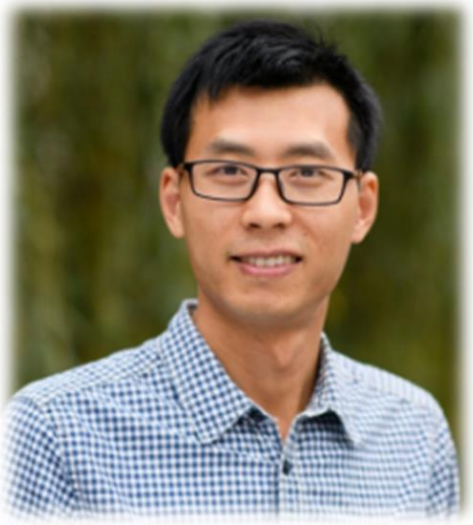
Literature Report V

Thioethers as Dichotomous Electrophiles for Site-Selective Silylation *via* C-S Bond Cleavage

Reporter: Shan-Shan Xun
Checker: Han Wang
Date: 2023-06-26

Chen, S.; Feng, Z. *et al. Angew. Chem. Int. Ed.* ***2023***, e202303470.

CV of Prof. Zhang Feng (冯璋)



Research Interest:

- Fluorine Chemistry
- Organic Synthesis Methodology

Background:

- **2006-2010** B.S., Southwest University
- **2010-2015** Ph.D., Shanghai Institute of Organic Chemistry, CAS
- **2015-2017** Postdoc., Princeton University
- **2017-now** Distinguished Researcher, Chongqing University

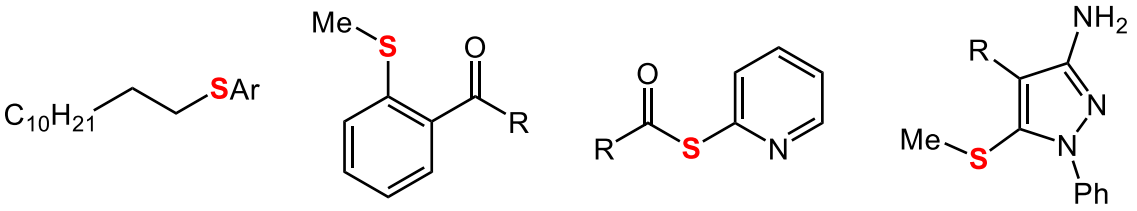
Contents

Introduction

The Activation or Functionalization of the C-S Bond

C-X Bond Dissociation Enthalpies (kcal/mol)

H_3C-H	H_3C-F	H_3C-Cl	H_3C-Br	H_3C-C_{sp3}	H_3C-N	H_3C-O	H_3C-S
438.6	459.7	350.7	291.8	307.8	356.0	385.7	**307.8**



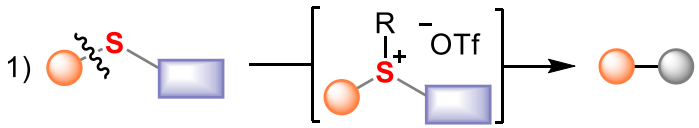
- **Widely found in natural products, pharmaceuticals and materials**
- **Commercially available**
- **Good substrates in synthesis**

Pan, F.; Shi, Z.-J. *ACS Catal*. **2014**, *4*, 280

Introduction

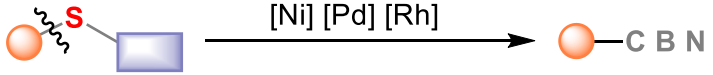
Transformations of Thioethers via C-S Bond Cleavage

A) The Cleavage of Activated *C-S* Bonds



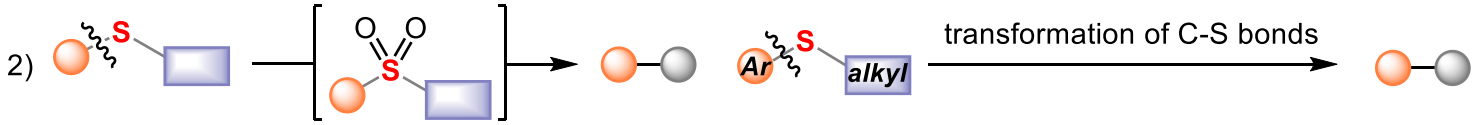
reactive sulfoniums as substrates

B) The Cleavage of Unreactive C-S Bond of Thioethers



direct transformation of thioethers

C) Only Selective Cleavage of the C(aryl)-S Bonds

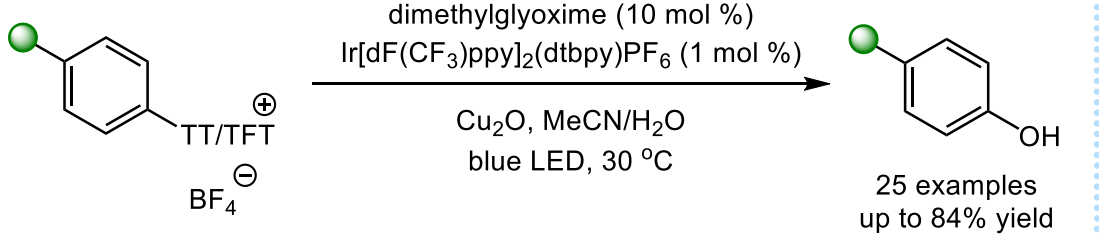


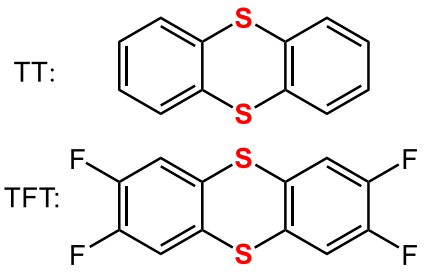
reactive sulfones as substrates

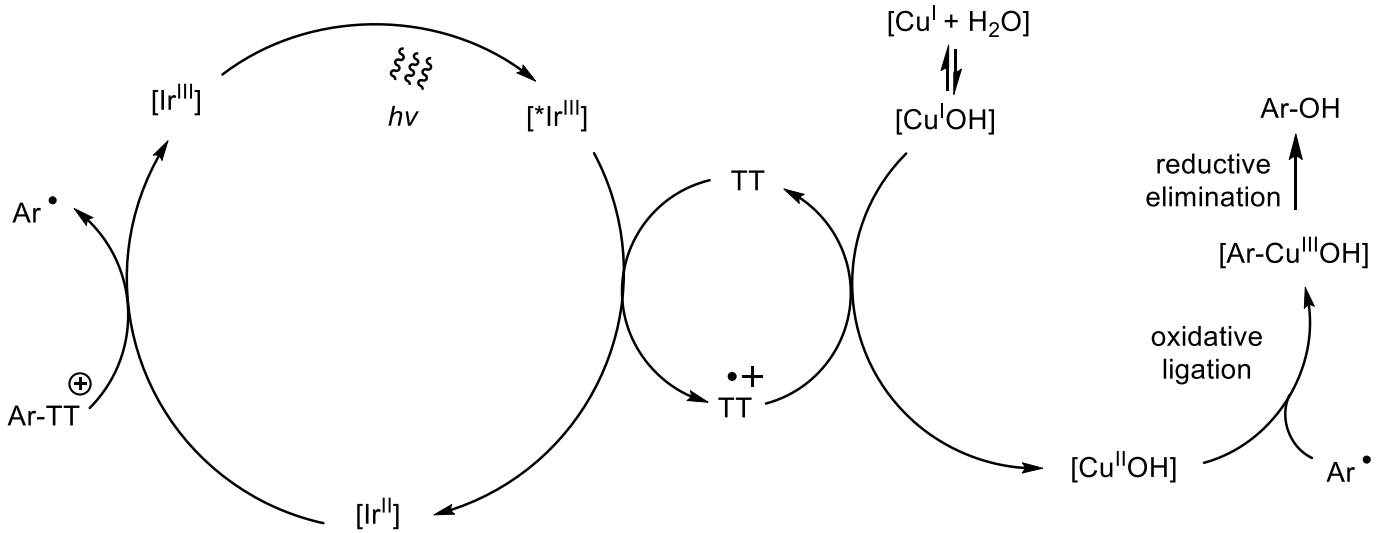
disadvantage: alkyl moiety cannot be utilized

Introduction

The Cleavage of Activated C-S Bonds (Sulfonium Salts)



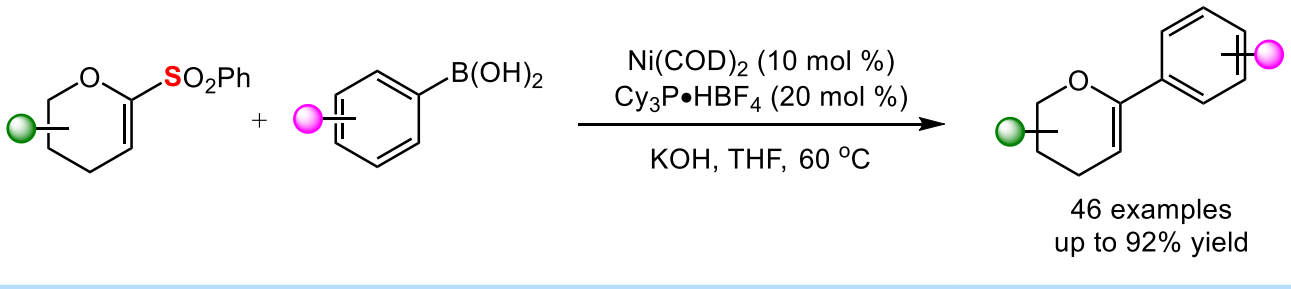


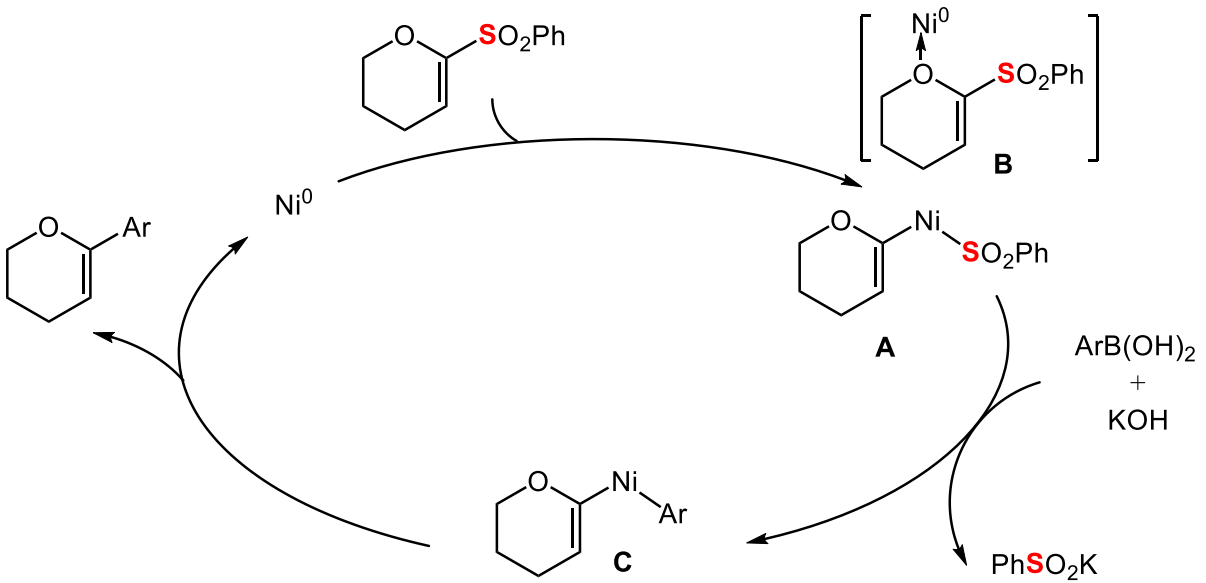


Sang, R.; Ritter, T. *Angew. Chem. Int. Ed*. **2019**, *58*, 16161

Introduction

The Cleavage of Activated C-S Bonds (Sulfones)





Gong, L.; Niu, D. *J. Am. Chem. Soc*. **2019**, *141*, 7680

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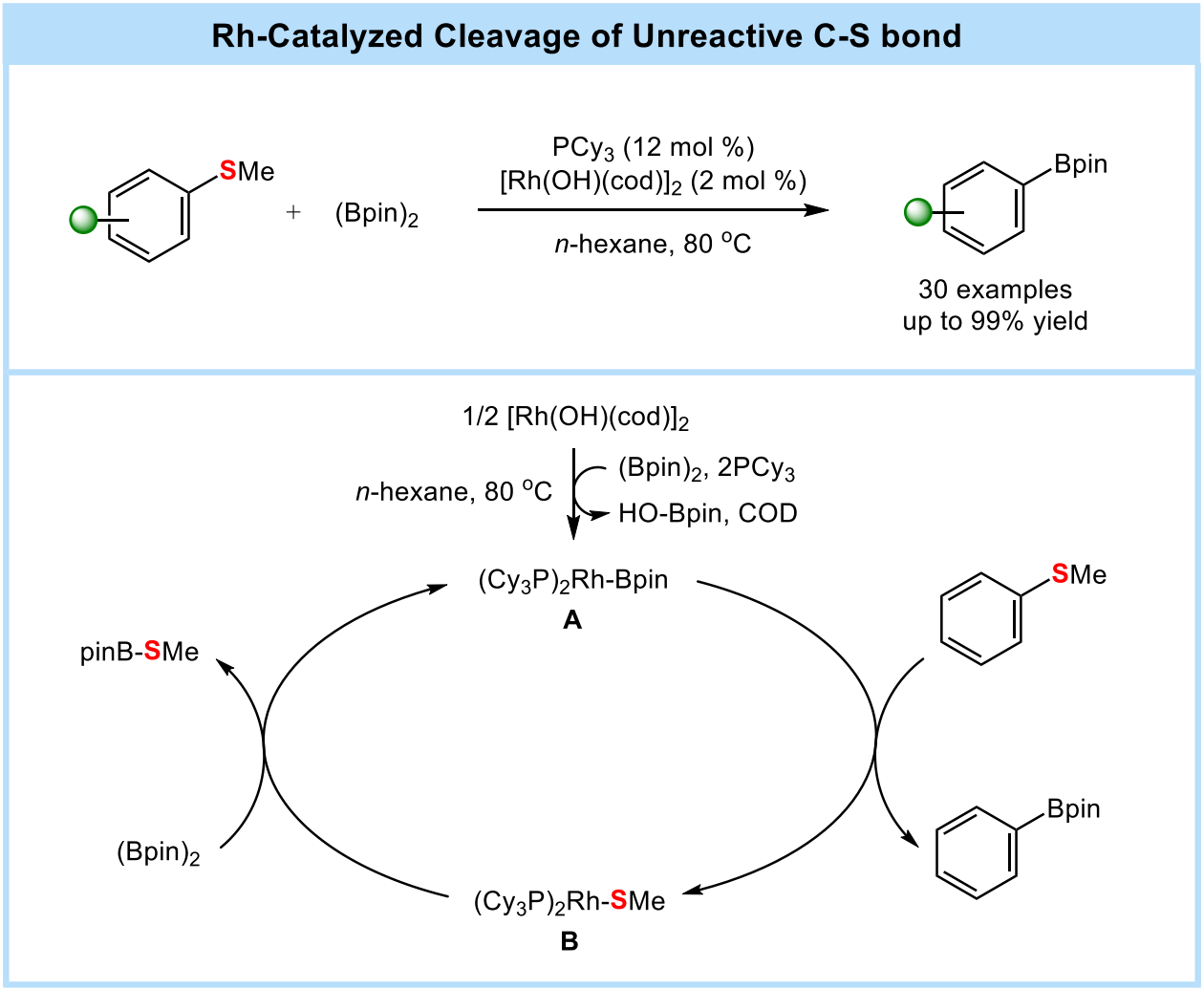
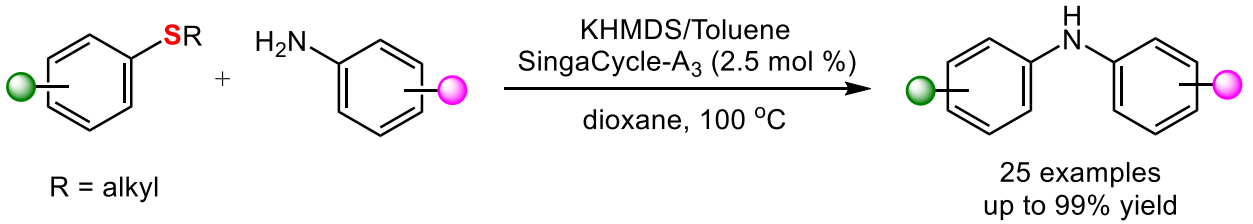


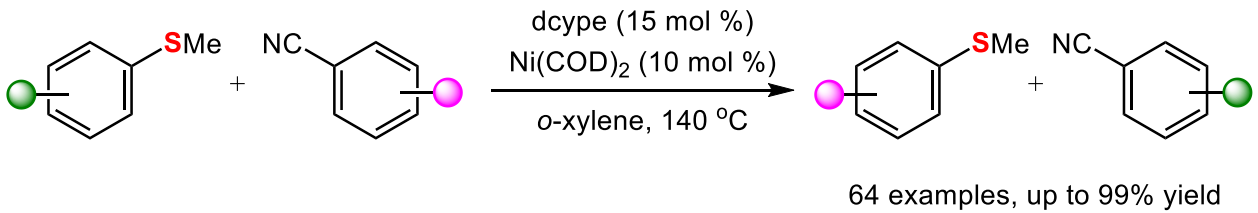
Uetake, Y.; Hosoya, T. *Org. Lett*. **2016**, *18*, 2758

Introduction

Pd-Catalyzed Cleavage of Unreactive C-S bond



Ni-Catalyzed Cleavage of Unreactive C-S bond



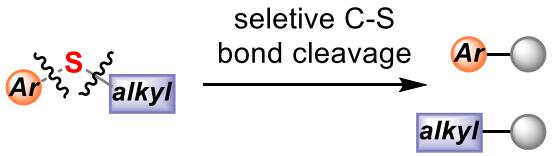
Sugahara, T.; Osuka, A. *Angew. Chem. Int. Ed*. **2014**, *53*, 9329
Delcaillau, T.; Morandi, B. *J. Am. Chem. Soc*. **2021**, *143*, 3723

Introduction

Transformations of Thioethers via C-S Bond Cleavage

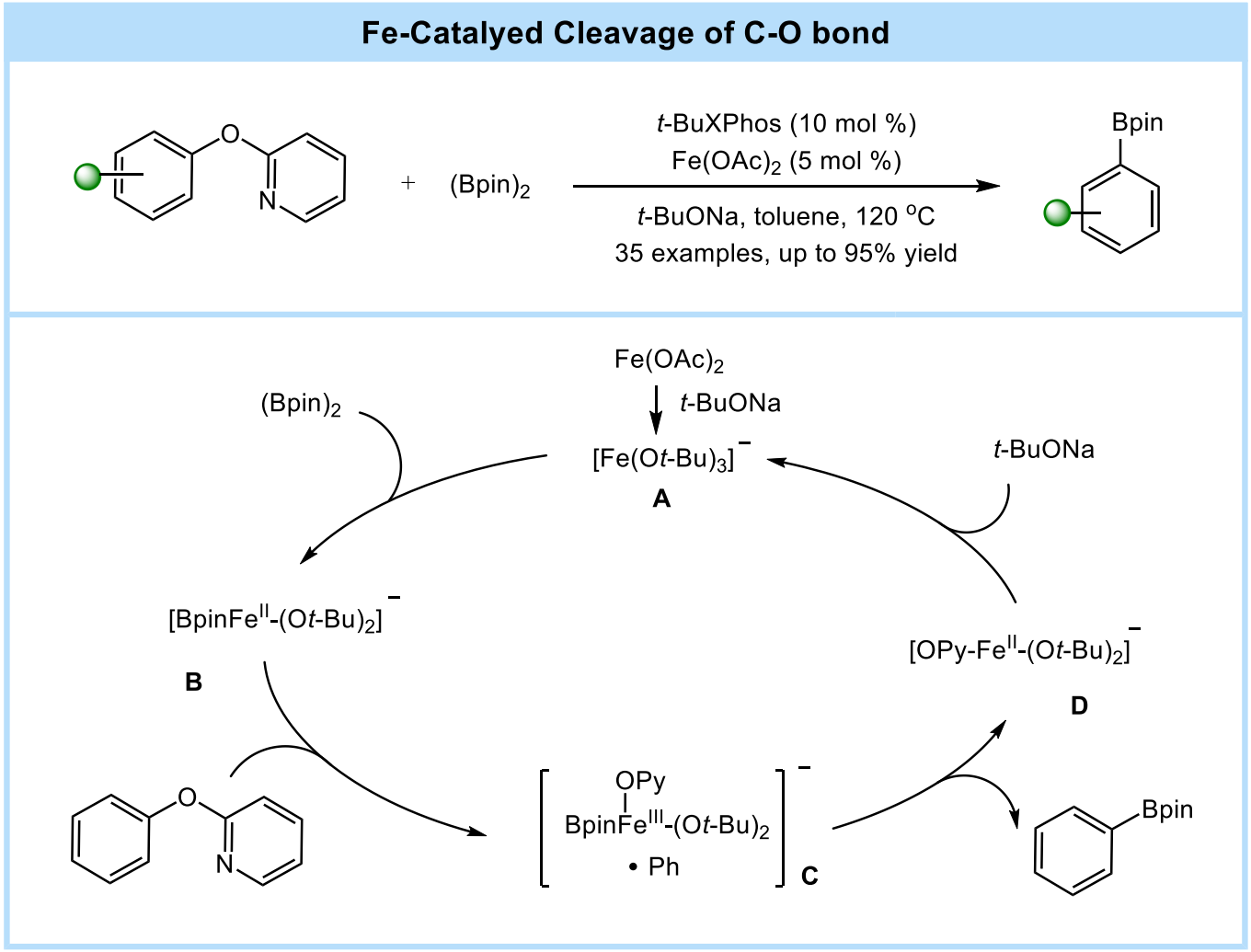
D) Direct transformation of thioethers for the C-Si formation

E) Using thioethers as dichotomous electrophiles



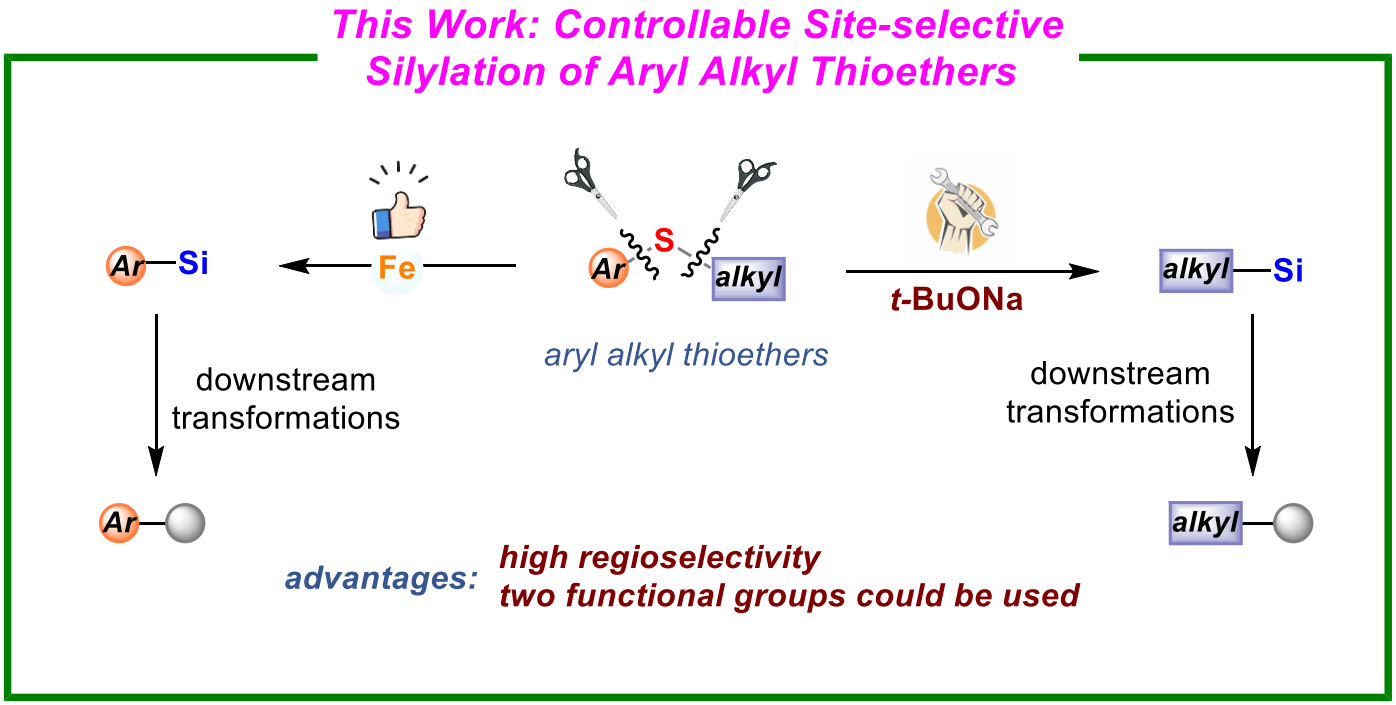
- Iron-catalyzed site-selective C-S bond cleavage of aryl alkyl sulfides
- Extremely challenging: strong dissociation energy of the C-S bond
  the uncontrollable reactivity of iron catalysis
- Iron-catalyzed site-selective C-S bond cleavage of aryl alkyl sulfides

Introduction

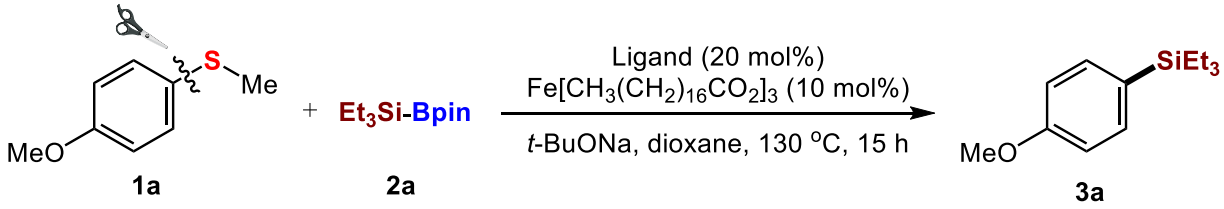


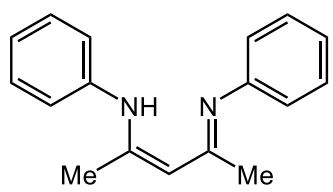
Zeng, X.; Feng, Z. *Org. Lett*. **2020**, *22*, 2950

Introduction

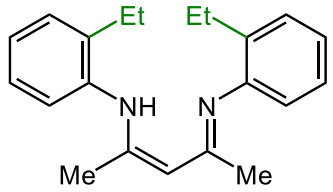


Optimization of Cyclopropanation Reaction

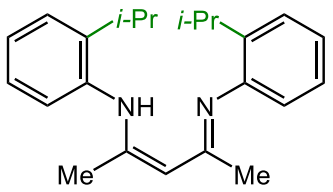




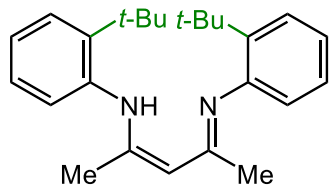
L1, 27%



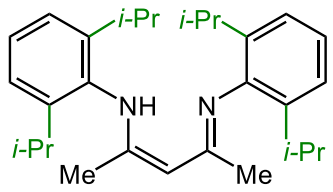
L2, 10%



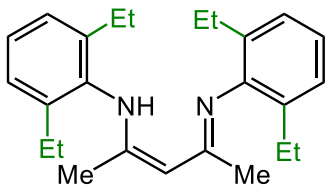
L3, 44%



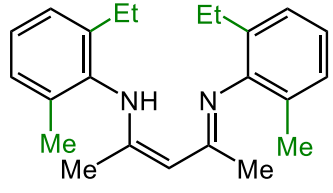
L4, 40%



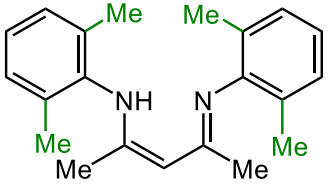
L5, trace



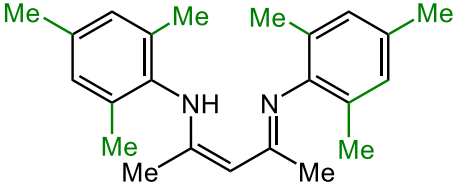
L6, 23%



L7, 62%



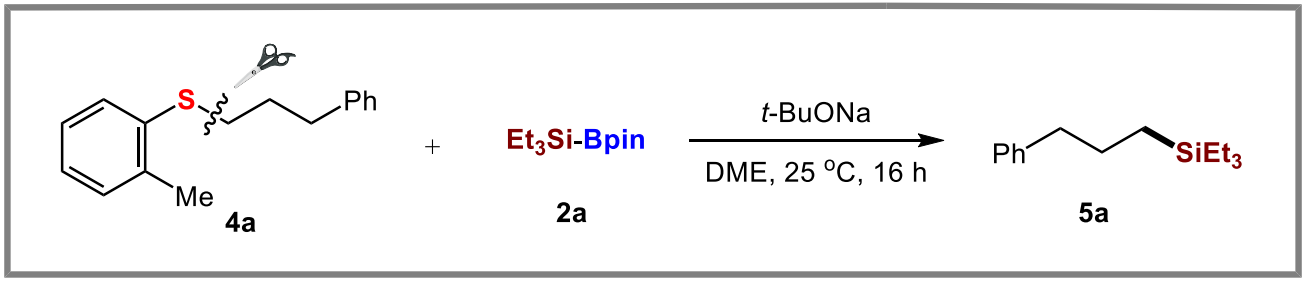
L8, 65%



L9, 84%[b]

[a]Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), **2a** (0.9 mmol, 4.5 equiv), $Fe[CH_3(CH_2)_{16}CO_2]_3$ (0.02 mmol, 0.1 equiv), ligand (0.04 mmol, 0.2 equiv), *t*-BuONa (0.5 mmol, 2.5 equiv), dioxane (1.0 mL), 130 °C, 15 h. [b]Dioxane (2.0 mL).

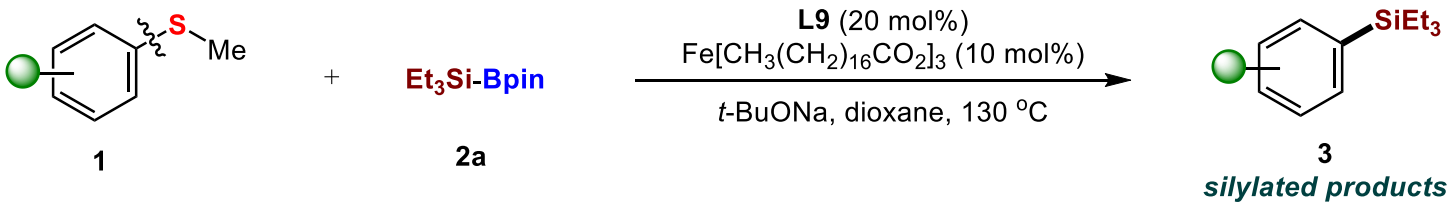
Optimization of Cyclopropanation Reaction



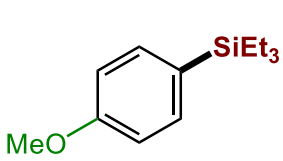
Entry[a]	[Fe]/ligand	base	Yield
1[b]	$Fe(OTf)_2$/**L9**	*t*-BuONa	96%
2	without	*t*-BuONa	99%
3	without	*t*-BuOK	54%
4	without	*t*-BuOLi	nd
5	without	MeOK	8%
6	without	MeONa	38%
7	without	MeOLi	nd
8	without	K_2CO_3	nd
9	without	NaOH	nd

[a]Reaction conditions: **4a** (0.2 mmol, 1.0 equiv), **2a** (0.45 mmol, 2.25 equiv), base (0.8 mmol, 4.0 equiv), DME (1.0 mL), 25 °C, 16 h. [b]**4a** (0.2 mmol, 1.0 equiv), **2a** (0.5 mmol, 2.5 equiv), $Fe(OTf)_2$ (0.02 mmol, 0.1 equiv), **L9** (0.04 mmol, 0.2 equiv), base (0.8 mmol, 4.0 equiv), DME (1.0 mL), 130 °C, 16 h.

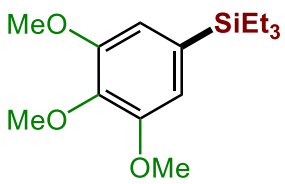
Substrate Scope



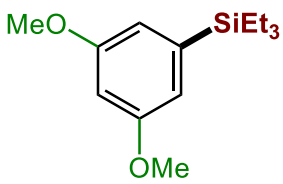
Substrates Scope



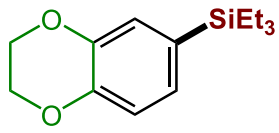
3a, 75%



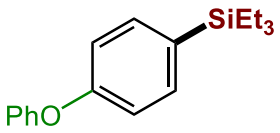
3b, 62%



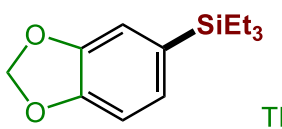
3c, 93%



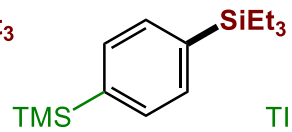
3d, 85%



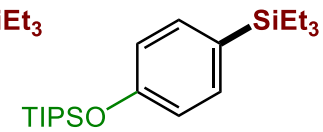
3e, 51%



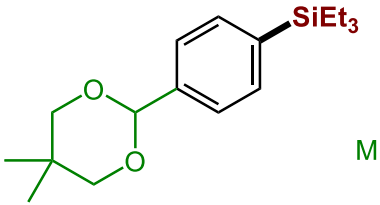
3f, 67%



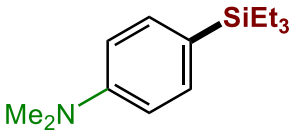
3g, 69%



3h, 75%



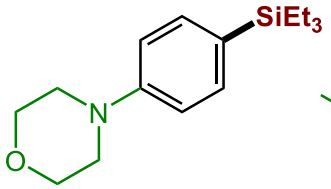
3i, 73%



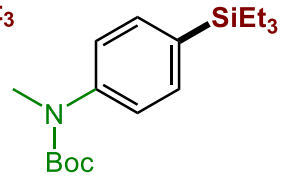
3j, 85%

Substrate Scope

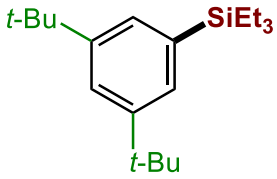
Substrates Scope



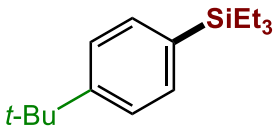
3k, 97%



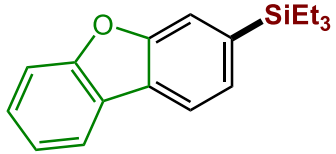
3l, 83%



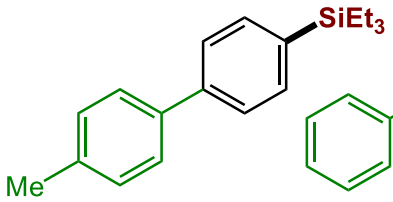
3m, 92%



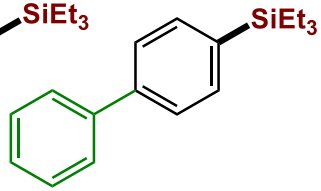
3n, 91%



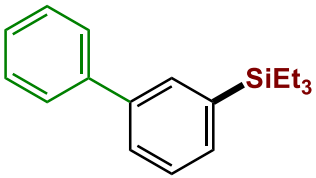
3o, 54%



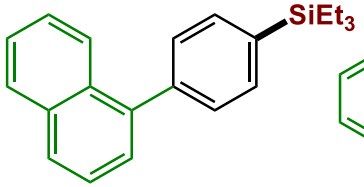
3p, 68%



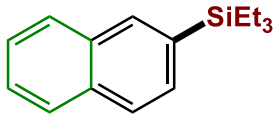
3q, 60%



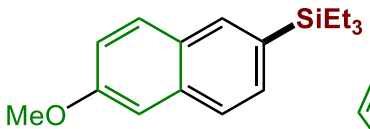
3r, 58%



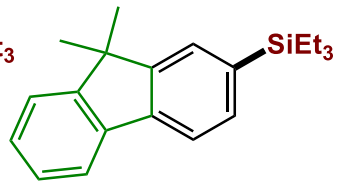
3s, 53%



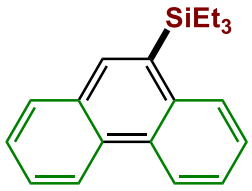
3t, 58%



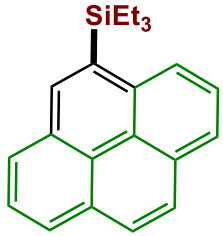
3u, 53%



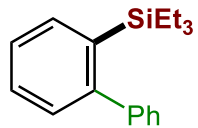
3v, 50%



3w, 70%

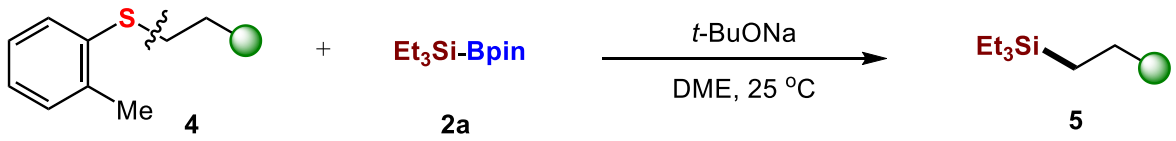


3x, 53%

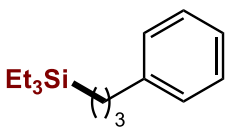


3y, 44%

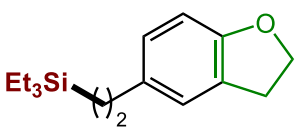
Substrate Scope



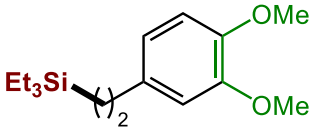
Substrates Scope



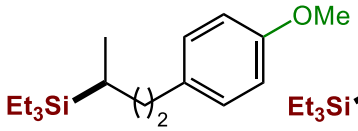
5a, 98%



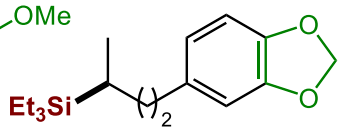
5b, 64%



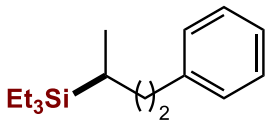
5c, 98%



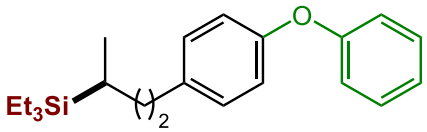
5d, 53%



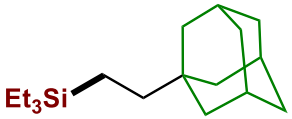
5e, 50%



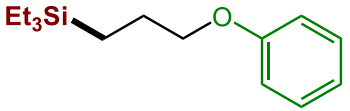
5f, 64%



5g, 56%

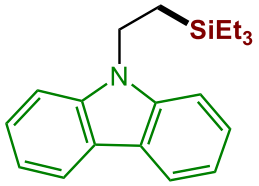


5h, 91%

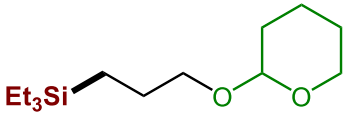


5i, 93%

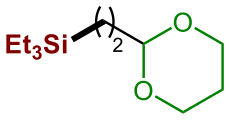
5j, 60%



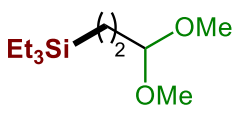
5k, 40%



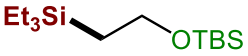
5l, 98%



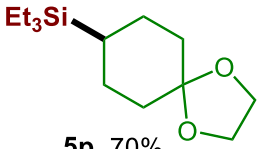
5m, 95%



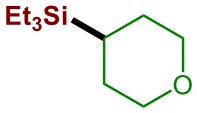
5n, 98%



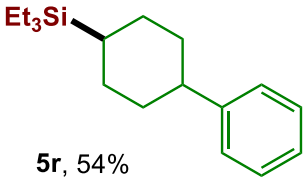
5o, 88%



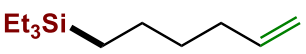
5p, 70%



5q, 79%



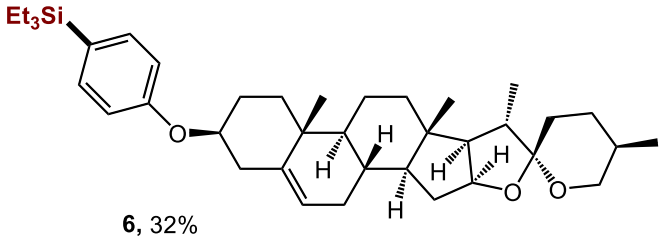
5r, 54%



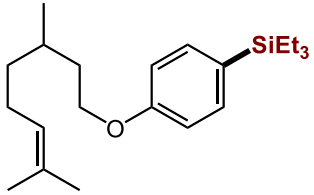
5s, 56%

Applications in Biomolecules

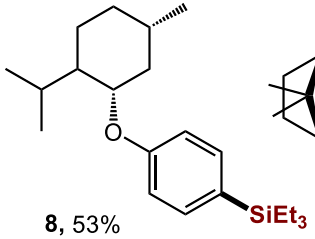
Applications in Biomolecules



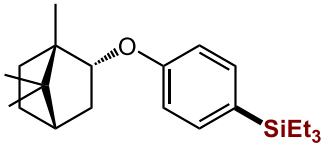
6, 32%
(from Diosgenin)



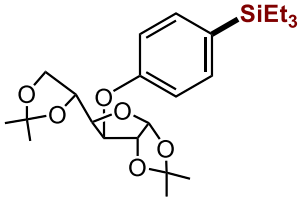
7, 69%
(from Citronellol)



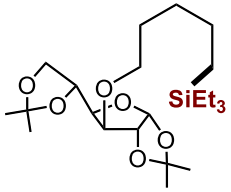
8, 53%
(from (+)-Menthol)



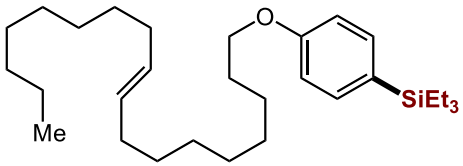
9, 53%
(from *L*-Borneol)



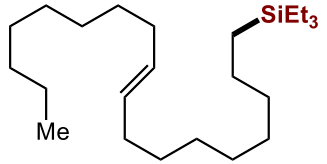
10, 55%
(from *Diacetone-D-glucose*)



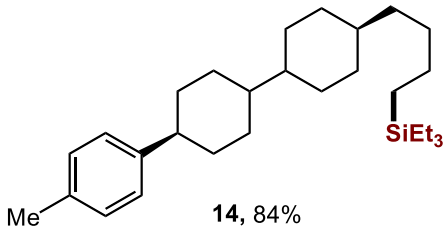
11, 47%
(from *Diacetone-D-glucose*)



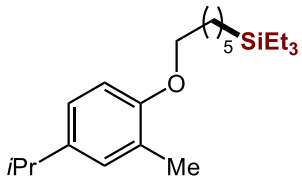
12, 67%
(from *Oleyl alcohol*)



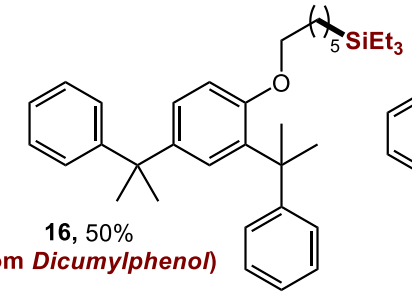
13, 92%
(from *Oleyl alcohol*)



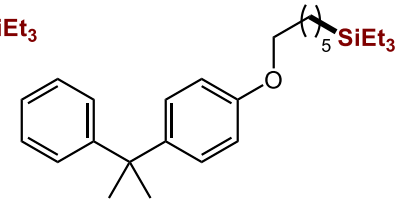
14, 84%
(from *liquid crystal building block*)



15, 87%
(from *Carvacrol*)



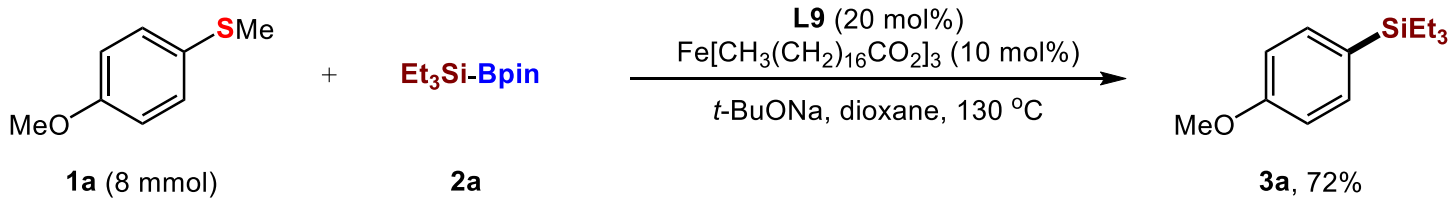
16, 50%
(from *Dicumylphenol*)



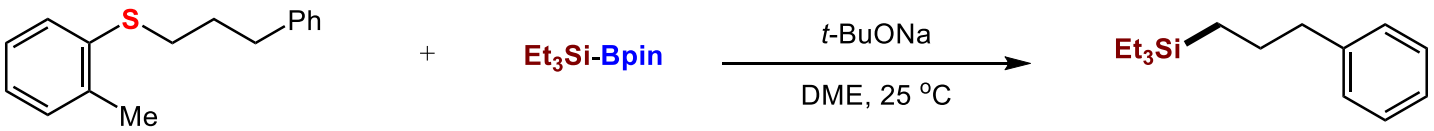
17, 76%
(from *Cumylphenol*)

Scale-up Reactions

Scale-up Reactions



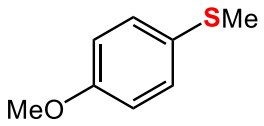
1a (8 mmol) **2a** **3a**, 72%



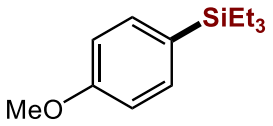
4a (6 mmol) **2a** **5a**, 96%

Experimental Mechanistic Studies

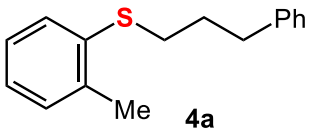
Radical Inhibition Experiments



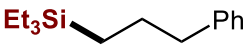
1a + Et_3Si-Bpin (**2a**) —*standard reaction conditions*, Fe, TEMPO (1.0 equiv)→



3a, 75%

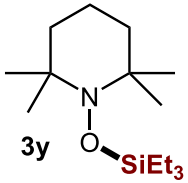


4a + Et_3Si-Bpin (**2a**) —*standard reaction conditions*, TEMPO (2.0 equiv)→



5a, 0%

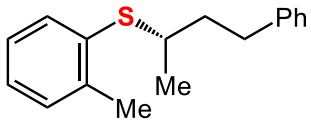
Et_3Si-Bpin (**2a**) —TEMPO (2.0 equiv), *t*-BuONa, DME, 25 °C→



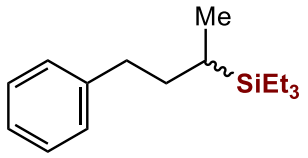
3y

HRMS(ESI): $C_{15}H_{34}ONSi$ (M+H), 272.2399

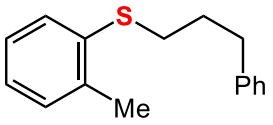
The Radical Pathway



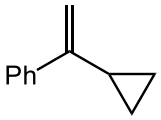
4f' (ee = 62%) + Et_3Si-Bpin (**2a**) —*t*-BuONa, DME, 25 °C→



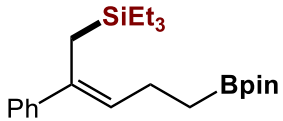
5f, 72% (ee = 6%)



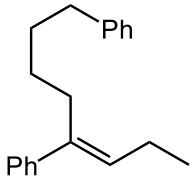
4a +



18 —Et_3Si-Bpin, *t*-BuONa, DME, 25 °C→



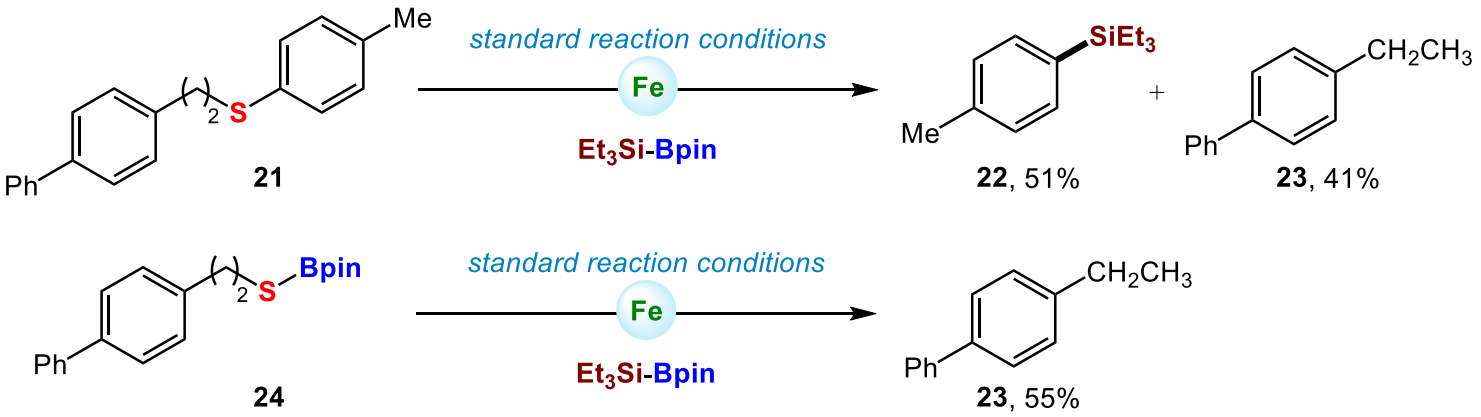
19, 89%



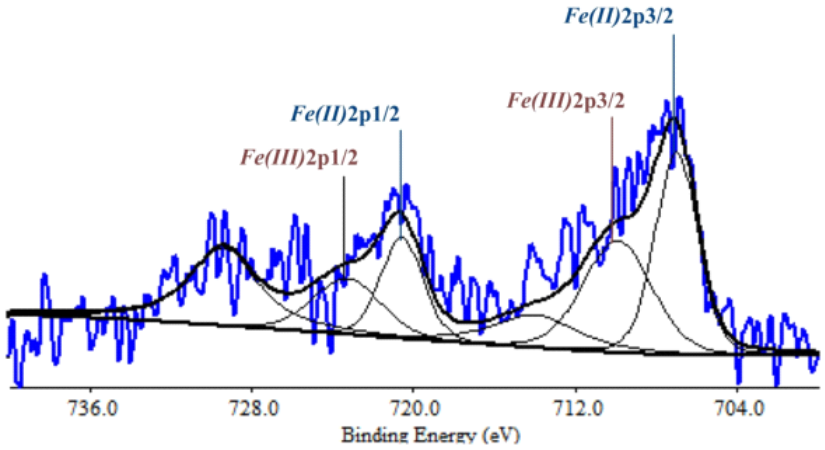
20, 0%

Experimental Mechanistic Studies

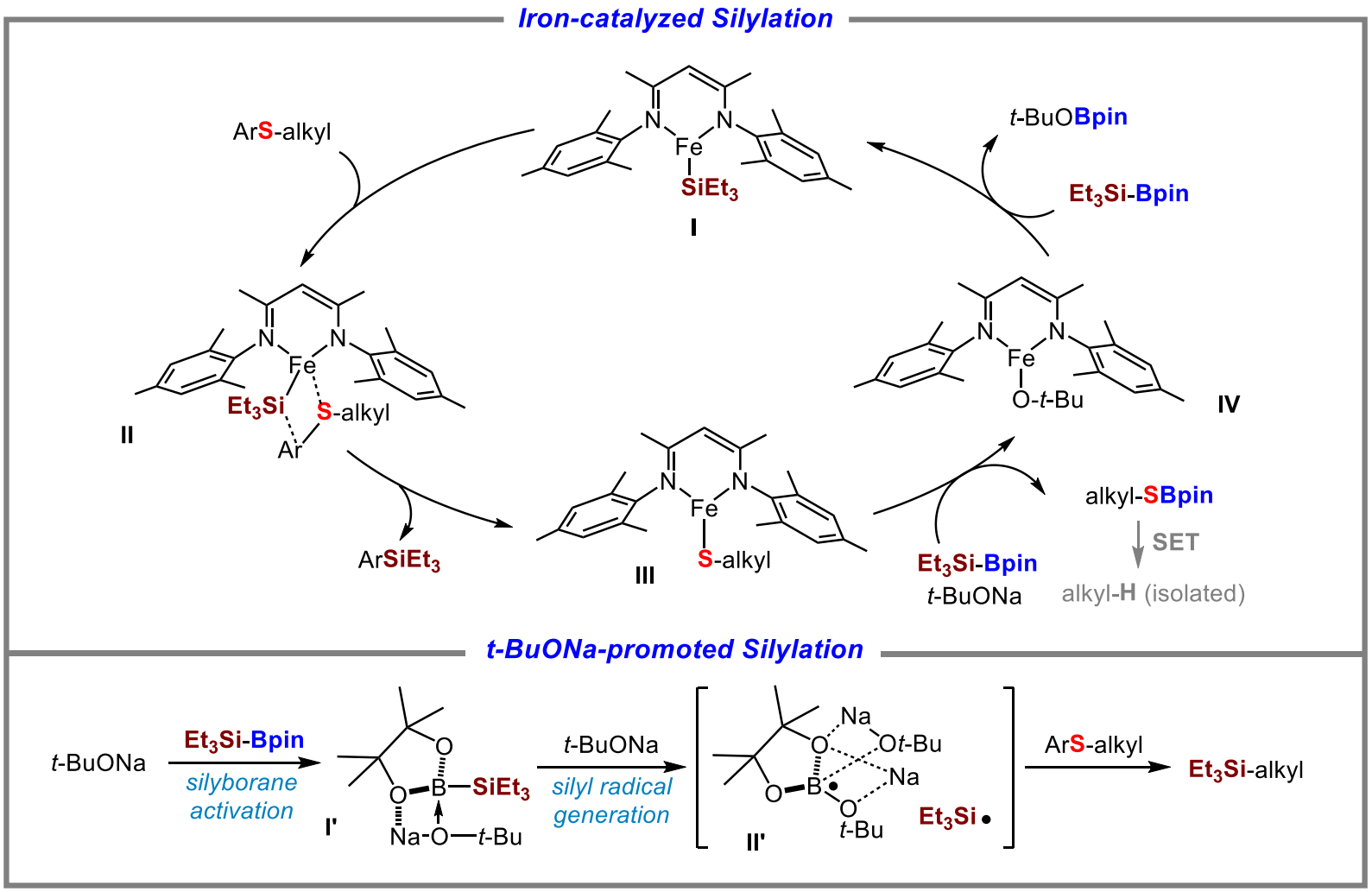
Determination of Possible Intermediates



XPS Experiments

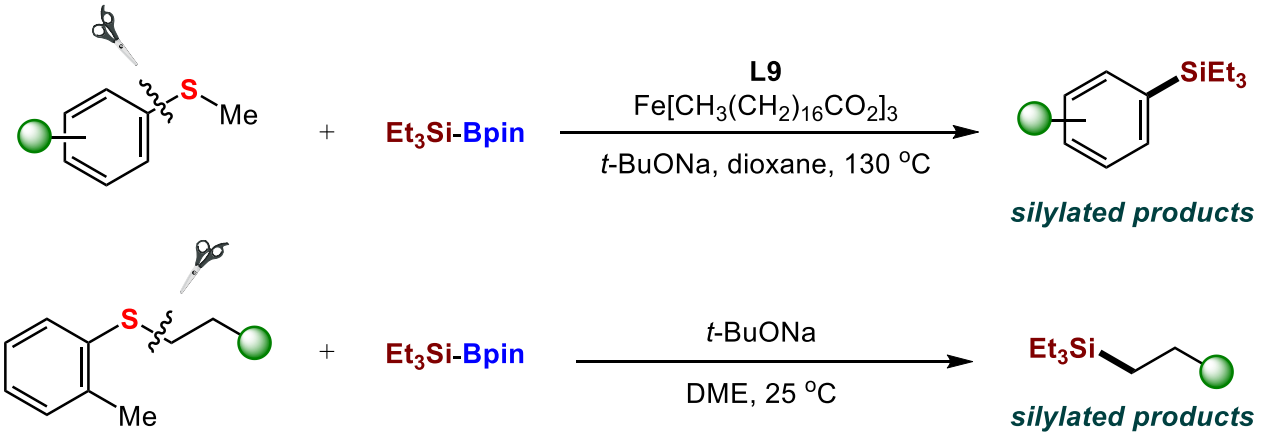


Proposed Mechanism



Summary

Controllable Site-selective Silylation of Aryl Alkyl Thioethers



- 57 Examples, excellent chemoselectivity
- Complement noble metal-catalyzed silylation of C-S bonds
- Offer new insights into the unique reactivity of iron catalysis
- Providing good opportunities for applications in drug development

Writing Strategy

☐ The First Paragraph

Importance of aryl alkyl sulfides

↓

Limitations of cleavage C-S bonds

↓

Challenge

- ✓ **Aryl alkyl sulfides are widely found in natural products, pharmaceutical molecules and materials. Many aryl alkyl sulfides are commercially available, enabling them as good substrates in synthesis.**
- ✓ **However, the strong affinity of sulfur atoms with metals significantly hinders the transformation of sulfides under transition metal catalysis. To address this issue, unreactive sulfides are always converted to active sulfonium salts and sulfoxides, which then perform downstream transformations.**
- ✓ **The C(aryl)-S bonds in aryl alkyl sulfides are usually preferentially cleaved, while the cleavage of the C(alkyl)-S bonds has been scarcely reported. Site-selective cleavage of the C-S bonds in aryl alkyl sulfides remains a long-standing challenge.**

Writing Strategy

☐ The Last Paragraph

Summary of this work

Advantages of the current method

Outlook of this work

- ✓ **In summary, we have developed iron-catalyzed and transition-metal-free site-selective silylation of aryl alkyl sulfides using the silylborane reagent as the silicon source.**
- ✓ **The silylation of C(aryl)-S and C(alkyl)-S bonds shows good efficiency, affording the corresponding silylated products with excellent chemoselectivity. Moreover, this protocol exhibits good functional group tolerance and enables the late-stage silylation of bioactive compounds, thus providing good opportunities for applications in drug discovery and development.**
- ✓ **These transformations can complement noble metal-catalyzed silylation of C-S bonds and also offer new insights into the unique reactivity of iron catalysis. Further studies are ongoing in our laboratory to understand the mechanisms of these reactions.**

Representative Examples

Radical clock experiments further demonstrated the radical nature of the C(alkyl)-S bond silylation, yielding the ring-opening silylated product instead of the alkylated product. (demonstrate：显示，证明；可替换近义词：prove, indicate, display, confirm, verify, illustrate)

To gain insight into the mechanism of the silylation of aryl alkyl sulfides, the radical inhibition experiments were first investigated using TEMPO as a radical scavenger. (为了深入了解)

In the C(alkyl)-S bond silylation reaction silylborane reagent was activated by using *t*-BuONa to yield complex I', which was then triggered by the additional *t*-BuONa to generate the silyl radical *via* a single-electron transfer process. (trigger：触发，引起)

Thanks
for your attention