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# Transition-Metal-Free Suzuki-Type Cross-Coupling Reaction of Benzyl Halides and Boronic Acids via 1,2-Metalate Shift

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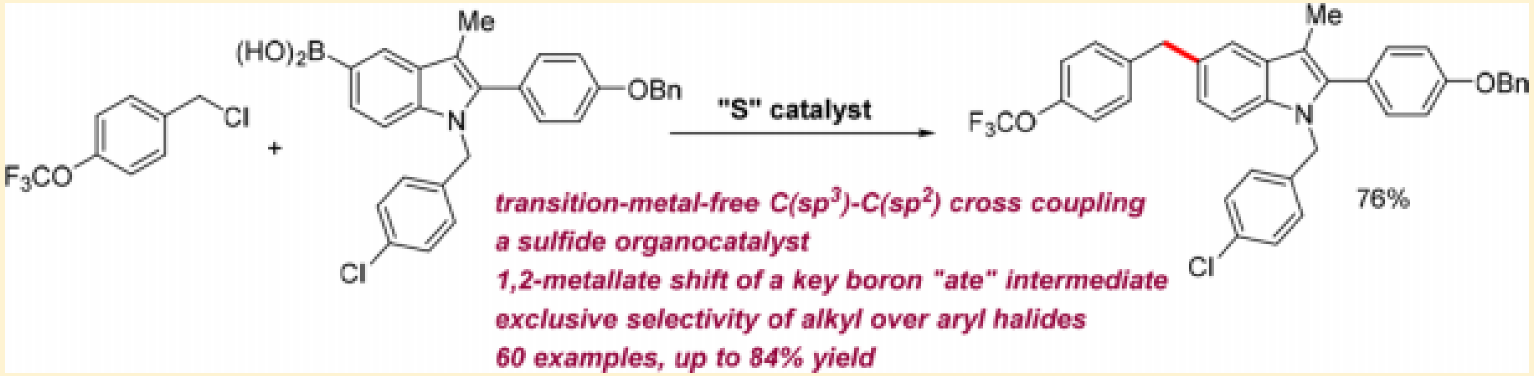
Supporting Information



Cite as: R. R. Merchant *et al*., *Science*
10.1126/science.aar7335 (2018).

# Modular radical cross-coupling with sulfones enables access to sp$^3$-rich (fluoro)alkylated scaffolds

**Rohan R. Merchant,[1*] Jacob T. Edwards,[1*] Tian Qin,[1*] Monika M. Kruszyk,[1] Cheng Bi,[1] Guanda Che,[2] Deng-Hui Bao,[2] Wenhua Qiao,[2] Lijie Sun,[2] Michael R. Collins,[3] Olugbeminiyi O. Fadeyi,[4†] Gary M. Gallego,[3] James J. Mousseau,[4] Philippe Nuhant,[4] Phil S. Baran[1‡]**

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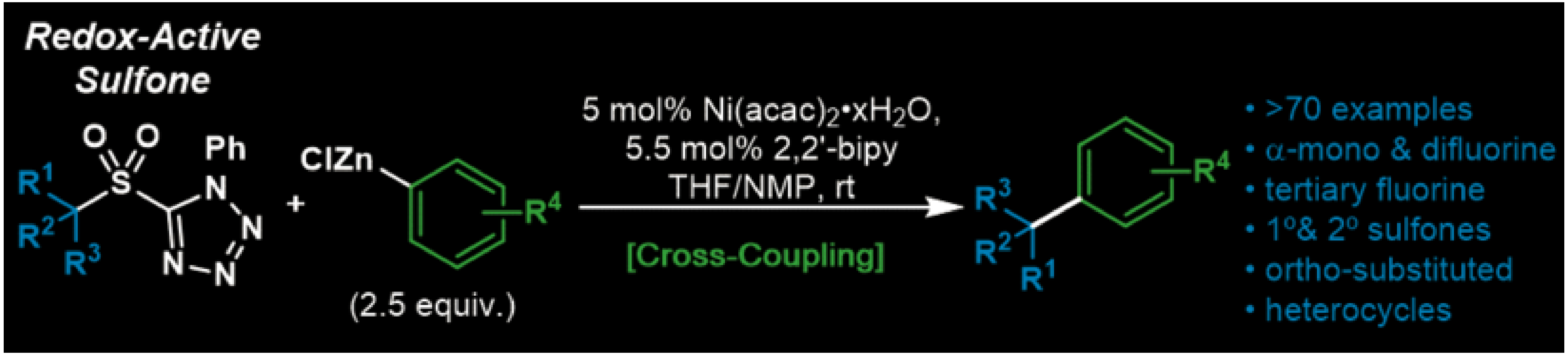
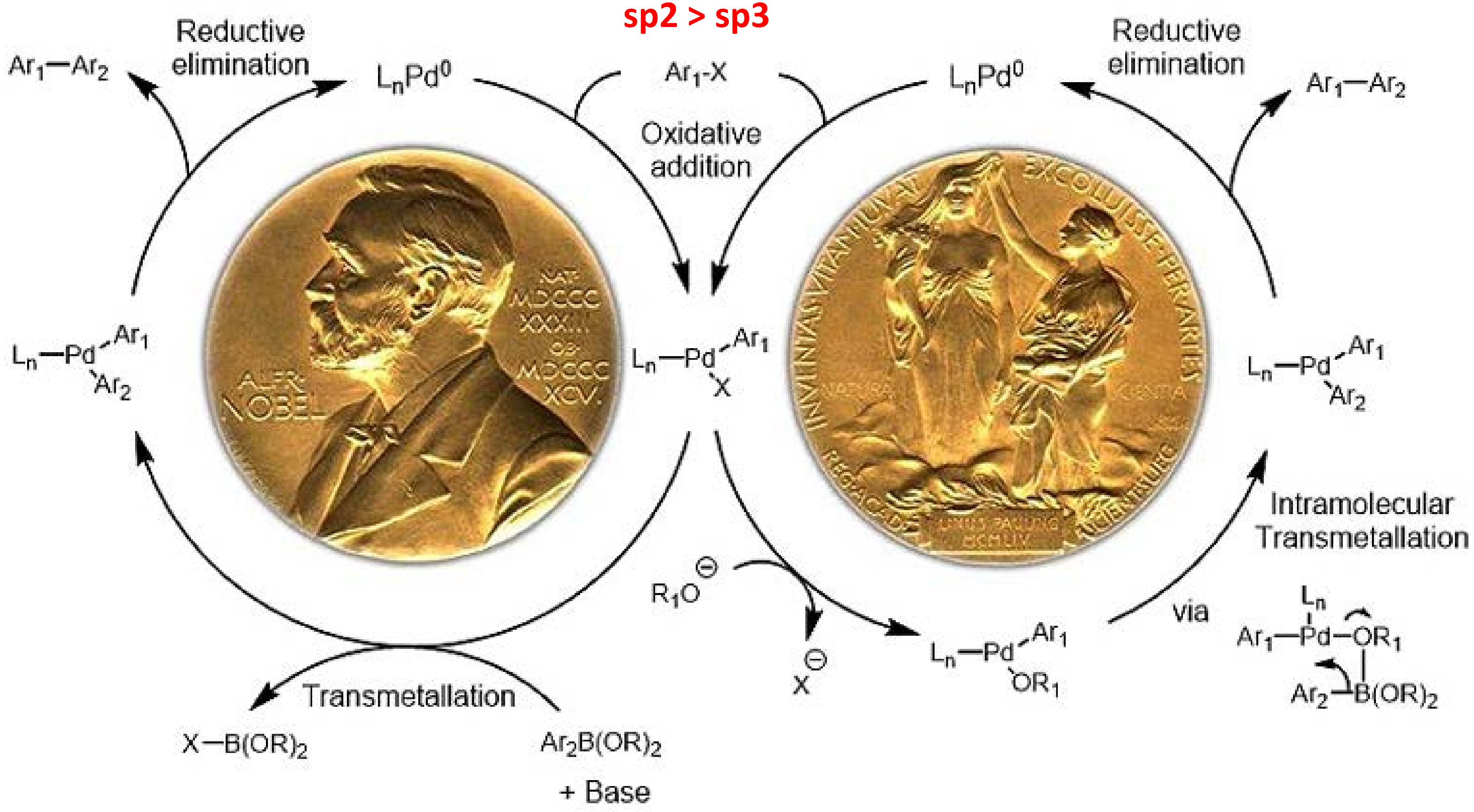


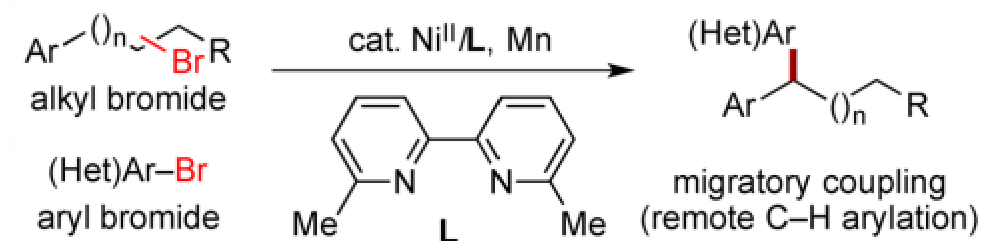
# Transition metal catalyzed mechanism

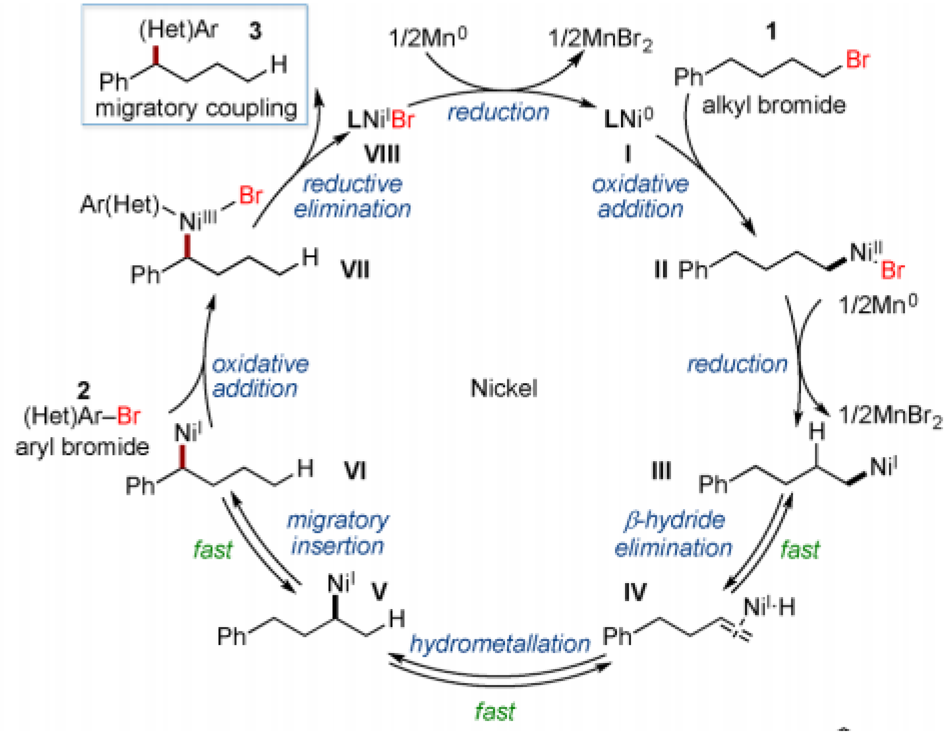
**sp2 > sp3**



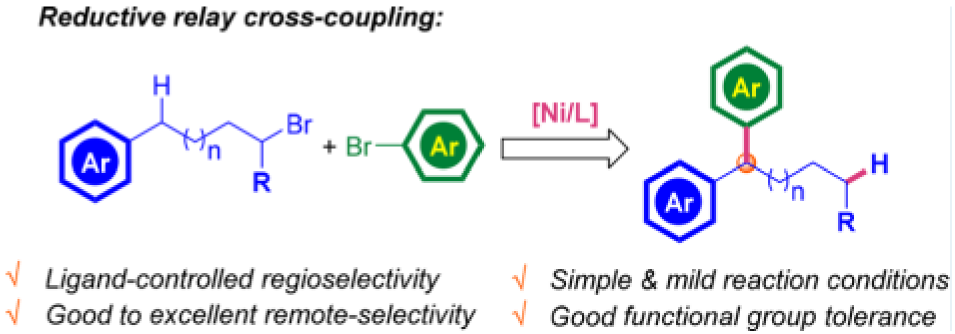
Shaolin Zhu *J. Am. Chem. Soc.* 2017, 139, 13929 −13935

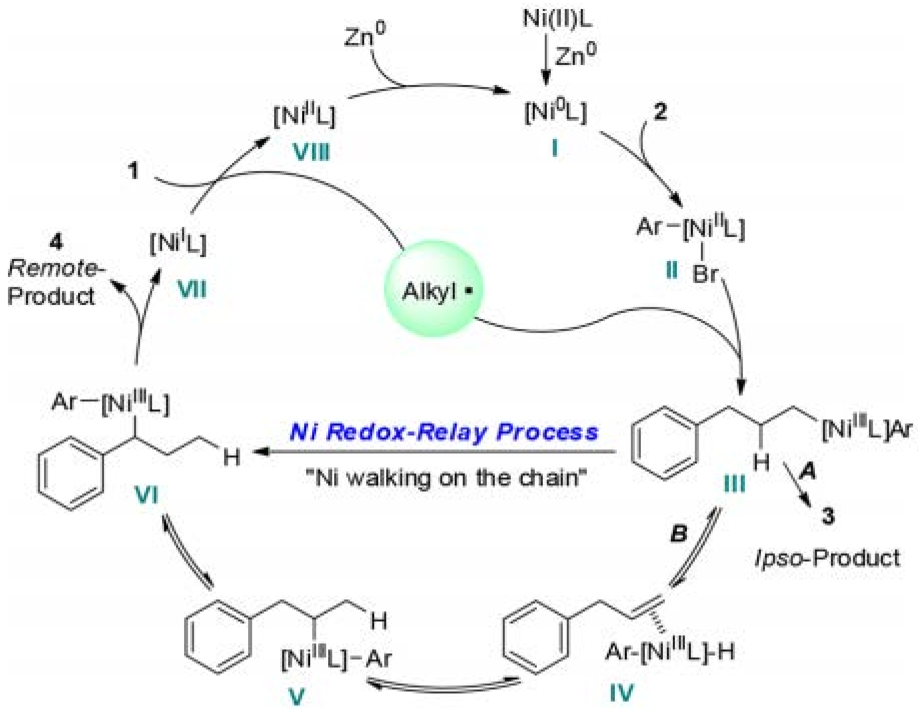
remote $sp^3$ C–H arylation via migratory cross-electrophile coupling



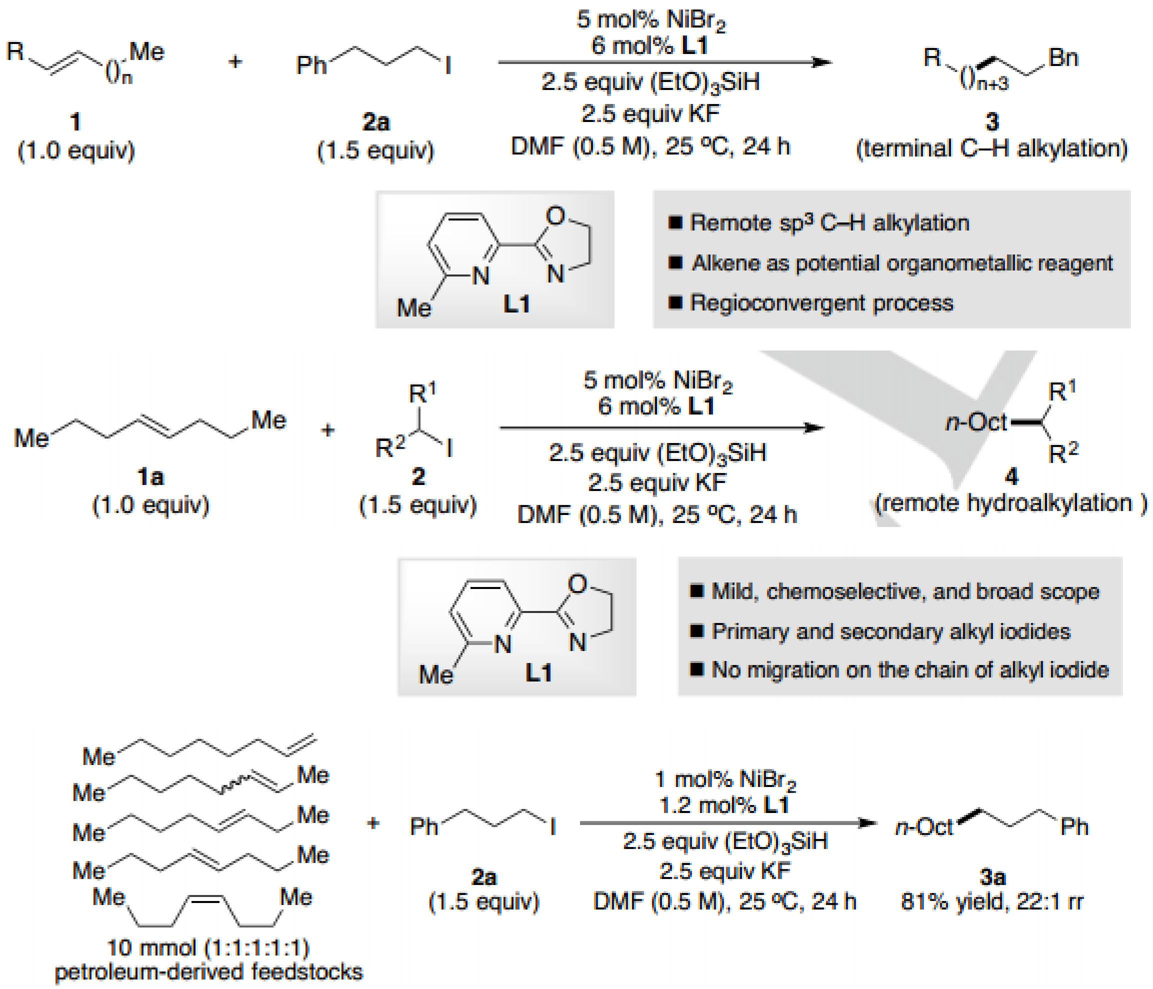

Guoyin Yin *ACS Catal.* 2018, 8, 310−313



# NiH-Catalyzed Reductive Relay Hydroalkylation: A Strategy for Remote sp$^3$ C–H Alkylation of Alkenes

Fang Zhou, Jin Zhu, Yao Zhang, and Shaolin Zhu*




**Scheme 1.** Regioconvergent experiment with lower catalyst loading.

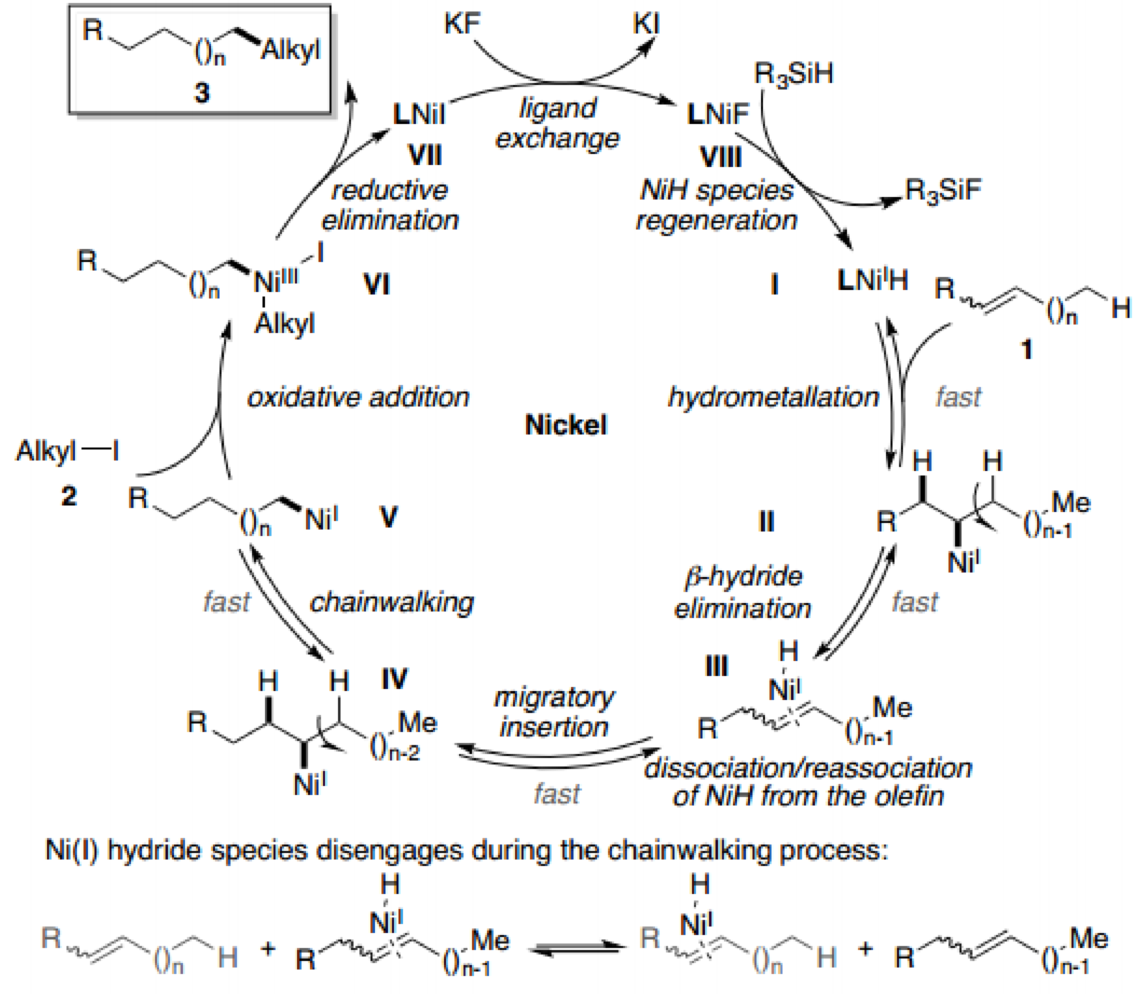



**Figure 2.** Proposed mechanism for remote hydroalkylation.

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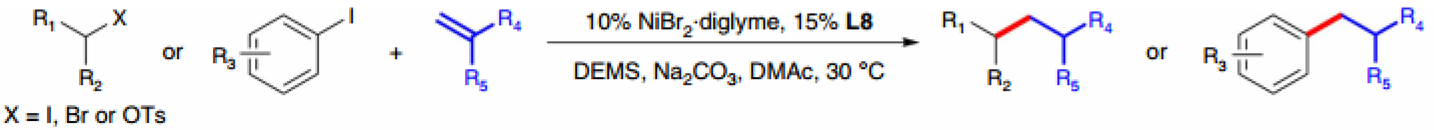
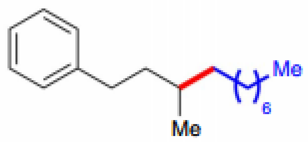
# Practical carbon–carbon bond formation from olefins through nickel-catalyzed reductive olefin hydrocarbonation

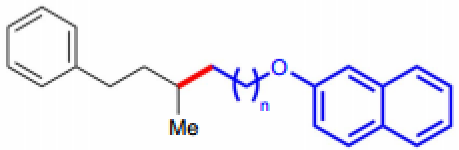
Xi Lu[1,2], Bin Xiao[1], Zhenqi Zhang[1], Tianjun Gong[1], Wei Su[1], Jun Yi[1], Yao Fu[1] & Lei Liu[2]

**Table 2 | Substrates scope for reductive olefin hydrocarbonation reaction.**

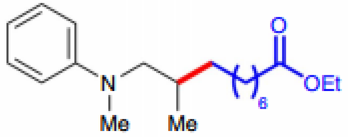


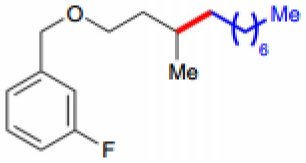
**3** (X = I) 82%*, 93%†



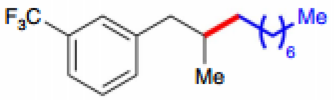
**4** (X = I) n = 3 66%*
**5** (X = I) n = 4 57%*
**6** (X = I) n = 10 70%*



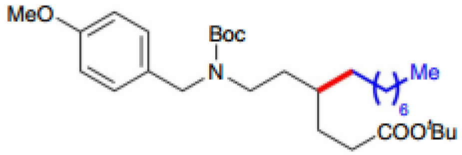
**7** (X = I) 67%*



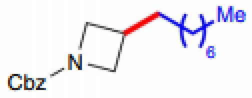
**8** (X = I) 57%†



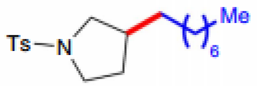
**9** (X = I) 92%†



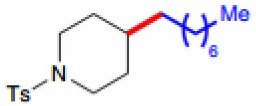
**10** (X = I) 45%†



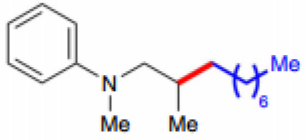
**11** (X = I) 55%†



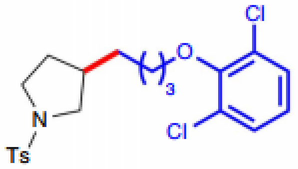
**12** (X = I) 88%†



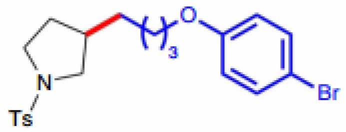
**13** (X = Br) 63%†

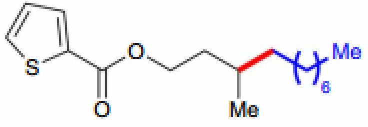


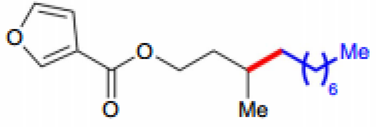
**14** (X = I) 89%†

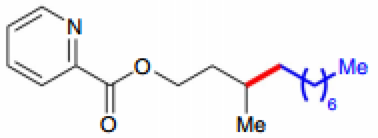


**15** (X = I) 50%†

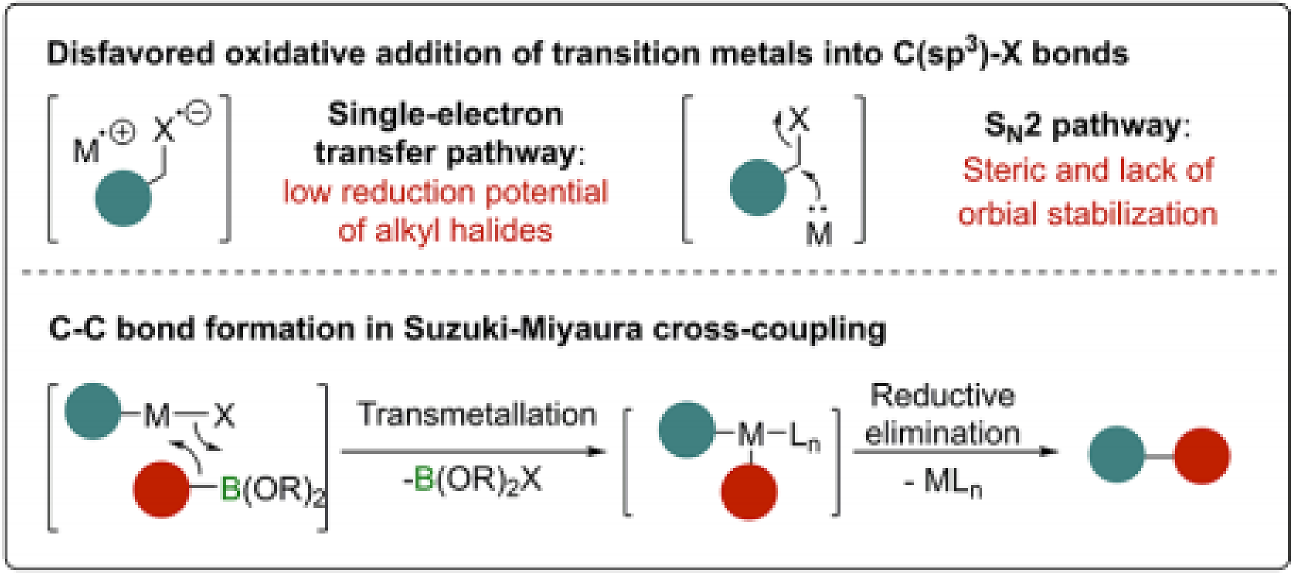








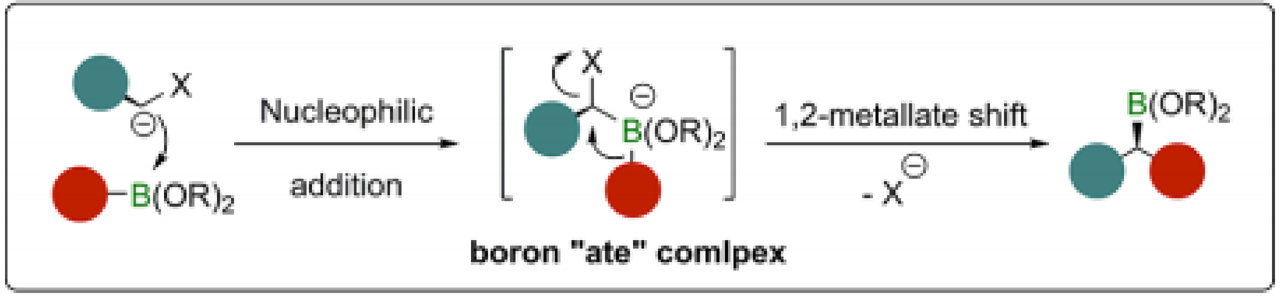
a) Transition-metal-catalyzed Cross-coupling




sp3 > sp2

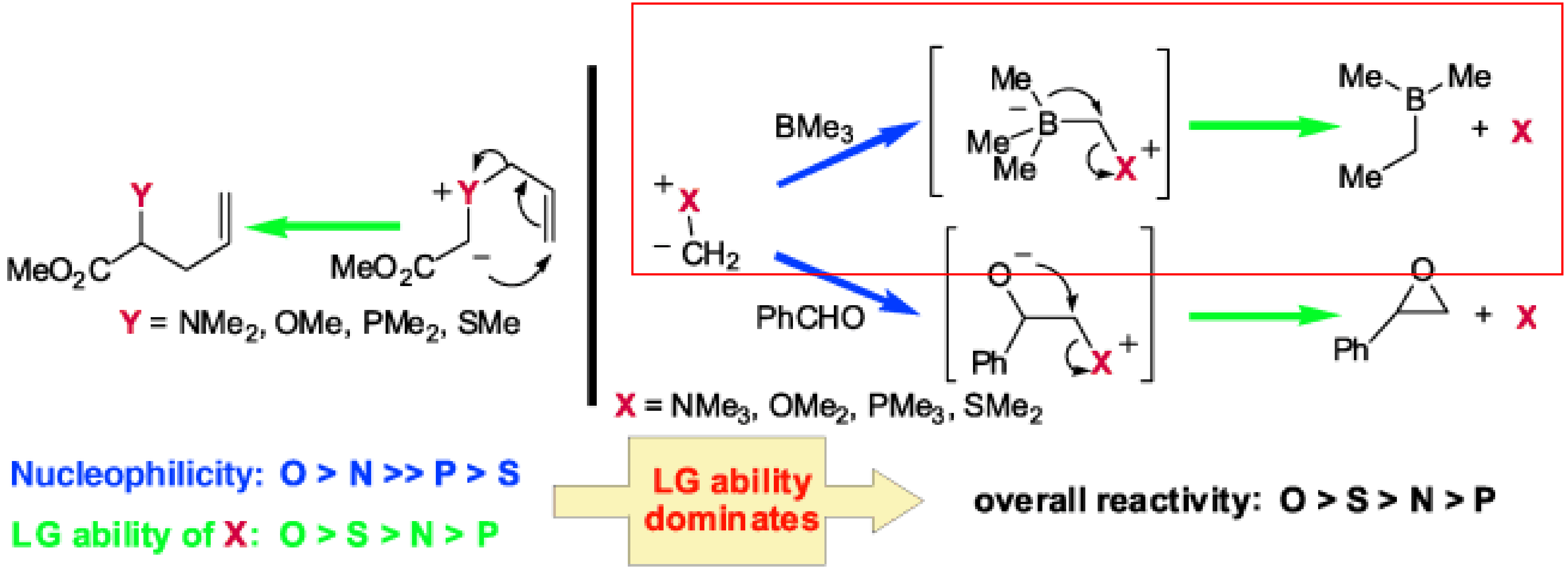
$S_N2$ > $S_NAr$

b) An alternative C-C bond forming mechanism of organoboron




Boronic acids and esters are mild Lewis acids that are able to accept a lone pair of electrons from carbon anions to form anionic boron-centered “ate” complexes.

Aggarwal, V. K. Angew. Chem., Int. Ed. 2005, 44, 5468.




donor/acceptor species

halide-substituted anions, carbenes, ylides

c) Proposed Sulfide-catalyzed Cross-coupling

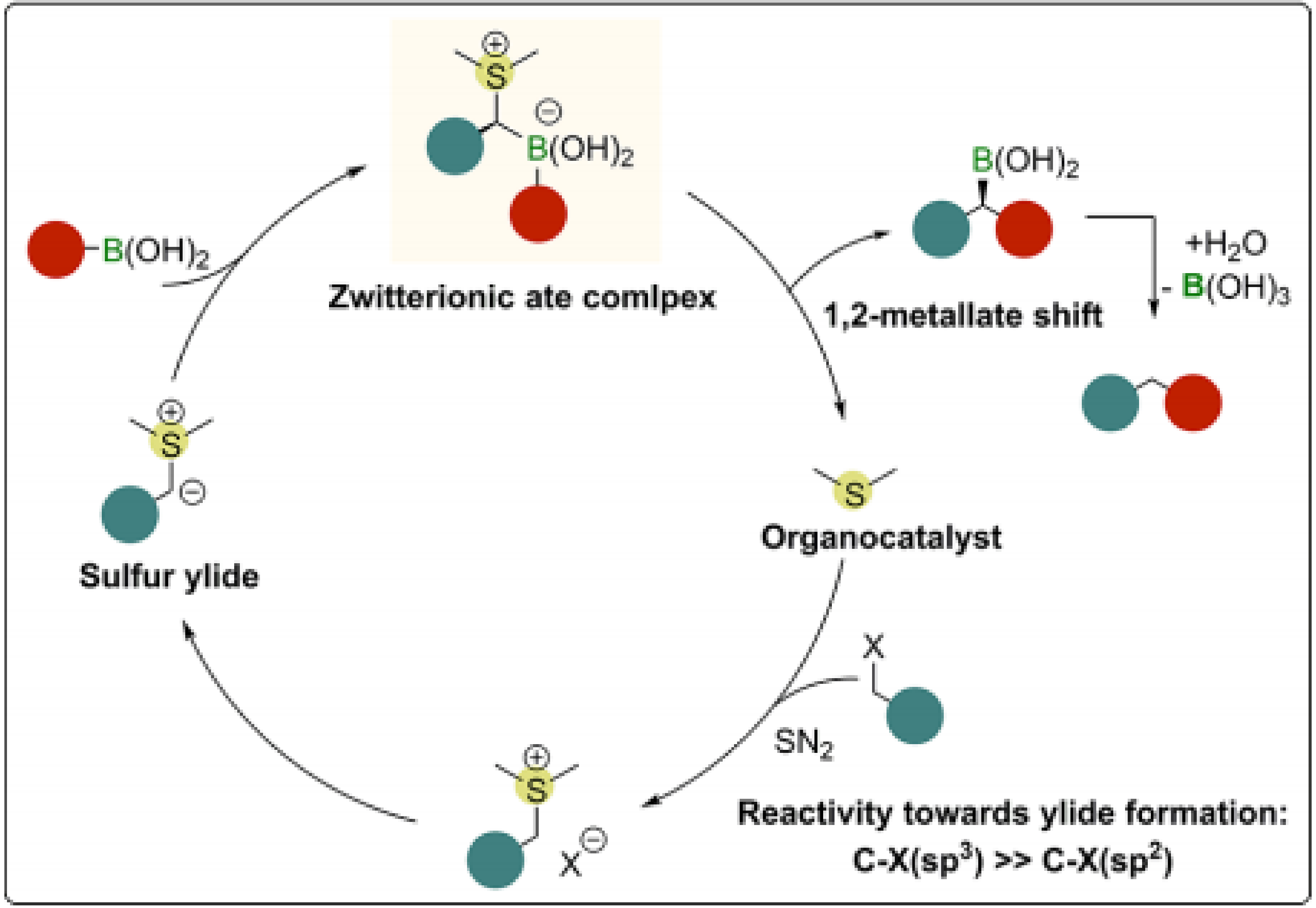
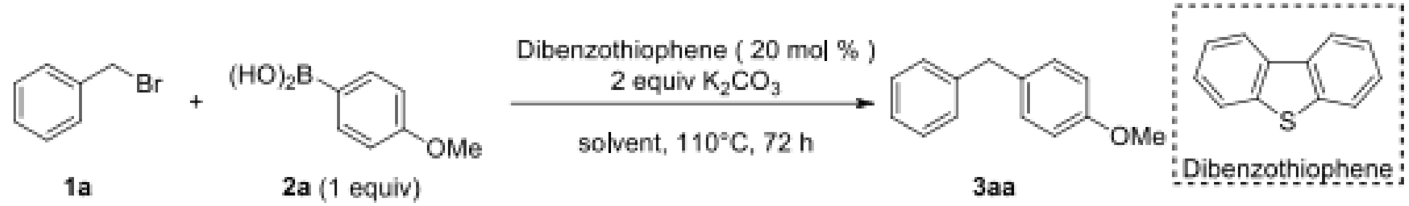


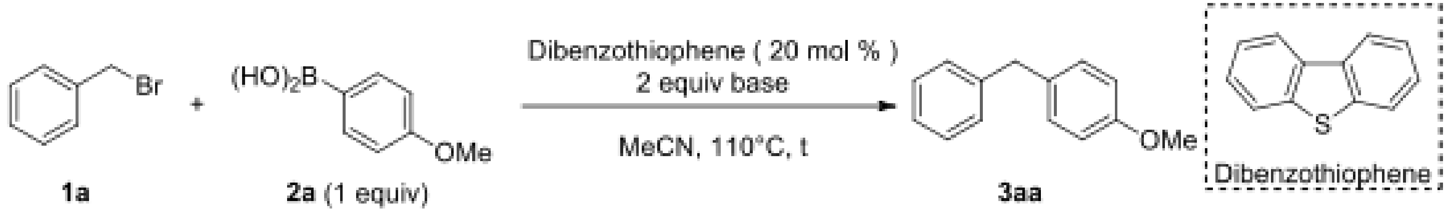
**Table S1.** Solvent screening




| entry | Solvent | yield[b] (%) |
|---|---|---|
| 1 | toluene | 3 |
| 2 | dioxane | 6 |
| 3 | THF | 5 |
| 4 | EA | trace |
| 5 | DMF | trace |
| 6 | DMPU | trace |
| 7 | DMSO | 0 |
| 8 | EtOH | 0 |
| 9 | MeCN | 13 |
| 10[a] | MeCN | 6 |

[a] The reaction was carried out without dibenzolthiophene.

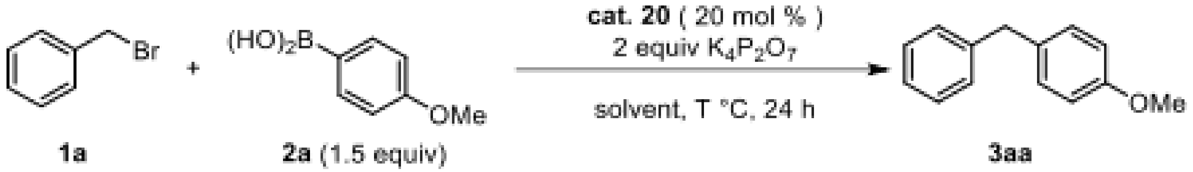
**Table S2.** Base screening




| entry | Base | Time | **1a** (remain) | yield[b] (%) |
|---|---|---|---|---|
| 1 | $K_3PO_4$ | 4h | 7 | 2 |
| 2 | $K_2HPO_4$ | 4h | 87 | 2 |
| 3 | $K_3PO_4$ | 72h | 0 | 2 |
| 4 | $K_2HPO_4$ | 72h | 30 | 17 |
| 5 | $K_2CO_3$ | 72h | 0 | 13 |
| 6[a] | $K_2CO_3$ | 4h | 75 | 2 |
| 7[a] | $K_2CO_3$ | 24h | 65 | 3 |
| 8 | $K_2CO_3$ | 24h | 4 | 10 |
| 9 | $K_4P_2O_7$ | 24h | 9 | 18 |

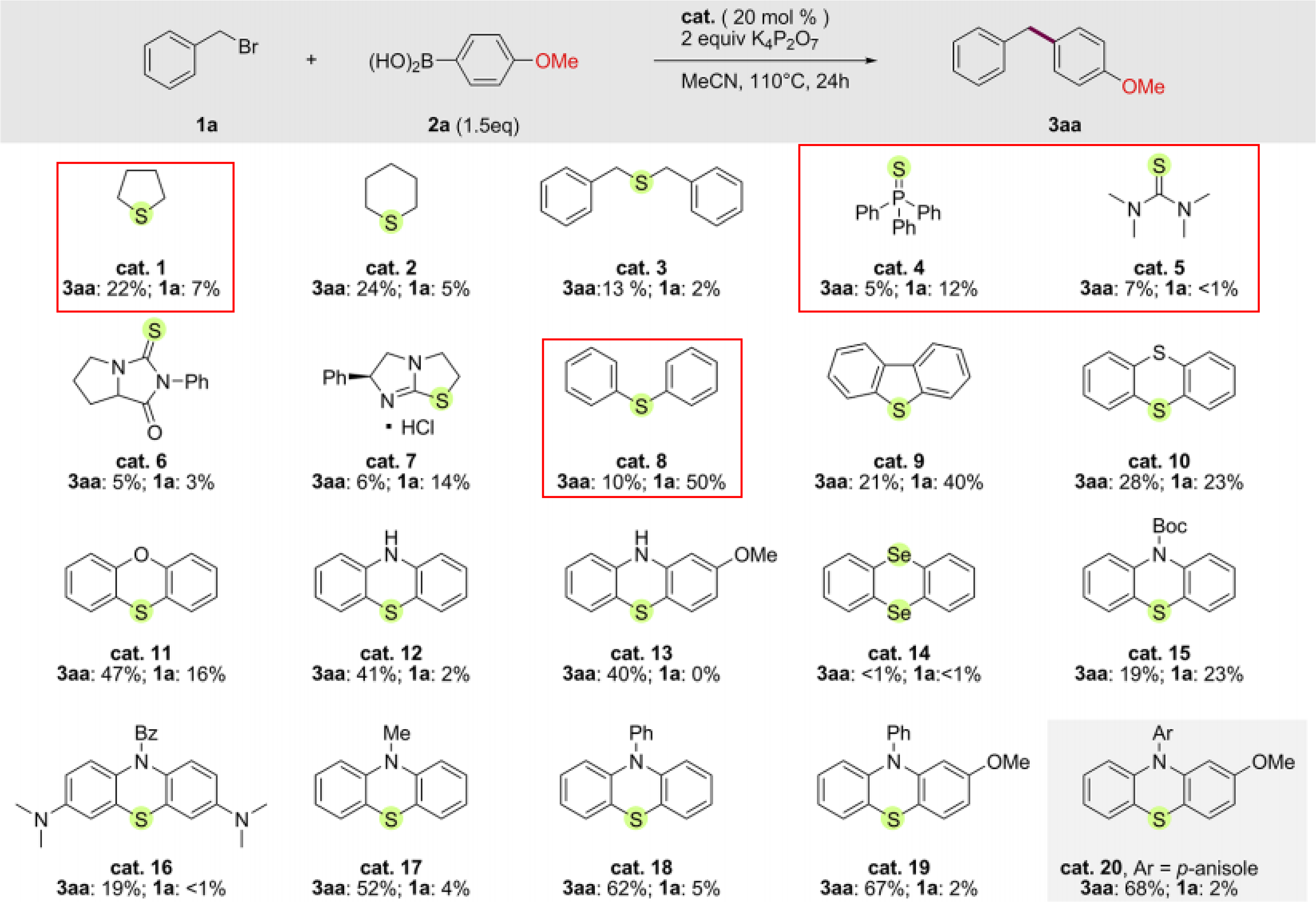
[a] The reaction was carried out with 20 mmol% base.

**Table S3.** Effect of temperature




| entry | T (°C) | yield[b] (%) |
|---|---|---|
| 1 | 110 | 68 |
| 2 | 80 | 54 |
| 3 | 60 | 26 |
| 4 | r.t. | 0.6 |

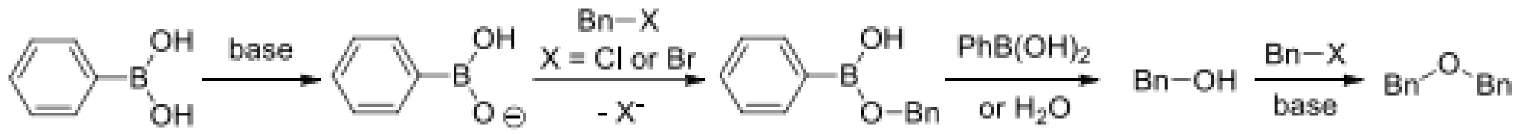
NOTE: a major side reaction was hydrolysis of benzyl halide (**Fig. S1A**). When dialkyl sulfide and **cat. 4-7** were tested, catalyst decomposition and deactivation was observed (**Fig. S1B**).

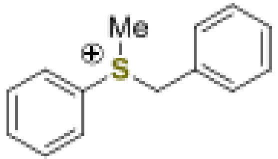


Br
(HO)2B
OMe
cat. ( 20 mol % )
2 equiv K4P2O7
MeCN, 110°C, 24h
OMe
1a
2a (1.5eq)
3aa
cat. 1
3aa: 22%; 1a: 7%
cat. 2
3aa: 24%; 1a: 5%
cat. 3
3aa:13 %; 1a: 2%
Ph Ph Ph
cat. 4
3aa: 5%; 1a: 12%
cat. 5
3aa: 7%; 1a: <1%
N-Ph
cat. 6
3aa: 5%; 1a: 3%
Ph
• HCl
cat. 7
3aa: 6%; 1a: 14%
cat. 8
3aa: 10%; 1a: 50%
cat. 9
3aa: 21%; 1a: 40%
cat. 10
3aa: 28%; 1a: 23%
cat. 11
3aa: 47%; 1a: 16%
cat. 12
3aa: 41%; 1a: 2%
OMe
cat. 13
3aa: 40%; 1a: 0%
cat. 14
3aa: <1%; 1a:<1%
Boc
cat. 15
3aa: 19%; 1a: 23%
Bz
cat. 16
3aa: 19%; 1a: <1%
Me
cat. 17
3aa: 52%; 1a: 4%
Ph
cat. 18
3aa: 62%; 1a: 5%
Ph
OMe
cat. 19
3aa: 67%; 1a: 2%
Ar
OMe
cat. 20, Ar = p-anisole
3aa: 68%; 1a: 2%

## Side reactions.

**A. Hydrolysis:**



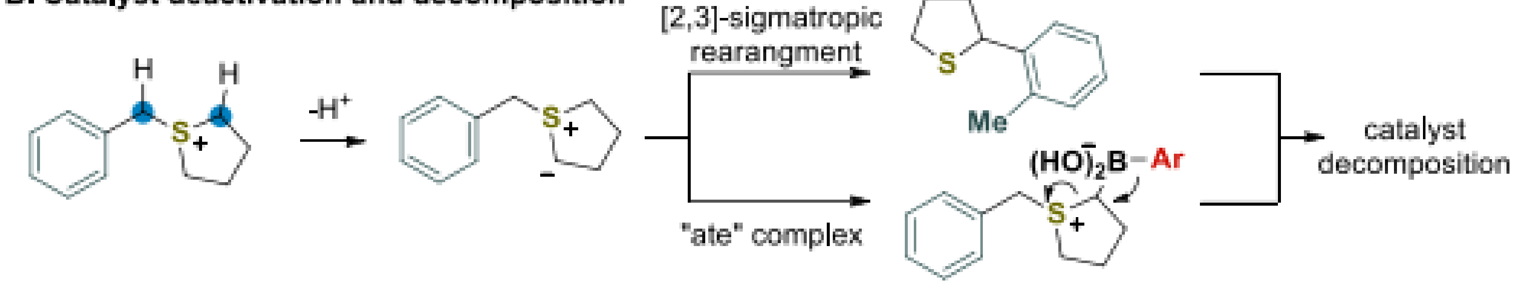

$pKa$ = 16.3 (DMSO)

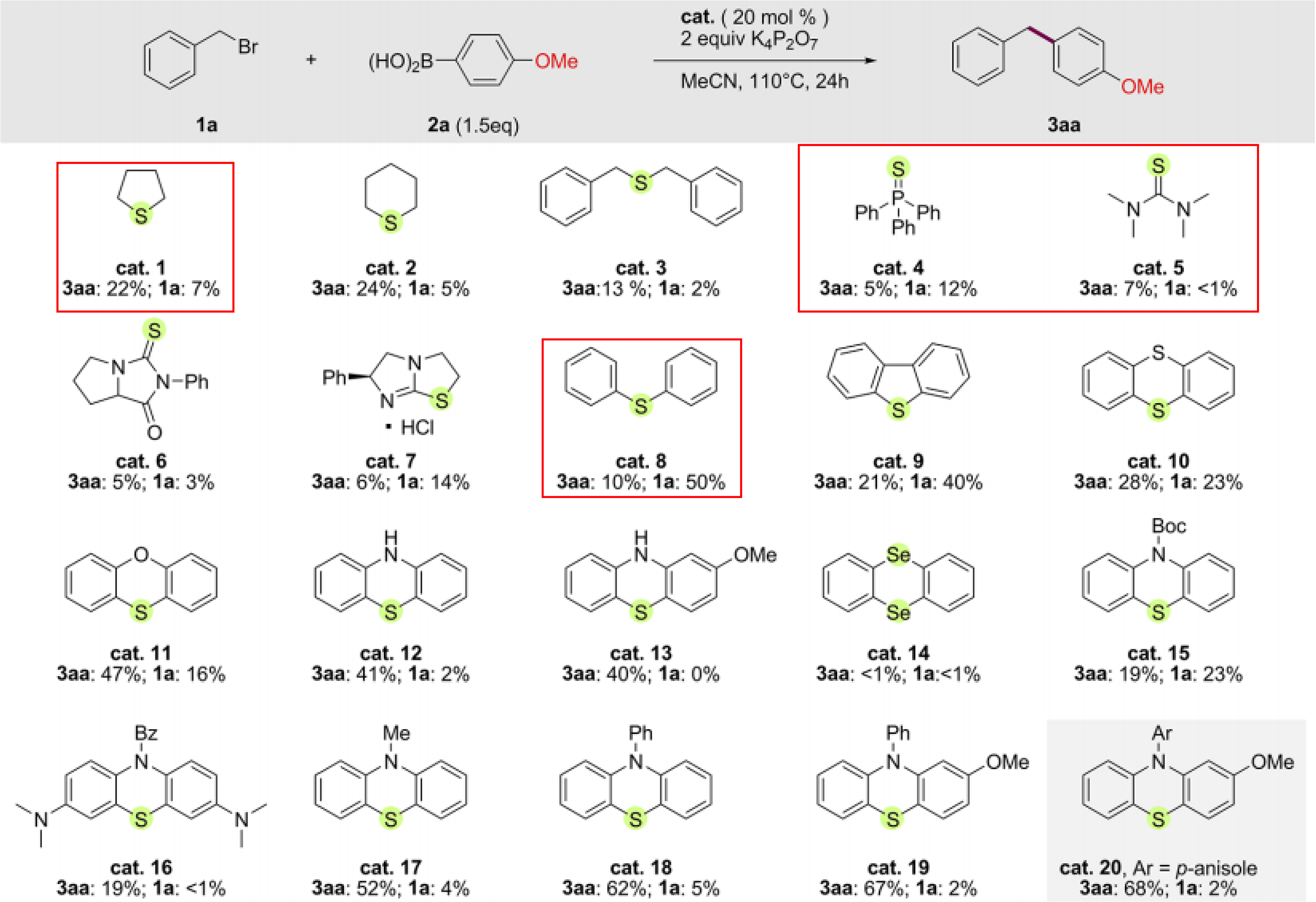
$B(OH)_3$

$pKa$ = 9.23 (in water)

| base: | $K_3PO_4$ | $K_2HPO_4$ | $K_2CO_3$ | $K_4P_2O_7$ |
|---|---|---|---|---|
| conjugate acid: | $HPO_4^{2-}$ | $H_2PO_4^-$ | $HCO_3^-$ | $HP_2O_7^{3-}$ |
| $pKa$: | 12.32 | 6.58 | 10.33 | 9.25 |

**B. Catalyst deactivation and decomposition**





Br
(HO)2B
OMe
cat. ( 20 mol % )
2 equiv K4P2O7
MeCN, 110°C, 24h
OMe
1a
2a (1.5eq)
3aa
cat. 1
3aa: 22%; 1a: 7%
cat. 2
3aa: 24%; 1a: 5%
cat. 3
3aa:13 %; 1a: 2%
cat. 4
3aa: 5%; 1a: 12%
cat. 5
3aa: 7%; 1a: <1%
cat. 6
3aa: 5%; 1a: 3%
cat. 7
3aa: 6%; 1a: 14%
cat. 8
3aa: 10%; 1a: 50%
cat. 9
3aa: 21%; 1a: 40%
cat. 10
3aa: 28%; 1a: 23%
cat. 11
3aa: 47%; 1a: 16%
cat. 12
3aa: 41%; 1a: 2%
cat. 13
3aa: 40%; 1a: 0%
cat. 14
3aa: <1%; 1a:<1%
cat. 15
3aa: 19%; 1a: 23%
cat. 16
3aa: 19%; 1a: <1%
cat. 17
3aa: 52%; 1a: 4%
cat. 18
3aa: 62%; 1a: 5%
cat. 19
3aa: 67%; 1a: 2%
cat. 20, Ar = p-anisole
3aa: 68%; 1a: 2%

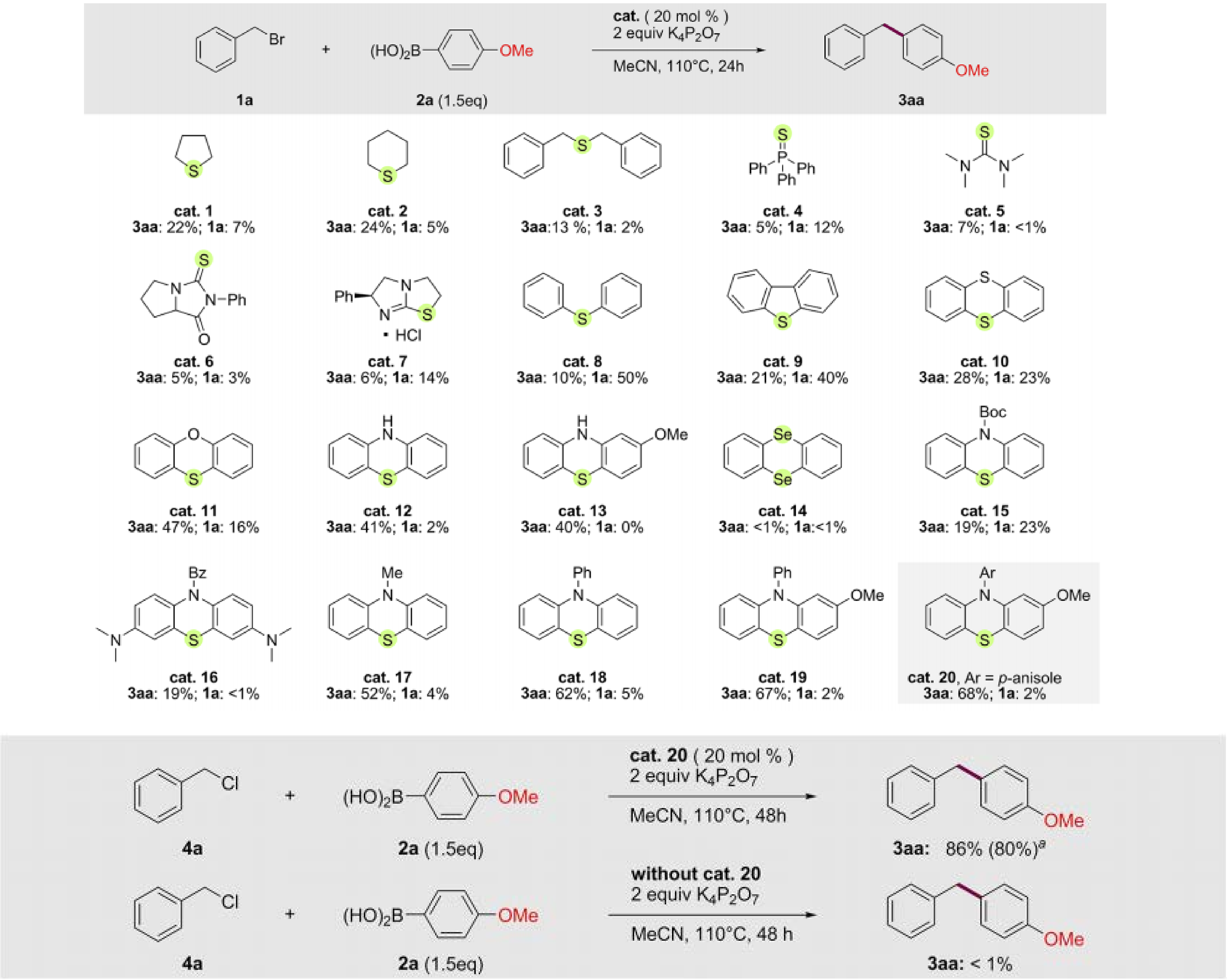
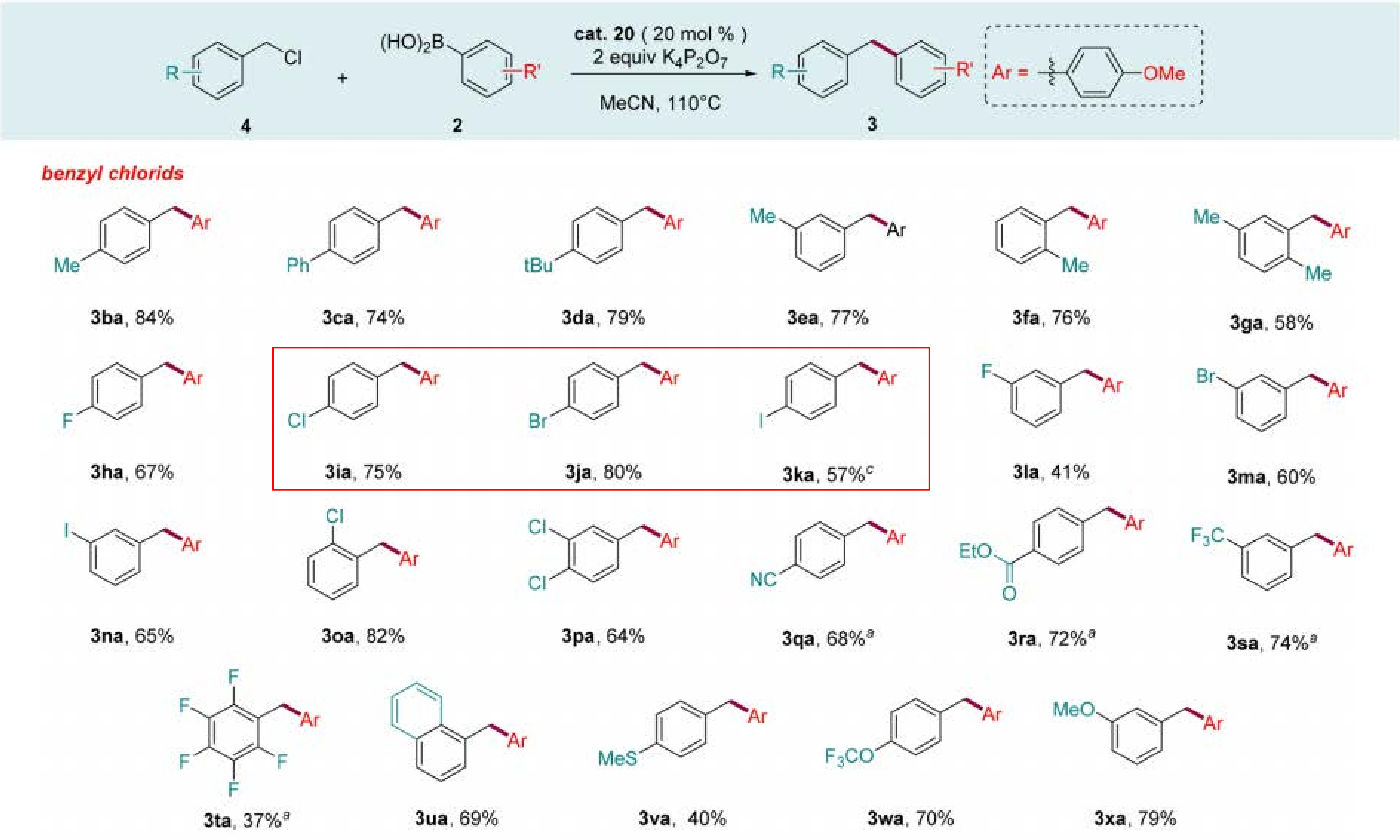
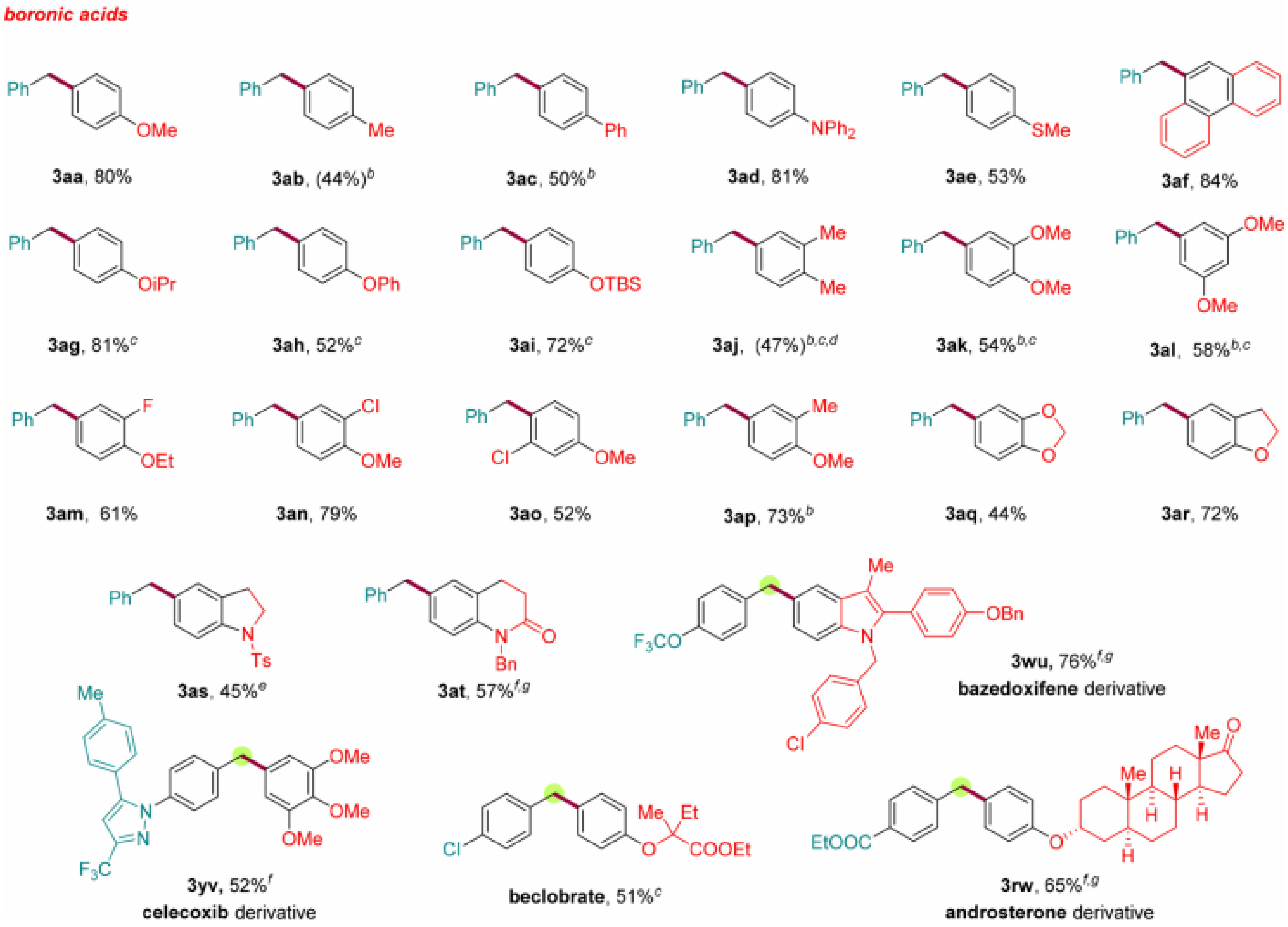

cat. ( 20 mol % )
2 equiv $K_4P_2O_7$
MeCN, 110°C, 24h
1a
2a (1.5eq)
3aa
cat. 1
3aa: 22%; 1a: 7%
cat. 2
3aa: 24%; 1a: 5%
cat. 3
3aa:13 %; 1a: 2%
cat. 4
3aa: 5%; 1a: 12%
cat. 5
3aa: 7%; 1a: <1%
cat. 6
3aa: 5%; 1a: 3%
cat. 7
3aa: 6%; 1a: 14%
cat. 8
3aa: 10%; 1a: 50%
cat. 9
3aa: 21%; 1a: 40%
cat. 10
3aa: 28%; 1a: 23%
cat. 11
3aa: 47%; 1a: 16%
cat. 12
3aa: 41%; 1a: 2%
cat. 13
3aa: 40%; 1a: 0%
cat. 14
3aa: <1%; 1a:<1%
cat. 15
3aa: 19%; 1a: 23%
cat. 16
3aa: 19%; 1a: <1%
cat. 17
3aa: 52%; 1a: 4%
cat. 18
3aa: 62%; 1a: 5%
cat. 19
3aa: 67%; 1a: 2%
cat. 20, Ar = p-anisole
3aa: 68%; 1a: 2%
cat. 20 ( 20 mol % )
2 equiv $K_4P_2O_7$
MeCN, 110°C, 48h
4a
2a (1.5eq)
3aa: 86% (80%)[a]
without cat. 20
2 equiv $K_4P_2O_7$
MeCN, 110°C, 48 h
4a
2a (1.5eq)
3aa: < 1%

**Table 1. Substrate Scope of the Transition-Metal-Free C(sp$^3$)−C(sp$^2$) Cross-Coupling Reaction**




boronic acids
3aa, 80%
3ab, (44%)[b]
3ac, 50%[b]
3ad, 81%
3ae, 53%
3af, 84%
3ag, 81%[c]
3ah, 52%[c]
3ai, 72%[c]
3aj, (47%)[b,c,d]
3ak, 54%[b,c]
3al, 58%[b,c]
3am, 61%
3an, 79%
3ao, 52%
3ap, 73%[b]
3aq, 44%
3ar, 72%
3as, 45%[e]
3at, 57%[f,g]
3wu, 76%[f,g]
bazedoxifene derivative
3yv, 52%[f]
celecoxib derivative
beclobrate, 51%[c]
3rw, 65%[f,g]
androsterone derivative

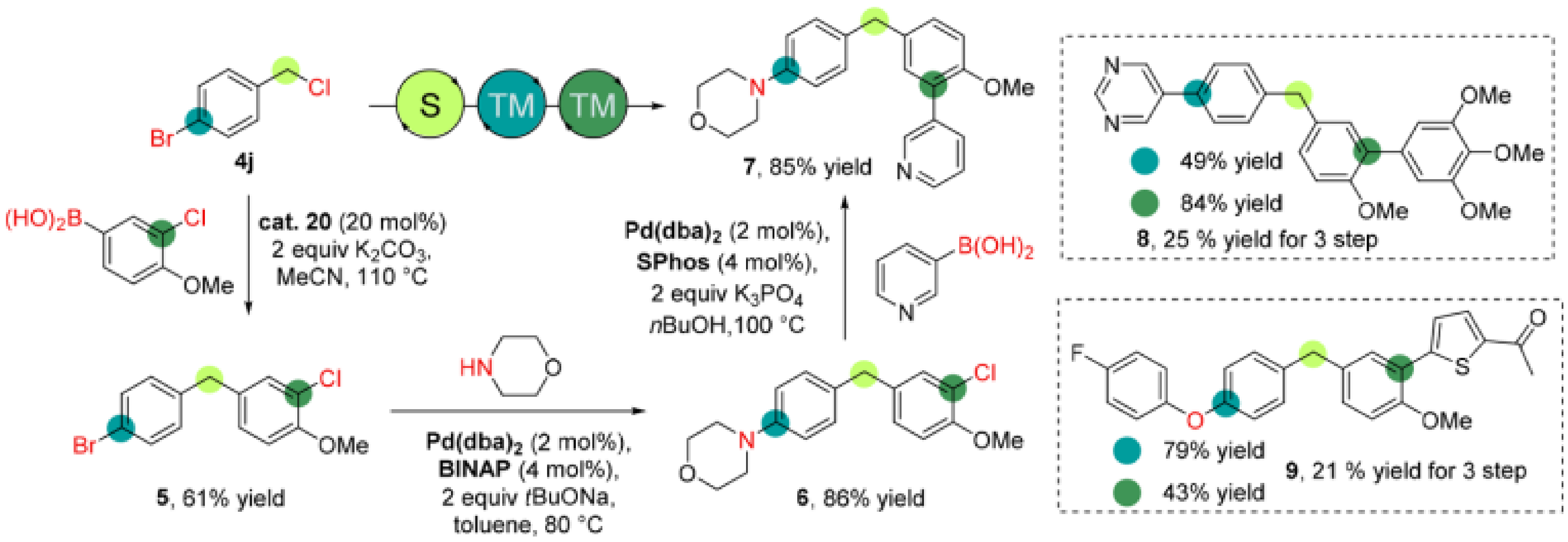
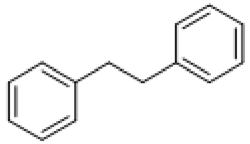
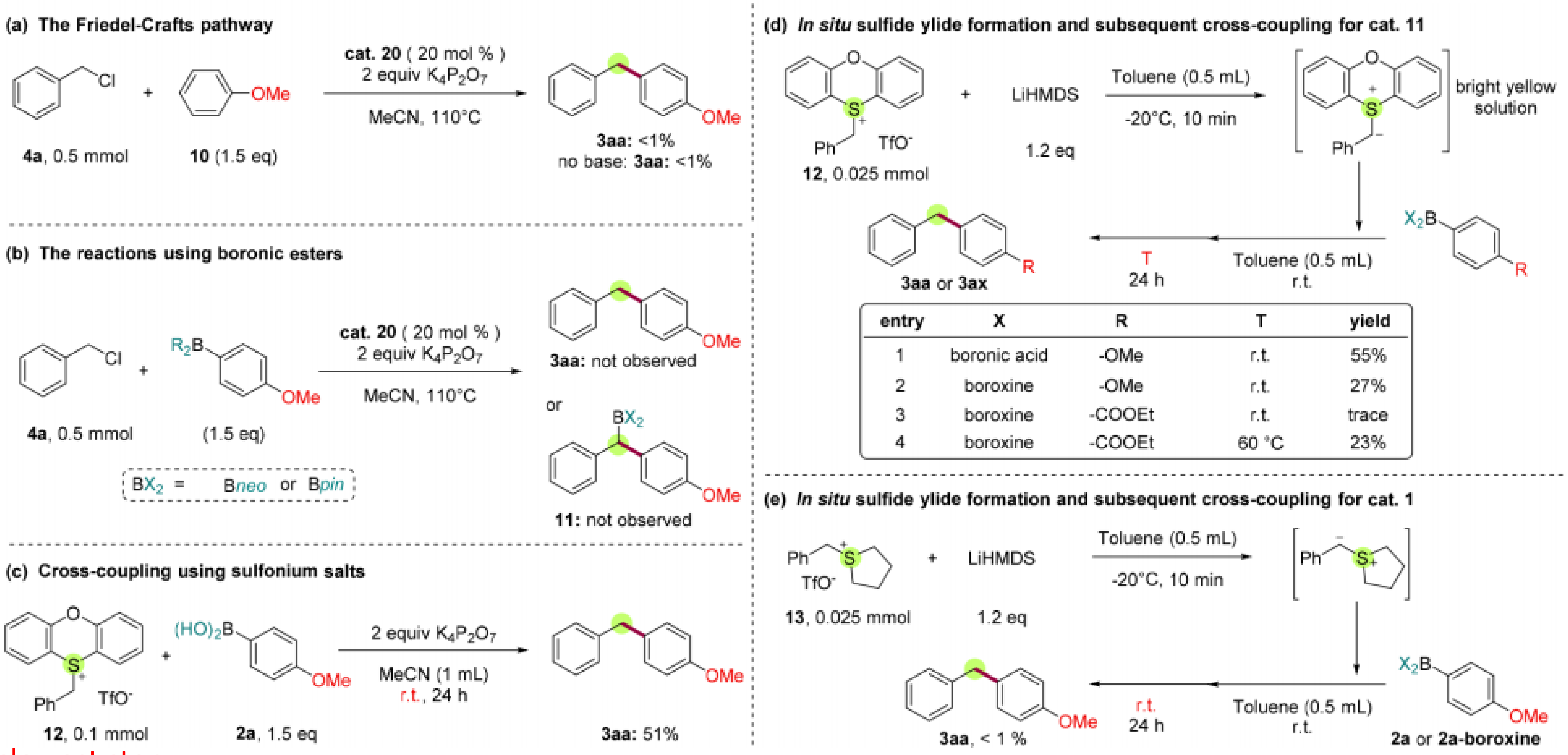



**Figure 3.** Modular synthesis of diaryl methane scaffolds using sequential cross-coupling reactions.

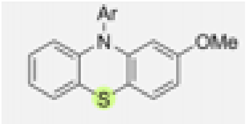





| entry | X | R | T | yield |
|---|---|---|---|---|
| 1 | boronic acid | -OMe | r.t. | 55% |
| 2 | boroxine | -OMe | r.t. | 27% |
| 3 | boroxine | -COOEt | r.t. | trace |
| 4 | boroxine | -COOEt | 60 °C | 23% |

slowest step

**Figure 4.** Mechanistic experiments.



Science REPORTS

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# Modular radical cross-coupling with sulfones enables access to sp$^3$-rich (fluoro)alkylated scaffolds

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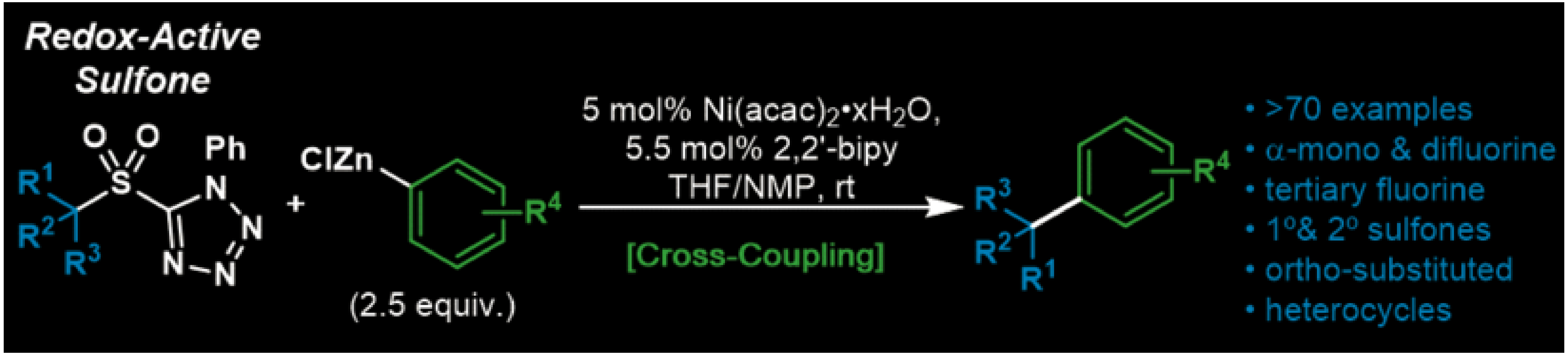


https://chemrxiv.org/

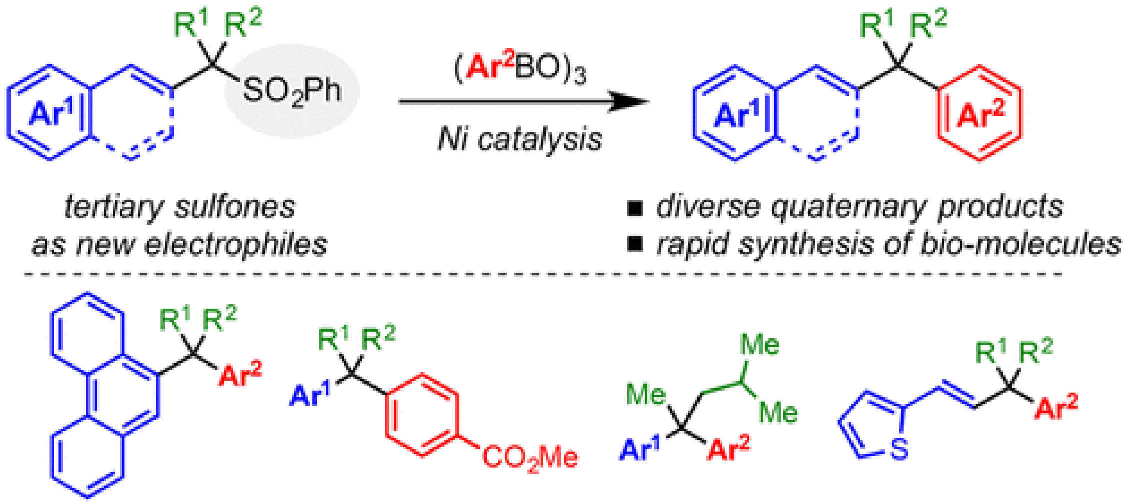
**Sulfones: A New Functional Group for Modular Radical Cross-Coupling**

http://science.sciencemag.org/content/early/2018/02/16/science.aar7335

**Modular radical cross-coupling with sulfones enables access to $sp^3$-rich (fluoro)alkylated scaffolds**

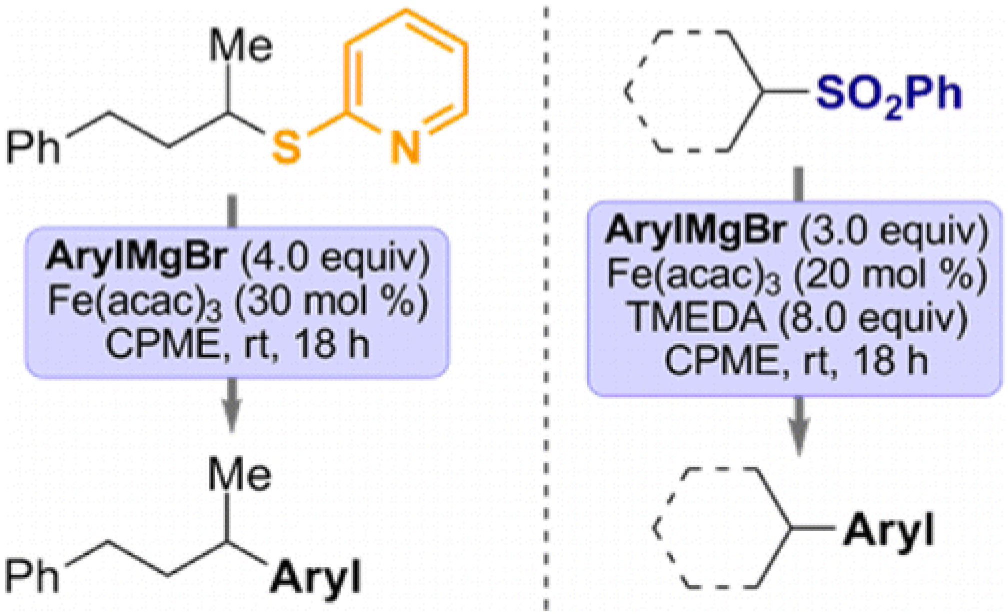
Masakazu Nambo, Cathleen M. Crudden

*J. Am. Chem. Soc. 2018, 140, 1, 78-81*



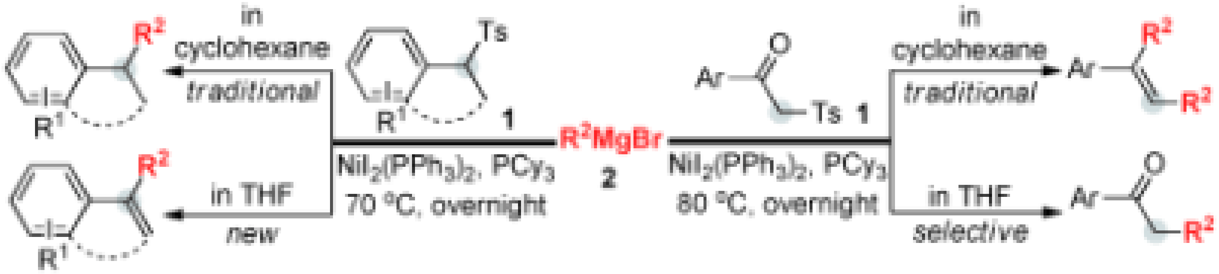

Scott E. Denmark

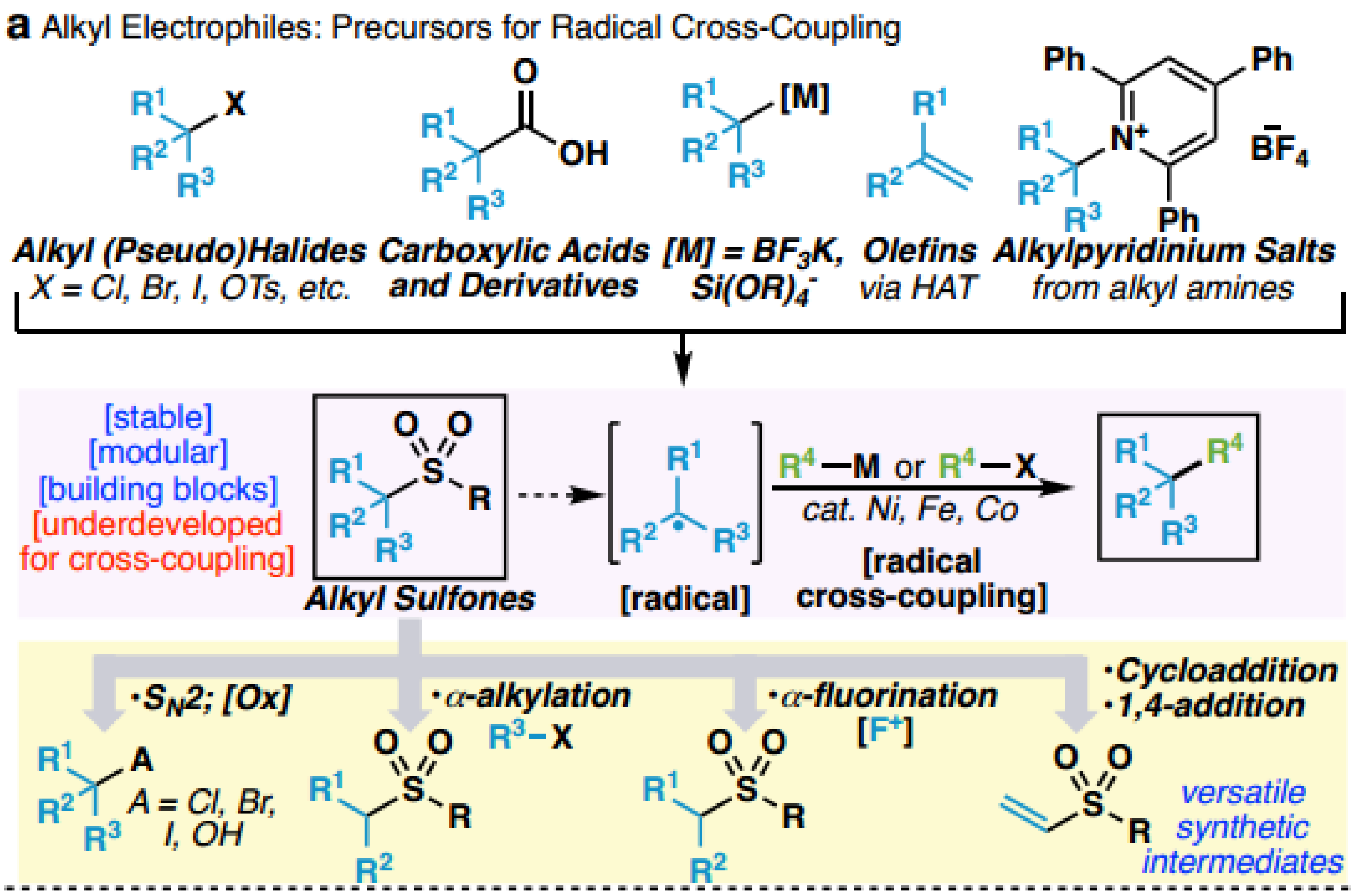
*J. Org. Chem. 2013. 78, 24, 12593-12628*

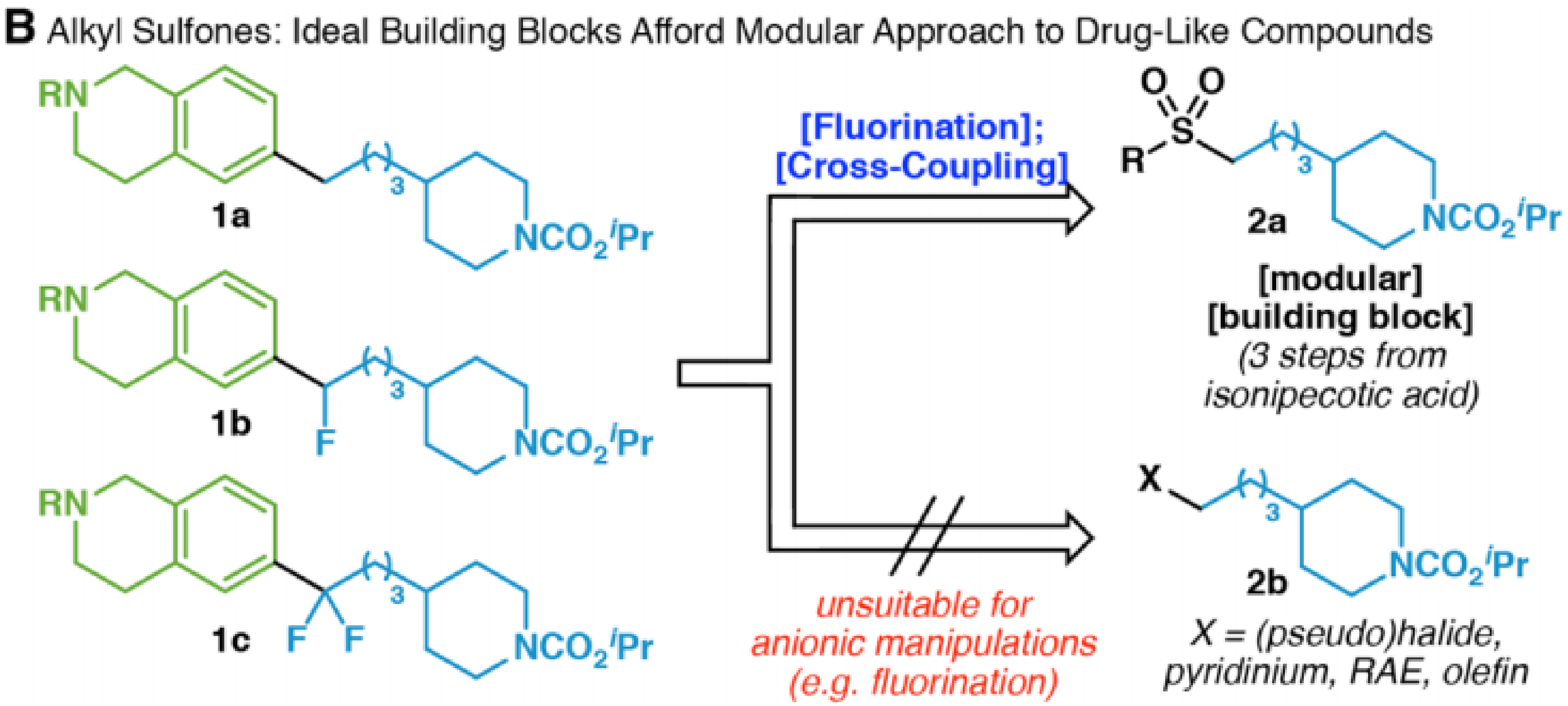



Jin-Heng Li

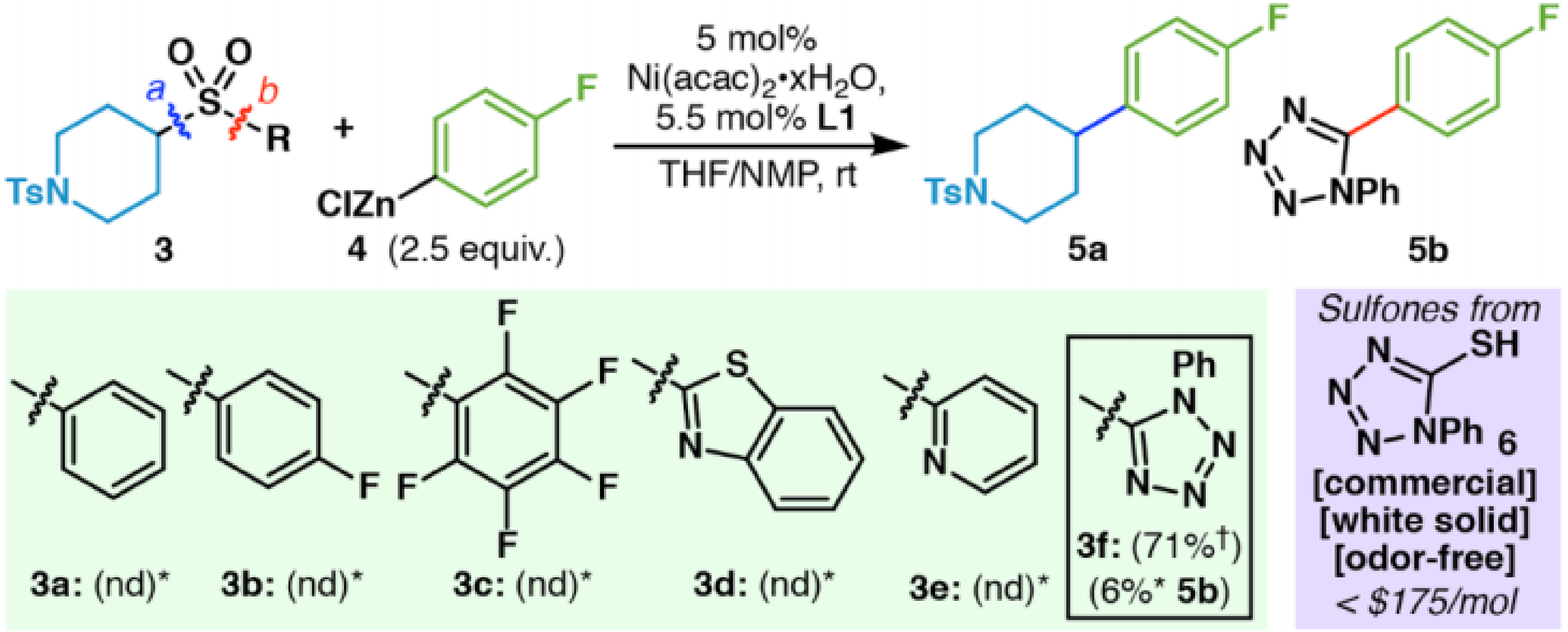
*Angew. Chem. Int. Ed. 51, 9909–9913 (2012)*




a Alkyl Electrophiles: Precursors for Radical Cross-Coupling
Alkyl (Pseudo)Halides
X = Cl, Br, I, OTs, etc.
Carboxylic Acids and Derivatives
[M] = BF3K, Si(OR)4-
Olefins
via HAT
Alkylpyridinium Salts
from alkyl amines
[stable]
[modular]
[building blocks]
[underdeveloped
for cross-coupling]
Alkyl Sulfones
[radical]
R4—M or R4—X
cat. Ni, Fe, Co
[radical
cross-coupling]
·SN2; [Ox]
A = Cl, Br, I, OH
·α-alkylation
R3–X
·α-fluorination
[F+]
·Cycloaddition
·1,4-addition
versatile
synthetic
intermediates

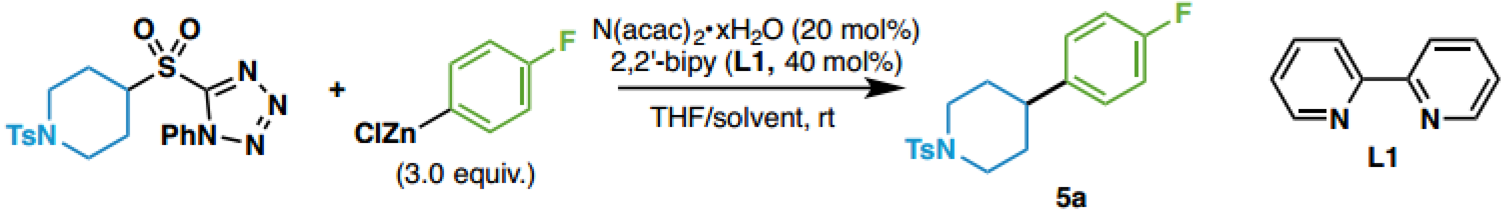

B Alkyl Sulfones: Ideal Building Blocks Afford Modular Approach to Drug-Like Compounds
RN
1a
NCO2iPr
1b
F
1c
F F
[Fluorination];
[Cross-Coupling]
unsuitable for
anionic manipulations
(e.g. fluorination)
O O
S
R
3
2a
[modular]
[building block]
(3 steps from
isonipecotic acid)
X
2b
X = (pseudo)halide,
pyridinium, RAE, olefin

**C** Initial Investigations and Optimization: Sulfones as Radical Cross-Coupling Electrophiles



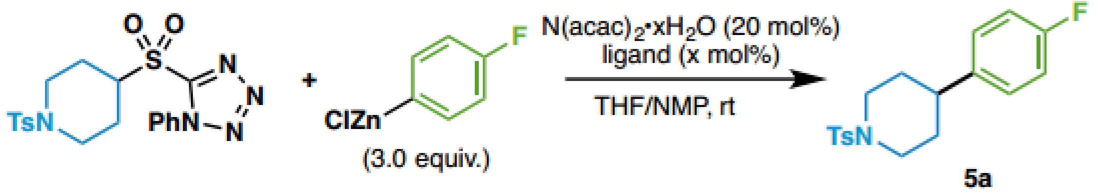

***Key finding:** Phenyl tetrazole (PT, **3f**) sulfones exclusively afford radical cross-coupling product under Ni-catalyzed Negishi arylation conditions*

*Evaluation of solvents* (**Table S1**).

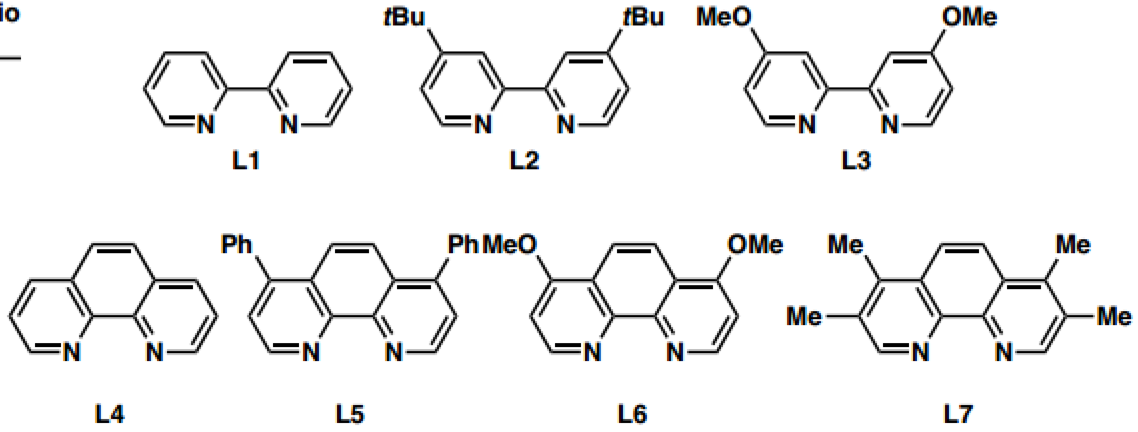



| Solvent | GC-FID Ratio (5a/IS) | $^{19}F$ NMR Yield (%) |
|---|---|---|
| THF | 0 | nd |
| $Et_2O$ | 0.03 | nd |
| $CH_2Cl_2$ | 0.02 | nd |
| 2-MeTHF | 0 | nd |
| PhMe | 0.02 | nd |
| MeCN | 0.04 | nd |
| **NMP** | **0.83** | **66** |
| DMPU | 0.41 | nd |
| 1,4-dioxane | 0.04 | nd |
| DMA | 0.67 | nd |

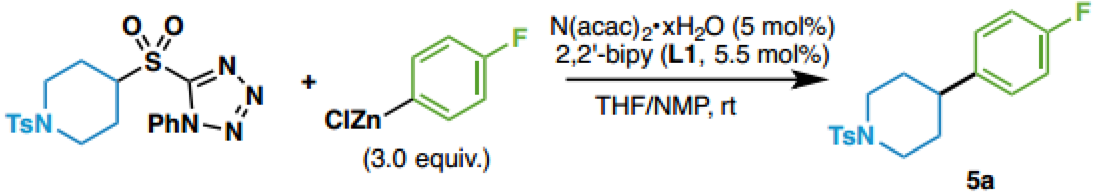
*Evaluation of ligands* (**Table S2**).




| Ligand | mol % | GC-FID Ratio (5a/IS) |
|---|---|---|
| L1 | 20 | 0.81 |
| L1 | 40 | 0.80 |
| L2 | 20 | 0.67 |
| L2 | 40 | 0.65 |
| L3 | 20 | 0.41 |
| L3 | 40 | 0.31 |
| L4 | 20 | 0.50 |
| L4 | 40 | 0.62 |
| L5 | 20 | 0.60 |
| L5 | 40 | 0.52 |
| L6 | 20 | 0.23 |
| L6 | 40 | 0.24 |
| L7 | 20 | 0.18 |
| L7 | 40 | 0.15 |



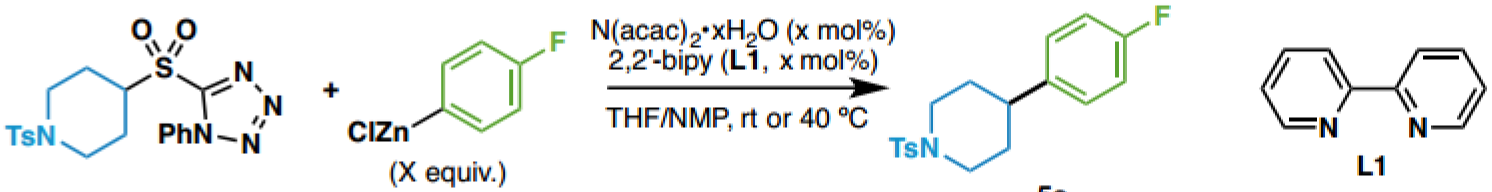
*Evaluation of Catalyst Concentration* (**Table S3**).




| NMP (mL) | GC-FID Ratio (5a/IS) |
|---|---|
| 0.50 | 1.07 |
| 0.68 | 1.11 |
| 1.00 | 1.07 |
| 1.40 | 1.01 |
| 1.70 | 1.11 |
| 2.00 | 1.02 |

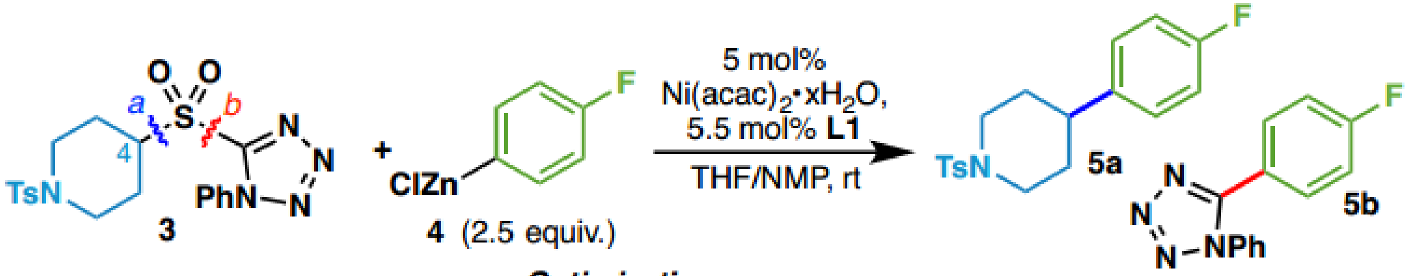
*Similar amounts of product formation are observed over a range of catalyst concentrations.*

*Evaluation of arylzinc loading* (**Table S4**).



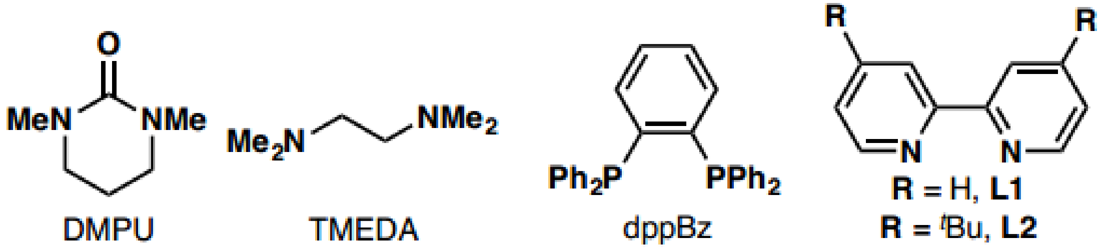

| Ni mol% (Ni/L ratio) | ArZnCl (equiv.) | T/°C | GC-FID Ratio (5a/IS) | Observation |
|---|---|---|---|---|
| 20% (1:2) | 3.0 | 40 | 0.59:1.0 | |
| 20% (1:2) | 3.0 | 40 | 0.85:1.0 | |
| 20% (1:1.1) | 3.0 | rt | 0.81:1.0 | |
| 10% (1:1.1) | 3.0 | rt | 1.0:1.0 | |
| **5% (1:1.1)** | **3.0** | **rt** | **1.1:1.0** | |
| **2.5% (1:1.1)** | **3.0** | **rt** | **1.1:1.0** | |
| 5% (1:1.1) | 3.0 | rt | 0.91:1.0 | |
| **5% (1:1.1)** | **2.5** | **rt** | **1.1:1.0** | **71% isolated yield** |
| 5% (1:1.1) | 2.0 | rt | 0.92:1.0 | |
| 5% (1:1.1) | 1.2 | rt | 0.48:1.0 | |
| 20% (1:1) | $Ph_2Zn$ (1.5) | rt | 0.64:1.0 | |

*Evaluation of alternative Ni sources, metal catalysts, and ligands* (**Table S5**).



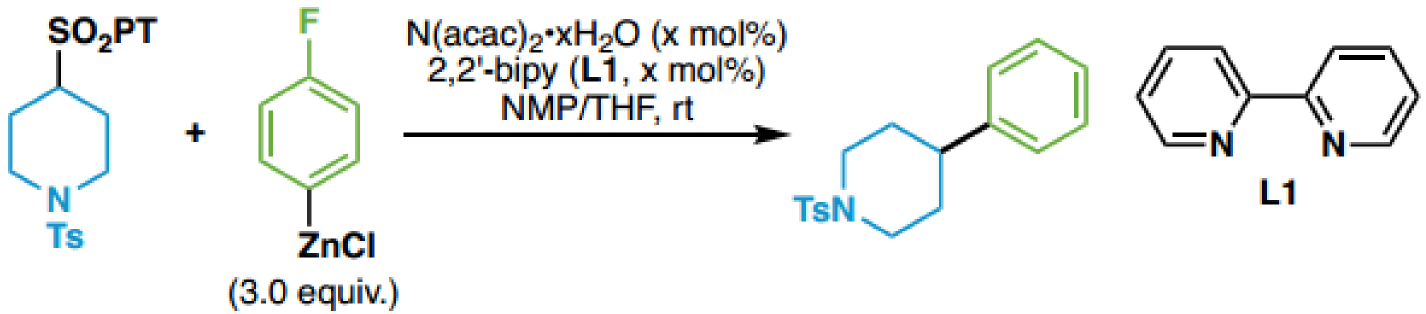

***Optimization***

| entry | deviation from above (R = **3f**) | **5a**[a] | **5b**[a] |
|---|---|---|---|
| 1 | $NiCl_2$•glyme, **L2**, DMF/THF, 40 °C | 46% | 20% |
| 2 | 20% Ni/40% **L1,** rt | 65% | 20% |
| 3 | 20% Ni/40% **L1**, rt, DMA | 55% | 31% |
| 4 | $Fe(acac)_3$, dppBz | trace | nd |
| 5 | $Fe(acac)_3$, DMPU | nd | 5% |
| 6 | $Fe(acac)_3$, TMEDA, CPME | nd | 10% |
| 7 | no ligandno | nd | 10% |
| 8 | Ni cat., no ligand | nd | nd |

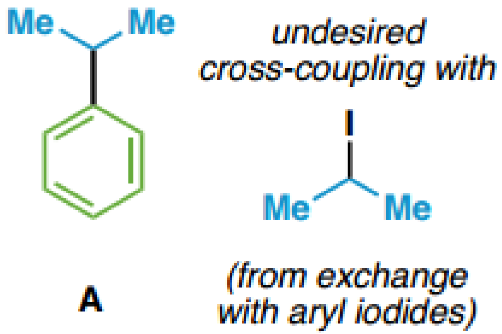



[a]Yields determined by $^{19}F$ NMR with 1-fluoronapthalene as an internal standard. [b]Isolated yield

*Alternative methods of arylzinc preparation (***Table S6***).*

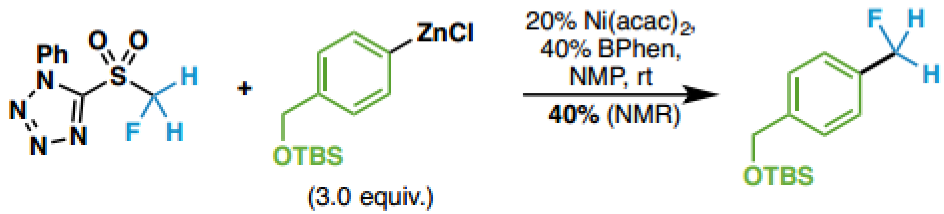



| RM | Ni/L (mol%) | Additive | NMR Yield |
|---|---|---|---|
| iPrMgCl•LiCl | 5/5.5 | – | 36% + 54% **A** |
| nBuLi | 5/5.5 | – | 20% |
| nBuLi | 5/5.5 | $MgBr_2$ (3 equiv.) | 10% |
| nBuLi | 5/5.5 | LiCl (3 equiv.) | 36% |
| **nBuLi** | **10/11** | **LiCl (3 equiv.)** | **66%** |



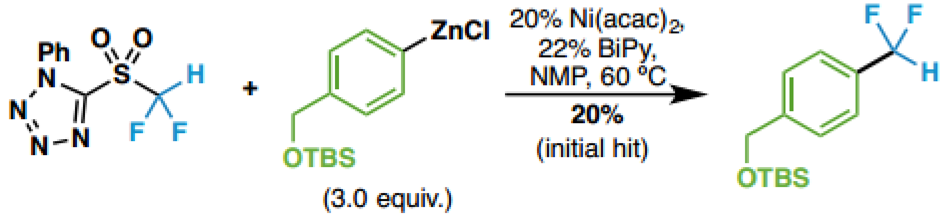

Arylzinc reagents were typically prepared from the corresponding aryl bromide via Mg insertion in the presence of LiCl followed by transmetallation with $ZnCl_2$ (**General Procedure E**) (*50*). In some cases, metal halogen exchange procedures with *n*-BuLi or *i*PrMgCl•LiCl were performed (*51*).

*Ligand screening for monofluoromethylation* (**Table S7**).




| Ligand | Ni/L (mol%) | T/°C | NMR Yield (%) |
|---|---|---|---|
| BiPy | 20 (1:1.1) | 60 | 20 |
| BiPy | 20 (1:1.1) | rt | 30 |
| BPhen | 20 (1:2) | 60 | 3 |
| BPhen | 20 (1:2) | rt | 40 |

*Ligand screening for difluoromethylation* (**Table S8**).




| Ligand | Ni/L (mol%) | T/°C | Yield (%) |
|---|---|---|---|
| BiPy | 20 (1:1.1) | 60 | 20 (isolated) |
| BPhen | 20 (1:2) | 60 | 59 (isolated) |
| BPhen | 20 (1:2) | rt | 58 (isolated) |
| BPhen | 5 (1:2) | rt | 51 (NMR) |

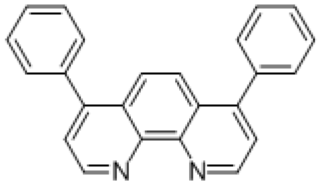
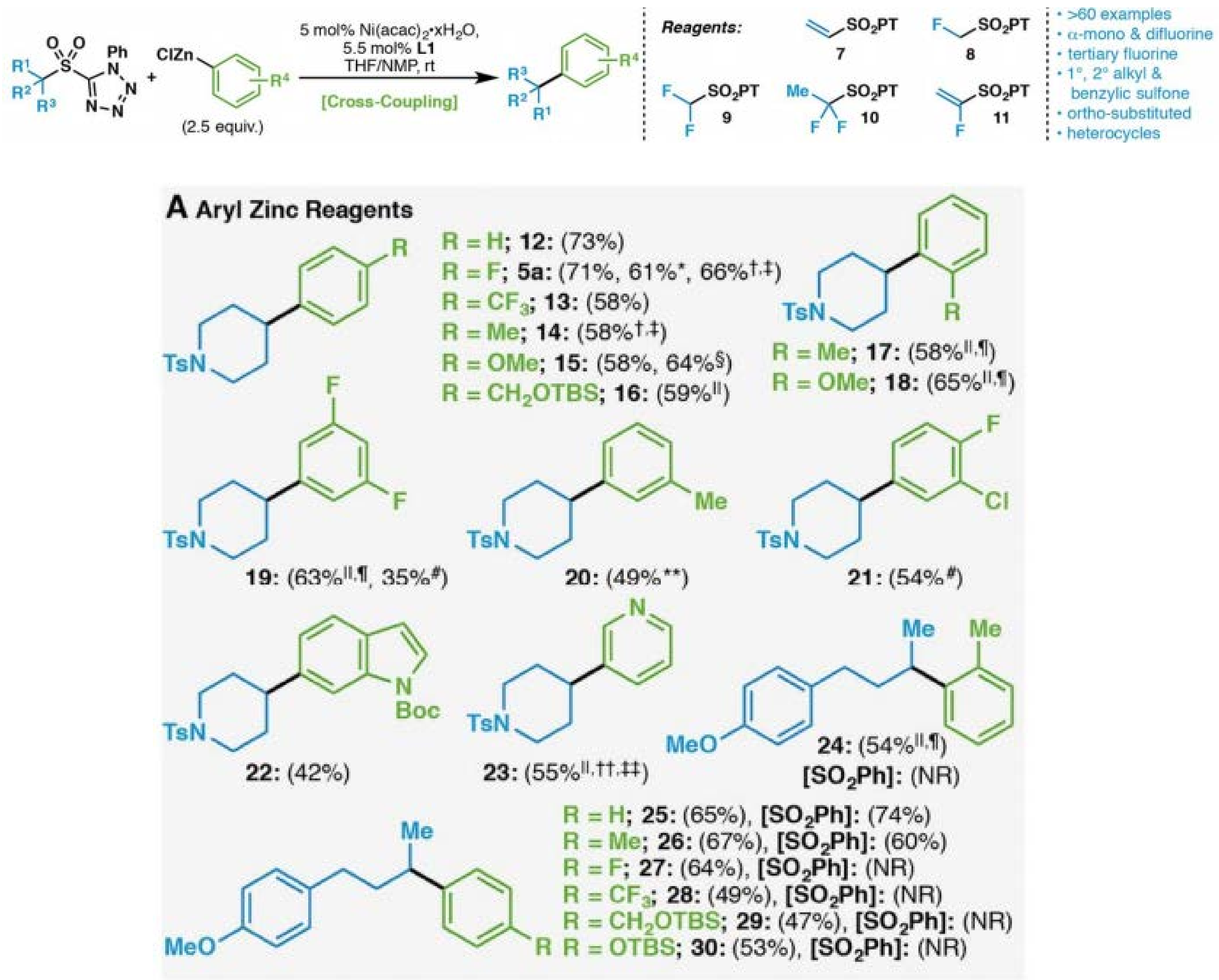
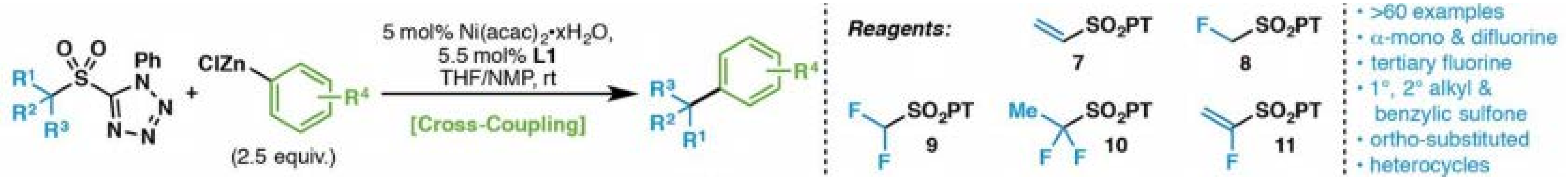
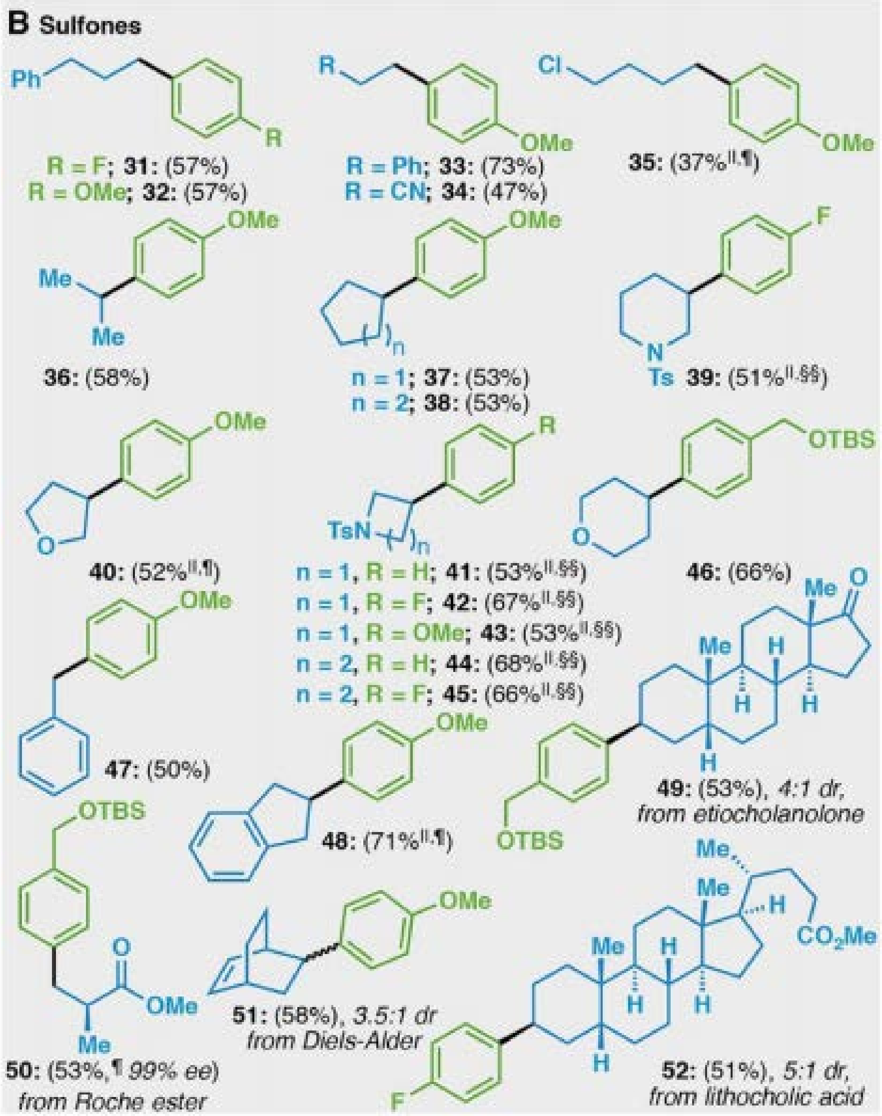
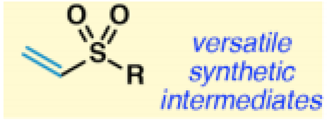


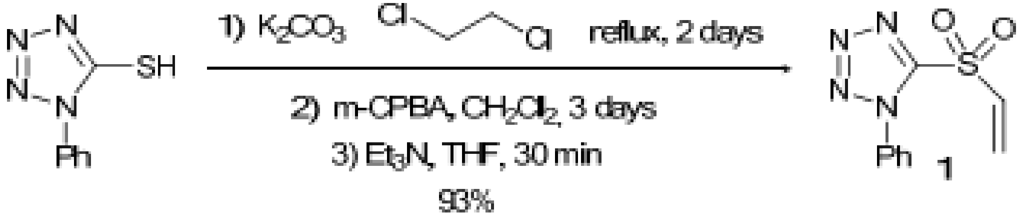
Fig. 2. Scope of the Ni-catalyzed cross-coupling of redox-active PT-sulfones.

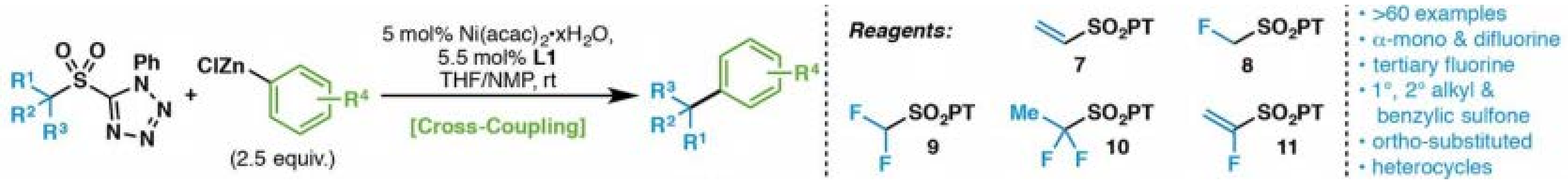


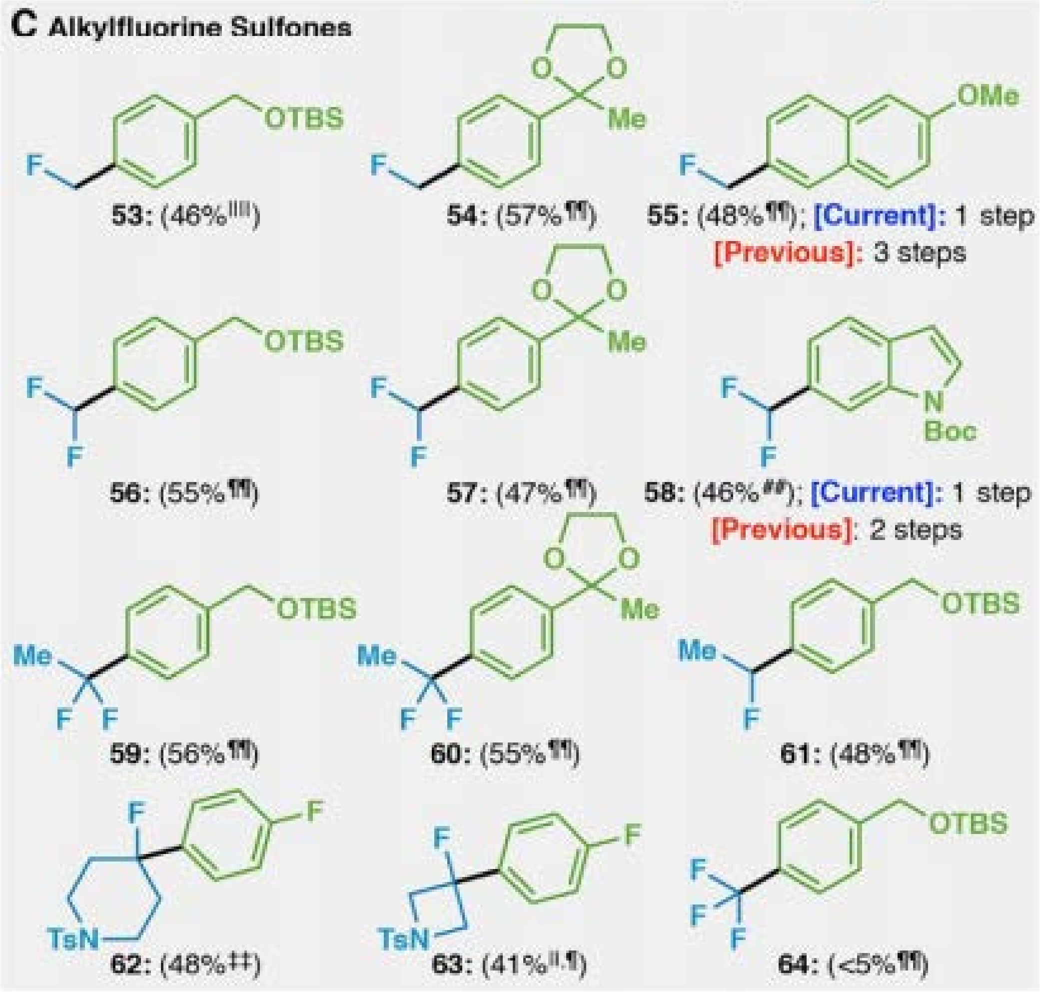

5 mol% Ni(acac)2•xH2O,
5.5 mol% L1
THF/NMP, rt
[Cross-Coupling]
(2.5 equiv.)
Reagents:
• >60 examples
• α-mono & difluorine
• tertiary fluorine
• 1°, 2° alkyl & benzylic sulfone
• ortho-substituted
• heterocycles

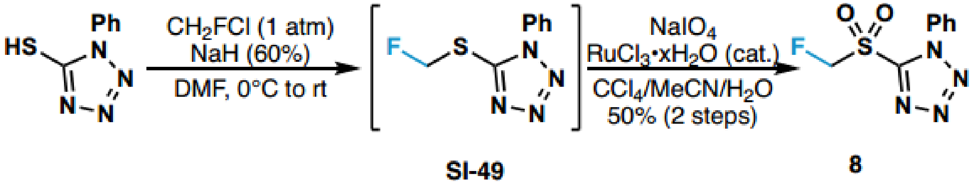

B Sulfones
R = F; 31: (57%)
R = OMe; 32: (57%)
R = Ph; 33: (73%)
R = CN; 34: (47%)
35: (37%||,¶)
36: (58%)
n = 1; 37: (53%)
n = 2; 38: (53%)
39: (51%||,§§)
40: (52%||,¶)
n = 1, R = H; 41: (53%||,§§)
n = 1, R = F; 42: (67%||,§§)
n = 1, R = OMe; 43: (53%||,§§)
n = 2, R = H; 44: (68%||,§§)
n = 2, R = F; 45: (66%||,§§)
46: (66%)
47: (50%)
48: (71%||,¶)
49: (53%), 4:1 dr,
from etiocholanolone
50: (53%,¶ 99% ee)
from Roche ester
51: (58%), 3.5:1 dr
from Diels-Alder
52: (51%), 5:1 dr,
from lithocholic acid

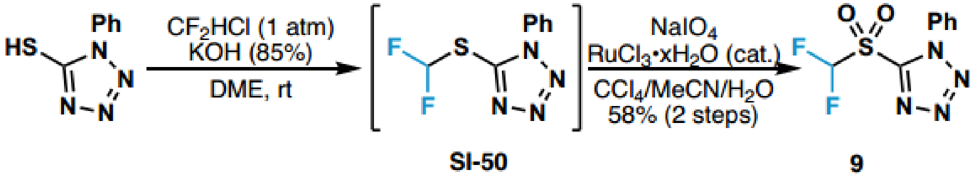

versatile
synthetic
intermediates

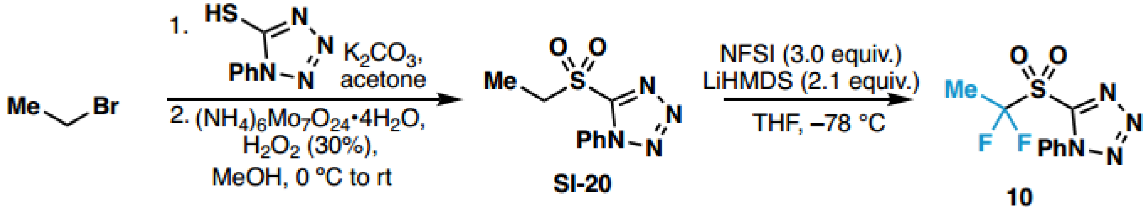

1) K2CO3 reflux, 2 days
2) m-CPBA, CH2Cl2, 3 days
3) Et3N, THF, 30 min
93%


5 mol% Ni(acac)2•xH2O,
5.5 mol% L1
THF/NMP, rt
[Cross-Coupling]
(2.5 equiv.)
Reagents:
7
8
9
10
11
• >60 examples
• α-mono & difluorine
• tertiary fluorine
• 1°, 2° alkyl & benzylic sulfone
• ortho-substituted
• heterocycles


C Alkylfluorine Sulfones
53: (46%||||)
54: (57%¶¶)
55: (48%¶¶); [Current]: 1 step
[Previous]: 3 steps
56: (55%¶¶)
57: (47%¶¶)
58: (46%##); [Current]: 1 step
[Previous]: 2 steps
59: (56%¶¶)
60: (55%¶¶)
61: (48%¶¶)
62: (48%‡‡)
63: (41%||,¶)
64: (<5%¶¶)


CH2FCl (1 atm)
NaH (60%)
DMF, 0°C to rt
SI-49
NaIO4
RuCl3•xH2O (cat.)
CCl4/MeCN/H2O
50% (2 steps)
8


CF2HCl (1 atm)
KOH (85%)
DME, rt
SI-50
NaIO4
RuCl3•xH2O (cat.)
CCl4/MeCN/H2O
58% (2 steps)
9


1. K2CO3, acetone
2. (NH4)6Mo7O24•4H2O, H2O2 (30%), MeOH, 0 °C to rt
SI-20
NFSI (3.0 equiv.)
LiHMDS (2.1 equiv.)
THF, –78 °C
10

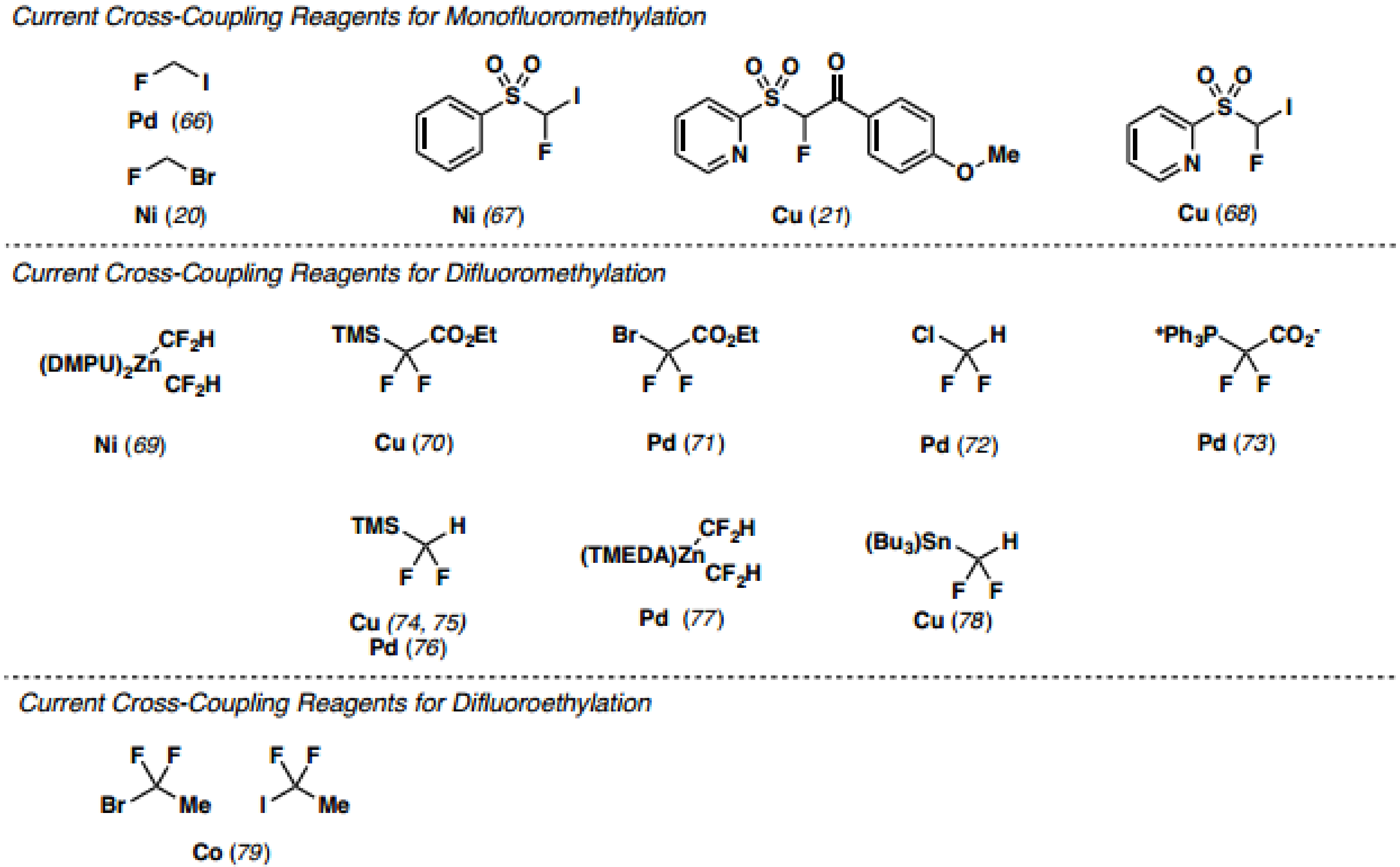



**Figure S24:** Reagents for mono and difluoromethylation and diethylfluorinations.

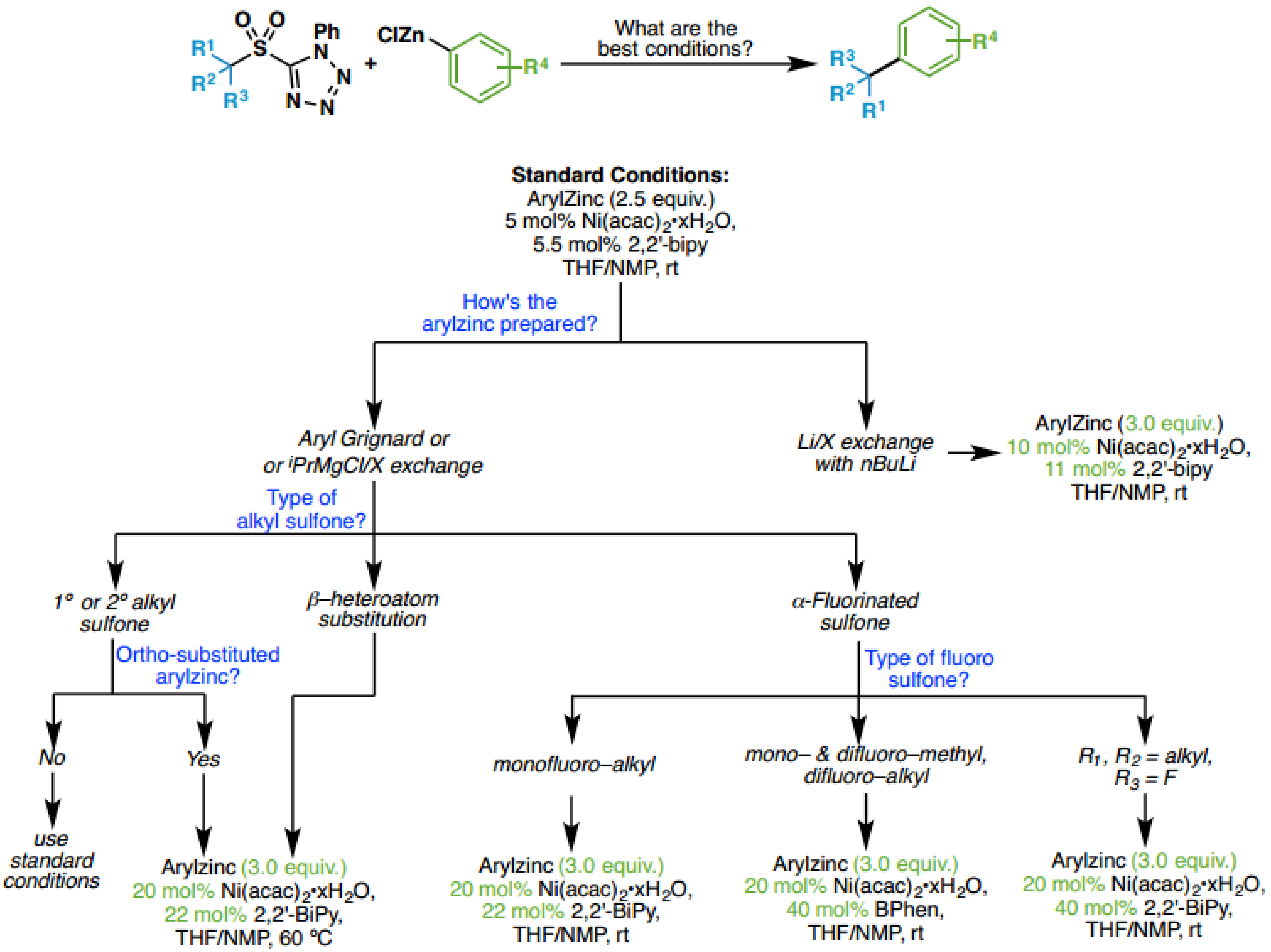
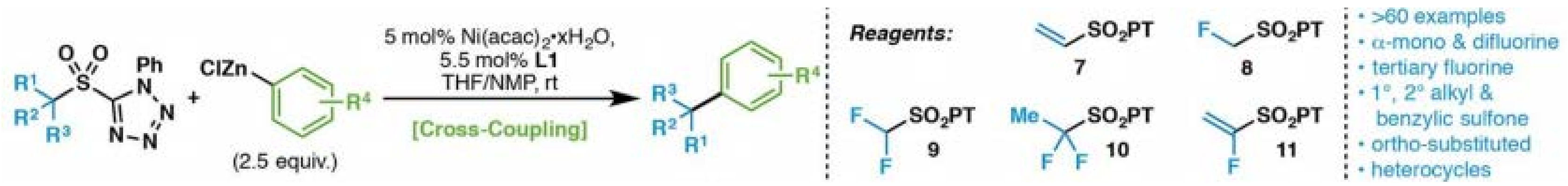
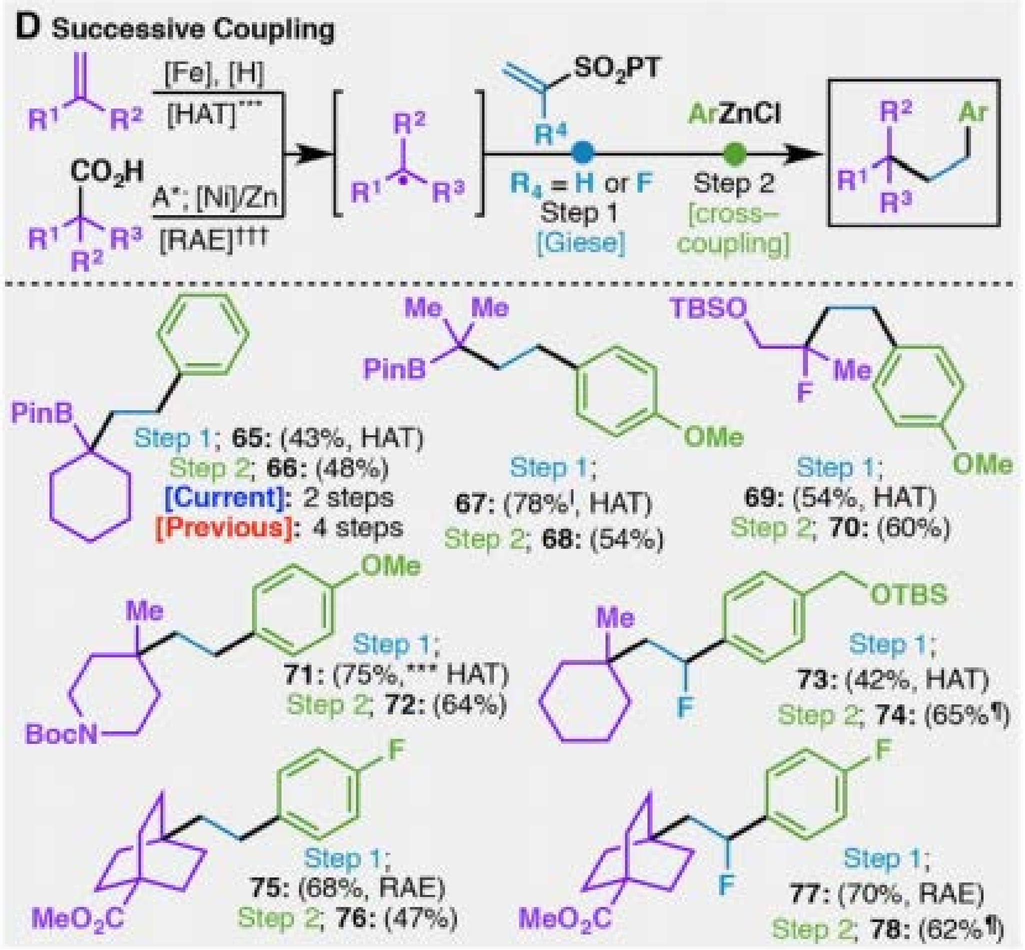
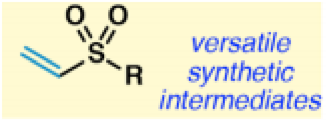
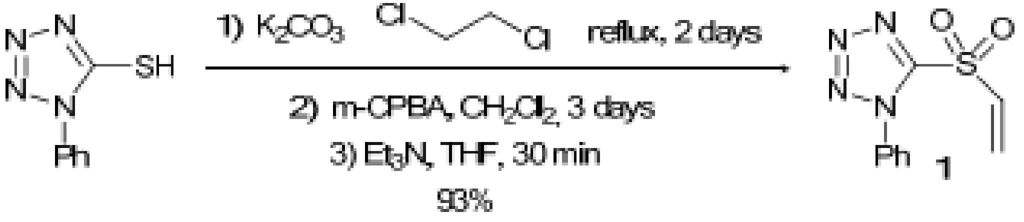


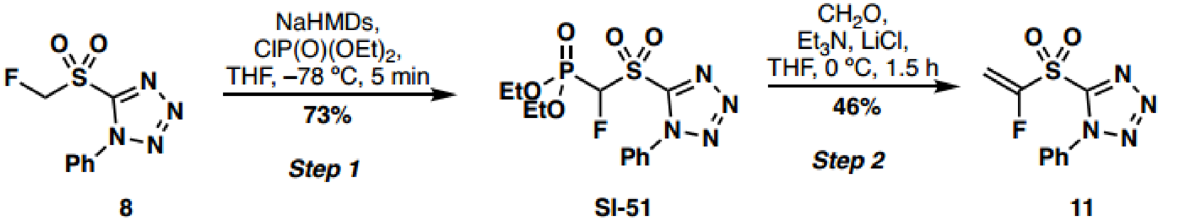

**Figure S8**: Flow chart for choosing reaction conditions.



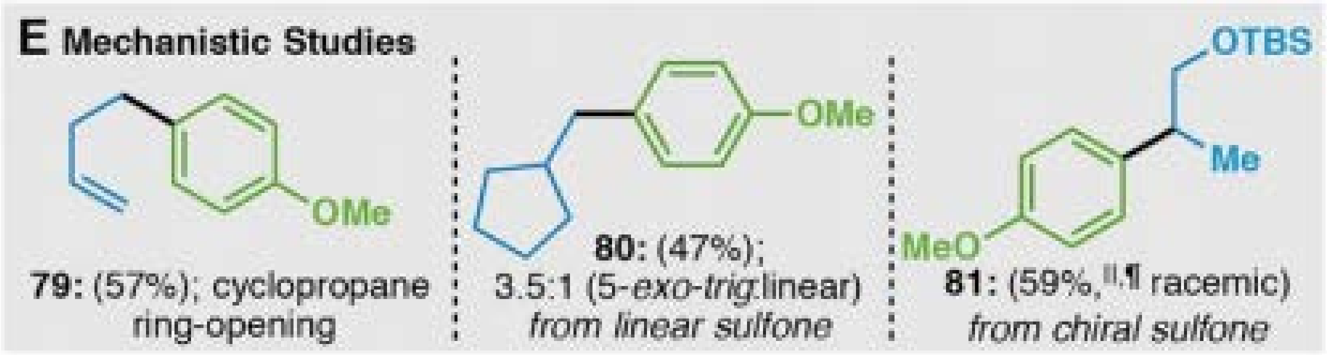



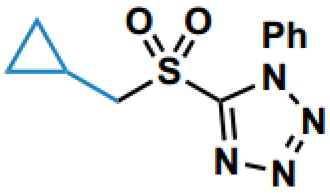



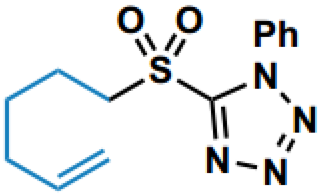




HAT, hydrogen atom transfer; A*, activation with Nhydroxyphthalimide (NHPI); RAE, redox-active ester

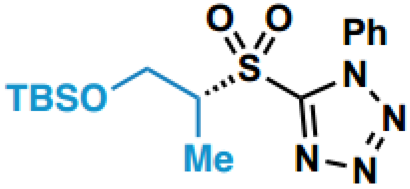



SI-25




SI-26




SI-27

79 (cyclopropane ring-opening)
80 (5-exo-trig cyclization)
81 (racemic product from a chiral sulfone)

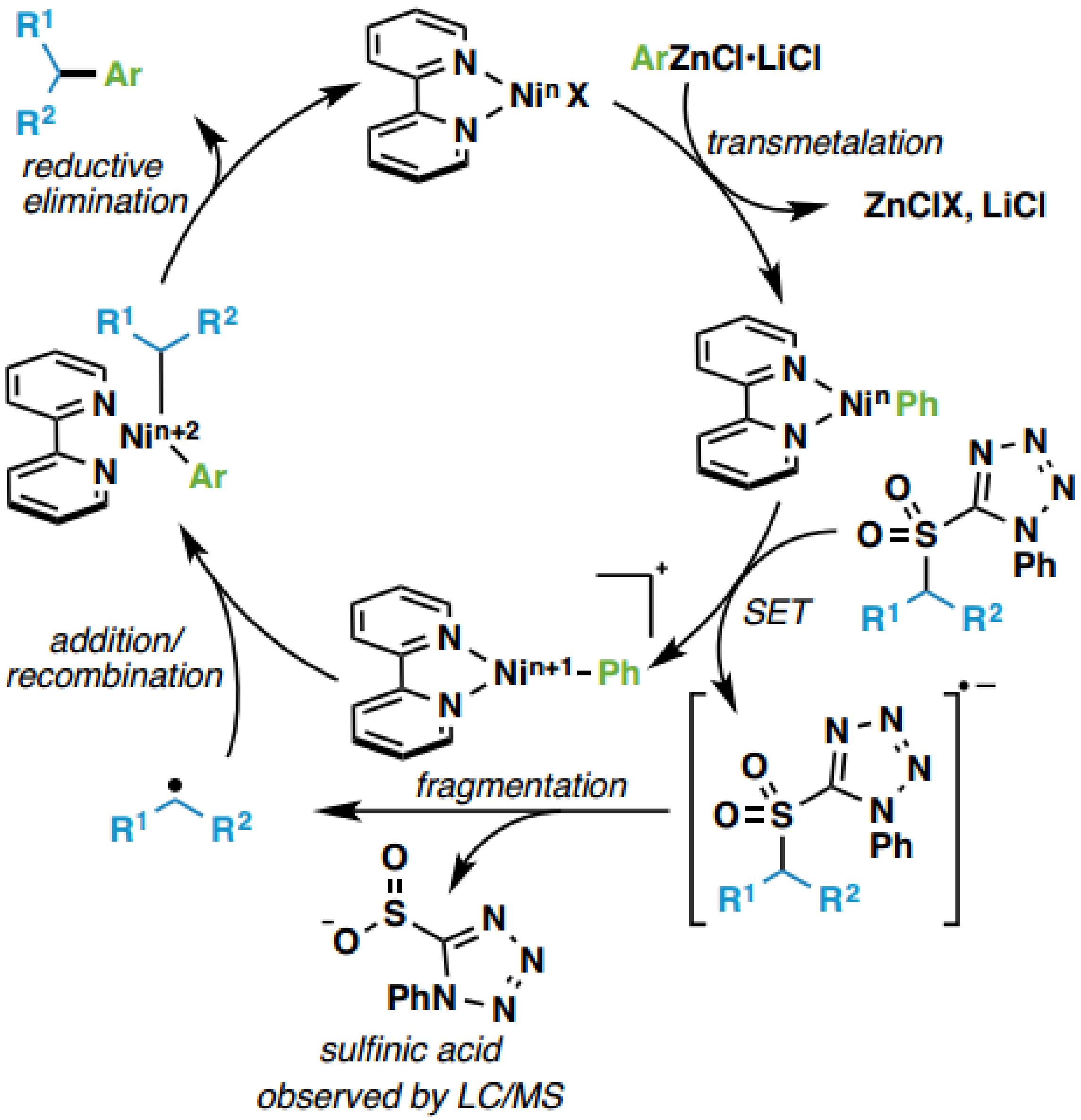



**Figure S9**: Possible catalytic cycle for the desulfonylative arylation. (*54-57*)

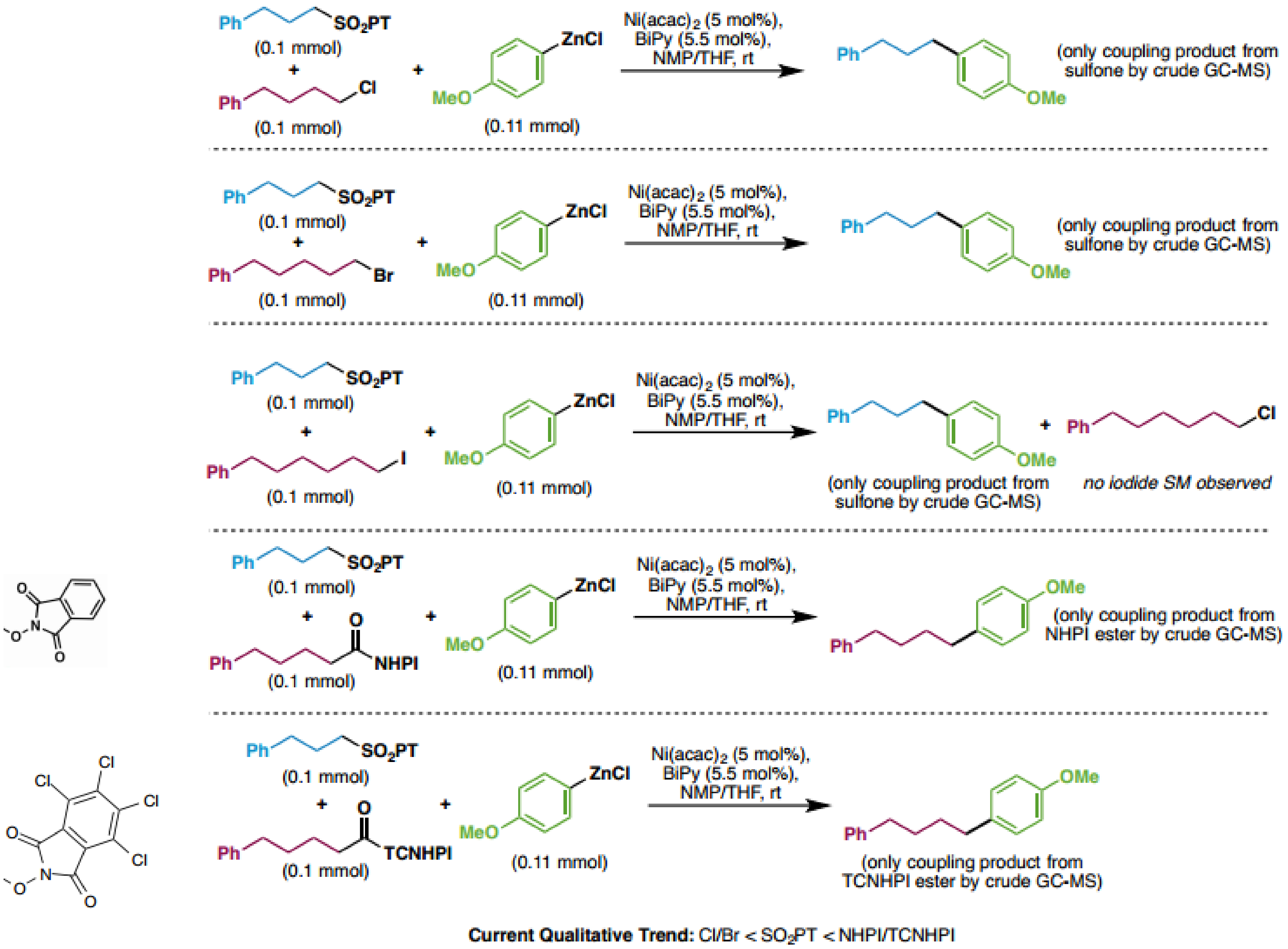
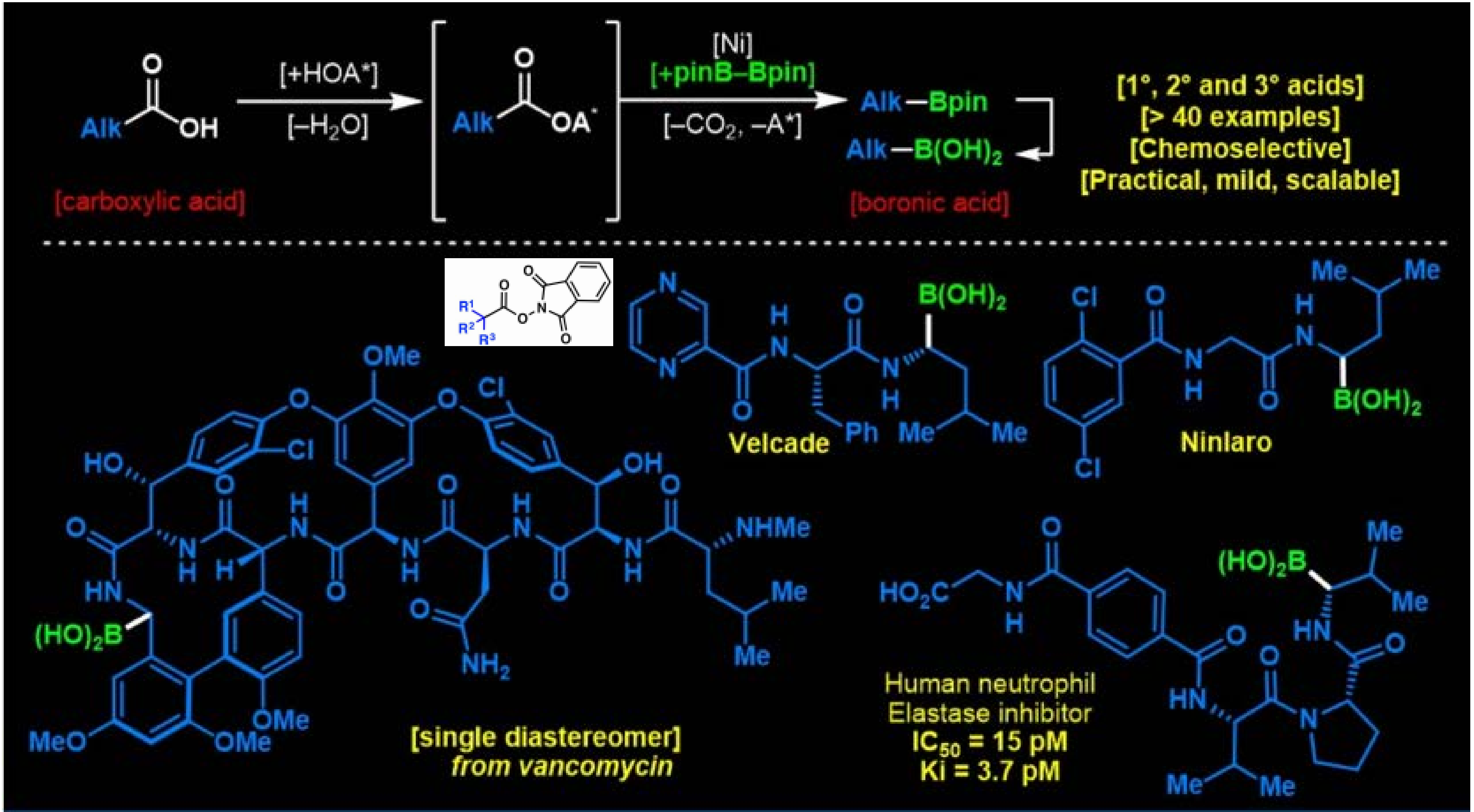



**Figure S1:** Competition experiments between alkyl electrophiles and PT-sulfone reagents.

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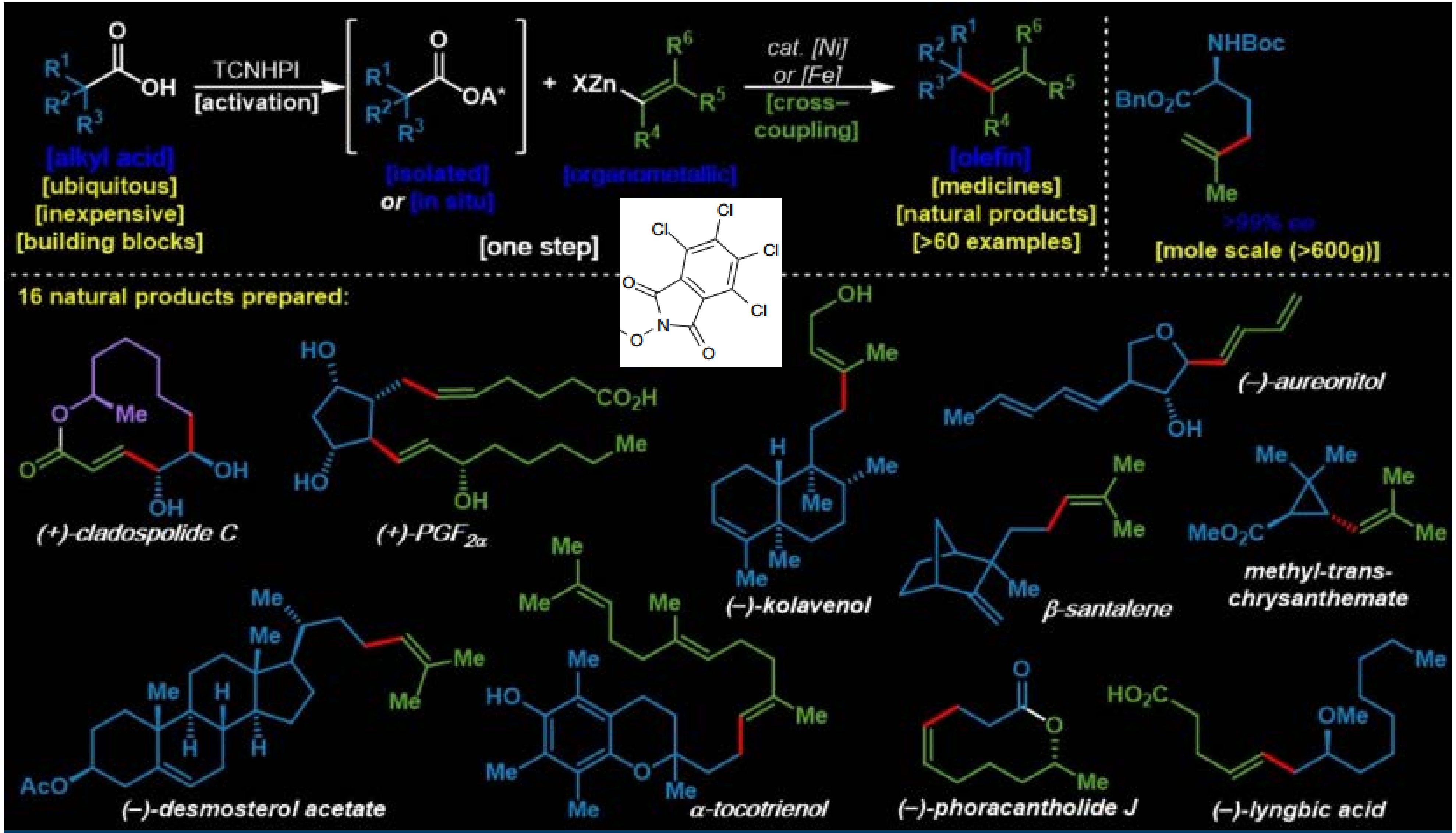


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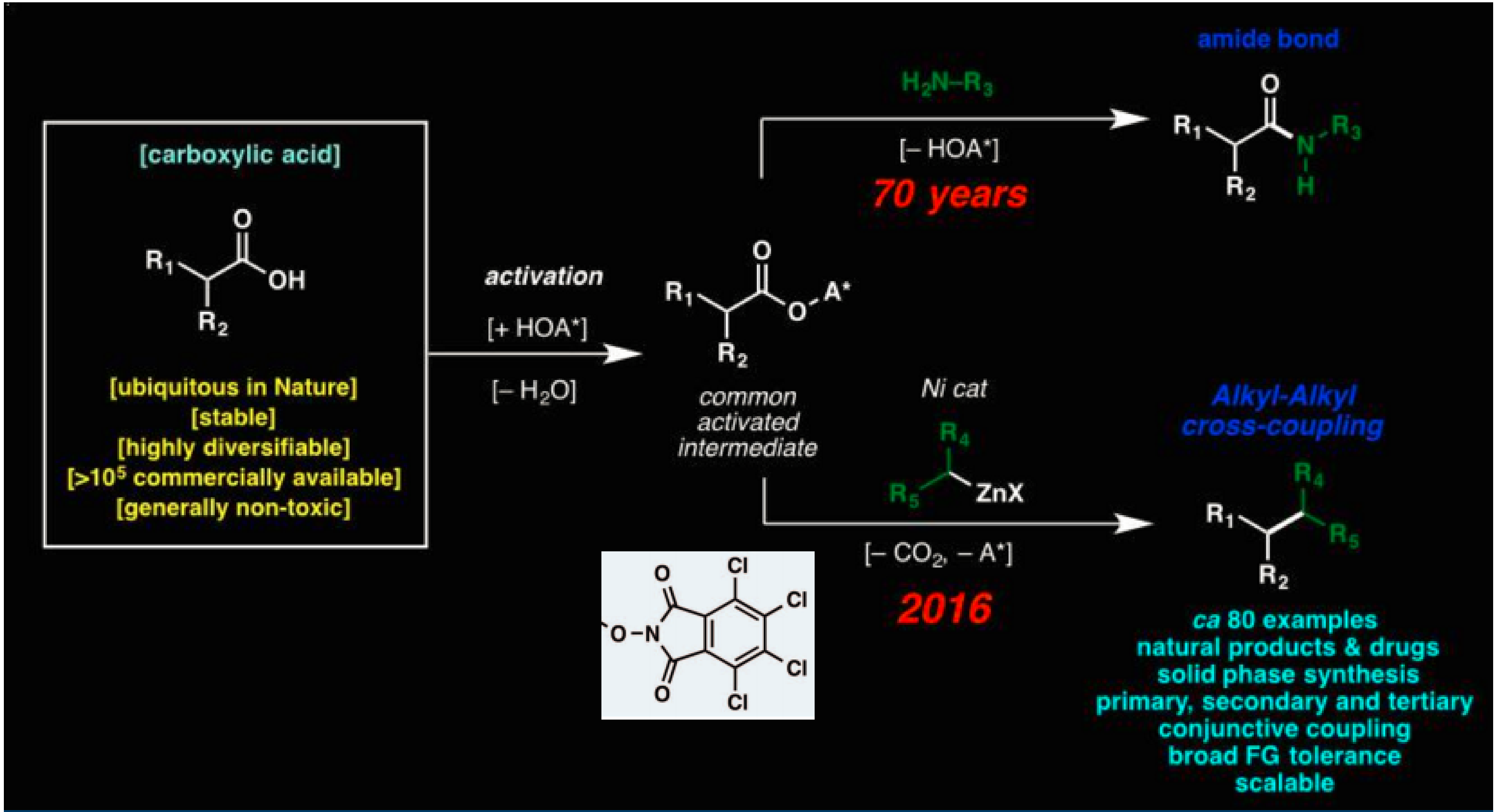


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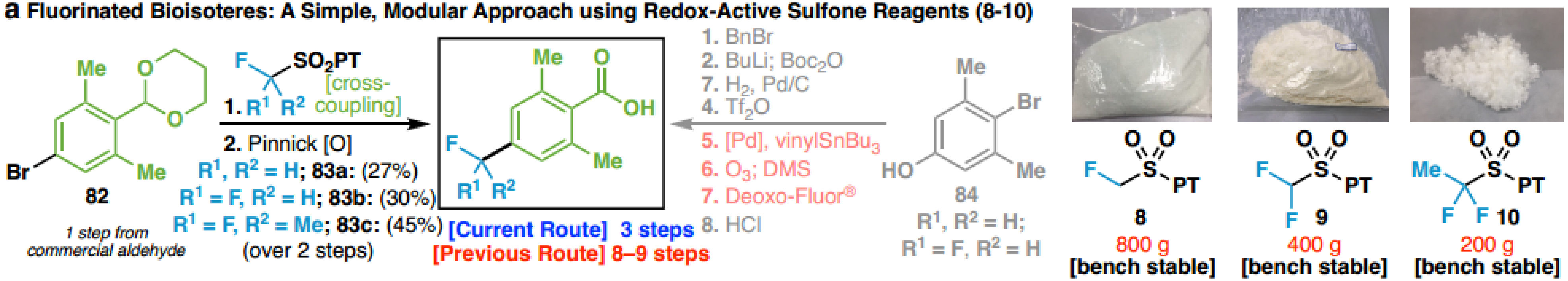
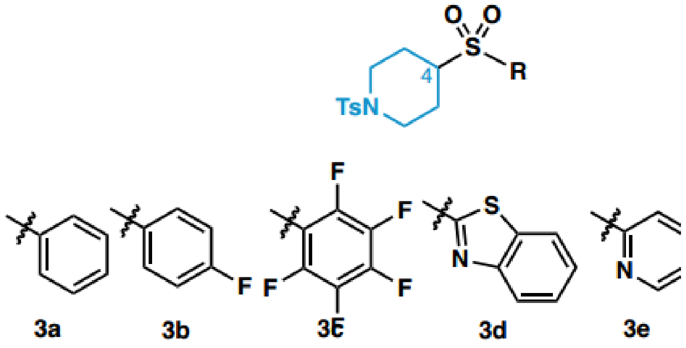
Fig. 3. Simplification of synthesis using sulfone-cross-coupling logic.

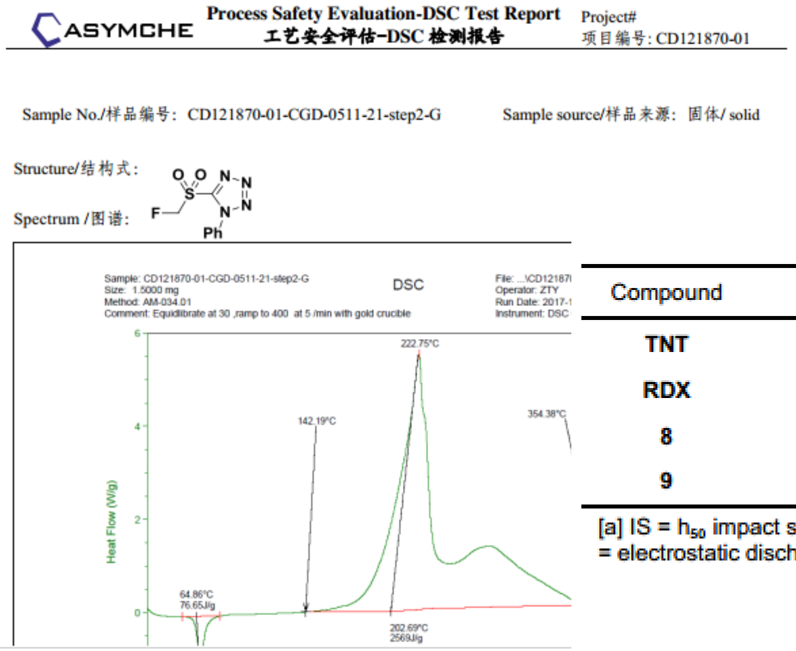




| | 3a | 3b | 3c | 3d | 3e |
|---|---|---|---|---|---|
| E(V) | −1.46 | −1.64 | −1.30 | −1.50 | −1.21 |
| [$^1H_4$]$^c$ | 2.81 | 2.81 | 3.06 | 3.39 | 3.43 |
| [$^{13}C_4$]$^c$ | 60.87 | 61.03 | – | 60.30 | 57.11 |

**Table S19**: Reduction potential and NMR shifts of sul


ASYMCHE Process Safety Evaluation-DSC Test Report
工艺安全评估-DSC 检测报告
Project#
项目编号: CD121870-01

Sample No./样品编号: CD121870-01-CGD-0511-21-step2-G Sample source/样品来源: 固体/ solid

Structure/结构式:

Spectrum /图谱:



| Compound | IS[a] [J] | FS[b] [N] | ESD[c] [J] |
|---|---|---|---|
| TNT | 15.1 | >360 | >0.25 |
| RDX | 6.2 | 141 | 0.125 |
| 8 | >34.2 | >360 | >0.25 |
| 9 | >34.2 | >360 | >0.25 |

[a] IS = $h_{50}$ impact sensitivity; [b] FS = friction sensitivity; [c] ESD = electrostatic discharge

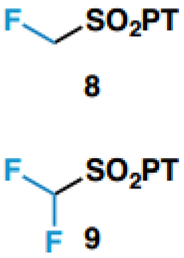
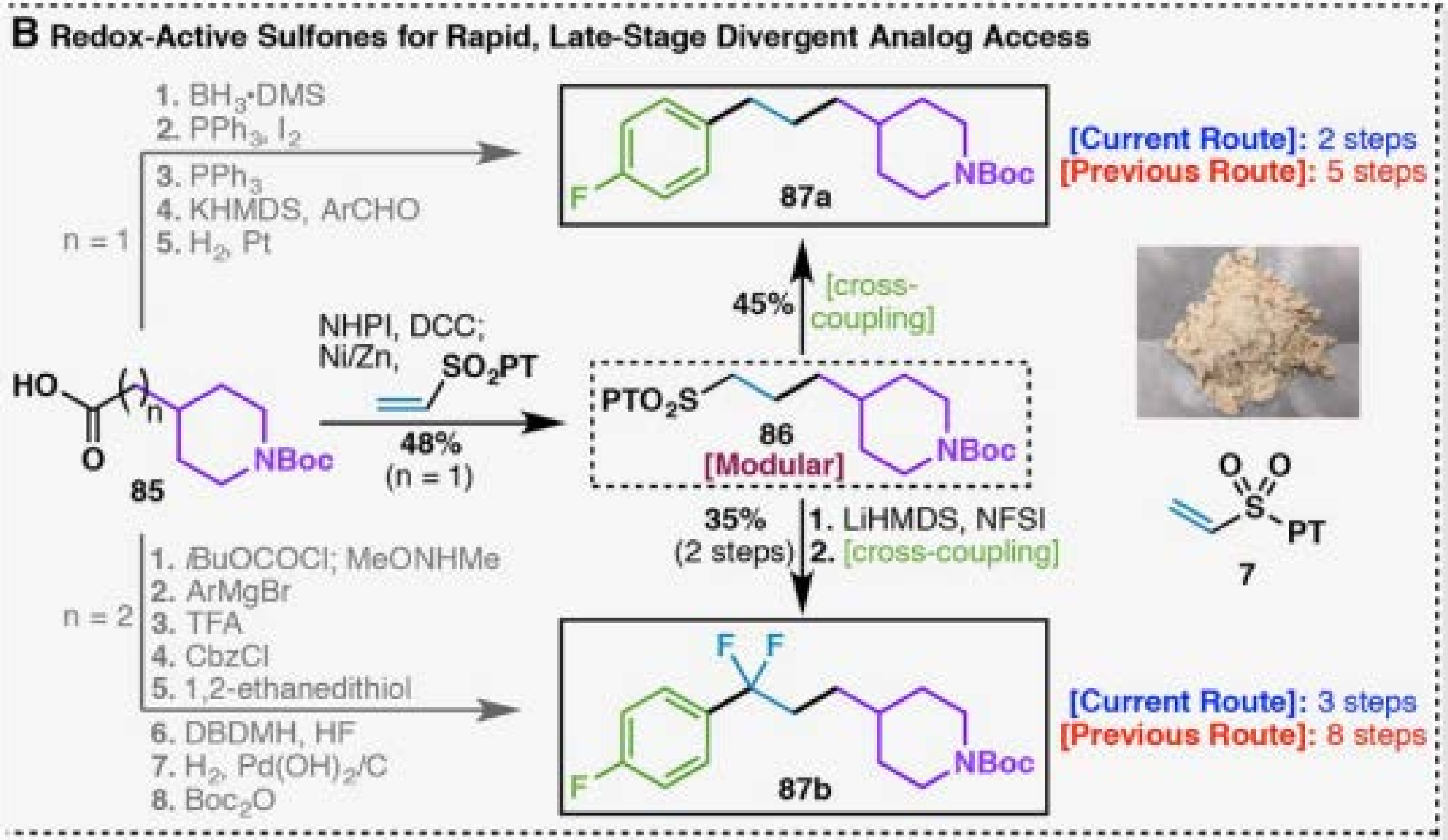
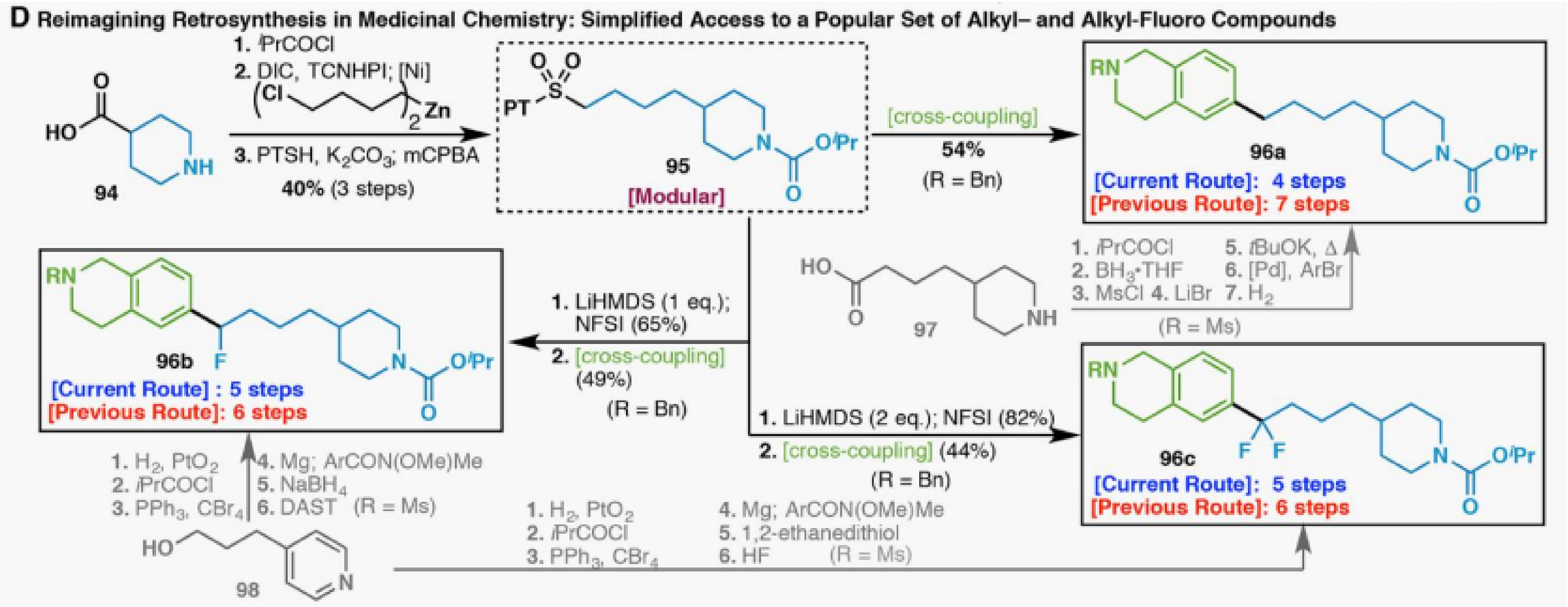
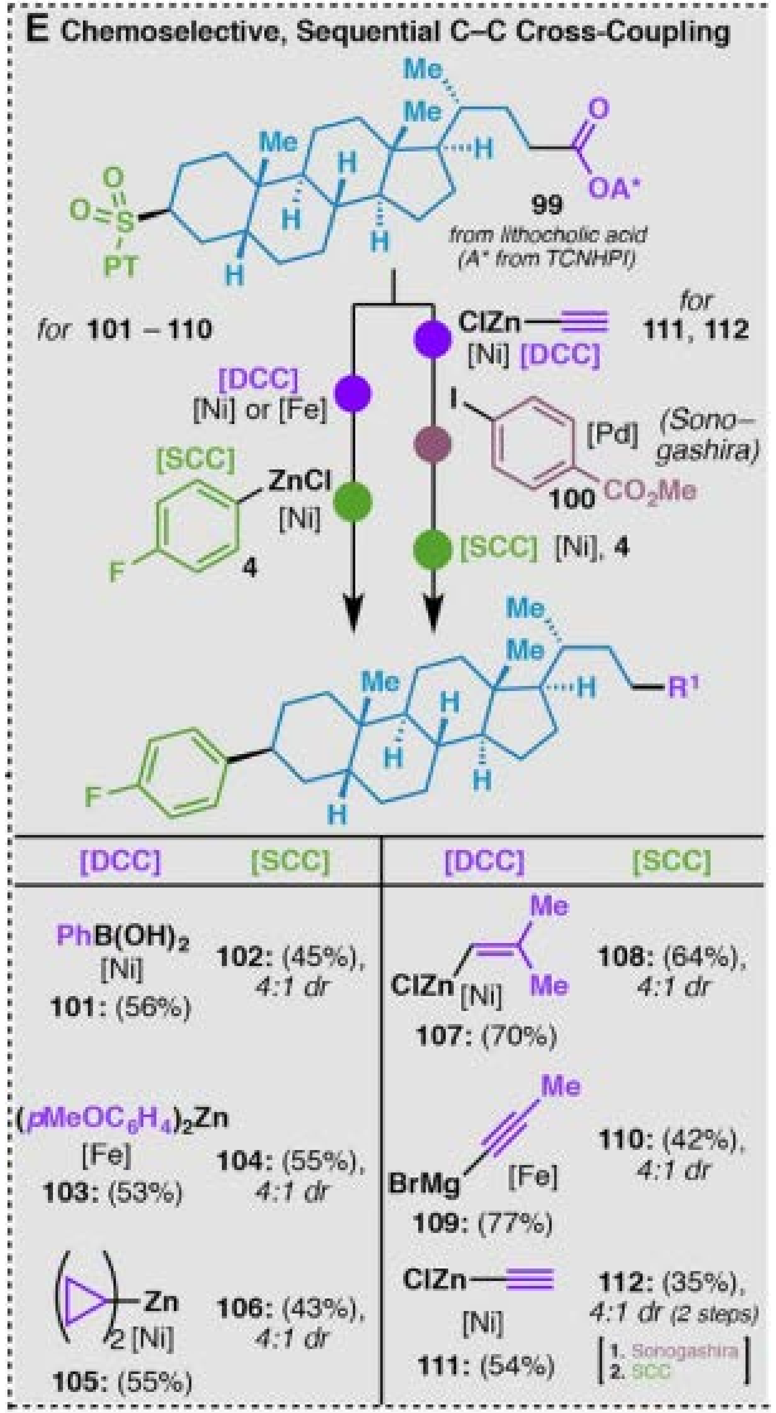


**Table S20**: Shock and friction sensitivity data for **8** and **9**


B Redox-Active Sulfones for Rapid, Late-Stage Divergent Analog Access
1. BH3•DMS
2. PPh3, I2
3. PPh3
4. KHMDS, ArCHO
5. H2, Pt
n = 1
87a
[Current Route]: 2 steps
[Previous Route]: 5 steps
45%
[cross-coupling]
NHPI, DCC;
Ni/Zn, SO2PT
48%
(n = 1)
85
86
[Modular]
35%
(2 steps)
1. LiHMDS, NFSI
2. [cross-coupling]
n = 2
1. iBuOCOCl; MeONHMe
2. ArMgBr
3. TFA
4. CbzCl
5. 1,2-ethanedithiol
6. DBDMH, HF
7. H2, Pd(OH)2/C
8. Boc2O
87b
[Current Route]: 3 steps
[Previous Route]: 8 steps
7

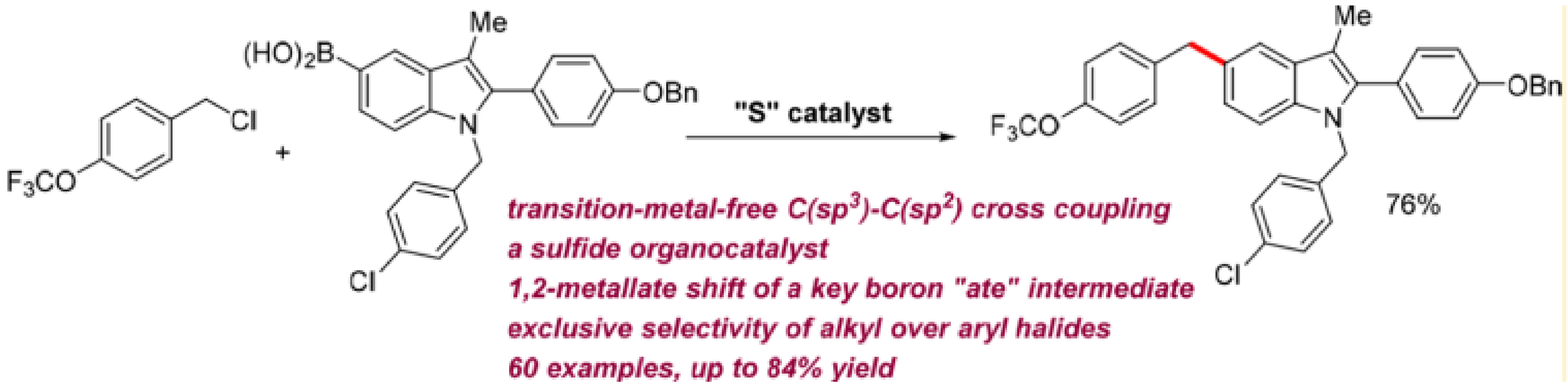
**C Fluorine Embedded, Successive Radical Cross-Coupling**


D Reimagining Retrosynthesis in Medicinal Chemistry: Simplified Access to a Popular Set of Alkyl– and Alkyl-Fluoro Compounds
1. iPrCOCl
2. DIC, TCNHPI; [Ni]
Cl Zn
3. PTSH, K2CO3; mCPBA
40% (3 steps)
HO
O
NH
94
PT
S
95
[Modular]
O^iPr
[cross-coupling]
54%
(R = Bn)
RN
96a
[Current Route]: 4 steps
[Previous Route]: 7 steps
1. iPrCOCl
2. BH3•THF
3. MsCl 4. LiBr
5. tBuOK, Δ
6. [Pd], ArBr
7. H2
(R = Ms)
97
1. LiHMDS (1 eq.); NFSI (65%)
2. [cross-coupling] (49%)
(R = Bn)
96b
[Current Route] : 5 steps
[Previous Route]: 6 steps
1. LiHMDS (2 eq.); NFSI (82%)
2. [cross-coupling] (44%)
(R = Bn)
96c
[Current Route]: 5 steps
[Previous Route]: 6 steps
1. H2, PtO2
2. iPrCOCl
3. PPh3, CBr4
4. Mg; ArCON(OMe)Me
5. NaBH4
6. DAST
(R = Ms)
1. H2, PtO2
2. iPrCOCl
3. PPh3, CBr4
4. Mg; ArCON(OMe)Me
5. 1,2-ethanedithiol
6. HF
(R = Ms)
98




DCC, decarboxylative cross-coupling;
SCC, desulfonylative cross-coupling;

*J. Am. Chem. Soc.* 2018, 140, 2693−2699



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