Radical reactions using α-aminoalkyl radicals as halogen-atom transfer agents

2021.09.04

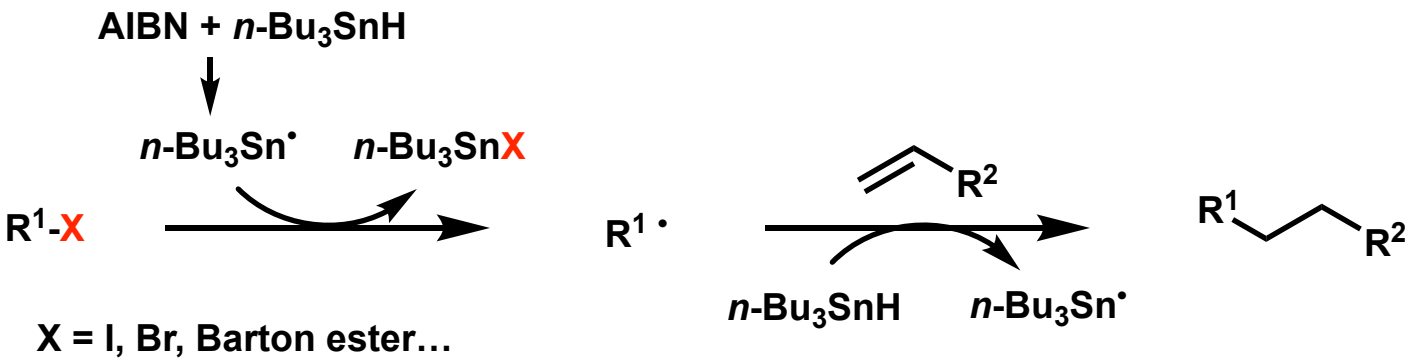
Toshiya Nagai

Contents

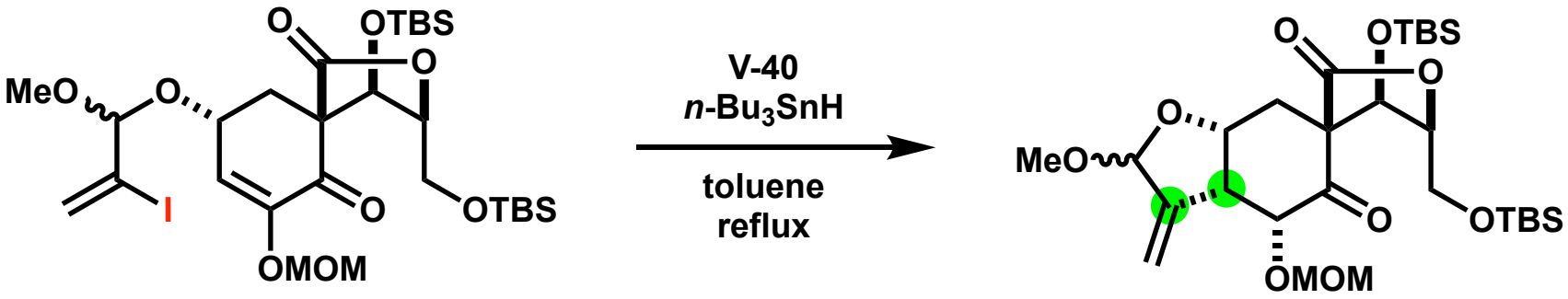
Contents

Radical Reaction

- Radical addition

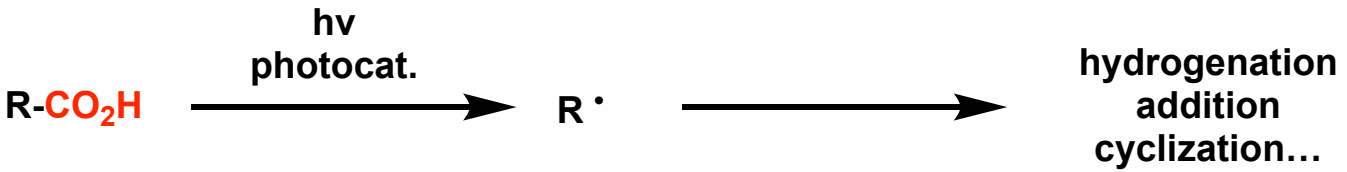


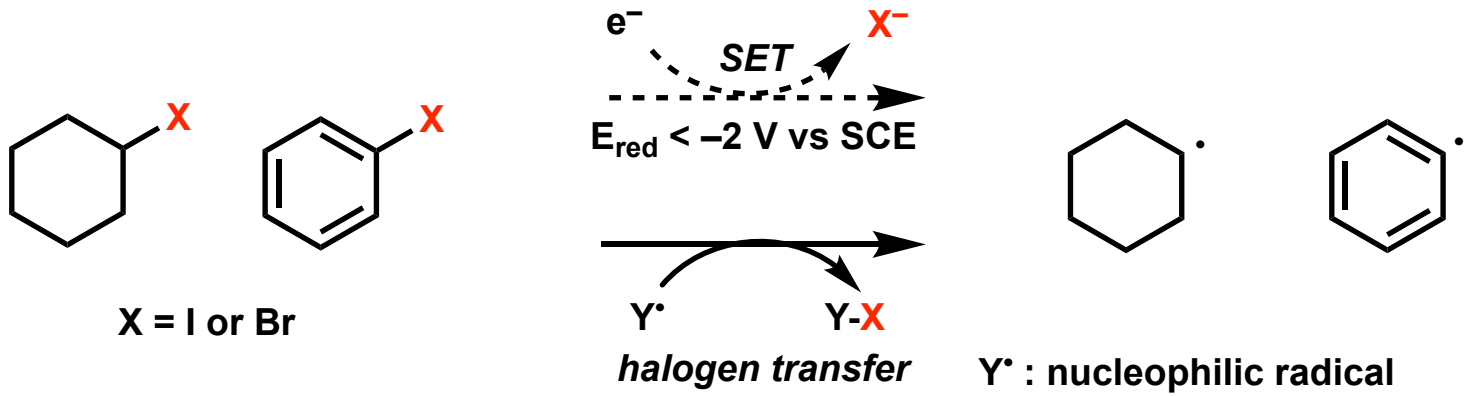
- Ueno-Stork-type cyclization



While radical reactions are extremely useful in total synthesis, they often require the use of highly toxic tin reagents.

Radical Reactions by Photoredox Catalysis

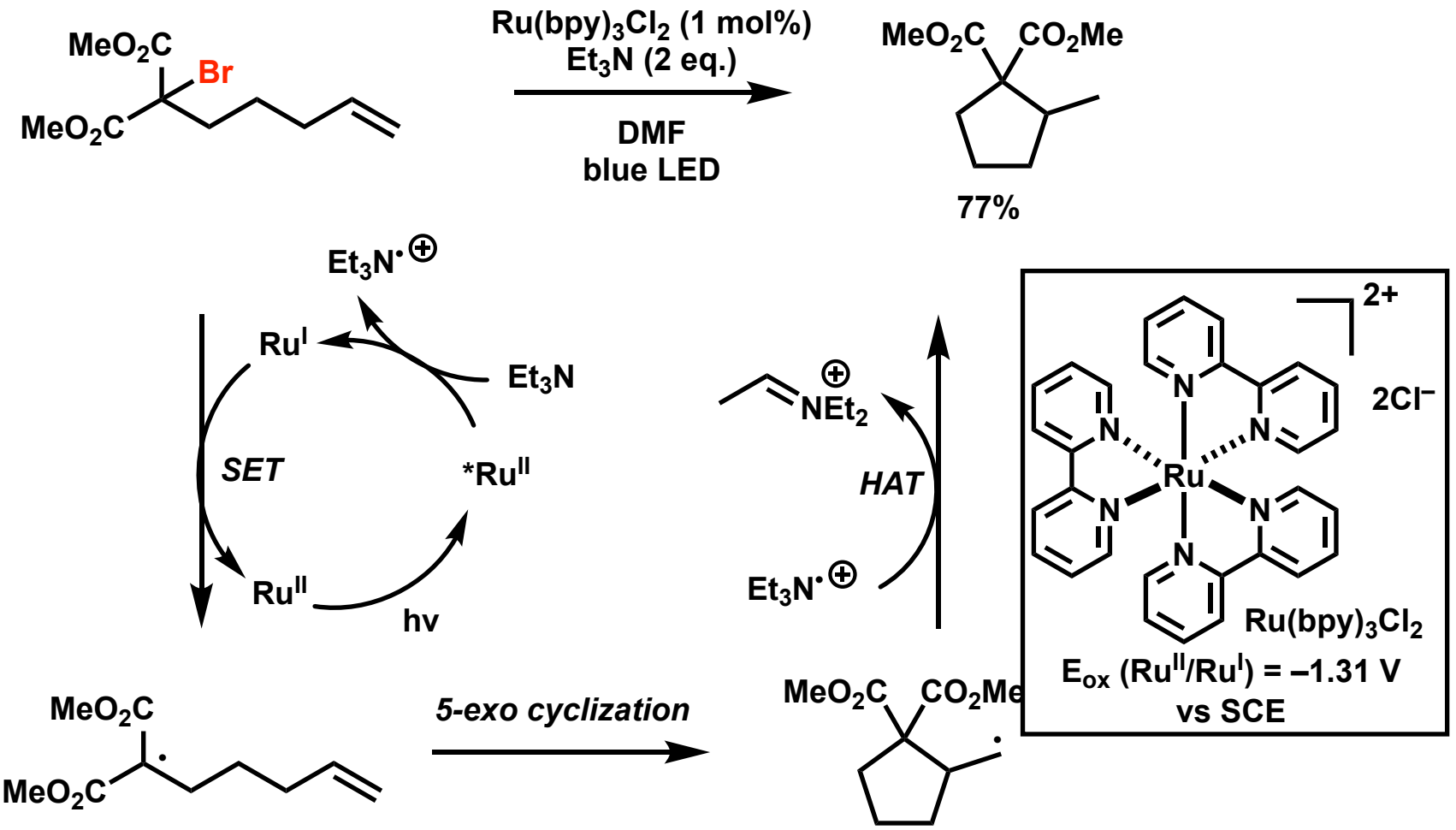




In general, radical generation from unactivated alkyl halide by SET is difficult, because of highly negative reduction potentials. On the other hand, radical generation by halogen transfer is relatively easy to proceed, as is the case with tin reagents.

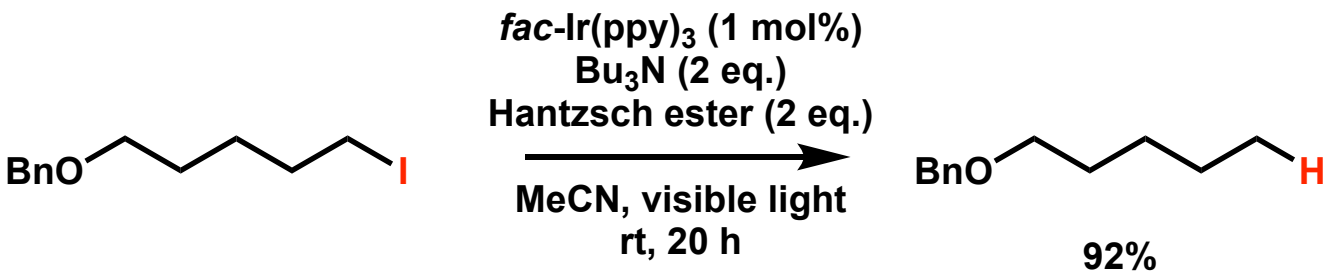
Constantin, T.; Zanini, M.; Regni, A.; Sheikh, N. S.; Julia, F.; Leonori, D. *Science* **2020**, *367*, 1021.

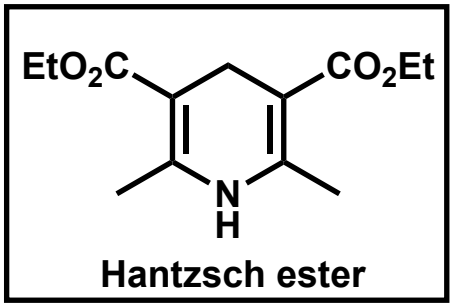
Radical Reaction with Malonate

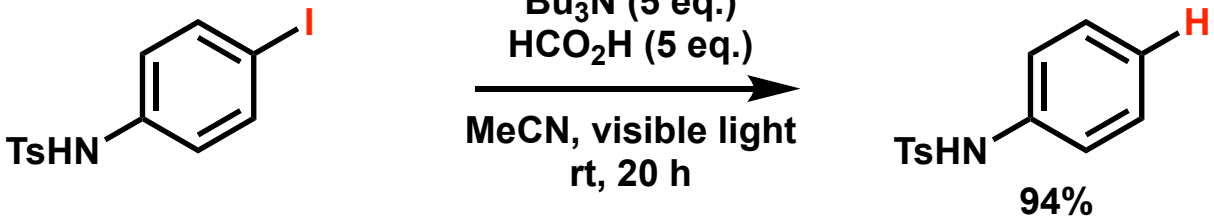


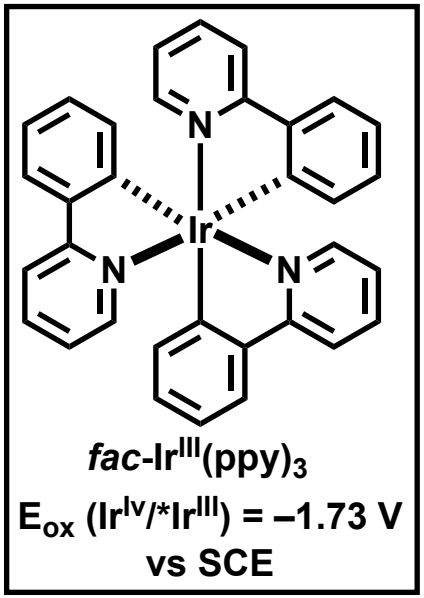
Tucker, J. W.; Nguyen, J. D.; Narayanam, J. M. R.; Krabbe, S. W.; Stephenson, C. R. J. *Chem. Commun.* **2010**, *46*, 4985.

Reduction of Alkyl and Aryl Iodide with Ir-Catalyst







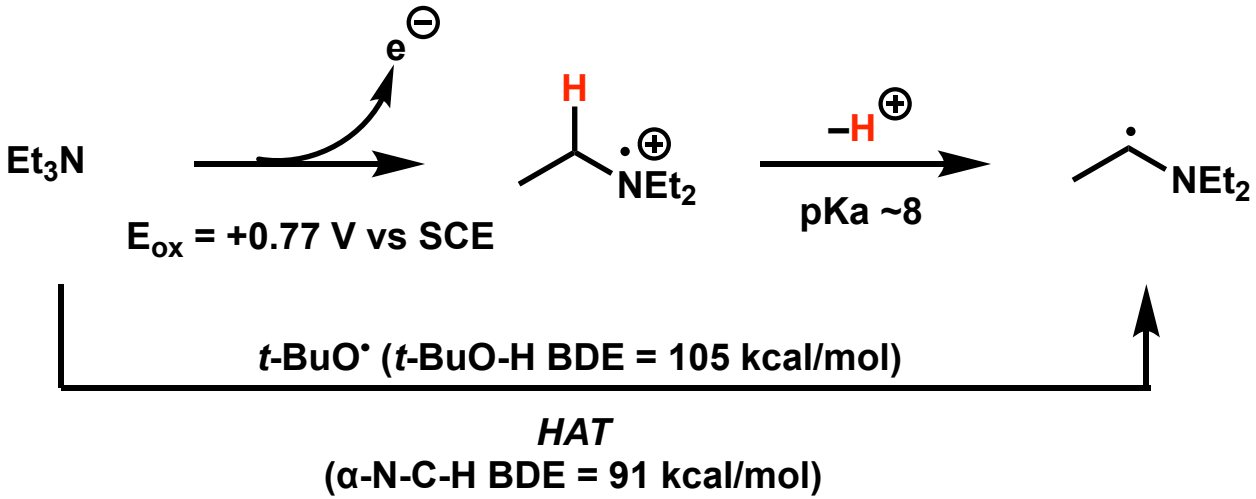


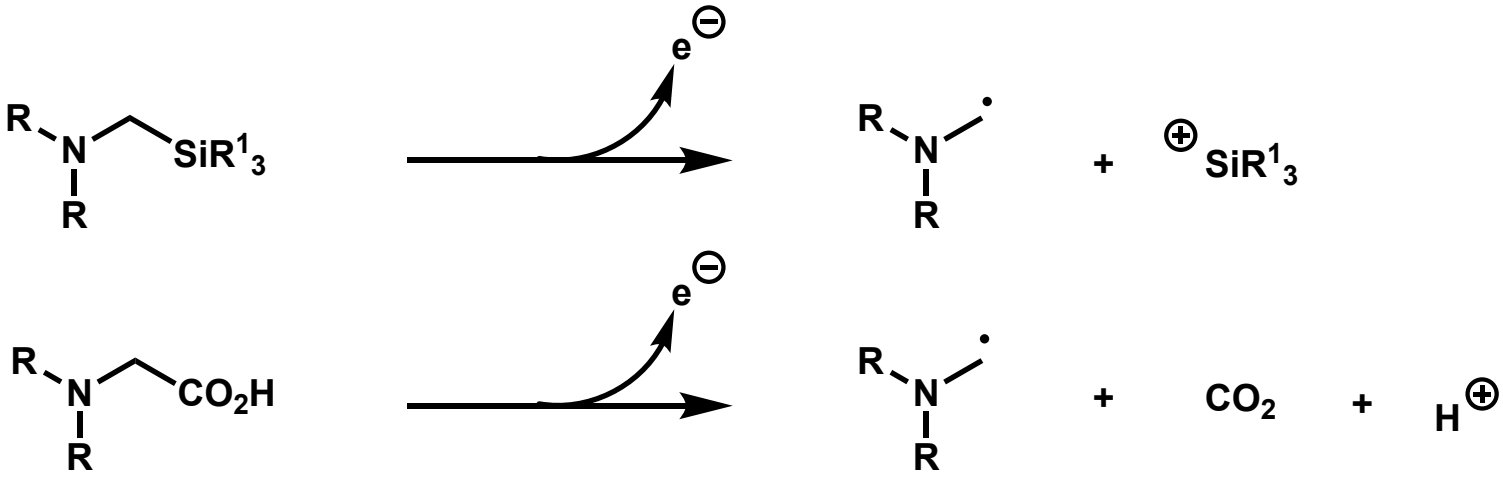
Strong reductant is needed to reduce alkyl and aryl iodide.

Nguyen, J. D.; D'Amato, E. M.; Narayanam, J. M. R.; Stephenson, C. R. J. *Nat. Chem.* **2012**, *4*, 854.

Contents

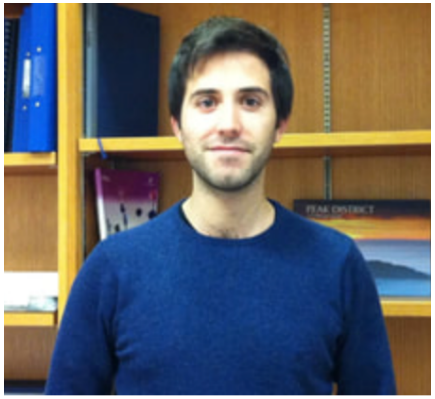
α-Aminoalkyl Radical





Nakajima, K.; Miyake, Y.; Nishibayashi, Y. *Acc. Chem. Res.* **2016**, *49*, 1946.

Prof. Daniele Leonori

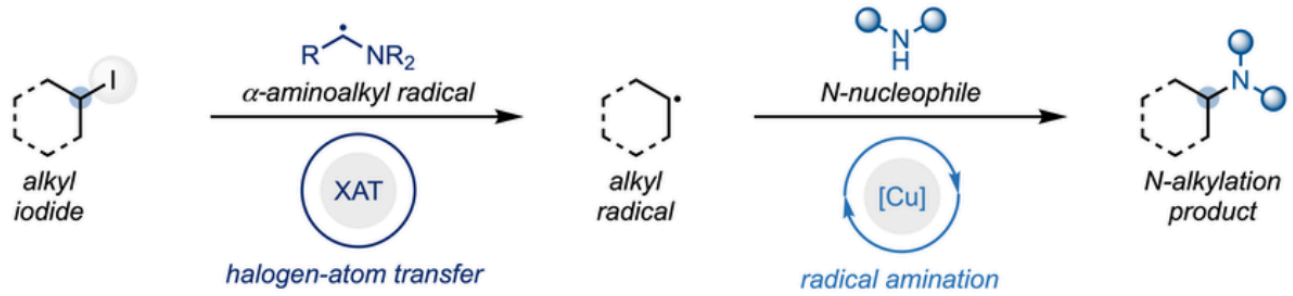


Career:

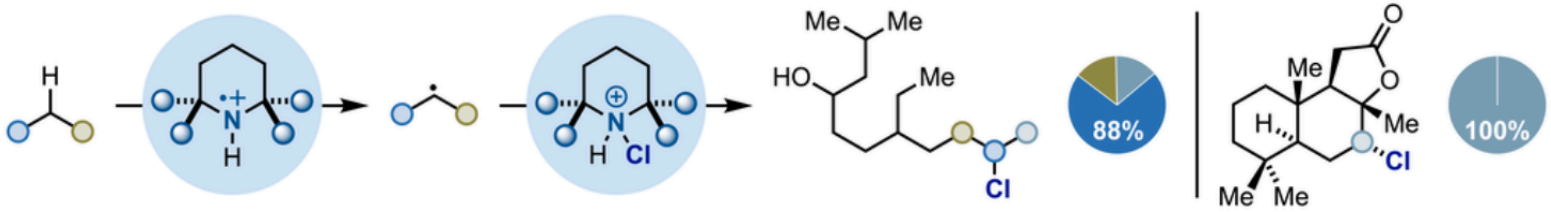
2007-2010 : PhD, University of Sheffield (Prof. Iain Coldham)
2010-2011 : Postdoc, RWTH-Aachen University (Prof. Magnus Rueping)
2011-2012 : Postdoc, Max Planck Institute (Prof. Peter H. Seeberger)
2012-2014 : Research Officer, University of Bristol (Prof. Varinder K. Aggarwal)
2014-2018 : Lecturer of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

Research topic: Development of reactions using α-aminoalkyl radical

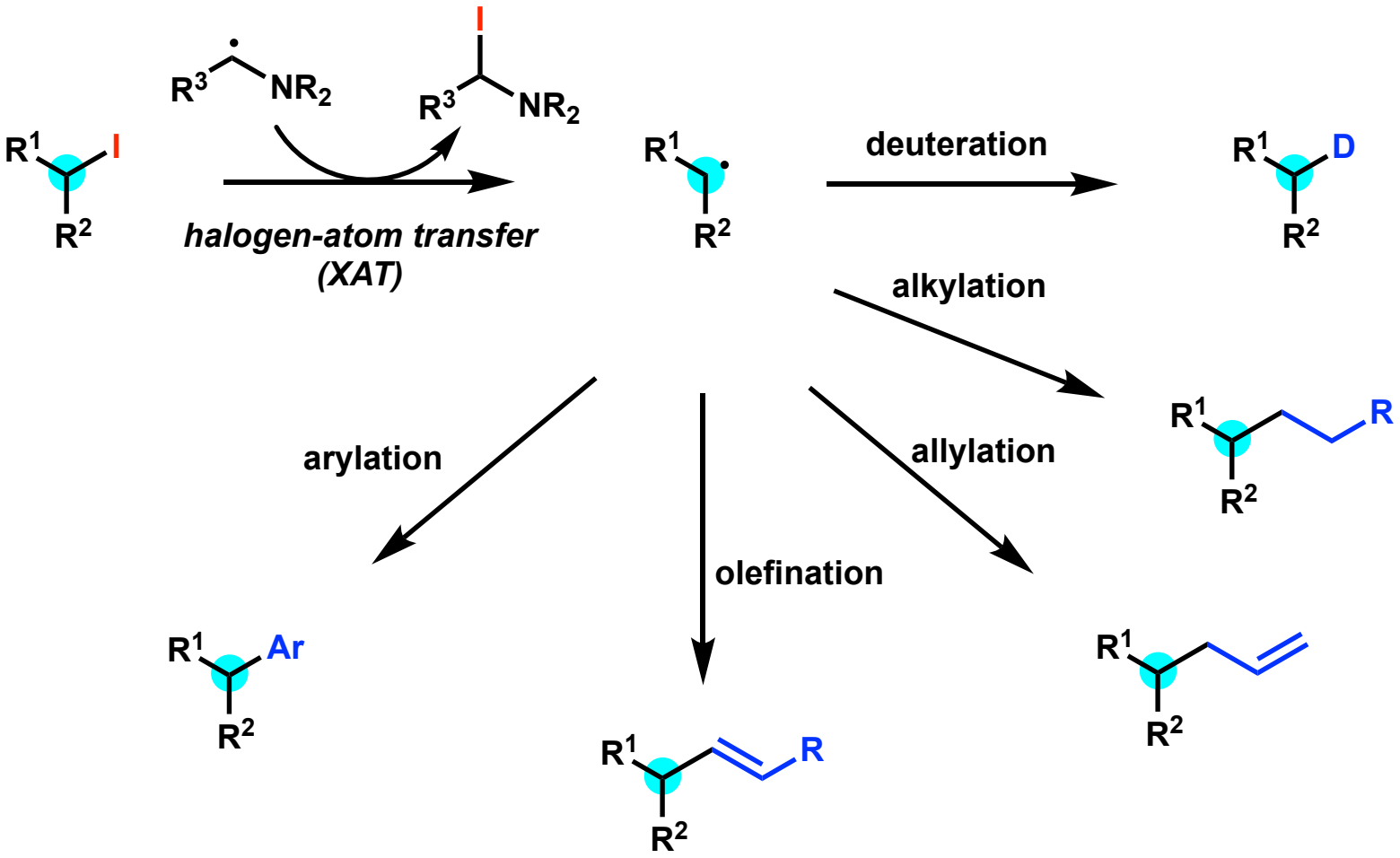
Nat. Catal. **2021**, *4*, 623–630



Angew. Chem. Int. Ed. **2021**, 60, 7132–7139

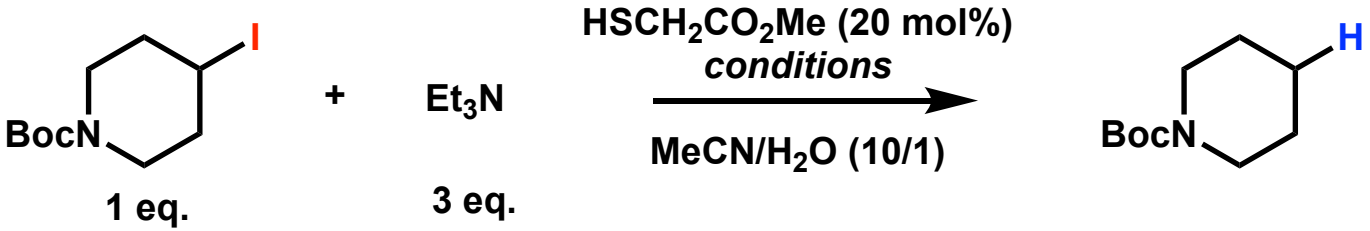


Transformations Using Alkyl and Aryl Halides

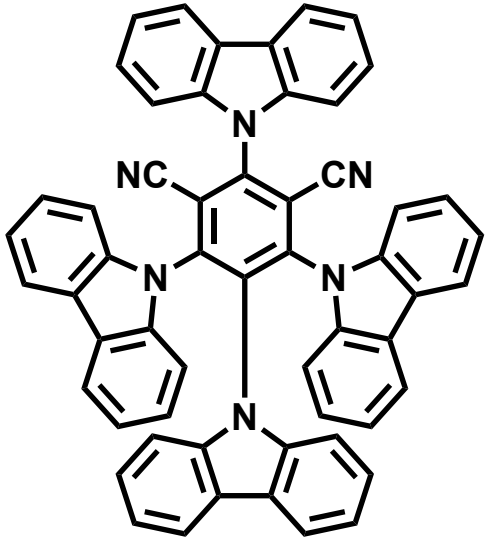


Constantin, T.; Zanini, M.; Regni, A.; Sheikh, N. S.; Julia, F.; Leonori, D. *Science* **2020**, *367*, 1021.

Conditions for α-Aminoalkyl Radical Generation



entry	conditions	yield
1	4CzIPN (5 mol%) blue LED, rt, 4 h	98%
2	$Ph_2C=O$ (1 eq.) UV-A LED, rt, 2 h	70%
3	$K_2S_2O_8$ (2 eq.) 70 °C, 2 h	40%
4	$(t\text{-BuO})_2$ (16 eq.) UV-A LED, rt, 16 h	67%

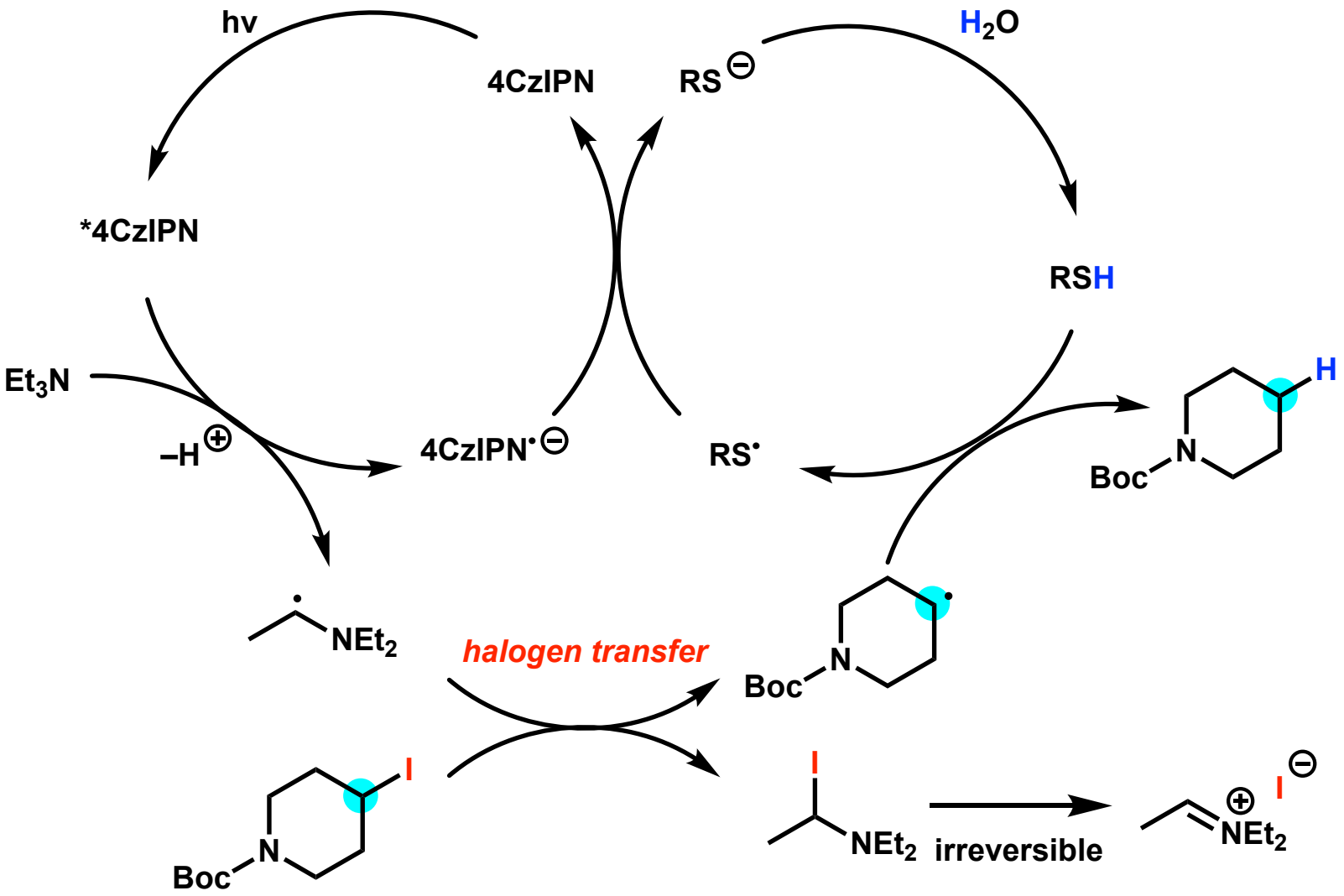


4CzIPN

E_{red} = +1.35 V vs SCE

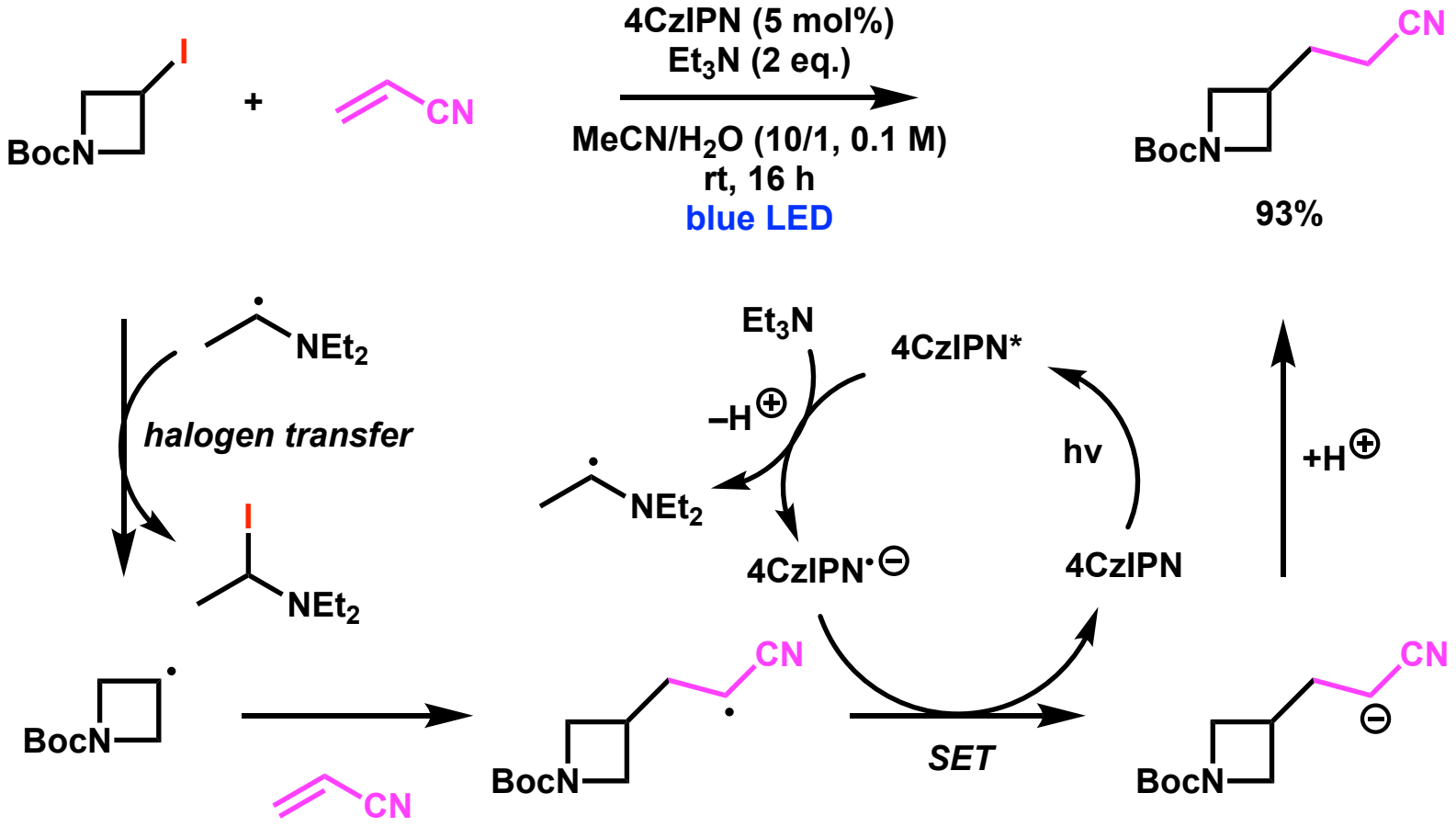
Constantin, T.; Zanini, M.; Regni, A.; Sheikh, N. S.; Julia, F.; Leonori, D. *Science* **2020**, *367*, 1021.

Proposed Mechanism for Photoredox-based Dehalogenation



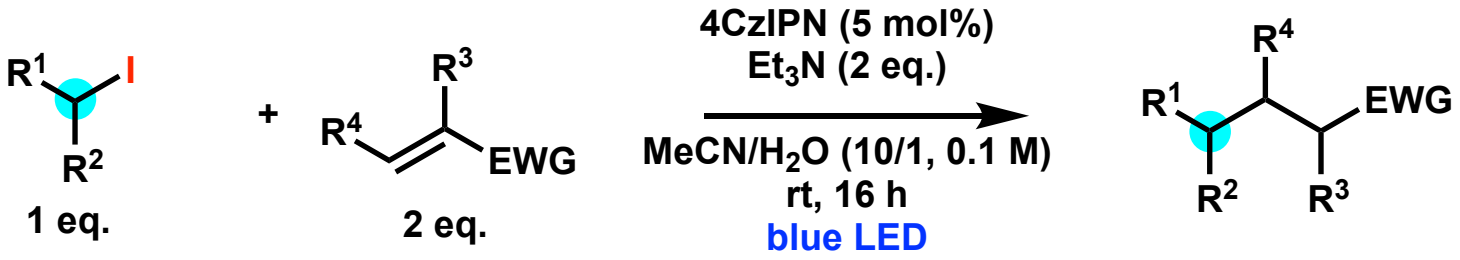
Constantin, T.; Zanini, M.; Regni, A.; Sheikh, N. S.; Julia, F.; Leonori, D. *Science* **2020**, *367*, 1021.

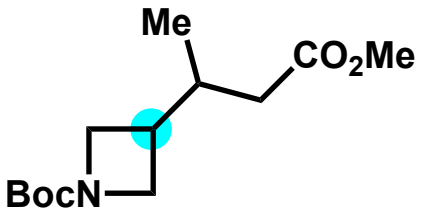
Giese Reaction with Alkyl Iodide



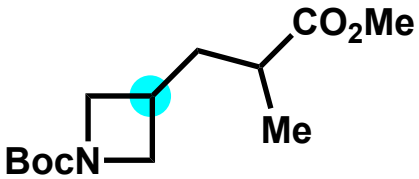
Constantin, T.; Zanini, M.; Regni, A.; Sheikh, N. S.; Julia, F.; Leonori, D. *Science* **2020**, *367*, 1021.

Giese Reaction with Alkyl Iodide

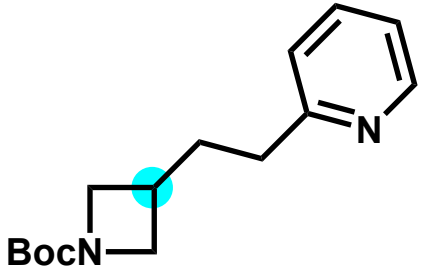




91%



quant.



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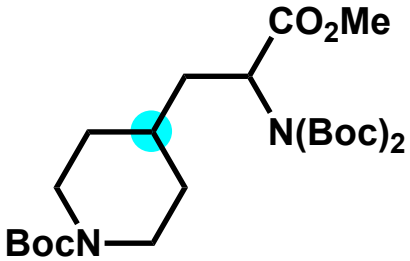

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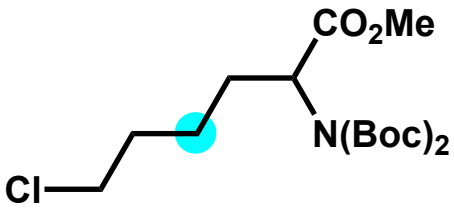

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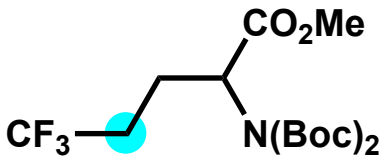
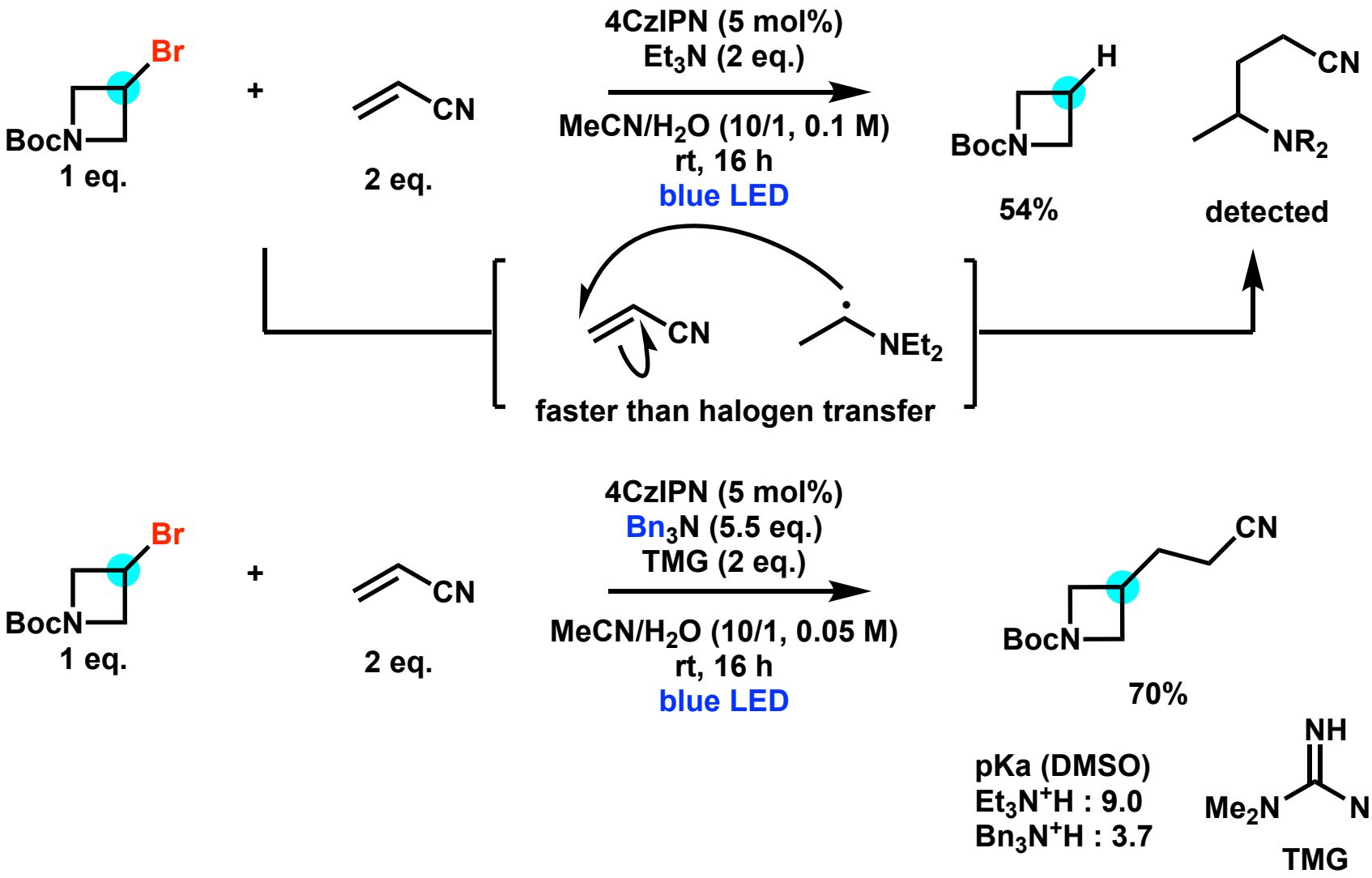


78%

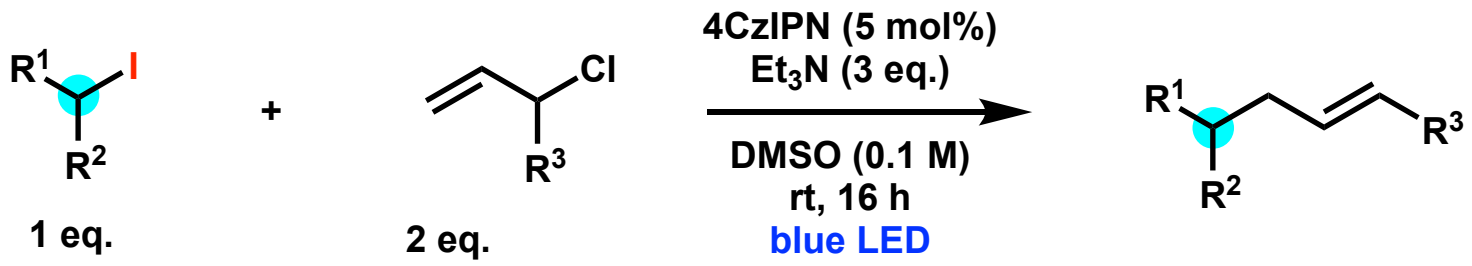
Constantin, T.; Zanini, M.; Regni, A.; Sheikh, N. S.; Julia, F.; Leonori, D. *Science* **2020**, *367*, 1021.

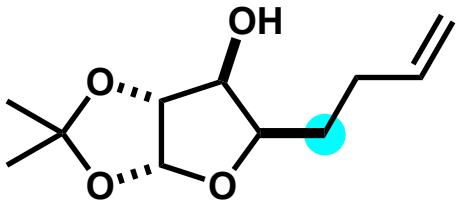
Giese Reaction with Alkyl Bromide



Constantin, T.; Zanini, M.; Regni, A.; Sheikh, N. S.; Julia, F.; Leonori, D. *Science* **2020**, *367*, 1021.

Allylation of Alkyl Iodide





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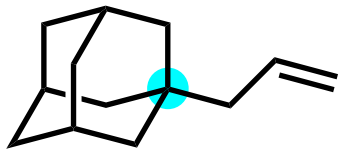

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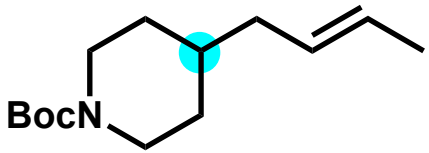
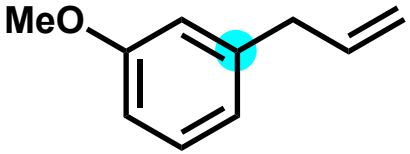
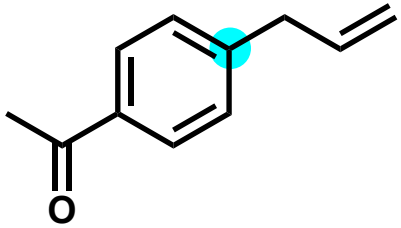


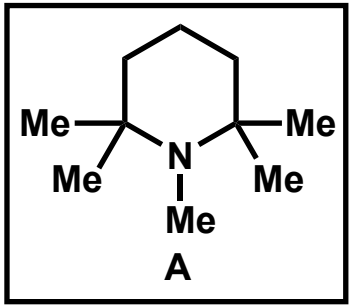
80% (*E*:*Z* = 1.4:1)



39%*



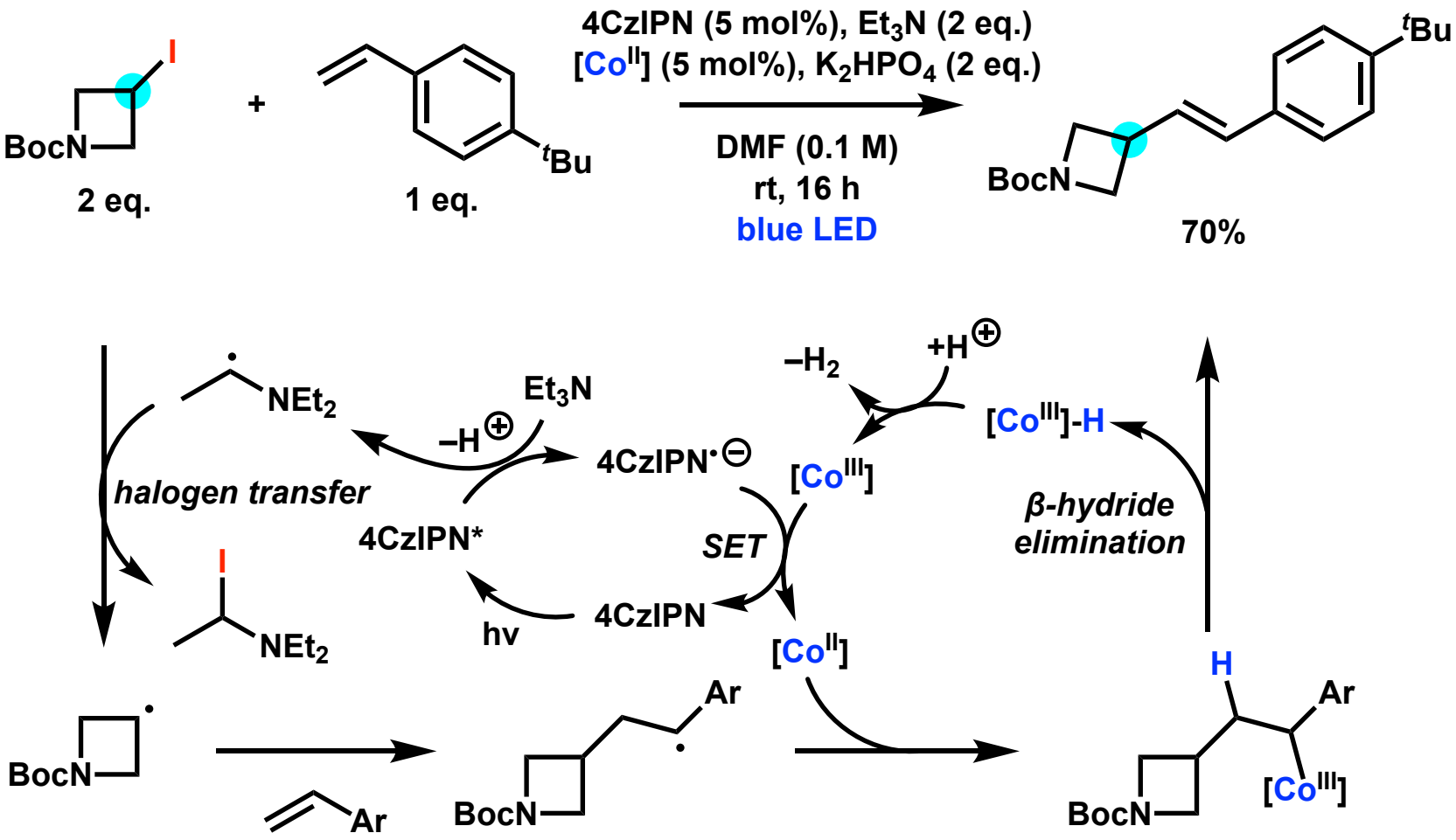
47%*



* A was used instead of Et_3N.

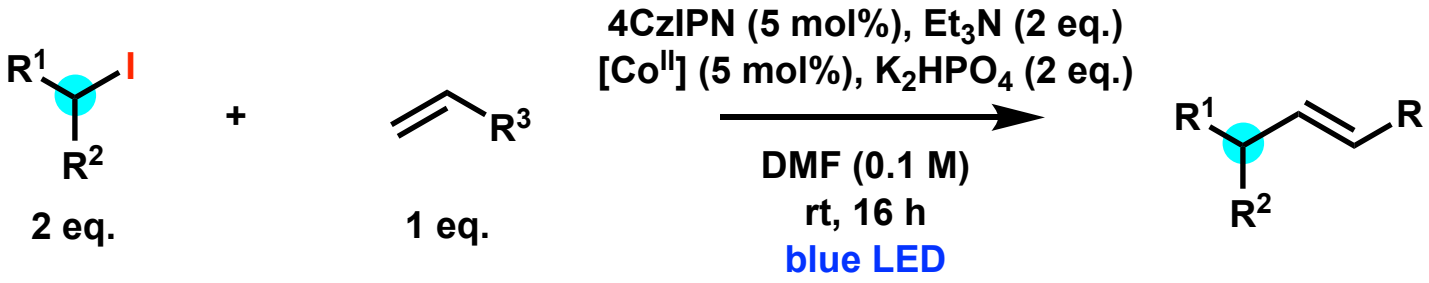
Constantin, T.; Zanini, M.; Regni, A.; Sheikh, N. S.; Julia, F.; Leonori, D. *Science* **2020**, *367*, 1021.

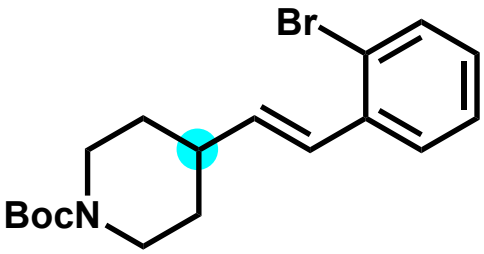
Heck-type Olefination of Alkyl Iodide



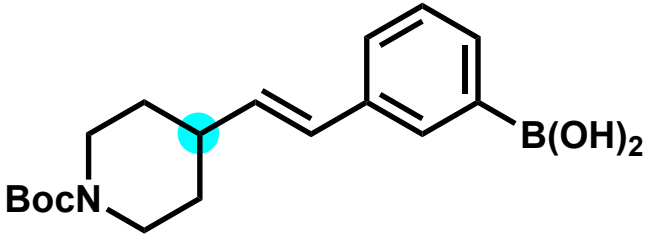
Constantin, T.; Zanini, M.; Regni, A.; Sheikh, N. S.; Julia, F.; Leonori, D. *Science* **2020**, *367*, 1021.

Scope for Olefination





79%



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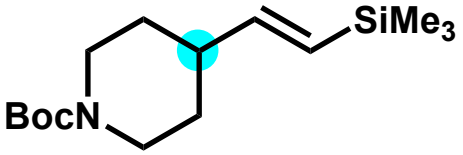
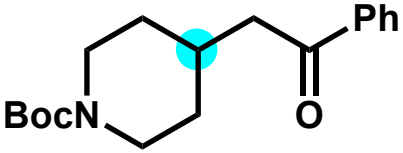
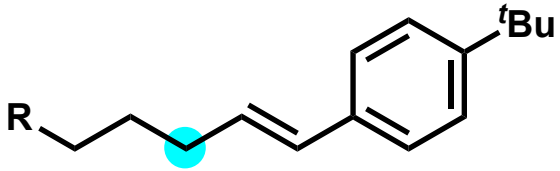


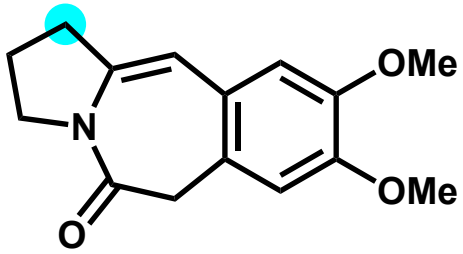
50% (E/Z = 16:1)



75%
from TMS enol ether



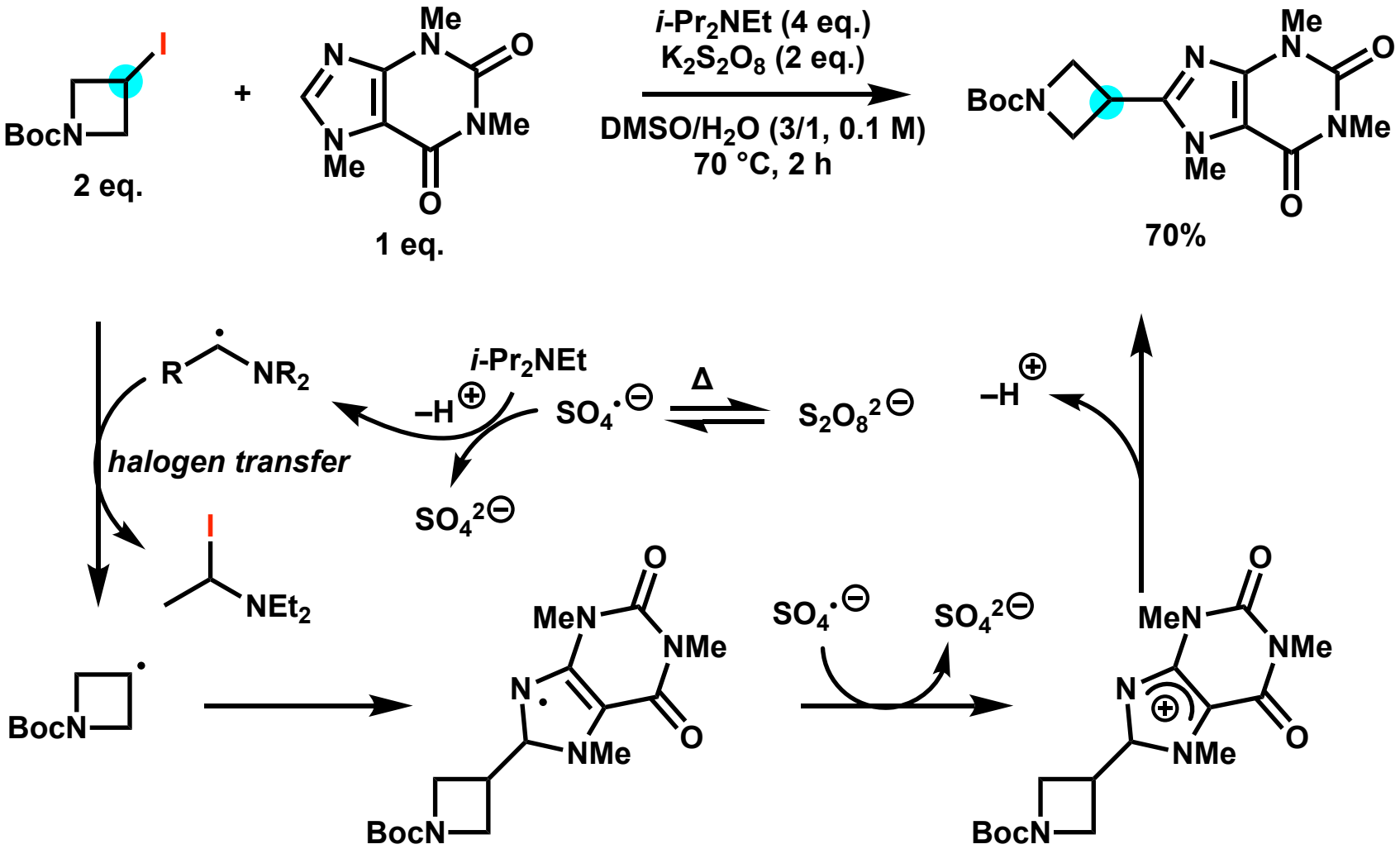
R = OH : 78%
R = Cl : 84%



82%

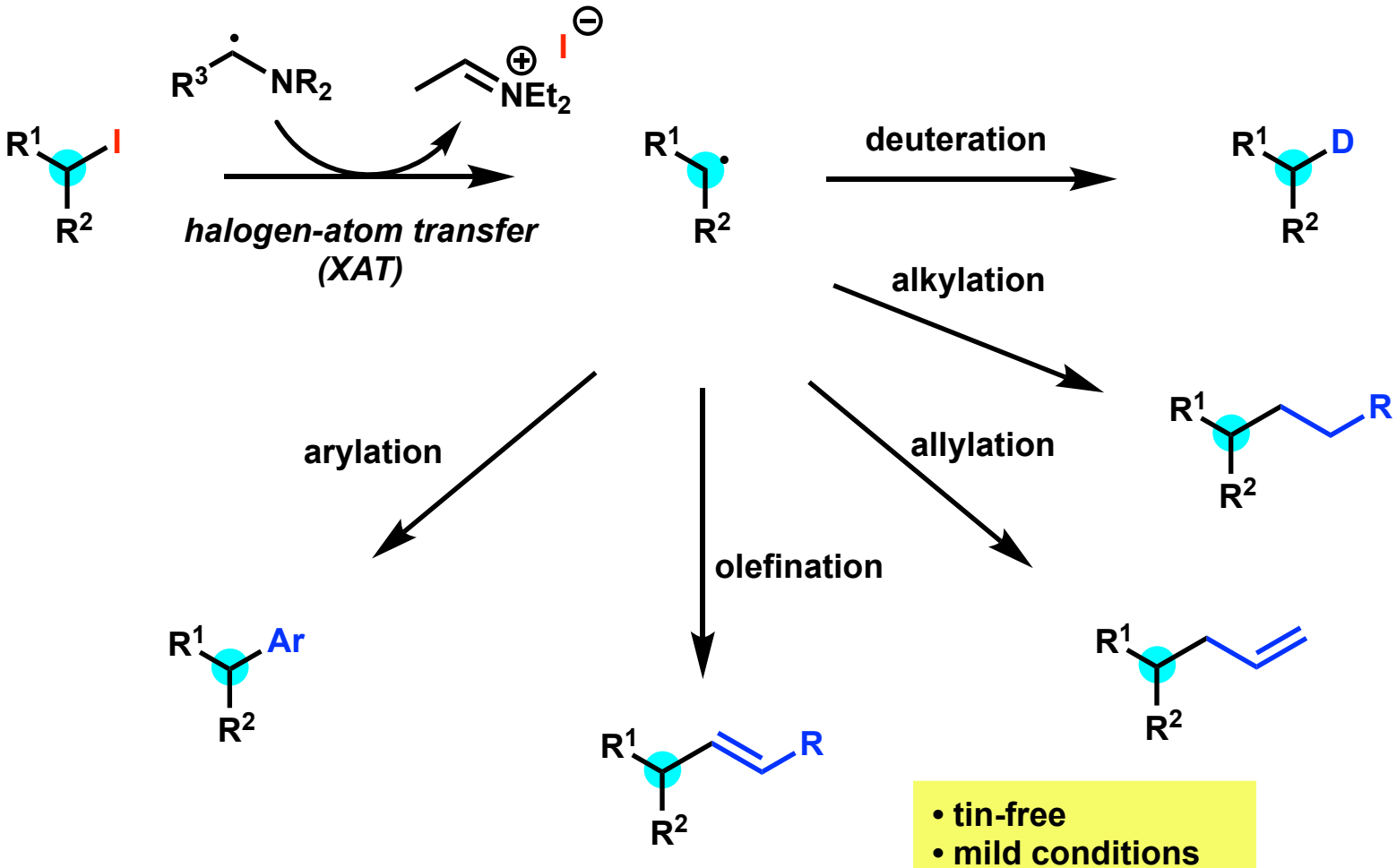
Constantin, T.; Zanini, M.; Regni, A.; Sheikh, N. S.; Julia, F.; Leonori, D. *Science* **2020**, *367*, 1021.

Arylation of alkyl iodide



Constantin, T.; Zanini, M.; Regni, A.; Sheikh, N. S.; Julia, F.; Leonori, D. *Science* **2020**, *367*, 1021.

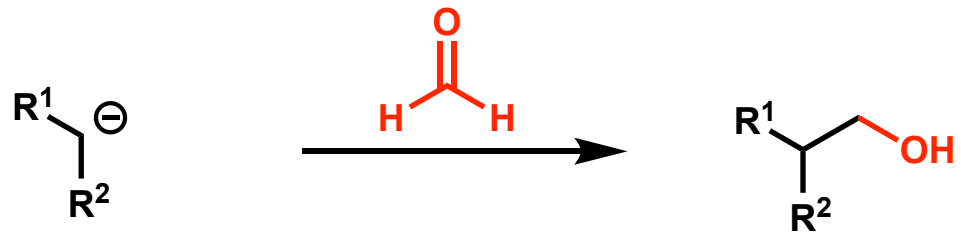
Summary-1

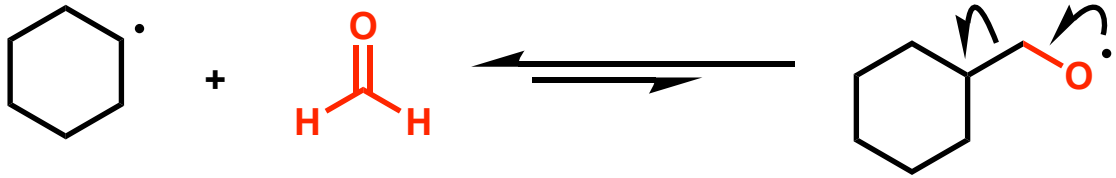


Constantin, T.; Zanini, M.; Regni, A.; Sheikh, N. S.; Julia, F.; Leonori, D. *Science* **2020**, *367*, 1021.

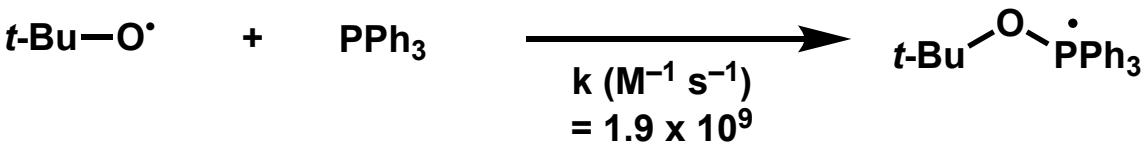
Contents

Hydroxymethylation using Formaldehyde



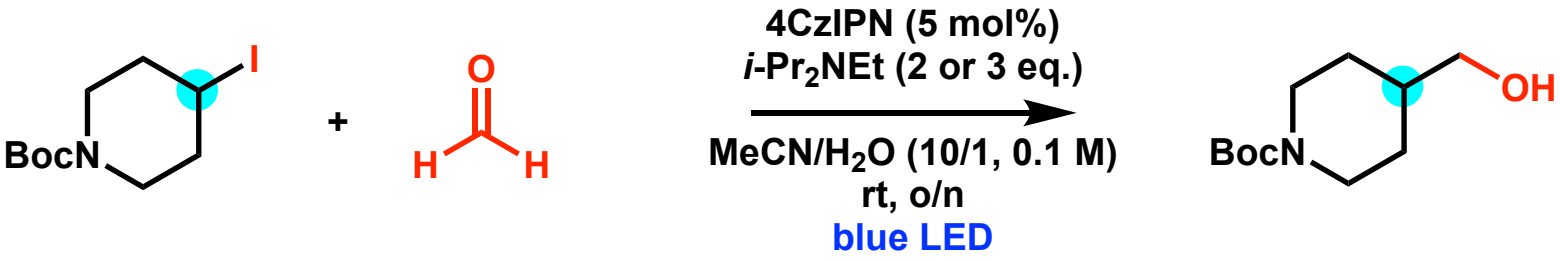


ΔG^0 : 4.8 kcal/mol
$\Delta G^{\ddagger}$: 9.9 kcal/mol



1. Caiger, L.; Sinton, C.; Constantin, T.; Douglas, J. J.; Sheikh, N. S.; Julia, F.; Leonori, D. *Chem. Sci.* **2021**, *12*, 10448.
2. Griller, D.; Ingold, K. U.; Patterson, L. K.; Scaiano, J. C.; Small, R. D. *J. Am. Chem. Soc.* **1979**, *101*, 3780.
3. Inial, A.; Morlet-Savary, F.; Lalevee, J.; Gaumont, A.-C.; Lakhbar, S. *Org. Lett.* **2020**, *22*, 4404.

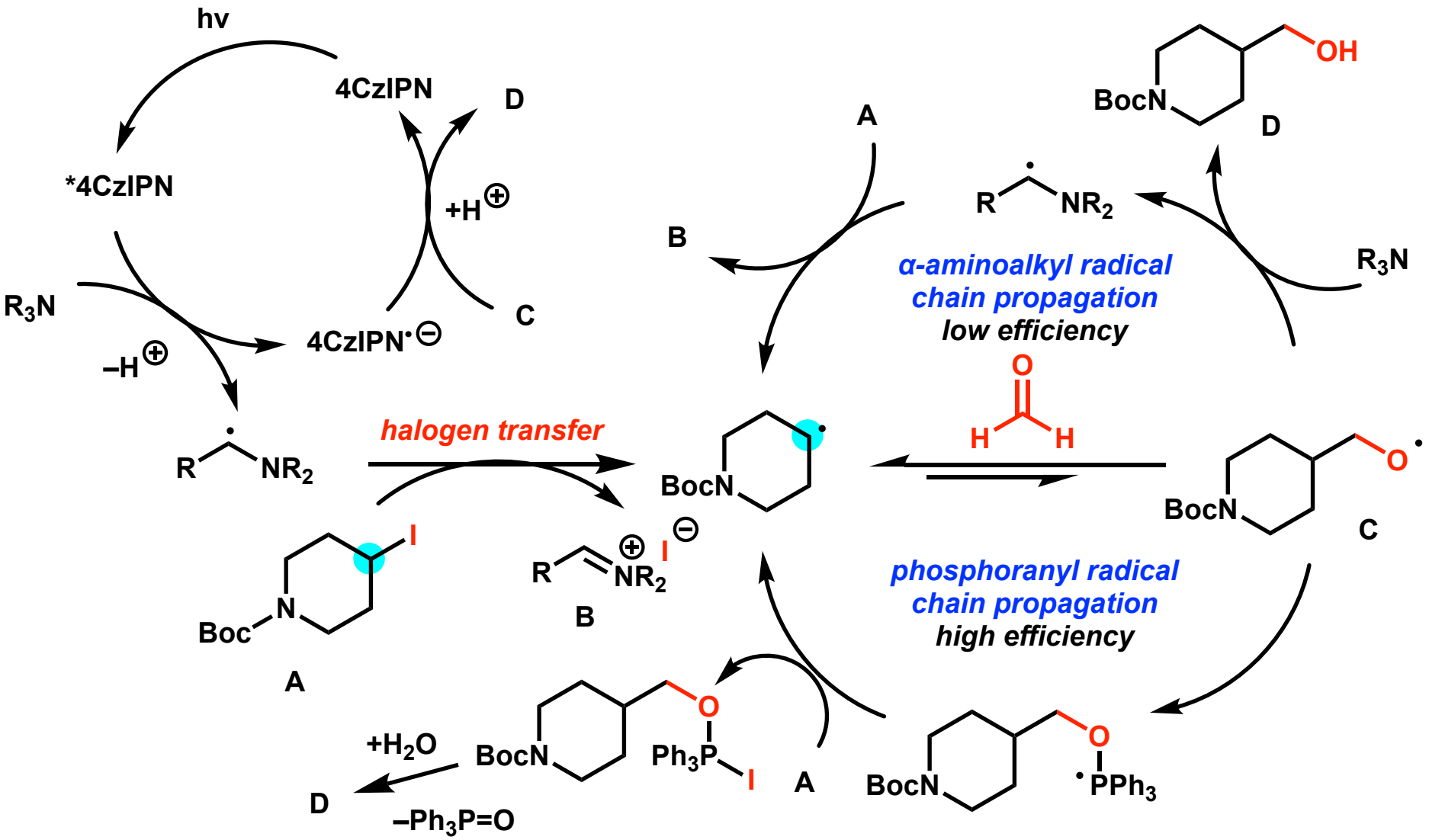
Reaction Optimization



entry	HCHO source	*i*-Pr_2NEt	additive	yield
1	$(HCHO)_n$ (4 eq.)	2 eq.	-	35%
2	$(HCHO)_n$ (4 eq.)	2 eq.	PPh_3 (2 eq.)	60%
3	HCHO aq. (10 eq.)	2 eq.	PPh_3 (2 eq.)	61%
4	HCHO aq. (10 eq.)	3 eq.	PPh_3 (3 eq.)	86%

Caiger, L.; Sinton, C.; Constantin, T.; Douglas, J. J.; Sheikh, N. S.; Julia, F.; Leonori, D. *Chem. Sci.* **2021**, *12*, 10448.

Proposed Mechanism of Hydroxymethylation



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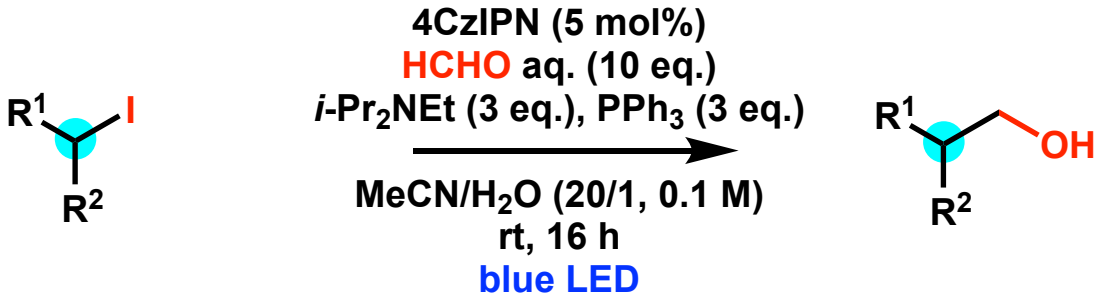
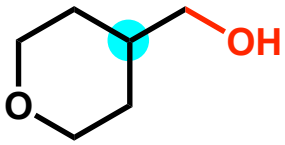
Scope for Hydroxymethylation





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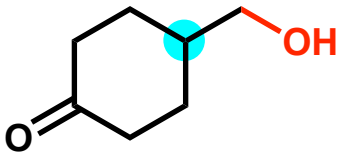

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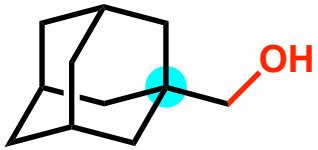

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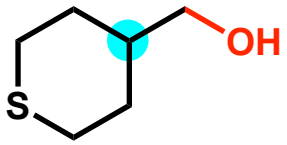

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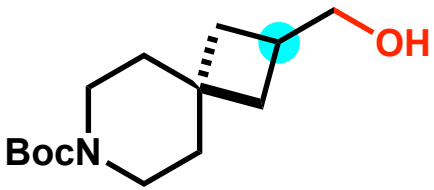

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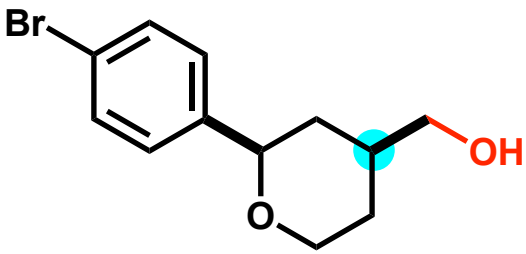

74% (dr: 3:1)

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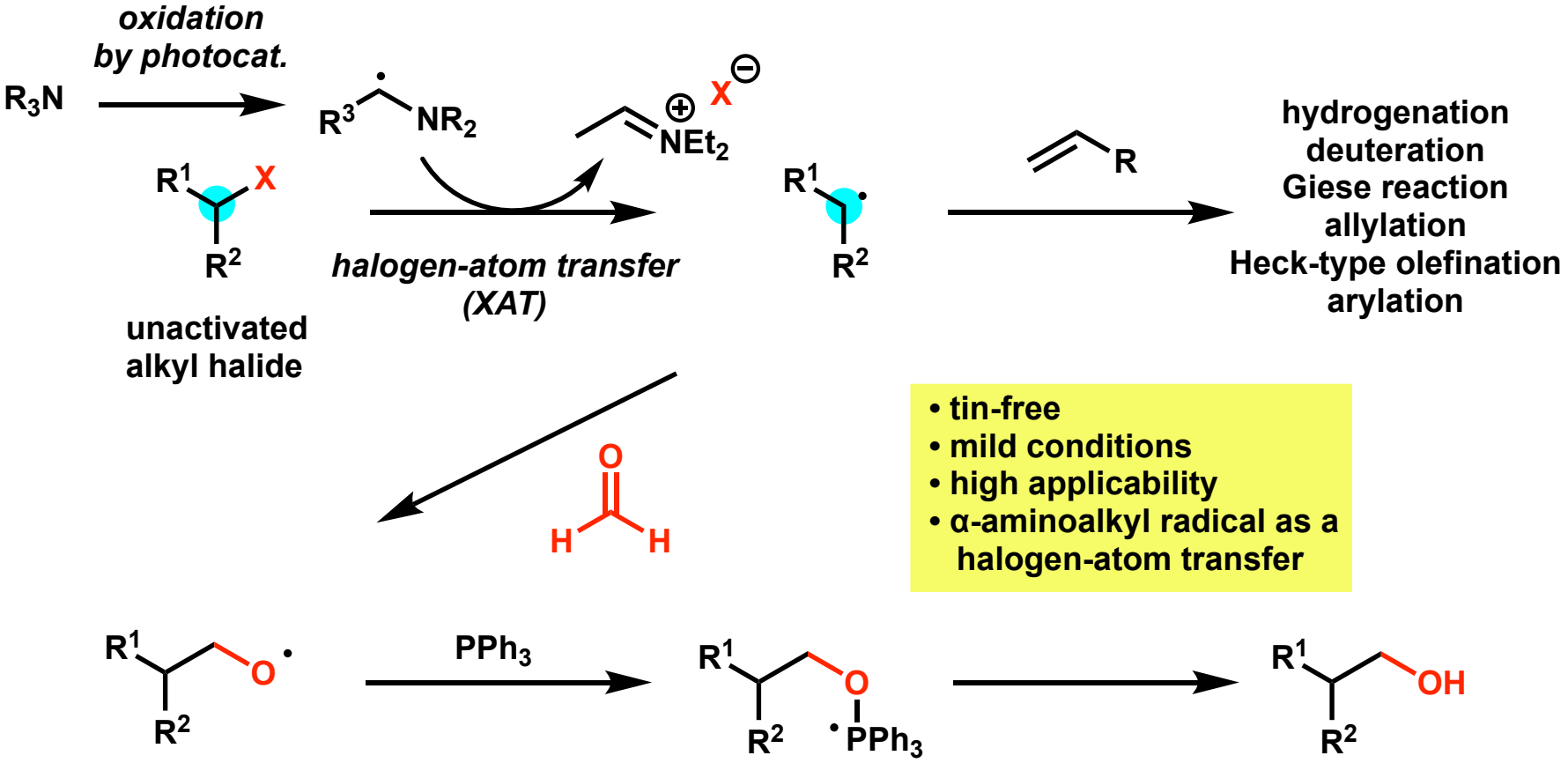
Summary-2



1. Constantin, T.; Zanini, M.; Regni, A.; Sheikh, N. S.; Julia, F.; Leonori, D. *Science* **2020**, *367*, 1021.
2. Caiger, L.; Sinton, C.; Constantin, T.; Douglas, J. J.; Sheikh, N. S.; Julia, F.; Leonori, D. *Chem. Sci.* **2021**, *12*, 10448.