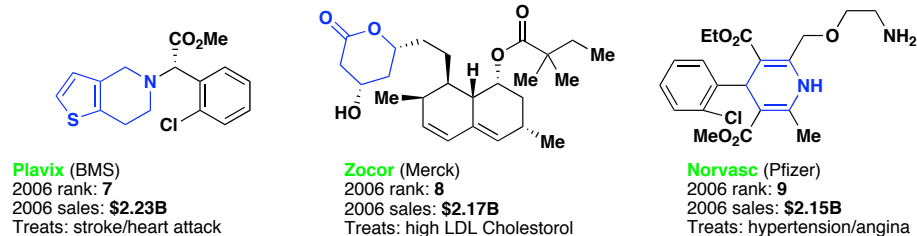
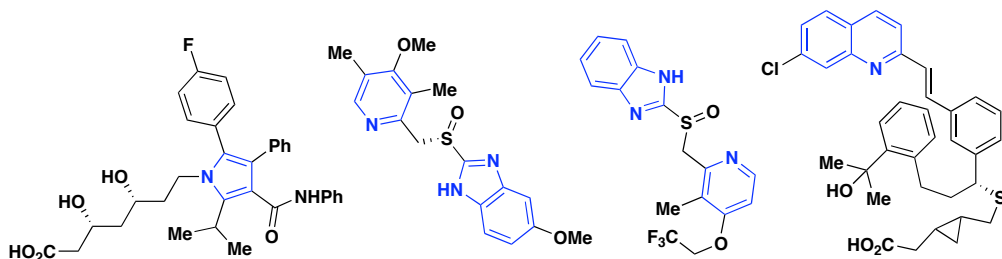
Isoindoles:



Beta-lactams:



Top 15 Brand-Name Pharmaceuticals with Heterocycles:



Top 21 Generic Pharmaceuticals with Heterocycles:

