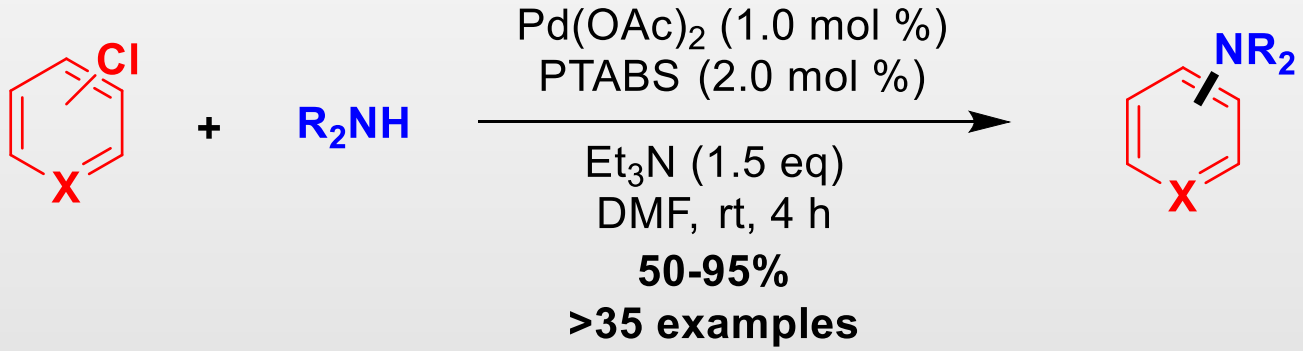
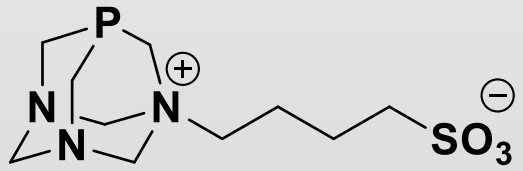
Pd/PTABS: Catalyst for Room Temperature Amination of Heteroarenes

Murthy Bandaru, S. S.; Bhilare, S.; Chrysochos, N.; Gayakhe, V.; Trentin, I.; Schulzke, C.; Kapdi, A. R.
Org. Lett. **2018**, *20* (2), 473.



PTABS:



Current Literature

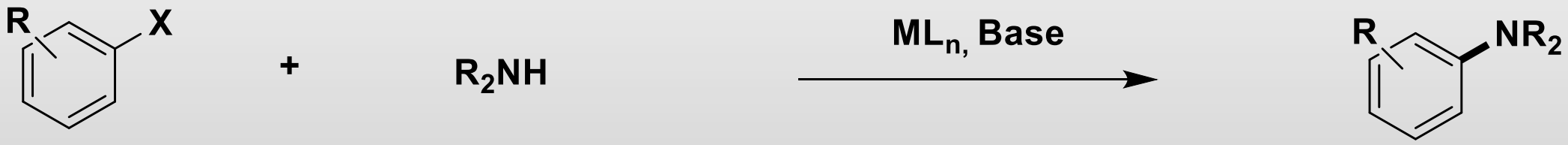
Joseph Lizza

5/26/2018

Outline

- Background
  - Aryl C-N Coupling Reactions
  - Arylchloride – Amine Coupling
  - Room Temperature Coupling of Arylchlorides and Amines
  - Introduction to the PTABS Ligand
- Title Paper
- Future Directions and Improvements
- Summary

Metal Catalyzed Aryl C-N Bond Formations

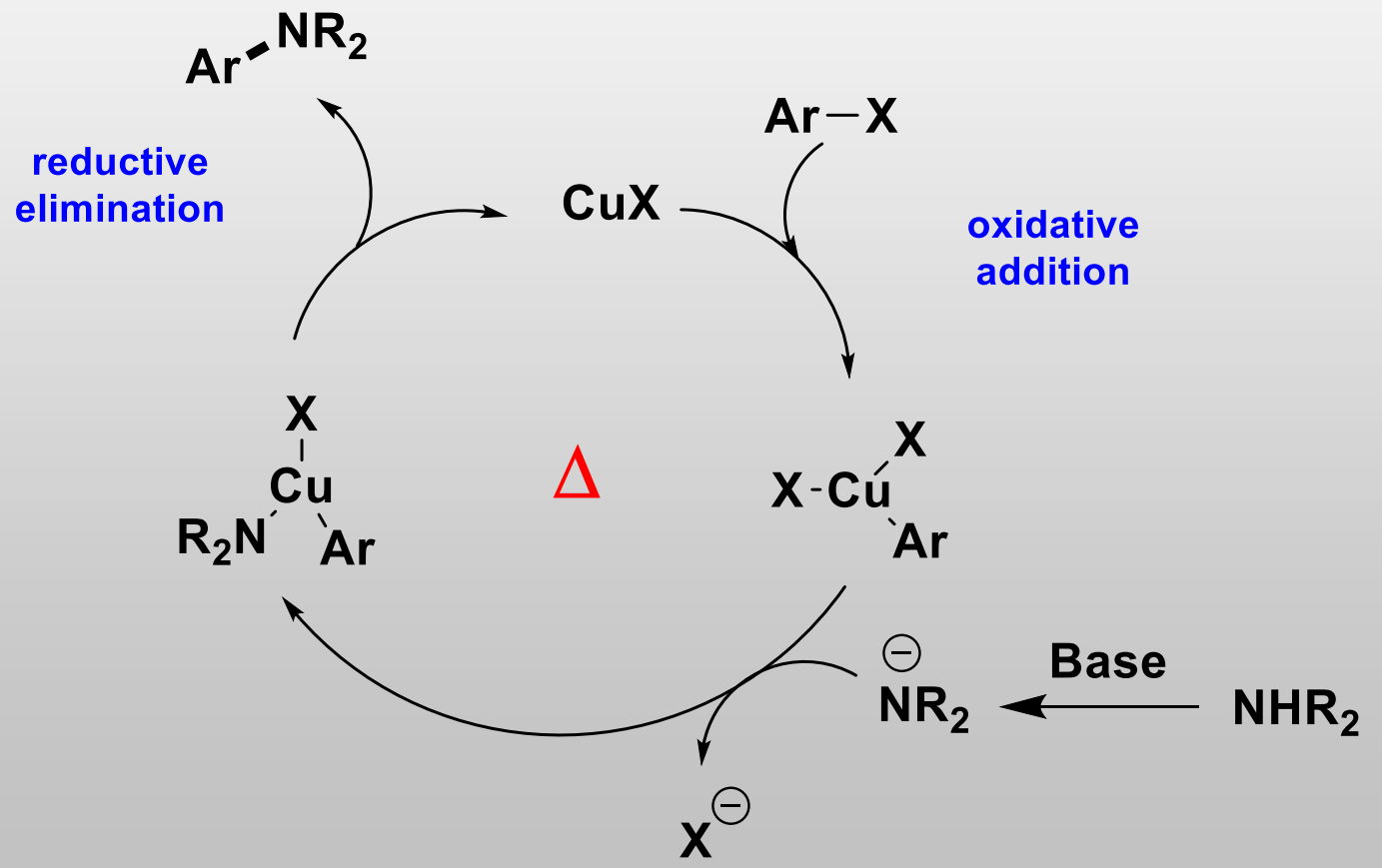


X = Cl, Br, I, OTf, OTs **R = Ar, Alkyl, H**

Ullman-Goldberg Reaction (1903)
M = Cu

- **Harsh conditions**
  >90 °C
  long reaction times
- Stoichiometric copper

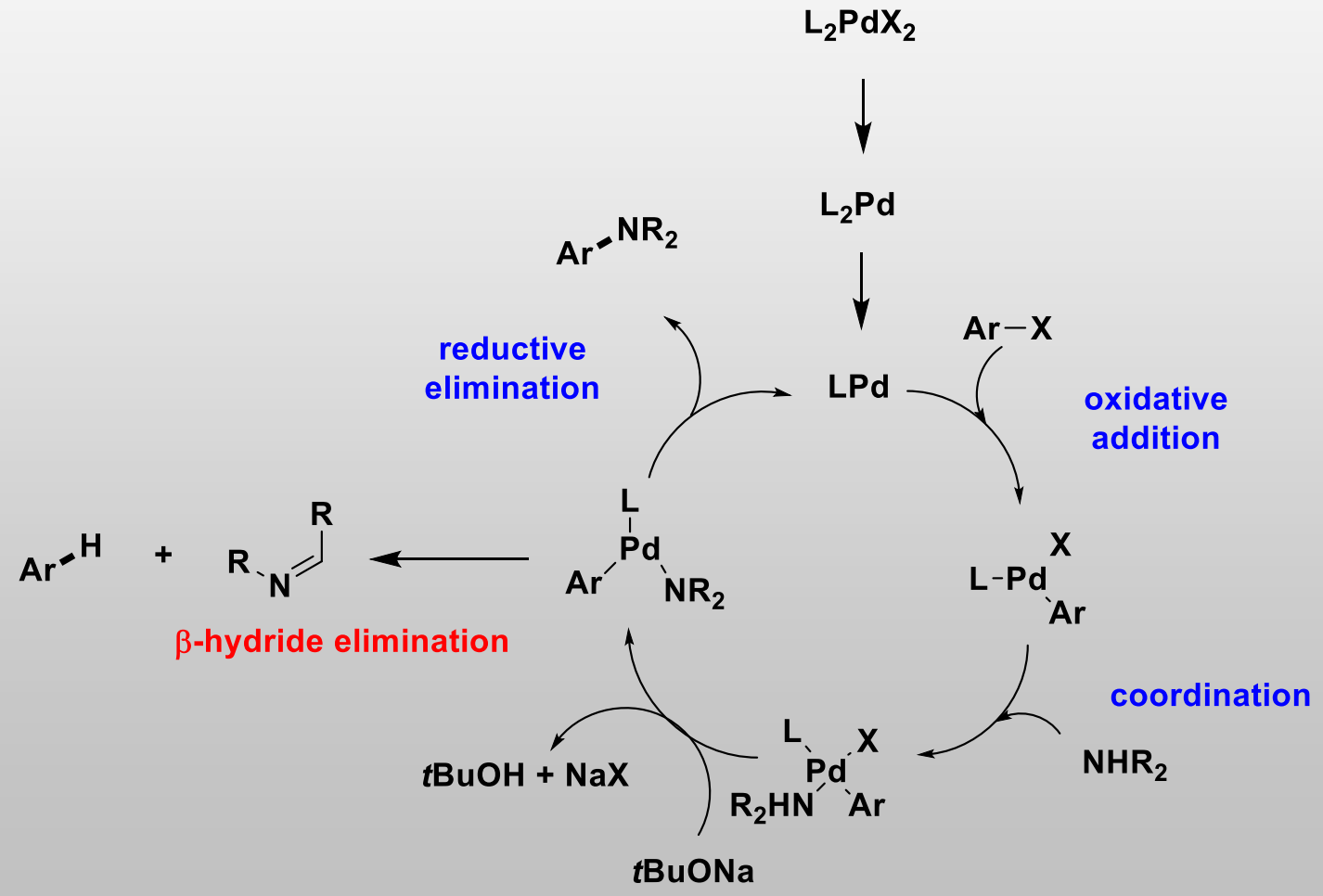
  but…
- Making a comeback (2002)



SynArchive

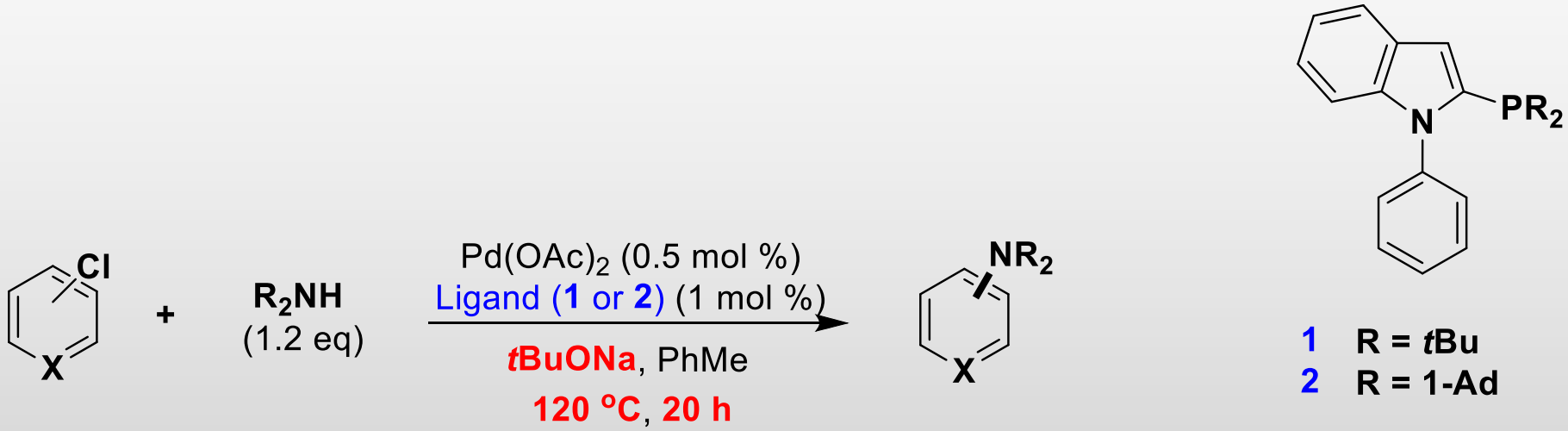
Buchwald-Hartwig Amination (1994)
M = Pd

- Robust and versatile
- Low catalyst loading
- Extensively modeled
- "Go-to" for aryl C-N bond formation

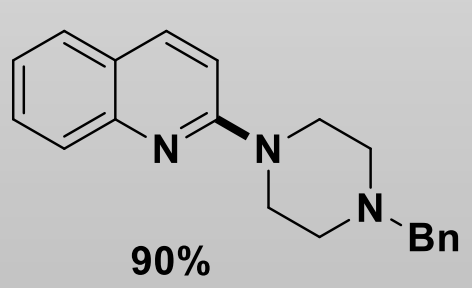


SynArchive

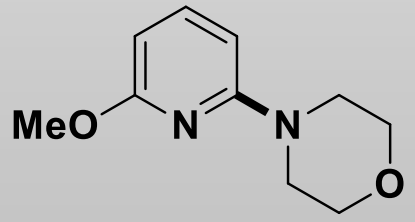
Heteroaryl Chloride – Amine Coupling



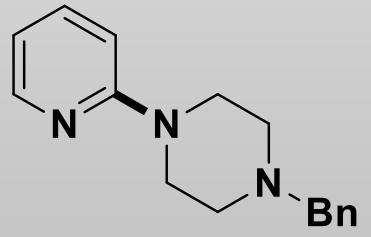
Representative Examples:



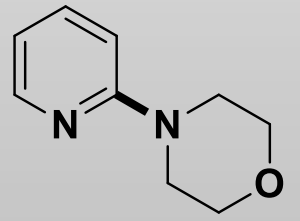
90%



99%



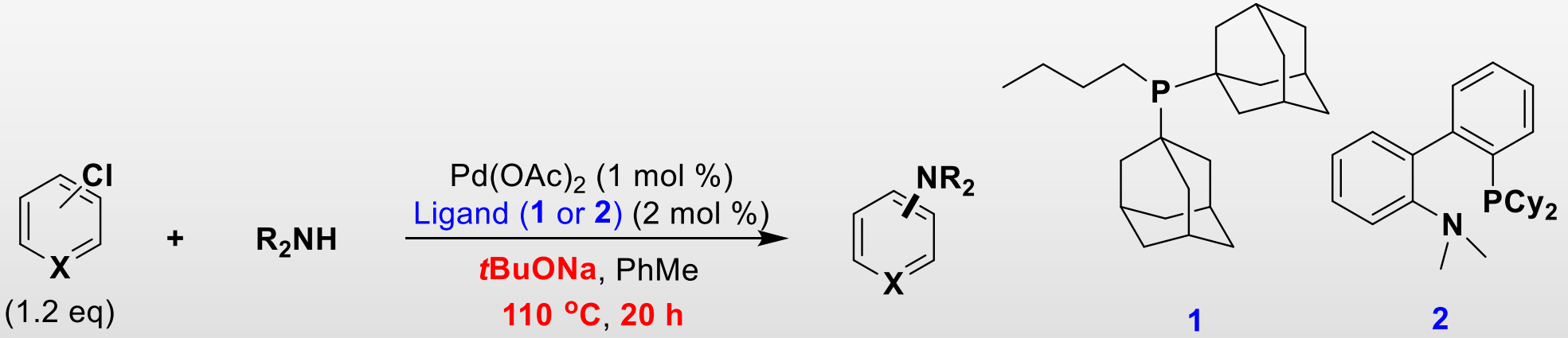
77% (2) 99% (1)



60% (2) 99% (1)

Beller et al. J. Mol. Catal. A Chem. 2002, 182–183, 515.

Heteroaryl Chloride – Amine Coupling



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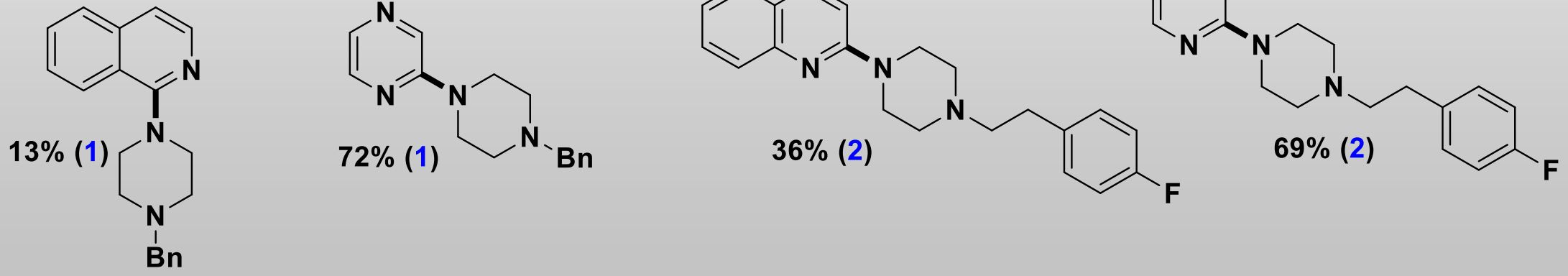
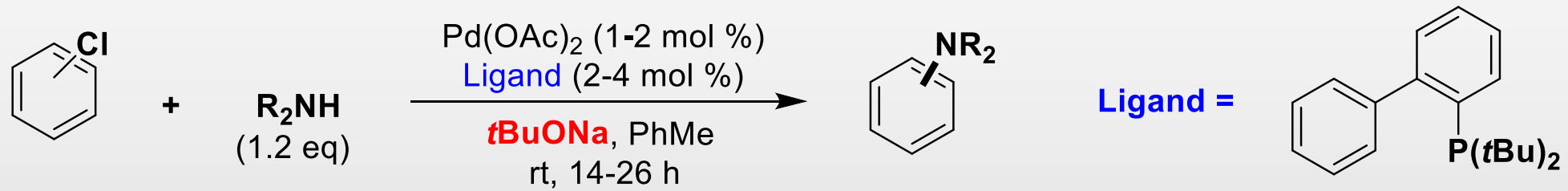


Beller et al. Tetrahedron Lett. 2004, 45 (10), 2057.

Room Temperature Aryl C-N Coupling



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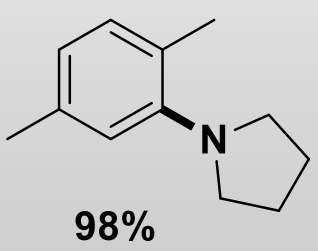
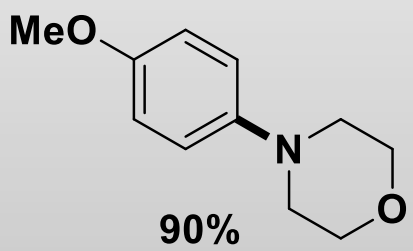
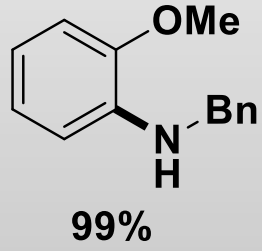
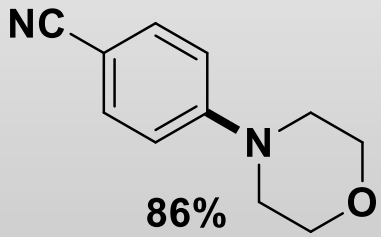




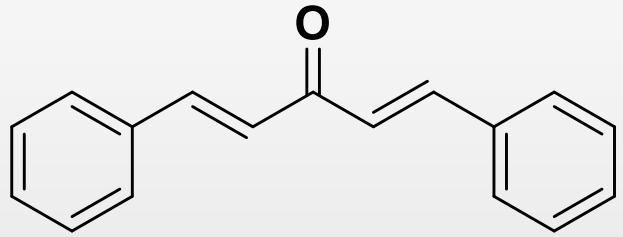


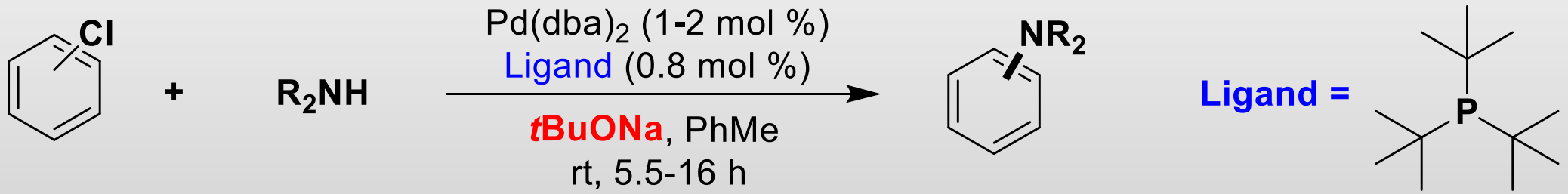


"inefficiency of the room-temperature reactions in the presence of bases weaker than *t*BuONa"

Buchwald et al. L. Angew. Chemie - Int. Ed. 1999, 38 (16), 2413.

Room Temperature Aryl C-N Coupling

dba = 



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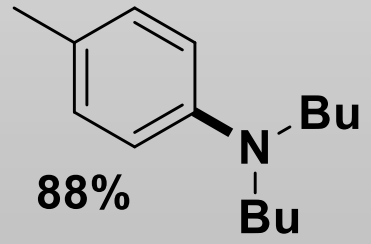
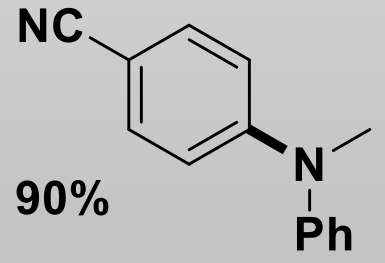
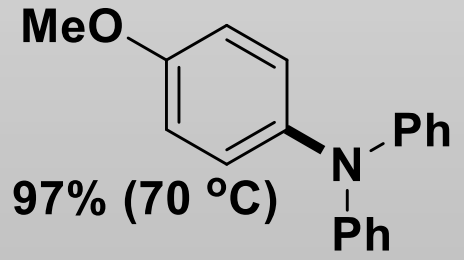
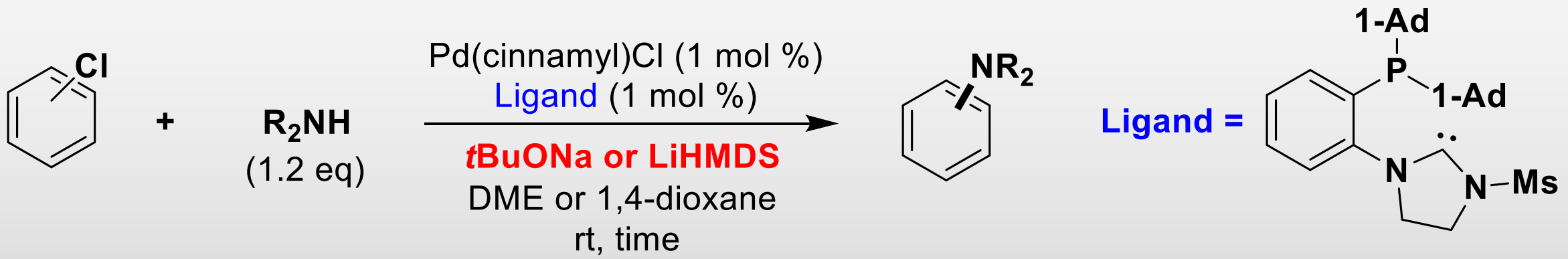






Hartwig et al. J. Org. Chem. 1999, 64 (15), 5575.

Room Temperature Aryl C-N Coupling



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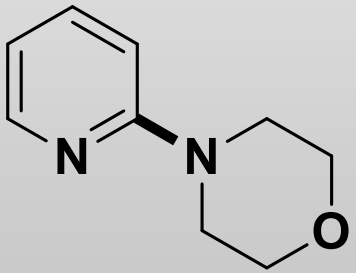
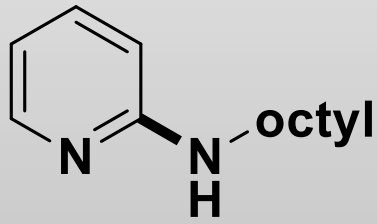


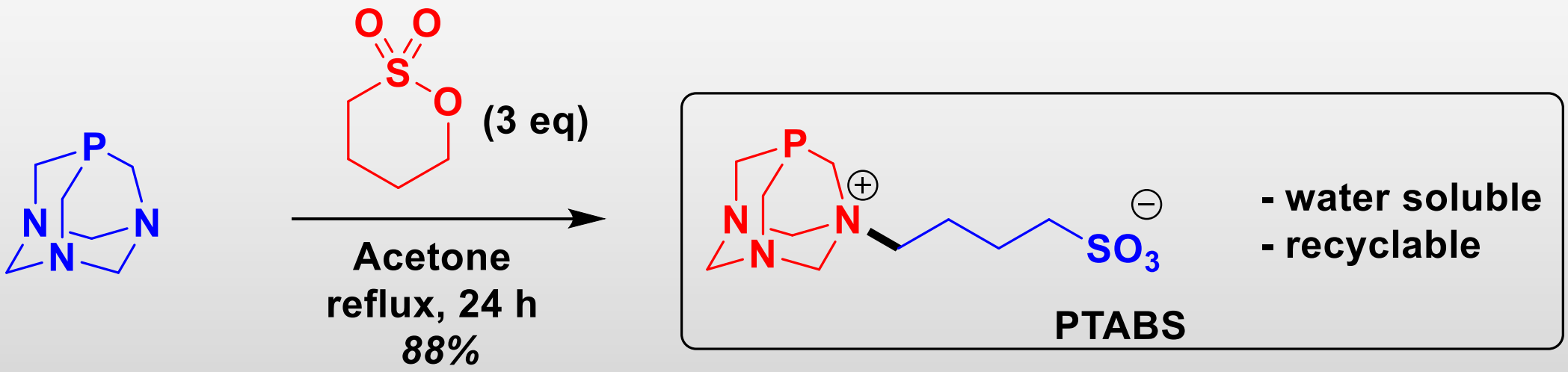
92%, *t*BuONa
DME, 19 h



91%, LiHMDS
1,4-dioxane, 1 min

Stradiotto et al. Organometallics 2013, 32 (21), 6148.

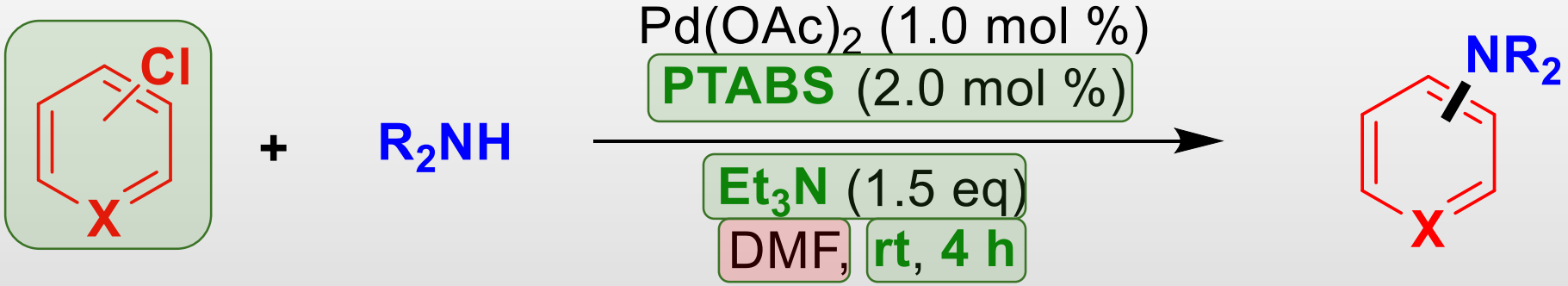
PTABS Ligand

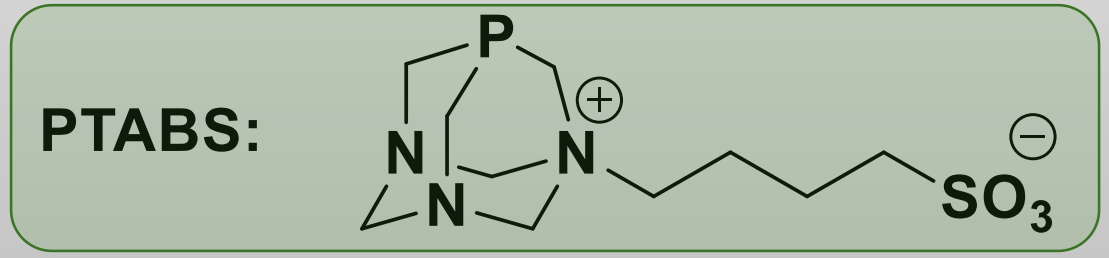


- ligand for Suzuki-Miyaura Reaction in water (*16 examples, 72-88% yield*)
Sonogashira Reaction in MeCN:water (*5 examples, 68-78% yield*)
Heck Reaction in MeCN:water (*synthesis of anti-viral drug BVDU*)

Kapdi et al. RSC Adv. 2016, 6 (87), 83820.

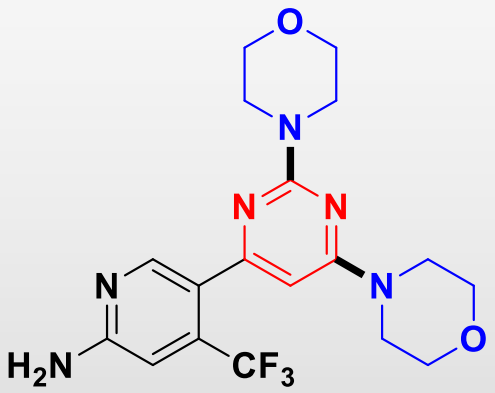
Title Paper



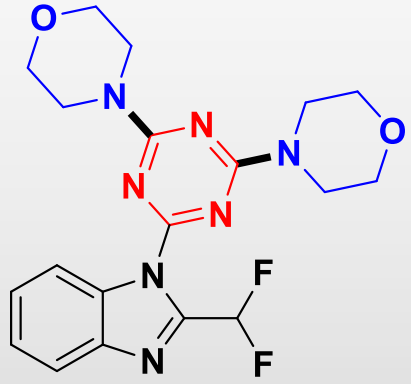


Kapdi et al. A. R. Org. Lett. 2018, 20 (2), 473.

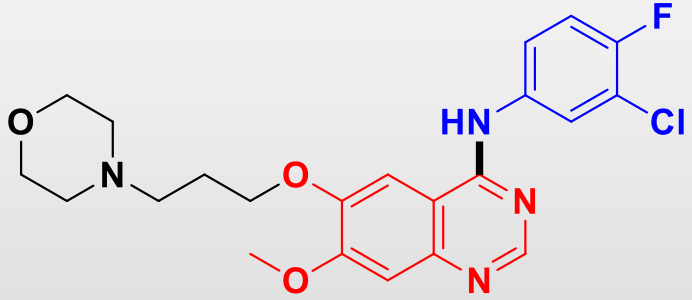
Relevant Pharmaceuticals



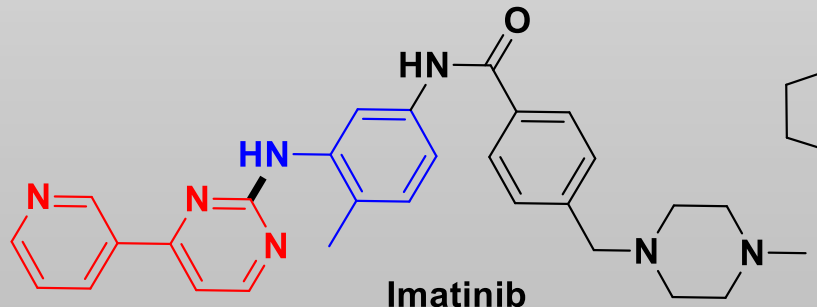
Buparilsib
(anticancer)



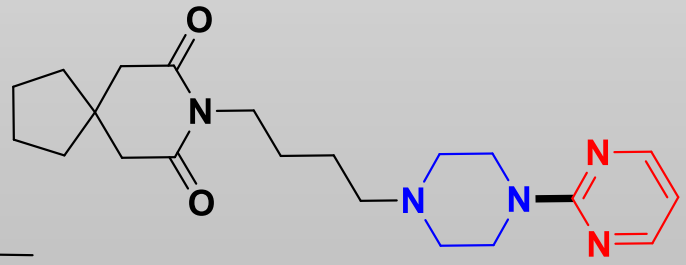
ZSTK474
(PI3K inhibitor)



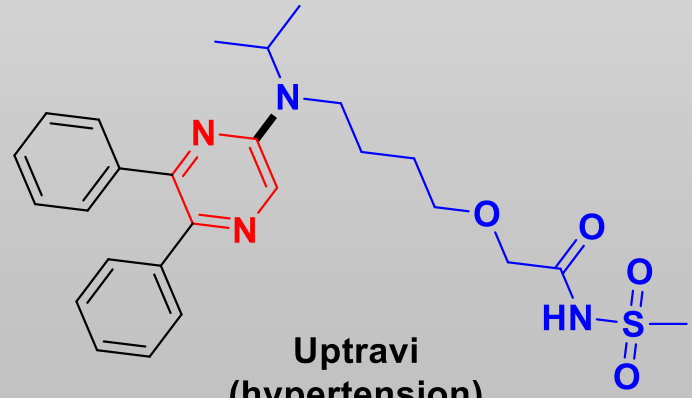
Gefitinib
(anticancer)



Imatinib
(anticancer)



BuSpar
(andipressant)



Uptravi
(hypertension)

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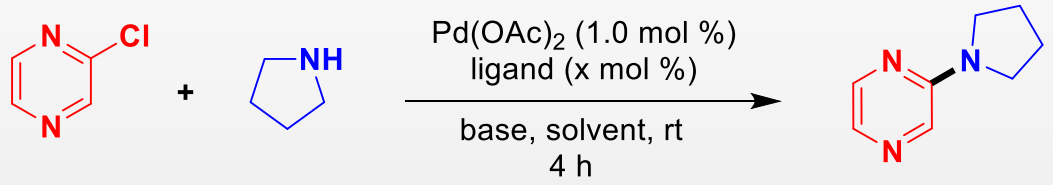
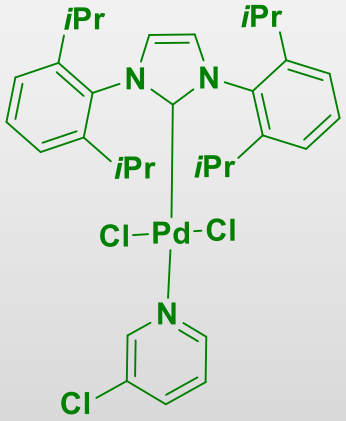
Ligand Screen / Optimization



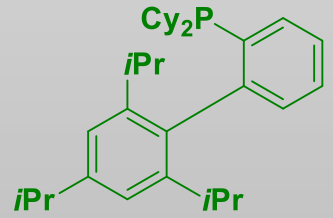
Amine eq	Ligand	Ligand Loading	Base (eq)	Solvent	Yield
2	-	-	-	DMF	0
2	PPh_3	1.0 mol %	-	DMF	30
2	XPhos	2.0 mol %	-	DMF	73
2	PEPPSI (1 mol %)	-	-	DMF	75
2	PTAPS	1.0 mol %	-	DMF	55
1.2	PTABS	1.0 mol %	K_2CO_3 (1.0)	DMF	72
1.2	PTABS	2.0 mol %	*t*BuOK (1.0)	DMF	74
1.2	PTABS	2.0 mol %	Et_3N (1.5)	DMF	88
1.2	PTABS	2.0 mol %	Et_3N (1.5)	H_2O	69
1.2	PTABS	2.0 mol %	Et_3N (1.5)	MeCN	72
1.2	PTABS	2.0 mol %	Et_3N (1.5)	H_2O:ACN	75

PTAPS

PTABS



PEPPSI



XPhos

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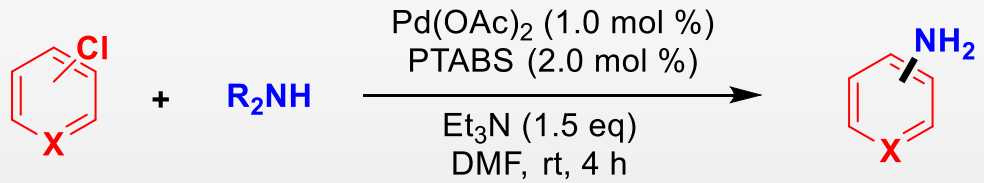
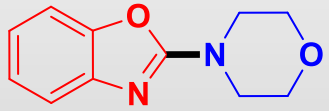
Scope





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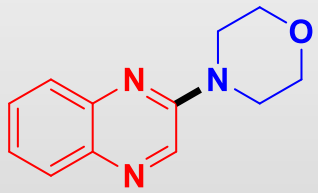

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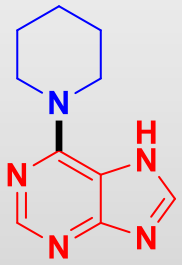

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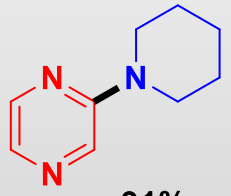

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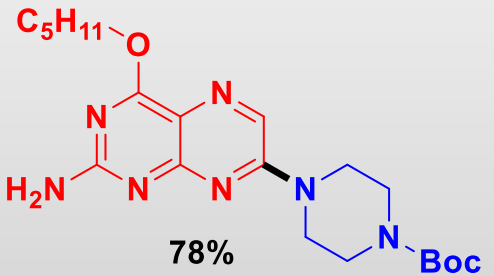

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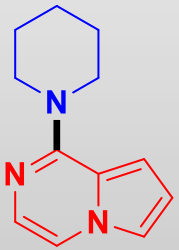

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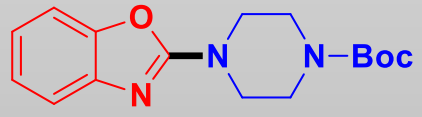

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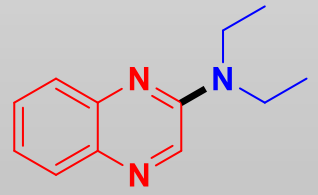

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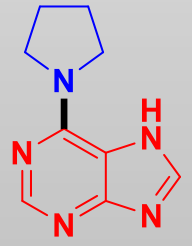

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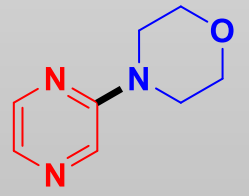

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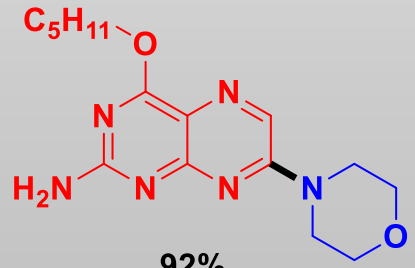

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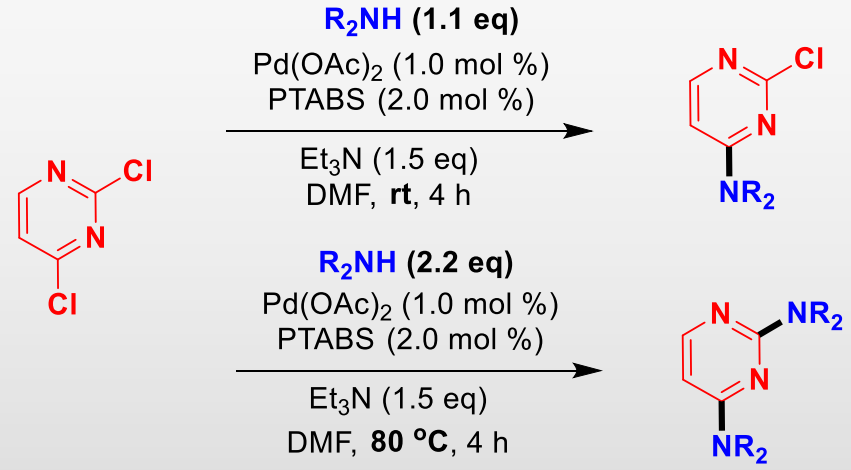
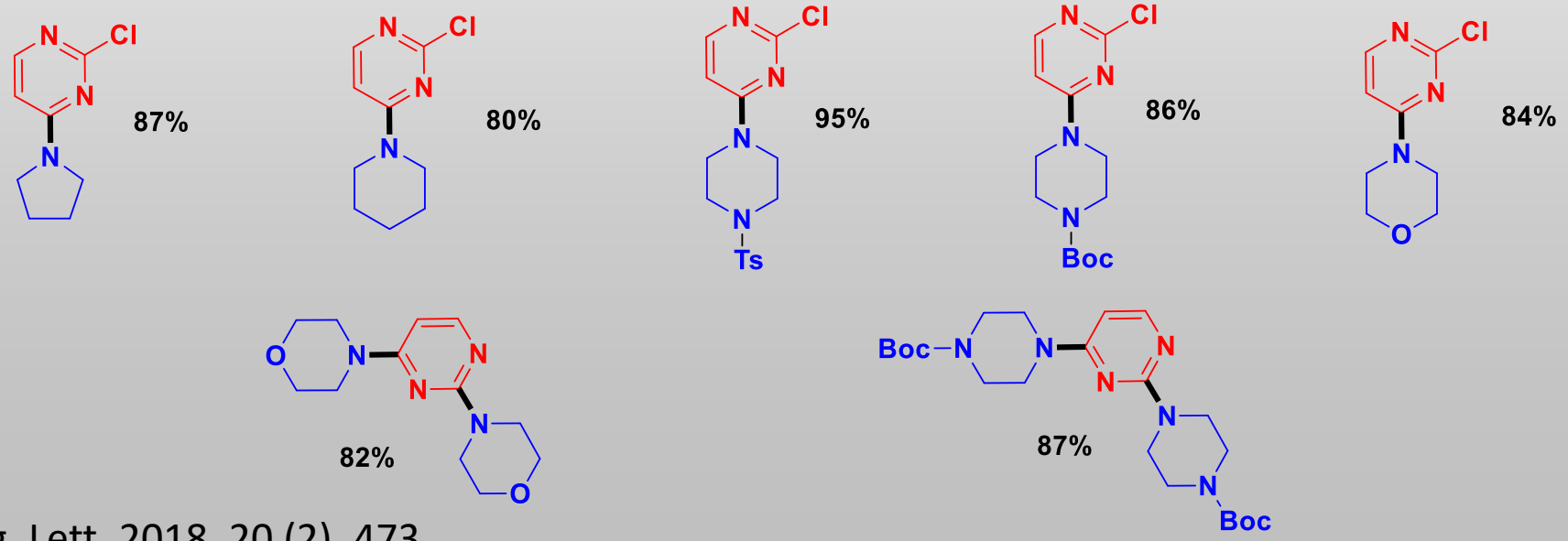
Monoselective Amination





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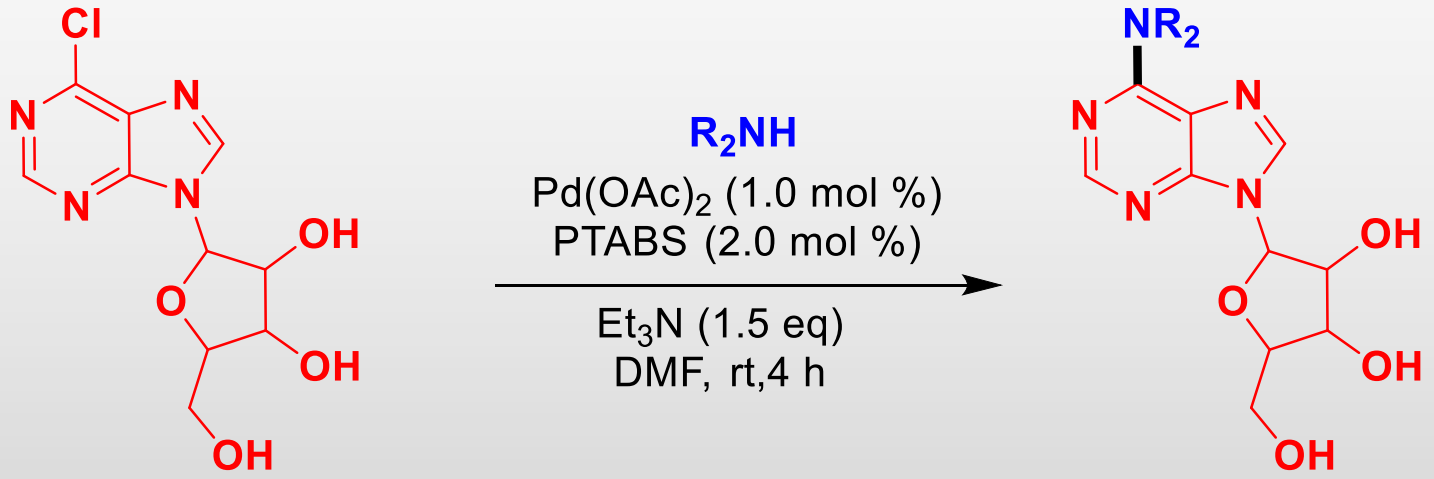
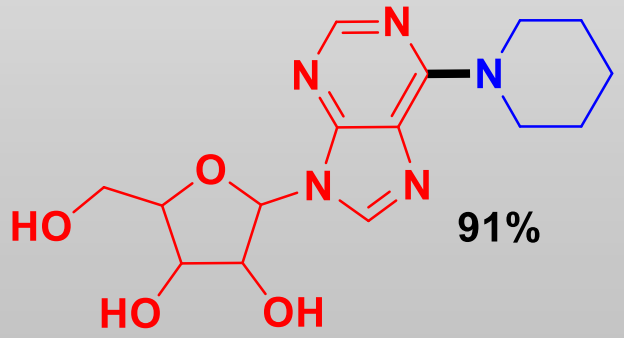
Furanosyl Purines





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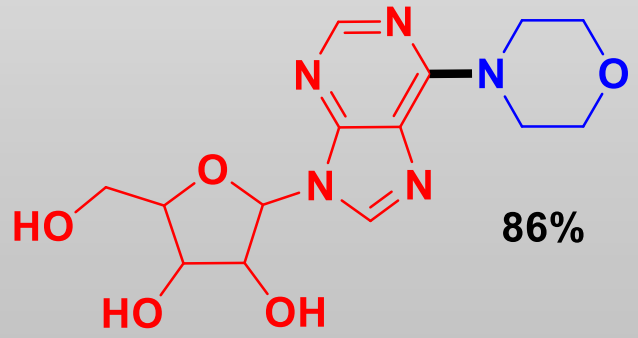

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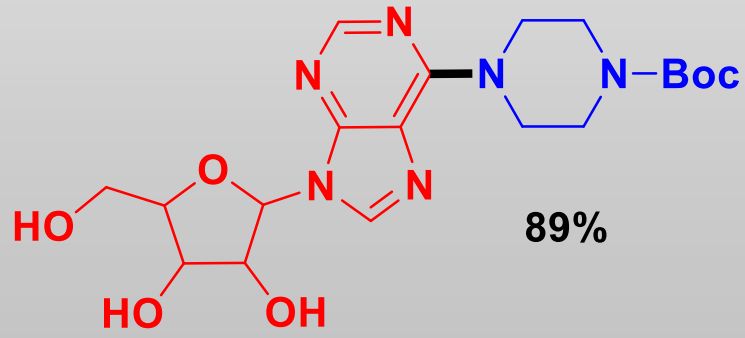
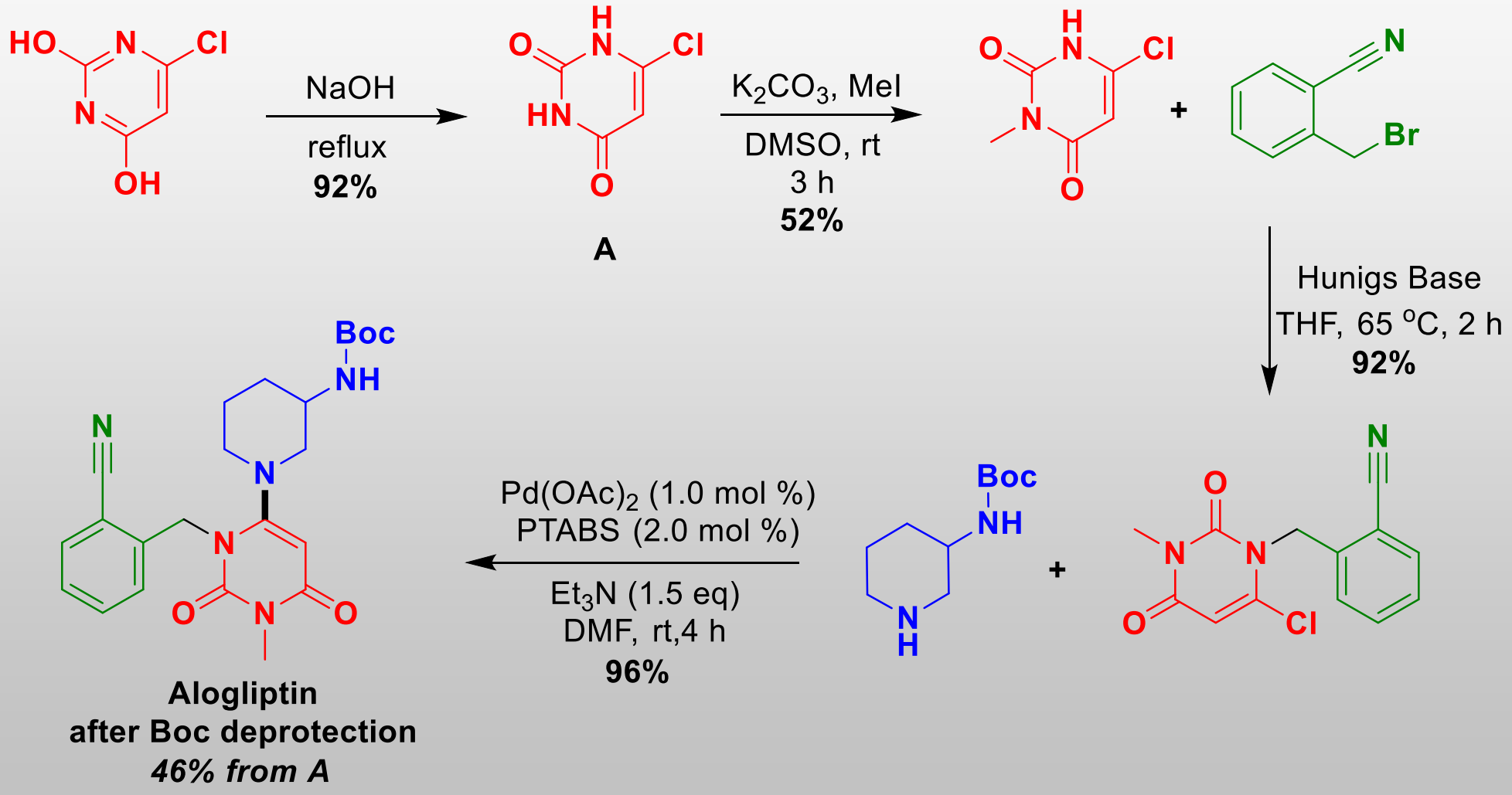


89%

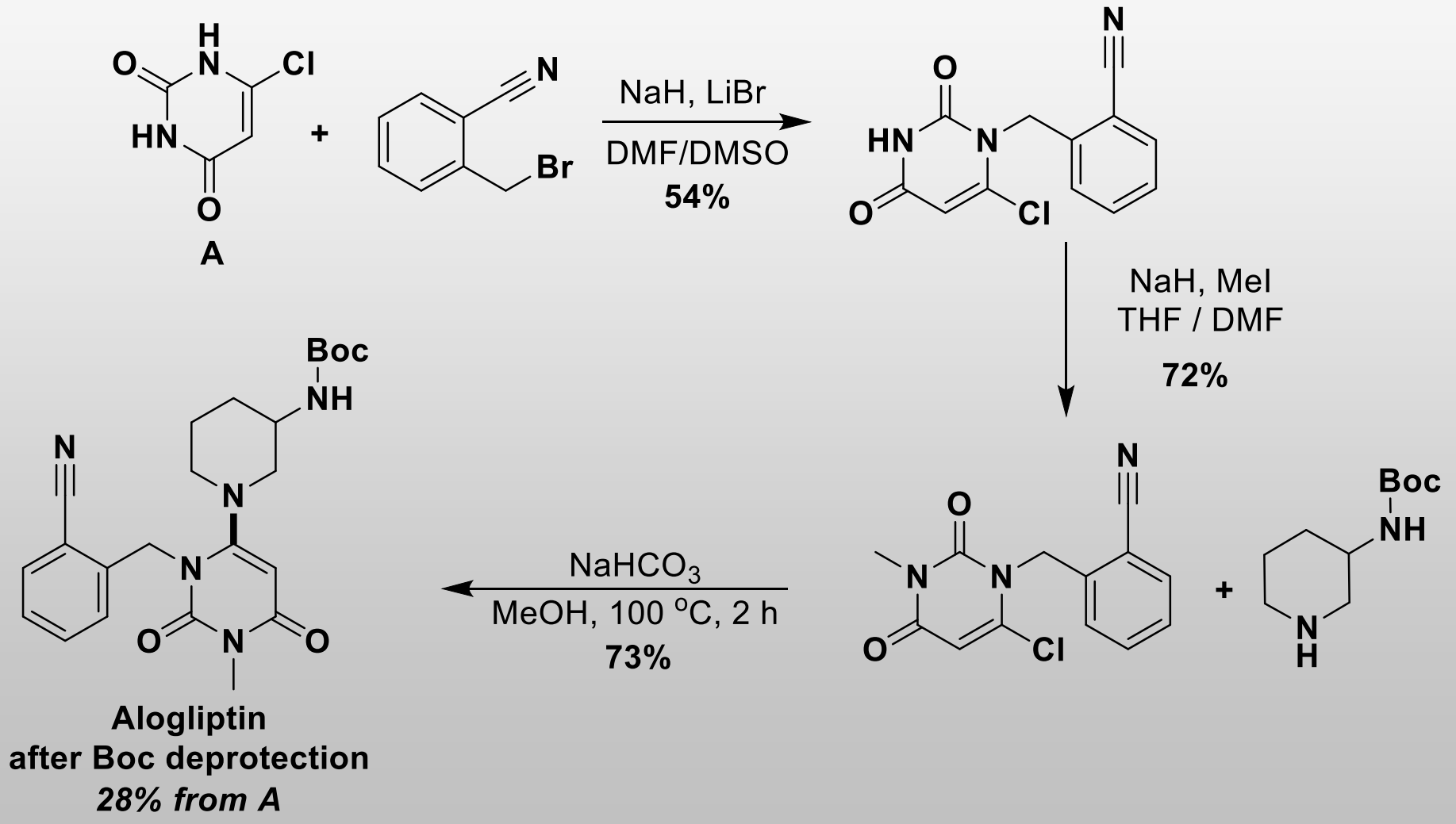
Kapdi et al. A. R. Org. Lett. 2018, 20 (2), 473.

Formal Synthesis of Alogliptin



Kapdi et al. A. R. Org. Lett. 2018, 20 (2), 473.

Previous Synthesis of Alogliptin



Feng et al. J. Med. Chem. 2007, 50 (10), 2297.

Future Directions

- Large Scale Application
- Primary Amines
- *Ortho* substituted heteroarenes
- Broader Amine Scope (substituted cyclic amines…)

Summary

- Heteroarylation of amines at room temperature
- Short reaction times
- Utilizing a recyclable, water-soluble catalyst
- Without use of strong base
- Broad scope of heteroaryl chlorides including unprotected nucleosides in good to excellent yields
- Synthesis of Alogliptin