Innovation & Sustainability in Process Chemistry

Parma 6-11-2024

Nitrogen Ring Walk:
a synthetic approach for substitution pattern alteration

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Otto Diels Institute for Organic Chemistry, CAU Kiel

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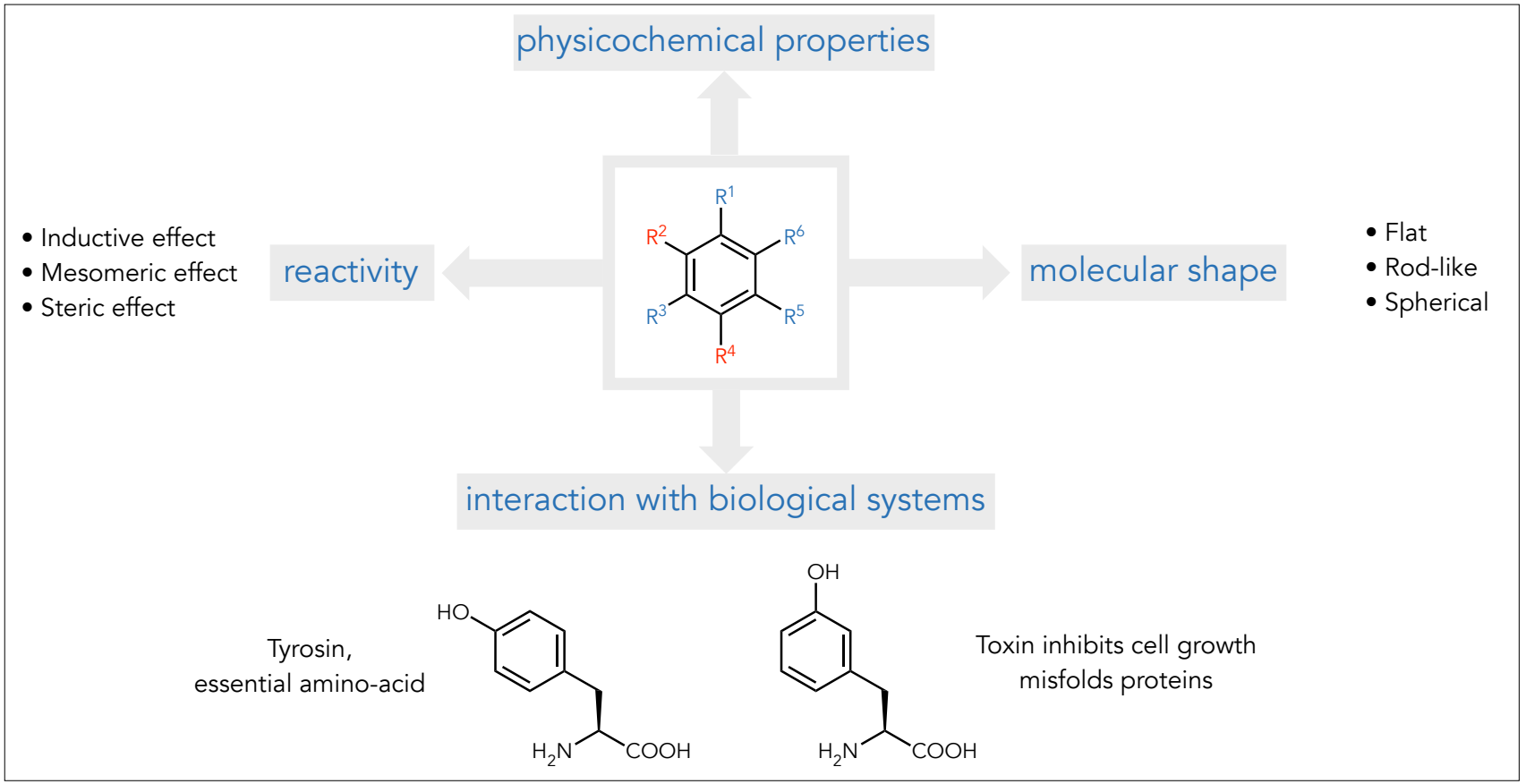
Benzene Substitution Pattern

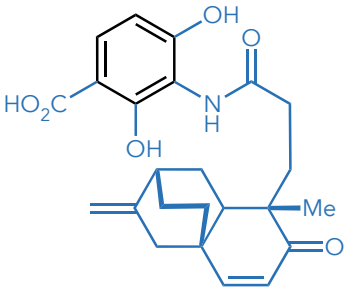


Proc. Natl Acad. Sci. USA **2007**, 16964

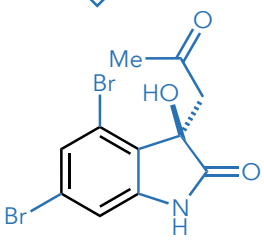
Origin & Control of Substitution Pattern

Natural product, Enzymatic reactions

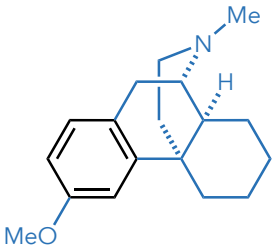
Enzymatic active site



Platencin



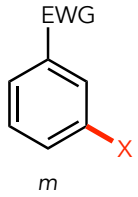
Convolutamydine



Dextromethorphan

Feedstock functionalization, S_EAr, Radical addition

Intrinsic recativity



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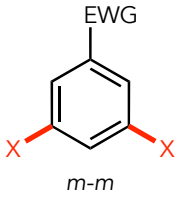

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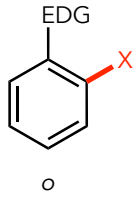

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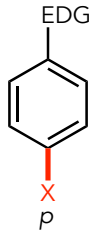

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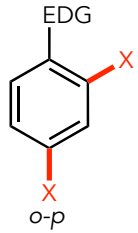

o-p

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Origin & Control of Substitution Pattern

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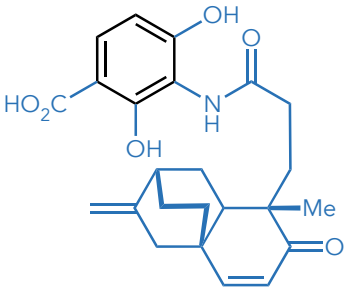
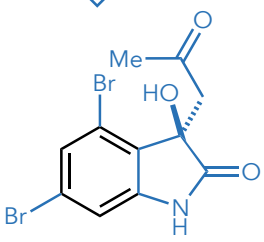
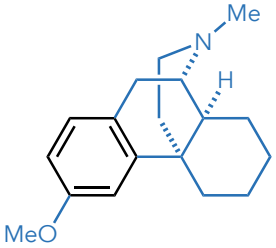
Enzymatic active site



Platencin



Convolutamydine



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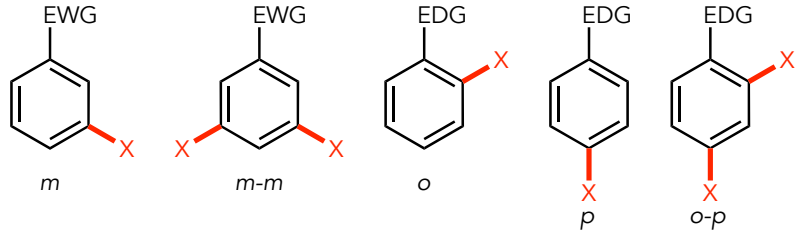
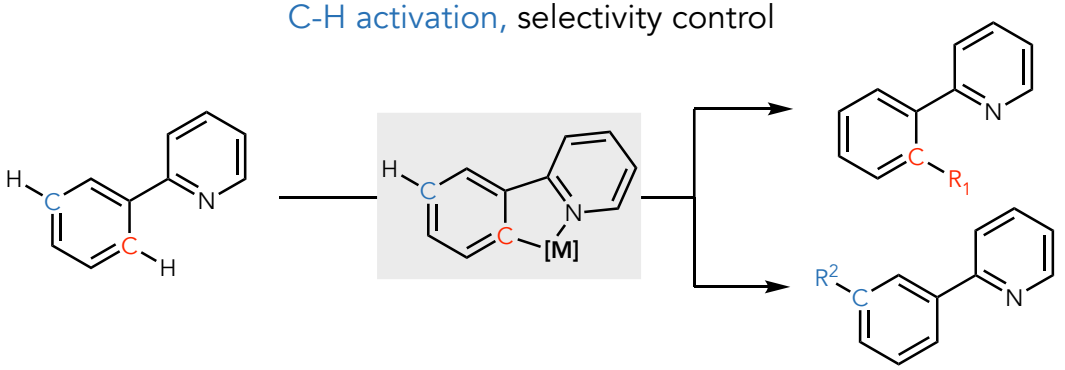


C-H activation, selectivity control



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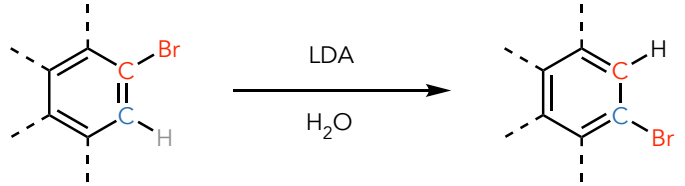
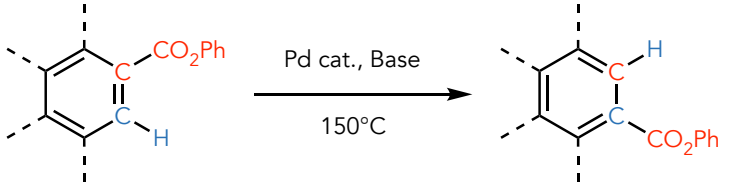
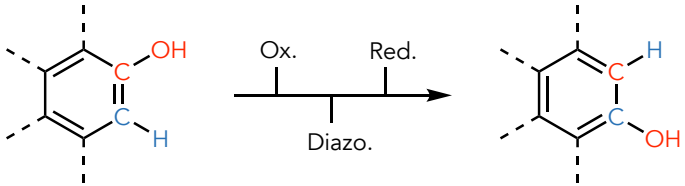
Synthetic Methods for Substitution Pattern Alteration



Halogen dance reaction
review: Erb *Tetrahedron* **2016**, 4973

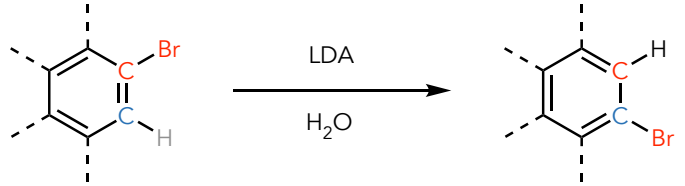


Yamaguci, *Sci. Adv.* **2020**, 6



Lumb, *Nat. Chem.* **2024**, 1193

Synthetic Methods for Substitution Pattern Alteration



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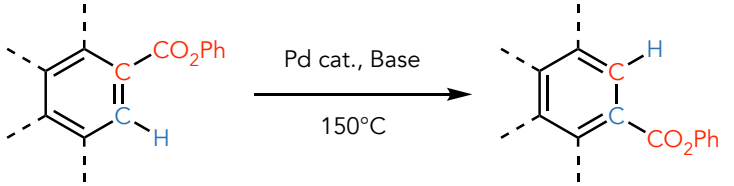
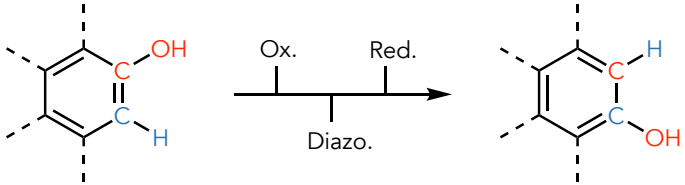
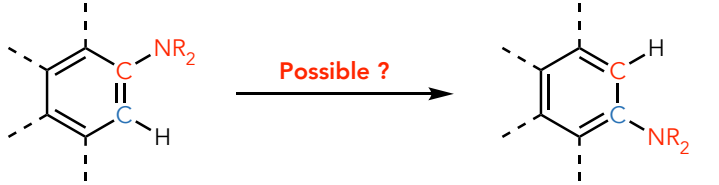


Yamaguci, *Sci. Adv.* **2020**, 6



Lumb, *Nat. Chem.* **2024**, 1193



New of synthetic strategy for Nitrogen Ring Walk

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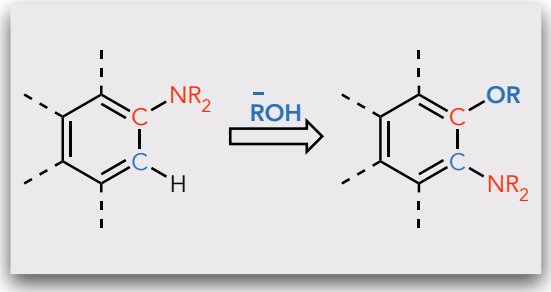
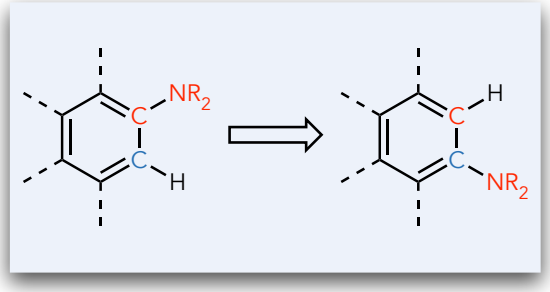
Road Map to Nitrogen Ring Walk

Synthesis of *ortho*-aminophenols

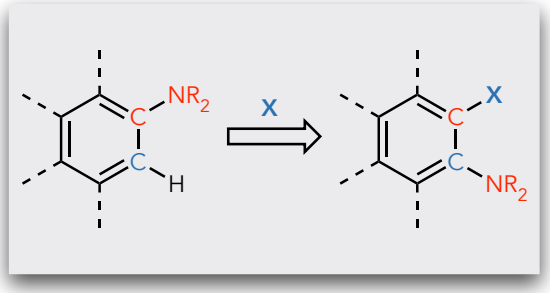


Angew. Chem. Int. Ed. **2023**, 62, e202310540

Nitrogen ring walk



Synthesis of *ortho*-functionalized Anilines



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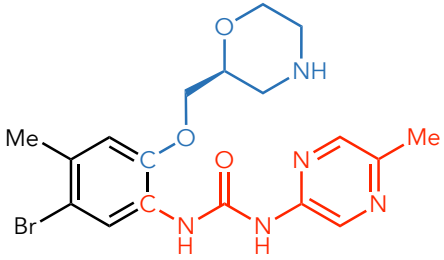
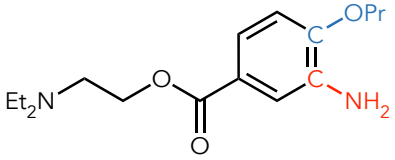
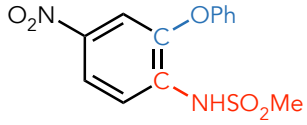
Synthesis of *ortho*-Aminophenols



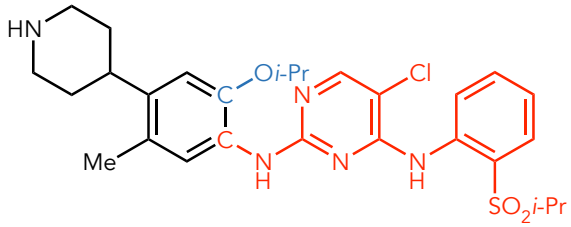
rabusertib (Eli Lilly)
anticancer



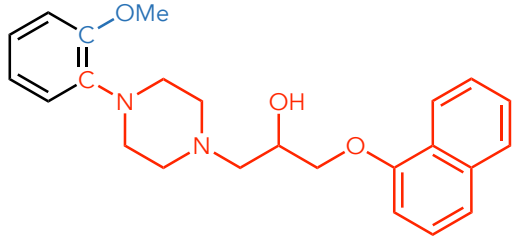
Proparacaine (POEN)
anesthetic



Nimesulide (Vifor)
anti-inflammatory



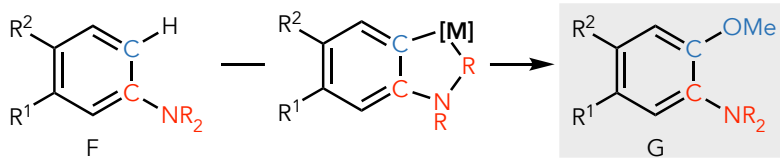
ceritinib (Novartis)
anticancer



naftopidil (Flivas)
α-1 blocker

Synthesis of *ortho*-Aminophenols

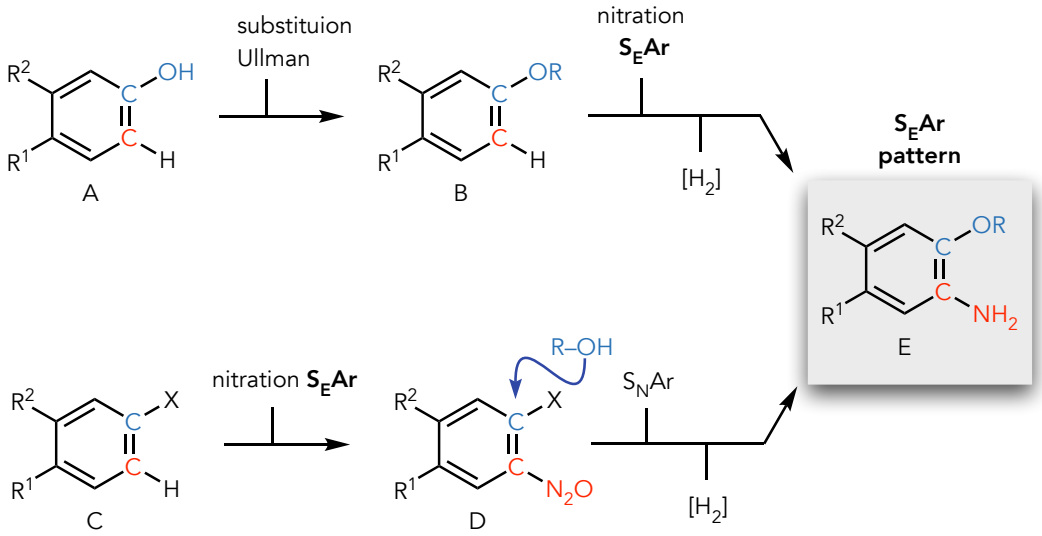
ortho-CH Etherification



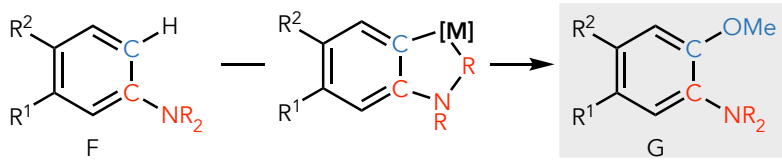
- Limited to HOMe, HOEt

Synthesis of *ortho*-Aminophenols

Current strategies



ortho-CH Etherification



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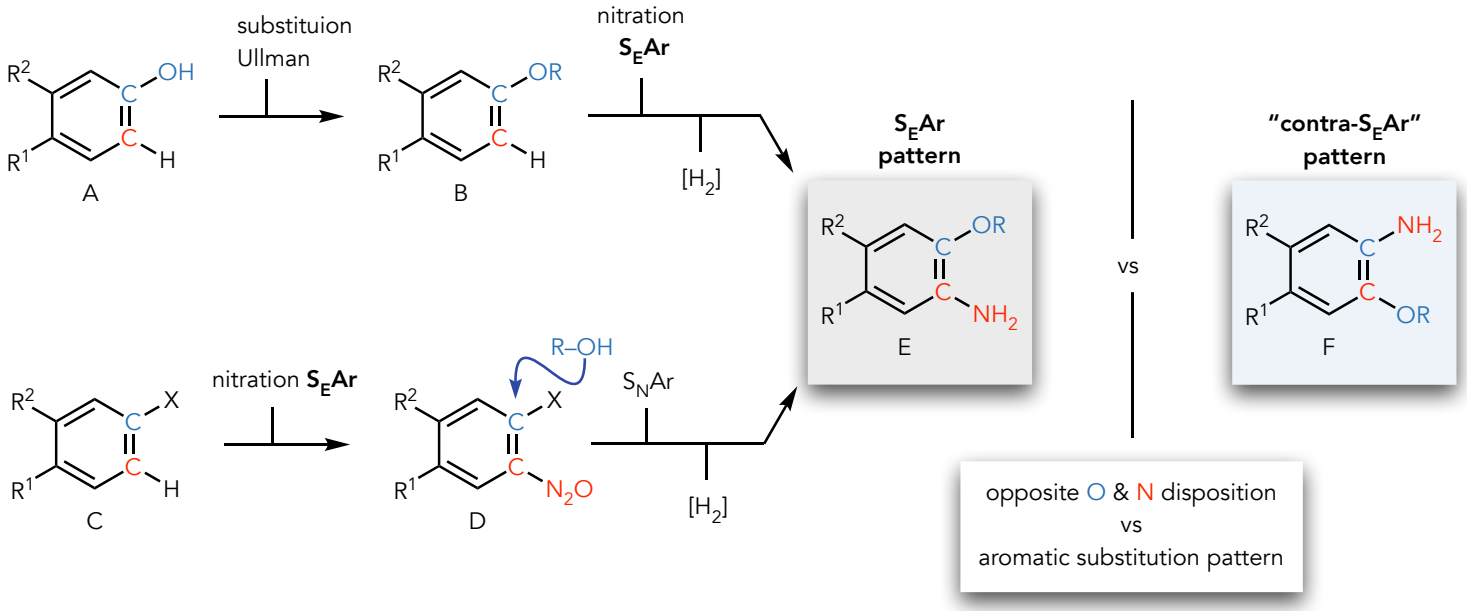
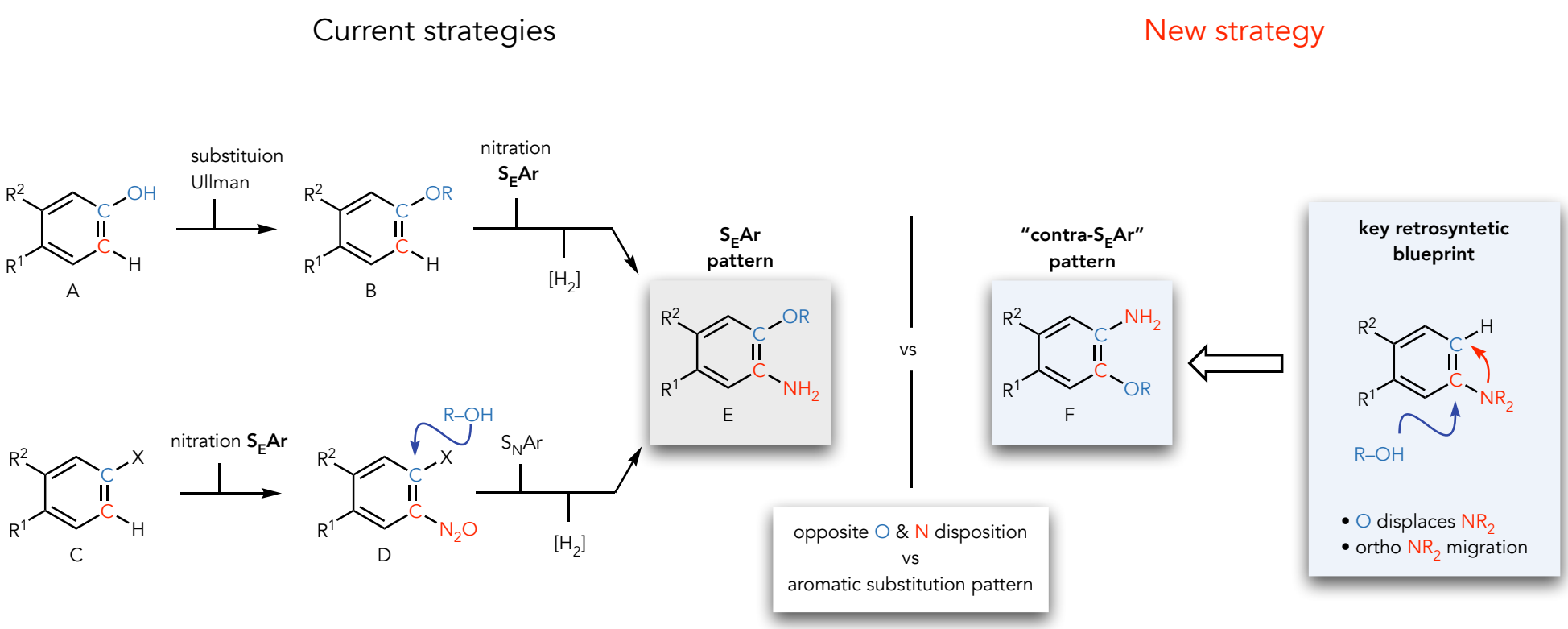
Synthesis of *ortho*-Aminophenols

Current strategies

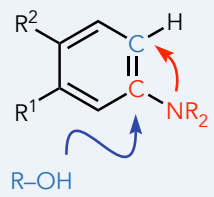


Synthesis of *ortho*-Aminophenols

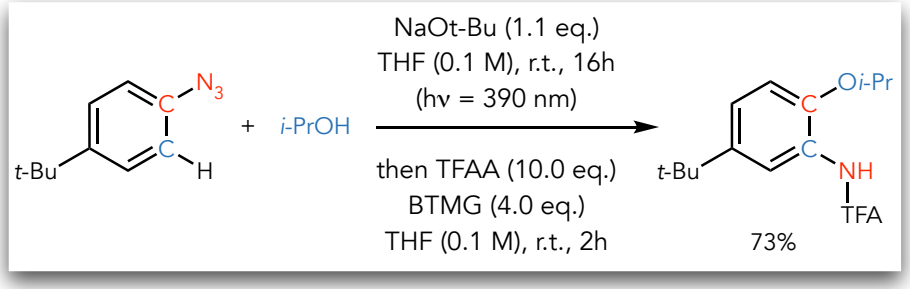


New Approach for the Synthesis of *ortho*-Aminophenols

key retrosyntetic blueprint



- O displaces NR_2
- ortho NR_2 migration



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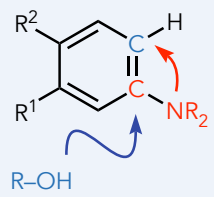

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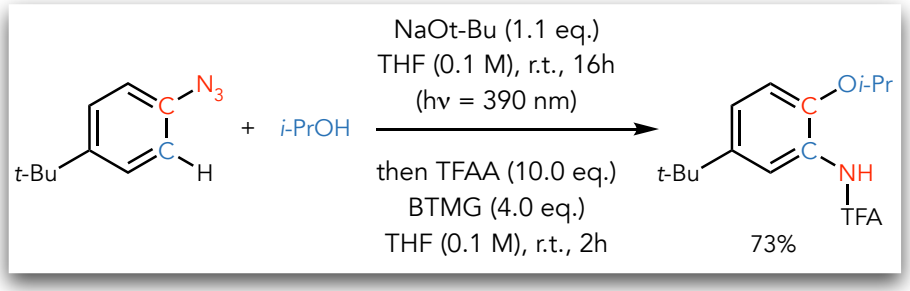
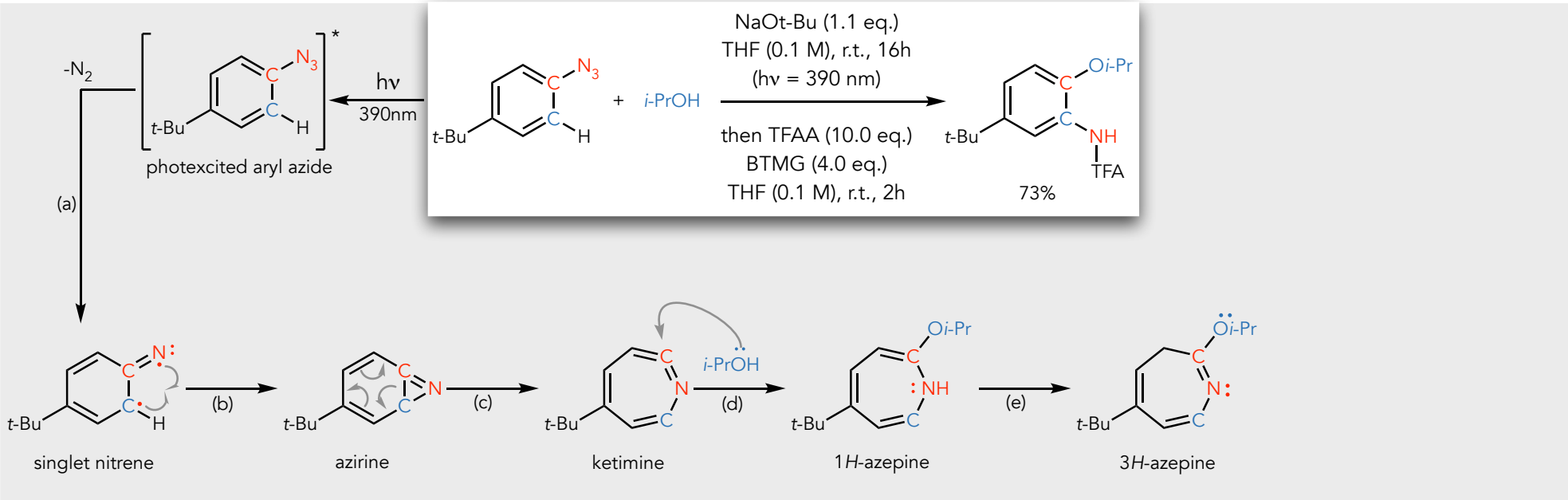


1) Metal free formal "*Ortho*-CH oxidation" of aryl azide

2) Nitrogen ring walk along the aromatic ring

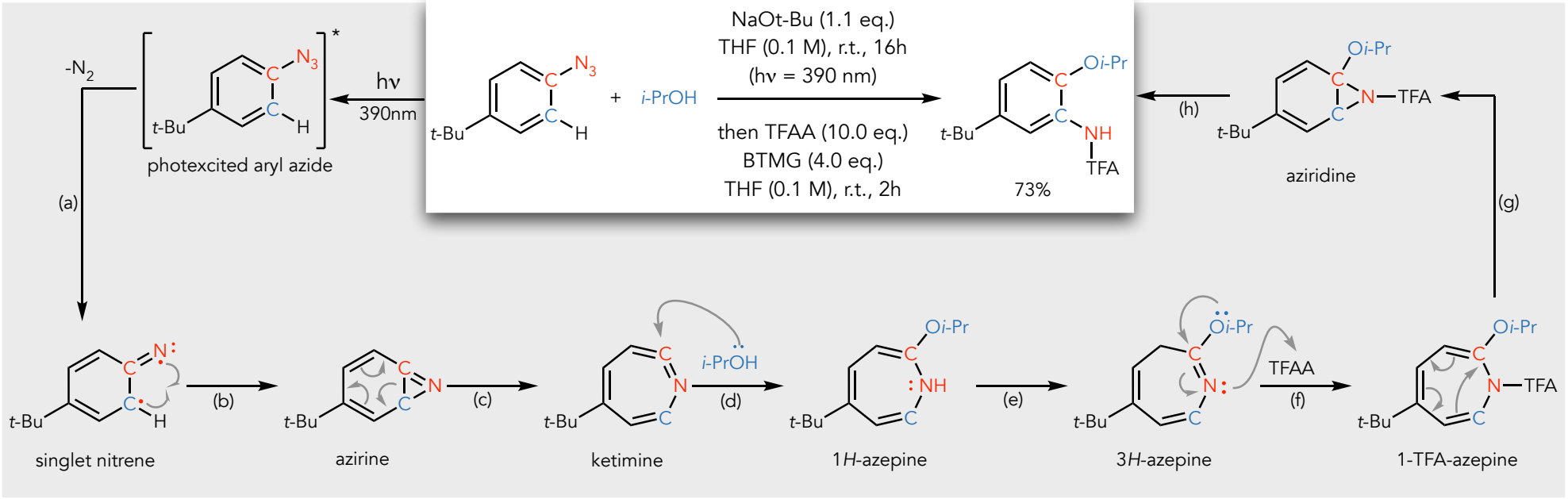
Reaction Mechanism



Breaking aromaticity

(a) singlet nitrene formation
(b) azirination
(c) 6π electrocyclization
(d) nucleophilic addition
(e) isomerization
(f) N-acylation
(g) 6π electrocyclization
(h) aromatization

Reaction Mechanism

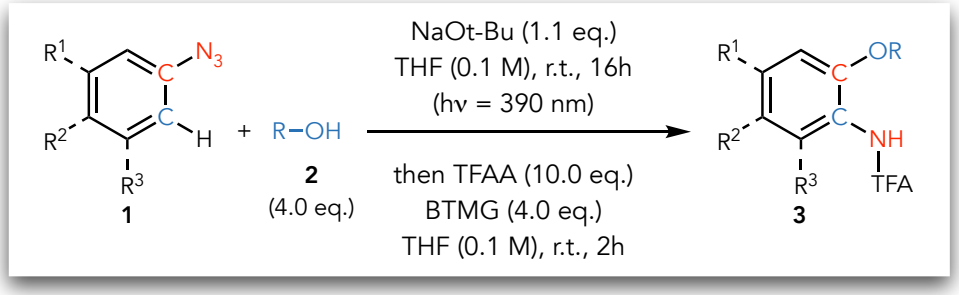


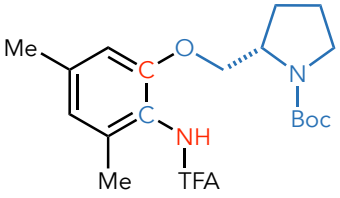
Breaking aromaticity

Re-building aromaticity

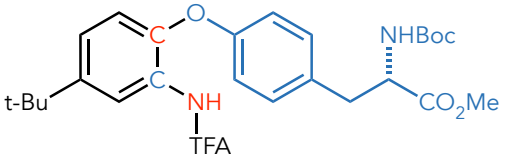
(a) singlet nitrene formation
(b) azirination
(c) 6π electrocyclization
(d) nucleophilic addition
(e) isomerization
(f) N-acylation
(g) 6π electrocyclization
(h) aromatization

Preparation of complex *ortho*-Aminophenols

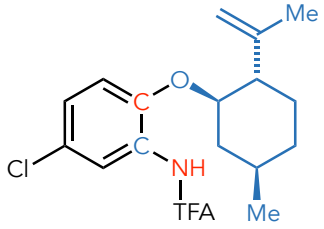




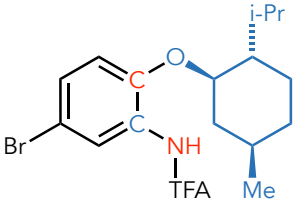
from Prolinol
82%



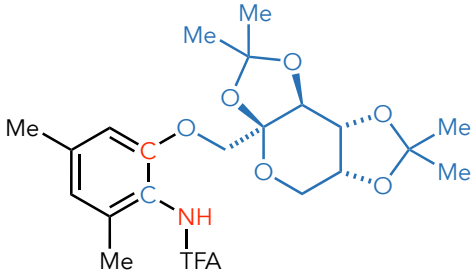
from L-tyrosine
55%



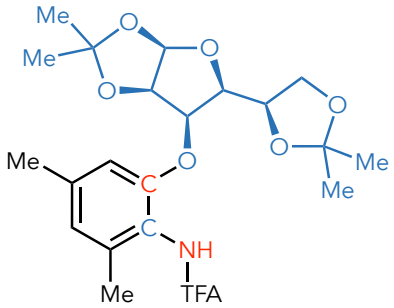
from (+) -isopulegol
30%



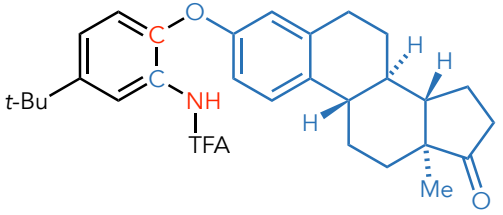
from (-)-Menthol
40%



from Topiramate
98%

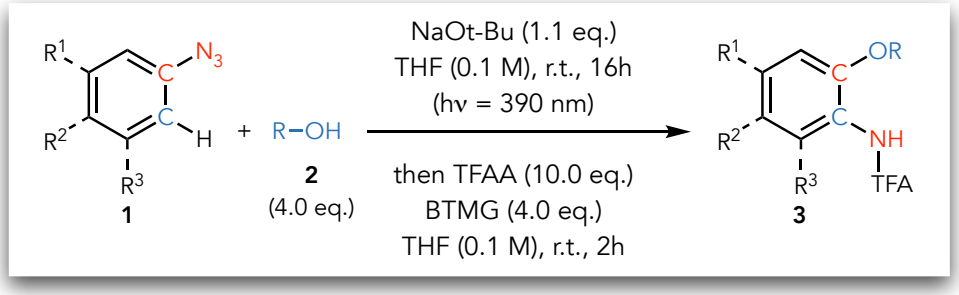


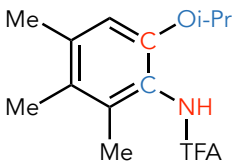
from D-glucofuranose
78%



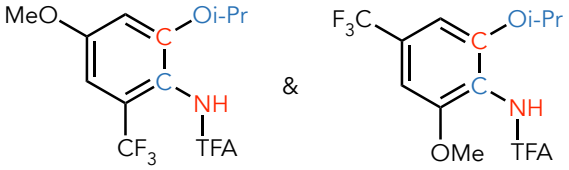
from Estrone
71%

Preparation of complex *ortho*-Aminophenols

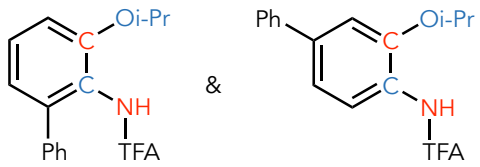




60%

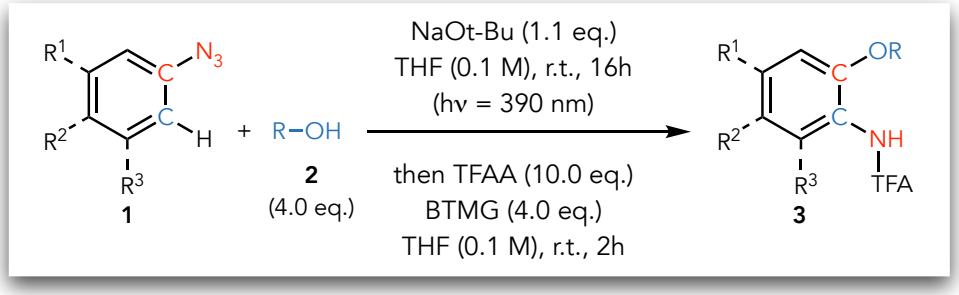


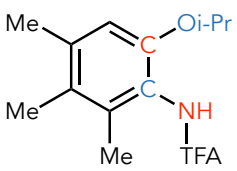
8.4 : 1; 66%



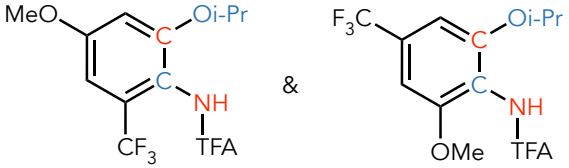
2 : 1; 55%

Synthesis of *ortho*-Aminophenols : Selectivity

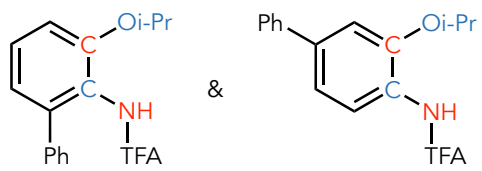




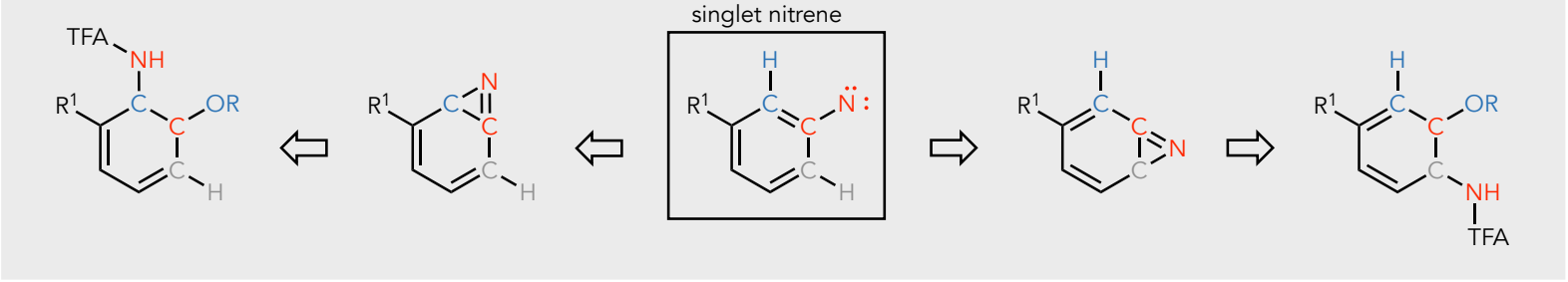
60%



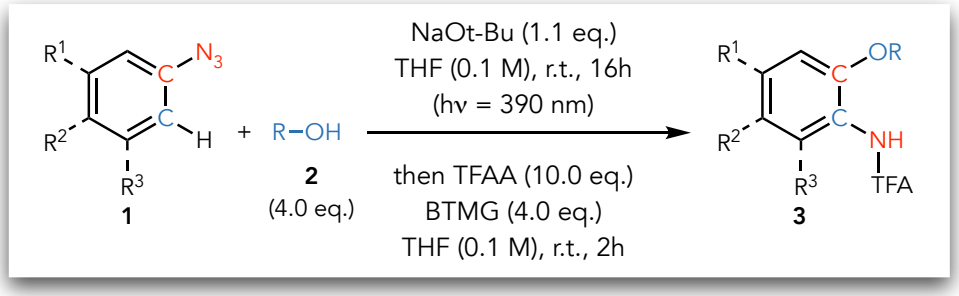
8.4 : 1; 66%

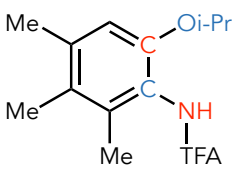


2 : 1; 55%



Application in Synthesis of Drugs





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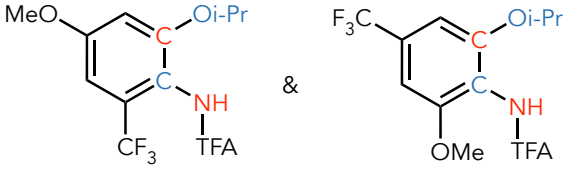
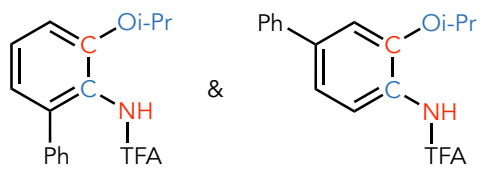
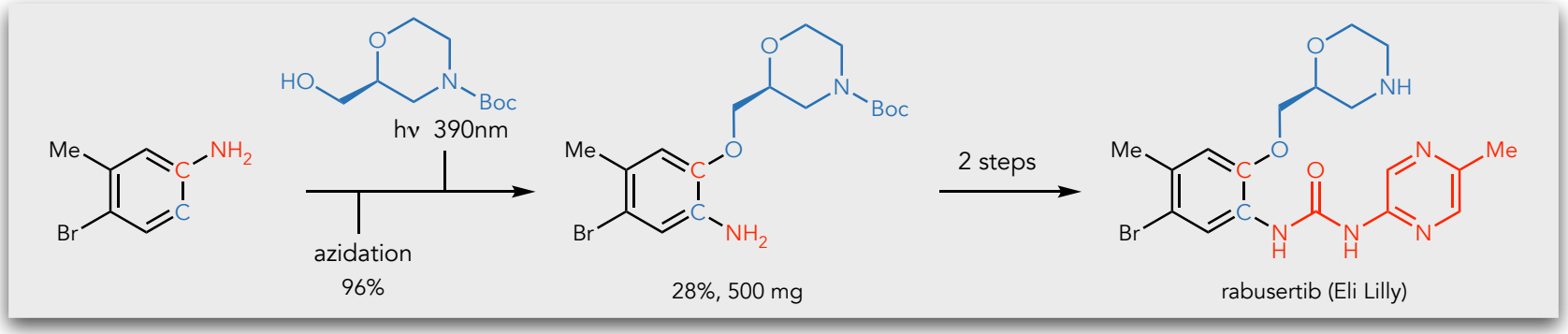


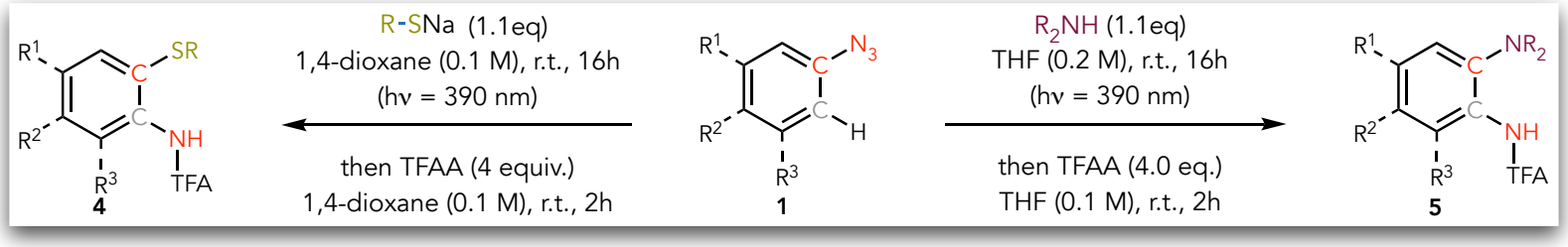
8.4 : 1; 66%

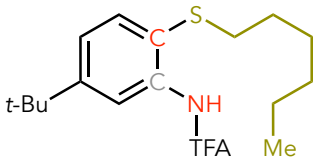


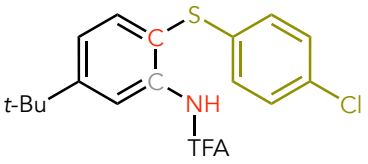
2 : 1; 55%

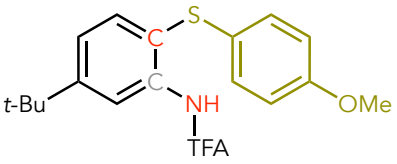


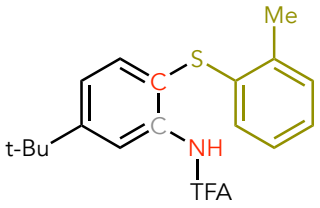
Extension to Nitrogen and Sulfur Nucleophiles

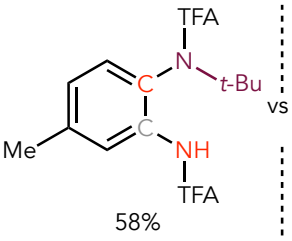


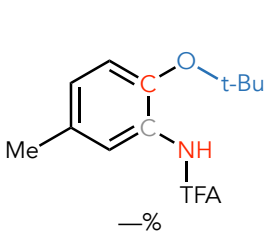

64%


45%


68%


72%


58%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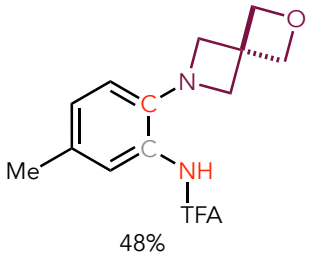
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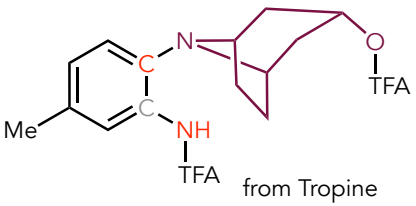
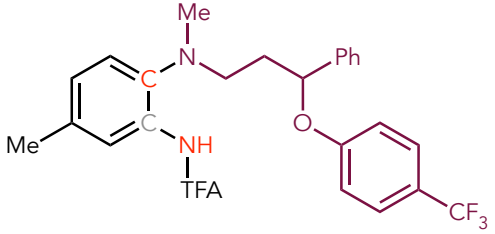
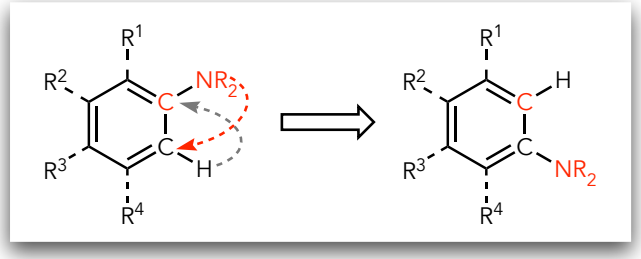

from Tropine
32%

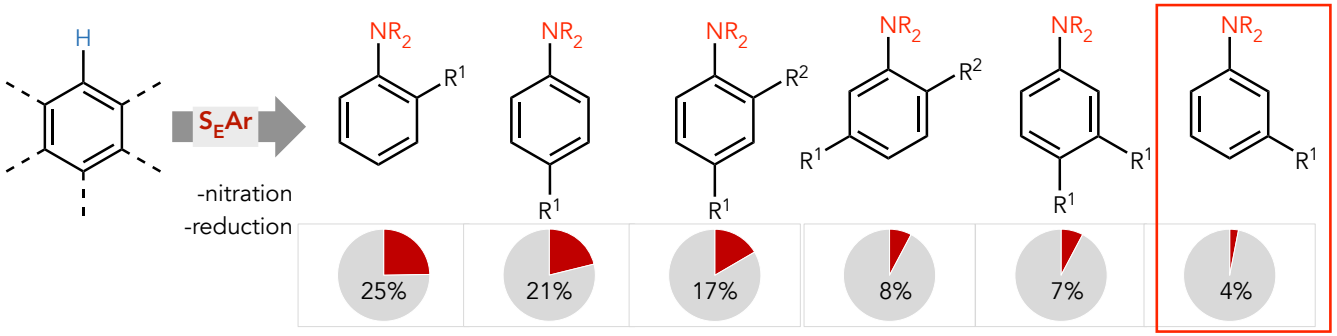

from Fluoxetine
61%

Substitution Pattern Alteration via Nitrogen Ring Walk

-Late Stage Exploration of Substitution Pattern Chemical Space



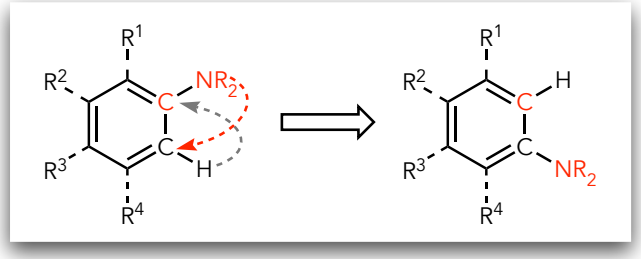
-Nitrogen contains molecule substitution pattern analysis



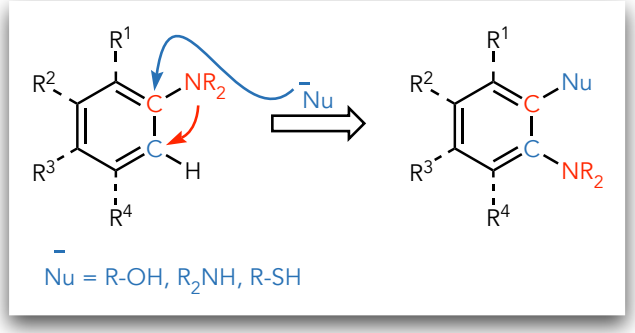
Unpublished

Substitution Pattern Alteration via Nitrogen Ring Walk

-Late Stage Exploration of Substitution Pattern Chemical Space



- substitution pattern alteration
-addition extra functionality



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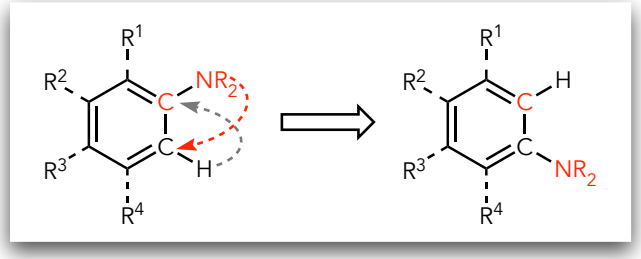
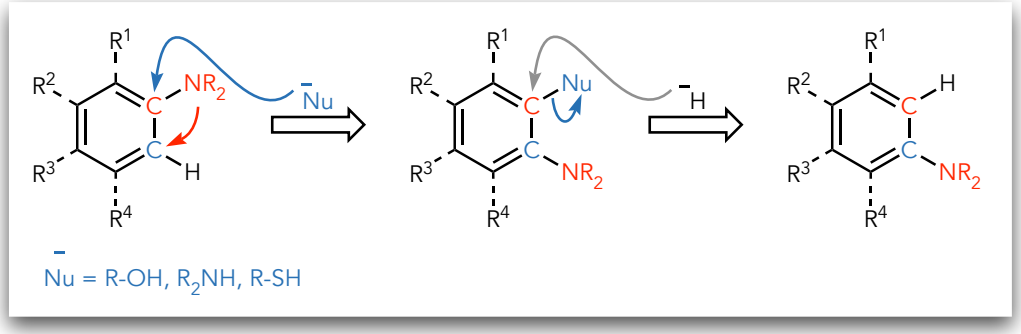
Substitution Pattern Alteration via Nitrogen Ring Walk

-Late Stage Exploration of Substitution Pattern Chemical Space



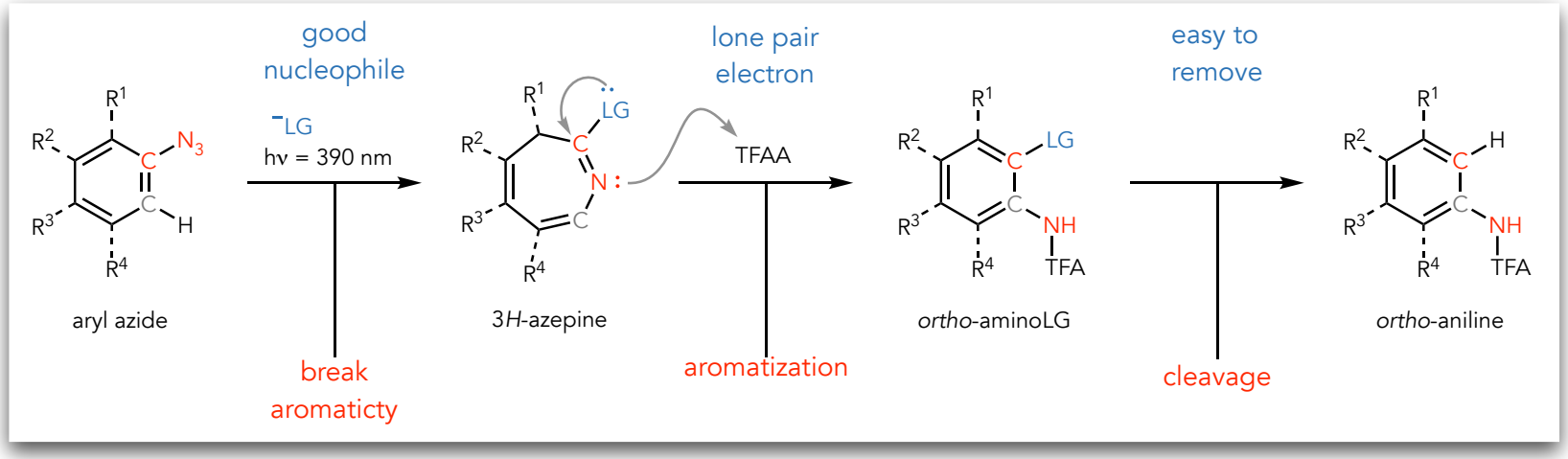
- substitution pattern alteration

-addition extra functionality

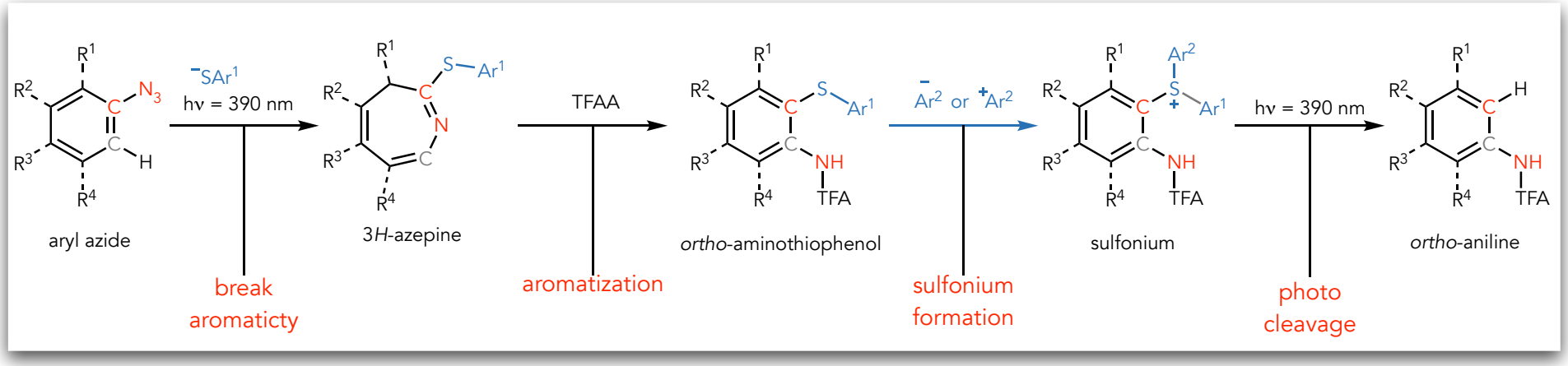


-remove of the extra functionality

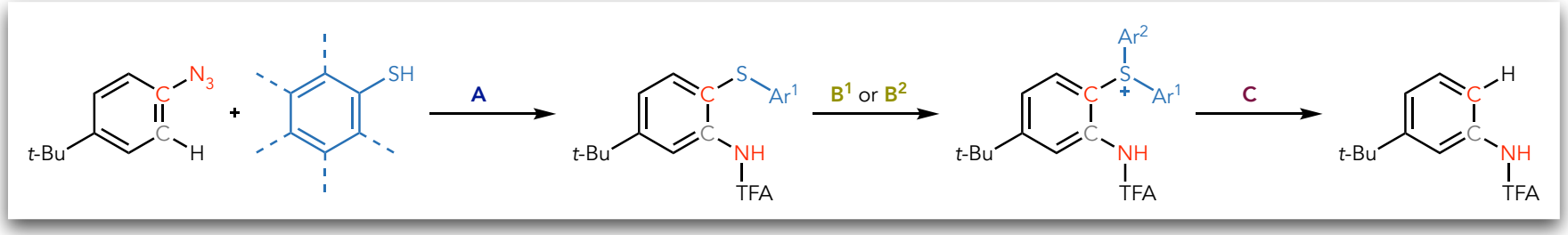
Synthetic Strategy and Reagent Design

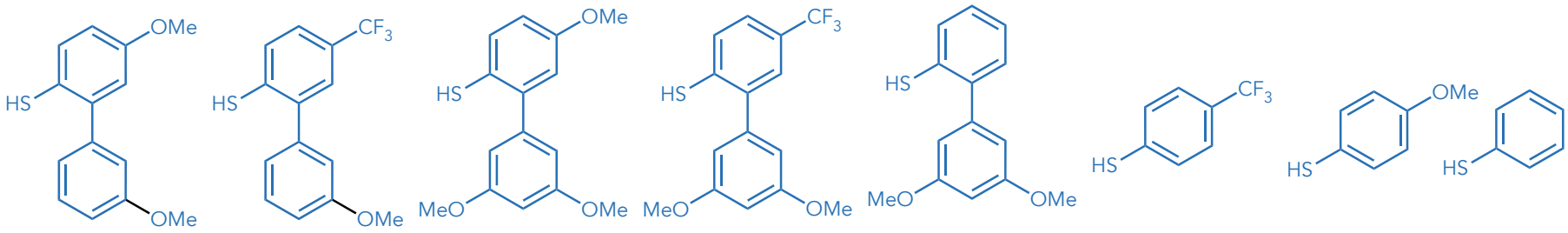


Synthetic Strategy and Reagent Design



Synthetic Strategy and Reagent Design





A: DMAP (1 eq.), 1,4-dioxane (0.05 M), hν =390nm, r.t., 16h *then* TFAA (4 eq.), r.t., 2h

B^1:NCS (1 eq.), $Bi(OTf)_3$ (1 eq.) 1:1 1,4-dioxane/MeCN (0.033 M), r.t., 6h

B^2:MeOTf (1.5 eq.) DCM (0.05 M), r.t., 8h.

C: Cs_2CO_3 (1 eq.), 1:1 MeOH/Acetone (0.05 M) ,hν =390 nm, r.t., 12h

Arstad, *J. Am. Chem. Soc.* **2018**, 11125; Zhang, *Org. Lett.* **2022**, 8417.

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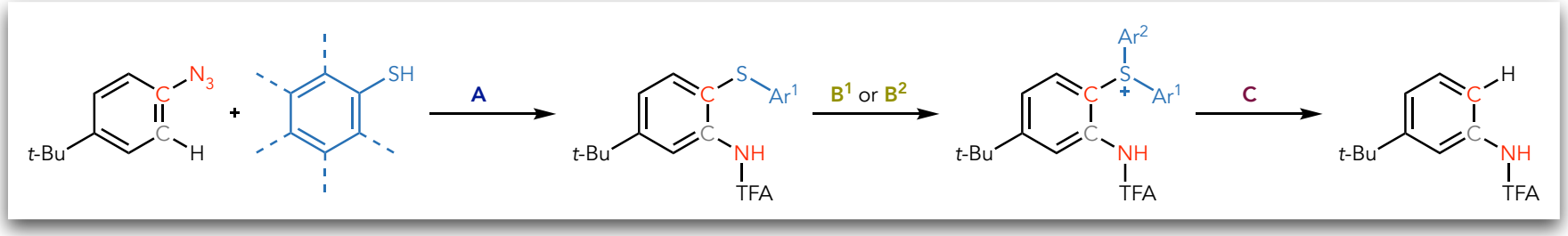
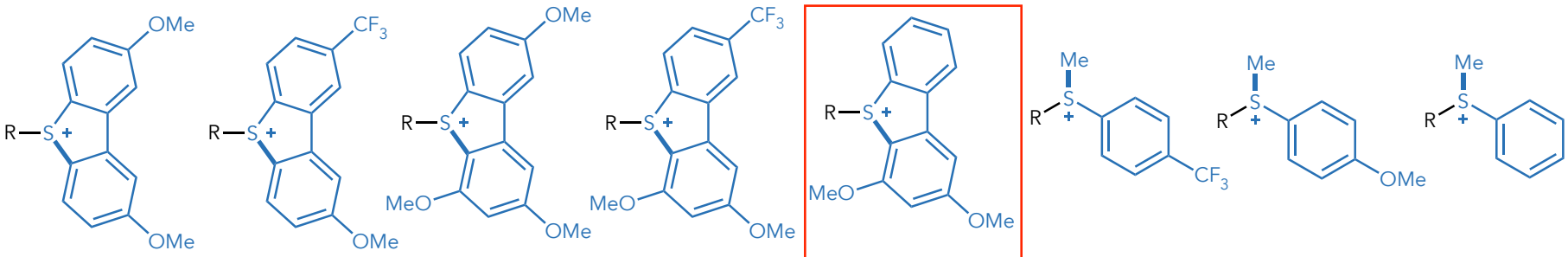
Synthetic Strategy and Reagent Design





A	**58%**	**49%**	**52%**	**43%**	**75%**	**48%**	**67%**	**65%**
B	**69%**	**68%**	**49%**	**26%**	**78%**	—	**100%**	—
C	**12% (insoluble)**	**39%**	**13%**	**5%**	**98%**	—	**<5%(insoluble)**	—

A: DMAP (1 eq.), 1,4-dioxane (0.05 M), hν =390nm, r.t., 16h *then* TFAA (4 eq.), r.t., 2h

B^1:NCS (1 eq.), $Bi(OTf)_3$ (1 eq.) 1:1 1,4-dioxane/MeCN (0.033 M), r.t., 6h

B^2:MeOTf (1.5 eq.) DCM (0.05 M), r.t., 8h.

C: Cs_2CO_3 (1 eq.), 1:1 MeOH/Acetone (0.05 M) ,hν =390 nm, r.t., 12h

Arstad, *J. Am. Chem. Soc.* **2018**, 11125; Zhang, *Org. Lett.* **2022**, 8417.

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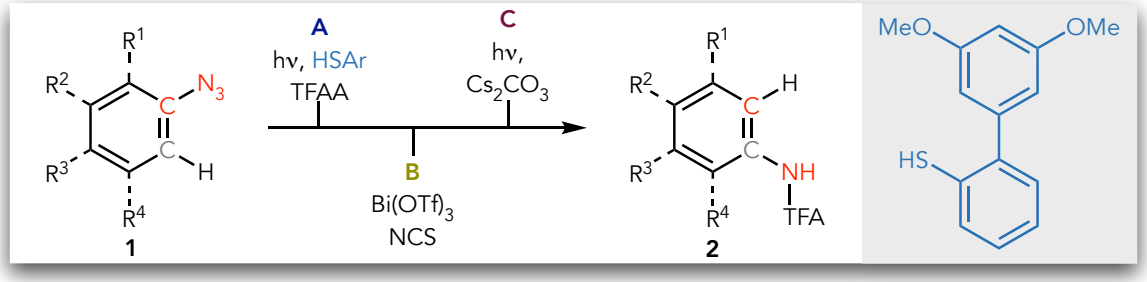
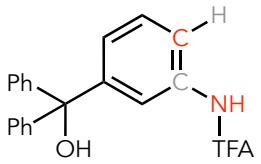
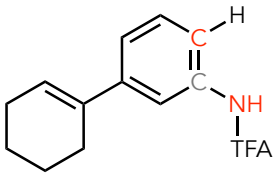
Scope of Nitrogen Ring Walk

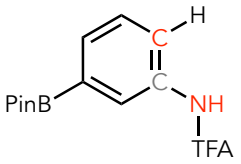




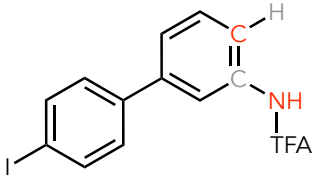
29%
(**A** 53%, **B** 76%, **C** 73%)



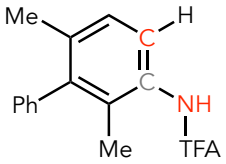
36%
(**A** 65%, **B** 75%, **C** 75%)



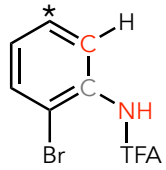
50%
(**A** 78%, **B** 67%, **C** 95%)



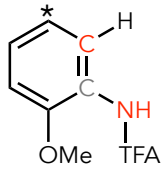
48%
(**A** 62%, **B** 78%, **C** 98%)



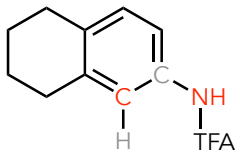
31%
(**A** 59%, **B** 55%, **C** 98%)



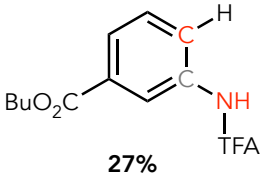
1 : 2, 36%
(**A** 56%, **B** 70%, **C** 92%)



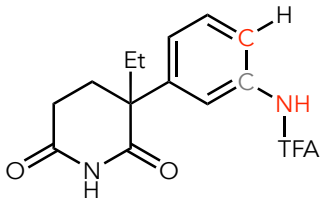
1 : 9, 50%
(**A** 79%, **B** 78%, **C** 96%)



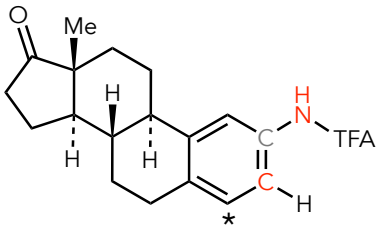
48%
(**A** 71%, **B** 78%, **C** 87%)



27%
(**A** 58%, **B** 76%, **C** 95%)
from Butamben



55%
(**A** 71%, **B** 81%, **C** 98%)
from Aminoglutethimide
1 gram scale



1 : 1, 26%
(**A** 59%, **B** —%, **C** 44%)
from Estrone

Unpublished

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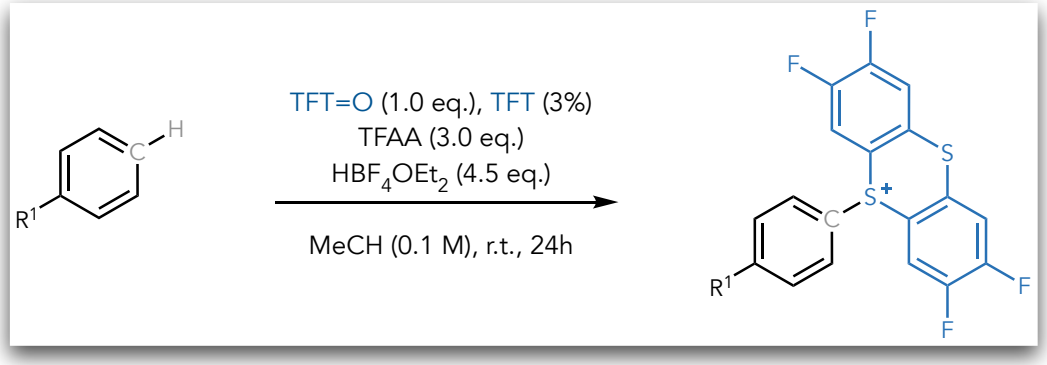
Ortho-diversification

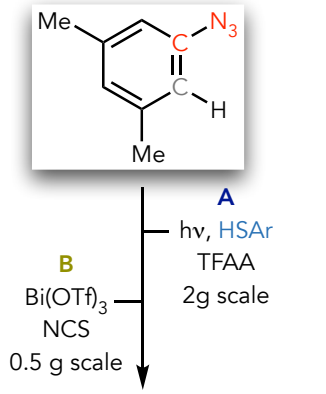
Ritter, *Nature*, **2019**, 223

Selective para- CH installation of Thianthrenium



Powerful Synthetic Handle

Ortho-diversification

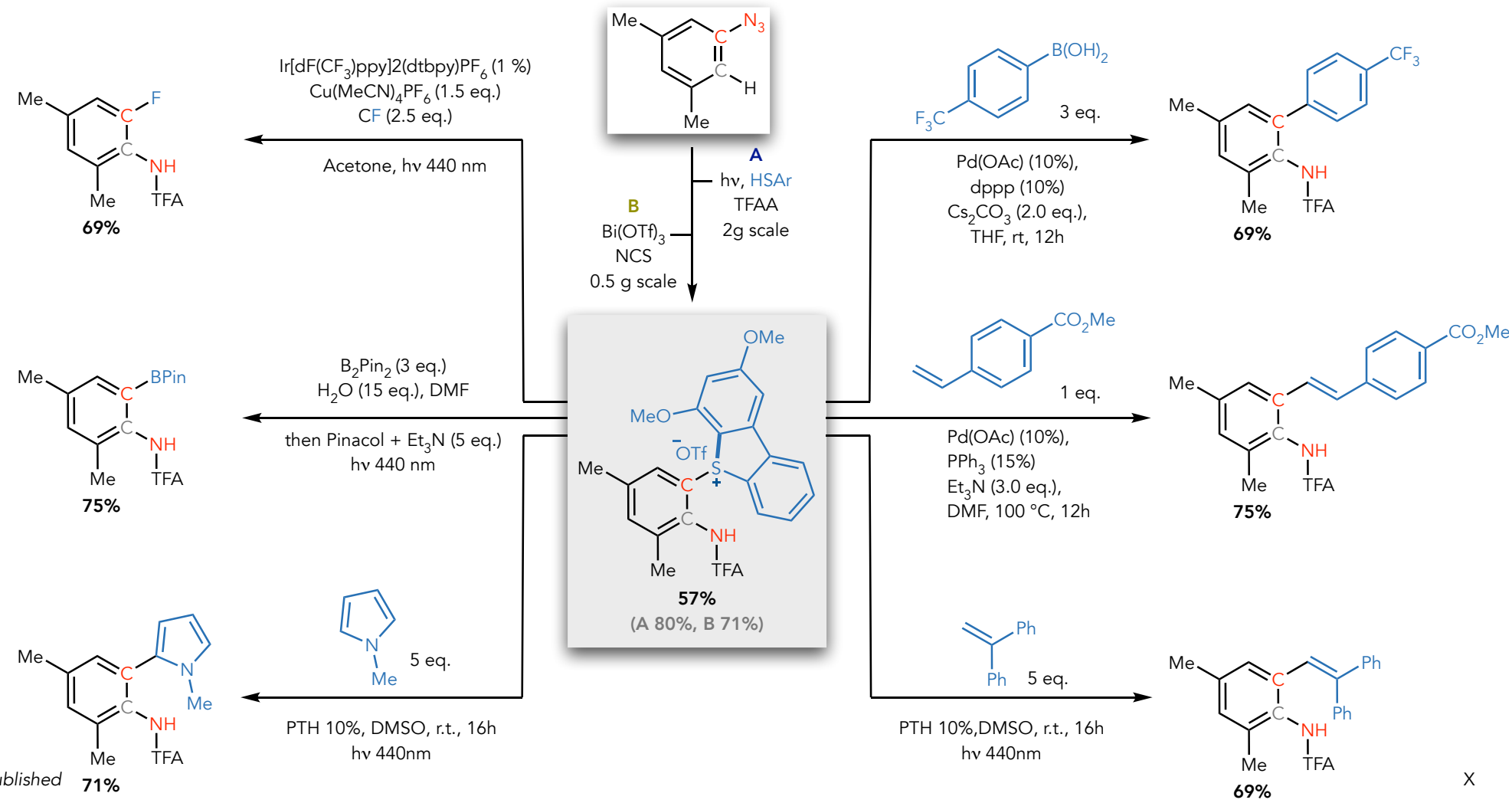


57%
(A 80%, B 71%)

Formal "Ortho- CH installation"
of sulfonium salt

Powerful Synthetic Handle

Ortho-diversification



Unpublished

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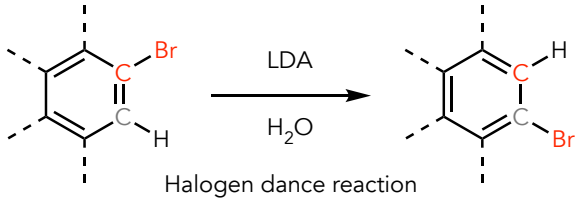
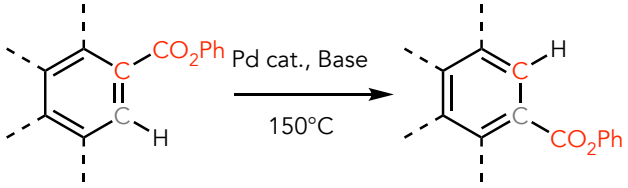
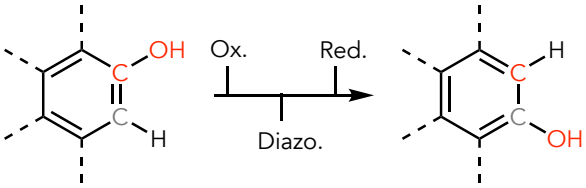
Substitution Pattern Alteration via Alkyl Group Ring Walk



Halogen dance reaction
review: Erb *Tetrahedron* **2016**, 4973

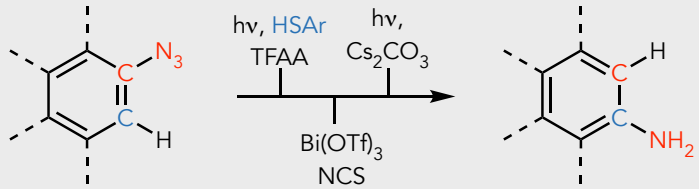


Yamaguci, *Sci. Adv.* **2020**, 6



Lumb, *Nat. Chem.* **2024**, 1193

New of synthetic strategy for Nitrogen Ring Walk



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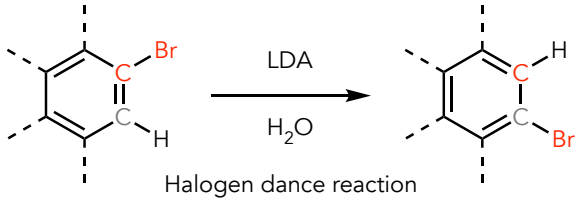
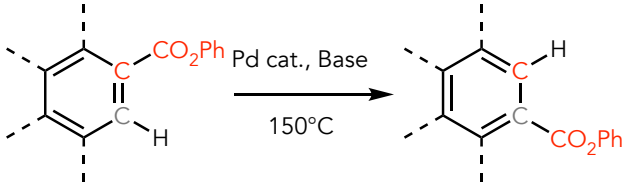
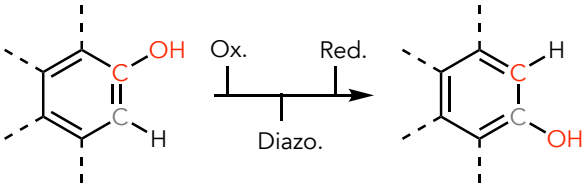
Substitution Pattern Alteration via Alkyl Group Ring Walk



Halogen dance reaction
review: Erb *Tetrahedron* **2016**, 4973

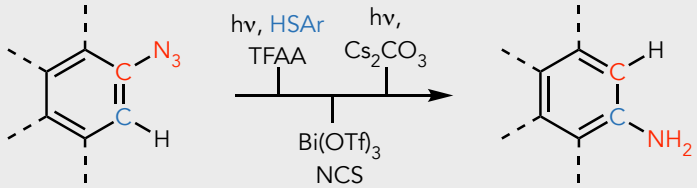


Yamaguci, *Sci. Adv.* **2020**, 6

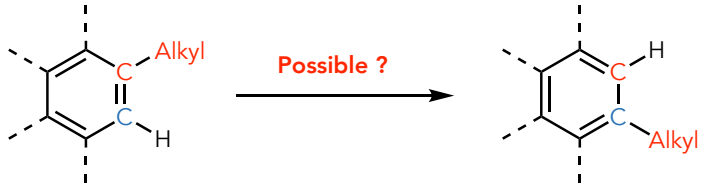


Lumb, *Nat. Chem.* **2024**, 1193

New of synthetic strategy for Nitrogen Ring Walk



New Methodology for Alkyl Group Ring Walk



Unpublished

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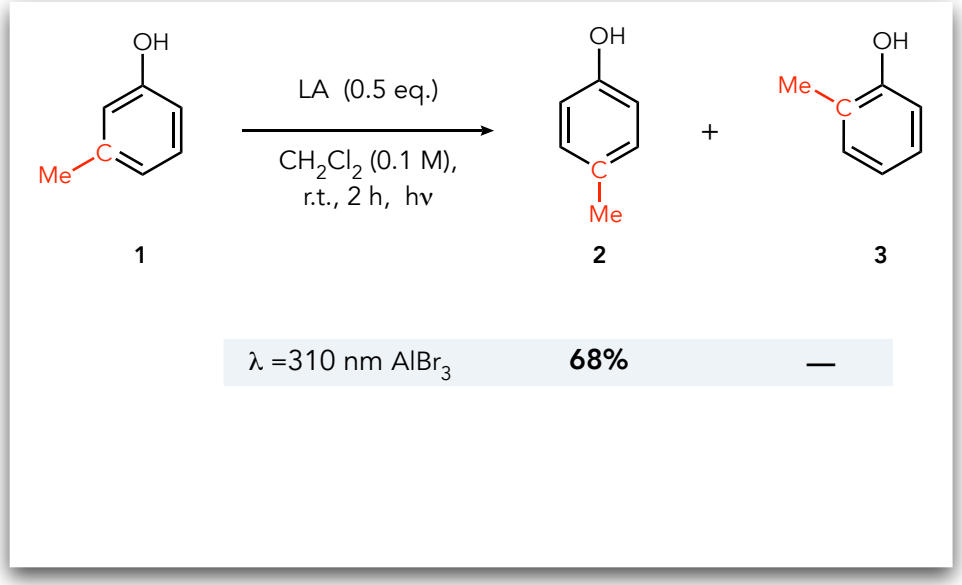
Substitution Pattern Alteration via Alkyl Group Ring Walk



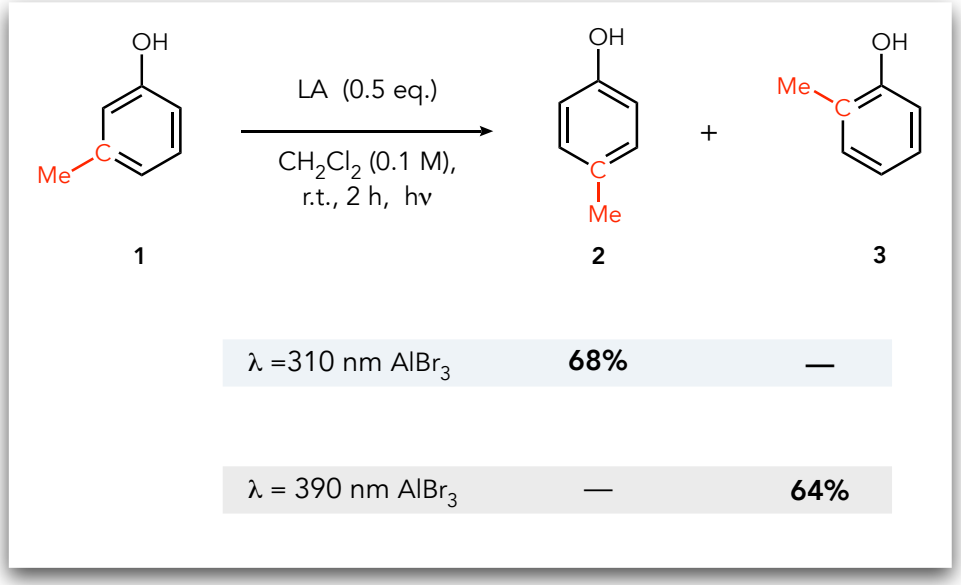
1 **2** **3**

λ =310 nm $AlBr_3$	**68%**	—

Unpublished

Child, *Chem. Comm.*, **1970**, 1581

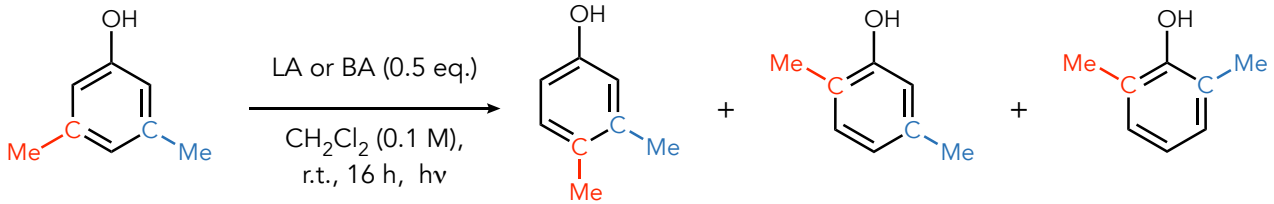
Substitution Pattern Alteration via Alkyl Group Ring Walk



1 **2** **3**

λ =310 nm $AlBr_3$	**68%**	—
λ = 390 nm $AlBr_3$	—	**64%**

Substitution Pattern Alteration via Alkyl Group Ring Walk

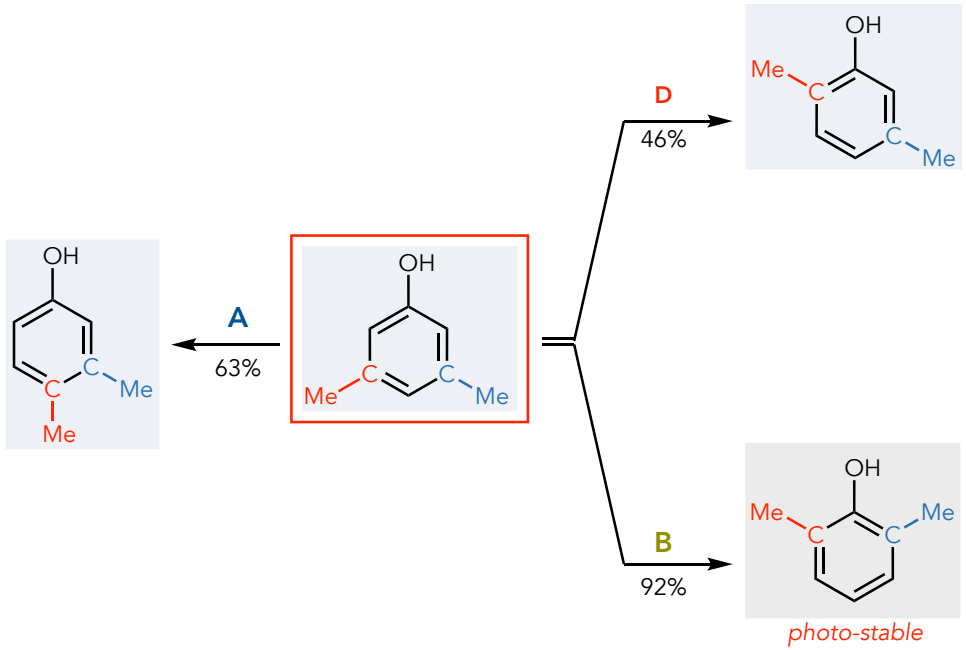


4 **5** **6** **7**

λ = 310 nm $AlBr_3$	**63%**	**11%**	—
λ = 390 nm $AlBr_3$	—	—	**96%**
λ = 390 nm TfOH	—	**59%**	—

Unpublished

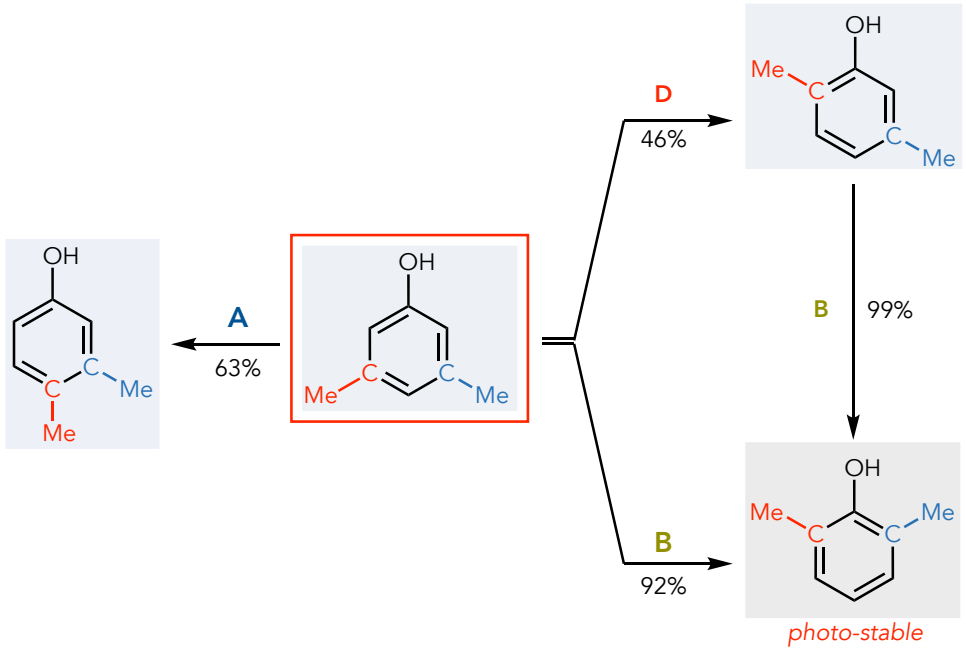
Alkyl Group Ring Walk: Systematic Analysis of Photo-stability



A	B	C	D
$AlBr_3$ (0.5 eq.), 310 nm, CH_2Cl_2 (0.1 M), r.t., 16 h	$AlBr_3$ (0.5 eq.), 390 nm CH_2Cl_2 (0.1 M), r.t., 16 h	TfOH (2-5 eq.), 390 nm $CHCl_3$ (0.1 M), r.t., 16 h	BCF (0.5 eq.), 390 nm CH_2Cl_2 (0.1 M), r.t., 16 h

X

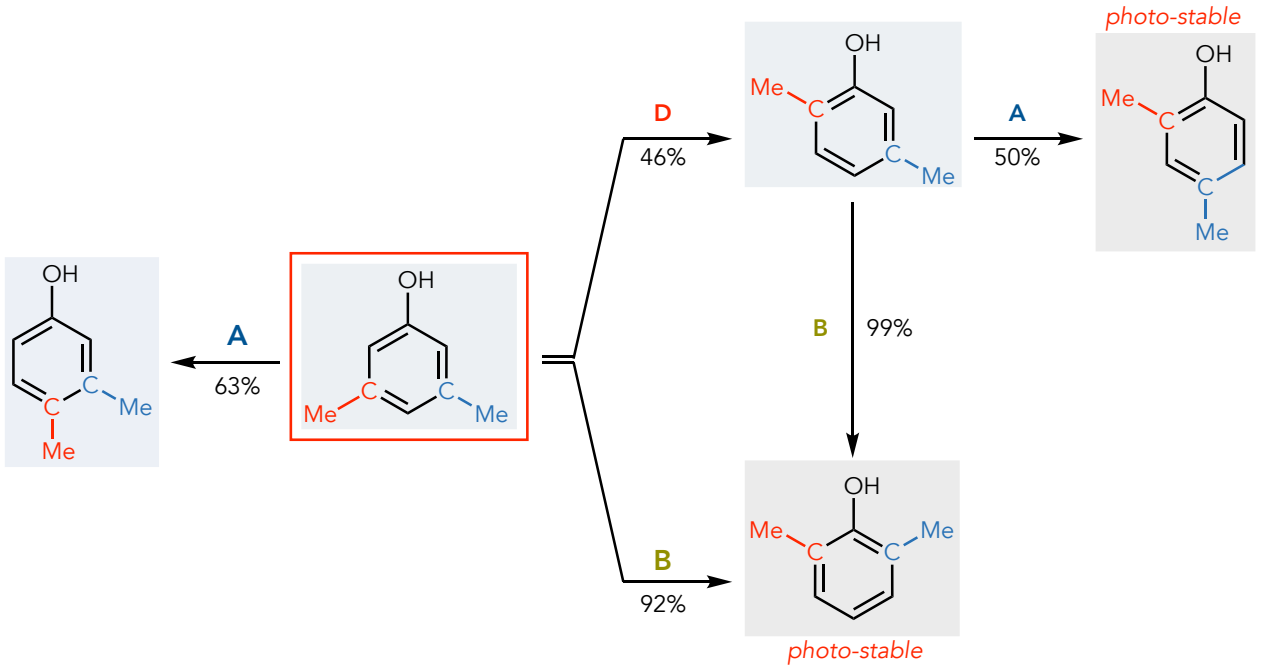
Alkyl Group Ring Walk: Systematic Analysis of Photo-stability



A	B	C	D
$AlBr_3$ (0.5 eq.), 310 nm, CH_2Cl_2 (0.1 M), r.t., 16 h	$AlBr_3$ (0.5 eq.), 390 nm CH_2Cl_2 (0.1 M), r.t., 16 h	TfOH (2-5 eq.), 390 nm $CHCl_3$ (0.1 M), r.t., 16 h	BCF (0.5 eq.), 390 nm CH_2Cl_2 (0.1 M), r.t., 16 h

X

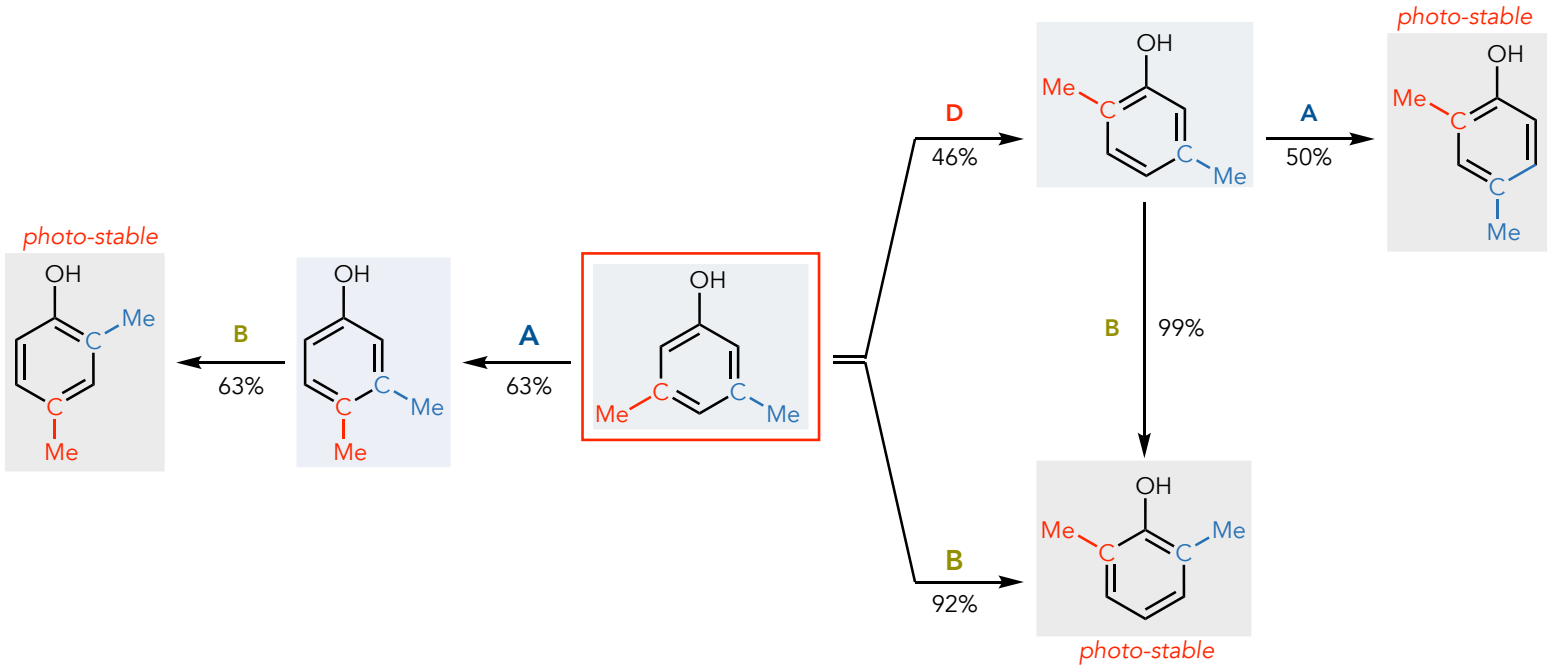
Alkyl Group Ring Walk: Systematic Analysis of Photo-stability



A	B	C	D
$AlBr_3$ (0.5 eq.), 310 nm, CH_2Cl_2 (0.1 M), r.t., 16 h	$AlBr_3$ (0.5 eq.), 390 nm CH_2Cl_2 (0.1 M), r.t., 16 h	TfOH (2-5 eq.), 390 nm $CHCl_3$ (0.1 M), r.t., 16 h	BCF (0.5 eq.), 390 nm CH_2Cl_2 (0.1 M), r.t., 16 h

X

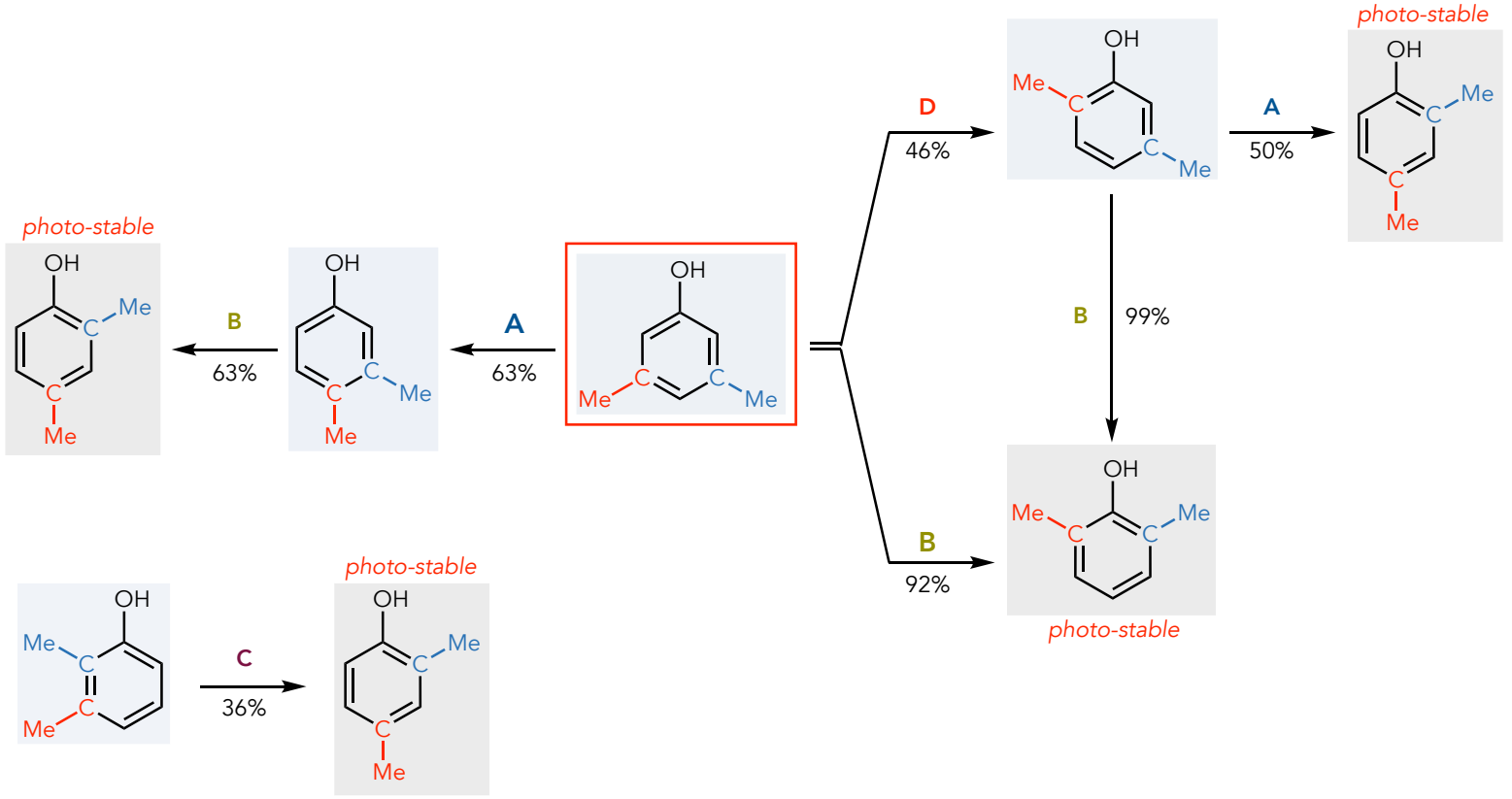
Alkyl Group Ring Walk: Systematic Analysis of Photo-stability



A	B	C	D
$AlBr_3$ (0.5 eq.), 310 nm, CH_2Cl_2 (0.1 M), r.t., 16 h	$AlBr_3$ (0.5 eq.), 390 nm CH_2Cl_2 (0.1 M), r.t., 16 h	TfOH (2-5 eq.), 390 nm $CHCl_3$ (0.1 M), r.t., 16 h	BCF (0.5 eq.), 390 nm CH_2Cl_2 (0.1 M), r.t., 16 h

X

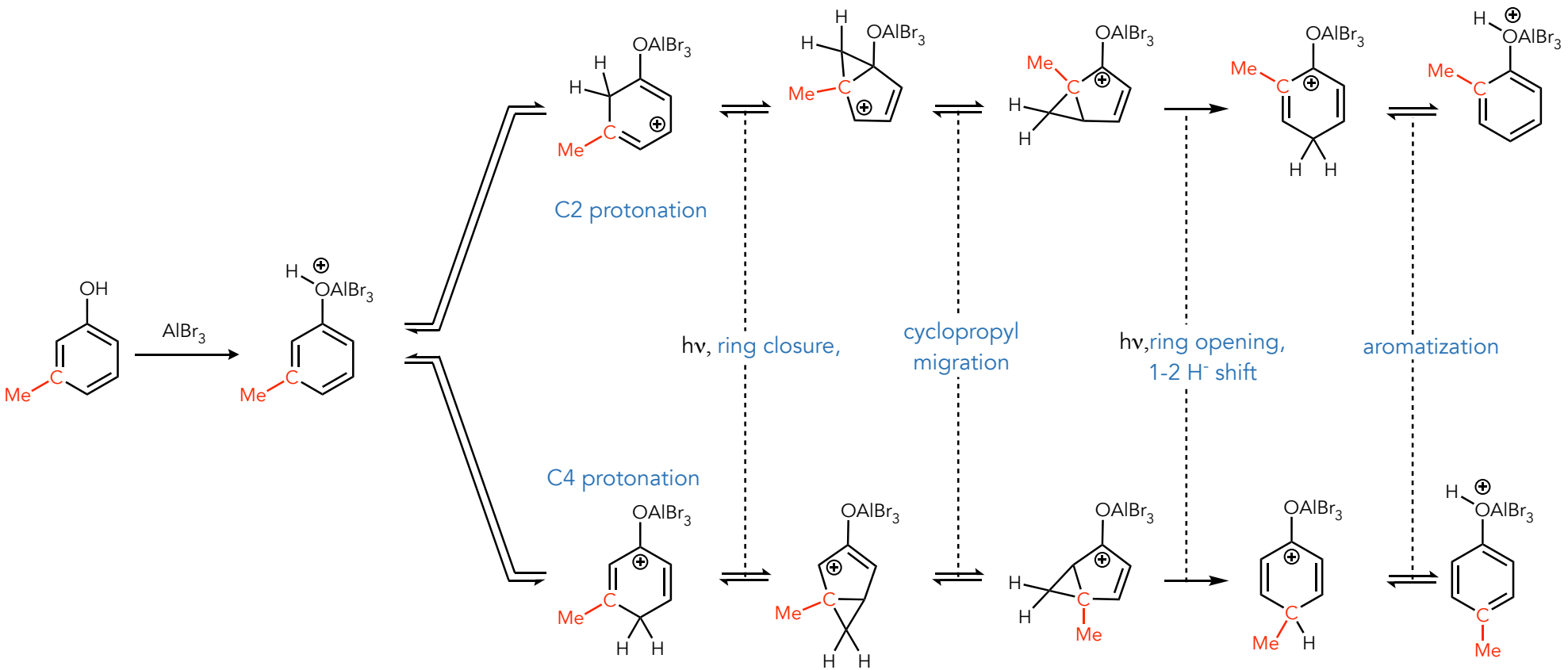
Alkyl Group Ring Walk: Systematic Analysis of Photo-stability



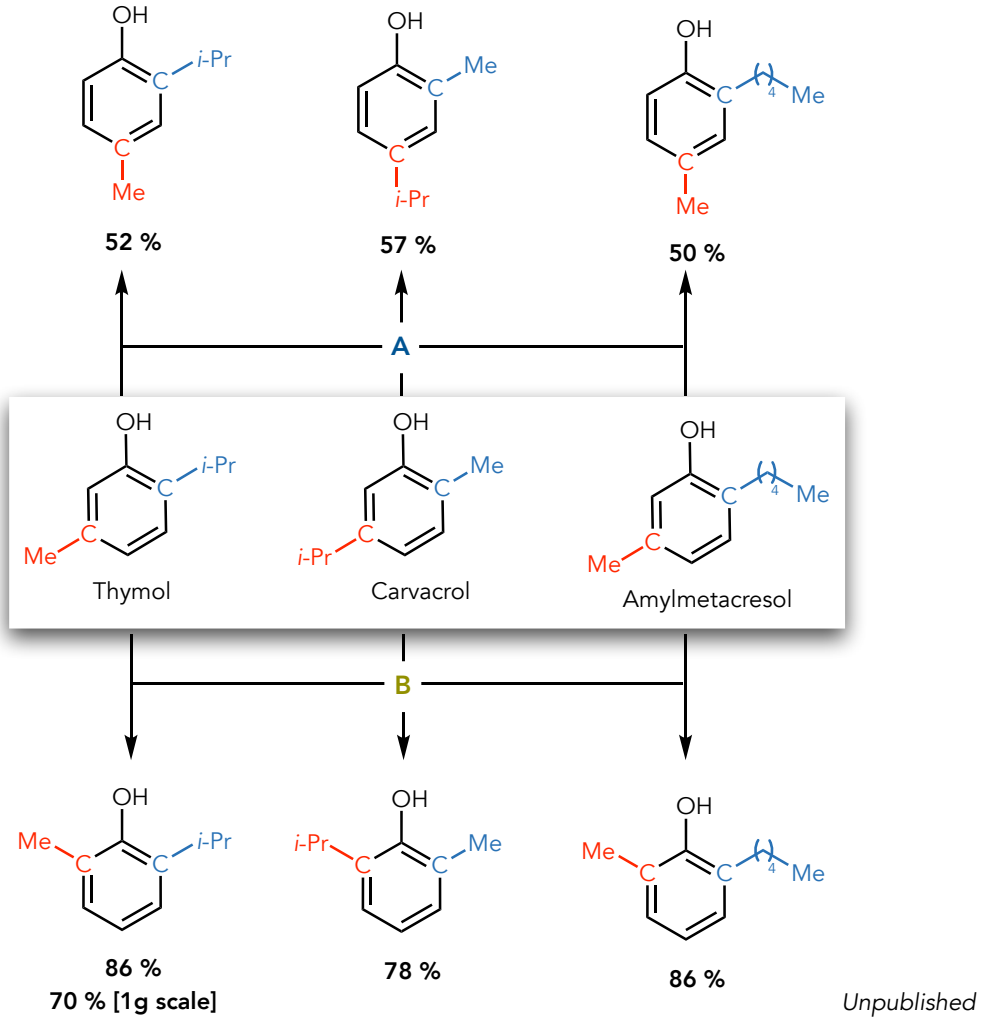
A	B	C	D
$AlBr_3$ (0.5 eq.), 310 nm, CH_2Cl_2 (0.1 M), r.t., 16 h	$AlBr_3$ (0.5 eq.), 390 nm CH_2Cl_2 (0.1 M), r.t., 16 h	TfOH (2-5 eq.), 390 nm $CHCl_3$ (0.1 M), r.t., 16 h	BCF (0.5 eq.), 390 nm CH_2Cl_2 (0.1 M), r.t., 16 h

X

Aryl-Alkyl Group Ring Walk - Mechanism



Alkyl Group Ring Walk : Scope



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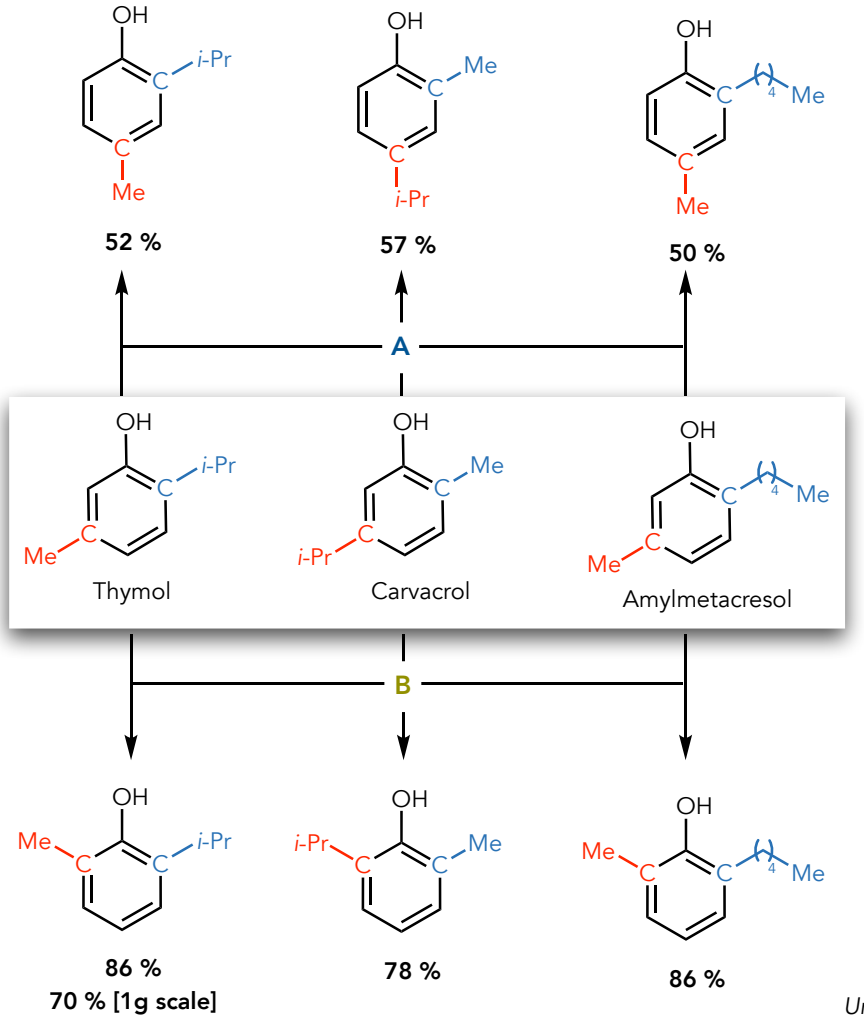

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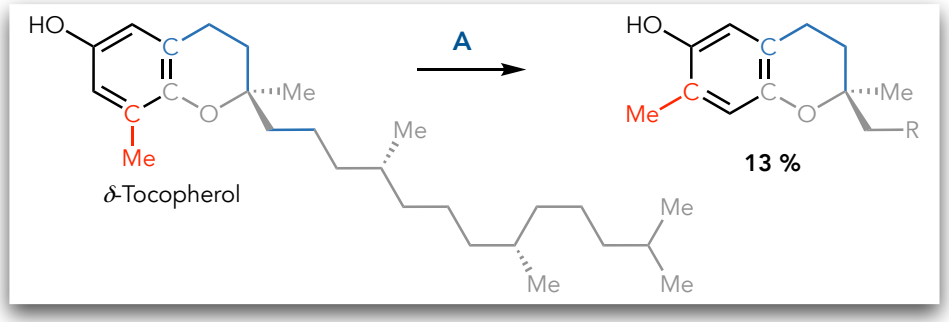
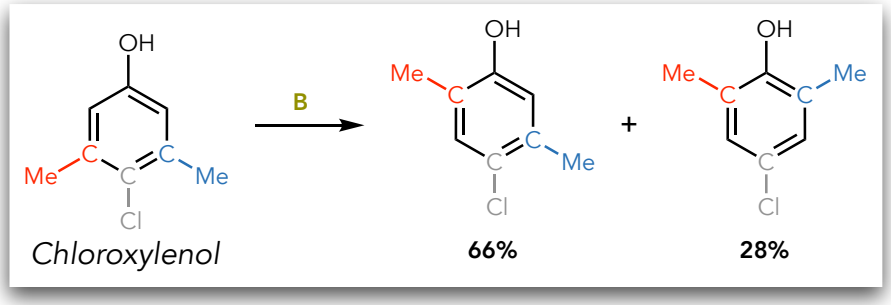
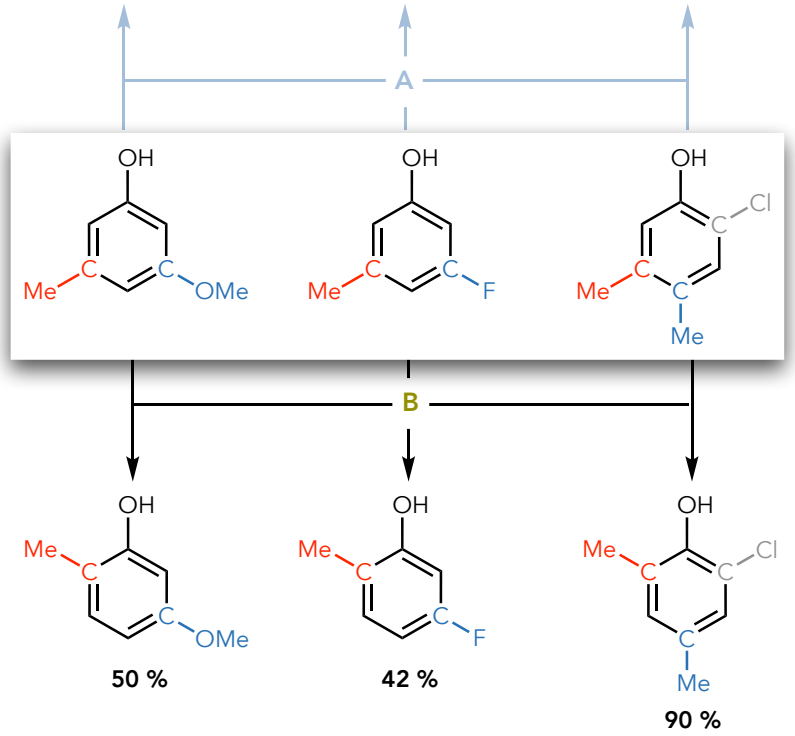




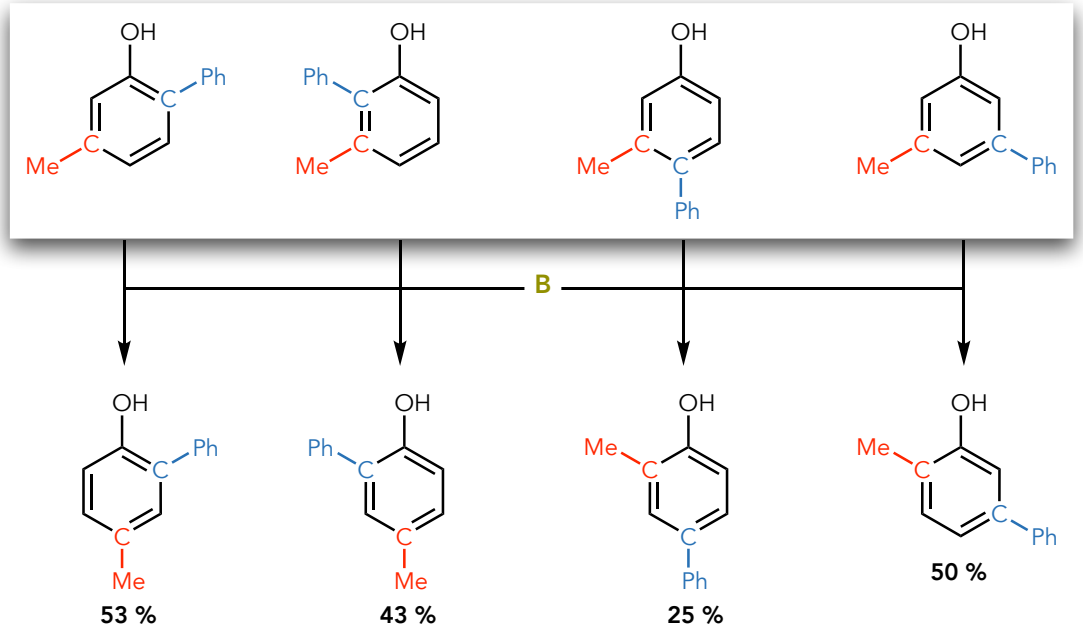
Substitution Pattern Alteration via Alkyl Group Ring Walk



A	B	C	D
$AlBr_3$ (0.5 eq.), 310 nm, CH_2Cl_2 (0.1 M), r.t., 16 h	$AlBr_3$ (0.5 eq.), 390 nm CH_2Cl_2 (0.1 M), r.t., 16 h	TfOH (2-5 eq.), 390 nm $CHCl_3$ (0.1 M), r.t., 16 h	BCF (0.5 eq.), 390 nm CH_2Cl_2 (0.1 M), r.t., 16 h

Unpublished

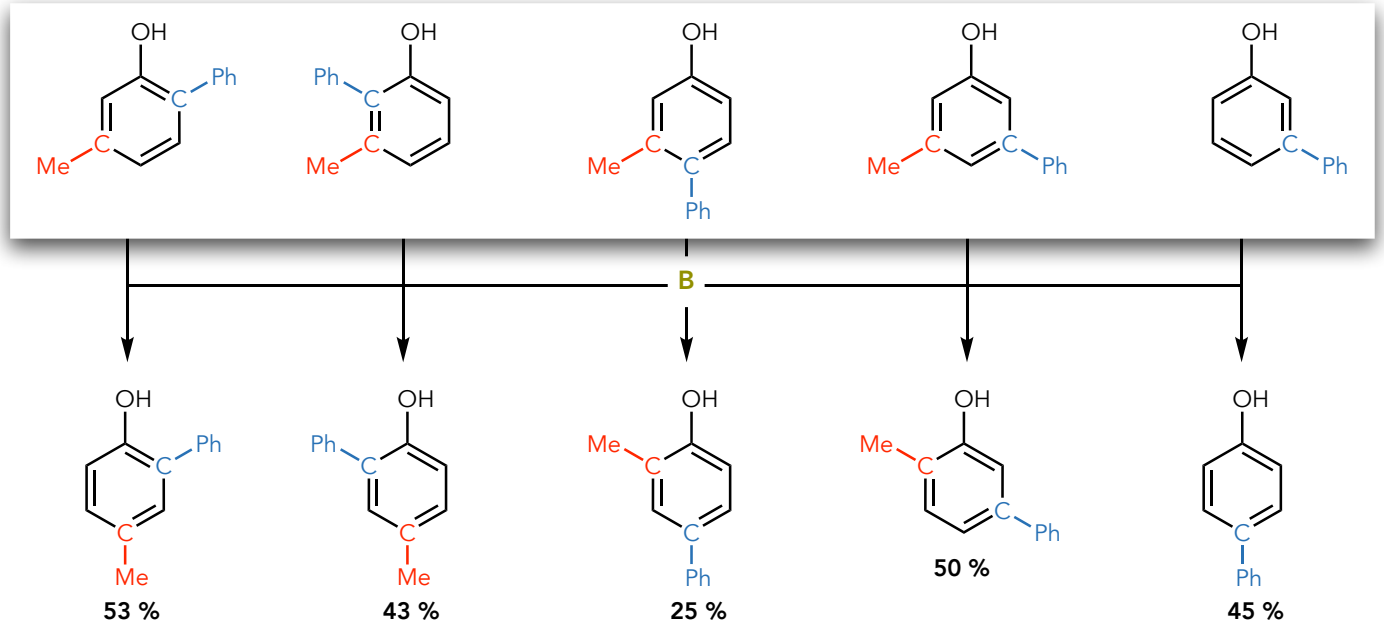
Alkyl Group Ring Walk : Scope



A	B	C	D	E
$AlBr_3$ (0.5 eq.), 310 nm, CH_2Cl_2 (0.1 M), r.t., 16 h	$AlBr_3$(0.5 eq.), 390 nm CH_2Cl_2 (0.1 M), r.t., 16 h	TfOH (2-5 eq.), 390 nm $CHCl_3$ (0.1 M), r.t., 16 h	BCF (0.5 eq.), 390 nm CH_2Cl_2 (0.1 M), r.t., 16 h	TfOH (2-5 eq.), 310 nm, CH_2Cl_2 (0.1 M), r.t., 16 h

Unpublished

Alkyl Group Ring Walk : Scope

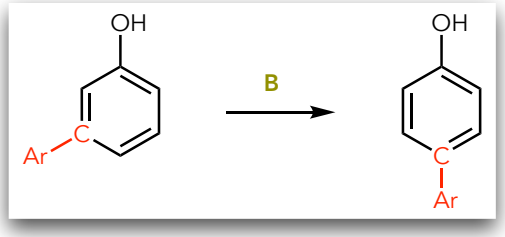


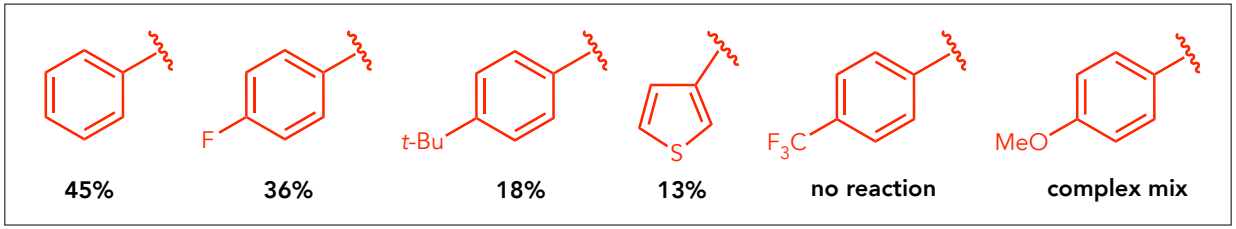
A	B	C	D	E
$AlBr_3$ (0.5 eq.), 310 nm, CH_2Cl_2 (0.1 M), r.t., 16 h	$AlBr_3$(0.5 eq.), 390 nm CH_2Cl_2 (0.1 M), r.t., 16 h	TfOH (2-5 eq.), 390 nm $CHCl_3$ (0.1 M), r.t., 16 h	BCF (0.5 eq.), 390 nm CH_2Cl_2 (0.1 M), r.t., 16 h	TfOH (2-5 eq.), 310 nm, CH_2Cl_2 (0.1 M), r.t., 16 h

X

Unpublished

*Substitution Pattern Alteration via **Aryl** Group Ring Walk*

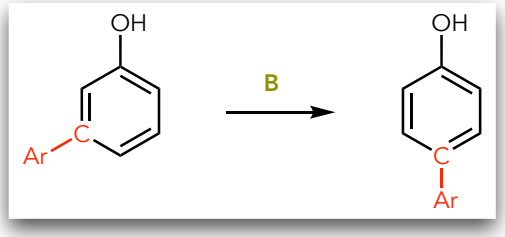


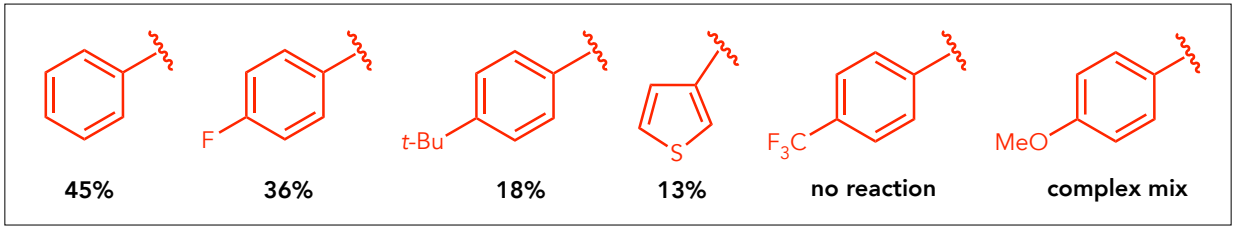


A	B	C	D	E
$AlBr_3$ (0.5 eq.), 310 nm, CH_2Cl_2 (0.1 M), r.t., 16 h	$AlBr_3$(0.5 eq.), 390 nm CH_2Cl_2 (0.1 M), r.t., 16 h	TfOH (2-5 eq.), 390 nm $CHCl_3$ (0.1 M), r.t., 16 h	BCF (0.5 eq.), 390 nm CH_2Cl_2 (0.1 M), r.t., 16 h	TfOH (2-5 eq.), 310 nm, CH_2Cl_2 (0.1 M), r.t., 16 h

X

*Substitution Pattern Alteration via **Aryl** Group Ring Walk*





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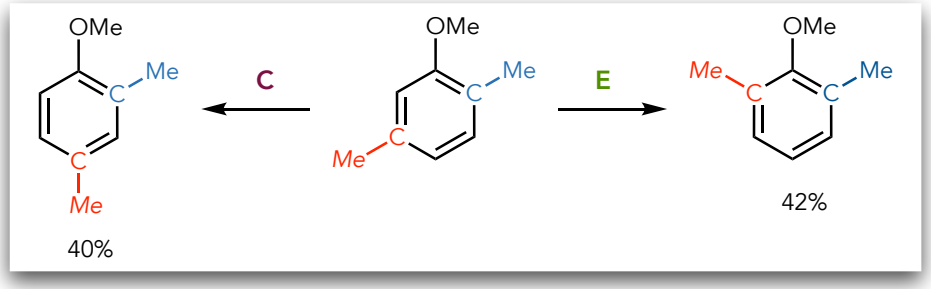
$AlBr_3$ (0.5 eq.), 310 nm, CH_2Cl_2 (0.1 M), r.t., 16 h	$AlBr_3$(0.5 eq.), 390 nm CH_2Cl_2 (0.1 M), r.t., 16 h	TfOH (2-5 eq.), 390 nm $CHCl_3$ (0.1 M), r.t., 16 h	BCF (0.5 eq.), 390 nm CH_2Cl_2 (0.1 M), r.t., 16 h	TfOH (2-5 eq.), 310 nm, CH_2Cl_2 (0.1 M), r.t., 16 h



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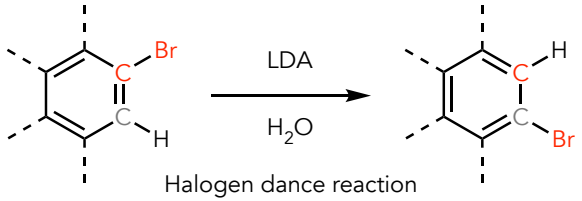
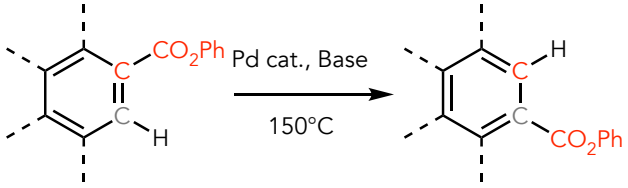
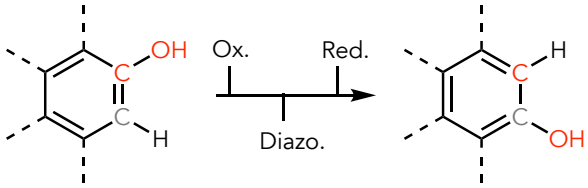
Substitution Pattern Alteration Reactions



Halogen dance reaction
review: Erb *Tetrahedron* **2016**, 4973

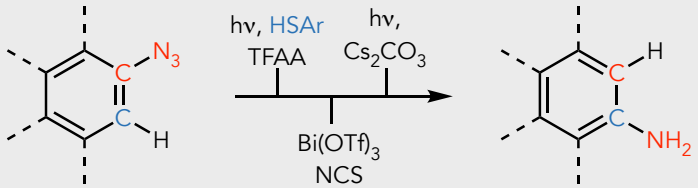


Yamaguci, *Sci. Adv.* **2020**, 6

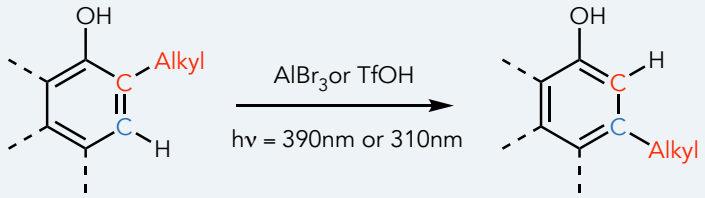


Lumb, *Nat. Chem.* **2024**, 1193

New of synthetic strategy for Nitrogen Ring Walk



New Methodology for Alkyl Group Ring Walk



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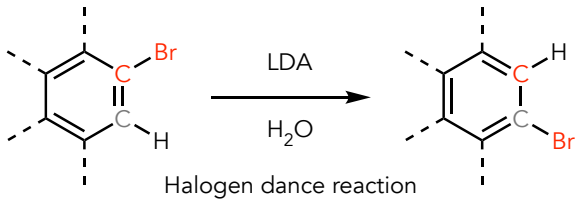
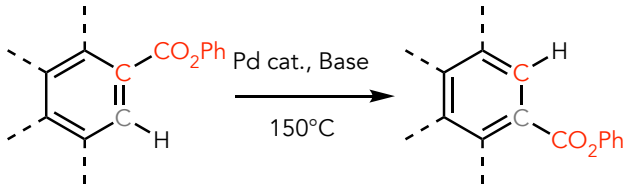
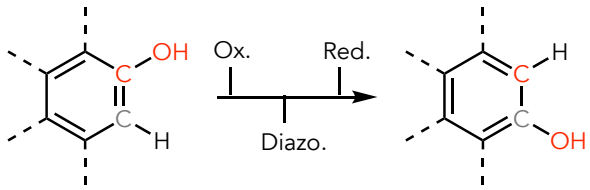
Substitution Pattern Alteration: Directionality



Halogen dance reaction
review: Erb *Tetrahedron* **2016**, 4973



Yamaguci, *Sci. Adv.* **2020**, 6

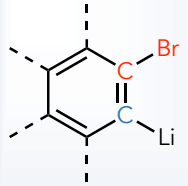


Lumb, *Nat. Chem.* **2024**, 1193

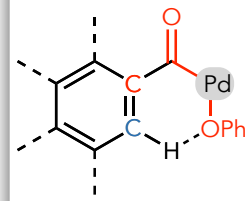
Deprotonation Equilibrium
by LDA

often lacks of directionality

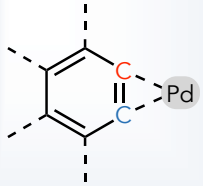
key intermidiate



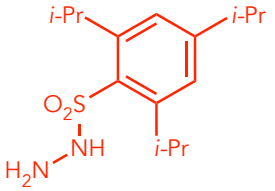
Thermodynamically driven CH activation
by Pd catalyst



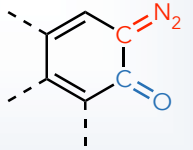
key intermidiate



Eletronically-sterically driven diazotization
by designed reagent



key intermidiate



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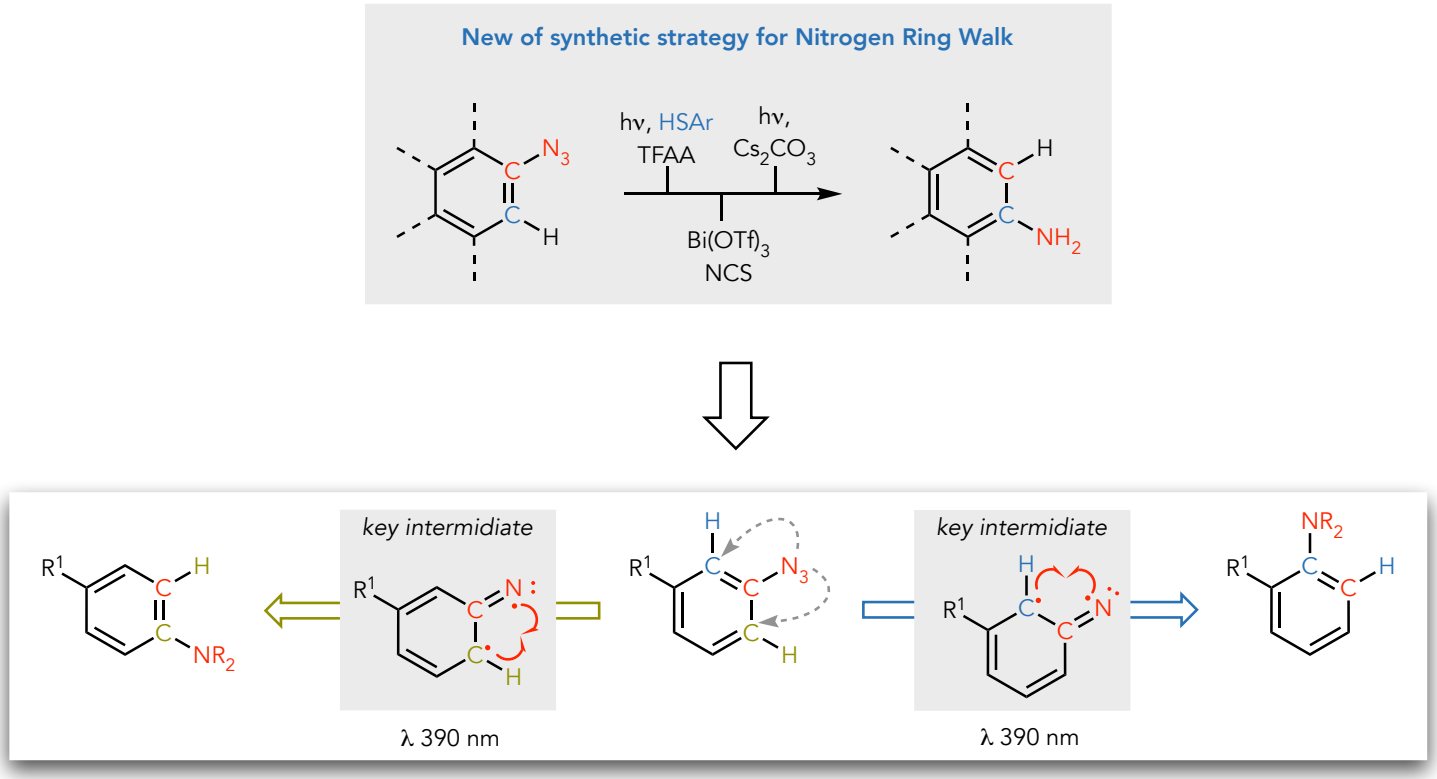
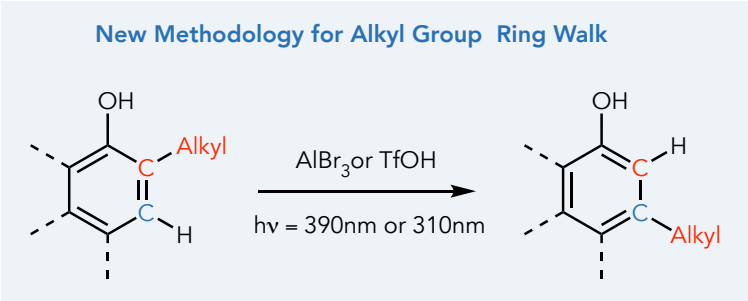
Substitution Pattern Alteration: Directionality

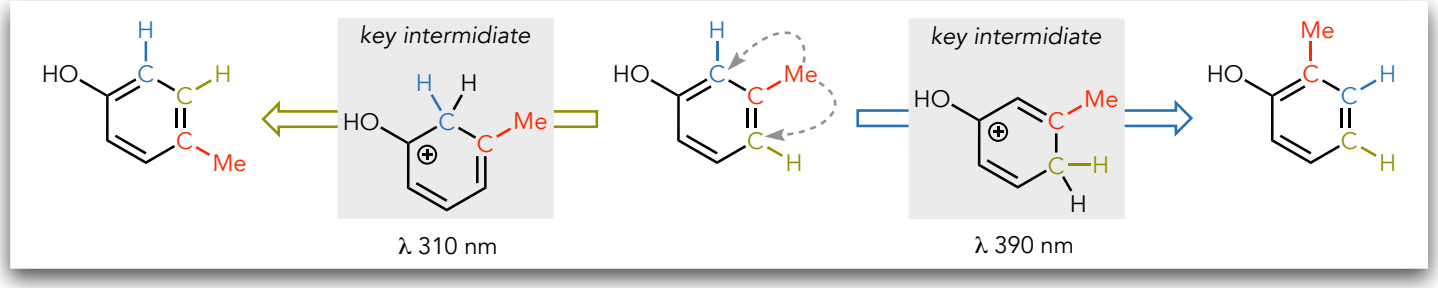


Single Nitrene delocalization-insertion

Inherent directionality

Substitution Pattern Alteration: Directionality





Protonation and Absorption are fundamental for the directionality

Group translocation can be controlled by different wave length

Unpublished

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Photochemistry for Benzene Substitution Pattern Alteration

Photochemistry Rearrangements :

Sustainable : Avoids precious metals like iridium, platinum, and ruthenium.

Energy Efficiency: No heat required, with the potential to harness solar light as an energy source (energy savings)

Atom Economy: Promotes highly efficient photochemical transformation, all atoms are already into the final product.

Proc. Natl Acad. Sci. USA **2007**, 16964

X

Acknowledgment

Institute of Organic Chemistry, RWTH Aachen University

Prof. Daniele Leonori

Nitrogen ring walk

Giovanni Lenardon

Xheila Yzeiri

Dr. Bo Liv

Alkyl ring walk

Maialen Alonso

Dr. Giovanni Leonardi

Baptist Roure

Dr. Enrique Arpa

The Organizers of Innovation & Sustainability in Process Chemistry for the invitation

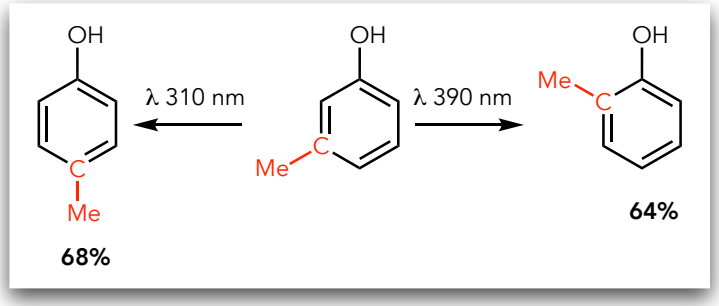
All of you for your kind attention

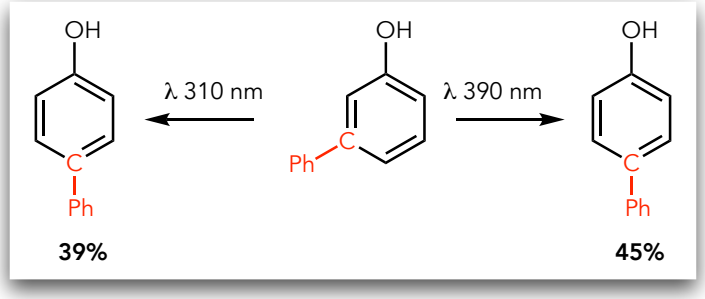
Moving soon to Otto Diels Institute for Organic Chemistry, Kiel, Germany

PhD and PDRA positions open to join the group

alessandro.ruffoni@RWTH-aachen.de

Selectivity





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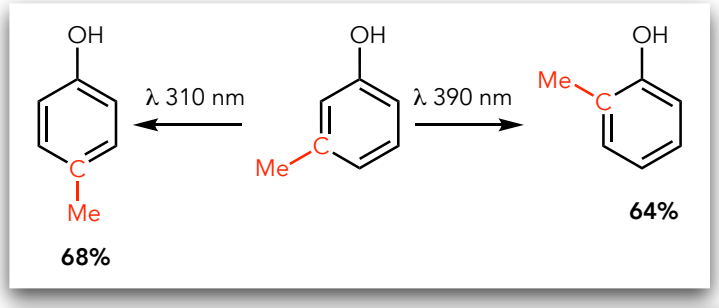
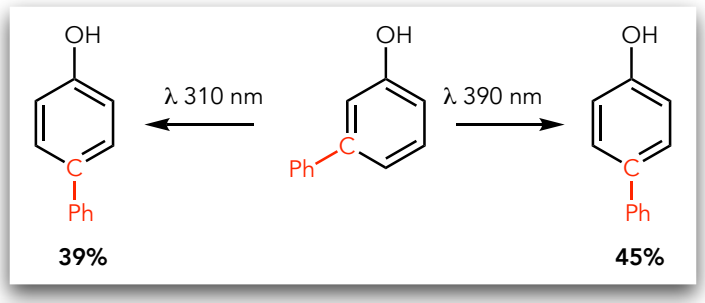
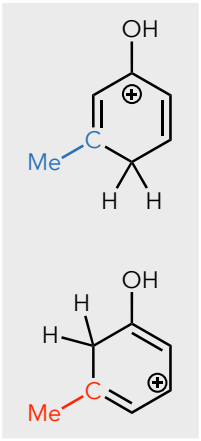
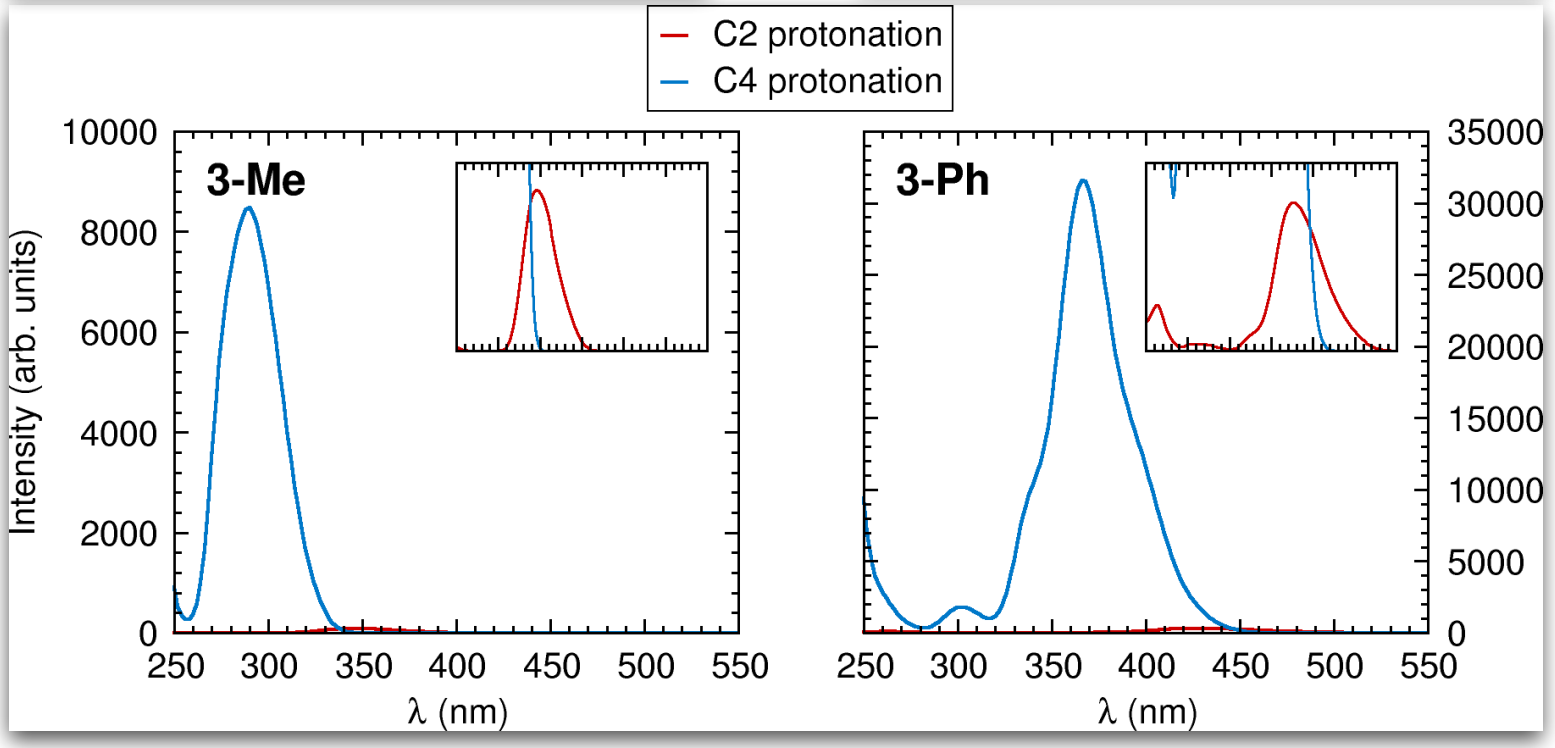
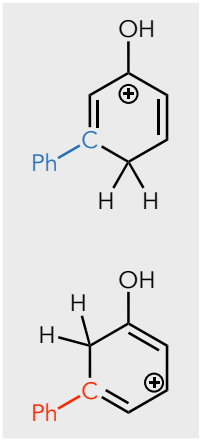
Selectivity





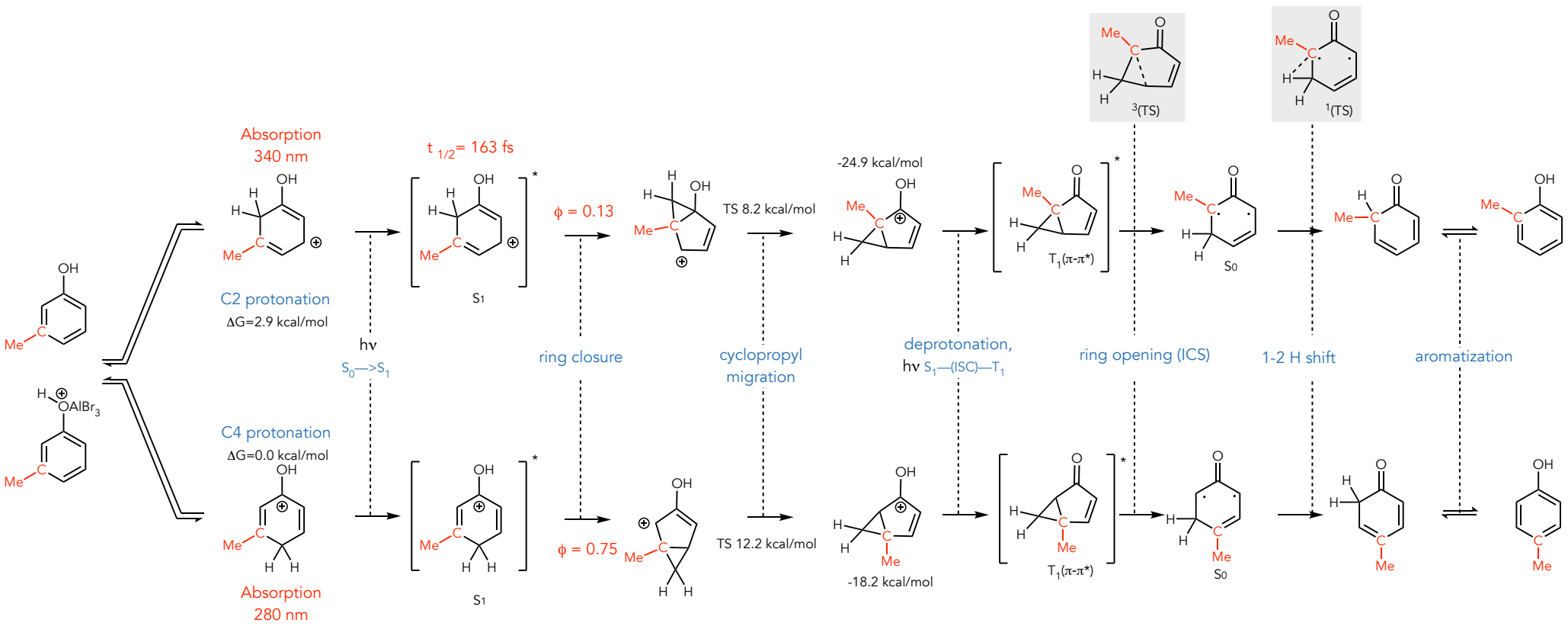






x

Alkyl Group Ring Walk - Mechanism



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