Safe, Scalable, Inexpensive, and Mild Nickel-Catalyzed Migita-like C–S Cross-Couplings in Recyclable Water

Yilin Cao[1,2], Julie Yu[2], Haobo Pang[2], Bruce H. Lipshutz[2]
[1]College of Creative Studies, University of California, Santa Barbara
[2]Department of Chemistry and Biochemistry, University of California, Santa Barbara

Introduction

Thioethers are widely distributed throughout nature, including being found in numerous physiologically active compounds (Figure 1). Unfortunately, Migita cross-couplings that lead to carbon-sulfur (C–S) bond formation remain challenging in several ways, including the typically high loadings of endangered Pd[1] catalysts attributed to strong coordination of thiolates to the metal, oftentimes leading to catalyst deactivation and hence, overall low efficiency.

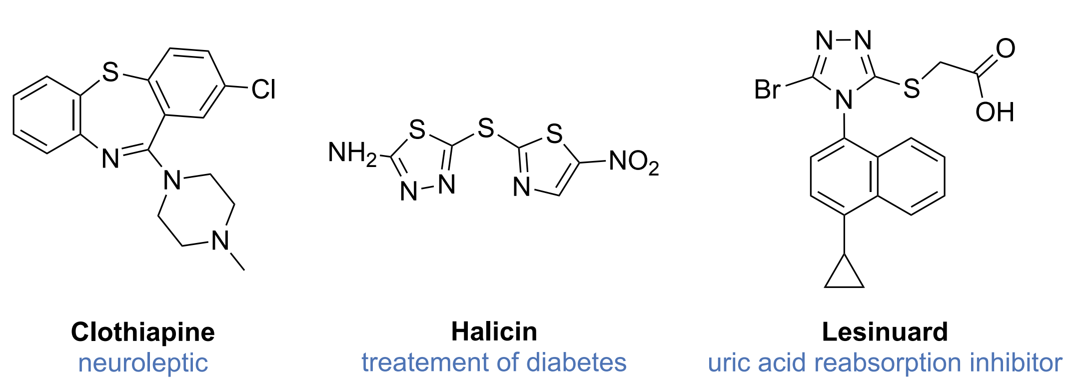


Figure 1. Selected examples of therapeutic agents bearing aromatic/heteroaromatic thioethers.

Challenge

- Use precious and expensive metals, such as Pd[2], Ir[3], and Ru[4].
- Most reactions reply on high temperatures in organic solvents[5].

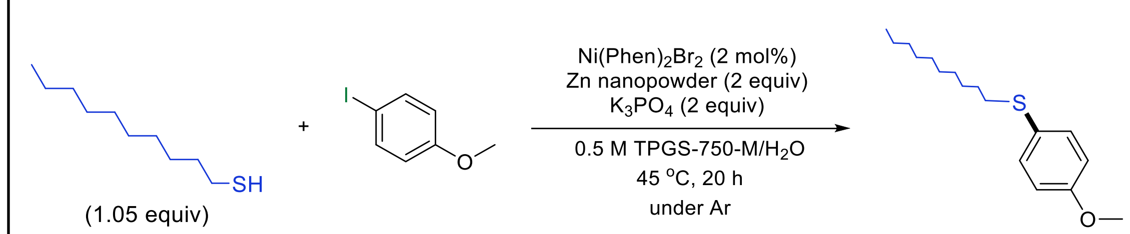
Goal

- Find an alternative protocol that replaces dangerously flammable and toxic organic solvents with safe, recyclable water.

This Protocol

- Describe a process that relies on low levels of base metal (nickel) catalysis enabled by aqueous micellar catalysis.

Optimization

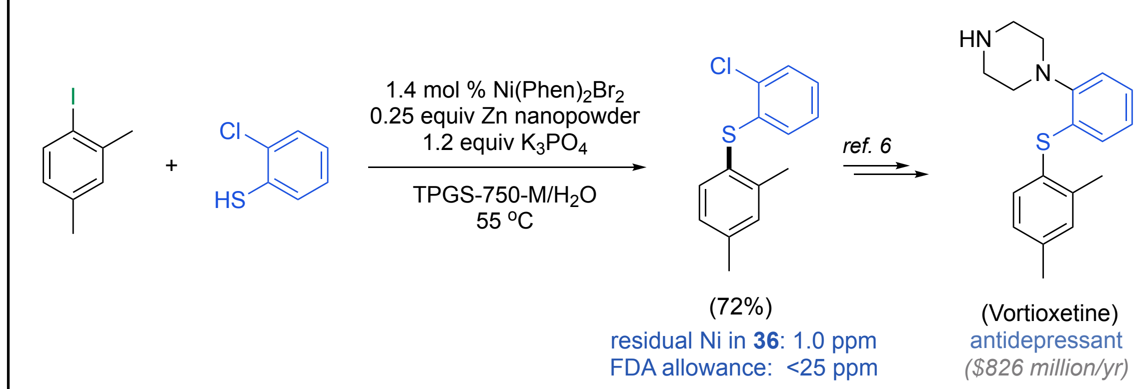


Entry	Ni(Phen)$_2$Br$_2$ (mol%)	Zn (equiv)	K_3PO_4 (equiv)	Conv. [%][b]
1	2 mol%	2	2	100
2	0.35 mol%	2	2	77
3	0.07 mol%	2	2	79
4	0.0035 mol%	2	2	53
5	2 mol%	2	1.2	100
6	2 mol%	2	0	0
7	2 mol%	2	2	6[c]
8	0.7 mol%	1	1.2	100
9	0.7 mol%	0.5	1.2	99
10	**0.7 mol%**	**0.25**	**1.2**	**94 (96)**
11	0.7 mol%	0.1	1.2	83
12	0.7 mol%	0.5	1.2	100
13	0.7 mol%	0.5	1.2	62[d]

[a] Scale of reaction: 0.25 mmol of 4-iodoanisole and 2 wt % TPGS-750-M/H2O (0.5 mL). [b] Conversion determined by 1H NMR. Isolated yields in parenthesis. [c] Run at rt (22 ° C). [d] Run in air; disulfide formed.

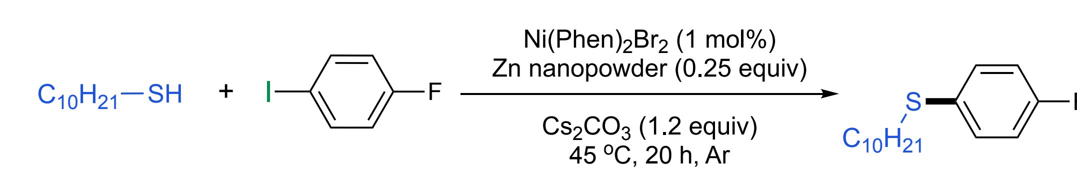
- Reducing pre-catalyst to 0.35 % or below decrease the yield (entries 2-4).
- Decrease the base to 1.2 equivalent did not affect the conversion (entry 5).
- The base was essential (entry 6).
- Decrease the temperature from 45 °C to 22 °C gave a significant reduction in yield (entry 7).
- Only 0.25 equivalents were required (entries 8–11).
- Reaction efficiency was reduced when air remained within the reaction vessel (entry 13).

Synthesis a Drug Precursor



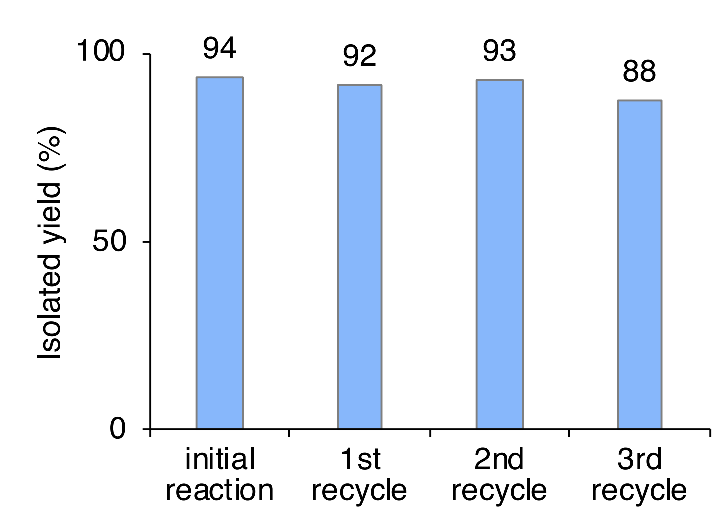
- Synthesis of a Vortioxetine Intermediate.
- Applicable to syntheses of targets in pharmaceutical area.
- Residual Metal Analysis: much **lower** residual nickel loading (1.0 ppm) compared to FDA guidelines (≤25 ppm).

E factor and Recycle



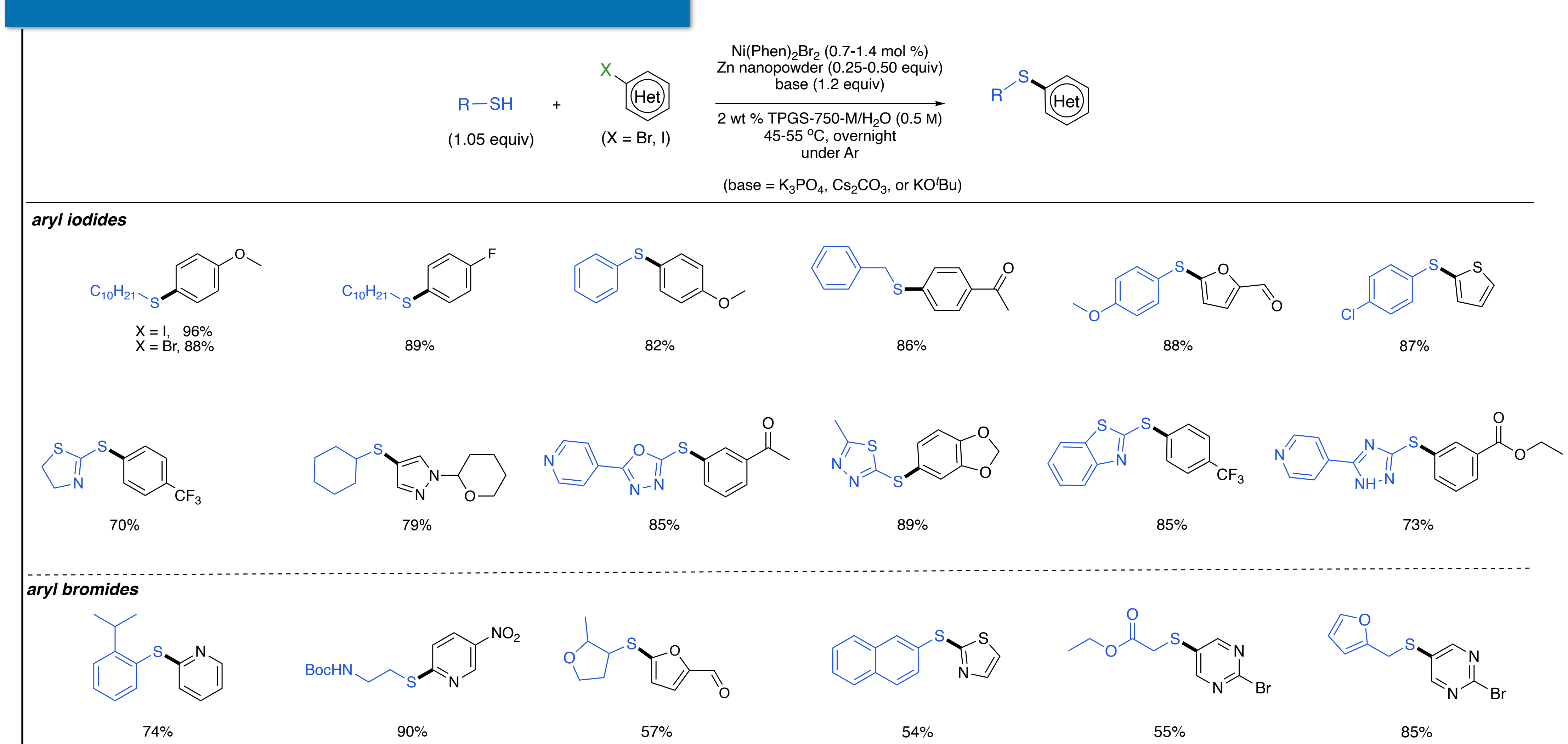
$$\text{E Factor} = \frac{\text{mass of total waste}}{\text{mass of product}}$$

E Factor (organic solvent) = 4.6
E Factor (including base, water) = 7.6



- E factor was only **4.6** (indicating a sustainable process is in hand for thioether bond formation..
- 2 wt % TPGS-750-M, could be **re-used in three** additional reactions to future minimizing generation of wastewater.

Substrate Scope



References

[1] T. Scattolin, E. Senol, G. Yin, Q. Guo, F. Schoenebeck, Angew. Chem. Int. Ed. 2018, 57, 12425–12429; Angew. Chem. 2018, 130, 12605– 12609.
[2] a) T. Norris, K. Leeman, Org. Process Res. Dev. 2008, 12, 869–876; b) J. M. Ganley, C. S. Yeung, J. Org. Chem. 2017, 82, 13557–13562.
[3] M. S. Oderinde, M. Frenette, D. W. Robbins, B. Aquila, J. W. Johannes, J. Am. Chem. Soc. 2016, 138, 1760–1763.
[4] S. D. Timpa, C. J. Pell, O. V. Ozerov, J. Am. Chem. Soc. 2014, 136, 14772–14779.
[5] "N,N-dimethylformamide - Substance Information - ECHA," A. C. Jones, W. I. Nicholson, H. R. Smallman, D. L. Browne, Org. Lett. 2020, 22, 7433–7438.
[6] Z. Boros, L. Nagy-Győr, K. Kátai-Fadgyas, I. Kőhegyi, I. Ling, T. Nagy, Z. Iványi, M. Oláh, G. Ruzsics, O. Temesi, B. Volk, J. Flow. Chem. 2019, 9, 101–113.

DOI: 10.1002/anie.202013017