The application of visible light mediated photoredox catalysis in organic transformations

Vu, Minh Duy

2018

Vu, M. D. (2018). The application of visible light mediated photoredox catalysis in organic transformations. Doctoral thesis, Nanyang Technological University, Singapore.

<https://hdl.handle.net/10356/89112>

<https://doi.org/10.32657/10220/47721>

The application of visible light mediated photoredox catalysis in organic transformations

VU MINH DUY

School of Physical and Mathematical Sciences

A thesis submitted to the Nanyang Technological University

in partial fulfillment of the requirement for the degree of

Doctor of Philosophy

2018

Statement of Originality

I hereby certify that the work embodied in this thesis is the result of original research, is free of plagiarised materials, and has not been submitted for a higher degree to any other University or Institution.

[Input Date Here]

21/02/2019
.....
Date

[Input Signature Here]

.....
[Input Name Here]

Vu Minh Duy

Supervisor Declaration Statement

I have reviewed the content and presentation style of this thesis and declare it is free of plagiarism and of sufficient grammatical clarity to be examined. To the best of my knowledge, the research and writing are those of the candidate except as acknowledged in the Author Attribution Statement. I confirm that the investigations were conducted in accord with the ethics policies and integrity standards of Nanyang Technological University and that the research data are presented honestly and without prejudice.

20-02-19

[Input Date Here]

.....
Date

[Input Supervisor Signature Here]

Liu Xuewei

.....
[Input Supervisor Name Here]

Authorship Attribution Statement

This thesis contains material from 2 papers published in the following peer-reviewed journal(s) where I was the first and/or corresponding author.

Chapter 3 is published as M. D. Vu, W.-L. Leng, H.-C. Hsu and X.-W. Liu. Alkene Synthesis Using Phosphonium Ylides as Umpolung Reagents. *Asian Journal of Organic Chemistry* **8**, 93-96 (2017). <https://doi.org/10.1002/ajoc.201800586>.

The contributions of the co-authors are as follows:

- I conducted most of the synthetic experiments, including reaction set-up, substrate preparation, product isolation and characterization. I prepared the manuscript drafts. The manuscript was revised by Dr Leng, Hao-Cheng Hsu and A/Prof Xue-Wei Liu.
- Dr Leng discussed the experimental results and assisted to prepare manuscript drafts.
- Hao-Cheng Hsu aided in substrate preparation (phosphonium salt synthesis and purification)
- A/Prof Xue-Wei Liu provided overall guidance for the project.
- All the laboratory work at the School of Physical and Mathematical Sciences.

Chapter 4 is published as M. D. Vu, M. Das and X.-W. Liu. Direct Aldehyde C_{sp2}-H Functionalization through Visible-Light Photoredox Catalysis. *Chemistry - A European Journal* **23**, 15899-15902 (2017). <https://doi.org/10.1002/chem.201704224>.

The contributions of the co-authors are as follows:

- I conducted most of the synthetic experiments, including reaction set-up, substrate preparation, product isolation and characterization. I prepared the manuscript drafts. The manuscript was revised by Mrinmoy Das and A/Prof Xue-Wei Liu.
- Mrinmoy Das carried out some examples of the substrate scope mentioned in Scheme 4.3.
- A/Prof Xue-Wei Liu provided overall guidance for the project.
- All the laboratory work at the School of Physical and Mathematical Sciences.

[Input Date Here]

21/02/2019
Date

[Input Signature Here]

[Input Name Here]

Vu Minh Duy

Acknowledgement

First and foremost, I would like to express my sincere gratitude towards my supervisor, Assoc. Prof. Liu Xue-Wei, for his guidance and support throughout my PhD study. I gratefully appreciate his valuable advices and opportunities that has been given to me through the years. This PhD thesis would not have been possible without all these help.

I would also like to thank for the support and kind assistance from all technical and administrative staffs in the Division of Chemistry and Biological Chemistry. Specifically, I greatly appreciate Ms. Goh Ee Ling for NMR experiment setup, Ms. Zhu Wen Wei for mass spectrometry analysis, Dr. Li Yongxin and Dr. Rakesh Ganguly for their expertise in X-ray crystallography analysis.

Additionally, I would like to thank Nanyang Technological University (NTU) for awarding me the prestigious Nanyang President Graduate Scholarship (NPGS) and giving me the opportunity to pursue my PhD degree.

My gratitude also extends to former and current members of the group, whom I have learnt many laboratory techniques and wide background knowledge in carbohydrate, glycoprotein, biochemistry and polymer chemistry.

Lastly, my appreciation would be incomplete without mentioning the support and encouragement my family has given me throughout the years. Their continuous support has given me the strength to persevere through this journey.

Table of Contents

Acknowledgement	1
Table of Contents	2
List of Abbreviations	4
Summary	6
Chapter 1 Introduction to Photoredox Catalysis and Its Recent Applications in Organic Chemistry	7
1.1 - An Introduction to Structure and Photophysical Properties of Photoredox Catalysts	8
1.2 - Photoredox Catalysis - Modes of Action	16
1.3 - Applications of Photoredox Catalysis in Organic Chemistry	20
1.4 - Thesis Proposal	36
1.5 - References	37
Chapter 2 Photoredox Mediated C-H Activation for Intermolecular Cross-Radical Radical Coupling with Ketyl Radicals	44
2.1 - Introduction	45
2.2 - Results and Discussion	50
2.3 - Conclusion	59
2.4 - Experimental Section	60
2.5 - References	91
Chapter 3 Alkene Synthesis through Umpolung of Phosphonium Ylides	94
3.1 - Introduction	95

	3.2 - Results and Discussion	98
	3.3 - Conclusion	107
	3.4 - Experimental Section	108
	3.5 - References	128
Chapter 4	Direct Aldehyde C_{sp2}-H Functionalization via Visible Light Mediated Photoredox Catalysis	130
	4.1 - Introduction	131
	4.2 - Results and Discussion	135
	4.3 - Conclusion	141
	4.4 - Experimental Section	142
	4.5 - References	157
	List of Publications and Conferences	160

List of Abbreviations

μL	microliter	DIPEA	N-diisopropylethylamine
Acr⁺	acridinium	DMA	dimethylacetamide
ATRA	atom transfer radical addition	dme	dimethoxyethane
BDE	bond-dissociation energy	DMF	dimethylformamide
Bn	benzyl	DMSO	dimethyl sulfoxide
Boc	<i>tert</i> -butoxycarbonyl	dr	diastereoisomeric ratio
bpy	2,2'-bipyridine	dtbbpy	4,4'-di- <i>tert</i> butyl-2,2'-bipyridine
brs	broad singlet	EDG	electron donating groups
Bz	benzoyl	equiv	equivalents
Calc.	calculated	Et	ethyl
CAN	cerium ammonium nitrate	EWG	electron withdrawing groups
CDCl₃	deuterated chloroform	<i>fac</i>-	facial
cod	1,5-cyclooctadiene	FGI	functional group
d	doublet		interconversion
DABCO	1,4-diazabicyclo-[2.2.2]-octane	HAT	hydrogen atom transfer
dba	dibenzylideneacetone	HFIP	1,1,1,3,3,3-hexafluoro
DCE	1,2-dichloroethane		isopropanol
DCM	dichloromethane	HWE	Horner–Wadsworth–Emmons
dd	doublet of doublets	Hz	hertz
DDQ	2,3-dichloro-5,6-dicyano- benzoquinone	IC	internal conversion
dF(CF₃)ppy	2-(2,4-difluorophenyl)-5- (trifluoromethyl)pyridine	ⁱPr	<i>iso</i> -propyl
DFT	density functional theory	ISC	intersystem crossing
		LED	light emitting diode
		M	mole per liter

Me	methyl	ppy	2-phenylpyridine
MeCN	acetonitrile	PRC	polarity reversal catalyst
MeOH	methanol	rr	regio-isomeric ratio
Mes	mesityl	s	singlet
MHz	megahertz	SCE	saturated calomel electrode
mL	milliliter	SET	single electron transfer
MLCT	metal to ligand charge transfer	t	triplet
mmol	millimoles	TBADT	tetra- <i>n</i> -butylammonium
mol%	mole percentage		decatungstate
NHC	N-heterocyclic carbene	^tBu	<i>tert</i> -butyl
PC	Photocatalyst	TEMPO	2,2,6,6-tetramethyl-1-
PCET	proton coupled electron transfer		piperidinyloxy
PET	photoinduced electron transfer	TIPS	tri- <i>iso</i> -propylsilyl
Ph	phenyl	TMS	trimethylsilyl
phen	1,10-phenanthroline	TMSCN	trimethylsilyl cyanide
PMB	<i>para</i> -methoxybenzyl	TTET	triplet-triplet energy transfer
PMP	<i>para</i> -methoxyphenyl	Δ	reflux or heat
ppm	part per million	δ	chemical shift

Summary

In the modern era of chemistry, photoredox catalysis has proven its usefulness in many synthetic applications. First of all, with the use of visible-light as the only activation source, several challenging organic transformations now could be successfully carried out at ambient conditions. Secondly, the remarkable redox regulatory capability of photoredox catalysts has facilitated a handful of difficult electron transfer processes, breaking conventional energy barrier by going through alternative pathways. The increasing number of reports on novel bond formation strategies has been ongoing through the last few decades. Therefore, the objective of my thesis is to develop new C-H functionalization methodologies and to probe new chemistry of traditional organic reagents under visible-light mediated photoredox conditions.

The thesis begins with an overview introduction about photoredox catalysis, including catalyst design and photophysical properties, mode of actions and break-through applications in organic synthesis during recent years. Subsequently, chapter 2 describes my work on allylic/benzylic C_{sp3}-H activation for intermolecular cross-radical radical couplings. The reaction outcome resembles Barbier type ketone alkylation for tertiary alcohol synthesis; nevertheless, the use of organometallic nucleophiles or strong reducing metals is avoided. In the next chapter, umpolung chemistry of traditional phosphorus ylide nucleophile was first explored in direct olefin synthesis. Finally, the last chapter concludes my thesis with catalytic aldehyde C_{sp2}-H activation for non-symmetrical ketone synthesis via two separate pathways, namely, olefin radical addition and nickel catalyzed cross-coupling reaction.

Introduction to Photoredox Catalysis and Its Recent Applications in Organic Chemistry

Abstract: This chapter introduces fundamental theory of photoredox catalysis, including structure and classification of recently employed photoredox catalysts, proposed reaction mechanisms and innovative reaction design, as well as significant applications of photoredox catalysis in organic chemistry. The chapter is then concluded with a thesis proposal that summarizes my ideas for the research discussed in this thesis.

1.1 - An Introduction to Structure and Photophysical Properties of Photoredox Catalysts

Photosensitizer was harnessed as catalyst for single electron transfer (SET) processes that facilitates organic transformation almost 40 years ago.¹ The overall working mechanism of a photosensitizer includes typical excitation and relaxation pathways. Upon absorbing a photon, the photosensitizer transforms into its excited state which subsequently relaxes back to its ground state via several pathways (**Figure 1.1**). At first, it can directly release a photon of equal or longer wavelength via the process called fluorescence. Secondly, it may undergo radiationless relaxation by internal conversion, in which the excited photosensitizer converts its potential energy to vibrational modes without affecting molecular spin state. In some cases, another radiationless relaxation pathway named intersystem-crossing could happen with a change in molecular spin state (*i.e.* singlet to triplet), following by phosphorescence. These mentioned pathways generally are not of interest in organic synthesis, because the energy package received from original photon absorption merely transforms to heat (or light), but not being delivered to any targeted substrate to trigger bond breaking/formation steps.

Figure 1.1 | Simplified energy diagram of photochemical properties of photosensitizer

Chemists have found that with some special design, photosensitizers could reside in a long-lived excited triplet state,² owing to low kinetic phosphorescence pathway. In those cases, the excited sensitizer might undergo electron transfer processes, either reduction or oxidation, to gain a more stable electronic configuration. Research has shown that the redox property of photoexcited sensitizer is much more potent than its ground state. For example, the ground state potential of the prototypical photosensitizer $\text{Ru}(\text{bpy})_3^{2+}$ is +1.29 V and -1.33 V for $E_{1/2}^{\text{III/II}}$ and $E_{1/2}^{\text{II/I}}$ (vs SCE) respectively, which means that both the oxidation of Ru(II) to Ru(III) and the reduction of Ru(II) to Ru(I) are thermodynamically unfavorable.³ In contrast, the similar potentials for the excited species $[\text{Ru}(\text{bpy})_3^{2+}]^*$ are -0.81 V and +0.77 V ($E_{1/2}^{\text{III/II}*}$ and $E_{1/2}^{\text{II*/I}}$ vs SCE).⁴ Hence, complex $\text{Ru}(\text{bpy})_3^{2+}$ could act as either strong oxidant or reductant in its photoexcited triplet state (**Figure 1.2**).

After being quenched via electron transfer, the photoredox catalyst ends up in an unstable oxidation state that is prone to another step of back electron transfer, recycling the catalyst and making the overall process redox-neutral (the catalyst donates one electron then accepts one electron and *vice versa*).

Based on the structural diversity of photosensitizers, they can be classified into three major groups: transition metal complexes, organic dyes and semiconductors. With the same working mechanism, although semiconductors have been employed in photocatalysis, they perform well mostly in environmental aspects⁵⁻⁷ such as water photolysis, CO_2 reduction and pollutant degradation, but rarely in organic synthesis. Therefore, within the scope of this dissertation, only transition metal complexes and organic dyes will be discussed in further details.

1.1a - Transition metal complexes

A wide variety of transition metal complexes are known as potent photosensitizers. For those complexes with low-lying π^* ligand orbitals, metal to ligand charge transfer (MLCT) can occur, resulting in a positive charge at metal center while the ligand takes a negative charge. Therefore, in the long-lived excited state, the complexes can undergo either oxidation (ligand donating one electron) or reduction (metal center accepting one electron).⁸

Figure 1.2| Redox quenching pathways of example polypyridyl complexes $[M(bpy)_3]^{2+}$

The most widely used complexes for photoredox catalysis are ruthenium (II) and iridium (III) based. With d^6 electron configuration,⁹ under ligand field theory, the complex is substitutionally inert with filled t_{2g} orbitals (**Figure 1.3**). This also reduces the occurrence of any background reactions attributed to Lewis acidity of the metal centers.

The photophysical properties as well as the stability of photocatalysts primarily depends on the metal center. Although both Ru^{2+} and Ir^{3+} complexes have d^6 configuration, being in a higher oxidation state, Ir^{3+} complexes have considerably better oxidative

potential. In addition, higher ligand field stabilization energy (LFSE, or Δ_o) in iridium complexes (means a larger LUMO-HOMO gap) results in a greater photonic input. Overall, Ir^{3+} complexes are more thermodynamically stable than Ru^{2+} complexes due to this fact.¹⁰⁻¹¹

Figure 1.3| Typical d^6 complexes electron configuration in ligand field theory

On the other hand, ligands also play vital roles in the design of photoredox catalyst. Based on the type of ligands used, these complexes can be classified into 2 categories, namely, homoleptic and heteroleptic. Homoleptic complexes, for instance, $[\text{Ru}(\text{bpy})_3]^{2+}$ and $\text{Ir}(\text{ppy})_3$, have the same ligands surrounding metal center, while heteroleptic complexes like $[\text{Ir}(\text{ppy})_2(\text{dtbbpy})]^+$ or $[\text{Ir}(\text{dFCF}_3\text{ppy})_2(\text{dtbbpy})]^+$ have different ligands (**Figure 1.4**). Due to larger spin orbit coupling that improves MLCT efficiency, iridium can accommodate heteroleptic ligand system better than ruthenium. In contrast, the majority of ruthenium photoredox catalysts are homoleptic complexes.

Figure 1.4| Examples of homoleptic and heteroleptic photoredox catalysts

One of the central advantages of transition metal based photoredox catalyst is the versatility of design allowed by ligand tailoring, thus altering the redox profile of the

complex in a desirable manner. Examples of 4 common photoredox catalysts are listed in **Table 1.1** below.

Table 1.1 | Redox profiles of common photoredox catalysts¹²

	bpy	ppy	dtbbpy	dFCF ₃ ppy
	Ru(bpy)₃²⁺	fac-Ir(ppy)₃	Ir(ppy)₂(dtbbpy)⁺	Ir(dFCF₃ppy)₂(dtbbpy)⁺
E (M⁺/M[*]) vs SCE	-0.81 V	-1.73 V	-0.96 V	-0.89 V
E (M[*]/M) vs SCE	+0.77 V	+0.31 V	+0.66 V	+1.21 V
τ_{1/2}	1100 ns	1900 ns	560 ns	2300 ns
λ_{abs}	452 nm	375 nm	410 nm	380 nm

It is obvious that the electron rich anionic ligand 2-phenylpyridine (ppy) significantly induces reductive ability in the catalyst compared to the neutral ligand 2,2'-bipyridine (bpy). Moreover, substituents on the ligand also affect the redox ability of the catalyst. Electron withdrawing groups such as –F and –CF₃ help to increase the oxidative potential, therefore, the catalyst Ir(dFCF₃ppy)₂(dtbbpy)⁺ is among the strongest oxidative iridium photoredox catalysts reported up to date.

To reduce the cost and to explore new catalytic properties, other organometallic complexes have also been employed as photoredox catalyst in recent years, especially from earth abundant elements (copper, iron, chromium and zirconium).¹³⁻¹⁹

1.1b - Organic dyes

Besides complexes of transition metals, a wide range of organic substances also possess the ability to convert light energy into chemical energy via redox processes (**Figure 1.6**).²⁰⁻²¹ In fact, organic photoredox catalysts have been applied in organic chemistry for several decades.²² Due to their ability to absorb visible-light, they exhibit a colorful appearance and hence are used massively in the dye industry. To compare with transition metal photoredox catalysts, organic dyes are relatively inexpensive, less toxic and widely available. This following section will introduce a few common classes of organic dyes (**Figure 1.5**) that have shown significant applications in organic synthesis.

Figure 1.5| Examples of organic dyes as photoredox catalysts

The most well-known type of organic photoredox is probably Xanthenes, which was employed in organic synthesis for over a century.²³ The representatives of this class are Fluorescein, Eosin Y, Rose Bengal and Rhodamin B. Because these dyes exhibit relatively balanced redox potentials in the excited state, they were widely employed in both reductive

as well as oxidative processes.²⁰ For instance, Eosin Y was utilized in benzylic oxidation (formal Kornblum oxidation),²⁴ oxidative removal of PMB protecting group,²⁵ sulfur oxidation to form disulfides and sulfoxides.²⁶⁻²⁷ Rose Bengal and Eosin Y also involved in dehydrogenative couplings as reported by König,²⁸ Tan and co-workers.²⁹ Furthermore, Scaiano,³⁰ Neumann and Zeitler demonstrated reductive cyclization of bis-enones.³¹ Several other protocols for reductive deoxygenation,³² desulfonylation³³ and dehalogenation³⁴ were also reported, marking xanthenes to be a highly versatile class of organic photoredox (comparable and alternative to $\text{Ru}(\text{bpy})_3^{2+}$ and $\text{Ir}(\text{ppy})_2(\text{dtbbpy})^+$).

Some organic dyes possess strong reducing power such as electron rich derivatives of anthracenes and pyrenes. With the excited state oxidation potential in the range of -2.0 V to -2.5 V vs SCE, these catalysts are known to be effective in ketone reduction, generating ketyl radicals.³⁵ In addition, Jamison demonstrated the use of *para*-terphenyl ($E^\circ = -2.63$ V vs SCE) for CO_2 reduction in direct synthesis of aminoacids.³⁶ Miyake and co-workers also developed strong organic photo-reductant in replacement of iridium complexes in a handful of organic transformations.³⁷

Figure 1.6| Quenching pathway of organic dyes

On the other hand, there are also powerful oxidative organic dyes. Fukuzumi developed acridinium salts³⁸ that was subsequently utilized by Nicewicz and co-workers³⁹ in many anti-Markovnikov additions to alkenes⁴⁰ and arene functionalization.⁴¹

Nevertheless, at the current state of improvement, organophotoredox still suffers significant drawbacks from deactivation pathways, due to the involvement of strong reagents or reactive intermediates.²⁰ This explains the requirement for higher catalyst loading in most of the cases compared with transition metal complexes (2-5 mol% vs 0.02-1 mol%). The mechanism of deactivation is generally irreversible nucleophilic addition or radical addition to the catalyst molecules, thus shutting down the catalytic cycles (**Figure 1.7**). In contrast to the inert transition metal complexes, these side reactions of organic dyes with nucleophilic reagents limit the substrate scope of the reactions. In the recent progress, more robust and efficient organophotoredox catalysts have been designed to tackle these challenges.

Figure 1.7| Deactivation pathway of organic photoredox catalysts

1.2 - Photoredox Catalysis - Modes of Action

1.2a - Electron transfer mechanism

Photoinduced electron transfer (PET) mechanism is the principal mode of activation that makes photoredox chemistry boom in recent decades. Excited photoredox catalysts possess both excellent oxidizing and reducing capabilities that allow great versatility in reaction design. The redox power of each catalyst or substrates is readily quantifiable by either measuring potentials of the half-reaction (cyclic voltammetry) or by theoretical calculation.⁴² Therefore, reaction design would then be facilitated by matching possible quenching substrates with suitable photoredox catalysts. For example, to reduce acetophenone ($E = -2.11$ V vs SCE) to a ketyl radical intermediate, one can use Ir(ppy)_3 via reductive quenching pathway ($E = -2.19$ V vs SCE) or any other photocatalyst that offers comparable reducing ability. As can be seen, novel reaction pathways are now predictable by anticipating feasibility of electron transfer steps.

Other than that, serendipitous quenching experiments could also reveal promising quenchers or feasible electron transfer processes, as described by MacMillan,⁴³ Glorius and co-workers.⁴⁴⁻⁴⁵ In 2011, the finding α -amine $\text{C}_{\text{sp}^3}\text{-H}$ arylation by MacMillan stimulated the whole era of new photoredox discoveries later on. Mechanism based luminescence screening helped Glorius to discover novel chemistry of triazole substrates.⁴⁶

Beyond this most well-known mechanism of photoredox catalysts, these photosensitizers were found to exhibit other capabilities in facilitating the desired transformation. Listed below in this section are energy transfer mechanism, hydrogen absorption mechanism and photoacid/Lewis acid mechanism.

1.2b - Energy transfer mechanism

Besides photoinduced electron transfer mode, some photoredox catalysts also offer an alternative activation mode which is energy transfer to targeted substrate. After intersystem crossing to a triplet state, the high energy photosensitizer molecules may undergo triplet-triplet energy transfer (TTET) with the ground state substrate molecules (**Figure 1.8**). Receiving the energy package, the substrate becomes activated and prone to chemical transformation.

Figure 1.8| Illustrating diagram for energy transfer between photosensitizer & substrate

Figure 1.9| a. Intramolecular [2+2] cycloaddition via energy transfer mechanism, b.

Electron transfer and energy transfer mechanism in a Nickel(II) complex

Yoon reported the intramolecular [2+2]-cycloaddition of styrene scaffolds in 2012 (**Figure 1.9a**).⁴⁷ This work features an interesting exclusion of SET facilitated radical cationic pathway that was previously discovered by the same group. The use of styrene substrates

with high oxidation potential ($> +1.40$ V vs SCE) precludes the radical cation cycloaddition pathway (oxidation potential of catalyst 1.21 V vs SCE). On the other hand, the catalyst's excited state triplet energy (E_T) is approximately equal to the one of common styrenes ($E_T \approx 60$ kcal·mol⁻¹), indicating that the catalyst might be capable of sensitizing triplet-state reactions of styrene upon irradiation with visible light. Additionally, MacMillan described a coupling protocol between carboxylic acids and aryl halides via co-operative nickel and photoredox catalysis.⁴⁸ Instead of modulating the oxidation state of nickel as reported in previous synergistic pathway,⁴⁹⁻⁵⁰ it was proved that energy transfer took place as the new activation mode in this coupling transformation (**Figure 1.9b**).

1.2c - Hydrogen atom transfer mechanism

Scheme 1.1 | The mechanism of hydrogen atom transfer via excited Eosin Y photocatalyst

Hydrogen atom transfer (HAT) process plays an important role in various C-H functionalization methodologies. Beside the bond strength differences that govern thermodynamic factor of the reaction, the polarity match between radicals (HAT acceptor) and substrate (HAT donor) is pivotal for kinetic consideration. Electrophilic radicals such as

thiyl, hydroxyl or carboxyl radicals have a high tendency to abstract hydrogen from C-H bonds, generating carbon centered radicals which can engage in useful secondary transformation. Recently, Wu and co-workers reported the use of Eosin-Y organic dye as a HAT catalyst in its photoexcited form (**Scheme 1.1**).⁵¹ In the mechanistic point of view, excited Eosin-Y might exist in the form that possesses an electrophilic hydroxyl free radical. Indeed, excited Eosin-Y shows a strong capability to activate a wide range of substrates including ether, thioether, alcohol, aldehyde, benzylic/allylic compounds and hydrocarbons.

1.2d - Photoacid catalyst and Lewis acid catalyst

Figure 1.10| Examples of recently reported photoredox catalysts acting as acid catalysts

Some organic substances can behave as acid catalysts in their excited state, hence, the term photoacid was introduced since 1976.⁵² Recently, Toshima and co-workers presented photoinduced glycosylation by the excited state of thiourea (**A**)-**Figure 1.10**.⁵³ Earlier this year, Wang demonstrated the photoacid property of excited Eosin-Y (**B**)-**Figure 1.10** in 2-deoxy-glycosides synthesis via addition of glycosyl donors to protected glycals.⁵⁴

In addition, the Meggers group has developed photosensitive iridium complexes with labile ligands such as acetonitrile (**C**)-**Figure 1.10**. The dissociation of these ligands creates empty sites on metal centers, thus allowing its Lewis acid functionality. Its dual role as photoredox catalyst and Lewis acid catalyst was successfully demonstrated in the asymmetric α -alkylation of carbonyl compounds.⁵⁵

1.3 - Applications of Photoredox Catalysis in Organic Chemistry

With the four modes of action discovered up to date, chemists have created, either through intentional design or serendipitous screening, a wide array of novel and useful organic transformations. This following section lists out these break-through applications of photoredox catalysis recently.

1.3a - Radical C-H activation and functionalization

One of the main principles in green chemistry emphasizes the preference of optimum atom economy in organic synthesis. The direct utilization of C-H instead of other pre-functionality for C-C or C-X bond formation is the true answer for that. However, it has always been a challenge to organic chemists to design new pathways as well as activation modes for mild, selective and predictable C-H activation protocols. The realm of C-H activation has witnessed significant progresses and improvement, from using stoichiometric activators to catalytic usage of either transition metal catalysts or organocatalysts. Radical C-H abstraction (Hydrogen atom transfer or HAT in short) is one of the mechanisms being favored in the past,⁵⁶ and with the development of photoredox chemistry, this strategy has been brought to a much greater advance.⁵⁷

The first classic example to mention is α -amine C_{sp3}-H functionalization.⁵⁸ Aliphatic amines are prone to single electron oxidation to give a radical cation. This species may undergo either deprotonation in presence of base, or hydrogen atom transfer (HAT) in the presence of an H-acceptor (**Figure 1.11**). In the former case, it gives a carbon centered radical that can be quenched by radicalphiles like olefins. On the other hand, the HAT process can generate an iminium cation, a highly electrophilic intermediate that can easily undergo nucleophilic addition.

Figure 1.11 | α -Amine C_{sp^3} -H functionalization mechanism

Stephenson and co-workers demonstrated a series of examples via photoredox aza-Henry reaction, using the carbanion derived from a nitroalkane to attack the iminium intermediate.⁵⁹ Rueping *et al.* reported the use of enamine,⁶⁰ and then copper acetylides as carbon nucleophiles.⁶¹ In addition, Rovis presented co-operative N-heterocyclic carbene catalyzed aldehyde umpolung for direct enantioselective acylation of amines.⁶² On the other hand, the synthetic potential of α -amino radicals was developed by Pandey and Reiser,⁶³ Nishibayashi,⁶⁴ Yoon⁶⁵ and MacMillan.⁴³ Subsequently, MacMillan developed β -ketone C_{sp^3} -H functionalization via dual photoredox and enamine catalysis.⁶⁶

In contrast to amine oxidative C-H functionalization, other functionalities that possess high oxidation potential, for instances, alcohol, ether, olefins, etc., undergo a similar mechanism with relative difficulty. Therefore, another C-H activation strategy is to use a HAT catalyst precursor that could be activated *in situ* via a SET event mediated by a photoredox catalyst. The examples of these HAT catalyst are thiols and quinuclidine, as pioneered by MacMillan and co-workers (**Figure 1.12**). Thiols have long been known as polarity reversal catalysts (PRC)⁶⁷ which efficiently increase the kinetic profile of a HAT process. With slightly higher acidity than alcohols, thiols can be deprotonated to thiolates, which can then undergo SET oxidation to form thiyl radicals, the active species to abstract

hydrogen from organic substrates. Due to electrophilic properties of thiyl radicals, they abstract hydrogen from nucleophilic carbon radicals (or hydridic C-H) relatively fast. Remarkable examples of direct C_{sp^3} -H allylic arylation,⁶⁸ α -Hydroxyl C_{sp^3} -H alkylation⁶⁹ and benzylic ether C_{sp^3} -H activation⁷⁰⁻⁷¹ were reported.

Figure 1.12| Synergistic catalysis between thiol/quinuclidine HAT and photoredox catalysts

The use of quinuclidine to replace thiols shows its advantage in 2 aspects. Firstly, although thiyl radical hydrogen abstraction is kinetically favored, the S-H bond ($BDE \approx 87\text{-}90 \text{ kcal}\cdot\text{mol}^{-1}$)⁷⁰ is relatively weak compared to an unactivated C-H bond that makes the process thermodynamically disfavored. In contrast, the N-H bond ($BDE \approx 100 \text{ kcal}\cdot\text{mol}^{-1}$)⁷² in the quinuclidinium ion is very strong. Together with the inherent electrophilic character of the quinuclidinium radical, the HAT process for quinuclidine catalyst is both kinetically and thermodynamically favored.⁶⁹ Moreover, unlike thiols, quinuclidine does not show a poisoning effect on transition metals, therefore, they could aid in co-operative metal

catalyzed coupling reactions. As a result, the secondary transformation after getting the desired carbon radical is widely expanded.⁷³

Nicewicz

Nicewicz & Alexanian

Figure 1.13| Organic dye Acridinium as photoredox catalyst in C-H functionalization

In the area of organophotoredox chemistry, Nicewicz successfully demonstrated strategies for C_{sp2}-H functionalization of electron rich aromatic substrates by using acridinium salts. Successful regioselective C_{sp2}-H amination⁴¹ and cyanation⁷⁴ were reported (Figure 1.13). Oxygen plays a vital role in these protocols as HAT catalyst precursors. Subsequently, Nicewicz's collaborative work with Alexanian on C_{sp3}-H azidation highlighted the use of phosphate salt as a cheap and non-toxic HAT catalyst precursor.⁷⁵

Glorius

Figure 1.14| Benzoate salts as HAT catalyst precursors

Since 2016, Glorius discovered the use of benzoate salts as direct precursors of benzoyloxy radicals which possess strong HAT power, owing to the high energy of the O-H bond (in benzoic acid) and the highly electrophilic property of the radical (Figure 1.14).

Successful examples include trifluoromethylthiolation ($-\text{SCF}_3$) of unactivated tertiary $\text{C}_{\text{sp}^3}\text{-H}$ ⁷⁶ and aldehyde $\text{C}_{\text{sp}^2}\text{-H}$ bonds.⁷⁷

Figure 1.15| Amidyl radicals as HAT acceptors

In 2016, Knowles⁷⁸ and Rovis⁷⁹ independently reported *in situ* formation of amidyl radicals via a PCET pathway, which then underwent intramolecular 1,5-hydrogen abstraction (Figure 1.15). This work was then expanded to distal $\text{C}_{\text{sp}^3}\text{-H}$ activation of carboxylic acid derivatives.⁸⁰

Figure 1.16| Chlorine radical as HAT acceptors

Trace chlorine radical formed by dual Nickel and photoredox catalysis activation could be utilized as efficient HAT acceptor, as reported by Doyle *et al.* (Figure 1.16).⁸¹

Figure 1.17| Minisci type heteroaryl functionalization

Moreover, there are several protocols that can facilitate C_{sp^2} -H functionalization via radical substitution, resembling the Minisci reaction reported since 1971 (**Figure 1.17**).⁸² By photoredox mediated single electron reduction of a diazonium salt, iodonium salt, aryl halides, etc., a handful of radical intermediates could be obtained (aryl/alkyl/acyl) for the substitution reaction. On the other hand, photoredox oxidation of carboxylate (followed by decarboxylation) and trifluoroborate could also generate alkyl and aryl radicals for a similar transformation.⁸³ Recently, the enantioselective version of the reaction was successfully developed by Phipps and co-workers.⁸⁴

Figure 1.18| Wide range of C-H bonds that could be functionalized via photoredox catalysis

Overall, synergistic photoredox catalysis has enabled a wide array of C-H activation/functionalization (**Figure 1.18**). Together with benign reaction condition and low catalytic loading of activators, these methodologies promise enormous synthetic application in the near future.

1.3b - Functional group interconversion

Apart from C-C bond formation processes, functional group interconversion (FGI) plays an important role in organic synthesis. Quick, efficient and sustainable methodologies for FGI are always of great interest. Visible-light mediated photoredox catalysis has successfully replaced a plethora of conventional methods by a greener and milder approach. In this section, major examples of FGI reactions will be discussed in reduction, oxidation and redox neutral categories.

With regards to reductive transformation, early photoredox reduction of sulfonium salts was reported in 1978 by Kellogg and co-workers.⁸⁵ By utilizing the Hantzsch ester as the terminal reductant, $\text{Ru}(\text{bpy})_3$ was found to be a potent photoredox catalyst to facilitate the cleavage of C-S bonds, forming carbon radicals.

Figure 1.19 | The reduction of halides via single electron transfer

Subsequently, the seminal work on reduction of activated halides was reported by Tanaka⁸⁶ (1984) and Fukuzumi⁸⁷ (1990) using $\text{Ru}(\text{bpy})_3\text{Cl}_2$, Kern and Sauvage⁸⁸ (1987) using $\text{Cu}(\text{dap})_2\text{BF}_4$ as the photocatalyst. However, the scope of the organohalides undergoing the photo induced reduction was still limited, because the reduction power of the photosensitizer was not improved. Over two decades later, Stephenson generalized the

protocol,⁸⁹ with significant improvements specifically for unactivated iodide reduction using a stronger reducing photoredox catalyst $\text{Ir}(\text{ppy})_3$.⁹⁰ The method altered traditional usage of highly toxic organotin reagents to generate carbon centered radicals from halides. Furthermore, these radical could be employed in reductive radical cyclization and atom transfer radical addition (ATRA) (**Figure 1.19**).⁹¹⁻⁹² The usage of organic sacrificial reductants such as tertiary amines or formate salts in these catalytic protocols is considered more environmentally friendly compared to metal hydrides.

The reduction of nitrogen containing functional groups is also of great use in organic synthesis (**Figure 1.20**). Nitrobenzene reduction to aniline derivatives was successfully reported by Hirao in 2004.⁹³ Liu developed a bio-compatible azide reduction method that works chemoselectively in aqueous media with extremely high functional group tolerance.⁹⁴ The method was applied on the reduction of DNA-link azide substrates.

Figure 1.20| Photoredox reduction of nitrogen-containing functional groups

Additionally, the conversion of the hydroxyl group to halide is of great interest because organic halides are favorable electrophiles in many organic transformations, from simple substitutions to eliminations and cross-coupling reactions. Among the mildest reported methods, the Appel reaction employs stoichiometric triphenyl phosphine together

with electrophilic halogen sources (CBr_4 , I_2).⁹⁵ However, the use of phosphine results in a considerable amount of waste and difficulty in by-product removal. In 2012, Stephenson invented an alternative photoredox catalytic protocol that works with both primary and secondary alcohols, delivering bromides and iodides with high functional group tolerance (**Figure 1.21**).⁹⁶ Proceeding via a different reactive intermediate, a Vilsmeier–Haack halogeniminium ion, the reaction eliminates the need for stoichiometric phosphine reagents.

Figure 1.21 | Direct conversion of alcohol to halide by photoredox catalysis

Figure 1.22 | Selected examples of photoredox oxidative transformation

The chemoselective oxidation of alcohols to carbonyl compounds have been well established using different protocols. The first photoredox protocol utilizing a ruthenium complex for the oxidation of benzylic alcohols dates back to 1984.⁹⁷ In this report, Cano-Yelo and Deronzier described the use of diazonium salts as the oxidative quencher for the ruthenium photoredox catalytic cycle. This method for alcohol oxidation has subsequently

been investigated by different groups. The most recent method features a metal-free condition with the use of 9-fluorenone as the photosensitizer and molecular oxygen in air as the terminal oxidant.⁹⁸

Beside alcohol oxidation, some organohalides were found to be oxidized to carbonyl functionality under photoredox conditions. For example, Jiao and co-workers reported aerobic oxidation of benzyl halides in 2011.⁹⁹ In addition, the oxidative interconversion of boronic acid derivatives to alcohols was developed by Xiao and Jorgensen.¹⁰⁰

In 2011, Stephenson demonstrated the photoredox oxidative deprotection of *para*-methoxybenzyl (PMB) ethers.¹⁰¹ The procedure could replace the use of super-stoichiometric strong oxidants such as DDQ or CAN.

In summary, photoredox catalysis does not only show its usefulness for bond formation methodologies, but it also plays significant roles in plenty of functional group interconversions. The oxidation, as well as reduction, of the key functional groups such as alcohol, halides, carboxylic acid, azide and nitro have been successfully developed with mild catalytic photoredox conditions. Nevertheless, there are still organic functional groups, for which, the photoredox reactivity (oxidative/ reductive processes) has not been fully discovered and utilized. One of them includes the classic phosphonium ylides, which are the subject of our study discussed in the next chapter.

1.3c - Metallaphotoredox catalysis for coupling reactions

Owing to the ability to modulate other substances' oxidation state via single electron transfer processes, photoredox catalysts are known to undergo synergistic catalysis with transition metal catalyst such as nickel, palladium or copper for a wide array of C-X and C-C bond formation.^{1, 102-105}

The conventional mechanism of transition metal catalyzed coupling reactions involves 3 elementary steps, namely, oxidative addition, transmetalation and reductive elimination. Because these steps usually alter the metal oxidation state by ± 2 , the typical catalytic processes cycle between M(0)-M(II) or M(II)-M(IV). With the introduction of photoredox catalyst on radicalphilic organometallic complexes, the oxidation state of (I) or (III) could be generated, which might lead to major changes in its chemistry (**Figure 1.23a**).

Figure 1.23 | (a) General overview of comparison between conventional transition metal catalysis and metallaphotoredox catalysis. (b) Energy diagram of reductive elimination

In 2015, co-operative metallaphotoredox catalysis for C-X bond formation was initiated by MacMillan's group. A series of aryl ethers were successfully synthesized via C-O bond formation employing an air stable nickel catalyst.⁵⁰ The study suggested an elusive mechanism that involves the formation of Ni(III) species through single electron oxidation. Since Ni(II) complexes have been known for their unfavorable endothermic reductive elimination in contrast to Pd complexes, DFT calculations and experimental evidences showed that the oxidized form of Ni(II), however, could accelerate this desirable process (**Figure 1.23b**). Given the high oxidation potential of Ir(dFCF₃ppy)₂(dtbbpy)PF₆, the formation of Ni(III) is thermodynamically allowed. It is noteworthy that the role of the photoredox catalyst does not only apply to Ni(II) oxidation, but it is also essential for Ni(I) reduction to Ni(0), thus closing the catalytic cycle. Therefore, the reaction would be considered as redox-neutral and does not require any stoichiometric sacrificial oxidant or reductant. This discovery has opened a new era of development for C-X bond construction later on.

Figure 1.24 | Experimental evidence for the necessity of light and photoredox catalyst in facilitating reductive elimination of an inert Ni(II) complex

In the context of C-N bond coupling, although the chemistry of copper and palladium in Ullman, Chan-Lam and Buchwald-Hartwig amination reactions has been well established in the past, it usually requires vigorous heating condition (>100°C). In 2016, a room temperature aryl amination protocol using air stable ligand-free Ni(II) salts together with a photoredox catalyst was successfully developed by MacMillan.⁴⁹ This remarkable

breakthrough applied the same mechanistic rationale as previously mentioned in the case of C-O bond formation. To address the issue of difficult reductive elimination of Ni(II) amine bound complex, a very low loading of [Ir] photocatalyst (0.02 mol%) was employed to facilitate the process. In a follow-up study, the amination scope was expanded to primary aryl amines (aniline derivatives) independently by Johannes *et al.*¹⁰⁶ One more example of C-N bond formation is by energy transfer mechanism.

In comparison to C-N and C-O bond formation, C-S coupling is generally less developed and more challenging when using transition metals due to the catalyst poisoning effect of thiols. In 2014, photoredox mediated nickel catalyzed cross-coupling of thiols with aryl and heteroaryl iodides via thiyl radicals was successfully reported by Johannes.¹⁰⁷ The mechanism for this reaction is slightly different from C-O or C-N coupling. Instead of SET oxidation of a nickel (II) complex, it was proposed that the thiyl radical first underwent radical abstraction by Ni(I) salt (following by SET reduction to Ni(II)) prior to oxidative addition. In addition, Manolikakes developed visible-light photoredox/nickel dual catalysis for the cross-coupling of sulfinic acid salts with aryl iodides.¹⁰⁸

Furthermore, visible light photoredox mediated C-P bond formation was also reported by Xiao and co-workers in 2015.¹⁰⁹ In this case, a P-centered radical from diarylphosphine oxides was generated *in situ* and underwent single electron transmetalation with the Ni(II) complex after oxidative addition, a similar mechanism to the aforementioned C-S coupling.

Overall, the key concept in reaction design is to obtain a transient Ni(III) complex that is much more prone to reductive elimination than a conventional Ni(II) complex. This can be done by either using a photoredox catalyst to modulate the nickel oxidation state through single electron transfer or trapping with radicals generated from photoredox

activation. By overcoming such limitations in nickel catalysis, a broadened usage and development of this methodology will be seen in the near future. One of the recent advances is the replacement of precious iridium in photosensitizer by organic dyes presented by Miyake in nickel catalyzed C-N and C-S coupling protocols.³⁷

Figure 1.25| Selected examples of C-X bond formation under metallaphotoredox condition

With a similar mechanistic rationale, dual nickel photoredox catalysis has been applied to forge C-C bonds in multiple catalytic cross-coupling reactions. The key step is the interception of a carbon centered radical by a Ni(II) complex after oxidative addition to generate a high energy Ni(III) species which can undergo facile reductive elimination. There

are several precursors and pathways to obtain these coupling fragment radicals. MacMillan reported the use of carboxylic acid, an abundant functionality presenting in plenty of natural products, via oxidative decarboxylation mediated by strong oxidizing photoredox catalyst like $\text{Ir}(\text{dFCF}_3\text{ppy})_2(\text{dtbbpy})\text{PF}_6$. The wide scope observed for the halide coupling partners (aryl, vinyl and alkyl) makes this dual catalysis strategy extremely useful in organic synthesis.¹¹⁰⁻¹¹³ In addition, other potential nucleophilic coupling partners have been developed, for examples, trifluoroborate (Molander¹¹⁴⁻¹¹⁵ *et al.*), silicate (Molander¹¹⁶ and Fensterbank¹¹⁷ *et al.*), alcohol derived oxalate ester (MacMillan¹¹⁸ *et al.*) or Hantzsch ester derivative (Molander¹¹⁹ and Nishibayashi¹²⁰ *et al.*).

Figure 1.26 | Selected examples of C-C bond formation under metallaphotoredox condition

A triple catalysis involving HAT, nickel and photoredox catalysts aid in C_{sp2} - C_{sp3} and C_{sp3} - C_{sp3} couplings was introduced by MacMillan.^{73, 121-122} In contrast to the oxidative radical generation strategy, the photoredox catalyst does not directly engage in substrate activation. Instead, it furnishes an active HAT catalyst species (quinuclidinium radical) that undergoes hydrogen abstraction to form coupling fragment radicals to intercept the Ni(II) complex. Moreover, reductive processes to generate radical fragments were reported in the cross-coupling of halides by Lei and co-workers.¹²³ This similar cross-electrophile coupling was demonstrated by MacMillan using stoichiometric organosilanes as bromide activators.¹²⁴

Other than nickel, photoredox catalysis has been successfully merged with a diverse range of transition metals, showing its power in redox modulation of organo-complexes. For example, recently copper catalyst has been employed in the co-operative protocols. In contrast to nickel chemistry, oxidative addition is a challenging barrier in copper catalysis. This issue has been solved by photoredox mediated radical oxidative addition to form Cu(III) species from Cu(I) or Cu(II). Numerous C-N and C-CF₃ bond formation methodologies using synergistic copper-photoredox catalysis were demonstrated by MacMillan,¹²⁵⁻¹²⁷ Hu,¹²⁸ and Sanford¹²⁹. Additionally, an increasing number of reports on the use of palladium, gold, cobalt, etc. merging with photoredox catalysis have been made over the last few years.¹⁰⁴

In summary, excellent redox regulatory capability of photoredox catalysts allows tremendous flexibility in reaction design, especially for transition metal catalysis. Highly reactive rare oxidation states of organo-complexes can be accessed in catalytic cycle, this significantly improves the kinetic profiles of the whole process. The broad range of metals utilized also means a substantial variety of new substrates can be employed for coupling protocols.

1.4 - Thesis Proposal

From the general introduction about photoredox catalysis and its recent application in organic transformations, it can be seen that the future of this new activation mode is wide open to tackle current challenging matters remaining in the synthetic field. To follow up, the objectives of my research work are to design C-H functionalization protocols for new classes of substrates, as well as to seek novel reaction pathways for classic reagents. This dissertation herein describes my work on 3 projects in separate chapters.

At first, a new route was proposed for cross radical coupling between allylic/benzylic/acyl radicals and ketyl radicals, which will be discussed in chapter 2. Based on the synergistic catalysis between HAT catalyst and photoredox catalyst, a cheap and widely available HAT catalyst, that furnishes the C_{sp^3} -H activation products, was developed. A wide array of bulky tertiary alcohols has been successfully synthesized in a “green” and efficient manner.

In chapter 3, a method to alter the chemistry of an old class of organic reagent - phosphonium ylide was proposed. It was hypothesized that the ylide (or phosphorane) could be acting as an electrophile (umpolung) for homo-/cross-coupling with another nucleophilic ylide molecule, generating alkenes of intriguing stereo-configuration.

The last chapter demonstrates my work on C_{sp^2} -H activation of aldehydes for C-C bond formation via two routes, namely, radical addition to electron deficient olefins and nickel catalyzed cross-coupling with aryl halides. These protocols allow direct access of non-symmetrical ketones from simple feedstock aldehydes under benign conditions with minimized undesirable decarbonylation products.

1.5 - References

1. Shaw, M. H.; Twilton, J.; MacMillan, D. W. C. *J. Org. Chem.* **2016**, *81*, 6898-6926.
2. Kalyanasundaram, K. *Coord. Chem. Rev.* **1982**, *46*, 159-244.
3. Juris, A.; Balzani, V.; Barigelletti, F.; Campagna, S.; Belser, P.; von Zelewsky, A. *Coord. Chem. Rev.* **1988**, *84*, 85-277.
4. Bock, C. R.; Connor, J. A.; Gutierrez, A. R.; Meyer, T. J.; Whitten, D. G.; Sullivan, B. P.; Nagle, J. *K. J. Am. Chem. Soc.* **1979**, *101*, 4815-4824.
5. Hoffmann, M. R.; Martin, S. T.; Choi, W.; Bahnmann, D. W. *Chem. Rev.* **1995**, *95*, 69-96.
6. Serpone, N.; Emeline, A. V. *J. Phys. Chem. Lett.* **2012**, *3*, 673-677.
7. Horst, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 812-847.
8. Tucker, J. W.; Stephenson, C. R. J. *J. Org. Chem.* **2012**, *77*, 1617-1622.
9. Incorvia, M. J.; Zink, J. I. *Inorg. Chem.* **1974**, *13*, 2489-2494.
10. Damrauer, N. H.; Cerullo, G.; Yeh, A.; Boussie, T. R.; Shank, C. V.; McCusker, J. K. *Science* **1997**, *275*, 54-57.
11. Dixon, I. M.; Collin, J.-P.; Sauvage, J.-P.; Flamigni, L.; Encinas, S.; Barigelletti, F. *Chem. Soc. Rev.* **2000**, *29*, 385-391.
12. Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322-5363.
13. Christopher, B. L.; Oliver, S. W. *Chem. Eur. J.* **2018**, *24*, 2039-2058.
14. Hernandez-Perez, A. C.; Collins, S. K. *Acc. Chem. Res.* **2016**, *49*, 1557-1565.
15. Reiser, O. *Acc. Chem. Res.* **2016**, *49*, 1990-1996.
16. Suva, P.; Oliver, R. *ChemCatChem* **2014**, *6*, 2477-2483.
17. Jing, Z.; Damien, C.; Frederic, D.; Pu, X.; Pierre, F. J.; Didier, G.; Jacques, L. *ChemCatChem* **2016**, *8*, 2227-2233.
18. Wiśniewska, J.; Marai, H.; Karocki, A.; Szaciłowski, K.; Kita, E.; Stasicka, Z. *J. Photochem. Photobiol. A: Chemistry* **2010**, *209*, 121-127.

19. Büldt, L. A.; Wenger, O. S. *Chem. Sci.* **2017**, *8*, 7359-7367.
20. Romero, N. A.; Nicewicz, D. A. *Chem. Rev.* **2016**, *116*, 10075-10166.
21. Davide, R.; Maurizio, F. *ChemCatChem* **2012**, *4*, 169-171.
22. Nicewicz, D. A.; Nguyen, T. M. *ACS Catal.* **2014**, *4*, 355-360.
23. Neckers, D. C.; Valdes-Aguilera, O. M. Photochemistry of the Xanthene Dyes. In *Advances in Photochemistry*, **2007**
24. Li, J.; Wang, H.; Liu, L.; Sun, J. *RSC Adv.* **2014**, *4*, 49974-49978.
25. Zheng, L.; Yi, Z.; Zheren, C.; Hao, S.; Xu, C. *Adv. Synth. Cat.* **2015**, *357*, 589-593.
26. Keshari, T.; Yadav, V. K.; Srivastava, V. P.; Yadav, L. D. S. *Green Chem.* **2014**, *16*, 3986-3992.
27. Ali, T.; Brian, D.; W., S. N. J.; Lech-Gustav, M.; Luc, B.; Volker, H.; Timothy, N. *Adv. Synth. Cat.* **2015**, *357*, 2180-2186.
28. Hari, D. P.; König, B. *Org. Lett.* **2011**, *13*, 3852-3855.
29. Pan, Y.; Kee, C. W.; Chen, L.; Tan, C.-H. *Green Chem.* **2011**, *13*, 2682-2685.
30. Ismaili, H.; Pitre, S. P.; Scaiano, J. C. *Catal. Sci. Technol.* **2013**, *3*, 935-937.
31. Matthias, N.; Kirsten, Z. *Chem. Eur. J.* **2013**, *19*, 6950-6955.
32. Gazi, S.; Ananthakrishnan, R. *Appl. Catal. B Environ.* **2011**, *105*, 317-325.
33. Deng-Tao, Y.; Qing-Yuan, M.; Jian-Ji, Z.; Ming, X.; Qiang, L.; Li-Zhu, W. *Eur. J. Org. Chem.* **2013**, *2013*, 7528-7532.
34. Matthias, N.; Stefan, F.; Burkhard, K.; Kirsten, Z. *Angew. Chem. Int. Ed.* **2011**, *50*, 951-954.
35. Hasegawa, E.; Takizawa, S.; Seida, T.; Yamaguchi, A.; Yamaguchi, N.; Chiba, N.; Takahashi, T.; Ikeda, H.; Akiyama, K. *Tetrahedron* **2006**, *62*, 6581-6588.
36. Seo, H.; Katcher, M. H.; Jamison, T. F. *Nat. Chem.* **2016**, *9*, 453-456.
37. Du, Y.; Pearson, R. M.; Lim, C.-H.; Sartor, S. M.; Ryan, M. D.; Yang, H.; Damrauer, N. H.; Miyake, G. M. *Chem. Eur. J.* **2017**, *23*, 10962-10968.
38. Fukuzumi, S.; Ohkubo, K. *Org. Biomol. Chem.* **2014**, *12*, 6059-6071.

39. Joshi-Pangu, A.; Lévesque, F.; Roth, H. G.; Oliver, S. F.; Campeau, L.-C.; Nicewicz, D.; DiRocco, D. A. *J. Org. Chem.* **2016**, *81*, 7244-7249.
40. Margrey, K. A.; Nicewicz, D. A. *Acc. Chem. Res.* **2016**, *49*, 1997-2006.
41. Romero, N. A.; Margrey, K. A.; Tay, N. E.; Nicewicz, D. A. *Science* **2015**, *349*, 1326-1330.
42. Roth, H. G.; Romero, N. A.; Nicewicz, D. A. *Synlett* **2016**, *27*, 714-723.
43. McNally, A.; Prier, C. K.; MacMillan, D. W. C. *Science* **2011**, *334*, 1114-1117.
44. N., H. M.; Adrián, G.-S.; Michael, T.; Basudev, S.; Frank, G. *Angew. Chem. Int. Ed.* **2016**, *55*, 4361-4366.
45. Collins, K. D.; Gensch, T.; Glorius, F. *Nat. Chem.* **2014**, *6*, 859-871.
46. Michael, T.; Adrián, G.-S.; Lena, P.; N., H. M.; Frank, G. *Angew. Chem. Int. Ed.* **2017**, *56*, 902-906.
47. Zhan, L.; P., Y. T. *Angew. Chem. Int. Ed.* **2012**, *51*, 10329-10332.
48. Welin, E. R.; Le, C.; Arias-Rotondo, D. M.; McCusker, J. K.; MacMillan, D. W. C. *Science* **2017**, *355*, 380-385.
49. Corcoran, E. B.; Pirnot, M. T.; Lin, S.; Dreher, S. D.; DiRocco, D. A.; Davies, I. W.; Buchwald, S. L.; MacMillan, D. W. C. *Science* **2016**, *353*, 279-283.
50. Terrett, J. A.; Cuthbertson, J. D.; Shurtleff, V. W.; MacMillan, D. W. C. *Nature* **2015**, *524*, 330-334.
51. Xuan-Zi, F.; Jia-Wei, R.; Hao-Lin, W.; Quan, Z.; Hong-Ping, D.; Da, T. J.; Cheng-Wen, X.; Li-Zhu, W.; Hai-Rong, T.; Jie, W. *Angew. Chem. Int. Ed.* **2018**, *57*, 8514-8518.
52. Ireland, J. F.; Wyatt, P. A. H., Acid-Base Properties of Electronically Excited States of Organic Molecules. In *Advances in Physical Organic Chemistry*, Gold, V., Ed. Academic Press: **1976**, *12*, 131-221.
53. Kimura, T.; Eto, T.; Takahashi, D.; Toshima, K. *Org. Lett.* **2016**, *18*, 3190-3193.
54. Gaoyuan, Z.; Ting, W. *Angew. Chem. Int. Ed.* **2018**, *57*, 6120-6124.

55. Huo, H.; Shen, X.; Wang, C.; Zhang, L.; Röse, P.; Chen, L.-A.; Harms, K.; Marsch, M.; Hilt, G.; Meggers, E. *Nature* **2014**, *515*, 100-103.
56. Yi, H.; Zhang, G.; Wang, H.; Huang, Z.; Wang, J.; Singh, A. K.; Lei, A. *Chem. Rev.* **2017**, *117*, 9016-9085.
57. Xie, J.; Jin, H.; Xu, P.; Zhu, C. *Tetrahedron Lett.* **2014**, *55*, 36-48.
58. Beatty, J. W.; Stephenson, C. R. J. *Acc. Chem. Res.* **2015**, *48*, 1474-1484.
59. Condie, A. G.; González-Gómez, J. C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2010**, *132*, 1464-1465.
60. Rueping, M.; Vila, C.; Koenigs, R. M.; Poscharny, K.; Fabry, D. C. *Chem. Commun.* **2011**, *47*, 2360-2362.
61. Magnus, R.; M., K. R.; Konstantin, P.; C., F. D.; Daniele, L.; Carlos, V. *Chem. Eur. J.* **2012**, *18*, 5170-5174.
62. DiRocco, D. A.; Rovis, T. *J. Am. Chem. Soc.* **2012**, *134*, 8094-8097.
63. Kohls, P.; Jadhav, D.; Pandey, G.; Reiser, O. *Org. Lett.* **2012**, *14*, 672-675.
64. Miyake, Y.; Nakajima, K.; Nishibayashi, Y. *J. Am. Chem. Soc.* **2012**, *134*, 3338-3341.
65. Ruiz Espelt, L.; Wiensch, E. M.; Yoon, T. P. *J. Org. Chem.* **2013**, *78*, 4107-4114.
66. Petronijević, F. R.; Nappi, M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2013**, *135*, 18323-18326.
67. P. Roberts, B. *Chem. Soc. Rev.* **1999**, *28*, 25-35.
68. Cuthbertson, J. D.; MacMillan, D. W. C. *Nature* **2015**, *519*, 74-77.
69. Jeffrey, J. L.; Terrett, J. A.; MacMillan, D. W. C. *Science* **2015**, *349*, 1532-1536.
70. Qvortrup, K.; Rankic, D. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 626-629.
71. Jeffrey, J. L.; Petronijević, F. R.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2015**, *137*, 8404-8407.
72. Liu, W.-Z.; Bordwell, F. G. *J. Org. Chem.* **1996**, *61*, 4778-4783.
73. Shaw, M. H.; Shurtleff, V. W.; Terrett, J. A.; Cuthbertson, J. D.; MacMillan, D. W. C. *Science* **2016**, *352*, 1304-1308.
74. McManus, J. B.; Nicewicz, D. A. *J. Am. Chem. Soc.* **2017**, *139*, 2880-2883.

75. Margrey, K. A.; Czaplyski, W. L.; Nicewicz, D. A.; Alexanian, E. J. *J. Am. Chem. Soc.* **2018**, *140*, 4213-4217.
76. Mukherjee, S.; Maji, B.; Tlahuext-Aca, A.; Glorius, F. *J. Am. Chem. Soc.* **2016**, *138*, 16200-16203.
77. Mukherjee, S.; Patra, T.; Glorius, F. *ACS Catal.* **2018**, *8*, 5842-5846.
78. Choi, G. J.; Zhu, Q.; Miller, D. C.; Gu, C. J.; Knowles, R. R. *Nature* **2016**, *539*, 268-271.
79. Chu, J. C. K.; Rovis, T. *Nature* **2016**, *539*, 272-275.
80. Chen, D.-F.; Chu, J. C. K.; Rovis, T. *J. Am. Chem. Soc.* **2017**, *139*, 14897-14900.
81. Shields, B. J.; Doyle, A. G. *J. Am. Chem. Soc.* **2016**, *138*, 12719-12722.
82. Minisci, F.; Bernardi, R.; Bertini, F.; Galli, R.; Perchinnunmo, M. *Tetrahedron* **1971**, *27*, 3575-3579.
83. Wang, C.-S.; Dixneuf, P. H.; Soulé, J.-F. *Chem. Rev.* **2018**, *118*, 7532-7585.
84. Proctor, R. S. J.; Davis, H. J.; Phipps, R. J. *Science* **2018**, *360*, 419-422.
85. Hedstrand, D. M.; Kruizinga, W. H.; Kellogg, R. M. *Tetrahedron Lett.* **1978**, *19*, 1255-1258.
86. Hironaka, K.; Fukuzumi, S.; Tanaka, T. *J. Chem. Soc. Perkin Trans. II* **1984**, 1705-1709.
87. Fukuzumi, S.; Mochizuki, S.; Tanaka, T. *J. Phys. Chem.* **1990**, *94*, 722-726.
88. Kern, J.-M.; Sauvage, J.-P. *J. Chem. Soc. Chem. Commun.* **1987**, 546-548.
89. Narayanam, J. M. R.; Tucker, J. W.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2009**, *131*, 8756-8757.
90. Nguyen, J. D.; D'Amato, E. M.; Narayanam, J. M. R.; Stephenson, C. R. J. *Nat. Chem.* **2012**, *4*, 854-859.
91. Wallentin, C.-J.; Nguyen, J. D.; Finkbeiner, P.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2012**, *134*, 8875-8884.
92. Nguyen, J. D.; Tucker, J. W.; Konieczynska, M. D.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2011**, *133*, 4160-4163.
93. Toshikazu, H.; Jun, S.; Naoki, O. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1763-1764.

94. Chen, Y.; Kamlet, A. S.; Steinman, J. B.; Liu, D. R. *Nat. Chem.* **2011**, *3*, 146-153.
95. Rolf, A. *Angew. Chem. Int. Ed.* **1975**, *14*, 801-811.
96. Dai, C.; Narayanam, J. M. R.; Stephenson, C. R. J. *Nat. Chem.* **2011**, *3*, 140-145.
97. Cano-Yelo, H.; Deronzier, A. *Tetrahedron Lett.* **1984**, *25*, 5517-5520.
98. Schilling, W.; Riemer, D.; Zhang, Y.; Hatami, N.; Das, S. *ACS Catal.* **2018**, *8*, 5425-5430.
99. Su, Y.; Zhang, L.; Jiao, N. *Org. Lett.* **2011**, *13*, 2168-2171.
100. You-Quan, Z.; Jia-Rong, C.; Xiao-Peng, L.; Liang-Qiu, L.; L., D. R.; Anker, J. K.; Wen-Jing, X. *Angew. Chem. Int. Ed.* **2012**, *51*, 784-788.
101. Tucker, J. W.; Narayanam, J. M. R.; Shah, P. S.; Stephenson, C. R. J. *Chem. Commun.* **2011**, *47*, 5040-5042.
102. Skubi, K. L.; Blum, T. R.; Yoon, T. P. *Chem. Rev.* **2016**, *116*, 10035-10074.
103. Parasram, M.; Gevorgyan, V. *Chem. Soc. Rev.* **2017**, *46*, 6227-6240.
104. Twilton, J.; Le, C.; Zhang, P.; Shaw, M. H.; Evans, R. W.; MacMillan, D. W. C. *Nat. Rev. Chem.* **2017**, *1*, 0052.
105. Lang, X.; Zhao, J.; Chen, X. *Chem. Soc. Rev.* **2016**, *45*, 3026-3038.
106. Oderinde, M. S.; Jones, N. H.; Juneau, A.; Frenette, M.; Aquila, B.; Tentarelli, S.; Robbins, D. W.; Johannes, J. W. *Angew. Chem. Int. Ed.* **2016**, *55*, 13219-13223.
107. Oderinde, M. S.; Frenette, M.; Robbins, D. W.; Aquila, B.; Johannes, J. W. *J. Am. Chem. Soc.* **2016**, *138*, 1760-1763.
108. Liu, N.-W.; Hofman, K.; Herbert, A.; Manolikakes, G. *Org. Lett.* **2018**, *20*, 760-763.
109. Jun, X.; Ting-Ting, Z.; Jia-Rong, C.; Liang-Qiu, L.; Wen-Jing, X. *Chem. Eur. J.* **2015**, *21*, 4962-4965.
110. Johnston, C. P.; Smith, R. T.; Allmendinger, S.; MacMillan, D. W. C. *Nature* **2016**, *536*, 322-325.
111. Zuo, Z.; Ahneman, D. T.; Chu, L.; Terrett, J. A.; Doyle, A. G.; MacMillan, D. W. C. *Science* **2014**, *345*, 437-440.

112. Noble, A.; McCarver, S. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2015**, *137*, 624-627.
113. Zuo, Z.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 5257-5260.
114. Tellis, J. C.; Primer, D. N.; Molander, G. A. *Science* **2014**, *345*, 433-436.
115. Primer, D. N.; Karakaya, I.; Tellis, J. C.; Molander, G. A. *J. Am. Chem. Soc.* **2015**, *137*, 2195-2198.
116. Jouffroy, M.; Primer, D. N.; Molander, G. A. *J. Am. Chem. Soc.* **2016**, *138*, 475-478.
117. Vincent, C.; Lise-Marie, C.; Etienne, D.; Jean-Philippe, G.; Cyril, O.; Louis, F. *Angew. Chem. Int. Ed.* **2015**, *54*, 11414-11418.
118. Zhang, X.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2016**, *138*, 13862-13865.
119. Gutiérrez-Bonet, Á.; Tellis, J. C.; Matsui, J. K.; Vara, B. A.; Molander, G. A. *ACS Catal.* **2016**, *6*, 8004-8008.
120. Kazunari, N.; Sunao, N.; Yoshiaki, N. *Angew. Chem. Int. Ed.* **2016**, *55*, 14106-14110.
121. Le, C.; Liang, Y.; Evans, R. W.; Li, X.; MacMillan, D. W. C. *Nature* **2017**, *547*, 79-83.
122. Jack, T.; Melodie, C.; A., D. D.; T., R. R.; W., D. I.; C., M. D. W. *Angew. Chem. Int. Ed.* **2018**, *57*, 5369-5373.
123. Duan, Z.; Li, W.; Lei, A. *Org. Lett.* **2016**, *18*, 4012-4015.
124. Zhang, P.; Le, C. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2016**, *138*, 8084-8087.
125. Liang, Y.; Zhang, X.; MacMillan, D. W. C. *Nature* **2018**, *559*, 83-88.
126. Kautzky, J. A.; Wang, T.; Evans, R. W.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2018**, *140*, 6522-6526.
127. Le, C.; Chen, T. Q.; Liang, T.; Zhang, P.; MacMillan, D. W. C. *Science* **2018**, *360*, 1010-1014.
128. Mao, R.; Frey, A.; Balon, J.; Hu, X. *Nat. Catal.* **2018**, *1*, 120-126.
129. Ye, Y.; Sanford, M. S. *J. Am. Chem. Soc.* **2012**, *134*, 9034-9037.

Photoredox mediated C-H activation for intermolecular cross-radical radical coupling with ketyl radicals

Abstract: Ketyl radicals, useful synthetic intermediates derived from ketones or aldehydes via single electron reduction, have long been employed in organic synthesis. However, the scope of the intermolecular cross radical-radical coupling of these species has been limited due to their tendency to dimerize under vigorous reaction conditions. Recent photoredox methodology developments features efficient pathways to obtain not only the ketyl radicals, but also a wide array of other possible radical coupling partners, for instance, allylic, benzylic and acyl radicals. Therefore, it is of great interest to develop a method for the cross radical-radical coupling, which will significantly broaden the synthetic utility of the ketyl radicals. The expected products of these reactions, highly substituted alcohols, resemble products achieved from the trivial Barbier carbonyl additions. On the other hand, by starting from feedstock and naturally derived chemicals without any pre-activation, it will be superior for the synthesis of challenging bulky tertiary alcohols in an industrial context.

2.1 - Introduction

The tertiary alcohol scaffold is prevalent in organic molecules, ranging from pharmaceutical and agrochemical compounds to natural products (**Figure 2.1**). Traditional synthesis of alcohols, specifically the tertiary alcohol, utilized the Barbier type carbonyl addition reactions developed in the last century.¹ Nevertheless, the organometallic reagents involved are pyrophoric and pose dangerous fire hazards upon air exposure. They are also highly reactive and usually exhibit low functional group tolerance in the preparation of complex molecules. Furthermore, the use of stoichiometric amounts of metallic reagents is unfavorable from environmental and sustainable aspects. Additionally, the nucleophilic addition of organometallic reagents to ketones is sometimes not straightforward as compared to the reaction of aldehydes, owing to the inherent steric congestion around carbonyl group and the strong basicity of the reagents. Hence, a range of undesirable side reactions, for example, ketone reduction and aldol condensation, usually leads to a complex mixture of products obtained.²

Figure 2.1| Examples of aryl tertiary alcohol occurrence in natural and artificial products

Figure 2.2| Overview of tertiary alcohol synthetic pathways

In the last few years, a handful of new methodologies for carbonyl addition have been invented to overcome such drawbacks (**Figure 2.2**). For examples, milder organometallic reagents were developed to eliminate the need for anhydrous reaction conditions. Plenty of carbonyl additions now can be done in aqueous solvent, even though stoichiometric usage of metals is still necessary.³⁻⁵ Moreover, methods involving transition metals such as nickel, copper and palladium catalyzed the reductive coupling between organohalides and carbonyl derivatives have been developed.⁶ Moving beyond traditional designs of carbonyl addition, Krische presented the first reductive coupling between olefin-derived nucleophiles and primary/secondary alcohols.⁷ The concept of using the unsaturated hydrocarbon as a carbanion equivalent was also demonstrated by Buchwald and Liu in the discovery of copper-catalyzed asymmetric alkylation of ketones.⁸ Subsequently, aldehydes were harnessed as latent alkyl carbanions for the additions to carbonyl compounds under ruthenium catalysis as reported by Li *et al.*⁹ (**Figure 2.3**).

The trend of reinventing the carbonyl addition reaction not only covered charge interaction mechanisms, but also extended to the field of radical chemistry (**Figure 2.4**). In 2016, Chi and co-workers demonstrated a metal-free process using a carbene catalyst to

facilitate the addition of benzyl halides to activated ketone substrates via a proposed radical pathway.¹⁰ Glorius discovered rare examples of intermolecular radical addition to carbonyl acceptors under photoredox conditions earlier this year.¹¹ On the other hand, carbonyl substrates can be transformed into ketyl radical intermediates, which undergo subsequent C-C bond formation, by samarium (II) halides - the potent single electron reductants.¹²⁻¹⁷

Figure 2.3| Remarkable inventions in carbonyl alkylation via transition metal catalysis using olefins or aldehydes as latent alkyl carbanions

Figure 2.4| Selected examples on the radical carbonyl alkylation

On the rise of photoredox chemistry over the last decade, the radical pathways that involve ketyl radicals have been developed extensively (**Figure 2.5a**). In 2013, Knowles and co-workers first reported the proton coupled electron transfer (PCET) approach to generate

challenging ketyl radicals. These intermediates then underwent intramolecular cyclization with olefin or imine functional groups.¹⁸⁻¹⁹ The formation of ketyl radical via photoredox catalysis was developed independently by Rueping through photoinduced electron transfer.²⁰⁻²² It was revealed that under *in situ* activation of a hole catalyst such as an ammonium cation or an acid, the carbonyl reduction potential significantly drops so that a wide array of photoredox catalysts can be employed to achieve the ketyl radicals. Under the reaction condition, these radicals were found to dimerize²¹, couple with α -amino radicals²⁰ and add to olefins²².

Figure 2.5 | Recent developments in ketyl radical chemistry. (a) Summary of carbonyl addition via radical approaches. **(b)** Recent application of synergistic photoredox and Hydrogen atom transfer catalysis in C-C bond formation processes via transient radicals. R: aryl or alkyl substituents. EWG: electron withdrawing groups. X: heteroatoms (O, N).

In 2016, Ngai *et al.* reported another utility of the ketyl radical - the intermolecular addition to electron deficient styrene derivatives.²³⁻²⁴ In comparison to olefin addition, cross

radical-radical coupling of ketyl radicals may show broader applications. However, they are rarely reported in literature. The previous success on intramolecular version was presented by Zhu in 2016 in an attempt to synthesize multi-substituted nitrogen heterocycles.²⁵ Another scarce example of intermolecular cross radical coupling between α -heteroatom (O, N) stabilized radicals and the ketyl radical was developed by Xiao and co-workers.²⁶ To the best of our knowledge, there has been no report on the use of simple transient radicals derived from hydrocarbon feedstock or natural sources in the analogous reaction.

In recent years, C-H activation is a promising and highly favorable process for synthesis because of minimal pre-functionalization required on the substrates.²⁷⁻²⁹ Being intrigued by elegant approaches to transient radicals demonstrated by MacMillan in various C-X and C-C bond formation protocols (**Figure 2.5b**),³⁰⁻³⁴ we questioned whether they can be applied in radical-radical cross coupling with ketyl radicals, leading to a quick access of bulkily substituted alcohols. The reaction would resemble a hydrocarbonation to ketones which exhibits absolute atom economy, and be of great interest in green chemistry.³⁵ In this chapter, we report our design of such a reaction and show its potential application in organic synthesis.

2.2 - Results and Discussion

Our model reactions between benzophenone (**2.2**) and cyclohexene (**2.3**) have been examined under various photoredox conditions (**Table 2.1**). The initial use of acid additives (*ie.* benzoic acid)²⁰⁻²¹ to facilitate ketone single electron reduction gave detrimental results. In contrast, base additives such as carbonate salts increased the reaction efficiency, possibly by accelerating the thiolate formation. In addition, protic solvents including alcohols or trace water gave rise to a dimerization product (**2.7**). The choice of thiol catalyst is a decisive factor in this protocol. From our screening results, we have concluded two optimized conditions, in which, both gave excellent yields of product in the model reactions (>85%). Condition A features the direct use of inexpensive potassium thioacetate without additional base, while condition B employs tri-isopropylsilanethiol together with potassium carbonate, all in 10 mol% loading. Although the triplet state benzophenone has been known as a hydrogen atom transfer catalyst that provides trace coupling product with cyclohexene, it is merely excited by the UV light, not by the blue light in our set-up. Our control experiments ruled out this pathway, reaffirming the necessity of all parameters.³⁶

A plausible mechanism for the ketone hydrocarbonation is delineated in **Figure 2.6**. After initial excitation by blue light (455 nm), the photosensitizer (**2.1**) transforms into its long-lived triplet excited-state (lifetime 1900 ns).³⁷⁻³⁸ Upon ketone oxidative quenching to generate the active ketyl radical, the photoredox catalyst turns to its higher oxidation state which exhibits a good oxidation power.³⁹ Consequently, single electron oxidation of thiolate to give the thiyl radical should be an thermodynamically favorable process. It is noteworthy that the reported reduction potential of typical aryl ketones lies in the range of -2.1 V to -1.5 V ($E_{\text{Ph}_2\text{CO}} = -1.87 \text{ V vs SCE}$) which is a workable range for the photoredox catalyst **2.1**.⁴⁰⁻⁴¹

We anticipated that the electrophilic thiyl radical would serve as a powerful hydrogen atom transfer catalyst which abstracts hydrogen from the allylic/benzylic C_{sp3}-H bonds (BDE for cyclohexene C-H_{allylic} = 83.2 kcal·mol⁻¹, BDE for toluene C-H_{benzylic} = 89.9 kcal·mol⁻¹).⁴²⁻⁴³ In fact, the presence of cyclohexenyl radical was confirmed by the isolation of the TEMPO trapping product **2.8**. The transient allylic/benzylic radical can undergo fast cross radical-radical coupling with ketyl radical to afford the desired tertiary alcohol product **2.4**.

Figure 2.6| Proposed mechanism for hydrocarbonation of ketone under photoredox condition. Cation [M⁺] can be a metal ion (K⁺ in the case of KSAC) or proton which has tendencies for ionic bond to ketyl radical intermediates.

Table 2.1 | Selected results for the optimization of reaction conditions

Entry	Photocatalyst (1 mol%)	HAT Catalyst (10 mol%)	Additive (10 mol%)	Results ^[a]
1	Ru(bpy) ₃ (PF ₆) ₂	HAT-1	K ₂ CO ₃	N.R.
2	Ru(phen) ₃ Cl ₂	HAT-1	K ₂ CO ₃	N.R.
3	Ir(ppy) ₂ (bpy)PF ₆	HAT-1	K ₂ CO ₃	Trace 2.4
4	Ir(ppy) ₂ (dtbbpy)PF ₆	HAT-1	K ₂ CO ₃	2.7
5	Ir(dFCF ₃ ppy) ₂ (dtbbpy)PF ₆	HAT-1	K ₂ CO ₃	N.D.
6	<i>fac</i> -Ir(ppy) ₃	HAT-1	K ₂ CO ₃	40% 2.4
7 ^[b]	<i>fac</i> -Ir(ppy) ₃	HAT-1	-	58% 2.4
8	<i>fac</i> -Ir(ppy) ₃	HAT-2	-	90% 2.4
9	<i>fac</i> -Ir(ppy) ₃	HAT-3	-	N.D.
10	<i>fac</i> -Ir(ppy) ₃	HAT-4	K ₂ CO ₃	85% 2.4
11	<i>fac</i> -Ir(ppy) ₃	HAT-5	K ₂ CO ₃	N.D.
12	-	-	-	N.R.
13 ^[c]	<i>fac</i> -Ir(ppy) ₃	HAT-2	-	N.R.
14	<i>fac</i> -Ir(ppy) ₃	-	-	2.7
15	-	HAT-2	-	N.R.

The reactions were carried out under inert atmosphere (Ar or N₂) using 0.2 mmol benzophenone and 1.0 mmol cyclohexene in 0.1 M acetone solution. [a] Isolated yield. [b] Reaction in DMSO 0.1 M solution. [c] Reaction in the dark. N.R. No reaction. N.D. Not determined, a complex mixture was obtained.

With the optimized conditions in hand, we first evaluated the scope of the carbonyl alkylation on a wide range of ketones (**Figure 2.7**). Diaryl ketones generally provided good coupling efficiency, in despite of steric hindrance. However, *ortho*-substituted aryl ketone (**2.16**) gave significantly lower yield compared with the *para*- and *meta*- counterpart (**2.12** and **2.14**). It is interesting that the benzylic C_{ssp3}-H bond on the ketone substrate (**2.12**, **2.16** and **2.18**) was not activated by the thiyl radical, hence, the selective cross-coupling with cyclohexene was observed. Strong electron donating substituents such as –OMe (**2.13**) or –NH₂ (**2.15**) present on the ketone substrates imposes negative impact to the reaction outcome. Although these substituents can stabilize the ketyl radical intermediates, they raise the energy barrier for single electron reduction process. The conversion of the ketone substrates in these cases was not completed even after 48 hours. A cyclic diaryl ketone gave a moderate yield of 48% (**2.17**), possibly because of a reduced steric shield which help to stabilize ketyl radical intermediate.

In addition, heterocyclic aryl ketones are viable substrates that produced bulky tertiary alcohols in moderate to good yields (59%-85%). Electron deficient heterocycles (pyridine in **2.21**, benzothiazole in **2.24**) and electron rich heterocycles (furan in **2.23**, indole in **2.25**) did not show any substantial effect in the reactivity. When these non-symmetrical ketones were employed, the alcohol products were obtained as a diastereoisomeric mixture (dr $\approx$ 1:1 in all the cases).

To our delight, aryl-alkyl ketones can undergo the cross-radical coupling reaction efficiently, although extended reaction times were required. This significantly broadens the range of tertiary alcohols that can be synthesized using our benign protocol. Ketones with cyclic alkyl (**2.26**) and linear alkyl (**2.29**) worked equally well. Moreover, benzylic ketone (**2.18**), branched primary and secondary alkyl ketones (**2.27** and **2.28**) also furnished tertiary

Figure 2.7 | Substrate scope evaluation for various ketones. All reactions were carried out under inert atmosphere of Argon, with 0.2 mmol ketone and 1.0 mmol cyclohexene for 12-16 hours, unless otherwise indicated. Yields given in parentheses are isolated yield. a, condition A using KSAc (10 mol%). b, condition B using tri-isopropylsilanethiol (10 mol%) and K₂CO₃ (10 mol%). Diastereoisomers were obtained

without selectivity ($dr \approx 1:1$) for all the cases using unsymmetrical ketones. *Reactions were carried out for 72 hours.

Figure 2.8| Substrate scope evaluation for various allylic and benzylic $\text{C}_{\text{sp}^3}\text{-H}$. All reactions were carried out under inert atmosphere of Argon, with 0.2 mmol benzophenone and 0.6 mmol olefin/alkyl benzene for 12-16 hours, unless otherwise indicated. Yields given in parentheses are isolated yield, a, condition A using KSAc (10 mol%). b, condition B using tri-isopropylsilanethiol (10 mol%) and K_2CO_3 (10 mol%). *Regioisomers were obtained, the main isomers are depicted in all cases. †Additional loading of olefin required (see Supplementary Information for more details). Blue circles indicate regioisomeric sites.

alcohols with synthetically useful yields (>50%). Additionally, trifluoro substituted acetophenone reacted, albeit slowly, to form trifluoromethyl tertiary alcohol (**2.19**). Even though significant effort has been made to optimize reaction conditions for the alkylation of dialkyl ketones and aldehydes, no desirable outcome has been achieved so far. It is presumably due to the high reduction potential of the dialkyl ketones and the short lifetime of the aldehyde derived ketyl radicals.

We next sought to expand this reaction from the model substrate - cyclohexene to other allylic/benzylic systems (**Figure 2.8**). Conjugated alkene - cycloheptatriene provided a good yield of 80% (**2.30**), owing to greater stability of the transient radical. Apart from that, cycloalkenes in various ring sizes, both cycloheptene (**2.31**) and *cis*-cyclooctene (**2.32**), gave reasonably good results (>60%). Heterocyclic alkenes with a polarized double bond, for examples, dihydropyran and dihydrofuran, furnished regioisomeric product mixtures due to the 1,3-allylic rearrangement. Notably, free-hydroxyl containing olefins can be viable substrates for the reaction as well, although a low yield was observed. It has been challenging to synthesize a carbanion equivalent with such unprotected hydroxyl presenting. Further successful examples with acyclic linear terminal (**2.39**), internal olefins (**2.38**) and branched olefin (**2.37**) reaffirm the applicability of our method.

Following our previous success in aldehyde C_{sp2}-H activation via the HAT process,⁴⁴ we have tested and achieved benzoin condensation type product (**2.40**) in the cross-radical coupling between an acyl radical and a ketyl radical. It is noteworthy that our protocol works not only on C_{sp3} allylic radicals, but also on different type of radical such as the C_{sp2} acyl radical. Moreover, a series of benzylic C_{sp3}-H substrates were successfully employed in the carbonyl alkylation. Tertiary (**2.41**) and secondary (both cyclic – **2.42** and acyclic – **2.43**, **2.44**) benzylic substrates gave moderate to good yields (50-82%). However, a primary

benzylic substrate only provided a low yield (**2.45**), attributed to the short-lived primary radical intermediate. In addition, it is of considerable value for the tolerance of a bromo substituent, which will allow multi-functionalization of the substrate. It has been problematic for the classical organometallic reagents in this aspect.

Figure 2.9| Application of the visible-light photoredox mediated hydrocarbonation. All

reactions were carried out under inert atmosphere of Argon, with 0.2 mmol ketone substrate and 0.6 mmol olefin/alkyl benzene for 24 hours, unless otherwise indicated. Yields given in parentheses are isolated yield. a, condition A using KSAc (10 mol%). b, condition B using tri-isopropylsilanethiol (10 mol%) and K_2CO_3 (10 mol%).

*Diastereoisomers were obtained. †Additional loading of olefin required (see Supplementary Information for

more details). ^{††}Mixture of regio-isomeric products were obtained; the yield is reported for the main isomer depicted. dr: diastereoisomeric ratio. rr: regioisomeric ratio. Blue circles indicate regioisomeric sites.

Finally, mild reaction condition, the central advantage of this protocol, has been demonstrated in late-stage diversification of advanced, highly functionalized synthetic intermediates and natural products. As being illustrated in **Figure 2.9**, Fenofibrate, a top-selling pharmaceutical for treatment of Hypercholesterolemia, successfully underwent the cross-radical coupling reaction, forming alcohol **2.46** in a moderate yield of 64%. The reaction is chemoselective at the carbonyl group, leaving the ester group intact. Furthermore, the potential pharmaceutical precursors (**2.47** and **2.48**) were smoothly synthesized in one step from inexpensive commercially available substrates.

More beneficially, alkene-containing natural products and derivatives may likewise be employed directly as carbanion equivalents for the carbonyl alkylation. Citronellyl acetate reacted with benzophenone with complete conversion, giving a mixture of regio-isomers, from which, the main isomer (**2.49**) was isolated and characterized. Naturally occurring terpenes such as α -Pinene and γ -Terpinene with multiple allylic C_{sp3}-H sites selectively reacted at the ring carbons to deliver the tertiary alcohol products in 53% and 40% respectively.

2.3 - Conclusion

In conclusion, we have developed a protocol for direct hydrocarbonation of aryl ketones to obtain various challenging tertiary alcohols. The reactions proceed via an intermolecular cross radical-radical coupling between a semi-persistent ketyl radical and a transient alkyl radical generated through HAT process using thiol catalyst and photoredox catalyst. Although aldehydes and dialkyl ketones do not undergo the reaction, several examples of aryl ketones were shown to react smoothly with tolerance of other functional groups.

Our catalytic method eliminates the need of pre-functionalization steps including halogenation and metalation, also avoids the usage of stoichiometric reactive reducing reagents. The quick modification of natural products as well as pharmaceuticals was demonstrated as examples of this mild and simple methodology.

2.4 - Experimental Section

Catalytic reactions were conducted under inert atmosphere. Commercially available chemicals were purchased and used without further purification unless otherwise stated. All reactions were monitored by TLC Silica gel 60 F₂₅₄ using fluorescence quenching (UV – 254 nm), basic potassium permanganate or phosphomolybdic acid staining method. Flash column chromatography for purification uses Silica gel 60 (40-63 μ m). Technical grade solvents were used for chromatography and distilled prior to use. High resolution mass spectrometry (HRMS) was recorded on a time-of-flight (TOF) machine. NMR spectra were recorded at 500 MHz or 400 MHz for ^1H ; 125 Hz or 100 Hz for ^{13}C nuclear. Chemical shifts (ppm) of all the peaks in ^1H -NMR were calibrated to either TMS residue peak (0 ppm) or trace chloroform peak (7.26 ppm) in CDCl_3 . Coupling constants (J) are given in Hz. Following abbreviations classify the multiplicity: s = singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, m = multiplet, brs = broad singlet. Blue light irradiation uses 34 W Blue LED H150 made by Kessil. Photoredox catalyst *fac*-Ir(ppy)₃ was prepared according to reported method.

2.4a - Procedure A

To an oven dried 8 mL vial equipped with a magnetic stirrer was added *fac*-Ir(ppy)₃ (1 mol%), ketone (0.2 mmol) (if solid), allylic/benzylic C_{sp3}-H substrate (2-5 equiv) (if solid) and potassium thioacetate (10 mol%). The vial was brought into a glovebox under Ar atmosphere and acetone (2 mL), ketone (0.2 mmol) (if liquid), allylic/benzylic C_{sp3}-H substrate (2-5 equiv) (if liquid) was added. The vial was sealed tightly, taken out from the glovebox and put under blue light irradiation from a 34 W LED (with an USB cooling fan). After 12-72 hours, the reaction mixture was concentrated under vacuum and subsequently purified by flash column chromatography (Ethylacetate/Hexane eluent) to afford the product of interest.

2.4b - Procedure B

To an oven dried 8 mL vial equipped with a magnetic stirrer was added *fac*-Ir(ppy)₃ (1 mol%), ketone (0.2 mmol) (if solid), allylic/benzylic C_{sp3}-H substrate (2-5 equiv) (if solid) and potassium carbonate (10 mol%). The vial was brought into a glovebox under Ar atmosphere, then acetone (2 mL), ketone (0.2 mmol) (if liquid), allylic/benzylic C_{sp3}-H substrate (2-5 equiv) (if liquid) and tri-isopropylsilanethiol (10 mol%) was added by using micropipette. The vial was sealed tightly, taken out from the glovebox and put under blue light irradiation from a 34 W LED (with an USB cooling fan). After 12-72 hours, the reaction mixture was concentrated under vacuum and subsequently purified by flash column chromatography (Ethylacetate/Hexane eluent) to afford the product of interest.

2.4c - Compound characterization

Following **Procedure A**. Ketone: 36.4 mg (0.2 mmol), *fac*-Ir(ppy)₃: 1.3 mg (1 mol%), KSAc: 2.3 mg (10 mol%), Acetone: 2 mL (0.1 M), Cyclohexene: 102 μ L (5 equiv). Reaction time: 12 hours. White solid obtained 47.6 mg (**90%**).

¹H-NMR (400 MHz; CDCl₃) δ 7.61-7.13 (m, 10H_{Ar}), 5.99-5.94 (m, 1H_{vinyl}), 5.51-5.48 (m, 1H_{vinyl}), 3.49-3.42 (m, 1H_{allylic}), 2.21 (brs, 1H_{OH}), 2.04-1.43 (m, 6H)

¹³C-NMR (100 MHz; CDCl₃) δ 146.9, 145.5, 133.8, 128.3, 128.0, 126.6, 126.4, 126.2, 126.0, 125.5, 79.4, 43.7, 25.3, 23.8, 22.0

HRMS for C₁₉H₂₀O [M+H]⁺ calc. 265.1592, found 265.1592

Following **Procedure A**. Ketone: 40.0 mg (0.2 mmol), *fac*-Ir(ppy)₃: 1.3 mg (1 mol%), KSAc: 2.3 mg (10 mol%), Acetone: 2 mL (0.1 M), Cyclohexene: 102 μ L (5 equiv). Reaction time: 12 hours. Colorless oil obtained 44.0 mg (**78%**). ¹H-NMR of crude reaction mixture shows **dr** = **1:1**

Mixture of 2 diastereoisomers

$^1\text{H-NMR}$ (500 MHz; CDCl_3) δ 7.57-7.53 (m, 2H_{Ar}), 7.44-7.41 (m, 2H_{Ar}), 7.33-7.14 (m, 3H_{Ar}), 7.00-6.92 (m, 2H_{Ar}), 6.00-5.94 (m, $1\text{H}_{\text{vinyllic}}$), 5.49-5.44 (m, $1\text{H}_{\text{vinyllic}}$), 3.43-3.37 (m, $1\text{H}_{\text{allylic}}$), 2.21 (brs, 1H_{OH}), 2.03-1.97 (m, $2\text{H}_{\text{allylic}}$), 1.80-1.39 (m, 4H)

$^{13}\text{C-NMR}$ (100 MHz; CDCl_3) δ 161.5 (d, $J_{\text{CF}} = 244$ Hz), 161.3 (d, $J_{\text{CF}} = 243$ Hz), 146.7, 145.4, 142.6 (d, $J_{\text{CF}} = 3.3$ Hz), 141.3 (d, $J_{\text{CF}} = 3.0$ Hz), 134.0, 134.0, 128.4, 128.1, 127.8 (d, $J_{\text{CF}} = 7.8$ Hz), 127.2 (d, $J_{\text{CF}} = 7.7$ Hz), 126.7, 126.3, 126.2, 126.1, 126.0, 125.4, 114.9 (d, $J_{\text{CF}} = 27.5$ Hz), 114.7 (d, $J_{\text{CF}} = 27.5$ Hz), 79.1, 43.8, 43.7, 25.2, 23.8, 23.7, 21.9

HRMS for $\text{C}_{19}\text{H}_{19}\text{FO}$ $[\text{M}+\text{H}]^+$ calc. 283.1498, found 283.1500

Following **Procedure A**. Ketone: 39.3 mg (0.2 mmol), *fac*-Ir(ppy)₃: 1.3 mg (1 mol%), KSAc: 2.3 mg (10 mol%), Acetone: 2 mL (0.1 M), Cyclohexene: 102 μL (5 equiv). Reaction time: 12 hours. Colorless oil obtained 47.3 mg (**85%**). $^1\text{H-NMR}$ of crude reaction mixture shows **dr** = **1:1**

Mixture of 2 diastereoisomers

$^1\text{H-NMR}$ (500 MHz; CDCl_3) δ 7.59-7.57 (m, 1H_{Ar}), 7.47-7.44 (m, 2H_{Ar}), 7.36-7.24 (m, 3H_{Ar}), 7.19-7.07 (m, 3H_{Ar}), 5.96-5.93 (m, $1\text{H}_{\text{vinyllic}}$), 5.52-5.46 (m, $1\text{H}_{\text{vinyllic}}$), 3.45-3.93 (m, $1\text{H}_{\text{allylic}}$), 2.29 (s, 1.5H_{Me}), 2.27 (s, 1.5H_{Me} of isomer), 2.18 (brs, 0.5H_{OH}), 2.17 (brs, 0.5H_{OH} of isomer), 2.02-1.97 (m, $2\text{H}_{\text{allylic}}$), 1.79-1.42 (m, 4H)

$^{13}\text{C-NMR}$ (125 MHz; CDCl_3) δ 147.0, 145.7, 143.9, 142.6, 136.1, 135.7, 133.6, 133.5, 129.0, 128.7, 128.2, 127.9, 126.6, 126.5, 126.4, 126.1, 125.9, 125.4, 125.3, 79.3, 79.2, 43.7, 43.6, 25.3, 23.8, 23.7, 22.0, 20.9

HRMS for $C_{20}H_{22}O$ $[M+H]^+$ calc. 279.1749, found 279.1754

Following **Procedure A**. Ketone: 42.4 mg (0.2 mmol), *fac*-Ir(ppy)₃: 1.3 mg (1 mol%), KSAc: 2.3 mg (10 mol%), Acetone: 2 mL (0.1 M), Cyclohexene: 102 μ L (5 equiv). Reaction time: 48 hours. Colorless oil obtained 29.4 mg (**50%**). ¹H-NMR of crude reaction mixture shows **dr** = **1:1**

Mixture of 2 diastereoisomers

¹H-NMR (500 MHz; CDCl₃) δ 7.56 (d, J = 7.6 Hz, 1H_{Ar}), 7.49 (d, J = 8.9 Hz, 1H_{Ar}), 7.43 (d, J = 7.6 Hz, 1H_{Ar}), 7.36 (d, J = 8.9 Hz, 1H_{Ar}), 7.30 (t, J = 7.6 Hz, 1H_{Ar}), 7.26 (t, J = 7.6 Hz, 1H_{Ar}), 7.18 (t, J = 7.3 Hz, 0.5H_{Ar}), 7.14 (t, J = 7.3 Hz, 0.5H_{Ar}), 6.84 (d, J = 8.9 Hz, 1H_{Ar}), 6.80 (d, J = 8.9 Hz, 1H_{Ar}), 5.97-5.93 (m, 1H_{vinyl}), 5.54-5.46 (m, 1H_{vinyl}), 3.77 (s, 1.5H_{Me}), 3.75 (s, 1.5H_{Me} (isomer)), 3.42-3.37 (m, 1H_{allylic}), 2.17 (brs, 0.5H_{OH}), 2.16 (brs, 0.5H_{OH}), 2.02-1.97 (m, 2H_{allylic}), 1.80-1.40 (m, 4H)

¹³C-NMR (125 MHz; CDCl₃) δ 158.2, 157.9, 147.1, 145.9, 139.1, 137.8, 133.6, 133.5, 128.2, 127.9, 127.2, 126.7, 126.6, 126.5, 126.4, 126.1, 125.9, 125.4, 113.6, 113.3, 79.2, 79.1, 55.2, 55.1, 43.9, 43.7, 25.3, 23.8, 22.0

HRMS for $C_{20}H_{22}O_2$ $[M+H]^+$ calc. 295.1698, found 295.1698

Following **Procedure A**. Ketone: 50.0 mg (0.2 mmol), *fac*-Ir(ppy)₃: 1.3 mg (1 mol%), KSAc: 2.3 mg (10 mol%), Acetone: 2 mL (0.1 M), Cyclohexene: 102 μ L (5 equiv). Reaction time: 12 hours. Colorless oil obtained 47.2 mg (**71%**). ¹H-NMR of crude reaction mixture shows **dr** = **1:1**

Mixture of 2 diastereoisomers

¹H-NMR (500 MHz; CDCl₃) δ 7.88-7.16 (m, 9H_{Ar}), 6.02-6.00 (m, 1H_{vinyl}), 5.49-5.38 (m, 1H_{vinyl}), 3.50-3.43 (m, 1H_{allylic}), 2.28 (brs, 1H_{OH}), 2.05-1.98 (m, 2H), 1.79-1.77 (m, 1H), 1.51-1.33 (m, 3H)

¹³C-NMR (125 MHz; CDCl₃) δ 148.0, 146.6, 146.2, 144.7, 134.6, 134.5, 130.5 (q, J_{C-F} = 32Hz, C_{Ar}-CF₃), 129.5, 128.9, 128.7, 128.5, 128.4, 128.2, 127.0, 126.6, 126.0, 125.7, 125.6, 125.4, 122.9 (q, CF₃), 79.2, 79.1, 43.8, 43.6, 25.3, 25.2, 23.7, 23.7, 21.9, 21.8

¹⁹F-NMR (376 MHz; CDCl₃) δ -62.41 (s), -62.40 (s)

HRMS for C₂₀H₁₉F₃O [M+Na]⁺ calc. 355.1286, found 355.1283

Following **Procedure A**. Ketone: 39.5 mg (0.2 mmol), *fac*-Ir(ppy)₃: 1.3 mg (1 mol%), KSAc: 2.3 mg (10 mol%), Acetone: 2 mL (0.1 M), Cyclohexene: 102 μ L (5 equiv). Reaction time: 12

hours. Colorless oil obtained 12.3 mg (**22%**). $^1\text{H-NMR}$ of crude reaction mixture shows **dr = 1:1**

Mixture of 2 diastereoisomers

$^1\text{H-NMR}$ (500 MHz; CDCl_3) δ 7.56-7.12 (m, 7H_{Ar}), 6.63 (d, $J = 8.6$ Hz, 1H_{Ar}), 6.59 (d, $J = 8.6$ Hz, 1H_{Ar}), 5.96-5.91 (m, $1\text{H}_{\text{vinyllic}}$), 5.58-5.45 (m, $1\text{H}_{\text{vinyllic}}$), 3.58 (brs, 2H_{NH_2}), 3.36-3.34 (m, $1\text{H}_{\text{allylic}}$), 2.13 (brs, 0.5H_{OH}), 2.10 (brs, 0.5H_{OH}), 2.02-1.96 (m, $2\text{H}_{\text{allylic}}$), 1.78-1.38 (m, 4H)

$^{13}\text{C-NMR}$ (125 MHz; CDCl_3) δ 147.2, 146.2, 144.8, 144.6, 137.0, 135.9, 133.3, 133.2, 128.1, 127.9, 127.2, 126.9, 126.8, 126.6, 126.3, 125.9, 125.4, 114.9, 114.8, 79.3, 79.2, 43.9, 43.7, 25.3, 23.9, 22.1

HRMS for $\text{C}_{19}\text{H}_{21}\text{NO}$ $[\text{M}+\text{H}]^+$ calc. 280.1701, found 280.1703

Following **Procedure A**. Ketone: 39.3 mg (0.2 mmol), *fac*-Ir(ppy)₃: 1.3 mg (1 mol%), KSAc: 2.3 mg (10 mol%), Acetone: 2 mL (0.1 M), Cyclohexene: 102 μL (5 eqv). Reaction time: 12 hours. Colorless oil obtained 29.0 mg (**52%**). $^1\text{H-NMR}$ of crude reaction mixture shows **dr = 1:1**

Diastereoisomer 1

$^1\text{H-NMR}$ (500 MHz; CDCl_3) δ 7.84-7.04 (m, 9H_{Ar}), 5.99-5.97 (m, $1\text{H}_{\text{vinyllic}}$), 5.74-5.59 (m, $1\text{H}_{\text{vinyllic}}$), 3.56-3.48 (m, $1\text{H}_{\text{allylic}}$), 2.33 (brs, 1H_{OH}), 2.16 (s, 3H_{Me}), 2.05-1.48 (m, 6H)

$^{13}\text{C-NMR}$ (125 MHz; CDCl_3) δ 145.5, 142.9, 136.6, 132.8, 132.5, 127.7, 127.1, 126.9, 126.8, 126.7, 126.4, 125.1, 80.4, 32.3, 25.2, 24.6, 22.2, 22.1

Diastereoisomer 2

¹H-NMR (500 MHz; CDCl₃) δ 7.60 (d, *J* = 7.6 Hz, 1H_{Ar}), 7.30-7.13 (m, 7H_{Ar}), 7.08 (d, *J* = 7.3 Hz, 1H_{Ar}), 6.03-6.00 (m, 1H_{vinyl}), 5.84-5.81 (m, 1H_{vinyl}), 3.35-3.30 (m, 1H_{allyl}), 2.19 (brs, 1H_{OH}), 2.17 (s, 3H_{Me}), 2.05-1.99 (m, 2H_{allyl}), 1.78-1.03 (4H)

¹³C-NMR (125 MHz; CDCl₃) δ 144.7, 143.0, 139.4, 134.2, 133.3, 127.4, 127.2, 127.1, 126.7, 126.2, 125.9, 124.8, 80.2, 44.4, 25.4, 24.1, 22.1, 22.0

HRMS for C₂₀H₂₂O [M+H]⁺ calc. 279.1749, found 279.1744

Following **Procedure B**. Ketone: 36.0 mg (0.2 mmol), *fac*-Ir(ppy)₃: 1.3 mg (1 mol%), K₂CO₃: 2.8 mg (10 mol%), tri-isopropylsilane thiol 4.4 μL (10 mol%), Acetone: 2 mL (0.1 M), Cyclohexene: 102 μL (5 equiv). Reaction time: 24 hours. Colorless oil obtained 25.2 mg (48%).

¹H-NMR (500 MHz; CDCl₃) δ 7.62-7.60 (m, 2H_{Ar}), 7.55 (d, *J* = 7.5 Hz, 1H_{Ar}), 7.51 (d, *J* = 7.3 Hz, 1H_{Ar}), 7.37-7.23 (4H_{Ar}), 6.22-6.20 (m, 1H_{vinyl}), 5.88-5.85 (m, 1H_{vinyl}), 3.12-3.06 (m, 1H_{allyl}), 2.08 (brs, 1H_{OH}), 1.92-1.24 (m, 5H), 0.67-0.59 (m, 1H)

¹³C-NMR (125 MHz; CDCl₃) δ 148.7, 147.0, 140.1, 139.8, 129.6, 128.9, 128.8, 127.9, 127.5, 126.9, 125.0, 123.2, 119.7, 119.6, 84.2, 44.5, 25.1, 23.9, 21.7

HRMS for C₁₉H₁₈O [M+H]⁺ calc. 263.1436, found 263.1427

Following **Procedure B**. Ketone: 39.3 mg (0.2 mmol), *fac*-Ir(ppy)₃: 1.3 mg (1 mol%), K₂CO₃: 2.8 mg (10 mol%), tri-isopropylsilane thiol 4.4 μ L (10 mol%), Acetone: 2 mL (0.1 M), Cyclohexene: 102 μ L (5 equiv). Reaction time: 72 hours. Light yellow oil obtained 30.1 mg (54%). ¹H-NMR of crude reaction mixture shows **dr = 1:1**

Mixture of 2 diastereoisomers

¹H-NMR (500 MHz; CDCl₃) δ 7.28-7.08 (m, 8H_{Ar}), 6.91-6.81 (m, 2H_{Ar}), 6.10-5.39 (m, 2H_{vinyl}), 3.32-3.13 (m, 2H_{Bn}), 2.83-2.69 (m, 1H_{allylic}), 2.08-1.22 (m, 7H)

¹³C-NMR (125 MHz; CDCl₃) δ 145.2, 144.4, 136.6, 136.5, 131.6, 131.4, 130.7, 130.6, 127.8, 127.7, 127.6, 127.5, 127.0, 126.5, 126.4, 126.3, 126.2, 126.1, 78.7, 78.5, 46.1, 45.7, 45.1, 45.1, 25.2, 25.1, 24.7, 23.9, 22.1, 22.0

HRMS for C₂₀H₂₂O [M+H]⁺ calc. 279.1749, found 279.1751

Following **Procedure A**. Ketone: 28.1 μ L (0.2 mmol), *fac*-Ir(ppy)₃: 1.3 mg (1 mol%), KSAc: 2.3 mg (10 mol%), Acetone: 2 mL (0.1 M), Cyclohexene: 102 μ L (5 equiv). Reaction time: 48 hours. Colorless oil obtained 14.0 mg (27%). ¹H-NMR of crude reaction mixture shows **dr = 1:1**

Diastereoisomer 1

¹H-NMR (500 MHz; CDCl₃) δ 7.58 (d, *J* = 7.7 Hz, 2H_{Ar}), 7.42-7.34 (m, 3H_{Ar}), 5.89-5.86 (m, 1H_{vinyl}), 5.06-5.03 (m, 1H_{vinyl}), 3.18-3.15 (m, 1H_{allylic}), 2.39 (brs, 1H_{OH}), 2.13-1.57 (m, 6H)

¹³C-NMR (125 MHz; CDCl₃) δ 138.1, 133.3, 128.4, 128.3, 126.2, 124.2, 125.5 (q, *J*_{CF} = 284.9 Hz, CF₃), 79.0 (q, *J*_{CF} = 27.4 Hz), 42.5, 24.7, 23.7 (q, *J*_{CF} = 2.2 Hz), 21.7

^{19}F -NMR (376 MHz; CDCl_3) δ -73.48

Diastereoisomer 2

^1H -NMR (500 MHz; CDCl_3) δ 7.55 (d, J = 7.7 Hz, 2H_{Ar}), 7.41-7.33 (m, 3H_{Ar}), 6.20-6.16 (m, 1H_{vinyl}), 5.93-5.91 (m, 1H_{vinyl}), 3.13-3.08 (m, $1\text{H}_{\text{allylic}}$), 2.61 (brs, 1H_{OH}), 2.00-1.97 (m, $2\text{H}_{\text{allylic}}$), 1.72-1.64 (m, 1H), 1.44-1.18 (m, 3H)

^{13}C -NMR (125 MHz; CDCl_3) δ 137.0, 136.0, 128.2, 128.0, 125.8, 123.5 (q, J_{CF} = 2.8 Hz), 78.9 (q, J_{CF} = 26.4 Hz), 126.0 (q, J_{CF} = 286 Hz, CF_3)

^{19}F -NMR (376 MHz; CDCl_3) δ -73.33

HRMS for $\text{C}_{14}\text{H}_{15}\text{F}_3\text{O}$ $[\text{M}+\text{Na}]^+$ calc. 279.0973, found 279.0974

Following **Procedure A**. Ketone: 50.2 mg (0.2 mmol), *fac*-Ir(ppy)₃: 1.3 mg (1 mol%), KSAc: 2.3 mg (10 mol%), Acetone: 2 mL (0.1 M), Cyclohexene: 102 μL (5 equiv). Reaction time: 24 hours. White solid obtained 38.0 mg (**57%**).

^1H -NMR (500 MHz; CDCl_3) δ 7.50 (d, J = 8.6 Hz, 2H_{Ar}), 7.37 (d, J = 8.6 Hz, 2H_{Ar}), 7.29 (d, J = 8.6 Hz, 2H_{Ar}), 7.24 (d, J = 8.6 Hz, 2H_{Ar}), 6.02-5.99 (m, 1H_{vinyl}), 5.44-5.42 (m, 1H_{vinyl}), 3.39-3.34 (m, $1\text{H}_{\text{allylic}}$), 2.22 (brs, 1H_{OH}), 2.05-1.97 (m, $2\text{H}_{\text{allylic}}$), 1.80-1.40 (m, 4H)

^{13}C -NMR (100 MHz; CDCl_3) δ 145.0, 143.6, 134.6, 132.7, 132.3, 128.5, 128.2, 127.5, 126.9, 125.5, 78.8, 43.5, 25.2, 23.7, 21.8

HRMS for $\text{C}_{19}\text{H}_{18}\text{Cl}_2\text{O}$ $[\text{M}+\text{H}]^+$ calc. 333.0813, found 333.0819

Following **Procedure A**. Ketone: 36.6 mg (0.2 mmol), *fac*-Ir(ppy)₃: 1.3 mg (1 mol%), KSAc: 2.3 mg (10 mol%), Acetone: 2 mL (0.1 M), Cyclohexene: 102 μ L (5 equiv). Reaction time: 12 hours. Colorless oil obtained 32.4 mg (**61%**). ¹H-NMR of crude reaction mixture shows **dr** = **1:1**

Mixture of 2 diastereoisomers

¹H-NMR (500 MHz; CDCl₃) δ 8.52-8.47 (m, 1H_{Ar}), 7.72-7.12 (m, 8H_{Ar}), 5.86-5.81 (m, 1H_{Vinyllic}), 5.73 (brs, 0.5H_{OH}), 5.35 (brs, 0.5H_{OH} (isomer)), 5.52-5.50 (m, 0.5H_{Vinyllic}), 5.18-5.16 (m, 0.5H_{Vinyllic} (isomer)), 3.49-3.44 (m, 1H_{allylic}), 2.07-1.20 (m, 6H)

¹³C-NMR (125 MHz; CDCl₃) δ 163.4, 162.7, 147.4, 147.1, 145.6, 145.1, 136.9, 136.8, 131.2, 130.6, 128.2, 128.1, 127.2, 127.1, 126.7, 126.5, 126.2, 125.9, 121.9, 121.7, 120.7, 120.4, 79.3, 79.0, 44.4, 44.2, 25.2, 25.1, 23.9, 23.5, 22.2, 22.1

HRMS for C₁₈H₁₉NO [M+H]⁺ calc. 266.1545, found 266.1547

Following **Procedure A**. Ketone: 37.7 mg (0.2 mmol), *fac*-Ir(ppy)₃: 1.3 mg (1 mol%), KSAc: 2.3 mg (10 mol%), Acetone: 2 mL (0.1 M), Cyclohexene: 102 μ L (5 equiv). Reaction time: 24 hours. Colorless oil obtained 32.0 mg (**59%**). ¹H-NMR of crude reaction mixture shows **dr** = **1:1**

Mixture of 2 diastereoisomers

¹H-NMR (500 MHz; CDCl₃) δ 7.62-6.89 (m, 8H_{Ar}), 6.03-6.00 (m, 0.5H_{vinyllic}), 5.91-5.88 (m, 0.5H_{vinyllic} (isomer)), 5.64-5.62 (m, 0.5H_{vinyllic}), 5.37-5.35 (m, 0.5H_{vinyllic} (isomer)), 3.33-3.23 (m, 1H_{allylic}), 2.61 (brs, 0.5H_{OH}), 2.40 (brs, 0.5H_{OH} (isomer)), 2.00-1.96 (m, 2H_{allylic}), 1.80-1.34 (m, 4H)

¹³C-NMR (125 MHz; CDCl₃) δ 153.1, 151.0, 145.9, 144.6, 134.2, 133.2, 128.2, 128.0, 126.9, 126.7, 126.6, 126.1, 126.0, 125.5, 125.2, 124.4, 123.9, 123.2, 122.8, 79.3, 79.0, 46.3, 46.2, 25.2, 25.1, 24.0, 23.9, 21.9, 21.7

HRMS for C₁₇H₁₈OS [M+H]⁺ calc. 271.1157, found 271.1158

Following **Procedure B**. Ketone: 34.4 mg (0.2 mmol), *fac*-Ir(ppy)₃: 1.3 mg (1 mol%), K₂CO₃: 2.8 mg (10 mol%), tri-isopropylsilane thiol 4.4 μL (10 mol%), Acetone: 2 mL (0.1 M), Cyclohexene: 102 μL (5 equiv). Reaction time: 48 hours. Colorless oil obtained 43.2 mg (85%). ¹H-NMR of crude reaction mixture shows **dr = 1:1**

Diastereoisomer 1

¹H-NMR (500 MHz; CDCl₃) δ 7.66-7.20 (m, 6H_{Ar}), 6.35-6.33 (m, 2H_{Ar}), 6.00-5.96 (m, 1H_{vinyllic}), 5.50-5.48 (m, 1H_{vinyllic}), 3.24-3.19 (m, 1H_{allylic}), 2.43 (brs, 1H_{OH}), 2.02-1.97 (m, 2H_{allylic}), 1.77-1.28 (m, 4H)

¹³C-NMR (125 MHz; CDCl₃) δ 158.5, 143.2, 141.7, 133.2, 128.0, 126.8, 126.3, 125.3, 110.2, 106.1, 77.4, 44.5, 25.2, 23.3, 21.8

Diastereoisomer 2

¹H-NMR (500 MHz; CDCl₃) δ 7.58-7.24 (m, 6H_{Ar}), 6.30-6.27 (m, 2H_{Ar}), 5.86-5.84 (m, 1H_{vinyl}), 5.35-5.33 (m, 1H_{vinyl}), 3.28-3.21 (m, 1H_{allylic}), 2.37 (brs, 1H_{OH}), 2.00-1.94 (m, 2H_{allylic}), 1.79-1.43 (m, 4H)

¹³C-NMR (125 MHz; CDCl₃) δ 157.6, 143.7, 141.6, 131.8, 128.0, 127.0, 126.1, 125.9, 110.0, 106.2, 77.7, 45.1, 25.1, 24.1, 21.9

HRMS for C₁₇H₁₈O₂ [M+H]⁺ calc. 255.1385, found 255.1381

Following **Procedure B**. Ketone: 47.9 mg (0.2 mmol), *fac*-Ir(ppy)₃: 1.3 mg (1 mol%), K₂CO₃: 2.8 mg (10 mol%), tri-isopropylsilane thiol 4.4 μL (10 mol%), Acetone: 2 mL (0.1 M), Cyclohexene: 102 μL (5 equiv). Reaction time: 24 hours. Colorless oil mixed white solid obtained 43.7 mg (**68%**). ¹H-NMR of crude reaction mixture shows **dr = 1:1**

Diastereoisomer 1 (colorless oil)

¹H-NMR (500 MHz; CDCl₃) δ 8.02 (d, *J* = 8.1 Hz, 1H_{Ar}), 7.82 (d, *J* = 7.9 Hz, 1H_{Ar}), 7.78-7.77 (m, 2H_{Ar}), 7.47-7.43 (m, 1H_{Ar}), 7.34-7.31 (m, 3H_{Ar}), 7.24-7.21 (m, 1H_{Ar}), 6.06-6.03 (m, 1H_{vinyl}), 5.47 (dd, *J*₁ = 2 Hz, *J*₂ = 10 Hz, 1H_{vinyl}), 3.79-3.75 (m, 1H_{allylic}), 3.36 (brs, 1H_{OH}), 2.03-1.37 (m, 6H)

¹³C-NMR (125 MHz; CDCl₃) δ 179.6, 153.5, 141.7, 135.6, 134.9, 128.2, 127.2, 125.8, 125.5, 125.4, 124.8, 123.1, 121.6, 80.7, 46.0, 25.2, 23.5, 21.5

Diastereoisomer 2 (white solid)

¹H-NMR (500 MHz; CDCl₃) δ 7.98 (d, *J* = 8.2 Hz, 1H_{Ar}), 7.85-7.81 (m, 3H_{Ar}), 7.45-7.24 (m, 5H_{Ar}), 5.96-5.93 (m, 1H_{vinyl}), 5.33-5.31 (m, 1H_{vinyl}), 3.66-3.63 (m, 1H_{allylic}), 3.42 (brs, 1H_{OH}), 2.04-1.57 (m, 6H)

¹³C-NMR (125 MHz; CDCl₃) δ 177.1, 153.0, 143.3, 135.4, 133.4, 128.4, 127.5, 125.9, 125.8, 125.3, 124.7, 123.0, 121.6, 80.8, 46.1, 25.1, 23.7, 21.8

HRMS for C₂₀H₁₉NOS [M+H]⁺ calc. 322.1266, found 322.1267

Following **Procedure B**. Ketone: 47.1 mg (0.2 mmol), *fac*-Ir(ppy)₃: 1.3 mg (1 mol%), K₂CO₃: 2.8 mg (10 mol%), tri-isopropylsilane thiol 4.4 μL (10 mol%), Acetone: 2 mL (0.1 M), Cyclohexene: 102 μL (5 equiv). Reaction time: 24 hours. Light yellow oil obtained 42.5 mg (67%). ¹H-NMR of crude reaction mixture shows **dr = 1:1**

Diastereoisomer 1 (colorless oil)

¹H-NMR (500 MHz; CDCl₃) δ 7.64-7.62 (m, 1H_{Ar}), 7.35 (brs, 1H_{Ar}), 7.28-7.08 (m, 7H_{Ar}), 6.68-6.66 (m, 1H_{Ar}), 6.15-6.07 (m, 2H_{vinyl}), 3.45 (s, 3H_{Me}), 3.29-3.24 (m, 1H_{allylic}), 2.42 (brs, 1H_{OH}), 2.08-1.98 (m, 2H_{allylic}), 1.79-1.06 (m, 4H)

¹³C-NMR (125 MHz; CDCl₃) δ 143.0, 142.6, 138.2, 134.6, 127.8, 127.2, 126.8, 126.6, 126.1, 121.5, 120.5, 119.3, 109.0, 100.8, 77.3, 45.2, 31.4, 25.4, 23.9, 21.8

Diastereoisomer 2 (light yellow oil)

¹H-NMR (500 MHz; CDCl₃) δ 7.63-7.61 (m, 1H_{Ar}), 7.35-7.08 (m, 8H_{Ar}), 6.69 (s, 1H_{Ar}), 5.85-5.83 (m, 1H_{vinyllic}), 5.50-5.48 (m, 1H_{vinyllic}), 3.44 (s, 3H_{Me}), 3.26-3.21 (m, 1H_{allylic}), 2.35 (brs, 1H_{OH}), 2.13-1.57 (m, 6H)

¹³C-NMR (125 MHz; CDCl₃) δ 143.4, 141.9, 138.1, 131.3, 127.8, 126.9, 126.8, 126.7, 126.4, 121.6, 120.6, 119.4, 109.1, 101.4, 78.4, 46.3, 31.7, 25.1, 24.8, 22.2

HRMS for C₂₂H₂₃NO [M+H]⁺ calc. 318.1858, found 318.1867

Following **Procedure B**. Ketone: 37.7 mg (0.2 mmol), *fac*-Ir(ppy)₃: 1.3 mg (1 mol%), K₂CO₃: 2.8 mg (10 mol%), tri-isopropylsilane thiol 4.4 μL (10 mol%), Acetone: 2 mL (0.1 M), Cyclohexene: 102 μL (5 equiv). Reaction time: 72 hours. Colorless oil obtained 31.4 mg (58%).

Mixture of 2 diastereoisomers

¹H-NMR (500 MHz; CDCl₃) δ 7.40-7.19 (m, 5H_{Ar}), 5.92-5.81 and 5.16-5.14 (m, 2H_{vinyllic}), 3.07-2.90 (m, 1H_{allylic}), 1.95-0.44 (m, 17H)

¹³C-NMR (125 MHz; CDCl₃) δ 144.0, 142.8, 132.7, 131.7, 127.4, 127.3, 127.1, 126.7, 126.5, 126.3, 126.2, 126.0, 80.2, 80.1, 45.1, 44.6, 41.6, 40.9, 27.7, 27.6, 27.1, 27.0, 26.8, 26.7, 26.6, 26.5, 26.4, 26.3, 25.3, 25.2, 24.2, 22.9, 22.2, 21.9

HRMS for C₁₉H₂₆O [M+H]⁺ calc. 271.2062, found 271.2066

Following **Procedure B**. Ketone: 30.0 μL (0.2 mmol), *fac*-Ir(ppy)₃: 1.3 mg (1 mol%), K₂CO₃: 2.8 mg (10 mol%), tri-isopropylsilane thiol 4.4 μL (10 mol%), Acetone: 2 mL (0.1 M), Cyclohexene: 102 μL (5 equiv). Reaction time: 72 hours. Colorless oil obtained, yield was estimated by ¹H-NMR (20 μL dibromomethane added as internal standard) due to difficult isolation from ketone substrate (**52%**).

Mixture of 2 diastereoisomers (with starting ketone impurity)

¹H-NMR (500 MHz; CDCl₃) δ 7.44-7.21 (m, 5H_{Ar}), 5.92-5.82 (m, 1.5H_{vinyl}), 5.26-5.20 (m, 0.5H_{vinyl}), 3.05-2.88 (m, 1H_{allylic}), 2.34-1.23 (m, 8H), 0.88-0.75 (m, 6H_{iPr})

¹³C-NMR (125 MHz; CDCl₃) δ 143.3, 142.3, 132.5, 131.4, 127.4, 127.3, 127.2, 127.1, 126.7, 126.4, 126.3, 126.1, 80.5, 42.1, 41.7, 34.8, 33.8, 25.2, 25.2, 24.4, 23.0, 22.2, 21.9, 17.6, 17.5, 16.9, 16.8

HRMS for C₁₆H₂₂O [M+H]⁺ calc. 231.1749, found 231.1746

Following **Procedure B**. Ketone: 32.5 mg (0.2 mmol), *fac*-Ir(ppy)₃: 1.3 mg (1 mol%), K₂CO₃: 2.8 mg (10 mol%), tri-isopropylsilane thiol 4.4 μL (10 mol%), Acetone: 2 mL (0.1 M), Cyclohexene: 102 μL (5 equiv). Reaction time: 72 hours. Colorless oil obtained 24.9 mg (**51%**).

Mixture of 2 diastereoisomers

¹H-NMR (500 MHz; CDCl₃) δ 7.41-7.19 (m, 5H_{Ar}), 6.01-5.82 (m, 1.5H_{vinyl}), 5.15-5.13 (m, 0.5H_{vinyl}), 2.67-2.47 (m, 1H_{allyl}), 1.98-1.15 (10H), 0.91-0.86 (m, 3H_{Me}), 0.67-0.65 (m, 3H_{Me})

¹³C-NMR (125 MHz; CDCl₃) δ 146.4, 145.1, 132.7, 132.4, 127.8, 127.7, 126.7, 126.2, 126.1, 125.9, 125.8, 125.7, 79.0, 78.9, 49.1, 47.6, 47.4, 47.1, 25.3, 25.2, 24.8, 24.7, 24.3, 24.2, 24.0, 23.7, 23.5, 22.0, 21.9

HRMS for C₁₇H₂₄O [M+Na]⁺ calc. 267.1725, found 267.1726

Following **Procedure B**. Ketone: 38.1 mg (0.2 mmol), *fac*-Ir(ppy)₃: 1.3 mg (1 mol%), K₂CO₃: 2.8 mg (10 mol%), tri-isopropylsilane thiol 4.4 μL (10 mol%), Acetone: 2 mL (0.1 M), Cyclohexene: 102 μL (5 equiv). Reaction time: 72 hours. Light yellow oil obtained 38.1 mg (70%).

Mixture of 2 diastereoisomers

¹H-NMR (500 MHz; CDCl₃) δ 7.40-7.20 (m, 5H_{Ar}), 5.98-5.80 (m, 1.5H_{vinyl}), 5.26-5.22 (m, 0.5H_{vinyl}), 2.74-2.52 (m, 1H_{allyl}), 1.99-1.14 (m, 17H), 0.87-0.80 (m, 3H)

¹³C-NMR (125 MHz; CDCl₃) δ 146.2, 144.9, 132.1, 132.0, 127.9, 127.8, 126.8, 126.3, 126.2, 126.0, 125.7, 125.6, 78.5, 78.4, 46.1, 45.8, 40.3, 39.1, 31.7, 29.8, 25.2, 25.2, 24.4, 23.5, 23.4, 22.6, 22.0, 21.9, 14.0

HRMS for C₁₉H₂₈O [M+H]⁺ calc. 273.2218, found 273.2217

Following **Procedure A**. Ketone: 36.4 mg (0.2 mmol), *fac*-Ir(ppy)₃: 1.3 mg (1 mol%), KSAc: 2.3 mg (10 mol%), Acetone: 2 mL (0.1 M), Cycloheptatriene (97% purity): 103.8 μ L (5 equiv). Reaction time: 16 hours. Colorless oil obtained 43.9 mg (**80%**).

¹H-NMR (400 MHz; CDCl₃) δ 7.42-7.18 (m, 10H_{Ar}), 6.71-6.70 (m, 2H), 6.23-6.20 (m, 2H), 5.39-5.36 (m, 2H), 2.64-2.61 (m, 1H_{allylic}), 2.49 (brs, 1H_{OH})

¹³C-NMR (100 MHz; CDCl₃) δ 146.3, 130.9, 128.4, 127.1, 126.3, 125.0, 122.9, 78.9, 47.7

HRMS for C₂₀H₁₈O [M+H]⁺ calc. 275.1436, found 275.1435

Following **Procedure A**. Ketone: 36.4 mg (0.2 mmol), *fac*-Ir(ppy)₃: 1.3 mg (1 mol%), KSAc: 2.3 mg (10 mol%), Acetone: 2 mL (0.1 M), Cycloheptene: 116.7 μ L (5 eqv). Reaction time: 16 hours. Colorless oil obtained 34.0 mg (**61%**).

¹H-NMR (400 MHz; CDCl₃) δ 7.54-7.51 (m, 4H_{Ar}), 7.33-7.28 (m, 4H_{Ar}), 7.20-7.16 (m, 2H_{Ar}), 5.88-5.81 (m, 1H_{vinyl}), 5.66 (dd, *J*₁ = 3.9 Hz, *J*₂ = 11.0 Hz, 1H_{vinyl}), 3.60-3.53 (m, 1H_{allylic}), 2.28 (brs, 1H_{OH}), 2.25-2.20 (m, 2H_{allylic}), 2.02-1.29 (m, 6H)

¹³C-NMR (100 MHz; CDCl₃) δ 146.7, 146.6, 133.5, 132.4, 128.2, 128.1, 126.4, 126.3, 126.0, 125.6, 81.0, 47.6, 30.6, 28.3, 28.2, 26.2

HRMS for C₂₀H₂₂O [M+H]⁺ calc. 279.1749, found 279.1750

Following **Procedure A**. Ketone: 36.4 mg (0.2 mmol), *fac*-Ir(ppy)₃: 1.3 mg (1 mol%), KSAc: 2.3 mg (10 mol%), Acetone: 2 mL (0.1 M), cis-Cyclooctene (94% purity): 78.2 μ L (3 equiv). Reaction time: 16 hours. Colorless oil obtained 36.8 mg (**63%**).

¹H-NMR (500 MHz; CDCl₃) δ 7.53-7.51 (m, 2H_{Ar}), 7.48-7.46 (m, 2H_{Ar}), 7.34-7.17 (m, 6H_{Ar}), 5.74-5.68 (m, 1H_{vinyl}), 5.53-5.49 (m, 1H_{vinyl}), 3.74-3.70 (m, 1H_{allylic}), 2.44-2.37 (m, 1H_{allylic}), 2.29 (brs, 1H_{OH}), 2.23-2.16 (m, 1H_{allylic}), 1.78-1.29 (m, 8H)

¹³C-NMR (125 MHz; CDCl₃) δ 146.9, 146.8, 130.0, 129.9, 128.2, 128.0, 126.5, 126.4, 126.1, 125.7, 80.0, 44.0, 30.0, 29.4, 27.1, 27.0, 25.5

HRMS for C₂₁H₂₄O [M+H]⁺ calc. 293.1905, found 293.1909

Regio-isomer 1

Regio-isomer 2

Following **Procedure A**. Ketone: 36.4 mg (0.2 mmol), *fac*-Ir(ppy)₃: 1.3 mg (1 mol%), KSAc: 2.3 mg (10 mol%), Acetone: 2 mL (0.1 M), 3,4-dihydro-2H-pyran: 54.7 μ L (3 equiv). Reaction time: 12 hours. Product obtained in total 45.3 mg (**85%**). ¹H-NMR of crude reaction mixture shows **rr = 3:1**

Regio-isomer 1 (white solid)

¹H-NMR (500 MHz; CDCl₃) δ 7.59-7.57 (m, 2H_{Ar}), 7.47-7.45 (m, 2H_{Ar}), 7.34-7.27 (m, 4H_{Ar}), 7.22-7.15 (m, 2H_{Ar}), 6.57 (dd, $J_1 = 6.4$ Hz, $J_2 = 1.9$ Hz, 1H_{vinyl}), 4.49-4.47 (m, 1H_{vinyl}), 4.13-4.09 (m, 1H), 3.91 (dt, $J_1 = 10.8$ Hz, $J_2 = 2.6$ Hz, 1H), 3.53-3.48 (m, 1H), 2.35 (brs, 1H_{OH}), 1.95-1.87 (m, 1H), 1.52-1.46 (m, 1H)

¹³C-NMR (125 MHz; CDCl₃) δ 148.7, 146.4, 144.8, 128.4, 128.1, 126.8, 126.4, 126.0, 125.3, 99.2, 78.5, 65.5, 38.7, 24.1

Regio-isomer 2 (colorless oil)

¹H-NMR (500 MHz; CDCl₃) δ 7.57-7.56 (m, 2H_{Ar}), 7.48-7.46 (m, 2H_{Ar}), 7.33-7.28 (m, 4H_{Ar}), 7.22-7.18 (m, 2H_{Ar}), 5.99-5.95 (m, 1H_{vinyl}), 5.43-5.40 (m, 1H_{vinyl}), 5.13-5.09 (m, 1H), 4.11-4.08 (m, 1H), 3.79 (dt, $J_1 = 3.5$ Hz, $J_2 = 11.3$ Hz, 1H), 3.20 (brs, 1H_{OH}), 2.42-2.34 (m, 1H), 1.92-1.88 (m, 1H)

¹³C-NMR (125 MHz; CDCl₃) δ 145.6, 143.7, 128.2, 128.0, 127.9, 126.8, 126.8, 126.6, 126.0, 125.8, 79.1, 78.1, 64.6, 25.0

HRMS for C₁₈H₁₈O₂ [M+H]⁺ calc. 267.1385, found 267.1385

35 (30%)^a

Following **Procedure A**. Ketone: 36.4 mg (0.2 mmol), *fac*-Ir(ppy)₃: 1.3 mg (1 mol%), KSAc: 2.3 mg (10 mol%), Acetone: 2 mL (0.1 M), 2-allyloxyethanol: 64.2 μL (3 equiv). Reaction time: 24 hours. White solid obtained 17.0 mg (**30%**).

¹H-NMR (500 MHz; CD₃OD) δ 7.56-7.54 (m, 2H_{Ar}), 7.40-7.38 (m, 2H_{Ar}), 7.29-7.26 (m, 2H_{Ar}), 7.22-7.10 (m, 4H_{Ar}), 5.80-5.72 (m, 1H_{vinyl}), 5.13-5.10 (m, 1H_{vinyl}), 4.65 (d, J = 7.9 Hz, 1H_{allyl}), 4.58 (brs, 1H_{OH}), 3.68-3.64 (m, 1H), 3.56 (t, J = 4.5 Hz, 2H), 3.44-3.40 (m, 1H)

¹³C-NMR (125 MHz; CD₃OD) δ 144.7, 143.2, 132.5, 125.8, 125.7, 125.1, 124.7, 124.6, 124.5, 117.4, 83.9, 78.1, 68.0, 59.4

HRMS for C₁₈H₂₀O₃ [M+Na]⁺ calc. 307.1310, found 307.1311

Following **Procedure B**. Ketone: 36.4 mg (0.2 mmol), *fac*-Ir(ppy)₃: 1.3 mg (1 mol%), K₂CO₃: 2.8 mg (10 mol%), tri-isopropylsilane thiol 4.4 μ L (10 mol%), Acetone: 2 mL (0.1 M), 3-methyl-2-buten-1-ol: 61.0 μ L (3 equiv). Reaction time: 24 hours. Colorless oil obtained 19.9 mg (**37%**).

¹H-NMR (500 MHz; CDCl₃) δ 7.63-7.14 (m, 10H_{Ar}), 5.37 (d, J = 9 Hz, 1H), 5.22 (d, J = 9 Hz, 1H), 3.17 (brs, 1H_{OH}), 1.82 (brs, 1H_{OH}), 1.61 (s, 3H_{Me}), 1.42 (s, 3H_{Me})

¹³C-NMR (125 MHz; CDCl₃) δ 145.6, 143.9, 138.7, 128.5, 127.9, 127.3, 126.9, 126.8, 126.4, 122.4, 80.2, 72.8, 26.0, 18.5

HRMS for C₁₈H₂₀O₂ [M+H]⁺ calc. 269.1542, found 269.1542

Regio-isomer 1 (E/Z mixture)

Regio-isomer 2

Following **Procedure B**. Ketone: 34.4 mg (0.2 mmol), *fac*-Ir(ppy)₃: 1.3 mg (1 mol%), K₂CO₃: 2.8 mg (10 mol%), tri-isopropylsilane thiol 4.4 μ L (10 mol%), Acetone: 2 mL (0.1 M), 3-methyl-1-pentene: 126.0 μ L (5 equiv). Reaction time: 16 hours. Colorless oil obtained 27.2 mg (**51%**). ¹H-NMR of crude reaction mixture shows **rr = 3.5:1**

Regio-isomer 1 (E/Z mixture)

¹H-NMR (400 MHz; CDCl₃) δ 7.51-7.20 (m, 10H_{Ar}), 5.08-5.00 (m, 1H_{vinyl}), 3.03 (d, *J* = 7.3 Hz, 2H_{allylic}), 2.55 (brs, 1H_{OH}), 2.15-1.96 (m, 2H_{Et}), 1.67 (s, 3H_{Me}), 1.00-0.90 (m, 3H_{Et})

¹³C-NMR (100 MHz; CDCl₃) δ 146.9, 143.7, 143.4, 137.6, 132.4, 130.0, 128.3, 128.1, 128.0, 126.7, 126.1, 126.0, 117.8, 117.0, 77.7, 40.6, 40.3, 32.7, 25.1, 23.2, 16.4, 12.8, 12.7

HRMS for C₁₉H₂₂O [M+H]⁺ calc. 267.1749, found 267.1752

Regio-isomer 1

Regio-isomer 2

Following **Procedure B**. Ketone: 36.4 mg (0.2 mmol), *fac*-Ir(ppy)₃: 1.3 mg (1 mol%), K₂CO₃: 2.8 mg (10 mol%), tri-isopropylsilane thiol 4.4 μ L (10 mol%), Acetone: 2 mL (0.1 M), 4-*cis*-octene: 70 mg (3 equiv). Reaction time: 24 hours. Colorless oil obtained 34.2 mg (**58%**).

Mixture of 2 regio-isomers

¹H-NMR (400 MHz; CDCl₃) δ 7.48-7.11 (m, 10H_{Ar}), 5.50-5.42 (m, 1H_{vinyl}), 5.20-5.14 (m, 1H_{vinyl}), 3.11-2.97 (m, 1H_{allylic}), 2.41 (brs, 1H_{OH}), 1.96-1.87 (m, 2H_{allylic}), 1.52-1.17 (m, 4H), 0.88-0.73 (m, 6H)

^{13}C -NMR (100 MHz; CDCl_3) δ 146.7, 146.0, 145.9, 136.4, 135.0, 128.7, 128.0, 127.9, 127.8, 126.5, 126.4, 126.3, 126.2, 126.1, 80.2, 80.1, 52.9, 50.6, 34.8, 31.1, 25.8, 22.6, 22.0, 20.9, 14.0, 13.9, 13.4, 12.5

HRMS for $\text{C}_{21}\text{H}_{26}\text{O}$ $[\text{M}+\text{H}]^+$ calc. 295.2062, found 295.2064

Regio-isomer 1

Regio-isomer 2

Following **Procedure B**. Ketone: 36.4 mg (0.2 mmol), *fac*-Ir(ppy)₃: 1.3 mg (1 mol%), K_2CO_3 : 2.8 mg (10 mol%), tri-isopropylsilane thiol 4.4 μL (10 mol%), Acetone: 2 mL (0.1 M), 1-octene: 70 mg (3 equiv). Reaction time: 24 hours. Colorless oil obtained 25.9 mg (**44%**).

Mixture of 2 regio-isomers

^1H -NMR (400 MHz; CDCl_3) δ 7.50-7.43 (m, 4H_{Ar}), 7.32-7.12 (m, 6H_{Ar}), 5.70-5.59 (m, 1H_{vinyl}), 5.30-5.20 (m, 0.5H_{vinyl}), 5.12-5.03 (m, 1H_{vinyl}), 3.20-3.14 (m, 0.5H), 3.00 (d, $J = 7.2$ Hz, 1H), 2.63 (brs, 0.5H_{OH}), 2.38 (brs, 0.5H_{OH}), 2.12-1.93 (m, 1H), 1.46-1.14 (m, 8H), 0.91-0.80 (m, 3H)

^{13}C -NMR (100 MHz; CDCl_3) δ 146.8, 146.5, 145.8, 137.8, 137.7, 135.7, 128.1, 128.0, 127.8, 126.8, 126.7, 126.5, 126.4, 126.0, 125.9, 124.2, 123.4, 118.2, 79.9, 76.8, 51.7, 45.6, 39.9, 32.6, 31.7, 31.5, 31.3, 29.2, 29.0, 28.2, 27.6, 27.4, 22.5, 22.4, 14.0

HRMS for $\text{C}_{21}\text{H}_{26}\text{O}$ $[\text{M}+\text{Na}]^+$ calc. 317.1881, found 317.1885

Following **Procedure B**. Ketone: 36.4 mg (0.2 mmol), *fac*-Ir(ppy)₃: 1.3 mg (1 mol%), K₂CO₃: 2.8 mg (10 mol%), tri-isopropylsilane thiol 4.4 μL (10 mol%), Acetone: 2 mL (0.1 M), Heptanal: 140.0 μL (5 equiv). Reaction time: 24 hours. Colorless oil obtained 23.7 mg (**40%**).

¹H-NMR (400 MHz; CDCl₃) δ 7.40-7.32 (m, 10H_{Ar}), 4.90 (brs, 1H_{OH}), 2.56 (t, *J* = 7.4 Hz, 2H), 1.49-1.12 (m, 8H), 0.83 (t, *J* = 7.0 Hz, 3H)

¹³C-NMR (100 MHz; CDCl₃) δ 211.3, 141.6, 128.4, 128.2, 128.1, 85.6, 38.5, 31.4, 28.6, 24.4, 22.4, 13.9

HRMS for C₂₀H₂₄O₂ [M+H]⁺ calc. 297.1855, found 297.1855

Following **Procedure B**. Ketone: 36.4 mg (0.2 mmol), *fac*-Ir(ppy)₃: 1.3 mg (1 mol%), K₂CO₃: 2.8 mg (10 mol%), tri-isopropylsilane thiol 4.4 μL (10 mol%), Acetone: 2 mL (0.1 M), 1,2,3,4-tetrahydronaphthalene: 136.0 μL (5 equiv). Reaction time: 16 hours. Colorless oil obtained 51.6 mg (**82%**).

¹H-NMR (400 MHz; CDCl₃) δ 7.63-7.54 (m, 4H_{Ar}), 7.34-7.05 (m, 8H_{Ar}), 6.79-6.75 (m, 1H_{Ar}), 6.51 (d, *J* = 7.9 Hz, 1H_{Ar}), 4.20 (t, *J* = 6.7 Hz, 1H_{benzylic}), 2.80-2.66 (m, 2H_{benzylic}), 2.11 (brs, 1H_{OH}), 2.03-1.44 (m, 4H)

¹³C-NMR (100 MHz; CDCl₃) δ 148.1, 146.0, 141.3, 134.8, 130.2, 129.2, 128.1, 128.0, 126.5, 126.4, 126.2, 126.1, 125.9, 125.0, 81.6, 45.8, 30.1, 26.3, 21.5

HRMS for C₂₃H₂₂O [M+H]⁺ calc. 315.1749, found 315.1747

Following **Procedure B**. Ketone: 36.4 mg (0.2 mmol), *fac*-Ir(ppy)₃: 1.3 mg (1 mol%), K₂CO₃: 2.8 mg (10 mol%), tri-isopropylsilane thiol 4.4 μL (10 mol%), Acetone: 2 mL (0.1 M), 1-bromo-4-butylbenzene: 176.4 μL (5 equiv). Reaction time: 16 hours. White solid obtained 39.5 mg (**50%**).

¹H-NMR (400 MHz; CDCl₃) δ 7.55 (d, *J* = 7.5 Hz, 2H_{Ar}), 7.36 (t, *J* = 7.4 Hz, 2H_{Ar}), 7.27-6.95 (m, 10H_{Ar}), 3.66 (dd, *J*₁ = 3.7 Hz, *J*₂ = 10.6 Hz, 1H_{benzylic}), 2.36 (brs, 1H_{OH}), 1.77-1.70 (m, 2H), 1.17-1.08 (m, 2H), 0.80 (t, *J* = 7.2 Hz, 3H)

¹³C-NMR (100 MHz; CDCl₃) δ 146.0, 145.9, 139.4, 131.8, 130.6, 128.3, 127.7, 126.9, 126.2, 126.2, 125.6, 120.2, 80.8, 53.4, 32.4, 20.9, 14.0

HRMS for C₂₃H₂₃O⁷⁹Br [M+H]⁺ calc. 395.1011, found 395.1006

Following **Procedure B**. Ketone: 36.4 mg (0.2 mmol), *fac*-Ir(ppy)₃: 1.3 mg (1 mol%), K₂CO₃: 2.8 mg (10 mol%), tri-isopropylsilane thiol 4.4 μL (10 mol%), Acetone: 2 mL (0.1 M), ethylbenzene: 122.5 μL (5 equiv). Reaction time: 48 hours. White solid obtained 35.2 mg (**61%**).

¹H-NMR (400 MHz; CDCl₃) δ 7.62-7.60 (m, 2H_{Ar}), 7.36-7.00 (m, 13H_{Ar}), 3.98 (q, *J* = 7.0 Hz, 1H_{benzylic}), 2.38 (brs, 1H_{OH}), 1.33 (d, *J* = 7.0 Hz, 3H_{Me})

¹³C-NMR (100 MHz; CDCl₃) δ 146.4, 145.7, 141.9, 129.5, 128.1, 127.7, 127.6, 126.6, 126.4, 126.2, 126.1, 125.7, 80.5, 47.6, 16.5

HRMS for C₂₁H₂₀O [M+Na]⁺ calc. 311.1412, found 311.1418

Following **Procedure B**. Ketone: 36.4 mg (0.2 mmol), *fac*-Ir(ppy)₃: 1.3 mg (1 mol%), K₂CO₃: 2.8 mg (10 mol%), tri-isopropylsilane thiol 4.4 μL (10 mol%), Acetone: 2 mL (0.1 M), 2,5-dimethyl furan: 106.5 μL (5 equiv). Reaction time: 48 hours. Colorless oil obtained 15.6 mg (**28%**).

¹H-NMR (400 MHz; CDCl₃) δ 7.47-7.19 (m, 10H_{Ar}), 5.77 (s, 2H_{Ar}), 3.59 (s, 2H_{benzylic}), 3.06 (brs, 1H_{OH}), 2.16 (s, 3H_{Me})

¹³C-NMR (100 MHz; CDCl₃) δ 151.4, 149.3, 146.2, 128.0, 126.9, 126.1, 109.4, 106.2, 77.6, 41.0, 13.5

HRMS for C₁₉H₁₈O₂ [M+Na]⁺ calc. 301.1204, found 301.1197

Following **Procedure B**. Ketone: 72.0 mg (0.2 mmol), *fac*-Ir(ppy)₃: 1.3 mg (1 mol%), K₂CO₃: 2.8 mg (10 mol%), tri-isopropylsilane thiol 4.4 μL (10 mol%), Acetone: 2 mL (0.1 M),

Cyclohexene: 102 μL (5 equiv). Reaction time: 24 hours. Colorless oil obtained 56.7 mg (64%). $^1\text{H-NMR}$ of crude reaction mixture shows **dr = 1:1**

Mixture of 2 diastereoisomers

$^1\text{H-NMR}$ (400 MHz; CDCl_3) δ 7.50-7.20 (m, 6H_{Ar}), 6.80-6.73 (m, 2H_{Ar}), 5.98-5.94 (m, $1\text{H}_{\text{vinylc}}$), 5.49-5.39 (m, $1\text{H}_{\text{vinylc}}$), 5.08-5.01 (m, 1H_{iPr}), 3.36-3.28 (m, $1\text{H}_{\text{allylic}}$), 2.18 (brs, 0.5H_{OH}), 2.16 (brs, 0.5H_{OH}), 2.01-1.95 (m, $2\text{H}_{\text{allylic}}$), 1.77-1.72 (m, 1H), 1.56 (s, 3H_{Me}), 1.54 (s, 3H_{Me}), 1.51-1.36 (m, 3H), 1.18-1.15 (m, 6H_{iPr})

$^{13}\text{C-NMR}$ (100 MHz; CDCl_3) δ 173.7, 173.6, 154.4, 154.1, 145.5, 144.3, 139.7, 138.5, 133.9, 133.8, 132.3, 131.8, 128.2, 128.0, 127.6, 127.0, 126.8, 126.3, 126.1, 118.5, 118.4, 79.0, 78.9, 78.8, 68.8, 68.7, 43.9, 43.6, 25.4, 25.3, 25.2, 23.7, 21.9, 21.5

HRMS for $\text{C}_{26}\text{H}_{31}\text{ClO}_4$ $[\text{M}+\text{H}]^+$ calc. 443.1989, found 443.1988

Following **Procedure B**. Ketone: 43.3 mg (0.2 mmol), *fac*- $\text{Ir}(\text{ppy})_3$: 1.3 mg (1 mol%), K_2CO_3 : 2.8 mg (10 mol%), tri-isopropylsilane thiol 4.4 μL (10 mol%), Acetone: 2 mL (0.1 M), *n*-propylbenzene: 84 μL (3 equiv). Reaction time: 48 hours. Colorless oil obtained 42.4 mg (63%).

Mixture of diastereoisomers

$^1\text{H-NMR}$ (500 MHz; CDCl_3) δ 7.57-7.02 (m, 14H_{Ar}), 3.60-3.53 (m, $1\text{H}_{\text{benzylic}}$), 2.41 (brs, 1H_{OH}), 1.82-1.76 (m, 2H), 0.77-0.72 (m, 3H)

^{13}C -NMR (125 MHz; CDCl_3) δ 146.0, 145.8, 145.0, 144.5, 139.5, 139.3, 132.5, 131.9, 130.1, 130.0, 128.4, 128.2, 127.9, 127.8, 127.7, 127.6, 127.4, 127.2, 126.9, 126.7, 126.6, 126.5, 126.4, 126.1, 125.7, 80.7, 80.6, 56.2, 56.1, 23.3, 23.2, 12.5

HRMS for $\text{C}_{22}\text{H}_{21}\text{ClO}$ $[\text{M}+\text{H}]^+$ calc. 337.1359, found 337.1354

Following **Procedure A**. Ketone: 36.4 mg (0.2 mmol), *fac*-Ir(ppy)₃: 1.3 mg (1 mol%), KSAc: 2.3 mg (10 mol%), Acetone: 2 mL (0.1 M), N-Boc-3,4-dihydro-2*H*-pyridine: 74.2 μL (2 eqv). Reaction time: 16 hours. Colorless oil obtained 42.4 mg (**58%**). Note: this product is moisture sensitive and can transform to hydrolyzed white solid product overnight, it must be kept in air-tight container.

^1H -NMR (400 MHz; CDCl_3) δ 7.59-7.14 (m, 10 H_{Ar}), 7.07-6.90 (m, 1 $\text{H}_{\text{vinyllic}}$), 4.68-4.56 (m, 1 $\text{H}_{\text{vinyllic}}$), 3.94-3.84 (m, 1H), 3.49-3.45 (m, 1H), 3.27-3.14 (m, 1H), 2.27 (brs, 1 H_{OH}), 1.80-1.71 (m, 1H), 1.58-1.51 (m, 1H), 1.47 (s, 9H)

^{13}C -NMR (100 MHz; CDCl_3) δ 146.5, 144.9, 130.0, 128.4, 128.1, 126.8, 126.4, 126.0, 125.3, 103.2, 80.9, 78.9, 40.9, 40.5, 28.3, 23.0

HRMS for $\text{C}_{23}\text{H}_{27}\text{NO}_3$ $[\text{M}+\text{H}]^+$ calc. 366.2069, found 366.2066

Following **Procedure B**. Ketone: 18.2 mg (0.1 mmol), *fac*-Ir(ppy)₃: 0.7 mg (1 mol%), K₂CO₃: 1.4 mg (10 mol%), tri-isopropylsilane thiol 2.2 μ L (10 mol%), Acetone: 2 mL (0.1 M), Citronellyl acetate: 40.0 mg (2 equiv). Reaction time: 24 hours. Ketone starting material was completely consumed and mixture of isomeric product was observed. Major product obtained as colorless oil 14.5 mg (**38%**). The remaining isomeric products were unsuccessfully purified and characterized due to very similar polarity.

Mixture of diastereoisomers

¹H-NMR (500 MHz; CDCl₃) δ 7.55-7.53 (m, 4H_{Ar}), 7.27-7.18 (m, 6H_{Ar}), 5.76 (d, *J* = 15.8 Hz, 1H_{vinyl}), 5.57-5.51 (m, 1H_{vinyl}), 4.14-4.06 (m, 2H_{CH₂OAc}), 2.50 (brs, 1H_{OH}), 2.03 (s, 3H_{Me}), 2.11-2.05 (m, 1H), 1.97-1.90 (m, 1H), 1.71-1.63 (m, 2H), 1.47-1.40 (m, 1H), 1.18 (s, 6H_{Me}), 0.92 (d, *J* = 6.6 Hz, 3H_{Me})

¹³C-NMR (125 MHz; CDCl₃) δ 171.2, 145.7, 139.8, 128.5, 127.2, 126.5, 126.3, 81.7, 62.9, 44.8, 40.3, 35.0, 30.3, 25.0, 24.9, 21.0, 19.5

HRMS for C₂₅H₃₂O₃ [M+Na]⁺ calc. 403.2249, found 403.2243

Following **Procedure A**. Ketone: 36.4 mg (0.2 mmol), *fac*-Ir(ppy)₃: 1.3 mg (1 mol%), KSAc: 2.3 mg (10 mol%), Acetone: 2 mL (0.1 M), α -pinene: 95.4 μ L (3 equiv). Reaction time: 16 hours. Colorless oil obtained 33.8 mg (**53%**).

$^1\text{H-NMR}$ (400 MHz; CDCl_3) δ 7.62 (d, $J = 7.4$ Hz, 2H_{Ar}), 7.43 (d, $J = 7.4$ Hz, 2H_{Ar}), 7.38-7.16 (m, 6H_{Ar}), 5.16-5.13 (m, $1\text{H}_{\text{vinyllic}}$), 3.52-3.49 (m, $1\text{H}_{\text{allylic}}$), 2.23 (s, 1H), 2.22-2.18 (m, 1H), 2.02-1.99 (m, 1H), 1.88-1.85 (m, 1H), 1.72 (s, 3H_{Me}), 1.57 (brs, 1H_{OH}), 1.24 (s, 3H_{Me}), 0.96 (s, 3H_{Me})

$^{13}\text{C-NMR}$ (100 MHz; CDCl_3) δ 151.4, 147.6, 145.9, 128.1, 128.0, 126.5, 126.1, 126.0, 125.7, 114.5, 80.2, 47.4, 47.1, 42.7, 42.1, 27.8, 26.3, 23.5, 20.6

HRMS for $\text{C}_{23}\text{H}_{26}\text{O}$ $[\text{M}+\text{H}]^+$ calc. 319.2062, found 319.2062

Following **Procedure B**. Ketone: 36.4 mg (0.2 mmol), *fac*-Ir(ppy)₃: 1.3 mg (1 mol%), K_2CO_3 : 2.8 mg (10 mol%), tri-isopropylsilane thiol 4.4 μL (10 mol%), Acetone: 2 mL (0.1 M), γ -Terpinene: 96.2 μL (3 equiv). Reaction time: 24 hours. Colorless oil obtained 25.5 mg (**40%**). Regio-isomeric ratio was determined by $^1\text{H-NMR}$ of crude mixture (**rr = 3:1**).

Mixture of regio-isomers

$^1\text{H-NMR}$ (500 MHz; CDCl_3) δ 7.66-7.15 (m, 10H_{Ar}), 5.78-5.33 (m, $2\text{H}_{\text{vinyllic}}$), 4.03-3.99 (m, $1\text{H}_{\text{allylic}}$), 2.79-2.49 (m, $3\text{H}_{\text{allylic}}$ and OH), 2.25-2.19 (m, 1H_{iPr} of isomer 1), 1.71 (s, 3H_{Me} of isomer 2), 1.16 (s, 3H_{Me} of isomer 1), 0.94-0.92 (m, 6H_{iPr} of isomer 1), 0.81 (d, $J = 6.8\text{ Hz}$, 3H_{iPr} of isomer 2), 0.69 (d, $J = 6.8$ Hz, 3H_{iPr} of isomer 2)

$^{13}\text{C-NMR}$ (125 MHz; CDCl_3) δ 146.4, 146.2, 146.1, 145.9, 144.0, 138.1, 133.0, 128.3, 128.0, 127.9, 127.8, 127.7, 126.7, 126.5, 126.4, 126.3, 126.2, 126.1, 121.9, 121.1, 118.8, 81.4, 80.6, 50.5, 48.6, 34.5, 33.2, 31.8, 28.6, 24.4, 23.7, 23.0, 21.5, 21.2, 20.1

HRMS for $\text{C}_{23}\text{H}_{26}\text{O}$ $[\text{M}+\text{H}]^+$ calc. 319.2062, found 319.2061

Following **Procedure A** (additional 1.2 equivalent of TEMPO scavenger). Ketone: 18.2 mg (0.2 mmol), *fac*-Ir(ppy)₃: 1.3 mg (2 mol%), KSAc: 1.2 mg (10 mol%), Acetone: 1 mL (0.1 M), Cyclohexene: 51 μ L (5 equiv). Reaction time: 12 hours. Colorless oil trapping product obtained.

¹H-NMR (500 MHz; CDCl₃) δ 5.94-5.92 (m, 1H_{vinyl}), 5.80-5.78 (m, 1H_{vinyl}), 4.25-4.21 (m, 1H_{allylic}), 2.01-0.85 (m, 24H)

¹³C-NMR (125 MHz; CDCl₃) δ 129.9, 129.1, 77.5, 40.3, 34.7 (brs), 34.3 (brs), 29.5, 25.4, 20.3 (brs), 19.8, 17.3

HRMS for C₁₅H₂₇NO [M+H]⁺ calc. 238.2171, found 238.2171

2.5 - References

1. Li, J. J., Barbier reaction. In *Name Reactions: A Collection of Detailed Mechanisms and Synthetic Applications Fifth Edition*, Springer International Publishing: Cham, **2014**, 21-22.
2. Hatano, M.; Ishihara, K. *Synthesis* **2008**, 2008, 1647-1675.
3. Zhou, F.; Li, C.-J. *Nat. Commun.* **2014**, 5, 4254-4261.
4. Keh, C. C. K.; Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2003**, 125, 4062-4063.
5. Li, C.-J. *Chem. Rev.* **2005**, 105, 3095-3166.
6. Toni, M.; Arkaitz, C.; Ruben, M. *Chem. Eur. J.* **2014**, 20, 8242-8258.
7. Nguyen, K. D.; Park, B. Y.; Luong, T.; Sato, H.; Garza, V. J.; Krische, M. J. *Science* **2016**, 354, 300-305.
8. Yang, Y.; Perry, I. B.; Lu, G.; Liu, P.; Buchwald, S. L. *Science* **2016**, 353, 144-150.
9. Wang, H.; Dai, X.-J.; Li, C.-J. *Nat. Chem.* **2016**, 9, 374-378.
10. Li, B.-S.; Wang, Y.; Proctor, R. S. J.; Zhang, Y.; Webster, R. D.; Yang, S.; Song, B.; Chi, Y. R. *Nat. Commun.* **2016**, 7, 12933-12940.
11. Pitzer, L.; Sandfort, F.; Strieth-Kalthoff, F.; Glorius, F. *J. Am. Chem. Soc.* **2017**, 139, 13652-13655.
12. Chciuk, T. V.; Anderson, W. R.; Flowers, R. A. *J. Am. Chem. Soc.* **2016**, 138, 8738-8741.
13. Kern, N.; Plesniak, M. P.; McDouall, J. J. W.; Procter, D. J. *Nat. Chem.* **2017**, 9, 1198-1204.
14. Szostak, M.; Fazakerley, N. J.; Parmar, D.; Procter, D. J. *Chem. Rev.* **2014**, 114, 5959-6039.
15. C., N. K.; P., E. S.; S., C. J. *Angew. Chem. Int. Ed.* **2009**, 48, 7140-7165.
16. Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, 96, 307-338.
17. Krief, A.; Laval, A.-M. *Chem. Rev.* **1999**, 99, 745-778.
18. Rono, L. J.; Yayla, H. G.; Wang, D. Y.; Armstrong, M. F.; Knowles, R. R. *J. Am. Chem. Soc.* **2013**, 135, 17735-17738.
19. Tarantino, K. T.; Liu, P.; Knowles, R. R. *J. Am. Chem. Soc.* **2013**, 135, 10022-10025.

20. Eleonora, F.; Anthony, M.; Masaki, N.; Sebastian, L.; Magnus, R. *Angew. Chem. Int. Ed.* **2016**, *55*, 6776-6779.
21. Masaki, N.; Eleonora, F.; Sebastian, L.; Zhen, J.; Magnus, R. *Angew. Chem. Int. Ed.* **2015**, *54*, 8828-8832.
22. Fava, E.; Nakajima, M.; Nguyen, A. L. P.; Rueping, M. *J. Org. Chem.* **2016**, *81*, 6959-6964.
23. Lee, K. N.; Lei, Z.; Ngai, M.-Y. *J. Am. Chem. Soc.* **2017**, *139*, 5003-5006.
24. Lee, K. N.; Ngai, M.-Y. *Chem. Commun.* **2017**, *53*, 13093-13112.
25. Li, W.; Duan, Y.; Zhang, M.; Cheng, J.; Zhu, C. *Chem. Commun.* **2016**, *52*, 7596-7599.
26. Ding, W.; Lu, L.-Q.; Liu, J.; Liu, D.; Song, H.-T.; Xiao, W.-J. *J. Org. Chem.* **2016**, *81*, 7237-7243.
27. Wencel-Delord, J.; Glorius, F. *Nat. Chem.* **2013**, *5*, 369-375.
28. Davies, H. M. L.; Morton, D. *J. Org. Chem.* **2016**, *81*, 343-350.
29. Yi, H.; Zhang, G.; Wang, H.; Huang, Z.; Wang, J.; Singh, A. K.; Lei, A. *Chem. Rev.* **2017**, *117*, 9016-9085.
30. Cuthbertson, J. D.; MacMillan, D. W. C. *Nature* **2015**, *519*, 74-77.
31. Loh, Y. Y.; Nagao, K.; Hoover, A. J.; Hesk, D.; Rivera, N. R.; Colletti, S. L.; Davies, I. W.; MacMillan, D. W. C. *Science* **2017**, *358*, 1182-1187.
32. Jeffrey, J. L.; Petronijević, F. R.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2015**, *137*, 8404-8407.
33. Qvortrup, K.; Rankic, D. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 626-629.
34. Hager, D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 16986-16989.
35. Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695-705.
36. Fréneau, M.; Hoffmann, N. *J. Photochem. Photobiol. C: Photochem. Rev.* **2017**, *33*, 83-108.
37. Jifu, S.; Wanhua, W.; Jianzhang, Z. *Chem. Eur. J.* **2012**, *18*, 8100-8112.
38. Hofbeck, T.; Yersin, H. *Inorg. Chem.* **2010**, *49*, 9290-9299.
39. Flamigni, L.; Barbieri, A.; Sabatini, C.; Ventura, B.; Barigelletti, F., Photochemistry and Photophysics of Coordination Compounds: Iridium. In *Photochemistry and Photophysics of*

Coordination Compounds II, Balzani, V.; Campagna, S., Eds. Springer Berlin Heidelberg: Berlin, Heidelberg, **2007**, 143-203.

40. Roth, H. G.; Romero, N. A.; Nicewicz, D. A. *Synlett* **2016**, 27, 714-723.
41. Wagner, P. J.; Truman, R. J.; Puchalski, A. E.; Wake, R. J. *Am. Chem. Soc.* **1986**, 108, 7727-7738.
42. Khursan, S. L.; Mikhailov, D. A.; Yanborisov, V. M.; Borisov, D. I. *React. Kinet. Catal. Lett.* **1997**, 61, 91-95.
43. Wu, Y.-D.; Wong, C.-L.; Chan, K. W. K.; Ji, G.-Z.; Jiang, X.-K. *J. Org. Chem.* **1996**, 61, 746-750.
44. Vu, M. D.; Das, M.; Liu, X.-W. *Chem. Eur. J.* **2017**, 23, 15899-15902.

Alkene Synthesis through Umpolung of Phosphonium Ylides

Abstract: In this chapter, we report an easy access to olefins through the umpolung of phosphonium ylides via photoredox catalysis. This well-known classical nucleophile was successfully transformed into an electrophile by single electron oxidation, followed by ylide-ylide coupling, achieving unusual (Z)-olefin selectivity as compared to the conventional Wittig olefination. The access to medium-sized ring olefins was also demonstrated, together with one-pot olefination from activated halides.

3.1 - Introduction

Phosphonium ylides, organic structures containing a C-P polarized double bond, were first synthesized over a century ago.¹ Since then, the reactivity of this class of compounds has been well investigated in both mechanistic and synthetic aspects.²⁻³ Being easily accessible from other functionalities such as organohalides and alcohols, the ylides have shown their wide applicability in a variety of organic transformations, in the role of nucleophiles. The ylide nucleophilicity was demonstrated through the reactions with typical electrophiles,⁴ for example, nitriles,⁵ diazo compounds,⁶ azides⁷ and acyl chlorides⁸ (**Figure 3.1**). Moreover, it was also utilized in Michael-type and Mannich-type reactions, with or without stereocontrol, to construct new C-C bonds.⁹

Figure 3.1| Examples of nucleophilicity of various phosphonium ylides

The most outstanding application of phosphonium ylides is undeniably the Wittig olefination, which was discovered by Georg Wittig in 1954.¹⁰ The reaction proceeds chemoselectively between an aldehyde or ketone and a phosphonium ylide (phosphorane) under mild condition, and so far is still one of the best choices for synthetic chemists to

approach alkenes. Nevertheless, the stereoselectivity of final olefin products is highly dependent on the starting phosphoranes (**Figure 3.2**). Extensive scope studies have shown that, under the classic Wittig reaction conditions, stabilized ylides usually give dominantly the (*E*)-alkene, while non-stabilized ylides give the (*Z*)-isomer.¹¹ The phenomenon was explained by many groups through experimental data as well as the DFT calculations.¹²⁻¹⁴ In order to achieve selectively the remaining isomer from the same type of ylides, chemists have developed modifications to the original Wittig reaction conditions. For example, Schlosser and co-workers successfully employed lithium salt effect to obtain (*E*)-alkene from non-stabilized ylides.¹⁵ More recently, Tian's modification allows tunable selectivity for semi-stabilized ylides.¹⁶ However, up to date, the synthesis of (*Z*)-alkenes, the isomer higher in energy and more difficult to obtain, from the stabilized phosphonium ylides is still elusive.

Figure 3.2| General selectivity outcomes of the classic Wittig olefination

Other than the Wittig reaction, the autoxidation of non-stabilized ylides to form symmetrical alkenes was reported in 1977;¹⁷ however, these reactions gave complex mixtures with a low yield of olefin. Noiret and co-workers then developed a symmetrical (*Z*)-olefin synthesis from non-stabilized phosphonium ylides through oxidation in 1996,¹⁸ in which, the classical Wittig reaction was believed to be the key step determining the selectivity in this coupling protocol. To the best of our knowledge, there has been no further extension to the less reactive stabilized phosphorane up to date.

Figure 3.3| Overview of Phosphonium ylide chemistry

Since 2008, the use of photosensitizers as redox-catalyst in organic transformations pioneered by Macmillan and co-workers has been growing tremendously.¹⁹⁻²⁰ Upon activated by visible light, the excited photoredox catalyst can undergo single electron transfer (SET) events, resulting in either oxidizing or reducing the organic substrate, leading to novel reactivity. Various examples of oxidative activation to form cationic radical from unsaturated system were nicely demonstrated by Fukuzumi,²¹ Nicewicz²² and Yoon²³ *et al.* Furthermore, the first application of photoredox chemistry on sulfonium ylides was reported by Xiao and co-workers for the cyclization of transient cationic radicals to form 3-acyl oxindoles.²⁴ Quick growth of the newly developed photoredox catalysis triggered our attention to discover new reactivity of the well-established phosphonium ylide chemistry. Our primary aim was to seek for novel umpolung reactivity of phosphonium ylides after undergoing the hypothesized single electron oxidation. In this chapter, we would like to present our unprecedented discovery on the selective formation of (*Z*)-alkene starting from stabilized and semi-stabilized ylides under visible-light mediated photoredox conditions (Figure 3.3).

3.2 - Results and Discussion

Our study was initiated by probing the reactivity of the commercially available phosphorane **3.1a** under photoredox condition (**Table 3.1**). The selection of photoredox catalysts was firstly limited to highly oxidative complexes such as Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ ($E_{1/2}^{ox} = 1.21$ V vs SCE)²⁵ and the acridinium organic dye ($E_{1/2}^{ox} = 2.06$ V vs SCE)²⁶ (entry 1-2). However, complex product mixtures were obtained, probably due to over oxidation. To our surprise, while screening with more reductive catalysts (entry 3-5), the alkene product **3.2aa** was obtained in good to excellent yields. Interestingly, strongly reducing photoredox catalyst such as Ir(ppy)₃ facilitated the selective formation of the (*E*)-alkene, while Ru complexes, on the other hand, gave predominantly the (*Z*)-isomer. Changing the ligand on the catalyst could affect the selectivity outcome. Despite possessing similar redox profiles, Ru(phen)₃Cl₂ gave exclusively the (*Z*)-isomer, while Ru(bpy)₃(PF₆)₂ resulted in a mixture of isomers. This interesting observation has not been rationalized yet. Solvent evaluation revealed that the transformation proceeded most efficiently in non-polar halogenated solvents (entry 6-10).

Control experiments have also been conducted to confirm the necessity of all the components and parameters. The presence of photo-catalyst is indeed crucial for this novel reactivity, since the reported photo-reactivity of phosphorane and related compounds undergo different pathways.²⁷

Apart from the phosphoranes, the phosphonium salts could also be utilized to give comparable results (deprotonation in situ using strong base *ie.* NaH or LiO^tBu). In the case of the semi-stabilized ylides, the phosphonium salts were applied directly in the presence of excess sodium hydride (in mineral oil) and a catalytic amount of a crown ether (**15C5**).²⁸

Table 3.1 | Selected results for the optimization of reaction conditions

Entry	Catalyst (1 mol%)	Solvent	Yields ^[a]
1	[Ir(dFCF ₃ ppy) ₂ (dtbbpy)]PF ₆	DCM	N.D.
2	MesAcr ⁺ Me	DCM	N.D.
3	Ir(dtbbpy) ₂ (ppy)PF ₆	DCM	28% (>20E:1Z)
4	Ir(ppy) ₃	DCM	50% (>20E:1Z)
5	[Ru(bpy) ₃](PF ₆) ₂	DCM	98% (1E:4Z)
6	Ru(phen) ₃ Cl ₂	DCM	95% (>20Z:1E)
7	Ru(phen) ₃ Cl ₂	THF	N.D.
8	Ru(phen) ₃ Cl ₂	CHCl ₃	89% (10Z:1E)
9	Ru(phen) ₃ Cl ₂	DMF	N.R.
10	Ru(phen) ₃ Cl ₂	MeCN	77% (>20Z:1E)
11 ^[b]	Ru(phen) ₃ Cl ₂	DCM	Trace
12 ^[c]	Ru(phen) ₃ Cl ₂	DCM	Trace
13 ^[d]	-	DCM	Trace

All reactions were carried out under open air at 0.1 mmol scale, using 34 W blue LED with cooling fan. [a]

Isolated yield of **3.2aa** was reported, olefin isomeric ratio was determined from analysis of 500 MHz ¹H-NMR spectra of crude mixture. [b] Reaction in the dark. [c] Reaction in Ar atmosphere. N.D. Not determined. N.R.

No reaction.

Scheme 3.1 | Homo-coupling scope of various phosphonium ylides, phosphonium salts and phosphonate. All reactions were carried out under open air at 0.1 mmol scale, using 34 W blue LED with cooling fan. Isolated yields were reported, and olefin isomeric ratios were determined from analyses of 500 MHz ¹H-NMR spectra of crude mixtures. (a) Starting from phosphonium salt. (b) Starting from HWE phosphonate.

(a) Medium-sized ring closing reactions

Structure related to Bio-active lactones:

(b) Cross-Coupling of Phosphorus Ylides/ Phosphonium Salts **(c) One-pot Reaction of Activated Halides** **Scheme 3.2| Intramolecular reaction and cross-coupling reaction of phosphonium ylides/****phosphonium salts.** All reactions were carried out under open air at 0.1 mmol scale, using 34 W blue LED

with cooling fan. Isolated yields were reported, and olefin isomeric ratios were determined from analyses of

500 MHz ^1H -NMR spectra of crude mixtures. **(a)** Examples of ring-closing reaction starting from simple diols.**(b)** Reactions between different phosphonium ylides (2:1 equiv). **(c)** One-pot reaction of activated halides

(bromides) (2:1 equiv).

With the optimized conditions in hand, we proceeded to evaluate the substrate scope of the reaction. In order to test for the reactivity of various types of ylides under photoredox condition, we started with the homo-coupling of the phosphonium ylides (or the phosphonium salt precursors) and the results are illustrated in **Scheme 3.1**. Generally, symmetrical alkenes could be obtained in good to excellent yields, predominantly with (*Z*)-selectivity. Keto-stabilized phosphoranes (**3.1b**, **3.1c**, **3.1d** and **3.1e**) underwent the coupling reaction smoothly to furnish (*Z*)-alkene as the major product in excellent yields, despite the electronic property difference of substituents on the benzene ring. Aliphatic keto-stabilized phosphorane (**3.1n**) also gave comparable result. On the other hand, ester-stabilized phosphoranes, as well as the Horner–Wadsworth–Emmons (HWE) phosphonate reagent gave high (*E*)-selectivity under the same conditions. Benzylic semi-stabilized phosphoranes (**3.1f**, **3.1g** and **3.1h**) could undergo reaction smoothly as well, albeit diminished selectivity. Interestingly, for the case of an allylic phosphorane (**3.1i**), which was supposed to deliver a tri-ene product, a subsequent *in situ* electrocyclic reaction occurred to yield a substituted 1,3-cyclohexadiene in a moderate yield.

Our substrate scope was also successfully extended to bis-ylides, via a ring-closing reaction for the syntheses of medium-sized cycloalkenes. Starting from simple aliphatic diols, 9- and 10-membered-ring dilactones were synthesized efficiently over 2 steps, thereby demonstrating the utility of our method (**Scheme 3.2a**). These lactones resemble reported bioactive natural products such as the families of Pyrenolides²⁹ and Stagonolides³⁰⁻³¹. Although moderate yields were achieved, the selectivity for the (*Z*)-isomer was almost exclusive and other side products observed were likely dimers and trimers (based on TLC and LC-MS). Further applications on the cross-coupling of the phosphorane (as well as the phosphonium salts) have also been demonstrated (**Scheme 3.2b**). It was found that the

phosphoranes formed *in situ* by deprotonation provided similar reaction efficiency and the excessive amount of the strong bases used did not have any adverse effect on the reaction. A few semi-stabilized ylides were tested under our reaction condition, and they could successfully furnish non-symmetrical stilbene analogues, predominantly in the (*Z*) form.

Notably, a series of challenging *cis*-1,4-ketoesters could also be synthesized with very high selectivity. Our results show that the cross-coupling between two different keto-stabilized ylides proceeded comparably well, yielding 1,4-dionenes. Moreover, with the aforementioned success in utilizing the phosphonium salts, we anticipated that the activated halides can be applied in the syntheses of olefins via an one-pot reaction. Indeed, (*Z*)-stilbenes were obtained from benzylic halides in synthetically useful yields. (*E*)-**3.4a** and (*E*)-**3.4b** were undetectable in the ^1H -NMR spectrum of the crude reaction mixture, as well as in the isolated products. Intriguingly, (*Z*) to (*E*) isomerization was observed while monitoring the formation of the stilbene **3.4c** during the course of the reaction. To the best of our knowledge, the direct synthesis of stilbene from benzyl halides was only reported in a recent work done by Walsh *et al.* so far.³²

In order to investigate the reaction mechanism, a cyclic voltammetry experiment was conducted to measure the oxidation potential of the model substrate **3.1a** ($E_{1/2}^{\text{ox}} = 1.12$ V vs SCE). It was found that single electron oxidation of the ylide by $[\text{Ru}(\text{phen})_3]^{3+}$ is thermodynamically favorable. This also indicates an oxidative quenching pathway of the excited photoredox catalyst $[\text{Ru}(\text{phen})_3]^{2+*}$ ($E_{1/2}^{\text{ox}} = 1.26$ V vs SCE). Hence, we hypothesized that, upon single electron oxidation, the cationic radical intermediate **I** will be intercepted by another ylide molecule present in the solution to form either cationic radical **II_A** (path A) or **II_B** (path B). The quenching of the cationic radical **II_A** with the anionic radical oxygen, followed by triphenylphosphine oxide elimination, facilitates the alkene formation. On the

other hand, the cationic radical **II_B** resulted from a S_N2-type reaction can undergo single electron reduction (**III_B**) and subsequent phosphine elimination to form the alkene product. However, ³¹P-NMR monitoring did not show any trace of PPh₃ during the course of the reaction, but Ph₃PO was observed instead. Therefore, we presume that path B is the operative pathway, even though the formation of the dioxygen-bridged-phosphine **III_A** has not been reported.

Scheme 3.3 | Plausible mechanism and explanations for the unique (Z)-selectivity

To explain the intriguing (*Z*)-selectivity in the majority of the cases, we have looked up seminal works on the possible isomerization of alkenes under visible-light photoredox conditions. The first visible-light photoredox up-hill catalysis reported by Weaver *et al.* features a facile isomerization of several (*E*)-aminoalkenes.³³ The work done by Gilmour and co-workers on Riboflavin catalyzed alkene isomerization presents another approach to (*Z*)-olefins from (*E*)-isomers.³⁴⁻³⁵ Additionally, Wang and co-workers reported the photo-isomerization of (*E*)-1,4-enediones under visible light.³⁶ Last but not least, Liang and co-workers demonstrated that the use of organic dye also helps to facilitate 1,4-enedione isomerization to achieve a favorable (*Z*)-configuration.³⁷ Therefore, the probability of our alkene products undergoing photo-isomerization cannot be excluded. However, while the reaction progress of the ylide **3.1a** was monitored (in NMR tube), the formation of *cis*-alkene **3.2aa** was continuously observed over time. The photo-isomerization test was also conducted, starting from purified (*E*)-**3.2aa**, only partial isomerization occurred under our optimized photoredox condition (**Figure 3.4**). Prolonged reaction time merely led to the decomposition of the alkene substrate. Hence, we propose that, apart from photo-isomerization, the approach of the ylides in the transition state may play a significant role to determine the observed selectivity. The phosphorane (nucleophile) and its cationic radical form (electrophile) should approach each other in such a way that the large substituents stay opposite in space to minimize steric repulsion. As a result, the dioxygen-bridge **III_A** intermediate will have a *cis*-conformation. Finally, the concerted removal of two phosphine oxide molecules gives rise to the (*Z*)-alkene product (**Scheme 3.3**).

Figure 3.4| Experimental evidence for the photoisomerization of alkene products

3.3 - Conclusion

In summary, a practically simple method to synthesize alkenes from phosphonium ylides (phosphoranes) or phosphonium salts was reported. Our reactions occur under very mild conditions, providing a unique (*Z*)-selectivity of the olefin products, starting from stabilized phosphoranes. The novelty of our methodology is to utilize a nucleophilic ylide as an electrophile (umpolung) in the coupling of two ylide molecules. This reactivity reversal effect on a classical ylide has not been observed in previous literature. Detailed mechanistic studies, further expansion to other type of ylides, as well as exploring different compatible nucleophiles have been carried out in our laboratory.

3.4 - Experimental Section

Catalytic reactions were conducted under open air condition. Commercially available chemicals were purchased and used without further purification. Freshly distilled dichloromethane solvent was used for the reaction. The reaction progress was monitored by TLC Silica gel 60 F₂₅₄ using fluorescence quenching (UV – 254 nm), KMnO₄ or p-anisaldehyde staining method. Column chromatography for purification uses Silica gel 60 (40-63 μ m). High resolution mass spectrometry (HRMS) was recorded on a time-of-flight (TOF) machine. NMR spectra were recorded at 500 MHz or 400 MHz for ¹H; 125 Hz or 100 Hz for ¹³C nuclear. Chemical shifts (ppm) of all the peaks in ¹H-NMR were calibrated to either TMS residue peak (0 ppm) or trace chloroform peak (7.26 ppm) in CDCl₃. Chemical shifts (ppm) of all the peaks in ¹³C-NMR were calibrated to CDCl₃ residue peak (77.00 ppm). Blue light source is from 34 W blue LED made by Kessil (Reactions in 5 W blue LED strip gave comparable results).

3.4a - General Procedure for the Synthesis of Alkene from Phosphorus Ylides (Procedure A)

To an oven-dry 8 mL vial equipped with a rubber septum and a magnetic stir bar was charged with Ru(phen)₃.Cl₂.H₂O (1 mol%) and phosphorane (1 equiv). Freshly distilled dichloromethane was then added to form an orange solution. The reaction mixture was stirred under blue LED irradiation for a period of time. The surrounding temperature was maintained at 30 °C by a cooling fan. Subsequently, the reaction mixture was concentrated in vacuo and purified by column chromatography.

3.4b - General Procedure for the synthesis of alkene from Phosponium Salts (Procedure B)

To an oven-dry 8 mL vial equipped with a rubber septum and a magnetic stir bar was charged with sodium hydride (60% stabilized in mineral oil) (2 equiv) and phosphonium salt (1 equiv). Freshly distilled dichloromethane was then added to form an orange solution. The crown ether *15C5* was added to the solution before it was left for stirring for about 15 minutes. Subsequently, $\text{Ru}(\text{phen})_3\text{Cl}_2 \cdot \text{H}_2\text{O}$ (1 mol%) was added. The reaction mixture was stirred under blue LED irradiation for a period of time. The surrounding temperature was maintained by a cooling fan. The reaction mixture was then concentrated in vacuo and purified by column chromatography.

3.4c - General procedure for the synthesis of alkene via one-pot reaction starting from activated halides (Procedure C)

To an oven-dry 8 mL vial equipped with a rubber septum and a magnetic stir bar was charged with triphenylphosphine and activated halides. The vial was evacuated and back-filled with nitrogen. Dry degassed dichloromethane was added and the reaction solution was left stirring overnight (12 hours). Subsequently, base was added into the solution. After 15 minutes, $\text{Ru}(\text{phen})_3\text{Cl}_2$ was added. The opened vial was irradiated by 34 W blue LED, cooling by a fan. Dry dichloromethane was topped-up frequently. After 4-12 hours, the reaction mixture was concentrated and purified by flash column chromatography.

3.4d - Product Characterization

Following **Procedure A**. Phosphorane: 40 mg, Photocatalyst: 0.7 mg, Solvent: 2 mL. Reaction time: 12 hours. Obtained white solid 13 mg (**98%**).

¹H-NMR (500 MHz; CDCl₃) δ 7.97-7.94 (m, 4H), 7.14-7.11 (m, 4H), 7.13 (s, 2H)

¹³C-NMR (125 MHz; CDCl₃) δ 190.8, 166.0 (d, J_{C-F} = 254.2 Hz), 135.4, 132.5 (d, J_{C-F} = 3.1 Hz), 131.3 (d, J_{C-F} = 9.7 Hz), 116.0 (d, J_{C-F} = 22.5 Hz)

HRMS for C₁₆H₁₀F₂O₂ [M+H]⁺ calc. 273.0727, found 273.0729.

Following **Procedure A**. Phosphorane: 42 mg, Photocatalyst: 0.7 mg, Solvent: 2 mL. Reaction time: 12 hours. Obtained yellow solid 15 mg (**99%**).

¹H-NMR (500 MHz; CDCl₃) δ 7.88-7.85 (m, 4H), 7.45-7.42 (m, 4H); 7.12 (s, 2H)

¹³C-NMR (125 MHz; CDCl₃) δ 191.1, 140.2, 135.5, 134.3, 130.0, 129.2

HRMS for C₁₆H₁₀Cl₂O₂ [M+H]⁺ calc. 305.0136 (³⁵Cl), found 305.0138.

Following **Procedure A**. Phosphorane: 41 mg, Photocatalyst: 0.7 mg, Solvent: 2 mL. Reaction time: 12 hours. Obtained yellow solid 13.6 mg (**92%**).

¹H-NMR (500 MHz; CDCl₃) δ 7.93-7.90 (m, 4H), 7.08 (s, 2H), 6.93-6.91 (m, 4H), 3.85 (s, 6H)

¹³C-NMR (125 MHz; CDCl₃) δ 191.1, 163.8, 135.1, 131.0, 129.4, 113.9, 55.5

HRMS for C₁₈H₁₆O₄ [M+H]⁺ calc. 297.1127, found 297.1129.

Following **Procedure A**. Phosphorane: 75.3 mg, Photocatalyst: 1.5 mg, Solvent: 3 mL.

Reaction time: 12 hours. Obtained colorless oil 8 mg (**35%**).

¹H-NMR (500 MHz; CDCl₃) δ 6.67 (2H, s), 1.49 (18H, s)

¹³C-NMR (125 MHz; CDCl₃) δ 164.4, 134.6, 81.7, 28.0

HRMS for C₁₂H₂₀O₄ [M+Na]⁺ calc. 251.1259, found 251.1257.

White solid obtained.

¹H-NMR (500 MHz; CDCl₃) δ 7.88-7.65 (m, 30H), 5.54 (d, *J*_{H-P} = 13.5 Hz, 4H), 3.94 (s, 4H), 1.45 (s, 4H)

¹³C-NMR (125 MHz; CDCl₃) δ 164.6, 135.2 (d, *J*_{C-P} = 2.5 Hz), 133.9 (d, *J*_{C-P} = 10 Hz), 130.3 (d, *J*_{C-P} = 12.5 Hz), 117.8 (d, *J*_{C-P} = 88.8 Hz), 66.0, 33.0 (d, *J*_{C-P} = 57.5 Hz), 24.8

³¹P-NMR (202 MHz; CDCl₃) δ 20.6

Following **Procedure B**. Phosphonium salt: 48 mg, Photocatalyst: 0.7 mg, Base NaH 60% in mineral oil: 8 mg, Crown ether *15C5* 5 μ L, Solvent: 3 mL. Reaction time: 20 hours. Obtained inseparable mixture of (*Z*) and (*E*) isomers, yellow solid 10 mg (**75%**).

(*Z*)-isomer

$^1\text{H-NMR}$ (500 MHz; CDCl_3) δ 8.10-8.07 (m, 4H), 7.54-7.40 (m, 4H), 6.81 (s, 2H)

$^{13}\text{C-NMR}$ (125 MHz; CDCl_3) δ 148.5, 137.7, 134.6, 130.4, 129.5, 123.7, 122.6

(*E*)-isomer

$^1\text{H-NMR}$ (500 MHz; CDCl_3) δ 8.41 (s, 2H), 8.17 (d, J = 8.4 Hz, 2H), 7.84 (d, J = 7.7 Hz, 2H), 7.58 (t, J = 7.9 Hz, 2H), 7.28 (s, 2H)

$^{13}\text{C-NMR}$ (125 MHz; CDCl_3) δ 138.1, 132.6, 129.8, 129.2, 122.9, 121.2

HRMS for mixture of $\text{C}_{14}\text{H}_{10}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$ calc. 271.0719, found 271.0719.

Following **Procedure B**. Bis-Phosphonium salt: 86 mg, Photocatalyst: 1.5 mg, Base NaH 60% in mineral oil: 20 mg, Crown ether *15C5* 5 μ L, Solvent: 5 mL. Reaction time: 24 hours. Obtained white solid 8.7 mg (**51%**).

$^1\text{H-NMR}$ (500 MHz; CDCl_3) δ 6.34 (s, 2H), 4.30-4.28 (m, 4H), 1.91-1.89 (m, 4H)

$^{13}\text{C-NMR}$ (125 MHz; CDCl_3) δ 165.6, 131.0, 65.0, 26.6

HRMS for $\text{C}_8\text{H}_{10}\text{O}_4$ $[\text{M}+\text{H}]^+$ calc. 171.0657, found 171.0656.

Following **Procedure B**. Phosphonium salt: 48 mg, Photocatalyst: 0.7 mg, Base NaH 60% in mineral oil: 8 mg, Crown ether *15C5* 5 μ L, Solvent: 3 mL. Reaction time: 12 hours. Obtained inseparable mixture of (*Z*) and (*E*) isomers, yellow solid 9.5 mg (**70%**).

(*Z*)-isomer

¹H-NMR (500 MHz; CDCl₃) δ 8.12 (d, *J* = 9 Hz, 4H), 7.34 (d, *J* = 9 Hz, 4H), 6.84 (s, 2H)

¹³C-NMR (100 MHz; CDCl₃) δ 142.8, 131.4, 129.7, 127.5, 124.3

(*E*)-isomer

¹H-NMR (500 MHz; CDCl₃) δ 8.27 (d, *J* = 9 Hz, 4H), 7.69 (d, *J* = 9 Hz, 4H), 7.30 (s, 2H)

HRMS for mixture of C₁₄H₁₀N₂O₄ [M+Na]⁺ calc. 293.0538, found 293.0536.

Following **Procedure B**. Phosphonium salt: 48 mg, Photocatalyst: 0.7 mg, Base NaH 60% in mineral oil: 8 mg, Crown ether *15C5* 5 μ L, Solvent: 3 mL. Reaction time: 12 hours. Obtained white solid 12 mg (**90%**). (The alkene product can isomerize during purification by chromatography. The ratio of isomers is deduced from crude NMR).

¹H-NMR (500 MHz; CDCl₃) δ 7.83 (d, *J* = 8.5 Hz, 4H), 7.24 (d, *J* = 8 Hz, 4H), 7.11 (s, 2H), 2.40 (s, 6H)

¹³C-NMR (125 MHz; CDCl₃) δ 192.1, 144.4, 135.4, 133.7, 129.4, 128.8, 21.7

HRMS for C₁₈H₁₆O₂ [M+Na]⁺ calc. 287.1048, found 287.1047.

Following **Procedure B**. Phosphonium salt: 46 mg, Photocatalyst: 0.7 mg, Base NaH 60% in mineral oil: 8 mg, Crown ether *15C5* 5 μ L, Solvent: 3 mL. Reaction time: 12 hours. Obtained colorless oil 7.5 mg (**68%**).

$^1\text{H-NMR}$ (500 MHz; CDCl_3) δ 7.08 (s, 2H), 4.24 (q, J = 7 Hz, 4H), 2.55 (s, 4H), 1.32 (t, J = 7 Hz, 6H)

$^{13}\text{C-NMR}$ (125 MHz; CDCl_3) δ 166.7, 133.1, 131.6, 60.8, 21.7, 14.3

HRMS for $\text{C}_{12}\text{H}_{16}\text{O}_4$ $[\text{M}+\text{H}]^+$ calc. 225.1127, found 225.1125.

Following **Procedure B**. Bis-Phosphonium salt: 43 mg, Photocatalyst: 0.7 mg, Base NaH 60% in mineral oil: 10 mg, Crown ether *15C5* 5 μ L, Solvent: 3 mL. Reaction time: 16 hours. Obtained white solid 4 mg (**44%**).

$^1\text{H-NMR}$ (500 MHz; CDCl_3) δ 6.48 (m, 2H), 5.23-5.17 (m, 1H), 5.00-4.96 (m, 1H), 4.07-4.02 (m, 1H), 1.97-1.89 (m, 1H), 1.84-1.83 (m, 1H), 1.38 (d, J = 6.6 Hz, 3H)

$^{13}\text{C-NMR}$ (125 MHz; CDCl_3) δ 166.3, 166.1, 133.0, 132.6, 73.8, 64.0, 29.6, 20.5

HRMS for $\text{C}_8\text{H}_{10}\text{O}_4$ $[\text{M}+\text{H}]^+$ calc. 171.0657, found 171.0657.

White solid obtained.

¹H-NMR (500 MHz; CDCl₃) δ 5.04-5.00 (m, 1H), 4.19 (t, *J* = 7 Hz, 2H), 3.80-3.74 (m, 4H), 1.98-1.87 (m, 2H), 1.26 (d, *J* = 6.5 Hz, 3H)

¹³C-NMR (125 MHz; CDCl₃) δ 166.9, 166.5, 69.8, 62.1, 34.2, 25.9, 25.6, 19.6

White solid obtained.

¹H-NMR (400 MHz; CDCl₃) δ 7.92-7.68 (m, 30H), 5.87-5.40 (4H, m), 4.80-4.75 (m, 1H), 4.05-3.94 (m, 2H), 1.73-1.64 (m, 2H), 0.95 (d, *J* = 6.2 Hz, 3H)

¹³C-NMR (100 MHz; CDCl₃) δ 164.4, 163.8, 135.0, 134.9, 134.8, 133.8, 133.7, 133.6, 133.5, 133.3, 130.1, 130.0, 128.5, 128.4, 118.0 (d, *J*_{C-P} = 4.1 Hz), 117.2 (d, *J*_{C-P} = 4.4 Hz), 71.4, 62.9, 33.6, 33.0 (d, *J*_{C-P} = 21.6 Hz), 32.5 (d, *J*_{C-P} = 23.7 Hz), 19.2

³¹P-NMR (162 MHz; CDCl₃) δ 20.6, 20.5

Following **Procedure A**. Phosphorane 1: 76 mg, Phosphorane 2: 41 mg, Photocatalyst: 0.7 mg, Solvent: 3 mL. Reaction time: 12 hours. Obtained yellow oil 16 mg (**60%**).

¹H-NMR (500 MHz; CDCl₃) δ 7.93-7.91 (m, 2H), 7.62-7.18 (m, 8H), 6.95 (d, *J* = 12 Hz, 1H), 6.34 (d, *J* = 12 Hz, 1H), 5.05 (s, 2H)

¹³C-NMR (125 MHz; CDCl₃) δ 194.0, 164.6, 141.7, 135.7, 135.0, 133.7, 128.8, 128.7, 128.5, 128.4, 128.3, 125.7, 67.0

HRMS for C₁₇H₁₄O₃ [M+Na]⁺ calc. 289.0841, found 289.0844.

Following **Procedure A**. Phosphorane 1: 82 mg, Phosphorane 2: 41 mg, Photocatalyst: 0.7 mg, Solvent: 3 mL. Reaction time: 12 hours. Obtained yellow solid 19 mg (**65%**).

¹H-NMR (500 MHz; CDCl₃) δ 7.88-7.86 (m, 2H), 7.28-7.17 (m, 5H), 6.91-6.88 (m, 3H), 6.27 (d, *J* = 12 Hz, 1H), 5.03 (s, 2H), 3.87 (s, 3H)

¹³C-NMR (125 MHz; CDCl₃) δ 192.5, 164.6, 164.0, 141.8, 135.0, 131.1, 128.9, 128.4, 128.3, 128.2, 125.1, 113.9, 66.8, 55.5

HRMS for C₁₈H₁₆O₄ [M+Na]⁺ calc. 319.0946, found 319.0946.

Following **Procedure A**. Phosphorane 1: 80 mg, Phosphorane 2: 41 mg, Photocatalyst: 0.7 mg, Solvent: 3 mL. Reaction time: 12 hours. Obtained white solid 17 mg (**61%**).

¹H-NMR (500 MHz; CDCl₃) δ 7.91-7.89 (m, 2H), 7.30-7.07 (m, 7H), 6.88 (d, *J* = 12.5 Hz, 1H), 6.31 (d, *J* = 12.5 Hz, 1H), 5.03 (s, 2H)

¹³C-NMR (125 MHz; CDCl₃) δ 192.5, 166.0 (d, *J*_{C-F} = 254 Hz), 164.4, 141.4, 134.8, 132.2 (d, *J*_{C-F} = 2.7 Hz), 131.4 (d, *J*_{C-F} = 9.3 Hz), 128.5, 128.4(d), 125.7, 116.0, 115.8, 67.0

HRMS for C₁₇H₁₃FO₃ [M+Na]⁺ calc. 307.0746, found 307.0743.

Following **Procedure A**. Phosphorane 1: 76 mg, Phosphorane 2: 36 mg, Photocatalyst: 0.7 mg, Solvent: 3 mL. Reaction time: 12 hours. Obtained light yellow oil 16.4 mg (**76%**).

¹H-NMR (500 MHz; CDCl₃) δ 7.92-7.90 (m, 2H), 7.58-7.54 (m, 1H), 7.47-7.44 (m, 2H), 6.87 (d, *J* = 11.5 Hz, 1H), 6.82 (d, *J* = 11.5 Hz, 1H), 1.18 (s, 9H)

¹³C-NMR (125 MHz; CDCl₃) δ 205.9, 194.5, 138.0, 135.9, 133.4, 132.1, 128.7, 128.5, 43.4, 26.0

HRMS for C₁₄H₁₆O₂ [M+Na]⁺ calc. 239.1048, found 239.1050.

Following **Procedure C**. Activated bromide 1: 44 mg, Activated bromide 2: 15.3 μL, Phosphine: 78 mg, Base NaH 60% in mineral oil: 15 mg. Photocatalyst: 0.7 mg, Solvent: 3mL. Reaction time: 12 hours + 5 hours. Obtained colorless crystal 18 mg (**59%**).

¹H-NMR (500 MHz; CDCl₃) δ 7.79-7.26 (m, 11H), 6.86 (d, *J* = 12 Hz, 1H), 6.68 (d, *J* = 12 Hz, 1H)

¹³C-NMR (100 MHz; CDCl₃) δ 138.0, 134.0, 133.4, 132.7, 132.1, 131.9, 128.9, 128.6, 128.2, 127.9, 127.7(d), 126.5, 126.2, 126.1, 125.9, 125.8, 123.8(q)

HRMS for C₁₉H₁₃F₃ [M+Na]⁺ calc. 321.0867, found 321.0867.

Following **Procedure C**. Activated bromide 2: 20 mg, Activated bromide 1: 24.0 μL , Phosphine: 78 mg, Base NaH 60% in mineral oil: 15 mg. Photocatalyst: 0.7 mg, Solvent: 3 mL. Reaction time: 12 hours + 8 hours. Obtained colorless oil 10 mg (**50%**).

$^1\text{H-NMR}$ (400 MHz; CDCl_3) δ 7.66-7.64 (m, 1H), 7.36-7.13 (m, 8H), 6.86 (d, $J = 12$ Hz, 1H), 6.78 (d, $J = 12$ Hz, 1H)

$^{13}\text{C-NMR}$ (100 MHz; CDCl_3) δ 141.3, 136.0, 134.4, 132.9, 132.2, 129.8, 128.9, 128.5, 127.8, 127.5, 126.0, 117.9, 112.3

HRMS for $\text{C}_{15}\text{H}_{11}\text{N}$ $[\text{M}+\text{H}]^+$ calc. 206.0970, found 206.0973.

Following **Procedure A**. Phosphorane: 70 mg, Photocatalyst: 1.5 mg, Solvent: 3 mL. Reaction time: 12 hours. Obtained colorless oil 12 mg (**70%**).

$^1\text{H-NMR}$ (400 MHz; CDCl_3) δ 6.85 (s, 2H), 4.25 (q, $J = 7.2$ Hz, 4H), 1.32 (t, $J = 7.2$ Hz, 6H)

$^{13}\text{C-NMR}$ (100 MHz; CDCl_3) δ 165.0, 133.6, 61.3, 14.1

HRMS for $\text{C}_8\text{H}_{12}\text{O}_4$ $[\text{M}+\text{Na}]^+$ calc. 195.0633, found 195.0633

Following **Procedure A**. Phosphorane: 82 mg, Photocatalyst: 1.5 mg, Solvent: 3 mL. Reaction time: 12 hours. Obtained white solid 23.7 mg (**80%**).

$^1\text{H-NMR}$ (400 MHz; CDCl_3) δ 7.38-7.36 (m, 10H), 6.93 (s, 2H), 5.23 (s, 4H)

$^{13}\text{C-NMR}$ (100 MHz; CDCl_3) δ 164.7, 135.2, 133.7, 128.6, 128.5, 128.3, 67.1

HRMS for $C_{18}H_{16}O_4$ $[M+Na]^+$ calc. 319.0946, found 319.0943.

Following **Procedure C**. Activated bromide: 15.3 μ L, Phosphine: 27 mg, Base NaH 60% in mineral oil: 5 mg, Photocatalyst: 0.7 mg, Solvent: 2 mL. Reaction time: 12 hours + 8 hours. Obtained light yellow oil 12 mg (**76%**).

1H -NMR (500 MHz; $CDCl_3$) δ 7.48-7.46 (m, 4H), 7.38-7.33 (m, 4H), 6.70 (s, 2H)

^{13}C -NMR (125 MHz; $CDCl_3$) δ 137.2, 132.0, 130.3, 128.8, 125.6 (q), 124.2 (q), 125.0, 123.9 (q), 130.9 (q)

HRMS for $C_{16}H_{10}F_6$ $[M+H]^+$ calc. 317.0765, found 317.0764.

Following **Procedure A**. Phosphorane 1: 22 mg, Phosphorane 2: 41 mg, Photocatalyst: 0.7 mg, Solvent: 3 mL. Reaction time: 12 hours. Obtained colorless oil 9.1 mg (**56%**).

1H -NMR (500 MHz; $CDCl_3$) δ 7.38-7.33 (m, 5H), 6.73 (d, J = 12 Hz, 1H), 6.07 (d, J = 12 Hz, 1H), 5.15 (s, 2H), 2.01-1.64 (m, 15H)

^{13}C -NMR (125 MHz; $CDCl_3$) δ 208.4, 165.2, 140.4, 135.2, 128.7, 128.5, 128.4, 125.5, 67.0, 46.2, 37.9, 36.4, 27.8

HRMS for $C_{21}H_{24}O_3$ $[M+Na]^+$ calc. 347.1623, found 347.1625.

Following **Procedure B**. Phosphonium salt 1: 87 mg, Phosphonium salt 2: 48 mg, Photocatalyst: 0.7 mg, Base LiO^tBu: 50 mg, Solvent: 3 mL. Reaction time: 12 hours. Obtained yellow oil mixture of 2 isomers 21 mg (**94%**).

(Z) isomer – Light yellow oil

¹H-NMR (500 MHz; CDCl₃) δ 8.09-8.03 (m, 2H), 7.54-7.52 (m, 1H), 7.36 (t, *J* = 8 Hz, 1H), 7.28-7.19 (m, 5H), 6.78 (d, *J* = 12 Hz, 1H), 6.60 (d, *J* = 12 Hz, 1H)

¹³C-NMR (125 MHz; CDCl₃) δ 148.3, 138.9, 136.0, 134.8, 133.1, 129.0, 128.7, 128.6, 127.8, 127.6, 123.8, 121.9

HRMS for C₁₄H₁₁NO₂ [M+H]⁺ calc. 226.0868, found 226.0872.

(E) isomer – Yellow solid

¹H-NMR (500 MHz; CDCl₃) δ 8.38-8.37 (m, 1H), 8.11-8.09 (m, 1H), 7.81-7.80 (m, 1H), 7.56-7.51 (m, 3H), 7.42-7.31 (m, 3H), 7.24 (d, *J* = 16.3 Hz, 1H), 7.14 (d, *J* = 16.3 Hz, 1H)

Following **Procedure A**. Phosphorane: 44 mg, Photocatalyst: 0.7 mg, Solvent: 2 mL. Reaction time: 10 hours. Obtained white solid mixture of 2 isomers 16.4 mg (**93%**).

(Z) isomer – White solid

¹H-NMR (500 MHz; CDCl₃) δ 6.59 (s, 2H), 2.04-1.68 (m, 30H)

¹³C-NMR (125 MHz; CDCl₃) δ 207.9, 134.5, 45.8, 37.9, 36.5, 27.9

HRMS for C₂₄H₃₂O₂ [M+H]⁺ calc. 353.2481, found 353.2480.

(*E*) isomer – White solid

¹H-NMR (500 MHz; CDCl₃) δ 7.45 (s, 2H), 2.07-1.69 (m, 30H)

3.4e - Cyclic Voltammetry Data

Equipment Model: EC-Lab ASCII

Working Electrode: Glassy Carbon

Auxiliary Electrode: Platinum

Reference Electrode: Platinum

Scan rate: 100 mV/s

$C_{\text{Ylide 3.1a}} = 0.9 \text{ mM}$

$C_{\text{Bu4NPF6}} = 0.1 \text{ M}$

$C_{\text{Ferrocene}} = 0.9 \text{ mM}$

3.4f - X-Ray Data of Compound 3.2aa

A colorless block-like specimen of $C_8H_{10}O_4$, approximate dimensions 0.300 mm x 0.320 mm x 0.400 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured.

The total exposure time was 0.26 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 18736 reflections to a maximum θ angle of 31.69° (0.68 Å resolution), of which 2685 were independent (average redundancy 6.978, completeness = 99.8%, $R_{\text{int}} = 7.21\%$, $R_{\text{sig}} = 4.42\%$) and 2012 (74.93%) were greater than $2\sigma(F^2)$. The final cell constants of $a = 8.9251(5)$ Å, $b = 7.7452(4)$ Å, $c = 12.2199(7)$ Å, $\beta = 110.046(4)^\circ$, volume = $793.55(8)$ Å³, are based upon the refinement of the XYZ-centroids of 3196 reflections above $20\sigma(I)$ with $4.858^\circ < 2\theta < 56.83^\circ$. Data were corrected for absorption effects using the Multi-Scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.899. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.9550 and 0.9660.

The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group $P 1 21/c 1$, with $Z = 4$ for the formula unit, $C_8H_{10}O_4$. The final anisotropic full-matrix least-squares refinement on F^2 with 109 variables converged at $R1 = 4.41\%$, for the observed data and $wR2 = 11.63\%$ for all data. The goodness-of-fit was 1.046. The largest peak in the final difference electron density synthesis was $0.302 \text{ e}^-/\text{\AA}^3$ and the largest hole was $-0.303 \text{ e}^-/\text{\AA}^3$ with an RMS deviation of $0.057 \text{ e}^-/\text{\AA}^3$. On the basis of the final model, the calculated density was 1.424 g/cm^3 and $F(000)$, 360 e^- .

Table 1. Sample and crystal data for liu141.

Identification code	liu141	
Chemical formula	C ₈ H ₁₀ O ₄	
Formula weight	170.16 g/mol	
Temperature	153(2) K	
Wavelength	0.71073 Å	
Crystal size	0.300 x 0.320 x 0.400 mm	
Crystal habit	colorless block	
Crystal system	monoclinic	
Space group	P 1 21/c 1	
Unit cell dimensions	a = 8.9251(5) Å	α = 90°
	b = 7.7452(4) Å	β = 110.046(4)°
	c = 12.2199(7) Å	γ = 90°
Volume	793.55(8) Å ³	
Z	4	
Density (calculated)	1.424 g/cm ³	
Absorption coefficient	0.115 mm ⁻¹	
F(000)	360	

Table 2. Data collection and structure refinement for liu141.

Theta range for data collection	2.43 to 31.69°
Index ranges	-13<=h<=13, -11<=k<=11, -18<=l<=18
Reflections collected	18736
Independent reflections	2685 [R(int) = 0.0721]
Coverage of independent reflections	99.8%
Absorption correction	Multi-Scan
Max. and min. transmission	0.9660 and 0.9550
Structure solution technique	direct methods
Structure solution program	XT, VERSION 2014/4
Refinement method	Full-matrix least-squares on F ²
Refinement program	SHELXL-2014/7 (Sheldrick, 2014)
Function minimized	$\sum w(F_o^2 - F_c^2)^2$
Data / restraints / parameters	2685 / 0 / 109
Goodness-of-fit on F²	1.046
Final R indices	2012 data; I>2σ(I) R1 = 0.0441, wR2 = 0.1046 all data R1 = 0.0649, wR2 = 0.1163
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0509P)^2+0.1367P]$ where $P=(F_o^2+2F_c^2)/3$
Largest diff. peak and hole	0.302 and -0.303 eÅ ⁻³
R.M.S. deviation from mean	0.057 eÅ ⁻³

3.4i - Alternative Light-Dark Experiment

Standard reaction condition using $\text{Ru}(\text{phen})_3\text{Cl}_2$	
Time Duration (min)	Integration of Alkene Product in Comparison to Internal Standard
0	0
20	0.32
40	0.32
60	0.63
100	0.63
140	1.05
180	1.05
220	1.42
260	1.42
320	1.83
380	1.83
440	2.31

Standard reaction condition using Ir(ppy) ₃	
Time Duration (min)	Integration of Alkene Product in Comparison to Internal Standard
0	0
20	1.1
40	1.1
60	1.6
100	1.6
140	2.0
180	2.0
220	2.6
260	2.6
320	2.9
380	2.9
440	3.0

3.5 - References

1. Michaelis, A.; Gimborn, H. V. *Berichte der deutschen chemischen Gesellschaft* **1894**, *27*, 272-277.
2. Kolodiazhnyi, O. I., Introduction. In *Phosphorus Ylides*, Wiley-VCH Verlag GmbH: **2007**, 1-8.
3. Johnson, A. W., *Ylides and imines of phosphorus*. J. Wiley: **1993**.
4. Appel, R.; Loos, R.; Mayr, H. *J. Am. Chem. Soc.* **2009**, *131*, 704-714.
5. Barnhardt, R. G.; McEwen, W. E. *J. Am. Chem. Soc.* **1967**, *89*, 7009-7014.
6. Tomilov, Y. V.; Platonov, D. N.; Dorokhov, D. V.; Nefedov, O. M. *Tetrahedron Lett.* **2007**, *48*, 883-886.
7. Ykman, P.; L'Abbé, G.; Smets, G. *Tetrahedron* **1971**, *27*, 845-849.
8. Rocha Gonsalves, A. M. A.; Cabral, A. M. T. D. P. V.; Pinho e Melo, T. M. V. D. D.; Gilchrist, T. L. *Synthesis* **1997**, *1997*, 673-676.
9. Kolodiazhnyi, O. I., C,P-Carbon-Substituted Phosphorus Ylides. In *Phosphorus Ylides*, Wiley-VCH Verlag GmbH: **2007**, 9-156.
10. Wittig, G.; Schöllkopf, U. *Chem. Ber.* **1954**, *87*, 1318-1330.
11. Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863-927.
12. Robiette, R.; Richardson, J.; Aggarwal, V. K.; Harvey, J. N. *J. Am. Chem. Soc.* **2006**, *128*, 2394-2409.
13. Vedejs, E.; Peterson, M. J., Stereochemistry and Mechanism in the Wittig Reaction. In *Topics in Stereochemistry*, John Wiley & Sons, Inc.: **2007**, 1-157.
14. Byrne, P. A.; Gilheany, D. G. *Chem. Soc. Rev.* **2013**, *42*, 6670-6696.
15. Schlosser, M.; Christmann, K. F. *Angew. Chem. Int. Ed.* **1966**, *5*, 126-126.
16. Dong, D.-J.; Li, H.-H.; Tian, S.-K. *J. Am. Chem. Soc.* **2010**, *132*, 5018-5020.
17. Pine, S. H.; Fujita, E. *J. Org. Chem.* **1977**, *42*, 1460-1461.
18. Poulain, S.; Noiret, N.; Patin, H. *Tetrahedron Lett.* **1996**, *37*, 7703-7706.

19. Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322-5363.
20. Shaw, M. H.; Twilton, J.; MacMillan, D. W. C. *J. Org. Chem.* **2016**, *81*, 6898-6926.
21. Fukuzumi, S.; Ohkubo, K. *Chem. Sci.* **2013**, *4*, 561-574.
22. Margrey, K. A.; Nicewicz, D. A. *Acc. Chem. Res.* **2016**, *49*, 1997-2006.
23. Ischay, M. A.; Yoon, T. P. *Eur. J. Org. Chem.* **2012**, *2012*, 3359-3372.
24. Xia, X.-D.; Lu, L.-Q.; Liu, W.-Q.; Chen, D.-Z.; Zheng, Y.-H.; Wu, L.-Z.; Xiao, W.-J. *Chem. Eur. J.* **2016**, *22*, 8432-8437.
25. Lowry, M. S.; Goldsmith, J. I.; Slinker, J. D.; Rohl, R.; Pascal, R. A.; Malliaras, G. G.; Bernhard, S. *Chem. Mater.* **2005**, *17*, 5712-5719.
26. Nicewicz, D. A.; Nguyen, T. M. *ACS Catal.* **2014**, *4*, 355-360.
27. Dankowski, M., Photochemistry of Phosphonium Salts, Phosphoranes and Ylides. In *Organophosphorus Compounds (1993)*, John Wiley & Sons, Ltd: **2006**, 325-343.
28. Bellucci, G.; Chiappe, C.; Moro, G. L. *Tetrahedron Lett.* **1996**, *37*, 4225-4228.
29. Nukina, M.; Sassa, T.; Ikeda, M. *Tetrahedron Lett.* **1980**, *21*, 301-302.
30. Evidente, A.; Cimmino, A.; Berestetskiy, A.; Andolfi, A.; Motta, A. *J. Nat. Prod.* **2008**, *71*, 1897-1901.
31. Evidente, A.; Cimmino, A.; Berestetskiy, A.; Mitina, G.; Andolfi, A.; Motta, A. *J. Nat. Prod.* **2008**, *71*, 31-34.
32. Zhang, M.; Jia, T.; Yin, H.; Carroll, P. J.; Schelter, E. J.; Walsh, P. J. *Angew. Chem. Int. Ed.* **2014**, *53*, 10755-10758.
33. Singh, K.; Staig, S. J.; Weaver, J. D. *J. Am. Chem. Soc.* **2014**, *136*, 5275-5278.
34. Metternich, J. B.; Gilmour, R. *J. Am. Chem. Soc.* **2015**, *137*, 11254-11257.
35. Metternich, J. B.; Gilmour, R. *J. Am. Chem. Soc.* **2016**, *138*, 1040-1045.
36. Xu, K.; Fang, Y.; Yan, Z.; Zha, Z.; Wang, Z. *Org. Lett.* **2013**, *15*, 2148-2151.
37. Wei, D.; Liang, F. *Org. Lett.* **2016**, *18*, 5860-5863.

Direct Aldehyde C_{sp2}-H Functionalization via Visible Light Mediated Photoredox Catalysis

Abstract: The development of methods for carbon–carbon bond formation under benign conditions is an ongoing challenge for synthetic chemists. In recent years, there has been considerable interest in using selective C–H activation as a direct route for generating reactive intermediates. In this chapter, the use of the visible-light mediated dual photoredox-organocatalysis is discussed as a mild and effective method for C_{sp2}–H activation of aldehydes, resulting in the generation of acyl radicals. These nucleophilic acyl radical species can undergo either addition to electrophilic alkenes or nickel catalyzed cross-coupling reaction to provide quick access to a broad range of unsymmetrical ketones, which are abundantly found in many organic building blocks.

4.1 - Introduction

Acyl radicals - useful transient synthetic intermediates have long been employed in organic synthesis.¹ Their nucleophilic nature has mostly been demonstrated in the Michael addition type reactions for the synthesis of 1,4-dioxo compounds.² The generation of this radical, however, has been a great challenge. The early examples utilized the C-X bond homo-cleavage, where X can be an easy leaving group.³⁻⁸ Those methods generally require high loading of a toxic organotin initiator, together with harsh heating conditions, which usually lead to an undesirable decarbonylation pathway. More elegant approaches make use of the direct C-O bond cleavage from carboxylic acid or the C-C bond cleavage from pyruvic acid derivatives under visible-light photoredox conditions (**Figure 4.1**).⁹⁻¹⁵ The atom economy as well as the substrate availability actually limits the synthetic application of these methods, despite mild reaction conditions. The acyl radicals, on the other hands, could also be prepared in situ by alkyl radical addition to CO.¹⁶⁻¹⁷ However, pressurized CO is required to ensure a good conversion rate, as such, special equipment is necessary.

Figure 4.1 | Photoredox mediated formation of acyl radicals via C-X and C-C bond cleavage

Overall, towards the view point of sustainable chemistry in recent decades, the direct selective C-H functionalization becomes more favourable route in organic synthesis. Consequently, it is of great interest to selectively activate C_{sp2}-H of aldehydes, especially under benign conditions, for useful organic transformations. The initial success in C-H activation of aldehydes, which mostly follows radical approaches, has been presented by several groups. The first example that used thiol as the polarity reversal catalyst (PRC) was demonstrated by Harris and Waters in 1953 (**Scheme 4.1a**).¹⁸ Since then, other types of PRC were utilized such as N-hydroxyphthalimide¹⁹⁻²⁰ and peroxides (sources of electrophilic O-radical)²¹⁻²² for more efficient abstraction of the aldehyde hydrogen. However, the common

Scheme 4.1| Introduction to acyl radical formation and C-H activation strategy via photoredox catalysis

drawback is that the radical initiation step usually takes place at elevated temperature or with excessive usage of reagents. In 2007, Fagnoni, Albini and co-workers successfully employed tetrabutylammonium decatungstate (TBADT) for activation under UV irradiation at room temperature (**Scheme 4.1a**).²³⁻²⁶ Nevertheless, the scope of the reactions was limited to only linear aldehydes because significant decarbonylation was observed in the case of branched aldehydes. More recently, the auto-oxidation of aldehydes has also been applied as a simple method of C_{sp2}-H activation by Caddick and co-workers in 2010 (**Scheme 4.1a**).²⁷ Despite the convenience of the catalyst free process, the reactions actually occur at a very slow rate, and the aldehydes are prone to overoxidation due to prolonged heating conditions in some cases. The most recent advanced method was presented by Maruoka *et al.* using hypervalent iodine as the initiator via a radical chain mechanism (**Scheme 4.1a**).²⁸⁻³⁰

Figure 4.2| Our proposed aldehyde activation pathway employed in electron-deficient olefin addition

The visible light mediated photoredox transformation of organic compounds has been attracting significant interest in recent years. MacMillan and co-workers pioneered in the use of co-operative catalytic system employing an organocatalyst (hydrogen atom transfer - HAT catalyst) and a photoredox catalyst (electron transfer catalyst) for the

selective C-H activation of several organic compounds (**Scheme 4.1b**). These methods well incorporated the PRC concept for C-H activation and the photoinduced electron transfer (PET) for catalyst activation as well as regeneration. Hence, a series of novel C-C bond formations were successfully performed under ambient conditions. Thiols were first chosen as the HAT catalyst for the dual catalytic cycle.³¹⁻³³ Subsequently, the selective functionalization of challenging unactivated C_{sp3}-H centers was accomplished by Glorius³⁴ using benzoyl radical as the HAT catalyst, Knowles³⁵ and Rovis³⁶ with proton-coupled electron transfer (PCET) concept to form amidyl radical as the HAT catalyst. Most recently, quinuclidine was also harnessed as the new powerful HAT catalyst that is able to abstract hydrogen from strong C_{sp3}-H bonds due to the high bonding energy of N-H bond (BDE = 100 kcal·mol⁻¹) of the quinuclidinium radical intermediate.³⁷

Being inspired by the work, our group would like to propose a strategy for the aldehyde C_{sp2}-H activation that provides direct access to acyl radicals, which can be employed in useful transformations (**Figure 4.2**). We anticipated that the C_{sp2}-H bond in aldehyde is significantly weak (BDE = 86-87 kcal·mol⁻¹)¹ and possible to undergo hydrogen atom abstraction by the quinuclidinium cationic radical.

4.2 - Results and Discussion

Our initial trial utilized benzaldehyde and 2-cyclohexeneone as the model substrates for optimization studies (**Table 4.1**). To our delight, the reaction gave a moderate yield of the desired adduct (**4.3aa**). To evaluate and compare the power of quinuclidine as the HAT catalyst, several experiments using different co-catalysts were carried out. Although the aliphatic thiols were reported as promising polarity reversal catalysts which can facilitate C_{sp2}-H activation of aldehydes, our results show that they are not compatible with the photoredox catalytic cycle (Entry 2-4). Additionally, a range of photoredox catalysts were also tested. Among Ru and Ir complexes, [Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆ has shown to be the best candidate. The result agrees with the electrochemistry potential measurement of the catalyst ($E_{1/2}^{\text{red}} = 1.21 \text{ V vs SCE}$) and supports the hypothesis that reductive quenching first occurs to oxidize quinuclidine ($E_{1/2}^{\text{ox}} = 1.10 \text{ V vs SCE}$) to the HAT active form. Our effort to further optimize the reaction conditions by varying solvents was unsuccessful. Entry 7-10 show that acetonitrile (MeCN) is the solvent of choice, while protic and more polar solvents such as MeOH, DMSO and DMF are not suitable for the reaction. Control experiments reinforce the necessity of both the catalysts as well as the visible light irradiation (entry 13-15). The auto-oxidation of the aldehyde was eliminated (entry 12) since the open-air reaction yield mainly carboxylic acid as the sole transformation of the aldehyde.

The poor reactivity of benzaldehyde is probably attributed to the weak nucleophilicity of the phenacyl radical. The reaction yield increased when a large excess of the aldehyde was used (entry 11). Therefore, we proceeded to evaluate the scope of the reaction using the optimized conditions as stated on various aldehydes and Michael acceptors (**Scheme 4.2**).

Table 4.1 | Selected results for the optimization of reaction conditions

Entry	Catalyst	Co-Catalyst	Solvent	Yields ^[a]
1	[Ir(dFCF ₃ ppy) ₂ (dtbbpy)]PF ₆	C1	MeCN	49%
2	[Ir(dFCF ₃ ppy) ₂ (dtbbpy)]PF ₆	C2	MeCN	-
3	[Ir(dFCF ₃ ppy) ₂ (dtbbpy)]PF ₆	C3	MeCN	-
4	[Ir(dFCF ₃ ppy) ₂ (dtbbpy)]PF ₆	C4	MeCN	-
5	[Ru(bpy) ₃](PF ₆) ₂	C1	MeCN	-
6	[Ir(ppy) ₂ (dtbbpy)]PF ₆	C1	MeCN	-
7	[Ir(dFCF ₃ ppy) ₂ (dtbbpy)]PF ₆	C1	DMSO	-
8	[Ir(dFCF ₃ ppy) ₂ (dtbbpy)]PF ₆	C1	DMF	-
9	[Ir(dFCF ₃ ppy) ₂ (dtbbpy)]PF ₆	C1	MeOH	-
10	[Ir(dFCF ₃ ppy) ₂ (dtbbpy)]PF ₆	C1	DCM	-
11 ^[b]	[Ir(dFCF ₃ ppy) ₂ (dtbbpy)]PF ₆	C1	MeCN	60%
12 ^[c]	[Ir(dFCF ₃ ppy) ₂ (dtbbpy)]PF ₆	C1	MeCN	-
13 ^[d]	[Ir(dFCF ₃ ppy) ₂ (dtbbpy)]PF ₆	-	MeCN	-
14	[Ir(dFCF ₃ ppy) ₂ (dtbbpy)]PF ₆	C1	MeCN	-
15	-	C1	MeCN	-

The reactions were carried out under inert atmosphere (Ar or N₂), using 0.1 mmol olefin and 0.3 mmol aldehyde in 0.3 M solution. [a] Isolated yield. [b] Using 5 equiv of aldehyde. [c] Reaction in open air. [d] Reaction in the dark.

Scheme 4.2| Substrate scope evaluation for the hydroacylation of electron-deficient

alkenes. Unless otherwise indicated, all the reactions were carried out in inert atmosphere (Ar or N₂) under irradiation of 34 W blue LED for 12-16 hours at room temperature (30 °C). 5 equiv of aldehyde was used. All the yields refer to isolated compounds. Gram scale reaction was done at 0.1 mol% photoredox catalyst and 1 mol% HAT catalyst loading for 48 hours.

The aromatic aldehydes generally gave low to moderate yields (**4.3ab** and **4.3fb**). On the other hand, the aliphatic aldehydes including both linear and branched chain reacted smoothly under the optimized conditions (**4.3db**, **4.3eb** and **4.3mb**). Interestingly, selective C_{sp2}-H activation was achieved in the presence of weaker benzylic C_{sp3}-H bonds (**4.3kb** and **4.3lb**).

Scheme 4.3 | Initial substrate scope evaluation for the cross-coupling of aldehyde to aryl bromide. Unless otherwise indicated, all the reactions were carried out under inert atmosphere (N₂) using freeze-pump-thaw technique. Fans are used to chill the reaction vials (30 °C).

In the case of the branched aldehydes, to our delight, there was only a trace amount of the decarbonylated product observed (GC-MS). Our method hence shows its superiority towards reported procedures using high energy activating sources (UV and heat). Gram scale reaction also performed well in a prolonged reaction time with the minimized usage of both catalysts (ca. 0.1 mol% [Ir] and 1.0 mol% quinuclidine) (**4.3eb**). The synthetic utility of this protocol has also been demonstrated by the success on a variety of olefin acceptors. Almost quantitative yields were obtained in the case of the α - β unsaturated ketones, including di-substituted (**4.3bh**) or cyclic structure (**4.3ba**). Other electron withdrawing

groups (EWG) such as sulfone (**4.3bf**) and cyanide are also well tolerated, although the conversion rate was rather low for the acrolein addition (**4.3bi**). To our surprise, cyclohexanecarboxyl radical was unable to open a cyclopropane ring (**4.3be**) – the starting material, diethyl cyclopropane-1,1-dicarboxylate, was fully recovered in this case.

Figure 4.3| Plausible mechanism for the cross-coupling of organic halides with aldehydes via triple catalytic pathway involving Ni, HAT and photoredox catalysts

The application of this C-H activation strategy can be extended to C-C bond formation by co-operative catalysis with Ni catalyzed cross-coupling of acyl radicals and organohalides (**Figure 4.3**). After initial screening, we found the optimized condition to be 1 mol% Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆, 1 mol% NiCl₂.dme together with 1.2 mol% ligand dtbbpy, 1.2 equivalent quinuclidine base in DMSO (0.05-0.10 M) over 24 hours. Nickel (0), which was generated in situ via reduction facilitated by photoredox catalyst and sacrificial quinuclidine, underwent oxidative addition with aryl bromides. The Ni(II) complex formed could trap the acyl radical, forming a Ni(III) species. This also induces reductive elimination to forge the desirable C-C bond and recycle the nickel catalyst.

The scope of our cross-coupling was evaluated on the electron-deficient bromo arene with various aliphatic aldehydes (**Scheme 4.3**). The initial yields were low to moderate, due to significant amount of the limiting substrate, in this case, the aryl bromides were reduced. The phenomenon was similarly observed by MacMillan through a hypothesized proto-dehalogenation pathway.³⁸ Although our preliminary results still need further optimization, we are glad to present the first example for direct cross-coupling of aldehydes with organohalides at ambient temperature, to the best of our knowledge.

Satyanarayana, 2016

Xiao, 2010

Xiao, 2008

Chang, 2005

Scheme 4.4 | Examples of palladium catalyzed direct acylation of organohalides

Prior work on the direct coupling of aldehyde generally required harsh reaction conditions (**Scheme 4.4**). Chang presented bimetallic Ru-Pd system for the direct coupling in 2005, nonetheless, a directing group on the aldehyde is necessary thus limiting the scope of aldehyde.³⁹ Seminal work done by Xiao and co-workers employed the Heck coupling modification under elevated temperature.⁴⁰ The strategy utilizes the formation of an enamine between the aldehyde substrate and pyrrolidine *in situ*. This enamine undergoes Heck coupling with aryl halides and then it is hydrolyzed during work-up to afford the

ketone final product. The most recent progress was reported by Satyanarayana, using equimolar silver and peroxide under heating conditions.⁴¹

4.3 - Conclusion

In conclusion, a mild and selective aldehyde C_{sp2}-H activation method was developed on the basis of co-operative organo-photoredox chemistry. The acyl radical formed under benign conditions, hence, CO extrusion to generate undesirable alkyl radical was avoided. The acyl radical successfully underwent either radical addition to electron deficient olefins, or cross coupling with aryl bromides, enabling short access to a series of non-symmetrical ketones. Further optimization for direct aldehyde cross-coupling as well as synthetic applications of the protocol are underway in our laboratory.

4.4 - Experimental Section

Catalytic reactions were conducted under inert atmosphere. Commercially available chemicals were purchased and used without further purification unless otherwise stated. Aldehydes were purified before the reaction by distillation. All reactions were monitored by TLC Silica gel 60 F₂₅₄ using fluorescence quenching (UV – 254 nm), potassium permanganate or p-anisaldehyde staining method. Flash column chromatography for purification uses Silica gel 60 (40-63 μ m). Technical grade solvents were used for chromatography and distilled prior to use. High resolution mass spectrometry (HRMS) was recorded on a time-of-flight (TOF) machine. NMR spectra were recorded at 500 MHz or 400 MHz for ^1H ; 125 Hz or 100 Hz for ^{13}C nuclear. Chemical shifts (ppm) of all the peaks in ^1H -NMR were calibrated to either TMS residue peak (0 ppm) or trace chloroform peak (7.26 ppm) in CDCl_3 . Coupling constants (J) are given in Hz. Following abbreviations classify the multiplicity: s = singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, m = multiplet. Blue light irradiation uses 34 W Blue LED H150 made by Kessil. Photoredox catalyst $\text{Ir}[\text{dF}(\text{CF}_3)\text{ppy}]_2(\text{dtbbpy})\text{PF}_6$ was prepared according to reported method by Bernhard and co-workers.⁴²

4.4a - Catalytic hydroacylation of electron-deficient alkene

To an oven dried 8 mL vial was charged with Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (1 mol%), quinuclidine (10 mol%) and alkene (1 equiv) (if it is in solid form at room temperature). The mixture was subsequently dissolved in anhydrous MeCN (0.3 M), followed by the addition of alkene substrate (if it is in liquid form at room temperature) and aldehyde (5 equiv)*. The light yellow solution was then degassed by either freeze-pump-thaw (3 cycles) or nitrogen purging (10 minutes) (both techniques gave comparable yields). The reaction vial was then refilled with N₂ and placed under blue light irradiation (34 W Kessil Aquarium LED light). The surrounding temperature was chilled by using a cooling fan placed on top. After 16 hours, the solvent was removed under vacuum and the oily residue was further purified by flash column chromatography (Ethyl acetate/Hexane) affording the compound of interest.

(*) In the case of volatile aldehyde such as EtCHO or ⁿBuCHO, they were added into the solution after degassing via a micro syringe.

4.4b - Co-operative Nickel catalyzed direct cross coupling of aldehydes with aryl bromides

To an oven dried 8 mL vial was charged with quinuclidine (1.2 equiv) and aryl halide (if it is in solid form at room temperature). The mixture was then dissolved in DMSO (0.1 M), followed by the addition of stock Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (1 mol%)* and stock NiCl₂.dme (1 mol%) in DMSO**. The aldehyde (5 equiv) was finally added to the reaction solution*** before it was degassed via freeze-pump-thaw technique (3 cycles) and refilled with nitrogen. The vial was placed under blue LED irradiation from 34 W Kessil Light and cooling by a small fan on top of the system. After 24 hours, the solution was washed with concentrated Na₂CO₃ solution and extracted by dichloromethane (4 times). Organic solvent was

evaporated, and the oily residue was further purified by flash column chromatography (Ethyl acetate/Hexane) affording the compound of interest.

*Stock solution of photoredox Catalyst: 11 mg of $\text{Ir}[\text{dF}(\text{CF}_3)\text{ppy}]_2(\text{dtbbpy})\text{PF}_6$ was dissolved in 1 mL DMSO in a glass vial. The vial was evacuated and refilled with nitrogen after each usage. The solution retains good catalytic activity even after several weeks.

**Stock solution of nickel catalyst: 11 mg of $\text{NiCl}_2\cdot\text{dme}$ and 16 mg of dtbbpy was dissolved in 1 mL DMSO in a glass vial. The resulting solution should be transparent and have light green color. The vial was evacuated and refilled with nitrogen after each usage. This stock solution can be used for 2 weeks.

***Volatile aldehyde (EtCHO) should be added after degassing.

4.4c - Compound characterization

(Scale 0.2 mmol) Obtained 41 mg (**71%**) white solid. Mixture of diastereoisomers.

¹H-NMR (500 MHz, CDCl₃) δ 7.31-7.27 (m, 4H), 7.22-7.19 (m, 7H), 3.95 (dd, $J_1 = 8.5$ Hz, $J_2 = 6$ Hz, 1H), 3.90 (dd, $J_1 = 6.5$ Hz, $J_2 = 7.8$ Hz, 1H), 3.74 (s, 3H), 3.67 (s, 3H), 3.63 (s, 3H), 3.59 (s, 3H), 3.37 (m, 2H), 3.09 (dd, $J_1 = 6.8$ Hz, $J_2 =$, 1H), 2.97-2.77 (m, 7H), 1.27 (d, $J = 7$ Hz, 3H), 1.25 (d, $J = 7$ Hz, 3H)

¹³C-NMR (125 MHz, CDCl₃) δ 202.5; 202.4; 171.8; 171.7; 168.8; 168.4; 146.0; 145.9; 128.5; 128.4; 126.8; 126.7; 126.3; 126.2; 54.2; 54.1; 52.7; 52.6; 52.1; 52.0; 51.0; 50.9; 34.9; 34.7; 32.0; 31.9; 21.9; 21.5.

HRMS: m/z for C₁₆H₂₀O₅ [M+H]⁺ calculated 293.1389, found 293.1387.

(Scale 0.2 mmol) Obtained 34 mg (**70%**) yellow oil. Spectra match with reported data.²⁸

¹H-NMR (400 MHz, CDCl₃) δ 4.10 (t, $J = 7$ Hz, 1H), 3.73 (s, 3H), 3.67 (s, 3H), 2.93-2.80 (m, 2H), 2.73-2.67 (m, 1H), 1.72-1.61 (m, 2H), 1.51-1.40 (m, 2H), 0.87 (t, $J = 7.5$ Hz, 3H), 0.80 (t, $J = 7.5$ Hz, 3H).

¹³C-NMR (100 MHz, CDCl₃) δ 206.5; 171.7; 168.7; 54.3; 54.1; 52.6; 52.0; 31.9; 24.2; 22.9; 11.6; 11.3.

HRMS: m/z for C₁₂H₂₀O₅ [M+Na]⁺ calculated 267.1208, found 267.1206.

(Scale 0.2 mmol) Obtained 42 mg (**92%**) colorless oil. Spectra match with reported data.⁴³

¹H-NMR (400 MHz, CDCl₃) δ 3.96 (dd, $J_1 = 8.2$ Hz, $J_2 = 6.4$ Hz, 1H), 3.73 (s, 3H), 3.67 (s, 3H), 2.96 (dd, $J_1 = 8.2$ Hz, $J_2 = 17.5$ Hz, 1H), 2.82 (dd, $J_1 = 6.4$ Hz, $J_2 = 17.5$ Hz, 1H), 2.53 (m, 2H), 2.18 (m, 1H), 0.92 (d, $J = 6.6$ Hz, 3H), 0.89 (d, $J = 6.6$ Hz, 3H).

¹³C-NMR (100 MHz, CDCl₃) δ 203.3; 171.8; 168.9; 54.2; 52.7; 52.0; 51.5; 32.0; 24.1; 22.4; 22.2.

HRMS: m/z for C₁₁H₁₈O₅ [M+Na]⁺ calculated 253.1052, found 253.1058.

(Scale 0.2 mmol) Obtained 37 mg (**93%**) white solid (mp. 58-59 °C)

(Scale 5 mmol) Obtained 0.7 g (**70%**). Spectra match with reported data.⁴⁴

¹H-NMR (400 MHz, CDCl₃) δ 3.99 (dd, $J_1 = 6.3$ Hz, $J_2 = 8.3$ Hz, 1H), 3.74 (s, 3H), 3.67 (s, 3H), 2.99 (dd, $J_1 = 8.3$ Hz, $J_2 = 17.6$ Hz, 1H), 2.84 (dd, $J_1 = 6.3$ Hz, $J_2 = 17.6$ Hz, 1H), 2.79-2.60 (m, 2H), 1.08 (t, $J = 7.3$ Hz, 3H).

¹³C-NMR (100 MHz, CDCl₃) δ 204.5; 171.8; 169.0; 53.5; 52.7; 52.0; 36.1; 32.2; 7.5.

HRMS: m/z for C₉H₁₄O₅ [M+H]⁺ calculated 203.0919, found 203.0915.

(Scale 0.2 mmol) Obtained 31 mg (**72%**) colorless oil. Spectra match with reported data.⁴³

¹H-NMR (400 MHz, CDCl₃) δ 4.16 (dd, $J_1 = 6.4$ Hz, $J_2 = 8.0$ Hz, 1H), 3.73 (s, 3H), 3.67 (s, 3H), 2.98-2.90 (m, 2H), 2.83 (dd, $J_1 = 6.4$ Hz, $J_2 = 17.4$ Hz, 1H), 1.16 (d, $J = 7.0$ Hz, 3H), 1.11 (d, $J = 6.7$ Hz, 3H).

¹³C-NMR (100 MHz, CDCl₃) δ 207.7; 171.7; 169.1; 52.7; 52.0; 51.9; 40.7; 32.3; 18.6; 17.8.

HRMS: m/z for C₁₀H₁₆O₅ [M+Na]⁺ calculated 239.0895, found 239.0898.

(Scale 0.2 mmol) Obtained 24 mg (**47%**) colorless oil. Spectra match with reported data.²⁶

¹H-NMR (400 MHz, CDCl₃) δ 3.99 (dd, $J_1 = 6.4$ Hz, $J_2 = 8.2$ Hz, 1H), 3.74 (s, 3H), 3.67 (s, 3H), 2.98 (dd, $J_1 = 8.2$ Hz, $J_2 = 17.6$ Hz, 1H), 2.83 (dd, $J_1 = 6.4$ Hz, $J_2 = 17.6$ Hz, 1H), 2.74-2.56 (m, 2H), 1.60-1.55 (m, 2H), 1.28-1.27 (m, 6H), 0.86-0.90 (m, 3H).

¹³C-NMR (100 MHz, CDCl₃) δ 203.9; 171.8; 169.0; 53.8; 52.7; 52.0; 42.7; 32.1; 31.5; 28.6; 23.3; 22.4; 14.0.

HRMS: m/z for C₁₃H₂₂O₅ [M+Na]⁺ calculated 281.1365, found 281.1368.

(Scale 0.2 mmol) Obtained 36 mg (**65%**) colorless oil. Spectra match with reported data.²⁶

¹H-NMR (400 MHz, CDCl₃) δ 7.30-7.26 (m, 2H), 7.20-7.17 (m, 3H), 3.98 (dd, $J_1 = 6.2$ Hz, $J_2 = 8.4$ Hz, 1H), 3.67 (s, 3H), 3.66 (s, 3H), 3.08-2.91 (m, 5H), 2.84 (dd, $J_1 = 6.2$ Hz, $J_2 = 17.6$ Hz, 1H).

¹³C-NMR (100 MHz, CDCl₃) δ 202.9; 171.8; 168.7; 140.6; 128.4; 128.3; 126.1; 53.8; 52.7; 52.0; 44.3; 32.1; 29.4.

HRMS: m/z for C₁₅H₁₈O₅ [M+Na]⁺ calculated 301.1052, found 301.1050.

(Scale 0.2 mmol) Obtained 43 mg (**66%**) yellow oil. Mixture of diastereoisomers.

¹H-NMR (400 MHz, CDCl₃) δ 4.16-4.08 (m, 1H), 3.74-3.67 (m, 6H), 2.97-2.77 (m, 3H), 1.76-1.63 (m, 1H), 1.46-1.37 (m, 1H), 1.22-0.97 (m, 8H), 0.91-0.87 (m, 12H).

¹³C-NMR (100 MHz, CDCl₃) δ 207.4; 207.2; 207.1 (3 different isomers, C=O); 171.7; 171.6; 169.1; 168.8 (O=C-O); The rest of C_{sp3} peak are complex, see spectra for more details.

HRMS: m/z for C₁₈H₃₂O₅ [M+Na]⁺ calculated 351.2147, found 351.2148.

(Scale 0.2 mmol) Obtained 42 mg (**81%**) light yellow oil. Spectra match with reported data.²⁸

¹H-NMR (400 MHz, CDCl₃) δ 4.14 (dd, *J*₁ = 6.4 Hz, *J*₂ = 8.0 Hz, 1H), 3.72 (s, 3H), 3.66 (s, 3H), 2.93 (dd, *J*₁ = 8.1 Hz, *J*₂ = 17.4 Hz, 1H), 2.81 (dd, *J*₁ = 6.4 Hz, *J*₂ = 17.4 Hz, 1H), 2.68-2.62 (m, 1H), 1.98-1.62 (m, 5H), 1.43-1.16 (m, 5H).

¹³C-NMR (100 MHz, CDCl₃) δ 206.8; 171.8; 169.1; 52.7; 52.1; 52.0; 50.6; 32.2; 28.9; 27.9; 25.7; 25.6; 25.3.

HRMS: m/z for C₁₃H₂₀O₅ [M+Na]⁺ calculated 279.1208, found 279.1207.

(Scale 0.2 mmol) Obtained 38 mg (**79%**) light yellow oil

¹H-NMR (400 MHz, CDCl₃) δ 4.10 (dd, $J_1 = 6.6$ Hz, $J_2 = 7.8$ Hz, 1H), 3.73 (s, 3H), 3.67 (s, 3H), 3.20-3.12 (m, 1H), 2.95 (dd, $J_1 = 7.8$ Hz, $J_2 = 17.4$ Hz, 1H), 2.83 (dd, $J_1 = 6.6$ Hz, $J_2 = 17.4$ Hz, 1H), 1.97-1.52 (m, 8H, merging with H₂O peak).

¹³C-NMR (100 MHz, CDCl₃) δ 206.3; 171.8; 169.1; 53.5; 52.7; 52.0; 51.1; 32.2; 29.9; 28.7; 26.0; 25.9.

HRMS: m/z for C₁₂H₁₈O₅ [M+Na]⁺ calculated 265.1052, found 265.1057.

(Scale 0.2 mmol) Obtained 30 mg (**60%**) light yellow oil. Spectra match with reported data.⁴⁵

¹H-NMR (400 MHz, CDCl₃) δ 8.04-8.02 (m, 2H), 7.62-7.58 (m, 1H), 7.51-7.47 (m, 2H), 4.89 (t, $J = 7.1$ Hz, 1H), 3.68 (s, 3H), 3.67 (s, 3H), 3.14-3.00 (m, 2H).

¹³C-NMR (100 MHz, CDCl₃) δ 194.0; 171.7; 169.2; 135.8; 133.7; 128.9; 128.8; 52.8; 52.1; 49.2; 33.1.

HRMS: m/z for C₁₃H₁₄O₅ [M+Na]⁺ calculated 273.0739, found 273.0742.

(Scale 0.2 mmol) Obtained 21 mg (**31%**) yellow oil.

¹H-NMR (400 MHz, CDCl₃) δ 7.91-7.89 (m, 2H), 7.65-7.63 (m, 2H), 4.82 (dd, $J_1 = 6.2$ Hz, $J_2 = 8.1$ Hz, 1H), 3.68 (s, 3H), 3.67 (s, 3H), 3.13 (dd, $J_1 = 8.1$ Hz, $J_2 = 17.5$ Hz, 1H), 3.03 (dd, $J_1 = 6.2$ Hz, $J_2 = 17.5$ Hz, 1H).

^{13}C -NMR (100 MHz, CDCl_3) δ 193.1; 171.7; 168.8; 134.6; 132.1; 130.4; 129.1; 52.9; 52.2; 49.2; 33.0.

HRMS: m/z for $\text{C}_{13}\text{H}_{13}\text{O}_5\text{Br}$ $[\text{M}+\text{Na}]^+$ calculated 350.9844 (using ^{79}Br), found 350.9848.

(Scale 0.2 mmol) Obtained 40 mg (**95%**) colorless oil.

^1H -NMR (400 MHz, CDCl_3) δ 3.22-3.17 (m, 1H), 2.93 (dd, $J_1 = 9.2$ Hz, $J_2 = 17.7$ Hz, 1H), 2.61-2.36 (m, 3H), 2.31 (dd, $J_1 = 4.4$ Hz, $J_2 = 17.7$ Hz, 1H), 1.98-1.63 (m, 6H), 1.43-1.17 (m, 5H), 1.06 (d, $J = 7.2$ Hz, 3H), 1.01 (t, $J = 7.2$ Hz, 3H).

^{13}C -NMR (100 MHz, CDCl_3) δ 216.6; 210.1; 49.5; 45.3; 39.5; 36.0; 29.0; 28.3; 25.9; 25.6; 16.9; 7.6.

HRMS: m/z for $\text{C}_{13}\text{H}_{22}\text{O}_2$ $[\text{M}+\text{H}]^+$ calculated 211.1698, found 211.1690.

(Scale 0.2 mmol) Obtained 13 mg (**38%**) colorless oil.

^1H -NMR (400 MHz, CDCl_3) δ 2.85-2.81 (m, 2H), 2.59-2.55 (m, 2H), 2.40-2.33 (m, 1H), 1.88-1.66 (m, 5H), 1.41-1.19 (m, 5H).

^{13}C -NMR (100 MHz, CDCl_3) δ 209.3; 119.2; 50.5; 35.7; 28.3; 25.7; 25.5; 11.5.

HRMS: m/z for $\text{C}_{10}\text{H}_{15}\text{NO}$ $[\text{M}+\text{H}]^+$ calculated 166.1232, found 166.1233.

(Scale 0.2 mmol) Obtained 54 mg (**96%**) light yellow solid. Spectra match with reported data.⁴⁶

¹H-NMR (400 MHz, CDCl₃) δ 7.91-7.89 (m, 2H), 7.68-7.64 (m, 1H), 7.59-7.55 (m, 2H), 3.38-3.34 (m, 2H), 2.95-2.91 (m, 2H), 2.36-2.30 (m, 1H), 1.81-1.64 (m, 5H), 1.34-1.15 (m, 5H).

¹³C-NMR (100 MHz, CDCl₃) δ 209.2; 139.1; 133.8; 129.3; 127.9; 50.8; 50.6; 32.8; 28.3; 25.6; 25.4.

HRMS: m/z for C₁₅H₂₀O₃S [M+Na]⁺ calculated 303.1031, found 303.1029.

(Scale 0.2 mmol) Obtained 36 mg (**99%**) light yellow oil. Spectra match with reported data.¹⁶

¹H-NMR (400 MHz, CDCl₃) δ 2.70-2.68 (m, 4H), 2.40-2.34 (m, 1H), 2.18 (s, 3H), 1.87-1.64 (m, 5H), 1.38-1.17 (m, 5H).

¹³C-NMR (100 MHz, CDCl₃) δ 212.6; 207.4; 50.7; 36.9; 34.1; 30.0; 28.5; 25.8; 25.6.

HRMS: m/z for C₁₁H₁₈O₂ [M+H]⁺ calculated 183.1385, found 183.1385.

(Scale 0.2 mmol) Obtained 41 mg (**99%**) white solid (mp. 54-55 °C). Spectra match with reported data.¹⁶

¹H-NMR (400 MHz, CDCl₃) δ 3.06-2.98 (m, 1H), 2.54-2.27 (m, 5H), 2.12-1.95 (m, 2H), 1.83-1.63 (m, 7H), 1.47-1.16 (m, 5H).

¹³C-NMR (100 MHz, CDCl₃) δ 213.5; 210.3; 49.5; 48.5; 42.9; 40.9; 28.7; 28.1; 27.5; 25.7; 25.4; 25.1.

HRMS: m/z for C₁₃H₂₀O₂ [M+H]⁺ calculated 209.1542, found 209.1545.

(Scale 0.2 mmol) Obtained 24 mg (**60%**) colorless oil. Spectra match with reported data.⁴⁷

¹H-NMR (500 MHz, CDCl₃) δ 7.95-7.94 (m, 2H), 7.61-7.58 (m, 1H), 7.50-7.47 (m, 2H), 3.84-3.80 (m, 1H), 2.75-2.70 (m, 1H), 2.51-2.40 (m, 3H), 2.13-2.09 (m, 2H), 1.90-1.82 (m, 2H).

¹³C-NMR (100 MHz, CDCl₃) δ 210.2; 200.4; 135.4; 133.5; 128.9; 128.4; 45.2; 43.2; 41.0; 28.4; 24.9.

HRMS: m/z for C₁₃H₁₄O₂ [M+H]⁺ calculated 203.1072, found 203.1074.

(Scale 0.1 mmol) Obtained 3 mg (**15%**) light yellow oil.

¹H-NMR (500 MHz, CDCl₃) δ 7.91-7.90 (m, 1H), 7.83-7.81 (m, 1H), 7.70-7.67 (m, 1H), 7.64-7.61 (m, 1H), 3.70 (q, *J* = 7.9 Hz, 1H), 1.96-1.92 (m, 4H), 1.76-1.64 (m, 4H).

¹³C-NMR (125 MHz, CDCl₃) δ 201.6; 140.5; 135.2; 132.4; 131.9; 129.3; 118.2; 111.4; 47.8; 29.8; 26.2.

HRMS: m/z for C₁₃H₁₃NO [M+Na]⁺ calculated 222.0895, found 222.0893.

(Scale 0.1 mmol) Obtained 11 mg (**47%**) white solid.

¹H-NMR (500 MHz, CDCl₃) δ 8.03 (s, 4H), 2.99 (t, *J* = 7.5 Hz, 2H), 2.64 (s, 3H), 1.75-1.72 (m, 2H), 1.39-1.32 (m, 8H), 0.90-0.88 (m, 3H).

¹³C-NMR (125 MHz, CDCl₃) δ 200.0; 197.5; 140.3; 140.0; 128.5; 128.2; 39.0; 31.6; 29.0; 26.9; 24.1; 22.5; 14.0.

HRMS: *m/z* for C₁₅H₂₀O₂ [M+H]⁺ calculated 233.1542, found 233.1545.

(Scale 0.1 mmol) Obtained 14 mg (**60%**) white solid.

¹H-NMR (500 MHz, CDCl₃) δ 8.02-7.98 (m, 4H), 3.29-3.23 (m, 1H), 2.64 (s, 3H), 1.90-1.83 (m, 4H), 1.53-1.25 (m, 6H).

¹³C-NMR (125 MHz, CDCl₃) δ 203.4; 197.5; 139.9; 139.7; 128.5; 128.4; 46.0; 29.2; 26.9; 25.9; 25.8.

HRMS: *m/z* for C₁₅H₁₈O₂ [M+Na]⁺ calculated 253.1204, found 253.1202.

(Scale 0.1 mmol) Obtained 6 mg (**25%**) colorless oil.

¹H-NMR (400 MHz, CDCl₃) δ 8.03 (s, 4H), 3.33-3.27 (m, 1H), 2.65 (s, 3H), 1.85-1.74 (m, 2H), 1.63-1.53 (m, 2H – merged peak with H₂O), 0.88 (t, *J* = 9.5 Hz, 6H).

¹³C-NMR (125 MHz, CDCl₃) δ 204.1; 197.5; 141.1; 139.9; 128.5; 128.3; 49.7; 26.9; 24.7; 11.8.

HRMS: *m/z* for C₁₄H₁₈O₂ [M+H]⁺ calculated 219.1385, found 219.1386.

(Scale 0.1 mmol) Obtained 11 mg (**51%**) colorless oil.

¹H-NMR (500 MHz, CDCl₃) δ 8.03 (s, 4H), 3.71 (q, *J* = 7.5 Hz, 1H), 2.64 (s, 3H), 1.95-1.89 (m, 4H), 1.75-1.66 (m, 4H).

¹³C-NMR (125 MHz, CDCl₃) δ 202.2; 197.6; 140.2; 139.9; 128.6; 128.4; 46.8; 29.8; 26.9; 26.3.

HRMS: *m/z* for C₁₄H₁₆O₂ [M+H]⁺ calculated 217.1229, found 217.1231.

(Scale 0.1 mmol) Obtained 9 mg (**36%**) white solid. Spectra match with reported data.⁴⁸

¹H-NMR (400 MHz, CDCl₃) δ 8.02 (s, 4H), 7.33-7.20 (m, 5H) (merging with CHCl₃ residue peak), 3.33 (t, *J* = 7.5 Hz, 2H), 3.08 (t, *J* = 7.5 Hz, 2H), 2.64 (s, 3H).

¹³C-NMR (100 MHz, CDCl₃) δ 198.7, 197.5; 140.9; 140.1; 140.0; 128.6; 128.5; 128.4; 128.2; 126.3; 40.8; 30.0; 26.9.

HRMS: *m/z* for C₁₇H₁₆O₂ [M+H]⁺ calculated 253.1229, found 253.1230.

(Scale 0.1 mmol) Obtained 9 mg (**49%**) white solid (mp. 71-72 °C). Spectra match with reported data.⁴⁹

¹H-NMR (500 MHz, CDCl₃) δ 8.03 (s, 4H), 3.04 (q, *J* = 7.0 Hz, 2H), 2.64 (s, 3H), 1.24 (t, *J* = 7.0 Hz, 3H).

¹³C-NMR (125 MHz, CDCl₃) δ 200.2; 197.5; 140.1; 140.0; 128.5; 128.2; 32.2; 26.9; 8.1.

HRMS: *m/z* for C₁₁H₁₂O₂ [M+H]⁺ calculated 177.0916, found 177.0912.

(Scale 0.2 mmol) Obtained 28 mg (**65%**) light yellow oil. Spectra match with reported data.⁵⁰⁻

51

¹H-NMR (500 MHz, CDCl₃) δ 4.11 (q, *J* = 7.5 Hz, 2H), 2.74 (t, *J* = 6.5 Hz, 2H), 2.56 (t, *J* = 6.5 Hz, 2H), 2.40-2.35 (m, 1H), 1.88-1.65 (m, 5H), 1.39-1.18 (m, 8H).

¹³C-NMR (125 MHz, CDCl₃) δ 212.1; 172.9; 60.5; 50.7; 35.0; 28.5; 27.9; 25.8; 25.6; 14.2.

HRMS: *m/z* for C₁₂H₂₀O₃ [M+Na]⁺ calculated 235.1310, found 235.1315.

(Scale 0.2 mmol) Obtained 30 mg (**70%**) light yellow oil. Spectra match with reported data.¹⁶

¹H-NMR (400 MHz, CDCl₃) δ 3.66 (s, 3H), 2.97-2.88 (m, 2H), 2.51-2.44 (m, 1H), 2.37-2.29 (m, 1H), 1.87-1.64 (m, 5H), 1.38-1.15 (m, 8H).

¹³C-NMR (100 MHz, CDCl₃) δ 211.9; 176.4; 51.8; 50.8; 43.8; 34.5; 28.4; 28.3; 25.8; 25.6; 25.5; 17.1.

HRMS: *m/z* for C₁₂H₂₀O₃ [M+Na]⁺ calculated 235.1310, found 235.1311.

(Scale 0.2 mmol) Obtained 30 mg (**63%**) light yellow oil.

¹H-NMR (500 MHz, CDCl₃) δ 3.83 (d, *J* = 6.7 Hz, 2H), 2.74 (t, *J* = 6.5 Hz, 2H), 2.57 (t, *J* = 6.5 Hz, 2H), 2.40-2.34 (m, 1H), 1.94-1.63 (m, 6H), 1.38-1.17 (m, 5H), 0.91 (d, *J* = 6.8 Hz, 6H).

¹³C-NMR (125 MHz, CDCl₃) δ 212.0; 173.0; 70.7; 50.7; 35.0; 28.4; 27.9; 27.7; 25.8; 25.6; 19.0.

HRMS: *m/z* for C₁₄H₂₄O₃ [M+Na]⁺ calculated 263.1623, found 263.1622.

(Scale 0.1 mmol) Obtained 9 mg (**50%**) light yellow oil.

¹H-NMR (500 MHz, CDCl₃) δ 7.89 (d, *J* = 7.7 Hz, 1H), 7.81 (d, *J* = 7.6 Hz, 1H), 7.70-7.67 (m, 1H), 7.65-7.62 (m, 1H), 2.89 (d, *J* = 6.8 Hz, 2H), 2.34-2.29 (m, 1H), 1.01 (d, *J* = 6.7 Hz, 6H).

¹³C-NMR (100 MHz, CDCl₃) δ 198.8; 140.7; 135.2; 132.5; 132.1; 129.2; 118.1; 111.0; 48.8; 25.0; 22.6.

HRMS: *m/z* for C₁₂H₁₃NO [M+H]⁺ calculated 188.1075, found 188.1079.

(Scale 0.2 mmol) Obtained 11 mg (**31%**) colorless oil. Spectra match with reported data.⁵²

¹H-NMR (400 MHz, CDCl₃) δ 7.99-7.97 (m, 2H), 7.59-7.56 (m, 1H), 7.48-7.44 (m, 2H), 3.28 (t, *J* = 6 Hz, 2H), 2.89 (t, *J* = 6 Hz, 2H), 2.26 (s, 3H).

¹³C-NMR (100 MHz, CDCl₃) δ 207.3; 198.5; 136.6; 133.2; 128.6; 128.1; 37.1; 32.4; 30.1.

HRMS: *m/z* for C₁₁H₁₂O₂ [M+H]⁺ calculated 177.0916, found 177.0920.

4.5 - References

1. Chatgililoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991-2070.
2. Boger, D. L.; Mathvink, R. J. *J. Org. Chem.* **1992**, *57*, 1429-1443.
3. Blakskjær, P.; Høj, B.; Riber, D.; Skrydstrup, T. *J. Am. Chem. Soc.* **2003**, *125*, 4030-4031.
4. Webster, R. D.; Bond, A. M. *J. Org. Chem.* **1997**, *62*, 1779-1787.
5. Kim, S.; Jon, S. Y. *Chem. Commun.* **1996**, 1335-1336.
6. Crich, D.; Yao, Q. *J. Org. Chem.* **1996**, *61*, 3566-3570.
7. Penn, J. H.; Liu, F. *J. Org. Chem.* **1994**, *59*, 2608-2612.
8. Ballestri, M.; Chatgililoglu, C.; Cardi, N.; Sommazzi, A. *Tetrahedron Lett.* **1992**, *33*, 1787-1790.
9. Zhang, M.; Ruzi, R.; Xi, J.; Li, N.; Wu, Z.; Li, W.; Yu, S.; Zhu, C. *Org. Lett.* **2017**, *19*, 3430-3433.
10. L., J. C.; G., D. A. *Angew. Chem. Int. Ed.* **2016**, *55*, 4040-4043.
11. Gu, L.; Jin, C.; Liu, J.; Zhang, H.; Yuan, M.; Li, G. *Green Chem.* **2016**, *18*, 1201-1205.
12. Lingling, C.; M., L. J.; C., M. D. W. *Angew. Chem. Int. Ed.* **2015**, *54*, 7929-7933.
13. Hanchu, H.; Guojin, Z.; Yiyun, C. *Angew. Chem. Int. Ed.* **2015**, *54*, 7872-7876.
14. Giulia, B.; Carlo, C.; Carl-Johan, W. *Angew. Chem. Int. Ed.* **2015**, *54*, 14066-14069.
15. Guo, L.-N.; Wang, H.; Duan, X.-H. *Org. Biomol. Chem.* **2016**, *14*, 7380-7391.
16. Ilhyong, R.; Akihiro, T.; Takahide, F.; Davide, R.; Maurizio, F.; Angelo, A. *Angew. Chem. Int. Ed.* **2011**, *50*, 1869-1872.
17. Ilhyong, R.; Noboru, S. *Angew. Chem. Int. Ed.* **1996**, *35*, 1050-1066.
18. Harris, E. F. P.; Waters, W. A. *Nature* **1952**, *170*, 212-213.
19. Recupero, F.; Punta, C. *Chem. Rev.* **2007**, *107*, 3800-3842.
20. Tsujimoto, S.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **2003**, *44*, 5601-5604.
21. Sharma, U. K.; Gemoets, H. P. L.; Schröder, F.; Noël, T.; Van der Eycken, E. V. *ACS Catal.* **2017**, *7*, 3818-3823.

22. Li, J.; Wang, D. Z. *Org. Lett.* **2015**, *17*, 5260-5263.
23. Silvia, E.; Daniele, D.; Maurizio, F.; Angelo, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 2531-2534.
24. Ravelli, D.; Zema, M.; Mella, M.; Fagnoni, M.; Albini, A. *Org. Biomol. Chem.* **2010**, *8*, 4158-4164.
25. Maurizio, F.; Filippo, B.; Alessandro, P.; Stefano, P.; Davide, R.; Roberto, B. *Adv. Synth. Cat.* **2014**, *356*, 753-758.
26. Filippo, B.; Davide, R.; Stefano, P.; Maurizio, F. *Adv. Synth. Cat.* **2015**, *357*, 3687-3695.
27. Chudasama, V.; Fitzmaurice, R. J.; Caddick, S. *Nat. Chem.* **2010**, *2*, 592-596.
28. A., M. S.; Asuka, U.; Sermadurai, S.; Tiexin, Z.; Keiji, M. *Angew. Chem. Int. Ed.* **2014**, *53*, 11060-11064.
29. Jiang, J.; Ramozzi, R.; Moteki, S.; Usui, A.; Maruoka, K.; Morokuma, K. *J. Org. Chem.* **2015**, *80*, 9264-9271.
30. Sermadurai, S.; Ryu, S.; Keiji, M. *Chem. Eur. J.* **2016**, *22*, 6552-6555.
31. Hager, D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 16986-16989.
32. Qvortrup, K.; Rankic, D. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 626-629.
33. Cuthbertson, J. D.; MacMillan, D. W. C. *Nature* **2015**, *519*, 74-78.
34. Mukherjee, S.; Maji, B.; Tlahuext-Aca, A.; Glorius, F. *J. Am. Chem. Soc.* **2016**, *138*, 16200-16203.
35. Choi, G. J.; Zhu, Q.; Miller, D. C.; Gu, C. J.; Knowles, R. R. *Nature* **2016**, *539*, 268-271.
36. Chu, J. C. K.; Rovis, T. *Nature* **2016**, *539*, 272-275.
37. Jeffrey, J. L.; Terrett, J. A.; MacMillan, D. W. *Science* **2015**, *349*, 1532-1536.
38. Shaw, M. H.; Shurtleff, V. W.; Terrett, J. A.; Cuthbertson, J. D.; MacMillan, D. W. C. *Science* **2016**, *352*, 1304-1308.
39. Sangwon, K.; Byungman, K.; Sukbok, C. *Angew. Chem. Int. Ed.* **2005**, *44*, 455-457.
40. Ruan, J.; Saidi, O.; Iggo, J. A.; Xiao, J. *J. Am. Chem. Soc.* **2008**, *130*, 10510-10511.
41. Suchand, B.; Satyanarayana, G. *J. Org. Chem.* **2016**, *81*, 6409-6423.

42. Lowry, M. S.; Goldsmith, J. I.; Slinker, J. D.; Rohl, R.; Pascal, R. A.; Malliaras, G. G.; Bernhard, S. *Chem. Mater.* **2005**, *17*, 5712-5719.
43. Chudasama, V.; Akhbar, A. R.; Bahou, K. A.; Fitzmaurice, R. J.; Caddick, S. *Org. Biomol. Chem.* **2013**, *11*, 7301-7317.
44. Starodubtseva, E. V.; Turova, O. V.; Vinogradov, M. G.; Gorshkova, L. S.; Ferapontov, V. A.; Struchkova, M. I. *Tetrahedron* **2008**, *64*, 11713-11717.
45. Mattson, A. E.; Bharadwaj, A. R.; Scheidt, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 2314-2315.
46. Chudasama, V.; Fitzmaurice, R. J.; Ahern, J. M.; Caddick, S. *Chem. Commun.* **2010**, *46*, 133-135.
47. Bennetau, B.; Krempp, M.; Dunoguès, J. *Synth. Commun.* **1994**, *24*, 77-83.
48. Lukas J., G.; Keya, G. *Eur. J. Org. Chem.* **2002**, *2002*, 3254-3267.
49. Sato, N.; Narita, N. *Synthesis* **2001**, *2001*, 1551-1555.
50. Eun-Ae, J.; Chul-Ho, J. *Eur. J. Org. Chem.* **2006**, *2006*, 2504-2507.
51. Kawamoto, T.; Uehara, S.; Hirao, H.; Fukuyama, T.; Matsubara, H.; Ryu, I. *J. Org. Chem.* **2014**, *79*, 3999-4007.
52. Lan, X.-W.; Wang, N.-X.; Zhang, W.; Wen, J.-L.; Bai, C.-B.; Xing, Y.; Li, Y.-H. *Org. Lett.* **2015**, *17*, 4460-4463.

List of Publications and Conferences

Publications

- 1. N-Linked Glycosyl Auxiliary-Mediated Native Chemical Ligation on Aspartic Acid: Application towards N-Glycopeptide Synthesis**
Angewandte Chemie International Edition, Volume 128, Issue 35, Pages 10519-10523
Authors: H. Chai, Dr. M.H.K. Le, M.D. Vu, Dr. K. Pasunooti, Prof. C.-F. Liu, Prof. X.-W. Liu
- 2. Direct Aldehyde C_{sp2}-H Functionalization through Visible-Light-Mediated Photoredox Catalysis**
Chemistry-A European Journal, Volume 23, Issue 63, Pages 15899-15902
Authors: M.D. Vu, M. Das, Prof. X.-W. Liu
- 3. Triflic Acid Catalyzed Tandem Allylic Substitution-Cyclization Reaction of Alcohols with Thiophenols - Facile Access to Polysubstituted Thiochromans**
ACS Omega, 2018, accepted (invited article)
Authors: M.D. Vu, C.Q. Foo, A. Sadeer, S.S. Shand, Y. Li and Dr. S.A. Pullarkat
- 4. Alkene Synthesis through Umpolung of Phosphonium Ylides**
Asian Journal of Organic Chemistry, 2018, accepted
Authors: M.D. Vu, W.-L. Leng, H.-C. Hsu and Prof. X.-W. Liu
- 5. Metal-Free Visible Light Photoredox Mediated Hydrocarbonation of Electron Rich Olefins**
Chemical Science, 2018, accepted
Authors: M. Das*, M.D. Vu* and Prof. X.-W. Liu (* the two authors contributed equally)
- 6. Photoredox Mediated Allylic/Benzylic C_{sp3}-H Activation for Intermolecular Cross-Radical Radical Coupling with Ketyl Radicals**
Manuscript under review
Authors: M.D. Vu, M. Das, Z.-E. Ang and Prof. X.-W. Liu
- 7. Recent advances in reagent-controlled stereoselective/stereospecific glycosylation**
Carbohydrate Research, 2018, accepted (review article)
Authors: H. Yao*, M.D. Vu* and Prof. X.-W. Liu (* the two authors contributed equally)

Conferences

1. **18th Tetrahedron Symposium - Asia Edition, Melbourne, Australia
& 100th Royal Australian Chemical Institute Centenary Congress, Melbourne, Australia (Jul 17)**

Presented on: Alkene synthesis via umpolung of Phosphonium ylides under visible-light mediated photoredox catalysis - One-pot olefination of activated halides

2. **19th IUPAC International Symposium on Organometallic Chemistry directed towards Organic Synthesis, Jeju, Korea (Jun 17)**

Presented on: Direct aldehyde C_{sp2}-H functionalization through visible-light-mediated photoredox catalysis

3. **14th International Symposium for Chinese Organic Chemists, Singapore (Dec 16)
& 17th Tetrahedron Symposium, Barcelona, Spain (Jun 16)**

Presented on: Visible-light induced glycal activation - α -Stereoselective synthesis of 2-deoxy-*O*-glycosides