Part I: N-heterocyclic carbene catalyzed
homoenolate addition of enals to nitroalkenes.
Part II: Palladium catalyzed N-heterocyclic
glycosides synthesis

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**NANYANG
TECHNOLOGICAL
UNIVERSITY**

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HOMOENOLATE ADDITION OF ENALS TO
NITROALKENES**

**PART II. PALLADIUM CATALYZED N-
HETEROCYCLIC GLYCOSIDES SYNTHESIS**

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SCHOOL OF PHYSICAL & MATHEMATICAL SCIENCES

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ABSTRACT

Part 1. N-heterocyclic carbene catalyzed highly diastereoselective and potentially multifunctional nitroester from α,β -unsaturated aldehyde and nitrodiene is described. Amongst the imidazolium carbene catalysts tested, sterically demanding 1,3-bis(2,6-diisopropyl phenyl)imidazolium chloride gave the best chemical yield and diastereoselectivity. A variety of aryl substituted cinnamaldehyde derivatives undergo smooth addition with aryl substituted nitrodiene to afford five carbon synthon frameworks with additional C=C double bond. To demonstrate the utility of this methodology, a few applications such as cyclopentanol and tetra- and trisubstituted tetraline derivatives were synthesized from the multifunctional nitroester. Furthermore, we have developed a chiral version of the homoenolate addition to nitroalkenes for the construction of highly enantio-enriched “5-carbon synthon” nitroester by using a chiral N-heterocyclic carbene catalyst. Various types of enals and nitroalkenes were well tolerated with the reaction conditions to afford the desired δ -nitroesters in excellent enantioselectivities.

Part 2. An efficient and highly stereoselective strategy for the synthesis of N-heterocyclic glycosides was developed. This method is based on a palladium catalyzed allylation, which allows formation of N-heterocyclic glycosyl linkages in moderate to good yields with excellent β -selectivity. The utility of this method was further demonstrated by expedient syntheses of bis-indole sugars that have potential as antiproliferative drugs from N-glycosyl isatine products.

INDEX OF ABBREVIATIONS

δ	chemical shift	DIBAL	diisobutylaluminum hydride -H
Δ	reflux or heat	DIPEA	N,N-Diisopropylethylamine
$^{\circ}\text{C}$	degree centigrade	DMAP	4-(N,N-dimethylamino) pyridine
Ac	acetyl	DME	dichloroethane
AcCl	acetyl chloride	DMF	N,N-dimethylformamide
AcOH	acetic acid	DMSO	dimethyl sulfoxide
ACN	acetonitrile	DPPB	1,4-bis(diphenylphosphino) butane
Aq	aqueous	<i>ee</i>	enantiomeric excess
Bn	benzyl	EI	electron ionization
Boc	<i>tert</i> -butoxycarbonyl	equiv	equivalent
brs	broad singlet	Et	ethyl
Bz	benzoic	ether	diethyl ether
calcd.	calculated	Et ₃ N	triethylamine
cat.	catalytic	EtOAc	ethylacetate
CDCl ₃	deuterated chloroform	EtOH	ethanol
CH ₂ Cl ₂	dichloromethane	Fmoc	fluorenylmethoxycarbonyl
CHCl ₃	chloroform	FTIR	fourier transfer infrared spectroscopy
cm ⁻¹	inverse centimeter	g	gram
d	doublet	h	hour (time)
DABCO	1,4-Diazabicyclo[2.2.2]octane	Hex	hexane
DCC	N,N'- dicyclohexylcarbodiimide	HRMS	high resolution mass spectroscopy
DCE	dichloroethane	Hz	hertz
dd	doublet of doublets	<i>i</i> Pr	isopropyl

IR	infrared	Ph	phenyl
<i>J</i>	coupling constants	PMB	<i>p</i> -methoxybenzyl
M	concentration (mol/L)	PMP	<i>p</i> -methoxyphenyl
m	multiplet	ppm	parts per million
M ⁺	parent ion peak(mass spectrum)	Py	pyridine
Me	methyl	q	quartet
MeOH	methanol	RBF	round bottom flask
Mes	2,4,6-trimethylbenzene	s	singlet
mg	milligram	sat	saturated
MHz	megahertz	t	triplet
min	minute	TBAF	Tetrabutylammonium fluoride
mL	milliliter	TBDPS	<i>tert</i> -butyldiphenylsilyl
mm	millimeter	TBS	<i>tert</i> -butyldimethylsilyl
mmol	millimoles	TFA	trifluoroacetic acid
mol	moles	THF	tetrahydrofuran
MS	mass spectrum	THP	tetrahydropyran
<i>n</i> Bu	<i>n</i> -butyl	TLC	thin layer chromatography
NBS	N-Bromosuccinimide	TMS	trimethylsilyl
NMR	nuclear magnetic Resonance	Ts	<i>p</i> -toluenesulfonyl
NMO	4-methylmorpholine <i>N</i> -oxide	^t Bu	<i>tert</i> -butyl
Nu	nucleophile	v	volume
OTf	trifluoromethanesulfonate		
<i>p</i>	<i>para</i>		
Pd/C	palladium on carbon		
Piv	pivaloyl; trimethylacetyl		

CHAPTER 1

Introduction: Recent Advances in N-Heterocyclic Carbene (NHC) Catalysed Reactions

1.1 NHC catalysed reactions *via* acyl anion intermediates

The carbon-carbon bond formation reactions play an essential role in organic synthesis. Compared with conventional chemical transformations, organocatalytic processes have attracted tremendous attentions^[1] from synthetic chemists due to their advantages such as low toxicity and cost of catalysis, operational simplicity, less air- and moisture-sensitive reaction conditions. In the late 1980s and early 1990s, Bertrand and Arduengo *et al.* independently isolated stable nucleophilic carbenes.^[2] The carbene molecule is constructed by a divalent carbon atom with six electrons only in its valence shell and exists in either a singlet or triplet state (Figure 1.1 **a, b**).

Figure 1.1 The singlet and triplet states of carbene

Singlet carbene, which contains an electron lone pair and a vacant p-orbital, possesses an ambiphilic character, whereas triplet carbene can be defined as diradical. When heteroatoms such as oxygen, nitrogen or sulphur are attached on either side of the carbene atom to and donate electron density into the vacant p-orbital, the carbene will become nucleophilic. Since the first isolation, many advances have been achieved in the field of catalysis by employing NHCs (N-heterocyclic carbenes). Traditionally NHCs are employed widely in coordination chemistry, olefin metathesis, and cross-coupling reactions^[3]. Other than acting as ligands to coordinate with transition metals, NHCs have been developed as

organocatalysts in the past years, leading to rapid evolution of the area of carbene organocatalysis. The increasingly wide utilization of NHCs in C-C bond formation has been realized by synthetic chemists; Figure 1.2 shows the general structures of NHCs as organocatalysts. They are categorized as imidazolylidene, imidazolinylidene, triazolylidene, and thiazolylidene. In this part, basic principles and recent advances about nucleophilic carbene are introduced.

Figure 1.2 General structures of nucleophilic carbenes

1.1.1 Benzoin condensation

The benzoin condensation was first disclosed in 1832 by Wöhler and Liebig, showing that the polarity of the carbonyl group of benzaldehyde can be reversed by cyanide (Scheme 1.1).^[4] This phenomenon of polarity reversal was defined as ‘Umpolung’,^[5] and the generated reactive nucleophilic species from aldehyde was named as acyl anion equivalent subsequently. In 1903, Lapworth proposed the plausible mechanism of cyanide catalyzed benzoin condensation (Scheme 1.1).^[6] The cyanide attacks the benzaldehyde followed by proton transfer to form the acyl anion intermediate. The reactive carbon anion then attacks another benzaldehyde to form the C-C bond.

Scheme 1.1 Lapworth's proposed mechanism of cyanide catalysed benzoin reaction

In 1943, Ukai *et al.* reported that thiazolium vitamin B1 (Figure 1.3) catalysed the homocondensation of aldehydes under basic conditions.^[7] This significant transformation makes enantioselective catalysis of benzoin condensation possible because further elaboration of the thiazolium salts allows installation of chirality elements.

Figure 1.3 Coenzyme thiamine (vitamin B1)

Breslow and co-workers illustrated the mechanism of the thiamine-catalysed benzoin reaction in 1958 (Scheme 1.2).^[8] The widely accepted concept 'Breslow intermediate' was proposed thereby. Firstly, the carbene catalyst adds to the carbonyl group of the aldehyde, followed by a proton transfer. The resulting nucleophilic acyl anion is named 'Breslow intermediate'.

Scheme 1.2 Breslow's proposed mechanism of the benzoin condensation

In 2003, an intramolecular benzoin condensation was reported by Suzuki and coworkers. The synthesis of preanthraquinone analogues was achieved from aldehyde-ketone starting materials through intramolecular benzoin cyclization under the catalysis of thiazolium bromide (Scheme 1.3).^[9] Later, Enders and Suzuki independently developed asymmetric intramolecular benzoin condensations *via* the catalysis of chiral triazolium salts **1-4**.^[10] Selected examples are listed in Scheme 1.4. The cyclization products α -hydroxyketones **5** could be obtained in good yields and enantioselectivities.

Scheme 1.3 Intramolecular cross-benzoin condensation of ketones and aldehydes

Scheme 1.4 Asymmetric intramolecular benzoin condensation

1.1.2 Stetter reaction

In the early 1970s, Stetter and coworkers first applied the ‘Umpolung’ reactivity of aldehyde to Michael acceptors. This new type of addition was named as Stetter reaction. The mechanism is shown in Scheme 1.5.^[11] The initial study showed that a range of aromatic and aliphatic aldehydes could be successfully transformed into acyl anions *via* cyanide or thiazolylidene carbene catalysis to serve as strong nucleophiles. This catalytic method has been widely used in preparing 1,4-diketones, 4-ketoesters and 4-ketonitriles by employing α,β -unsaturated ketones, esters, and nitriles as Michael acceptors (Scheme 1.6).^[12]

Scheme 1.5 Proposed mechanism for thiazolium catalysed Stetter reaction

Scheme 1.6 Stetter reaction with activated alkenes

Stetter products act as versatile intermediates in the synthesis of cyclopentanone derivatives^[13] and heterocycles.^[14] One pot synthesis of multi-substituted products were therefore achieved starting from simple reactants. For example, a smart one-pot four-component synthesis of pyrrole derivatives has been developed by Müller and co-workers (scheme 1.7).^[15] The synthesis started from Sonogashira coupling followed by isomerization to form an α,β -unsaturated ketone *in situ*. The subsequent Stetter reaction with an aromatic aldehyde was catalysed by the thiamine catalyst to afford a 1,4-diketone, which underwent Paal-Knorr reaction to furnish the multi-substituted pyrrole.

Scheme 1.7 One-pot synthesis of pyrrole derivatives.

The first asymmetric Stetter reaction was developed by Ender and co-workers in 1989 (Scheme 1.8).^[16] The chalcone **7** was acylated with *n*-butanal **6** to form the 1,4-diketone **8** but with only 39% enantiomeric excess and 4% yield. The sila-Stetter reaction was reported by Scheidt group in 2004 (Scheme 1.9).^[17] This is the first time that ‘Umplong’ reactivity was combined with 1,2-silyl group shift (Brook rearrangement) to generate the acyl anion species. This catalytic methodology was meaningful in expanding the Stetter reaction through starting with acylsilanes as tunable acyl anion precursors.

Scheme 1.8

Scheme 1.9 Sila-Stetter reaction

The first intramolecular Stetter reaction was illustrated by Ciganek and co-workers in 1995, using a thiazolium precatalyst **9** (Scheme 1.10).^[18] One year later, Enders *et al.* successfully realized the asymmetric intramolecular Stetter reaction in the presence of chiral triazolium catalyst **10**, providing the cyclization product 1,4-ketoester in good yield with moderate *ee*.^[19] The enantioselectivity was further improved by Rovis *et al.* using triazolium catalysts **11** and **12** (Figure 1.4).^[20] Peptide **13** with a thiazolium residue was employed in Stetter cyclization as well, resulting 64-76% *ee*, although the chiral center is not close to the nucleophilic carbene.^[21]

Scheme 1.10 The intramolecular Stetter reaction

Figure 1.4 Selected catalysts for asymmetric intramolecular Stetter reaction.

1.2 NHC catalysed reactions *via* activated carboxylate intermediates

1.2.1 Internal redox

Another reactive intermediate generated from α -functionalized aldehydes in reactions catalyzed by NHC is an activated carboxylate, which was first illustrated by Bode's group in 2004 (Scheme 1.11a).^[22] The mechanism is shown in Scheme 1.12. β -Hydroxy esters were synthesized diastereoselectively from α,β -unsaturated epoxides. In preceding studies, stoichiometric oxidants were needed to form the carboxylate-azolium adducts, while the epoxide functionality introduced made the intramolecular redox reaction possible.^[23] The resulting intermediate undergoes an internal redox reaction to form **carboxylic** esters or amino esters (Scheme 1.11b) from readily available starting materials. Concurrently, a similar transformation was performed starting from α -haloaldehydes by Rovis and co-workers (Scheme 1.11c).^[24] The halogen was installed as a leaving group at the α position

of the aldehyde, so that the Breslow intermediate can be transformed into enol after elimination of the halogen atom and then into acylazolium through subsequent tautomerization. Thereafter, Scheidt *et al.* reported the catalytic formation of an activated carboxylate from an α,β -unsaturated aldehyde to provide the corresponding saturated ester (Scheme 1.11d).^[25] The resulting homoenolate was transformed into an electrophilic carboxylate after protonation, which is trapped by a nucleophile such as an alcohol.

Scheme 1.12 Proposed mechanism for the internal redox reaction of α,β -epoxyaldehyde

Scheme 1.11

The NHC-catalysed redox esterification was extended to ring opening and ring expansion reactions through carbon-carbon bond breaking and cyclization pathways. Bode pioneered this area of research by subjecting formylcyclopropanes to umplong conditions, yielding acyclic esters (Scheme 1.13a).^[26] Both esters and thioesters can be provided in high yield and good enantiomeric excess. The triazolium pre-catalyst with N-mesityl substituent proved effective in suppressing the benzoin condensation. Later, You extended this strategy to formyl acyl cyclopropanes to yield the corresponding 3,4-dihydro- α -pyrones through intramolecular cyclization (Scheme 1.13b).^[27] The extra carbonyl group extended the conjugation system and thus led to the formation of a ketone enolate under the catalysis of the same triazolium salt used in Bode's methodology. The enolate served as an internal nucleophile to attack the aldehyde carbon to afford the six-membered lactone and regenerate the catalyst. Succinimide derivatives were also obtained through the same ring expansion

from four-membered formyl β -lactams as demonstrated previously by You (Scheme 1.13c).^[28] Notably, a pharmaceutically valuable spiro bicyclic diamine skeleton was obtained with retention of chirality from 4-formyl spiro β -lactam.

Scheme 1.13

1.3 NHC catalysed reactions *via* homoenolate intermediates

Figure 1.5 Enolate and homoenolate

The enolate intermediate is a versatile species in many chemical transformations, which is typically generated through deprotonation of the α carbon of the carbonyl group by using strong alkali metal amide bases. While an enolate contains a nucleophilic center at the α position of the carbonyl group, a homoenolate possess a nucleophilic center at the β position.

The species is stabilized by delocalization of the negative charge to the carbonyl group (Figure 1.5).^[29] The discovery of homoenolate dates back to the early 1960s. Recently, with the development of NHC chemistry, people found metal free way to generate homoenolate species and apply them in annulation reactions and C-C bond formations. Starting from α, β -unsaturated aldehyde, conjugated Breslow intermediates can be obtained under NHC catalysis (Scheme 1.14). Electron transfer from the conjugated Breslow intermediate leads to the generation of many reactive species, such as acyl anion, enolate and homoenolate equivalents. Compared with the acyl carbon, the negatively charged β -carbon is more reactive since the sterically bulky carbene moiety blocks the reaction pathway at the acyl position. After trapping by an electrophile, the homoenolate becomes an enol-NHC adduct which undergoes tautomerization to form the activated carboxylate equivalent. A subsequent nucleophilic attack releases the carbene catalyst and generates the esterification product. If electrophilic and nucleophilic moieties are installed in the same molecule, the above-mentioned reaction pathway results in annulation. In this way, the α, β -unsaturated aldehyde can serve as a 1,3-dipole when activated by NHC catalysts.

Scheme 1.14 Reactive species derived from α, β -unsaturated aldehydes with N-heterocyclic carbene

In 2004, Glorius^[30] and Bode^[31] independently published research works on catalytic generation of homoenolate derived from α, β -unsaturated aldehydes (Scheme 1.15). Both of them used a trimethylphenyl substituted carbene precatalyst to generate the homoenolate, which was further captured by a simple aldehyde to stereoselectively form synthetically valuable γ -lactone with *cis* configuration. Bode proposed that the catalyst should be properly selected in order to activate the β -carbon, block the acyl position, and prevent the protonation of the β -position, which hampers the homoenolate addition to other electrophiles. In the absence of other electrophiles, the enals undergo homo-dimerisation to yield the corresponding γ -lactones. No 1,2 addition product was observed under their conditions.

Scheme 1.15 First catalytic generation of homoenolate using NHC precatalyst

1.3.1 Reactions of homoenolates with various electrophiles

Since the first catalytic generation of homoenolate, many researchers have engaged in the development of more electrophiles to harness this intermediate. Bode first extended his

work to sulfonyl imine, making a new synthesis method for lactams (Scheme 1.16b).^[32] Nair and co-workers applied the homoenolate strategy to enones. The reaction proceeded in an intramolecular aldol manner followed by decarboxylation to yield 3,4-trans-disubstituted-1-aryl cyclopentenones instead of the desired acyl cyclopentanones (Scheme 1.16c).^[33] As normal ketones (except for α,α,α -trifluoroacetophenone)^[34] failed to afford annulation product with homoenolates, Nair *et al.* employed 1,2-diketones as electrophiles and successfully synthesized spirocyclic ketones (**17**, Scheme 1.16d).^[35] In the continuation of the development of other Michael acceptors, Nair further applied homoenolate species to nitroalkenes, furnishing the γ -nitroester **18** in good yield and stereoselectivity (Scheme 1.16e).^[36] Another two biofunctional transformations were realized by Scheit and Ying to afford γ - and β - amino esters through addition with nitrones (**19**, Scheme 1.16f)^[37] and nitrosobenzenes (**20**, Scheme 1.16g).^[38] Scheidt *et al.* developed another C-N bond formation strategy by a formal [3+2] cycloaddition of homoenolates with diazenes, furnishing pyrazolidinones **21** as a single regioisomer (Scheme 1.16).^[39] A novel [8 + 3] cycloaddition was achieved by Nair through employing tropones as annulation partner to prepare bicyclic δ -lactones (**22**, Scheme 1.16i).^[40] Scheidt developed the first homoenolate addition to β , γ -unsaturated α -ketoesters. A Lewis acid $\text{Ti}(\text{O}^i\text{Pr})_4$ served as a significant co-catalyst to activate the ketoesters. This compatibility of Lewis acid and Lewis base (NHC) offers innovative approach to the dual activation in conjugate addition of homoenolate.^[41] The NHC catalytic method also provides a straightforward synthesis of β -aryl/alkylsulfanyl thioesters by homoenolate addition. Yadav illustrated C-S bond formation between a homoenolate and an organic disulfide, which involves thioetherification and thioesterification process in one step to afford a biologically potent di-sulphur containing compound **24** (Scheme 1.16k).^[42]

aldehydes **imines** **enones** **diketones** **nitroalkenes** **nitrones**

nitrosobenzenes **diazenes** **tropones** **ketoesters** **disulfides** **Scheme 1.16** Reactions of homoenolates with various electrophiles

1.3.2 Cooperative Lewis acid and NHC catalysis

The combination of a metal salt or complex as a Lewis acid and an NHC as a Lewis base to generate new reactivity in organic reaction has been an interesting but challenging topic since the strong coordination between the NHC and the metal inhibits their catalytic activities. However, with a proper choice of the Lewis acid, the NHC and the Lewis acid complex tend to dissociate and play their own roles to activate the reactants. Scheidt has successfully employed magnesium(II) tert-butoxide together with chiral triazolium salt in the formal [3 + 2] cycloaddition of a homoenolate with N-acyl hydrazones to construct γ -lactam derivatives. In the absence of Lewis acid, the products were formed in low to moderate yields and selectivities with incomplete conversion of the reactant. This result suggested that the Lewis acid played a significant role in enhancing the reactivity of the N-acyl hydrazones.^[43] The reaction scheme and proposed catalytic cycle are shown in Scheme 1.17. Firstly, the α,β -unsaturated aldehyde is activated by the NHC to form the homoenolate equivalent **26**. The homoenolate then serves as a nucleophile to attack the hydrazine **30**, which is activated by $\text{Mg}(\text{O}^t\text{Bu})_2$ to form a chelate species **31**. After the C–C bond formation, the enol intermediate **27** undergoes tautomerization followed by release of $\text{Mg}(\text{II})$ alkoxide. Subsequent intramolecular cyclization of **28** affords the γ -lactam **29** and regenerates the NHC.

Another example by Scheidt shows that Lewis acid mediated homoenolate annulation with chalcones would reverse the facial selectivity through preorganization of the starting material (Scheme 1.18).^[44] Amongst the Lewis acids they screened, zinc and scandium triflates completely inhibited the reaction, while titanium(IV) iso-propoxide was compatible with this carbene-catalyzed homoenolate annulation process. The reaction intermediate underwent an intramolecular aldol reaction to form the cyclopentane ring, after which

decarboxylation proceeded to provide the cyclopentene product **32** with *cis* stereochemistry. Interestingly, in the presence of a substoichiometric amount of 2-propanol (20 mol %), the yield was improved with a shorter reaction time.

Scheme 1.17 Proposed reaction cycle of homoenolate annulation with N-acyl hydrazones

Scheme 1.18 Homoenolate annulation with chalcones.

As a continuation of their work, Scheidt and co-workers further employed a chiral titanium Lewis acid **33** as a co-catalyst together with an achiral imidazolium catalyst. Under the co-catalysis of the NHC and the chiral titanium alkoxid, the product *cis* γ -butyrolactone was obtained with 60% ee (Scheme 1.19).^[44] When an achiral Ti(O^{*i*}Pr) Lewis acid was used together with a novel tryptophan-derived triazolium **34**, the homoenolate 1,4-addition was preferred to 1,2-addition (Scheme 1.20).^[45] The corresponding cyclopentene was obtained in good yield and enantioselectivity. In the proposed transition state, conjugate addition was preferred because of the preorganization of the homoenolate and the enal by titanium.

Scheme 1.19 Homoenolate annulation with N-acyl hydrazones

Scheme 1.20 Enal dimerization by co-catalysis

Another function of Lewis acid is to activate otherwise unreactive coupling partners. α,β -unsaturated ketoesters can be activated by $\text{Ti}(\text{O}^i\text{Pr})_4$ to undergo cyclization with a homoenolate to afford multisubstituted cyclopentanes in good to excellent diastereoselectivities and enantioselectivities (Scheme 1.21).^[46]

Scheme 1.21 Assembly of highly substituted cyclopentanol.

1.4 NHC catalysed reactions *via* enolate intermediates

In 2006, Bode and co-workers developed a new method to generate enolate from α,β -unsaturated aldehyde, which serves as a highly reactive dienophile to be captured by an α,β -unsaturated N-sulfonyl imine.^[47] Starting from a homoenolate, an activated carboxylate equivalent can be generated when an external electrophile adds to the β -position. However, if the homoenolate undergoes protonation of the β -position by an internal hydrogen transfer, the enolate equivalent could be generated (Scheme 1.22). In their initial study, the imidazole carbene pre-catalyst always led to the formation of γ -lactone, which was formed by the dimerization of enal. In contrast, when hindered triazolium salts were used, the desired azadiene Diels–Alder reaction proceeded successfully, affording the [4+2] cycloaddition products, dihydropyridinones, in good yields with excellent enantioselectivity. Furthermore, they introduced a new triazolium salt **35**, named Bode catalyst which could effectively

increase the yield and afford up to 99% *ee* for a wide range of substrates. In their proposed mechanism, the *cis*-diastereoselectivity is derived from an *endo* transition state, and the bulky NHC catalyst makes the desired reaction pathway operative.

Scheme 1.22 Proposed mechanism for triazolium catalyzed Diels–Alder reaction of enolate and N-sulfonyl imine

Scheme 1.23

Later on, Bode extended his work to use an α -haloaldehyde as an enolate precursor which served as a dienophile to undergo oxodiene Diels-Alder reaction, affording a dihydropyranone in outstanding enantioselectivity (Scheme 1.23).^[48]

Scheidt reported an intramolecular Diels-Alder cycloaddition involving an enolate intermediate to yield bicyclic enol ester **36** with high diastereo- and enantioselectivity (Scheme 1.24).^[49] Studer also used the same starting material to generate the enol intermediate which further underwent *in situ* oxidation to obtain the Michael acceptor. This Michael acceptor was further attacked by an external nucleophile **37** to form another enolate and underwent subsequent intramolecular Michael reaction, furnishing the corresponding 1,2,3-trisubstituted indane derivative **38** (Scheme 1.24).^[50]

Scheme 1.24 Intramolecular Diels–Alder reaction *via* enolate

Ketene was also employed as an enolate precursor under NHC catalysis. Ye *et al.* demonstrated the formation of enantiomerically enriched δ -lactones *via* [4+2] cycloaddition of ketenes with enones (Scheme 1.25a).^[51] Later he employed this enolate precursor for

Staudinger type [2+2] cycloaddition reaction with a protected imine to afford a β -lactam in good yield and excellent enantioselectivity (Scheme 1.25 b).^[52]

Scheme 1.25

1.5 NHC catalysed transesterification reactions

In 2002, Nolan^[53] and Hedrick^[54] independently reported the first transesterification reactions catalysed by NHC. The corresponding new ester was formed in excellent yield (Scheme 1.26a). NHC-catalysed transesterification was found to have high selectivity towards primary alcohols in comparison with secondary alcohols. When a vinyl ester **39** was subjected to the reaction with a 1:1 mixture of primary and secondary alcohols, the corresponding esters **40** and **41** were formed in a ratio of 20:1 (Scheme 1.26b). The first asymmetric version was reported by Suzuki and co-workers using a vinyl propionate with a secondary alcohol, resulting in 19% *ee*.^[55]

Scheme 1.26

In 2005, Movassaghi and Schmidt reported a novel amidation of unactivated esters with amino alcohols by free IMes catalysis.^[56] In their study, the carbene–alcohol complexes with hydrogen bonding **42** and **43** was isolated for the first time. As shown in Scheme 1.27, the transesterification with alcohol followed by a rapid O to N transfer afforded the corresponding amide.

Scheme 1.27 NHC catalysed transesterifications with amino alcohols

NHC activated methyl ester could also react with benzoin or benzaldehydes to form γ – butyrolactones (Scheme 1.28).^[57] Although the mechanism of this cascade reaction is still not very clear as to whether the reaction pathway is a transesterification followed by a Michael addition or a tandem Michael addition/lactonization, this methodology provides a fast and efficient protocol for the synthesis of γ,γ -difunctionalized γ -butyrolactones in moderate to good yields.

Scheme 1.28 NHC catalysed access to γ -butyrolactones

1.6 My thesis work

The unique homoenolate intermediate derived from an enal via NHC catalysis has become a popular synthetic building block since the first reports of Bode and Glorius. This unpolunged three carbon synthon was involved in many carbon-carbon bond forming or carbon-heteroatom bond forming events with a variety of electrophiles. Since the chiral NHC precatalysts are readily available and easily modified, more useful synthetic skeletons

could be catalysed with high stereo and enantioselectivities. In the first part of this thesis, we present the development of NHC-catalysed addition of enals to nitroalkenes via homoenolate intermediate. Chapter 2 describes a diastereoselective homoenolate addition to nitrodienes and a mechanistic study on the reaction was carried out. Chapter 3 describes an enantioselective version of the synthesis “5-carbon synthon” multifunctional nitroester by homoenolate addition of enals to various nitroalkenes. Previously unreactive enals were well tolerated in the presence of the modified Bode catalyst. Further transformations were also accomplished to prove the utility of this methodology.

1.7 References

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CHAPTER 2

N-Heterocyclic Carbene Mediated Homoenolate Addition of Enals to Nitrodienes: Scope and Limitations

2.1 Introduction

Over the past few years, N-heterocyclic carbene catalysis involving reactive intermediates such as acyl anion,^[1] homoenolate,^[2] enolate^[3] and activated carboxylate^[4] (Scheme 2.1), has emerged as an intense research area in organic chemistry. Each intermediate exhibits distinctive reactivity under suitable reaction conditions.

Scheme 2.1 NHC-mediated generation of reactive intermediates from α,β -unsaturated aldehydes

Among these intermediates, the reactive homoenolate intermediate was first disclosed by Bode^[2a] and Glorius^[2b] independently in 2004. Since then, a massive extension has been made for the development of various electrophiles in order to accomplish important structural motifs through this intermediate. For example, aldehydes,^[2a-2c] enones,^[2d-2f] imines,^[2g-2j] 1,2-diketones,^[2k] nitrones,^[2l] ketoesters,^[2m] and nitrostyrenes^[2n] have been employed in the presence of suitable N-heterocyclic carbenes under basic conditions. In 2009, Nair *et al*, first reported NHC-catalyzed, stereoselective Michael addition of enals to β -nitrostyrene *via* the homoenolate intermediate.^[2n]

Recently, Rovis and Scheidt *et al*, developed a highly efficient and enantioselective intermolecular Stetter reaction of enals with nitroalkenes.^[5] Nitroalkene is probably one of the most versatile electrophiles for further structural elaboration due to the presence of the unique $-\text{NO}_2$ functionality.^[6] The aim of our research is to extend Nair's strategy^[2n] to conjugated nitroalkenes in order to broaden the scope of useful functionalized nitroolefins. Attractively, this Michael adduct contains $-\text{NO}_2$ functionality with an extra "C=C" double bond, which could be useful for further transformations such as metathesis and electrophilic cyclization reactions under appropriate conditions (Scheme 2.2). We describe here a highly-stereoselective synthesis of multifunctional nitroesters **2.4** from α,β -unsaturated aldehydes and nitrodienes *via* NHC catalyzed homoenolate addition.

Scheme 2.2 Multifunctional nitroester synthesis

2.2 Results and discussion

2.2.1 Optimization of reaction conditions

In the last few years, Michael addition of various types of nucleophiles to nitrodienes have been extensively investigated.^[7] However, no report of NHC-catalyzed homoenolate addition to nitrodiene has been achieved in highly stereoselective manner. Initial investigations were carried out on the reaction of cinnamaldehyde **2.1a** (2.0 equiv)

with nitrodiene **2.2a** (1.0 equiv) catalyzed by various imidazolium based NHC catalysts **2.3a-2.3f** (0.15 equiv) by using K₂CO₃ (0.2 equiv) as a base in anhydrous THF-MeOH (9:1) at 70 °C, which was similar to the condition developed by Nair.^[2n] The results are depicted in Table 2.1. Amongst the NHC-catalysts, **2.3a** furnished a good yield of 56% after 18 h. However, the diastereoselectivity was only modest (dr = 4.5:1). Other bases like DBU, DIPEA and Et₃N were completely inactive for this reaction when catalyst **2.3a** was used (entries 7-9). When the more nucleophilic catalyst **2.3b** was used, the product was obtained with a similar diastereomeric ratio (dr = 4.5:1) but in a slightly lower yield (entry 2). To further increase the selectivity, more sterically demanding catalysts including 1,3-bis(2,6-diisopropyl phenyl)imidazolium chloride **2.3c** and 1,3-bis(2,6-diisopropyl phenyl)imidazolinium chloride **2.3d** were tested. Interestingly, the yield of the ester **2.4a** dramatically decreased to less than 10% but diastereomeric ratio increased to >30:1 when the catalyst **2.3c** was used (entry 3). The catalyst **2.3d** also furnished **2.4a** in good diastereoselectivity but in a moderate yield (entry 4). Catalysts **2.3e** and **2.3f** were completely inactive for this reaction. The mesityl substituted imidazolium catalysts^[8] **2.3a** and **2.3b** were much more reactive compared to **2.3c** and **2.3d** while the diastereoselectivities were not satisfactory. The catalyst **2.3d** was observed to be more reactive than **2.3c** presumably due to its higher nucleophilicity nature as discussed by Nair *et al.* Therefore both steric and electronic factor are to be considered in order to obtain good yield and diastereoselectivity. The highest yield was obtained when KHCO₃ (0.2 equiv) was used as a base (entries 11-12). Finally, potassium or sodium benzoate (0.2 equiv) as an additive was also tested along with K₂CO₃ (0.2 equiv) under anhydrous conditions, which result in moderate yields of **2.4a** with slightly lower diastereoselectivity after 12 h (entries 13-14). PhCO₂K (0.2 equiv) produced **2.4a** in a lower yield (entry 15). A lower loading (0.1 equiv) of **2.3c** and KHCO₃ (0.2 equiv) furnished **2.4a** in similar yield and diastereoselectivity (entry

16). The more nucleophilic catalyst **2.3d** was also examined in the presence of KHCO_3 as a base, which resulted in a lower yield of **2.4a** (entry 17). Excess aldehyde (2.0 equiv) was necessary to guarantee good yields of the nitroester product **2.4a** (entry 18), because saturated ester of cinnamaldehyde was always formed as a major byproduct along with desired product. In summary, the optimum conditions for the homoenolate addition to nitrodiene involved a suspended solution of NHC-catalyst **2.3c** (0.10 equiv), cinnamaldehyde **2.1a** (2.0 equiv), nitrodiene **2.2a** (1.0 equiv), and KHCO_3 (0.2 equiv) in anhydrous THF-MeOH (0.13 M; 9:1). Under these conditions, the nitroester **2.4a** was obtained in 63% yield after 12 h at 70 °C with good diastereoselectivity. It is worth mentioning that the reaction did not provide any product at room temperature and not even a trace amount of 1,6-addition adduct has been observed during the whole optimization study.

Table 2.1. Optimization of reaction conditions for the nitroester synthesis

Entry	Catalyst	Base	Additive	Time (h)	Yield of 2.4a (%) ^b	Dr (<i>syn:anti</i>) ^c
1	2.3a	K ₂ CO ₃	---	18	56	4.5:1
2	2.3b	K ₂ CO ₃	---	12	53	4.5:1
3	2.3c	K ₂ CO ₃	---	24	<10	>30:1
4	2.3d	K ₂ CO ₃	---	12	42	>30:1
5	2.3e	K ₂ CO ₃	---	24	trace	--
6	2.3f	K ₂ CO ₃	---	24	0	--
7	2.3a	DBU	---	24	0	--
8	2.3a	DIPEA	---	24	0	--
9	2.3a	Et ₃ N	---	24	0	--
10	2.3c	KOH	---	5	30	--
11	2.3c	NaHCO ₃	---	12	53	>30:1
12 ^d	2.3c	KHCO ₃	---	8	64(66)	>30:1
13 ^e	2.3c	K ₂ CO ₃	PhCO ₂ K	12	53	>15:1
14 ^e	2.3c	K ₂ CO ₃	PhCO ₂ Na	12	51	>15:1
15	2.3c	--	PhCO ₂ K	24	31	--
16 ^f	2.3c	KHCO ₃	---	12	63	>30:1
17	2.3d	KHCO ₃	---	12	44	---
18 ^g	2.3c	KHCO ₃	---	12	41	>30:1

^a. Reaction condition: All the reactions are conducted with 15 mol% catalyst **2.3c**, 20 mol% base KHCO₃ in THF-MeOH (9:1) at 70 °C; ^b. Isolated yield; ^c. Diastereomeric ratio is determined from ¹H-NMR. Diastereoisomer could not be isolated by column chromatography as R_f factor is same for both diastereoisomer; ^d. Yield in parenthesis refers as NMR yield using CH₂Br₂ as an internal standard. ^e. 20 mol% of potassium benzoate is added as additive along with base K₂CO₃ (20 mol%); ^f. IPr-HCl-catalyst 10 mol% and KHCO₃ 20 mol% are used; ^g. 1.0 equiv. of cinnamaldehyde is used.

2.2.2 Substrate scope

With the optimized conditions in hand, we stepped forward to the investigation of the scope and limitations of various α,β -unsaturated aldehydes with nitrodiene **2.2a** (Table 2.2). All aryl enals substituted at 2, 3 or 4-positions, participated in the reaction to afford the desired products in good yields and diastereoselectivities. Interestingly, alkyl

substituted aldehyde (*i.e.* crotonaldehyde) was completely unreactive (entry 6). Next, we extended the reaction to other nitrodienes **2.2b-2.2e** substituted with electron rich and electron poor aryl groups (entries 8-21). Good to excellent yields and diastereoselectivities of **2.4** were observed in most of the cases, with the exception of heteroaryl-substituted enals, which gave moderate diastereoselectivities under the same conditions (entries 7 & 19). The nitrodiene substituted with electron poor 4-chlorophenyl group **2.2e** gave a moderate yield but excellent diastereoselectivity (entry 21). It is significant to mention that just as Nair interpreted, only aryl substituted nitrodiene and enals gave the products with good to excellent yields for this reaction. An alkyl-substituted nitrodiene did not provide any homoenolate addition product **2.4v** (entry 22). After successful development of homoenolate addition to nitrodiene with good to excellent diastereoselectivity, we attempted to extend this protocol to nitroenyne systems. Unfortunately, no trace amount of the desired addition product was observed by the ¹H-NMR of the crude reaction mixture under the same optimized reaction conditions. Instead, the aldehyde was mainly converted to the corresponding saturated ester.

Table 2.2 Exploration the substrate scope of enals **2.1** and nitrodienes **2.2** in the synthesis of multifunctional nitroester **2.4^a**

Entry	R ₁	R ₂	Products	Yield (%) ^b	dr (<i>syn:anti</i>) ^c
1	Ph	Ph	2.4a	63	>30:1
2	4-MeC ₆ H ₄	Ph	2.4b	68	>30:1
3	4-BrC ₆ H ₄	Ph	2.4c	77	>30:1
4	3-BrC ₆ H ₄	Ph	2.4d	68	>30:1
5	2-OMeC ₆ H ₄	Ph	2.4e	67	>30:1
6	CH ₃	Ph	2.4f	---	---
7	2-Furyl	Ph	2.4g	65	10:1
8	Ph	4-OMeC ₆ H ₄	2.4h	63	30:1
9	4-MeC ₆ H ₄	4-OMeC ₆ H ₄	2.4i	76	28:1
10	4-BrC ₆ H ₄	4-OMeC ₆ H ₄	2.4j	78	28:1
11	2-OMeC ₆ H ₄	4-OMeC ₆ H ₄	2.4k	69	>30:1(4:1) ^d
12	4-MeC ₆ H ₄	2-OMeC ₆ H ₄	2.4l	72	>30:1
13	2-OMeC ₆ H ₄	2-OMeC ₆ H ₄	2.4m	68	>30:1
14	2-ClC ₆ H ₄	2-OMeC ₆ H ₄	2.4n	68	>30:1
15	4-ClC ₆ H ₄	2-OMeC ₆ H ₄	2.4o	65	>30:1
16	4-BrC ₆ H ₄	2-OMeC ₆ H ₄	2.4p	67	>30:1
17	4-FC ₆ H ₄	2-OMeC ₆ H ₄	2.4q	42	>30:1
18	4-OMeC ₆ H ₄	2-OMeC ₆ H ₄	2.4r	65	>30:1
19	2-Thiophenyl	2-OMeC ₆ H ₄	2.4s	51	12:1
20	3-BrC ₆ H ₄	4-MeC ₆ H ₄	2.4t	73	>30:1
21	4-MeC ₆ H ₄	4-ClC ₆ H ₄	2.4u	41	>30:1
22	Ph	CH ₃	2.4v	---	---

^aReaction procedure: All reactions are carried out with aldehyde (2.0 equiv), nitrodiene (1.0 equiv), catalyst 2.3c (0.1 equiv) and KHCO_3 (0.2 equiv) in 0.13 (M) THF-MeOH (9:1 ratio) at 70 °C; ^b yield obtained after column chromatography; ^c dr ratio is determined from $^1\text{H-NMR}$ analysis, Diastereoisomer for all the cases could not be isolated by column chromatography as R_f factor is same for both *anti* and *syn* adduct; ^d dr ratio in parenthesis is observed when catalyst $\text{IMes}\cdot\text{HCl}$ is used.

2.2.3 Application

To establish the importance of this methodology, we performed a few reactions with Michael adducts **2.4** containing an extra C=C double bond. Halogen induced Friedel-Crafts type alkylation^[9] reaction and metal catalyzed hydroarylation reaction^[10] were tested. The reaction of the adduct **2.4h**, which containing an electron-rich 4-methoxystyryl moiety, with NBS and $\text{Sm}(\text{OTf})_3$ in DCM at 0°C afforded tetrasubstituted tetralin derivative **2.6** (Scheme 2.3). Another Michael adduct **2.4r** was refluxed in DCE-cyclohexane in the presence of $\text{Bi}(\text{OTf})_3$ (5 mol%), which furnished a hydroarylated product **2.7** in excellent yield with 2:1 diastereoselectivity (Scheme 2.3).

Scheme 2.3 Application towards the synthesis of substituted tetralin derivatives

Next we attempted synthesis of a highly substituted cyclopentanol derivative. Firstly, we carried out the reduction of the ester **2.4a** using DIBAL-H in toluene to afford the corresponding alcohol **2.8**. Subsequent DMP-oxidation provided an ester **2.9** in an excellent yield. By using the enamine catalyst **CAT-A**, compound **2.9** smoothly converted to a cyclopentanol **2.10** in almost quantitative yield. (Scheme 2.4).

Reagent and condition: a. DIBAL-H, Toluene, 40 °C, 68%; b. DMP, DCM, rt, 89%; c. CAT-A (10 mol%), DABCO (10 mol%), DCM, 0 °C, 98%.

Scheme 2.4 Synthesis of cyclopentanol from Michael adduct **2.4a**

2.2.4 Mechanism investigation

On the basis of control experiments, the reaction mechanism is proposed (Scheme 2.5). Initially, the deprotonated aryl imidazolium catalyst **2.3c** reacts with enals to form intermediate **I**, followed by proton transfer to form Breslow intermediate **II**. Next, this intermediate converts to homoenolate intermediate **III**. The intermediate **IV** was furnished by a nucleophilic attack of homoenolate to the nitrodiene **2.2**. Finally, MeOH acts as an acylating agent and gives the multifunctional nitroester **2.4** with the regeneration of carbene **2.3c**.

Scheme 2.5 Proposed reaction mechanism

2.3 Conclusion

In conclusion, we have developed a highly diastereoselective homoenolate addition of enals to nitrodienes to afford multifunctional five carbon synthons, unsaturated nitroesters, in good yields. A salient feature of this methodology is that the reaction provides exclusively 1,4-Michael addition product. No trace amount of 1,6-adduct was ever observed during the entire study. We have shown a few applications by employing electrophilic cyclization reactions to provide highly functionalized tetralin derivatives.

2.4 Experimental section

α,β -unsaturated aldehydes such as *trans*-4-methoxycinnamaldehyde, *trans*-2-methoxycinnamaldehyde and *trans*-cinnamaldehyde were purchased from suppliers and were used without any further purification. Other cinnamaldehyde derivatives were prepared from the standard literature procedures.^[12] Nitrodienes (**2.2a-2.2f**) and nitroenyne (**2.2g**) substrates were prepared from the standard literature procedures.^[13] All the imidazolium and imidazolinium NHC catalysts **2.3a-2.3f** were purchased from commercial suppliers. Freshly distilled THF over sodium benzophenone ketyl was used

for all the reactions. ACS grade MeOH (99.98%) was used directly as received. KHCO_3 was purchased from (GCE) local chemical suppliers and used as received.

General procedure for the synthesis of multifunctional nitro ester **2.4a**:

To a well-stirred solution of cinnamaldehyde (75 mg, 0.57 mmol, 2.0 equiv) and nitrodiene (50 mg, 0.29 mmol, 1.0 equiv) in 2.2 mL dry THF-MeOH {0.13 (M) C, 9:1}, 1,3-bis(2,6-diisopropyl phenyl) imidazolium chloride **2.3c** (12 mg, 0.029 mmol, 0.1 equiv) and KHCO_3 (6 mg, 0.06 mmol, 0.2 equiv) were added and allowed to stir at 70 °C under nitrogen atmosphere. Progress of the reaction was monitored by TLC. On completion (8 h), the reaction mixture was diluted with 2-4 mL ethyl acetate and filtered through celite. After removal of the combined solvents under reduced pressure, the crude reaction mixture was subjected to purification by flash column chromatography directly using EtOAc/petroleum-ether as an eluent to provide nitroester **2.4a** in 61 mg (63%) with good diastereoselectivity (dr >30:1).

4-Nitromethyl-3,6-diphenyl-hex-5-enoic acid methyl ester (**2.4a**):

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 7.43-7.20 (m, 8H), 7.13 (d, $J = 7.3$ Hz, 2H), 6.51 (d, $J = 15.6$ Hz, 1H), 5.78 (dd, $J = 16.0, 9.6$ Hz, 1H), 4.47 (dd, $J = 12.4, 6.4$ Hz, 1H), 4.16 (dd, $J = 12.0, 8.7$ Hz, 1H), 3.62 (s, 3H), 3.48-3.37 (m, 2H), 2.84 (dd, $J = 15.6, 7.3$ Hz, 1H), 2.75 (dd, $J = 15.8, 7.3$ Hz, 1H). $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz): δ 171.9, 138.1, 136.1, 135.5, 128.6 (4C), 128.5 (2C), 128.1, 127.6, 126.5 (2C), 123.2, 78.5, 51.8, 45.9, 43.2, 37.8. HRMS (EI) calcd for $\text{C}_{20}\text{H}_{21}\text{NO}_4$, 340.1549 m/z ($\text{M}+\text{H}$) $^+$; Found, 340.1555 m/z .

4-Nitromethyl-6-phenyl-3-*p*-tolyl-hex-5-enoic acid methyl ester (**2.4b**):

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 7.40-7.23 (m, 5H), 7.15 (d, J = 7.8 Hz, 2H), 7.01 (d, J = 8.2 Hz, 2H), 6.51 (d, J = 15.6 Hz, 1H), 5.80 (dd, J = 16.0, 9.6 Hz, 1H), 4.46 (dd, J = 12.4, 6.0 Hz, 1H), 4.15 (dd, J = 12.0, 8.7 Hz, 1H), 3.62 (s, 3H), 3.45-3.32 (m, 2H), 2.86-2.65 (m, 2H), 2.34 (s, 3H). $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz): δ 172.2, 137.5, 136.4, 135.6, 135.2, 129.5 (2C), 128.8 (2C), 128.6 (2C), 128.3, 126.7 (2C), 123.6, 78.7, 52.0, 46.1, 43.0, 38.0, 21.2. HRMS (EI) calcd for $\text{C}_{21}\text{H}_{23}\text{NO}_4$, 354.1705 m/z ($\text{M}+\text{H}$) $^+$; Found, 354.1714 m/z .

3-(4-Bromo-phenyl)-4-nitromethyl-6-phenyl-hex-5-enoic acid methyl ester (2.4c):

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 7.48 (d, J = 7.3 Hz, 2H), 7.36-7.23 (m, 5H), 7.02 (d, J = 8.0 Hz, 2H), 6.51 (d, J = 15.6 Hz, 1H), 5.72 (dd, J = 15.6, 9.6 Hz, 1H), 4.43 (dd, J = 12.4, 6.0 Hz, 1H), 4.18 (dd, J = 11.4, 7.8 Hz, 1H), 3.62 (s, 3H), 3.43-3.32 (m, 2H), 2.80 (dd, J = 15.6, 6.4 Hz, 1H), 2.72 (dd, J = 16.0, 7.3 Hz, 1H). $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz): δ 171.6, 137.1, 135.9, 135.8, 131.8 (2C), 130.2 (2C), 128.7 (2C), 128.2, 126.4 (2C), 122.6, 121.6, 78.1, 51.9, 45.7, 42.6, 37.7. HRMS (EI) calcd for $\text{C}_{20}\text{H}_{20}\text{BrNO}_4$, 418.0654 m/z ($\text{M}+\text{H}$) $^+$; Found, 418.0661 m/z .

3-(3-Bromo-phenyl)-4-nitromethyl-6-phenyl-hex-5-enoic acid methyl ester (2.4d):

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 7.45-7.42 (m, 1H), 7.34-7.20 (m, 7H), 7.08 (d, J = 7.8 Hz, 1H), 6.52 (d, J = 16.0 Hz, 1H), 5.74 (dd, J = 16.0, 9.6 Hz, 1H), 4.46 (dd, J = 12.0, 6.0 Hz, 1H), 4.19 (dd, J = 12.0, 8.0 Hz, 1H), 3.64 (s, 3H), 3.43-3.37 (m, 2H), 2.81 (dd, J = 16.0, 6.8 Hz, 1H), 2.72 (dd, J = 16.0, 7.2 Hz, 1H). $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz): δ 171.5, 140.7, 135.9, 131.6, 130.8, 130.2, 128.7 (3C), 128.2, 127.2, 126.5 (3C), 122.7, 78.2, 51.9, 45.7,

42.9, 37.6. HRMS (EI) calcd for $C_{20}H_{20}BrNO_4$, 418.0654 m/z ($M+H$)⁺; Found, 418.0654 m/z .

3-(2-Methoxy-phenyl)-4-nitromethyl-6-phenyl-hex-5-enoic acid methyl ester (2.4e):

2.4 e

¹H-NMR ($CDCl_3$, 400 MHz): δ 7.31-7.21 (m, 6H), 7.02-6.89 (m, 3H), 6.48 (d, J = 16.0 Hz, 1H), 5.80 (dd, J = 16.0, 10.0 Hz, 1H), 4.59 (dd, J = 12.4, 5.5 Hz, 1H), 4.12 (dd, J = 12.8, 9.6 Hz, 1H), 4.08-4.02 (m, 1H), 3.82 (s, 3H), 3.62 (s, 3H), 3.46-3.39 (m, 1H), 2.84 (dd, J = 16.0, 8.2 Hz, 1H), 2.69 (dd, J = 16.0, 7.3 Hz, 1H). ¹³C-NMR ($CDCl_3$, 100 MHz): δ 172.2, 156.9, 136.4, 135.0, 128.7, 128.5 (2C), 128.4, 127.8, 126.7, 126.4 (2C), 124.0, 120.5, 110.8, 78.2, 55.3, 51.7, 45.7, 37.3, 34.8. HRMS (EI) calcd for $C_{21}H_{23}NO_5$, 370.1654 m/z ($M+H$)⁺; Found, 370.1647 m/z .

3-Furan-2-yl-4-nitromethyl-6-phenyl-hex-5-enoic acid methyl ester (2.4g):

2.4 g

¹H-NMR ($CDCl_3$, 400 MHz): δ 7.40-7.22 (m, 6H), 6.51 (d, J = 16.0 Hz, 1H), 6.35-6.32 (m, 1H), 6.13 (d, J = 3.2 Hz, 1H), 5.86 (dd, J = 16.0, 10.0 Hz, 1H), 4.54 (dd, J = 12.0, 6.0 Hz, 1H), 4.32 (dd, J = 12.0, 9.0 Hz, 1H), 3.66 (s, 3H), 3.62-3.55 (m, 1H), 3.42-3.37 (m, 1H), 2.72 (dd, J = 7.8, 4.6 Hz, 2H). ¹³C-NMR ($CDCl_3$, 100 MHz): δ 171.5, 152.6, 142.2, 136.1, 135.6, 128.5 (2C), 128.0, 126.5 (2C), 123.4, 110.3, 107.8, 78.4, 51.8, 45.4, 36.7, 35.9. HRMS (EI) calcd for $C_{18}H_{19}NO_5$, 352.1161 m/z ($M+Na$)⁺; Found, 352.1173 m/z .

6-(4-Methoxy-phenyl)-4-nitromethyl-3-phenyl-hex-5-enoic acid methyl ester (2.4h):

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 7.38-7.26 (m, 3H), 7.24 (d, J = 8.6 Hz, 2H), 7.14-7.11 (m, 2H), 6.84 (d, J = 8.2 Hz, 2H), 6.45 (d, J = 16.0 Hz, 1H), 5.63 (dd, J = 15.6, 9.6 Hz, 1H), 4.45 (dd, J = 12.0, 6.0 Hz, 1H), 4.14 (dd, J = 12.0, 8.6 Hz, 1H), 3.79 (s, 3H), 3.61 (s, 3H), 3.44-3.32 (m, 2H), 2.83 (dd, J = 16.0, 7.8 Hz, 1H), 2.74 (dd, J = 16.0, 7.3 Hz, 1H). $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz): δ 172.2, 159.7, 138.4, 135.0, 129.1, 128.8 (3C), 127.8 (2C), 127.7 (2C), 121.0, 114.2 (2C), 78.7, 55.5, 52.0, 46.1, 43.4, 37.9. HRMS (EI) calcd for $\text{C}_{21}\text{H}_{23}\text{NO}_5$, 392.1474 m/z ($\text{M}+\text{Na}$) $^+$; Found, 392.1471 m/z .

6-(4-Methoxy-phenyl)-4-nitromethyl-3-*p*-tolyl-hex-5-enoic acid methyl ester (2.4i):

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 7.24 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 8.2 Hz, 2H), 7.01 (d, J = 8.0 Hz, 2H), 6.84 (d, J = 8.0 Hz, 2H), 6.45 (d, J = 16.0 Hz, 1H), 5.63 (dd, J = 16.0, 10.0 Hz, 1H), 4.45 (dd, J = 12.0, 6.0 Hz, 1H), 4.13 (dd, J = 12.0, 8.6 Hz, 1H), 3.80 (s, 3H), 3.62 (s, 3H), 3.41-3.35 (m, 2H), 2.80-2.70 (m, 2H), 2.34 (s, 3H). $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz): δ 172.0, 159.5, 137.2, 135.1, 134.7, 129.2 (2C), 129.0, 128.4 (2C), 127.6 (2C), 121.0, 114.0 (2C), 78.6, 55.2, 51.7, 46.0, 42.8, 37.8, 21.0. HRMS (EI) calcd for $\text{C}_{22}\text{H}_{25}\text{NO}_5$, 406.1630 m/z ($\text{M}+\text{Na}$) $^+$; Found, 406.1639 m/z .

3-(4-Bromo-phenyl)-6-(4-methoxy-phenyl)-4-nitromethyl-hex-5-enoic acid methyl ester (2.4j):

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 7.47 (d, J = 8.2 Hz, 2H), 7.24 (d, J = 8.2 Hz, 2H), 7.02 (d, J = 8.2 Hz, 2H), 6.85 (d, J = 8.2 Hz, 2H), 6.45 (d, J = 16.0 Hz, 1H), 5.56 (dd, J = 15.6, 9.6 Hz, 1H), 4.42 (dd, J = 12.0, 6.4 Hz, 1H), 4.17 (dd, J = 12.0, 8.0 Hz, 1H), 3.80 (s, 3H), 3.61 (s, 3H), 3.43-3.30 (m, 2H), 2.80 (dd, J = 16.0, 7.4 Hz, 1H),

2.71 (dd, $J = 16.0, 7.8$ Hz, 1H). ^{13}C -NMR (CDCl_3 , 100 MHz): δ 171.6, 159.6, 137.3, 135.2, 131.7 (2C), 130.3 (2C), 128.7, 127.7 (2C), 121.6, 120.2, 114.1 (2C), 78.3, 55.2, 52.0, 45.8, 42.6, 37.7. HRMS (EI) calcd for $\text{C}_{21}\text{H}_{22}\text{BrNO}_5$, 448.0760 m/z ($\text{M}+\text{H}$) $^+$; Found, 448.0759 m/z .

6-(4-Methoxy-phenyl)-3-(2-methoxy-phenyl)-4-nitromethyl-hex-5-enoic acid methyl ester (2.4k):

^1H -NMR (CDCl_3 , 400 MHz): δ 7.26-7.20 (m, 3H), 7.01 (dd, $J = 7.8, 1.6$ Hz, 1H), 6.95-6.83 (m, 2H), 6.81 (d, $J = 8.2$ Hz, 2H), 6.42 (d, $J = 16.0$ Hz, 1H), 5.65 (dd, $J = 16.0, 10.0$ Hz, 1H), 4.58 (dd, $J = 12.8, 5.6$ Hz, 1H), 4.09 (dd, $J = 12.8, 10.0$ Hz, 1H), 4.07-4.01 (m, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.61 (s, 3H), 3.45-3.36 (m, 1H), 2.83 (dd, $J = 16.0, 8.2$ Hz, 1H), 2.68 (dd, $J = 16.0, 7.3$ Hz, 1H). ^{13}C -NMR (CDCl_3 , 100 MHz): δ 172.2, 159.4, 156.9, 134.4, 129.1, 128.7, 128.3, 127.6 (2C), 126.8, 121.6, 120.4, 113.8 (2C), 110.7, 78.3, 55.23, 55.20, 51.6, 45.7, 37.3, 34.7. HRMS (EI) calcd for $\text{C}_{22}\text{H}_{25}\text{NO}_6$, 422.1580 m/z ($\text{M}+\text{Na}$) $^+$; Found, 422.1590 m/z .

6-(2-Methoxy-phenyl)-4-nitromethyl-3-*p*-tolyl-hex-5-enoic acid methyl ester (2.4l):

^1H -NMR (CDCl_3 , 400 MHz): δ 7.30 (dd, $J = 7.3, 1.4$ Hz, 1H), 7.26-7.21 (m, 1H), 7.14 (d, $J = 7.8$ Hz, 2H), 7.04 (d, $J = 8.0$ Hz, 2H), 6.96-6.85 (m, 2H), 6.80 (d, $J = 16.0$ Hz, 1H), 5.84 (dd, $J = 16.0, 9.6$ Hz, 1H), 4.43 (dd, $J = 12.4, 6.4$ Hz, 1H), 4.14 (dd, $J = 12.4, 8.7$ Hz, 1H), 3.83 (s, 3H), 3.61 (s, 3H), 3.44-3.35 (m, 2H), 2.82 (dd, $J = 16.0, 7.3$ Hz, 1H), 2.74 (dd, $J = 16.0, 7.8$ Hz, 1H), 2.34 (s, 3H). ^{13}C -NMR (CDCl_3 , 100 MHz): δ 172.1, 156.8, 137.2, 135.1, 130.4, 129.2 (2C), 129.0, 128.6 (2C), 127.1, 125.3, 124.0,

120.6, 111.0, 78.6, 55.4, 51.7, 46.5, 42.8, 38.0, 21.0. HRMS (EI) calcd for $C_{22}H_{25}NO_5$, 406.1630 m/z ($M+Na$)⁺; Found, 406.1629 m/z .

3,6-Bis-(2-methoxy-phenyl)-4-nitromethyl-hex-5-enoic acid methyl ester (2.4m):

¹H-NMR ($CDCl_3$, 400 MHz): δ 7.30-7.18 (m, 3H), 7.05 (dd, J = 7.8, 4.0 Hz, 1H), 6.95-6.83 (m, 4H), 6.78 (d, J = 16.0 Hz, 1H), 5.83 (dd, J = 16.0, 9.6 Hz, 1H), 4.57 (dd, J = 12.8, 6.0 Hz, 1H), 4.14-4.07 (m, 2H), 3.83 (s, 3H), 3.81 (s, 3H), 3.62 (s, 3H), 3.45-3.41 (m, 1H), 2.85 (dd, J = 16.0, 7.8 Hz, 1H), 2.71 (dd, J = 16.0, 7.8 Hz, 1H). ¹³C-NMR ($CDCl_3$, 100 MHz): δ 172.3, 157.0, 156.7, 130.0, 128.9, 128.8, 128.2, 127.0, 126.9, 125.4, 124.6, 120.5, 120.4, 110.9, 110.7, 78.2, 55.4, 55.2, 51.6, 46.2, 37.4, 34.6. HRMS (EI) calcd for $C_{22}H_{25}NO_6$, 422.1580 m/z ($M+Na$)⁺; Found, 422.1580 m/z .

3-(2-Chloro-phenyl)-6-(2-methoxy-phenyl)-4-nitromethyl-hex-5-enoic acid methyl ester (2.4n):

¹H-NMR ($CDCl_3$, 400 MHz): δ 7.40 (d, J = 8.0 Hz, 1H), 7.30-7.16 (m, 5H), 6.92-6.84 (m, 2H), 6.76 (d, J = 16.0 Hz, 1H), 5.90 (dd, J = 16.0, 9.6 Hz, 1H), 4.70 (dd, J = 12.2, 4.6 Hz, 1H), 4.23-4.13 (m, 2H), 3.81 (s, 3H), 3.60 (s, 3H), 3.50-3.42 (m, 1H), 2.87 (dd, J = 16.0, 6.9 Hz, 1H), 2.75 (dd, J = 16.0, 8.0 Hz, 1H). ¹³C-NMR ($CDCl_3$, 100 MHz): δ 171.6, 156.8, 136.6, 134.5, 130.6, 130.1, 129.2, 129.1, 128.6, 127.2, 126.9, 125.1, 124.0, 120.6, 111.0, 78.2, 55.4, 51.8, 46.7, 38.5, 37.8. HRMS (EI) calcd for $C_{21}H_{22}ClNO_5$, 404.1265 m/z ($M+H$)⁺; Found, 404.1265 m/z .

3-(4-Chloro-phenyl)-6-(2-methoxy-phenyl)-4-nitrophenylmethyl-hex-5-enoic acid methylester (2.4o):

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 7.31 (d, $J = 8.0$ Hz, 2H), 7.30-7.21 (m, 2H), 7.10 (d, $J = 8.7$ Hz, 2H), 6.92-6.85 (m, 2H), 6.78 (d, $J = 16.0$ Hz, 1H), 5.78 (dd, $J = 16.0, 9.6$ Hz, 1H), 4.40 (dd, $J = 12.0, 6.8$ Hz, 1H), 4.17 (dd, $J = 12.0, 8.2$ Hz, 1H), 3.83 (s, 3H), 3.60 (s, 3H), 3.43-3.36 (m, 2H), 2.81 (dd, $J = 16.0, 6.8$ Hz, 1H), 2.73 (dd, $J = 16.0, 8.2$ Hz, 1H). $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz): δ 171.6, 156.8, 136.8, 133.4, 130.8, 130.0 (2C), 129.2, 128.7 (2C), 127.2, 125.0, 123.4, 120.6, 110.9, 78.2, 55.4, 51.8, 46.3, 42.5, 37.9. HRMS (EI) calcd for $\text{C}_{21}\text{H}_{22}\text{ClNO}_5$, 426.1084 m/z ($\text{M}+\text{Na}$) $^+$; Found, 426.1082 m/z .

3-(4-Bromo-phenyl)-6-(2-methoxy-phenyl)-4-nitrophenylmethyl-hex-5-enoic acid methyl ester (2.4p):

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 7.46 (d, $J = 8.0$ Hz, 2H), 7.27-7.22 (m, 2H), 7.04 (d, $J = 8.0$ Hz, 2H), 6.92-6.82 (m, 2H), 6.78 (d, $J = 16.0$ Hz, 1H), 5.77 (dd, $J = 15.6, 9.2$ Hz, 1H), 4.40 (dd, $J = 12.3, 6.8$ Hz, 1H), 4.17 (dd, $J = 12.0, 8.2$ Hz, 1H), 3.83 (s, 3H), 3.60 (s, 3H), 3.42-3.36 (m, 2H), 2.82 (dd, $J = 16.0, 6.8$ Hz, 1H), 2.75 (dd, $J = 16.0, 7.8$ Hz, 1H). $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz): δ 171.7, 156.8, 137.3, 131.7 (2C), 130.9, 130.5 (2C), 129.2, 127.2, 125.0, 123.3, 121.6, 120.6, 111.0, 78.2, 55.4, 51.8, 46.3, 42.6, 37.9. HRMS (EI) calcd for $\text{C}_{21}\text{H}_{22}\text{BrNO}_5$, 470.0579 m/z ($\text{M}+\text{Na}$) $^+$; Found, 470.0582 m/z .

3-(4-Fluoro-phenyl)-6-(2-methoxy-phenyl)-4-nitrophenylmethyl-hex-5-enoic acid methyl ester (2.4q):

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 7.32-7.23 (m, 2H), 7.18-7.14 (m, 2H), 7.07-7.01 (m, 2H), 6.94-6.88 (m, 2H), 6.81 (d, $J = 16.0$ Hz, 1H), 5.81 (dd, $J = 16.0, 9.6$ Hz, 1H), 4.44 (dd, $J = 12.0, 6.9$ Hz, 1H), 4.19 (dd, $J = 12.0, 8.0$ Hz, 1H), 3.85 (s, 3H), 3.62 (s, 3H), 3.50-3.35 (m, 2H), 2.84 (dd, $J = 16.0, 6.8$ Hz, 1H), 2.75 (dd, $J = 16.0, 8.2$ Hz, 1H). $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz): δ 171.7, 162.0 (d, $J = 245.2$ Hz, 1C), 156.8, 134.0 (d, $J = 15.2$ Hz, 1C), 130.7, 130.3, 130.2, 129.2, 127.2, 125.0, 123.5, 120.6, 115.5, 115.3, 110.9, 78.3, 55.4, 51.7, 46.4, 42.4, 38.1. HRMS (EI) calcd for $\text{C}_{21}\text{H}_{22}\text{FNO}_5$, 410.1380 m/z ($\text{M}+\text{Na}$) $^+$; Found, 410.1387 m/z .

6-(2-Methoxy-phenyl)-3-(4-methoxy-phenyl)-4-nitromethyl-hex-5-enoic acid methyl ester (2.4r):

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 7.30 (d, 7.8 Hz, 1H), 7.26-7.21 (m, 1H), 7.08 (d, $J = 8.2$ Hz, 2H), 6.92-6.85 (m, 4H), 6.80 (d, $J = 16.4$ Hz, 1H), 5.83 (dd, $J = 16.0, 9.6$ Hz, 1H), 4.43 (dd, $J = 12.0, 6.4$ Hz, 1H), 4.16 (dd, $J = 12.0, 8.2$ Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.61 (s, 3H), 3.41-3.30 (m, 2H), 2.80 (dd, $J = 16.0, 7.3$ Hz, 1H), 2.73 (dd, $J = 16.0, 7.8$ Hz, 1H). $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz): δ 172.0, 158.8, 156.8, 130.3, 130.1, 129.7 (2C), 129.0, 127.1, 125.2, 123.9, 120.6, 113.8 (2C), 110.9, 78.5, 55.4, 55.2, 51.7, 46.6, 42.3, 38.1. HRMS (EI) calcd for $\text{C}_{22}\text{H}_{25}\text{NO}_6$, 422.1580 m/z ($\text{M}+\text{Na}$) $^+$; Found, 422.1584 m/z .

6-(2-Methoxy-phenyl)-4-nitromethyl-3-thiophen-2-yl-hex-5-enoic acid methyl ester (2.4s):

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 7.38 (dd, $J = 7.4$, 1.4 Hz, 1H), 7.27-7.22 (m, 2H), 6.99 (d, $J = 5.0$, 3.6 Hz, 1H), 6.95-6.83 (m, 4H), 6.02 (dd, $J = 16.0$, 10.0 Hz, 1H), 4.48 (dd, $J = 12.0$, 6.4 Hz, 1H), 4.26 (dd, $J = 12.0$, 8.0 Hz, 1H), 3.85 (s, 3H), 3.84-3.79 (m, 1H), 3.64 (s, 3H), 3.48-3.36 (m, 1H), 2.81 (dd, $J = 16.0$, 7.3 Hz, 1H), 2.74 (dd, $J = 16.0$, 7.6 Hz, 1H). $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz): δ 171.4, 156.7, 141.0, 130.8, 129.1, 127.2, 127.0, 126.7, 126.5, 124.7, 123.2, 120.5, 110.9, 78.2, 55.3, 51.7, 46.0, 39.5, 38.7. HRMS (EI) calcd for $\text{C}_{19}\text{H}_{21}\text{NO}_5\text{S}$, 398.1038 m/z ($\text{M}+\text{Na}$) $^+$; Found, 398.1049 m/z .

3-(3-Bromo-phenyl)-4-nitromethyl-6-*p*-tolyl-hex-5-enoic acid methyl ester (2.4t):

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 7.45-7.42 (m, 1H), 7.30 (t, $J = 3.2$ Hz, 1H), 7.25-7.18 (m, 3H), 7.13 (d, $J = 7.8$ Hz, 2H), 7.07 (d, $J = 7.8$ Hz, 1H), 6.48 (d, $J = 15.6$ Hz, 1H), 5.68 (d, $J = 15.6$, 9.6 Hz, 1H), 4.44 (dd, $J = 12.0$, 6.4 Hz, 1H), 4.18 (dd, $J = 12.0$, 8.2 Hz, 1H), 3.63 (s, 3H), 3.42-3.32 (m, 2H), 2.80 (dd, $J = 16.0$, 7.3 Hz, 1H), 2.71 (dd, $J = 16.0$, 7.4 Hz, 1H), 2.34 (s, 3H). $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz): δ 171.6, 140.7, 138.2, 135.7, 133.2, 131.6, 130.8, 130.1, 129.4 (2C), 127.3, 126.4 (2C), 122.8, 121.5, 78.3, 51.9, 45.8, 42.9, 37.7, 21.2. HRMS (EI) calcd for $\text{C}_{21}\text{H}_{22}\text{BrNO}_4$, 432.0810 m/z ($\text{M}+\text{H}$) $^+$; Found, 432.0821 m/z .

6-(4-Chloro-phenyl)-4-nitromethyl-3-*p*-tolyl-hex-5-enoic acid methyl ester (2.4u):

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 7.29-7.20 (m, 4H), 7.14 (d, $J = 8.2$ Hz, 2H), 7.00 (d, $J = 8.0$ Hz, 2H), 6.45 (d, $J = 16.0$ Hz, 1H), 5.77 (dd, $J = 15.6$, 9.1 Hz, 1H), 4.47 (dd, $J = 12.4$, 6.0 Hz, 1H), 4.15 (dd, $J = 12.4$, 9.1 Hz, 1H), 3.62 (s, 3H), 3.42-3.30 (m, 2H), 2.80 (dd, $J = 15.6$, 7.3 Hz, 1H), 2.72 (dd, $J = 16.0$, 7.3 Hz, 1H), 2.34 (s, 3H). $^{13}\text{C-NMR}$

(CDCl₃, 100 MHz): δ 171.9, 137.4, 134.9, 134.6, 134.1, 133.7, 129.3 (2C), 128.8 (2C), 128.3 (2C), 127.6 (2C), 124.3, 78.5, 51.8, 45.9, 42.8, 37.8, 21.0. HRMS (EI) calcd for C₂₁H₂₂ClNO₄, 410.1135 m/z (M+Na)⁺; Found, 410.1128 m/z .

Recation procedure for the synthesis of 2-Bromotetraline compound **2.6**^[10]

To a well-stirred solution of the nitroester compound **2.4h** (30 mg, 0.081mmol) in dichloromethane (1 mL), Sm(OTf)₃ (5.0 mg, 0.1 equiv) and NBS (16 mg, 1.1 equiv) were added and the mixture was allowed to stir at 0 °C. After 30 min, the reaction was quenched with H₂O and extracted with Et₂O. The combined organic layer was washed with brine and dried over Na₂SO₄. After removal of the solvents under reduced pressure, the crude mixture was subjected to purification by flash column chromatography using EtOAc and petroleum-ether mixture as eluent to obtain white solid **2.6** in (32 mg) 87% yield.

[3-Bromo-4-(4-methoxy-phenyl)-2-nitromethyl-1,2,3,4-tetrahydro-naphthalen-1-yl]-acetic acid methyl ester (**2.6**):

¹H-NMR (CDCl₃, 400 MHz): δ 7.22-7.15 (m, 2H), 7.12-7.03 (m, 3H), 6.93 (d, J = 8.0 Hz, 2H), 6.60 (d, J = 7.8 Hz, 1H), 4.92 (dd, J = 13.7, 5.0 Hz, 1H), 4.84 (dd, J = 13.7, 4.0 Hz, 1H), 4.42-4.35 (m, 2H), 3.84 (s, 3H), 3.66 (s, 3H), 3.62-3.58 (m, 1H), 3.25-3.15 (m, 1H), 3.00 (dd, J = 16.0, 7.3 Hz, 1H), 2.80 (dd, J = 16.0, 5.0 Hz, 1H). ¹³C-NMR (CDCl₃,

100 MHz): δ 171.7, 158.9, 138.35, 136.34, 133.5, 130.2 (2C), 129.0, 127.5 (2C), 127.1, 114.0 (2C), 78.2, 57.4, 55.2, 53.1, 51.9, 47.1, 41.1, 38.8. HRMS (EI) calcd for C₂₁H₂₂BrNO₅, 448.0760 m/z (M+H)⁺; Found, 448.0760 m/z .

Reaction procedure for the synthesis of tetrasubstituted tetraline compound **2.7**^[11]

To a stirred solution of nitroester compound **2.4r** (30 mg, 0.075 mmol) in mixed solvent dichloromethane and cyclohexane (2 mL), Bi(OTf)₃ (3 mg, 0.004 mmol) was added and the reaction mixture was refluxed for 3 hrs. After completion, the reaction mixture was concentrated and directly subjected to column chromatography to furnish the tetrasubstituted tetraline compound **2.7** (26 mg) in 86% yield with diastereomeric ratio 2:1.

[6-Methoxy-4-(2-methoxy-phenyl)-2-nitromethyl-1,2,3,4-tetrahydro-naphthalen-1-yl]-acetic acid methyl ester (2.7):

¹H-NMR (CDCl₃, 400 MHz): δ 7.27-7.22 (m, 1H), 7.14 (d, *J* = 8.6 Hz, 0.66H), 7.09 (d, *J* = 8.2 Hz, 0.34H), 6.98-6.80 (m, 3H), 6.78-6.70 (m, 1H), 6.38 (d, *J* = 2.8 Hz, 0.34H), 6.28 (d, *J* = 2.8 Hz, 0.66H), 4.55-4.42 (m, 2H), 4.40-4.32 (m, 0.34H), 4.27 (dd, *J* = 12.0, 7.3 Hz, 0.66H), 3.81 (s, 1.98H), 3.75 (s, 1.02H), 3.73 (s, 1.02H), 3.71 (s, 1.98H), 3.64 (s, 3H), 3.31-3.24 (m, 1H), 2.86-2.70 (m, 3H), 2.32-2.20 (m, 1H), 2.05-1.84 (m, 1H). ¹³C-NMR of mixture (CDCl₃, 100 MHz): δ 172.5, 172.2, 158.4, 158.0, 157.2, 141.0, 139.3, 133.5, 132.3, 130.3, 130.0, 129.4, 129.2, 128.4, 127.9, 127.8, 120.8, 120.77, 114.0, 113.7, 112.8, 112.2, 111.1, 110.7, 80.1, 78.3, 55.3, 55.0, 51.84, 51.79, 42.2, 41.3, 38.1, 37.1, 32.5, 27.9. HRMS (EI) calcd for C₂₂H₂₅NO₆, 422.1580 *m/z* (M+Na)⁺; Found, 422.1588 *m/z*.

Reaction procedure for the synthesis of alcohol 2.8

In a two-neck round bottom flask fitted with a reflux condenser, **nitroester 2.4a** (230 mg, 0.678 mmol) was dissolved in toluene (10 mL) and 1.5 mL DIBAL-H (1.0 M in toluene, 1.492 mmol) was added slowly in 5 min at room temperature. After addition, the reaction mixture was warmed to 40 °C. After 3 h, the reaction mixture was cooled to rt and then quenched with MeOH-toluene mixture (2 mL) to obtain solid slurry. Next,

the solid slurry was subjected to filtration through celite and solid was washed with ethyl acetate (3 X 10 mL). The combined organic layer was dried with Na₂SO₄, evaporated and purified to furnish alcohol **2.8** (143 mg) in 68% yield.

4-Nitromethyl-3,6-diphenyl-hex-en-1-ol (2.8):

¹H-NMR (CDCl₃, 400 MHz): δ 7.36-7.22 (m, 8H), 7.14 (d, *J* = 8.2 Hz, 2H), 6.48 (d, *J* = 16.0 Hz, 1H), 5.85 (dd, *J* = 15.6, 9.6 Hz, 1H), 4.47 (dd, *J* = 12.0, 6.0 Hz, 1H), 4.17 (dd, *J* = 12.0, 9.0 Hz, 1H), 3.63-3.57 (m, 1H), 3.50-3.44 (m, 1H), 3.40-3.32 (m, 1H), 3.10-3.04 (m, 1H), 2.06-2.00 (m, 2H). ¹³C-NMR (CDCl₃, 100 MHz): δ 138.9, 136.3, 134.7, 128.9 (2C), 128.6 (2C), 128.58 (2C), 127.9, 127.4, 126.4 (2C), 124.2, 78.7, 60.3, 46.8, 43.7, 35.9. HRMS (EI) calcd for C₁₉H₂₁NO₃, 334.1419 *m/z* (M+Na)⁺; Found, 334.1423 *m/z*.

Reaction procedure for the synthesis of aldehyde 2.9

In a two-neck round bottom flask, alcohol **2.8** (120 mg, 0.386 mmol) in dry DCM (5 mL) was treated with DMP (200 mg, 0.463 mmol) at rt. Then, the reaction mixture was slowly warmed to room temperature and stirred for 1-2 h. After completion, reaction mixture was quenched with aq. NaHCO₃ and aq. Na₂S₂O₃ solution (2 mL, 1:1 ratio by v/v) and extracted with DCM (2 X 10 mL). After removal of the combined solvents under reduced pressure, the crude reaction mixture was subjected to purification by flash column chromatography directly using EtOAc/petroleum-ether as an eluent to provide aldehyde **2.9** in 106 mg (89%) with single *syn*-diastereoisomer.

4-Nitromethyl-3,6-diphenyl-hex-5-enal (2.9):

$^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz): δ 200.1, 137.9, 135.9, 135.6, 128.8 (2C), 128.7 (4C), 128.2, 127.8, 126.4 (2C), 123.0, 78.3, 47.0, 46.0, 40.8. HRMS (EI) calcd for $\text{C}_{19}\text{H}_{19}\text{NO}_3$, 332.1263 m/z ($\text{M}+\text{Na}$) $^+$; Found, 332.1262 m/z .

Reaction procedure for the synthesis of cyclopentanol **2.10**

To a stirred solution of compound **2.9** (20 mg, 0.065 mmol) and catalyst **CAT-A** (4.2 mg, 0.2 equiv) in DCM (1 mL) was added DABCO (1.0 mg, 0.0065 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 24 h under N_2 atmosphere. After completion, the reaction mixture was concentrated and directly used for column chromatography to obtain cyclopentanol **2.10** in excellent yield (98%).

2-Nitro-4-phenyl-3-styryl-cyclopentanol (**2.10**):

(m, 0.74H), 3.52-3.37 (m, 0.52H), 3.01-2.94 (m, 0.74H), 2.84-2.74 (m, 0.26H), 2.70-2.60 (m, 0.74H), 2.55 (d, $J = 5.0$ Hz, 0.74H), 2.30 (d, $J = 4.6$ Hz, 0.26H), 2.20-2.11 (m, 0.74H), 2.00-1.96 (m, 0.26H). $^{13}\text{C-NMR}$ of major isomer **6** (CDCl_3 , 100 MHz): δ 141.3, 136.4, 133.5, 128.7 (2C), 128.5 (2C), 127.78, 127.7 (2C), 127.0, 126.5, 126.3 (2C), 92.8, 71.8, 52.5, 47.0, 40.6. HRMS (EI) calcd for $\text{C}_{19}\text{H}_{19}\text{NO}_3$, 332.1263 m/z ($\text{M}+\text{Na}$) $^+$; Found, 332.1277 m/z .

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CHAPTER 3

**N-Heterocyclic Carbene Catalyzed
Homoenolate Addition of Enals to
Nitroalkenes: Asymmetric Synthesis of 5-
Carbon Synthon δ -Nitroester**

3.1 Introduction

In the recent years, a homoenolate catalytically generated from an α,β -unsaturated aldehyde by N-heterocyclic carbene (NHC) has found broad applications as an important intermediate in organic synthesis, especially in Michael addition reactions.^[1] In 2004, Bode^[2] and Glorius^[3] reported the formation of a homoenolate derived from an enal under NHC catalysis, which was further captured by an aldehyde to form a lactone. Later, tremendous studies have been made to harness the homoenolate equivalent by various electrophiles, affording synthetically valuable skeletons.^[4] Nitroalkene has been widely used as Michael acceptor due to its high reactivity and potential for further elaboration, of the versatile NO₂ functionality.^[5] Based on reaction types, the synthetic method for nitroketone from nitroalkene via C-C bond formation could be categorized as (i) Stetter reaction to access β -nitroketone (3-carbon synthon), (ii) conventional Michael addition to access γ -nitroketone (4-carbon synthon) and (iii) NHC derived homoenolate addition reaction to access δ -nitroketone (5-carbon synthon) (Figure 3.1).

Figure 3.1 Reaction category to access ‘3-5 Carbon-synthon’ nitroketone

Schiedt *et al.* first developed a chiral thiourea-catalyzed addition of a preformed thiozolium carbinol to a nitroalkene to access a β -nitro ketone with fluoride anion as a promoter, albeit in moderate enantioselectivity.^[6] Rovis group has disclosed a highly enantioselective intermolecular Stetter reaction with nitroalkenes by employing a

specially designed fluorine substituted triazolium precatalyst.^[7] The above mentioned methods, however, all afforded the “3-carbon synthon” β -nitroketones. The synthetic protocol for accessing chiral “4-carbon synthon” γ -nitroketones are also achieved by asymmetric Michael additions of enolizable carbonyl compounds to nitroalkenes.^[8] In addition, the synthesis of γ -nitroketoesters and γ -nitroketoamides has also been achieved by nucleophilic addition of 1,2-ketoester and 1,2-ketoanilides to nitroolefins, respectively.^[9] In 2009, the research group led by Nair first disclosed the protocol for constructing “5-carbon synthon” δ -nitroester through addition of homoenolate derived from α,β -unsaturated aldehydes to β -nitrostyrenes under the catalysis of achiral NHC precatalyst.^[4n] In the last few years, our group has also worked on the development of novel organic synthetic methodology involving NHC catalysis.^[10] In the continuation of our previous research, we envisioned that the enantioenriched δ -nitroester can be obtained by a straightforward coupling of enals with a variety of nitroalkenes such as nitrodienes, nitroenynes and β -nitrostyrenes by using chiral carbene catalyst (Figure 3.1).

3.2 Results and discussion

3.2.1 Optimization of reaction conditions

In the beginning of our study, chiral imidazolinium pre-catalysts **3.3a-3.3d** were employed in enantioselective addition of cinnamaldehyde **3.1a** to nitrodiene **3.2a**. Only the catalyst **3.3d** successfully provided the desired product **3.4a**, albeit in 36% yield with 19% enantioselectivity of the major *syn* diastereoisomer (Table 3.1, entries 1-4).^[11] Next, more NHC catalysts were tested. The triazolium catalyst **3.3e**, with KHCO_3 as a base, resulted in a low yield of **3.4a** with poor dr of the major *anti* stereoisomer (Table 3.1, entry 5). By changing the catalyst to **3.3f**, the yield was improved to 65% with 86% ee of the major *anti* diastereoisomer (Table 3.1, entry 6). Screening of solvents and bases

showed that a combination of toluene: MeOH (20:1) and KHCO_3 gives the best result^[12] (Table 3.1, entry 7 & 17). Triazolium catalysts **3.3f** and **3.3g** gave **3.4a** in comparable diastereoselectivities (**3.3f**: dr = 5.5:1; **3.3g**: dr = 6:1) and enantioselectivities (**3.3f**: 94%; **3.3g**: 95%). In order to improve the diastereoselectivity further, the reaction was set up at a lower temperature (0 °C). However, this just resulted in a decreased yields with no improvement of diastereoselectivity. Thus we choose the chiral NHC catalyst **3.3g** for substrate scope expansion (Table 3.2). It is noteworthy that even a trace amount of Stetter product was not observed by the ^1H -NMR analysis of the crude product.

Table 3.1 Optimization of the reaction^a

Entry	precatalyst, Solvent, Base	dr (<i>anti:syn</i>) ^b	Yield (%) ^c	ee (%) ^d
1 ^e	3.3a-3.3c , THF, K ₂ CO ₃	--	NR	--
2 ^e	3.3a-3.3d , THF, DBU	--	NR	--
3 ^e	3.3d , THF, K ₂ CO ₃	1:4	24	ND
4 ^e	3.3d , THF, KHCO ₃	1:4	36	19 ^f
5	3.3e , THF, KHCO ₃	1.4:1	23	ND
6	3.3f , THF, KHCO ₃	1:7:1	65	86
7	3.3f, Toluene, KHCO₃	5.5:1	81	94
8	3.3f , Xylene, KHCO ₃	5.5:1	67	91
9	3.3f , Mesitylene, KHCO ₃	6:1	58	95
10	3.3f , C ₆ H ₅ CF ₃ , KHCO ₃	4:1	59	86
11	3.3f , DCM, KHCO ₃	1.8:1	82	87
12	3.3f , Toluene, DIPEA	3:1	60	87
13	3.3f , Toluene, DMAP	3:1	81	87
14	3.3f , Toluene, NaOAc	5.5:1	69	94
15	3.3f , Toluene, K ₂ CO ₃	5.5:1	54	94
16	3.3f , Toluene, Cs ₂ CO ₃	5.5:1	51	93
17	3.3g, Toluene, KHCO₃	6:1	82	95

^aReaction conditions: all reactions are conducted with 2.0 equiv of aldehyde **3.1a** and 1.0 equiv of nitrodiene **3.2a** for 24 h in the presence of 10 mol% chiral catalyst and 20 mol% base. ^b Diastereomeric ratio determined from ¹H-NMR. ^c Combined yield after column chromatography. ^d Enantiomeric excess determined from HPLC by using chiral column of major *anti* diastereoisomer only. ^eReactions are carried out at 70 °C. ^fEnantiomeric excess of major *syn* diastereoisomer.

3.2.2 Substrate scope

Table 3.2 Scope of the reaction with nitrodienes^a

Entry	R ₁	R ₂	Yield (%) ^b	dr(<i>anti</i> : <i>syn</i>) ^c	ee ^d (%)
1	Ph	Ph	3.4a , 82	6:1	95
2	4-MeC ₆ H ₄	Ph	3.4b , 81	9:1	94
3 ^e	4-FC ₆ H ₄	Ph	3.4c , 81	10:1	99
4 ^e	4-MeC ₆ H ₄	4-ClC ₆ H ₄	3.4d , 68	7:1	92
5 ^e	4-BrC ₆ H ₄	2-furyl	3.4e , 72	10:1	97
6 ^f	H	Ph	3.4f , 48	-	82
7 ^f	CH ₃	Ph	3.4g , 52	5:1	96
8	2-furyl	CH ₃	3.4h , 86	6:1	97

^aReactions performed with 2.0 equiv of **3.1** and 1.0 equiv of **3.2** for 24 h. ^b Isolated yield after column chromatography. ^c Diastereomeric ratio determined from ¹H-NMR of crude reaction mixture. ^d Enantiomeric excess determined by HPLC analysis by using chiral column for major *anti* diastereoisomer only. ^e Major *anti* diastereoisomer are isolated in pure form by column chromatography. ^f 3.0 equiv aldehyde used in two portions in 48 h reaction time.

The substrate scope of this reaction shows good compatibility with various α,β -unsaturated aldehydes as well as nitrodienes bearing aromatic, aliphatic and hetero-aromatic functional groups (Table 3.2). Both electron-rich and electron-deficient α,β -unsaturated aromatic aldehydes are reactive, affording the desired products in good yields with excellent enantioselectivities (Table 3.2, entries 2-5). Aliphatic α,β -unsaturated aldehydes including acrolein also provided the desired products in moderate yields and good enantioselectivity (Table 3.2, entries 6 & 7). Unsaturated aldehydes

bearing a furyl group also worked well with aliphatic nitrodiene, giving the desired product **3.4h** in a good yield and excellent *ee* (Table 3.2, entry 8). It is interesting that this catalytic methodology exclusively provides 1,4-*anti* Michael addition product. Not even a trace amount of 1,6-Michael addition product was formed in the given examples (Table 3.2).

After successful development of homoenolate addition to nitrodiene, another interesting family of nitroalkenes, i.e., nitroenyne was also evaluated under the same optimized reaction conditions (Table 3.3). Aromatic and hetero-aromatic enals were effectively involved in this catalytic transformation, furnishing the products in good to excellent enantioselectivity (81-97%) with diastereoselectivity up to 12:1 (Table 3.3, entries 1-4). Interestingly, even acrolein afforded the desired product in a modest yield but in good *ee* (Table 3.3, entry 5).

Table 3.3 Scope of the reaction with nitroenyne family^a

Entry	R ₁	R ₂	Yield (%) ^b	dr (<i>anti</i> : <i>syn</i>) ^c	Ee (%) ^d
1 ^e	Ph	Ph	3.6a , 70	12:1	94
2	4-MeC ₆ H ₄	4-BrC ₆ H ₄	3.6b , 67	10:1	81
3	2-OMe C ₆ H ₄	4-OMeC ₆ H ₄	3.6c , 68	9:1	81
4	2-Furyl	4-OMeC ₆ H ₄	3.6d , 78	10:1	97
5 ^f	H	4-OMeC ₆ H ₄	3.6e , 51	-	83

^aReactions performed with 2.0 equiv of **3.1** and 1.0 equiv of **3.5** for 24-48 h. ^b Combined yield after column chromatography. ^c dr ratio determined from ¹H-NMR of the crude reaction mixture. ^d Enantiomeric excess determined from HPLC by using chiral column for major *anti* diastereoisomer only. ^e Reaction time 48 h. ^f 3.0 equiv acrolein used in two portions for 48 h.

Table 3.4 Substrates scope with β -Nitrostyrenes^a

<div style="display: flex; align-items: center; justify-content: center;"> <div style="text-align: center;"> $\begin{array}{c} \text{R}_1\text{-CH=CH-C(=O)H} \\ \mathbf{3.1} \\ + \\ \text{R}_2\text{-CH=CH-NO}_2 \\ \mathbf{3.7} \end{array}$ </div> <div style="text-align: center; margin: 0 20px;"> $\xrightarrow[\text{rt, 24 h, 0.2 (M) C}]{\begin{array}{c} 10 \text{ mol\% Cat. } \mathbf{3.3g} \\ 20 \text{ mol\% KHCO}_3 \\ \text{Toluene:MeOH (20:1)} \end{array}}$ </div> <div style="text-align: center;"> $\begin{array}{c} \text{O}_2\text{N-CH}_2\text{-CH(R}_1\text{)-CH(R}_2\text{)-CH}_2\text{-C(=O)OMe} \\ \mathbf{3.8} \end{array}$ </div> </div>					
Entry	R ₁	R ₂	Yield (%) ^b	dr (<i>anti</i> : <i>syn</i>) ^c	ee (%) ^d
1 ^e	Ph	Ph	3.8a , 66	5:1	99
2 ^f	4-OMeC ₆ H ₄	4-ClC ₆ H ₄	3.8b , 58	6:1	91
3	4-OMeC ₆ H ₄	Ph	3.8c , 78	4.5:1	95
4 ^f	4- ^t BuC ₆ H ₄	4-MeC ₆ H ₄	3.8d , 63	5:1	97
5	4-ClC ₆ H ₄	2-OMeC ₆ H ₄	3.8e , 73	10:1	95
6 ^f	4-ClC ₆ H ₄	4-MeC ₆ H ₄	3.8f , 62	10:1	93
7 ^f	4-NO ₂ C ₆ H ₄	Ph	3.8g , 61	9:1	81
8 ^g	H	4-MeC ₆ H ₄	3.8h , 52	-	81
9 ^g	H	3-OMeC ₆ H ₄	3.8i , 51	-	86
10	Ph	Cyclohexyl	NR	-	-

^aReactions performed with 2.0 equiv of **3.1** and 1.0 equiv of **3.7** for 24 h. ^b Combined yield after column chromatography. ^c Diastereomeric ratio determined from ¹H-NMR or HPLC of the crude reaction mixture. ^d Enantiomeric excess determined from HPLC by using chiral column for major *anti* diastereoisomer only. ^e Reaction time 48 h. ^f Major *anti* diastereoisomer are isolated in pure form by column chromatography. ^g 3.0 equiv acrolein used in two portions for 48 h.

Finally we applied the present reaction conditions β -nitrostyrene derivatives. Similarly, all the enals gave rise to multifunctional nitroesters **3.8** with *anti* diastereoselectivity as the major isomer (Table 3.4). Electron-rich and electron-deficient enals reacted smoothly with the substituted nitrostyrenes in good yields with excellent enantioselectivity (95–99%), except that 4-nitro cinnamaldehyde showed modest enantioselectivity (81%). Unsubstituted α,β -unsaturated aldehyde, i.e., acrolein, furnished the desired Michael addition products with 4- and 3-substituted β -

nitrostyrenes in good selectivity (Table 3.4, entry 8, 81% *ee* & entry 9, 86% *ee*). When aliphatic nitroalkene such as β -cyclohexylnitroalkene was employed as the electrophile, the reaction failed to provide the desired addition product (Table 3.4, entry 10). The relative and absolute stereochemistry of **3.4d** and **3.8b** are confirmed by single X-ray crystal analysis (Figure 3.2).^[13]

Figure 3.2 X-ray crystal structure of the compound **3.4d** and **3.8b**

3.2.3 Applications

To demonstrate the utility of the present methodology, we performed a few further transformations of the product to construct some synthetically useful building blocks. Reduction of δ -nitroester **3.8f** afforded alcohol **3.9**, which was further oxidized to aldehyde **3.10**. By treating with DABCO, the aldehyde **3.10** was transformed into a cyclopentanol **3.11** with a 3:1 diastereoselectivity. The major diastereoisomer of **3.11** was obtained in 71% yield after purification (Scheme 3.1). Another transformation was the reduction of the nitro group of the compound **3.8h**, which was followed by

cyclization to a δ -lactam **3.12** in 81% yield and 76% *ee* under hydrogen atmosphere in the presence of Raney nickel (Scheme 3.2).^[14]

Scheme 3.1 Transformation of δ -nitroester into cyclopentanol

Scheme 3.2 Transformation of δ -nitroester into δ -lactam (RaNi=Raney nickel)

3.2.4 Mechanism investigation

In order to figure out the stereoselectivity of the reaction, we listed the transition states below. When the *Si* face of homoenolate attacks the *Si* face of β -Nitroalkenes, or the *Re* face of homoenolate attacks the *Re* face of β -Nitroalkenes, there will be a steric hindrance between the R_2 group and the phenol group of the catalyst. Therefore, the pathway for the formation of *anti* isomer is preferred over the *syn* isomer.

Figure 3.3 The proposed transition states

3.3 Conclusion

In conclusion, we have developed a methodology for the synthesis of highly enantio-enriched “5-carbon synthon” multifunctional nitroester by using a chiral N-heterocyclic carbene catalyst. The reaction tolerates a broad range of substrates scope for the synthesis of a chiral nitroester compounds containing one extra C=C and C $\equiv$ C in a straightforward and efficient manner. All types of enals are well tolerated with variety of nitroalkenes such as nitrodienes, nitroenynes and nitrostyrenes, affording the desired products in good to excellent enantioselectivities under mild reaction conditions. The homoenolate-addition product can be further transformed into multi-functionalized cyclopentanol and δ -lactams, which are versatile skeletons in organic synthesis.

3.4 Experimental section

All reactions were conducted using oven-dried glassware under an atmosphere of Nitrogen (N₂). Commercial grade reagents were used without further purification. Solvents were dried and distilled following usual protocols. Flash chromatography was carried out using Silica gel (230-400 mesh). TLC was performed on aluminum-backed plates coated with Silica gel 60 with F₂₅₄ indicator. The ¹H NMR spectra were measured with 400 MHz, and ¹³C NMR spectra were measured with 400 (100 MHz), using CDCl₃ as solvent. ¹H NMR chemical shifts are expressed in parts per million (δ) downfield to CHCl₃ (δ = 7.26), ¹³C NMR chemical shifts are expressed in parts per million (δ) relative to the central CDCl₃ resonance (δ = 77.0). Coupling constants in ¹H NMR are in Hz. The following abbreviations classify the multiplicity: s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, dd = doublet of doublet. HR-MS (ESI) spectra were recorded on a Waters Q-ToF premierTM mass spectrometer.

α,β -Unsaturated aldehydes such as *trans*-4-methoxycinnamaldehyde, *trans*-2-methoxycinnamaldehyde and *trans*-cinnamaldehyde were purchased from suppliers and were used without any further purification. Other cinnamaldehyde derivatives were prepared from the standard literature procedure.^[1] Nitrodienes, nitroenynes and nitrostyrenes starting materials were prepared from the standard literature procedures and well characterized comparing with literature data.^[2] All the achiral imidazolium and imidazolinium NHC catalysts were purchased from commercial suppliers. Chiral imidazolinium carbene catalysts^[3] **3.3a-3.3d** and triazolium carbene catalysts^[4] were prepared from standard known literature procedure. Freshly distilled THF over sodium benzophenone ketyl were used for all the reactions. Toluene and MeOH (99.98%) was used directly as received. KHCO₃ was purchased from (GCE) local chemical suppliers and used as received.

Crystal Structure of racemic nitroester compound 6-(4-Methoxy-phenyl)-3-(2-methoxy-phenyl)-4-nitromethyl-hex-5-enoic acid methyl ester:

The relative stereochemistry was confirmed from the single X-ray crystal structure of racemic nitroester compound: 6-(4-Methoxy-phenyl)-3-(2-methoxy-phenyl)-4-nitromethyl-hex-5-enoic acid methyl ester.

Reaction procedure for the synthesis of racemic *syn* nitroester compounds:

To a well-stirred solution of cinnamaldehyde (75 mg, 0.57 mmol, 2.0 equiv) and nitrodiene **3.2a** (50 mg, 0.29 mmol, 1.0 equiv) in 2.2 mL dry THF-MeOH {0.13 (M) C, 10:1}, 1,3-bis(2,6-diisopropyl phenyl) imidazolium chloride (12 mg, 0.029 mmol, 0.1 equiv) and KHCO_3 (6 mg, 0.06 mmol, 0.2 equiv) were added and allowed to stir at 70 °C under nitrogen atmosphere. Progress of the reaction was monitored by TLC. On completion (12 h), the reaction mixture was diluted with 2-4 mL ethyl acetate and filtered through a pad of celite. After removal of the combine solvents under reduced pressure, the crude reaction mixture was subjected to purification by flash column chromatography directly using EtOAc/petroleum-ether (60-80 °C) as an eluent to provide nitroester ***syn*-3.4a** in 61 mg (63%) with a major *syn* diastereoselectivity (dr = 30:1).

Spectral data of all racemic *syn* nitroester compounds:

(±)-*syn* 3.4a, (±)-*syn* 3.4d and 6-(4-Methoxy-phenyl)-3-(2-methoxy-phenyl)-4-nitromethyl-hex-5-enoic acid methyl ester

(±) *syn* 3.4a

63% yield; dr (*syn:anti*) ratio = 30:1; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz):

δ 7.43-7.20 (m, 8H), 7.13 (d, $J = 7.3$ Hz, 2H), 6.51 (d, $J = 15.6$ Hz, 1H), 5.78 (dd, $J = 16.0, 9.6$ Hz, 1H), 4.47 (dd, $J = 12.4, 6.4$ Hz, 1H), 4.16 (dd, $J = 12.0, 8.7$ Hz, 1H), 3.62 (s, 3H), 3.48-3.37 (m, 2H), 2.84 (dd, $J = 15.6, 7.3$ Hz, 1H), 2.75 (dd, $J = 15.8, 7.3$ Hz, 1H). $^{13}\text{C-NMR}$

(CDCl_3 , 100 MHz): δ 171.9, 138.1, 136.1, 135.5, 128.6 (4C), 128.5 (2C), 128.1, 127.6, 126.5 (2C), 123.2, 78.5, 51.8, 45.9, 43.2, 37.8. HRMS (EI) calcd for $\text{C}_{20}\text{H}_{21}\text{NO}_4$, 340.1549 m/z ($\text{M}+\text{H}$) $^+$; Found, 340.1555 m/z .

(±)-6-(4-Chloro-phenyl)-4-nitromethyl-3-p-tolyl-hex-5-enoic acid methyl ester [(±)-*syn* 3.4d]:

(±)-*syn* 3.4d

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz): d 7.29-7.20 (m, 4H), 7.14 (d, $J = 8.2$ Hz, 2H), 7.00 (d, $J = 8.0$ Hz, 2H), 6.45 (d, $J = 16.0$ Hz, 1H), 5.77 (dd, $J = 15.6, 9.1$ Hz, 1H), 4.47 (dd, $J = 12.4, 6.0$ Hz, 1H), 4.15 (dd, $J = 12.4, 9.1$ Hz, 1H), 3.62 (s, 3H), 3.42-3.30 (m, 2H), 2.80 (dd, $J = 15.6, 7.3$ Hz, 1H), 2.72 (dd, $J = 16.0, 7.3$ Hz, 1H), 2.34 (s, 3H).

$^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz): d 171.9, 137.4, 134.9, 134.6, 134.1, 133.7, 129.3 (2C), 128.8 (2C), 128.3 (2C), 127.6 (2C), 124.3, 78.5, 51.8, 45.9, 42.8, 37.8, 21.0. HRMS (EI) calcd for $\text{C}_{21}\text{H}_{22}\text{ClNO}_4$, 410.1135 m/z ($\text{M}+\text{Na}$) $^+$; Found, 410.1128 m/z .

6-(4-Methoxy-phenyl)-3-(2-methoxy-phenyl)-4-nitromethyl-hex-5-enoic acid methyl ester:

Prepared according to the general procedure: 69% yield; dr (*syn:anti*) ratio = >30:1; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 7.26-7.20 (m, 3H), 7.01 (dd, $J = 7.8, 1.6$ Hz, 1H), 6.95-6.83 (m, 2H), 6.81 (d, $J = 8.2$ Hz, 2H), 6.42 (d, $J = 16.0$ Hz, 1H), 5.65 (dd, $J = 16.0, 10.0$ Hz, 1H), 4.58 (dd, $J = 12.8, 5.6$ Hz, 1H), 4.09 (dd, $J = 12.8, 10.0$ Hz, 1H), 4.07-4.01 (m, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.61 (s, 3H), 3.45-3.36 (m, 1H), 2.83 (dd, $J = 16.0, 8.2$ Hz, 1H), 2.68 (dd, $J = 16.0, 7.3$ Hz, 1H). $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz): δ 172.2, 159.4, 156.9, 134.4, 129.1, 128.7, 128.3, 127.6 (2C), 126.8, 121.6, 120.4, 113.8 (2C), 110.7, 78.3, 55.23, 55.20, 51.6, 45.7, 37.3, 34.7. HRMS (EI) calcd for $\text{C}_{22}\text{H}_{25}\text{NO}_6$, 422.1580 m/z ($\text{M}+\text{Na}$) $^+$; Found, 422.1590 m/z .

General Reaction Procedure for the Synthesis of Chiral Nitroester Compounds **3.4**, **3.6** and **3.8**:

(5a*R*,10b*S*)-2-(2,6-diethylphenyl)-4,5a,6,10b-tetrahydroindeno[2,1-b][1,2,4] triazole [4,3-d][1,4]oxazin-2-ium tetrafluoroborate **3.3g** (7 mg, 0.02 mmol, 0.1 equiv), KHCO_3 (4 mg, 0.03 mmol, 0.2 equiv), nitrodiene **3.2a** (30 mg, 0.17 mmol, 1.0 equiv) were added to a 10 mL flask fitted with N_2 balloon. Next, cinnamaldehyde **3.1a** (45 mg, 0.34 mmol, 2.0 equiv) dissolving in 0.8 mL toluene was added to the reaction mixture and followed by 0.05 mL MeOH. After 24 h, the reaction mixture was diluted with 2-3 mL EA and finally purified by column chromatography to afford homoenolate addition product **3.4a** in 82% yield with *anti* diastereoisomer as a major one (dr = 6:1).

For racemic reaction, compounds **3.4a** and **3.4b** are prepared by using achiral imidazolium carbene catalyst (IPr.HCl or IMes.HCl) and KHCO_3 as a base under the modified reaction procedure developed by Nair.^[5] For all other racemic compounds, (5a*R*, 10b*S*)-2-(2,6-diethylphenyl)-4,5a,6,10b-tetrahydroindeno[2,1-b][1,2,4]triazolo[4,3-d][1,4]oxazin-2-ium tetrafluoroborate **3.3g** and (5a*S*, 10b*R*)-2-(2,6-

diethylphenyl)-4,5a,6,10b-tetrahydroindeno[2,1-b][1,2,4]triazolo[4,3-d][1,4]oxazin-2-ium tetrafluoroborate **3.3g'** are mixed together in 1:1 proportionate and performed the reaction. (Few cases, due to inaccurate addition of two chiral catalysts **3.3g** and **3.3g'**, the area appeared in the HPLC chromatogram is not exactly equal).

Spectral Data of All Chiral Nitroester Compounds **3.4**, **3.6** and **3.8**:

4-Nitromethyl-3,6-diphenyl-hex-5-enoic acid methyl ester (**3.4a**):

Prepared according to the general procedure: 82% yield; dr (*anti:syn*) ratio = 6:1; 95% ee; $[\alpha]_D^{21} = -49.3$ ($c = 0.011$ g/ml, CHCl_3); HPLC analysis: Chiralcel OD-H column, 90:10 hexane/*iso*-propanol, 1.0 mL/min, Major: 11.2 min, minor: 17.01 min; **$^1\text{H-NMR}$** (CDCl_3 , 400 MHz): δ 7.40-7.23 (m, 10H), 6.58 (d, $J = 15.56$ Hz, 1H), 6.00 (dd, $J = 16, 9.6$ Hz, 1H), 4.20 (dd, $J = 12.0, 10.0$ Hz, 1H), 4.11 (dd, $J = 12.0, 3.6$ Hz, 1H), 3.40 (s, 3H), 3.30-3.15 (m, 2H), 2.86 (dd, $J = 16.04, 5.52$ Hz, 1H), 2.60 (dd, $J = 16.04, 8.2$ Hz, 1H); **$^{13}\text{C-NMR}$** (CDCl_3 , 100 MHz): δ 172.0, 140.4, 135.9, 135.5, 129.2 (2C), 128.6 (2C), 128.1, 127.7, 127.6 (2C), 126.5 (2C), 125.8, 78.7, 51.6, 48.4, 44.0, 39.9; **HRMS** (EI) calcd for $\text{C}_{20}\text{H}_{21}\text{NO}_4$, 362.1368 m/z (M^+Na^+); Found, 362.1372 m/z .

4-Nitromethyl-6-phenyl-3-*p*-tolyl-hex-5-enoic acid methyl ester (**3.4b**):

Prepared according to the general procedure: 81% yield; dr (*anti:syn*) ratio = 9:1; 94% ee; $[\alpha]_D^{21} = -51.05$ ($c = 0.012$ g/ml, CHCl_3); HPLC analysis: Chiralcel OD-H column, 90:10 hexane/*iso*-propanol, 1.0 mL/min, Major: 9.6 min, minor: 11.1 min; **$^1\text{H-NMR}$** (CDCl_3 , 400 MHz): δ 7.38-7.20 (m, 5H), 7.16-7.11

(m, 4H), 6.57 (d, $J = 16.0$ Hz, 1H), 5.99 (dd, $J = 16.0, 9.1$ Hz, 1H), 4.19 (dd, $J = 12.4, 10.0$ Hz, 1H), 4.12 (dd, $J = 12.4, 4.1$ Hz, 1H), 3.40 (s, 3H), 3.25-3.12 (m, 2H), 2.84 (dd, $J = 16.0, 5.0$ Hz, 1H), 2.57 (dd, $J = 16.0, 8.7$ Hz, 1H), 2.33 (s, 3H). **$^{13}\text{C-NMR}$** (CDCl_3 , 100 MHz): δ 172.0, 137.3, 137.2, 135.9, 135.4, 129.8 (2C), 128.5 (2C), 128.0, 127.4 (2C), 126.5 (2C), 126.0, 78.8, 51.5, 48.4, 43.6, 39.9, 21.0; **HRMS** (EI) calcd for $\text{C}_{21}\text{H}_{23}\text{NO}_4$, 376.1525 m/z (M^+Na^+); Found, 376.1527 m/z .

3-(4-Fluoro-phenyl)-4-nitromethyl-6-phenyl-hex-5-enoic acid methyl ester (3.4c):

Prepared according to the general procedure: 81% yield; dr (*anti:syn*) ratio = 10:1; Major *anti* diastereoisomer was isolated in pure form by column chromatography; 99% ee; $[\alpha]_{\text{D}}^{21} = -43.96$ ($c = 0.011$ g/ml, CHCl_3); HPLC analysis: Chiralcel OD-H column, 90:10 hexane/*iso*-propanol, 1.0 mL/min, Major: 12.6 min, minor:

16.6 min; **$^1\text{H-NMR}$** (CDCl_3 , 400 MHz): δ 7.38-7.22 (m, 7H), 7.08-7.02 (m, 2H), 6.58 (d, $J = 16.0$ Hz, 1H), 5.99 (dd, $J = 16.0, 8.7$ Hz, 1H), 4.24-4.10 (m, 2H), 3.43 (s, 3H), 3.25-3.15 (m, 2H), 2.85 (dd, $J = 16.0, 4.6$ Hz, 1H), 2.55 (dd, $J = 16.0, 8.4$ Hz, 1H); **$^{13}\text{C-NMR}$** (CDCl_3 , 100 MHz): δ 171.9, 162.0 (d, $J = 245$ Hz, 1C), 136.1 (d, $J = 3.8$ Hz, 1C), 135.8, 135.7, 129.2, 129.1, 128.6 (2C), 128.2, 126.5 (2C), 125.5, 116.2, 116.0, 78.6, 51.6, 48.3, 43.3, 39.9; **HRMS** (EI) calcd for $\text{C}_{20}\text{H}_{20}\text{NO}_4\text{F}$, 380.1274 m/z (M^+Na^+); Found, 380.1289 m/z .

6-(4-Chloro-phenyl)-4-nitromethyl-3-*p*-tolyl-hex-5-enoic acid methyl ester (3.4d):

Prepared according to the general procedure: 68% yield; dr (*anti:syn*) ratio = 7:1; Major *anti* diastereoisomer was isolated in pure form by column chromatography; 92% ee; $[\alpha]_D^{21} = -46.02$ ($c = 0.011$ g/ml, CHCl_3); HPLC analysis: Chiralpak IC column, 98:2 hexane/*iso*-propanol, 0.5 mL/min, Major: 39.3 min, minor: 41.4 min; **$^1\text{H-NMR}$** (CDCl_3 , 400 MHz): δ 7.27 (m, 4H), 7.20-7.10 (m, 4H), 6.52 (d, $J = 16.0$ Hz, 1H), 5.97 (dd, $J = 16.0, 9.1$ Hz, 1H), 4.18 (dd, $J = 11.9, 9.6$ Hz, 1H), 4.12 (dd, $J = 11.9, 3.6$ Hz, 1H), 3.41 (s, 3H), 3.25-3.12 (m, 2H), 2.81 (dd, $J = 16.0, 5.5$ Hz, 1H), 2.57 (dd, $J = 16.0, 8.2$ Hz, 1H), 2.33 (s, 3H); **$^{13}\text{C-NMR}$** (CDCl_3 , 100 MHz): δ 172.0, 137.4, 137.1, 134.4, 134.0, 133.7, 129.8 (2C), 128.7 (2C), 127.7 (2C), 127.4 (2C), 126.8, 78.7, 51.6, 48.4, 43.5, 39.9, 21.0; **HRMS** (EI) calcd for $\text{C}_{21}\text{H}_{22}\text{NO}_4\text{Cl}$, 410.1135 m/z (M^+Na)⁺; Found, 410.1144 m/z .

3-(4-Bromo-phenyl)-6-furan-2-yl-4-nitromethyl-hex-5-enoic acid methyl ester

(3.4e):

Prepared according to the general procedure: 72% yield; dr (*anti:syn*) ratio = 10:1; Major *anti* diastereoisomer was isolated in pure form by column chromatography; 92% ee; $[\alpha]_D^{21} = -58.54$ ($c = 0.011$ g/ml, CHCl_3); HPLC analysis: Chiralcel OD-H column, 90:10 hexane/*iso*-propanol, 1.0 mL/min, Major: 13.2 min, minor: 19.3 min; **$^1\text{H-NMR}$** (CDCl_3 , 400 MHz): δ 7.48 (d, $J = 8.6$ Hz, 2H), 7.34 (s, 1H), 7.13 (d, $J = 8.6$ Hz, 2H), 6.45-6.20 (m, 3H), 5.90 (dd, $J = 15.6, 9.1$ Hz, 1H), 4.25-4.05 (m, 2H), 3.46 (s, 3H), 3.28-3.10 (m, 2H), 2.85 (dd, $J = 15.6, 3.7$ Hz, 1H), 2.55 (dd, $J = 15.6, 3.6$ Hz, 1H); **$^{13}\text{C-NMR}$** (CDCl_3 , 100 MHz): δ 171.6, 151.2, 142.3, 139.3, 132.3 (2C), 129.4 (2C), 123.9, 123.6, 121.6, 111.4, 109.0, 78.4, 51.6, 47.7, 43.5, 39.5; **HRMS** (EI) calcd for $\text{C}_{18}\text{H}_{18}\text{NO}_5\text{Br}$, 408.0447 m/z (M^+H)⁺; Found, 408.0447 m/z .

4-Nitromethyl-6-phenyl-hex-5-enoic acid methyl ester (3.4f):

Prepared according to the general procedure: 48% yield; 82% ee;

$[\alpha]_D^{21} = -0.981$ ($c = 0.012$ g/ml, CHCl_3); HPLC analysis: Chiralcel

OD-H column, 90:10 hexane/*iso*-propanol, 1.0 mL/min, Major:

20.2 min, minor: 28.7 min; **$^1\text{H-NMR}$** (CDCl_3 , 400 MHz): δ 7.38-

7.22 (m, 5H), 6.50 (d, $J = 16.0$ Hz, 1H), 5.89 (dd, $J = 16.0, 9.1$ Hz, 1H), 4.47-4.36 (m,

2H), 3.63 (s, 3H), 3.15-3.01 (m, 1H), 2.50-2.34 (m, 2H), 1.94-1.87 (m, 1H), 1.80-1.72

(m, 1H); **$^{13}\text{C-NMR}$** (CDCl_3 , 100 MHz): δ 173.1, 136.0, 134.4, 128.5 (2C), 128.0, 126.4

(2C), 126.3, 79.7, 51.7, 41.8, 31.3, 26.9; **HRMS** (EI) calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_4$, 286.1055 m/z

(M^+Na^+); Found, 286.1064 m/z .

3-Methyl-4-nitromethyl-6-phenyl-hex-5-enoic acid methyl ester (3.4g):

Prepared according to the general procedure: 52% yield; dr

(*anti*:*syn*) ratio = 5:1; 96% ee; $[\alpha]_D^{21} = +21.44$ ($c = 0.005$ g/ml,

CHCl_3); HPLC analysis: Chiralcel OD-H column, 90:10

hexane/*iso*-propanol, 1.0 mL/min, Major: 15.9 min, minor: 21.9

min; **$^1\text{H-NMR}$** (CDCl_3 , 400 MHz): δ 7.38-7.22 (m, 5H), 6.47 (d, $J = 16.0$ Hz, 1H), 5.96

(dd, $J = 16.0, 9.1$ Hz, 1H), 4.58 (dd, $J = 12.0, 5.0$ Hz, 1H), 4.40 (dd, $J = 11.4, 10.0$ Hz,

1H), 3.62 (s, 3H), 3.0-2.92 (m, 1H), 2.55-2.48 (m, 1H), 2.25-2.12 (m, 2H), 1.06 (d, $J =$

6.8 Hz, 3H); **$^{13}\text{C-NMR}$** (CDCl_3 , 100 MHz): δ 172.7, 136.0, 134.9, 128.5 (2C), 127.9,

126.4 (2C), 125.4, 78.3, 51.6, 47.5, 38.7, 32.3, 18.0; **HRMS** (EI) calcd for $\text{C}_{15}\text{H}_{19}\text{NO}_4$,

300.1212 m/z (M^+Na^+); Found, 300.1229 m/z .

3-Furan-2-yl-4-nitromethyl-hept-5-enoic acid methyl ester (3.4h):

Prepared according to the general procedure: 86% yield; dr (*anti:syn*) ratio = 6:1; 97% ee; $[\alpha]_{\text{D}}^{21} = -66.6$ ($c = 0.011$ g/ml, CHCl_3); HPLC analysis: Chiralcel OD-H column, 90:10 hexane/*iso*-propanol, 1.0 mL/min, Major: 9.8 min, minor: 10.6

min; **$^1\text{H-NMR}$** (CDCl_3 , 400 MHz): δ 7.35 (s, 1H), 6.30-6.28 (m, 1H), 6.14 (d, $J = 3.4$ Hz, 1H), 5.71-5.62 (m, 1H), 5.28-5.20 (m, 1H), 4.18-4.12 (m, 2H), 3.60 (s, 3H), 3.28-3.22 (m, 1H), 3.12-3.05 (m, 1H), 2.74 (dd, $J = 16.0, 5.5$ Hz, 1H), 2.62 (dd, $J = 16.0, 9.1$ Hz, 1H), 1.68 (d, $J = 6.4$ Hz, 3H); **$^{13}\text{C-NMR}$** (CDCl_3 , 100 MHz): δ 171.9, 153.2, 142.1, 132.2, 127.1, 110.2, 107.5, 78.5, 51.7, 46.1, 37.4, 37.1, 17.9; **HRMS** (EI) calcd for $\text{C}_{13}\text{H}_{17}\text{NO}_5$, 290.1004 m/z (M^+Na^+); Found, 290.1015 m/z .

4-Nitromethyl-3,6-diphenyl-hex-5-ynoic acid methyl ester (3.6a):

Prepared according to the general procedure: 70% yield; dr (*anti:syn*) ratio = 12:1; 94% ee; $[\alpha]_{\text{D}}^{21} = +2.18$ ($c = 0.011$ g/ml, CHCl_3); HPLC analysis: Chiralcel OD-H column, 90:10 hexane/*iso*-propanol, 1.0 mL/min, Major: 11.1 min, minor: 16.7 min; **$^1\text{H-NMR}$** (CDCl_3 , 400 MHz): δ 7.43-7.25 (m, 10H), 4.37 (dd,

$J = 12.8, 9.6$ Hz, 1H), 4.23 (dd, $J = 12.4, 4.6$ Hz, 1H), 3.73-3.67 (m, 1H), 3.52 (s, 3H), 3.42-3.36 (m, 1H), 3.24 (dd, $J = 16.0, 4.6$ Hz, 1H), 2.82 (dd, $J = 16.0, 10.0$ Hz, 1H); **$^{13}\text{C-NMR}$** (CDCl_3 , 100 MHz): δ 171.8, 139.5, 131.8 (2C), 129.1 (2C), 128.6, 128.3 (2C), 127.9, 127.6 (2C), 122.0, 86.2, 84.9, 77.5, 51.7, 43.8, 39.2, 37.3; **HRMS** (EI) calcd for $\text{C}_{20}\text{H}_{19}\text{NO}_4$, 360.1212 m/z (M^+Na^+); Found, 360.1221 m/z .

6-(4-Bromo-phenyl)-4-nitromethyl-3-*p*-tolyl-hex-5-ynoic acid methyl ester (3.6b):

Prepared according to the general procedure: 67% yield; dr (*anti:syn*) ratio = 10:1; 81% ee; $[\alpha]_{\text{D}}^{21} = +9.34$ ($c = 0.01$ g/mL, CHCl_3); HPLC analysis: Chiralcel OD-H column, 90:10 hexane/*iso*-propanol, 1.0 mL/min, Major: 9.7 min, minor: 11.0 min; **$^1\text{H-NMR}$** (CDCl_3 , 400 MHz): δ 7.44 (d, $J = 8.0$ Hz, 2H), 7.27 (d, $J = 8.0$ Hz, 2H), 7.17-7.12 (m, 4H), 4.34 (dd, $J = 12.8, 9.6$ Hz, 1H), 4.21 (dd, $J = 12.4, 4.6$ Hz, 1H), 3.69-3.62 (m, 1H), 3.54 (s, 3H), 3.37-3.30 (m, 1H), 3.19 (dd, $J = 16.0, 5.0$ Hz, 1H), 2.79 (dd, $J = 16.0, 9.6$ Hz, 1H), 2.33 (s, 3H); **$^{13}\text{C-NMR}$** (CDCl_3 , 100 MHz): δ 171.8, 137.7, 136.2, 133.2 (2C), 131.6 (2C), 129.8 (2C), 127.4 (2C), 122.9, 121.0, 86.3, 85.1, 77.4, 51.7, 43.4, 39.3, 37.3, 21.0; **HRMS** (EI) calcd for $\text{C}_{21}\text{H}_{20}\text{NO}_4\text{Br}^{81}$, 454.0453 m/z (M^+Na^+); Found, 454.0421 m/z .

6-(4-Methoxy-phenyl)-3-(2-methoxy-phenyl)-4-nitromethyl-hex-5-ynoic acid methyl ester (3.6c):

Prepared according to the general procedure: 68% yield; dr (*anti:syn*) ratio = 9:1; 81% ee; $[\alpha]_{\text{D}}^{21} = +4.89$ ($c = 0.012$ g/mL, CHCl_3); HPLC analysis: Chiralcel OD-H column, 90:10 hexane/*iso*-propanol, 1.0 mL/min, Major: 11.3 min, minor: 22.1 min; **$^1\text{H-NMR}$** (CDCl_3 , 400 MHz): δ 7.34 (d, $J = 8.6$ Hz, 2H), 7.30-7.18 (m, 2H), 6.95-6.87 (m, 2H), 6.82 (d, $J = 8.6$ Hz, 2H), 4.40

(dd, $J = 12.2, 9.6$ Hz, 1H), 4.20 (dd, $J = 12.8, 5.0$ Hz, 1H), 3.98-3.87 (m, 1H), 3.86 (s, 3H), 3.79 (s, 3H), 3.73-3.65 (m, 1H), 3.51 (s, 3H), 3.20 (dd, $J = 16.0, 5.0$ Hz, 1H), 2.97 (dd, $J = 16.4, 9.6$ Hz, 1H); **$^{13}\text{C-NMR}$** (CDCl_3 , 100 MHz): δ 172.4, 159.6, 157.2, 133.2 (2C), 129.3, 128.9, 127.1, 120.9, 114.4, 113.8 (2C), 111.0, 85.5, 84.2, 78.0, 55.4, 55.2,

51.5, 37.4 (2C), 35.7; **HRMS** (EI) calcd for C₂₂H₂₃NO₆, 420.1423 m/z (M⁺Na)⁺; Found, 420.1425 m/z .

3-Furan-2-yl-6-(4-methoxy-phenyl)-4-nitromethyl-hex-5-ynoic acid methyl ester (3.6d):

Prepared according to the general procedure: 78% yield; dr (*anti:syn*) ratio = 10:1; 97% ee; $[\alpha]_D^{21} = +12.2$ ($c = 0.012$ g/ml, CHCl₃); HPLC analysis: Chiralpak IC column, 95:5hexane/*iso*-propanol, 1.0 mL/min, Major: 18.9 min, minor: 19.5 min; **¹H-NMR** (CDCl₃, 400 MHz): δ 7.37-7.30 (m, 3H), 6.82 (d, $J = 8.2$ Hz, 2H), 6.31 (dd, $J = 3.2, 1.8$ Hz, 1H), 6.24 (d, $J = 3.2$ Hz, 1H), 4.42 (dd, $J = 12.8, 9.1$ Hz, 1H), 4.33 (dd, $J = 12.8, 5.0$ Hz, 1H), 3.79 (s, 3H), 3.78-3.73 (m, 1H), 3.61 (s, 3H), 3.60-3.52 (m, 1H), 3.12 (dd, $J = 16.0, 5.0$ Hz, 1H), 2.86 (dd, $J = 16.0, 9.6$ Hz, 1H); **¹³C-NMR** (CDCl₃, 100 MHz): δ 171.6, 159.8, 152.2, 142.4, 133.2 (2C), 114.0, 113.8 (2C), 110.4, 108.0, 86.0, 83.0, 77.3, 55.2, 51.8, 37.6, 36.9, 35.5; **HRMS** (EI) calcd for C₁₉H₁₉NO₆, 380.1110 m/z (M⁺Na)⁺; Found, 380.1117 m/z .

6-(4-Methoxy-phenyl)-4-nitromethyl-hex-5-ynoic acid methyl ester (3.6e):

Prepared according to the general procedure: 51% yield; 83% ee; $[\alpha]_D^{21} = -37.72$ ($c = 0.006$ g/ml, CHCl₃); HPLC analysis: Chiralpak IC column, 95:5 hexane/*iso*-propanol, 1.0 mL/min, Major: 24.5 min, minor: 30.1 min; **¹H-NMR** (CDCl₃, 400 MHz): δ 7.32 (d, $J = 8.6$ Hz, 2H), 6.82 (d, $J = 8.6$ Hz, 2H), 4.55 (dd, $J = 12.4, 7.8$ Hz, 1H), 4.47 (dd, $J = 12.4, 6.9$ Hz, 1H), 3.80 (s, 3H), 3.69 (s, 3H), 3.58-3.50 (m, 1H), 2.72-2.54 (m, 2H), 2.06-1.96 (m, 1H), 1.92-1.80 (m, 1H); **¹³C-NMR** (CDCl₃, 100 MHz): δ 172.9, 159.7, 133.2 (2C), 114.2, 113.9 (2C), 85.1, 83.7, 78.4, 55.2,

51.8, 31.2, 30.8, 27.1; **HRMS** (EI) calcd for $C_{15}H_{17}NO_5$, 314.1004 m/z (M^+Na)⁺; Found, 314.1014 m/z .

5-Nitro-3,4-diphenyl-pentanoic acid methyl ester (3.8a):

Prepared according to the general procedure: 66% yield; dr (*anti:syn*) ratio = 5:1; 99% ee; $[\alpha]_D^{21} = +51.2$ ($c = 0.011$ g/ml, $CHCl_3$); HPLC analysis: Chiralcel OD-H column, 98:2hexane/*iso*-propanol, 1.0 mL/min, Major: 23.8 min, minor: 24.8 min; **¹H-NMR** ($CDCl_3$, 400 MHz): δ 7.40-7.20 (m, 10H), 4.47 (dd, $J = 12.8, 11.4$, 1H), 4.21 (dd, $J = 12.8, 4.6$ Hz, 1H), 3.72-3.65 (m, 1H), 3.42-3.35 (m, 1H), 3.37 (s, 3H), 2.51 (dd, $J = 16.0, 10.5$ Hz, 1H), 2.40 (dd, $J = 16.0, 4.6$ Hz, 1H); **¹³C-NMR** ($CDCl_3$, 100 MHz): δ 171.7, 140.2, 137.5, 129.14 (2C), 129.10 (2C), 128.1, 128.0 (2C), 127.8, 127.6 (2C), 79.5, 51.4, 49.6, 45.4, 39.5; **HRMS** (EI) calcd for $C_{18}H_{19}NO_4$, 336.1212 m/z (M^+Na)⁺; Found, 336.1231 m/z .

4-(4-Chloro-phenyl)-3-(4-methoxy-phenyl)-5-nitro-pentanoic acid methyl ester (3.8b):

(3.8b): Prepared according to the general procedure: 58% yield; dr (*anti:syn*) ratio = 6:1; Major *anti* diastereoisomer was isolated in pure form by column chromatography; 91% ee; $[\alpha]_D^{21} = +62.2$ ($c = 0.010$ g/ml, $CHCl_3$); HPLC analysis: Chiralpak IC column, 95:5 hexane/*iso*-propanol, 1.0 mL/min, Minor: 20.7 min, major: 26.1 min; **¹H-NMR** ($CDCl_3$, 400 MHz): δ 7.34 (d, $J = 8.2$ Hz, 2H), 7.26-7.19 (m, 4H), 6.90 (d, $J = 8.2$ Hz, 2H), 4.42 (dd, $J = 12.8, 11.4$ Hz, 1H), 4.23 (dd, $J = 13.3, 4.6$ Hz, 1H), 3.79 (s, 3H), 3.68-3.61 (m, 1H), 3.40 (s, 3H), 3.34-3.27 (m, 1H), 2.46 (dd, $J = 16.0, 10.5$ Hz, 1H), 2.35 (dd, $J = 16.0, 4.6$ Hz, 1H); **¹³C-NMR** ($CDCl_3$, 100 MHz): δ 171.6, 159.0, 136.3, 133.9, 131.6, 129.4 (2C), 129.3 (2C), 128.6 (2C), 114.5 (2C), 79.3, 55.2,

51.5, 49.2, 44.6, 39.4; **HRMS** (EI) calcd for $C_{19}H_{20}NO_5Cl$, 400.0928 m/z (M^+Na)⁺; Found, 400.0921 m/z .

3-(4-Methoxy-phenyl)-5-nitro-4-phenyl-pentanoic acid methyl ester (3.8c):

Prepared according to the general procedure: 78% yield; dr (*anti:syn*) ratio = 4.5:1; 95% ee; $[\alpha]_D^{21} = +3.31$ (c = 0.012 g/ml, $CHCl_3$); HPLC analysis: Chiralcel OD-H column, 93:7 hexane/*iso*-propanol, 1.0 mL/min, Minor: 13.7 min, major: 17.1 min; **¹H-NMR** ($CDCl_3$, 400 MHz): δ 7.38-7.20 (m, 7H), 6.90 (d, $J = 8.2$ Hz, 2H), 4.47 (t, $J = 11.4$ Hz, 1H), 4.24 (dd, $J = 12.8, 4.0$ Hz, 1H), 3.79 (s, 3H), 3.67-3.59 (m, 1H), 3.39 (s, 3H), 3.38-3.30 (m, 1H), 2.46 (dd, $J = 16.0, 10.5$ Hz, 1H), 2.37 (dd, $J = 16.0, 4.6$ Hz, 1H); **¹³C-NMR** ($CDCl_3$, 100 MHz): δ 171.8, 158.9, 137.7, 132.0, 129.1 (2C), 128.6 (2C), 128.1, 128.0 (2C), 114.5 (2C), 79.6, 55.2, 51.4, 49.9, 44.6, 39.6; **HRMS** (EI) calcd for $C_{19}H_{21}NO_5$, 366.1317 m/z (M^+Na)⁺; Found, 366.1318 m/z .

3-(4-tert-Butyl-phenyl)-5-nitro-4-p-tolyl-pentanoic acid methyl ester (3.8d):

Prepared according to the general procedure: 63% yield; dr (*anti:syn*) ratio = 5:1; Major *anti* diastereoisomer was isolated in pure form by column chromatography; 97% ee; $[\alpha]_D^{21} = +17.3$ (c = 0.012 g/ml, $CHCl_3$); HPLC analysis: Chiralcel OD-H column, 98:2 hexane/*iso*-propanol, 0.5 mL/min, Minor: 16.1 min, major: 18.9 min; **¹H-NMR** ($CDCl_3$, 400 MHz): δ 7.37 (d, $J = 8.2$ Hz, 2H), 7.25-7.12 (m, 6H), 4.43 (t, $J = 12.8$ Hz, 1H), 4.20 (dd, $J = 12.8, 4.6$ Hz, 1H), 3.67-3.60 (m, 1H), 3.38 (s, 3H), 3.37-3.31 (m, 1H), 2.48 (dd, $J = 16.0, 10.0$ Hz, 1H), 2.40 (dd, $J = 16.0, 4.6$ Hz, 1H), 2.32 (s, 3H), 1.32 (s, 9H); **¹³C-NMR** ($CDCl_3$, 100 MHz): δ 171.9, 150.5, 137.8, 137.2, 134.6, 129.8 (2C), 127.9 (2C), 127.2 (2C), 126.0 (2C), 79.8, 51.4,

49.4, 44.9, 39.6, 34.5, 31.3 (3C), 21.0; **HRMS** (EI) calcd for $C_{23}H_{29}NO_4$, 406.1994 m/z (M^+Na)⁺; Found, 406.1982 m/z .

3-(4-Chloro-phenyl)-4-(2-methoxy-phenyl)-5-nitro-pentanoic acid methyl ester

(3.8e): Prepared according to the general procedure: 73% yield; dr (*anti:syn*) ratio = 10:1; 95% ee; $[\alpha]_D^{21} = +5.32$ ($c = 0.012$ g/ml, $CHCl_3$); HPLC analysis: Chiralcel OD-H column, 98:2 hexane/*iso*-propanol, 1.0 mL/min, Minor: 14.0 min, major: 16.5 min; **¹H-NMR** ($CDCl_3$, 400 MHz): δ 7.35 (d, $J = 8.6$ Hz, 2H), 7.33-

7.23 (m, 3H), 7.19 (dd, $J = 8.0, 1.8$ Hz, 1H), 6.96-6.90 (m, 2H), 4.73 (t, $J = 11.4$ Hz, 1H), 4.17 (dd, $J = 12.4, 4.12$ Hz, 1H), 3.95-3.93 (m, 1H), 3.93 (s, 3H), 3.76-3.56 (m, 1H), 3.38 (s, 3H), 2.48 (dd, $J = 15.6, 10.0$ Hz, 1H), 2.39 (dd, $J = 16.0, 4.6$ Hz, 1H); **¹³C-NMR** ($CDCl_3$, 100 MHz): δ 171.8, 157.6, 139.5, 133.3, 129.4, 129.25, 129.21 (2C), 124.8, 121.0 (2C), 111.3 (2C), 77.5, 55.5, 51.4 (2C), 43.0, 39.4; **HRMS** (EI) calcd for $C_{19}H_{20}NO_5Cl$, 400.0928 m/z (M^+Na)⁺; Found, 400.0927 m/z .

3-(4-Chloro-phenyl)-5-nitro-4-*p*-tolyl-pentanoic acid methyl ester (3.8f):

Prepared according to the general procedure: 62% yield; dr (*anti:syn*) ratio = 10:1; Major *anti* diastereoisomer was isolated in pure form by column chromatography; 93% ee; $[\alpha]_D^{21} = +55.0$ ($c = 0.012$ g/ml, $CHCl_3$); HPLC analysis: Chiralpak IC column, 95:5 hexane/*iso*-propanol, 1.0 mL/min, Minor: 13.5 min, major:

16.8 min; **¹H-NMR** ($CDCl_3$, 400 MHz): δ 7.35 (d, $J = 8.6$ Hz, 2H), 7.26 (d, $J = 8.2$ Hz, 2H), 7.16 (m, 4H), 4.44 (t, $J = 12.0$ Hz, 1H), 4.19 (dd, $J = 12.8, 4.1$ Hz, 1H), 3.65-3.57 (m, 1H), 3.40 (s, 3H), 3.39-3.31 (m, 1H), 2.48-2.39 (m, 2H), 2.33 (s, 3H); **¹³C-NMR** ($CDCl_3$, 100 MHz): δ 171.6, 138.9, 138.0, 134.0, 133.5, 129.9 (2C), 129.3 (2C), 129.1

(2C), 127.8 (2C), 79.4, 51.5, 49.2, 44.8, 39.3, 21.0; **HRMS** (EI) calcd for $C_{19}H_{20}NO_4Cl$, 384.0979 m/z (M^+Na)⁺; Found, 384.0972 m/z .

5-Nitro-3-(4-nitro-phenyl)-4-phenyl-pentanoic acid methyl ester (3.8g):

3.8g

Prepared according to the general procedure: 61% yield; dr (*anti:syn*) ratio = 9:1; Major *anti* diastereoisomer was isolated in pure form by column chromatography; 81% ee; $[\alpha]_D^{21} = +7.66$ ($c = 0.011$ g/ml, $CHCl_3$); HPLC analysis: Chiralpak IC column, 90:10 hexane/*iso*-propanol, 1.0 mL/min, Minor: 44.2 min, major:

66.9 min; **¹H-NMR** ($CDCl_3$, 400 MHz): δ 8.25 (d, $J = 8.7$ Hz, 2H), 7.53 (d, $J = 8.7$ Hz, 2H), 7.42-7.26 (m, 5H), 4.51 (dd, $J = 12.8, 10.5$ Hz, 1H), 4.21 (dd, $J = 12.0, 4.6$ Hz, 1H), 3.76-3.70 (m, 1H), 3.61-3.54 (m, 1H), 3.42 (s, 3H), 2.57-2.46 (m, 2H); **¹³C-NMR** ($CDCl_3$, 100 MHz): δ 171.1, 148.0, 147.5, 136.6, 129.4 (2C), 128.9 (2C), 128.6, 128.0 (2C), 124.3 (2C), 79.0, 51.7, 49.1, 45.0, 38.9; **HRMS** (EI) calcd for $C_{18}H_{18}N_2O_6$, 381.1063 m/z (M^+Na)⁺; Found, 381.1066 m/z .

5-Nitro-4-*p*-tolyl-pentanoic acid methyl ester (3.8h):

3.8h

Prepared according to the general procedure: 52% yield; 81% ee; $[\alpha]_D^{21} = +18.9$ ($c = 0.010$ g/ml, $CHCl_3$); HPLC analysis: Chiralcel OD-H column, 98:2 hexane/*iso*-propanol, 1.0 mL/min, Major: 30.0 min, minor: 33.4 min; **¹H-NMR** ($CDCl_3$, 400

MHz): δ 7.14 (d, $J = 8.2$ Hz, 2H), 7.06 (d, $J = 8.2$ Hz, 2H), 4.60-4.51 (m, 2H), 3.61 (s, 3H), 3.49-3.41 (m, 1H), 2.32 (s, 3H), 2.19 (t, $J = 7.8$ Hz, 2H), 2.11-2.02 (m, 1H), 2.00-1.89 (m, 1H); **¹³C-NMR** ($CDCl_3$, 100 MHz): δ 173.0, 137.6, 134.9, 129.7 (2C), 127.4 (2C), 80.6, 51.6, 43.2, 31.3, 28.0, 21.0; **HRMS** (EI) calcd for $C_{13}H_{17}NO_4$, 274.1055 m/z (M^+Na)⁺; Found, 274.1051 m/z .

4-(3-Methoxy-phenyl)-5-nitro-pentanoic acid methyl ester (**3.8i**):

Prepared according to the general procedure: 51% yield; 86%

ee; $[\alpha]_D^{21} = +7.60$ ($c = 0.011$ g/mL, CHCl_3); HPLC analysis:

Chiralcel OD-H column, 93:7 hexane/*iso*-propanol, 1.0 mL/min,

Major: 25.1 min, minor: 35.2 min; **$^1\text{H-NMR}$** (CDCl_3 , 400

MHz): δ 7.28-7.24 (m, 1H), 6.83-6.70 (m, 3H), 4.56 (d, $J = 7.8$ Hz, 2H), 3.80 (s, 3H),

3.63 (s, 3H), 3.50-3.43 (m, 1H), 2.20 (t, $J = 7.8$ Hz, 2H), 2.12-2.02 (m, 1H), 2.00-1.92

(m, 1H); **$^{13}\text{C-NMR}$** (CDCl_3 , 100 MHz): δ 173.0, 160.0, 139.6, 130.1, 119.6, 113.6,

112.8, 80.4, 55.2, 51.6, 43.5, 31.2, 27.9; **HRMS** (EI) calcd for $\text{C}_{13}\text{H}_{17}\text{NO}_5$, 290.1004 m/z

(M^+Na^+); Found, 290.1006 m/z .

Synthetic transformation of **3.8f** to cyclopentanol **3.11**

Reaction procedure for the synthesis of alcohol **3.9**

In a two-neck round bottom flask, nitroester **3.8f** (100 mg, 0.280 mmol) was dissolved in toluene (4 mL) and slowly 0.61 mL DIBAL-H (1.0 M in toluene, 0.61 mmol) was added at room temperature. After addition, the reaction mixture was warmed at 40 °C. After 3 h, the reaction mixture was cooled to rt and then quenched with MeOH-toluene mixture (1 mL) to obtain solid slurry. Next, the solid slurry was subjected to filtration through celite and solid was washed with ethyl acetate (3 X 10 mL) three times. The combined organic layer was dried with Na_2SO_4 , evaporated and purified to furnish alcohol **3.9** (0.067 g) in 72% yield.

3-(4-Chloro-phenyl)-5-nitro-4-*p*-tolyl-pentan-1-ol (3.9):

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 7.35 (d, J = 8.2 Hz, 2H), 7.21 (d, J = 8.2 Hz, 2H), 7.16-7.11 (m, 4H), 4.40 (t, J = 12.4 Hz, 1H), 4.19 (dd, J = 12.4, 4.1 Hz, 1H), 3.61-3.54 (m, 1H), 3.35-3.29 (m, 1H), 3.16-3.10 (m, 1H), 3.04-2.98 (m, 1H), 2.32 (s, 3H), 1.71-1.53 (m, 2H). $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz): δ 139.7, 137.6, 134.9, 133.2, 129.7 (2C), 129.3 (2C), 129.2 (2C), 127.8 (2C), 79.8, 59.9, 49.9, 44.9, 36.6, 21.0.

Reaction procedure for the synthesis of aldehyde 3.10

In a two-neck round bottom flask, alcohol **3.9** (60 mg, 0.18 mmol) was treated with DMP (90 mg, 0.22 mmol) in dry DCM (3 mL) at 0°C. Then, the reaction mixture was slowly warmed at room temperature and stirred for 1-2 h. After completion, reaction mixture was quenched with aq. NaHCO_3 and aq. $\text{Na}_2\text{S}_2\text{O}_3$ solution (2 mL, 1:1 ratio by v/v) and then extracted with DCM (2X 10 mL). After removal of the combine solvents under reduced pressure, the crude reaction mixture was subjected to purification by flash column chromatography directly using EtOAc/petroleum-ether (60-80°C) as an eluent to provide aldehyde **3.10** in 49 mg (82%) with single *anti* diastereoisomer.

3-(4-Chloro-phenyl)-5-nitro-4-*p*-tolyl-pentanal (3.10):

$[\alpha]_{\text{D}}^{21} = +29.3$ (c = 0.010 g/mL, CHCl_3); $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 9.35 (s, 1H), 7.36 (d, J = 8.6 Hz, 2H), 7.27 (d, J = 8.6 Hz, 2H), 7.18-7.12 (m, 4H), 4.45 (t, J = 12.4 Hz, 1H), 4.21 (dd, J = 12.4, 4.0 Hz, 1H), 3.66-3.58 (m, 1H), 3.51-3.43 (m, 1H), 2.72-

2.26 (m, 1H), 2.50 (dd, $J = 17.8, 4.0$ Hz, 1H), 2.33 (s, 3H). ^{13}C -NMR (CDCl_3 , 100 MHz): δ 199.4, 139.1, 138.3, 134.0, 133.6, 130.0 (2C), 129.5 (2C), 129.1 (2C), 127.8 (2C), 79.3, 49.2, 48.5, 42.6, 21.1. HRMS (EI) calcd for $\text{C}_{18}\text{H}_{18}\text{ClINO}_3$, 332.1053 m/z ($\text{M}+\text{H}$) $^+$; Found, 332.1042 m/z .

Reaction procedure for the synthesis of cyclopentanol 3.11

To a stirred solution of compound **3.10** (30 mg, 0.090 mmol) in DCM (1.0 mL) was added DABCO (1 mg, 0.1 equiv) at 0 °C. The reaction mixture was stirred at 0 °C for 48 h under N_2 atmosphere. After completion, the reaction mixture was concentrated and directly used for column chromatography to obtain cyclopentanol **3.11** in a major diastereoisomer in 71% yield (21 mg). The structure of major diastereoisomer **3.11** was ascertained by 2D-NMR. Other minor isomer was not characterized.

3-(4-Chloro-phenyl)-5-nitro-4-*p*-tolyl-cyclopentanol (3.11):

dr ratio = 3:1; Major diastereoisomer **3.11** was isolated in pure form by column chromatography; 94% ee; $[\alpha]_{\text{D}}^{24} = +65.2$ ($c = 0.01$ g/mL, CHCl_3); HPLC analysis: Chiralcel OD-H column, 90:10 hexane/*iso*-propanol, 1.0 mL/min, Minor: 9.6 min, major: 14.7 min; ^1H -NMR (CDCl_3 , 400 MHz): δ 7.07 (d, $J = 8.2$ Hz, 2H), 6.92 (d, $J = 8.2$ Hz, 2H), 6.81 (d, $J = 8.0$ Hz, 2H), 6.69 (d, $J = 8.0$ Hz, 2H), 5.19 (dd, $J = 7.6, 6.4$ Hz, 1H), 4.98-4.95 (m, 1H), 4.05 (t, $J = 8.2$ Hz, 1H), 3.71-3.65 (m, 1H), 2.80 (d, $J = 3.2$ Hz, 1H), 2.72-2.65 (m, 1H), 2.34-2.26 (m, 1H), 2.23 (s, 3H). ^{13}C -NMR (CDCl_3 , 100 MHz):

δ 137.8, 136.9, 133.4, 132.3, 129.7 (2C), 128.9 (2C), 128.1 (2C), 128.0 (2C), 96.6, 76.5, 52.7, 46.2, 37.2, 20.9. HRMS (EI) calcd for $C_{18}H_{18}ClNO_3$, 332.1053 m/z ($M+H$)⁺; Found, 332.1082 m/z .

Synthetic transformation of **3.8h** to δ -lactam **3.12**

Reaction procedure for the synthesis of δ -lactam **3.12**

To a solution of the nitroester compound **3.8h** (100 mg, 0.400 mmol) in MeOH (5 mL) was added RaNi (0.1 mL). The reaction mixture was hydrogenated at 100 psi for 72 h at 70 °C. The catalyst was filtered and concentrated. After purification by column chromatography, the title compound δ -lactam, 5-*p*-Tolyl-piperidine-2-one, **3.12** was obtained as a white solid in 81% yield and 76% ee. **5-*p*-Tolyl-piperidine-2-one (3.12):** 81% yield; 76% ee; $[\alpha]_D^{24} = -112.17$ ($c = 0.01$ g/mL, CHCl_3); HPLC analysis: Chiralcel OD-H column, 90:10 hexane/*iso*-propanol, 1.0 mL/min, Major: 15.832 min, minor: 17.4 min; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 7.17–7.12 (m, 4H), 6.71 (s, 1H), 3.50–3.43 (m, 1H), 3.34 (t, $J = 11.4$ Hz, 1H), 3.10–2.99 (m, 1H), 2.52–2.45 (m, 2H), 2.33 (s, 3H), 2.10–2.01 (m, 2H). $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz): δ 172.1, 138.7, 136.7, 129.3 (2C), 126.8 (2C), 48.6, 39.1, 31.2, 27.8, 20.9. HRMS (EI) calcd for $C_{12}H_{15}NO$, 190.1232 m/z ($M+H$)⁺; Found, 190.1226 m/z .

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Crystal Structure of racemic nitroester compound 6-(4-Methoxy-phenyl)-3-(2-methoxy-phenyl)-4-nitromethyl-hex-5-enoic acid methyl ester:

Table 1. Crystal data and structure refinement for liu83.

Identification code	liu83	
Empirical formula	C ₂₂ H ₂₅ N O ₆	
Formula weight	399.43	
Temperature	103(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 9.4383(8) Å	$\alpha = 90^\circ$.
	b = 9.5427(7) Å	$\beta = 92.592(2)^\circ$.
	c = 23.068(2) Å	$\gamma = 90^\circ$.
Volume	2075.5(3) Å ³	
Z	4	
Density (calculated)	1.278 Mg/m ³	
Absorption coefficient	0.093 mm ⁻¹	
F(000)	848	
Crystal size	0.40 x 0.40 x 0.38 mm ³	
Theta range for data collection	1.77 to 30.65°.	
Index ranges	-13 ≤ h ≤ 13, -13 ≤ k ≤ 13, -32 ≤ l ≤ 32	
Reflections collected	45904	
Independent reflections	6382 [R(int) = 0.0453]	
Completeness to theta = 30.65°	99.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9655 and 0.9637	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	6382 / 0 / 265	
Goodness-of-fit on F ²	1.112	
Final R indices [I > 2σ(I)]	R1 = 0.0607, wR2 = 0.1446	
R indices (all data)	R1 = 0.0719, wR2 = 0.1546	
Largest diff. peak and hole	0.647 and -0.335 e.Å ⁻³	

Crystal structure of the chiral compound 3.4d:

Table 1. Crystal data and structure refinement for liu82.

Identification code	liu82
Empirical formula	C ₂₁ H ₂₂ Cl N O ₄
Formula weight	387.85
Temperature	103(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)
Unit cell dimensions	a = 7.3797(5) Å α = 90°. b = 5.6954(4) Å β = 98.308(5)°. c = 23.2777(17) Å γ = 90°.
Volume	968.10(12) Å ³
Z	2
Density (calculated)	1.331 Mg/m ³
Absorption coefficient	0.224 mm ⁻¹
F(000)	408
Crystal size	0.40 x 0.18 x 0.12 mm ³
Theta range for data collection	1.77 to 28.45°.
Index ranges	-9 ≤ h ≤ 9, -7 ≤ k ≤ 7, -29 ≤ l ≤ 31
Reflections collected	10652
Independent reflections	4759 [R(int) = 0.0608]
Completeness to theta = 28.45°	98.5 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9737 and 0.9158
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	4759 / 1 / 247
Goodness-of-fit on F ²	1.015
Final R indices [I > 2σ(I)]	R1 = 0.0665, wR2 = 0.1360
R indices (all data)	R1 = 0.1209, wR2 = 0.1692
Absolute structure parameter	0.16(11)
Largest diff. peak and hole	0.424 and -0.297 e.Å ⁻³

Crystal structure of the chiral compound 3.8b:

Table 1. Crystal data and structure refinement for liu86.

Identification code	liu86	
Empirical formula	C ₁₉ H ₂₀ Cl N O ₅	
Formula weight	377.81	
Temperature	103(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 5.6919(2) Å	α = 90°.
	b = 10.6547(4) Å	β = 90°.
	c = 30.5750(12) Å	γ = 90°.
Volume	1854.24(12) Å ³	
Z	4	
Density (calculated)	1.353 Mg/m ³	
Absorption coefficient	0.235 mm ⁻¹	
F(000)	792	
Crystal size	0.40 x 0.06 x 0.04 mm ³	
Theta range for data collection	3.28 to 30.23°.	
Index ranges	-8 ≤ h ≤ 7, -15 ≤ k ≤ 13, -43 ≤ l ≤ 41	
Reflections collected	31114	
Independent reflections	5402 [R(int) = 0.0492]	
Completeness to theta = 30.23°	98.2 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9906 and 0.9117	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	5402 / 0 / 237	
Goodness-of-fit on F ²	1.029	
Final R indices [I > 2σ(I)]	R1 = 0.0398, wR2 = 0.0808	
R indices (all data)	R1 = 0.0582, wR2 = 0.0881	
Absolute structure parameter	0.04(6)	
Largest diff. peak and hole	0.204 and -0.224 e.Å ⁻³	

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12. The use of stronger bases and the high concentration of MeOH in the reaction medium, the yields of desired product 3.4a are less, this might be due to base induced slow decomposition of products. Rovis *et al* also addressed the similar type of observation, see: ref. [7c].
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CHAPTER4

Introduction: Recent Developments in N-glycosylation strategy

4.1 Introduction of glycosidic bond synthesis

Carbohydrates are important building blocks of nature which are present in all organisms in the form of glycosides, glycoconjugates, and polysaccharides. In natural products, sugar units are connected to each other or to other molecules via glycosidic bonds. With the rapid development of biomedical science and pharmacology, the synthesis of all kinds of bioactive glycosides is the key step for further studies. Therefore, highly stereoselective synthetic methods of C-, N-, and O-glycosidic bonds formation are in exigent need. Pioneering works on glycosidic bond formation were reported by Michael^[1] in 1879 and Fischer^[2] in 1893, followed by the ground-breaking work of Koenigs and Knorr,^[3] in which glycosyl halides were employed as glycosyl donors. After those early studies, a massive collection of methodologies has been developed to achieve efficient access to glycosidic bond formations with excellent anomeric selectivity.

The chemical glycosylation methods usually refers to the delivery of the glycosyl moiety of a glycosyl donor to a glycosyl acceptor (usually a nucleophile). The leaving group and protecting group installed on the donor play vital roles in anomeric selectivity control.^[4–6] Glycosyl donors derived from pyranoses and furanoses are commonly generated by oxygen-exchange reactions.^[4a, 7, 8] Scheme 4.1, (a) shows the acid-catalyzed Fischer–Helferich glycosylation method in a direct way to replace anomeric oxygen atom and Scheme 4.1, (b) shows the Koenigs–Knorr method, where a glycosyl halide serves as the donor. On the other hand, alkylation of the anomeric hydroxyl group under basic conditions directly affords the O-glycosylation product irreversibly (Scheme 4.1, c).^[4a, 7, 8] A pre-formed glycosyl trichloroacetimidates are also commonly used in efficient and highly stereoselective glycosylation since the strong electron withdrawing nature of the trichloroacetimidate group promotes the generation of an oxocarbenium

ion. Meanwhile, the steric hindrance of such protecting groups enhances the anomeric selectivity to some extent (Scheme 4.1, d).^[9-13]

Scheme 4.1 Generation of glycosidic and saccharide bonds

Another commonly used sugar substrates in glycosylation reactions are glycals, which possess a double bond between carbon atoms 1 and 2 (Scheme 4.2). The electrophilic oxygen, nitrogen, and sulfur containing compounds undergo nucleophilic attack to form a three membered ring on the sugar scaffold, which, upon ring opening process through pathway **a** or **b**, is transformed into the corresponding glycoside.^[14-21] The glycal donor can be converted into a Michael acceptor through installation of an electron withdrawing group at the C2 position, such as 2-nitro group, thus undergoing Michael addition to form the corresponding 2-deoxyglycoside (Scheme 4.2, pathway **c**).^[22]

Scheme 4.2 Glycals as donors for the generation of glycosidic bonds

4.2 Transition Metal-Catalyzed Glycosylation

With the development of automated solid phase carbohydrate synthesis by Seeberger^[23, 24] and fluororous-based carbohydrate microarrays by Pohl,^[25,26] mild and efficient reaction conditions have become a new trend in research area of carbohydrate chemistry. Transition metal catalysts play significant roles in green chemistry, because they allow mild reaction conditions, high synthetic efficiency as well as reduction of side products. In many cases, well-designed ligand-transition metal complexes enable stereoselectivity control. In Schmidt's statement,^[27] efficient glycosylation must meet the following three requirements: 1) low catalyst loading for donor activation; 2) the glycosylation process must be stereo-controlled with high yields; and 3) the method must be applicable on a large scale.

4.2.1 Palladium catalysed O-glycosylations

Palladium complexes are powerful catalysts for many synthetic transformations such as hydrogenation, cross-coupling, and C-H activation reactions.^[28] Recently, palladium complexes have started to play a significant role in stereocontrolled glycosylations.

The group led by Feringa reported the first palladium-catalyzed stereoselective O-glycosylation by using glycosyl acetate as a donor in 1999 (Scheme 4.3, a).^[29] The catalytically generated allyl-palladium active species was the key intermediate, which was further attacked by a nucleophile such as an alcohol to afford the O-glycosylation product with retention of the stereochemistry. Later in 2003, in the continuation of their research work, ester groups such as formate (Scheme 4.3, b) and benzoate (Scheme 4.3, c) groups were also employed as leaving groups installed on pyranone ring for palladium-catalysed O-glycosylation with excellent stereospecificity.^[30]

Scheme 4.3 Palladium-catalyzed stereoselective O-glycosylation using glycosyl ester donors

O'Doherty and co-workers also illustrated that, with *tert*-butylcarbonate as leaving group on pyranone, the reaction occurs much faster with complete retention of stereochemistry (Scheme 4.4, a and b).^[31,32] In the proposed reaction mechanism, the decarboxylation of the carbonate group was suggested to be the driving force.

Scheme 4.4 Palladium-catalyzed stereoselective O-glycosylation using glycosyl carbonate donors

In the continuation of their work, O'Doherty further applied this palladium catalysed allylation to the synthesis of oligosaccharides.^[33] As shown in Scheme 4.5, disaccharide **4.5** and trisaccharide **4.7** were synthesised following two or three time of the Pd-catalyzed glycosylation. A subsequent reduction of **4.5** by employing sodium borohydride afforded **4.8** in 88% yield, which was further dihydroxylated or reduced to provide disaccharides **4.9** and **4.10**, respectively. Similarly, trisaccharides **4.12** and **4.13** were also prepared following the same procedure.^[33]

Glycal donors, which have been widely used in Ferrier rearrangement, are also important donors in transition metal-catalysed glycosylation reactions. Interestingly, in the glycosylation involving glycal donors, the palladium catalyst strongly affects the anomeric selectivity rather than the stereochemical nature of the glycosyl donor itself. For example, palladium acetate and 2-di(*tert*-butyl)phosphinobiphenyl (DTBBP) complex leads to the generation of β -glycosides **4.15**, while trimethyl phosphite ligand provides α -anomer **4.16** in the same reaction. The possible explanation for the stereocontrol by the palladium catalyst is outlined in Scheme 4.6.^[34] Starting from glycal **4.14**, the reaction goes through a common retention pathway through an intermediate **4.17** to afford β -anomer when DTBBP was employed as the ligand, while α -anomer is

obtained through path A–D in the presence of P(OMe)_3 as ligand, involving intermediates **4.18** and **4.19**. Moreover, the authors believed a Zn(II) ion present in the reaction plays a role in the dual activation of the acceptor and the leaving group.

Scheme 4.5 *De novo* synthesis of 1,6 linked disaccharides and trisaccharides

Scheme 4.6 Proposed mechanism for α,β selectivity of glycosylation controlled by ligand

Recently, glycal imidates **4.20** was employed as glycosyl donors in palladium-catalyzed stereoselective glycosylation by Nguyen.^[35] The trichloroacetimidate group

was found to play an essential role in mediating the anomeric selectivity. In their proposed mechanism (Scheme 4.7), the palladium-phosphine complex is coordinated by both the nitrogen atom of the imidate group and the double bond of the glucal **4.20** to generate the intermediate **4.23**, which further undergo oxidative insertion form the oxonium palladium complex **4.24** was generated. The bulky palladium complex causes a steric hindrance at the β -face so that the nucleophile prefers to attack the intermediate **4.24** from the α -face to afford **4.25**. Deoxypalladation followed by dissociation provides α -glycoside **4.22**.

Scheme 4.7 Palladium-catalyzed stereoselective O-glycosylation using glycal imidate donors

4.2.2 Palladium catalysed N-glycosylations

Although palladium catalyzed C-, O-glycosylation have been well studied, N-glycosylation via a catalytically generated Pd- π -allyl intermediate has been rarely reported. In 1992, Sinou and co-workers reported the first palladium(0) catalyzed protocol to access 2,3-unsaturated nucleoside analogues with good stereoselectivities (Figure 4.1).^[36] In the year of 2002, Trost and co-workers revealed a Pd-catalyzed N-glycosylation of bis-indole lactam pro-aglycon with high stereo- and

chemoselectivity^[37]. As shown in Scheme 4.8, the (bis)indole lactam undergo allylation with galactose- and fucose-derived glycals to afford staurosporine derivatives **4.27** and **4.29** with monosubstitution. The authors reasoned that allylation preferentially occurs at the more acidic indolic N-H moiety, which is the one linearly conjugated with the carbonyl group.

Figure 4.1 Sinou's strategy of Pd(0) catalyzed N-glycosylation

Scheme 4.8 Trost's strategy for synthesis of staurosporine derivatives **4.27** and **4.29**

In 2006, O'Doherty and co-workers successfully prepared homoadenosine analogues starting from pyranone through direct palladium-catalyzed N-glycosylation.^[38] Their protocol started from Pd-catalyzed N-glycosylation of Boc-protected pyranone **4.30**

with 6-chloropurine **4.31**, which exclusively afforded the β isomer **4.32** in high yield (Scheme 3). Reduction of the enone **4.32** with NaBH₄ followed by Myers' reductive rearrangement furnished an olefin **4.34**. Subsequent dihydroxylation of **4.34** through oxidation with OsO₄/NMO afforded a compound **4.35**, which was further transformed into **4.37** through exposure to ammonia and then to TBAF. Starting from **4.33**, another homoadenosine analogue (*ent*)-**2** (compound **4.40**) was also prepared in three steps (Scheme 4.9).

Scheme 4.9 O'Doherty's strategy for the synthesis of homoadenosine analogues (*ent*)-**1** and (*ent*)-**2**

Scheme 4.10 Nguyen's strategy for the stereoselective synthesis of α - and β -N-glycosyl trichloroacetamides and the proposed mechanism

In 2007, Nguyen *et al.* developed a novel method for the stereoselective synthesis of α - and β -N-glycosyl trichloroacetamides through glycal imide rearrangement via palladium(II) catalysis (Scheme 4.10).^[39] The α - and β -selectivity of the product is subject to the nature of the palladium catalyst. In their proposed mechanism, a cationic palladium $\text{Pd}(\text{CH}_3\text{CN})_4(\text{BF}_4)_2$ prefers to ionize the imide group to furnish an allylic cation **4.43**. Subsequent nucleophilic attack of the trichloroamide species to **4.43** from the α -face generates the α -N-glycosydic bond. On the other hand, the neutral $\text{Pd}(\text{PhCN})_2\text{Cl}_2$ -TTMPP-salicylaldehyde complex catalyzes the formation of β -glycosides in a different reaction pathway. Firstly the double bond of glycal is activated

by the coordination of the palladium complex to form **4.45**. Secondly, the imidate nitrogen attacks at the C1 position to form a cyclized intermediate **4.46**, followed by Grob-like fragmentation and dissociation to release the β -glycoside **4.44 β** .

Scheme 4.11 Liu's palladium catalyzed decarboxylative allylation strategy toward synthesis of β -N-glycosides and the proposed mechanism

In 2014, our group reported a highly stereoselective strategy for the formation of N-glycosyl imidazole analogues by palladium catalysis.^[40] This one-pot reaction involves a sequence of carbamation, decarboxylation and allylation between the glycal donor and the CDI analogue acceptor. In the absence of the palladium catalyst, the reaction affords α -N-glycoside through decarboxylation followed by nucleophilic attack of imidazole anion to the C1 position from the axial orientation. On the other hand, the reaction using

$\text{Pd(PPh}_3)_4$ involves coordination of the palladium center to the double bond of glycal and the lone pair of the imidazole nitrogen atom. The key intermediate **4.49** is with the palladium center being located at the β -face. Subsequent decarboxylative oxidative addition releases an imidazolyl palladium the imidazole species **4.50**, which further undergoes reductive elimination to furnish the β -isomer **4.51**.

4.3 Recent developments in synthesis of N-glycosylated indigo and its isomers

Figure 4.2 The structures of indigo, isoindigo and indirubin

Recently N-glycosylated bis-indole compounds start to play an important role in the pharmaceutical research area. There are three major kinds of bis-indole structures, that is, indigo, isoindigo and indirubin (Figure 4.2). People have been using indigo and its bromo-substituted derivatives as dyes for a long time. The precursors of these colourants such as isatin can be extracted from plants and fungi. Besides natural extraction, there are also many synthetic methods developed for synthesizing indigo derivatives.

Figure 4.3 Structures of Asashin A, B, and C

In 2002, Laatsch *et al.* successfully isolated Akashins A, B and C (Figure 4.3), which exist in terrestrial *Streptomyces* spp.^[41] The indigo moiety is linked to a sugar residue via a N-glycosidic bond. Compared with non-glycosylated indigo, these Akashins shows higher antiproliferative activity toward various human tumor cell lines. Another well-known isomer of indigo is indirubin,^[42] which is an important ingredient of Danggui Longhui Wan, a traditional chinese medicine that has been proved therapeutic towards myelocytic leukemia.^[43] Till now, indirubin and its derivatives have been used as potent inhibitors of several kinases such as glycogen synthase kinase-3 (GSK-3) and cyclin-dependent kinases (CDKs).^[44, 45]

In the last decade, tremendous methods have been developed for the synthesis of indigoid derivatives, including glycosylated molecules. Herein we introduce some important synthetic protocols for the synthesis of these bioactive molecules, including indigo, isoindigo, and indirubin glycosides.

4.3.1 Synthesis of N-Glycosylated indigo, indirubin and isoindigo

Langer and co-workers firstly reported an elegant synthesis of N-glycosylated indigo (Scheme 4.12).^[46] N-Benzylindigo **4.53** was used as O-nucleophile, which underwent O-glycosylation with rhamnosyl trichloroacetimidate **4.54** in the presence of a Lewis

acid to afford **4.55**. With a longer reaction time, the O-glycoside **4.55** underwent an O→N rearrangement to furnish the desired N-glycosylated indigo **4.56**. However, this strategy has its own limitation that the O→N rearrangement can only happen when pivaloyl protected rhamnose was employed as the glycosyl donor. Furthermore, the following attempts on deprotection of the sugar moiety was unsuccessful.

Scheme 4.12 Synthesis of protected N-glycosylated indigo

In the continuation of their previous work, Langer proceeded to synthesize more hydrophilic deprotected indigo-N-glycosides (Scheme 4.13).^[47] Indigo was first oxidized into a diacetate **4.58**, which further underwent elimination to form dehydroindigo **4.59**. A TMS-protected rhamnose **4.60** was treated with TMSI to form rhamnosyliodide in situ, which further underwent N-glycosylation to furnish **4.61** with the anomeric selectivity of $\alpha:\beta=2:1$. Further treatment of **4.61** with NaO^tBu in MeOH provided the deprotected indigo-N-glycoside **4.62**.

Scheme 4.13 Synthesis of deprotected N-glycosylated indirubin

Langer also reported the first synthesis of N-glycosylated indirubin (Scheme 4.14).^[48] The core building block was an N-glycosylated isatin **4.66**, which was obtained through a Friedel-Crafts reaction of N-glycosyl aniline **4.65** with oxalyl chloride mediated by aluminum trichloride. The β -isomer of the N-glycosylated isatin **4.66** further underwent nucleophilic addition with indoxylacetate to form the desired deprotected N-glycosyl indirubin **4.67**.

Scheme 4.14 Synthesis of N-glycosylated indirubin

Starting from an N-glycosylated isatin, an N-glycosylated isoindigo can be synthesised in one step via condensation with oxindole in the presence of acid.^[49] As shown in

Scheme 4.15, non-substituted and bromo- and nitro- substituted N-glycosylated isoindigos were prepared by this method.

Scheme 4.15 Synthesis of N-glycosylated isoindigo derivatives

4.4 Conclusion

As discussed above, many methods for the synthesis of sugar- substituted bis-indoles (like indigo, isoindigo and indirubin) have been developed recently. A antitumor activity studies of these glycosides have shown the importance of sugar residues for cancer therapy. Whereas many synthetic methods have been reported for the N-glycosylated bis-indoles, straightforward and highly stereoselective strategies for C-N bond formation to construct this kind of molecules have been rare. Following recent trends in transition metal catalysis, many efficient and stereocontrolled methodologies for O, C, N-glycosylation have been achieved. Therefore, the transition metal catalyzed allylation strategy could be applied for the synthesis of many bioactive N-glycosylated bisindoles by employing glycals as sugar donors.

4.5 References

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CHAPTER 5

Palladium Catalyzed Glycosylation: Novel Synthetic Approach to Diverse N-Heterocyclic Glycosides

5.1 Introduction

N-Heterocyclic glycosides and glycoconjugates widely exist in many natural products and play significant roles in many biological processes.^[1] Nucleosides, in particular, have great potential as antitumor and antiviral drugs because their functions manipulating genetic processes involving *N*-glycosidic linkages.^[2] Due to their biological importance, nucleosides have attracted much attention. With the development of glycobiology, an increasing number of *N*-glycosylated heterocycle-containing structures, such as Akashin A^[3] and Staurosporine,^[4] have been found to be valuable in the pharmaceutical field (Figure 5.1). Moreover, the activities of some other bioactive natural products such as bis-indole-containing compounds can be significantly increased by incorporating a sugar moiety through an *N*-glycosidic bond.^[5] However, to date, there are very few synthetic methods to construct this kind of glycosidic linkages.^[6] Transition metals have demonstrated their catalytic capability for the formation of *C*-*N* bonds with high efficiency and selectivity.^[7] Among them, palladium has been the most widely used catalyst. Many good methods for *C*-*N* bonds formation have been developed based on palladium catalyzed reactions.^[8]

Figure 5.1 Natural products containing *N*-glycosylated bis-indole structure

For *N*-heterocyclic glycosylation, we preferred glycal type donors since the coordination between the palladium catalyst and the double bond in the sugar ring could potentially lead to improved stereoselectivity through a classic Ferrier rearrangement and provide versatile synthetic building blocks for further functionalization.^[9] The difficulties of generating Pd- π -allyl intermediates and their poor reactivities as glycosyl donors have limited the development of palladium catalyzed glycosylation.^[10] The trifluoroacetyl group,^[11] which can increase donor by acting as a good leaving group, was therefore introduced to solve these problems. Meanwhile, various coordinating groups such as imidate^[12] and cyano^[13] are widely used to exert stereo-control in glycosylations while picoloyl group offers an alternative for glycosylation as a good leaving and directing group.^[14] Our group has been focusing on palladium-catalyzed glycosylation using glycal derivatives for several years. Various acceptors have been successfully employed to construct different types of glycosidic bonds with a Pd- π -allyl intermediate as donor.^[8f,15] As a further expansion of this strategy, herein, we report a palladium-catalyzed glycosylation reaction involving diverse *N*-heterocyclic nucleophiles including isatins, imide as well as imidazole analogues.

5.2 Results and discussion

5.2.1 Optimization of reaction conditions

Table 5.1 Optimization of the reaction conditions with isatine acceptor^a

Entry	Ligand	Solvent	Temp.(°C)	Yield(%) ^b	$\beta:\alpha$ ^c
1	JohnPhos	ACN	70	-	-
2	SPhos	ACN	70	-	-
3	DPPF	ACN	70	35	6:1
4	RuPhos	ACN	70	-	-
5	DPPB	ACN	70	50	9:1
6	DPPB	Toluene	70	39	N.D.
7	DPPB	Toluene	Reflux	42	7:1
8	DPPB	CH ₂ Cl ₂	Reflux	12	N.D.
9	DPPB	THF	70	87	8.8:1
10 ^d	DPPB	THF	70	85	8.8:1

^a Unless otherwise specified, all reactions were carried out with 0.1 mmol **5.1a**, 0.2 mmol **5.2a**, 10% Pd(PPh₃)₄, 20% DPPB in 3 mL solvent for 24 hours. ^b Isolated yield. ^c All the ratios were determined by ¹H-NMR. ^d The reaction was carried out for 12 h.

In our initial attempts, a model study was conducted using compounds **5.1a** as the glycosyl donor and **5.2a** as the acceptor with Pd(PPh₃)₄ as the catalyst. Reaction optimization was first carried out by screening various ligands in anhydrous acetonitrile at 70 °C. The results are depicted in Table 5.1. Among the ligands we examined, JohnPhos, SPhos and RuPhos failed to catalyze this reaction (entries 1, 2 and 4), while DPPF successfully furnished the desired *N*-glycosylation product in 35% yield with incomplete conversion of **5.1a** (entry 3). DPPB was found to be the best ligand to afford 50% yield after 24 h with incomplete conversion of the starting material (entry 5). The stereoselectivity observed by NMR analysis of the crude product was $\beta:\alpha = 9:1$. The major isomer could be easily purified by column chromatography and the

stereochemistry of the anomeric center was confirmed by X-ray diffraction crystallographic analysis.^[16] In our attempts to improve the yield, the solvents were screened. Poor yields were obtained when the reactions were carried out in toluene at both 70 °C and reflux conditions due to the poor solubility of the reactants (entries 6 and 7). CH₂Cl₂ was also unable to give a good yield (entry 8). To our delight, the yield was improved significantly when THF was used (entry 9). Reducing the reaction time from 24 h to 12 h resulted in no significant change in the yield (entry 10). Therefore, the optimized reaction conditions were concluded as follows: the reaction was performed with compound **5.1a** (1.0 equiv) and isatin **5.2a** (2.0 equiv) in the presence of Pd(PPh₃)₄ (0.1 equiv) and DPPB (0.2 equiv) in THF at 70 °C for 12 h.

5.2.2 Substrate scope

With the optimized reaction conditions in hand, we proceeded to examine the scope and limitations of this method. The results are summarized in Scheme 5.1. A range of isatin nucleophiles with various substituents on the aromatic ring were screened. The reaction with an unsubstituted isatin resulted in better selectivity, albeit lower yield (**5.3b**). When we employed other isatins bearing electron-donating groups, good yields were obtained, with slightly diminished selectivities (**5.3c**, **5.3d**). Isatins bearing electron-withdrawing groups, such as 5-Cl, 5- NO₂ or 5-CF₃ were also screened but they failed to give the *N*-glycosides. Next, we synthesized various glycosyl donors to examine the effect of protecting groups. Exclusive β -selectivities were detected with moderate-to-good yields when electron-donating protecting groups were used (**5.3e**-**5.3i**). We further employed our reaction conditions to other types of *N*-nucleophiles. Imidazole and its derivatives were then investigated to further expand the substrate scope. When compound **5.1a** was utilized as the donor, imidazole, 2-methylimidazole,

4,5-diphenylimidazole, benzimidazole, and pyrazole successfully provided the corresponding N-glycosides in good yields and excellent selectivities (**5.3j-5.3n**).

Scheme 5.1. Substrate scope of *N*-glycosylation with glucal donors ^{a,b,c}

^a Unless otherwise specified, all reactions were carried out with 0.1 mmol **5.1**, 0.2 mmol **5.2**, 10% $\text{Pd(PPh}_3)_4$, 20% DPPB in 3 mL THF at 70 °C for 12 h. ^b Isolated yield.

^c All the ratios were determined by $^1\text{H-NMR}$.

Later on, we employed α -type 2,3-unsaturated hexopyranoside **5.1'**^[17] as donor^[8a], which was proved to be effective in achieving the desired α -*N*-glycosides (Scheme 5.2). Exclusive α -selectivities were obtained in all reactions (**5.3'a**–**5.3'd**) with compound **5.1'** as the starting material and the stereochemistry of compound **5.3'c** was confirmed by X-ray diffraction crystallographic analysis.^[18]

Scheme 5.2. Substrate scope of *N*-glycosylation with hexopyranoside donor ^{a,b,c,d}

^a Unless otherwise specified, all reactions were carried out with 0.1 mmol **5.1'**, 0.2 mmol **5.2**, 10% $\text{Pd(PPh}_3)_4$, 20% DPPB in 3 mL THF at 70 °C for 12 h. ^b Isolated yield. ^c All the ratios were determined by $^1\text{H-NMR}$. ^d Compound **5.1'** is unstable even stored at -20 °C.

5.2.3 Proposed mechanism

On the basis of the experimental results, a plausible reaction mechanism is outlined in Scheme 5.3. Initially, palladium is coordinated simultaneously to the nitrogen of the picoloyl group as well as the double bond of glucal at β -face to generate an intermediate

II (Scheme 5.3, a). Next, cleavage of the picoloyl ester moiety affords the π -allyl Pd species **III**. Subsequent coordination of the *N*-nucleophile to the palladium with concurrent N-H deprotonation by the picolate anion gives intermediate **IV**. Finally, the β -*N*-glycoside is obtained through C-N reductive elimination with concomitant regeneration of the palladium catalyst **I**. When α -type 2,3-unsaturated hexopyranoside **5.1'** is employed as donor, the key intermediate is formed with α -orientation by a double coordination of palladium to compound **5.1'** (Scheme 5.3, b). The α -isomer is generated by a similar pathway.

Scheme 5.3. Plausible mechanism for the synthesis of *N*-glycosides

5.2.4 Synthesis of *N*-glycosylated indirubins

In order to demonstrate the applicability of our method, *N*-glycosylated isatins were chosen as precursors to construct the indirubin analogues.^[5c] Potentially biological active *N*-glycosylated indirubins **5.4a**, **5.4b** and **5.4c** were successfully synthesized in good yields (Scheme 5.4).

Scheme 5.4. Synthesis of Indirubin *N*-Glycosides **5.4a**, **5.4b** and **5.4c**

5.3 Conclusion

In conclusion, we have successfully developed an efficient methodology for the stereoselective synthesis of *N*-heterocyclic glycosides. This strategy is based on a palladium-catalyzed allylation reaction with various *N*-nucleophiles. Glucal and α -type 2,3-unsaturated hexopyranoside donors equipped with *O*-picoloyl group successfully furnished the corresponding β - and α -anomers respectively. The reaction tolerated different kinds of protecting groups on glycosyl donors as well as a wide variety of acceptors such as isatins, imides and imidazole derivatives. Most of the substrates could

yield the desired products in good-to-excellent yields and stereoselectivities. The applicability of our methodology was demonstrated by synthesizing the glycosylated indirubins, which are potent inhibitors toward various kinases.^[5]

5.4 Experimental section

5.4.1 General Techniques

Unless otherwise specified, all reactions were carried out in oven-dried (>120 °C) glassware equipped with a magnetic stir bar and a rubber septum under a positive pressure of nitrogen or argon. Air- or moisture-sensitive reagents were transferred to the reaction vessel under positive pressure of nitrogen or argon via syringe or stainless steel cannula. Reactions were run at 70 °C unless otherwise noted in the experimental procedure, and reported reaction temperatures refer to the external temperatures measured for the bath in which the reaction vessel was immersed. Heating was obtained through the use of a silicone oil bath. “Concentration” refers to the removal of solvent using a Buchi rotary evaporator equipped with a portable vacuum pump. Removal of residual solvents was accomplished by evacuation of the container for a period of 12-20 hours using a high vacuum line maintained at 0.1-1.0 Torr.

5.4.2 Reagents and Solvents

Unless otherwise specified, all commercial reagents, solvents, and solutions were used without further purification with the following exceptions. Tetrahydrofuran was purified *via* distillation from sodium benzophenone ketyl. Dichloromethane and toluene was purified *via* distillation from calcium hydride.

5.4.3 Chromatography

Analytical thin-layer chromatography (TLC) was performed using Merck 0.25 mm silica gel plates with a 254 nm fluorescent indicator. Plates were developed in a covered chamber visualized with ultraviolet light, followed by staining of the plate with either *p*-anisaldehyde solution, ceric ammonium molybdate solution, or potassium permanganate solution, and heating. The term “flash chromatography” refers to column chromatography using Merck silica gel 60 (230-400 mesh), with a description of the eluent used noted in parenthesis following the description of purification.

5.4.4 Physical and Spectroscopic Data

Proton and Carbon NMR spectra were measured on a Bruker ACF-300, Bruker DPX-400, and Bruker AMX-500 nuclear magnetic resonance spectrometers. ^1H NMR spectra are reported as chemical shifts in parts per million (ppm) as referenced from a residual solvent peak (chloroform: δ 7.26 unless otherwise noted) and coupling constants (J) are reported in Hertz. The reported chemical shifts are tabulated in one of the following format: multiplicity, coupling constant(s), number of protons. Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, td = triplet of doublets, qd = quartet of doublets, m = multiplet. Proton-decoupled ^{13}C NMR spectra are reported as chemical shifts in parts per million (ppm) as referenced to residual solvent peaks (chloroform: δ 77.0). Infrared spectra were measured on a Restige-21 (Shimadzu) Fourier Transform Spectrometer (FT-IR) using material applied as a thin film on a NaCl plate and are reported as wavenumbers (cm^{-1}). Optical rotations were measured at 589 nm (Na-D line) on a Jasco P-2000 digital polarimeter using solutions of chloroform. All values are reported in the following format: $[\alpha]_{\text{D}}$ = specific rotation (concentration of the solution reported in units of 10 mg sample per 1 mL solvent, solvent used). High-resolution mass

spectroscopy (HRMS) services were recorded on a Waters Q-ToF premier™ mass spectrometer.

5.4.5 Procedures

Experimental for preparation of compound 5.1'

DMAP (0.5 equiv.) and DCC (1.3 equiv.) were added to a suspension of picolinic acid (1.1 equiv.) in CH_2Cl_2 (2.0 M) in an ice-water bath. After stirring at 0 °C for 30 min, a solution of ((2*R*,3*S*)-3-acetoxy-6-hydroxy-3,6-dihydro-2*H*-pyran-2-yl)methyl acetate (1.0 equiv.) in CH_2Cl_2 (2.0 M) was added to the mixture. The reaction mixture was stirred at 0 °C for 2 h before dilution with Et_2O and filtration with Celite. After removal of solvent, the residue was purified by flash column chromatography on silica gel with EtOAc /hexane to give compound **5.1'** (α : β = 5.5:1). The α isomer was separated in 81% yield as a yellow solid. m.p. 95-97°C; $[\alpha]_{\text{D}}^{22} = 11.7$ ($c = 1.0$ in CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ 8.82-8.81 (m, 1H), 8.17 (d, $J = 7.8$ Hz, 1H), 7.89 (td, $J = 7.7, 1.7$ Hz, 1H), 7.55-7.51 (m, 1H), 6.65-6.64 (m, 1H), 6.13 (d, $J = 10.0$ Hz, 1H), 6.04 (ddd, $J = 10.2, 2.7, 2.1$ Hz, 1H), 5.49-5.46 (m, 1H), 4.31-4.21 (m, 3H), 2.10 (s, 3H), 2.05 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 170.8, 170.3, 164.0, 150.1, 147.7, 137.1, 131.3, 127.2, 125.5, 125.5, 89.5, 69.2, 64.7, 62.4, 20.9, 20.7 ppm. HRMS (ESI) calcd. for $\text{C}_{16}\text{H}_{17}\text{NO}_7\text{Na}$ [$\text{M}+\text{Na}$]: 358.0903, found: 358.0907.

General procedure for synthesis of *N*-glycosides 5.3a-5.3n

Picolinates **5.1** (0.1 mmol), nucleophiles **5.2** (0.2 mmol), $\text{Pd}(\text{PPh}_3)_4$ (0.01 mmol) and

DPPB (0.02 mmol) were dissolved in THF (3 mL) in a schlenk tube under nitrogen atmosphere. The solution was heated at 70 °C for 12 h. Then THF was removed under reduced pressure and the residue was purified by flash column chromatography to give *N*-glycosides **5.3a-5.3n** in 40% to 98% yields.

General procedure for synthesis of *N*-glycosides **5.3'a-5.3'd**

Picolinate **5.1'** (0.1 mmol), nucleophiles **5.2** (0.2 mmol), $\text{Pd(PPh}_3)_4$ (0.01 mmol) and DPPB (0.02 mmol) were dissolved in THF (3 mL) in a schlenk tube under nitrogen atmosphere. The solution was heated at 70 °C for 12 h. Then THF was removed under reduced pressure and the residue was purified by flash column chromatography to give *N*-glycosides **5.3'a-5.3'd** in 41% to 83% yields.

Synthesis of *N*-glycosides and characterization of new compounds

1-((4*aR*,6*R*,8*aS*)-2-(4-methoxyphenyl)-4,4*a*,6,8*a*-tetrahydropyrano[3,2- d][1,3]dioxin-6-yl)-5-methylindoline-2,3-dione (**5.3a**)

According to the general procedure, the solution of (2*R*,4*aR*,8*S*,8*aS*)-2-(4-methoxyphenyl)-4,4*a*,8,8*a*-tetrahydropyrano[3,2-*d*][1,3]dioxin-8-yl picolinate **5.1a** (36.9 mg, 0.100 mmol), 5-methylindoline-2,3-dione (32.2 mg, 0.200 mmol), $\text{Pd(PPh}_3)_4$ (11.6 mg, 0.0100 mmol) and DPPB (9.5 mg, 0.020 mmol) in THF (3 mL) was stirred at 70 °C for 12 h and then purified by flash column chromatography to give desired product **5.3a** (35.3 mg, 85%, $\beta:\alpha = 8.8:1$) as an orange solid. $^1\text{H NMR}$ (500 MHz, CDCl_3): δ 7.47

(s, 1H), 7.44 (d, $J = 8.7$ Hz, 2H), 7.38 (d, $J = 8.7$ Hz, 1H), 7.02 (d, $J = 8.1$ Hz, 1H), 6.92 (d, $J = 6.9$ Hz, 2H), 6.49-6.47 (m, 1H), 6.39 (d, $J = 10.3$ Hz, 1H), 5.74 (dt, $J = 10.4, 2.0$ Hz, 1H), 5.65 (s, 1H), 4.49-4.47 (m, 1H), 4.31 (dd, $J = 10.4, 4.6$ Hz, 1H), 3.98-3.94 (m, 1H), 3.86-3.82 (m, 4H), 2.35 (s, 3H) ppm; ^{13}C NMR (125 MHz, CDCl_3): δ 182.3, 160.4, 157.8, 146.6, 138.8, 134.2, 133.0, 129.5, 127.5, 126.3, 125.8, 118.0, 113.8, 112.8, 102.3, 74.6, 71.7, 68.7, 55.4, 20.7 ppm. IR (NaCl): 2929, 1737, 1620, 1489, 1089 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{23}\text{H}_{22}\text{NO}_6$ $[\text{M}+\text{H}]$: 408.1447, found: 408.1455.

1-((4aR,6R,8aS)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxin-6-yl)indoline-2,3-dione (5.3b)

According to the general procedure, the solution of (2*R*,4*aR*,8*S*,8*aS*)-2-(4-methoxyphenyl)-4,4*a*,8,8*a*-tetrahydropyrano[3,2-*d*][1,3]dioxin-8-yl picolinate **5.1a** (36.9 mg, 0.100 mmol), indoline-2,3-dione (29.4 mg, 0.200 mmol), $\text{Pd}(\text{PPh}_3)_4$ (11.6 mg, 0.0100 mmol) and DPPB (9.5 mg, 0.020 mmol) in THF (3 mL) was stirred at 70 °C for 12 h and then purified by flash column chromatography to give desired product **5.3b** (22.8 mg, 58%, $\beta:\alpha = 12.3:1$) as an orange solid. ^1H NMR (400 MHz, CDCl_3): δ 7.66, (dd, $J = 7.4, 0.8$ Hz, 1H), 7.58 (td, $J = 7.8, 1.3$ Hz, 1H), 7.46-7.43 (m, 2H), 7.19-7.13 (m, 2H), 6.93-6.89 (m, 2H), 6.51-6.49 (m, 1H), 6.41 (d, $J = 10.3$ Hz, 1H), 5.76 (dt, $J = 10.3, 2.1$ Hz, 1H), 5.65 (s, 1H), 4.51-4.47 (m, 1H), 4.32 (dd, $J = 10.2, 4.5$ Hz, 1H), 4.00-3.94 (m, 1H), 3.88-3.81 (m, 4H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 182.1, 160.3, 157.6, 148.8, 138.3, 133.1, 129.5, 127.5, 126.1, 125.6, 124.3, 117.9, 113.8, 113.0, 102.3, 77.3, 74.5, 71.8, 68.7, 55.3 ppm. IR (NaCl): 2930, 1733, 1622, 1485, 1079 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{22}\text{H}_{20}\text{NO}_6$ $[\text{M}+\text{H}]$: 394.1291, found: 394.1296.

5-isopropyl-1-((4*aR*,6*R*,8*aS*)-2-(4-methoxyphenyl)-4,4*a*,6,8*a*-tetrahydropyrano[3,2-*d*][1,3]dioxin-6-yl)indoline-2,3-dione (5.3c)

According to the general procedure, the solution of

(2*R*,4*aR*,8*S*,8*aS*)-2-(4-methoxyphenyl)-4,4*a*,8,8*a*-

tetrahydropyrano[3,2-*d*][1,3]dioxin-8-yl picolinate **5.1a**

(36.9 mg, 0.100 mmol), 5-isopropylindoline-2,3-dione (37.8 mg, 0.200 mmol), Pd(PPh₃)₄ (11.6 mg, 0.0100 mmol) and DPPB (9.5 mg, 0.020 mmol) in THF (3 mL) was stirred at 70 °C for 12 h and then purified by flash column chromatography to give desired product **5.3c** (28.3 mg, 65%, β : α = 4:1) as an orange oil. ¹H NMR (400 MHz, CDCl₃): δ 7.55 (d, J = 1.8 Hz, 1H), 7.45-7.44 (m, 3H), 7.05 (d, J = 8.2 Hz, 1H), 6.92-6.90 (m, 2H), 6.49-6.48 (m, 1H), 6.39 (d, J = 10.3 Hz, 1H), 5.75 (dt, J = 10.3, 2.2 Hz, 1H), 5.65 (s, 1H), 4.49-4.47 (m, 1H), 4.31 (dd, J = 10.3, 4.6 Hz, 1H), 3.96 (dq, J = 13.2, 4.7 Hz, 1H), 3.86-3.81 (m, 4H), 2.91 (heptet, J = 6.9 Hz, 1H), 1.24 (d, J = 7.0 Hz, 6H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 182.4, 160.3, 157.9, 146.8, 145.4, 136.7, 133.0, 129.5, 127.6, 126.3, 123.4, 118.0, 113.8, 112.9, 102.3, 74.6, 71.7, 68.7, 55.4, 33.5, 23.8 ppm. IR (NaCl): 2940, 1739, 1630, 1486, 1095, 1029, 829 cm⁻¹; HRMS (ESI) calcd. for C₂₂H₂₀NO₆ [M+H]: 394.1291, found: 394.1296.

1-((4*aR*,6*R*,8*aS*)-2-(4-methoxyphenyl)-4,4*a*,6,8*a*-tetrahydropyrano[3,2-*d*][1,3]dioxin-6-yl)-4-methylindoline-2,3-dione (5.3d)

According to the general procedure, the solution of

(2*R*,4*aR*,8*S*,8*aS*)-2-(4-methoxyphenyl)-4,4*a*,8,8*a*-

tetrahydropyrano[3,2-*d*][1,3]dioxin-8-yl picolinate **5.1a**

(36.9 mg, 0.100 mmol), 4-methylindoline-2,3-dione (32.2 mg, 0.200 mmol), Pd(PPh₃)₄ (11.6 mg, 0.0100 mmol) and DPPB (9.5 mg, 0.020 mmol) in THF (3 mL) was stirred at 70 °C for 12 h and then purified by flash column chromatography to give desired product

5.3d (24.9 mg, 61%, $\beta:\alpha = 5.3:1$) as a yellow solid. ^1H NMR (400 MHz, CDCl_3): δ 7.45-7.40 (m, 3H), 6.95-6.90 (m, 4H), 6.50-6.49 (m, 1H), 6.38 (d, $J = 10.3$ Hz, 1H), 5.74 (ddd, $J = 10.3, 2.5, 1.8$ Hz, 1H), 5.65 (s, 1H), 4.50-4.46 (m, 1H), 4.31 (dd, $J = 10.2, 4.5$ Hz, 1H), 3.99-3.93 (m, 1H), 3.87-3.81 (m, 4H), 2.59 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 182.6, 160.3, 157.6, 148.8, 141.6, 137.5, 132.8, 129.5, 127.5, 126.5, 126.4, 116.2, 113.8, 110.2, 102.3, 77.3, 74.6, 71.8, 68.7, 55.3, 18.3 ppm. IR (NaCl): 2932, 1734, 1621, 1476, 1089, 800 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{23}\text{H}_{22}\text{NO}_6$ $[\text{M}+\text{H}]$: 408.1447, found: 408.1442.

1-((2*R*,5*S*,6*R*)-6-(((tert-butyldimethylsilyl)oxy)methyl)-5-((4-methoxybenzyl)oxy)-5,6-dihydro-2H-pyran-2-yl)indoline-2,3-dione (5.3e)

According to the general procedure, the solution of (2*R*,3*S*,4*S*)-2-(((tert-butyldimethylsilyl)oxy)methyl)-3-((4-methoxybenzyl)oxy)-3,4-dihydro-2H-pyran-4-yl picolinate

5.1b (48.6 mg, 0.100 mmol), indoline-2,3-dione (29.4 mg, 0.200 mmol), $\text{Pd}(\text{PPh}_3)_4$ (11.6 mg, 0.0100 mmol) and DPPB (9.5 mg, 0.020 mmol) in THF (3 mL) was stirred at 70 $^\circ\text{C}$ for 12 h and then purified by flash column chromatography to give desired product **5.3e** (41.7 mg, 82%, $\beta:\alpha = 100:0$) as an orange oil; $[\alpha]_{\text{D}}^{22} = +104.5$ ($c = 1.0$ in CHCl_3); ^1H NMR: (400 MHz, CDCl_3): δ 7.62 (dd, $J = 8.0, 1.3$ Hz, 1H), 7.48 (td, $J = 7.8, 1.3$ Hz, 1H), 7.30 (d, $J = 8.6$ Hz, 2H), 7.13-7.11 (m, 2H), 6.93-6.89 (m, 2H), 6.34-6.29 (m, 2H), 5.76 (dt, $J = 10.2, 1.8$ Hz, 1H), 4.63 (dd, $J = 30.1, 11.1$ Hz, 2H), 4.43-4.39 (m, 1H), 3.93 (dd, $J = 11.6, 3.4$ Hz, 1H), 3.85 (dd, $J = 11.5, 1.6$ Hz, 1H), 3.82 (s, 3H), 3.76-3.73 (m, 1H), 0.86 (s, 9H), 0.02 (s, 3H), -0.06 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 182.7, 159.5, 157.5, 149.1, 138.0, 133.1, 130.0, 129.5, 126.1, 125.2, 123.9, 117.8, 114.2, 114.0, 78.9, 76.8, 71.7, 68.4, 61.9, 55.3, 25.9, 18.3, -5.3, -5.4 ppm. IR (NaCl): 3030, 1745, 1611, 1479, 1059, 755 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{28}\text{H}_{35}\text{NO}_6\text{SiNa}$ $[\text{M}+\text{Na}]$: 532.2131,

found: 532.2130.

**1-((4*aR*,6*R*,8*aS*)-2,2-di-tert-butyl-4,4*a*,6,8*a*-tetrahydropyrano[3,2-
d][1,3,2]dioxasilin-6-yl)indoline-2,3-dione (5.3f)**

According to the general procedure, the solution of (4*aR*,8*S*,8*aS*)-2,2-di-tert-butyl-4,4*a*,8,8*a*-tetrahydropyrano[3,2-
d][1,3,2]dioxasilin-8-yl picolinate **5.1c** (39.1 mg, 0.100 mmol), indoline-2,3-dione (29.4 mg, 0.200 mmol), Pd(PPh₃)₄ (11.6 mg, 0.0100 mmol) and DPPB (9.5 mg, 0.020 mmol) in THF (3 mL) was stirred at 70 °C for 12 h and then purified by flash column chromatography to give desired product **5.3f** (29.9 mg, 72%, $\beta:\alpha = 100:0$) as a yellow solid. m.p. 158-160 °C; $[\alpha]_D^{22} = +70.1$ ($c = 1.0$ in CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.64 (dd, $J = 7.5, 0.9$ Hz, 1H), 7.56 (td, $J = 7.8, 1.3$ Hz, 1H), 7.15 (t, $J = 7.5$ Hz, 1H), 7.09 (d, $J = 8.0$ Hz, 1H), 6.42 (dd, $J = 4.3, 2.4$ Hz, 1H), 6.3 (dt, $J = 10.3, 1.7$ Hz, 1H), 5.70 (dt, $J = 10.3, 2.0$ Hz, 1H), 4.67-4.63 (m, 1H), 4.20 (dd, $J = 8.8, 3.8$ Hz, 1H), 3.94-3.85 (m, 2H), 1.09 (s, 9H), 1.02 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 182.2, 157.6, 148.8, 138.3, 136.3, 125.5, 124.7, 124.2, 117.9, 113.3, 75.5, 69.7, 66.4, 27.4, 27.0, 22.7, 20.1 ppm. IR (NaCl): 3034, 1755, 1639, 1489, 1261, 1087, 689 cm⁻¹; HRMS (ESI) calcd. for C₂₂H₂₉NO₅SiNa [M+Na]: 438.1713, found: 438.1695.

**1-((2*R*,5*S*,6*R*)-5-(benzyloxy)-6-((benzyloxy)methyl)-5,6-dihydro-2H-pyran-2-
yl)indoline-2,3-dione (5.3g)**

according to the general procedure, the solution of (2*R*,3*S*,4*S*)-
3-(benzyloxy)-2-((benzyloxy)methyl)-3,4-dihydro-2H-pyran-
4-yl picolinate **5.1d** (43.1 mg, 0.100 mmol), indoline-2,3-dione (29.4 mg, 0.200 mmol), Pd(PPh₃)₄ (11.6 mg, 0.0100 mmol) and DPPB (9.5 mg, 0.020 mmol) in THF (3 mL) was stirred at 70 °C for 12 h and then purified by flash column

chromatography to give desired product **5.3g** (36.0 mg, 79%, $\beta:\alpha = 100:0$) as an orange oil; $[\alpha]_D^{22} = +107.1$ ($c = 1.0$ in CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.63 (dq, $J = 7.4$, 0.6 Hz, 1H), 7.51-7.46 (m, 1H), 7.37-7.27 (m, 10H), 7.15-7.10 (m, 2H), 6.38-6.32 (m, 2H), 5.81 (dt, $J = 10.2$, 1.8 Hz, 1H), 4.69 (d, $J = 11.4$ Hz, 1H), 4.59 (d, $J = 12.3$ Hz, 1H), 4.56 (d, $J = 11.8$ Hz, 1H), 4.47 (d, $J = 12.0$ Hz, 1H), 4.39 (ddd, $J = 8.7$, 4.6, 2.0 Hz, 1H), 3.93 (ddd, $J = 8.8$, 4.0, 2.1 Hz, 1H), 3.83 (dd, $J = 11.1$, 4.1 Hz, 1H), 3.76 (dd, $J = 11.1$, 2.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 182.6, 157.4, 149.0, 138.2, 138.1, 137.7, 132.7, 128.5, 128.3, 128.0, 127.9, 127.7, 127.6, 126.4, 125.3, 124.0, 117.9, 113.9, 78.0, 76.8, 73.5, 71.9, 69.3, 68.8 ppm. IR (NaCl): 3030, 2922, 2868, 1741, 1614, 1469, 1350, 1292, 1095, 752, 698 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{28}\text{H}_{26}\text{NO}_5$ $[\text{M}+\text{H}]$: 456.1811, found: 456.1813.

1-((4aR,6R,8aS)-2,2-dimethyl-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxin-6-yl)indoline-2,3-dione (5.3h)

According to the general procedure, the solution of (4aR,8S,8aS)-2,2-dimethyl-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3]dioxin-8-yl picolinate **5.1g** (29.1 mg, 0.100 mmol), indoline-2,3-dione (29.4 mg, 0.200 mmol), $\text{Pd}(\text{PPh}_3)_4$ (11.6 mg, 0.0100 mmol) and DPPB (9.5 mg, 0.020 mmol) in THF (3 mL) was stirred at 70 °C for 12 h and then purified by flash column chromatography to give desired product **5.3h** (12.6 mg, 40%, $\beta:\alpha = 100:0$) as an orange oil; $[\alpha]_D^{22} = +117.9$ ($c = 1.0$ in CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ 7.65 (dd, $J = 7.5$, 0.8 Hz, 1H), 7.58 (td, $J = 7.8$, 1.4 Hz, 1H), 7.16 (td, $J = 7.6$, 0.6 Hz, 1H), 7.12 (d, $J = 8.0$ Hz, 1H), 6.46-6.44 (m, 1H), 6.25 (d, $J = 10.3$, 1H), 5.71 (ddd, $J = 10.3$, 2.6, 1.9 Hz, 1H), 4.33-4.30 (m, 1H), 3.93 (dd, $J = 9.3$, 4.0 Hz, 1H), 3.86-3.75 (m, 2H), 1.59 (s, 3H), 1.47 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 182.1, 157.6, 148.8, 138.3, 133.7, 125.9, 125.6, 124.2, 117.9, 113.0, 100.3, 72.9, 67.2, 62.4, 29.1, 19.2 ppm. IR (NaCl):

2930, 2866, 1733, 1514, 1476, 1108, 921, 745, 723 cm^{-1} ; HRMS (ESI) calcd. For $\text{C}_{17}\text{H}_{17}\text{NO}_5\text{Na}$ [$\text{M}+\text{Na}$]: 338.1004, found: 338.0996.

1-((4a'*R*,6'*R*,8a'*S*)-4',4a',6',8a'-tetrahydrospiro[cyclohexane-1,2'-pyrano[3,2-d][1,3]dioxin]-6'-yl)indoline-2,3-dione (5.3i)

According to the general procedure, the solution of (4a'*R*,8'*S*,8a'*S*)-4',4a',8',8a'-tetrahydrospiro[cyclohexane-1,2'-pyrano[3,2-d][1,3]dioxin]-8'-yl picolinate **5.1f** (33.1 mg, 0.100 mmol), indoline-2,3-dione (29.4 mg, 0.200 mmol), $\text{Pd}(\text{PPh}_3)_4$ (11.6 mg, 0.0100 mmol) and DPPB (9.5 mg, 0.020 mmol) in THF (3 mL) was stirred at 70 °C for 12 h and then purified by flash column chromatography to give desired product **5.3i** (27.8 mg, 78%, $\beta:\alpha = 100:0$) as a yellow solid. m.p. 178-180 °C; $[\alpha]_{\text{D}}^{22} = +96.1$ ($c = 1.0$ in CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ 7.65 (dd, $J = 7.8, 0.8$ Hz, 1H), 7.58 (td, $J = 7.8, 1.8$ Hz, 1H), 7.16 (td, $J = 7.6, 0.6$ Hz, 1H), 7.11 (d, $J = 8.0$ Hz, 1H), 6.45-6.44 (m, 1H), 6.27 (d, $J = 10.3$ Hz, 1H), 5.70 (ddd, $J = 10.3, 2.6, 1.8$ Hz, 1H), 4.56-4.53 (m, 1H), 3.92 (dd, $J = 9.3, 4.0$ Hz, 1H), 3.86-3.76 (m, 2H), 2.10-2.03 (m, 1H), 1.97-1.96 (m, 1H), 1.69-1.41 (m, 8H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 182.2, 157.6, 148.8, 138.3, 134.0, 125.8, 125.5, 124.2, 117.9, 113.1, 100.5, 73.1, 66.3, 61.7, 38.0, 27.8, 25.6, 22.7, 22.6 ppm. IR (NaCl): 2937, 2858, 1745, 1614, 1469, 1099, 925, 754, 734 cm^{-1} ; HRMS (ESI) calcd. For $\text{C}_{20}\text{H}_{22}\text{NO}_5$ [$\text{M}+\text{H}$]: 356.1498, found: 356.1498.

1-((4a*R*,6*R*,8a*S*)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxin-6-yl)-1*H*-imidazole (5.3j)

According to the general procedure, the solution of
(2*R*,4*aR*,8*S*,8*aS*)-2-(4-methoxyphenyl)-4,4*a*,8,8*a*-
tetrahydropyrano[3,2-*d*][1,3]dioxin-8-yl picolinate **5.1a**

(36.9 mg, 0.100 mmol), imidazole (13.6 mg, 0.200 mmol), Pd(PPh₃)₄ (11.6 mg, 0.0100 mmol) and DPPB (9.5 mg, 0.020 mmol) in THF (3 mL) was stirred at 70 °C for 12 h and then purified by flash column chromatography to give desired product **5.3j** (23.6 mg, 75%, $\beta:\alpha = 8:1$) as a white solid. m.p. 160-162 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.67 (s, 1H), 7.46-7.41 (m, 2H), 7.10(s, 1H), 7.04 (s, 1H), 6.94-6.88 (m, 2H), 6.38 (d, $J = 10.2$ Hz, 1H), 6.18-6.14 (m, 1H), 5.88 (ddd, $J = 10.2, 2.4, 1.9$ Hz, 1H), 5.60 (s, 1H), 4.44-4.38 (m, 1H), 4.29 (dd, $J = 10.0, 4.2$ Hz, 1H), 3.94-3.87 (m, 1H), 3.86-3.79 (m, 4H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 160.3, 136.5, 132.8, 130.0, 129.4, 127.5, 125.6, 117.3, 113.7, 102.2, 81.1, 74.1, 71.6, 68.7, 55.3 ppm; IR (NaCl): 2941, 2881, 1614, 1517, 1249, 1095 cm⁻¹; HRMS (ESI) calcd. for C₁₇H₁₉O₄N₂ [M+H]: 315.1345; found: 315.1345.

**1-((4*aR*,6*R*,8*aS*)-2-(4-methoxyphenyl)-4,4*a*,6,8*a*-tetrahydropyrano[3,2-
d][1,3]dioxin-6-yl)-2-methyl-1*H*-imidazole (5.3k)**

According to the general procedure, the solution of
(2*R*,4*aR*,8*S*,8*aS*)-2-(4-methoxyphenyl)-4,4*a*,8,8*a*-
tetrahydropyrano[3,2-*d*][1,3]dioxin-8-yl picolinate **5.1a** (36.9

mg, 0.100 mmol), 2-methylimidazole (16.4 mg, 0.200 mmol), Pd(PPh₃)₄ (11.6 mg, 0.0100 mmol) and DPPB (9.5 mg, 0.020 mmol) in THF (3 mL) was stirred at 70 °C for 12 h and then purified by flash column chromatography to give desired product **5.3k** (28.9 mg, 88%, $\beta:\alpha = 12.4:1$) as a white solid. m.p. 136-138 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.46-7.41 (m, 2H), 6.93-6.88 (m, 4H), 6.35 (d, $J = 10.3$ Hz, 1H), 6.12-6.08

(m, 1H), 5.77 (ddd, $J = 10.3, 2.4, 2.0$ Hz, 1H), 5.59 (s, 1H), 4.42-4.36 (m, 1H), 4.28 (dd, $J = 10.0, 4.2$ Hz, 1H), 3.90 (ddd, $J = 10.3, 8.4, 4.4$ Hz, 1H), 3.86-3.78 (m, 4H), 2.46 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): 160.2, 145.1, 132.2, 129.4, 127.5, 127.4, 125.8, 116.7, 113.6, 102.0, 80.1, 74.1, 71.5, 68.6, 55.2, 13.1 ppm; IR (NaCl): 2970, 2933, 2879, 1614, 1517, 1417, 1249, 1092 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{21}\text{O}_4\text{N}_2$ $[\text{M}+\text{H}]$: 329.1501; found: 329.1501.

**1-((4*aR*,6*R*,8*aS*)-2-(4-methoxyphenyl)-4,4*a*,6,8*a*-tetrahydropyrano[3,2-
d][1,3]dioxin-6-yl)-4,5-diphenyl-1*H*-imidazole (5.3l)**

According to the general procedure, the solution of (2*R*,4*aR*,8*S*,8*aS*)-2-(4-methoxyphenyl)-4,4*a*,8,8*a*-tetrahydropyrano[3,2-*d*][1,3]dioxin-8-yl picolinate **5.1a** (36.9 mg, 0.100 mmol), 4,5-diphenylimidazole (44.1 mg, 0.200 mmol), $\text{Pd}(\text{PPh}_3)_4$ (11.6 mg, 0.0100 mmol) and DPPB (9.5 mg, 0.020 mmol) in THF (3 mL) was stirred at 70 °C for 12 h and then purified by flash column chromatography to give desired product **5.3l** (32.2 mg, 69%, $\beta:\alpha = 100:0$) as a yellow solid. m.p. 189-191 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.76 (s, 1H), 7.49-7.38 (m, 9H), 7.23-7.12 (m, 3H), 6.91-6.86 (m, 2H), 6.27 (d, $J = 10.2$ Hz, 1H), 5.88-5.84 (m, 1H), 5.76 (dt, $J = 10.2, 2.2$ Hz, 1H), 5.56 (s, 1H), 4.33-4.28 (m, 1H), 4.26 (dd, $J = 9.6, 3.8$ Hz, 1H), 3.86-3.73 (m, 5H) ppm; ^{13}C NMR (100 MHz, CDCl_3): 160.2, 138.6, 135.3, 134.1, 132.4, 131.2, 129.8, 129.5, 128.9(2C), 128.1(2C), 127.5, 126.8, 126.6, 125.8, 113.7, 102.1, 79.5, 74.1, 71.6, 68.7, 55.3 ppm; IR (NaCl): 2983, 2940, 2874, 1620, 1523, 1467, 1253, 1100 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{29}\text{H}_{27}\text{O}_4\text{N}_2$ $[\text{M}+\text{H}]$: 467.1971; found: 467.1973.

1-((4*aR*,6*R*,8*aS*)-2-(4-methoxyphenyl)-4,4*a*,6,8*a*-tetrahydropyrano[3,2-d][1,3]dioxin-6-yl)-1*H*-benzo[d]imidazole (5.3m)

According to the general procedure, the solution of (2*R*,4*aR*,8*S*,8*aS*)-2-(4-methoxyphenyl)-4,4*a*,8,8*a*-tetrahydropyrano[3,2-d][1,3]dioxin-8-yl picolinate **5.1a** (36.9 mg, 0.100 mmol), benzimidazole (23.6 mg, 0.200 mmol), Pd(PPh₃)₄ (11.6 mg, 0.0100 mmol) and DPPB (9.5 mg, 0.020 mmol) in THF (3 mL) was stirred at 70 °C for 12 h and then purified by flash column chromatography to give desired product **5.3m** (35.7 mg, 98%, $\beta:\alpha = 36:1$) as a white solid. ¹H NMR (400 MHz, CDCl₃): δ 7.89-7.76 (m, 1H), 7.58-7.48 (m, 1H), 7.48-7.40 (m, 2H), 7.36-7.27 (m, 2H), 6.95-6.88 (m, 2H), 6.50-6.41 (m, 2H), 5.95-5.86 (m, 1H), 5.63 (s, 1H), 4.54-4.47 (m, 1H), 8.40-7.92 (m, 1H), 4.30 (dd, $J = 10.4, 4.6$ Hz, 1H), 4.00 (ddd, $J = 10.2, 8.6, 4.7$ Hz, 1H), 3.87-3.77 (m, 4H) ppm; ¹³C NMR (100 MHz, CDCl₃): 160.3, 133.2, 129.5, 127.5, 125.6, 123.5, 122.9, 120.7, 113.7, 110.7, 102.2, 80.5, 74.3, 71.7, 68.7, 55.3 ppm; IR (NaCl): 2968, 2937, 2871, 1615, 1520, 1466, 1254, 1095 cm⁻¹; HRMS (ESI) calcd. for C₂₁H₂₁N₂O₄ [M+H]: 365.1501, found: 365.1497.

1-((4*aR*,6*R*,8*aS*)-2-(4-methoxyphenyl)-4,4*a*,6,8*a*-tetrahydropyrano[3,2-d][1,3]dioxin-6-yl)-1*H*-pyrazole (5.3n)

According to the general procedure, the solution of (2*R*,4*aR*,8*S*,8*aS*)-2-(4-methoxyphenyl)-4,4*a*,8,8*a*-tetrahydropyrano[3,2-d][1,3]dioxin-8-yl picolinate **5.1a** (36.9 mg, 0.100 mmol), 1*H*-pyrazole (13.6 mg, 0.200 mmol), Pd(PPh₃)₄ (11.6 mg, 0.0100 mmol) and DPPB (9.5 mg, 0.020 mmol) in THF (3 mL) was stirred at 70 °C for 12 h and then purified by flash column chromatography to give desired product **5.3n**

(28.9 mg, 92%, $\beta:\alpha = 100:0$) as a white solid. m.p. 155-157 °C; $[\alpha]_D^{22} = +82.7$ ($c = 1.0$ in CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ 7.62 (d, $J = 1.48$ Hz, 1H), 7.58 (d, $J = 2.4$ Hz, 1H), 7.44 (d, $J = 8.7$ Hz, 2H), 6.92-6.89 (m, 2H), 6.39-6.34 (m, 3H), 5.93-5.89 (m, 1H), 5.59 (s, 1H), 4.46-4.43 (m, 1H), 4.30 (dd, $J = 10.1, 4.4$ Hz, 1H), 3.95 (ddd, $J = 12.9, 8.5, 4.5$ Hz, 1H), 3.87-3.80 (m, 4H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 160.3, 140.8, 132.3, 129.7, 128.3, 127.5, 125.7, 113.8, 107.0, 102.2, 85.1, 74.3, 71.6, 68.8, 55.3 ppm. IR (NaCl): 2922, 2852, 2353, 1517 1384, 1253, 1095, 1033, 819, 761 cm^{-1} ; HRMS (ESI) calcd. For $\text{C}_{17}\text{H}_{19}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]$: 315.1345, found: 315.1349.

((2R,3S,6S)-3-acetoxy-6-(2,3-dioxindolin-1-yl)-3,6-dihydro-2H-pyran-2-yl)methyl acetate (5.3'a)

According to the general procedure, the solution of (2R,3S,4S)-3-acetoxy-2-(acetoxymethyl)-3,4-dihydro-2H-pyran-4-yl picolinate **5.1'** (33.5 mg, 0.100 mmol), indoline-2,3-dione (29.4 mg, 0.200 mmol), $\text{Pd}(\text{PPh}_3)_4$ (11.6 mg, 0.0100 mmol) and DPPB (9.5 mg, 0.020 mmol) in THF (3 mL) was stirred at 70 °C for 12 h and then purified by flash column chromatography to give desired product **5.3'a** (15.5 mg, 43%, $\alpha:\beta = 100:0$) as an orange oil; $[\alpha]_D^{22} = +23.0$ ($c = 1.0$ in CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.66 (dd, $J = 7.5, 0.9$ Hz, 1H), 7.60 (td, $J = 8.0, 1.4$ Hz, 1H), 7.34 (d, $J = 8.1$ Hz, 1H), 7.18 (td, $J = 7.6, 0.6$ Hz, 1H), 6.22 (ddd, $J = 18.3, 2.9, 2.0$ Hz, 1H), 6.16 (ddd, $J = 10.3, 2.2, 1.4$ Hz, 1H), 6.00 (q, $J = 2.1$ Hz, 1H), 5.32-5.29 (m, 1H), 4.37-4.32 (m, 1H), 4.19-4.14 (m, 2H), 2.14 (s, 3H), 2.01 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 182.3, 170.6, 170.2, 157.8, 150.1, 138.4, 128.6, 126.9, 125.5, 124.3, 117.9, 112.8, 74.7, 71.6, 64.1, 62.1, 21.0, 20.7 ppm. IR (NaCl): 3025, 1741, 1729, 1689, 1622, 1431, 1323, 1283, 1089, 752 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{18}\text{NO}_7$ $[\text{M}+\text{H}]$: 360.1083, found: 360.1088.

((2R,3S,6S)-3-acetoxy-6-(5-methyl-2,3-dioxindolin-1-yl)-3,6-dihydro-2H-pyran-2-yl)methyl acetate (5.3'b)

According to the general procedure, the solution of (2R,3S,4S)-3-acetoxy-2-(acetoxymethyl)-3,4-dihydro-2H-pyran-4-yl picolinate **5.1'** (33.5 mg, 0.100 mmol), 5-methylindoline-2,3-dione (32.2 mg, 0.200 mmol), Pd(PPh₃)₄ (11.6 mg, 0.0100 mmol) and DPPB (9.5 mg, 0.020 mmol) in THF (3 mL) was stirred at 70 °C for 12 h and then purified by flash column chromatography to give desired product **5.3'b** (15.3 mg, 41%, $\alpha:\beta = 100:0$) as an orange oil; $[\alpha]_D^{22} = +10.9$ ($c = 1.0$ in CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 7.46 (s, 1H), 7.40 (dd, $J = 8.2, 1.2$ Hz, 1H), 7.22 (d, $J = 8.2$ Hz, 1H), 6.21 (ddd, $J = 10.3, 2.9, 2.0$ Hz, 1H), 6.14 (ddd, $J = 10.3, 2.2, 1.4$ Hz, 1H), 5.98 (q, $J = 2.1$ Hz, 1H), 5.32-5.29 (m, 1H), 4.36-4.31 (m, 1H), 4.19-4.13 (m, 2H), 2.34 (s, 3H), 2.14 (s, 3H), 2.02 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 182.5, 170.6, 170.2, 158.0, 148.0, 138.9, 134.1, 128.6, 127.0, 125.7, 117.9, 112.6, 74.7, 71.6, 64.2, 62.1, 21.0, 20.7, 20.6 ppm. IR (NaCl): 2926, 1737, 1622, 1489, 1371, 1230, 1026 cm⁻¹; HRMS (ESI) calcd. For C₁₉H₁₉NO₇Na [M+Na]: 396.1059, found: 396.1065.

((2R,3S,6S)-3-acetoxy-6-(1,3-dioxoisindolin-2-yl)-3,6-dihydro-2H-pyran-2-yl)methyl acetate (5.3'c)

According to the general procedure, the solution of (2R,3S,4S)-3-acetoxy-2-(acetoxymethyl)-3,4-dihydro-2H-pyran-4-yl picolinate **5.1'** (33.5 mg, 0.100 mmol), isoindoline-1,3-dione (29.4 mg, 0.200 mmol), Pd(PPh₃)₄ (11.6 mg, 0.0100 mmol) and DPPB (9.5 mg, 0.020 mmol) in THF (3 mL) was stirred at 70 °C for 12 h and then purified by flash column chromatography to give desired product **5.3'c** (29.8 mg, 83%, $\alpha:\beta = 100:0$) as a white solid. m.p. 134-136 °C; $[\alpha]_D^{22} = -70.9$ ($c = 1.0$ in CHCl₃); ¹H NMR (400 MHz, CDCl₃):

δ 7.90 (dd, $J = 5.5, 3.1$ Hz, 2H), 7.78 (dd, $J = 5.5, 3.1$ Hz, 2H), 6.16-6.13 (m, 2H), 5.89-5.85 (m, 1H), 5.42 (dq, $J = 9.0, 2.1$ Hz, 1H), 4.38 (ddd, $J = 8.9, 4.4, 2.6$ Hz, 1H), 4.26 (dd, $J = 12.3, 4.5$ Hz, 1H), 4.16 (dd, $J = 12.3, 2.5$ Hz, 1H), 2.13 (s, 3H), 2.06 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 170.8, 170.4, 167.8, 134.6, 131.7, 129.6, 125.1, 123.8, 72.2, 70.5, 64.7, 62.7, 21.1, 20.8 ppm. IR (NaCl): 2926, 1722, 1371, 1238, 723 cm^{-1} ; HRMS (ESI) calcd. For $\text{C}_{18}\text{H}_{18}\text{NO}_7$ [$\text{M}+\text{H}$]: 360.1083, found: 360.1085.

((2*R*, 3*S*, 6*S*)-3-acetoxy-6-(2-phenyl-1*H*-imidazol-1-yl)-3,6-dihydro-2*H*-pyran-2-yl)methyl acetate (5.3'd**)**

According to the general procedure, the solution of (2*R*,3*S*,4*S*)-3-acetoxy-2-(acetoxymethyl)-3,4-dihydro-2*H*-pyran-4-yl picolinate **5.1'** (32.2 mg, 0.100 mmol), 2-phenyl-1*H*-imidazole (28.8 mg, 0.200 mmol), $\text{Pd}(\text{PPh}_3)_4$ (11.6 mg, 0.0100 mmol) and DPPB (9.5 mg, 0.020 mmol) in THF (3 mL) was stirred at 70 °C for 12 h and then purified by flash column chromatography to give desired product **5.3'd** (16.8 mg, 47%, $\alpha:\beta = 100:0$) as a colourless oil; $[\alpha]_{\text{D}}^{22} = +135.0$ ($c = 1.0$ in CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ 7.83 (dd, $J = 8.1, 1.7$ Hz, 2H), 7.44-7.50 (m, 3H), 7.24 (d, $J = 1.2$ Hz, 1H), 7.15 (d, $J = 0.9$ Hz, 1H), 6.19 (dt, $J = 10.6, 1.7$ Hz, 1H), 6.00 (m, 1H), 5.95 (ddd, $J = 10.1, 3.0, 1.9$ Hz, 1H), 5.40 (dq, $J = 9.2, 1.8$ Hz, 1H), 4.30 (dd, $J = 12.2, 5.8$ Hz, 1H), 4.19 (dd, $J = 12.2, 2.5$ Hz, 1H), 4.10 (dq, $J = 11.7, 2.6$ Hz, 1H), 2.15 (s, 3H), 2.04 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 170.7, 170.1, 130.6, 130.0, 129.3, 129.1, 128.7, 128.4, 126.0, 119.5, 76.4, 68.6, 64.7, 62.7, 21.0, 20.8 ppm. IR (NaCl): 2926, 1725, 1430, 1321, 698 cm^{-1} ; HRMS (ESI) calcd. For $\text{C}_{19}\text{H}_{21}\text{N}_2\text{O}_5$ [$\text{M}+\text{H}$]: 357.1450, found: 357.1445.

General procedure for synthesis of indirubin *N*-glycosides **5.4a-5.4c**

The solution of the glycosyl isatine (1.0 equiv), indoxyl acetate (1.2 equiv) and sodium carbonate (2.0-4.0 equiv) was stirred under argon atmosphere for 4 h at room temperature.^[1] The colour of the solution changed from red to violet. The mixture was concentrated under reduced pressure. Column chromatography of the residue gave the indirubin glycosides as violet solid or oil.

(*Z*)-1'-((4*aR*,6*R*,8*aS*)-2-(4-methoxyphenyl)-4,4*a*,6,8*a*-tetrahydropyrano[3,2-*d*][1,3]dioxin-6-yl)-[2,3'-biindolinylidene]-2',3-dione (**5.4a**)

According to general procedure, the solution of glycosyl isatine **5.3b** (20.0 mg, 0.0510 mmol), indoxyl acetate (10.0 mg, 0.0610 mmol), and sodium carbonate (13.0 mg, 0.100 mmol) in MeOH (3 mL) was stirred under argon atmosphere at rt for 4 h and then purified by flash column chromatography to give desired product **5.4a** (18.6

mg, 72%) as a violet solid. m.p. 189-191 °C; $[\alpha]_D^{22} = -289.8$ ($c = 1.0$ in CHCl_3); ^1H NMR (500 MHz, CDCl_3): δ 10.52 (s, 1H), 8.95 (d, $J = 7.6$ Hz, 1H), 7.75 (d, $J = 7.5$ Hz, 1H), 7.54-7.50 (m, 1H), 7.46 (d, $J = 8.7$ Hz, 2H), 7.31-7.26 (m, 1H), 7.19-7.12 (m, 2H), 7.03 (dd, $J = 7.5, 13.8$ Hz, 2H), 6.94-6.91 (m, 2H), 6.63 (dd, $J = 2.4, 5.1$ Hz, 1H), 6.38 (d, $J = 10.3$ Hz, 1H), 5.79 (dt, $J = 10.3, 2.1$ Hz, 1H), 5.67 (s, 1H), 4.55 (t, $J = 3.6$ Hz, 1H), 4.34 (dd, $J = 10.3, 4.6$ Hz, 1H), 4.06-4.01 (m, 1H), 3.90-3.85 (m, 1H), 3.82 (s, 3H) ppm; ^{13}C NMR (125 MHz, CDCl_3): δ 188.1, 170.5, 160.3, 151.5, 139.9, 138.8, 137.0, 131.9, 129.6, 128.9, 127.6, 127.2, 125.5, 125.4, 123.2, 121.9, 121.5, 120.0, 113.8, 112.0, 110.7, 105.8, 102.3, 74.8, 71.7, 68.9, 55.4 ppm. IR (NaCl): 2920, 2867, 1656, 1453, 1322, 1090, 997 cm^{-1} ; HRMS (ESI) calcd. For $\text{C}_{30}\text{H}_{25}\text{N}_2\text{O}_6$ $[\text{M}+\text{H}]$: 509.1713, found: 509.1687.

(Z)-1'-((2R,5S,6R)-5-(benzyloxy)-6-((benzyloxy)methyl)-5,6-dihydro-2H-pyran-2-yl)-[2,3'-biindolinylidene]-2',3-dione (5.4b)

According to general procedure, the solution of glycosyl isatine **5.3g** (30.0 mg, 0.0660 mmol), indoxyl acetate (14.1 mg, 0.0790 mmol), and sodium carbonate (14.0 mg, 0.132 mmol) in MeOH (3 mL) was stirred under argon atmosphere at rt for 4 h and then

purified by flash column chromatography to give desired product **5.4b** (25.1 mg, 75%) as a violet solid. m.p. 193-195 °C; $[\alpha]_D^{22} = +41.5$ ($c = 1.0$ in CHCl_3); ^1H NMR (500 MHz, CDCl_3): δ 10.52 (s, 1H), 8.92 (d, $J = 7.7$ Hz, 1H), 7.74 (d, $J = 7.4$ Hz, 1H), 7.51 (t, $J = 7.6$ Hz, 1H), 7.36-7.21 (m, 11H), 7.15-7.12 (m, 2H), 7.04-6.99 (m, 2H), 6.49 (s, 1H), 6.31 (d, $J = 10.2$ Hz, 1H), 5.85 (d, $J = 10.2$ Hz, 1H), 4.71 (d, $J = 11.4$ Hz, 1H), 4.61-4.57 (m, 2H), 4.49 (d, $J = 12.1$ Hz, 1H), 4.40 (d, $J = 7.8$ Hz, 1H), 4.00 (m, 1H), 3.85-3.78 (m, 2H) ppm; ^{13}C NMR (125 MHz, CDCl_3): δ 188.2, 170.3, 151.5, 139.6, 139.2, 138.3, 137.8, 137.0, 131.4, 129.0, 128.5, 128.3, 128.0, 127.9, 127.8, 127.7, 127.6, 125.4, 125.3, 122.9, 121.7, 121.4, 120.1, 111.9, 111.4, 106.3, 78.2, 76.5, 73.5, 71.7, 69.8, 69.2 ppm. IR (NaCl): 2922, 2856, 1668, 1606, 1463, 1317, 1203, 1093, 1041 cm^{-1} ; HRMS (ESI) calcd. For $\text{C}_{36}\text{H}_{30}\text{N}_2\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]$: 593.2052, found: 593.2079.

(Z)-1'-((2S, 5S, 6R)-5-hydroxy-6-(hydroxymethyl)-5,6-dihydro-2H-pyran-2-yl)-5'-methyl-[2,3'-biindolinylidene]-2',3-dione (5.4c)

According to general procedure, the solution of glycosyl isatine **5.3'b** (20.0 mg, 0.0540 mmol), indoxyl acetate (11.0 mg, 0.0640 mmol), and sodium carbonate (22.9 mg, 0.216 mmol) in MeOH (3 mL) was stirred under argon atmosphere at rt for 4 h and then

purified by flash column chromatography to give desired product **5.4c** (15.9 mg, 73%) as a violet oil. $[\alpha]_D^{22} = -652.3$ ($c = 1.0$ in CHCl_3); ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ

11.14 (s, 1H), 8.72 (s, 1H), 7.65 (d, $J = 7.5$ Hz, 1H), 7.58 (t, $J = 7.1$ Hz, 1H), 7.42 (d, $J = 8.0$ Hz, 1H), 7.33 (d, $J = 8.1$ Hz, 1H), 7.10 (d, $J = 7.8$ Hz, 1H), 7.04 (t, $J = 7.4$ Hz, 1H), 6.18-6.12 (m, 2H), 5.99-5.96 (m, 1H), 5.29 (d, $J = 5.8$ Hz, 1H), 4.62 (t, $J = 5.5$ Hz, 1H), 4.04-4.02 (m, 1H), 3.65-3.62 (m, 2H), 3.52-3.46 (m, 1H), 2.34 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO): δ 188.9, 170.1, 152.9, 139.3, 139.2, 137.7, 134.7, 131.2, 129.8, 125.4, 124.9, 121.9, 121.6, 119.5, 114.0, 111.1, 105.8, 77.1, 73.8, 62.2, 61.4, 21.5 ppm. IR (NaCl): 2930, 2873, 1676, 1429, 1287, 1203, 1022 cm^{-1} ; HRMS (ESI) calcd. For $\text{C}_{23}\text{H}_{20}\text{N}_2\text{O}_5\text{Na}$ [$\text{M}+\text{Na}$]: 427.1270, found: 427.1265.

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X-ray structure of compound 5.3a (CCDC number 1016860)

Table 1. Sample and crystal data for compound 5.3a.

Identification code	liu125s
Chemical formula	C ₂₃ H ₂₁ NO ₆
Formula weight	407.41
Temperature	103(2) K
Wavelength	0.71073 Å
Crystal size	0.240 x 0.340 x 0.360 mm
Crystal habit	orange block
Crystal system	monoclinic
Space group	P 1 21 1
Unit cell dimensions	a = 8.0658(10) Å b = 6.9998(8) Å c = 17.278(3) Å
	$\alpha = 90^\circ$ $\beta = 90.698(6)^\circ$ $\gamma = 90^\circ$
Volume	975.4(2) Å ³
Z	2
Density (calculated)	1.387 g/cm ³
Absorption coefficient	0.101 mm ⁻¹
F(000)	428

Table 2. Data collection and structure refinement for compound 5.3a.

Theta range for data collection	2.36 to 28.33°
Index ranges	-10 ≤ h ≤ 10, -9 ≤ k ≤ 9, -19 ≤ l ≤ 23
Reflections collected	11817
Independent reflections	4748 [R(int) = 0.0285]
Coverage of independent reflections	99.8%
Absorption correction	multi-scan
Max. and min. transmission	0.9760 and 0.9650
Refinement method	Full-matrix least-squares on F ²
Refinement program	SHELXL-2013 (Sheldrick, 2013)
Function minimized	$\sum w(F_o^2 - F_c^2)^2$
Data / restraints / parameters	4748 / 1 / 273
Goodness-of-fit on F ²	1.057
Final R indices	4243 data; I > 2σ(I) R1 = 0.0402, wR2 = 0.1040 all data R1 = 0.0471, wR2 = 0.1137
Weighting scheme	w = 1/[σ ² (F _o ²) + (0.0714P) ² + 0.0281P] where P = (F _o ² + 2F _c ²)/3
Absolute structure parameter	0.2(5)
Largest diff. peak and hole	0.281 and -0.252 eÅ ⁻³
R.M.S. deviation from mean	0.063 eÅ ⁻³

X-ray structure of compound 5.1' (CCDC number 1047594)

Table 1. Sample and crystal data for liu135.

Identification code	liu135
Chemical formula	C ₁₆ H ₁₇ NO ₇
Formula weight	335.30 g/mol
Temperature	296(2) K
Wavelength	0.71073 Å
Crystal size	0.020 x 0.020 x 0.300 mm
Crystal habit	colorless needle
Crystal system	orthorhombic
Space group	P 21 21 21
Unit cell dimensions	a = 5.4622(9) Å b = 14.704(3) Å c = 20.875(4) Å
Volume	1676.6(5) Å ³
Z	4
Density (calculated)	1.328 g/cm ³
Absorption coefficient	0.105 mm ⁻¹
F(000)	704

$$\begin{aligned} \alpha &= 90^\circ \\ \beta &= 90^\circ \\ \gamma &= 90^\circ \end{aligned}$$

Table 2. Data collection and structure refinement for liu135.

Theta range for data collection	1.69 to 26.43°
Index ranges	-6 ≤ h ≤ 6, -18 ≤ k ≤ 18, -25 ≤ l ≤ 26
Reflections collected	18677
Independent reflections	3434 [R(int) = 0.0811]
Coverage of independent reflections	99.9%
Absorption correction	multi-scan
Max. and min. transmission	0.9980 and 0.9690
Refinement method	Full-matrix least-squares on F ²
Refinement program	SHELXL-2014/6 (Sheldrick, 2014)
Function minimized	$\sum w(F_o^2 - F_c^2)^2$
Data / restraints / parameters	3434 / 0 / 219
Goodness-of-fit on F ²	0.983
Final R indices	1845 data; I > 2σ(I)
	all data
	R1 = 0.0496, wR2 = 0.1134
Weighting scheme	w = 1/[σ ² (F _o ²) + (0.0759P) ² + 0.3946P] where P = (F _o ² + 2F _c ²)/3
	R1 = 0.1277, wR2 = 0.1671
Absolute structure parameter	2.0(9)
Largest diff. peak and hole	0.181 and -0.274 eÅ ⁻³
R.M.S. deviation from mean	0.070 eÅ ⁻³

X-ray structure of compound 5.3'c (CCDC number 1047605)

Table 1. Sample and crystal data for liu134.

Identification code	liu134
Chemical formula	C ₁₈ H ₁₇ NO ₇
Formula weight	359.32 g/mol
Temperature	103(2) K
Wavelength	0.71073 Å
Crystal size	0.120 x 0.140 x 0.420 mm
Crystal habit	colorless needle
Crystal system	monoclinic
Space group	P 1 21 1
Unit cell dimensions	$a = 11.4475(7)$ Å $b = 5.2192(3)$ Å $c = 13.9822(8)$ Å
Volume	830.92(8) Å ³
Z	2
Density (calculated)	1.436 g/cm ³
Absorption coefficient	0.112 mm ⁻¹
F(000)	376

Table 2. Data collection and structure refinement for liu134.

Theta range for data collection	2.43 to 31.07°
Index ranges	-16 ≤ h ≤ 16, -7 ≤ k ≤ 7, -20 ≤ l ≤ 20
Reflections collected	16177
Independent reflections	5321 [R(int) = 0.0593]
Coverage of independent reflections	99.8%
Absorption correction	multi-scan
Max. and min. transmission	0.9870 and 0.9550
Refinement method	Full-matrix least-squares on F ²
Refinement program	SHELXL-2014/6 (Sheldrick, 2014)
Function minimized	$\sum w(F_o^2 - F_c^2)^2$
Data / restraints / parameters	5321 / 1 / 237
Goodness-of-fit on F ²	1.008
Final R indices	4262 data; I > 2σ(I) R1 = 0.0483, wR2 = 0.1031 all data R1 = 0.0676, wR2 = 0.1150
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0453P)^2 + 0.0560P]$ where $P = (F_o^2 + 2F_c^2)/3$
Largest diff. peak and hole	0.296 and -0.214 eÅ ⁻³
R.M.S. deviation from mean	0.055 eÅ ⁻³

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16. For more details, see CCDC number 1016860.
17. For more details, see CCDC number 1047594.
18. For more details, see CCDC number 1047605.

APPENDIX

Facile synthesis of solid electrolyte for lithium ion batteries

Lithium ion batteries have become a hot research topic because of its high energy density, portability and operational voltage.^[1] In order to achieve high ionic conductivities, organic solvents and lithium salts complexes have always been used as the electrolytes.^[2] However, it is not perfect because of the drawbacks such as leakage, volatility, spontaneous combustion, limited temperature range of operation, and lack of mechanical stability.^[2] To achieve a better safety of lithium ion batteries, scientists have been focusing on the study of solid polymer electrolytes (SPEs) which have the advantages such as nonvolatility, low flammability, chemical and electrochemical stability, and widely tunable shape conformations.^[1,3] In previous studies, high molecular weight poly ethylene oxide (PEO) was widely used as an SPE material, however, the low ionic conductivity arising from its high crystallinity restricts its development.^[4] To overcome this shortcoming, the crystallinity of SPE must be decreased. One of the solutions is to use lower molecular weight PEO, which is dimensionally unstable as it is in a liquid or lipidic state.^[5] To attain a good ionic conductivity as well as a dimensional stability, several modifications have been developed in SPEs studies, such as block copolymer electrolytes,^[6] composite polymer electrolytes,^[7] pore-filling polymer electrolytes,^[8] and network polymer electrolytes.^[9]

Compared with linear polymers, the star-shaped polymers possess a lower crystallinity, a smaller chain entanglement and a larger chain mobility.^[10] Therefore, star-shaped polymer complexes are the promising SPEs with enhanced ionic conductivities and dimensional stabilities. Herein, we introduce our strategy of preparing PEG-polysiloxane complex and PEG modified graphene oxide as SPE materials.

1. Polyhedral oligomeric silsesquioxanes (POSS)-PEG

As a special inorganic material with a definite nano-sized structure, POSS can be integrated with polymers to afford hybrid functional materials with improved mechanical properties, thermal stabilities, oxidation resistances, flame resistances, and glass transition temperatures.^[11] We envisaged to explore an efficient and facile protocol to access POSS-PEG solid electrolyte and in this section three different procedures are introduced.

As shown in Scheme 1, triethoxy-*p*-tolylsilane **3** was obtained *via* Grignard reaction, followed by hydrolysis and condensation in the presence of hydrochloric acid to furnish modified POSS **4**.^[12,13] After treated with NBS, modified POSS with bromine substitution (compound **5**) was obtained which proceeded to couple with PEG and generated compound **6**. However, when aryltrialkoxysilane **3** was subjected to acidic conditions, the desired condensation product **4** was generated in a low yield hence hindered the scaling up.

Scheme 1. Synthesis of POSS-PEG compound 6

In order to achieve a higher yield, we tried a second reaction procedure (Scheme 2). Compound **8** was prepared from **7** in a very high yield, and the cross-linked compound **10** was obtained from 3-aminopropyltriethoxysilane **9**. **8** and **10** was subjected in NMP at 80°C for 8 h, providing a jelly like product. The following dehydration offered the dry material.

Scheme 2. Synthesis of POSS-PEG compound 11

We have also designed and tested the synthesis plan shown in scheme 3. Firstly, hydrolysis and condensation of (3-chloropropyl) trimethoxysilane **12** provided POSS **13**, which was collected as a white solid. The cubic silsesquioxane core then underwent nucleophilic attack by deprotonated PEG to afford POSS-PEG **14**.^[14]

Scheme 3. Synthesis of POSS-PEG compound **14**

2. Graphene oxide (GO)-PEG

Graphene oxide (GO) is an important derivative of graphene. Unlike graphene, which is consisted of sp^2 -hybridized carbon, graphene oxide contains a range of residuals either on its basal planes or at the edges, such as carboxyl, epoxide and hydroxyl groups. This structure makes its mechanical strength different to other nano-sheet materials.^[15] Therefore, we envisaged that the coupling of GO with PEG may afford a new solid electrolyte for lithium ion batteries.

As shown in scheme 4, protected PEG **17** was synthesised according to a reported procedure, followed by deprotection of the amino group under an acidic condition to afford **18**.^[16] The free amino group then underwent condensation with the carboxyl group on GO to furnish final GO-PEG complex **11**.^[17]

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