# Denmark Group Meeting

## Palladium catalyzed Dearomatization Reaction

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## Electrophilic rearrangement of amides

**Bo Peng**

**11th Feb. 2014**


https://maps.google.com

# Palladium catalyzed Dearomatization Reaction

&

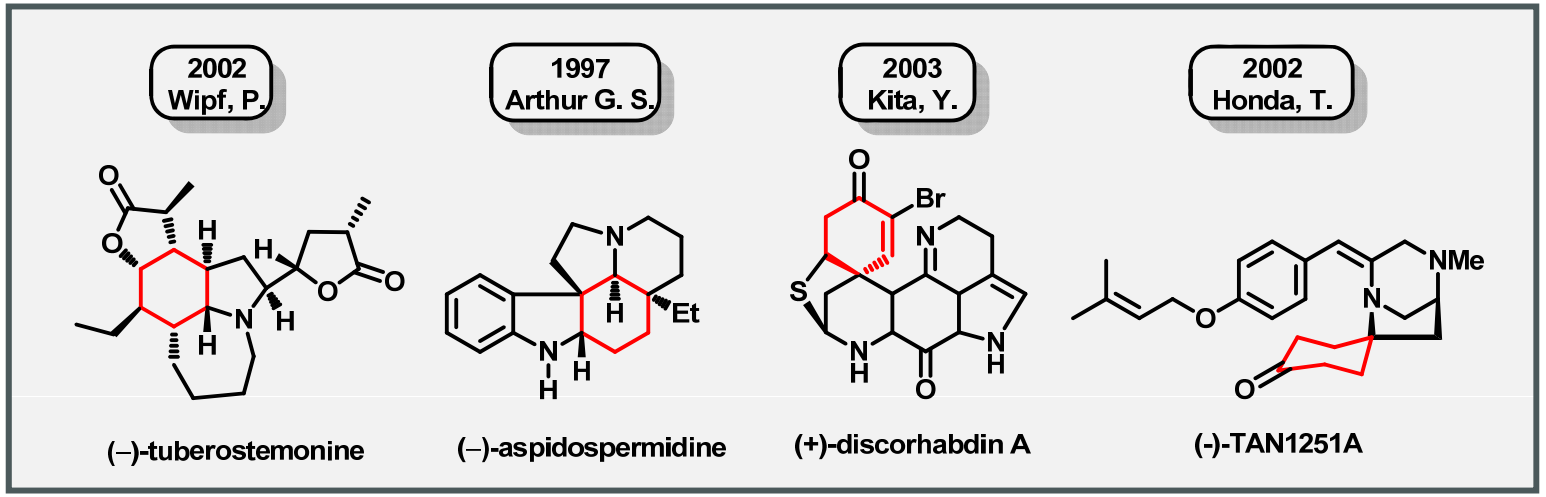
# Electrophilic rearrangement of amides

# Palladium catalyzed Dearomatization Reaction: **background**

## Dearomatization Reaction

**Starting material**
**Aromatic compounds**

**product**
**Alicyclic compounds**

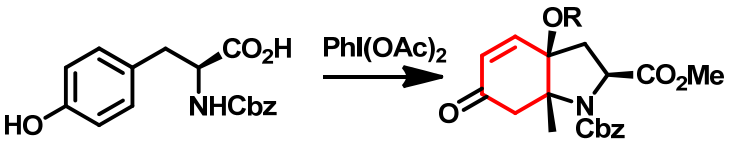



**Natural products**

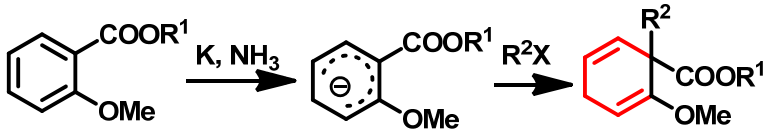
a) Roche, S. P.; Porco, J. A., Jr. *Angew. Chem.,Int. Ed.* **2011**, *50*, 4068-4093; b). Pouysegu, L.; Deffieux, D.; Quideau, S. *Tetrahedron* **2010**, *66*, 2235–2261.

# Palladium catalyzed Dearomatization Reaction: **background**

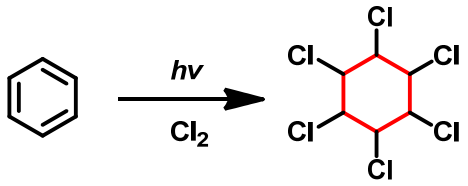
## 1. oxidative dearomatization



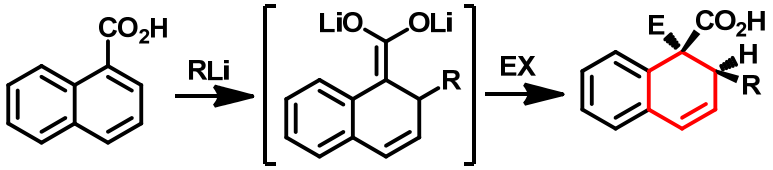

## 2. reductive dearomatization



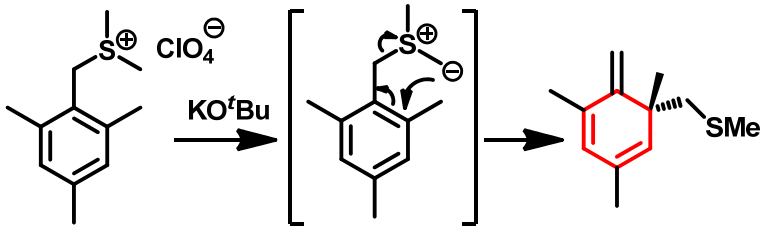

## 3. photocatalyzed dearomatization



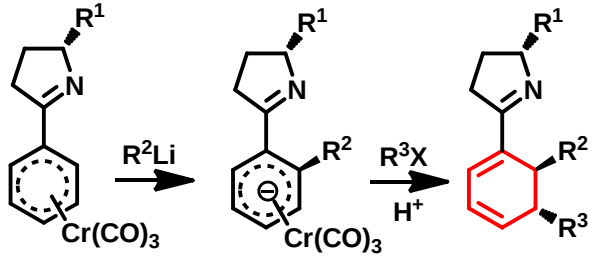

## 4. nucleophilic additive dearomatization



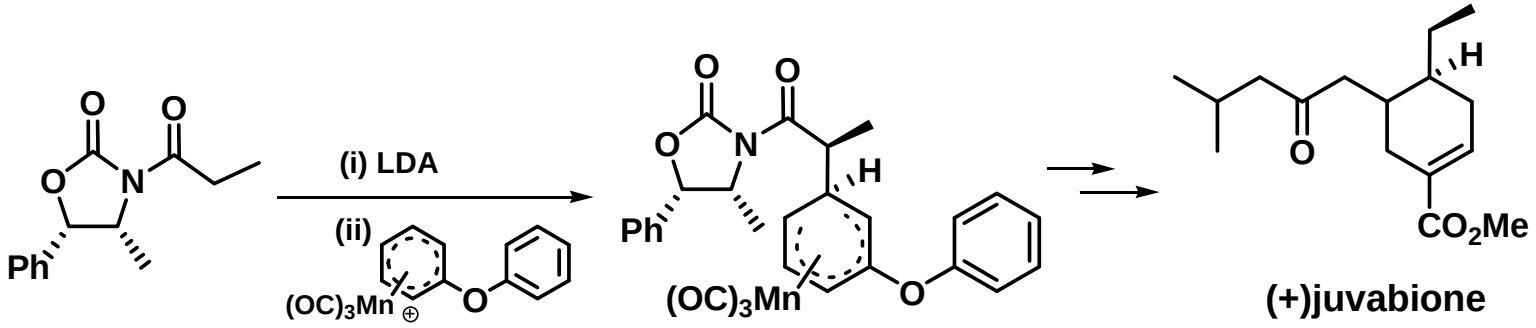

## 5. σ -rearrangement dearomatization




## 6. transition metals promoted dearomatization

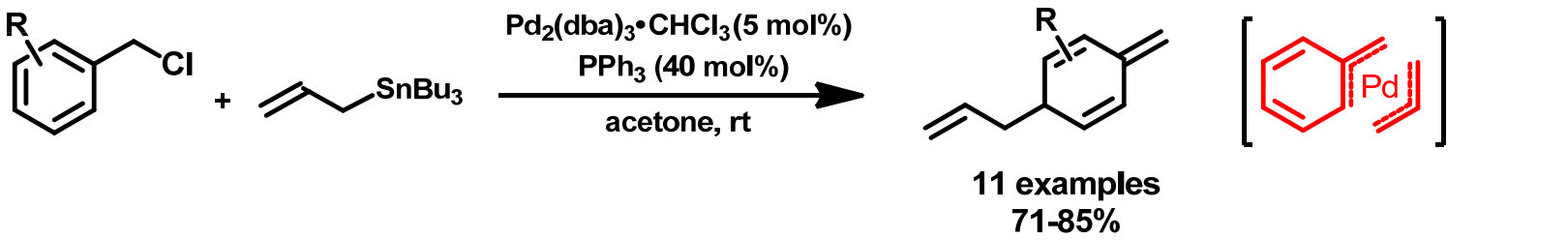


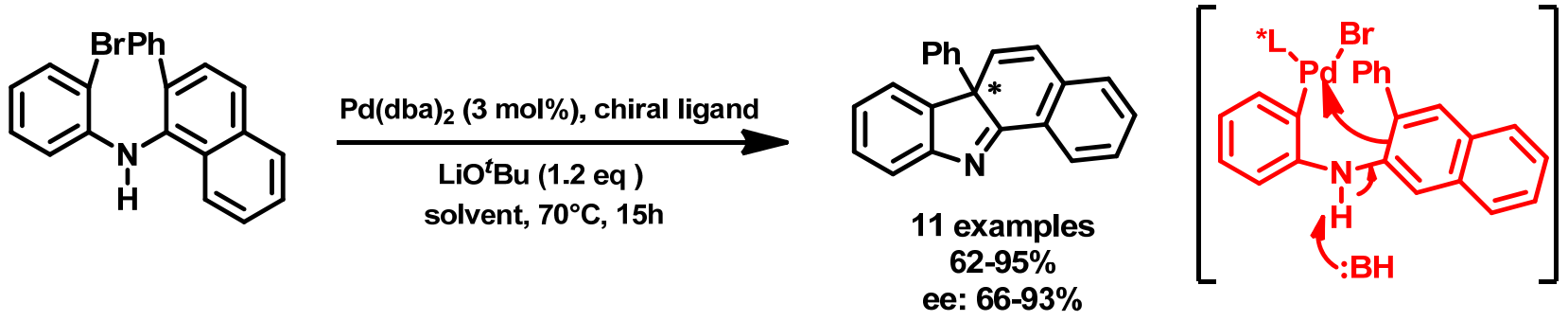
## Application of $[(\eta^6\text{-Arene})\ Mn(CO)_3]^+$




Miles, W. H.; Brinkman, H. R. *Tetrahedron Lett*. **1992**, *33*, 589

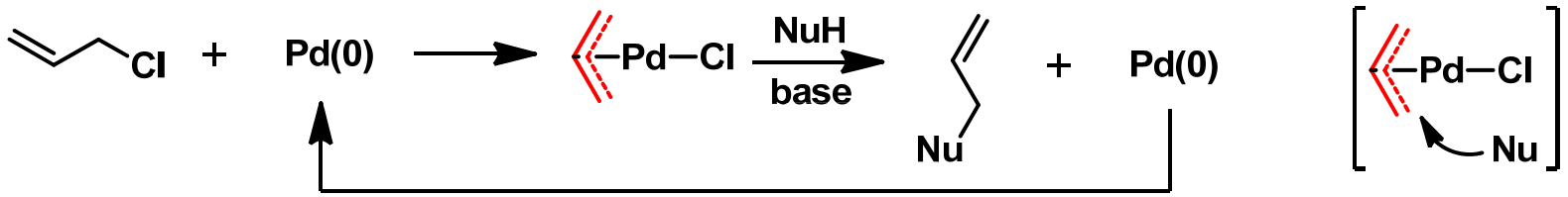
## Palladium catalyzed dearomatization reactions



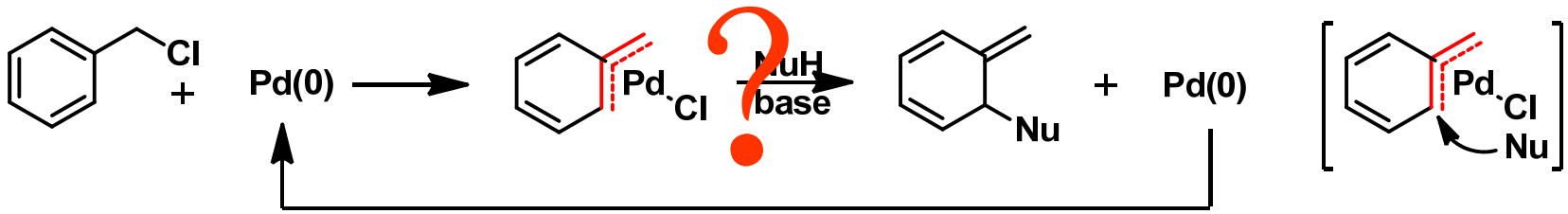




a). Bao, M.; Nakamura, H.; Yamamoto, Y. *J. Am. Chem. Soc.*, **2001**, *123,* 759; b). Fortanet, J. G.; Kessler, F.; Buchwald, S. L. *J. Am. Chem. Soc.*, **2009**, *131,* 6676

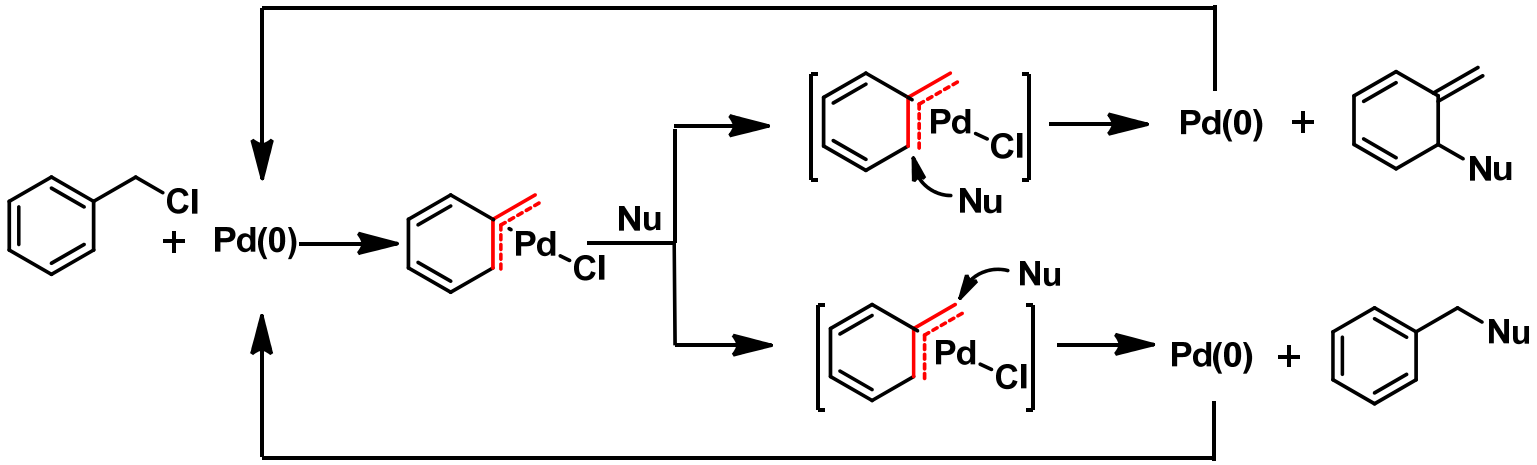
## Tsuji-Trost reaction



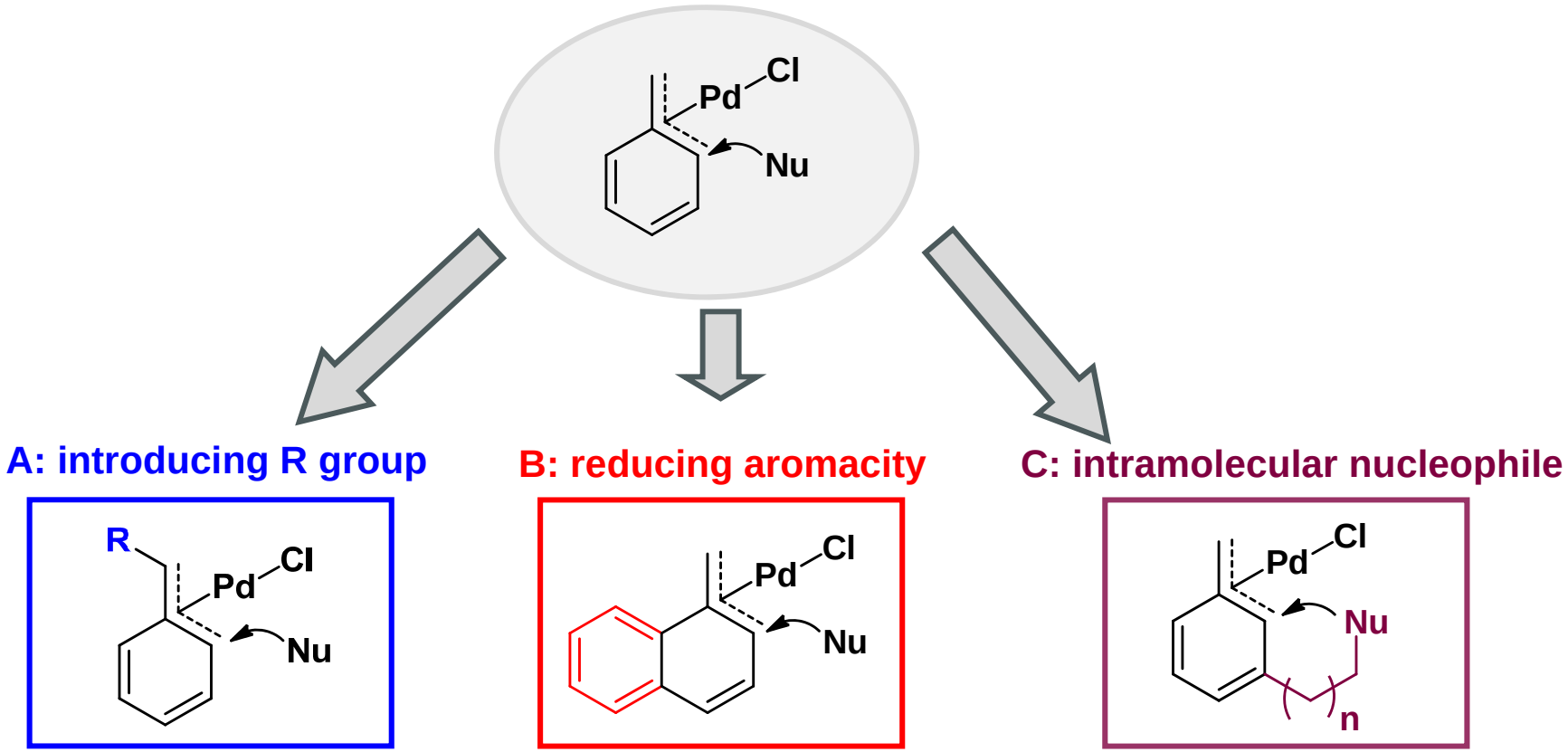

## Palladium catalyzed Nucleophilic Dearomatization ?



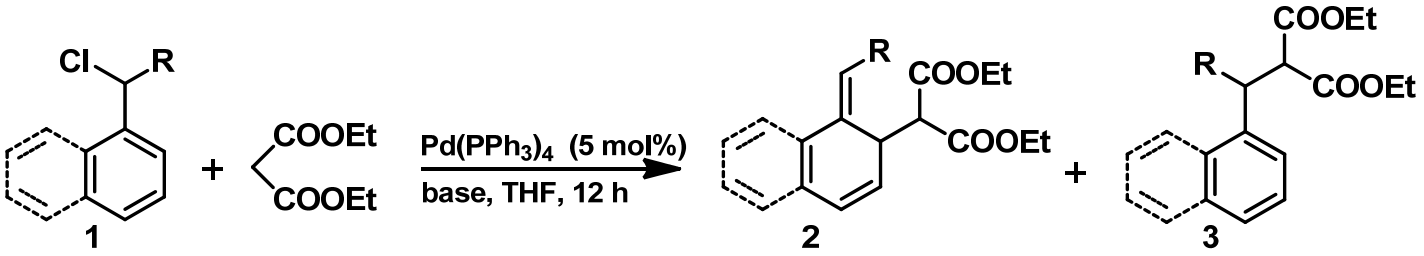
**Regional Selectivity ?**

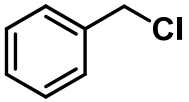
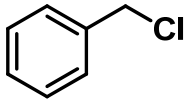
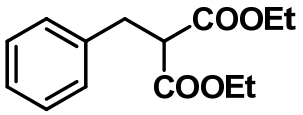
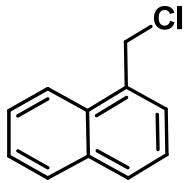
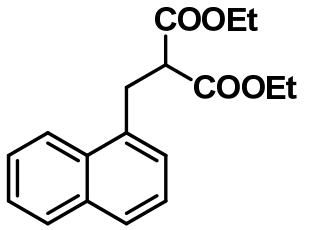
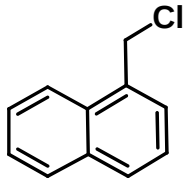
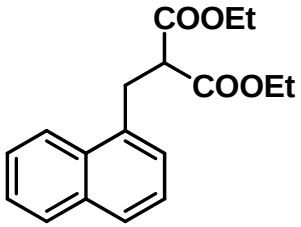


## Possible solutions

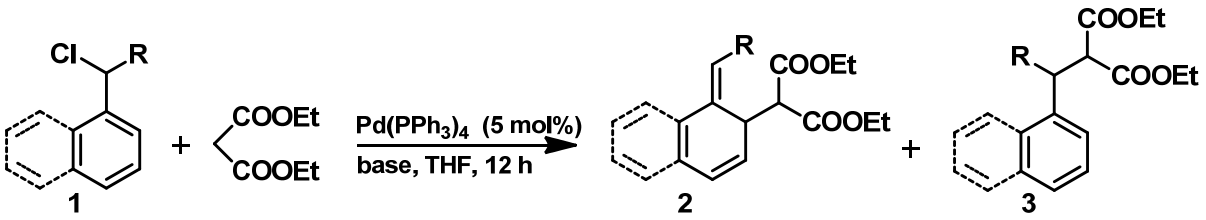


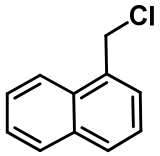
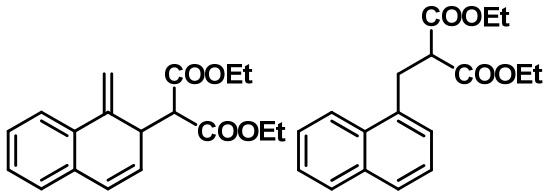
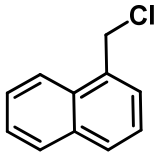
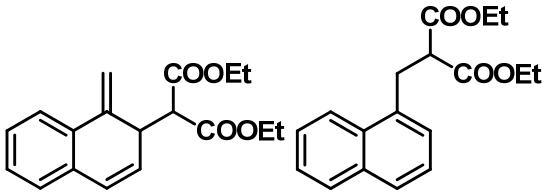
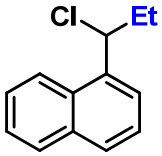
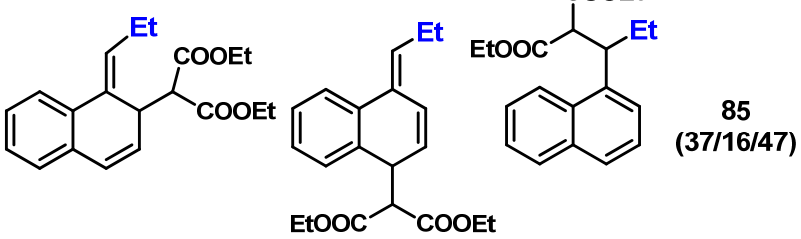
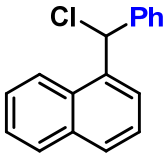
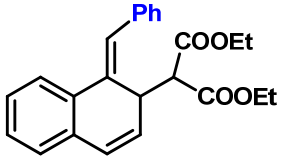
# Palladium catalyzed Dearomatization Reaction: **exploration**



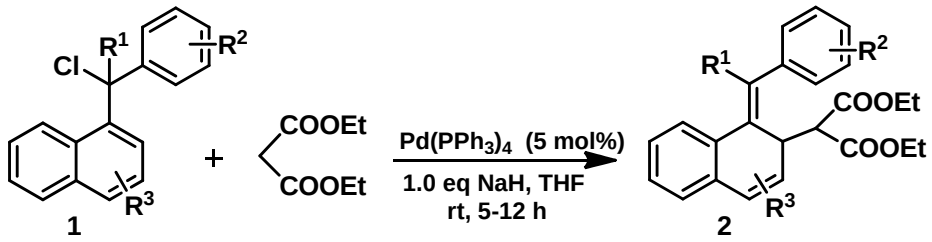

| entry | substrate | base | temp [°C] | product | yield [%] |
|---|---|---|---|---|---|
| 1 |  | NaH | rt | —— | NR |
| 2 |  | NaH | 50 |  | > 99 |
| 3 |  | NaH | rt |  | > 99 |
| 4 |  | NaH | -20 - rt |  | > 99 |

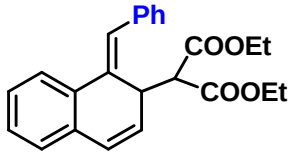
# Palladium catalyzed Dearomatization Reaction: **exploration**



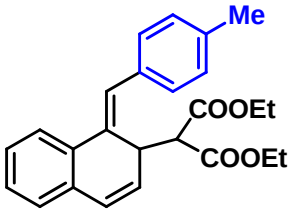

| entry | substrate | base | temp [°C] | product | yield [%] |
|---|---|---|---|---|---|
| 5 |  | $K_3PO_4$ | -20 - rt |  | 95 (5/95) |
| 6 |  | $Cs_2CO_3$ | -20 - rt |  | 87 (7/93) |
| 7 |  | NaH | rt |  | 85 (37/16/47) |
| 8 |  | NaH | rt |  | 90 |

# Palladium catalyzed Dearomatization Reaction: **scope study**

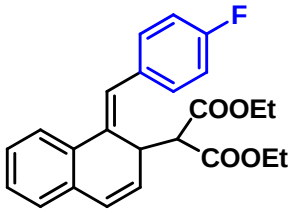


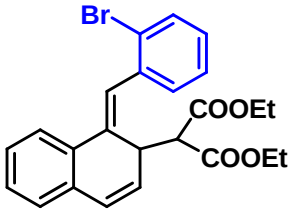

2a, 93%



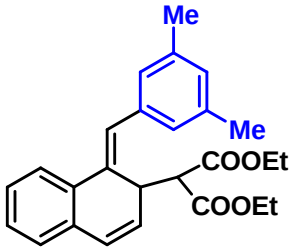

2b, 86%



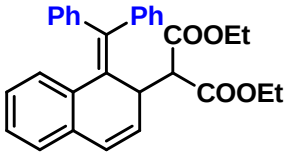

2c, 92%



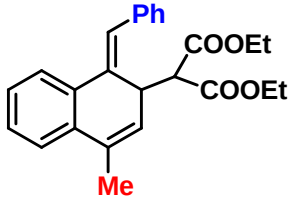

2d, 71%



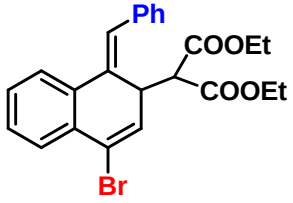

2e, 63%



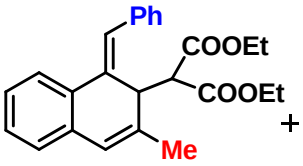

2e, 75%



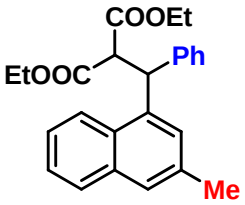

2f, 90%




2g, 72%

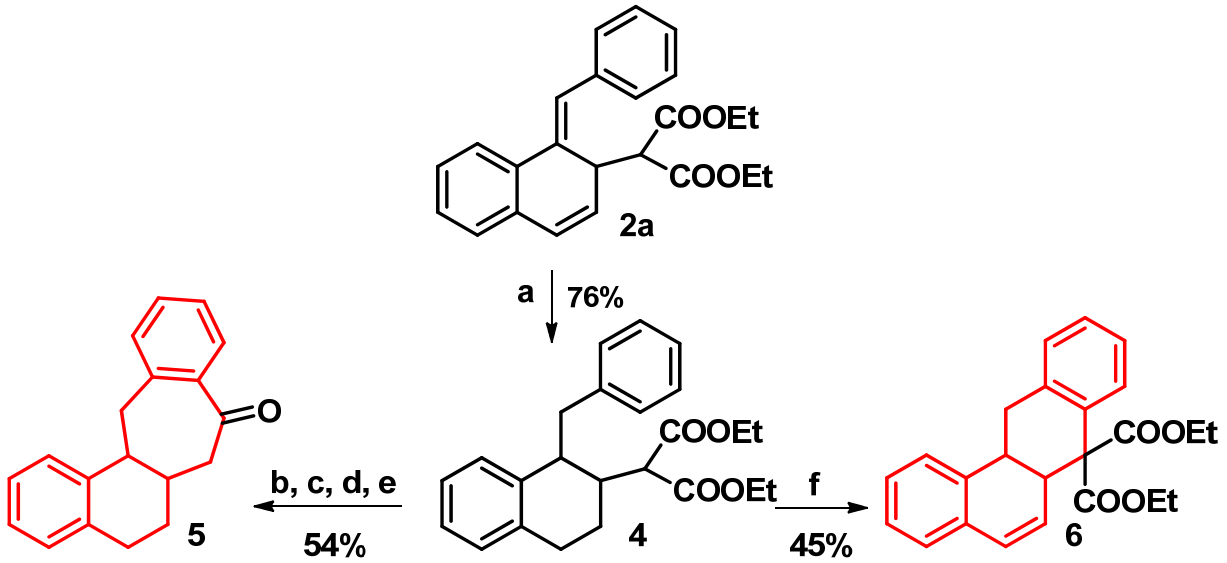



2h, 30%

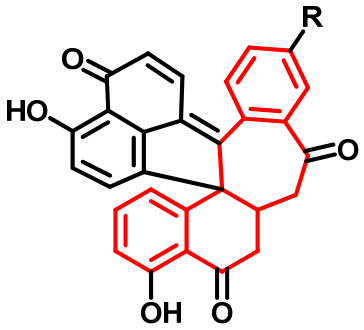



3h, 64%

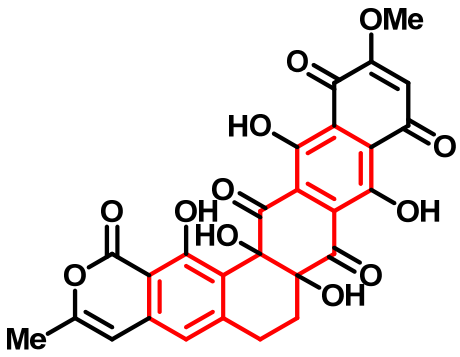
# Application to Tetracyclic Compounds




Reaction conditions: (a) Pd/C, $H_2$ (1 atm.), THF, rt; (b) KOH, EtOH, rt; (c) HCl, $H_2O$, rt; (d) 170 °C;
(e) $PCl_5$, $SnCl_4$, DCM, -20 °C; (f) $Mn(OAc)_3$•H2O, HOAc, 140 °C

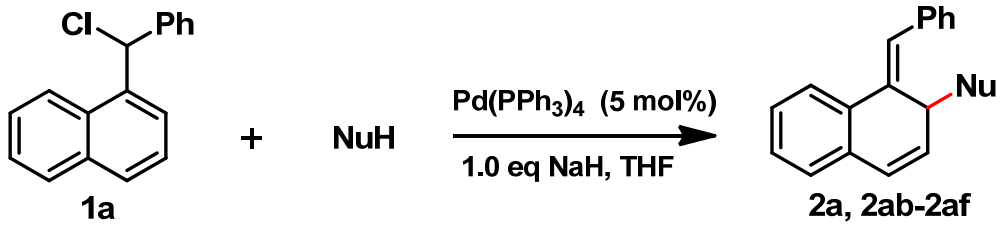


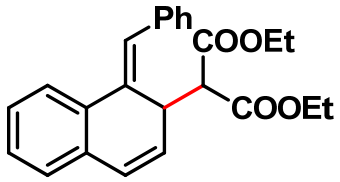

R = H, dalesconol A
R = OH, dalesconol B



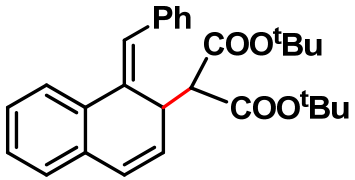

Collinone

# Palladium catalyzed Dearomatization Reaction: **Nu scope**

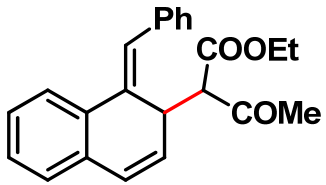


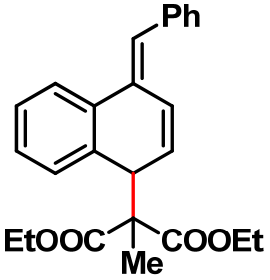

rt, 6 h
2a, 93%



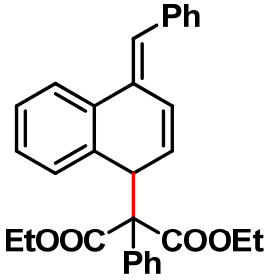

rt, 7 h
2ab, 91%



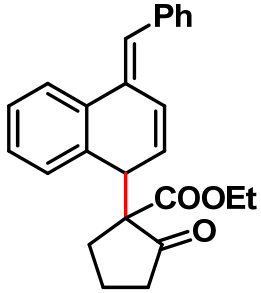

50 °C, 72 h
2ac, 42%, 1/1 dr




rt, 6 h
2ad, 92%

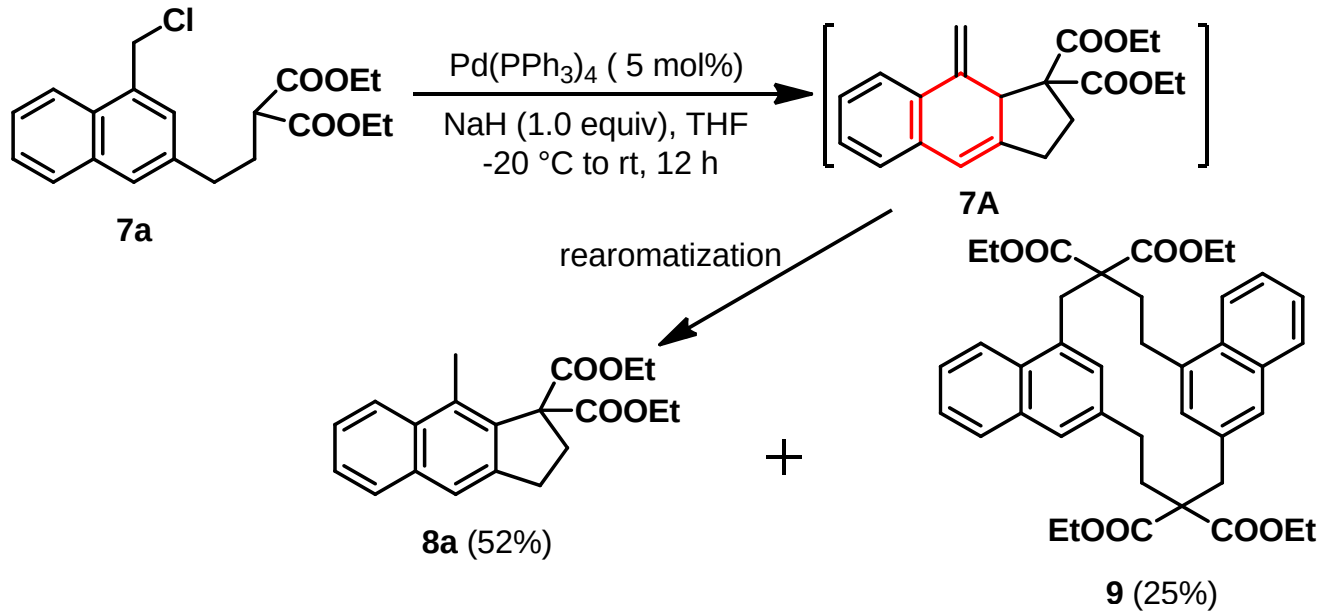


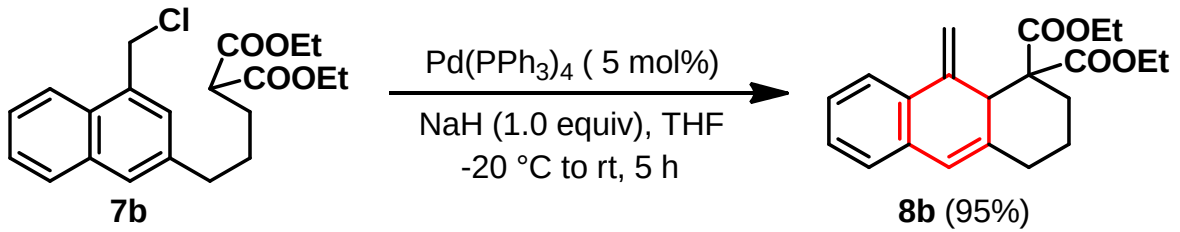

rt, 96 h
2ae, 67%



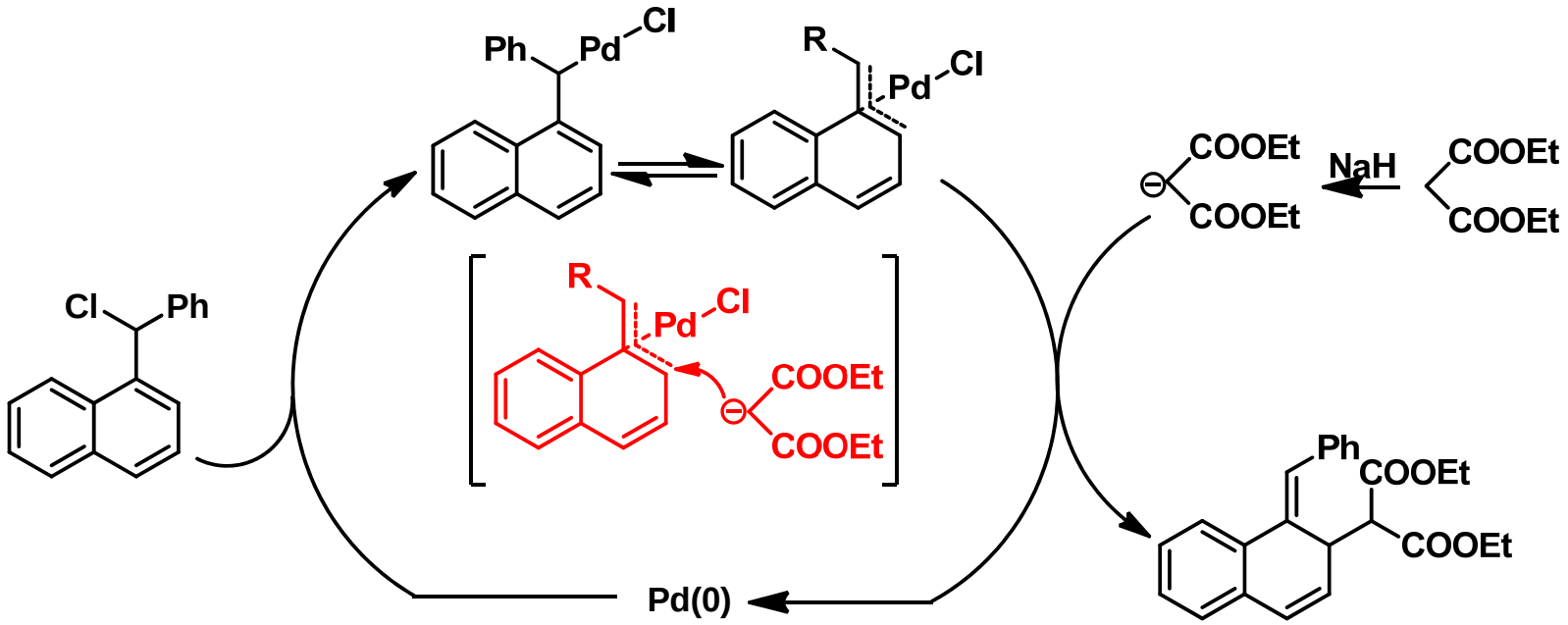

50 °C, 12 h
2af, 71%, 3/2 dr

## Intramolecular palladium catalyzed dearomatization

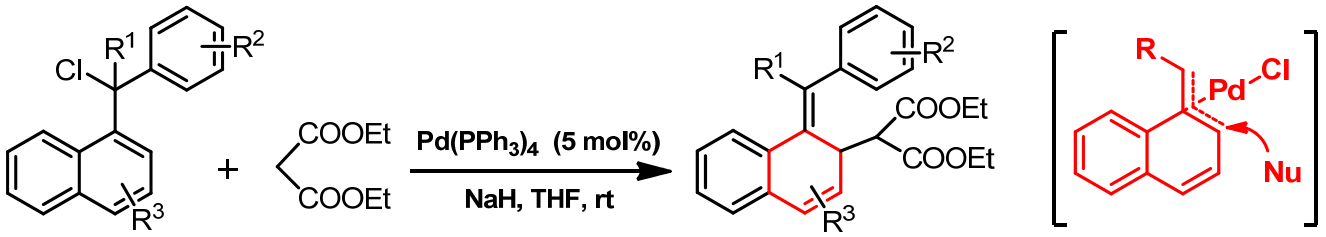


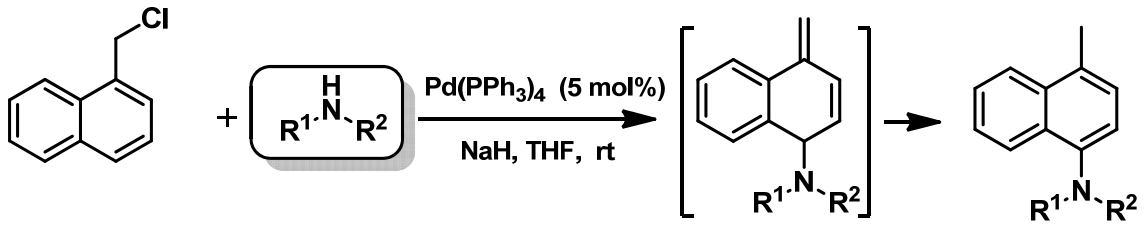
**Possible mechanism**



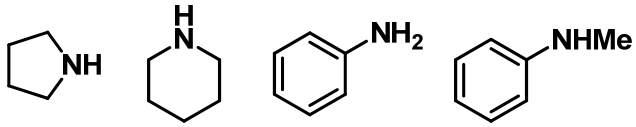
## summary




## recent progress




Nu:




a) Peng, B.; Zhang, S.; Yu, X.; Feng, X.; Bao, M. *Org. Lett.* **2011**, *13*, 5402-5405; b). Zhang, S.; Wang, Y.; Feng, X. *J. Am. Chem. Soc.* **2012**, *134*, 5492−5495.

# Palladium catalyzed Dearomatization Reaction

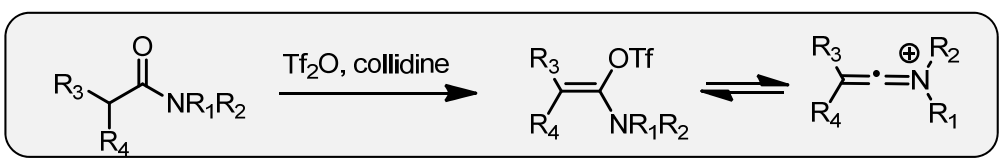
&

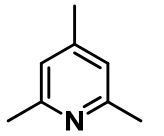
# Electrophilic rearrangement of amides

# Electrophilic rearrangement of amides: **background**

## *Keteniminium Chemistry*

Generation of Keteniminium Salt

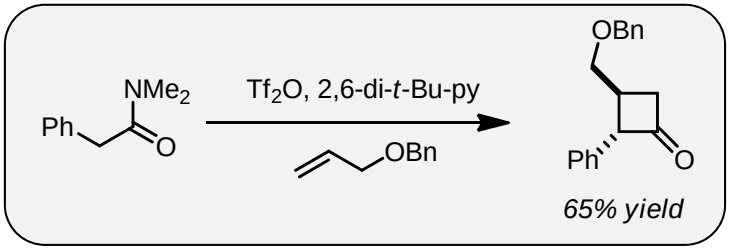


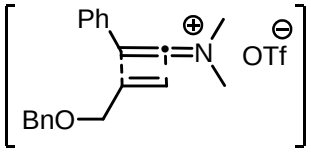




**2,4,6-collidine**

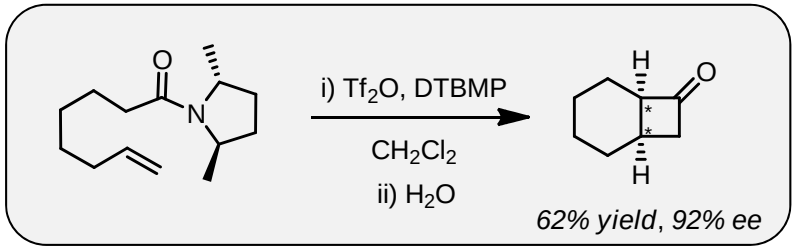
[2+2] cycloaddition of Keteniminium Salt

Intermolecular



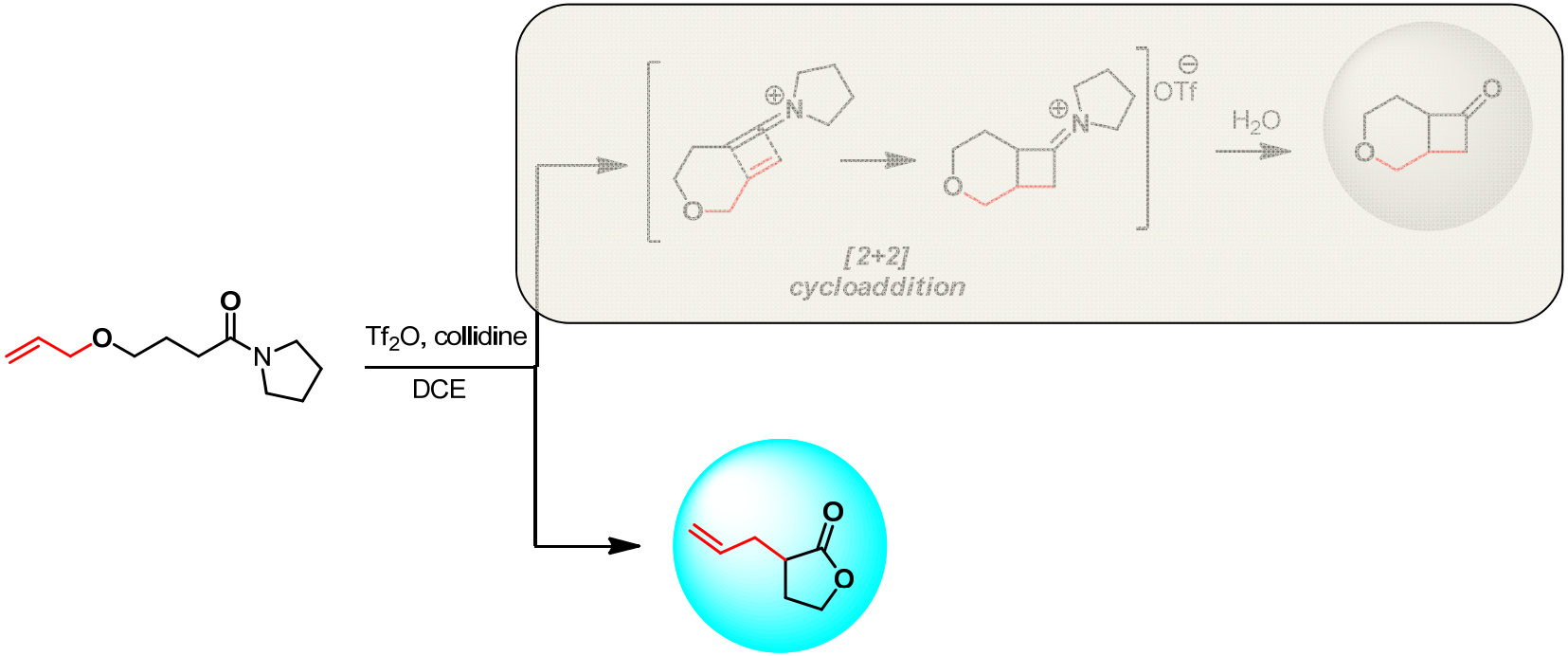




Intramolecular



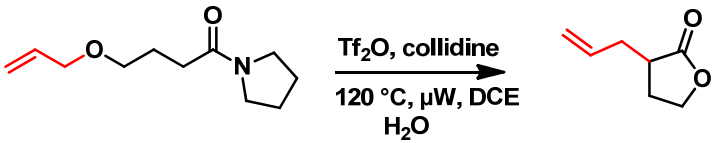

Snider B.B. *Chem. Rev.* **1988**, *88*, 793

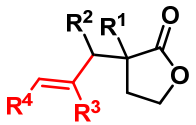
## Rational design VS Serendipitous result



# Electrophilic rearrangement of amides: **background**

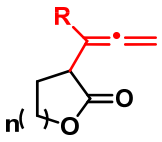
**2009 Claire, Vivi**



33%- 90%

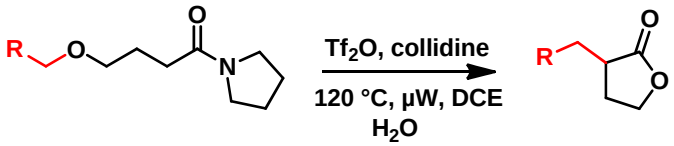
12 examples

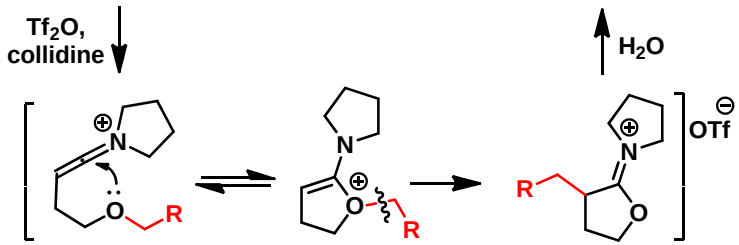


40%- 70%

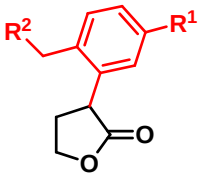
6 examples

**2010 Vivi, Claire**



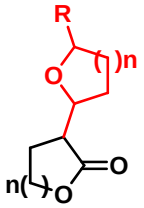




*Keteniminum induced Claisen Rearrangement*



31%- 90%

9 examples



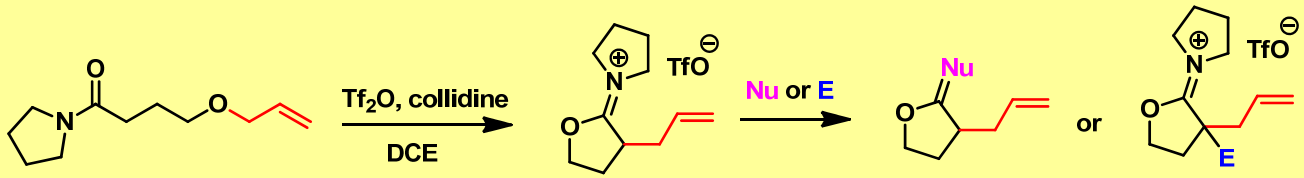
40%- 76%

6 examples

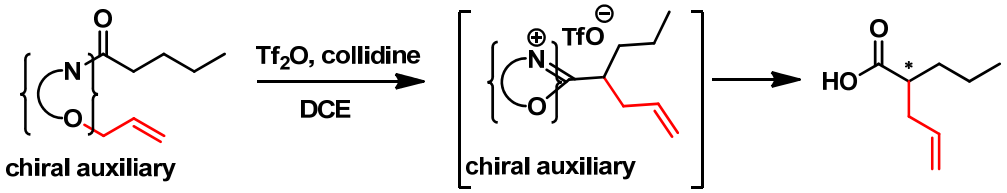
b). Madelaine C., Valerio V., Maulide N., *Angew. Chem. Ed.* **2010**, *49*, 1583-1586; c). Valerio V., Madelaine C., Maulide N., *Chem. Eur. J.* **2011**, *17*, 4742-4745.

# Electrophilic rearrangement of amides: **content**

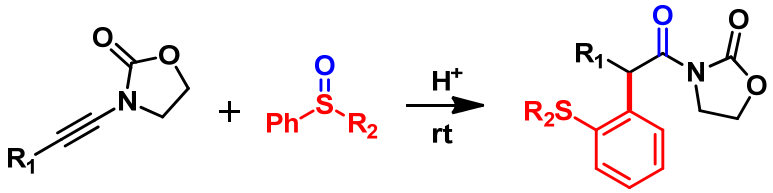
## Part 1. Nucleophilic/electrophilic capture of in-situ generated iminium ethers



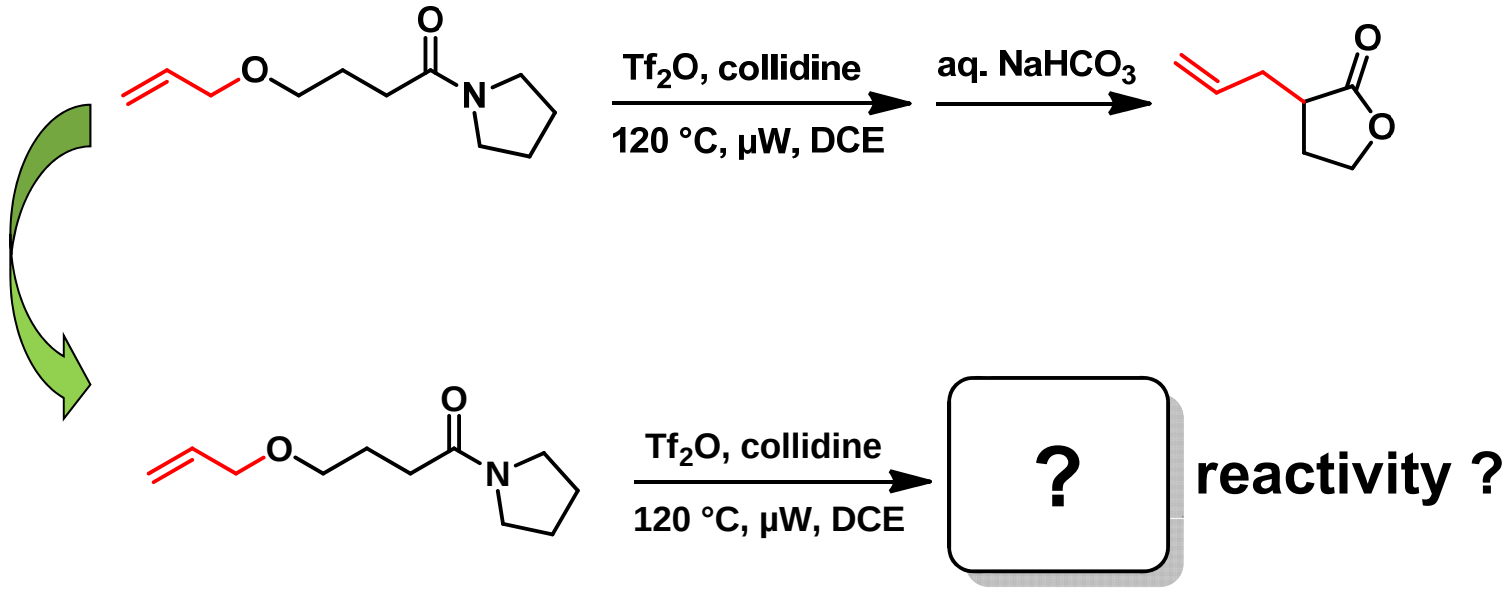

## Part 2. Development of Asymmetric α-Allylation



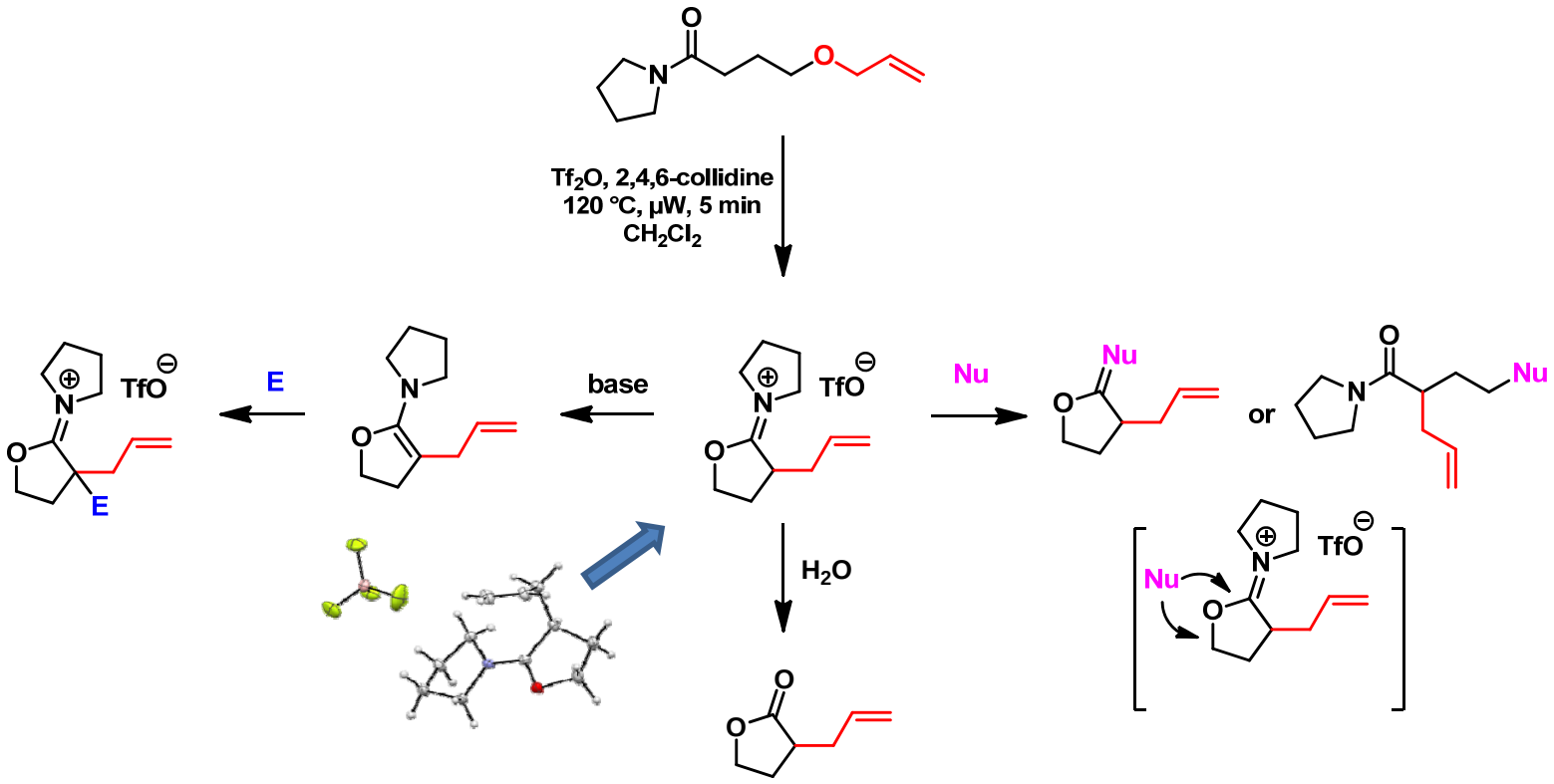

## Part 3. Development of A Brønsted Acid-Catalyzed Redox Arylation



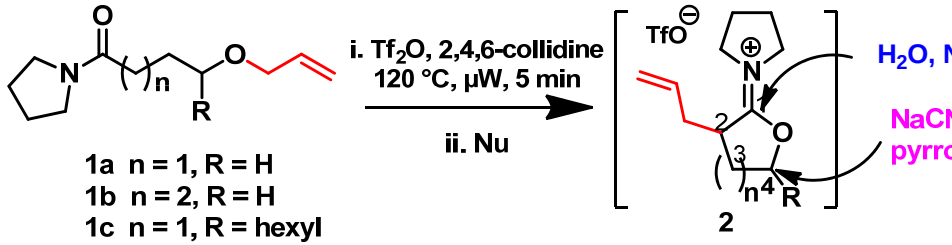
***Previous discovery:***



***Dual Nucleophilic/Electrophilic Capture of Iminium ether:***

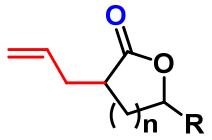


## *scope of substrates*

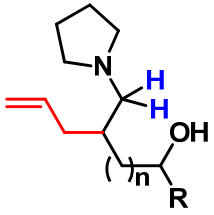



1a n = 1, R = H
1b n = 2, R = H
1c n = 1, R = hexyl

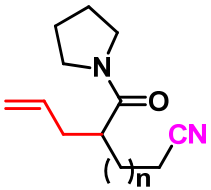
2



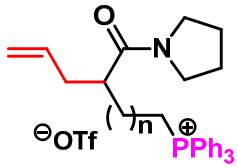
3a, 90%
3b, 57%
3c, 71%, d.r. 5:1
Nu = $H_2O$
aq. $NaHCO_3$, rt, 16 h



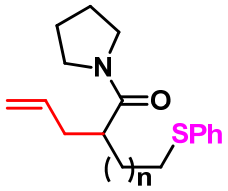
4a, 72%
4b, 41%
4c, 73%, d.r. > 9:1
Nu = $NaBH_4$
rt, 16 h



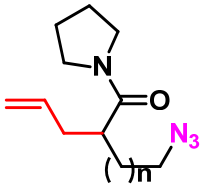
5a, 62%
5b, 82%
Nu = NaCN
120 °C, 5 min



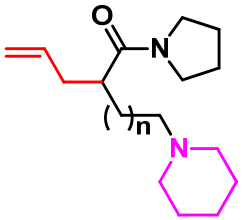
6a, 58%
6b, 40%
Nu = $PPh_3$
120 °C, 1 h



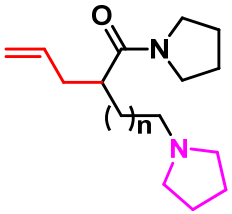
7a, 72%
7b, 85%
Nu =NaSPh
120 °C, 5 min



8a, 56%
8b, 42%
Nu = $NaN_3$
rt, 24 h

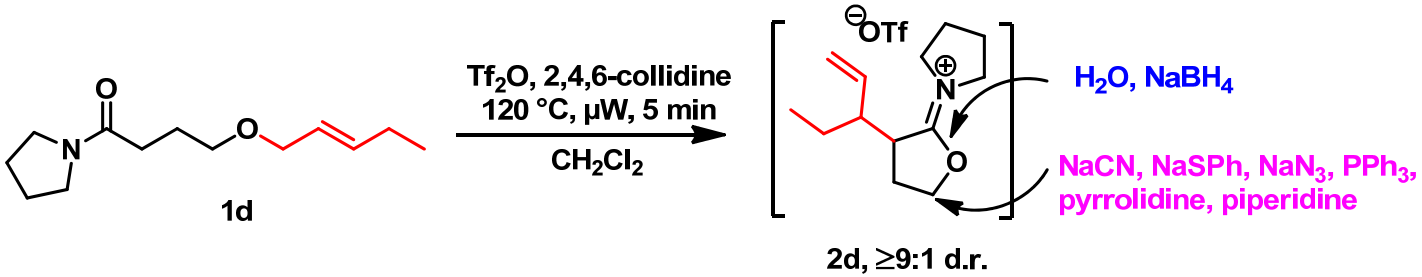


9a, 73%
9b, 47%
Nu = piperidine
120 °C, 5 min



10a, 47%
10b, 46%
Nu = pyrrolidine
120 °C, 5 min

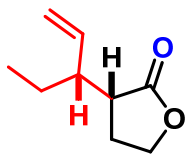
## *reactions of diastereomeric enriched iminium ether 2d*




2d, ≥9:1 d.r.

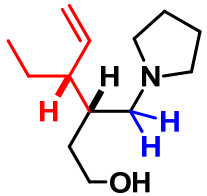
---

$H_2O$



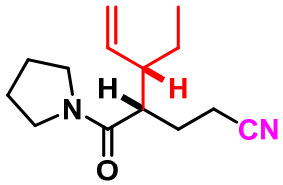
3d 78%, 9:1 d.r.

$NaBH_4$



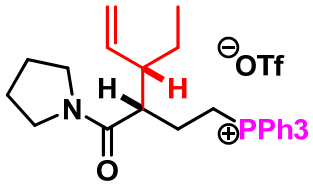
4d 62%, 7:1 d.r.

NaCN



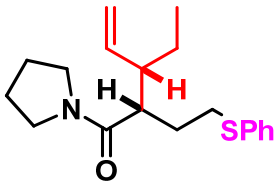
5d 62%, 7:3 d.r.

$PPh_3$



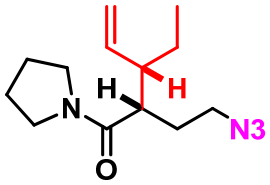
6d 48%, 5:1 d.r.

NaSPh



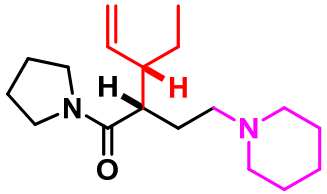
7d 40%, 7:3 d.r.

$NaN_3$



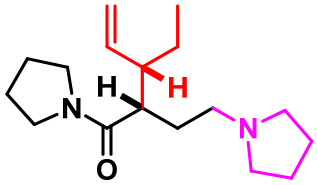
8d 28%, 7:3 d.r.

piperidine



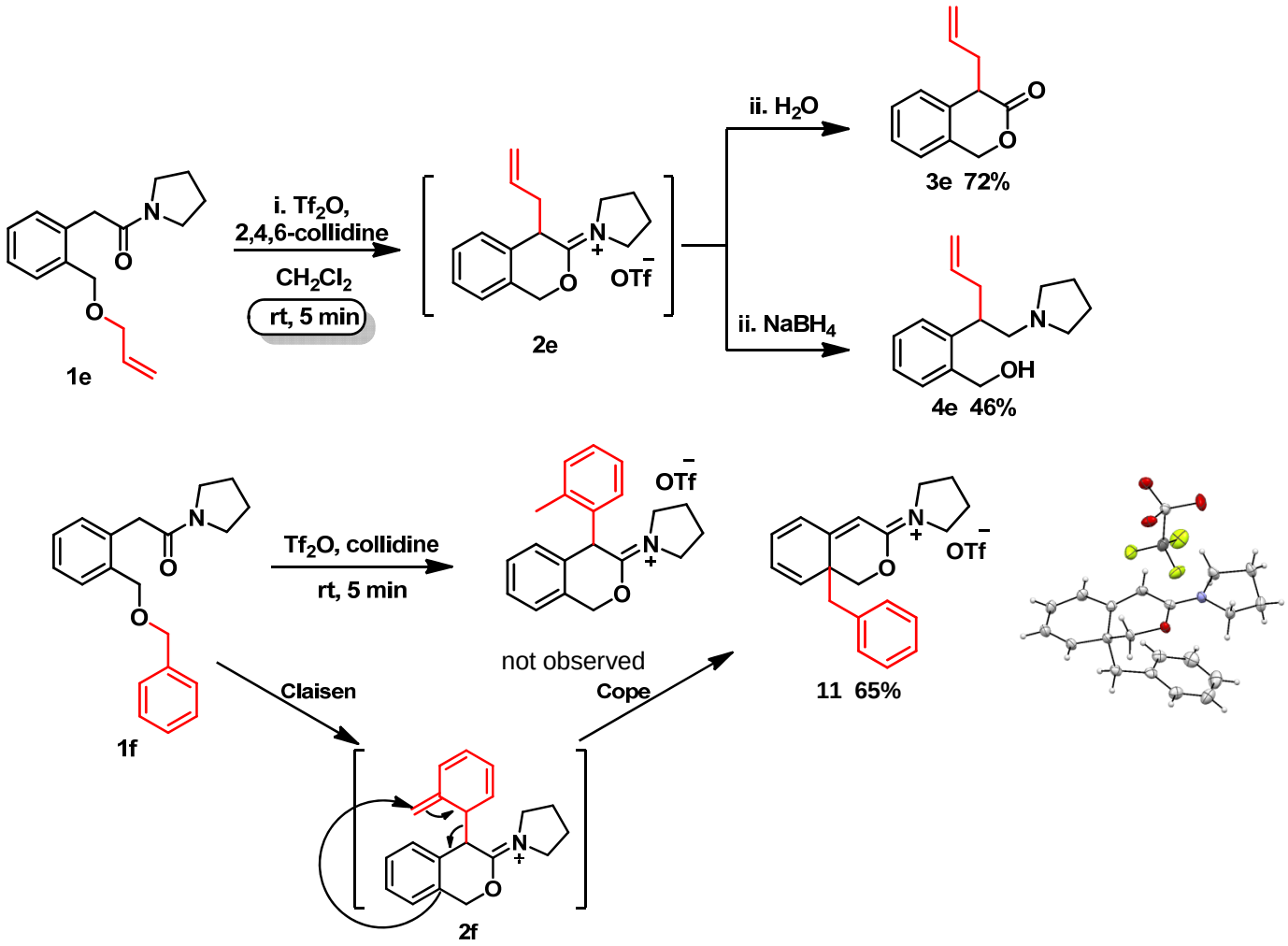
9d 54%, 2:1 d.r.

pyrrolidine

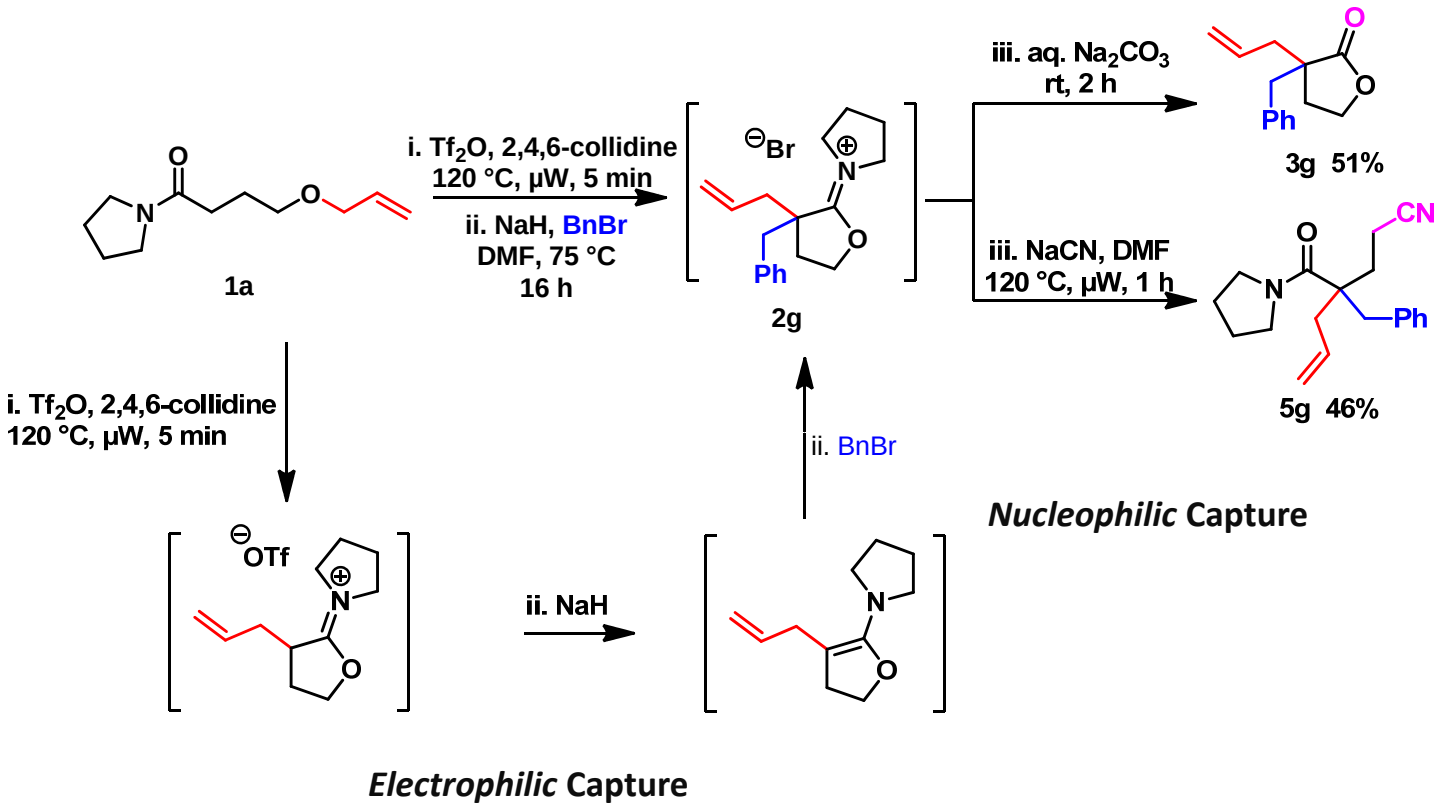


10d 31%, 2:1 d.r.

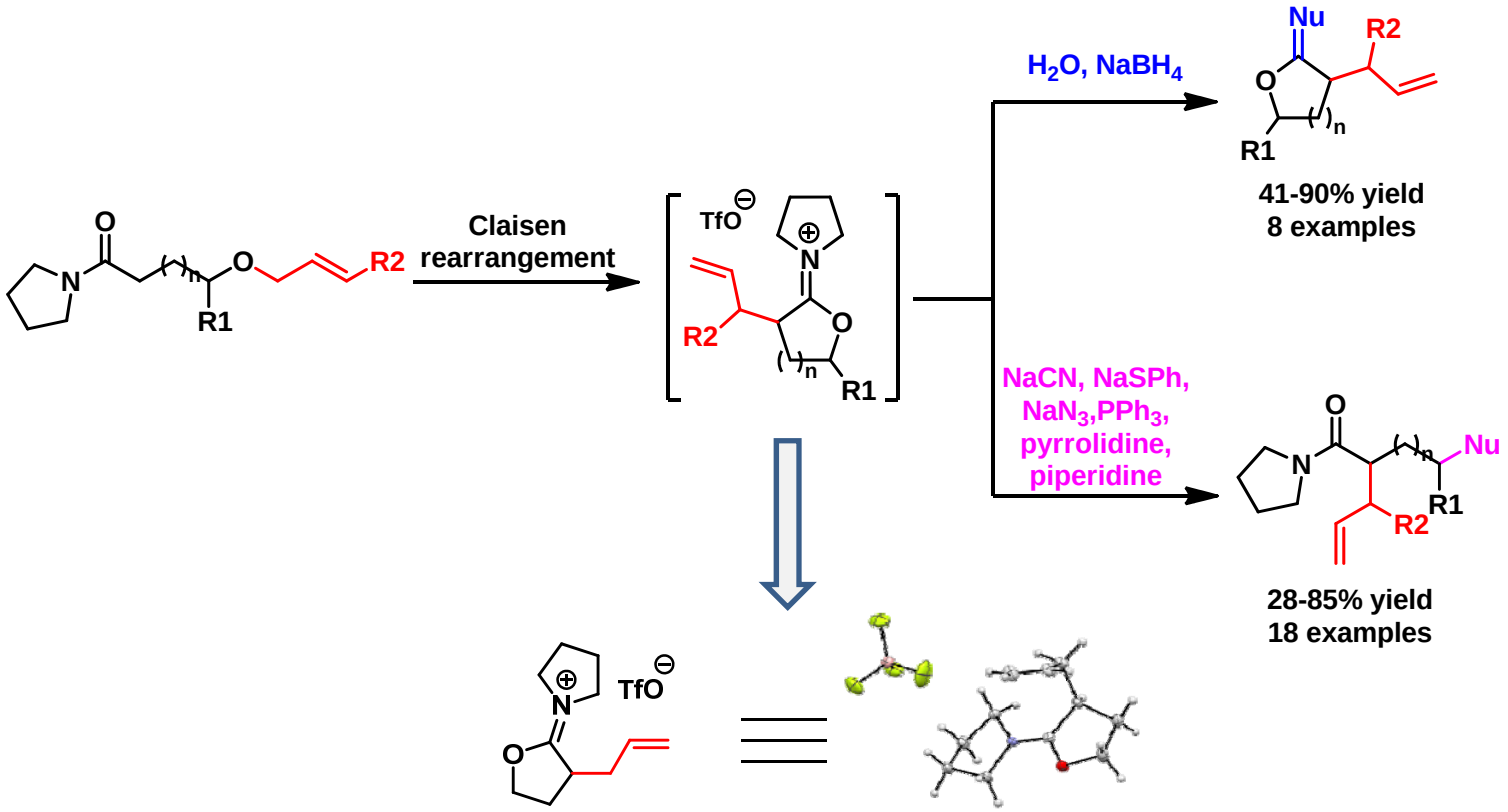
## Dearomatisation inspired by Ji Woong's SM



***Tandem Electrophilic/Nucleophilic trap of In-Situ Generated Iminium Ethers***



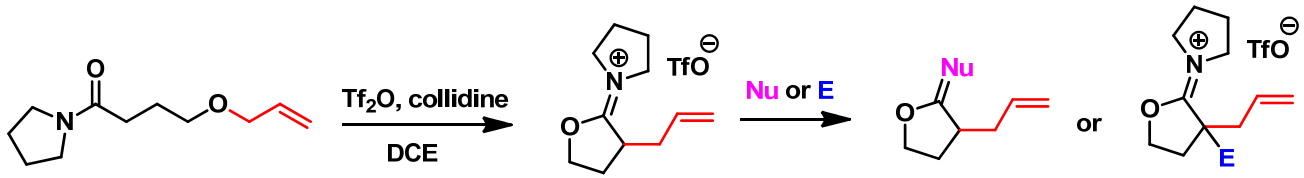
# summary



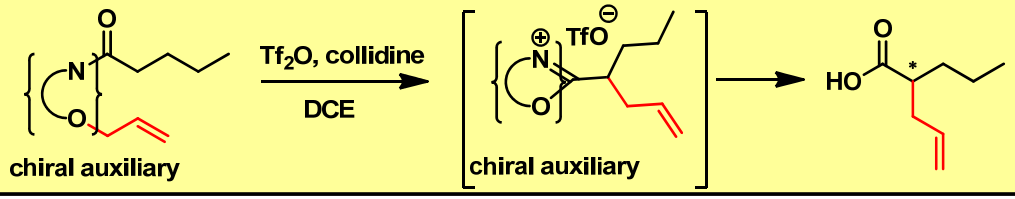

e) Peng B., ODonovan D. H., Jurberg I. D., Maulide N. *Chem. Eur. J.* **2012**, *18*, 16292 – 16296

# Electrophilic rearrangement of amides: **content**

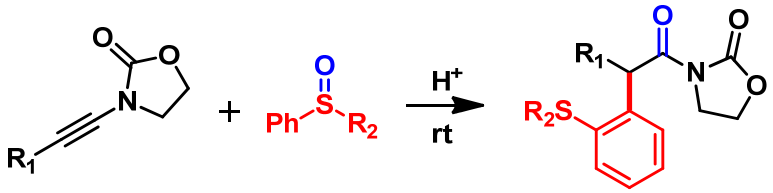
## Part 1. Nucleophilic/electrophilic capture of in-situ generated iminium ethers



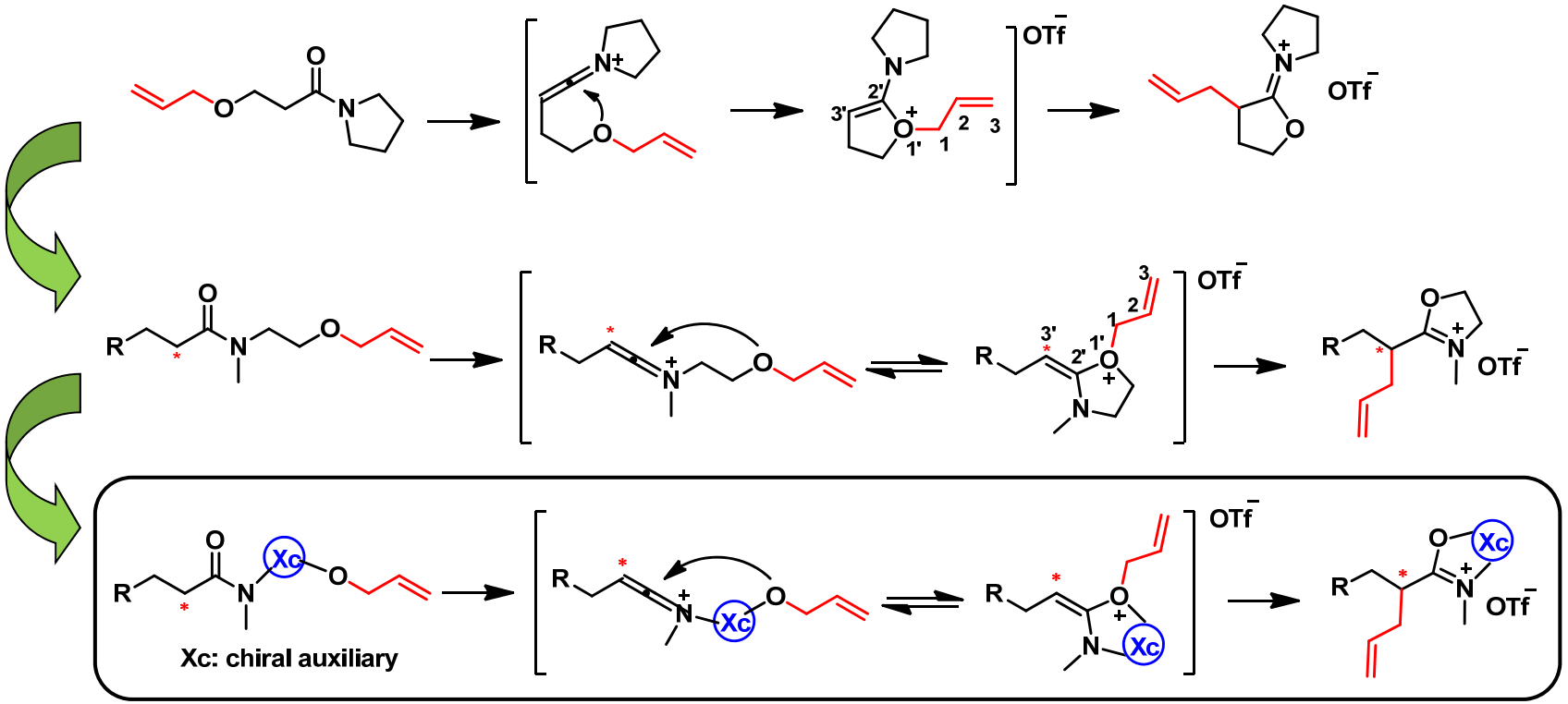

## Part 2. Development of Asymmetric α-Allylation




## Part 3. Development of A Brønsted Acid-Catalyzed Redox Arylation



***Previous discovery:***




**Asymmetric α-Allylation**

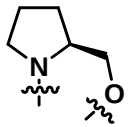
# Part 2. Development of Asymmetric a-Allylation

**With Danny**


1a, 1b and 2a

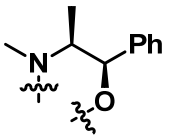
3a,3b and 4a

| entry | substrate | base (2.0 eq.) | Product (yield) |
|---|---|---|---|
| 1 | 1a | 2,4,6-collidine | 3a (---) |
| 2 | 1b | 2,4,6-collidine | 3b (---) |
| 3 | 2a | 2,4,6-collidine | 4a (16%) |
| 4 | 2a | 2-fluoropyridine | 4a (> 95%) |

Xc = 

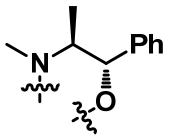

1a

L-prolinol




1b

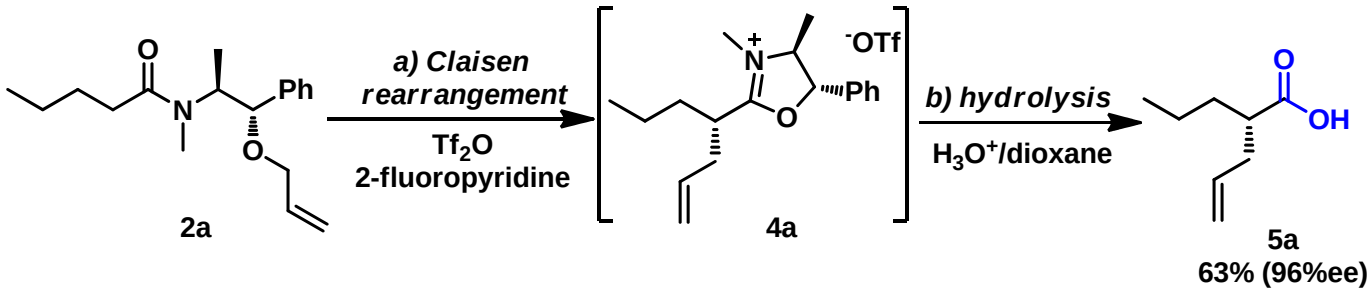
(1*R*,2*S*)-pseudoephedrine

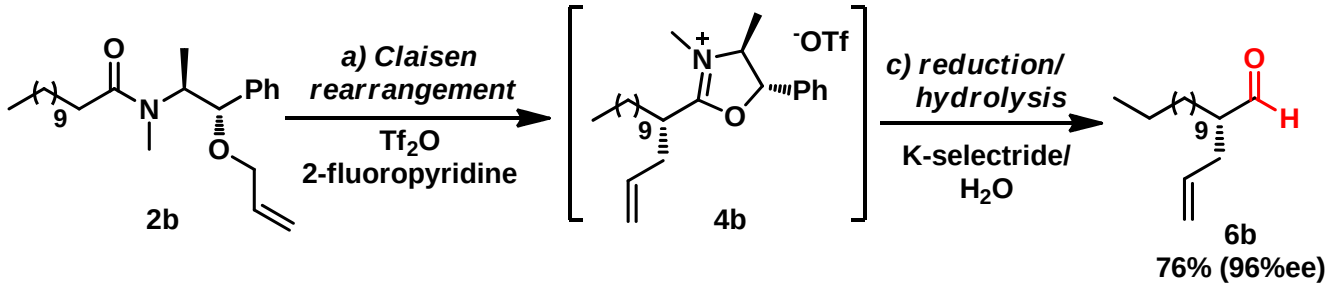



2a

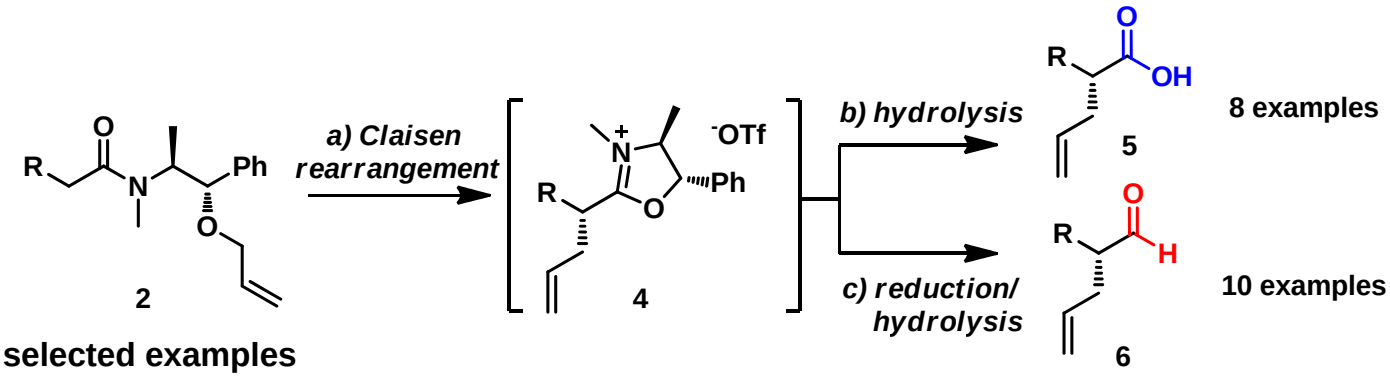
(1*S*,2*S*)-pseudoephedrine

## *Remove auxiliary towards α-allylated carboxylic acid and aldehyde*



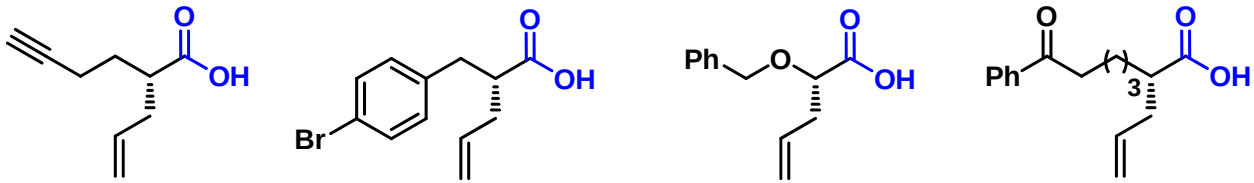




a): $Tf_2O$ (1.5 eq), 2-fluoropyridine (2.0 eq), DCM, 0 °C, 12 h;
b): $H_2SO_4$/dioxane ($1/_1$), 100 °C, 24 h;
c): K-selectride (3.0 eq), -78 °C to rt, 3 h, then silica/DCM/$H_2O$, rt, 12 h.




**selected examples**

***in situ* hydrolysis to carboxylic acids**



**5c**
**75%(88%ee)**



**5d**
**43%(88%ee)[b,c]**

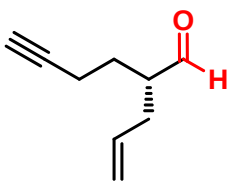


**5g**
**47%(94%ee)**

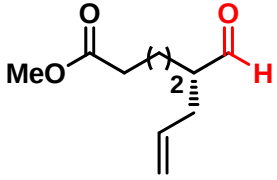


**5h**
**80%(95%ee)**

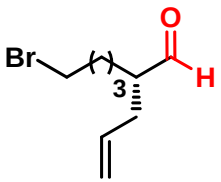
***in situ* reduction/hydrolysis to aldehydes**



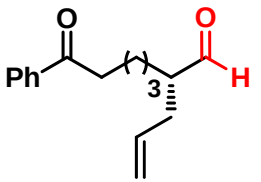
**6c**
**68%(90%ee)**



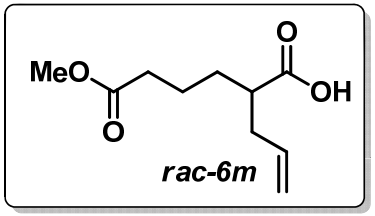
**6m**
**87% (90%ee)[b,e]**

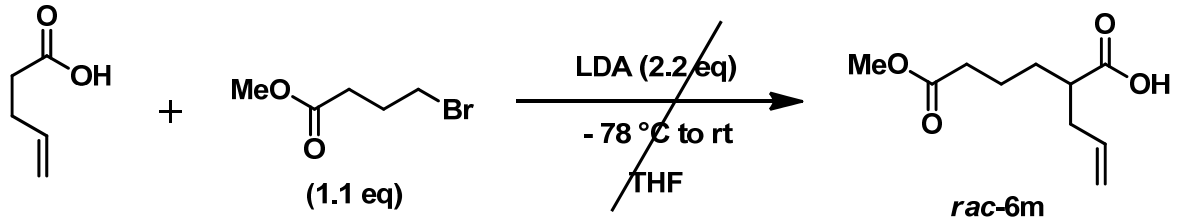


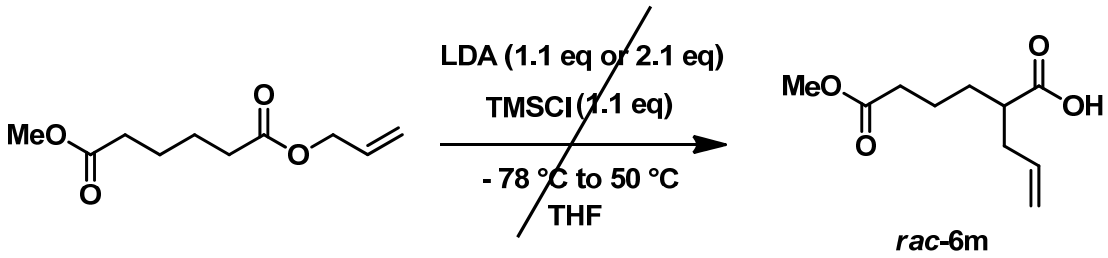
**6k**
**55% (90%ee)[b,e]**

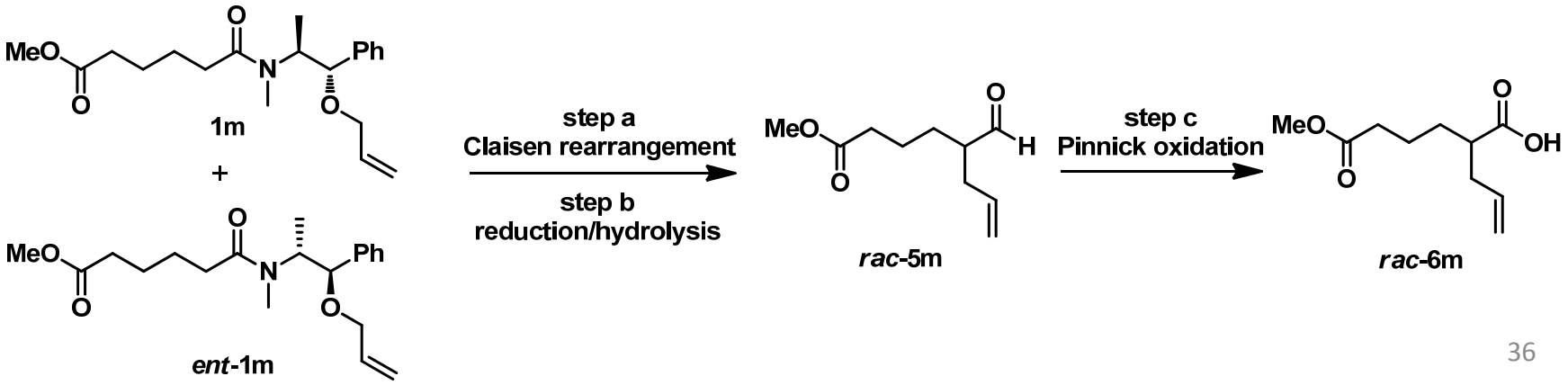


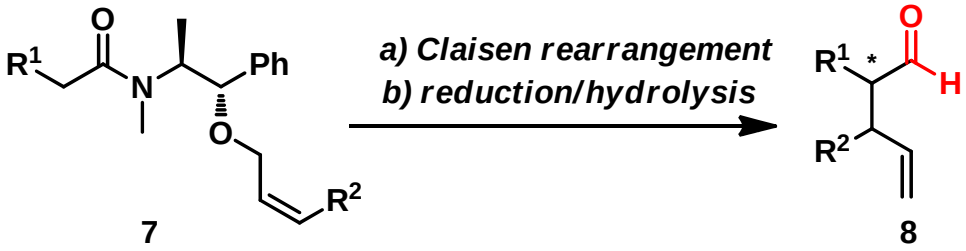
**6h**
**54%(91%ee)[e]**

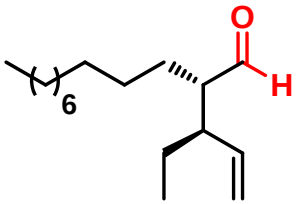

MeO
O
O
OH
rac-6m


OH
MeO
Br
(1.1 eq)
LDA (2.2 eq)
- 78 °C to rt
THF
rac-6m

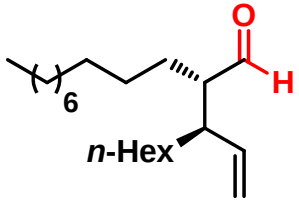

MeO
LDA (1.1 eq or 2.1 eq)
TMSCl (1.1 eq)
- 78 °C to 50 °C
THF
rac-6m


MeO
Ph
N
1m
+
ent-1m
step a
Claisen rearrangement
step b
reduction/hydrolysis
rac-5m
step c
Pinnick oxidation
rac-6m

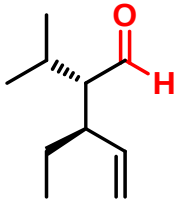


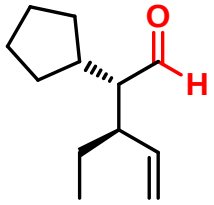

8a, 72%
(d.r. 3.2/1, 94% ee)



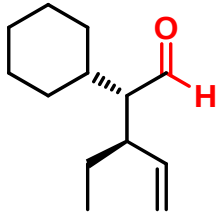

8b, 67%
(d.r. 2.6/1, 93% ee)



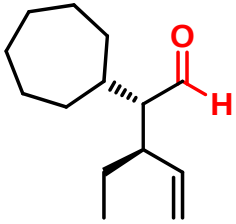

8c, 42%
(d.r. 3.7/1, 94% ee)



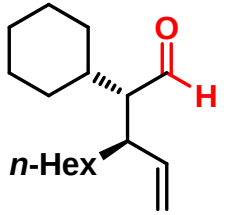

8d, 65%[b]
(d.r. 4.3/1, 94% ee)




8e, 82%[c]
(d.r. 5.3/1, 93% ee)

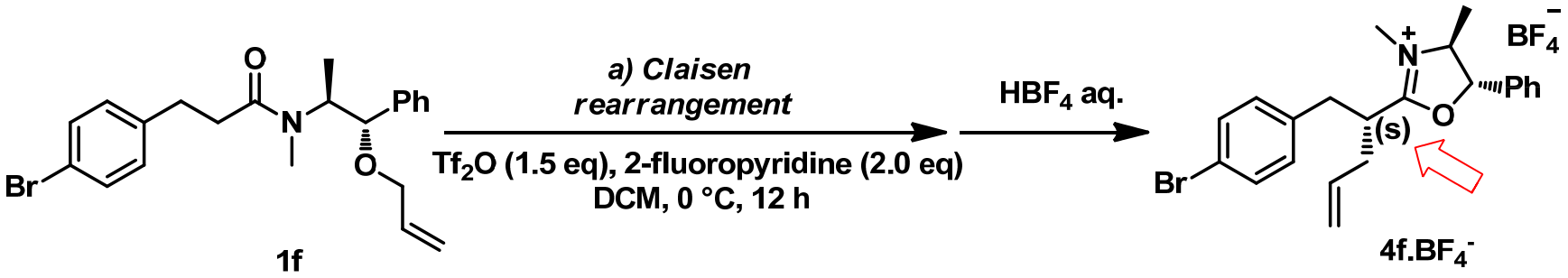


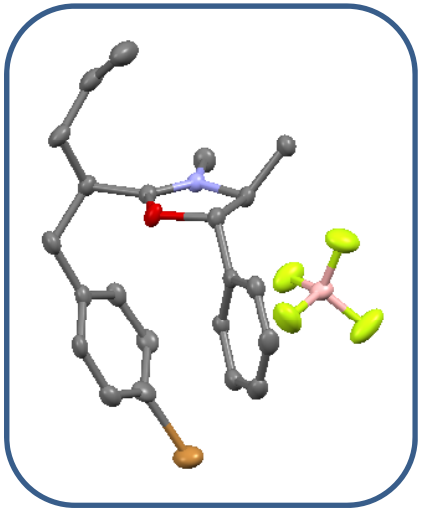

8f, 53%
(d.r. 5.7/1, 92% ee)

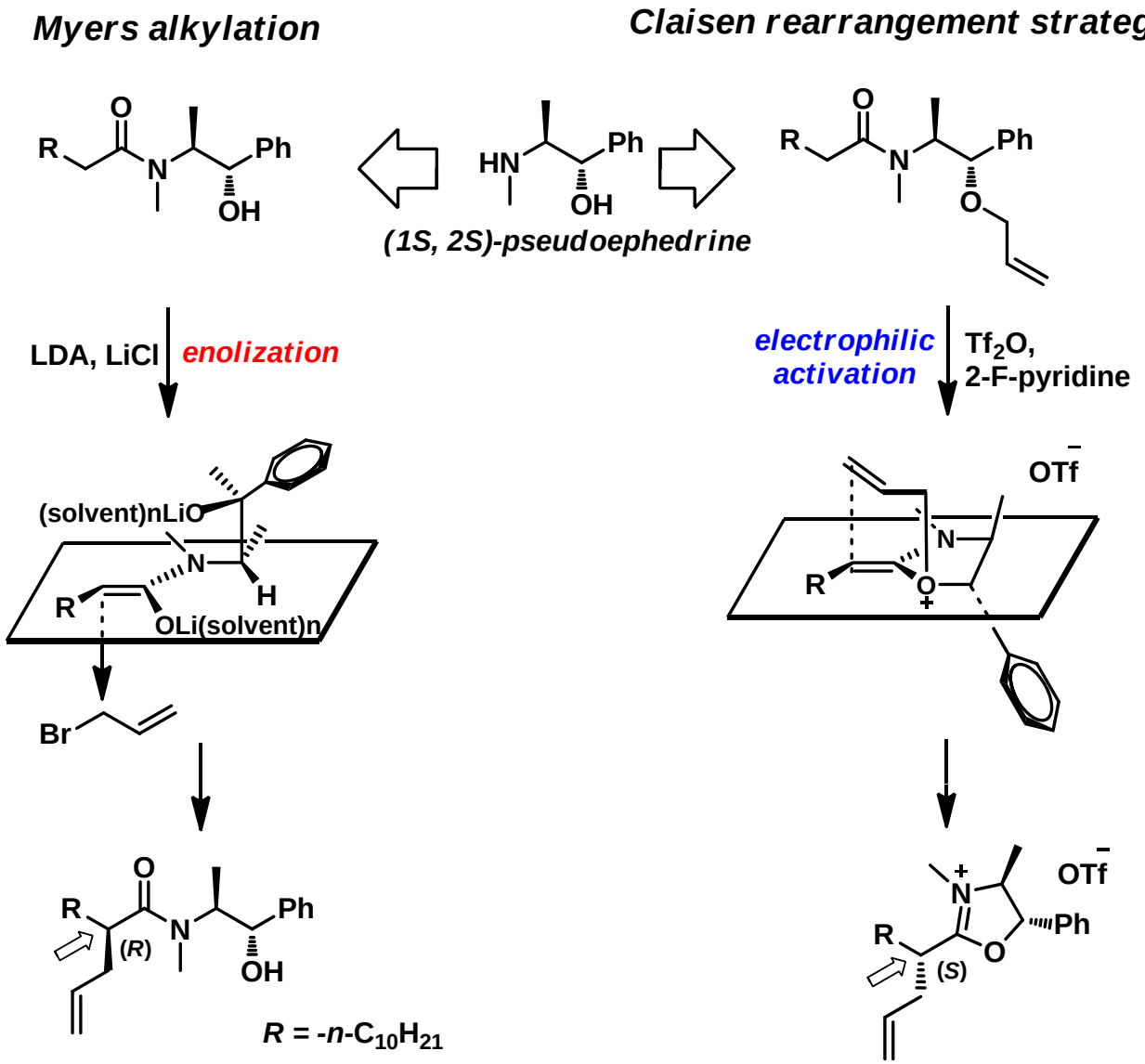



8g, 69%[c]
(d.r. 3.2/1, 87% ee)

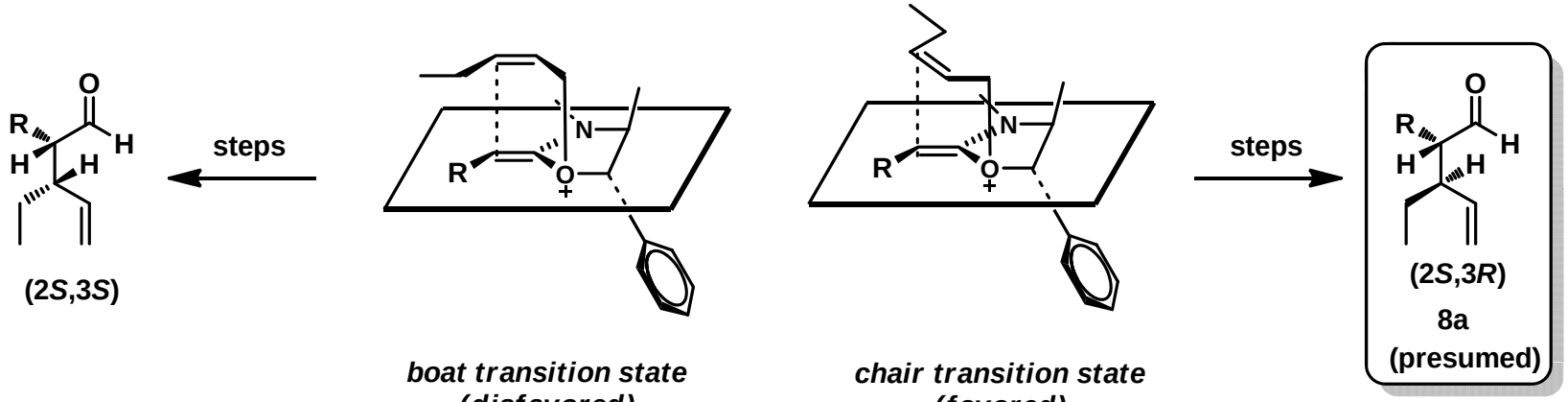
***Single-crystal X-ray determination of the absolute configuration***

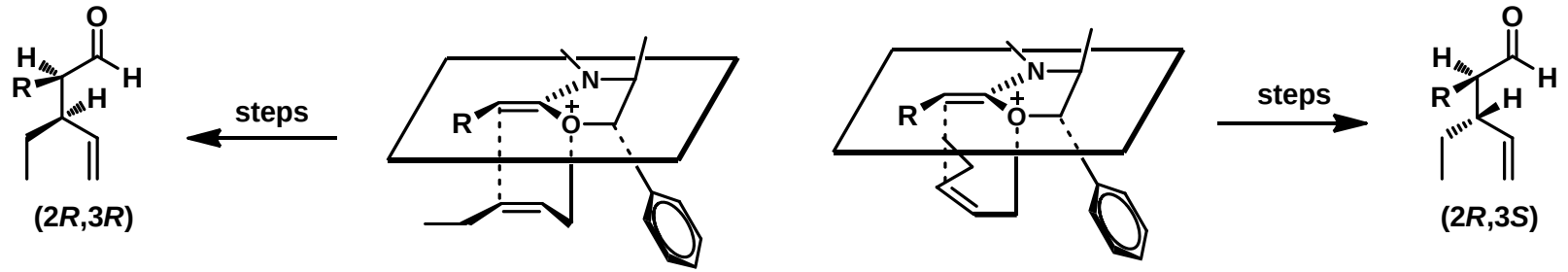



Myers alkylation
Claisen rearrangement strategy
(1S, 2S)-pseudoephedrine
LDA, LiCl
enolization
electrophilic activation
Tf2O, 2-F-pyridine
(solvent)nLiO
OLi(solvent)n
OTf
Br
R = -n-C10H21

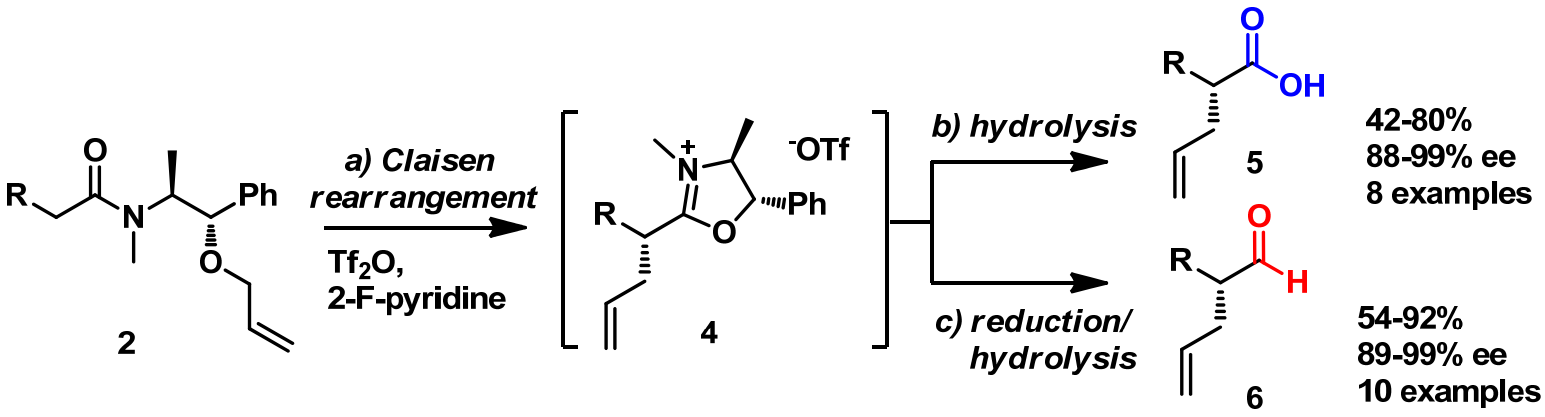
## *Mechanistic proposal for the observed diastereo- and enantioselectivity*




*R* = -*n*-$C_{10}H_{21}$

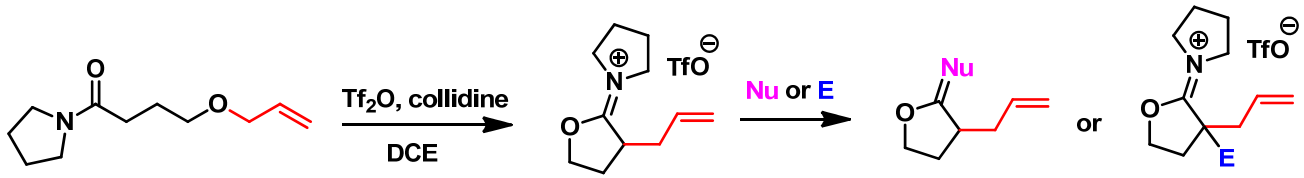
# summary



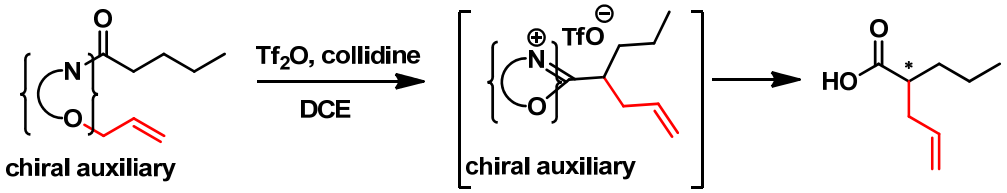

Peng, B.; Geerdink, D.; Maulide, N. *J. Am. Chem. Soc.* **2013**, *135*, 14968−14971

# Electrophilic rearrangement of amides: **content**

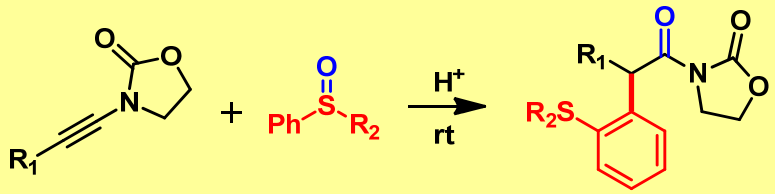
## Part 1. Nucleophilic/electrophilic capture of in-situ generated iminium ethers



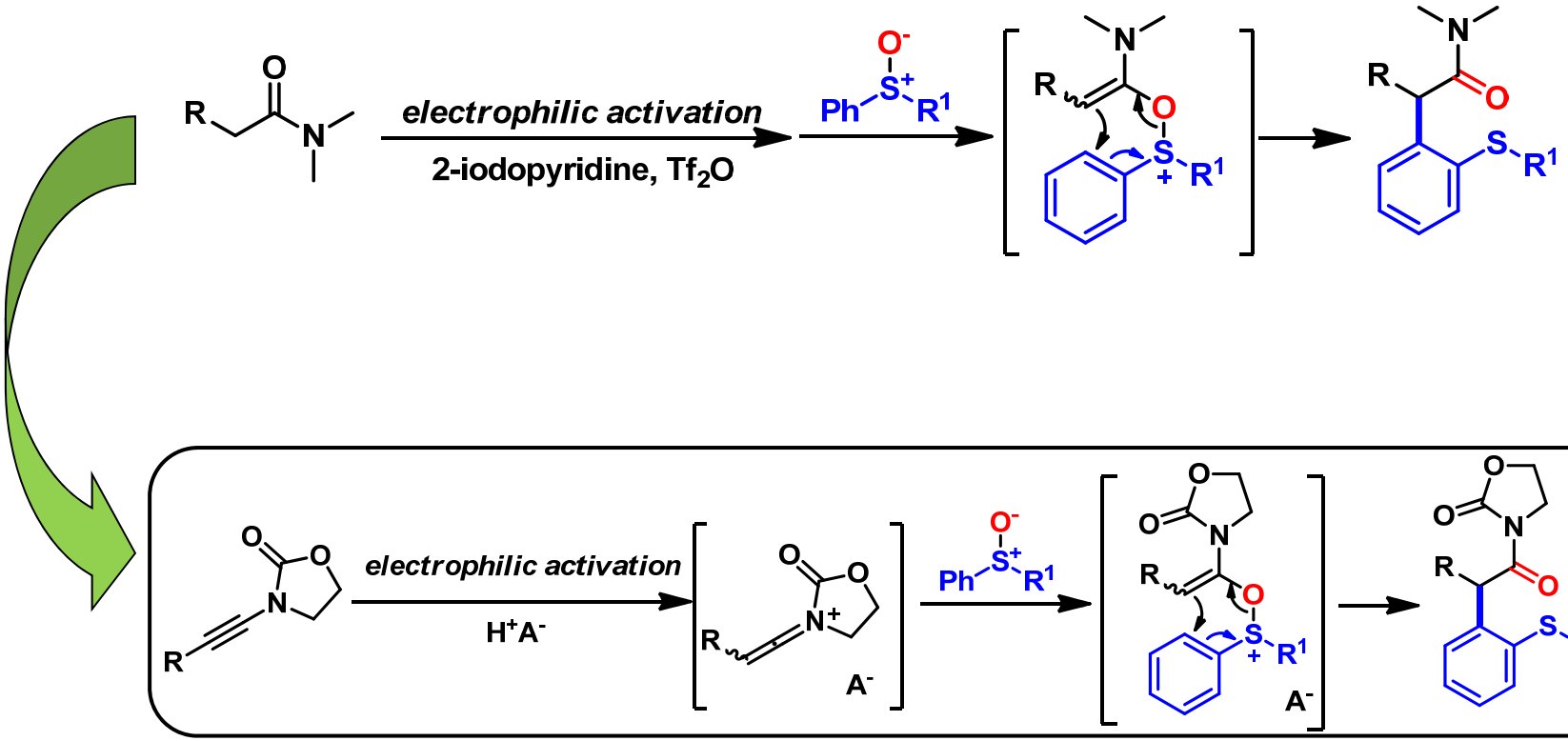

## Part 2. Development of Asymmetric α-Allylation



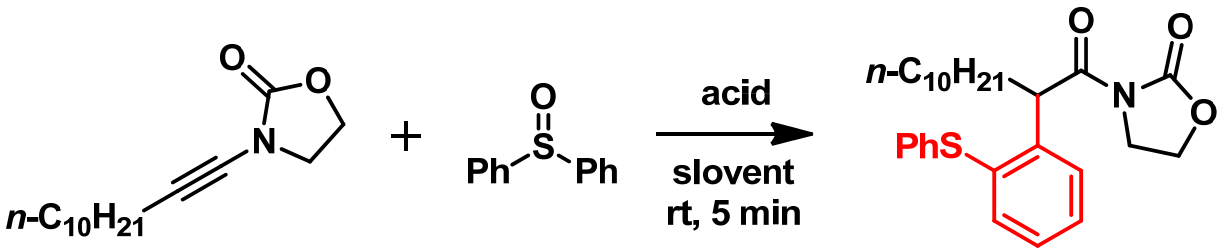

## Part 3. Development of A Brønsted Acid-Catalyzed Redox Arylation



***Previous work:***



# Part 4. Development of A Brønsted Acid-Catalyzed Redox Arylation



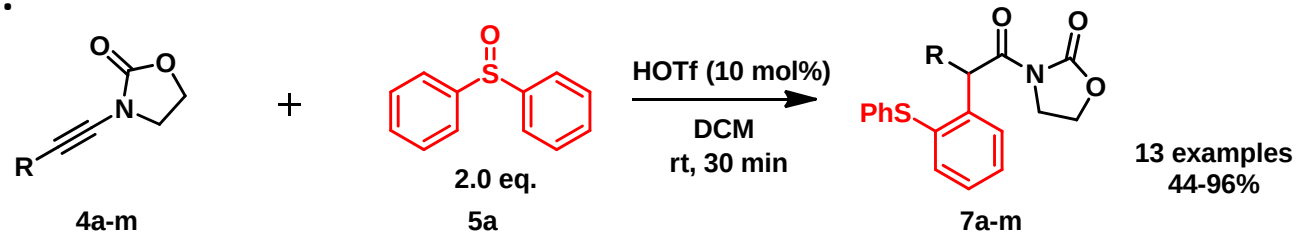

4a 5a 7a

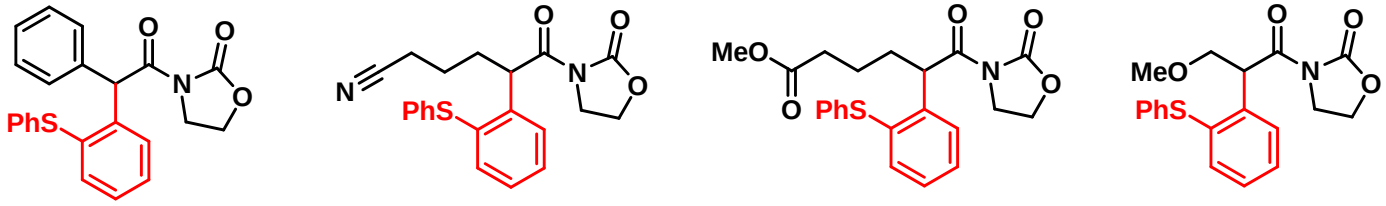
| entry | acid(eq) | amount of nucleophile | solvent | yield |
|---|---|---|---|---|
| 1 | HOTf(1.0 eq) | 1.0 eq | DCM | 89% |
| 2 | TFA(1.0 eq) | 1.0 eq | DCM | NR |
| 3 | HOTf(0.2 eq) | 1.0 eq | DCM | 90% |
| 4 | HOTf(1.0 eq) | 2.0 eq | DCM | > 95% |
| 5 | HOTf(1.0 eq) | 1.0 eq | toluene | 74% |
| 6 | HOTf(0.1 eq) | 2.0 eq | DCM | > 95% |

# Part 4. Development of A Brønsted Acid-Catalyzed Redox Arylation

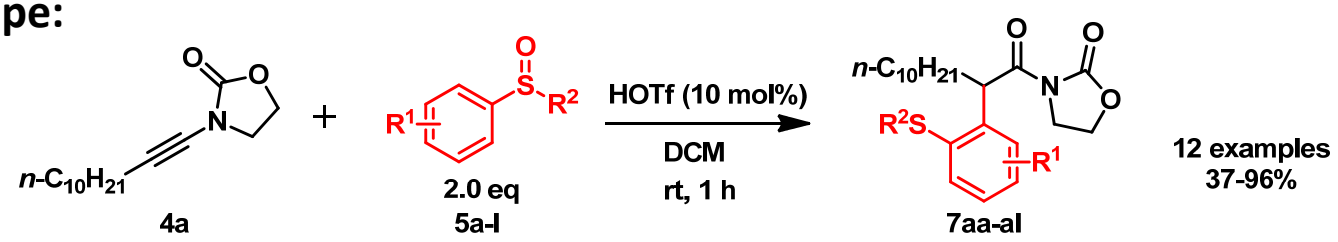
**With Huang and Xie**

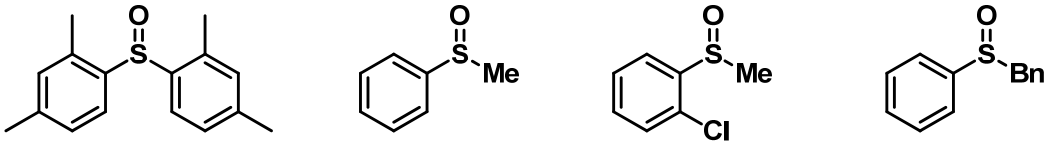
## Substrate scope:



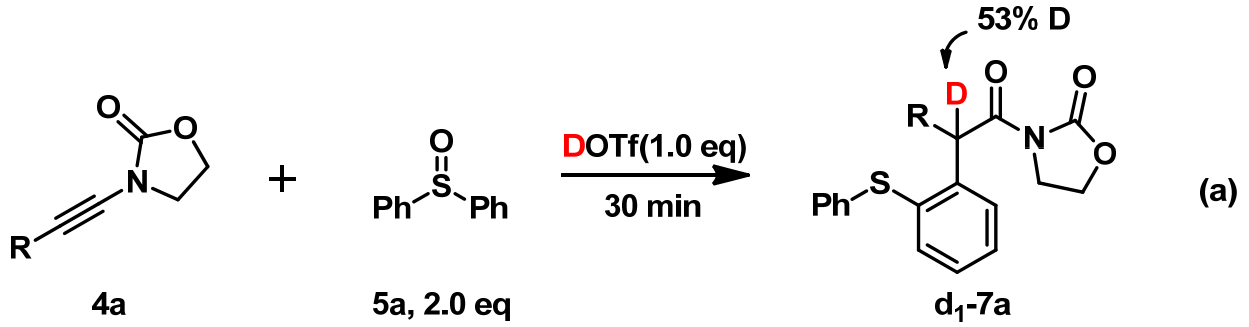

## Nucleophile scope:

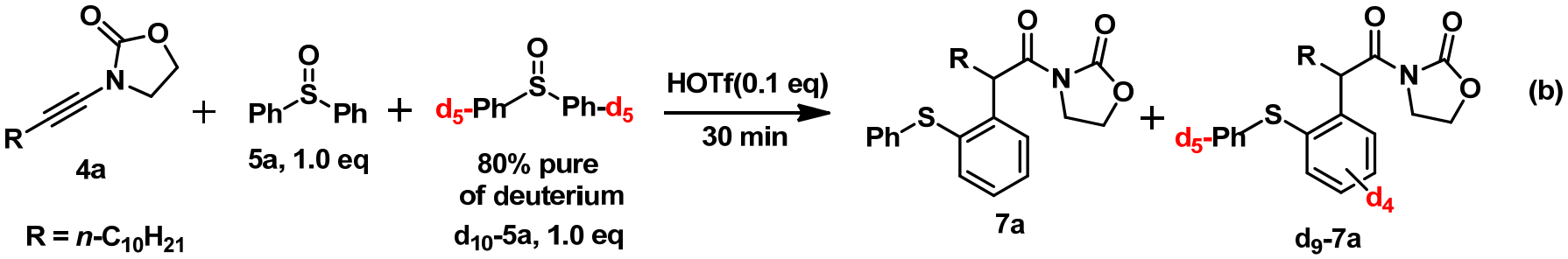


**With Huang and Xie**

**labelling experiments:**

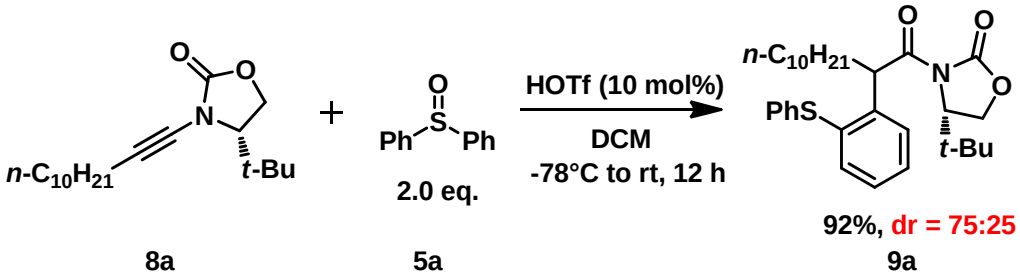



7a : $d_9$-7a = 63 : 37

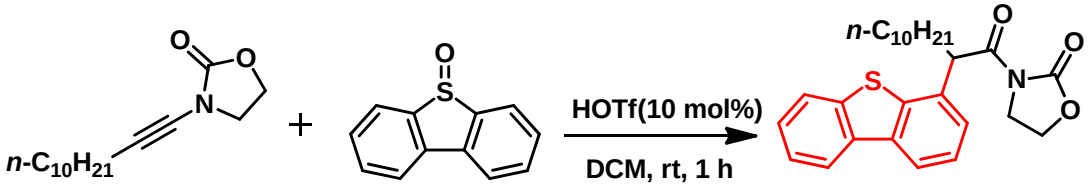
**With Huang and Xie**

## Asymmetric arylation reaction



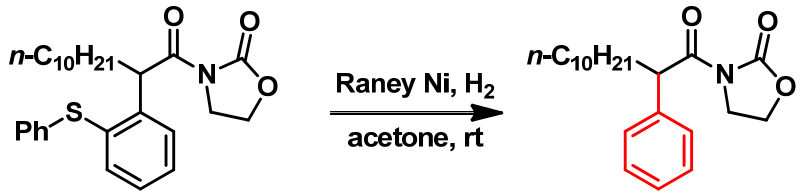

8a 5a 9a

## Synthesis of a dibenzothiophene:



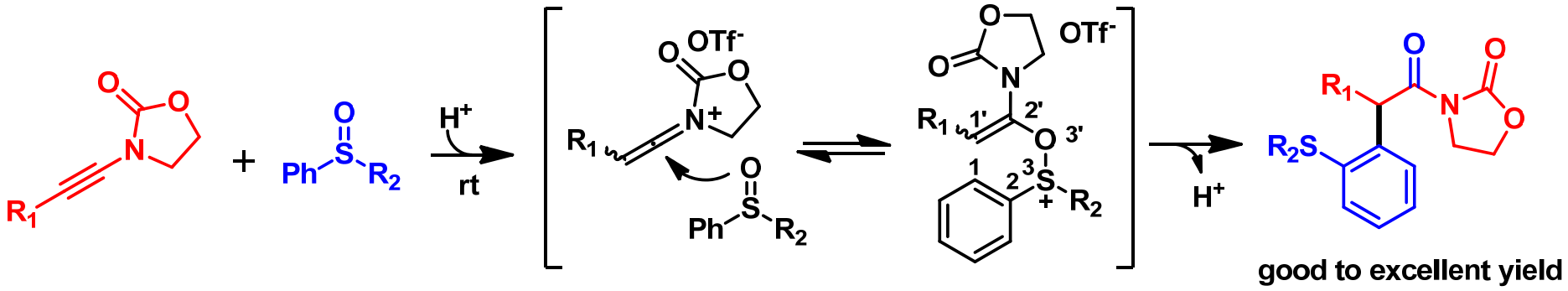

4a 5n 7an, 72%

## Elaboration of products:




7a 10, 89%

# summary



# Acknowledgements

Prof. Ming Bao

Prof. Nuno Maulide