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Sulfenate Anion Catalysis: Reactions And Precatalysts Development

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Sulfenate Anion Catalysis: Reactions And Precatalysts Development

Abstract
Organocatalysts have been a hot area of exploration, due to both concept novelty and significant reactivity. Multiple mechanisms have been proved and used to design new organocatalysts. Examples include thioureas, which have been designed to accelerate chemical transformation through hydrogen bonds. Initially found by Schering and Hoffman-La, prolines have been widely used in asymmetric aldol reactions. This dissertation investigated an unprecedented organocatalyst: sulfenate anions.

In Chapter 1, sulfenate anions are introduced as a new type of organocatalyst. It has been well established that the sulfenate anions act both as nucleophiles and leaving groups. For prove-of-concept, a variety of benzyl halides were successfully coupled to form stilbenes. More challenging sulfenate anions precatalysts, including DMSO performed well in these catalytic reactions. Preliminary mechanistic studies were conducted, identifying α-deprotenated sulfoxide as the resting state.

In Chapter 2, we further investigated the sulfenate anions capability as organocatalysts. Due to the instability of sulfenate anions in air, sulfoxides precursors are usually used and generate sulfenate anions in situ through base induced beta-hydrogen elimination or thermolysis. tert-Butyl sulfoxides were examined as a new type of organocatalysts precursor with iso-butylene as a byproduct. It is noteworthy that sulfenate anions generated from tert-butyl sulfoxides remain stable in high temperature under inert atmosphere and retain similar reactivity compared with sulfenate anions formed using general conditions in the model reaction of benzyl halides coupling.

In Chapter 3, further research was performed in exploring the reaction possibility of sulfenate anions. A cross-coupling reaction of benzyl halides and benzaldehydes derivatives was achieved to form alkyne compounds. A broad scope of alkyne products, including multiple functional groups and heterocycles, demonstrated the value of sulfenate anion catalysts in synthetic chemistry. The reactivity of different functionalized sulfenate anions and sulfoxide precatalysts were examined. Further optimization was conducted to overcome multiple side reactions. Moreover, preliminary mechanism study revealed the role of sulfenate anions in the reaction.

In Chapter 4, convenient scalable sulfenate anions precatalysts were developed and their utility demonstrated in a scalable alkyne synthesis.

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SULFENATE ANION CATALYSIS: REACTIONS AND PRECATALYSTS

DEVELOPMENT

Mengnan Zhang

A DISSERTATION

in

Chemistry

Presented to the Faculties of the University of Pennsylvania

in

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2017

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SULFENATE ANION CATALYSIS: REACTIONS AND PRECATALYSTS
DEVELOPMENT

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ABSTRACT

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DEVELOPMENT

Mengnan Zhang
Patrick J. Walsh

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CHAPTER 1 Phenyl Sulfenate Anion Catalyzed Stilbene Formation from Benzyl Halides
## CHAPTER 2 tert-Butyl Phenyl Sulfoxide as a Traceless Sulfenate Anion Precatalyst

2.1 Introduction .............................................................................................................42
   2.1.1 Introduction to Sulfenate Anions Generation .................................................42
   2.1.2 Phenyl Sulfenate Anion Catalysis and Precatalyst Improvement ...............44

2.2 Results and Discussions .......................................................................................45
   2.2.1 Optimization of tert-Butyl Phenyl Sulfoxide Precatalysts in Stilbene Formation .........................................................................................................................46
   2.2.2 Substrate Scope of Stilbenes Formation from Benzyl Halides Catalyzed by Sulfenate Anions ...........................................................................................................48
   2.2.3 Gram Scale Reaction .......................................................................................50

2.3 Conclusion ...............................................................................................................51

2.4 Experimental Section ............................................................................................51

2.5 References .............................................................................................................60

## CHAPTER 3 Sulfenate Anion Organocatalytic Synthesis of Alkynes

3.1 Introduction .............................................................................................................63
   3.1.1 General Approaches for Alkynes Synthesis ...................................................63
   3.1.2 Our Approach to Alkyne Synthesis through Sulfenate Anion Catalysis .....65

3.2 Results and Discussion .........................................................................................67
   3.2.1 Optimization of Sulfenate Anion Catalyzed Alkyne Synthesis .................67
   3.2.2 Substrate Scope of Benzyl Chlorides in Diaryl Acetylene Synthesis .......71
3.2.3 Substrate Scope of Benzaldehydes in the Diaryl Acetylene Synthesis .....72
3.2.4 Gram Scale Reaction .................................................................................74
3.2.5 Special Substrates .......................................................................................75
3.2.6 Preliminary Mechanistic Study.................................................................76
3.3 Conclusion ...................................................................................................78
3.4 Experimental Section ..................................................................................78
3.5 References....................................................................................................102

CHAPTER 4 Sulfenate Anion Precatalyst Development for Alkyne Synthesis on
Gram Scale.........................................................................................................106

4.1 Introduction ..................................................................................................106
  4.1.1 Introduction to Alkyne Chemistry .............................................................106
  4.1.2 Introduction of Sulfenate Anions and Precatalysts.................................107
4.2 Results and Discussion ...............................................................................110
4.4 Conclusion ..................................................................................................111
4.3 Experimental Section .................................................................................112
4.5 References....................................................................................................115

APPENDICES .....................................................................................................119

Appendix A1 NMR Spectra Relevant to Chapter 1 .............................................119
Appendix A2. NMR Spectra Relevant to Chapter 2 ............................................134
Appendix A3 NMR Spectra Relevant to Chapter 3 ............................................149
Appendix A4 NMR Spectra Relevant to Chapter 4 ............................................184
LIST OF TABLES

Table 1-1. Optimization of the formation of stilbene 1.3a from benzyl chloride 1.1a ....... 5

Table 1-2. Comparison of computed bond metrics, Mayer bond orders and natural. charges. .................................................................................................................................32

Table 1-3. Optimized coordinates of PhS(=O)CH2Ph......................................................33

Table 1-4. Optimized coordinates of [PhS(=O)CHPh]– anion isomer A. .........................34

Table 1-5. Optimized coordinates of [PhS(=O)CHPh]– anion isomer A’. .........................35

Table 1-6. Optimized coordinates of [PhS(=O)CHPh]K(18-crown-6)(THF). .................36

Table 2-1. Optimization of sulfenate anion catalyzed trans-stilbene (2.3a) formation from benzyl chloride (2.1a).a ..................................................................................................................47

Table 3-1. Optimization of diaryl acetylene (3.3a) synthesis of benzyl chloride (3.1a) and benzaldehyde (2a). ........................................................................................................68

Table 3-2. Base and solvent screening for alkyne synthesis catalyzed by sulfenate....100
LIST OF SCHEMES

Scheme 1-1. Sulfenate anions and conjugate acids.......................................................... 1

Scheme 1-2. Palladium promotes the tri-catalytic cycle with sulfenate anion as the leaving group in cycle B and nucleophile in cycle C.......................................................... 2

Scheme 1-3. Proposed mechanism of sulfenate anion catalyzed coupling of benzyl halides to form symmetrical stilbenes.......................................................... 3

Scheme 1-4. Substrate scope of sulfenate anion-catalyzed trans-stilbene formation from benzyl halides.......................................................... 8

Scheme 1-5. 2,2′,6,6′-Tetrachloro stilbene formation on gram scale.......................... 9

Scheme 1-6. Methyl phenyl sulfoxide (1.4b), dibenzyl sulfoxide (1.4c) and DMSO (1.4d) as precatalysts in trans-stilbene (1.3a) forming reactions.............................................10

Scheme 1-7. Preliminary mechanistic investigations into sulfenate anion catalyzed stilbene formation.......................................................... 11

Scheme 1-8. Monitoring rest state of the catalytic reaction...........................................23

Scheme 2-1. Sulfenic acid and its conjugate base, sulfenate anion...............................42

Scheme 2-2. Sulfenate anions generation methods..........................................................43

Scheme 2-3. Proposed mechanism for sulfenate anions catalyzed trans-stilbenes formation from benzyl halides.......................................................... 45

Scheme 2-4. Substrate scope of stilbenes formation from benzyl halides catalyzed by sulfenate anions.......................................................... 50

Scheme 2-5. trans-1,2-Di(α-naphthyl)ethylene formation on gram scale..................50

Scheme 3-1. Synthetic approaches to alkynes (A-D) and sulfenate anions (E)........64

Scheme 3-2. Proposed mechanism of the sulfenate anion catalyzed generation of stilbenes (Cycle A) and diaryl acetylenes (Cycle B)..................................................66

Scheme 3-3. Proposed reaction for generation of dibenzyl ether byproduct via Cannizzaro reaction.......................................................... 67

Scheme 3-4. Byproduct formation using benzyl sulfoxide as precatalyst.......................71

Scheme 3-5. Substrate scope of benzyl chlorides in diaryl acetylene synthesis...........72

Scheme 3-6. Substrate scope of benzaldehydes in diaryl acetylene synthesis.............73

Scheme 3-7. Gram scale reactions..........................................................................................74
**Scheme 3-8.** Special substrates applied in sulfenate-anion-catalyzed alkyne synthesis. ...........................................................................................................................................76

**Scheme 3-9.** Preliminary mechanistic study of sulfenate anion-catalyzed diaryl acetylene formation. ...........................................................................................................................................76

**Scheme 4-1.** Reactions catalyzed by sulfenate anions. .........................................................108

**Scheme 4-2.** Sulfenate anions generation methods. ...............................................................110

**Scheme 4-3.** Solid precatalyst preparation and catalytic reaction. ......................................111
LIST OF FIGURES

Figure 1-1. Thermal ellipsoid plot of K(18-crown-6)(THF)[PhS(=O)CHPh] at 30% probability. ..........................................................12

Figure 1-2. In-situ NMR spectra of the catalytic reaction in Scheme 1-8. ..................24

Figure 1-3. 13C NMR of PhS(=O)13CH2Ph treated with 1.0 (upper) and 2.0 (lower) equivalents of KCH2Ph. Resonances at 67.57(5) and 25.37(5) ppm are due to residual protoio THF ..........................................................25

Figure 1-4. 1H NMR spectra of PhS(=O)CH2Ph with increasing equivalents of KO'Bu in THF-d8. Resonances at 3.58 and 1.73 ppm are due to residual protoio THF. ..................26

Figure 1-5. 13C NMR spectra of PhS(=O)CH2Ph with increasing equivalents of KO'Bu in THF-d8. Resonances at 67.57(5) and 25.37(5) ppm are due to residual protoio THF. .....27

Figure 1-6. Variable temperature 1H NMR of PhS(=O)13CH2Ph and 4.0 equivalents of KO'Bu between 240-300 K in THF-d8, showing the diastereotopic benzylic proton (upper) and the tert-butanol (lower) resonance. ..........................................................29

Figure 1-7. Variable temperature 13C NMR of PhS(=O)13CH2Ph and 4.0 equivalents of KO'Bu between 240-300 K in THF-d8. ..........................................................30

Figure 1-8. Structure of Isomer A and A' in Table 1-2. ........................................33

Figure A1.1 500 MHz 1H and 125 MHz 13C{1H} NMR of 1.3a in CDCl3..................120
Figure A1.2 500 MHz 1H and 125 MHz 13C{1H} NMR of 1.3b in CDCl3..................121
Figure A1.3 500 MHz 1H and 125 MHz 13C{1H} NMR of 1.3c in CDCl3..................122
Figure A1.4 500 MHz 1H and 125 MHz 13C{1H} NMR of 1.3d in CDCl3..................123
Figure A1.5 500 MHz 1H and 125 MHz 13C{1H} NMR of 1.3e in CDCl3..................124
Figure A1.6 500 MHz 1H and 125 MHz 13C{1H} NMR of 1.3f in CDCl3..................125
Figure A1.7 500 MHz 1H and 125 MHz 13C{1H} NMR of 1.3g in CDCl3..................126
Figure A1.8 500 MHz 1H and 125 MHz 13C{1H} NMR of 1.3h in CDCl3..................127
Figure A1.9 500 MHz 1H and 125 MHz 13C{1H} NMR of 1.3i in CDCl3..................128
Figure A1.10 500 MHz 1H and 125 MHz 13C{1H} NMR of 1.3j in CDCl3..................129
Figure A1.11 500 MHz 1H and 125 MHz 13C{1H} NMR of 1.3k in CDCl3..................130
Figure A1.12 500 MHz 1H and 125 MHz 13C{1H} NMR of 1.3l in CDCl3..................131
Figure A1.13 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of $^{1.3m}$ in CDCl$_3$ .................132
Figure A1.14 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of $^{1.3n}$ in CDCl$_3$ .................133
Figure A2.1 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of $^{2.3a}$ in CDCl$_3$ ....................135
Figure A2.2 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of $^{2.3b}$ in CDCl$_3$ ....................136
Figure A2.3 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of $^{2.3c}$ in CDCl$_3$ ....................137
Figure A2.4 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of $^{2.3d}$ in CDCl$_3$ ....................138
Figure A2.5 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of $^{2.3e}$ in CDCl$_3$ ....................139
Figure A2.6 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of $^{2.3f}$ in THF-$d_8$ .....................140
Figure A2.7 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of $^{2.3g}$ in CDCl$_3$ ....................141
Figure A2.8 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of $^{2.3h}$ in CDCl$_3$ ....................142
Figure A2.9 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of $^{2.3i}$ in CDCl$_3$ ....................143
Figure A2.10 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of $^{2.3j}$ in CDCl$_3$ ....................144
Figure A2.11 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of $^{2.3k}$ in CDCl$_3$ ....................145
Figure A2.12 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of $^{2.3l}$ in CDCl$_3$ ....................146
Figure A2.13 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of $^{2.3m}$ in CDCl$_3$ ....................147
Figure A2.14 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of $^{2.3n}$ in CDCl$_3$ ....................148
Figure A3.1 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of $^{3.3a}$ in CDCl$_3$ ....................150
Figure A3.2 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of $^{3.3b}$ in CDCl$_3$ ....................151
Figure A3.3 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of $^{3.3c}$ in CDCl$_3$ ....................152
Figure A3.4 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of $^{3.3d}$ in CDCl$_3$ ....................153
Figure A3.5 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of $^{3.3e}$ in CDCl$_3$ ....................154
Figure A3.6 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of $^{3.3f}$ in CDCl$_3$ ....................155
Figure A3.7 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of $^{3.3g}$ in CDCl$_3$ ....................156
Figure A3.8 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of $^{3.3h}$ in CDCl$_3$ ....................157
Figure A3.9 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of $^{3.3i}$ in CDCl$_3$ ....................158
Figure A3.10 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of 3.3j in CDCl$_3$ .................................. 159
Figure A3.11 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of 3.3k in CDCl$_3$ ................................. 160
Figure A3.12 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of 3.3l in CDCl$_3$ ................................. 161
Figure A3.13 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of 3.3m in CDCl$_3$ ................................. 162
Figure A3.14 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of 3.3n in CDCl$_3$ ................................. 163
Figure A3.15 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of 3.3o in CDCl$_3$ ................................. 164
Figure A3.16 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of 3.3p in CDCl$_3$ ................................. 165
Figure A3.17 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of 3.3q in CDCl$_3$ ................................. 166
Figure A3.18 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of 3.3r in CDCl$_3$ ................................. 167
Figure A3.19 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of 3.3s in CDCl$_3$ ................................. 168
Figure A3.20 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of 3.3t in CDCl$_3$ ................................. 169
Figure A3.21 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of 3.3u in CDCl$_3$ ................................. 170
Figure A3.22 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of 3.3v in CDCl$_3$ ................................. 171
Figure A3.23 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of 3.3w in CDCl$_3$ ................................. 172
Figure A3.24 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of 3.3x in CDCl$_3$ ................................. 173
Figure A3.25 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of 3.3y in CDCl$_3$ ................................. 174
Figure A3.26 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of 3.6a in CDCl$_3$ ................................. 175
Figure A3.27 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of 3.6b in CDCl$_3$ ................................. 176
Figure A3.28 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of 3.3dx in CDCl$_3$ ............................... 177
Figure A3.29 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of 3.3dy in CDCl$_3$ ............................... 178
Figure A3.30 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of 3.3gf in CDCl$_3$ ............................... 179
Figure A3.31 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of 3.3mo in CDCl$_3$ .............................. 180
Figure A3.32 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of 3.I in CDCl$_3$ ................................. 181
Figure A3.33 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of 3.H in CDCl$_3$ ................................. 182
Figure A3.34 500 MHz $^1$H and 125 MHz $^{13}$C{${^1}$H} NMR of 3.H' in CDCl$_3$ ............................... 183
Figure A4.1 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 4.4 in CDCl$_3$..........................185

Figure A4.2 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 4.7 in CDCl$_3$..........................186
CHAPTER 1 Phenyl Sulfenate Anion Catalyzed Stilbene Formation from Benzyl Halides.

1.1 Introduction

1.1.1 Introduction to Sulfenate Anions

Sulfenate anions, along with the conjugate acids, sulfenic acids (Scheme 1-1), exhibit a broad range of biological properties, especially in cysteine oxidation to form sulfur containing compounds, such as sulfenamides and sulfonic acids. Small molecule sulfenic acids are highly reactive and difficult to isolate unless sterically protected or stabilized by hydrogen bonds.

![Scheme 1-1. Sulfenate anions and conjugate acids.](image)

In the biological process, sulfenate anions were key intermediates to form multiple compounds. In synthetic chemistry, sulfenate anions also played as a critical and reactive intermediates in sulfoxides formation, trapped by a variety of electrophiles, via organic or metal catalyzed processes.
1.1.2 Reactions of Sulenate Anions

Due to the nucleophilicity of sulenate anions, sulfoxides and sulfenic acid esters could be generated by S- and O- alkylation, controlled by reaction conditions and substrates.\textsuperscript{4} With proper additives introduced, alkanesulfoxides were achieved with excellent yield and enantioselectivity (up to 99%).\textsuperscript{5} With the current trend in transition metal catalysis, palladium catalyzed arylation and allylic substitution have been achieved with sulenate anions generated from different precursors by us\textsuperscript{6} and other groups.\textsuperscript{7}

1.1.3 Our Approach Using Sulenate Anions as Organocatalysts

![Scheme 1-2](image)

 Scheme 1-2. Palladium promotes the tri-catalytic cycle with sulenate anion as the leaving group in cycle B and nucleophile in cycle C.

Despite the long history of discovery and study of sulenate anions as key intermediates, no previous work has been done in exploring the capability of sulenate anions as catalysts. In an early published palladium-catalyzed triple relay reaction converting aryl benzyl sulfoxides to diaryl sulfoxides,\textsuperscript{6} we found the sulenate anions as
the key intermediates, acting as both leaving groups in cycle B and nucleophiles undergoing transmetallation in cycle C, eventually forming a C-S bond (Scheme 1-2). Inspired by this character, we proposed the possibility of utilizing sulfenate anions as organocatalysts in the following catalytic cycle to couple benzyl halides to form stilbene derivatives. We set out to test the feasibility of the hypothesis.

**Scheme 1-3.** Proposed mechanism of sulfenate anion catalyzed coupling of benzyl halides to form symmetrical stilbene.

We started from benzyl sulfoxide 1.A as the precatalysts (Scheme 1-3). With proper base introduced, the α-deprotonated benzylic sulfoxide would react with benzyl halides to form intermediate 1.D. Deprotonation of the β-C–H of 1.D was envisioned to
proceed via an E2 elimination generating *trans*-stilbene and expelling the sulfenate anion catalyst 1.F. Sulfenate anions are known to undergo nucleophilic substitution with benzyl halides,\textsuperscript{4} regenerating sulfoxide 1.A and completing the catalytic cycle. The sulfenate anion 1.F is the smallest structural unit carried through this catalytic cycle.\textsuperscript{8}

1.2 Results and Discussion

1.2.1 Optimization of Sulfenate Anion Catalyzed Stilbene Generation

We initiated the reaction optimization on the basis of previous sulfenate anions cross-coupling work. The pK\textsubscript{a} of benzyl sulfoxide is 27.2 in DMSO,\textsuperscript{9} thus, a number of strong bases with compatible conjugate acid pK\textsubscript{a} (LiO\textsubscript{t}Bu, NaO\textsubscript{t}Bu, KO\textsubscript{t}Bu, Li\textsubscript{N}(SiMe\textsubscript{3})\textsubscript{2}, NaN(SiMe\textsubscript{3})\textsubscript{2}, and KN(SiMe\textsubscript{3})\textsubscript{2}) were selected, with 0.1 mmol benzyl chloride 1.1a and 10 mol % of sulfoxide precatalyst 1.4a loading at 80 °C in solvent cyclopentyl methyl ether (CPME) for 12 hours. Assay yields through NMR indicated KO\textsubscript{t}Bu as the leading base in stilbene 1.3a generation (Table 1-1, entries 1-6). Analysis of reactions shown that both LiO\textsubscript{t}Bu and NaO\textsubscript{t}Bu resulted in unreacted 1.1a (Table 1-1, entries 2-3). However, amide bases led to decomposition of starting materials and formation of byproducts (Table 1-1, entries 4-6). A further decrease in 1.4a loading to 2.5 mol % retain high yield (Table 1-1, entries 7-8). We next focused on identification of more suitable solvents. Screens conducted with 1.0 mol % 1.4a indicated CPME as the optimal solvent (Table 1-1, entries 9-14). Reduction in base equivalents or temperature resulted in lower yields (Table 1-1, entries 15-16). An attempt to increase the concentration from 0.1 M to 0.2 M caused formation of benzyl *tert*-butyl ether, the direct S\textsubscript{N}2 product of KO\textsubscript{t}Bu and benzyl chloride (Table 1-1, entry 17). In the absence of sulfoxide precatalyst 1.4a no stilbene
formation was observed (Table 1-1, entry 18). In conclusion of Table 1-1, the optimized conditions of phenyl sulenate anion catalyzed stilbenes formation from benzyl halides was found to be 2.5 mol % benzyl phenyl sulfoxide precatalyst 1.4a, 3.0 equiv KOtBu in CPME at 80 °C for 12 h.

Table 1-1. Optimization of the formation of stilbene 1.3a from benzyl chloride 1.1a.a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>Catalyst (mol %)</th>
<th>1.3a Assay yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LiO\textsuperscript{t}Bu</td>
<td>CPME</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>NaO\textsuperscript{t}Bu</td>
<td>CPME</td>
<td>10</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>KO\textsuperscript{t}Bu</td>
<td>CPME</td>
<td>10</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>LiN(SiMe\textsubscript{3})\textsubscript{2}</td>
<td>CPME</td>
<td>10</td>
<td>41</td>
</tr>
<tr>
<td>5</td>
<td>NaN(SiMe\textsubscript{3})\textsubscript{2}</td>
<td>CPME</td>
<td>10</td>
<td>51</td>
</tr>
<tr>
<td>6</td>
<td>KN(SiMe\textsubscript{3})\textsubscript{2}</td>
<td>CPME</td>
<td>10</td>
<td>81</td>
</tr>
<tr>
<td>7</td>
<td>KO\textsuperscript{t}Bu</td>
<td>CPME</td>
<td>5</td>
<td>100</td>
</tr>
<tr>
<td>8</td>
<td>KO\textsuperscript{t}Bu</td>
<td>CPME</td>
<td>2.5</td>
<td>100 (95\textsuperscript{b})</td>
</tr>
<tr>
<td>9</td>
<td>KO\textsuperscript{t}Bu</td>
<td>CPME</td>
<td>1</td>
<td>74</td>
</tr>
<tr>
<td>10</td>
<td>KO\textsuperscript{t}Bu</td>
<td>Toluene</td>
<td>1</td>
<td>57</td>
</tr>
</tbody>
</table>
Under the optimized conditions in entry 8 (Table 1-1), the scope of benzyl halide coupling to form stilbenes catalyzed by phenyl sulfenate anion was examined (Scheme 1-4). Both benzyl chloride 1.1 and benzyl bromide 1.2 derivatives were investigated if the starting materials were available. In general, the optimal condition favored benzyl chlorides over benzyl bromides, since the latter tended to undergo direct S_N2 reaction with base to form benzyl tert-butyl ether. This is likely due to the fact that bromine is a better leaving group than chloride. For the purpose of eliminating background reaction, 5 mol % 1.4a was applied. trans-Stilbene 1.3a was generated in 95% and 81% yield from benzyl chloride 1.1a and benzyl bromide 1.2a, respectively. Slightly electron-donating groups, 4-methyl and 4-tert-butyl benzyl halides generated substituted stilbenes in average to good yields (Scheme 1-4, 1.3b-c, 62-84%). However, a strong electron-
donating group, such as 4-methoxybenzyl chloride, decreased the yield to 31\% (Scheme 1-4, 1.3d). This observation is likely due to the decreased \( \alpha \)-proton acidity of benzylic sulfoxides and lower \( \beta \)-proton reactivity of intermediate D (Scheme 1-3). Substrates bearing simple electron-withdrawing groups resulted in good to excellent yields (Scheme 1-4, 1.3e-f, 66-99\%). Unfortunately, some substrates with base sensitive strong electron-withdrawing groups, like 4-CF\(_3\), 4-NO\(_2\) and 4-CN led to no desired products, due to the substrate decomposition. Our optimized conditions could also tolerate ortho-substituted substrates, from 2-F-C\(_6\)H\(_4\)CH\(_2\)-Cl (Scheme 1-4, 1.1g, 73\%) to more sterically hindered 2-Me-C\(_6\)H\(_4\)CH\(_2\)-Cl (Scheme 1-4, 1.1h, 92\% yield) and (1-naphthyl)CH\(_2\)-Cl (Scheme 1-4, 1.1i, 80\% yield). Even 2,6-dichlorobenzyl chloride gave tetrachloro stilbene in high yield (Scheme 1-4, 1.3j, 88\%). Meta-substituents exhibited great reactivity (Scheme 1-4, 1.3k-m, 68-89\%). The 3-CF\(_3\) substituted benzyl bromide formed 1.2m in 68\% yield when KO\( ^\text{Bu}\) was decreased to 2.0 equiv, due to the base sensitivity of the functional group. More challenging substrate 2-(chloromethyl)pyridine (Scheme 1-4, 1.1n) did not react under our standard conditions. A stronger base KH and longer reaction time (24 h) at higher temperature 110 °C facilitated the formation of 1.3n in 54\% yield.
Scheme 1-4. Substrate scope of sulenate anion-catalyzed trans-stilbene formation from benzyl halides.

5 mol % 1.4a loading. 0.2 mmol KO'Bu. KH as the base, 110 °C for 24 h.
1.2.3 Gram Scale Synthesis

To demonstrate the scalability of this phenyl sulenate anion catalyzed reaction, synthesis of 1.2j on 7.0 mmol scale with 2.5 mol % of sulfoxide 1.4a was performed (Scheme 1-5) under the optimized condition. 2,2',6,6'-Tetrachloro trans-stilbene 1.3j was isolated in 92% yield, demonstrating the reaction is scalable.

![Scheme 1-5. 2,2',6,6'-Tetrachloro stilbene formation on gram scale.](image)

1.2.4 Expansion of Sulfoxide Precatalysts in Stilbene Formation

Based on the proposed mechanism in Scheme 1-3, related precatalysts could be imagined. The $pK_a$ of methyl phenyl sulfoxide (1.4b) is significantly higher than benzyl aryl sulfoxides. A stronger base, KH, therefore, was required to generate the catalyst. The expected byproduct of catalyst formation, styrene, was observed ($^1$H NMR). With 5 mol % phenyl methyl sulfoxide, stilbene was generated in 92% yield$^{10}$ (Scheme 1-6A). Using 10 mol % dibenzyl sulfoxide (1.4c), 1.3a was afforded in 92% yield (Scheme 1-6B). Dimethyl sulfoxide (DMSO, 1.4d, 10 mol %), a common organic solvent, was also a viable precatalyst when combined with KH, affording 71% yield$^{10}$ (Scheme 1-6C).
1.2.5 Preliminary Mechanism Study of Sulfenate Anions Catalysis

We next set out to gain insight into the mechanism of the catalytic coupling. Upon reaction of stoichiometric benzyl phenyl sulfoxide (1.4a) with 1.0 equiv benzyl chloride (1.1a) under basic conditions, 1,2-diphenylethyl phenyl sulfoxide11 was (1.4e) observed (2%) along with trans-stilbene (91%, 1.3a, Scheme 1-7A). When independently synthesized 1.4e was used as catalyst, 98% yield of stilbene (1.3a) was obtained (Scheme 1-7B), suggesting sulfoxide 1.4e is an intermediate in the catalytic reaction. Furthermore, when 1.4e was combined with stoichiometric 4-methylbenzyl chloride (1.1b) under the standard reaction conditions, trans-stilbene, 4,4'-dimethyl trans-stilbene (1.3b),
and 4-methylbenzyl phenyl sulfoxide (1.4f, 52% yield) were generated (Scheme 1-7C), suggesting that phenylsulfenate anion is formed from 1.4e. These results supported the mechanism proposed in Scheme 1-3.

Scheme 1-7. Preliminary mechanistic investigations into sulfenate anion catalyzed stilbene formation.

To investigate the resting state of this unique system, we conducted the reaction using benzyl chloride (1.1a) under standard conditions but at 50 °C. The reaction was quenched with 30 equiv of water after 30 min. Benzyl phenyl sulfoxide 1.4a was isolated in 87% yield, suggesting that resting state is benzyl phenyl sulfoxide or its conjugate base. The reaction was then conducted in THF-\textit{d}_8 and monitored by \textit{^1}H NMR. No resonances for benzyl phenyl sulfoxide were observed. Furthermore, combining benzyl phenyl sulfoxide with KO\textsuperscript{t}Bu and monitoring the reaction by NMR also indicates sulfoxide
deprotonation. These results are consistent with the relative pKa's of benzyl phenyl sulfoxide (pKa 27.2 in DMSO) and tert-butanol (pKa 32.2 in DMSO). These data indicate the deprotonated sulfoxide is catalyst resting state. Moreover, recent Density Functional Theory (DFT) calculations by Toscano and Adamo's confirmed our hypothesis. To form 1.4e, reactants must overcome an energy barrier of 20.5 kcal/mol.\textsuperscript{12}

Figure 1-1. Thermal ellipsoid plot of K(18-crown-6)(THF)[PhS(=O)CHPh] at 30% probability.

To further characterize the catalyst resting state, Dr. Haolin Yin deprotonated benzyl phenyl sulfoxide 1.4a with KCH\textsubscript{2}Ph. Single crystals suitable for a crystallographic study were obtained after addition of 18-crown-6 and layering with hexanes.\textsuperscript{13} The solid state structure of the product, K(18-crown-6)(THF)[PhS(=O)CHPh], is monomeric with a potassium cation coordinated to both the α-carbon and oxygen atoms of the anion (Figure 1-1). The sp\textsuperscript{2} nature of the benzylic carbon was evident from the short S–C bond of 1.691(2) Å, compared to the 1.837(2) Å C–S distance in the reported benzylic
sulfoxide \{2-[(NMe_2)CHMe]C_6H_4}S(=O)CH_2Ph.\textsuperscript{14} A gas-phase DFT calculation at B3LYP/6-31G* level was performed on [PhS(O)CHPh]\textsuperscript{−} and corresponding neutral sulfoxide, PhS(O)CH_2Ph. The computed models showed a 0.166 Å shortening of the O bond upon benzylic de-protonation. This result, together with the X-ray structure, is supportive of multiple bond character of S–C(Bn) bond in the deprotonated sulfoxide anion.\textsuperscript{15}

1.3 Conclusion

In summary, we hypothesized that sulfenate anions could act as catalytic intermediates in organocatalytic reactions. This hypothesis was founded upon their ability to act as both leaving groups and as nucleophiles. As proof of concept, we developed the base-promoted conversion of benzyl halides to \textit{trans}-stilbenes catalyzed by sulfenate anions. Furthermore, we have shown that a variety of sulfoxide precatalysts, including DMSO, can promote this reaction with loadings of 1–10 mol %. Reactivity studies provide support for the intermediacy of sulfenate anions and strong evidence that the catalyst resting state is the deprotonated sulfoxide. Based on these studies, we offer that sulfenate anions have significant potential in organocatalysis. Related reactions catalyzed by this novel class of catalysts are currently under investigation.

1.4 Experimental Section

General Methods
All reactions were carried out under dry nitrogen. Anhydrous cyclopentyl methyl ether (CPME), dioxane and dichloroethane were purchased from Sigma-Aldrich and directly used without further purification. Toluene, dimethoxyethane (DME) and THF were dried through activated alumina columns. Unless otherwise stated, reagents were commercially available and used as purchased without further purification. Chemicals were purchased from Sigma-Aldrich, Acros, Alfa Aesar, TCI or Matrix Scientific, and solvents were purchased from Fisher Scientific. The progress of the reactions was monitored by thin-layer chromatography using Whatman Partisil K6F 250 μm precoated 60 Å silica gel plates and visualized by short-wave ultraviolet light as well as by treatment with iodine. Flash chromatography was performed with silica gel (230–400 mesh, Silicycle). The NMR spectra were obtained using a Brüker 500 MHz Fourier-transform NMR spectrometer. Chemical shifts are reported in units of parts per million (ppm) downfield from tetramethylsilane (TMS), and all coupling constants are reported in hertz.

**General Procedure:** To an oven-dried microwave vial equipped with a stir bar was added benzyl phenyl sulfoxide (1.4a, 0.54 mg, 0.0025 mmol) and KOtBu (33.6 mg, 0.30 mmol, 3.0 equiv) in a nitrogen filled dry box followed by 1.0 mL dry CPME. The microwave vial was sealed with a vial cap with a rubber insert and the sealed vial was removed from the dry box. Benzyl chloride (1.1a 11.5 μL, 0.10 mmol) was then added by microsyringe under nitrogen protection. Note that if the benzylic halide is a solid, it was added to the reaction vial before sealed in the dry box. The reaction mixture was heated to 80 °C in an oil bath and stirred for 12 h. The sealed vial was cooled to room temperature, opened to air, and the reaction mixture was passed through a short pad of
silica gel then rinsed with 10 mL ethyl acetate. The solvent was removed under reduced pressure. The resulting residue was purified by flash chromatography as outlined below.

**(E)-Stilbene (1.3a):** The reaction was performed following the General Procedure with benzyl phenyl sulfoxide (1.4a, 0.54 mg, 0.0025 mmol, from a stock solution), benzyl chloride (1.1a, 11.5 μL, 0.10 mmol) and KOtBu (33.6 mg, 0.30 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (1.3a, 8.6 mg, 95% yield) as a white solid. The spectroscopic data match the previously reported data.  

**(E)-Stilbene (1.3a) (from benzyl bromide):** The reaction was performed following the General Procedure with benzyl phenyl sulfoxide (1.4a, 0.54 mg, 0.0025 mmol, from a stock solution), benzyl bromide (1.2a, 12.0 μL, 0.10 mmol) and KOtBu (33.6 mg, 0.30 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (1.3a, 7.3 mg, 81% yield) as a white solid. The spectroscopic data match the previously reported data.  

**(E)-4,4′-Dimethylstilbene (1.3b):** The reaction was performed following the General Procedure with benzyl phenyl sulfoxide (1.4a, 0.54 mg, 0.0025 mmol, from a stock solution), 4-methylbenzyl chloride (1.1b, 13.5 μL, 0.10 mmol) and KOtBu (33.6 mg, 0.30 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (1.3b, 8.7 mg, 84% yield) as a white solid. The spectroscopic data match the previously reported data.
(E)-4,4'-Dimethylstilbene (1.3b) (from 4-methylbenzyl bromide): The reaction was performed following the General Procedure with benzyl phenyl sulfoxide (1.4a, 1.08 mg, 0.005 mmol, from a stock solution), 4-methylbenzyl bromide (1.2b, 18.5 mg, 0.10 mmol) and KOtBu (33.6 mg, 0.30 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (1.3b, 6.5 mg, 62% yield) as a white solid. The spectroscopic data match the previously reported data.8

(E)-4,4'-Di(tert-butyl)stilbene (1.3c): The reaction was performed following the General Procedure with benzyl phenyl sulfoxide (1.4a, 1.08 mg, 0.005 mmol, from a stock solution), 4-tert-butylbenzyl bromide (1.2c, 18.5 μL, 0.10 mmol) and KOtBu (33.6 mg, 0.30 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (1.3c, 10.3 mg, 70% yield) as a white solid. The spectroscopic data match the previously reported data.16

(E)-4,4'-Dimethoxystilbene (1.3d): The reaction was performed following the General Procedure with benzyl phenyl sulfoxide (1.4a, 1.08 mg, 0.005 mmol, from a stock solution), 4-methoxybenzyl chloride (1.1d, 13.5 μL, 0.10 mmol) and KOtBu (33.6 mg, 0.30 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes:EtOAc = 10:1) to give the product (1.3d, 3.6 mg, 31% yield) as a white solid. The spectroscopic data match the previously reported data.8
(E)-4,4'-Difluorostilbene (1.3e): The reaction was performed following the General Procedure with benzyl phenyl sulfoxide (1.4a, 0.54 mg, 0.0025 mmol, from a stock solution), 4-fluorobenzyl chloride (1.1e, 12 µL, 0.10 mmol) and KO'Bu (33.6 mg, 0.30 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (1.3e, 8.8 mg, 81% yield) as a white solid. The spectroscopic data match the previously reported data.⁸

(E)-4,4'-Difluorostilbene (1.3e) (from 4-fluorobenzyl bromide): The reaction was performed following the General Procedure with benzyl phenyl sulfoxide (1.4a, 1.08 mg, 0.005 mmol, from a stock solution), 4-fluorobenzyl bromide (1.2e, 12.5 µL, 0.10 mmol) and KO'Bu (33.6 mg, 0.30 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (1.3e, 7.2 mg, 66% yield) as a white solid. The spectroscopic data match the previously reported data.⁸

(E)-4,4'-Dichlorostilbene (1.3f): The reaction was performed following the General Procedure with benzyl phenyl sulfoxide (1.4a, 0.54 mg, 0.0025 mmol, from a stock solution), 4-chlorobenzyl chloride (1.1f, 16.1 mg, 0.10 mmol) and KO'Bu (33.6 mg, 0.30 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (1.3f, 12.4 mg, 99% yield) as a white solid. The spectroscopic data match the previously reported data.⁸
(E)-2,2′-Difluorostilbene (1.3g): The reaction was performed following the General Procedure with benzyl phenyl sulfoxide (1.4a, 0.54 mg, 0.0025 mmol, from a stock solution), 2-fluorobenzyl chloride (1.1g, 12.0 μL, 0.10 mmol) and KOtBu (33.6 mg, 0.30 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (1.3g, 7.9 mg, 73% yield) as a white solid. The spectroscopic data match the previously reported data.  

(E)-2,2′-Dimethylstilbene (1.3h): The reaction was performed following the General Procedure with benzyl phenyl sulfoxide (1.4a, 0.54 mg, 0.0025 mmol, from a stock solution), 2-methylbenzyl chloride (1.1h, 13.5 μL, 0.10 mmol) and KOtBu (33.6 mg, 0.30 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (1.3h, 9.6 mg, 92% yield) as a white solid. The spectroscopic data match the previously reported data.  

(E)-1,2-Di(1-naphthyl)ethylene (1.3i): The reaction was performed following the General Procedure with benzyl phenyl sulfoxide (1.4a, 0.54 mg, 0.0025 mmol, from a stock solution), 1-(chloromethyl)naphthalene (1.1i, 17.7 mg, 0.10 mmol) and KOtBu (33.6 mg, 0.30 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (1.3i, 11.2 mg, 80% yield) as a white solid. The spectroscopic data match the previously reported data.
(E)-2,2',6,6'-Tetrachlorostilbene (1.3j): The reaction was performed following the General Procedure with benzyl phenyl sulfoxide (1.4a, 0.54 mg, 0.0025 mmol, from a stock solution), 2,6-dichlorobenzyl chloride (1.1j, 19.6 mg, 0.10 mmol) and KOtBu (33.6 mg, 0.30 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (1.3j, 14.0 mg, 88% yield) as a white solid. The spectroscopic data match the previously reported data.8

(E)-3,3'-Dimethylstilbene (1.3k): The reaction was performed following the General Procedure with benzyl phenyl sulfoxide (1.4a, 1.08 mg, 0.005 mmol, from a stock solution), 3-methylbenzyl bromide (1.2k, 14.0 μL, 0.10 mmol) and KOtBu (33.6 mg, 0.30 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (1.3k, 7.8 mg, 75% yield) as a white solid. The spectroscopic data match the previously reported data.8

(E)-3,3'-Difluorostilbene (1.3l): The reaction was performed following the General Procedure with benzyl phenyl sulfoxide (1.4a, 0.54 mg, 0.0025 mmol, from a stock solution), 3-fluorobenzyl chloride (1.1l, 12.1 μL, 0.10 mmol) and KOtBu (33.6 mg, 0.30 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (1.3l, 9.6 mg, 89% yield) as a white solid. The spectroscopic data match the previously reported data.17
(E)-3,3′-Ditrifluoromethylstilbene (1.3m): The reaction was performed following the General Procedure with benzyl phenyl sulfoxide (1.4a, 0.54 mg, 0.0025 mmol, from a stock solution), 3-trifluoromethylbenzyl bromide (1.2m, 15.5 μL, 0.10 mmol) and KOtBu (22.4 mg, 0.20 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (1.3m, 10.8 mg, 68% yield) as a white solid. The spectroscopic data match the previously reported data.18

1,2-Trans-bis(2-pyridyl)ethylene (1.3n): To an oven-dried microwave vial equipped with a stir bar was added benzyl phenyl sulfoxide (1.4a, 1.08 mg, 0.005 mmol, from a stock solution), 2-(Chloromethyl)pyridine hydrochloride (1.1n, 16.4 mg, 0.10 mmol) and KH (16 mg, 0.40 mmol, 4.0 equiv) in a nitrogen filled dry box followed by 1.0 mL dry CPME. The microwave vial was sealed with a vial cap with a rubber insert and the sealed vial removed from the dry box. The reaction mixture was heated to 110 °C in an oil bath and stirred for 24 h. The sealed vial was cooled to room temperature, opened to air, and the reaction mixture was passed through a short pad of silica gel. The pad was then rinsed with 20 mL ethyl acetate. The volatile materials were removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (eluted with hexanes:EtOAc = 1:1) to give the product (1.3n, 4.9 mg, 54% yield) as a white solid. The spectroscopic data match the previously reported data.19

Gram scale reaction
**E)-2',2',6,6'-Tetrachlorostilbene (1.3j, gram scale):** To a three-necked round bottom flask equipped with a condenser under a nitrogen atmosphere was added benzyl phenyl sulfoxide (1.4a, 37.8 mg, 0.175 mmol), 2,6-dichlorobenzyl chloride (1.1j, 1.37 g, 7.0 mmol) and KO\textsubscript{t}Bu (2.35 g, 21 mmol) and the flask was subjected to 3 cycles of vacuum/back fill with nitrogen. Then 70 mL dry CPME were added via syringe. The flask was sealed by a glass plug with grease. The reaction was heated to 80 °C and stirred for 12 h under nitrogen. The reaction mixture was passed through a short pad of silica gel, and eluted with 150 mL ethyl acetate. The volatile materials were removed under reduced pressure and the residue was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (1.3j, 1.03 g, 93% yield) as a white solid. The spectroscopic data match the above reported data.\textsuperscript{8}

**Sulfoxide precatalyst investigation.**

**Methyl Phenyl Sulfoxide 1.4b Precatalyst:** To an oven-dried microwave vial equipped with a stir bar was added methyl phenyl sulfoxide (1.4b, 0.7 mg, 0.005 mmol, from a stock solution) and KH (12.0 mg, 0.30 mmol, 3.0 equiv) in a nitrogen filled dry box followed by 1.0 mL dry CPME. The microwave vial was sealed with a vial cap with a rubber insert and the sealed vial removed from the dry box. Benzyl chloride (1.1a, 11.5 μL, 0.10 mmol) was then added by syringe under nitrogen. The reaction mixture was heated to 80 °C in an oil bath and stirred for 12 h. The sealed vial was cooled to room temperature, opened to air, and the reaction mixture was passed through a short pad of silica gel then rinsed with 10 mL ethyl acetate. The volatile materials were removed under reduced pressure and the residue was purified by flash chromatography on silica gel (eluted hexanes) to give the product (1.3a, 7.9 mg) as
a white solid. Due to the styrene generation, only 95% of benzyl chloride was taken into catalytic reaction. The maximum yield is 8.6 mg. Therefore, the yield is 92% (7.9 mg/8.6 mg * 100% = 92%).

**Dibenzyl Sulfoxide 1.4b Precatalyst:** To an oven-dried microwave vial equipped with a stir bar was added dibenzyl sulfoxide (1.4b, 2.3 mg, 0.010 mmol) and KN(SiMe₃)₂ (60.0 mg, 0.30 mmol, 3.0 equiv) in a nitrogen filled dry box followed by 1.0 mL dry CPME. The microwave vial was sealed with a vial cap with a rubber insert and the sealed vial removed from the dry box. Benzyl chloride (1.1a, 11.5 μL, 0.10 mmol) was then added by syringe under nitrogen. The reaction mixture was heated to 80 °C in an oil bath and stirred for 12 h. The sealed vial was cooled to room temperature, opened to air, and the reaction mixture was passed through a short pad of silica gel then rinsed with 10 mL ethyl acetate. The volatile materials were removed under reduced pressure and the residue was purified by flash chromatography on silica gel (eluted hexanes) to give the product (1.1a, 8.3 mg, 92% yield) as a white solid.

**Dimethyl Sulfoxide 1.4c Precatalyst:** To an oven-dried microwave vial equipped with a stir bar was added methyl phenyl sulfoxide (1.4c, 0.7 μL, 0.010 mmol, from a stock solution) and KH (12.0 mg, 0.30 mmol, 3.0 equiv) in a nitrogen filled dry box followed by 1.0 mL dry CPME. The microwave vial was sealed with a vial cap with a rubber insert and the sealed vial removed from the dry box. Benzyl chloride (1.1a, 11.5 μL, 0.10 mmol) was then added by syringe under nitrogen. The reaction mixture was heated to 80 °C in an oil bath and stirred for 12 h. The sealed vial was cooled to room temperature, opened to air, and the reaction mixture was passed through a short pad of silica gel then rinsed with 10 mL ethyl acetate. The volatile
materials were removed under reduced pressure and the residue was purified by flash chromatography on silica gel (eluted hexanes) to give the product (1.3a, 5.1 mg) as a white solid. Due to the consumption of 2 equiv. benzyl chloride and generation of two equiv. styrene, only 80% of benzyl chloride can form the product. The maximum yield is 7.2 mg. Therefore, the yield is 71% (5.1 mg/7.2 mg * 100% = 71%).

**Mechanism Study**

**Resting State Investigation**

An experiment to investigate the resting state was run in J. Young NMR tube with THF-d₆. To an oven-dried J. Young NMR tube was added benzyl phenyl sulfoxide (1.4a, 1.08 mg, 0.005 mmol, from a stock solution), benzyl chloride 1.1a (11.5 μL, 0.10 mmol) and KOtBu (33.6 mg, 0.30 mmol) and 0.75 mL dry THF-d₆ in a nitrogen filled dry box. The J. Young NMR tube was sealed and removed from dry box (Scheme 1-8). The reaction mixture was heated to 80 °C in an oil bath for 10 minutes and monitored by NMR. No resonance of neutral benzyl phenyl sulfoxide was observed.

![Scheme 1-8. Monitoring rest state of the catalytic reaction.](image-url)
To an oven-dried J. Young NMR tube was added PhS(=O)\(^{13}\)CH\(_2\)Ph (1.4a', 10.9 mg, 0.05 mmol), KCH\(_2\)Ph (6.5 mg, 0.05 mmol) and 0.75 mL dry THF-\(d_8\) in a nitrogen filled dry box. The J. Young NMR tube was sealed and removed from dry box. The mixture was monitored by \(^{13}\)C NMR (Figure 1-3). Then in the dry box, more KCH\(_2\)Ph (6.5 mg, 0.05 mmol) was added into the J. Young NMR tube. The resulting \(^{13}\)C NMR remained the same in 80-50 ppm range. Indicating addition of excess KCH\(_2\)Ph did not lead to further deprotonation.

**Figure 1-2.** In-situ NMR spectra of the catalytic reaction in Scheme 1-8.
Figure 1-3. $^{13}$C NMR of PhS(=O)13CH2Ph treated with 1.0 (upper) and 2.0 (lower) equivalents of KCH2Ph. Resonances at 67.57(5) and 25.37(5) ppm are due to residual protio THF.
To an oven-dried J. Young NMR tube was added benzyl phenyl sulfoxide (1.4a, 10.8 mg, 0.05 mmol) and 0.75 mL dry THF-$d_8$ in a nitrogen filled dry box. The J. Young NMR tube was sealed and removed from dry box. The mixture was monitored by $^1$H NMR. Then in the dry box, more KOtBu (amount shown in Figure 1-4) was added into the J. Young NMR tube. The resulting $^1$H NMR was layered in Figure 1-4. The benzylic proton disappeared with 2.0 equiv. KOtBu added, indicating a fast exchange between neutral sulfoxide and anionic sulfoxide mediated by tert-butanol.

![Figure 1-4. $^1$H NMR spectra of PhS(=O)CH$_2$Ph with increasing equivalents of KOtBu in THF-$d_8$. Resonances at 3.58 and 1.73 ppm are due to residual protio THF.](image)
To an oven-dried J. Young NMR tube was added PhS(=O)\(^{13}\)CH\(_2\)Ph (1.4a*, 10.9 mg, 0.05 mmol) and 0.75 mL dry THF-\(d_8\) in a nitrogen filled dry box. The J. Young NMR tube was sealed and removed from dry box. The mixture was monitored by \(^{13}\)C NMR. Then in the dry box, more KO\(^t\)Bu (amount shown in Figure 1-5) was added into the J. Young NMR tube. The resulting \(^{13}\)C NMR was layered in Figure 1-5. The benzylic carbon (labeled by \(^{13}\)C) broadened with KO\(^t\)Bu added, indicating a fast exchange between neutral sulfoxide and anionic sulfoxide mediated by \textit{tert}-butanol.

\textbf{Figure 1-5.} \(^{13}\)C NMR spectra of PhS(=O)\(^{13}\)CH\(_2\)Ph with increasing equivalents of KO\(^t\)Bu in THF-\(d_8\). Resonances at 67.57(5) and 25.37(5) ppm are due to residual protio THF.
To an oven-dried J. Young NMR tube was added PhS(=O)$^{13}$CH$_2$Ph ($1.4a^*$, 10.9 mg, 0.05 mmol), KO'Bu (22.4 mg, 0.2 mmol) and 0.75 mL dry THF-$d_8$ in a nitrogen filled dry box. The J. Young NMR tube was sealed and removed from dry box. The mixture was monitored by $^1$H NMR under 300K-240K (Figure 1-6). In variable temperature $^1$H NMR, the diastereotopic benzylic proton resonance appeared at $\sim$ 250 K and 3.89 and 3.71 ppm (d, $J = 167$ Hz, $^{13}$C split). Meanwhile, the resonance of tert-butanol appeared at 13.15 ppm.
Figure 1-6. Variable temperature $^1$H NMR of PhS(=O)$^{13}$CH$_2$Ph and 4.0 equivalents of KO'Bu between 240-300 K in THF-$d_8$, showing the diastereotopic benzylic proton (upper) and the tert-butanol (lower) resonance.

Deprotonation of PhS(=O)$^{13}$CH$_2$Ph with KCH$_2$Ph generated K[PhS(=O)$^{13}$CHPh], which exhibited 2 broad diastereotopic benzylic carbon resonances at 71.9 and 56.7 ppm in THF-$d_8$ (See Figure 1-3). When benzyl phenyl sulfoxide was treated with excess KO'Bu, only one broad $^{13}$C resonance at 63.5 ppm was observed (See Figure 1-5), suggesting a fast exchange between two species mediated by tert-butanol.

To further support the presence of deprotonated sulfoxide, variable temperature $^{13}$C NMR experiments were performed (See Figure 1-7). To an oven-dried J. Young NMR tube was added PhS(=O)$^{13}$CH$_2$Ph (1.4a', 10.9 mg, 0.05 mmol), KO'Bu (22.4 mg, 0.2 mmol) and 0.75 mL dry THF-$d_8$ in a nitrogen filled dry box. The J. Young NMR tube was sealed and removed from dry box. The mixture was monitored by $^{13}$C NMR under 300K-240K. The decoalescence of the benzylic carbon was observed at ~275 K, corresponding to a barrier of 11.5 kcal mol$^{-1}$. Thus, the fast exchange was demonstrated
and the equilibrium lies to the deprotonated sulfoxide, proving its role as the resting state in catalytic cycle.

**Figure 1-7.** Variable temperature $^{13}$C NMR of PhS(=O)\(^{13}\)CH\(_2\)Ph and 4.0 equivalents of KO'Bu between 240-300 K in THF-d\(_8\).

Rotational barrier is calculated according to the equations below.

$$k_c = \frac{\pi}{\sqrt{2}} \Delta v_{AB}$$

$$\Delta G^\ddagger = RT \ln \left( \frac{kT}{\kappa_c h} \right)$$
**Synthesis of [PhS(=O)CHPh]K(18-crown-6)(THF).** To a 2 mL THF solution containing PhS(=O)CH$_2$Ph (1.4a, 0.108 g, 0.500 mmol, 1.00 equiv) cooled to -25 °C, a 2 mL cold(-25 °C) THF solution containing KBn (0.065 g, 0.500 mmol, 1.00 equiv) was added, leading to an instant color change to yellow. The mixture was allowed to warm up to room temperature and stirred for 1 h. Then a 2 mL THF solution containing 18-crown-6 (0.132 g, 0.500 mmol, 1.00 equiv) was added to the reaction mixture. After stirring for another 0.5 h, the resulting yellow solution was filtered through Celite packed in a pipette filter. The solution was concentrated to 2 mL under reduced pressure and layered with 3 mL hexanes. Storage of the layered solution under -25 °C overnight led to the precipitation of yellow solids. The products were collected on a medium size fritted filter and dried under reduced pressure for 1 h. Yield: 0.267 g, 0.453 mmol, 91%. Single crystals suitable for X-ray diffraction analysis (Figure 1-1) were obtained by storing a THF/Hexanes layered solution under -25 °C overnight.

Instead of two enantiomers, two diastereomers were observed in solution. The difference between solid crystal structure and solution behavior may origin from potassium coordination to oxygen. In solid structure, the cation was chelated by both oxygen and the benzylic carbon. Therefore, the chirality of the ionic carbon was interfered by the sulfur configuration. While in solution, since the lone pair of electrons on the ionic carbon was free of potassium coordination, the two chiral centers were independent, expressing two diastereomers.

**Computational Details**

Gaussian 09 Rev. A.02 was used for all electronic structure calculations. The B3LYP hybrid DFT method was employed, with 6-31G* basis set for all other atoms. The
frequency calculation indicated that the geometry was the minimum (no imaginary frequencies). Molecular orbitals were rendered with the program Chemcraft v1.6,\textsuperscript{21} at an isovalue of 0.03. Natural bond orbital analysis and Mayer bond orders\textsuperscript{22} were calculated with Gaussian with keyword pop=(nbo,full) and IOp(6/80=1), respectively.

\textit{Table 1-2.} Comparison of computed bond metrics, Mayer bond orders and natural charges.

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*Isomer A’ anion is 1.1 kcal mol\textsuperscript{-1} higher in free energy than A. The optimized geometry of A and A’ are shown below Figure 1-9.
**Figure 1-8.** Structure of Isomer A and A’ in Table 1-2.

**Table 1-3.** Optimized coordinates of PhS(=O)CH2Ph.

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Table 1-4. Optimized coordinates of [PhS(=O)CHPh] anion isomer A.

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\caption{Optimized coordinates of [PhS(=O)CHPh]⁻ anion isomer A⁻.}
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Table 1-6. Optimized coordinates of [PhS(=O)CHPh]K(18-crown-6)(THF).

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</table>

1.5 References


10. a) In this case, due to the styrene generation, only 95% of benzyl chloride was taken into catalytic reaction. b) In this case, due to styrene generation from both methyls of DMSO, only 80% of benzyl chloride was taken into catalytic reaction.


15. Crystallographic data (excluding structure factors) for the structure K(18-crown-6)(THF)[PhS(=O)CHPh] have been deposited with Cambridge Data Centre as supplementary publication. The deposition number is CCDC 1007043. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax:(+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).


CHAPTER 2 tert-Butyl Phenyl Sulfoxide as a Traceless Sulfenate Anion Precatalyst

2.1 Introduction

2.1.1 Introduction to Sulfenate Anions Generation

Sulfenate anions and their conjugate acids, sulfenic acids (Scheme 2-1), are highly reactive intermediates in biochemistry\(^1\) and organic synthesis.\(^2\) In organic chemistry, sulfenate anions can be trapped with alkyl halides to afford sulfoxides. Due to the high reactivity of sulfenate anions, they are quite unstable under most conditions. Therefore, sulfoxide precursors were developed for in-situ generation for sulfenate anions through multiple methods (Scheme 2-2). Strong base induced methods were widely used, including β-H elimination\(^3\) (Scheme 2-2A) and ring opening/manipulation process\(^4\) (Scheme 2-2B). Recently, fragmentation methods triggered by heat\(^5\) (Scheme 2-2C) or weak bases\(^6\) (Scheme 2-2D) were developed, broadening the reaction scope through mild conditions. Addition-elimination chemistry requires specially designed structure for leaving group, azaheterocycles (Scheme 2-2E),\(^7\) limiting the applications for such methods. Within the realm of transition metal catalysis, palladium catalyzed sulfenate anion preparation has drawn great attention. Poli and Madec developed Pd-
catalyzed sulfenate anion generation via [2,3]-sigmatropic rearrangement (Scheme 2-2F). Our group has also been involved in the palladium catalyzed synthesis of diary sulfoxides starting with benzyl sulfoxide precursors (Scheme 2-2G).

\[ \text{(A)} \quad \text{ArSO} \overset{\text{Base}}{\rightarrow} \text{R} \quad \text{R}^+ \quad \text{ArSO}^- \]

\[ \text{(B)} \quad \text{SO} \overset{\text{Base}}{\rightarrow} \text{H} \quad \text{CHO} \quad \text{ArSO}^- \]

\[ \text{(C)} \quad \text{ArSO} \overset{\text{Heat}}{\rightarrow} \text{R} \quad \text{R}^+ \quad \text{ArSOH} \quad \text{Base} \quad \text{ArSO}^- \]

\[ \text{(D)} \quad \text{SO} \overset{\text{SiMe}_3}{\rightarrow} \text{H}_2\text{C} = \text{CH}_2 + \text{TMSF} + \text{RSO}^- \]

\[ \text{(E)} \quad \text{Ar} \quad \text{Nu}^- \quad \text{Nu}^- \quad \text{ArSO}^- \]

\[ \text{(F)} \quad \text{ArSO} \overset{\text{Pd}}{\rightarrow} \text{ArSO} \quad \text{Pd} \quad \text{ArSO}^- \]

\[ \text{(G)} \quad \text{ArSO} \overset{\text{Pd}}{\rightarrow} \text{Ar} \quad \text{ArBr} \quad \text{ArSO}^- \]

**Scheme 2-2.** Sulfenate anions generation methods.
2.1.2 Phenyl Sulfenate Anion Catalysis and Precatalyst Improvement

In the examples above, sulfenate anions act as leaving groups, but once generated, behave as nucleophiles in subsequent reactions. Inspired by this, we recognized their potential to act as organocatalysts. As proof of concept, benzyl phenyl sulfoxide was applied as a precatalyst in coupling of benzyl halides to form symmetrical trans-stilbenes under basic conditions (Scheme 2-3).\textsuperscript{10} In this process, a variety of trans-stilbenes could be prepared in good to excellent yields with catalyst loadings as low as 2.5 mol %.

The proposed mechanism for the sulfenate anion-catalyzed coupling of benzyl halides is illustrated in Scheme 2-3. Beginning with benzyl phenyl sulfoxide (Scheme 2-3, 2.A), deprotonation by KO\textsubscript{t}Bu generates the anion (Scheme 2-3, 2.B), which was demonstrated to be the catalyst resting state. The anion 2.B undergoes nucleophilic substitution with benzyl halide (Scheme 2-3, 2.C) to form sulfoxide 2.D. Deprotonation of the β-position of 2.D is followed by elimination to generate the double bond in 2.E with very high trans selectivity and the sulfenate anion 2.F. A rather serious limitation to use of benzyl phenyl sulfoxide (Scheme 2-3, 2.A) as precatalyst is that the first turnover installs a phenyl group on the trans-stilbene. In cases where the benzylic halide (2.C) is other than benzyl chloride or bromide, the first cycle forms an unsymmetrical stilbene (PhCH=CHAr, 2.E’) that is usually difficult to separate from the desired symmetric trans-stilbene, ArCH=CHAr (Scheme 2-3, 2.E). To make the sulfenate anion catalyzed synthesis of trans-stilbenes more attractive, we envisioned entry into the catalytic cycle at the sulfenate anion, 2.F.

Inspired by previous sulfenate anions work, we developed a second-generation sulfenate anion precatalyst that avoids contamination of the first cycle. The precatalyst,
tert-butyl phenyl sulfoxide (Scheme 2-3), undergoes base promoted elimination to generate phenyl sulfenate anion and isobutylene as a gaseous byproduct (Scheme 2-3), completely avoiding purification issues.

![Scheme 2-3. Proposed mechanism for sulfenate anions catalyzed trans-stilbenes formation from benzyl halides.](image)

2.2 Results and Discussions
2.2.1 Optimization of tert-Butyl Phenyl Sulfoxide Precatalysts in Stilbene Formation

To explore the use of tert-butyl phenyl sulfoxide as precatalyst, we initially employed conditions for our catalytic coupling of benzyl chlorides using KO\textsuperscript{t}Bu and benzyl phenyl sulfoxide precatalyst at 80 °C for 12 h. Under these conditions, tert-butyl phenyl sulfoxide (2.4a, 2.5 mol %) afforded only 33% assay yield of trans-stilbene (2.3a, Table 2-1, entry 1). The low yield was due to the reaction of benzyl chloride 2.1a with KO\textsuperscript{t}Bu via a S\textsubscript{N}2 process to generate benzyl tert-butyl ether.\textsuperscript{11} We hypothesized that the low conversion to the desired stilbene was due to the slower E2 elimination of tert-butyl phenyl sulfoxide to afford the sulenate anion. To address this issue, we conducted the reaction in two stages. First, the precatalyst tert-butyl phenyl sulfoxide 2.4a was heated with 3.0 equiv KO\textsuperscript{t}Bu in CPME at 80 °C for 30 min before addition of benzyl chloride 2.1a for the coupling. The assay yield of trans-stilbene (2.3a) increased to 43% (Table 2-1, entry 2). Elevating the pre-heating temperature to 110 °C followed by cooling the reaction mixture, addition of benzyl chloride 2.1a and heating to 80 °C for the coupling led to 97% assay yield of trans-stilbene (Table 2-1, entry 3). Decreasing the catalyst loading to 1 mol % under otherwise identical conditions yielded 69% trans-stilbene (Table 2-1, entry 4). Lowering the coupling temperature to 50 °C, resulted in formation of the product with 94% 2.3a assay yield (Table 2-1, entry 5). Finally, we found that lowering the base loading to 2.0 equiv provided a slightly higher yield (96%) of trans-stilbene 2.3a under more economical conditions (Table 2-1, entry 6). Unfortunately, attempts to increase the reaction concentration from 0.1 M to 0.2 M led to increased tert-butyl phenyl ether (Table 2-1, entry 7). The assay yield of 2.3a remained at 96% when the coupling time was cut to 6 h (Table 2-1, entry 8 vs. 6). Further decreasing the
coupling time to 4 h caused a drop in the assay yield to 88% (Table 2-1, entry 9). Therefore, the optimized reaction conditions for \textit{tert}-butyl phenyl sulfoxide 2.4a catalyzed \textit{trans}-stilbenes formation from benzyl halides is 2.5 mol % precatalyst and 2.0 equiv of KO\textsuperscript{t}Bu in CPME preheated at 110 °C for 30 min, followed by addition of benzyl halides and heating at 50 °C for 6 h.

The most surprising finding during the optimization process is that the sulfenate anion, generated at 110 °C, seems to be stable under these conditions in the absence of trapping reagents, at least for short periods of time.\textsuperscript{12}

\textit{Table 2-1.} Optimization of sulfenate anion catalyzed \textit{trans}-stilbene (2.3a) formation from benzyl chloride (2.1a).\textsuperscript{a}

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<td>110 (\rightarrow) 50</td>
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2.2.2 Substrate Scope of Stilbene Formation from Benzyl Halides Catalyzed by Sulfenate Anions

With the optimized conditions in hand, we set out to explore the substrate scope (Scheme 2-4). In general, benzyl chloride derivatives are better substrates than benzyl bromides, because the latter undergo more rapid S_N2 reactions with the base to generate benzyl tert-butyl ethers. To compensate for the increase reactivity of benzyl bromide derivatives, 5 mol % precatalyst loading was employed with these substrates. Benzyl chloride and bromide gave trans-stilbene (2.3a) in 94% and 76% yield, respectively. Benzyl chlorides with substituents at para position (2.3b, 2.3d, 2.3e, 2.3f) were found to give higher yields at 80 °C and in some cases with 3.0 equiv of base (2.1b and 2.1d). Electron-donating groups increased the pK_a of the benzylic protons of intermediates A and D (Scheme 2-3) making them more difficult substrates. For example, only 71% of 2.3b was obtained. Substrates bearing electron withdrawing groups were better coupling partners. For example, 4,4'-difluorostilbene (2.3d), 4,4'-dichlorostilbene (2.3e) and 4,4'-dibromostilbene (2.3f) were produced in 60–97% yield. Compounds 2.3e and 2.3f could be easily elaborated by standard cross-coupling methods.

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<td>88</td>
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^a Reactions performed using 1.0 equiv of 2.1a on a 0.2 mmol scale in CPME. ^b Crude yield determined by 1H NMR using 0.1 mmol CH₂Br₂ as internal standard. ^c Before benzyl chloride was added, base and precatalyst 2.4a were pre-heated at 80 °C for 30 min. ^d Before benzyl chloride was added, base and precatalyst were pre-heated at 110 °C for 30 min. ^e 0.4 mmol of 2.1a. ^f Isolated yield.
Reactions were performed using 1.0 equiv of 2.1 and 2.0 equiv of base on a 0.2 mmol scale. \(^b\) 5 mol % precatalyst loading. \(^c\) 80 °C. \(^d\) 3.0 equiv KO'Bu used. \(^e\) KH used as base and reaction run for 24 h at 110 °C.
**Scheme 2-4.** Substrate scope of stilbenes formation from benzyl halides catalyzed by sulenate anions.

More sterically hindered substrates, such as 2-methyl benzyl chloride (2.3h) and 1-(chloromethyl)naphthalene (2.1i), afforded 2.3h and 2.3i in 86% and 85% yields, respectively. Di-ortho-substituted 2,6-dichlorobenzyl chloride was an excellent substrate, leading to *trans*-stilbene 2.3j 98% yield. Benzyl halides substituted at the *meta* position with Me, F, or CF<sub>3</sub> groups were good substrates, giving 2.3k, 2.3l and 2.3m in 89%, 89% and 84% yield, respectively. Heterocycle-containing stilbenes usually exhibit interesting photochemical properties, but are more challenging to synthesize.<sup>13</sup> Heterocyclic 2-(chloromethyl)pyridine did not couple under our optimized condition. Using non-nucleophilic KH, however, generated the product 2.3n, but only in 39% yield.

### 2.2.3 Gram Scale Reaction

To demonstrate the potential utility of this approach, we performed the coupling of 1-(chloromethyl)naphthalene (2.1i, 8.4 mmol, 1.48 g), to the *trans*-stilbene (2.3i) in 88% yield (Scheme 2-5), suggesting the reaction is scalable.

![Scheme 2-5](image)

**Scheme 2-5.** *trans*-1,2-Di(α-naphthyl)ethylene formation on gram scale.
2.3 Conclusion

In summary, trans-stilbenes are widely used as industrial dyes, laser-dyes, and optoelectronic materials\textsuperscript{14} and significant effort has been devoted to their synthesis\textsuperscript{15-19}. We have developed an organocatalytic method for their preparation that addresses a deficiency in our prior precatalyst, wherein a catalytic amount of an inseparable impurity was generated in the first catalytic cycle. The precatalyst introduced herein, tert-butyl phenyl sulfoxide, undergoes base promoted E2 elimination to generate the sulfenate anion catalyst and a gaseous byproduct. Interestingly, the sulfenate anion generated under these conditions appears to survive the 110 °C precatalyst activation stage\textsuperscript{12}, as judged by its ability to generate trans-stilbenes in up to 98% yield. Current efforts are focused on the application of sulfenate anion catalysts to other reactions.

2.4 Experimental Section

General Methods: All reactions were carried out under dry nitrogen. Anhydrous cyclopentyl methyl ether (CPME) was purchased from Sigma-Aldrich and directly used without further purification. Unless otherwise stated, reagents were commercially available and used as purchased without further purification. Chemicals were purchased from Sigma-Aldrich, Acros, Alfa Aesar or Matrix Scientific, and solvents were purchased from Fisher Scientific. The progress of the reactions was monitored by thin-layer chromatography using Whatman Partisil K6F 250 μm precoated 60 Å silica gel plates and visualized by short-wave ultraviolet light as well as by treatment with iodine. Flash chromatography was performed with silica gel (230–400 mesh, Silicycle). The NMR spectra were obtained using a Brüker 500 MHz Fourier-transform NMR spectrometer.
Chemical shifts are reported in units of parts per million (ppm) downfield from tetramethylsilane (TMS), and all coupling constants are reported in hertz. Reactions were conducted in 2–5 mL microwave vials that were purchased from VWR International.

**Preparation of Sulfoxides:** Sulfoxides were prepared according to the literature procedures.²⁰

**General Procedure for catalysis:** To an oven-dried microwave vial equipped with a stir bar was added phenyl tert-butyl sulfoxide (2.4a, 0.91 mg, 0.005 mmol) and KOtBu (44.8 mg, 0.40 mmol, 2.0 equiv), under nitrogen atmosphere followed by 2.0 mL dry CPME. The microwave vial was sealed and heated to 110 °C for 30 min. When the solution turned to pale yellow, benzyl chloride (2.1a, 24 μL, 0.20 mmol) was added by syringe under nitrogen atmosphere under room temperature. Note that if the benzylic halide is a solid, it was dissolved in 0.5 mL CPME and added as a solution under nitrogen atmosphere. The reaction mixture was heated to 50 °C by oil bath and stirred for 6 h. The sealed vial was cooled to room temperature, opened to air, and the reaction mixture was passed through a short pad of silica gel. The pad was then rinsed with 10 mL ethyl acetate and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (2.3a, 16.9 mg, 94% yield) as a white solid. The spectroscopic data match the previously reported data.¹⁹
\((E)\)-Stilbene \((2.3a)\): The reaction was performed following the General Procedure with phenyl \textit{tert}-butyl sulfoxide \((2.4a, 0.91 \text{ mg}, 0.005 \text{ mmol}, \text{from a stock solution})\), benzyl chloride \((2.1a, 24 \mu \text{L}, 0.20 \text{ mmol})\) and KO\textsuperscript{t}Bu (44.8 mg, 0.40 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product \((2.3a, 16.9 \text{ mg}, 94\% \text{ yield})\) as a white solid. The spectroscopic data match the previously reported data.\textsuperscript{19}

\((E)\)-Stilbene \((2.3a)\) \textit{from benzyl bromide}: The reaction was performed following the General Procedure with phenyl \textit{tert}-butyl sulfoxide \((2.4a, 1.82 \text{ mg}, 0.010 \text{ mmol}, \text{from a stock solution})\), benzyl bromide \((2.2a, 24.0 \mu \text{L}, 0.20 \text{ mmol})\) and KO\textsuperscript{t}Bu (44.8 mg, 0.40 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product \((2.3a, 13.7 \text{ mg}, 76\% \text{ yield})\) as a white solid. The spectroscopic data match the previously reported data.\textsuperscript{19}

\((E)\)-4,4\textsuperscript{'}-Dimethylstilbene \((2.3b)\): The reaction was performed following the General Procedure with phenyl \textit{tert}-butyl sulfoxide \((2.4a, 0.91 \text{ mg}, 0.005 \text{ mmol}, \text{from a stock solution})\), 4-methylbenzyl chloride \((2.1b, 27 \mu \text{L}, 0.20 \text{ mmol})\) and KO\textsuperscript{t}Bu (67.2 mg, 0.60 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product \((2.3b, 14.8 \text{ mg}, 71\% \text{ yield})\) as a white solid. The spectroscopic data match the previously reported data.\textsuperscript{19}
(E)-4,4'-Dimethylstilbene (2.3b) (from 4-methylbenzyl bromide): The reaction was performed following the General Procedure with phenyl tert-butyl sulfoxide (2.4a, 1.81 mg, 0.010 mmol, from a stock solution), 4-methylbenzyl bromide (2.2b, 37.0 mg, 0.20 mmol) and KOtBu (44.8 mg, 0.40 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (2.3b, 12.1 mg, 58% yield) as a white solid. The spectroscopic data match the previously reported data.19

(E)-4,4'-Di(tert-butyl)stilbene (2.3c): The reaction was performed following the General Procedure with phenyl tert-butyl sulfoxide (2.4a, 1.82 mg, 0.010 mmol, from a stock solution), 4-tert-butylbenzyl bromide (2.1c, 37 μL, 0.20 mmol) and KOtBu (44.8 mg, 0.40 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (2.3c, 18.1 mg, 62% yield) as a white solid. The spectroscopic data match the previously reported data.21

(E)-4,4'-Difluorostilbene (2.3d): The reaction was performed following the General Procedure with phenyl tert-butyl sulfoxide (2.4a, 0.91 mg, 0.005 mmol, from a stock solution), 4-fluorobenzyl chloride (2.1e, 24 μL, 0.20 mmol) and KOtBu (67.2 mg, 0.60 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (2.3d, 17.5 mg, 81% yield) as a white solid. The spectroscopic data match the previously reported data.19
**(E)-4,4'-Difluorostilbene (2.3d) (from 4-fluorobenzyl bromide):** The reaction was performed following the General Procedure with phenyl tert-butyl sulfoxide (2.4a, 1.82 mg, 0.010 mmol, from a stock solution), 4-fluorobenzyl bromide (2.3d, 25 μL, 0.20 mmol) and KO'Bu (44.8 mg, 0.40 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (2.3d, 14.5 mg, 67% yield) as a white solid. The spectroscopic data match the previously reported data.\(^{19}\)

**(E)-4,4'-Dichlorostilbene (2.3e):** The reaction was performed following the General Procedure with phenyl tert-butyl sulfoxide (2.4a, 0.91 mg, 0.005 mmol, from a stock solution), 4-chlorobenzyl chloride (2.1e, 32.2 mg, 0.20 mmol) and KO'Bu (44.8 mg, 0.40 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (2.3e, 24.2 mg, 97% yield) as a white solid. The spectroscopic data match the previously reported data.\(^{19}\)

**(E)-4,4'-Dibromostilbene (2.3f):** The reaction was performed following the General Procedure with phenyl tert-butyl sulfoxide (2.4a, 0.91 mg, 0.005 mmol, from a stock solution), 4-bromobenzyl chloride (2.1f, 41.1 mg, 0.20 mmol) and KO'Bu (44.8 mg, 0.40 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (2.3f, 22.6 mg, 67% yield) as a white solid. The spectroscopic data match the previously reported data.\(^{22}\)
**E-4,4'-Dibromostilbene (2.3f)** (from 4-bromobenzyl bromide): The reaction was performed following the General Procedure with phenyl tert-butyl sulfoxide (2.4a, 1.82 mg, 0.010 mmol, from a stock solution), 4-bromobenzyl bromide (2.2f, 50 mg, 0.20 mmol) and KOtBu (44.8 mg, 0.40 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (2.3f, 20.1 mg, 60% yield) as a white solid. The spectroscopic data match the previously reported data.\(^{22}\)

**E-2,2'-Difluorostilbene (2.3g)**: The reaction was performed following the General Procedure with phenyl tert-butyl sulfoxide (2.4a, 0.91 mg, 0.005 mmol, from a stock solution), 2-fluorobenzyl chloride (2.1g, 24.0 μL, 0.20 mmol) and KOtBu (44.8 mg, 0.40 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (2.3g, 19.7 mg, 91% yield) as a white solid. The spectroscopic data match the previously reported data.\(^{19}\)

**E-2,2'-Dimethylstilbene (2.3h)**: The reaction was performed following the General Procedure with phenyl tert-butyl sulfoxide (2.4a, 0.91 mg, 0.005 mmol, from a stock solution), 2-methylbenzyl chloride (2.1h, 27.0 μL, 0.20 mmol) and KOtBu (67.2 mg, 0.60 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (2.3h, 17.9 mg, 86% yield) as a white solid. The spectroscopic data match the previously reported data.\(^{19}\)
(E)-1,2-Di(1-naphthyl)ethylene (2.3i): The reaction was performed following the General Procedure with phenyl tert-butyl sulfoxide (2.4a, 0.91 mg, 0.005 mmol, from a stock solution), 1-(chloromethyl)naphthalene (2.1i, 35.4 mg, 0.20 mmol) and KOtBu (44.8 mg, 0.40 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (2.3i, 23.8 mg, 85% yield) as a white solid. The spectroscopic data match the previously reported data.¹⁹

(E)-2,2',6,6'-Tetrachlorostilbene (2.3j): The reaction was performed following the General Procedure with phenyl tert-butyl sulfoxide (2.4a, 0.91 mg, 0.005 mmol, from a stock solution), 2,6-dichlorobenzyl chloride (2.1j, 39.2 mg, 0.20 mmol) and KOtBu (44.8 mg, 0.40 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (2.3j, 31.2 mg, 98% yield) as a white solid. The spectroscopic data match the previously reported data.¹⁹

(E)-3,3'-Dimethylstilbene (2.3k): The reaction was performed following the General Procedure with phenyl tert-butyl sulfoxide (2.4a, 0.91 mg, 0.005 mmol, from a stock solution), 3-methylbenzyl chloride (2.1k, 27.0 μL, 0.20 mmol) and KOtBu (67.2 mg, 0.60 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (2.3k, 18.5 mg, 89% yield) as a white solid. The spectroscopic data match the previously reported data.¹⁹
(E)-3,3'-Difluorostilbene (2.3l): The reaction was performed following the General Procedure with phenyl tert-butyl sulfoxide (2.4a, 0.91 mg, 0.005 mmol, from a stock solution), 3-fluorobenzyl chloride (2.1l, 24.0 μL, 0.20 mmol) and KO\text{tBu} (44.8 mg, 0.40 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (2.3l, 19.2 mg, 89% yield) as a white solid. The spectroscopic data match the previously reported data.\textsuperscript{22}

(E)-3,3'-Ditrifluoromethylstilbene (2.3m): The reaction was performed following the General Procedure with phenyl tert-butyl sulfoxide (2.4a, 1.82 mg, 0.010 mmol, from a stock solution), 3-trifluoromethylbenzyl bromide (2.2m, 31.0 μL, 0.20 mmol) and KO\text{tBu} (44.8 mg, 0.40 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (2.3m, 26.6 mg, 84% yield) as a white solid. The spectroscopic data match the previously reported data.\textsuperscript{17c}

1,2-trans-Bis(2-pyridyl)ethylene (2.3n): To an oven-dried microwave vial equipped with a stir bar was added phenyl tert-butyl sulfoxide (2.4a, 0.91 mg, 0.005 mmol, from a stock solution), 2-(chloromethyl)pyridine hydrochloride (2.1n, 32.8 mg, 0.20 mmol) and KH (32 mg, 0.80 mmol, 4.0 equiv) in a nitrogen filled dry box followed by 2.0 mL dry CPME. The microwave vial was sealed with a vial cap with a rubber insert and the sealed vial removed from the dry box. The reaction mixture was heated to 110 °C in an oil bath and stirred for 24 h. The sealed vial was cooled to room temperature, opened to
air, and the reaction mixture was passed through a short pad of silica gel. The pad was then rinsed with 10 mL ethyl acetate. The volatile materials were removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (eluted with hexanes:EtOAc = 1:1) to give the product (2.3n, 7.1 mg, 39% yield) as a white solid. The spectroscopic data match the previously reported data.\textsuperscript{23}

**Gram scale reaction.**

\begin{center}
(\textit{E})-1,2-Di(1-naphthyl)ethylene (2.3i): To a three-necked round bottom flask equipped with a condenser under a nitrogen atmosphere was added phenyl tert-butyl sulfoxide (2.4a, 38.3 mg, 0.18 mmol), KO\textsuperscript{t}Bu (1.89 g, 16.8 mmol) and the flask was subjected to 3 cycles of vacuum/back fill with nitrogen. Two other necks were sealed with rubber septa. Then 50 mL dry CPME were added via a syringe through the rubber septum. The rubber septa were replaced with greased glass stoppers. The reaction mixture was heated to 110 °C and stirred for 30 min under nitrogen. The flask was then transferred to a 50 °C oil bath and 1.48 g 1-(chloromethyl)naphthalene 2.1i dissolved in 34 mL of CPME was added via a syringe with nitrogen protection. The reaction mixture was heated at 50 °C for 6 h then passed through a short pad of silica gel, and eluted with 150 mL ethyl acetate. The volatile materials were removed under reduced pressure and the residue was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (2.3i, 1.04 g, 88% yield) as a white solid. The spectroscopic data match the reported data.\textsuperscript{19}
\end{center}
2.5 References


CHAPTER 3 Sulfenate Anion Organocatalytic Synthesis of Alkynes

3.1 Introduction

3.1.1 General Approaches for Alkynes Synthesis

The carbon-carbon triple bond of alkynes is among the most useful functional groups in chemistry and plays a significant role in modern society. Alkynes occur in natural products and marketed pharmaceuticals. For example, naturally occurring calicheamicin is a highly reactive antitumor agent while norethynodrel was the first oral contraceptive and Efazirenz is an antiretroviral introduced by Merck. Alkynes can be transformed into a vast array of value added organic compounds by well-established stoichiometric methods or in the presence of metal catalysts or organocatalysts. A renewed interest in alkyne chemistry stems from emerging applications in organic materials. Alkynes are vital in the synthesis of π-conjugated oligomers and polymers with applications in photonics, optoelectronics, and molecular electronics, to name a few. As a result of the long-standing interest in the reactions of alkynes, their synthesis is of fundamental importance.

The majority of alkyne syntheses can be categorized by three general approaches. The first forms the triple bond from isolated reagents, which include the pioneering and very useful Corey-Fuchs reaction with aldehyde substrates (Scheme 3-1A). Similarly, the Seyferth-Gilbert (Scheme 3-1B) and Bestmann-Ohira homologations employ aldehydes or ketones for terminal/internal alkyne generation (Scheme 3-1B). Although these methods are reliable, they are stoichiometric and use harsh (n-BuLi) or
potentially explosive reagents (diazo) or precursors ($\text{TsN}_3$). The second approach involves elimination reactions that form one or two $\pi$-bonds of the alkyne (Scheme 3-1C). These methods employ starting materials with the carbon-carbon framework already in place, making them more labor intensive and less attractive. Finally, beautiful work to elaborate existing carbon-carbon triple bonds is well documented, most notably the Sonogashira cross-coupling and alkyne metathesis. Notably absent from known approaches are methods to directly convert readily available starting materials into functionalized alkynes under catalytic conditions. Such transformations would form all three bonds of the alkyne from substrates that do not possess preexisting triple bonds.

Scheme 3-1. Synthetic approaches to alkynes (A-D) and sulfinic anions (E).
Herein we introduce the first organocatalytic method to prepare a variety of diaryl alkynes from simple aryl or heteroaryl aldehydes and benzyl halide derivatives. Advantages of this catalytic approach over well-established methods include avoidance of transition metal catalysts and the issues associated with metal residues, mild conditions, and use of readily available and inexpensive reagents.

### 3.1.2 Our Approach to Alkyne Synthesis through Sulfenate Anion Catalysis

We envisioned sulfenate anions as novel catalysts potentially suitable for the synthesis of alkynes. Sulfenate anions and their conjugate bases, sulfenic acids (Scheme 3-1E) are relatively unexplored, highly reactive species proposed to be transient intermediates in organic and biochemistry. We, and others, observed that sulfenate anions possess the ability to act both as nucleophiles and leaving groups in palladium catalyzed arylation reactions. This observation inspired us to hypothesize that they could also behave as catalysts. As proof-of-concept we developed the first sulfenate anion catalyzed reaction, the coupling of benzyl halides to afford trans-stilbenes (Scheme 3-2, cycle A). To access higher value alkynes, we envisioned the catalytic coupling of benzaldehyde derivatives with benzyl halides, as depicted in a proposed catalytic cycle (Scheme 3-2, cycle B). Generation of the sulfenate anions 3.A under basic conditions in the presence of benzyl halides (3.B) will result in benzylation to give sulfoxide 3.C via an S_N2 reaction pathway. Deprotonation of the sulfoxide by base generates a nucleophile (3.D). Key to the success of this process is control of the relative rates of reaction of the deprotonated sulfoxide 3.D with the two electrophilic coupling partners. The reaction with benzyl chloride, leads to stilbenes and consumes
two equivalents of starting material (Scheme 3-2, cycle A). In the presence of benzaldehyde derivatives, addition of the deprotonated sulfoxide to the aldehyde 3.G provides β-hydroxy sulfoxide 3.H after proton transfer. Base promoted elimination of hydroxide from 3.H is proposed to generate the vinyl sulfoxide 3.I, which can undergo a second elimination to produce the desired alkyne, regenerate the sulfenate anion, and close cycle B.

**Scheme 3-2.** Proposed mechanism of the sulfenate anion catalyzed generation of stilbenes (Cycle A) and diaryl acetylenes (Cycle B).
3.2 Results and Discussion

3.2.1 Optimization of Sulfenate Anion Catalyzed Alkyne Synthesis

To explore the viability of the proposed catalytic cycle B in Scheme 3-2, we initiated the reaction discovery process with the coupling of benzaldehyde 3.2a and benzyl chloride 3.1a to form diphenyl acetylene 3.3a in the presence of six bases [LiO\(\text{tBu}\), NaO\(\text{tBu}\), K\(\text{tBu}\), LiN(SiMe\(_3\))\(_2\), NaN(SiMe\(_3\))\(_2\) and KN(SiMe\(_3\))\(_2\)] in four different solvents [THF, DME, dioxane and cyclopentyl methyl ether (CPME)] for 10 h at 80 °C. To simplify the screening we chose 10 mol % benzyl phenyl sulfoxide 3.4a as the catalyst (Scheme 3-2C, \(\text{Ar}^1 = \text{Ph}\)) rather than entering the catalytic cycle by generating the sulfenate anion (Scheme3-2A). In this initial screen the combination of 3.0 equiv. KO\(\text{tBu}\) in THF was the most promising. When conducted on lab scale (0.1 mmol) diphenyl acetylene 3.3a was generated in 20% assay yield (AY, as determined by GC, Table 3-1, entry 1). Byproducts identified from this reaction include \textit{trans}-stilbene, derived from coupling of benzyl chloride (8%), and dibenzyl ether (62%). Dibenzyl ether was presumably generated from benzyl chloride and benzyl alcohol, the latter of which could arise from a Cannizzaro reaction with benzaldehyde promoted by KO\(\text{tBu}\) (Scheme 3-3). Consistent with this hypothesis, use of 3-methyl benzyl chloride (\(\text{Ar}^1 = \text{3-Tol}\)) generated the unsymmetrical dibenzyl ether, 3-TolCH\(_2\)OCH\(_2\)Ph. Byproduct \textit{tert}-butyl benzoate was detected by gas chromatography.

\[
\text{Ar}^1\text{Cl} + \text{PhCHO} \xrightarrow{\text{Ko\text{tBu}}} \text{Ar}^1\text{CH} = \text{O} + \text{PhCH} \equiv \text{O} + \text{PhCH} \equiv \text{O} + \text{O} \text{Bu}
\]

\textbf{Scheme 3-3.} Proposed reaction for generation of dibenzyl ether byproduct via Cannizzaro reaction.
Based on these observations, we decided to limit the exposure of the substrates to the base by slow addition of a 2:1 ratio of benzaldehyde to benzyl chloride. Slow addition of the substrates to the catalyst and KO'Bu mixture led to 41% AY of diphenyl acetylene (Table 3-1, entry 2). Increasing the substrates stock solution concentration to 0.5 M benzyl chloride 3.1a resulted in 65% assay yield (Table 3-1, entry 3). Further increasing the concentration of the substrates solution to 1.0 M resulted in reduced AY (Table 3-1, entry 4). It should be noted that although the slow addition decreased the formation of byproducts trans-stilbene and dibenzyl ether, we have been unable to completely eliminate their formation.

**Table 3-1.** Optimization of diaryl acetylene (3.3a) synthesis of benzyl chloride (3.1a) and benzaldehyde (2a).a

<table>
<thead>
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<th>Entry</th>
<th>3.1a:3.2a:base</th>
<th>3.4, R1/R2</th>
<th>Time(h)</th>
<th>3.3a (%)b</th>
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<td>1:2:3</td>
<td>Ph/CH₂Ph</td>
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<td>20</td>
</tr>
<tr>
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<td>Ph/CH₂Ph</td>
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<td>41</td>
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<tr>
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<td>1:2:3</td>
<td>Ph/CH₂Ph</td>
<td>10</td>
<td>65</td>
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<tr>
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<td>Ph/CH₂Ph</td>
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<td>73(72h)</td>
</tr>
</tbody>
</table>

a Reactions performed using 10 mol % catalyst, 3.0 equiv of base with a stock solution of 1.0 equiv of benzyl chloride 3.1a and 2.0 equiv of benzaldehyde 3.2a on a 0.5 mmol scale. One tenth of the stock solution was added to reaction mixture every one tenth of reaction time. b Determined by GC analysis of the crude reaction mixture. c Reactions performed without slow addition on a 0.1 mmol scale. d 0.1 mmol scale. e 1.0 mmol scale. f Extra base added for catalyst activation. g 20 mol % catalyst loading. h Isolated yield.

We next examined the influence of catalyst structure on performance, as judged by assay yield. Thus, employing Ar-S(O)CH₂Ph with the Ar supporting 4-OMe, 4-Me, 4-F, 4-CF₃, 1-naphthyl and 2-pyridyl indicated that the parent phenyl was as good or better than the other catalysts (Table 3-1, entry 3 3.4a vs. 5–10 3.4b-g). Use of the aliphatic c-
Hex-S(O)CH₂Ph led to 18% AY (Table 3-1, entry 11, **3.4h**). Thus, the parent S-Ph-based catalyst was used for the remainder of this study.

With the optimized catalyst, the reaction time was examined. It was found that the reaction using benzyl phenyl sulfoxide reached completion in 1 h at 80 °C, giving 67% conversion (Table 3-1, entry 12–13). Changing the ratios of benzyl chloride, benzaldehyde and base revealed the optimal conditions employed 3.0 equiv of KO'Bu with 1 : 2 ratio of benzyl chloride to benzaldehyde (Table 3-1, entry 12 vs. 14-16).

Although benzyl sulfoxide proved to be a good catalyst, its use is problematic in combination with other benzyl chloride derivatives. Benzyl sulfoxide will lead to a phenyl-substituted alkyne in the first turnover, PhC≡CAr², which is difficult to separate from the desired product, Ar¹C≡CAr² (Scheme 3-4). To avoid this problem, a better strategy is to enter the catalytic cycle at the sulfenate anion A. We, therefore, examined different precatalyst **3.4i-k** to generate the sulfenate anion through E2 elimination and found 2-phenylethyl phenyl sulfoxide **3.4k** outperformed (AY = 68%) other sulfenate anion precatalysts (48–55% AY, Table 3-1, entry 17–19). Raising the catalyst loading to 20 mol % rendered 73% diphenyl acetylene AY (Table 3-1, entry 20). To compensate for the 0.2 equiv base consumed in conversion of the precatalyst to the catalyst, 3.2 equiv of base were employed. Thus, our standard conditions involve 20 mol % 2-phenylethyl phenyl sulfoxide precatalyst **3.4k** and 3.2 equivalents of KO'Bu with slow addition of coupling partners as a stock solution containing 0.5 M benzyl chloride (limiting reagent) and 2.0 equiv aldehyde to 20 mol % sulfenate anion precursor in THF at 80 °C for 1 h.
Scheme 3-4. Byproduct formation using benzyl sulfoxide as precatalyst.

3.2.2 Substrate Scope of Benzyl Chlorides in Diaryl Acetylene Synthesis

\[
\begin{align*}
\text{Ar}_2^+ \quad \text{O} & \quad \text{byproduct} \\
\text{Ph} & \quad \equiv \quad \text{Ar}_2^+ \\
\text{RSO}^- & \quad \text{desired product} \\
\text{Ar}_1^- \quad \equiv \quad \text{Ar}_2^+
\end{align*}
\]

3.2.2 Substrate Scope of Benzyl Chlorides in Diaryl Acetylene Synthesis

\[
\begin{align*}
\text{Ar}_2^+ \quad \text{Cl} + \quad \text{PhCO} & \quad 20 \text{ mol} \% \quad \text{3.4k} \\
\text{3.2a} & \quad \text{3.2 equiv KO}^\text{Bu} \\
\text{THF, 80 ºC, 1 h} & \quad \rightarrow \\
\text{3.3} & \quad \text{3.3a, 72%} \\
\text{3.3b, 61%} & \quad \text{3.3c, 69%} \\
\text{3.3d, 77%} & \quad \text{3.3e, 70%} \\
\text{3.3f, 69%} & \quad \text{3.3g, 73%} \\
\text{3.3h, 23%} & \quad \text{3.3i, 69%} \\
\text{3.3j, 68%} & \quad \text{3.3k, 65%} \\
\text{3.3l, 62%} & \quad \text{3.3m, 53%}
\end{align*}
\]
Scheme 3-5. Substrate scope of benzyl chlorides in diaryl acetylene synthesis.

With the optimized conditions, we next investigated the scope of the alkyne synthesis with a series of benzyl chlorides (Scheme 3-5). Electron-donating groups on the benzyl chloride, such as 4-Me, 4-tBu and 4-OMe provided 61–77% isolated yields (3.3b–3.3d). Substrates bearing 4-F, 4-Cl, and 4-Br afforded the corresponding products 69–73% yield (3.3e–3.3g). The bulkier 2-TolCH₂Cl was a poor substrate (3.3h, 23% yield) due to steric hindrance. Smaller substituents, such as 2-F (3.3i, 63%) or 1-naphthyl (3.3j, 68%) derived benzyl halides exhibited better reactivity. Benzyl chlorides substituted at the 3-position with Me, F, or CF₃ furnished alkyne products in 53–65% yield (3.3k–3.3m).

3.2.3 Substrate Scope of Benzaldehydes in the Diaryl Acetylene Synthesis

Aldehyde coupling partners were next examined (Scheme 3-6). Benzaldehydes with electron-donating (4-OMe and 4-SMe, 61–70% yield, 3.3d and 3.3n) and withdrawing substituents (4-F, 4-Cl, 4-Br, 4-CF₃, 67–76%, 3.3e–3.3g, 3.3o) readily furnished alkyne products. However, 4-CO₂Me benzaldehyde resulted in poor yield, due to the basic reaction conditions. With 1- and 2-naphthyl aldehydes, 81 and 75% yield (3.3j and 3.3q), respectively, were obtained. Heterocyclic 3-(1-pyrrolyl) benzaldehyde gave corresponding the alkyne in 76% yield (3.3r). Interestingly, a 3-hydroxy group was tolerated, providing alkyne (3.3s) in 66% yield without formation of the benzyl ether. Base-sensitive 3-cyano benzaldehyde also gave the desired product in 68% yield. We were particularly interested in applying our method to heterocycles. We were pleased to
find that 2-pyridyl, 3-pyridyl, 5-isoquinillnlyl, 2-furanyl and 2-thienyl substituted alkynes could be accessed in moderate to good yields (3u-3y, 54–80%). Under our current conditions, 4-NO$_2$-benzaldehyde, indole-5-carboxaldehyde and 5-imidazolecarboxaldehyde were not tolerated.

Scheme 3-6. Substrate scope of benzadehydes in diaryl acetylene synthesis.
3.2.4 Gram Scale Reaction

The scalability of this novel alkyne synthesis was evaluated by performing four reactions with 8 mmol benzyl chlorides 3.1 and 10 mol % precatalyst 3.4k (Scheme 3-7). The reaction with 4-methoxy benzyl chloride and 2-furaldehyde resulted in formation of the desired product in 78% yield (3.3dx, 1.23 g). Very similar results were obtained with
2-thiofurfural (3.3dy, 75% yield, 1.28 g). Coupling of 4-bromobenzyl chloride with 4-chlorobenzaldehyde proceeded smoothly in 71% yield (3.3gf, 2.06 g). Synthesis of this alkyne by Sonogashira coupling reaction could be complicated by the presence of the aryl bromide. Product 3.3gf could be easily elaborated using cross-coupling chemistry. With the more challenging 3-trifluoromethyl benzyl chloride coupling under the standard conditions with 4-trifluoromethyl benzaldehyde provided the alkyne product in 56% yield (3.3mo, 1.42 g). These results indicate the reactions perform better on scale.

### 3.2.5 Special Substrates

Diynes are important precursors to polycyclic aromatic hydrocarbons synthesis.\(^{14}\) We therefore applied our method to \(\alpha,\alpha'\)-dichloro-\(m\)-xylene 3.5a, which gave the double-coupling product 3.6a in 42% yield (Scheme 3-8A). In addition to benzyl chlorides, preliminary studies with the allyl chloride derivative 1,1-diphenyl-3-chloro-1-propene 3.5b were undertaken. In combination with benzaldehyde under conditions optimized for benzyl chlorides, the desired enyne 3.6b was generated in 46% yield (Scheme 3-8B).
**Scheme 3-8.** Special substrates applied in sulfenate-anion-catalyzed alkyne synthesis.

### 3.2.6 Preliminary Mechanistic Study

**(A)**

\[
\text{Scheme 3-9. Preliminary mechanistic study of sulfenate anion-catalyzed diaryl acetylene formation.}
\]
To gain insight into the mechanism of the catalytic alkyne synthesis, we set out to investigate the catalyst resting state. The reaction between benzyl chloride and benzaldehyde was performed under the standard conditions except the reaction was quenched with H₂O after only 15 min. Among the sulfur-containing compounds, the (Z)-vinyl sulfoxide 3.I (Scheme 3-2) was isolated in 62% yield as a single diastereomer. Benzyl phenyl sulfoxide (33%, Scheme 3-2) was also observed by ¹H NMR. Based on these findings, the vinyl sulfoxide 3.I is the most likely resting state for the catalyst. Independently synthesized vinyl sulfoxide (3.I) was shown to generate diphenyl acetylene under basic conditions in 94% yield (Scheme 3-9).

To probe the water elimination step of the proposed mechanism, both threo- and erythro-2-phenylsulfinyl-1,2-diphenyl-1-ethanol (3.H, 3.H') were synthesized by NaIO₄ oxidation of corresponding sulfides, which were generated from reactions of thiophenol with either cis- or trans-stilbene oxide.¹⁵ When threo- or erythro-2-phenylsulfinyl-1,2-diphenyl-1-ethanol were treated with 2 equiv base and quenched with 4-methoxy benzyl chloride, diphenyl acetylene was generated via elimination in 81–82% yield (Scheme 3-9B). 4-Methoxy benzyl phenyl sulfoxide was also isolated in 70–73% yield (Scheme 3-9B), suggesting sulfenate anion was generated during the reactions. Treatment of either threo- or erythro-2-phenylsulfinyl-1,2-diphenyl-1-ethanol with only 1.0 equiv of KO'Bu resulted in 32–38% conversion to vinyl sulfoxide and 52–57% benzyl phenyl sulfoxide. Formation of benzyl phenyl sulfoxide suggests that the condensation between the deprotonated sulfoxide and the aldehyde is reversible (Scheme 3-9C). The reversible condensation between the deprotonated sulfoxide and benzaldehyde derivative suggests that the preferred diastereomer leading to elimination to generate the vinyl
sulfoxide can be accessed. These results lend credence to the proposed reaction mechanism in Scheme 3-2.

3.3 Conclusion

In summary, we developed the first organocatalytic approach to synthesize alkynes from benzyl chlorides and benzaldehyde derivatives. The reaction is catalyzed by sulfenate anions and leads to diaryl and heteroaryl aryl alkynes in moderate to good yields. The method is scalable and can be conducted with reduced loading of the organocatalysts. Preliminary mechanistic studies demonstrate that the catalyst resting state is \((Z)\)-vinyl sulfoxide. It is particularly noteworthy that this method provides diaryl acetylenes, which are usually synthesized by the Sonogashira coupling of terminal alkynes. The advantage of our method over this well-known cross-coupling reaction is that it does not employ costly transition metals or designer phosphine ligands, does not require the synthesis of a terminal alkyne precursors, and circumvents problems associated with metal residues that can be problematic in the pharmaceutical and electronics industries.

3.4 Experimental Section

General Methods: All reactions were carried out under dry nitrogen. Anhydrous tetrahydrofuran (THF) was purchased from Sigma-Aldrich and directly used without further purification. Unless otherwise stated, reagents were commercially available and used as purchased without further purification. Chemicals were purchased from Sigma-Aldrich, Acros, Alfa Aesar or Matrix Scientific. Aldehydes were newly purchased or distilled under nitrogen atmosphere. The progress of the reactions was monitored by
thin-layer chromatography using Whatman Partisil K6F 250 μm precoated 60 Å silica gel plates and visualized by short-wave ultraviolet light as well as by treatment with iodine. Flash chromatography was performed with silica gel (230–400 mesh, Silicycle). The NMR spectra were obtained using a Bruker 500 MHz Fourier-transform NMR spectrometer. Chemical shifts are reported in units of parts per million (ppm) downfield from tetramethylsilane (TMS), and all coupling constants are reported in hertz. Reactions were conducted in 2–5 mL microwave vials that were purchased from VWR International.

**Preparation of sulfoxides:** Sulfoxides were prepared according to the literature procedures.¹⁶

**General Procedure for catalysis:** To an oven-dried microwave vial equipped with a stir bar was added 2-phenylethyl phenyl sulfoxide (3.4k, 23 mg, 0.10 mmol) and KOtBu (180 mg, 1.60 mmol, 3.2 equiv), under a nitrogen atmosphere followed by 1.0 mL dry THF. The microwave vial was sealed with a rubber septum and an aluminum cap. The vial was then heated at 80 °C for 10 minutes for catalyst activation. The benzyl chloride (3.1a, 58 μL, 0.50 mmol) and the benzaldehyde (3.2a, 105 μL, 1.0 mmol) were combined with 1.0 mL dry THF and loaded into a 1.0 mL syringe. This stock solution was added to the reaction vial in a portionwise fashion (0.1 mL every 6 minutes). The reaction mixture was therefore heated for 1 h in total, cooled to room temperature, and opened to air. The reaction mixture was vacuumed filtered through a plug of Celite packed in a 15 mL Buchner funnel into a 100 mL round bottom flask. The pad was then rinsed with 20 mL ethyl acetate and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (eluted with
hexanes) to give the product (3.3a, 64.2 mg, 72% yield) as a white solid. The spectroscopic data match the previously reported data.\textsuperscript{17}

**Diphenyl acetylene (3.3a):** The reaction was performed following the General Procedure with 2-phenylethyl phenyl sulfoxide (3.4k, 23 mg, 0.10 mmol) and KO\textsuperscript{t}Bu (180 mg, 1.60 mmol). The stock solution was made with benzyl chloride (3.1a, 58 \( \mu \)L, 0.50 mmol) and benzaldehyde (3.2a, 105 \( \mu \)L, 1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (3.3a, 64.2 mg, 72% yield) as a white solid. The spectroscopic data match the previously reported data.\textsuperscript{17}

**1-Methyl-4-(phenylethynyl)benzene (3.3b):** The reaction was performed following the General Procedure with 2-phenylethyl phenyl sulfoxide (3.4k, 23 mg, 0.10 mmol) and KO\textsuperscript{t}Bu (180 mg, 1.60 mmol). The stock solution was made with 4-methyl benzyl chloride (3.1b, 63 \( \mu \)L, 0.50 mmol) and benzaldehyde (3.2a, 105 \( \mu \)L, 1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (3.3b, 58.6 mg, 61% yield) as a white solid. The spectroscopic data match the previously reported data.\textsuperscript{18}

**1-(1,1-Dimethylethyl)-4-(2-phenylethynyl)benzene (3.3c):** The reaction was performed following the General Procedure with 2-phenylethyl phenyl sulfoxide (3.4k, 23 mg, 0.10 mmol) and KO\textsuperscript{t}Bu (180 mg, 1.60 mmol). The stock solution was made with 4-\textit{tert}-butyl benzyl chloride (3.1c, 97 \( \mu \)L, 0.50 mmol) and benzaldehyde (2a, 105 \( \mu \)L, 1.0 mmol). The crude product
was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (3.3c, 80.8 mg, 69% yield) as a white solid. The spectroscopic data match the previously reported data.\(^1\)

**4-Methoxy-1-(phenylethynyl)benzene (3.3d):** The reaction was performed following the General Procedure with 2-phenylethyl phenyl sulfoxide (3.4k, 23 mg, 0.10 mmol) and KOtBu (180 mg, 1.60 mmol). The stock solution was made with 4-methoxy benzyl chloride (3.1d, 68 μL, 0.50 mmol) and benzaldehyde (3.2a, 105 μL, 1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (3.3d, 80.2 mg, 77% yield) as a white solid. The spectroscopic data match the previously reported data.\(^1\)

**1-Fluoro-4-(phenylethynyl)benzene (3.3e):** The reaction was performed following the General Procedure with 2-phenylethyl phenyl sulfoxide (3.4k, 23 mg, 0.10 mmol) and KOtBu (180 mg, 1.60 mmol). The stock solution was made with 4-fluoro benzyl chloride (3.1e, 60 μL, 0.50 mmol) and benzaldehyde (3.2a, 105 μL, 1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (3.3e, 68.7 mg, 70% yield) as a white solid. The spectroscopic data match the previously reported data.\(^1\)

**1-Chloro-4-(phenylethynyl)benzene (3.3f):** The reaction was performed following the General Procedure with 2-phenylethyl phenyl sulfoxide (3.4k, 23 mg, 0.10 mmol) and KOtBu (180 mg, 1.60 mmol). The stock solution was made with 4-chloro benzyl chloride (3.1f, 80.5 mg, 0.50 mmol)
and benzaldehyde (3.2a, 105 μL, 1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (3.3f, 73.4 mg, 69% yield) as a white solid. The spectroscopic data match the previously reported data.\textsuperscript{19}

1-Bromo-4-(phenylethynyl)benzene (3.3g): The reaction was performed following the General Procedure with 2-phenylethyl phenyl sulfoxide (3.4k, 23 mg, 0.10 mmol) and KO\textsuperscript{t}Bu (180 mg, 1.60 mmol). The stock solution was made with 4-bromo benzyl chloride (3.1g, 102.7 mg, 0.50 mmol) and benzaldehyde (3.2a, 105 μL, 1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (3.3g, 93.9 mg, 73% yield) as a white solid. The spectroscopic data match the previously reported data.\textsuperscript{19}

1-Methyl-2-(phenylethynyl)benzene (3.3h): The reaction was performed following the General Procedure with 2-phenylethyl phenyl sulfoxide (3.4k, 23 mg, 0.10 mmol) and KO\textsuperscript{t}Bu (180 mg, 1.60 mmol). The stock solution was made with 2-methyl benzyl chloride (3.1h, 67 μL, 0.50 mmol) and benzaldehyde (3.2a, 105 μL, 1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (3.3h, 22.1 mg, 23% yield) as a white solid. The spectroscopic data match the previously reported data.\textsuperscript{18}

1-Fluoro-2-(phenylethynyl)benzene (3.3i): The reaction was performed following the General Procedure with 2-phenylethyl phenyl sulfoxide (3.4k, 23 mg, 0.10 mmol) and KO\textsuperscript{t}Bu (180 mg, 1.60 mmol).
The stock solution was made with 2-fluoro benzyl chloride (3.1i, 60 μL, 0.50 mmol) and benzaldehyde (3.2a, 105 μL, 1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (3.3i, 61.8 mg, 63% yield) as a white solid. The spectroscopic data match the previously reported data.

1-(Phenylethynyl)naphthalene (3.3j): The reaction was performed following the General Procedure with 2-phenylethyl phenyl sulfoxide (3.4k, 23 mg, 0.10 mmol) and KO\textsubscript{t}Bu (180 mg, 1.60 mmol). The stock solution was made with 1-(chloromethyl) naphthalene (3.1j, 88 mg, 0.50 mmol) and benzaldehyde (3.2a, 105 μL, 1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (3.3j, 77.6 mg, 68% yield) as a white solid. The spectroscopic data match the previously reported data.\textsuperscript{18}

1-Methyl-3-(phenylethynyl)benzene (3.3k): The reaction was performed following the General Procedure with 2-phenylethyl phenyl sulfoxide (3.4k, 23 mg, 0.10 mmol) and KO\textsubscript{t}Bu (180 mg, 1.60 mmol). The stock solution was made with 3-methyl benzyl chloride (3.1k, 67 μL, 0.50 mmol) and benzaldehyde (3.2a, 105 μL, 1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (3.3k, 62.5 mg, 65% yield) as a white oil. The spectroscopic data match the previously reported data.\textsuperscript{18}

1-Fluoro-3-(phenylethynyl)benzene (3.3l): The reaction was performed following the General Procedure with 2-phenylethyl phenyl sulfoxide (3.4k, 23 mg, 0.10 mmol) and KO\textsubscript{t}Bu (180 mg, 1.60 mmol).
The stock solution was made with 3-fluoro benzyl chloride (3.1l, 61 μL, 0.50 mmol) and benzaldehyde (3.2a, 105 μL, 1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (3.3l, 60.1 mg, 62% yield) as a white oil. The spectroscopic data match the previously reported data.21

1-(2-Phenylethynyl)-3-(trifluoromethyl)benzene (3.3m): The reaction was performed following the General Procedure with 2-phenylethyl phenyl sulfoxide (3.4k, 23 mg, 0.10 mmol) and KOtBu (180 mg, 1.60 mmol). The stock solution was made with 3-(trifluoromethyl) benzyl chloride (3.1m, 78 μL, 0.50 mmol) and benzaldehyde (3.2a, 105 μL, 1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (3.3m, 65.3 mg, 53% yield) as a white oil. The spectroscopic data match the previously reported data.21

4-Methoxy-1-(phenylethynyl)benzene (3.3d) (from 4-methoxybenzaldehyde): The reaction was performed following the General Procedure with 2-phenylethyl phenyl sulfoxide (3.4k, 23 mg, 0.10 mmol) and KOtBu (180 mg, 1.60 mmol). The stock solution was made with benzyl chloride (3.1a, 58 μL, 0.50 mmol) and 4-methoxybenzaldehyde (3.2d, 121 μL, 1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (3.3d, 63.5 mg, 61% yield) as a white solid. The spectroscopic data match the previously reported data.17

4-Methylthio-1-(phenylethynyl)benzene (3.3n): The reaction was performed following the General Procedure with 2-phenylethyl phenyl sulfoxide (3.4k, 23 mg, 0.10 mmol) and KOtBu (180 mg,
1.60 mmol). The stock solution was made with benzyl chloride (3.1a, 58 μL, 0.50 mmol) and 4-methylthiobenzaldehyde (3.2n, 133 μL, 1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (3.3n, 78.5 mg, 70% yield) as a white solid. The spectroscopic data match the previously reported data.22

1-Fluoro-4-(phenylethynyl)benzene (3.3e) (from 4-fluorobenzaldehyde): The reaction was performed following the General Procedure with 2-phenylethyl phenyl sulfoxide (3.4k, 23 mg, 0.10 mmol) and KOtBu (180 mg, 1.60 mmol). The stock solution was made with benzyl chloride (3.1a, 58 μL, 0.50 mmol) and 4-fluoro benzaldehyde (3.2e, 108 μL, 1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (3.3e, 65.7 mg, 67% yield) as a white solid. The spectroscopic data match the previously reported data.17

1-Chloro-4-(phenylethynyl)benzene (3.3f) (from 4-chlorobenzaldehyde): The reaction was performed following the General Procedure with 2-phenylethyl phenyl sulfoxide (3.4k, 23 mg, 0.10 mmol) and KOtBu (180 mg, 1.60 mmol). The stock solution was made with benzyl chloride (3.1a, 58 μL, 0.50 mmol) and 4-chlorobenzaldehyde (3.2f, 140.6 mg, 1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (3.3f, 78.7 mg, 74% yield) as a white solid. The spectroscopic data match the previously reported data.19
1-Bromo-4-(phenylethynyl)benzene (3.3g) (from 4-bromobenzaldehyde): The reaction was performed following the General Procedure with 2-phenylethyl phenyl sulfoxide (3.4k, 23 mg, 0.10 mmol) and KOtBu (180 mg, 1.60 mmol). The stock solution was made with benzyl chloride (3.1a, 58 μL, 0.50 mmol) and 4-bromobenzaldehyde (3.2g, 185 mg, 1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (3.3g, 97.7 mg, 76% yield) as a white solid. The spectroscopic data match the previously reported data.\(^\text{19}\)

1-(Phenylethynyl)naphthalene (3.3j) (from 1-naphthaldehyde): The reaction was performed following the General Procedure with 2-phenylethyl phenyl sulfoxide (3.4k, 23 mg, 0.10 mmol) and KOtBu (180 mg, 1.60 mmol). The stock solution was made with benzyl chloride (3.1a, 58 μL, 0.50 mmol) and 1-naphthaldehyde (3.2j, 136 μL, 1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (3.3j, 92.5 mg, 81% yield) as a white solid. The spectroscopic data match the previously reported data.\(^\text{18}\)

1-(2-Phenylethynyl)-4-(trifluoromethyl)benzene (3.3o): The reaction was performed following the General Procedure with 2-phenylethyl phenyl sulfoxide (3.4k, 23 mg, 0.10 mmol) and KOtBu (180 mg, 1.60 mmol). The stock solution was made with benzyl chloride (3.1a, 58 μL, 0.50 mmol) and 4-(trifluoromethyl)benzaldehyde (3.2o, 137 μL, 1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (3.3o, 88.6 mg, 72% yield) as a white solid. The spectroscopic data match the previously reported data.\(^\text{19}\)
1-(4-Methoxycarbonylphenyl)-2-phenylacetylene (3.3p): The reaction was performed following the General Procedure with 2-phenylethyl phenyl sulfoxide (3.4k, 23 mg, 0.10 mmol) and KOtBu (180 mg, 1.60 mmol). The stock solution was made with benzyl chloride (3.1a, 58 μL, 0.50 mmol) and methyl 4-formylbenzoate (3.2p, 164 mg, 1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes:EtOAc = 100:1) to give the product (3.3p, 36.6 mg, 31% yield) as a white solid. The spectroscopic data match the previously reported data.18

2-(2-Phenylethynyl)naphthalene (3.3q): The reaction was performed following the General Procedure with 2-phenylethyl phenyl sulfoxide (3.4k, 23 mg, 0.10 mmol) and KOtBu (180 mg, 1.60 mmol). The stock solution was made with benzyl chloride (3.1a, 58 μL, 0.50 mmol) and 2-naphthaldehyde (3.2q, 156 mg, 1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (3.3q, 85.6 mg, 75% yield) as a white solid. The spectroscopic data match the previously reported data.21

1-[3-(2-Phenylethynyl)phenyl]pyrrole (3.3r): The reaction was performed following the General Procedure with 2-phenylethyl phenyl sulfoxide (3.4k, 23 mg, 0.10 mmol) and KOtBu (180 mg, 1.60 mmol). The stock solution was made with benzyl chloride (3.1a, 58 μL, 0.50 mmol) and 3-(1H-pyrrol-1-yl)benzaldehyde (3.2r, 172 mg, 1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (92.5 mg, 76% yield) as a white solid; m.p. = 69 – 71 °C. 1H NMR (500 MHz, CDCl3): δ 7.55 – 7.53 (m, 3H), 7.38 – 7.30 (m, 6H), 7.07 (t, J = 2.5 Hz, 2H), 6.34 (t, J = 2.5 Hz,
2H) ppm; $^{13}$C($^1$H) NMR (125 MHz, CDCl$_3$): 140.7, 131.6, 129.5, 128.6, 128.5, 128.4, 124.6, 123.2, 122.9, 120.2, 119.1, 110.7, 90.2, 88.6 ppm; IR (thin film): 3150, 3130, 3100, 3070, 1940, 1603, 1582, 1498, 1488, 1441, 1345, 1257, 1085, 1074, 1028, 887, 788, 757, 727, 691, 684 cm$^{-1}$; HRMS calculated for C$_{18}$H$_{14}$N 244.1126, found 240.1125 [M+H$^+$].

1-Phenyl-2-(m-hydroxyphenyl)acetylene (3.3s): The reaction was performed following the General Procedure with 2-phenylethyl phenyl sulfoxide (3.4k, 23 mg, 0.10 mmol) and KO'Bu (292 mg, 2.60 mmol). Note that an extra equivalent of base was used to deprotonate the phenolic hydroxyl group. The stock solution was made with benzyl chloride (3.1a, 58 μL, 0.50 mmol) and 3-hydroxybenzaldehyde (3.2s, 122 mg, 1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes:EtOAc = 10:1) to give the product (3.3s, 64.1 mg, 66% yield) as a white solid. The spectroscopic data match the previously reported data.$^{23}$

(3-Cyanophenyl)phenylacetylene (3.3t): The reaction was performed following the General Procedure with 2-phenylethyl phenyl sulfoxide (3.4k, 23 mg, 0.10 mmol) and KO'Bu (180 mg, 1.60 mmol). The stock solution was made with benzyl chloride (3.1a, 58 μL, 0.50 mmol) and 3-cyanobenzaldehyde (3.2t, 131 mg, 1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (3.3t, 69.1 mg, 68% yield) as a white solid. The spectroscopic data match the previously reported data.$^{22}$
**2-(2-phenylethynyl)pyridine (3.3u):** The reaction was performed following the General Procedure with 2-phenylethyl phenyl sulfoxide (3.4k, 23 mg, 0.10 mmol) and KO\textsubscript{t}Bu (180 mg, 1.60 mmol). The stock solution was made with benzyl chloride (3.1a, 58 μL, 0.50 mmol) and 2-pyridinecarboxaldehyde (3.2u, 96 μL, 1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes:EtOAc = 10:1) to give the product (3.3u, 48.4 mg, 54% yield) as a white solid. The spectroscopic data match the previously reported data.\textsuperscript{24}

**3-(2-Phenylethynyl)pyridine (3.3v):** The reaction was performed following the General Procedure with 2-phenylethyl phenyl sulfoxide (3.4k, 23 mg, 0.10 mmol) and KO\textsubscript{t}Bu (180 mg, 1.60 mmol). The stock solution was made with benzyl chloride (3.1a, 58 μL, 0.50 mmol) and 3-pyridinecarboxaldehyde (3.2v, 94 μL, 1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes:EtOAc = 10:1) to give the product (3.3v, 62.7 mg, 70% yield) as a white solid. The spectroscopic data match the previously reported data.\textsuperscript{18}

**(5-Isoquinolinyl)phenylacetylene (3.3w):** The reaction was performed following the General Procedure with 2-phenylethyl phenyl sulfoxide (3.4k, 23 mg, 0.10 mmol) and KO\textsubscript{t}Bu (180 mg, 1.60 mmol). The stock solution was made with benzyl chloride (3.1a, 58 μL, 0.50 mmol) and isoquinoline-5-carboxaldehyde (3.2w, 157 mg, 1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes:EtOAc = 10:1) to give the product (3.3w, 83.7 mg, 73% yield) as a white oil. \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): δ 9.23 (s, 1H), 8.62 (d, J = 6 Hz, 1H), 8.14 (d, J = 6 Hz, 1H), 7.87 (d, J = 7.5 Hz, 2H), 7.62 (dd,
\[ J = 7.5, 2.5 \text{ Hz, 2H}, 7.51 (t, J = 8.5 \text{ Hz, 1H}), 7.38 – 7.36 (m, 3H) \text{ ppm}; ^{13}\text{C}[^{1}\text{H}] \text{ NMR (125 MHz, CDCl}_3)\]: 152.6, 143.8, 135.8, 133.8, 131.5, 128.6, 128.3, 128.2, 127.8, 126.5, 122.6, 120.1, 118.7, 95.3, 85.8 ppm; IR (thin film): 3062, 2215, 1612, 1598, 1579, 1571, 1492, 1442, 1381, 1368, 1024, 829, 755, 691 cm\text{^{-1}}; \text{ HRMS calculated for C}_{17}\text{H}_{12}\text{N} 230.0969, \text{ found } 230.0975 [\text{M+H}]^+.\]

**2-(2-Phenylethynyl)furan (3.3x):** The reaction was performed following the General Procedure with 2-phenylethyl phenyl sulfoxide (3.4k, 23 mg, 0.10 mmol) and KO\text{Bu} (180 mg, 1.60 mmol). The stock solution was made with benzyl chloride (3.1a, 58 \mu\text{L}, 0.50 mmol) and 2-furaldehyde (3.2x, 83 \mu\text{L}, 1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (3.3x, 67.3 mg, 80% yield) as a pale yellow oil. The spectroscopic data match the previously reported data.\textsuperscript{25}

**2-(2-Phenylethynyl)thiophene (3.3y):** The reaction was performed following the General Procedure with 2-phenylethyl phenyl sulfoxide (3.4k, 23 mg, 0.10 mmol) and KO\text{Bu} (180 mg, 1.60 mmol). The stock solution was made with benzyl chloride (3.1a, 58 \mu\text{L}, 0.50 mmol) and 2-thiophenecarboxaldehyde (3.2y, 94 \mu\text{L}, 1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (3.3y, 70.9 mg, 77% yield) as a white solid. The spectroscopic data match the previously reported data.\textsuperscript{18}

**1,3-Bis(2-phenylethynyl)benzene (3.6a):** The reaction was performed following the General Procedure with 2-phenylethyl phenyl sulfoxide (3.4k, 23 mg, 0.10 mmol) and
KO\textsubscript{t}Bu (360 mg, 3.20 mmol). The stock solution was made with 1,3-bis(chloromethyl)benzene (3.5a, 88 mg, 0.50 mmol) and benzaldehyde (3.2a, 210 μL, 2.0 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (3.6a, 58.5 mg, 42% yield) as a white solid. The spectroscopic data match the previously reported data.\textsuperscript{26}

1,1',4-Triphenylbut-3-en-1-yne (3.6b): The reaction was performed following the General Procedure with 2-phenylethyl phenyl sulfoxide (3.4k, 23 mg, 0.10 mmol) and KO\textsubscript{t}Bu (180 mg, 1.60 mmol). The stock solution was made with 1,1-diphenyl-3-chloro-1-propene (3.5b, 115 mg, 0.50 mmol) and benzaldehyde (3.2a, 105 μL, 1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (3.6b, 64.5 mg, 46% yield) as a white solid. The spectroscopic data match the previously reported data.\textsuperscript{27}

2-(2-(4-Methoxyphenyl)ethynyl)furan (3.3dx) (gram scale reaction): To an oven-dried Schlenk flask equipped with a stir bar was added 2-phenylethyl phenyl sulfoxide (3.4k, 184 mg, 0.80 mmol) and KO\textsubscript{t}Bu (2.87 g, 25.6 mmol, 3.2 equiv) under nitrogen atmosphere, followed by 17.0 mL dry THF via syringe. The Schlenk flask neck was equipped with a condenser, whose top was connected to a nitrogen line, with side arm closed. And the flask was then heated at 80 °C for 10 minutes for catalyst activation. 4-Methoxy benzyl chloride 3.1d (1.08 mL, 8.0 mmol) and 2-furaldehyde 3.2x (1.33 mL, 16.0 mmol) were diluted to 15.0 mL with dry THF and loaded into a syringe. This stock solution was added to the
vial every 6 minutes through the sidearm. The reaction was heated for 1 h and then cooled to room temperature, opened to air. The reaction mixture was vacuumed filtered through a plug of Celite packed in a 15 mL Buchner funnel into a 100 mL round bottom flask. The pad of Celite was then rinsed with 50 mL ethyl acetate, the filtrates combined, and the volatile materials removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (3.3dx, 1.23 g, 78% yield) as a pale yellow oil. The spectroscopic data match the previously reported data.28

2-(2-(4-Methoxyphenyl)ethynyl)thiophene (3.3dy) (gram scale synthesis): To an oven-dried Schlenk flask equipped with a stir bar was added 2-phenylethyl phenyl sulfoxide (3.4k, 184 mg, 0.80 mmol) and KOtBu (2.87 g, 25.6 mmol, 3.2 equiv), under nitrogen atmosphere followed by 17.0 mL dry THF via syringe. The Schlenk flask neck was equipped with a condenser, whose top was connected to a nitrogen line, with side arm closed. And the flask was then heated at 80 °C for 10 minutes for catalyst activation. 4-Methoxy benzyl chloride 3.1d (1.08 mL, 8.0 mmol) and 2-thiophenecarboxaldehyde 3.2y (1.50 mL, 16.0 mmol) was diluted to 15.0 mL with dry THF and loaded to a syringe as the stock solution. 1.5 mL stock solution was added to the vial every 6 minutes through the sidearm. The reaction was heated for 1 h and then cooled to room temperature, opened to air. The reaction mixture was vacuumed filtered through a plug of Celite packed in a 15 mL Buchner funnel into a 100 mL round bottom flask. The pad was then rinsed with 50 mL ethyl acetate and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the
product (3.3dy, 1.28 g, 75% yield) as a white solid. The spectroscopic data match the previously reported data.28

1-(4-Bromophenyl)-2-(4-chlorophenyl)ethyne (3.3gf) (gram scale synthesis): To an oven-dried 100 Schlenk flask equipped with a stir bar was added 2-phenylethyl phenyl sulfoxide (3.4k, 184 mg, 0.80 mmol) and KOtBu (2.87 g, 25.6 mmol, 3.2 equiv) under nitrogen atmosphere, followed by 17.0 mL dry THF via syringe. The Schlenk flask neck was equipped with a condenser, whose top was connected to a nitrogen line, with side arm closed. And the flask was then heated at 80 °C for 10 minutes for catalyst activation. 4-Bromo benzyl chloride 3.1g (1.64 g, 8.0 mmol) and 3.2f 4-chlorobenzaldehyde (2.25 g, 16.0 mmol) was diluted to 15.0 mL with dry THF and loaded to a syringe as the stock solution. 1.5 mL stock solution was added to the vial every 6 minutes through the sidearm. The reaction was heated for 1 h and then cooled to room temperature, opened to air. The reaction mixture was vacuumed filtered through a plug of Celite packed in a 15 mL Buchner funnel into a 100 mL round bottom flask. The pad was then rinsed with 50 mL ethyl acetate and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (3.3gf, 2.06 g, 71% yield) as a white solid. The spectroscopic data match the previously reported data.29

1-(3-Trifluoromethyl)-2-(4-trifluorophenyl)ethyne (3.3mo) (gram scale synthesis): To an oven-dried Schlenk flask equipped with a stir bar was added 2-phenylethyl phenyl sulfoxide (3.4k, 184 mg, 0.80 mmol) and KOtBu (2.87 g, 25.6 mmol, 3.2 equiv), under nitrogen atmosphere followed by 17.0 mL dry THF via syringe. The Schlenk flask neck
was equipped with a condenser, whose top was connected to a nitrogen line, with side arm closed. And the flask was then heated at 80 °C for 10 minutes for catalyst activation. 3-Trifluoromethyl benzyl chloride 3.1m (1.24 mL, 8.0 mmol) and 4-(trifluoromethyl)benzaldehyde 3.2o (2.19 mL, 16.0 mmol) was diluted to 15.0 mL with dry THF and loaded to a syringe as the stock solution. 1.5 mL stock solution was added to the vial every 6 minutes through the sidearm. The reaction was heated for 1 h and then cooled to room temperature, opened to air. The reaction mixture was vacuumed filtered through a plug of Celite packed in a 15 mL Buchner funnel into a 100 mL round bottom flask. The pad was then rinsed with 50 mL ethyl acetate and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (3.3mo, 1.41 g, 56% yield) as a white oil. ¹H NMR (500 MHz, CDCl₃): δ 7.80 (s, 1H), 7.68 (d, J = 7.5 Hz, 1H), 7.63 – 7.56 (m, 5H), 7.45 (t, J = 7.5 Hz, 1H), 7.51 (t, J = 4 Hz, 1H) ppm; ¹³C{¹H} NMR (125 MHz, CDCl₃): 134.8, 131.9, 131.1 (q, J_C-F = 31.2 Hz), 130.4 (q, J_C-F = 32.5 Hz), 129.0, 128.5 (q, J_C-F = 3.7 Hz), 126.5, 125.4 (q, J_C-F = 3.7 Hz), 125.2 (q, J_C-F = 3.7 Hz), 123.9 (q, J_C-F = 270 Hz), 123.7 (q, J_C-F = 270 Hz), 123.6 ppm; IR (thin film): 3076, 1616, 1434, 1343, 1324, 1129, 1169, 1067, 842, 902, 707, 695 cm⁻¹; HRMS calculated for C₁₆H₈F₆ 314.0530, found 314.0535 [M]+.

Mechanism Study
**Scheme 3-9, I**: \((Z)-1,2\text{-Diphenyl-1-(phenylsulphinyl)ethene}\) was synthesized according to literature\(^ {15}\) with diphenyl acetylene (3.56 g, 20 mmol) and thiophenol (2.04 mL, 20 mmol). The resulting sulfide was oxidized with sodium periodate (4.28 g, 20 mmol) in 70 mL MeOH:H\(_2\)O = 19:1 for 12 h, giving \((Z)-1,2\text{-diphenyl-1-(phenylsulphinyl)ethene}\) (3.16 g, 52%); m.p. = 125 – 127 °C. \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 7.42 (s, 1H), 7.38 – 7.29 (m, 6H), 7.25 (t, \(J = 7.57\) Hz, 2H), 7.20 – 7.15 (m, 5H), 6.88 (d, \(J = 7.57\) Hz, 2H) ppm; \(^{13}\)C\({}^1\)H\) NMR (125 MHz, CDCl\(_3\)): 145.5, 142.5, 133.8, 131.8, 131.0, 129.7, 129.6, 129.5, 128.75, 128.72, 128.68, 128.64, 128.3, 125.3 ppm; IR (thin film): 3056, 1443, 1082, 1053, 750, 692 cm\(^{-1}\); HRMS calculated for C\(_{20}\)H\(_{17}\)OS 305.1000, found 314.0997 [M+H]\(^+\). The vinyl sulfoxide isolated from reaction was demonstrated as the same compound with \((Z)-1,2\text{-diphenyl-1-(phenylsulphinyl)ethene}\) by comparing \(^1\)H and \(^{13}\)C\({}^1\)H\) NMR spectra.

**Scheme 3-9, H**: Both threo- and erythro-2-phenylsulfinyl-1,2-diphenyl-1-ethanol were synthesized according to literature.\(^ {15}\)

**Resting state study:**

To an oven-dried microwave vial equipped with a stir bar was added 2-phenylethyl phenyl sulfoxide (3.4k, 23 mg, 0.10 mmol) and KO\(^{\text{tBu}}\) (180 mg, 1.60 mmol, 3.2 equiv), under a nitrogen atmosphere followed by 1.0 mL dry THF. The microwave
The vial was sealed with a rubber septum and an aluminum cap. The vial was then heated at 80 °C for 10 minutes for catalyst activation. The benzyl chloride (3.1a, 58 μL, 0.50 mmol) and the benzaldehyde (3.2a, 105 μL, 1.0 mmol) were combined with 1.0 mL dry THF and loaded into a 1.0 mL syringe. This stock solution was added to the reaction vial in a portionwise fashion (0.1 mL every 6 minutes). At the 12th minute and the first 3 doses of stock solution, the rest stock solution was injected into reaction mixture at once and the reaction was quenched 3 min later. The reaction mixture was filtered through Celite. The reaction mixture was vacuumed filtered through a plug of Celite packed in a 15 mL Buchner funnel into a 100 mL round bottom flask. The pad was then rinsed with 20 mL ethyl acetate and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (eluted with hexanes:EtOAc = 4:1) to give (Z)-1,2-diphenyl-1-(phenylsulphinyl)ethene (I, 18.8 mg, 62% yield) as a white solid and benzyl phenyl sulfoxide (7.2 mg, 33% yield) as a white solid.

**Studies of Reaction Intermediates.**

Scheme 3-9A: To an oven-dried microwave vial equipped with a stir bar was added (Z)-1,2-diphenyl-1-(phenylsulphinyl)ethene I (Scheme 3-9, 30.4 mg, 0.1 mmol) and KOtBu (33.6 mg, 0.30 mmol, 3.0 equiv) under a nitrogen atmosphere, followed by 2.0 mL dry THF via syringe. The microwave vial was sealed with rubber septum and aluminum cap, and heated to 80 °C for 60 min. The sealed vial was cooled to room temperature and opened to air. The reaction mixture was passed through a short pad of silica gel. The pad was then rinsed with 10 mL ethyl acetate and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give diphenyl acetylene J (Scheme 3-9, 16.7 mg, 94% yield) as a white solid.
Scheme 3-9B: To an oven-dried microwave vial equipped with a stir bar was added *erythro*-2-phenylsulfinyl-1,2-diphenyl-1-ethanol **H** (Scheme 3-9, 33.2 mg, 0.1 mmol) and KO'Bu (22.4 mg, 0.20 mmol, 2.0 equiv) under nitrogen atmosphere, followed by 2.0 mL dry THF via syringe. The microwave vial was sealed with rubber septum and aluminum cap, and heated to 80 °C for 10 min. The sealed vial was cooled to room temperature, quenched with 4-methoxy benzyl chloride (28 µL, 0.20 mmol, 2.0 equiv), and opened to air. The reaction mixture was passed through a short pad of silica gel, the pad was rinsed with 10 mL ethyl acetate, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (eluted with hexanes) to give diphenyl acetylene **J** (Scheme 3-9, 14.6 mg, 82% yield) as a white solid. The column was then eluted with hexanes:EtOAc = 2:1 to give 4-methoxy-benzyl phenyl sulfoxide **C’** (Scheme 3-9, 17.2 mg, 70% yield) as a white solid.

Scheme 3-9B’: To an oven-dried microwave vial equipped with a stir bar was added *erythro*-2-phenylsulfinyl-1,2-diphenyl-1-ethanol **H’** (Scheme 3-9, 33.2 mg, 0.1 mmol) and KO'Bu (22.4 mg, 0.20 mmol, 2.0 equiv) under nitrogen atmosphere, followed by 2.0 mL dry THF via syringe. The microwave vial was sealed with rubber septum and aluminum cap, and heated to 80 °C for 10 min. The sealed vial was cooled to room temperature, quenched with 4-methoxy benzyl chloride (28 µL, 0.20 mmol, 2.0 equiv), and opened to air. The reaction mixture was passed through a short pad of silica gel, the pad was rinsed with 10 mL ethyl acetate, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (eluted with
hexanes) to give diphenyl acetylene J (Scheme 3-9, 14.4 mg, 81% yield) as a white solid. The column was then eluted with hexanes:EtOAc = 2:1 to give 4-methoxy-benzyl phenyl sulfoxide C' (Scheme 3-9, 18.0 mg, 73% yield) as a white solid.

Scheme 3-9C: To an oven-dried microwave vial equipped with a stir bar was added erythro-2-phenylsulfinyl-1,2-diphenyl-1-ethanol H (Scheme 3-9, 33.2 mg, 0.1 mmol) and 1 equiv. KO'Bu (11.2 mg, 0.10 mmol, 1.0 equiv) under a nitrogen atmosphere, followed by 2.0 mL dry THF via syringe. The microwave vial was sealed with rubber septum and aluminum cap, and heated to 80 °C for 10 min. The sealed vial was cooled to room temperature and opened to air. The reaction mixture was passed through a short pad of silica gel. The pad was then rinsed with 10 mL ethyl acetate and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (eluted with hexanes:EtOAc = 4:1) to give the (Z)-1,2-diphenyl-1-(phenylsulphinyl)ethene I (Scheme 3-9, 11.6 mg, 38% yield) as a white solid. The column was then eluted with hexanes:EtOAc = 2:1 to give benzyl phenyl sulfoxide C (Scheme 3-9, 11.2 mg, 52 %) as a white solid.

Scheme 3-9C': To an oven-dried microwave vial equipped with a stir bar was added threo-2-phenylsulfinyl-1,2-diphenyl-1-ethanol H' (Scheme 3-9, 33.2 mg, 0.1 mmol) and KO'Bu (11.2 mg, 0.10 mmol, 1.0 equiv), under nitrogen atmosphere followed by 2.0 mL dry THF. The microwave vial was sealed with rubber septum and aluminum cap, and heated to 80 °C for 10 min. The sealed vial was cooled to room temperature and opened to air. The reaction mixture was passed through a short pad of silica gel. The pad was
then rinsed with 10 mL ethyl acetate and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (eluted with hexanes:EtOAc = 4:1) to give the (Z)-1,2-diphenyl-1-(phenylsulphinyl)ethene \( \text{I} \) (Scheme 3-9, 9.7 mg, 32% yield) as a white solid. The column was then eluted with hexanes:EtOAc = 2:1 to give benzyl phenyl sulfoxide \( \text{C} \) (Scheme 3-9, 12.3 mg, 57 %) as a white solid.

**High-throughput Experimentation Screenings**

**Set up:**

Experiments were set up in a glove box under a nitrogen atmosphere. A 24-well aluminum block containing 1 mL glass vials was dosed with 1 µmol benzyl phenyl sulfoxide \( \text{3.4a} \), in THF. The solvent was removed to dryness using a GeneVac. Next, base (30 µmol) in THF was added to the vials. The solvent was again removed to dryness using a GeneVac and a parylene stir bar was then added to each reaction vial. Benzyl chloride \( \text{3.1a} \), 10 µmol/reaction), benzaldehyde \( \text{3.2a} \), 20 µmol/reaction) and biphenyl (1 µmol/reaction, used as an internal standard to measure HPLC yields) were then dosed together into each reaction vial as a solution in each solvent (100 µL, 0.1 M). The 24-well plate was then sealed and stirred for 10 h at 80 °C.

**Work up:**

The plate was cooled to room temperature. Upon opening the plate to air, 500 µL of acetonitrile was added into each vial. The plate was covered again and the vials stirred for 10 min to ensure good homogenization. Into a separate 24-well LC block was
added 700 μL of acetonitrile, followed by 40 μL of the diluted reaction mixtures. The LC block was then sealed with a silicon-rubber storage mat and mounted on an automated HPLC instrument for analysis.

Base and solvent screening

**Base:** LiO’Bu, NaO’Bu, KO’Bu, LiN(SiMe₃)₂, NaN(SiMe₃)₂, KN(SiMe₃)₂.

**Solvent:** THF, DME, dioxane, CPME.

*Table 3-2.* Base and solvent screening for alkyne synthesis catalyzed by sulfenate anions.

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3.5 References


CHAPTER 4 Sulfenate Anion Precatalyst Development for Alkyne Synthesis on Gram Scale

4.1 Introduction

4.1.1 Introduction to Alkyne Chemistry

Widely occurring in biochemistry and materials science, alkynes have drawn much attention. Compounds like enediyne antibiotics show great pharmaceutical activity.\(^1\) Also, π-conjugated oligomers built from arylalkyne motifs exhibit attractive properties in electronic materials.\(^2\) As a basic functional group in organic chemistry, the triple bond provides a variety of reaction possibilities, making alkynes significant building blocks and intermediates in synthetic chemistry.\(^3\) Reduction of alkynes provide direct methods towards alkene derivatives.\(^4\) Some alkynes can be oxidized into esters and diketones.\(^5\) Reactions with CO, alcohols and amines lead to generation of α,β-unsaturated esters and amides.\(^6\) Intermolecular or intramolecular addition to alkynes can lead to carbocyclic compounds, including heterocycles.\(^7\)

Alkynes can be prepared through multiple routes. The most traditional methods for alkyne synthesis are eliminations, including catalytic dehydrogenation, dehydrohalogenation, and heat or base-induced heteroatoms elimination from the corresponding alkenes.\(^8\) However, this method is not widely utilized in synthetic chemistry due to substrates availability. The Corey-Fuchs reaction provides an alternative alkyne preparation approach from readily accessible aldehydes.\(^9\) Similarly, Seyferth-Gilbert homologation employs aldehydes or ketones for terminal/internal alkynes generation.\(^10\) Unfortunately, both of these routes require consumption of

106
stoichiometric amount of reagents, triphenylphosphine or dimethyl (diazomethyl)phosphonate. Catalytic methods are more popular in synthetic chemistry, including transition metal catalyzed cross coupling of terminal alkynes, haloalkynes or metal alkynides,\textsuperscript{11} and alkyne metathesis.\textsuperscript{12} Cross coupling reactions often require involvement of noble transition metal Pd catalyst. Similar to olefin metathesis, alkyne metathesis utilizes redistribution between alkyne molecules.\textsuperscript{7} For both types of reactions, existing triple bonds in substrates are necessary. In other words, both of the reactions can only modify triple bonds, rather than generating triple bonds.

4.1.2 Introduction of Sulfenate Anions and Precatalysts

These methods mentioned above are useful, but they are limited by harsh conditions or the need to prepare reagents. We previously introduced the first catalytic method to prepare carbon-carbon triple bonds from precursors that do not contain such linkages (Scheme 4-1B).\textsuperscript{13d} By coupling benzaldehyde and benzyl chloride derivatives under basic conditions with an organocatalyst, good yields of alkynes are obtained. The catalyst, a highly reactive sulfenate anion, is readily generated under the reaction conditions from air-stable precursors. This method represents an attractive organocatalytic alternative to well-established stoichiometric approaches to alkynes and transition metal-based alkyne functionalization methods.
In recent years, sulfenate anions, along with the conjugated acids, sulfenic acids have drawn wide attention in organic and biochemistry due to their high reactivity. We have reported application of sulfenate anions as organocatalysts in formation of symmetric stilbenes and unsymmetrical diaryl acetylenes (Scheme 4-1), taking advantage of the sulfenate anions ability to act as both nucleophiles and leaving groups. Meanwhile, we and others have expanded sulfoxide syntheses utilizing sulfenate anions as intermediates through $S_N$2 or transition metal catalyzed cross coupling reactions. Unlike relatively inert sulfonate anions and thiophenolate anions which are usually air stable and commercial available, sulfenate anions cannot be isolated as sodium or lithium salts, due to the high reactivity. Therefore, sulfenate anions precursors are required for either application. Schwan and Poli use $\beta$-sulfinyl esters as the sufenate anion precursors (Scheme 4-2A). However, such precursors slowly decomposed when exposed to air, making it hard to store them for long periods of time. Perrio group and our group have developed tert-butyl sulfoxide as a sulfenate anion precursor (Scheme 4-2B). High temperatures (over 110 $^\circ$C) are required for the leaving of iso-butylene to form sulfenate anions, making it hard to use low boiling point solvent, such as THF in certain scenarios. Fluoride triggered elimination strategies of 2-
(trimethylsilyl)ethyl sulfoxides to liberate sulfenate anion intermediates provided a new possibility for precatalysts (Scheme 4-2C).\textsuperscript{16d-e,18} However, these precatalysts performed terribly in alkyne synthesis, likely due to the introduction of more impurities into reactions. We employed 2-phenylethyl phenyl sulfoxide as a precatalyst in the organocatalytic synthesis of alkynes (Scheme 4-2D).\textsuperscript{13d} This precatalyst could be kept in air for long periods of time without decomposition and it is easily activated by bases like KO\textsuperscript{t}Bu at room temperature through β-hydrogen elimination to release the sulfenate anion. The resulting alkene, styrene, does not seem to become involved in the alkyne forming reaction. Despite these advantages, 2-phenylethyl phenyl sulfoxide is dense and sticky yellow oil at room temperature. This physical property leads to great difficulties in accurately weighing and transferring the sulfenate anion precatalyst. In consideration of the above factors, we decided to develop a solid substitute of 2-phenylethyl phenyl sulfoxide as a new sulfenate anion precatalyst for the alkyne synthesis.
4.2 Results and Discussion

After comparing with sulfenate anions precursors in Scheme 4-2, the 2-arylethyl aryl sulfoxides skeleton was selected due to its stability and ease of preparation and activation under desired reaction conditions. Sulfoxides can be obtained through oxidation of corresponding sulfides, which, in turn, was generated from thiophenol and styrene derivatives (Scheme 4-3A). Based on the optimization in Chapter 3 Table 3-1, several candidates, such as 4-methoxyphenyl sulfenate anion and 4-fluorophenyl sulfenate anion are considered good substituents for phenyl sulfenate anion, given the similarly good yields for diphenyl acetylene synthesis. To change the physical property under room temperature, we tested multiple combinations of thiophenol derivatives and
styrene derivatives, and considering the cost of the reagents, we found that 1-methoxy-4-(4-methylphenethylsulfinyl) benzene 4.4 as a good substitute of 2-phenylethyl phenyl sulfoxide as a white solid, which could be prepared in large lab scale.

\[
\text{Scheme 4-3. Solid precatalyst preparation and catalytic reaction.}
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Next we examined the catalytic reactivity 4.4 in alkyne synthesis. 4-methoxybenzyl chloride 4.5 and 4-bromobenzadehyde 4.6 were chosen to test the reaction in gram scale (Scheme 4-3B). The reaction resulted in comparable yield (4.7, 57%) with our previous report even in 5-gram scale, proving the practicability and scalability of sulfenate anions catalyzed alkyne synthesis.

4.4 Conclusion

In summary, a more practical and convenient sulfenate anion precatalyst 1-methoxy-4-(4-methylphenethylsulfinyl)benzene was developed, as a solid state compound. Catalytic reactivity of such compound was tested, proving the scalability of the alkyne synthesis from benzyl chlorides and benzaldehydes.
4.3 Experimental Section

1-Methoxy-4-(4-methylphenethylsulfinyl)benzene (4.4). To a 250 mL round bottle flask quipped with a 25 x 10 mm, Teflon-coated, octagonal magnetic stir bar, 125 mL deionized water was added through a volumetric cylinder. 25 mmol 4-methylstyrene (4.2, 3.4 mL) and 27.5 mmol 4-methoxythiophenol (4.1, 3.4 mL) were introduced to the round bottle flask through 5 mL syringes with needles. The round bottle flask was then capped with a septum and heated up to 50 °C in an oil bath. After 12 h, the reaction was cooled to room temperature. The aqueous reaction was extracted with two 100-mL portions of ethyl acetate with a 250-mL separatory funnel. The combined organic layer was washed with two 120-mL portions of saturated K₂CO₃ solution to remove unreacted thiophenol. After washed with 120-mL brine, the organic layer was dried over 10 g MgSO₄, and filtered through a 30-mL sintered glass Büchner funnel (medium porosity, 30 mm diameter). The MgSO₄ was rinsed with dichloromethane twice (2*30 mL) and the combined filtrate was concentrated through rotary evaporation with 40 °C water bath in a 250-mL round bottle flash. The obtained crude sulfide (4.3) product was oxidized without further purification. To the 250-mL round bottle flask, 80-mL methanol and 4 mL deionized water was added with a 25 x 10 mm, tefloncoated, octagonal magnetic stir bar. The round bottle flask was put onto a stir plate and 26.6 mmol NaIO₄ (25.3 g) was weighted and introduced to the round bottle flask in several small portions while stirring. After stirring the reaction under room temperature for 12 h, large amount of white precipitation formed. The mixture was filtered through a 30-mL sintered glass Büchner funnel (medium porosity, 30 mm diameter). The white
precipitation was rinsed with dichloromethane twice (2*20 mL) and the combined filtrate was concentrated through rotary evaporation with 40 °C water bath. The residue was transferred to a 250-mL separatory funnel and 100 mL dichloromethane was added. Then it was washed by two 100-mL portions of saturated NaS2O3 solution to remove unreacted NaIO4. After washed with 100-mL brine, the organic layer was dried over 10 g MgSO4, and filtered through a 30-mL sintered glass Büchner funnel (medium porosity, 30 mm diameter). The MgSO4 was rinsed with dichloromethane twice (2*30 mL) and the combined filtrate was concentrated through rotary evaporation with 40 °C water bath. The resulted crude product was dissolved in a minimum amount of dichloromethane and loaded onto a column of silica gel prepared as a slurry in 2:1 hexanes-ethyl acetate. Elution with 2:1 hexanes-ethyl acetate affords pure product. The fractions contained with pure product were combined and solvent was removed through rotary evaporation with a 40 °C water bath. Further concentration at room temperature, 0.05 mmHg for 12 h affords 5.4 g (79%) sulfoxide (4.4) as a white solid. 4.4 has the following physical and spectroscopic data: Rf = 0.3 (hexanes : EtOAc = 2:1). 1H NMR (CDCl3, 500 MHz): δ 7.56 (d, J = 10 Hz, 2H), 7.07 (dd, J = 15, 5 Hz, 4H), 7.02 (d, J = 10 Hz, 2H), 3.84 (s, 3H), 3.03-2.96 (m, 3H), 2.88-2.83 (m, 1H), 2.30 (s, 3H). 13C NMR (CDCl3, 125 MHz): δ 161.8, 136.1, 135.6, 134.5, 129.3, 128.3, 125.9, 58.5, 55.4, 27.8, 20.9. IR (thin film): 3461, 2919, 1594, 1578, 1515, 1495, 1304, 1252, 1088 1029. Melting point: 72-73 °C. HRMS calc for C16H19O2S [M+H]+: 275.1106, found 275.1107.

1-(4-bromoophenyl)-2-(4-methoxyphenyl)-ethyne (4.7). To an oven-dried 250 mL Schlenk flask equipped with a 25 x 10 mm, Teflon-coated, octagonal magnetic stir bar, 3 mmol (0.82 g) 1-methoxy-4-(4-methylphenethylsulfinyl)benzene (4.4) was weighed. The Schlenk flask
was then transferred into glove box. 96 mmol (10.8 g) KO\textsubscript{t}Bu was weighted to the Schlenk flask and 60 mL anhydrous tetrahydrofuran was added through a volumetric cylinder. A yellow slurry was formed. Side arm was closed and the main neck was capped with a rubber septum. An anhydrous tetrahydrofuran solution of 0.5 M 4-methoxybenzyl chloride (4.5) and 1.0 M 4-bromobenzaldehyde (4.6) was prepared. 60 mL of such solution was filled into ten 6-mL syringes equipped with long needles. Each syringe contains 6 mL of the above solution. The Schlenk flask and 10 syringes were removed from glove box. The Schlenk flask was connected to N\textsubscript{2} line through the side arm. The N\textsubscript{2} flow to tuned to maximum with the side arm open. The septum of the main neck was removed and quickly replaced with a condenser tube with chill water on, whose top was connected to another N\textsubscript{2} line. Once the condenser was connected and N\textsubscript{2} flow open, the side arm was close and the corresponding N\textsubscript{2} line was removed. The Schlenk flask was heated up in an 80 °C oil bath with stirring. Every 6 minutes, 6 mL of the stock solution of 4-methoxybenzyl chloride 4.5 and 4-bromobenzaldehyde 4.6 was injected into the Schlenk flask through the sidearm. The reaction was heated for 1 h and cooled to room temperature, opened to air. The reaction mixture was filtered through a 50-mL sintered glass Büchner funnel to remove some of the precipitation. The Schlenk flask was rinsed with 30 mL ethyl acetate. The combined organic slurry was concentrated through rotary evaporation with 40 °C water bath. 50 g silica gel was packed into a column (64 mm diameter) with ethyl acetate. The concentrated slurry was loaded to the top of the silica gel and eluted with 300 mL ethyl acetate. The elution was collected with a round bottle flask. Thus, most of the precipitation was removed. The combined elution was then again concentrated through rotary evaporation with 40 °C water bath. The resulted crude product was purified with hexanes through column chromatography, to give product 4.7 4.9g (57%) as a white solid. 4.7 has the following
physical and spectroscopic data: Rf = 0.6 (hexanes). $^1$H NMR (CDCl$_3$, 500 MHz): δ 7.45 (dd, $J = $10, 5 Hz, 4H), 7.36 (d, $J = $10 Hz, 2H), 6.87 (d, $J = $10 Hz, 2H), 3.82 (s, 3H). $^{13}$C NMR (CDCl$_3$, 125 Hz): δ 159.8, 133.1, 132.9, 131.5, 122.6, 122.1, 115.0, 114.1, 90.6, 87.0, 55.3. IR (thin film): 2965, 2840, 1604, 1513, 1391, 1287, 1252, 1178, 1108, 1030, 823. Melting point: 148-150 °C. HRMS calc for C$_{15}$H$_{12}$BrO [M+H$^+$]: 287.0072, found 287.0081.

4.5 References


APPENDICES

Appendix A1 NMR Spectra Relevant to Chapter 1
Figure A1.1 500 MHz 1H and 125 MHz 13C(1H) NMR of 1.3a in CDCl₃.
Figure A1.2 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 1.3b in CDCl$_3$. 
Figure A1.3 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 1.3c in CDCl$_3$. 

122
Figure A1.5 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 1.3d in CDCl$_3$. 

123
Figure A1.5 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 1.3e in CDCl$_3$. 
Figure A1.6 500 MHz \(^1\)H and 125 MHz \(^{13}\)C\(^{1}\)H NMR of 1.3f in CDCl\(_3\).
Figure A1.7 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 1.3g in CDCl$_3$. 
Figure A1.8 500 MHz $^1$H and 125 MHz $^{13}$C[$^1$H] NMR of 1.3h in CDCl$_3$. 
Figure A1.9 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 1.3i in CDCl$_3$. 
**Figure A1.10** 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 1.3j in CDCl$_3$. 
Figure A1.11 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 1.3k in CDCl$_3$. 
Figure A1.12 500 MHz $^1$H and 125 MHz $^{13}$C{$^1$H} NMR of 1.3l in CDCl$_3$. 
Figure A1.13 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 1.3m in CDCl₃.
Figure A1.14 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 1.3n in CDCl$_3$. 
Appendix A2. NMR Spectra Relevant to Chapter 2
Figure A2.1 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 2.3a in CDCl$_3$. 
Figure A2.2 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 2.3b in CDCl$_3$. 
Figure A2.3 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 2.3c in CDCl$_3$. 
Figure A2.4 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 2.3d in CDCl$_3$. 
Figure A2.5 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 2.3e in CDCl$_3$. 
**Figure A2.6** 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 2.3f in THF-$_d_8$. 
Figure A2.7 500 MHz $^1\text{H}$ and 125 MHz $^{13}\text{C}$($^1\text{H}$) NMR of 2.3g in CDCl$_3$. 

141
Figure A2.8 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 2.3h in CDCl$_3$. 
Figure A2.9 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 2.3i in CDCl₃.
Figure A2.10 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 2.3j in CDCl$_3$. 
Figure A2.11 500 MHz $^1$H and 125 MHz $^{13}$C[$^1$H] NMR of 2.3k in CDCl$_3$. 

145
Figure A2.12 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 2.3l in CDCl$_3$. 
Figure A2.13 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 2.3m in CDCl$_3$. 
Figure A2.14 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 2.3n in CDCl$_3$. 
Appendix A3 NMR Spectra Relevant to Chapter 3
Figure A3.1 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 3.3a in CDCl$_3$. 
Figure A3.2 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 3.3b in CDCl$_3$. 
Figure A3.3 500 MHz $^1$H and 125 MHz $^{13}$C$^1$H NMR of 3.3c in CDCl$_3$. 
Figure A3.4 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 3.3d in CDCl$_3$. 
Figure A3.5 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 3.3e in CDCl$_3$. 
Figure A3.6 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 3.3f in CDCl$_3$. 
Figure A3.7 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 3.3g in CDCl$_3$. 
Figure A3.8 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 3.3h in CDCl$_3$. 

![Diagram of molecular structure](image)
Figure A3.9: 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 3.3i in CDCl$_3$. 
Figure A3.10 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 3.3j in CDCl$_3$. 
Figure A3.11 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 3.3k in CDCl$_3$. 

![NMR Spectrum Diagram](image-url)
Figure A3.12 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 3.3l in CDCl$_3$. 
Figure A3.13 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 3.3m in CDCl$_3$. 
Figure A3.14 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 3.3n in CDCl$_3$. 
Figure A3.15 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 3.3o in CDCl$_3$. 
Figure A3.16 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 3.3p in CDCl$_3$. 
**Figure A3.17** 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 3.3q in CDCl$_3$. 
Figure A3.18 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 3.3r in CDCl$_3$. 
Figure A3.19 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 3.3s in CDCl$_3$. 
Figure A3.20 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 3.3t in CDCl$_3$. 
Figure A3.21 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 3.3u in CDCl$_3$. 
Figure A3.22 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 3.3v in CDCl$_3$. 
Figure A3.23 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 3.3w in CDCl$_3$. 
Figure A3.24 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 3.3x in CDCl$_3$. 
Figure A3.25 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 3.3y in CDCl₃.
Figure A3.26 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 3.6a in CDCl$_3$. 
Figure A3.27 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 3.6b in CDCl$_3$. 
Figure A3.28 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 3.3dx in CDCl$_3$. 
Figure A3.29 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 3.3dy in CDCl$_3$. 
**Figure A3.30** 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 3.3gf in CDCl$_3$. 
Figure A3.31 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 3.3mo in CDCl$_3$. 
Figure A3.32 500 MHz $^1$H and 125 MHz $^{13}$C{$^1$H} NMR of 3.1 in CDCl$_3$. 
Figure A3.33 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 3.H in CDCl$_3$. 
Figure A3.34 500 MHz $^1\text{H}$ and 125 MHz $^{13}\text{C}(^1\text{H})$ NMR of $3.\text{H}'$ in CDCl$_3$. 
Appendix A4 NMR Spectra Relevant to Chapter 4
Figure A4.1 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 4.4 in CDCl$_3$. 
Figure A4.2 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 4.7 in CDCl$_3$. 