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Oxidation of Thiols to Disulfides using an Environmentally “Green” Organocatalyst and New Mechanistic Insights

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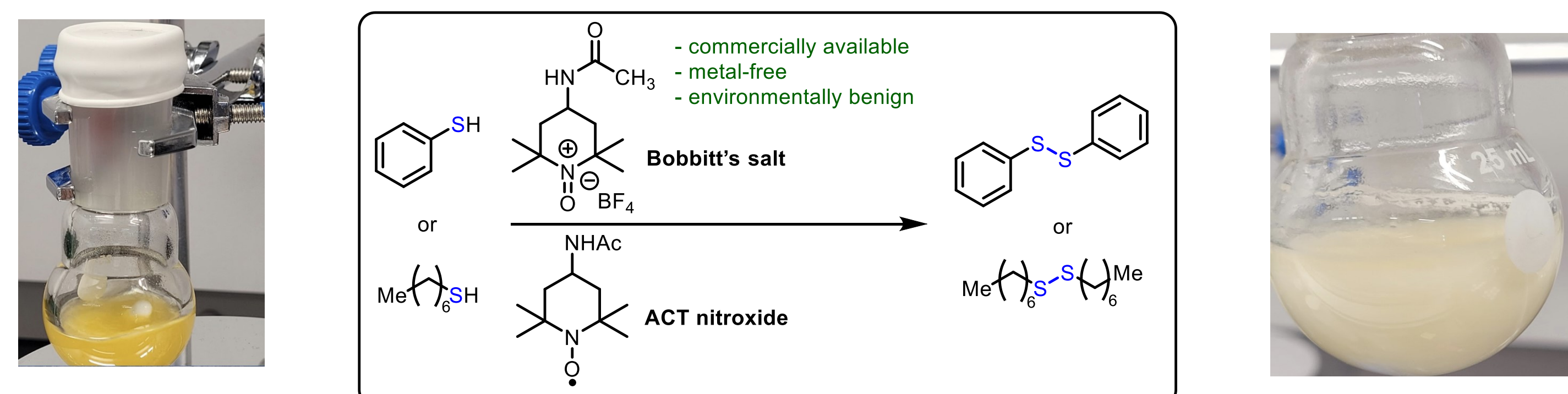
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Chemoselective Oxidation of Thiols to Disulfides with Bobbitt's Salt

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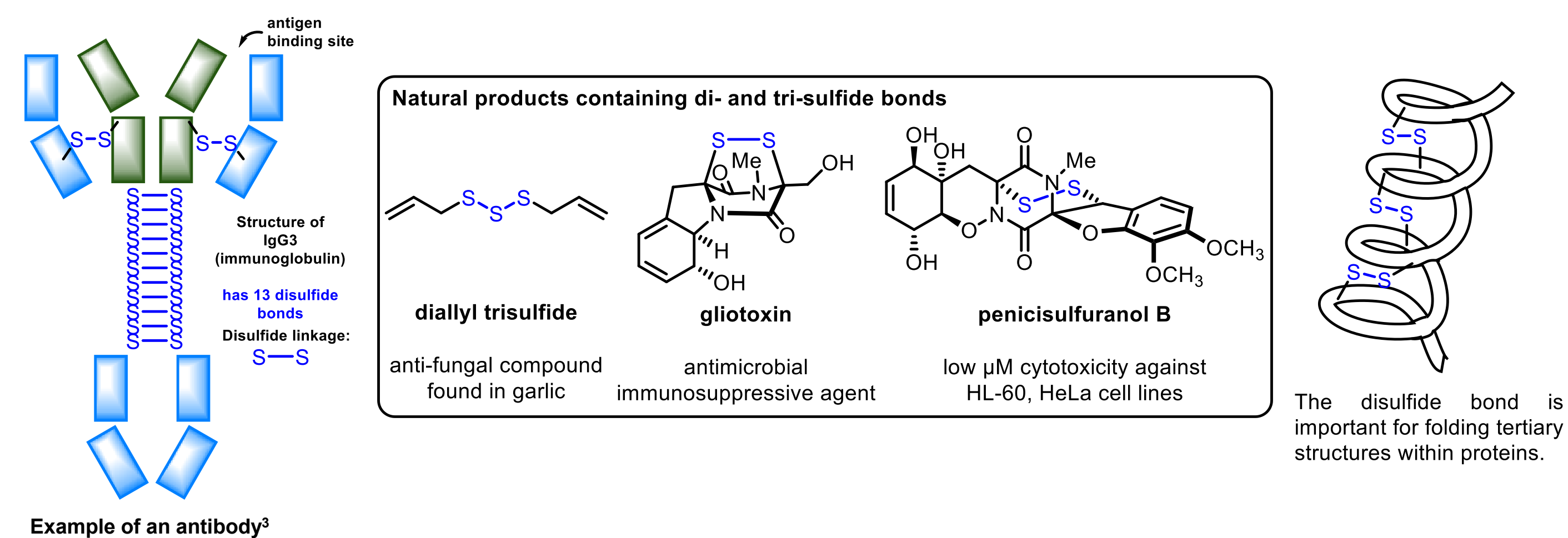
Abstract



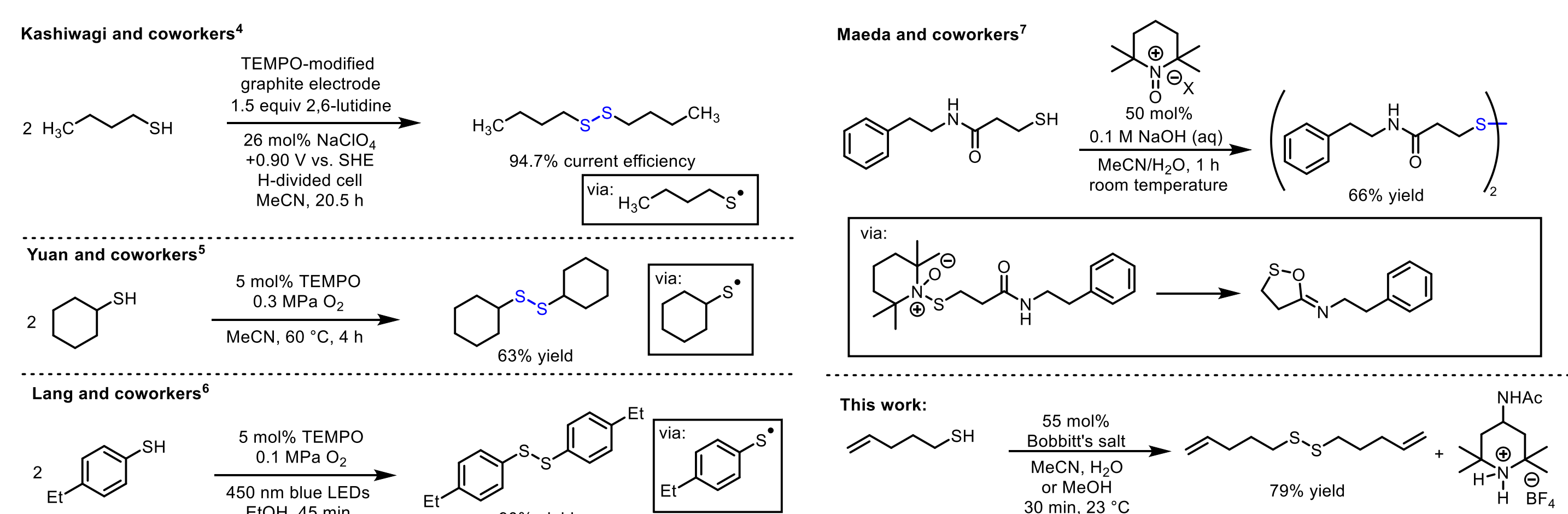
The oxidation of various aryl and aliphatic thiols with Bobbitt's salt has been investigated. The reaction is remarkably chemoselective and can be accomplished in the presence of free amines and alcohols to afford the corresponding disulfide products in good to excellent yields (71–99%). Combined experimental and computational studies reveal the oxidation takes place via a hydrogen atom transfer (HAT) process with concomitant, and unexpected deoxygenation of the oxoammonium cation, which differs from prototypical thiol couplings that proceed via thiol radicals.

Introduction

Disulfide bonds play a critical role in several biological processes, including structural stabilization of proteins such as insulin, enzymes¹, and many others. Additionally, their occurrence on the lining of antibodies², in the antigen binding sites allow for a redox-dual-response that trigger when reactive oxygen species alter the conditions of the cell. The ROS – sensitive trait of disulfide bonds produce a prodrug delivery system make them highly demandable in the medical, pharmaceutical, and agrochemical industry.¹ However, contemporary methods used to create these bonds, often using iodine oxidants or metal catalysts, result in halogenated and metal waste, and are often not chemoselective. Therefore, our goal is to develop mild methods for the selective formation of disulfide bonds using environmentally benign and metal-free organocatalysts, without incurring environmental damage.



Typical Approaches to Disulfides using TEMPO

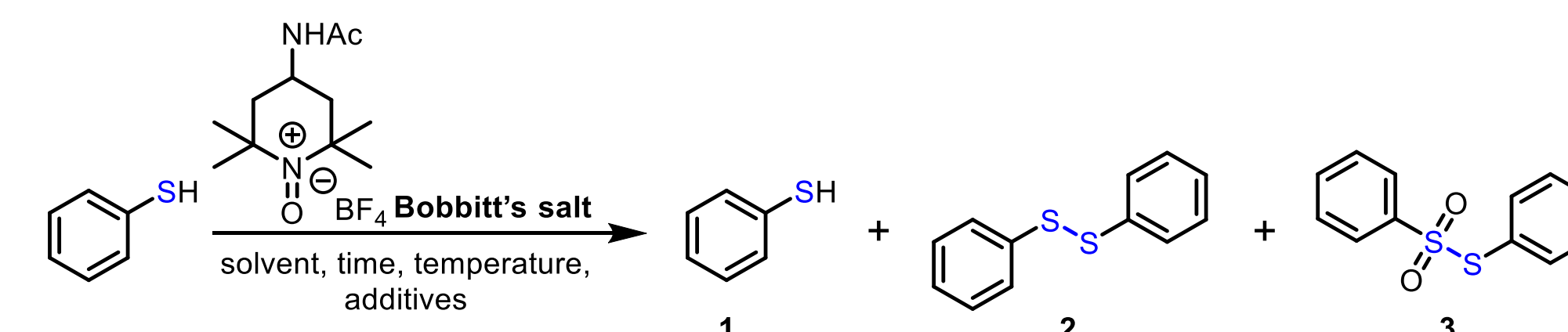


- Require O₂ and/or visible light (460 nm)
- Aliphatic systems are challenging
- Tolerates free phenols and anilines
- Oxidations are proposed to proceed via thiyl radicals

- No O₂ or UV-Vis light required
- Polar solvents expedite reaction
- Aliphatic systems are well tolerated
- High degree of chemoselectivity for thiols, faster alcohol or amine oxidations
- Electrocatalytic methods are also possible

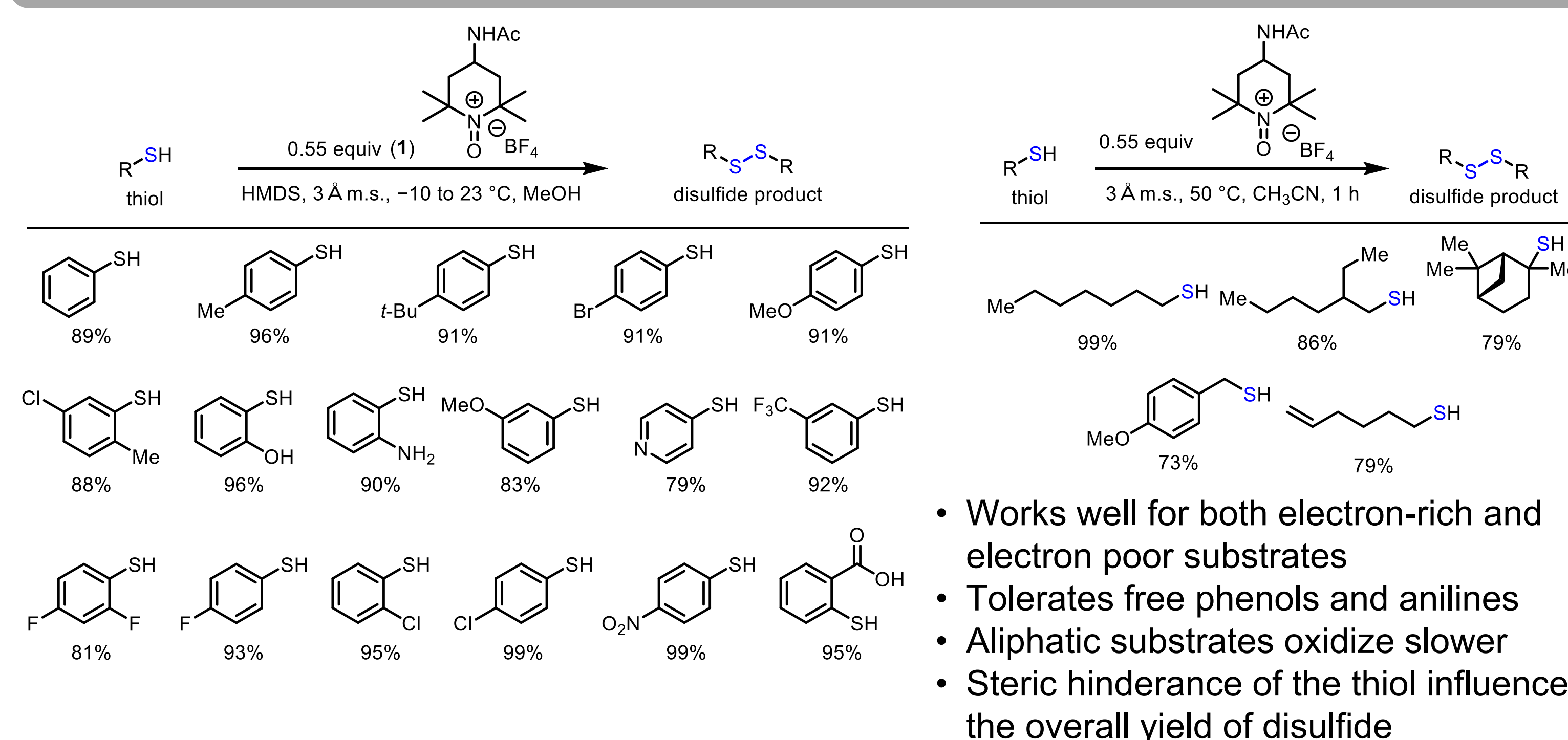
Optimization of the Oxidation

Optimization of the oxidation of thiophenol (1) to diphenyl disulfide (2) & thiosulfinate (3) via Bobbitt's salt

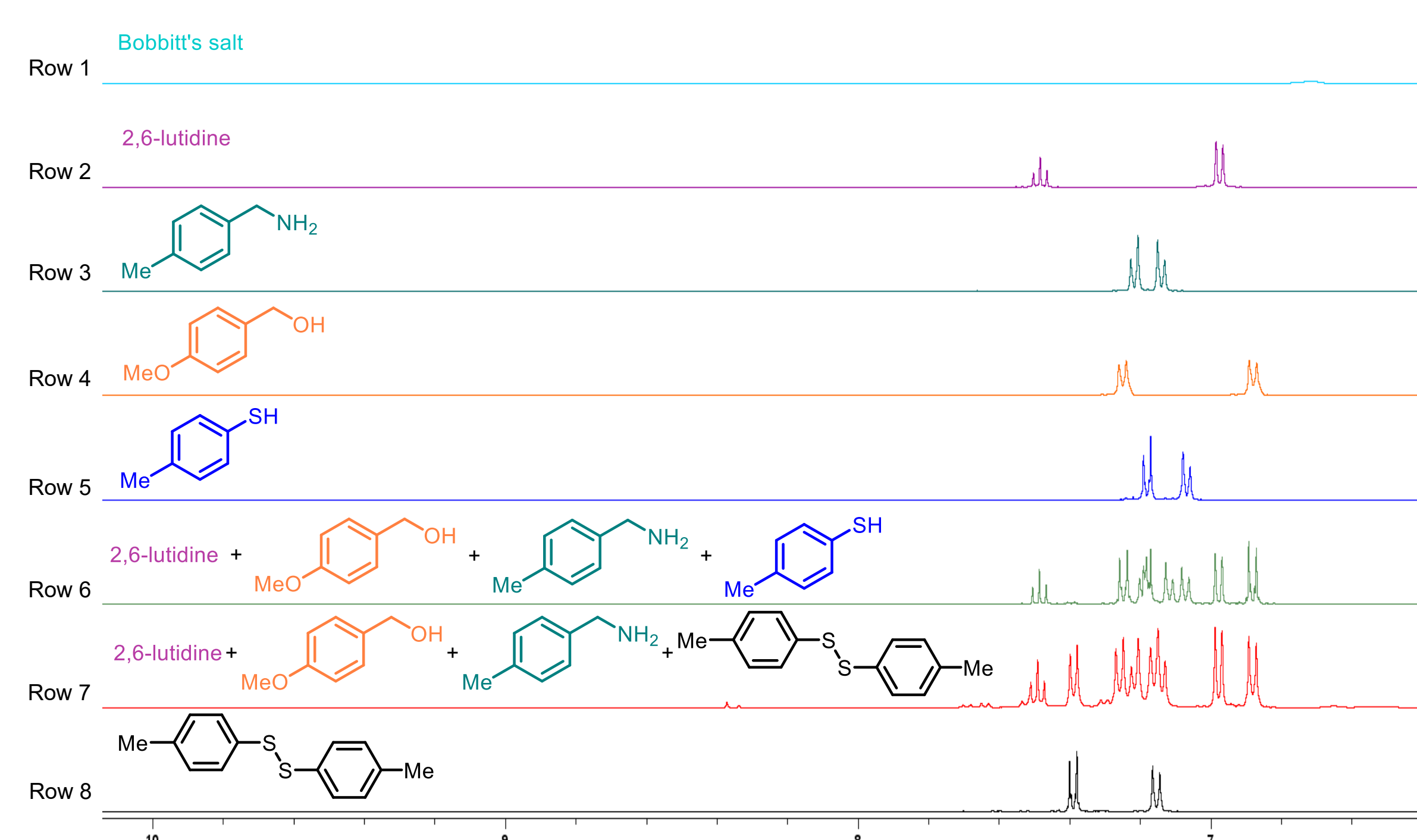


Entry	Equiv of Bobbitt's salt	Solvent	Time (h)	Temperature (°C)	Additives	% Conversion 1:2:3	Isolated Yield
1	1.2	CH ₂ Cl ₂	1.5	23	-	10:87:3	56%
2	1.2	PhCH ₃	1.5	23	-	33:67:0	19%
3	1.2	EtOAc	1.5	23	-	59:40:1	n.d.
4	1.2	MTBE	1.5	23	-	58:40:2	n.d.
5	1.2	Et ₂ O	1.5	23	-	29:67:4	38%
6	1.2	MeCN	1.5	23	-	0:93:7	69%
7	1.2	H ₂ O	1.5	23	-	0:100:0	76%
8	0.75	MeCN	1.5	23	-	n.d.	85%
9	0.5	MeCN	1	23	-	0:92:8	n.d.
10	0.5	MeCN	12	23	0.5 equiv 2,6-lutidine	0:92:8	n.d.
11	0.5	MeCN/H ₂ O (8:2)	12	23	1 equiv NaHCO ₃	18:72:10	n.d.
12	0.5	MeCN	0.33	23	1 equiv DBU	0:95:5	n.d.
13	0.55	Dry MeCN	0.5	-10 to 23	3 Å m.s., 1 equiv 2,6-lutidine	n.d.	76%
14	0.55	Dry CH ₃ OH	0.5	-10 to 23	3 Å m.s., 1 equiv HMDS	n.d.	89%

Substrate Scope for Oxidation to Disulfides



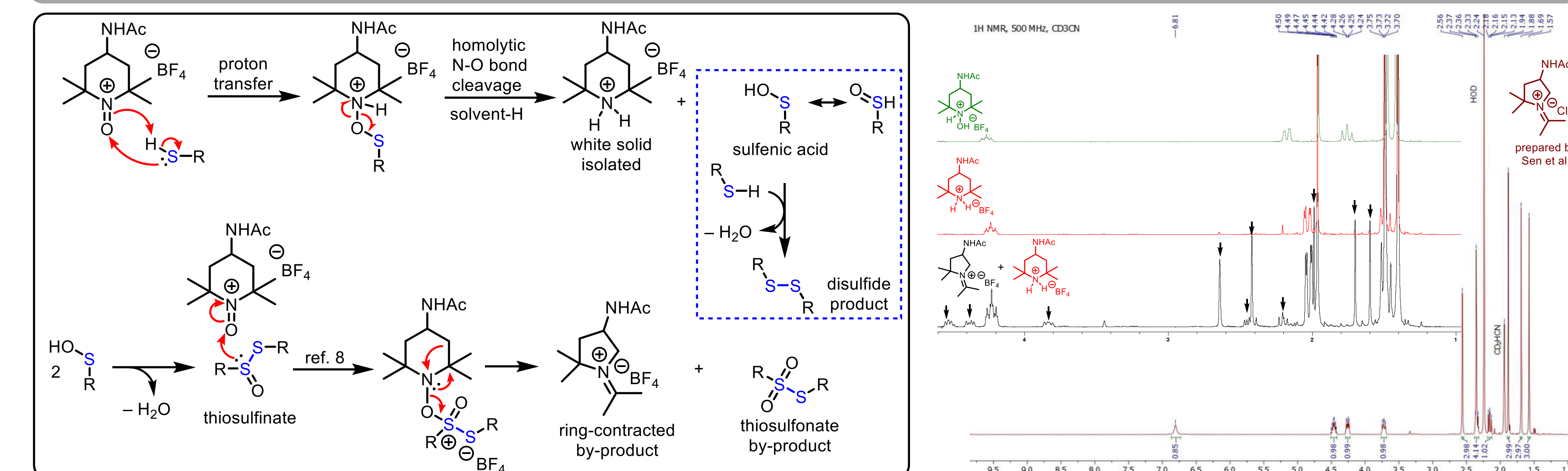
¹H NMR Analysis of a Competitive Oxidation



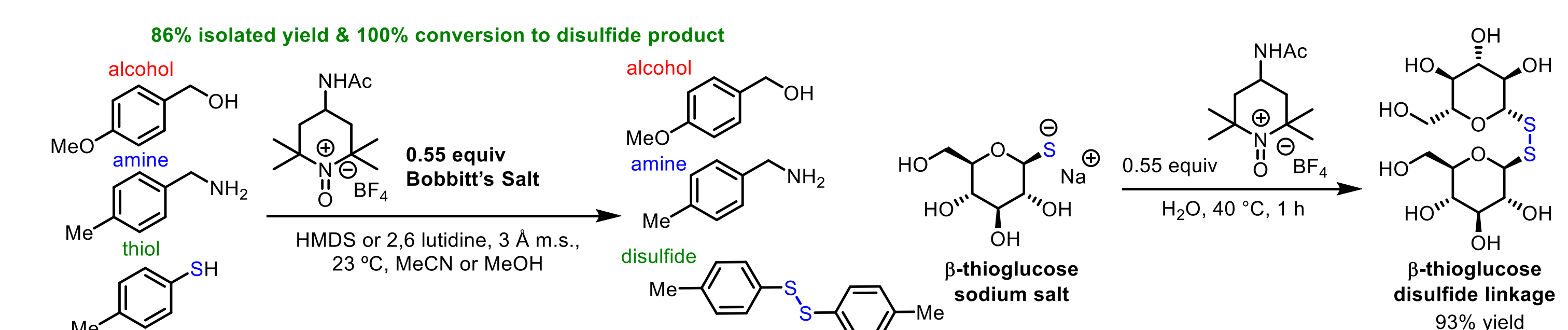
Reactions were conducted on 0.1 mmol scale under argon atmosphere in a rubber septum-capped NMR tube w/ MeCN as solvent + lutidine base.

Results show row 7 displays no imine, aldehyde or nitrile compounds, only diphenyl disulfide

Mechanistic Considerations



Evaluation of Chemoselectivity of the Oxidation



Competitive oxidation of alcohols, amines and thiols with Bobbitt's salt shows that the thiol preferentially oxidizes amidst common oxidizable functional groups.

Conclusions and Future Work

The Lambert research group has successfully developed a chemoselective oxidation of thiols to disulfides. Our methodology employs a cheap and environmentally friendly oxidant to achieve good to excellent yields (71–99%) of disulfides and has a wide substrate scope. The course of the reaction takes an unusual path resulting in deoxygenation of the parent oxoammonium salt oxidant as revealed from experimental and computational mechanistic investigations. Furthermore, recent advancements from our efforts have allowed us to develop electrocatalytic reaction using nitroxide derivatives such as ACT to afford the desired disulfides. Future endeavors of our group involve the employment of this method in efforts to affect late-stage disulfide formation in the epidithiodiketopiperazine class of natural products to construct their central disulfide bridges.

Acknowledgements

- Old Dominion University Perry Honors College Program for Undergraduate Research and Scholarships (PURS; K.V.V. & O.M.W.)
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