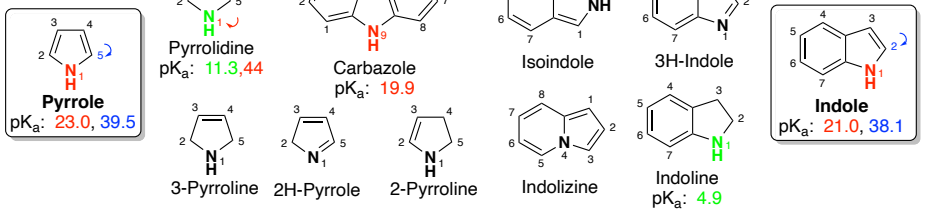
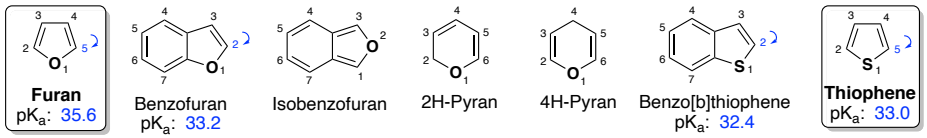
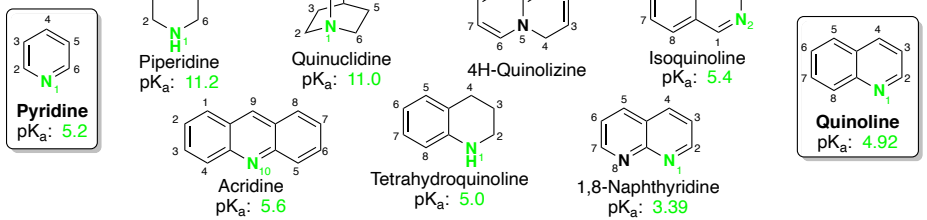
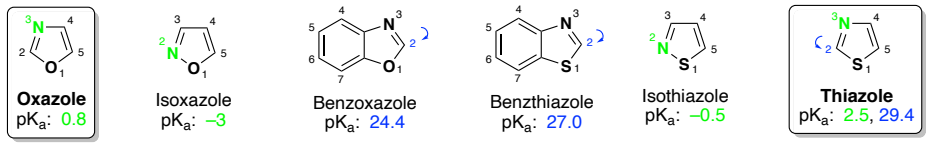
Essentials of Heterocyclic Chemistry-I

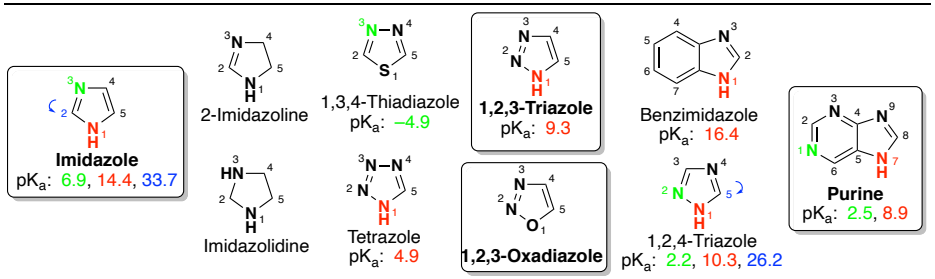
Deprotonation of N–H, Deprotonation of C–H, Deprotonation of Conjugate Acid

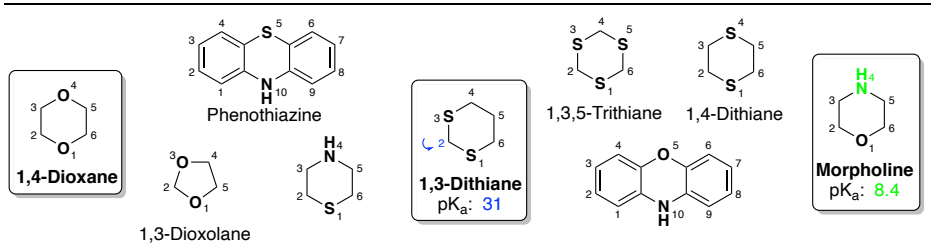


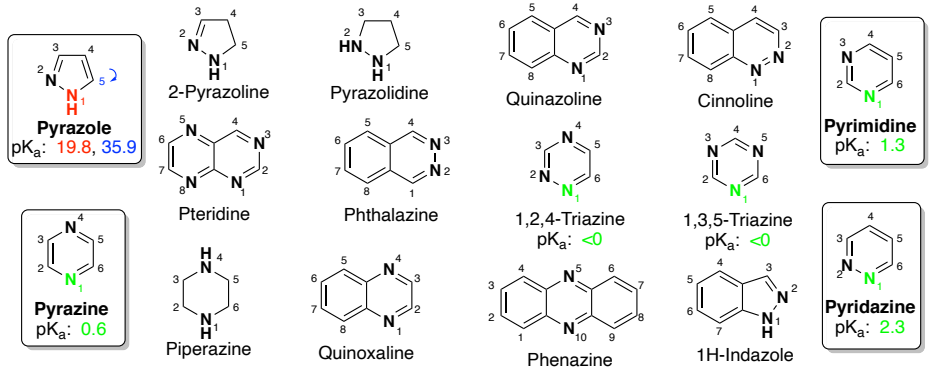










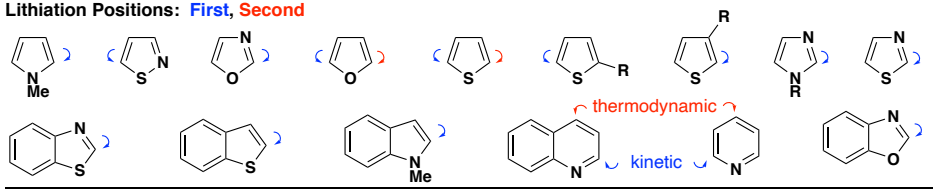


Effects of Substitution on Pyridine Basicity:

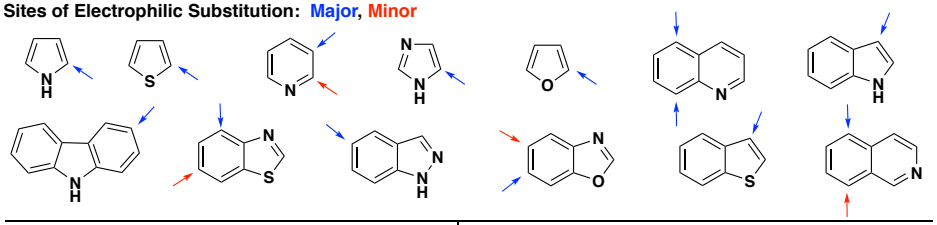


	Me	^{t}Bu	NH_2	NHAc	OMe	SMe	Cl	Ph	vinyl	CN	NO_2	$CH(OH)_2$
2-position	6.0	5.8	6.9	4.1	3.3	3.6	0.7	4.5	4.8	–0.3	–2.6	3.8
3-position	5.7	5.9	6.1	4.5	4.9	4.4	2.8	4.8	4.8	1.4	0.6	3.8
4-position	6.0	6.0	9.2	5.9	6.6	6.0	3.8	5.5	5.5	1.9	1.6	4.7

Lithiation Positions: First, Second



Sites of Electrophilic Substitution: Major, Minor



Lipinski Rule of Five:

Christopher Lipinski (retired from Pfizer) formulated a set of criteria fulfilled in most orally available drugs.

1. No more than **five** hydrogen bond donors.
2. No more than **ten** hydrogen bond acceptors.
3. A molecular weight under **500**.
4. A LogP (partition coefficient) value under **five**.

Heterocyclic Aromaticity Values:

	% (of PhH)	β-value		% (of PhH)	β-value
pyridine	82	0.058	indole		0.047
tetrazole	80		benzothiophene		0.044
pyrazole	61		imidazole	43	0.042
quinoline	61	0.052	pyrrole	37	0.039
isoquinoline		0.051	benzofuran		0.036
pyrazine	75	0.049	thiophene	45	0.032
1,2,5-triazole	71		isoindole		0.029
pyrimidine	67	0.049	furan	12	0.007
pyridazine	65		isobenzofuran		0.002

Medicinal Chemistry Glossary:

ED_{50}: Dose required to yield maximum therapeutic effect in 50% of test animals.

Efficacy: Description of the relative intensity with which agonists vary in the response they produce, even with similar affinity.

Homologue: A compound belonging to a series of compounds differing from each other by a repeating unit (i.e. a CH_2, a peptide residue, etc.).

Intrinsic activity: The maximal stimulatory response induced by a compound relative to that of a given reference comopund.

LD_{50}: Dose required to kill 50% of test animals.

Partition coefficient (LogP): Log_{10} of the ratio of a compound's concentration in 1-octanol vs. water at equilibrium. A LogP<0 means that a compound is more soluble in water than in 1-octanol.

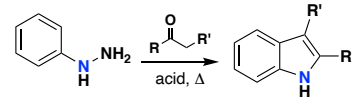
Pharmacophore: The ensemble of steric and electronic features that is necessary to ensure the optimal supramolecular interactions with a specific biological target structure and to trigger (or block) its biological response. This is not a real molecule or moiety, but rather an abstract concept that is considered the largest common denominator shared by a set of active molecules.

Potency: The dose of a drug required to produce a specific effect of given intensity as compared to a standard reference.

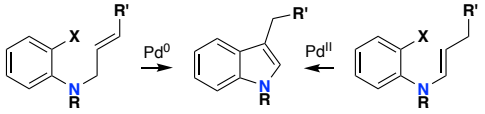
Therapeutic index: LD_{50}/ED_{50}

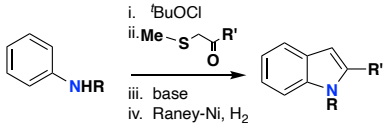
Essentials of Heterocyclic Chemistry-I

Indoles:

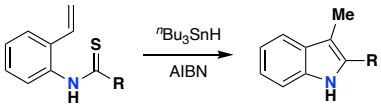


Fischer Indole Synthesis

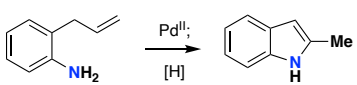




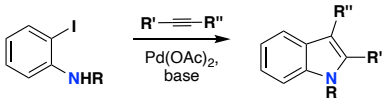
Gassman Indole Synthesis



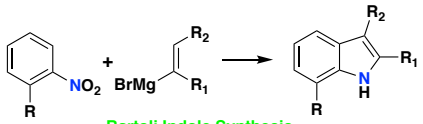
Fukuyama Indole Synthesis



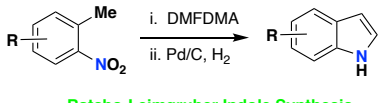
Hegedus Indole Synthesis



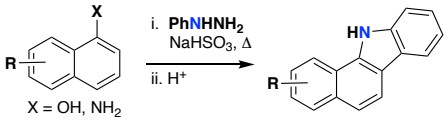
Larock Indole Synthesis



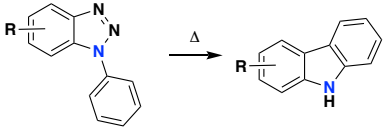
Bartoli Indole Synthesis



Batcho-Leimgruber Indole Synthesis



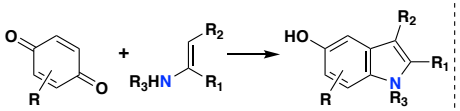
Bucherer Carbazole Synthesis



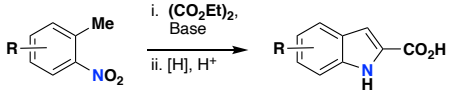
Graebe-Ullmann Carbazole Synthesis



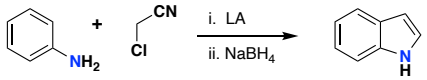
Madelung Indole Synthesis



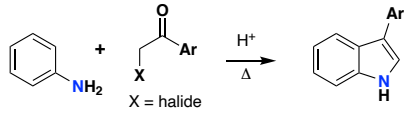
Nenitzescu Indole Synthesis



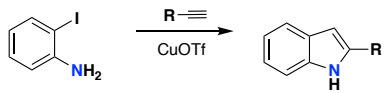
Reissert Indole Synthesis



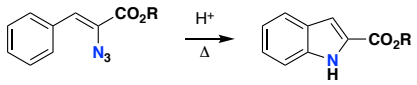
Sugasawa Indole Synthesis



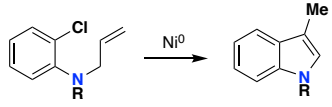
Bischler Indole Synthesis



Castro Indole Synthesis

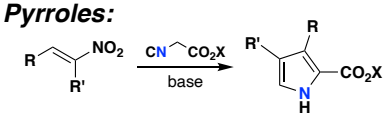


Hemetsberger Indole Synthesis

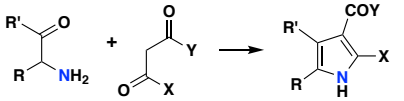


Mori-Ban Indole Synthesis

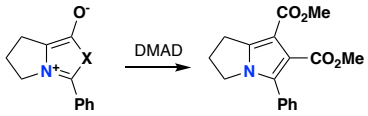
Pyrroles:



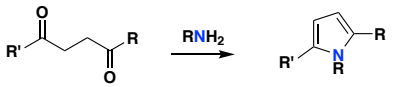
Barton-Zard Pyrrole Synthesis



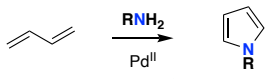
Knorr Pyrrole Synthesis



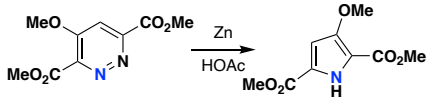
Huisgen Pyrrole Synthesis



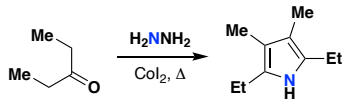
Paal-Knorr Pyrrole Synthesis



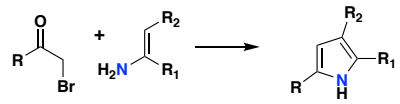
Wacker Pyrrole Synthesis



Boger Pyrrole Synthesis



Piloty Pyrrole Synthesis

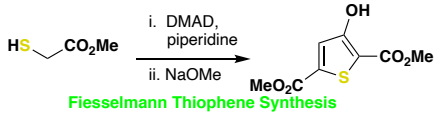


Hantzsch Pyrrole Synthesis

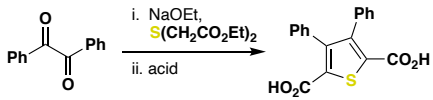
Thiophenes:



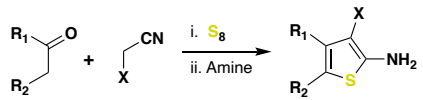
Paal Thiophene Synthesis



Fiesselmann Thiophene Synthesis

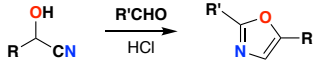


Hinsberg Thiophene Synthesis

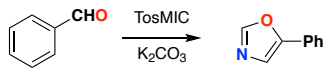


Gewald Aminothiophene Synthesis

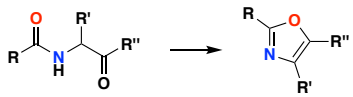
Oxazoles and Isoxazoles:



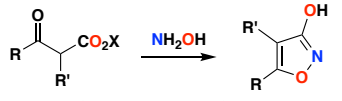
Fisher Oxazole Synthesis



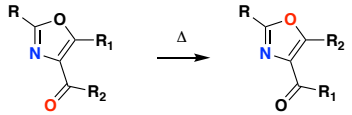
van Leusen Oxazole Synthesis



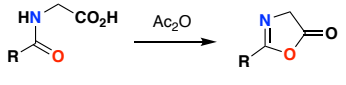
Robinson-Gabriel Oxazole Synthesis



Claisen Isoxazole Synthesis



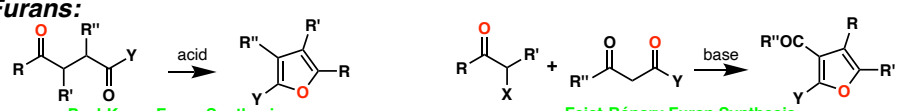
Cornforth Rearrangement



Erlenmeyer-Plöchl Azlactone Synthesis

Essentials of Heterocyclic Chemistry-II

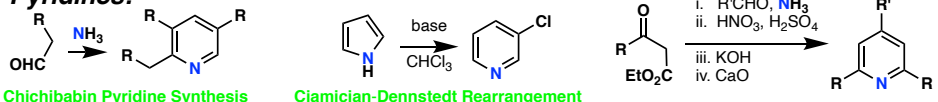
Furans:



Paal-Knorr Furan Synthesis

Feist-Bénary Furan Synthesis

Pyridines:



Chichibabin Pyridine Synthesis

Ciamician-Dennstedt Rearrangement

Hantzsch Pyridine Synthesis



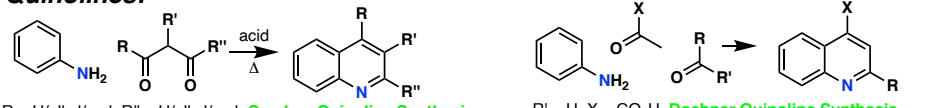
Guareschi-Thorpe Pyridine Synthesis

Bohlmann-Rahtz Pyridine Synthesis

Kröhnke Pyridine Synthesis

Boger Pyridine Synthesis

Quinolines:



R = H/alkyl/aryl, R'' = H/alkyl/aryl Combes Quinoline Synthesis
R = O-alkyl/aryl, R'' = H/alkyl/aryl Conrad-Limpach Reaction
R = H/alkyl/aryl, R'' = O-alkyl Knorr Quinoline Synthesis

R' = H, X = CO_2H Doebner Quinoline Synthesis
R' = X = Me Riehm Quinoline Synthesis



Friedländer Quinoline Synthesis

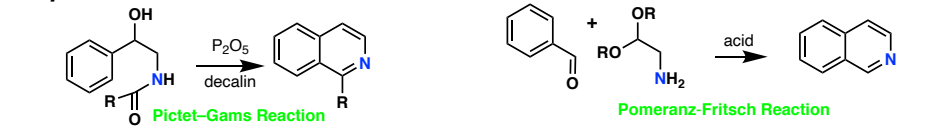
Gould-Jacobs Reaction



Meth–Cohn Quinoline Synthesis

Pfitzinger Quinoline Synthesis

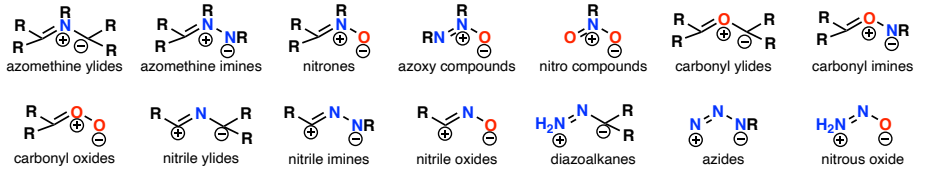
Isoquinolines:



Pictet–Gams Reaction

Pomeranz-Fritsch Reaction

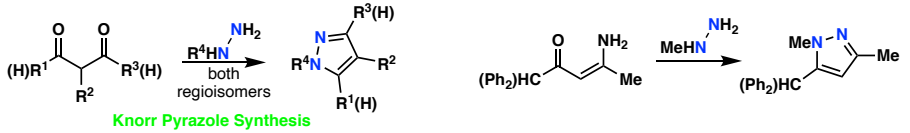
Useful 1,3-dipoles:



azomethine ylides | azomethine imines | nitrones | azoxy compounds | nitro compounds | carbonyl ylides | carbonyl imines

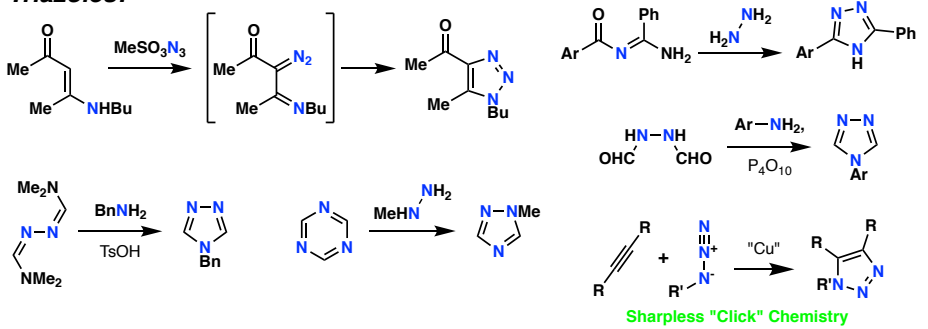
carbonyl oxides | nitrile ylides | nitrile imines | nitrile oxides | diazoalkanes | azides | nitrous oxide

Diazoles:



Knorr Pyrazole Synthesis

Triazoles:



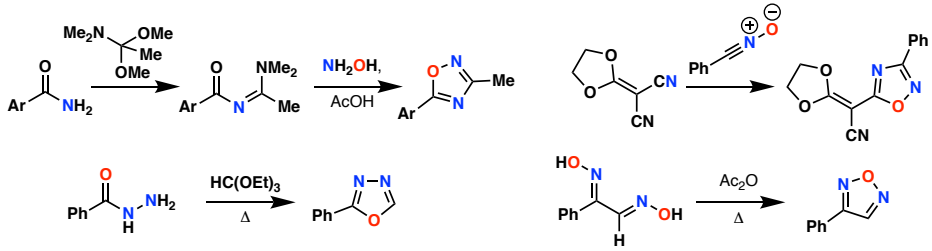
Sharpless "Click" Chemistry

Tetrazoles:

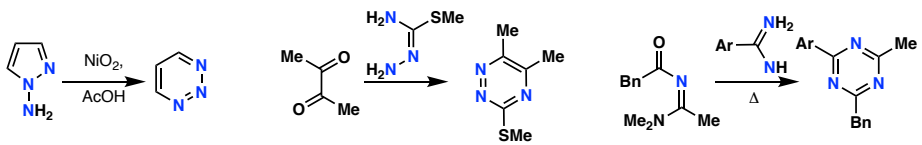


Passerini Synthesis

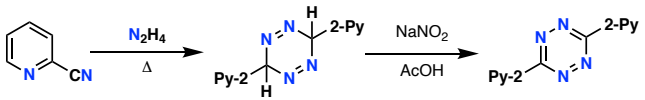
Oxadiazoles:

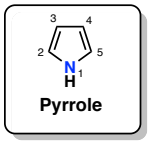


Triazanes:



1,2,4,5-Tetrazines:





Pyrrole

NMR Spectral Parameters

^{1}H ($CDCl_3$) ppm

H-3, H-4: 6.22

H-2, H-5: 6.68

^{13}C ($CDCl_3$)

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)

$J_{C2\text{-}H}$ 183.28 $J_{C3\text{-}H}$ 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

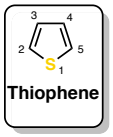
C3-C4: 1.417 C3-H: 1.077

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



Thiophene

NMR Spectral Parameters

^{1}H (C_6D_{12}) ppm

H-3, H-4: 6.96

H-2, H-5: 7.20

^{13}C (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)

$J_{C2\text{-}H}$ 185 $J_{C3\text{-}H}$ 168

Structural Properties

(Determined by gas-phase microwave spectra)

Bond Lengths (Å)

S-C2: 1.714

C2-C3: 1.369

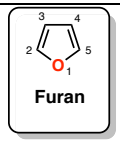
C3-C4: 1.423

Bond Angles

C2-S-C5: 92

S-C2-C3: 111

C2-C3-C4: 112



Furan

NMR Spectral Parameters

^{1}H ($CDCl_3$) ppm

H-3, H-4: 6.24

H-2, H-5: 7.29

^{13}C (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)

$J_{C2\text{-}H}$ 201 $J_{C3\text{-}H}$ 175

Structural Properties

(Determined by microwave spectra)

Bond Lengths (Å)

O-C2: 1.362

C2-C3: 1.361

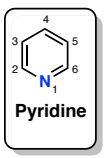
C3-C4: 1.430

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



Pyridine

NMR Spectral Parameters

^{1}H ($CDCl_3$) ppm

H-3: 7.25

H-4: 7.64

H-2: 8.60

^{13}C ($CDCl_3$)

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)

$J_{C2\text{-}H}$ 179 $J_{C3\text{-}H}$ 163 $J_{C4\text{-}H}$ 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

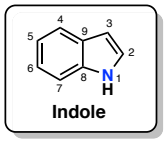
Bond Angles

C6-N-C5: 116.9

N-C2-C3: 123.8

C2-C3-C4: 118.5

C3-C4-C5: 118.4



Indole

NMR Spectral Parameters

^{1}H ($CDCl_3$) 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

^{13}C ($CDCl_3$)

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

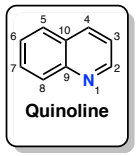
Bond Angles

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



Quinoline

NMR Spectral Parameters

^{1}H (CCl_4) 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

^{13}C ($CDCl_3$) 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 NiS_2PEt_2 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

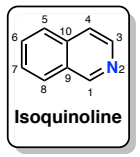
Bond Angles

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



Isoquinoline

NMR Spectral Parameters

^{1}H (CCl_4) 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

^{13}C ($CDCl_3$) 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

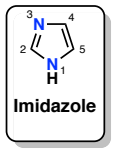
Bond Angles

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



Imidazole

NMR Spectral Parameters

^{1}H (D_2O) ppm

H-4, H-5: 7.14

H-2: 7.73

^{13}C (D_2O) 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

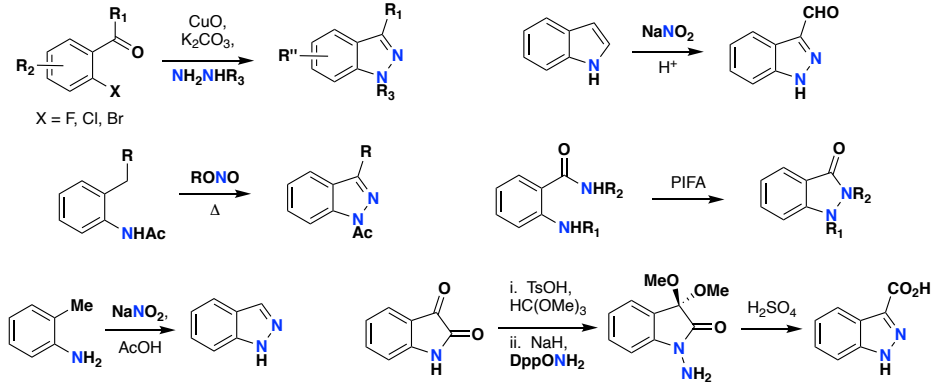
N1-C2-N3: 111.3

C2-N3-C4: 105.4

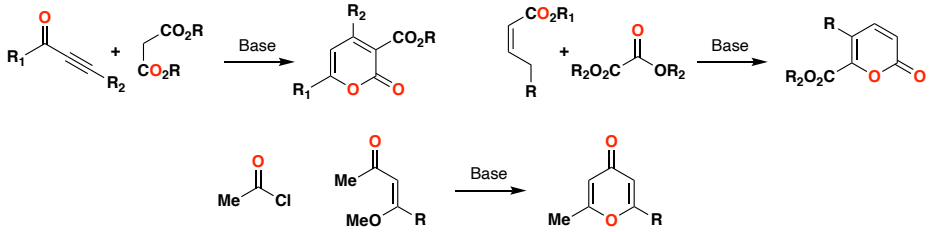
N3-C4-C5: 109.8

C4-C5-N1: 106.3

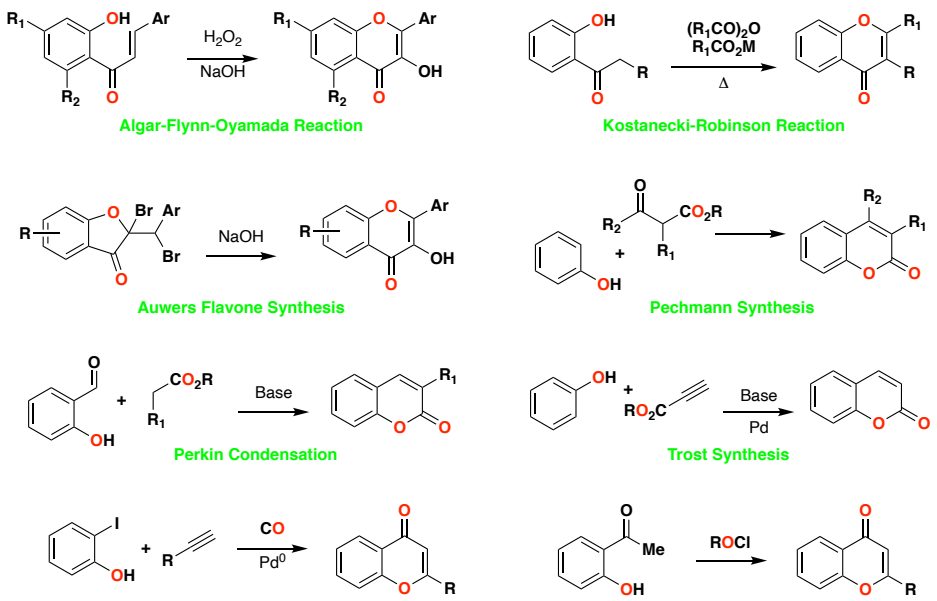
Indazoles:



Pyrones:



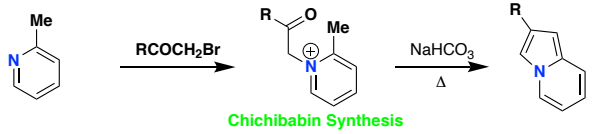
Chromanones and Coumarins:



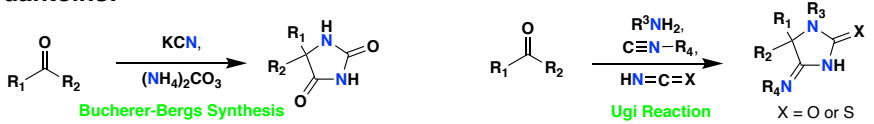
Purines:



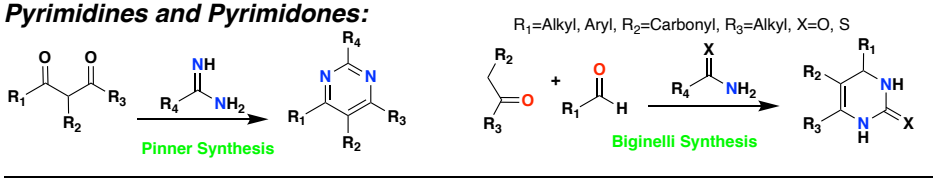
Indolizidines:



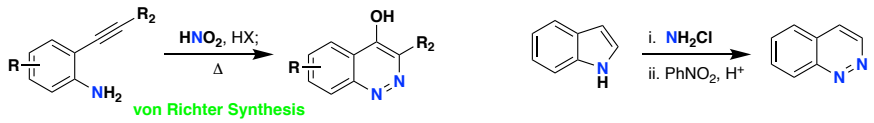
Hydantoins:



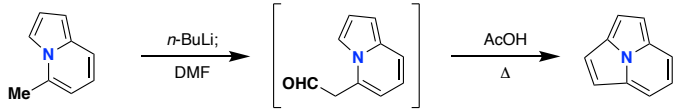
Pyrimidines and Pyrimidones:



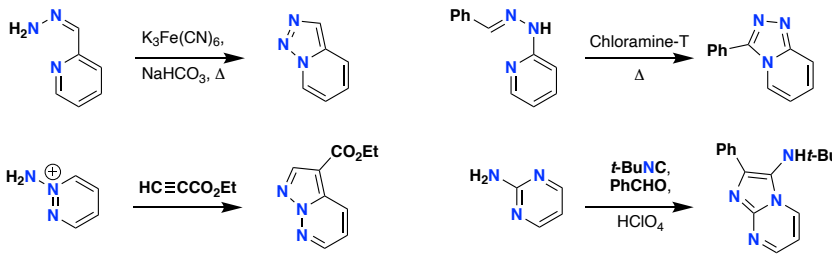
Cinnolines:



Cyclazines:



Triazolopyridines:



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

ArMgCl + **Ar'NO_2** —($FeCl_2$, $NaBH_4$)→ **ArNHAr'** — *J. Am. Chem. Soc.* **2002**, *124*, 9390

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

$ArB(OH)_2$ + **RYH** (Y = NH, O, S) —("Cu Source", Base)→ **ArYR**

Tetrahedron Lett. **1998**, *39*, 2933
Tetrahedron Lett. **1998**, *39*, 2937
Tetrahedron Lett. **1998**, *39*, 2941
Org. Lett. **2000**, *2*, 2019
Tetrahedron Lett. **2001**, *42*, 3415
Tetrahedron Lett. **2003**, *44*, 1691
Tetrahedron Lett. **2003**, *44*, 3359

Applicable to a wide variety of nucleophilic partners, including phenols, amines, anilines, amides, imides, ureas, carbamates, sulfonamides, thiols, and thiophenols. Can use a variety of heterocycles, including imidazoles, pyrazoles, triazoles, tetrazoles, benzimidazoles, and indazoles. Even styryl boronic acids are tolerated in the reaction. α-Amino esters can be arylated in good yields and purines have been shown to react selectively at N-9. Catalytic reactions can be performed and a wide variety of copper sources, ligands, and bases can be used.

$ArB(OH)_2$ + **PhthNOH** —("Cu source", Pyr, DCE)→ **ArONPhth** — *Org. Lett.* **2001**, *3*, 139

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

ArX (X = I, Br, Cl) + **RYHZ** (Y = N, O, S; Z = C, H) —("Cu Source", Base)→ **ArYRZ**

J. Am. Chem. Soc. **1997**, *119*, 10539
J. Am. Chem. Soc. **1998**, *120*, 12459
Tetrahedron Lett. **1999**, *40*, 2657
J. Org. Chem. **1999**, *64*, 670
Tetrahedron Lett. **2000**, *41*, 1283
Tetrahedron Lett. **2001**, *42*, 4791
J. Am. Chem. Soc. **2001**, *123*, 7727
Synlett. **2002**, 231
Synlett. **2002**, 427
Org. Lett. **2002**, *4*, 581
Org. Lett. **2002**, *4*, 973
Org. Lett. **2002**, *4*, 3517
Org. Lett. **2002**, *4*, 3703
J. Am. Chem. Soc. **2002**, *124*, 7421
J. Am. Chem. Soc. **2002**, *124*, 11684
Org. Lett. **2003**, *5*, 793
Org. Lett. **2003**, *5*, 133

Applicable to a wide variety of nucleophilic partners, including anilines, phenols, thiophenols, aliphatic alcohols, thiols, amines, amino alcohols, amino acids, amino esters, guanidines, amides, diamines, hydrazones, carbazoles, imidazoles, indoles, acylhydrazides, pyrroles, pyrazoles, benzimidazoles, indazoles, azaindoles, and carbamates. The aryl ring can be a wide variety of heterocycles and the reaction tolerates a wide range of substituents, including electron-donating and electron-withdrawing groups. Inter- and intramolecular reactions are both possible. Unprotected functionality of all sorts is tolerated. Various ring sizes can be formed/are tolerated in the reaction. A wide variety of copper sources and oxidation states work in the reaction. A variety of bases and ligands can be used and the reaction can even be run with catalytic copper loadings.

J. Org. Chem. **2005**, 70, 5164. *Tetrahedron*, **2005**, 61, 6553. *Synlett*, **2006**,18, 3105. *Tetrahedron*, **2006**, 62, 4435. *Tetrahedron*, **2006**, 62, 4756. *J. Org. Chem.* **2007**, 72, 2737. *Tetrahedron Letters*, **2007**, 48, 6573. *Angew. Chem. Int. Ed.* **2007**, *46, 934*. *J. Org. Chem.* ***2007***, 72, 3863. *Org. Lett.* **2007**, 9, 643. *Tetrahedron Letters*, ***2007***, *48, 7199*.

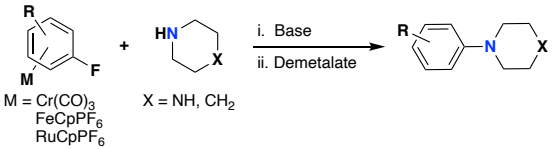
$ArSnR_3$ + **YNHZ** (Z = C, H) —("Cu Source", Base)→ **ArNYZ** — *Tetrahedron Lett.* **2002**, *43*, 3091

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

ArX (X = Cl, Br) + **NaOR** (R = alkyl) —(Ni(0))→ **ArOR**

J. Org. Chem. **1997**, *62*, 5413
J. Am. Chem. Soc. **1997**, *199*, 6054

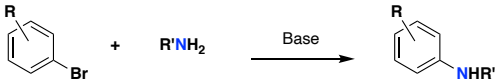
Various nucleophilic parters can be used, specifically alkoxides, silyloxides, anilines, and amines. A variety of electron-withdrawing and electron-donating groups are tolerated on the aromatic ring.



M = $Cr(CO)_3$, $FeCpPF_6$, $RuCpPF_6$ X = NH, CH_2

Tetrahedron Lett. **1993**, *34*, 1395
J. Org. Chem. **1996**, *61*, 6581
Tetrahedron Lett. **1996**, *37*, 8487
Tetrahedron Lett. **1997**, *38*, 5123
J. Am. Chem. Soc. **1997**, *119*, 6488

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 susbstitution on the aromatic ring is tolerable.



J. Org. Chem. **1987**, *52*, 2619

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:

ArX (X = I, Br, Cl) + **RYHZ** (Y = N, O, S; Z = C, H) —("Pd Source", Base)→ **ArYRZ**

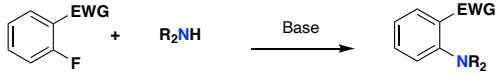
Tetrahedron Lett. **1995**, *36*, 3609
Angew. Chem. Int. Ed. **1995**, *34*, 1348
J. Org. Chem. **1996**, *61*, 1133
J. Am. Chem. Soc. **1996**, *118*, 7215, 7217
J. Org. Chem. **1996**, *61*, 7240
Tetrahedron **1996**, *52*, 7525
J. Org. Chem. **1997**, *62*, 1264, 1268
J. Am. Chem. Soc. **1997**, *119*, 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

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.

Ar_3BiX_2 (X = Cl, O_2CR') + **RYHZ** (Y = N, O; Z = C, H) —(Cu(II))→ **ArYRZ**

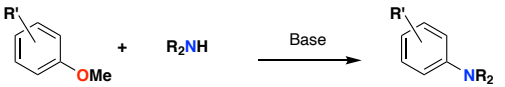
Tetrahedron Lett. **1986**, *27*, 3615
Synthesis. **1994**, 775
Tetrahedron. **1997**, *53*, 4137
Tetrahedron. **1999**, *55*, 1341

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.



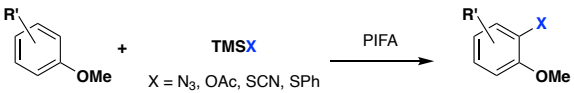
Tetrahedron Lett. **1996**, *37*, 7343
J. Chem. Soc. Perkin Trans. 1. **1997**, 2229
J. Org. Chem. **1997**, *62*, 3874

Various amines and electron-withdrawing groups can be used.



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

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



X = N_3, OAc, SCN, SPh

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

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.

For Reviews on the Subject See:

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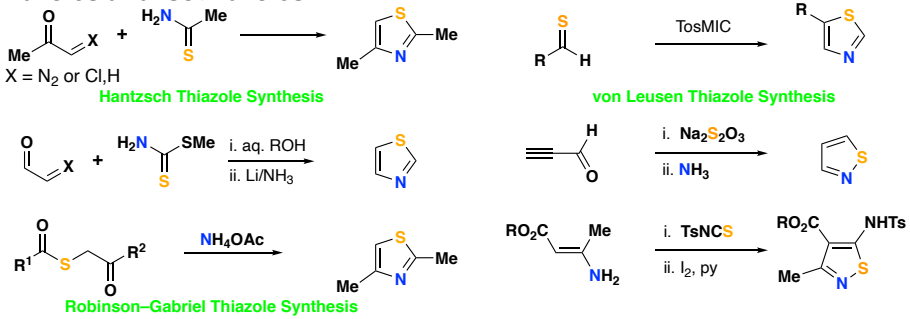
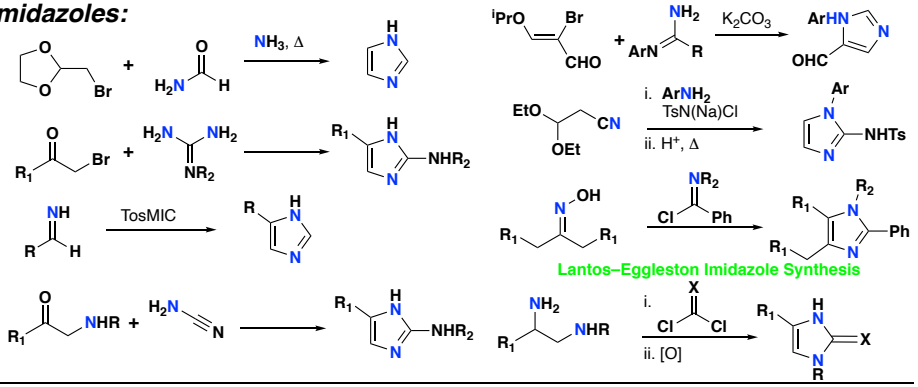
2. Koser, G. F. "C-Heteroatom-Bond Forming Reactions" *Top. Curr. Chem.* **2003**, *224*, 137 – 172.
3. Muci, A. R.; Buchwald, S. L. "Practical Palladium Catalysts for C-N and C-O Bond Formation" *Top. Curr. Chem.* **2002**, *219*, 131 – 209.
4. Hartwig, J. F. "Palladium-Catalyzed Amination of Aryl Halides: Mechanism and Rational Catalyst Design" *Synlett.* **1997**, 329 – 340.
5. Hartwig, J. F. "Transition Metal Catalyzed Synthesis of Arylamines and Aryl Ethers from Aryl Halides and Triflates: Scope and Mechanism" *Angew. Chem. Int. Ed.* **1998**, *37*, 2046 – 2067.
6. 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.
7. Hartwig, J. F. "Carbon–Heteroatom Bond-Forming Reductive Eliminations of Amines, Ethers, and Sulfides" *Acc. Chem. Res.* **1998**, *31*, 852 – 860.
8. Frost, C. G.; Mendonça, P. "Recent developments in aromatic heteroatom coupling reactions" *J. Chem. Soc. Perkin Trans. 1.* **1998**, 2615 – 2623.
9. Yang, B. H.; Buchwald, S. L. "Palladium-catalyzed amination of aryl halides and sulfonates" *J. Organometallic Chem.* **1999**, *576*, 125 – 146.
10. Belfield, A. J.; Brown, G. R.; Foubister, A. J. "Recent Synthetic Advances in the Nucleophilic Amination of Benzenes" *Tetrahedron.* **1999**, *55*, 11399 – 11428.
11. Hartwig, J. F. "Approaches to catalyst discovery. New carbon-heteroatom and carbon-carbon bond formation" *Pure Appl. Chem.* **1999**, *71*, 1417 – 1423.
12. Prim, D.; Campagnew, J.-M.; Joseph, D.; Andrioletti, B. "Palladium-catalysed reactions of aryl halides with soft, non-organometallic nucleophiles" *Tetrahedron.* **2002**, *58*, 2041 – 2075.

Essentials of Heterocyclic Chemistry-IV

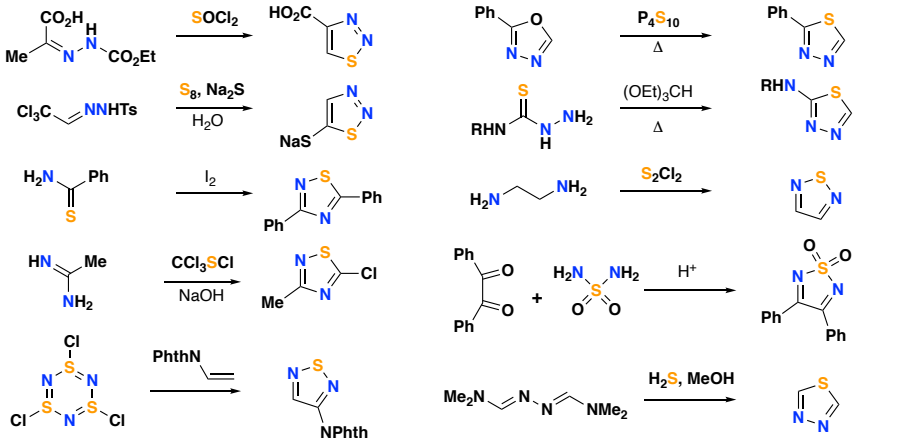
Thiazoles and Isothiazoles:



Imidazoles:



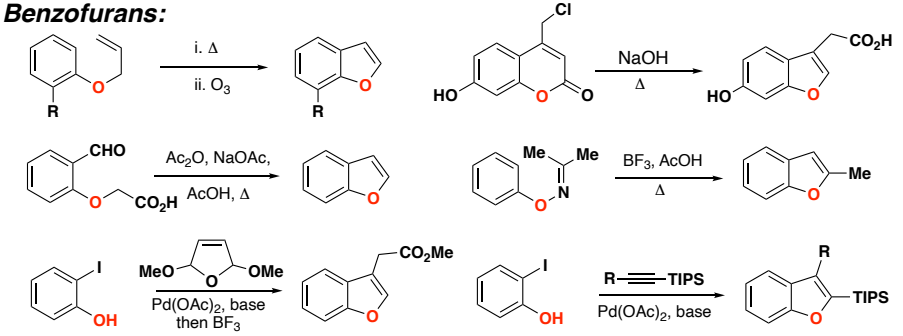
Thiadiazoles:



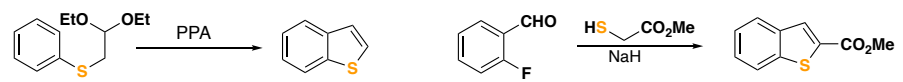
Oxetanes:



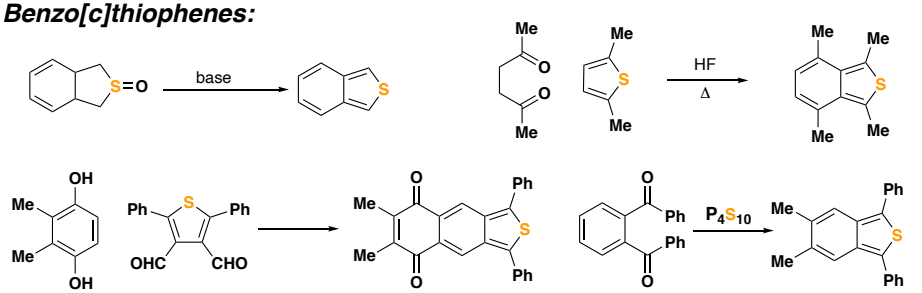
Benzofurans:



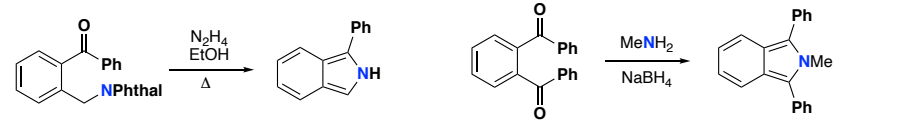
Benzothiophenes:



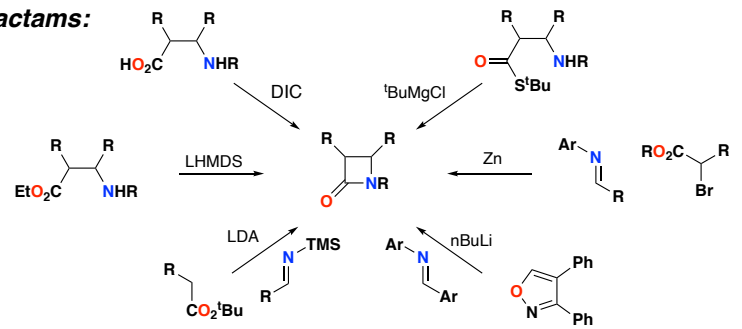
Benzo[c]thiophenes:



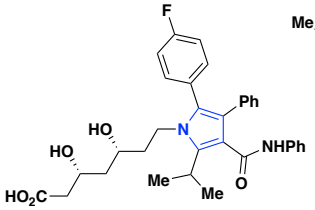
Isoindoles:



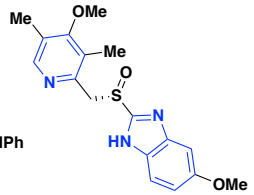
Beta-lactams:



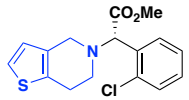
Top 15 Brand-Name Pharmaceuticals with Heterocycles:



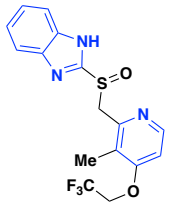
Lipitor (Pfizer)
2008 rank: **1**
2008 sales: **$5.88B**
Treats: high LDL cholesterol



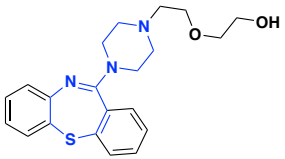
Nexium (Astra-Zeneca)
2008 rank: **2**
2008 sales: **$4.79B**
Treats: heartburn/esophigitis



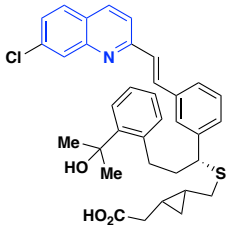
Plavix (BMS)
2008 rank: **3**
2008 sales: **$3.80B**
Treats: stroke/heart attack



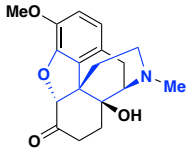
Prevacid (TAP)
2008 rank: **5**
2008 sales: **$3.30B**
Treats: gastric reflux



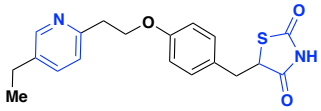
Seroquel (Astra-Zeneca)
2008 rank: **6**
2008 sales: **$2.91B**
Treats: schizophrenia/bipolar mania



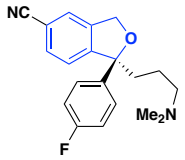
Singulair (Merck)
2008 rank: **7**
2008 sales: **$2.90B**
Treats: asthma



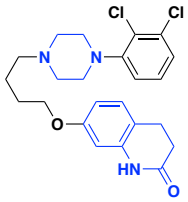
Oxycontin (Purdue)
2008 rank: **9**
2008 sales: **$2.5B**
Treats: moderate to severe pain



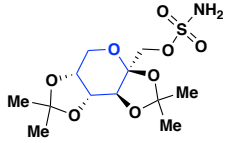
Actos (Eli Lilly)
2008 rank: **10**
2008 sales: **$2.45B**
Treats: type 2 diabetes



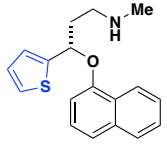
Lexapro (Forest)
2008 rank: **11**
2008 sales: **$2.41B**
Treats: depression and anxiety



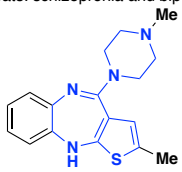
Abilify (Otsuka)
2008 rank: **12**
2008 sales: **$2.37B**
Treats: schizoprenia and bipolar mania



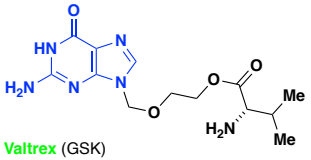
Topamax (J & J)
2008 rank: **13**
2008 sales: **$2.18B**
Treats: seizures and migranes



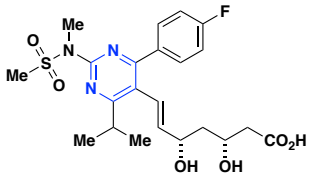
Cymbalta (Eli Lilly)
2008 rank: **14**
2008 sales: **$2.17B**
Treats: depression



Zyprexa (Eli Lilly)
2008 rank: **15**
2008 sales: **$1.75B**
Treats: schizophrenia/bipolar mania

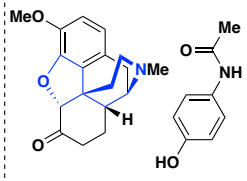


Valtrex (GSK)
2008 rank: **16**
2008 sales: **$1.68B**
Treats: shingles, cold sores and genital herpes

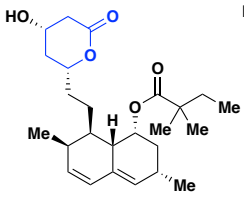


Crestor (AstraZeneca)
2008 rank: **17**
2008 sales: **$1.68B**
Treats: high LDL cholesterol

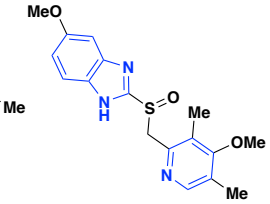
Top 19 Generic Pharmaceuticals with Heterocycles:



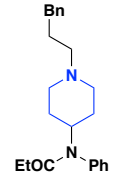
Hydrocodone/ Acetaminophen
2008 rank: **1**
2008 sales: **$1.78B**
Treats: pain



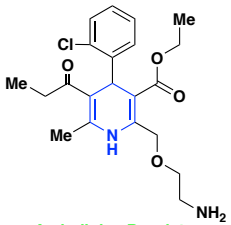
Simvastatin
2008 rank: **2**
2008 sales: **$1.45B**
Treats: cholesterol



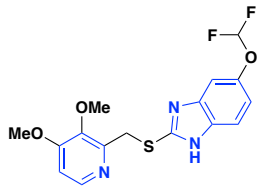
Omeprazole
2008 rank: **4**
2008 sales: **$1.15B**
Treats: heartburn



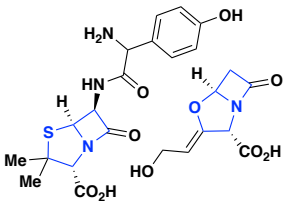
Fentanyl
2008 rank: **6**
2008 sales: **$1.00B**
Treats: pain



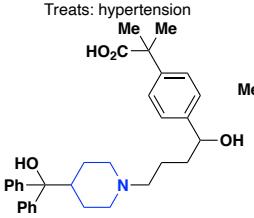
Amlodipine Besylate
2008 rank: **7**
2008 sales: **$0.96B**
Treats: hypertension



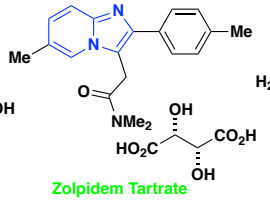
Pantoprazole
2008 rank: **8**
2008 sales: **$0.95B**
Treats: esophagus inflammation and erosion



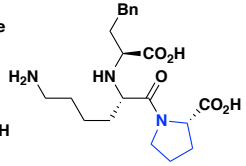
Amoxicillin/ Pot Clav
2008 rank: **10**
2008 sales: **$0.81B**
Treats: bacterial infections



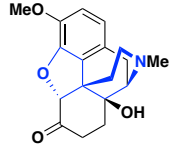
Fexofenadine
2008 rank: **11**
2008 sales: **$0.77B**
Treats: allergies



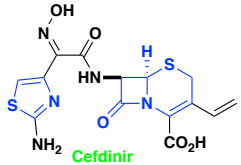
Zolpidem Tartrate
2008 rank: **12**
2008 sales: **$0.74B**
Treats: insomnia



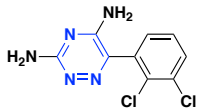
Lisinopril
2008 rank: **14**
2008 sales: **$0.69B**
Treats: hypertension



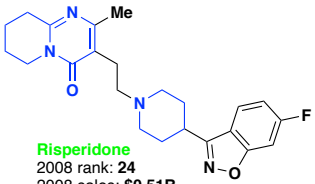
Oxycodone
2008 rank: **15**
2008 sales: **$0.68B**
Treats: pain



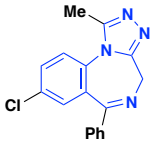
Cefdinir
2008 rank: **17**
2008 sales: **$0.59B**
Treats: infections



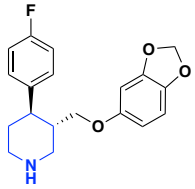
Lamotrigine
2008 rank: **20**
2008 sales: **$0.54B**
Treats: seizures and bipolar disorder



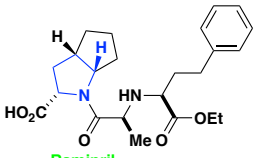
Risperidone
2008 rank: **24**
2008 sales: **$0.51B**
Treats: schizoprenia and bipolar mania



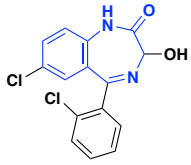
Alprazolam
2008 rank: **25**
2008 sales: **$0.47B**
Treats: anxiety, panic



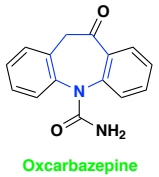
Paroxetine
2008 rank: **29**
2008 sales: **$0.36B**
Treats: depression, panic



Ramipril
2008 rank: **31**
2008 sales: **$0.34B**
Treats: hypertension and heart disease



Lorazepam
2008 rank: **32**
2008 sales: **$0.34B**
Treats: anxiety



Oxcarbazepine
2008 rank: **35**
2008 sales: **$0.33B**
Treats: seizures