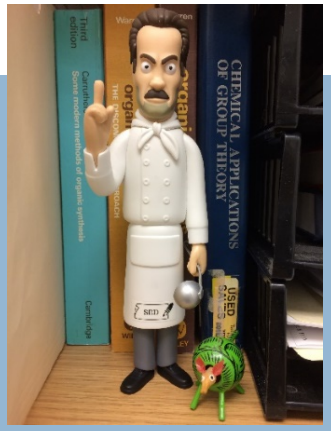
Five Years in the Denmark Lab

A Coming of Age Story

Kevin A. Robb

October 16, 2018



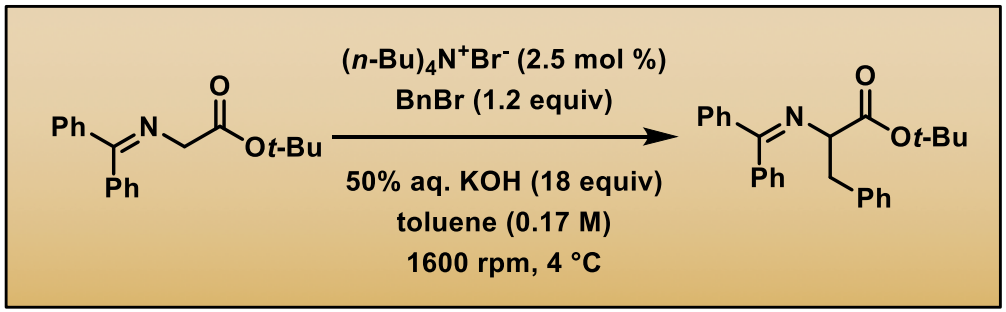
Tonight's Outline

- Phase Transfer Catalysis
  - Development of PT-Catalyzed Anionic Oxy-Cope Rearrangement
  - Synthesis of an Azahelicene-Derived Scaffold for APTC
- Lewis Base Catalysis
  - Enantioselective Sulfenocyclization of Polyenes
    - Mechanistic Investigation
  - Enantioselective Sulfenofunctionalization of Alkenylboronates

- Will not be covered:
  - Bisoxazoline Synthesis

Phase Transfer Catalysis

- Transfer reagent (e.g. quaternary ammonium salt) facilitates the transport of ionic intermediates between immiscible phases
- Example (O'Donnell alkylation)



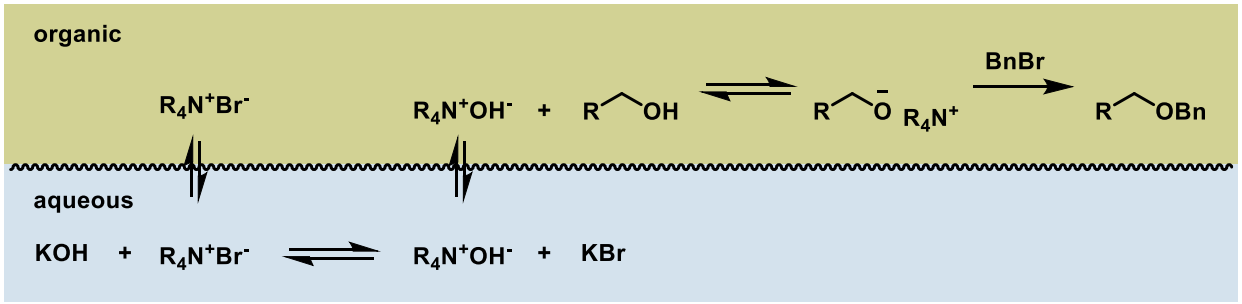
- $t_{1/2}$ (catalyzed) = 14 min
- $t_{1/2}$ (control) = 6.5 days

- Benefits:
  - Decreased volumes of organic solvents
  - More environmentally benign reagents
- PTC reactions proceed through one of two general mechanisms
  - Starks Extraction mechanism
  - Makosza Interfacial mechanism

Starks, C. M.; Liotta, C. L.; Halpern, M. *Phase-Transfer Catalysis: Fundamentals, Applications, and Industrial Perspectives*. Chapman & Hall: New York, 1994.
Denmark, S. E. and Henle, J. J. *Chemical Science* **2015**, *6*, 2211.

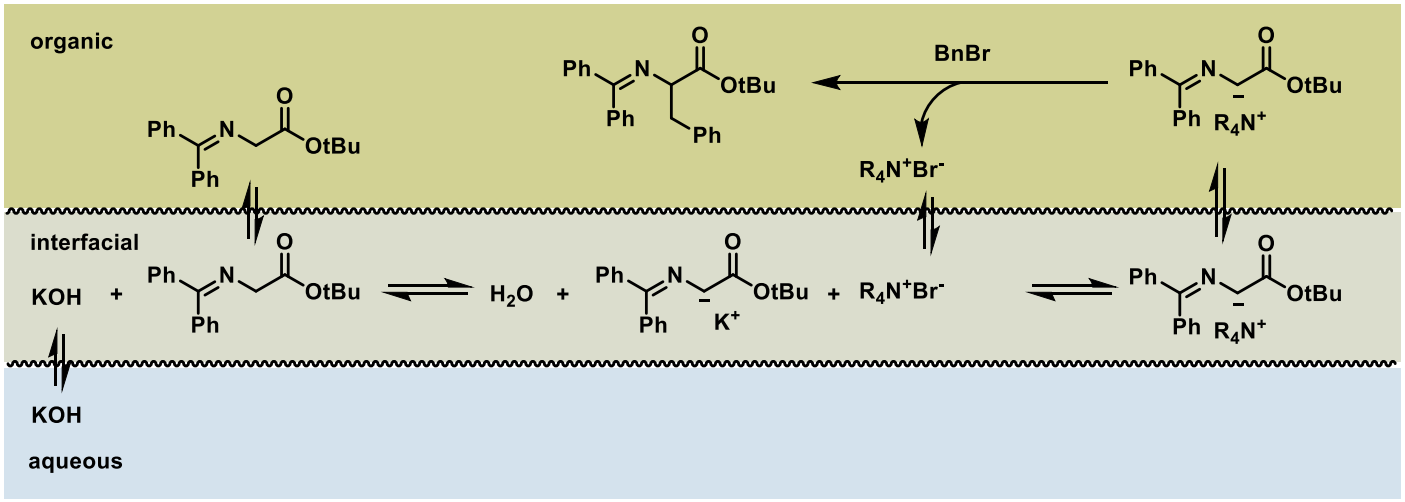
General PTC Mechanisms

- Extraction Mechanism
  - e.g. *O*-alkylation of alkoxides (Williamson ether synthesis)



- Intrinsic rate-limited
- Catalyst role = extraction of inorganic ions into organic phase
- Stir rate independent

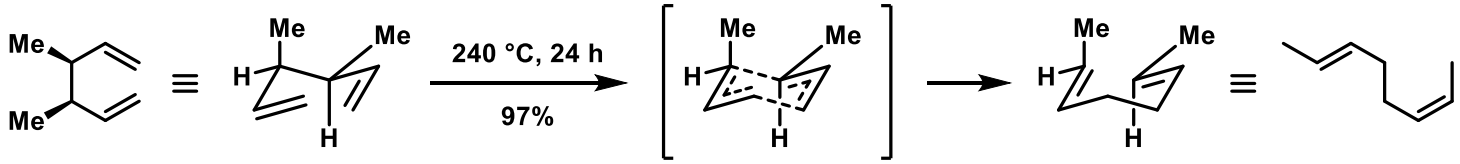
- Interfacial Mechanism
  - e.g. α-alkylation of carbonyl compounds



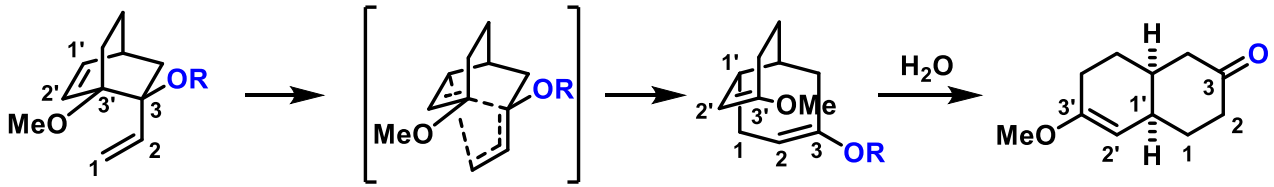
- Transport rate-limited
- Catalyst role = desolvation (RDS)
- Reaction rate is stir rate dependent

The Cope Rearrangement

- [3,3]-sigmatropic rearrangement of 1,5-dienes
  - Driving force: formation of more substituted olefins



- Variation: oxy-Cope rearrangement
  - Driving force: formation of enol



Alcohol 1a (R = H)
Alkoxide 2a (R = K)

Table I. Activation Parameters for Oxy-Cope Rearrangement

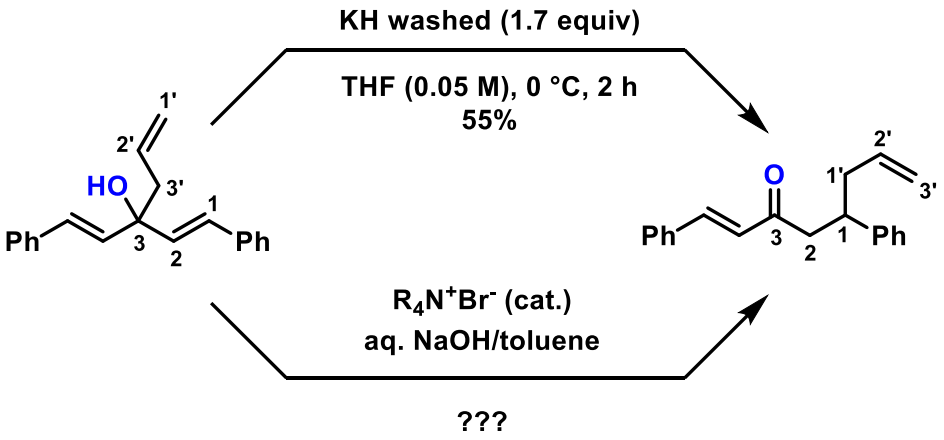
Substrate	E_a (kcal/mol)	Log A (sec^{-1})	Temp range, °K	Entry
1a	35.9 ± 1.8	12.6 ± 0.6	448–488	A
2a (M = K)	19.4 ± 0.7	10.3 ± 0.4	283–328	B
2a (M = K)[a]	18.2 ± 0.1	11.5 ± 0.1	253–278	C

- *Anionic* oxy-Cope rearrangement results in *dramatic* rate increase!
- Increased electron density

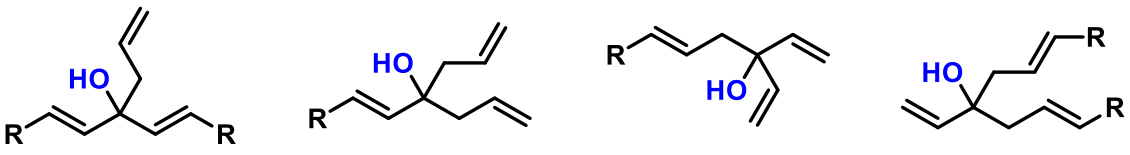
Evans, D.A. et al. *J. Am. Chem. Soc.* **1975**, *97*, 4765.

Candidate for PTC?

- Research Objectives:
  - Establish viability of phase transfer catalyzed anionic oxy-Cope rearrangement (i.e. demonstrate catalytic activity and no/low background conversion)

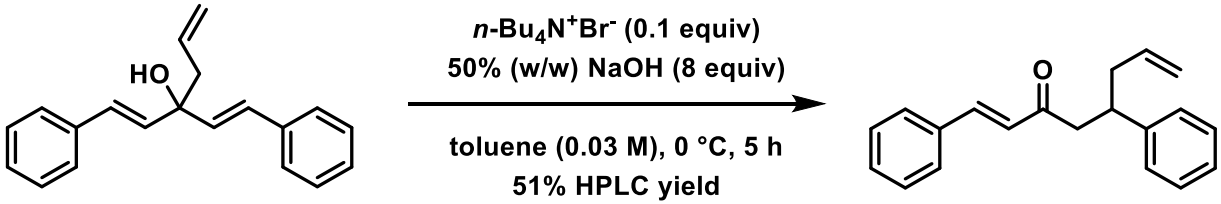


  - Investigate asymmetric variant using chiral ammonium salts for the desymmetrization of tertiary alcohols



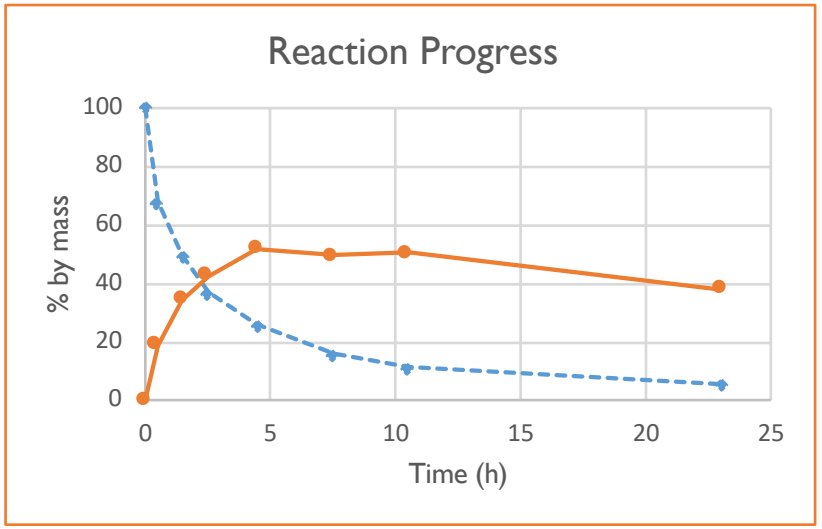
Reactivity (Class 1)

- Successful rearrangement under PTC conditions

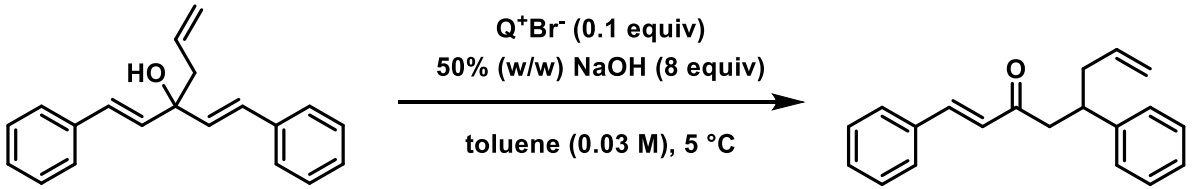


[Sub.] in toluene	Yield
0.060 M	43%
0.030 M	51%
0.015 M	62%

- No background reaction observed
- Utility limited by unproductive self-condensation reactions

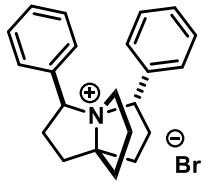


Investigation of Enantioselective Reaction



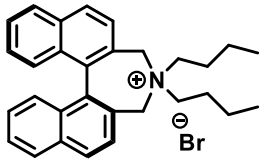
- Unlike TBAB, all chiral catalysts showed low/no activity

aza-propellane

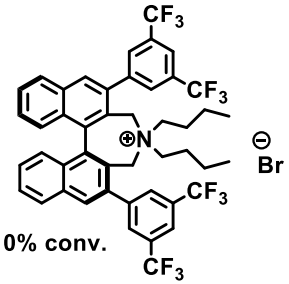


10% max. yield (2 h)
e.r. = 50:50

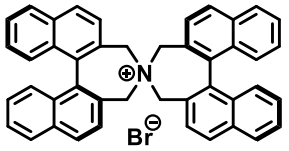
Maruoka



31% max. yield (9 d)
e.r. = 50:50

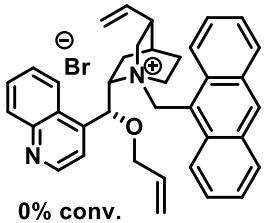


0% conv.



0% conv.

***Cinchona*-derived**



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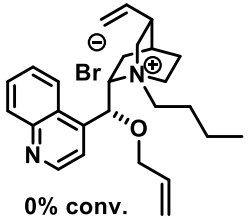

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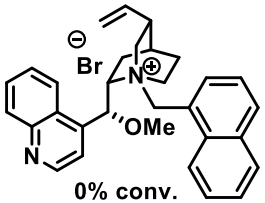

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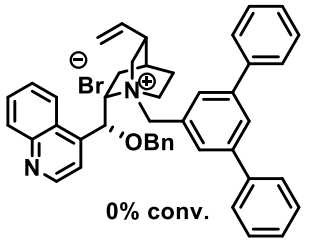

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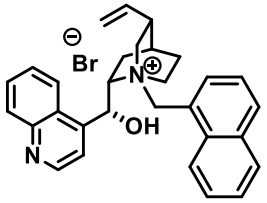

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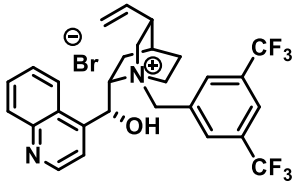

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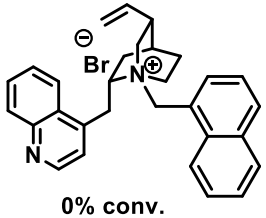

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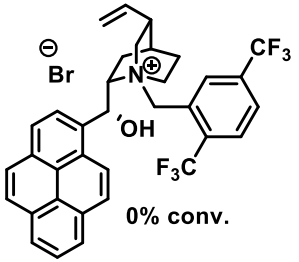
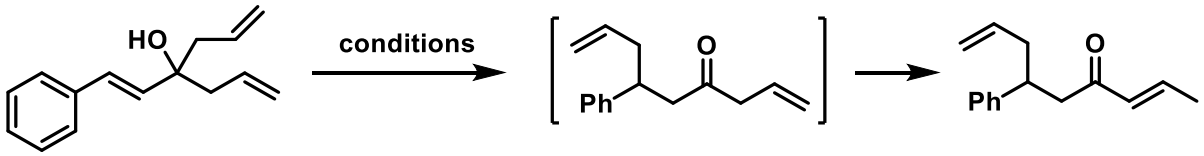


0% conv.

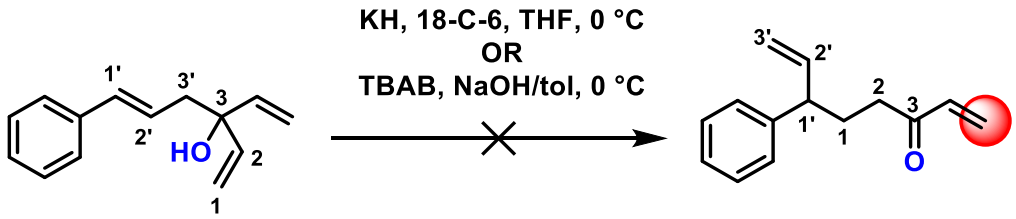
Reactivity (Class 2 & 3)

- Class 2
  - No conversion under PTC conditions

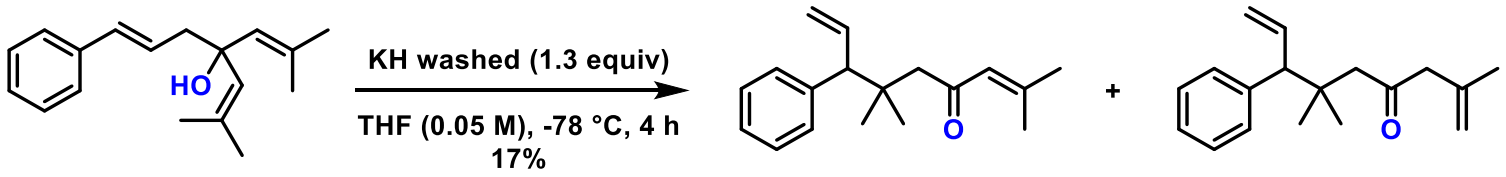


conditions	Yield
KH, 18-C-6, 0 °C	31%
"PTC"	0%

- Class 3
  - Unproductive pathways dominate

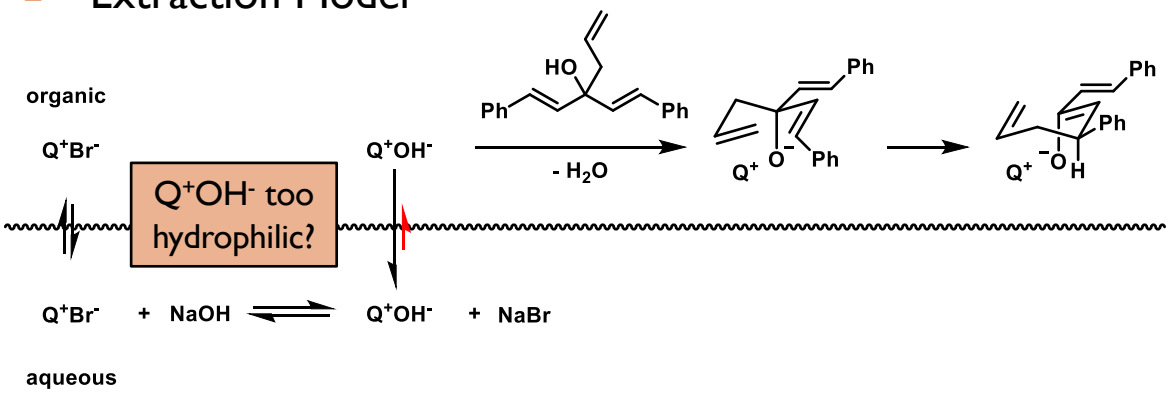


- Full conversion under both conditions
- Only polymeric products observed



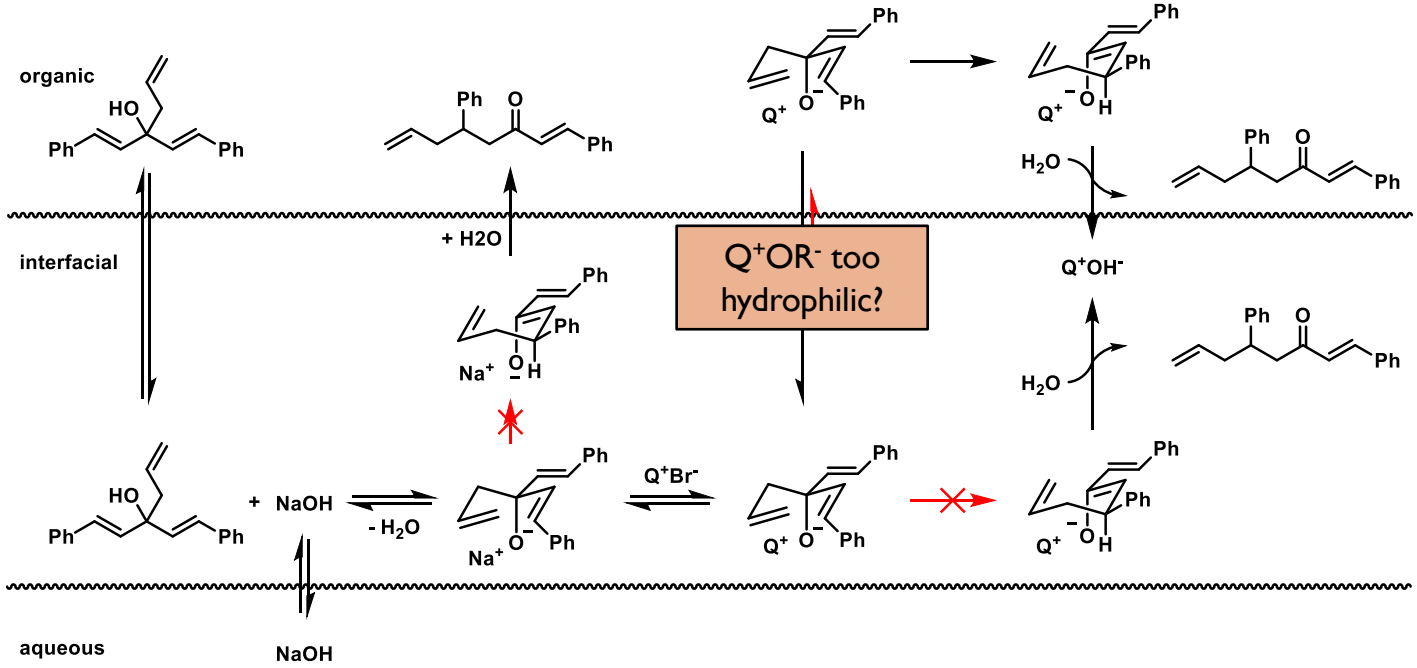
Mechanistic Proposals

- Extraction Model



- Common for alkoxide intermediates
- Explains lack of background conversion
- Rate of extraction dependent on Q^+

- Interfacial Model



- Q^+OR^- must desolvate prior to rearrangement
- Rate of desolvation dependent on Q^+

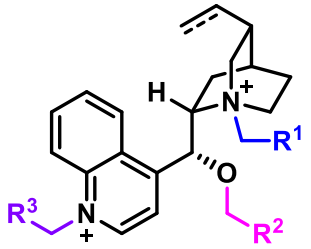
Summary - PT-Catalyzed oxy-Cope Rearr.

- A phase transfer catalyzed anionic oxy-Cope rearrangement was demonstrated for a limited substrate scope
- Synthetic utility is hindered by unproductive self-condensation pathways
- Catalysts other than tetraalkylammonium salts were largely ineffective
  - No asymmetric induction was observed

Quaternary ammonium salts in APTC

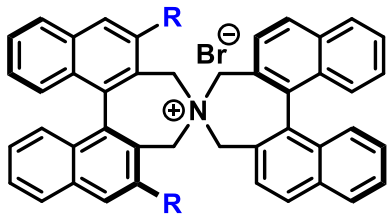
- In addition to usual considerations, solubility properties and base-stability of salt must be taken into account
- Asymmetric PTC is dominated by just two catalyst scaffolds

Cinchona alkaloid-derived



- derived from cheap natural products
- low synthetic overhead
- several points of diversification
- general method for diversifying aryl moiety remains a challenge

Maruoka type

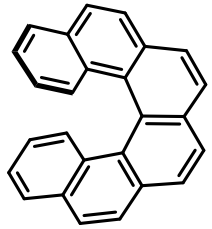


- derived from BINOL
- high synthetic overhead
- no risk of racemization
- one meaningful point of diversification

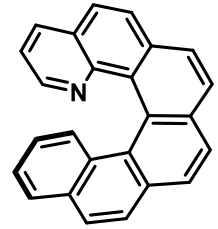
- What to do when libraries based on these scaffolds fail to produce high enantioselectivity in a reaction of interest?

Helicenes

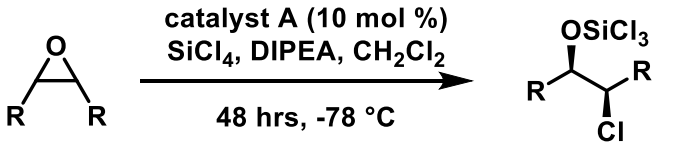
- Molecules containing five or more *ortho*-fused aryl or heteroaryl rings
- Adopt 3D-helical structure, with significant barrier to inversion for systems containing six rings or more
- Display high rigidity and thermal stability
- Highly polarizable, amenable to charge-transfer complexation
- Heteroatom-containing helicenes can be asymmetric catalysts!



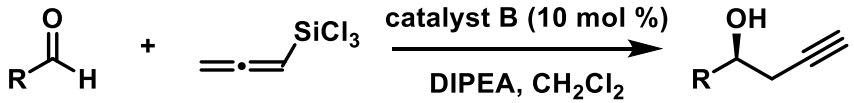
P-(+)-hexahelicene



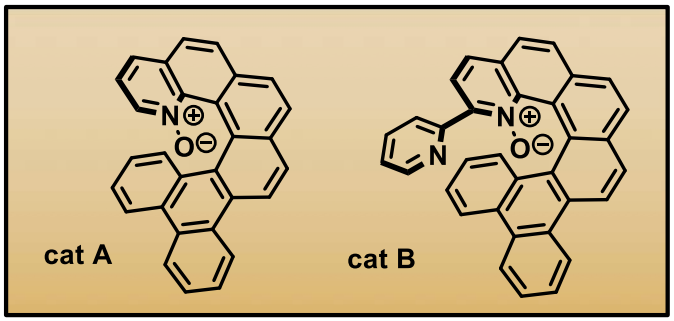
M-(-)-1-aza[6]helicene



63-84% yield
up to 97:3 e.r.



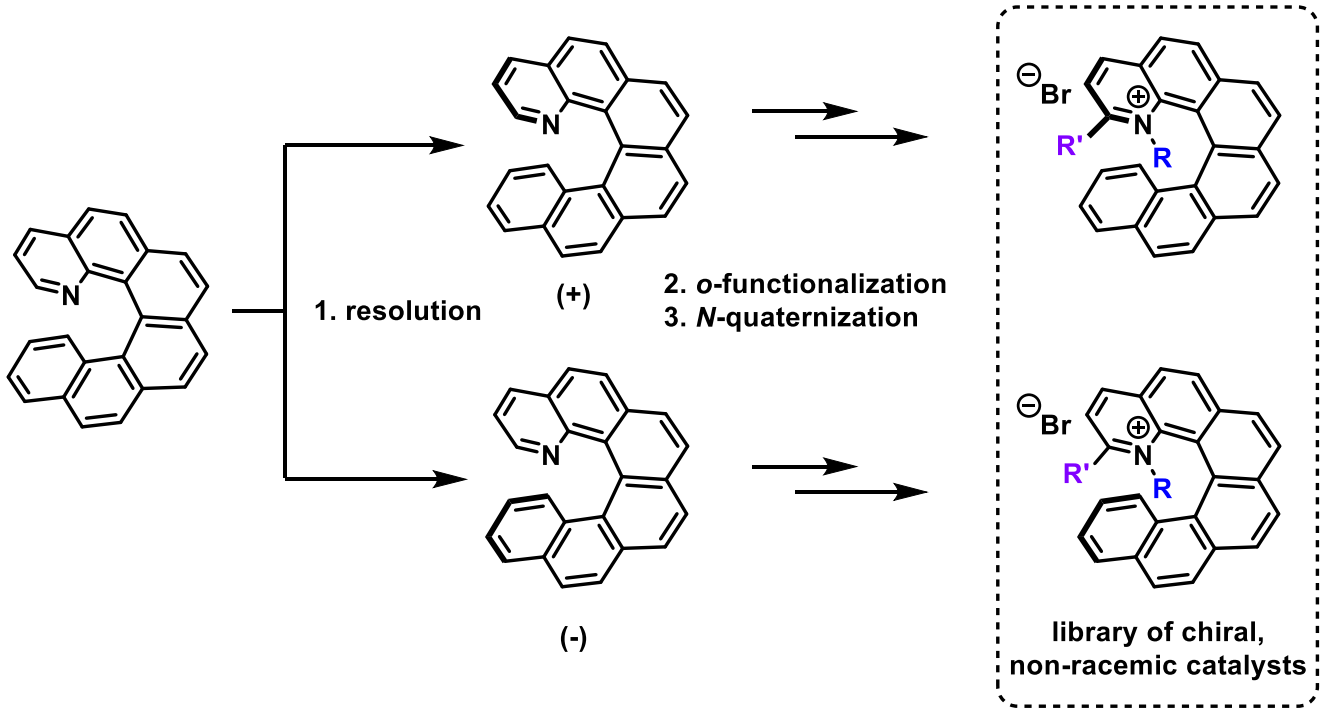
55-98% yield
up to 98:2 e.r.



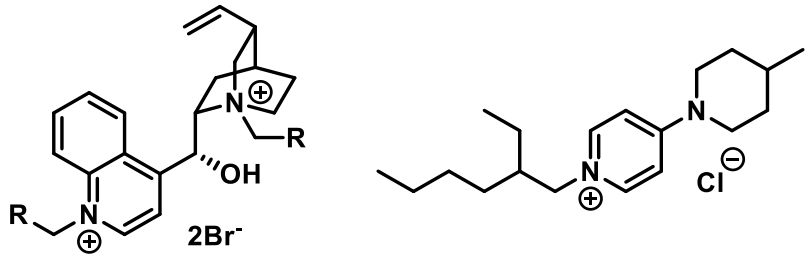
Takenaka, N. et al. *Angew. Chem. Int. Ed.* **2008**, *47*, 9708.
Takenaka, N. et al. *Org. Lett.* **2011**, *13*, 1654.

N-Quaternized Azahelicenes

- Interested in the development of a general catalyst scaffold based on the unique architecture of the azahelicene



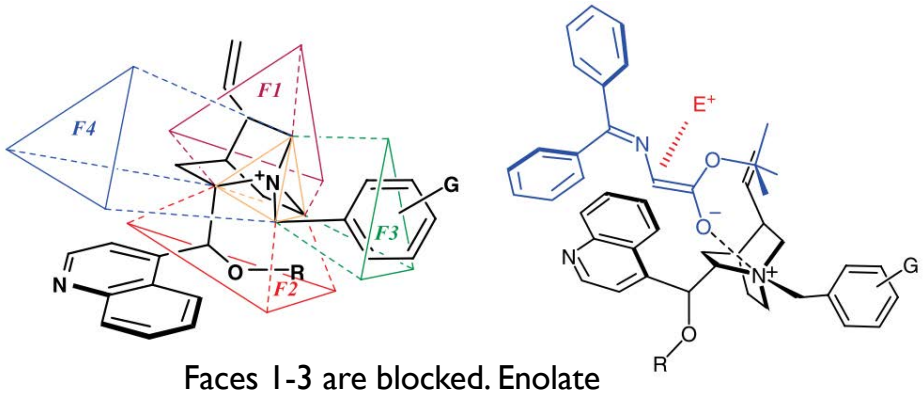
- Pyridinium salts are competent PTCs



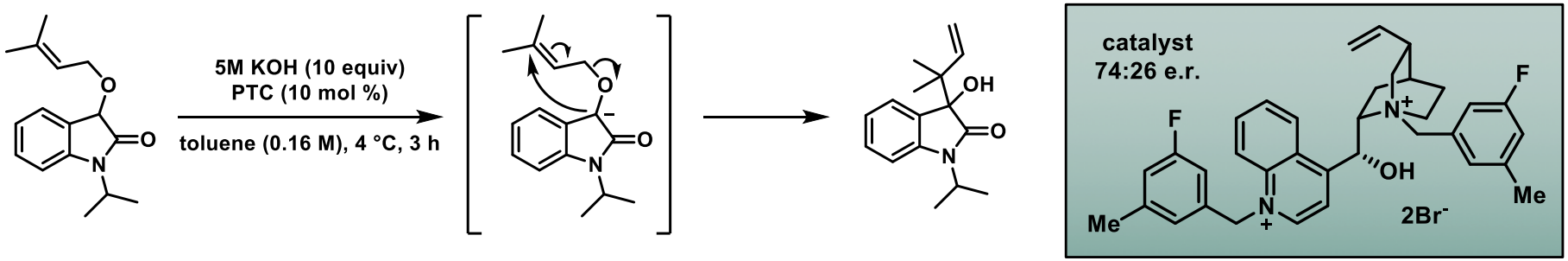
Brunelle, D. J.; Singleton, D. A. *Tetrahedron Lett.* **1984**, *25*, 3383.
Xiang, B., Yasuda, N. et al. *Angew. Chem. Int. Ed.* **2014**, *53*, 8375.

Why helicenes?

- Very high e.r. values (>99:1) are obtainable for most intermolecular APTC reactions
- Challenging to obtain high e.r. for intramolecular reactions
  - Steric screening model no longer applies



Faces 1-3 are blocked. Enolate must approach from face 4.



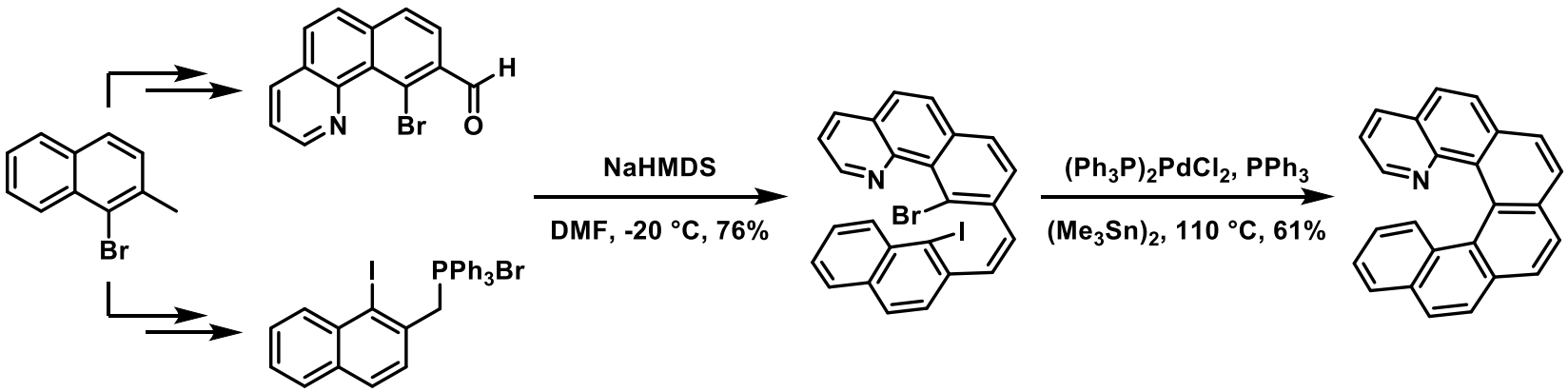
- Azahelicenes display helical chirality
  - Hypothesis: "continuously chiral" catalyst may be more selective for intramolecular PTC

Cullen, L. R. Thesis, **2015**.

Park, H.-G. and Jeong, B.-S. In *Cinchona Alkaloids in Synthesis and Catalysis*. Wiley: 2009, p 131-169.

Research Objectives

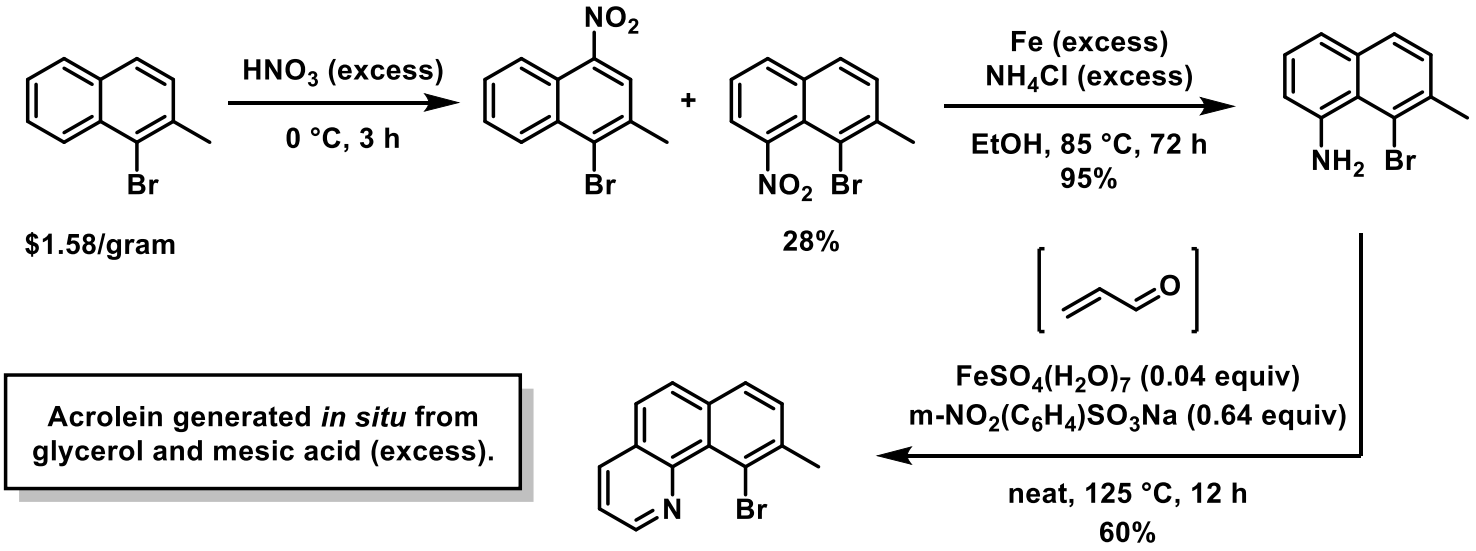
- Generate a library of novel phase transfer catalysts via *N*-quaternization of azahelicenes
- Establish the efficiency and selectivity of these catalysts in a known benchmark reaction (O'Donnell alkylation)
- Test catalysts for activity/selectivity in several intramolecular PTC reactions
- Synthetic strategy:
  - *Z*-selective Wittig reaction, intramolecular cross-coupling



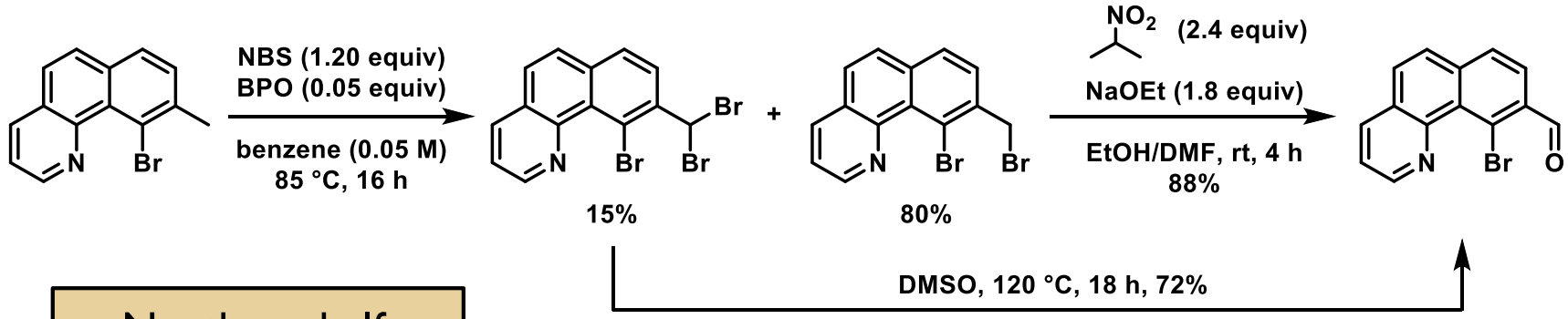
Takenaka, N. et al. *Angew. Chem. Int. Ed.* **2008**, *47*, 9708.

Northern Half

- Pyridine construction



- Aldehyde construction

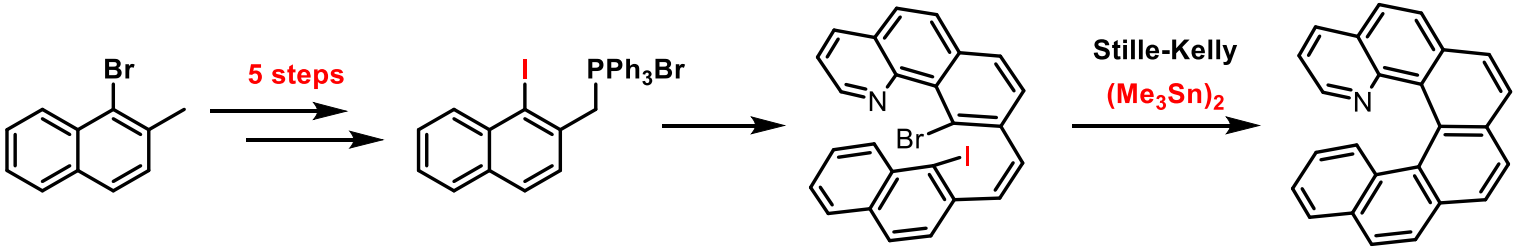


Northern half:
5 steps, 11% overall

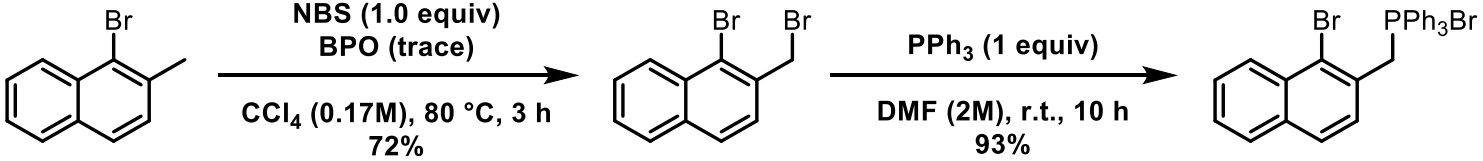
Tsubaki, K. et al. *Tetrahedron: Asymmetry* **2007**, 18, 1017.
Takenaka, N. et al. *Angew. Chem. Int. Ed.* **2008**, *47*, 9708.

Southern Half and Union

- Literature route:



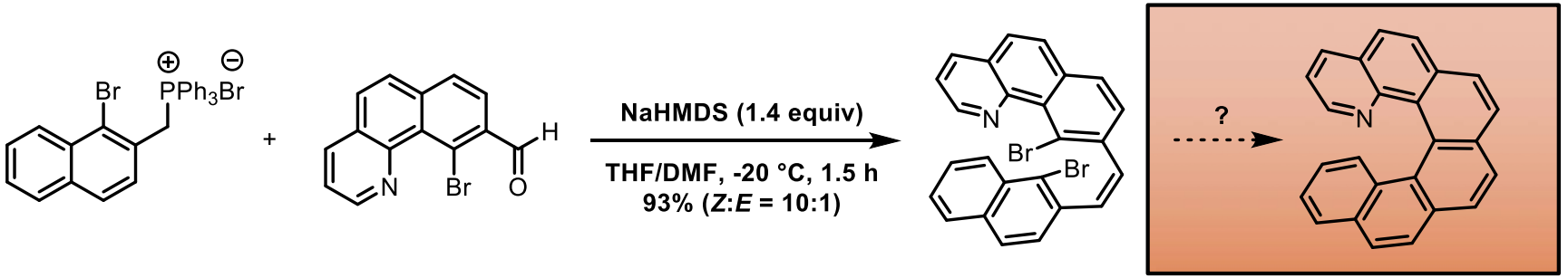
- Target revision:



$1.58/gram

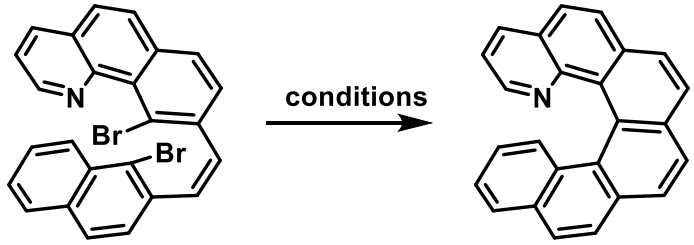
Southern half:
2 steps, 67% overall

- Wittig Olefination:



Endgame

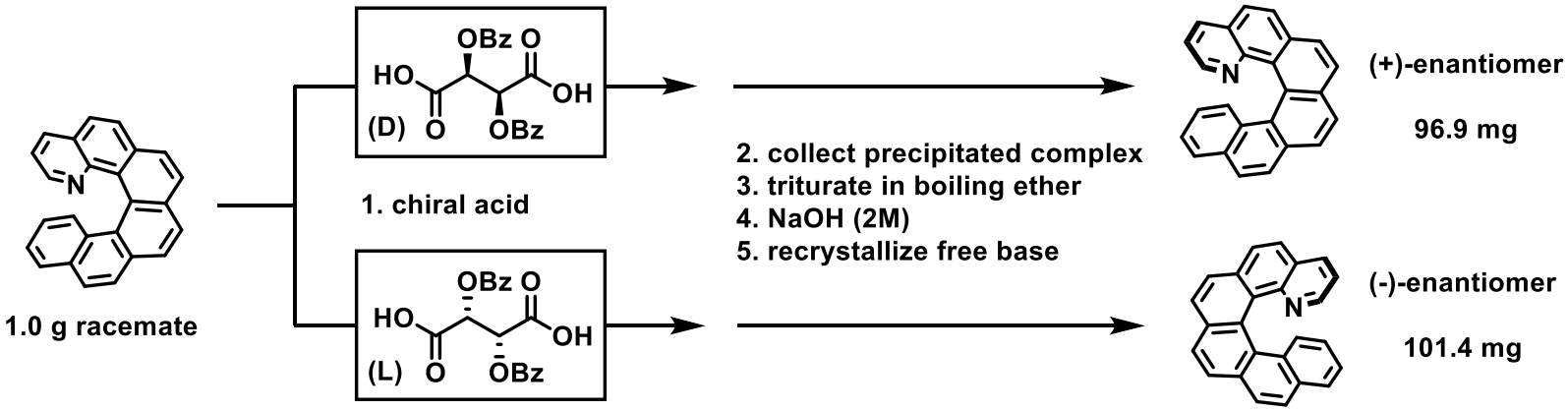
- Intramolecular coupling
  - Novel method to access helicenes (nickel-mediated coupling)



Conditions	Yield of **7**
Cu (4.3 equiv), DMF, 150 °C, 24 h	0%
$NiCl_2$ (1.6 equiv), PPh_3 (5.7 equiv), NaI (1.9 equiv), Zn (10.1 equiv), DMF, 60 °C to 75 °C, 12 h	73%

  - 9 total steps (7 LLS), 7% overall yield, 4.5 grams synthesized

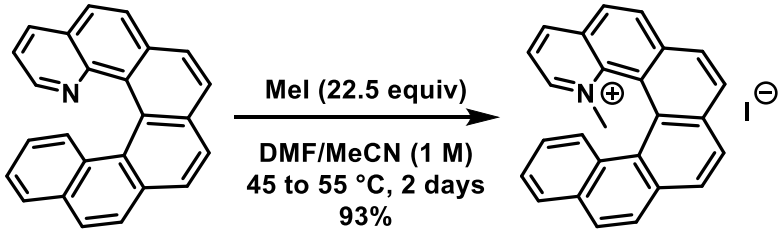
- Resolution by known procedure



Stará, I. G., Starý, I. et al. *Angew. Chem. Int. Ed.* **2008**, *47*, 3188.

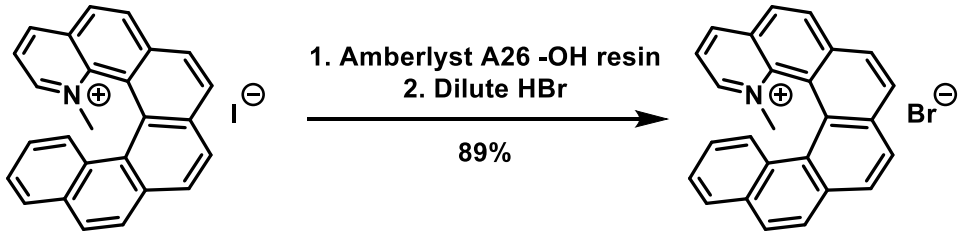
Preparation and Assessment of Catalysts

- Alkylation

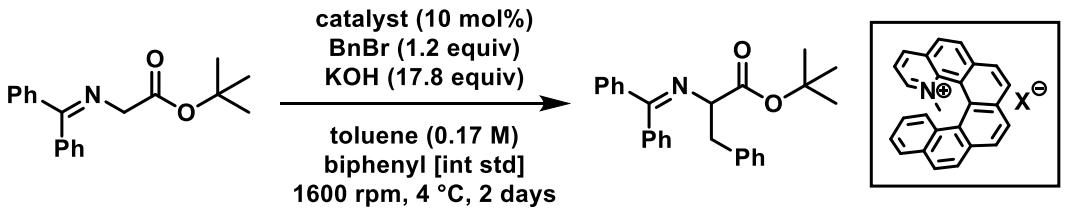


Electrophile	Yield
Methyl iodide	93%
Allyl bromide	0%
Ethyl bromide	0%
Benzyl bromide	0%
Benzyl triflate	0%

- Ion exchange (I to Br)



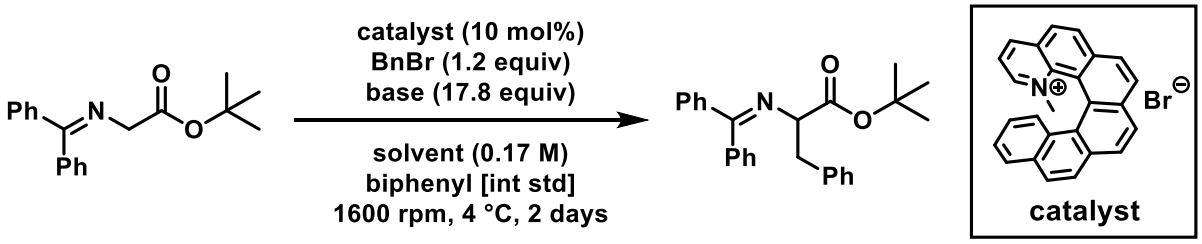
- Test for activity in O'Donnell reaction



Catalyst	Yield
None	6%
X = I	13%
X = Br	62%

Optimization of Reaction Conditions

- Base and solvent screen
  - Using TFT as the solvent and/or CsOH as the base all led to comparable yields of **2**
  - Background conversion was lowest with original conditions

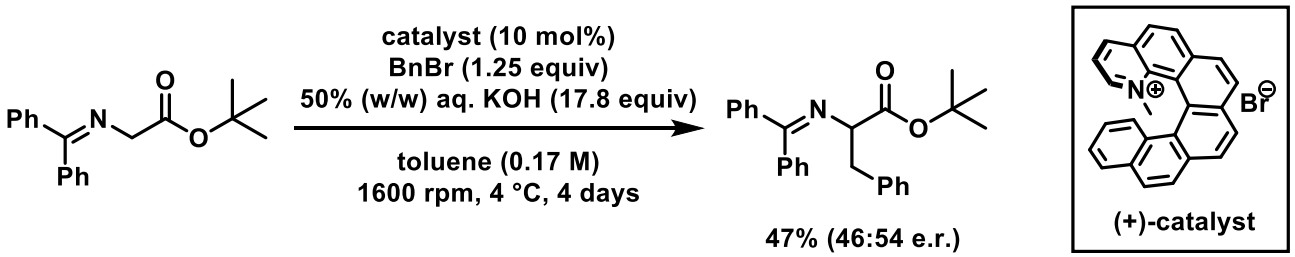


Base	Solvent	Additive	Yield[b]	Control Yield[b]
KOH (50% w/w aq)	toluene	none	62%	6%
KOH (50% w/w aq)	toluene	KBr (0.5 equiv)	29%	6%
KOH (50% w/w aq)	TFT[a]	none	66%	21%
CsOH (80% w/w aq)	toluene	none	57%	28%
CsOH (80% w/w aq)	TFT	none	64%	37%
K_2CO_3 (sat. aq)	toluene	none	0%	0%
K_2CO_3 (sat. aq)	TFT	none	0%	0%

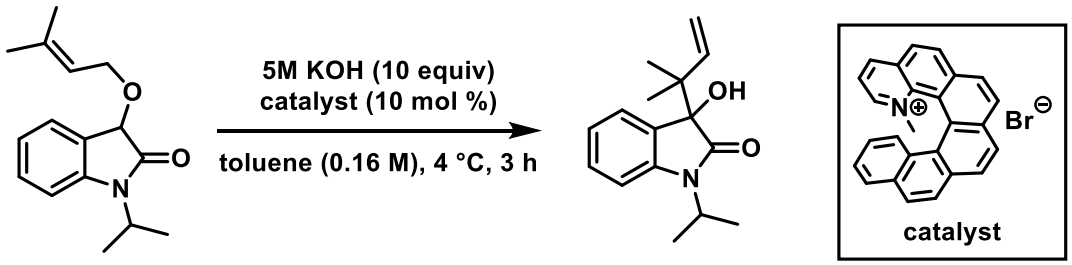
[a] TFT = α,α,α-trifluorotoluene. [b] Determined by analytical HPLC using biphenyl as an internal standard.

Assessment of Enriched Catalyst

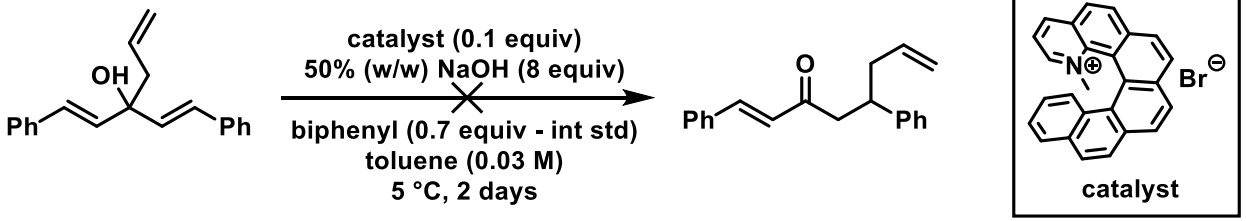
- (+)-catalyst accessed thru same alkylation/ion exchange sequence
- Displayed poor activity (slow) and poor selectivity in intermolecular PTC reaction



- No activity observed in intramolecular PTC reactions



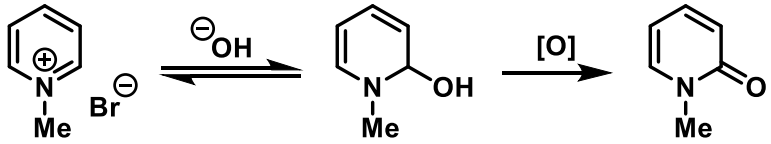
Same rate as background (no catalysis)



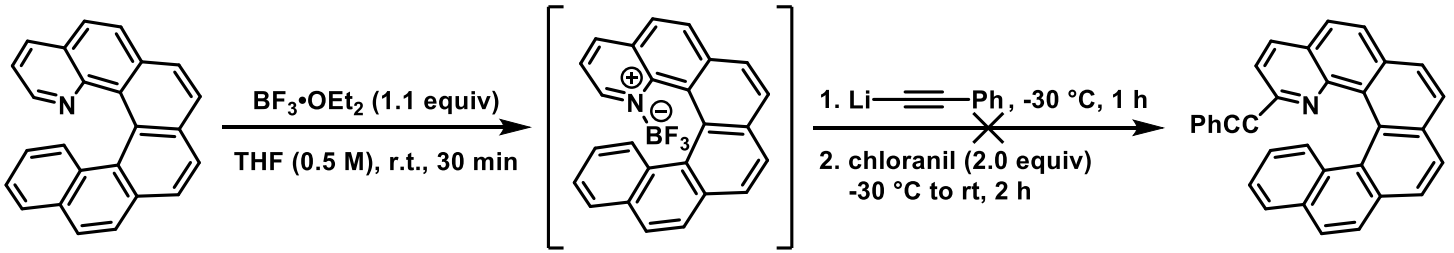
No conversion

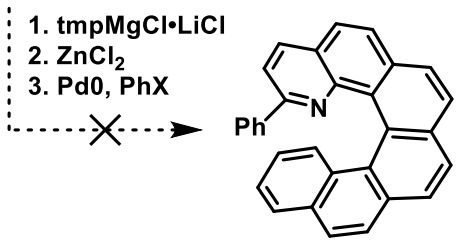
Catalyst Stability

- Quaternary pyridinium salts can decompose in aqueous hydroxide
  - 2-position susceptible to nucleophilic attack



- Potential solution: prepare *ortho*-substituted derivatives
- Unsuccessful route: functionalization of BF_3 adduct



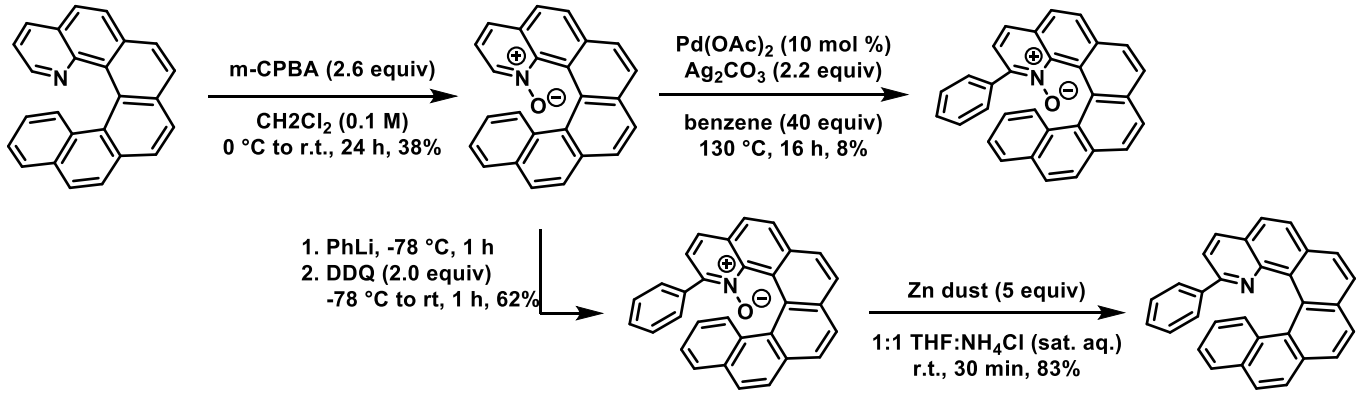


Eicher, T.; Hauptmann, S.; Speicher, A. In *The Chemistry of Heterocycles*; Wiley: 2012, p 345-406.
Knochel, P. et al. *Angew. Chem. Int. Ed.* **2010**, *49*, 5451.
Knochel, P. et al. *Synthesis* **2014**, *46*, 1374.

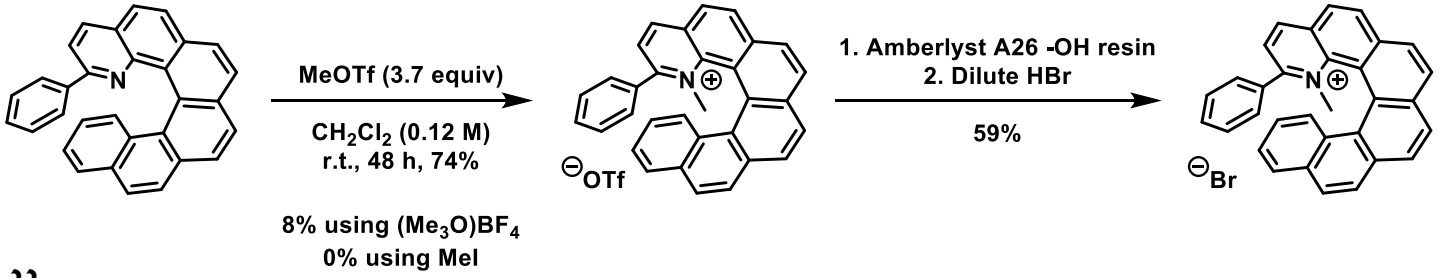
Synthesis/Evaluation of ortho-Arylated Catalyst

- Successful route: functionalization of *N*-oxide

Oxidant	Yield
m-CPBA[a]	38%
TFPAA	12%
DMDO	0%
H_2O_2	0%



- Catalyst Synthesis:

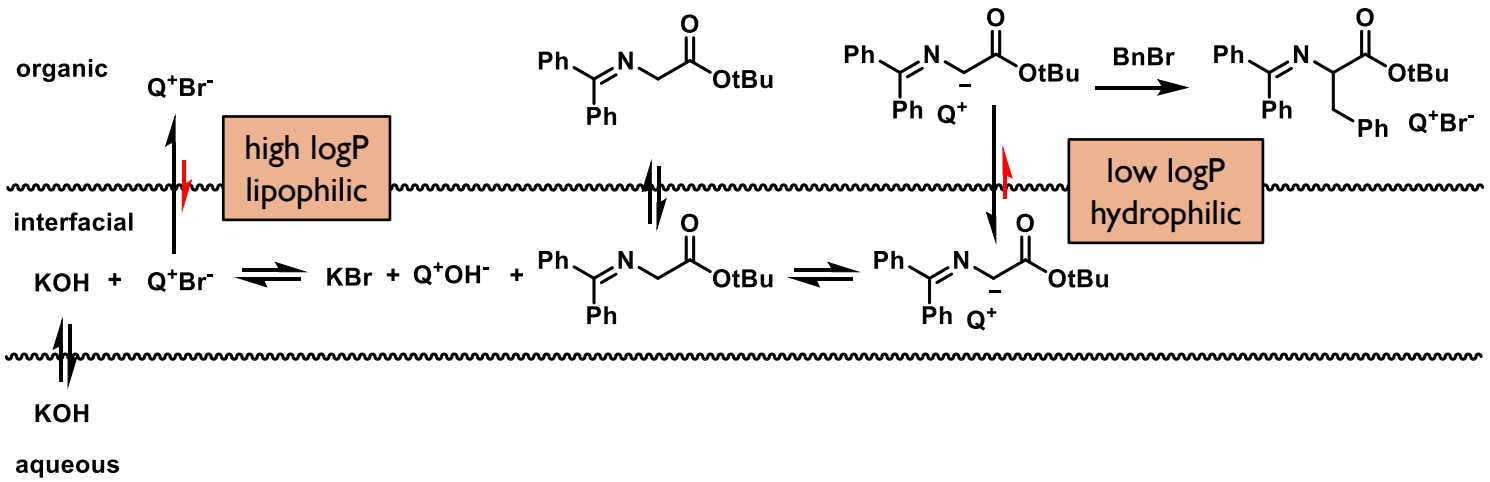


- Active??
  - **NO** catalytic activity observed in O'Donnell alkylation!
  - Conversion resulted from background reaction only

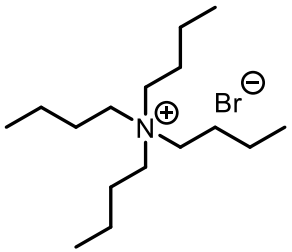
Takenaka, N. et al. *Organic Letters* **2011**, *13*, 1654.

Discussion - Catalyst Lipophilicity

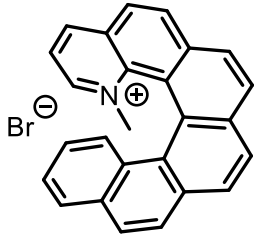
- logP: measure of relative affinity of Q^+X^- for the organic vs. aqueous phase



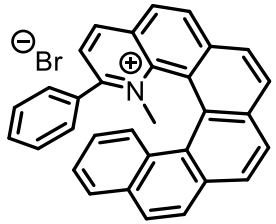
- Computed ClogP(o/w) values:



TBAB
ClogP = 6.569

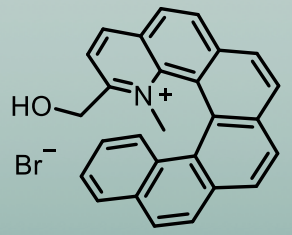


Cat. 2-H
ClogP = 7.674



Cat. 2-Ph
ClogP = 9.384

Future Direction?



Cat. 2-CH_2OH
ClopP = 6.902

Structures minimized with B3LYP/LACVP*

Calculations by Dr. Jeremy J. Henle

Summary - Azahelicene PTC Scaffold

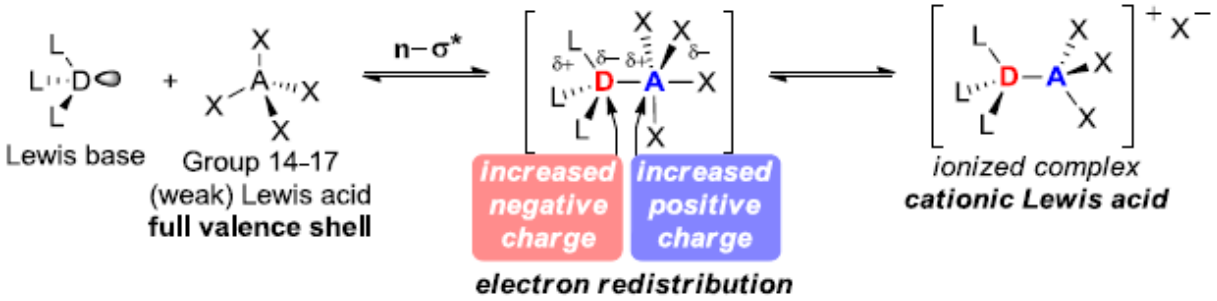
- The syntheses of several novel azahelicene-based *N*-methylpyridinium halides have been reported (racemic and enantiopure)
  - Accompanied by a novel method of accessing 1-aza[6]helicene via nickel-mediated cross coupling
- Catalytic activity of one of these compounds has been established for the α-alkylation of carbonyl compounds under hydroxide-mediated PTC conditions
- Synthetic utility is hampered by:
  - high synthetic overhead
  - difficulty of late-stage diversification
  - possible catalyst decomposition
  - poor asymmetric induction

Tonight's Outline

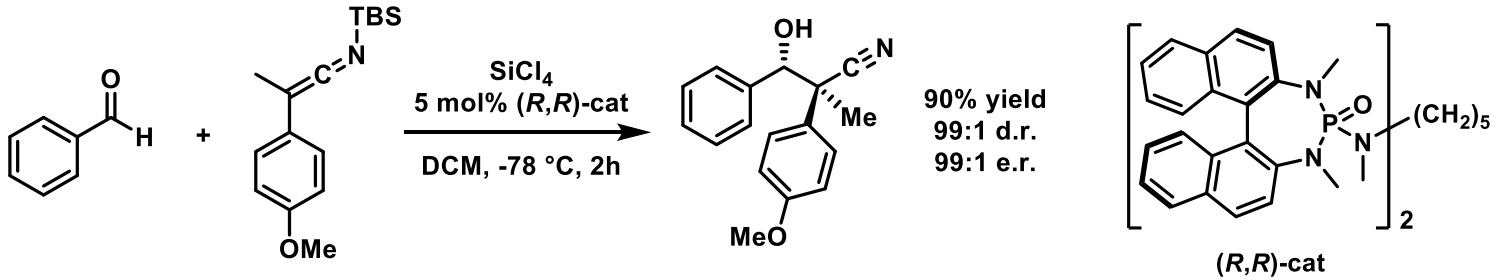
- Phase Transfer Catalysis
  - Development of PT-Catalyzed Anionic Oxy-Cope Rearrangement
  - Synthesis of an Azahelicene-Derived Scaffold for APTC
- Lewis Base Catalysis
  - Enantioselective Sulfenocyclization of Polyenes
    - Mechanistic Investigation
  - Enantioselective Sulfenofunctionalization of Alkenylboronates

- Will not be covered:
  - Bisoxazoline Synthesis

Lewis Base Catalysis

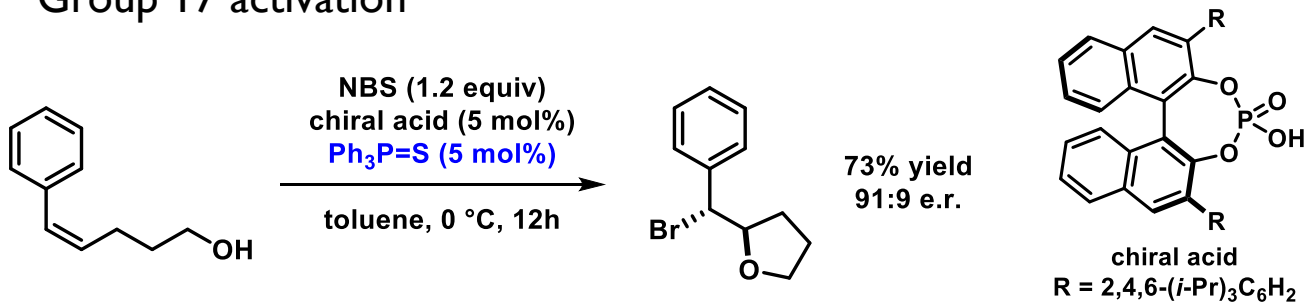


- Group 14 activation



Denmark, S. E. et al. *J. Am. Chem. Soc.* **2007**, 129(48), 14864-14865.

- Group 17 activation

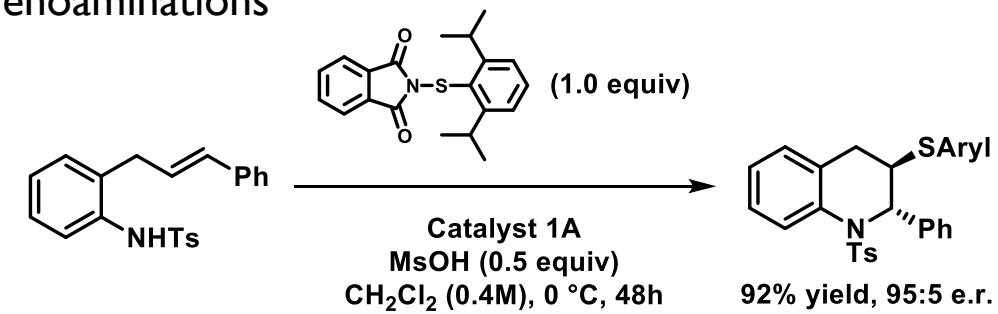


Denmark, S. E. et al. *Org. Lett.* **2012**, 14(1), 256-259.

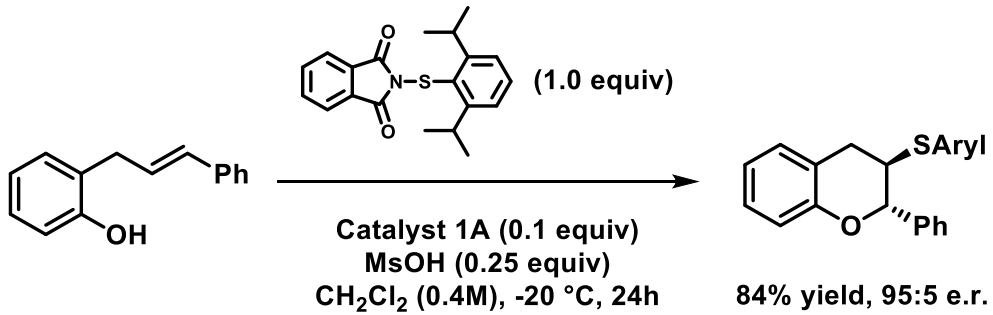
Denmark, S. E. and Beutner, G. L. In *Lewis Base Catalysis in Organic Synthesis*; Wiley-VCH Verlag GmbH & Co. KGaA: 2016, p. 31.
Chi, H. M. Doctoral Thesis

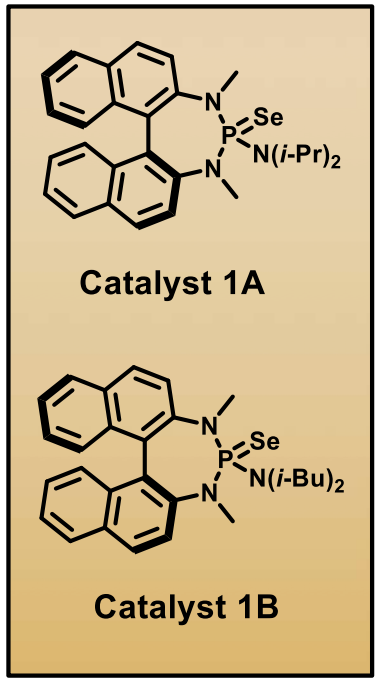
Lewis Base Activation: Group 16

- Sulfenoaminations

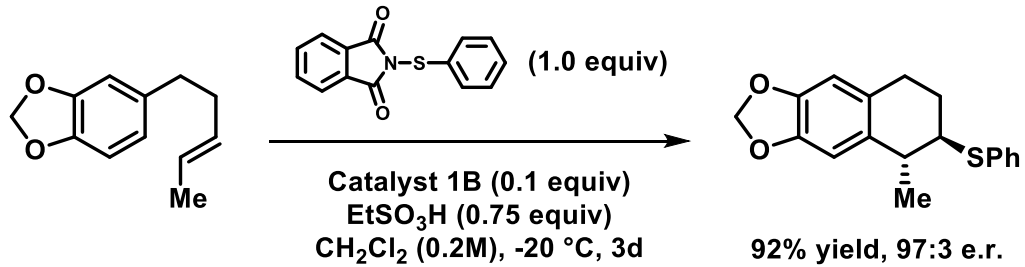


- Oxysulfenylations



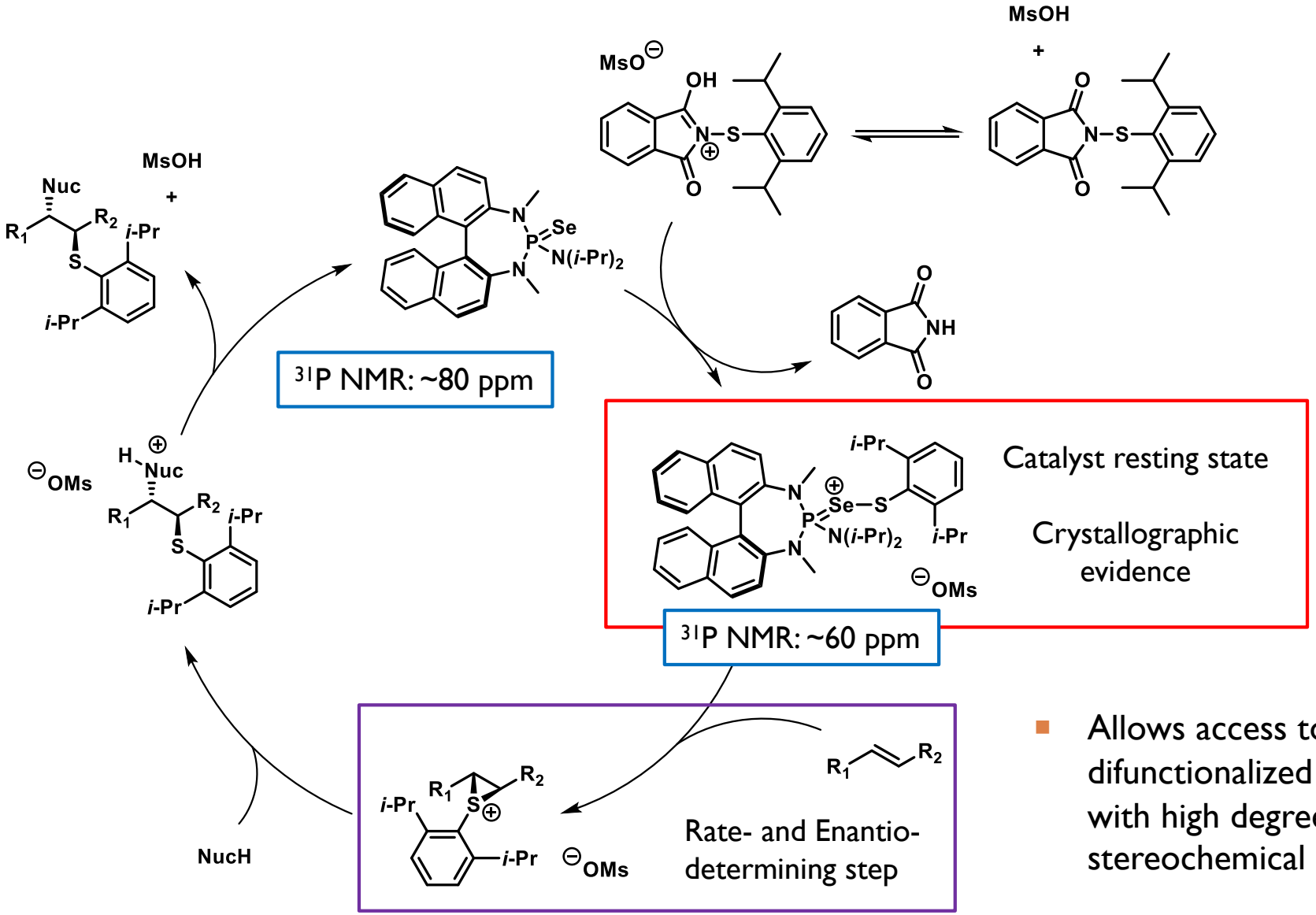


- Carbosulfenylations



Chi, H. M. and Denmark, S. E. *J. Org. Chem.* **2017**, 82(7), 3826-3843.
Kornfilt, D. J.-P. and Denmark, S. E. *J. Org. Chem.* **2017**, 82(6), 3192-3222.
Jaunet, A. and Denmark, S. E. *J. Am. Chem. Soc.* **2013**, 135(17), 6419-6422.

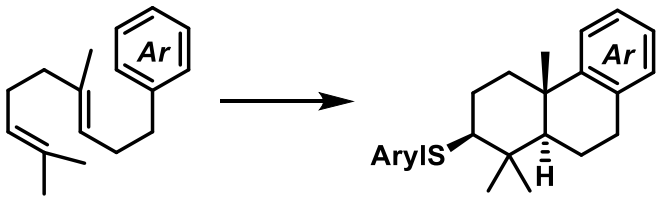
Group 16 Activation: Mechanism



- Allows access to 1,2-difunctionalized products with high degree of stereochemical control

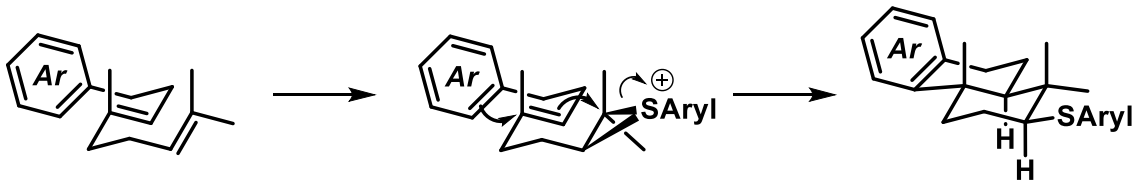
Denmark, S. E. et al. *Nat. Chem.* **2014**, 6(12), 1056-1064.

Proposal: Polyene Sulfenocyclization

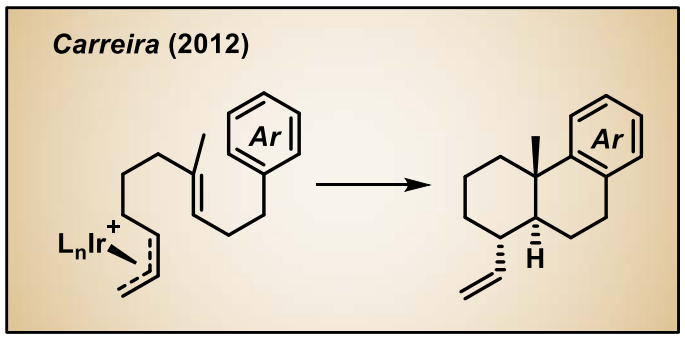


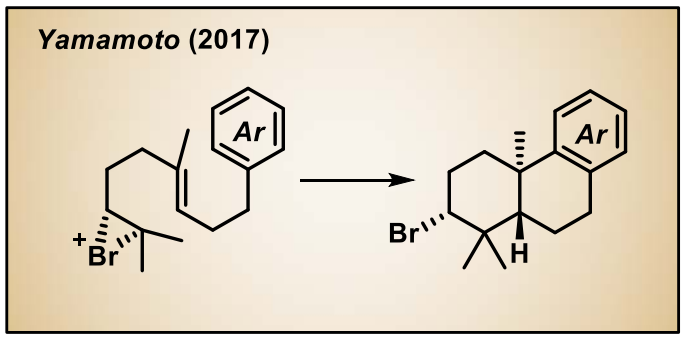
- Biomimetic
- Diastereoselective transformation
- Rapid generation of *complexity*
- W. S. Johnson, E. E. van Tamelen, E. J. Corey, others

- Via:



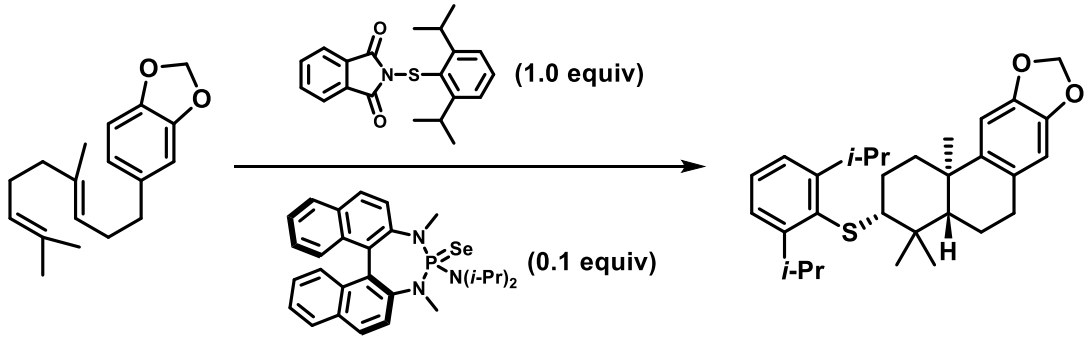
- Catalytic, enantioselective polyene cyclizations:



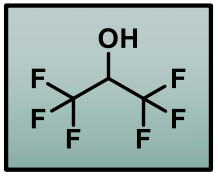


Sarlah, D. et al. *Org. Biomol. Chem.* **2016**, 14(24), 5454-5467.
Yamamoto, H. et al. *J. Am. Chem. Soc.* **2017**, 139(4), 1460-1463.
Carreira, E. M. et al. *J. Am. Chem. Soc.* **2012**, 134(50), 20276-20278.

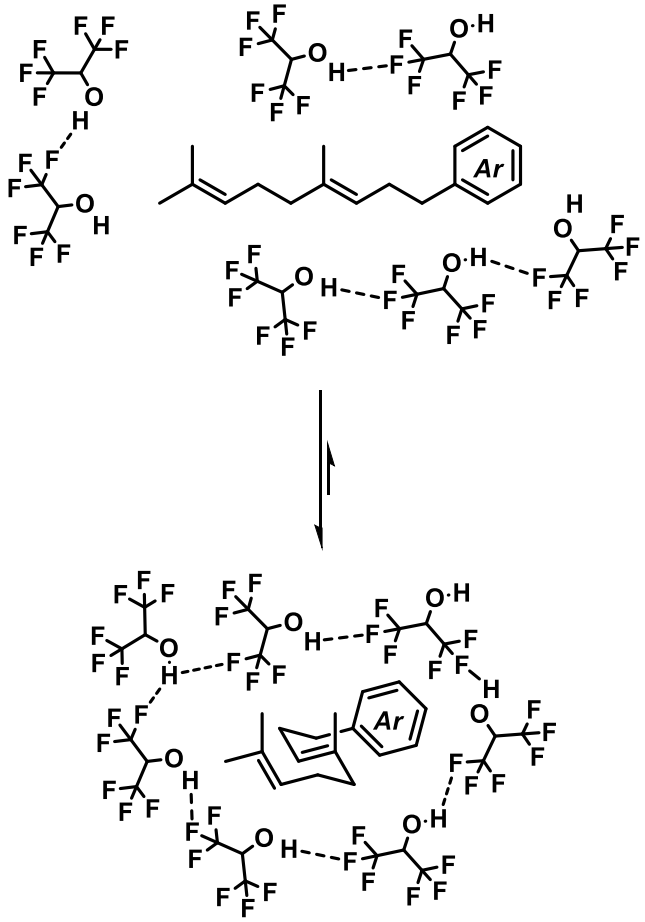
Optimization: Solvent Screen



Entry	MsOH equiv.	Solvent	Temp.	Results
1	0.4	CH_2Cl_2	-20 °C	Full conv, complex mixture (3d)
2	0.4	Toluene	-20 °C	No conversion (5d)
3	0.4	$MeNO_2$	-20 °C	Full conv, complex mixture (2d)
4	0.4	PhCl	-20 °C	< 5% conv (5d)
5	0.4	TFT	-20 °C	Full conv, complex mixture (2d)
6	0.4	MeCN	-20 °C	Incomplete, complex mixture (2d)
7	0	HFIP	0 °C	Clean conv (2h)

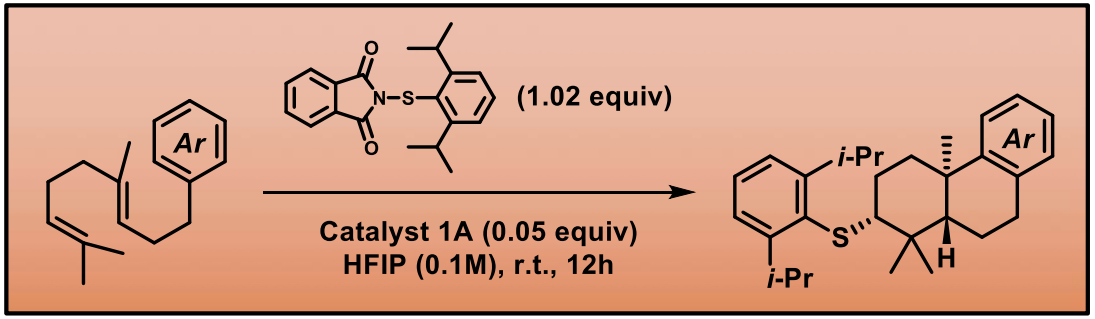


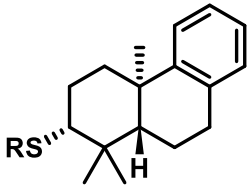
- Solvophobic effects → cleaner reaction
- Removal of MsOH → better FG tolerance



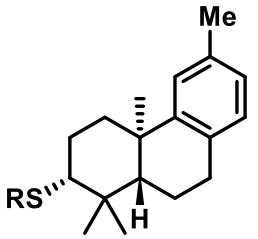
Kuo Zhao

Scope of Transformation



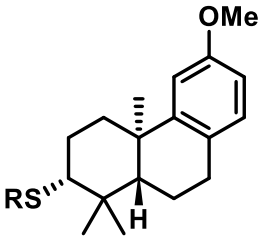


60%, 90:10 e.r.

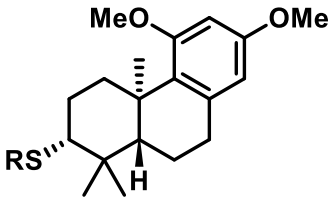


60%, 90:10 e.r.

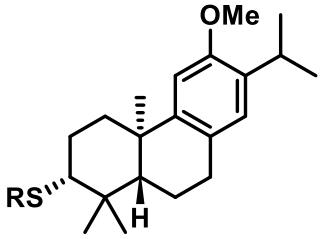
- Isolated yields of analytically pure material; e.r. determined by HPLC.



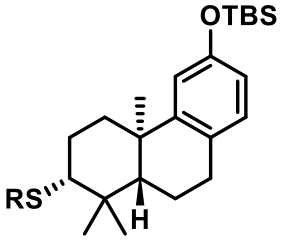
59%, 92:8 e.r.



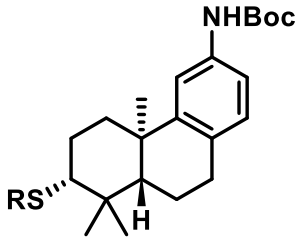
78%, 90:10 e.r.



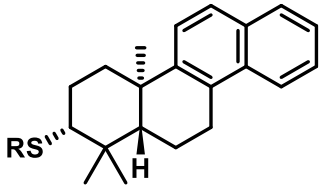
68%, 92:8 e.r.



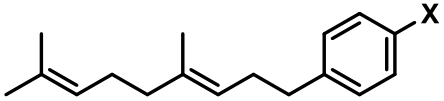
71%, 93:7 e.r.



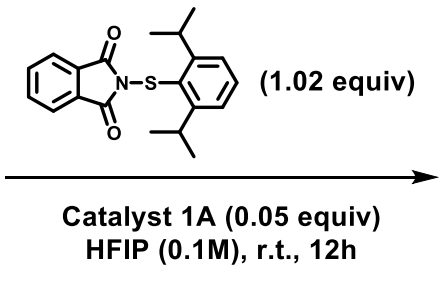
78%, 92:8 e.r.



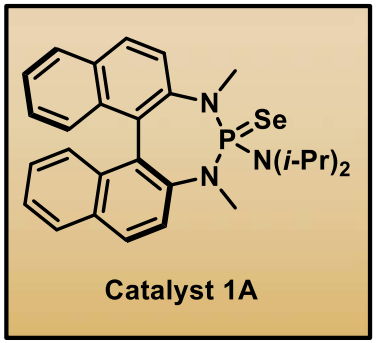
59%, 92:8 e.r.



X = F, Cl



complex mixture

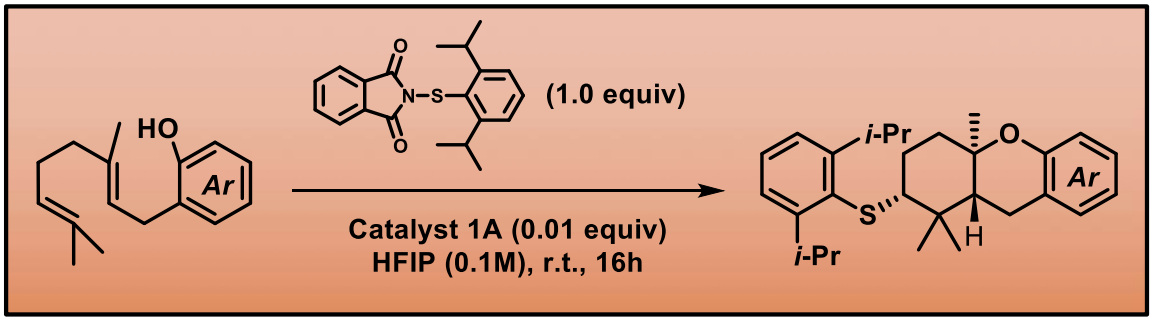


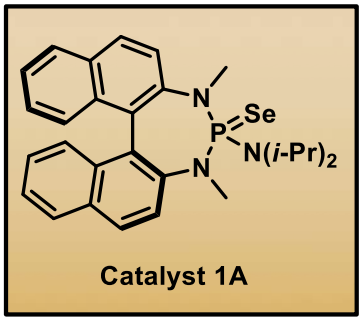
Catalyst 1A

- All electron neutral/rich compounds cyclize efficiently

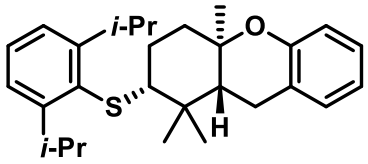
Zhonglin Tao, Kevin A. Robb, Kuo Zhao, and Scott E. Denmark. *J. Am. Chem. Soc.* **2018**, 140(10), 3569-3573.

Scope of Transformation

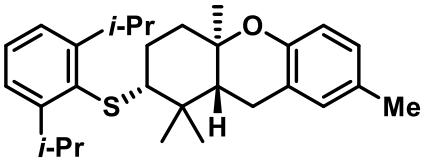




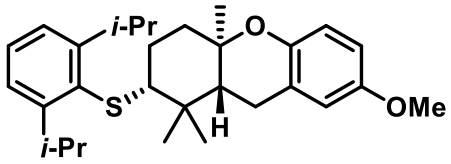
- Isolated yields of analytically pure material; e.r. determined by HPLC.



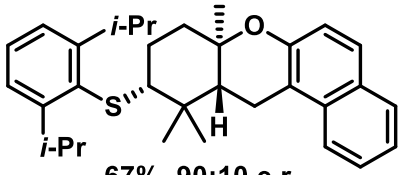
72%, 93:7 e.r.



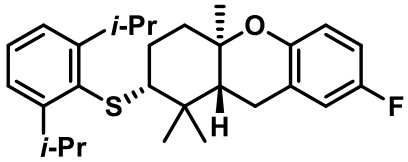
71%, 92:8 e.r.



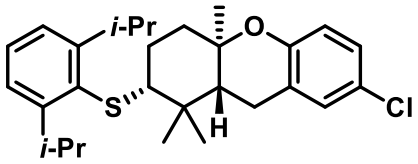
80%, 91:9 e.r.



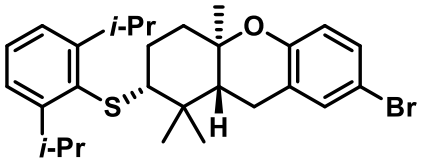
67%, 90:10 e.r.



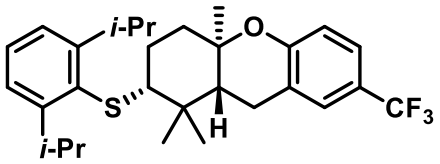
77%, 92:8 e.r.



79%, 91:9 e.r.



77%, 92:8 e.r.



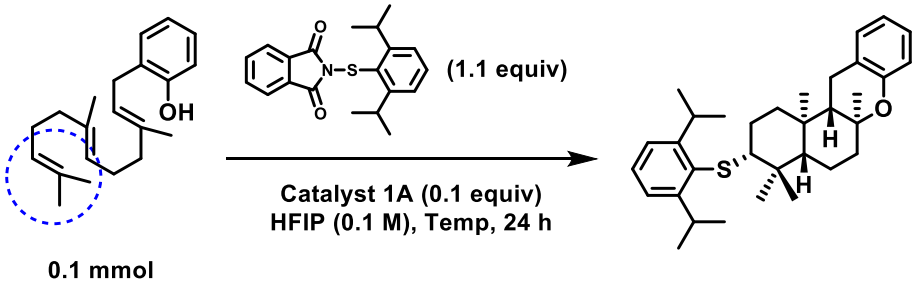
76%, 91:9 e.r.

- Diverse phenols serve as effective terminal nucleophiles

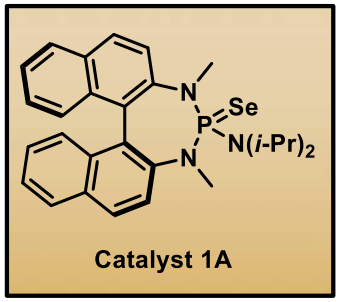
Zhonglin Tao, Kevin A. Robb, Kuo Zhao, and Scott E. Denmark. *J. Am. Chem. Soc.* **2018**, 140(10), 3569-3573.

Scope: Trienes

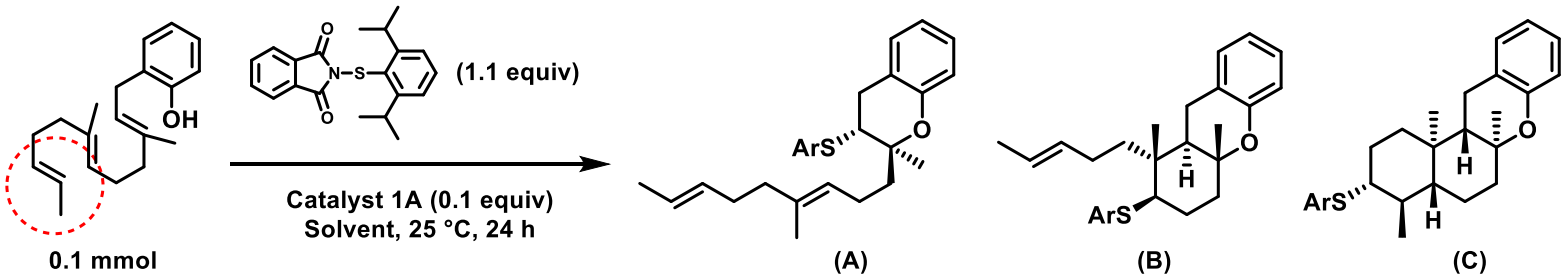
- Cyclization of trienes afforded complex mixtures which were difficult to purify



Temp	Yield
25 °C	<10%
0 °C	<30%



- Preparation of desmethyl analog did not improve site-selectivity

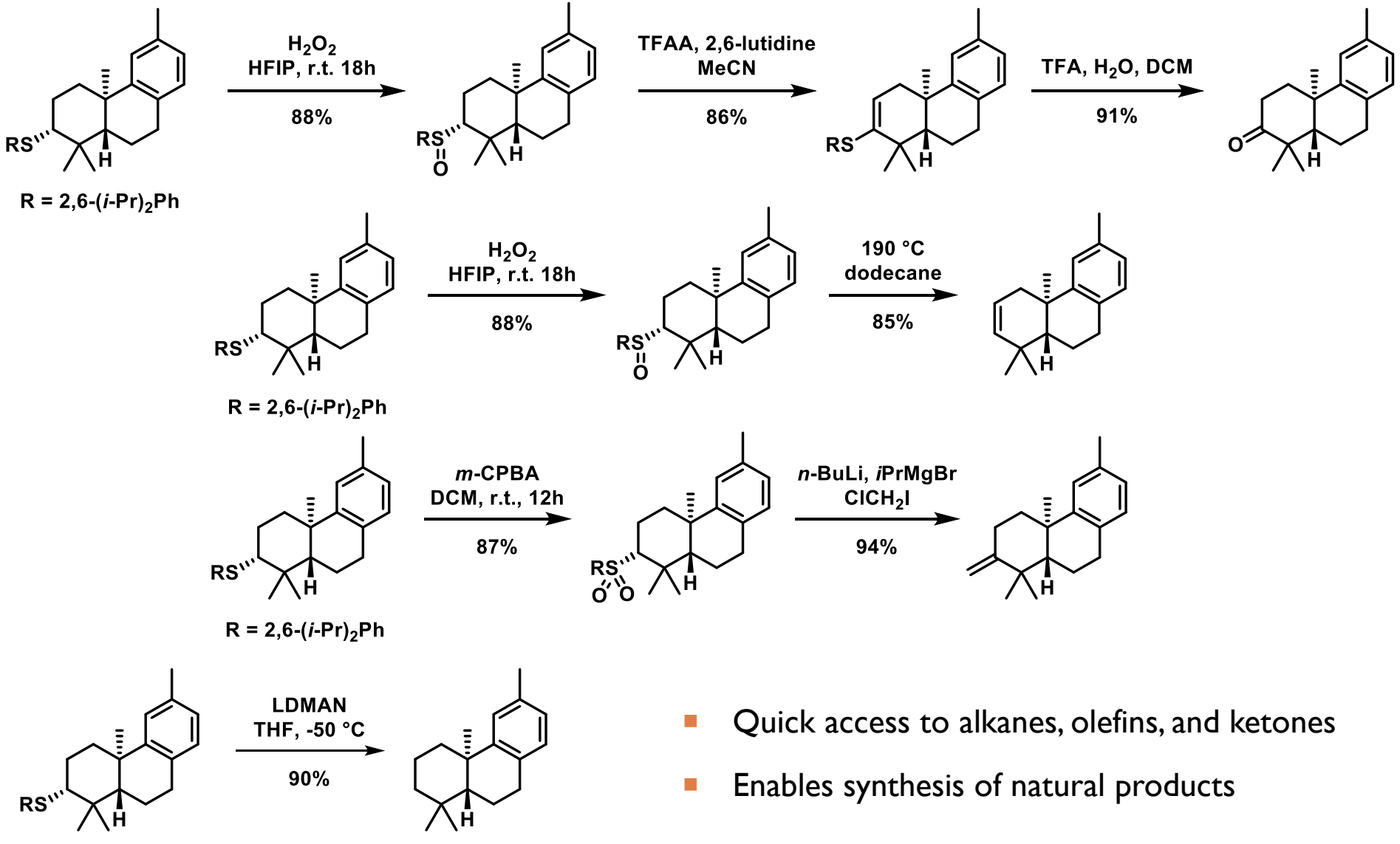


Solvent	A	B	C	Isolated yield of C
DCM (w/ MsOH)	Yes	Yes	Yes	<10%
TFE	Yes	No	No	---
HFIP	No	Yes	Yes	<30%
$(CF_3)_3COH$	No	No	No	---
$CF_3(CF_2)_2CH_2OH$	Yes	Yes	No	---

- Best results still obtained in HFIP

Unpublished results.

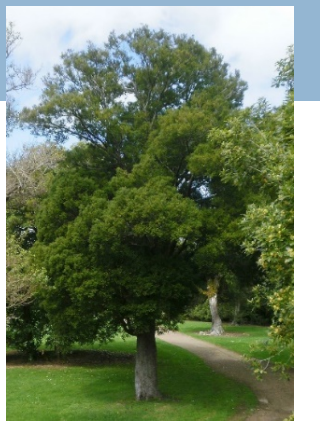
Product Diversification



- Quick access to alkanes, olefins, and ketones
- Enables synthesis of natural products

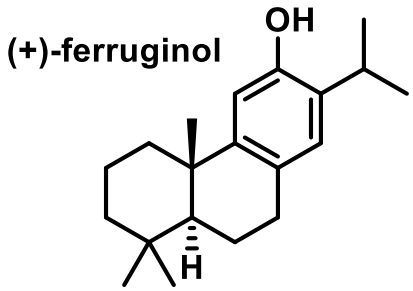
Zhonglin Tao, Kevin A. Robb, Kuo Zhao, and Scott E. Denmark. *J. Am. Chem. Soc.* **2018**, 140(10), 3569-3573.

Natural Product Showcase



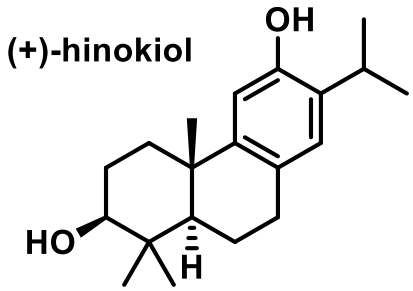
Ferruginol

- Diterpene first isolated in 1939 from the bark resin of *P. ferruginea* (Miro tree), New Zealand
- Anti-fungal and anti-bacterial activity

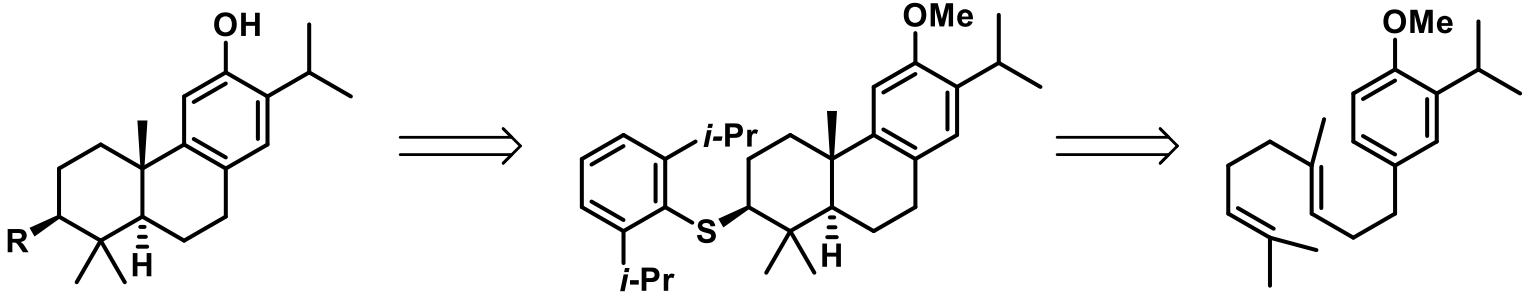


Hinokiol

- Diterpene first isolated in 1933 from *C. obtusa* (hinoki cypress), central Japan
- Anti-inflammatory and anti-parasitic activity

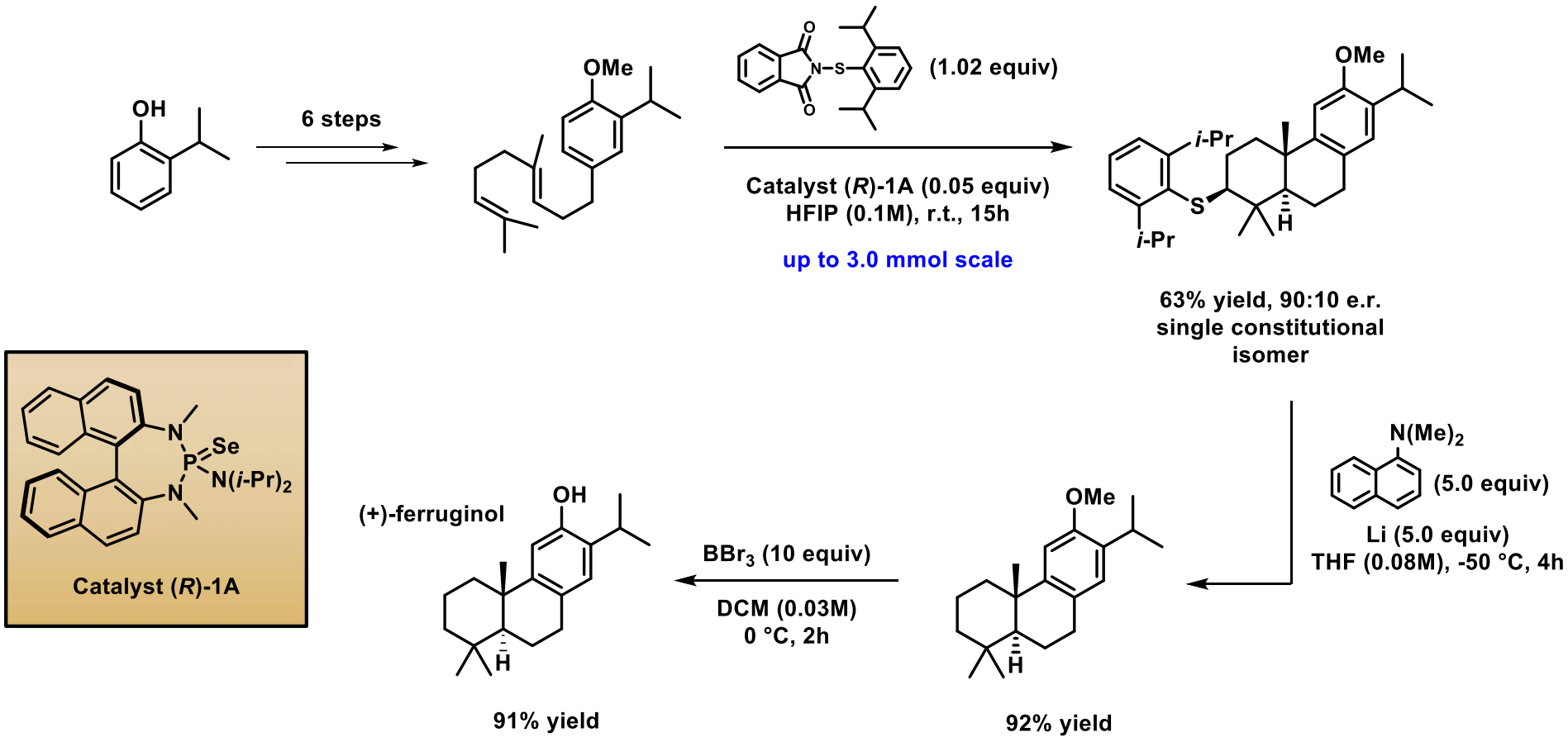


Retrosynthetic analysis



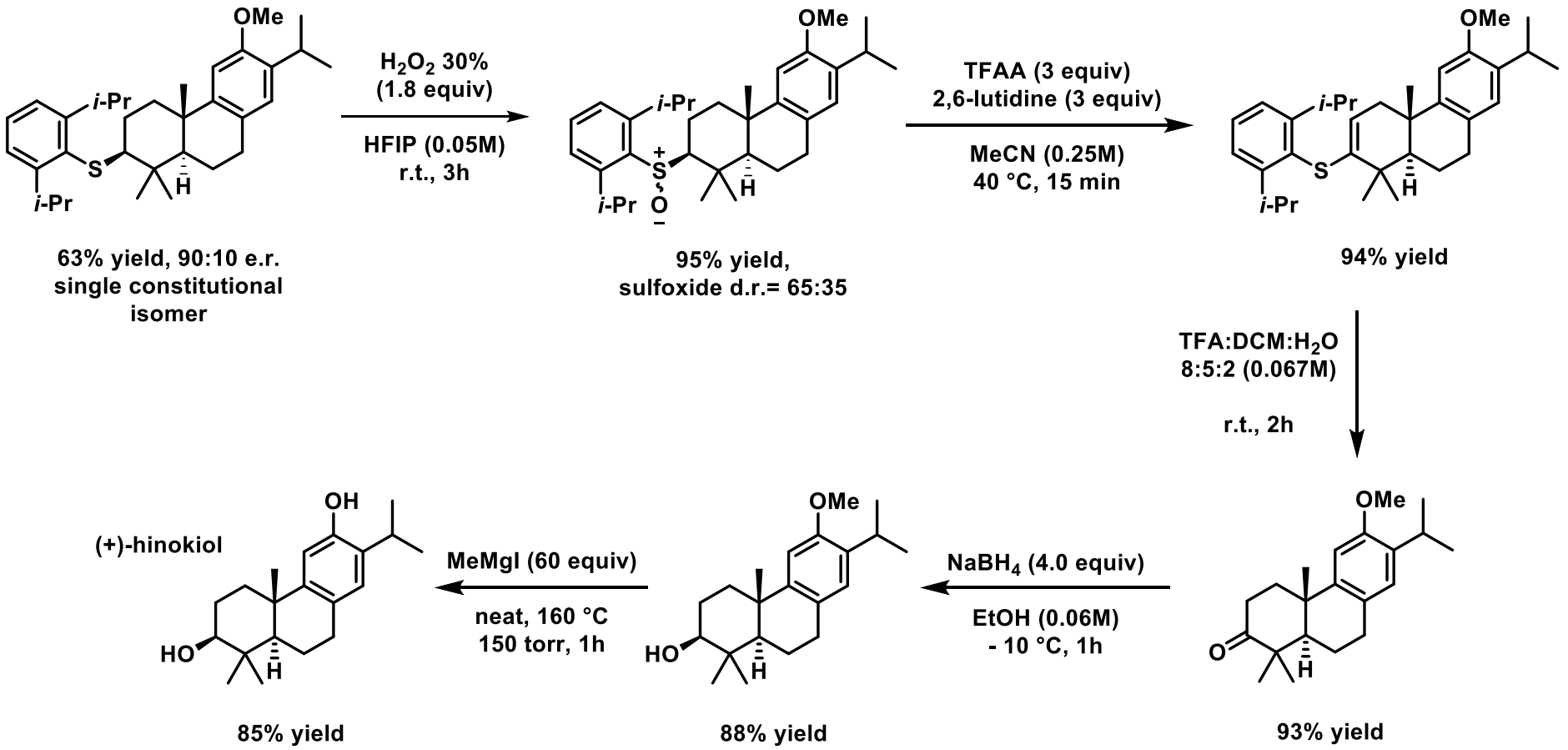
Brandt, C.W. and Neubauer, L. G. *J. Chem. Soc.* **1939**, 1031-1037.
Yoshiki, Y. and Ishiguro, T. *Yakugaku Zasshi* **1933**, 53, 73-151.

Forward Route: Ferruginol



Zhonglin Tao, Kevin A. Robb, Kuo Zhao, and Scott E. Denmark. *J. Am. Chem. Soc.* **2018**, 140(10), 3569-3573.

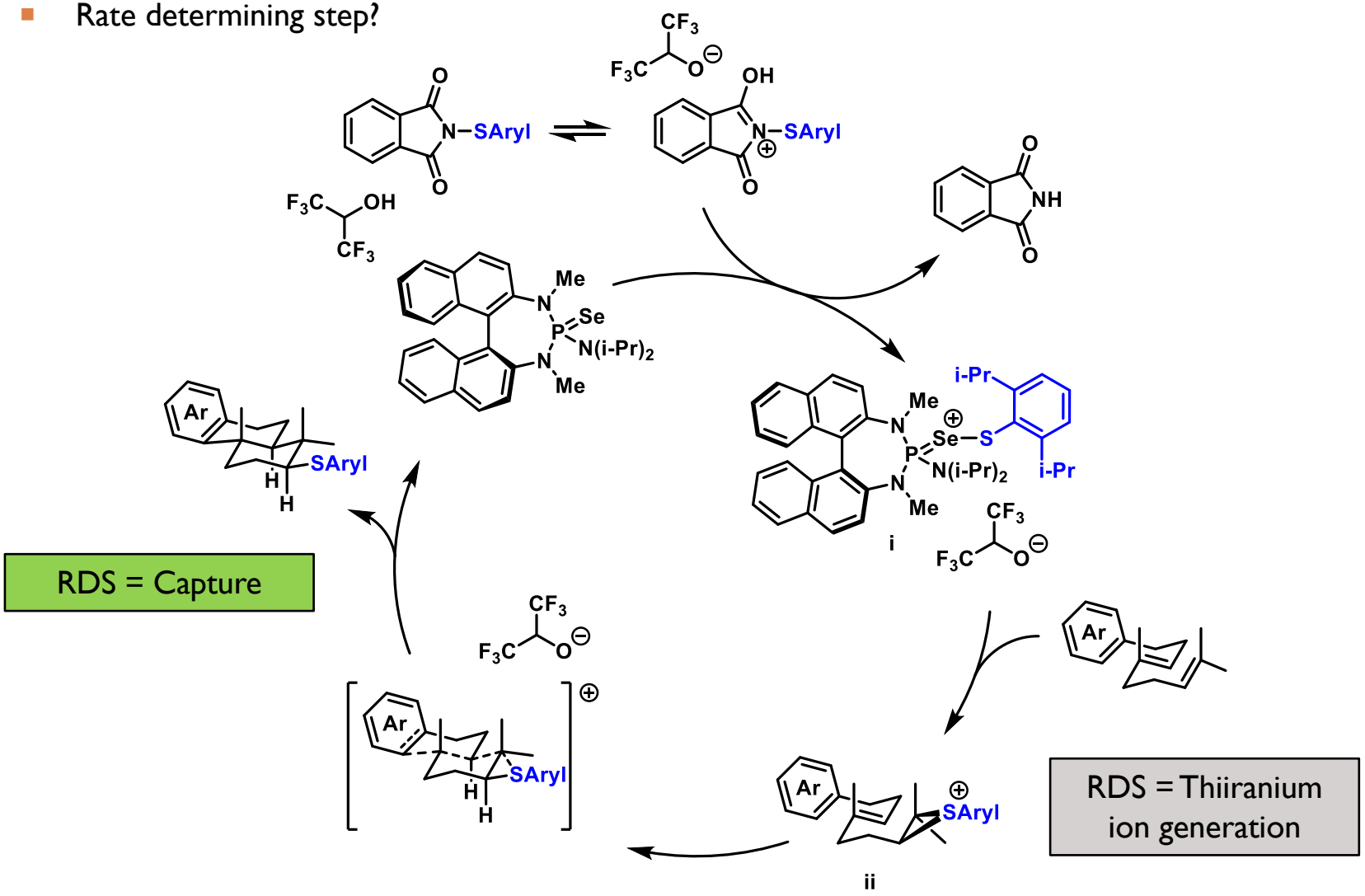
Forward Route: Hinokiol



Zhonglin Tao, Kevin A. Robb, Kuo Zhao, and Scott E. Denmark. *J. Am. Chem. Soc.* **2018**, 140(10), 3569-3573.

Polyene Cyclization: Mechanism

- Proposed to follow general mechanism for LB catalyzed reactions
  - Rate determining step?



Influence of Terminating Group

- W. S. Johnson (1973)
  - Rate increases for more electron-rich arenes

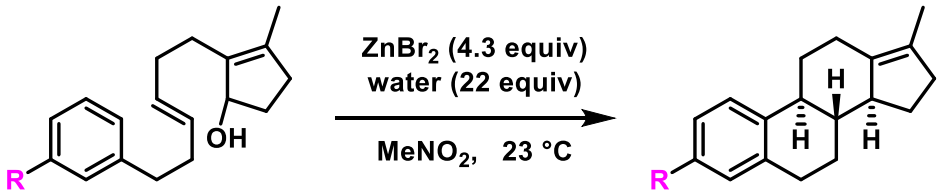
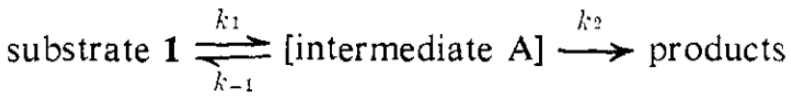


Table I. Relative Cyclization Rates[a] of Substrate **1** (R′ = H)

R	σ^a	k_{rel}
CF_3	0.54	1
Cl	0.23	3.12
H	0.00	5.90
CH_3	−0.17	6.50
OCH_3	−0.27	6.70

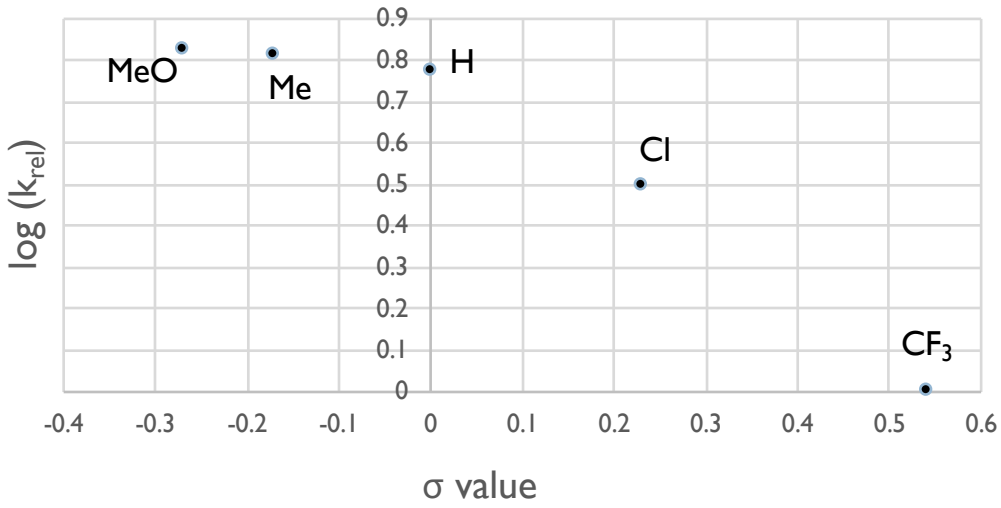
  - Curvature of Hammett plot suggests a change in RDS



  - Conclusion:

> Thus, the dependence of para:ortho ratios on the leaving group,[13] the second-order anchimeric assistance in a two-step scheme, the relatively low value of ρ, and the absence of products derived from an intermediate bicyclic cation are most easily accommodated by a mechanism involving the concerted formation of two rings.

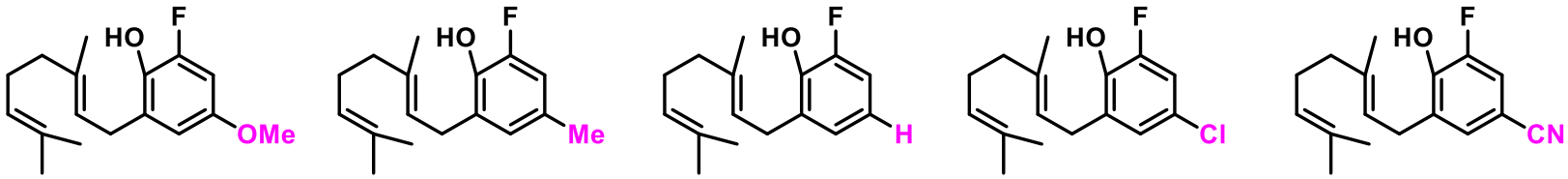
Hammett Plot



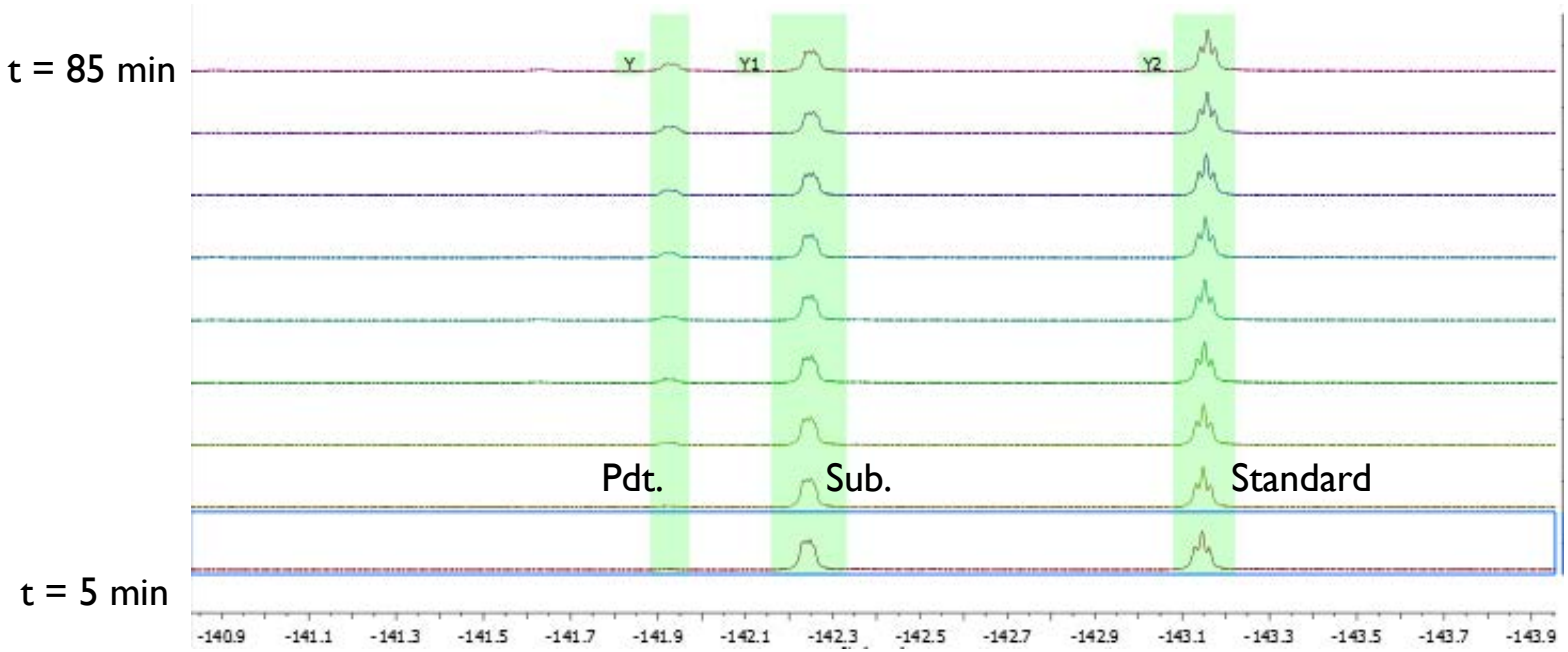
Johnson, W. S. et al. *J. Am. Chem. Soc.* **1973**, 95(22), 7502-7504.

Experimental Design

- Prepare *ortho*-geranylphenols with varying electronics
  - Substrates are also ortho-fluorinated for ^{19}F NMR monitoring

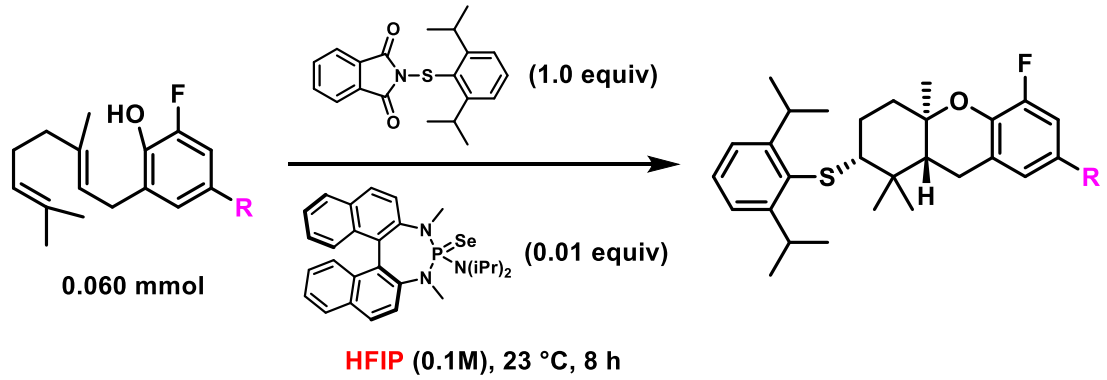


- Obtain rate data from quantitative ^{19}F NMR integrations over time

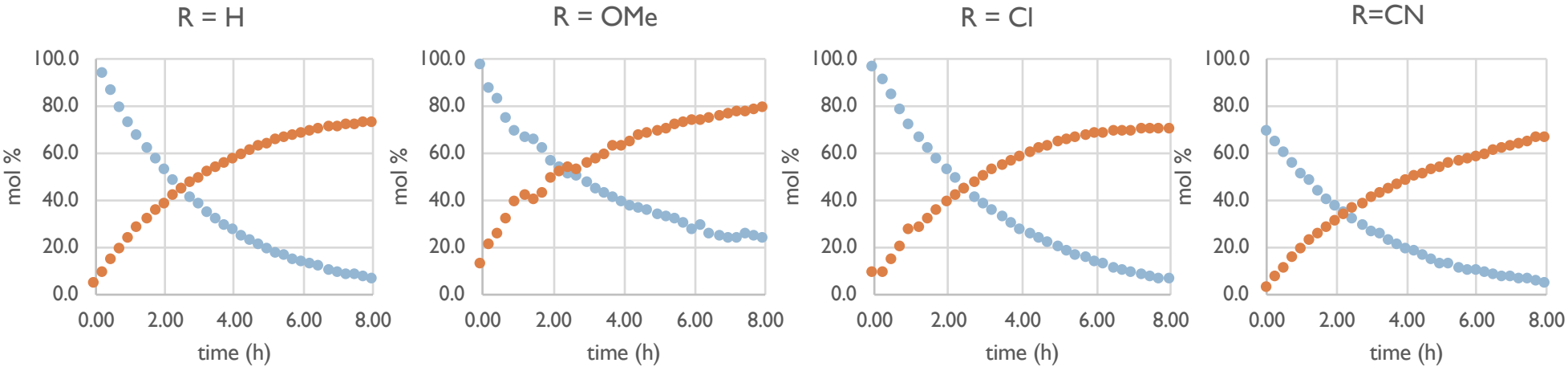


Results

- Collection of ^{19}F NMR rate data required *solvent suppression* of HFIP
  - Used 1,2-difluorobenzene as an internal standard
  - Overlapping SM/Pdt signals for R = Me prevented data collection



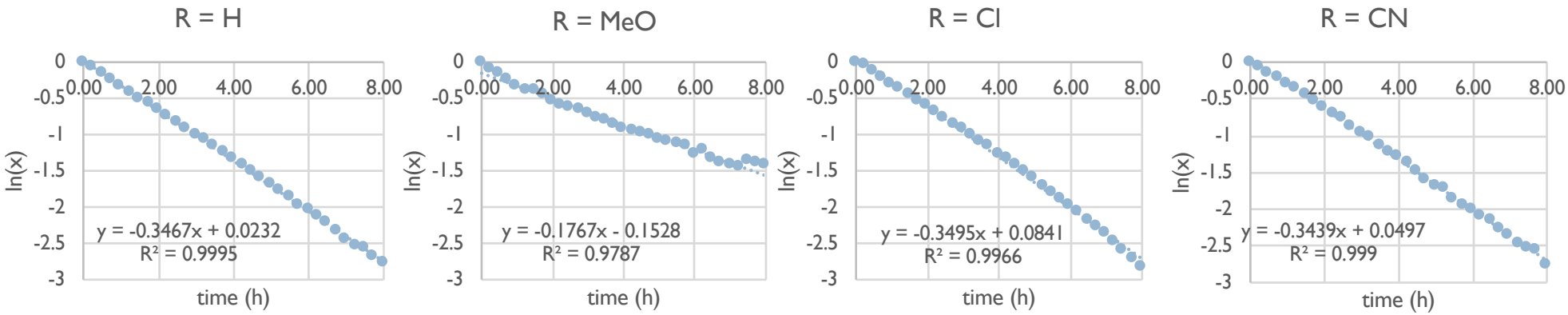
- Results shown are an average of two runs (except for R = CN)



Unpublished results.

Analysis/Interpretation

- 1st order decay plots:

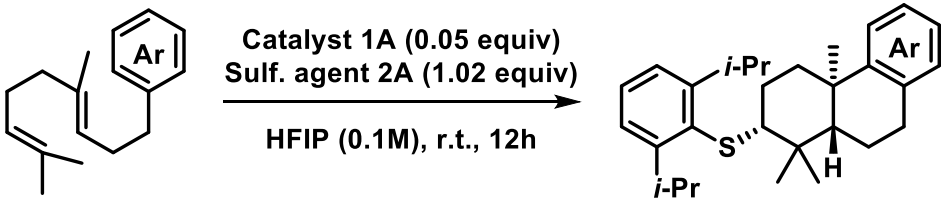


- Conclusions:
  - Unlike Johnson's study, electron-withdrawing R had no effect on rate
  - Suggests RDS is still thiiranium ion generation
    - Alternatively, nucleophilicity of *ortho*-fluorophenols may be affected very little by *para*-substituent
  - R = MeO behavior is curious
    - *Slower* than other substrates, which was unexpected
    - Also, doesn't appear to be quite first-order

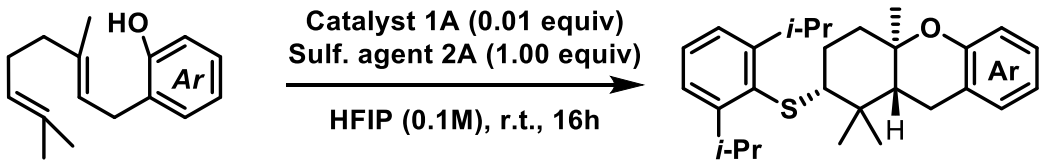
Substrate	k_{obs}
R = H	0.3467 min^{-1}
R = MeO	0.1767 min^{-1}
R = Cl	0.3495 min^{-1}
R = CN	0.3439 min^{-1}

Unpublished results.

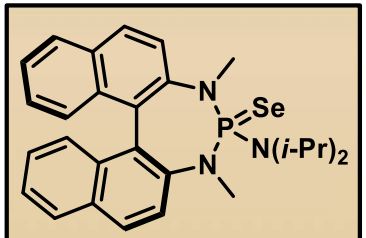
Summary: Polyene Cyclization



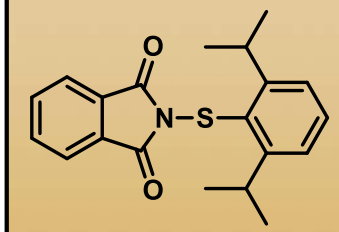
8 examples
59-78% yield, 90:10 e.r.



8 examples
67-80% yield, 90:10 e.r.

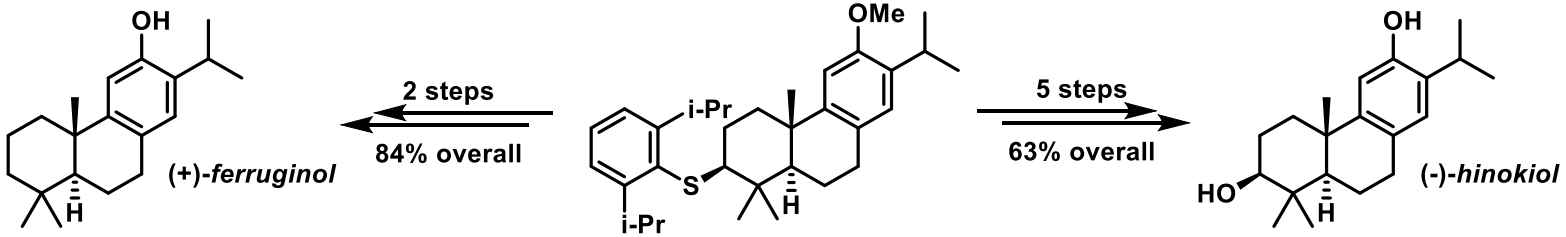


Catalyst 1A



Sulf. Agent 2A

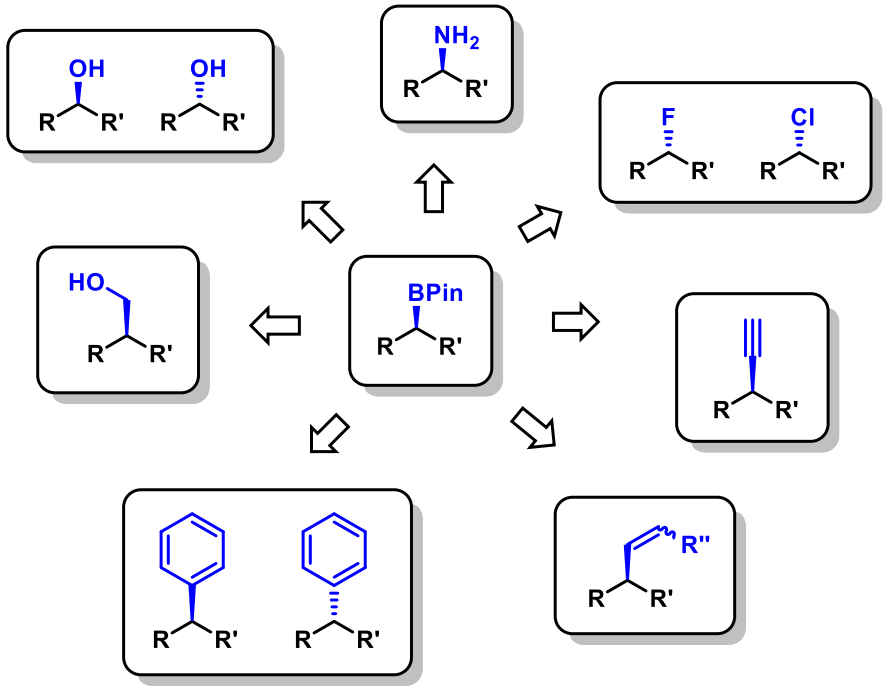
- complete cyclizations
- mild conditions
- operationally simple
- high yields and e.r.
- unmodified polyene substrates
- initiation event installs useful FG handle



- We have developed a Lewis base-catalyzed, enantioselective sulfenocyclization of polyenes
- Sulfide products are rapidly derivatized
- Current/future directions: longer polyenes and exploring different terminal nucleophiles

Chiral boronic esters

- Chiral, non-racemic alkyl boronic esters are versatile synthetic intermediates

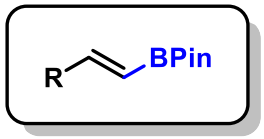


- Numerous preparative methods have been reported
  - More common: products containing a single stereogenic center (boron-bearing carbon)
  - Less common: products containing two or more stereogenic centers

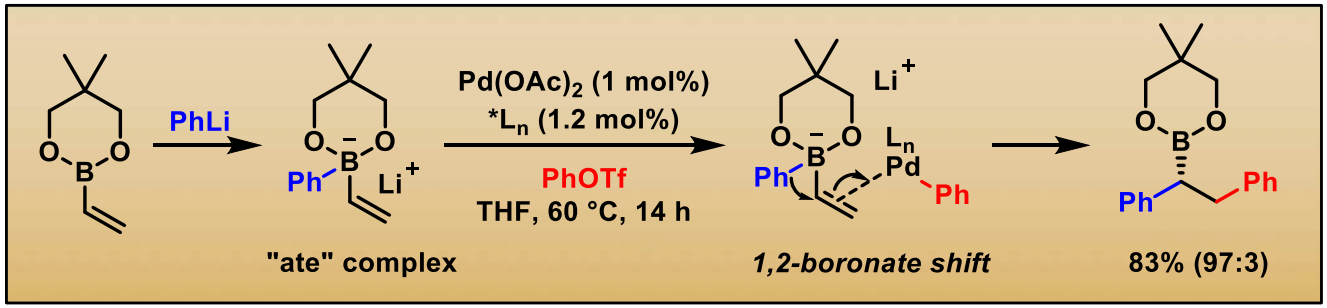
Aggarwal, V. K. et al. *Angew. Chem. Int. Ed.* **2017**, 56(39), 11700-11733.

Boronate shift: C(sp^2)–B to C(sp^3)–B

- Alkenyl boronic esters
  - Easy to synthesize (hydroboration of alkynes, etc.)
  - Methods for converting to chiral, alkyl boronic esters are desirable



- *Morken* (2016)

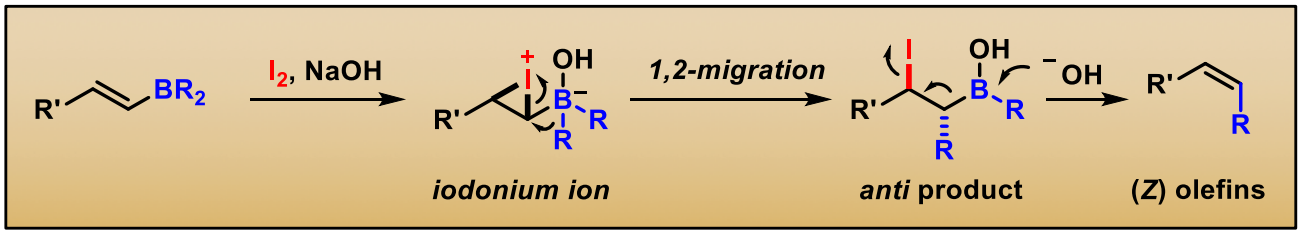


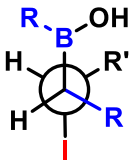
  - Benefits: high yields/selectivities, good scope of migrating groups and aryl triflates
  - Limitation: only amenable to unsubstituted vinyl "ate" complex → sets only *one* center

Morken, J. P. et al. *Science* **2016**, 351(6268), 70-74.

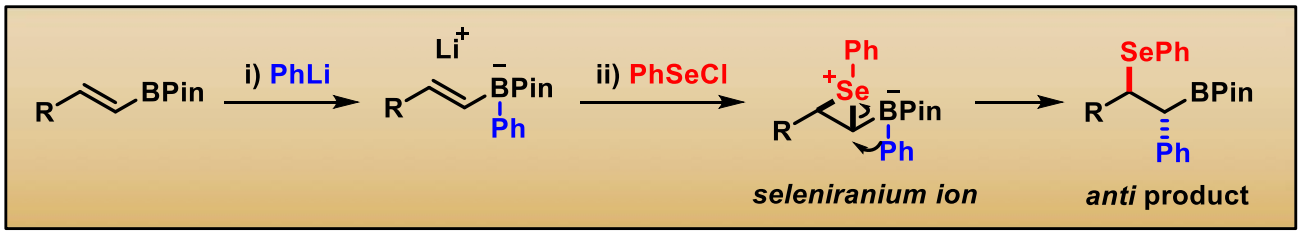
Diastereoselective Functionalization

- Generation of tricyclic "onium" ion from vinyl boronate induces 1,2-shift
  - Results in 1,2-*anti* functionalized products
  - *Zweifel* (1967)

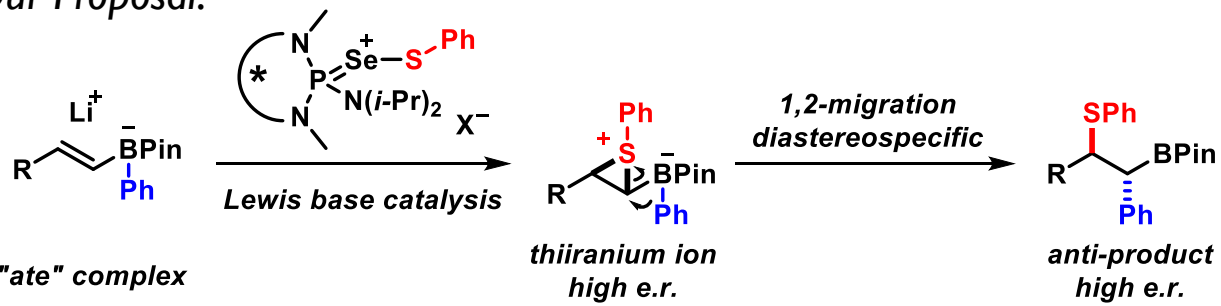




  - *Aggarwal* (2017)

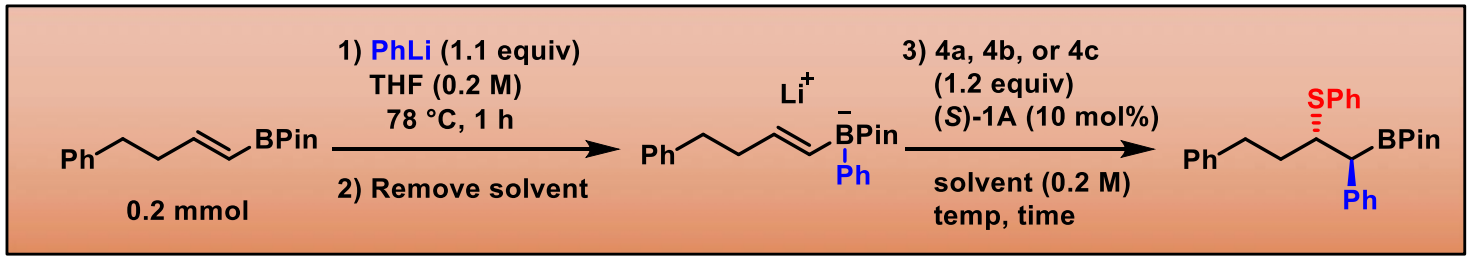


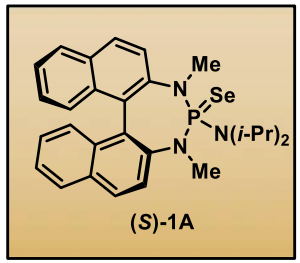
  - *Our Proposal*:



Zweifel, G. et al. *J. Am. Chem. Soc.* **1967**, 18(14), 3652.
Aggarwal, V. K. et al. *Synthesis* **2017**, 49(15), 3323.
Aggarwal, V. K. et al. *Chem. Commun.* **2017**, 53(36), 4922.

Reaction optimization

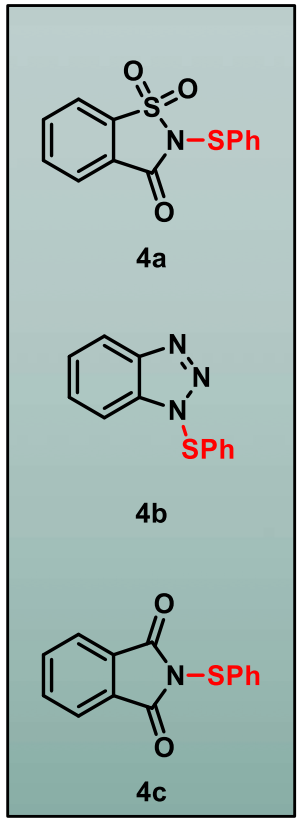




- Caveat: boronate decomposes under acidic conditions

Entry	S.A. 4	Cat.	Solv.	Temp. (°C)	Time (h)	Yield	e.r.
1	4a	--	CH_2Cl_2	–78	3	56% [a]	--
2	4a	1A	CH_2Cl_2	–78	3	68% [a]	55:45
3	4b	--	CH_2Cl_2	–78	18	11% [b]	--
4	4b	1A	CH_2Cl_2	–78	18	16% [b]	57:43
5	4c	--	CH_2Cl_2	–20	36	31% [b]	--
6	4c	1A	CH_2Cl_2	–20	36	37% [b]	53:47

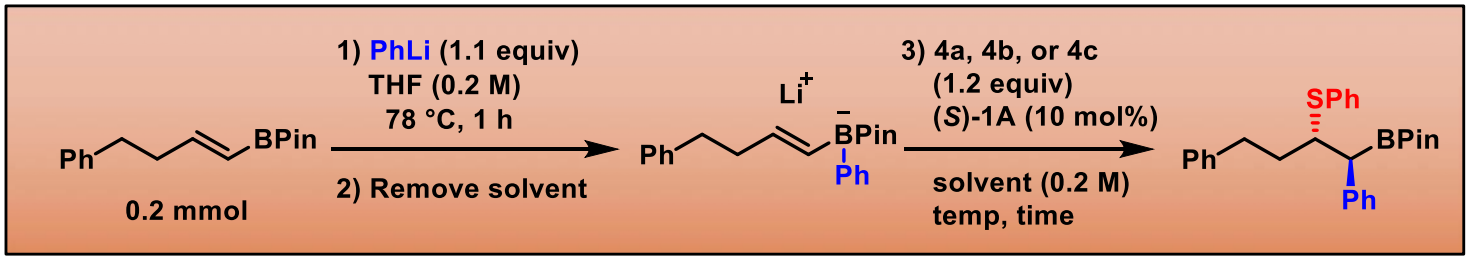
[a] Yield of isolated alcohol product from oxidation. [b] NMR yield of pinacol boronate.

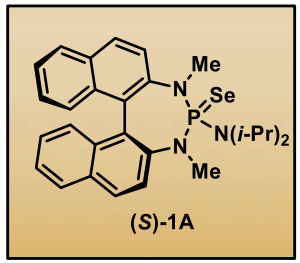


- No catalysis observed in DCM
- Alkenylboronate complex is too reactive

Zhonglin Tao, Kevin A. Robb, Jesse L. Panger, and Scott E. Denmark. Manuscript submitted.

Reaction optimization

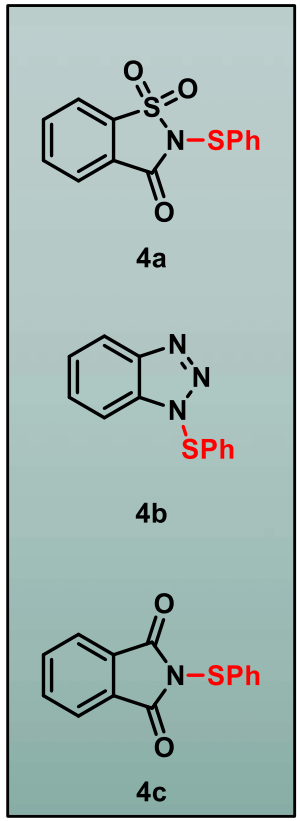




(S)-1A

Entry	S.A. 4	Cat.	Solv.	Temp. (°C)	Time (h)	Yield	e.r.
7	4a	--	MeOH	–60	24	10% [b]	--
8	4a	1A	MeOH	–60	24	47% [a]	94:6
9	4a	--	EtOH	–60	24	14% [b]	--
10	4a	1A	EtOH	–60	24	80% [a]	98:2
11	4b	--	EtOH	–20	24	7% [b]	--
12	4b	1A	EtOH	–20	24	10% [b]	--
13	4b	--	TFE	–20	2	10% [b]	--
14	4b	1A	TFE	–20	2	32% [b]	85:15
15	4c	--	HFIP	0	2	0% [c]	--
16	4c	1A	HFIP	0	2	27% [a,c]	83:17

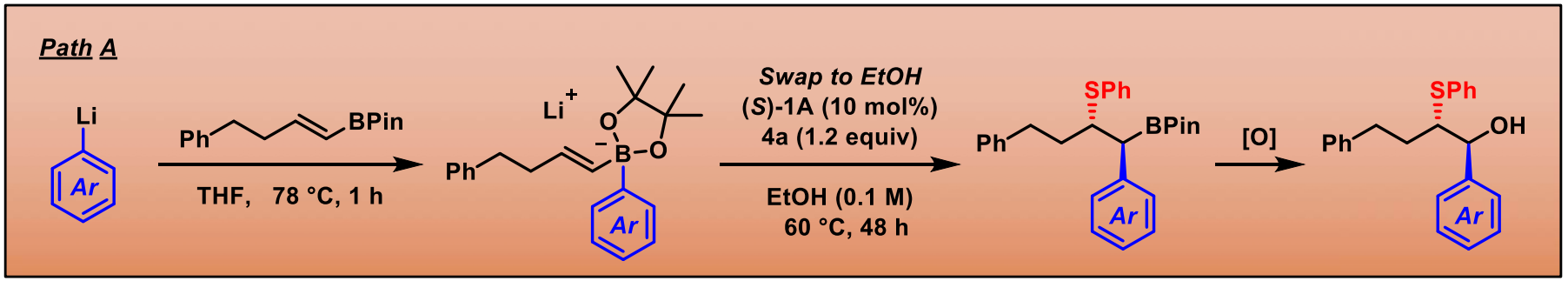
[a] Yield of isolated alcohol product from oxidation. [b] NMR yield of pinacol boronate. [c] Decomposition of boronate observed.



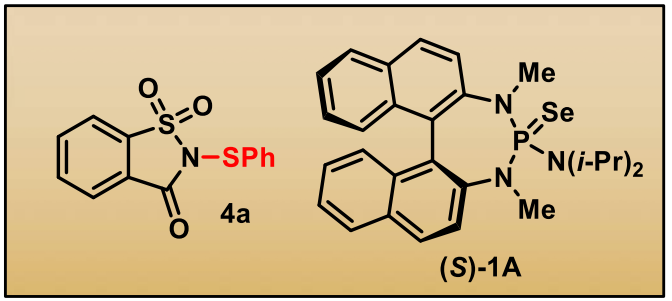
- Polar protic solvents mitigate background reactivity
- Ideal combination is *saccharin-derived 4a* in *ethanol*

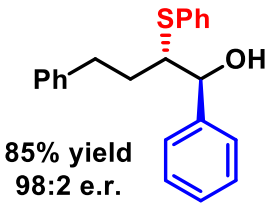
Zhonglin Tao, Kevin A. Robb, Jesse L. Panger, and Scott E. Denmark. Manuscript submitted.

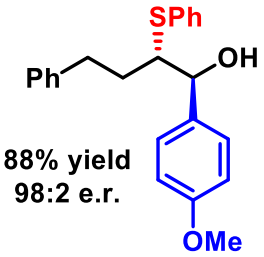
Scope of Migrating Group

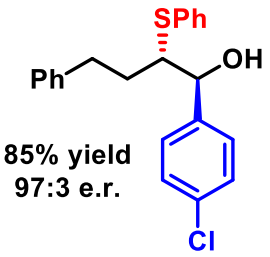


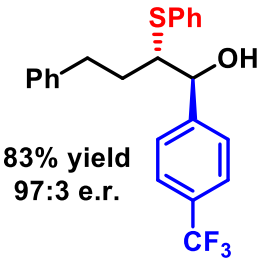
- Isolated yields of analytically pure material over 2 steps.
- All reactions run on 1.00 mmol scale; e.r. determined by HPLC.

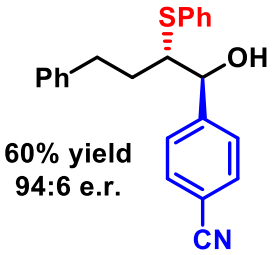


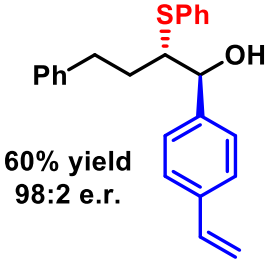


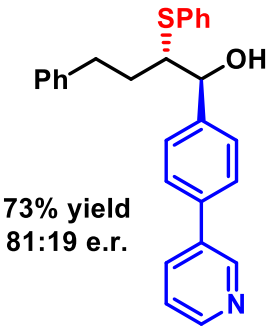


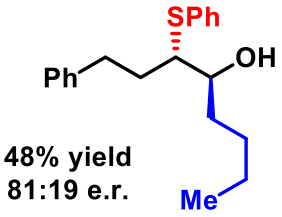


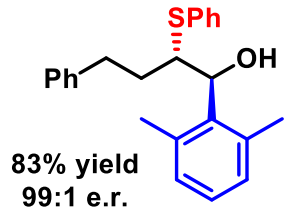


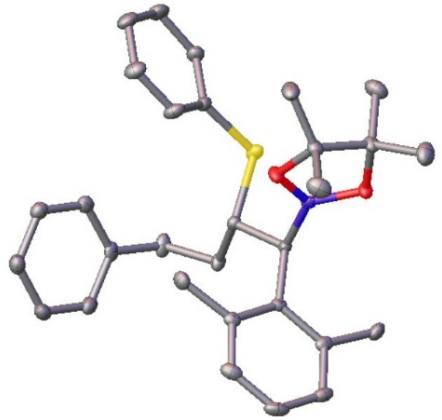






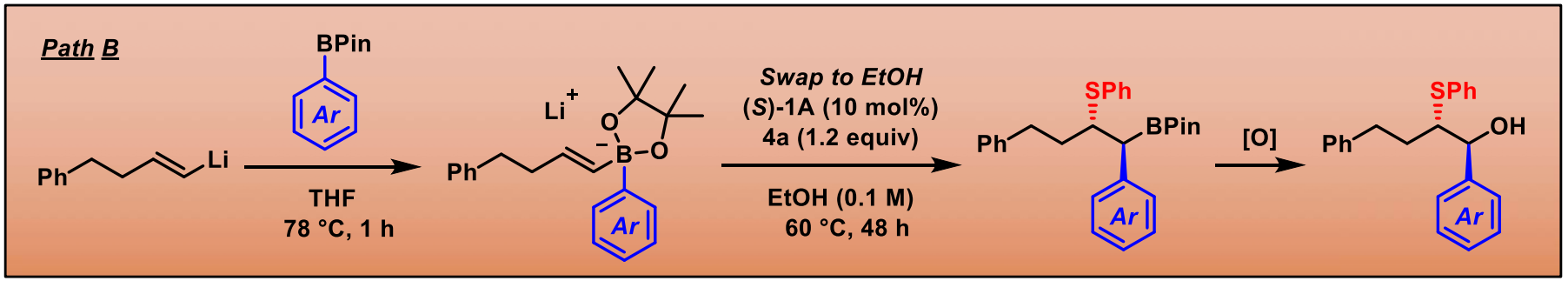




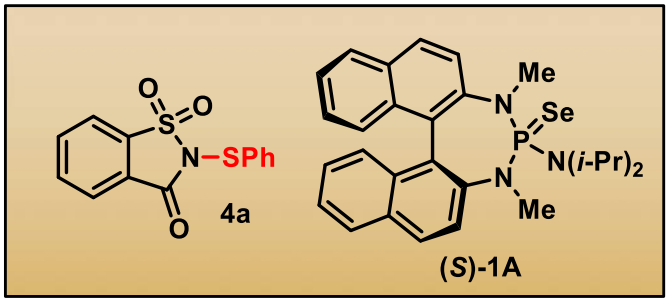


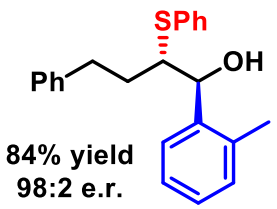
Zhonglin Tao, Kevin A. Robb, Jesse L. Panger, and Scott E. Denmark. Manuscript submitted.

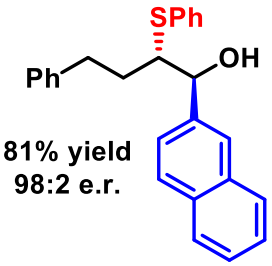
Scope of Migrating Group

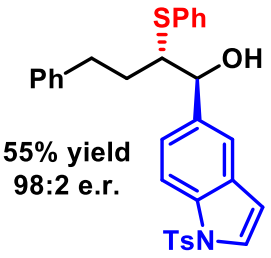


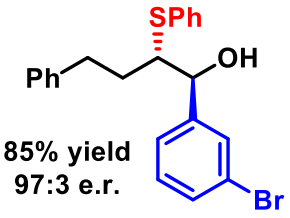
- Isolated yields of analytically pure material over 2 steps.
- All reactions run on 1.00 mmol scale; e.r. determined by HPLC.

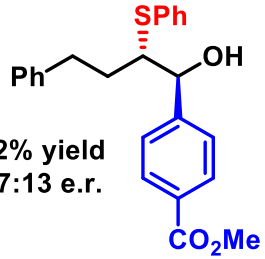








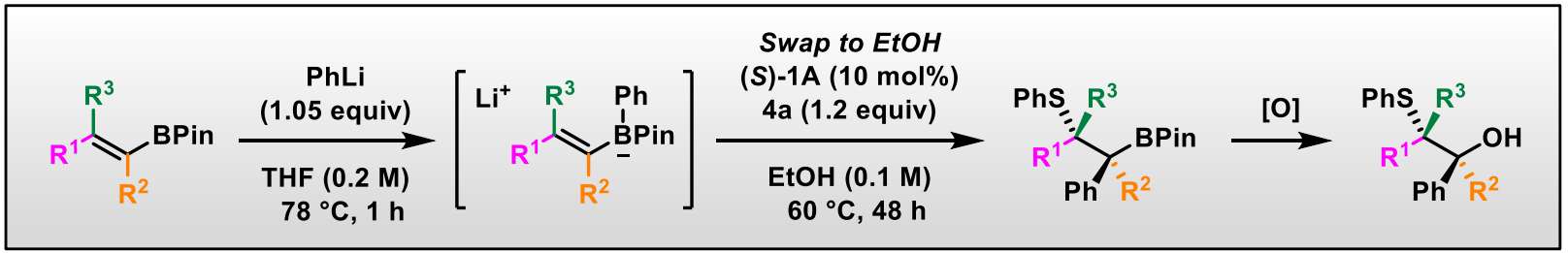




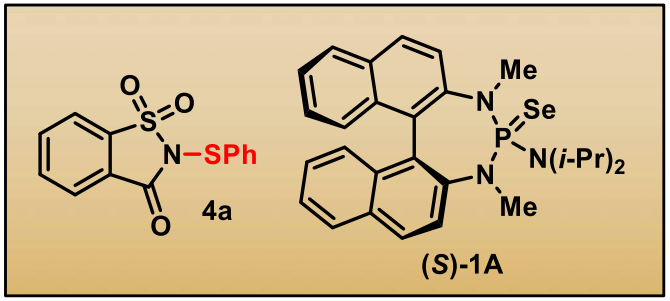
- Electronically diverse aryl groups
- Sterically demanding aryl groups
- Heteroaryl and alkyl groups

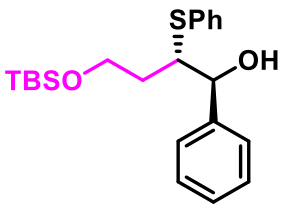
Zhonglin Tao, Kevin A. Robb, Jesse L. Panger, and Scott E. Denmark. Manuscript submitted.

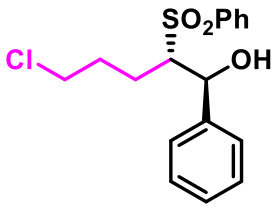
Scope of Alkenylborane

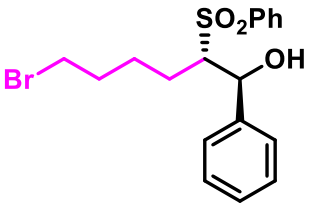


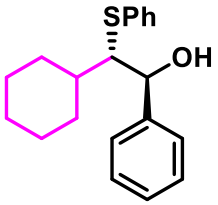
- Isolated yields of analytically pure material over 2 steps.
- All reactions run on 1.00 mmol scale; e.r. determined by HPLC.




65%, 96:4 er


83%, 98:2 er


81%, 98:2 er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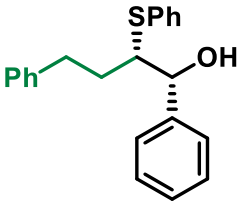
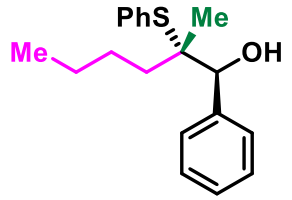
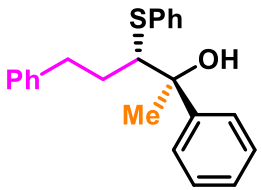
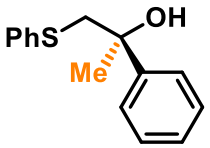
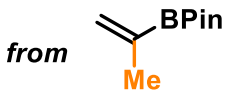
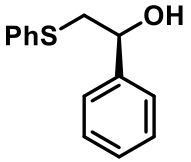

61%, 68:32 er


27%, 54:46


76%, 96:4 er


74%, 95:5 er

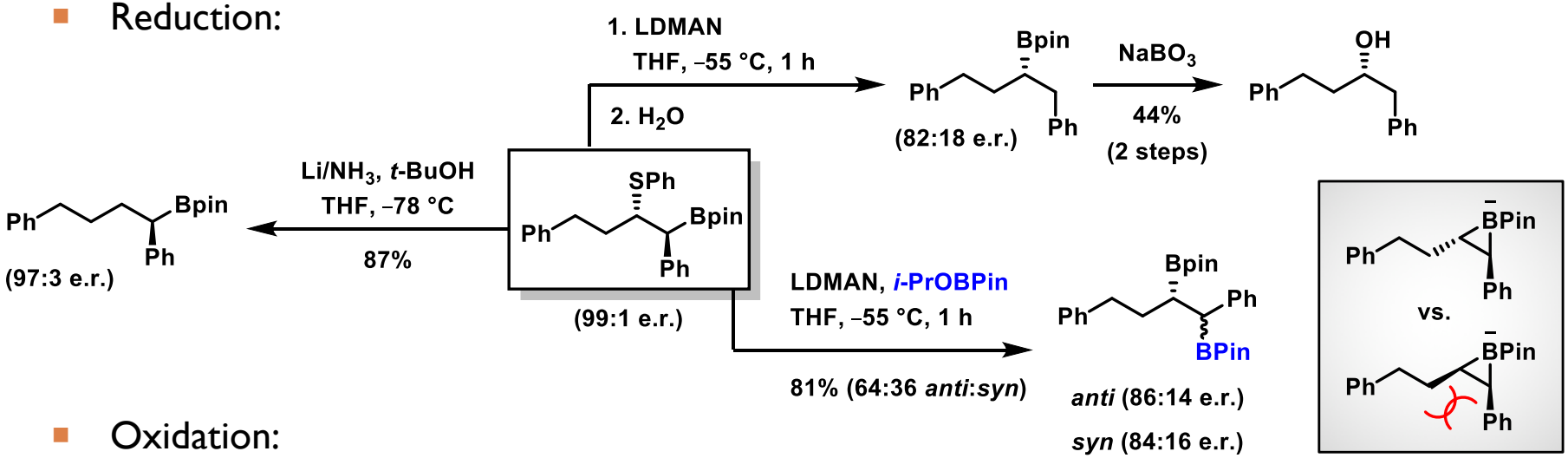



60%, 84:16

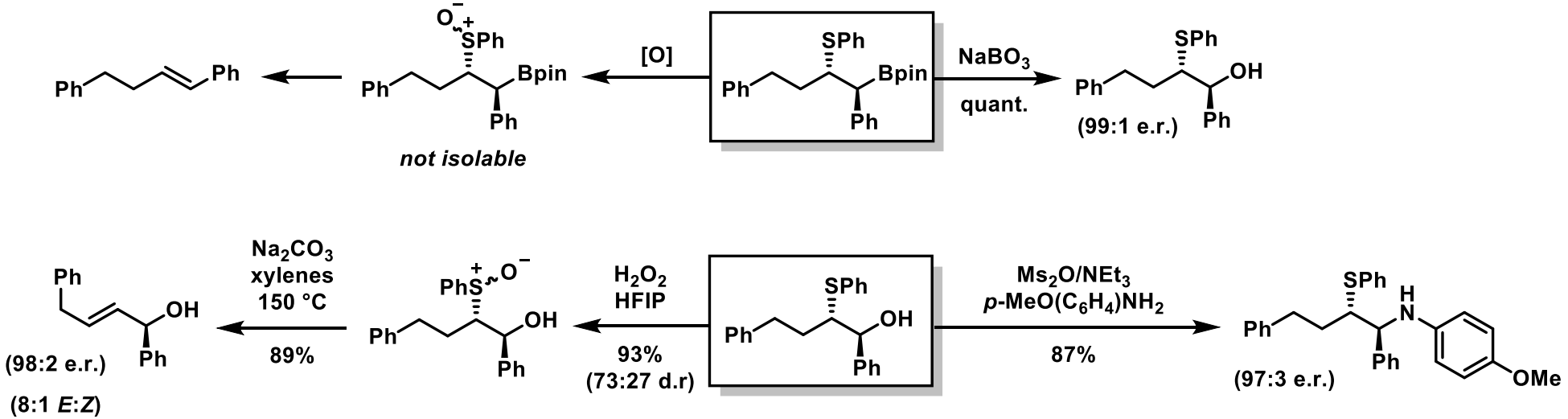
Zhonglin Tao, Kevin A. Robb, Jesse L. Panger, and Scott E. Denmark. Manuscript submitted.

Product Manipulations

- Reduction:



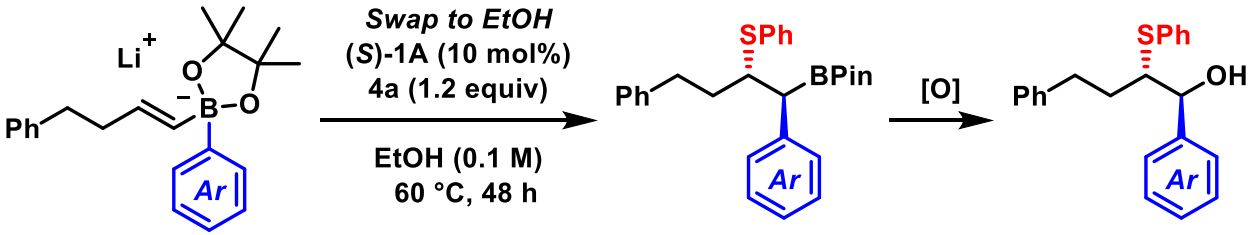
- Oxidation:



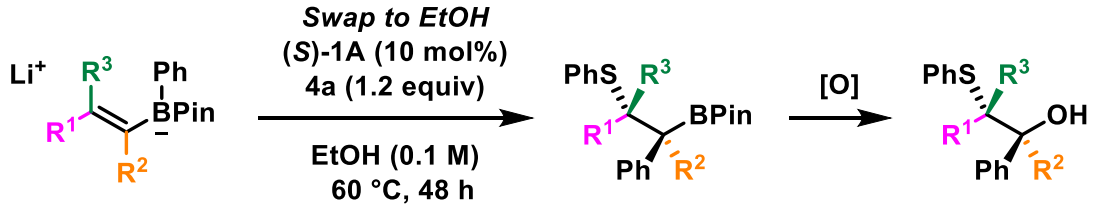
Zhonglin Tao, Kevin A. Robb, Jesse L. Panger, and Scott E. Denmark. Manuscript submitted.

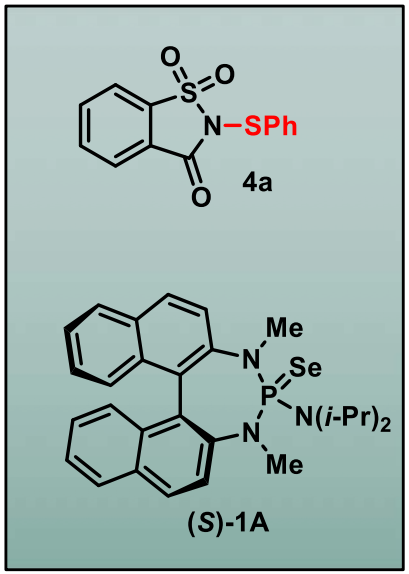
Summary: Boronate functionalization

- 14 examples, 32–88%, 81:19 to 99:1 e.r.



- 9 examples, 27–90%, 54:46 to 99:1 e.r.

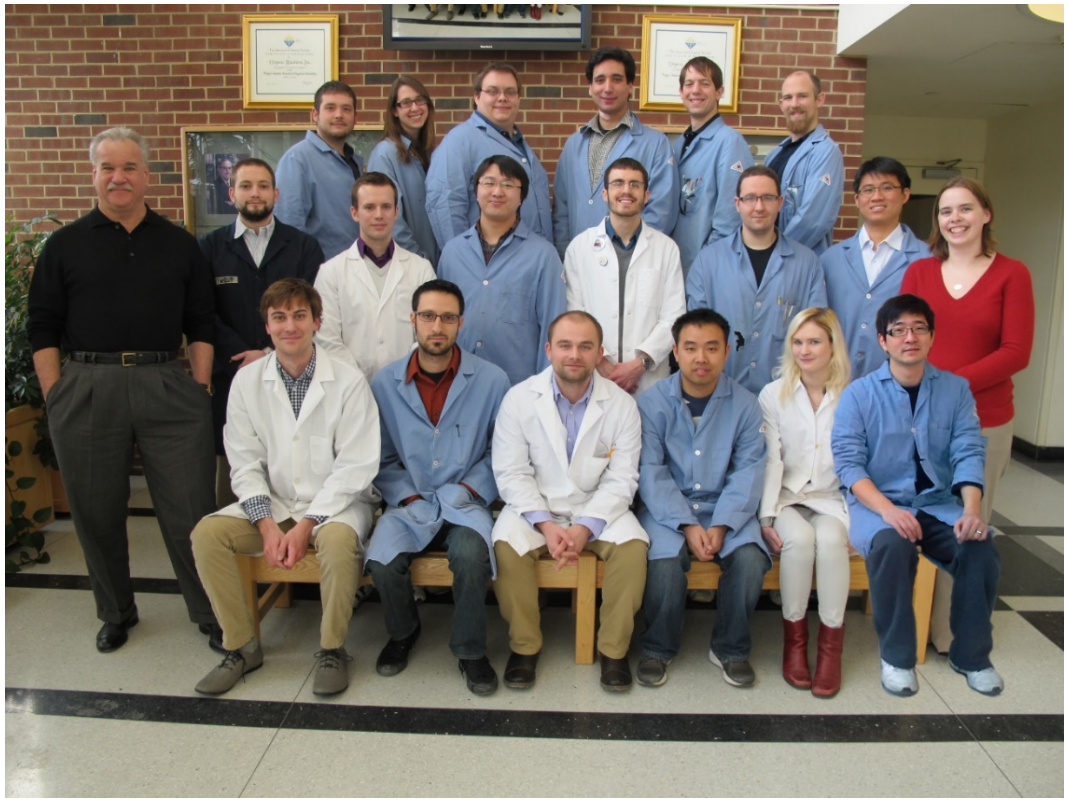




- A method for preparing α-thiolated boranes was presented
  - Enantio- and diastereoselective, vicinal stereogenic centers
  - Secondary and tertiary alkylboranes
  - Readily available starting materials

Acknowledgements (Part 1)

- Prof. Scott Denmark
- Denmark Group
- PTC Subgroup
  - Dr. Lindsey Kryger
  - Dr. Jeremy Henle
  - Craig Seymour

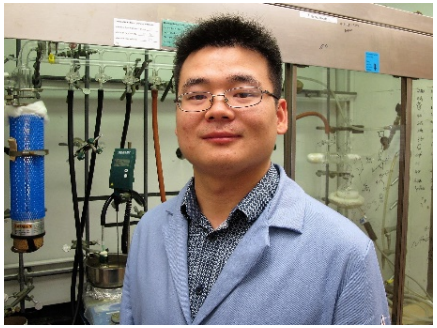


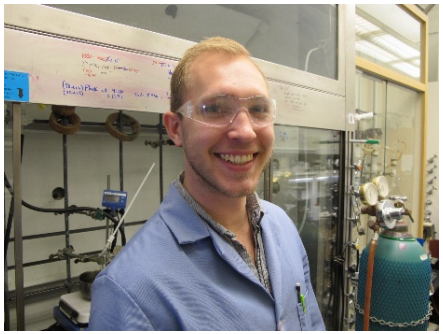
Group Problem: Who's Photoshopped in??

- Keck Foundation

Acknowledgements (Part 2)

- Prof. Scott Denmark
- Denmark Group
- Lewis Base Subgroup
  - Dr. Zhonglin Tao
  - Kuo Zhao
  - Jesse Panger
- Dr. Lingyang Zhu



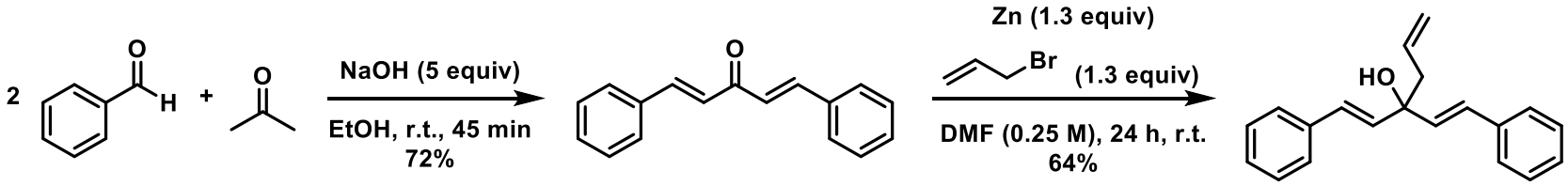


- National Institutes of Health
- R. C. Fuson Memorial Travel Fund
- Seemon Pines Travel Award

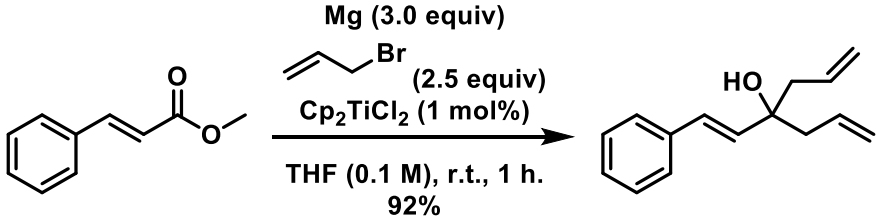
Supplementary Material

Substrate Synthesis

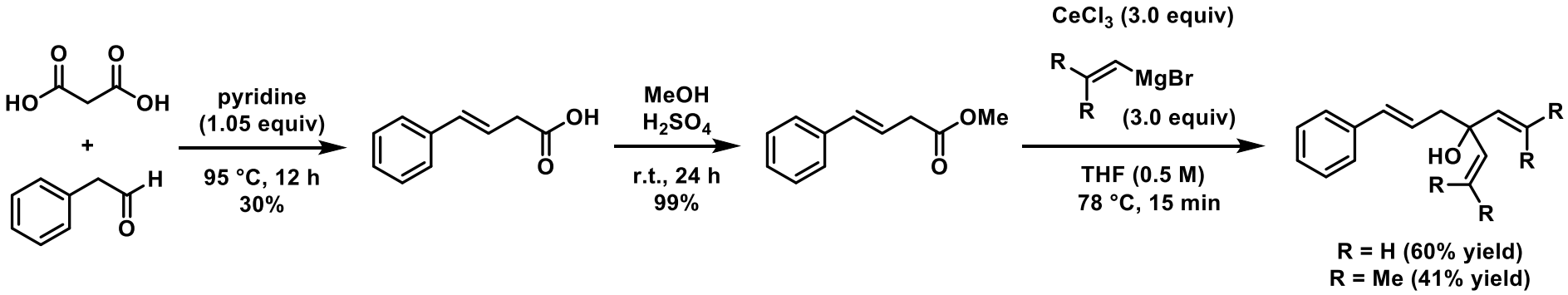
- Class 1



- Class 2

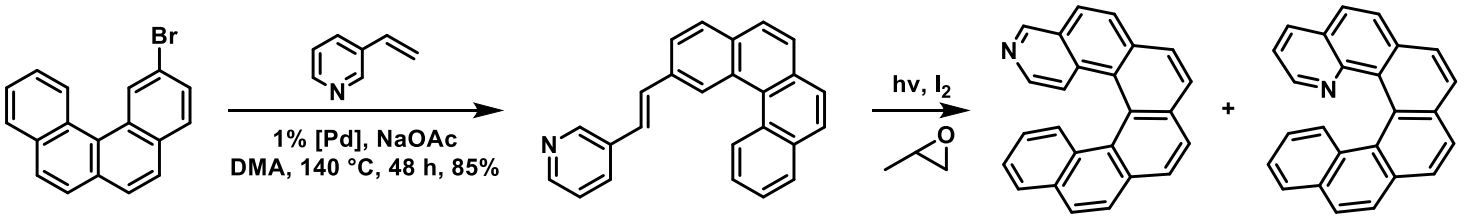


- Class 3

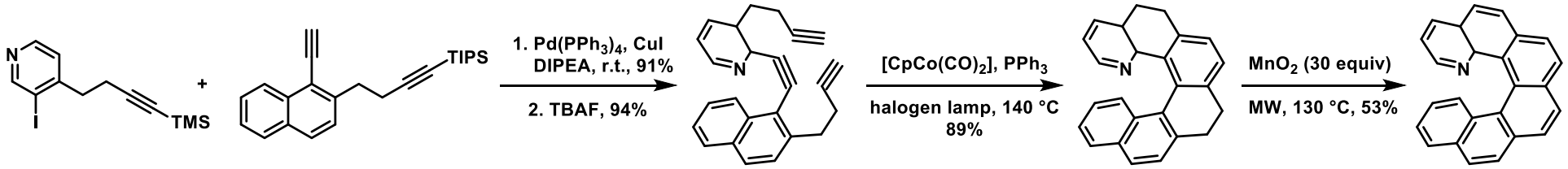


Other azahelicene syntheses

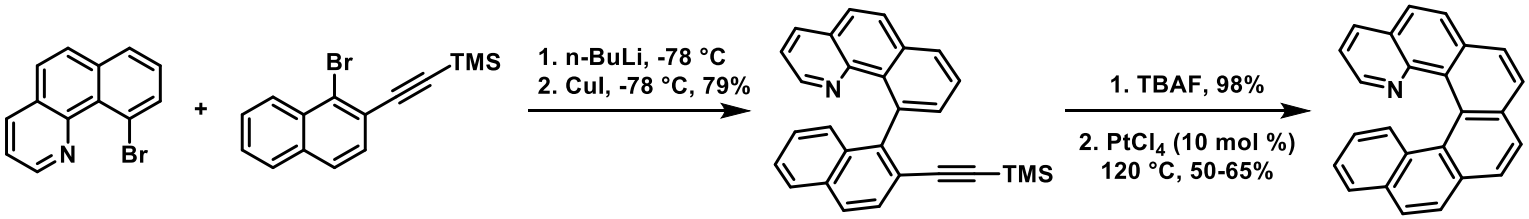
- Mallory photocyclization (Hassine et al. 2008)



- [2+2+2] triyne cyclization (Stará, Starý, et al. 2008)



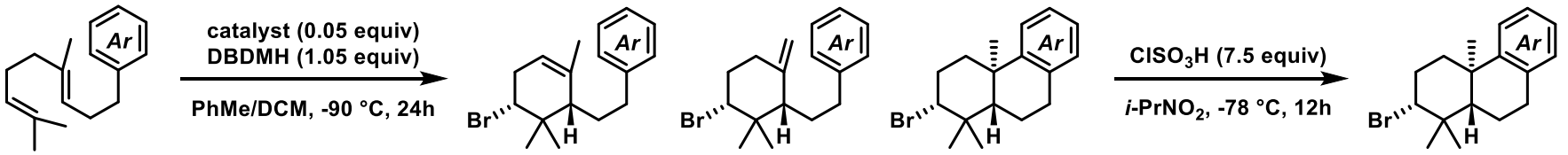
- Alkyne cycloisomerization (Fuchter et al. 2013)

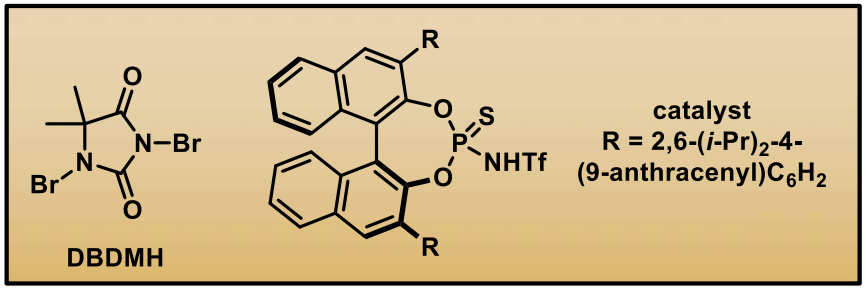


Hassine, B. B. et al. *Tetrahedron Lett.* **2008**, *49*, 1455.
Stará, I. G., Starý, I. et al. *Angew. Chem. Int. Ed.* **2008**, *47*, 3188.
Fuchter, M. J. et al. *Org. Lett.* **2013**, *15*, 1706.

Catalytic, Enantioselective Polyene Cyclizations

- Yamamoto (2017)



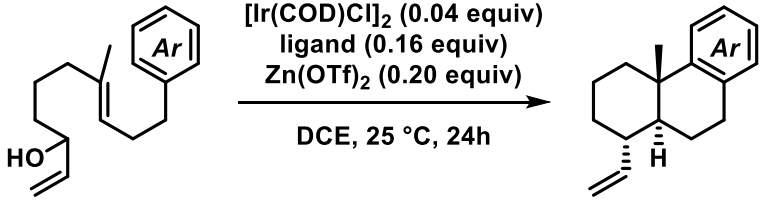


- unmodified polyene substrates
- initiation event installs FG

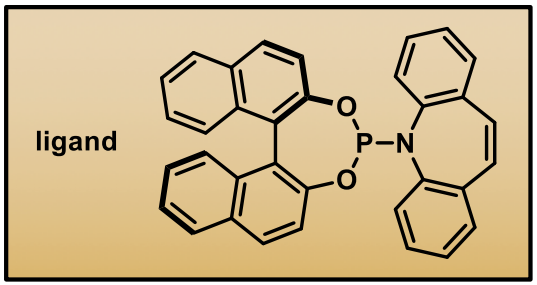
13 examples
41-98% yield over two steps
approx. 90:10 e.r.

- incomplete cyclizations
- requires harsh acid
- not operationally simple
- variable yields

- Carreira (2012)



9 examples
69-93% yield
> 99:1 e.r.

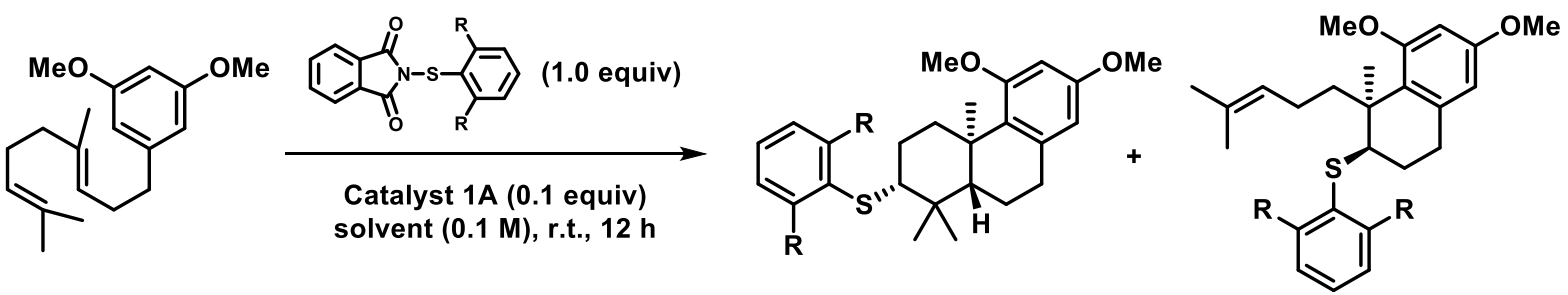


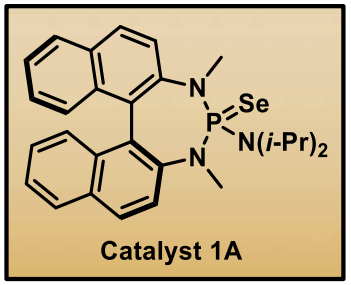
- complete cyclizations
- mild conditions
- operationally simple
- high yields and e.r.

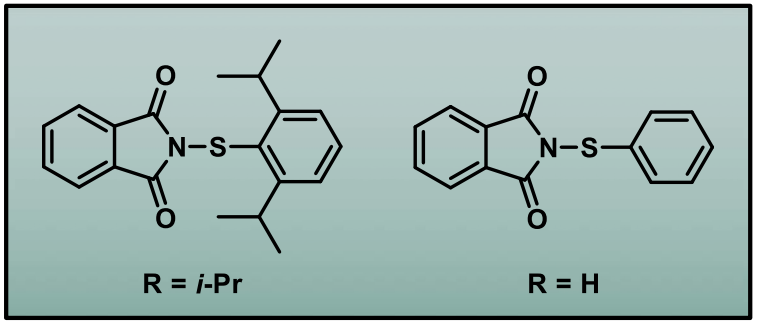
- modified substrates
- no FG handle installed at C2 position

Sarlah, D. et al. *Org. Biomol. Chem.* **2016**, 14(24), 5454-5467.
Yamamoto, H. et al. *J. Am. Chem. Soc.* **2017**, 139(4), 1460-1463.
Carreira, E. M. et al. *J. Am. Chem. Soc.* **2012**, 134(50), 20276-20278.

Further Optimization

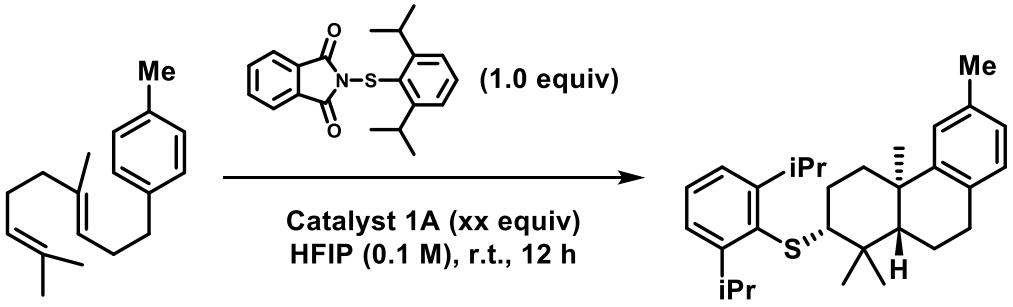






Entry	Solvent	Sulf. Agent	Product Ratio
1	HFIP	R = *i*-Pr	10:1
2	HFIP	R = H	5:1
3	CH_2Cl_2	R = *i*-Pr	2:1

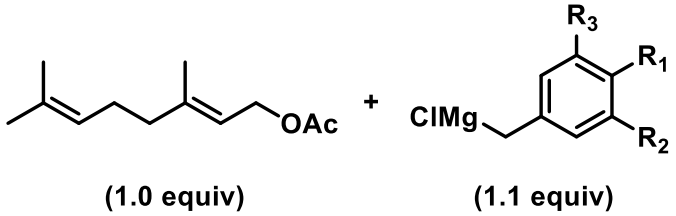
- Entry 3 run w/ MsOH (0.4 equiv)



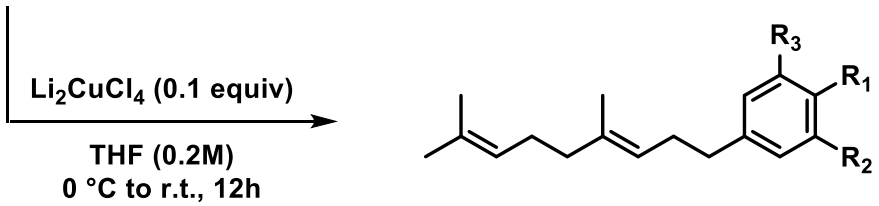
Entry	Cat. Loading (equiv)	e.r.	Yield
1	0.01	91:9	67%
2	0.025	91:9	73%
3	0.05	91:9	79%
4	0.10	92:8	80%

Kuo Zhao

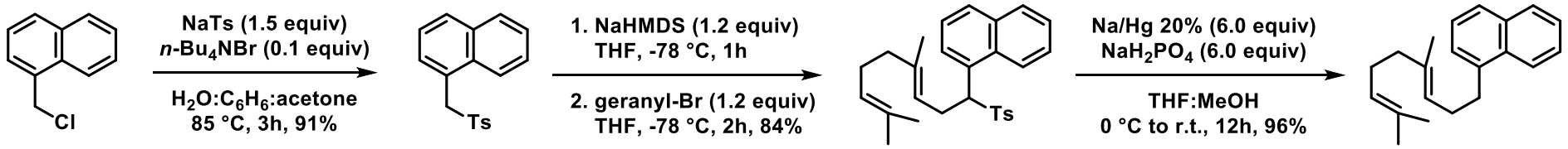
Substrate Synthesis

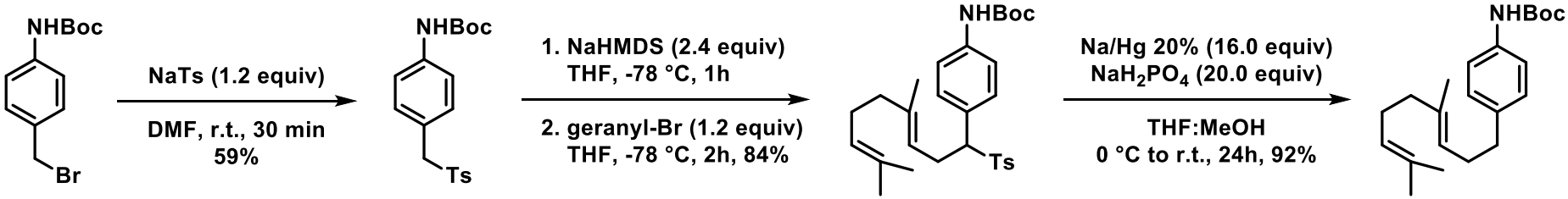


(1.0 equiv) (1.1 equiv)



R_1	R_2	R_3	Yield
H	H	H	98%
Me	H	H	77%
OMe	H	H	95%
H	OMe	OMe	74%
OMe	*i*-Pr	H	87%

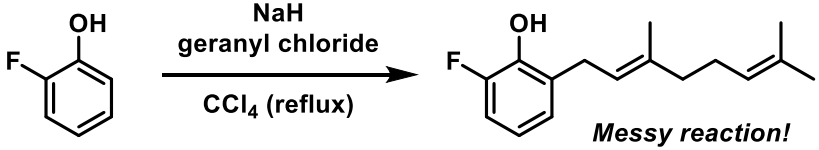




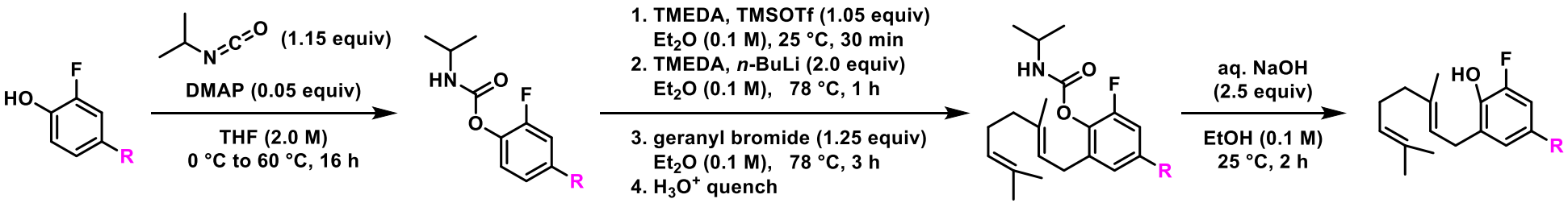
Zhonglin Tao, Kevin A. Robb, Kuo Zhao, and Scott E. Denmark. *J. Am. Chem. Soc.* **2018**, 140(10), 3569-3573.

Substrate Synthesis

- Direct alkylation of *ortho*-fluorophenols
  - After 3 columns, still unacceptable purity



- 3-Step workaround:



Substrate	Step 1 yield	Step 2 yield	Step 3 yield
R = H	92%	40%	88%
R = Me	88%	54%	89%
R = MeO	89%	39%	87%
R = Cl	87%	17%	83%
R = CN	89%	10%	60%

Adapted from: Hoppe, D. et al. *Synthesis* **2006**, 10, 1578-1589.