N-heterocyclic carbene-catalyzed single-electron-transfer radical processes for reductive coupling reactions

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**N-Heterocyclic Carbene-Catalyzed Single-Electron-Transfer
Radical Processes for Reductive Coupling Reactions**

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N-Heterocyclic Carbene-Catalyzed Single-Electron-Transfer Radical Processes for Reductive Coupling Reactions

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ABSTRACT

This thesis focuses on exploring single-electron-transfer (SET) reductive coupling reactions catalyzed by N-heterocyclic carbene (NHC) organocatalysts. It contained five chapters:

Chapter 1 gives a brief introduction to NHC-catalyzed electron-pair transfer reactions involving different key intermediates, and recent discoveries on NHC-catalyzed SET process and relating reactions.

Chapter 2 describes a carbene-catalyzed reductive coupling reaction for β -nitroalkenes. The reaction pathway includes SET process mimicking the thiamine pyrophosphate (TPP)-catalyzed oxidative decarboxylation of pyruvate in living systems. The SET process starts from Breslow intermediate of nitroalkene to generate corresponding nitroalkene radical anion for further transforming to homocoupling product. For the first time, the presence of radical anion intermediate in NHC-organocatalytic system is revealed.

Chapter 3 introduces a carbene-catalyzed reductive cross-coupling of nitrobenzyl bromides with nitroalkenes via SET process and formal 1,4-addition. Control experiments prove that the reaction initiates from the SET process between nitrobenzyl bromide and Breslow intermediate. The nitrobenzyl bromide first obtains one electron, and the elimination of bromide takes place during the following generation of corresponding nitrobenzyl radical intermediate for further transformation. The bromo group serves as a leaving group in this reaction. The reaction pathway shows a new activation mode in NHC-organocatalysis.

Chapter 4 describes a carbene-catalyzed reductive cross-coupling of nitrobenzyl bromides with ketones or imines via SET process and formal 1,2-addition. This reaction utilizes the nitrobenzyl radical intermediate, which generates via single-electron reduction of nitrobenzyl bromide and elimination of bromide, to react with α,β -unsaturated ketoesters,

isatins and sulfonyl imines. The reaction provides tertiary alcohols and tertiary amines as the desired products, and the products are further transformed to other interesting molecules including nature product. This work expands the utilization of our NHC-catalyzed SET process.

Chapter 5 develops an efficient carbene-catalyzed cascade process for the synthesis of indane ring systems. The reaction includes the initial SET process for the formal 1,4-addition of nitrobenzyl radical to nitroalkene, and follows another SET process to give corresponding anion intermediate, then the intramolecular Michael addition and protonation takes place to form the indane derivative. The diastereoselectivities of the reaction are excellent that for each of the products, only one diastereomer can be observed. This work demonstrates the synthetic utilization of our NHC-catalyzed new activation mode which involving SET process as key process.

PUBLICATIONS

1. Synthesis of Indanes via Carbene-Catalyzed Single-Electron-Transfer Processes and Cascade Reactions.

Yuhuang Wang, Xingxing Wu and Yonggui Robin Chi*

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2. Carbene-Catalyzed Reductive Coupling of Nitrobenzyl Bromide and Nitroalkene via Single-Electron-Transfer (SET) process and Formal 1,4-Addition.

Yuhuang Wang, Yu Du, Xuan Huang, Xingxing Wu, Yuexia Zhang, Song Yang, and Yonggui Robin Chi.

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3. Carbene-catalysed reductive coupling of nitrobenzyl bromides and activated ketones or imines via single-electron-transfer process.

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11. β -Functionalization of Carboxylic Anhydrides with β -Alkyl Substituents through Carbene Organocatalysis

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ABBREVIATIONS

Ac	acetyl
Ad	adamantly
AIBN	2,2'-azo <i>bisisobutyronitrile</i>
Ar	Aryl
Boc	<i>tert</i> -butoxycarbonyl
Bu	Butyl
Bn	benzyl
bpy	2,2'-bipyridine
Bz	Benzoyl
Cat	Catalyst
CV	Cyclic voltammetry
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
2,3-DHQ	2,3-dihydropyridine
DIEA/DIPEA	<i>N,N</i> -diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
de	distereomeric excess
ECE	Electron transfer-chemical reaction-electron transfer

EDA	electron donor-acceptor
ee	enantiomeric excess
Equiv	equivalent
EPR	electron paramagnetic resonance
ESI	electrospray ionization
ESR	electron spin resonance
EWG	electron-withdrawing group
FcE	ferrocene electrode
HRMS	high-resolution mass spectrometry
IPA	isopropyl alcohol
<i>i</i> Pr	isopropyl
IR	infrared
IR	infrared
LDA	lithium diisopropylamide
LG	leaving group
<i>m</i> -CPBA	<i>meta</i> -chloroperbenzoic acid
MAO	Monoamine oxidase
MBH	Morita-Baylis-Hillman
Mes	mesityl
MOM	methoxymethyl
Ms	mesyl (methanesulfonyl)
NBS	<i>N</i> -bromosuccinimide
NHC	<i>N</i> -heterocyclic carbene
NMDA	<i>N</i> -methyl-D-aspartate
NMO	<i>N</i> -methylmorpholine oxide

NMR	nuclear magnetic resonance
Nu	nucleophile
OTf	trifluoromethanesulfonate
Ox	oxidant
OAc	acetocyl
Ph	Phenyl
<i>p</i> -TsOH	<i>p</i> -toluenesulfonic acid
Red	reductant
rt	room temperature
SCE	saturated calomel electrode
SET	single electron transfer
Sub	substrate
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxyl
TLC	thin layer chromatography
TMS	Trimethylsilyl
TMEDA	tetramethylethyldiamine
TPP	Thiamine pyrophosphate
Ts	tosyl
UV	ultraviolet
α	alpha
β	beta
γ	gamma
δ	delta
σ	sigma
μ	mu

ν	nu
π	pi
ω	omega

Chapter 1

Introduction

1.1 Introduction on N-Heterocyclic Carbene Catalysts

N-heterocyclic carbenes (NHCs) is a class of neutral compounds containing divalent carbene central carbon and at least one nitrogen atom in a cyclic structure. Based on the pioneer contributions of Wanzlick and co-workers¹ on the stability of nucleophilic carbenes and the first phosphinocarbene reported by Bertrand and co-workers² in 1988, Arduengo et al.³ obtained the first stable crystal of an N-heterocyclic carbene in 1991 (Fig. 1.1). These above milestones boosted the enthusiasm on the researching of N-heterocyclic carbene catalysis over the past decades, and no doubtfully this catalysis route played an outstanding role in synthetic chemistry.⁴ To fulfill the demands of synthetic chemistry, the chemists had developed many different NHCs and applied them in organocatalysis to develop new synthetic methodologies, and these existing NHCs include four general types of structures: 1) imidazolydinene, 2) imidazolinylidene, 3) thiazolylidene, 4) triazolylidene.

Fig. 1.1 First stable crystal N-heterocyclic carbene and general N-heterocyclic carbenes

As an organocatalyst, N-heterocyclic carbene always bears a divalent carbon as the carbene center along with two heteroatoms (N, N or N, S) adjacent to the carbene center. In the singlet carbene, the central carbene carbon atom probably hybridized as the sp^2 hybridization, where the lone pair electrons occupy one of the sp^2 orbital and the remaining p orbital stays unoccupied. The two adjacent heteroatoms served as σ -electron-withdrawing substituents due to the electronegativity which is stronger than carbon, and π -electron-donating substituents by p- π conjugation (Fig. 1.2). NHCs benefit a lot from the “push-pull” effect caused by π -donating and σ -withdrawing properties of amino groups. Heteroatom

donor groups on a carbene center may produce some energy unbalance on the originally degenerate orbitals of center carbon, thus enhancing the nucleophilicity of the carbon atom and thermodynamic stability.⁵ These properties make NHCs become the nucleophilic catalysts and can be regenerated by elimination to finish the catalytic circle at the end of the reactions.

Fig. 1.2 Properties of N-heterocyclic carbenes

The bulky group substituted on nitrogen atom provides possibilities for NHCs to prevent deactivation by dimerization. By change the substituents on the structures, researchers can adjust the nucleophilicity of NHCs, and the introduction of chiral substituents can lead to stereoselectivity control. These properties allow chemists to design and synthesis a lot of chiral and achiral NHC catalysts and use them to develop a great many of synthetic methodologies. To briefly introduce the skeleton of the reaction mechanisms, the process of the reactions catalyzed by NHCs usually start from the nucleophilic addition of NHCs to the substrates following by transformation towards one of the below key intermediates: a) acyl anions, b) homoenolates, c) acylazoliums; d) enolates, e) α,β -unsaturated acylazoliums, f) vinyl enolates, then these key intermediates react with other substrates to achieve further transformations (Fig. 1.3).

Fig. 1.3 Different NHC-bound intermediates

1.2 Catalysis Involving Acyl Anions

1.2.1 Benzoin Condensation

The coupling of benzaldehyde to benzoin catalyzed by cyanide reported by Wöhler and Liebig⁶ in 1832 is named as benzoin condensation. In 1943, Ugai and co-workers⁷ first discovered that thiazolium salt can also catalyze the coupling of benzaldehyde to benzoin product. And based on pioneer's work, Breslow⁸ proposed a widely acceptable mechanism model for the benzoin reaction catalyzed by thiazolium involving a key intermediate called “Breslow intermediate” (Scheme 1.1).

Scheme 1.1 Mechanism of benzoin condensation catalyzed by thiazolium salt.

Later in 1966, Sheehan^{9a} et al. first achieved the asymmetric benzoin condensation by introduced chiral NHC catalyst and 22% ee was obtained, years later they improved the selectivity to 51% ee by adjusting the structure of chiral NHC.^{9b} Encouraged by the success of asymmetric condensation, the study of asymmetric benzoin condensation attracted more and more attentions. Many highly efficient chiral NHC catalysts were developed to utilize in this field achieving the enantioselectivities on up to 99% ee (Fig. 1.4).¹⁰

Fig. 1.4 Selected chiral NHC catalysts utilized in asymmetric benzoin condensation.

1.2.2 Stetter Reactions

The reversibility of benzoin condensation provided opportunities for acyl anion intermediate to nucleophilic attack other electrophiles such as Michael accepters. In early 1970s, Stetter¹¹ first achieved the Michael addition of acyl anion to the substrates of Michael accepters, giving a new route to the synthesis of 1,4-bifunctional compounds (Scheme 1.2). Enders et al.¹² first achieved the asymmetric intermolecular Stetter reaction catalyzed by chiral thiazolium salt, allowing the enantioselectivity only in 39% ee (Scheme 1.3). Then great efforts have been made in the study of asymmetric intermolecular Stetter reaction by several research groups using different chiral NHC catalysts and achieve high

enantioselectivities.¹³ The result was summarized in **Scheme 1.4**.

Scheme 1.2 Reaction process of Stetter reaction

Scheme 1.3 First asymmetric intermolecular Stetter reaction.

Scheme 1.4 Summary of asymmetric Stetter reactions.

Intramolecular Stetter reactions are also very important and receive a lot of attentions. The first intramolecular Stetter reaction was reported by Ciganek¹⁴ in 1995, and Enders¹⁵ achieved the first asymmetric intramolecular Stetter reaction. Since then, excellent studies have been done by scientists to develop asymmetric Stetter reaction for the synthesis of chiral fused ring compounds (Scheme 1.5).¹⁶

Scheme 1.5 asymmetric intramolecular Stetter reactions.

1.3 Reactions Involving Homo-enolates.

Although α,β -unsaturated aldehydes are usually used as electrophiles in NHC catalysis, the usage of enals in NHC catalysis shows another important reactivity.¹⁷ While being nucleophilic-attacked by N-heterocyclic carbenes, enals can give interesting different reactivity compare with saturated aldehydes. The reaction system gives extended Breslow intermediate, and the β -carbon of enal change the reactivity from electrophilic to nucleophilic, achieve a^3-d^3 umpolung due to the conjugated system of the Breslow intermediate (Scheme 1.6).

Scheme 1.6 The formation process of homo-enolate intermediates.

In 2004, Glorius^{17a} and Bode^{17b} simultaneously reported the same process for the formation of lactones from enals and simple aldehydes via homo-enolate activation mode (Scheme 1.7). This methodology was the pioneer work of this field.

The diagram illustrates the central role of a **homoenolate intermediate** in the synthesis of diverse molecules:

- Top Left:** Reaction with a substituted cyclopentenone derivative (Ar , R_1 , R_2) yields a bicyclic product.
- Top Right:** Reaction with a furan-substituted enone yields a complex polycyclic ether product.
- Middle Left:** Reaction with a diazo compound ($\text{R}^1\text{-C(=O)-N=N-R}^2$) yields a cyclic urea derivative.
- Middle Right:** Reaction with a carbonyl compound ($\text{R}_1\text{-C(X)=R}_2$, where $\text{X} = \text{O or NR}$) yields a cyclic ketone or imine derivative.
- Bottom Left:** Reaction with a diazo compound yields another cyclic urea derivative.
- Bottom Right:** Reaction with a diazo compound yields a bicyclic product with stereochemical control indicated by wedges and dashes.

Scheme 1.8 Summary of homoenolate activation reactions.

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developed by our group²⁰ in 2013 also provided NHC-bound homoenolate intermediate. In this process, the NHC attacked the ester group to form acylazolium. After that, successive twice deprotonation can give such intermediate.

Scheme 1.9 Other activation mode for the activation of homoenolate intermediate.

1.4 Reactions Involving acylazolium intermediates.

The first example involving acylazolium intermediate in the reaction pathway was the transesterification reported by Smith and co-workers in 1994 (Scheme 1.10).²¹ Quite a lot of reactions catalyzed by NHCs can generate acylazolium intermediates in the reaction pathway, and the catalytic circle finishes by trapping the acylazolium intermediates using nucleophiles and regenerating NHCs. Transesterification promoted by NHCs is a useful reaction that was widely investigated by chemists. Many kinds of substrate can transform to corresponding esters by transesterifications (Scheme 1.11).²²

Scheme 1.10 Transesterification promoted by NHC

Scheme 1.11 Transesterification of different substrates catalyzed by NHCs.

An important application of transesterifications promoted by NHCs is kinetic resolution of racemic alcohols and amines (Scheme 1.12). This application of transesterifications was initiated reported by Suzuki²³ and Maruoka²⁴ in the kinetic resolution of secondary alcohols, and then spreaded to more different alcohols and amines with excellent results.²⁵

Scheme 1.12 Application of transesterifications in kinetic resolution.

1.5 Catalysis involving enolate intermediates.

Glorius and co-workers²⁶ observed β -lactones byproduct when they studied the homoenolate activation of enals and ketones catalyzed by NHC. Their further research on this side reaction lead to the discovery of a new activation mode called enolate activation. The key point of the generation of this intermediate from homoenolate is the β -protonation process (Scheme 1.13).

Scheme 1.13 First example of enolate activation

This type of nucleophilic intermediates with great reactivity thus attracted great attention from chemists. Besides enals, many different types of substrate have been developed as the precursors of this intermediate. The α -chloroaldehydes²⁷ and α -chloroaldehyde bisulfites²⁸ can transform to enolate by elimination of HCl of the corresponding Breslow intermediates; the direct addition of NHC to ketenes²⁹ can form enolate intermediates; deprotonation of acylazoliums can also formulate the enolate intermediate, and the acylazoliums come from oxidative process of Breslow intermediate³⁰ of simple aldehydes or activation of saturated esters³¹ (Scheme 1.14).

Scheme 1.14 Different NHC-bound enolate intermediate precursors

The enolate intermediates bearing versatile reactivities that can undergo several

annulation reactions such [4 + 2] cycloaddition, [2 + 2] cycloaddition, [3 + 2] cycloaddition and [2 + 2 + 2] cycloaddition with different reaction partners (Scheme 1.15).²⁷⁻³¹

Scheme 1.15 Versatile reactivities of enolate intermediates.

1.6 Catalysis involving α,β -unsaturated acylazoliums.

The α,β -unsaturated acylazolium intermediate is a Michael acceptor which became one of the most investigated NHC-bound intermediates over the past few years. The first contribution of this intermediate was reported by Zeitler^{22d} towards the generation of α,β -unsaturated esters from ynals catalyzed by NHC. In 2010, Studer et al.³² first reported NHC-bound α,β -unsaturated acylazolium intermediate as a Michael acceptor for the synthesis of δ -lactones. They combined enals with NHC to form the Breslow intermediate, follow by oxidation to form unsaturated acylazolium intermediate and reaction with 1,3-dicarbonyl compounds to generate the desired products (Scheme 1.16).

Scheme 1.16 First example of α,β -unsaturated acylazolium as a Michael acceptor.

α,β -Unsaturated acylazolium intermediates can generate from different substrates based on different formation processes. The formation of these intermediates from ynals^{31,33} and α -bromo enols³⁴ undergoes internal redox processes. Direct addition of NHC to α,β -unsaturated acyl fluorides,^{35a, b} esters,^{35a, c} in situ generated mixed anhydrides^{35d} and further elimination of the corresponding leaving groups are alternative methods. Finally, enals^{32,36} can also serve as precursors for these intermediates by the oxidization of corresponding Breslow intermediates (Scheme 1.17). The generated unsaturated acylazoliums were further reacted with different nucleophiles majorly following [3 + 3] annulation reaction to form six-membered ring products.³³⁻³⁶

Scheme 1.17 Different types of α,β -unsaturated acylazolium precursors.

1.7 Catalysis involving vinyl enolate intermediates

Thanks to the conjugative effect, when γ -proton exists on α,β -unsaturated acylazolium intermediate, this intermediate can undergo a deprotonation process to form a new conjugated intermediate called vinyl enolate showing nucleophilicity on both α - and γ -position. In 2011, Ye and co-workers³⁷ reported the first vinyl enolate activation by nucleophilic addition of NHC catalyst to α,β -unsaturated ketenes in situ generated from dehydrohalogenation of corresponding acyl chlorides, and underwent the [4 + 2] cycloaddition with ketones (Scheme 1.18).

Scheme 1.18 First example of vinyl enolate activation.

Besides α,β -unsaturated ketenes, other kinds of substrates can serve as the precursors of vinyl enolate intermediates. The intermediates can generate by internal redox reaction of corresponding α -bromo enals³⁸ and γ -leaving group enals³⁹. Oxidation of Breslow intermediate generated from corresponding β -methyl enals followed by γ -deprotonation can also generate the vinyl enolates.⁴⁰ The carbon-carbon activation of cyclobutenones catalyzed by NHC catalysts can undergo ring-opening process to formulate such intermediates⁴¹ (Scheme 1.19). This kind of active intermediates have been used to develop numerous of synthetic methodologies including annulations and α -functionalizations.

Scheme 1.19 Other substrates as precursors of vinyl enolate intermediates.

1.8 Introduction on SET Process Catalyzed by NHCs

As was described above, N-heterocyclic carbene organocatalysis is one of the most investigated fields that numerous of synthetic methodologies have been developed for the

synthetic chemistry. Many types of substrates can be activated by NHCs to react with different kinds of reaction partners following different activation modes to generate a great number of useful molecules. And what's more, the reaction mechanism is also well studied by chemist. However, when focusd on the reaction pathway, one can find that all the reactions mentioned above generally follow electron-pair transfer processes, and to the best of our knowledge, there are only a few examples catalyzed by NHCs undergo single-electron transfer process.

Single-electron transfer is a radical generation procedure that transfers one electron from electron-rich molecules to electron-poor species to form two radicals. Such a process was first described by Kornblum^{42a} and Russell^{42b} in their independent studies of the specific $S_{RN}1$ reaction pathway. The first and key step of this mechanism is the SET process from nucleophile (Y^-) to the oxidative substrate (RX) (Scheme 1.20, eq 1).

Scheme 1.20 Mechanistic pathway of $S_{RN}1$ reaction

The SET process is widely involved in organic reactions. The most investigated catalysis field involving SET process is visible light photoredox catalysis. In recent years, SET process attracts more and more attention along with the great development of photoredox catalysis. Most of the visible light photoredox reactions utilize polypyridyl complexes of ruthenium and iridium as metal catalysts, and the exemplar structure of these metal complexes, tris(2,2'-bipyridine) ruthenium(II) ($Ru(bpy)_3^{2+}$), is presented in Fig 1.6a.⁴³ Not only metal catalyst, organic dyes such as methylene blue and eosin Y, can also serve as catalysts in visible light photoredox catalysts (Fig 1.6b).⁴⁴

Fig. 1.6 a) Typical structure of metal complex photocatalysis; b) Selected examples of organic dyes.

Photoredox catalytic reactions have two general pathways: oxidative quenching cycle and reductive quenching cycle. It's no doubt that the generation of excited state catalyst $[\text{cat}]^*$ initiated the catalytic cycle. These two different pathways were categorized by the primary direction of the SET process between $[\text{cat}]^*$ and other species. In an oxidative quenching cycle, the single-electron transfers from the excited state catalyst $[\text{cat}]^*$ to **sub** or **[ox]** to quench to $[\text{cat}]^{*+}$ and generate $\text{sub}^{\bullet-}$ or $[\text{ox}]^{\bullet-}$ respectively for further transformations, and the catalytic turnover step is another SET process from reductive species to $[\text{cat}]^{*+}$ to regenerate ground state catalyst $[\text{cat}]$. In this catalytic pathway, the catalyst served as an excited state reductant. In contrast, in a reductive quenching cycle, the catalyst served as an excited state oxidant that the primary direction of SET process is from reductive species to excited state catalyst $[\text{cat}]^*$ to quench to $[\text{cat}]^{*-}$, and the turnover step is another SET process from $[\text{cat}]^{*-}$ to oxidative species to regenerate ground state catalyst (Scheme 1.21).

Scheme 1.21 Two general mechanism pathways of photoredox catalysis.

Thiamine pyrophosphate (TPP) is a co-factor of enzymes that can catalyze the oxidative decarboxylation of pyruvate to become an acetylation agent for the acetylation of CoASH to CoAS-Ac in living system.⁴⁵ This vitamin B₁ derivative is a thiazolium derivative, and it can be deprotonated to form a thiazolylidene and act as a NHC catalyst. This enzyme catalysis procedure is believed to utilize SET process as key process in the mechanistic pathway. In this procedure, the NHC generated from deprotonation of TPP activates the pyruvate to undergo a decarboxylation process to form corresponding Breslow intermediate **I**, and this Breslow intermediate further undergo SET process to transfer one electron to $[\text{Fe}_4\text{S}_4]^+$ to form radical cation intermediate **II**, which is oxidized through another SET process to form acylazolium to act as acetylation agent for CoASH to transform to CoASAc and regenerate NHC (Scheme 1.22).⁴⁶ Based on this catalytic cycle, chemists believe that NHC catalysis can undergo SET process to form interesting radical intermediate to occur different reaction to synthesize useful molecules.

Scheme 1.22 PPT-mediated SET process in living system.

In 2008, Studer et al.⁴⁷ reported biomimetic oxidations of aldehydes to form TEMPO

esters catalyzed by N-heterocyclic carbenes. In the reaction mechanism, the NHC first activate aldehyde to generate Breslow intermediate, and then SET from this intermediate to TEMPO generated radical cation and $\text{TEMPO}^\cdot$. Then the deprotonation of radical cation by $\text{TEMPO}^\cdot$ generated the neutral radical intermediate. Another SET from such an intermediate to second TEMPO generated acylazolium intermediate and $\text{TEMPO}^\cdot$, finally, the transesterification of acylazolium with TEMPO generated the corresponding TEMPO ester and regenerated the NHC catalyst (Scheme 1.23).

Scheme 1.23 Biomimetic oxidations of aldehydes catalyzed by NHC.

In 2015, Rehbein⁴⁸ and co-workers did further studies about the mechanistic pathway of benzoin condensation. By electron paramagnetic resonance (EPR) studies, they observed the exiting Breslow intermediate-like radical cation intermediates. Based on these results, they demonstrated that the benzoin condensation maybe partially undergoes SET process, and described a revised catalytic cycle involving SET process. In the revised catalytic cycle, the benzoin product partially generated following the consecutive ionic procedure. In

another pathway, the SET process from anion intermediate **I** or Breslow intermediate **II** to aldehyde generated radical anion **III** and radical cation **IV**, the radical-radical coupling of **III** and **IV** follow by elimination of NHC also generated the benzoin products (Scheme 1.24).

Scheme 1.24 Revised catalytic cycle of benzoin condensation

In 2014, the Rovis' group^{49a} and our group^{49b} simultaneously developed the asymmetric β -hydroxylation of α,β -unsaturated aldehydes using nitrobenzene derivatives catalyzed by NHC. The reaction provided a series of optically active β -hydroxyl esters. In the catalytic cycle, the aldehydes were first activated by NHC to generate Breslow intermediate **I**, then SET to nitrobenzene derivatives generated radical anion **II** and radical cation **III**, the radical-radical coupling of **II** and **III** form the intermediate **IV**, and elimination of nitrosobenzene derivatives generated the intermediate **V**, finally the intermediate worked up by CH_3OH to form the β -hydroxyl esters and regenerated the NHC. In this reaction, the byproduct α,β -unsaturated ester, which formulate via two times SET processes, was not easy to prevent (Scheme 1.25).

Scheme 1.25 β-hydroxylation of enals using nitrobenzene derivatives catalyzed by NHC.

Based on these results, Rovis' group⁵⁰ developed a methodology for the synthetic of optically active 3,4-disubstituted cyclopentanones from α,β-unsaturated aldehydes via SET process in 2015. They proposed a catalytic cycle involving SET processes that at the beginning, the NHC nucleophilic attacked the aldehyde to formulate the Breslow intermediate **I**, then SET from **I** to 4-nitropyridine N-oxide generated radical anion **II** and radical cation **III**, the radical cation **III** then attacked the β-carbon of second Breslow intermediate **I** to form dimerization intermediate **IV**, then a second SET process occurred from **IV** to **II** to generate acyl azolium intermediate **VI**, cyclization of **VI** to release the first molecule of NHC generated the cyclopentanone intermediate **VII**, cyclopentanone **VII** was then attacked by H₂O to release the second molecule of NHC and from the cyclopentanone **VIII**, decarboxylation of **VIII** generated the 3,4-disubstituted cyclopentanone derivatives.

Scheme 1.26 Asymmetric synthesis of 3,4-disubstituted cyclopentanones involving SET process catalyzed by NHC.

In 2017, Ye and co-workers⁵¹ reported a [3+2] cyclization of dioxindoles and enals via SET process catalyzed by NHC. Mechanistically, NHC first activates the enal to form Breslow intermediate **I**, then transfer one electron to 4-nitropyridine N-oxide to generate radical anion **II** and radical cation **III**. Then dioxindole transfer one electron to radical anion **II** to generate radical intermediate **IV**, after that, the radical-radical coupling of **II** and **IV** generated the intermediate **V**, then intermediate **V** underwent further transformations to form the lactones and regenerate the NHCs (Scheme 1.27).

Scheme 1.27 [3+2] annulations of dioxindoles and enals via SET process catalyzed by NHC.

1.9 Summary and Research Design

As was described above, N-heterocyclic carbene organocatalysis was well investigated over the past decades. As nucleophilic organocatalysts, NHCs can nucleophilically attack a lot of different kinds of substrates to generate versatile active intermediates including electrophilic intermediates and nucleophilic ones, and these active intermediates can react with series of reaction partners to synthesize different useful molecules via consecutive ionic reactions. For most of these polarity reactions, the reaction mechanisms were also well described.

However, when it comes to NHC-catalyzed reactions involving SET process in the catalytic cycle, many great challenges still remain. While compared with electron-pair transfer chemistry, very few examples toward this field were reported in the literature. After

SET process NHC-bound intermediates react with other active species, and NHC-bound radical intermediates will generate. This kind of intermediate bear greatly different properties, thus can undergo specific reactions. The several successful examples encourage the chemists to pay more attentions to this field to discover more knowledge to enrich this chemistry.

In the catalytic cycle of the successful examples, we can see that Breslow intermediate can serve as a reductant transferring one electron to an oxidative species to generate corresponding radical intermediate, which is the key step of these catalytic reactions. In other words, Breslow intermediates are single-electron reductants. Inspired by these results, we consider to introduce different oxidative species to the reaction system to discover more synthetic methodologies involving SET process catalyzed by N-heterocyclic carbenes.

1.10 References

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Chapter 2

N-Heterocyclic Carbene Organocatalytic Reductive β,β -Coupling Reactions of Nitroalkenes via Radical Intermediates

2.1 Introduction

2.1.1 Nitroalkenes in N-Heterocyclic Carbene Catalysis

With a strong π -electron withdrawing nitro group conjugates with C-C double bond, the nitroalkenes can serve as excellent Michael acceptors and electron deficient cycloaddition partners in organic synthesis. Much attention has been paid to the role of nitroalkenes as Michael acceptors and cycloaddition partners since the transformation of the nitro group can facilitate further structural elaboration.¹

As good electrophiles, nitroalkenes also serve as useful reaction partners in NHC organocatalysis. The nitroalkenes served as Michael acceptors undergo Stetter reactions with Breslow intermediates to generate β -nitro ketones, which was developed by the research groups of Scheidt^{2a} and Rovis^{2b-d} (Scheme 2.1a). Nair,^{3a} Rovis^{3b} and Liu's^{3c} groups reported their own methodologies about the 1,4-addition of homoenolates to nitroalkenes for the synthesis of δ -nitro esters (Scheme 2.1b). Enders and co-workers⁴ reported that the enolate intermediates could undergo Michael addition to nitroalkenes in the [2+3] annulations, such as α -chloroaldehydes with nitrovinylindoles catalyzed by NHCs (Scheme 2.1c).

Scheme 2.1 Nitroalkenes serve as reaction partners in NHC organocatalysis

Beside the role of reaction partners, the nitroalkenes can also be nucleophilically attacked by NHCs followed by reacting with other electrophiles to form useful molecules. In 2010, Yadav et al.^{5a} reported a [2+2] cycloaddition of nitroalkenes with aryl isothiocyanates for the synthesis of β -thiolactams catalyzed by NHC. One of the possible pathway was that, NHCs first attacked the nitroalkenes to form NHC-bound intermediates, then these intermediates attacked the C=S double bonds following by further transformations to provide the β -thiolactams (Scheme 2.2a). Ye and co-workers^{5b} reported an NHC catalyzed Morita-Baylis-Hillman (MBH) reaction of nitroalkenes to azodicarboxylates (Scheme 2.2b). In the same year, using the same activation mode, they developed a [4+2] cycloaddition of nitroalkenes with oxodienes for the synthesis of dihydropyran derivatives (Scheme 2.2c).^{5c}

Scheme 2.2 Nitroalkenes activated by NHCs to react with other electrophiles.

2.1.2 Reductive β,β -Coupling of β -Nitroalkenes.

Nitro containing compounds are usually served as precursors of other molecules such as oximes and amines, thus the reduction of nitro containing compounds attracted much attention from chemists. A series of reduction system has been developed for the reduction of nitro group to different groups.⁶ In 1917, Sonn and Schellenberg^{7a} first obtained a unexpected side-product which was confirmed as reductive β,β -dimerization of β -nitrostyrene when they reduced β -nitrostyrene by hydrogenation catalyzed by platinum.

Later in 1923, Kohler and Drake^{7b} investigated the hydrogenation of β -nitrostyrene under different solvents and different catalysts such as palladium, platinum and nickel catalysts and found that this reductive dimerization product always obtained as a byproduct in all the cases they tried. Not only in catalytic hydrogenations, but also in the reduction of nitroalkenes under other reduction systems such as enzymes,^{7c} TiCl_3 ,^{7d-e} SmI_2 ,^{7f} even in the Michael addition reaction of Grignard reagents to nitroalkenes,^{7g} the corresponding dimers always generated as reaction byproducts. The proposed mechanism for the formation of this dimer is that, SET firstly from reductant to nitroalkenes to form nitroalkene radical anion intermediate, then radical-radical dimerization and following protonation takes place to give the dimer product (Scheme 2.3).

Scheme 2.3 The reductive coupling of nitroalkenes and the proposed mechanism.

In electrochemistry, the reductive coupling product can also be generated by electrolyze of the corresponding nitroalkenes including aliphatic nitroalkenes^{8a} and aromatic nitroalkenes^{8b} (Scheme 2.4). The electrohydrodimerization product generates from the same pathway as reductive coupling by reductants. The current density is an important parameter for this reaction pathway. The EPR spectrum of *t*-butyl nitroalkene radical anion intermediate in the reaction system supports the generation pathway (Fig. 2.1).

Scheme 2.4 The Electrohydrodimerization of nitroalkenes.

Fig. 2.1 EPR spectrum of *t*-butyl nitroalkene radical anion.

2.1.3 Our Proposal.

Because nitroalkene can easily obtain one electron to generate corresponding radical anion to form a radical dimerization product, and Breslow intermediates are electron-rich species, we proposed that Breslow intermediates can serve as a reductant which can reduce the nitroalkenes to form β,β -dimerization products via SET process (Scheme 2.5).

Scheme 2.5 The proposal of SET process from Breslow intermediate to nitroalkenes

2.2 Results and Discussions

We used methyl 4-formylbenzoate **2-1a** as aldehyde and β -nitrostyrene **2-2a** as nitroalkene to test the possibility of the reductive dimerization (Table 1). Our initial study was carried out in CH₃OH at 0 °C using DIEA as base and thiazolium salt **2-A** as catalyst mimicking TPP in nature.⁹ The dimerization product **2-3a** was produced in trace yield (entry 1). Then we tried triazolium salt **2-B~2-D** and another thiazolium salt **2-E** as catalysts. To our delight, we found that pyrrolidone-derived triazolium salt **2-D** that bearing an electron-withdrawing group C₆F₅ gave the desired product in 94% yield (entry 4). When used chiral NHCs **2-F** and **2-G** as catalysts, the dimer was generated in 14% and 85% yields, respectively, but without any observed diastereoselectivities (entries 6,7). As was showed in the research proposal, the aldehyde in this reaction formed Breslow intermediate under the action of NHC, then oxidize by nitroalkenes to generate acylazolium intermediate via two SET processes, and finally trapped by MeOH to form the corresponding ester and regenerate the NHC catalyst. For this reason, the aldehyde may be another important parameter in this reaction. Then we introduced aromatic aldehydes **2-1b**, **2-1c** to serve as the reductants instead of **2-1a**. All these aldehydes led to form the dimer **3a** in moderate yields, and no better results were obtained (entries 8-9). When aliphatic aldehyde **2-1d** was used as reductant, only trace product could be obtained (entry 10). The diastereomeric ratio (dr) of all these reactions is approximately 2.5: 1, and the soluble *dl*-**3a** is the major diastereomer while the insoluble *meso*-**3a** is the minor one.

Table 2.1 Condition Optimization^a

entry	NHC	aldehyde	2-3a yield (%)		2-3a dr ^c
			<i>dl</i> + <i>meso</i>	<i>dl</i> ^b	
1	2-A	2-1a	~5	/	/
2	2-B	2-1a	10	8	/
3	2-C	2-1a	17	14	/
4	2-D	2-1a	94	66	71:29
5	2-E	2-1a	13	9	/
6	2-F	2-1a	14	12 ^d	/
7	2-G	2-1a	85	62 ^d	72:28
8	2-D	2-1b	58	38	70:30
9	2-D	2-1c	75	51	71:29
10	2-D	2-1d	< 5	/	/

^a Unless otherwise noted, reactions were carried out at 0 °C using **1** (0.2 mmol), **2a** (0.3 mmol), catalyst (0.02 mmol), DIEA (0.04 mmol) and 2 mL MeOH. Yields and drs were determined via ¹H NMR analysis. ^b Isolated yields of *dl*-**3a**. ^c dr refers to *dl* over *meso*. ^d No enantioselectivity.

With the optimized reaction condition in hand, we turn our attention to the reaction scope. The key results were summarized in Table 2.2. We first examined the reductive coupling of aromatic nitroalkenes using **2-1a** as the model aldehydes under the condition as table 2-1, entry 4. We found that electron-donating groups substituted on the *para*-position of benzene ring gave the dimerization products in good yields (**2-3b** and **2-3c**). Electron-withdrawing groups placed on *para*- or *meta*-position on the benzene ring also led to the desired products in good yields (**2-3d**~**2-3g**). The β -naphthyl substituted substrate also worked fine under such condition (**2-3h**). When heteroaryl substituted nitroalkenes were introduced to this catalytic reaction, the corresponding β,β -reductive dimerization products were also afforded in high yields (**2-3i**~**2-3l**). It was interesting that the substrates containing

unprotected hydroxy group could also lead to the coupling product, although the reaction yield was only moderate (**2-3m**). β,β -Disubstituted nitroalkene, a substrate with large steric hindrance could also work smoothly under the standard condition to give the desired product in moderate yield (**2-3m**).

Table 2.2 Substrates scope.

^a Unless otherwise noted, yields are isolated total yields, drs (*dl* over *meso*) were determined via ¹H NMR analysis. ^b Based on isolated *dl* and *meso*-**3h** (slight dissolves in DMSO). ^c Yields obtained when using **2-1a** as the model aldehyde.

Then we investigated the β,β -reductive coupling of aliphatic nitroalkenes under the standard condition as in Table 2.1, entry 4. Unfortunately, in these cases, the yields of corresponding desired products were very low (**2-3o**~**2-3s**, yields showed in parentheses), and the Stetter products² generated from Michael addition of Breslow intermediates to the nitroalkenes became the major products. To our delight, after we had turned back to screen the reaction conditions, we found that by using heteroaryl aldehyde **2-1c** as reductant, the reaction outcome could be greatly improved. Specifically, the desired products **2-3** was obtained as major products in moderate yields, although the competing Stetter adducts were still obtained in lower yields.

For all the different nitroalkenes introduced in this catalytic reaction, the diastereomeric ratios (drs) were between 1.5: 1 to 4: 1, and the *dl* isomers were the major products. The relative configurations of major diastereomers were determined by the X-ray crystallographic analysis of *dl*-**2-3d**, and the X-ray structure of *dl*-**2-3d** was showed in Figure 2.1.

Fig. 2.1 Crystall structure of cross-coupling product **2-3d**.

2.3 Mechanistic Study.

As described in the research proposal, we proposed that the generation of the reductive

coupling product **2-3** involved SET process; the radical intermediates were the key intermediates of the mechanistic pathway. To confirm the radical process, we paid attention to detecting and analyzing the proposed radical intermediates and proceeded some radical clock experiments for understanding the reaction mechanism.

2.3.1. EPR Study of the Radical Anions

We tried to detect the proposed radical anion intermediates by EPR study. To our delight, we found that in the reactions of several different nitroalkenes, the EPR signal could be detected, which demonstrated that radical intermediates generated in the reaction procedure. With β -isopropyl nitroethene as nitroalkene, the detected EPR signal coincided with the simulated EPR signal of the corresponding proposed β -isopropyl-nitroethene-derived radical anion intermediate (Fig. 2.2), which confirmed the existing of proposed radical anion in the reaction systems.

Fig. 2.2. (Black line) EPR spectrum of the anionic radical derived from β -isopropyl nitroethylene obtained in methanol under the catalytic reaction condition and analyzed at $22(\pm 2)$ °C. (Red line, bottom) Simulated spectrum based on hyperfine coupling constants of $1N = 13.025$ G, $1H_a = 8.775$ G, $1H_b = 2.80$ G, $1H_c = 6.375$ G and $6H = 0.275$ G, and with a linewidth of 0.15 G.

The same process using α -methyl- β -nitrostyrene, β,β -dimethyl nitroethene and β -n-butyl nitroethene in the EPR studies under the standard condition could also show the EPR signal.

But due to the difficulty of simulating the EPR spectrum of the corresponding radical anion intermediates, we didn't analyze these EPR spectrum (Fig. 2.3).

Fig. 2.3 EPR spectra of the anion radicals of (a) α -methyl- β -nitrostyrene, (b) β,β -dimethyl nitroethylene, and (c) β -n-butyl nitroethylene.

2.3.2 Radical Clock Experiments.

In amine catalysis for aldehyde α -functionalization via SET mechanism, MacMillan^{10a} and Melchiorre^{10b} have used “radical clock” experiments¹⁰ to investigate the presence of proposed radical intermediates. To further understand the reaction mechanism, we synthesized both *cis*- and *trans*- β -cyclopropyl nitroethenes to do radical clock experiments. When we used nitroalkene **2-5** as substrate under the standard reaction condition, we found that the reductive coupling product was not observed. Instead, the reaction majorly gave the α,β -unsaturated ketone **2-7** in high yield. This product generated via the elimination of HNO_2 of the Stetter product **2-6**. Interestingly, when we used *cis*-**2-5** as the substrate, the α,β -unsaturated ketone **2-7** gave both *cis*- and *trans*- diastereoisomers, and the yields of *cis*- and *trans*- isomers were 70% and 17%, respectively (Scheme 2.6).

Scheme 2.6 Reaction outcome of *cis*-**2-5** as nitroalkene.

The generation of *trans*-**2-7** may come from the isomerization of *cis*-**2-5** to *trans*-**2-5** via radical process, follow by Stetter reaction and elimination. The proposed radical pathway was that: at the beginning, the nitroalkene *cis*-**2-5** obtained one electron via SET process to form the radical anion *cis*-**2-8**, then radical ring-opening of the cyclopropane took place to form radical anion **2-9** following by ring-closing to give the radical anion *trans*-**2-8**; finally, this radical anion lost one electron to transform to *trans*-isomer (Scheme 2.7). This experiment provided strong evidence to support our propose that the reaction took place via radical process.

Scheme 2.7 Proposed pathway of *cis/trans* isomerization of nitroalkene **2-5**.

2.3.3 Reaction Pathway

Based on the above mechanistic studies, we proposed a mechanistic cycle for our reductive coupling reaction of nitroalkenes. At the beginning, the NHC attacked the aldehyde **2-1** formed Breslow intermediate **I**, then SET from **I** to nitroalkene **2-2** generated radical cation **II** and radical anion **III**. Then the deprotonation of radical cation **II** generated the radical intermediate **VI** while radical anion 1,4-addition to second molecule of nitroalkene **2-2** generated radical anion intermediate **V**. After that, second SET process occurred from radical **VI** to radical anion **V** followed by protonation to give the reductive coupling product **2-3**, and the radical **VI** transformed to acylazolium intermediate, which was trapped by CH₃OH to give the corresponding ester and regenerated NHC to finish the catalytic cycle (Scheme 2.8). This proposed mechanism is in consistence well with the ECE (electron transfer-chemical reaction-electron transfer) pathway of reductive β,β-coupling of electron deficient alkenes in electrochemistry.¹² However, because the intermediate **V** was not confirmed by experimental study, another possible pathway that generated via radical-radical dimerization as described in the research proposal can not be ruled out.

Scheme 2.8 Proposed mechanism for the reductive coupling reaction

2.4 Summary.

In summary, we have developed the first reaction of reductive β,β -dimerization of nitroalkenes catalyzed by NHC. The reaction proceeds via SET process that mimicking the oxidative decarboxylation of pyruvates catalyzed by TPP in nature. The nitroalkenes serve as single-electron acceptors instead of Michael acceptors which they usually serve as. The aldehydes act as reductants with themselves oxidized to form corresponding esters after the reaction. This methodology is quite different that the generation of radical intermediate shows different reactivities comparing with electron-pair transfer chemistry, which will significantly expand the development of organocatalysis by providing a new orientation for chemists to develop new reactions.

2.5 Experimental Section

2.5.1 General Information.

Commercially available materials purchased from Alfa Aesar or Aldrich was used as received. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a Bruker AV400 (400 MHz) spectrometer. Chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethylsilane (δ 0.00). ^1H NMR splitting patterns are designated as singlet

(s), doublet (d), triplet (t), quartet (q), dd (doublet of doublets); m (multiplets), and etc. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker AV400 (100 MHz) spectrometer. High resolution mass spectral analysis (HRMS) was performed on Waters Q-TOF Premier mass spectrometer. X-ray crystallography analysis was performed on Bruker X8 APEX X-ray diffractometer. Continuous wave X-band EPR spectra was obtained with a Bruker ELEXSYS E500 EPR spectrometer in a silica flat cell. Flash chromatography was performed using Merck silica gel 60 with distilled solvents. Analytical thin-layer chromatography (TLC) was carried out on Merck 60 F254 pre-coated silica gel plate (0.2 mm thickness). Visualization was performed using a UV lamp.

2.5.2 General Qrocedure for the Catalytic Reductive β,β -Coupling of Nitroalkenes:

To a dry Schlenk tube equipped with a magnetic stir bar, was added aldehyde **1** (0.20 mmol), nitroalkene **2-2** (0.30 mmol) and triazolium salt **2-D** (15 mg, 0.04 mmol), then the tube was closed with a septum. Methanol (2.0 mL) was added and the resulting solution was degassed 3 times (freeze-pump-thaw: cooled in liquid nitrogen and degassed via vacuum evacuation (5 min), backfilled with nitrogen, and warm to room temperature). *N,N*-diisopropylethylamine (35 μL , 0.20 mmol) was added at 0°C and the reaction mixture was stirred at this temperature till nitroalkene was completely consumed (12~24 h, monitored by TLC). For most of aromatic nitroalkenes (**2-2a**~**2-2i**, **2-2k**~**2-2m**), after filtration, the filtrate was purified via column chromatography on silica gel to afford *dl*-**2-3**, and the precipitate was suspended in boiling MeOH, filtered to afford *meso*-**2-3**. For other

nitroalkenes (**2-2j**, **2-2n~2-2r**), the mixture was concentrated under reduced pressure, and the resulting crude residue was purified via column chromatography on silica gel to afford the coupling dimer **2-3**.

2.5.2 Procedure for the Synthesis of Radical-Clock Containing Nitroalkenes:

($\pm$)-*cis*- and ($\pm$)-*trans*-(2-(benzyloxymethyl)cyclopropyl)carboxaldehyde **2-11** were prepared following the procedures described in the literature.¹³ To a dry round bottom flask was added carboxaldehyde **2-11** (950 mg, 5.0 mmol), nitromethane (540 μ L, 10.0 mmol), and 1:1 THF/*t*-BuOH (5.0 mL). This solution was cooled to 0 °C and potassium *tert*-butoxide (135 mg, 1.2 mmol) added in one portion. The reaction was then stirred at 0 °C for 1 h then warmed to room temperature and stirred for 12 h. After completion, saturated aqueous NH₄Cl solution (10 mL) was added to quench the reaction and then extracted with CH₂Cl₂ (3 $\times$ 10 mL). The combined organic extracts were then dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. After drying the crude residue under vacuum for 1 h, CH₂Cl₂ (10.0 mL) was added followed by cooling to 0 °C. Et₃N (1.46 mL, 10.5 mmol) was added followed by the slow dropwise addition of trifluoroacetic anhydride (0.77 mL, 5.5 mmol). After stirring for 1 h at 0 °C the reaction was allowed to warm to room temperature and stirred an additional 2 h. The reaction was diluted with CH₂Cl₂ (10 mL) followed by the addition of saturated aqueous NH₄Cl solution (15 mL). After separation, the aqueous layer was extracted with CH₂Cl₂ (2 $\times$ 10 mL), and the combined organic extracts were dried over anhydrous Na₂SO₄, filtered, concentrated under reduced pressure. The brown residue was purified by flash column chromatography (1:6 EtOAc: hexane) on silica gel to afford nitroalkene **2-5** as colorless oil (yield > 90%).

(((*cis*-2-((*E*)-2-nitrovinyl)cyclopropyl)methoxy)methyl)benzene
(*cis*-2-5): ¹H NMR (400 MHz, CDCl₃) δ 0.85 (dt, *J* = 5.2, 5.8 Hz, 1H),

1.33 (dt, $J = 5.2, 8.2$ Hz, 1H), 1.71-1.83 (m, 2H), 3.34 (m, 1H), 3.75 (m, 1H), 4.46 (d, $J = 12.0$ Hz, 1H), 4.56 (d, $J = 12.0$ Hz, 1H), 7.00-7.10 (m, 1H), 7.15 (d, $J = 13.1$ Hz, 1H), 7.26-7.38 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3) δ 14.0, 16.1, 21.8, 68.9, 73.1, 127.8, 127.9, 128.5, 137.6, 138.7, 144.8; HRMS (ESI) calcd. for $\text{C}_{13}\text{H}_{15}\text{NO}_3\text{H}^+$: 234.1125, found: 234.1125.

(((*trans*-2-((*E*)-2-nitrovinyl)cyclopropyl)methoxy)methyl)benzene

(*trans*-2-5): ^1H NMR (400 MHz, CDCl_3) δ 1.00 (dt, $J = 8.6, 5.0$ Hz,

1H), 1.11 (ddd, $J = 8.6, 6.4, 5.0$ Hz, 1H), 1.47-1.60 (m, 2H), 3.36 (dd, $J = 10.5, 6.5$ Hz, 1H), 3.55 (dd, $J = 10.5, 5.5$ Hz, 1H), 4.51 (s, 2H), 6.81 (dd, $J = 13.2, 10.5$ Hz, 1H), 7.09 (d, $J = 13.2$ Hz, 1H), 7.26-7.38 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3) δ 14.2, 17.0, 23.3, 71.4, 72.8, 127.6, 127.7, 128.4, 137.5, 137.9, 146.9; HRMS (ESI) calcd. for $\text{C}_{13}\text{H}_{15}\text{NO}_3\text{H}^+$: 234.1125, found: 234.1123.

2.5.2 Procedure of Radical Clock Experiments:

The general procedure of radical clock experiments was followed using aldehyde **2-1a** (33 mg, 0.20 mmol), nitroalkene **2-5** (47 mg, 0.20 mmol), triazolium salt **2-D** (15 mg, 0.04 mmol), DIEA (35 μL , 0.20 mmol) and methanol (2.0 mL) (reaction time 36 h). Purification by flash column chromatography (eluent: EtOAc: *n*-hex = 1: 7) afforded the title compound **2-7** as colorless oil.

***cis*-methyl 4-(2-((-2-((benzyloxy)methyl)cyclopropyl)acryloyl)benzoate (*cis*-2-7):** ^1H

NMR (400 MHz, CDCl_3) δ 0.70 (q, $J = 5.7$ Hz, 1H), 1.04 (dt, $J = 5.4, 8.2$ Hz, 1H), 1.58 (m, 1H), 2.20 (q, $J = 7.7$ Hz, 1H),

3.31 (dd, $J = 10.4, 8.4$ Hz, 1H), 3.47 (dd, $J = 10.4, 6.4$ Hz, 1H), 3.95 (s, 3H), 4.42 (AB, $J = 12.0$ Hz, 2H), 5.66 (s, 1H), 5.72 (d, $J = 1.0$ Hz, 1H), 7.18-7.30 (m, 5H), 7.72 (d, $J = 8.4$ Hz,

2H), 8.04 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 7.9, 17.8, 17.9, 52.4, 69.2, 72.4, 126.3, 127.4, 127.6, 128.2, 129.26, 129.3, 132.9, 138.2, 141.5, 145.3, 166.3, 197.3; HRMS (ESI) calcd. for $\text{C}_{22}\text{H}_{22}\text{O}_4\text{H}^+$: 351.1591, found: 351.1590.

(*trans*-2-7): ^1H NMR (400 MHz, CDCl_3) δ 0.89 (m, 2H), 1.38 (m, 1H), 1.83 (dt, $J = 8.2, 5.4$ Hz, 1H), 3.40 (dd, $J = 10.4, 6.8$ Hz, 1H), 3.52 (dd, $J = 10.4, 6.3$ Hz, 1H), 3.95 (s, 3H), 4.55 (s, 2H), 5.48 (s, 1H), 5.59 (s, 1H), 7.25-7.38 (m, 5H), 7.78 (d, $J = 8.4$ Hz, 2H), 8.09 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 13.1, 17.9, 21.7, 52.4, 72.6, 73.1, 122.3, 127.6, 127.7, 128.4, 129.2, 129.4, 133.1, 138.4, 141.4, 148.6, 166.3, 197.1; HRMS (ESI) calcd. for $\text{C}_{22}\text{H}_{22}\text{O}_4\text{H}^+$: 351.1591, found: 351.1591.

Characterization of products:

2-Formyl-1-methylimidazole (2-1c): 2-Formyl-1-methylimidazole **1c** was prepared following the procedure described in the literature.¹⁴ Yellow oil, R_f 0.25, (eluent: CH_2Cl_2 : MeOH = 40: 1); ^1H NMR (400 MHz, CDCl_3) δ 4.03 (s, 3H), 7.12 (s, 1H), 7.28 (s, 1H), 9.83 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 34.9, 127.3, 131.4, 143.7, 182.1; HRMS (ESI) calcd. for $\text{C}_5\text{H}_6\text{N}_2\text{OH}^+$: 111.0553, found: 111.0553.

Dimethyl terephthalate (2-4a): White solid, R_f 0.32 (eluent: EtOAc: n -hex = 1: 9); mp 108–110 °C (EtOAc/ n -hex); ^1H NMR (400 MHz, CDCl_3) δ 3.95 (s, 6H), 8.11 (s, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 52.4, 129.5, 133.9, 166.3; HRMS (ESI) calcd. for $\text{C}_{10}\text{H}_{10}\text{O}_4\text{H}^+$: 195.0652, found: 195.0652.

Methyl 1-methyl-1*H*-imidazole-2-carboxylate (2-4c): Colorless oil, R_f 0.14

(eluent: EtOAc: *n*-hex = 3: 1); ^1H NMR (400 MHz, CDCl_3) δ 3.94 (s, 3H), 4.03 (s, 3H), 7.05 (s, 1H), 7.15 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 35.8, 52.2, 126.3, 129.5, 136.5, 159.6; **HRMS (ESI)** calcd. for $\text{C}_6\text{H}_8\text{N}_2\text{O}_2\text{H}^+$: 141.0659, found: 141.0660.

4,5-Dimethyl-3-(pentafluorophenyl)thiazol-3-ium perchlorate (2-E):

Thiazolium salt catalyst **E** was prepared following the procedures described in the literatures.^{15,16} White solid, ^1H NMR (400 MHz, DMSO-d_6) δ 2.35 (s, 3H), 2.61 (s, 3H), 10.46 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.4, 144.1 (m), 142.6, 141.6 (m), 138.9 (m), 136.4 (m), 135.0, 111.5 (m), 12.1, 10.7; **HRMS (ESI)** calcd. for $\text{C}_{11}\text{H}_7\text{F}_5\text{NS}^+$: 280.0214, found: 280.0214.

(1,4-Dinitrobutane-2,3-diyl)dibenzene (2-3a)^{17,18}: Major (*dl*) isomer:

White solid, 66% yield (30 mg). R_f 0.39 (eluent: EtOAc: *n*-hex = 1: 7); mp 99–101 °C (EtOAc/*n*-hex); IR (KBr) 1547, 1381, 694 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 3.96 (quint, J = 5.4 Hz, 2H), 4.57 and 4.74 (ABX, J_{AB} = 13.2 Hz, J_{AX} = 7.4 Hz, J_{BX} = 6.2 Hz, 4H), 6.75–6.88 (m, 4H), 7.23–7.32 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 45.4, 77.2, 128.5, 128.7, 129.0, 134.0; **HRMS (ESI)** calcd. for $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_4\text{H}^+$: 301.1183, found: 301.1183.

Minor (*meso*) isomer: White solid, 24% yield (11 mg). ^1H NMR (400 MHz, DMSO-d_6) δ 3.83 (m, 2H), 4.21 (dd, J = 12.9, 3.5 Hz, 2H), 4.91 (m, 2H), 7.33 (t, J = 7.2 Hz, 2H), 7.41 (t, J = 7.2 Hz, 4H), 7.53 (d, J = 7.2 Hz, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 47.3, 79.3, 128.5, 128.6, 129.4, 138.1.

4,4'-(1,4-Dinitrobutane-2,3-diyl)bis(methylbenzene) (2-3b): Major (*dl*)

isomer: White solid, 65% yield (32 mg). R_f 0.34 (eluent: EtOAc: *n*-hex = 1: 5); mp 129–130 °C (EtOAc/*n*-hex); ^1H NMR (400 MHz, CDCl_3) δ 2.33 (s, 6H), 3.91 (quint, $J = 5.3$ Hz, 2H), 4.52 and 4.69 (ABX, $J_{AB} = 13.1$ Hz, $J_{AX} = 7.4$ Hz, $J_{BX} = 6.2$ Hz, 4H), 6.70 (d, $J = 8.0$ Hz, 4H), 7.08 (d, $J = 8.0$ Hz, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.1, 45.0, 77.3, 128.9, 129.3, 130.9, 138.3; HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_4\text{H}^+$: 329.1496, found: 329.1496.

Minor (*meso*) isomer: White solid, 20% yield (10 mg). ^1H NMR (400 MHz, DMSO-d_6) δ 2.30 (s, 6H), 3.74 (m, 2H), 4.18 (dd, $J = 12.8, 3.6$ Hz, 2H), 4.85 (m, 2H), 7.21 (d, $J = 7.9$ Hz, 4H), 7.39 (d, $J = 7.9$ Hz, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.2, 47.1, 79.4, 128.5, 130.0, 135.1, 137.6.

4,4'-(1,4-Dinitrobutane-2,3-diyl)bis(methoxybenzene) (2-3c)¹⁷:

Major (*dl*) isomer: White solid, 65% yield (35 mg). R_f 0.15 (eluent: EtOAc: *n*-hex = 1: 5); mp 125–126 °C (EtOAc/*n*-hex); ^1H NMR (400 MHz, CDCl_3) δ 3.79 (s, 6H), 3.87 (quint, $J = 5.2$ Hz, 2H), 4.50 and 4.67 (ABX, $J_{AB} = 13.0$ Hz, $J_{AX} = 7.4$ Hz, $J_{BX} = 7.4$ Hz, 4H), 6.72 (dt, $J = 8.8, 2.3$ Hz, 4H), 6.80 (dt, $J = 8.8, 2.3$ Hz, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 44.7, 55.2, 77.5, 114.0, 125.7, 130.2, 159.6; HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_6\text{H}^+$: 361.1394, found: 361.1395.

Minor (*meso*) isomer: White solid, 24% yield (13 mg). ^1H NMR (400 MHz, DMSO-d_6) δ 3.72 (m, 2H), 3.76 (s, 6H), 4.18 (dd, $J = 12.7, 3.3$ Hz, 2H), 4.83 (m, 2H), 6.96 (d, $J = 8.6$ Hz, 4H), 7.42 (d, $J = 8.6$ Hz, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 46.9, 55.5, 79.5, 114.7, 129.7, 129.9, 159.3.

4,4'-(1,4-Dinitrobutane-2,3-diyl)bis(bromobenzene) (2-3d): Major*(dl)* isomer: White solid, 63% yield (43 mg). R_f 0.21 (eluent: EtOAc: *n*-hex = 1: 5); mp 138–139 °C (EtOAc/*n*-hex); ^1H NMR (400 MHz, CDCl_3) δ 3.91 (quint, J = 5.5 Hz, 2H), 4.54 and 4.70 (ABX, J_{AB} = 13.1Hz, J_{AX} = 7.4 Hz, J_{BX} = 6.0 Hz, 4H), 6.70 (dt, J = 8.5, 2.2 Hz, 4H), 7.43 (dt, J = 8.5, 2.2 Hz,4H); ^{13}C NMR (100 MHz, CDCl_3) δ 44.9, 76.9, 123.0, 130.4, 132.1, 132.8; HRMS (ESI)calcd. for $\text{C}_{16}\text{H}_{14}\text{Br}_2\text{N}_2\text{O}_4\text{H}^+$: 456.9393, found: 456.9395.Minor (*meso*) isomer: White solid, 24% yield (16 mg). ^1H NMR (400 MHz, DMSO-d_6) δ 3.84 (m, 2H), 4.29 (dd, J = 13.0, 3.4 Hz, 2H), 4.89 (m, 2H), 7.50 (d, J = 8.4 Hz, 4H), 7.62(d, J = 8.4 Hz, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 46.4, 79.0, 121.8, 130.9, 132.3,

137.5.

4,4'-(1,4-Dinitrobutane-2,3-diyl)bis(chlorobenzene) (2-3e): Major*(dl)* isomer: White solid, 65% yield (34 mg). R_f 0.13 (eluent: EtOAc: *n*-hex = 1: 7); mp 154–155 °C (EtOAc/*n*-hex); ^1H NMR (400 MHz, CDCl_3) δ 3.92 (quint, J = 5.5 Hz, 2H), 4.55 and 4.70 (ABX, J_{AB} = 13.1 Hz, J_{AX} = 7.4 Hz, J_{BX} = 6.0 Hz, 4H), 6.76 (dt, J = 8.5, 2.2 Hz, 4H), 7.27 (dt, J = 8.5, 2.2 Hz, 4H); ^{13}C NMR(100 MHz, CDCl_3) δ 44.9, 77.0, 129.1, 130.1, 132.3, 134.8; HRMS (ESI) calcd. for $\text{C}_{16}\text{H}_{14}\text{Cl}_2\text{N}_2\text{O}_4\text{H}^+$: 369.0403, found: 369.0404.Minor (*meso*) isomer: White solid, 27% yield (14 mg). ^1H NMR (400 MHz, DMSO-d_6) δ 3.86 (m, 2H), 4.29 (dd, J = 13.2, 3.3 Hz, 2H), 4.90 (m, 2H), 7.49 (d, J = 8.4 Hz, 4H), 7.56(d, J = 8.4 Hz, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 46.4, 79.0, 129.4, 130.6, 133.2,

137.1.

4,4'-(1,4-Dinitrobutane-2,3-diyl)bis((trifluoromethyl)benzene) (2-3f):

3f): Major (*dl*) isomer: White solid, 57% yield (37 mg). R_f 0.24 (eluent:

EtOAc: *n*-hex = 1: 6); mp 137–138 °C (EtOAc/*n*-hex); ^1H NMR (400

MHz, CDCl_3) δ 4.07 (quint, $J = 5.6$ Hz, 2H), 4.63 and 4.77 (ABX, $J_{AB} = 13.2$ Hz, $J_{AX} = 7.4$ Hz, $J_{BX} = 4.5$ Hz, 4H), 6.98 (d, $J = 8.1$ Hz, 4H), 7.56 (d, $J = 8.1$ Hz, 4H); ^{13}C NMR (100 **MHz, CDCl_3)** δ 45.3, 76.8, 123.5 (q, $J = 271$ Hz), 125.9 (q, $J = 3.6$ Hz), 129.2, 131.2 (q, $J = 32.7$ Hz), 138.0; **HRMS (ESI)** calcd. for $\text{C}_{18}\text{H}_{14}\text{F}_6\text{N}_2\text{O}_4\text{H}^+$: 437.0931, found: 437.0930.

Minor (*meso*) isomer: White solid, 28% yield (18 mg). ^1H NMR (400 MHz, DMSO-d_6) δ 4.05 (m, 2H), 4.33 (dd, $J = 13.3, 3.5$ Hz, 2H), 5.00 (m, 2H), 7.81 (t, $J = 9.6$ Hz, 8H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 46.5, 78.8, 124.6 (q, $J = 270$ Hz), 126.3 (q, $J = 3.7$ Hz), 129.1 (q, $J = 31.5$ Hz), 129.7, 142.8.

3,3'-(1,4-Dinitrobutane-2,3-diyl)bis(bromobenzene) (2-3g):

Major (*dl*) isomer: White solid, 61% yield (42 mg). R_f 0.26 (eluent: EtOAc: *n*-

hex = 1: 5); mp 115–116 °C (EtOAc/*n*-hex); ^1H NMR (400 **MHz,**

CDCl_3) δ 3.91 (quint, $J = 5.4$ Hz, 2H), 4.56 and 4.70 (ABX, $J_{AB} = 13.2$ Hz, $J_{AX} = 7.4$ Hz, $J_{BX} = 6.0$ Hz, 4H), 6.75–7.50 (m, 8H); ^{13}C NMR (100 **MHz, CDCl_3)** δ 45.1, 76.7, 122.9, 127.5, 130.3, 131.9, 132.0, 136.0; **HRMS (ESI)** calcd. for $\text{C}_{16}\text{H}_{14}\text{Br}_2\text{N}_2\text{O}_4\text{H}^+$: 456.9393, found: 456.9391.

Minor (*meso*) isomer: White solid, 29% yield (20 mg). ^1H NMR (400 MHz, DMSO-d_6) δ 3.88 (m, 2H), 4.29 (dd, $J = 13.1, 3.4$ Hz, 2H), 4.94 (m, 2H), 7.38 (t, $J = 7.8$ Hz, 2H), 7.54 (d, $J = 7.8$ Hz, 4H), 7.82 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 46.5, 78.9, 122.7, 127.9, 131.3, 131.5, 140.8.

2,2'-(1,4-Dinitrobutane-2,3-diyl)dinaphthalene (2-3h): Major (*dl*)isomer: White solid, 65% yield (39 mg). R_f 0.20 (eluent: EtOAc: *n*-hex = 1: 7); mp 121–122 °C (EtOAc/*n*-hex); ^1H NMR (400 MHz,

CDCl_3) δ 4.22 (quint, J = 5.3 Hz, 2H), 4.67 and 4.86 (ABX, J_{AB} = 13.2 Hz, J_{AX} = 7.4 Hz, J_{BX} = 6.5 Hz, 4H), 6.85–7.83 (m, 14H); ^{13}C NMR (100 MHz, CDCl_3) δ 45.7, 77.3, 126.2, 126.69, 126.71, 127.7, 127.8, 128.4, 128.6, 131.5, 132.9, 133.0; HRMS (ESI) calcd. for $\text{C}_{24}\text{H}_{20}\text{N}_2\text{O}_4\text{H}^+$: 401.1496, found: 401.1496.

Minor (*meso*) isomer: White solid, 27% yield (16 mg). ^1H NMR (400 MHz, DMSO-d_6) δ 4.14 (m, 2H), 4.34 (dd, J = 12.9, 3.2 Hz, 2H), 5.08 (m, 2H), 7.57 (m, 4H), 7.82 (d, J = 8.4 Hz, 2H), 7.94 (t, J = 8.4 Hz, 4H), 8.03 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 47.4, 79.4, 125.9, 126.8, 127.0, 128.15, 128.19, 129.3, 133.1, 133.4, 135.7.

3,3'-(1,4-dinitrobutane-2,3-diyl)dipyridine (2-3i): Major (*dl*) isomer:Brown oil, 64% yield (29 mg). R_f 0.12 (eluent: EtOAc: *n*-hex = 3: 1); ^1H NMR (400 MHz, CDCl_3) δ 4.02 (quint, J = 5.7 Hz, 2H), 4.65 and 4.80

(ABX, J_{AB} = 13.1 Hz, J_{AX} = 7.4 Hz, J_{BX} = 6.8 Hz, 4H), 7.11 (dt, J = 8.0, 2.0 Hz, 2H), 7.24 (dd, J = 8.0, 4.8 Hz, 2H), 8.21 (d, J = 2.0 Hz, 2H), 8.58 (dd, J = 4.8, 1.6 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 43.3, 123.6, 129.8, 135.9, 150.0, 150.3; HRMS (ESI) calcd. for $\text{C}_{14}\text{H}_{14}\text{N}_4\text{O}_4\text{H}^+$: 303.1088, found: 303.1088.

Minor (*meso*) isomer: White solid, 24% yield (11 mg). ^1H NMR (400 MHz, DMSO-d_6) δ 3.98 (m, 2H), 4.42 (dd, J = 13.3, 3.9 Hz, 2H), 4.98 (m, 2H), 7.46 (dd, J = 7.9, 4.8 Hz, 2H), 8.00 (dt, J = 7.9, 1.8 Hz, 2H), 8.55 (dd, J = 4.8, 1.5 Hz, 2H), 8.66 (d, J = 1.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 43.8, 78.2, 124.0, 133.1, 135.4, 149.4, 149.8.

2,2'-(1,4-dinitrobutane-2,3-diyl)difuran (2-3j): Brown oil of an inseparable *meso-dl* mixture, 86% yield (36 mg). R_f 0.26 (eluent: EtOAc: *n*-hex = 1: 5); **HRMS (ESI)** calcd. for $C_{12}H_{12}N_2O_6H^+$: 281.0768, found: 281.0768. Major (*dl*) isomer: **1H NMR (400 MHz, $CDCl_3$)** δ 4.13 (m, 2H), 4.60-4.74 (m, 4H), 6.10 (d, J = 3.3 Hz, 2H), 6.33 (dd, J = 3.3, 1.8 Hz, 2H), 7.35 (d, J = 1.8 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 38.9, 75.0, 109.0, 110.6, 142.9, 148.4. Minor (*meso*) isomer: **1H NMR (400 MHz, $CDCl_3$)** δ 4.05 (m, 2H), 4.32 (dd, J = 13.0, 3.8 Hz, 2H), 4.60 (m, 2H), 6.33 (2H), 6.35 (dd, J = 3.2, 1.8 Hz, 2H), 7.44 (d, J = 1.8 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 39.2, 76.3, 110.2, 110.8, 143.5, 148.5.

2,2'-(1,4-dinitrobutane-2,3-diyl)dithiophene (2-3k): Major (*dl*) isomer: Brown oil, 77% yield (36 mg). R_f 0.25 (eluent: EtOAc: *n*-hex = 1: 5); **1H NMR (400 MHz, $CDCl_3$)** δ 4.31 (m, 2H), 4.61 and 4.77 (ABX, J_{AB} = 13.4 Hz, J_{AX} = 7.3 Hz, J_{BX} = 7.0 Hz, 4H), 6.74 (d, J = 3.6 Hz, 2H), 6.98 (dd, J = 5.1, 3.6 Hz, 2H), 7.28 (dd, J = 5.1, 1.0 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 41.0, 77.4, 125.9, 127.2, 127.7, 135.5; **HRMS (ESI)** calcd. for $C_{12}H_{12}N_2O_4S_2H^+$: 313.0311, found: 313.0310. Minor (*meso*) isomer: White solid, 9% yield (4 mg). **1H NMR (400 MHz, $CDCl_3$)** δ 4.12 (m, 2H), 4.46 (dd, J = 13.0, 3.7 Hz, 2H), 4.53 (m, 2H), 7.02 (dd, J = 5.0, 3.5 Hz, 2H), 7.06 (dd, J = 3.5, 1.0 Hz, 2H), 7.35 (dd, J = 5.0, 1.0 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 43.8, 79.5, 126.4, 127.6, 127.7, 138.5.

2,2'-(1,4-dinitrobutane-2,3-diyl)bis(1H-indole) (2-3l): Major (*dl*) isomer: White solid, 61% yield (35 mg). R_f 0.28 (eluent: EtOAc: *n*-hex = 1: 3); **1H NMR (400 MHz, $CDCl_3$)** δ 4.11 (m, 2H), 4.52 and 4.63 (ABX, J_{AB} = 13.1 Hz, J_{AX} = 8.1 Hz, J_{BX} = 6.3 Hz, 4H), 6.23 (s, 2H), 7.14

(t, $J = 7.4$ Hz, 2H), 7.22 (t, $J = 7.6$ Hz, 2H), 7.31 (d, $J = 8.0$ Hz, 2H), 7.56 (d, $J = 7.8$ Hz, 2H), 8.20 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 39.2, 76.3, 103.3, 111.2, 120.68, 120.74, 123.1, 127.6, 131.0, 136.2; HRMS (ESI) calcd. for $\text{C}_{20}\text{H}_{18}\text{N}_4\text{O}_4\text{H}^+$: 379.1401, found: 379.1400.

Minor (*meso*) isomer: White solid, 23% yield (13 mg). ^1H NMR (400 MHz, DMSO-d_6) δ 4.18 (brs, 2H), 4.48 (d, $J = 11.8$ Hz, 2H), 4.97 (brs, 2H), 6.43 (brs, 2H), 7.01 (brs, 2H), 7.11 (brs, 2H), 7.43 (d, $J = 6.5$ Hz, 2H), 7.51 (d, $J = 6.5$ Hz, 2H), 11.38 (brs, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 40.5, 77.9, 101.5, 111.4, 119.2, 120.0, 121.4, 127.6, 134.5, 136.6.

2,2'-(1,4-dinitrobutane-2,3-diyl)diphenol (2-3m): Major (*dl*) isomer:

Brown oil, 38% yield (19 mg). R_f 0.24 (eluent: EtOAc: *n*-hex = 1: 2); ^1H NMR (400 MHz, CDCl_3) δ 4.50 (quint, $J = 5.8$ Hz, 2H), 4.84 (m, 4H), 5.35 (brs, 2H), 6.65-6.78 (m, 6H), 7.09 (dt, $J = 1.7, 7.7$ Hz, 2H); ^{13}C NMR (100

MHz, CDCl_3) δ 39.8, 76.4, 115.9, 120.9, 122.2, 129.2, 129.8, 153.3; HRMS (ESI) calcd. for $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_6\text{H}^+$: 333.1081, found: 333.1081.

Minor (*meso*) isomer: White solid, 16% yield (8 mg). ^1H NMR (400 MHz, DMSO-d_6) δ 4.20 (m, 2H), 4.23 (dd, $J = 12.6, 4.0$ Hz, 2H), 4.98 (t, $J = 11.5$ Hz, 2H), 6.81 (t, $J = 7.4$ Hz, 2H), 6.85 (d, $J = 7.4$ Hz, 2H), 7.13 (dt, $J = 1.5, 7.6$ Hz, 2H), 7.27 (brs, 2H), 9.86 (brs, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 77.5, 115.8, 119.4, 123.1, 128.9, 129.9, 155.6.

(2,3-Dimethyl-1,4-dinitrobutane-2,3-diyl)dibenzene (2-3n): White solid

of an inseparable *meso-dl* mixture, 65% yield (32 mg). R_f 0.35 (eluent: EtOAc: *n*-hex = 1: 5); mp 125–126 °C (EtOAc/*n*-hex); HRMS (ESI) calcd.

for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_4\text{H}^+$: 329.1496, found: 329.1496. Major (*dl*) isomer: ^1H NMR (400 MHz, CDCl_3) δ 1.71 (s, 6H), 4.61 (d, $J = 12.2$ Hz, 2H), 4.81 (d, $J = 12.2$ Hz, 2H), 6.95-7.35 (m,

10H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.0, 48.3, 81.1, 127.8, 128.03, 128.5, 136.7. Minor (*meso*) isomer: ^1H NMR (400 MHz, CDCl_3) δ 1.63 (s, 6H), 4.35 (d, $J = 12.1$ Hz, 2H), 5.27 (d, $J = 12.1$ Hz, 2H), 7.10-7.35 (m, 10H); ^{13}C NMR (100 MHz, CDCl_3) δ 20.8, 48.5, 81.5, 127.9, 127.98, 128.45, 137.2.

5,6-Bis(nitromethyl)decane (2-3o): **2-3o** was obtained in 36% yield (14 mg) along with Stetter product **2-10o** in 44% yield. Major isomer of **2-3o**:

Colorless oil, R_f 0.40 (eluent: EtOAc: *n*-hex = 1: 8); ^1H NMR (400 MHz, CDCl_3) δ 0.92 (t, $J = 6.9$ Hz, 6H), 1.24-1.47 (m, 12H), 2.40 (m, 2H), 4.34 (dd, $J = 6.4, 12.3$ Hz, 2H), 4.39 (dd, $J = 6.8, 12.3$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 13.8, 22.6, 27.9, 29.3, 38.6, 76.8; HRMS (ESI) calcd. for $\text{C}_{12}\text{H}_{24}\text{N}_2\text{O}_4\text{H}^+$: 261.1809, found: 261.1810.

Minor isomer of **2-3o**: Colorless oil, R_f 0.36 (eluent: EtOAc: *n*-hex = 1: 8); ^1H NMR (400 MHz, CDCl_3) δ 0.91 (t, $J = 6.8$ Hz, 6H), 1.22-1.52 (m, 12H), 2.41 (m, 2H), 4.35 (d, $J = 6.6$ Hz, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 13.8, 22.5, 28.2, 29.2, 38.6, 76.9.

1-(1-Methyl-1*H*-imidazol-2-yl)-2-(nitromethyl)hexan-1-one (2-10o):

Colorless oil, R_f 0.24 (eluent: EtOAc: *n*-hex = 1: 3); ^1H NMR (400 MHz, CDCl_3) δ 0.87 (t, $J = 7.0$ Hz, 3H), 1.28-1.90 (m, 6H), 4.01 (s, 3H), 4.55 (dd, $J = 4.3, 15.0$ Hz, 1H), 4.56 (m, 1H), 4.97 (dd, $J = 10.7, 15.0$ Hz, 1H), 7.08 (s, 1H), 7.19 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 13.7, 22.6, 28.8, 29.7, 36.2, 44.8, 75.1, 127.6, 129.7, 142.1, 191.2; HRMS (ESI) calcd. for $\text{C}_{11}\text{H}_{17}\text{N}_3\text{O}_3\text{H}^+$: 240.1343, found: 240.1343.

2,5-Dimethyl-3,4-bis(nitromethyl)hexane (2-3p): **2-3p** was obtained in 58%

yield (20 mg) along with Stetter product **2-10p** in 36% yield. Major isomer of

2-3p: Colorless oil, R_f 0.46 (eluent: EtOAc: *n*-hex = 1: 5); ^1H NMR (400

MHz, CDCl₃) δ 0.97 (d, J = 6.8 Hz, 6H), 1.03 (d, J = 6.8 Hz, 6H), 1.84 (m, 2H), 2.41 (m, 2H), 4.31 (dd, J = 4.1, 13.4 Hz, 2H), 4.39 (dd, J = 7.1, 13.4 Hz, 2H); **¹³C NMR (100 MHz, CDCl₃)** δ 19.1, 19.9, 29.5, 42.9, 75.2; **HRMS (ESI)** calcd. for C₁₀H₂₀N₂O₄H⁺: 233.1496, found: 233.1496.

Minor isomer of **2-3p**: R_f 0.40 (eluent: EtOAc: *n*-hex = 1: 5); **¹H NMR (400 MHz, CDCl₃)** δ 0.85 (d, J = 6.8 Hz, 6H), 1.05 (d, J = 6.8 Hz, 6H), 1.90 (m, 2H), 2.42 (m, 2H), 4.35 (dd, J = 6.1, 13.7 Hz, 2H), 4.43 (dd, J = 4.8, 13.7 Hz, 2H); **¹³C NMR (100 MHz, CDCl₃)** δ 17.9, 21.7, 28.1, 44.1, 75.5.

3-Methyl-1-(1-methyl-1*H*-imidazol-2-yl)-2-(nitromethyl)butan-1-one

(2-10p): Colorless oil, R_f 0.10 (eluent: EtOAc: *n*-hex = 1: 5); **¹H NMR (400**

MHz, CDCl₃) δ 0.90 (d, J = 6.9 Hz, 3H), 1.07 (d, J = 6.9 Hz, 3H), 2.35 (dq, J = 5.3, 6.9, 6.9 Hz, 1H), 4.01 (s, 3H), 4.52 (ddd, J = 3.4, 5.3, 11.3 Hz, 1H), 4.53 (dd, J = 3.4, 14.8 Hz, 1H), 5.03 (dd, J = 11.3, 14.8 Hz, 1H), 7.07 (s, 1H), 7.19 (s, 1H); **¹³C NMR**

(100 MHz, CDCl₃) δ 18.6, 20.9, 29.3, 36.2, 50.2, 72.8, 127.5, 129.6, 142.5, 191.1; **HRMS**

(ESI) calcd. for C₁₀H₁₅N₃O₃H⁺: 226.1186, found: 226.1186.

(1,4-Dinitrobutane-2,3-diyl)dicyclohexane (2-3q): **2-3q** was obtained in

66% yield (31 mg) along with Stetter product **2-10q** in 20% yield. **2-3q:**

White solid of an inseparable *meso-dl* mixture, R_f 0.39 (eluent: EtOAc: *n*-

hex = 1: 7); mp 83–85 °C (EtOAc/*n*-hex); **¹H NMR (400 MHz, CDCl₃)** δ 0.85–1.85 (m,

22H), 2.36–2.54 (m, 2H), 4.20–4.54 (m, 4H); **¹³C NMR (100 MHz, CDCl₃)** δ 26.02, 26.04,

26.2, 26.3, 26.5, 28.9, 29.9, 29.93, 32.0, 38.6, 39.7, 41.7, 43.4, 75.2, 76.0; **HRMS (ESI)**

calcd. for C₁₆H₂₈N₂O₄H⁺: 313.2122, found: 313.2123.

2-Cyclohexyl-1-(1-methyl-1H-imidazol-2-yl)-3-nitropropan-1-one (2-**10q):** Colorless oil, R_f 0.28 (eluent: EtOAc: *n*-hex = 1: 3); ^1H NMR (400**MHz, CDCl_3) δ 0.90-1.30 (m, 6H), 1.59-1.78 (m, 4H), 1.88-1.98 (m, 1H),**

4.01 (s, 3H), 4.52 (ddd, $J = 3.4, 5.7, 11.4$ Hz, 1H), 4.55 (dd, $J = 3.4, 15.0$ Hz, 1H), 5.02 (dd, $J = 11.4, 15.0$ Hz, 1H), 7.07 (s, 1H), 7.20 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 25.9, 26.2, 26.3, 29.4, 31.3, 36.3, 39.1, 49.8, 73.4, 127.5, 129.6, 142.6, 191.2; **HRMS (ESI)** calcd. for $\text{C}_{13}\text{H}_{19}\text{N}_3\text{O}_3\text{H}^+$: 266.1499, found: 266.1500.

Methyl 4-(2-cyclohexyl-3-nitropropanoyl)benzoate (2-11):

White solid, R_f 0.23 (eluent: EtOAc: *n*-hex = 1: 7); ^1H -NMR (400 MHz, CDCl_3) δ 0.87-1.78 (m, 11H), 3.96 (s, 3H), 4.18 (ddd, $J = 3.4,$

5.2, 10.5 Hz, 1H), 4.57 (dd, $J = 3.4, 14.8$ Hz, 1H), 5.09 (dd, $J = 10.5, 14.8$ Hz, 1H), 8.04 (d, $J = 8.5$ Hz, 2H), 8.17 (d, $J = 8.5$ Hz, 2H) ppm; ^{13}C -NMR (100 MHz, CDCl_3) δ 25.7, 26.1, 26.2, 29.6, 31.4, 39.1, 49.2, 52.4, 73.5, 128.3, 130.0, 134.2, 139.9, 166.0, 199.4 ppm; **HRMS (ESI)** calcd. for $\text{C}_{17}\text{H}_{21}\text{NO}_5\text{H}^+$: 320.1492, found: 320.1492.

2,2,3,3-Tetramethyl-1,4-dinitrobutane (2-3r): 2-3r was obtained in 33% yield(10 mg) along with Stetter product **2-10r** in 10% yield. **2-3r:** White solid, R_f 0.37 (eluent: EtOAc: *n*-hex = 1: 5); mp 65–66 °C (EtOAc/*n*-hex); ^1H NMR (400

MHz, CDCl_3) δ 1.13 (s, 12H), 4.38 (s, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 20.5, 40.2, 82.9; **HRMS (ESI) calcd. for $\text{C}_8\text{H}_{16}\text{N}_2\text{O}_4\text{H}^+$: 205.1183, found: 205.1183.**

2,2-Dimethyl-1-(1-methyl-1H-imidazol-2-yl)-3-nitropropan-1-one (2-**10r):** Colorless oil, R_f 0.26 (eluent: EtOAc: *n*-hex = 1: 5); ^1H NMR (400**MHz, CDCl_3) δ 1.47 (s, 6H), 3.99 (s, 3H), 5.43 (s, 2H), 6.98 (s, 1H), 7.07**

(s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 23.3, 36.6, 47.2, 84.0, 126.3, 128.1, 141.3, 192.0; HRMS (ESI) calcd. for $\text{C}_9\text{H}_{13}\text{N}_3\text{O}_3\text{H}^+$: 212.1030, found: 212.1032.

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Chapter 3

Carbene-Catalyzed Reductive Coupling of Nitrobenzyl Bromide and Nitroalkene via Single-Electron-Transfer (SET) Process and Formal 1,4-Addition

3.1 Introduction

3.1.1 4-Nitrobenzyl Compounds in Radical Chemistry

4-Nitrobenzyl compounds **3-1** are a class of active compounds that are extensively studied by electrochemical and chemical methods. These molecules can easily obtain one electron to form radical anion intermediates, and thus these radical anions are very reactive due to the weakness of C-X single bond, and they can dissociate anions to form corresponding radical intermediates (Scheme 3.1).¹ The electron initially transfers to the conjugated π -system NO₂ and phenyl ring, followed by delivering to the C-X σ -bond to eliminate X⁻ and generate the radical intermediate.² In electrochemistry, the single electrons are provided by irradiating under electron linear accelerator. The electrochemical studies indicated that the bond energies of the C-X σ -bond effects the dissociations of the radical anions, thus determines the reaction rate.¹

Scheme 3.1 Formulation of 4-nitrobenzyl radicals from corresponding 4-nitrobenzyl compounds.

In radical chemistry, the single electron is transferred from the electron-rich spaces in the reaction system. In some cases of substitution reactions of 4-nitrobenzyl compounds, the substitution of the leaving groups by nucleophiles proceeds via SET process instead of S_N2 process.³ In these cases, the SET process occurs from the nucleophile to the 4-nitrobenzyl compound to generate the radical anion intermediates to initiate the reaction, then the dissociation of the leaving group generates the radical intermediate, which acts as an electrophile to react with another nucleophile via 1,6-addition to generate the corresponding

radical anion intermediates. Finally, the SET process from this radical anion to another molecule of 4-nitrobenzyl compound gives the substitution product.

Scheme 3.2 Substitution reactions of 4-nitrobenzyl compounds proceed via radical anion intermediates.

In recent years, photoredox catalysis has attracted more and more attention from chemists.⁴ 4-Nitrobenzyl bromide derivatives can serve as a benzylation agent in photoredox catalysis catalyzed by ruthenium complex^{5a} and iridium complex^{5b}. The key process for this chemistry is the irradiation of visible light to the metal catalyst which induce the metal catalyst to the excited state, then SET process initiate the reaction. The 4-nitrobenzyl bromide derivatives get one electron from the radical anion intermediates, then elimination of the bromide give the key 4-nitrobenzyl radical intermediates (Scheme 3.3).

Scheme 3.3 Macmillan's α -benzylation of aldehydes via photoredox catalyzed by $\text{Ru}(\text{bpy})_3^{2+}$.

Without photocatalyst, the 4-nitrobenzyl bromide derivatives can also serve as benzylation agents in photoredox chemistry. These catalyst-free photoredox reactions were developed by Melchiorre and co-workers.⁶ The key process of these reactions is that, the amine-catalyst activate the aldehyde or ketone to generate enamine intermediate, which serve as a donor to interact with 4-nitrobenzyl bromide, which act as an acceptor, to generate electron donor-acceptor (EDA) complex. When this key intermediate undergoes visible light irradiation, a SET process takes place and generate a radical ions pair, then dissociates the Br^- to form benzyl radical and iminium radical. Finally, radical-radical coupling follow by hydrolysis to give the α -benzylation product (Scheme 3.4).

Scheme 3.4 Donor-acceptor complex in photochemistry developed by Melchiorre.

3.1.2 Our Proposal.

As was described above, the 4-nitrobenzyl bromide derivatives are good single-electron oxidants which can easily obtain single electron and further dissociate to generate the 4-benzyl radicals. In our previous study, we achieved the NHC catalyzed reductive coupling of nitroalkenes, and the key point of this reaction is the single electron reduction of nitroalkenes to generate nitroalkene radical anions as key intermediates. Based on previous results, we propose that Breslow intermediates can serve as a single-electron reductant that SET to 4-nitrobenzyl bromide followed by dissociating the bromide to form 4-nitrobenzyl radical, which can react with nitroalkene radical anion via radical-radical coupling⁷ process to form a reductive cross-coupling product (Scheme 3.5).

Scheme 3.5 Research proposal of cross-coupling of 4-nitrobenzyl bromide and nitroalkene.

3.2 Results and Discussions

Our initial study used 4-nitrobenzyl bromide **3-1k** and β -nitrostyrene **3-2a** as substrates to investigate the reductive cross coupling reaction. Similar with the reductive dimerization of nitroalkenes, the reaction used 10 mol % **3-C1** as NHC-catalyst, methyl 4-formylbenzoate **3-3a** as aldehyde, and carried out at 0 °C in CH₃OH. The research proposal indicated that the reaction produced one equivalent of hydrobromide (HBr), so we modified the amount of base DIPEA from catalytic amount to stoichiometric amount: 200 mol %. To our delight, the desired cross coupling product **3-4k** was obtained as major product in 42% yield along with small amounts of reduction product 4-nitrotoluene and reductive dimerization of 4-nitrobenzyl bromide and β -nitrostyrene as side products (Scheme 3.6, a). Substituents on α -position of 4-nitrobenzyl bromide can decrease the dissociation energies of C-X bond by stabilizing the resulting benzyl radical,² that makes the corresponding 4-nitrobenzyl bromide more active. Inspired by this, we introduced α,α -dimethyl 4-nitrobenzyl bromide as substrate in order to suppress the side reactions. It was fortunate that in this case, the desired coupling product **3-4a** was isolated in 81% yield, while both

of the two dimerization products were not observed (Scheme 3.6, b). The structure of cross-coupling product **3-4a** was confirmed by X-ray crystallographic analysis (Fig. 3.1).

Scheme 3.6 Reductive coupling reactions of 4-nitrobenzyl bromides and β -nitrostyrene.

Fig. 3.1 Crystall structure of cross-coupling product **3-4a**.

Then we used dimethyl 4-nitrobenzyl bromide **3-1a** instead of **3-1k** as substrate to optimized the reaction conditions, and the key results were summarized in table 3.1. First we investigated achiral electron-deficient NHCs **3-C1**~**3-C4** derived from different lactames, and we found that pyrrolidone-derived catalyst provided the desired product **3-4a** in 81% yield (entry 1), which was the best result. Other N-C₆F₅ substituted triazolium

salts gave worse results, **3-4a** were obtained in 21-69% yields (entries 2-4). Investigation of different bases proved that DIEA was the most suitable one, while other bases could also give the desired product in moderate yields (entries 1, 5, 6). When we used toluene as a solvent instead of CH₃OH, the desired product was given in 76% yield. In this case, 10 equivalents CH₃OH should be added to trapped the acylazolium intermediate (entry 7). It is surprising that, reducing the reaction concentration could improve the reaction yield to 91% (entry 8). The NHC loading could be reduced to 5% without any decrease of yield of **3-4a**, which was isolated in 87% yield (entry 9). Further reducing the loading of NHC to 1 mol % result in a bit drop of the reaction yield (entry 10). Without NHC, the reaction could not occur (entry 11).

Table 3.1 Condition Optimization.

CC1(C)C(Br)C=C(C1)C(=O)O + O=Cc1ccc([N+](=O)[O-])cc1
 $\xrightarrow[\text{solvent, 0 } ^\circ\text{C, degas}]{\text{NHC, 200 mol \% base}}$
CC1(C)C(C(=O)O)C=C(C1)C(=O)O + CCOC(=O)c1ccc([N+](=O)[O-])cc1

3-1a, 0.15 mmol **3-2a**, 0.1 mmol
 + ArCHO (**3-3**, 0.15 mmol), CH₃OH

3-C1 **3-C2** **3-C3**, X = CH₂ **3-C4**, X = O ArCHO (**3-3**)

entry	NHC, mol%	base	solvent (mL)	yield (%) ^a
1	3-C1 , 10	DIEA	CH ₃ OH (1)	81
2	3-C2 , 10	DIEA	CH ₃ OH (1)	21
3	3-C3 , 10	DIEA	CH ₃ OH (1)	55
4	3-C4 , 10	DIEA	CH ₃ OH (1)	69
5	3-C1 , 10	K ₂ CO ₃	CH ₃ OH (1)	53
6	3-C1 , 10	DBU	CH ₃ OH (1)	68
7 ^c	3-C1 , 10	DIEA	toluene (1)	76
8	3-C1 , 10	DIEA	CH ₃ OH (2)	91
9	3-C1 , 5	DIEA	CH ₃ OH (2)	92(87) ^b
10	3-C1 , 1	DIEA	CH ₃ OH (2)	63
11	no NHC	DIEA	CH ₃ OH (2)	no reaction

^aYield (based on **2a**) was estimated via ¹H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. ^b Isolated yield in parentheses. ^c10 equivalents CH₃OH was used.

With the optimized reaction conditions in hand, we turn our attention to the reaction scopes. At the beginning, we used β -nitrostyrene **3-2a** as the model substrate to try different functionalized nitrobenzyl bromides (Table 3.2). We observed that α,α -disubstituted 4-nitrobenzyl bromides as substrates worked very effectively in this reaction, giving the desired products in 76~87% yields (**3-4a~3-4d**). Mono-substituted nitrobenzyl bromides were then studied (**3-4e~3-4j**, **3-4i**). Placing the alkyl group (**3-4e**, **3-4f**) and aryl group (**3-4g**) on the benzylic carbon of nitrobenzyl bromide led to good reaction outcomes. Mono-substituted nitrobenzyl bromide containing unsaturated units (**3-4h**) and electron-withdrawing group (**3-4j**) worked fine as well. It was interesting that when using non-substituted nitroalkene as substrate, the corresponding coupling product could only obtain in moderated yield (**3-4k**, **3-4l**), and the drop of the reaction yields of these two examples probably due to the generated corresponding benzyl radicals without any substituent on the benzylic carbon which were less stable compared with the substituted ones.⁸ Moving of the nitro group from para-position to ortho-position would not effect the reaction outcomes, and the corresponding reductive products obtained in similar yields compared with the corresponding para-nitroalkenes (**3-4l** vs. **3-4k**, **3-4m** vs. **3-4e**).

The generality of nitroalkenes in this reaction were then evaluated using α,α -dimethyl nitrobenzyl bromide **3-1a** as the model substrate (Table 3.3). We first placed various substituents on different positions of the phenyl ring of nitroalkene. Nitroalkenes bearing electron-withdrawing group on the para- (**3-6a~3-6d**), meta-position (**3-6i**, **3-6j**) and (**3-6l**) all worked well in this reaction, giving the corresponding reductive coupling products in moderate to good yields. Nitroalkenes bearing electron-donating groups on the para- (**3-6f~3-6g**) and meta-position (**3-6k**) work fine as well, although in para-position substituted cases we needed to enhance the amount of nitrobenzyl bromide **3-1a** and aldehyde **3** from 1.5 equiv. to 2.0 equiv. to achieve moderate yields. Unprotected hydroxy group addressed on the nitroalkene was well tolerated, gave the desired product in 70% yield (**3-6h**).

Table 3.2 Examples of Nitrobenzyl Bromides.

^a Reaction condition as in Table 1, entry 9. ^b Isolated yield. ^c For **3-4c**, **3-4e**~**3-4j**, **3-4m**, dr between 1.1:1 and 1.2:1, determined via ¹H NMR.

Placing unsaturated units on the ortho-position of the β -nitrostyrene did not lead to the ring-closing products. Instead, the reaction stopped on the reductive coupling step, and provided the corresponding products in good to excellent yields (**3-6m**~**3-6o**). The fused ring substituted (β -naphthyl) nitroalkene also worked well in our cross-coupling reaction (**3-6p**). The heteroaryl substituted nitroalkenes introduced as substrates provided the desired products in moderate yields (**3-6q**~**3-6s**). Finally, we evaluated the alkyl nitroalkenes, but unfortunately, the examples we had tried were ineffective in the reaction, and the desired product could not obtain at all. In these cases, the nitrobenzyl bromide was reduced while alkyl nitroalkene remained unchanged.

^aReaction condition as in Table 1, entry 9. ^bIsolated yield. ^c0.2 mmol **3-1a**, 0.2 mmol **3-3** were used.

3.3.1 Control Experiments for Mechanistic Insights.

3.3.1 Control Experiments for Mechanistic Insights.

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3.7, a). It indicated that the nitrogroup substituted on para- or ortho-position of benzyl bromide was important for the benzyl bromide to undergo proposed SET process to generate the benzyl radical, which ensured the reductive coupling reaction to occur. Changing the α -bromide substituted on the nitrobenzyl bromide to other leaving groups such as Cl, OTs (**3-9a** and **3-9b**) led to the desired product with similar yields compared with bromide, which demonstrated that the α -leaving group had less effects to the SET process that from Breslow intermediate to nitrobenzyl compounds (Scheme 3.7, b).

Scheme 3.7 Control experiments for mechanistic insights.

As was described in the research proposal, the proposed generation process of desired product was radical-radical coupling process (Scheme 3.5). But when we introduced 1,1-dibromoethyl-4-nitrobenzene **3-10** as nitrobenzyl bromide in the reaction, the reaction outcome was totally different from the case that using normal nitrobenzyl bromides. In this case, the desired cross-coupling product **3-12** was not observed, instead, the nitrobenzyl bromide **3-10** transformed to 4-nitrostyrene **3-11** in 87% yield, while the β -nitrostyrene **3-2a** was fully recovered after the reaction (Scheme 3.7, c). The possible generation pathway of 4-nitrostyrene **3-11** was showed in Scheme 3.8. the SET from Breslow intermediate **3-A** to nitrobenzyl bromide **3-10** generated radical anion **3-C₁**, and this intermediate

dissociated to generated radical intermediate **3-D₁**, and through direct elimination of bromo radical or under second SET process, this radical intermediate reduced to nitrobenzyl anion followed by elimination of bromide which both gave the 4-nitrostyrene **3-11**. This phenomenon suggests that the single-electron transfer from Breslow intermediate to nitrobenzyl bromide and following dissociation to form radical intermediate initiated the reaction, and the intermediate generated from nitrobenzyl bromide 1,4-addition to nitroalkene provided the cross-coupling product.

Scheme 3.8 The generation pathway of 4-nitrostyrene **3-11** from 1-dibromoethyl-4-nitrobenzene.

The cyclic voltammetry spectra of a) α,α -dimethyl-4-nitrobenzyl bromide **3-1a**; b) 4-nitrobenzyl bromide **3-1k**; c) β -nitrostyrene **3-2a** provided further evidence for the confirmation of the reaction starting from reduction of nitrobenzyl bromides (Fig. 3.2). From the spectra, we could see that the reduction potentials E_{red} for nitrobenzyl bromides to obtain the first electron to generate radical intermediate were higher than that of nitroalkenes (**3-1a**, ~ -0.85 V, **3-1k**, ~ -0.90 V, **3-2a**, ~ -1.0 V), which suggests that nitrobenzyl bromides were easier to reduce by obtaining one electron than nitroalkenes, thus confirmed that the coupling step was 1,4-addition of nitrobenzyl radical or anion intermediate to nitroalkenes rather than radical-radical coupling process. And the similar reduction potential of nitrobenzyl bromide

3-1k and nitroalkene **3-2a** led to low yield of **3-4k** along with a small amount of nitroalkene dimer was produced as byproduct (Scheme 3.6).

Figure 3.2 Cyclic voltammograms of 5 mM substrates in CH₃CN at glassy carbon disk (1.0 mm diameter, working electrode), counter electrode: platinum electrode, reference electrode: saturated calomel electrode (SCE); 0.1 M tetrabutylammonium tetrafluoroborate, scan rate of $\nu = 1.0$ V/s; a) substrate: α,α -dimethyl-4-nitrobenzyl bromide **3-1a**; b) 4-nitrobenzyl bromide **3-1k**; c) β -nitrostyrene **3-2a**

To determine whether the cross-coupling process to nitroalkene came from the radical conjugated addition⁹ of nitrobenzyl radical intermediate or Michael addition of nitrobenzyl anion intermediate, we tried to deprotonate 4-nitrocumene **3-13** to form corresponding benzyl anion for Michael addition to nitrostyrene **3-2a** in CH₃OH to form the cross-coupling product **3-4a**. The base we had tried (CH₃ONa, DIPEA, DBU) all could not lead to the desired product (Scheme 3.9, a). It demonstrated that under our condition, the benzyl anion intermediate was easy to be protonated to quench the reaction. Based on this, we think the Michael addition pathway is less possible. What's more, when nitrobenzyl

bromide **3-14a** or **3-14b** as substrate, the reaction provided the result, yielding the product **3-15a** and **3-15b** in 32% yield and 18% yield, respectively. The yield of the product **3-15a** derived from a secondary carbon addition to nitroalkene was higher than the product **3-15b** derived from corresponding primary carbon (Scheme 3.9, b). These results suggest that the coupling step likely proceeded via radical conjugated addition rather than Michael addition, because anion conjugated addition is more sensitive to the steric hindrance.

Scheme 3.9 Control experiments for mechanistic insights.

3.3.2 Proposed Reaction Pathways.

Based on the above mathematic studies, we proposed two reaction pathways for the reductive cross-coupling of nitrobenzyl bromide with nitroalkenes (Scheme 3.10). At the beginning NHC nucleophilic attacked the aldehyde **3-3** to generate the Breslow intermediate **3-A**, then the single-electron reducing of nitrobenzyl bromide **3-1a** to nitrobenzyl anion intermediate **3-C** via SET process initiated the reaction. And after the SET process, the Breslow intermediate transformed to radical cation **3-B**. Then heterolytic cleavage of C-Br σ -bond of radical anion **3-C** generated the neutral radical intermediate **3-D**. The coupling process of radical **3-D** with nitrostyrene **3-2a** has two possible pathways. The first one was radical pathway. In this pathway, radical **3-D** conjugated addition to

nitrostyrene **3-2a** generated radical intermediate **3-E**, then **3-E** further reduced to anion intermediate **3-F** via second SET process, finally, protonation of anion **3-F** provided the coupling product **3-4a** (Scheme 3.10, possible pathway #1). The other possible pathway was anion Michael addition pathway, in which the radical **3-D** first further reduced to the benzyl anion intermediate **3-H** via second SET process, then this benzyl anion underwent a Michael addition to nitroalkene **3-2a** follow by protonation to give the coupling product **3-4a** (Scheme 3.10, possible pathway #2). Our control experiments suggest that the radical conjugated addition pathway (possible pathway #1) is the more possible one, while the Michael addition pathway (possible pathway #2) cannot be completely ruled out.

Scheme 3.10 Proposed reaction pathways.

The radical cation intermediate **3-B** underwent a deprotonation process followed by loss of one electron to intermediates **3-D** or **3-E** via second SET process generated acylazolinium intermediate **3-G**, which was trapped by CH_3OH to generate the ester **3-5** and regenerate NHC to finish the catalytic cycle.

3.4 Synthetic Transformations of our Products.

The reductive cross-coupling products were easily transformed to other useful molecular

via reduction conditions (Scheme 3.11). For example, the product **3-4a** could be reduced to diamine **3-16** under Zn-HOAc-HCl reduction system in excellent yield, and the product **3-4j-a** (one diastereomer) can be reductively cyclized to form 2-piperidone derivative **3-17** in 86% yield. And the lactam **3-17** were widely found as core ring structure in biological active alkaloids and pharmaceuticals.¹⁰

Scheme 3.11 Synthetic transformations of our products.

3.5 Summary.

In summary, we have developed an NHC catalyzed reductive cross-coupling reaction of 4-nitrobenzyl bromides and nitroalkenes under mild conditions. The reaction initiate from the reductive elimination of nitrobenzyl bromides via SET process to generate nitrobenzyl radical intermediates. The product was generated by a formal 1,4-addition process. In this reaction, the α -carbon of nitrobenzyl bromide was umpolung from electrophilic carbon to nucleophilic carbon, which usually achieved via the pre-formed organometallic reagents. We believe that this work will provide opportunities for chemists to get more achievements towards NHC-catalyzed reactions.

3.6 Experimental Section

3.5.1 General Information.

Commercially available materials purchased from Alfa Aesar or Aldrich was used as received. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a Bruker AV400 (400 MHz) spectrometer. Chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethylsilane (δ 0.00). ^1H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), dd (doublet of doublets); m (multiplets), etc. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker AV400 (100 MHz) spectrometer. High resolution mass spectral analysis (HRMS) was performed on Waters Q-TOF Premier mass spectrometer. X-ray crystallography analysis was performed on Bruker X8 APEX X-ray diffractometer. Flash chromatography was performed using Merck silica gel 60 with distilled solvents. Analytical thin-layer chromatography (TLC) was carried out on Merck 60 F254 pre-coated silica gel plate (0.2 mm thickness). Visualization was performed using a UV lamp.

3.5.2 General Procedures for the catalytic reductive coupling reactions.

To a dry Schlenk tube equipped with a magnetic stir bar, was added benzyl bromide **3-1** (0.15 mmol), nitroalkene **3-2** (0.10 mmol), aldehyde **3-3** (0.15 mmol) and triazolium salt **3-C1** (1.8 mg, 0.005 mmol), then the tube was closed with a septum. Methanol (2.0 mL) was added and the resulting solution was degassed 3 times (freeze-pump-thaw: cooled in

liquid nitrogen and degassed via vacuum evacuation (5 min), backfilled with nitrogen, and warm to room temperature). N,N-diisopropylethylamine (35 μ L, 0.2 mmol) was added at 0 $^{\circ}$ C and the reaction mixture was stirred at this temperature overnight. Then the resulting mixture was concentrated under reduced pressure, and the residue was purified via column chromatography on silica gel to afford the coupling product **3-4** or **3-6**.

3.5.3 Further Transformations of the Products.

Reduced of product 4a to diamine 3-16

To a stirred solution of compound **3-4a** (31.4 mg, 0.1 mmol) in CH_3OH (1 ml) was added Zn powder (130 mg, 2 mmol) follow by the addition of a mixture of 1N HCl (0.8 ml) and HOAc (0.4 ml). After the reaction was completed, the zinc powder was filtered out and the filtrate was concentrated by rotary evaporator. The residue was dissolved in DCM, the resulting solution was neutralized by sat. NaHCO_3 , separated and the aqueous layer was extract by DCM, the combine organic layers was washed with brine, dried over Na_2SO_4 and concentrated, the residue was purified by column chromatography (eluent: $\text{CH}_3\text{OH}:\text{CH}_2\text{Cl}_2 = 1:10$, with 1% $\text{NH}_3\cdot\text{H}_2\text{O}$, dried over Na_2SO_4) to afford the amine **3-16** (24.4 mg, 96%) as a colourless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.29-7.18 (m, 3H), 7.10-7.06 (m, 4H), 6.65-6.59 (m, 2H), 3.00-2.90 (m, 1H), 2.87-2.77 (m, 2H), 2.46 (brs, 4H), 1.23 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 144.2, 140.3, 138.6, 130.3, 127.9, 127.4, 126.6, 114.8, 61.2, 42.0, 40.0, 29.3, 24.3; IR (ν cm^{-1}) 3362, 3030, 2964, 1616, 1516, 1452, 1384, 1286, 1190, 927, 754, 708; HRMS (ESI) calcd. for $\text{C}_{17}\text{H}_{23}\text{N}_2$ ($\text{M}+\text{H}$) $^{+}$: 255.1861, Found: 155.1860.

Formations lactam 17 by reductive cyclization of 3-4j-a.

To a stirred solution of compound **3-4j-a** (37.2 mg, 0.1 mmol) in CH₃OH solution was added Zn powder (130 mg, 2 mmol) follow by the addition of a mixture of 1N HCl (0.8 ml) and HOAc (0.4 ml). The resulting mixture was allowed to stir overnight. Then the reaction was concentrated by rotary evaporator, the residue was dissolved in CH₃OH and then K₂CO₃ (50 mg) was added and the resulting mixture was allowed to stir overnight. The K₂CO₃ was filtered, the filtrate was concentrated and the residue was purified by column chromatography (eluent: CH₃OH:CH₂Cl₂ = 1:20, with 1% NH₃•H₂O, dried over Na₂SO₄) to afford piperidinone **3-17** (22.9 mg, 86%) as a white solid. Mp 203-204 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.24-7.16 (m, 3H), 6.86-6.78 (m, 2H), 6.64-6.46 (m, 5H), 3.83 (brs, 2H), 3.67-3.51 (m, 2H), 3.44-3.34 (m, 2H), 2.82 (dd, *J* = 18.0, 6.0 Hz, 1H), 2.66 (dd, *J* = 17.9, 5.6 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 172.6, 145.3, 139.5, 129.6, 129.4, 128.4, 128.1, 127.0, 114.9, 43.9, 43.6, 42.6, 35.9; IR (ν cm⁻¹) 3361, 3028, 2912, 1651, 1632, 1518, 1494, 1450, 1332, 1244, 1186, 1128, 827, 754, 700; HRMS (ESI) calcd. for C₁₇H₁₉N₂O (M+H)⁺: 267.1497, Found: 267.1492.

3.5.4 Substrates preparation.**General procedure A for the synthesis of benzylbromides 3-1.**

To a round bottom flask with a magnetic stir bar was added **S** (5 mmol), NBS (1.068 g, 6 mmol), (PhCOO)₂ (20 mg) and CCl₄ (10 ml). Then the resulting mixture was warmed to reflux and stirred. After the reaction was completed, the reaction was cooled to room temperature and washed with water, brine, dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography to afford benzylbromide **3-1**.

1-(2-Bromopropan-2-yl)-4-nitrobenzene (3-1a). The nitro compound **S** was treated following the general procedure **A** (eluent: AcOEt:Hexane = 1:20) to give the title compound **3-1a** in 78% yield. ¹H NMR (400 MHz, CDCl₃) δ 8.22-8.16 (m, 2H), 7.80-7.75 (m, 2H), 2.20 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 153.7, 147.2, 127.0, 123.7, 61.0, 35.3.

1-(3-Bromopentan-3-yl)-4-nitrobenzene (3-1b). The nitro compound **S** was prepared according to the literature's procedure¹² from pentan-3-ylbenzene. Then the nitro compound **S** was treated following the general procedure **A** (eluent: AcOEt:Hexane = 1:20) to give the title compound **3-1b**, 2 steps, 48% overall yield. ¹H NMR (400 MHz, CDCl₃) δ 8.22-8.15 (m, 2H), 7.76-7.68 (m, 2H), 2.31 (q, *J* = 7.2 Hz, 4H), 0.93 (q, *J* = 7.2 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 151.0, 147.1, 128.6, 123.4, 76.7, 37.4, 10.4.

1-(2-Bromobutan-2-yl)-4-nitrobenzene (3-1c). The nitro compound **S** was prepared according to the literature's procedure¹³ from corresponding amine. Then the nitro compound **S** was treated following the general procedure **A** (eluent: AcOEt:Hexane = 1:20) to give the title compound **3-1c**, 2 steps, 62% overall yield. ¹H NMR (400 MHz, CDCl₃) δ 8.22-8.16 (m, 2H), 7.76-7.70 (m, 2H), 2.41-

2.28 (m, 2H), 2.17 (s, 3H), 0.94 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 152.6, 127.8, 123.6, 67.9, 40.4, 31.5, 10.8.

1-(1-bromocyclohexyl)-4-nitrobenzene (3-1d). The nitro compound **S** was prepared according to the literature's procedure⁴ from corresponding amine. Then the nitro compound **S** was treated following the general procedure **A** (eluent: AcOEt:Hexane = 1:20) to give the title compound **3-1d**, 2 steps, 56% overall yield. ^1H NMR (400 MHz, CDCl_3) δ 8.23-8.17 (m, 2H), 7.77-7.72 (m, 2H), 2.58-2.50 (m, 2H), 2.07-1.88 (m, 4H), 1.78-1.66 (m, 3H), 1.40-1.28 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 153.5, 147.1, 127.1, 123.8, 68.9, 40.9, 25.0, 23.7.

1-(1-bromopropyl)-4-nitrobenzene (3-1f). The nitro compound **S** was prepared according to the literature's procedure⁴ from corresponding amine. Then the nitro compound **S** was treated following the general procedure **A** (eluent: AcOEt:Hexane = 1:20) to give the title compound **3-1f**, 2 steps, 56% overall yield. ^1H NMR (400 MHz, CDCl_3) δ 8.24-8.17 (m, 2H), 7.58-7.52 (m, 2H), 4.88 (t, $J = 7.3$ Hz, 1H), 2.35-2.24 (m, 1H), 2.22-2.11 (m, 1H), 2.17 (s, 3H), 1.03 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 149.2, 147.7, 128.4, 124.1, 54.6, 33.1, 12.9

General procedure B for the synthesis of benzylbromide 3-1 from corresponding alcohol.

Ketone **S** (5 mmol) was dissolved in CH_3OH (20 ml) and the solution was cooled to 0 °C and stirred, then NaBH_4 (227 mg, 6 mmol) was added in portions. After that, the resulting

mixture was warm to room temperature and stirred. After the reaction was completed, the reaction was quenched with saturated NH_4Cl , then the solvent was evaporated and water (20 ml) was added, then the resulting aqueous solution was extracted with EtOAc (3×10 ml), the combined organic layers was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give the alcohol **M**, which was used without further purification.

The obtained alcohol **M** was dissolved in Et_2O (10 ml) and stirred, then to the resulting solution was added PBr_3 (0.24 ml, 2.5 mmol) dropwise at 0°C . The resulting mixture was allowed to warm to room temperature and stir. After the reaction was completed, the reaction was cautiously quenched with water at 0°C , the organic layer was separated and the aqueous layer was extracted with Et_2O (3×10 ml), the combined organic layers was washed with NaHCO_3 and brine, dried over Na_2SO_4 and then concentrated under reduced pressure. The residue was purified by column chromatography to give benzylbromide **3-1**.

Preparation of 1-(1-bromobut-3-en-1-yl)-4-nitrobenzene (**3-1h**).

The alcohol **M** was synthesis from aldehyde **S** follow the literature's procedure¹⁴. The alcohol **M** was treated with PBr_3 follow the general procedure **B** (eluent: AcOEt:Hexane = 1:20) to give the benzyl bromide **1h**, 2 steps, 36% overall yield. ^1H NMR (400 MHz, CDCl_3) δ 8.23-8.17 (m, 2H), 7.59-7.53 (m, 2H), 5.76-5.64 (m, 1H), 5.17-5.08 (m, 2H), 4.98 (t, $J = 7.5$ Hz, 1H), 3.07-2.87 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 148.6, 147.7, 133.7, 128.5, 124.1, 119.2, 51.1, 43.8.

Preparation of 1-Bromo-6-nitro-1,2,3,4-tetrahydronaphthalene (**3-1i**).

The corresponding ketone substrate was oxidized from corresponding amine according to the literature's procedure¹⁵. The ketone was treated follow the general procedure **B** (eluent: AcOEt:Hexane = 1:20) to afford the benzylbromide **3-1i**, 3 steps, 38% overall yield. ¹H NMR (400 MHz, CDCl₃) δ 7.98-7.92 (m, 2H), 7.49 (d, *J* = 8.2 Hz, 1H), 5.20 (d, *J* = 3.6 Hz, 1H), 3.10-3.00 (m, 1H), 2.97-2.86 (m, 1H), 2.46-2.38 (m, 1H), 2.30-2.10 (m, 2H), 2.00-1.92 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 147.3, 143.9, 138.0, 131.8, 124.5, 121.1, 48.6, 32.8, 28.8, 18.3.

Preparation of benzyl bromide Ethyl 3-bromo-3-(4-nitrophenyl)propanoate (**3-1j**).

To solution of diisopropyl amine (0.91g, 9 mmol) in dry THF (10 ml) was added butyllithium (1.6 M in hexane, 5.7 ml, 9 mmol) at -78 °C under nitrogen. The mixture was kept at this temperature for 1 h, then a solution of ethyl acetate (660 mg, 7.5 mmol) in dry THF (5 ml) was added at low temperature. After it stirred for 1 h at -78 °C, a solution of aldehyde **S** (1.36g, 9 mmol) in dry THF (10 ml) was added. After the mixture was stirred for another 1 h, sat. NH₄Cl solution was added and the aqueous layer was extracted with ethyl acetate (3×10 ml), the combined extracts were dried and evaporated in vacuum. The residue was purified by column chromatography to give the alcohol **M**. Then the alcohol **M** was treated with PBr₃ follow the general procedure **B** (eluent: AcOEt:Hexane = 1:20) to give the benzylbromide **3-1j** in 48% overall yield. ¹H NMR (400 MHz, CDCl₃) δ 8.24-8.18 (m, 2H), 7.63-7.57 (m, 2H), 5.40 (t, *J* = 7.8 Hz, 1H), 4.20-4.06 (m, 2H), 3.34 (dd, *J* = 16.3, 8.1 Hz, 1H), 3.22 (dd, *J* = 16.4, 7.2 Hz, 1H), 1.22 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 169.2, 147.8, 128.5, 124.2, 61.5, 45.3, 44.5, 14.2.

Preparation of nitrobenzyl bromide 1-(1-bromoallyl)-4-nitrobenzene (3-14a) (E)-1-(3-bromoprop-1-en-1-yl)-4-nitrobenzene (3-14b).

To a stirred solution of 4-nitrobenzaldehyde **S** (755 mg, 5.0 mmol) in dried THF (20 mL) was added vinylmagnesium bromide solution (1.0 M in THF, 6.0 mL, 6.0 mmol) dropwise at -78 °C. Then the resulting mixture was allowed to warm to -50 °C and stir for 40 min, and the reaction was quenched by saturated NH_4Cl (10 mL). The organic phase was separated and the aqueous layer was extracted with EtOAc, the combined organic layers was washed with brine, dried over Na_2SO_4 , the solvent was removed under reduced pressure, the residue was purified by column chromatography (eluent: AcOEt:Hexane = 1:6) to afford the alcohol **M** (823 mg, 92%).

To a stirred solution of alcohol **M** (358 mg, 2.0 mmol) and CBr_4 (995 mg, 3.0 mmol) in DCM (10 mL) was added a solution of PPh_3 (787 mg, 3.0 mmol) in DCM (5 mL) dropwise at 0 °C. Then the resulting mixture was allowed to stir for 30 min. Then the solvent was removed and a mixture of diethyl ether and hexane (1:1, 20 mL) was added, the resulting solid was filter and wash with hexane, the filtrate was concentrated in vacuum, the residue was purified by column chromatography (eluent: AcOEt:Hexane = 1:20) to give benzyl bromide **3-14a** (123 mg, 26%) and allyl bromide **3-14b** (250 mg, 51%).

1-(1-Bromoallyl)-4-nitrobenzene (3-14a). ^1H NMR (400 MHz, CDCl_3)

δ 8.24-8.18 (m, 2H), 7.64-7.58 (m, 2H), 6.35-6.28 (m, 1H), 5.65-5.60 (m, 1H), 5.33 (dd, J = 16.8, 2.8 Hz, 1H), 5.28 (dd, J = 10.1, 2.9 Hz, 1H); ^{13}C

NMR (100 MHz, CDCl_3) δ 147.7, 147.3, 136.8, 128.9, 124.1, 118.7, 51.9.

General procedure C for the synthesis of nitroalkenes 3-2 from corresponding aldehydes.

The procedure was following the literature's procedure.¹⁶ To a stirred solution of aldehyde **S** (5.0 mmol) in THF (12 ml) and nitromethane (915 mg, 15.0 mmol) was added KOH (420 mg, 7.5 mmol, in H_2O 3.0 ml) at 0 °C and the mixture was stirred for 15 min. The reaction was quenched with satd. NH_4Cl , and the mixture was extract with AcOEt, The organic layers was washed successively with water and brine, dried over Na_2SO_4 . The solvent was removed under reduced pressure to give the crude alcohol **M**, which was used without further purification.

To a solution of the above alcohol **M** in pyridine (20 ml) was added Ac_2O (765 mg, 7.5 mmol) and DMAP (122 mg, 1 mmol) in pyridine (2 ml) at 0 °C and the mixture was stirred for 30 min. The reaction was quenched with satd. NaHCO_3 , and the mixture was extract with CH_2Cl_2 . The organic layer was washed successively with water and brine, and dried over anhyd. Na_2SO_4 . The solvent was removed under reduced pressure and the residue was purified by column chromatography to give nitroalkene **3-2**.

Preparation of nitrostyrene 3-2h.

To a stirred solution of dial **S** (1.34g, 10 mmol) in a mixture of 95% EtOH (10 ml) and THF (30 ml) was added NaBH₄ (95 mg, 2.5 mmol) at 0 °C with continuous stirring for 30 min. Then the reaction mixture was stirred at 0 °C for 6h while the temperature was maintained at 0 °C. After the reaction was completed, the reaction mixture was neutralized with 2 M HCl to PH = 5, then the solvent was evaporated, water (50 ml) was added to the residue then the resulting aqueous solution was extracted with EtOAc. The combined organic layers were washed with brine, dry over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: AcOEt:Hexane = 1:3) to afford corresponding mono-alcohol **M1** (1.08g, 79%).

The obtained alcohol **M1** (1.08g, 7.9 mmol) was dissolved in DCM (50 ml), 2,3-DHP (1.0 g, 11.9 mmol) was added follow by the addition of p-CH₃PhSO₃H (200 mg) and the reaction mixture was stirred for 1 h. Then the resulting mixture was washed with sat. NaHCO₃, brine, dried over Na₂SO₄ and then concentrated to give the residue, which was purified by column chromatography to give the aldehyde **M2** (1.56 g, 90%). Then the aldehyde **M2** was treated follow the general procedure **C** (eluent: AcOEt:Hexane = 1:8) to afford nitroalkene **M3** (1.05g, 56%).

The obtained nitroalkene **M3** (1.05g, 4.0 mmol) was dissolved in acetone (20 ml) and stirred, then HCl (2M in H₂O, 10 mL, 20 mmol) was added, then the reaction was allowed to stir at room temperature for 3h. Then the resulting mixture quenched with NaOH (2M in H₂O, 10 mL) follow by extracted with Et₂O, the combined organic layers was washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The residue was

purified by column chromatography (eluent: AcOEt:Hexane = 1:4) to give the nitroalkene **3-2h** as a white solid (616 mg, 86%). ^1H NMR (400 MHz, CDCl_3) δ 7.99 (d, J = 13.6 Hz, 1H), 7.58 (d, J = 13.7 Hz, 1H), 7.55-7.52 (m, 2H), 7.47-7.42 (m, 2H), 4.76 (s, 2H) 1.97 (brs, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 145.5, 138.9, 137.1, 129.5, 127.6, 129.3, 64.6.

Preparation of nitrostyrene **3-2n**.

The aldehyde **M** was synthesis from aldehyde **S** according to the literature's procedure¹⁷. The obtained aldehyde **M** was treated follow the general procedure **C** (eluent: AcOEt:Hexane = 1:8) to give the nitroalkene **3-2n** as a white solid (18% in total yield). ^1H NMR (400 MHz, CDCl_3) δ 8.42 (d, J = 13.5 Hz, 1H), 7.55-7.43 (m, 4H), 7.33 (td, J = 7.6, 1.5 Hz, 1H), 3.74 (s, 2H), 0.15 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 138.3, 137.4, 136.4, 132.2, 130.3, 129.0, 127.9, 127.8, 102.7, 88.9, 25.0, -0.0.

3.5.5 Characterization of the Products.

1-(2-Methyl-4-nitro-3-phenylbutan-2-yl)-4-nitrobenzene (**3-4a**).

Following the general procedure, the title compound **3-4a** (27.5 mg, 87%) was purified by column chromatography (eluent: AcOEt:Hexane = 1:4) to be obtained as a white solid, mp 127-128 °C (colourless crystal, 131-132 °C); ^1H NMR (400 MHz, CDCl_3) δ 8.22-8.17 (m, 2H), 7.54-7.49 (m, 2H), 7.31-7.27 (m, 2H), 7.10-7.04 (m, 2H), 4.77 (dd, J = 12.6, 11.8 Hz, 1H), 4.37 (dd, J = 12.9, 4.2 Hz, 1H), 3.85 (dd, J = 11.5, 4.2 Hz, 1H), 1.42 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 154.4, 146.8, 135.6, 129.5, 128.4, 128.2, 127.4, 123.8, 76.6, 54.5, 41.5, 28.2, 24.1; IR (ν cm^{-1}) 3032,

2974, 2922, 2852, 1599, 1557, 1514, 1454, 1378, 1346, 1207, 1115, 1091, 1012, 856, 763, 704; **HRMS (ESI)** calcd. for $C_{17}H_{18}N_2O_4Na$ ($M+Na$)⁺: 337.1164, Found: 337.1167.

1-(3-Ethyl-1-nitro-2-phenylpentan-3-yl)-4-nitrobenzene (3-4b).

Following the general procedure, the title compound **3-4b** (27.9 mg, 81%) was purified by column chromatography (eluent: AcOEt:Hexane = 1:4)

to be obtained as a white solid, mp 132-133 °C; **¹H NMR (400 MHz, CDCl₃)** δ 8.17-8.12 (m, 2H), 7.25-7.14 (m, 5H), 6.68-6.62 (m, 2H), 4.81 (dd, J = 12.6, 4.2 Hz, 1H), 4.45 (dd, J = 12.5, 11.6 Hz, 1H), 3.85 (dd, J = 11.5, 4.2 Hz, 1H), 2.12-1.95 (m, 2H), 1.82 (hext, J = 7.3 Hz, 1H), 1.66 (hext, J = 7.4 Hz, 1H), 0.96 (t, J = 7.3 Hz, 3H), 0.85 (t, J = 7.4 Hz, 3H); **¹³C NMR (100 MHz, CDCl₃)** δ 149.8, 146.7, 135.6, 129.6, 129.3, 128.1, 123.1, 77.2, 50.6, 47.5, 26.4, 26.4, 8.3, 8.1; **IR (ν cm⁻¹)** 3035, 2972, 2883, 1603, 1557, 1517, 1454, 1380, 1346, 1215, 1112, 850, 754, 704; **HRMS (ESI)** calcd. for $C_{19}H_{22}N_2O_4Na$ ($M+Na$)⁺: 365.1477, Found: 365.1470.

1-(3-Methyl-1-nitro-2-phenylpentan-3-yl)-4-nitrobenzene (3-4c).

Following the general procedure, the title compound **3-4c** (25.1 mg, 76%, total yield of two diastereomers) was purified by column chromatography (eluent: AcOEt:Hexane = 1:4) to give diastereomers **3-4c-a** and **3-4c-b**, dr 1.1:1, determined by ¹H NMR spectroscopy.

Diastereomer **3-4c-a**, white solid, mp 135-136 °C; **¹H NMR (400 MHz, CDCl₃)** δ 8.21-8.17 (m, 2H), 7.57-7.51 (m, 2H), 7.36-7.28 (m, 3H), 7.20-7.14 (m, 2H), 4.76 (t, J = 12.4 Hz, 1H), 4.18 (dd, J = 12.9, 3.9 Hz, 1H), 3.86 (dd, J = 11.8, 3.9 Hz, 1H), 1.98 (hext, J = 7.3 Hz, 1H), 1.41-1.30 (m, 1H), 1.36 (s, 3H), 0.52 (t, J = 7.4 Hz, 3H); **¹³C NMR (100 MHz, CDCl₃)** δ 152.5, 146.8, 135.7, 129.8, 128.5, 128.2, 128.0, 123.9, 55.3, 45.2, 33.9, 18.8, 8.3;

IR (ν cm^{-1}) 3032, 2970, 2933, 2879, 1604, 1556, 1520, 1379, 1348, 1215, 1115, 852, 754, 702; **HRMS (ESI)** calcd. for $\text{C}_{18}\text{H}_{21}\text{N}_2\text{O}_4$ ($\text{M}+\text{H}$) $^+$: 329.1501, Found: 329.1499.

Diastereomer **3-4c-b**, white solid, mp 148-149 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.15-8.09 (m, 2H), 7.30-7.25 (m, 2H), 7.21-7.12 (m, 3H), 6.85-6.79 (m, 2H), 4.78 (dd, J = 13.0, 5.6 Hz, 1H), 4.73 (dd, J = 12.8, 10.1 Hz, 1H), 3.77 (dd, J = 10.2, 5.6 Hz, 1H), 2.07 (hext, J = 7.3 Hz, 1H), 1.75 (hext, J = 7.3 Hz, 1H), 1.42 (s, 3H), 0.70 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 151.4, 146.5, 135.8, 129.4, 128.5, 128.2, 127.9, 123.3, 76.6, 55.3, 45.4, 31.4, 21.0, 8.8; **IR** (ν cm^{-1}) 3028, 2974, 2929, 1604, 1556, 1517, 1454, 1379, 1348, 1217, 1012, 856, 754, 702; **HRMS (ESI)** calcd. for $\text{C}_{18}\text{H}_{21}\text{N}_2\text{O}_4$ ($\text{M}+\text{H}$) $^+$: 329.1501, Found: 329.1499.

1-Nitro-4-(1-(2-nitro-1-phenylethyl)cyclohexyl)benzene (3-4d).

Following the general procedure, the title compound **3-4d** (30.4 mg, 86%) was purified by column chromatography (eluent: AcOEt:Hexane = 1:4)

to be obtained as a white solid, mp 124-125 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.18 (d, J = 8.5 Hz, 2H), 7.33-7.15 (m, 5H), 6.85-6.75 (m, 2H), 4.66 (dd, J = 12.6, 4.5 Hz, 1H), 4.57 (t, J = 11.8 Hz, 1H), 3.63 (dd, J = 11.0, 4.3 Hz, 1H), 2.46 (d, J = 12.0 Hz, 1H), 2.13 (d, J = 12.8 Hz, 1H), 1.67-1.53 (m, 4H), 1.25-1.02 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 149.3, 146.6, 135.3, 129.5, 128.2, 128.1, 123.5, 76.4, 55.8, 45.9, 35.2, 33.8, 26.0, 22.2, 22.0; **IR** (ν cm^{-1}) 3030, 2978, 2930, 2956, 1606, 1558, 1516, 1454, 1380, 1349, 1217, 1012, 856, 756, 701; **HRMS (ESI)** calcd. for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_4\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 377.1477, Found: 377.1472.

1-Nitro-4-(4-nitro-3-phenylbutan-2-yl)benzene (3-4e). Following the general procedure, the title compound **3-4e** (25.8 mg, 86%, total yield of two diastereomers), was purified by column chromatography (eluent:

AcOEt:Hexane = 1:4) to give diastereomers **3-4e-a** and **3-4e-b**, dr 1.1:1, determined by ^1H NMR spectroscopy.

Diastereomer **3-4e-a**, white solid, mp 116-117 °C (colourless crystal, mp 123-124 °C); ^1H NMR (400 MHz, CDCl_3) δ 8.26-8.21 (m, 2H), 7.46-7.41 (m, 2H), 7.39-7.31 (m, 3H), 7.23-7.18 (m, 2H), 4.52 (dd, J = 12.6, 10.3 Hz, 1H), 4.30 (dd, J = 12.6, 4.9 Hz, 1H), 3.65 (td, J = 10.2, 5.0 Hz, 1H), 3.15 (ddd, J = 13.9, 10.2, 6.9 Hz, 1H), 1.13 (d, J = 6.9 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 151.5, 147.4, 137.4, 129.2, 128.4, 128.3, 128.2, 124.5, 79.3, 50.9, 43.4, 20.2; IR (ν cm^{-1}) 3032, 2972, 2927, 2857, 1604, 1552, 1516, 1454, 1379, 1348, 1182, 1109, 1012, 856, 758, 702; HRMS (ESI) calcd. for $\text{C}_{16}\text{H}_{17}\text{N}_2\text{O}_4$ ($\text{M}+\text{H}$) $^+$: 301.1188, Found: 301.1187.

Diastereomer **3-4e-b**, white solid, mp 97-98 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.06-8.01 (m, 2H), 7.22-7.06 (m, 3H), 7.12-7.07 (m, 2H), 6.92-6.86 (m, 2H), 4.81 (dd, J = 12.6, 6.4 Hz, 1H), 4.68 (dd, J = 12.6, 8.9 Hz, 1H), 3.73 (td, J = 8.5, 1.9 Hz, 1H), 3.25 (pent, J = 7.4 Hz, 1H), 1.43 (d, J = 7.0 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 150.6, 146.9, 136.9, 128.9, 128.8, 128.3, 128.0, 123.6, 78.5, 50.4, 43.1, 19.4; IR (ν cm^{-1}) 3030, 2960, 2924, 2854, 1604, 1556, 1516, 1454, 1379, 1346, 1317, 1280, 1217, 1111, 1076, 1014, 856, 759, 700; HRMS (ESI) calcd. for $\text{C}_{16}\text{H}_{17}\text{N}_2\text{O}_4$ ($\text{M}+\text{H}$) $^+$: 301.1188, Found: 301.1187.

1-Nitro-4-(1-nitro-2-phenylpentan-3-yl)benzene. (3-4f). Following the general procedure, the title compound **3-4f** (24.8 mg, 79%, total yield of two diastereomers) was purified by column chromatography (eluent:

AcOEt:Hexane = 1:4) to give diastereomers **3-4f-a** and **3-4f-b**, dr 1.1:1, determined by ^1H NMR spectroscopy.

Diastereomer **3-4f-a**, white solid, mp 164-165 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.28-8.23 (m, 2H), 7.45-7.41 (m, 2H), 7.40-7.29 (m, 3H), 7.25-7.20 (m, 2H), 4.47 (dd, J = 12.5, 10.6 Hz, 1H), 4.22 (dd, J = 12.5, 4.7 Hz, 1H), 3.68 (dt, J = 10.6, 4.6 Hz, 1H), 2.88 (td, J =

10.7, 3.7 Hz, 1H), 1.55-1.40 (m, 2H), 0.58 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 149.6, 147.4, 137.9, 129.2, 129.1, 128.3, 128.1, 124.4, 79.6, 51.1, 50.2, 27.0, 11.9; IR (ν cm^{-1}) 3031, 2962, 2927, 1602, 1550, 1516, 1382, 1346, 1215, 1101, 850, 752, 698; HRMS (ESI) calcd. for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_4\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 337.1164, Found: 337.1163.

Diastereomer **3-4f-b**, white solid, mp 113-114 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.06-8.01 (m, 2H), 7.20-7.14 (m, 3H), 7.05-6.99 (m, 2H), 6.86-6.78 (m, 2H), 4.81 (dd, $J = 12.6$, 7.0 Hz, 1H), 4.63 (dd, $J = 12.8$, 8.3 Hz, 1H), 3.82 (q, $J = 7.6$ Hz, 1H), 2.98 (ddd, $J = 10.7$, 7.3, 4.6 Hz, 1H), 1.98-1.87 (m, 1H), 1.78-1.66 (m, 1H), 0.78 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 148.3, 147.0, 136.7, 129.9, 128.7, 128.5, 128.0, 123.4, 78.6, 50.6, 49.0, 26.2, 12.1; IR (ν cm^{-1}) 3030, 2966, 2934, 1607, 1556, 1518, 1454, 1379, 1346, 1182, 1109, 852, 796, 700; HRMS (ESI) calcd. for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_4\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 337.1164, Found: 337.1163.

(3-Nitro-1-(4-nitrophenyl)propane-1,2-diyl)dibenzene (3-4g).

Following the general procedure, the title compound **4g** (31.2 mg, 86%, total yield of two diastereomers) was purified by column chromatography (eluent: AcOEt:Hexane = 1:4) to give diastereomers **3-4g-a** and **3-4g-b**, dr 1.2:1, determined by ^1H NMR spectroscopy.

Diastereomer **3-4g-a**, white solid, mp 152-153 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.97-7.93 (m, 2H), 7.48-7.38 (m, 4H), 3.04-3.28 (m, 3H), 7.22-7.14 (m, 5H), 4.65-4.54 (m, 2H), 4.43-4.33 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 149.1, 146.6, 140.0, 137.2, 129.9, 129.1, 129.0, 128.4, 128.3, 128.2, 128.1, 127.9, 124.0, 123.8, 79.9, 55.2, 48.3; IR (ν cm^{-1}) 3062, 3030, 2922, 2850, 1604, 1595, 1552, 1514, 1454, 1379, 1346, 1217, 1111, 851, 831, 748, 700, 630; HRMS (ESI) calcd. for $\text{C}_{21}\text{H}_{18}\text{N}_2\text{O}_4\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 385.1164, Found: 337.1164.

Diastereomer **3-4g-b**, white solid, mp 168-169 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.27-8.21 (m, 2H), 7.67-7.62 (m, 2H), 7.23-7.10 (m, 9H), 7.08-7.03 (m, 1H), 4.64-4.57 (m, 1H),

4.53-4.46 (m, 1H), 4.43-4.36 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 149.2, 147.3, 139.9, 137.1, 128.9, 128.9, 128.9, 128.2, 128.1, 128.0, 127.3, 124.7, 79.8, 55.0, 48.2; IR ($\nu\text{ cm}^{-1}$) 3065, 3028, 2927, 2850, 1597, 1552, 1518, 1454, 1379, 1346, 1215, 1111, 1076, 856, 842, 756, 700; HRMS (ESI) calcd. for $\text{C}_{21}\text{H}_{18}\text{N}_2\text{O}_4\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 385.1164, Found: 337.1164.

1-Nitro-4-(1-nitro-2-phenylhex-5-en-3-yl)benzene (3-4h). Following the general procedure, the title compound **3-4h** (24.7 mg, 76%, total yield of two diastereomers) was purified by column chromatography

(eluent: AcOEt:Hexane = 1:6) to give diastereomers **3-4h-a** and **3-4h-b**, dr 1.1:1, determined by ^1H NMR spectroscopy.

Diastereomer **3-4h-a**, white solid, mp 142-142 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.27-8.22 (m, 2H), 7.44-7.30 (m, 5H), 7.26-7.23 (m, 2H), 5.35 (ddt, $J = 17.1, 10.0, 7.2$ Hz, 1H), 4.83 (d, $J = 9.8$ Hz, 1H), 4.74 (dd, $J = 17.1, 1.4$ Hz, 1H), 4.48 (dd, $J = 12.5, 10.6$ Hz, 1H), 4.26 (dd, $J = 12.5, 4.6$ Hz, 1H), 3.73 (td, $J = 10.6, 4.6$ Hz, 1H), 3.10 (td, $J = 10.2, 4.7$ Hz, 1H), 2.30-2.15 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 149.0, 147.4, 137.5, 134.4, 129.4, 129.2, 128.5, 128.1, 124.4, 118.0, 79.4, 49.6, 49.3, 38.3. IR ($\nu\text{ cm}^{-1}$) 3068, 3030, 2929, 2849, 1621, 1598, 1551, 1511, 1455 1380, 1346, 1215, 1108, 1078, 856, 756, 698; HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_4\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 349.1164, Found: 349.1171.

Diastereomer **3-4h-b**, colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 8.08-8.01 (m, 2H), 7.23-7.16 (m, 3H), 7.04-6.98 (m, 2H), 6.85-6.78 (m, 2H), 5.56 (ddt, $J = 17.0, 10.1, 6.8$ Hz, 1H), 5.09-4.99 (m, 2H), 4.81 (dd, $J = 12.6, 7.4$ Hz, 1H), 4.62 (dd, $J = 12.6, 8.0$ Hz, 1H), 3.89 (dd, $J = 14.6, 7.4$ Hz, 1H), 3.19 (dd, $J = 6.0, 6.4$ Hz, 1H), 2.64-2.57 (m, 1H), 2.51-2.41 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 147.7, 147.0, 136.0, 134.7, 130.1, 129.5, 128.7, 128.2, 123.4, 118.4, 78.4, 48.1, 48.1, 37.4; IR ($\nu\text{ cm}^{-1}$) 3072, 3028, 2931, 2850, 1623, 1600, 1552, 1458 1380, 1346, 1218, 1110, 1080, 856, 754, 699; HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_4\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 349.1164, Found: 349.1171.

6-Nitro-1-(2-nitro-1-phenylethyl)-1,2,3,4-tetrahydronaphthalene (3-4i).

Following the general procedure, the title compound **3-4i** (26.7 mg, 82%, total yield of two diastereomers) was purified by column chromatography (eluent: AcOEt:Hexane = 1:4) to give diastereomers **3-4i-a** and **3-4i-b**, dr 1.2 :1, determined by ^1H NMR spectroscopy.

Diastereomer **3-4i-a**, white solid, mp 135-136 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.04 (dd, $J = 8.4, 2.2$ Hz, 1H), 8.00-7.97 (m, 1H), 7.37 (d, $J = 8.4$ Hz, 1H), 7.34-7.28 (m, 3H), 7.14-7.10 (m, 2H), 4.74 (dd, $J = 12.5, 9.4$ Hz, 1H), 4.62 (dd, $J = 12.5, 6.2$ Hz, 1H), 3.82 (td, $J = 9.0, 6.3$ Hz, 1H), 3.24 (pent, $J = 4.5$ Hz, 1H), 2.86-2.78 (m, 2H), 1.88-1.78 (m, 1H), 1.73-1.62 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 146.9, 145.1, 140.0, 137.2, 130.5, 129.1, 128.2, 128.1, 124.8, 120.6, 79.4, 47.7, 41.3, 28.5, 24.2, 18.0; IR (ν cm^{-1}) 3030, 2972, 2879, 1552, 1518, 1454, 1348, 1217, 1090, 1020, 908, 852, 756, 702; HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_4\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 349.1164, Found: 349.1168.

Diastereomer **3-4i-b**, white solid, mp 148-149 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.96 (d, $J = 2.0$ Hz, 1H), 7.83 (dd, $J = 8.6, 2.3$ Hz, 1H), 7.34-7.28 (m, 3H), 7.14-7.10 (m, 2H), 7.03 (d, $J = 8.5$ Hz, 1H), 4.87 (dd, $J = 12.7, 11.2$ Hz, 1H), 4.56 (dd, $J = 12.8, 4.6$ Hz, 1H), 4.05 (ddd, $J = 11.4, 7.0, 4.6$ Hz, 1H), 3.26 (dd, $J = 12.3, 6.1$ Hz, 1H), 2.86 (t, $J = 6.3$ Hz, 1H), 2.00-1.90 (m, 1H), 1.89-1.80 (m, 1H), 1.77-1.69 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 146.6, 144.5, 139.6, 137.7, 129.5, 129.0, 128.2, 128.1, 124.4, 120.6, 76.3, 47.9, 42.8, 29.4, 24.8, 19.8; IR (ν cm^{-1}) 3026, 2972, 2880, 1552, 1517, 1454, 1346, 1215, 1092, 1019, 906, 853, 756, 702; HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_4\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 349.1164, Found: 349.1168.

Ethyl 5-nitro-3-(4-nitrophenyl)-4-phenylpentanoate (3-4j).

Following the general procedure, the title compound **3-4j** (23.9 mg, 64%, total yield of two diastereomers) was purified by column chromatography (eluent: AcOEt:Hexane = 1:3) to give diastereomers **3-4j-a** and **3-4j-b**, dr 1.1:1, determined by ^1H NMR spectroscopy.

Diastereomer **3-4j-a**, white solid, mp 154-155 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.27-8.22 (m, 2H), 7.55-7.49 (m, 2H), 7.42-7.31 (m, 3H), 7.29-7.25 (m, 2H), 4.51 (dd, J = 12.6, 10.4 Hz, 1H), 4.21 (dd, J = 12.7, 4.4 Hz, 1H), 3.91-3.80 (m, 2H), 3.77-3.68 (m, 1H), 3.61-3.53 (m, 1H), 2.55-2.42 (m, 2H), 1.01 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.8, 148.3, 147.6, 136.8, 129.5, 129.1, 128.7, 128.1, 124.4, 79.1, 60.9, 49.4, 45.3, 39.3, 14.1; IR (ν cm^{-1}) 3036, 2962, 2922, 1714, 1600, 1551, 1514, 1379, 1350, 1286, 1219, 1109, 1014, 957, 856, 760, 700; HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{21}\text{N}_2\text{O}_6$ ($\text{M}+\text{H}$) $^+$: 373.1400, Found: 373.1408.

Diastereomer **3-4j-a**, colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 8.07-8.02 (m, 2H), 7.25-7.18 (m, 3H), 7.07-7.01 (m, 2H), 6.86-6.80 (m, 2H), 4.75 (dd, J = 12.9, 7.3 Hz, 1H), 4.63 (dd, J = 12.8, 8.1 Hz, 1H), 4.11-3.98 (m, 2H), 3.89 (q, J = 7.3 Hz, 1H), 3.68 (dt, J = 8.6, 6.7 Hz, 1H), 2.85 (dd, J = 15.9, 6.5 Hz, 1H), 2.69 (dd, J = 15.9, 8.7 Hz, 1H), 1.14 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.8, 147.2, 146.8, 135.5, 129.8, 128.8, 128.7, 128.4, 123.5, 78.0, 61.2, 48.1, 44.3, 38.1, 14.2; IR (ν cm^{-1}) 3032, 2981, 2926, 2852, 1732, 1691, 1604, 1557, 1519, 1377, 1346, 1280, 1165, 1111, 1029, 957, 856, 754, 703; HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{21}\text{N}_2\text{O}_6$ ($\text{M}+\text{H}$) $^+$: 373.1400, Found: 373.1408.

1-Nitro-4-(3-nitro-2-phenylpropyl)benzene (3-4k).

Following the general procedure, the title compound **3-4k** (15.1 mg, 53%) was purified by column chromatography (eluent: AcOEt:Hexane = 1:5) to be obtained as a colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 8.09-8.04 (m, 2H), 7.32-7.27

(m, 3H), 7.17-7.12 (m, 2H), 7.10-7.06 (m, 2H), 4.65 (d, $J = 7.6$ Hz, 2H), 3.82-3.75 (m, 1H), 3.16 (dd, $J = 13.6, 5.8$ Hz, 1H), 3.06 (dd, $J = 13.6, 9.3$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 145.6, 137.7, 130.1, 129.3, 128.3, 127.7, 123.8, 79.7, 45.8, 39.6; IR (ν cm^{-1}) 3065, 3032, 2970, 2922, 2847, 1604, 1552, 1514, 1454, 1379, 1348, 1201, 1109, 1082, 1016, 850, 761, 698; HRMS (ESI) calcd. for $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_4\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 309.0851, Found: 309.0853.

1-Nitro-2-(3-nitro-2-phenylpropyl)benzene (3-4l). Following the general procedure, the title compound **3-4l** (17.8 mg, 62%) was purified by column chromatography (eluent: AcOEt:Hexane = 1:4) to be obtained as a colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 7.93 (dd, $J = 8.1, 1.3$ Hz, 1H), 7.43 (td, $J = 7.5, 1.4$ Hz, 1H), 7.36 (td, $J = 7.8, 1.5$ Hz, 1H), 7.30-7.23 (m, 2H), 7.16-7.12 (m, 2H), 7.09 (dd, $J = 7.6, 1.3$ Hz, 1H), 4.76 (dd, $J = 12.6, 9.0$ Hz, 1H), 4.67 (dd, $J = 12.6, 6.3$ Hz, 1H), 3.88 (tt, $J = 8.6, 6.6$ Hz, 1H), 3.39 (dd, $J = 13.5, 6.8$ Hz, 1H), 3.23 (dd, $J = 13.6, 8.4$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 149.5, 138.4, 133.1, 132.7, 129.2, 128.2, 128.1, 127.6, 125.3, 79.6, 45.3, 37.1; IR (ν cm^{-1}) 3064, 3030, 2953, 2922, 2982, 1608, 1554, 1516, 1454, 1379, 1346, 1201, 1176, 1085, 858, 786, 763, 700; HRMS (ESI) calcd. for $\text{C}_{15}\text{H}_{15}\text{N}_2\text{O}_4$ ($\text{M}+\text{H}$) $^+$: 287.1032, Found: 287.1035.

1-Nitro-2-(4-nitro-3-phenylbutan-2-yl)benzene (3-4m). Following the general procedure, the title compound **3-4m** (27.1 mg, 79%, total yield of two diastereomers) was purified by column chromatography (eluent: AcOEt:Hexane = 1:4) to give diastereomers **3-4m-a** and **3-4m-b**, dr 1.1:1, determined by ^1H NMR spectroscopy.

Diastereomer **3-4m-a**, colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 7.78 (dd, $J = 8.2, 1.2$ Hz, 1H), 7.69-7.59 (m, 2H), 7.44 (ddd, $J = 8.2, 7.2, 1.6$ Hz, 1H), 7.40-7.35 (m, 2H),

7.34-7.28 (m, 2H), 4.74 (dd, $J = 12.7, 10.9$ Hz, 1H), 4.25 (dd, $J = 12.7, 4.1$ Hz, 1H), 3.68 (td, $J = 11.0, 4.0$ Hz, 1H), 3.62-3.53 (m, 1H), 1.08 (d, $J = 6.7$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 150.5, 138.1, 137.9, 133.4, 129.2, 128.3, 128.2, 128.2, 124.4, 79.7, 51.6, 36.9, 21.1; IR ($\nu \text{ cm}^{-1}$) 3030, 2978, 2924, 1606, 1552, 1523, 1454, 1379, 1344, 1205, 1111, 1029, 976, 854, 756, 702, 673; HRMS (ESI) calcd. for $\text{C}_{16}\text{H}_{17}\text{N}_2\text{O}_4$ ($\text{M}+\text{H}$) $^+$: 301.1188, Found: 301.1199.

Diastereomer **3-4m-b**, colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 7.54 (dd, $J = 8.1, 1.1$ Hz, 1H), 7.47 (td, $J = 8.0, 1.1$ Hz, 1H), 7.38 (dd, $J = 7.9, 1.1$ Hz, 1H), 7.25-7.19 (m, 1H), 7.17-7.08 (m, 3H), 7.98-7.92 (m, 2H), 4.87 (dd, $J = 12.9, 4.9$ Hz, 1H), 4.70 (dd, $J = 12.7, 9.7$ Hz, 1H), 3.90-3.75 (m, 2H), 1.47 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 150.0, 138.1, 137.8, 132.6, 128.9, 128.8, 127.8, 127.8, 127.5, 124.2, 78.8, 50.1, 37.3, 19.5; IR ($\nu \text{ cm}^{-1}$) 3030, 2974, 2922, 2874, 1607, 1552, 1716, 1454, 1379, 1346, 1201, 1109, 1080, 852, 750, 700; HRMS (ESI) calcd. for $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_4$ ($\text{M}+\text{H}$) $^+$: 201.1188, Found: 301.1199.

1-Fluoro-4-(3-methyl-1-nitro-3-(4-nitrophenyl)butan-2-yl)benzene (3-6a). Following the general procedure, the title compound **3-6a** (26.9 mg, 81%) was purified by column chromatography (eluent: AcOEt:Hexane = 1:4) to be obtained as a

white solid, mp 119-120 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.23-8.17 (m, 2H), 7.53-7.46 (m, 2H), 7.08-7.02, (m, 2H), 7.01-6.94 (m, 2H), 4.71 (dd, $J = 12.3, 12.3$ Hz, 1H), 4.38 (dd, $J = 12.9, 4.2$ Hz, 1H), 3.84 (dd, $J = 11.7, 4.2$ Hz, 1H), 1.41 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 162.5 (d, $J = 247.3$ Hz), 154.0, 146.8, 131.4 (d, $J = 3.3$ Hz), 131.0 (d, $J = 8.0$ Hz), 127.4, 123.8, 115.5 (d, $J = 21.4$ Hz), 76.6, 53.9, 41.4, 28.0, 24.2; ^{19}F NMR (376 MHz, CDCl_3) δ -113.7-(-113.9) (m). IR ($\nu \text{ cm}^{-1}$) 3084, 2978, 2898, 2850, 1604, 1558, 1522, 1471, 1438, 1377, 1348, 1228, 1163, 1107, 1098, 1012, 856, 761, 739, 692, 635; HRMS (ESI) calcd. for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_4\text{F}$ ($\text{M}+\text{H}$) $^+$: 333.1251, Found: 333.1244.

1-Chloro-4-(3-methyl-1-nitro-3-(4-nitrophenyl)butan-2-yl)benzene (3-6b). Following the general procedure, the title compound **3-6b** (26.5 mg, 76%) was purified by column chromatography (eluent: AcOEt:Hexane = 1:4) to be obtained as a white solid, mp 148-149 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.23-8.16 (m, 2H), 7.52-7.46 (m, 2H), 7.28-7.24 (m, 2H), 7.03-6.97 (m, 2H), 4.71 (dd, $J = 12.5, 12.2$ Hz, 1H), 4.38 (dd, $J = 13.0, 4.2$ Hz, 1H), 3.83 (dd, $J = 11.7, 4.2$ Hz, 1H), 1.41 (s, 3H), 1.30 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 153.9, 146.9, 134.2, 134.1, 130.7, 128.7, 127.4, 123.8, 76.4, 54.0, 41.4, 28.1, 24.2; IR ($\nu \text{ cm}^{-1}$) 3032, 2974, 2921, 2850, 1597, 1554, 1514, 1435, 1377, 1348, 1115, 1091, 1012, 856, 753, 702; HRMS (ESI) calcd. for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_4$ ($\text{M}+\text{H}$) $^+$: 349.0955, Found: 349.0971.

1-Bromo-4-(3-methyl-1-nitro-3-(4-nitrophenyl)butan-2-yl)benzene (3-6c). Following the general procedure, the title compound **3-6c** (31.1 mg, 79%) was purified by column chromatography (eluent: AcOEt:Hexane = 1:4) to be obtained as a white solid, mp 163-164 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.23-8.17 (m, 2H), 7.53-7.47 (m, 2H), 7.44-7.38 (m, 2H), 6.97-6.92 (m, 2H), 4.71 (dd, $J = 12.8, 11.9$ Hz, 1H), 4.36 (dd, $J = 13.0, 4.1$ Hz, 1H), 3.81 (dd, $J = 11.6, 4.1$ Hz, 1H), 1.40 (s, 3H), 1.30 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 153.8, 146.9, 134.7, 131.6, 131.0, 127.4, 123.9, 122.3, 76.3, 54.1, 41.3, 28.1, 24.2; IR ($\nu \text{ cm}^{-1}$) 3030, 2968, 2922, 2852, 1597, 1554, 1514, 1489, 1435, 1377, 1348, 1115, 1076, 1010, 856, 821, 700; HRMS (ESI) calcd. for $\text{C}_{17}\text{H}_{17}\text{N}_2\text{O}_4\text{BrNa}$ ($\text{M}+\text{Na}$) $^+$: 415.0269, Found: 415.0270.

1-(3-Methyl-1-nitro-3-(4-nitrophenyl)butan-2-yl)-4-(trifluoromethyl)benzene (3-6d). Following the general/

procedure, the title compound **3-6d** (23.4 mg, 65%) was purified by column chromatography (eluent: AcOEt:Hexane = 1:4) to be

obtained as a white solid, mp 158-159 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.25-8.18 (m, 2H), 7.59-7.48 (m, 4H), 7.24-7.19 (m, 2H), 4.77 (dd, *J* = 13.0, 11.9 Hz, 1H), 4.40 (dd, *J* = 13.2, 4.2 Hz, 1H), 3.93 (dd, *J* = 11.7, 4.1 Hz, 1H), 1.43 (s, 3H), 1.31 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 153.6, 147.0, 139.9, 130.4, 129.8, 127.3, 125.4 (t, *J* = 3.8 Hz), 123.9, 76.2, 54.3, 41.4, 28.2, 24.1; ¹⁹F NMR (376 MHz, CDCl₃) δ -62.7; IR (ν cm⁻¹) 3018, 2978, 2923, 1605, 1558, 1519, 1454, 1377, 1350, 1327, 1215, 1170, 1120, 1070, 856, 752, 996; HRMS (ESI) calcd. for C₁₈H₁₈N₂O₄F₃ (M+Na)⁺: 383.1219, Found: 383.1210.

1-Methyl-4-(3-methyl-1-nitro-3-(4-nitrophenyl)butan-2-yl)benzene (3-6e). Following the general procedure, the title

compound **3-6e** (23.0 mg, 75%) was purified by column chromatography (eluent: AcOEt:Hexane = 1:4) to be obtained as a white solid, mp 151-152

°C; ¹H NMR (400 MHz, CDCl₃) δ 8.23-8.16 (m, 2H), 7.54-7.48 (m, 2H), 7.08 (d, *J* = 7.9 Hz, 2H), 6.95 (d, *J* = 8.0 Hz, 2H), 4.74 (dd, *J* = 12.4, 11.9 Hz, 1H), 4.35 (dd, *J* = 12.8, 4.2 Hz, 1H), 3.81 (dd, *J* = 11.6, 4.2 Hz, 1H), 2.31 (s, 3H), 1.41 (s, 3H), 1.29 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 154.5, 146.7, 137.9, 132.5, 129.3, 129.1, 127.4, 123.7, 76.7, 54.2, 41.5, 28.3, 24.1, 21.2; IR (ν cm⁻¹) 3032, 2970, 2920, 2857, 1600, 1556, 1514, 1377, 1348, 1205, 1122, 1089, 856, 806, 758, 692; HRMS (ESI) calcd. for C₁₈H₂₁N₂O₄ (M+H)⁺: 329.11501, Found: 329.1514.

1-Methoxy-4-(3-methyl-1-nitro-3-(4-nitrophenyl)butan-2-yl)benzene (3-6f). Following the general procedure, expect increasing the amount of nitrobenzyl bromide **3-1a** and aldehyde **3-3** to 0.2 mmol, the title compound **3-6f** (24.8 mg, 72%) was purified by column chromatography (eluent: AcOEt:Hexane = 1:3) to be obtained as a white solid, yield, mp 129-130 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.22-8.16 (m, 2H), 7.53-7.47 (m, 2H), 7.01-6.95 (m, 2H), 6.83-6.77 (m, 2H), 4.71 (dd, *J* = 12.2, 12.2 Hz, 1H), 4.35 (dd, *J* = 12.7, 4.2 Hz, 1H), 3.83-3.76 (m, 4H), 2.31 (s, 3H), 1.40 (s, 3H), 1.29 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 159.4, 154.5, 146.7, 130.5, 127.4, 123.7, 113.8, 76.8, 55.4, 53.9, 41.6, 28.2, 24.1; IR (ν cm⁻¹) 3071, 2957, 2924, 2855, 1604, 1555, 1514, 1463, 1379, 1331, 1296, 1182, 1120, 1087, 1033, 856, 829, 757, 692; HRMS (ESI) calcd. for C₁₈H₂₀N₂O₅Na (M+Na)⁺: 367.1270, Found: 367.1275.

1-(Allyloxy)-4-(3-methyl-1-nitro-3-(4-nitrophenyl)butan-2-yl)benzene (3-6g). Following the general procedure except increasing the amount of nitrobenzyl bromide **3-1a** and aldehyde **3-3** to 0.2 mmol, the title compound **3-6g** (26.0 mg, 70%) was purified by column chromatography (eluent: AcOEt:Hexane = 1:4) to be obtained as a white solid, mp 159-160 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.22-8.16 (m, 2H), 7.53-7.47 (m, 2H), 7.00-6.94 (m, 2H), 6.84-6.78 (m, 2H), 6.10-5.98 (m, 1H), 5.40 (dd, *J* = 17.3, 1.3 Hz, 1H), 5.29 (dd, *J* = 10.5, 1.0 Hz, 1H), 4.70 (t, *J* = 12.3 Hz, 1H), 4.52-4.47 (m, 2H), 4.35 (dd, *J* = 12.7, 4.2 Hz, 1H), 3.79 (dd, *J* = 11.6, 4.1 Hz, 1H), 1.40 (s, 3H), 1.29 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 158.4, 154.5, 146.7, 133.2, 130.5, 127.6, 127.4, 123.7, 118.0, 114.6, 76.8, 68.9, 53.9, 41.6, 28.2, 24.2; IR (ν cm⁻¹) 3078, 2954, 2924, 2852, 1625, 1600, 1548, 1514, 1462, 1381, 1350, 1246, 1192, 1089, 1031, 948, 858, 761, 698; HRMS (ESI) calcd. for C₂₀H₂₂N₂O₅Na (M+Na)⁺: 393.1426, Found: 393.1428.

(4-(3-Methyl-1-nitro-3-(4-nitrophenyl)butan-2-yl)phenyl)methanol (3-6h). Following the general procedure expect increasing the amount of nitrobenzyl bromide **1a** and aldehyde **3-3** to 0.2 mmol, the title compound **3-6h** (24.0 mg, 70%) was purified by column chromatography (eluent: AcOEt:Hexane = 1:2) to be obtained as a white solid, mp 130-131 °C; **¹H NMR (400 MHz, CDCl₃)** δ 8.22-8.16 (m, 2H), 7.54-7.49 (m, 2H), 7.30-7.26 (m, 2H), 7.10-7.04 (m, 2H), 4.76 (dd, *J* = 12.6, 11.6 Hz, 1H), 4.66 (s, 2H), 4.36 (dd, *J* = 12.9, 4.2 Hz, 1H), 3.85 (dd, *J* = 11.7, 4.1 Hz, 1H), 1.84 (brs, 1H), 1.41 (s, 3H), 1.30 (s, 3H); **¹³C NMR (100 MHz, CDCl₃)** δ 154.3, 146.8, 140.8, 134.9, 129.6, 127.4, 126.9, 123.8, 76.6, 64.9, 54.3, 41.5, 28.3, 24.0; **IR (ν cm⁻¹)** 3398, 2974, 2922, 2851, 1604, 1556, 1514, 1379, 1348, 1298, 1115, 1089, 1012, 856, 758, 702; **HRMS (ESI)** calcd. for C₁₈H₂₀N₂O₅Na (M+Na)⁺: 367.1270, Found: 367.1272.

1-Bromo-3-(3-methyl-1-nitro-3-(4-nitrophenyl)butan-2-yl)benzene (3-6i). Following the general procedure, the title compound **3-6i** (28.3 mg, 72%) was purified by column chromatography (eluent: AcOEt:Hexane = 1:4) to be obtained as a white solid, mp 114-115 °C; **¹H NMR (400 MHz, CDCl₃)** δ 8.23-8.18 (m, 2H), 7.54-7.46 (m, 2H), 7.44-7.39 (m, 1H), 7.23 (t, *J* = 3.8 Hz, 1H), 7.16 (t, *J* = 7.8 Hz, 1H), 7.00 (d, *J* = 7.8 Hz, 1H), 4.71 (dd, *J* = 13.0, 11.8 Hz, 1H), 4.36 (dd, *J* = 13.1, 4.1 Hz, 1H), 3.81 (dd, *J* = 11.5, 4.1 Hz, 1H), 1.42 (s, 3H), 1.30 (s, 3H); **¹³C NMR (100 MHz, CDCl₃)** δ 153.7, 146.8, 138.0, 132.4, 131.3, 129.8, 127.8, 127.2, 123.7, 122.4, 76.1, 54.1, 41.3, 28.1, 23.9; **IR (ν cm⁻¹)** 3031, 2974, 2922, 2851, 1597, 1556, 1514, 1475, 1433, 1346, 1265, 1089, 1012, 854, 736, 700; **HRMS (ESI)** calcd. for C₁₇H₁₇N₂O₄BrNa (M+Na)⁺: 415.0269, Found: 415.0270.

1-(3-Methyl-1-nitro-3-(4-nitrophenyl)butan-2-yl)-3-nitrobenzene (3-6j). Following the general procedure, the title **3-6j** (23.0 mg, 64%) was purified by column chromatography (eluent: AcOEt:Hexane = 1:3) to be obtained as a white solid, mp 148-149

°C; **¹H NMR (400 MHz, CDCl₃)** δ 8.25-8.20 (m, 2H), 8.19-8.14 (m, 1H), 7.55-7.50 (m, 2H), 7.48 (t, J = 8.0 Hz, 1H), 7.42-7.37 (m, 1H), 4.81 (dd, J = 13.1, 11.9 Hz, 1H), 4.46 (dd, J = 13.2, 4.0 Hz, 1H), 3.99 (dd, J = 11.8, 4.0 Hz, 1H), 1.46 (s, 3H), 1.36 (s, 3H); **¹³C NMR (100 MHz, CDCl₃)** δ 153.2, 148.2, 147.0, 138.0, 135.5, 129.5, 127.3, 124.0, 123.3, 76.1, 54.3, 41.4, 27.9, 24.2; **IR (ν cm⁻¹)** 3031, 2976, 2924, 1604, 1556, 1529, 1439, 1377, 1348, 1176, 1091, 1012, 856, 792, 734, 698; **HRMS (ESI)** calcd. for C₁₇H₁₇N₃O₆Na (M+Na)⁺: 382.1015, Found: 382.1018.

1-Methoxy-3-(3-methyl-1-nitro-3-(4-nitrophenyl)butan-2-yl)benzene (3-6k). Following the general procedure, the title compound **3-6k** (25.2 mg, 73%) was purified by column chromatography (eluent: AcOEt:Hexane = 1:4) to be obtained as

a white solid, mp 104-105 °C; **¹H NMR (400 MHz, CDCl₃)** δ 8.22-8.16 (m, 2H), 7.55-7.49 (m, 2H), 7.19 (t, J = 7.9 Hz, 1H), 6.80 (dd, J = 8.2, 2.4 Hz, 1H), 6.66 (d, J = 7.7 Hz, 1H), 6.60 (t, J = 1.8 Hz, 1H), 4.74 (dd, J = 12.8, 11.6 Hz, 1H), 4.35 (dd, J = 13.0, 4.2 Hz, 1H), 3.82 (dd, J = 11.5, 4.2 Hz, 1H), 3.75 (s, 3H), 1.43 (s, 3H), 1.31 (s, 3H); **¹³C NMR (100 MHz, CDCl₃)** δ 159.4, 154.4, 146.8, 137.2, 129.4, 127.4, 123.7, 121.7, 116.1, 112.9, 76.6, 55.3, 54.5, 41.5, 28.3, 24.2; **IR (ν cm⁻¹)** 3082, 2872, 2939, 2837, 1602, 1556, 1514, 1495, 1435, 1379, 1348, 1261, 1115, 1042, 858, 787, 734, 702; **HRMS (ESI)** calcd. for C₁₈H₂₁N₂O₅ (M+H)⁺: 345.1450, Found: 345.1445.

1-Bromo-2-(3-methyl-1-nitro-3-(4-nitrophenyl)butan-2-yl)benzene (3-6l). Following the general procedure, the title compound **3-6l** (35.0 mg, 89%) was purified by column chromatography (eluent: AcOEt:Hexane = 1:4) to be obtained as a white solid, mp 150-151 °C;

¹H NMR (400 MHz, CDCl₃) δ 8.26-8.21 (m, 2H), 7.68-7.61 (m, 3H), 7.32 (td, *J* = 7.5, 0.8 Hz, 1H), 7.20-7.14 (m, 2H), 4.76-4.64 (m, 2H), 4.28 (dd, *J* = 11.3, 2.2 Hz, 1H), 1.46 (s, 3H), 1.33 (s, 3H); **¹³C NMR (100 MHz, CDCl₃)** δ 154.3, 146.9, 135.7, 134.0, 129.6, 128.4, 128.1, 127.6, 127.6, 123.9, 76.8, 51.0, 42.5, 28.4, 23.0; **IR (ν cm⁻¹)** 3066, 2978, 2885, 2854, 1597, 1556, 1519, 1469, 1435, 1377, 1348, 1298, 1193, 1089, 1022, 856, 753, 700; **HRMS (ESI)** calcd. for C₁₇H₁₈N₂O₄Br (M+H)⁺: 393.0450, Found: 393.0444.

1-Ethynyl-2-(3-methyl-1-nitro-3-(4-nitrophenyl)butan-2-yl)benzene (3-6m). Following the general procedure, except increasing the amount of nitrobenzyl bromide **3-1a** and aldehyde **3-3** to 0.2 mmol, the title compound **3-6m** (30.8 mg, 91%) was purified by column

chromatography (eluent: AcOEt:Hexane = 1:4) to be obtained as a white solid, mp 124-125 °C; **¹H NMR (400 MHz, CDCl₃)** δ 8.26-8.21 (m, 2H), 7.67-7.63 (m, 2H), 7.57 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.36 (t, *J* = 7.2 Hz, 1H), 7.30-7.26 (m, 1H), 7.20-7.15 (m, 1H), 4.83-4.65 (m, 2H), 4.26 (dd, *J* = 12.0, 2.6 Hz, 1H), 3.49 (s, 1H), 1.44 (s, 3H), 1.30 (s, 3H); **¹³C NMR (100 MHz, CDCl₃)** δ 154.3, 146.8, 133.2, 133.0, 133.0, 128.6, 128.1, 128.0, 127.7, 127.5, 127.2, 126.6, 126.5, 123.8, 76.7, 54.6, 41.8, 28.5, 24.2; **IR (ν cm⁻¹)** 3292, 3031, 2964, 2924, 2854, 2126, 1597, 1557, 1518, 1377, 1348, 1215, 1114, 1087, 1012, 856, 759, 702; **HRMS (ESI)** calcd. for C₁₉H₁₈N₂O₄Na (M+Na)⁺: 361.1164, Found: 361.1176.

Trimethyl(3-(2-(3-methyl-1-nitro-3-(4-nitrophenyl)butan-2-yl)phenyl)prop-1-yn-1-yl)silane (3-6n).

Following the general procedure except increasing the amount of nitrobenzyl bromide **1a** and aldehyde **3** to 0.2 mmol, the title compound **3-6n** (31.9 mg, 79%) was purified by column chromatography (eluent: AcOEt:Hexane = 1:4) to be obtained as a colorless oil; **¹H NMR (400 MHz, CDCl₃)** δ 8.24-8.18 (m, 2H), 7.61-7.53 (m, 3H), 7.30 (td, J = 7.5, 1.2 Hz, 1H), 7.23 (td, J = 7.6, 1.4 Hz, 1H), 7.04 (dd, J = 7.7, 1.0 Hz, 1H), 4.68 (dd, J = 13.0, 11.3 Hz, 1H), 4.37 (dd, J = 13.0, 4.3 Hz, 1H), 4.16 (dd, J = 11.2, 4.3 Hz, 1H), 3.76 (d, J = 18.9 Hz, 1H), 3.66 (d, J = 18.9 Hz, 1H), 1.49 (s, 3H), 1.33 (s, 3H), 0.19 (s, 9H); **¹³C NMR (100 MHz, CDCl₃)** δ 154.4, 146.9, 136.5, 134.2, 129.9, 128.4, 127.7, 127.1, 126.9, 123.8, 103.6, 88.5, 77.5, 47.5, 42.3, 28.3, 24.4, 24.1, 0.1; **IR (ν cm⁻¹)** 3032, 2962, 2921, 2849, 2175, 1604, 1556, 1520, 1377, 1348, 1249, 1217, 1114, 1024, 844, 758, 700; **HRMS (ESI)** calcd. for C₂₃H₂₉N₂O₄Si (M+H)⁺: 425.1897, Found: 425.1906.

(3-Methyl-1-nitro-3-(4-nitrophenyl)butan-2-yl)-2-vinylbenzene (3-6o).

Following the general procedure except increasing the amount of nitrobenzyl bromide **3-1a** and aldehyde **3-3** to 0.2 mmol, the title compound **3-6o** (31.8 mg, 86%) was purified by column chromatography (eluent: AcOEt:Hexane = 1:4) to be obtained as a colorless oil; **¹H NMR (400 MHz, CDCl₃)** δ 8.22-8.16 (m, 2H), 7.54-7.48 (m, 2H), 7.44-7.39 (m, 1H), 7.30-7.23 (m, 2H), 7.14 (dd, J = 17.2, 10.9 Hz, 1H), 7.09-7.03 (m, 1H), 5.54 (dd, J = 17.2, 1.3 Hz, 1H), 5.40 (dd, J = 10.9, 1.3 Hz, 1H), 4.75 (dd, J = 13.7, 12.4 Hz, 1H), 4.38-4.31 (m, 2H), 1.43 (s, 3H), 1.23 (s, 3H); **¹³C NMR (100 MHz, CDCl₃)** δ 154.5, 146.8, 140.4, 135.5, 133.5, 128.2, 128.0, 127.6, 127.5, 126.8, 123.7, 118.2, 77.1, 47.8, 42.5, 28.1, 23.9. **IR (ν cm⁻¹)** 3068, 2978, 2898, 1626, 1604, 1556, 1520, 1435, 1346, 1298, 1215, 1189, 1012, 912, 856,

771, 732, 698; **HRMS (ESI)** calcd. for $C_{19}H_{20}N_2O_4Na$ ($M+Na$)⁺: 363.1321, Found: 393.1319.

2-(3-Methyl-1-nitro-3-(4-nitrophenyl)butan-2-

yl)naphthalene(3-6p). Following the general procedure except

increasing the amount of nitrobenzyl bromide **3-1a** and aldehyde

3-3 to 0.2 mmol, the title compound **3-6p** (31.8 mg, 87%) was purified by column chromatography (eluent: AcOEt:Hexane = 1:4) to be obtained as a white solid, mp 143-144 °C; **¹H NMR (400 MHz, CDCl₃)** δ 8.24-8.17 (m, 2H), 7.85-7.74 (m, 3H), 7.58-7.53 (m, 3H), 7.52-7.46 (m, 2H), 7.17 (dd, $J = 8.5, 1.5$ Hz, 1H), 4.89 (dd, $J = 12.6, 12.0$ Hz, 1H), 4.45 (dd, $J = 13.0, 4.1$ Hz, 1H), 4.01 (dd, $J = 11.5, 4.1$ Hz, 1H), 1.47 (s, 3H), 1.35 (s, 1H); **¹³C NMR (100 MHz, CDCl₃)** δ 154.3, 146.8, 133.2, 133.0, 133.0, 128.6, 128.1, 128.0, 127.7, 127.5, 127.2, 126.6, 126.5, 123.8, 76.7, 54.6, 41.8, 28.5, 24.2; **IR (ν cm⁻¹)** 3057, 3022, 2959, 2924, 2855, 1599, 1557, 1514, 1469, 1377, 1346, 1215, 1115, 1089, 1014, 858, 819, 758, 702; **HRMS (ESI)** calcd. for $C_{21}H_{21}N_2O_4$ ($M+H$)⁺: 365.1501, Found: 365.1499.

2-(3-Methyl-1-nitro-3-(4-nitrophenyl)butan-2-yl)thiophene (3-6q).

Following the general procedure, the title compound **3-6q** (24.4 mg,

76%) was purified by column chromatography (eluent: AcOEt:Hexane

= 1:4) to be obtained as a yellow solid, mp 120-121 °C; **¹H NMR (400 MHz, CDCl₃)** δ 8.23-8.17 (m, 2H), 7.58-7.52 (m, 2H), 7.20 (d, $J = 5.1$ Hz, 1H), 6.93 (dd, $J = 5.1, 3.6$ Hz, 1H), 6.82 (d, $J = 3.4$ Hz, 1H), 4.66 (dd, $J = 12.7, 11.5$ Hz, 1H), 4.39 (dd, $J = 12.8, 3.8$ Hz, 1H), 4.18 (dd, $J = 11.4, 3.8$ Hz, 1H), 1.51 (s, 3H), 1.37 (s, 3H); **¹³C NMR (100 MHz, CDCl₃)** δ 154.2, 146.8, 138.2, 127.6, 127.3, 126.9, 125.4, 123.9, 78.0, 50.3, 41.6, 28.0, 24.2; **IR (ν cm⁻¹)** 3035, 2974, 2924, 2852, 1604, 1556, 1514, 1433, 1377, 1348, 1217, 1091,

1012, 852, 758, 700; **HRMS (ESI)** calcd. for $C_{15}H_{17}N_2O_4S$ ($M+H$)⁺: 321.0909, Found: 321.0916.

2-(3-Methyl-1-nitro-3-(4-nitrophenyl)butan-2-yl)furan (3-6r).

Following the general procedure, the title compound **3-6r** (20.1 mg, 66%) was purified by column chromatography (eluent: AcOEt:Hexane = 1:4) to be obtained as a white solid, mp 115-116 °C; **¹H NMR (400 MHz, CDCl₃)** δ 8.23-8.17 (m, 2H), 7.56-7.51 (m, 2H), 7.35 (d, J = 1.1 Hz, 1H), 6.30 (dd, J = 3.0, 2.1 Hz, 1H), 6.11 (d, J = 3.2 Hz, 1H), 4.73 (dd, J = 12.7, 11.5 Hz, 1H), 4.25 (dd, J = 12.9, 3.7 Hz, 1H), 3.99 (dd, J = 11.3, 3.6 Hz, 1H), 1.44 (s, 3H), 1.35 (s, 3H); **¹³C NMR (100 MHz, CDCl₃)** δ 154.2, 150.2, 146.8, 142.6, 127.1, 123.9, 110.6, 109.8, 75.3, 48.4, 41.7, 28.4, 24.1; **IR (ν cm⁻¹)** 3020, 2976, 2922, 1604, 1558, 1517, 1375, 1350, 1215, 1149, 1016, 854, 754, 700, 669; **HRMS (ESI)** calcd. for $C_{15}H_{17}N_2O_5$ ($M+H$)⁺: 305.1137, Found: 305.1140.

3-(3-Methyl-1-nitro-3-(4-nitrophenyl)butan-2-yl)pyridine (3-6s).

Following the general procedure, the title compound **3-6s** (19.3 mg, 61%) was purified by column chromatography (eluent: AcOEt:Hexane = 1:3) to be obtained as a colorless oil; **¹H NMR (400 MHz, CDCl₃)** δ 8.53 (dd, J = 4.7, 1.2 Hz, 1H), 8.38 (d, J = 1.9 Hz, 1H), 8.23-8.18 (m, 2H), 7.53-7.48 (m, 2H), 7.39 (dt, J = 8.0, 2.0 Hz, 1H), 7.24 (dd, J = 7.9, 4.8 Hz, 1H), 4.76 (dd, J = 13.0, 11.7 Hz, 1H), 4.44 (dd, J = 13.1, 4.2 Hz, 1H), 3.87 (dd, J = 11.6, 4.2 Hz, 1H), 1.44 (s, 3H), 1.32 (s, 3H); **¹³C NMR (100 MHz, CDCl₃)** δ 153.4, 150.8, 149.6, 147.0, 136.3, 131.5, 127.3, 124.0, 123.3, 76.0, 52.3, 41.4, 27.8, 24.2. **IR (ν cm⁻¹)** 3032, 2976, 2924, 2851, 1597, 1556, 1514, 1429, 1379, 1348, 1217, 1117, 1091, 1026, 856, 752, 717, 700; **HRMS (ESI)** calcd. for $C_{16}H_{18}N_3O_4$ ($M+H$)⁺: 316.1297, Found: 316.1297.

Using bromide **3-14a** or **3-14b** as the substrates:

Following the general procedure, using bromide **3-14a** or **3-14b** (0.3 mmol), nitrostyrene **3-2a** (0.2 mmol), aldehyde **3-3** (0.3 mmol) as substrates, NHC **3-C1** (0.01 mmol) as catalyst, DIEA (0.4 mmol) as base and CH₃OH (4 ml) as solvent, the reaction gave similar outcome: 1-Nitro-4-(5-nitro-4-phenylpent-1-en-3-yl)benzene (**3-15a**) and 1-Nitro-4-(5-nitro-4-phenylpent-1-en-1-yl)benzene (**3-15b**) was purified by column chromatography (eluent: AcOEt:Hexane = 1:6) to be obtained in 32% (20.2 mg, total yield of two diastereomers) and 18% (11.2 mg) yields, respectively.

1-Nitro-4-(5-nitro-4-phenylpent-1-en-3-yl)benzene (3-15a).

Diastereomer **3-15a-a**, white solid, mp 115-116 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.23-8.17 (m, 2H), 7.35-7.28 (m, 5H), 7.09-7.03 (m, 2H), 5.84

(ddd, *J* = 17.1, 10.2, 8.4 Hz, 1H), 5.12 (d, *J* = 10.3 Hz, 1H), 4.99 (d, *J* = 17.0 Hz, 1H), 4.58 (dd, *J* = 12.8, 8.6 Hz, 1H), 4.52 (dd, *J* = 12.8, 6.1 Hz, 1H), 3.85 (td, *J* = 8.4, 6.1 Hz, 1H), 3.77 (t, *J* = 8.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 148.6, 147.3, 136.2, 135.9, 129.0, 129.0, 128.6, 128.4, 124.3, 119.3, 52.7, 9.2; IR (ν cm⁻¹) 3080, 3032, 2922, 1631, 1697, 1552, 1517, 1454, 1379, 1346, 1182, 1109, 985, 926, 854, 837, 854, 704, 650; HRMS (ESI) calcd. for C₁₇H₁₇N₂O₄ (M+H)⁺: 313.1188, Found: 313.1187.

Diastereomer **3-15a-b**, white solid, mp 95-96 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.03-7.98 (m, 2H), 7.19-7.10 (m, 5H), 7.01-6.96 (m, 2H), 6.06 (td, *J* = 16.7, 9.8 Hz, 1H), 5.34 (td, *J* = 16.0, 0.8 Hz, 1H), 5.28 (dd, *J* = 10.0, 0.8 Hz, 1H), 4.88 (dd, *J* = 12.9, 5.3 Hz, 1H), 4.67 (dd, *J* = 13.0, 9.6 Hz, 1H), 3.91-3.82 (m, 1H), 3.68 (t, *J* = 10.0 Hz, 1H); ¹³C NMR

(100 MHz, CDCl₃) δ 148.5, 146.8, 137.4, 136.9, 129.0, 128.8, 128.1, 123.9, 119.2, 79.3, 54.8, 48.6; IR (ν cm⁻¹) 3082, 3030, 2922, 2792, 1639, 1599, 1552, 1519, 1545, 1433, 1379, 1346, 1217, 1109, 931, 852, 831, 754, 700, 655; HRMS (ESI) calcd. for C₁₇H₁₇N₂O₄ (M+H)⁺: 313.1188, Found: 313.1187.

1-Nitro-4-(5-nitro-4-phenylpent-1-en-1-yl)benzene (3-15b).

Colorless oil; ¹H NMR (400 MHz, CDCl₃) δ 8.16-8.11 (m, 2H), 7.40-7.34 (m, 4H), 7.33-7.28 (m, 1H), 7.25-7.20 (m, 2H), 6.47 (d, J = 15.8 Hz, 1H), 6.20 (td, J = 15.8, 7.3 Hz, 1H), 4.67 (dd, J = 12.4, 7.6 Hz, 1H), 4.62 (dd, J = 12.5, 7.6 Hz, 1H), 3.68 (pent, J = 7.4 Hz, 1H), 2.74-2.64 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 147.0, 143.4, 138.7, 131.5, 131.0, 129.3, 128.1, 127.6, 126.8, 124.1, 80.0, 44.1, 37.1; IR (ν cm⁻¹) 3076, 3030, 2922, 2861, 1651, 1596, 1548, 1514, 1454, 1379, 1340, 1182, 1109, 972, 858, 761, 744, 700, 651; HRMS (ESI) calcd. for C₁₇H₁₇N₂O₄ (M+H)⁺: 313.1188, Found: 313.1187.

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Chapter 4

Carbene-catalyzed Reductive Coupling of Nitrobenzyl Bromides and Activated Ketones or Imines via Single-electron-transfer Process

4.1 Introduction

4.1.1 NHC-Catalyzed Radical Reactions.

The NHC-organocatalysis was growing very fast over the past decades, and a great number of novel synthetic methodologies via different catalytic activation modes were developed by chemists and utilized in organic synthesis.¹ However, almost all the existing methodologies contained electron-pair transfer as the key process, and the example of the reaction containing SET process in the possible pathway were very few in the literature. Fortunately, recent years, contributed by Studer,² Rehbein³, Rovis,⁴ Ye,⁵ and our groups,⁶ the NHC-catalyzed reactions containing SET process were widely studied, and several interesting reactions were developed, these reactions proceed via the reaction pathway mimicking the TPP-catalyzed oxidative decarboxylation of pyruvate in living system.⁷ The NHC-catalyzed reactions involving SET process would generate interesting intermediates bearing special relativities compared with the intermediates generated via electron-pair transfer ones. The development of NHC-catalyzed radical reaction would be an important component in NHC-catalysis.

4.1.2 Our Proposal.

Our previous work described a reductive cross coupling of nitrobenzyl bromides with nitroalkenes via SET process catalyzed by NHC organocatalyst. The proposed reaction pathway was that, nitrobenzyl bromide underwent single-electron reduced via SET process followed by debromination gave the nitrobenzyl radical intermediate, then this radical conjugated addition to nitroalkenes provided the cross-coupling products. The desired product generated from a formal 1,4-addition process (Scheme 4.1).⁸

Scheme 4.1 Proposed pathway of our previous work of 1,4-addition of benzyl radical to nitroalkenes.

The ketone and imine derivatives can be attacked by radicals.⁸ The general reaction pathway underwent a formal 1,2-addition process: radical nucleophilic attacked the carbon-hetero double bond to general corresponding heteroatom-center radical intermediate, which was then further reduced to anion followed by protonation to give the adduct (Scheme 4.2).

Scheme 4.2 Radical 1,2-addition of alkyl radical to carbon-carbon double bond.

Inspired by this radical 1,2-addition process and our previous radical 1,4-addition process, we proposed that the nitrobenzyl radical that was generated in our previous reaction system can also react with ketones or imines via a formal 1,2-addition process to generate the corresponding reductive cross-coupling products (Scheme 4.3).

Scheme 4.3 Proposed 1,2-addition of benzyl radical to C=X double bond.

4.2 Results and Discussions

4.2.1 Reductive Coupling with α,β -unsaturated-ketoester

We first introduced α,β -unsaturated ketoester **4-2a** as the coupling partner, and used this ketone with 4-nitrobenzyl **4-1a** as model substrate to optimize the reaction condition. Key results were described in Table 4.1. We found that under similar conditions of the reductive coupling reaction of nitrobenzyl bromide with nitroalkenes: 1.5 equiv. of **4-1a**, 1.5 equiv. aldehyde **4-3a** as reductant, 5 mol% **4-C1** as catalyst, 150 mol% DIPEA as base, carried out in CH₃OH at rt, the desired coupling product **4-4a** was produced in 75% yield (entry 1). With the absent of NHC (entry 2), aldehyde (entry 3), the desired product could not be observed. And using benzyl bromide without nitro-group on the phenyl ring, the reaction also could not occur (entries 4-6). And when introducing non-substituted (entry 7) or electron-rich (entry 8) aldehydes as reductants, the reaction yield were significantly dropped, giving the desired product **4-4a** in very low yields. Electron-rich thiazolium salt **4-C2**, **4-C4** (entries 9, 10) and diazolium **4-C4** (entry 11) as catalysts also provided **4-4a** in very low yields, and thiazolium salt **4-C5** was inactive in this catalytic reaction.

Table 4.1 Conditional Optimization.^a

<div style="display: flex; justify-content: space-around; align-items: flex-start;"> <div style="text-align: center;"> <p>4-1a, 0.15 mmol</p> </div> <div style="text-align: center;"> <p>4-2a, 0.1 mmol</p> </div> </div> <p style="text-align: center;">5 mol % NHC precursor 150 mol % DIPEA CH₃OH, rt, 8h</p> <div style="display: flex; justify-content: space-around; align-items: flex-start;"> <div style="text-align: center;"> <p>4-4a</p> </div> <div style="text-align: center;"> <p>+ ArCO₂CH₃ (4-5)</p> </div> </div> <div style="border: 1px dashed gray; padding: 5px; margin-top: 10px;"> <div style="display: flex; justify-content: space-around;"> <div style="text-align: center;"> <p>R₁ = NO₂, 4-1a CF₃, 4-1b H, 4-1c CH₃O, 4-1d</p> </div> <div style="text-align: center;"> <p>R₂ = CO₂CH₃, 4-3a H, 4-3b CH₃O, 4-3c</p> </div> <div style="text-align: center;"> <p>Ar = C₆F₅, 3-C1 Ph, 3-C2 Mes, 3-C3</p> </div> <div style="text-align: center;"> <p>4-C4</p> </div> <div style="text-align: center;"> <p>4-C5</p> </div> </div> </div>				
entry	benzyl bromide	aldehyde	NHC	yield (%) ^a
1	4-1a	4-3a	3-C1	78(75) ^b
2	4-1a	4-3a	w/o	ND
3	4-1a	w/o	3-C1	ND
4	4-1b	4-3a	3-C1	ND
5	4-1c	4-3a	3-C1	ND
6	4-1d	4-3a	3-C1	ND
7	4-1a	4-3b	3-C1	36
8	4-1a	4-3c	3-C1	27
9	4-1a	4-3a	3-C2	35
10	4-1a	4-3a	3-C3	29
11	4-1a	4-1a	3-C4	23
12	4-1a	4-1a	3-C5	ND

^a**4-1a** to **4-1d** (0.15 mmol), **4-2a** (0.10 mmol, 19.0 mg), NHC pre-catalyst **4-C1** to **4-C5** (5 mol %), aldehyde **3** (0.15 mmol), DIPEA (0.15 mmol, 25 μ l), CH₃OH (1.0 ml), 8 h. Yields were estimated via ¹H NMR analysis. ^bIsolated yield after SiO₂ chromatography.

With optimized conditions in hand, we turn our attention to examine the generality of the substrates. We first utilized α,β -unsaturated ketoester **4-2a** as the model substrate to test the different nitrobenzyl bromides. Similar with our previous research on reductive coupling with nitroalkenes, the nitro group substituted on para- and ortho-position of the phenyl ring was both tolerated in the reaction, giving the corresponding products in good yields (**4-4a** and **4-4b**, respectively), while substitution on meta-position could not lead to the desired product at all. Introducing one additional substituent to meta- or ortho-position of para-nitrobenzyl bromide also work fine, giving the desired product in moderated yields (**4-4c**, **4-4d**). Not only para-nitrobenzyl bromide, but the ortho-nitrobenzyl bromide bearing additional functional group on para-position (**4-4e~4-4h**) or meta-position (**4-4i**) also gave

positive results as well. Both electron-withdrawing (such as $-\text{CN}$, $-\text{CO}_2\text{CH}_3$, $-\text{COCH}_3$, $-\text{Cl}$) and electron-donating groups (such as $-\text{CH}_3\text{O}$) as additional substituent were tolerated, and substitution containing unprotected hydroxy group had less effect on the reaction yield (**4-4h**). In the preparation of Grignard reagents, these electron-withdrawing group were sensitive, thus alkyl halide bearing these usually could not be used as substrates.⁹ Placing two additional strong electron-donating group on the substrate also led to the desired product in moderate yield (**4-4j**). Placing substituents on para-nitrobenzyl bromide could also proceed smoothly even if high steric hindrance on the benzyl carbon was presented, providing the desired tertiary alcohols in good yields (**4-4k**, **4-4l**).

Table 4.2 Reaction Scope of nitrobenzyl bromides^a

^aReaction condition as in Table 4.1, entry 1. ^bIsolated yield.

Then the generality of α,β -unsaturated ketoesters was investigated utilizing para-nitrobenzyl bromide **4-1a** as model substrate (Table 4.3). We found that α,β -unsaturated

ketoesters bearing electron-withdrawing groups or electron-donating groups on ortho-, meta-, or para-position of β -phenyl ring were all tolerated, the corresponding tertiary alcohols were obtained in good yields (**4-4m~4-4r**). β -Hetero-aryl substituted α,β -unsaturated ketoester also worked fine (**4-4s**). The phenyl unit could also be replaced to phenylethenyl (**4-4t**) and phenylethyl unit (**4-4u**), and the corresponding tertiary alcohols were provided in good yields. Replacing the unsaturated unit from carbon-carbon double bond to phenyl group also provided the desired product in moderate yield (**4-4v**). However, when the unsaturated unit was changed to a saturated one, the cross-coupling product could not be observed. The replacement of carbon-carbon double with carbon-carbon triple bond in the ketoester substrates **4-2** worked smoothly as well, and the desired product were obtained in good yields (**4-4x~4-4z**).

Table 4.3 Reaction Scope of α,β -Unsaturated Ketoesters^a

^aReaction condition as in Table 4.1, entry 1. ^bIsolated yield.

The reductive cross-coupling product could be easily transformed to other useful molecules (Scheme 4.4). For example, the nitro group of product **4-4b** could be reduced to amine group, and the resulting intermediate would undergo an intramolecular cyclization to give lactam **4-4b-1** containing a quinolone core structure, which was the core structure in many nature products and bioactive molecules.¹⁰ What's more, the product **4-4b** could undergo a epoxidation procedure by the oxidation of mCPBA to give the corresponding product **4-4b-2** in 87% yield with excellent diastereoselectivity (only one diastereomer was observed). And when treated with PBr₃, the hydroxy group in tertiary alcohol **4-4b** could undergo a formal 1,3-migration procedure to generate a γ -hydroxy- α,β -unsaturated ester **4-4b-3**.

Scheme 4.4 Synthetic transformations of coupling product **4-4b**.

4.2.2 Reductive Coupling with isatins

Besides α,β -unsaturated ketoesters, the isatins derivatives were also introduced to reductive coupling with nitrobenzyl bromides to synthesis the corresponding tertiary alcohols under our standard reaction conditions. First we screened the generality of nitrobenzyl bromides **4-1** using benzyl protected isatin **4-6a** as model substrate (Table 4.4). Under our standard conditions, the para-nitrobenzyl bromide and para-nitrobenzyl bromides with additional functional group on meta- or ortho-position proceed successfully,

and the desired products were isolated in good yields (**4-7a~4-7c**). Ortho-nitrobenzyl bromide and ortho-nitrobenzyl bromide bearing additional substituent on para- or meta-position led to provide the desired products in good yields as well (**4-7d~4-7i**). The unprotected hydroxy group was tolerated in the reaction (**4-7h**). α,α -Methyl-4-nitrobenzyl bromide a substrate could also provide the corresponding tertiary alcohol in good yield (**4-7j**).

Table 4.4 Reaction Scope of nitrobenzyl bromides^{a, b}

^aReaction condition as in Table 4.1, entry 1. ^bIsolated yield.

Then the scope of isatin derivatives was investigated (Table 4.5). All the isatins bearing electron-withdrawing and electron-donating groups on 5-position were suitable for the reductive coupling reaction, providing the desired products in good yields (**4-7k~4-7p**). 7-Position substituted isatins worked fine as well, and the corresponding tertiary alcohols was obtained in good yields (**4-7q, 4-7r**). 5,7-Dichloro isatin as a substrate led to the desired product in 80% yield (**4-7s**). Other protecting group (such as methyl group) protected isatins

and unprotected isatins were also suitable for the coupling reaction, leading to the desired product in good yields (**4-7t**, **4-7t**).

Table 4.5 Reaction Scope of isatins^{a, b}

^aReaction condition as in Table 4.1, entry 1. ^bIsolated yield.

The cross-coupling product **4-7u** could be produced in gram scale without any loss of the reaction yield (72% vs. 76%), and this product could serve as a synthon for the synthesis of neocryptolepine **4-7u-2**. Neocryptolepine is a nature product that isolated from the bark of roots of *Cryptolepis sanguinolenta*,¹¹ and this nature product and its analogs bear a strong astiplasmodial activity against *Plasmodium falciparum* chloroquine-resistant strains.¹²

Scheme 4.5 Transformation of product **4-7u** to nature product neocryptolepine **7u-2**

4.2.3 Reductive Coupling with imines

To further expand the generality of our reaction system, we introduced sulfonyl imine **4-8a** as a reaction partner. To our delight, the desired reductive coupling product **4-9a** was provided in 67% yield. Then the reaction scope of coupling with imines was evaluated (Table 4.6). The nitrobenzyl bromide derivatives which were successfully used in the coupling reaction with activated ketones were also suitable for coupling reaction with sulfonyl imines to generate corresponding tertiary amines in moderate yields (**4-9a~4-9h**). Placing the substituents on the phenyl ring of sulfonyl imines worked fine as well (**4-9i**, **4-9j**).

Table 4.6 Reaction Scope with Imines.^{a, b}

^aReaction condition as in Table 4.1, entry 1. ^bIsolated yield.

The structures of the reductive coupling products were confirmed via X-ray crystallographic analysis of tertiary alcohols **4-4w** and **4-7l**.

Fig. 4.1 Crystall structure of cross-coupling product **4-4w** and **4-7l**.

4.3 Mechanistic Study.

4.3.1 Proposed Reaction Pathway.

Based on our previous work towards the reductive coupling of nitrobenzyl bromides with nitroalkenes,^{6c} we proposed a possible reaction pathway for this catalytic reaction. The reaction starts from the generation of Breslow intermediate **4-A** by nucleophilic attack of NHC catalyst to aldehyde. Then SET process occurred between Breslow intermediate **4-A** and nitrobenzyl bromide **4-1a** to generate corresponding radical cation **4-B** and radical anion **4-C**, and the elimination of bromide from **4-C** generated the key radical intermediate **4-D**. Similar with the formal 1,4-addition to nitroalkenes, the generation of coupling product **4-4** also had two possible pathways: radical pathway and anion pathway. For the radical pathway, the 1,2-addition of radical intermediate **4-D** to ketones **4-2** generated radical intermediate **4-E**, then this radical further reduced via a second SET process to form anion intermediate **4-F**. Finally, protonation of anion **4-F** provided the desired tertiary alcohol **4-4**. The anion pathway was that the radical intermediate **4-D** first got one electron from reducing species generating the nitrobenzyl anion intermediate **4-H**, then anion intermediate **4-H** nucleophilic 1,2-addition to ketone **4-2** followed by protonation provided the desired product **4-4**. In the NHC catalytic cycle, the radical cation **4-B** further oxidized

to provided the acylazolium intermediate **4-G**, which was trapped by CH₃OH to give the corresponding ester and regenerated the NHC.

Scheme 4.6 Proposed Reaction Pathway.

4.3.2 Control Experiment.

To further confirm the proposed reaction pathway, we desired some control experiments to investigate the reaction mechanism. In the reaction outcome of our model reaction (Table 4.1, entry 1), we found that beside the tertiary alcohol **4-4a** as the major product, we also got 42% 4-nitrotoluene **4-10a** as side product (Scheme 4.7a). This side product likely generated from further reducing and protonation of radical **4-D**. As this reducing product was formed, we tried to estimate the possibility of nucleophilic 1,2-addition of benzyl anion **4-H** to ketones. We introduced 4-nitrotoluene to serve as a substrate instead of 4-nitrobenzyl bromide, and found that under the standard condition, the desired product could not be obtained (Scheme 4.7b). When we mixed the nitrotoluene **4-10a** and ketone **4-2a** and treated the mixture with 3.0 equivalent of NaOCH₃, we also could not observe the desired product. These results indicate that the anion 1,2-addition pathway is less possible.

There is another possibility that the ketone **4-2a** first reduced to corresponding α -hydroxy ester **4-11a**,¹³ then the enolate from deprotonation of ester **4-11a** underwent a S_N2

substitution reaction with nitrobenzyl bromide **4-1a** to give the tertiary alcohol **4-4a**. However, the corresponding reducing product **4-11a** from ketone **4-2a** was not observed under our standard conditions (Scheme 4.7a), and replacing ketone **4-2a** by alcohol **4-11a** to proceed under our standard conditions also could not lead to the desired product **4-4a** (Scheme 4.7d). We also measured the reduction potential of substrates **4-1a**, **4-2a** and **4-6a** by cyclic voltammerty experiments at the same conditions, and the results showed that the reduction potential of nitrobenzyl bromide **4-1a** was much higher than that of ketones **4-2a** and **4-6a** (-1.18 V of **4-1a** VS -1.47 of **4-2a** and -1.38 of **4-6a**, Fig. 4.2), which indicated that nitrobenzyl bromide was easier to be reduced. Those results demonstrated that the possibility of S_N2 substitution reaction could be roled out.

Finally, as the 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was usually served as a radical trapping agent which was used to confirm the generation of radical in the reactions via trapping the in situ generation of radical intermediate in radical reactions,¹⁴ we added TEMPO as an additive to our model reaction as in Table 4.1, entry 1 (Scheme 4.7e). In this case, the desired coupling product **4-4a** was not observed, and we obtained the radical trapping product **4-12a** in 7% yield which probably generated from radical-radical coupling of TEMPO with nitrobenzyl radical **4-D**, which provided strong evidence for the generation of benzyl radical intermediate. And the reduced product of nitrobenzyl bromide still provided in 45% yield, which suggest that the nucleophilic attacking pathway was less possible, thus suggest that radical addition of **4-D** to ketone **4-2** was the more possible reaction pathway.

Scheme 4.7 Control experiments.

Fig. 4.2 Cyclic voltammograms of 5 mM substrates in CH₃CN at glassy carbon disk (1.0 mm diameter, working electrode), counter electrode: platinum electrode, reference electrode: ferrocene electrode (FcE); 0.5 M *n*-Bu₄NPF₆, scan rate of $\nu = 1.0$ V/s

4.4 Summary.

In summary, we had successfully expanded our NHC-catalyzed SET precess containing reaction system to ketones and imines via formal 1,2-addition process. The more reasonable reaction pathway was the nitrobenzyl radical which generated via SET process, underwent formal 1,2-addition process to carbon-heteroatom double bond. The reaction scope was very widely with a lot of special functional groups tolerated in the reaction. The coupling products could further transform to other useful molecules including nature product. This methodology provide an opportunity for chemist to have a deep understanding about NHC-organocatalysis.

4.5 Experimental Section

4.5.1 General Information.

All reactions were carried out under standard conditions using N₂ as shielding gas with magnetic stirring. Analytical thin layer chromatography (TLC) was performed with TLC plates. All reactions and column chromatography were monitored by thin layer chromatography with UV light at 254 nm and colorized with ethanol solution of phosphomolybdic acid, followed by heating using a heat gun. All products could be purified by column chromatography using ethyl acetate and hexane as eluent. Organic solutions were concentrated by rotary evaporation. All solvents were freshly distilled before use. ¹H and ¹³C NMR chemical shifts are reported in CDCl₃ solution of the compound by Bruker AV-400 MHz instruments and marked in ppm relative to tetramethylsilane (TMS) (0) and CDCl₃ (77.0 ppm) as standard. The following abbreviations are used to describe peak patterns where appropriate: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Coupling constants (*J*) are reported in Hertz (Hz). High resolution mass spectral analysis (HRMS) was performed on Waters Q-TOF Premier mass spectrometer. X-ray

crystallography analysis was performed on Bruker X8 APEX X-ray diffractionmeter.

4.5.2 General Procedures for the catalytic reductive coupling reactions.

To a dry Schlenk tube equipped with a magnetic stir bar, was added benzyl bromide **4-1** (0.15 mmol), nitroalkene **2-2** (or **4-6**, **4-8**) (0.10 mmol), aldehyde **4-3a** (0.15 mmol) and triazolium salt **4-C1** (1.8 mg, 0.005 mmol), then the tube was closed with a septum. Methanol (1.0 mL) was added and the resulting solution was evacuated and refill with N₂. N,N-diisopropylethylamine (25 μ L, 0.15 mmol) was added and the reaction mixture was stirred at room temperature for 8 hours. Then the resulting mixture was concentrated under reduced pressure, and the residue was purified via column chromatography on silica gel to afford the coupling product **4-4**, **4-7** or **4-9**.

4.5.3 Substrates preparation.

Generation procedure for the preparation of substrates **4-1**

General procedure A.

The NBS (1.2 equiv) and AIBN (0.1 equiv) were added into the solution of the corresponding 2- or 4-nitro-toluene. The reaction was refluxed until the starting material was fully transferred into product via monitoring of TLC. The reaction was poured into cold water. The resulting solution was extracted with ether three times. The organic layer was collected and dried over Na₂SO₄ and concentrated under reduced pressure. The crude product could be purified by column chromatography.

General procedure B.

PBr₃ (0.5 eq) was added carefully into solution of alcohol (1.0 eq) in Et₂O at 0°C. The resulting mixture was allowed to stir at rt until the starting material was fully transferred into product via monitoring of TLC. The reaction mixture was carefully quenched with water and the resulting solution was extracted with ether three times. The organic layer was collected, dried over Na₂SO₄ and concentrated under reduced pressure. The crude product could be purified by column chromatography.

General procedure for the preparation of substrates 4-2**For alkene ketoesters**

To a solution of methylpyruvate (1 eq., 15 mmol/mL) and benzaldehyde (1 eq., 15 mmol/mL) in methanol was added at 0 °C a solution of potassium hydroxide (1.5 eq., 5 mmol/mL) in methanol. The first two-thirds of alkali were added dropwise, then the ice-bath was removed and the rest of the potassium hydroxide was run rapidly to complete the condensation before precipitation of potassium pyruvate could occur. The mixture was held at 40 °C for 1h and then at 0 °C overnight. The solvent was removed in vacuo and the solid was filtered and washed with a little cold methanol to give the potassium salt as a yellow solid.

A saturated solution of potassium salt (1 eq., 0.5 mmol/mL) in water at 40°C was rapidly poured into an excess of 1.6 M HCl. The acid precipitated from water was filtered and dissolved in CH₂Cl₂, dried (Na₂SO₄) and the solvent evaporated in vacuo. Without further

purification, the residue was dissolved in methanol (to 4 mmol / mL) and sulfuric acid (98 %, 0.05 eq.) was added. The mixture was refluxed overnight. The cooled mixture was concentrated in vacuo, diluted with CH₂Cl₂ and washed with saturated brine. The aqueous phase was extracted with CH₂Cl₂, dried (Na₂SO₄) and the solvent evaporated in vacuo. The yellow solid was recrystallized from hexane to give the ester product.

For alkyne ketoesters

An oven-dried round-bottomed flask tube equipped with a stirrer bar was evacuated while hot and allowed to cool under nitrogen. The flask was first charged with CuI (0.02 eq.), TMEDA (0.05 eq.) and ethyl-2-chloro-2-oxoacetate (1.2 eq.) followed by alkyne (1.0 eq.), Et₃N (3 eq.) and dry THF (conc. 0.2 mmol/mL). The reaction mixture was stirred at room temperature under nitrogen overnight. Saturated NaHCO₃ solution (25 mL) was added and the mixture was extracted with EA (30 mL), dried over (Na₂SO₄) and concentrated in vacuo. The residue was purified by flash column chromatography.

General procedure for the preparation of substrates 4-6

Under a nitrogen atmosphere, NaH (1 eq.) was added portion-wise into a solution of isatin (1 eq., 0.5 mmol/mL) in DMF at 0 °C. After 15 minutes, benzyl bromide (1.4 eq.) was added and the reaction mixture was stirred for 30 minutes at room temperature. Water was added to precipitate the product, which was filtered and washed with hexane to give the protected isatin.

Synthetic transformations

The procedure for synthesis of compound 4-4b-1:

The solution of **4-4b** (0.2 mmol, 65 mg, 1.0 eq.) in AcOH was added iron powder (1.2 mmol, 61 mg, 6.0 eq.) and then the reaction system was heated to reflux for 4 h. The solution was cooled to room temperature and neutralized with aq. NaHCO₃, the reaction was extracted three times with ethyl acetate. The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and evaporated under reduced pressure. The product **4-4b-1** could be obtained in 90% yield through isolation by silica gel column chromatography to give as a white solid; m.p. 185–187 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.66 (d, *J* = 8.0 Hz, 1H), 7.26–7.18 (m, 7H), 7.06–7.02 (m, 1H), 6.87–6.79 (m, 2H), 6.17 (d, *J* = 8.0 Hz, 1H), 4.17 (s, 1H), 3.34 (d, *J* = 7.2 Hz, 1H), 3.18 (d, *J* = 7.6 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 172.8, 136.0, 131.2, 129.0, 128.5, 128.0, 128.0, 127.6, 126.8, 124.0, 122.4, 115.6, 72.1, 38.9; IR (ν cm⁻¹) 3325, 1686, 1489, 1366, 1315, 1150, 1088, 748; HRMS (ESI) calcd. For C₁₇H₁₅NNaO₂ [M+Na]⁺: 288.0995, Found: 288.0987.

The procedure for synthesis of compound 4-4b-2:

Under a nitrogen atmosphere, a solution of **4-4b** (0.2 mmol, 65 mg, 1.0 eq.) in DCM (4.0 mL, 0.05 M) was added to MCPBA (0.4 mmol, 68.4 mg, 2.0 equiv) at 0 °C. After the full conversion of 4b, the reaction was quenched with saturated solution of NaHCO₃. Then the

organic phase was separated, and the aqueous phase was extracted with Et₂O three times. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography to afford product **4-4b-2** in 87% yield. Colorless liquid; ¹H NMR (400 MHz, CDCl₃) δ 7.82-7.80 (m, 1H), 7.46-7.35 (m, 3H), 7.33-7.29 (m, 3H), 7.10-7.08 (m, 2H), 3.84 (s, 3H), 3.74 (d, *J* = 2.0 Hz, 1H), 3.63 (s, 2H), 3.43 (d, *J* = 20 Hz, 1H), 3.22 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 173.2, 150.9, 135.8, 133.2, 132.3, 129.3, 128.5, 128.4, 128.1, 125.7, 124.7, 75.3, 64.4, 54.6, 53.5, 36.5; HRMS (ESI) calcd. For C₁₈H₁₇NNaO₆ [M+Na]⁺: 366.0948, Found: 366.0945.

The procedure for synthesis of compound 4-4b-3:

Under a nitrogen atmosphere, to a stirred solution of compound **4-4b** (0.2 mmol, 65 mg, 1.0 eq.) in Et₂O (1.0 mmol / mL) was added PBr₃ (0.1 mmol, 27 mg, 1.0 eq.) dropwise at 0 °C, then the reaction was allowed to warm to room temperature and stirred. After the reaction was completed, it was cautiously treated with water at 0 °C and then the resulting solution was stirred for 4 h. The organic layer containing the corresponding alcohol compound **4-4b-3** was separated, washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by column chromatography to afford product **4-4b-3** in 81% yield. Colorless liquid; ¹H NMR (400 MHz, CDCl₃) δ 7.91-7.88 (dd, *J* = 8.0 Hz, 1.2 Hz, 1H), 7.44-7.40 (m, 1H), 7.36-7.28 (m, 6H), 7.17-7.14 (m, 2H), 5.55 (d, *J* = 8.8 Hz, 1H), 4.19 (d, *J* = 16.4, 1H), 4.07 (d, *J* = 16.8 Hz, 1H), 3.64 (s, 3H), 2.24 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 167.2, 149.4, 145.0, 141.4, 133.5, 132.9, 130.5, 129.1, 128.9, 128.4,

127.3, 126.3, 124.6, 71.0, 52.2, 29.6; **IR** (ν cm^{-1}) 3464, 1717, 1524, 1350, 1219, 1115, 1015, 702; **HRMS (ESI)** calcd. For $\text{C}_{18}\text{H}_{17}\text{NNaO}_5$ $[\text{M}+\text{Na}]^+$: 350.0999, Found: 350.0997.

The total synthesis of neocryptolepine 4-7u-2:

The solution of **4-7u** (0.3 mmol, 85 mg, 1.0 eq.) in AcOH was added the iron powder (1.8 mmol, 92 mg, 6.0 eq.) and then the reaction system was heated to reflux for 12 h. The solution was neutralized with an aq. solution of NaHCO_3 , the reaction was extracted three times with ethyl acetate. The combined organic solution was washed with brine, dried over Na_2SO_4 , filtered and evaporated under the reduce pressure. The product **4-7u-1** could be obtained in 85% yield through isolation by silica gel column chromatography. **^1H NMR (400 MHz, DMSO)** δ 11.7 (s, 1H), 9.05 (s, 1H), 8.26 (d, $J = 7.6$ Hz, 1H), 8.11 (d, $J = 7.6$ Hz, 1H), 7.98 (d, $J = 8.4$ Hz, 1H), 7.74-7.70 (m, 1H), 7.55-7.46 (m, 3H), 7.29-7.25 (m, 1H); **^{13}C NMR (100 MHz, DMSO)** δ 152.9, 146.3, 141.5, 128.6, 128.2, 127.5, 127.0, 123.7, 122.7, 121.8, 120.3, 119.6, 117.9, 110.9.

Under a nitrogen atmosphere, CH_3I was added into a solution of compound **4-7u-1** in toluene. The reaction was heated to 130 $^\circ\text{C}$ in a sealed tube for 4 h. The solvent was removed under reduce pressure. The nature product neocryptolepine could be obtained in 80% yield through isolation by silica gel column chromatograph. **^1H NMR (400 MHz, CDCl_3)** δ 8.54 (s, 1H), 8.06 (d, $J = 7.6$ Hz, 1H), 8.00 (d, $J = 8.0$ Hz, 1H), 7.78-7.74 (m, 3H), 7.55 (t, $J = 7.6$ Hz, 1H), 7.47-7.43 (m, 1H), 7.23 (d, $J = 7.2$ Hz, 1H), 4.38 (s, 3H); **^{13}C NMR (100 MHz, CDCl_3)** δ 156.3, 155.5, 137.0, 130.4, 130.0, 129.3, 128.2, 128.1, 124.0, 121.9, 121.0, 120.8, 119.8, 117.7, 114.1, 33.0.

Characterization of cross-coupling products.

(E)-Methyl 2-hydroxy-2-(4-nitrobenzyl)-4-phenylbut-3-enoate**(4-4a).** White solid; m.p. 100-102 °C; ^1H NMR (400 MHz, CDCl_3)

δ 8.13 (d, $J = 8.4$ Hz, 2H), 7.43-7.38 (m, 4H), 7.35-7.31 (t, $J = 8.8$ Hz, 2H), 7.29-7.26 (m, 1H), 6.83 (d, $J = 15.6$ Hz, 1H), 6.38 (d, $J = 15.6$ Hz, 1H), 3.80 (s, 3H), 3.47 (s, 1H), 3.32 (d, $J = 13.2$ Hz, 1H), 3.16 (d, $J = 13.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.2, 147.4, 143.6, 140.8, 131.4, 128.5, 128.3, 125.4, 123.0, 78.6, 53.4, 45.4; IR (ν cm^{-1}) 3495, 1736, 1520, 1346, 1130, 976, 856, 694; HRMS (ESI) calcd. For $\text{C}_{18}\text{H}_{17}\text{NNaO}_5$ $[\text{M}+\text{Na}]^+$: 350.0999, Found: 350.1003.

(E)-Methyl 2-hydroxy-2-(2-nitrobenzyl)-4-phenylbut-3-enoate (4-4b). Colorless liquid; ^1H NMR (400 MHz, CDCl_3) δ 7.79 (s, 1H), 7.50-

7.46 (dt, $J = 0.8$ Hz, 8.0 Hz, 1H), 7.43-7.41 (dd, $J = 1.2$ Hz, 7.6 Hz, 1H), 7.39-7.29 (m, 6H), 6.73 (d, $J = 16.0$ Hz, 1H), 6.34 (d, $J = 15.6$ Hz, 1H), 3.78 (s, 3H), 3.62 (s, 2H), 3.48 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.4, 151.1, 136.0, 133.4, 132.0, 131.0, 129.7, 128.6, 128.5, 128.0, 128.0, 126.7, 124.5, 77.7, 53.4, 40.3; HRMS (ESI) calcd. For $\text{C}_{18}\text{H}_{17}\text{NNaO}_5$ $[\text{M}+\text{Na}]^+$: 350.0999, Found: 350.1018.

(E)-Methyl 2-(3-chloro-4-nitrobenzyl)-2-hydroxy-4-phenylbut-**3-enoate (4-4c).** Colorless liquid; ^1H NMR (400 MHz, CDCl_3) δ

7.81 (d, $J = 8.4$ Hz, 1H), 7.46 (d, $J = 1.6$ Hz, 1H), 7.40-7.38 (m, 2H), 7.36-7.23 (dd, $J = 1.2$ Hz, 8.0 Hz, 2H), 7.32-7.26 (m, 2H), 6.84 (d, $J = 15.6$ Hz, 1H), 6.36 (d, $J = 16.0$ Hz, 1H), 3.82 (s, 3H), 3.49 (s, 1H), 3.26 (d, $J = 13.6$ Hz, 1H), 3.09 (d, $J = 13.6$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.0, 146.6, 142.3, 135.8, 133.7, 131.3, 129.4, 128.7, 128.5, 128.2, 126.8, 125.3, 77.6, 53.4, 44.5; HRMS (ESI) calcd. For

$C_{18}H_{16}ClNNaO_5$ $[M+Na]^+$: 384.0609, Found: 384.0608.

(E)-Methyl 2-(2-cyano-4-nitrobenzyl)-2-hydroxy-4-phenylbut-3-enoate (4-4d). Colorless liquid; 1H NMR (400 MHz, $CDCl_3$) δ 8.45

(d, $J = 2.4$ Hz, 1H), 8.34-8.31 (dd, $J = 2.4$ Hz, 8.4 Hz, 1H), 7.73 (d, J

= 8.8 Hz, 1H), 7.39-7.27 (m, 5H), 6.69 (d, $J = 15.6$ Hz, 1H), 6.44 (d, $J = 16.0$ Hz, 1H), 3.89

(s, 3H), 3.61 (s, 1H), 3.51 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 146.7, 146.2,

135.5, 133.3, 131.8, 128.7, 128.4, 127.5, 127.3, 126.8, 126.5, 116.3, 115.6, 77.3, 53.8, 42.9;

HRMS (ESI) calcd. For $C_{19}H_{16}N_2NaO_5$ $[M+Na]^+$: 375.0951, Found: 375.0959.

(E)-Methyl 2-(4-cyano-2-nitrobenzyl)-2-hydroxy-4-phenylbut-3-

enoate (4-4e). White solid; m.p. 131–133 °C; 1H NMR (400 MHz,

$CDCl_3$) δ 8.08 (d, $J = 1.6$ Hz, 1H), 7.75-7.23 (dd, $J = 1.6$ Hz, 8.0 Hz,

1H), 7.58 (d, $J = 8.0$ Hz, 1H), 7.33-7.32 (m, 5H), 6.68 (d, $J = 15.6$ Hz, 1H), 6.28 (d, $J =$

15.6 Hz, 1H), 3.81 (s, 3H), 3.67 (d, $J = 2.4$ Hz, 2H) 3.49 (d, $J = 13.2$ Hz, 1H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 173.9, 151.1, 135.5, 135.2, 134.8, 134.6, 131.7, 128.7, 128.3, 128.0,

127.6, 126.8, 116.5, 112.4, 77.4, 53.7, 40.2; **IR** (ν cm^{-1}) 3502, 2237, 1732, 1539, 1361,

1215, 972, 748; **HRMS (ESI)** calcd. For $C_{19}H_{17}N_2O_5$ $[M+H]^+$: 353.1132, Found: 353.1131.

(E)-Methyl 4-(2-hydroxy-2-(methoxycarbonyl)-4-phenylbut-

3-en-1-yl)-3-nitrobenzoate (4-4f). Colorless liquid; 1H NMR

(400 MHz, $CDCl_3$) δ 8.43 (d, $J = 1.6$ Hz, 1H), 8.13-8.10 (dd, $J =$

2.0 Hz, 8.0 Hz, 1H), 7.52 (d, $J = 8.0$ Hz, 1H), 7.35-7.25 (m, 5H), 6.72 (d, $J = 15.6$ Hz, 1H),

6.32 (d, $J = 16.0$ Hz, 1H), 3.94 (s, 3H), 3.79 (s, 3H), 3.66 (d, $J = 2.0$ Hz, 2H), 3.50 (s, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 164.9, 151.0, 135.8, 134.5, 133.8, 132.4, 131.4,

130.3, 128.6, 128.2, 128.1, 126.8, 125.5, 77.6, 53.5, 52.6, 40.3; **HRMS (ESI)** calcd. For

$C_{20}H_{19}NNaO_7$ $[M+Na]^+$: 408.1054, Found: 408.1054.

(E)-Methyl 2-(4-acetyl-2-nitrobenzyl)-2-hydroxy-4-phenylbut-3-enoate (4-4g). White solid; m.p. 108–110 °C; 1H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, J = 2.0 Hz, 1H), 8.05–8.02 (dd, J = 2.0 Hz, 8.0 Hz, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.36–7.29 (m, 4H), 7.28–7.23 (m, 1H),

6.71 (d, J = 16.0 Hz, 1H), 6.32 (d, J = 16.0 Hz, 1H), 3.80 (s, 3H), 3.71–3.63 (dd, J = 9.6 Hz, 13.2 Hz, 2H), 3.51 (s, 1H), 2.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.5, 174.1, 151.2, 136.7, 135.7, 134.6, 134.0, 131.4, 130.9, 128.6, 128.2, 128.0, 126.8, 124.3, 77.6, 53.6, 40.3, 26.6; IR (ν cm^{-1}) 3507, 1732, 1536, 1362, 1257, 1165, 748, 694; HRMS (ESI) calcd. For $C_{20}H_{19}NNaO_6$ $[M+Na]^+$: 392.1105, Found: 392.1114.

(E)-Methyl 2-hydroxy-2-(4-(hydroxymethyl)-2-nitrobenzyl)-4-phenylbut-3-enoate (4-4h). White solid; m.p. 106–108 °C; 1H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.48 (d, J = 1.2 Hz, 1H),

7.46 (d, J = 1.2 Hz, 1H), 7.42–7.23 (m, 6H), 6.73 (d, J = 15.6 Hz, 1H), 6.36 (d, J = 15.6 Hz, 1H), 4.73 (s, 2H), 3.78 (s, 3H), 3.60 (s, 2H), 3.49 (s, 1H), 1.90 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 151.1, 141.4, 136.0, 133.6, 131.0, 129.9, 128.7, 128.6, 128.5, 128.0, 126.8, 122.5, 77.7, 63.7, 53.5, 40.1; IR (ν cm^{-1}) 3256, 1748, 1535, 1362, 1250, 1165, 1049, 694; HRMS (ESI) calcd. For $C_{19}H_{19}NNaO_6$ $[M+Na]^+$: 380.1105, Found: 380.1111.

(E)-Methyl 2-(5-chloro-2-nitrobenzyl)-2-hydroxy-4-phenylbut-3-enoate (4-4i). White solid; m.p. 215–217 °C; 1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 8.4 Hz, 1H), 7.44 (d, J = 6.0 Hz, 1H), 7.37–7.30

(m, 5H), 7.27–7.24 (m, 1H), 6.74 (d, J = 16.0 Hz, 1H), 6.31 (d, J = 16.0 Hz, 1H), 3.80 (s,

3H), 3.64 (d, $J = 12.0$ Hz, 1H), 3.56 (d, $J = 11.6$ Hz, 1H) 3.49 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.2, 149.3, 138.2, 135.8, 133.4, 131.9, 131.3, 128.6, 128.1, 128.1, 126.8, 125.9, 77.6, 53.6, 40.1; IR ($\nu \text{ cm}^{-1}$) 3480, 1717, 1516, 1350, 1258, 1138, 976, 853; HRMS (ESI) calcd. For $\text{C}_{18}\text{H}_{16}\text{ClNNaO}_5$ $[\text{M}+\text{Na}]^+$: 384.0609, Found: 384.0616.

(E)-Methyl 2-(4,5-dimethoxy-2-nitrobenzyl)-2-hydroxy-4-phenylbut-3-enoate (4-4j). White solid; m.p. 116–118 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.45 (s, 1H), 7.37-7.29 (m, 4H), 7.26-7.23 (m,

1H), 6.87 (s, 1H), 6.73 (d, $J = 15.6$ Hz, 1H), 6.38 (d, $J = 16.0$ Hz, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 3.79 (s, 3H), 3.69 (d, $J = 14.0$ Hz, 1H), 3.58 (d, $J = 14.0$ Hz, 1H), 3.57 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.6, 151.8, 147.7, 143.1, 136.0, 130.7, 128.7, 128.6, 128.0, 126.7, 124.4, 115.0, 108.0, 77.8, 56.2, 56.2, 53.4, 40.5; IR ($\nu \text{ cm}^{-1}$) 3445, 1740, 1524, 1300, 1223, 1061, 769, 532; HRMS (ESI) calcd. For $\text{C}_{20}\text{H}_{21}\text{NNaO}_7$ $[\text{M}+\text{Na}]^+$: 410.1210, Found: 410.1199.

(E)-Methyl 2-hydroxy-2-((4-nitrophenyl)(phenyl)methyl)-4-phenylbut-3-enoate (4-4k). White solid; ^1H NMR (400 MHz, CDCl_3) δ 8.14-8.00 (m, 6H), 7.73-7.63 (m, 4H), 7.48-7.46 (m, 2H),

7.39-7.09 (m, 16H), 6.82-6.73 (m, 2H), 6.29-6.25 (m, 2H), 4.91 (s, 1H), 4.70 (s, 1H), 4.69 (s, 1H), 3.85 (s, 1H), 3.72 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.4, 174.2, 150.2, 147.8, 147.1, 140.8, 138.5, 137.8, 136.1, 135.9, 132.2, 132.0, 130.9, 130.2, 130.0, 129.2, 129.1, 128.8, 128.7, 128.6, 128.6, 128.5, 128.5, 128.3, 128.3, 128.1, 128.0, 127.6, 127.2, 126.9, 126.7, 126.7, 123.8, 123.4, 123.2, 80.3, 57.7, 57.6, 55.9, 53.5, 53.4; IR ($\nu \text{ cm}^{-1}$) 3483, 1714, 1515, 1356, 1257, 1134, 976, 853; HRMS (ESI) calcd. For $\text{C}_{24}\text{H}_{21}\text{NNaO}_5$ $[\text{M}+\text{Na}]^+$: 425.1234, Found: 425.1238.

(E)-Methyl 2-hydroxy-2-(2-(4-nitrophenyl)propan-2-yl)-4-phenylbut-3-enoate (4-4l). White solid; m.p. 167–169 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.12 (d, $J = 9.2$ Hz, 2H), 7.58 (d, $J = 8.8$ Hz, 2H), 7.39 (d, $J = 7.2$ Hz, 2H), 7.34 (t, $J = 7.2$ Hz, 2H), 7.28–7.25 (m, 1H), 6.82 (d, $J = 16.0$ Hz, 1H), 6.48 (d, $J = 15.6$ Hz, 1H), 3.70 (s, 3H), 3.49 (s, 1H), 1.61 (s, 3H), 1.50 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.2, 152.4, 146.5, 136.3, 132.2, 128.7, 128.7, 128.0, 126.7, 126.1, 122.4, 81.7, 53.1, 46.6, 24.6, 23.9; IR (ν cm^{-1}) 3480, 2959, 1717, 1516, 1350, 1258, 1138, 853; HRMS (ESI) calcd. For $\text{C}_{20}\text{H}_{21}\text{NNaO}_5$ $[\text{M}+\text{Na}]^+$: 378.1312, Found: 378.1307.

(E)-Methyl 4-(2-fluorophenyl)-2-hydroxy-2-(4-nitrobenzyl)but-3-enoate (4-4m). White solid; m.p. 123–125 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.13 (d, $J = 8.4$ Hz, 2H), 7.43–7.39 (m, 3H), 7.24–7.21 (m, 1H), 7.11 (t, $J = 7.6$ Hz, 1H), 7.07–7.02 (m, 1H), 6.95 (d, $J = 15.6$ Hz, 1H), 6.51 (d, $J = 16.0$ Hz, 1H), 3.81 (s, 3H), 3.49 (s, 1H), 3.32 (d, $J = 13.2$ Hz, 1H), 3.16 (d, $J = 13.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.1, 161.8, 159.3, 147.2, 143.2, 131.5 (d, $J = 22.6$ Hz), 131.2, 129.4 (d, $J = 33.8$ Hz), 128.2 (d, $J = 11.3$ Hz), 124.1 (t, $J = 15.0$ Hz), 124.1, 123.7 (d, $J = 54.1$ Hz), 123.2, 115.9 (d, $J = 82.7$ Hz), 77.8, 53.4, 45.0; IR (ν cm^{-1}) 3510, 1747, 1740, 1520, 1346, 1112; HRMS (ESI) calcd. For $\text{C}^{18}\text{H}^{16}\text{FNNaO}_5$ $[\text{M}+\text{Na}]^+$: 368.0905, Found: 368.0909.

(E)-Methyl 2-hydroxy-4-(2-methoxyphenyl)-2-(4-nitrobenzyl)but-3-enoate (4-4n). Colorless liquid; ^1H NMR (400 MHz, CDCl_3) δ 8.15–8.11 (dt, $J = 2.4$ Hz, 9.6 Hz, 2H), 7.44–7.40 (m, 3H), 7.26–7.323 (m, 1H), 7.12 (d, $J = 16.0$ Hz, 1H), 6.93 (t, $J = 7.6$ Hz, 1H), 6.87 (d, $J = 16.0$ Hz, 1H), 6.42 (d, $J = 16.0$ Hz, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.44 (s, 1H), 3.32 (d, J

= 13.6 Hz, 1H), 3.17 (d, J = 13.6 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.3, 157.0, 147.1, 143.5, 131.2, 129.3, 129.2, 127.2, 126.1, 124.8, 123.1, 120.6, 111.0, 78.0, 55.4, 53.2, 45.1; IR ($\nu\text{ cm}^{-1}$) 3495, 1736, 1520, 1346, 1246, 1103, 976, 745; HRMS (ESI) calcd. For $\text{C}_{19}\text{H}_{19}\text{NNaO}_6$ $[\text{M}+\text{Na}]^+$: 380.1105, Found: 380.1106.

(E)-Methyl 4-(3-fluorophenyl)-2-hydroxy-2-(4-nitrobenzyl)but-3-enoate (4-4o). White solid; m.p. 89–91 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.13 (d, J = 7.6 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.32–7.28 (m, 1H), 7.13 (d, J = 8.0 Hz, 1H), 7.11–7.08 (dd, J = 2.0 Hz, 10.0 Hz, 1H), 6.99–6.94 (dt, J = 1.6 Hz, 10.8 Hz, 1H), 6.80 (d, J = 15.6 Hz, 1H), 6.40 (d, J = 15.6 Hz, 1H), 3.81 (s, 3H), 3.49 (s, 1H), 3.32 (d, J = 14.4 Hz, 1H), 3.15 (d, J = 14.4 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.0, 164.30, 161.9, 147.2, 143.1, 138.2 (d, J = 30.1 Hz), 131.2, 130.2, 130.1 (d, J = 7.5 Hz), 123.2, 122.8, 122.8, 114.9 (d, J = 79.0 Hz), 113.1 (d, J = 82.7 Hz), 77.6, 53.4, 45.1; IR ($\nu\text{ cm}^{-1}$) 3503, 3075, 1740, 1520, 1346, 1130, 961, 698; HRMS (ESI) calcd. For $\text{C}_{18}\text{H}_{16}\text{FNNaO}_5$ $[\text{M}+\text{Na}]^+$: 368.0905, Found: 368.0899.

(E)-Methyl 2-hydroxy-4-(3-methoxyphenyl)-2-(4-nitrobenzyl)but-3-enoate (4-4p). Colorless liquid; ^1H NMR (400 MHz, CDCl_3) δ 8.13 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.8 Hz, 2H), 7.27–7.23 (m, 1H), 6.98 (d, J = 7.6 Hz, 1H), 6.91 (s, 1H), 6.84 (d, J = 2.4 Hz, 1H), 6.79 (d, J = 16.0 Hz, 1H), 6.37 (d, J = 15.6 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.45 (s, 1H), 3.31 (d, J = 13.6 Hz, 1H), 3.15 (d, J = 13.6 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.2, 159.9, 147.2, 143.3, 137.3, 131.2, 131.0, 129.7, 129.1, 123.2, 119.4, 113.7, 112.3, 77.7, 55.3, 53.4, 45.1; IR ($\nu\text{ cm}^{-1}$) 3507, 2920, 1736, 1520, 1246, 1026, 860, 698; HRMS (ESI) calcd. For $\text{C}_{19}\text{H}_{19}\text{NNaO}_6$ $[\text{M}+\text{Na}]^+$: 380.1105, Found: 380.1094.

(E)-Methyl 4-(4-fluorophenyl)-2-hydroxy-2-(4-nitrobenzyl)but-3-enoate (4-4q). White solid; m.p. 135–137 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.13 (d, J = 8.0 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.36 (t, J = 6.4 Hz, 2H), 7.04–7.00 (m, 2H), 6.80 (d, J = 15.6 Hz, 1H), 6.31 (d, J = 15.6 Hz, 1H), 3.81 (s, 3H), 3.47 (s, 1H), 3.31 (d, J = 13.6 Hz, 1H), 3.14 (d, J = 13.2 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.1, 147.2, 143.2, 132.1 (d, J = 11.3 Hz), 131.2, 129.9, 128.4 (d, J = 30.1 Hz), 123.2, 115.6 (d, J = 79.0 Hz), 77.6, 53.4, 45.1; IR (ν cm^{-1}) 3499, 1754, 1520, 1346, 1215, 1130, 856, 694; HRMS (ESI) calcd. For $\text{C}_{18}\text{H}_{16}\text{FNNaO}_5$ $[\text{M}+\text{Na}]^+$: 368.0905, Found: 368.0921.

(E)-Methyl 2-hydroxy-4-(4-methoxyphenyl)-2-(4-nitrobenzyl)but-3-enoate (4-4r). White solid; m.p. 114–116 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.13 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 6.76 (d, J = 16.4 Hz, 1H), 6.24 (d, J = 16.0 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.44 (s, 1H), 3.31 (d, J = 13.6 Hz, 1H), 3.14 (d, J = 13.2 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.3, 159.7, 147.1, 143.4, 131.2, 130.4, 128.0, 126.5, 123.2, 114.1, 77.7, 55.3, 53.3, 45.1; IR (ν cm^{-1}) 3487, 1724, 1528, 1126, 1042, 980, 752, 690; HRMS (ESI) calcd. For $\text{C}_{19}\text{H}_{19}\text{NNaO}_6$ $[\text{M}+\text{Na}]^+$: 380.1105, Found: 380.1097.

(E)-Methyl 2-hydroxy-2-(4-nitrobenzyl)-4-(thiophen-2-yl)but-3-enoate (4-4s). White solid; m.p. 98–100 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.13 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 4.8 Hz, 1H), 6.98–6.97 (m, 3H), 6.22 (d, J = 15.6 Hz, 1H), 3.80 (s, 3H), 3.47 (s, 1H), 3.29 (d, J = 13.2 Hz, 1H), 3.14 (d, J = 13.6 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.0, 147.2, 143.2, 140.9, 131.2, 128.0, 127.6, 126.9, 125.0, 124.4, 123.2, 77.4, 53.4, 45.1; IR (ν

cm^{-1}) 3375, 2237, 1706, 1529, 1192, 1115, 856, 698; **HRMS (ESI)** calcd. For $\text{C}_{16}\text{H}_{15}\text{NNaO}_5\text{S}$ $[\text{M}+\text{Na}]^+$: 356.0563, Found: 356.0569.

(3E,5E)-Methyl 2-hydroxy-2-(4-nitrobenzyl)-6-phenylhexa-3,5-dienoate (4-4t). White solid; m.p. 141–143 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.14 (d, J = 8.4 Hz, 2H), 7.41–7.39 (m, 4H), 7.34–7.30 (m,

2H), 7.24–7.22 (m, 1H), 6.81–6.75 (m, 1H), 6.65–6.58 (m, 2H), 5.98 (d, J = 14.8 Hz, 1H), 3.79 (s, 3H), 3.41 (s, 1H), 3.27 (d, J = 13.6 Hz, 1H), 3.11 (d, J = 13.6 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.1, 147.2, 143.3, 136.9, 134.4, 132.4, 131.4, 131.2, 128.7, 127.9, 127.2, 126.5, 123.2, 77.6, 53.3, 45.0; **IR** (ν cm^{-1}) 3487, 2920, 1735, 1520, 1269, 1130, 991, 694; **HRMS (ESI)** calcd. For $\text{C}_{20}\text{H}_{19}\text{NNaO}_5$ $[\text{M}+\text{Na}]^+$: 376.1155, Found: 376.1157.

(E)-Methyl 2-hydroxy-2-(4-nitrobenzyl)-6-phenylhex-3-enoate (4-4u). Colorless liquid; ^1H NMR (400 MHz, CDCl_3) δ 8.11 (d, J =

8.8 Hz, 2H), 7.34 (d, J = 8.8 Hz, 2H), 7.29 (d, J = 7.6 Hz, 2H), 7.20–7.13 (m, 3H), 5.97–5.90 (m, 1H), 5.63 (d, J = 15.6 Hz, 1H), 3.74 (s, 3H), 3.26 (s, 1H), 3.16 (d, J = 13.2 Hz, 1H), 3.01 (d, J = 13.6 Hz, 1H), 2.69 (t, J = 7.6 Hz, 2H), 2.41–2.35 (dd, J = 7.6 Hz, 15.2 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.5, 147.1, 143.7, 141.4, 131.6, 131.2, 130.3, 128.5, 128.3, 125.9, 123.1, 77.3, 53.1, 44.8, 35.3, 33.7; **IR** (ν cm^{-1}) 3483, 1736, 1520, 1346, 1207, 1111, 976, 689; **HRMS (ESI)** calcd. For $\text{C}_{20}\text{H}_{21}\text{NNaO}_5$ $[\text{M}+\text{Na}]^+$: 378.1312, Found: 378.1318.

Methyl 2-hydroxy-3-(4-nitrophenyl)-2-phenylpropanoate (4-4v).

White solid; m.p. 99–101 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.09 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 7.2 Hz, 2H), 7.40–7.33 (m, 5H), 3.78 (s, 3H), 3.69 (s, 1H), 3.60 (d, J = 13.6 Hz, 1H), 3.36 (d, J = 13.6 Hz, 1H); ^{13}C NMR (100 MHz,

CDCl₃) 174.2, 147.4, 143.6, 140.8, 131.4, 128.5, 128.3, 125.4, 123.0, 78.6, 53.4, 45.4; **IR** (ν cm⁻¹) 3507, 2920, 1736, 1520, 1346, 1261, 1111, 698; **HRMS (ESI)** calcd. For C₁₆H₁₅NNaO₅ [M+Na]⁺: 324.0842, Found: 324.0837.

Methyl 2-hydroxy-5,5-dimethyl-2-(4-nitrobenzyl)hex-3-ynoate (4-4w). White solid; m.p. 110–112 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.15 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H), 3.85 (s, 3H), 3.36 (s, 1H), 3.32 (d, J = 13.2 Hz, 1H), 3.16 (d, J = 13.6 Hz, 1H), 1.18 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 172.3, 147.3, 142.9, 131.6, 123.0, 95.7, 76.4, 70.9, 53.7, 45.5, 30.6, 27.4; **HRMS (ESI)** calcd. For C₁₆H₁₉NNaO₅ [M+Na]⁺: 328.1155, Found: 328.1161.

Methyl 4-cyclohexyl-2-hydroxy-2-(4-nitrobenzyl)but-3-ynoate (4-4x). White solid; m.p. 135–137 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.17 (dt, J = 2.0 Hz, 8.8 Hz, 2H), 7.48–7.45 (dd, J = 2.0 Hz, 8.8 Hz, 2H), 3.85 (s, 3H), 3.38 (s, 1H), 3.33 (d, J = 13.6 Hz, 1H), 3.25 (d, J = 13.6 Hz, 1H), 2.42–2.35 (m, 1H), 1.76–1.73 (m, 2H), 1.65–1.62 (m, 3H), 1.53–1.40 (m, 2H), 1.38–1.19 (m, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 172.3, 147.3, 142.8, 131.6, 123.0, 91.7, 77.8, 70.9, 53.7, 45.5, 32.1, 28.9, 25.7, 24.7; **IR** (ν cm⁻¹) 3507, 2928, 1728, 1508, 1350, 1076, 856, 590; **HRMS (ESI)** calcd. For C₁₈H₂₁NNaO₅ [M+Na]⁺: 354.1312, Found: 354.1309.

Methyl 4-(cyclohex-1-en-1-yl)-2-hydroxy-2-(4-nitrobenzyl)but-3-ynoate (4-4y). Colorless liquid; ¹H NMR (400 MHz, CDCl₃) δ 8.15 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H), 6.13 (t, J = 1.6 Hz, 1H), 3.85 (s, 3H), 3.45 (s, 1H), 3.37 (d, J = 13.2 Hz, 1H), 3.28 (d, J = 13.6

Hz, 1H), 2.11-2.05 (m, 4H), 1.65-1.54 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 172.0, 147.3, 142.7, 137.0, 131.6, 123.1, 119.4, 88.3, 83.7, 71.2, 53.8, 45.4, 28.7, 25.6, 22.1, 21.3; IR ($\nu\text{ cm}^{-1}$) 3499, 2932, 2218, 1744, 1261, 1219, 1084, 856; HRMS (ESI) calcd. For $\text{C}_{18}\text{H}_{19}\text{NNaO}_5$ $[\text{M}+\text{Na}]^+$: 352.1155, Found: 352.1168.

Methyl 2-hydroxy-2-(2-(4-nitrophenyl)propan-2-yl)-4-phenylbut-3-ynoate (4-4z). White solid; m.p. 130–132 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.15 (d, J = 8.8 Hz, 2H), 7.70 (d, J = 8.4 Hz, 2H), 7.46-7.44 (m, 2H), 7.36-7.32 (m, 3H), 3.78 (s, 3H), 3.75 (s, 1H),

1.70 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.9, 151.2, 146.8, 131.8, 129.0, 128.9, 128.4, 122.5, 121.8, 86.7, 85.8, 77.6, 53.7, 46.8, 24.7, 24.4; IR ($\nu\text{ cm}^{-1}$) 3476, 1721, 1512, 1350, 1273, 1088, 856, 702; HRMS (ESI) calcd. For $\text{C}_{20}\text{H}_{19}\text{NNaO}_5$ $[\text{M}+\text{Na}]^+$: 376.1155, Found: 376.1168.

1-Benzyl-3-hydroxy-3-(4-nitrobenzyl)indolin-2-one (4-7a). White solid; m.p. 163–165 °C; ^1H (400 MHz, CDCl_3) δ 7.87 (d, J = 8.8 Hz, 2H), 7.32 (dd, J = 7.2 Hz, 0.4 Hz, 1H), 7.23-7.03 (m, 5H), 7.04 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 7.2 Hz, 2H), 6.58 (d, J = 7.6 Hz, 1H), 4.92 (d,

J = 16.0 Hz, 1H), 4.47 (d, J = 16.0 Hz, 1H), 4.27 (s, 1H) 3.50-3.39 (dd, J = 32.4 Hz, 12.8 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 177.4, 147.0, 142.4, 141.6, 134.7, 131.1, 130.2, 128.7, 128.6, 127.8, 127.0, 124.3, 123.3, 123.0, 109.7, 77.2, 44.4, 43.8; IR ($\nu\text{ cm}^{-1}$) 3318, 1701, 1612, 1346, 1296, 1111, 853, 760; HRMS (ESI) calcd. For $\text{C}_{22}\text{H}_{18}\text{N}_2\text{NaO}_4$ $[\text{M}+\text{Na}]^+$: 397.1159, Found: 397.1168.

1-Benzyl-3-(3-chloro-4-nitrobenzyl)-3-hydroxyindolin-2-one (4-7b).

White solid; m.p. 156–158 °C; ^1H (400 MHz, CDCl_3) δ 7.57 (d, $J = 7.6$ Hz, 1H), 7.33 (d, $J = 8.8$ Hz, 1H), 7.25–7.21 (m, 4H), 7.14–7.10 (m, 2H), 6.94–6.90 (m, 3H), 6.63 (d, $J = 7.6$ Hz, 1H), 4.97 (d, $J = 15.6$ Hz, 1H), 4.51 (d, $J = 15.6$ Hz, 1H), 4.09 (s, 1H), 3.42 (d, $J = 12.8$ Hz, 1H), 3.31 (d, $J = 12.8$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 177.2, 146.5, 142.4, 140.7, 134.7, 133.6, 130.4, 129.4, 128.8, 128.3, 127.9, 126.8, 126.6, 125.2, 124.3, 123.4, 109.9, 76.9, 44.0, 43.8; IR (ν cm^{-1}) 3379, 1709, 1524, 1470, 1339, 1184, 883, 760; HRMS (ESI) calcd. For $\text{C}_{22}\text{H}_{17}\text{ClN}_2\text{NaO}_4$ $[\text{M}+\text{Na}]^+$: 431.0769, Found: 431.0765.

2-((1-Benzyl-3-hydroxy-2-oxoindolin-3-yl)methyl)-5-

nitrobenzonitrile (4-7c). White solid; m.p. 159–161 °C; ^1H (400 MHz, CDCl_3) δ 8.34 (d, $J = 2.4$ Hz, 1H), 8.14–8.11 (dd, $J = 8.4$ Hz, 2.4 Hz, 1H), 7.55 (d, $J = 8.8$ Hz, 1H), 7.56–7.24 (m, 4H), 7.19–7.17 (m, 3H), 7.09–7.05 (m, 1H), 6.74 (d, $J = 8.0$ Hz, 1H), 4.93 (d, $J = 15.6$ Hz, 1H), 4.72 (d, $J = 15.6$ Hz, 1H), 3.65 (d, $J = 13.6$ Hz, 1H), 3.50 (d, $J = 13.2$ Hz, 1H), 3.38 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 176.7, 146.7, 144.9, 142.0, 134.9, 132.8, 130.6, 128.8, 128.0, 127.9, 127.5, 127.4, 126.5, 124.8, 123.5, 115.9, 115.8, 109.8, 76.2, 44.1, 42.5; IR (ν cm^{-1}) 3437, 2236, 1701, 1612, 1350, 1281, 1080, 745; HRMS (ESI) calcd. For $\text{C}_{23}\text{H}_{18}\text{N}_3\text{O}_4$ $[\text{M}+\text{H}]^+$: 400.1292, Found: 400.1293.

1-Benzyl-3-hydroxy-3-(2-nitrobenzyl)indolin-2-one (4-7d).

White solid; m.p. 193–195 °C; ^1H (400 MHz, CDCl_3) δ 7.84 (d, $J = 8.0$ Hz, 2H), 7.48–7.37 (m, 3H), 7.29–7.24 (m, 3H), 7.19–7.15 (m, 1H), 7.12 (d, $J = 1.2$ Hz, 2H), 7.03–6.96 (m, 2H), 6.62 (d, $J = 7.6$ Hz, 1H), 4.92 (d, $J = 15.6$ Hz, 1H), 4.67 (d, $J = 16.0$ Hz, 1H), 4.02 (d, $J = 14.0$ Hz, 1H), 3.48 (d, $J = 14.0$ Hz, 1H), 3.39 (s, 1H); ^{13}C

NMR (100 MHz, CDCl₃) δ 177.4, 150.3, 142.2, 135.1, 134.2, 132.4, 129.9, 129.2, 128.8, 128.2, 127.6, 127.2, 124.9, 124.3, 123.3, 109.6, 76.4, 43.9, 40.0; **HRMS (ESI)** calcd. For C₂₂H₁₉N₂O₄ [M+H]⁺: 375.1139, Found: 375.1136.

4-((1-Benzyl-3-hydroxy-2-oxoindolin-3-yl)methyl)-3-

nitrobenzonitrile (4-7e). White solid; m.p. 189–191 °C; ¹H (400 MHz,

CDCl₃) δ 8.11 (s, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 1H),

7.30–7.16 (m, 7H), 7.09–7.02 (m, 2H), 6.72 (d, *J* = 8.0 Hz, 1H), 4.89 (d, *J*

= 16.8 Hz, 1H), 4.67 (d, *J* = 16.8 Hz, 1H), 3.98 (d, *J* = 14.4 Hz, 1H), 3.56 (d, *J* = 14.4 Hz,

1H), 3.12 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 176.7, 150.2, 142.0, 136.7, 135.3, 135.0,

134.9, 134.6, 130.4, 128.9, 128.4, 128.0, 127.4, 124.1, 123.6, 116.4, 112.6, 109.8, 76.0,

44.0, 40.2; **IR** (ν cm⁻¹) 3379, 2237, 1705, 1535, 1346, 1192, 1080, 644; **HRMS (ESI)** calcd.

For C₂₃H₁₇N₃NaO₄ [M+Na]⁺: 422.1111, Found: 422.1119.

Methyl 4-((1-benzyl-3-hydroxy-2-oxoindolin-3-yl)methyl)-3-

nitrobenzoate (4-7f). White solid; m.p. 174–176 °C; ¹H (400 MHz,

CDCl₃) δ 8.44 (s, 1H), 8.06–8.04 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H), 7.50

(d, *J* = 8.0 Hz, 1H), 7.28–7.12 (m, 6H), 7.03–6.97 (m, 2H), 6.65 (d, *J*

= 8.0 Hz, 1H), 4.89 (d, *J* = 15.6 Hz, 1H), 4.66 (d, *J* = 15.6 Hz, 1H), 4.00 (d, *J* = 13.6 Hz,

1H), 3.95 (s, 3H), 3.63 (s, 1H), 3.54 (d, *J* = 13.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ

177.2, 164.9, 150.1, 142.1, 135.0, 134.5, 134.0, 132.7, 130.4, 130.1, 128.8, 128.6, 127.7,

127.2, 125.9, 124.2, 123.4, 109.7, 76.3, 52.6, 44.0, 40.1; **HRMS (ESI)** calcd. For

C₂₄H₂₀N₂NaO₆ [M+Na]⁺: 455.1214, Found: 455.1222.

3-(4-Acetyl-2-nitrobenzyl)-1-benzyl-3-hydroxyindolin-2-one (4-7g).

White solid; m.p. 149–151 °C; ^1H (400 MHz, CDCl_3) δ 8.34 (s, 1H), 7.96 (d, $J = 8.0$ Hz, 1H), 7.53 (d, $J = 8.0$ Hz, 1H), 7.24–7.17 (m, 6H), 7.05–6.98 (m, 2H), 6.66 (d, $J = 8.0$ Hz, 1H), 4.90 (d, $J = 15.6$ Hz, 1H), 4.65 (d, $J = 16.0$ Hz, 1H), 3.99 (d, $J = 13.2$ Hz, 1H), 3.80 (s, 1H), 3.56 (d, $J = 13.2$ Hz, 1H), 2.59 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 195.5, 177.2, 150.3, 142.0, 136.7, 135.0, 134.7, 134.1, 131.3, 130.1, 128.7, 128.6, 127.7, 127.2, 124.6, 124.1, 123.5, 109.7, 76.3, 43.9, 40.0, 26.5; IR (ν cm^{-1}) 3279, 1694, 1535, 1362, 1258, 1177, 1080, 756; HRMS (ESI) calcd. For $\text{C}_{24}\text{H}_{20}\text{N}_2\text{NaO}_5$ $[\text{M}+\text{Na}]^+$: 439.1264, Found: 439.1268.

1-Benzyl-3-hydroxy-3-(4-(hydroxymethyl)-2-nitrobenzyl)-indolin-2-one (4-4h).

White solid; m.p. 175–177 °C; ^1H (400 MHz, CDCl_3) δ 7.85 (s, 1H), 7.45 (d, $J = 8.0$ Hz, 1H), 7.39 (d, $J = 8.0$ Hz, 1H), 7.30–7.24 (m, 3H), 7.20–7.14 (m, 3H), 7.07–7.05 (m, 1H), 7.00–6.97 (m, 1H), 6.64 (d, $J = 8.0$ Hz, 1H), 4.90 (d, $J = 15.6$ Hz, 1H), 4.72 (d, $J = 3.2$ Hz, 2H), 4.67 (d, $J = 16.0$ Hz, 1H), 3.95 (d, $J = 13.6$ Hz, 1H), 3.95 (d, $J = 14.0$ Hz, 1H), 3.35 (s, 1H), 2.19 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 177.4, 150.2, 142.1, 141.7, 135.2, 134.3, 130.4, 129.9, 128.9, 128.8, 128.1, 127.7, 127.3, 124.2, 123.3, 122.9, 109.6, 76.3, 63.6, 43.9, 39.8; IR (ν cm^{-1}) 3514, 3402, 1713, 1535, 1358, 1173, 999, 745; HRMS (ESI) calcd. For $\text{C}_{23}\text{H}_{20}\text{N}_2\text{NaO}_5$ $[\text{M}+\text{Na}]^+$: 427.1264, Found: 427.1266.

1-Benzyl-3-(4,5-dimethoxy-2-nitrobenzyl)-3-hydroxyindolin-2-one (4-4i).

White solid; m.p. 207–209 °C; ^1H (400 MHz, CDCl_3) δ 7.48 (s, 1H), 7.29–7.21 (m, 3H), 7.19–7.17 (m, 1H), 7.14–7.09 (m, 3H), 7.02–6.99 (m, 1H), 6.79 (s, 1H), 6.64 (d, $J = 7.6$ Hz, 1H), 4.95 (d, $J = 16.0$ Hz, 1H), 4.67 (d, $J = 15.6$ Hz, 1H), 4.08 (d, $J = 13.6$ Hz, 1H), 3.91 (s, 3H), 3.79 (s, 3H), 3.45 (d, $J =$

13.6 Hz, 1H), 3.32 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 177.5, 152.2, 147.9, 142.5, 142.4, 135.2, 129.9, 129.0, 128.8, 127.7, 127.0, 124.4, 123.8, 123.1, 115.4, 109.6, 108.3, 77.2, 56.3, 56.2, 43.9, 40.2; IR (ν cm^{-1}) 3348, 2935, 1694, 1524, 1273, 1061, 799, 756; HRMS (ESI) calcd. For $\text{C}_{24}\text{H}_{22}\text{N}_2\text{NaO}_6$ $[\text{M}+\text{Na}]^+$: 457.1370, Found: 457.1369.

1-Benzyl-3-hydroxy-3-(2-(4-nitrophenyl)propan-2-yl)indolin-2-one

(4-7j). White solid; m.p. 143–145 °C; ^1H (400 MHz, CDCl_3) δ 7.98 (d, J = 8.8 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.24 (t, J = 3.2 Hz, 3H), 7.18 (t, J = 7.8 Hz, 1H), 7.08 (d, J = 4.4 Hz, 2H), 6.91 (t, J = 7.6 Hz, 1H), 6.68

(d, J = 6.8 Hz, 1H), 6.62 (d, J = 8.0 Hz, 1H), 4.86 (d, J = 15.6 Hz, 1H), 4.49 (d, J = 15.6 Hz, 1H), 3.06 (s, 1H), 1.68 (s, 3H), 1.53 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 177.3, 151.1, 146.5, 143.2, 135.1, 129.9, 128.9, 128.7, 128.4, 127.8, 127.4, 125.5, 122.4, 122.3, 109.1, 80.0, 45.0, 44.0, 22.8, 22.2; IR (ν cm^{-1}) 3433, 1694, 1512, 1346, 1177, 1111, 853, 702; HRMS (ESI) calcd. For $\text{C}_{24}\text{H}_{23}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$: 403.1652, Found: 403.1661.

1-Benzyl-5-chloro-3-hydroxy-3-(4-nitrobenzyl)indolin-2-one (4-4k).

White solid; m.p. 159–161 °C; ^1H (400 MHz, CDCl_3) δ 7.91 (d, J = 8.8 Hz, 2H), 7.37 (d, J = 2.0 Hz, 1H), 7.26–7.12 (m, 4H), 7.07 (d, J = 8.8 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 6.49 (d, J = 8.4 Hz, 1H), 4.89 (d, J = 16.0

Hz, 1H), 4.46 (d, J = 16.0 Hz, 1H), 4.00 (s, 1H), 3.47–3.39 (dd, J = 18.4 Hz, 12.4 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 176.9, 147.2, 141.0, 140.9, 134.3, 131.1, 130.3, 130.1, 128.9, 128.7, 128.0, 126.9, 124.8, 123.2, 110.8, 77.2, 44.4, 44.0; IR (ν cm^{-1}) 3460, 1721, 1609, 1520, 1350, 1061, 829, 737; HRMS (ESI) calcd. For $\text{C}_{22}\text{H}_{17}\text{ClN}_2\text{NaO}_4$ $[\text{M}+\text{Na}]^+$: 431.0769, Found: 431.0772.

1-Benzyl-5-bromo-3-hydroxy-3-(4-nitrobenzyl)indolin-2-one (4-7l).

White solid; m.p. 173–175 °C; ^1H (400 MHz, CDCl_3) δ 7.91 (d, $J = 1.6$ Hz, 2H), 7.50 (d, $J = 0.8$ Hz, 1H), 7.34–7.32 (dd, $J = 8.4$ Hz, 2.0 Hz, 1H), 7.21–7.12 (m, 3H), 7.07 (d, $J = 8.4$ Hz, 2H), 6.82 (d, $J = 7.6$ Hz, 2H), 6.45 (d, $J = 8.4$ Hz, 1H), 4.89 (d, $J = 15.6$ Hz, 1H), 4.46 (d, $J = 15.6$ Hz, 1H), 3.72 (s, 1H), 3.46–3.38 (dd, $J = 20.0$ Hz, 12.8 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 176.6, 147.2, 141.5, 140.9, 134.3, 133.1, 131.1, 130.6, 128.7, 128.0, 127.6, 126.9, 123.2, 116.1, 111.2, 77.1, 44.5, 44.0; HRMS (ESI) calcd. For $\text{C}_{22}\text{H}_{17}\text{BrN}_2\text{NaO}_4$ $[\text{M}+\text{Na}]^+$: 475.0264, Found: 475.0268.

1,3-Dibenzyl-3-hydroxy-5-(trifluoromethyl)indolin-2-one (4-7m).

White solid; m.p. 136–138 °C; ^1H (400 MHz, CDCl_3) δ 7.90 (d, $J = 8.4$ Hz, 2H), 7.62 (s, 1H), 7.50 (d, $J = 8.0$ Hz, 1H), 7.24–7.14 (m, 3H), 7.03 (d, $J = 8.8$ Hz, 2H), 6.86 (d, $J = 7.6$ Hz, 2H), 6.67 (d, $J = 8.0$ Hz, 1H), 4.93 (d, $J = 15.6$ Hz, 1H), 4.52 (d, $J = 15.6$ Hz, 1H), 4.31 (s, 1H), 3.47–3.39 (dd, $J = 18.4$ Hz, 12.4 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 177.5, 147.2, 145.3, 140.7, 134.0, 131.1, 129.4, 128.8, 128.1–127.8 (q, $J = 15.04$ Hz), 127.0, 125.9, 125.6, 125.3, 123.2, 122.6, 121.6 (d, $J = 11.28$ Hz), 109.6, 76.9, 44.4, 44.1; IR (ν cm^{-1}) 3341, 1709, 1520, 1346, 1165, 1119, 833, 698; HRMS (ESI) calcd. For $\text{C}_{23}\text{H}_{17}\text{F}_3\text{N}_2\text{NaO}_4$ $[\text{M}+\text{Na}]^+$: 465.1033, Found: 465.1023.

1,3-Dibenzyl-3-hydroxy-5-(trifluoromethoxy)indolin-2-one (4-7n).

White solid; m.p. 147–149 °C; ^1H (400 MHz, CDCl_3) δ 7.91 (d, $J = 8.4$ Hz, 2H), 7.25–7.16 (m, 4H), 7.06 (d, $J = 8.4$ Hz, 3H), 6.88 (d, $J = 7.2$ Hz, 2H), 6.57 (d, $J = 8.4$ Hz, 1H), 4.92 (d, $J = 15.6$ Hz, 1H), 4.51 (d, $J = 16.0$ Hz, 1H), 4.03 (s, 1H), 3.41 (dd, $J = 29.6$ Hz, 12.8 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 177.3 (d, $J = 15.0$ Hz), 147.2, 145.1, 140.9 (d, $J = 33.8$ Hz), 134.3, 131.1, 130.1, 128.8, 128.1, 127.0, 123.2 (d, $J = 26.3$ Hz), 121.8, 119.2, 118.4, 116.7, 110.4, 77.3, 44.1,

44.5; **IR** (ν cm^{-1}) 3352, 1717, 1520, 1350, 1215, 1150, 817, 698; **HRMS** (ESI) calcd. For $\text{C}^{23}\text{H}^{18}\text{F}^3\text{N}^2\text{O}^5$ $[\text{M}+\text{H}]^+$: 459.1162, Found: 459.1147.

1-Benzyl-3-hydroxy-5-methoxy-3-(4-nitrobenzyl)indolin-2-one (4-7o).

White solid; m.p. 206–208 °C; ^1H (400 MHz, CDCl_3) δ 7.91 (d, J = 8.8 Hz, 2H), 7.20–7.07 (m, 5H), 6.97 (d, J = 2.4 Hz, 1H), 6.84 (d, J = 7.2 Hz, 2H), 6.72 (dd, J = 8.4 Hz, 2.4 Hz, 1H), 6.47 (d, J = 8.4 Hz, 1H),

4.89 (d, J = 15.6 Hz, 1H), 4.45 (d, J = 15.6 Hz, 1H), 3.77 (s, 3H), 3.41 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 176.8, 156.4, 147.1, 141.5, 135.8, 134.9, 131.2, 129.7, 128.6, 127.8, 127.0, 123.1, 114.6, 111.5, 110.3, 77.4, 55.8, 44.6, 44.0; **IR** (ν cm^{-1}) 3298, 1709, 1601, 1516, 1342, 1277, 1015, 694; **HRMS** (ESI) calcd. For $\text{C}_{23}\text{H}_{20}\text{N}_2\text{NaO}_5$ $[\text{M}+\text{Na}]^+$: 427.1264, Found: 427.1266.

1-Benzyl-3-hydroxy-5-methyl-3-(4-nitrobenzyl)indolin-2-one (4-7p).

White solid; m.p. 205–207 °C; ^1H (400 MHz, CDCl_3) δ 7.89 (d, J = 8.4 Hz, 2H), 7.20–7.11 (m, 4H), 7.06–7.00 (m, 3H), 6.83 (d, J = 7.2 Hz, 2H), 6.46 (d, J = 8.0 Hz, 1H), 4.90 (d, J = 16.0 Hz, 1H), 4.45 (d, J = 15.6 Hz,

1H), 3.63 (s, 1H), 3.47–3.37 (dd, J = 27.6 Hz, 12.8 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 177.0, 147.0, 141.6, 140.1, 134.9, 133.0, 131.1, 130.5, 128.6, 128.5, 127.7, 127.0, 125.0, 123.0, 109.5, 77.2, 44.5, 43.9, 21; **IR** (ν cm^{-1}) 3545, 1724, 1497, 1346, 1280, 1049, 818, 698; **HRMS** (ESI) calcd. For $\text{C}_{23}\text{H}_{20}\text{N}_2\text{NaO}_4$ $[\text{M}+\text{Na}]^+$: 411.1315, Found: 411.1318.

1-Benzyl-7-chloro-3-hydroxy-3-(4-nitrobenzyl)indolin-2-one (4-7q).

White solid; m.p. 156–158 °C; ^1H (400 MHz, CDCl_3) δ 7.90 (d, J = 8.8 Hz, 2H), 7.26–7.12 (m, 5H), 7.08–7.03 (m, 3H) 6.85 (d, J = 7.2 Hz, 2H), 5.10 (dd, J = 26.0 Hz, 16.0 Hz, 2H), 4.24 (s, 1H) 3.45–3.34 (dd, J = 31.2 Hz, 12.5 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 178.1, 147.1, 141.0, 138.5, 136.4, 132.8, 131.6, 131.2, 128.4, 127.3, 126.3, 124.3, 123.2, 123.1, 116.0, 76.3, 44.9, 44.4; IR (ν cm^{-1}) 3395, 1709, 1520, 1454, 1346, 1161, 1065, 737; HRMS (ESI) calcd. For $\text{C}_{22}\text{H}_{17}\text{ClN}_2\text{NaO}_4$ $[\text{M}+\text{Na}]^+$: 431.0769, Found: 431.0768.

1-Benzyl-3-hydroxy-7-methyl-3-(4-nitrobenzyl)indolin-2-one (4-7r).

White solid; m.p. 205–207 °C; ^1H (400 MHz, CDCl_3) δ 7.95 (d, J = 8.8 Hz, 2H), 7.25 (d, J = 5.6 Hz, 1H), 7.17–6.79 (m, 7H), 6.66 (d, J = 7.2 Hz, 2H), 5.10 (d, J = 16.8 Hz, 1H), 4.86 (d, J = 16.8 Hz, 1H), 4.23 (s, 1H), 3.47–3.37 (dd, J = 26.6 Hz, 12.8 Hz, 2H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 178.4, 147.1, 141.8, 140.5, 136.6, 134.2, 131.4, 129.4, 128.6, 127.3, 125.2, 123.5, 123.1, 122.3, 120.5, 76.7, 45.0, 44.5, 18.4; IR (ν cm^{-1}) 3395, 1701, 1520, 1346, 1184, 1065, 1030, 741; HRMS (ESI) calcd. For $\text{C}_{23}\text{H}_{20}\text{N}_2\text{NaO}_4$ $[\text{M}+\text{Na}]^+$: 411.1315, Found: 411.1318.

1-Benzyl-4,7-dichloro-3-hydroxy-3-(4-nitrobenzyl)indolin-2-one (4-7s).

White solid; m.p. 185–187 °C; ^1H (400 MHz, CDCl_3) δ 7.86 (d, J = 8.4 Hz, 2H), 7.21–7.18 (m, 1H), 7.14–7.10 (m, 3H), 7.06–7.03 (m, 3H), 6.75 (d, J = 7.6 Hz, 2H), 5.18–5.05 (dd, J = 37.6 Hz, 16.2 Hz, 2H), 4.00 (d, J = 12.4 Hz, 1H), 3.81 (s, 1H), 3.48 (d, J = 12.8 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 176.7, 147.2, 140.8, 140.4, 136.1, 133.8, 130.6, 130.5, 128.4, 127.5, 127.3, 126.2, 125.3, 123.4, 114.6, 77.6, 44.9, 41.1; HRMS (ESI) calcd. For $\text{C}_{22}\text{H}_{16}\text{Cl}_2\text{N}_2\text{NaO}_4$ $[\text{M}+\text{Na}]^+$: 465.0379, Found: 465.0370.

3-Hydroxy-1-methyl-3-(4-nitrobenzyl)indolin-2-one (4-7t).

White solid; m.p. 147–149 °C; ^1H (400 MHz, CDCl_3) δ 7.98 (d, $J = 8.8$ Hz, 2H), 7.32–7.27 (m, 1H), 7.19–7.07 (m, 4H), 6.69 (d, $J = 8.0$ Hz, 1H), 3.84 (s, 1H), 3.42 (d, $J = 12.8$ Hz, 1H), 3.26 (d, $J = 12.8$ Hz, 1H), 3.03 (s, 3H);

^{13}C NMR (100 MHz, CDCl_3) δ 177.4, 147.0, 142.9, 141.9, 131.1, 130.1, 128.5, 124.3, 123.2, 122.9, 108.6, 77.2, 44.5, 26.1; IR ($\nu \text{ cm}^{-1}$) 3364, 1701, 1516, 1342, 1223, 1103, 1011, 756; HRMS (ESI) calcd. For $\text{C}_{16}\text{H}_{15}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$: 299.1026, Found: 299.1026.

Ethyl 3-(4-nitrobenzyl)-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide (4-9a).

White solid; m.p. 165–167 °C; ^1H (400 MHz, CDCl_3) δ 8.16 (d, $J = 8.4$ Hz, 2H), 7.88 (d, $J = 8.0$ Hz, 1H), 7.80 (d, $J = 8.0$ Hz, 1H), 7.55 (t, $J = 7.6$ Hz, 1H), 7.65 (t, $J = 7.6$ Hz, 2H), 7.50 (d, $J = 8.4$ Hz, 2H), 5.64 (s, 1H), 4.34–4.25 (m, 2H), 3.63 (d, $J = 13.2$ Hz, 1H), 3.33 (d, $J = 13.6$ Hz, 1H), 1.33 (t, $J = 7.2$ Hz, 3H);

^{13}C NMR (100 MHz, CDCl_3) δ 69.1, 64.0, 45.4, 14.1, 168.5, 147.5, 141.9, 137.9, 135.8, 133.7, 131.6, 130.9, 124.7, 123.4, 121.8; IR ($\nu \text{ cm}^{-1}$) 3535, 2283, 1759, 1559, 1327, 1283, 1168, 853; HRMS (ESI) calcd. For $\text{C}_{17}\text{H}_{16}\text{N}_2\text{NaO}_6\text{S}$ $[\text{M}+\text{Na}]^+$: 399.0621, Found: 399.0623.

Ethyl 3-(3-chloro-4-nitrobenzyl)-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide (4-9b).

White solid; m.p. 131–133 °C; ^1H (400 MHz, CDCl_3) δ 7.86–7.81 (m, 3H), 7.76–7.72 (m, 1H), 7.68–7.64 (m, 1H), 7.53 (d, $J = 1.6$ Hz), 7.42–7.40 (dd, $J = 8.2$ Hz, 1.8 Hz, 1H), 5.67 (s, 1H),

4.37–4.29 (m, 2H), 3.56 (d, $J = 13.6$ Hz, 1H), 3.27 (d, $J = 13.6$ Hz, 1H), 1.36 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.3, 147.1, 140.9, 137.9, 135.9, 133.8, 131.0, 130.0, 127.0, 125.5, 124.6, 121.8, 68.9, 64.2, 44.8, 14.2; IR ($\nu \text{ cm}^{-1}$) 3507, 1709, 1535, 1304, 1165,

1030, 984, 856; **HRMS (ESI)** calcd. For $C_{17}H_{15}ClN_2NaO_6S$ $[M+Na]^+$: 433.0232, Found: 433.0229.

Ethyl 3-(4-cyano-2-nitrobenzyl)-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide (4-9c). White solide; m.p. 162–164 °C; 1H (400 MHz, $CDCl_3$) δ 8.13 (d, $J = 1.6$ Hz, 1H), 7.84–7.82 (m, 1H), 7.77–7.73 (m, 3H), 7.67–7.61 (m, 2H), 5.72 (s, 1H), 4.38–4.18 (m, 3H), 3.64 (d, $J = 14.4$ Hz, 1H), 1.33 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 150.6, 136.7, 135.6, 135.2, 135.0, 133.9, 133.6, 131.2, 128.4, 124.9, 121.8, 116.3, 113.1, 68.5, 64.6, 40.2, 13.8; ν 3507, 2237, 1740, 1535, 1308, 1234, 1165, 853; **HRMS (ESI)** calcd. For $C_{18}H_{16}N_3O_6S$ $[M+H]^+$: 402.0754, Found: 402.0760.

Ethyl 3-(4-(methoxycarbonyl)-2-nitrobenzyl)-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide (4-9d). White solide; m.p. 206–208 °C; 1H (400 MHz, $CDCl_3$) δ 8.48 (d, $J = 2.0$ Hz, 1H), 8.12–8.10 (dd, $J = 8.0$ Hz, 1.6 Hz, 1H), 7.85–7.82 (m, 1H), 7.73 (t, $J = 7.4$ Hz, 2H), 7.65–7.63 (m, 1H), 7.58 (d, $J = 8.0$ Hz, 1H), 5.71 (s, 1H), 4.35–4.15 (m, 3H), 3.95 (s, 3H), 3.62 (d, $J = 14.4$ Hz, 1H), 1.31 Hz (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 164.7, 150.5, 137.0, 135.6, 134.2, 133.8, 133.0, 132.7, 131.0, 130.9, 125.9, 125.1, 121.7, 68.7, 64.5, 52.7, 40.3, 13.8; **IR** (ν cm^{-1}) 3507, 1721, 1535, 1296, 1273, 1184, 1107, 764; **HRMS (ESI)** calcd. For $C_{19}H_{18}N_2NaO_8S$ $[M+Na]^+$: 457.0676, Found: 457.0622.

Ethyl 3-(4-acetyl-2-nitrobenzyl)-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide (4-9e). Colorless liquid; ^1H (400 MHz, CDCl_3)

δ 8.38 (s, 1H), 8.04-8.02 (dd, $J = 8.0$ Hz, 1.6 Hz, 1H), 7.84 (d, $J = 8.0$, 1H), 7.74 (t, $J = 7.4$ Hz, 2H), 7.66-7.61 (dd, $J = 12.4$ Hz, 8.0 Hz, 2H), 5.71 (s,

1H), 4.36-4.16 (m, 3H), 3.62 (d, $J = 14.0$ Hz, 1H), 2.63 (s, 3H), 1.32 (t, $J = 7.0$ Hz, 3H);

^{13}C NMR (100 MHz, CDCl_3) δ 195.3, 168.7, 150.7, 137.2, 137.1, 135.6, 134.5, 133.8,

133.1, 131.3, 131.1, 125.1, 124.5, 121.7, 68.7, 64.5, 40.3, 26.6, 13.8; IR ($\nu \text{ cm}^{-1}$) 3507, 1709,

1535, 1304, 1165, 1030, 856, 571; HRMS (ESI) calcd. For $\text{C}_{19}\text{H}_{18}\text{N}_2\text{NaO}_7\text{S}$ $[\text{M}+\text{Na}]^+$:

441.0727, Found: 441.0732.

Ethyl 3-(4-(hydroxymethyl)-2-nitrobenzyl)-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide (4-9f).

Colorless liquid; ^1H (400 MHz, CDCl_3) δ 7.86-7.83 (m, 2H), 7.74-7.70

(m, 2H), 7.64-7.60 (m, 1H), 7.46 (s, 2H), 5.71 (s, 1H), 4.75 (d, $J = 2.8$ Hz, 2H), 4.34-4.14

(m, 3H), 3.54 (d, $J = 14.4$ Hz, 1H), 2.02 (s, 1H), 1.31 (t, $J = 7.0$ Hz); ^{13}C NMR (100 MHz,

CDCl_3) δ 169.0, 150.6, 142.3, 137.3, 135.5, 134.0, 133.7, 130.9, 130.3, 127.3, 125.2,

122.8, 121.6, 69.0, 64.3, 63.6, 40.1, 13.8; IR ($\nu \text{ cm}^{-1}$) 3310, 3078, 1721, 1535, 1296, 1184,

1030, 764; HRMS (ESI) calcd. For $\text{C}_{18}\text{H}_{18}\text{N}_2\text{NaO}_7\text{S}$ $[\text{M}+\text{Na}]^+$: 429.0727, Found: 429.0719.

Ethyl 3-(4,5-dimethoxy-2-nitrobenzyl)-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide (4-9g).

Colorless liquid; ^1H (400 MHz, CDCl_3) δ 7.87 (d, $J = 8.0$ Hz, 1H), 7.76-

7.70 (m, 2H), 7.64-7.60 (m, 1H), 7.46 (s, 1H), 6.90 (s, 1H), 5.78 (s, 1H), 4.36 (d, $J = 14.4$

Hz, 1H), 4.32-4.15 (m, 2H), 3.92 (s, 3H), 3.87 (s, 3H), 3.49 (d, $J = 14.4$ Hz, 1H), 1.32 (t, J

$= 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 169.2, 152.2, 148.2, 142.6, 137.7, 135.6,

133.5, 130.7, 125.5, 123.2, 121.6, 115.3, 108.1, 69.0, 64.2, 56.4, 56.3, 40.5, 13.8; **IR** (ν cm^{-1}) 3507, 2237, 1740, 1535, 1308, 1234, 1165, 853; **HRMS** (ESI) calcd. For $\text{C}_{19}\text{H}_{20}\text{N}_2\text{NaO}_8\text{S}$ $[\text{M}+\text{Na}]^+$: 459.0833, Found: 459.0839.

Ethyl 3-(2-(4-nitrophenyl)propan-2-yl)-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide (4-9h).

Colorless liquid; ^1H (400 MHz, CDCl_3) δ 8.13 (d, $J = 8.8$ Hz, 2H), 7.84-7.82 (m, 1H), 7.77-7.74 (m, 1H), 7.70-7.63 (m, 2H), 7.51-7.49 (d, $J = 9.2$ Hz, 2H), 5.69 (s, 1H), 4.21-4.16 (dd, $J = 14.4$ Hz, 7.2 Hz, 2H), 1.74 (s, 3H), 1.49 (s, 3H), 1.23 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.5, 150.6, 146.9, 136.4, 134.5, 132.6, 130.8, 129.1, 127.7, 122.6, 121.7, 74.7, 63.7, 47.6, 25.1, 25.0, 13.9; **IR** (ν cm^{-1}) 3287, 1728, 1520, 1350, 1254, 1177, 1034, 756; **HRMS** (ESI) calcd. For $\text{C}_{19}\text{H}_{20}\text{N}_2\text{NaO}_6\text{S}$ $[\text{M}+\text{Na}]^+$: 427.0934, Found: 427.0940.

Ethyl 5-methyl-3-(4-nitrobenzyl)-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide (4-9i). White solide; m.p. 181–183 °C; ^1H (400

MHz, CDCl_3) δ 8.17-8.15 (dd ($J = 6.8$ Hz, 2.0 Hz, 2H), 7.69-7.4 (m, 2H), 7.51 (d, $J = 8.8$ Hz, 2H), 7.44 (d, $J = 7.6$ Hz, 1H), 5.60 (s, 1H), 4.33-4.24 (m, 2H), 3.62 (d, $J = 13.6$ Hz, 1H), 3.31 (d, $J = 13.6$ Hz, 1H), 2.54 (s, 3H), 1.32 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.5, 147.5, 144.9, 142.0, 138.5, 133.2, 131.8, 131.6, 124.9, 123.4, 121.5, 69.0, 63.9, 45.4, 22.0, 14.1; **IR** (ν cm^{-1}) 3456, 1736, 1601, 1524, 1346, 1184, 1053, 698; **HRMS** (ESI) calcd. For $\text{C}_{18}\text{H}_{18}\text{N}_2\text{NaO}_6\text{S}$ $[\text{M}+\text{Na}]^+$: 413.0778, Found: 413.0786.

Ethyl 5-methoxy-3-(4-nitrobenzyl)-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide (4-9j). White solide; m.p. 166–168 °C; ^1H

(400 MHz, CDCl_3) δ 8.16 (d, $J = 8.4$ Hz, 2H), 7.70 (d, $J = 8.8$ Hz, 1H), 7.51 (d, $J = 8.8$ Hz, 2H), 7.28 (d, $J = 2.0$ Hz, 2H), 7.13–7.11 (dd, $J = 8.4$

Hz, 2.0 Hz, 1H), 5.62 (s, 1H), 4.35–4.23 (m, 2H), 3.94 (s, 3H), 3.60 (d, $J = 13.2$ Hz, 1H),

3.32 (d, $J = 13.6$ Hz, 1H), 1.33 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.4,

164.0, 147.5, 141.9, 140.7, 131.6, 127.8, 123.4, 123.2, 117.0, 109.4, 68.7, 63.9, 56.1, 45.4,

14.1; IR ($\nu \text{ cm}^{-1}$) 3507, 1740, 1589, 1520, 1346, 1180, 1015, 745; HRMS (ESI) calcd. For

$\text{C}_{18}\text{H}_{18}\text{N}_2\text{NaO}_7\text{S}$ $[\text{M}+\text{Na}]^+$: 429.0727, Found: 429.0732.

2,2,6,6-Tetramethyl-1-((4-nitrobenzyl)oxy)piperidine (4). White

solid; m.p. 60–62 °C; ^1H (400 MHz, CDCl_3) δ 8.21–8.19 (dd, $J = 7.0$ Hz, 1.8 Hz, 2H), 7.50 (d, $J = 8.8$ Hz, 2H), 4.93 (s, 2H), 1.56–1.47 (m,

5H), 1.38–1.35 (m, 1H), 1.21 (s, 6H), 1.17 (s, 6H); ^{13}C NMR (100 MHz,

CDCl_3) δ 147.1, 146.0, 127.4, 123.5, 60.1, 39.7, 33.0, 20.3, 17.0; IR ($\nu \text{ cm}^{-1}$) 3483, 2936,

1601, 1516, 1342, 1011, 841, 737; HRMS (ESI) calcd. For $\text{C}_{16}\text{H}_{24}\text{N}_2\text{NaO}_3$ $[\text{M}+\text{Na}]^+$:

315.1679, Found: 315.16793.

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Chapter 5

Synthesis of Indanes via Carbene-Catalyzed Single-Electron-Transfer (SET) Process and Cascade Reactions

5.1 Introduction

5.1.1 Indanyl core containing molecules.

Indane (2,3-dihydro-1*H*-indene) ring system, a fused combination of aromatic benzene ring and aliphatic cyclopentane ring, is an attractive scaffold which was widely found in commercially available pharmaceuticals and nature products. For instance, Indantadol, a mono-substituted indane, can serve as an NMDA (N-methyl-D-aspartate) receptor antagonist and MAO (monoamine oxidase) inhibitor, and it is a potential drug for neuropathic pain and chronic cough treatment.¹ Disubstituted indane indatraline act as an amine uptake inhibitor that block the transport of methamphetamine to nerve terminals.² Trisubstituted indane caraphenol B is a nature product which is isolated from the dried roots of *caragana sinica*, a traditional Chinese medicine for the treatment of hypertension and contusion (Scheme 5.1).³ Some special molecules containing this skeleton have been used as efficient organocatalysts⁴ and ligands⁵.

Scheme 5.1 Structure of indane ring and selected examples of nature products containing indanyl core.

This bicyclic scaffold provides great biologically active possibilities by installing versatile substituents in different directionalities. By modifying the substituents, chemists can easily modify the biological activities of the target molecule, which provide opportunity

for chemists to develop new bioactive drugs.⁶ It is an attractive skeleton that the development of methodologies for the synthesis of indanyl core is extremely important. To date, a great number of approaches were developed to synthesize the indane derivatives, and these methods were including carbocyclization processes, ring contraction methods, ring expansion approaches and substituted functionalization of indane precursors.⁷

5.1.2 Our proposal

Our previous work has developed a NHC catalyzed reductive cross coupling reaction of nitrobenzyl bromide with nitroalkenes via SET process and formal 1,4-addition. The proposed reaction pathway was that at the beginning, the nitrobenzyl bromide underwent a single-electron reduced via SET process follow by elimination of bromide to give the nitrobenzyl radical intermediate, then this radical intermediate attacked the nitroalkene via a formal 1,4-addition process to provide a radical intermediate, which was further reduced to give the anion intermediate, finally, the protonation of anion intermediate provided the reductive coupling product (Scheme 5.2).⁸

Scheme 5.2 Proposed pathway of our previous reductive coupling of nitrobenzyl bromide and nitroalkenes.

We proposed that if we introduce a Michael acceptor unit to the ortho-position of phenyl ring of the nitroalkene, this modified nitroalkene may undergo a formal 1,4-addition by benzyl radical intermediate and an SET process to generate corresponding anion

intermediate, and this anion intermediate will undergo an intramolecular Michael addition to give a ring-closing product (Scheme 5.3). This ring-closing type is a 5-exo-trig process, and according to Baldwin's rule⁹, this ring-closure case is favored. This proposed cascade procedure¹⁰ will give an efficient pathway for the synthesis of indane derivatives.

Scheme 5.3 Proposed cascade reaction

5.2 Results and discussion

We used α,α -dimethyl 4-nitrobenzyl bromide **5-1a** and modified nitroalkene **5-2a** as model substrates to optimize the reaction conditions. Key results were summarized in Table 5.1. Fortunately, when we used methyl 4-formylbenzoate **5-3** as a reductant, 5 mol% pyrrolidone-derived NHC **5-C1** as catalyst, 2 equivalent of DIEA as base and carried out in CH₃OH at 0 °C, the desired cascade product **5-4a** was provided in 86% yield (entry 1), along with excellent diastereoselectivity (only one diastereomer was obtained). As was confirmed in our previous work, only electron-deficient NHC-catalysts were efficient for the reaction, so other N-C₆F₅ substituted NHC precursors **5-C2**~**5-C4** were tried, but no better results could be obtained (entries 2~4). The use of inorganic base K₂CO₃ and stronger organic base DBU also provided the desired product in moderated yields (entries 5~6). Using toluene as a solvent along with 10 equivalent of CH₃OH as additive provided the desired product **5-4a** in good yield, but worse than the case of using CH₃OH as solvent (entry 7). When NHC precursor was absent, the reaction could not occur (entry 8).

Table 5.1 Condition Optimization

entry	NHC	base	solvent	yield (%) ^a
1	5-C1	DIEA	CH ₃ OH	88(86) ^b
2	5-C2	DIEA	CH ₃ OH	31
3	5-C3	DIEA	CH ₃ OH	42
4	5-C4	DIEA	CH ₃ OH	59
5	5-C1	K ₂ CO ₃	CH ₃ OH	53
6	5-C1	DBU	CH ₃ OH	46
7 ^c	5-C1	DIEA	toluene	75
8	w/o NHC	DIEA	CH ₃ OH	no reaction

^aYield (based on **2a**) was estimated via ¹H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. ^b Isolated yield in parentheses. ^c10 equivalents CH₃OH was used.

With the optimized reaction conditions in hand, we then investigated the generalities of this cascade reaction. At the beginning, the scope of Nitrobenzyl bromides was evaluated using modified nitroalkene **5-2a** as model substrate. α,α -Disubstituted nitrobenzyl bromides as substrates proceeded excellently in this cascade reaction, and the desired products were isolated in 86~90% yields (**5-4a**~**5-4d**). Nitrobenzyl bromides bearing one substituent on α -position also work fine under our standard conditions, yielding the desired product in 79~88% (**5-4e**~**5-4h**). α -Substituent containing unsaturated unit or electron-withdrawing functional group was also tolerated in this reaction (**5-4g** and **5-4h**). α -Non-substituted nitrobenzyl bromide was also suitable for this reaction, provided the corresponding indane derivative **5-4i** in 48% yield. Moving the nitro group to the ortho-position could also lead to the desired products without any loss of the reaction yields (**5-4j** and **5-4k**). The low yields of non-substituted nitrobenzyl bromides compared to α -

substituted nitrobenzyl bromides were likely due to the lower stability of the corresponding nitrobenzyl radical intermediates.¹¹

Table 5.2 Examples of Nitrobenzyl Bromides^{a,b}

^aReaction condition as in Table 1, entry 1. ^bIsolated yield. ^cFor **5-4d**–**5-4h**, **5-4k**, dr between 1.1:1 and 1.2:1, determined via ¹H NMR.

Then we turn our attention to evaluate the generality of modified nitroalkenes. When α,β -unsaturated ester was used as a Michael acceptor unit to nitroalkene, either electron-withdrawing or electron-donating substituents on the phenyl ring all worked excellently, providing the desired product in high yields (**5-4l**–**5-4n**). α,β -Unsaturated ketone as Michael acceptor unit worked fine as well, but the yield was slightly dropped (**5-4o**). Electron-withdrawing and electron-donating substituents placed on the para-position of phenyl ring of the Michael acceptor unit were all tolerated, producing the desired annulation products in moderate yields (**5-4p**–**5-4s**). Functional group substituted on meta-position of

Michael acceptor unit was also suitable for the reaction (**5-4t**). The aryl ring on the Michael acceptor unit could be changed to heteroaryl rings without any loss of the reaction yields (**5-4u~5-4w**). Alkyl group replaced aryl ring on the Michael acceptor unit work fine as well, giving the desired product in 72% yield (**5-4x**). Finally, we found that α,β -unsaturated nitrile could also be served as the Michael acceptor unit in this reaction, and the desired product was provided in 63% yields.

Table 5.3 Examples of Modified Nitroalkenes.^{a,b}

^aReaction condition as in Table 1, entry 1. ^bIsolated yield.

The structures of the cascade annulation products were confirmed by the X-ray crystallographic analysis of the single-crystal of product **5-4o** (Fig. 5.1), CCDC 1560178.

The cascade annulation product **5-4a** could be reduced by hydrogenation catalyzed by

Raney Nickel under 10 atm to corresponding amine, which could undergo intramolecular transesterification to form a tricyclic amide **5-6** in quantity yield. And **5-4o** could be transformed to a fused ring product **5-7** in 83% yield via a reductive amination annulation process (Scheme 5.4).

Fig. 5.1 Crystallation structure of product **5-4o**.

Scheme 5.4 Synthetic Transformations of **5-5a** and **5-5o**.

5.3 Proposed Reaction Pathway.

The proposed reaction pathway was described in Scheme 5.5. At the beginning, NHC nucleophilic attacked the aldehyde **5-3** to generate Breslow intermediate **5-A**, then the single-electron was transferred from Breslow intermediate **5-A** to nitrobenzyl bromide **5-**

1a generating corresponding radical cation **5-B** and radical anion **5-C**. Heterolytic cleavage of radical **5-C** released bromide and generated radical intermediate **5-D**, and this radical **5-D** underwent a formal 1,4-addition to modified nitroalkene **5-2a** and follow by an SET process to generate anion intermediate **5-E**, then intramolecular Michael addition formed indane derived anion intermediate **5-F**, finally, the protonation of **5-F** gave the desired product **5-4a**. In the catalytic cycle, radical cation **5-B** underwent a deprotonation and SET process to generate acylazolium intermediate **5-G**, and this intermediate was trapped by CH₃OH to give the corresponding carboxylic ester and regenerate NHC to finish the catalytic cycle.

Scheme 5.5 Proposed Reaction Pathways.

5.4 Summary

In summary, we have developed an NHC-catalyzed cascade annulation reaction for the synthesis of indane derivatives. SET from Breslow intermediate to nitrobenzyl bromide generates nitrobenzyl radical intermediate which initiate the reaction. The cascade reaction undergoes a formal 1,4-addition follow by intramolecular Michael addition to give the indane derivatives. The diastereoselectivities of the products are excellent, since for each of the products only one diastereomer can be obtained. The reaction scope is rather

extensive that many sensitive functional groups are tolerated. This synthetic methodology is an important complement of our NHC-catalyzed radical chemistry.

5.5 Experimental section

5.5.1 General Information

Commercially available materials purchased from Alfa Aesar or Aldrich was used as received. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a Bruker AV400 (400 MHz) spectrometer. Chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethylsilane (δ 0.00). ^1H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), dd (doublet of doublets); m (multiplets), etc. All first-order splitting patterns were assigned base on the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker AV400 (100 MHz) spectrometer. High resolution mass spectral analysis (HRMS) was performed on Waters Q-TOF Premier mass spectrometer. X-ray crystallography analysis was performed on Bruker X8 APEX X-ray diffractometer. Flash chromatography was performed using Merck silica gel 60 with distilled solvents. Analytical thin-layer chromatography (TLC) was carried out on Merck 60 F254 pre-coated silica gel plate (0.2 mm thickness). Visualization was performed using a UV lamp.

5.5.2 General Procedures for the catalytic cascade reactions.

To a dry Schlenk tube equipped with a magnetic stir bar, was added benzyl bromide **5-1** (0.15 mmol), nitroalkene **5-2** (0.10 mmol), aldehyde **5-3** (0.15 mmol) and triazolium salt **5-C1** (1.8 mg, 0.005 mmol), then the tube was closed with a septum. Methanol (2.0 mL) was added and the resulting solution was degassed 3 times (freeze-pump-thaw: cooled in liquid nitrogen and degassed via vacuum evacuation (5 min), backfilled with nitrogen, and warm to room temperature). *N,N*-diisopropylethylamine (35 μ L, 0.2 mmol) was added at 0 $^{\circ}$ C and the reaction mixture was stirred at this temperature overnight. Then the resulting mixture was concentrated under reduced pressure, and the residue was purified via column chromatography on silica gel to afford the coupling product **5-4**.

5.5.3 Further Transformations of the Products.

To a test tube was added stirred bar and Raney Ni (100 mg, wet weight), the wet Raney was washed by CH_3OH for three times, then compound **5-4a** (41.2 mg, 0.1 mmol) in CH_3OH solution was added, and the resulting solution was hydrogenated at 10 atm for 48 h. Then the catalyst was filtered and washed with CH_3OH , the filtrate was concentrated under reduced pressure to give amide **5-6** (30.3 mg, 99%) as a white solid, m.p. 229-231 $^{\circ}$ C; ^1H NMR (400 MHz, CDCl_3) δ 7.26-7.21 (m, 1H), 7.16-7.10 (m, 2H), 6.98-6.90 (m, 3H), 6.63-6.57 (m, 2H), 6.08 (s, 1H), 4.07 (d, J = 6.4 Hz, 1H), 3.61 (brs, 2H), 3.49-3.24 (m, 1H), 3.28 (s, 1H), 2.69 (dd, J = 17.0, 9.6 Hz, 1H), 2.32 (d, J = 17.0 Hz, 1H), 1.31 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 176.66, 146.06, 144.53, 141.75, 137.54, 127.99, 127.22, 127.01, 124.48, 115.03, 63.31, 61.95, 44.11, 40.56, 37.03, 27.32, 25.68; IR (ν cm^{-1}) 3408, 3090, 2889, 1732, 1599, 1548, 1518, 1348, 1290, 1240, 1213, 1159, 1096, 1022,

860, 705; **HRMS (ESI)** calcd. For $C_{20}H_{23}N_2O$ $[M+H]^+$: 307.1810, Found: 307.1816.

To a stirred solution of compound **5-4o** (44.4 mg, 0.1 mmol) in CH_3OH solution was added Zn powder (130 mg, 2 mmol) follow by the addition of a mixture of 1N HCl (0.8 ml) and HOAc (0.4 ml). The resulting mixture was allowed to stir overnight. Then the reaction was concentrated by rotary evaporator, the residue was dissolved in CH_3OH and then K_2CO_3 (50 mg) was added and the resulting mixture was allowed to stir overnight. The K_2CO_3 was filtered, the filtrate was concentrated and the residue was purified by column chromatography (eluent: $CH_3OH:CH_2Cl_2 = 1:20$, with 1% $NH_3 \cdot H_2O$, dried over Na_2SO_4) to afford piperidinone **5-7** (31.7 mg, 83%) as a white solid, m.p. 176-178 °C; **1H NMR (400 MHz, $CDCl_3$)** δ 7.76-7.70 (m, 2H), 7.37-7.29 (m, 3H), 7.17-7.12 (m, 1H), 7.11-7.07 (m, 1H), 7.06-7.01 (m, 2H), 6.99 (t, $J = 7.4$ Hz, 1H), 6.65-6.59 (m, 3H), 4.75-4.71 (m, 1H), 3.80 (s, 1H), 3.47 (t, $J = 7.5$ Hz, 1H), 3.25 (ddd, $J = 16.9, 8.7, 2.4$ Hz, 1H), 3.11-3.05 (m, 1H), 2.72 (brs, 2H), 1.47 (s, 3H), 1.33 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 170.9, 147.4, 144.2, 142.9, 138.3, 134.6, 130.4, 128.4, 127.9, 127.8, 127.3, 127.1, 126.3, 124.2, 114.9, 81.5, 62.2, 45.9, 43.0, 41.1, 27.9, 25.7; **IR (ν cm^{-1})** 3409, 3339, 2961, 2901, 1656, 1608, 1508, 1359, 1306, 1289, 1182, 1033, 828, 742, 701; **HRMS (ESI)** calcd. for $C_{26}H_{27}N_2$ $(M+H)^+$: 367.2174, Found: 367.2170.

5.5.4 Substrates preparation.

General procedure for the synthesis of modified nitroalkenes **5-2**

The modified nitroalkenes were synthesized follow the literature's procedure.¹²

Ethyl (E)-3-(4-methoxy-2-((E)-2-nitrovinyl)phenyl)acrylate (5-**2n). ¹H NMR (400 MHz, CDCl₃) δ 8.34 (d, *J* = 13.5 Hz, 1H), 7.90**

(d, *J* = 15.7 Hz, 1H), 7.60 (d, *J* = 8.7 Hz, 1H), 7.45 (d, *J* = 13.4 Hz, 1H), 7.04 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.01-6.09 (m, 1H), 6.28 (d, *J* = 15.7 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 1H), 3.87 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 166.5, 161.0, 139.8, 139.4, 136.0, 131.0, 129.9, 128.3, 121.1, 118.1, 112.8, 60.9, 55.7, 14.4; **HRMS (ESI)** calcd. for C₁₄H₁₆NO₅ (M+H)⁺: 278.1028, Found: 278.1031.

(E)-3-(2-((E)-2-Nitrovinyl)phenyl)-1-phenylprop-2-en-1-one (5-2o).**¹H NMR (400 MHz, CDCl₃) δ 8.42 (d, *J* = 13.5 Hz, 1H), 8.09 (d, *J* = 15.5**

Hz, 1H), 8.07-8.02 (m, 2H), 7.75 (d, *J* = 7.7 Hz, 1H), 7.65-7.45 (m, 7H), 7.43 (d, *J* = 15.5 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 189.7, 140.4, 139.3, 137.8, 136.5, 136.1, 133.4, 132.0, 130.5, 130.0, 128.9, 128.8, 128.7, 128.5, 127.2; **HRMS (ESI)** calcd. for C₁₇H₁₄NO₃ (M+H)⁺: 280.0974, Found: 280.0969.

(E)-1-(4-Bromophenyl)-3-(2-((E)-2-nitrovinyl)phenyl)prop-2-en-**1-one (5-2p). ¹H NMR (400 MHz, CDCl₃) δ 8.40 (d, *J* = 13.5 Hz, 1H),****8.09 (d, *J* = 15.4 Hz, 1H), 7.92-7.87 (m, 2H), 7.74 (d, *J* = 7.2 Hz, 1H),**

7.68-7.63 (m, 2H), 7.60-7.48 (m, 4H), 7.38 (d, *J* = 15.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 188.4, 140.9, 139.3, 136.4, 136.2, 136.0, 132.2, 132.0, 130.7, 130.2, 130.0, 128.8, 128.6, 128.5, 126.4; **HRMS (ESI)** calcd. for C₁₇H₁₂NO₃BrNa (M+Na)⁺: 378.9898, Found: 379.9908.

(E)-1-(4-fluorophenyl)-3-(2-((E)-2-nitrovinyl)phenyl)prop-2-en-1-one (5-2q). ^1H NMR (400 MHz, CDCl_3) δ 8.40 (d, $J = 13.5$ Hz, 1H), 8.11-8.03 (m, 3H), 7.74 (d, $J = 7.7$ Hz, 1H), 7.61-7.46 (m, 4H), 7.40 (d, $J = 15.5$ Hz, 1H), 7.21-7.15 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 187.9, 160.0 (d, $J = 255.8$ Hz), 140.6, 139.2, 136.3, 136.1, 134.1, (d, $J = 2.8$ Hz), 132.0, 131.4, (d, $J = 9.4$ Hz), 130.6, 129.9, 128.6 (d, $J = 25.7$ Hz), 126.6, 116.2, 116.0; **HRMS (ESI)** calcd. for $\text{C}_{17}\text{H}_{13}\text{NO}_3\text{F}$ ($\text{M}+\text{H}$) $^+$: 298.0879, Found: 298.0879.

(E)-3-(2-((E)-2-Nitrovinyl)phenyl)-1-(p-tolyl)prop-2-en-1-one (5-2r). ^1H NMR (400 MHz, CDCl_3) δ 8.41 (d, $J = 13.5$ Hz, 1H), 8.07 (d, $J = 15.5$ Hz, 1H), 7.98-7.92 (m, 2H), 7.75 (d, $J = 7.6$ Hz, 1H), 7.60-7.40 (m, 5H), 7.35-7.30 (m, 2H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 189.2, 144.4, 140.0, 139.2, 136.6, 136.2, 135.2, 131.9, 130.4, 129.9, 129.6, 128.9, 128.8, 128.5, 127.3, 21.8; **HRMS (ESI)** calcd. for $\text{C}_{18}\text{H}_{16}\text{NO}_3$ ($\text{M}+\text{H}$) $^+$: 294.1130, Found: 294.1121.

(E)-1-(4-Methoxyphenyl)-3-(2-((E)-2-nitrovinyl)phenyl)prop-2-en-1-one (5-2s). ^1H NMR (400 MHz, CDCl_3) δ 8.43 (d, $J = 13.5$ Hz, 1H), 8.09-8.02 (m, 3H), 7.74 (d, $J = 7.6$ Hz, 1H), 7.60-7.40 (m, 5H), 7.03-6.97 (m, 2H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 187.8, 163.9, 139.5, 139.1, 136.6, 136.2, 131.9, 131.0, 130.6, 130.3, 129.7, 128.7, 128.4, 127.1, 114.1, 55.6; **HRMS (ESI)** calcd. for $\text{C}_{18}\text{H}_{16}\text{NO}_4$ ($\text{M}+\text{H}$) $^+$: 310.1079, Found: 310.1085.

(E)-1-(3-Bromophenyl)-3-(2-((E)-2-nitrovinyl)phenyl)prop-2-en-1-one (5-2t). ^1H NMR (400 MHz, CDCl_3) δ 8.40 (d, $J = 13.5$ Hz, 1H), 8.14 (d, $J = 1.7$ Hz, 1H), 8.10 (d, $J = 15.5$ Hz, 1H), 7.97-7.93 (m, 1H), 7.78-7.71 (m, 2H), 7.61-7.54 (m, 2H), 7.52-7.47 (m, 2H), 7.40 (t, $J = 7.8$ Hz, 1H), 7.38 (d, $J = 15.5$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 188.1, 141.2, 139.5, 139.3, 136.2, 136.1,

135.9, 132.0, 131.7, 130.8, 130.5, 130.1, 128.7, 128.5, 127.2, 126.3, 123.3; **HRMS (ESI)** calcd. for $C_{17}H_{12}NO_3BrNa$ ($M+Na$)⁺: 379.9898, Found: 379.9897.

(E)-1-(Furan-2-yl)-3-(2-((E)-2-nitrovinyl)phenyl)prop-2-en-1-one (5-2u). ¹H NMR (400 MHz, CDCl₃) δ 8.41 (d, *J* = 13.5 Hz, 1H), 8.12 (d, *J* = 15.6 Hz, 1H), 7.75 (d, *J* = 7.7 Hz, 1H), 7.67 (s, 1H), 7.60-7.45 (m, 4H),

7.38-7.30 (m, 2H), 6.64-6.59 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 177.3, 153.5, 147.1, 139.6, 139.3, 136.2, 136.1, 131.9, 130.6, 130.0, 128.8, 128.5, 126.3, 118.4, 112.9; **HRMS (ESI)** calcd. for $C_{15}H_{12}NO_4$ ($M+H$)⁺: 270.0766, Found: 270.0768.

(E)-3-(2-((E)-2-Nitrovinyl)phenyl)-1-(thiophen-2-yl)prop-2-en-1-one (5-2w). ¹H NMR (400 MHz, acetone-*d*₆) δ 8.48 (d, *J* = 13.4 Hz, 1H), 8.18 (d, *J* = 3.6 Hz, 1H), 8.13 (d, *J* = 15.4 Hz, 1H), 8.00 (d, *J* = 7.7 Hz, 1H),

7.96 (d, *J* = 4.8 Hz, 1H), 7.89-7.82 (m, 2H), 7.69 (d, *J* = 15.4 Hz, 1H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.28 (t, *J* = 4.4 Hz, 1H); ¹³C NMR (100 MHz, acetone-*d*₆) δ 181.9, 146.5, 140.6, 139.8, 136.9, 136.4, 135.9, 134.0, 132.6, 131.4, 131.1, 129.6, 129.6, 129.4, 127.1; **HRMS (ESI)** calcd. for $C_{15}H_{12}NO_3S$ ($M+H$)⁺: 286.0538, Found: 286.0545.

(E)-4-(2-((E)-2-Nitrovinyl)phenyl)but-3-en-2-one (5-2x). ¹H NMR (400 MHz, CDCl₃) δ 8.35 (d, *J* = 13.5 Hz, 1H), 7.82 (d, *J* = 15.8 Hz, 1H), 7.65 (d, *J* = 13.5 Hz, 1H), 7.60-7.45 (m, 2H), 6.64 (d, *J* = 15.9 Hz, 1H);

¹H NMR (400 MHz, CDCl₃) δ 197.5, 139.3, 138.7, 135.8, 132.0, 131.5, 130.5, 129.7, 128.5, 28.3; **HRMS (ESI)** calcd. for $C_{12}H_{12}NO_3$ ($M+H$)⁺: 218.0817, Found: 218.0821.

(E)-3-(2-((E)-2-Nitrovinyl)phenyl)acrylonitrile (5-2y). ^1H NMR (400 MHz, CDCl_3) δ 8.26 (d, $J = 13.5$ Hz, 1H), 7.74 (d, $J = 16.4$ Hz, 1H), 7.61-7.50 (m, 4H), 7.47 (d, $J = 13.5$ Hz, 1H), 5.88 (d, $J = 16.4$ Hz, 1H); ^1H NMR (400 MHz, CDCl_3) δ 146.6, 139.7, 135.0, 134.4, 132.1, 131.4, 129.3, 128.5, 127.6, 117.3, 101.5; HRMS (ESI) calcd. for $\text{C}_{11}\text{H}_9\text{N}_2\text{O}_4$ ($\text{M}+\text{H}$) $^+$: 201.0664, Found: 201.0668.

5.5.5 Characterization of products 5-4.

(±)-Ethyl 2-((1R,2R,3R)-2-nitro-3-(2-(4-nitrophenyl)propan-2-yl)-2,3-dihydro-1H-inden-1-yl)acetate (5-4a). Following the general procedure, the title compound **5-4a** (35.5 mg, 86%) was purified by column chromatography (eluent: AcOEt:Hexane = 1:4) to be obtained as a white solid, m.p. 144-146 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.19-8.13 (m, 2H), 7.41-7.36 (m, 2H), 7.28 (t, $J = 7.4$ Hz, 1H), 7.18 (t, $J = 7.4$ Hz, 1H), 7.05 (d, $J = 7.6$ Hz, 1H), 6.83 (d, $J = 7.6$ Hz, 1H), 5.22 (d, $J = 7.3$ Hz, 1H), 4.21-4.11 (m, 2H), 4.03 (s, 1H), 3.69-3.61 (m, 1H), 2.83 (dd, $J = 17.6, 5.5$ Hz, 1H), 2.38 (dd, $J = 17.6, 9.5$ Hz, 1H), 1.48 (s, 3H), 1.46 (s, 3H), 1.26 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.4, 153.8, 146.8, 142.2, 140.3, 128.6, 127.7, 127.4, 126.2, 123.7, 123.1, 92.1, 61.2, 61.2, 44.2, 42.2, 34.0, 26.6, 26.4, 14.2; IR (ν cm^{-1}) 3072, 2970, 2941, 1728, 1607, 1548, 1516, 1479, 1348, 1186, 1095, 1014, 855, 760, 704; HRMS (ESI) calcd. for $\text{C}_{22}\text{H}_{25}\text{N}_2\text{O}_6$ ($\text{M}+\text{H}$) $^+$: 413.1713, Found: 413.1719.

(±)-Ethyl 2-((1R,2R,3R)-2-nitro-3-(3-(4-nitrophenyl)pentan-3-yl)-2,3-dihydro-1H-inden-1-yl)acetate (5-4b). Following the general procedure, the title compound **5-4b** (39.8 mg, 90%) was purified by column chromatography (eluent: AcOEt:Hexane = 1:4) to

be obtained as a white solid, m.p. 130-132 °C;; ^1H NMR (400 MHz, CDCl_3) δ 8.02-7.97 (m, 2H), 7.42 (d, J = 7.1 Hz, 1H), 7.36-7.27 (m, 2H), 7.09-7.02 (m, 2H), 6.89 (d, J = 7.2 Hz, 1H), 5.21 (d, J = 6.9 Hz, 1H), 4.16-4.04 (m, 2H), 3.93 (s, 1H), 2.68 (dd, J = 17.6, 4.9 Hz, 1H), 2.45-2.37 (m, 1H), 2.27-2.17 (m, 3H), 2.15-2.01 (m, 2H), 1.22 (t, J = 7.2 Hz, 3H), 1.22 (t, J = 7.2 Hz, 3H), 1.04 (t, J = 7.3 Hz, 3H), 0.78 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.1, 150.2, 146.6, 142.8, 140.6, 128.6, 128.1, 127.6, 126.7, 123.0, 122.9, 92.1, 61.1, 57.4, 47.6, 43.6, 33.3, 26.6, 26.2, 14.2, 8.1, 8.1; IR (ν cm^{-1}) 3072, 2976, 2937, 2881, 1732, 1602, 1549, 1522, 1462, 1426, 1373, 1348, 1325, 1303, 1261, 1202, 1182, 1094, 1013, 951, 856, 756, 700; HRMS (ESI) calcd. for $\text{C}_{24}\text{H}_{29}\text{N}_2\text{O}_6$ ($\text{M}+\text{H}$) $^+$: 441.2026, Found: 441.2031.

(±)-Ethyl 2-((1R,2R,3R)-2-nitro-3-(2-(4-nitrophenyl)butan-2-yl)-2,3-dihydro-1H-inden-1-yl)acetate (**5-4c**). Following the general procedure, the crude product was purified by flash column chromatography (EtOAc:Hexane = 1:4) to afford the diastereomers of

title compound (36.6 mg, 86%, total yield of **5-4c-a** and **5-4c-b**, dr 1.1:1, determined by ^1H NMR spectroscopy.

5-4c-a, white solid, m.p. 160-162 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.16-8.11 (m, 2H), 7.28-7.22 (m, 3H), 7.12-7.07 (m, 1H), 7.00 (d, J = 7.6 Hz, 1H), 6.49 (d, J = 7.6 Hz, 1H), 5.43 (d, J = 7.2 Hz, 1H), 4.22-4.13 (m, 2H), 3.95 (s, 1H), 3.46-3.38 (m, 1H), 2.81 (dd, J = 17.6, 5.4 Hz, 1H), 2.38 (dd, J = 17.6, 9.7 Hz, 1H), 2.26-2.15 (m, 1H), 1.98-1.89 (m, 1H), 1.40 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H), 0.69 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.4, 151.4, 146.7, 142.2, 140.2, 128.6, 128.3, 127.6, 126.2, 123.5, 123.0, 91.9, 61.8, 61.2, 45.9, 44.1, 33.9, 33.1, 20.7, 14.2, 8.6; IR (ν cm^{-1}) 3068, 2972, 2927, 2879, 1730, 1607, 1549, 1516, 1466, 1375, 1348, 1192, 1099, 1020, 856, 763, 709; HRMS (ESI) calcd. for $\text{C}_{23}\text{H}_{27}\text{N}_2\text{O}_6$ ($\text{M}+\text{H}$) $^+$: 427.1869, Found: 427.1866.

5-4c-b, white solid, m.p. 120-122 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.23-8.18 (m, 2H), 7.45-7.40 (m, 2H), 7.36-7.27 (m, 3H), 7.10-7.06 (m, 1H), 4.98 (d, $J = 7.3$ Hz, 1H), 4.16 (qd, $J = 7.1, 1.8$ Hz, 1H), 4.11 (s, 1H), 3.88-3.80 (m, 1H), 2.83 (dd, $J = 17.6, 5.4$ Hz, 1H), 2.34 (dd, $J = 17.6, 9.7$ Hz, 1H), 2.15-2.05 (m, 1H), 1.98-1.88 (m, 1H), 1.24 (s, 3H), 1.24 (t, $J = 7.4$ Hz, 3H), 0.71 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.5, 152.3, 146.7, 142.6, 140.5, 128.6, 127.9, 127.7, 126.8, 123.8, 123.2, 92.7, 61.3, 60.8, 46.2, 44.5, 34.0, 32.7, 19.7, 14.2, 8.6; IR (ν cm^{-1}) 3071, 2978, 2941, 1734, 1604, 1547, 1519, 1375, 1348, 1288, 1217, 1150, 1022, 858, 752, 708; HRMS (ESI) calcd. for $\text{C}_{22}\text{H}_{25}\text{N}_2\text{O}_6$ ($\text{M}+\text{H}$) $^+$: 427.1869, Found: 427.1866.

(±)-Ethyl 2-((1R,2R,3R)-2-nitro-3-(1-(4-nitrophenyl)cyclohexyl)-2,3-dihydro-1H-inden-1-yl)acetate (5-4d). Following the general procedure, the title compound **5-4d** (39.1 mg, 86%) was purified by column chromatography (eluent: $\text{AcOEt}:\text{Hexane} = 1:4$) to be obtained as a colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 8.09-8.03 (m, 2H), 7.30-7.22 (m, 2H), 7.20-7.10 (m, 2H), 6.94-6.87 (m, 2H), 5.30 (d, $J = 6.6$ Hz, 1H), 4.19-4.08 (m, 2H), 3.76 (s, 1H), 2.75-2.65 (m, 1H), 2.63-2.55 (m, 1H), 2.30-2.20 (m, 2H), 1.90-1.80 (m, 2H), 1.75-1.55 (m, 3H), 1.49-1.32 (m, 2H), 1.24 (t, $J = 7.2$ Hz, 3H), 1.15-1.02 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.2, 149.2, 146.6, 142.5, 140.1, 128.7, 128.6, 127.5, 126.7, 123.4, 122.9, 91.6, 61.1, 45.8, 43.8, 35.3, 34.8, 33.4, 26.0, 22.1, 22.1, 14.2; IR (ν cm^{-1}) 3058, 2973, 2942, 1726, 1602, 1549, 1513, 1346, 1182, 1092, 1011, 852, 758, 708; HRMS (ESI) calcd. for $\text{C}_{25}\text{H}_{29}\text{N}_2\text{O}_6$ ($\text{M}+\text{H}$) $^+$: 453.2026, Found: 453.2030.

(±)-Ethyl

2-((1R,2R,3R)-2-nitro-3-((R)-4-

nitrophenyl)(phenyl)methyl)-2,3-dihydro-1H-inden-1-yl)acetate

(5-4e). Following the general procedure, the crude product was purified by flash column chromatography (EtOAc:Hexane = 1:3) to

afford the title compound (40.9 mg, 88%) as a white solid consisting of two diastereomers (d.r. 1.1:1, as determined by ^1H NMR spectroscopy); m.p. 154-156 °C; ^1H NMR (400 MHz, CDCl_3) (mixture of two diastereomers, both isomers quoted) δ 8.21-8.17 (m, 2H), 8.16-8.12 (m, 2H), 7.50-7.46 (m, 2H), 7.38-7.33 (m, 4H), 7.32-7.27 (m, 6H), 7.26-7.21 (m, 2H), 7.17-7.14 (m, 2H), 7.13-7.08 (m, 2H), 7.03-6.97 (m, 2H), 6.34 (d, $J = 7.6$ Hz, 1H), 6.29 (d, $J = 7.6$ Hz, 1H), 5.24 (dd, $J = 7.0, 1.2$ Hz, 1H), 5.24 (dd, $J = 7.0, 1.5$ Hz, 1H), 4.69-4.62 (m, 2H), 4.22-4.00 (m, 8H), 2.94-2.86 (m, 2H), 2.53 (dd, $J = 8.5, 2.7$ Hz, 1H), 2.48 (dd, $J = 8.5, 2.7$ Hz, 1H), 1.26 (t, $J = 7.1$ Hz, 3H), 1.25 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) (mixture of two diastereomers, both isomers quoted) δ 171.4, 171.4, 149.4, 149.3, 147.1, 147.1, 141.2, 141.1, 140.8, 140.7, 140.3, 140.2, 129.6, 129.6, 129.1, 128.9, 128.7, 128.6, 128.5, 128.0, 127.9, 127.8, 127.7, 125.8, 125.5, 124.4, 124.0, 123.3, 123.1, 92.9, 92.7, 61.3, 54.9, 53.5, 53.4, 43.2, 43.0, 33.9, 33.8, 14.2; IR (ν cm^{-1}) 3068, 2972, 2941, 1734, 1718, 1607, 1597, 1541, 1523, 1491, 1377, 1348, 1292, 1192, 1172, 1113, 1013, 864, 766, 764, 708, 702; HRMS (ESI) calcd. for $\text{C}_{26}\text{H}_{25}\text{N}_2\text{O}_6$ ($\text{M}+\text{H}$) $^+$: 461.1713, Found: 461.1719.

(±)-Ethyl 2-((1R,2R,3R)-2-nitro-3-((S)-1-(4-nitrophenyl)propyl)-2,3-dihydro-1H-inden-1-yl)acetate (5-4f). Following the general

procedure, the crude product was purified by flash column chromatography (EtOAc:Hexane = 1:4) to afford the title compound

(35.1 mg, 84%) as a colorless oil consisting of two diastereomers (d.r. 1.2:1, as determined by ^1H NMR spectroscopy). ^1H NMR (400 MHz, CDCl_3) (mixture of two diastereomers,

both isomers quoted) δ 8.18-8.13 (m, 2H), 8.10-8.05 (m, 2H), 7.40-7.36 (m, 1H), 7.35-7.28 (m, 2H), 7.27-7.22 (m, 3H), 7.20-7.15 (m, 1H), 7.09-6.99 (m, 4H), 6.90 (d, $J = 7.5$ Hz, 1H), 5.38 (dd, $J = 7.0, 1.5$ Hz, 1H), 5.07 (dd, $J = 6.7, 0.8$ Hz, 1H), 4.22-4.12 (m, 4H), 4.04 (d, $J = 6.5$ Hz, 1H), 3.98 (d, $J = 8.1$ Hz, 1H), 3.68 (dd, $J = 9.2, 6.2$ Hz, 1H), 3.46 (dd, $J = 9.2, 6.3$ Hz, 1H), 2.98 (ddd, $J = 10.8, 6.6, 4.6$ Hz, 1H), 2.88-2.83 (m, 3H), 2.42 (dd, $J = 17.6, 9.4$ Hz, 1H), 2.38 (dd, $J = 17.6, 9.5$ Hz, 1H), 2.11-1.97 (m, 2H), 1.96-1.82 (m, 2H), 1.26 (t, $J = 7.1$ Hz, 3H), 1.25 (t, $J = 7.1$ Hz, 3H), 0.82 (t, $J = 7.4$ Hz, 3H), 0.79 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) (mixture of two diastereomers, both isomers quoted) δ 171.4, 171.3, 149.0, 148.8, 147.2, 141.9, 141.3, 140.9, 140.7, 129.4, 129.1, 128.5, 128.5, 128.0, 127.9, 125.7, 125.4, 124.0, 123.7, 123.3, 123.2, 93.1, 92.1, 61.2, 55.3, 54.9, 51.3, 50.3, 43.6, 43.5, 33.7, 33.5, 26.5, 26.1, 14.2, 12.2, 12.0; IR ($\nu \text{ cm}^{-1}$) 3076, 2968, 2936, 2878, 1732, 1605, 1602, 1549, 1522, 1458, 1346, 1294, 1180, 1110, 1028, 858, 754, 702; HRMS (ESI) calcd. for $\text{C}_{22}\text{H}_{25}\text{N}_2\text{O}_6$ ($\text{M}+\text{H}$) $^+$: 413.1713, Found: 413.1709.

(±)-Ethyl 2-((1R,2R,3R)-2-nitro-3-((S)-1-(4-nitrophenyl)but-3-en-1-yl)-2,3-dihydro-1H-inden-1-yl)acetate (5-4g). Following the general procedure, the crude product was purified by flash column chromatography (EtOAc:Hexane = 1:4) to afford the title compound

(33.6 mg, 79%) as a colorless oil consisting of two diastereomers (d.r. 1.2:1, as determined by ^1H NMR spectroscopy). ^1H NMR (400 MHz, CDCl_3) (mixture of two diastereomers, both isomers quoted) δ 8.13-8.09 (m, 2H), 8.09-8.04 (m, 2H), 7.41-7.37 (m, 1H), 7.36-7.24 (m, 3H), 7.23-7.15 (m, 3H), 7.08-6.97 (m, 5H), 5.65-5.52 (m, 2H), 5.39 (dd, $J = 7.0, 1.0$ Hz, 1H), 5.14 (d, $J = 6.8$ Hz, 1H), 5.08-4.97 (m, 4H), 4.22-4.12 (m, 4H), 4.09 (d, $J = 6.2$ Hz, 1H), 4.05 (d, $J = 7.1$ Hz, 1H), 3.50 (dt, $J = 9.5, 6.2$ Hz, 1H), 3.40 (dt, $J = 9.4, 6.5$ Hz, 1H), 3.22 (dt, $J = 9.8, 5.9$ Hz, 1H), 3.10 (dt, $J = 8.7, 6.6$ Hz, 1H), 2.87-2.57 (m, 6H), 2.41 (dd, $J = 17.3, 9.7$ Hz, 1H), 2.37 (dd, $J = 17.1, 9.6$ Hz, 1H), 1.26 (t, $J = 7.1$ Hz, 3H), 1.26 (t,

$J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) (mixture of two diastereomers, both isomers quoted) δ 171.3, 171.3, 148.2, 147.3, 147.2, 141.7, 141.5, 141.0, 140.4, 134.6, 134.5, 129.4, 129.1, 128.6, 128.6, 128.1, 128.0, 125.5, 125.4, 123.8, 123.7, 123.3, 118.7, 118.3, 93.1, 91.5, 61.2, 54.5, 54.3, 49.2, 48.3, 43.6, 43.6, 37.6, 37.3, 33.7, 33.5, 14.2; IR (ν cm^{-1}) 3080, 2972, 2936, 2875, 1729, 1665, 1602, 1548, 1523, 1364, 1348, 1294, 1182, 1118, 1020, 921, 858, 748, 722, 701; HRMS (ESI) calcd. for $\text{C}_{23}\text{H}_{25}\text{N}_2\text{O}_6$ ($\text{M}+\text{H}$) $^+$: 425.1713, Found: 425.1717.

(±)-Ethyl (S)-3-((1R,2R,3R)-3-(2-ethoxy-2-oxoethyl)-2-nitro-2,3-dihydro-1H-inden-1-yl)-3-(4-nitrophenyl)propanoate (5-4h).

Following the general procedure, the crude product was purified by flash column chromatography (EtOAc:Hexane = 1:2) to afford the title compound (37.9 mg, 81%) as a colorless oil consisting of two diastereomers (d.r. 1.2:1, as determined by ^1H NMR spectroscopy). ^1H NMR (400 MHz, CDCl_3) (mixture of two diastereomers, both isomers quoted) δ 8.17-8.12 (m, 2H), 8.10-8.05 (m, 2H), 7.41-7.38 (m, 1H), 7.37-7.28 (m, 4H), 7.25-7.19 (m, 1H), 7.13-7.08 (m, 2H), 7.07-6.99 (m, 3H), 5.34 (dd, $J = 7.1, 1.2$ Hz, 1H), 5.07 (d, $J = 6.7$ Hz, 1H), 4.21-4.12 (m, 4H), 4.10-4.07 (m, 1H), 4.06-3.05 (m, 5H), 3.77-3.66 (m, 2H), 3.57-3.50 (m, 1H), 3.44-3.37 (m, 1H), 2.98 (dd, $J = 16.0, 5.9$ Hz, 1H), 2.92-2.75 (m, 5H), 2.42 (dd, $J = 17.6, 9.6$ Hz, 1H), 2.36 (dd, $J = 17.6, 9.6$ Hz, 1H), 1.26 (t, $J = 7.1$ Hz, 3H), 1.25 (t, $J = 7.1$ Hz, 3H), 1.14 (t, $J = 7.2$ Hz, 3H), 1.11 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) (mixture of two diastereomers, both isomers quoted) δ 171.3, 171.1, 170.8, 170.7, 147.6, 147.5, 147.2, 141.5, 141.0, 140.9, 139.9, 129.2, 128.9, 128.9, 128.9, 128.3, 128.2, 125.5, 125.4, 124.1, 123.8, 123.5, 123.5, 92.7, 91.6, 61.3, 61.2, 61.2, 61.1, 54.5, 54.1, 44.9, 44.3, 43.7, 43.5, 38.1, 37.9, 33.7, 33.5, 14.2, 14.2, 14.1; IR (ν cm^{-1}) 3078, 2984, 2940, 2876, 1736, 1605, 1551, 1522, 1348, 1254, 1175, 1111, 1026, 856, 756, 726, 702; HRMS (ESI) calcd. for $\text{C}_{24}\text{H}_{27}\text{N}_2\text{O}_8$ ($\text{M}+\text{H}$) $^+$: 471.1767, Found:

471.1764.

(±)-Ethyl 2-((1R,2S,3R)-2-nitro-3-(4-nitrobenzyl)-2,3-dihydro-1H-inden-1-yl)acetate (**5-4i**). Following the general procedure, the title compound **5-4i** (18.7 mg, 48%) was purified by column chromatography (eluent: AcOEt:Hexane = 1:4) to be obtained as a

colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 8.18-8.14 (m, 2H), 7.32-7.26 (m, 3H), 7.25-7.21 (m, 1H), 7.15 (d, $J = 7.2$ Hz, 1H), 7.00 (d, $J = 7.2$ Hz, 1H), 5.21 (dd, $J = 7.3, 3.6$ Hz, 1H), 4.23-4.14 (m, 3H), 4.09 (dd, $J = 15.1, 7.5$ Hz, 1H), 3.17-3.03 (m, 2H), 2.80 (dd, $J = 17.2, 6.5$ Hz, 1H), 2.50 (dd, $J = 17.2, 8.5$ Hz, 1H), 1.27 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.2, 147.2, 145.4, 141.5, 140.3, 130.2, 128.6, 128.4, 124.4, 124.0, 123.9, 92.6, 61.3, 49.6, 43.3, 39.3, 34.2, 14.2; IR (ν cm^{-1}) 3066, 2988, 2936, 2875, 1736, 1605, 1552, 1520, 1458, 1346, 1254, 1180, 1108, 1028, 857, 751, 702; HRMS (ESI) calcd. for $\text{C}_{20}\text{H}_{21}\text{N}_2\text{O}_6$ ($\text{M}+\text{H}$) $^+$: 385.1400, Found: 385.1406.

(±)-Ethyl 2-((1R,2S,3R)-2-nitro-3-(2-nitrobenzyl)-2,3-dihydro-1H-inden-1-yl)acetate (**5-4j**). Following the general procedure, the title compound **4k** (19.8 mg, 51%) was purified by column chromatography (eluent: AcOEt:Hexane = 1:4) to be obtained as a colorless oil; ^1H NMR

(400 MHz, CDCl_3) δ 8.04 (dd, $J = 8.2, 1.1$ Hz, 1H), 7.57 (dd, $J = 7.5, 1.2$ Hz, 1H), 7.46 (dd, $J = 8.2, 1.3$ Hz, 1H), 7.32-7.24 (m, 3H), 7.19-7.15 (m, 1H), 7.14-7.10 (m, 1H), 5.32 (dd, $J = 7.2, 3.4$ Hz, 1H), 4.30 (dd, $J = 15.0, 7.5$ Hz, 1H), 4.25-4.16 (m, 3H), 3.52 (dd, $J = 13.7, 6.0$ Hz, 1H), 3.06 (dd, $J = 13.7, 9.4$ Hz, 1H), 2.83 (dd, $J = 17.1, 6.6$ Hz, 1H), 2.49 (dd, $J = 17.1, 8.4$ Hz, 1H), 1.27 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.3, 149.3, 142.1, 140.1, 133.6, 133.3, 132.7, 128.6, 128.5, 128.4, 125.7, 124.5, 123.7, 92.7, 61.2, 49.3, 43.3, 37.0, 34.3, 14.3; IR (ν cm^{-1}) 3081, 2978, 2922, 2847, 1736, 1608, 1552, 1524, 1379,

1348, 1251, 1169, 1026, 863, 791, 752, 698; **HRMS (ESI)** calcd. for $C_{20}H_{21}N_2O_6$ ($M+H$)⁺: 385.1400, Found: 385.1399.

(±)-Ethyl 2-((1R,2R,3R)-2-nitro-3-((S)-1-(2-nitrophenyl)ethyl)-2,3-dihydro-1H-inden-1-yl)acetate (**5-4k**). Following the general procedure, the crude product was purified by flash column chromatography (EtOAc:Hexane = 1:4) to afford the title compound (31.4 mg, 78%) as a

colorless oil consisting of two diastereomers (d.r. 1.2:1, as determined by 1H NMR spectroscopy). 1H NMR (400 MHz, $CDCl_3$) (mixture of two diastereomers, both isomers quoted) δ 7.79-7.74 (m, 2H), 7.67-7.58 (m, 2H), 7.57-7.53 (m, 1H), 7.51-7.47 (m, 1H), 7.46-7.38 (m, 2H), 7.34-7.27 (m, 3H), 7.26-7.21 (m, 1H), 7.16-7.07 (m, 3H), 6.70 (d, J = 7.5 Hz, 1H), 5.51 (dd, J = 7.3, 2.7 Hz, 1H), 5.11 (d, J = 6.5 Hz, 1H), 4.31-4.06 (m, 7H), 3.94 (d, J = 10.3 Hz, 1H), 3.82 (pent, J = 7.0 Hz, 1H), 3.43 (ddt, J = 10.2, 6.9, 6.9 Hz, 1H), 2.95 (dd, J = 17.5, 5.8 Hz, 1H), 2.86 (dd, J = 17.3, 6.1 Hz, 1H), 2.50 (dd, J = 9.1, 1.7 Hz, 1H), 2.45 (dd, J = 9.1, 1.9 Hz, 1H), 1.40 (d, J = 6.8 Hz, 6H), 1.29 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of two diastereomers, both isomers quoted) δ 171.4, 171.2, 150.2, 150.1, 141.5, 141.4, 141.2, 140.8, 138.4, 137.8, 133.3, 133.0, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.7, 126.3, 124.8, 124.7, 124.5, 123.4, 123.3, 93.5, 91.3, 61.2, 61.2, 56.4, 55.4, 43.9, 43.2, 36.2, 36.0, 34.3, 33.7, 20.7, 17.9, 14.3, 14.2; **IR** (ν cm^{-1}) 3066, 2982, 2936, 2887, 1732, 1607, 1551, 1524, 1481, 1458, 1354, 1296, 1254, 1179, 1028, 854, 787, 752, 669; **HRMS (ESI)** calcd. for $C_{21}H_{23}N_2O_6$ ($M+H$)⁺: 399.1556, Found: 399.1555.

(±)-Ethyl

2-((1R,2R,3R)-5-fluoro-2-nitro-3-(2-(4-nitrophenyl)propan-2-yl)-2,3-dihydro-1H-inden-1-yl)acetate

(5-4l). Following the general procedure, the title compound 5-4l (35.1 mg, 81%) was purified by column chromatography (eluent:

AcOEt:Hexane = 1:4) to be obtained as a white solid, m.p. 134-136 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.20-8.15 (m, 2H), 7.43-7.38 (m, 2H), 7.03-6.93 (m, 3H), 7.20-7.15 (m, 1H), 6.54 (dd, *J* = 8.6, 1.7 Hz, 1H), 5.21 (dd, *J* = 7.3, 1.0 Hz, 1H), 4.22-4.10 (m, 2H), 4.05 (s, 1H), 3.64-3.56 (m, 1H), 2.77 (dd, *J* = 17.5, 5.6 Hz, 1H), 2.36 (dd, *J* = 17.6, 9.4 Hz, 1H), 1.48 (s, 3H), 1.46 (s, 3H), 1.25 (t, *J* = 17.6, 9.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 171.2, 162.3 (d, *J* = 246.2 Hz), 153.4, 146.9, 142.6 (d, *J* = 8.0 Hz), 137.8 (d, *J* = 2.6 Hz), 127.4, 124.3 (d, *J* = 8.9 Hz), 123.8, 115.7 (d, *J* = 22.6 Hz), 113.4 (d, *J* = 23.2 Hz), 92.3, 61.3, 60.8 (d, *J* = 2.1 Hz), 43.5, 42.1, 34.1, 26.5, 26.4, 14.2; ¹⁹F NMR (376 MHz, CDCl₃) δ -113.9.1-(-114.1) (m); IR (ν cm⁻¹) 3076, 2968, 2924, 1680, 1624, 1516, 1458, 1379, 1349, 1288, 1267, 1190, 831, 765, 708; HRMS (ESI) calcd. for C₂₂H₂₄N₂O₆F (M+H)⁺: 415.1669, Found: 415.1664.

(±)-Ethyl

2-((1R,2R,3R)-5-methyl-2-nitro-3-(2-(4-nitrophenyl)propan-2-yl)-2,3-dihydro-1H-inden-1-yl)acetate

(5-4m). Following the general procedure, the title compound 5-4m (35.1 mg, 83%) was purified by column chromatography

(eluent: AcOEt:Hexane = 1:4) to be obtained as a white solid, m.p. 124-126 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.18-8.13 (m, 2H), 7.41-7.36 (m, 2H), 7.09 (d, *J* = 7.4 Hz, 1H), 6.92 (d, *J* = 7.8 Hz, 1H), 6.69 (s, 1H), 5.17 (dd, *J* = 7.2, 0.8 Hz, 1H), 4.20-4.10 (m, 2H), 3.97 (s, 1H), 3.61-3.53 (m, 1H), 2.79 (dd, *J* = 17.7, 5.5 Hz, 1H), 2.33 (dd, *J* = 17.6, 9.5 Hz, 1H), 2.28 (s, 3H), 1.49 (s, 3H), 1.44 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 171.4, 153.9, 146.7, 140.5, 139.3, 137.4, 129.5, 127.4, 126.9, 123.6, 122.8, 92.4,

61.2, 61.0, 43.9, 42.1, 34.0, 26.8, 26.3, 21.5, 14.2; **IR** (ν cm^{-1}) 3078, 2974, 2921, 2845, 1738, 1608, 1550, 1521, 1378, 1353, 1282, 1208, 1199, 1126, 1026, 868, 722; **HRMS (ESI)** calcd. for $\text{C}_{23}\text{H}_{27}\text{N}_2\text{O}_6$ ($\text{M}+\text{H}$) $^+$: 427.1869, Found: 427.1870.

($\pm$)-Ethyl 2-((1R,2R,3R)-5-methoxy-2-nitro-3-(2-(4-nitrophenyl)propan-2-yl)-2,3-dihydro-1H-inden-1-yl)acetate (**5-4n**). Following the general procedure, the title compound **5-4n** (37.1 mg, 84%) was purified by column

chromatography (eluent: AcOEt:Hexane = 1:3) to be obtained as a white solid, m.p. 148-150 $^{\circ}\text{C}$; **^1H NMR (400 MHz, CDCl_3)** δ 8.19-8.14 (m, 2H), 7.43-7.38 (m, 2H), 6.94 (dd, J = 8.4, 0.4 Hz, 1H), 6.81 (dd, J = 8.4, 2.4 Hz, 1H), 6.32 (d, J = 2.1 Hz, 1H), 5.21 (dd, J = 7.3, 1.0 Hz, 1H), 4.22-4.10 (m, 2H), 3.98 (s, 1H), 3.68 (s, 3H), 3.64-3.56 (m, 1H), 2.76 (dd, J = 17.6, 5.7 Hz, 1H), 2.33 (dd, J = 17.6, 9.5 Hz, 1H), 1.47 (s, 3H), 1.46 (s, 3H), 1.25 (t, J = 7.2 Hz, 3H); **^{13}C NMR (100 MHz, CDCl_3)** δ 171.4, 159.3, 153.9, 146.7, 141.8, 134.1, 127.5, 123.7, 123.7, 114.1, 112.0, 92.5, 61.2, 61.0, 55.4, 43.5, 42.2, 34.3, 26.7, 26.3, 14.2; **IR** (ν cm^{-1}) 3078, 2970, 2922, 2835, 1735, 1604, 1552, 1512, 1371, 1348, 1192, 1097, 1082, 1015, 856, 732, 706; **HRMS (ESI)** calcd. for $\text{C}_{23}\text{H}_{27}\text{N}_2\text{O}_7$ ($\text{M}+\text{H}$) $^+$: 443.1818, Found: 443.1822.

($\pm$)-2-((1R,2R,3R)-2-nitro-3-(2-(4-nitrophenyl)propan-2-yl)-2,3-dihydro-1H-inden-1-yl)-1-phenylethan-1-one (**5-4o**). Following the general procedure, the title compound **5-4o** (34.6 mg, 66%) was purified by column chromatography (eluent: AcOEt:Hexane = 1:4)

to be obtained as a white solid, m.p. 192-194 $^{\circ}\text{C}$; **^1H NMR (400 MHz, CDCl_3)** δ 8.20-8.15 (m, 2H), 7.93-7.89 (m, 2H), 7.60-7.55 (m, 1H), 7.48-7.40 (m, 4H), 7.28 (t, J = 7.5 Hz, 1H),

7.18 (t, $J = 7.5$ Hz, 1H), 7.09 (d, $J = 7.6$ Hz, 1H), 6.83 (d, $J = 7.6$ Hz, 1H), 5.34 (d, $J = 7.3$ Hz, 1H), 4.06 (s, 1H), 4.01-3.93 (m, 1H), 3.43 (d, $J = 18.6, 5.1$ Hz, 1H), 3.15 (d, $J = 18.6, 8.8$ Hz, 1H), 1.51 (s, 3H), 1.50 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 197.5, 154.0, 146.8, 142.8, 140.5, 136.4, 133.7, 128.8, 128.6, 128.1, 127.6, 127.5, 126.2, 123.7, 123.2, 92.5, 61.4, 43.6, 42.2, 38.7, 26.6, 26.4; IR (ν cm^{-1}) 3068, 3028, 2988, 2922, 2883, 1681, 1597, 1547, 1512, 1448, 1350, 1325, 1288, 1215, 1112, 1096, 1001, 987, 850, 760, 744, 687; HRMS (ESI) calcd. for $\text{C}_{26}\text{H}_{25}\text{N}_2\text{O}_5$ ($\text{M}+\text{H}$) $^+$: 445.1763, Found: 445.1768.

($\pm$)-1-(4-Bromophenyl)-2-((1R,2R,3R)-2-nitro-3-(2-(4-nitrophenyl)propan-2-yl)-2,3-dihydro-1H-inden-1-yl)ethan-1-one (**5-4p**). Following the general procedure, the title compound **5-4p** (34.6 mg, 66%) was purified by column chromatography (eluent: AcOEt:Hexane = 1:4) to be obtained as a white solid, m.p. 206-208 °

C; ^1H NMR (400 MHz, CDCl_3) δ 8.20-8.14 (m, 2H), 7.79-7.74 (m, 2H), 7.62-7.57 (m, 2H), 7.44-7.38 (m, 2H), 7.28 (t, $J = 7.5$ Hz, 1H), 7.19 (t, $J = 7.5$ Hz, 1H), 7.06 (d, $J = 7.6$ Hz, 1H), 6.84 (d, $J = 7.6$ Hz, 1H), 5.31 (d, $J = 7.3$ Hz, 1H), 4.05 (s, 1H), 3.97-3.89 (m, 1H), 3.38 (dd, $J = 18.6, 4.9$ Hz, 1H), 3.09 (dd, $J = 18.6, 9.0$ Hz, 1H), 1.51 (s, 3H), 1.50 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 196.5, 153.9, 146.8, 142.5, 140.5, 135.1, 132.2, 129.6, 129.0, 128.6, 127.7, 127.5, 126.3, 123.7, 123.1, 92.4, 61.3, 43.5, 42.2, 38.7, 26.6, 26.4; IR (ν cm^{-1}) 3058, 3023, 2965, 2897, 1684, 1583, 1552, 1514, 1350, 1290, 1215, 1070, 987, 849, 758, 702; HRMS (ESI) calcd. for $\text{C}_{26}\text{H}_{24}\text{N}_2\text{O}_5\text{Br}$ ($\text{M}+\text{H}$) $^+$: 523.0869, Found: 523.0862.

(±)-1-(4-Fluorophenyl)-2-((1R,2R,3R)-2-nitro-3-(2-(4-nitrophenyl)propan-2-yl)-2,3-dihydro-1H-inden-1-yl)ethan-1-one (5-4q). Following the general procedure, the title compound **5-4q** (30.1 mg, 65%) was purified by column chromatography (eluent: AcOEt:Hexane = 1:4) to be obtained as a yellow solid, m.p. 177-

179 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.20-8.14 (m, 2H), 7.96-7.91 (m, 2H), 7.44-7.39 (m, 2H), 7.28 (t, $J = 7.5$ Hz, 1H), 7.19 (t, $J = 7.5$ Hz, 1H), 7.22-7.06 (m, 3H), 6.84 (d, $J = 7.6$ Hz, 1H), 5.32 (dd, $J = 7.3, 0.4$ Hz, 1H), 4.05 (s, 1H), 3.98-3.90 (m, 1H), 3.40 (dd, $J = 18.6, 5.0$ Hz, 1H), 3.10 (dd, $J = 18.5, 9.0$ Hz, 1H), 1.51 (s, 3H), 1.50 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 195.9, 166.2 (d, $J = 255.2$ Hz), 153.9, 146.8, 142.6, 140.5, 132.8 (d, $J = 3.0$ Hz), 130.8 (d, $J = 9.6$ Hz), 128.6, 127.6, 127.5, 126.2, 123.7, 123.1, 116.0 (d, $J = 22.1$ Hz), 92.5, 61.3, 43.5, 42.2, 38.6, 26.6, 26.4; $^{19}\text{F NMR}$ (376 MHz, CDCl_3) δ -104.1-(-104.2) (m); IR (ν cm^{-1}) 3072, 3026, 2983, 2921, 28913, 1686, 1599, 1553, 1508, 1346, 1290, 1232, 1219, 1157, 1096, 1001, 987, 856, 847, 760, 704; HRMS (ESI) calcd. for $\text{C}_{26}\text{H}_{24}\text{N}_2\text{O}_5\text{F}$ ($\text{M}+\text{H}$) $^+$: 463.1669, Found: 463.1672.

(±)-2-((1R,2R,3R)-2-Nitro-3-(2-(4-methylphenyl)propan-2-yl)-2,3-dihydro-1H-inden-1-yl)-1-(p-tolyl)ethan-1-one (5-4r). Following the general procedure, the title compound **5-4r** (32.3 mg, 71%) was purified by column chromatography (eluent: AcOEt:Hexane = 1:4) to be obtained as a yellow solid, m.p. 173-175 °C; $^1\text{H NMR}$ (400

MHz, CDCl_3) δ 8.20-8.15 (m, 2H), 7.83-7.79 (m, 2H), 7.45-7.40 (m, 2H), 7.30-7.22 (m, 3H), 7.20-7.15 (m, 1H), 7.08 (d, $J = 7.6$ Hz, 1H), 6.82 (d, $J = 7.6$ Hz, 1H), 5.33 (dd, $J = 7.4, 0.8$ Hz, 1H), 4.05 (s, 1H), 4.01-3.93 (m, 1H), 3.40 (dd, $J = 18.5, 5.1$ Hz, 1H), 3.12 (dd, $J = 18.5, 8.8$ Hz, 1H), 2.40 (s, 3H), 1.50 (s, 3H), 1.49 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 197.1, 154.0, 146.7, 144.7, 142.9, 140.5, 133.9, 129.5, 128.6, 128.3, 127.5, 127.5, 126.2,

123.7, 123.2, 92.6, 61.4, 43.6, 42.2, 38.5, 26.6, 26.4, 21.8; **IR** (ν cm^{-1}) 3066, 3032, 2972, 2900, 1678, 1605, 1549, 1514, 1421, 1350, 1325, 1290, 1223, 1180, 1115, 1003, 980, 856, 781, 702; **HRMS (ESI)** calcd. for $\text{C}_{27}\text{H}_{27}\text{N}_2\text{O}_5$ ($\text{M}+\text{H}$) $^+$: 459.1920, Found: 459.1916.

($\pm$)-1-(4-Methoxyphenyl)-2-((1R,2R,3R)-2-nitro-3-(2-(4-nitrophenyl)propan-2-yl)-2,3-dihydro-1H-inden-1-yl)ethan-1-one (5-4s). Following the general procedure, the title compound **5-4s** (32.8 mg, 69%) was purified by column chromatography (eluent: AcOEt:Hexane = 1:3) to be obtained as a yellow solid, m.p. 189-

191 °C; **^1H NMR (400 MHz, CDCl_3)** δ 8.20-8.15 (m, 2H), 7.92-7.86 (m, 2H), 7.45-7.40 (m, 2H), 7.28 (t, J = 7.5 Hz, 1H), 7.18 (t, J = 7.5 Hz, 1H), 7.08 (d, J = 7.6 Hz, 1H), 6.94-6.89 (m, 2H), 6.81 (d, J = 7.6 Hz, 1H), 5.31 (d, J = 7.4, 0.8 Hz, 1H), 4.04 (s, 1H), 4.01-3.94 (m, 1H), 3.86 (s, 3H), 3.37 (dd, J = 18.2, 5.1 Hz, 1H), 3.09 (dd, J = 18.3, 8.8 Hz, 1H), 1.50 (s, 3H), 1.49 (s, 3H); **^{13}C NMR (100 MHz, CDCl_3)** δ 195.9, 164.0, 154.0, 146.8, 143.0, 140.5, 130.5, 129.5, 128.6, 127.5, 127.5, 126.2, 123.7, 123.3, 114.0, 92.6, 61.4, 55.7, 43.7, 42.3, 38.3, 26.6, 26.4; **IR** (ν cm^{-1}) 3071, 3030, 2978, 2926, 2881, 1682, 1603, 1541, 1508, 1421, 1348, 1251, 1180, 1102, 1015, 986, 856, 837, 760, 708; **HRMS (ESI)** calcd. for $\text{C}_{27}\text{H}_{26}\text{N}_2\text{O}_6\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 497.1689, Found: 497.1689.

($\pm$)-1-(3-Bromophenyl)-2-((1R,2R,3R)-2-nitro-3-(2-(4-nitrophenyl)propan-2-yl)-2,3-dihydro-1H-inden-1-yl)ethan-1-one (5-4t). Following the general procedure, the title compound **5-4t** (36.1 mg, 69%) was purified by column chromatography (eluent:

AcOEt:Hexane = 1:4) to be obtained as a yellow solid, m.p. 194-196 °C; **^1H NMR (400**

MHz, CDCl₃) δ 8.20-8.14 (m, 2H), 8.03 (t, J = 1.6 Hz, 1H), 7.84-7.79 (m, 1H), 7.71-7.67 (m, 1H), 7.44-7.39 (m, 2H), 7.33 (t, J = 7.5 Hz, 1H), 7.29 (t, J = 7.5 Hz, 1H), 7.19 (t, J = 7.6 Hz, 1H), 7.07 (d, J = 7.5 Hz, 1H), 6.83 (d, J = 7.5 Hz, 1H), 5.32 (d, J = 7.3 Hz, 1H), 4.06 (s, 1H), 3.96-3.89 (m, 1H), 3.40 (dd, J = 18.7, 4.8 Hz, 1H), 3.09 (dd, J = 18.8, 9.1 Hz, 1H), 1.51 (s, 3H), 1.50 (s, 3H); **¹³C NMR (100 MHz, CDCl₃)** δ 196.2, 153.8, 146.8, 142.4, 140.5, 138.0, 136.6, 131.2, 130.5, 128.6, 127.7, 127.5, 126.7, 126.3, 123.7, 123.2, 123.1, 92.4, 61.2, 43.5, 42.2, 38.8, 26.6, 26.4; **IR (ν cm⁻¹)** 3066, 3032, 2972, 2901, 2881, 1678, 1605, 1549, 1514, 1428, 1350, 1321, 1290, 1218, 1180, 1112, 1088, 980, 851, 781, 702; **HRMS (ESI)** calcd. for C₂₆H₂₃N₂O₅Na (M+Na)⁺: 545.0688, Found: 545.0691.

(±)-1-(Furan-2-yl)-2-((1R,2R,3R)-2-nitro-3-(2-(4-nitrophenyl)propan-2-yl)-2,3-dihydro-1H-inden-1-yl)ethan-1-one (5-4u). Following the general procedure, the title compound **5-4u** (29.6 mg, 68%) was purified by column chromatography (eluent: AcOEt:Hexane = 1:4) to be obtained as a white solid, m.p. 178-

180 °C; **¹H NMR (400 MHz, CDCl₃)** δ 8.19-8.14 (m, 2H), 7.56 (s, 1H), 7.44-7.38 (m, 2H), 7.28 (t, J = 7.5 Hz, 1H), 7.21-7.15 (m, 2H), 7.07 (d, J = 7.5 Hz, 1H), 6.83 (d, J = 7.5 Hz, 1H), 6.55-6.51 (m, 1H), 5.27 (d, J = 7.3 Hz, 1H), 4.04 (s, 1H), 3.94-3.86 (m, 1H), 3.31 (dd, J = 18.4, 5.3 Hz, 1H), 3.00 (dd, J = 18.4, 8.9 Hz, 1H), 1.50 (s, 3H), 1.48 (s, 3H); **¹³C NMR (100 MHz, CDCl₃)** δ 186.3, 153.9, 152.2, 146.9, 142.6, 140.4, 128.6, 127.6, 127.5, 126.2, 125.6, 123.7, 123.2, 117.7, 112.6, 92.4, 61.3, 43.0, 42.2, 38.2, 26.6, 26.4; **IR (ν cm⁻¹)** 3132, 3108, 3058, 3026, 2978, 2927, 2890, 1677, 1599, 1553, 1509, 1468, 1400, 1352, 1240, 1156, 1089, 1054, 1001, 986, 852, 793, 754, 688; **HRMS (ESI)** calcd. for C₂₄H₂₃N₂O₆ (M+H)⁺: 435.1556, Found: 435.1559.

(±)-1-(Furan-3-yl)-2-((1R,2R,3R)-2-nitro-3-(2-(4-nitrophenyl)propan-2-yl)-2,3-dihydro-1H-inden-1-yl)ethan-1-one (5-4v). Following the general procedure, the title compound **5-4v** (26.6 mg, 61%) was purified by column chromatography (eluent: AcOEt:Hexane = 1:5) to be obtained as a white solid, m.p. 152-154 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.20-8.15 (m, 2H), 7.98 (s, 1H), 7.45-7.37 (m, 3H), 7.28 (t, *J* = 7.5 Hz, 1H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.05 (d, *J* = 7.5 Hz, 1H), 6.83 (d, *J* = 7.5 Hz, 1H), 6.75 (d, *J* = 1.1 Hz, 1H), 5.26 (d, *J* = 7.3 Hz, 1H), 4.04 (s, 1H), 3.96-3.89 (m, 1H), 3.21 (dd, *J* = 18.2, 5.3 Hz, 1H), 2.88 (dd, *J* = 18.2, 8.8 Hz, 1H), 1.50 (s, 3H), 1.48 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 191.9, 153.9, 147.6, 146.8, 144.6, 142.6, 140.4, 128.6, 127.7, 127.5, 127.3, 126.2, 123.7, 123.2, 108.5, 92.4, 61.4, 43.1, 42.2, 40.1, 26.6, 26.4; IR (ν cm⁻¹) 3140, 3066, 3026, 2963, 2924, 2850, 1674, 1599, 1553, 1508, 1478, 1394, 1346, 1159, 1094, 1034, 999, 874, 856, 766, 706; HRMS (ESI) calcd. for C₂₆H₂₅N₂O₅ (M+H)⁺: 435.1556, Found: 435.1555.

(±)-2-((1R,2R,3R)-2-Nitro-3-(2-(4-nitrophenyl)propan-2-yl)-2,3-dihydro-1H-inden-1-yl)-1-(thiophen-2-yl)ethan-1-one (5-4w). Following the general procedure, the title compound **5-4w** (28.5 mg, 63%) was purified by column chromatography (eluent: AcOEt:Hexane = 1:5) to be obtained as a white solid, m.p. 168-170 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.20-8.15 (m, 2H), 7.66 (d, *J* = 4.4 Hz, 2H), 7.44-7.39 (m, 2H), 7.28 (t, *J* = 7.4 Hz, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.11 (t, *J* = 4.4 Hz, 1H), 7.08 (d, *J* = 7.6 Hz, 1H), 6.83 (d, *J* = 7.6 Hz, 1H), 5.29 (d, *J* = 7.3 Hz, 1H), 4.05 (s, 1H), 3.98-3.91 (m, 1H), 3.38 (dd, *J* = 18.1, 5.3 Hz, 1H), 3.07 (dd, *J* = 18.2, 8.8 Hz, 1H), 1.50 (s, 3H), 1.49 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 190.1, 153.9, 146.8, 143.4, 142.6, 140.4, 134.4, 132.5, 128.6, 128.4, 127.6, 127.5, 126.2, 123.7, 123.2, 92.4, 61.4, 43.4, 42.2, 39.1,

26.6, 26.4; **IR** (ν cm^{-1}) 3078, 3028, 2968, 2921, 2878, 1659, 1604, 1549, 1514, 1416, 1348, 1219, 1096, 1059, 1012, 916, 851, 752, 723; **HRMS (ESI)** calcd. for $\text{C}_{24}\text{H}_{23}\text{N}_2\text{O}_5\text{S}$ ($\text{M}+\text{H}$) $^{+}$: 451.1328, Found: 451.1331.

(±)-1-((1R,2R,3R)-2-Nitro-3-(2-(4-nitrophenyl)propan-2-yl)-2,3-dihydro-1H-inden-1-yl)propan-2-one (5-4x). Following the general procedure, the title compound **5-4x** (27.6 mg, 53%) was purified by column chromatography (eluent: AcOEt:Hexane = 1:2)

to be obtained as a white solid, m.p. 202-204 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.19-8.14 (m, 2H), 7.42-7.37 (m, 2H), 7.26 (t, J = 7.5 Hz, 1H), 7.16 (t, J = 7.5 Hz, 1H), 7.00 (d, J = 7.6 Hz, 1H), 6.80 (d, J = 7.6 Hz, 1H), 5.18 (d, J = 7.4 Hz, 1H), 4.02 (s, 1H), 3.79-3.70 (m, 1H), 2.91 (dd, J = 18.8, 4.9 Hz, 1H), 2.53 (dd, J = 18.8, 9.3 Hz, 1H), 2.16 (s, 3H), 1.47 (s, 3H), 1.46 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 205.9, 153.9, 146.8, 142.5, 140.4, 128.6, 127.6, 127.5, 126.2, 123.7, 123.0, 92.2, 61.0, 43.4, 43.3, 42.1, 30.3, 26.6, 26.4; **IR** (ν cm^{-1}) 3088, 3018, 2978, 2926, 2884, 1730, 1597, 1545, 1518, 1427, 1354, 1165, 1093, 1016, 957, 856, 760, 704; **HRMS (ESI)** calcd. for $\text{C}_{21}\text{H}_{23}\text{N}_2\text{O}_5$ ($\text{M}+\text{H}$) $^{+}$: 483.1607, Found: 483.1615.

(±)-2-((1R,2R,3R)-2-Nitro-3-(2-(4-nitrophenyl)propan-2-yl)-2,3-dihydro-1H-inden-1-yl)acetonitrile (5-4y). Following the general procedure, the title compound **5-4y** (23.1 mg, 63%) was purified by

column chromatography (eluent: AcOEt:Hexane = 1:2) to be obtained as a white solid, m.p. 224-226 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.22-8.18 (m, 2H), 7.45-7.40 (m, 2H), 7.37-7.34 (m, 2H), 7.25-7.21 (m, 1H), 6.78 (d, J = 7.7 Hz, 1H), 6.19 (dd, J = 7.5, 2.4 Hz, 1H), 4.21 (d, J = 2.2 Hz, 1H), 3.61 (q, J = 7.5 Hz, 1H), 2.66 (dd, J = 16.9, 8.9 Hz, 1H), 2.56 (dd, J = 16.9, 7.0 Hz, 1H), 1.45 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 153.6, 146.9, 140.1, 139.9, 129.5, 129.2, 128.8, 127.4, 126.3, 123.9, 123.6, 122.2, 117.2, 91.2,

60.6, 43.8, 42.2, 27.0, 25.8, 18.3; **IR** (ν cm^{-1}) 3089, 3023, 2968, 2936, 2889, 2249, 1604, 1597, 1551, 1512, 1458, 1354, 1346, 1250, 1115, 1094, 1015, 856, 766, 700; **HRMS (ESI)** calcd. for $\text{C}_{20}\text{H}_{20}\text{N}_3\text{O}_4$ ($\text{M}+\text{H}$)⁺: 366.1454, Found: 366.1450.

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