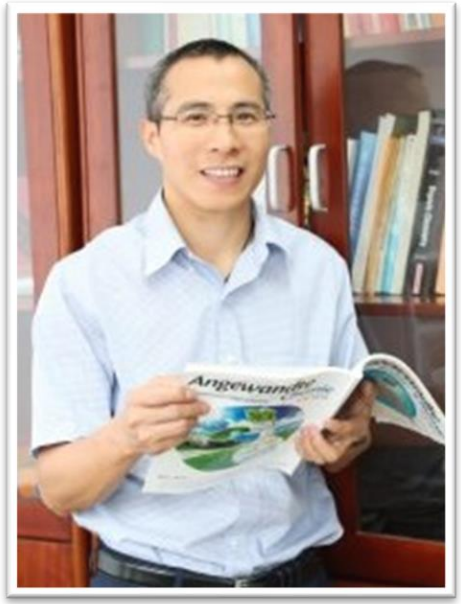
Literature Report 8

Cu(I)-Catalyzed Chemo- and Enantioselective Desymmetrizing C-O Bond Coupling of Acyl Radicals

Reporter: Han Wang
Checker: Shan-Shan Xun
Date: 2023.04.17

Yu, Z.-L.; Liu, X.-Y.* *et al*. *J. Am. Chem. Soc.* **2023**, *145*, 6535-6545.

CV of Dr. Xin-Yuan Liu



Background:

- **1997-2001** B.S., Anhui Normal University
- **2001-2004** M.S., SIOC
- **2006-2010** Ph.D., University of Hong Kong
- **2010-2012** Postdoc., The Scripps Research Institute
- **2012-2018** Associate Prof., Southern University of Science and Technology
- **2018-now** Full Professor, Southern University of Science and Technology

Research:

✓ **Design of Cu/Chiral Anion Catalysis for Radical-Initiated Asymmetric Chemistry**.

Contents

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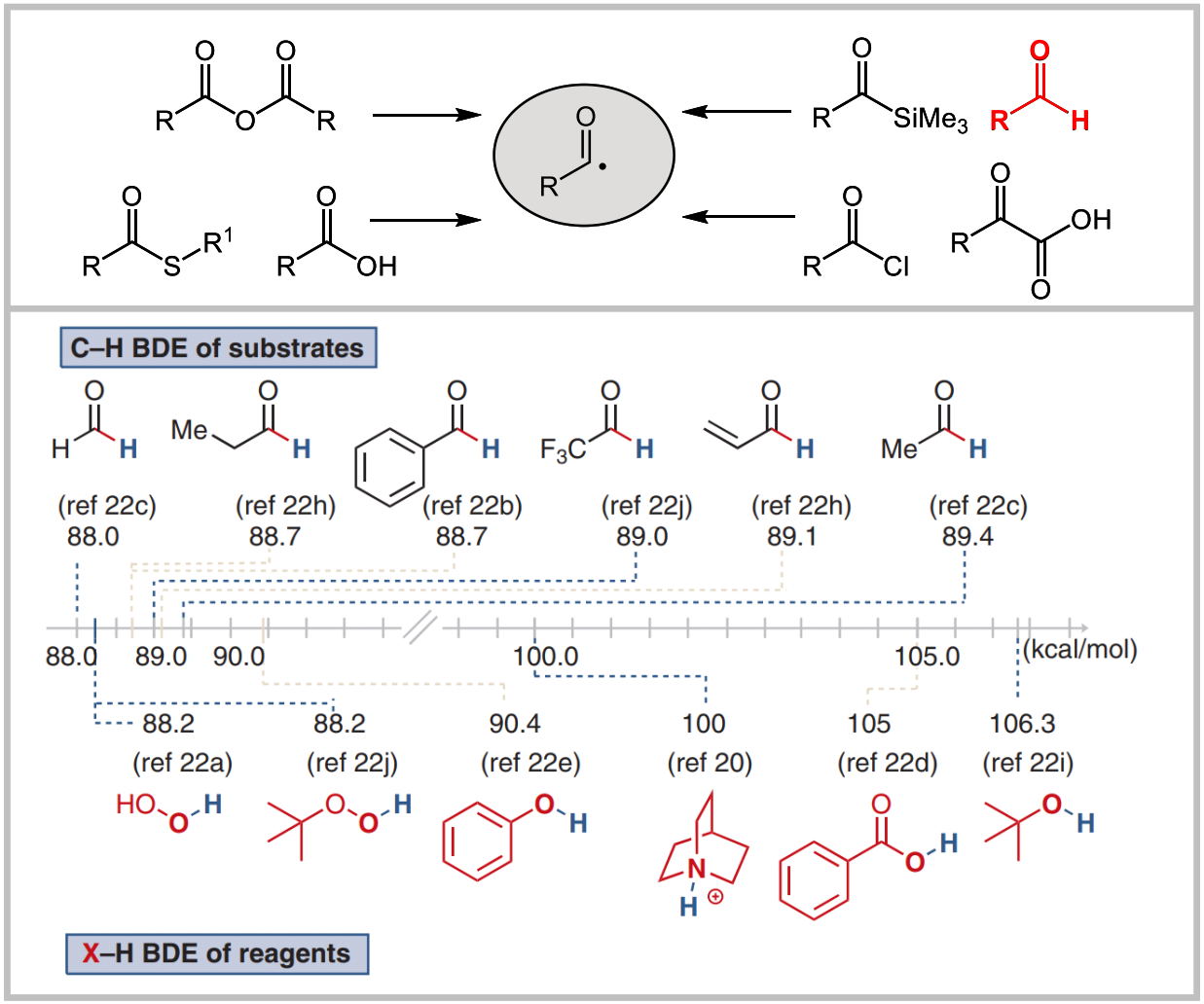

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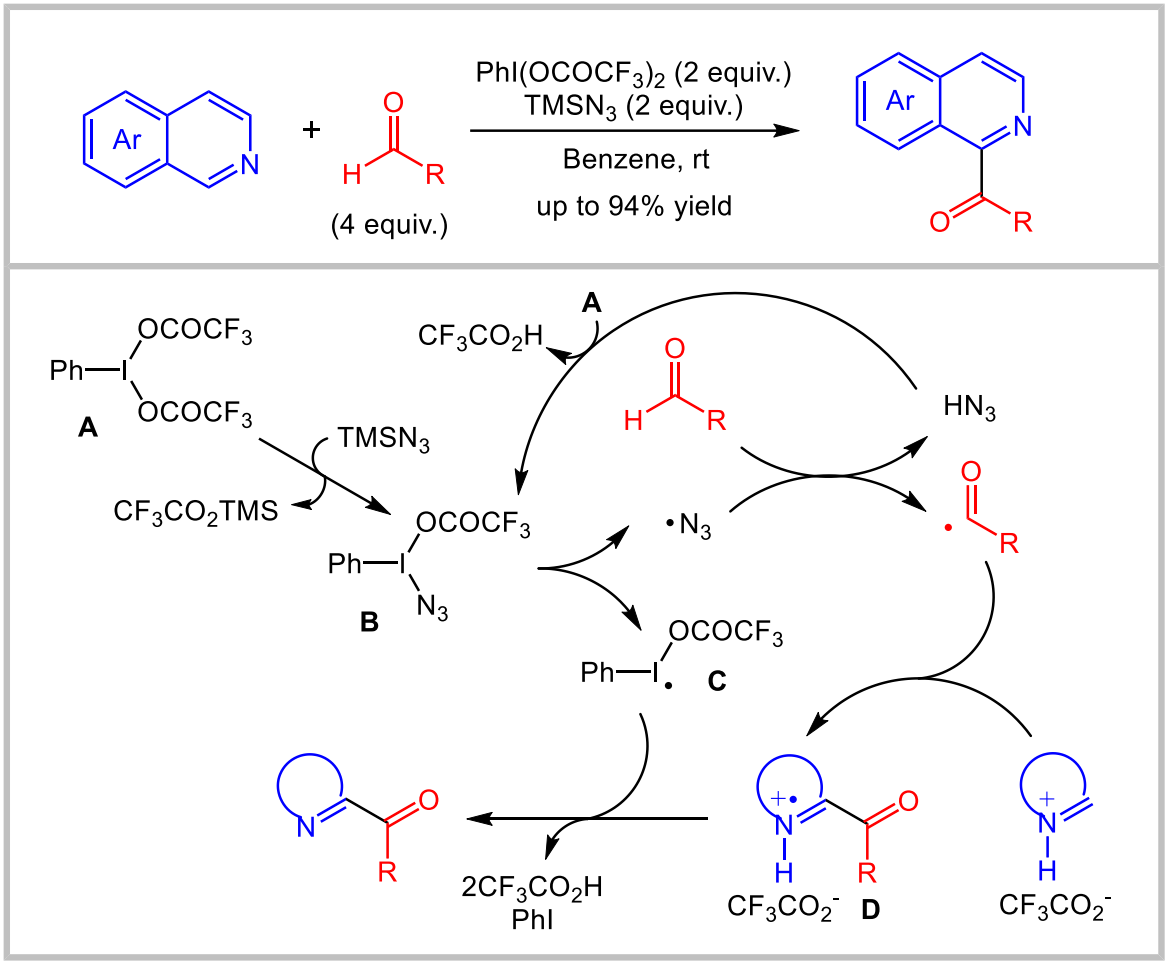
Introduction

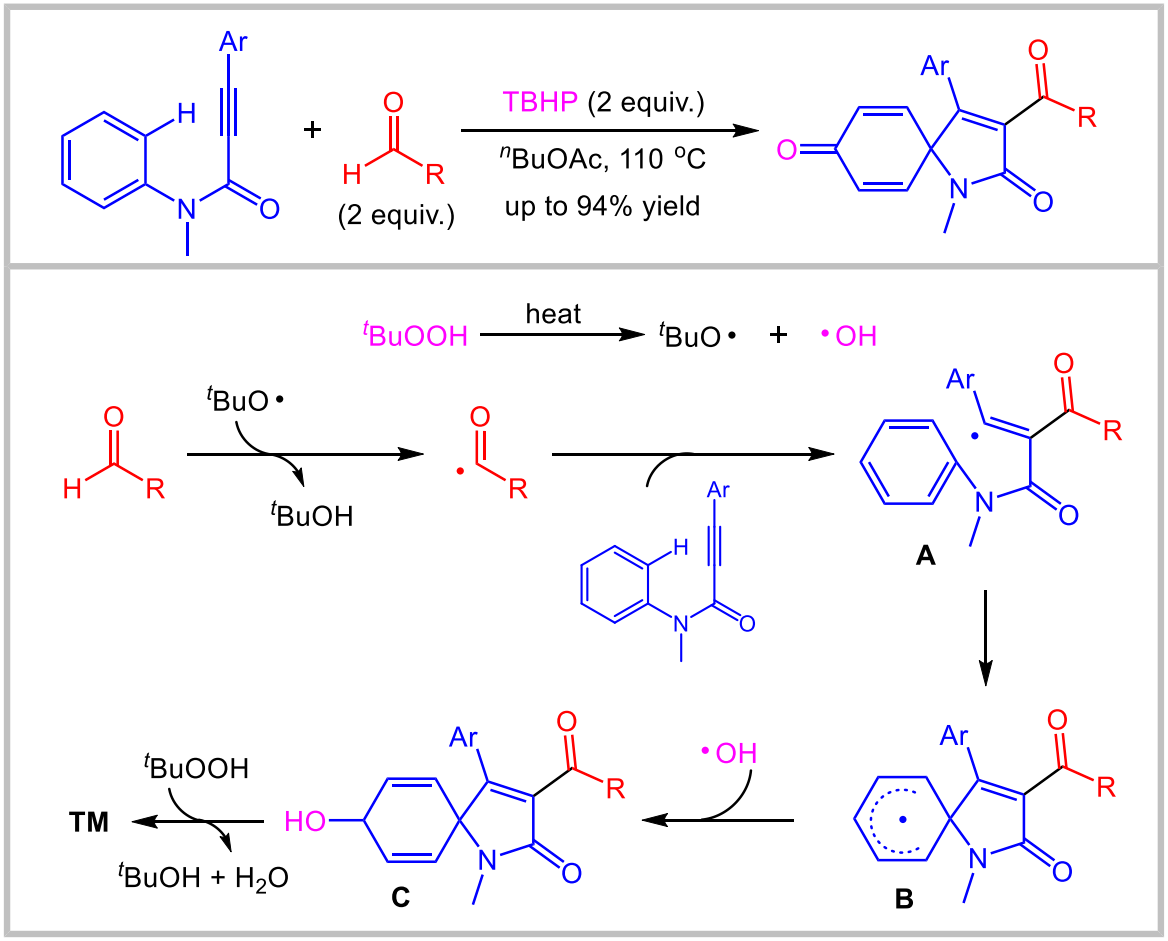
Acyl Radicals Generated by Thermal Means



Matcha, K.; Antonchick, A. P. *Angew. Chem. Int. Ed.* **2013**, *52,* 2082.

Introduction

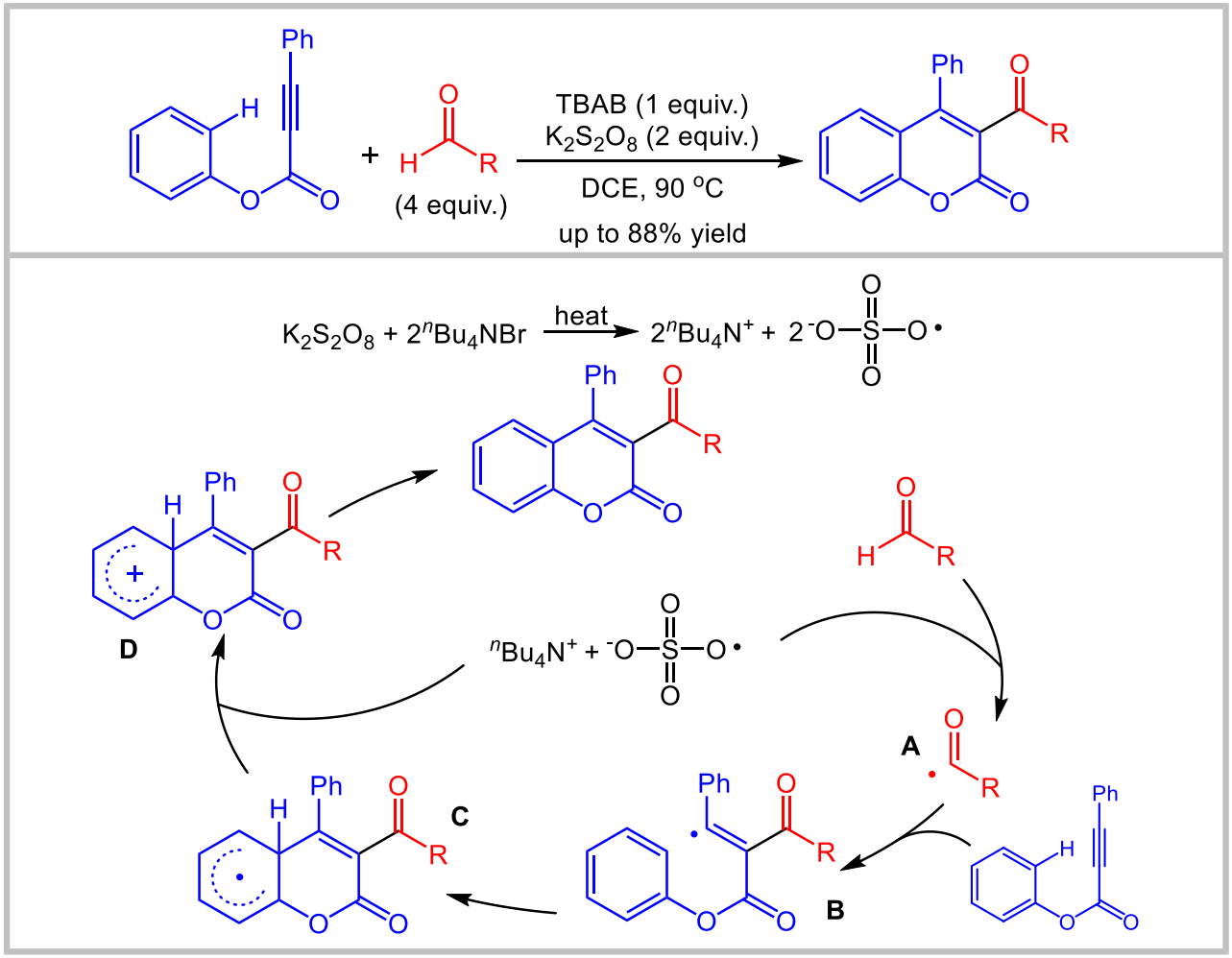
Acyl Radicals Generated by Thermal Means



Ouyang, X.-H.; Li, J.-H. *J. Org. Chem.* **2014**, *79,* 4582.

Introduction

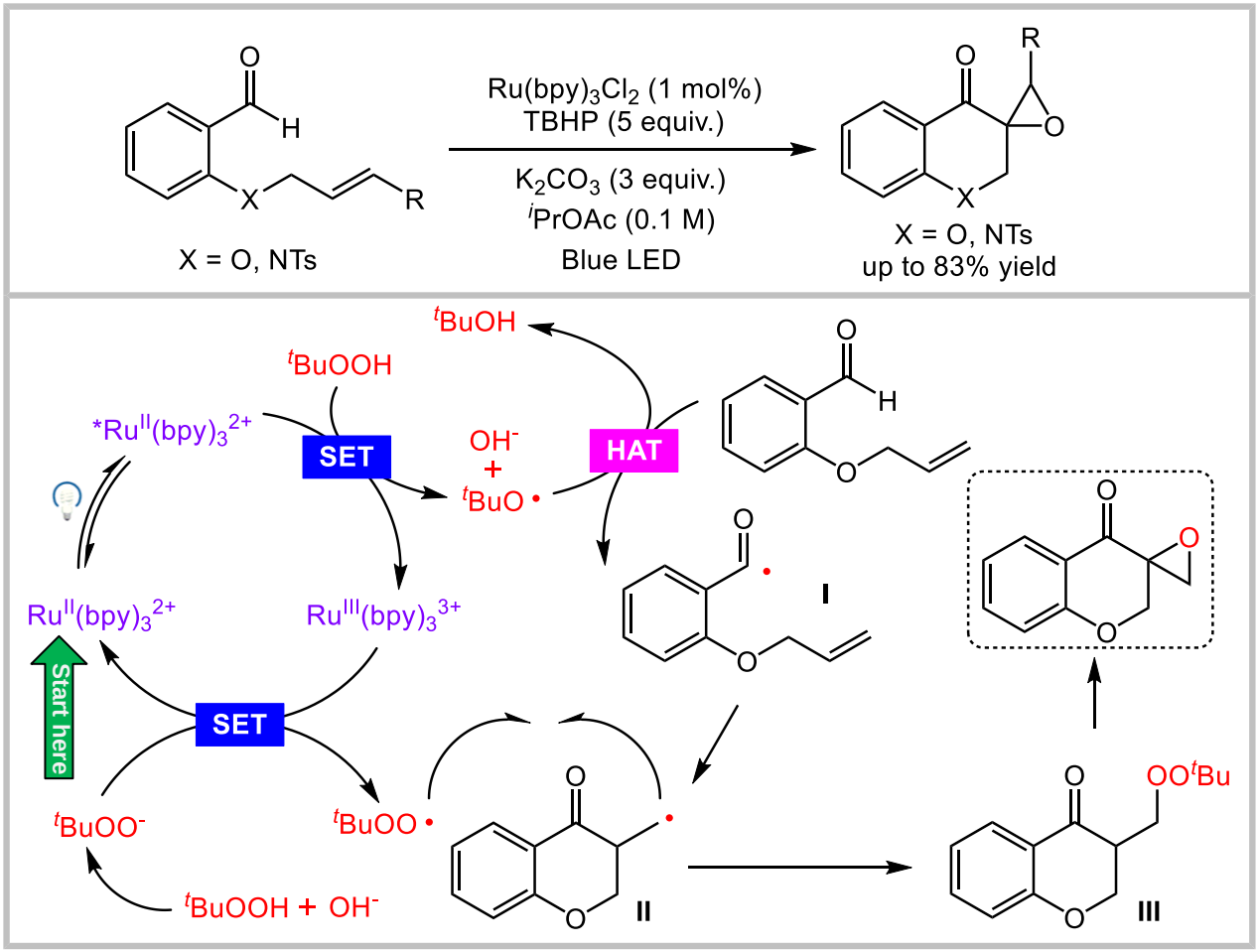
Acyl Radicals Generated by Thermal Means



Wu, Y.-J.; Mi, X. *J. Org. Chem.* **2015**, *80*, 148.

Introduction

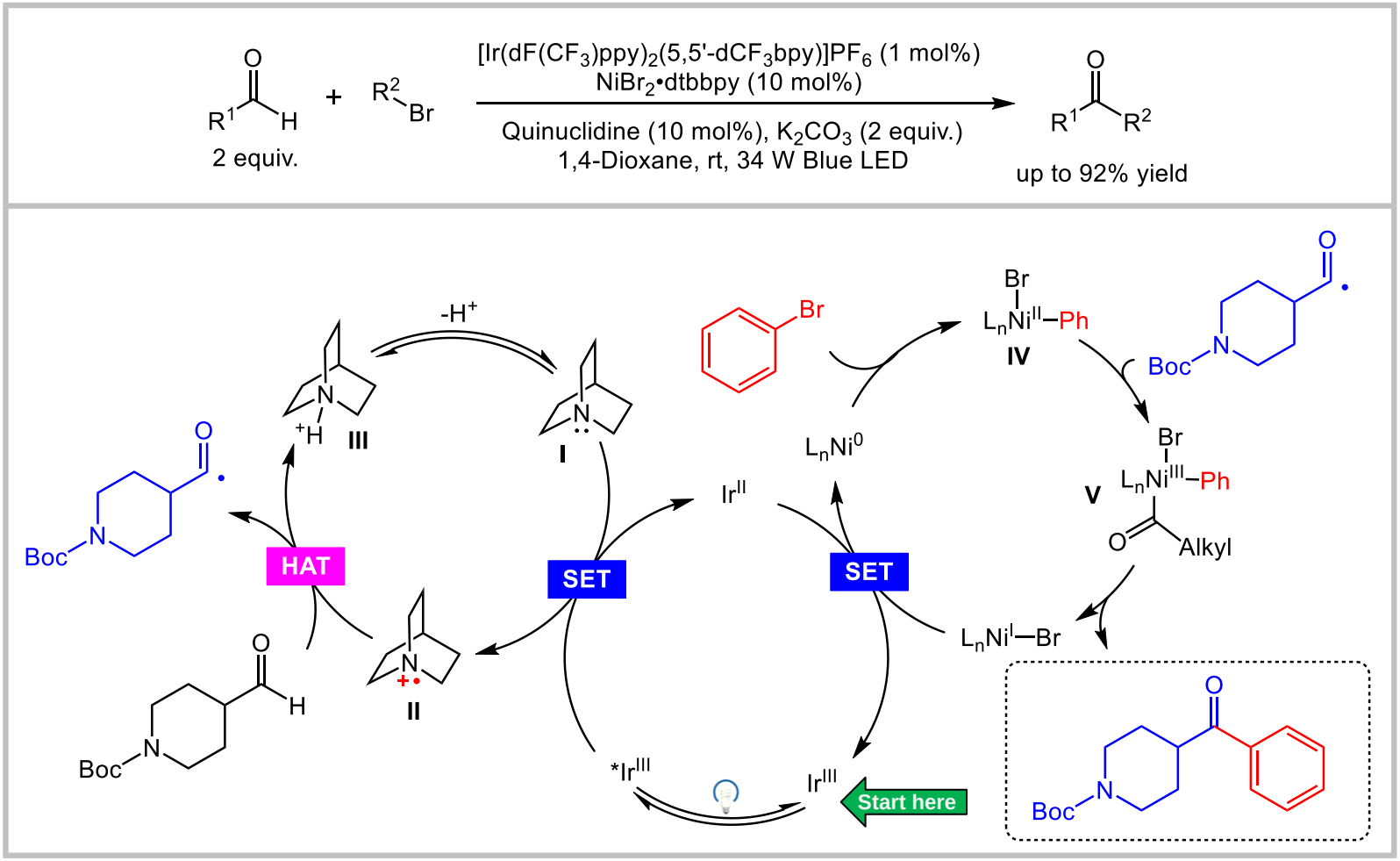
Acyl Radicals Generated by Visible-light Photocatalysis



Jung, S.; Hong, S. *Adv. Synth. Catal.* **2017**, *359*, 3945.

Introduction

Acyl Radicals Generated by Visible-light Photocatalysis



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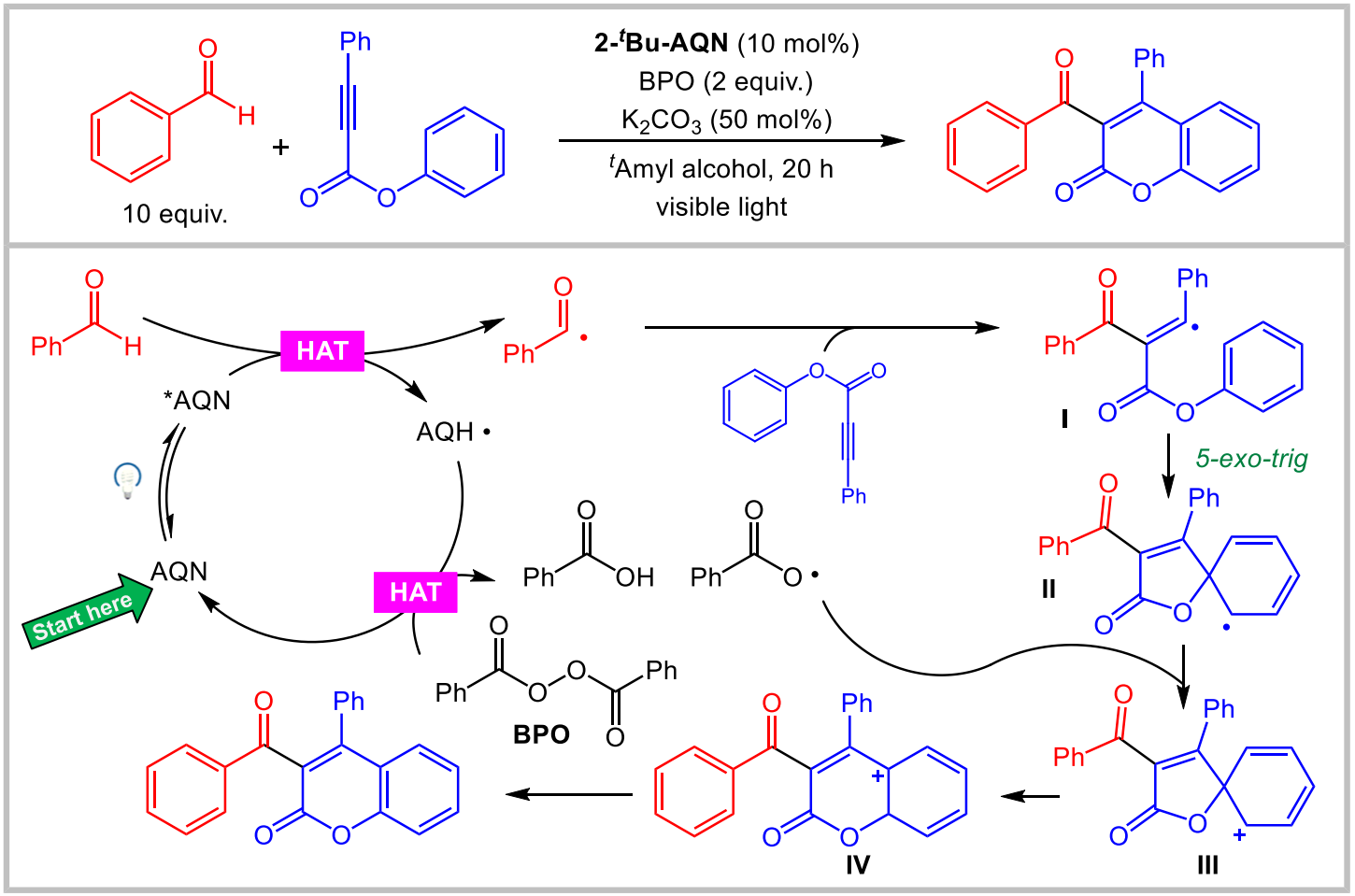
Introduction

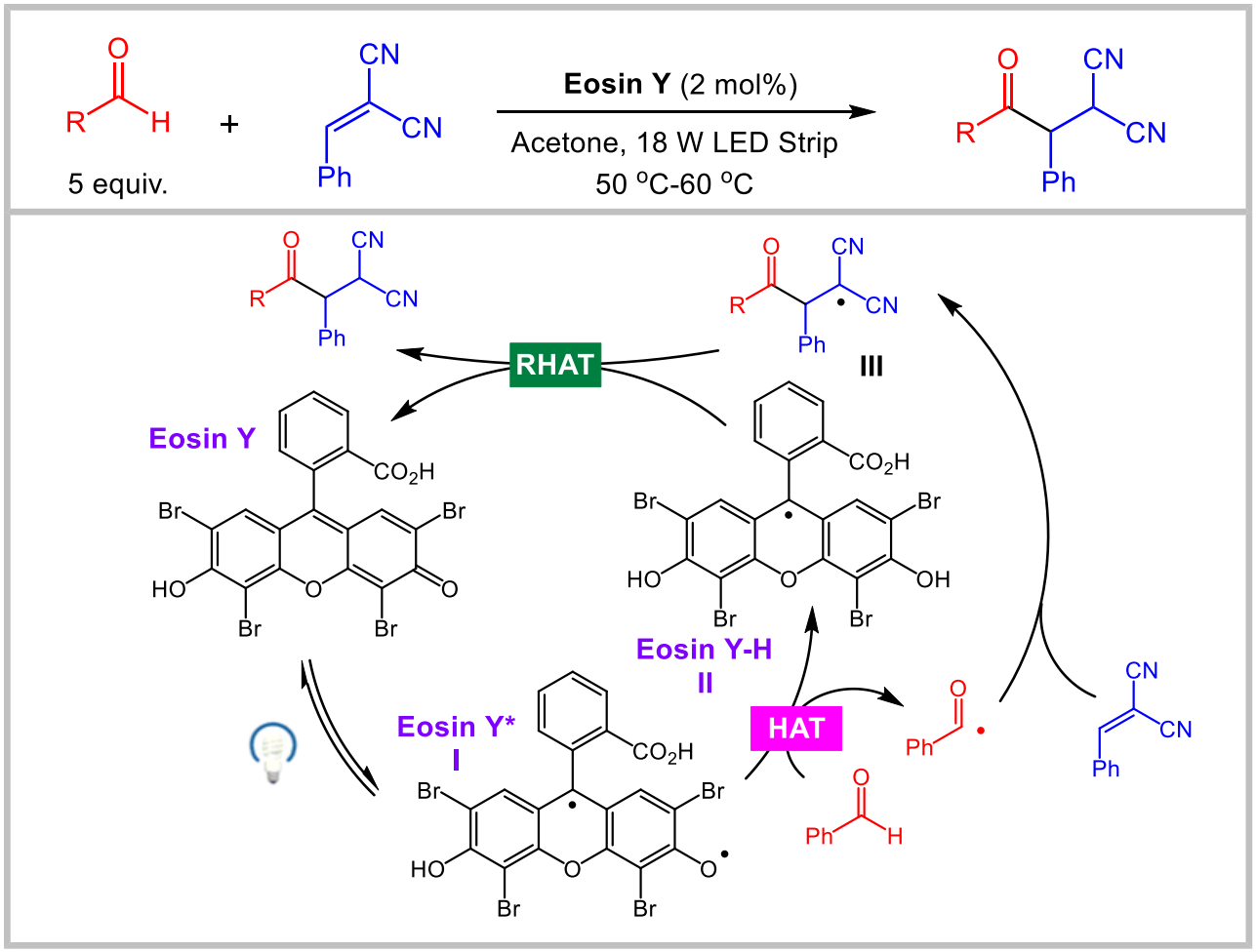
Acyl Radicals Generated by Visible-light Photocatalysis



Kawaai, K.; Itoh, A. *J. Org. Chem.* **2018**, *83*, 1988.

Introduction

Acyl Radicals Generated by Visible-light Photocatalysis



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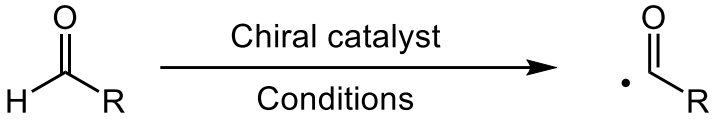
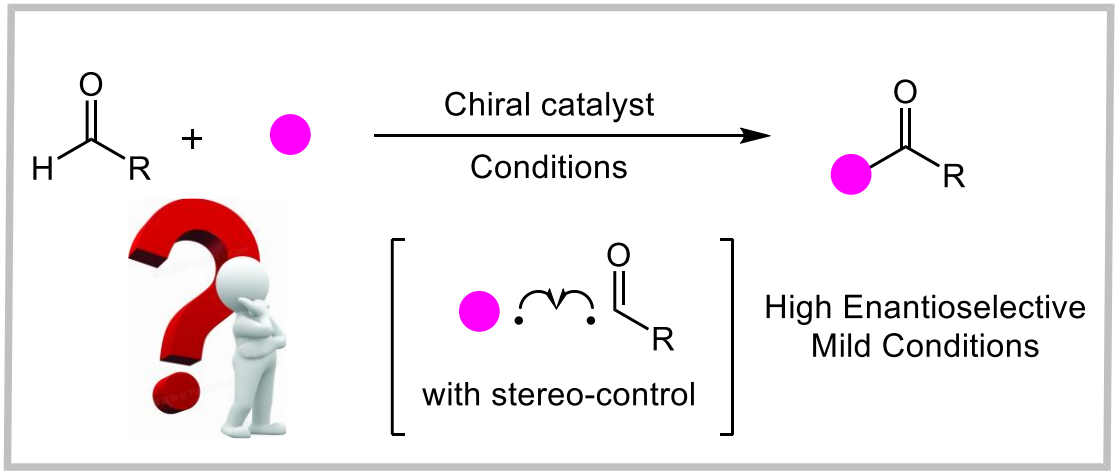
Introduction

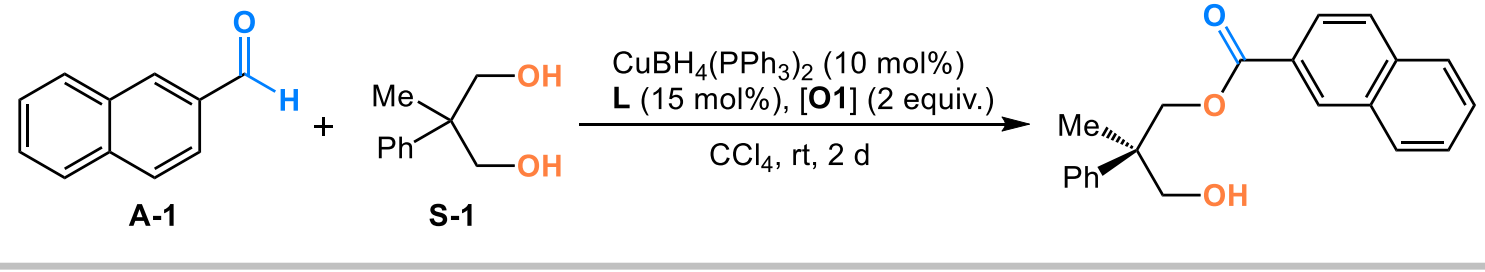


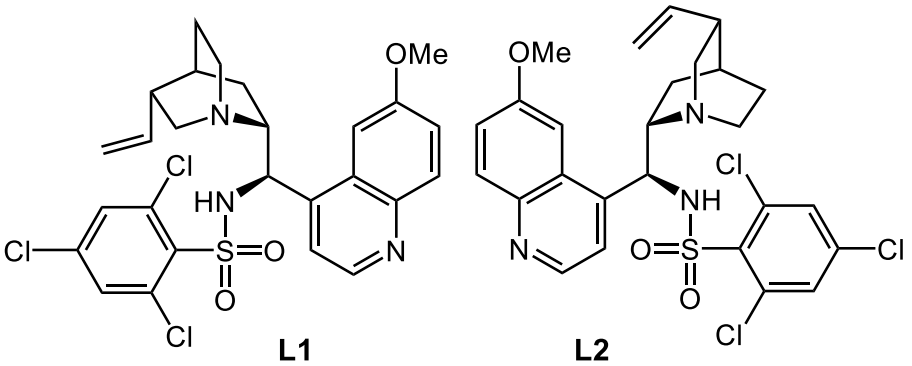
High Atom Economy
Ready Availability
High Stability

High Reaction Temperature
Finite Asymmetric Versions



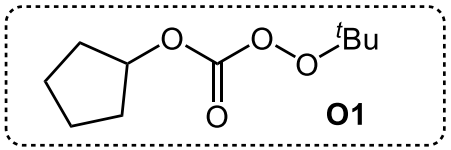
Optimization of Reaction Parameters

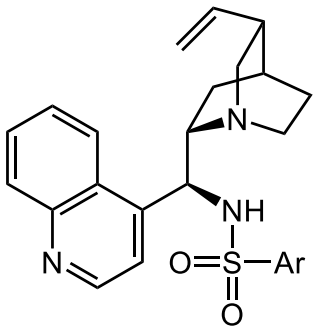




76% yield, 93% ee

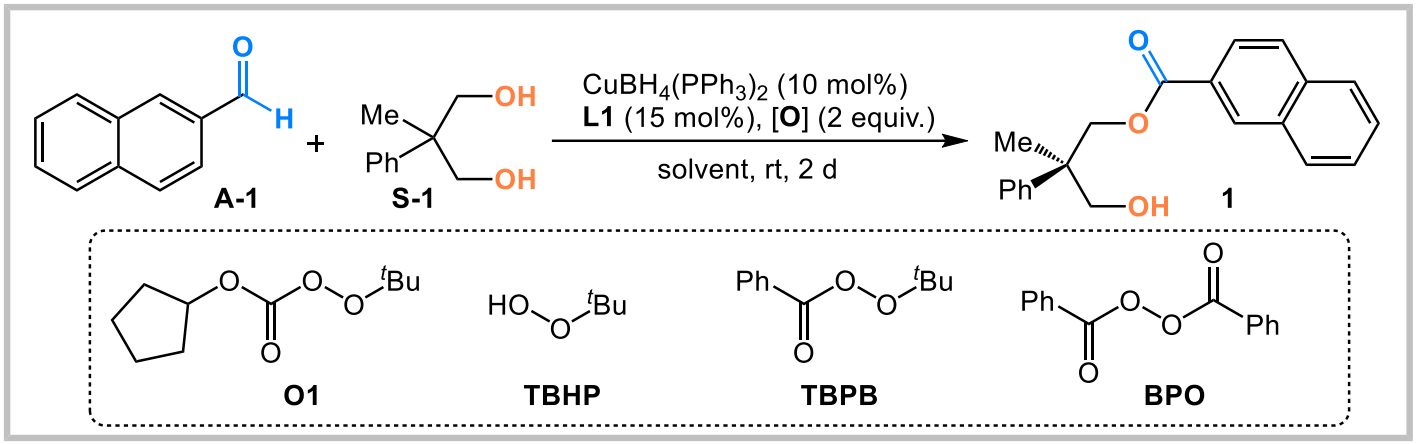
68% yield, 89% ee





L3, Ar = Ph	46% yield, -72% ee
L4, Ar = 4-NO_2Ph	30% yield, -73% ee
L5, Ar = 2,4,6-Me_3Ph	67% yield, -86% ee
L6, Ar = 2,4,6-F_3Ph	60% yield, -83% ee
L7, Ar = 2,4,6-Cl_3Ph	67% yield, -87% ee

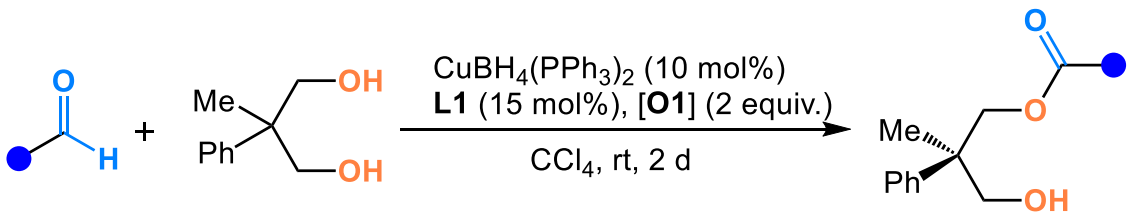
Optimization of Reaction Parameters

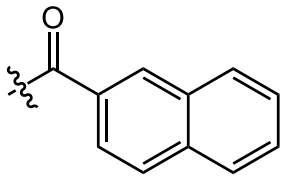


Entry[a]	[O]	Solvent	Yield [%]	Ee [%]
1	**O1**	DCM	6	80
2	**O1**	EA	8	85
3	**O1**	MTBE	9	61
4	**O1**	$CHCl_3$	trace	-
5	**O1**	CCl_4	76	93
6	TBHP	CCl_4	30	38
7	TBPB	CCl_4	17	69
8	BPO	CCl_4	trace	-

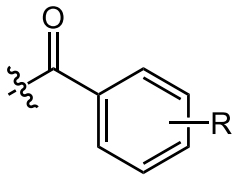
[a] The reaction was conducted with **A-1** (0.2 mmol), **S-1** (1.5 equiv.), $CuBH_4(PPh_3)_2$ (10 mol%), **L** (15 mol%), and [**O**] (2.0 equiv) in anhydrous solvent (4 mL) at rt for 2 days under Ar. Yield was based on ^1H NMR analysis of the crude product using 1,3,5-trimethoxybenzene as an internal standard; ee values were based on chiral HPLC analysis.

Scope of Aldehydes

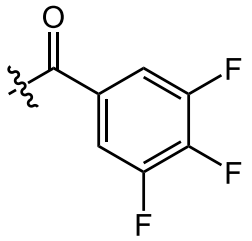




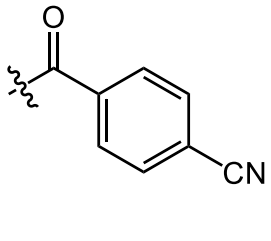
1, 72%, 93% ee



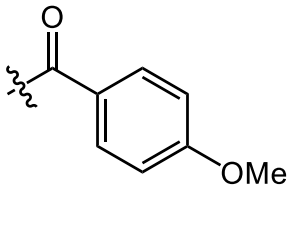
2, R = H, 86%, 92% ee
3, R = 4-Me, 81%, 93% ee
4, R = 3-Me, 84%, 93% ee
5, R = 2-Me, 68%, 90% ee
6, R = 4-F, 80%, 93% ee
7, R = 4-Cl, 80%, 94% ee
8, R = 4-Br, 75%, 93% ee
9, R = 3-Br, 63%, 92% ee
10, R = 4-I, 76%, 93% ee
11, R = 2-I, 20%, 90% ee



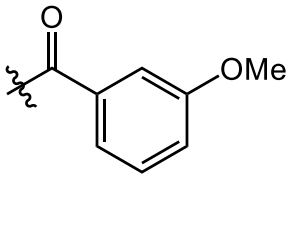
12, 68%, 93% ee



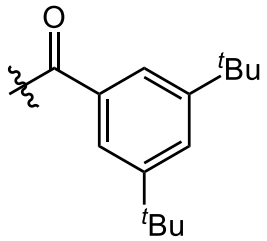
13, 68%, 84% ee



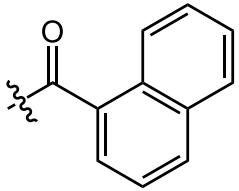
14, 76%, 92% ee



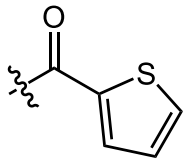
15, 79%, 93% ee



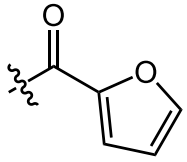
16, 76%, 88% ee



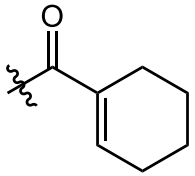
17, 69%, 85% ee



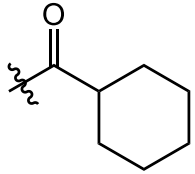
18, 80%, 94% ee



19, 58%, 92% ee

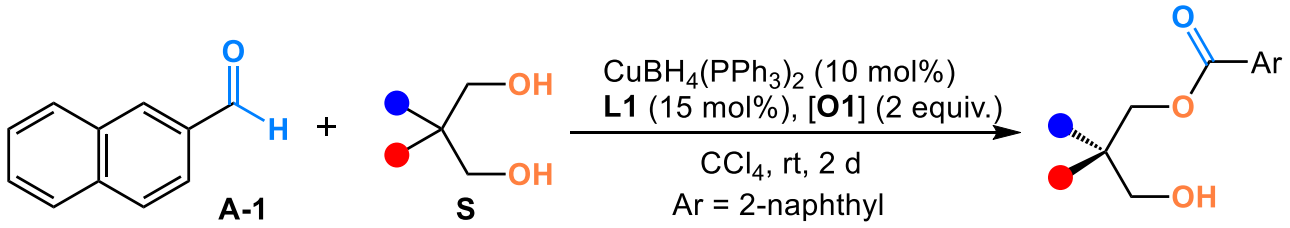


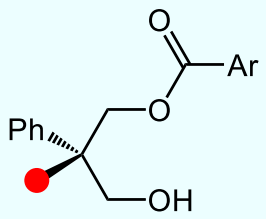
20, 62%, 86% ee

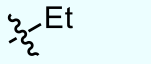


21, 59%, 79% ee

Scope of 1,3-Diols

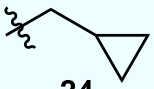




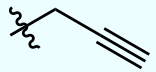


22
76%, 93% ee

23
89%, 95% ee

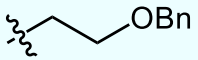


24
75%, 95% ee



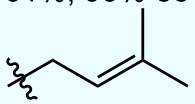
25
61%, 93% ee

26
73%, 86% ee

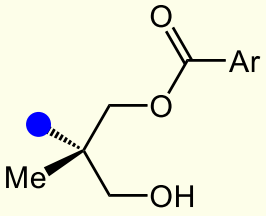


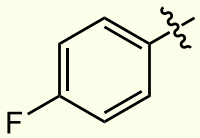
27
66%, 90% ee

28
78%, 96% ee

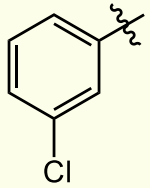


29
75%, 93% ee

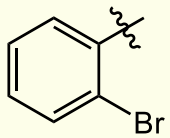




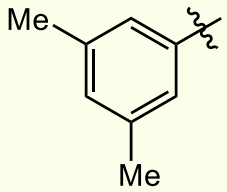
30, 62%, 87% ee



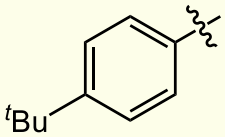
31, 59%, 87% ee



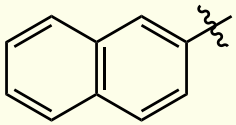
32, 78%, 85% ee



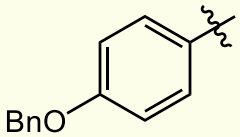
33, 70%, 94% ee



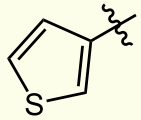
34, 80%, 90% ee



35, 74%, 94% ee



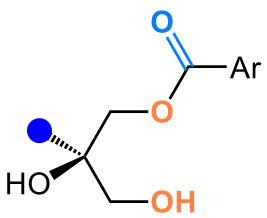
36, 68%, 94% ee



37, 71%, 90% ee

Substrate Scopes

Glycerol & 2-substituted-1,2,3-triols



Ar = 2-naphthyl
(**38-43**)

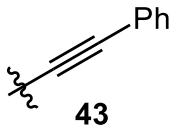
38
71%, 95% ee

39
77%, 96% ee

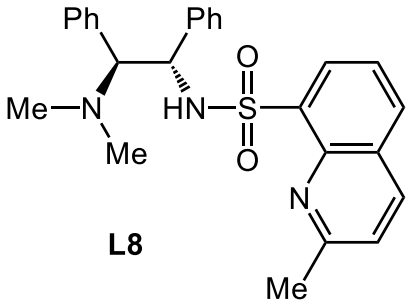
40
67%, 93% ee

41
68%, 97% ee

42
71%, 97% ee

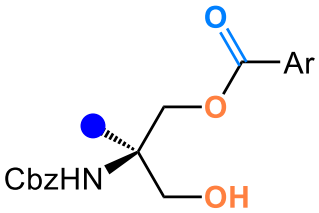


43
85%, 89% ee



L8

Serinol & 2-substituted-serinols

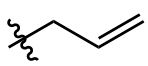


Ar = 2-naphthyl
(**44-48**)

44
71%, 94% ee

45
81%, 98% ee

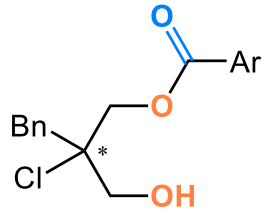
46
65%, 95% ee



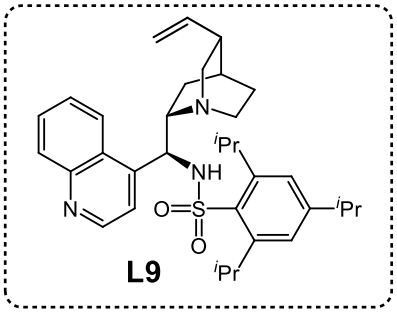
47
50%, 95% ee

48
78%, 98% ee

2-Chloro-1,3-diol

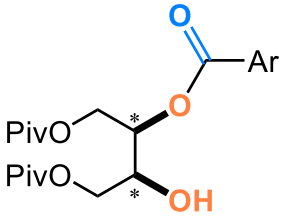


Ar = 2-naphthyl
49, 72%, 85% ee



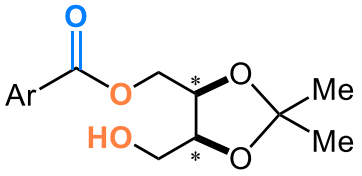
L9

meso 1,2-diol



Ar = 2-naphthyl
50, 74%, 85% ee

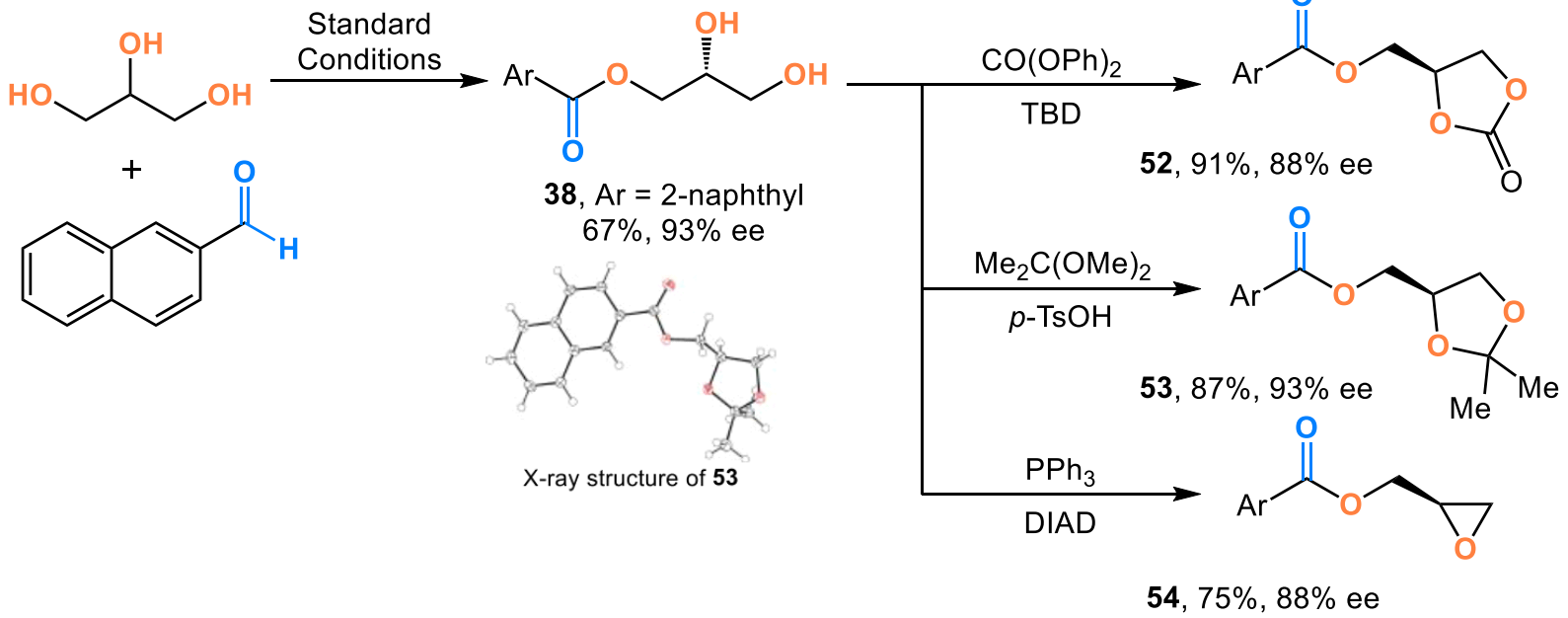
meso 1,4-diol



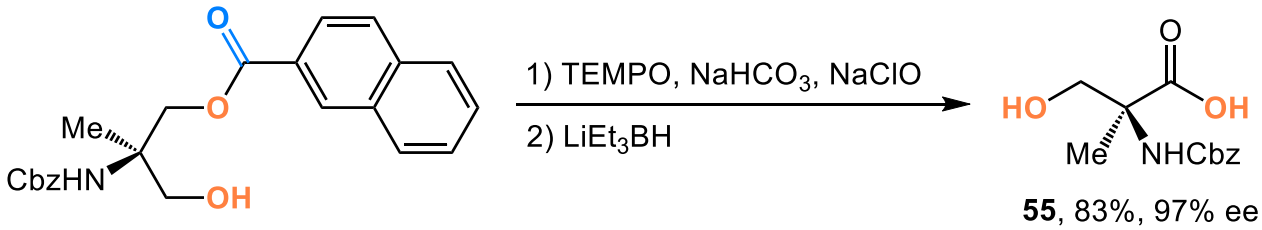
Ar = 2-naphthyl
51, 60%, 87% ee

Synthetic Application

A. Transforming glycerol into C3 building blocks

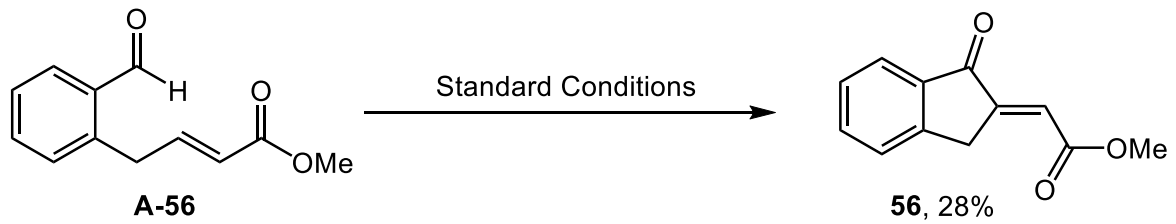


B. Synthesis of Cbz-protected (*S*)-methylserine



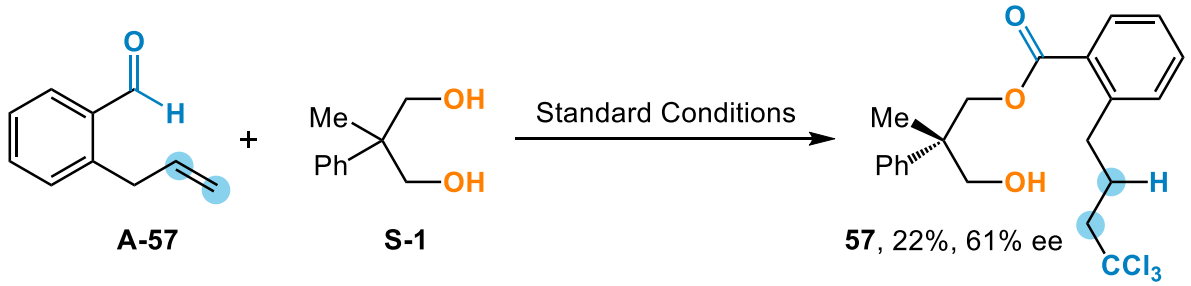
Mechanistic Investigations

A. Intramolecular trap of acyl radicals



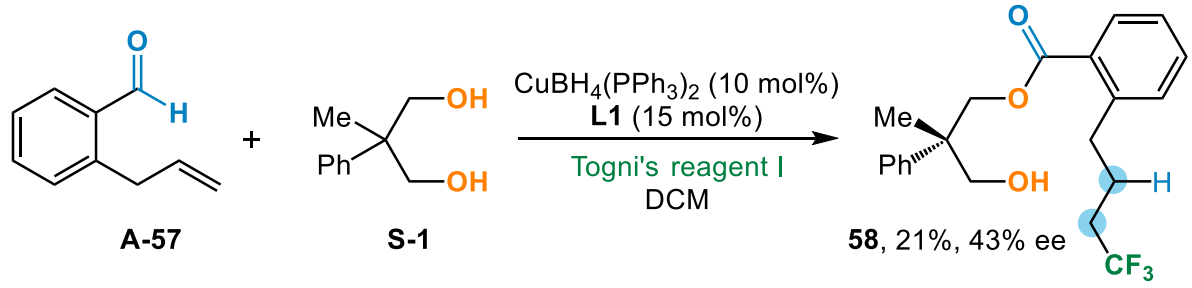
A-56 **56**, 28%

B. Alternative acyl radical generation with trichloromethyl radicals



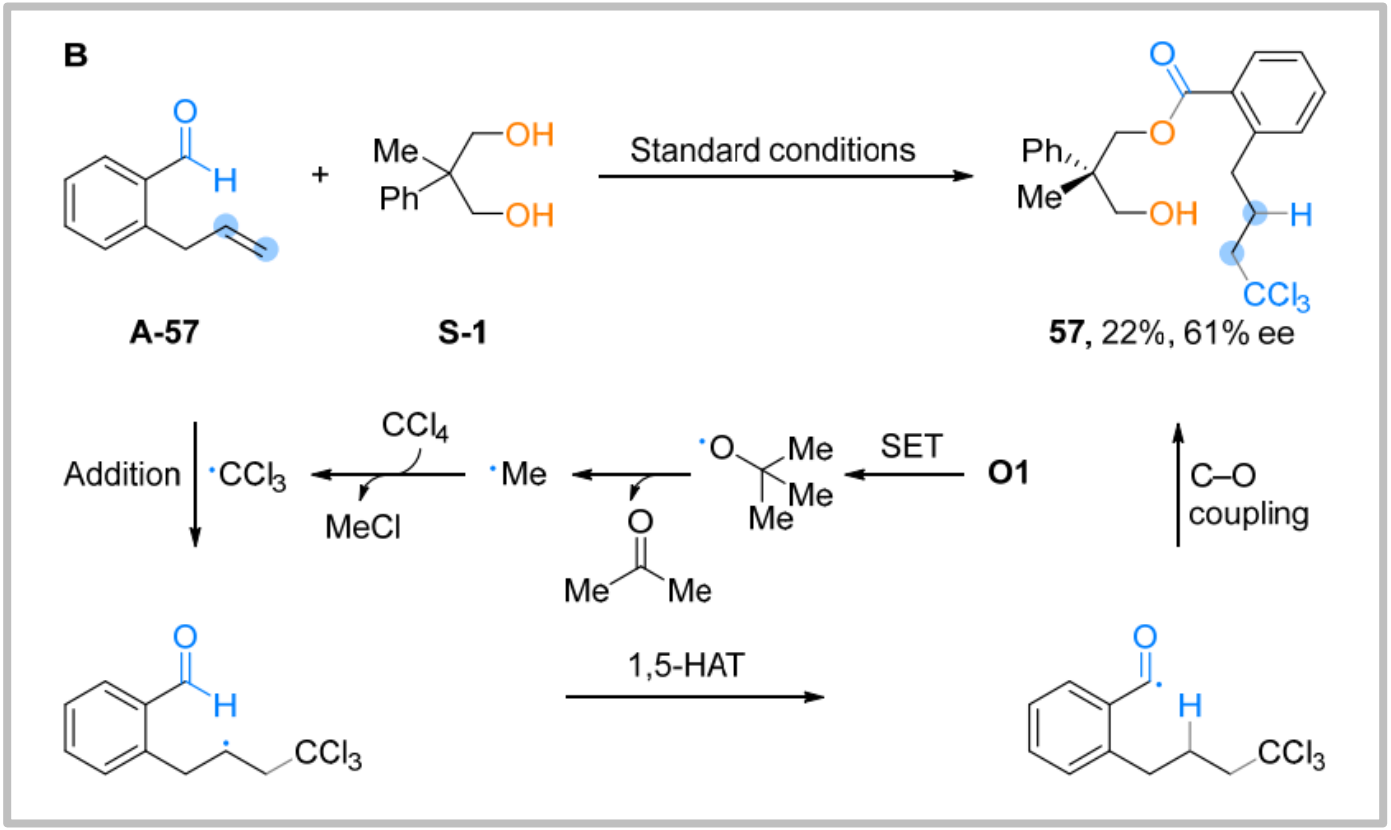
A-57 **S-1** **57**, 22%, 61% ee

C. Alternative acyl radical generation with trifluoromethyl radicals

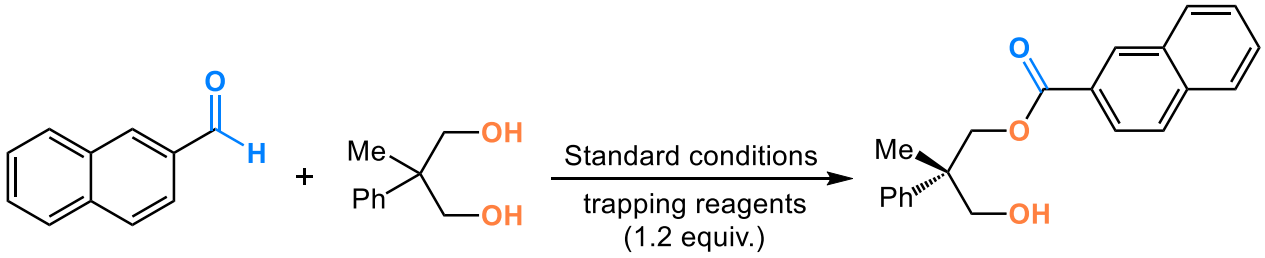


A-57 **S-1** **58**, 21%, 43% ee

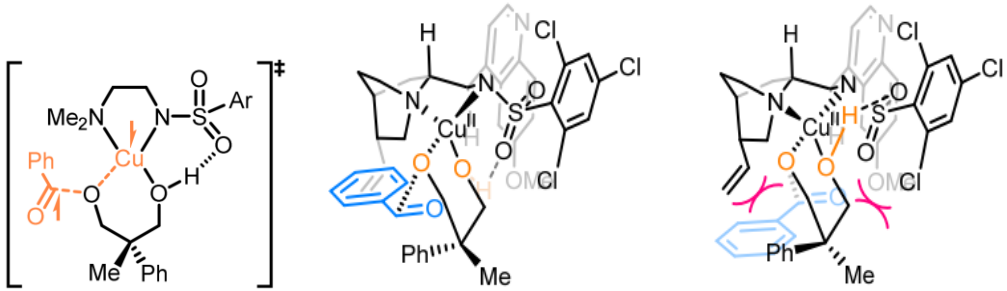
Mechanistic Investigations



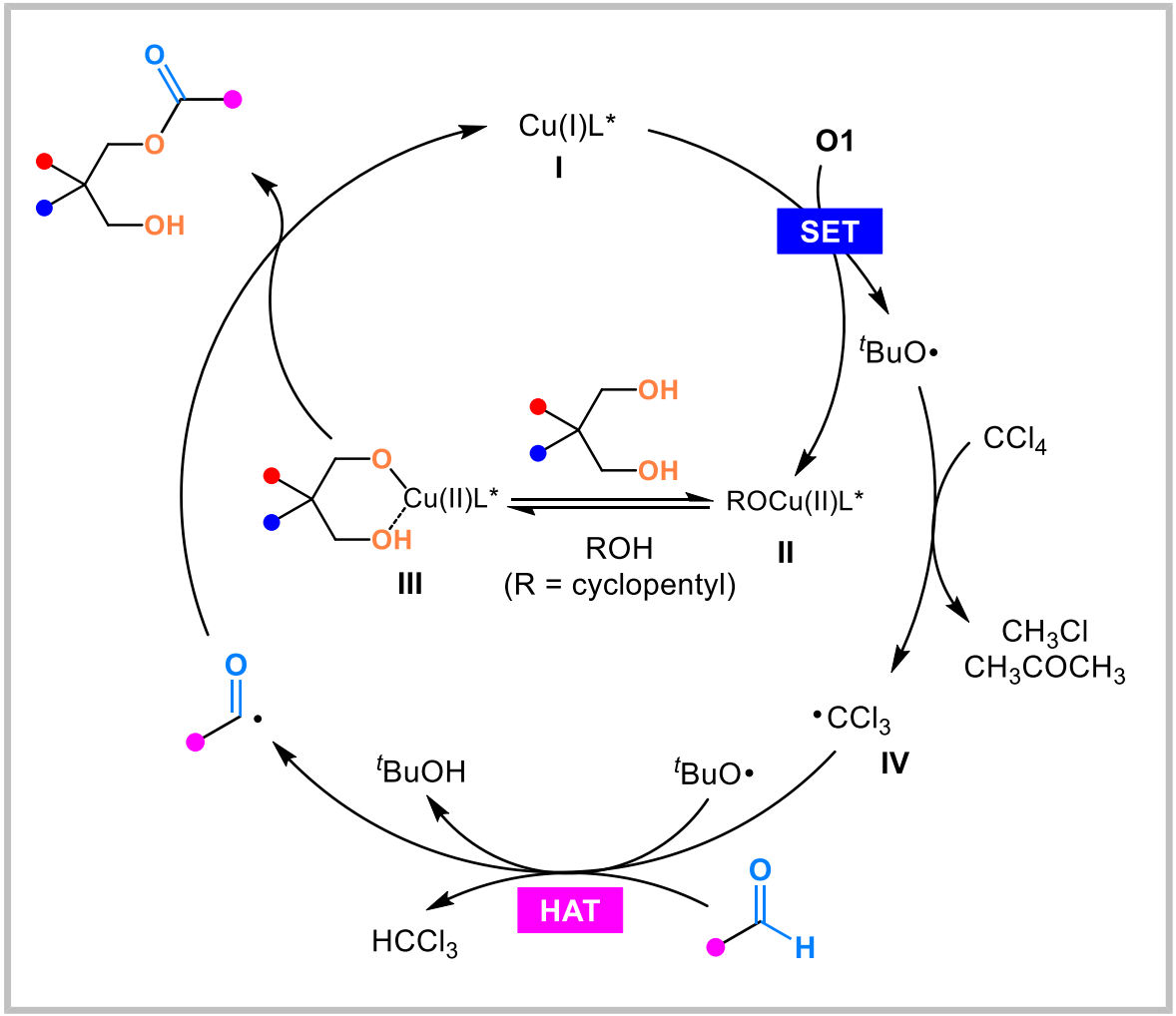
Mechanistic Investigations



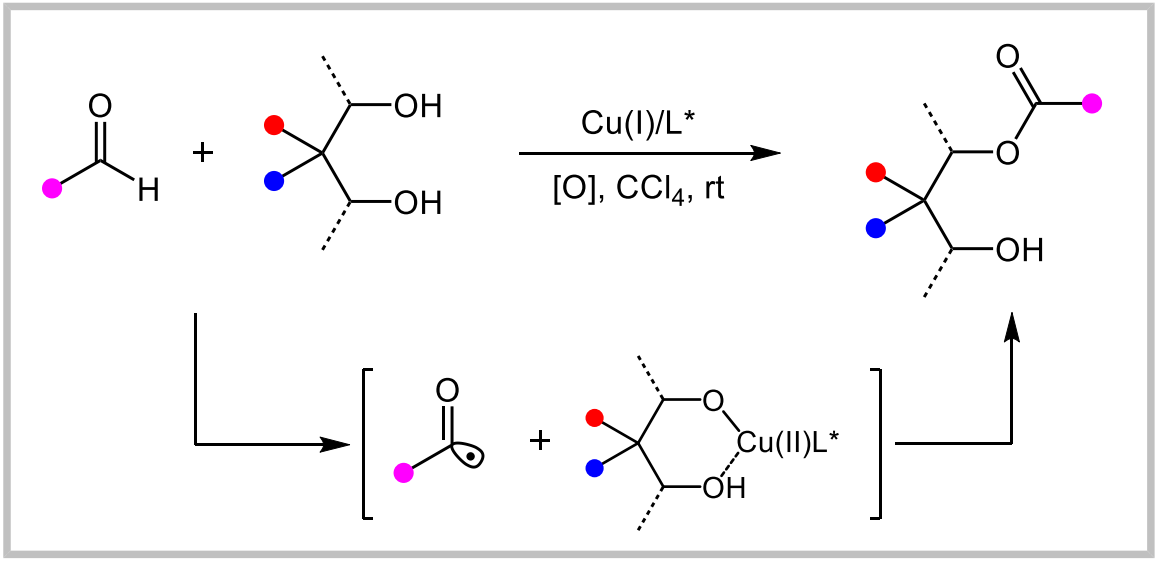
Trapping reagents	Yield of 1	Ee of 1
BHT	Trace	-
TEMPO	Trace	-



Proposed Mechanism



Summary



- Efficient remote enantiocontrol of reactions involving acyl radicals
- A convenient and practical platform for biomass industry
- >50 Examples, up to 89% yield, up to 98% ee

Writing Strategy

➢ Introduction

The importance of asymmetric radical reactions

Progress on asymmetric radical reactions

Shortcomings in asymmetric acyl radical reactions

- Asymmetric radical reactions, which are one of the most challenging areas of modern organic synthesis and asymmetric catalysis, provide a vital tool for preparing various enantioenriched molecules, thanks to their great functional group compatibility, high reactivity, and low steric hindrance sensitivity. Tremendous progress has been made in this field over the past few decades……
- For conjugated allenyl radicals, highly enantioselective cyanation and alkynylation reactions have also been achieved recently by Bao, Liu, and our group indepen-dently.
- By contrast, acyl radicals, which possess stabilities in between benzyl and isolated alkyl radicals, have so far remained uninvestigated for transition-metal-catalyzed enantioselective functionalization. This is despite that acyl radicals play an integral role in organic synthesis, and their formation and application in a controlled and efficient manner have long been a goal of chemists.

Writing Strategy

➢ The Last Paragraph

Summary of the work

Applications, mechanism and prospection

- In summary, we have developed a copper-catalyzed enantioselective desymmetrizing radical C-O bond coupling of aldehydes with prochiral or meso alcohols. The reaction features a remarkably broad alcohol scope, covering 2,2-dicarbosubstituted 1,3-diols, 2-substituted-2-chloro-1,3-diols, 2-substituted 1,2,3-triols, 2-substituted serinols, glycerol, serinol, meso 1,2- and 1,4-diols, of which most are challenging substrates for known chemo-catalytic enantioselective desymmetrization methods.
- More importantly, this reaction provides a convenient and practical platform for the fast valorization of biomass industry-relevant alcohols such as glycerol and its derivative serinol as well as erythritol. Mechanistic studies support a radical reaction mechanism with the participation of carbon tetrachloride solvent. The results of this work would encourage further efforts in developing various enantioselective functionalization of acyl radicals using chiral transition-metal catalysis.

Representative Examples

- Although aldehydes are appealing acyl group precursors, their use in intermolecular chemocatalytic enantioselective desymmetrization of alcohols has hitherto remained rare. (现今罕见，替换now… is limited，finite)
- Aryl, heteroaryl, and alkyl aldehydes all are viable substrates for this reaction. (是可行的底物)
- A general chemocatalytic desymmetrization method exhibiting such a broad substrate scope has, to the best of our knowledge, been rare, thus constituting an excellent complementary approach to these known protocols. (使用插入语，替代从句)

Acknowledgement

Thanks
for your attention