

# Radical-Based Arylation Methods

## Homolytic Aromatic Substitution

**Benjamin Wyler**

**Topic Review in Group Renaud**

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# Radical-Based Arylation Methods

$S_{RN}1$  Reactions

Homolytic  
Aromatic  
Substitution

Reaction of Aryl  
Radicals with  
Acceptors

## Literature

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- > Studer, A.; Bossart, M. in *Radicals in Organic Synthesis*, Vol. 2, eds P. Renaud, M. P. Sibi, Wiley-VCH Verlag GmbH, Weinheim, 2001, 62–80.
- > Vaillard, S. E.; Schulte, B.; Studer, A. in *Modern Arylation Methods*, ed. L. Ackermann, Wiley-VCH Verlag GmbH, Weinheim, 2009, 475–535.
- > Vaillard, S. E.; Studer, A. in *Encyclopedia of Radical in Chemistry, Biology and Materials*, Online, eds C. Chatgililoglu, A. Studer, John Wiley & Sons, Ltd., 2012.
- > Studer, A.; Bossart, M. *Tetrahedron* **2001**, 57, 9649–9667. (*Radical aryl migration reactions*)

# Radical-Based Arylation Methods

**S<sub>RN</sub>1 Reactions**

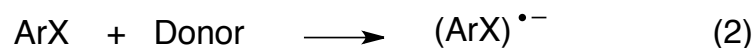
Homolytic  
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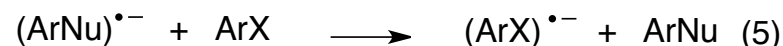
# S<sub>RN</sub>1 Reactions (Unimolecular Radical Nucleophilic Substitution)



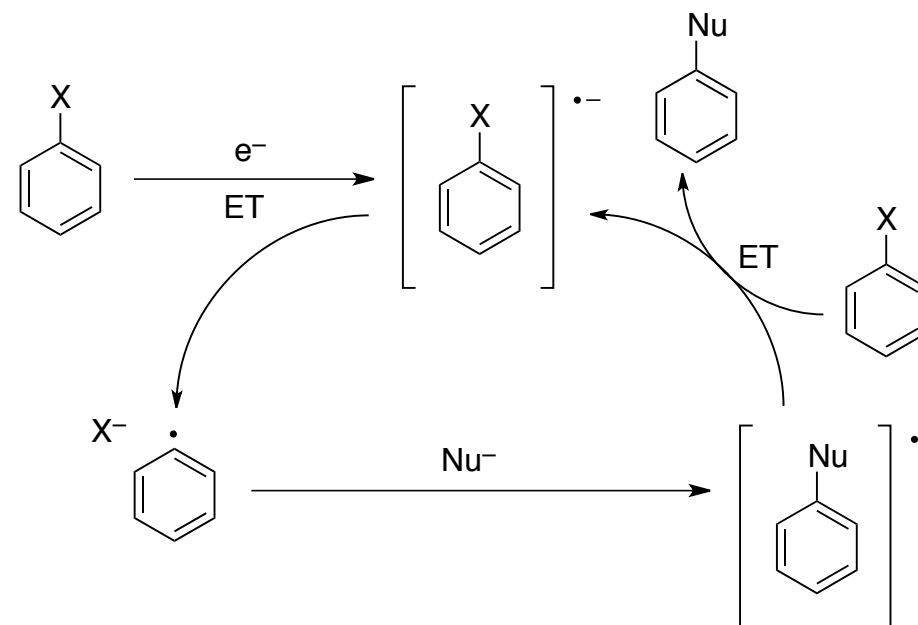
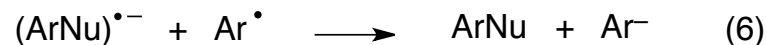
## INITIATION



## PROPAGATION



## TERMINATION



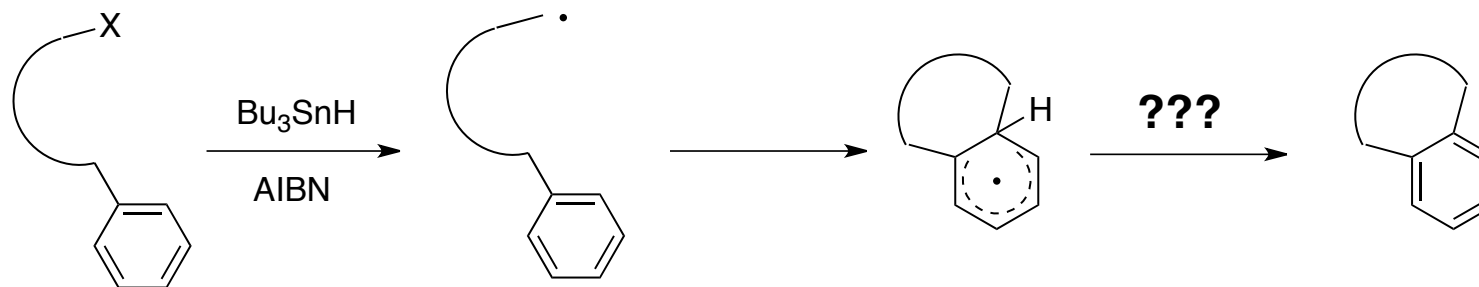
# Radical-Based Arylation Methods

$S_{RN}1$  Reactions

**Homolytic  
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Reaction of Aryl  
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# Mechanism of the homolytic aromatic substitution reaction with $\text{Bu}_3\text{SnH}$ and AIBN

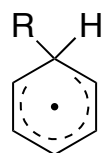
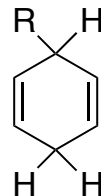
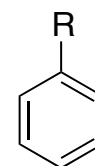


Several different possible mechanisms were proposed by A. K. J. Beckwith, **1995**

- I. Disproportionation or hydrogen-atom transfer from  $\text{Bu}_3\text{SnH}$  followed by oxidation of cyclohexadiene derivatives during work-up
- II. 'pseudo'  $\text{S}_{\text{RN}}1$  mechanism (as proposed by Bowman *et al.* *Tetrahedron* **1991**, 47, 10119)
- III. Oxidation of cyclohexadiene radical by AIBN (suggested by Curran *et al.* *Tetrahedron* **1994**, 50, 7343)

# Mechanism of the homolytic aromatic substitution reaction with $\text{Bu}_3\text{SnH}$ and AIBN

- I. Disproportionation or hydrogen-atom transfer from  $\text{Bu}_3\text{SnH}$  followed by oxidation of cyclohexadiene derivatives during work-up

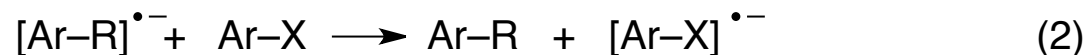
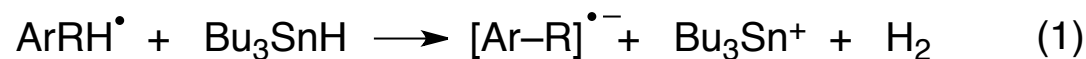
**A****B****C**

- yield higher than 50%
- no D-incorporation when using  $\text{Bu}_3\text{SnD}$
- Oxidation of dihydro-type systems as **B** is not fast in this system

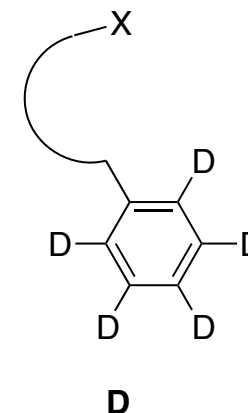


# Mechanism of the homolytic aromatic substitution reaction with Bu<sub>3</sub>SnH and AIBN

## II. 'pseudo S<sub>RN</sub>1' mechanism (as proposed by Bowman *et al.*)

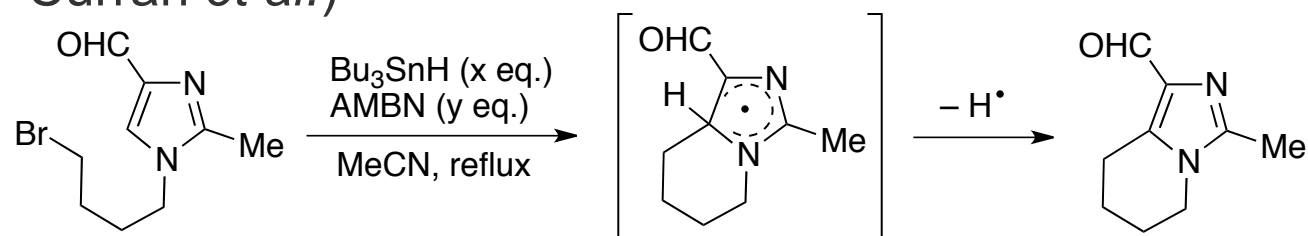


- if equation (1) is involved, with deuterated compound **D** HD should be formed
- no HD detected in mass spectrometry, NMR or Raman spectroscopy

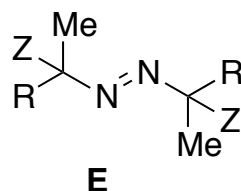


# Mechanism of the homolytic aromatic substitution reaction with Bu<sub>3</sub>SnH and AIBN

## III. Oxidation of cyclohexadiene radical by AIBN (as suggested by Curran *et al.*)



- Bu<sub>3</sub>SnH not regenerated (x = 2.2 to 0.5, y = 1.0) → no hydrogen-atom transfer between Bu<sub>3</sub>Sn• and ArRH•
- Stoichiometric amount of “initiator” needed (x = const., y = various, if y < 1.0 → incomplete)
- in cyclization reactions with 1.1 eq. Bu<sub>3</sub>SnH and 1.3 eq. of AIBN, only 0.3 eq. N<sub>2</sub> was detected



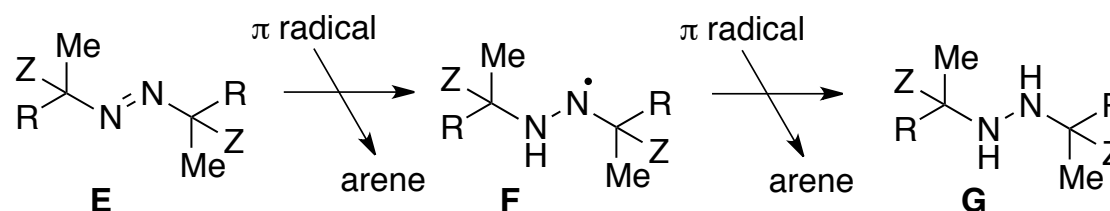
AIBN: R = Me, Z = CN

AMBN: R = Et, Z = CN

AIBMe: R = Me, Z = CO<sub>2</sub>Me

# Mechanism of the homolytic aromatic substitution reaction with Bu<sub>3</sub>SnH and AIBN

## III. Oxidation of cyclohexadiene radical by AIBN (as suggested by Curran *et al.*)



- reduced AIBN or AMBN derivatives (**G**) are unstable and decompose
- reduced AIBMe derivative (**G**) was recently isolated from a Bu<sub>3</sub>SnH-mediated cyclization onto pyrazole

(*Tetrahedron Letters* **2002**, 43, 4191–4193)

AIBN: R = Me, Z = CN
AMBN: R = Et, Z = CN
AIBMe: R = Me, Z = CO <sub>2</sub> Me

# Homolytic Aromatic Substitution

## 1. Intermolecular Substitution

1.1 Aromatic Substitution with Nucleophilic C-centered Radicals

1.2 Aromatic Substitution with Electrophilic C- and N-centered Radicals

1.3 *ipso* Substitution/Aryl Migration

## 2. Intramolecular Substitution

2.1 Aromatic Substitution with Aryl and Nucleophilic C-centered Radicals

2.2 Aromatic Substitution with Electrophilic C-centered Radicals

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## 2. Intramolecular Substitution

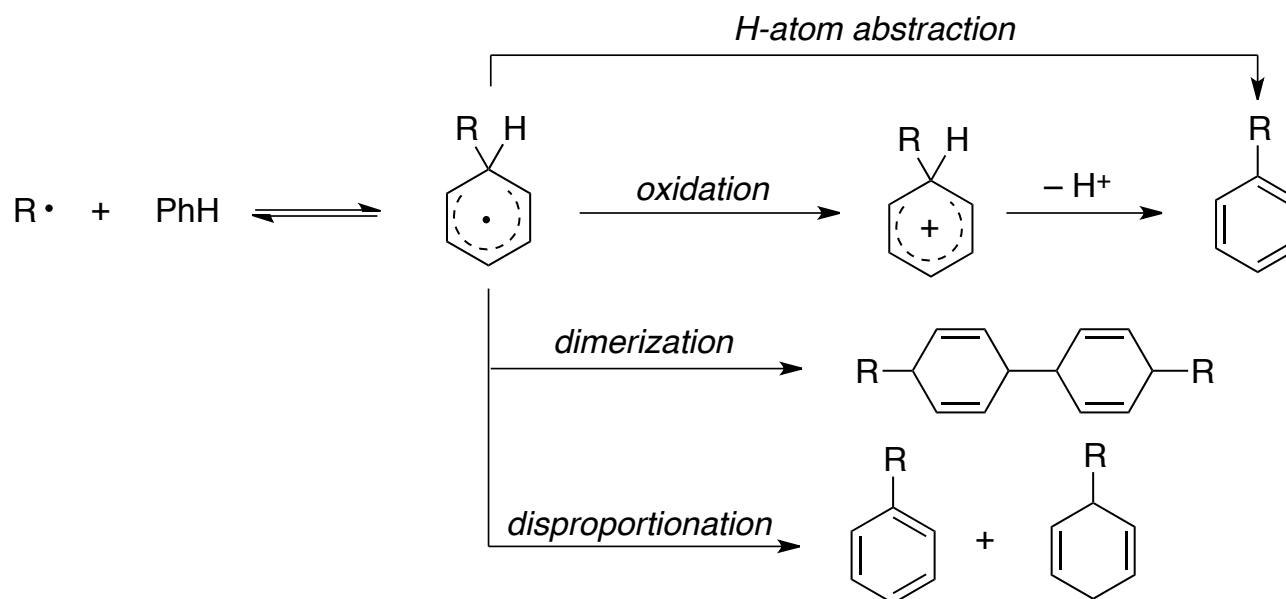
2.1 Aromatic Substitution with Aryl and Nucleophilic C-centered Radicals

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2.3 *ipso* Substitution/Aryl Migration

## Addition to benzene

- > Reaction of an nucleophilic radical with benzene



- > Rate constant for the addition of *n*-butyl radical at 79 °C is  $3.8 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$ . This is far below the rate of an efficient radical reaction  $\rightarrow$  side reactions occurring!

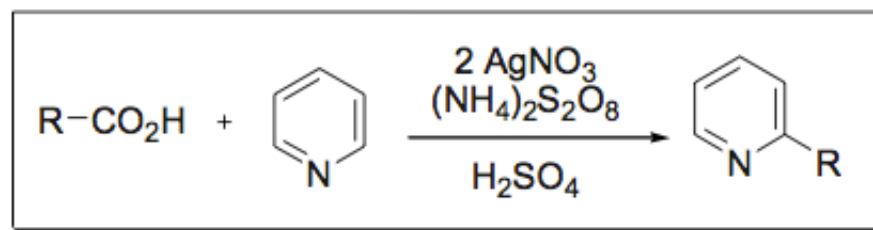
## Regioselectivity of radical addition to substituted benzene derivatives



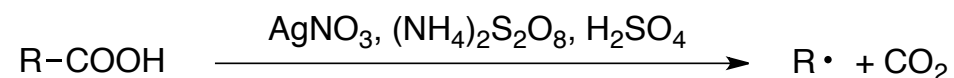
Substituent X	<i>ortho</i>	<i>meta</i>	<i>para</i>
OMe	38.0	31.0	31.0
Cl	0	66.8	33.2
CO <sub>2</sub> Me	0	4.5	95.5
CN	7.4	4.7	87.9

- > (Regioselective) substitution of nucleophilic C-centered radicals only efficient on electron-poor benzene derivatives
- > Not synthetically useful

## Minisci reaction (1970ies)



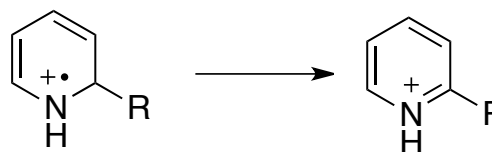
- I. Oxidative Decarboxylation with silver(I)salt and oxidizing reagent



- II. Nucleophilic attack onto protonated arene

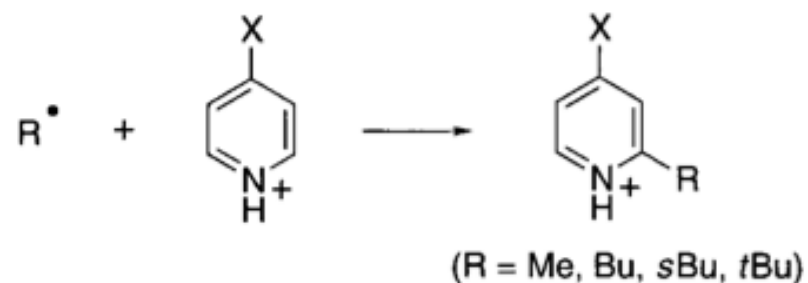


- III. Oxidation/Rearomatization





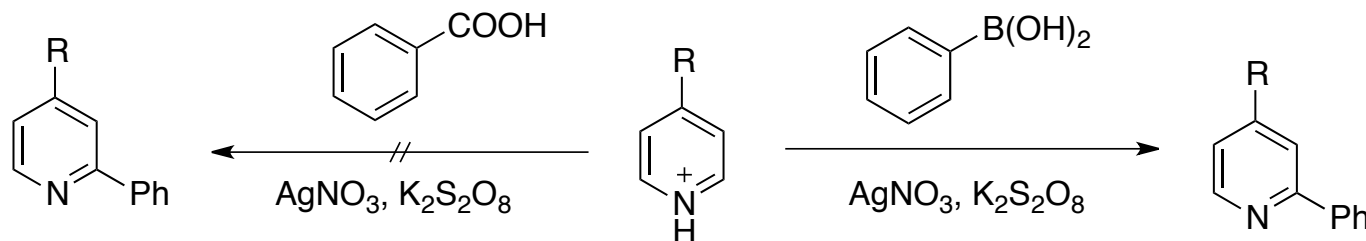
## Relative rates of Minisci reaction



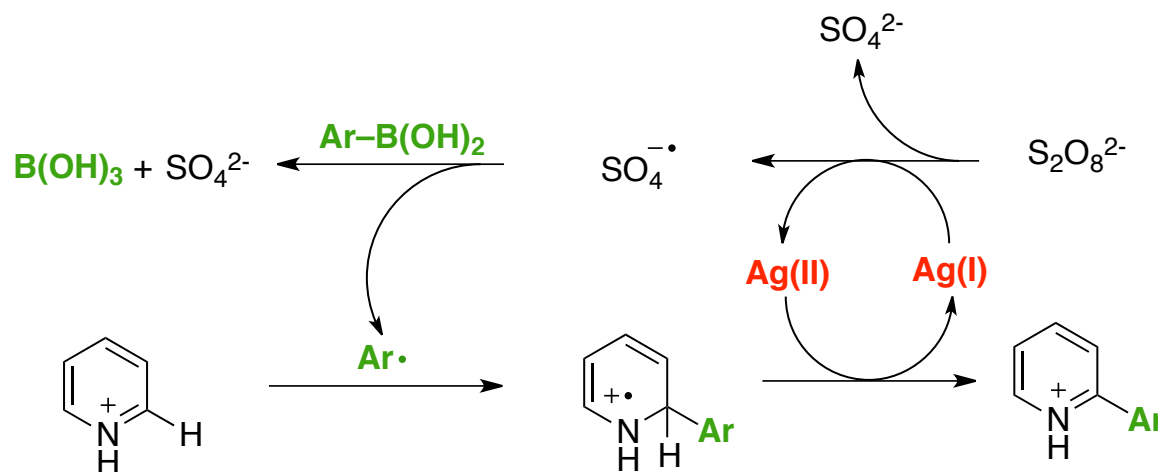
X	Me <sup>•</sup>	Bu <sup>•</sup>	sBu <sup>•</sup>	tBu <sup>•</sup>
CN	12.5	20.3	259.0	1890
COMe	3.6	5.6	55.6	144
Cl	2.4	–	–	11.1
H	1	1	1	1
Me	0.5	0.3	0.3	0.15
OMe	0.3	0.1	0.02	0.005

- > Electron-rich radical (R<sup>•</sup>) and Electron-poor arene
- > <sup>•</sup>CH<sub>2</sub>CN do not react with protonated pyridines

## Borono-Minisci reaction

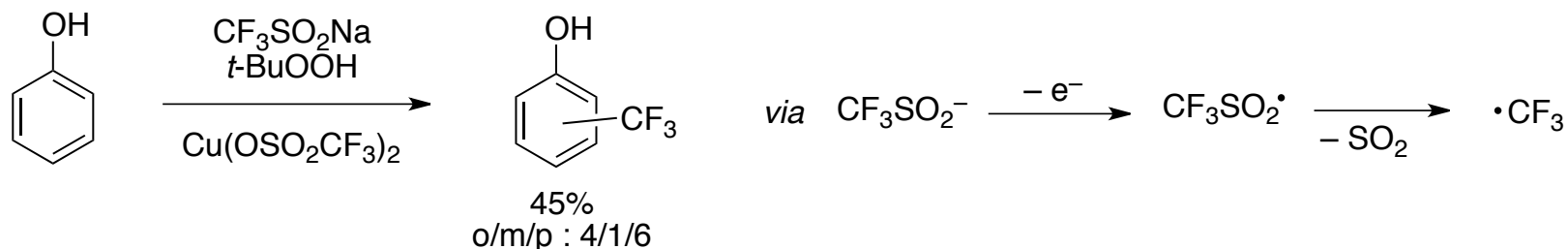


R = *t*-Bu  
 62% + 23% rsm

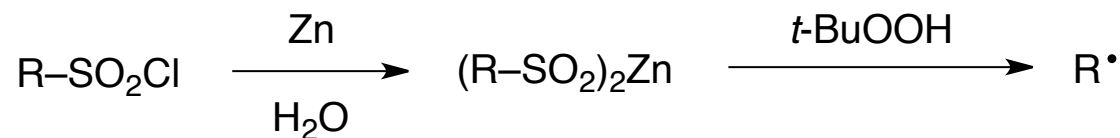


## Zinc sulphinate salts as radical precursors for Minisci-type reaction

- > Sodium sulphinate salts by Langlois and coworkers, 1991

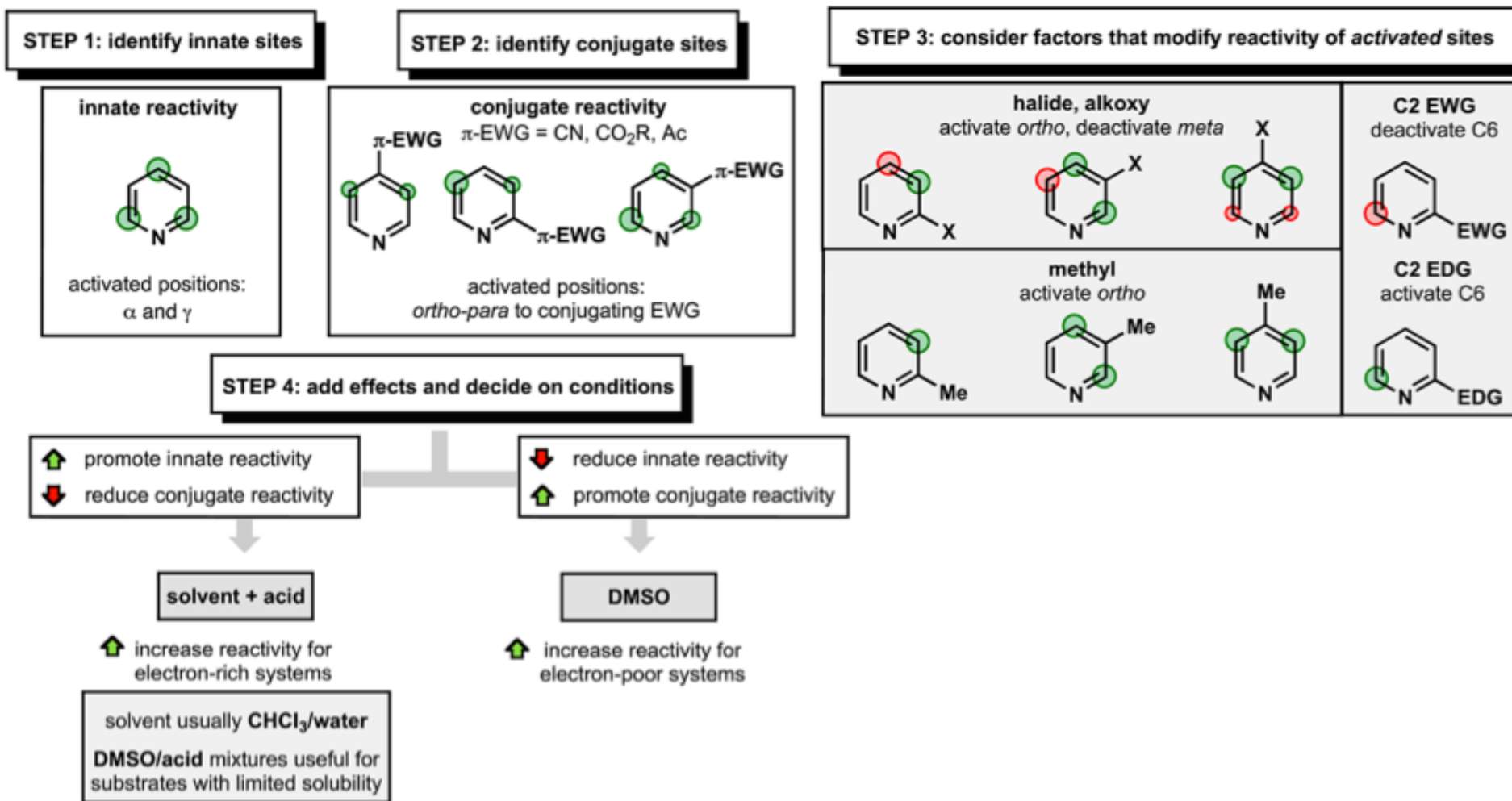


- > Zinc sulphinate salts by Baran and coworkers, 2012

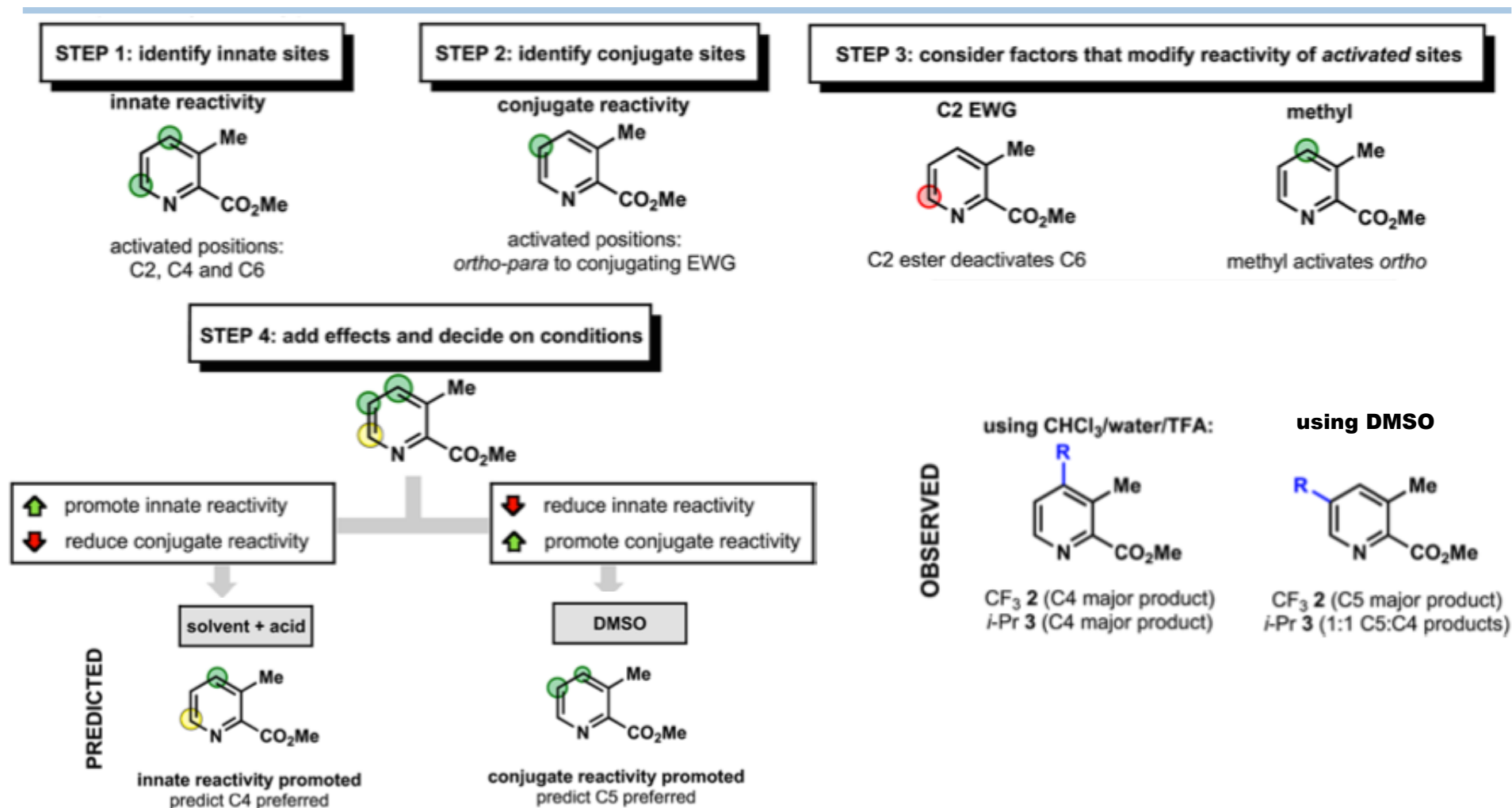


R group	Acronym	Amount prepared	Sigma-Aldrich catalogue number
-CF <sub>3</sub> (X-ray)	TFMS (A)	>500 g	L510106
-CF <sub>2</sub> H (X-ray)	DFMS (B)	>500 g	L510084
-CH <sub>2</sub> CF <sub>3</sub>	TFES (C)	>100 g	L511234
-CH <sub>2</sub> F	MFMS (D)	37 g	—
-CH(CH <sub>3</sub> ) <sub>2</sub>	IPS (E)	>200 g	L511161
-(CH <sub>2</sub> CH <sub>2</sub> O) <sub>3</sub> CH <sub>3</sub>	TEGS (F)	20 g	—

# Radical-based regioselective C–H functionalization of electron-deficient heteroarenes

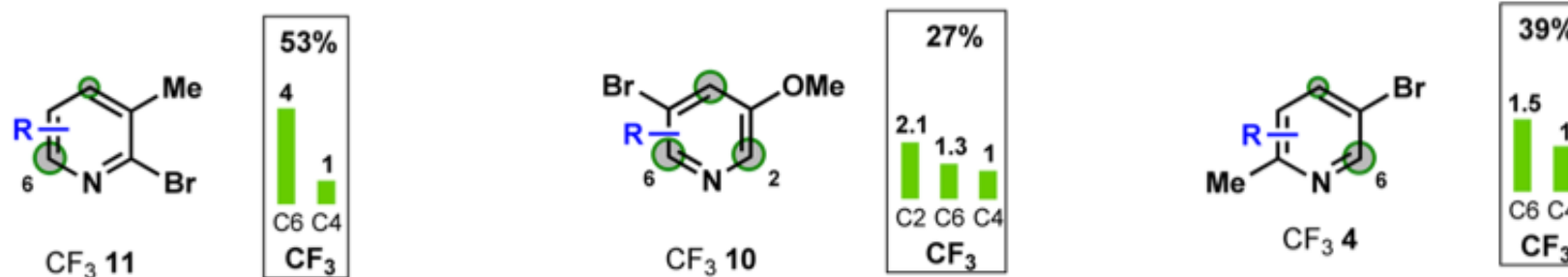


# Radical-based regioselective C–H functionalization of electron-deficient heteroarenes

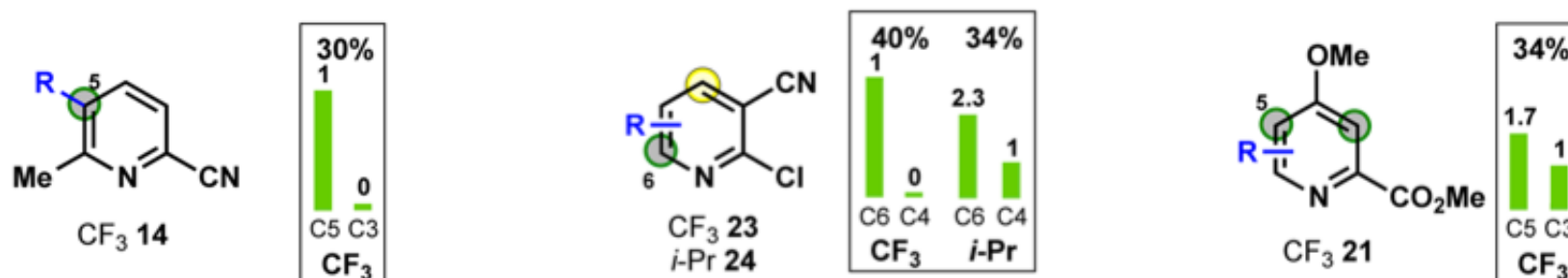


# Radical-based regioselective C–H functionalization of electron-deficient heteroarenes

- > Predictable selectivity in CHCl<sub>3</sub>/H<sub>2</sub>O or CHCl<sub>3</sub>/H<sub>2</sub>O/TFA; innate reactivity dominates

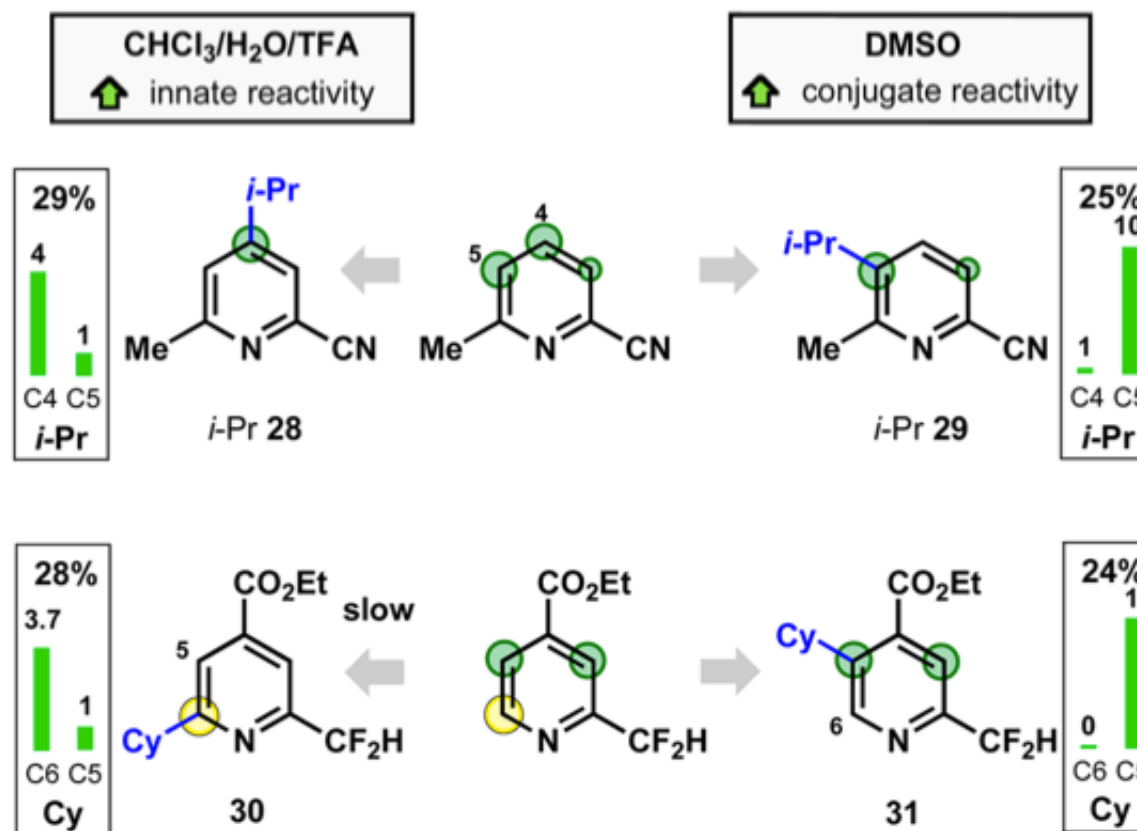


- > Predictable selectivity in DMSO; conjugate reactivity dominates

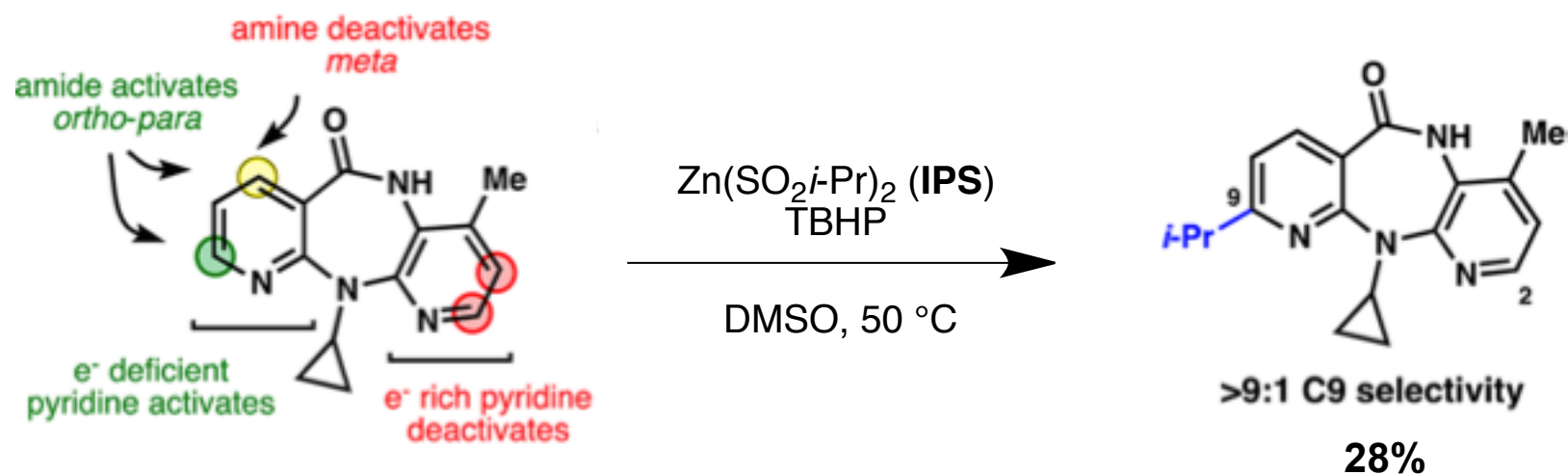


# Radical-based regioselective C–H functionalization of electron-deficient heteroarenes

- > Tuning regioselectivity with solvent choice



# Radical-based regioselective C–H functionalization of electron-deficient heteroarenes



Viramune<sup>®</sup>, Nevirapine  
by Boehringer Ingelheim



# Homolytic Aromatic Substitution

## 1. Intermolecular Substitution

1.1 Aromatic Substitution with Nucleophilic C-centered Radicals

1.2 Aromatic Substitution with Electrophilic C- and N-centered Radicals

1.3 *ipso* Substitution/Aryl Migration

## 2. Intramolecular Substitution

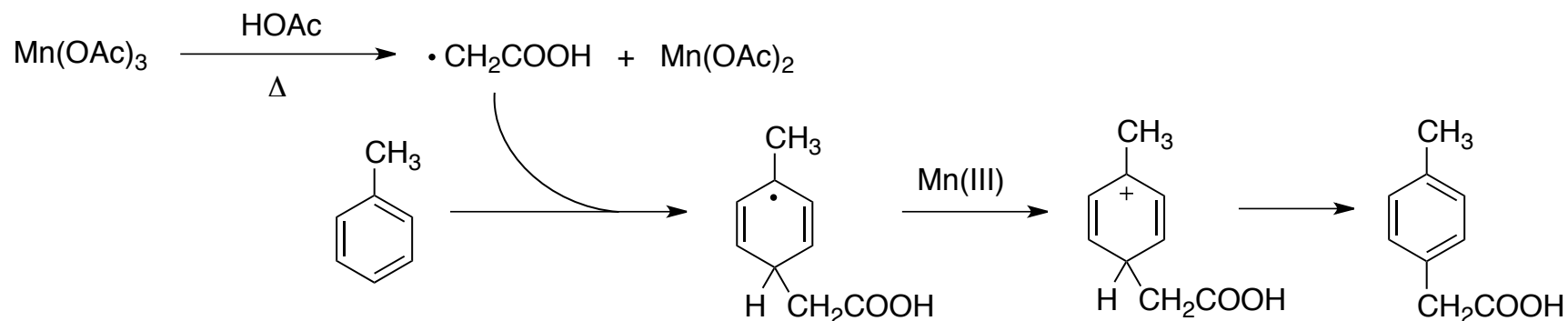
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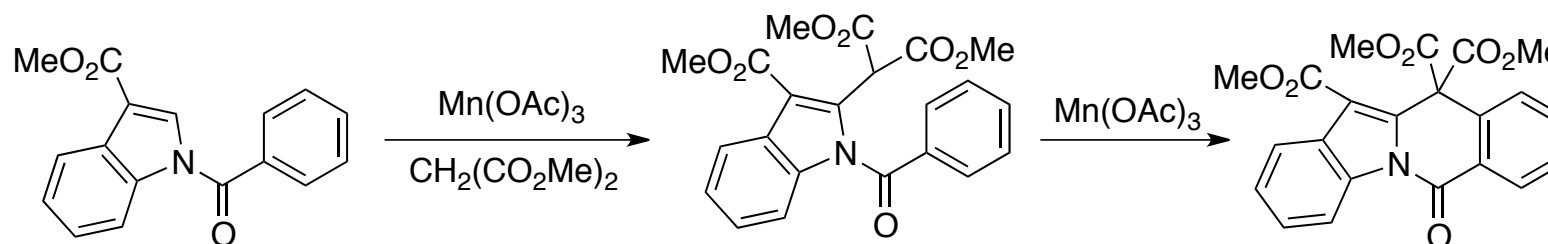
2.3 *ipso* Substitution/Aryl Migration

## Manganese(III)acetate–initiated reaction

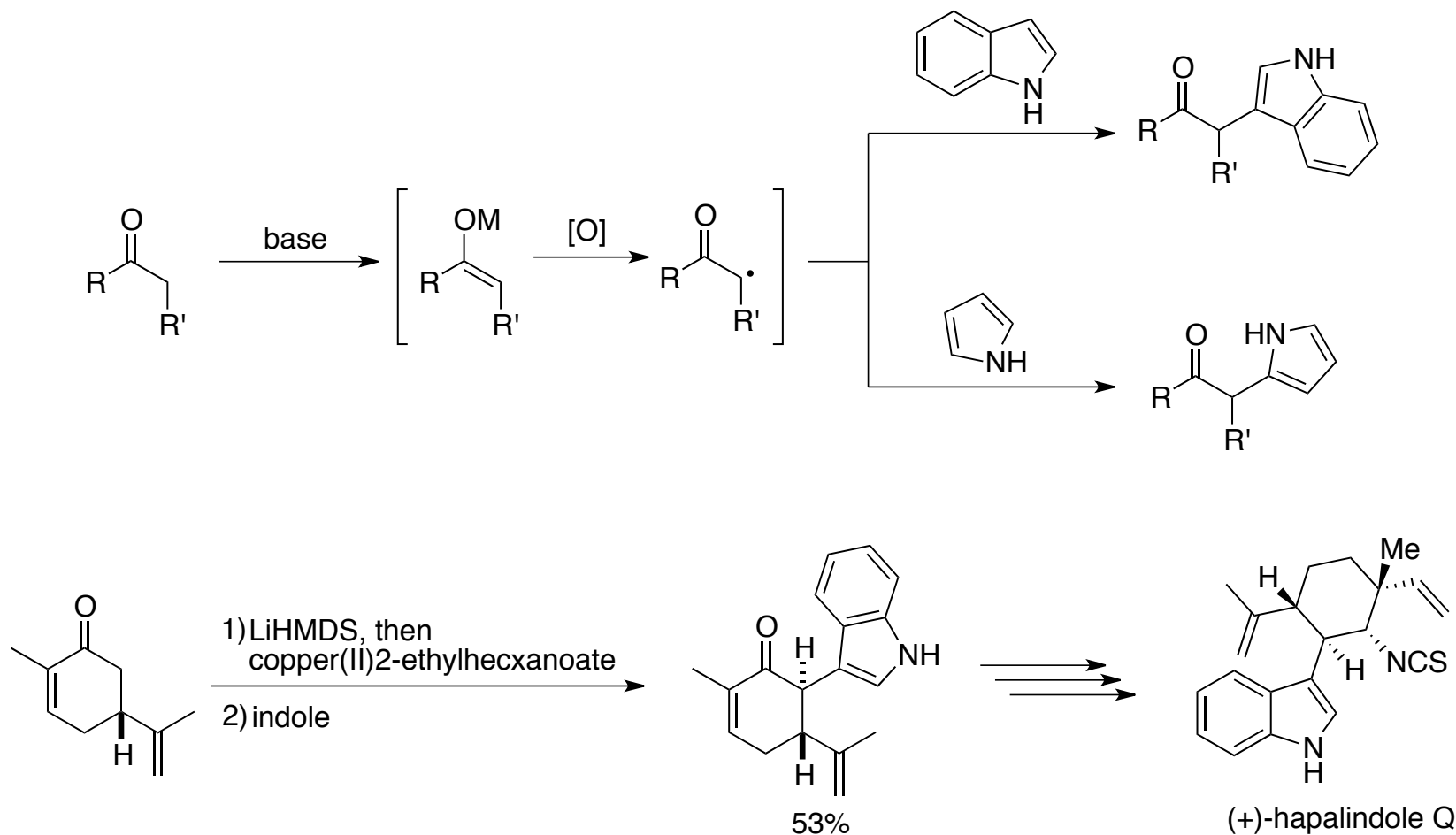
### > Heiba *et al.* 1969



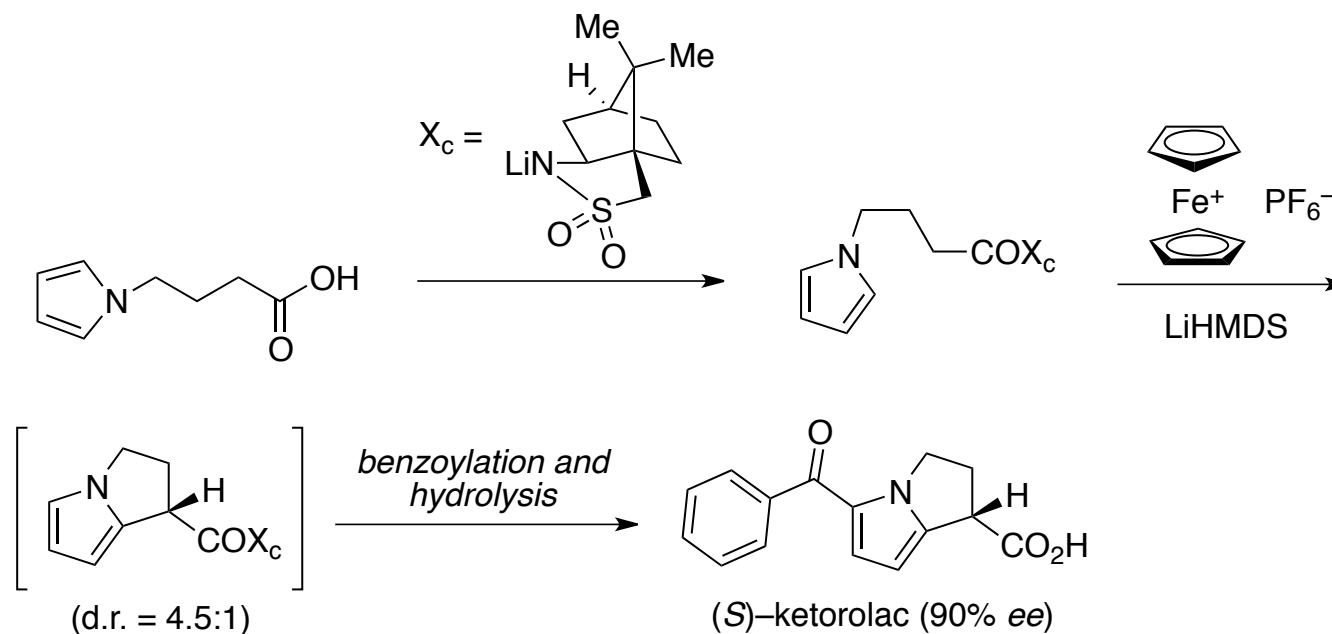
### > Chuang an Wang 1994



# Oxidation of Li-enolates and its application to natural product synthesis



# Direct coupling of pyrroles with carbonyl compounds



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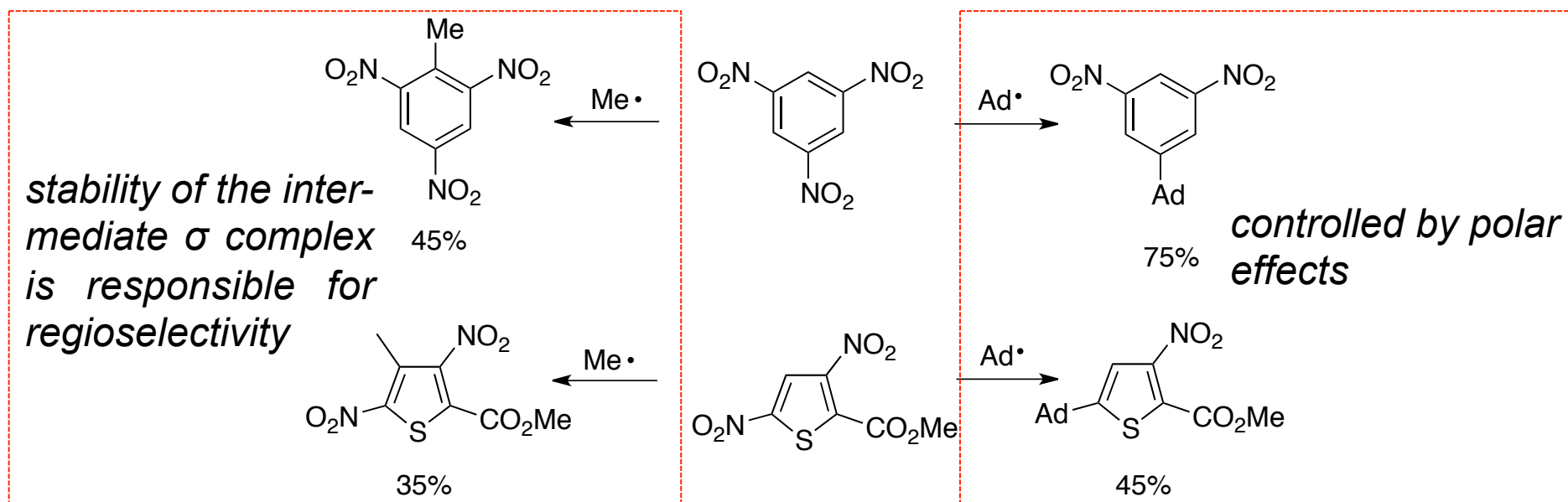
2.2 Aromatic Substitution with Electrophilic C-centered Radicals

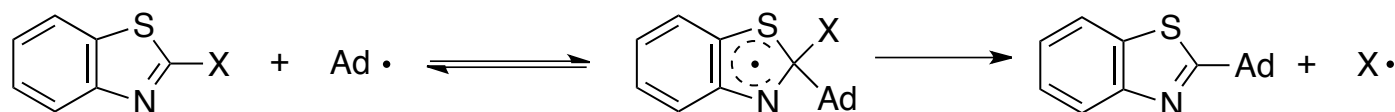
2.3 *ipso* Substitution/Aryl Migration

## Intermolecular *ipso* substitution

### Requirements:

- > most often nucleophilic radicals in combination with electrophilic arenes
- > replacing group should be small to allow *ipso* attack
- > must behave as a good radical leaving group



***ipso* substitution in benzothiazole**

X	conversion (%)	yield (%) <sup>a</sup>
NO <sub>2</sub>	100	95
PhSO <sub>2</sub>	100	80
PhSO	100	80
PhCO	100	55
MeS	50	60
MeO	10	40
Br	50	70

<sup>a</sup> based on reacted SM

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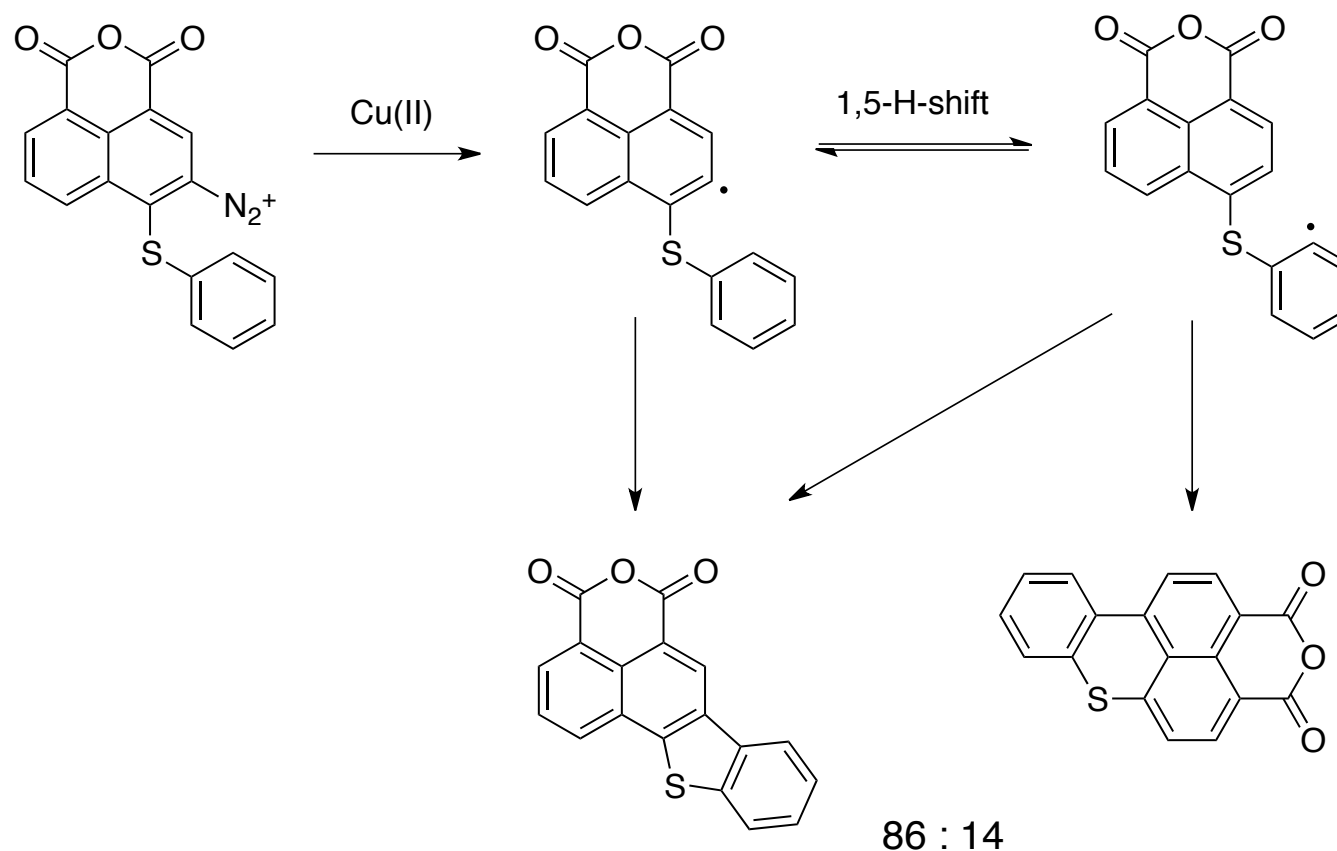
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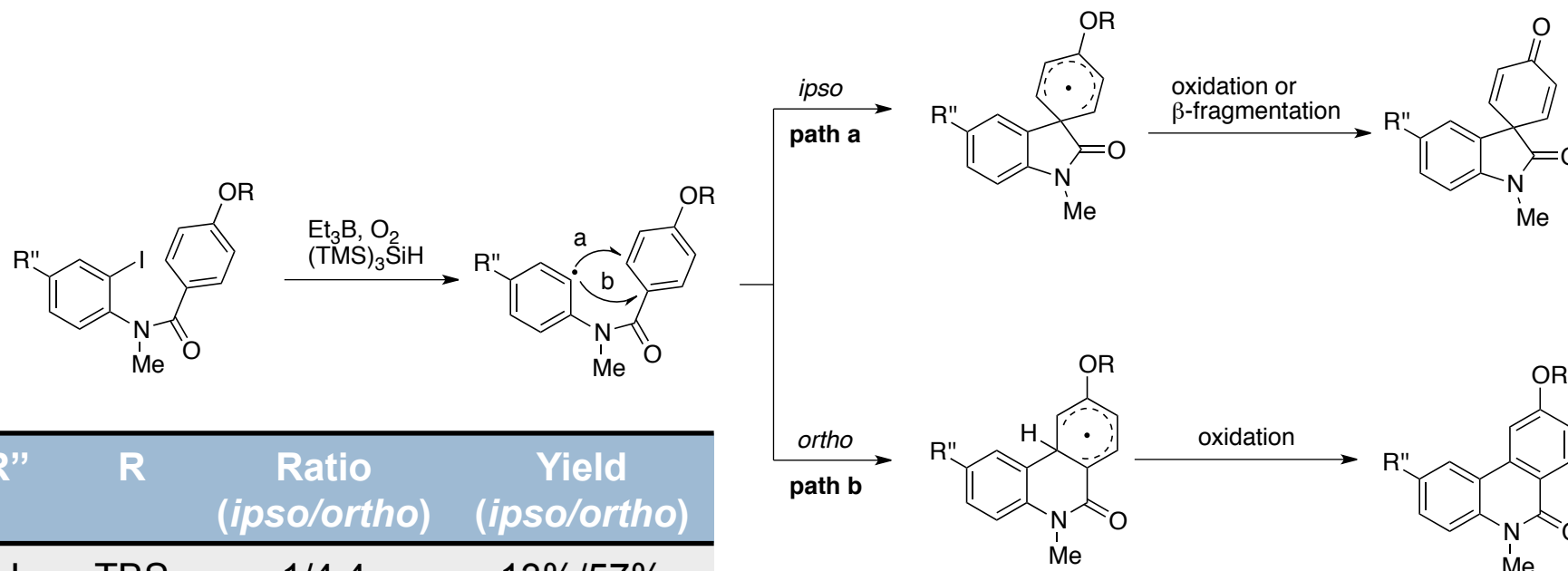


## Pschorr reaction and its application

- > Intramolecular version of Gomberg-Bachmann reaction

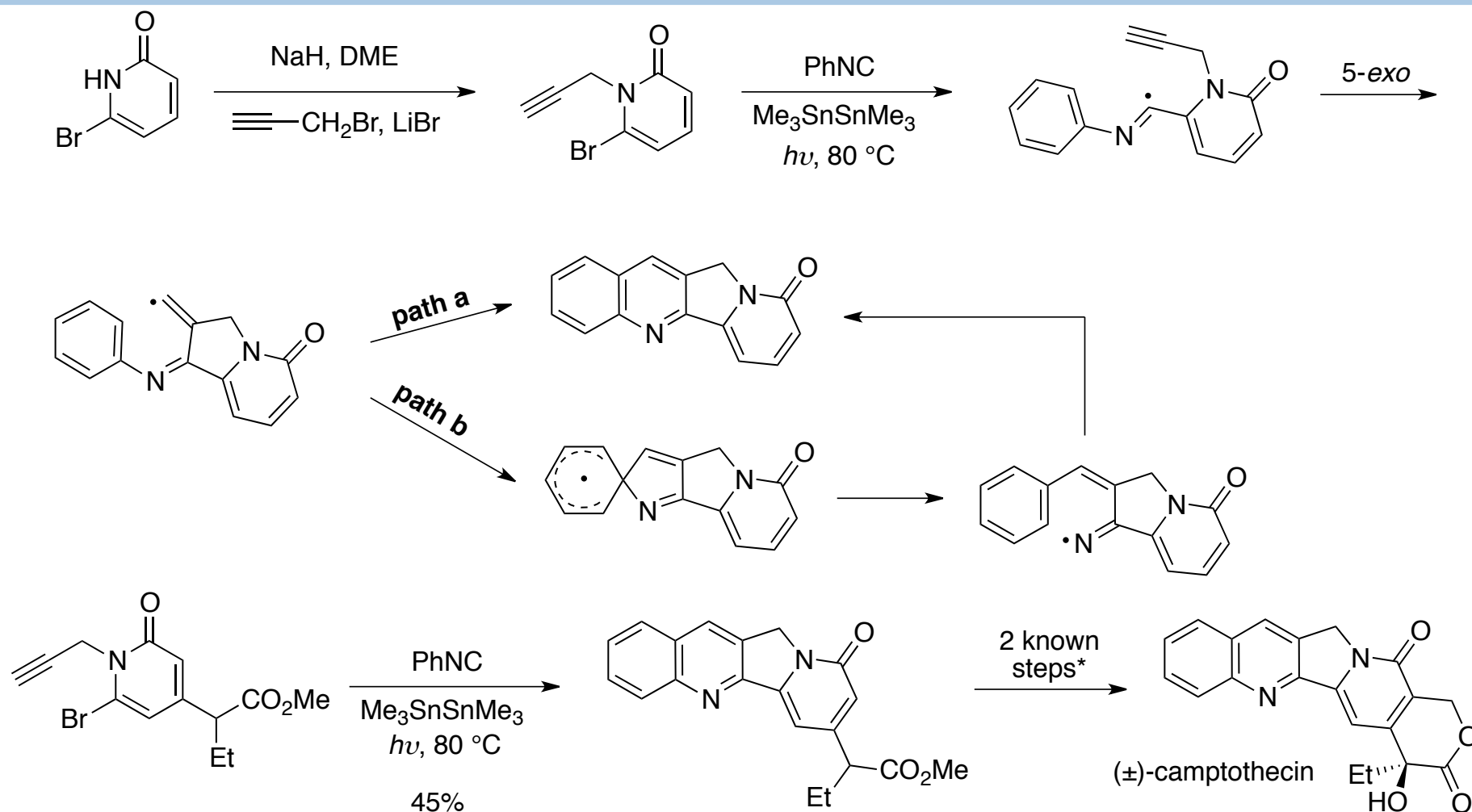


# Radical cyclization approach to spirocyclohexadienones

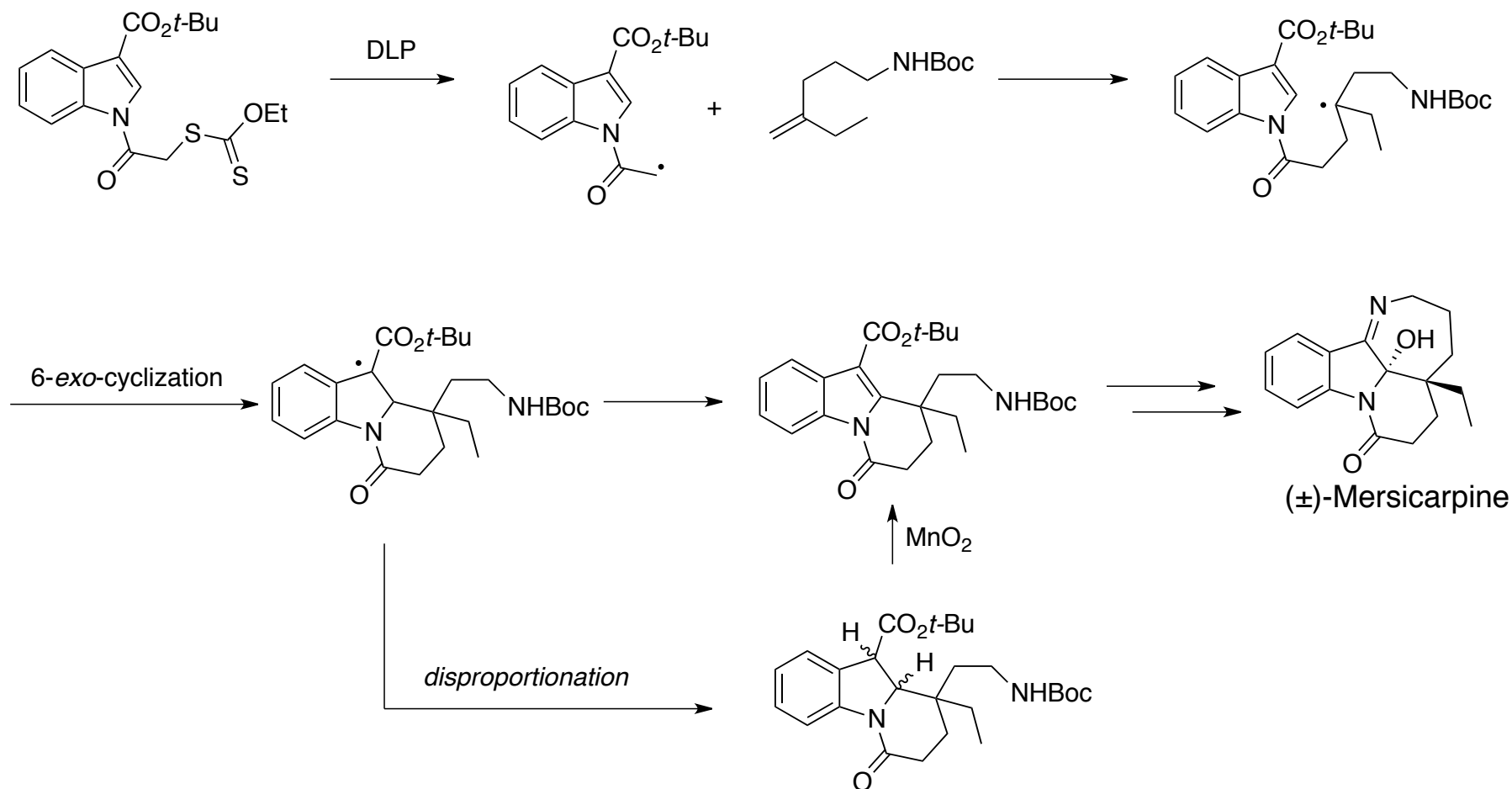


R''	R	Ratio ( <i>ipso</i> / <i>ortho</i> )	Yield ( <i>ipso</i> / <i>ortho</i> )
H	TBS	1/4.4	13%/57%
H	Tr	2.2/1	43%/nd
H	Bz	1.5/1	29%/nd
H	Me	1/2.6	15%/38%
Me	Tr	1/0	53%

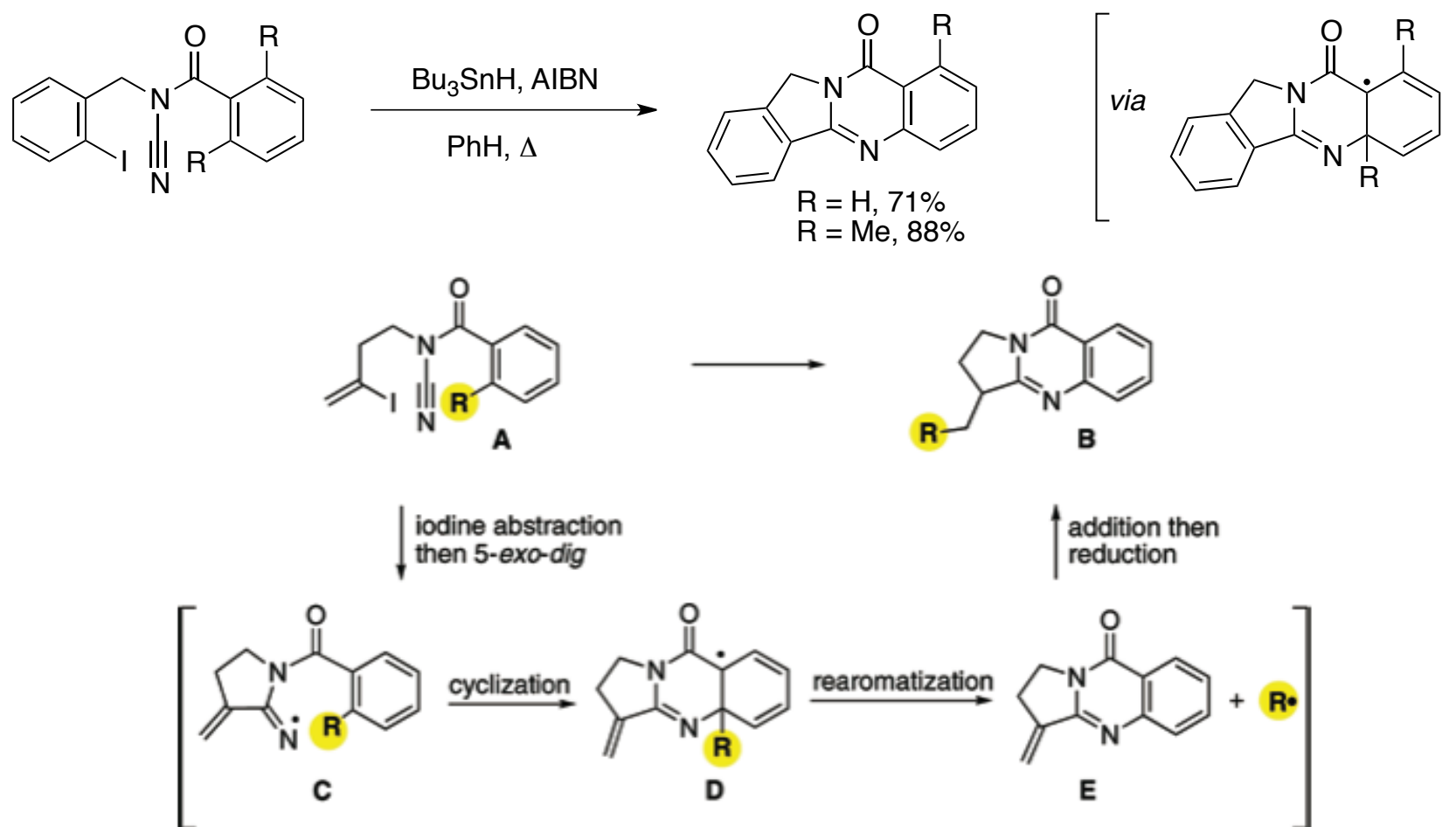
## New 4+1 radical annulations



# A Flexible, Convergent Approach to Polycyclic Indole Structures: Formal Synthesis of (±)-Mersicarpine.



# Radical migration of substituents of aryl groups on quinazolinones derived from *N*-acyl cyanamides



# Radical migration of substituents of aryl groups on quinazolinones derived from *N*-acyl cyanamides

Substrate	Solvent	Product	Yield (%)
	PhH		45
	<i>t</i> -BuOH		47
	PhH		52
	PhH		24
	<i>t</i> -BuOH		55
	PhH		58
	<i>t</i> -BuOH		69

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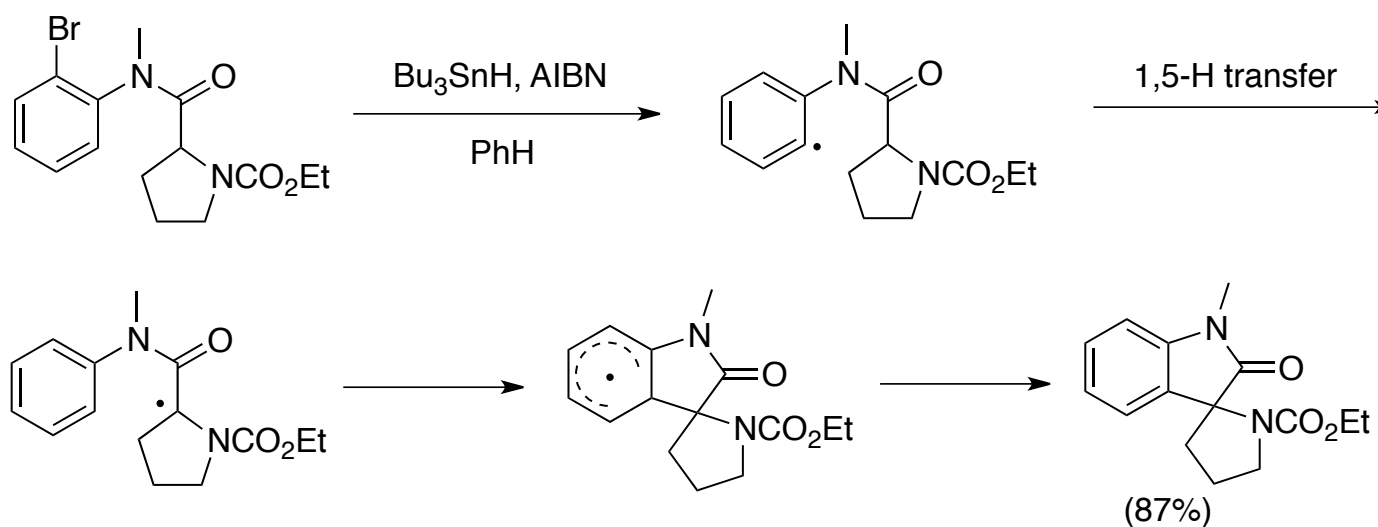
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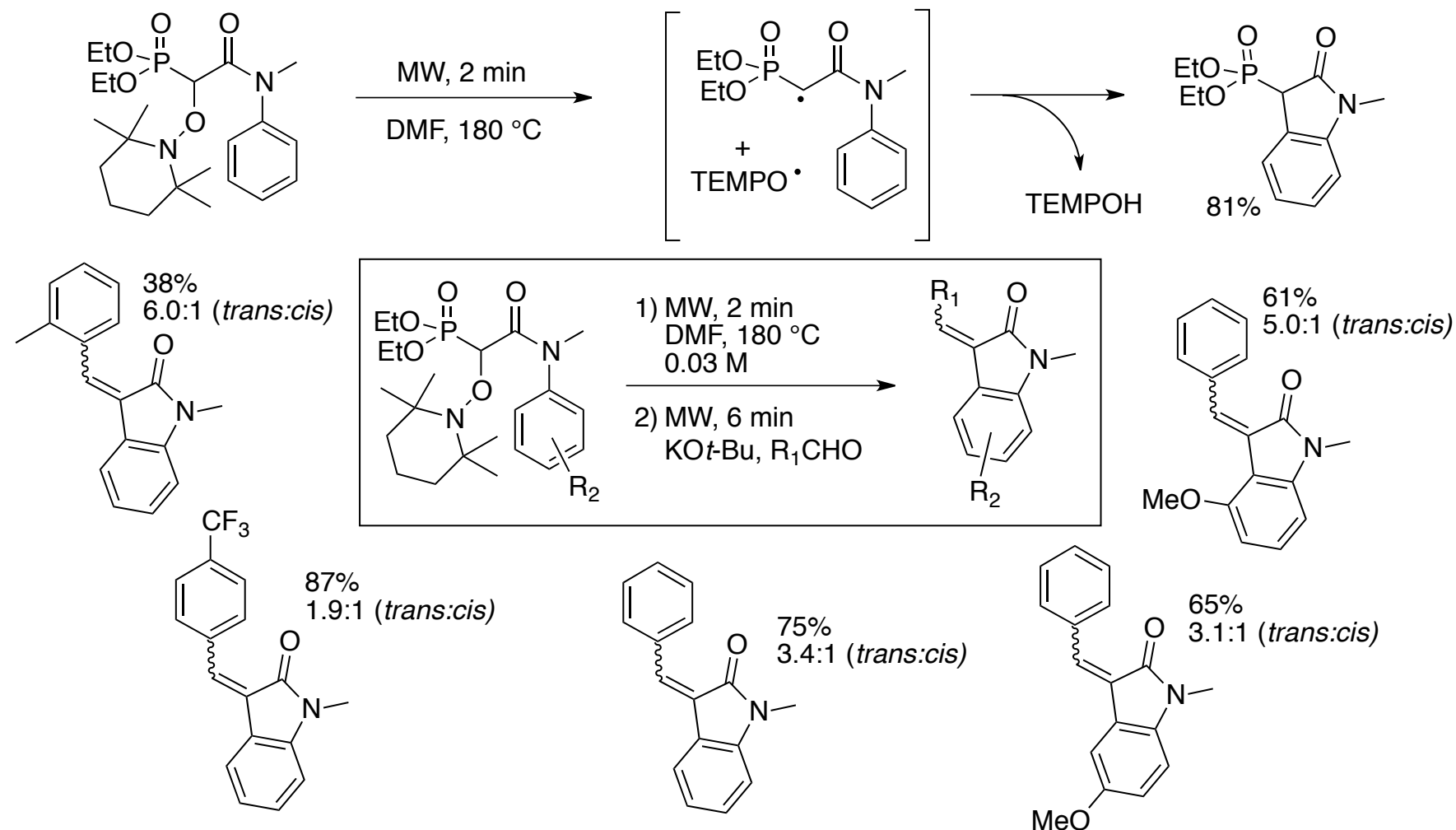
2.3 *ipso* Substitution/Aryl Migration

# Tandem radical translocation and homolytic aromatic substitution





# One-pot homolytic aromatic substitutions/HWE olefinations



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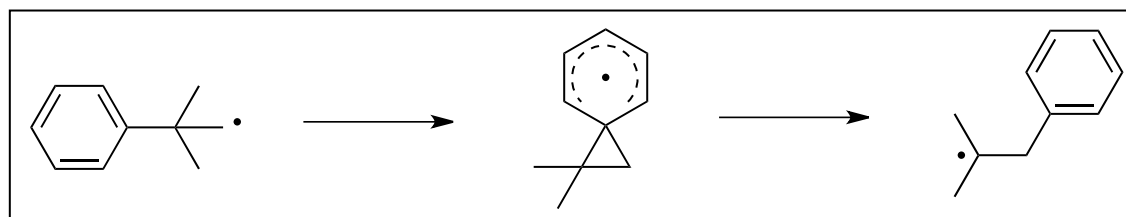
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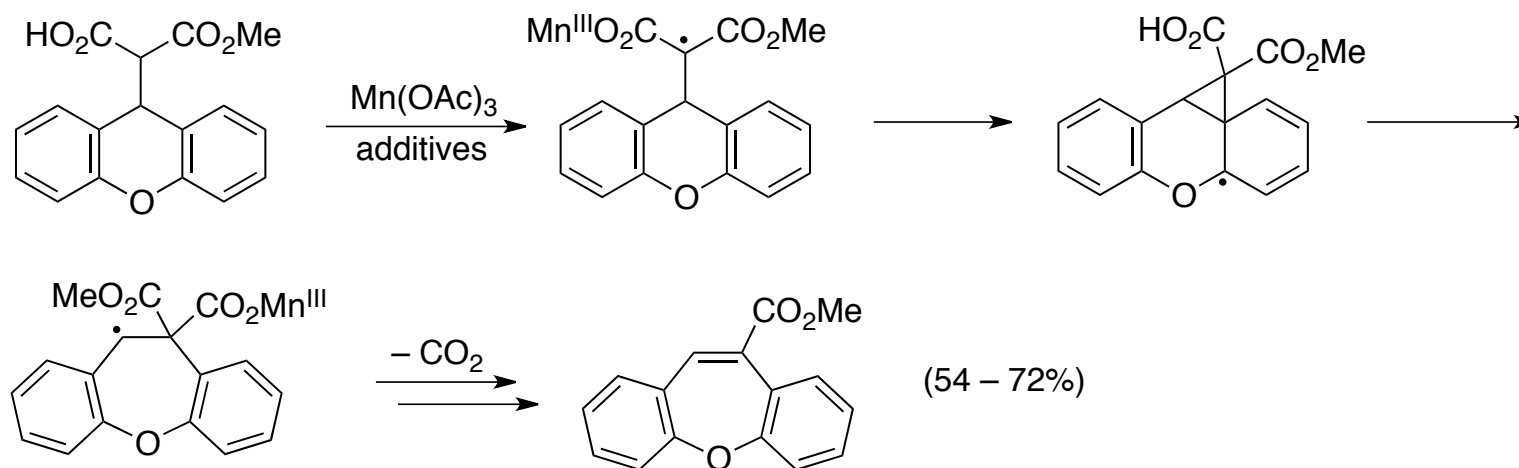
2.2 Aromatic Substitution with Electrophilic C-centered Radicals

2.3 *ipso* Substitution/Aryl Migration

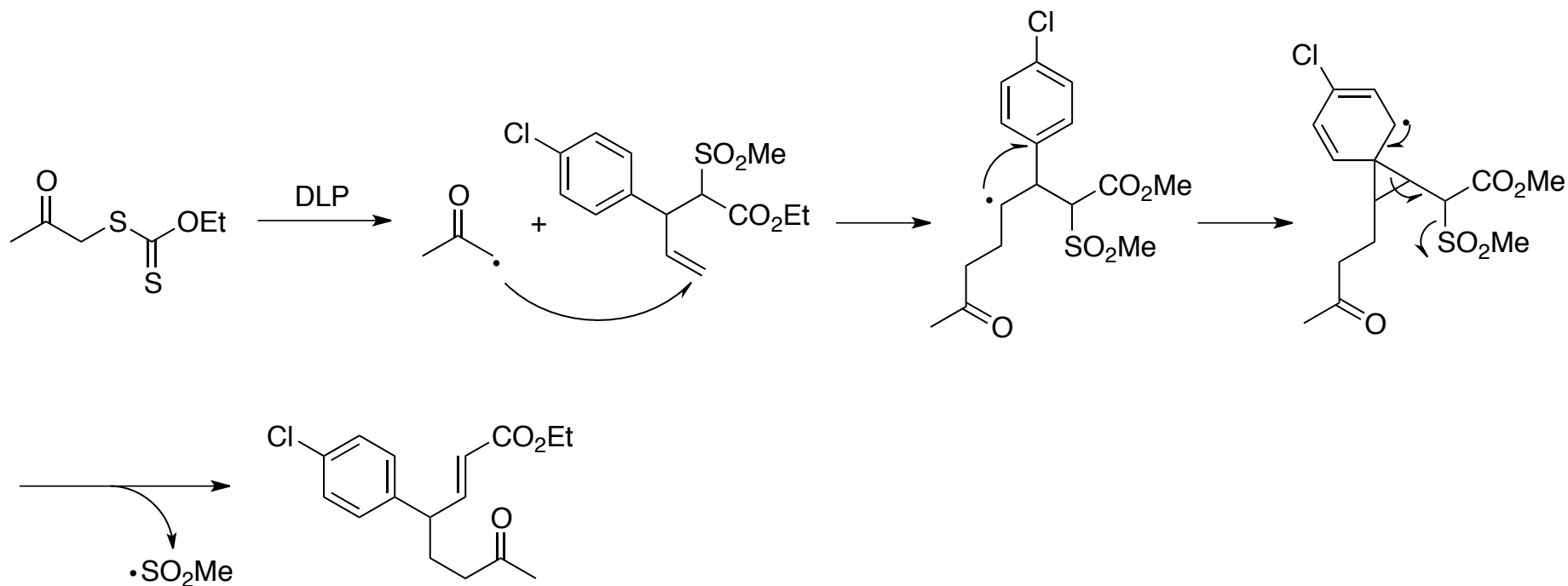
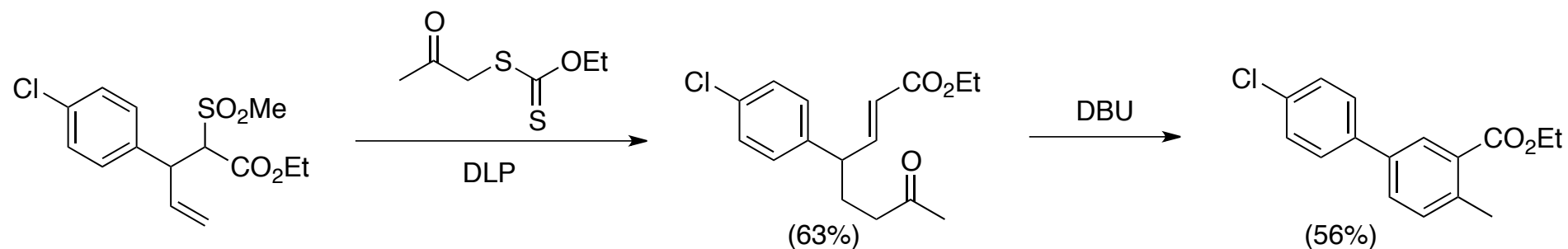
# 1,2-phenyl migration (neophyl rearrangement) to oxepines



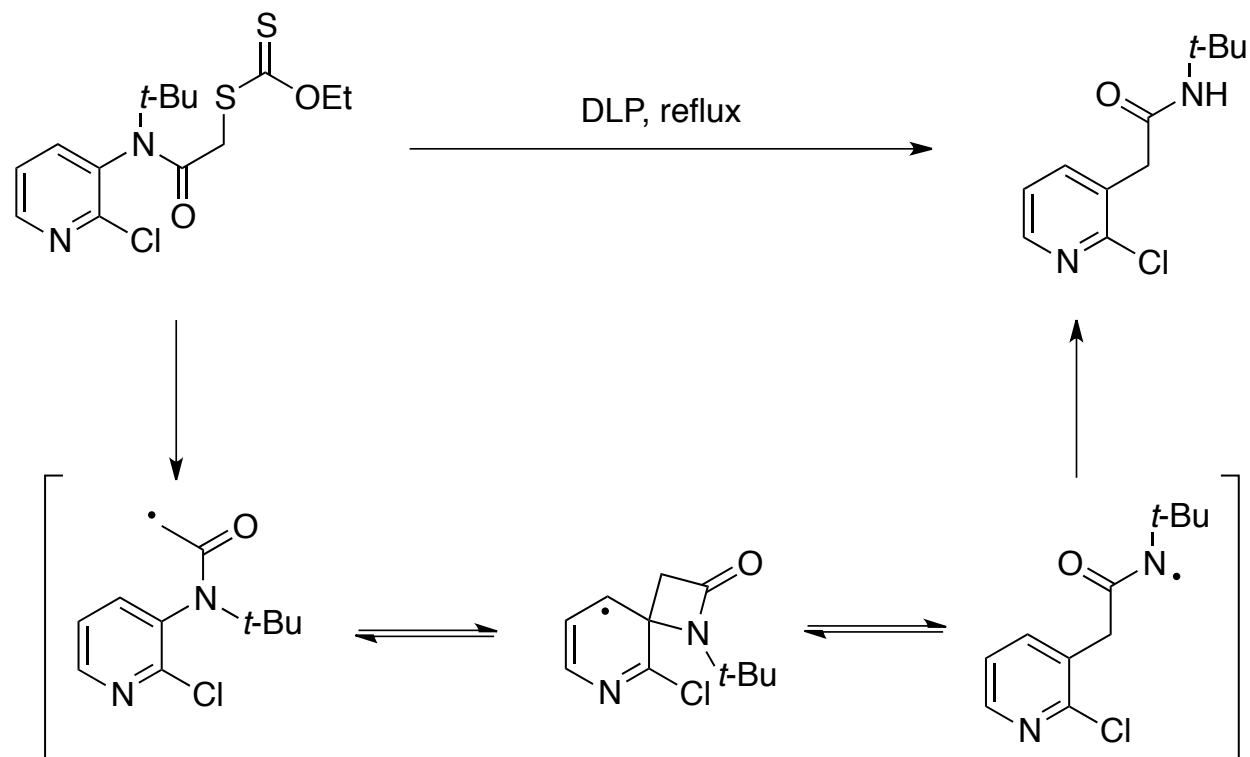
- Neophyl rearrangement is a relatively slow process ( $k = 762 \text{ s}^{-1}$  at  $25 \text{ }^\circ\text{C}$ )  $\rightarrow$  used as radical clock



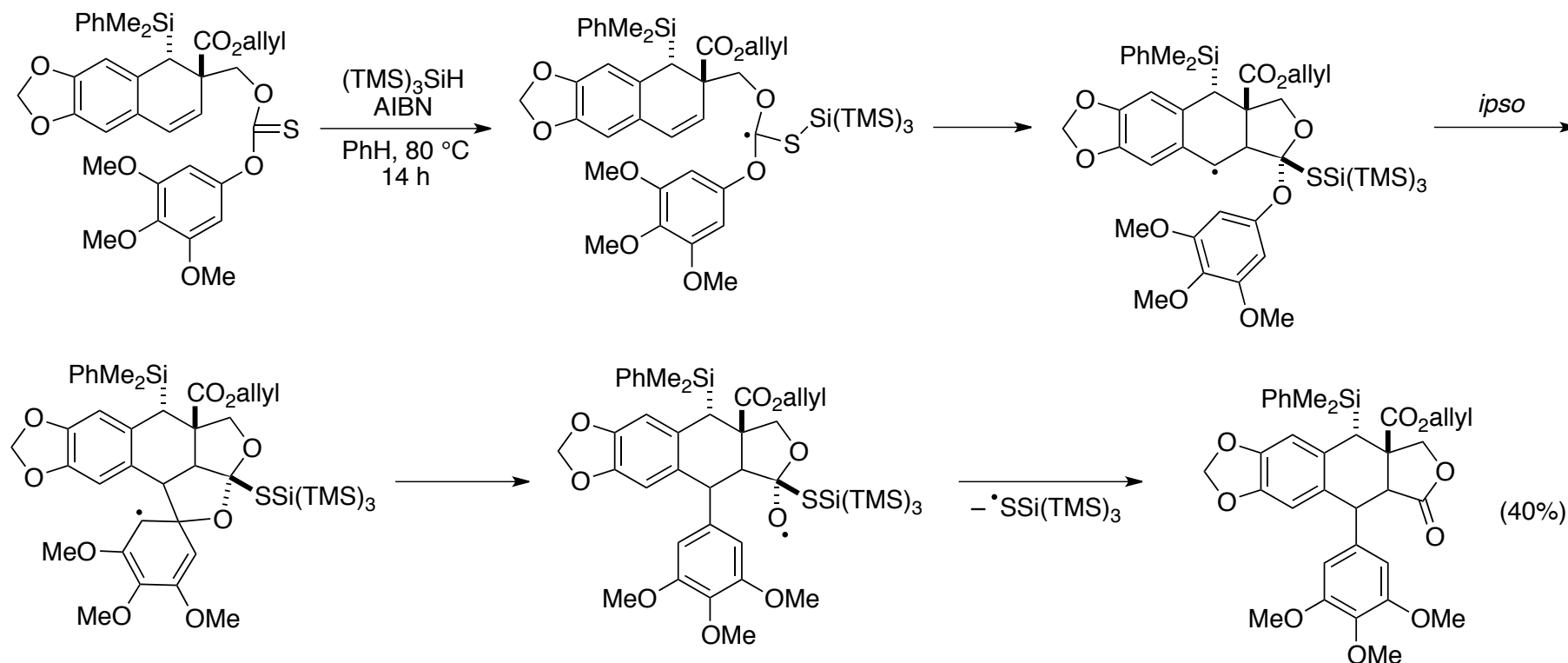
# A convergent radical-based route to biaryls (1,2-phenyl migration)



# 1,3-aryl migration from *N*- to *C*-centered radicals

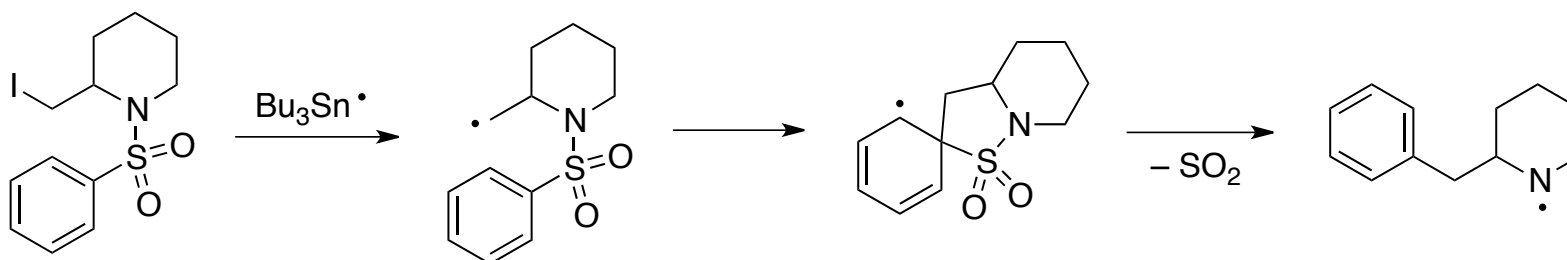


# 1,4-aryl migration from C- to C-centered radicals (The intramolecular carboxyarylation approach to podophyllotoxin)

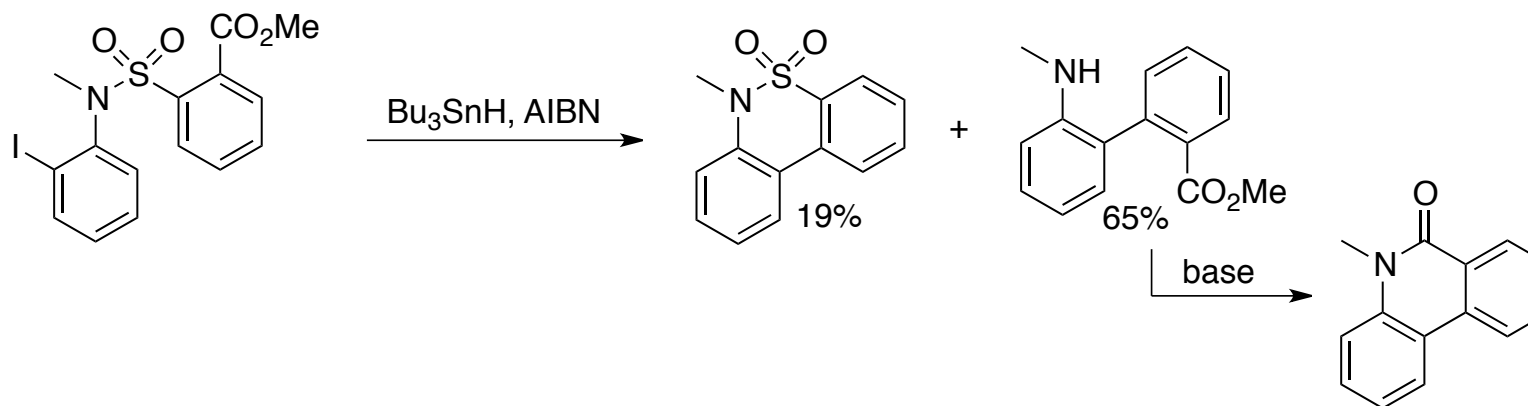


# 1,4-aryl migration from sulfur in sulfonamides to carbon

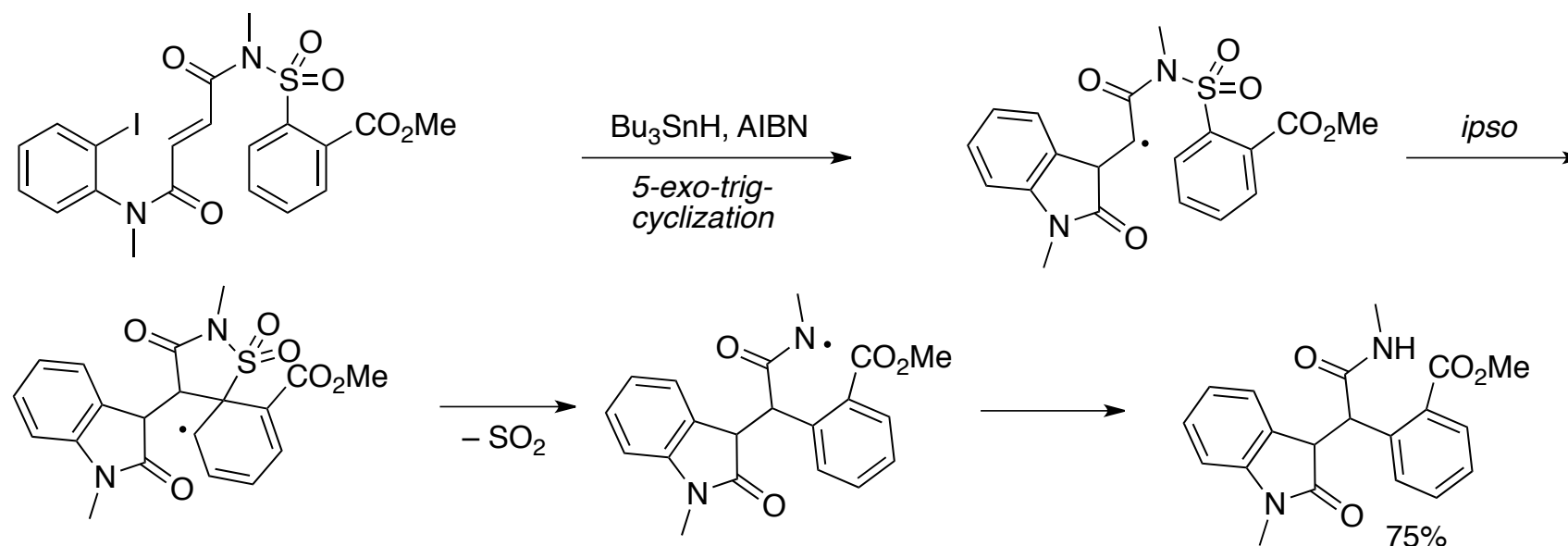
- > First report on 1,4-aryl migration on sulfonamides by Speckamp and Loven



- > Novel Route to Biaryls by Motherwell and Pennell

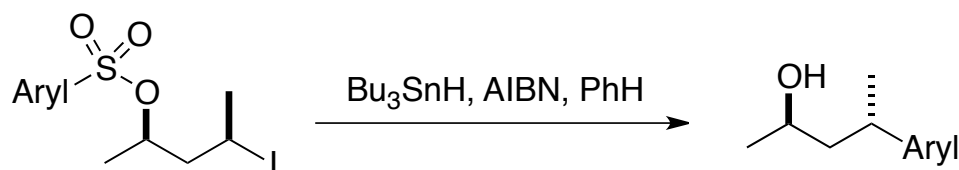


# Domino radical cyclization/Smiles rearrangement combination (1,4-aryl migration)

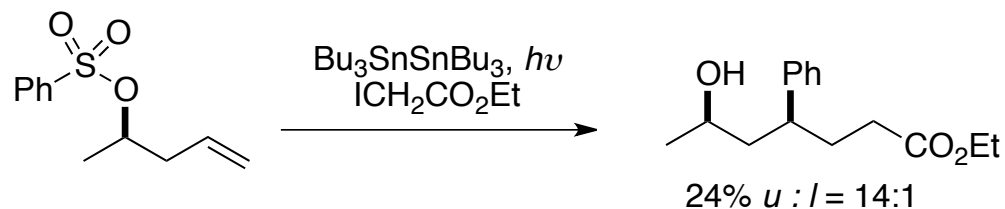
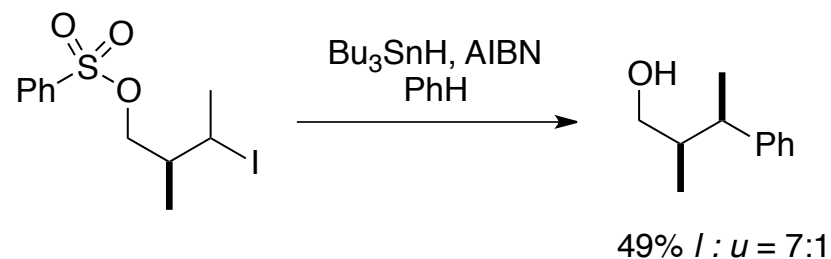




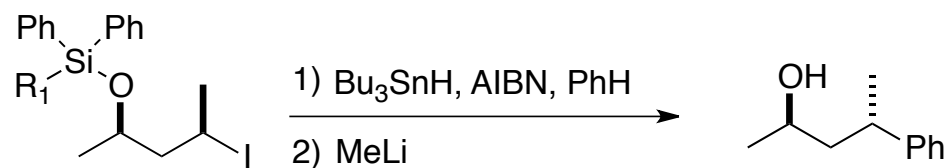
## Stereoselective aryl migration from sulfonates to carbon (1,5-aryl migration)



Aryl	Yield (%)	Ratio
Ph	76	13:1
4-FC <sub>6</sub> H <sub>4</sub>	59	10:1
4-MeOC <sub>6</sub> H <sub>4</sub>	50	9:1

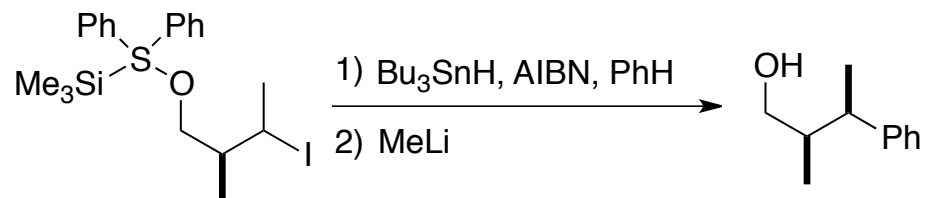


# Stereoselective phenyl migration from silyl ethers to carbon (1,5-aryl migration)



$\text{R}_1$	Yield (%)	Ratio ( <i>u</i> : <i>l</i> )
$\text{Me}_3\text{Sn}$	35 <sup>a</sup>	10 : 1
$\text{Me}_3\text{Si}$	70	10 : 1
<i>t</i> -Bu	33	6 : 1
Ph	37	6 : 1

<sup>a</sup> 30% of  $\text{S}_{\text{H}i}$ -product formed



17% *l* : *u* = 6:1

