

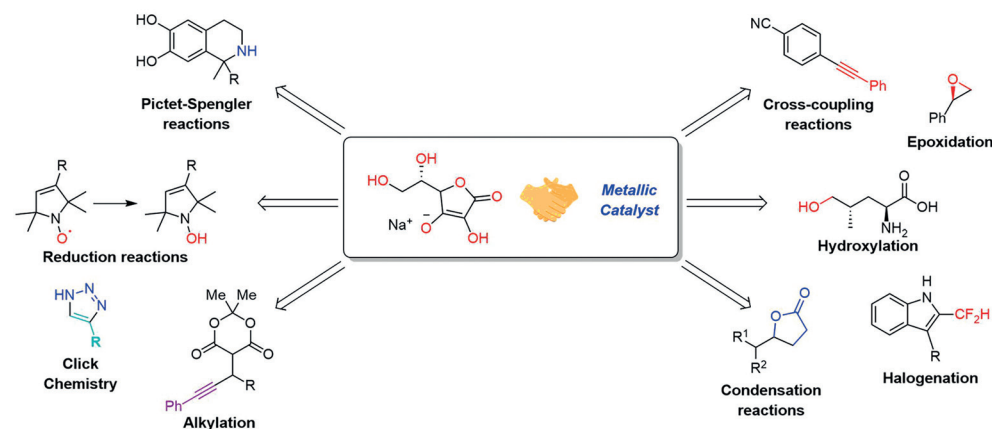
# The Diverse Applications of Sodium L-Ascorbate as a Reducing Agent in Organic Synthesis

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Received: 16.08.2024

Accepted after revision: 09.12.2024

Published online: 04.03.2025 (Version of Record)

DOI: 10.1055/s-0040-1720162; Art ID: SO-2024-08-0033-GR

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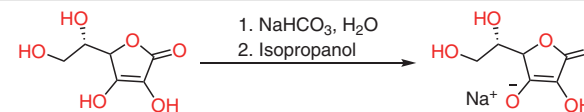
**Abstract** Sodium L-ascorbate is an inexpensive and non-hazardous organic salt derived from ascorbic acid that is widely applied as a reducing agent in diverse industrial processes and occurs naturally in some plants and animals. In organic synthesis it can participate in a variety of reactions, playing different roles as a secondary or main reactant to promote a wide range of chemical transformations, being most commonly used along with metallic catalysts. This graphical review highlights some of the numerous applications of sodium ascorbate as a reactant in organic reactions.

**Key words** sodium L-ascorbate, reduction, catalysis, photocatalysis, synthesis

Sodium L-ascorbate is an organic sodium salt that occurs as a white to slightly yellowish powder, is readily soluble in water and is only very slightly soluble in ethanol. In aqueous solutions it exhibits pH values of 5.6 to 7.0 or higher.<sup>1</sup> It can be obtained by dissolution of ascorbic acid (vitamin C) in water followed by the addition of an equivalent amount of sodium bicarbonate, which generates effervescence. Upon completion of the effervescence, sodium ascorbate can be precipitated by the addition of isopropanol (Scheme 1).<sup>2</sup>

Being an inexpensive, environmentally friendly and non-hazardous compound, ascorbate is widely applied as an antioxidant in pharmaceutical manufacturing, the food industry and in the production of cosmetics.<sup>3</sup> It also acts as a coenzyme and a reducing agent, occurs as a metabolite in some plants and animals and shows in vitro cytotoxic effects in malignant cell lines, of which melanoma cells are particularly susceptible.<sup>4</sup>

In organic synthesis, its most common employment is to induce click chemistry reactions,<sup>5</sup> but it can also be applied in a variety of chemical transformations under different reaction conditions, both as a secondary reactant or as a main reactant. Due to its reducing power, sodium ascorbate is commonly used along with a metallic catalyst for the purpose of reducing it to its most active form, contributing to increased reaction yields. The reducing activity of ascorbate also serves to avoid the formation of undesired byproducts. In addition to conventional metallic catalysts, the ascorbic acid sodium salt can also help to activate photocatalysts, participating in the formation of free radicals to promote photoredox-catalyzed reactions,<sup>6</sup> and plays a role in electrochemical reactions.<sup>7</sup> This graphical review provides a detailed overview of the many applications of sodium L-ascorbate as a reactant in organic chemistry through history.



**Scheme 1** Formation of sodium L-ascorbate from ascorbic acid

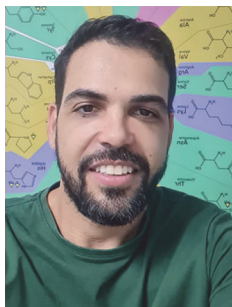
## Biosketches



**Leticia Ribeiro Magalhães** received her chemistry degree from the Federal University of Rio Grande do Norte in 2019. Currently, she is a pharmacy student and an undergraduate

researcher at the same institution under the supervision of Prof. A. K. Jordão and Prof. E. G. Barbosa. Her work involves the synthesis of potentially bioactive heterocyclic com-

pounds.



**Euzebio Guimarães Barbosa** received his Ph.D. in chemistry from Campinas University (UNICAMP) in 2011 under the

supervision of Prof. Marcia Miguel Castro Ferreira. Currently he is a professor at the Federal University of Rio Grande do

Norte. His research interests focus on medicinal chemistry and computer-aided drug design.



**Alessandro Kappel Jordão** received his Ph.D. in chemistry from Fluminense Federal University (UFF) in 2010 under the

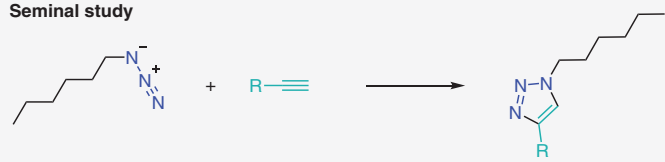
supervision of Prof. Vitor Francisco Ferreira and Prof. Anna Claudia. Currently, he is a professor at the Federal University

of Rio Grande do Norte. His research interests focus on the synthesis of heterocyclic compounds.

## Notable features

- Most common application.
- Click chemistry method.
- Cu(I)-catalyzed reactions to produce 1,4-disubstituted 1,2,3-triazoles.
- Sodium ascorbate reduces Cu(II) from diverse sources to Cu(I) in situ.
- Wide reaction scope.

## Seminal study



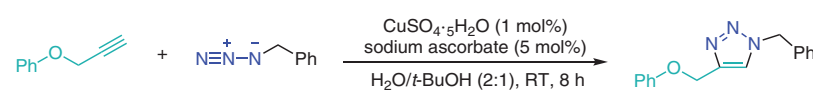
(8a) Huisgen, *Angew. Chem. Int. Ed.* **1963**, *2*, 565.

## Further reading

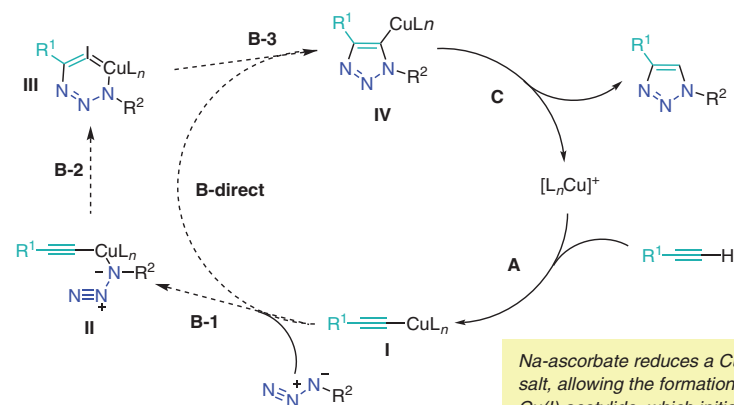
Additional seminal work:  
(8c) Huisgen, *Angew. Chem. Int. Ed.* **1963**, *2*, 633.

## Click chemistry:

(8d) Sharpless, *Angew. Chem. Int. Ed.* **2001**, *40*, 2004  
(8e) Pore, *Chem. Asian J.* **2011**, *6*, 2696.  
(8f) Meldal, *Chem. Rev.* **2008**, *108*, 2952.

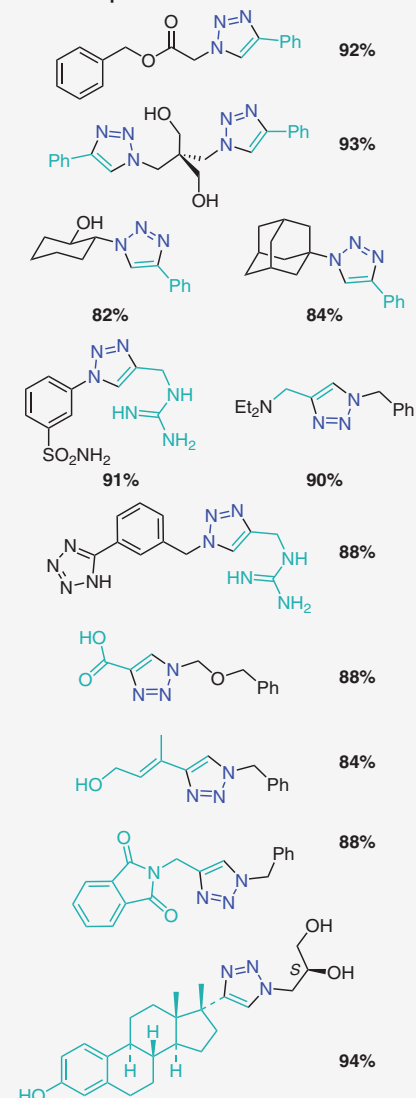
Synthesis of 1,4-disubstituted 1,2,3-triazoles using CuSO<sub>4</sub>·5H<sub>2</sub>O as the Cu(II) source

## Proposed catalytic cycle for Cu(I)-catalyzed ligation

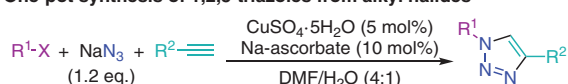


(5) Fokin, Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 2596.

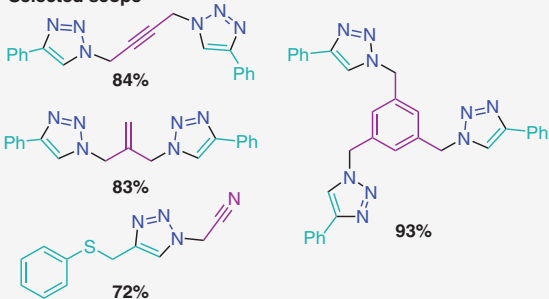
## Selected scope



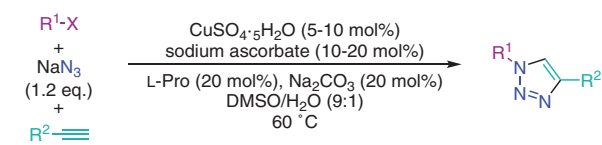
## One-pot synthesis of 1,2,3-triazoles from alkyl halides



## Selected scope



(8b) Fokin, *Org. Lett.* **2004**, *6*, 3897.



## Selected scope

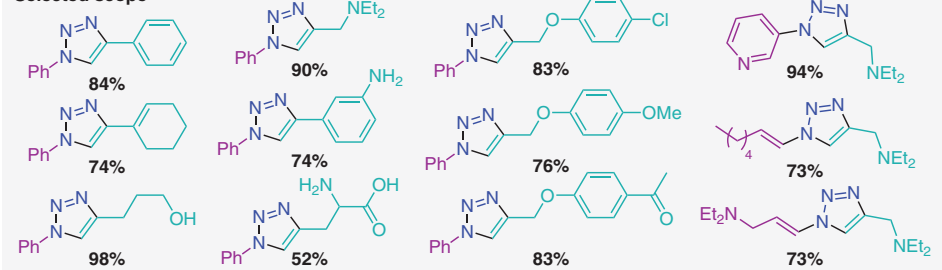
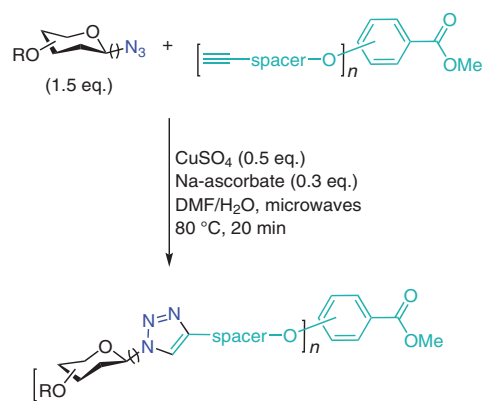
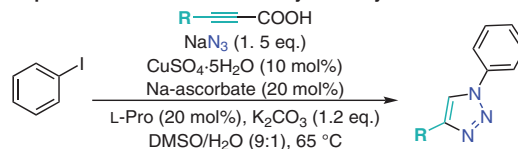
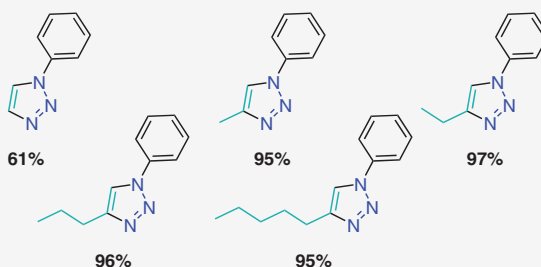


Figure 1 1,3-Dipolar cycloaddition, part I<sup>5,8a-f</sup>

**Microwave-assisted synthesis of triazole glycodendrimers**


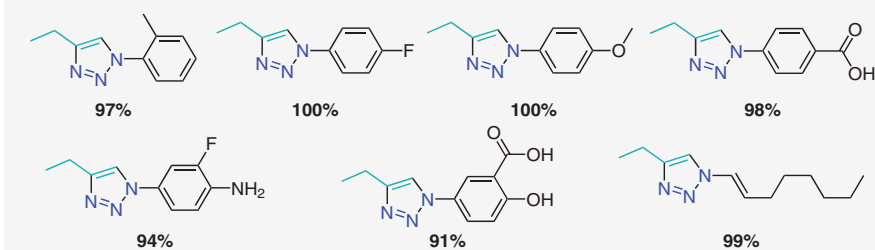
Microwave conditions reduce reaction time and yield only divalent products.

(9a) Liskamp, Pieters, *Eur. J. Org. Chem.* **2005**, 3182.

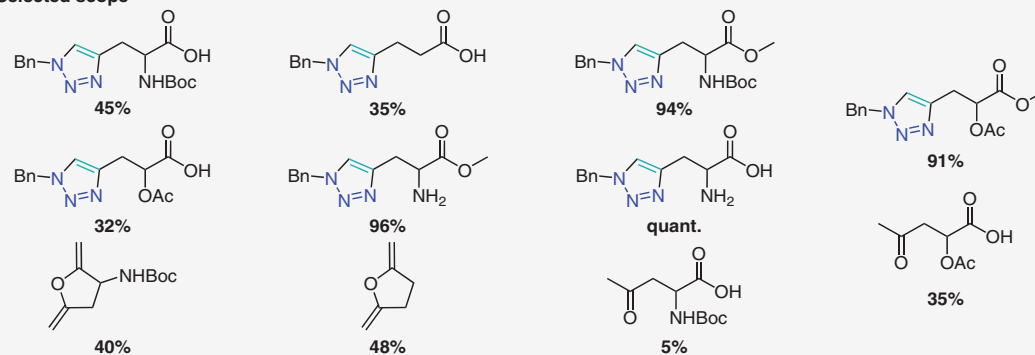
**One-pot azide formation–decarboxylation–cycloaddition**

**Selected scope**


(9b) Kolarovic, *J. Org. Chem.* **2011**, 76, 2613.

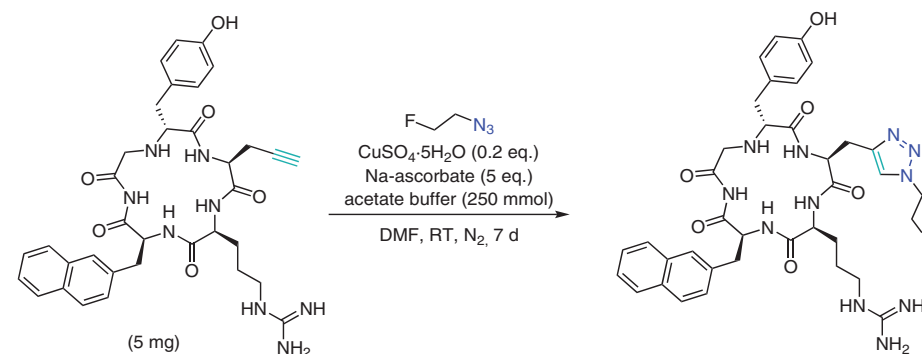
**One-pot azide formation–decarboxylation–cycloaddition with different iodide coupling partners**

**Selected scope**

**Click reaction of alkyonic acids yielding product mixtures**


Enol lactones are formed under the same conditions applied for Cu(I)-catalyzed cycloaddition of terminal alkynes and azides.

**Selected scope**


(9c) Mindt, *J. Org. Chem.* **2007**, 72, 10247.

**Synthesis of a triazole-containing peptide**


(9d) George, *J. Labelled Compd. Radiopharm.* **2013**, 56, 679.

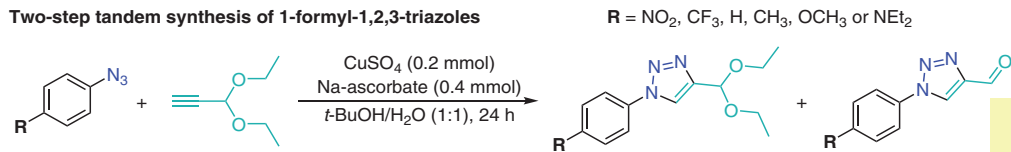
**Further reading**

Microwave organic synthesis:  
 (9e) Lidström, *Tetrahedron* **2001**, 57, 9225.  
 (9f) Bogdal, *Microwave-Assisted Organic Synthesis: One Hundred Reaction Procedures* **2005**.  
 (9g) Sagar, *Curr. Org. Chem.* **2021**, 25, 2378.

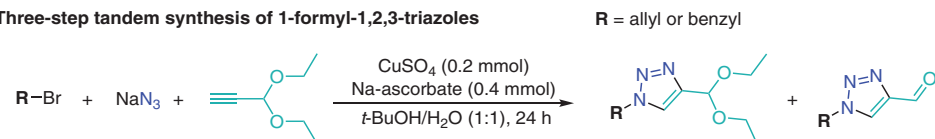
Peptides and click chemistry  
 (9h) Skwarczynski, *Molecules* **2013**, 18, 13148.  
 (9i) Chaiken, *Molecules* **2013**, 18, 9797.  
 (9j) Agouram, *Molecules* **2021**, 26, 2937.

**Figure 2** 1,3-Dipolar cycloaddition, part II<sup>9a–j</sup>

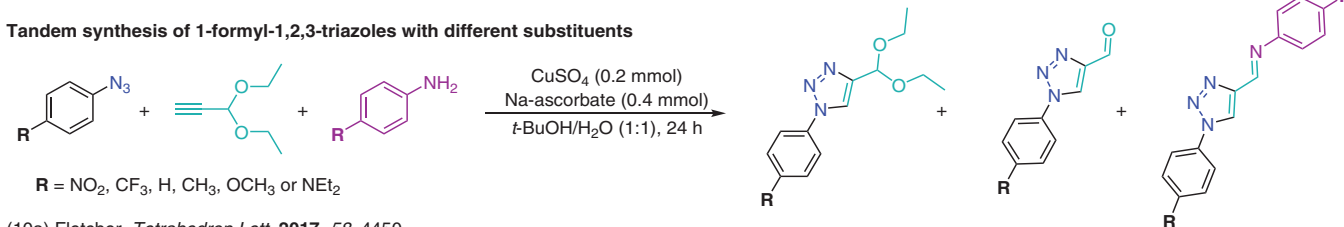
## Two-step tandem synthesis of 1-formyl-1,2,3-triazoles



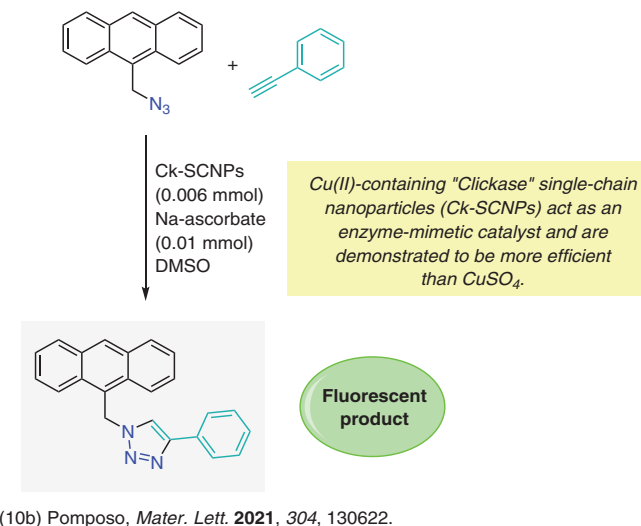
## Three-step tandem synthesis of 1-formyl-1,2,3-triazoles



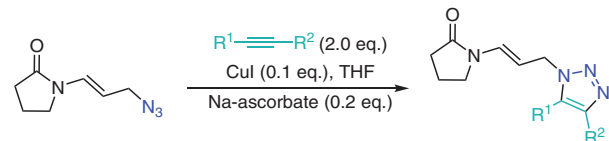
## Tandem synthesis of 1-formyl-1,2,3-triazoles with different substituents

(10a) Fletcher, *Tetrahedron Lett.* **2017**, *58*, 4450.

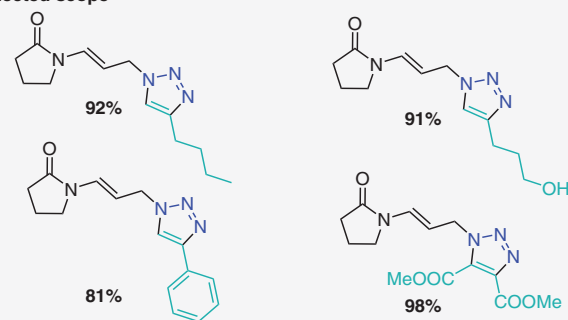
## Fluorogenic click reaction

(10b) Pomposo, *Mater. Lett.* **2021**, *304*, 130622.

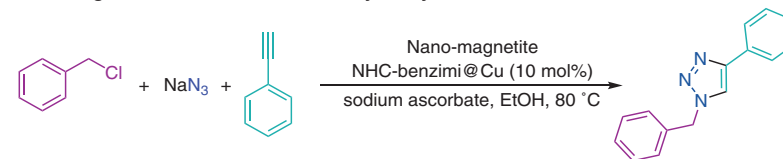
## 1,2,3-Triazole synthesis with mono- and disubstituted alkynes



## Selected scope

(10c) Maio, *Tetrahedron Lett.* **2021**, *102*, 132536.

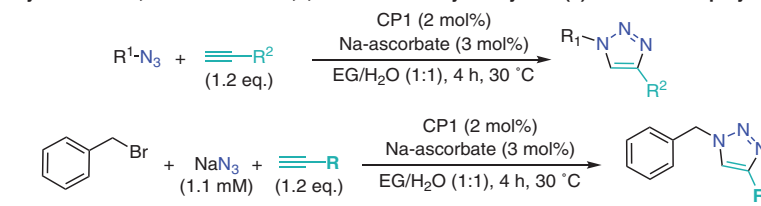
## Nano-magnetite NHC-benzimi@Cu-catalyzed synthesis of 1,4-disubstituted 1,2,3-triazoles



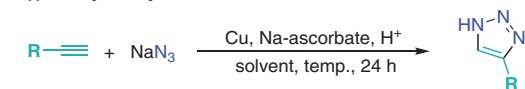
A magnetically recyclable catalyst is used as the Cu(II) source which is easy to recover and can be reused without appreciable loss of activity.

(10d) Patil, *Catal. Lett.* **2021**, *152*, 1854.

## Synthesis of 1,4-disubstituted 1,2,3-triazoles catalyzed by a Cu(II) coordination polymer

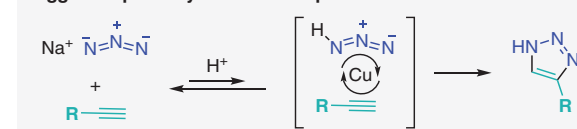
(10e) Puzari, *Sci. Rep.* **2022**, *12*, 14613.

## Cu(I)-catalyzed synthesis of 4-substituted-1H-1,2,3-triazoles



Cu-catalyzed azide-alkyne cycloaddition to form 4-substituted-1H-1,2,3-triazoles reported for the first time.

## Suggested pathway of the developed reaction

(10f) Gazvoda, *J. Org. Chem.* **2022**, *87*, 4018.

## Further reading

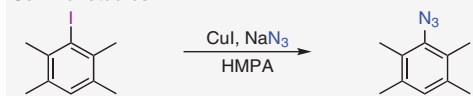
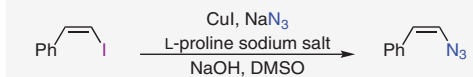
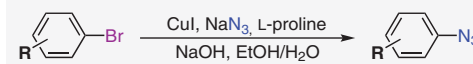
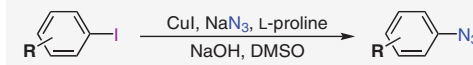
- Nanocatalysts and nanomagnetic materials  
(10g) Polshettiwar, Asefa (Eds.), *Nanocatalysis: Synthesis and Applications* **2013**.  
(10h) Yamaguchi, Hirohata, Stadler (Eds.), *Nanomagnetic Materials: Fabrication, Characterization and Application* **2021**.  
(10i) Gun'ko, *Nanomaterials* **2014**, *4*, 222.

Figure 3 1,3-Dipolar cycloaddition, part III<sup>10a-i</sup>

## Notable features

- Synthesis of aryl azides and amines.
- Commonly copper(I)-catalyzed reactions.
- Wide reaction scope.

## Seminal studies

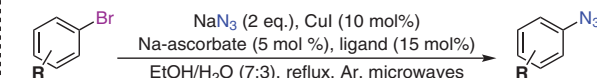
(11a) Suzuki, *Bull. Chem. Soc. Jpn.* **1980**, 53, 1765.(11b) Ma, *J. Chem. Soc., Chem. Commun.* **2004**, 888.

## Further reading

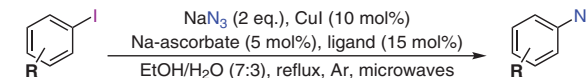
Additional seminal work:

(11h) Scriven, Turnbull, *Chem. Rev.* **1988**, 88, 298.(11i) Thomas, *Angew. Chem. Int. Ed.* **2003**, 42, 5400.

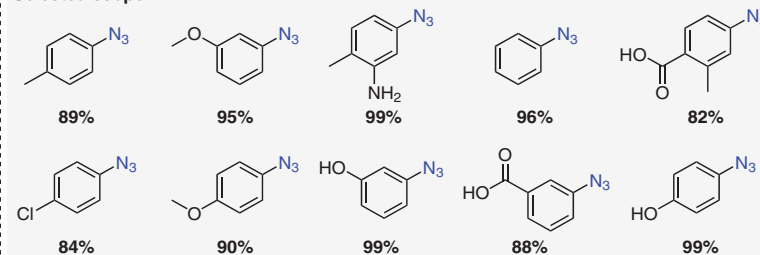
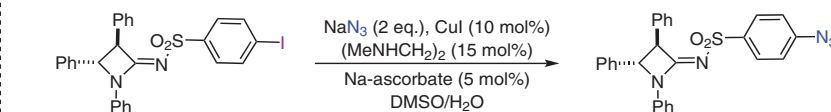
## Synthesis of aryl azides from aryl halides



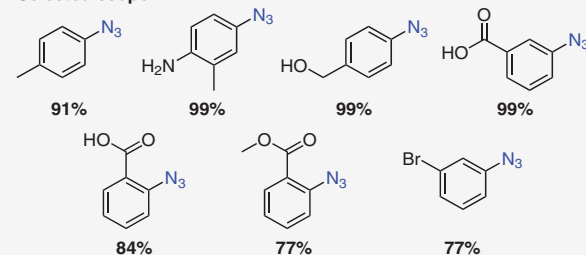
Sodium ascorbate helps to achieve total conversion of the products by its stabilizing effect on the copper catalyst.



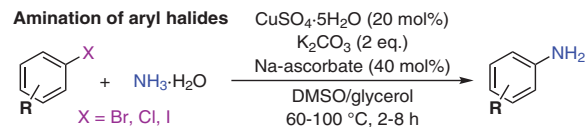
## Selected scope

(11c) Liang, *Synlett* **2005**, 2209.(11d) Fokin, *Angew. Chem. Int. Ed.* **2006**, 45, 3157.

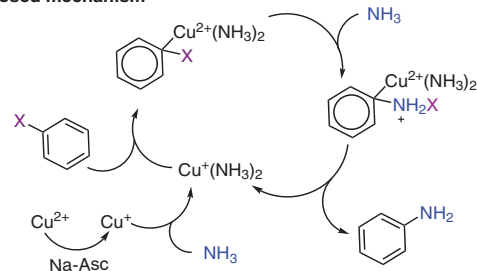
## Selected scope

(11e) Flood, *Angew. Chem. Int. Ed.* **2008**, 47, 2649.

## Amination of aryl halides



## Proposed mechanism

(11f) Wang, *Chin. J. Chem.* **2013**, 31, 501.

## Selected scope

X = Br		R	Yield (%)
R	Yield (%)		
4-Br	83	85%	85%
4-Cl	78		
2-Cl	50	80%	80%
4-COMe	88		
3-NO <sub>2</sub>	80	80%	80%
H	72		
4-Me	47	80%	80%
3-Me	45		
4-MeO	37	80%	80%
3-MeO	40		
4-NH <sub>2</sub>	15	80%	80%

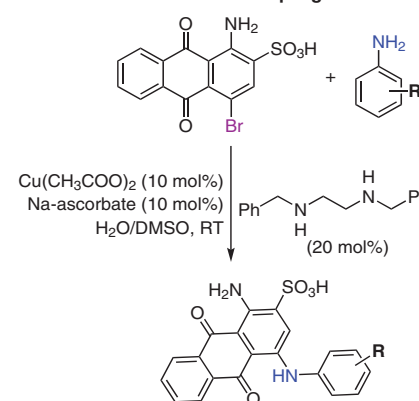
## X = Cl

R	Yield (%)
4-NO <sub>2</sub>	69
2-NO <sub>2</sub>	65
3-NO <sub>2</sub>	67
2,4-NO <sub>2</sub>	75, 43

## X = I

R	Yield (%)
4-Br	85, 37
4-COMe	90, 50
2-Cl	54
H	83, 35
4-Me	70
2-Me	45
4-MeO	58

## Ligand-assisted Ullmann cross-coupling reaction

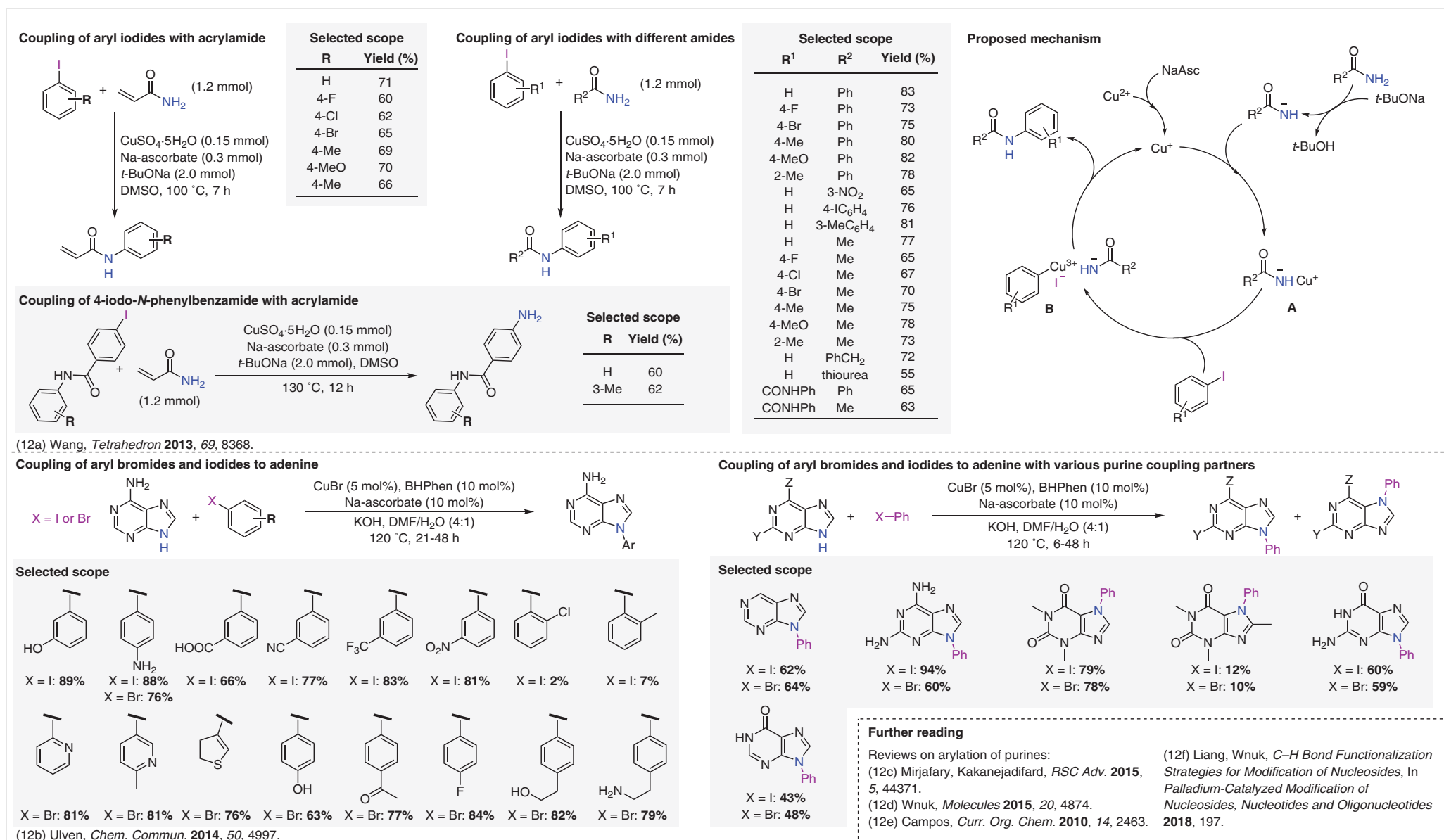
(11g) Lu, *Chin. J. Chem. Eng.* **2016**, 24, 1000.

## Selected scope

R	Yield (%)
4-SO <sub>3</sub> H	99.1
2-Me, 4-SO <sub>3</sub> H	99.5
2-COOH	99.0
4-COOH	100
3-SO <sub>3</sub> H	99.7
2,5-OMe	91.1
4-OMe	100
3-COOH, 5-NH <sub>2</sub>	100
3-COOH	99.7
4-OH	100
2-COOH, 4-Cl	99.8
3-NO <sub>2</sub>	99.8
2,4,5-Me	97.7
3-Me	100

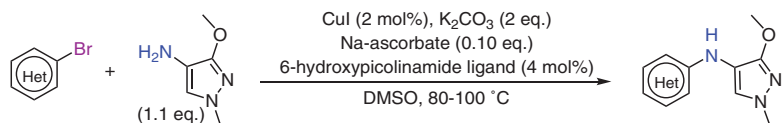
Figure 4 Substitution of aromatic halides with nitrogen nucleophiles, part I<sup>11a-i</sup>





**Figure 5** Substitution of aromatic halides with nitrogen nucleophiles, part II<sup>12a-f</sup>

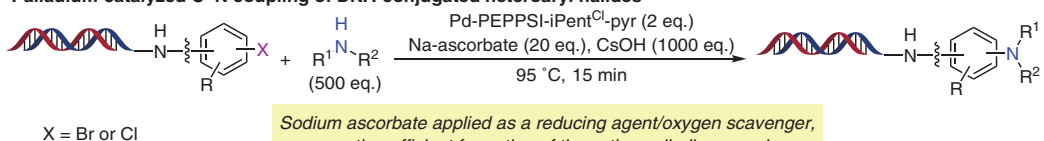
## Coupling of heteroaryl bromides with 4-aminopyrazoles



Sodium ascorbate ensures reliable activation of Cu catalysts, prevents side reactions when substrates that form electron-rich products are used and efficiently enables maximum reaction rates.

(13a) Singer, *Org. Process Res. Dev.* **2019**, *8*, 1538.

## Palladium-catalyzed C–N coupling of DNA-conjugated heteroaryl halides

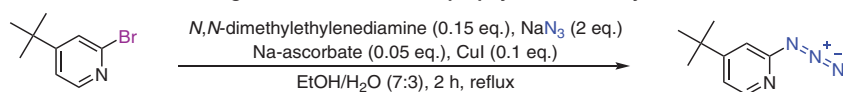


X = Br or Cl

Sodium ascorbate applied as a reducing agent/oxygen scavenger, promoting efficient formation of the active palladium species.

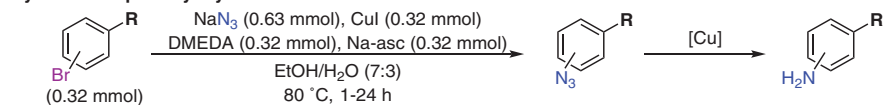
(13b) Chen, Simmons, *Bioconjugate Chem.* **2020**, *31*, 770.

## Synthesis of an intermediate during formation of a bis-zinc-porphyrin chemical system

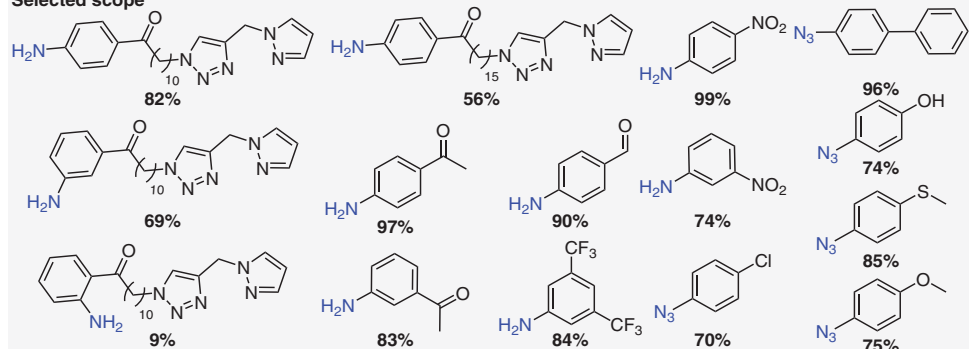


(13c) Kahlal, Gramage-Doria, *Eur. J. Org. Chem.* **2023**, *26*, e202300621.

## Synthesis of primary aryl amines and azides from bromobenzenes

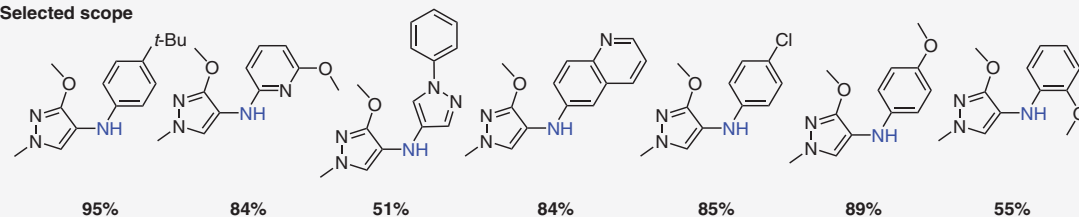


## Selected scope

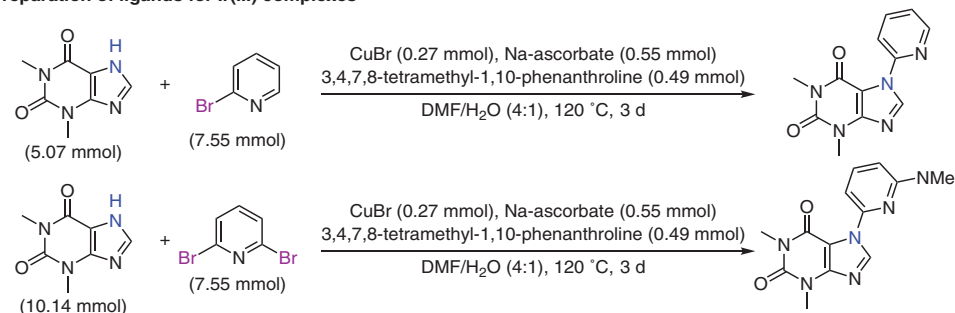


(13e) Roemer, *Adv. Synth. Catal.* **2022**, *364*, 2957.

## Selected scope

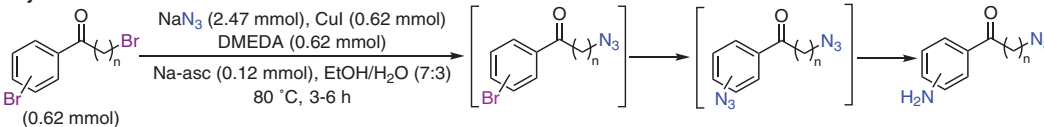


## Preparation of ligands for Ir(III) complexes



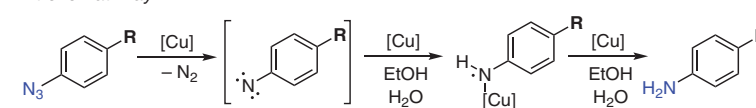
(13d) Biffis, *Eur. J. Inorg. Chem.* **2022**, e202200484.

## Synthesis of versatile amine-azides

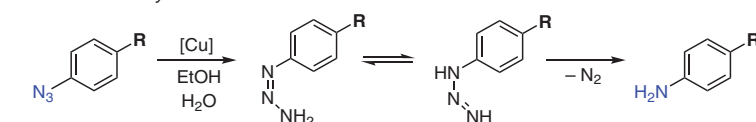


## Proposed mechanisms

## Nitrene Pathway



## Triazene Pathway



## Selected scope

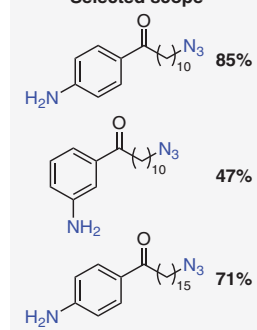


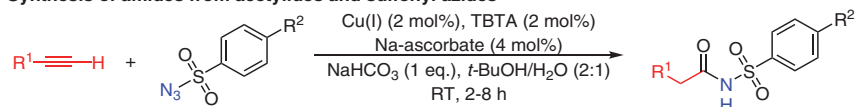
Figure 6 Substitution of aromatic halides with nitrogen nucleophiles, part III<sup>13a-e</sup>



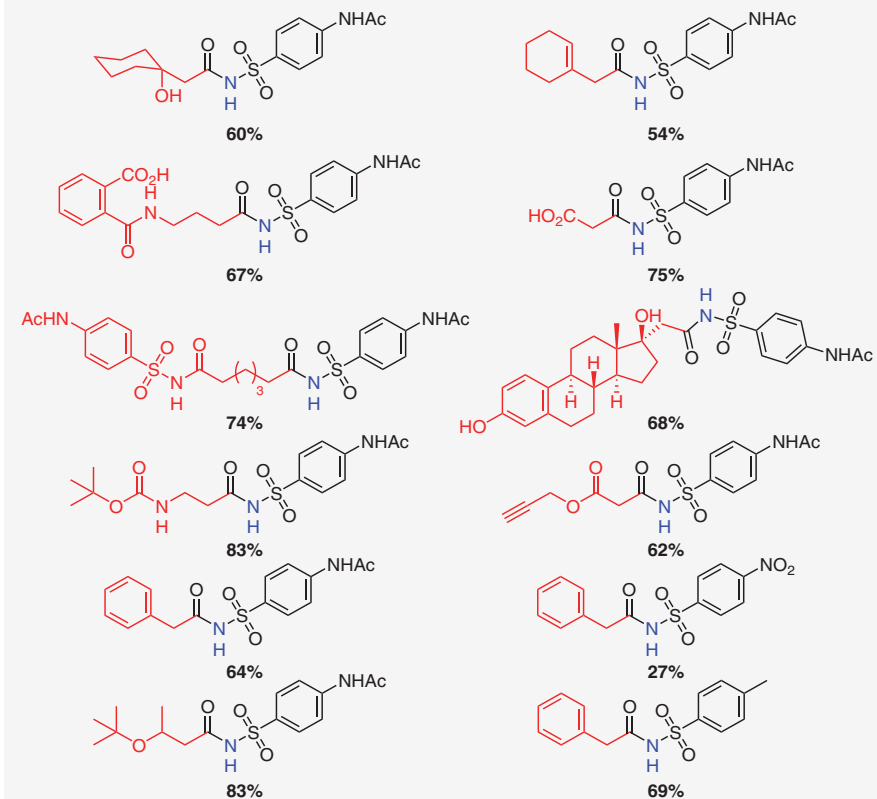
## Notable features

- Azide reduction to form primary or secondary amines.
- Sodium ascorbate reduces metallic catalysts in situ to an active form.
- Diverse reaction conditions.

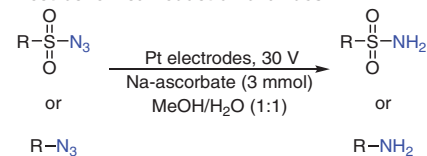
## Synthesis of amides from acetylides and sulfonyl azides



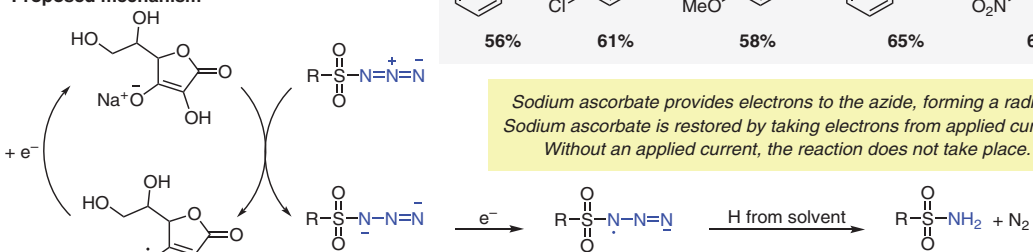
## Selected scope

(14a) Fokin, *Angew. Chem. Int. Ed.* **2006**, *45*, 3154.

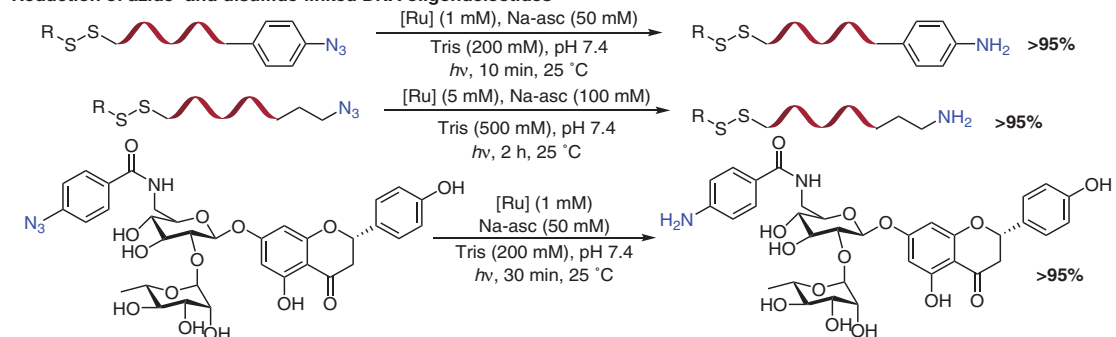
## Electrochemical reduction of azides



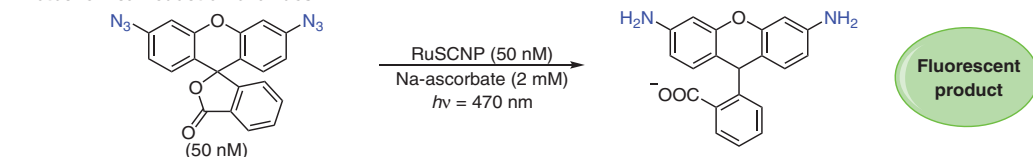
## Proposed mechanism

(7) Deena, *Orient. J. Chem.* **2022**, *38*, 1236.

## Reduction of azide- and disulfide-linked DNA oligonucleotides

(14b) Liu, *Nat. Chem.* **2011**, *3*, 146.

## Photochemical reduction of azides

(14c) Zimmerman, *J. Am. Chem. Soc.* **2020**, *142*, 4565.Figure 7 Reduction reactions, part I<sup>7,14a-c</sup>

## Notable features

- Reduction of nitrogenated compounds and oxygen radicals.
- Sodium ascorbate reduces directly or activates a metallic catalyst.

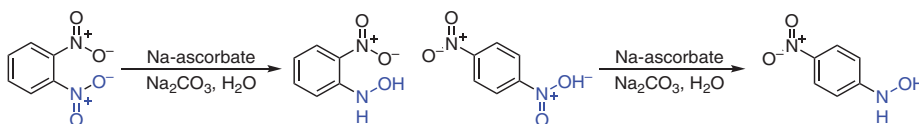
## Further reading

Reviews on reduction of nitro and nitroso compounds:  
 (15i) Dixon, Morejón, In *Comprehensive Organic Synthesis II* **2014**, 479.  
 (15j) Jost, Benaglia, *Org. Process Res. Dev.* **2018**, *22*, 430.  
 (15k) Sassykova, *Orient. J. Chem.* **2019**, *35*, 22.

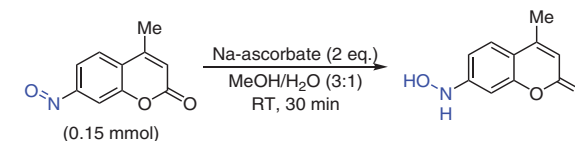
A review on radical reduction:

(15l) Gebicki, *Amino Acids* **2010**, *39*, 1131.

## Reduction of nitro or nitroso compounds to hydroxylamines

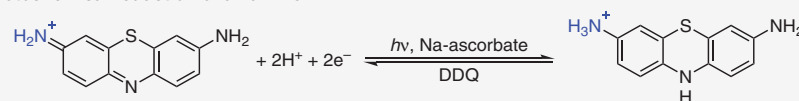


(15a) Bryant, Dyal, *Aust. J. Chem.* **1989**, *42*, 2275.



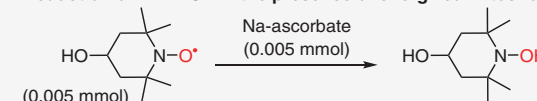
(15b) Sabot, Renard, *Eur. J. Org. Chem.* **2015**, 7992.

## Photochemical reduction of an amine



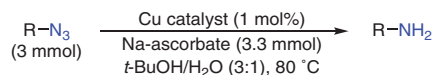
(15c) Akkaya, *Angew. Chem. Int. Ed.* **2011**, *50*, 9826.

## Reduction of TEMPOL in the presence of energized mitochondria



(15d) Murphy, *Free Radic. Biol. Med.* **2008**, *44*, 1406.

## Azide reduction with an organometallic catalyst

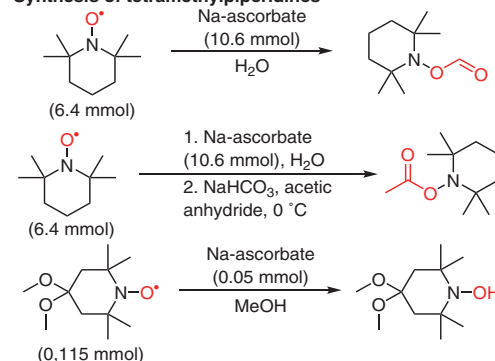


## Selected scope

R	Yield (%)
C <sub>6</sub> H <sub>5</sub> SO <sub>2</sub>	95
4-MeC <sub>6</sub> H <sub>4</sub> SO <sub>2</sub>	92
4-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> SO <sub>2</sub>	95
4-H <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> SO <sub>2</sub>	98
C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	23
C <sub>6</sub> H <sub>5</sub>	15

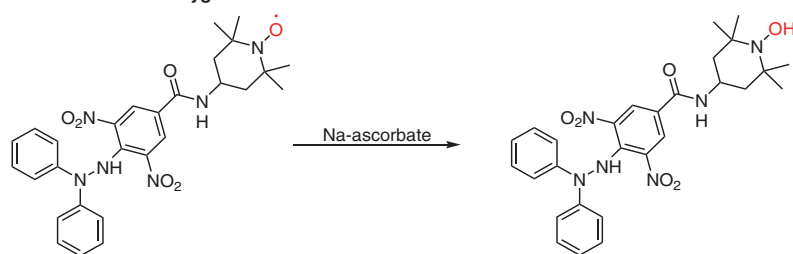
(15e) Emmanuvel, *J. Organomet. Chem.* **2021**, *931*, 121627. (15f) Anderson, Corrie *J. Chem. Soc., Perkin Trans. 2* **1992**, 1027.

## Synthesis of tetramethylpiperidines



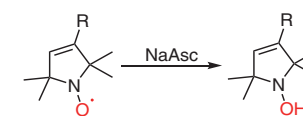
(15f) Anderson, Corrie *J. Chem. Soc., Perkin Trans. 2* **1992**, 1027.

## One-electron reduction of an oxygen radical



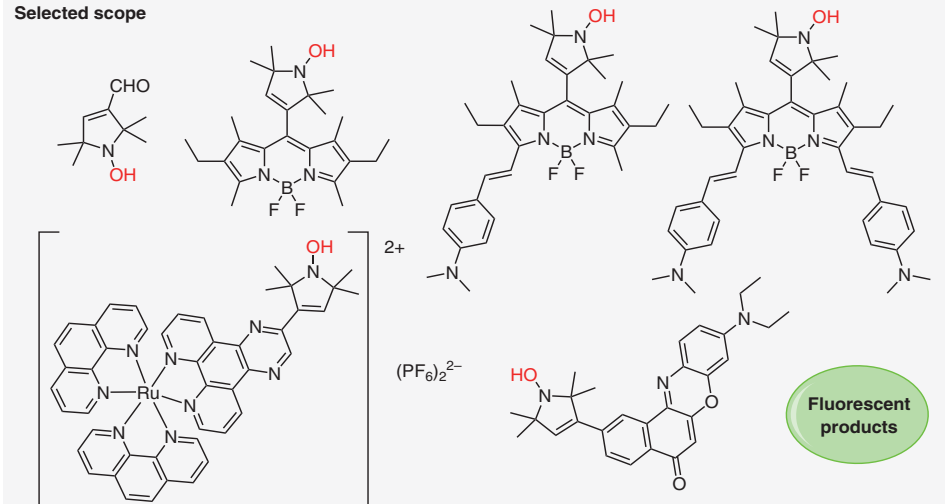
(15g) Gilbert, *J. Chem. Soc., Perkin Trans. 2* **2001**, 1453.

## Synthesis of fluorescent dyes



Sodium ascorbate was used to reduce molecules containing oxygen radicals resulting in products with increased fluorescence and long-wavelength emission, being potentially useful for biological and clinical applications.

## Selected scope



(15h) Hideg, *Dyes Pigm.* **2010**, *87*, 218.

Figure 8 Reduction reactions, part II<sup>15a-l</sup>

## Notable features

- Sulfonylmethylation, acylation, addition of a ring to a triple bond and addition of an alcohol to a double bond.
- Sodium ascorbate added to avoid oxidation or to activate a metallic catalyst.

## Further reading

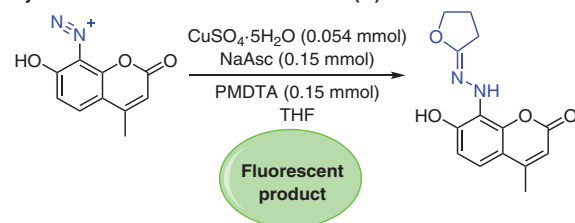
Reviews on acylation reactions:

(16f) Gotor-Fernández, Gotor, In *Green Biocatalysis* **2016**, 231.

(16g) Piazzolla, *Tetrahedron Lett.* **2018**, 59, 2615.

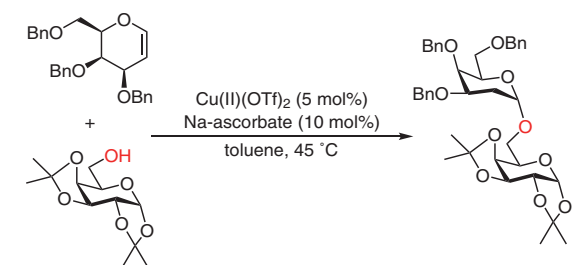
(16h) Taylor, Bull, In *Comprehensive Organic Synthesis II* **2014**, 427.

## Synthesis of a new chemosensor for Fe(III)



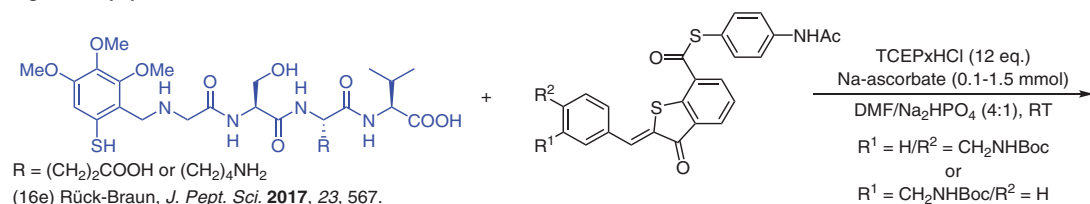
(16a) Hamukoshi, *ARKIVOC* **2023**, (viii), 202312030.

## Glycosylation of parabenzylated galactal



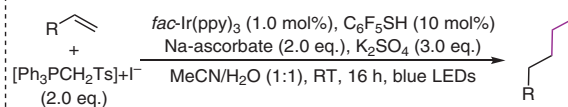
(16b) Grimaud, Galan, *Org. Lett.* **2020**, 22, 1991.

## Ligation of peptides and thioesters

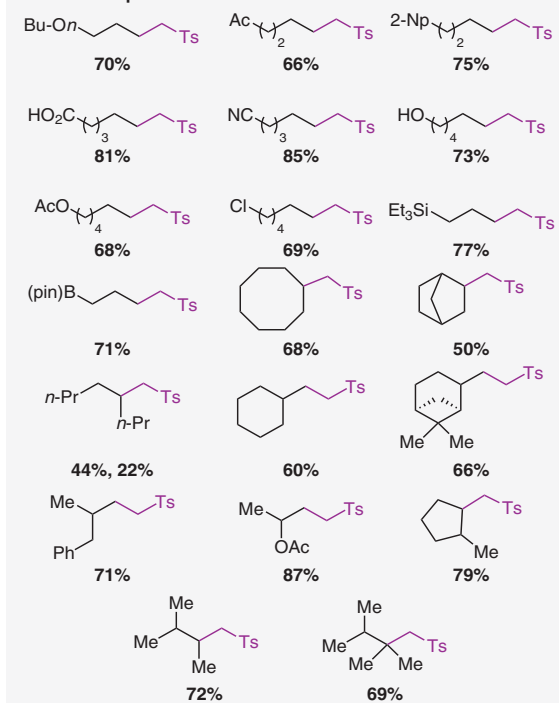


(16e) Rück-Braun, *J. Pept. Sci.* **2017**, 23, 567.

## 1,2-Hydro(sulfonylmethylation) of alkenes

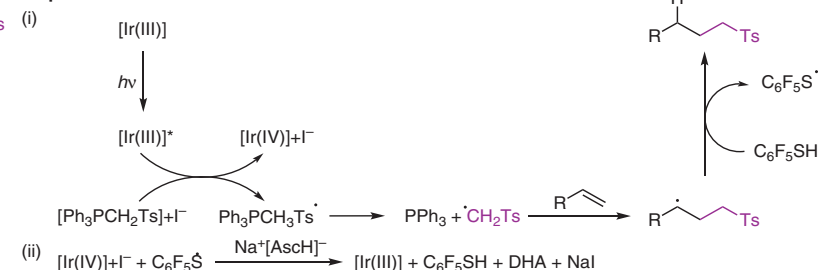


## Selected scope

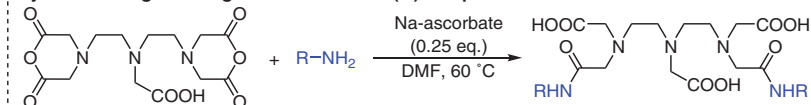


(16c) Miura, Murakami, *Chem. Lett.* **2020**, 49, 1382.

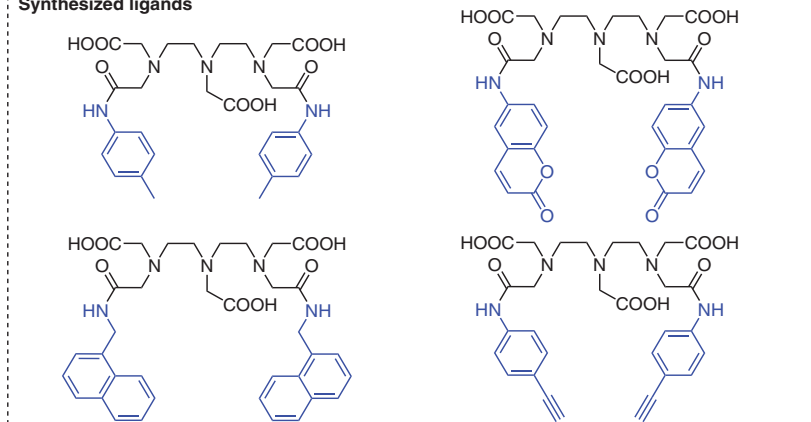
## Proposed mechanism



## Synthesis of ligands to generate lanthanide(III) complexes



## Synthesized ligands



(16d) Parac-Vogt, *Eur. J. Inorg. Chem.* **2013**, 2629.

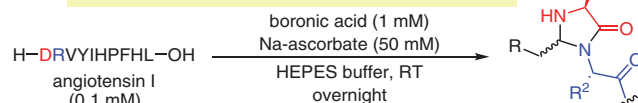
## Selected scope

- $R = (\text{CH}_2)_2\text{COOH}$ ,  $R^1 = \text{H}$ ,  $R^2 = \text{CH}_2\text{NHBoc}$
- $R = (\text{CH}_2)_2\text{COOH}$ ,  $R^1 = \text{CH}_2\text{NHBoc}$ ,  $R^2 = \text{H}$
- $R = (\text{CH}_2)_4\text{NH}_2$ ,  $R^1 = \text{H}$ ,  $R^2 = \text{CH}_2\text{NHBoc}$
- $R = (\text{CH}_2)_4\text{NH}_2$ ,  $R^1 = \text{CH}_2\text{NHBoc}$ ,  $R^2 = \text{H}$

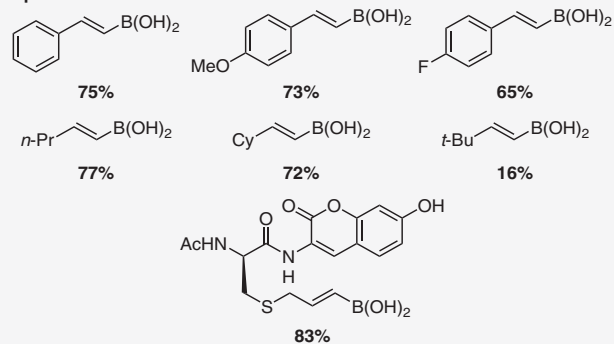
Figure 9 Addition reactions, part I<sup>16a-h</sup>

## Protein modification with vinylboronic acids

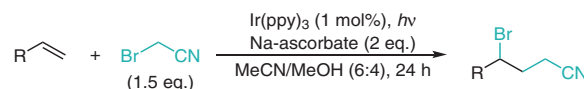
Sodium ascorbate is applied as a pro-oxidant reagent.



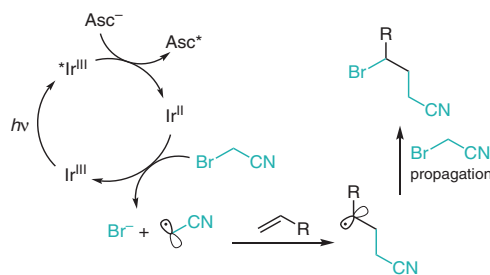
## Scope of boronic acids

(17a) Ball, *Chem. Commun.* **2017**, 53, 1622.

## Cyanomethylation reactions



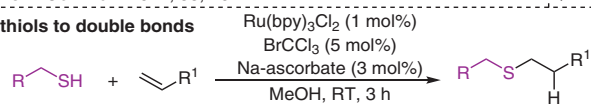
## Proposed mechanism



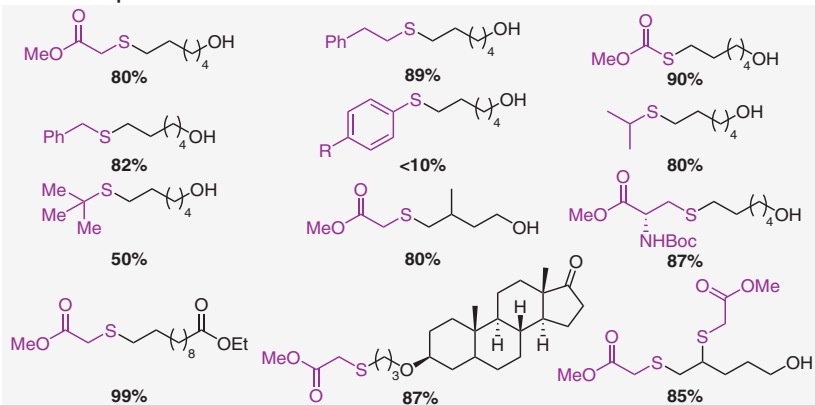
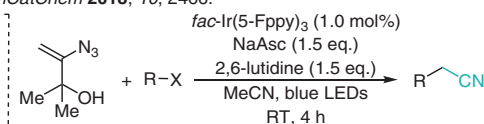
The iridium catalyst is excited by radiation and reduced by sodium ascorbate, allowing it to react with aliphatic olefins.

(17c) Kokotos, *ChemCatChem* **2018**, 10, 2466.

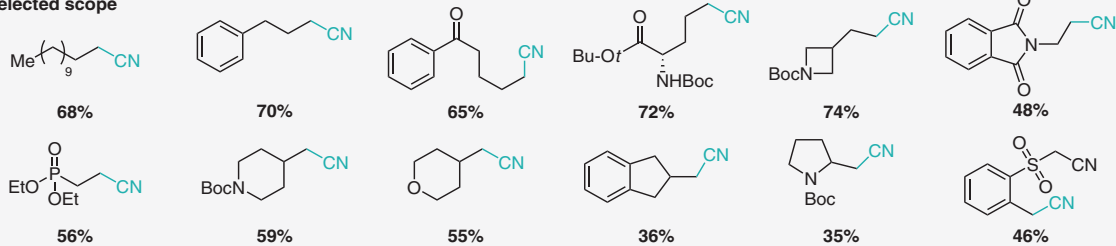
## Addition of thiols to double bonds



## Selected scope

(17b) Stephenson, *Tetrahedron* **2014**, 70, 4264.

## Selected scope

(17d) Donald, *Chem. Sci.* **2019**, 10, 5832.

## Notable features

- Sodium ascorbate as a reducing and pro-oxidant agent.
- Visible-light-induced photoredox catalysis.
- Mild reaction conditions.

## Further reading

- Cyanomethylation:
- (17e) Rossi, Inesi, *Mini-Rev. Org. Chem.* **2005**, 2, 79.
  - (17f) Ahmad, *New J. Chem.* **2020**, 44, 17177.

Figure 10 Addition reactions, part II<sup>17a-f</sup>

## Notable features

- Addition of alkyl halides to double or triple bonds.
- Sodium ascorbate reacting directly or activating photocatalysis.
- Wide reaction scope.

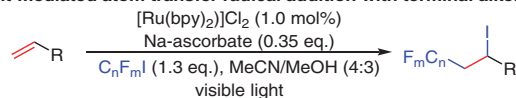
## Further reading

- Atom transfer radical addition:  
(18c) Noels, *Top. Organomet. Chem.* **2004**, *11*, 155.  
(18d) Severin, *Chimia* **2012**, *66*, 386.

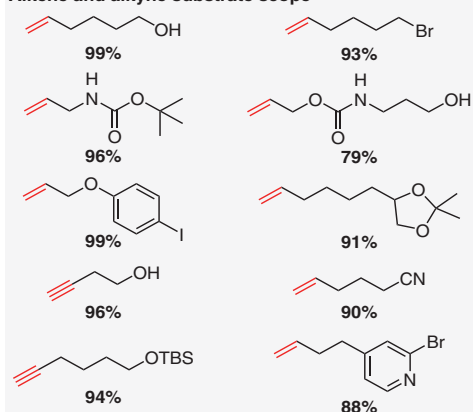
## Heck coupling:

- (18e) Alonso, Nájera, In *Science of Synthesis: Water in Organic Synthesis* **2012**, 535.  
(18f) Bräse, de Meijere, In *Metal-Catalyzed Cross-Coupling Reactions* **2004**, 217.

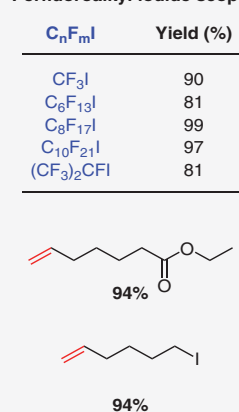
## Visible-light-mediated atom transfer radical addition with terminal alkenes and alkynes



## Alkene and alkyne substrate scope

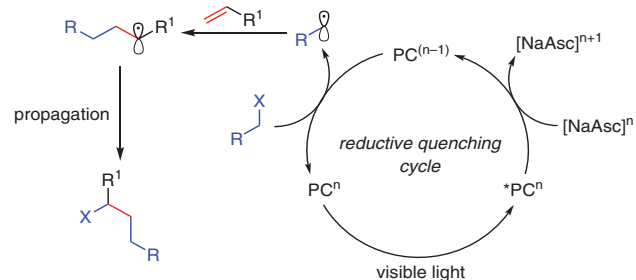


## Perfluoroalkyl iodide scope



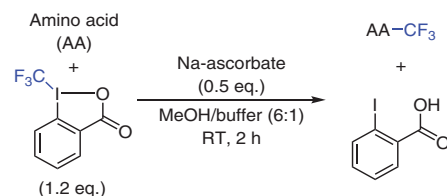
## Proposed mechanism

The photocatalyst (PC) is initially activated by visible light, then reduced by sodium ascorbate. The PC converts perfluoroalkyl iodides into electrophilic free radicals, which undergo addition to the alkene or alkyne.



(6) Stephenson, *J. Am. Chem. Soc.* **2012**, *134*, 8875.

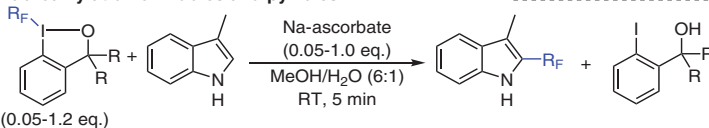
## Fluoroalkylation of amino acid derivatives



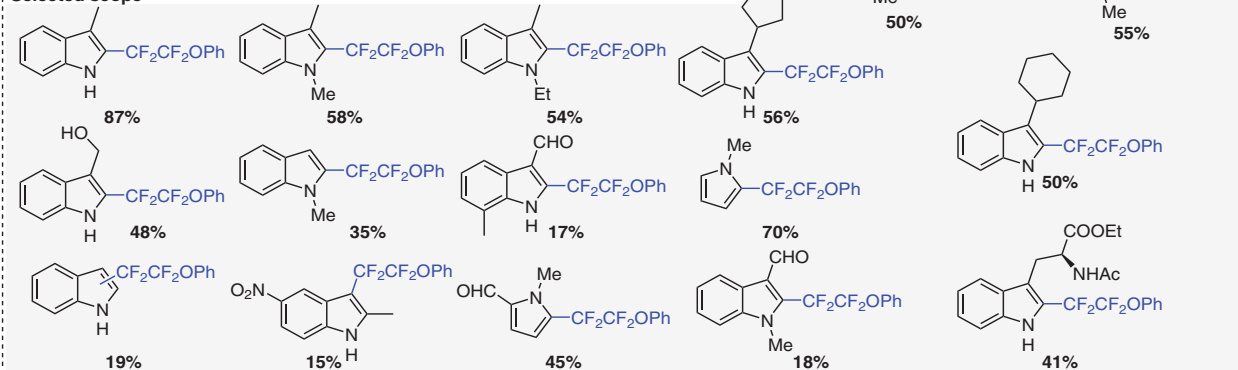
## Selected scope

Amino acid	Yield (%)
N-AcTrp	56
N-AcTyr	11, 18 (pH 9)
Phe	4 (pH 9)
His-HCl	2 (pH 5), 11 (pH 9)

## Fluoroalkylation of indoles and pyrroles

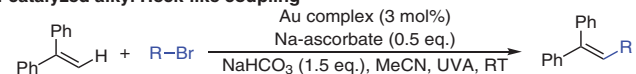


## Selected scope

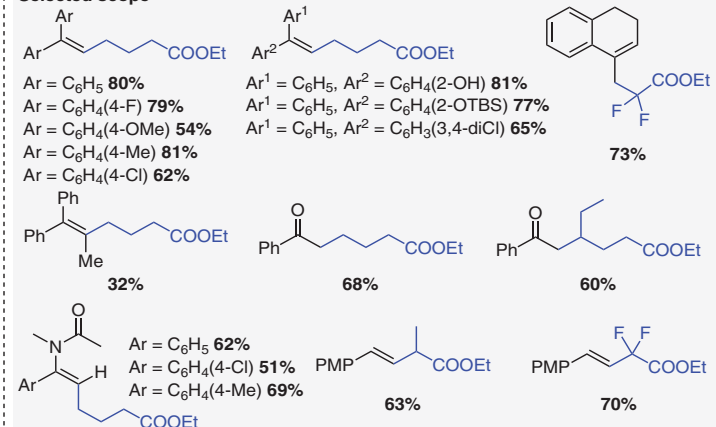


(18b) Novák, Beier, *Chem. Eur. J.* **2019**, *25*, 15779.

## Gold-catalyzed alkyl Heck-like coupling



## Selected scope



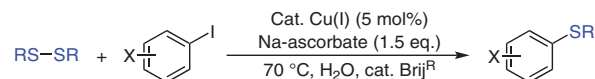
(18a) Hashmi, *Chem. Eur. J.* **2016**, *22*, 12646.

Figure 11 Addition reactions, part III<sup>6,18a-f</sup>

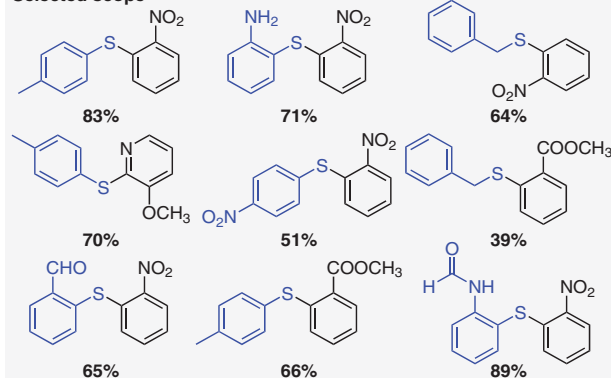
## Notable features

- Sodium ascorbate activates a metallic catalyst or acts as antioxidant.
- Wide reaction scope.
- Metallic or organometallic compounds as catalysts.

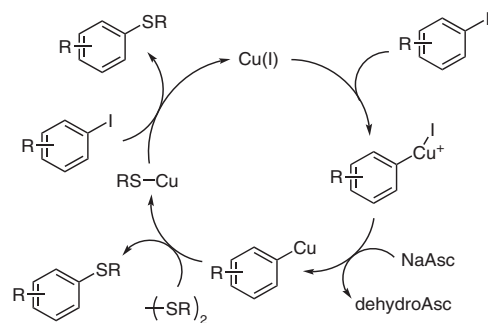
## Reductive cross-coupling of disulfides with aryl iodides



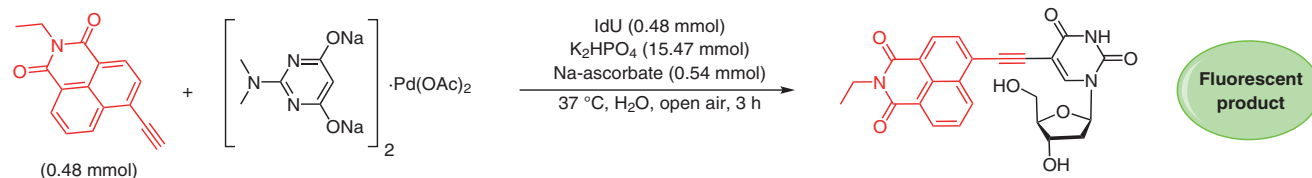
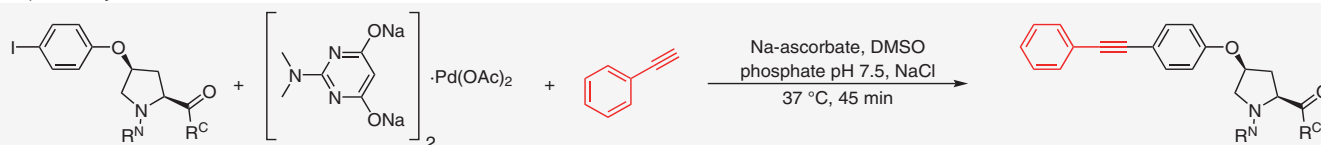
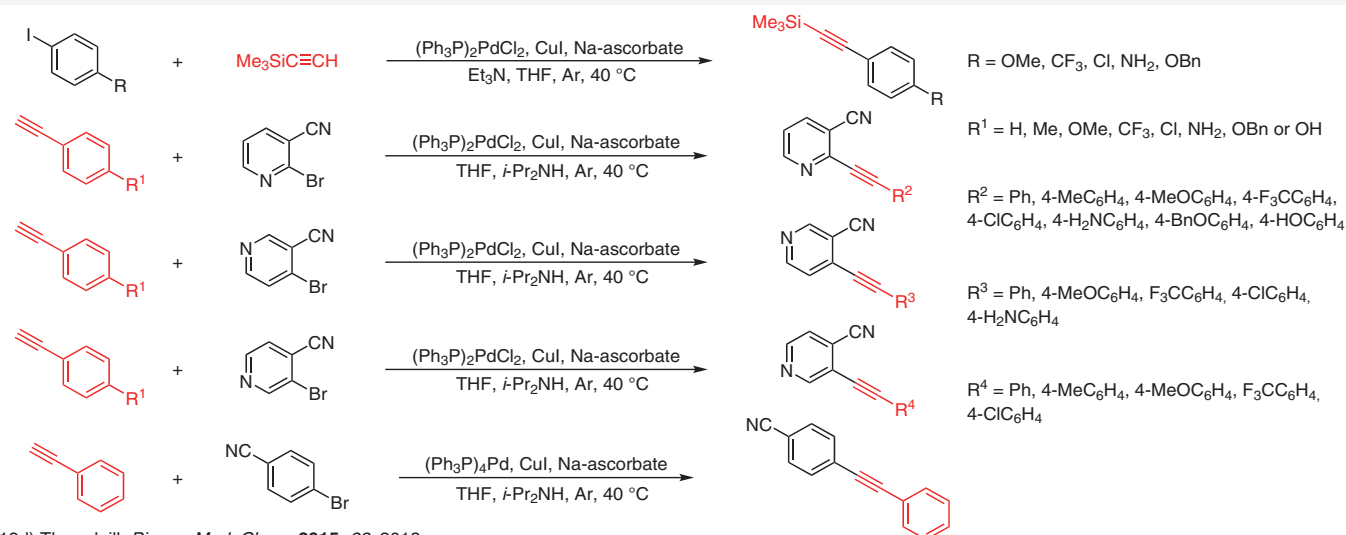
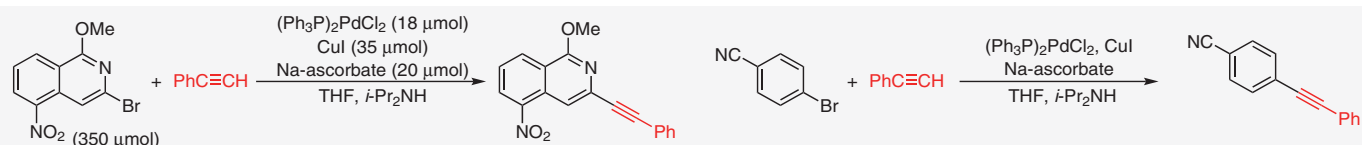
## Selected scope



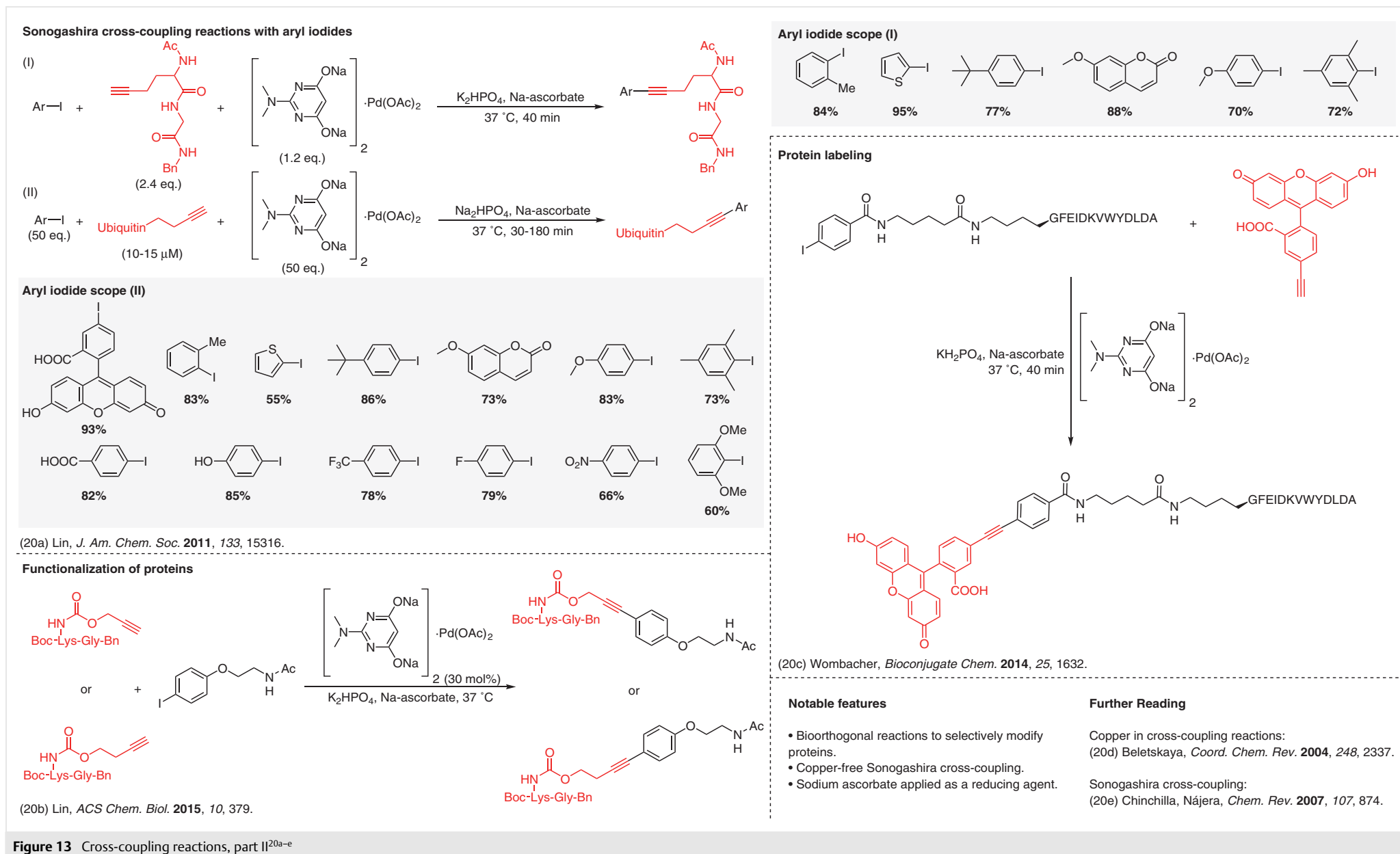
## Proposed mechanism

(19a) Srogl, *Chem. Commun.* **2010**, 46, 4387.

## Sonogashira cross-coupling

(19b) Yuan, *Synth. Commun.* **2014**, 44, 1007.(19c) Zondlo, *J. Am. Chem. Soc.* **2013**, 135, 4333.(19d) Threadgill, *Bioorg. Med. Chem.* **2015**, 23, 3013.(19e) Threadgill, *Bioorg. Med. Chem.* **2015**, 23, 5891.Figure 12 Cross-coupling reactions, part I<sup>19a-e</sup>

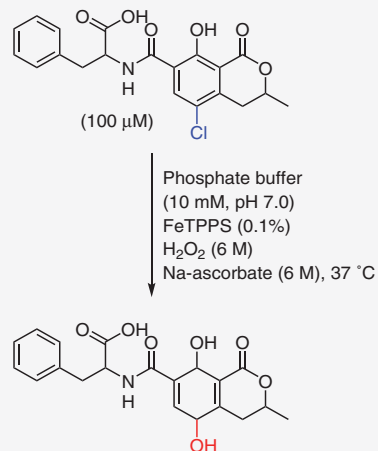


Figure 13 Cross-coupling reactions, part II<sup>20a-e</sup>

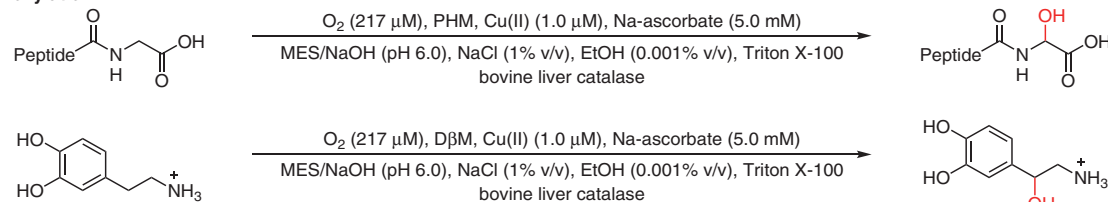
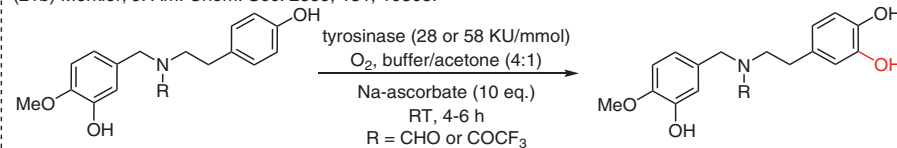
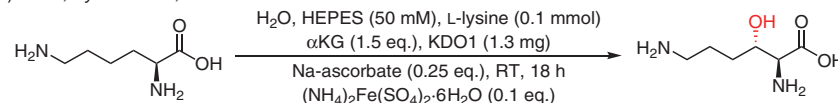
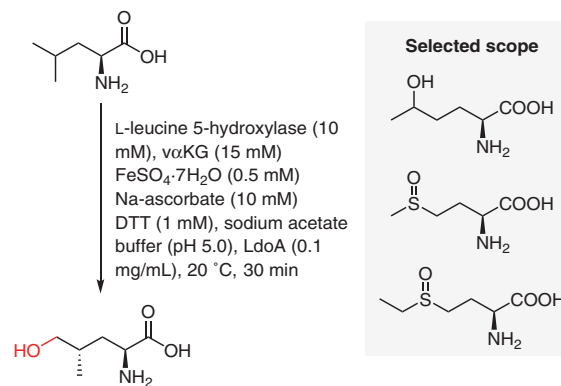
## Notable features

- Hydroxylation through oxygen reduction or hydroxy addition.
- Sodium ascorbate as a cofactor for enzymatic activity.

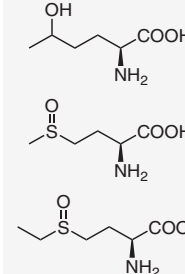
## First example



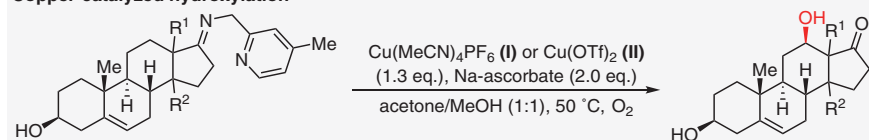
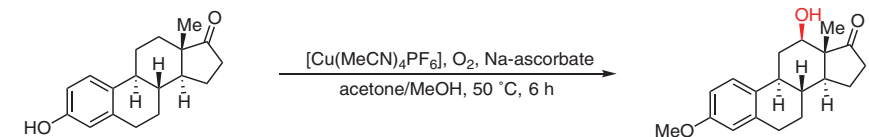
## Enzymatic hydroxylation

(21b) Merkle, *J. Am. Chem. Soc.* **2009**, *131*, 10308.(21c) Tozzi, *Synlett* **2010**, 1919.(21d) Zaparucha, *ChemCatChem* **2014**, *6*, 3012.(21e) Hibi, *Appl. Microbiol. Biotechnol.* **2013**, *97*, 2467.

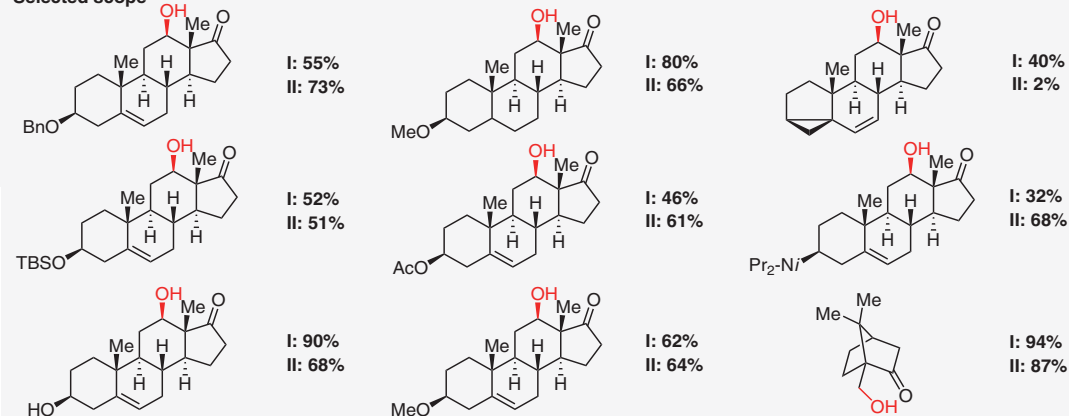
## Selected scope

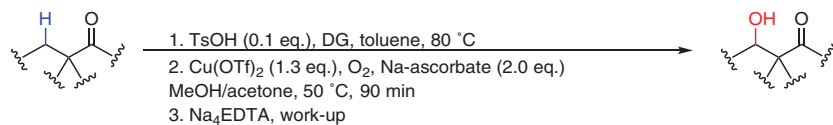


## Copper-catalyzed hydroxylation

(21f) Baran, *J. Am. Chem. Soc.* **2015**, *137*, 13776.(21g) Zhao, *Nat. Commun.* **2019**, *10*, 4015.

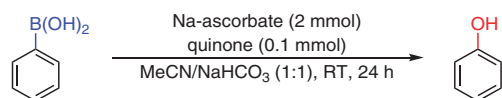
## Selected scope

Figure 14 Hydroxylation reactions, part I<sup>21a-g</sup>

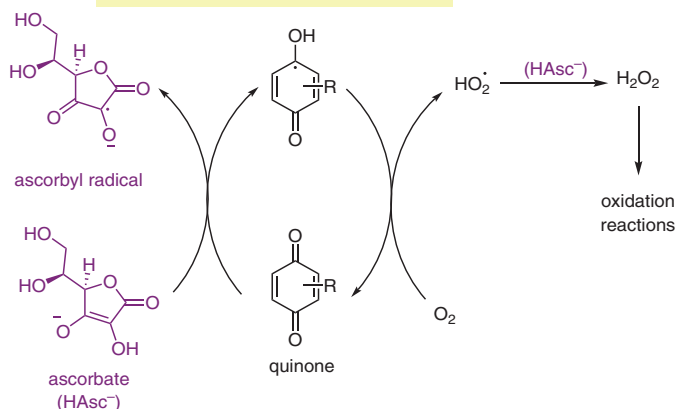
**Site-selective Cu-mediated hydroxylation of pentacyclic triterpenoids**


Selectivity was determined by different directing groups (DG).

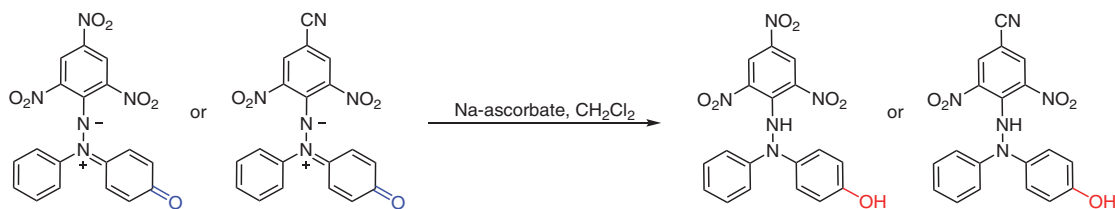
(22a) Mu, *Nat. Commun.* **2020**, *11*, 4371.

**Hydroxylation of phenylboronic compounds**

**Proposed mechanism**

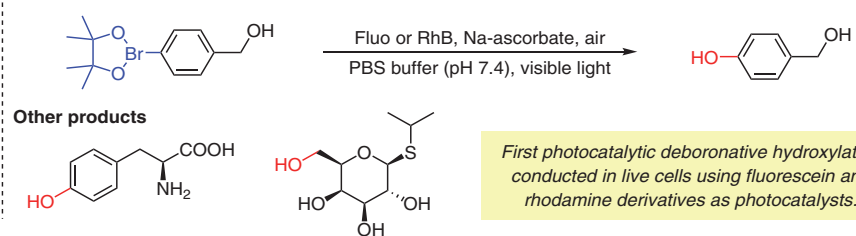
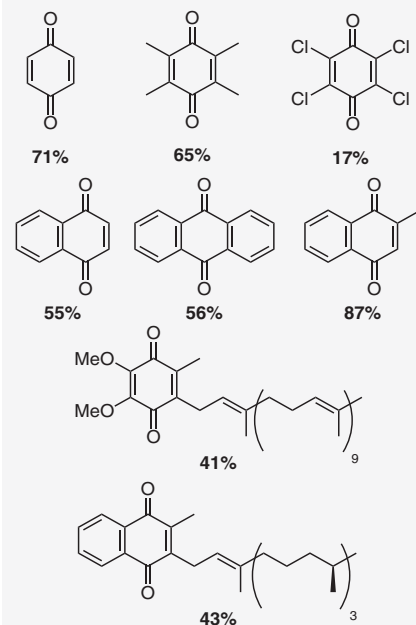
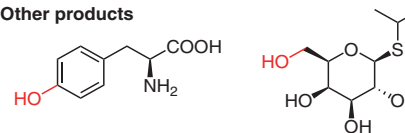
Sodium ascorbate was used to mimic the enzymatic quinone redox cycling.



(22b) Carrillo, *Chem. Commun.* **2015**, *51*, 7027.

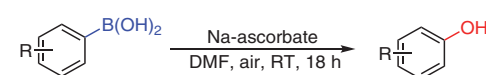
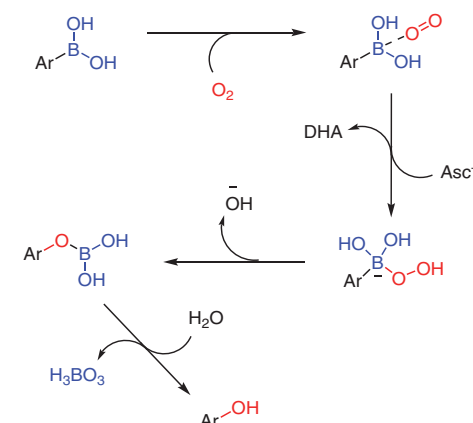
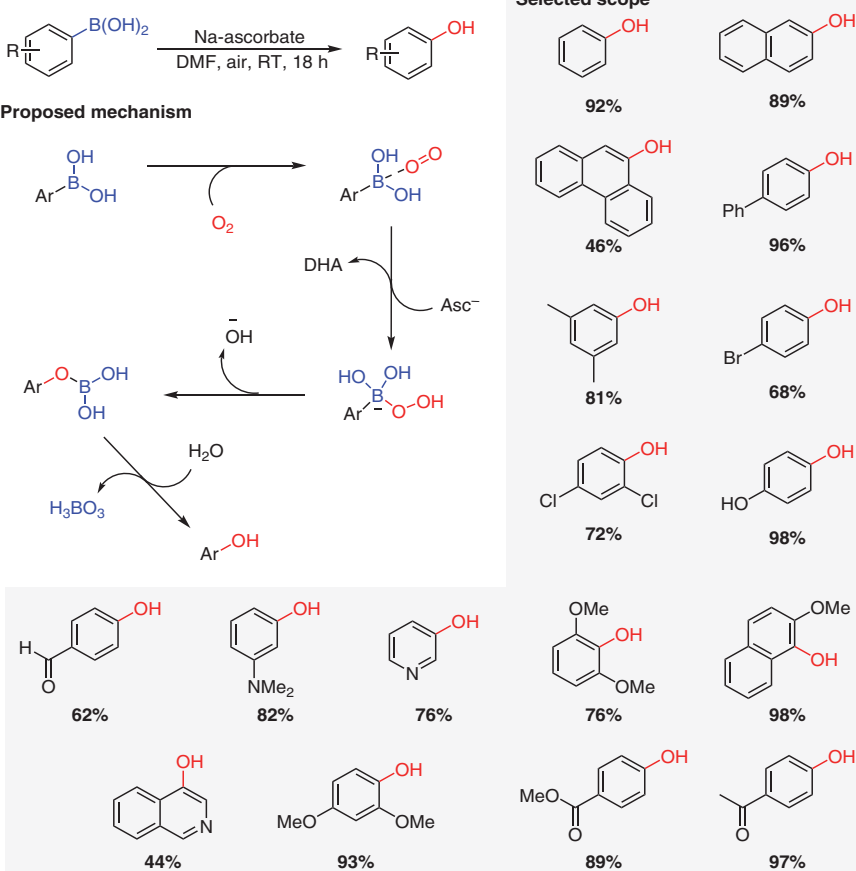
**Hydroxylation by redox reactions**


(22c) Ionita, *Aust. J. Chem.* **2007**, *60*, 173.

**Quinone scope**

**Other products**


First photocatalytic deboronative hydroxylation conducted in live cells using fluorescein and rhodamine derivatives as photocatalysts.

(22d) Xu, Chen, *Angew. Chem. Int. Ed.* **2019**, *58*, 561.


**Proposed mechanism**

**Selected scope**


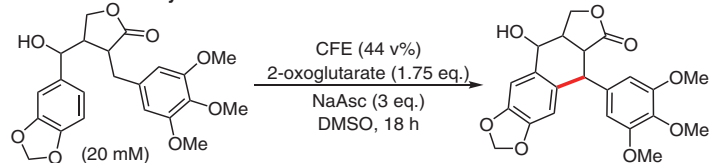
(22e) Cozzi, *Org. Chem. Front.* **2018**, *5*, 1573.

**Figure 15** Hydroxylation reactions, part II<sup>22a-e</sup>

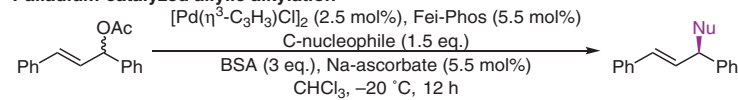
## Notable features

- Reactions conducted by metallic catalysts.
- Sodium ascorbate participates in an oxidative quenching cycle.

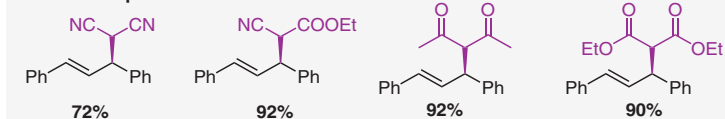
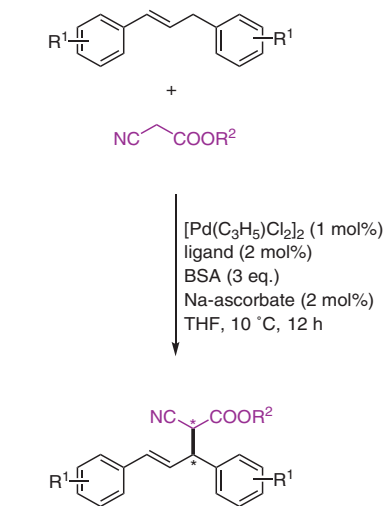
## Friedel-Crafts alkylation

(23a) Kroutil, Fuchs, *Angew. Chem. Int. Ed.* **2019**, *58*, 8226.

## Palladium-catalyzed allylic alkylation



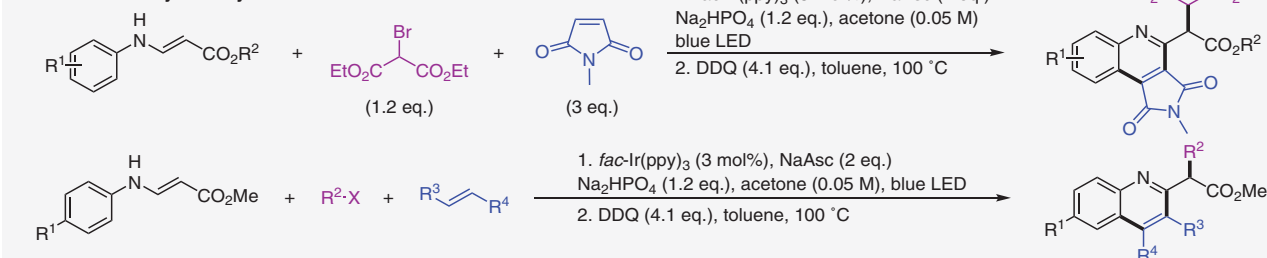
## Selected scope

(23b) Xu, *RSC Adv.* **2016**, *6*, 45495.(23c) Xu, *ChemCatChem* **2014**, *7*, 75.

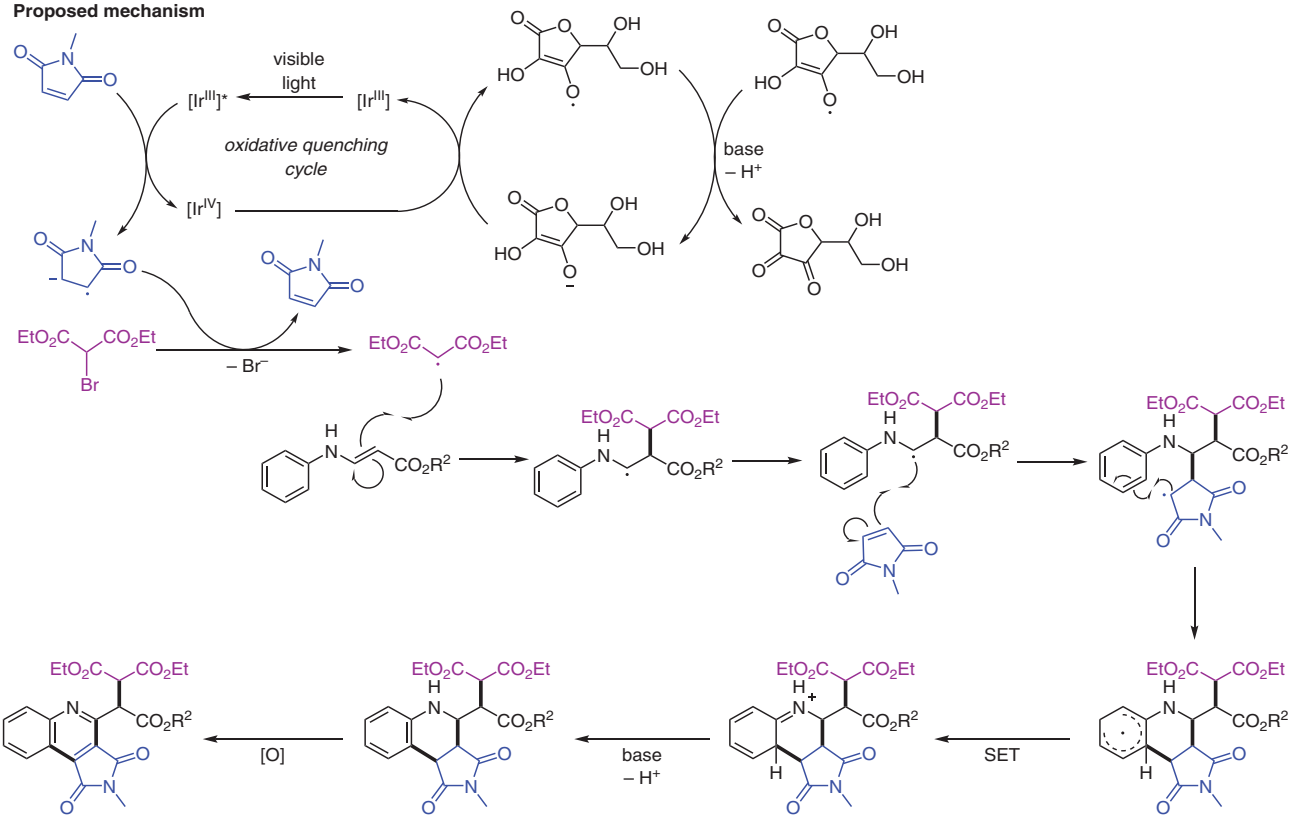
## Selected scope

R <sup>1</sup>	R <sup>2</sup>	Yield (%)
H	Et	87
H	Me	65
H	<i>i</i> -Pr	60
H	<i>n</i> -Bu	70
H	<i>t</i> -Bu	77
H	Bn	85
<i>p</i> -Cl	Et	63
<i>o</i> -Me	Et	52
<i>o</i> -Me	Me	42
<i>m</i> -Br	Me	60
<i>m</i> -Br	Et	81
<i>m</i> -Cl	Me	69
<i>m</i> -Cl	Et	85
<i>o</i> -Cl	Me	95
<i>p</i> -Me	Me	44
<i>p</i> -Me	Et	51
<i>m</i> -Br	<i>i</i> -Pr	72
<i>m</i> -Br	<i>t</i> -Bu	79
<i>m</i> -Br	<i>n</i> -Bu	75

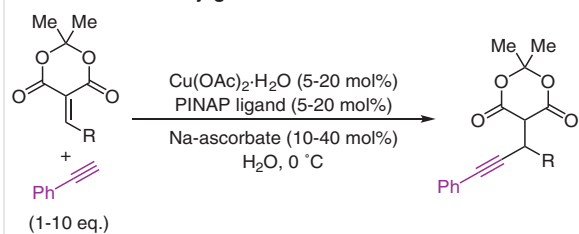
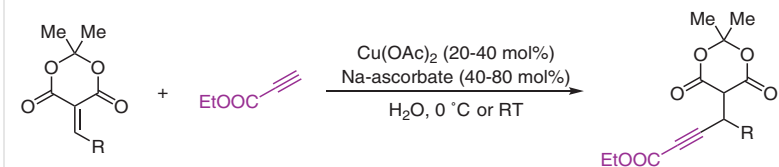
## Photoredox-catalyzed alkylation



## Proposed mechanism

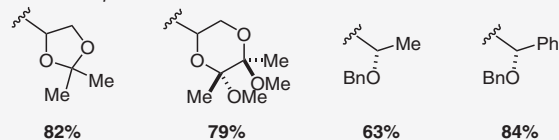
(23d) Park, *Adv. Synth. Catal.* **2018**, *360*, 3553.Figure 16 Alkylation reactions, part I<sup>23a-d</sup>

## Enantioselective conjugate addition to Meldrum's acid derivatives

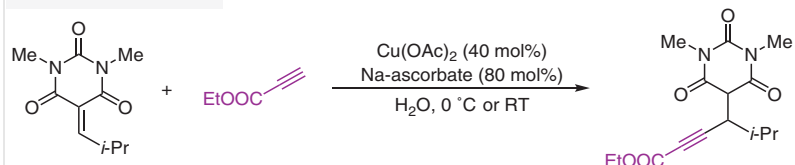
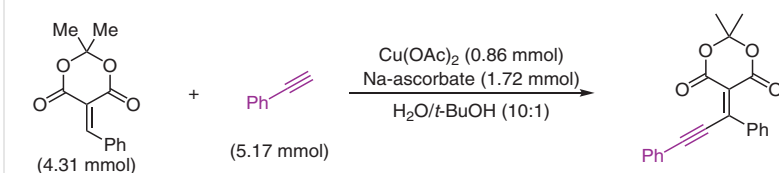
(24a) Carreira, *J. Am. Chem. Soc.* **2005**, *127*, 9682.

Selected scope	
Achiral acceptors	
R	Yield (%)
<i>i</i> -Pr	92
<i>c</i> -Hex	84
<i>c</i> -Pr	65
Et	54
<i>i</i> -Bu	90
(CH <sub>2</sub> ) <sub>2</sub> Ph	61
<i>n</i> -pentyl	74

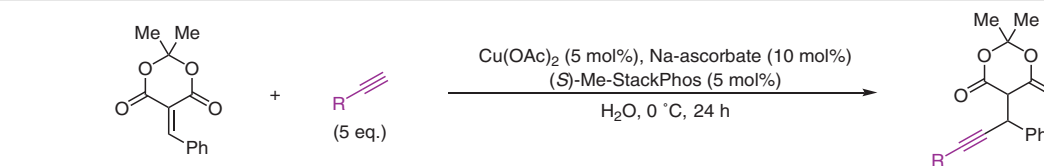
## Chiral acceptors



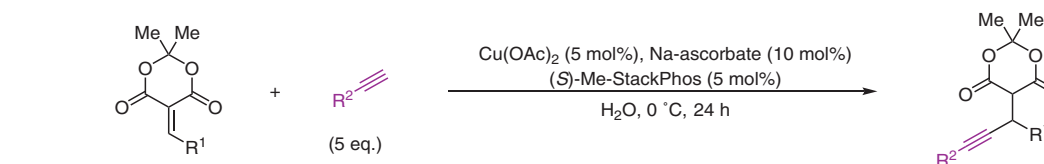
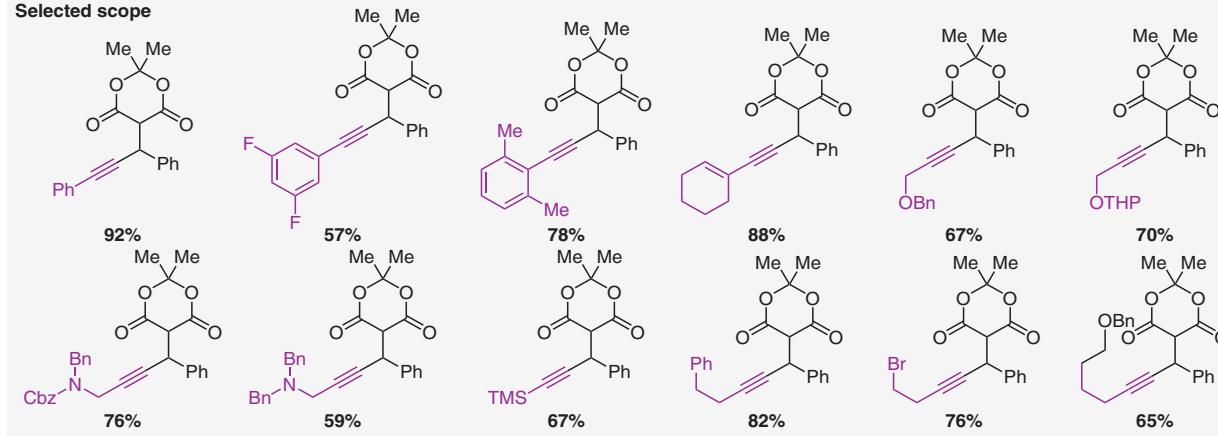
A barbituric acid derivative was also tested and confirmed to be useful as a substrate for the reaction.

(24b) Carreira, *Angew. Chem. Int. Ed.* **2007**, *46*, 4964.(24c) Tellitu, Domínguez, *ARKIVOC* **2010**, (iii), 7.

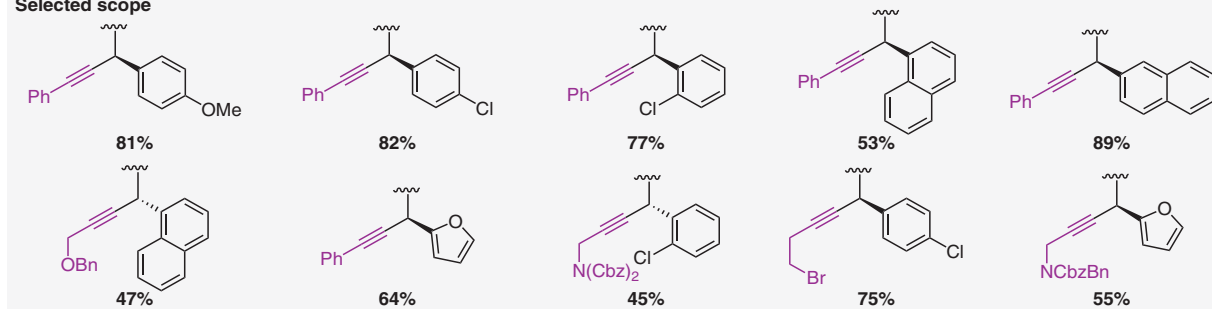
Selected scope	
R	Yield (%)
<i>i</i> -Pr	94
C <sub>6</sub> H <sub>11</sub>	81
<i>c</i> -Pr	79
<i>i</i> -Bu	85
Et	83
Ph	64
<i>m</i> -tol	87
<i>i</i> -Pr	93

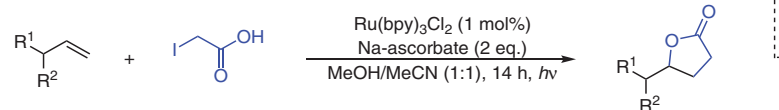
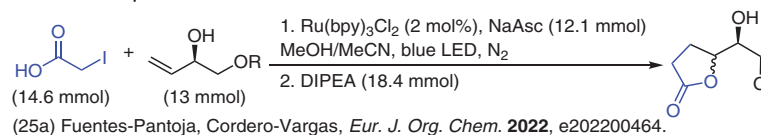


## Selected scope

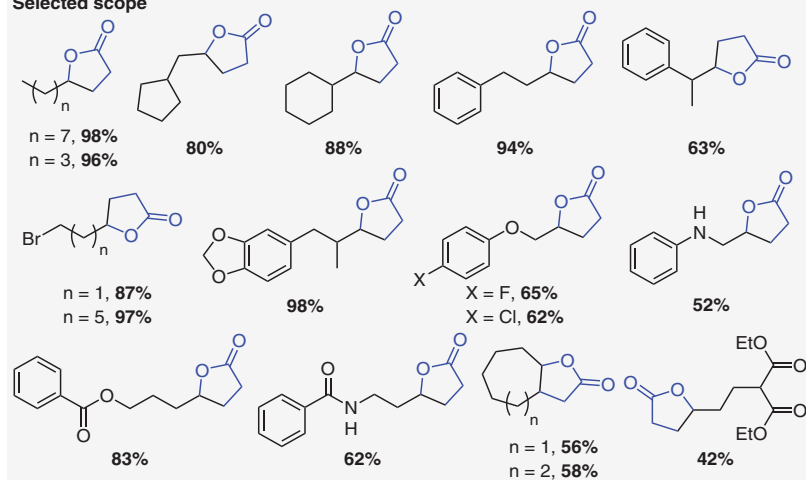


## Selected scope

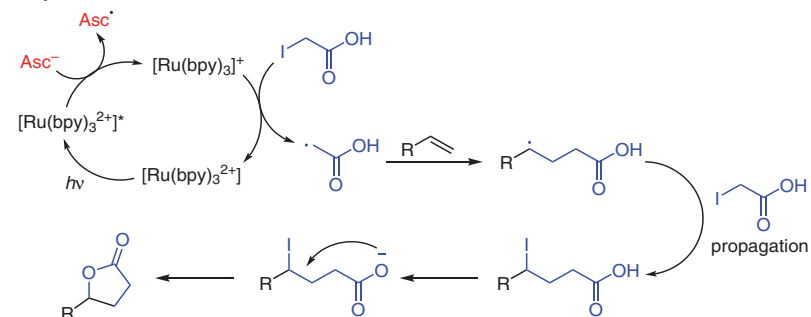
(24d) Aponick, *J. Am. Chem. Soc.* **2017**, *139*, 3352.Figure 17 Alkylation reactions, part II<sup>24a-d</sup>

Formation of  $\gamma$ -lactones from alkenes

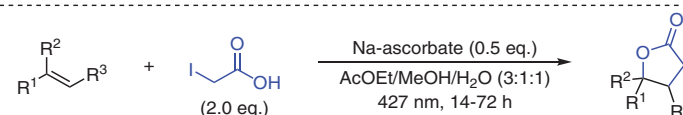
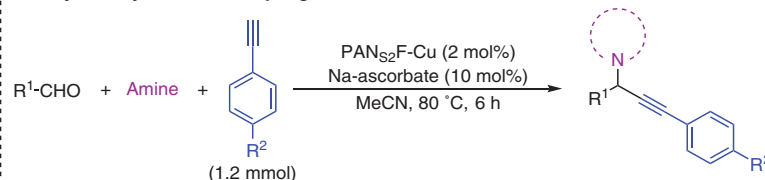
## Selected scope



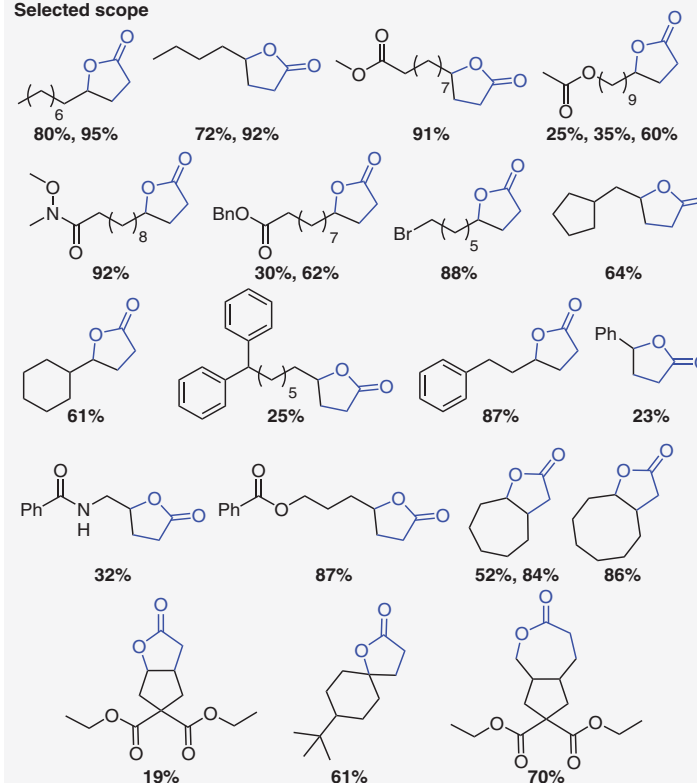
## Proposed mechanism

(25b) Kokotos, *Org. Lett.* **2018**, *20*, 36.

## Aldehyde–alkyne–amine coupling reaction



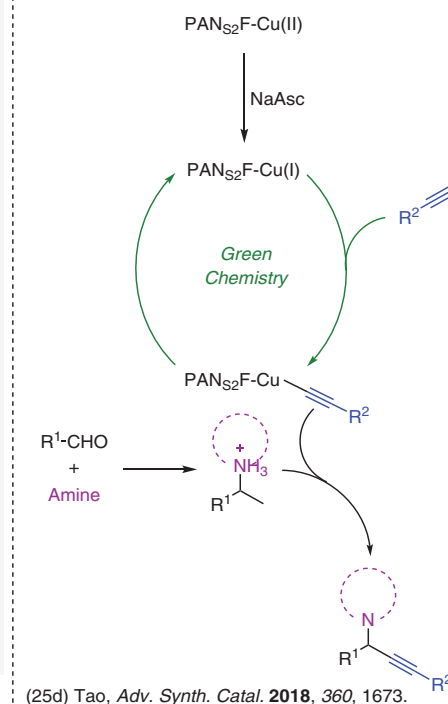
## Selected scope

(25c) Renaud, Kokotos, *Chem. Eur. J.* **2024**, *30*, e202400253.

## Selected scope

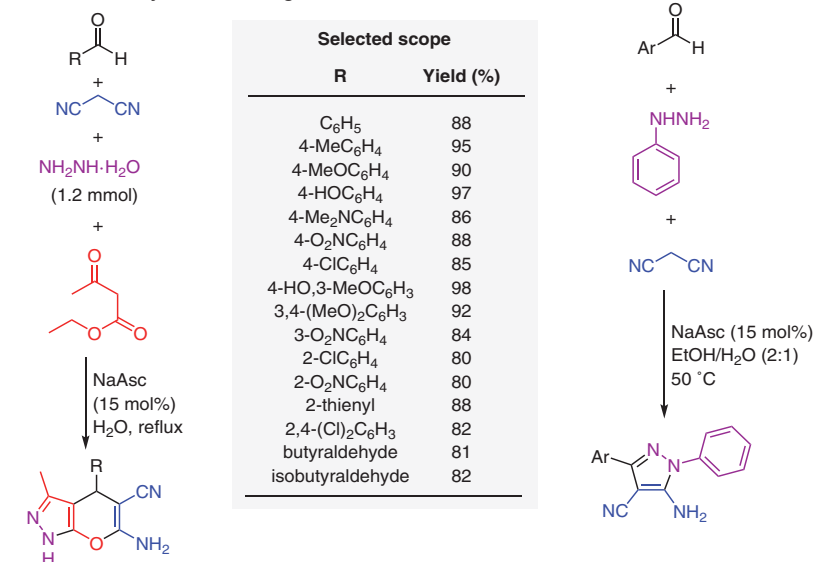
R <sup>1</sup>	Amine	R <sup>2</sup>	Yield (%)
H	pyrrolidine	H	96
H	diethylamine	H	92
H	dibutylamine	H	92
isopropyl	pyrrolidine	H	94
isopropyl	pyrrolidine	Me	93
isobutyl	pyrrolidine	H	95
Ph	pyrrolidine	H	83
Ph	pyrrolidine	Me	84
4-MeC <sub>6</sub> H <sub>4</sub>	pyrrolidine	H	80
4-MeOC <sub>6</sub> H <sub>4</sub>	pyrrolidine	H	78
4-PhC <sub>6</sub> H <sub>4</sub>	pyrrolidine	H	75
4-BrC <sub>6</sub> H <sub>4</sub>	pyrrolidine	H	85
4-ClC <sub>6</sub> H <sub>4</sub>	pyrrolidine	H	88

## Proposed mechanism

(25d) Tao, *Adv. Synth. Catal.* **2018**, *360*, 1673.Figure 18 Condensation reactions, part I<sup>25a-d</sup>



## Ascorbate-catalyzed Knoevenagel condensation



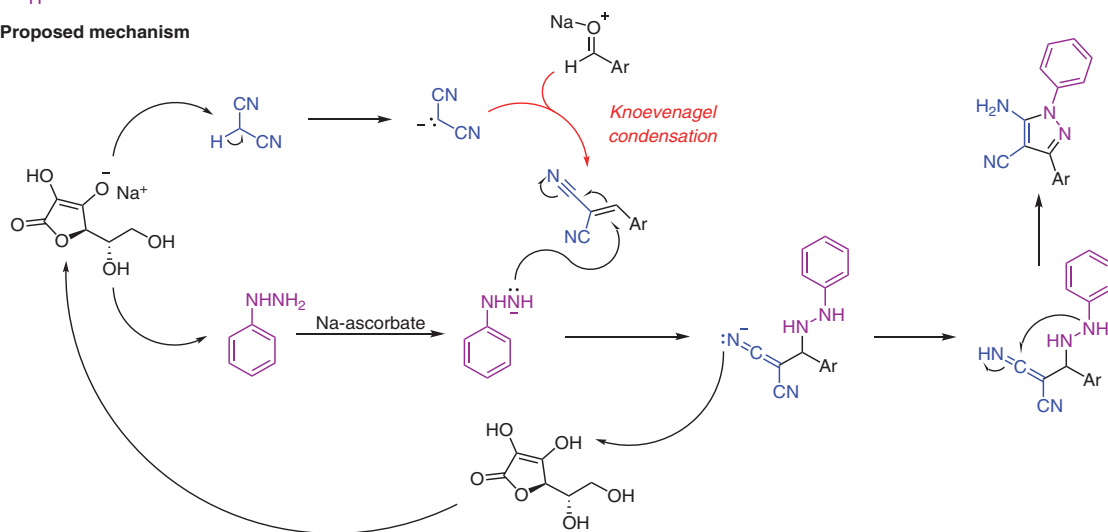
## Selected scope

R	Yield (%)
C <sub>6</sub> H <sub>5</sub>	88
4-MeC <sub>6</sub> H <sub>4</sub>	95
4-MeOC <sub>6</sub> H <sub>4</sub>	90
4-HOC <sub>6</sub> H <sub>4</sub>	97
4-Me <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	86
4-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	88
4-ClC <sub>6</sub> H <sub>4</sub>	85
4-HO,3-MeOC <sub>6</sub> H <sub>3</sub>	98
3,4-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	92
3-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	84
2-ClC <sub>6</sub> H <sub>4</sub>	80
2-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	80
2-thienyl	88
2,4-(Cl) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	82
butyraldehyde	81
isobutyraldehyde	82

## Selected scope

Ar	Yield (%)
C <sub>6</sub> H <sub>5</sub>	98
4-MeC <sub>6</sub> H <sub>4</sub>	95
4-MeOC <sub>6</sub> H <sub>4</sub>	97
4-HOC <sub>6</sub> H <sub>4</sub>	95
4-Me <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	88
4-O <sub>2</sub> N-C <sub>6</sub> H <sub>4</sub>	90
4-ClC <sub>6</sub> H <sub>4</sub>	98
4-BrC <sub>6</sub> H <sub>4</sub>	96
4-FC <sub>6</sub> H <sub>4</sub>	92
4-HO,3-MeOC <sub>6</sub> H <sub>3</sub>	98
3,4-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	95
3-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	86
2-ClC <sub>6</sub> H <sub>4</sub>	92
2-HOC <sub>6</sub> H <sub>4</sub>	92
2-MeOC <sub>6</sub> H <sub>4</sub>	93
2-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	88
2-thienyl	93
3-indolyl	91

## Proposed mechanism

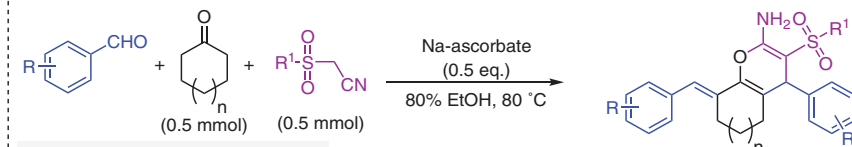
(26a) Kiyani, *Res. Chem. Intermed.* **2018**, *44*, 2761.

## Notable features

- Sodium ascorbate used as catalyst.
- Three- and four-component condensations.
- Wide reaction scope.
- Mild reaction conditions.

## Further reading

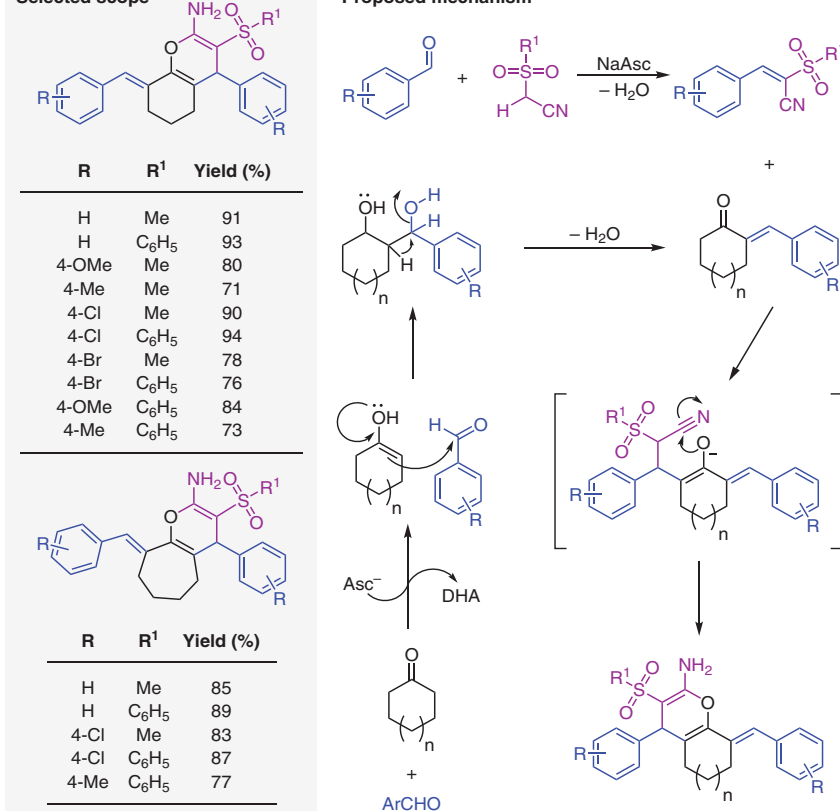
- (26c) Majumdar, *Tetrahedron* **2012**, *68*, 5693.
- (26d) Khare, *Orient. J. Chem.* **2019**, *35*, 423.
- (26e) van Schijndel, *Green Chem. Lett. Rev.* **2020**, *13*, 349.
- (26f) Heravi, *Monatsh. Chem.* **2020**, *151*, 439.



## Selected scope

R	R <sup>1</sup>	Yield (%)
H	Me	91
H	C <sub>6</sub> H <sub>5</sub>	93
4-OMe	Me	80
4-Me	Me	71
4-Cl	Me	90
4-Cl	C <sub>6</sub> H <sub>5</sub>	94
4-Br	Me	78
4-Br	C <sub>6</sub> H <sub>5</sub>	76
4-OMe	C <sub>6</sub> H <sub>5</sub>	84
4-Me	C <sub>6</sub> H <sub>5</sub>	73

## Proposed mechanism



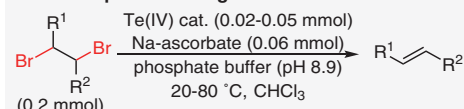
R	R <sup>1</sup>	Yield (%)
H	Me	85
H	C <sub>6</sub> H <sub>5</sub>	89
4-Cl	Me	83
4-Cl	C <sub>6</sub> H <sub>5</sub>	87
4-Me	C <sub>6</sub> H <sub>5</sub>	77

(26b) Nizhamu, *Res. Chem. Intermed.* **2020**, *46*, 3217.Figure 19 Condensation reactions, part II<sup>26a-f</sup>

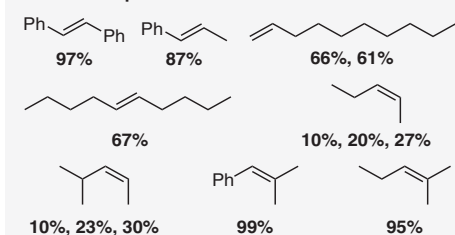
## Notable features

- Amination by a sodium ascorbate mediated reduction of an azide.
- Halogenation by photoredox catalysis.
- Mild reaction conditions.

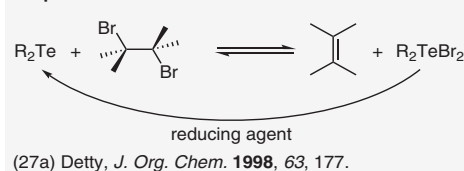
## First example of dehalogenation



## Selected scope



## Proposed mechanism



## Further reading

- Reviews on dehalogenation:  
(27g) Fetzner, *Appl. Microbiol. Technol.* **1998**, *50*, 633.  
(27h) Castro, *Rev. Env. Contam. Toxicol.* **1998**, *155*, 1.

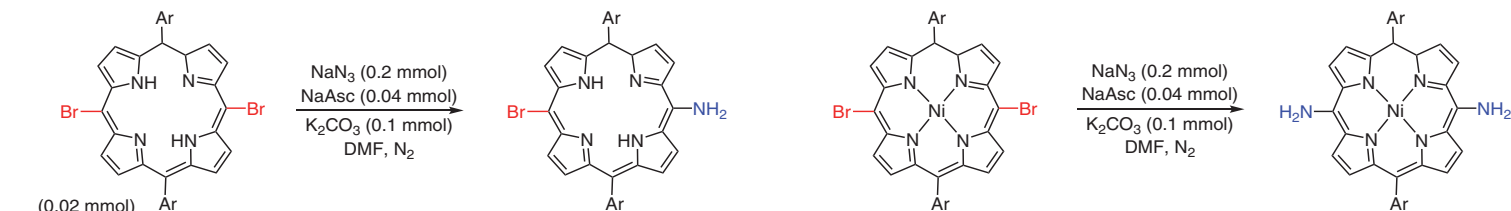
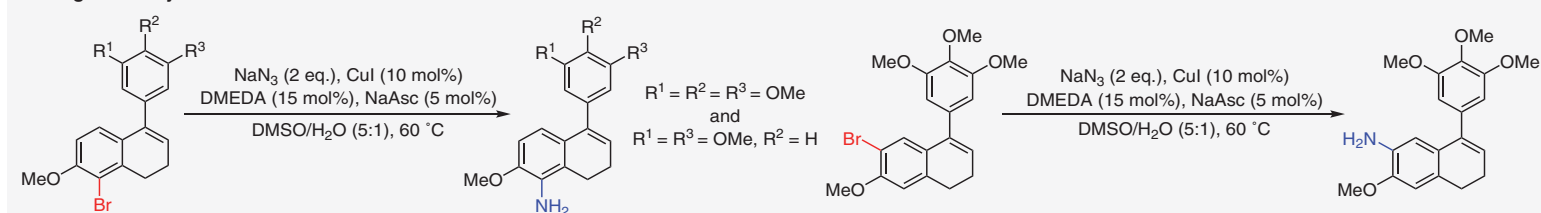
## Reviews on amination:

- (27i) Jørgensen, *Chem. Rev.* **1998**, *98*, 1689.  
(27j) Beller, *Synlett* **2002**, 1579.  
(27k) Knochel, *Eur. J. Org. Chem.* **2007**, 4166.  
(27l) Chusov, *Chem. Rev.* **2019**, *119*, 11857.

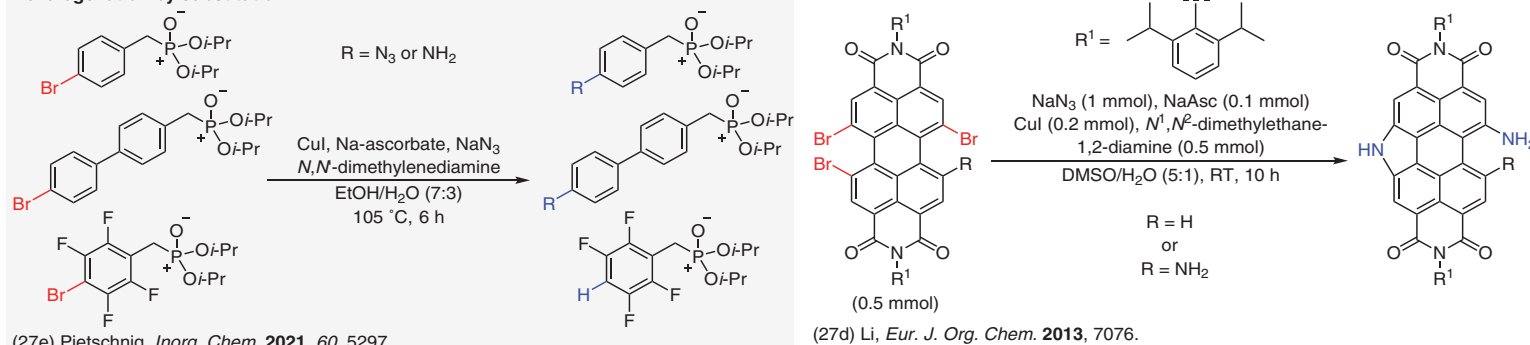
## Reviews on halogenation:

- (27m) Ibrahim, Togni, *J. Chem. Soc., Chem. Commun.* **2004**, 1147.  
(27n) Murphy, *J. Appl. Microb.* **2003**, *94*, 539.

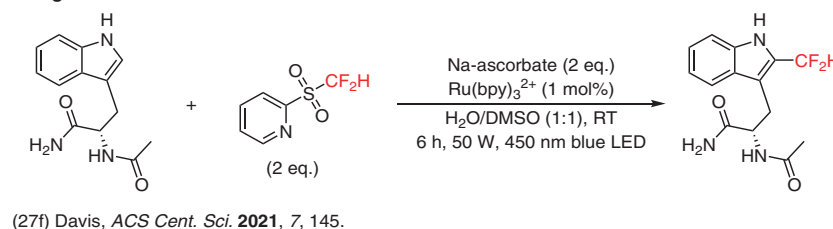
## Dehalogenation by amination



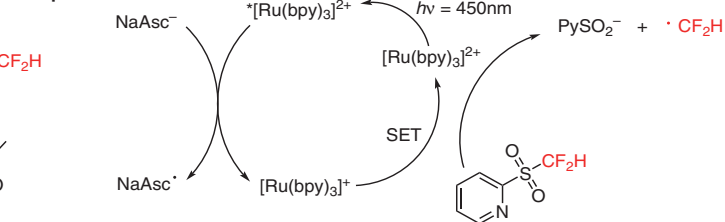
## Dehalogenation by substitution



## Halogenation reaction



## Proposed mechanism

Figure 20 Alkyl halide reactions<sup>27a-n</sup>

## Notable features

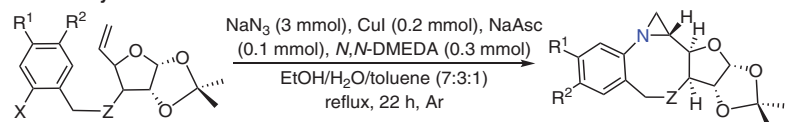
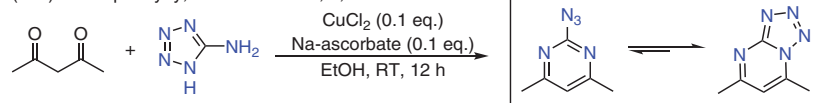
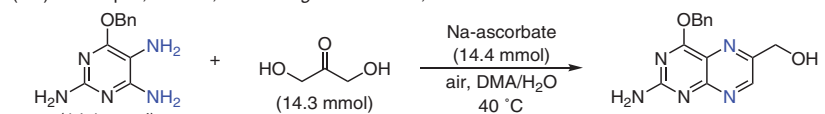
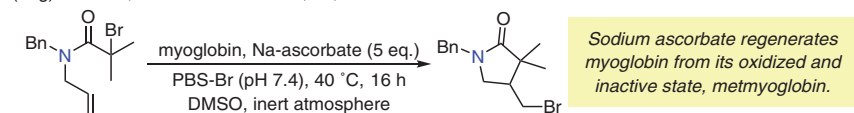
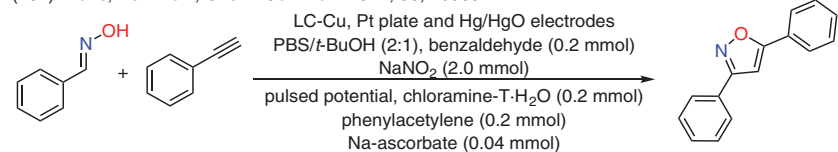
- Ascorbate presence increases catalytic activity, promotes basic reaction environment and avoids side products.
- Formation of *N*- and *O*-heterocycles.

## Further reading

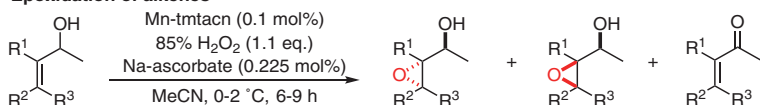
Epoxidation reviews:

(28m) Burgess, *Chem. Rev.* **2003**, *103*, 2457.(28n) Jørgensen, *Chem. Rev.* **1989**, *89*, 431.

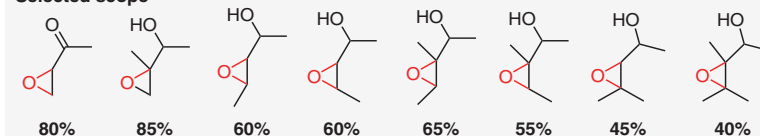
Pictet–Spengler reaction:

(28o) Stöckigt, Waldmann, *Angew. Chem. Int. Ed.* **2011**, *50*, 8538.**N**-Heterocycle formation(28e) Chattopadhyay, *RSC Adv.* **2014**, *4*, 4155.(28f) Baudequin, Achelle, *Eur. J. Org. Chem.* **2013**, 5591.(28g) Moschel, *J. Med. Chem.* **2004**, *47*, 3887.(28h) Bruns, Pellizzoni, *Chem. Commun.* **2022**, *58*, 10989.(28i) He, *Nat. Commun.* **2023**, *14*, 5088.

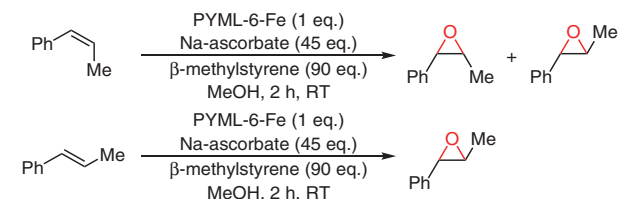
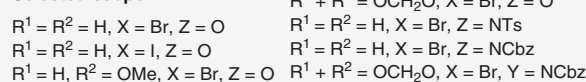
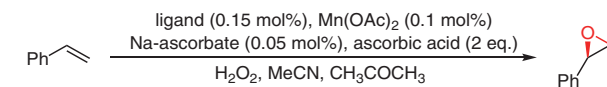
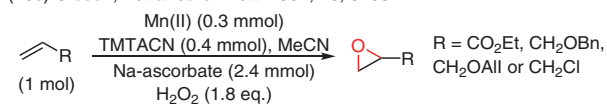
## Epoxidation of alkenes



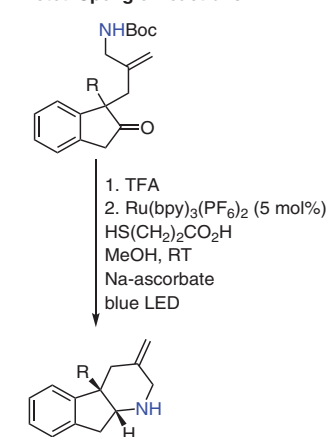
## Selected scope

(28a) Kilic, *J. Org. Chem.* **2009**, *74*, 1135.

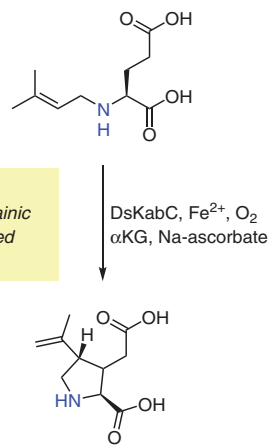
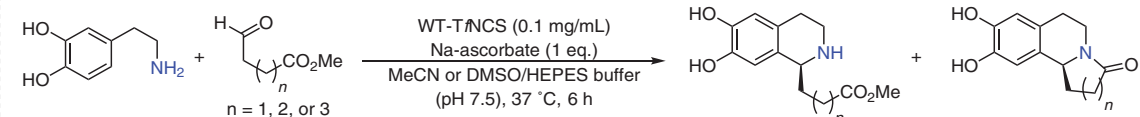
## Selected scope

(28b) Ohno, *Chem. Lett.* **1989**, *18*, 611.(28c) Gibson, *Tetrahedron Lett.* **2002**, *43*, 3795.(28d) Riss, *Org. Biomol. Chem.* **2008**, *6*, 4567.

## Pictet–Spengler reactions

(28k) Meijer, Harrity, *Chem. Eur. J.* **2024**, *30*, e202400116.

Chemoenzymatic cyclization of prekainic acid, also conducted with bacteria.

(28j) Moore, *Angew. Chem. Int. Ed.* **2019**, *131*, 8542.(28l) Hailes, *Chem. Commun.* **2018**, *54*, 1323.

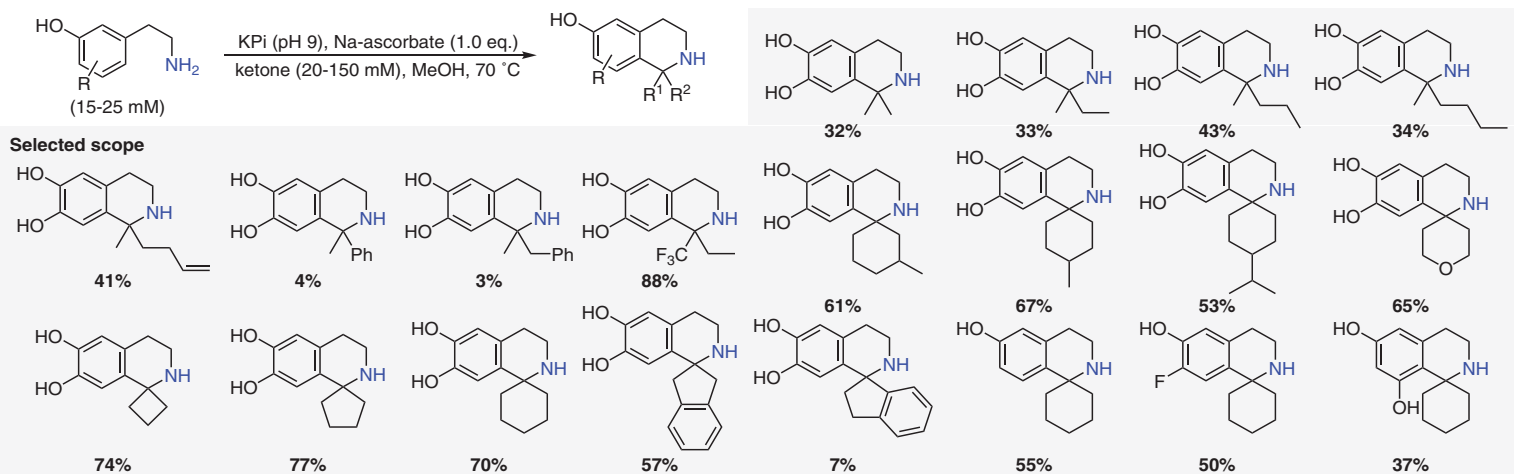
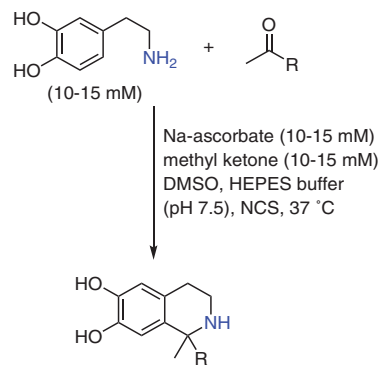
## Selected scope

R	Yield (%)
Ph	55
4-F <sub>3</sub> CC <sub>6</sub> H <sub>4</sub>	58
4-MeC <sub>6</sub> H <sub>4</sub>	53
4-MeOC <sub>6</sub> H <sub>4</sub>	53
3-MeOC <sub>6</sub> H <sub>4</sub>	52
CO <sub>2</sub> Et	57

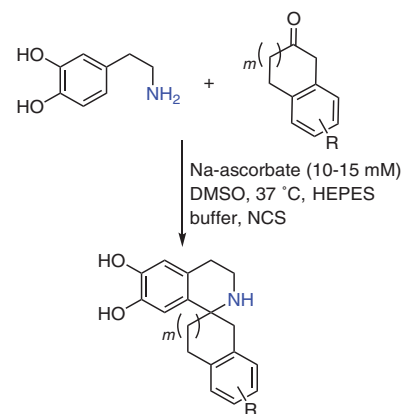
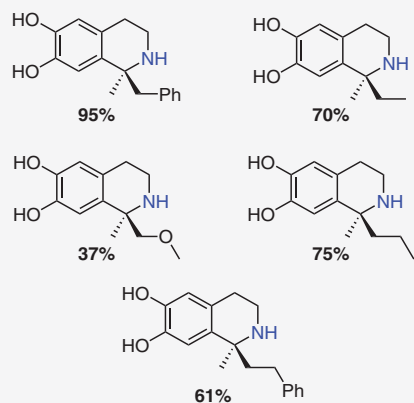
Figure 21 Formation of heterocycles, part I<sup>28a–o</sup>

## Pictet–Spengler reactions

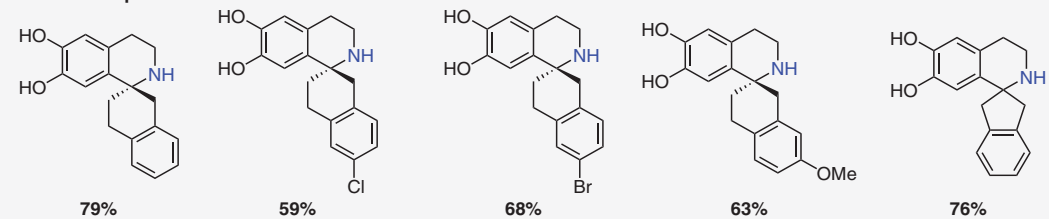
Enzymatic Pictet–Spengler reaction using norclaurine synthase as the catalyst to obtain non-natural tetrahydroisoquinoline alkaloids.

(29a) Hailes, *J. Org. Chem.* **2019**, *84*, 7702.

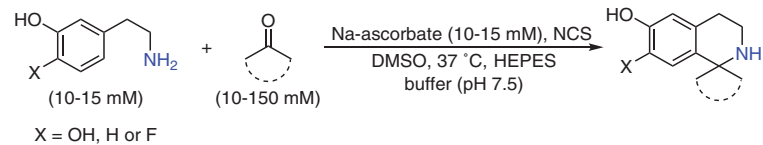
## Selected scope



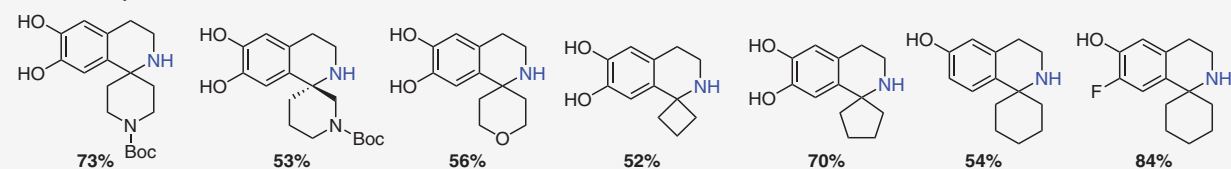
## Selected scope



## cyclic ketones

(29b) Hailes, *ACS Catal.* **2021**, *11*, 131.

## Selected scope

Figure 22 Formation of heterocycles, part II<sup>29a,b</sup>

## Conflict of Interest

The authors declare no conflict of interest.

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