Background

Polysubstituted heterocycles represent some of the most important compounds in the realm of pharmaceutical and material sciences. New and more efficient ways to selectively produce these molecules are of great importance and one approach is though the use of polyhalo heterocycles.

Consider:

Nucleophilic Substitution

S$_n$Ar or S$_n$(AE)

S$_n$(EA)

SET Mechanism can also be operative (S$_{Rh}$(1))

S$_n$(ANORC) Addition of Nucleophile, Ring Opening, Ring Closure

Cross Coupling

Virtually all types of cross coupling have been utilized in regioselective cross coupling reactions: Kumada, Negishi, Sonogashira, Stille, Suzuki, Hiyama, etc.

In all of these examples, the oxidative addition of the metal to the heterocycle is the selectivity determining steps and is frequently considered to be irreversible. This addition highly resembles a nucleophilic substitution and it frequently follows similar regioselectivities in traditional S$_n$Ar reactions. The regioselectivity of cross coupling reaction in polyhalo heterocycles do not always follow the BDE’s of the corresponding C-X bonds.

Meric and Houk have determined that the oxidative addition in palladium catalyzed cross coupling reactions is determined by the distortion energy of the C-X bond (related to BDE) and the interaction of the LUMO of the heterocycle to the HOMO of the Pd species.
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Predicting Reactivity

The Handy Method

Handy and coworkers disclosed an experimental method in 2006 for predicting the regiochemical outcome of multiply halogenated heterocycles using $^1$H-NMR of the dehalogenated substrate. The proton that displays the largest chemical shift implies it is attached to the most electron deficient carbon atom and, therefore, the preferred site of cross coupling. While this method is not foolproof (it does not take into account steric, directing groups, or interactions noted by Merlic), it is a good start for predicting regioselectivities of cross coupling reactions.

*Chem. Comm.* **2006**, *299*

Pyroles

- Due to the electron rich nature, $S_n$Ar reactions do not readily take place without strong EWGs.
- Cross coupling reactions occur fastest at the 2/5 positions, in accord with chemical shift prediction.
- Monocoupling in 2,5 dihalo substrates is difficult, but 3,4 dihalo substrates can be easily controlled on steric grounds.

* Tetrahedron **2005**, *61*, 5831
* Tet. Lett. **2009**, *49*, 1698
* Tet. Lett. **2003**, *44*, 4443

Pyroles can also be selectively monoarylated at C-2 under C-H activation conditions.

- Like pyrrole, $S_n$Ar is very difficult without strong EWG's
- Cross coupling occurs first at C-2, with C-4 to C-7 reacting before electron rich C-3. A C-2 vs C-4/7 has not been reported.

*JACS* **2006**, *128*, 4972

Indole

Orthogonally, the 3-position could be selectively exchanged with t-BuLi.


The C-H activation conditions for pyrrole are also successful on indole and tolerates aryl bromides.
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**Haloselectivity of Heterocycles**

*Will Gutekunst*

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**Furan**

- Not as resistant as pyrole, but S_{Ar} reactions still do not readily take place without strong EWGs.
- Cross coupling reactions occur fastest at the 2/5 positions, in accord with chemical shift prediction.
- Halogenated furans have general stability problems, making cross couplings sometimes troublesome.

*Synlett 1998, 11, 1185*

Furfural can be selectively arylated in the 5- position directly.

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**Thiophene**

- A better substrate for S_{Ar} than furan and two orders of magnitude more reactive than benzene, but not many examples of haloselective reactions.
- Cross coupling reactions occur fastest at the 2/5 positions and the 3/4 much slower. Selectivity on 2,5 dihalothiophenes is scarcely obtained though some success has been seen with Sonogashira reaction and cases with substrate bias.

*Synlett 2000, 4, 459*

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**Benzofuran**

- Like indole, S_{Ar} is uncommon on benzofuran.
- Cross coupling also mimics indole first at C-2, with C-4 to C-7 reacting before electron rich C-3. Seems to follow Handy rules, though selectivity among C-4 through C-7 is unknown.

*Eur. JOC 2008, 5, 801*

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**Synthesis 2003, 6, 925**
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Benzothiophene

- S_2Ar occurs readily on benzothiophenes, but they have some strange reactions with nucleophiles.
- Cross coupling also mimics indole: first at C-2, with C-4 to C-7 reacting before C-3.

JOC 1973, 88,1365

Synthesis 2002, 2, 213

1,2-Azoles

- Selective S_2Ar reactions are only known with EWGs on the 4-position, but strongly favors substitution at the 5-position over the 3. This can be rationalized by both innate electronics (seen by NMR) and conjugation to the EWG.
- Cross coupling also follows Handy rules: first at C-5, then at C-2 and lastly C-3.

JOC 1964, 29, 660

Syn. Comm. 2008, 38, 674


Tetrahedron 2007, 63, 56

Attempts to displace the second chloride leads to mixtures with ring opened products.

Pyrazole shows similar reactivity, with a bromide being displaced before an iodide.

The remaining two bromides were unreactive in further Sonogashira couplings, even at higher temps.
Haloselectivity of Heterocycles

1,3-Azoles

- $S_N Ar$ reactions occur readily at C-2, though not very well at C-4/5 without assistance, and trends are not general among the series.
- Cross coupling also does not follow the Handy rules, with usual order of cross coupling being 2>D>4.
- Also note that the relative order chemical shifts switches in oxazole.

![Chem. Pharm. Bull. 1996, 44, 1831](image)

Regioselective Mg-Halogen exchange was observed of this dibromo thiophene.

Heterocycles 2007, 72, 293

1,3 azoles selectively C-H arylate at C-5 or C-2

![Bioorg. Med. Chem. Lett. 2006, 16, 6078](image)


Workers at Merck recently disclosed specific ligands to override and reinforce substrate bias in the 1,3-azoles in a screen of ~200 achiral phosphines.

![JOC 2010, 75, 1733](image)

JOC 2010, 75, 1733

Similar or better results were obtained for imidazoles, but selective C-4/C-5 over C-2 Suzuki couplings of dihalo thiophenes was not observed in any cases. No C-4 vs C-5 studies were undertaken.

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Some Relative Rates of Azines (Joule and Mills 4th Edition)

For EtO\(_2\) at 20°C

<table>
<thead>
<tr>
<th>Compound</th>
<th>Rate Constant</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.7x10^2</td>
</tr>
<tr>
<td>2</td>
<td>7.3x10^3</td>
</tr>
<tr>
<td>3</td>
<td>5.3x10^4</td>
</tr>
<tr>
<td>4</td>
<td>5.4x10^4</td>
</tr>
<tr>
<td>5</td>
<td>5.8x10^4</td>
</tr>
<tr>
<td>6</td>
<td>1.3x10^8</td>
</tr>
</tbody>
</table>

Pyridine

- Pyridines readily undergo S\(_2\)Ar, usually faster at C-4 than C-2/6, but highly dependent on nucleophile and conditions. C-3/5 react much slower.
- Cross coupling reactions occur fastest at the 2/6 positions followed by C-4 and C-3/5 much slower, much in accord with the Handy predictions. Mono substitution can usually be achieved with 2,6-dihalo and 3,5-dihalo pyridines.

\[ \text{Cl} + \text{Ar} \rightarrow \text{Cl} + \text{Ar} \]

Pyridines reaction under S\(_2\)Ar conditions

<table>
<thead>
<tr>
<th>Compound</th>
<th>Reaction Conditions</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhB(OH)(_2)</td>
<td>K(_2)CO(_3), THF reflux</td>
<td>61%</td>
</tr>
<tr>
<td>BnNH(_2)</td>
<td></td>
<td>140°C, 93%</td>
</tr>
</tbody>
</table>

OL 2003, 5, 3131

Pyridines reaction under cross coupling conditions

<table>
<thead>
<tr>
<th>Compound</th>
<th>Reaction Conditions</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>PdCl(_2)(PPh(_3))</td>
<td>90%</td>
</tr>
</tbody>
</table>

JMC 2000, 43, 4288

Usefully, Li-Halogen exchange is slow at 2/6 positions due to lone pair repulsion

<table>
<thead>
<tr>
<th>Compound</th>
<th>Reaction Conditions</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Br</td>
<td>n-BuLi, -100°C;</td>
<td>85%</td>
</tr>
<tr>
<td></td>
<td>D(_2)SO(_4)</td>
<td></td>
</tr>
</tbody>
</table>

ACIEE 2002, 41, 3901
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Haloselectivity of Heterocycles

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Quinoline/ Isoquinoline

- $S_N$Ar reactions of quinoline mimic pyridine largely, with C-4=C-2 generally preferred, but usually dependent on reaction conditions. Isoquinoline reacts fastest at C-1 followed by C-3 in $S_N$Ar.
- Cross coupling reactions in quinoline strongly favor the 2 position followed by 4. Regioselectivity between the other positions has not been well investigated. Preference of 1 vs 3 is well established in isoquinolines, but other positions not as well.

Pyridazine/Pyrazine

- $S_N$Ar reactions occur readily at all of the positions. All sites are degenerate on pyrazine, and the 4-position is most activated for nucleophilic attack, despite NMR chemical shift.
- Selective cross coupling reactions have not been well studied on pyridazine, but modest selectivity can be obtained from 3,6-dichloro compounds.

JOC 1999, 64, 453

Tetrahedron 2001, 57, 2507

JOC 2002, 67, 9392


**Haloselectivity of Heterocycles**

**Pyrimidine**

- Pyrimidines readily undergo S$_2$Ar at the 2 and 4/6 positions. 4/6 being generally more reactive, but is very sensitive to reaction conditions. The 3-position is greatly deactivated relative to the others.
- Cross coupling reactions occur fastest at the 4/6 positions followed by C-2 and C-5 much slower, in direct contrast to the Handy predictions.

![Chemical reaction diagram]

**Benzannelated Diazines**

- S$_2$Ar reactions occur readily at all of the heterocyclic positions. Behavior seems to be similar to the diazine counterparts, i.e. C-4 more reactive than C-2 in quinoxalines, C-4=C-3 in cinnoline.
- Cross coupling reactions have not been well studied on these systems, but the few examples mimic the corresponding diazines well.

![Chemical reaction diagram]

**Lithium reagents can directly add into C-4/6, which can be oxidized back to aromaticity easily**

![Chemical reaction diagram]
**Purine**

- Purines can participate in $S_n$Ar reactions at all carbon centers. For 9-H purines, the order of reactivity is 6>8>2. For substitution at 9, reactivity changes to 8>6>2.
- Cross coupling reactions usually occur fastest at the 6 position, though C-8 becomes competitive in some cases. C-2 is slowest.

![Chemical structures and reactions](image)


C-8 can be directly functionalized to give highly flexible syntheses of trisubstituted purines

![Chemical structures and reactions](image)

*OL 2006, 8, 5389

Misc Examples

- **Cl~Cl**
  - **JMC 2010, 53, 52**
  - DCM, Et$_2$Ni-Pr
  - KCN, DMSO

- **Cl~Cl**
  - **JMC 2009, 52, 655**
  - BnNH$_2$

- **Cl~Cl**
  - **Tet. Lett. 2006, 47, 8917**
  - Single regioisomer (no yields reported)

- **Cl~Cl**
  - **OL 2007, 9, 4673**
  - PhB(OH)$_2$

- **Cl~Cl**
  - **OPRD 2006, 10, 512**
  - LiHMDS

*Synlett 2004, 6, 889*
Conclusions

Selective reactions of polyhaloheterocycles has proven to be a very powerful method for synthesis of functionalized heterocycles. Frequently cross-coupling and S$_4$Ar are complementary methods, with C-H functionalization rapidly growing. While the prediction of regioselectivity is difficult to rationalize at times, common trends are seen in certain heterocyclic motifs and can be extrapolated to more complex situations, though, screening seems to still be needed for many cases. Future directions are in the ligand controlled cross coupling and further development of C-H activation reactions.

Key References

Cross coupling reviews:
- *Tetrahedron* 2005, 61, 2245
- *Synthesis* 2009, 9, 1405

Computational Analysis of Polyhalo Heterocycles
- *JACS*, 2007, 129, 12664
- *JACS*, 2009, 131, 6632

Handy Predictions