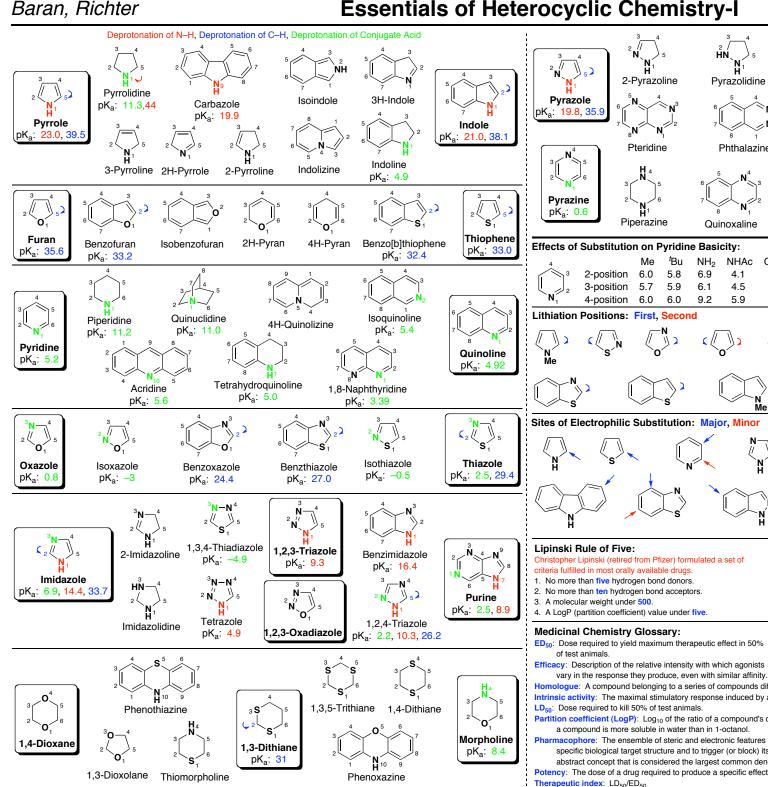
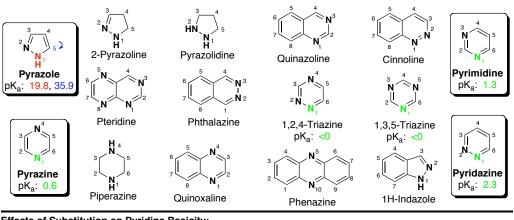
# **Essentials of Heterocyclic Chemistry-I**

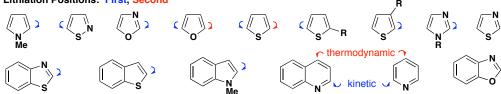
## Heterocyclic Chemistry

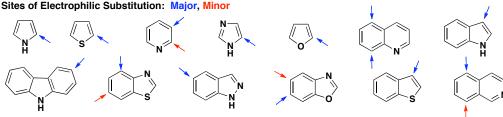




#### Effects of Substitution on Pyridine Basicity:

4													CH(OH) <sub>2</sub>
$N_1$	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





pyridine

tetrazole

pyrazole

quinoline

pyrazine

pyrimidine

pyridazine

isoquinoline

1,2,5-triazole

**Heterocyclic Aromaticity Values:** 

82

80

61

61

75

71

67

% (of PhH) β-value

0.058 indole

0.052

0.051

0.049

0.049

benzothiophene

imidazole

benzofuran

thiophene

isoindole

isobenzofuran

pyrrole

furan

% (of PhH) β-value

12

0.047

0.044

0.042

0.039

0.036

0.032

0.029

0.007

ED<sub>50</sub>: Dose required to yield maximum therapeutic effect in 50%

Efficacy: Description of the relative intensity with which agonists

Homologue: A compound belonging to a series of compounds differing from each other by a repeating unit (i.e. a CH2, a peptide residue, etc.). Intrinsic activity: The maximal stimulatory response induced by a compound relative to that of a given reference comopund.

Partition coefficient (LogP): Log<sub>10</sub> of the ratio of a compound's concentration in 1-octanol vs. water at equilibrium. A LogP<0 means that

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.

## Indoles:

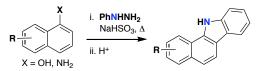
$$\begin{array}{c|c}
 & O \\
 & R' \\
 & R' \\
 & A \\
 & A$$

**Fukuyama Indole Synthesis** 

$$\begin{array}{c|c} & Pd^{ll}; & \hline \\ NH_2 & [H] & H \end{array}$$

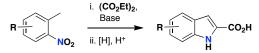
**Hegedus Indole Synthesis** 

**Bartoli Indole Synthesis** 



**Bucherer Carbazole Synthesis** 

**Madelung Indole Synthesis** 



**Reissert Indole Synthesis** 

$$\begin{array}{c|cccc} & & & & & & & & Ar \\ & + & & & & & & & & \\ & NH_2 & & & & & & & & \\ & X = \text{halide} & & & & & & & \\ \end{array}$$

**Bischler Indole Synthesis** 

$$\begin{array}{c|c} CO_2R & \xrightarrow{H^+} & CO_2R \\ \hline & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ \end{array}$$

**Hemetsberger Indole Synthesis** 

$$\begin{array}{c|c} X & R' \\ \hline \\ Pd^0 & \\ \hline \\ R & R \end{array}$$

#### **Gassman Indole Synthesis**

**Larock Indole Synthesis** 

**Batcho-Leimgruber Indole Synthesis** 

**Graebe-Ullmann Carbazole Synthesis** 

$$0 + R_3 + R_1 + R_2 + R_2 + R_3 +$$

**Nenitzescu Indole Synthesis** 

Sugasawa Indole Synthesis

$$\begin{array}{c|c}
I & R = \\
\hline
CuOTf & R
\end{array}$$

#### **Castro Indole Synthesis**

**Huisgen Pyrrole Synthesis** 

**Barton-Zard Pyrrole Synthesis** 

**Paal-Knorr Pyrrole Synthesis** 

**Knorr Pyrrole Synthesis** 

$$\begin{array}{c|c} \text{MeO} & \text{CO}_2\text{Me} \\ \hline \text{MeO}_2\text{C} & \text{N} \end{array} \begin{array}{c} \text{OMe} \\ \hline \text{HOAC} \\ \text{MeO}_2\text{C} & \text{N} \\ \end{array}$$

**Boger Pyrrole Synthesis** 

#### Thiophenes:

#### Oxazoles and Isoxazoles:

Fisher Oxazole Synthesis

**Robinson-Gabriel Oxazole Synthesis** 

R<sub>1</sub> 
$$\Delta$$
 R<sub>2</sub>  $R_1$   $A$   $R_1$   $A$   $R_2$   $R_1$   $R_2$   $R_2$   $R_1$   $R_2$   $R_2$   $R_1$ 

#### van Leusen Oxazole Synthesis

Claisen Isoxazole Synthesis

**Erlenmeyer-Plöchl Azlactone Synthesis** 

# Furans:

#### Pyridines:

Ciamician-Dennstedt Rearrangement

Kröhnke Pyridine Synthesis

#### Quinolines:

$$\begin{array}{c|c} & & & \\ &$$

R = H/alkyl/aryl, R" = H/alkyl/aryl Combes Quinoline Synthesis R = O-alky/aryl, R" = H/alkyl/aryl Conrad-Limpach Reaction

Friedländer Quinoline Synthesis



Meth-Cohn Quinoline Synthesis

R' = H, X = CO<sub>2</sub>H Doebner Quinoline Synthesis R' = X = Me Riehm Quinoline Synthesis

#### Isoquinolines:

#### Useful 1,3-dipoles:

carbonyl oxides

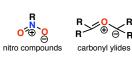


nitrile ylides





nitrile oxides





#### Diazoles:

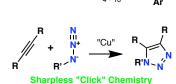
$$(H)R^{1} \xrightarrow{R^{3}(H)} R^{3}(H) \xrightarrow{R^{4}HN} R^{4}N \xrightarrow{R^{4}N} R^{2}$$

$$(Ph_{2})HC \xrightarrow{Me} R^{2}$$

$$(Ph_{2})HC \xrightarrow{Me} R^{2}$$

$$(Ph_{2})HC \xrightarrow{Me} R^{2}$$

#### Triazoles:



#### Tetrazoles:

#### Oxadiazoles:

#### Triazanes:

#### 1,2,4,5-Tetrazines:

$$\begin{array}{c|c}
 & N_2H_4 \\
\hline
N & A \\
\hline
N & N \\
N & N \\
\hline
N & N \\
N & N \\
\hline
N & N \\
N & N \\
\hline
N & N \\
N & N \\
\hline
N & N \\
N & N \\
\hline
N & N \\
N & N \\
\hline
N & N \\
N & N \\$$



**NMR Spectral Parameters** 

<sup>1</sup>H (CDCI<sub>3</sub>) ppm H-3. H-4: 6.22 H-2. H-5: 6.68 13C (CDCI<sub>3</sub>) 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

 $J_{24}$  1.491  $J_{12}$  2.579  $J_{2.5}$  1.845  $J_{1.3}$  2.458 C-H Coupling Constants (Hz) J<sub>C2-H</sub> 183.28 J<sub>C3-H</sub> 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** <sup>1</sup>H (CDCl<sub>3</sub>) 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 (CDCI<sub>3</sub>)

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  $J_{13}2.0$   $J_{37}0.7$   $J_{47}0.9$   $J_{67}8.1$  $J_{1.4}$  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** 

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** 

<sup>1</sup>H (C<sub>6</sub>D<sub>12</sub>) ppm H-3. H-4: 6.96 H-2, H-5: 7.20 13C (acetone-d<sub>6</sub>) 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<sub>C2-H</sub> 185 J<sub>C3-H</sub> 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** 

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 <sup>13</sup>C (CDCl<sub>3</sub>) ppm

<sup>1</sup>H (CCI<sub>4</sub>) 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<sub>2</sub>PEt<sub>2</sub> 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** 

<sup>1</sup>H (CDCl<sub>3</sub>) ppm H-3, H-4: 6.24 H-2, H-5: 7.29 13C (acetone-d<sub>6</sub>) 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<sub>C2-H</sub> 201 J<sub>C3-H</sub> 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

Isoquinoline

**NMR Spectral Parameters** 

<sup>1</sup>H (CCI<sub>4</sub>) 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 (CDCI<sub>3</sub>) 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** 

<sup>1</sup>H (CDCI<sub>3</sub>) ppm H-3: 7.25 H-4: 7.64 H-2: 8.60 13C (CDCI<sub>3</sub>) C-3: 123.46 C-4: 135.58

C-2 149.59 H-H Coupling Constants (Hz)

 $J_{23}4.93$   $J_{26}-0.03$ J<sub>24</sub> 1.80 J<sub>3.5</sub> 1.44  $J_{2.5}$  1.00  $J_{3.4}$  7.66

C-H Coupling Constants (Hz) J<sub>C2-H</sub> 179 J<sub>C3-H</sub> 163 J<sub>C4-H</sub> 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 Imidazole

**NMR Spectral Parameters** <sup>1</sup>H (D<sub>2</sub>O) ppm

H-4, H-5: 7.14 H-2: 7.73

13C (D<sub>2</sub>O) 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:

$$R_{2} \xrightarrow{\text{II}} X$$

$$X = F, CI, Br$$

$$CuO, K_{2}CO_{3}, N_{1} N_{2}NHR_{3}$$

$$R'' \xrightarrow{\text{II}} N_{R_{3}}$$

$$R'' \xrightarrow{\text{II}} N_{R_{3}}$$

$$\begin{array}{c|c} & & & \text{CHO} \\ \hline \\ N \\ H \\ \end{array} \begin{array}{c} & & \text{NaNO}_2 \\ \hline \\ H^{\dagger} \\ \end{array} \begin{array}{c} & & \text{CHO} \\ \\ N \\ H \\ \end{array}$$

### Pyrones:

$$R_1$$
 $R_2$ 
 $CO_2R$ 
 $R_1$ 
 $R_2$ 
 $CO_2R$ 
 $R_3$ 
 $R_4$ 
 $R_2$ 
 $R_4$ 
 $R_2$ 
 $R_4$ 
 $R_4$ 
 $R_5$ 
 $R_5$ 
 $R_6$ 
 $R_6$ 
 $R_7$ 
 $R_7$ 
 $R_8$ 
 $R_8$ 
 $R_9$ 
 $R_9$ 

#### Chromanones and Coumarins:

$$R_1$$
 OH Ar  $H_2O_2$  NaOH  $R_2$  OH

**Kostanecki-Robinson Reaction** 

Algar-Flynn-Oyamada Reaction

**Auwers Flavone Synthesis** 

**Trost Synthesis** 

#### Purines:

#### Indolizidines:

#### Hydantoins:

$$\begin{array}{c} O \\ R_1 \\ R_2 \\ \hline \\ HN = C = X \\ \hline \\ Ugi \ Reaction \\ \end{array} \begin{array}{c} R_1 \\ R_2 \\ \hline \\ R_4 \\ \hline \\ X = O \ or \ S \\ \end{array}$$

## Pyrimidines and Pyrimidones:



$$R_1$$
=Alkyl, Aryl,  $R_2$ =Carbonyl,  $R_3$ =Alkyl, X=O, S

 $R_1$ 
 $R_2$ 
 $R_3$ 
 $R_4$ 
 $R_$ 

#### Cinnolines:

$$\begin{array}{c|c} R_2 & OH \\ \hline R & \hline \\ \hline NH_2 & NH_2 \\ \hline \end{array}$$
 von Richter Synthesis

#### Cyclazines:

#### Triazolopyridines:

# **Essentials of Heterocyclic Chemistry-III**

#### Useful Methods of Forming Aryl C-N and C-O Bonds:

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

$$ArB(OH)_2$$
 +  $RYH$   $\xrightarrow{"Cu Source"}$   $ArYR$   
 $Y = NH, O, S$ 

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.  $\alpha$ -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.

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 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 cooper loadinos.

J. Org. Chem. 2005, 70, 5164. Tetrahedron, 2005, 61, 6553. Synlett, 2006, 18, 3105.
 J. 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.

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 aryl stannanes. Nucleophilic partners include amines, anilines, indazoles, benzimiazolones, pyridones, and aryl amides.

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.

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.

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. Ora. 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.

Various amines and electron-withdrawing groups can be used.

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

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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# Thiazoles and Isothiazoles:

#### von Leusen Thiazole Synthesis

$$= \bigvee_{0}^{H} \frac{\text{i. Na}_{2}S_{2}O_{3}}{\text{ii. NH}_{3}}$$

#### Imidazoles:

#### Thiadiazoles:

$$\begin{array}{c} \text{CO}_2\text{H} \\ \text{Me} \\ \text{N} \\ \text{N} \\ \text{CO}_2\text{Et} \\ \end{array} \xrightarrow{\begin{array}{c} \text{SOCI}_2 \\ \text{N} \\ \text{SOCI}_2 \\ \end{array}} \xrightarrow{\begin{array}{c} \text{HO}_2\text{C} \\ \text{N} \\ \text{N} \\ \text{SOCI}_2 \\ \end{array}} \xrightarrow{\begin{array}{c} \text{N} \\ \text{SOCI}_2 \\ \end{array}} \xrightarrow{\begin{array}{c} \text{N} \\ \text{N}$$

## Oxetanes:

#### Benzofurans:

i. 
$$\Delta$$
ii.  $O_3$ 
R

CHO

Ac<sub>2</sub>O, NaOAc,

Me

## Benzothiophenes:

#### Benzo[c]thiophenes:

#### Isoindoles:

# Beta-lactams: LHMDS

2006 sales: \$1.66B

Treats: schizophrenia/bipolar mania

2006 sales: \$1.54B

Treats: schizophrenia/bipolar mania

2006 sales: \$1.52B

Treats: seizures and migranes

2006 sales: \$0.22B

Treats: ulcers

2006 sales: \$0.22B

Treats: depression

2006 sales: \$0.22B

Treats: edema, hypertension

#### Heterocyclic Chemistry Top 15 Brand-Name Pharmaceuticals with Heterocycles: Top 21 Generic Pharmaceuticals with Heterocycles: MeO HO HO, ĆO₂H Amoxicillin/ Pot Clav Oxycodone 2006 rank: 4 Hydrocodone/ Simvastatin F<sub>3</sub>C<sub>3</sub> 2006 rank: 2 HO<sub>2</sub>C Acetaminophen 2006 rank: 6 2006 sales: \$1.39M 2006 rank: 1 2006 sales: \$1.18B Prevacid (TAP) Singulair (Merck) Lipitor (Pfizer) Nexium (Astra-Zeneca) 2006 sales: \$0.93B Treats: cholesterol 2006 sales: \$1.62M Treats: pain 2006 rank: 3 2006 rank: **5** 2006 rank: 1 2006 rank: 2 Treats: antibiotic Treats: pain 2006 sales: \$6.58B 2006 sales: \$4.06B 2006 sales: \$3.31B 2006 sales: \$2.48B Treats: high LDL cholestorol Treats: heartburn/esophigitis Treats: gastric reflux Treats: asthma HO<sub>2</sub>C CO<sub>2</sub>Me EtO<sub>2</sub>C CO<sub>2</sub>Me ΗÒ EtOC N. MeO<sub>2</sub>C Plavix (BMS) Zocor (Merck) Norvasc (Pfizer) 2006 rank: 8 2006 rank: 9 2006 rank: 7 Clopidogrel 2006 rank: 13 Lisinopril 2006 rank: 9 **Fentanyl** 2006 sales: \$2.23B 2006 sales: \$2.17B 2006 sales: \$2.15B Omeprazole 2006 rank: 8 2006 rank: 7 2006 rank: 12 Treats: stroke/heart attack Treats: high LDL Cholestorol Treats: hypertension/angina 2006 sales: \$0.91B 2006 sales: \$0.84B 2006 sales: \$0.73B 2006 sales: \$0.63B 2006 sales: \$0.64B Treats: allergies Treats: pain Treats: hypertension Treats: stroke, heart Treats: heartburn attack MeO Lexapro (Forest) Seroquel (Astra-Zeneca) Protonix (Wyeth) 2006 rank: 10 2006 rank: 11 2006 rank: 12 2006 sales: \$2.10B 2006 sales: \$2.07B 2006 sales: \$2.02B **Paroxetine** Alprazolam Warfarin Lorazepam Treats: depression and anxiety Treats: schizophrenia/bipolar mania Treats: esophagitis 2006 rank: 14 2006 rank: 18 2006 rank: 25 2006 rank: 26 2006 sales: \$0.62B 2006 sales: \$0.43B 2006 sales: \$0.36B 2006 sales: \$0.34B Treats: depression, panic Treats: anxiety, panic Treats: anxiety Treats: hypertension NMe<sub>2</sub> Ambien (Sanofi Aventis) , HO₂Ç Actos (Eli Lilly) Avandia (GSK) 2006 rank: 13 2006 rank: 14 2006 rank: 17 Cephalexin 2006 rank: 31 Quinapril 2006 rank: **31** Hydrochlorothiazide Clonazepam 2006 sales: \$1.94B 2006 sales: \$1.93B 2006 sales: \$1.66B 2006 rank: 30 2006 rank: 33 Treats: insomnia Treats: type 2 diabetes Treats: type 2 diabetes 2006 sales: \$0.30B 2006 sales: \$0.30B 2006 sales: \$0.27B 2006 sales: \$0.24B Treats: fluid buildup Treats: antibiotic Treats: seizures, panic Treats: hypertension H<sub>2</sub>NO<sub>2</sub>S Topamax (J & J) Risperdal (J & J) Zyprexa (Eli Lilly) Ciprolfloxacin HCI Diltiazem **Furosemide** Citalopram HBr 2006 rank: 19 2006 rank: 18 2006 rank: 20 2006 rank: 38 2006 rank: 42 2006 rank: 43 2006 rank: 45

2006 sales: \$0.23B

Treats: hypertension, angina