Copper-Catalyzed Amino Oxygenation of Alkenes and Dienes:

An Amino-Initiation Pathway Using *O*-Benzoylhydroxylamines

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07.30.19

Ph.D. Dissertation Work

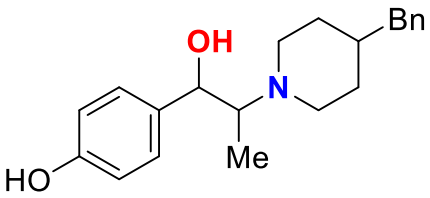
SED Group Meeting

Duke UNIVERSITY | DEPARTMENT OF Chemistry

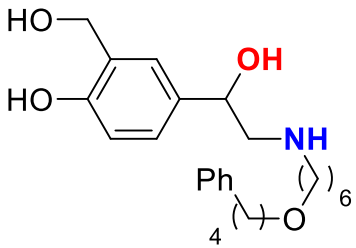
WANG LAB Duke

Importance of Nitrogen–Carbon Bond Formation

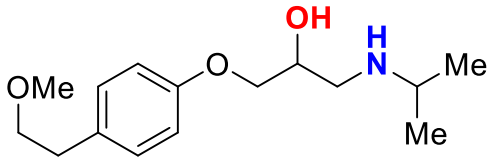
- 2016 Top 100 Drugs (Number of Prescriptions)
  - 81% Contain at least one C–N bond
  - 46% Contain at least one free (non-conjugated) nitrogen



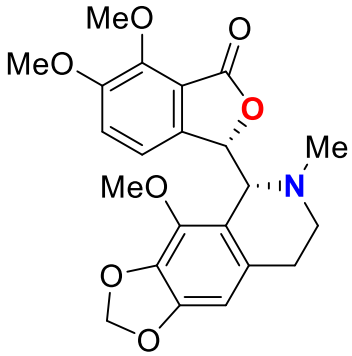
Ifenprodil
(neuronal pain)



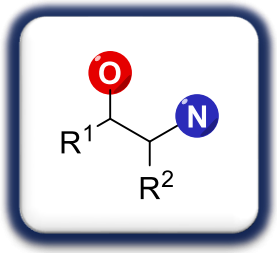
Salmeterol [Advair]
(asthma/COPD)

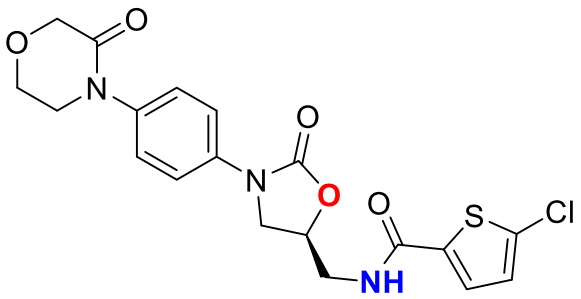


Metoprolol [Lopressor]
(high blood pressure)



Noscapine
(anti-tumor)



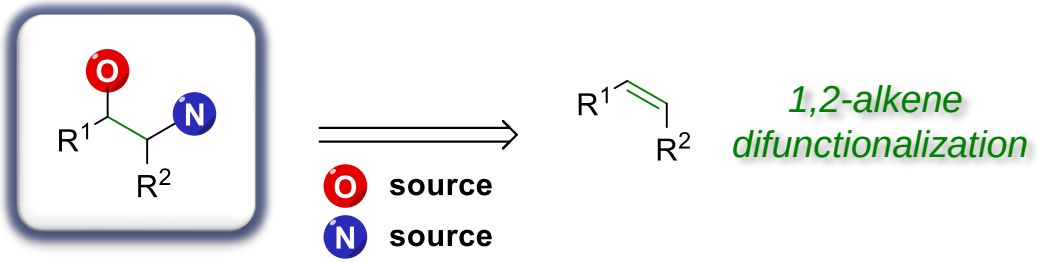


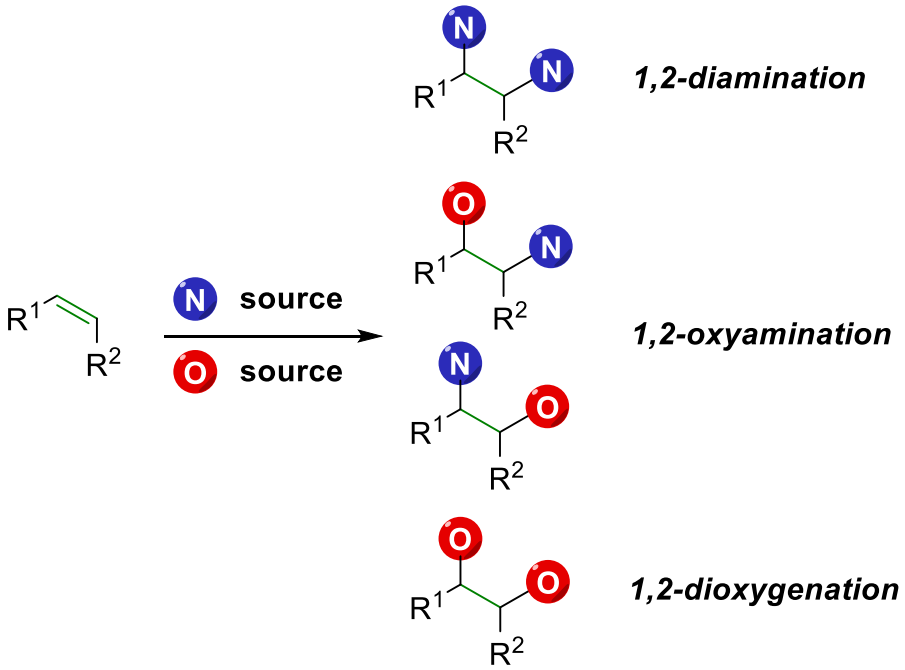
Rivaroxaban [Xarelto]
(anticoagulant)

- C–N bond formation accounts for 37% of drug discovery reactions

Roughley, S.D.; Jordan, A.M. *J. Med. Chem.* **2011**, *54*, 3451–3479.

Alkene Oxyamination Strategy





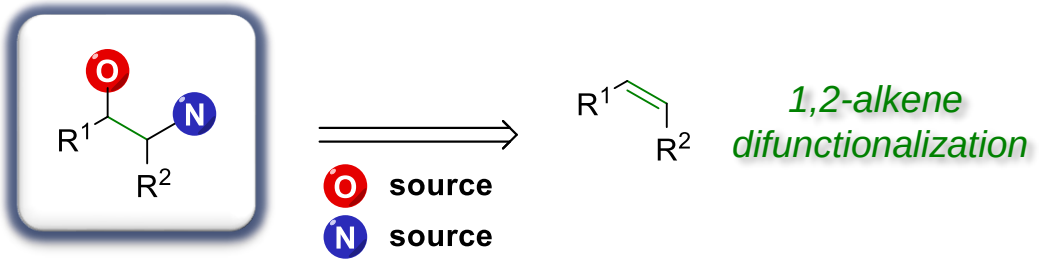
Advantages:

- Alkenes are feedstock chemicals
- Single-step functionalization
- Modular approach

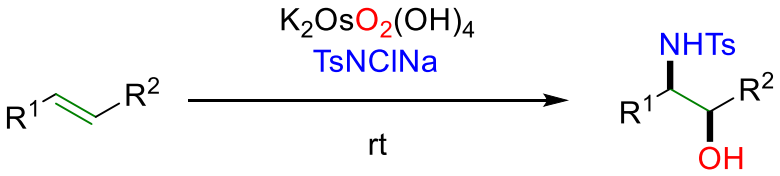
Challenges:

- Chemo- and regioselectivity due to two nucleophilic moieties
- Diversity of generated products
- Robust/straightforward reactivity

Notable Alkene 1,2-Oxyamination Methods

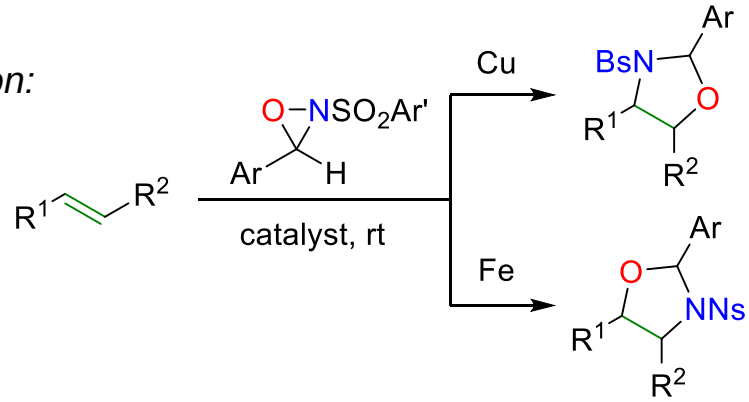


Sharpless:



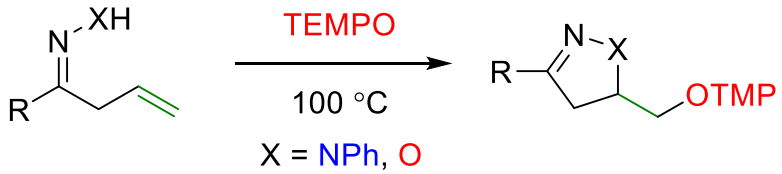
J. Am. Chem. Soc. **1975**, *97*, 2305–2307.
J. Org. Chem. **1976**, *41*, 177–179.
Angew. Chem. Int. Ed. **1996**, *35*, 451–454.

Yoon:



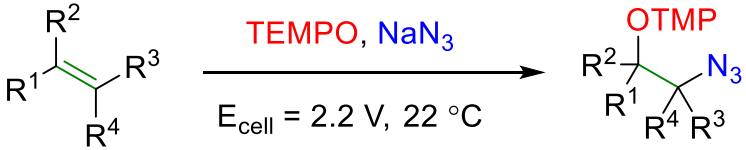
J. Am. Chem. Soc. **2007**, *129*, 1866–1867.
J. Am. Chem. Soc. **2010**, *132*, 4570–4571.

Han:



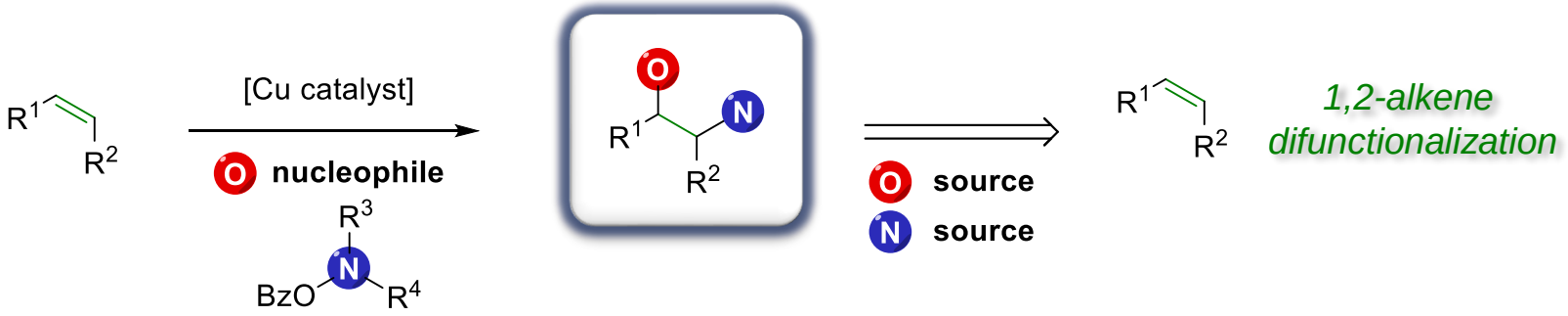
Angew. Chem. Int. Ed. ***2012***, *51*, 8816–8820.
J. Org. Chem. **2013**, *78*, 10692–10704.

Lin:



J. Am. Chem. Soc. **2018**, *140*, 12511–12520.

Alkene Oxyamination Strategy



Electrophilic nitrogen* allows for *cooperative reactivity with nucleophiles

O-Benzoylhydroxylamines:

- Effective for 2° or 3° amines
- Oxidized form of nitrogen
- Effective with Cu catalysts
- Scalable and benchtop stable

Advantages:

- Alkenes are feedstock chemicals
- Single-step functionalization
- Modular approach

Challenges:

- Chemo- and regioselectivity due to two nucleophilic moieties
- Diversity of generated products
- Robust/straightforward reactivity

Notable Alkene Lactonization Efforts

Halogen

X = Br, Cl, I

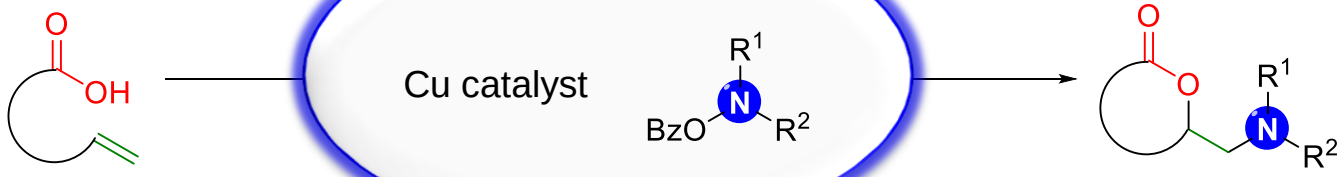
Tetrahedron **2004**, *60*, 5273–5308.
Angew. Chem. Int. Ed. **2012**, *51*, 10938–10953.

Sulfonamide

X = $NHSO_2Ar$

Org. Lett. **2011**, *13*, 5830–5833.
Chem. Commun. **2014**, *50*, 6913–6916.

Amine



Chalcogen

X = S, Se

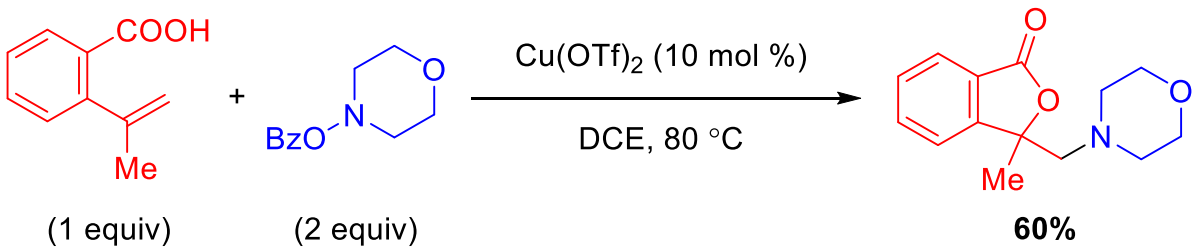
Org. Lett. **2007**, *9*, 3801–3804.
Tetrahedron Lett. **2015**, *56*, 2843–2852.

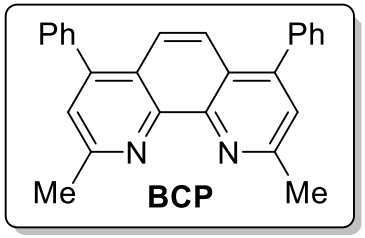
Additional

X = CF_3, N_3, SO_2Ar

Angew. Chem. Int. Ed. **2013**, *52*, 12655–12658.
J. Am. Chem. Soc. **2015**, *137*, 8069–8077.

Alkene Amino Lactonization Optimization



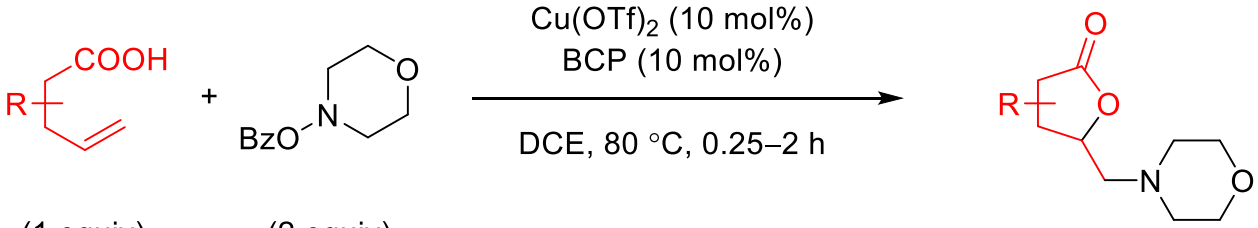


Entry	Change from standard conditions	Yield[a] (%)
1	Run using $[Cu(OTf)]_2$·tol instead of $Cu(OTf)_2$	60
2	Run using $CuCl_2$ instead of $Cu(OTf)_2$	40
3	Run using $Cu(acac)_2$ instead of $Cu(OTf)_2$	21
4	Run in CF_3Ph instead of DCE	41
5	Run in Dioxane instead of DCE	32
6	Run in CH_3CN instead of DCE	22
7	Run at 100 °C instead of 80 °C	64
8	Added BINAP (10 mol %)	54
9	Added BQ (10 mol %)	74
10	**Added BCP (10 mol %)**	**84 (75)[b]**

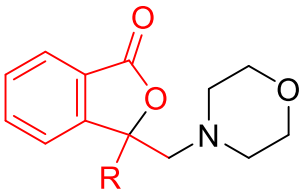
Reactions run on 0.2 mmol scale. [a]Yields determined by ^1H NMR spectroscopy with CH_2Br_2 as a quantitative internal standard. [b]Isolated yield on 0.4 mmol scale shown in parentheses.

Hemric, B.N.; Shen, K.; Wang, Q. *J. Am. Chem. Soc.* **2016**, *138*, 5813–5816.

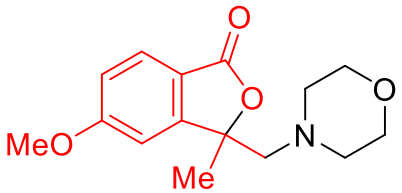
Alkene Amino Lactonization: Oxygen Scope



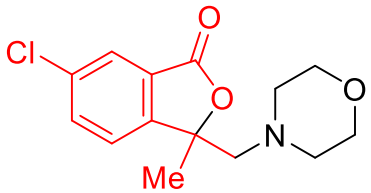
(1 equiv) (2 equiv)



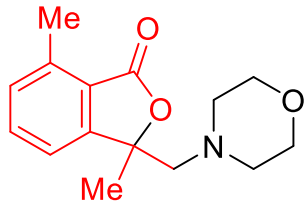
75%, R = Me
82%, R = Ph
43%,[a] R = H



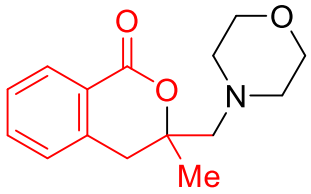
73%



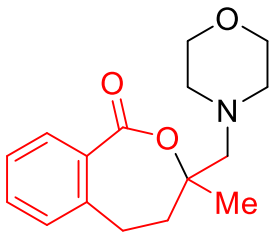
72%



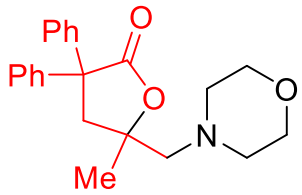
77%



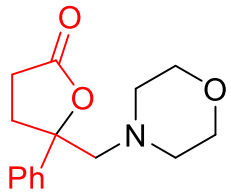
89%



27%



55%



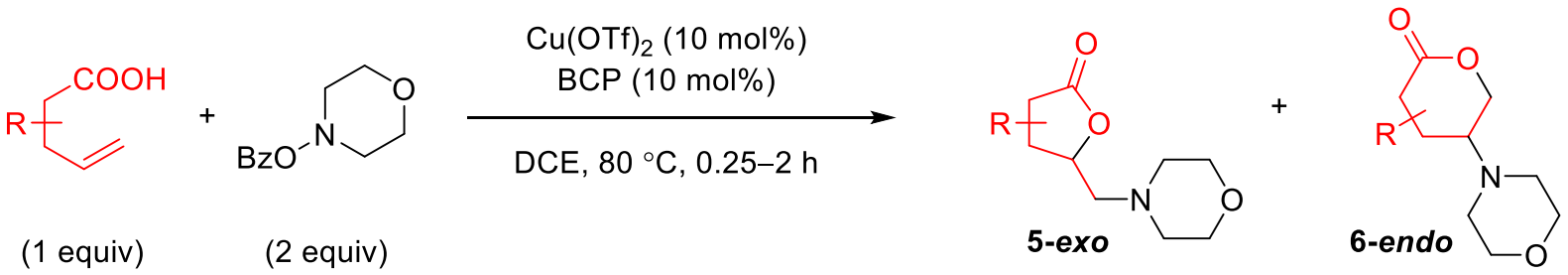
45%[a]

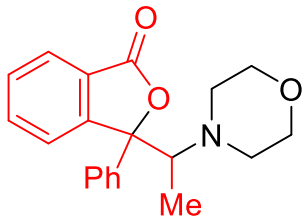
Isolation yields on 0.4 mmol scale. [a]Run without BCP. [b]dr = diastereomeric ratio, as determined by ^{1}H NMR of the crude mixture. [c]Observed by GCMS. [d]Determined by Xray crystallography.

Hemric, B.N.; Shen, K.; Wang, Q. *J. Am. Chem. Soc.* **2016**, *138*, 5813–5816.

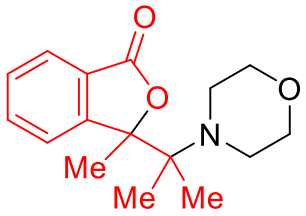
With Dr. Kun Shen

Alkene Amino Lactonization: Oxygen Scope

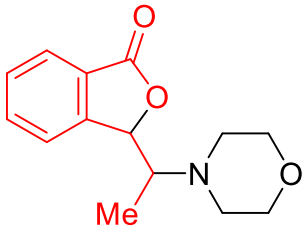




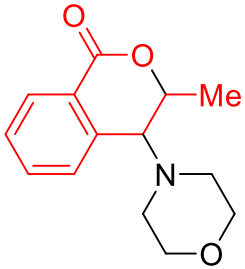
99% (dr = 1.4:1)[b]



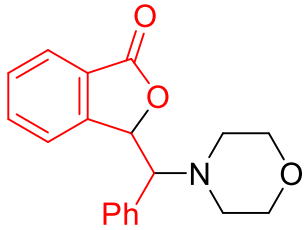
10%



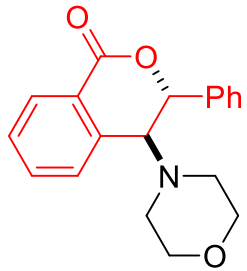
55% (dr = 1.8:1)[b] from *E*
46% (dr = 1.8:1)[b] from *Z*



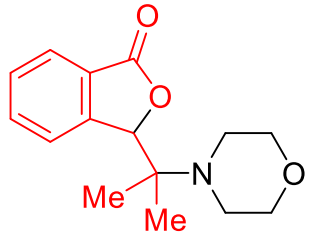
trace[c] from *E*
trace[c] from *Z*



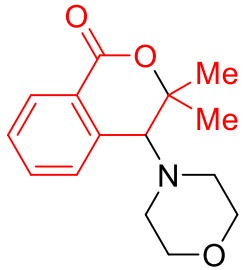
trace[c] from *E*
trace[c] from *Z*



58%[d] from *E*
30% from *Z*



30%



16%

Isolation yields on 0.4 mmol scale. [a]Run without BCP. [b]dr = diastereomeric ratio, as determined by ^{1}H NMR of the crude mixture. [c]Observed by GCMS. [d]Determined by Xray crystallography.

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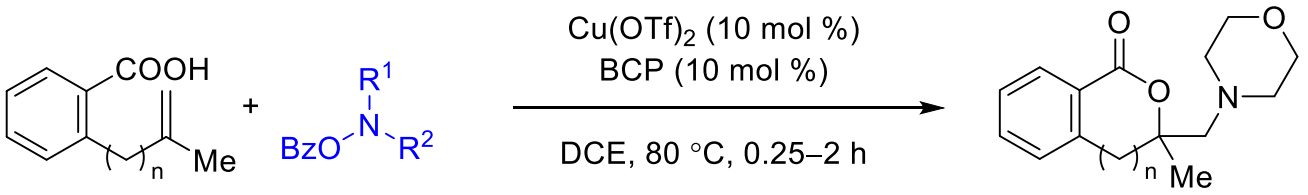
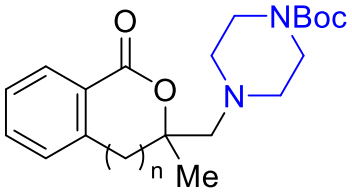
With Dr. Kun Shen

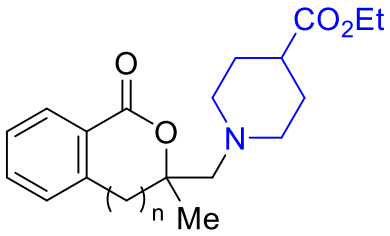
Alkene Amino Lactonization: Amine Scope



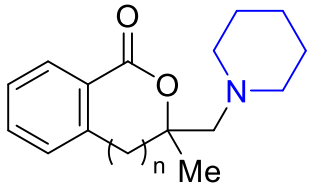
(1 equiv) (2 equiv)



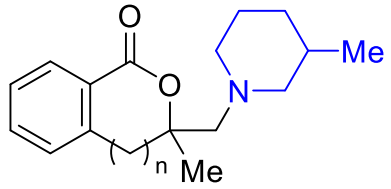
71%, n = 0
70%, n = 1



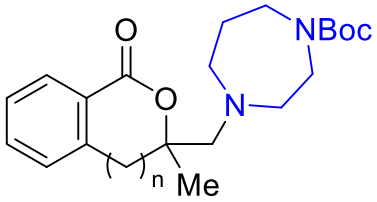
59%, n = 0
49%, n = 1



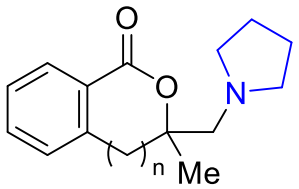
51%, n = 0
51%, n = 1



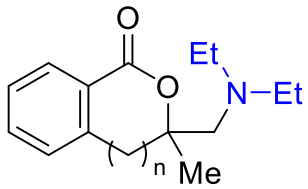
57% (dr = 1:1)[b] n = 0
50% (dr = 1:1)[b] n = 1



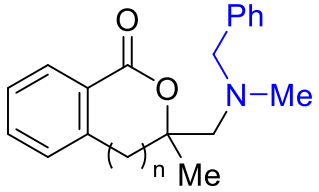
44%,[a] n = 0
35%,[a] n = 1



32%,[a] n = 0
26%,[a] n = 1



46%,[a] n = 0
39%,[a] n = 1

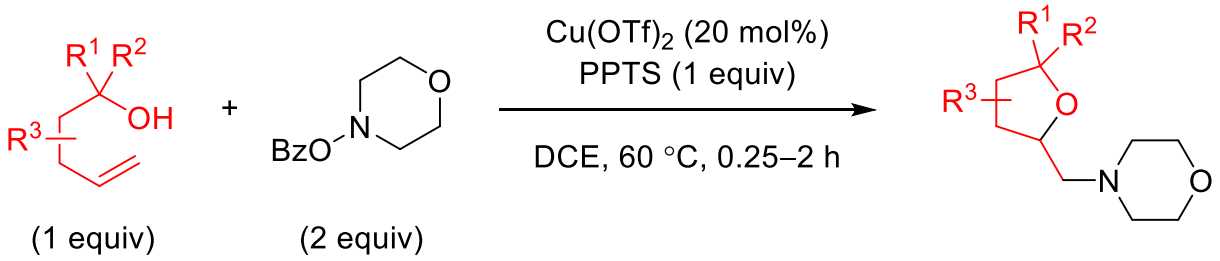


45%,[a] n = 0
28%,[a] n = 1

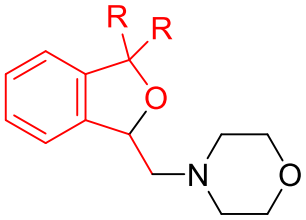
Isolated yields on 0.4 mmol scale. [a]Run with 20 mol% $Cu(OTf)_2$ and without BCP. [b]dr = diastereomeric ratio, as determined by ^1H NMR of the crude mixture.

Hemric, B.N.; Shen, K.; Wang, Q. *J. Am. Chem. Soc.* **2016**, *138*, 5813–5816.

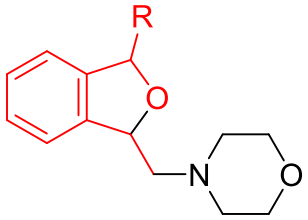
Alkene Amino Etherification: Alcohol Scope



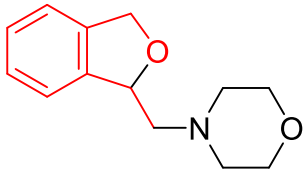
Representative Examples



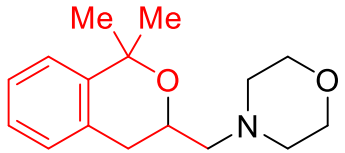
76%, R = Me
48%, R = Ph



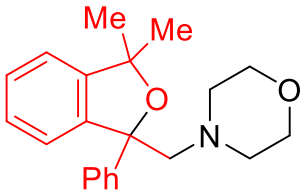
55% (dr = 1.3:1)[a] R = Me
66% (dr = 1.1:1)[a] R = Ph



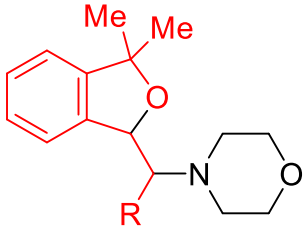
38%



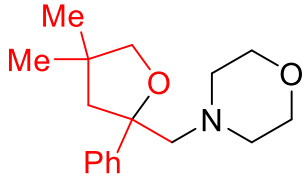
47%



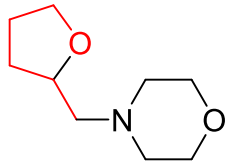
52%



70% (dr = 2.1:1)[a] R = Me[b]
33% (dr = 1.2:1)[a] R = Ph[b]



62%



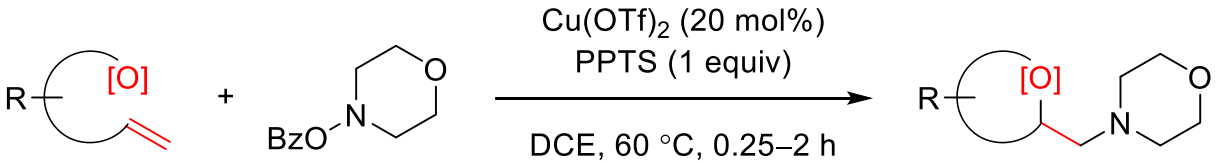
24%

Isolation yields on 0.4 mmol scale. [a]dr = diastereomeric ratio, as determined by ^{1}H NMR of the crude mixture. [b]Starting from the *E* isomer.

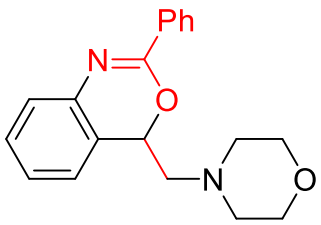
Hemric, B.N.; Chen, A.W.; Wang, Q. *J. Org. Chem*. **2019**, *84*, 1468–1488.

With Andy Chen

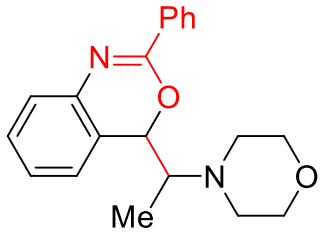
Alkene Amino Oxygenation: Oxygen Source Scope



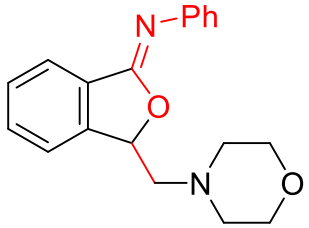
(1 equiv) (2 equiv)



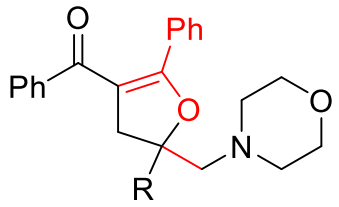
52%



60% (2.5:1)[a]
from *E*

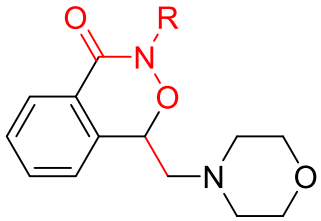


35%

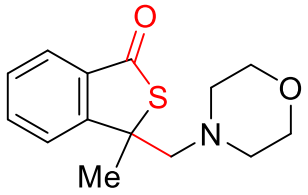


31%, R = Me
NR, R = H

50% (0.4 mmol)
50% (2 mmol)



NR, R = Me
NR, R = Ph



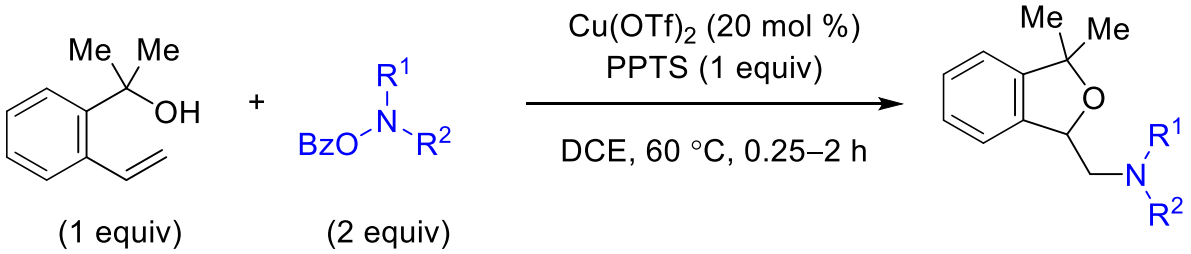
16%

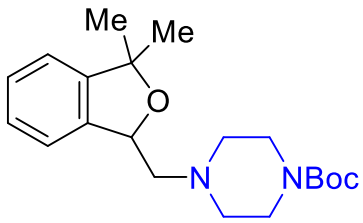
Isolation yields on 0.4 mmol scale. [a]dr = diastereomeric ratio, as determined by ^{1}H NMR of the crude mixture.

Hemric, B.N.; Chen, A.W.; Wang, Q. *J. Org. Chem*. **2019**, *84*, 1468–1488.

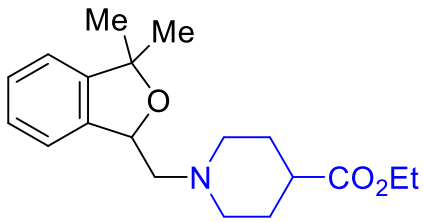
With Andy Chen

Alkene Amino Etherification: Amine Scope

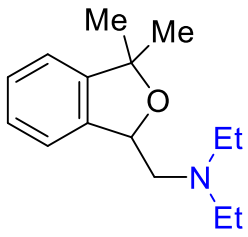




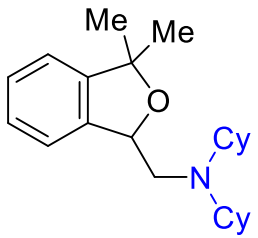
63%



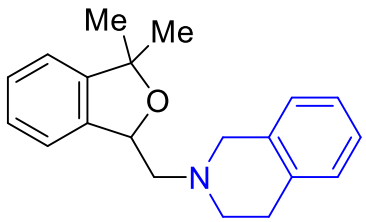
70%



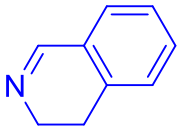
56%



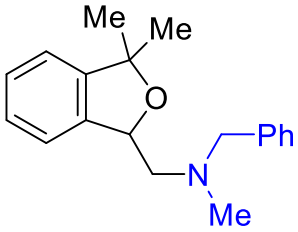
ND



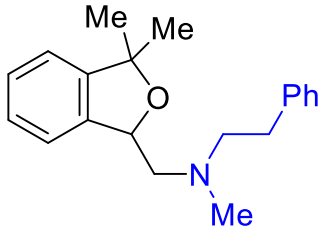
ND



Only product observed



37%



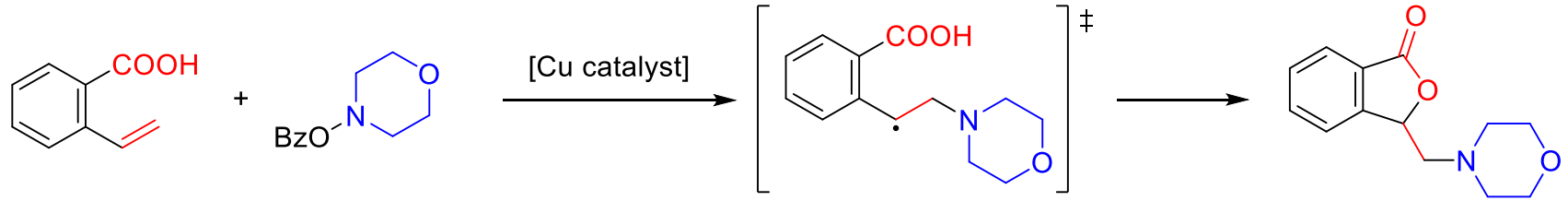
72%

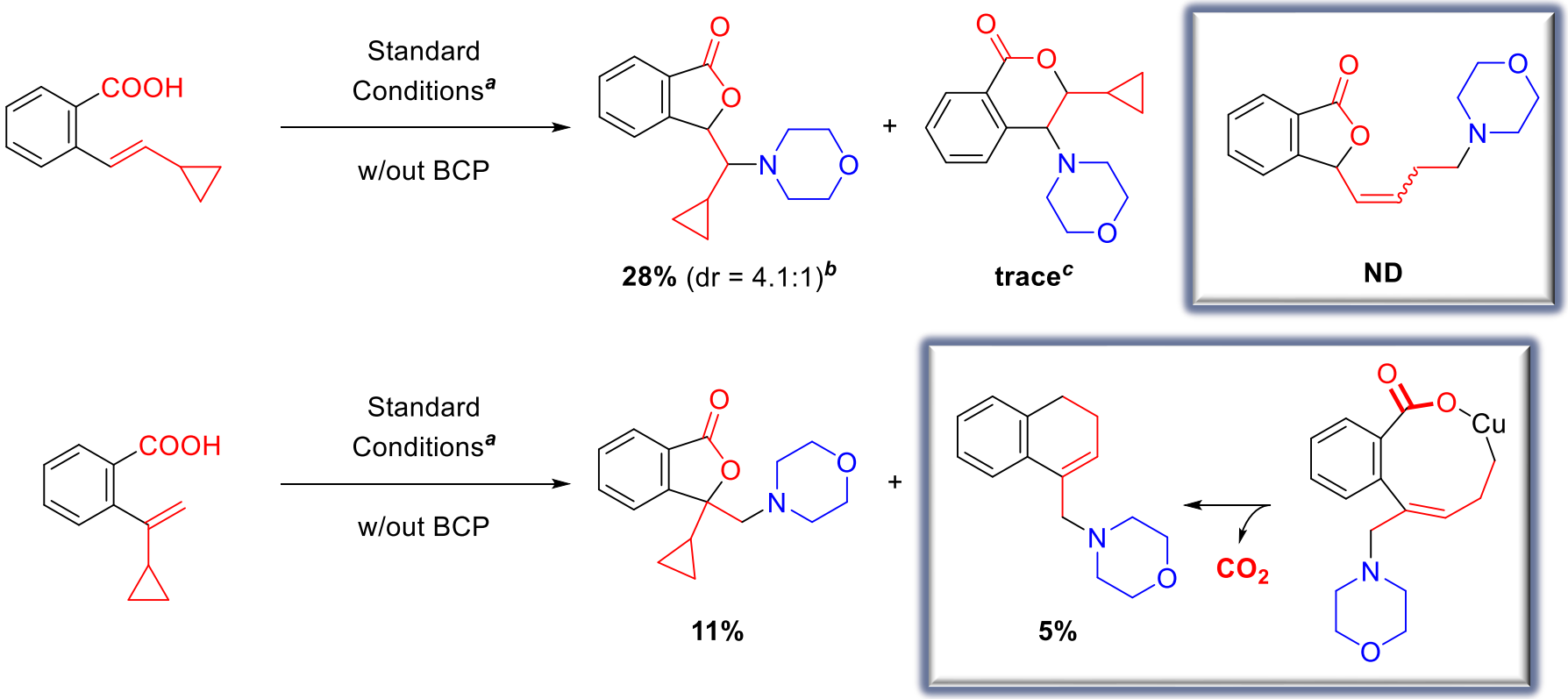
Isolated yields on 0.4 mmol scale.

Hemric, B.N.; Chen, A.W.; Wang, Q. *J. Org. Chem*, **2019**, *84*, 1468–1488.

With Andy Chen

Mechanistic Insight: Radical Clock Studies



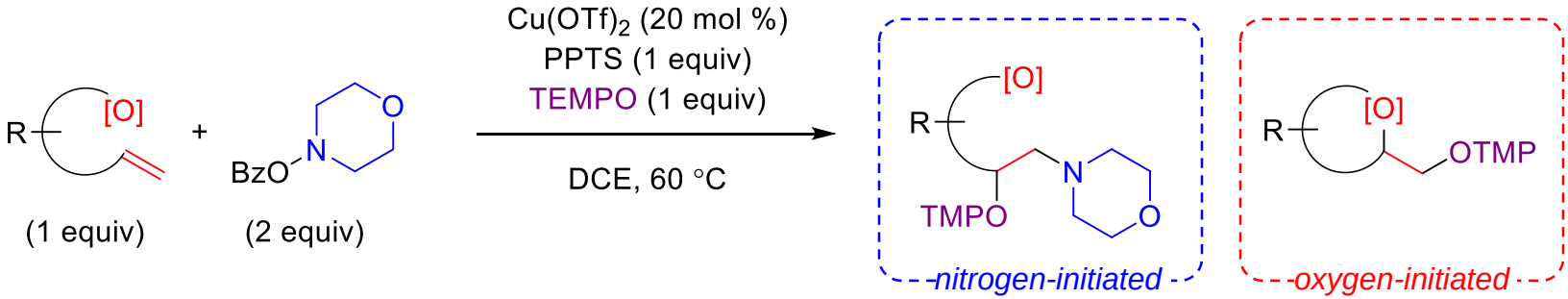


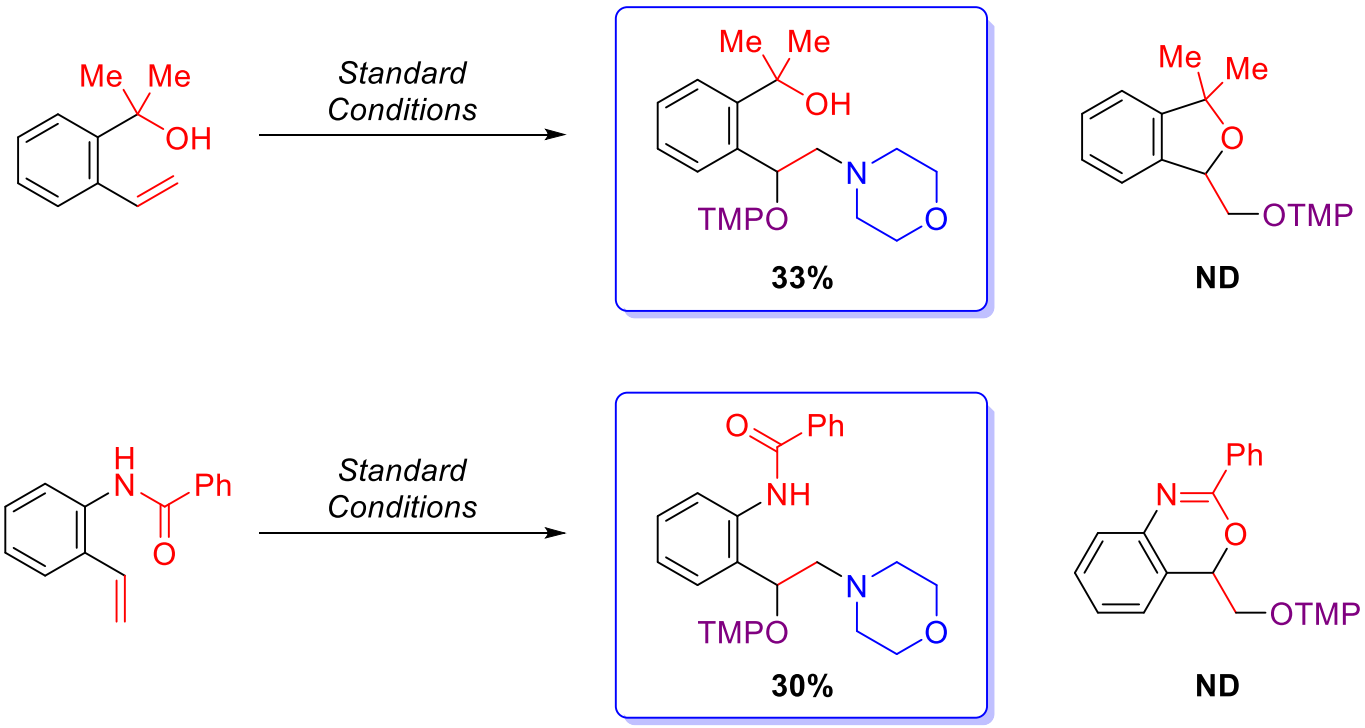
Isolated Yields. [a]Standard reaction conditions: carboxylic acid (0.4 mmol, 1.0 equiv), *O*-benzoylhydroxylamine (2.0 equiv), $Cu(OTf)_2$ (10 mol%), DCE (2 mL), 80 °C. [b]dr = diastereomeric ratio, as determined by ^1H NMR of the crude mixture. [c]Observed by GCMS.

Liwosz, T.W.; Chemler, S.R. *Org. Lett.* **2013**, *15*, 3034–3037.

Hemric, B.N.; Shen, K.; Wang, Q. *J. Am. Chem. Soc.* **2016**, *138*, 5813–5816.

Mechanistic Insight: Radical Trapping

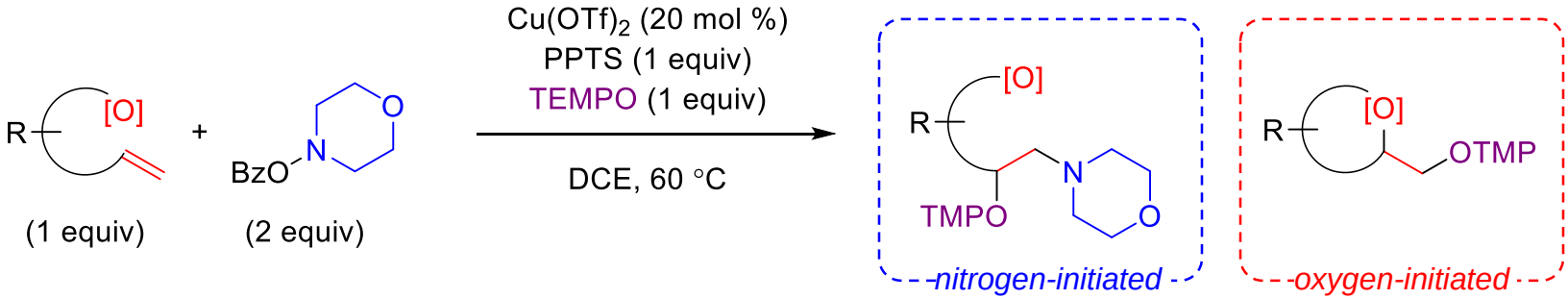


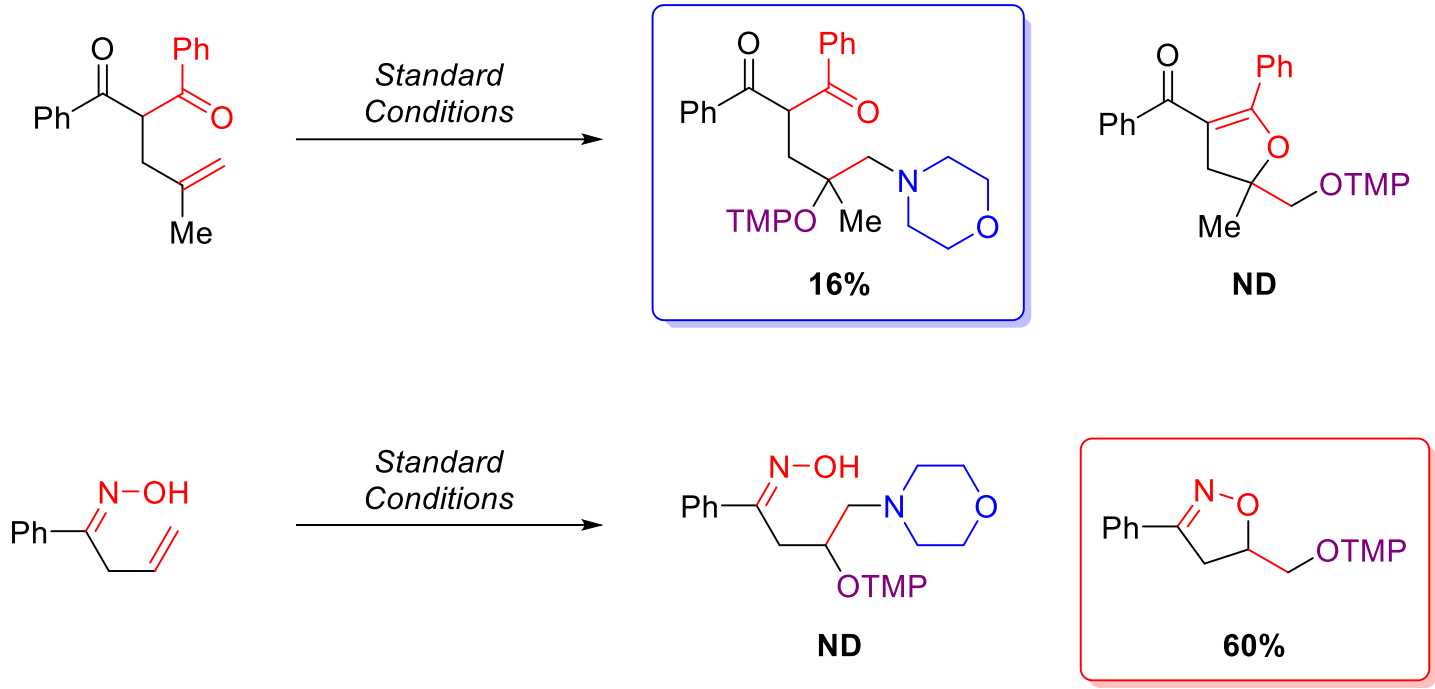


Isolated yields on 0.4 mmol scale.

Hemric, B.N.; Chen, A.W.; Wang, Q. *J. Org. Chem*, **2019**, *84*, 1468–1488.

Mechanistic Insight: Radical Trapping

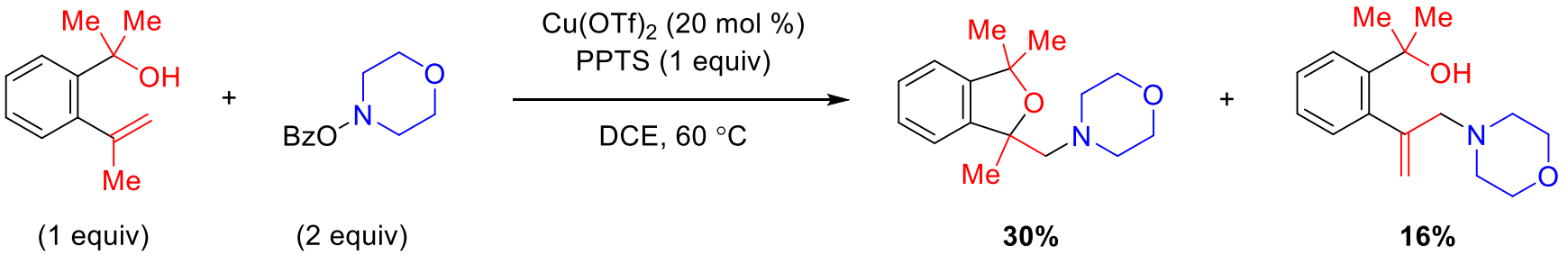


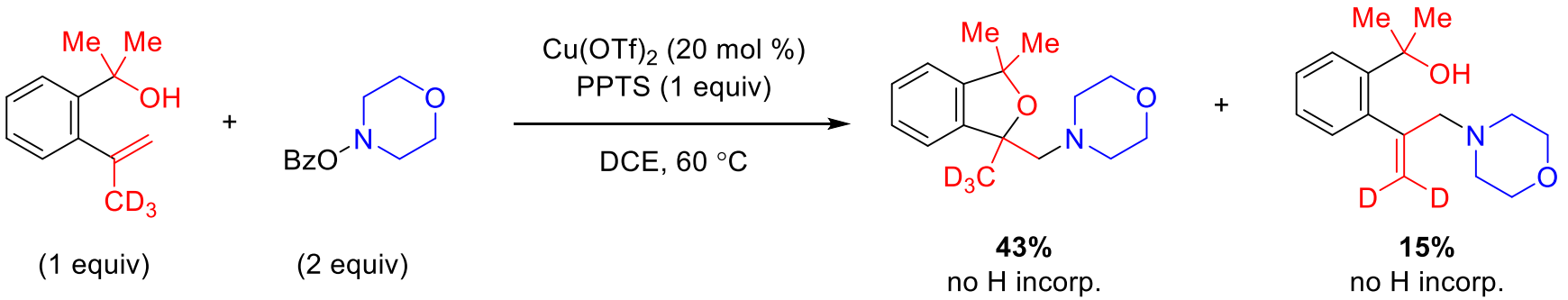


Isolated yields on 0.4 mmol scale.

Hemric, B.N.; Chen, A.W.; Wang, Q. *J. Org. Chem*, **2019**, *84*, 1468–1488.

Mechanistic Insight: Elimination Pathway

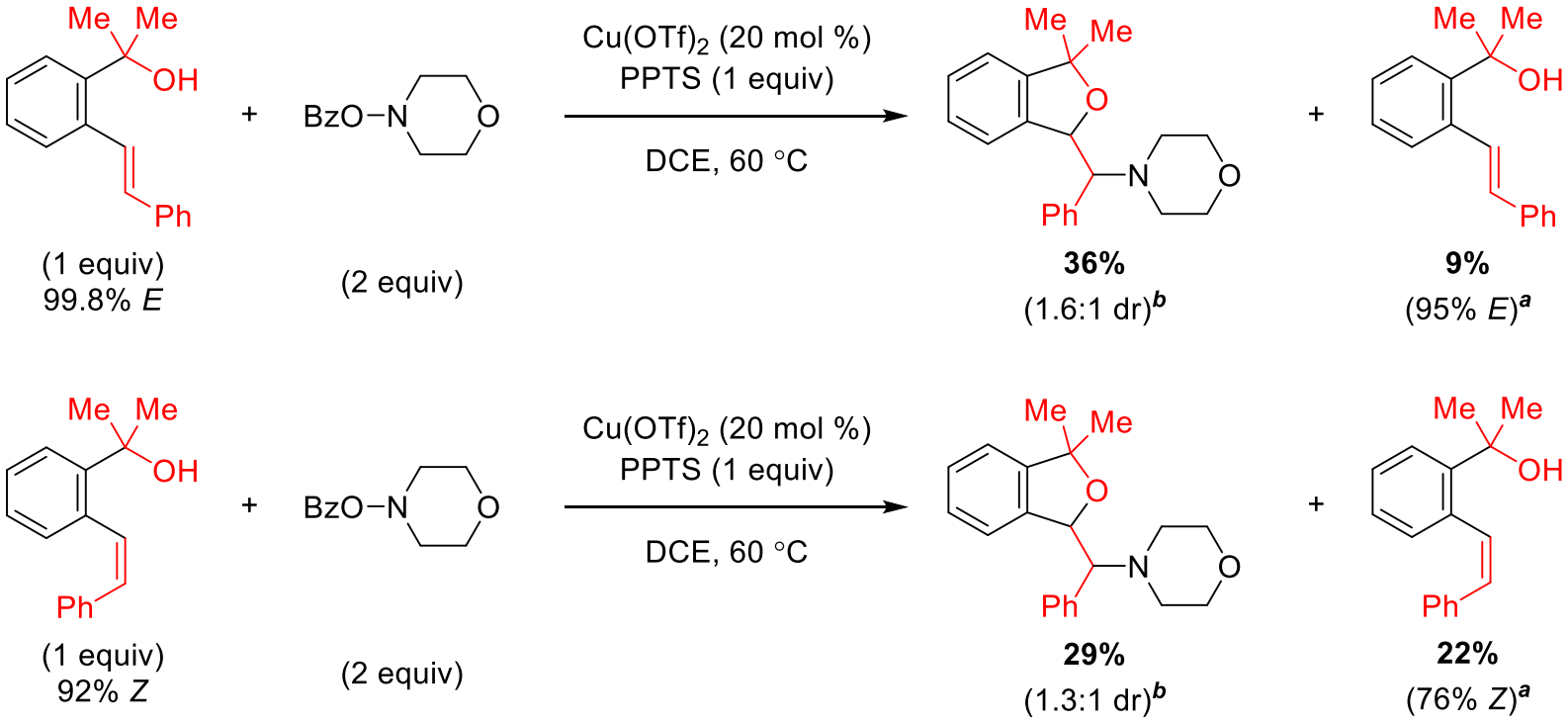




Isolated yields on 0.4 mmol scale.

Hemric, B.N.; Chen, A.W.; Wang, Q. *J. Org. Chem*, **2019**, *84*, 1468–1488.

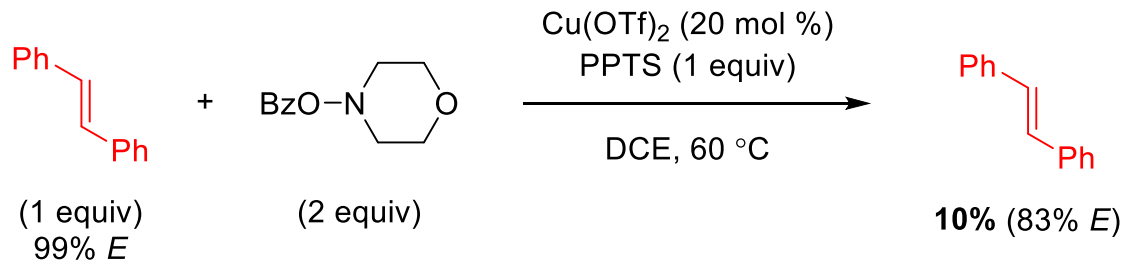
Mechanistic Insight: Alkene Addition Reversibility



Isolated yields on 0.4 mmol scale. Geometric purities determined by GCMS.

Hemric, B.N.; Chen, A.W.; Wang, Q. *J. Org. Chem*, **2019**, *84*, 1468–1488.

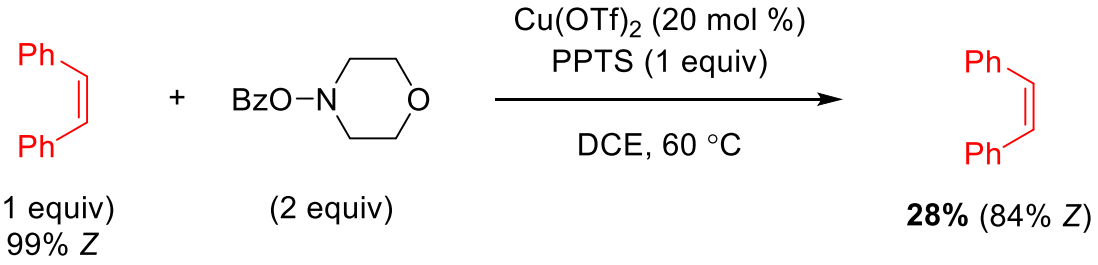
Mechanistic Insight: Alkene Addition Reversibility



(1 equiv)
99% *E*

(2 equiv)

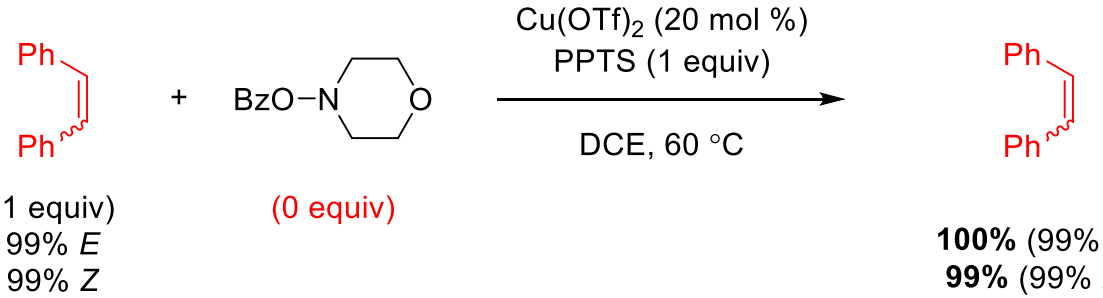
10% (83% *E*)



(1 equiv)
99% *Z*

(2 equiv)

28% (84% *Z*)



(1 equiv)
99% *E*
99% *Z*

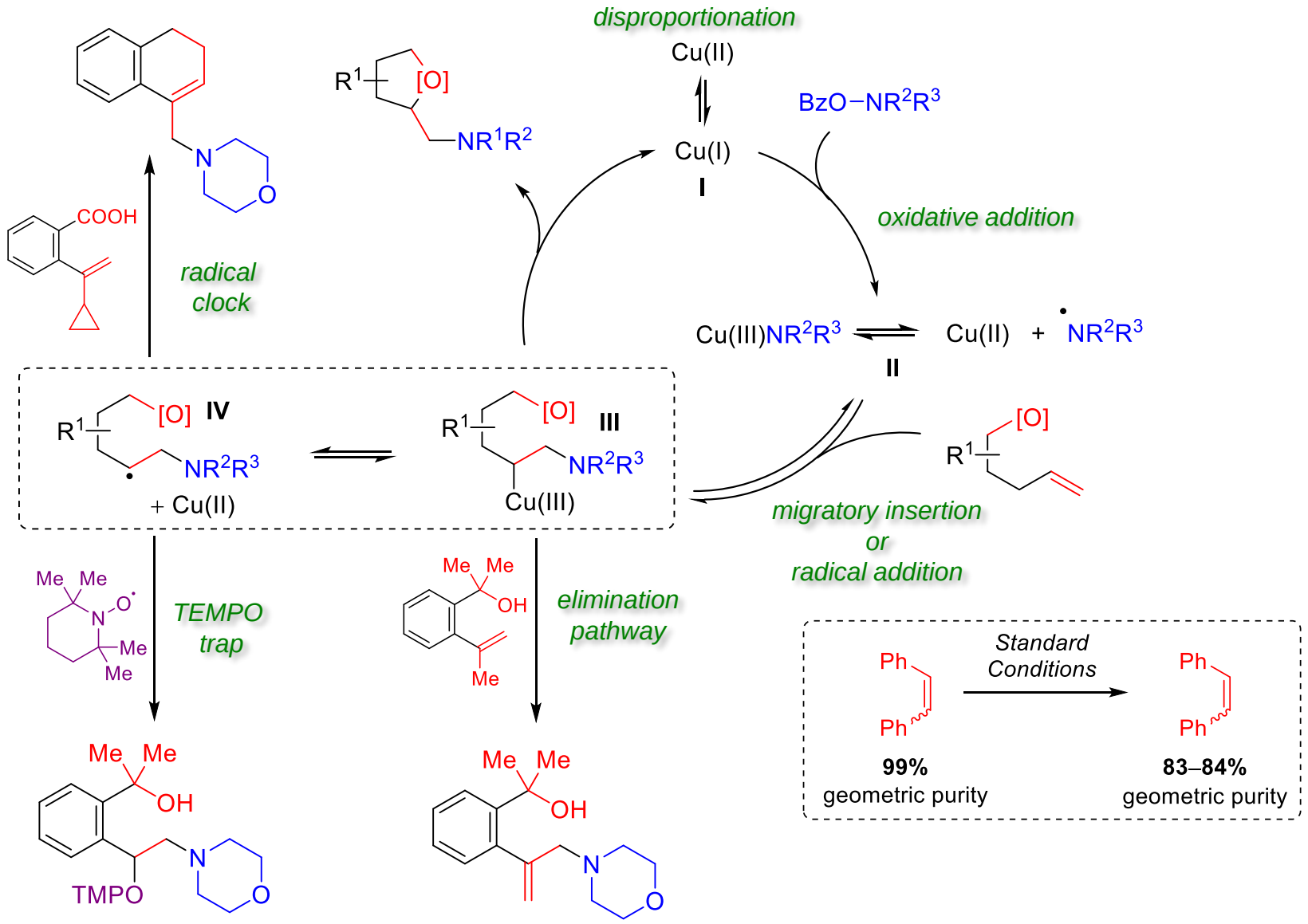
(0 equiv)

100% (99% *E*)
99% (99% *Z*)

Isolated yields on 0.4 mmol scale. Geometric purities determined by GCMS.

Hemric, B.N.; Chen, A.W.; Wang, Q. *J. Org. Chem*, **2019**, *84*, 1468–1488.

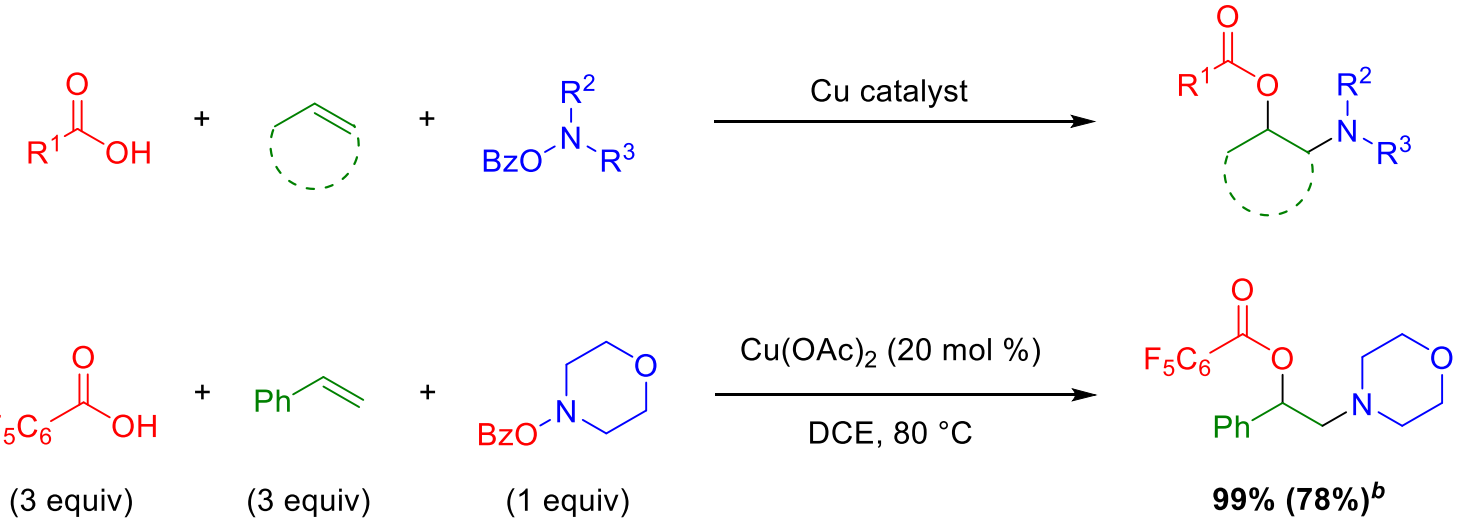
Proposed Catalytic Cycle



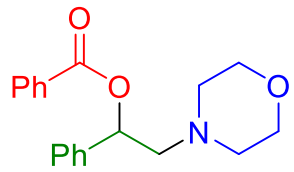
Hemric, B.N.; Shen, K.; Wang, Q. *J. Am. Chem. Soc.* **2016**, *138*, 5813–5816.

Hemric, B.N.; Chen, A.W.; Wang, Q. *J. Org. Chem*, **2019**, *84*, 1468–1488.

Three-Component Amino Oxygenation



Entry	COOH (equiv)	Alkene (equiv)	Hydroxylamine (equiv)	Yield[a] (%)
1	1	1	1	42
2	1	1	3	45
3	3	1	1	71
4	1	3	1	82
5	1	3	3	99
6	**3**	**3**	**1**	**99 (78)[b]**

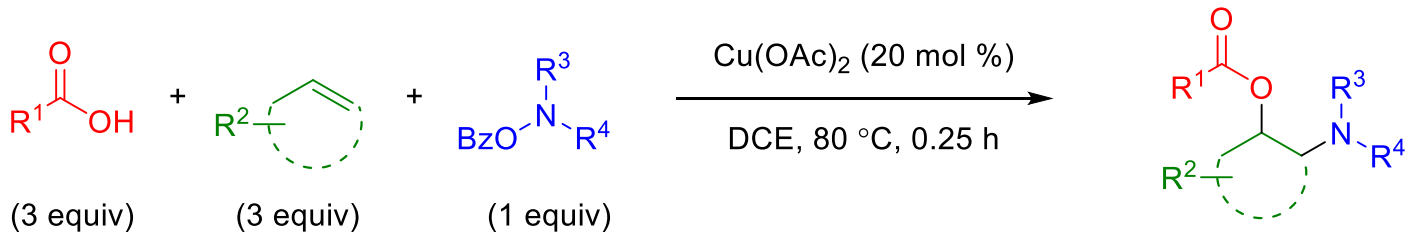


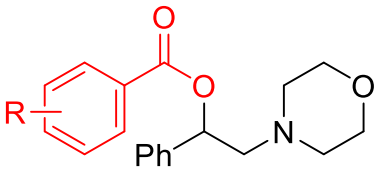
In absence of excess carboxylic acid, benzoic acid from hydroxylamine will trap.

[a]Yields determined by ^{1}H NMR spectroscopy with CH_2Br_2 as a quantitative internal standard. [b]Isolation yield on 0.4 mmol scale shown in parentheses.

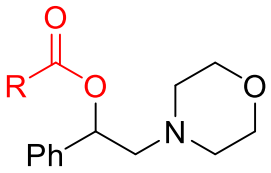
Hemric, B.N.; Wang, Q. *Beilstein J. Org. Chem.* **2016**, *12*, 22–28.

Three-Component Amino Oxygenation: Alkene Scope

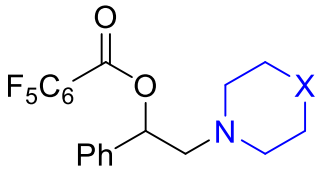




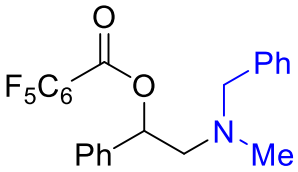
78%, R = 2,3,4,5,6-F
77%, R = 3,5-NO_2
40%, R = H



40%, R = CH_2Cl
32%, R = Me
34%, R = allyl



73%, X = NBoc
68%, X = $CHCO_2Et$
49%, X = CH_2

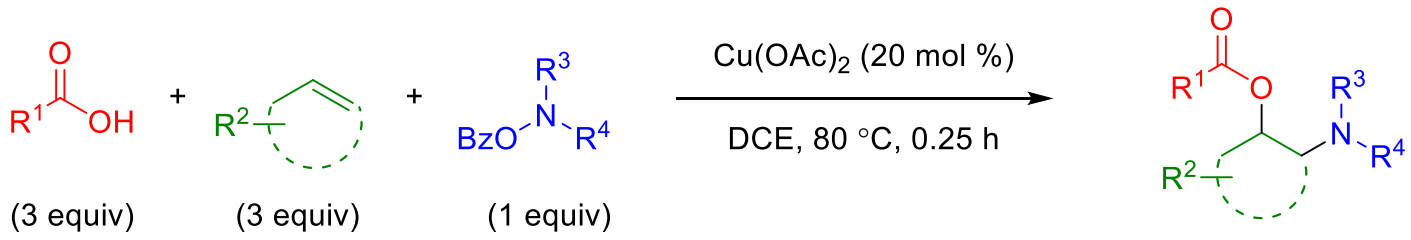


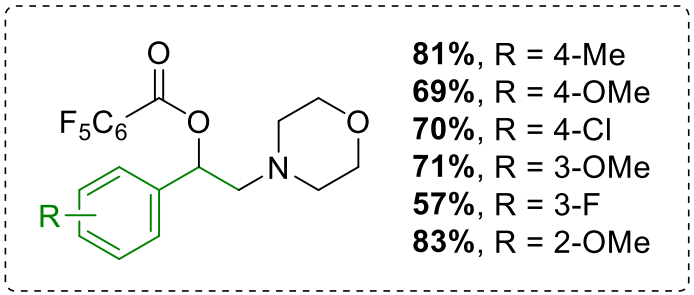
23%

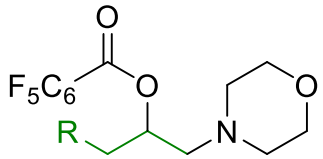
Isolated yields on 0.4 mmol scale. [a]dr = diastereomeric ratio, as determined by ^1H NMR of the crude mixture. [b]Relative stereochemistry determined by X-ray crystallography.

Hemric, B.N.; Wang, Q. *Beilstein J. Org. Chem*. **2016**, *12*, 12–22.

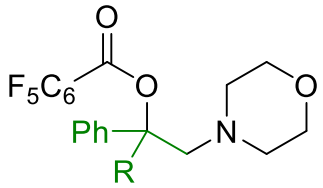
Three-Component Amino Oxygenation: Alkene Scope



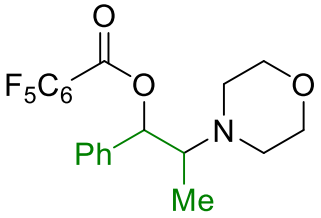




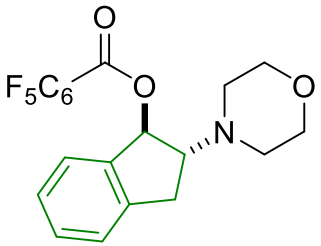
19%, R = TMS
ND, R = CN



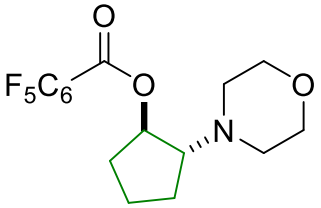
<15%, R = Me
ND, R = Ph



69% (dr = 1:1)[a]
from *E*



89% (dr = 7:1)[ab]

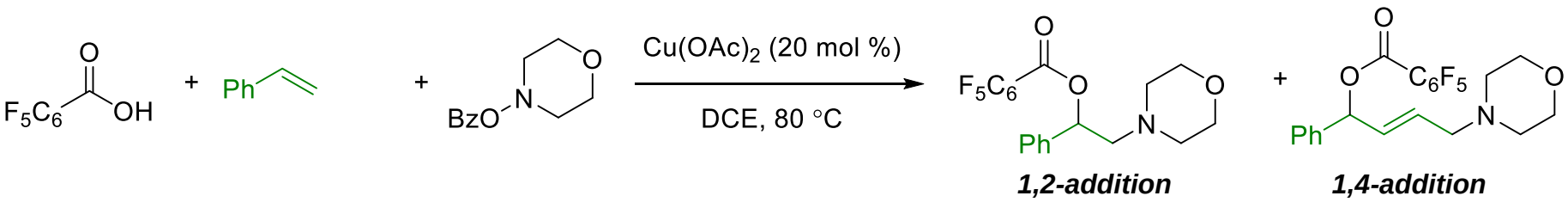


35% (dr = >20:1)[a]

Isolated yields on 0.4 mmol scale. [a]dr = diastereomeric ratio, as determined by ^{1}H NMR of the crude mixture. [b]Relative stereochemistry determined by X-ray crystallography.

Hemric, B.N.; Wang, Q. *Beilstein J. Org. Chem*. **2016**, *12*, 12–22.

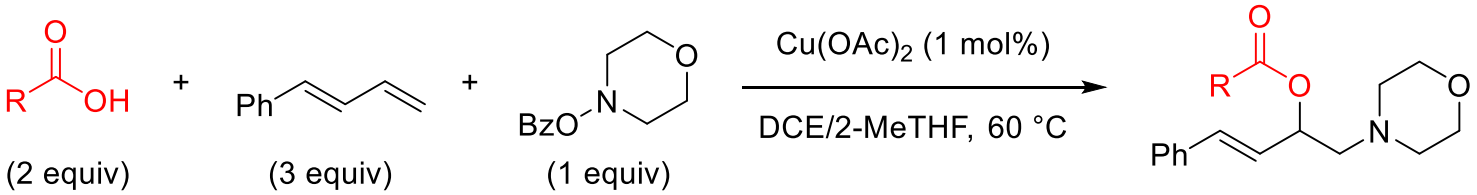
Three-Component Amino Oxygenation of Dienes

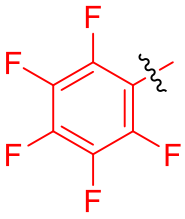


Entry	Equiv			Cu(OAc)$_2$ (mol %)	solvent	Temp (°C)	Yield[a] (%)	
							1,2	**1,4**
1	3	3	1	20	DCE	80	46	20
2	2	3	1	20	DCE	80	50	12
3	2	3	1	1	DCE	80	47	18
4	2	3	1	1	DCE	60	48	21
5	2	3	1	1	2-MeTHF	60	56 (60)[b]	2
5	2	3	1	1	DCE/2-MeTHF (1:1)	60	62[b]	7

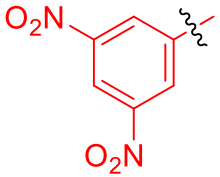
[a]Determined by quantitative ^{19}F NMR with 1,2,4,5-tetrafluorobenzene as an internal standard. [b]Isolated yield on 0.2 mmol scale

Three-Component Diene Amino Oxygenation: Acid Scope

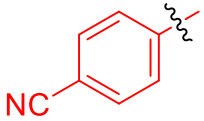




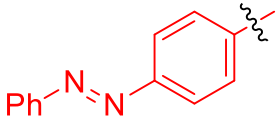
65%



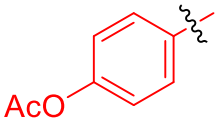
63%



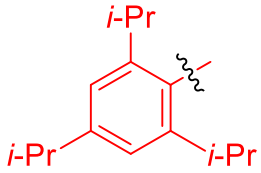
59%



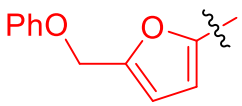
36%[a]



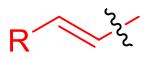
50%[b]



71%[ab]

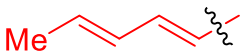


57%[b]



61%,[ab] R = H
43%,[ab] R = Ph

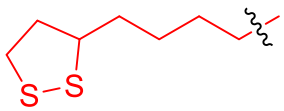
34%



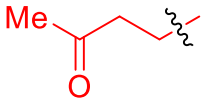
21%[ab]

57%[b]

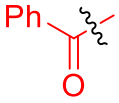
51%, R = Cl
55%,[b] R = SPh



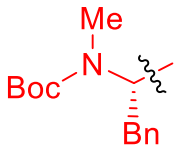
32%[b]



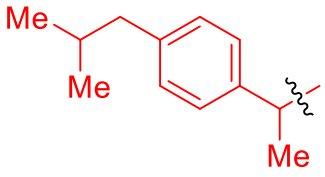
55%[b]



27%



58%[b] (1:1 dr)[c]



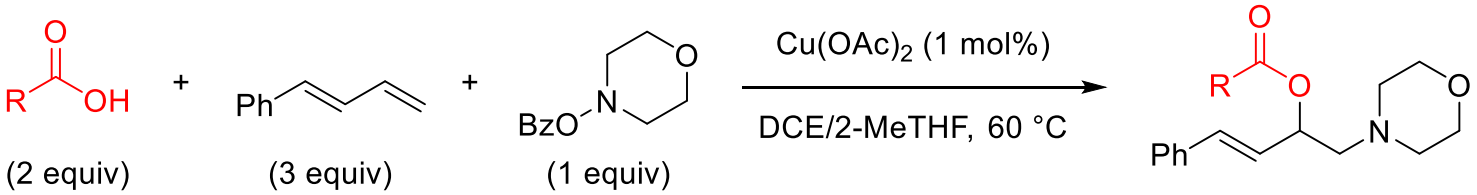
46%[ab] (1:1 dr)[d]

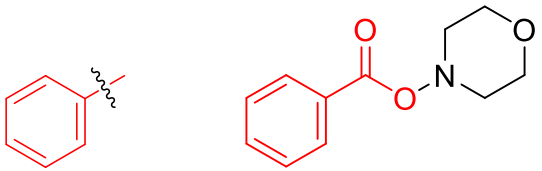
Isolated yields as average of two runs on 0.4 mmol scale. [a]Run with morpholino 3,4,5-trimethoxybenzoate. [b]Run without 2-MeTHF. Run with dr = diastereomeric ratio; [d]determined by chiral HPLC of the crude mixture, [e]determined by ^{1}H NMR of the crude mixture.

Hemric, B.N.; Chen, A.W.; Wang, Q. *Manuscript in review.*

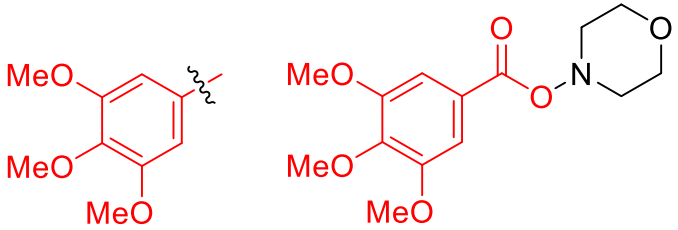
With Andy Chen

Three-Component Diene Amino Oxygenation: Acid Scope



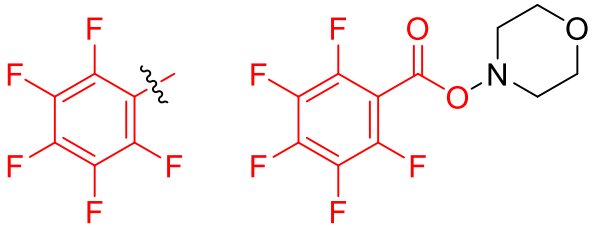


76%[b]



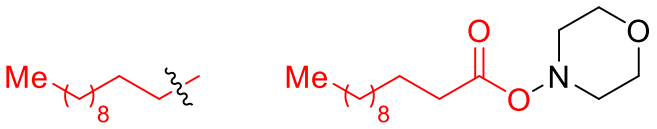
63%[b]

76%[b] with matching LG



65%

64% with matching LG



48%[b]

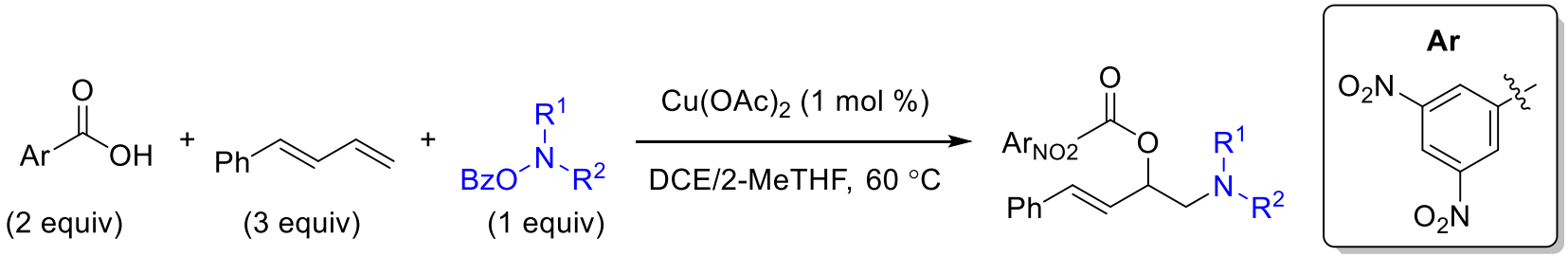
69%[b] with matching LG

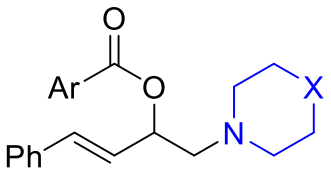
Isolated yields as average of two runs on 0.4 mmol scale. [a]Run with morpholino 3,4,5-trimethoxybenzoate. [b]Run without 2-MeTHF. Run with dr = diastereomeric ratio; [d]determined by chiral HPLC of the crude mixture, [e]determined by ^{1}H NMR of the crude mixture.

Hemric, B.N.; Chen, A.W.; Wang, Q. *Manuscript in review.*

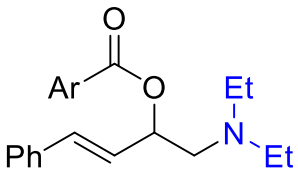
With Andy Chen

Three-Component Diene Amino Oxygenation: Amine Scope

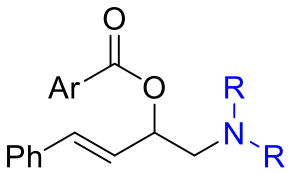




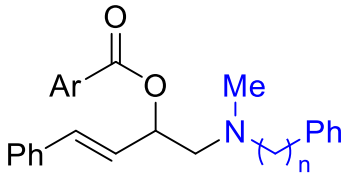
61%, X = NBoc
50%, X = $CHCO_2Et$
40%, X = CH_2



30%[a]



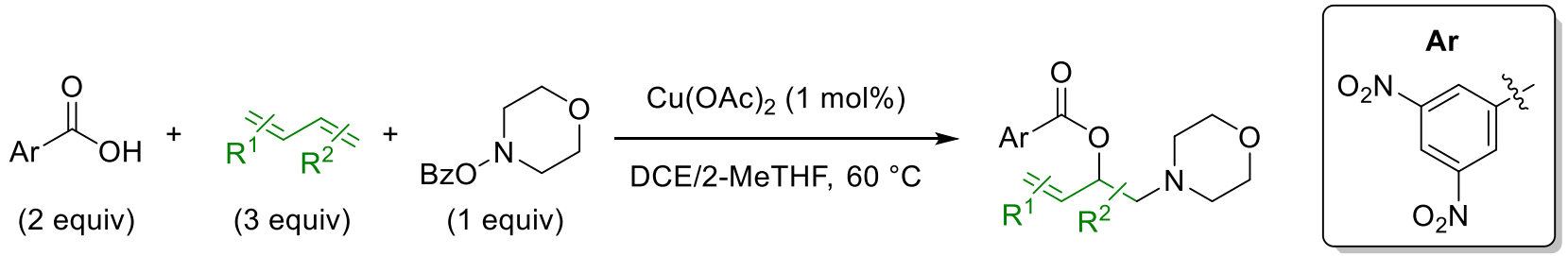
ND, R = Bn
ND, R = Cy

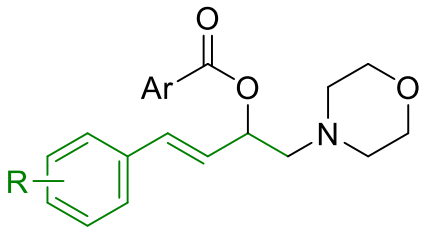


36%,[a] n = 1
47%,[a] n = 2

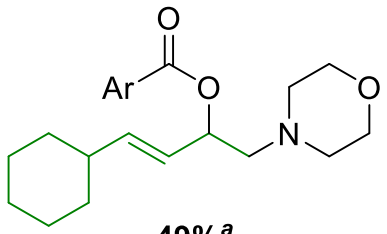
Isolated yields as average of two runs on 0.4 mmol scale. [a]Run without 2-MeTHF.

Three-Component Diene Amino Oxygenation: Diene Scope

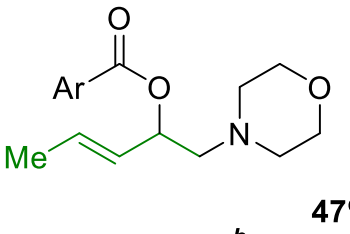




52%, R = 4-Me
56%, R = 4-Ph
ND, R = 4-NMe_2
trace, R = 4-OMe
57%, R = 4-Cl
64%, R = 4-Br
63%, R = 3-OMe
53%, R = 3-CF_3
43%, R = 2-OMe
57%, R = 2-Cl

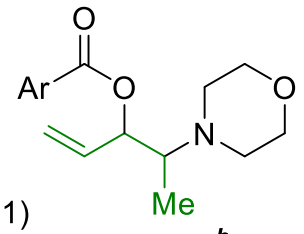


49%[a]

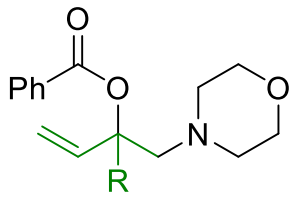


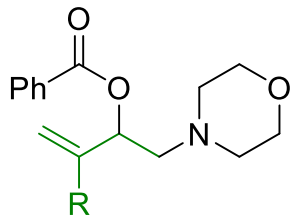
(14:1 E:Z)[b]

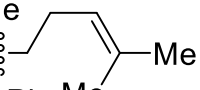
47% (5:1)

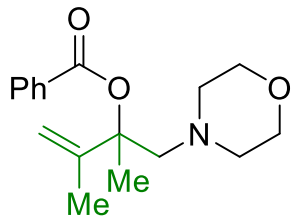


(1.3:1 dr)[b]





73%,[c] (6:1)[b] R = Me
61%,[c] (3:1)[b] R = 
39%,[acd] (8:1)[b] R = Ph



49%

Isolated yields as average of two runs on 0.4 mmol scale. [a]Second run on 0.2 mmol scale. [b]Determined through ^{1}H NMR of the crude reaction. [c]Run without 2-MeTHF. [d]Yield of major isomer. [e]Determined by chiral HPLC of the crude reaction. [f]Starting from 1.2:1 *E*:*Z* diene. [g]Determined by ^{1}H NMR of the crude reaction eluted through silica gel to remove **2x**.

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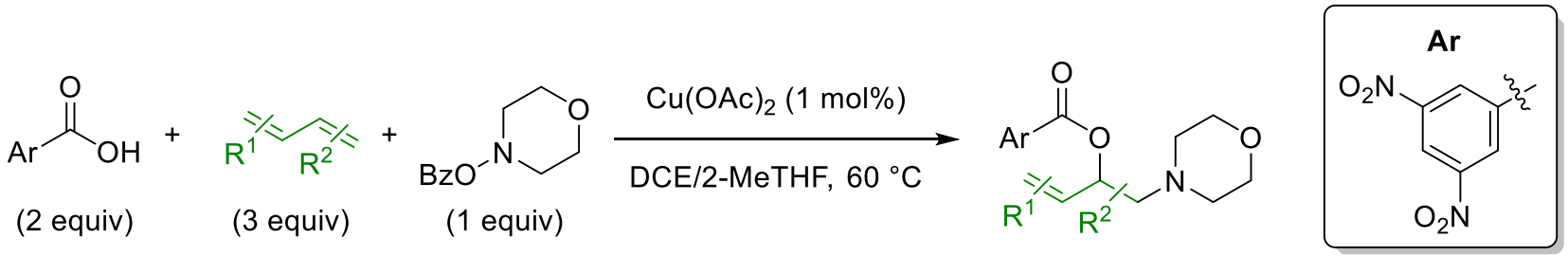
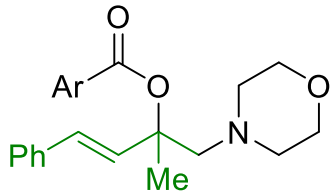
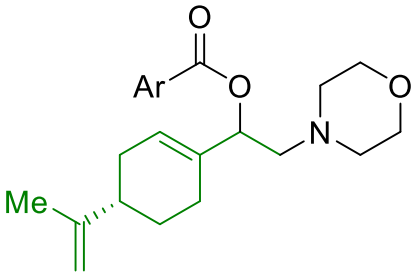
Three-Component Diene Amino Oxygenation: Diene Scope

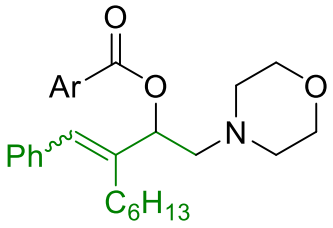




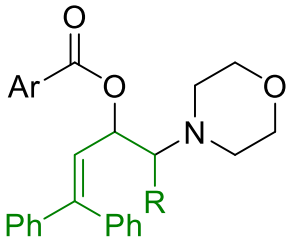
ND



32% (1.3:1 dr)[e]

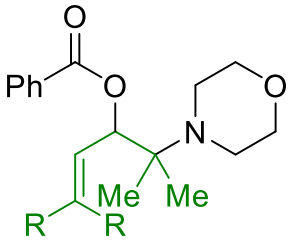


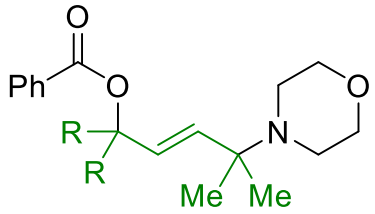
49% (3:1 E:Z)[b]



59%, R = H

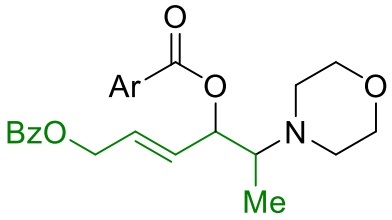
60%,[f] (1:1 dr)[b] R = Me



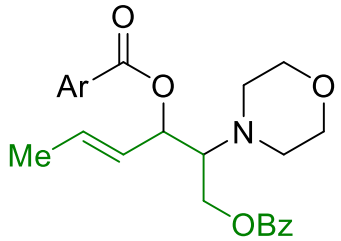


59%,[ce] (>20:1) R = Ph

76%,[c] (8:1) R = Me



(1.4:1 dr)[g]



26% (3.5:1)[g]

(1.9:1 dr)[g]

Isolated yields as average of two runs on 0.4 mmol scale. [a]Second run on 0.2 mmol scale. [b]Determined through ^{1}H NMR of the crude reaction. [c]Run without 2-MeTHF. [d]Yield of major isomer. [e]Determined by chiral HPLC of the crude reaction. [f]Starting from 1.2:1 *E*:*Z* diene. [g]Determined by ^{1}H NMR of the crude reaction eluted through silica gel to remove **2x**.

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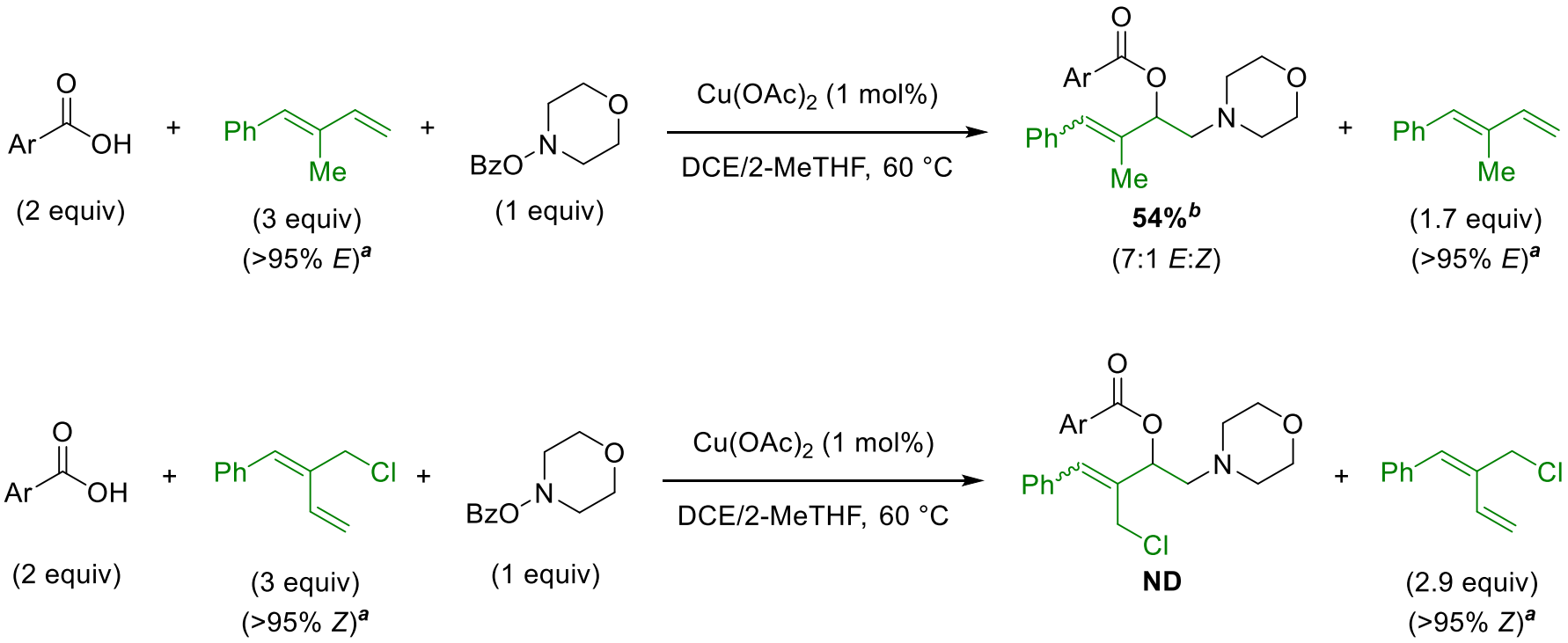
Three-Component Diene Amino Oxygenation: *E* vs *Z* Dienes



Isolated yields on 0.4 mmol scale. [a]Determined through ^{1}H NMR of the crude reaction. [b]Average of two runs.

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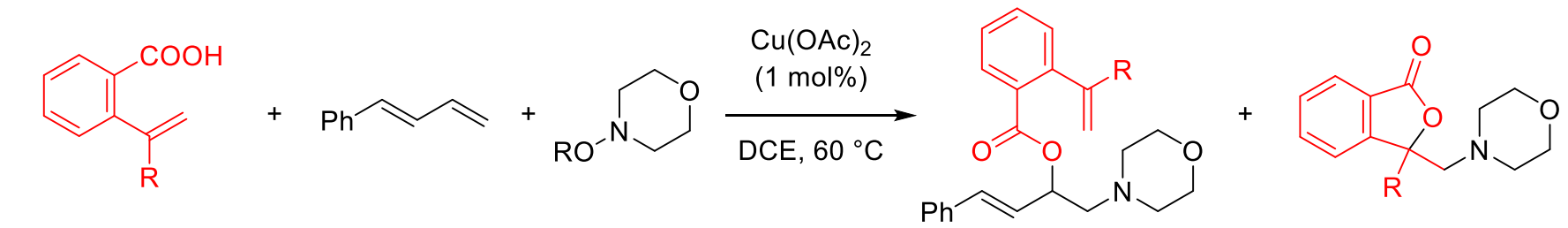
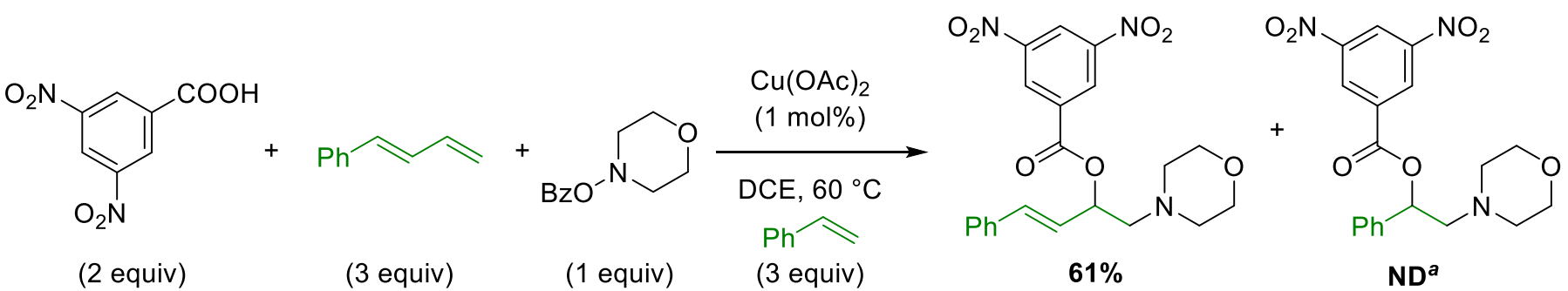
Selectivity for Dienes over Alkenes



(2 equiv) (3 equiv) (1 equiv)

58%, R = H
55%, R = Me

trace,[a] R = H
trace,[b] R = Me



(2 equiv) (3 equiv) (1 equiv) (3 equiv)

61%

ND[a]

Isolated yields as an average of two runs on 0.4 mmol scale. R = 3,4,5-trimethoxybenzoate. [a]Observed in >40:1 ratio by ^{1}H NMR. [b]Observed by GCMS. [c]ND = not detected by GCMS.

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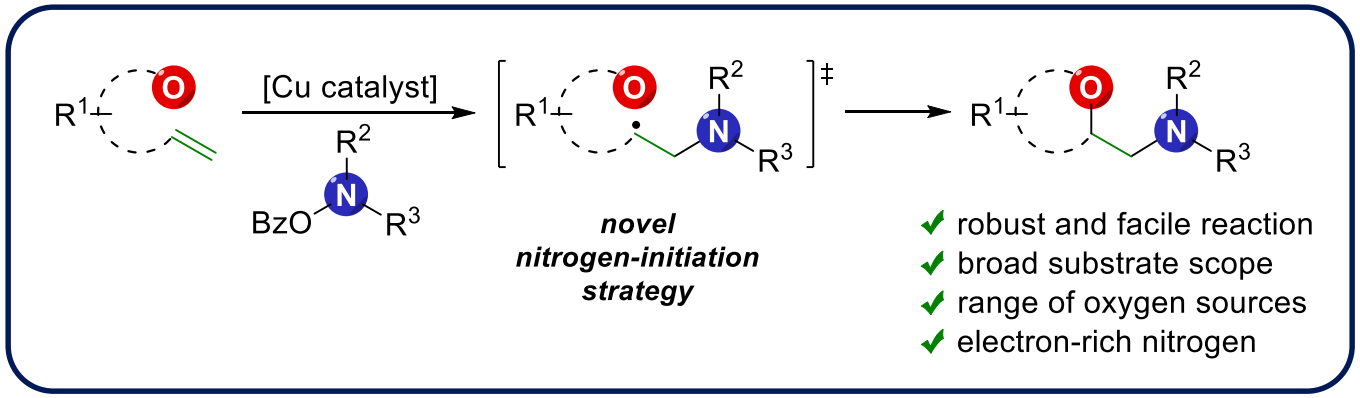
Summary


[Cu catalyst]
R2
N
BzO
R3
R1
O
‡
novel
nitrogen-initiation
strategy
robust and facile reaction
broad substrate scope
range of oxygen sources
electron-rich nitrogen

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