Direct Synthesis of Diverse 2-Aminobenzo[*b*]thiophenes via Palladium-Catalyzed Carbon-Sulfur Bond Formation Using $Na_2S_2O_3$ as the Sulfur Source

Chuanwei Hou, Qian He, and Chunhao Yang

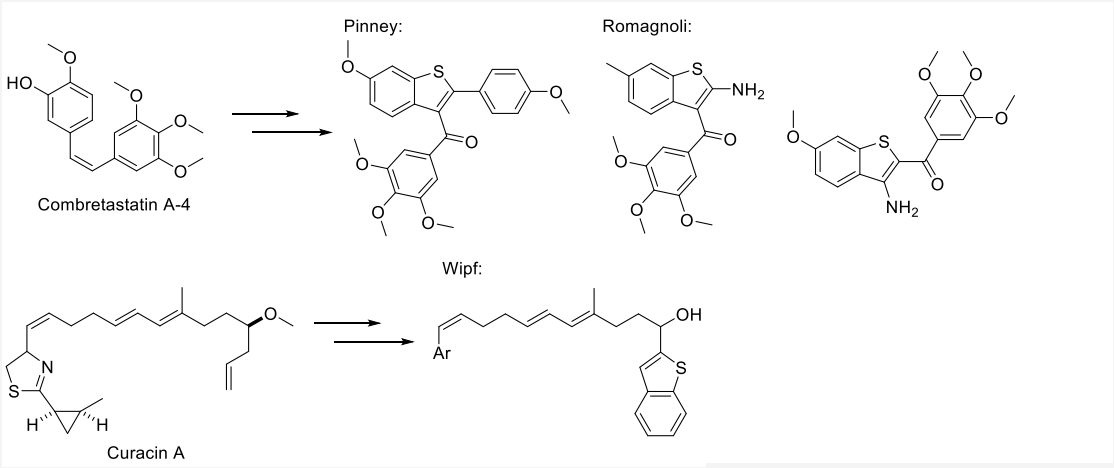
Shanghai Institute of Materia Medica, Chinese Academy of Scineces

Org. Lett. **2014**, *16*, 5040.

Celeste Alverez
Current Literature
10/11/2014

Benzothiophenes

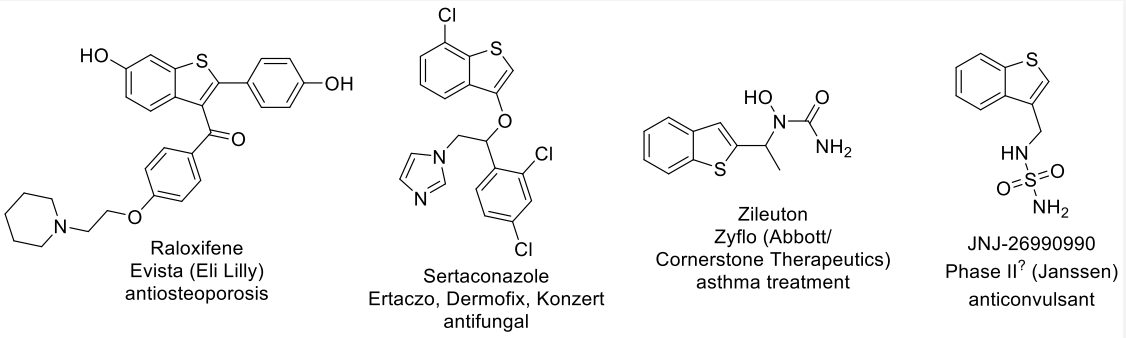
- A privileged scaffold
- Used as a replacement in some natural product analogs:



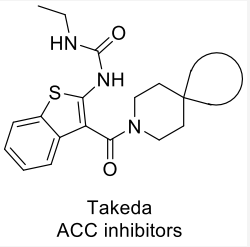
Bioorg. Med. Chem. Lett. **1999**, *9*, 1081-1086. *J. Am. Chem. Soc.* **2000**, *122*, 9391-9395. *J. Med. Chem.* **2007**, *50*, 2273-2277.

Benzothiophenes

- Widely used in biologically active molecules

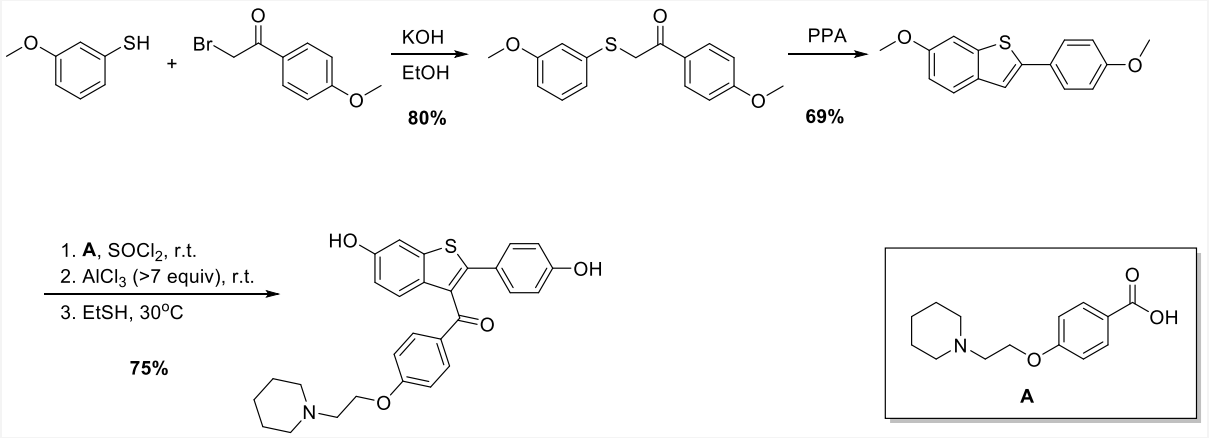


- Many reports of benzothiophenes in literature as bioactive molecules
  - Selective estrogen receptor modulators
  - Acetyl-CoA carboxylase inhibitors
  - HIV-1 RT inhibitors
  - Antidepressants
  - Tubulin polymerization inhibitors



Raloxifene

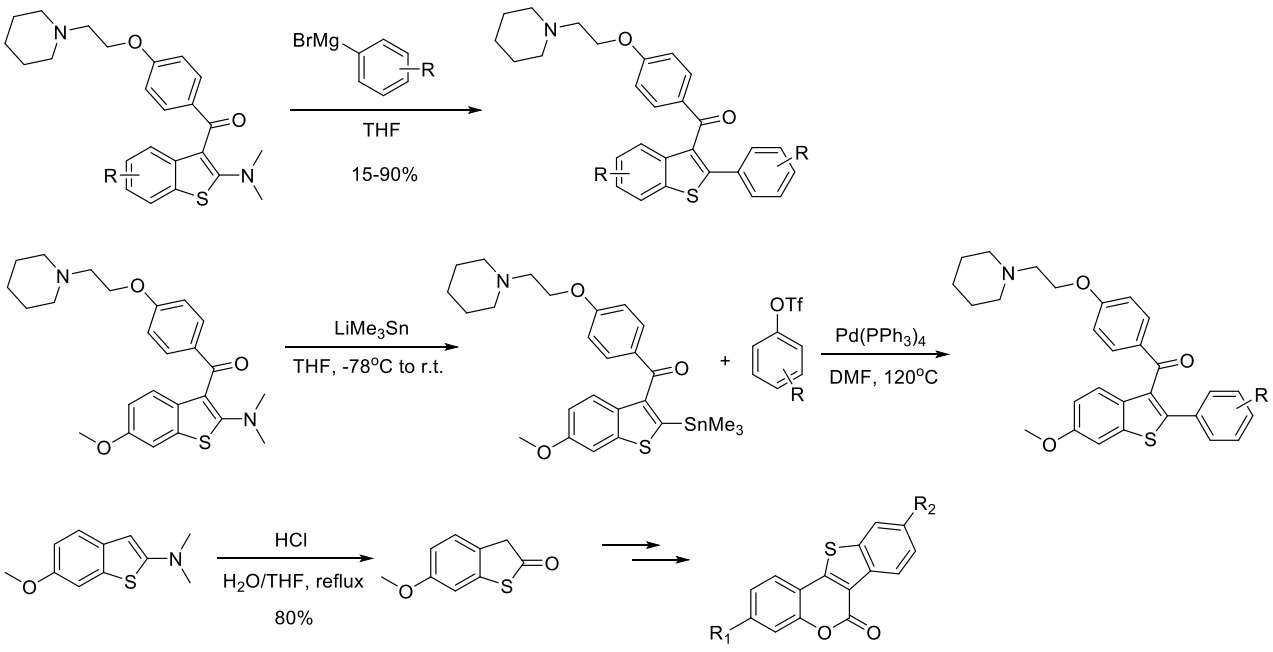
- Eli Lilly blockbuster osteoporosis drug
- A selective oestrogen receptor modulator (SERM)
- Also used as a preventative for invasive breast cancer in post-menopausal women
- Benzothiophene core
- Early synthesis:



MedlinePlus. http://www.nlm.nih.gov/medlineplus (accessed Oct 7, 2014).
J. Med. Chem. **1984,** *27,* 1057-1066.

2-Amino benzothiophene in Raloxifene synthesis

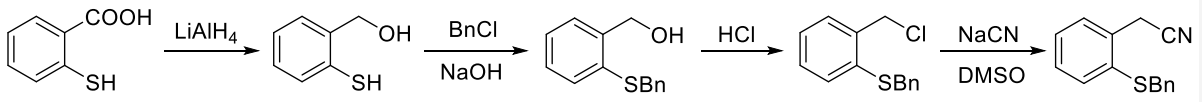
- Routes to Raloxifene and analogs via the *N,N*-dimethyl-2-aminobenzothiophene have been proposed:

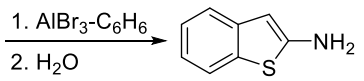


J. Med. Chem. **1997,** *40,* 146.
Bioorg. Med. Chem. **2003,** *11,* 3449.
J. Med. Chem. **1998,** *41,* 1272.

Approaches to 2-amino benzothiophenes

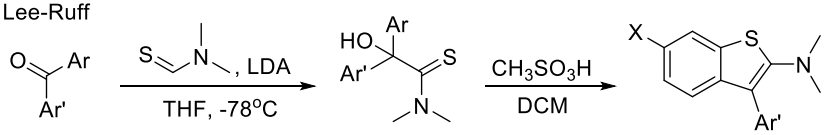
Wollner





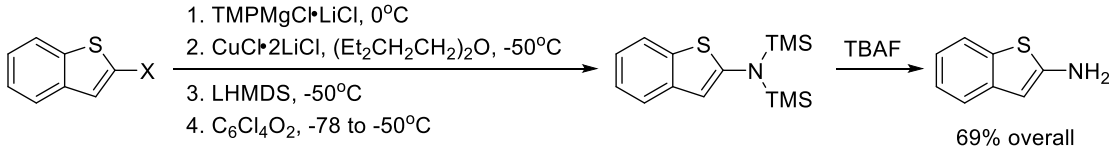
5 steps, 48% overall

Lee-Ruff



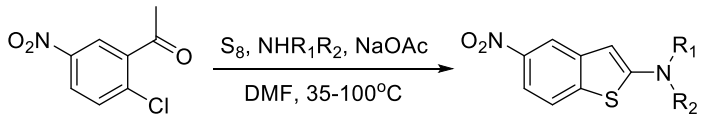
6 examples
25-80%

Knochel



69% overall

Jasinski

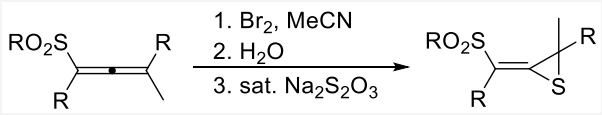


12 examples
7-49%

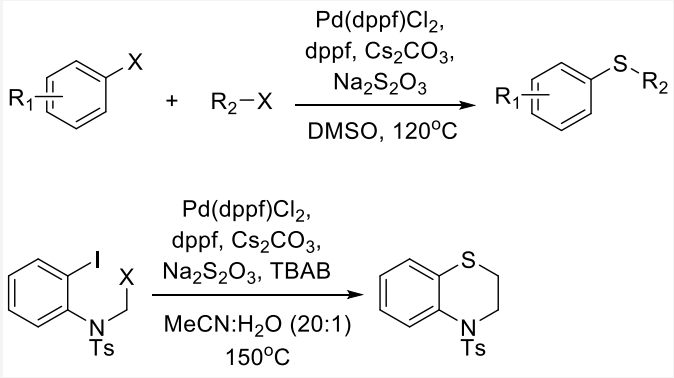
J. Org. Chem. **1965,** *30,* 4074.
Can. J. Chem. **1987,** *65,* 1800.
Angew. Chem., Int. Ed. **2006,** *45,* 7838.
Tetrahedron **2010,** *66,* 2474.

$Na_2S_2O_3$

- Recently used as sulfur source in synthesis of organosulfur compounds
- Ma: formation of 1-sulfonyl alkylidenethiiranes



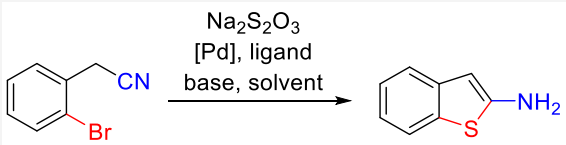
- Jiang: double C-S bond formations



- Advantages: odorless, stable, inexpensive, does not poison Pd catalyst

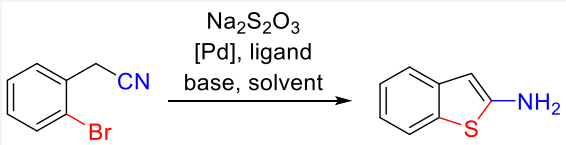
Angew. Chem., Int. Ed. **2007**, *46*, 4379.
Org. Lett., **2014**, 16, *1212*.
Org. Lett., **2013**, *15*, 2594.

Optimization



entry	catalyst (10 mol%)	ligand (5 mol%)	base (3 equiv)	solvent	additive	temp	yield (%)
1	$Pd(dppf)Cl_2$	dppf	Cs_2CO_3	DMF	--	140°C	36
2	$Pd(OAc)_2$	dppf	Cs_2CO_3	DMF	--	140°C	17
3	$Pd(MeCN)_2Cl_2$	dppf	Cs_2CO_3	DMF	--	140°C	21
4	$Pd(dppf)Cl_2$	dppf	Cs_2CO_3	DMF	H_2O (0.4 mL)	140°C	29
5	$Pd(dppf)Cl_2$	dppf	Cs_2CO_3	DMF	H_2O (0.2 mL)	140°C	28
6	$Pd(dppf)Cl_2$	dppf	Cs_2CO_3	DMF	H_2O (0.4 mL), TBAB	140°C	33
7	$Pd(dppf)Cl_2$	dppf	Cs_2CO_3	DMF	H_2O (0.2 mL), TBAB	140°C	43
8	$Pd(dppf)Cl_2$	dppf	K_2CO_3	DMF	H_2O, TBAB	140°C	24
9	$Pd(dppf)Cl_2$	dppf	KOAc	DMF	H_2O, TBAB	140°C	trace
10	$Pd(dppf)Cl_2$	dppf	tBuOK	DMF	H_2O, TBAB	140°C	trace
11	$Pd(dppf)Cl_2$	JohnPhos	Cs_2CO_3	DMF	H_2O, TBAB	140°C	17
12	$Pd(dppf)Cl_2$	$P(tBuO)_3$	Cs_2CO_3	DMF	H_2O, TBAB	140°C	30
13	$Pd(dppf)Cl_2$	dppf	Cs_2CO_3	DMF	glycol	140°C	50
14	$Pd(dppf)Cl_2$	dppf	Cs_2CO_3	DMF	DETA	140°C	trace
15	$Pd(dppf)Cl_2$	dppf	Cs_2CO_3	DMSO	glycol	140°C	17
16	$Pd(dppf)Cl_2$	dppf	Cs_2CO_3	NMP	glycol	140°C	42
17	$Pd(dppf)Cl_2$	dppf	Cs_2CO_3	glycol	--	140°C	trace
18	$Pd(dppf)Cl_2$	dppf (15 mol%)	Cs_2CO_3	DMF	glycol	140°C	64
19	$Pd(dppf)Cl_2$	dppf (15 mol%)	Cs_2CO_3	DMF	glycol	120°C	20

Optimization



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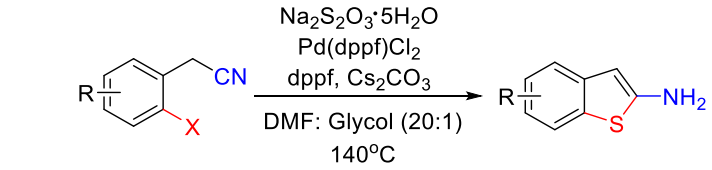
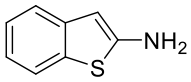
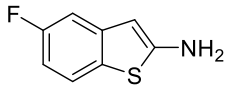
4	$Pd(dppf)Cl_2$	dppf	Cs_2CO_3	DMF	H_2O (0.4 mL)	140°C	29
5	$Pd(dppf)Cl_2$	dppf	Cs_2CO_3	DMF	H_2O (0.2 mL)	140°C	28
6	$Pd(dppf)Cl_2$	dppf	Cs_2CO_3	DMF	H_2O (0.4 mL), TBAB	140°C	33
7	$Pd(dppf)Cl_2$	dppf	Cs_2CO_3	DMF	H_2O (0.2 mL), TBAB	140°C	43
8	$Pd(dppf)Cl_2$	dppf	K_2CO_3	DMF	H_2O, TBAB	140°C	24
9	$Pd(dppf)Cl_2$	dppf	KOAc	DMF	H_2O, TBAB	140°C	trace
10	$Pd(dppf)Cl_2$	dppf	tBuOK	DMF	H_2O, TBAB	140°C	trace
11	$Pd(dppf)Cl_2$	JohnPhos	Cs_2CO_3	DMF	H_2O, TBAB	140°C	17
12	$Pd(dppf)Cl_2$	$P(tBuO)_3$	Cs_2CO_3	DMF	H_2O, TBAB	140°C	30
13	$Pd(dppf)Cl_2$	dppf	Cs_2CO_3	DMF	glycol	140°C	50
14	$Pd(dppf)Cl_2$	dppf	Cs_2CO_3	DMF	DETA	140°C	trace
15	$Pd(dppf)Cl_2$	dppf	Cs_2CO_3	DMSO	glycol	140°C	17
16	$Pd(dppf)Cl_2$	dppf	Cs_2CO_3	NMP	glycol	140°C	42
17	$Pd(dppf)Cl_2$	dppf	Cs_2CO_3	glycol	--	140°C	trace
18	$Pd(dppf)Cl_2$	dppf (15 mol%)	Cs_2CO_3	DMF	glycol	140°C	64
19	$Pd(dppf)Cl_2$	dppf (15 mol%)	Cs_2CO_3	DMF	glycol	120°C	20

Synthesis of 2-amino benzothiophenes

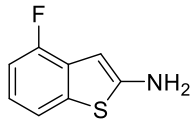




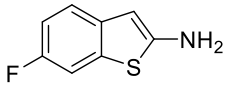
X = Br, **64%**
X = Cl, **26%**
X = I, **47%**



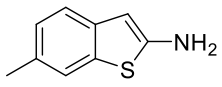
X = Br, **46%**



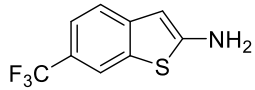
X = Br, **50%**



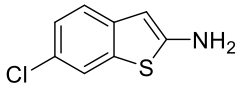
X = Br, **50%**



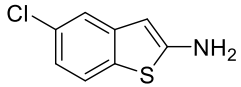
X = Br, **60%**



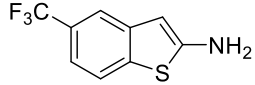
X = Br, **29%**



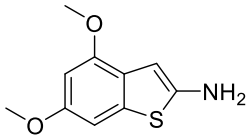
X = Br, **47%**



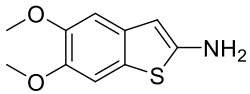
X = Br, **40%**



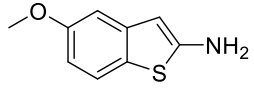
X = Br, **49%**



X = Br, **39%**

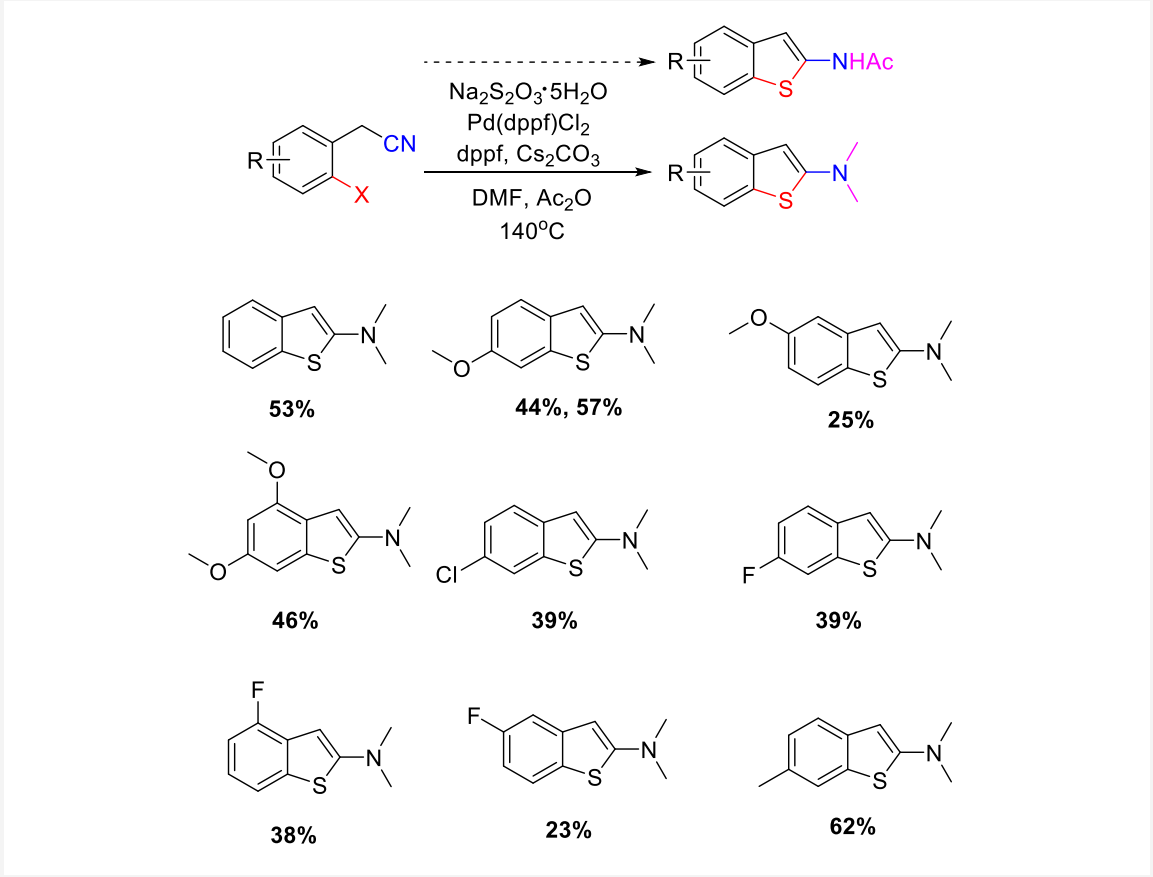


X = Br, **32%**
X = I, **39%**

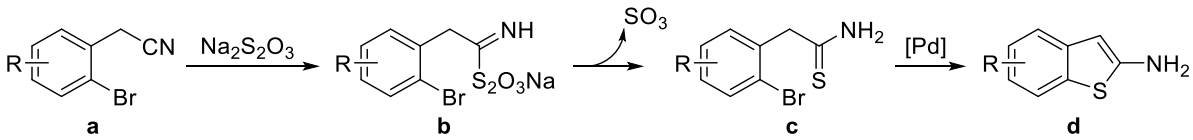


X = Br, **40%**

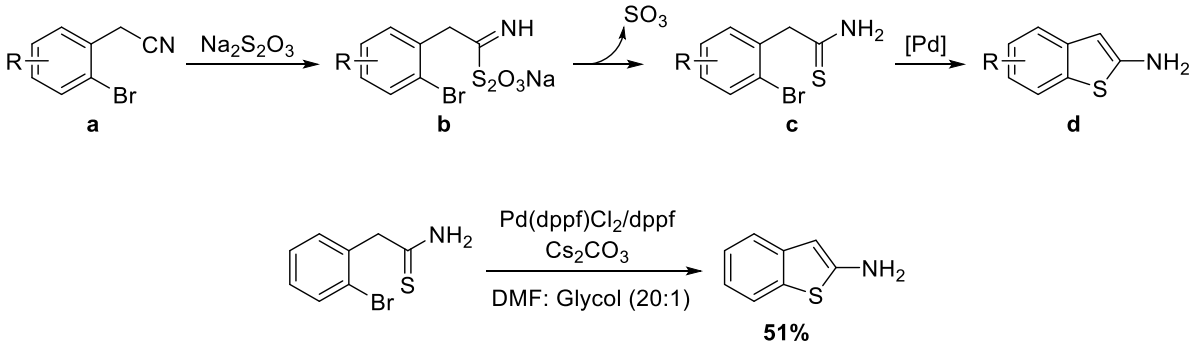
Synthesis of *N,N*-dimethyl-2-amino benzothiophenes



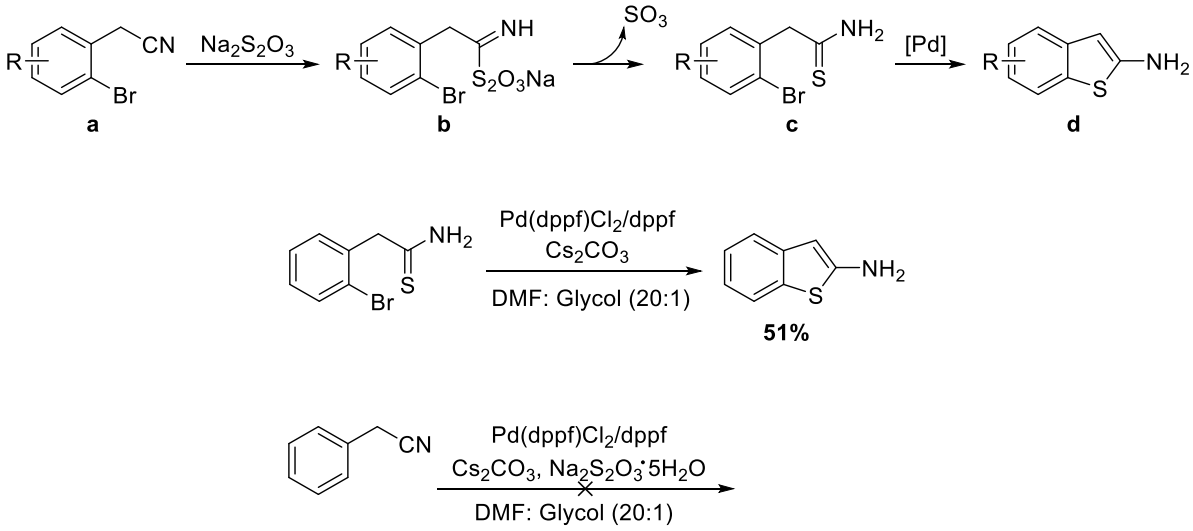
Proposed mechanism 1



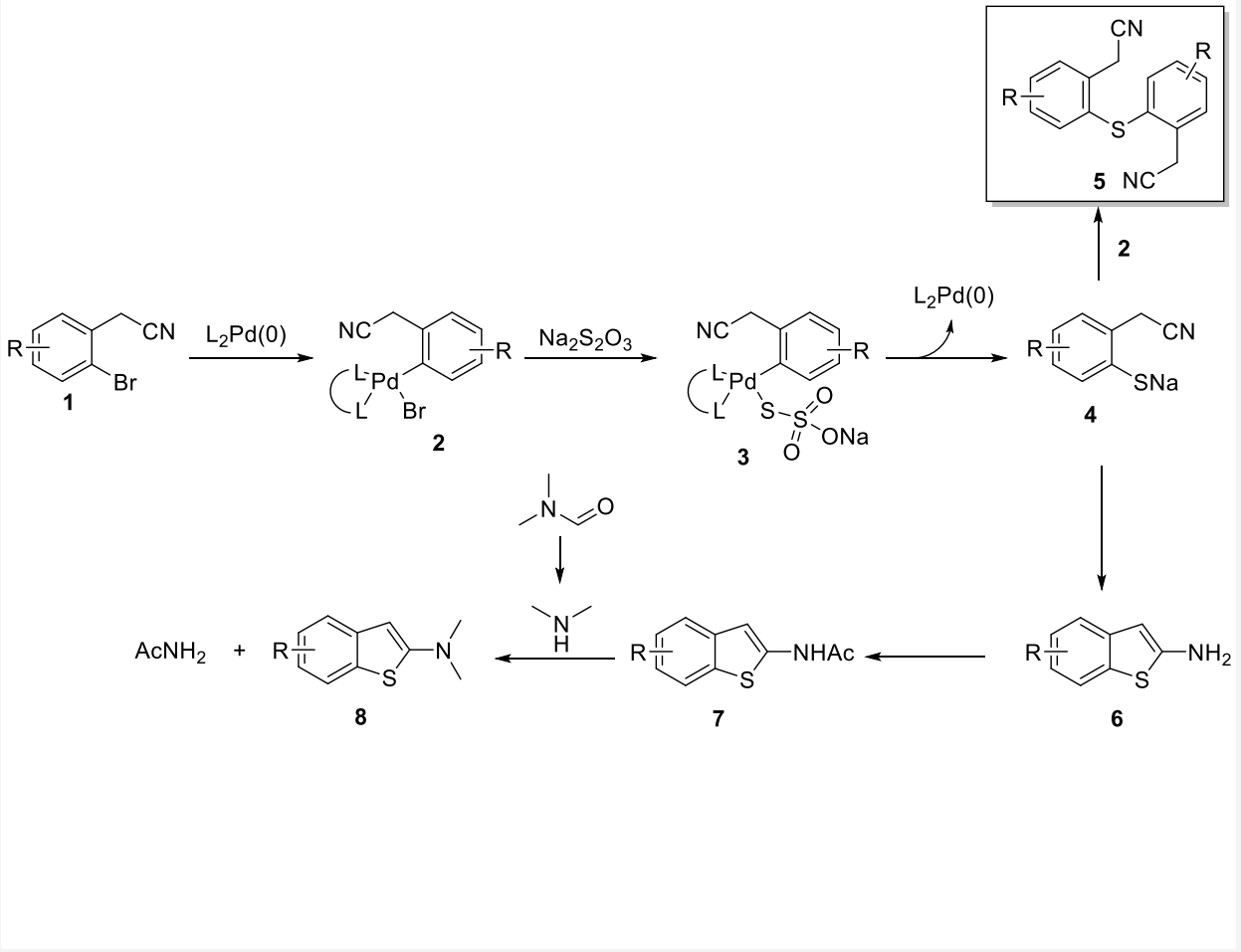
Proposed mechanism 1



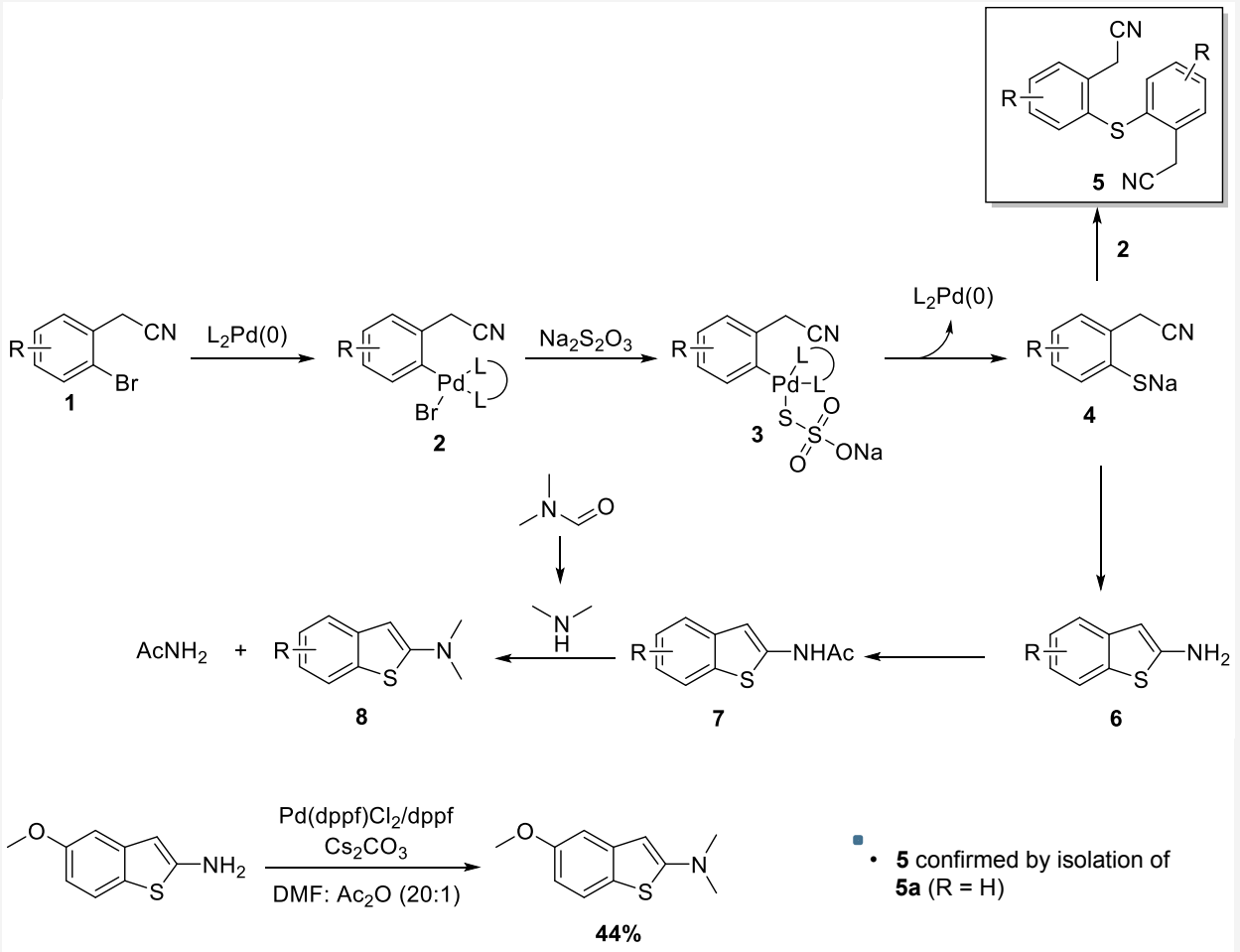
Proposed mechanism 1



Proposed mechanism



Proposed mechanism



- **5** confirmed by isolation of **5a** (R = H)

Conclusions
Future Work

- Direct access to 2-aminobenzothiophene
- Utilizes an odorless sulfur source
- Ease of procedure to useful building block "should make this approach attractive for chemists"

- Broadening of the scope of the reaction
- Utilize in the synthesis of a known bioactive molecule, such as Raloxifene, to show how this can improve its synthesis/production