Baran Group Meeting

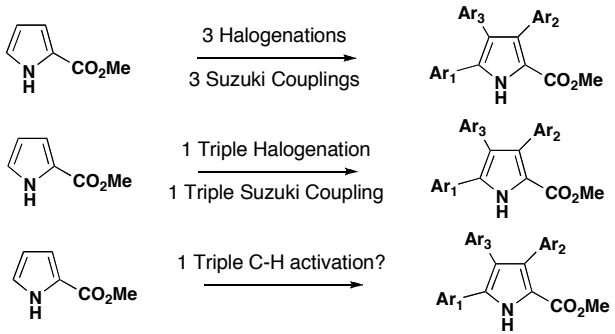
Haloselectivity of Heterocycles

Will Gutekunst

Background

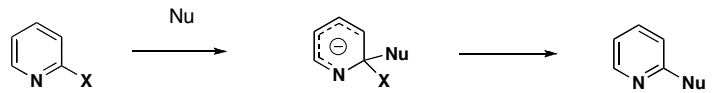
Polysubstituted heterocycles represent some of the most important compounds in the realm of pharmaceutical and material sciences. New and more efficient ways to selectively produce these molecules are of great importance and one approach is though the use of polyhalo heterocycles.

Consider:



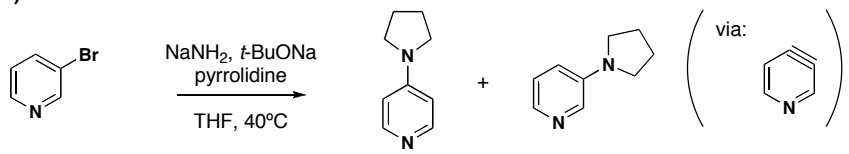
Nucleophilic Substitution

S_NAr or S_N(AE)



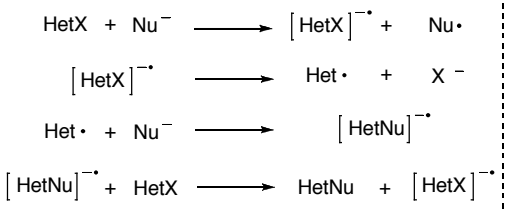
Meisenheimer Complex

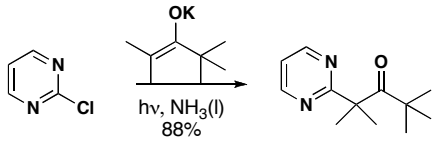
S_N(EA)



Tetrahedron **1982**, *38*, 427

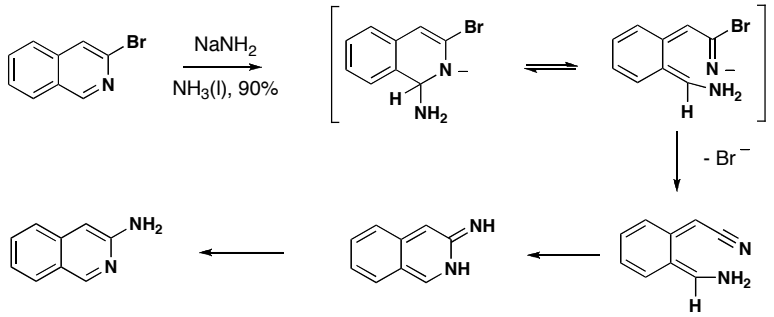
SET Mechanism can also be operative ($S_{RN}1$)





JOC **1981**, *46*, 294

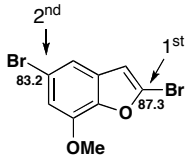
S_N(ANRORC) Addition of Nuclophile, Ring Opening, Ring Closure

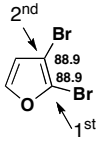


Cross Coupling

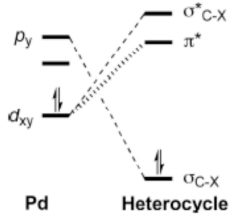
Virtually all types of cross coupling have been utilized in regioselective cross coupling reactions: Kumada, Negishi, Sonogashira, Stille, Suzuki, Hiyama, etc.

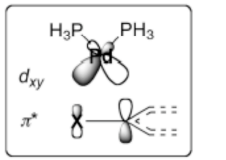
In all of these examples, the oxidative addition of the metal to the heterocycle is the selectivity determining steps and is frequently considered to be irreversible. This addition highly resembles a nucleophilic substitution and it frequently follows similar regioselectivities in traditional S_NAr reactions.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





Merlic 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.





Secondary orbital interaction

JACS, **2007**, *129*, 12664; *JACS*, **2009**, *131*, 6632

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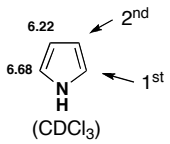
Predicting Reactivity

The Handy Method

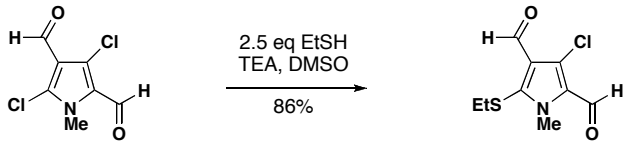
Handy and coworkers disclosed an experimental method in 2006 for predicting the regiochemical outcome of multiply halogenated heterocycles using ^{1}H-NMR of the dehalogenated substrate. The proton that displays the largest chemical shift implies it is attached to the most electron deficient carbon atom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

Chem. Comm. **2006**, 299

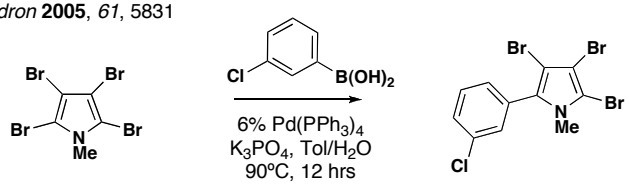
Pyrroles



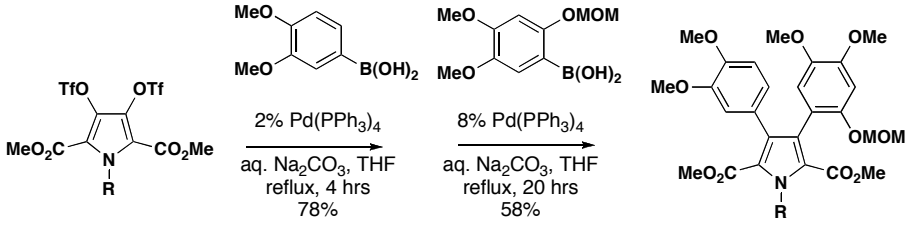
- Due to the electron rich nature, S_NAr reactions do not readily take place without strong EWGs.
- Cross coupling reactions occur fastest at the 2/5 positions, in accord with chemical shift prediction.
- Monocoupling in 2,5 dihalo substrates is difficult, but 3,4 dihalo substrates can be easily controlled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



Tetrahedron **2005**, *61*, 5831

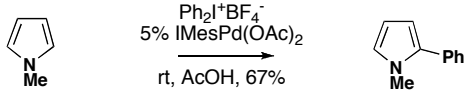


Tet. Lett. **2009**, *49*, 1698



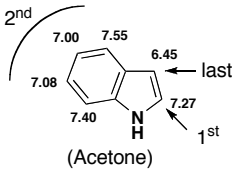
Tet. Lett. **2003**, *44*, 4443

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

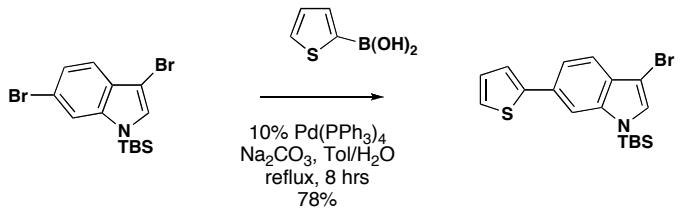


JACS **2006**, *128*, 4972

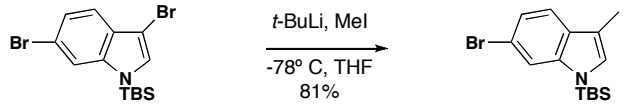
Indole



- Like pyrrole, S_NAr 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.

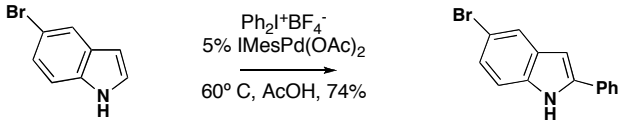


Orthogonally, the 3-position could be selectively exchanged with *t*-BuLi.



Chem. Pharm. Bull. **1996**, *44*,1831

The C-H activation conditions for pyrrole are also successful on indole and tolerates aryl bromides



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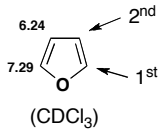
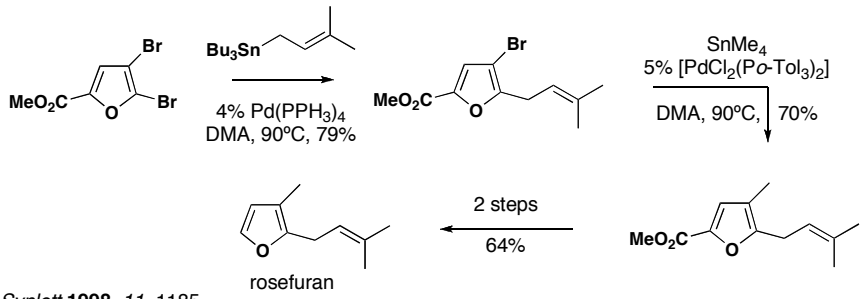
Furan

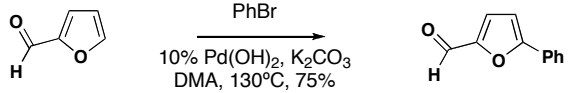


- Not as resistant as pyrrole, but S_NAr reactions still do not readily take place without strong EWGs.
- Cross coupling reactions occur fastest at the 2/5 positions, in accord with chemical shift prediction.
- Halogenated furans have general stability problems, making cross couplings sometimes troublesome.



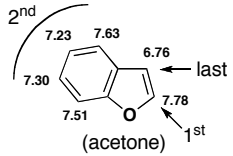
Synlett **1998**, *11*, 1185

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

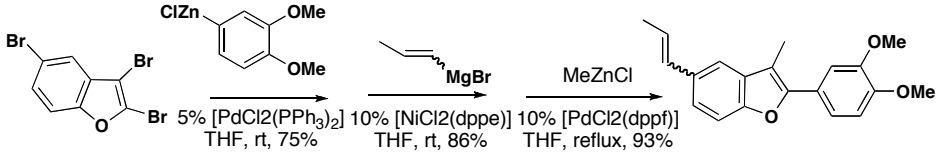


JOC **2005**, *70*, 7578

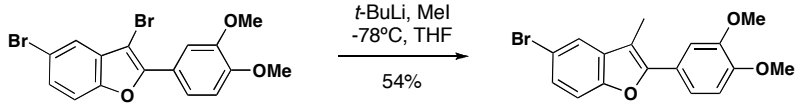
Benzofuran



- Like indole, S_NAr 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.

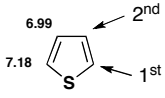


Much like the dibromo indole, after the first Negishi coupling, the lithium halogen exchange at C-3 is favored.

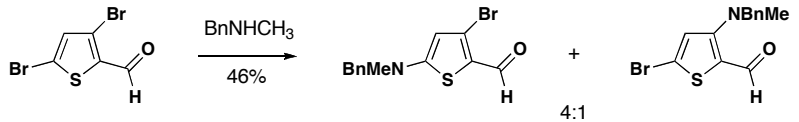


Synthesis **2003**, *6*, 925

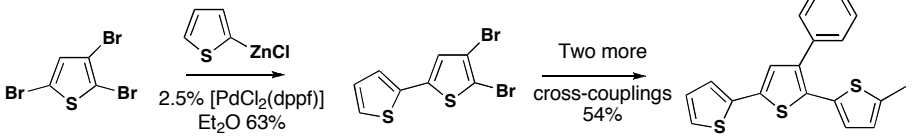
Thiophene



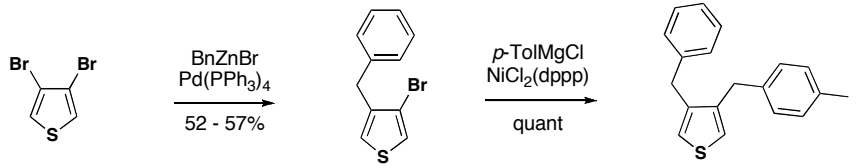
- A better substrate for S_NAr than furan and two orders of magnitude more reactive than benzene, but not many examples of haloselective reactions.
- Cross coupling reactions occur fastest at the 2/5 positions and the 3/4 much slower. Selectivity on 2,5 dihalothiophenes is scarcely obtained though some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



Synlett **2000**, *4*, 459

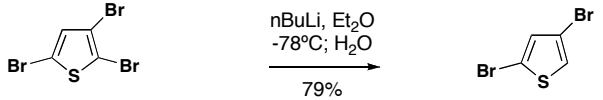


Eur. JOC **2008**, *5*, 801



Tet. Lett. **1980**, *21*, 4017

Again, Lithium Halogen Exchange shows a different regioselection



Thiophenes, pg 693

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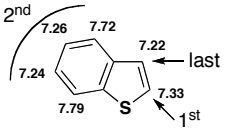
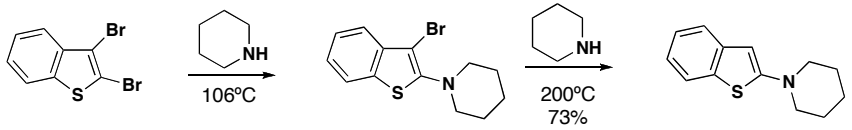
Benzothiophene

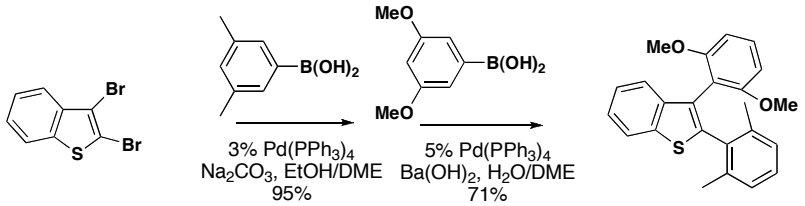


(CCl_4)

- S_NAr 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

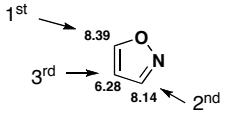


Synthesis **2002**, *2*, 213

1,2-Azoles



N-methyl pyrazole ($CDCl_3$)

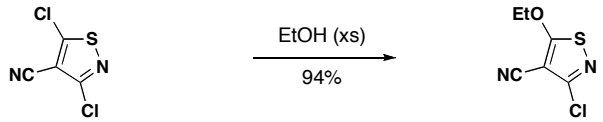


Isoxazole (CS_2)

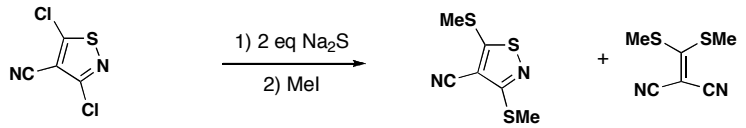


Isothiazole (CCl_4)

- Selective S_NAr 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.

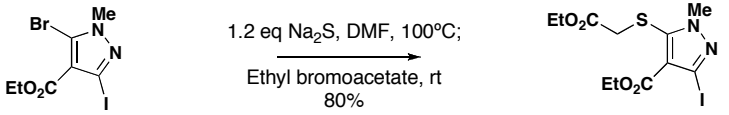


Attempts to displace the second chloride leads to mixtures with ring opened products.

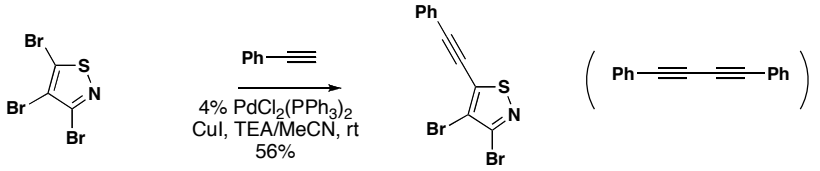


JOC **1964**, *29*, 660

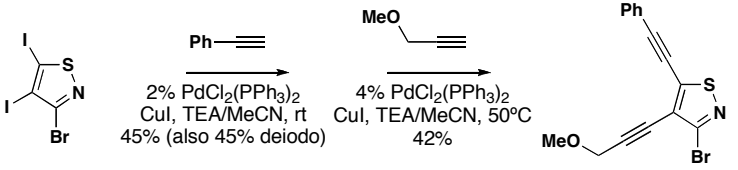
Pyrazole shows similar reactivity, with a bromide being displaces before an iodide.



Syn. Comm. **2008**, *38*, 674

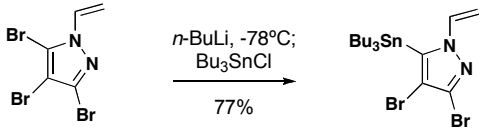


The remaining two bromides were unreactive in further Sonogashira couplings, even at higher temps



Russ. Chem. Bull. **1998**, *47*, 537

Tribromopyrazoles also lithiate at the most reactive C-5



Tetrahedron **2007**, *63*, 56

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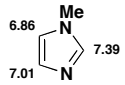
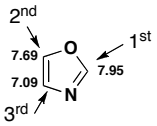
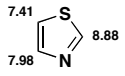
1,3-Azoles



N-methyl imidazole ($CDCl_3$)

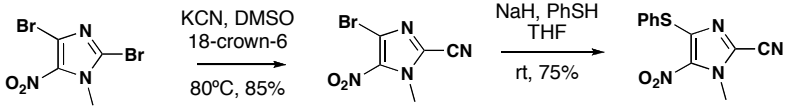


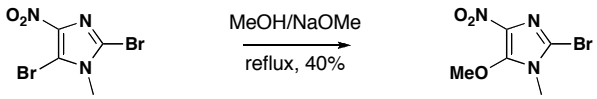
Oxazole (CCl_4)



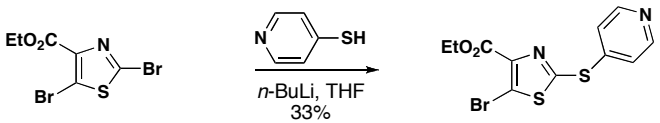
Thiazole ($CDCl_3$)

- S_NAr 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>5>4, Also note that the relative order chemical shifts switches in oxazole.

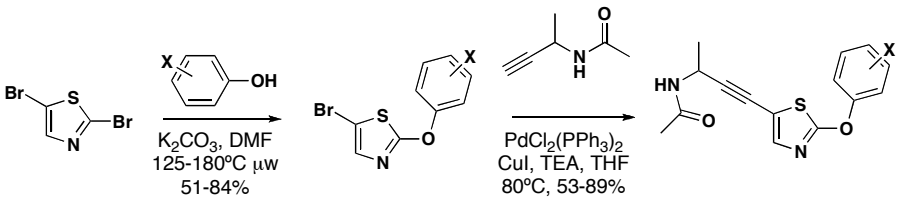




J. Het. Chem **2000**, *37*, 119

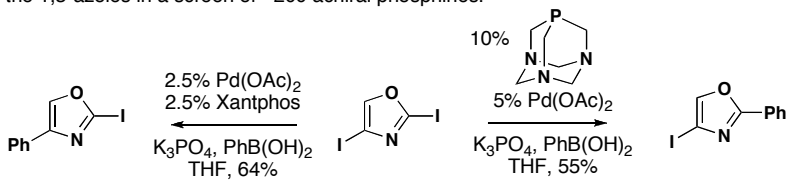


Heterocycles **2007**, *72*, 293



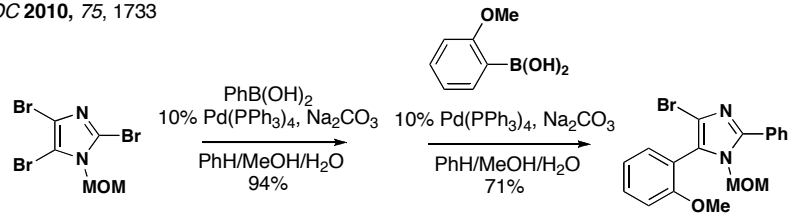
Bioorg. Med. Chem. Lett. **2006**, *16*, 6078

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.



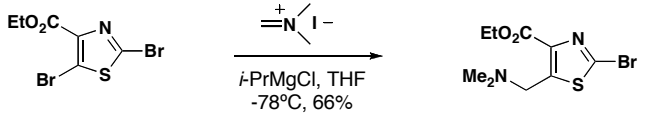
Similar or better results were obtained for imidazoles, but selective C-4/C-5 over C-2 Suzuki couplings of dihalo thiophenes was not observed in any cases. No C-4 vs C-5 studies were undertaken.

JOC **2010,** *75*, 1733



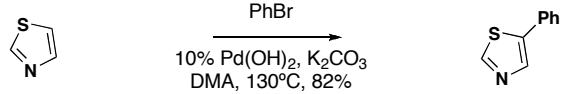
Chem. Pharm. Bull. **1996**, *44*, 1831

Regioselective Mg-Halogen exchange was observed of this dibromothiophene.

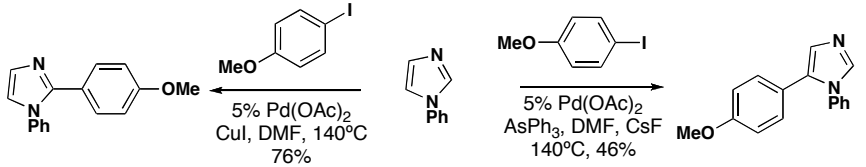


Heterocycles **2007**, *72*, 293

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



JOC **2005**, *70*, 7578



JOC **2005**, *70*, 3997, *Eur. JOC* **2006**, 1379

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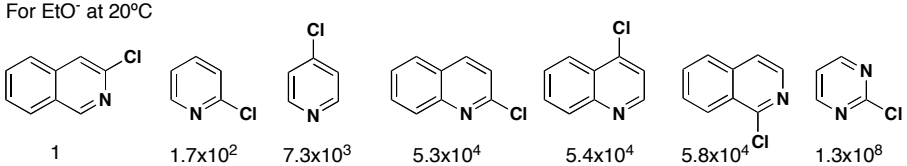
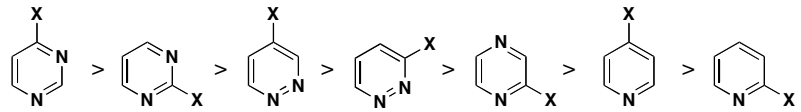
Haloselectivity of Heterocycles

Will Gutekunst

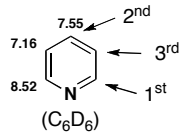
Some Relative Rates of Azines (Joule and Mills 4th Edition)

For EtO^- at 20ºC

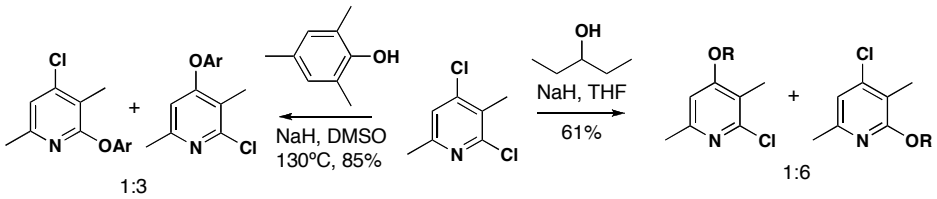


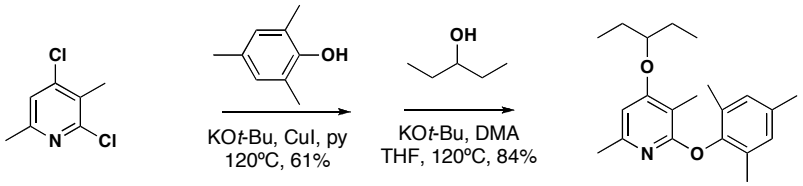


Pyridine

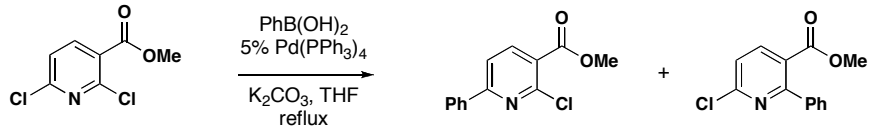


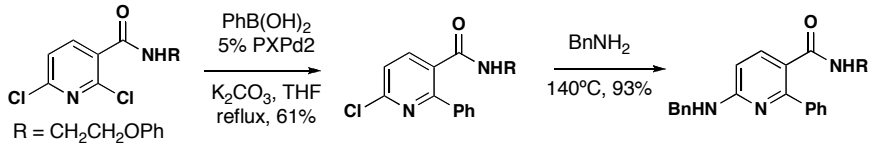
- Pyridines readily undergo S_NAr, usually faster at C-4 than C-2/6, but highly dependent on nucleophile and conditions. C-3/5 react much slower.
- Cross coupling reactions occur fastest at the 2/6 positions followed by C-4 and C-3/5 much slower, much in accord with the Handy predictions. Mono substitution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



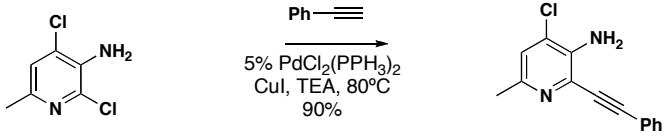


OPRD **2008**, *12*, 411

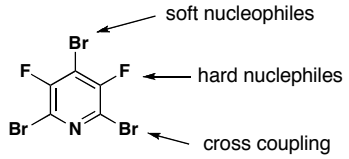




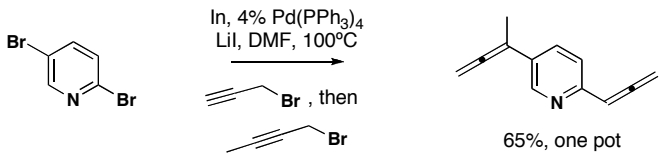
OL **2003**, *5*, 3131



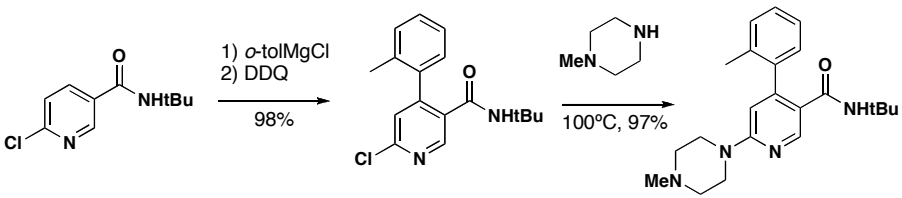
JMC **2000**, *43*, 4288



Tetrahedron **2005**, *61*, 2245

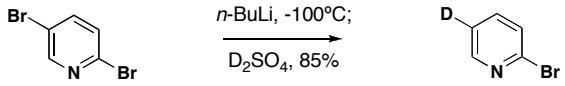


ACIEE **2002**, *41*,3901



JOC **2006**, *71*, 2000

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



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Haloselectivity of Heterocycles

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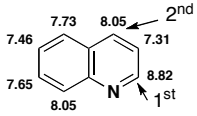
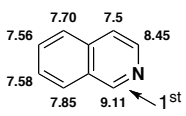
Quinoline/ Isoquinoline

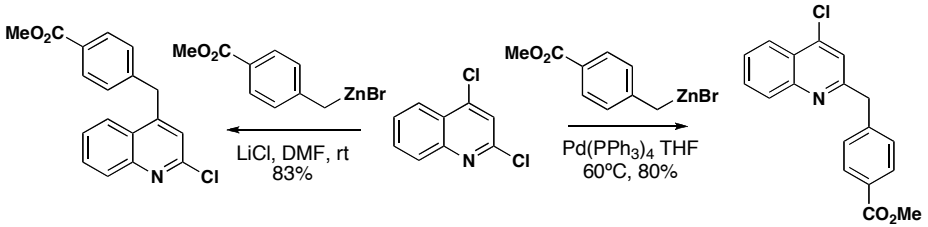


Quinoline (CCl_4)

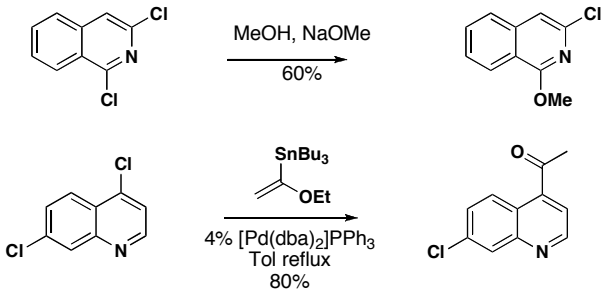


Isoquinoline (CCl_4)

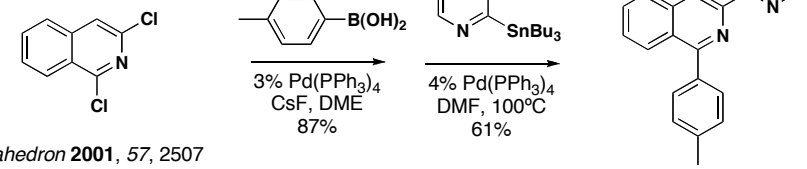
- S_NAr reactions of quinoline mimic pyridine largely, with C-4>C-2 generally preferred, but usually dependent on reaction conditions. Isoquinoline reacts fastest at C-1 followed by C-3 in S_NAr.
- Cross coupling reactions in quinoline strongly favor the 2 position followed by 4. Regioselection between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



JOC **1999**, *64*, 453

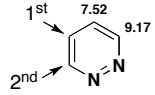


Tetrahedron **2001**, *57*, 2507



Tetrahedron **2001**, *57*, 2507

Pyridazine/Pyrazine

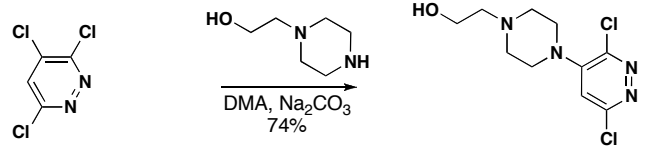


Pyridazine (C_6D_6)

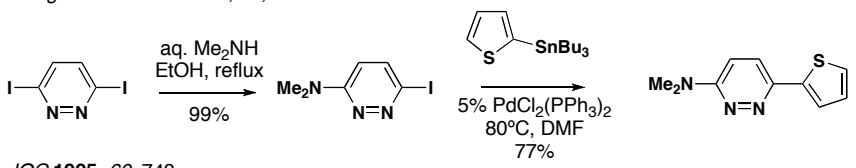


Pyrazine (C_6D_6)

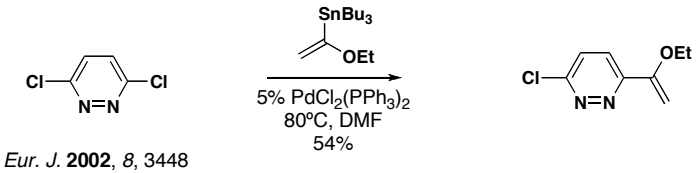
- S_NAr reactions occur readily at all of the positions. All sites are degenerate on pyrazine, and the 4-position is most activated for nucleophilic attack, despite NMR chemical shift.
- Selective cross coupling reactions have not been well studied on pyridazine, but modest selectivity can be obtained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



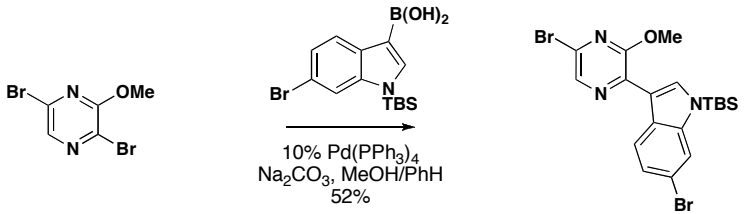
Bioorg. Med. Chem. **2009**, *17*, 621



JOC **1995**, *60*, 748



Chem. Eur. J. **2002**, *8*, 3448



JOC **2002**, *67*, 9392

Haloselectivity of Heterocycles

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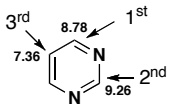
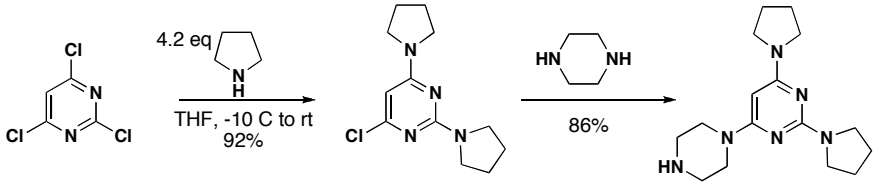
Pyrimidine

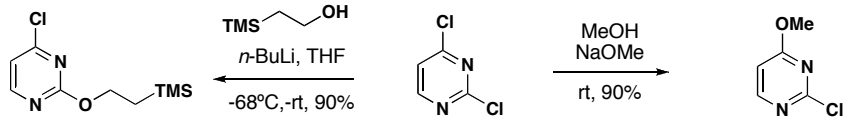


Pyrimidine (C_6D_6)

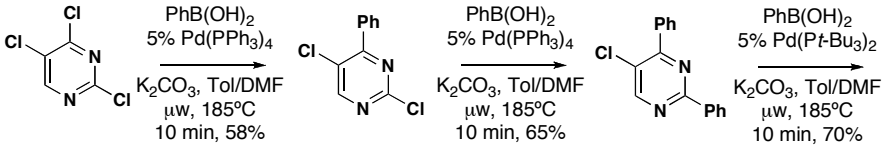
- Pyrimidines readily undergo S_NAr at the 2 and 4/6 positions. 4/6 being generally more reactive, but is very sensitive to reaction conditions. The 3-position is greatly deactivated relative to the others.
- Cross coupling reactions occur fastest at the 4/6 positions followed by C-2 and C-5 much slower,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



OPRD **2006**, *10*, 921

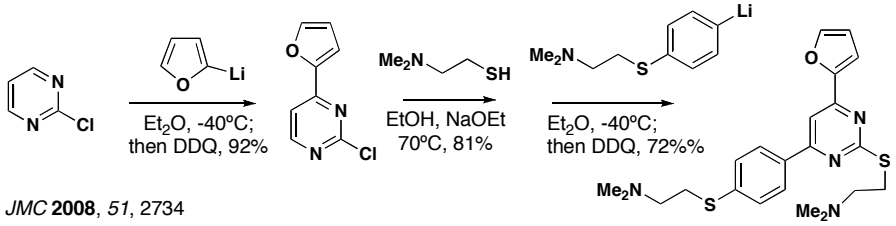


Chem. Soc. Perkin 2 **1989**, 1499; *J. Het. Chem.* **1994**, *31*, 989



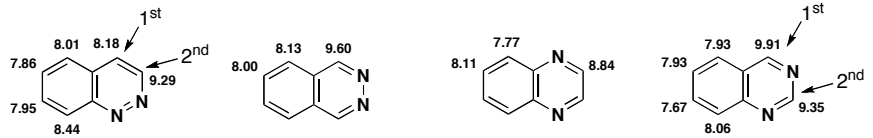
Tet. Lett. **2006**, *47*, 4415

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



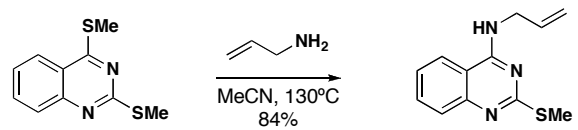
JMC **2008**, *51*, 2734

Benzannelated Diazines

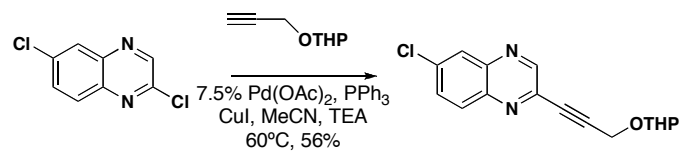


Cinnoline ($CDCl_3$) Phthalazine (acetone) Quinoxaline ($CDCl_3$) Quinazoline ($CDCl_3$)

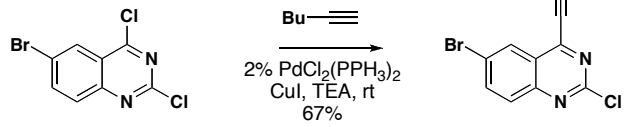
- S_NAr reactions occur readily at all of the heterocyclic positions. Behavior seems to be similar to the diazine counterparts, ie C-4 more reactive than C-2 in quinazolines, C-4>C-3 in cinnoline.
- Cross coupling reactions have not been well studied on these systems, but the few examples mimic the corresponding diazines well.



JMC **1993**, *36*, 2196



J. Chem. Soc. Perkin 1 **2001**, 978



Acta Chem. Scand. **1996**, *50*, 914

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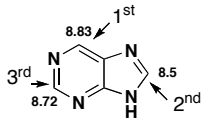
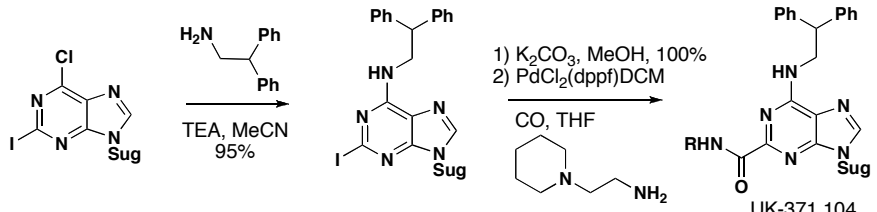
Purine

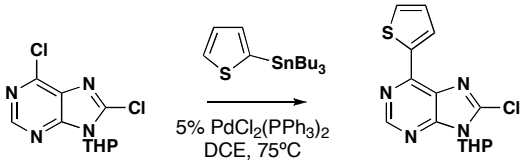


Purine (D_2O)

- Purines can participate in S_NAr 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.

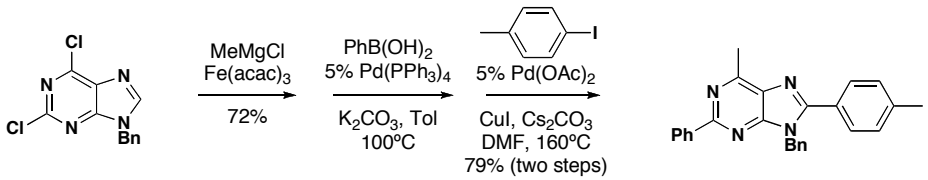


OPRD **2008**, *12*, 575

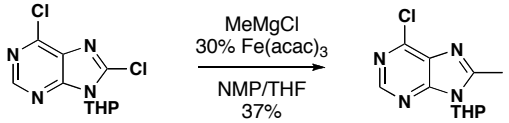


Acta Chem. Scand. **1999**, *53*, 366

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

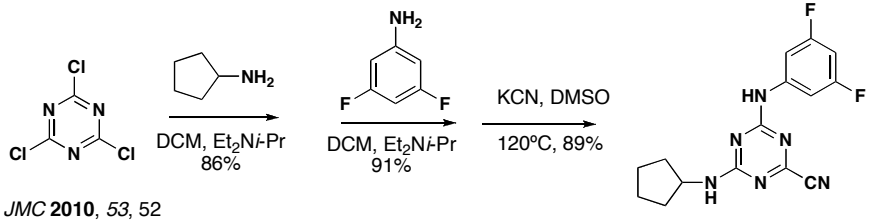


OL **2006**, *8*, 5389

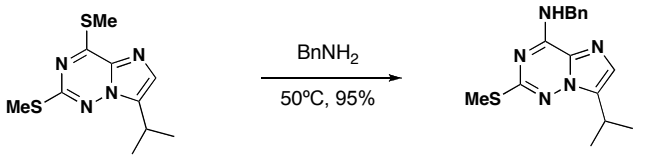


Synlett **2004**, *6*, 889

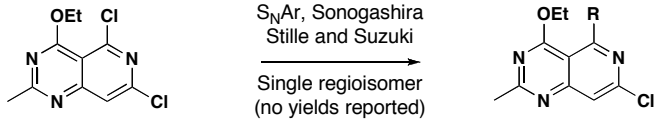
Misc Examples



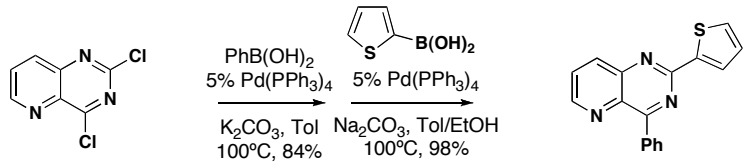
JMC **2010**, *53*, 52



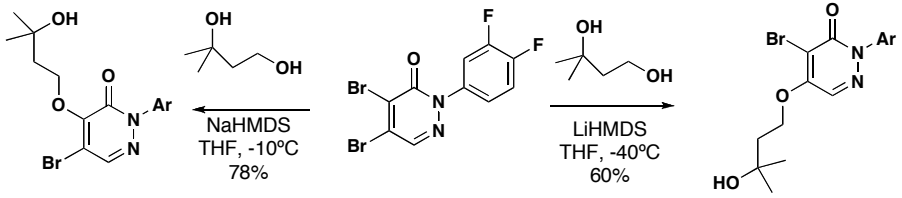
JMC **2009**, *52*, 655



Tet. Lett. **2006**, *47*, 8917



OL **2007**, *9*, 4673



OPRD **2006**, *10*, 512

Conclusions

Selective reactions of polyhaloheterocycles has proven to be a very powerful method for synthesis of functionalized heterocycles. Frequently cross-coupling and S_NAr 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.

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