

# Literature Report III

## Iron-catalyzed Remote Functionalization of Inert C(sp<sup>3</sup>)-H Bonds of Alkenes via 1,n-Hydrogen-Atom-Transfer by C-Centered Radical Relay

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Reporter: Yu-Qing Bai

Checker: Xiao-Qing Wang

Date: 2020-12-07

Wang, X.-S. *et al. Chem. Sci.* **2020**, *11*, 10437.

# CV of Prof. Xi-Sheng Wang

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## Background:

- ❑ **1995–1999** B.S., Jilin University
- ❑ **2000–2005** Ph.D., SIOC
- ❑ **2005–2008** Postdoc., Kyoto University, Japan
- ❑ **2008–2011** Research Assistant, TSRI, USA
- ❑ **2011-Now** Professor, USTC

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## Research:

- Transition metal catalyzed carbon-fluorine bond formation reaction
- Transition metal catalyzed inert bond activation
- Asymmetric synthesis of fluorinated organic compounds catalyzed by transition metals or small organic molecules
- Exploration of a novel reaction catalyzed by transition metals and its application in the synthesis of natural products

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**1** Introduction

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**2** Remote Functionalization of Inert C(sp<sup>3</sup>)-H Bonds

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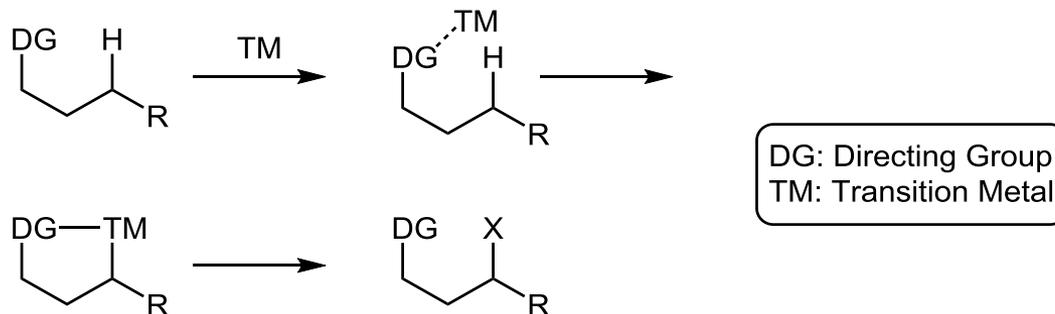
**3** Summary

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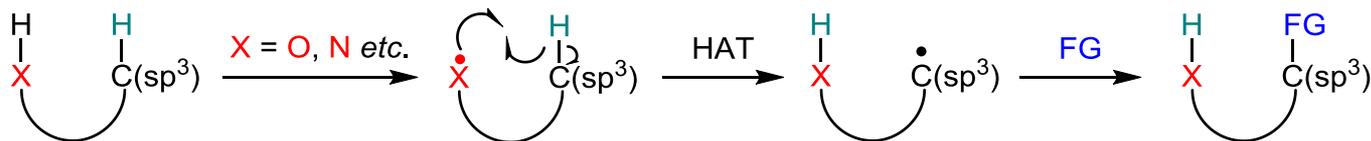
# Introduction

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## Transition-Metal-Catalyzed C-H Activation

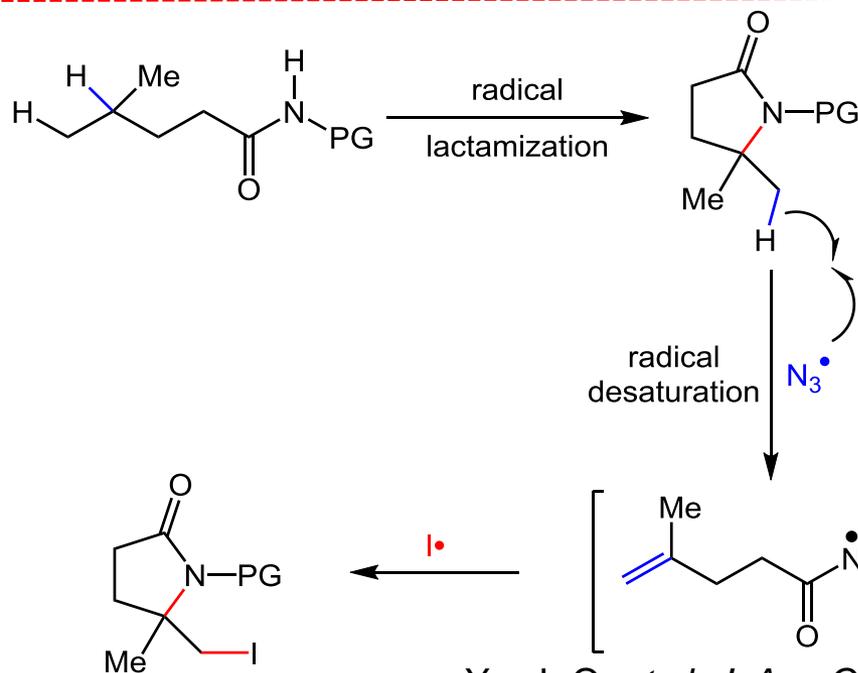
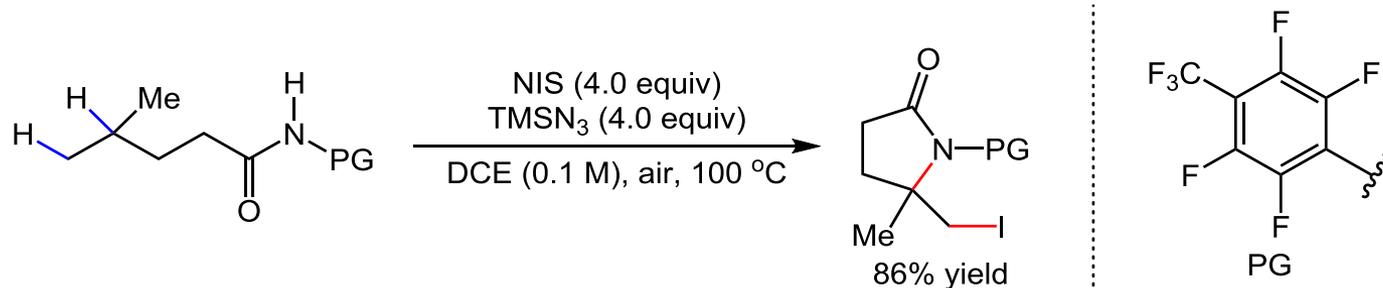


## Remote C(sp<sup>3</sup>)-H Bond Functionalization via HAT Process



# Introduction

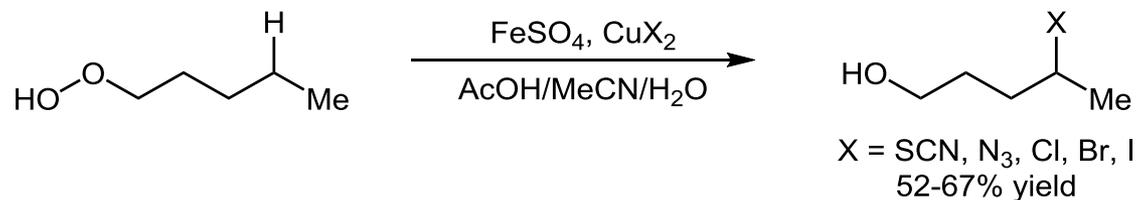
## Nitrogen Radicals Homolysis of N-X Bonds



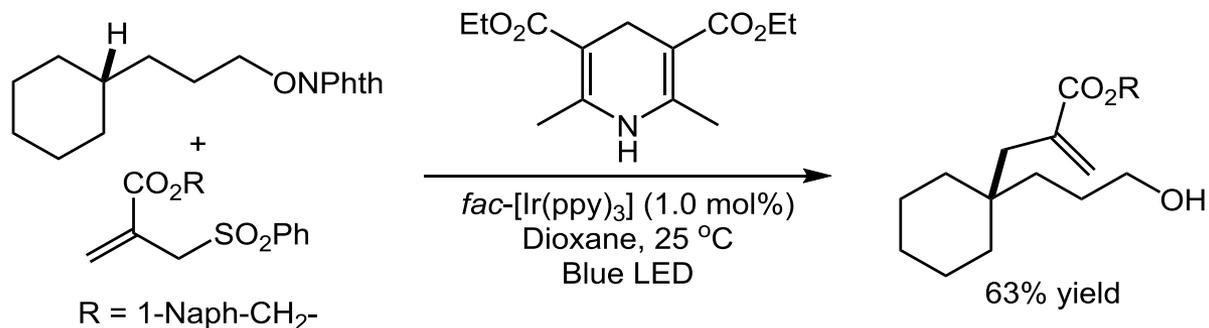
Yu, J.-Q. *et al.* *J. Am. Chem. Soc.* **2015**, 137, 5871

# Introduction

## Oxygen Radicals Reduction of O-X Bonds

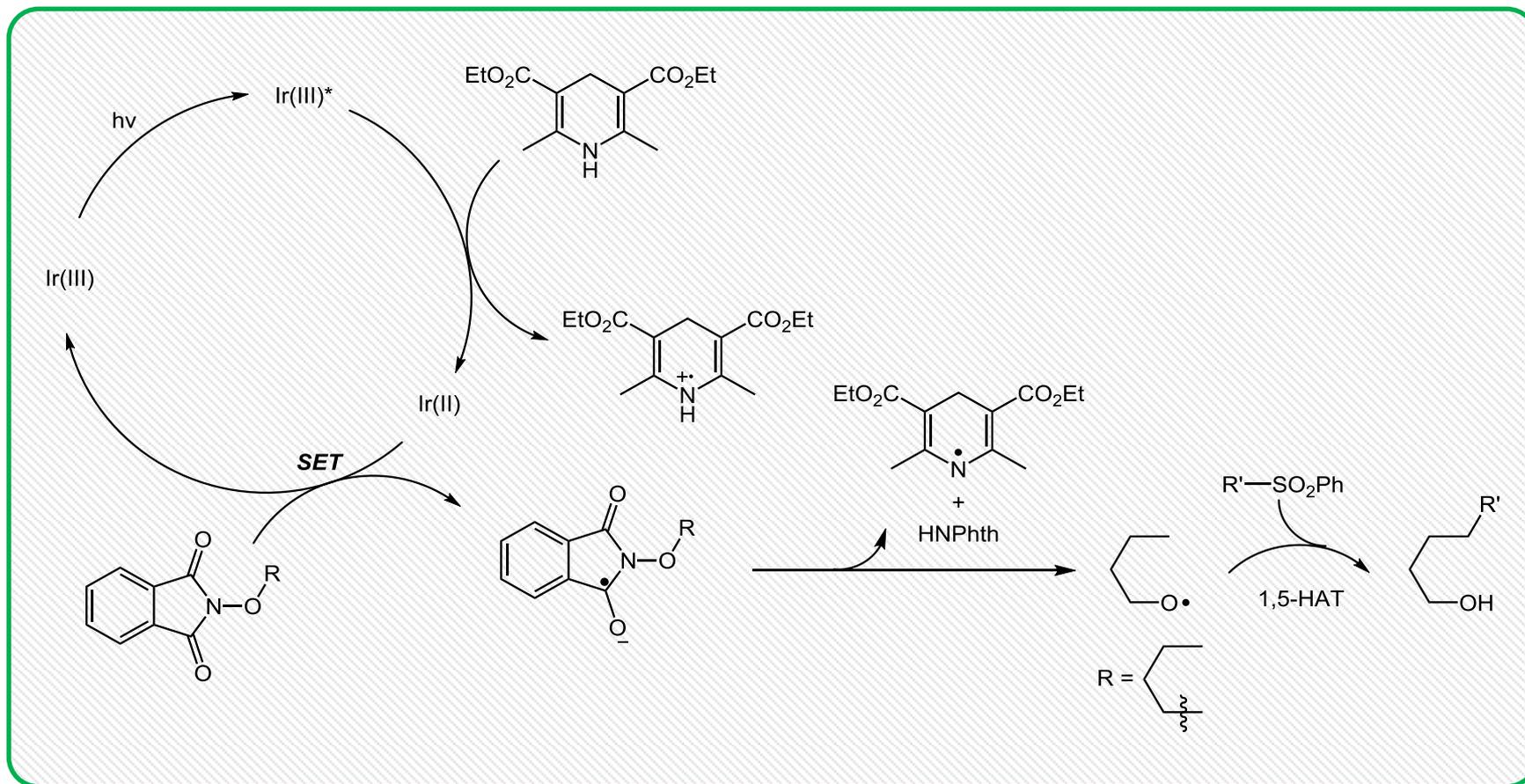


Cekovic, Z. *et al. Tetrahedron Lett.* **1982**, 23, 3791



Chen, Y. *et al. Angew. Chem. Int. Ed.* **2016**, 128, 1904

# Introduction



Chen, Y. *et al. Angew. Chem. Int. Ed.* **2016**, 128, 1904

# Introduction

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Radical Addition to Unsaturated C=C Bonds



**Carbon-Centered Radicals**

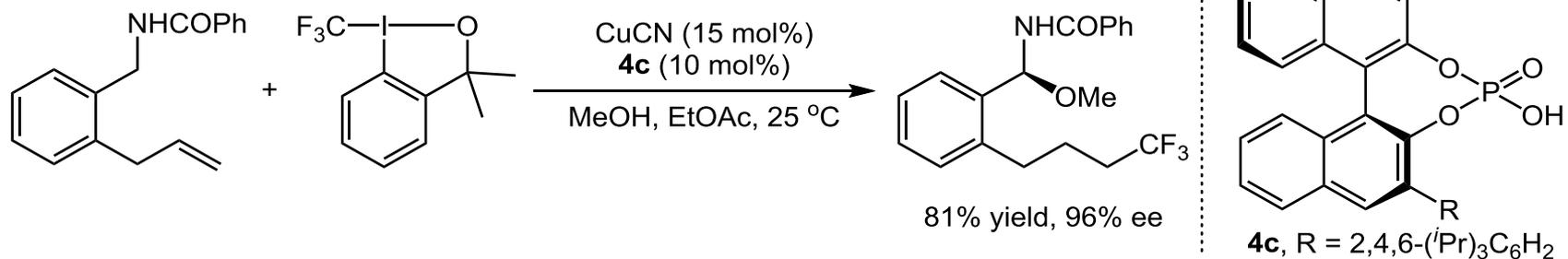


**HAT Rate Constant  
Bond Dissociation Energies**

**Weaker Driving Force for Remote Functionalization**

# Introduction

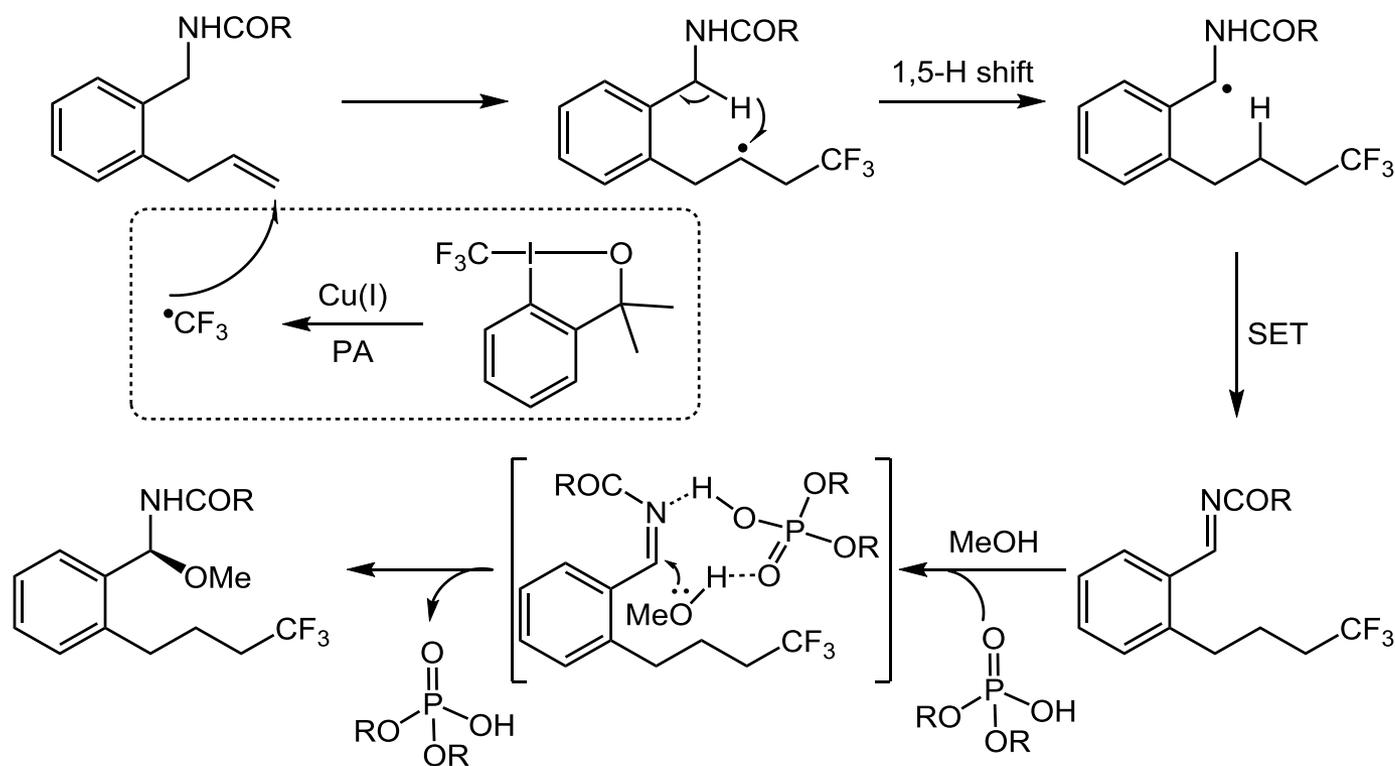
## Carbon Radicals Copper Catalysis



Liu, X.-Y. *et al.* *Angew. Chem. Int. Ed.* **2014**, *53*, 11890

# Introduction

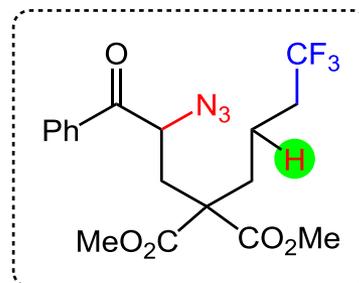
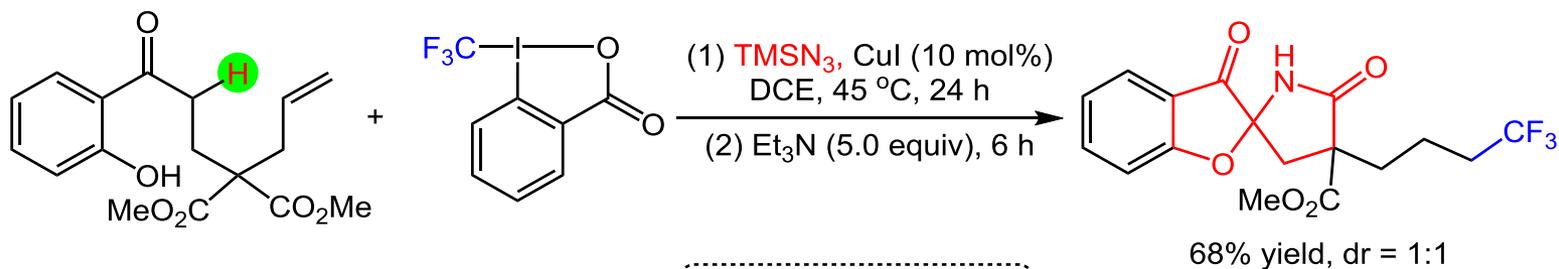
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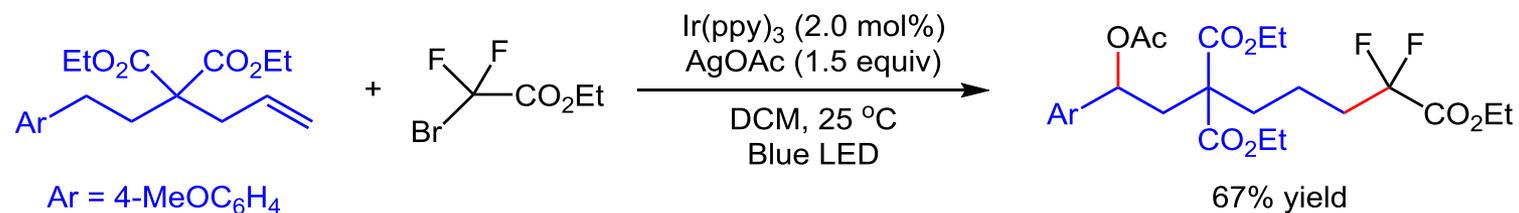
## Carbon Radicals Copper Catalysis



Liu, X.-Y. *et al.* *ACS Catal.* **2015**, *5*, 2826

# Introduction

## Carbon Radicals Visible-Light Mediation

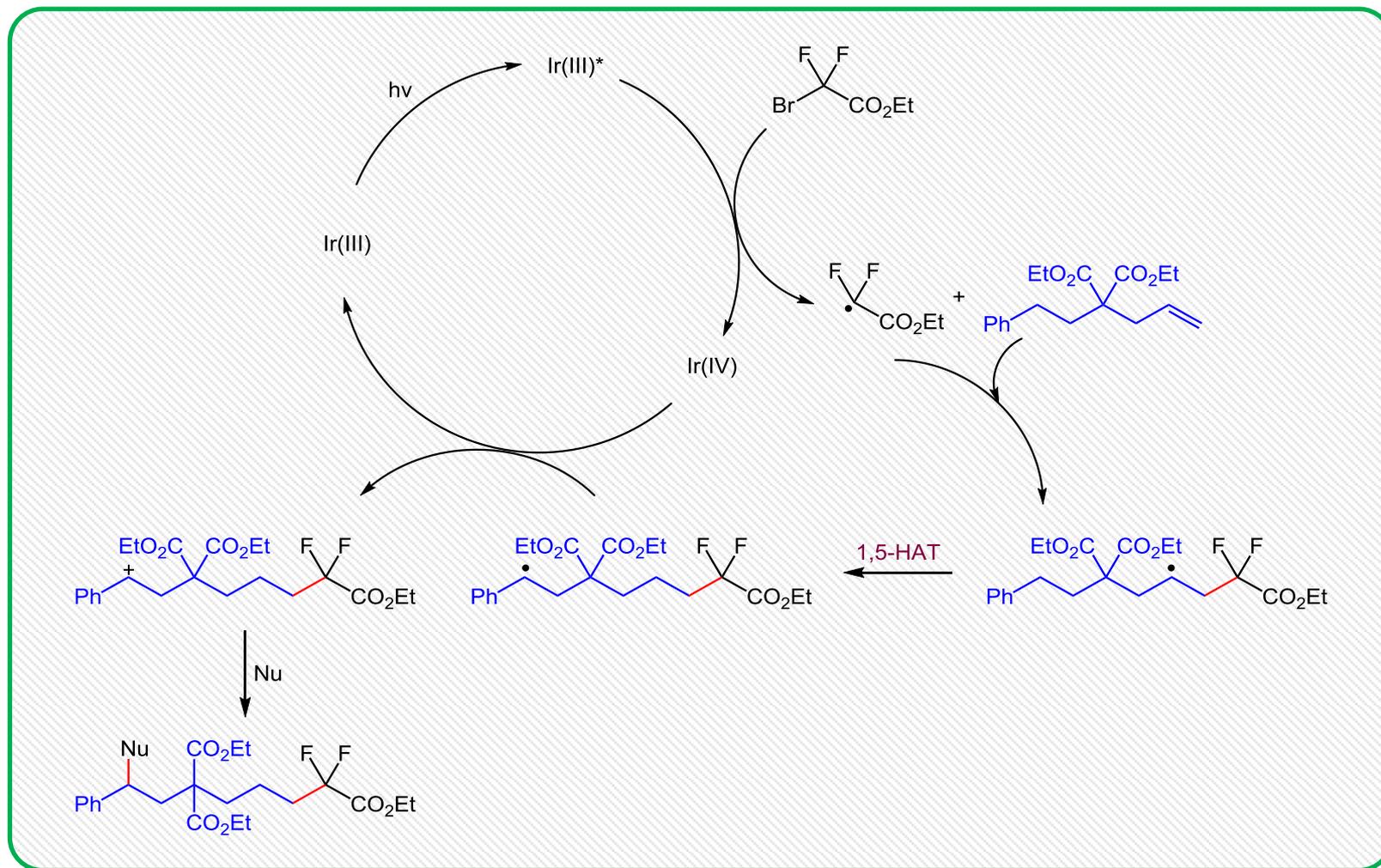


Nevado, C. *et al.* *ACS Catal.* **2018**, 8, 6401



Ma, Y.-N. *et al.* *Org. Lett.* **2019**, 21, 9228

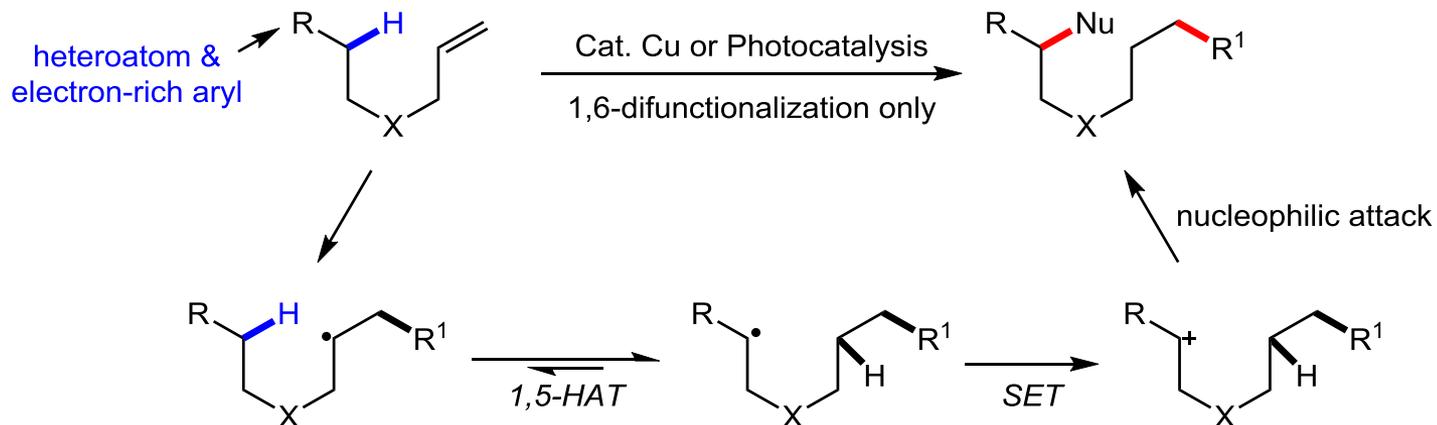
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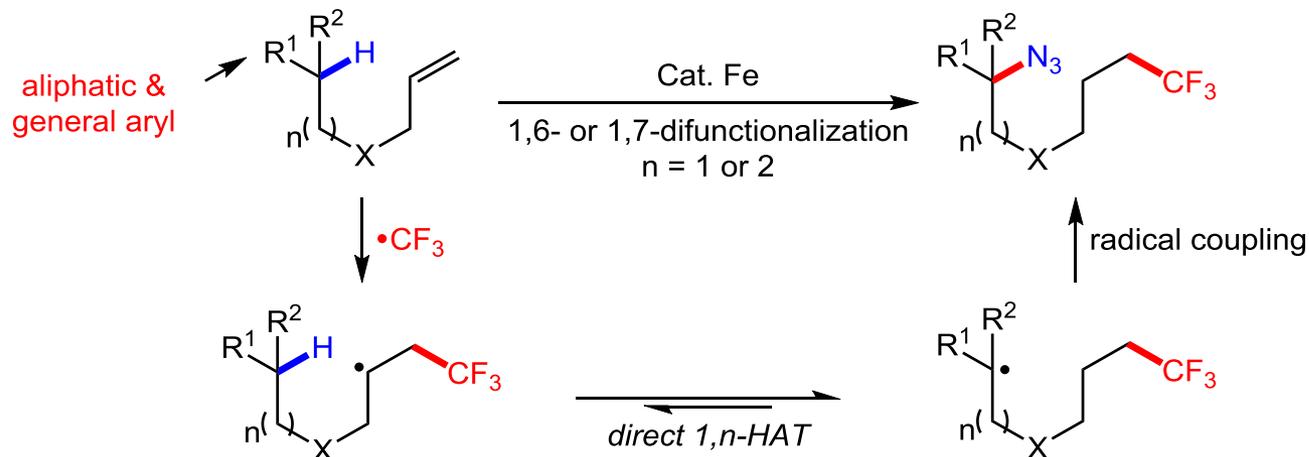
Nevado, C. *et al.* *ACS Catal.* **2018**, *8*, 6401

# Introduction

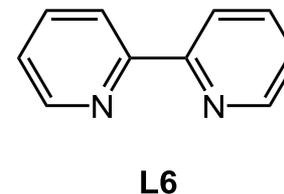
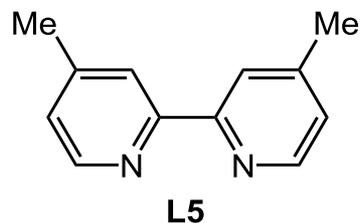
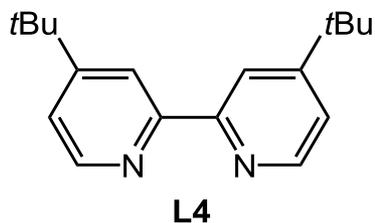
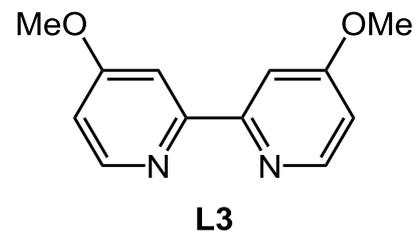
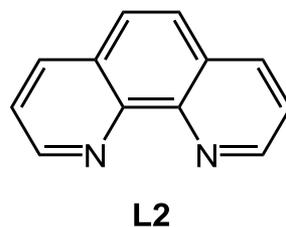
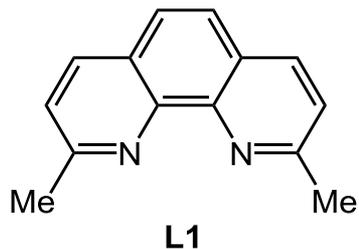
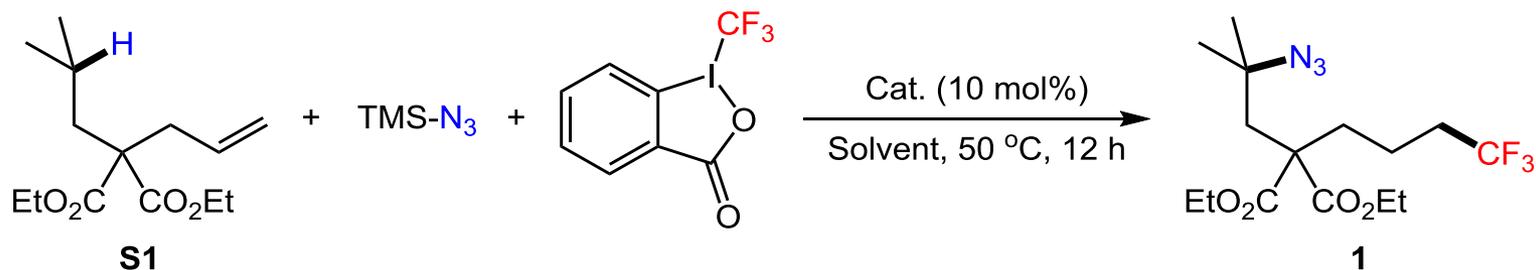
a Previous works: Selective cleavage of *relatively active* C(sp<sup>3</sup>)-H bonds



b This work: Selective cleavage of *inert* C(sp<sup>3</sup>)-H bonds



# Optimization of reaction conditions



# Optimization of reaction conditions

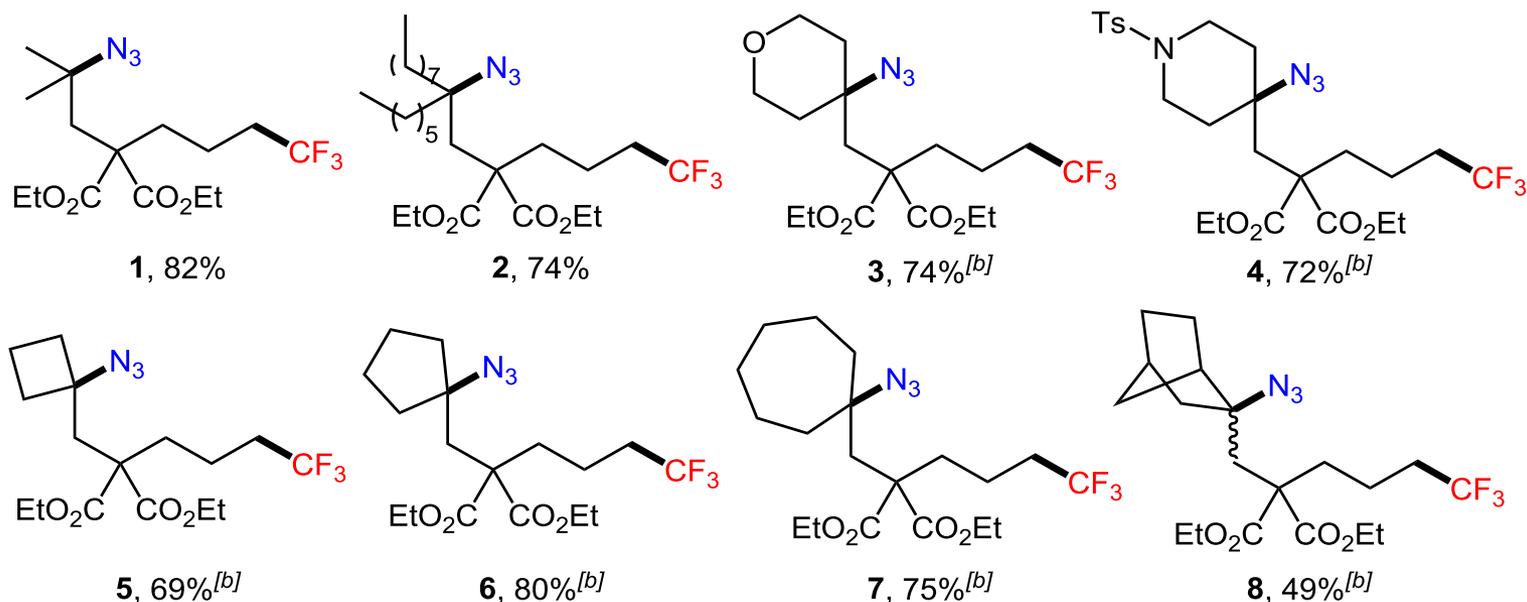
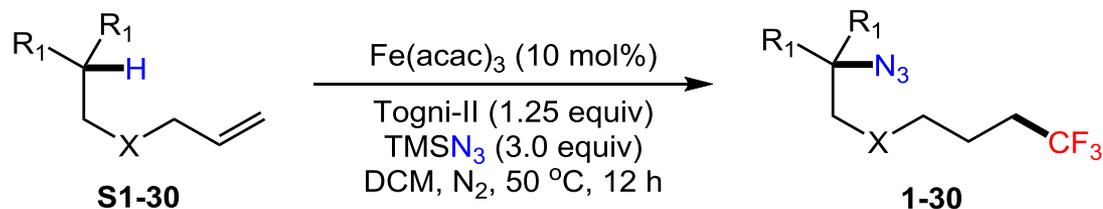
Entry <sup>a</sup>	Cat.	Ligand	Solvent	Yield [%]
1	Fe(acac) <sub>3</sub>	L1	DCM	75
2	Fe(acac) <sub>3</sub>	L2	DCM	68
3	Fe(acac) <sub>3</sub>	L3	DCM	79
4	Fe(acac) <sub>3</sub>	L4	DCM	71
5	Fe(acac) <sub>3</sub>	L5	DCM	72
6	Fe(acac) <sub>3</sub>	L6	DCM	70
7	Fe(acac) <sub>3</sub>	-	DCM	84 (82)
8	Fe(acac) <sub>3</sub>	-	DCE	82
9	Fe(acac) <sub>3</sub>	-	MeCN	73
10	Fe(acac) <sub>3</sub>	-	Toluene	55
11	Fe(acac) <sub>3</sub>	-	MeOH	Trace
12	Fe(acac) <sub>3</sub>	-	DMA	57
13	Fe(acac) <sub>3</sub>	-	1,4-dioxane	59

# Optimization of reaction conditions

Entry <sup>a</sup>	Cat.	Ligand	Solvent	Yield [%]
7	Fe(acac) <sub>3</sub>	-	DCM	84 (82)
14	Fe(OTf) <sub>2</sub>	-	DCM	18
15	Fe <sub>2</sub> (SO <sub>4</sub> ) <sub>3</sub>	-	DCM	57
16	Fe(acac) <sub>2</sub>	-	DCM	55
17	Fe(OAc) <sub>2</sub>	-	DCM	50
18	FeCl <sub>2</sub>	-	DCM	42
19	FeF <sub>2</sub>	-	DCM	72
20	-	-	DCM	0

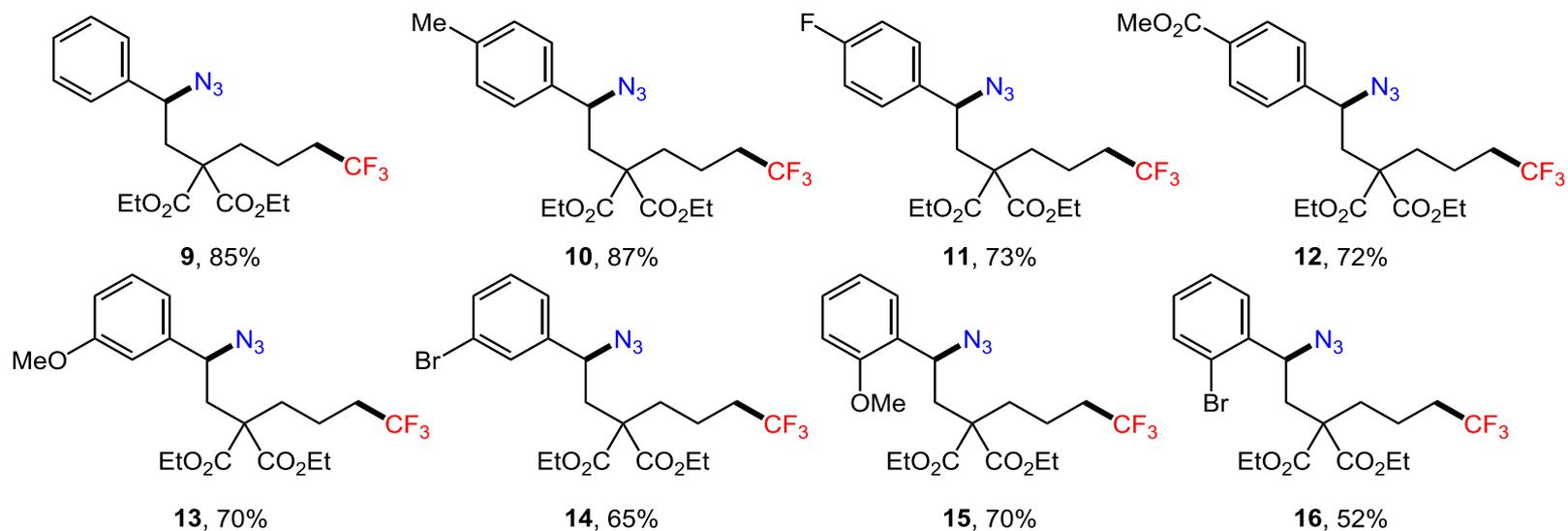
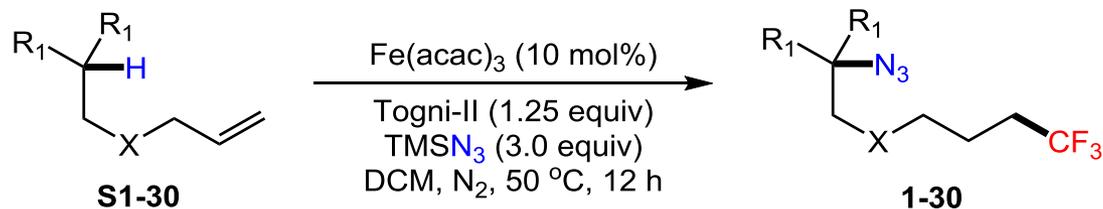
<sup>a</sup> Reaction conditions: **S1** (0.1 mmol), TMSN<sub>3</sub> (0.3 mmol), Togni-II (0.125 mmol), catalyst (10 mol%), solvent (1.0 mL), 50 °C, N<sub>2</sub>, 12 h. <sup>1</sup>H NMR yield using CH<sub>2</sub>Br<sub>2</sub> as the internal standard. Isolated yield in parantheses.

# Scope of the substrates



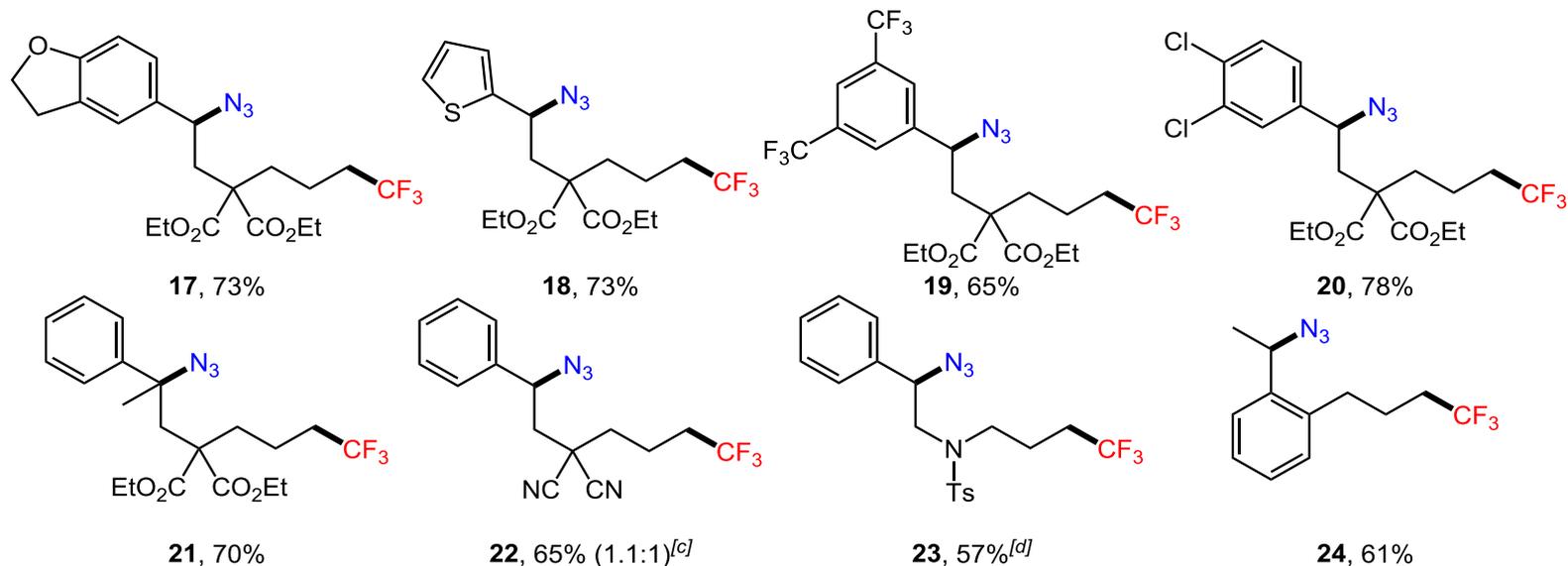
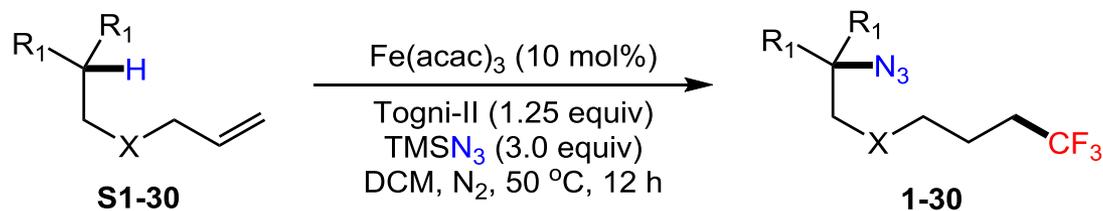
<sup>a</sup> Reaction conditions: substrate (0.2 mmol), TMSN<sub>3</sub> (3.0 equiv), Togni-II (1.25 equiv), Fe(acac)<sub>3</sub> (10 mol%), DCM (2.0 mL), N<sub>2</sub>, 50 °C, 12 h. Isolated yields. <sup>b</sup> 10 mol% of FeF<sub>2</sub> was used. <sup>c</sup> 1,6- : 1,2- = 1.1:1. <sup>d</sup> 1,4-dioxane was used as solvent.

# Scope of the substrates



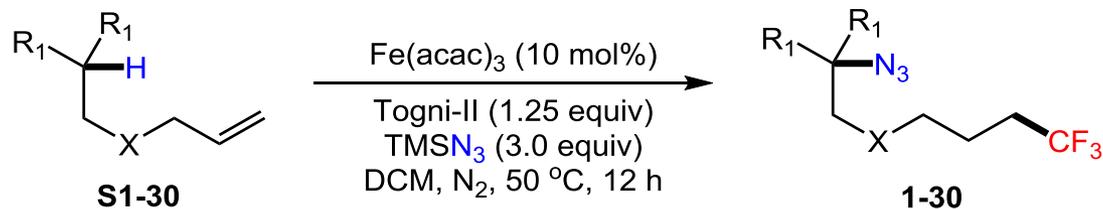
<sup>a</sup> Reaction conditions: substrate (0.2 mmol), TMSN<sub>3</sub> (3.0 equiv), Togni-II (1.25 equiv), Fe(acac)<sub>3</sub> (10 mol%), DCM (2.0 mL), N<sub>2</sub>, 50 °C, 12 h. Isolated yields. <sup>b</sup> 10 mol% of FeF<sub>2</sub> was used. <sup>c</sup> 1,6- : 1,2- = 1.1:1. <sup>d</sup> 1,4-dioxane was used as solvent.

# Scope of the substrates

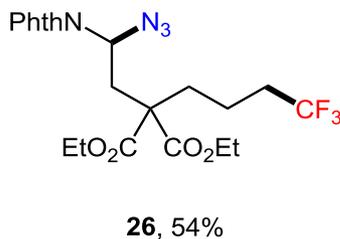
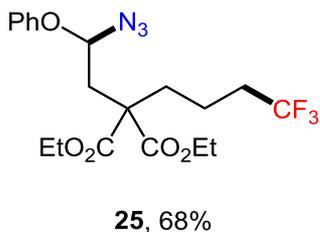


<sup>a</sup> Reaction conditions: substrate (0.2 mmol), TMSN<sub>3</sub> (3.0 equiv), Togni-II (1.25 equiv), Fe(acac)<sub>3</sub> (10 mol%), DCM (2.0 mL), N<sub>2</sub>, 50 °C, 12 h. Isolated yields. <sup>b</sup> 10 mol% of FeF<sub>2</sub> was used. <sup>c</sup> 1,6- : 1,2- = 1.1:1. <sup>d</sup> 1,4-dioxane was used as solvent.

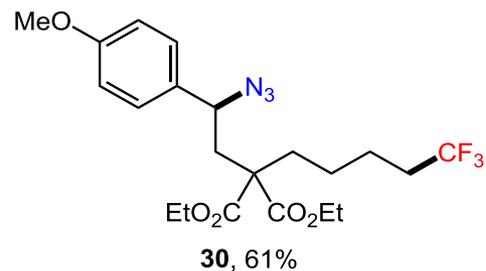
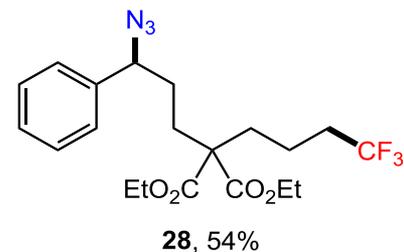
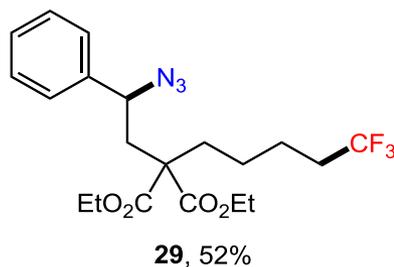
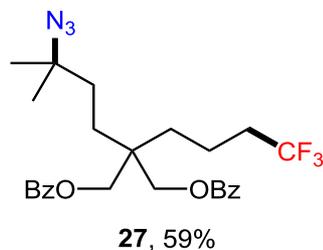
# Scope of the substrates



heteroatom-adjacent

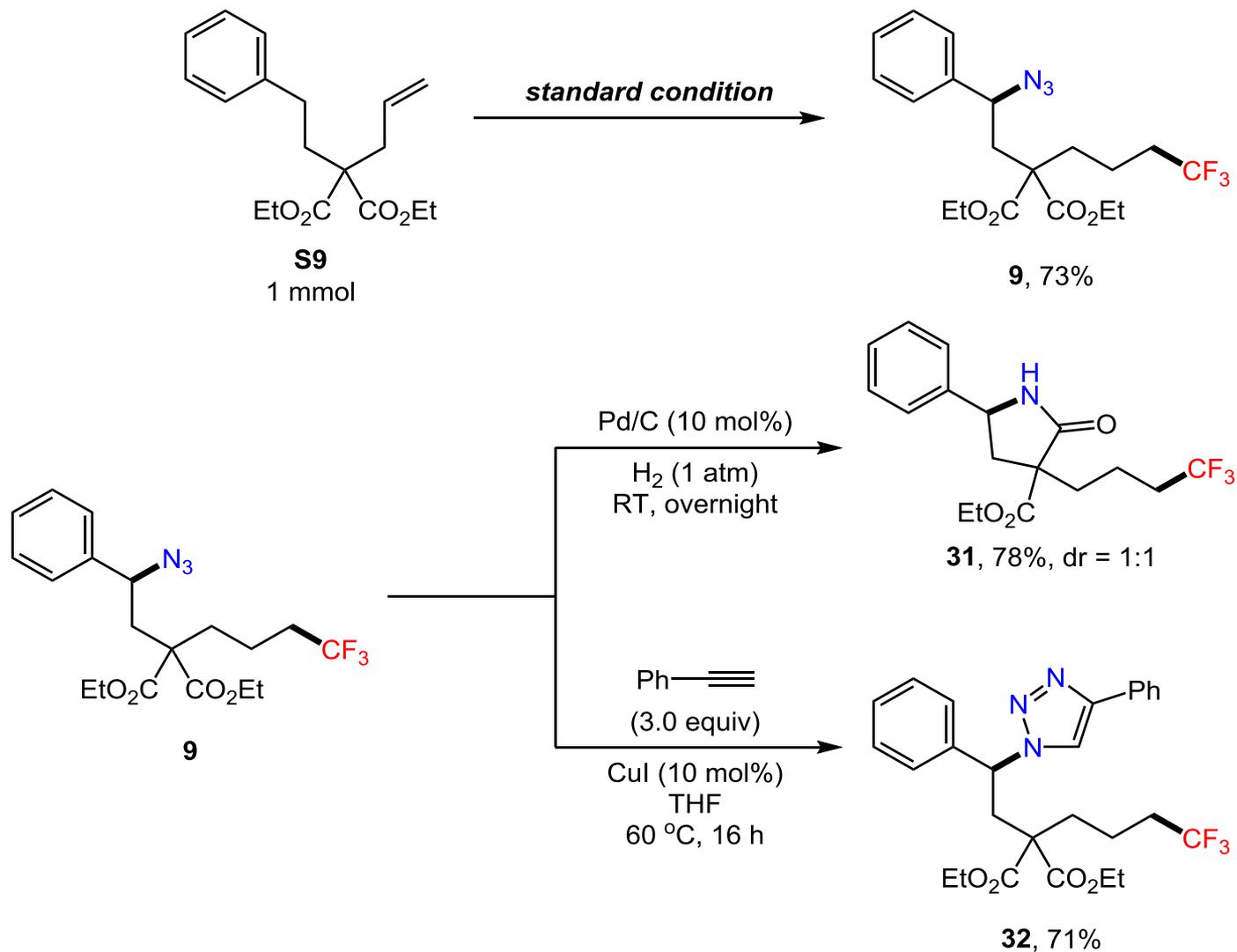


1,7-azidotrifluoromethylation

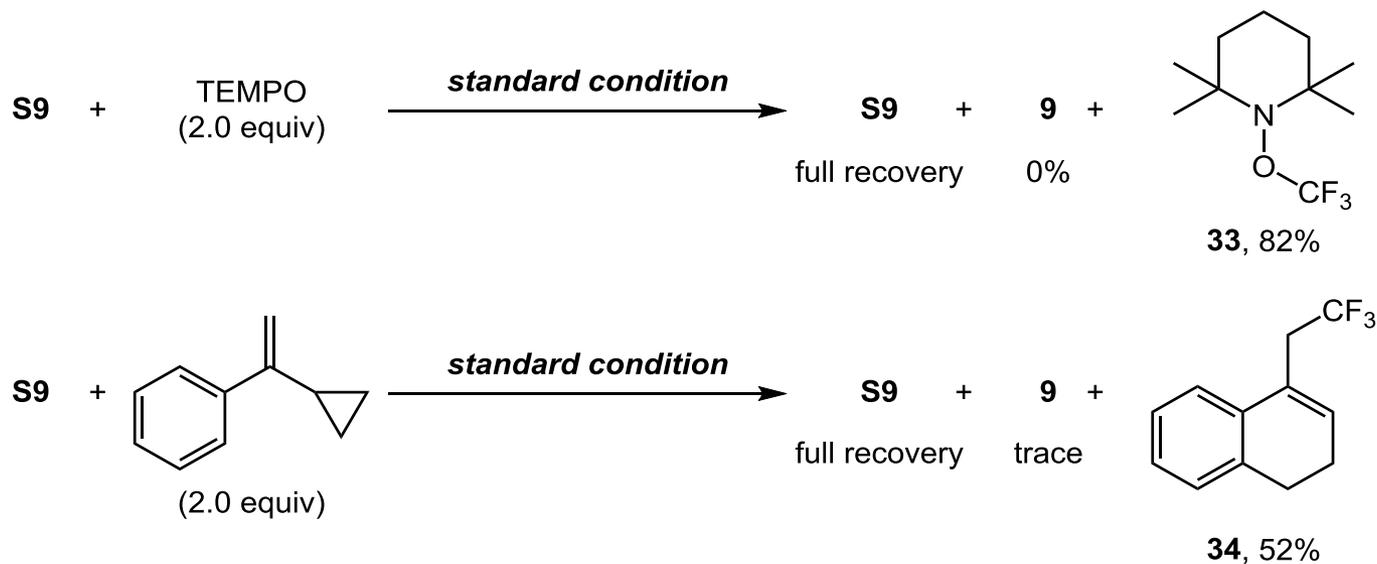


<sup>a</sup> Reaction conditions: substrate (0.2 mmol), TMSN<sub>3</sub> (3.0 equiv), Togni-II (1.25 equiv), Fe(acac)<sub>3</sub> (10 mol%), DCM (2.0 mL), N<sub>2</sub>, 50 °C, 12 h. Isolated yields. <sup>b</sup> 10 mol% of FeF<sub>2</sub> was used. <sup>c</sup> 1,6- : 1,2- = 1.1:1. <sup>d</sup> 1,4-dioxane was used as solvent.

# Scale-up reaction and derivative studies



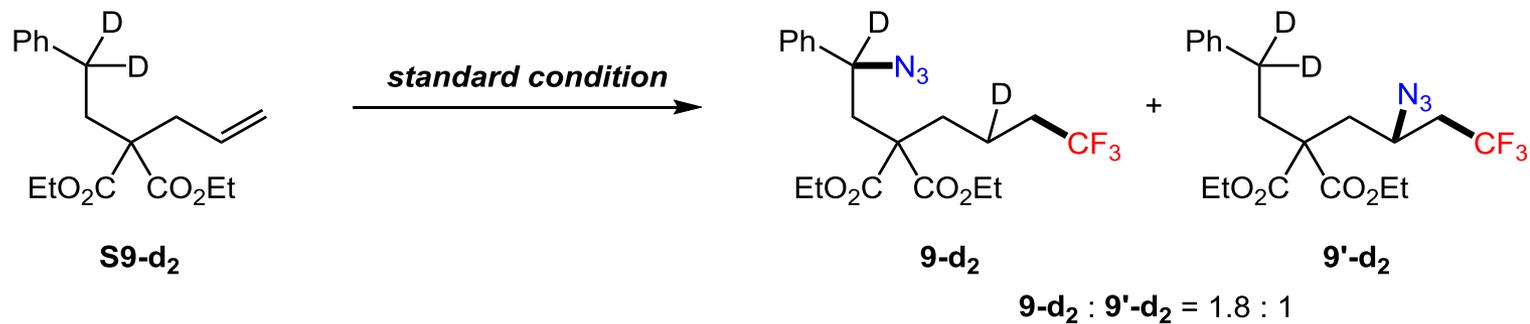
# Elementary mechanistic studies



# Deuterium labelling experiments

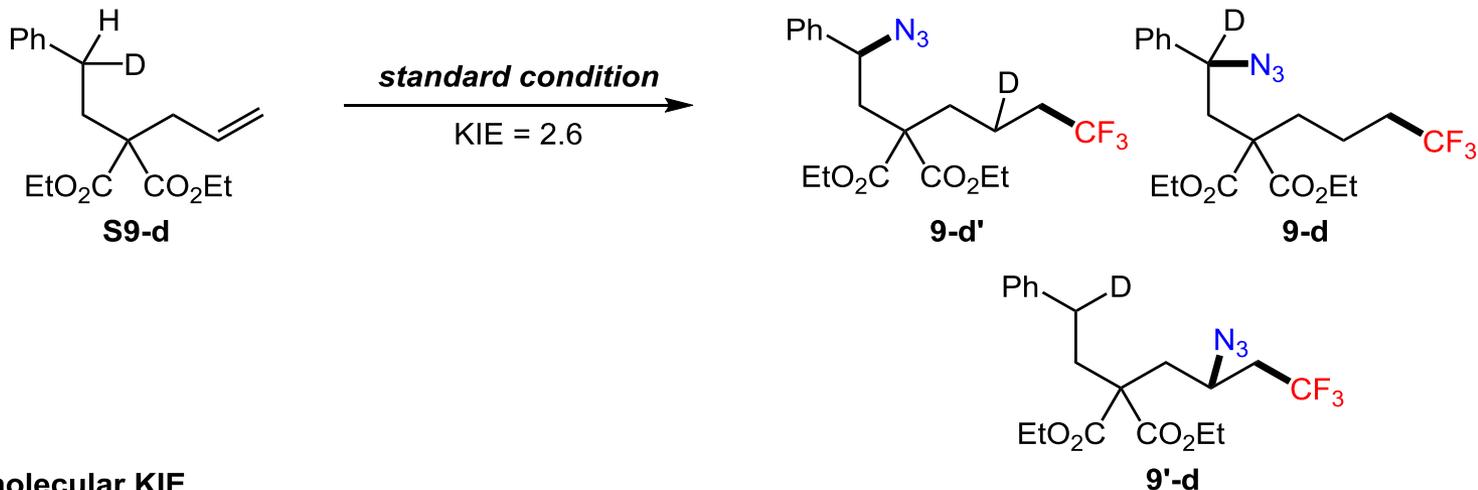
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a Radical [1,5]-deuterium transfer

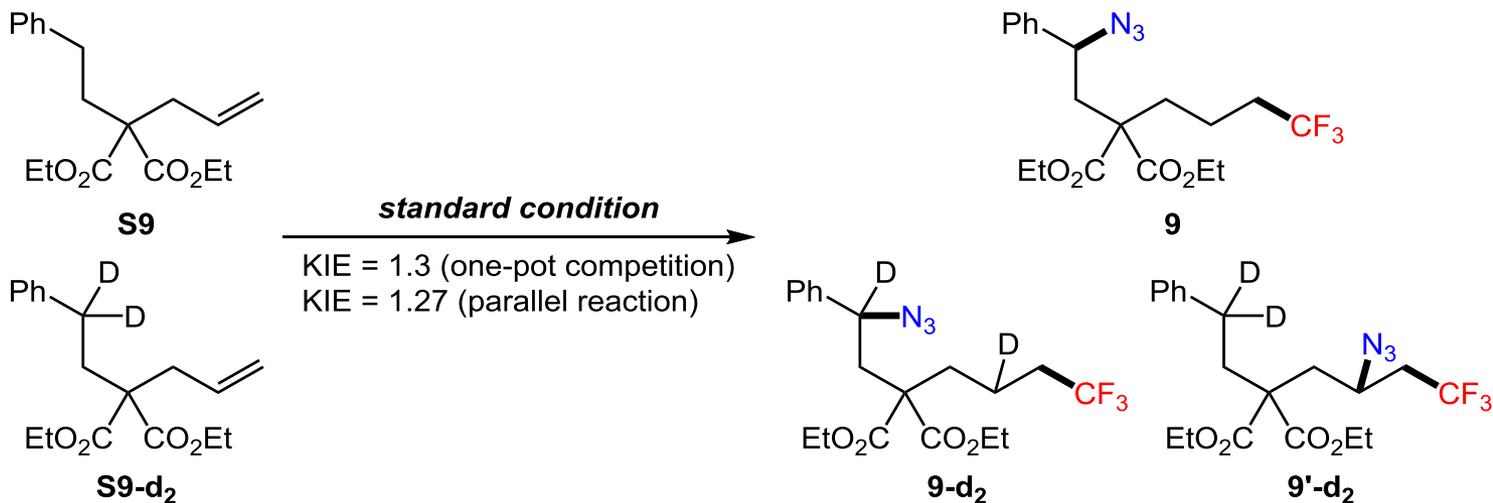


# Deuterium labelling experiments

## b Intramolecular KIE

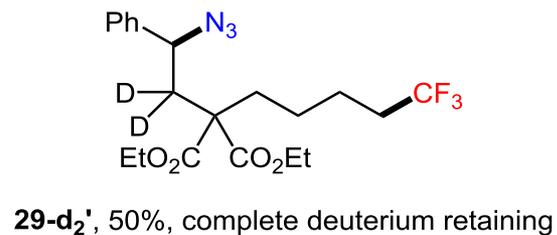
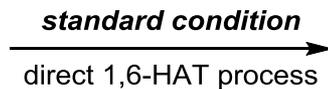
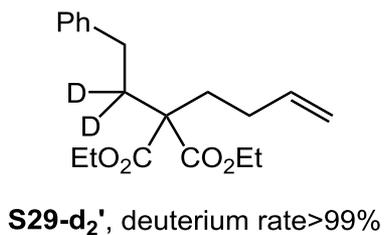
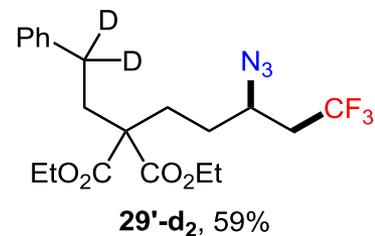
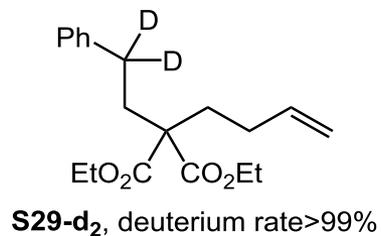


## c Intermolecular KIE

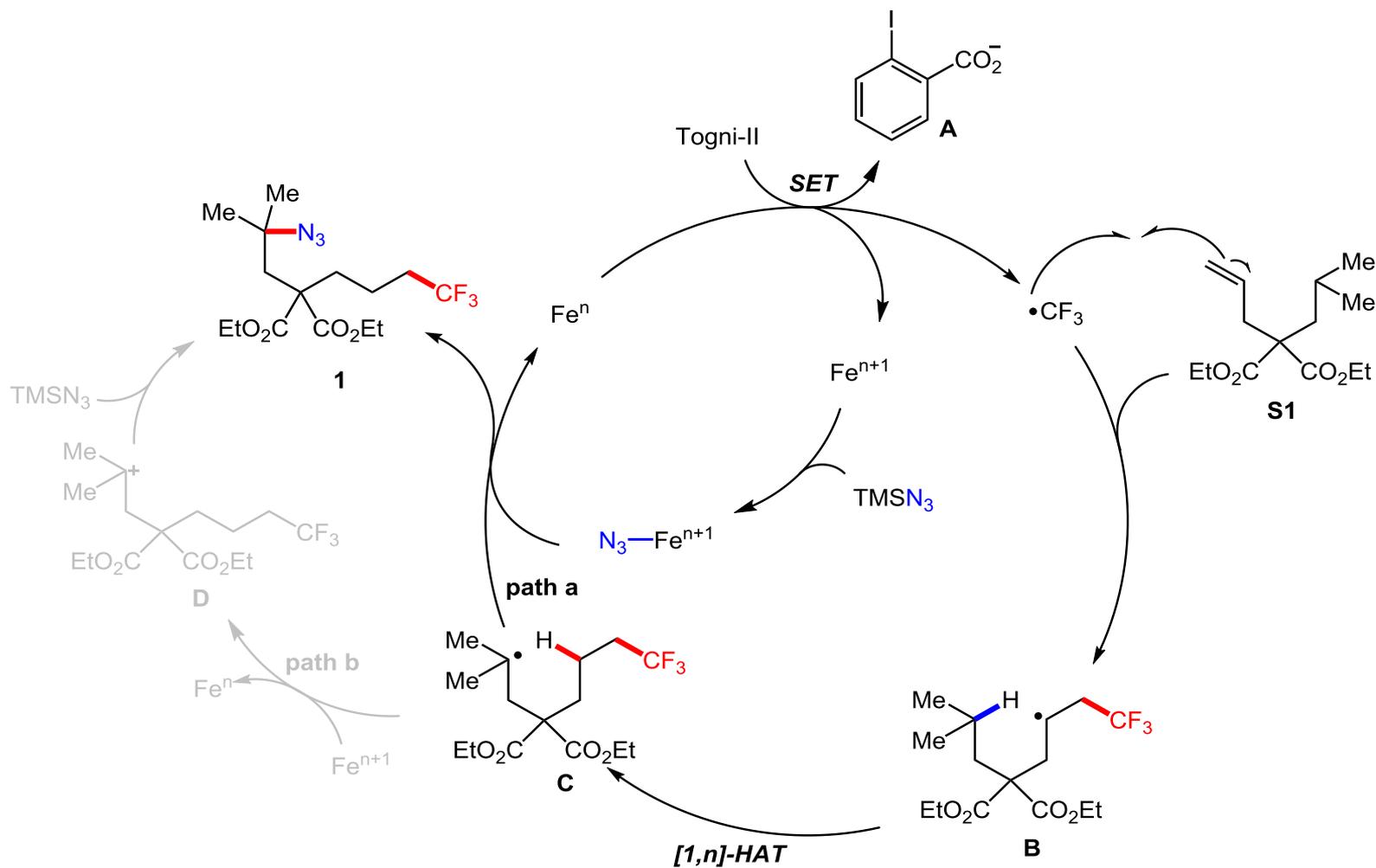


# Deuterium labelling experiments

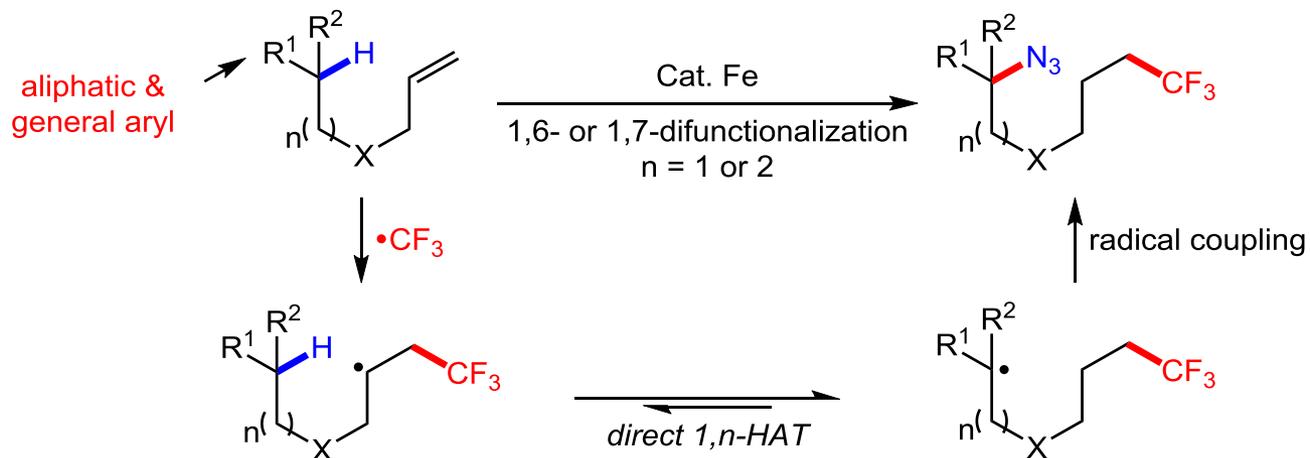
## d Direct [1,6]-hydrogen atom transfer



# Proposed mechanism



# Summary



- ◆ The first example of iron-catalyzed remote azidation of inert C(sp<sup>3</sup>)-H bonds by C-centered radical relay;
- ◆ Remote 1,6- and 1,7-azidotrifluoromethylation of alkenes;
- ◆ Highly catalytic reactivity, mild conditions, excellent functional group tolerance and great regioselectivity.

# The first paragraph

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## Writing strategy

**The importance of constructing complex functional molecules**



**The importance of transition-metal-catalyzed C-H functionalization**



**The advantages of hydrogen-atom-transfer compared to traditional C-H activation**

# The first paragraph

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The facile construction of complex functional molecules in a straightforward, efficient and practical manner from easily available materials is a major target and challenge in organic synthesis. Transition-metal-catalyzed C–H functionalization is a highly step- and atom-economic tactic to synthesise target molecules with structural complexity and diversity and it has been developed as one of the most ideal methods meeting the requirements of synthetic chemistry. Indeed, the direct functionalization of C–H bonds is emerging as a powerful strategy for retrosynthetic disconnection in the total synthesis of complex molecules, especially for the omnipresent inert C(sp<sup>3</sup>)–H bonds in basic chemical raw materials.

# The first paragraph

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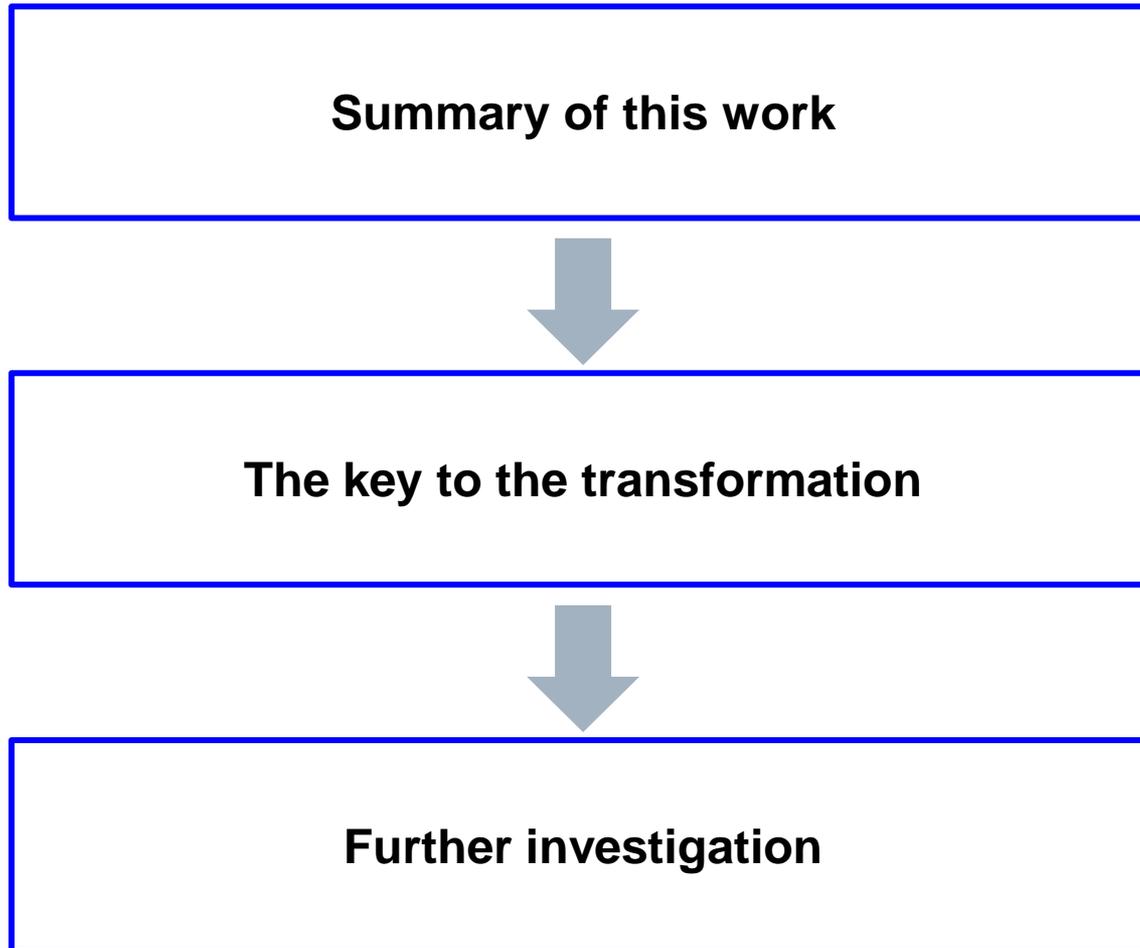
As an alternative approach to traditional C(sp<sup>3</sup>)-H activation, where metallacycles are usually formed in five-, six-membered rings and restricted mostly for vicinal functionalization of primary C(sp<sup>3</sup>)-H bonds, hydrogen-atom-transfer (HAT) through a radical pathway has been used as an efficient tool to activate the remote C(sp<sup>3</sup>)-H bond selectively.

Of note is that, as the target inert C(sp<sup>3</sup>)-H bond is almost impossible to distinguish from ubiquitous C-H bonds on the alkyl chain, 1,n (normally 1,5)-hydrogen-atom-transfer (HAT) offers a reliable solution for selective cleavage of remote C(sp<sup>3</sup>)-H bonds in a highly chemo- and site-selective fashion. In addition, the radical relay strategy offers a complementary path to direct functionalization of steric-hindered tertiary C(sp<sup>3</sup>)-H bonds, which still remains a significant challenge in traditional transition-metal-catalyzed C-H activation reactions.

# The last paragraph

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## Writing strategy



# The last paragraph

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In summary, we have developed the first example of iron-catalyzed remote azidation of inert C(sp<sup>3</sup>)–H bonds by sp<sup>3</sup> C-centered radical relay; remote 1,6- and 1,7-azidotrifluoromethylation of alkenes were successfully achieved. This method demonstrates high catalytic reactivity, mild conditions, excellent functional group tolerance and great regioselectivity. The key to the transformation is that iron plays the dual role of a radical initiator to promote the generation of CF<sub>3</sub>· and a terminator where iron<sup>III</sup>–azide can oxidize the *in situ* generated remote carbon radical and incorporate the azide functionality via azido–ligand-transfer. Deuterium studies revealed the direct 1,n- (n = 5, 6) HAT process. Further investigation of functionalization on fully linear chains and utilization of this strategy to construct potentially bioactive molecules is still underway in our laboratory.

# Representative examples

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This azidotrifluoromethylation was achieved in an iron-catalyzed system, **demonstrating** high catalytic reactivity, mild conditions, and excellent regioselective control (mostly >20 : 1). (表现)

Our study **commenced with** diethyl 2-allyl-2-isobutylmalonate S1 as the pilot substrate, Togni-II agent as the trifluoroalkylating reagent and TMSN3 as the azide source in the presence of a catalytic amount of iron salts. (以…开始)

It was found that **a significant amount of** 1,2-difunctionlizational byproducts was generated. (大量的)

**Collectively**, these results demonstrated that the C–H cleavage through HAT is not reversible and this step is not the rate determining step. (总而言之)

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***Thanks  
for your attention***