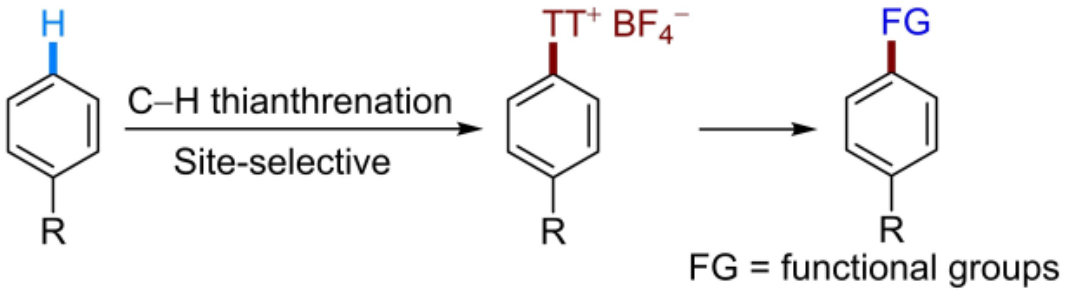
THE YANG
RESEARCH GROUP

Late-Stage Aromatic Functionalization via Aryl Sulfonium Salts



Lili Zhang

2022.12.9

Author Introduction

Tobias Ritter

2015-至今 教授，德国马克斯普朗克煤炭研究所；

2006 – 2015 助理教授，副教授，教授，哈佛大学；

2004 – 2006 博士后，加州理工学院，**Robert H. Grubbs**教授；

2004 博士，瑞士苏黎世联邦理工学院，**Erick M. Carreira**教授；

1999 硕士，德国布伦瑞克工业大学；

1975 出生于德国。

- 有机氟化学
- 复杂分子的后期官能化

Research Topics:

- Late-Stage Functionalization
- Late-Stage Fluorination
- Unappreciated redox reactivity of palladium

THE YANG RESEARCH GROUP

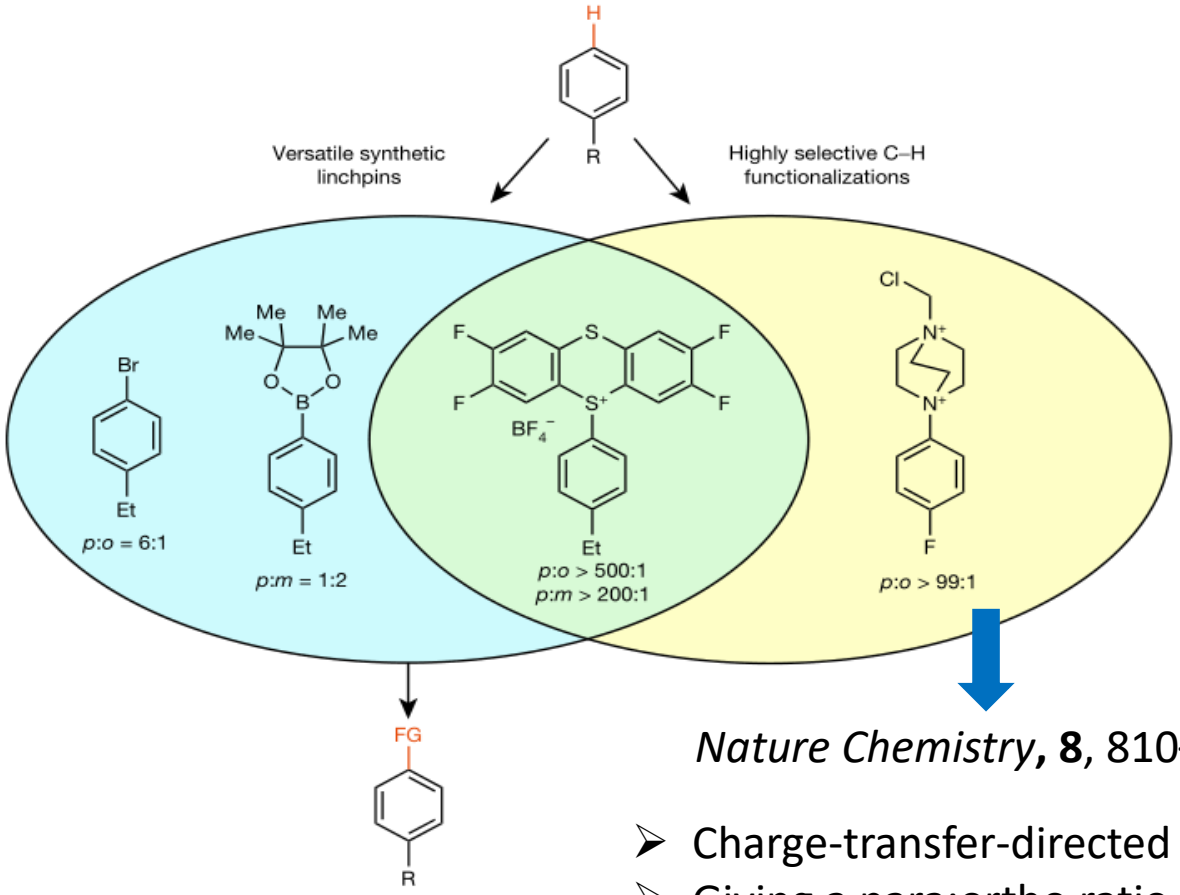
目 录

1. 背景

Site-selective and versatile aromatic C–H functionalization by thianthrenation

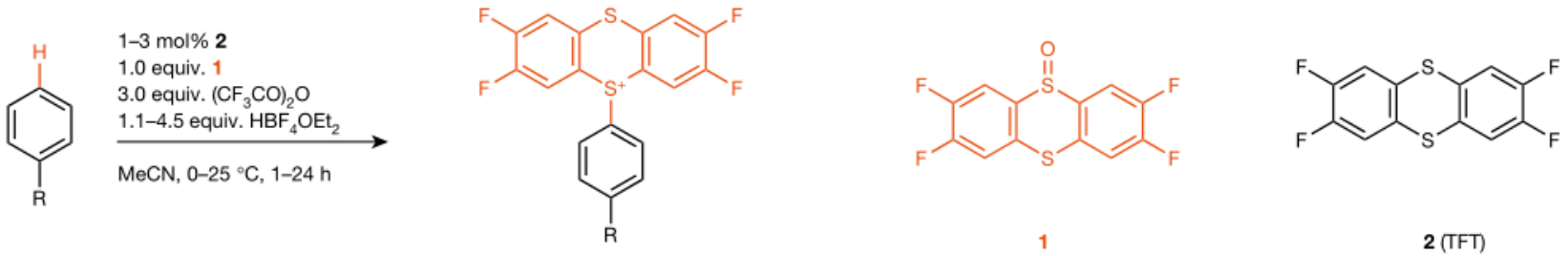
Nature.2019, 567, 223–228

Florian Berger[1], Matthew B. Plutschack[1], Julian Riegger[1], Wanwan Yu[1], Samira Speicher[1], Matthew Ho[1], Nils Frank[1] & Tobias Ritter[1]*



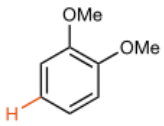
Nature Chemistry, **8**, 810–815 (2016)

- Charge-transfer-directed radical substitution;
- Giving a para:ortho ratio of p:o > 99:1;
- Aryl-TEDAs are of low synthetic value.

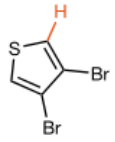


1

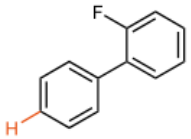
2 (TFT)



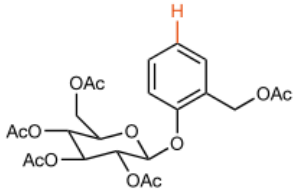
3
76%[a]



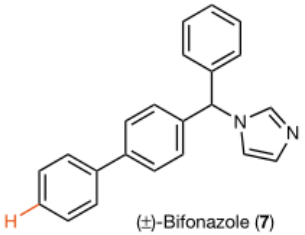
4
68%



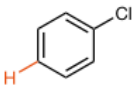
5
85%



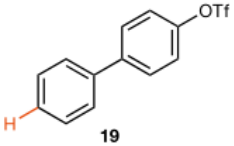
Salicin pentaacetate (**6**)
94%[b]



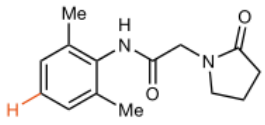
(±)-Bifonazole (**7**)
87%[c]



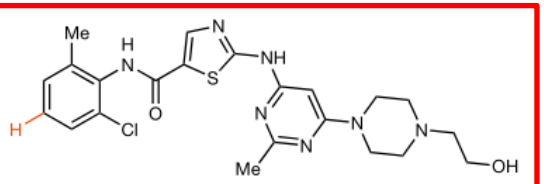
18
86%[c]



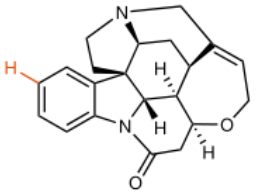
19
66%



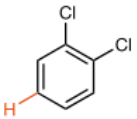
Nefiracetam (**20**)
63%[b]



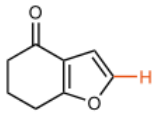
Dasatinib (**21**)
80%[c]



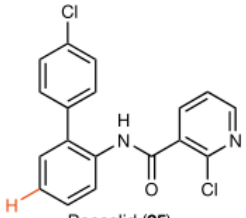
Strychnine (**22**)
64%



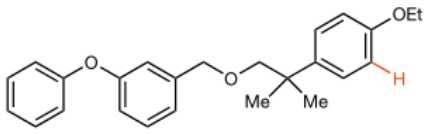
23
20%[c]



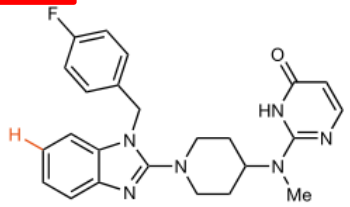
24
64%



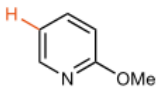
Boscalid (**25**)
95%



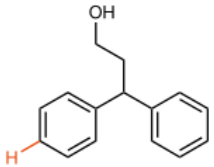
Etofenprox (**26**)
84%[a]



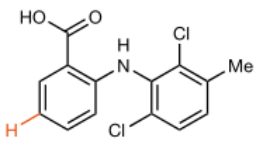
Mizolastine (**27**)
62%[g]



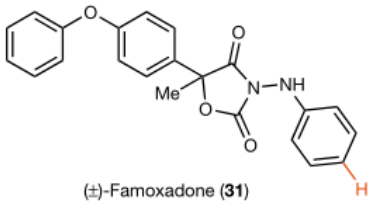
28
87%[e]



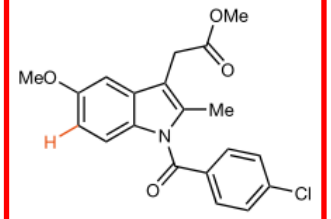
29
76%[f]



Meclofenamic acid (**30**)
87%[a]

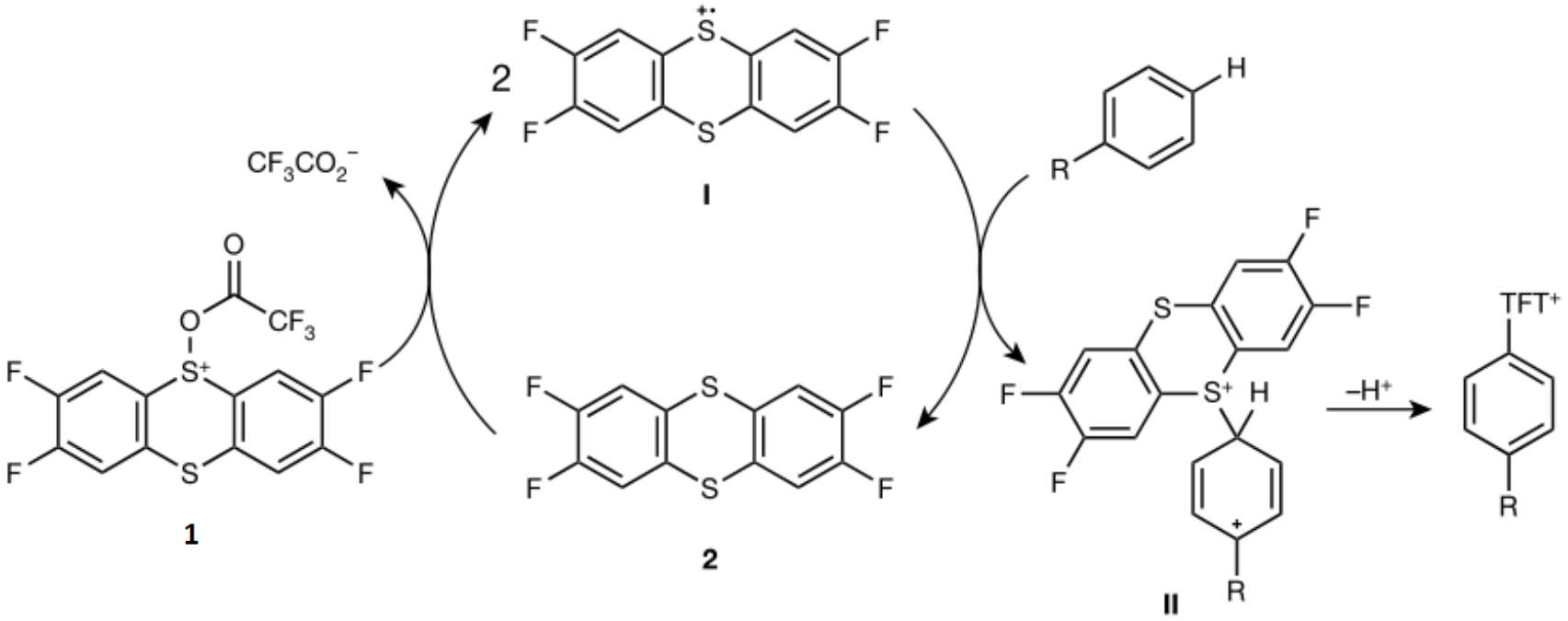


(±)-Famoxadone (**31**)
81%[a]

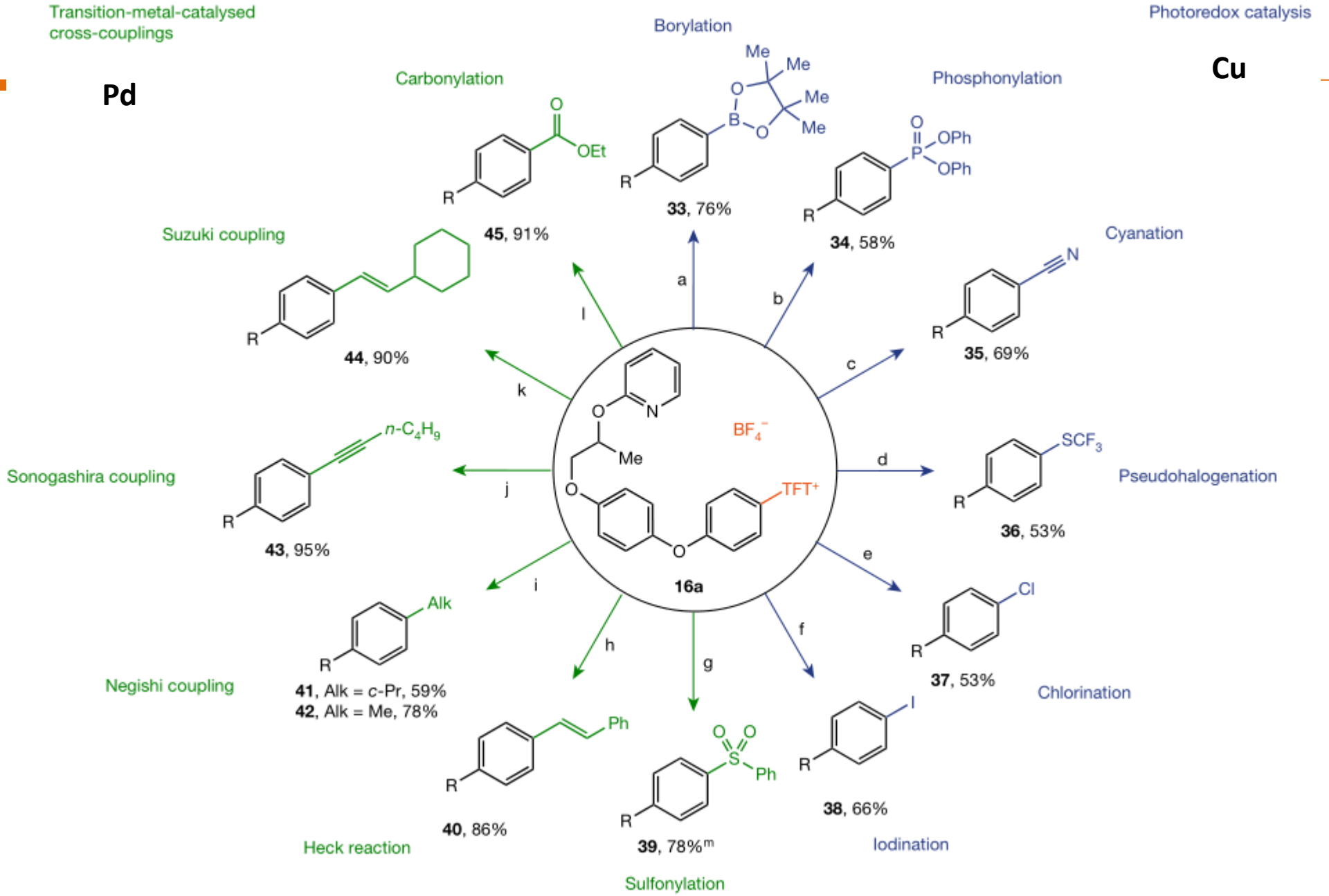


Indometacin methylester (**32**)
85%[a]

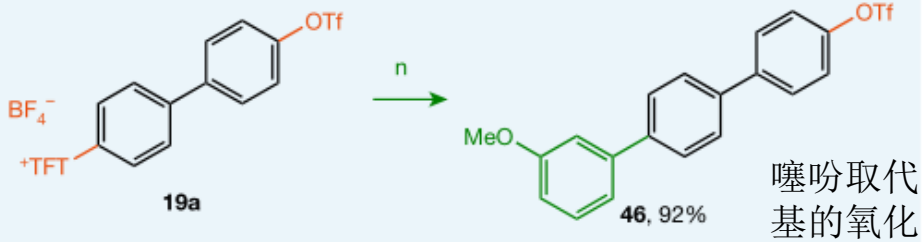
Proposed Mechanism



1. TFT 氧化物1和TFT 2歧化产生自由基阳离子
2. 自由基加成生成过渡态II
3. II歧化或II被I单电子氧化后脱质子化


Transition-metal-catalysed cross-couplings
Pd
Photoredox catalysis
Cu
Borylation
Carbonylation
Phosphonylation
Suzuki coupling
Cyanation
Sonogashira coupling
Pseudohalogenation
Negishi coupling
Chlorination
Heck reaction
Iodination
Sulfonylation
45, 91%
33, 76%
34, 58%
44, 90%
35, 69%
43, 95%
36, 53%
41, Alk = c-Pr, 59%
42, Alk = Me, 78%
37, 53%
40, 86%
39, 78%m
38, 66%
16a
BF4−
TFT+
a
b
c
d
e
f
g
h
i
j
k
l

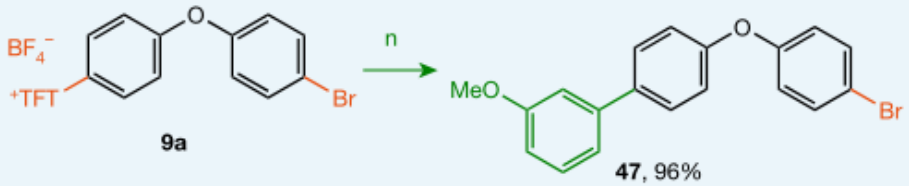
Competition with (pseudo-) halides in Suzuki coupling



19a

46, 92%

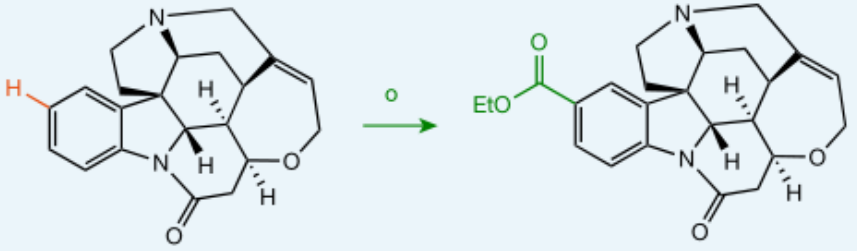
噻吩取代基的氧化加成更快



9a

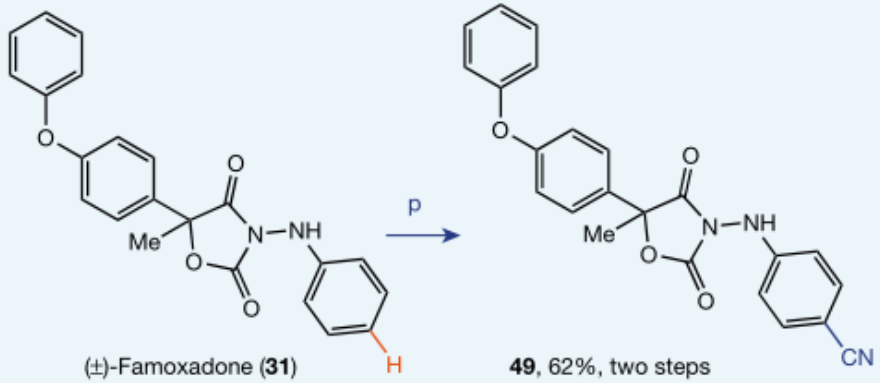
47, 96%

Functional-group tolerance



Strychnine (**22**)

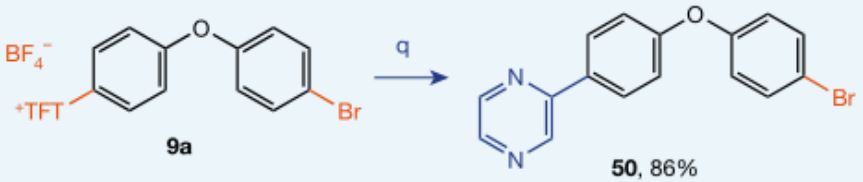
48, 48%, two steps



(±)-Famoxadone (**31**)

49, 62%, two steps

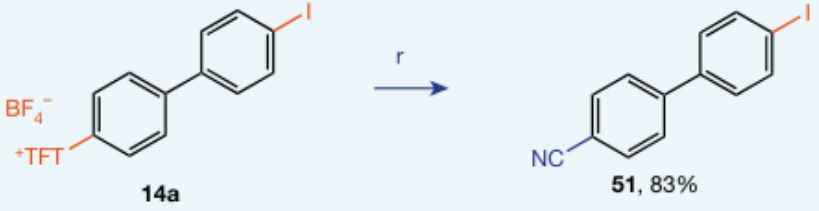
Minisci-type C–H arylation



9a

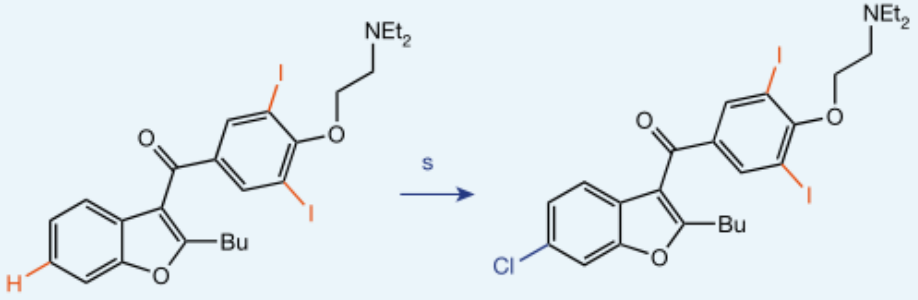
50, 86%

Competition with aryliodides in photoredox catalysis



14a

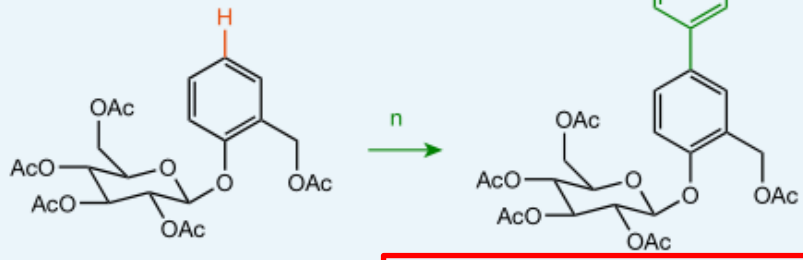
51, 83%



Amiodarone (**12**)

52, 50%, two steps

Scalability (25 g scale)



Salicin pentaacetate (**6**)

53, 75%, two steps, **2** (TFT) recovered: 76%

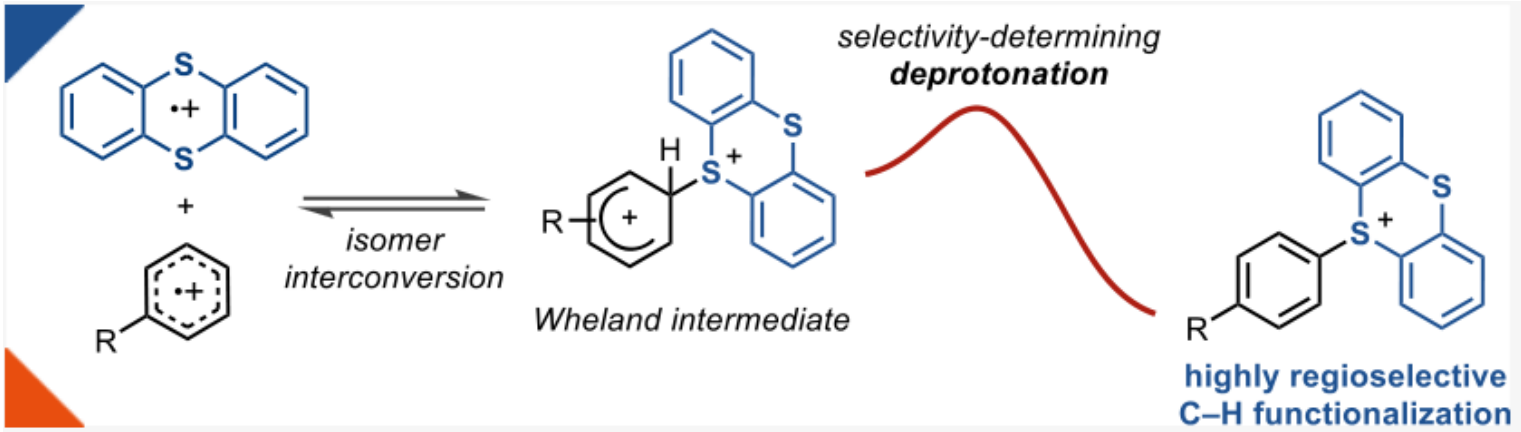
1. 背景

JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
J. Am. Chem. Soc. 2021, 143, 16041−16054
pubs.acs.org/JACS
Article

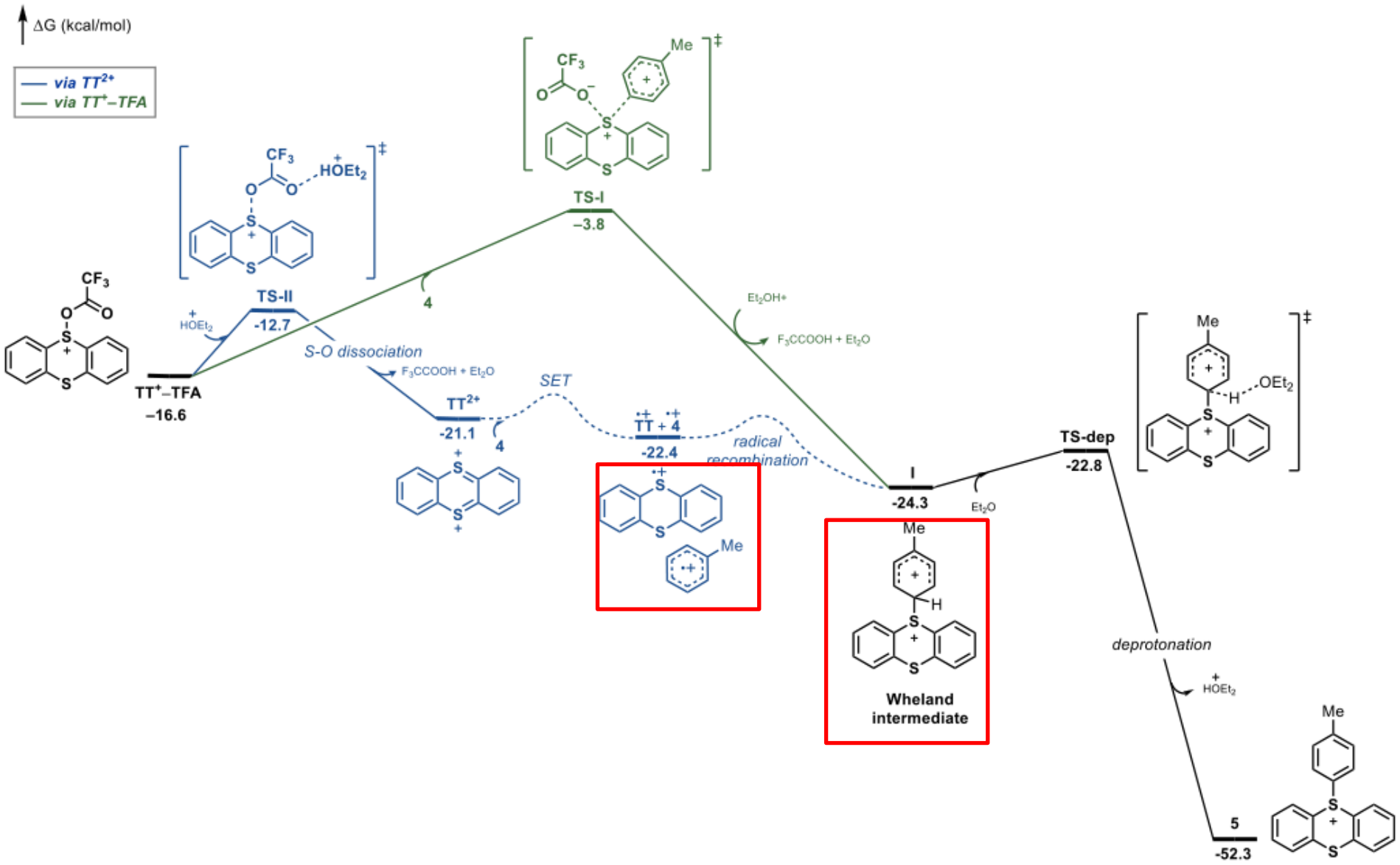
High Site Selectivity in Electrophilic Aromatic Substitutions: Mechanism of C−H Thianthrenation

Fabio Juliá,[§] Qianzhen Shao,[§] Meng Duan,[§] Matthew B. Plutschack, Florian Berger, Javier Mateos, Chenxi Lu, Xiao-Song Xue, K. N. Houk,* and Tobias Ritter*

Cite This: J. Am. Chem. Soc. 2021, 143, 16041−16054
Read Online



在不可逆脱质子化之前，不同的惠兰型中间体的
可逆相互转化是高区域选择性的原因


ΔG (kcal/mol)
via TT2+
via TT+–TFA
TT+–TFA
–16.6
TS-II
-12.7
TS-I
–3.8
TT2+
-21.1
TT + 4
-22.4
I
-24.3
TS-dep
-22.8
5
-52.3
4
S-O dissociation
SET
radical recombination
deprotonation
F3CCOOH + Et2O
Et2OH+
Et2O
Wheland intermediate

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目 录

- 背景
- 光参与的芳基硫盐的官能化反应
- 无光参与的芳基硫盐的官能化反应
- 其他课题组的相关工作
- 总结与展望

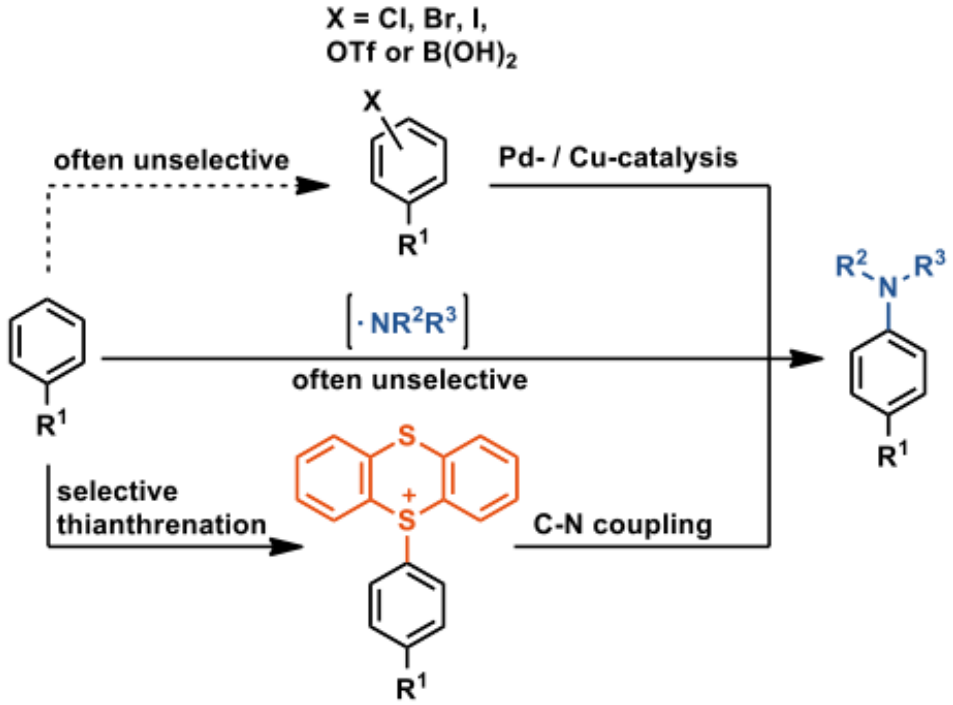
2. 光参与的芳基硫盐的官能化反应

J. Am. Chem. Soc. 2019, 141, 13346−13351

JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
Cite This: J. Am. Chem. Soc. 2019, 141, 13346−13351
pubs.acs.org/JACS

C−N Cross-Couplings for Site-Selective Late-Stage Diversification via Aryl Sulfonium Salts

Pascal S. Engl,‡ Andreas P. Häring,‡ Florian Berger, Georg Berger, Alberto Pérez-Bitrián, and Tobias Ritter*



传统方法：

Buchwald−Hartwig couplings

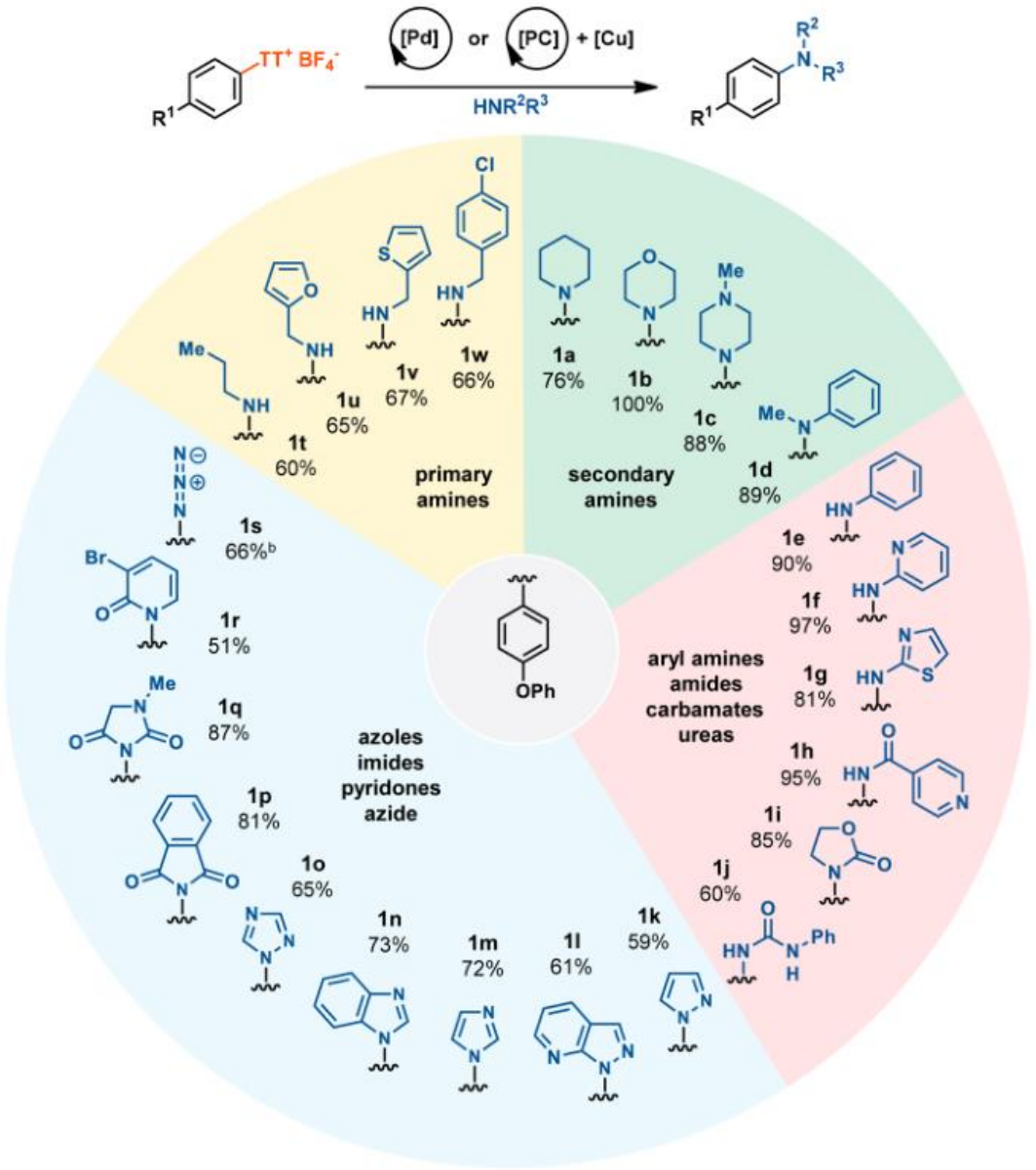
Ullmann-type couplings

Chan−Lam couplings

Minisci reaction

选择性差

Scope of Substrates



Method A

1 mol% $[Pd_2(dba)_3]$
2 mol% RuPhos
1.5 equiv. HNR^2R^3
2 eqiuv. Cs_2CO_3
DMF, 90 °C, 20 h

Method B

1 mol% $[(PdAlPhos)_2COD]$
1.5 equiv. HNR^2R^3
2 equiv. DBU
THF, 70 °C, 16 h

Method C

5 mol% $[Ru(bipy)_3](PF_6)_2$
1 equiv. $[Cu(MeCN)_4]BF_4$
3 equiv. HNR^2R^3
3 equiv. NMe_4OH or NaH
MeCN:DMSO (1:1)
blue LED (60W), 15 °C, 8 h

Method D

3 mol% $[Ir(ppy)_3]$
1 equiv. $[Cu(MeCN)_4]BF_4$
1.5 equiv. HNR^2R^3
2 equiv. K_2CO_3
MeCN, blue LED (60W)
15 °C, 8 h

- 伯烷基胺
- 仲烷基胺
- 芳基胺
- 酰胺
- 氨基酯类
- 含氮杂环

当量铜

2. 光参与的芳基硫盐的官能化反应

GDCh Communications Angewandte International Edition Chemie

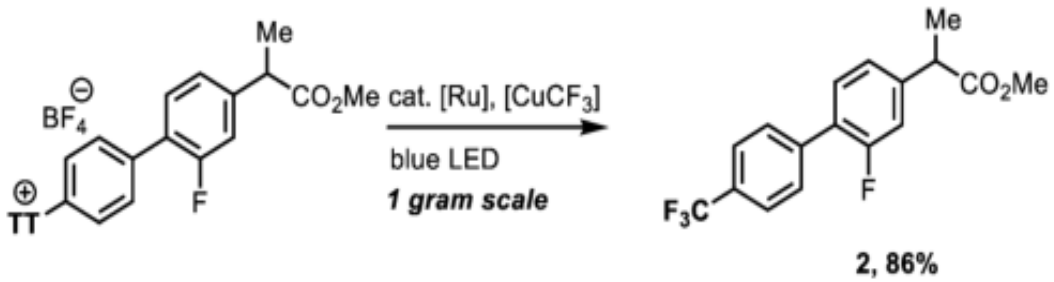
Trifluoromethylation

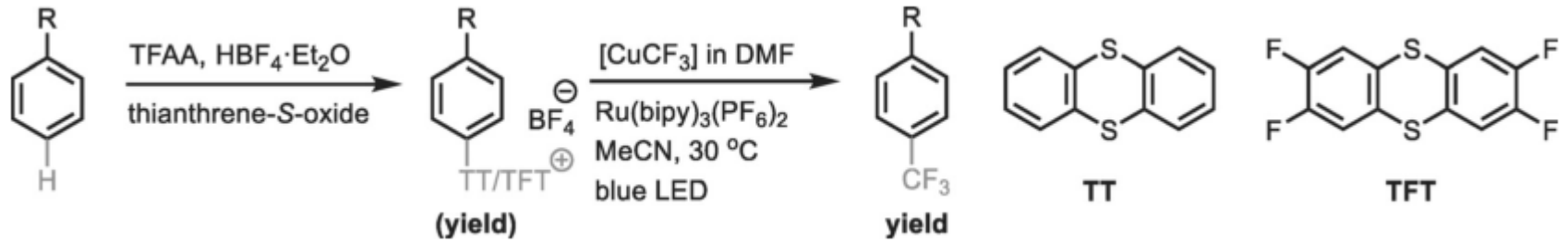
International Edition: DOI: 10.1002/anie.201906672
German Edition: DOI: 10.1002/ange.201906672

Aryl Sulfonium Salts for Site-Selective Late-Stage Trifluoromethylation

*Fei Ye, Florian Berger, Hao Jia, Joseph Ford, Alan Wortman, Jonas Börgel, Christophe Genicot, and Tobias Ritter**

Angew. Chem. Int. Ed. 2019, 58, 14615 –14619

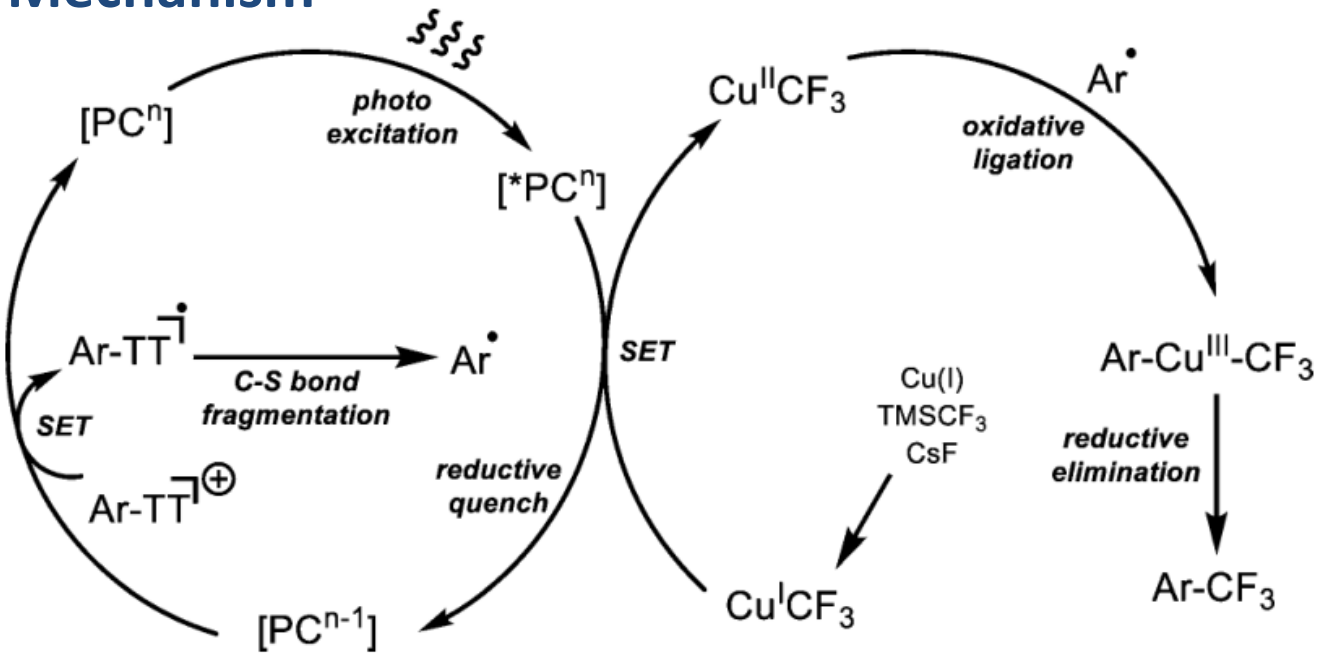




Reaction conditions for the second step:

CuSCN (1.5 equiv), CsF (2.0 equiv), TMSCF3 (1.5 equiv) in DMF (c = 0.3m) at 23℃ for 30 min, followed by addition of aryl (tetrafluoro)thianthrenium salts (0.2–0.3 mmol), Ru(bipy)3(PF6)2 (2 mol %) in MeCN (c = 0.2m), blue LED (34 W), 30℃, 3 h. 当量Cu

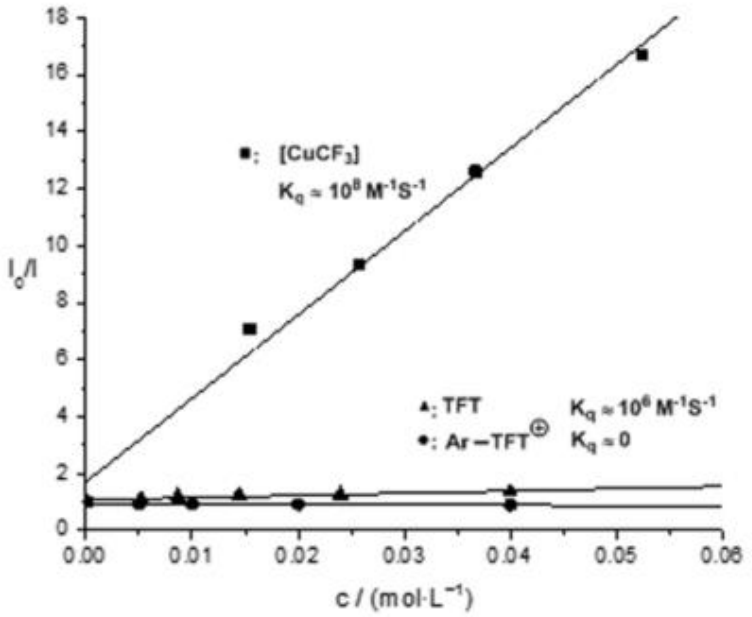
Proposed Mechanism



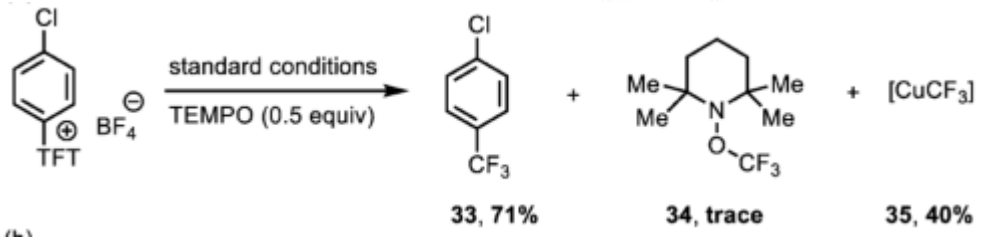
Mechanistic Investigation

- Stern–Volmer analysis

光激发的PC催化剂被
[CuCF3]试剂猝灭得更快



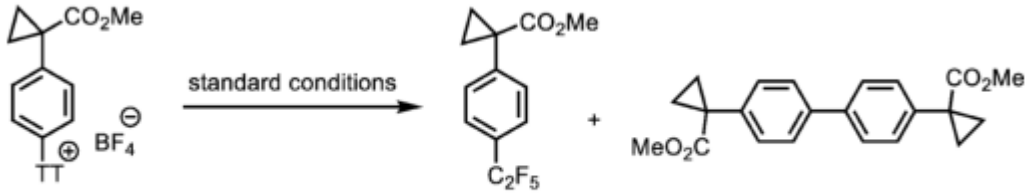
- TEMPO trapping experiments



33, 71% 34, trace 35, 40%

without TEMPO 33, 77%

- Biaryl formation from aryl thianthrenium salt



13, 66% 36, 14%

2. 光参与的芳基硫盐的官能化反应

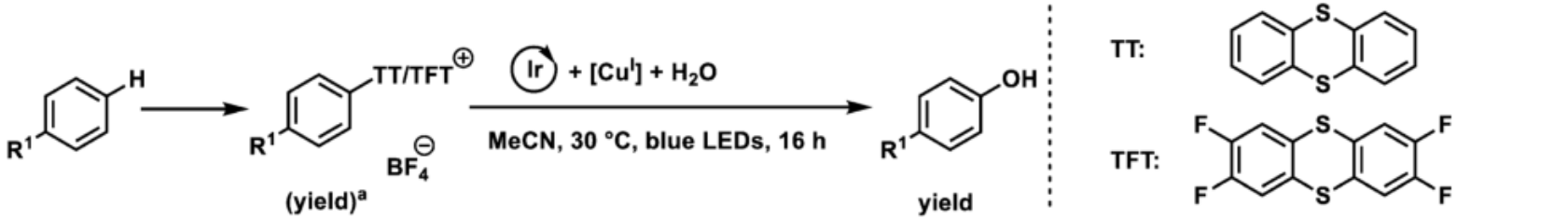
Angew. Chem. Int. Ed. 2019, 58, 16161 –16166

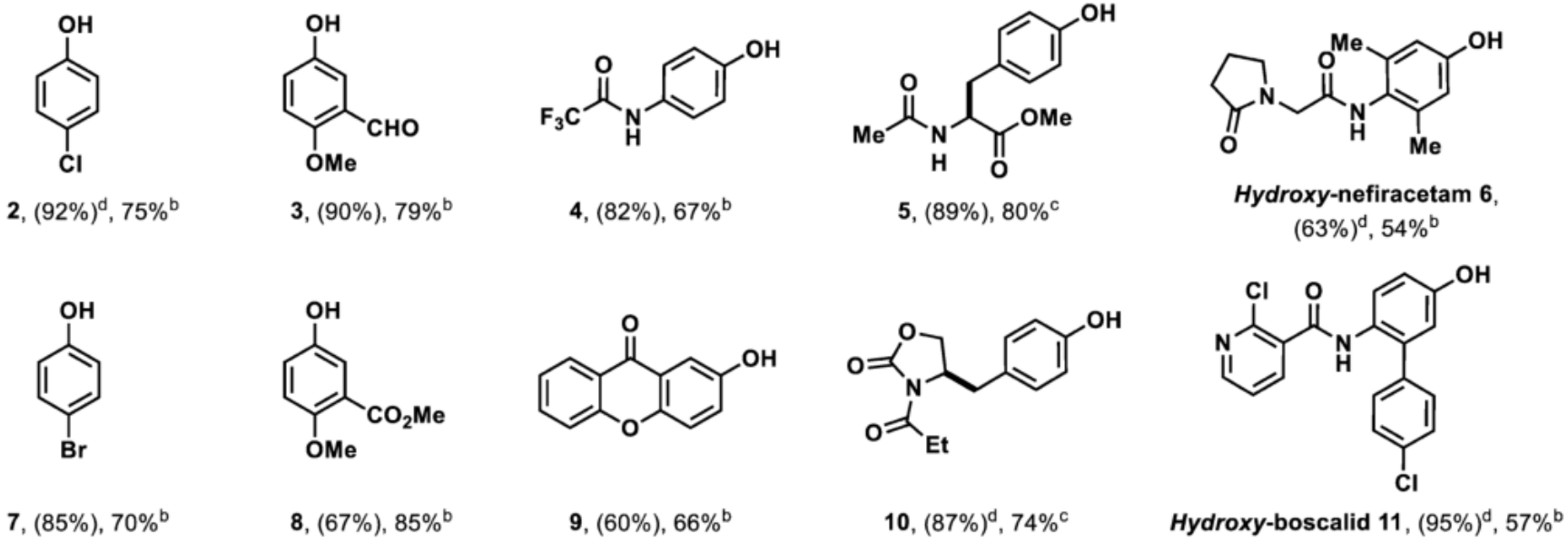
C–H Functionalization Hot Paper

International Edition: DOI: 10.1002/anie.201908718
German Edition: DOI: 10.1002/ange.201908718

Site-Selective C–H Oxygenation via Aryl Sulfonium Salts

*Ruocheng Sang, Stamatis E. Korkis[+], Wanqi Su[+], Fei Ye, Pascal S. Engl, Florian Berger, and Tobias Ritter**





2, (92%)[d], 75%[b]

3, (90%), 79%[b]

4, (82%), 67%[b]

5, (89%), 80%[c]

***Hydroxy*-nefiracetam 6**, (63%)[d], 54%[b]

7, (85%), 70%[b]

8, (67%), 85%[b]

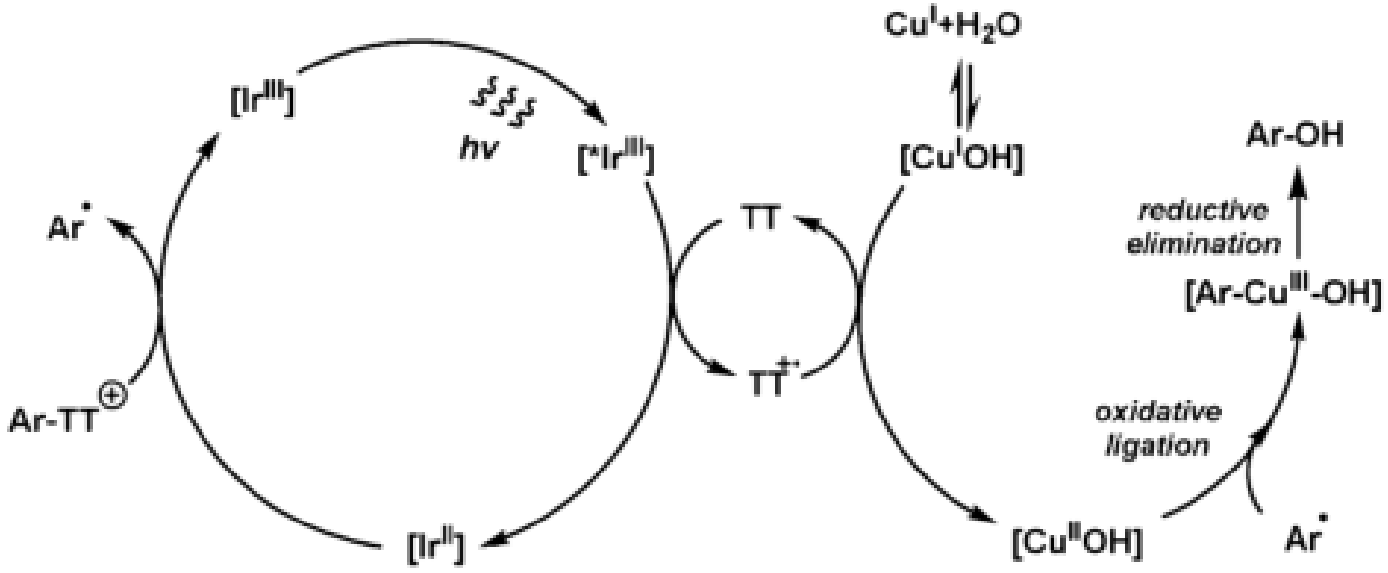
9, (60%), 66%[b]

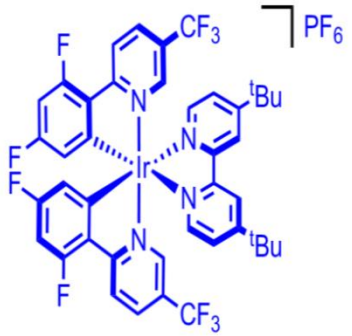
10, (87%)[d], 74%[c]

***Hydroxy*-boscalid 11**, (95%)[d], 57%[b]

thianthrenium salt (1.0 equiv), [Ir[dF(CF3)ppy]2(dtbpy)PF6] (1 mol %), CuTC (1.5 equiv), H2O (20 equiv), MeCN, blue LED(34 W), 30oC, 16 h.

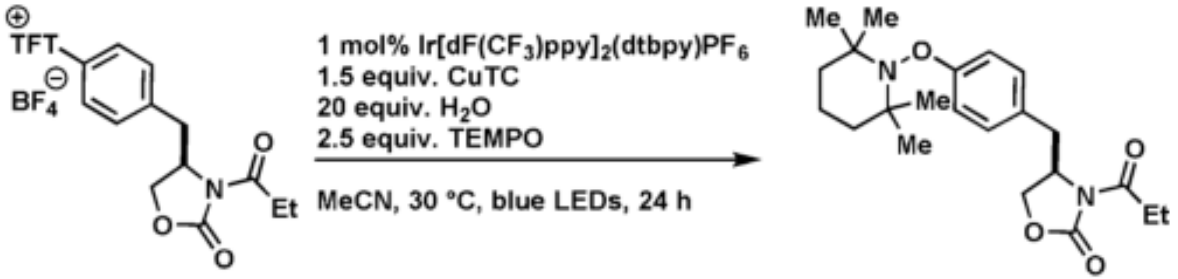
Proposed Mechanism





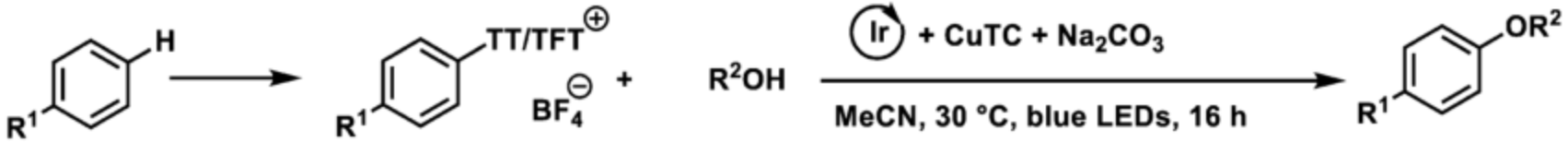
Stern–Volmer实验显示，噻蒽对激发态PC的还原猝灭比噻蒽盐的氧化猝灭快。
并且，形成的铱（II）对于芳基噻蒽鎓盐的还原具有合适的还原电位。

- **Radical trapping experiment**

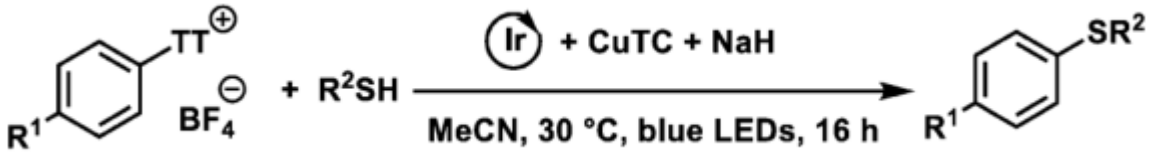


醚化反应和硫醚化反应

◆ Site-selective etherification of arenes



◆ Site-selective thioetherification of arenes



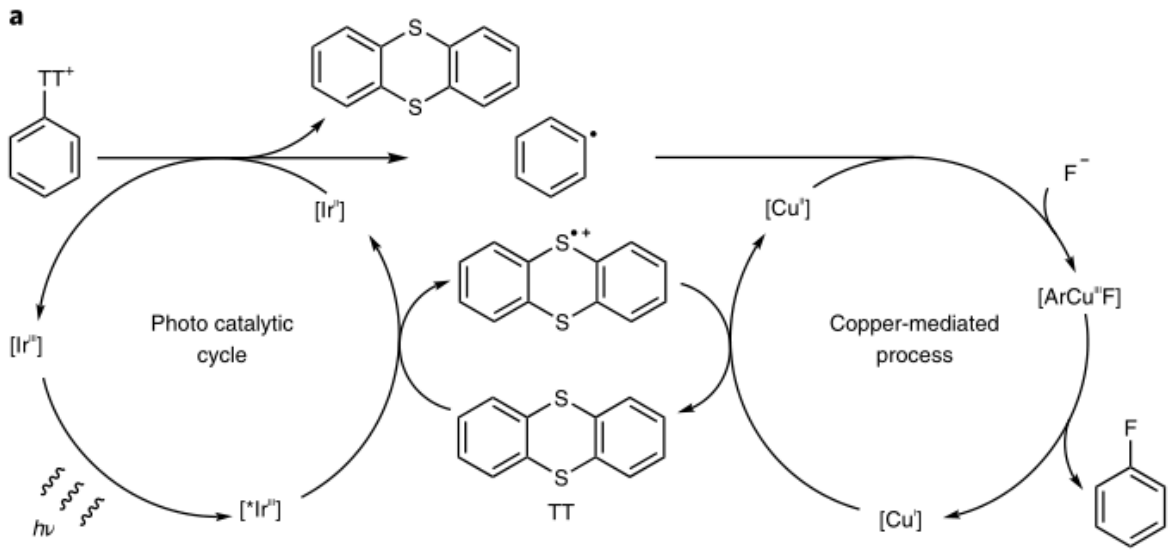
2. 光参与的芳基硫盐的官能化反应

ARTICLES
https://doi.org/10.1038/s41557-019-0353-3
nature chemistry

Ritter.NC.2020.56-62

Photoredox catalysis with aryl sulfonium salts enables site-selective late-stage fluorination

Jiakun Li[1], Junting Chen[1], Ruocheng Sang[1], Won-Seok Ham[1], Matthew B. Plutschack[1], Florian Berger[1], Sonia Chabbra[2], Alexander Schnegg[2], Christophe Genicot[3] and Tobias Ritter[1]*



2. 光参与的芳基硫盐的官能化反应

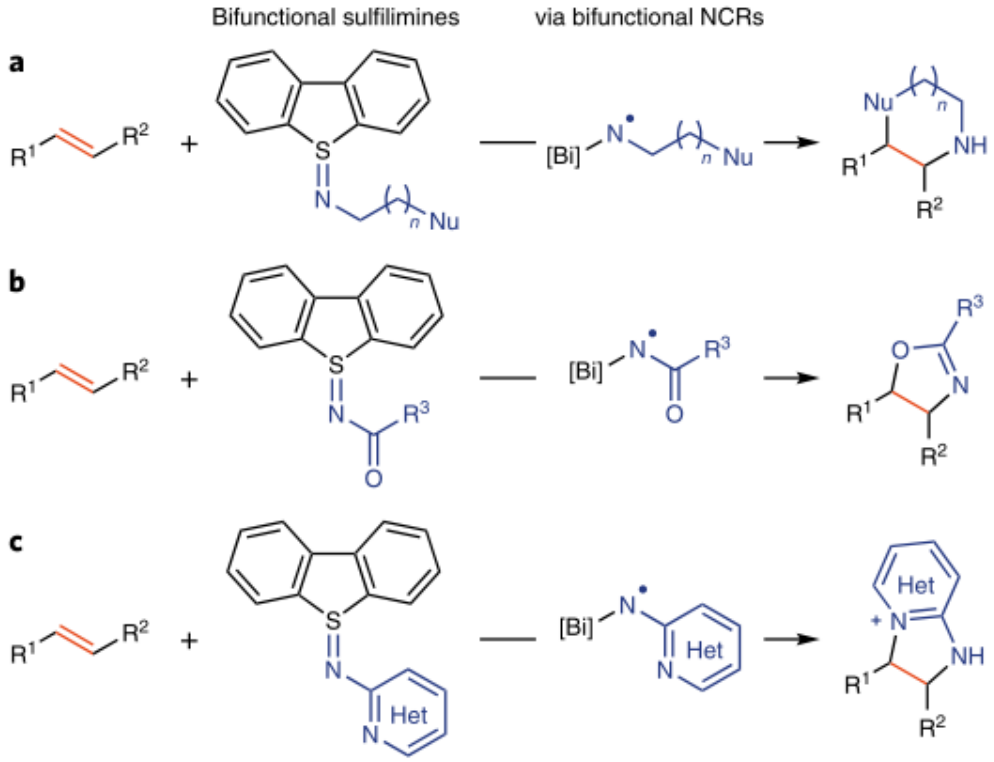
ARTICLES
https://doi.org/10.1038/s41557-022-00997-y
Nature Chemistry.14.2022.898–904
nature chemistry

Check for updates

OPEN

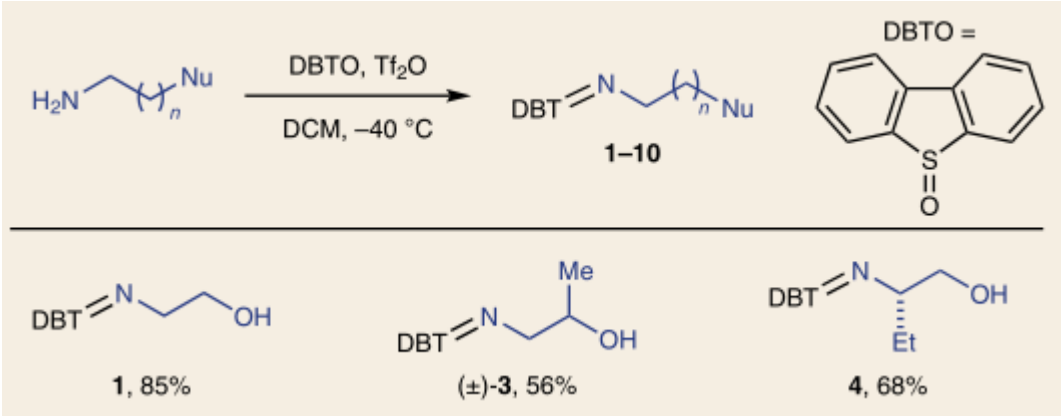
Bifunctional sulfilimines enable synthesis of multiple N-heterocycles from alkenes

Qiang Cheng[1], Zibo Bai[1], Srija Tewari[1,2] and Tobias Ritter[1,2]



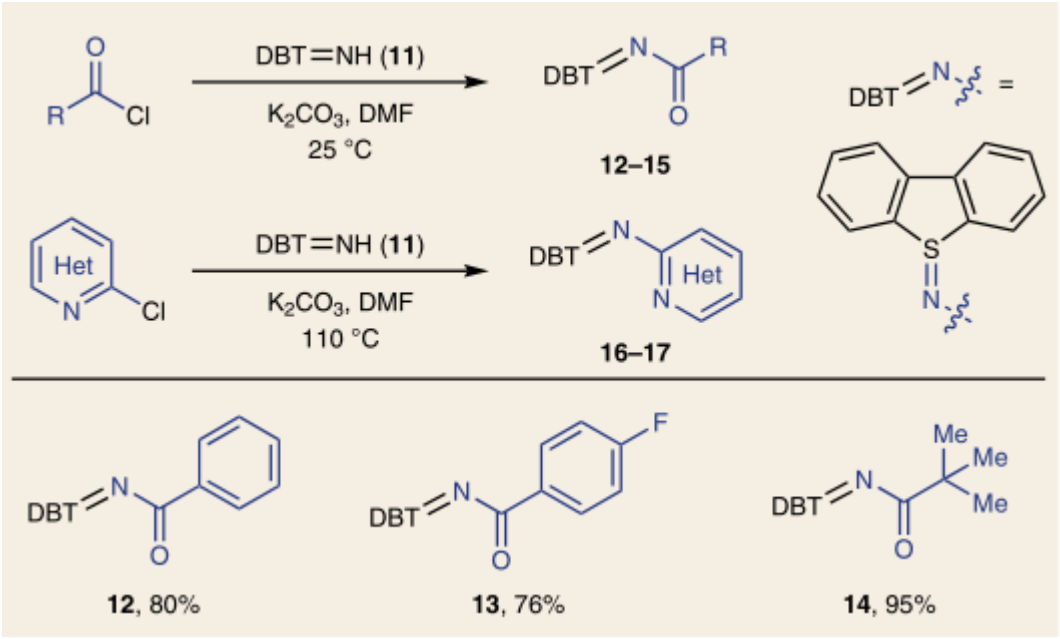
亚胺类化合物的合成

伯胺

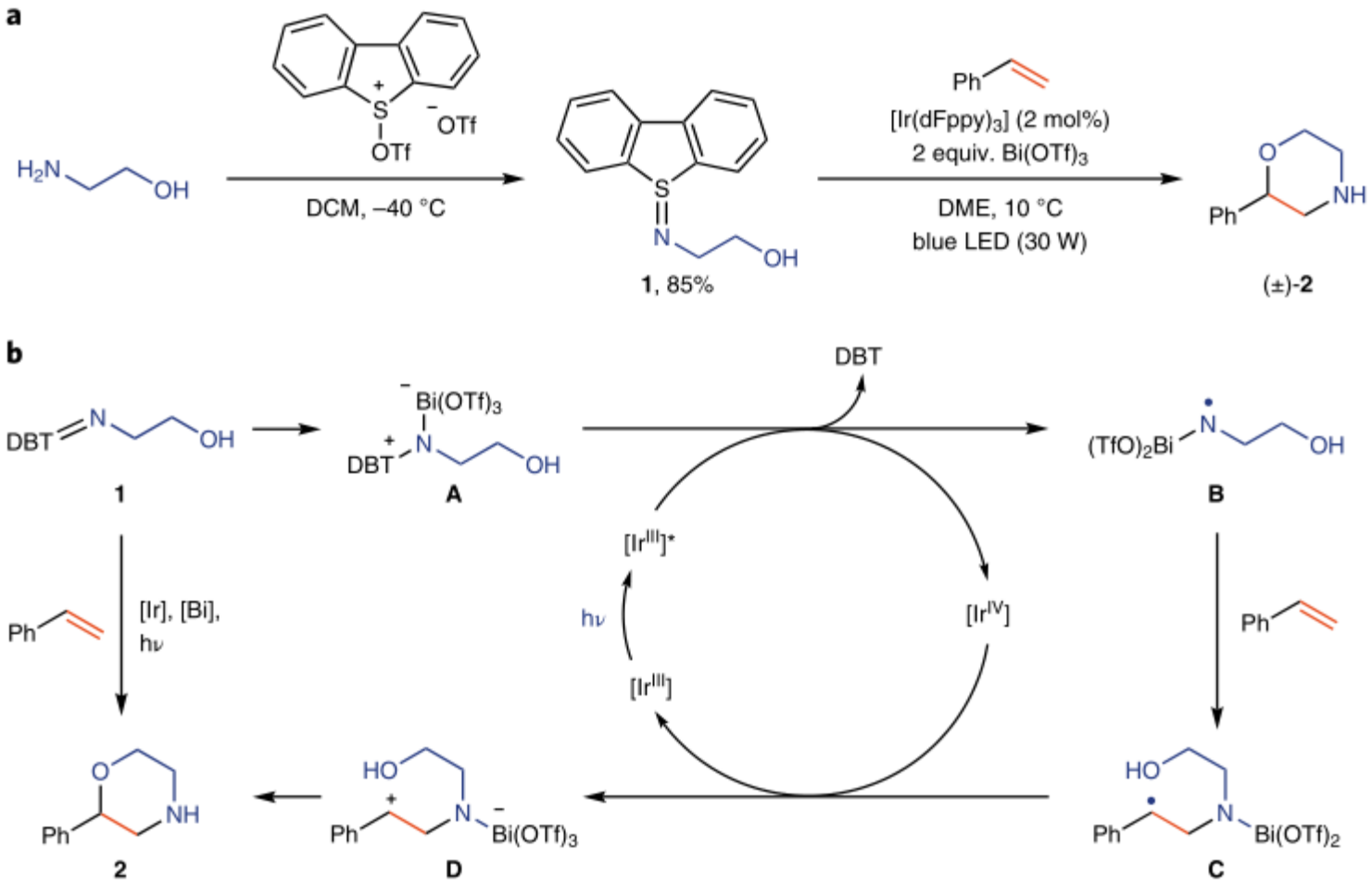


酰氯

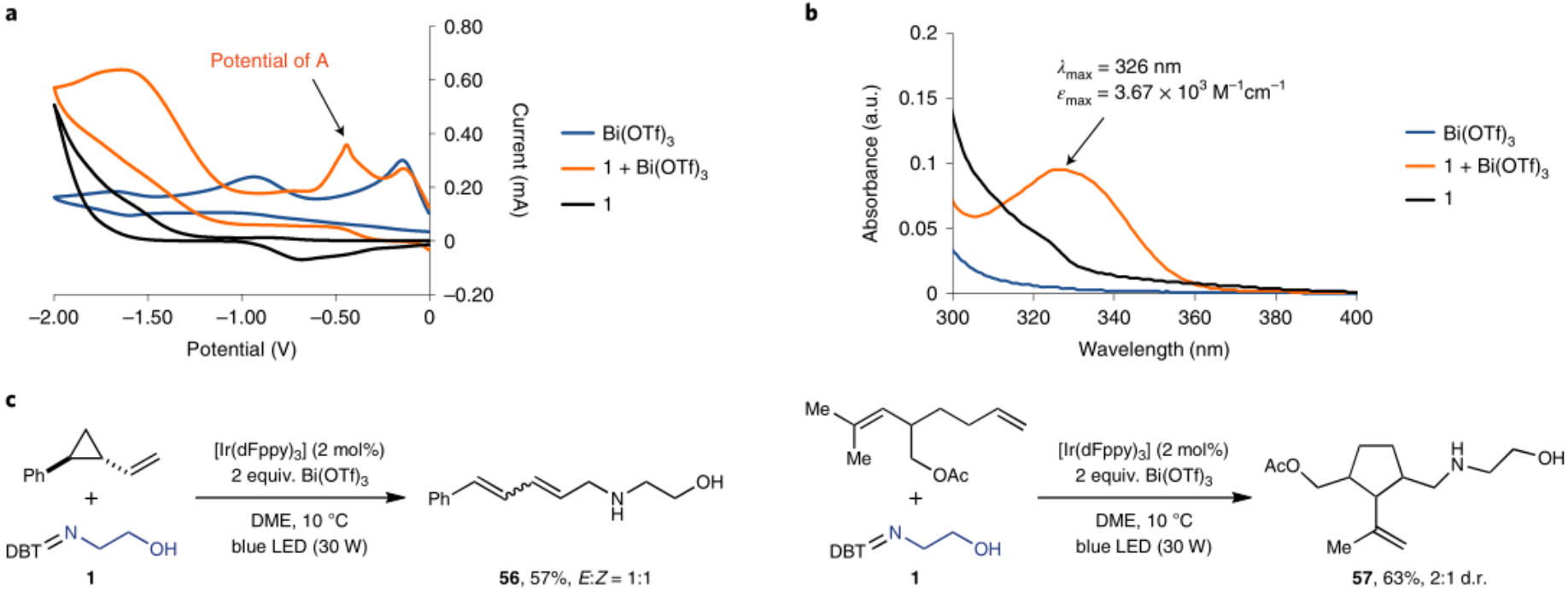
芳基氯



Proposed Mechanism



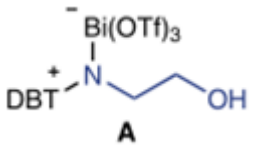
Mechanistic Investigations



A：循环伏安法，1+Bi(OTf)3在Ep=−0.4V vs.Ag/AgCl有峰；

B：紫外-可见光谱326 nm处有吸收峰，证明加合物A的存在；

C：自由基钟实验证明氮自由基的存在。



THE YANG RESEARCH GROUP

目 录

- 背景
- 光参与的芳基硫盐的官能化反应
- 无光参与的芳基硫盐的官能化反应
- 其他课题组的相关工作
- 总结与展望

3. 无光参与的芳基硫盐的官能化反应

无金属参与的芳基硫盐氟化反应

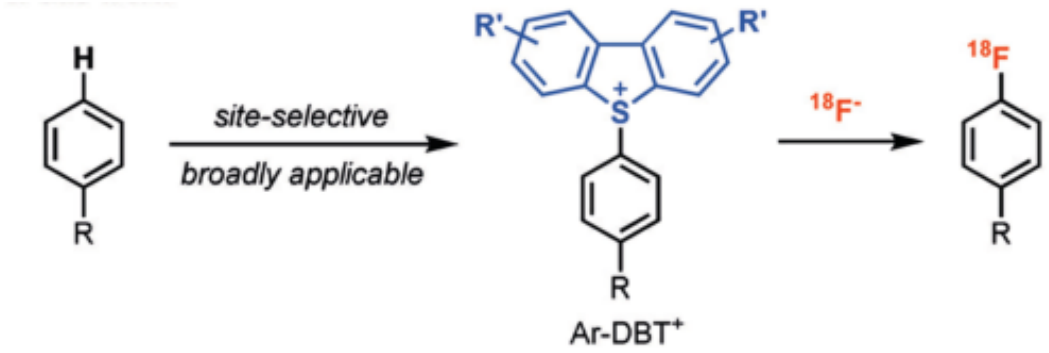
Fluorination

International Edition: DOI: 10.1002/anie.201912567
German Edition: DOI: 10.1002/ange.201912567

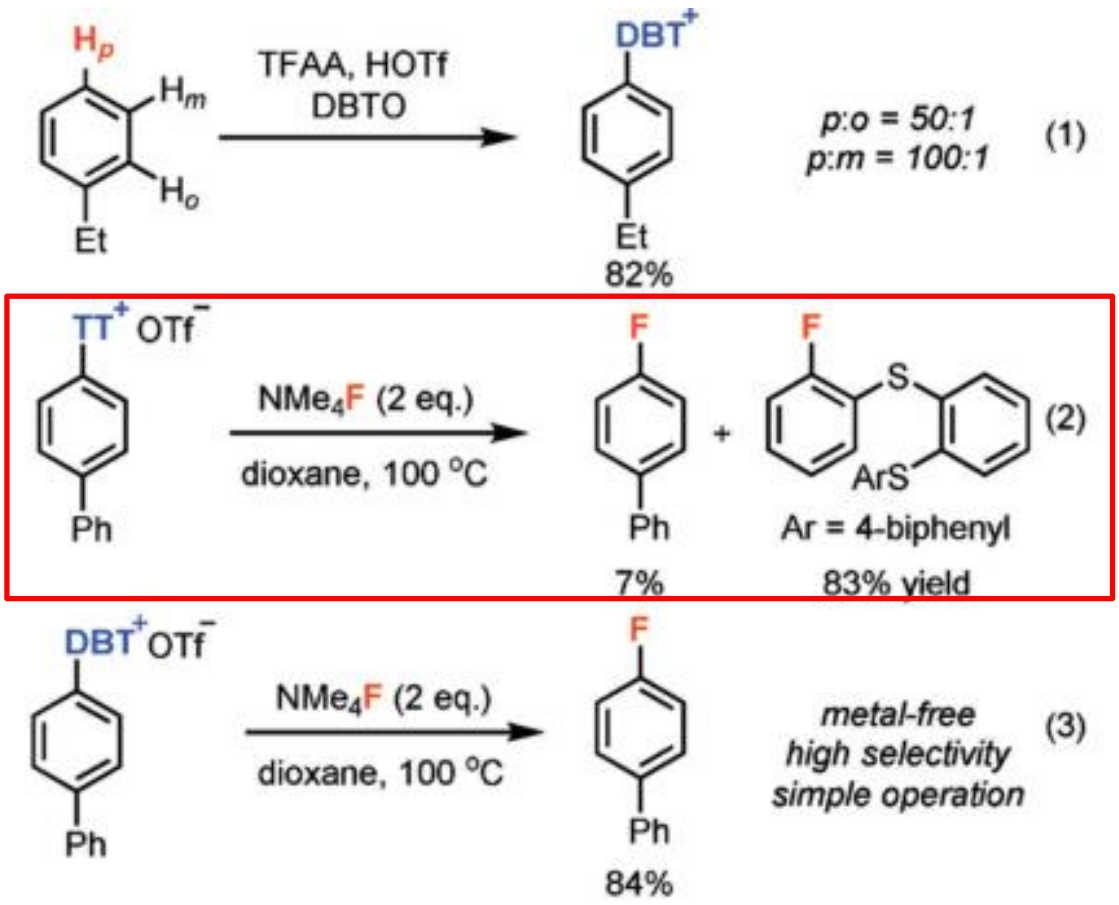
Site-Selective Late-Stage Aromatic [^{18}F]Fluorination via Aryl Sulfonium Salts

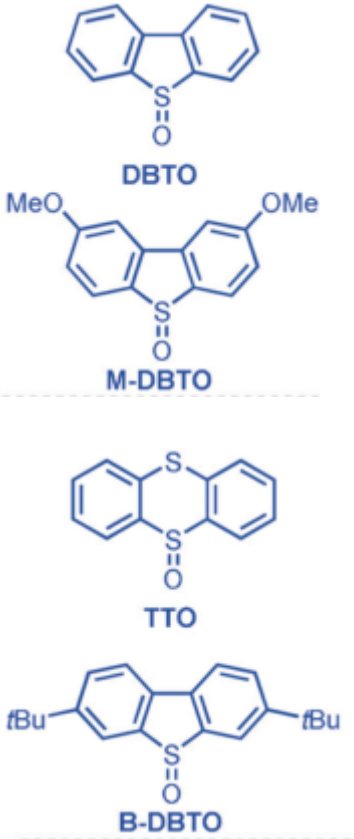
Angew. Chem. Int. Ed. 2020, 59, 1956 –1960

*Peng Xu[+], Da Zhao[+], Florian Berger, Aboubakr Hamad, Jens Rickmeier, Roland Petzold, Mykhailo Kondratiuk, Kostiantyn Bohdan, and Tobias Ritter**



无金属参与的芳基硫盐氟化反应





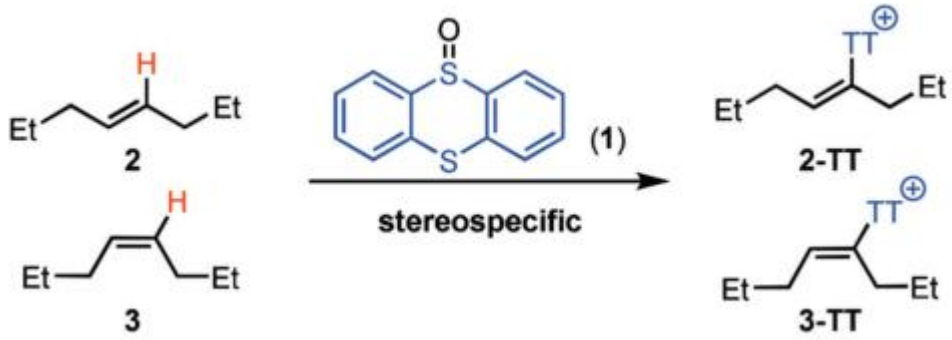
3. 无光参与的芳基硫盐的官能化反应

VIP C–H Functionalization Very Important Paper

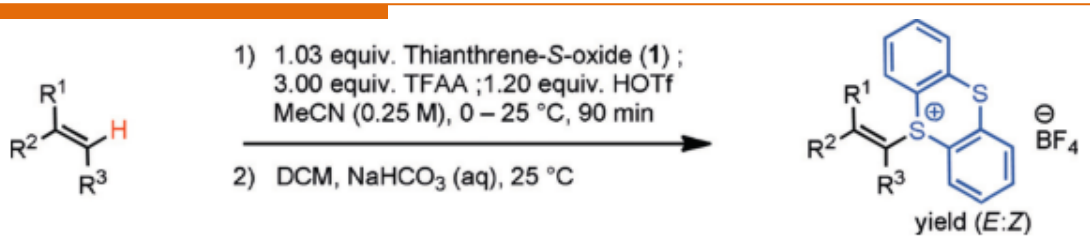
International Edition: DOI: 10.1002/anie.201914215
German Edition: DOI: 10.1002/ange.201914215

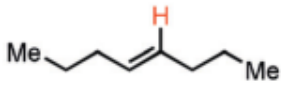
Regio- and Stereoselective Thianthrenation of Olefins To Access Versatile Alkenyl Electrophiles Angew. Chem. Int. Ed. 2020, 59, 5616 –5620

*Junting Chen, Jiakun Li, Matthew B. Plutschack, Florian Berger, and Tobias Ritter**

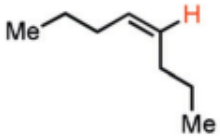


Regioselective C(sp2)-H thianthrenation of unactivated alkenes





2, 95% (<1:50)

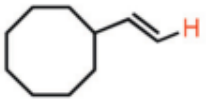


3, 98% (>49:1)[b]

4, 93% (20:1)[b]

5, 76% (17:1)

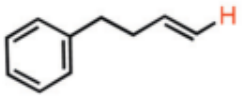
6, 80% (13:1)



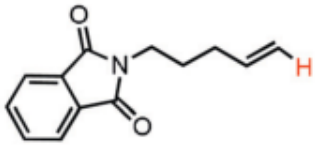
7, 64% (>50:1)

8, >99% (17:1)

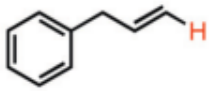
9, 71% (16:1)[b,c]



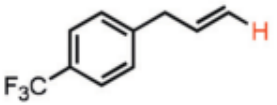
10, 72% (22:1)



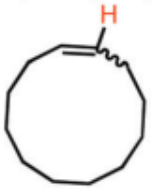
11, 72% (>50:1)[d,e]



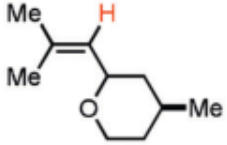
12, 76% (>50:1)



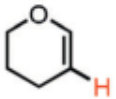
13, 77% (>50:1)



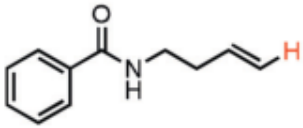
14, 68%[f,h](≈1:1)



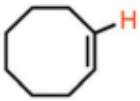
15, 75%[g]



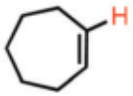
16, 88%[g]



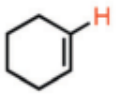
17, 68% (>50:1)



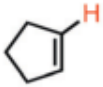
18, 74%[e,g,h]



19, 75%[g]



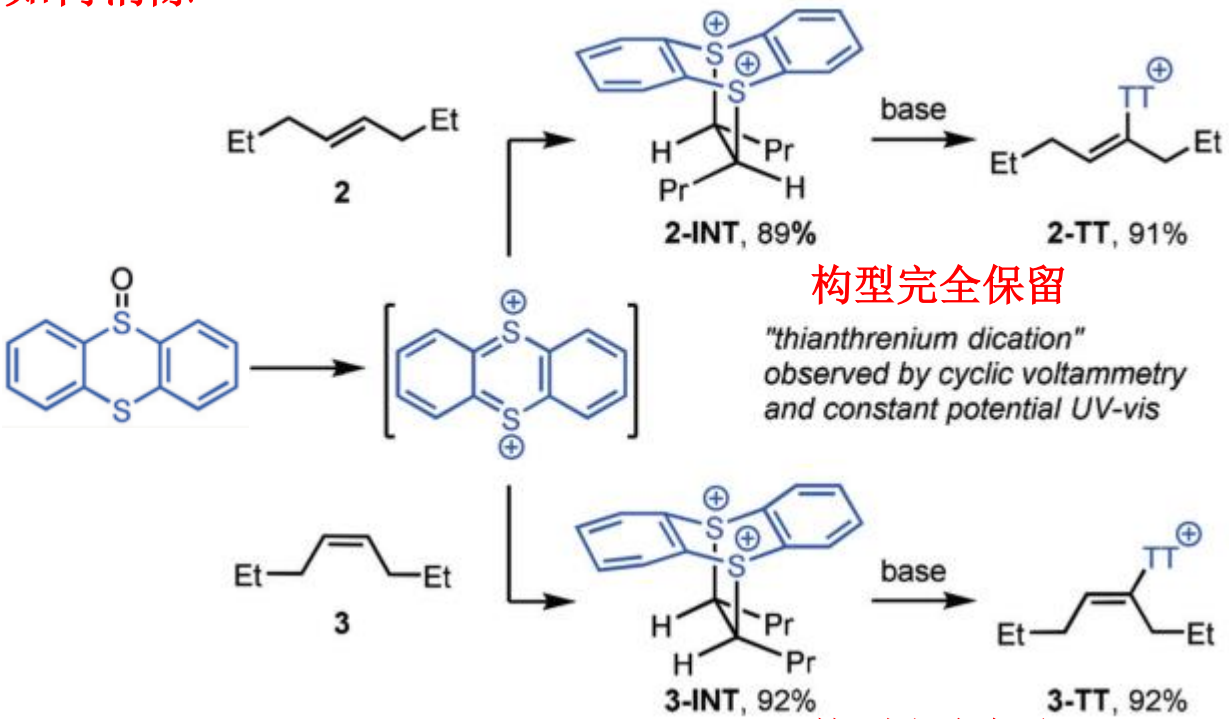
20, 60%[g,h]



21, 74%[g,h]

Proposed Mechanism

噻蒽二价离子or噻蒽自由基阳离子？
如何环加成？
如何消除？

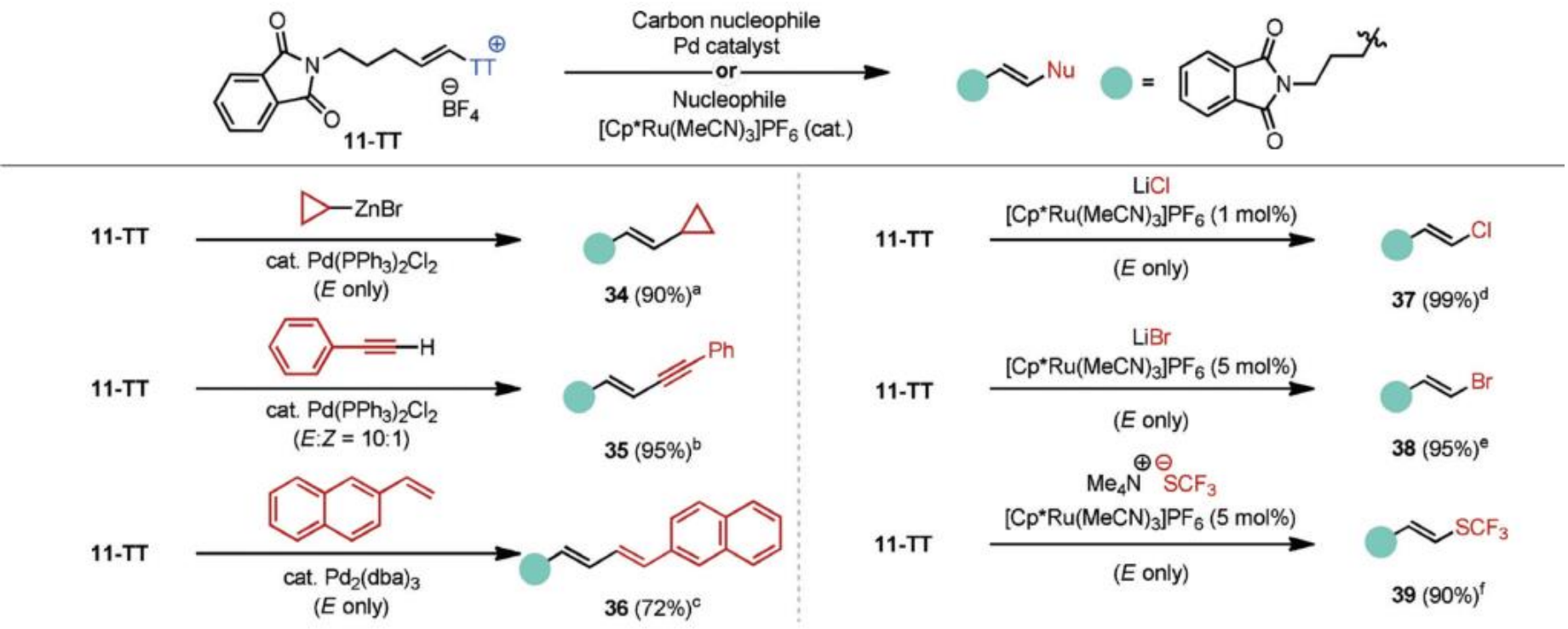


E2？
不符合反式共平面规则

E1？
构型完全保留

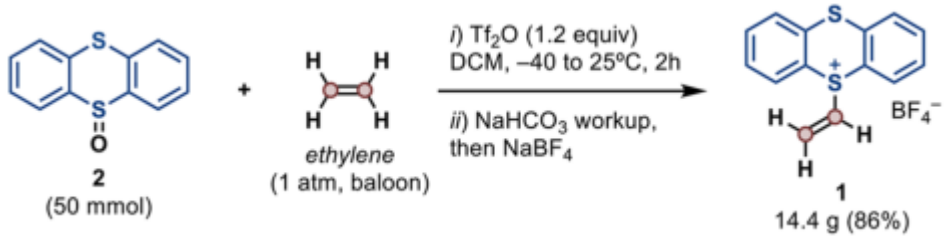
Consistent with all data is an E1cBirr（单分子共轭碱消除） mechanism where rate-determining deprotonation is followed by a rapid elimination.

Derivatizations of alkenyl thianthrenium salts



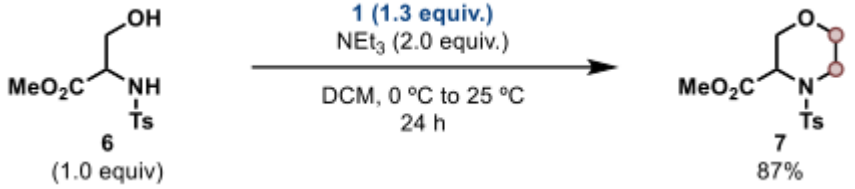
3. 无光参与的芳基硫盐的官能化反应

J. Am. Chem. Soc. 2021, 143, 12992−12998

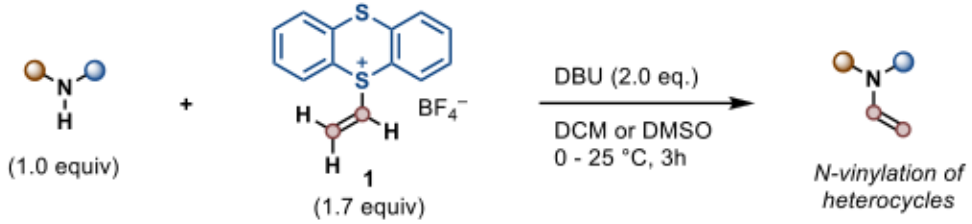


multigram scale

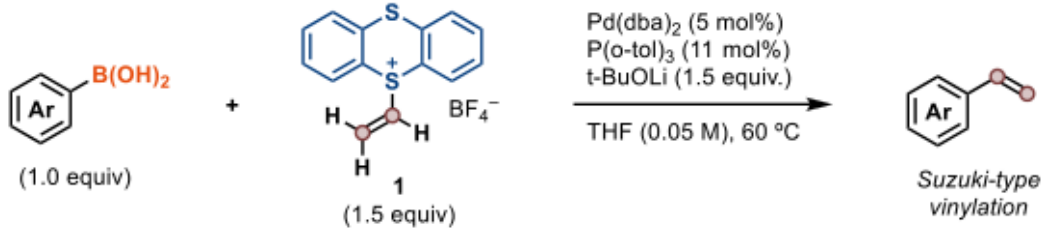
◆ The Annulation of Heterocycles.



◆ Vinylation of N-Heterocycles



◆ Suzuki-Type Vinylation



3. 无光参与的芳基硫盐后期官能化反应

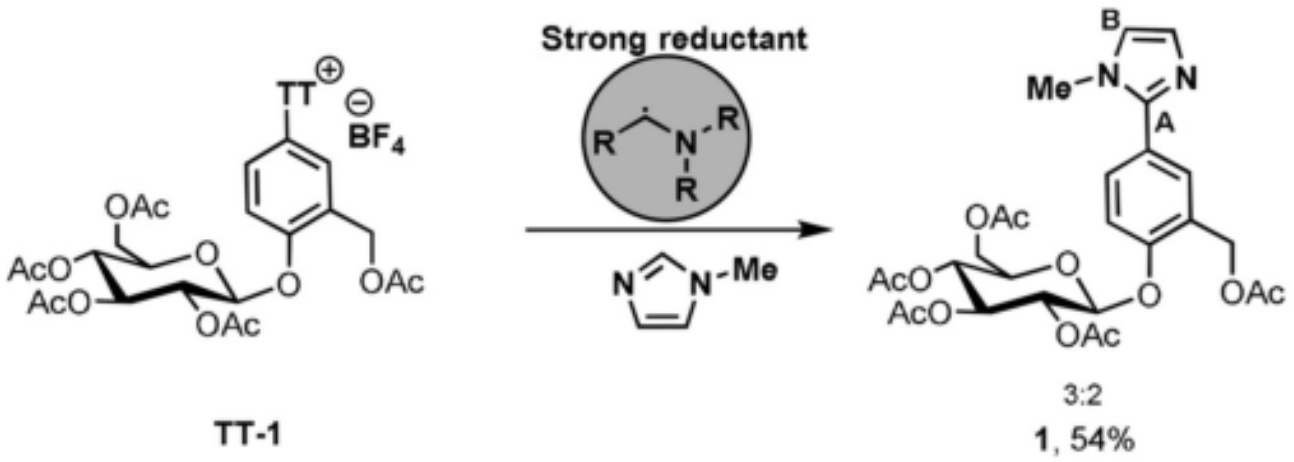
GDCh Communications Angewandte International Edition Chemie

Heteroarylation Hot Paper

How to cite: *Angew. Chem. Int. Ed.* **2021**, *60*, 13609–13613
International Edition: doi.org/10.1002/anie.202103085
German Edition: doi.org/10.1002/ange.202103085

Late-Stage Heteroarylation of Hetero(aryl)sulfonium Salts Activated by α-Amino Alkyl Radicals

*Eva Maria Alvarez, Teresa Karl, Florian Berger, Luca Torkowski, and Tobias Ritter**

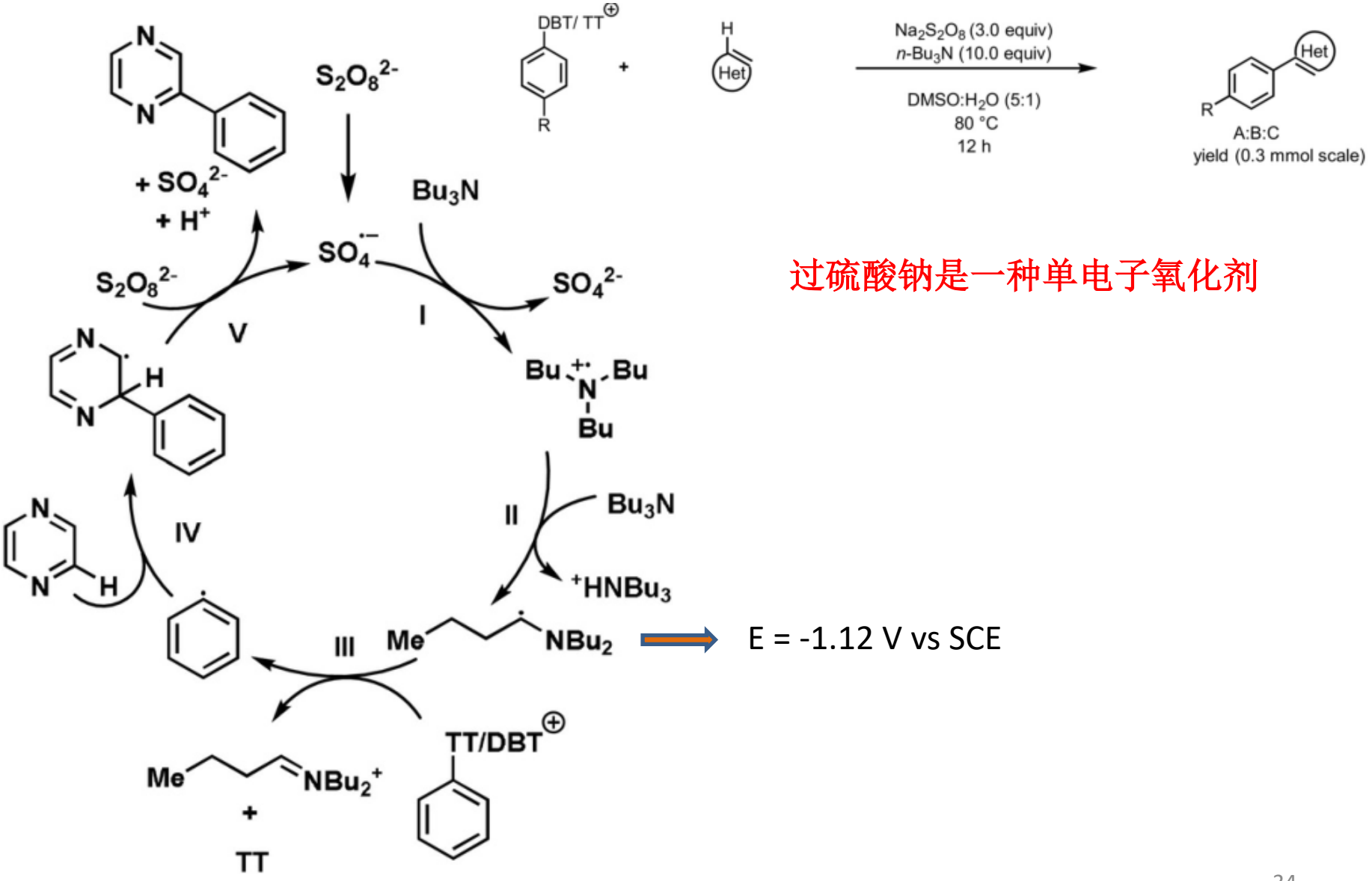


TT-1

3:2
1, 54%

- New mode of activation of sulfonium salts
- Operationally simple
- No transition metal catalyst
- Air and moisture insensitive

Proposed Mechanism



过硫酸钠是一种单电子氧化剂

E = -1.12 V vs SCE

3. 无光参与的芳基硫盐的官能化反应

JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

J. Am. Chem. Soc. 2021, 143, 7909−7914

pubs.acs.org/JACS

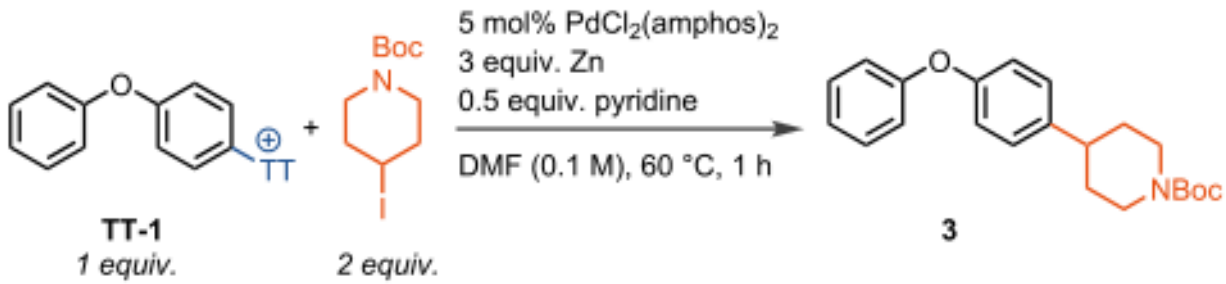
Communication

Site-Selective C−H alkylation of Complex Arenes by a Two-Step Aryl Thianthrenation-Reductive Alkylation Sequence

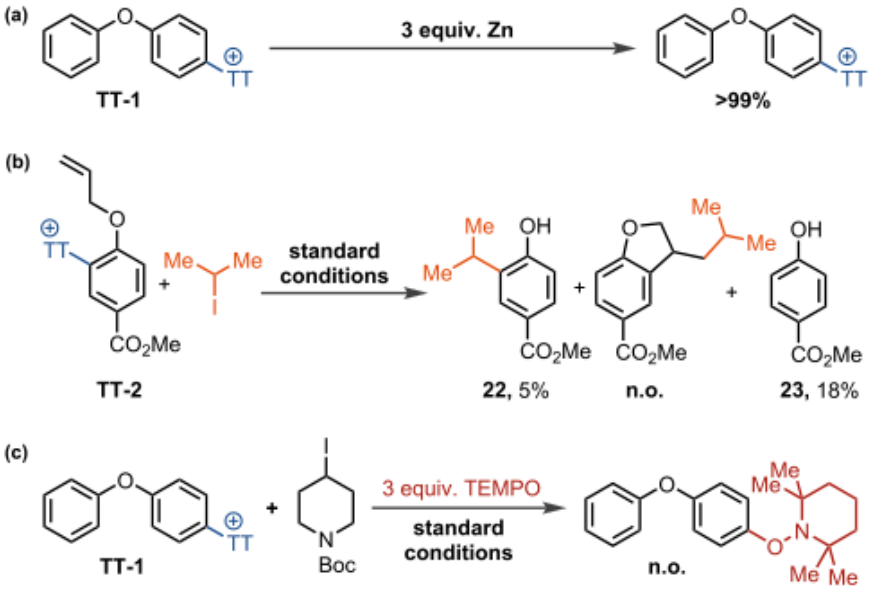
Beatrice Lansbergen, Paola Granatino, and Tobias Ritter*

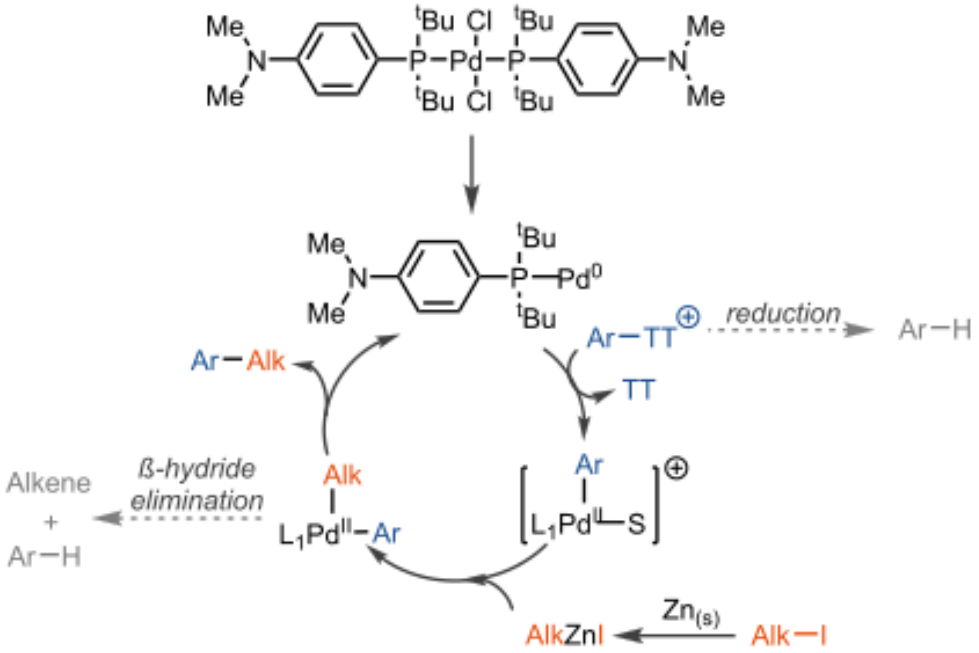
Cite This: *J. Am. Chem. Soc.* 2021, 143, 7909−7914

Read Online



Mechanistic Investigation and Proposed Mechanism





E(PhTT+/PhTT•) = −1.5 V vs SCE

E(Zn2+/Zn) = −0.76 V vs SCE

E(n-BuI/BuI•) = −2.5 V vs SCE

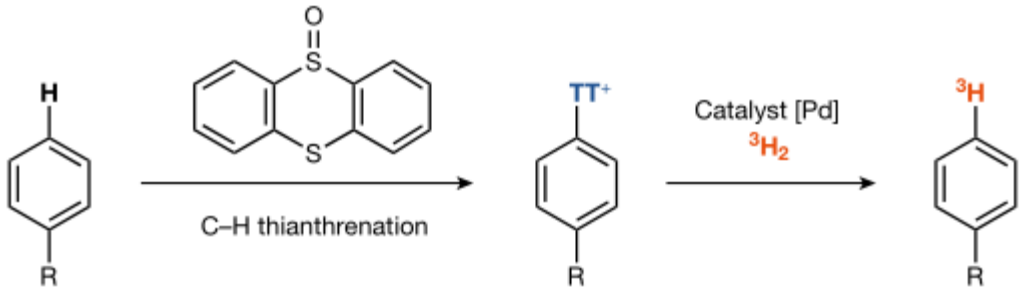
锌存在下烷基碘在5分钟内加氢脱卤，转化率为90%

3. 无光参与的芳基硫盐的官能化反应

Article

Tritiation of aryl thianthrenium salts with a molecular palladium catalyst

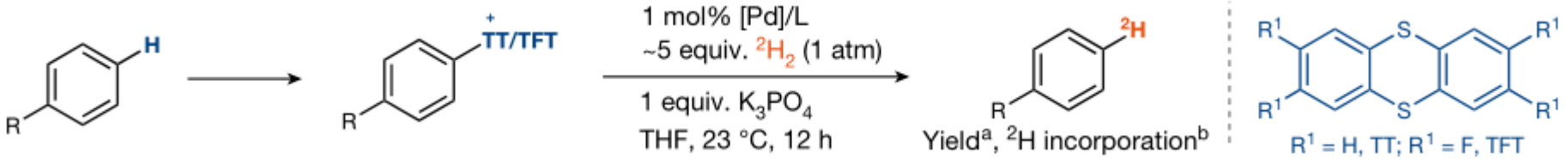
https://doi.org/10.1038/s41586-021-04007-y
Da Zhao[1], Roland Petzold[1], Jiyao Yan[1,2], Dieter Muri[3] & Tobias Ritter[1]✉



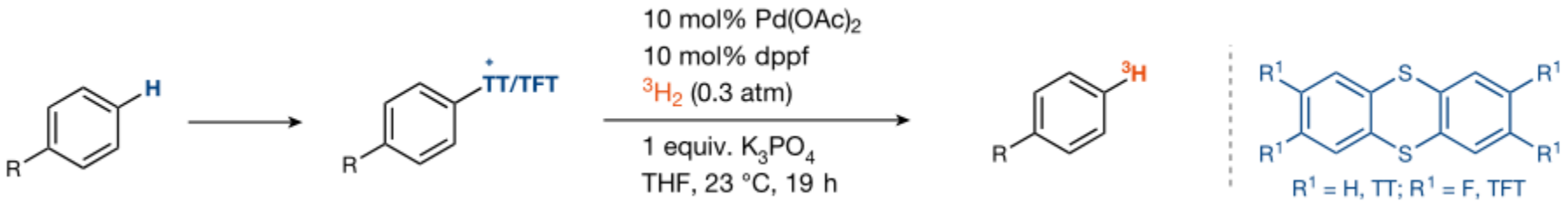
- 氚标记是研究药物的药代动力学和药效学特性、放射自显影、受体结合和受体占有率研究的关键工具；
- 氚气是制备标记分子的首选氚源；
- 均相钯催化剂用于氢解反应；
- 不需要惰性气氛或干燥条件。

Scope of Substrates

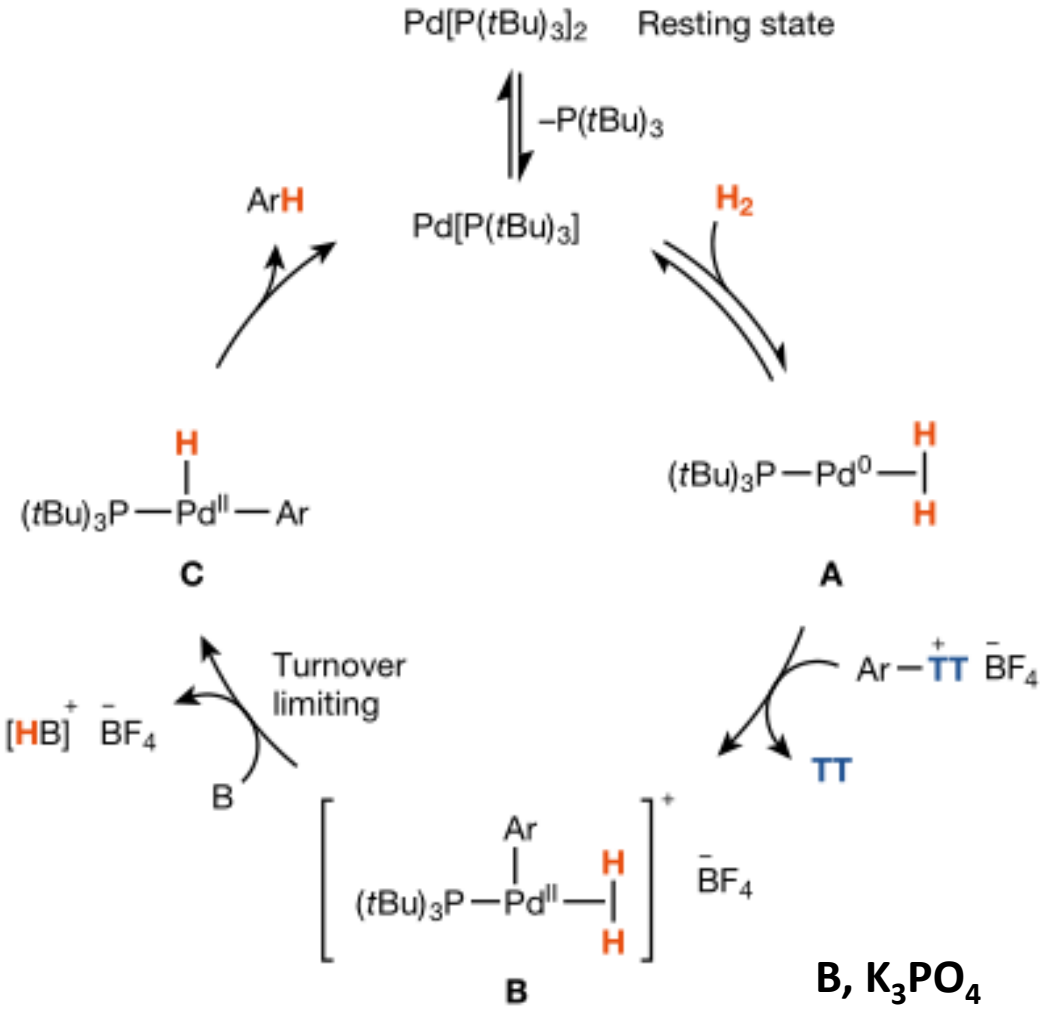
- Reductive deuteration of thianthrenium salts



- Reductive tritiation of thianthrenium salts



Proposed Mechanism



3. 无光参与的芳基硫盐的官能化反应

GDCh Communications Angewandte International Edition Chemie www.angewandte.org

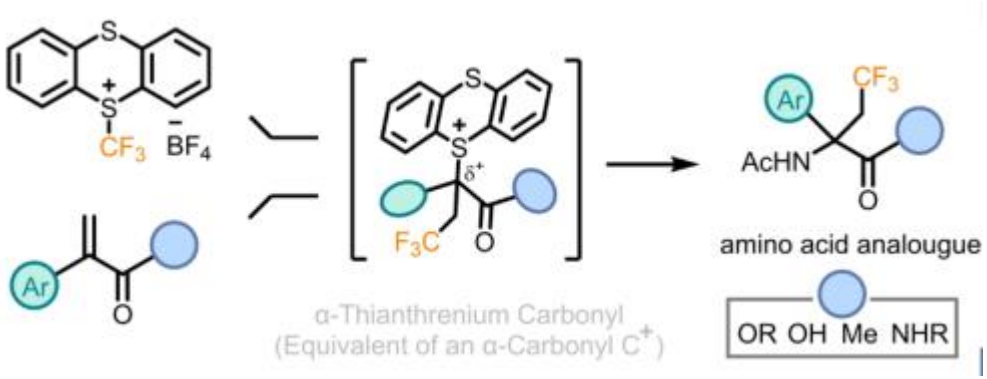
How to cite: *Angew. Chem. Int. Ed.* **2022,** *61*, e202208978
International Edition: doi.org/10.1002/anie.202208978
German Edition: doi.org/10.1002/ange.202208978

Synthetic Methods

α-Thianthrenium Carbonyl Species: The Equivalent of an α-Carbonyl Carbocation

*Hao Jia and Tobias Ritter**

Angew. Chem. Int. Ed. 2022, 61, e202208978



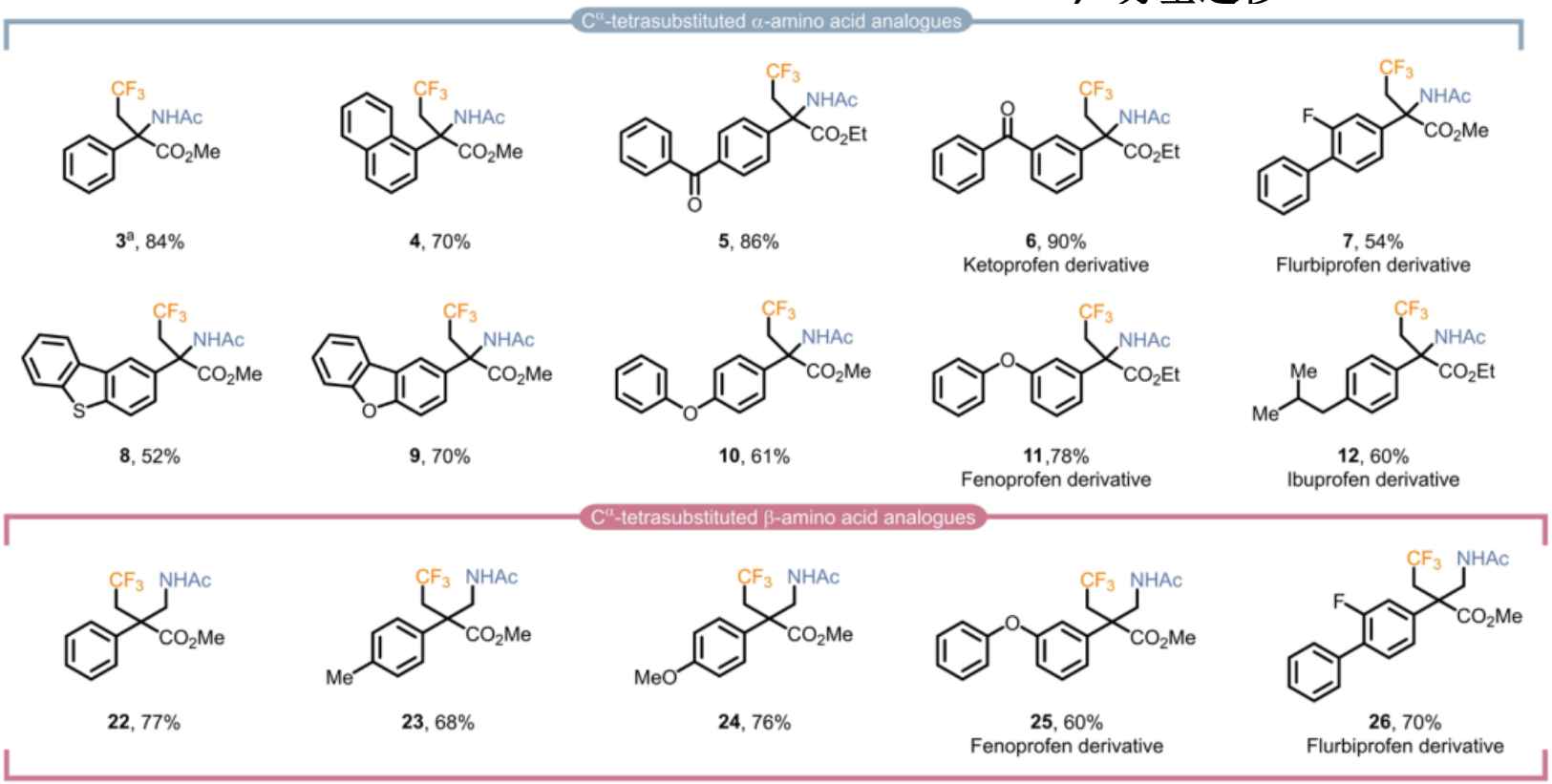
α-噻蒽鎓基化合物

等价物

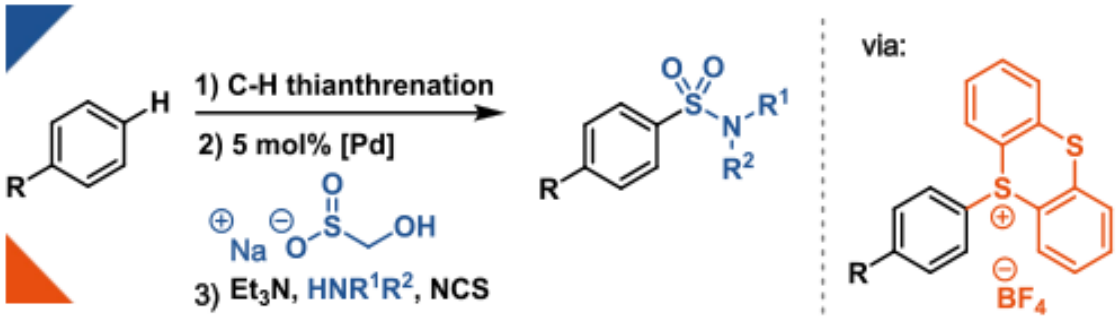
α-鎓基碳阳离子

Scope of Substrates

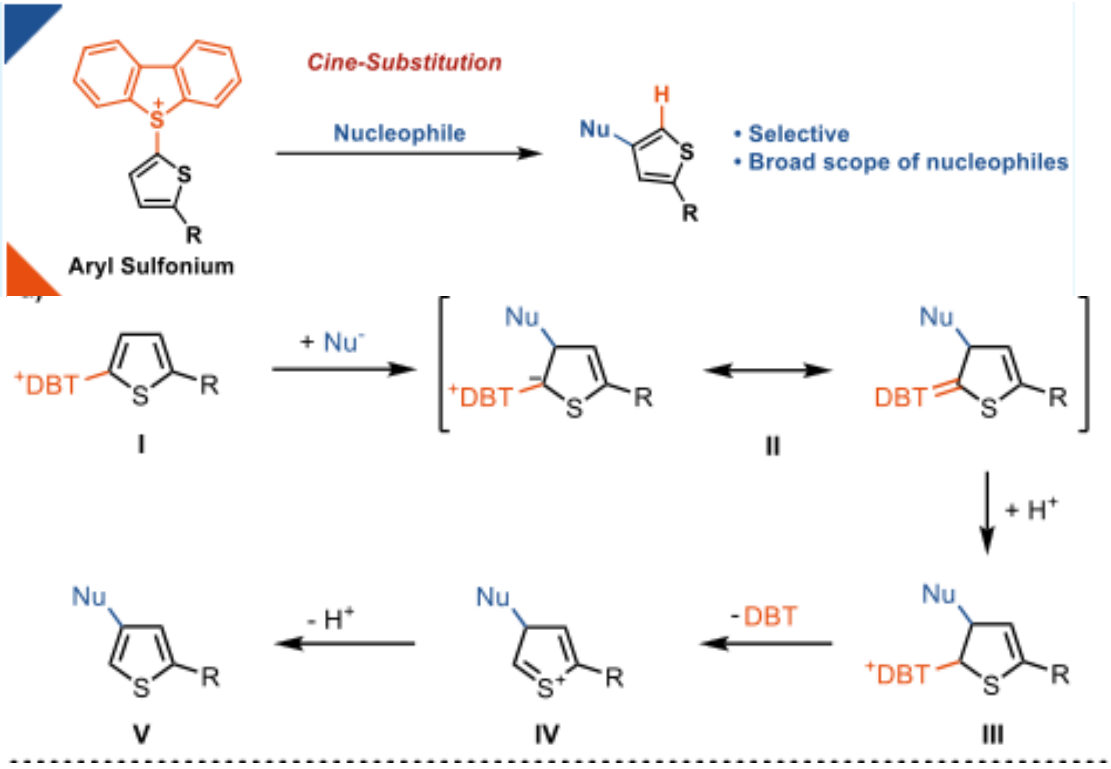
1,2-芳基迁移



3. 无光参与的芳基硫盐的官能化反应



Org. Lett. 2020, 22, 4593−4596



Org. Lett. 2020, 22, 5671−5674

亲核试剂：
酰亚胺、三唑、吡唑、咪唑、乙内酰脲和吡啶酮

THE YANG RESEARCH GROUP

目 录

- 背景
- 光参与的芳基硫盐的官能化反应
- 无光参与的芳基硫盐的官能化反应
- 其他课题组的相关工作
- 总结与展望

4. 其他课题组的相关工作

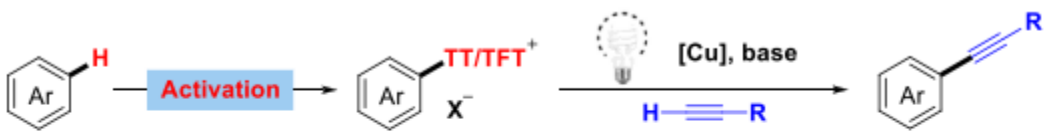
OL Organic Letters

pubs.acs.org/OrgLett Letter

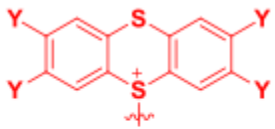
Photoinduced Copper-Catalyzed Site-Selective C(sp^2)–C(sp) Cross-Coupling via Aryl Sulfonium Salts

Lei Liang,* Hong-Ying Niu,* Ren-Long Li, Yao-Fei Wang, Jin-Kai Yan, Chang-Gong Li, and Hai-Ming Guo

Cite This: *Org. Lett.* 2020, 22, 6842–6846 Read Online



Ar = arenes and drug molecules, R = (hetero)aryl and alkyl, X = BF_4 or CF_3CO_2



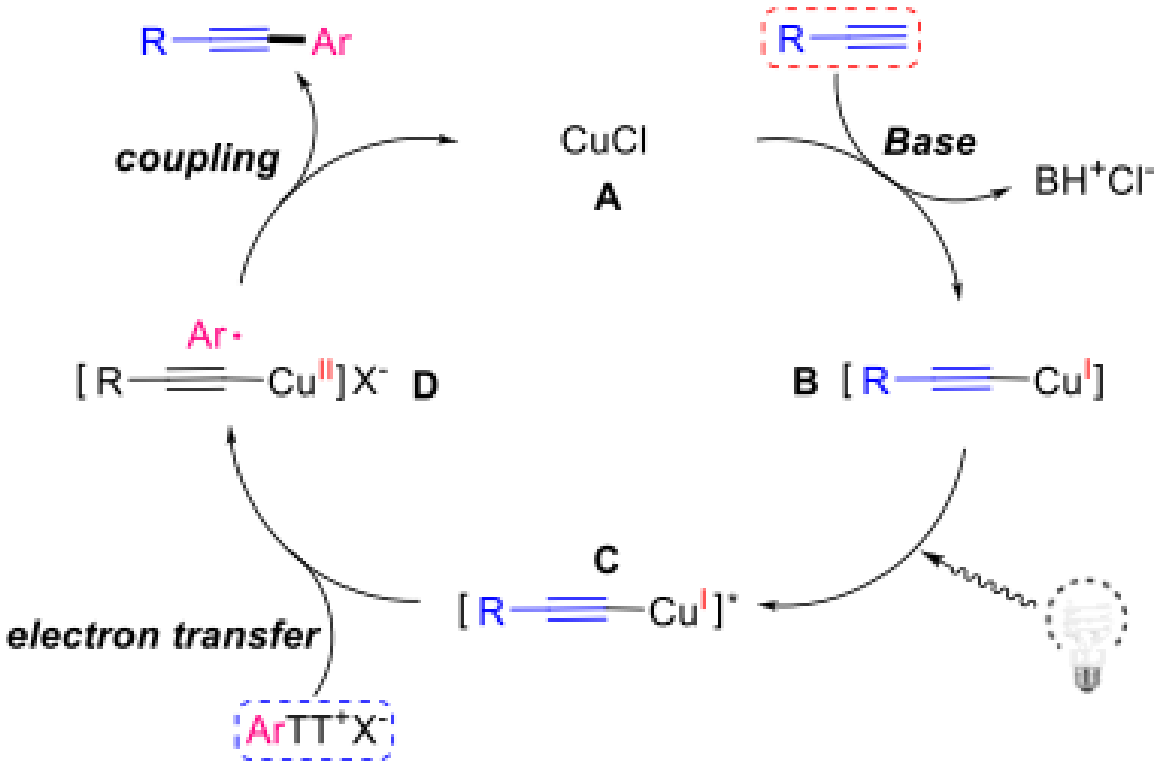
TT: Y = H
TFT: Y = F

- Site-selective alkynylation
- Low-cost copper catalysis
- Excellent chemoselectivity
- Mild condition
- Broad substrate scope, 35 examples
- Modification of drug molecules

Cu-catalyzed Sonogashira-type reaction

Lei Liang,* Hai-Ming Guo. Org. Lett. 2020, 22, 6842−6846

Proposed Mechanism



Lei Liang,* Hai-Ming Guo. Org. Lett. 2020, 22, 6842−6846

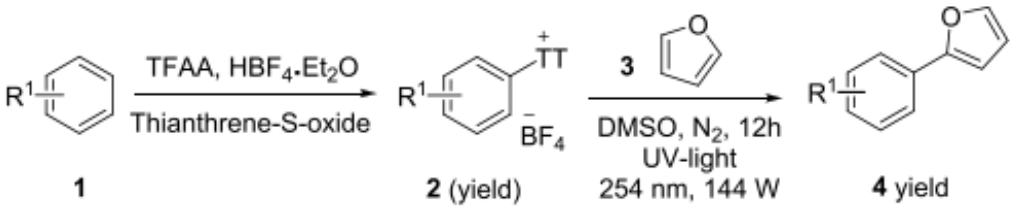
4. 其他课题组的相关工作

OL Organic Letters

pubs.acs.org/OrgLett Letter

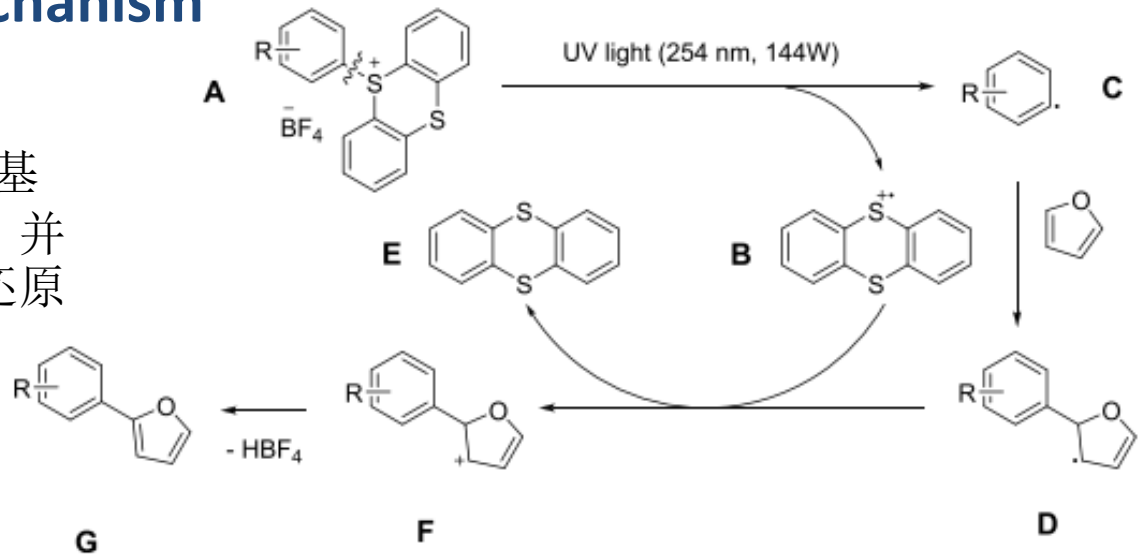
Photochemical (Hetero-)Arylation of Aryl Sulfonium Salts

Yue Zhao, Congjun Yu, Wenjing Liang, and Frederic W. Patureau*



Proposed Mechanism

UV light 激发芳基硫盐发生均裂，并未发生单电子还原



Yue Zhao, Congjun Yu, Wenjing Liang, and Frederic W. Patureau. Org. Lett. 2021, 23, 6232−6236

4. 其他课题组的相关工作

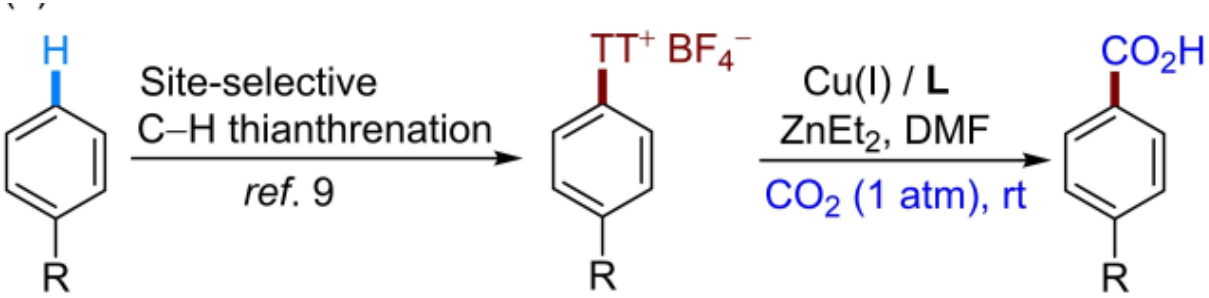
GDCh Communications Angewandte International Edition Chemie www.angewandte.org

Carboxylation Reactions Hot Paper

How to cite:
International Edition: doi.org/10.1002/anie.202212975
German Edition: doi.org/10.1002/ange.202212975

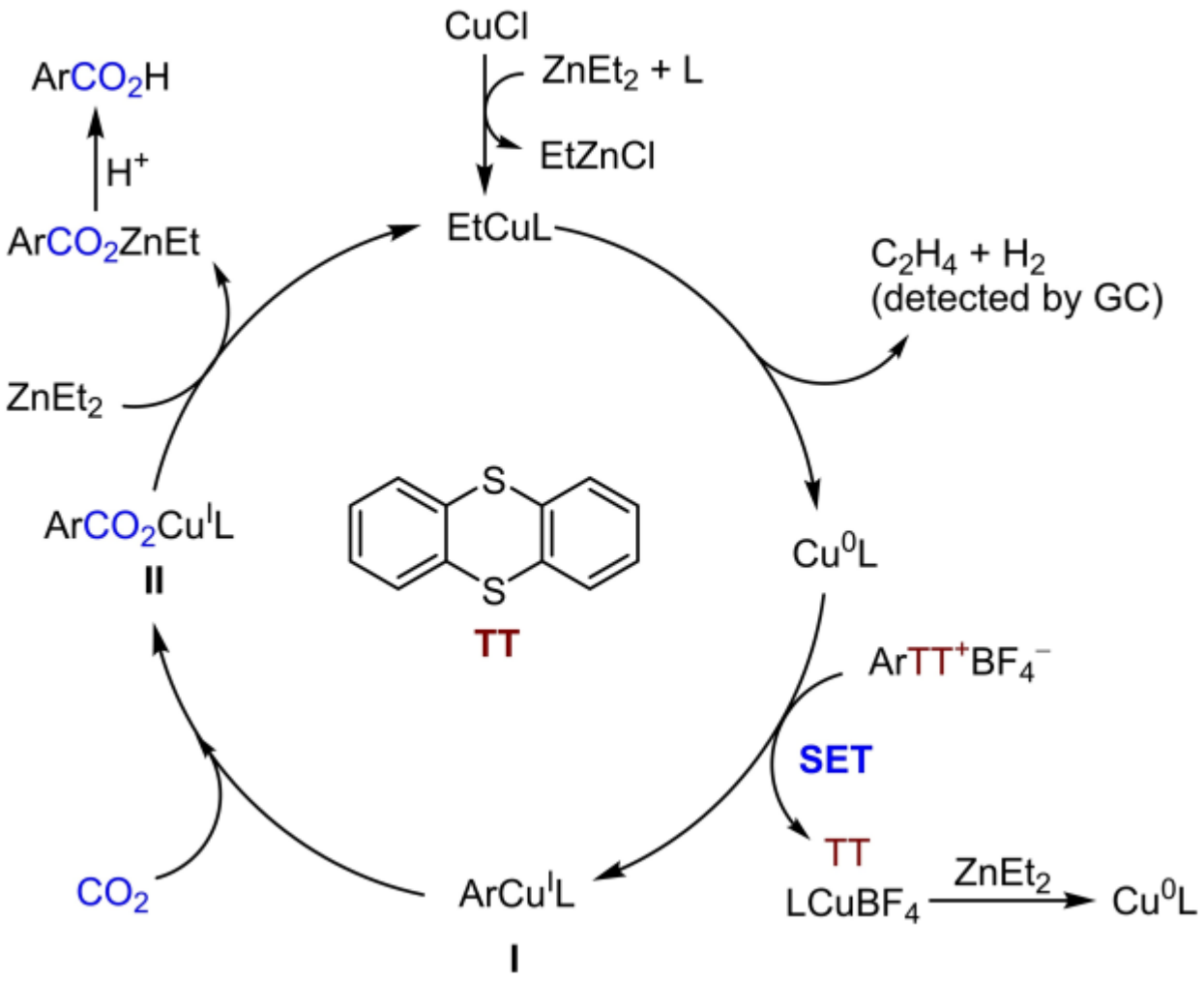
Copper-Catalyzed Carboxylation of Aryl Thianthrenium Salts with CO_2

*Shibiao Tang, Xiaobo Zhao, Lidong Yang, Bin Li, and Baiquan Wang**



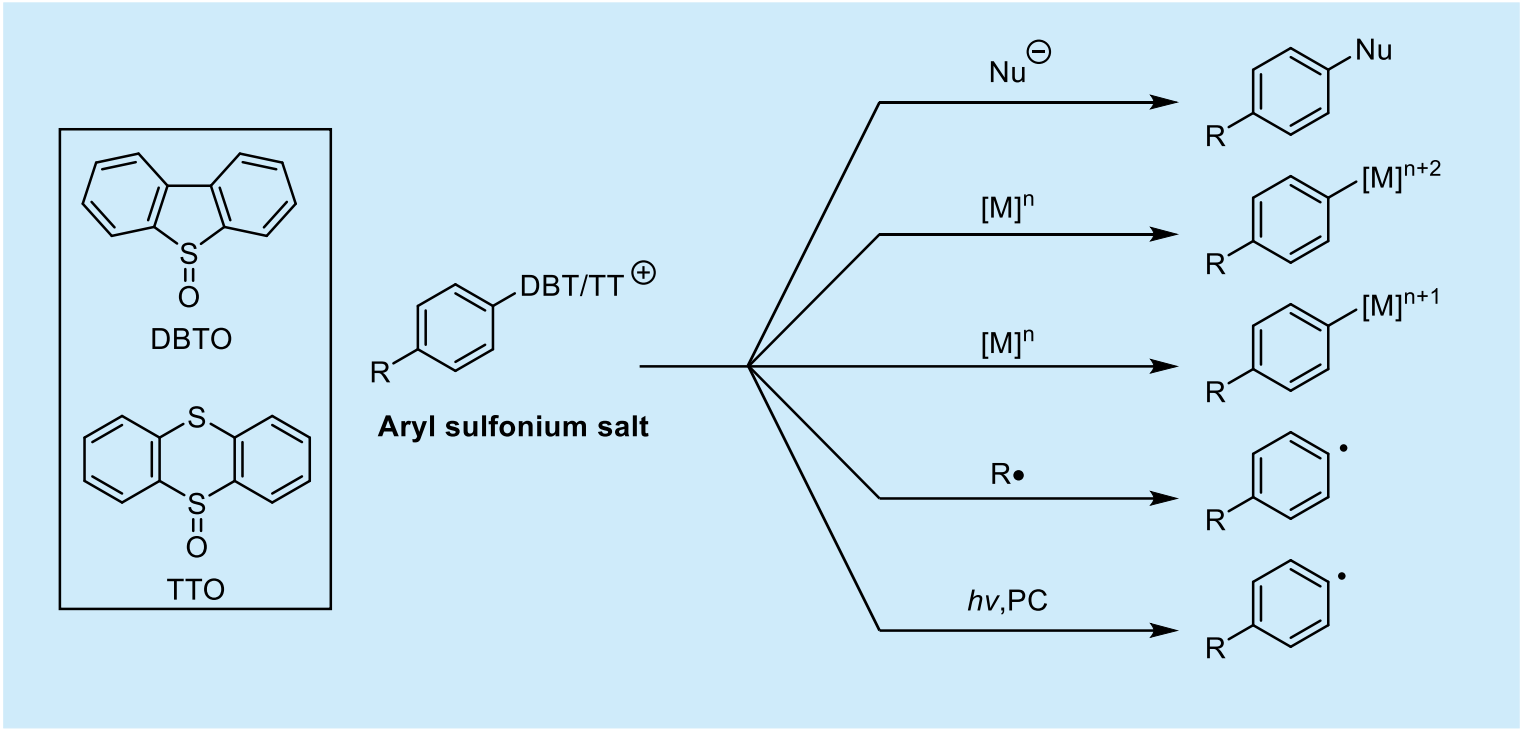
Angew. Chem. Int. Ed. **2022**, e202212975

Proposed Mechanism



Angew. Chem. Int. Ed. **2022**, e202212975

5.总结


DBTO
TTO
DBT/TT
R
Aryl sulfonium salt
Nu
[M]n
[M]n
R•
hv,PC
Nu
[M]n+2
[M]n+1
R
R
R
R
R

Thanks!