

Cleavage of Olefins Using Photoexcited Nitroarenes

**2023.11.25. Literature Seminar
M2 Hisahiro Morozumi**

Contents

- 1. Introduction**
- 2. Reaction of Photoexcited Nitroarenes toward olefins**
- 3. Cleavage of Olefins Using Photoexcited Nitroarenes**
nature

Article

Photoexcited nitroarenes for the oxidative cleavage of alkenes

Alessandro Ruffoni^{1,3}, Charlotte Hampton^{2,3}, Marco Simonetti²✉ & Daniele Leonori¹✉

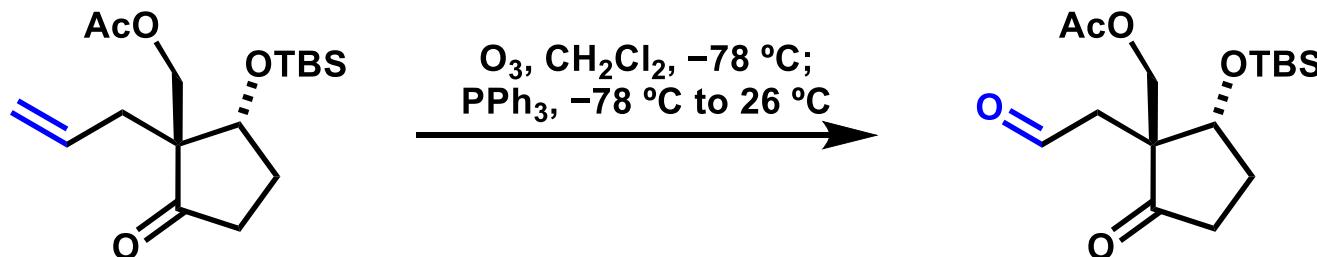
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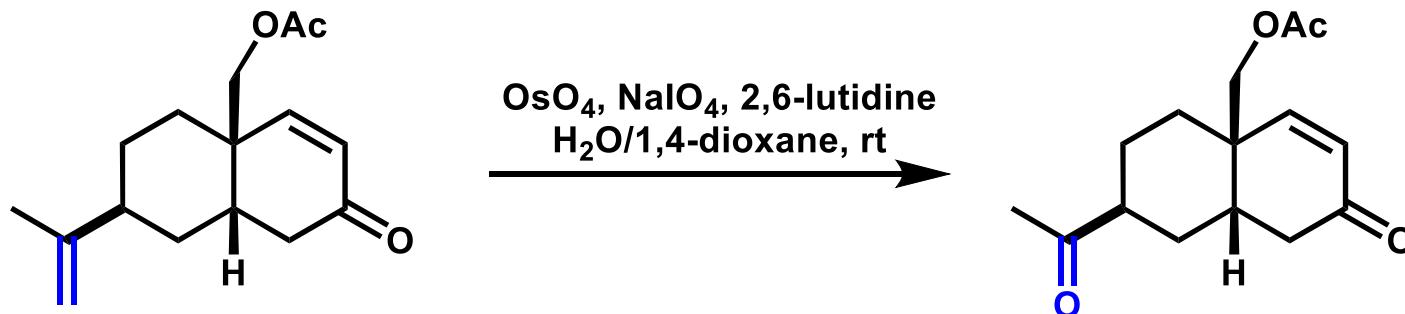
Cleavage of Olefins

- Example of cleavage of olefins in total synthesis

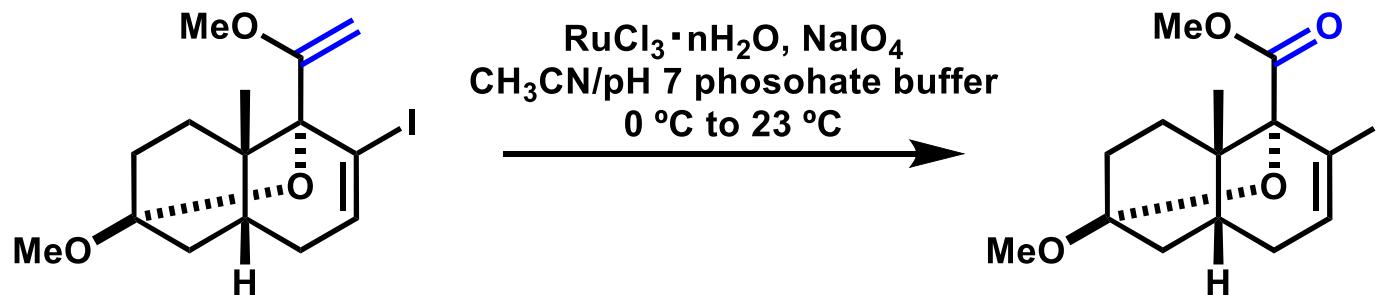
1. Ozonolysis



2. Lemieux-Johnson oxidation



3. Oxidation using other transition metal oxides



1) Watanabe, Y.; Morozumi, H.; Mutoh, H.; Hagiwara, K.; Inoue, M. *Angew. Chem. Int. Ed.* **2023**, 62, e202309688.

2) Urabe, D.; Nakagawa, Y.; Mukai, K.; Fukushima, K. Aoki, N.; Itoh, H.; Nagatomo, M.; Inoue, M. *J. Org. Chem.* **2018**, 83, 13888-13910.

Problems of Existing Methods

There are some problems with these oxidation methods.

1. Ozonolysis

- High toxicity
- Extreme oxidizing power
 - Less chemoselectivity
- Difficult to control the equivalent

2. Lemieux-Johnson oxidation

- High toxicity
- Toxic waste
- High cost
- High oxidizing power

3. Oxidation using other transition metal oxides

- Yield mixtures of products of various oxidation degrees (due to over-oxidation)
- High cost

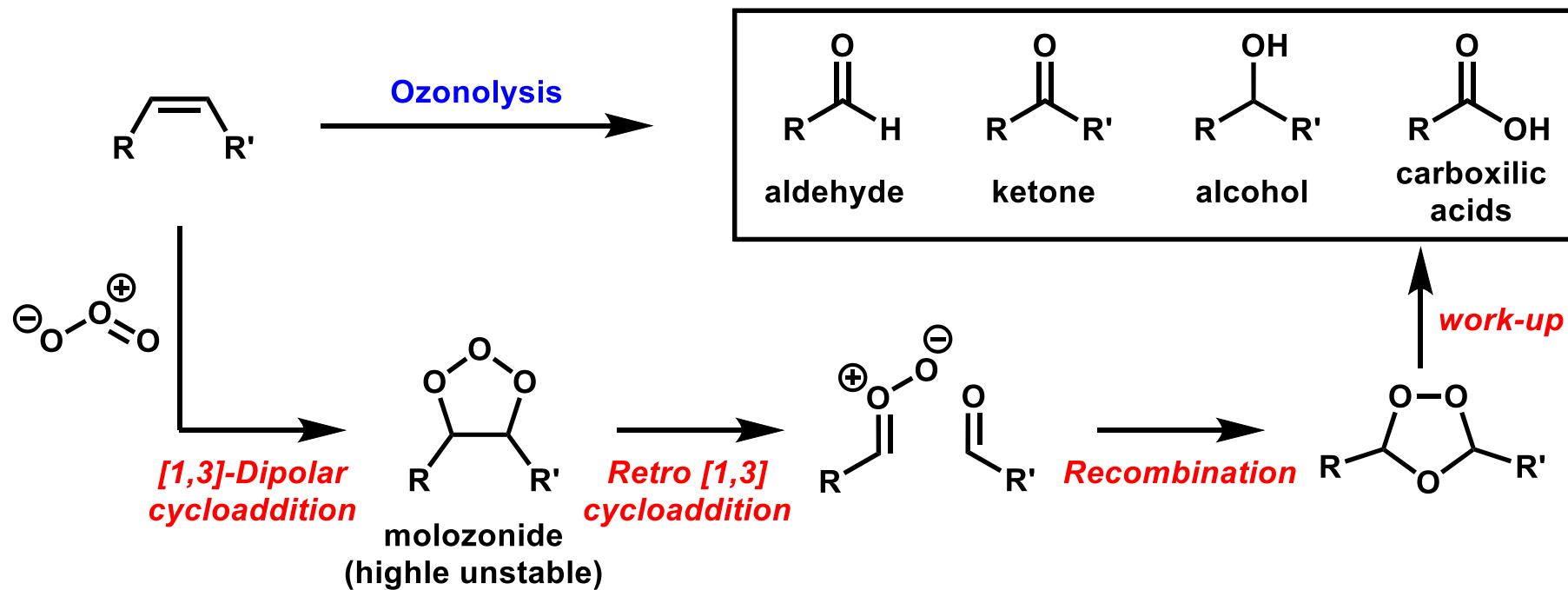
There is a need to develop a **safe, inexpensive** method
for oxidative cleavage of olefins **chemoselectively**.

Contents

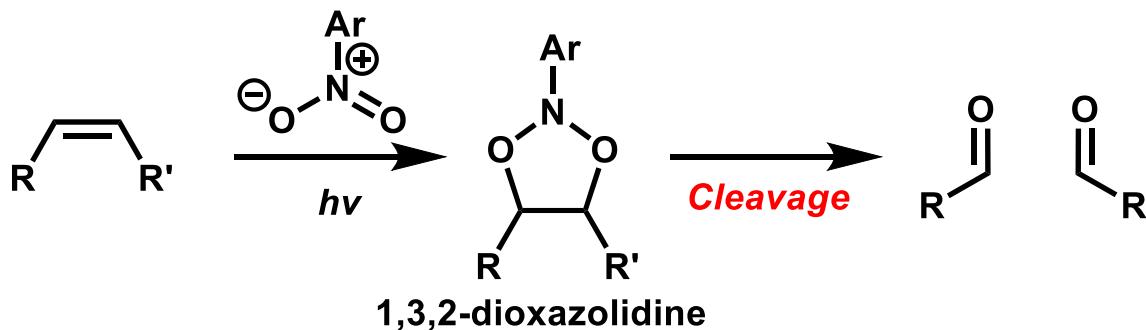
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Nitroarenes as Ozone Surrogates

Ozonolysis for the oxidative cleavage of olefins

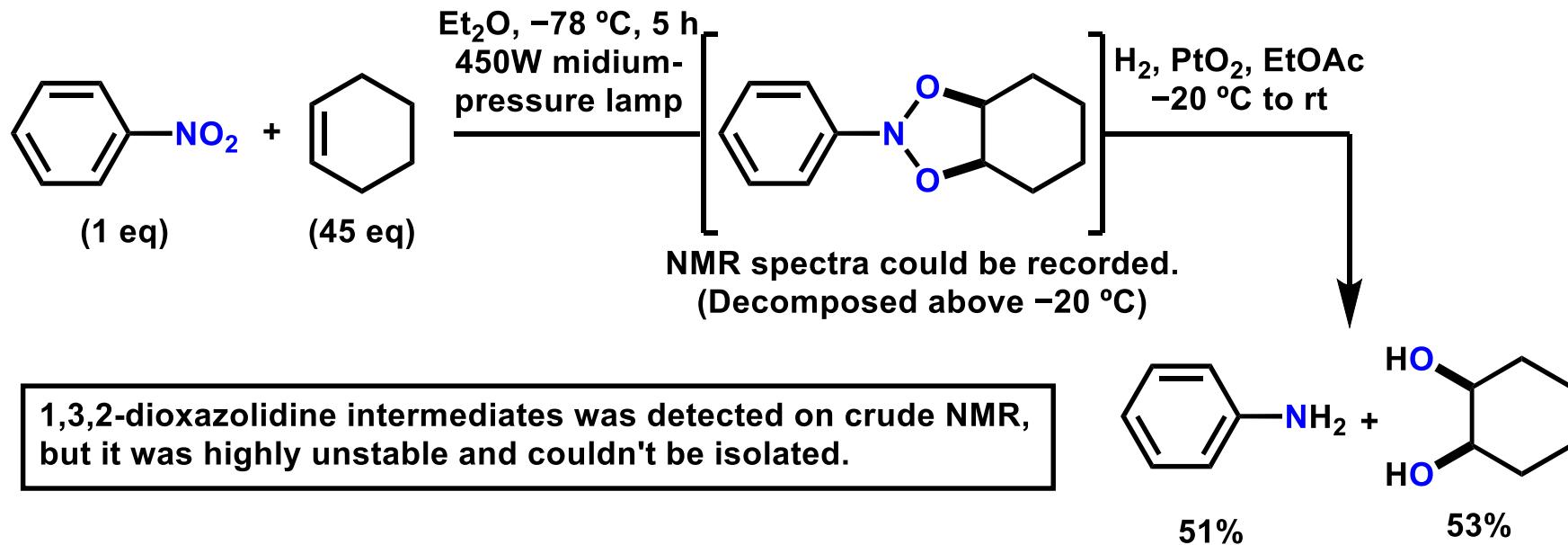


Is it possible to use Nitroarens as a substitute for ozone...?

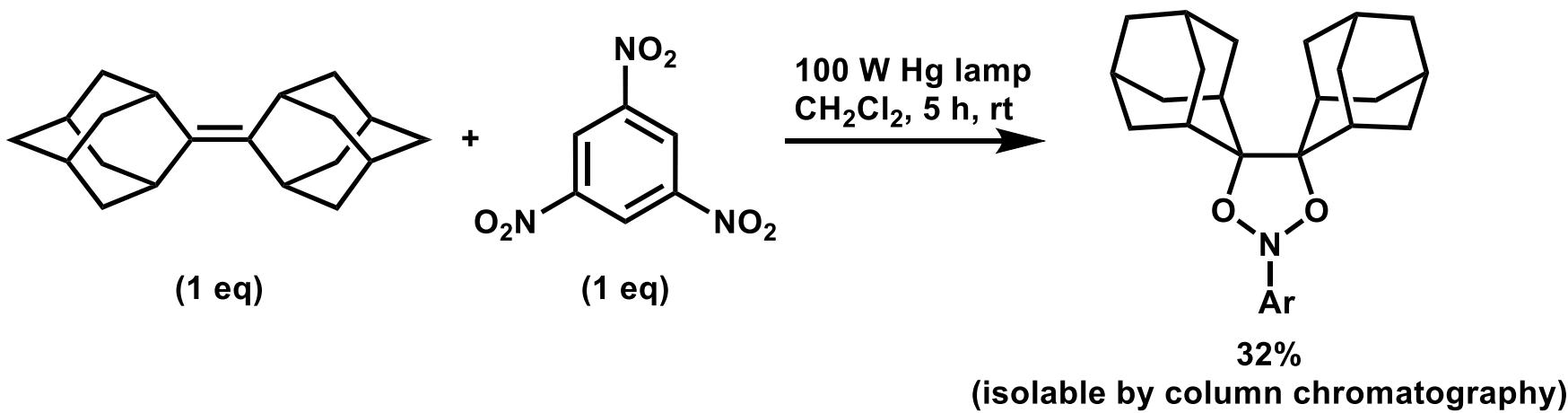


1,3,2-dioxazolidine

- Initial detection of the 1,3,2-dioxazolidine intermediate¹⁾



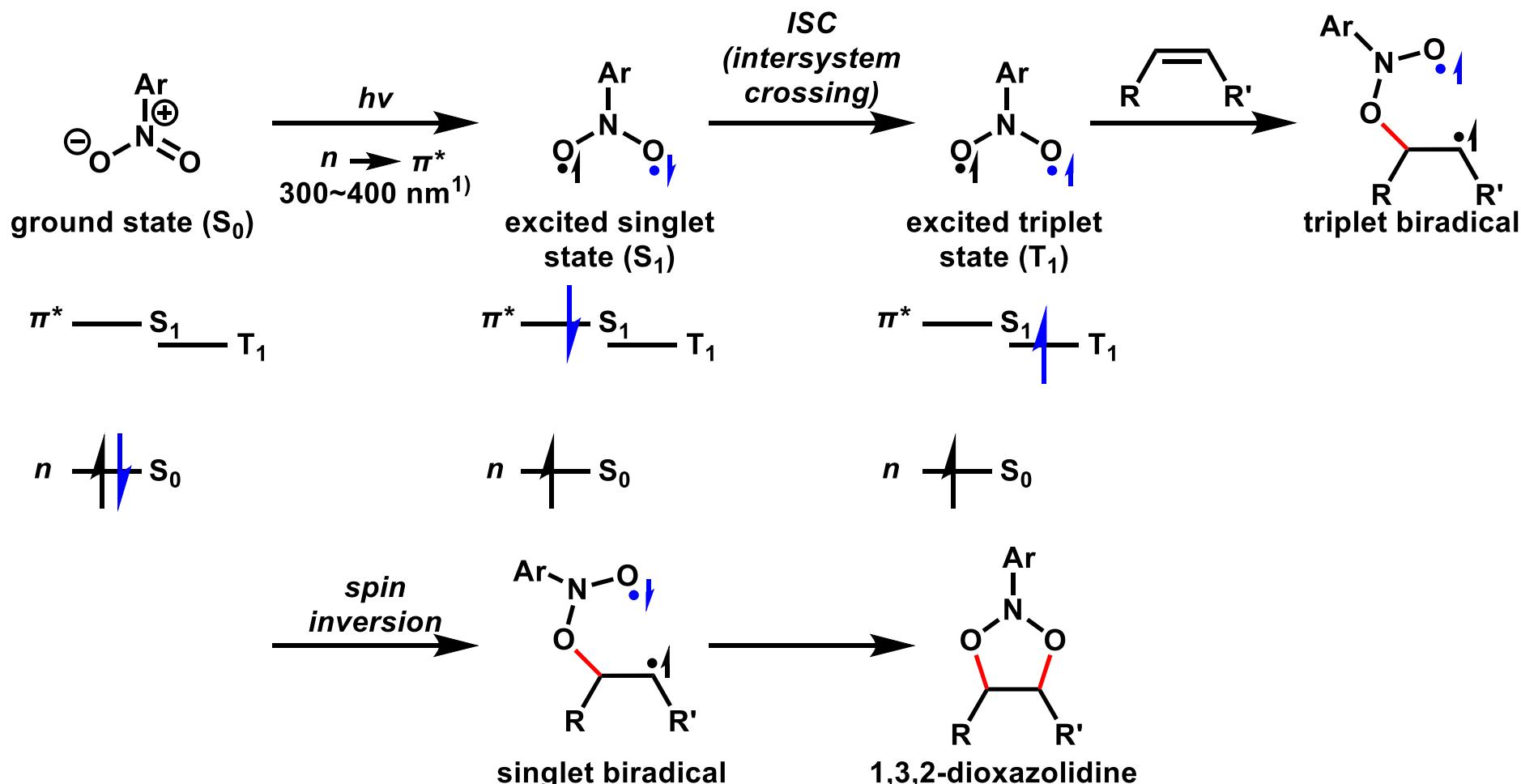
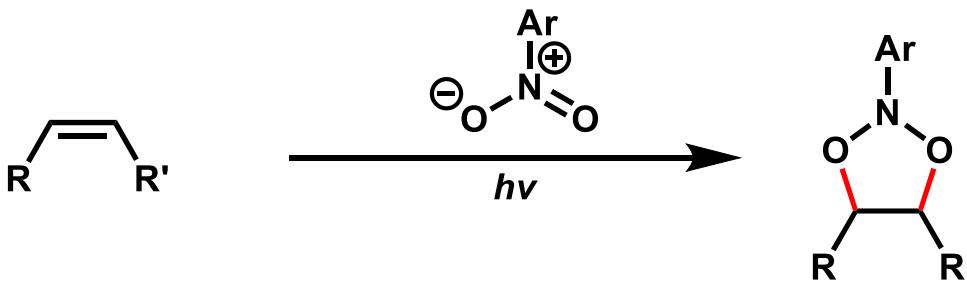
- Isolation of the 1,3,2-dioxazolidine intermediate²⁾



1) Charlton, J. L.; Liao, C. C.; De Mayo, P. J. *J. Am. Chem. Soc.* **1971**, 93, 2463-2471.

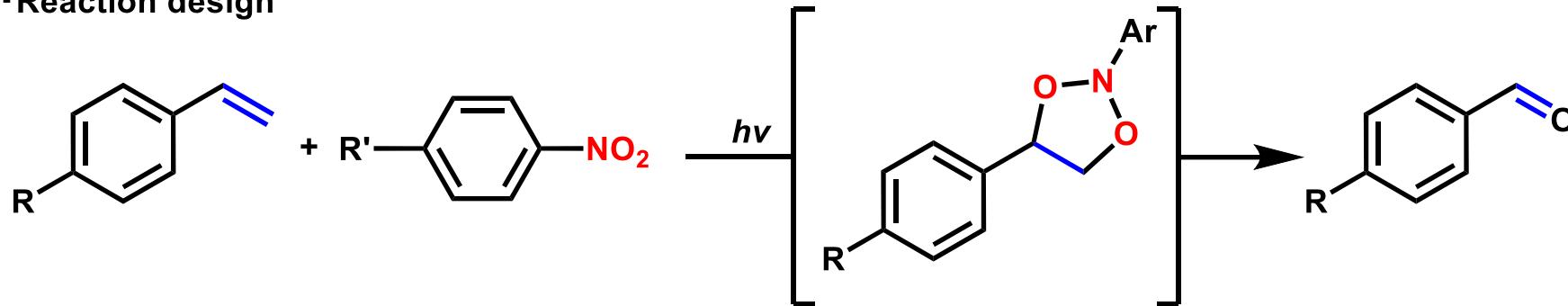
2) Okada, K.; Saito, Y.; Oda, M. *J. Chem. Soc. Chem. Commun.* **1992**, 1721-1732.

Proposed Reaction Mechanism

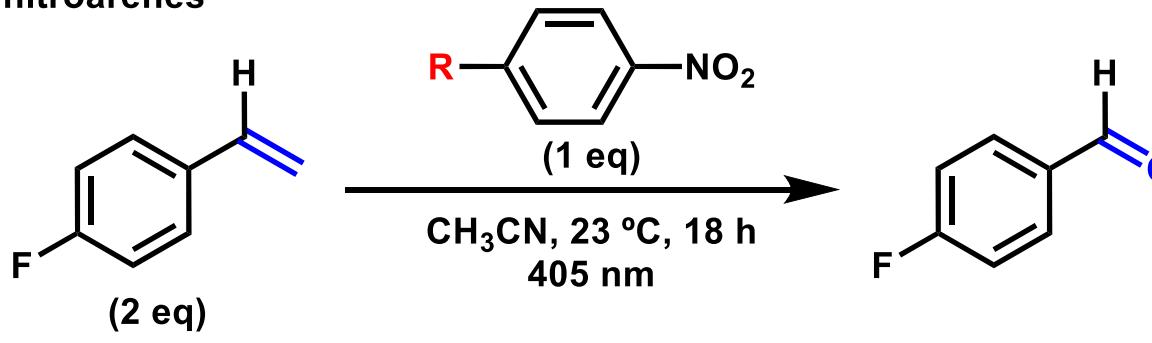


Cleavage of Olefins by Parasram Group

- Reaction design



- Optimization of nitroarenes



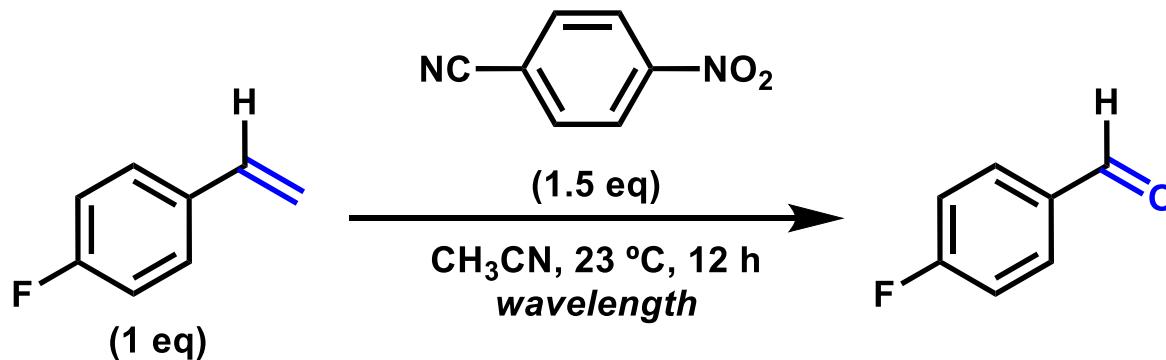
entry	R	$\sigma_{\text{para}}^{2)}$	yield
1	NH ₂	-0.66	0%
2	OMe	-0.27	8%
3	H	0	37%
4	CF ₃	0.54	83%
5	CN	0.66	88%
6	NO ₂	0.78	52%

Electron-withdrawing group improve reaction efficiency.

1) Wise, D. E.; Gogarnou, E. S.; Duke, A. D.; Paolillo, J. M.; Vacala, T. L.; Huassin, W. A.; Parasram, M. *J. Am. Chem. Soc.* **2022**, *144*, 15437-15442.

2) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165-195.

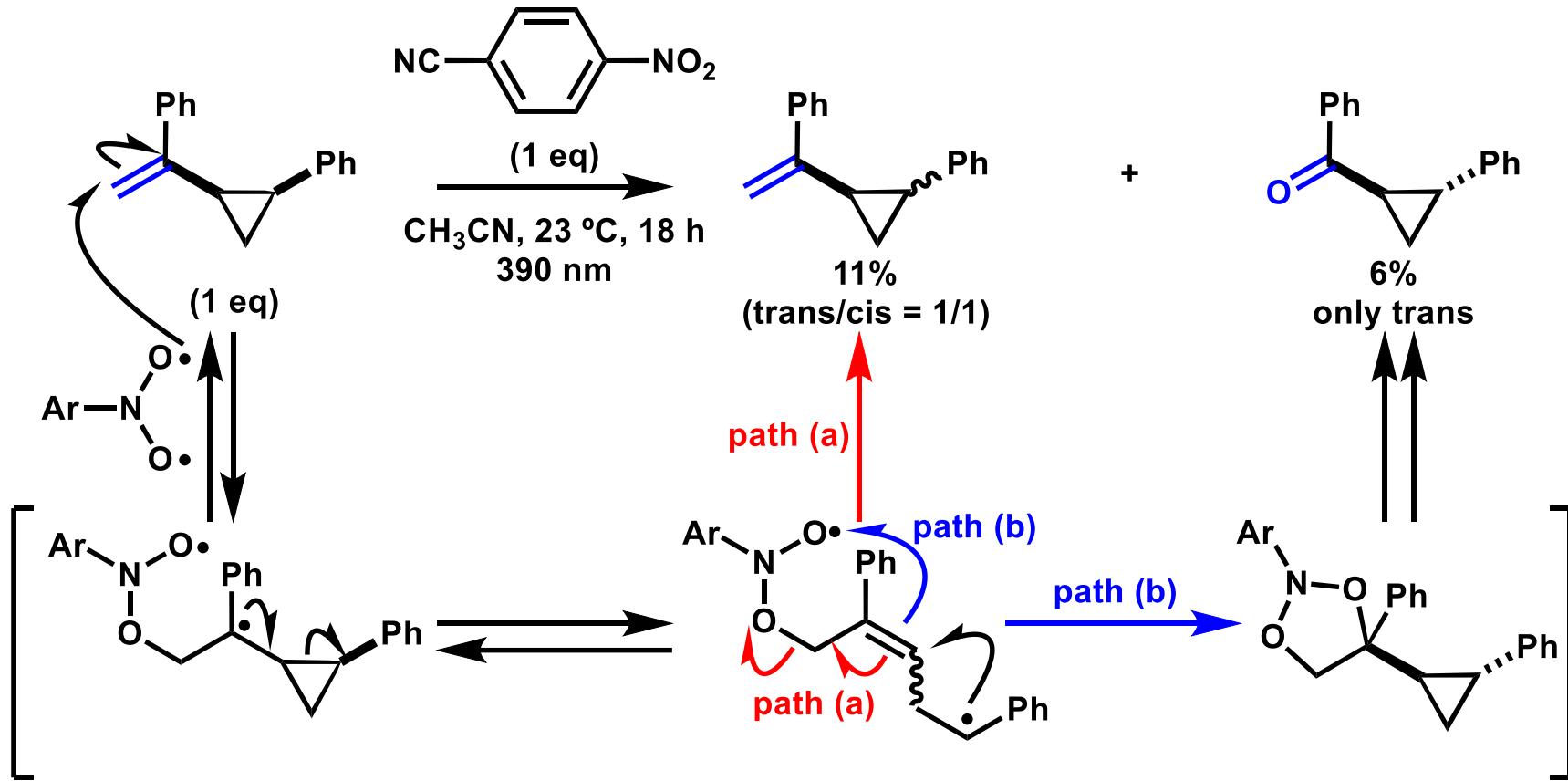
Optimization of Reaction Conditions (2)



entry	wavelength	yield
1	390 nm	71%
2	405 nm	65%
3	427 nm	67%
4	440 nm	55%
5	456 nm	25%
6	no light	no reaction

Mechanistic Study (1)

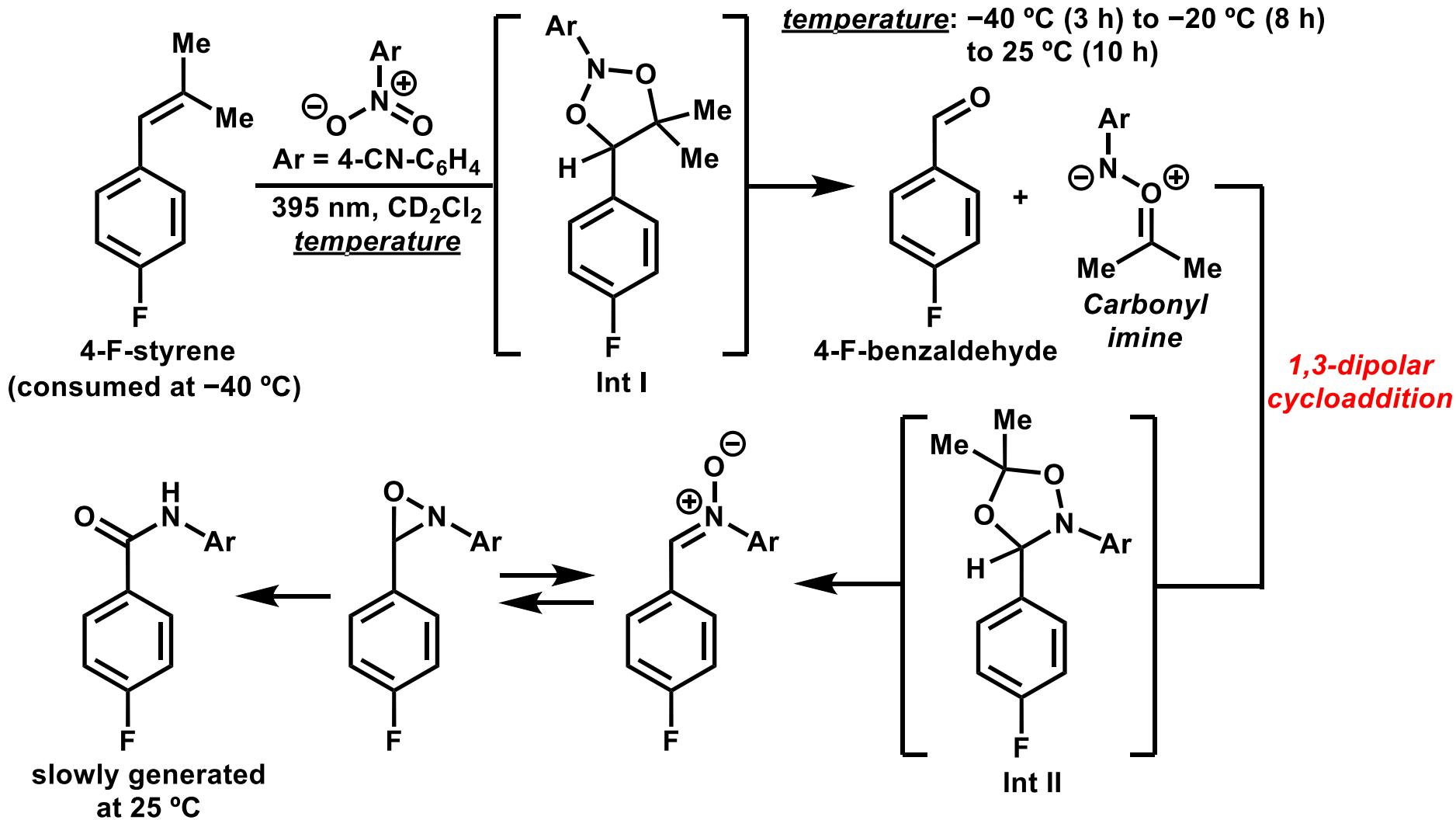
1. Radical clock studies



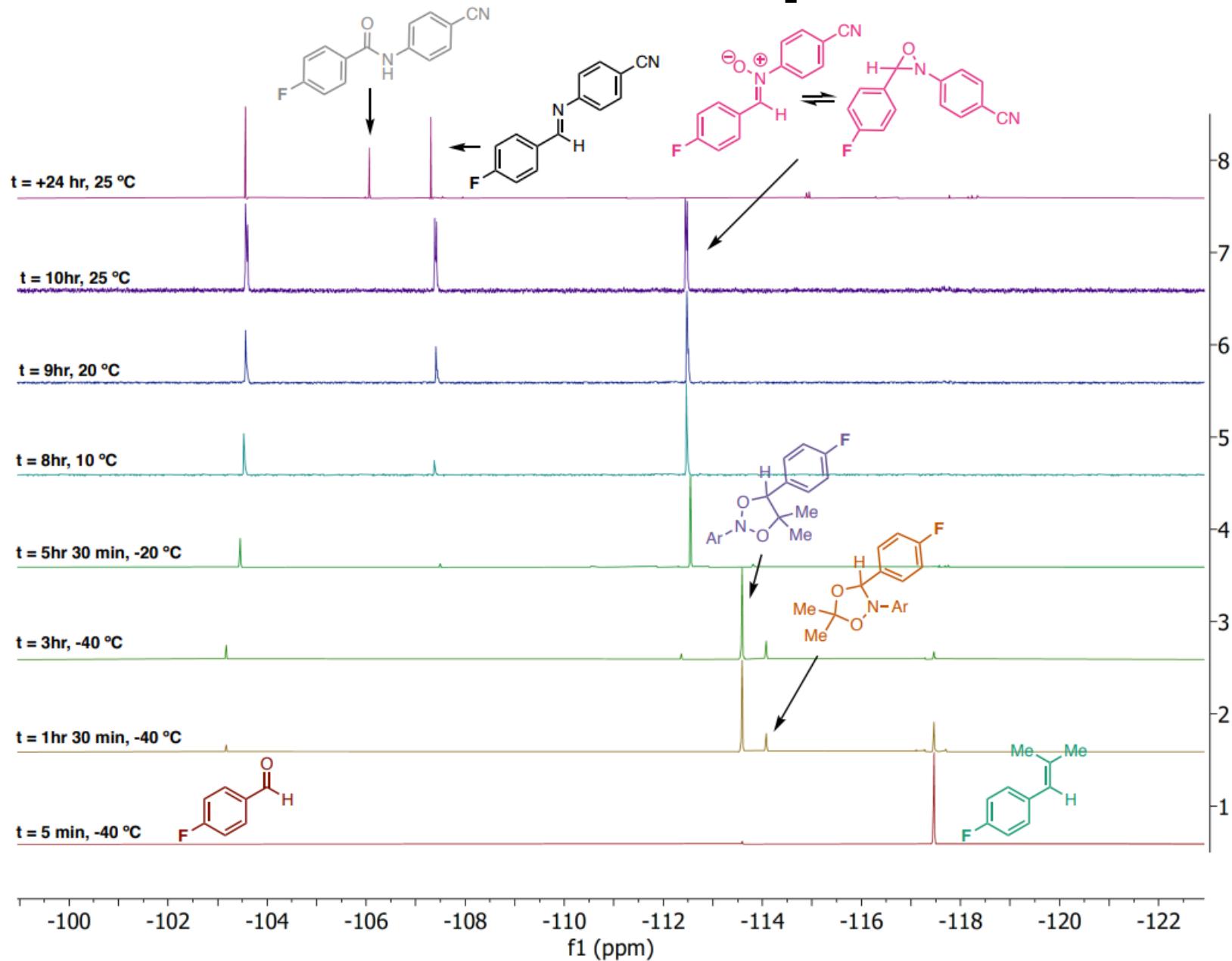
The ring-opened product was not detected, but the stereoisomer was obtained.

Mechanistic Study (2)

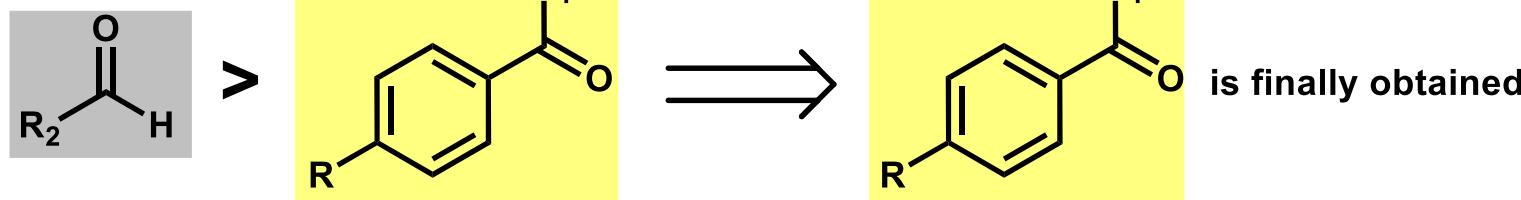
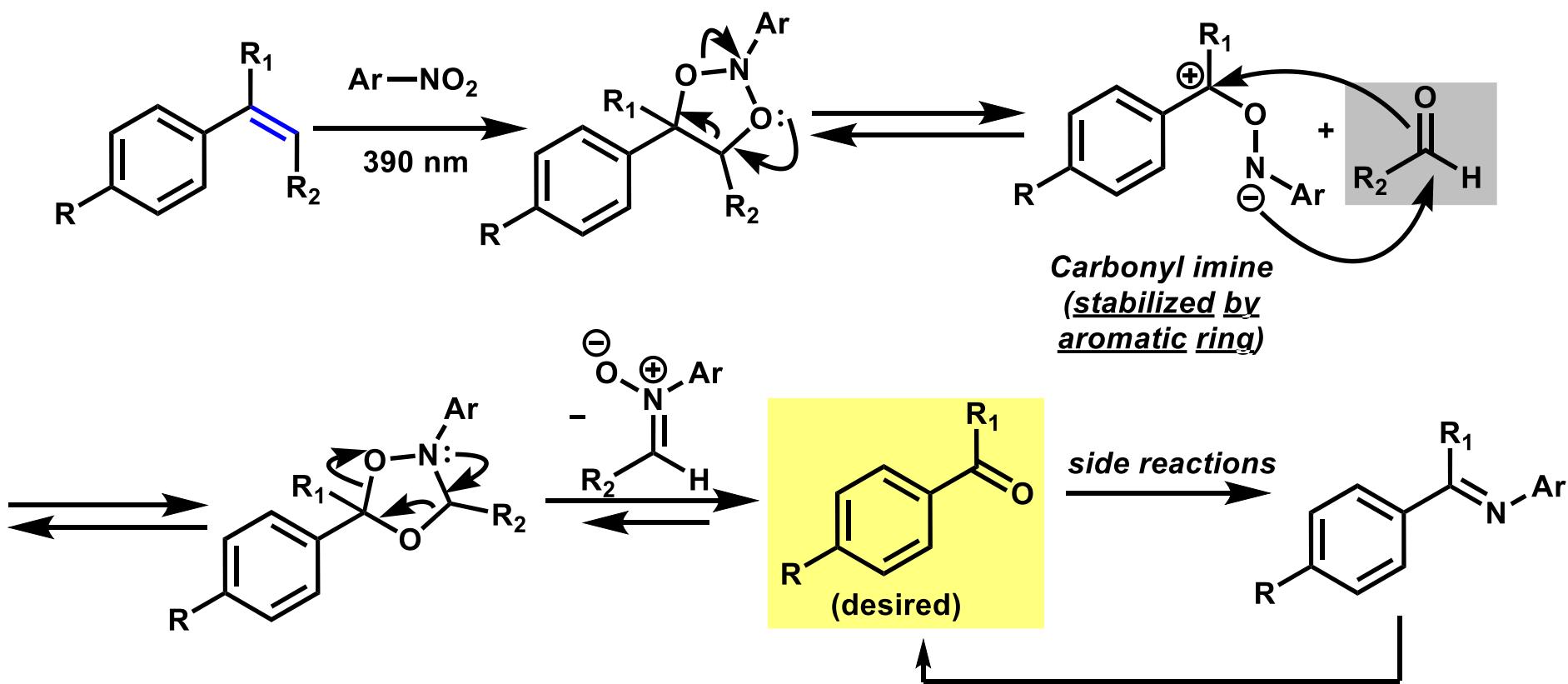
2. PhotoNMR monitoring of the intermediates and evidence for byproducts.



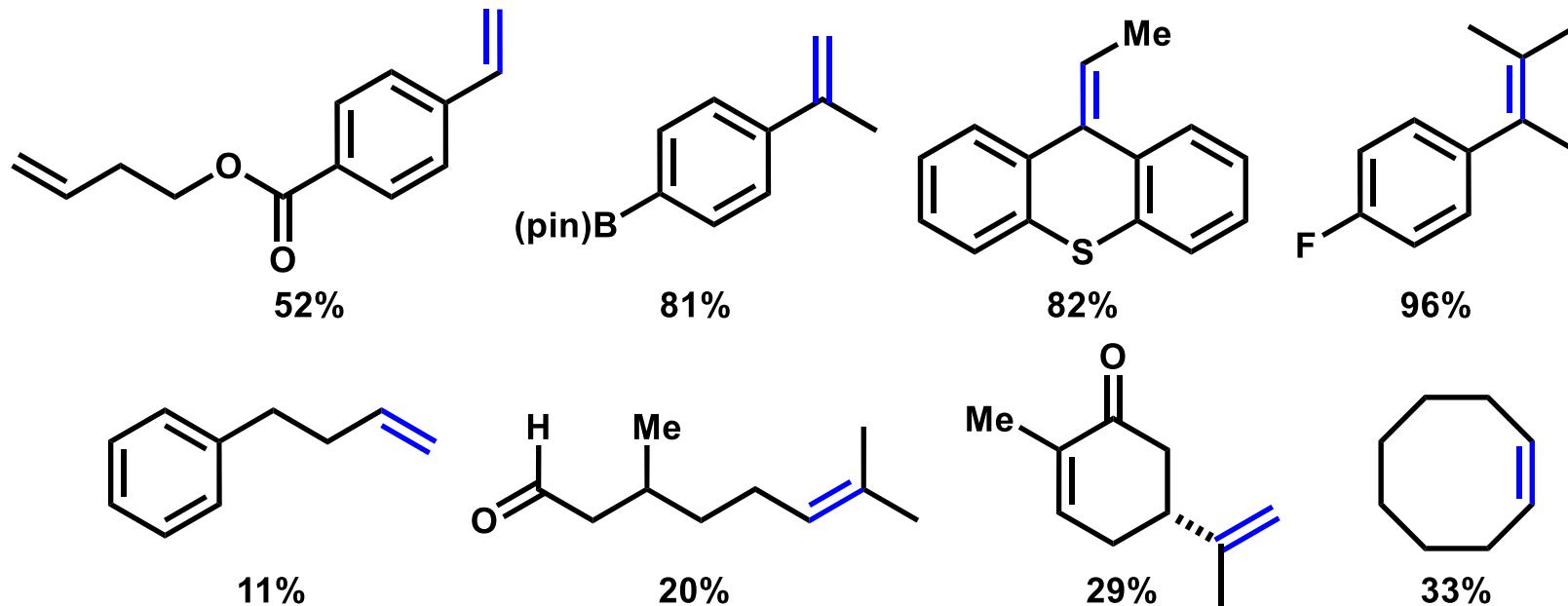
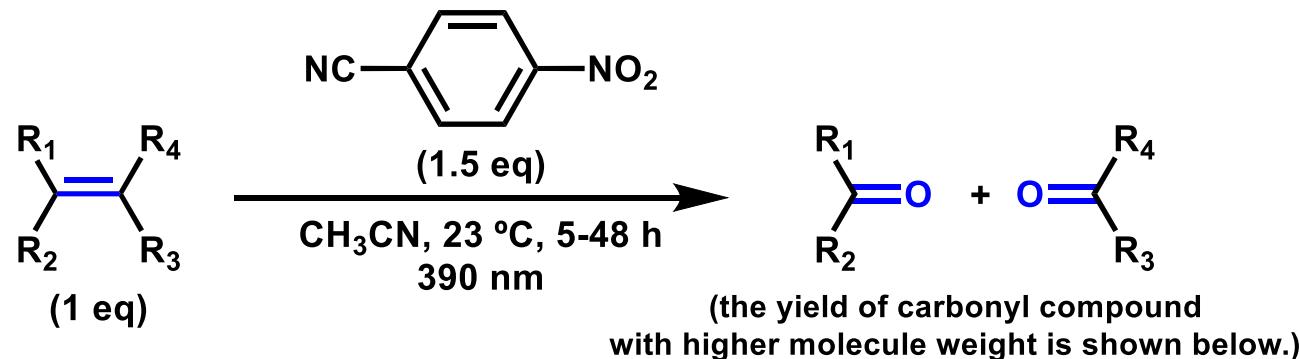
19F PhotoNMR Spectra



Proposed Reaction Mechanism



Substrate Scope



In the oxidative cleavage reaction of unconjugated olefins, yields were significantly lower. Especially, the reaction of terminal alkenes to give aldehyde products led to diminished yields.

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Alessandro Ruffoni^{1,3}, Charlotte Hampton^{2,3}, Marco Simonetti²✉ & Daniele Leonori¹✉

Introduction of Prof. Daniele Leonori



Career:

2007-2010 : PhD, University of Sheffield (Prof. Iain Coldham)
2010-2011 : Postdoc, RWTH-Aachen University (Prof. Magnus Rueping)
2011-2012 : Postdoc, Max Planck Institute (Prof. Peter H. Seeberger)
2012-2014 : Research Officer, University of Bristol (Prof. Varinder K. Aggarwal)
2014-2018 : Lecturer of Organic Chemistry, University of Manchester
2018-2020 : Reader in Organic Chemistry, University of Manchester
2020-2022 : Professor of Organic Chemistry, University of Manchester
2022- : Professor of Organic Chemistry, RWTH-Aachen University

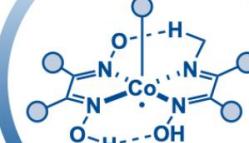
Research topic:

- (1) Development of nitrogen radical generation method
- (2) Dehydrogenation reaction using cobalt catalyst
- (3) Reaction development using XAT reaction
- (4) Borylation using boron radicals

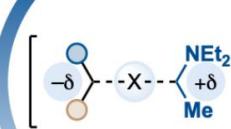
nitrogen
radicals



cobalt
desaturation



halogen-atom
transfer



boryl
radicals



radical strategies
for C–N bond
assembly

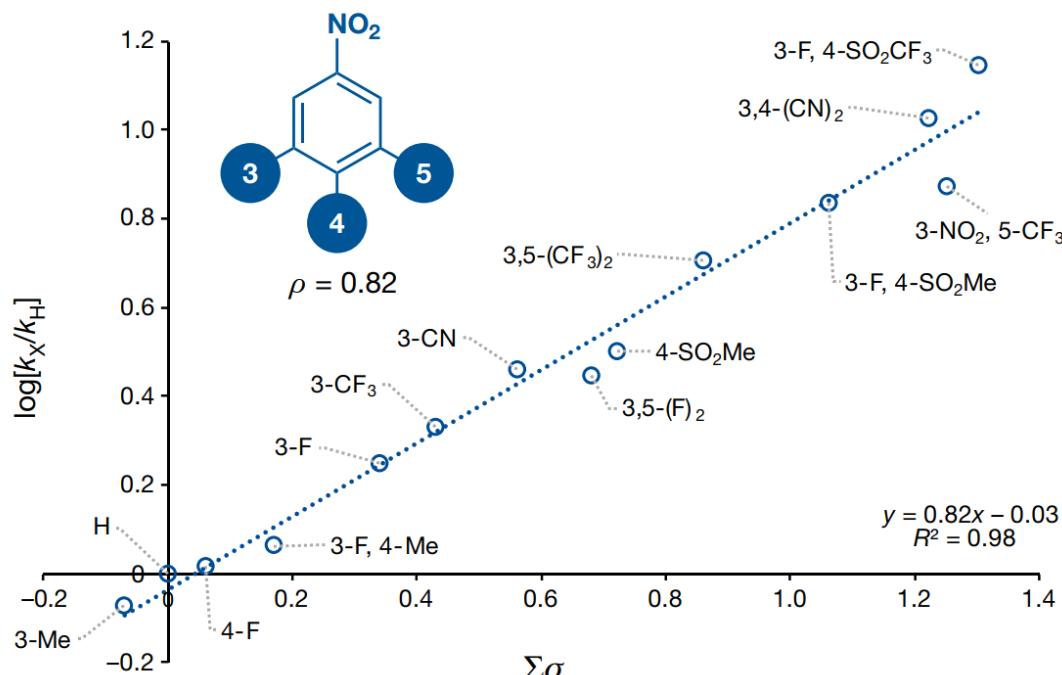
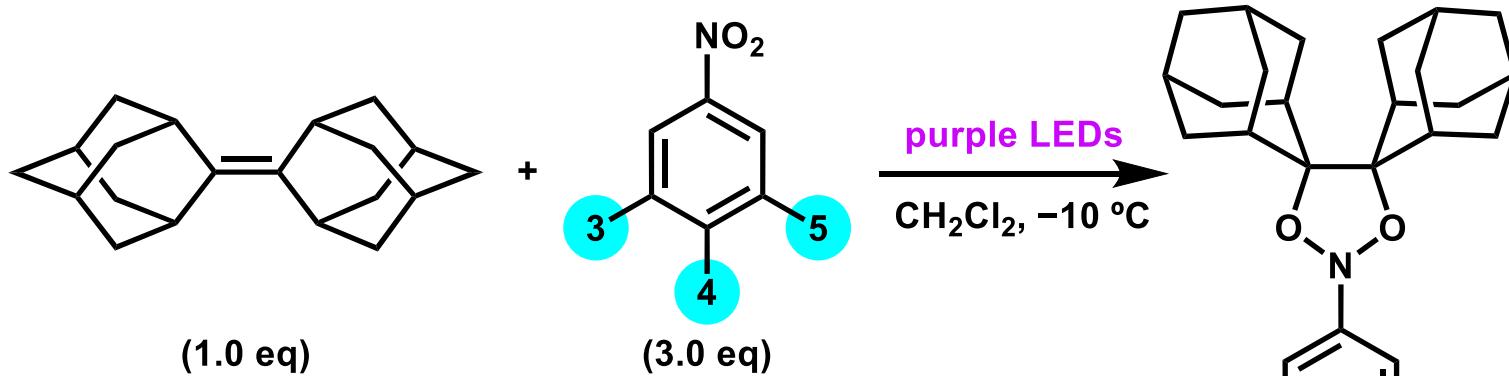
desaturative
approaches to
aromatic synthesis

novel strategies
for carbon radical
generation

radical blueprints
for aromatic
C–H borylations



Hammett Plot Analysis



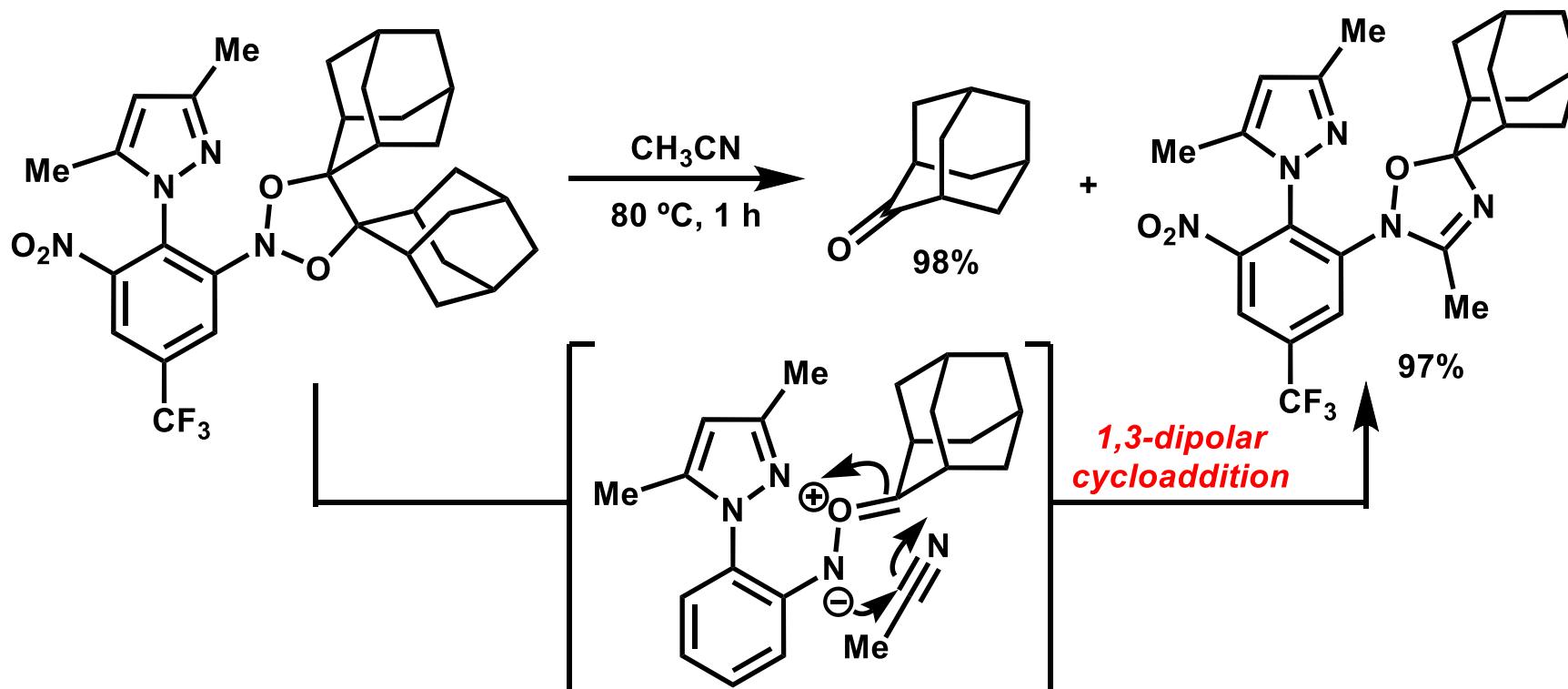
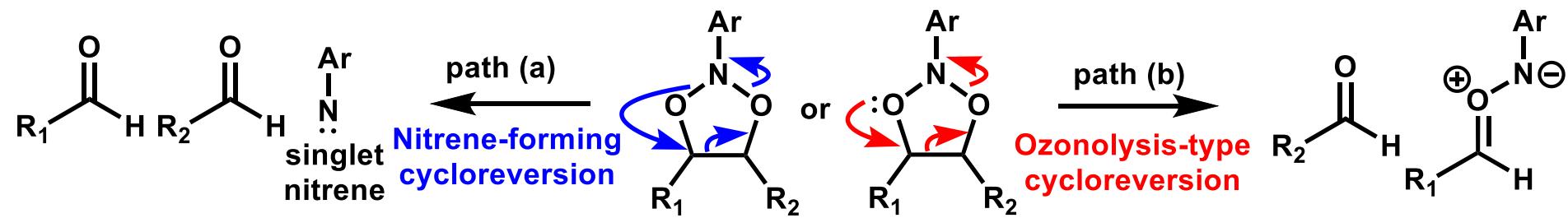
k_X : initial rates of disappearance of substituted nitroarenes

k_H : initial rates of disappearance of nitrobenzene

Electron-withdrawing groups accelerate the cycloaddition.

Mechanistic Study of Cycloreversion

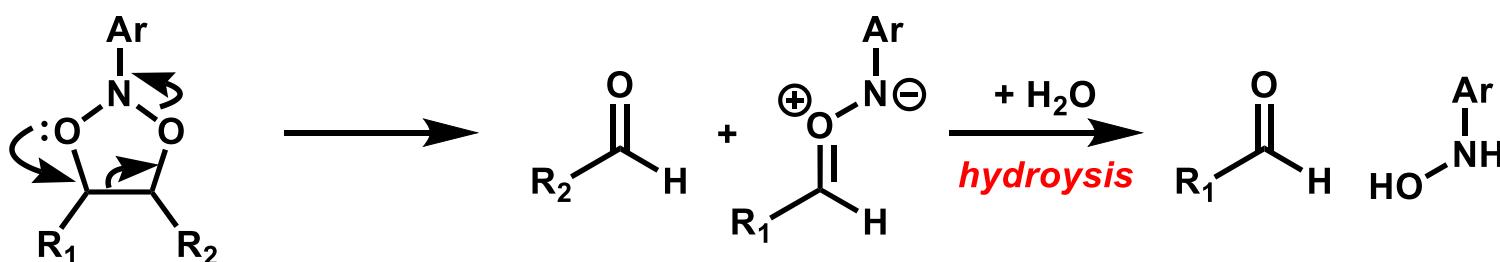
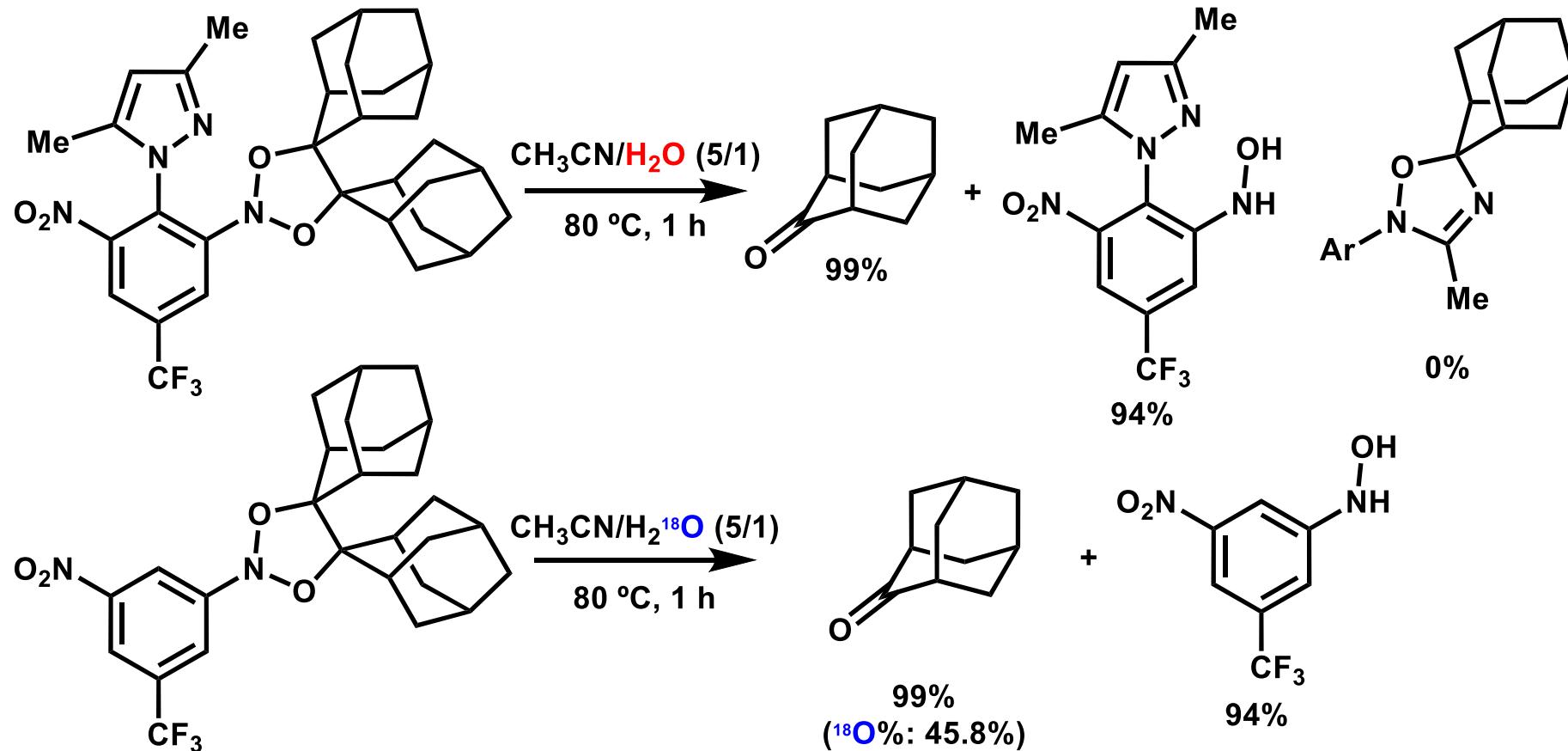
Possible reaction pathway:



It was found that cycloreversion was proceeded via path (b).

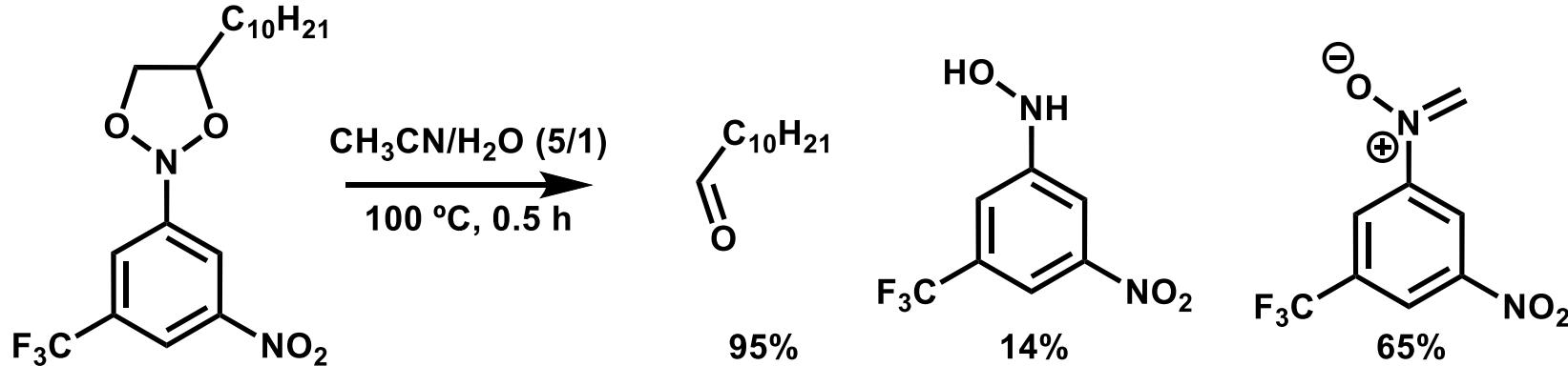
Hydrolysis of Carbonyl Imine

The reaction was also conducted with aqueous condition.

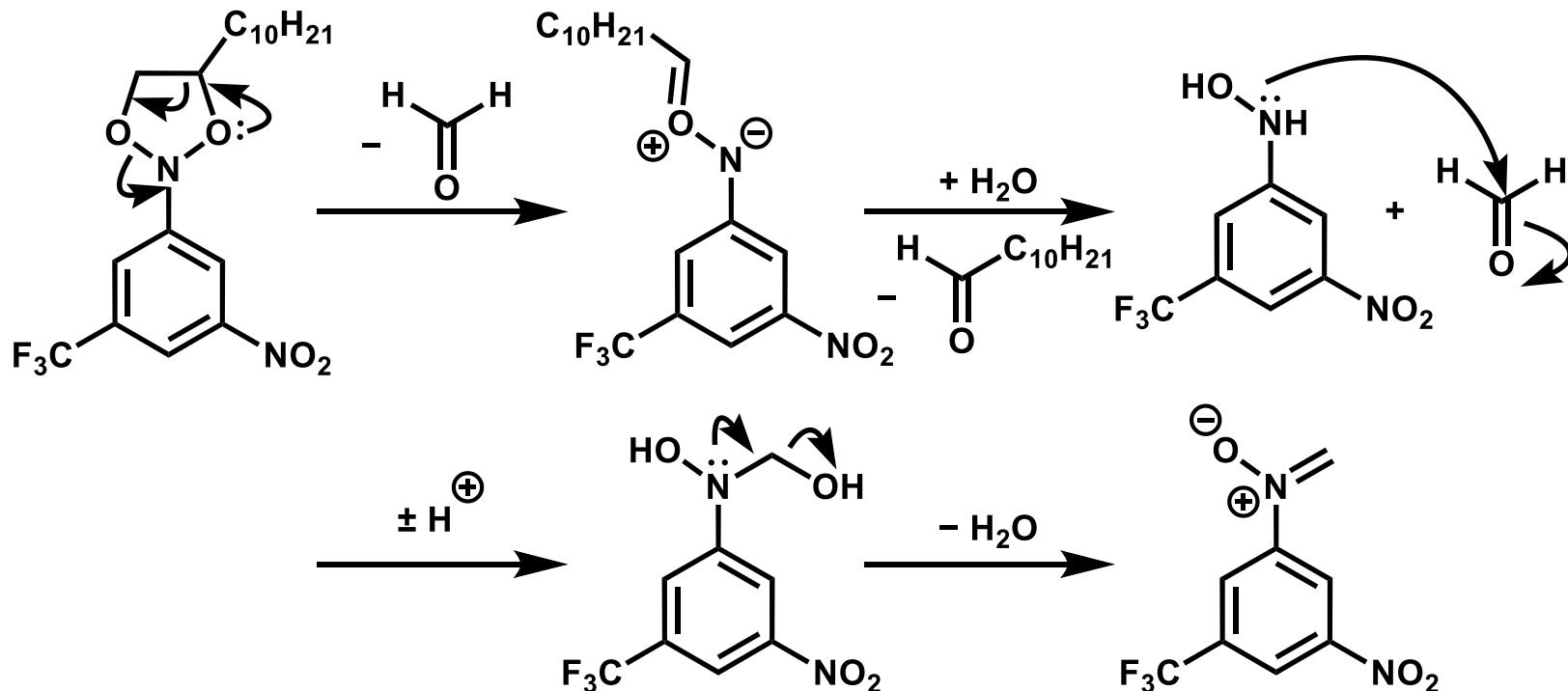


Generated carbonyl amine is quickly hydrolyzed.

Formation of Nitrone (1)

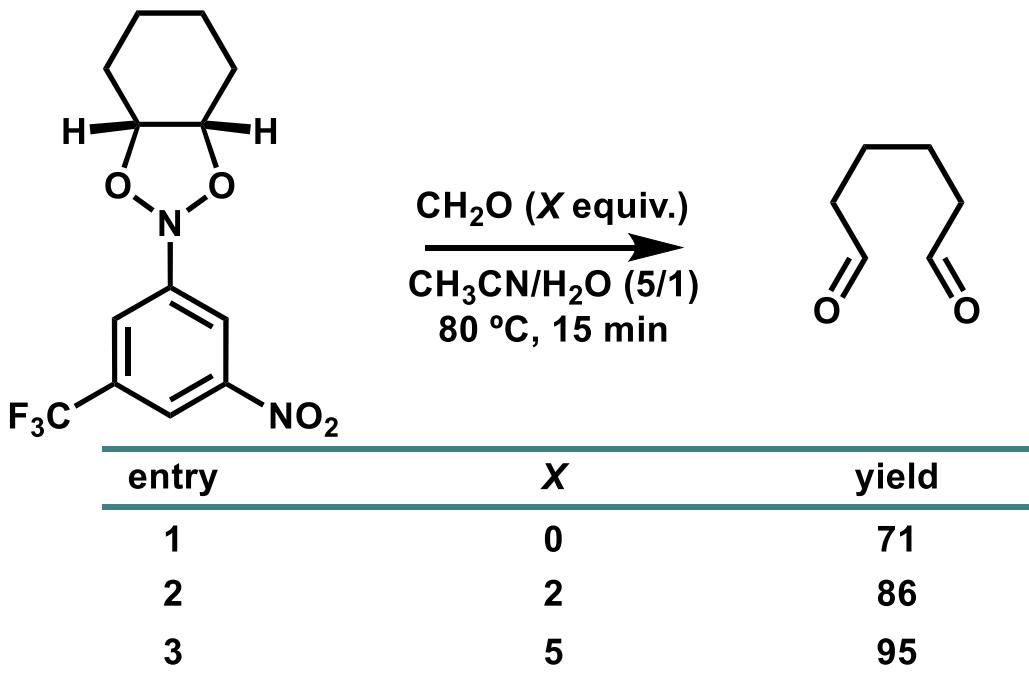


<proposed reaction mechanism>

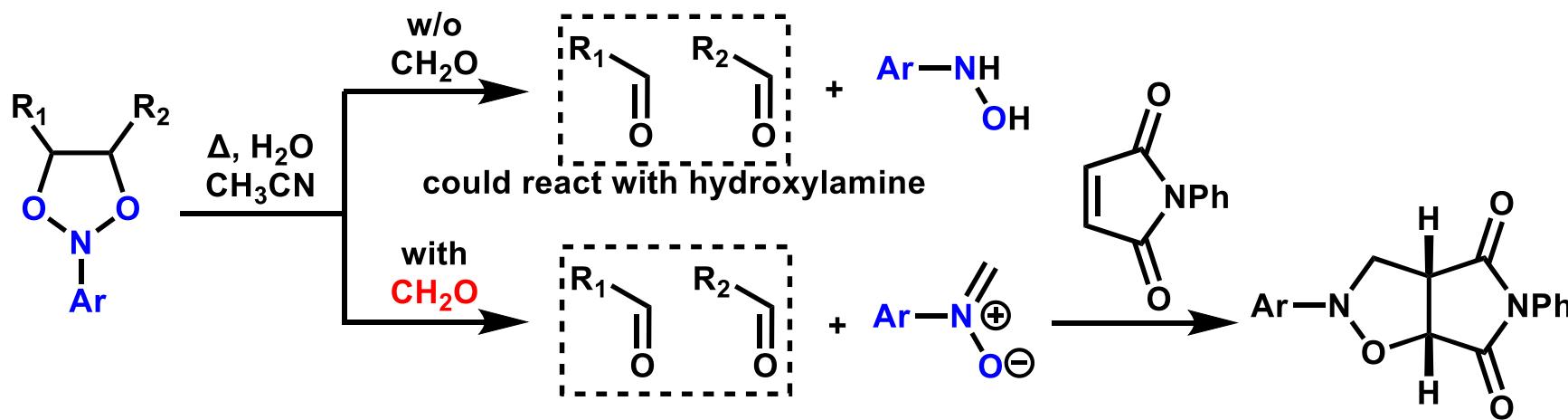


Nitrone was produced between *N*-arylhdroxylamine and CH_2O *in situ*.
Then, a strategy was developed to trap *N*-arylhdroxylamine by CH_2O to avoid side reactions.

Formation of Nitrone (2)

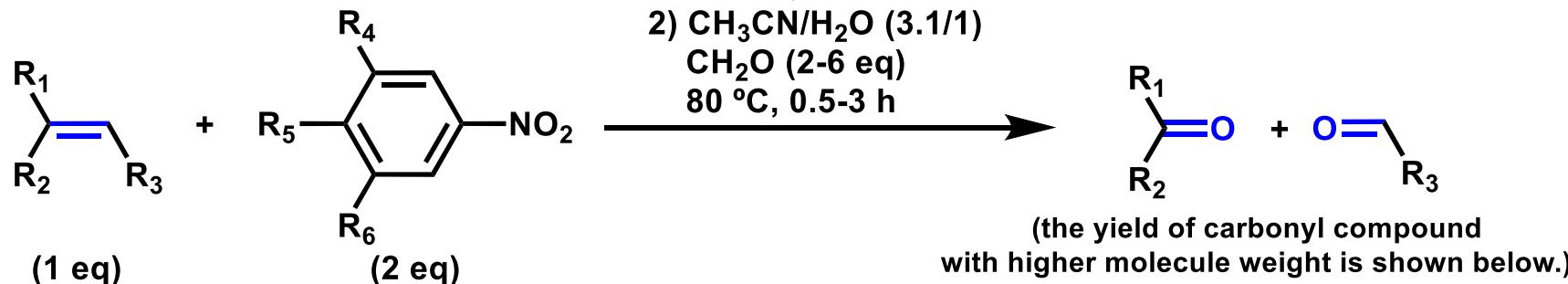


<the role of CH_2O >

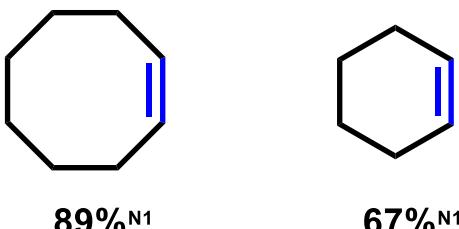


CH_2O reacts as a "quencher" of hydroxylamine.

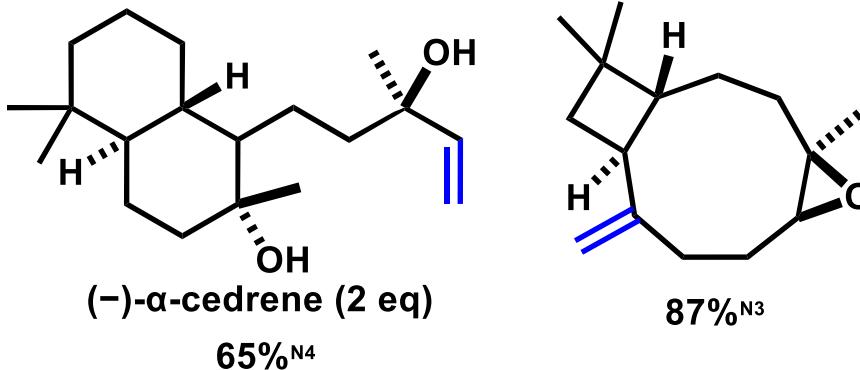
Substrate Scope (Solv. : EtOAc)



$\text{R} = \text{CO}_2\text{H} : 70\%^{\text{N}3}$
 $\text{R} = \text{CN} : 82\%^{\text{N}3}$
 $\text{R} = \text{Br} : 78\%^{\text{N}3}$
 $\text{R} = \text{NPhth} : 82\%^{\text{N}3}$
 $\text{R} = \text{B(pin)} : 70\%^{\text{N}3}$



$(\text{R}_1, \text{R}_2) = (\text{OMe, H}) : 89\%^{\text{N}2}$
 $(\text{R}_1, \text{R}_2) = (\text{CF}_3, \text{H}) : 98\%^{\text{N}3}$
 $(\text{R}_1, \text{R}_2) = (\text{H, Me}) : 83\%^{\text{N}2}$
 $(\text{R}_1, \text{R}_2) = (\text{H, Ph}) : 94\%^{\text{N}3}$



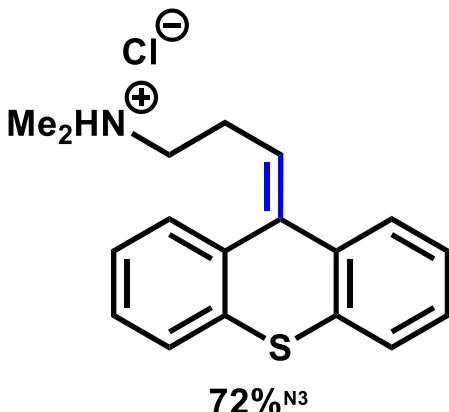
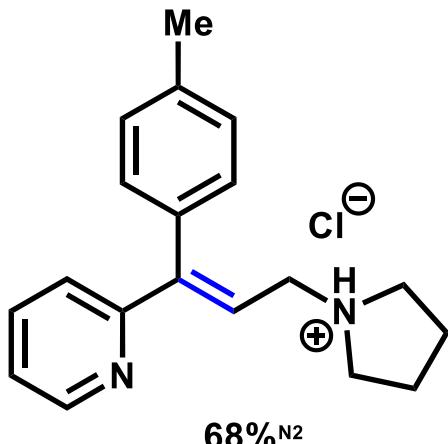
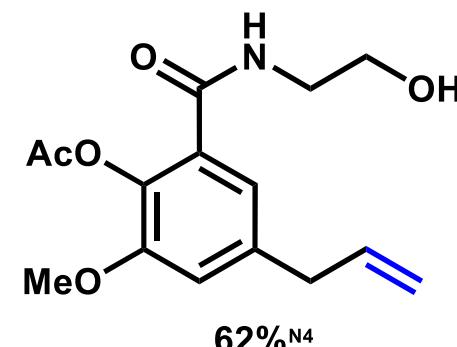
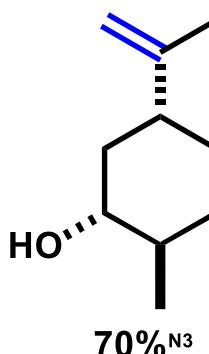
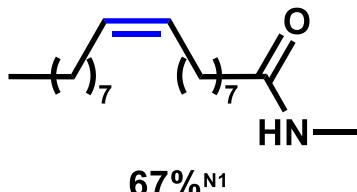
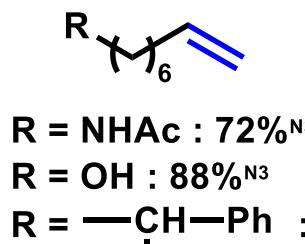
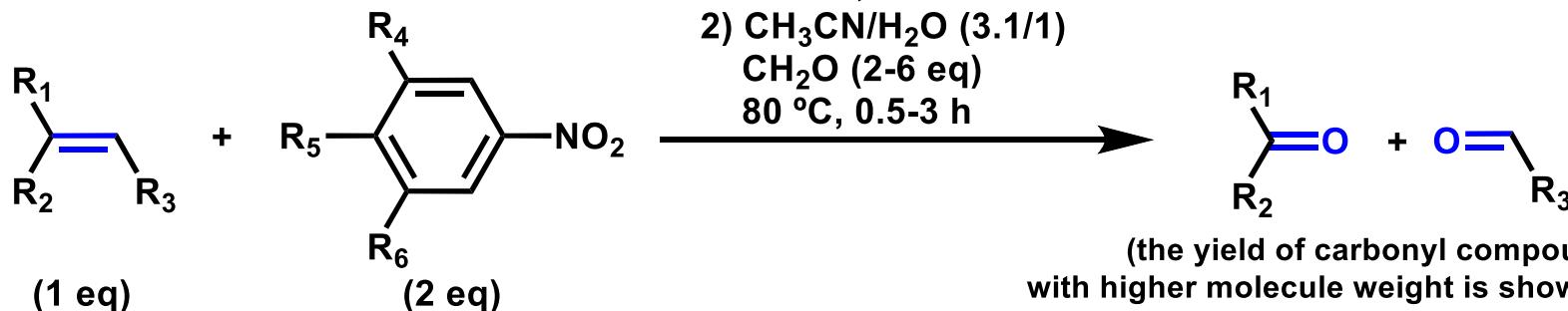
	R_4	R_5	R_6
N1	CF_3	H	CF_3
N2	CN	CN	H
N3	NO_2	H	CF_3
N4	F	SO_2CF_3	H

$\Sigma\sigma: \text{N}4 > \text{N}3 > \text{N}2 > \text{N}1$

Substrate Scope (Solv. : CH₂Cl₂ and HFIP)

1) purple LEDs
 CH₂Cl₂, HFIP (1-4 eq)
 -30 °C, 12-24 h

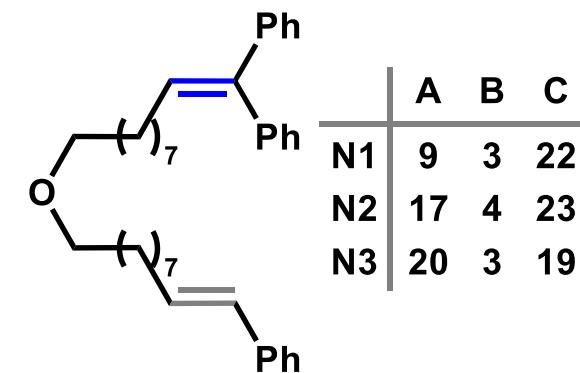
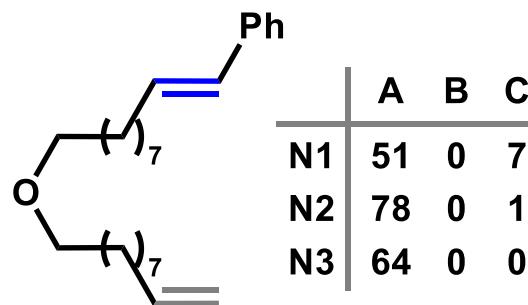
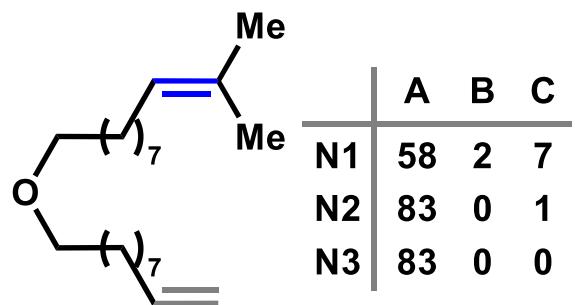
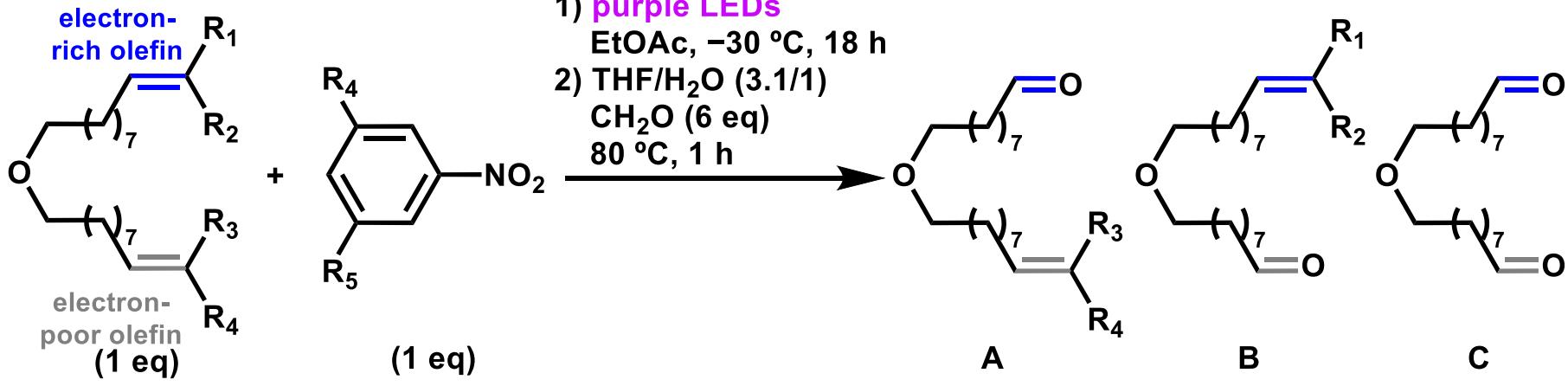
2) CH₃CN/H₂O (3.1/1)
 CH₂O (2-6 eq)
 80 °C, 0.5-3 h



	R ₄	R ₅	R ₆
N1	CF ₃	H	CF ₃
N2	F	SO ₂ CH ₃	H
N3	NO ₂	H	CF ₃
N4	F	SO ₂ CF ₃	H

$\Sigma\sigma: N4 > N3 > N2 > N1$

Stereoselectivity of Olefin Cleavage



Site selectivity depends on the electronic nature of the nitroarene and the two alkenes.
 Therefore, the selectivity increases when using less-electrophilic nitroarenes.

	R ₄	R ₅
N1	NO ₂	CF ₃
N2	F	H
N3	H	H

$\Sigma\sigma: N1 > N2 > N3$

→ reactivity of *N: N1 > N2 > N3

Comparison with Other Methods

conditions A

- 1) purple LEDs, N1, EtOAc, -30 °C, 24 h
- 2) CH₃CN/H₂O (3.1/1), CH₂O (2 eq), 80 °C, 1 h

conditions B

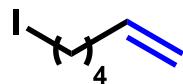
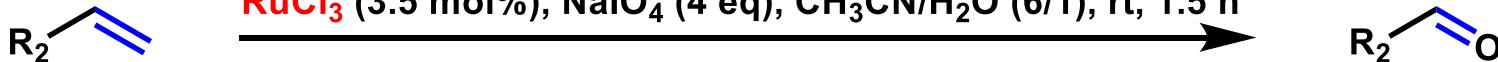
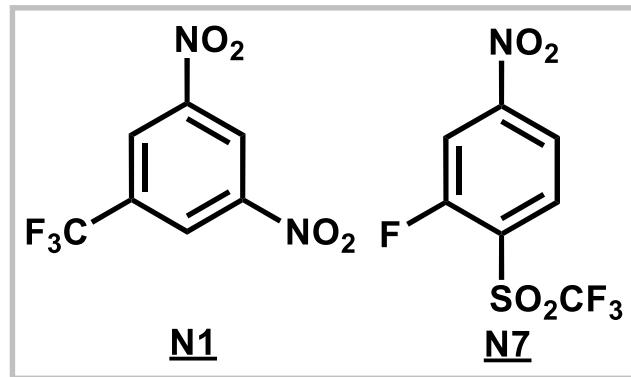
- 1) purple LEDs, N7, CH₂Cl₂, HFIP (2 eq), -30 °C, 24 h
- 2) CH₃CN/H₂O (3.1/1), CH₂O (4 eq), 80 °C, 1 h

conditions C²⁾

OsO₄ (2 mol%), 2,6-lutidine (2 eq), NaIO₄ (4 eq)
Dioxane/H₂O (3/1), rt, 2 h

conditions D³⁾

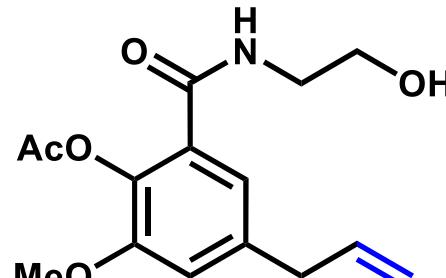
RuCl₃ (3.5 mol%), NaIO₄ (4 eq), CH₃CN/H₂O (6/1), rt, 1.5 h



conditions	A	C	D
yield	57%	1%	3%



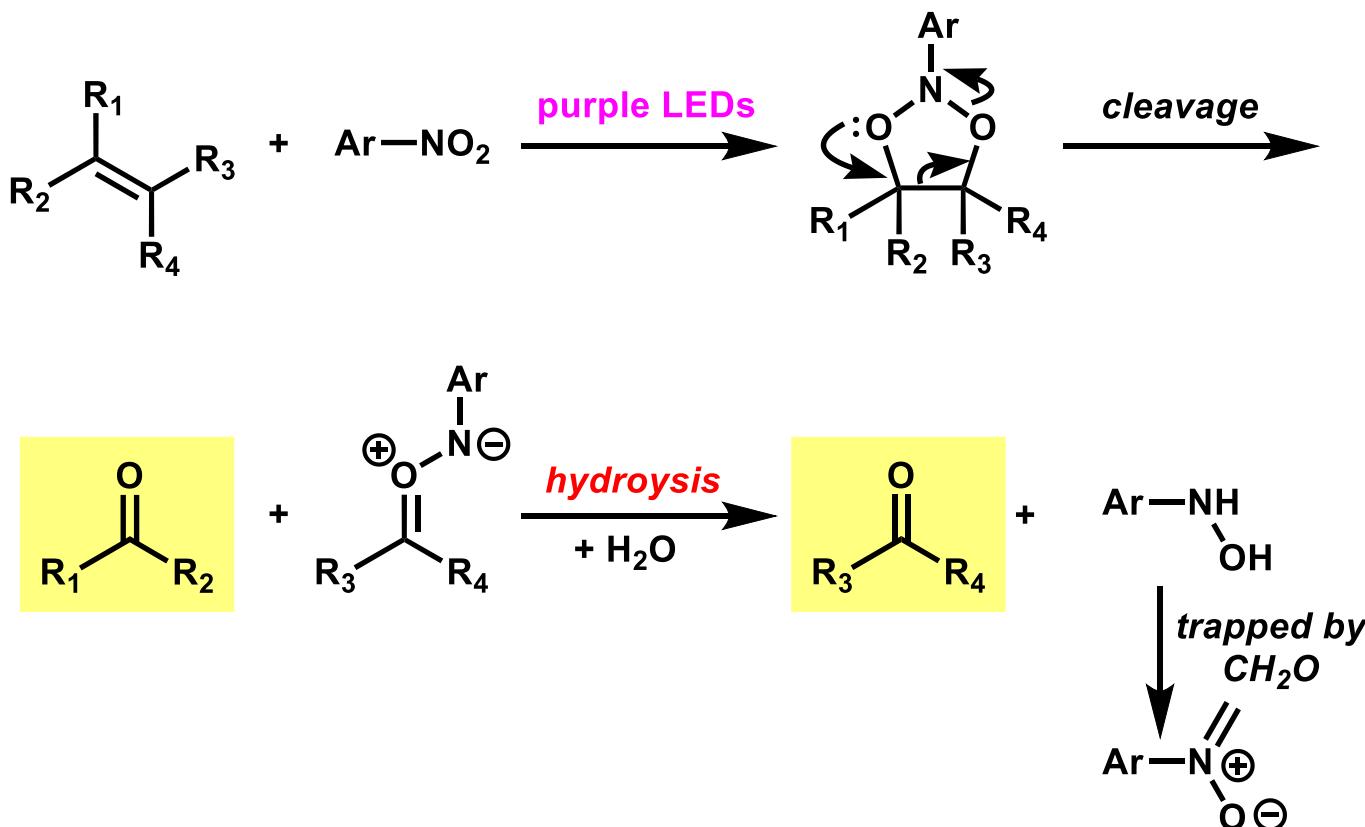
conditions	A	C	D
yield	85%	1%	26%



conditions	A	C	D
yield	62%	1%	5%

The authors state that the reaction conditions they used might not always be optimal ones for these substrates and improved results might be obtained upon individual optimization. However, it is possible that a newly developed method using nitroarene could be useful to perform oxidative cleavage of previously inaccessible substrates.

Summary



By using less-electrophilic nitroarenes, site-selective olefin cleavage was achieved.