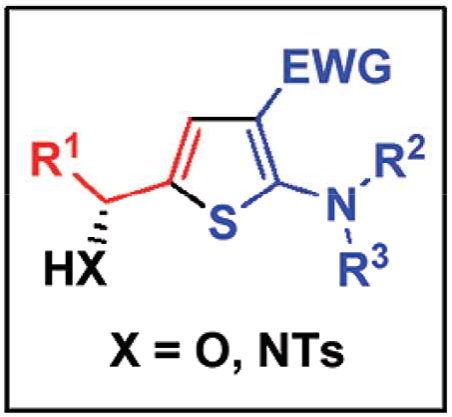
Optically Active Thiophenes: Organocatalytic One-pot Methodology

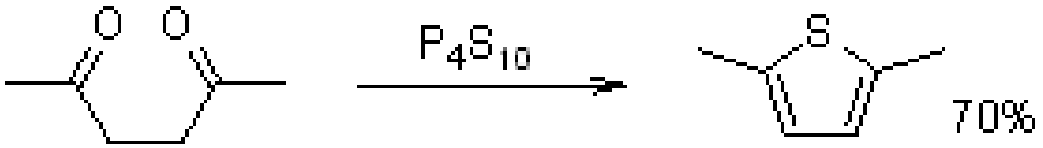
Org. Lett. **2012**, 10.1021/ol203237r



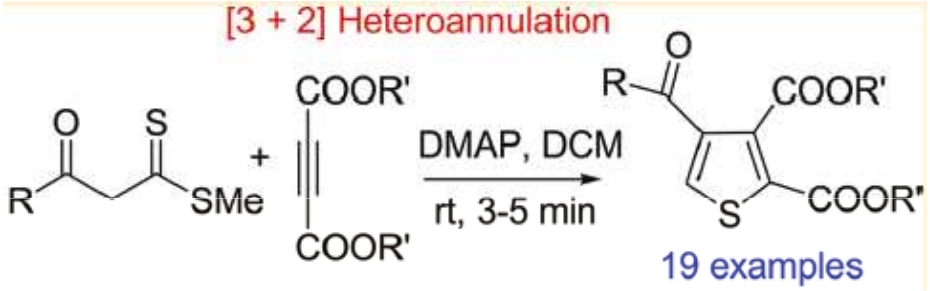
Lars Krogager Ransborg
Łukasz Albrecht
Christian F. Weise
Jesper R. Bak
Karl Anker Jørgensen

Jaime Gálvez

Pall-Knorr Thiophene Synthesis

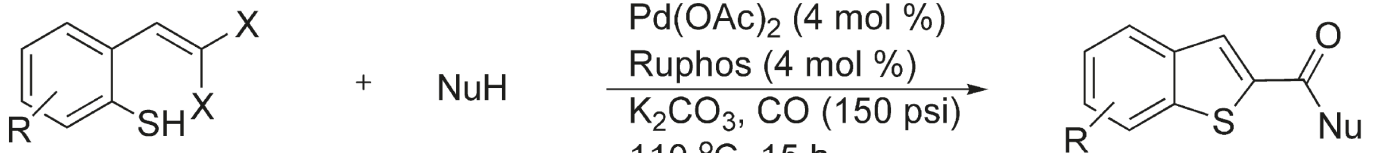


Organocatalyzed Synthesis



J. Org. Chem. **2011**, *76*, 8009-8014

Metal-Catalyzed Synthesis



R = electron-donating or -withdrawing groups

X = Br or Cl

alcohols, phenol, amines

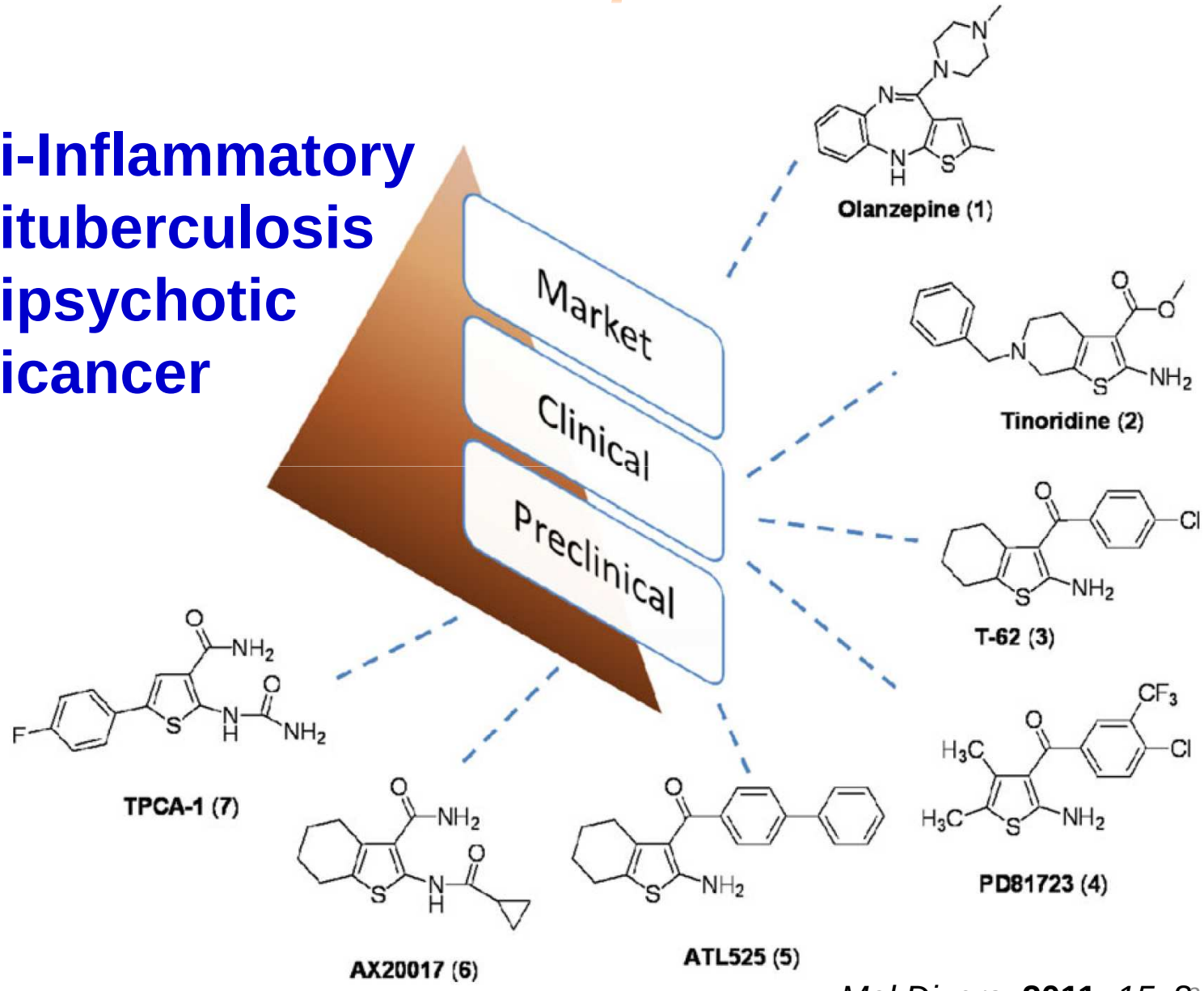
15 examples

24-73% yields

Org. Lett. **2011**, *13*, 2868-2871

2-aminothiophenes

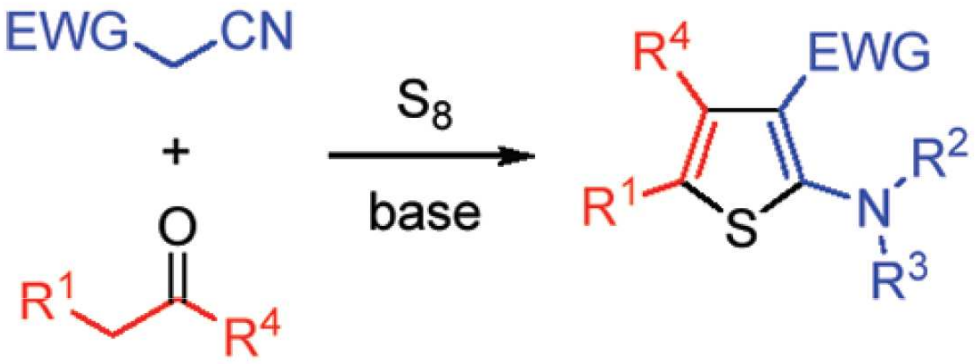
Anti-Inflammatory
Antituberculosis
Antipsychotic
Anticancer



Mol Divers, **2011**, *15*, 3–33

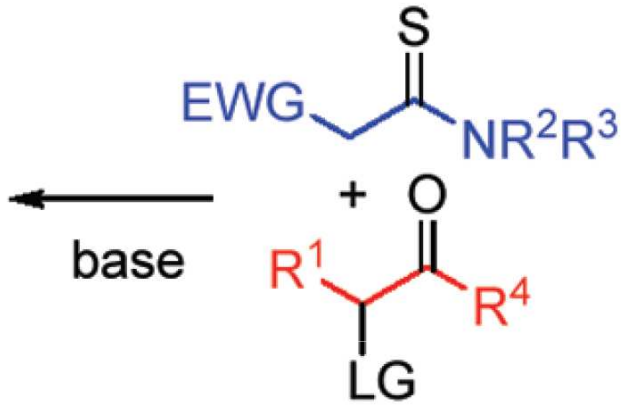
Synthesis of 2-aminothiophenes

Gewald Synthesis

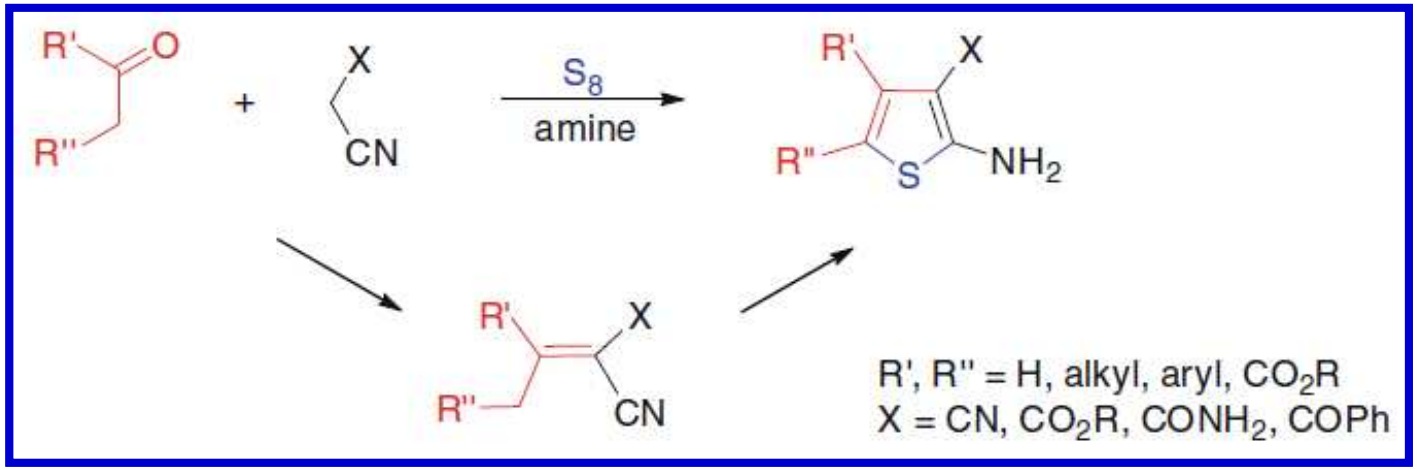


- Elemental sulfur as sulfur source
- Limited to primary amines ($R^2 = R^3 = H$)
- Well studied

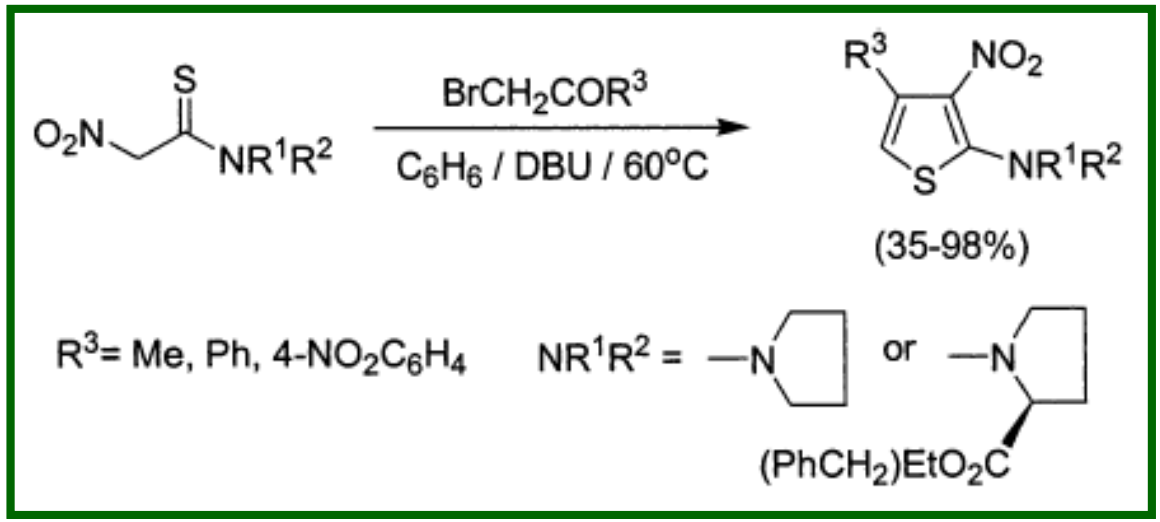
Thioamide approach



- Thioamides as sulfur source
- Requires LG
- Limited recognition



Mol Divers. **2011**, *15*, 3–33
ARKIVOC **2010**, 209-246



Chem. Rev. **2003**, *103*, 197-227

Limitation

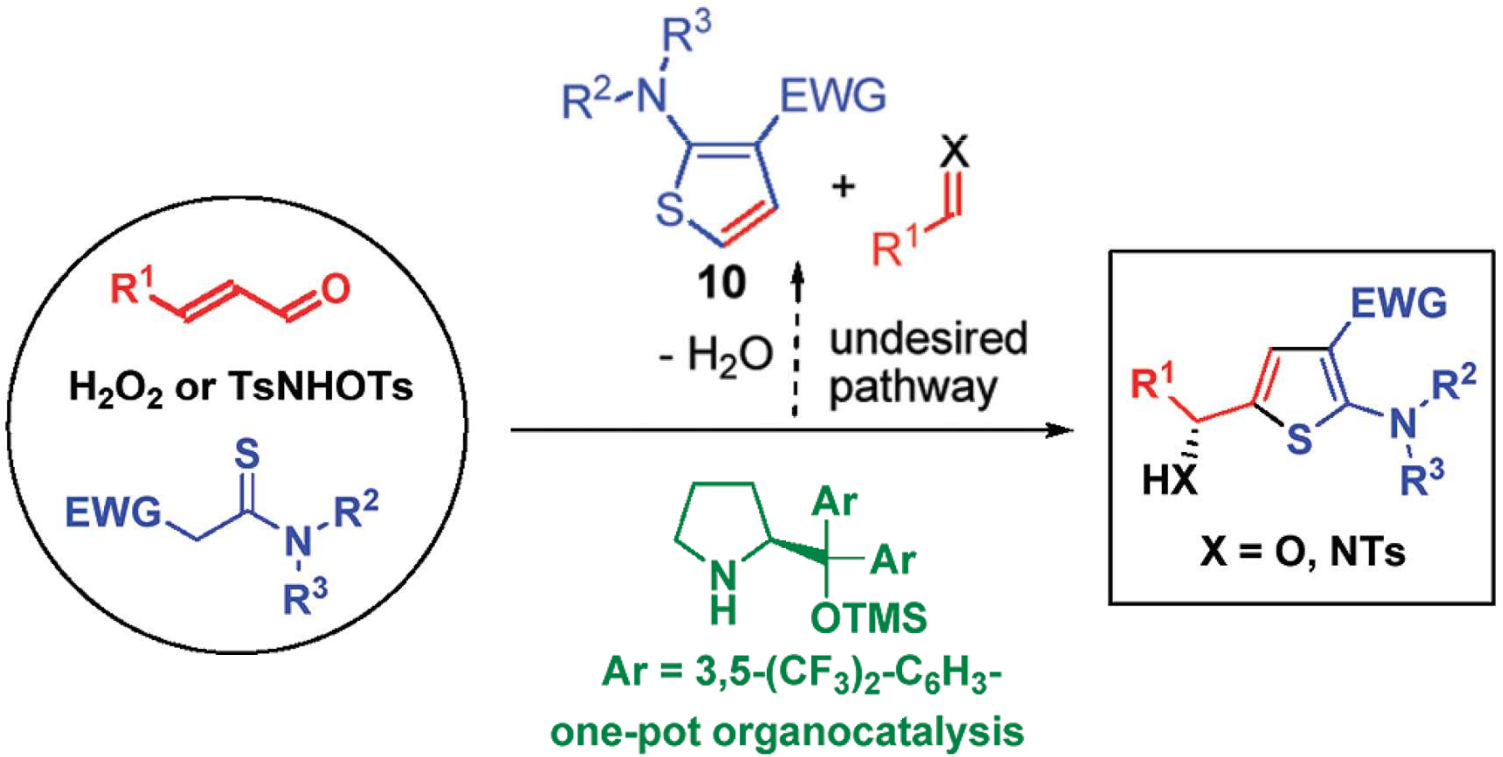
- Availability of asymmetric annulative strategies.

- Strategies based on functionalization of prochiral heteroaromatic starting materials.

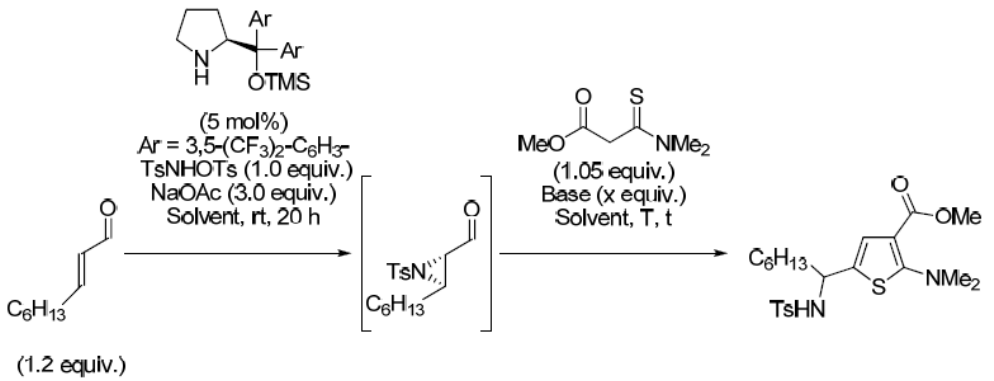
Challenge

- A direct strategy for the formation of optically active polysubstituted thiophenes from acyclic precursors.

- Overcome the possible and undesired elimination pathway

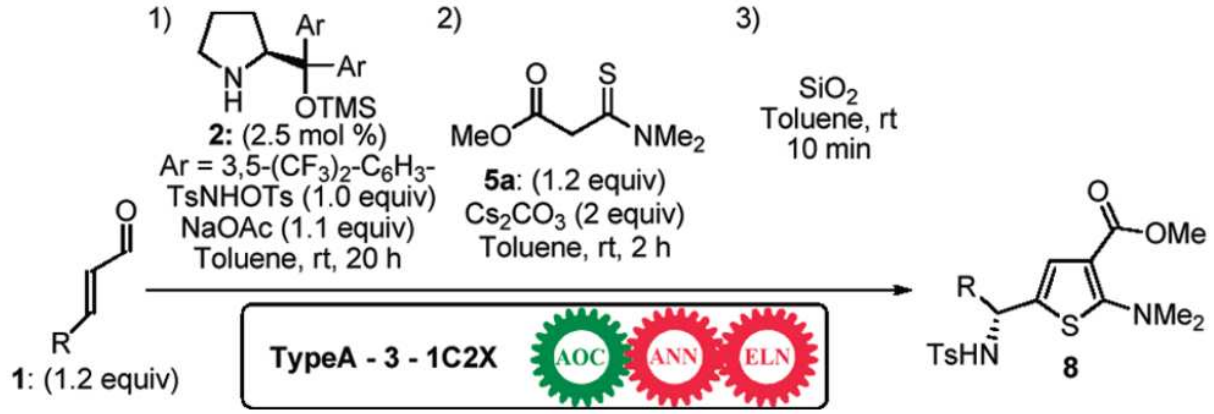


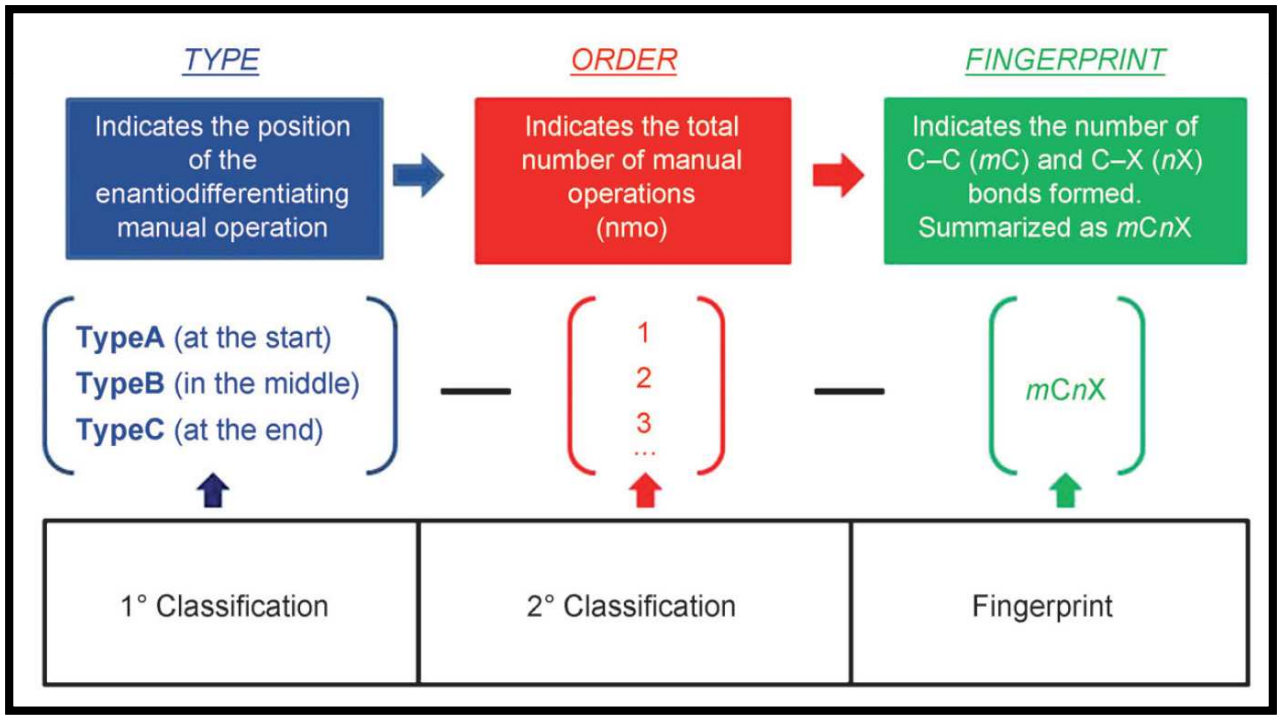
OPTIMIZATION



entry	base (equiv)	solvent	temperature [°C]	time [hours]	aziridine conversion [%][a]	yield [%] (NMR-yield [%][b])	ee [%]
1	DBU (1.0)	CH_2Cl_2	40	22	94	- (41)	-
2	MTBD (1.0)	CH_2Cl_2	40	22	>95	- (48)	-
3	DBU (1.0)	toluene	60	2.5	>95	- (37)	-
4	-	toluene	60	22	30	- (27)	-
5	Cs_2CO_3 (1.0)	toluene	60	22	>95	55 (71)	-
6	Cs_2CO_3 (2.0)	toluene	60	2	>95	- (77)	-
7	Cs_2CO_3 (3.0)	toluene	60	2.5	>95	67 (86)	95
8	Cs_2CO_3 (3.0)	CH_2Cl_2	40	2	>95	- (decomp)	-
9	K_2CO_3 (3.0)	toluene	60	2.5	>95	- (decomp)	-
10	DIPEA (3.0)	toluene	60	22	92	- (38)	-
11	$CsOH·H_2O$ (3.0)	toluene	60	2.5	>95	42 (90)	95
12	K_3PO_4 (3.0)	toluene	60	2.5	75	- (50)	-
13	Cs_2CO_3 (3.0)[c]	toluene	60	2	>95	58 (83)	-
14	CsOAc (3.0)[c]	toluene	60	22	>95	- (40)	-
15	Cs_2CO_3 (3.0)[d]	toluene	60	2	>95	- (71)	-
16	Cs_2CO_3 (2.0)[d]	toluene	60	2	>95	70 (75)	-
17	Cs_2CO_3 (2.0)[e]	toluene	60	2	>95	73 (87)	-
18	Cs_2CO_3 (2.0)[e][f]	toluene	60	2	>95	72 (91)	94
19	Cs_2CO_3 (2.0)[e][f]	toluene	rt	2[g]	>95	72 (91)	94
20	Cs_2CO_3 (2.0)[e][f]	toluene	rt	2[h]	>95	91 (91)	96

[a] Determined by ^{1}H NMR [b] NMR-yield calculations based on product to nucleophile ratio [c] 1 eq NaOAc in aziridination step [d] 1.5 equiv nucleophile used [e] 1.2 equiv nucleophile used [f] 2.5 mol% catalyst used [g] Followed by 30 min reaction with AcOH [h] Followed by 30 min reaction with SiO_2





asymmetric organocatalysis AOC

annulations ANN

elimination reaction ELN

Angew. Chem. Int. Ed. **2011**, *50*, 8492 – 8509

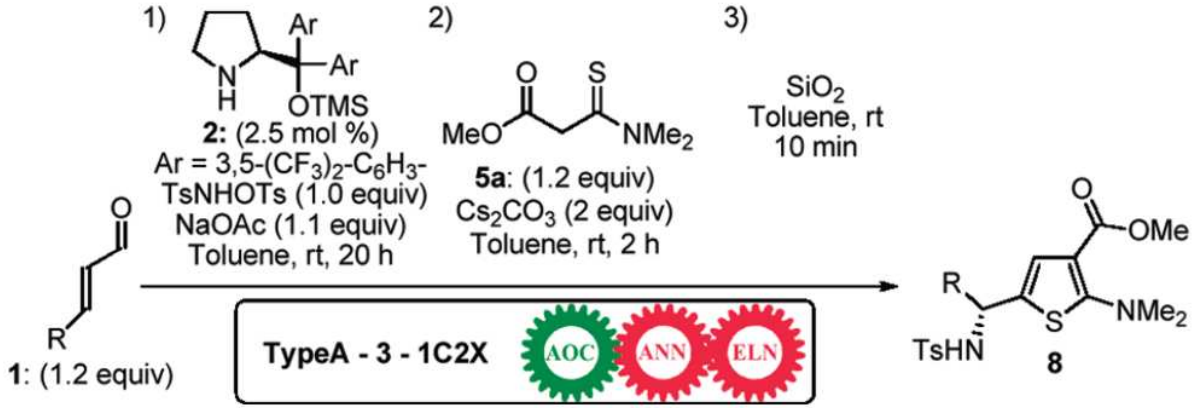


Table 1. Aldehyde Scope for the Formation of Aminoalkylthiophenes **8**[a]

entry	R	product	yield [%]	ee[b] [%]
1	Hex	**8a**	91	96
2	Pr	**8b**	83	95
3	*i*Pr	**8c**	92	93
4[c]	Me	**8d**	80	89
5	(*E*)-Hex-3-enyl	**8e**	81	95
6	(*Z*)-Hex-3-enyl	**8f**	60	94
7	$CH_2OTBDMS$	**8g**	82	96
8	CH_2CH_2Ph	**8h**	83	92

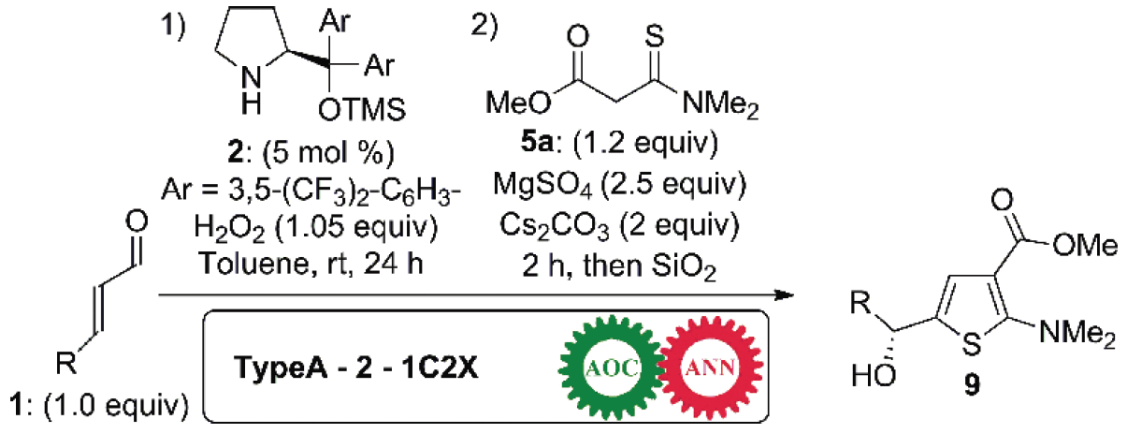
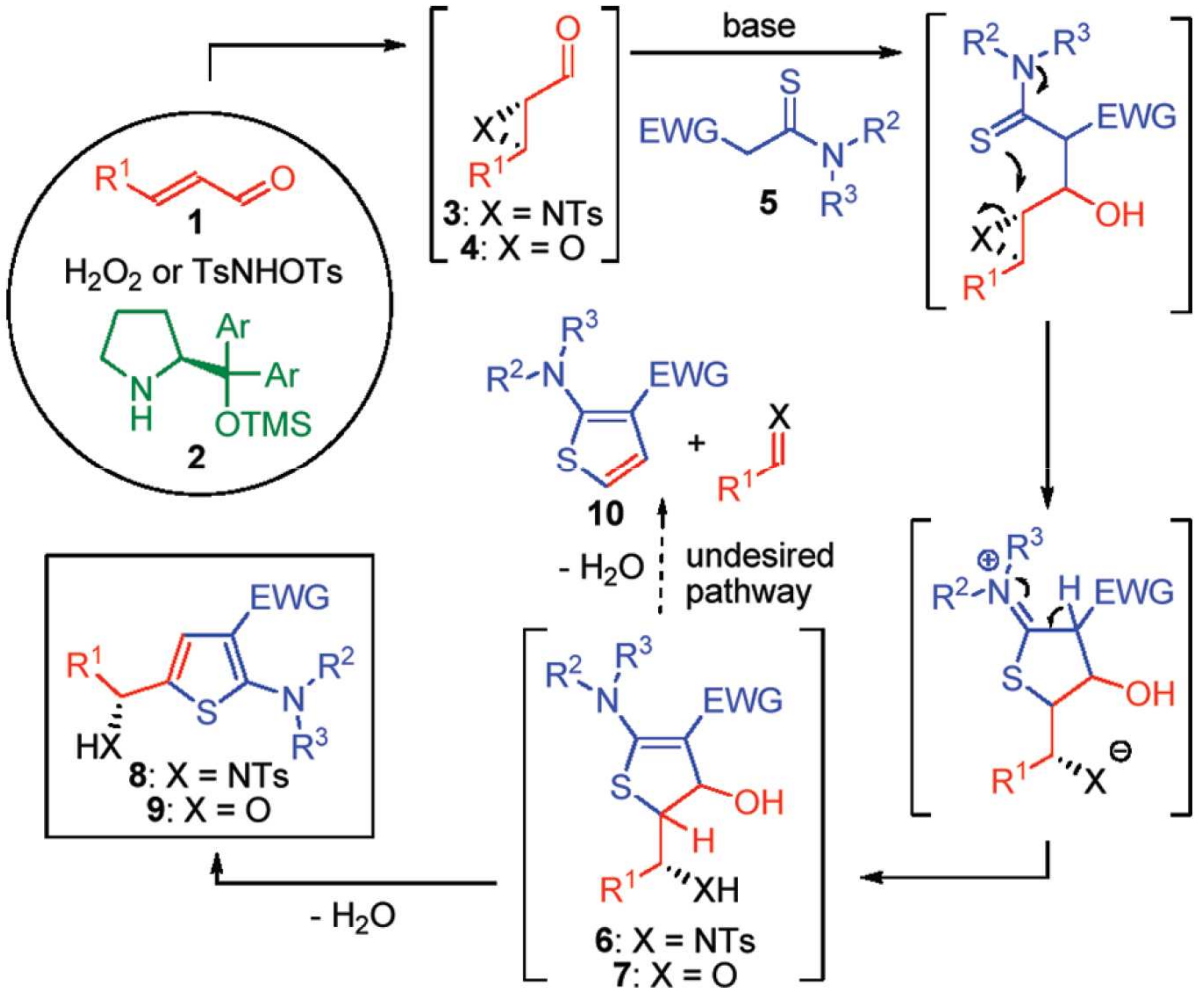


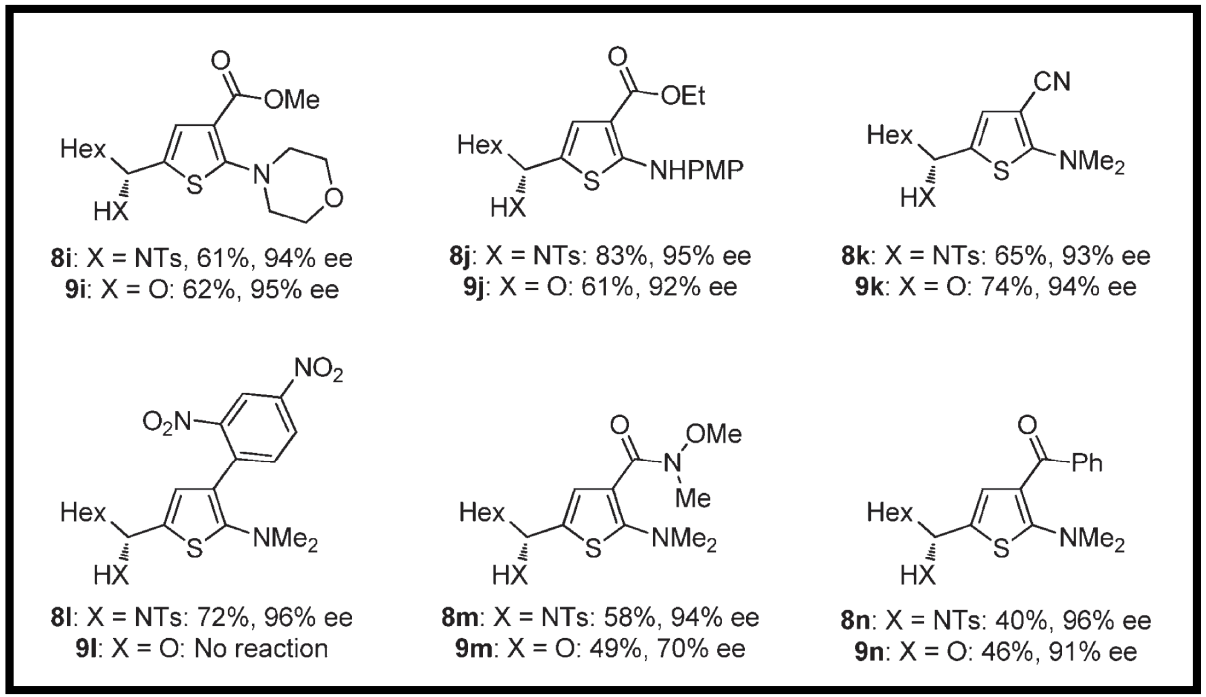
Table 2. Aldehyde Scope for the Formation of Hydroxyalkylthiophenes **9**[a]

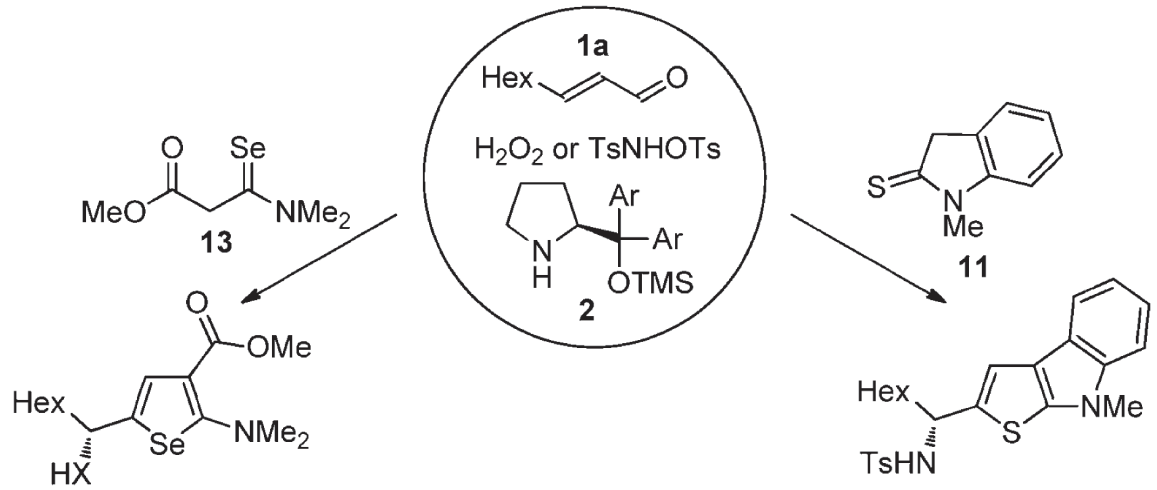
entry	R	product	yield [%]	ee[b] [%]
1	Hex	**9a**	75	94
2	Pr	**9b**	74	94
3	*i*Pr	**9c**	61	98
4[c]	Ph	**9d**	33	86
5	(*E*)-Hex-3-enyl	**9e**	73	96
6	(*Z*)-Hex-3-enyl	**9f**	40	92
7	$CH_2OTBDMS$	**9g**	71	96
8	CH_2CH_2Ph	**9h**	72	94

Organocatalytic One-Pot Mechanism



J. Am. Chem. Soc. **2005**, *127*, 6964-6965
Acc. Chem. Res. **2012**, 10.1021/ar200149w


8i: X = NTs, 61%, 94% ee
9i: X = O: 62%, 95% ee
8j: X = NTs: 83%, 95% ee
9j: X = O: 61%, 92% ee
8k: X = NTs: 65%, 93% ee
9k: X = O: 74%, 94% ee
8l: X = NTs: 72%, 96% ee
9l: X = O: No reaction
8m: X = NTs: 58%, 94% ee
9m: X = O: 49%, 70% ee
8n: X = NTs: 40%, 96% ee
9n: X = O: 46%, 91% ee


1a
H2O2 or TsNHOTs
2
13
11
14a: X = NTs: 87%, 96% ee
14b: X = O: 73%, 90% ee
12: 43%, 95% ee

CONCLUSIONS

An efficient and highly stereoselective one-pot methodology for the synthesis of optically active thiophenes, thieno[2,3-b]indoles, and selenophenes has been described.

Highly enantioselective amino-catalyzed epoxidation or aziridination reaction, combined with a ring annulation, to afford the target compounds.

These reactions can be carried out under mild reaction conditions and are based on the application of convenient, easily obtainable reagents.

Wide functional group tolerance resulting in the high substitution diversity of the final aromatic framework.

“Inquisitive young people are the most important element in chemistry research”
Professor Karl Anker Jørgensen

Merci Beaucoup!
Thank You!
Gracias!