METAL-FREE REGIO- AND STEREOSELECTIVE VICINAL DIFUNCTIONALISATION OF DIENYL CARBAMATES

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Metal-free regio- and stereoselective vicinal difunctionalisation of dienyl carbamates

DOCTORAL THESIS

Supervised by

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UNIVERSITAT ROVIRA i VIRGILI

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WE STATE that the present study, entitled "*Metal-free regio- and stereoselective vicinal difunctionalisation of dienyl carbamates*", presented by **Irene Giménez Nueno** for the award of the degree of Doctor and European Mention, has been carried out under our supervision at the Department of Analytical Chemistry and Organic Chemistry of this University.

Tarragona, 4th June 2019

Prof. Sergio Castillón Miranda

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Italia para visitaros a ti y a Alberto!! Y ahora mi querida Macarena. Creo que eres la persona a la que más veces habría matado durante la tesis. Pero también sé que cuando dentro de unos años recuerde esta tesis, tu imagen llorando porque te habían regalado una tele será lo primero que me venga a la mente… Muchas gracias por ser la mejor amiga del mundo, aunque de vez en cuando seas una tortura. ¡¡Te quiero mucho!!

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Al nacer era el hombre más rico del mundo, pero al morir seré el más pobre. Gastaré todo lo que tengo en viajar por el mundo, en buenas conversaciones, en dormir solo y en dormir acompañado. Lo gastaré en aprender cosas nuevas y en perfeccionar las que ya conozco. Como ves, el hombre más rico del mundo nace cada segundo. La riqueza no se mide en dinero, se mide en tiempo. Y no tienes más remedio que gastarlo.

Así que, gástalo bien.

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"Education is the most powerful weapon which you can use to change the world"

Nelson Mandela

A la educación pública

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ABBREVIATIONS

	Δ	Thermal heating
A	**Ac**	Acetyl
	aq	Aqueous
	Ar	Aryl
B	**:B**	Base
	BINOL	1,1'-Bi-2-naphthol
	Bn	Benzyl
	Boc	*tert*-Butyloxycarbonyl
	BOX	Bisoxazoline
	brs (NMR)	Broad signal
	BTI	[Bis(trifluoroacetoxy)iodo]benzene
	Bu	Butyl
	^{t}Bu	*tert*-Butyl
	Bz	Benzoyl
C	**ºC**	Degree Celsius
	***m*CBA**	*meta*-Chlorobenzoic acid
	Cbz	Benzyloxycarbonyl
	Conv	Conversion
	***m*CPBA**	*meta*-Chloroperoxybenzoic acid
D	**d** (NMR)	Doublet
	DCE	Dichloroethane
	DFT	Density functional theory
	DIB	(Diacetoxyiodo)benzene
	DIBAL	Diisobutyl aluminium hydride
	DIPEA	*N*,*N*-Diisopropylethylamine
	DMAP	4-Dimethylaminopyridine
	DMF	Dimethylformamide
	DMSO	Dimethyl sulfoxide
	dr	Diastereomeric ratio

E	**EDG**	Electron donating group
	ee	Enantiomeric excess
	equiv.	Equivalents
	ESI	Electrospray ionisation
	Et	Ethyl
	EWG	Electron withdrawing group
H	**hυ**	Photochemical irradiation
	HFIP	Hexafluoro-2-propanol
	HMRS	High mass resolution spectrometry
	HOMO	Highest occupied molecular orbital
	HPLC	High performance liquid chromatography
	HTIB	[Hydroxy(tosyloxy)iodo]benzene
I	**IR**	Infrared
J	***J***	Coupling constant
L	**L**	Ligand
	LA	Lewis acid
	LG	Leaving group
	LUMO	Lowest unoccupied molecular orbital
M	**M**	Molarity
	m (NMR)	Multiplet
	Me	Methyl
	Mes	Mesityl, 2,4,6-trimethylphenyl
	MO	Molecular orbital
	M.p.	Melting point
	M.S.	Molecular sieves
	Ms	Mesyl, methanesulfonyl
	MTBE	Methyl *tert*-butyl ether
	m/z	Mass under charge

N	**NA**	Not applicable
	NBS	*N*-Bromosuccinimide
	ND	Not detected
	NMR	Nuclear magnetic resonance
	Nu	Nucleophile
P	**PG**	Protecting group
	Ph	Phenyl
	Phth	Phthalimide
	PIDA	(Diacetoxyiodo)benzene
	PIFA	[Bis(trifluoroacetoxy)iodo]benzene
	Piv	Pivaloyl
	^{i}Pr	*iso*-Propyl
	Py	Pyridine
Q	**q** (NMR)	Quadruplet
R	**rac**	Racemic
	Rf	Retention factor
	r.t.	Room temperature
S	**s**	Selectivity
	s (NMR)	Singlet
	sat	Saturated
	SES	2-(Trimethylsilyl)ethanesulfonyl
	SM	Starting material
T	**t** (NMR)	Triplet
	TAI	Trichloroacetyl isocyanate
	TBAF	Tetra-*n*-butylammonium fluoride
	TBDPS	*tert*-Butyldiphenylsilyl
	Tces	2,2,2-Trichloroethoxysulfonyl
	temp	Temperature
	Tf	Triflyl, trifluoromethanesulfonyl
	TFAA	Trifluoroacetic anhydride

	THF	Tetrahydrofuran
	TLC	Thin layer chromatography
	TM	Transition metal
	TMS	Trimethylsilyl
	TS	Transition state
	Ts	Tosyl, *p*-toluenesulfonyl
	***p*-TsOH**	*para*-Toluenesulfonic acid
U	**UHP**	Urea hydrogen peroxide
V	**v/v**	Volume/volume percentage

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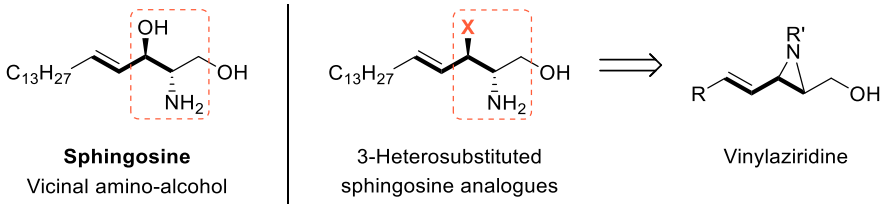
SUMMARY

The present PhD work aimed at developing new synthetic methodologies for the regio- and stereoselective preparation of unsaturated vicinal hetero-amino moieties as common structural components in relevant lipids occurring in nature, such as Sphingosine (**Scheme i**).[i] The proposed retrosynthetic pathway involved the formation of a key vinylaziridine intermediate from readily available dienols, followed by ring-opening with different nucleophilic sources to give access to 3-heterosubstituted sphingosine analogues (**Scheme i**).



Scheme i. Proposed retrosynthetic pathway for the stereoselective preparation of unsaturated vicinal hetero-amino moiety related to relevant lipids occurring in nature.

Our group had previously reported a regio- and stereoselective silver-catalysed aziridination of dienols using trispyrazolylborate ligands and PhINTs as a nitrene source.[ii] Along these lines, the stereoselective preparation of unsaturated vicinal amino-alcohols was also achieved via rhodium-catalysed intramolecular oxyamination of dienyl carbamates **A**.[iii]

Within this context, the increased concern in developing greener processes for already known chemical transformations has favoured the use of hypervalent iodine reagents as interesting surrogates of transition metal catalysts.[iv] Thus, several metal-free strategies concerning the intramolecular aziridination of alkenes via *in-situ*

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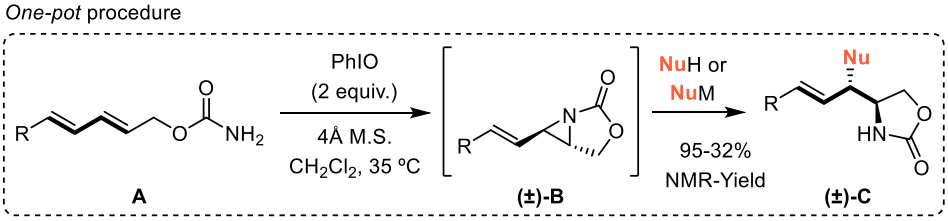
i D. Plano, S. Amin, A. K. Sharma, *J. Med. Chem.* **2014**, *57*, 5509–5524.

ii a) J. Llaveria, Á. Beltrán, M. M. Díaz-Requejo, M. I. Matheu, S. Castillón, P. J. Pérez, *Angew. Chem. Int. Ed.* **2010**, *49*, 7092–7095. b) J. Llaveria, Á. Beltrán, W. M. C. Sameera, A. Locati, M. M. Díaz-Requejo, M. I. Matheu, S. Castillón, F. Maseras, P. J. Pérez, *J. Am. Chem. Soc.* **2014**, *136*, 5342–5350.

iii J. Guasch, Y. Díaz, M. I. Matheu, S. Castillón, *Chem. Commun.* **2014**, *50*, 7344–7347.

iv a) A. Yoshimura, V. V. Zhdankin, *Chem. Rev.* **2016**, *116*, 3328–3435. b) T. Wirth, *Angew. Chem. Int. Ed.* **2005**, *44*, 3656–3665.

formation of iminoiodanes from sulfonamides and carbamates derivatives have recently appeared at the literature.[v] Inspired by these pioneering publications, PhIO mediated intramolecular aziridination of dienyl carbamates **A** was accomplished under metal-free conditions (**Scheme ii**). Subsequent regioselective ring-opening of intermediate vinylaziridine **(±)-B** with different external nucleophiles gave access to a set of hetero-substituted oxazolidinones **(±)-C** as single diastereomers.



Scheme ii. *One-pot* metal-free regio- and stereoselective aziridination/ring-opening of dienyl carbamates **A** in the presence of O-, X-, S- and N-nucleophiles.

In order to gain further insight into the mechanistic details, a computational study on PhIO mediated diene **A** aziridination was carried out by Dr. I. Funes-Ardoiz and Prof. F. Maseras (ICIQ) (**Figure i**). According to the calculated free energy profile, after the reported formation of transient iminoiodane **D**,[v(a,b)] C-O bond rotation places reactive alkene in close proximity to nitrogen atom. Then, intermediate **E** proceeds through a concerted and asynchronous transition state **TS E-F** stabilised by dispersion interactions between phenyl ring at hypervalent iodine reagent and distal double bond from dienyl moiety that ultimately generates vinylaziridine **(±)-B** (R = Me) upon final energy decay.

[v] a) A. Padwa, T. Stengel, *Org. Lett.* **2002**, *4*, 2137–2139. b) R. M. Moriarty, S. Tyagi, *Org. Lett.* **2010**, *12*, 364–366. c) Q.-H. Deng, J.-C. Wang, Z.-J. Xu, C.-Y. Zhou, C.-M. Che, *Synthesis* **2011**, 2959–2967.

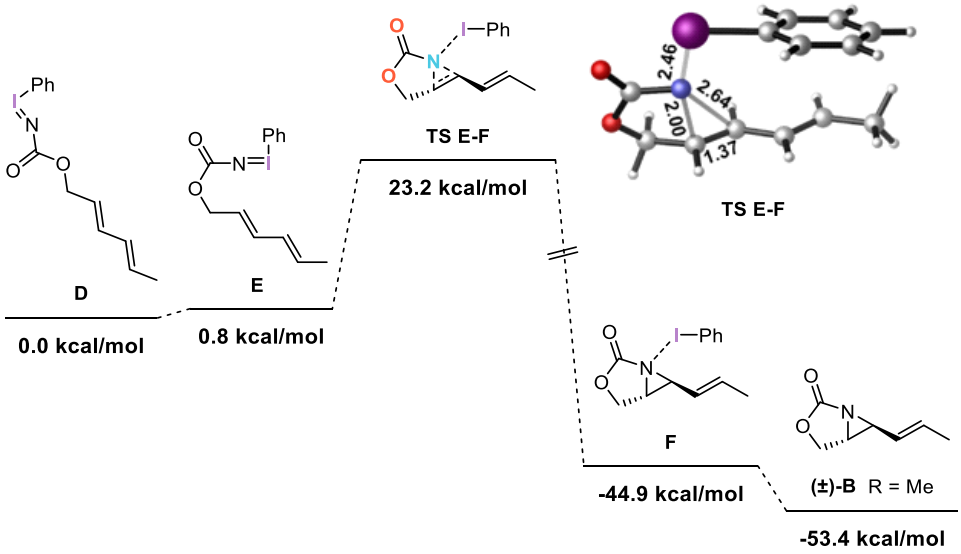
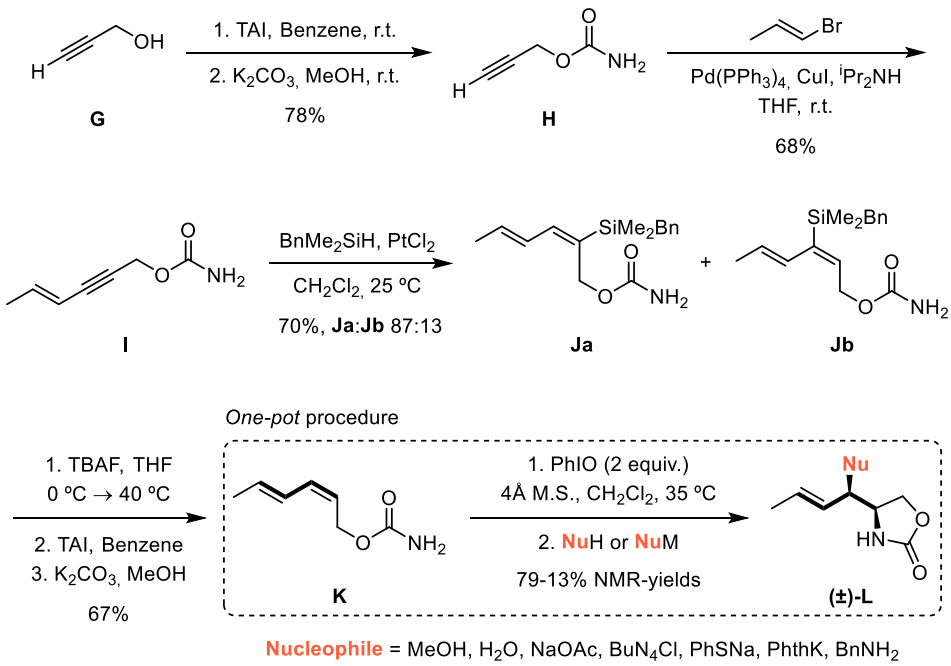


Figure i. Free energy profile for vinylaziridine **(±)-B** (R = Me) formation from iminoiodane **D**. The structure of calculated concerted transition state **TS E-F** is depicted in an inset, with relevant bond distances in Å.

As part of our general interest on the synthesis of structurally modified sphingosine analogues for cancer treatment, we envisioned the possibility of applying the PhIO-mediated aziridination/ring-opening methodology to the preparation of new compounds bearing substituents in a *syn*-relative configuration starting from (2*Z*,4*E*)-hexa-2,4-dien-1-yl carbamate **K** (**Scheme iii**).

Thus, starting from commercially available propargyl alcohol **G**, carbamate **K** was synthesised in a four step procedure via Sonogashira coupling with *trans*-1-bromo-propene followed by platinum-catalysed hydrosilylation of conjugated enyne **I** intermediate (**Scheme iii**).[ii,vi] Subsequent PhIO-mediated intramolecular aziridination/ring-opening under optimised conditions furnished the corresponding hetero-substituted oxazolidinones **(±)-L** with excellent *syn*-selectivity albeit in lower yields (**Scheme iii**).

[vi] D. A. Rooke, E. M. Ferreira, *Angew. Chem. Int. Ed.* **2012**, *51*, 3225–3230.



Scheme iii. Synthetic route for the preparation of (2*Z*,4*E*)-hexa-2,4-dien-1-yl carbamate **K** and subsequent application to the PhIO mediated aziridination/ring-opening methodology.

On the other hand, general methods for the asymmetric aziridination of alkenes rely either on the addition of metal-nitrenes to olefins in the presence of chiral ligands or on the organocatalysed reaction of amines with α,β-unsaturated carbonyl compounds.[vii] Chiral λ³-iodanes have recently emerged as a versatile eco-friendly alternative to transition metal complexes for the enantioselective synthesis of a wide range of biologically active structures.[viii] However, to the best of our knowledge, only two reports concerning the stereoselective aziridination of olefinic substrates in the presence of optically pure hypervalent iodine reagents have been published to date.[v(c),ix]

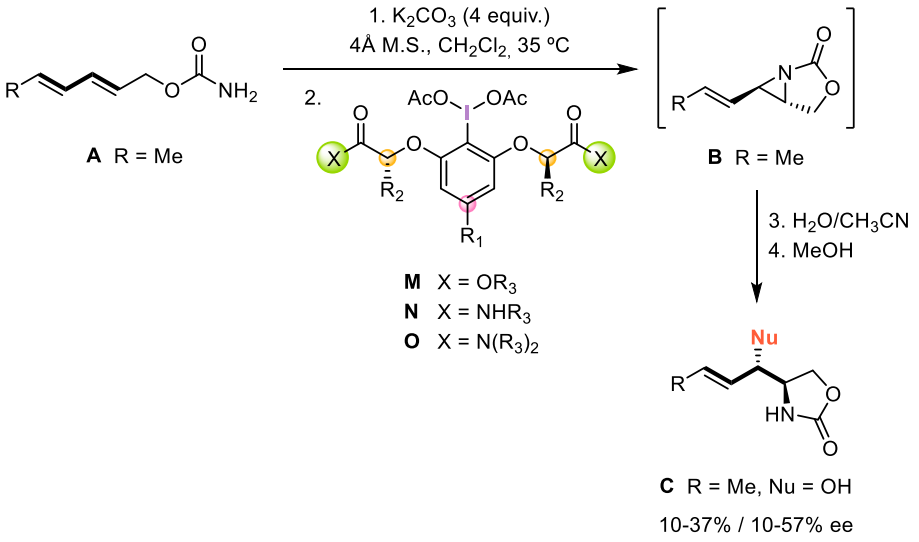
With this objective in mind, we have developed a *one-pot* procedure for the metal-free asymmetric aziridination of model dienyl carbamate **A** (R = Me) in the presence

[vii] L. Degennaro, P. Trinchera, R. Luisi, *Chem. Rev.* **2014**, *114*, 7881–7929.

[viii] a) A. Flores, E. Cots, J. Bergès, K. Muñiz, *Adv. Synth. Catal.* **2019**, *361*, 2–25. b) H. Liang, M. A. Ciufolini, *Angew. Chem. Int. Ed.* **2011**, *50*, 11849–11851.

[ix] R. D. Richardson, M. Desaize, T. Wirth, *Chem. Eur. J.* **2007**, *13*, 6745–6754.

of preformed (diacetoxyiodo)arenes **M**, **N** and **O** bearing two chiral lactate units attached to the central aromatic ring (**Scheme iv**). Subsequent regioselective ring-opening rendered hydroxy-substituted oxazolidinones **C** (R = Me and Nu = OH) up to 57% ee for λ^3-arenes bearing terminal ester groups.



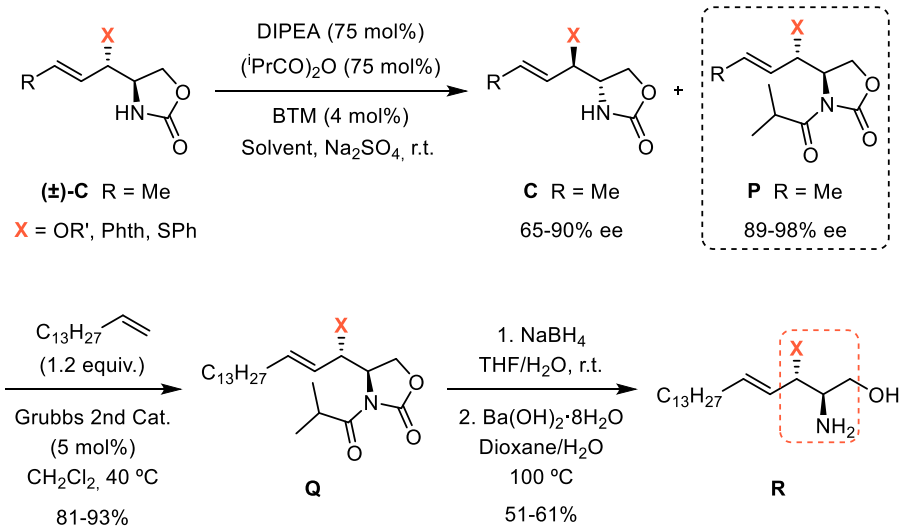
Scheme iv. Asymmetric aziridination of model dienyl carbamate **A** (R = Me) in the presence of lactate-based chiral hypervalent iodine reagents **M**, **N** and **O**.

Alternatively, enantioenriched vicinal hetero-amino compounds **C** (R = Me) could also be prepared upon kinetic resolution of racemic *anti*-oxazolidinones **(±)-C** (R = Me) intermediate (**Scheme v**) Inspired by a previous report from Birman and co-workers,[x] we developed an (*R*)-BTM organocatalysed *N*-acylation of oxyaminated products **(±)-C** (R = Me, X = OR') that relied on the formation of C=O-cation interactions between the starting material and the acylated catalyst to stabilise reactive diastereomeric transition state.[xi] To our delight, *N*- and *S*-substituted oxazolidinones **(±)-C** (R = Me, X = Phth, SPh) also underwent kinetic resolution under optimised conditions furnishing both unreacted starting materials **C** (R = Me, X = Phth, SPh)

[x] a) V. B. Birman, H. Jiang, X. Li, L. Guo, E. W. Uffman, *J. Am. Chem. Soc.* **2006**, *128*, 6536–6537. b) X. Yang, V. D. Bumbu, P. Liu, X. Li, H. Jiang, E. W. Uffman, L. Guo, W. Zhang, X. Jiang, K. N. Houk, V. B. Birman, *J. Am. Chem. Soc.* **2012**, *134*, 17605–17612.

[xi] J. Guasch, I. Giménez-Nueno, I. Funes-Ardoiz, M. Bernús, M. I. Matheu, F. Maseras, S. Castillón, Y. Díaz, *Chem. Eur. J.* **2018**, *24*, 4635–4642.

and acylated products **P** (R = Me, X = Phth, SPh) in high enantioselectivities. Moreover, in order to illustrate the usefulness of the methodology, 3-heterosubstituted sphingosine analogues **R** were synthesised via cross-metathesis and subsequent deprotection of the polar head (**Scheme v**).

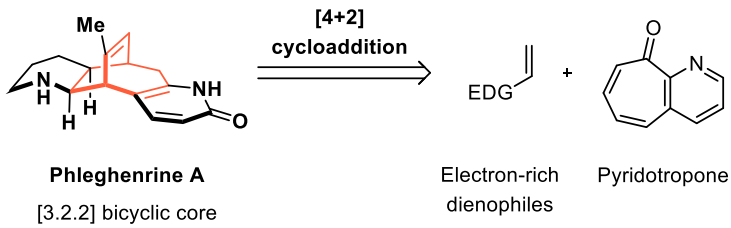


Scheme v. Organocatalysed kinetic resolution of racemic *anti*-oxazolidinones **(±)-C** (R = Me) and final synthesis of sphingosine analogues **R** via cross-metathesis and deprotection.

Therefore, two different methodologies for the preparation of unsaturated vicinal hetero-amino moiety have been developed. The first one relied on the sequential PhIO mediated intramolecular aziridination/ring-opening of dienyl carbamates **A** and subsequent kinetic resolution of racemic oxazolidinone intermediates **(±)-C** (R = Me) whereas the second involved the enantioselective synthesis of vinylaziridines **B** in the presence of chiral hypervalent iodine reagents. To date, excellent enantioselectivities have been achieved for the organocatalysed kinetic resolution of several hetero-substituted oxazolidinones **(±)-C** (R = Me). However, despite promising preliminary results, further optimisation of the asymmetric protocol concerning the *in-situ* oxidation of iodine-(I) precursors is still needed.

On the other hand, the last chapter of the present PhD work describes the research carried out during a predoctoral stay at UC Berkeley under the supervision

of Prof. R. Sarpong, aiming at the total synthesis of phleghenrine alkaloids for their biological evaluation as palliative drugs for Alzheimer's disease.[xii] The proposed retrosynthetic pathway envisioned the formation of phleghenrine [3.2.2] bicyclic core via an Inverse-Electron Demand Diels-Alder reaction (IEDDA) of pyridotropone with electron-rich dienophiles (**Scheme vi**).[xiii]



Scheme vi. Proposed retrosynthetic pathway for the preparation of phleghenrine [3.2.2] bicyclic core via Inverse-Electron Demand Diels-Alder reaction.

The screening of different Lewis acids demonstrated that $ZnBr_2$ and CuCl salts efficiently promoted the [4+2] cycloaddition of pyridotropone **T** and enecarbamate **S** to furnish the *endo* bicyclo[3.2.2]nonane **U*endo*** as the major product in high yields as a single regioisomer (**Scheme vii** a).[xiv] Unfortunately, the development of the asymmetric version of this IEDDA reaction in the presence of bisoxazoline ligands was unsuccessful. The protocol was amenable to terminal vinyl ethers and enamine derivatives (**Scheme vii** b). However, more substituted olefins proved to be challenging substrates, rendering the corresponding cycloadducts in lower yields.[xiv]

In all the cases, the electron-donating group from the dienophile partner took up β-position with respect to the carbonyl group from pyridotropone **T**, leading to bicyclo[3.2.2]nonanes with an incorrect disposition of the heteroatomic substituents for the final preparation of phleghenrine alkaloids (**Scheme vii** a). Disappointingly,

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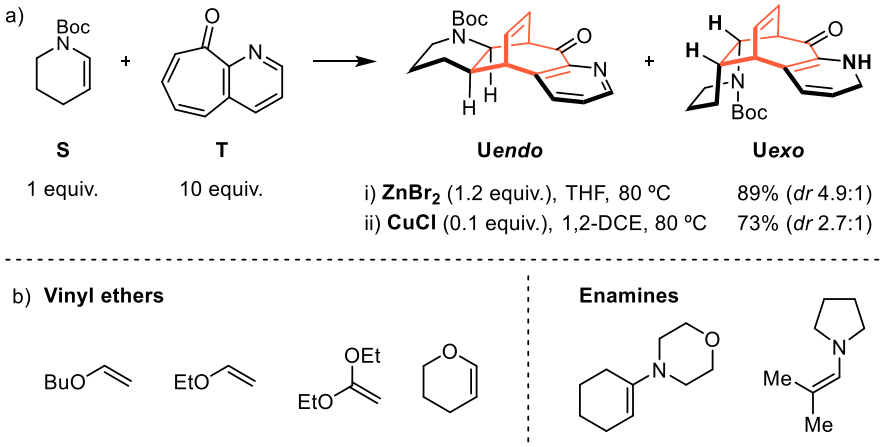
[xii] L.-B. Dong, X.-D. Wu, X. Shi, Z.-J. Zhang, J. Yang, Q.-S. Zhao, *Org. Lett.* **2016**, *18*, 4498–4501.

[xiii] a) P. Li, H. Yamamoto, *J. Am. Chem. Soc.* **2009**, *131*, 16628–16629. b) P. Li, H. Yamamoto, *Chem. Commun.* **2010**, *46*, 6294–6295. c) R. L. Funk, G. L. Bolton, *J. Am. Chem. Soc.* **1986**, *108*, 4655–4657.

[xiv] P. J. Gritsch, I. Gimenez-Nueno, L. Wonilowicz, R. Sarpong, *J. Org. Chem.* **2019**, DOI 10.1021/acs.joc.9b00899.

efforts to reverse the observed regioselectivity for the cycloaddition reaction have been fruitless to date.



Scheme vii. a) Lewis acid screening for the [4+2] cycloaddition of pyridotropone **T** with enecarbamate **S.** b) Dienophile scope for former cycloaddition reaction.

Therefore, the Lewis acid promoted regio- and stereoselective preparation of different substituted bicyclo[3.2.2]nonanes using pyridotropone **T** as a diene has been accomplished. Moreover, current on-going studies seek to apply this methodology to the synthesis of complex molecules.

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CHAPTER I

GENERAL INTRODUCTION

UNIVERSITAT ROVIRA I VIRGILI
METAL-FREE REGIO- AND STEREOSELECTIVE VICINAL DIFUNCTIONALISATION OF DIENYL CARBAMATES
Irene Giménez Nueno

1.1. Hypervalent iodine reagents

Iodine is an eco-friendly and relatively inexpensive element with a wide range of applications in chemistry, biochemistry, material science and medicine.[1] Its world's total reserves are estimated in 15 million metric tons, mainly located in Chile and Japan. Similar to other halogen members, iodine exists in nature as part of inorganic or organic species depending on whether it bonds to heteroatomic elements or carbon atoms. Moreover, in the case of organic compounds, it occurs under different oxidation states such as +I, as exemplified by aryl, vinyl or alkyl iodides, or +III and +V, observed for the so called hypervalent iodine reagents.

The first preparation of a hypervalent iodine reagent was reported by a German chemist in 1885.[2] However, it was not until the last years of the past century that hypervalent iodine compounds emerged as powerful reagents in organic synthesis for selective oxidative transformations of complex molecules.[3,4] Their environmentally benign character along with mild reaction conditions make them interesting alternatives to transition metal catalysts. Since then, hypervalent iodine chemistry has experience an impressive development driven by the increased concern in designing greener synthetic methodologies.

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1 F. C. Küpper, M. C. Feiters, B. Olofsson, T. Kaiho, S. Yanagida, M. B. Zimmermann, L. J. Carpenter, G. W. Luther III, Z. Lu, M. Jonsson, L. Kloo, *Angew. Chem. Int. Ed.* **2011**, *50*, 11598–11620.

2 a) C. Willgerodt, *J. Prakt. Chem.* **1885**, *33*, 154–160. b) A. Varvoglis, *Tetrahedron* **2010**, *66*, 5739–5744.

3 a) *Hypervalent Iodine Chemistry*; T. Wirth, Ed.; *Top. Curr. Chem.* **2016**, *373*, 1–310. b) V. V. Zhdankin, *Hypervalent Iodine Chemistry: Preparation, Structure and Synthetic Application of Polyvalent Iodine Compounds*; John Wiley & Sons Ltd.: New York, USA, **2014**. c) *Hypervalent Iodine Chemistry: Modern Developments in Organic Synthesis*; T. Wirth, Ed.; *Top. Curr. Chem.* **2003**, *224*, 1–248. d) A. Varvoglis, *Hypervalent Iodine in Organic Synthesis*; Academic Press: London, UK, **1997**. e) A. Varvoglis, *The Organic Chemistry of Polycoordinated Iodine*; VCH Publishers, Inc.: New York, USA, **1992**.

4 a) A. Yoshimura, V. V. Zhdankin, *Chem. Rev.* **2016**, *116*, 3328–3435. b) V. V. Zhdankin, P. J. Stang, *Chem. Rev.* **2008**, *108*, 5299–5358. c) V. V. Zhdankin, P. J. Stang, *Chem. Rev.* **2002**, *102*, 2523–2584. d) F. V. Singh, T. Wirth, *Chem. Asian J.* **2014**, *9*, 950–971. e) T. Wirth, *Angew. Chem. Int. Ed.* **2005**, *44*, 3656–3665. f) T. Dohi, Y. Kita, *Chem. Commun.* **2009**, 2073–2085. g) M. Ochiai, K. Miyamoto, *Eur. J. Org. Chem.* **2008**, 4229–4239. h) L. F. Silva, Jr., B. Olofsson, *Nat. Prod. Rep.* **2011**, *28*, 1722–1754.

General structure and main classes of iodine(III) reagents are depicted in **Figure 1.1**.[4a-c] λ³-Iodanes display a T-shaped structure within a pseudo trigonal bipyramidal geometry. In the case of trivalent iodine derivatives with general formula RIL_2, the less electronegative carbon substituent is placed in the equatorial position along with iodine lone pairs whereas heteroatom ligands are linked to the central atom by the apical positions. The nearly linear L–I–L bond is known as "hypervalent bond" and its highly polarised nature is responsible for the characteristic electrophilic reactivity of hypervalent iodine reagents.

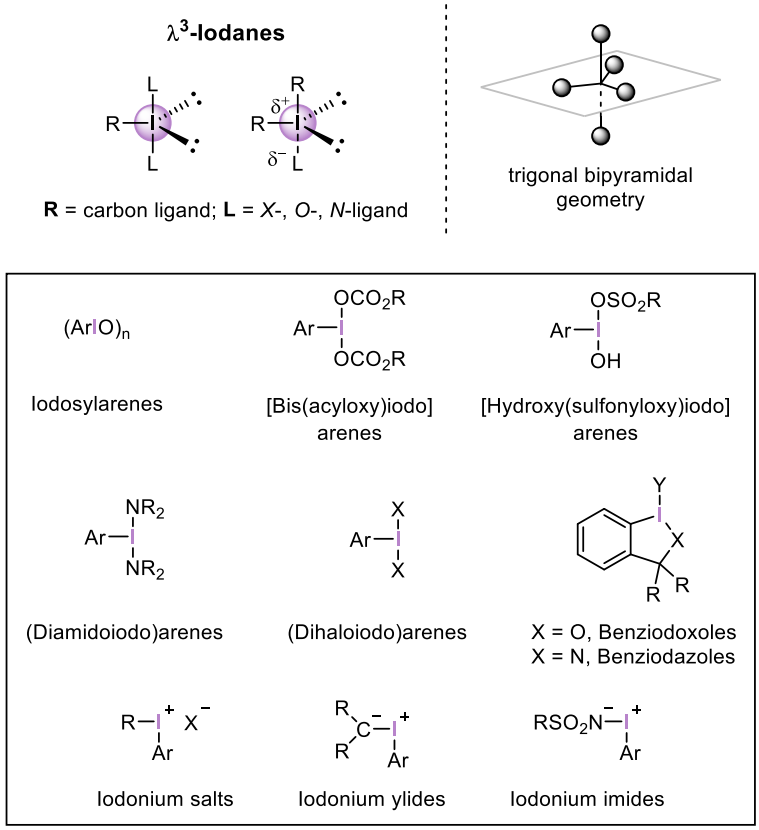

Figure 1.1. λ³-Iodanes: general structure and main classes.

Alternatively, iodonium salts, with general formula R_2IL, present an anionic ligand weakly bonded to the positively charged iodine atom and two carbon substituents arranged in a 90º angle.

[Bis(acyloxy)iodo]arenes and [hydroxy(sulfonyloxy)iodo]arenes are common terminal oxidants in organic synthesis. Among them, commercially available (diacetoxyiodo)benzene (PIDA or DIB), [bis(trifluoroacetoxy)iodo]benzene (PIFA or BTI) and [hydroxy(tosyloxy)iodo]benzene (Koser's reagent or HTIB) are widely used as precursors of other hypervalent iodine(III) reagents.

On the other hand, the polymeric structure of iodosylbenzene, a readily synthesised iodosylarene, make it highly insoluble in common organic solvents whereas nitrogen-containing iodine derivatives lack thermal stability even at low temperatures and are usually *in situ* generated in the reaction medium. In addition, hypervalent iodine halides are also difficult to handle: (difluoroiodo)arenes display a hygroscopic character while (dichloroiodo)arenes are light-sensitive.

Among heterocyclic iodine(III) compounds, benziodoxoles stand out as versatile "atom-transfer" reagents.[5] Their planar structure and the heterocyclic bridging of equatorial and axial positions favour a better overlapping between iodine non-bonding electrons ant benzene π-orbitals, thus conferring thermal stability to the hypervalent iodine reagent. Remarkable reactivities through diverse chemical transformations have already been reported for peroxide, azido, cyano, trifluoromethyl or alkynyl substituted benziodoxoles. Moreover, to date, several compounds bearing different heteroatoms or alternative ring sizes have also been studied.

Although iodonium salts are formally eight-electron iodine cationic species,[6] they are usually classified as hypervalent iodine reagents due to the strong secondary interactions between positively charged iodine atom and the counter-anion in their crystal structure. Highly electrophilic aryl,[7] alkenyl,[8] alkynyl[9] and fluoroalkyl containing iodonium salts commonly react via coupling reactions or nucleophile

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5 a) J. P. Brand, D. F. González, S. Nicolai, J. Waser, *Chem. Commun.* **2011**, *47*, 102–115. b) V. V. Zhdankin, *Curr. Org. Synth.* **2005**, *2*, 121–145. c) J. Charpentier, N. Früh, A. Togni, *Chem. Rev.* **2015**, *115*, 650–682.

6 M. S. Yusubov, A. V. Maskaev, V. V. Zhdankin, *Arkivoc* **2011**, *i*, 370–409.

7 E. Merritt, B. Olofsson, *Angew. Chem. Int. Ed.* **2009**, *48*, 9052–9070.

8 M. Ochiai, *J. Organomet. Chem.* **2000**, *611*, 494–508.

9 V. V. Zhdankin, P. J. Stang, *Tetrahedron* **1998**, *54*, 10927–10966.

additions. Likewise, structurally related iodonium ylides and iminoiodanes are efficient carbene and nitrene precursors respectively.

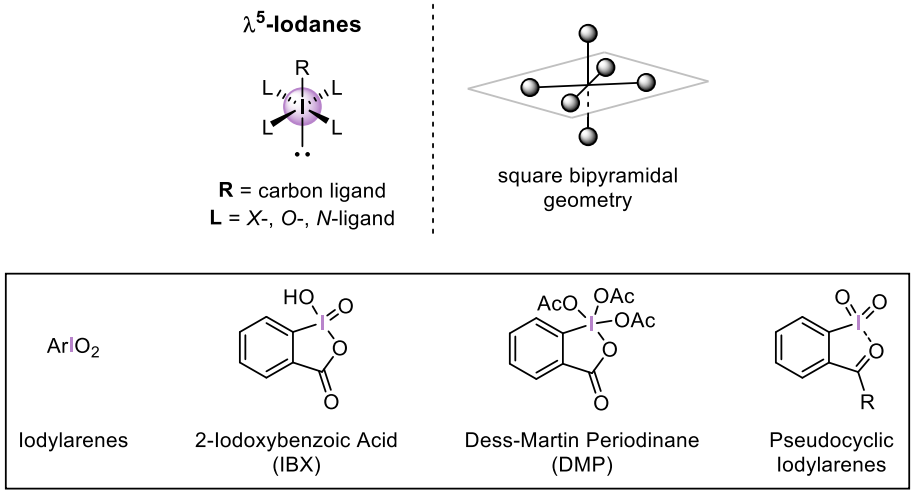

Figure 1.2. λ5-Iodanes: general structure and main classes.

General structure and main classes of iodine(V) reagents are depicted in **Figure 1.2**.[4a-c,10] λ5-Iodanes present two orthogonal L–I–L hypervalent bonds located in the basal positions of a distorted square bipyramid whereas carbon ligand and iodine lone pair take up apical positions. Pentavalent iodine compounds are commonly used as oxidants in organic synthesis. In particular, commercially available 2-iodoxybenzoic acid (IBX) and Dess-Martin periodinane (DMP) have been reported to mediate oxidation of complex molecules.[10]

[10] a) V. V. Zhdankin, *J. Org. Chem.* **2011**, *76*, 1185–1197. b) U. Ladziata, V. V. Zhdankin, *Arkivoc* **2006**, *ix*, 26–58.

1.2. Hypervalent bond and mutual ligand influence

In 1969, J. I. Musher formally classified hypervalent compounds as "*those molecules formed by elements in Groups 15-18 of the periodic table in any of their valences other than their lowest stable chemical valence*".[11] According to this definition, previously described polyvalent iodine reagents can be considered as hypervalent compounds since central iodine atom occurs in oxidation state +III and +V. However, the electronic properties of hypervalent iodine reagents just as the structural nature of hypervalent bond have received much discussion in the past and some authors have questioned the accuracy of the hypervalent term to refer to this class of compounds.[12]

Alternatively, hypervalent compounds can also be described as those molecules having Lewis structures with more than eight-electrons in the central atom valence shell,[12] as it is the case of model aryl iodine(III) **1** (**Figure 1.3**). Therefore, these compounds are considered exceptions to the *octet rule* postulated by G. N. Lewis.[13] When taking into account the polar nature of hypervalent bond,[3,4] two equivalent resonance forms **1a** and **1b** can be depicted (**Figure 1.3**).[12] Thus, resulting cationic iodine species obey the *octet rule* however, depending on the electronegativity of the ligands linked to the central iodine atom, such resonance structures may not be fully accurate.

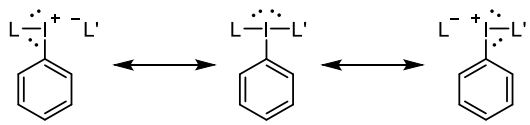

Figure 1.3. Lewis structure (**1**) and resonance forms (**1a**, **1b**) of model aryl iodine(III).

Based on preliminary definitions of hypervalent molecules, different theoretical studies were carried out in order to describe the structural nature of hypervalent bond. In accordance with the concept of hybridization, the bonding at the central atom of hypervalent compounds was initially described as an sp^3d^n hybrid

11 J. I. Musher, *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 54–68.
12 R. J. Gillespie, B. Silvi, *Coord. Chem. Rev.* **2002**, *233–234*, 53–62.
13 G. N. Lewis, *J. Am. Chem. Soc.* **1916**, *38*, 762–785.

combination of atomic orbitals. However, subsequent ab initio calculations for PCl_5 and SF_6 molecules ruled out former explanation.[12] Likewise, Varvoglis and co-workers confirmed the small contribution of *d*-orbitals to the molecular binding energy of $PhICl_2$ and $PhIF_2$ polyvalent iodine reagents.[14]

Hypervalent bond in aryl iodine(III) compounds **1** (**Figure 1.3**) is currently described using a simple qualitative molecular orbital model.[12,15,16] Thus, taking into account the electronic structure of iodine [Kr] $4d^{10}$ $5s^2$ $5p^5$, one filled 5p-orbital from iodine atom interacts with two half-filled p-orbitals from the ligands (L and L'), forming a 3-centre 4-electron delocalised structure (**Figure 1.4** a). In addition, central iodine atom retains two electron lone pairs and shares the remaining electron through a regular σ-bond with the aromatic ring (**Figure 1.4** a).

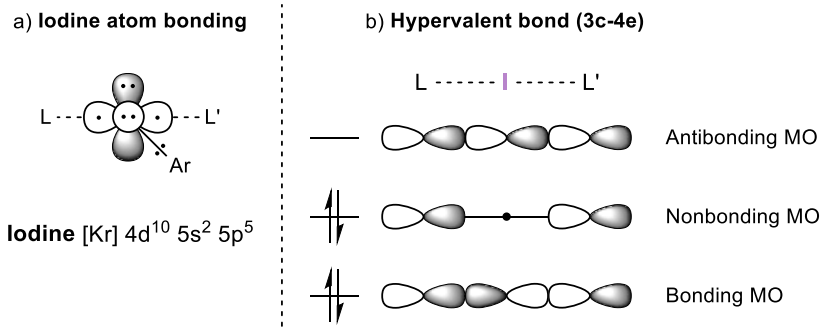

Figure 1.4. Model aryl iodine(III). a) General bonding around iodine atom. b) Hypervalent bond: 3-centre 4-electron bond.

The resulting linear L–I–L' hypervalent bond incorporates three molecular orbitals (**Figure 1.4** b). Whereas the two electrons occupying the bonding MO are delocalised through the bond, the node present at the nonbonding MO prevent electrons' movement, leading to a charge distribution that makes hypervalent bonds highly polarised, longer and weaker than regular covalent bonds.

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14 V. E. Mylonas, M. P. Sigalas, G. A. Katsoulos, C. A. Tsipis, A. G. Varvoglis, *J. Chem. Soc. Perkin Trans. 2* **1994**, 1691–1696.

15 J. T. Su, W. A. Goddard III, *J. Am. Chem. Soc.* **2005**, *127*, 14146–14147.

16 P. K. Sajith, C. H. Suresh, *Inorg. Chem.* **2012**, *51*, 967–977.

As mentioned before, structural definition of hypervalent bond is a highly controversial topic. Although generally accepted as a 3-centre 4-electron bond (**Figure 1.4** b), some authors have claimed that the two electrons contained in the non-bonding MO should not be considered as part of iodine electronic shell since the electronic density is mainly located over ligand substituents.[12] Therefore, from this point of view, central iodine atoms from polyvalent molecules obey Lewis' *octet rule*. Nevertheless, for the sake of clarity, scientific community has widely embrace the hypervalent term to refer to this class of iodine compounds.[3,4]

On the other hand, stability of iodine(III) reagents has been directly related to the mutual *trans* influence of ligands through linear hypervalent bond.[16,17] In 1966, Pidcock and co-workers defined the *trans* influence of a ligand for a transition metal complex as *"the extent to which that ligand* (L) *weakens the bond trans to itself* (M–L') *in the equilibrium state"* (**Figure 1.5** a).[18] Likewise, main group element coordination complexes always display a similar *trans* effect when central atom is not at its highest valence and formally retains the ns^2 lone pair,[19] as it is the case for organo-λ^3-iodanes. In addition, due to the structural properties of hypervalent bond, the L ligand only influences M–L' binding through iodine 5p-orbital conferring exclusive inductive character upon the mentioned mutual ligand effect (**Figure 1.5** b).[16,17]

Based on experimental data, ligand order of *trans* influence for organo-λ^3-iodanes can be stablished (**Figure 1.5** c).[17a] Combinations of either two moderate or a large and a small *trans*-influencing ligands lead to stable hypervalent iodine compounds, as exemplified by commercially available (diacetoxyiodo)benzene and Koser's reagent respectively. However, the unfavourable combination of two strong *trans*-influencing ligands around central iodine atom results in the labile nature of $PhI(OMe)_2$, even at room temperature.[20]

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17 a) M. Ochiai, T. Sueda, K. Miyamoto, P. Kiprof, V. V. Zhdankin, *Angew. Chem. Int. Ed.* **2006**, *45*, 8203–8206. b) P. K. Sajith, C. H. Suresh, *Inorg. Chem.* **2013**, *52*, 6046–6054. c) P. Kiprof, *Arkivoc* **2005**, *iv*, 19–25.

18 a) A. Pidcock, R. E. Richards, L. M. Venanzi, *J. Chem. Soc. A* **1966**, 1707–1710. b) T. G. Appleton, H. C. Clark, L. E. Manzer, *Coord. Chem. Rev.* **1973**, *10*, 335–422. c) F. R. Hartley, *Chem. Soc. Rev.* **1973**, *2*, 163–179.

19 E. M. Shustorovich, Y. A. Buslaev, *Inorg. Chem.* **1976**, *15*, 1142–1147.

20 B. C. Schardt, C. L. Hill, *Inorg. Chem.* **1983**, *22*, 1563–1565.

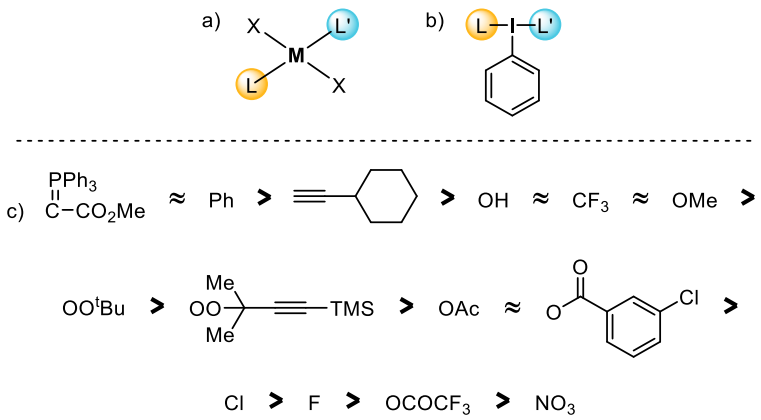

Figure 1.5. Mutual ligand influence. a) Transition metal complex. b) Hypervalent iodine(III) reagent. c) Ligand order of decreasing *trans* influence.

Along these lines, it has been proposed that observed aggregation of iodosylbenzene monomers into polymeric structures[21] **2** and formation of μ-oxo-bridged diiodanyl compounds **3** are direct consequences of unstable *trans* ligand influence through linear hypervalent bond (**Scheme 1.1** a). Moreover, a recent report by A. Boldyrev, V. Zhdankin and co-workers demonstrated the occurrence of a dative bond in iodosylbenzene and *N*-tosyl iodonium imide molecules, instead of the commonly represented double bond.[22] Under former description, the nature of the hypervalent bond is explained as a result of donor-acceptor interactions between occupied and unoccupied electronic levels and, therefore, both central iodine atoms obey Lewis' *octet rule*.[22,23]

In addition, the chemical behaviour of benziodoxoles **4** and benziodazoles **6** upon ligand exchange has been studied on the basis of mutual ligand effect (**Scheme 1.1** b). Thus, when hydroxy substituted benziodoxole **4** was reacted with *tert*-butyl hydroperoxide, heterocyclic iodine(III) **5** was synthesised in high yields.[24] In contrast,

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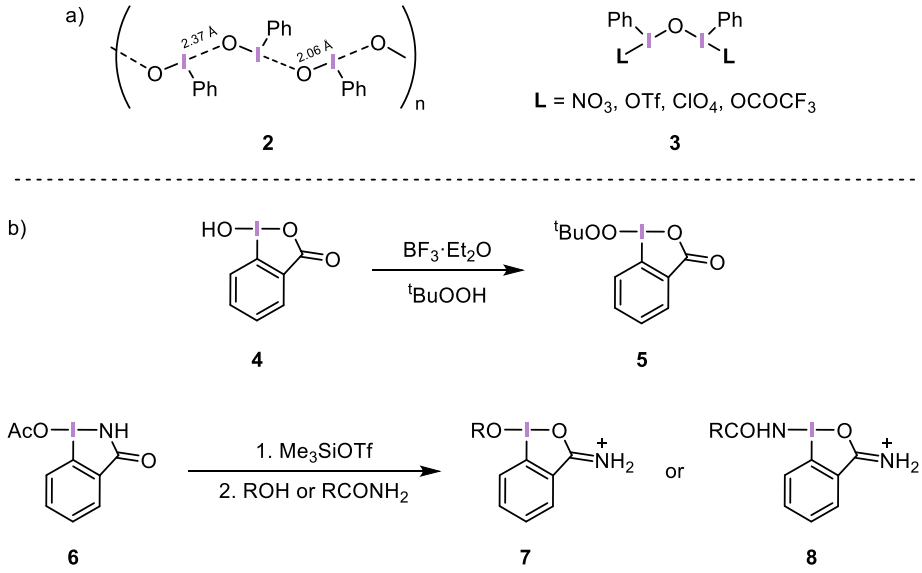
21 C. J. Carmalt, J. G. Crossley, J. G. Knight, P. Lightfoot, A. Martín, M. P. Muldowney, N. C. Norman, A. G. Orpen, *J. Chem. Soc. Chem. Commun.* **1994**, 2367–2368.

22 A. S. Ivanov, I. A. Popov, A. I. Boldyrev, V. V. Zhdankin, *Angew. Chem. Int. Ed.* **2014**, *53*, 9617–9621.

23 G. A. Landrum, N. Goldberg, R. Hoffmann, R. M. Minyaev, *New. J. Chem.* **1998**, 883–890.

24 M. Ochiai, T. Ito, Y. Masaki, M. Shiro, *J. Am. Chem. Soc.* **1992**, *114*, 6269–6270.

when acetoxy benziodazole **6** was used as starting material for a related ligand exchange reaction, rearranged iminiobenziodoxoles **7** or **8** were obtained.[25]



Scheme 1.1. a) Polymeric structure of iodosylbenzene **2** and dimeric structure of μ-oxo-bridged diiodanyl compounds **3**. b) Ligand exchange reactions for benziodoxoles **4** and benziodazoles **6**.

These observations can be rationalised by means of the ligand *trans* effect. Experimental data and theoretical calculations have shown the greater *trans*-influence of benziodazolone group in comparison with benziodoxolone group.[16,17a] Therefore, in order to accommodate strong *trans*-influencing ligands such as alcohols or amides, benziodazole ring **6** needs to rearrange into iminiobenziodoxoles **7** and **8** to minimise unfavourable ligand combination.

[25] a) V. V. Zhdankin, R. M. Arbit, M. McSherry, B. Mismash, V. G. Young, *J. Am. Chem. Soc.* **1997**, *119*, 7408–7409. b) V. V. Zhdankin, R. M. Arbit, B. J. Lynch, P. Kiprof, V. G. Young, *J. Org. Chem.* **1998**, *63*, 6590–6596.

1.3. Reactivity overview for organo-λ^3-iodanes

Organo-λ^3-iodanes have traditionally been used in organic synthesis as terminal oxidants for metal-catalysed processes. However, their highly electrophilic nature and remarkable leaving group ability make them interesting eco-friendly alternatives to transition metal complexes. To date, several metal-free iodine(III)-mediated oxidative transformations have been developed with high levels of regio- and stereocontrol.[3,4a-c,26] In addition, chiral hypervalent iodine compounds have recently emerged as powerful reagents for the asymmetric preparation of complex molecules.[27]

In general, iodine(III)-mediated transformations can be divided in formal functional group oxidation,[28] α-substitution of carbonyl compounds,[29] alkene derivatisation,[30] C-H bond functionalisation and oxidative rearrangements.[31]

Formal functional group oxidation

Stoichiometric and catalytic oxidations of functional groups such as alcohols, amines, oximes, thioethers and organic phosphines can be performed in the presence of different hypervalent iodine reagents (**Scheme 1.2**) In particular, common methodologies for alcohol oxidation involve the use of (diacetoxyiodo)benzene in combination with $BF_3{\cdot}EtO_2$ as Lewis acid or catalytic amounts of 2,2,6,6-tetramethylpiperidine-1-oxyl radical (TEMPO) as well as KBr-activated iodosylbenzene in water.[28a,b] In addition, the iodine(III)-mediated oxidative cleavage of alkenes **9** to form aldehydes **10** and carboxylic acids **11** has also been reported (**Scheme 1.2**). Benzylic or allylic positions are prone to oxidation upon treatment with PhIO or $PhI(OAc)_2$ along with radical initiators (**Scheme 1.2**) whereas the

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26 Z. Zheng, D. Zhang-Negrerie, Y. Du, K. Zhao, *Sci. China Chem.* **2014**, *57*, 189–214.

27 a) A. Flores, E. Cots, J. Bergès, K. Muñiz, *Adv. Synth. Catal.* **2019**, *361*, 2–25. b) H. Liang, M. A. Ciufolini, *Angew. Chem. Int. Ed.* **2011**, *50*, 11849–11851.

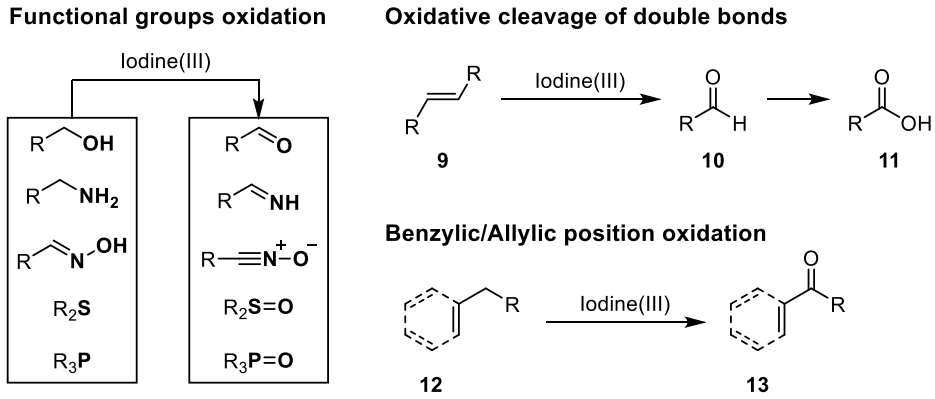
28 a) M. Uyanik, K. Ishihara, *Chem. Commun.* **2009**, 2086–2099. b) H. Tohma, Y. Kita, *Adv. Synth. Catal.* **2004**, *346*, 111–124. c) L. Pouységu, D. Deffieux, S. Quideau, *Tetrahedron* **2010**, *66*, 2235–2261. d) S. Rodríguez, P. Wipf, *Synthesis* **2004**, 2767–2783.

29 E. A. Merritt, B. Olofsson, *Synthesis* **2011**, 517–538.

30 a) R. M. Romero, T. H. Wöste, K. Muñiz, *Chem. Asian J.* **2014**, *9*, 972–983. b) M. Fujita, *Tetrahedron Lett.* **2017**, *58*, 4409–4419.

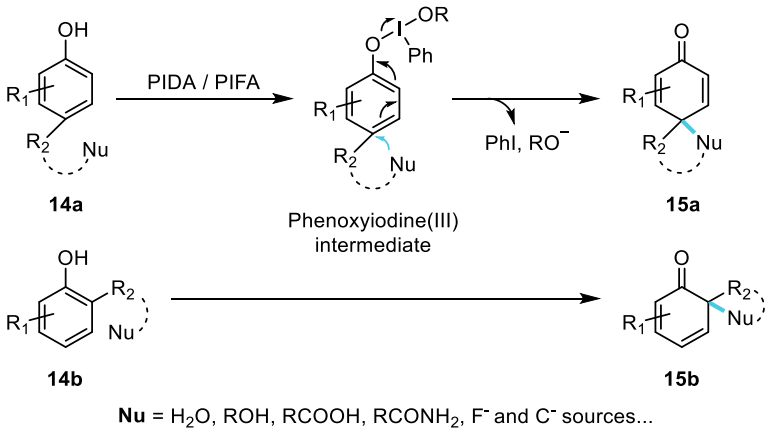
31 F. V. Singh, T. Wirth, *Synthesis* **2013**, 2499–2511.

oxidation of unactivated C-H bonds in alkyl chains can be promoted by stable *tert*-butyl-peroxybenziodoxole **5** to yield the corresponding carbonyl compounds.



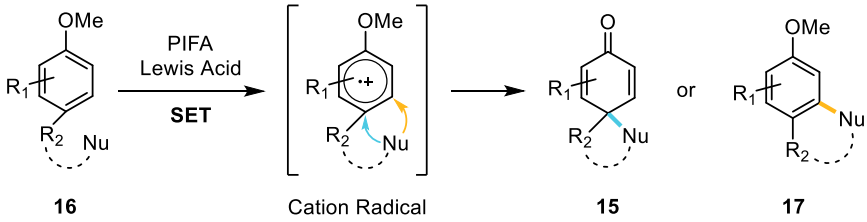
Scheme 1.2. Iodine(III)-mediated oxidation of organic compounds.

λ³-iodanes-induced oxidative dearomatization of phenolic substrates is a powerful tool for natural product synthesis.[28c] A general mechanism for this transformation is depicted in **Scheme 1.3**. Thus, *para*- and *ortho*-substituted phenols **14a** and **14b** undergo ligand exchange with PIDA or PIFA to furnish the corresponding phenoxyiodine(III) intermediates, that upon concomitant reductive elimination and nucleophile addition give access to dienones **15a** and **15b**. Several external and internal *O*-, *N*-, *F*- or *C*-nucleophiles have been successfully tested in former oxidative dearomatization of compounds **14a** and **14b**.



Scheme 1.3. Iodine(III)-mediated oxidative dearomatization of phenols **14a** and **14b**.

Along these lines, *C*-substituted dienones **15** can also be prepared by means of oxidative coupling of electron-rich arenes (**Scheme 1.4**).[28d] In this case, the reaction involves an intermediate cation radical generated from phenolic ethers **16** via PIFA-promoted single electron transfer (SET) in polar solvents. Final nucleophile addition yields either dearomatized product **15** or oxidative coupling compound **17**. Therefore, this methodology is particularly useful for rapid complexity introduction in synthesis upon intramolecular binding of electron-rich aryl rings.

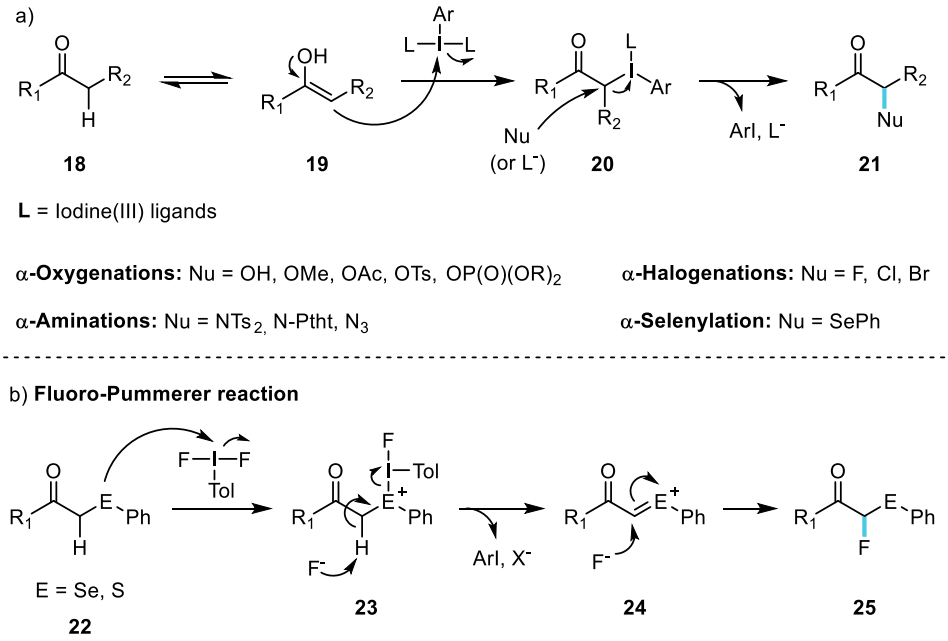


Nu = Electron rich aromatic rings, β-dicarbonyl compounds, N_3^-, AcO^-, ArS^-, SCN^- anions...

Scheme 1.4. Iodine(III)-mediated oxidative coupling of electron-rich arenes **16**.

a-Functionalisation of carbonyl compounds

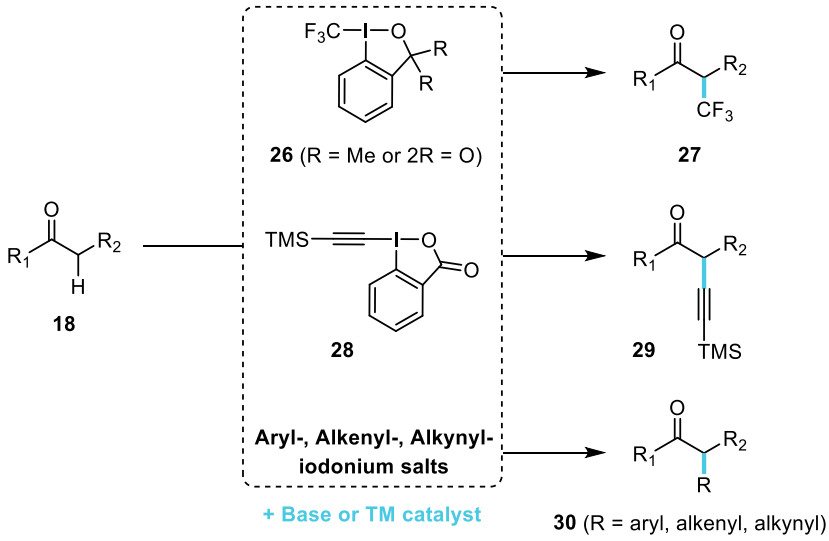
α-Functionalisation of carbonyl compounds is a versatile strategy in organic chemistry for straightforward complexity introduction. Iodine(III) reagents successfully promote α-oxygenations, aminations, halogenations and even selenylations of differently substituted carbonyl compounds **18** (**Scheme 1.5** a).[29] According to proposed mechanism, after initial keto-enol tautomerism, enol **19** coordinates to λ³-iodane via ligand exchange to furnish intermediate **20**. Then, due to the remarkable leaving group ability of hypervalent iodine, external nucleophiles or ligands released during the process effect its displacement upon reductive elimination rendering carbonyl derivatives **21** with a newly formed carbon-heteroatom bond.



Scheme 1.5. a) General mechanism for λ^3-iodanes-promoted α-functionalisation of carbonyl compounds **18**. b) Fluoro-Pummerer-type reaction for sulphur and selenium-containing carbonyl compounds **22**.

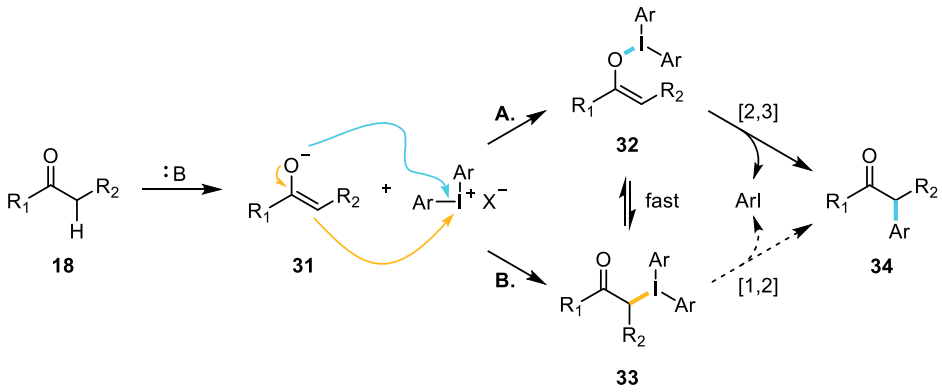
A specific example of α-functionalisation of carbonyl compounds uses phenylthio amides and esters **22** (E = S) as starting materials for fluoro-Pummerer-type reaction (**Scheme 1.5** b).[4a,29] Sequential heteroatom coordination to iodine(III) and α-deprotonation generates key cationic-thial intermediate **24** (E = S) which undergoes nucleophile addition of fluorine ions present in the reaction medium. Moreover, (difluoroiodo)toluene also mediates α-substitution of selenium analogues **22** (E = Se) under mild conditions (**Scheme 1.5** b).

The introduction of *C*-substituents at the adjacent position of a carbonyl group has been achieved by means of heterocyclic iodine(III) compounds and iodonium salts (**Scheme 1.6**). Togni's reagents[5c] **26** and alkynyl benziodoxole **28** respectively transfer trifluoromethyl and ethynyl moieties into carbonyl derivatives **18**.[5a,29] Likewise, base-mediated electrophilic arylation, alkenylation or alkynylation of carbonyl-containing starting materials **18** upon treatment with the corresponding iodonium salt effectively furnish functionalised products **30**.[6-9]



Scheme 1.6. Iodine(III)-mediated α-trifluoromethylation, arylation, alkenylation and alkynylation of carbonyl compounds **18**.

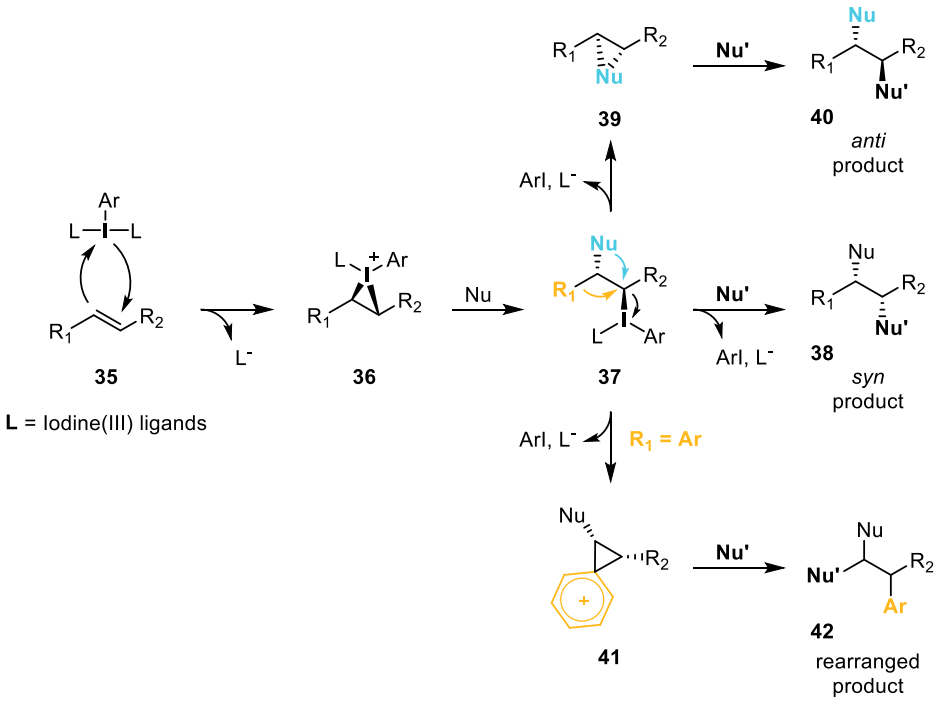
Mechanistic studies on iodonium salts mediated α-arylation of carbonyl compounds identified two isoenergetic intermediates that could converge into final product **34** following different reductive elimination pathways (**Scheme 1.7**, pathways A and B).[29] Thus, oxygen-bonded enol **32** undergoes [2,3] rearrangement to yield α-substituted carbonyl compound **34**, whereas carbon-linked analogue **33** alternatively evolves via reductive elimination to give **34** and aryl iodide. However, the fast equilibration between intermediates **32** and **33** biases the formation of functionalised products **34** through the favoured [2,3] rearrangement.



Scheme 1.7. Proposed mechanism for α-arylation of carbonyl compounds **18**.

Alkene derivatisation

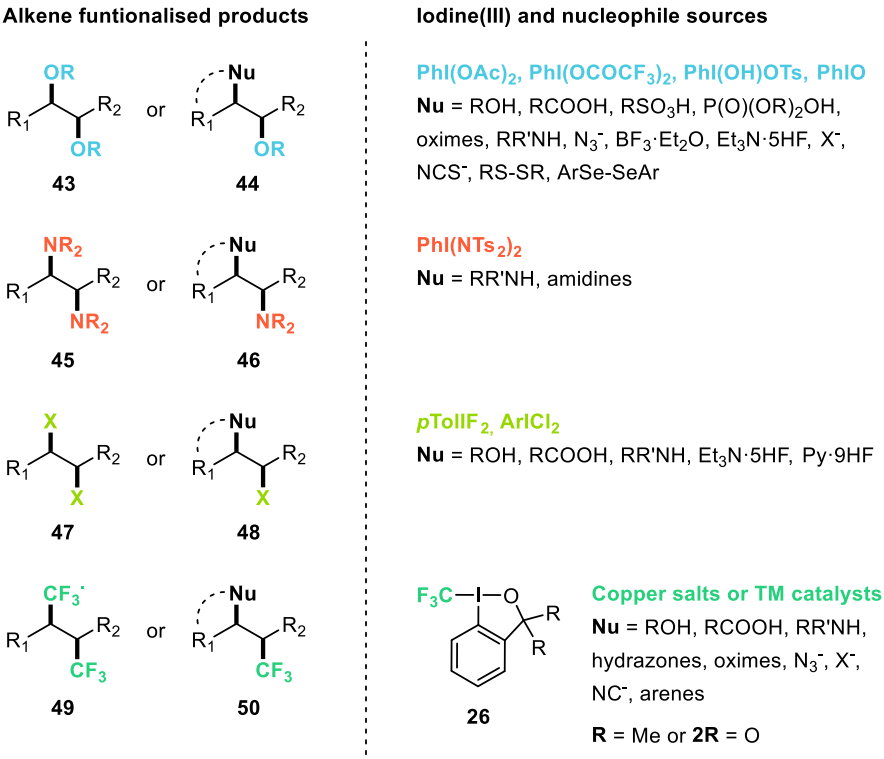
Oxidative vicinal difunctionalisation of double bonds in the presence of λ³-iodanes is a versatile transformation that allows the stereoselective introduction of two functional groups in a 1,2 array within a single step. Both ionic and radical pathways have been proposed for final product formation, especially in the case of chloro- and azido-substituted compounds.[30a] Some mechanistic aspects of iodine(III)-mediated alkene derivatisation are depicted in **Scheme 1.8**.[30b] Thus, when ionic pathway is considered, key iodonium specie **36** is originated from the coordination of electron deficient hypervalent iodine atom to the π-orbital of the double bond in olefin **35**. It has been described that initial ligand dissociation from iodine centre enhances its electrophilic character favouring the generation of cyclic iodonium **36** which is subsequently opened by external nucleophiles or released ligands to furnish iodane intermediate **37**.



Scheme 1.8. Mechanistic aspects of iodine(III)-mediated alkene **35** functionalisation.

Syn- or *anti*-difunctionalised products **38** and **40** respectively resulted from either clean intermolecular S_N2 replacement of hypervalent iodine moiety or intramolecular

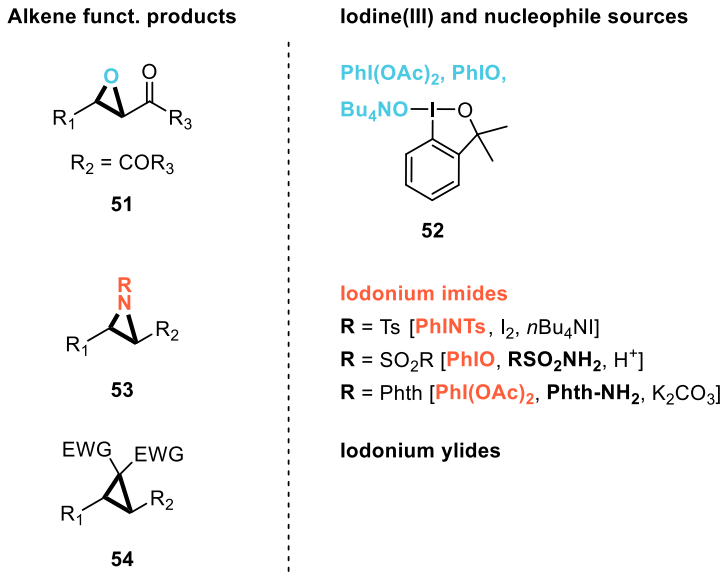
nucleophilic displacement followed by ring-opening pathway, respectively (**Scheme 1.8**). Alternatively, for aryl substituted alkenes, 1,2 migration of phenyl moiety via intermediate formation of phenonium ion **41** leads to rearranged product **42** (**Scheme 1.8**).[31]



Scheme 1.9. Vicinal difunctionalised products **43**-**50** prepared via iodine(III)-mediated oxidative alkene **35** derivatisation with internal and external nucleophiles.

According to previous mechanistic considerations, a wide range of selective vicinal difunctionalised products have been obtained depending on the selected hypervalent iodine compound or whether internal or external nucleophiles were used (**Scheme 1.9**).[4a-c,30a] Oxygen-containing λ³-iodanes are versatile reagents for double bond derivatisation. Amino-, halogen-, sulphur-, phosphorous- or selenium-substituted products can be synthesised, sometimes via *in situ* formation of respective

unstable hypervalent iodine(III) compounds.[32] In addition, $PhI(NTs_2)_2$ or its analogues effectively mediate alkene **35** amination[32] whereas di-halogenated and mono-halogenated products **47** and **48** arise from double bond functionalisation in the presence of (dihaloiodo)arenes and nucleophiles. Recently, Togni's reagents **26** have also been reported as powerful reagents for trifluoromethyl group transfer into alkene's moiety.[5c] Likewise, alkynes have also been used as starting materials for iodine(III)-mediated vicinal difunctionalisation.[4a-c]



Scheme 1.10. Iodine(III)-mediated intermolecular epoxidation, aziridination and cyclopropanation of alkene **35**.

Finally, oxidative alkene functionalisation can also give access to epoxides, aziridines or cyclopropanes depending on reaction conditions (**Scheme 1.10**).[4a-c,e] Thus, oxiranes **51** were synthesised from α,β-unsaturated compounds in the presence of $PhI(OAc)_2$, PhIO or benziodoxole **52**. Preformed or *in situ* generated iminoiodanes lead to *N*-substituted aziridines **53** via nitrene insertion into double bond under metal-free or transition metal catalysed conditions whereas cyclopropanes **54** can be easily obtained by inter- or intra-molecular reaction of alkenes and electron withdrawing group-stabilised iodonium ylides.

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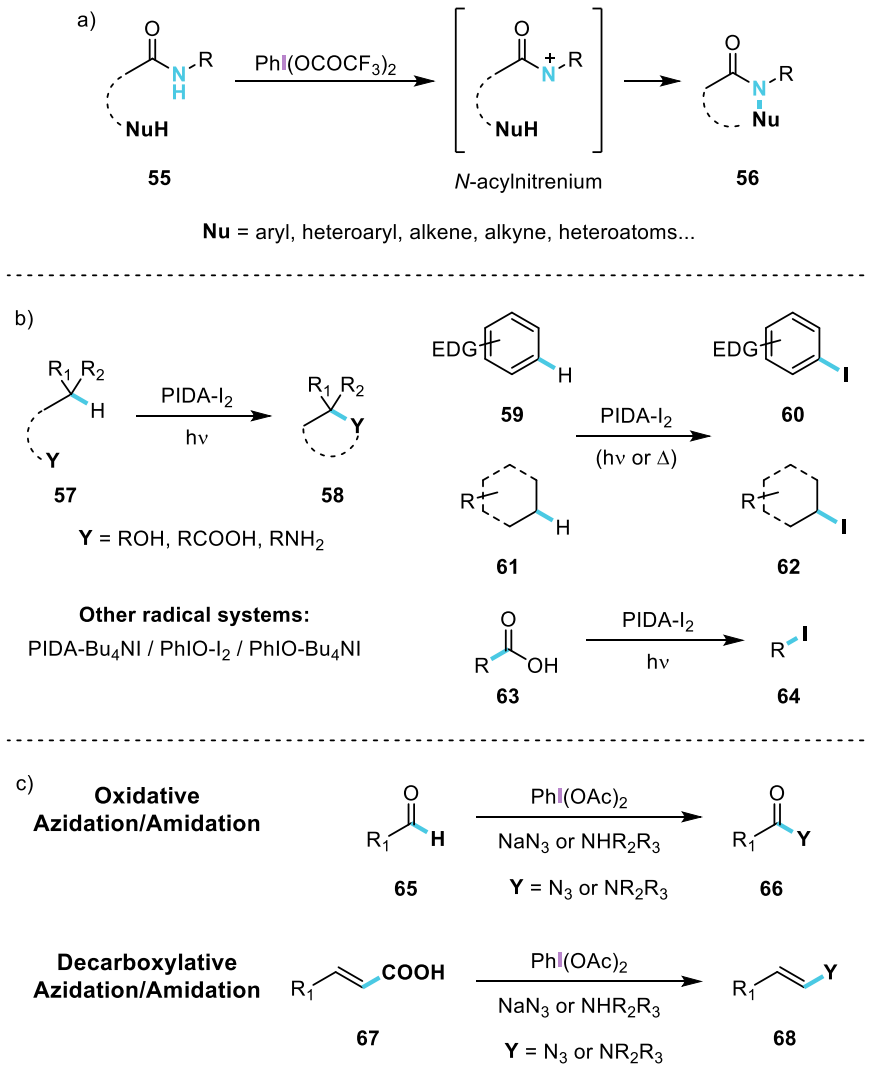
32 K. Muñiz, In *Hypervalent Iodine Chemistry*; T. Wirth, Ed.; *Top. Curr. Chem.* **2016**, *373*, 105–134.

C-H bond functionalisation

In the frame of iodine(III)-mediated chemistry, C-H bond functionalisation is the most versatile transformation, involving a wide range of reaction conditions, functional groups and mechanisms. In many cases, commercially available $PhI(OCOCF_3)_2$ and $PhI(OAc)_2$ are the reagents of choice, whether they act as the actual oxidants or as precursors of other λ^3-iodanes (**Scheme 1.11**).[4a-c,e]



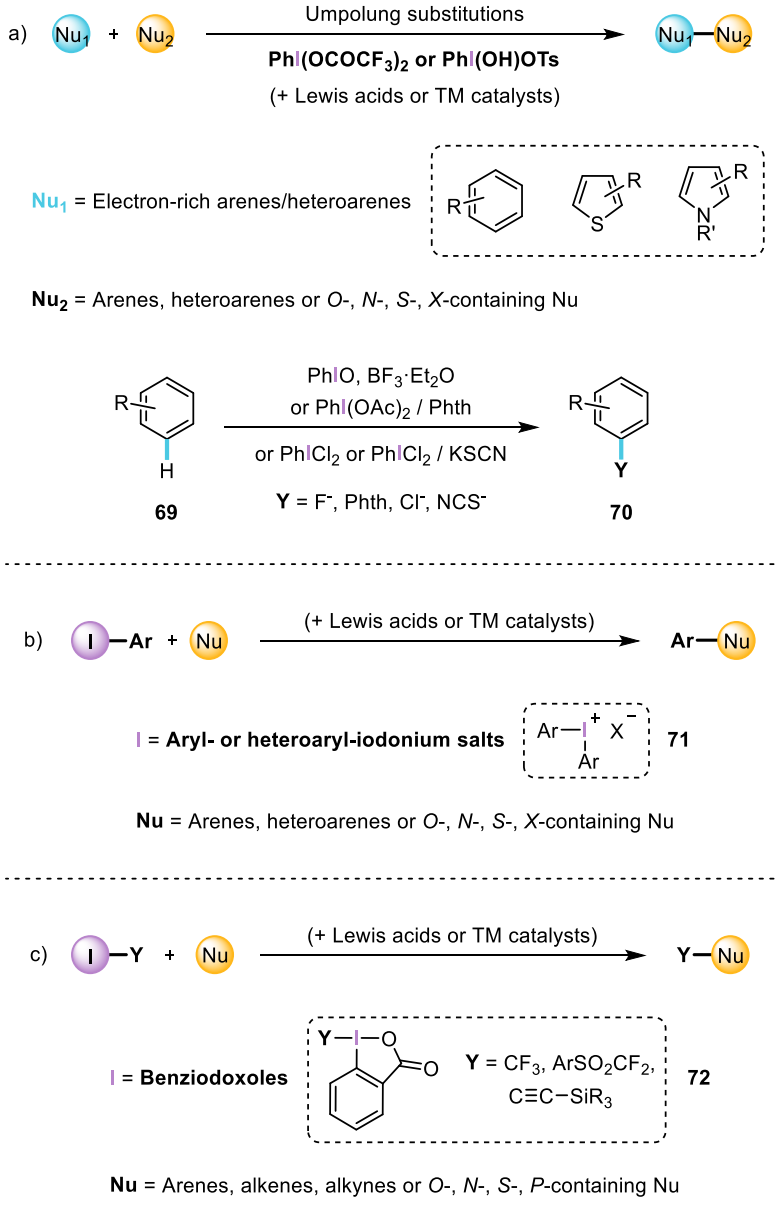
Scheme 1.11. PIFA- and PIDA-induced C-H bond functionalisation. a) PIFA-mediated oxidative cationic cyclisation of compounds **55**. b) PIDA-promoted radical C-H functionalisation. c) Oxidative azidation/amidation of aldehydes **65** and carboxylic acids **67**.

A remarkable example of C-H bond functionalisation is the PIFA-mediated cyclisation of amides **55** into *N*-containing heterocycles **56** of different sizes.[32] Mechanistic studies demonstrated that cationic *N*-acylnitrenium intermediate is the key active specie for the amidation of aryl, heteroaryl, alkenyl or alkynyl moieties and different heteroatoms (**Scheme 1.11** a).

On the other hand, in the presence of alcohols, carboxylic acids and amines, the combination of PIDA with molecular I_2 has been studied as a powerful radical-initiating system, generating oxygen- and nitrogen-centred radicals.[4a-c] Thus, intramolecular cyclisations of different hydrocarbon structures **57** have been reported for PIDA-I_2 system under photochemical conditions (**Scheme 1.11** b). Likewise, this reagent system also mediates the oxidative iodination of electron-rich arenes **59** and alkanes **61** upon irradiation or heating whereas decarboxylative decomposition of carboxylic acid **63** give access to terminal iodoalkanes **64** (**Scheme 1.11** b).

As mentioned before, [bis(acyloxy)iodo]benzenes are commonly used as precursors for the *in situ* generation of unstable hypervalent iodine(III) reagents, as it is the case for the oxidative azidation or amidation of aldehydes **65** in the presence of $PhI(OAc)_2$ and the corresponding nitrogen source. (**Scheme 1.11** c).[4a-c] A related synthetic methodology involves the transformation of α,β-unsaturated carboxylic acids **67** into *N*-substituted alkenes **68** upon PIDA-mediated decarboxylative decomposition (**Scheme 1.11** c).[4a-c] Moreover, preformed cyano- and azido-benziodoxoles represent an practical alternative to unstable *N*-containing λ^3-iodanes for C-H bond functionalisation of different functional groups.[5a,b]

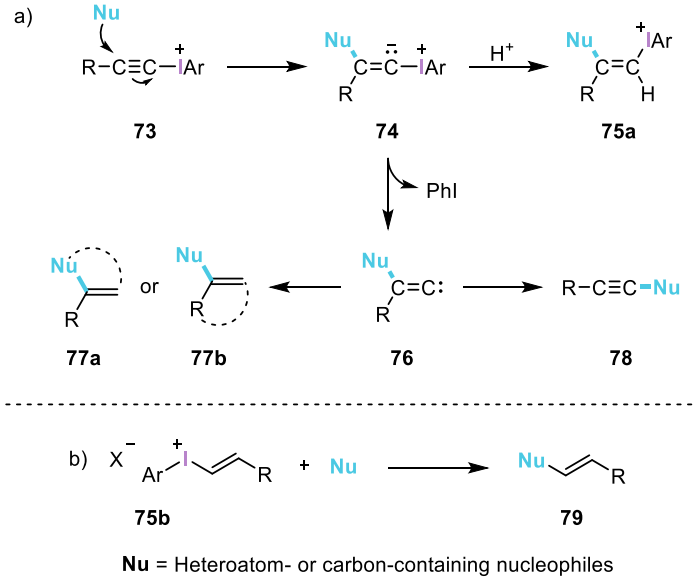
Several strategies for aromatic C-H bond functionalisation have also been reported at the literature. Thus, an alternative application to iodine(III)-mediated oxidative coupling of phenolic ethers **16** (**Scheme 1.4**) involves the related binding of electron-rich arenes, thiophenes and pyrroles with aromatic compounds or several heteroatomic nucleophiles in the presence of PIFA or Koser's reagent (**Scheme 1.12** a).[4a-c] Moreover, the oxidative introduction of fluoro, phthalimido, chloro and thiocyanate moieties has also been accomplished upon treatment of arene **69** with different combinations of λ^3-iodanes and the corresponding nucleophilic source (**Scheme 1.12** a).[4a-c]



Scheme 1.12. Iodine(III)-mediated Csp^2/Csp-H bond functionalisation. a) Umpolung substitutions of electron-rich arenes and heteroarenes. b) Oxidative functionalisations involving aryl- and heteroaryl iodonium salts **71**. c) Group-transfer reactions with trifluoromethyl-, (phenylsulfonyl)difluoromethyl- and alkynyl-benziodoxoles **72**.

In a similar way, aryl- and heteroaryl-iodonium salts **71** promoted the oxidative functionalisation of aromatic compounds or heteroatomic substrates (**Scheme 1.12**

b).[6,7] Along these lines, trifluoromethyl, (phenylsulfonyl)difluoromethyl- and alkynyl-benziodoxoles **72** have also been reported to react with arenes, alkenes and alkynes in the presence of a Lewis acid or a transition metal catalyst to form new C-C bonds via group-transfer reactions. (**Scheme 1.12** c).[5] Likewise, oxidative functionalisation of heteroatomic nucleophiles can also be performed upon treatment with these iodine(III) reagents.(**Scheme 1.12** c).[5]



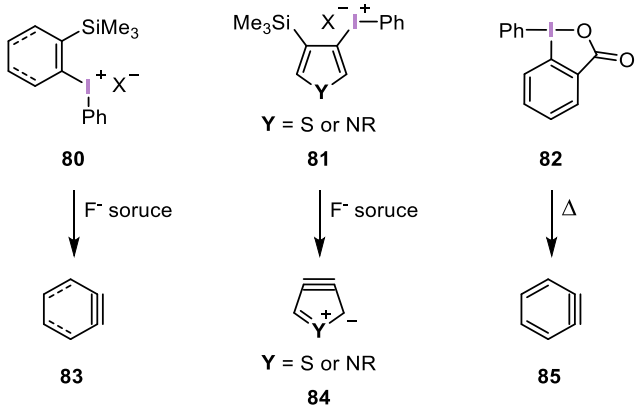
Scheme 1.13. a) General mechanism for the reaction of alkynyliodonium salts **73** with nucleophiles. b) Reactivity of alkenyliodonium salts **75b** with nucleophiles.

Alkynyliodonium salts **73** are commonly used as powerful alkylating reagents as exemplified by the α-functionalisation of carbonyl compounds **18** (**Scheme 1.6**). Under an alternative mechanism, their remarkable electrophilic nature favours nucleophile conjugated addition to the triple bond to furnish alkylideneiodonium ylides **74** (**Scheme 1.13** a).[4a,6,9] These highly reactive species can evolve through two different pathways: either they get protonated, giving access to substituted alkenyliodonium salts **75a** or they undergo reductive elimination of PhI group, generating alkylidene carbenes **76**. Final intramolecular 1,5-carbene insertion into nucleophilic moiety or alkylic side chain yields cyclic compounds **77a** and **77b** whereas linear alkyne **78** is formed upon 1,2-nucleophile shift.

On the other hand, a similar electrophilic behaviour has been observed for alkenyliodonium salts **75b** which undergo nucleophilic substitutions with heteroatoms or carbon-containing nucleophiles via S_N2, S_N1 or Michael addition-elimination pathways (**Scheme 1.13** b).[4a,6] Mechanistic aspects of such alkenylation reactions have been largely discussed and whether a stereoselective S_N2 addition-elimination or the formation of the corresponding vinylic cation take place depends on alkene substitution.[8]

Iodine(III)-mediated oxidative rearrangements

Finally, hypervalent iodine(III) reagents can also promote ring-contractions and expansions as well as other types of oxidative rearrangements such as Hoffmann and Claisen rearrangements.[31] In addition, they can participate in cycloaddition reactions upon trapping the *in situ* generated benzyne analogues **83**, **84** and **85** with dienes to furnish the corresponding adducts.[4a-c] These highly reactive intermediates can be synthesised from *ortho*-trimethylsilyl-substituted aryl-, alkenyl- and heteroaryl-iodonium salts **80** and **81** in the presence of different fluoride sources or upon thermal decomposition of phenylbenziodoxole **82** (**Scheme 1.14**).



Scheme 1.14. *In-situ* preparation of benzyne analogues **83**, **84** and **85** from *ortho*-trimethylsilyl-substituted iodonium salts **80** and **81** and phenylbenziodoxole **82**.

In situ reuse of hypervalent iodine reagents

Despite impressive development of hypervalent iodine chemistry in the past years, λ^3-iodanes-mediated transformations suffer from low atom-economy which has hampered their use in industrial applications. Thus, in order to reduce the important amounts of co-product waste generated during the process, re-oxidation of the aryl iodide would be highly recommended (**Figure 1.6**).[33]

From a synthetic point of view, a careful choice of terminal oxidant is needed to selectively regenerate the reduced iodine reagent while undesired oxidation of starting material was avoided (**Figure 1.6**).[4d,f,g] Initial achievements in such direction led to the electrochemical re-oxidation of aryl iodide. Later, *m*-CPBA emerged as the terminal oxidant of choice for the catalytic cycle.

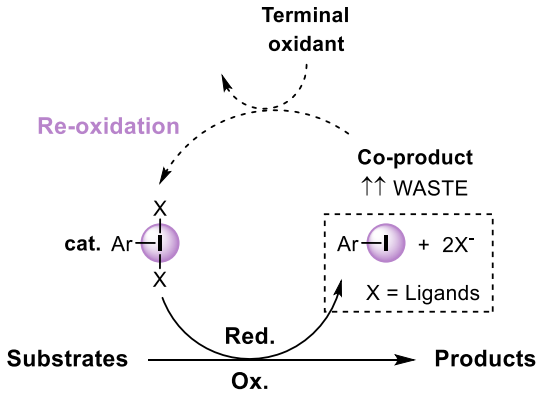


Figure 1.6. General mechanism for iodine(III)-catalysed oxidative functionalisations: *in-situ* reuse of hypervalent iodine reagents.

On the other hand, stoichiometric methodologies have benefitted from the recent preparation of polymer- and ion-supported hypervalent iodine compounds since regeneration of reduced iodine reagent was accomplished by simple filtration or extraction from the reaction medium and subsequent re-oxidation for its further reuse.[4a,g,34]

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33 R. D. Richardson, T. Wirth, *Angew. Chem. Int. Ed.* **2006**, *45*, 4402–4404.

34 M. S. Yusubov, V. V. Zhdankin, *Curr. Org. Synth.* **2012**, *9*, 247–272.

UNIVERSITAT ROVIRA I VIRGILI
METAL-FREE REGIO- AND STEREOSELECTIVE VICINAL DIFUNCTIONALISATION OF DIENYL CARBAMATES
Irene Giménez Nueno

CHAPTER II

AIMS AND OBJECTIVES

UNIVERSITAT ROVIRA I VIRGILI
METAL-FREE REGIO- AND STEREOSELECTIVE VICINAL DIFUNCTIONALISATION OF DIENYL CARBAMATES
Irene Giménez Nueno

Aims and objectives

The present PhD work aims at developing new synthetic methodologies for the regio- and stereoselective preparation of unsaturated vicinal hetero-amino moieties as common structural components in relevant lipids occurring in nature (**Figure 2.1**). This objective stems from the group's general interest in synthesising sphingosine analogues to test them as SphK1 inhibitors for cancer treatment.[35]

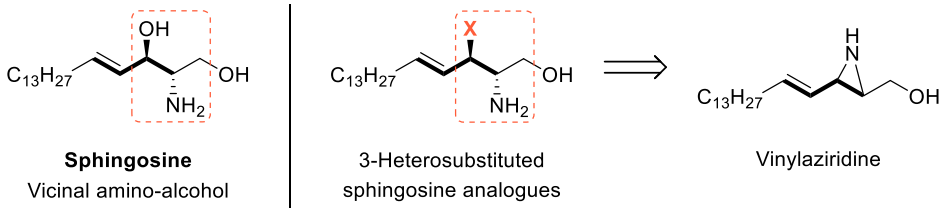

Figure 2.1. Proposed retrosynthetic pathway for the stereoselective preparation of unsaturated vicinal hetero-amino moiety related to relevant lipids occurring in nature.

The results have been divided in four chapters:

Chapter III. The main objective of this chapter concerns the development of a metal-free strategy for the regio- and stereoselective aziridination/ring-opening of dienyl carbamates in the presence of hypervalent iodine reagents to furnish unsaturated racemic oxazolidinones bearing desired vicinal hetero-amino moiety. For this purpose, the following aspects will be explored:

- Screening of common hypervalent iodine reagents for the *one-pot* metal-free regioselective aziridination/ring-opening of model dienyl carbamate and further optimisation of reaction conditions.
- Mechanistic calculations on iodine(III)-mediated aziridination.
- Study of the reaction scope for differently substituted dienyl carbamates.
- Preparation of unsaturated 1,2-difunctionalised products via ring-opening of intermediate vinylaziridine with *O*-, *N*-, *X*- and *S*-nucleophiles.

[35] D. Plano, S. Amin, A. K. Sharma, *J. Med. Chem.* **2014**, *57*, 5509–5524.

Chapter IV. The aim of this chapter involves the study of the asymmetric synthesis of vinylaziridines using chiral iodine(III) reagents. For this purpose, the following aspects will be explored:

- Literature analysis of already reported lactate-based iodine(III) reagents.
- Optimisation of reaction conditions for $PhI(OAc)_2$ mediated aziridination and *in situ* ring-opening of model dienyl carbamate, including additives screening.
- Preliminary study of the asymmetric aziridination of model dienyl carbamate under lactate-based iodine(III) catalysis.

Chapter V. The main objective of this chapter concerns the organocatalysed kinetic resolution of racemic oxazolidinones (chapter III) for the enantioselective preparation of sphingosine analogues bearing alternative heteroatomic substituents at position 3. For this purpose, the following aspects will be explored:

- Study of the effect of protecting group for the organocatalysed kinetic resolution of hydroxy-substituted oxazolidinones.
- Mechanistic calculations on the origin of the asymmetric induction.
- Generalisation of the kinetic resolution protocol for *N*- and *S*-containing starting materials.
- Optimisation of the cross-metathesis reaction for the derivatisation of enantioenriched oxazolidinones with different aliphatic chains.
- Final deprotection of sphingosine analogues.

Chapter VI. This chapter contains the general procedures and experimental data from previous sections.

Chapter VII. In addition, the last chapter of the present PhD work describes the research carried out during a predoctoral stay at UC Berkeley under the supervision of Prof. Richmond Sarpong, concerning the total synthesis of phleghenrine alkaloids for their biological evaluation as palliative drugs for Alzheimer's disease (**Figure 2.2**).[36] For this purpose, the following aspects will be explored:

[36] L.-B. Dong, X.-D. Wu, X. Shi, Z.-J. Zhang, J. Yang, Q.-S. Zhao, *Org. Lett.* **2016**, *18*, 4498–4501.

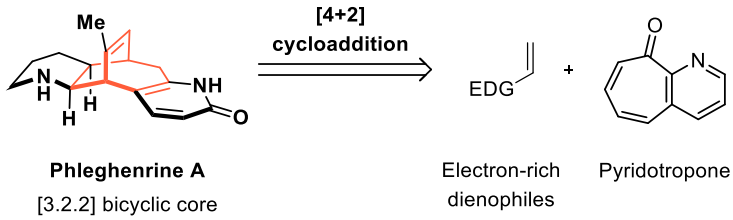

Figure 2.2. Proposed retrosynthetic pathway for the preparation of phleghenrine [3.2.2] bicyclic core via inverse-electron demand Diels-Alder reaction.

- Direct preparation of phleghenrine [3.2.2] bicyclic core via inverse-electron demand Diels-Alder reaction using pyridotropone as diene.
- Optimisation of cycloaddition conditions, including Lewis acids' screening.
- Study of the reaction scope for different electron-rich dienophiles.

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CHAPTER III

ONE-POT METAL-FREE REGIOSELECTIVE DIENE AZIRIDINATION/RING-OPENING

UNIVERSITAT ROVIRA I VIRGILI
METAL-FREE REGIO- AND STEREOSELECTIVE VICINAL DIFUNCTIONALISATION OF DIENYL CARBAMATES
Irene Giménez Nueno

3.1. Introduction

3.1.1. Aziridines and vinylaziridines

Traditionally considered as epoxide equivalents, aziridines are the smallest class of *N*-containing saturated heterocycles.[37,38] Ubiquitous motif in nature, they are part of many important synthetic targets such as biologically active natural products,[39] pharmaceutical drugs,[40] chiral auxiliaries[41] or catalysts ligands[41] (**Figure 3.1**). Aziridines reactivity is driven by their highly strained structure (they present 60º bond angles instead of the commonly observed 109.5º for sp^3 hybridised atoms). Thus, their constrained ring geometry in combination with the electron-withdrawing nature of the nitrogen atom make them prone to ring-opening reactions via C-N bond cleavage (**Figure 3.1**).[41,42] Thus, aziridines are versatile building blocks in organic synthesis as precursors of vicinal amines, amino-alcohols, amino-acids, amino-sugars

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37 a) A. Padwa, In *Comprehensive Heterocyclic Chemistry III*; A. R. Katrizky, C. A. Ramsden, E. F. V. Scriven, R. J. K. Taylor, Eds.; Elsevier: New York, USA, **2008**; Chap. *1*, pp. 1–104. b) *Aziridines and Epoxides in Organic Synthesis*; A. K. Yudin, Ed.; Wiley-VCH: Weinheim, Germany, **2006**. c) A. Padwa, S. Murphree, In *Progress in Heterocyclic Chemistry*; G. W. Gribble, J. A. Joule, Eds.; Elsevier Science: Oxford, England, **2003**; Vol. *15*, pp. 75–99. d) B. Zwanenburg, P. ten Holte, In *Stereoselective Heterocyclic Synthesis III*; P. Metz, Ed.; *Top. Curr. Chem.* **2001**, *216*, 93–124.

38 a) S. Sabir, G. Kumar, J. L. Jat, *Asian J. Org. Chem.* **2017**, *6*, 782–793. b) S. Jarzyński, S. Leśniak, *Chem. Heterocycl. Compd.* **2016**, *52*, 353–355. c) L. Degennaro, P. Trinchera, R. Luisi, *Chem. Rev.* **2014**, *114*, 7881–7929. d) H. Pellissier, *Adv. Synth. Catal.* **2014**, *356*, 1899–1935. e) H. Pellissier, *Tetrahedron* **2010**, *66*, 1509–1555. f) G. S. Singh, M. D'hooghe, N. De Kimpe, *Chem. Rev.* **2007**, *107*, 2080–2135. g) J. B. Sweeney, *Chem. Soc. Rev.* **2002**, *31*, 247–258.

39 a) F. M. D. Ismail, D. O. Levitsky, V. M. Dembitsky, *Eur. J. Med. Chem.* **2009**, *44*, 3373–3387. b) C. Botuha, F. Chemla, F. Ferreira, A. Pérez-Luna, In *Heterocycles in Natural Product Synthesis*; K. C. Majumdar, S. K. Chattopadhyay, Eds.; Wiley-VCH: Weinheim, Germany, **2011**; Part I, pp. 3–39. c) P. A. S. Lowden, In *Aziridines and Epoxides in Organic Synthesis*; A. K. Yudin, Ed.; Wiley-VCH: Weinheim, Germany, **2006**; pp. 399–441.

40 a) V. H. Dahanukar, L. A. Zavialov, *Curr. Opin. Drug Dis. Dev.* **2002**, *5*, 918–927. b) G. S. Singh, *Mini-Reviews in Med. Chem.* **2016**, *16*, 892–904. c) S. Fürmeier, J. O. Metzger, *Eur. J. Org. Chem.* **2003**, 649–659.

41 W. McCoull, F. A. Davis, *Synthesis* **2000**, 1347–1365.

42 a) X. E. Hu, *Tetrahedron* **2004**, *60*, 2701–2743. b) P. Lu, *Tetrahedron* **2010**, *66*, 2549–2560. c) S. Stanković, M. D'hooghe, S. Catak, H. Eum, M. Waroquier, V. Van Speybroeck, N. De Kimpe, H.-J. Ha, *Chem. Soc. Rev.* **2012**, *41*, 643–665.

and azaheterocycles which, in turn, are pivotal intermediates for the preparation of more complex molecules (**Figure 3.1**).[43]

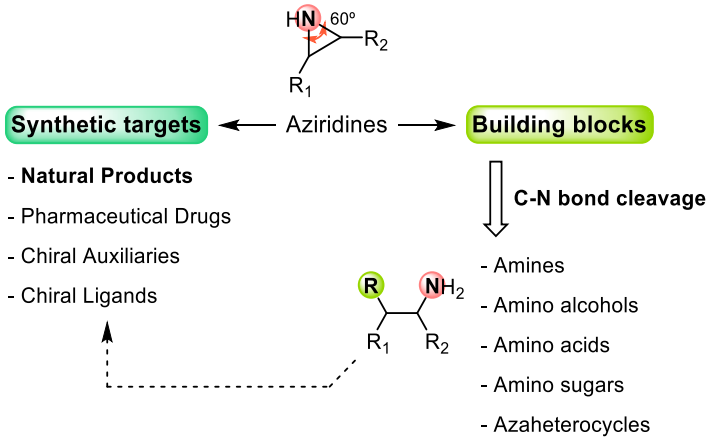

Figure 3.1. Aziridines in organic synthesis.

Among biological active compounds containing aziridine units, Mitomycin C is a powerful antitumor agent that promotes DNA alkylation upon bioreductive activation of its quinone moiety and subsequent heterocycle cleavage (**Figure 3.2**).[38g,44] In 2001, R. S. Coleman and co-workers reported the total synthesis of the naturally occurring anticancer agent Azinomycin A upon stereoselective preparation of its azabicyclic core (**Figure 3.2**).[45] A common structural feature of the Azinomycin family is the presence of an aziridine, an epoxide and a substituted naphthalene unit all of which play a central role in their DNA cross-linking ability (**Figure 3.2**).[46] Thus, non-covalent interactions between the naphthalene moiety and the DNA helix guide

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43 a) B. Darses, R. Rodrigues, L. Neuville, M. Mazurais, P. Dauban, *Chem. Commun.* **2017**, *53*, 493–508. b) R. H. Dodd, *Molecules* **2000**, *5*, 293–298.

44 a) S. E. Wolkenberg, D. L. Boger, *Chem. Rev.* **2002**, *102*, 2477–2496. b) T. Fukuyama, L. Yang, *J. Am. Chem. Soc.* **1989**, *111*, 8303–8304. c) P. D. Bass, D. A. Gubler, T. C. Judd, R. M. Williams, *Chem. Rev.* **2013**, *113*, 6816–6863.

45 a) R. S. Coleman, J. Li, A. Navarro, *Angew. Chem. Int. Ed.* **2001**, *40*, 1736–1739. b) R. S. Coleman, J.-S. Kong, T. E. Richardson, *J. Am. Chem. Soc.* **1999**, *121*, 9088–9095. c) R. S. Coleman, J.-S. Kong, *J. Am. Chem. Soc.* **1998**, *120*, 3538–3539.

46 K. Nagaoka, M. Matsumoto, J. Oono, K. Yokoi, S. Ishizeki, T. Nakashima, *J. Antibiot.* **1986**, *39*, 1527–1532.

direct nucleophile ring-opening by DNA purine bases.[47] In addition, two other members of this class of natural products, aromatic polyketides Azicemicins A and B, exert moderate inhibiting activity against gram-positive bacteria and mycobacteria (**Figure 3.2**).[48] Interestingly, isotope-tracer experiments have proved that Azicemicins' aziridine ring is biologically synthesised from aspartic acid.[49] Finally, the antibacterial properties of Madurastatin A1 have also been related to its *N*-acyl aziridine moiety (**Figure 3.2**).[50]

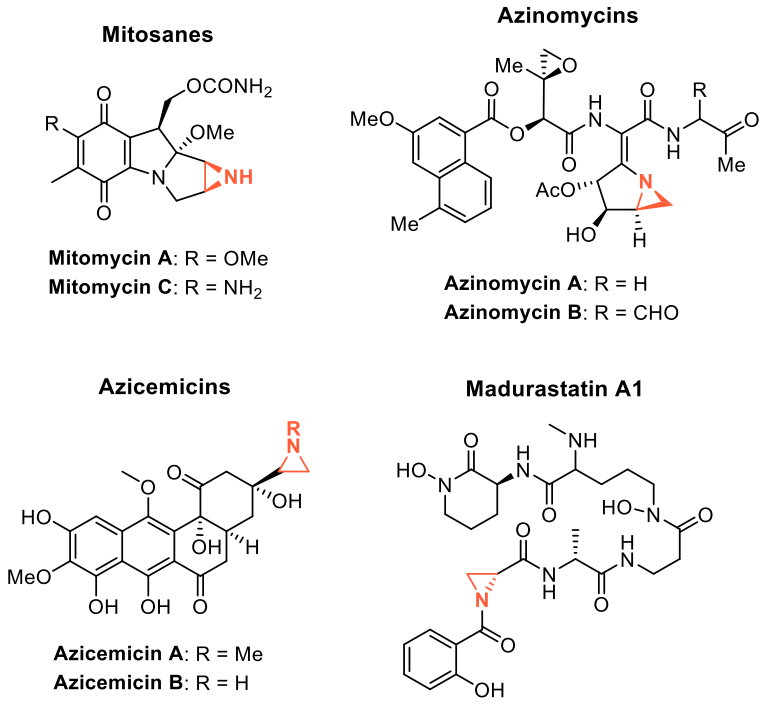

Figure 3.2. Aziridine-containing natural products.

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47 a) C. A. S. Landreau, R. C. LePla, M. Shipman, A. M. Z. Slawin, J. A. Hartley, *Org. Lett.* **2004**, *6*, 3505–3507. b) J. Foulke-Abel, H. Agbo, H. Zhang, S. Mori, C. M. H. Watanabe, *Nat. Prod. Rep.* **2011**, *28*, 693–704.

48 a) T. Tsuchida, R. Sawa, Y. Takahashi, H. Iinuma, T. Sawa, H. Naganawa, T. Takeuchi, *J. Antibiot.* **1995**, *48*, 1148–1152. b) T. Tsuchida, H. Iinuma, N. Kinoshita, T. Ikeda, T. Sawa, M. Hamada, T. Takeuchi, *J. Antibiot.* **1995**, *48*, 217–221.

49 Y. Ogasawara, H. Liu, *J. Am. Chem. Soc.* **2009**, *131*, 18066–18068.

50 K. Harada, K. Tomita, K. Fujii, K. Masuda, Y. Mikami, K. Yazawa, H. Komaki, *J. Antibiot.* **2004**, *57*, 125–135.

Besides the already mentioned chemical properties of aziridines, the presence of an exocyclic olefin, as in vinyl and methylene aziridines, or an alkynyl moiety, as in ethynylaziridines, alfa to the three-membered heterocycle further expands their versatile application in organic synthesis.[51,52] Thus, neighbouring multiple bond can stabilise any incipient charges or radicals generated upon aziridine ring-opening, take part into intramolecular rearrangements or being functionalised with external reagents without aziridine alteration.

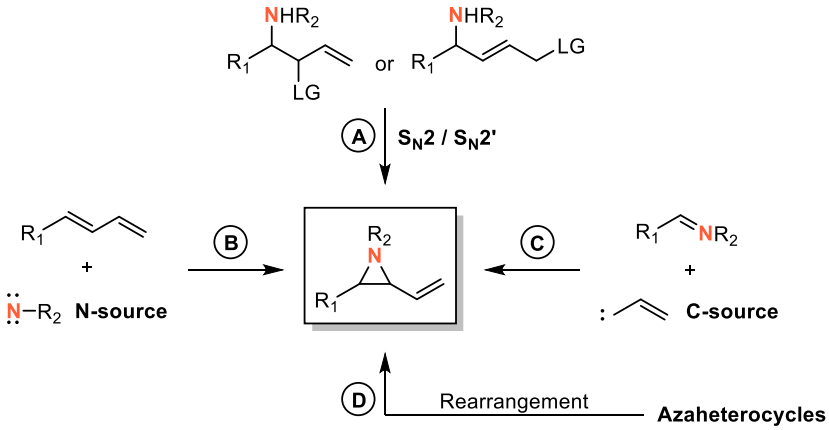

Figure 3.3. General methods for the synthesis of vinylaziridines.

Vinylaziridines have been traditionally synthesised upon intramolecular S_N2 or S_N2' leaving group displacement from starting materials containing double bonds (**Figure 3.3**, A).[51] However, in the past years, the addition of nitrene equivalents into conjugated dienes or allyl carbenes into imino compounds respectively have received much attention resulting in the recent development of asymmetric strategies for the preparation of vinylaziridines (**Figure 3.3**, B and C).[51] Alternatively, larger heterocycles can also rearrange under different reaction conditions to yield three-membered aziridines with an adjacent vinyl moiety (**Figure 3.3**, D).[51]

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51 a) H. Ohno, In *Aziridines and Epoxides in Organic Synthesis*; A. K. Yudin, Ed.; Wiley-VCH: Weinheim, Germany, **2006**; pp. 37–71. b) H. Ohno, *Chem. Rev.* **2014**, *114*, 7784–7814.

52 C. S. Adams, C. D. Weatherly, E. G. Burke, J. M. Schomaker, *Chem. Soc. Rev.* **2014**, *43*, 3136–3163.

3.1.2. Iminoiodanes as nitrene precursors

Nitrenes are neutral monovalent species with six electrons in their valence shell.[43a,53] Initially generated upon thermal or photochemical extrusion of molecular nitrogen from organic azides, their highly reactive nature and poor selectivity hampered a widespread application in organic synthesis for C-N bond formation. However, nitrene chemistry has benefitted from the recent studies on transition metal catalysed transformations. Thus, upon stabilisation of the free nitrene species as metallonitrene complexes, efficient protocols for alkane amination and olefin aziridination have been developed for the preparation of *N*-containing products (**Figure 3.4**).[43a,53,54,55]

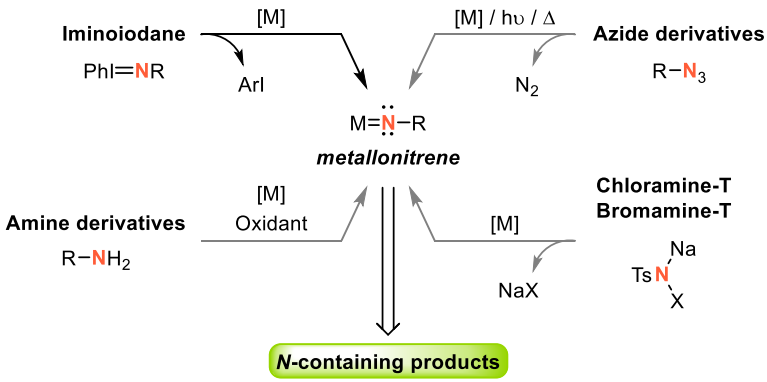

Figure 3.4. Nitrene sources for the preparation of *N*-containing compounds.

To date, according to the literature, four different types of nitrene precursors have been described for the generation of reactive intermediate metallonitrene species (**Figure 3.4**).[55] Iminoiodanes are a class of hypervalent iodine compounds that effectively transfer nitrogen moiety into the metal centre. Moreover,

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53 G. Dequirez, V. Pons, P. Dauban, *Angew. Chem. Int. Ed.* **2012**, *51*, 7384–7395.

54 a) P. Dauban, R. H. Dodd, *Synlett* **2003**, 1571–1586. b) J. W. W. Chang, T. M. U. Ton, P. W. H. Chan, *Chem. Rec.* **2011**, *11*, 331–357.

55 a) P. Dauban, B. Darses, A. Jarvis, In *Comprehensive Organic Synthesis II*; P. Knochel, Ed.; Elsevier: Oxford, England, **2014**; Vol *7*, pp. 538–604. b) S. Minakata, Y. Takeda, K. Kiyokawa, In *Methods and Applications of Cycloaddition Reactions in Organic Synthesis*; N. Nishiwaki, Ed.; John Wiley & Sons, Inc.: Hoboken, New Jersey, USA, **2014**; pp. 67–88. c) S. Fantauzzi, A. Caselli, E. Gallo, *Dalton Trans.* **2009**, 5434–5443. d) J. A. Halfen, *Curr. Org. Chem.* **2005**, *9*, 657–669.

metallonitrenes can also be *in situ* synthesised upon treatment of amine derivatives with oxidant reagents such as PhIO or $PhI(OAc)_2$. Alternatively, transformations of organic azides or *N*-haloamine salts such as Chloramine-T or Bromamine-T acting as nitrene sources have been reported.[55]

As mentioned before, an efficient method for the preparation of vinylaziridines involves the addition of nitrene equivalents into conjugated dienes (**Figure 3.3**).[51] Iminoiodanes, in particular [*N*-(*p*-toluenesulfonyl)imino]phenyliodane (PhINTs),[56] are the nitrene sources of choice for olefin aziridination due to the benign character of hypervalent iodine compounds, easy handling and remarkable chemical performance in the presence of different metal catalyst.[43a,54,57] However, the polymeric structure of PhINTs **86** makes it poorly soluble in commonly used organic solvents which has prevented its widespread synthetic application (**Figure 3.5**).[58]

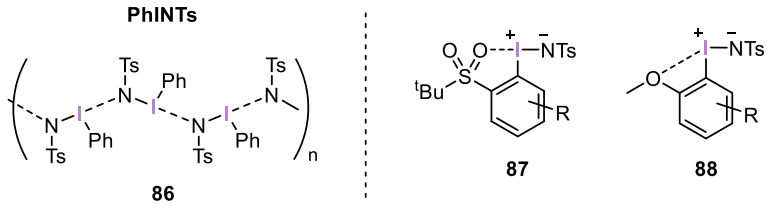

Figure 3.5. Polymeric structure of PhINTs **86** and intramolecular interactions in *ortho*-substituted iminoiodanes **87** and **88**.

In order to overcome this disadvantage, *ortho*-substituted analogues **87** and **88** have been prepared and tested for nitrene group transfer (**Figure 3.5**). As expected, the effective redirection of secondary I···N bonds in polymer **86** into intramolecular interactions between the iodine atom and the *ortho*-group in compounds **87** and **88**

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56 Y. Yamada, T. Yamamoto, M. Okawara, *Chem. Lett.* **1975**, 361–362.

57 a) D. Karila, R. H. Dodd, *Curr. Org. Chem.* **2011**, *15*, 1507–1538. b) P. Müller, C. Fruit, *Chem. Rev.* **2003**, *103*, 2905–2919.

58 a) A. K. Mishra, M. M. Olmstead, J. J. Ellison, P. P. Power, *Inorg. Chem.* **1995**, *34*, 3210–3214. b) J. D. Protasiewicz, *Acta Crystallogr. C* **1996**, *52*, 1570–1572. c) M. Boucher, D. Macikenas, T. Ren, J. D. Protasiewicz, *J. Am. Chem. Soc.* **1997**, *119*, 9366–9376.

leads to a solubility enhancement.[59] Moreover, the existing protocols for the preparation of PhINTs and other commonly used *N*-sulfonyl iminoiodanes lack of reproducibility and often involve tedious purification steps. This results in the low quality of iodonium imides and hampers their performance as nitrene precursor for the aziridination reaction.[54a]

An alternative methodology to circumvent the aforementioned experimental issues arise from the *in situ* preparation of iminoiodanes. Pioneering works by P. Dauban and R. H. Dodd concerning the intramolecular copper-catalysed aziridination of olefinic sulfonamides[60] and Du Bois' intramolecular rhodium-catalysed C-H insertion for the transformation of alkyl carbamates to oxazolidinones,[61] proved the feasibility of this strategy. In both cases, commercially available (diacetoxyiodo)benzene was used as the terminal oxidant for the effective formation of iminoiodanes. Iodosylbenzene has also been reported to mediate oxidation of amine into iodonium imines. Efficient protocols for its depolymerisation involved the addition of catalytic amounts of Lewis acids, halogen anions or transition metal complexes.[62]

3.1.3. Synthesis of vinylaziridines via metal-catalysed nitrene insertion into conjugated dienes

A general mechanism for transition-metal catalysed diene aziridination using iminoiodanes as nitrene precursors is depicted in **Figure 3.6** a. Thus, after initial formation of the metallonitrene intermediate via iminoiodane reduction,

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59 a) V. V. Zhdankin, J. D. Protasiewicz, *Coord. Chem. Rev.* **2014**, *275*, 54–62. b) D. Macikenas, E. Skrzypczak-Jankun, J. D. Protasiewicz, *J. Am. Chem. Soc.* **1999**, *121*, 7164–7165. c) B. V. Meprathu, J. D. Protasiewicz, *Tetrahedron* **2010**, *66*, 5768–5774. d) A. Yoshimura, V. N. Nemykin, V. V. Zhdankin, *Chem. Eur. J.* **2011**, *17*, 10538–10541.

60 P. Dauban, R. H. Dodd, *Org. Lett.* **2000**, *2*, 2327–2329.

61 C. G. Espino, J. Du Bois, *Angew. Chem. Int. Ed.* **2001**, *40*, 598–600.

62 a) R. M. Moriarty, S. Tyagi, *Org. Lett.* **2010**, *12*, 364–366. b) J. Cui, Q. Jia, R.-Z. Feng, S.-S. Liu, T. He, C. Zhang, *Org. Lett.* **2014**, *16*, 1442–1445. c) H. Tohma, S. Takizawa, T. Maegawa, Y. Kita, *Angew. Chem. Int. Ed.* **2000**, *39*, 1306–1308. d) H. Tohma, T. Maegawa, S. Takizawa, Y. Kita, *Adv. Synth. Catal.* **2002**, *344*, 328–337.

regioselective nitrene insertion into a double bond from the conjugated diene takes place, yielding the desired vinylaziridine.

The stereoselectivity of the aziridination step has been traditionally related to the electronic structure of the nitrene valence shell (**Figure 3.6** b). A concerted addition mechanism via singlet nitrene species has been envisioned for rhodium- and silver-stabilised metallonitrenes, with complete retention of double bond configuration. On the contrary, mixtures of *cis*/*trans* aziridines are commonly observed under copper catalysis presumably due to radical processes arising from triplet nitrene states.[43a]

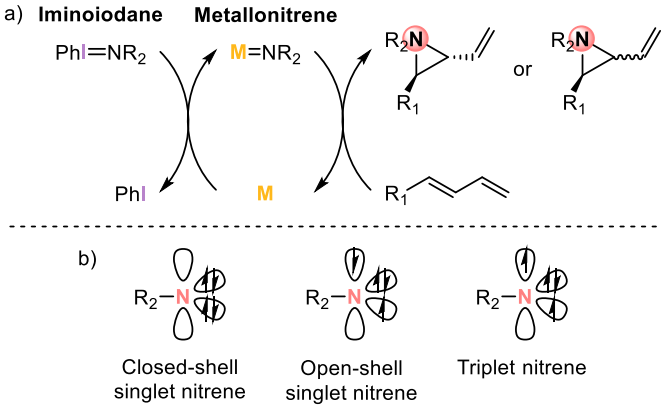

Figure 3.6. a) General mechanism for TM-catalysed diene aziridination using iminoiodanes as nitrene precursors. b) Electronic structure of a nitrene valence shell.

Recent DFT calculations proved the occurrence of minimum energy crossing points (MECP) within the diene aziridination energy profile that allowed spin-crossing from triplet nitrene species to singlet nitrene intermediates.[63] Thus, from triplet metallonitrene complex, the placement of these MECP in the overall reaction energy profile for a specific transition-metal catalyst determines whether aziridine is formed in a stereospecific manner.

[63] a) J. Llaveria, Á. Beltrán, W. M. C. Sameera, A. Locati, M. M. Díaz-Requejo, M. I. Matheu, S. Castillón, F. Maseras, P. J. Pérez, *J. Am. Chem. Soc.* **2014**, *136*, 5342–5350. b) L. Maestre, W. M. C. Sameera, M. M. Díaz-Requejo, F. Maseras, P. J. Pérez, *J. Am. Chem. Soc.* **2013**, *135*, 1338–1348.

3.1.3.1. Metal-catalysed intermolecular diene aziridination

PhINTs as nitrene source

Inspired by the pioneering examples of copper-catalysed alkene aziridination using PhINTs as nitrene source,[64] J. G. Knight and co-workers applied the aforementioned methodology to the preparation of vinylaziridines.[65] Thus, in the presence of copper-(II) acetylacetonate catalyst **91**, they were able to selectively synthesise cyclic vinylaziridines **90** and **94** in moderate yields (50-60%) (**Scheme 3.1**). Alternatively, a racemic nitridomanganese complex **92** has also been reported for the preparation of cyclic vinylaziridines **90** in the presence of pyridine, *p*-toluenesulfonic anhydride and pyridine-*N*-oxide (**Scheme 3.1** a).[66]

In 1995, T. Hudlicky and co-workers completed the enantioselective total synthesis of (+)-Pancratistain from dienyl acetonide **95** (**Scheme 3.1** b). After the preparation of the vinylaziridine intermediate **96** under copper-catalysed conditions, the key formation C-C bond between A and C rings was carried out by aziridine ring-opening in the presence of phenyl cyano cuprate reagents.[67] Later, this group reported a similar aziridination protocol for the synthesis of the hexahydroazepine core of natural product Balanol from dienyl acetonide **95**.[68] Moreover, the formal synthesis of Angelastin A[69] and the preparation of aziridino epoxides[70] has been described upon treatment of cyclic dienes **89** with $Cu(acac)_2$ catalyst **91** and PhINTs as nitrene precursor.

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64 a) D. A. Evans, M. M. Faul, M. T. Bilodeau, *J. Org. Chem.* **1991**, *56*, 6744–6746. b) D. A. Evans, M. M. Faul, M. T. Bilodeau, B. A. Anderson, D. M. Barnes, *J. Am. Chem. Soc.* **1993**, *115*, 5328–5329. c) D. A. Evans, M. T. Bilodeau, M. M. Faul, *J. Am. Chem. Soc.* **1994**, *116*, 2742–2753. d) Z. Li, K. R. Conser, E. N. Jacobsen, *J. Am. Chem. Soc.* **1993**, *115*, 5326–5327.

65 J. G. Knight, M. P. Muldowney, *Synlett* **1995**, 949–951.

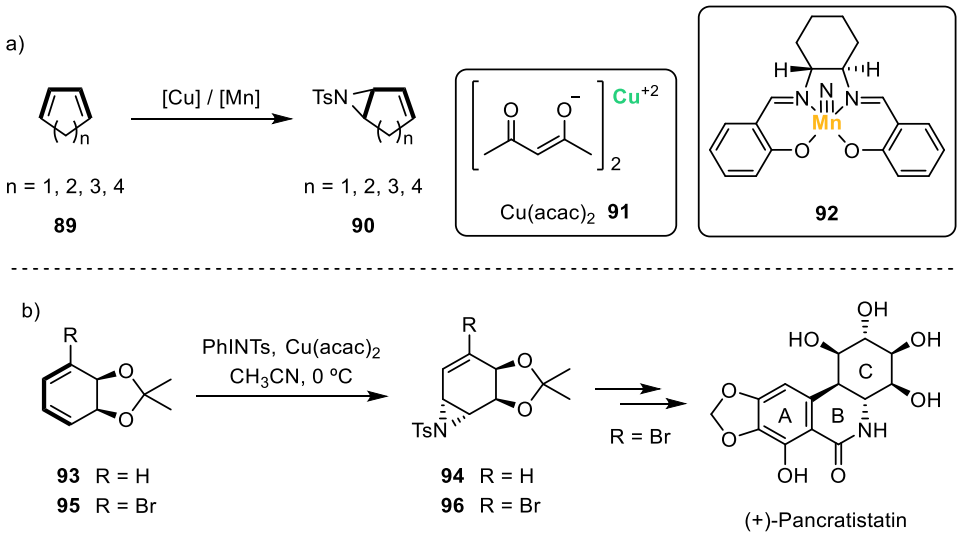
66 M. Nishimura, S. Minakata, S. Thongchant, I. Ryu, M. Komatsu, *Tetrahedron Lett.* **2000**, *41*, 7089–7092.

67 a) X. Tian, T. Hudlicky, K. Königsberger, *J. Am. Chem. Soc.* **1995**, *117*, 3643–3644. b) T. Hudlicky, X. Tian, K. Königsberger, R. Maurya, J. Rouden, B. Fan, *J. Am. Chem. Soc.* **1996**, *118*, 10752–10765.

68 J. Gilmet, B. Sullivan, T. Hudlicky, *Tetrahedron* **2009**, *65*, 212–220.

69 E. Baron, P. O'Brien, T. D. Towers, *Tetrahedron Lett.* **2002**, *43*, 723–726.

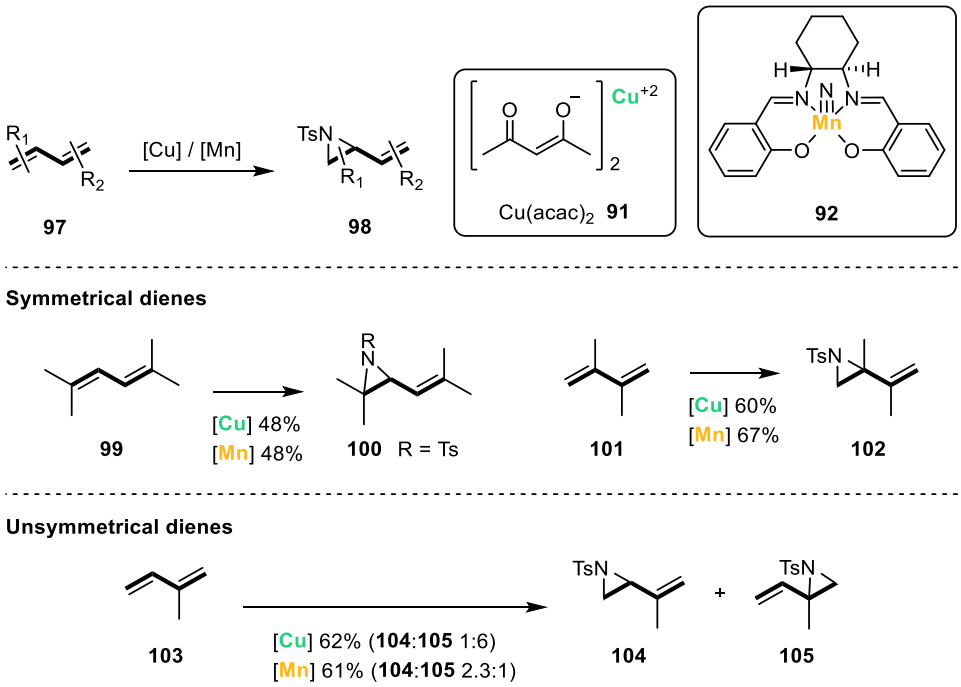
70 D. Sureshkumar, S. Maity, S. Chandrasekaran, *J. Org. Chem.* **2006**, *71*, 1653–1657.



Scheme 3.1. a) Cu- and Mn-catalysed aziridination of cyclic dienes **89** using PhINTs as nitrene source. b) Enantioselective total synthesis of (+)-Pancratistain from diene-diol **95**.

Along these lines, acyclic dienes **97** have also been employed as starting materials for the synthesis of vinylaziridines **98** (**Scheme 3.2**).[65,66] Similar aziridination yields were obtained for symmetrical dienes **99** and **101** under copper or manganese catalysis. However, unsymmetrical 1,3-butadiene **103** gave divergent regioselectivities depending on the nature of the transition-metal catalysts used. Thus, in the case of copper-(II) acetylacetonate **91**, predominant aziridination of the more electron-rich double bond **105** occurred whereas reaction at the less substituted alkene **104** was observed for the racemic nitridomanganese complex **92**, probably due to the remarkable steric hinderance around metal atom.

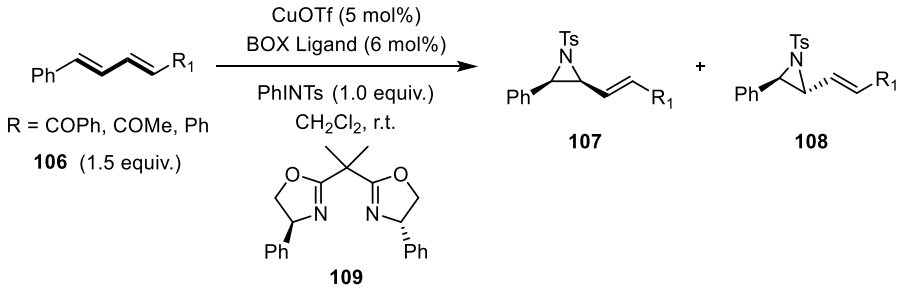
In addition, preliminary attempts towards the asymmetric synthesis of vinylaziridines from 2-*tert*-butyl-1,3-butadiene were carried out using a chiral version of catalyst complex **92** in the presence of pyridine, *p*-toluenesulfonic anhydride and pyridine-*N*-oxide, albeit with low enantioselectivities (40% ee).[66]



Scheme 3.2. Cu- and Mn-catalysed aziridination of symmetrical **99** and **101** and unsymmetrical **103** acyclic dienes using PhINTs as nitrene source.

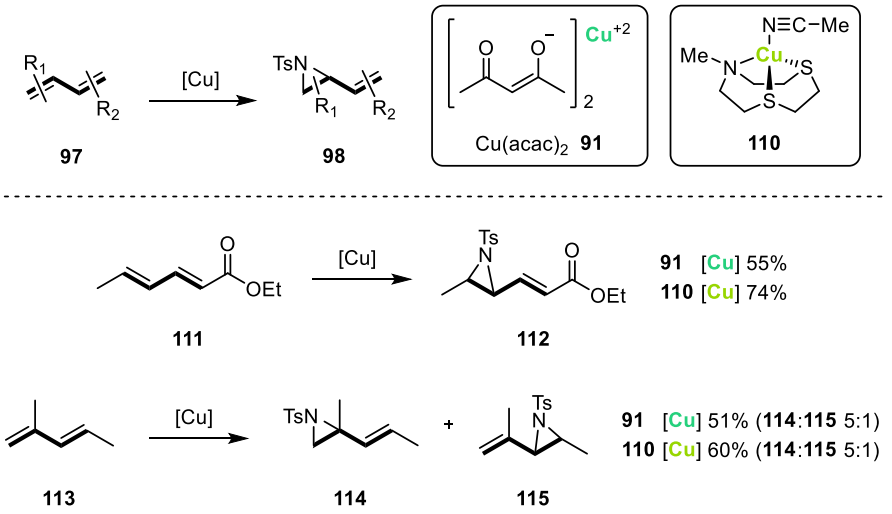
Alternatively, J. Xu and co-workers successfully applied Evans' bisoxazoline-copper complexes[64b] to induce enantiocontrol over aziridine generation (**Scheme 3.3**)[71] In general, ketone-substituted dienes **106** (R = COPh, COMe) selectively yielded *cis*-aziridines **107** up to 80% ee for BOX ligand **109**. On the contrary, nearly racemic mixtures of *trans*/*cis* vinylaziridines were obtained when diphenyl butadiene **106** (R = Ph) was used as starting material. In the light of major formation of *cis*-product **107** from *trans* double bonds, a stepwise mechanism was proposed. Thus, after initial nitrene insertion into conjugated diene, the resulting radical intermediate was able to rotate to place both olefinic substituents in a *cis*-array, minimising the steric hindrance with the neighbour copper ligand. Subsequent cyclisation step gave access to final product *cis*-vinylaziridine **107**.

[71] L. Ma, D.-M. Du, J. Xu, *Chirality* **2006**, *18*, 575–580.



Scheme 3.3. Asymmetric synthesis of vinylaziridines **107** and **108** catalysed by bisoxazoline-copper complexes.

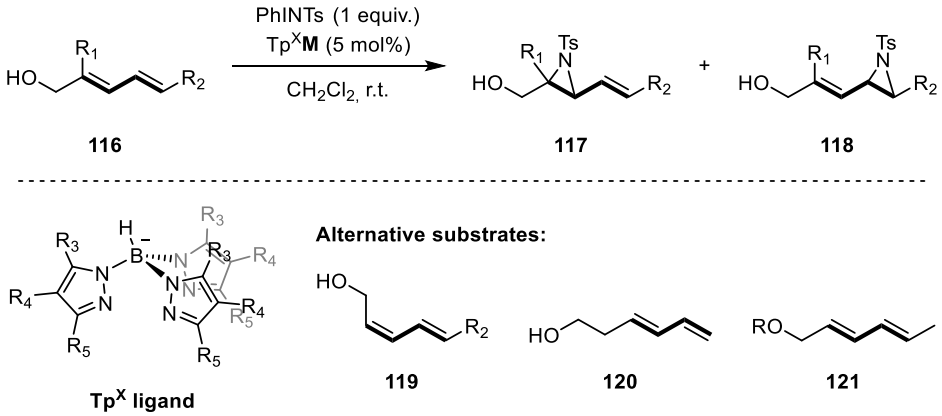
Rational ligand design revealed the high performance of copper-(I) 1-methyl-1-aza-4,8-dithiacyclodecane complex **110** for the aziridination of conjugated double bonds **97** in the presence of PhINTs as nitrene source (**Scheme 3.4**).[72] When compared to Cu(acac)$_2$ **91**, catalyst **110** displays greater turnover numbers thanks to the additional stability provided by the macrocyclic ligand. Moreover, similar regioselectivity was encountered for the reaction of ethyl sorbate **111** and 2-methyl-1,3-pentadiene **113** under both copper catalytic systems.[65,72]



Scheme 3.4. Regioselective Cu-catalysed aziridination of unsymmetrical dienes **111** and **113**.

[72] R. R. Conry, A. A. Tipton, W. S. Striejewske, E. Erkizia, M. A. Malwitz, A. Caffaratti, J. A. Natkin, *Organometallics* **2004**, *23*, 5210–5218.

On the other hand, our group tested a set of trispyrazolylborate ligands (Tp^X ligands) for the regio- and stereoselective synthesis of vinylaziridines from dienols **116** (**Scheme 3.5**).[63a,73] In the presence of PhINTs as nitrene precursor, both copper and silver complexes furnished vinylaziridine **117** as the major product, with regioselectivities up to 90:10. However, full *trans*-stereocontrol over aziridination formation was only achieved under silver catalysed conditions. The study of the reaction scope for differently substituted dienols **116** gave access to diastereomerically pure vinylaziridines **117** that could be further transformed into 1,2-difunctionalised compounds upon ring-opening reaction with O-, N- or S-nucleophiles. In addition, previous retention of double bond configuration under silver catalysis was also observed for *cis*-alkenes **119** (**Scheme 3.5**).[63a,73]



Scheme 3.5. Regio- and stereoselective silver-catalysed aziridination of dienols **116** using trispyrazolylborate ligands and PhINTs as nitrene source.

In order to explain the observed regioselectivity, the influence of the allylic alcohol moiety from diene **116** in the final reaction outcome was studied. Thus, when homoallylic dienol **120** and protected dienol **121** were treated under the optimised conditions (**Scheme 3.5**), exclusive distal double bond aziridination or decreased regiocontrol over corresponding proximal vinylaziridine formation were obtained respectively, proving the directing effect of the alcohol group. Moreover, DFT

[73] J. Llaveria, Á. Beltrán, M. M. Díaz-Requejo, M. I. Matheu, S. Castillón, P. J. Pérez, *Angew. Chem. Int. Ed.* **2010**, *49*, 7092–7095.

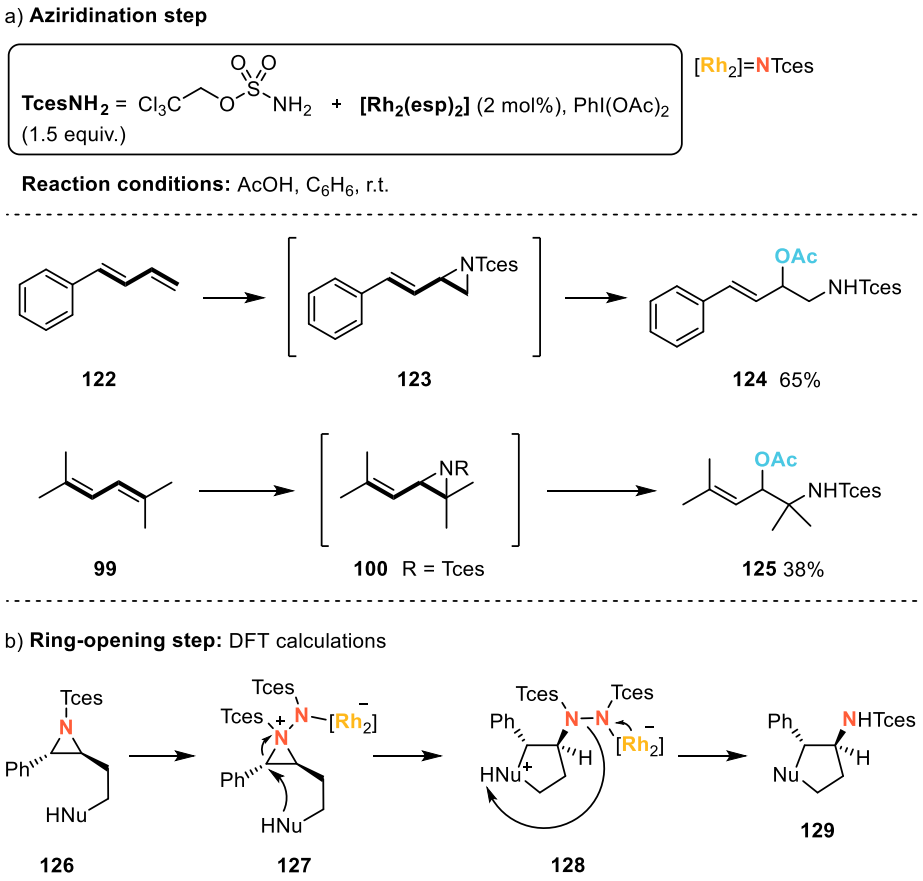
calculations further confirmed the substrate-controlled character of this silver-catalysed methodology.[63a]

In situ formed iminoiodanes as nitrene source

As mentioned before, iminoiodanes can be in situ generated upon oxidation of amine derivatives with hypervalent iodine reagents (**Figure 3.4**).[55] Along these lines, the group of P. Dauban reported a rhodium-catalysed alkene oxyamination in the presence of 2,2,2-trichloroethyl sulfamate ($TcesNH_2$) and (diacetoxyiodo)benzene as nitrene source for the initial intermolecular aziridination step (**Scheme 3.6** a).[74] In particular, dienes **122** and **99** yielded intermediate vinylaziridines **123** and **100** (R = Tces) respectively as single regioisomers when treated under optimised reaction conditions. Subsequent *in situ* S_N2 ring-opening with acetate ligands released from iodine(III) compound furnished oxyaminated products **124** and **125**.

From a mechanistic point of view, the formation of aziridine **126** as the key intermediate in the Rh-catalysed oxyamination process was confirmed by ^{1}H-NMR spectroscopy (**Scheme 3.6** b). Moreover, theoretical calculations pointed out the activating role of metallonitrene $[Rh_2]$=NTces upon N-N bond formation during the ring-opening step (**Scheme 3.6** b).[74b] Thus, aziridinium ring **127** underwent nucleophile attack followed by concomitant intramolecular protonation and metallonitrene elimination to furnish final difunctionalised products **129**.

[74] a) G. Dequirez, J. Ciesielski, P. Retailleau, P. Dauban, *Chem. Eur. J.* **2014**, *20*, 8929-8933. b) J. Ciesielski, G. Dequirez, P. Retailleau, V. Gandon, P. Dauban, *Chem. Eur. J.* **2016**, *22*, 9338–9347.

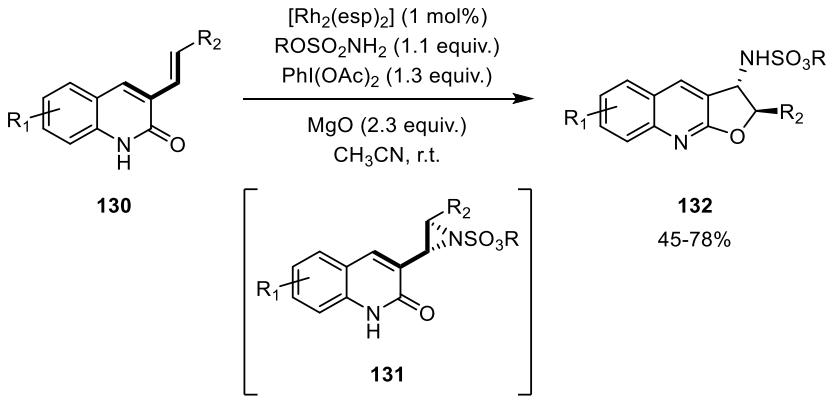


Scheme 3.6. Rhodium-catalysed oxyamination of dienes **122** and **99** via regioselective alkene aziridination and *in situ* ring-opening.

The preparation of biologically relevant 2,3-dihydrofuro[2,3-b]quinolines **132** has been achieved via *one-pot* rhodium-catalysed aziridination of 3-alkenylquinolones **130** and subsequent intramolecular ring-opening (**Scheme 3.7**).[75] As in previous examples, a mixture of 2,2,2-trichloroethyl sulfamate ($TcesNH_2$) and $PhI(OAc)_2$ was used as nitrene source for the stereoselective preparation of intermediate vinylaziridine **131**. Furthermore, the authors developed the asymmetric version of this cascade protocol driven by supramolecular hydrogen-bonding interactions between the starting material **130** and lactam-containing chiral ligands from a dirhodium complex. Alternatively, $TcesNH_2$ has also been employed in combination

[75] F. Zhong, T. Bach, *Chem. Eur. J.* **2014**, *20*, 13522–13526.

with PhIO as oxidant agent for the copper-catalysed *trans*-selective aziridination of methyl sorbate in the presence of *N*-heterocyclic carbene ligands.[76]



Scheme 3.7. *One-pot* rhodium-catalysed stereoselective diene aziridination/intramolecular ring-opening of 3-alkenylquinolones **130**.

Tamiflu ((-)-Oseltamivir phosphate) is a marketed drug for the treatment of influenza. In 2008, B. M. Trost and co-workers developed a concise route towards the enantioselective synthesis of (-)-Oseltamivir that relied on the regio- and stereoselective aziridination of diene **133**, obtained from palladium-catalysed allylic alkylation of a commercially available racemic bicyclic lactone (**Scheme 3.8**).[77] Unfortunately, no regiocontrol over aziridination step was observed under common copper catalysts whereas silver and gold complexes lead to low conversions. Moreover, the need for further straightforward aziridine deprotection limited the available number of amine derivatives for *in situ* nitrene formation.[38g] Eventually, [Rh_2esp_2] catalyst, 2-(trimethylsilyl)ethanesulfonamide ($SESNH_2$) and $PhI(OCO^tBu)_2$ were found to selectively furnished vinylaziridine **134** in high yields. Next, oxyaminated product **135**, bearing the characteristic substitution of (-)-Oseltamivir core, was generated upon Lewis acid mediated ring-opening of intermediate **134** with 3-pentanol.

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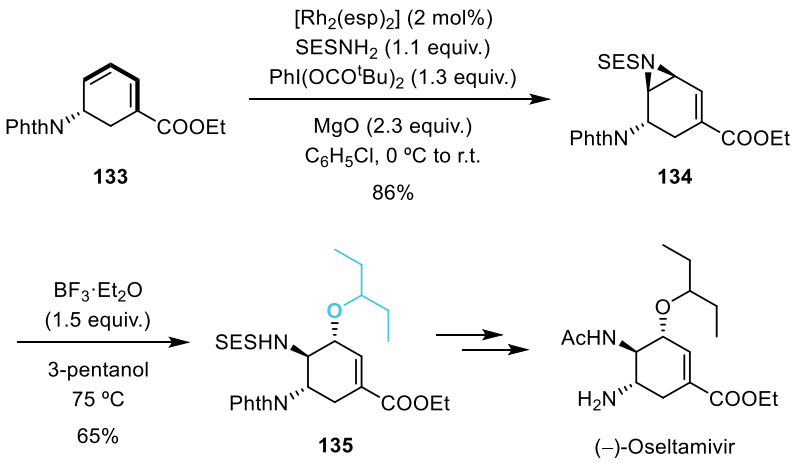
76 Q. Xu, D. H. Appella, *Org. Lett.* **2008**, *10*, 1497–1500.

77 a) B. M. Trost, T. Zhang, *Angew. Chem. Int. Ed.* **2008**, *47*, 3759–3761. b) B. M. Trost, T. Zhang, *Chem. Eur. J.* **2011**, *17*, 3630–3643.



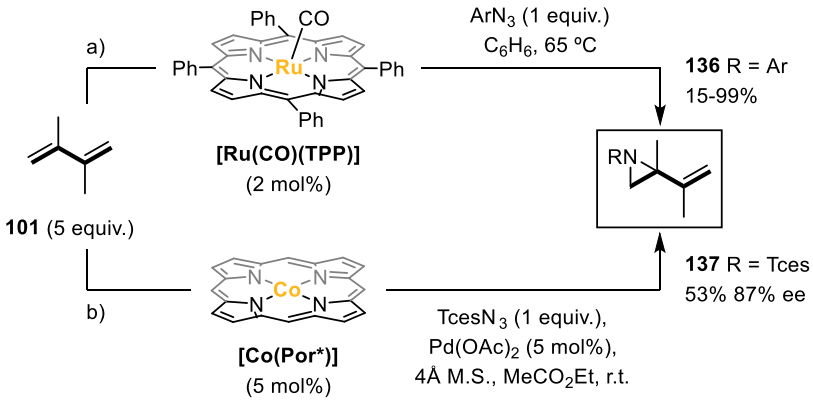
Scheme 3.8. Enantioselective total synthesis of (-)-Oseltamivir.

Organo-azides as nitrene source

Organo-azides have also been reported as powerful nitrene precursors under transition-metal catalysed conditions (**Figure 3.4**).[55] Their main advantage over iminoiodanes is the sole formation of molecular nitrogen gas as a reaction side product instead of the important amounts of iodobenzene waste generated for hypervalent iodine reagents. Along these lines, different substituted aryl azides have been used in combination with ruthenium-porphyrin catalyst [Ru(CO)(TPP)] for the preparation of *N*-aryl vinylaziridines **136** with variable yields (**Scheme 3.9** a).[78] Moreover, using this protocol, aziridination of diphenyl butadiene **106** (R = Ph) occurred with retention of double bond configuration and unsymmetrical dienes **103** and **113** reacted at the less sterically hindered olefin whereas C-H amination was observed when cyclohexadiene was tested as starting material. Alternatively, diene **101** formed Tces-substituted vinylaziridine **137** in moderate yields and high enantiomeric excess when treated with optically pure cobalt-porphyrin [Co(Por*)] and catalytic amounts of $Pb(OAc)_2$ (**Scheme 3.9** b).[79]

[78] C. Piangiolino, E. Gallo, A. Caselli, S. Fantauzzi, F. Ragaini, S. Cenini, *Eur. J. Org. Chem.* **2007**, 743–750.

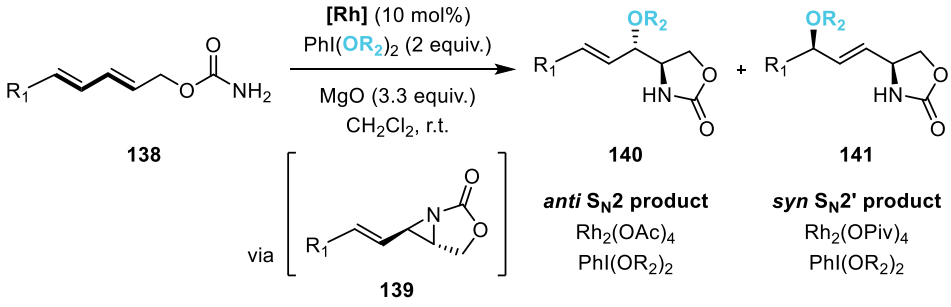
[79] V. Subbarayan, J. V. Ruppel, S. Zhu, J. A. Perman, X. P. Zhang, *Chem. Commun.* **2009**, 4266–4268.



Scheme 3.9. Ru- and Co-porphyrin complexes for the aziridination of diene **101** with aryl azides (ArN_3) and 2,2,2-trichloroethoxysulfonyl azide ($TcesN_3$).

3.1.3.2. Metal-catalysed intramolecular diene aziridination

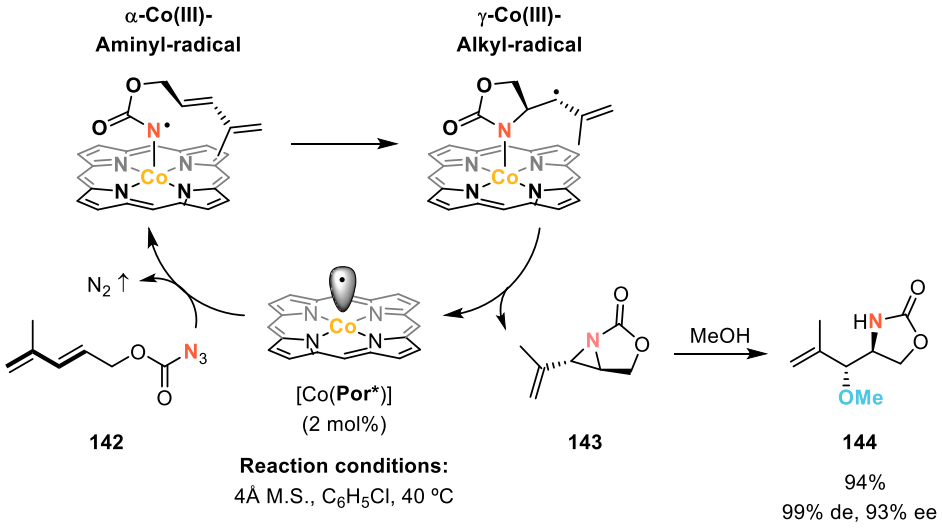
Within the context of meta-catalysed diene aziridination, intramolecular methodologies have recently emerged as powerful protocols to overcome regioselectivity issues. In addition, the possibility for *in situ* formation of iminoiodanes from simple amine derivatives and eco-friendly oxidants such as $PhI(OAc)_2$ or PhIO has favoured to broaden the substrate scope of this process.[43a,54,57]



Scheme 3.10. Rhodium-catalysed regio- and stereoselective oxyamination of dienyl carbamates **138** via bicyclic vinylaziridines **139**.

In 2014, our group developed a tandem rhodium-catalysed intramolecular aziridination/ring-opening of dienyl carbamates **138** under mild conditions (**Scheme**

3.10).[80] Outstanding catalyst-control over the regioselectivity of the ring-opening step (S_N2 vs. S_N2') was observed for the *in situ* reaction of transient vinylaziridine **139** with the carboxylate ligands released in the reaction mixture from the hypervalent iodine reagent ($PhI(OR_2)_2$. Thus, in the case of *anti*-S_N2 oxyaminated compounds **140**, dirhodium complex $Rh_2(OAc)_4$ played a dual role as nitrene stabiliser for the stereoselective metallonitrene insertion into conjugated diene **138** and as Lewis acid for the activation of intermediate vinylaziridine **139**. On the contrary, when $Rh_2(OPiv)_4$ was used, the coordination of manganese to aziridine nitrogen atom guides nucleophilic attack towards S_N2' addition furnishing *syn*-difunctionalised product **141**. Moreover, in order to illustrate the usefulness of the methodology, the racemic synthesis of natural occurring sphingosine from oxyaminated product **140** ($R_1 = C_{13}H_{27}$) was accomplished.



Scheme 3.11. Proposed stepwise mechanism for the cobalt-catalysed radical asymmetric aziridination of dienyl azidoformate **142.**

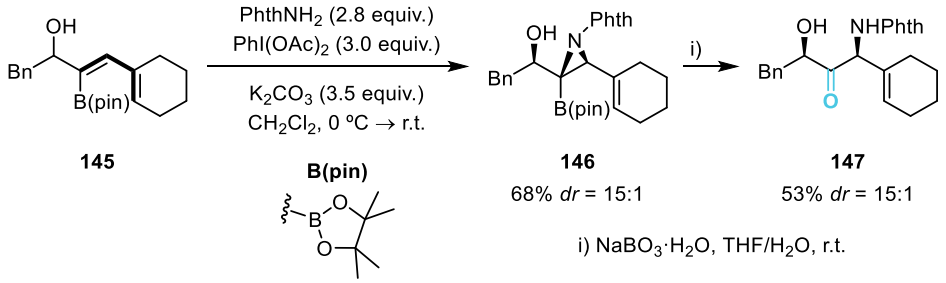
Following on from their studies on cobalt-porphyrin complexes,[79] the group of X. P. Zhang reported the catalytic asymmetric intramolecular aziridination of dienyl azidoformate **142** using a cobalt-based metalloradical catalyst [Co(Por*)] (**Scheme 3.11**).[81] A stepwise mechanism was proposed for the intramolecular cyclisation of

[80] J. Guasch, Y. Díaz, M. I. Matheu, S. Castillón, *Chem Commun* **2014**, *50*, 7344–7347.
[81] H. Jiang, K. Lang, H. Lu, L. Wojtas, X. P. Zhang, *J. Am. Chem. Soc.* **2017**, *139*, 9164–9167.

starting material **142** into vinylaziridine **143**. According to it, after initial coordination of nitrene equivalent to the central cobalt atom upon molecular nitrogen extrusion, the resulting α-Co(III)-aminyl-radical underwent enantioselective 5-*exo-trig* cyclisation to generate intermediate γ-Co(III)-alkyl-radical. Subsequent 3-*exo-tet* cyclisation gave access to [3.1.0] bicyclic vinylaziridine **143** which was *in situ* opened with methanol to furnish oxyaminated product **144** in high yields and selectivities. Therefore, the diastereoselectivity of this aziridination protocol ultimately depended on the feasibility of C-C bond rotation at the carbon centered radical.

3.1.4. Synthesis of vinylaziridines via metal-free intermolecular nitrogen addition into conjugated dienes

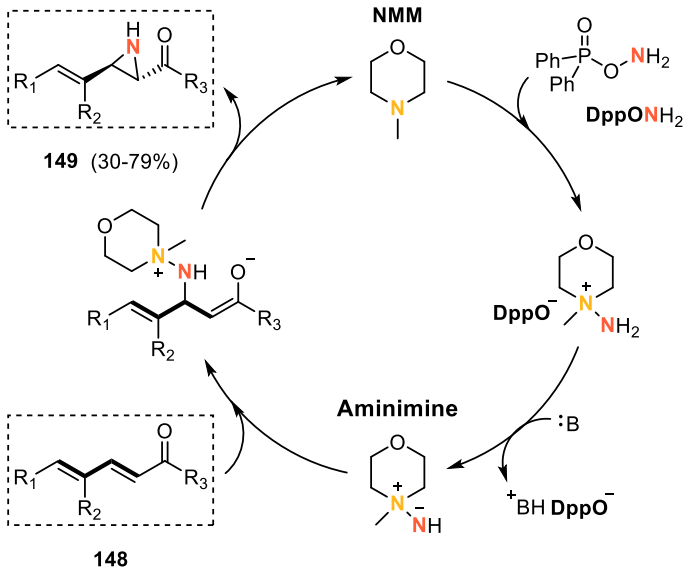
Hypervalent iodine reagents represent an eco-friendly alternative to transition metal complexes. The increased interest in developing metal-free methodologies has favoured the production of an important number of publications related to λ^3-iodane-mediated transformations.[3,4] Within this field, the replacement of highly toxic $Pb(OAc)_4$ by $PhI(OAc)_2$ has been successfully applied to the aziridination of different substituted alkenes with *N*-amino heterocycles as nitrogen sources.[82]



Scheme 3.12. Metal-free diastereoselective aziridination of 2-B(pin)-substituted allylic dienol **145** in the presence of $PhI(OAc)_2$ and K_2CO_3.

[82] a) J. Li, J.-L. Liang, P. W. H. Chan, C.-M. Che, *Tetrahedron Lett.* **2004**, *45*, 2685–2688. b) L. B. Krasnova, A. K. Yudin, *Org. Lett.* **2006**, *8*, 2011–2014. c) E. Zhang, Y.-Q. Tu, C.-A. Fan, X. Zhao, Y.-J. Jiang, S.-Y. Zhang, *Org. Lett.* **2008**, *10*, 4943–4946. d) M. Zibinsky, T. Stewart, G. K. S. Prakash, M. A. Kuznetsov, *Eur. J. Org. Chem.* **2009**, 3635–3642. e) R. D. Richardson, M. Desaize, T. Wirth, *Chem. Eur. J.* **2007**, *13*, 6745–6754.

Along these lines, metal-free diastereoselective aziridination of 2-B(pin)-substituted dienol **145** with *N*-aminophthalimide was accomplished using stoichiometric amounts of $PhI(OAc)_2$ to furnish unaltered boronate ester **146** as a single regioisomer (**Scheme 3.12**).[83] Subsequent oxidative ring-opening of intermediate vinylaziridine **146** gave access to synthetically useful 1,3-aminohydroxy-2-ketones **147** in moderate yields. In addition, A. K. Yudin and co-workers described a similar metal-free aziridination protocol for terminal dienes **103** under electrochemical conditions with minimal background olefin oxidation.[84]



Scheme 3.13. Tertiary amine-promoted regio- and stereoselective aziridination of unsaturated carbonyl compounds **148**.

A completely different metal-free strategy for the synthesis of vinylaziridines **149** relied in the preparation of an intermediate *N*-*N* ylide (aminimine) as a nucleophilic

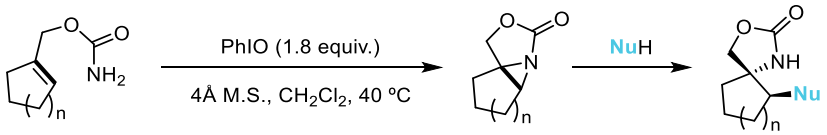
[83] J. Hernández-Toribio, M. M. Hussain, K. Cheng, P. J. Carroll, P. J. Walsh, *Org. Lett.* **2011**, *13*, 6094–6097.

[84] T. Siu, A. K. Yudin, *J. Am. Chem. Soc.* **2002**, *124*, 530–531.

nitrogen source (**Scheme 3.13**).[85] In this case, aziridination occurred via aminimine conjugated addition into dienones **148** and subsequent ring-closure with complete regioselectivity for α,β-double bond functionalisation. Unsaturated carbonyl compounds **148** bearing aryl and alkyl moieties generally furnished unprotected vinylaziridines **149** in high yields, whereas electron-withdrawing substituents were less tolerated under the optimised reaction conditions.

3.1.5. Iodine(III)-mediated metal-free intramolecular aziridination of olefinic substrates

Within the context of hypervalent iodine chemistry, pioneering metal-free strategies concerning olefin aziridination relied on the *in situ* preparation of iminoiodanes from different amine derivatives.[57a] In 2002, A. Padwa and co-workers published an intramolecular aziridination of cycloalkenyl carbamates **150** and **152** using PhIO as an oxidant agent as part of their study on rhodium-catalysed stereoselective indole aminoxygenation (**Scheme 3.14**).[86] Unexpectedly, during control experiments, smooth cyclisation of the carbamoyl nitrene intermediate with electron-rich olefins **150** and **152** under metal-free conditions was observed. Subsequent addition of external nucleophiles gave access to vicinal difunctionalised products **154** displaying completely *anti*-selectivity which supported the formation of transient aziridines **151** and **153**.



150 n = 1
152 n = 2

151 n = 1 71%
153 n = 2 78%

154
NuH: **MeOH, LiBr, RNH$_2$**
with H$^+$ or LA catalyst

Scheme 3.14. Iodine(III)-mediated metal-free intramolecular aziridination of cycloalkenyl carbamates **150** and **152**.

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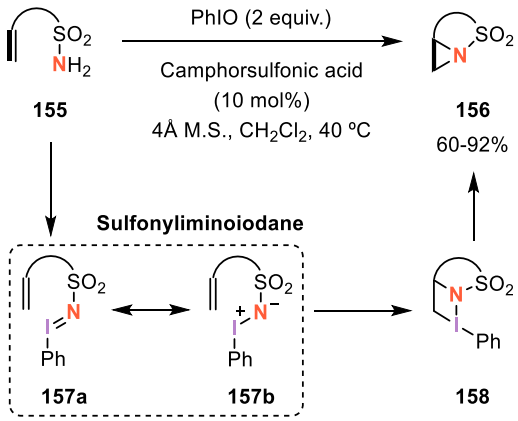
[85] A. Armstrong, R. D. C. Pullin, C. R. Jenner, J. N. Scutt, *J. Org. Chem.* **2010**, *75*, 3499–3502.

[86] a) A. Padwa, T. Stengel, *Org. Lett.* **2002**, *4*, 2137–2139. b) A. Padwa, A. C. Flick, C. A. Leverett, T. Stengel, *J. Org. Chem.* **2004**, *69*, 6377–6386.

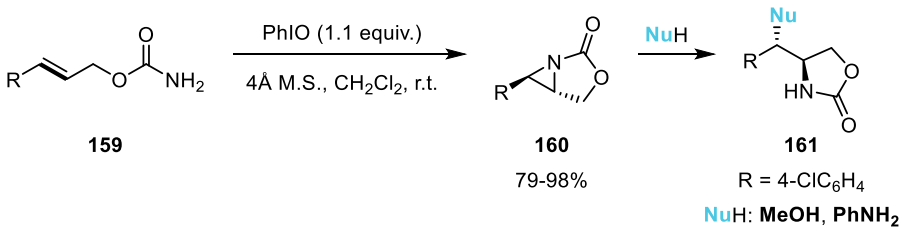
In addition, related alkenyl sulfonamides **155** also underwent intramolecular aziridination under metal-free conditions, as demonstrated by R. M. Moriarty and co-workers (**Scheme 3.15**).[62a] However, reaction scope was limited to conformationally rigids systems that guaranteed the intramolecular proximity of *in situ* generated sulfonyliminoiodane **157a** and the neighbouring olefin moiety. Based on literature reports and experimental data, the authors proposed a formal [2+2] cycloaddition of iminoiodane ionic form **157b** to furnish intermediate azaiodoniocyclobutane **158** which, upon reductive elimination, rendered bicyclic aziridines **156** in moderate to good yields.



Scheme 3.15. Metal-free intramolecular aziridination of conformationally rigid alkenyl sulfonamides **155** using iodosylbenzene as oxidant agent.

Finally, C.-M. Che and co-workers reported a metal-free intramolecular aziridination of allylic carbamates **159** in the presence of iodosylbenzene as oxidant agent (**Scheme 3.16**).[87] Although the protocol worked well for styrene derivatives, slightly lower aziridine **160** yields were observed when alkyl-substituted allylic carbamates **159** were used as starting materials. Interestingly, the development of a *one-pot* procedure for the intramolecular aziridination/ring-opening of *p*-chloro-styrene with external nucleophiles allowed the straightforward preparation of vicinal difunctionalised products **161**.

[87] Q.-H. Deng, J.-C. Wang, Z.-J. Xu, C.-Y. Zhou, C.-M. Che, *Synthesis* **2011**, 2959–2967.



Scheme 3.16. Iodosylbenzene promoted metal-free intramolecular aziridination of allylic carbamates **159**.

3.1.6. Iminobromanes as alternative reagents for the metal-free intramolecular aziridination of olefinic substrates

λ³-Bromanes, bromo-(III) species closely related to hypervalent iodine reagents, have very recently proved to effectively promote several oxidative transformations under metal-free conditions such as alkynyl coupling reactions, Hofmann rearrangements or transylidation with *N*-containing heterocycles.[88] In 2007, M. Ochiai and co-workers reported the first preparation and characterisation of *N*-sulfonyl-iminobromane **163** upon treatment of difluoro-λ³-bromane **162** with trifluoromethane sulfonamide in acetonitrile (**Scheme 3.17**).[89] The resulting compound **163** was a white stable solid, soluble in common organic solvents, that successfully mediated metal-free olefin aziridination in high yields and selectivities.

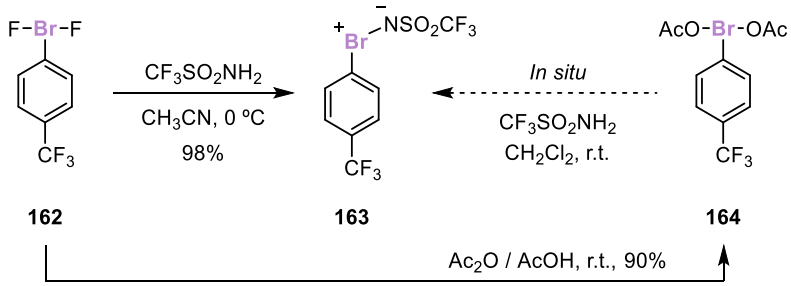
Some years later, the same group described an alternative strategy for the *in situ* preparation of *N*-sulfonyl-iminobromane **163** as part of a study on intermolecular alkene aziridination (**Scheme 3.17**).[90] The protocol involved the initial treatment of precursor **162** with an equimolar mixture of Ac_2O/AcOH to furnish intermediate diacetoxybromobenzene **164** via ligand exchange. Then, in the presence of trifluoromethane sulfonamide and differently substituted olefins, λ³-bromane **164** effectively yielded the corresponding aziridine products via transient iminobromane

88 a) U. Farooq, A.-H. A. Shah, T. Wirth, *Angew. Chem. Int. Ed.* **2009**, *48*, 1018–1020. b) M. Ochiai, K. Miyamoto, S. Hayashi, W. Nakanishi, *Chem. Commun.* **2010**, *46*, 511–521.

89 M. Ochiai, T. Kaneaki, N. Tada, K. Miyamoto, H. Chuman, M. Shiro, S. Hayashi, W. Nakanishi, *J. Am. Chem. Soc.* **2007**, *129*, 12938–12939.

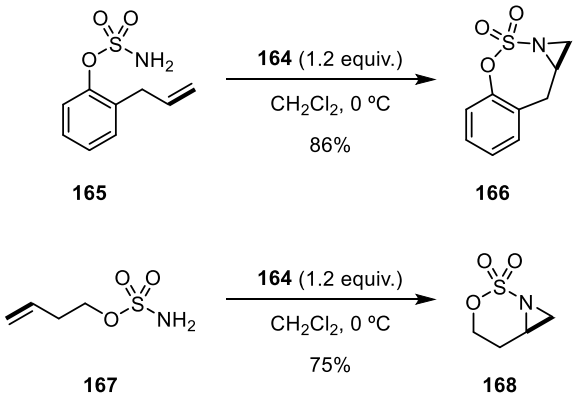
90 Md. M. Hoque, K. Miyamoto, N. Tada, M. Shiro, M. Ochiai, *Org. Lett.* **2011**, *13*, 5428–5431.

163 formation. Interestingly, this *one-pot* procedure was equally efficient as that consisting in premixing diacetoxybromobenzene **164** with sulfonamide derivative.[90]



Scheme 3.17. Synthesis of stable iminobromane reagent **163** from difluoro-λ³-bromane **162** or *in situ* preparation of **163** in the presence of hypervalent diacetoxybromobenzene **164**.

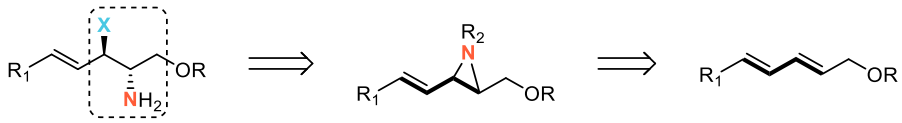
Encouraged by the successful performance of iminobromane **163** as imido group donor for the intermolecular aziridination of olefinic substrates, the authors applied this methodology to the intramolecular cyclisation of alkenyl sulfamates **165** and **167** (**Scheme 3.18**).[90] As expected, stoichiometric amounts of diacetoxybromobenzene **164** efficiently furnished bicyclic aziridines **166** and **168** in 86% and 75% yield respectively without detection of C-H aminated side product.



Scheme 3.18. Metal-free intramolecular aziridination of alkenyl sulfamates **165** and **167** via *in situ* formation of *N*-sulfonyl-iminobromane intermediate.

3.2. Aims and objectives

As part of a program aiming at developing new synthetic methodologies for the preparation of unsaturated vicinal amino-alcohols related to relevant lipids occurring in nature, *trans*-difunctionalised compounds **169** were envisioned to arise from the regioselective ring-opening of vinylaziridine **170**. This key intermediate, in turn, could be accessed by means of an intramolecular metal-free stereoselective aziridination of dienol derivatives **171** containing a nitrene source (**Scheme 3.19**).



169 **170** **171**

Scheme 3.19. Retrosynthetic strategy for the preparation of the unsaturated vicinal hetero-amino moiety in **169** via regioselective ring-opening of key intermediate vinylaziridine **170**.

Previous work in the group involved the rhodium-catalysed regio- and stereoselective oxyamination of dienyl carbamates **138** to give oxazolidinones **140** or **141** (**Scheme 3.10**).[80] Under these reaction conditions, bicyclic vinylaziridine intermediate **139** undergoes *in situ* ring-opening with the carboxylate ligands present in the reaction medium. This fact prevents the application of the protocol to the general introduction of nucleophilic functionalities at will. Therefore, an alternative strategy that guarantees aziridine stability would be desirable for the preparation of differently 1,2-disubstituted products in a divergent and straightforward manner. Herein we describe the *one-pot* metal-free regioselective aziridination/ring-opening of dienes **171**.

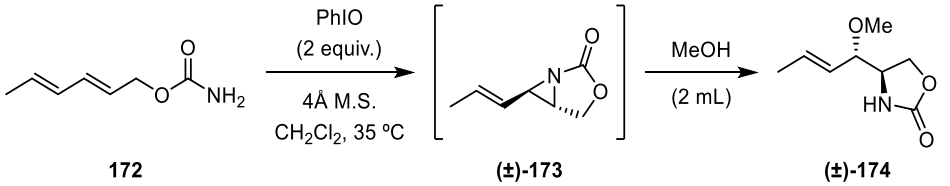
3.3. Results and discussion

3.3.1. Optimisation of aziridination reaction conditions

According to previous work developed by Dr. Joan Guasch, model carbamate **172** (readily obtained from commercially available (2*E*,4*E*)-hexa-2,4-dien-1-ol)[61] underwent an intramolecular aziridination in the presence of PhIO[91] and 4Å

[91] H. Saltzman, J. G. Sharefkin, *Org. Syn. Coll.* **1973**, *5*, 658–659.

molecular sieves in CH_2Cl_2 with modest yields (**Scheme 3.20** and **Table 3.1**).[92] The vinylaziridine generated **(±)-173** was stable under reaction conditions although not isolable, being convenient to directly treat it with a nucleophile agent to finally obtain the ring-opening product. Therefore, after complete consumption of the starting material was observed by TLC, methanol was added to the reaction mixture to furnish substituted oxazolidinone **(±)-174** (**Scheme 3.20**).



Scheme 3.20. Initial conditions for the *one-pot* intramolecular aziridination/ring-opening of model carbamate **172**.

Optimisation of the reaction conditions was carried out by an initial screening of solvents. In order to maximise PhIO solubility,[93] CH_2Cl_2, 1,2-DCE and CH_3CN were initially selected (**Table 3.1**, entries 1-3). The notorious difference between yields for the *one-pot* aziridination/ring-opening protocol led us to explore other common solvents in organic synthesis (**Table 3.1**, entries 4-8). Unfortunately, none of them improved the previous results obtained and dichloromethane remained as the solvent of choice for oxazolidinone **(±)-174** preparation. Moreover, higher concentrations proved to be detrimental for final product **(±)-174** formation (**Table 3.1**, entry 9).

In order to select the most suitable desiccant agent for the intramolecular aziridination step, $MgSO_4$ and Na_2SO_4 were tested using dichloromethane as optimised solvent (**Table 3.1**, entries 10 and 11). However, an important decrease in final yields was observed in both cases. Finally, a temperature screening led to no further improvements (**Table 3.1**, entries 12 and 13).

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92 J. Guasch (**2015**). *Regio- and Enantioselective Synthesis of Unsaturated Amino Alcohols, Amino Ketones and Diamines as Valuable Intermediates in Organic Synthesis*. Ph.D. Thesis. Universitat Rovira i Virgili, Tarragona, Spain.

93 R. M. Moriarty, J. W. Kosmeder II, Iodosylbenzene; *E-EROS Encyclopedia of Reagents for Organic Synthesis.*

Coincidentally, the optimised conditions for the intramolecular aziridination of model carbamate **172** with PhIO were those initially tested: CH_2Cl_2 (0.04M), 4Å molecular sieves and 35ºC. Disappointingly, only a maximum moderate yield over the two steps of 61% was obtained after this initial screening, even though complete conversion of starting material was confirmed by ^{1}H-NMR.

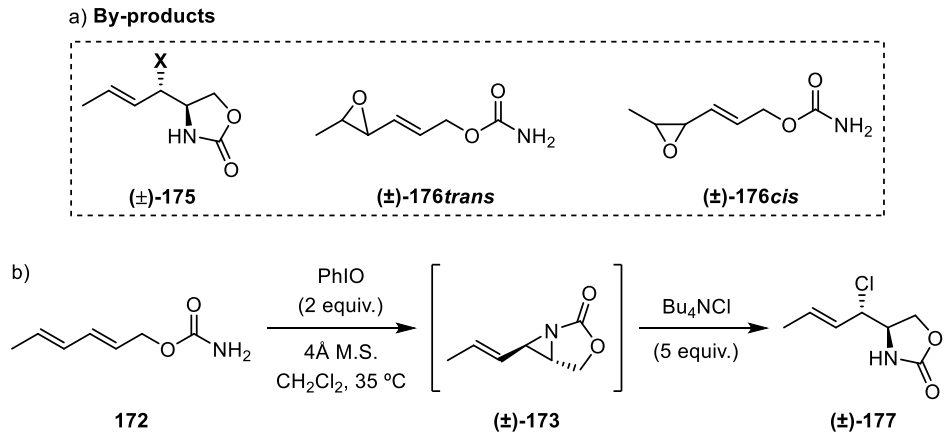
Table 3.1. Intramolecular aziridination of dienyl carbamate **172** with PhIO. Optimisation of reaction conditions.[a]

Entry	Solvent (M)	Desiccant agent	Temp (ºC)	Yield (%)[b]
1	CH_2Cl_2 (0.04)	4Å M.S.	35	56
2	1,2-DCE (0.04)	4Å M.S.	35	61
3	CH_3CN (0.04)	4Å M.S.	35	18
4	Toluene (0.04)	4Å M.S.	35	15
5	Benzene (0.04)	4Å M.S.	35	13
6	CF_3-Benzene (0.04)	4Å M.S.	35	C.M.[c]
7	THF (0.04)	4Å M.S.	35	C.M.[c]
8	1,4-Dioxane (0.04)	4Å M.S.	35	C.M.[c]
9	CH_2Cl_2 (0.10)	4Å M.S.	35	18
10	CH_2Cl_2 (0.04)	$MgSO_4$	35	18
11	CH_2Cl_2 (0.04)	Na_2SO_4	35	14
12	CH_2Cl_2 (0.04)	4Å M.S.	r.t.	35
13	CH_2Cl_2 (0.04)	4Å M.S.	Reflux	52
14[d]	CH_2Cl_2 (0.04)	4Å M.S.	35	32
15	CH_2Cl_2 (0.04)	-	35	26
16[e]	**CH_2Cl_2 (0.04)**	**4Å M.S.**	**35**	**95(70)**
17[e,f]	CH_2Cl_2 (0.04)	-	35	-
18[e,g]	CH_2Cl_2 (0.04)	-	35	C.M.[c]

[a] Carbamate **172** (1 equiv.), PhIO (2 equiv.), desiccant agent (100 mg per 0.1 mmol carbamate **172**). MeOH as quenching agent (2 mL). [b] Determined by ^{1}H NMR spectroscopy using 1,3-dinitrobenzene as internal standard (isolated yield). [c] Complex Mixture. [d] 10 mol% of radical inhibitor BHT. [e] Recrystallised carbamate **172** (1 equiv.). [f] $PhI(OAc)_2$ (2 equiv.). [g] $PhI(OCOCF_3)_2$ (2 equiv.).

Thoughtful analysis of the reaction crude NMR spectra revealed the presence of three by-products, a mixture of epoxides **(±)-176*trans*** and **(±)-176*cis*** (≤5% NMR-

yield) and an unidentified compound **(±)-175** (up to 20% NMR-yield) possessing the characteristic signals of a ring-opened product bearing a nucleophilic functionality displaying no signals on ^{1}H-NMR (**Scheme 3.21** a). As it was suspected that dichloromethane could decompose under the optimised conditions and release chloride ions,[94] a solution of $Bu_4N^+Cl^-$ in CH_2Cl_2 was added to the reaction mixture after formation of the intermediate vinylaziridine **(±)-173** (**Scheme 3.21** b). Final product was fully characterised by NMR Spectroscopy and Mass Spectrometry and undoubtedly assigned to the proposed chloro-substituted oxazolidinone **(±)-177**.



Scheme 3.21. a) Detected by-products **(±)-175**, **(±)-176*trans*** and **(±)-176*cis*** for PhIO mediated aziridination reaction. b) Intramolecular aziridination of **172** with PhIO and *in situ* ring-opening with Bu_4NCl.

Whereas epoxide by-products were consistently obtained in all reactions, the yield of the chloro-derivative proved erratic and significantly varied depending on the reaction batch. Therefore, it was clear that, in order to improve the performance of the aziridination step, removal of the chloride ion source was needed to minimise the formation of oxazolidinone **(±)-177**.

Initial efforts focused on the solvent as the most plausible chloride ion source. Chlorinated solvents have been reported to form either Cl radicals or HCl that *in situ* opened fused-ring intermediates with a similar chemical structure than that of vinylaziridine **(±)-173**.[94] Taking into account this piece of information, PhIO

[94] S. C. Bergmeier, D. M. Stanchina, *J. Org. Chem.* **1997**, *62*, 4449–4456.

mediated aziridination was carried out in the presence of a radical inhibitor, BHT (**Table 3.1**, entry 14). However, no improvement on final yield was observed after overnight stirring while a relevant percentage of chlorine oxazolidinone **(±)-177** was still generated.

As part of the ongoing study, molecular sieves were easily discarded as the chloride ion source by removing them from the reaction mixture (**Table 3.1**, entry 15). Once more, the NMR crude showed the characteristic signals for the chlorinated by-product **(±)-177**. Moreover, the low 26% yield obtained for the methoxy substituted oxazolidinone **(±)-174** proved the determinant role of the desiccant agent in the final outcome of the aziridination reaction.

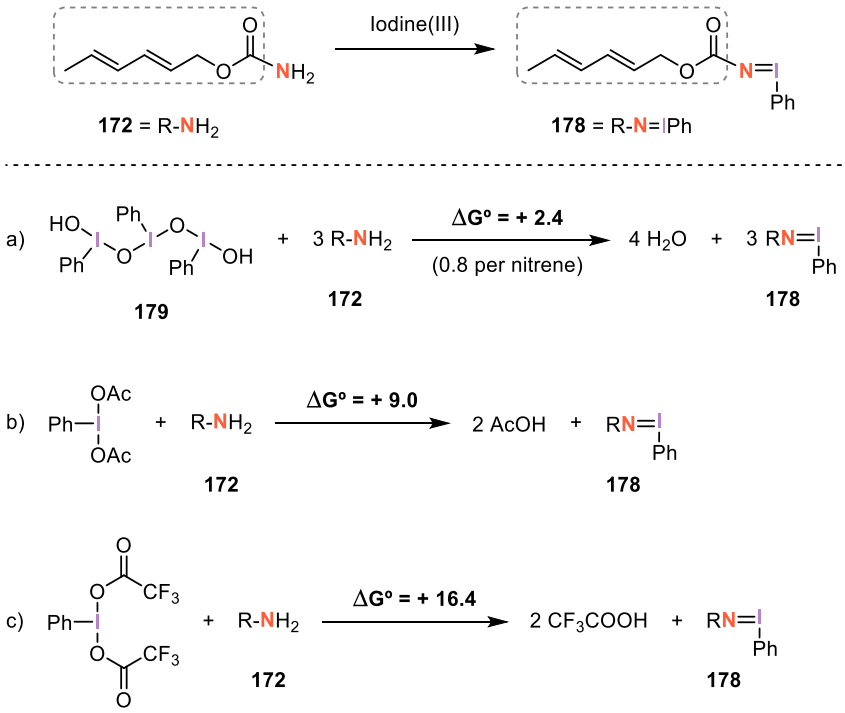
Additionally, studies on hypervalent iodine reagent decomposition using differently aged iodosylbenzene batches or variable amounts of PhIO were carried out under optimised conditions. However, the fact that yields for chlorinated by-product **(±)-177** remained stable in both cases confirmed that this starting material was not the searched ion source.

At that point, carbamate **172** had not been initially considered as a plausible chlorine ion source since, after purification by column chromatography, no perceptible impurities were present in its ^{1}H-NMR spectra. However, to our delight, when recrystallised starting material was treated with PhIO under optimised reaction conditions, the yield over the two steps for the desired methoxy oxazolidinone **(±)-174** increased up to 95% with no detection of chlorinated by-product **(±)-177** in the NMR crude (**Table 3.1**, entry 16).

Looking for further explanation for these results, different batches of carbamates **172** were analysed by Mass Spectrometry. Even though all the starting material batches seemed pure by ^{1}H-NMR, secondary unidentified mass peaks appeared in some cases displaying the characteristic isotopic pattern for chloro-containing molecules. Thus, it was envisioned that chlorine ions could be somehow generated during carbamate synthesis since chloro-containing reagents were involved. However, full structure assignment of such compounds was not achieved.

Two alternative sources of hypervalent iodine reagents, commercially available (diacetoxyiodo)benzene (PIDA) and [bis(trifluoroacetoxy)iodo]benzene (PIFA), were also tested for the *one-pot* aziridination/ring-opening of model substrate **172** (**Table 3.1**, entries 17 and 18). Disappointingly, none of them furnished the desired oxazolidinone product **(±)-174** but unreacted dienyl carbamate **172** was recovered in the case of PIDA whereas PIFA induced starting material decomposition.

In order to gain further insight into mechanistic details, a computational study on PhIO mediated diene aziridination was carried out by Dr. I. Funes-Ardoiz and Prof. F. Maseras (ICIQ)



Scheme 3.22. Thermodynamics of iminoiodane **178** formation from a) PhIO trimer **179**, b) $PhI(OAc)_2$ and c) $PhI(OCOCF_3)_2$. Free energies in kcal/mol.

As mentioned before, physical and chemical properties of iodosylbenzene are directly related to its polymeric nature (**Scheme 1.1 a**). From a theoretical point of view, an earlier publication on PhIO mediated alkene epoxidation employed a simplified trimeric structure of iodosylbenzene to model the observed net of

intermolecular secondary interactions between iodine and oxygen atoms.[95] On the other hand, *in situ* formed iminoiodanes have been previously reported as the reactive species in metal-free aziridination of olefinic substrates.[62a,86] However, to the best of our knowledge, no computational studies on their exact role during heterocycle formation have been published yet.

In the present case, a thermodynamic analysis on iodine(III)-mediated iminoiodane **178** formation confirmed the endergonic character of this transformation for PhIO (**Scheme 3.22** a). Thus, when model dienyl carbamate **172** was reacted in the presence of trimeric iodosylbenzene **179**, iodonium imide **178** was generated along with water as the only side product, consuming 0.8 kcal per nitrene. However, water removal from the reaction medium by means of 4Å molecular sieves favours equilibrium displacement towards product **178** formation and its subsequent cyclisation into vinylaziridine **(±)-173** (**Table 3.1**, entry 16). On the contrary, $PhI(OAc)_2$- and $PhI(OCOCF_3)_2$-mediated reactions proved to be more energetically demanding as corroborated by experimental data from aziridination optimisation (**Scheme 3.22** b and c and **Table 3.1**, entries 17 and 18).

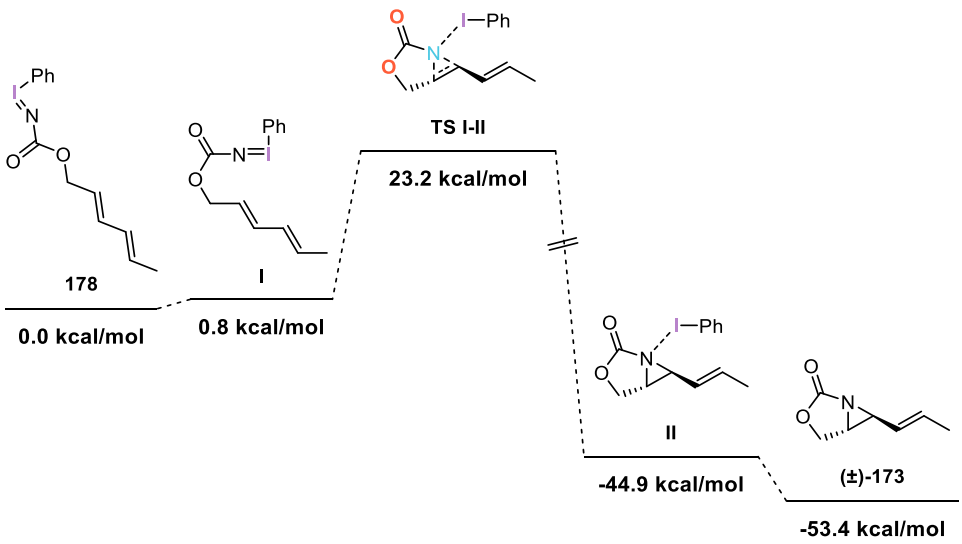


Figure 3.7. Free energy profile for aziridine **(±)-173** formation from iminoiodane **178**.

[95] G. Barea, F. Maseras, A. Lledós, *New J. Chem.* **2003**, *27*, 811–817.

The overall mechanism for aziridine **(±)-173** formation from iminoiodane **178** was next studied (**Figure 3.7**). Thus, initial rotation of C-O bond in compound **178** allocates reactive alkene moiety in close proximity to nitrogen atom, with an energy gain of 0.8 kcal/mol. Then, intermediate **I** proceeds through a concerted transition state **TS I-II** stabilised by dispersion interactions between parallel phenyl ring from hypervalent iodine reagent and the distal double bond at dienyl group (**Figure 3.7** and **Figure 3.8** left). Interestingly, a higher energy conformer **TS I-II'** with the aforementioned phenyl ring pointing out was also encountered for this transformation (**Figure 3.8** right). The generation of both C-N bonds takes place in an asynchronous manner to furnish intermediate **II** with the corresponding energy decay. Subsequent iodosylbenzene dissociation gives access the desired vinylaziridine **(±)-173**.

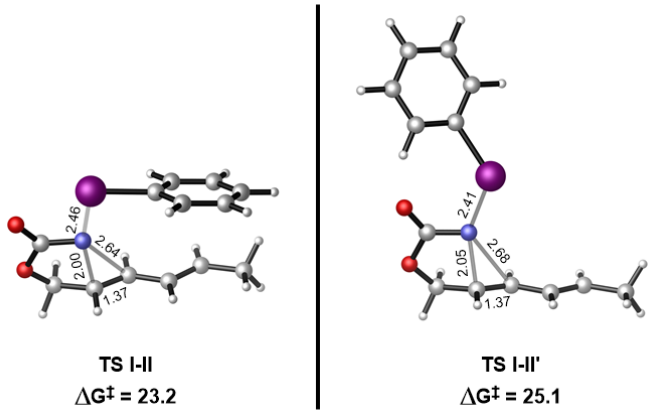
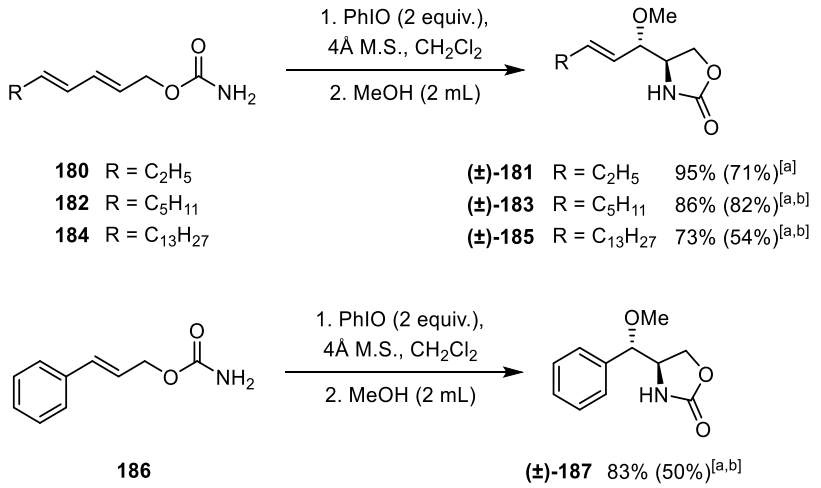


Figure 3.8. 3D structures of the concerted transition state **TS I-II** and its conformer **TS I-II'** for aziridine **(±)-173** formation from iminoiodane **178**. Relevant bond distances in Å and free energies in kcal/mol.

Finally, in order to study the reaction scope, three dienyl carbamates **180**, **182** and **184** with longer aliphatic chains and cinnamyl derivative **186** were reacted under optimised conditions from **Table 3.1**, entry 16 (**Scheme 3.23**). To our delight, remarkable yields were obtained in all the cases for methoxy-substituted oxazolidinones **(±)-181**, **(±)-183**, **(±)-185**, and **(±)-187** under longer reaction times or increased temperatures.



Scheme 3.23. Reaction scope for longer dienyl carbamates **180**, **182** and **184** and cinnamyl carbamate **186** under optimised conditions. [a] NMR-yield: determined by ^{1}H NMR spectroscopy using 1,3-dinitrobenzene as internal standard (isolated yield). [b] Reaction was performed under reflux.

3.3.2. Nucleophile scope for the ring-opening step. Synthesis of *anti*-substituted oxazolidinones

One of the main advantages of the present metal-free intramolecular aziridination procedure was the possibility of selecting external nucleophiles to perform the ring-opening step, providing differently substituted oxazolidinones. According to previous strategies,[41,42,96,97] several oxygen, nitrogen, and sulphur nucleophiles were chosen in order to explore the reaction scope, furnishing synthetically useful intermediates. Moderate to high yields were achieved after optimisation of reaction conditions for each nucleophile.

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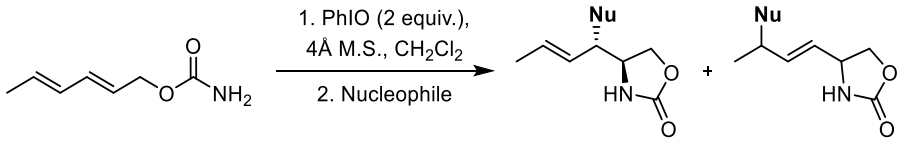
96 a) L. A. Boralsky, D. Marston, R. D. Grigg, J. C. Hershberger, J. M. Schomaker, *Org. Lett.* **2011**, *13*, 1924–1927. b) C. S. Adams, L. A. Boralsky, I. A. Guzei, J. M. Schomaker, *J. Am. Chem. Soc.* **2012**, *134*, 10807–10810.

97 a) F. Duran, L. Leman, A. Ghini, G. Burton, P. Dauban, R. H. Dodd, *Org. Lett.* **2002**, *4*, 2481–2483. b) G. Malik, A. Estéoule, P. Retailleau, P. Dauban, *J. Org. Chem.* **2011**, *76*, 7438–7448.

Firstly, different *O*-nucleophiles were tested. Since the reaction had already been optimised for MeOH, water was selected as an alternative *O*-nucleophile. A main drawback for this ring-opening step was the presence of molecular sieves in the medium, since they trapped the water leading to low reaction yields (**Table 3.2**, entry 1). Disappointingly, when they were removed from the reaction mixture previously to nucleophile addition, any further improvement on final yield was observed (**Table 3.2**, entry 2).

Table 3.2. PhIO mediated intramolecular aziridination of model dienyl carbamate **172** and *in situ* ring-opening with *O*-nucleophiles.[a]



172

Nu = OH **(±)-188**
Nu = OAc **(±)-190**

Nu = OH **189**

Entry	Nu	Ring-opening step	S_N2 product yield (%)[b]	S_N2' product yield (%)[b]
1	OH	H_2O drops	14	-
2	OH	H_2O drops[c]	9	-
3	OH	K_2CO_3, H_2O, 0 ºC	≤5	≤5
4	OH	KOH, DMSO/CH_2Cl_2	≤5	-
5	**OH**	**H_2O/CH_3CN**	**70**	**11**
6	OAc	NaOAc	-	-
7	OAc	KOAc	-	-
8	OAc	CsOAc	40	-
9	**OAc**	**NaOAc, 15-Crown-5**	**50**	**-**
10	OAc	KOAc, 18-Crown-6	C.M.[d]	

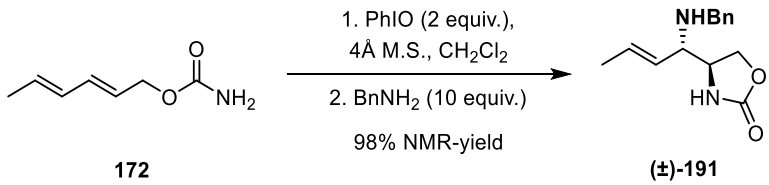
[a] Carbamate **172** (1 equiv.), PhIO (2 equiv.), 4Å M.S. (100 mg per 0.1 mmol carbamate **172**), CH_2Cl_2 (0.04M), 35ºC. **Nu** = OAc, XOAc (5 equiv.), crown ether (1 equiv.). [b] Determined by ^{1}H NMR spectroscopy using 1,3-dinitrobenzene as internal standard. [c] Molecular Sieves were removed from the crude mixture. [d] Complex Mixture.

At that point, two different basic media were tested as nucleophiles (**Table 3.2**, entries 3 and 4). Even though the formation of a two-phase system was avoided in the second case by addition of DMSO, the process took place in very low conversion.

Finally, hydroxy-substituted oxazolidinone **(±)-188** was generated in a promising 70% yield using a mixture of H_2O drops in MeCN, along with a small percentage of the S_N2' ring-opening product **189** (**Table 3.2**, entry 5). Washing the crude mixture with MeOH instead of CH_2Cl_2 during work-up filtration through a pad of celite was crucial for the final success of the procedure due to the high polarity of compounds **(±)-188** and **189**.

Additionally, *in situ* formed vinylaziridine **(±)-173** was treated with three different acetate salts to obtain another *O*-containing analogue. However, only CsOAc provided the desired acetoxy substituted product **(±)-190** (**Table 3.2**, entries 6-8). A commonly applied strategy to enhance salts solubility in organic solvents is the addition of the corresponding crown ethers to the reaction mixture. To our delight, when NaOAc and catalytic amounts of 15-crown-5 ether were added to the reaction mixture, oxazolidinone **(±)-190** was synthesised in a moderate 50% yield whereas a complex mixture was observed in the case of the potassium salt and its corresponding additive (**Table 3.2**, entries 9 and 10). Interestingly, removal of the crown ether from the crude mixture for purification purposes was achieved by washing it with a NaCl aqueous solution to generate the corresponding sodium complex.

For the introduction of *N*-nucleophiles, benzylamine and phthalimide were selected. The ring-opening reaction proceeded smoothly when liquid benzylamine was directly added to the reaction mixture, providing oxazolidinone **(±)-191** in an excellent 98% NMR-yield over the two steps (**Scheme 3.24**).

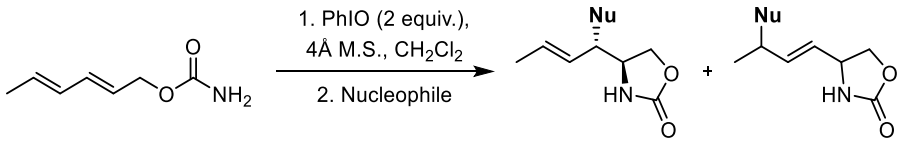


Scheme 3.24. PhIO mediated intramolecular aziridination of model dienyl carbamate **172** and *in situ* ring-opening with benzylamine.

However, phthalimide proved to be a more challenging nucleophile that required an intense optimisation work. Initial studies proved that solid phthalimide was unreactive under the reaction conditions (**Table 3.3**, entry 1). Likewise, unhopeful

results were obtained for potassium phthalimide salt, which furnished oxazolidinone **(±)-192** in rather low yields both at room temperature and at 35ºC (**Table 3.3**, entries 2 and 3).

Table 3.3. PhIO mediated intramolecular aziridination of model dienyl carbamate **172** and *in situ* ring-opening with *N*- and *S*-nucleophiles.[a]



172

Nu = Phth **(±)-192**
Nu = SPh **(±)-193**
Nu = SPh **194**

Entry	Nu	Ring-opening step	S_N2 product yield (%)[b]	S_N2' product yield (%)[b]
1	Phth	Phthalimide	C.M.[c]	
2	Phth	PhthK, r.t.	26	-
3	Phth	PhthK, 35 ºC	12	-
4	**Phth**	**PhthK, 18-Crown-6**	**52**	**-**
5	Phth	PhthK, 18-Crown-6/CH_3CN	C.M.[c]	
6	SPh	PhSH	≤5	32
7	SPh	PhSH[d]	18	26
8	SPh	PhSNa	C.M.[c]	
9	SPh	PhSNa/CH_3CN	26	-
10	SPh	PhSNa/DMF	23	-
11	SPh	PhSNa, 15-Crown-5	55	-
12	SPh	PhSNa, 15-Crown-5/CH_3CN	C.M.[c]	
13	**SPh**	**$PhSNHEt_3$**	**63**	**-**

[a] Carbamate **172** (1 equiv.), PhIO (2 equiv.), 4Å M.S. (100 mg per 0.1 mmol carbamate **172**), CH_2Cl_2 (0.04M), 35ºC. **Nu** = Phth, Phthalimide/PhthK (10 equiv.), crown ether (1 equiv.). **Nu** = SPh, PhSH/PhSNa/$PhSNEt_3$ (10 equiv.), crown ether (1 equiv.). [b] Determined by ^1H NMR spectroscopy using 1,3-dinitrobenzene as internal standard. [c] Complex Mixture. [d] PhSH was added dropwise.

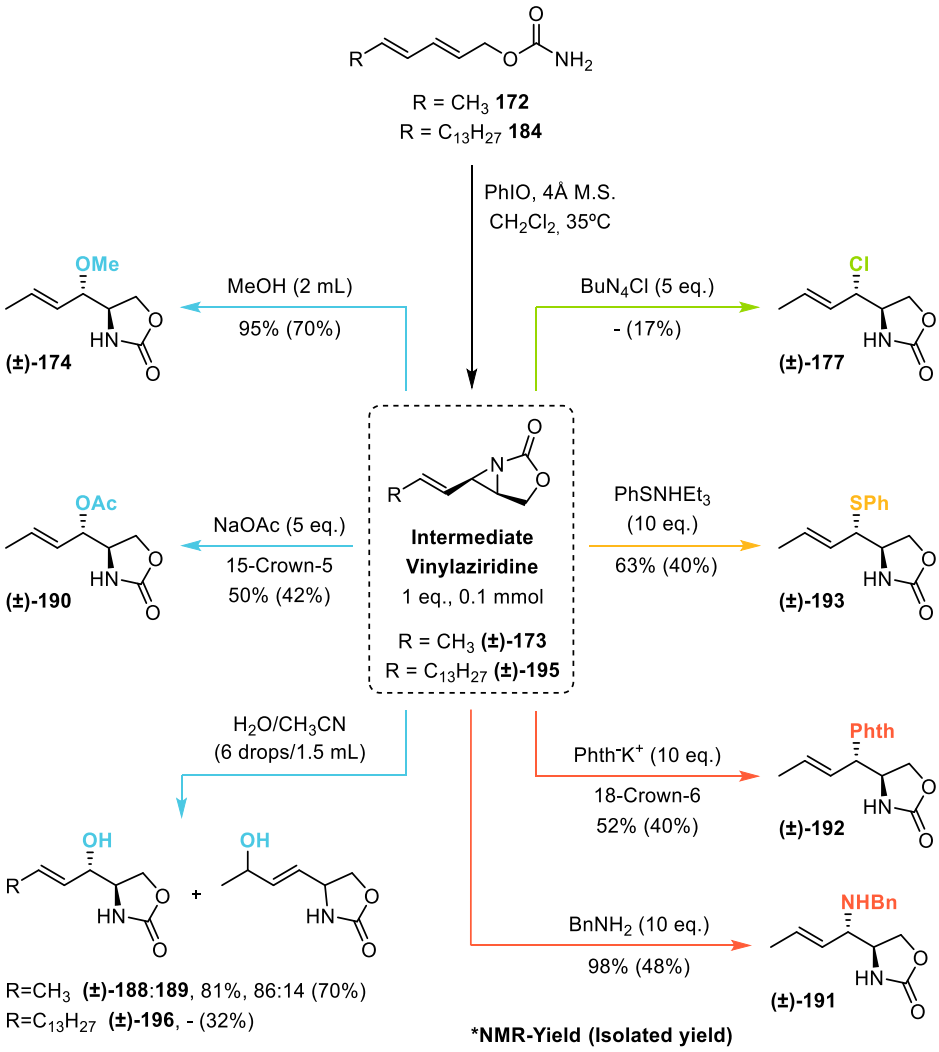
The main drawback of the present ring-opening strategy was the low solubility of the potassium salt in dichloromethane, the solvent of choice for the aziridination step. Alternatively, vinylaziridine intermediate **(±)-173** was treated with solid

potassium phthalimide and catalytic amounts of 18-crown-6 to favour salt solubilisation, providing the desired oxazolidinone **(±)-192** in a moderate 52% yield (**Table 3.3**, entry 4). Disappointingly, no further improvement on final yields was achieved when a solution of potassium phthalimide and crown ether in acetonitrile was used as nucleophile (**Table 3.3**, entry 5).

The introduction of *S*-nucleophiles was initially tackled by using thiophenol (**Table 3.3**, entry 6). Preliminary results suggested that the soft and slightly acid character of this nucleophile favoured S_N2' ring-opening product **194** over the desired S_N2 oxazolidinone **(±)-193**. In fact, slow addition of PhSH led to a substantial increase in the formation of S_N2 product **(±)-193** (**Table 3.3**, entry 7).

Then, considering the previous optimisation, PhSNa salt was tested as a nucleophile for the ring-opening step. However, no nucleophile incorporation was observed when intermediate vinylaziridine **(±)-173** was directly treated with the solid salt (**Table 3.3**, entry 8). Moreover, several attempts to solubilise PhSNa in different organic solvents were unsuccessful (**Table 3.3**, entries 9 and 10). Thus, applying former nitrogen-nucleophile incorporation strategy, solid PhSNa was added to the reaction mixture along with catalytic amounts of 15-crown-5 providing the desired oxazolidinone **(±)-193** in a moderate 55% yield (**Table 3.3**, entry 11). Once more, the use of a solution of solid PhSNa and crown ether in acetonitrile revealed to be detrimental for the final outcome of the reaction (**Table 3.3**, entry 12). Further improvement of ring-opening yield was achieved by selecting $PhSNHEt_3$ as nucleophile, furnishing oxazolidinone **(±)-193** in a fairly good 63% yield (**Table 3.3**, entry 13).

A summary of the optimised procedures and isolated yields for the preparation of *anti*-substituted oxazolidinones via PhIO mediated aziridination/ring-opening of (2*E*,4*E*)-hexa-2,4-dien-1-yl carbamate **172** are displayed in **Scheme 3.25**. In addition, this methodology was applied to the preparation of the sphingosine precursor **(±)-196** upon treatment of long-chain dienyl carbamate **184** with PhIO and subsequent ring-opening using a mixture of H_2O/CH_3CN. Despite the modest 32% yield observed for the formation of oxazolidinone **(±)-196**, this example clearly illustrates protocol versatility for the synthesis of unsaturated amino alcohols and analogous vicinal difunctionalised products (**Scheme 3.19**).



Scheme 3.25. PhIO mediated intramolecular aziridination of (2*E*,4*E*)-hexa-2,4-dien-1-yl carbamate **172** and *in situ* ring-opening with *O*-, *X*- *S*- and *N*-nucleophiles and straightforward preparation of sphingosine precursor **(±)-196**.

3.3.3. Synthesis of (2*Z*,4*E*)-hexa-2,4-dien-1-yl carbamate as starting material.

As part of our increased interest on the synthesis of structurally modified SK1 inhibitors for cancer treatment, we envisioned the possibility of applying the PhIO mediated aziridination/ring-opening methodology to the preparation of new sphingosine analogues bearing substituents in a *syn*-relative configuration starting from (2*Z*,4*E*)-hexa-2,4-dien-1-yl carbamate **201**.

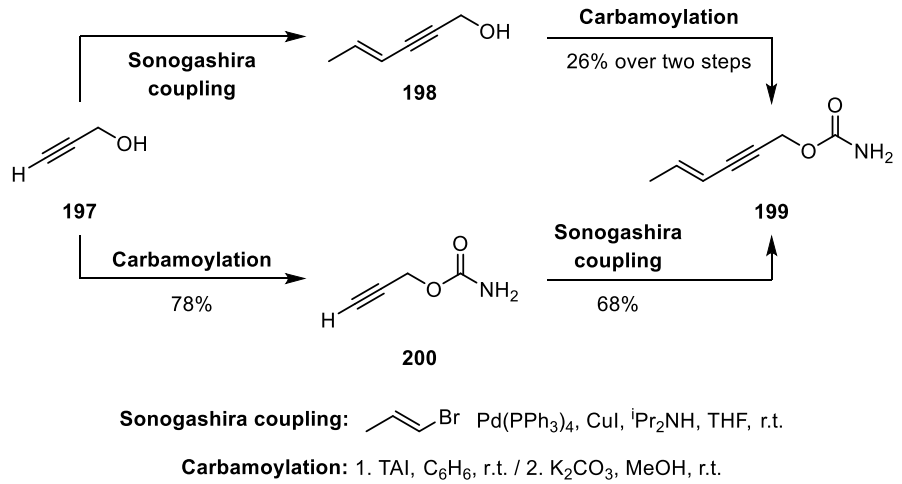
The initial proposal for the synthesis of carbamate **201** was coupling the propargyl alcohol with *trans*-1-bromo-1-propene using a Sonogashira reaction followed by a selective hydrogenation of the triple bond and a final carbamoylation of the hydroxyl moiety, as previously reported by our group.[73] However, the reduction of the triple bond to form a *cis*-double bond did not proceed as expected and it was necessary to study alternative routes for the synthesis of targeted carbamate **201**.

Sonogashira coupling and carbamoylation reaction

According to the aforementioned synthetic strategy, propargyl alcohol **197** was submitted to a Sonogashira coupling reaction with *trans*-1-bromo-1-propene in the presence of CuI and $^{i}(Pr)_2NH$, using tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$) as catalyst (**Scheme 3.26**). After overnight stirring, the crude NMR showed quantitative formation of alcohol **198** along with diisopropylamine signals and some impurities at the aromatic region, lately assigned by ^{31}P-NMR to triphenylphosphine and triphenylphosphine oxide. However, successive attempts to isolate alcohol **198** proved to be difficult do to its unstable nature under purification conditions.

In order to overcome product decomposition, alcohol **198** was directly submitted to the carbamoylation reaction after amine elimination with an aqueous work-up. Thus, crude mixture containing alcohol **198** was treated with a solution of trichloroacetyl isocyanate (TAI) in dry benzene followed by methanolysis of the intermediate product in the presence of K_2CO_3 to furnish carbamate **199** in a 26% yield over two steps (**Scheme 3.26**). In this case, purification was easily achieved using a mixture of 5:95 AcOEt/Hexanes to remove triphenylphosphine and its oxide

counterpart. Nevertheless, the observed poor yield for final carbamate **199** was probably due to operational problems related to the low boiling point of alcohol intermediate **198** (b.p. = 90.5-91.5 ºC).[98]



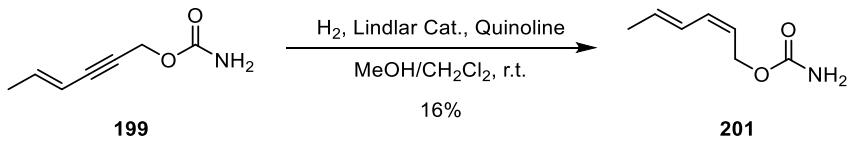
Scheme 3.26. Initial strategy for the synthesis of carbamate **199** involving a Sonogashira coupling and a carbamoylation reaction.

Eventually, an alternative synthetic route inverting previous sequence was proposed to avoid alcohol intermediate **198** evaporation. Consequently, carbamoylation reaction of propargyl alcohol **197** was performed in first place followed by the coupling reaction with *trans*-1-bromo-propene obtaining in both cases higher isolated yields (78% and 68% respectively) (**Scheme 3.26**). Moreover, for experimental reasons, (*E*)-Hex-4-en-2-yn-1-yl carbamate **199** was prepared in a 45% yield over two steps performing a single purification after both transformations.

Triple bond reduction

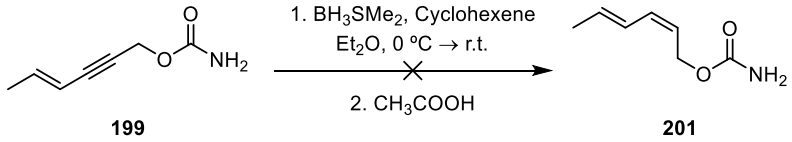
Initial attempts for triple bond reduction involved the direct hydrogenation of alkyne **199** in the presence of hydrogen gas, Lindlar Catalyst and quinoline (**Scheme 3.27**). After 2h stirring, the crude NMR showed the desired diene **201** as the major product. However, partially or completely hydrogenated by-products were observed as well, proving that the present reduction strategy was rather difficult to control.

[98] L. Crombie, S. H. Harper, R. J. D. Smith, *J. Chem. Soc.* **1957**, 2754–2760.



Scheme 3.27. Chemoselective alkyne **199** hydrogenation.

Alternatively, alkyne **199** was submitted to hydroboration reaction using BH_3SMe_2 in the presence of cyclohexene, as previously reported in the literature (**Scheme 3.28**).[99] Intermediate product was subsequently hydrolysed with acetic acid in a *one-pot* procedure to obtain diene **201**. However, reaction did not proceed as expected and the crude mixture mainly consisted of starting material and small amounts of side products.



Scheme 3.28. *One-pot* hydroboration/hydrolysis of alkyne **199**.

Ferreira and co-workers published in 2012 a platinum-catalysed hydrosilylation reaction of internal alkynes that furnished *E*-silylenones in high yields and selectivities.[100] To our delight, when alkyne **199** was treated with triethylsilane in the presence of $PtCl_2$, β/γ-substituted vinylsilanes **202a** and **202b** were obtained in an overall 65% yield (**Scheme 3.29**). However, selected TBAF deprotecting conditions did not yield diene **201**, even under longer reaction times or using tetrabutylammonium fluoride trihydrate at 80ºC.[101]

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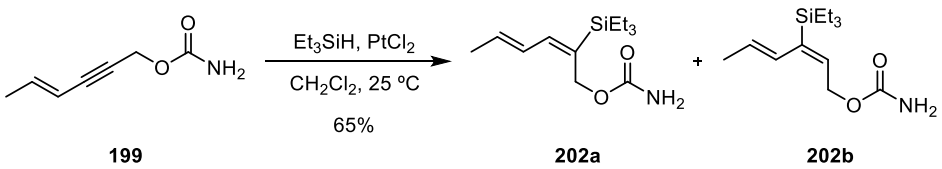
[99] a) S. Wattanasin, F. G. Kathawala, *J. Org. Chem.* **1985**, *50*, 3810–3815. b) M. Egger, P. Pellett, K. Nickl, S. Geiger, S. Graetz, R. Seifert, J. Heilmann, B. König, *Chem. Eur. J.* **2008**, *14*, 10978–10984.

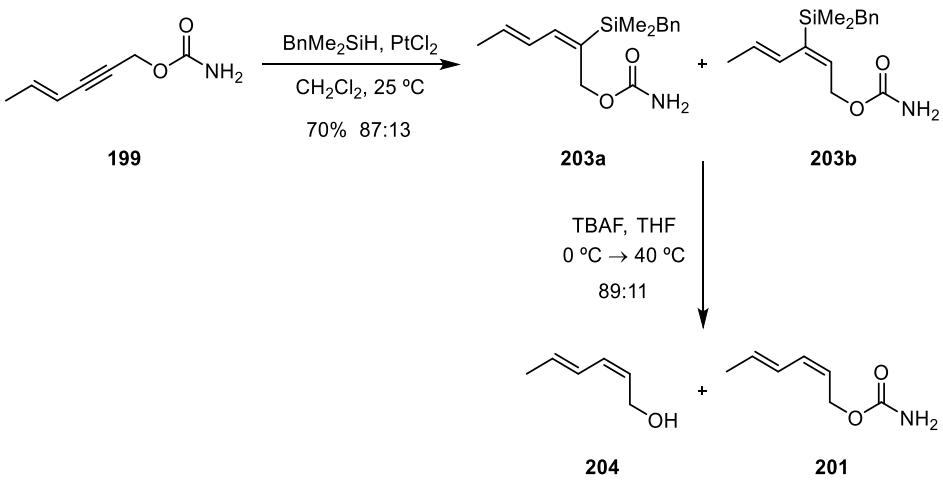
[100] D. A. Rooke, E. M. Ferreira, *Angew. Chem. Int. Ed.* **2012**, *51*, 3225–3230.

[101] H. Zhou, C. Moberg, *Org. Lett.* **2013**, *15*, 1444–1447.



Scheme 3.29. Platinum-catalysed hydrosilylation of alkyne **199**.

Finally, an extensive search into the literature led to the protodesilylation of $BnMe_2Si$-substituted double bonds. Thus, alkynyl carbamate **199** was reacted with benzylchlorodimethylsilane using Ferreira's conditions to afford an 87:13 mixture of regioisomers **203a** and **203b** (**Scheme 3.30**). To our delight, when vinylsilanes **203a** and **203b** were treated overnight with TBAF in anhydrous THF, an 89:11 mixture of dienol **204** and carbamate **201** was clearly observed in the crude NMR spectra. However, isolated yields were extremely low due to the high volatility of alcohol **204** (b.p. = 90 ºC).[102]

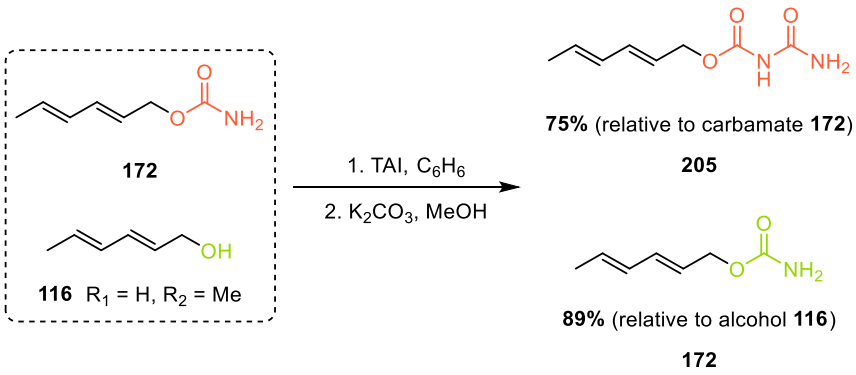


Scheme 3.30. Platinum-catalysed hydrosilylation of alkyne **199** followed by TBAF deprotection.

At this point, a *one-pot* protodesilylation/carbamoylation strategy was envisioned in order to directly transform volatile alcohol **204** into the desired product **201**, improving reaction yields. However, it was unclear whether the already formed

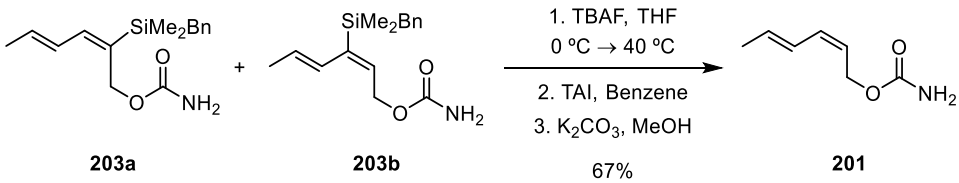
[102] L. A. Paquette, G. D. Crouse, A. K. Sharma, *J. Am. Chem. Soc.* **1982**, *104*, 4411–4423.

carbamate will be unreactive under carbamoylation conditions. With this purpose, a control experiment with a 1:1 mixture of readily available dienyl carbamate **172** and dienol **116** (R_1 = H, R_2 = Me) in the presence of trichloroacetyl isocyanate (TAI) was carried out (**Scheme 3.31**). To our delight, alcohol **116** was transformed into the desired product **172** in high yield. Unfortunately, carbamate **172** was also carbamoylated to afford compound **205** as a side product.



Scheme 3.31. Control experiment for carbamoylation reaction using an equimolar mixture of dienyl carbamate **172** and dienol **116**.

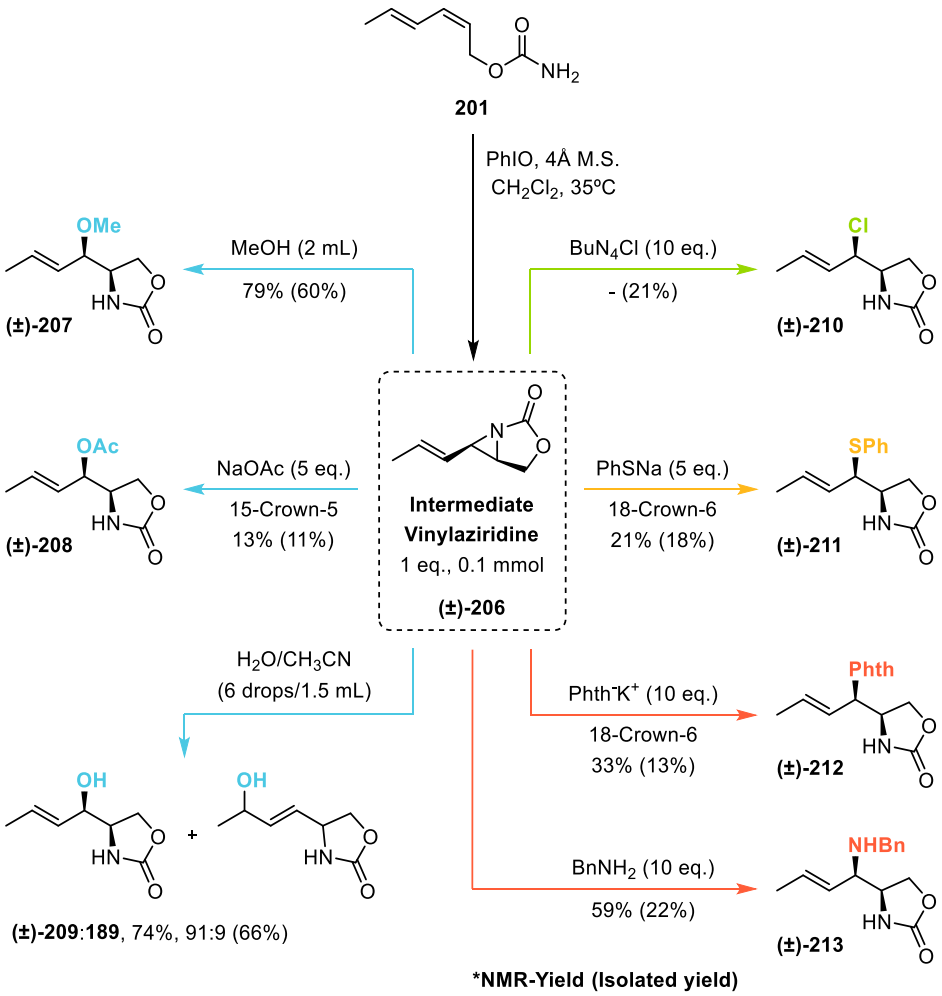
Finally, the mixture of vinylsilanes **203a** and **203b** was submitted to *one-pot* TBAF protodesilylation/carbamoylation reaction under the optimised conditions to afford *cis-trans* dienyl carbamate **201** in moderate yield (**Scheme 3.32**). Double bond configurations were unequivocally assigned by ^{1}H-NMR and nOe experiments whereas carbamate structure was confirmed by HRMS.



Scheme 3.32. *One-pot* TBAF protodesilylation/carbamoylation of vinylsilanes **203a** and **203b**.

3.3.4. Synthesis of *syn*-substituted oxazolidinones

Applying the previously optimised strategy, (2*Z*,4*E*)-hexa-2,4-dien-1-yl carbamate **201** was submitted to PhIO mediated aziridination/ring-opening reaction using the already studied *O*-, *X*-, *S*- and *N*-nucleophiles to furnish a set of *syn*-substituted oxazolidinones **(±)-207**-**(±)-213** (**Scheme 3.33**).



Scheme 3.33. PhIO mediated intramolecular aziridination of (2*Z*,4*E*)-hexa-2,4-dien-1-yl carbamate **201** and *in situ* ring-opening with *O*-, *X*- *S*- and *N*-nucleophiles.

In general, *syn*-substituted oxazolidinones **(±)-207**-**(±)-213** were obtained in somewhat lower yields than the related *trans*-products **(±)-174**-**(±)-193** (**Scheme**

3.25 and **Scheme 3.33**). In fact, theoretical calculations predicted a higher free energy barrier for the formation of *syn*-vinylaziridine **(±)-206** as a result of decreased dispersion interactions between phenyl ring from hypervalent iodine reagent and the distal double bond in (2*Z*,4E)-carbamate **201**.

Among oxygen nucleophiles, methanol and water rendered the corresponding *syn*-oxazolidinones **(±)-207** and **(±)-209** in synthetically useful yields whereas only traces of acetoxy-substituted product **(±)-208** were recovered from the reaction mixture upon NaOAc addition (**Scheme 3.33**). Interestingly, based on NMR data, both carbamates **172** and **201** furnished S_N2' ring-opening product **189** as the same diastereomer. Moreover, similar to the tendency observed for (2*E*,4*E*)-carbamate **172**, tetrabutylammonium chloride proved to be a poor nucleophile for the ring-opening reaction of intermediate vinylaziridine **(±)-206** (**Scheme 3.33**).

On the other hand, the synthesis of phenyl sulfanyl oxazolidinone **(±)-211** was specially challenging since only formation of chloro-substituted compound **(±)-210** was observed when $PhSNHEt_3$ salt was used as nucleophile. Upon screening of reaction conditions, sodium thiophenolate was found to furnish the desired sulfur-containing compound **(±)-211**, although in modest yield (**Scheme 3.33**). Finally, *in situ* formed vinylaziridine **(±)-206** underwent ring-opening with different nitrogen-containing nucleophiles rendering the corresponding *syn*-oxazolidinones **(±)-212** and **(±)-213** in 33% and 59% NMR-yields respectively (**Scheme 3.33**). Disappointingly, despite remarkable performance of benzyl amine in the preparation of *anti*-substituted product **(±)-191**, the analogous *syn*-compound **(±)-213** was obtained in rather low yield.

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CHAPTER IV

ASYMMETRIC DIENE AZIRIDINATION USING CHIRAL IODINE(III) REAGENTS

UNIVERSITAT ROVIRA I VIRGILI
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Irene Giménez Nueno

4.1. Introduction

In the past few years, important efforts have been made in the development of new asymmetric routes for the preparation of enantioenriched building blocks that will enable future chiral syntheses of natural occurring products and commercially available drugs. As commonly observed in Nature, the biological activity of sphingosine and its analogues strongly depends on their chiral chemical structure.[35] To date, moderate to good yields have been achieved for the metal-free regio and stereoselective aziridination/ring-opening of dienyl carbamates **172** (*See Chapter III*). However, an asymmetric system rendering enantioenriched unsaturated vicinal hetero-amino moieties as precursors of optically pure sphingosine derivatives is still missing.

General methods for asymmetric alkene aziridination rely either on the addition of metal-nitrenes to alkenes in the presence of chiral ligands or on the organocatalysed reaction of amines with α,β-unsaturated carbonyl compounds.[38c-e] In this context, hypervalent iodine reagents have been traditionally used as oxidant agents for the preparation of iminoiodanes such as PhI=NTs or for the *in situ* generation of metallonitrene from sulfonamide, sulfamate or carbamate derivatives and the corresponding metal catalyst.[57] However, chiral λ^3-iodanes have recently emerged as a versatile eco-friendly alternative to transition metal complexes for the enantioselective synthesis of a wide range of biologically active structures via dearomatisation of phenolic substrates, α-functionalisation of carbonyl compounds or alkene derivatisation.[27,103]

4.1.1. Chiral λ^3-iodanes for asymmetric synthesis

In 1997, T. Wirth and co-workers reported the enantioselective synthesis of α-oxytosylated ketones and vicinal difunctionalised styrenes in the presence of optically

[103] a) S. Ghosh, S. Pradhan, I. Chatterjee, *Beilstein J. Org. Chem.* **2018**, *14*, 1244–1262. b) M. Fujita, *Heterocycles* **2018**, *96*, 563–594. c) R. Kumar, T. Wirth, In *Hypervalent Iodine Chemistry*; T. Wirth, Ed.; *Top. Curr. Chem.* **2016**, *373*, 243–262. d) F. Berthiol, *Synthesis* **2015**, *47*, 587–603. e) A. Parra, S. Reboredo, *Chem. Eur. J.* **2013**, *19*, 17244–17260. f) M. Ngatimin, D. W. Lupton, *Aust. J. Chem.* **2010**, *63*, 653–658.

pure Koser's reagent **217** (**Figure 4.1** a).[104] This publication entailed the first example of an stereoselective transformation mediated by chiral hypervalent iodine compounds. Since then, important efforts have been made towards the development of new chiral structures that enable novel metal-free asymmetric protocols under stoichiometric or catalytic conditions (**Figure 4.1** a).[27,103]

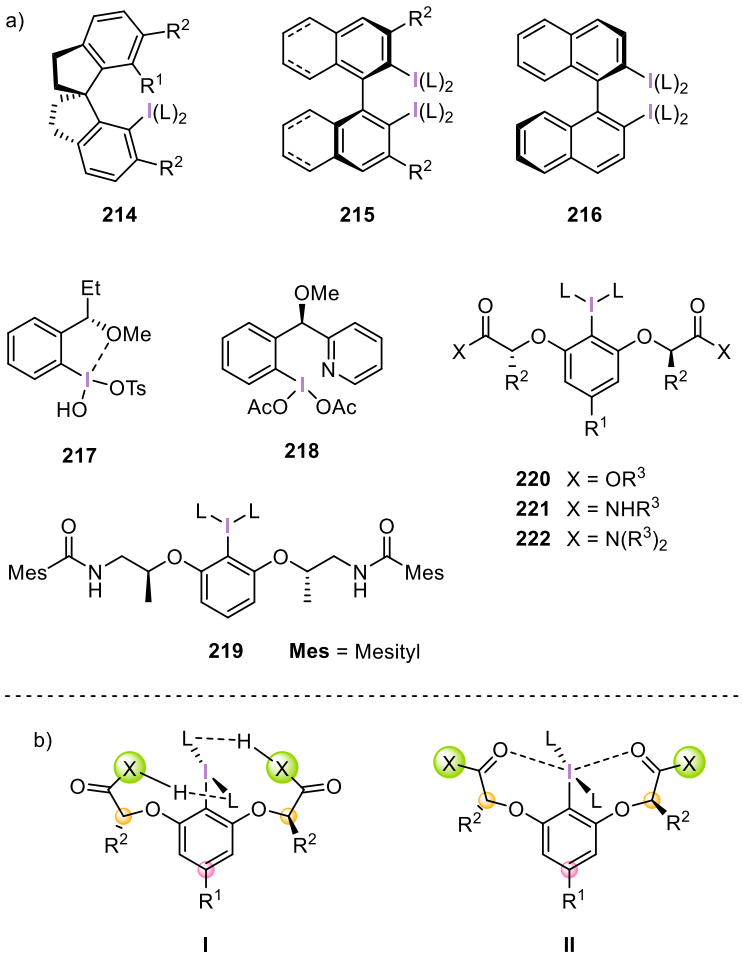

Figure 4.1. a) Selected examples of chiral λ³-iodanes. b) Proposed supramolecular assemblies **I** and **II** for lactate-based chiral aryliodine(III) reagents **220**-**222**.

[104] a) T. Wirth, U. H. Hirt, *Tetrahedron Asymmetry* **1997**, *8*, 23–26. b) U. H. Hirt, M. F. H. Schuster, A. N. French, O. G. Wiest, T. Wirth, *Eur. J. Org. Chem.* **2001**, 1569–1579.

To date, three different classes of chiral λ³-iodanes have been reported in the literature: carbon-based spirocyclic compounds **214**,[105] C_2-symmetric biaryl reagents **215** and **216**[106] and aryliodine(III) structures bearing adjacent stereogenic centres **217**-**222** (**Figure 4.1** a).[27,103] Among them, 2-iodo-resorcinol-systems containing two lactic acid units **220**-**222** have received much attention due to their versatile nature and straightforward introduction of chemical modifications (R_1, R_2 and X). Moreover, a related resorcinol-amino-alcohol system **219** has also been described for the oxidative dearomatisation of phenolic substrates.[107] In both cases, readily available chiral-pool groups were placed in close proximity to iodine atom in the resorcinol ring to enhance the transmission of stereochemical information to the reactive centre.

Chirally-modified Koser's reagent **217** represents an earlier example of hypervalent iodine-mediated supramolecular stereoinduction (**Figure 4.1** a).[104] Thus, intramolecular ether chelation to the iodine centre enhances its electrophilic character while creates a rigid stereochemical environment that prompted asymmetric control over styrene derivatisation and arylketone α-functionalisation.

Along these lines, preliminary studies on the mode of action of privileged resorcinol-lactate systems **220**-**222** suggested the formation of supramolecular helical structures that created a chiral environment around iodine atom (**Figure 4.1** b).[27a] Thus, the proposed three-dimensional assemblies arose from the H-bonding of secondary amides **221** with λ³-iodane ligands (structure **I**) or the coordination of lactic carbonyl moieties in **220** or **222** with electron-poor iodine centre (structure **II**). Eventually, X-ray analysis have demonstrated the presence of such intramolecular H-bonding interactions for amide-containing λ³-iodanes.[107,108] In addition, final stereodifferentiation for a specific organic substrate can be efficiently tuned by a

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105 T. Dohi, A. Maruyama, N. Takenaga, K. Senami, Y. Minamitsuji, H. Fujioka, S. B. Caemmerer, Y. Kita, *Angew. Chem. Int. Ed.* **2008**, *47*, 3787–3790.

106 S. Quideau, G. Lyvinec, M. Marguerit, K. Bathany, A. Ozanne-Beaudenon, T. Buffeteau, D. Cavagnat, A. Chénedé, *Angew. Chem. Int. Ed.* **2009**, *48*, 4605–4609.

107 M. Uyanik, T. Yasui, K. Ishihara, *Angew. Chem. Int. Ed.* **2013**, *52*, 9215–9218.

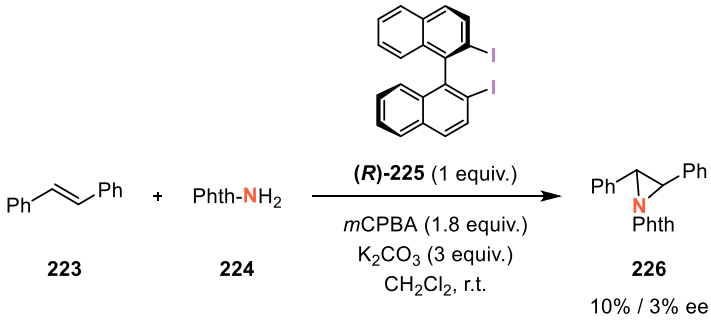
108 a) S. Haubenreisser, T. H. Wöste, C. Martínez, K. Ishihara, K. Muñiz, *Angew. Chem. Int. Ed.* **2016**, *55*, 413–417. b) K. Muñiz, L. Barreiro, R. M. Romero, C. Martínez, *J. Am. Chem. Soc.* **2017**, *139*, 4354–4357.

careful selection of electronic and steric properties of aryl and alkyl substituents at the stereogenic centres in lactate units.[30b]

4.1.2. Iodine(III)-mediated asymmetric aziridination of olefins

As previously mentioned, enantioenriched aziridines have been traditionally prepared by metal- or organocatalysed stereoselective addition of nitrene equivalents to double bonds.[38c-e] However, despite the impressive development of chiral hypervalent iodine chemistry in the past two decades, publications concerning the metal-free asymmetric aziridination of olefinic substrates via iminoiodane formation are scarce.

Inspired by an early report on the catalytic aziridination of styrene derivatives using 4-iodoanisole and *m*CPBA as an oxidant agent,[109] T. Wirth and co-workers attempted a related asymmetric aziridination of stilbene **223** with *N*-amino phthalimide **224** via *in situ* oxidation of chiral binaphthyl precursor **(*R*)-225** (**Scheme 4.1**).[82c] Unfortunately, the desired *trans*-aziridine **226** was formed in very low yields with no enantiocontrol.

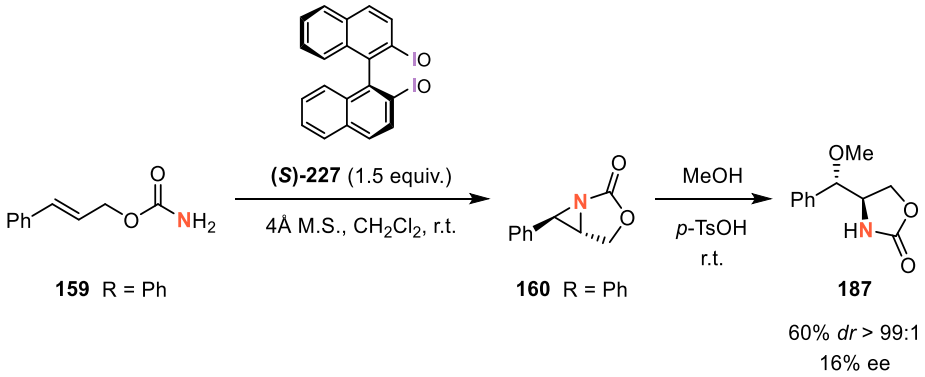


Scheme 4.1. *In situ* oxidation of chiral binaphthyl precursor **(*R*)-225** for the asymmetric aziridination of stilbene **223** with *N*-amino phthalimide **224**.

Few years later, as part of their work on PhIO-mediated intramolecular aziridination of allylic carbamates (*See Chapter III*, **Scheme 3.16**), C.-M. Che and co-workers applied pre-oxidised chiral binaphthyl iodine(III) reagent **(*S*)-227** to the *one-*

[109] J. Li, P. W. H. Chan, C.-M. Che, *Org. Lett.* **2005**, *7*, 5801–5804.

pot synthesis of oxyaminated products **187** via ring-opening of the aziridine intermediate **160** (R = Ph) (**Scheme 4.2**).[87] However, despite remarkable diastereoselectivity, only a 16% ee was obtained after two steps.



Scheme 4.2. Enantioselective aziridination/ring-opening of allylic carbamate **159** (R = Ph) using pre-oxidised chiral binaphthyl iodine(III) reagent **(*S*)-227**.

4.1.3. Relevant examples of asymmetric alkene difunctionalisation using chiral iodine(III) reagents

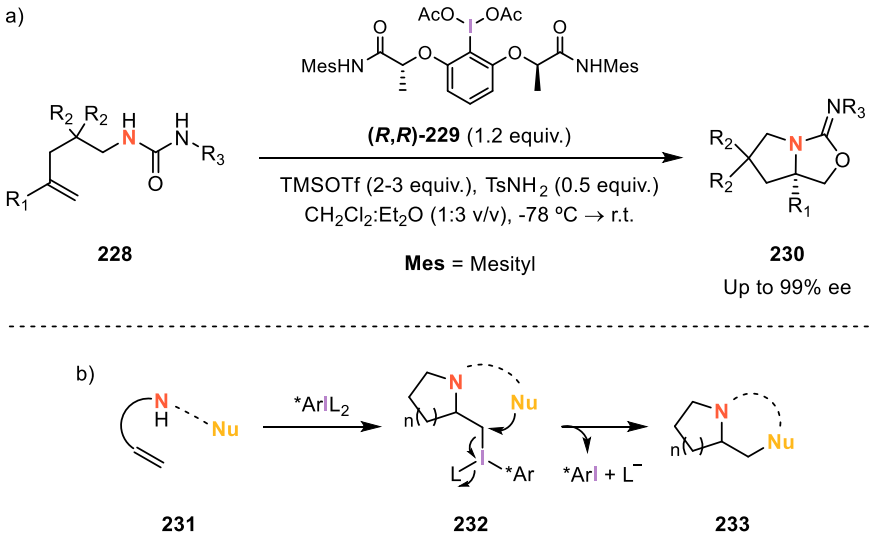
Alternatively, chiral iodine(III) reagents have also been employed for the asymmetric introduction of nucleophilic nitrogen sources into double bonds via alkene difunctionalisation. The mechanistic aspects of this transformation have already been described in the general introduction of this Ph.D. work (*See Chapter I*, **Scheme 1.8**).[30] Literature examples concerning the stereoselective addition of *N*-substituents to olefinic substrates using optically pure λ³-iodanes can be divided in oxyaminations, diaminations, amino-fluorinations, thioaminations and amino-arylations.

Oxyaminations

In 2012, T. Wirth and co-workers reported the enantioselective intramolecular oxyamination of urea derivatives **228** under stoichiometric amounts of lactate-based reagent **(*R,R*)-229** preactivated with TMSOTf (**Scheme 4.3** a).[110]

[110] U. Farid, T. Wirth, *Angew. Chem. Int. Ed.* **2012**, *51*, 3462–3465.

Stereodifferentiation of prochiral faces from starting materials **228** by chiral iodine(III) compound **(*R*,*R*)-229** allowed the formation of a set of bicyclic products **230** with up to 99% ee. Subsequent nitrogen deprotection and basic cleavage of the isourea heterocycle intermediate gave access to enantioenriched vicinal amino-alcohols. The protocol was amenable to different backbone substitutions whereas variable results were obtained when alternative nitrogen sources were used.

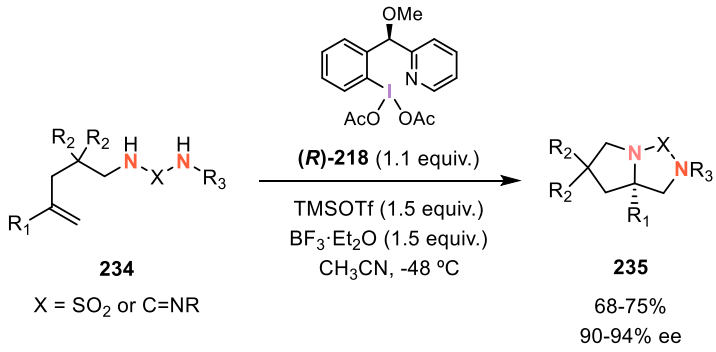


Scheme 4.3. a) Enantioselective intramolecular oxyamination of urea derivatives **228** towards bicyclic products **230**. b) Proposed mechanism for chiral iodine(III)-mediated intramolecular cyclisation of binucleophilic substrates **231**.

According to the general mechanism for alkene difunctionalisation proposed in **Scheme 1.8** (*See Chapter I*), binucleophilic substrate **231** undergoes initial addition of nitrogen source upon chiral iodine(III) activation of double bond (**Scheme 4.3** b). The attached hypervalent iodine atom in intermediate **232** displays excellent leaving group ability, favouring second nucleophilic attack and concomitant reductive elimination to furnish final bicyclic product **233**.

Diaminations

The preparation of a new chiral λ³-iodane **(*R*)-218** bearing a pyridine ring in close proximity to the iodine centre provided an efficient approach for the intramolecular asymmetric diamination of tethered alkenes **234** (**Scheme 4.4**).[111] Secondary interactions between nitrogen and iodine atoms restricted the conformational flexibility of iodine(III) reagent **(*R*)-218** favouring bicyclic product **235** formation in high yields and enantioselectivities. Both sulfonamide and guanidine derivatives were well tolerated whereas cyclisation reaction only proceed for starting materials **234** containing phenyl-substituted backbones and Cbz-protected terminal amines. Moreover, comparable enantiocontrol was observed for the intramolecular diamination of tethered alkenes **234** under catalytic conditions, using 20 mol% of iodine(I) precatalyst and $NaBO_3 \cdot 4H_2O$ as an oxidant agent.



Scheme 4.4. Intramolecular asymmetric cyclisation of tethered diamino alkenes **234**.

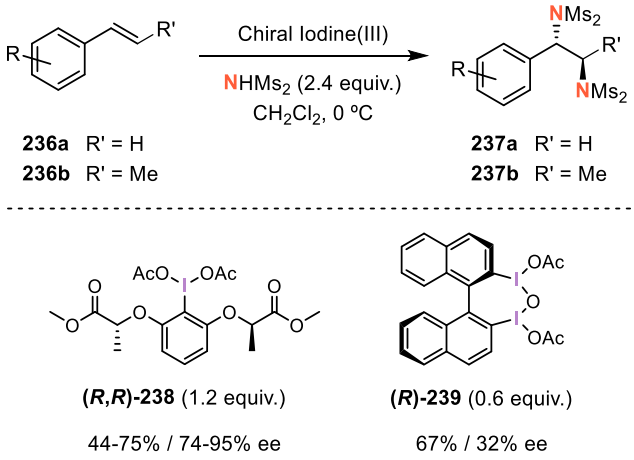
In 2011, K. Muñiz and co-workers reported the enantioselective diamination of styrene derivatives **236** under intermolecular control (**Scheme 4.5**).[112] Two different chiral iodine(III) reagents, **(*R,R*)-238** and **(*R*)-239**, were tested for alkene difunctionalisation in the presence of bismesylimide as external nitrogen source. However, only lactate-base λ³-iodane **(*R,R*)-238** rendered diaminated products **237**

[111] P. Mizar, A. Laverny, M. El-Sherbini, U. Farid, M. Brown, F. Malmedy, T. Wirth, *Chem. Eur. J.* **2014**, *20*, 9910–9913.

[112] a) C. Röben, J. A. Souto, Y. González, A. Lishchynskyi, K. Muñiz, *Angew. Chem. Int. Ed.* **2011**, *50*, 9478–9482. b) J. A. Souto, Y. González, A. Iglesias, D. Zian, A. Lishchynskyi, K. Muñiz, *Chem. Asian J.* **2012**, *7*, 1103–1111. c) C. Röben, J. A. Souto, E. C. Escudero-Adán, K. Muñiz, *Org. Lett.* **2013**, *15*, 1008–1011.

in synthetically useful yields and selectivities. The protocol was successfully applied to styrenes **236a** containing both electron-donating and electron-withdrawing groups and related indene, whereas no enantiocontrol was achieved for aliphatic double bonds. Moreover, versatile building blocks could be prepared upon deprotection of the vicinal diamino moiety in **237a** under reductive reaction conditions.

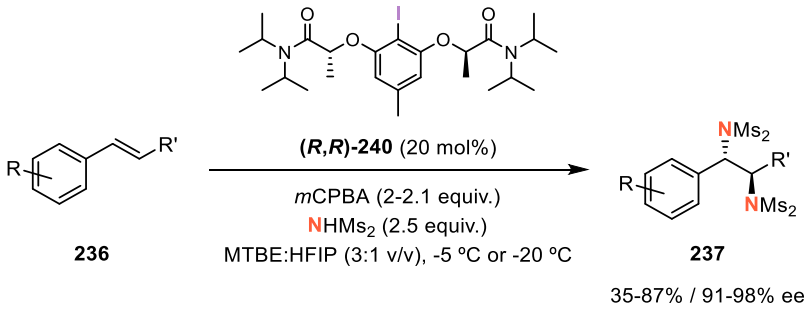
A tentative mechanism was proposed based on the observed *anti*-relationship for *β*-methyl styrene diaminated products **236b** (**Scheme 4.5**).[112a] Thus, according to the general pathways for alkene difunctionalisation (*See Chapter I*, **Scheme 1.8**), regioselective ring-opening of a transient aziridinium ring via nucleophilic attack at the benzylic position will give access to compounds **237b** in high enantioselectivities with *anti*-absolute configuration.



Scheme 4.5. Enantioselective intermolecular diamination of styrene derivatives **236** using chiral iodine(III) reagents **(*R,R*)-238** and **(*R*)-239**.

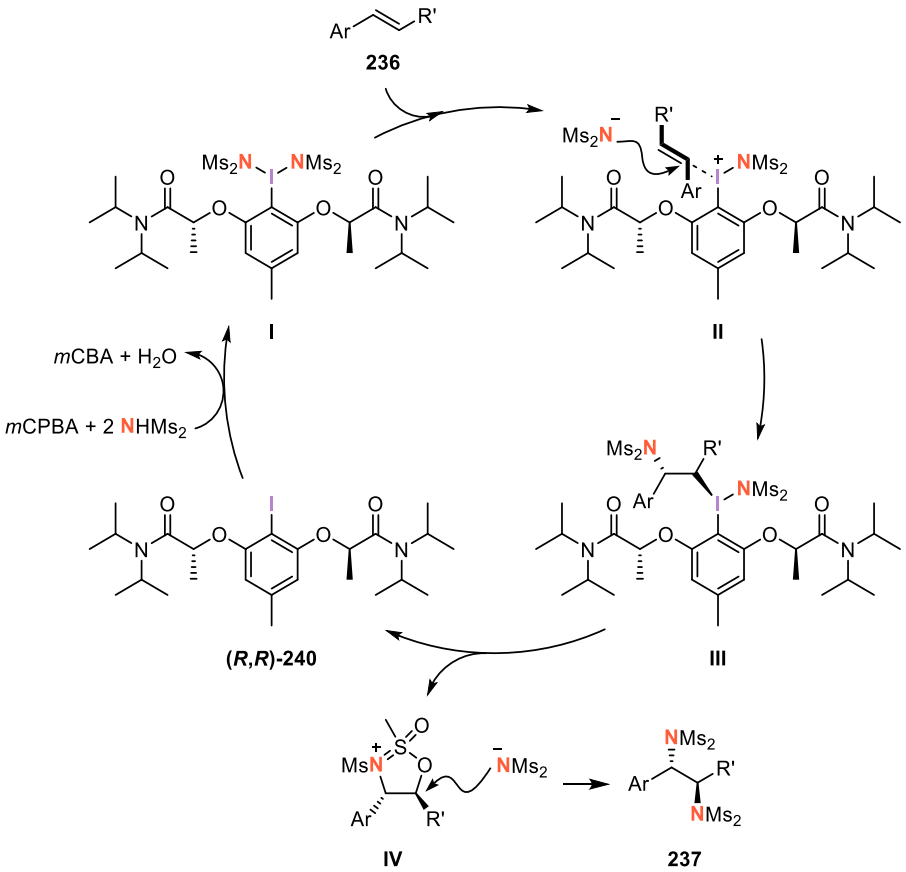
The catalytic version of this enantioselective transformation was published by the same group few years later (**Scheme 4.6**).[108b] Thus, chiral iodine(I) precursor **(*R,R*)-240** efficiently catalyses the intermolecular diamination of styrene derivatives **236** up to 98% ee, using *m*CPBA as a terminal oxidant and bismesylimide as an external nitrogen source. A careful selection of solvent mixture minimises background olefin epoxidation while avoids commonly used hazardous chlorinated solvents. Both external and internal alkenes **236** were tolerated under optimised reaction conditions furnishing difunctionalised products **237** with identical absolute

configuration at benzylic carbon. Interestingly, complete catalyst control was observed for starting materials **236** bearing preinstalled chiral substituents.



Scheme 4.6. Iodine(I/III)-catalysed enantioselective intermolecular diamination of styrene derivatives **236**.

The catalytic cycle proposed started with initial oxidation of chiral iodine(I) precursor **(*R*,*R*)-240** under stoichiometric amounts of *m*CPBA and bismesylimide (**Scheme 4.7**).[108b] X-ray analysis have demonstrated the supramolecular arrangement of a related hypervalent iodine reagent via intramolecular H-bonding interactions between an external water molecule and carbonyl moieties from the lactate units and acetate ligands.[108b] Therefore, after styrene **236** coordination, helical chirality around the iodine centre induces differentiation of enantiotopic alkene faces for subsequent nucleophilic attack, furnishing intermediate **III** in high enantioselectivities. Then, the intramolecular addition of the mesyl group triggered precatalyst **(*R*,*R*)-240** regeneration via reductive elimination and concomitant formation of cyclic compound **IV** which undergoes regioselective ring-opening to give access to final *anti*-diaminated product **237**.

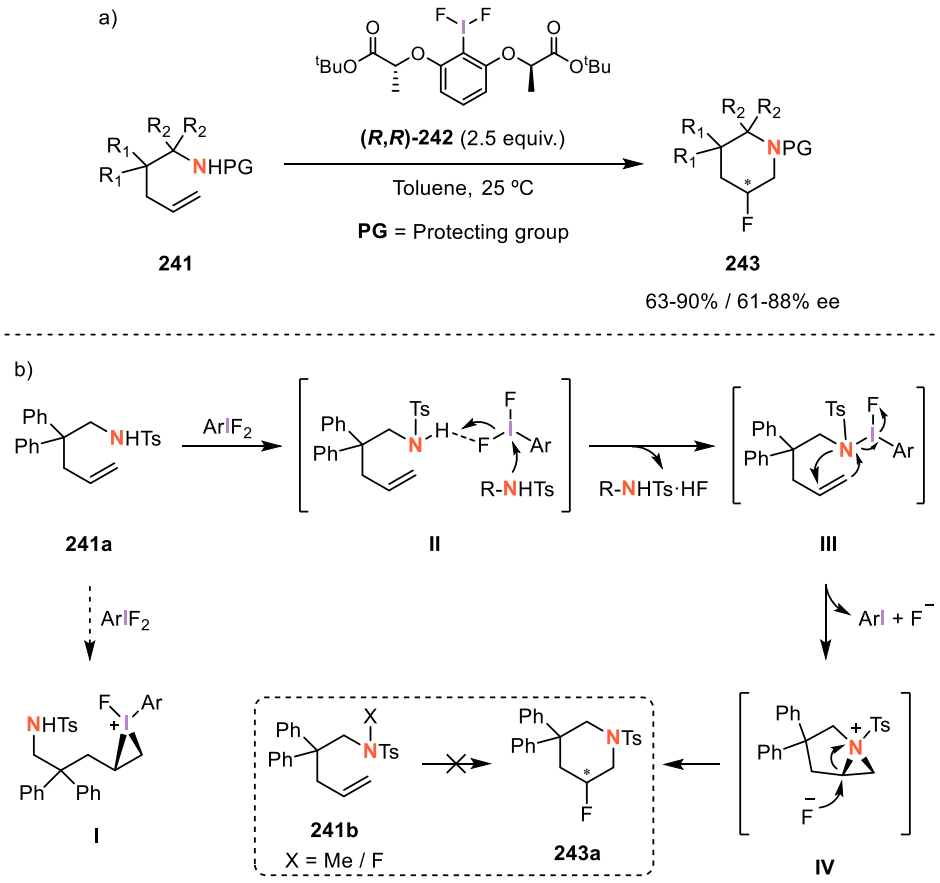


Scheme 4.7. Proposed catalytic cycle for the enantioselective diamination of styrene derivatives **236** using chiral iodine(I) precursor **(*R*,*R*)-240**.

Amino-fluorinations

In 2013, C. Nevado and co-workers reported the asymmetric amino-fluorination of pentenyl amines **241** using stoichiometric amounts of lactate-based (difluoroiodo)arene **(*R*,*R*)-242** (**Scheme 4.8** a).[113] The resulting 3-fluoro piperidines **243** were prepared as single regioisomers in high yields and remarkable selectivities via intramolecular 6-*endo*-cyclisation of differently monoprotected substrates **241**. Unfortunately, the protocol was restricted to terminal amino-alkenes **241** bearing aromatic substituents at the aliphatic backbone.

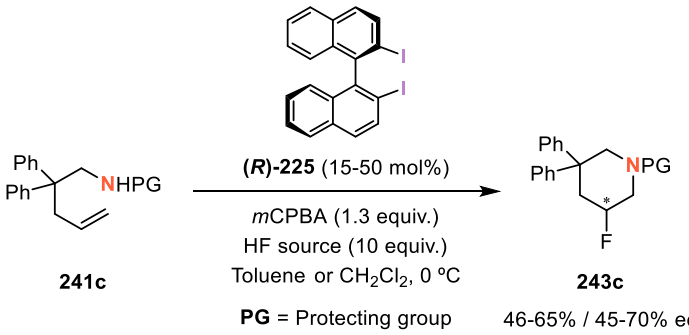
[113] W. Kong, P. Feige, T. de Haro, C. Nevado, *Angew. Chem. Int. Ed.* **2013**, *52*, 2469–2473.



Scheme 4.8. a) Regio- and enantioselective amino-fluorination of pentenyl amines **241** using lactate-based (difluoroiodo)arene **(*R*,*R*)-242**. b) Proposed mechanism for the observed 6-*endo*-cyclisation of tethered amino-alkenes **241a**.

A plausible mechanism for the observed 6-*endo*-cyclisation of tethered amino-alkenes **241a** was proposed based on experimental data (**Scheme 4.8** b).[113] The expected formation of iodonium ring **I**[30] was initially dismissed due to the unreactive nature of *N*,*N*-disubstituted starting materials **241b** under optimised conditions, which highlighted the crucial role of the secondary amine proton in the reaction mechanism. The suggested alternative pathway involved the oxidation of sulfonamide moiety via hydrogen bond-assisted ligand exchange to generate key intermediate **III**. Subsequent intramolecular cyclisation gave access to aziridinium ring **IV** which underwent *in situ* cleavage by fluoride anions released from iodine(III) reagent **(*R*,*R*)-242** to finally furnish β-fluoro piperidine **243a**.

A similar mechanism involving the generation of aziridinium intermediate **IV** was proposed for the asymmetric amino-fluorination of related pentenyl amines **241c** under catalytic conditions (**Scheme 4.9**).[114] In this case, chiral binaphthyl precursor **(*R*)-225** was *in situ* oxidised with *m*CPBA to render 3-fluoro piperidines **243c** in moderate yields and selectivities, using HF as a nucleophilic fluoride source. Both tosyl and nosyl *N*-protecting groups were tolerated under the reaction conditions, although diminished enantiomeric ratios were observed for nitro-containing sulfonamides. Interestingly, a completely lack of asymmetric control was encountered when phenyl rings at the substrate backbone were replaced by methyl groups, suggesting the formation of π-π interactions between the iodine(III) catalyst and the starting material **241c**.



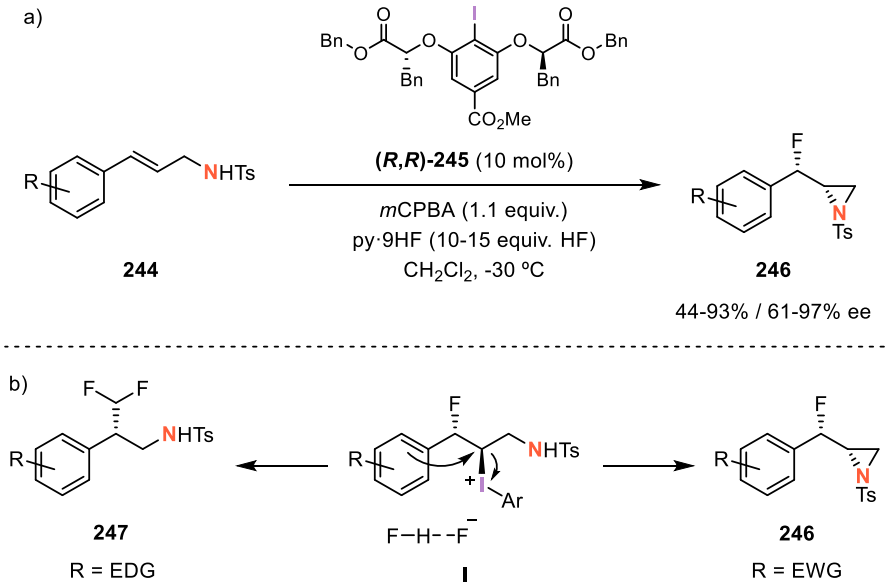
Scheme 4.9. Asymmetric amino-fluorination of pentenyl amines **241c** catalysed by chiral binaphthyl precursor **(*R*)-225**.

Along these lines, E. Jacobsen and co-workers have recently reported the catalytic enantioselective amino-fluorination of allylic amines **244** using lactate-based iodine(I) precursor **(*R,R*)-245** in the presence of *m*CPBA as terminal oxidant and py·9HF as a nucleophilic fluoride source (**Scheme 4.10** a).[115] *Syn*-*β*-flouroaziridines **246** were obtained in high yields and selectivities for a wide range of electron deficient cinnamyl tosylamide derivatives **244**. Subsequent regioselective ring-opening with *O*-, *N*-, *X*- and *S*-nucleophiles gave access to versatile building blocks bearing three adjacent heteroatomic substituents. Moreover, upon study of alternative carbonyl-

[114] S. Suzuki, T. Kamo, K. Fukushi, T. Hiramatsu, E. Tokunaga, T. Dohi, Y. Kita, N. Shibata, *Chem. Sci.* **2014**, *5*, 2754–2760.

[115] K. M. Mennie, S. M. Banik, E. C. Reichert, E. N. Jacobsen, *J. Am. Chem. Soc.* **2018**, *140*, 4797–4802.

based *N*-protecting groups, the formation of 1,2-oxyfluoro compounds was encountered as a result of the intramolecular cyclisation of neighbouring oxygen atom. Interestingly, phenethyl amine analogues **244** containing electron donating moieties at the aromatic ring underwent phenonium ion rearrangement from common iodonium intermediate **I**, furnishing difluorinated products **247** (**Scheme 4.10** b).[115]



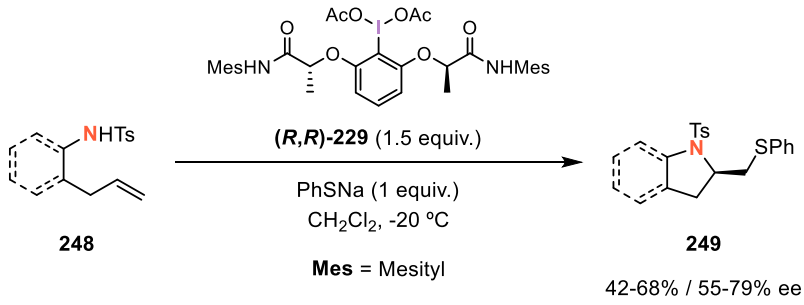
Scheme 4.10. a) Catalytic enantioselective amino-fluorination of cinnamyl tosylamide derivatives **244** using lactate-based iodine(I) precursor **(*R*,*R*)-245**. b) Divergent formation of *syn*-*β*-flouroaziridines **246** and rearranged difluorinated products **247** from common iodonium intermediate **I**.

Thioamination

In 2016, T. Wirth and co-workers published the thioamination of sulfonamide derivatives **248** using stoichiometric amounts of chiral lactate-based iodine(III) reagent **(*R*,*R*)-229** and sodium thiophenolate as nucleophilic source (**Scheme 4.11**).[116] Selective alkene activation over sulphur oxidation gave access to enantioenriched pyrrolidine and indoline ring systems **249** in moderate yields.

[116] P. Mizar, R. Niebuhr, M. Hutchings, U. Farooq, T. Wirth, *Chem. Eur. J.* **2016**, *22*, 1614–1617.

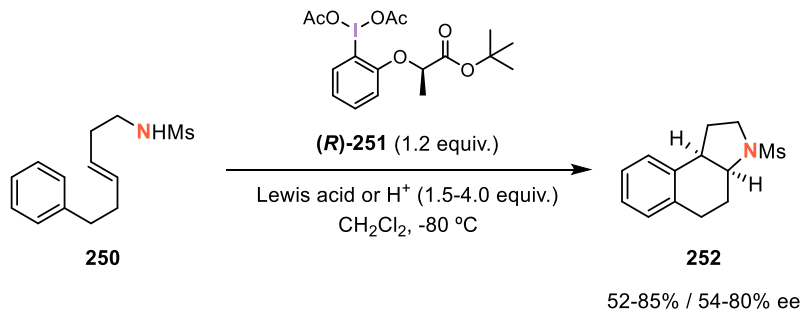
Notably, increased asymmetric control was encountered for cyclic starting materials **248**.



Scheme 4.11. Asymmetric thioamination of sulfonamide derivatives **248** using chiral lactate-based iodine(III) reagent **(*R*,*R*)-229**.

Amino-arylation

Enantioenriched hexahydrobenz[e]indole **252** was prepared in the presence of preactivated chiral λ³-iodane **(*R*)-251** bearing a single lactate arm via intramolecular amino-arylation of methanesulfonyl amide **250** (**Scheme 4.12**).[117] Asymmetric control was achieved upon coordination of the electrophilic iodine centre into the preferred enantiotopic alkene face and subsequent internal addition of terminal sulfonamide in *anti*-fashion. Then, final hypervalent iodine displacement by aryl moiety furnished observed *syn*-fused products **252**.

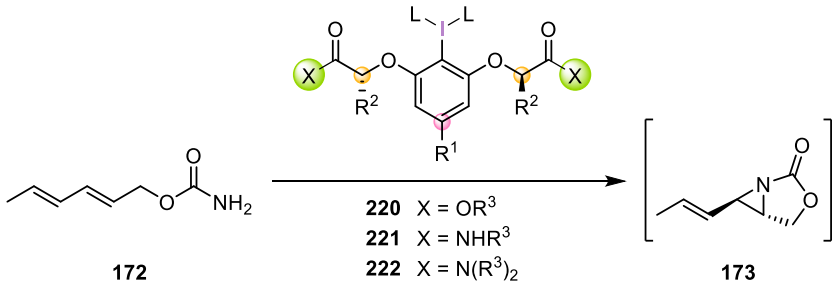


Scheme 4.12. Enantiomeric preparation of hexahydrobenz[e]indole **252** via intramolecular amino-arylation of methanesulfonyl amide **250**.

[117] M. Shimogaki, M. Fujita, T. Sugimura, *Angew. Chem. Int. Ed.* **2016**, *55*, 15797–15801.

4.2. Aims and objectives

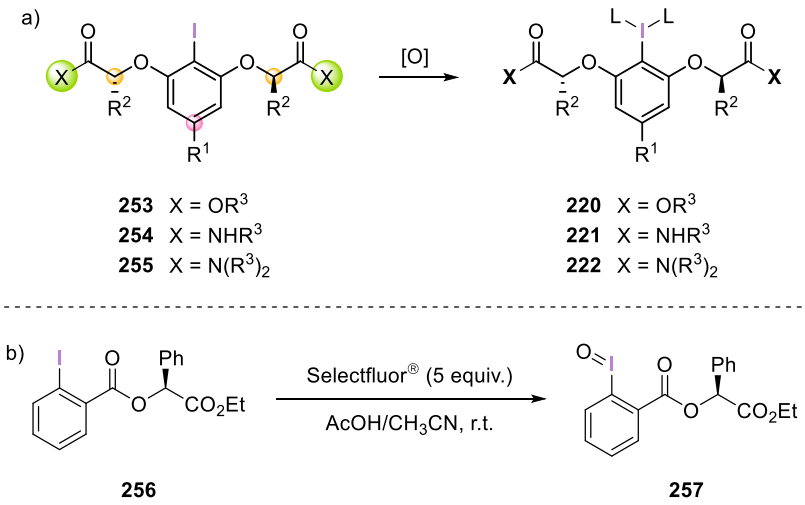
As part of a program aimed at developing new synthetic strategies for the preparation of unsaturated vicinal hetero-amino moieties, the application of lactate based λ³-iodanes **220-222** to the enantiomeric aziridination of model dienyl carbamate **172** was envisioned (**Scheme 4.13**). According to the literature, the reported supramolecular assembly of these chiral hypervalent iodine reagents could induce asymmetric control over the formation of key vinylaziridine intermediate **173**.[107,108] Therefore, the study of several iodine(I) precursors bearing different substituted lactate units was proposed in order to use them as mediators for diene **172** aziridination.



Scheme 4.13. Proposed asymmetric intramolecular aziridination of model dienyl carbamate **172** in the presence of lactate-based λ³-iodanes reagents **220**-**222**.

4.3. Results and discussion

With this objective in mind, the initial oxidation of lactate-based iodine(I) reagents **253-255** was tackled to subsequently perform the asymmetric aziridination of model dienyl carbamate **172** (**Scheme 4.14** a). A common strategy for the preparation of iodosylbenzene consists in a basic treatment of commercially available $PhI(OAc)_2$ using a 3N NaOH aq. solution.[91] Unfortunately, due to the chemical structure of these chiral reagents **253-255**, strong basic conditions must be avoided. In fact, to the best of our knowledge, only one example of an isolated chiral iodosylbenzene analogue has been reported in the literature (**Scheme 4.14** b).[110] In this case, iodine(I) precursor **256** was oxidised in the presence of Selectfluor® and $AcOH/CH_3CN$ as a solvent system, leading to chiral iodine(III) reagent **257** which was directly used after work-up without any further purification.

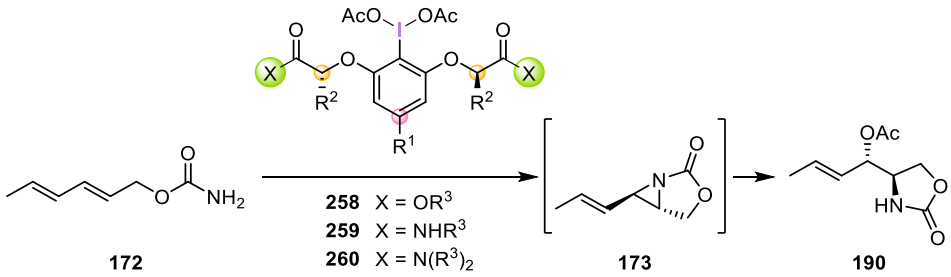


Scheme 4.14. a) General oxidation of lactate-based chiral iodine(I) reagents **253**-**255**. b) Reported procedure for the preparation of chiral iodosylbenzene analogue **257**.

Alternatively, we turned our attention into widely applied (diacetoxyiodo)arenes **258-260** as promoters for the asymmetric aziridination protocol (**Scheme 4.15**).[110,116,117,118,119] Thus, dienyl carbamate **172** would be treated with chiral iodine(III) compounds **258**-**260** to furnish enantioenriched vinylaziridine **173** which, based on our previous studies, would be expected to be *in situ* opened by the acetoxy ligands present in the reaction medium to render *anti*-oxazolidinone **190**. Therefore, commercially available $PhI(OAc)_2$ was selected for the newly required optimisation of racemic aziridination conditions.

[118] a) M. Fujita, S. Okuno, H. J. Lee, T. Sugimura, T. Okuyama, *Tetrahedron Lett.* **2007**, *48*, 8691–8694. b) M. Fujita, Y. Ookubo, T. Sugimura, *Tetrahedron Lett.* **2009**, *50*, 1298–1300. c) M. Fujita, Y. Yoshida, K. Miyata, A. Wakisaka, T. Sugimura, *Angew. Chem. Int. Ed.* **2010**, *49*, 7068–7071. d) M. Fujita, M. Wakita, T. Sugimura, *Chem. Commun.* **2011**, *47*, 3983–3985.

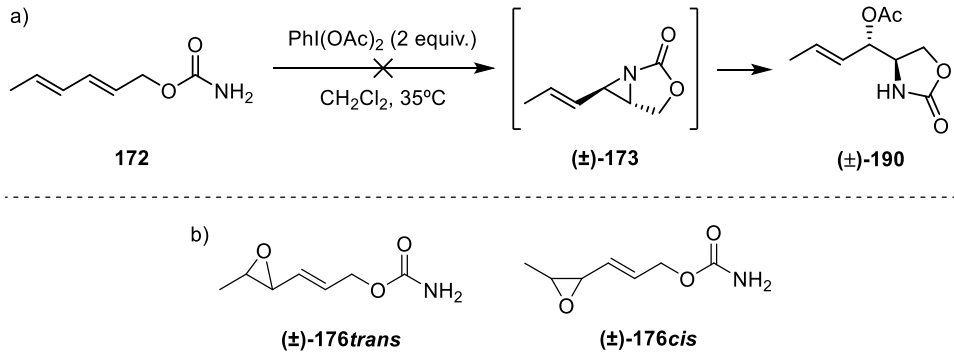
[119] a) U. Farid, F. Malmedy, R. Claveau, L. Albers, T. Wirth, *Angew. Chem. Int. Ed.* **2013**, *52*, 7018–7022. b) F. Malmedy, T. Wirth, *Chem. Eur. J.* **2016**, *22*, 16072–16077.



Scheme 4.15. Proposed asymmetric aziridination of model dienyl carbamate **172** in the presence of (diacetoxyiodo)arenes **258**-**260**.

4.3.1. PhI(OAc)$_2$-mediated intramolecular diene aziridination

As starting point, PhIO-mediated aziridination conditions were applied to the analogous reaction using (diacetoxyiodo)benzene as alternative oxidant source (**Scheme 4.16**).

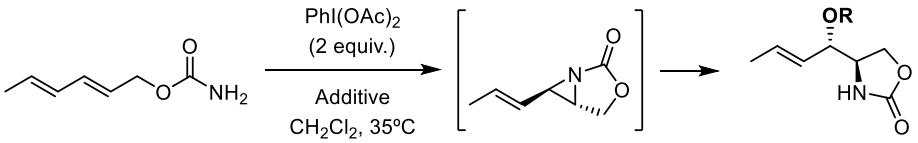


Scheme 4.16. a) Starting reaction conditions for PhI(OAc)$_2$-mediated aziridination/ring-opening of model dienyl carbamate **172**. b) Detected reaction side products: epoxides **(±)-176*trans*** and **(±)-176*cis***.

Thus, 1 equivalent of carbamate **172** was treated with 2 equivalents of PhI(OAc)$_2$ in dry CH_2Cl_2 at 35ºC (**Scheme 4.16** a). After overnight stirring, racemic oxazolidinone **(±)-190** was expected, assuming that acetoxy ligands present in the reaction medium would directly perform the ring-opening step. Unfortunately, as previously reported in chapter III of this Ph.D. work, unreacted starting material **172** was mainly recovered along with a ≤5% of **(±)-176*trans*** and **(±)-176*cis*** epoxide

mixture (**Scheme 4.16** b and **Table 4.1**, entry 1).[82e] Indeed, remarkable formation of these by-products was observed when the reaction was performed at higher temperatures. Therefore, the need for additives to assist $PhI(OAc)_2$-mediated intramolecular aziridination/ring-opening of dienyl carbamate **172** was clear.

Table 4.1. NMR-yields for the intramolecular aziridination/ring-opening of carbamate **172** with commercially available $PhI(OAc)_2$. Additives screening.[a]



172 **(±)-173** **(±)-190** R = Ac; **(±)-174**[b] R = Me

Entry	Additive (equiv.)	Conv. (%)	NMR-yields (%)[c]	
			Oxazolidinone (±)-190/(±)-174	Epoxide mixture (±)-176*trans*+(±)-176*cis*
1	-	≤5	-	≤5
2	$BF_3{\cdot}Et_2O$ (4)	100	C.M.[d]	C.M.[d]
3	CF_3SO_3H (4)	100	C.M.[d]	C.M.[d]
4[b]	**K_2CO_3 (4)**	**76**	**≤5**	**≤5**
5	MgO (4)	100	C.M.[d]	C.M.[d]
6	NaOAc (4)	17	-	13
7	KOAc (4)	12	-	7
8[b]	Cs_2CO_3 (4)	61	≤5	≤5
9	NaH (2)	100	C.M.[d]	C.M.[d]
10	LDA (2)	44	C.M.[d]	C.M.[d]
11	TBD (4)	≤5	-	-

[a] Carbamate **172** (1 equiv.), $PhI(OAc)_2$ (2 equiv.), CH_2Cl_2 (0.04M), 35ºC, overnight. [b] MeOH as quenching agent (2 mL). [c] Determined by ^{1}H-NMR spectroscopy using 1,3-dinitrobenzene as internal standard. [d] Complex mixture. S.M = starting material. LDA = lithium diisopropylamide. TBD = triazabicyclodecene.

According to previous results, a commonly used Lewis acid, boron trifluoride diethyl etherate,[117,118] and an organic acid which has been reported to activate diacetoxylated hypervalent iodine catalysts, triflic acid,[110,119] were selected as acid

additives (**Table 4.1**, entries 2 and 3). Thus, when carbamate **172** was treated with $PhI(OAc)_2$ in the presence of $BF_3{\cdot}Et_2O$ or TfOH, complete conversion of the starting material was observed. However, neither desired oxazolidinone **(±)-190** nor epoxides **(±)-176*trans*** and **(±)-176*cis*** were detected in any cases.

On the other hand, when K_2CO_3 was used as basic additive for the intramolecular aziridination of carbamate **172**,[82e,83,109120] oxazolidinone **(±)-174** was generated in low yields (**Table 4.1**, entry 4). Unexpectedly, an external nucleophile was required for the ring-opening step since intramolecular aziridine **(±)-173** was still observed in the TLC after overnight stirring. Therefore, readily available methanol was selected as nucleophile for the optimization process.

At this stage of the study, it was clear that a basic reaction medium was required for the model carbamate **172** to be productively transformed into the key iminoiodane intermediate **178**. Thus, four different inorganic bases were initially tested under optimised conditions (**Table 4.1**, entries 5-8). Surprisingly, MgO triggered starting material **172** decomposition (**Table 4.1**, entry 5), whereas no aziridination was observed in the presence of acetate salts, but important amounts of epoxides **(±)-176*trans*** and **(±)-176*cis*** were produced instead during the reaction (**Table 4.1**, entries 6 and 7). Moreover, Cs_2CO_3 provided similar results to those obtained for the analogous potassium salt, with oxazolidinone **(±)-174** formed in low yields upon methanol quenching after overnight stirring (**Table 4.1**, entries 4 and 8). Along these lines, complex mixtures were recovered after addition of strong bases such as lithium diisopropylamide or sodium hydride (**Table 4.1**, entries 9 and 10).

Alternatively, in order to circumvent the low solubility of inorganic salts, dienyl carbamate **172** was submitted to the aziridination reaction in the presence of triazabicyclodecene (TBD), a commercially available organic base (**Table 4.1**, entry 11). However, unreacted starting material **172** was mainly recovered after overnight stirring. Therefore, base screening did not provide any improved results and K_2CO_3 remained as the base of choice for $PhI(OAc)_2$-mediated aziridination/ring-opening experiments (**Table 4.1**, entry 4).

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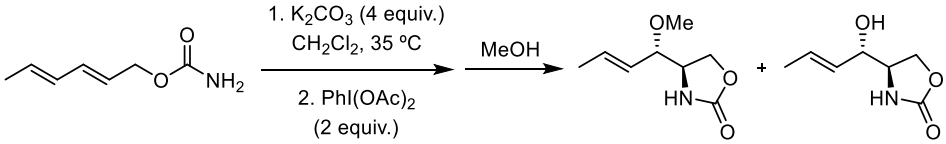
120 R.-H. Mei, Z.-G. Liu, H. Cheng, L. Xu, F.-P. Wang, *Org. Lett.* **2013**, *15*, 2206–2209.

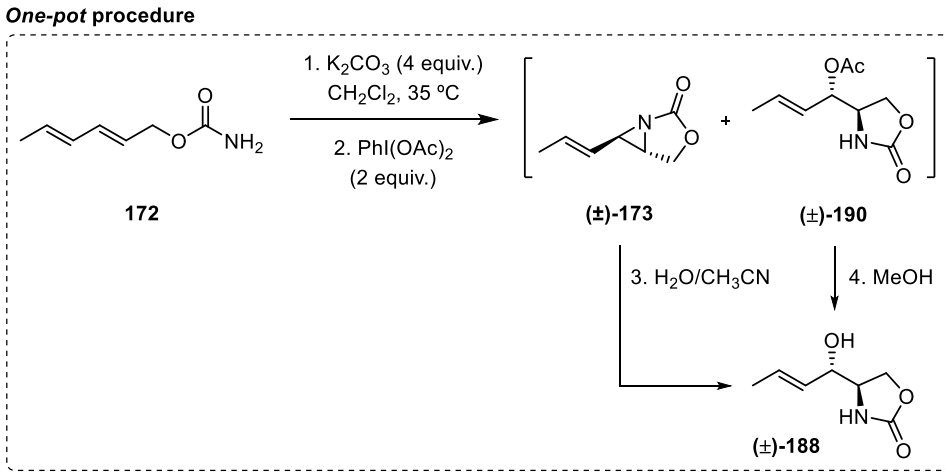
Regardless of the important effort made in the development of the $PhI(OAc)_2$-mediated aziridination/ring-opening protocol, calculated NMR-yields for the overall process were extremely low in all the cases. However, reported signals for the starting material **172**, the **(±)-176*trans*** and **(±)-176*cis*** epoxides and the final oxazolidinone **(±)-174** were clearly observed in the NMR-spectra. Product's waste during work-up or an incomplete solubilisation of the crude mixture in deuterated solvents for NMR studies due to its heterogeneous nature were pointed out as plausible reasons for the low yields obtained.

Finally, direct purification was envisioned to overcome this problem. To our delight, when the aziridination/ring-opening crude mixture was purified by column chromatography, hydroxy substituted oxazolidinone **(±)-188** was obtained as major product in a 60% yield along with methoxy oxazolidinone **(±)-174**, unreacted starting material **172** and a small amounts of epoxides **(±)-176*trans*** and **(±)-176*cis*** mixture (**Scheme 4.17**).



Scheme 4.17. Isolated yields for $PhI(OAc)_2$-mediated intramolecular aziridination/ring-opening of model dienyl carbamate **172**.

Moreover, it was found that initially expected acetoxy substituted oxazolidinone **(±)-190** was as well formed under the optimised conditions and subsequently deprotected upon addition of MeOH to the basic reaction medium. Therefore, in order to generate a single final product, a slightly modified strategy for the ring-opening step was envisioned (**Scheme 4.18**). Thus, aziridination crude containing vinylaziridine **(±)-173** and acetoxy oxazolidinone **(±)-190** was firstly reacted with water in acetonitrile. Then, the so obtained mixture of oxazolidinones **(±)-188** and **(±)-190** was treated with methanol to render hydroxyl substituted oxazolidinone **(±)-188** as the solely product in a 67% yield (**Table 4.2**, entry 1).



Scheme 4.18. Modified strategy for $PhI(OAc)_2$-mediated intramolecular aziridination/ring-opening of model dienyl carbamate **172**.

Carrying on with the optimisation process, carbamate **172** was reacted in the presence of 4Å molecular sieves assuming that the removal of the water generated from the decomposition of the H_2CO_3 formed along the aziridination reaction would favour iminoiodane **178** synthesis (*See Chapter III*, **Scheme 3.22**), (**Table 4.2**, entry 2). To our delight, a 78% yield for the overall mixture of ring-opening products (60% for **(±)-188** and 18% for **(±)-190**) was obtained due to an incomplete deprotection of intermediate acetoxy oxazolidinone **(±)-190**. In addition, a control experiment performed in the absence of K_2CO_3 but using molecular sieves proved again that a basic medium was needed for the aziridination reaction to proceed (**Table 4.2**, entry 3).

Then, with the asymmetric process in mind and taking into account that enantioselective transformations are generally favoured by low temperatures, aziridination/ring-opening reaction was carried out at room temperature with slightly decrease in the overall yield of ring-opening products (**Table 4.2**, entry 4). Moreover, in order to minimise future chiral iodine reagent's waste, (diacetoxyiodo)benzene concentration was adjusted to 1.1 equivalents (**Table 4.2**, entries 5 and 6). Disappointingly, reaction yields dropped dramatically, even under longer reaction times or in the presence of higher amounts of base.

Table 4.2. Isolated yields for $PhI(OAc)_2$-mediated intramolecular aziridination/ring-opening of model dienyl carbamate **172**. Study of desiccant agent, base equivalents and temperature effect.[a]

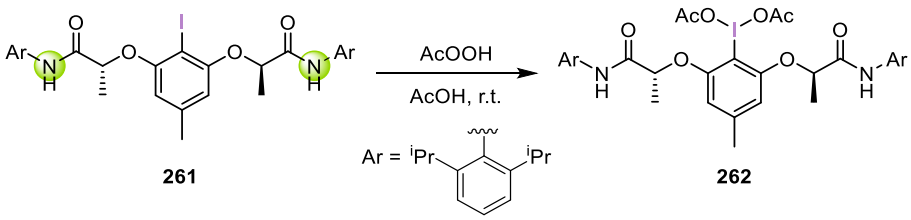
Entry	Additive	Desiccant agent	Temp (ºC)	Time (h)[b]	Yield (%)[c] (±)-188 ((±)-190)
1	K_2CO_3	-	35	72	67
2	K_2CO_3	4Å M.S.	35	24	60 (18)
3	-	4Å M.S.	35	72	-
4	K_2CO_3	4Å M.S.	r.t.	72	65 (5)
5[d]	K_2CO_3	4Å M.S.	r.t.	120	34
6[d,e]	K_2CO_3	4Å M.S.	r.t.	72	31
7[f]	**K_2CO_3**	**4Å M.S.**	**r.t.**	**72**	**71 (16)**
8[f,g]	K_2CO_3	4Å M.S.	r.t.	72	43 (23)

[a] Carbamate **172** (1 equiv.), K_2CO_3 (4 equiv.), 4Å M.S. (100 mg per 0.1 mmol carbamate **172**), $PhI(OAc)_2$ (2 equiv.), CH_2Cl_2 (0.04M). H_2O/CH_3CN (6 drops:1.5 mL) and MeOH (2 mL) as quenching agents. [b] Aziridination step. [c] Isolated yield. [d] $PhI(OAc)_2$ (1.1 equiv.). [e] K_2CO_3 (8 equiv.). [f] Deoxygenated CH_2Cl_2 (0.04M). [g] 4Å M.S. (400 mg per 0.1 mmol carbamate **172**).

Additionally, as previously mentioned, **(±)-176*trans*** and **(±)-176*cis*** epoxide mixture has been constantly obtained as an inherent by-product for the $PhI(OAc)_2$-mediated aziridination/ring-opening reaction of model carbamate **172** in yields up to 24%.[82e] Attempting to lower this epoxide formation, the aziridination reaction was performed in deoxygenated CH_2Cl_2, furnishing **(±)-176*trans*** and **(±)-176*cis*** by-products in a reduced 6% yield and the overall ring-opening products in a remarkable 87% (71% for **(±)-188** and 16% for **(±)-190**) (**Table 4.2**, entry 7). Unfortunately, no improvement was observed when increased equivalents of molecular sieves were added to the reaction medium (**Table 4.2**, entry 8).

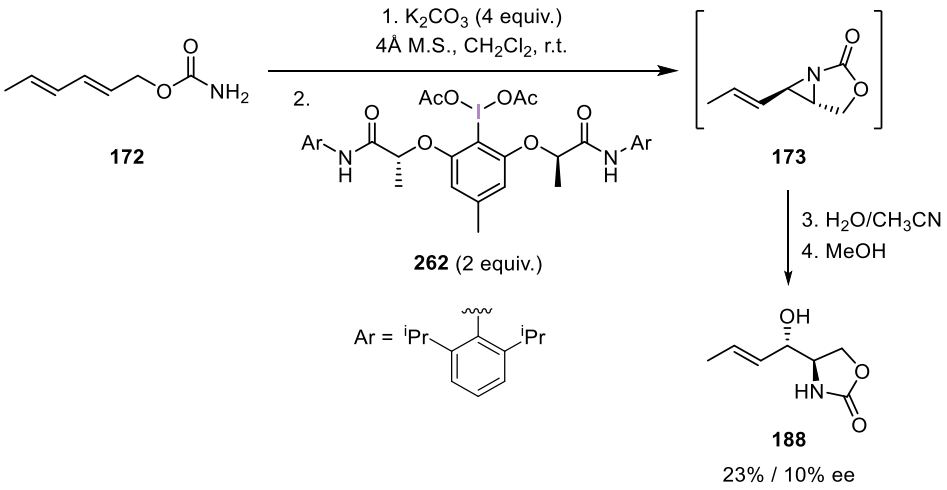
4.3.2. Initial studies on diene asymmetric aziridination using chiral iodine(III) reagents

With the optimised conditions for $PhI(OAc)_2$-mediated aziridination/ring-opening reaction in hand, oxidation of amide-containing iodine(I) reagent **261** was tackled (**Scheme 4.19**). Thus, chiral precursor **261** was treated with a solution of peracetic acid in acetic acid at room temperature.[108a] After overnight stirring, NMR crude showed an approximate 88:12 mixture of chiral hypervalent iodine reagent **262** and its precursor **261**. Purification was effected by recrystallisation from hexane/CH_2Cl_2 as previously reported. However, pure iodine(III) compound **262** was only obtained in low yields.



Scheme 4.19. Oxidation of amide-containing chiral iodine(I) precursor **261** using a solution of peracetic acid in acetic acid at room temperature.

Preliminary attempts for the asymmetric aziridination of model dienyl carbamate **172** in the presence of 1.1 equivalents of chiral (diacetoxyiodo)arene **262** at room temperature were unsuccessful furnishing mainly unreacted starting material **172** and reduced iodine(I) precursor **261** after overnight stirring. However, when carbamate **172** was treated with 2 equivalents of iodine(III) reagent **262**, hydroxy substituted oxazolidinone **188** was obtained in a 23% yield and 10% ee, proving the feasibility of desired intramolecular cyclisation despite the remarkable bulkiness of lactated-based chiral compound **262**. (**Scheme 4.20**).

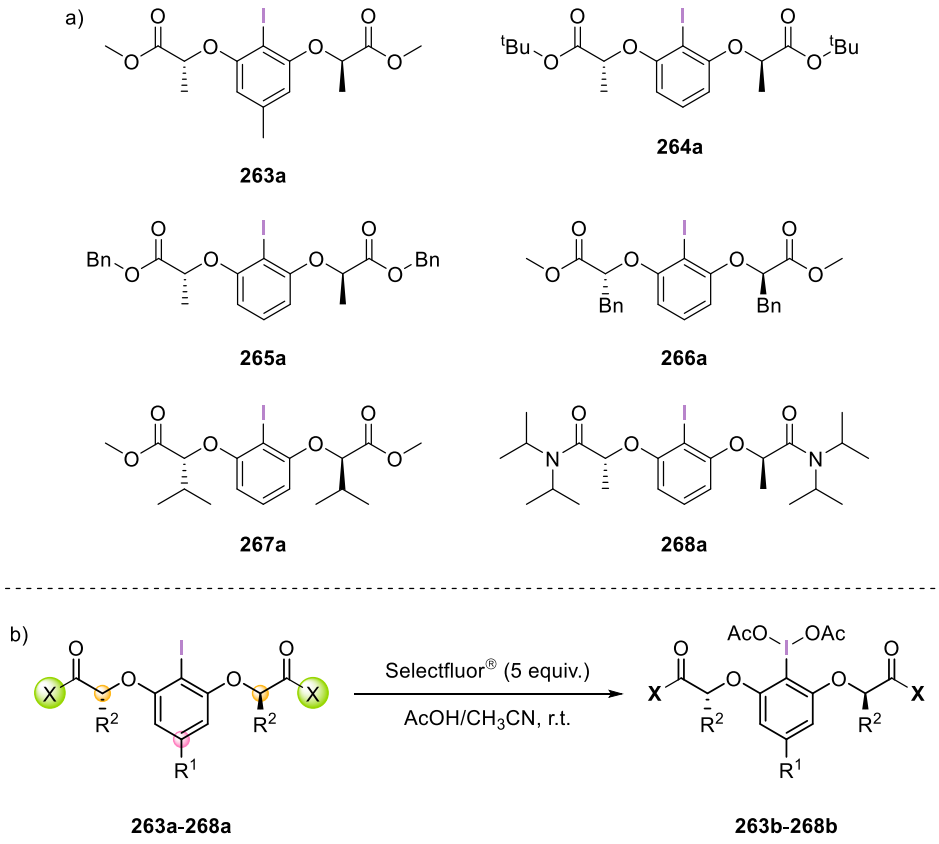


Scheme 4.20. Asymmetric aziridination of model dienyl carbamate **172** in the presence of amide-containing chiral hypervalent iodine reagent **262**.

Subsequent analysis of the chemical structure of chiral (diacetoxyiodo)arene reagent **262** identified two critical moieties that may be affected under reaction conditions (**Scheme 4.20**). Thus, deprotonation of the acid amide proton by K_2CO_3 could compete with the crucial removal of the acetic acid generated during iminoiodane **178** formation (*See Chapter III*, **Scheme 3.22**). On the other hand, basic reaction medium might alter the chiral centre adjacent to a carbonyl group in compound **262**, hampering the enantioselective formation of vinylaziridine **173**.

At this stage of the asymmetric study, the use of alternative chiral iodine(III) reagents bearing an ester moiety **263b**-**267b** or a tertiary substituted amide **268b** was envisioned to test their efficiency under basic reaction conditions (**Scheme 4.21**). Therefore, a set of lactate-based precursors **263a**-**268a** were prepared by initial Mitsunobu reaction of 2-iodo-resorcinol with different lactic acid derivatives (**Scheme 4.21** a).[108] Then, they were readily oxidised in the presence of Selectfluor® and AcOH/CH_3CN as solvent system and further purified upon aqueous work-up to furnish variable crude mixtures of iodine(I) **263a**-**268a**/iodine(III) **263b**-**268b** respectively (**Scheme 4.21** b).[110,121]

[121] C. Ye, B. Twamley, J. M. Shreeve, *Org. Lett.* **2005**, *7*, 3961–3964.



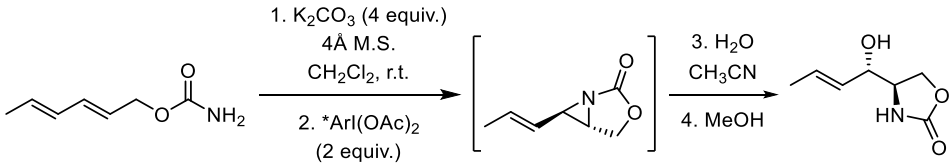
Scheme 4.21. a) Chiral iodine(I) precursors bearing an ester moiety **263a**-**267a** or a tertiary substituted amide **268a**. b) Oxidation protocol for lactate-based reagents **263a**-**268a**.

Table 4.3 displays the preliminary results for the asymmetric aziridination of model dienyl carbamate **172** using chiral iodosylbenzene analogue **257** and lactate-based hypervalent iodine reagents **263b**-**268b** (**Scheme 4.14** and **Scheme 4.21**). To our delight, hydroxy-substituted oxazolidinone **188** was successfully obtained in remarkable enantiomeric excess for chiral iodine(III) compounds **264b**-**267b** bearing different ester moieties (**Table 4.3**, entries 1-4). Disappointingly, decreased asymmetric control was exerted by tertiary amide **268b** (**Table 4.3**, entry 5) whereas λ^3-iodanes **257** and **263b** proved to be unreactive under the optimised aziridination conditions (**Table 4.3**, entries 6 and 7).

Obtained low yields can be rationalised taking into account that chiral hypervalent iodine compounds **257** and **263b**-**268b** were used without any further

purification after oxidation step. *In situ* formation of these λ³-iodanes under both stoichiometric or catalytic conditions could improve overall reaction rates. However, to date, unsuccessful results have been observed when *m*CPBA or Selectfluor® were tested as terminal oxidants due to important diene epoxidation.[82e,122]

Table 4.3. Asymmetric aziridination of model dienyl carbamate **172** using chiral iodosylbenzene analogue **257** and lactate-based iodine(III) compounds **263b**-**268b**.[a]

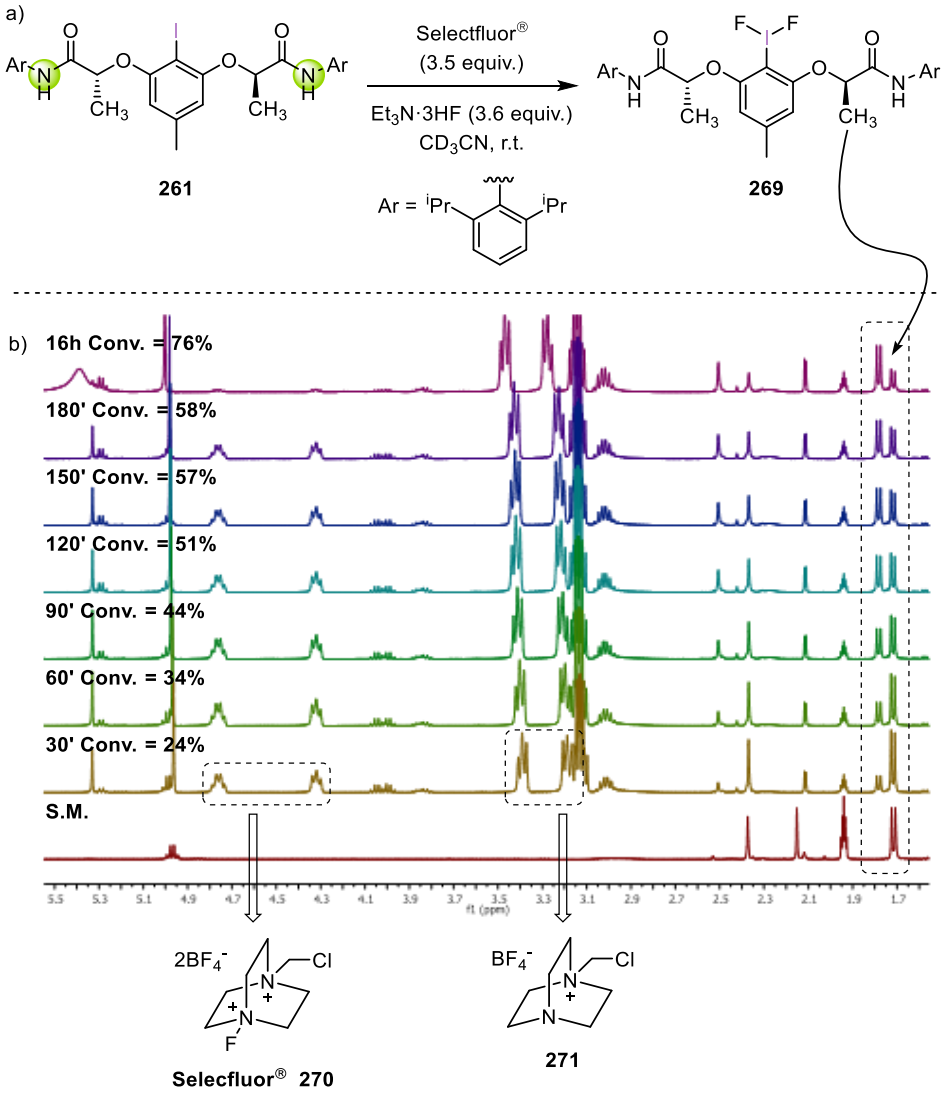


Entry	I(III)-reagent	Yield (%)[b]	ee (%)[c]
1	264b	33	47
2	265b	37	49
3	266b	18	31
4	267b	27	57
5	268b	10	14
6	257	-	-
7	263b	-	-

[a] Carbamate **172** (1 equiv.), K_2CO_3 (4 equiv.), 4Å M.S. (100 mg per 0.1 mmol carbamate **172**), $PhI(OAc)_2$ (2 equiv.), CH_2Cl_2 (0.04M), r.t. H_2O/CH_3CN (6 drops:1.5 mL) and MeOH (2 mL) as quenching agents. [b] Isolated yield. [c] Determined by chiral HPLC-TOF.

Alternatively, we hypothesised that the initial coordination of model dienyl carbamate **172** with hypervalent iodine reagent to generate the iminoiodane intermediate could be accomplished in the absence of base for (difluoroiodo)arenes.[113] Therefore, iodine(I) precursor **261** was oxidised in the presence of Selectfluor® and $Et_3N{\cdot}3HF$, as previously reported (**Scheme 4.22** a).[121] However, efforts to isolate difluorinated compound **269** were unsuccessful, even under inert conditions.

[122] W. Zhong, S. Liu, J. Yang, X. Meng, Z. Li, *Org. Lett.* **2012**, *14*, 3336–3339.



Scheme 4.22. a) Oxidation of amide-containing chiral iodine(I) precursor **261** using a mixture of Selectfluor® and $Et_3N·3HF$. b) NMR-study on (difluoroiodo)arene **269** preparation. Conv. = conversion. S.M. = starting material.

In order to confirm the formation of (difluoroiodo)arene **269**, an NMR-study was carried.[123] Thus, an NMR-tube was charged with the corresponding iodine(I) precursor **261**, Selectfluor® **270** and $Et_3N·3HF$ using deuterated acetonitrile as

[123] J. C. Sarie, C. Thiehoff, R. J. Mudd, C. G. Daniliuc, G. Kehr, R. Gilmour, *J. Org. Chem.* **2017**, *82*, 11792–11798.

solvent and NMR-spectra were recorded every 30 minutes during 3 hours (**Scheme 4.22** b). Reaction conversion was calculated based on signal integration from methyl groups at the stereogenic centres. Furthermore, characteristic signals from Selectfluor® **270** and its reduced form **271** were also monitored (**Scheme 4.22** b). After 3 hours, nearly half of the starting material **261** had been transformed into desired difluorinated λ^3-iodane **269**. Moreover, upon overnight stirring, conversion increased up to 76% and complete consumption of Selectfluor® **270** was observed. However, even though (difluoroiodo)arene **269** was clearly detected, subsequent product isolation was extremely complicated probably due to its unstable nature towards visible light and atmospheric moisture.

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CHAPTER V

ORGANOCATALYSED KINETIC RESOLUTION OF HETEROSUBSTITUTED OXAZOLIDINONES

UNIVERSITAT ROVIRA I VIRGILI
METAL-FREE REGIO- AND STEREOSELECTIVE VICINAL DIFUNCTIONALISATION OF DIENYL CARBAMATES
Irene Giménez Nueno

5.1. Introduction

5.1.1. Sphingosine kinase as a new target for cancer treatment

Sphingolipids are an important family of bioactive metabolites involved in different cellular processes. Recent studies have proved their central role in cancer regulation via a dynamic balance between ceramide (Cer) and sphingosine-1-phospate (S1P) that determines cells fate (**Figure 5.1**).[35,124] Along these lines, high concentrations of sphingosine-1-phosphate have been detected in many cancer tissues, relating this metabolite with cancer progression and drug-resistance. Moreover, new approaches for cancer treatment based on the increase of endogenous ceramide levels in human body have successfully induced cancer cell apoptosis.[125]

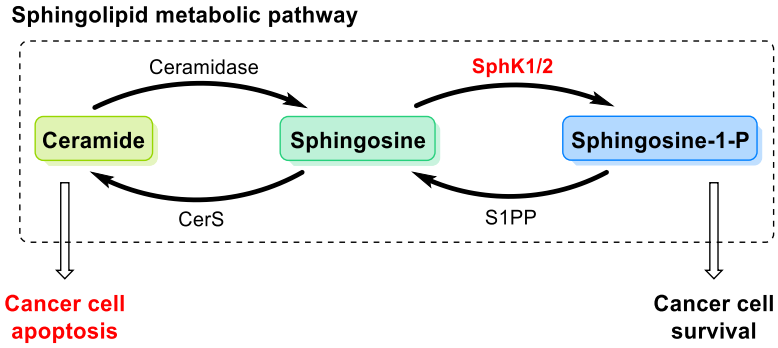

Figure 5.1. Sphingolipid metabolic pathway.

Sphingosine kinase 1 (SphK1) is a key enzyme within the sphingolipid metabolic pathway that catalyses the phosphorylation of sphingosine (Sph) into sphingosine-1-phosphate (**Figure 5.1**).[35] Thus, its inhibition will shift the Cer/S1P rheostat towards ceramide accumulation, leading to cancer cell apoptosis. As a result, SphK1 has recently emerged as an interesting target for novel cancer therapies.[124]

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[124] a) X. Zheng, W. Li, L. Ren, J. Liu, X. Pang, X. Chen, D. Kang, J. Wang, G. Du, *Pharmacol. Ther.* **2019**, *195*, 85–99. b) B. Ogretmen, *Nature Rev. Cancer* **2018**, *18*, 33–50. c) A. Adan-Gokbulut, M. Kartal-Yandim, G. Iskender, Y. Baran, *Curr. Med. Chem.* **2013**, *20*, 108–122.

[125] J. W. Antoon, J. Liu, A. P. Ponnapakkam, M. M. Gestaut, M. Foroozesh, B. S. Beckman, *Cancer Chemother. Pharmacol.* **2010**, *65*, 1191–1195.

In the past years, many efforts have been made in the development of SphK1 inhibitors. Conventional approaches focused on molecules that interacted with the ATP binding site of the enzyme.[126] However, this strategy led to non-selective drugs since many types of human kinases present a rather similar ATP domain. Consequently, drug design prompted into the study of a new family of compounds that efficiently targeted the substrate pocket of the SphK1 with remarkable levels of selectivity over its isoform SphK2 and encouraging inhibition activity.[127]

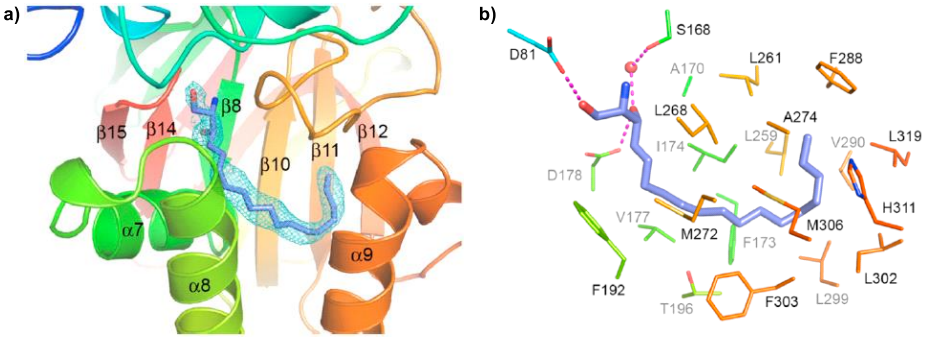

Figure 5.2. a) Sphingosine binding mode in the *C*-terminal domain (CTD) of SphK1. b) Specific interactions between sphingosine molecule and amino-acids residues contained at the SphK1 binding pocket.[128]

Along these lines, a recent report on the crystal structure of SphK1 has enlightened the molecular basis of enzyme/substrate interactions.[128] The catalytic domain of SphK1 is placed in the cleft between *N*-terminal domain (NTD) and *C*-terminal domain (CTD) with Sph located in a J-shaped tunnel in the CTD (**Figure 5.2** a). According to experimental observations, an induced fit mechanism was proposed for substrate placement inside the binding pocket of the enzyme through a lipid gate located between helix 7 and 8. In addition, Asp.178 emerged as a key amino-acid residue acting as a general base for the phosphorylation process via hydrogen bond formation with the sphingosine polar-head (**Figure 5.2** b). These

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126 T. P. Mathews, A. J. Kennedy, Y. Kharel, P. C. Kennedy, O. Nicoara, M. Sunkara, A. J. Morris, B. R. Wamhoff, K. R. Lynch, T. L. Macdonald, *J. Med. Chem.* **2010**, *53*, 2766–2778.

127 a) M. Cao, C. Ji, Y. Zhou, W. Huang, W. Ni, X. Tong, J.-F. Wei, *Int. J. Mol. Med.* **2018**, *41*, 2450–2460. b) M. R. Pitman, M. Costabile, S. M. Pitson, *Cell. Signal.* **2016**, *28*, 1349–1363.

128 Z. Wang, X. Min, S.-H. Xiao, S. Johnstone, W. Romanow, D. Meininger, H. Xu, J. Liu, J. Dai, S. An, S. Thibault, N. Walker, *Structure* **2013**, *21*, 798–809.

results have triggered the investigation on highly specific SphK1 inhibitors for cancer treatment, achieving high levels of selectivity and promising pharmacokinetics parameters.[129]

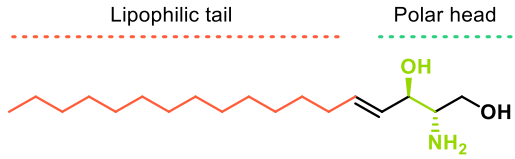


Figure 5.3. Chemical structure of natural sphingosine.

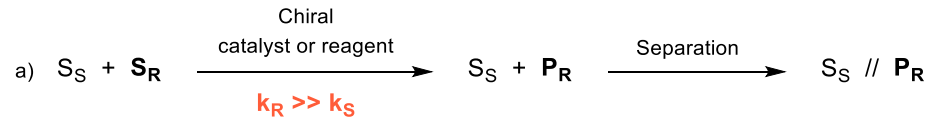
From a biological point of view, three different types of compounds are currently under study for SphK1 inhibition: natural products with reported activity against cancer processes, sphingosine-based drugs and non-lipidic small molecules.[35] On the other hand, taking into account the chemical structure of the sphingosine, three well differentiated regions can be established: a polar head bearing a vicinal amino-alcohol moiety, a lipophilic tail formed by a hydrocarbon chain and a linker between them (**Figure 5.3**). To date, structural modifications on each region have led to families of new sphingosine analogues that may serve as SphK1 inhibitors for cancer therapies.[130]

[129] D. J. Gustin, Y. Li, M. L. Brown, X. Min, M. J. Schmitt, M. Wanska, X. Wang, R. Connors, S. Johnstone, M. Cardozo, A. C. Cheng, S. Jeffries, B. Franks, S. Li, S. Shen, M. Wong, H. Wesche, G. Xu. T. J: Carlson, M. Plant, K. Morgenstern, K. Rex, J. Schmitt, A. Coxon, N. Walker, F. Kayser, Z. Wang, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 4608–4616.

[130] a) J. A. Morales-Serna, J. Llaveria, Y. Diaz, M. I. Matheu, S. Castillon, *Curr. Org. Chem.* **2010**, *14*, 2483–2521. b) M. Escudero-Casao, A. Cardona, R. Beltrán-Debón, Y. Díaz, M. I. Matheu, S. Castillón, *Org. Biomol. Chem.* **2018**, *16*, 7230–7235. c) Z. Dai, T. K. Green, *J. Org. Chem.* **2014**, *79*, 7778–7784. d) D. J. Baek, N. MacRitchie, N. J. Pyne, S. Pyne, R. Bittman, *Chem. Commun.* **2013**, *49*, 2136–2138. e) S. Ballereau, N. Andrieu-Abadie, N. Saffon, Y. Génisson, *Tetrahedron* **2011**, *67*, 2570–2578. f) L. Wong, S. S. L. Tan, Y. Lam, A. J. Melendez, *J. Med. Chem.* **2009**, *52*, 3618–3626.

5.1.2. Enantioselective preparation of vicinal amino-alcohol moiety via kinetic resolution

Vicinal amino-alcohols are among the most recurrent chemical structures in natural products including substituted amino-acids, lipids or sugars.[131] Their ability to be protected or chemically converted into other functionalities has generated increased interest for their use as drug precursors. Therefore, important efforts have been made in the development of new methodologies allowing the stereoselective synthesis of β-amino alcohols via preinstalled functional group derivatisation, heteroatom addition or direct oxyamination of alkenes.[55a,131] In this context, despite the high efficiency of some asymmetric protocols, the kinetic resolution of racemic mixtures still remains as a competitive tool for the preparation of enantioenriched vicinal amino-alcohols.[132]



b) $s = \frac{\ln [1 - C*(1+ee')]}{\ln [1 - C*(1-ee')]} = \frac{\ln [(1-C)*(1-ee)]}{\ln [(1-C)*(1+ee)]}$ (eq. 1) $C = \frac{ee}{ee + ee'} * 100$ (eq. 2)

ee: measured enantiomeric excess for the recovered starting material
ee': measured enantiomeric excess for the product

Figure 5.4. a) General mechanism for a kinetic resolution. b) Selectivity factor (s) (eq. 1) and reaction conversion (C) (eq. 2) for a kinetic resolution.

A kinetic resolution is a process based on the different reaction rates of the two enantiomers from a racemic mixture towards a specific chemical transformation

[131] a) S. C. Bergmeier, *Tetrahedron* **2000**, *56*, 2561–2576. b) O. K. Karjalainen, A. M. P. Koskinen, *Org. Biomol. Chem.* **2012**, *10*, 4311–4326. c) C. E. I. Knappke, A. Jacobi von Wangelin, *ChemCatChem* **2010**, *2*, 1381–1383. d) T. J. Donohoe, C. K. A. Callens, A. Flores, A. R. Lacy, A. H. Rathi, *Chem. Eur. J.* **2011**, *17*, 58–76.

[132] J. M. Keith, J. F. Larrow, E. N. Jacobsen, *Adv. Synth. Catal.* **2001**, *343*, 5–26.

mediated by a chiral reagent (**Figure 5.4** a).[133,134] Ideally, after 50% conversion of the starting material, one of the enantiomers from the racemate (S_S + S_R) is fully transformed into the desired product (P_R) whereas the other enantiomer remains unreacted (S_S). Subsequent isolation of final compounds can be easily achieved by column chromatography.

The efficiency of the kinetic resolution is calculated by the selectivity factor (s), which is a correlation between the reaction conversion (C) and the enantiomeric excesses (ee or ee') (**Figure 5.4** b). Thus, processes with selectivities greater than 10 are generally considered as synthetically useful. Unfortunately, an inherent limitation of the kinetic resolution is its low atom-economy since a maximum 50% yield for the enantioenriched product can be achieved.

In 2006, V. Birman and co-workers[135] published the organocatalysed kinetic resolution of oxazolidinone rings **(±)-272** in the presence of (*R*)-BTM catalyst via a stereoselective *N*-acylation that furnished enantioenriched unreacted starting material **272** and acylated product **273** as precursors of vicinal aminol-alcohols (**Scheme 5.1** a).[136] The methodology strongly depended on the nature of the substituents attached to the reactive nitrogen centre. Thus, substrates **(±)-272a-c** bearing aryl, ester and alkynyl moieties successfully underwent kinetic resolution

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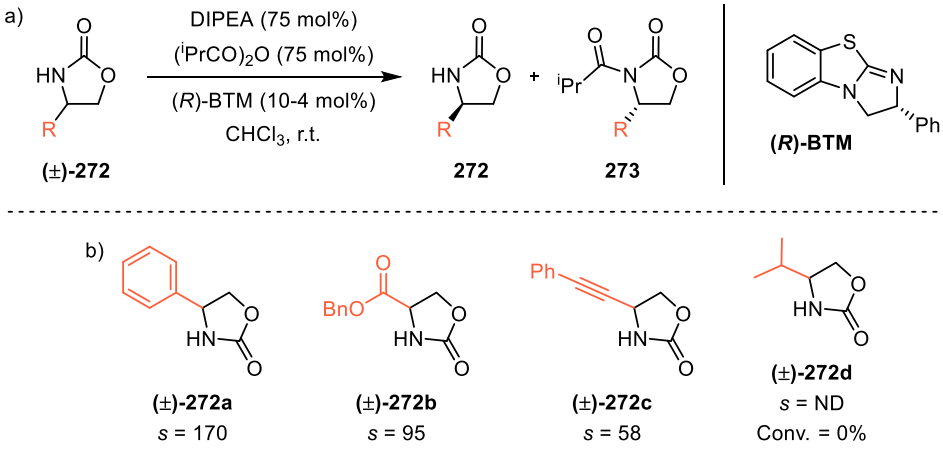
133 a) H. B. Kagan, J. C. Fiaud, In *Topics in Stereochemistry*; E. L. Eliel, S. H. Wilen, Eds.; John Wiley & Sons, Inc.: New York, USA, **1988**; Chap. *4*, pp. 249–330. b) *Separation of Enantiomers: Synthetic Methods*; M. Todd, Ed.; Wiley-VCH: Weinheim, Germany, **2014**. c) E. Vedejs, M. Jure, *Angew. Chem. Int. Ed.* **2005**, *44*, 3974–4001. d) H. Pellissier, *Adv. Synth. Catal.* **2011**, *353*, 1613–1666.

134 a) R. Gurubrahamam, Y.-S. Cheng, W.-Y. Huang, K. Chen, *ChemCatChem* **2016**, *8*, 86–96. b) V. P. Krasnov, D. A. Gruzdev, G. L. Levit, *Eur. J. Org. Chem.* **2012**, 1471–1493. c) C. E. Müller, P. R. Schreiner, *Angew. Chem. Int. Ed.* **2011**, *50*, 6012–6042.

135 For selected examples on amidine-based catalysed kinetic resolutions of alcohols and carboxylic acids see: a) V. B. Birman, E. W. Uffman, H. Jiang, X. Li, C. J. Kilbane, *J. Am. Chem. Soc.* **2004**, *126*, 12226–12227. b) X. Li, P. Liu, K. N. Houk, V. B. Birman, *J. Am. Chem. Soc.* **2008**, *130*, 13836–13837. c) X. Yang, V. B. Birman, *Adv. Synth. Catal.* **2009**, *351*, 2301–2304. d) X. Yang, P. Liu, K. N. Houk, V. B. Birman, *Angew. Chem. Int. Ed.* **2012**, *51*, 9638–9642.

136 a) V. B. Birman, H. Jiang, X. Li, L. Guo, E. W. Uffman, *J. Am. Chem. Soc.* **2006**, *128*, 6536–6537. b) X. Yang, V. D. Bumbu, P. Liu, X. Li, H. Jiang, E. W. Uffman, L. Guo, W. Zhang, X. Jiang, K. N. Houk, et al., *J. Am. Chem. Soc.* **2012**, *134*, 17605–17612.

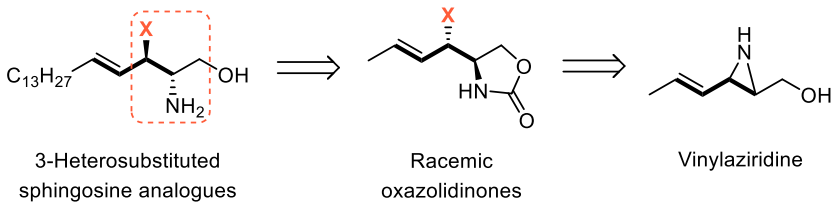
under optimised condition whereas isopropyl-substituted oxazolidinone **(±)-272d** proved to be unreactive when treated with the (*R*)-BTM-organocatalyst (**Scheme 5.1** b). Later theoretical calculations demonstrated that the favoured diastereomeric transition state presented cation-π-interactions between the acylated thiazolium ring from the catalyst and the corresponding π-orbitals from Csp^2/Csp groups directly linked to the oxazolidinone ring.[136b]



Scheme 5.1. a) General protocol for the organocatalysed kinetic resolution of oxazolidinones **(±)-272** as precursors of enantioenriched vicinal amino-alcohols in the presence of (*R*)-BTM catalyst. b) Substrate scope for the kinetic resolution reaction.

5.2. Aims and objectives

Inspired by Birman's report, an alternative route for the enantioselective preparation of vicinal hetero-amino moieties involving the organocatalysed kinetic resolution of the racemic oxazolidinones obtained from PhIO mediated aziridination/ring-opening protocol was envisioned (**Scheme 5.2**). Even though our substrates lacked a Csp^2/Csp functionality at the adjacent position of the reactive nitrogen atom, we expected that a careful selection of the substituents around the oxazolidinone ring allowed desired asymmetric control. Moreover, in order to illustrate the usefulness of this methodology, the synthesis of 3-heterosubstituted sphingosine analogues via cross-metathesis reaction was also attempted.



Scheme 5.2. Proposed retrosynthetic strategy for the preparation of enantioenriched unsaturated vicinal hetero-amino moieties via kinetic resolution of racemic oxazolidinones.

5.3. Results and discussion

The following study on the reaction scope for the organocatalysed kinetic resolution of differently heterosubstituted racemic oxazolidinones has been carried out in collaboration with Dr. J. Guasch. Moreover, the final preparation of sphingosine analogues via cross-metathesis reaction has been performed in collaboration with M. Bernús.[137]

5.3.1. Organocatalysed kinetic resolution of *O*-substituted oxazolidinones

In order to overcome the already mentioned lack of Csp^2/Csp functionalities directly linked to the oxazolidinone ring, the derivatisation of hydroxy-substituted oxazolidinone **(±)-188** with four different acyl-protecting groups was carried out to furnish compounds **(±)-274a-d** (**Table 5.1**).[92] To our delight, all four protected oxazolidinones **(±)-274a-d** underwent the desired organocatalysed kinetic resolution in synthetically useful selectivities. Thus, benzoyl-, acetyl- and *p*-OMeBz-derivatives **(±)-274a-c** afforded *N*-acylated products **(*R*,*S*)-275a-c** in similar enantioselectivities whereas pivaloyl analogue **(±)-274d** provided slightly lower ee values (**Table 5.1**, entries 1-4). However, when methoxy-substituted oxazolidinone **(±)-174** obtained from PhIO mediated aziridination was selected as starting material, no reaction was observed after 24 h stirring (**Table 5.1**, entry 5). These results confirmed that the efficiency of the kinetic resolution was controlled by the acyl-protecting group from the substrate, as previously envisioned.

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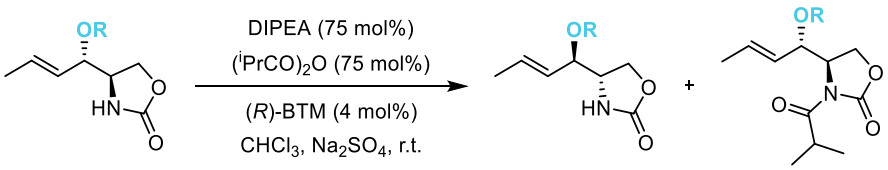
137 J. Guasch, I. Giménez-Nueno, I. Funes-Ardoiz, M. Bernús, M. I. Matheu, F. Maseras, S. Castillón, Y. Díaz, *Chem. Eur. J.* **2018**, *24*, 4635–4642.

Table 5.1. Protecting group screening for the organocatalysed kinetic resolution of *O*-substituted racemic oxazolidinones **(±)-274a-d** and **(±)-174**.



(±)-274a-d / (±)-174 **(*S*,*R*)-274a-d** **(*R*,*S*)-275a-d**

Entry	SM (R)	Time (h)	Conv. (%)[b]	ee (P/S)[c]	s[d]
1	**(±)-274a** (R = Bz)	4	43	96/73	108
2	**(±)-274b** (R = Ac)	5	46	92/79	60
3	**(±)-274c** (R = *p*MeOBz)	4	46	91/79	50
4	**(±)-274d** (R = Piv)	5.5	42	89/65	35
5	**(±)-174** (R = Me)	24	-	-	-

[a] Oxazolidinone **(±)-274** (0.1 mmol), (*R*)-BTM (4 mol%), $(^{i}PrCO)_2O$ (75 mol%), DIPEA (75 mol%), Na_2SO_4 (100 mg/0.1 mmol oxazolidinone **(±)-274**), $CHCl_3$ (0.2M). [b] Determined by ^1H NMR spectroscopy. [c] Product/starting material ee ratio. The ee was determined by chiral HPLC.

In this context, a computational study on the origin of the asymmetric control for the present kinetic resolution was carried by Dr. Funes-Ardoiz and Prof. F. Maseras (ICIQ) applying a similar protocol to that previously reported by Houk and co-workers for the analysis of the role of cation-π interactions in the efficiency of a related system.[136b] Thus, for the organocatalysed *N*-acylation of compound **(±)-275a**, the most stable conformers for the two diastereomeric transition states corresponding to each enantiomer from the racemate are depicted in **Figure 5.5**. The energy difference between the **TS-(*R*,*S*)-274a** and **TS-(*S*,*R*)-274a** structures is 4.7 kcal/mol. Despite the computed value overestimates the experimental result (the reported $s_{exp} = 108$ would correspond to a ΔΔG of 2.8 kcal/mol) the trend is clearly reproduced (**Table 5.1**, entry 1 and **Figure 5.5**).

The main structural difference between **TS-(*R*,*S*)-274a** and **TS-(*S*,*R*)-274a** lie in the interactions between the chain attached to the oxazolidinone ring and the acylated catalyst (**Figure 5.5**). Thus, for **TS-(*R*,*S*)-274a**, the carbonyl moiety of the benzoate group is directly pointing towards the cationic BTM ring which stabilises this transition state with respect to **TS-(*S*,*R*)-274a**, where this interaction cannot take

place due to the opposite orientation of the side chain. Therefore, these results are in agreement with the inactivity of methoxy-substituted oxazolidinone **(±)-174** under optimised kinetic resolution conditions.

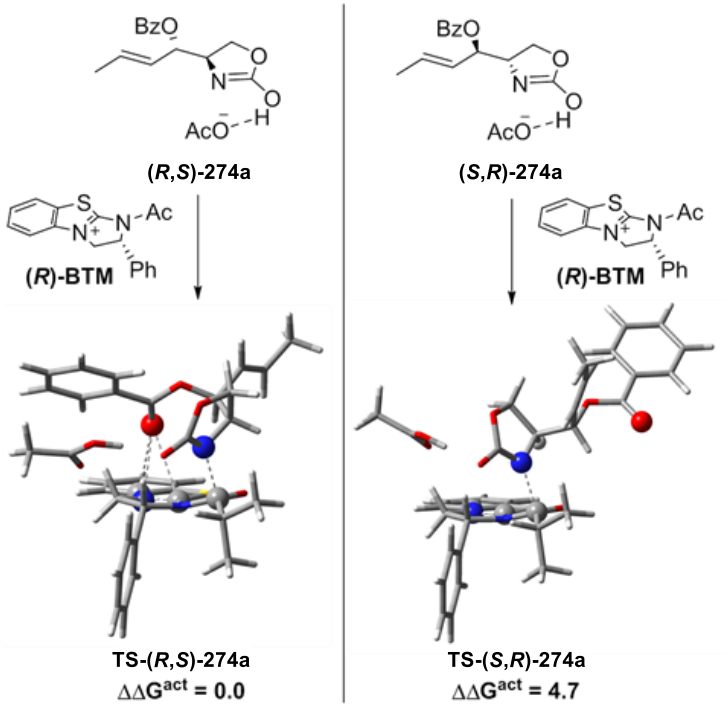


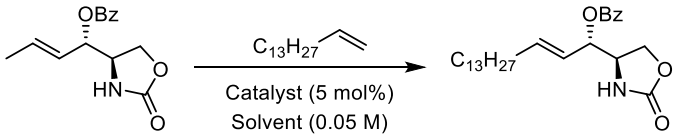
Figure 5.5. 3D structures for the diastereomeric transition states of the *N*-acylation of compound **(±)-274a** by (*R*)-BTM-Ac catalyst. Free energies are given in kcal/mol.

To illustrate the usefulness of the developed oxyamination/kinetic resolution methodology, we applied it to the enantioselective synthesis of sphingolipid analogues. A cross-metathesis reaction of acylated-oxazolidinone intermediate **(*R*,*S*)-275a** with terminal alkenes was envisaged for the introduction of different aliphatic side chains.[138] Therefore, in order to optimise the transformation conditions, readily available racemic benzoyl-derivative **(±)-274a** and 1-pentadecene were selected as

[138] a) H. Hasegawa, T. Yamamoto, S. Hatano, T. Hakogi, S. Katsumura, *Chem. Lett.* **2004**, *33*, 1592–1593. b) S. Torssell, P. Somfai, *Org Biomol Chem* **2004**, *2*, 1643–1646. c) A. N. Rai, A. Basu, *Org. Lett.* **2004**, *6*, 2861–2863. d) T. Yamamoto, H. Hasegawa, T. Hakogi, S. Katsumura, *Org. Lett.* **2006**, *8*, 5569–5572. e) P. Ghosal, V. Kumar, A. K. Shaw, *Tetrahedron* **2010**, *66*, 7504–7509.

coupling partners. Initial catalyst screening proved that a 5 mol% of Grubbs catalyst 2nd generation successfully furnished elongated product **(±)-276** (**Table 5.2**, entries 1-3). Moreover, final adjustment of solvent, reaction temperature and olefin equivalents rendered sphingosine precursor **(±)-276** in a remarkable 81% yield and good *E*:*Z* ratios (**Table 5.2**, entries 4-7).

Table 5.2. Cross-metathesis of oxazolidinone **(±)-274a**. Catalyst type, solvent, reaction temperature and terminal olefin equivalents screening.

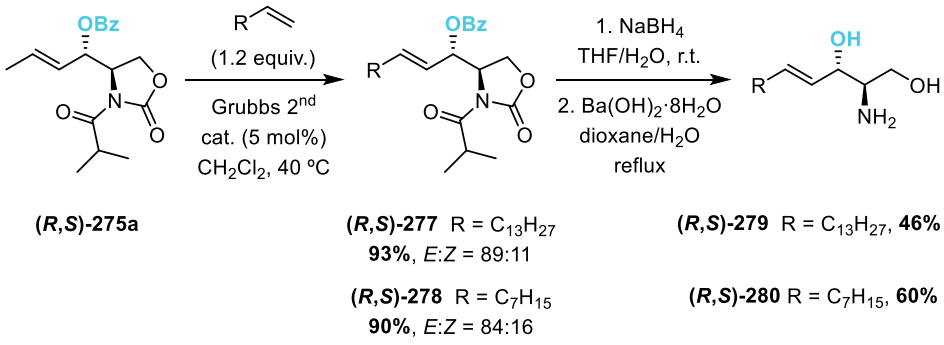


(±)-274a **(±)-276**

Entry	Catalyst[b]	Solvent	Temp (ºC)	Yield (%)	*E*:*Z* (%)
1	G-I	Toluene	55	-[c]	-[c]
2	G-II	Toluene	55	60	83:17
3	HG-II	Toluene	55	46	85:15
4	G-II	CF_3-Benzene	55	48	84:16
5	G-II	CH_2Cl_2	55	71	85:15
6	G-II	CH_2Cl_2	40	77	86:14
7[d]	**G-II**	**CH_2Cl_2**	**40**	**81**	**84:16**

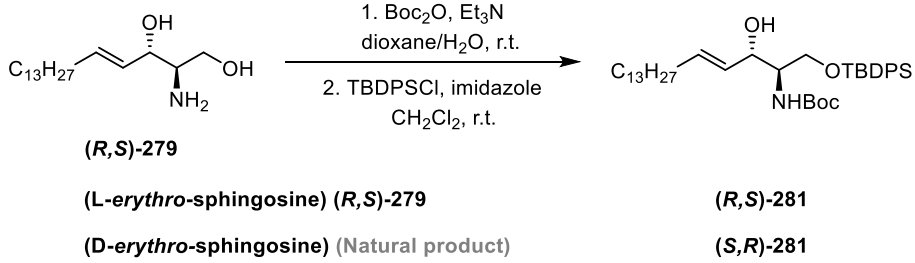
[a] **General conditions:** Oxazolidinone **(±)-274a** (1 equiv.), 1-pentadecene (10 equiv.), catalyst (5 mol%), solvent (0.05 M). [b] **G-I**: Grubbs catalyst 1st generation. **G-II**: Grubbs catalyst 2nd generation. **HG-II**: Hoveyda-Grubbs catalyst 2nd generation. [c] No reaction. [d] 1-Pentadecene (1.2 equiv.).

With the optimised conditions for the cross-metathesis reaction in hand, double bond functionalisation from enantioenriched acylated-oxazolidinone **(*R*,*S*)-275a** with commercially available 1-pentadecene and 1-nonene rendered intermediates **(*R*,*S*)-277** and **(*R*,*S*)-278** in high yields and good *E*:*Z* ratios (**Scheme 5.3**). Moreover, subsequent polar head deprotection with $NaBH_4$ and $Ba(OH)_2 \cdot 8H_2O$ in a two-step procedure gave final access to L-*erythro*-sphingosine **(*R*,*S*)-279** and clavaminol H derivative **(*R*,*S*)-280**.



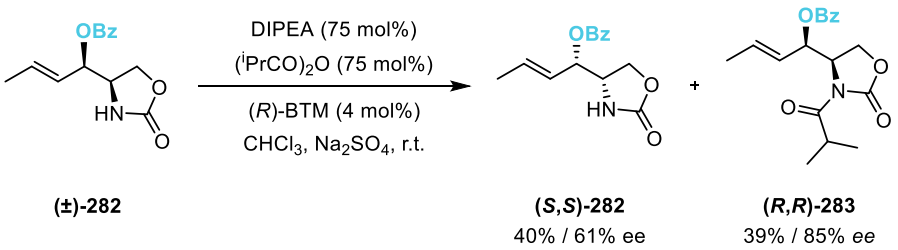
Scheme 5.3. Enantioselective synthesis of L-*erythro*-sphingosine **(*R,S*)-279** and clavaminol H derivative **(*R,S*)-280** from common acylated-oxazolidinone **(*R,S*)-275a** via cross-metathesis.

The absolute configuration of compound (***R,S***)-**279** was assigned by comparison of the HPLC traces recorded under identical conditions of derivatives (***R,S***)-**281** and (***S,R***)-**281**, obtained from (***R,S***)-**279** and natural commercially available sphingosine, respectively (**Scheme 5.4**). The results demonstrated that the application of tandem (*R*)-BTM catalysed kinetic resolution/cross-metathesis protocol to racemic oxazolidinone **(±)-274a** afforded synthetic sphingosine **(*R,S*)-279** with the opposite configuration than that of the natural occurring product.



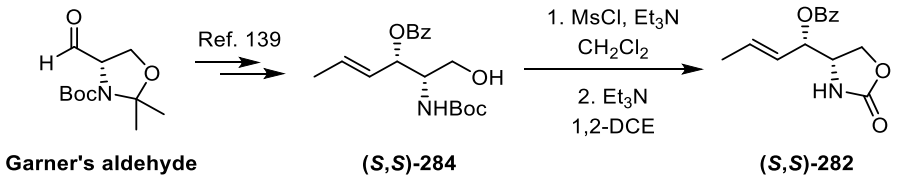
Scheme 5.4. Assignment of the absolute configuration of synthetic sphingosine **(*R,S*)-279**.

Alternatively, *syn*-benzoyl-substituted oxazolidinone **(±)-282** was prepared upon direct functionalisation of the related hydroxy derivative **(±)-209**, previously obtained from PhIO mediated aziridination/ring-opening strategy (**Scheme 3.33**). Then, this substrate was submitted to (*R*)-BTM-catalysed kinetic resolution under optimised conditions generating the acylated product **(*R,R*)-283** in 39% yield and 85% ee, along with the unreacted starting material **(*S,S*)-282** in 40% yield and 61% ee (**Scheme 5.5**).



Scheme 5.5. Kinetic resolution of *syn*-substituted oxazolidinone **(±)-282**.

The absolute configuration of compound **(*S*,*S*)-282**, prepared by kinetic resolution of **(±)-282**, was assigned by comparison with the same product obtained from Garner's aldehyde (**Scheme 5.6**).[139] With this purpose, *in situ* derivatisation of terminal alcohol from intermediate **(*S*,*S*)-284** with mesyl chloride triggered the intramolecular cyclisation of the Boc protecting group to furnish desired *syn*-substituted oxazolidinone **(*S*,*S*)-282.**[140]



Scheme 5.6. Synthesis of compound **(*S*,*S*)-282** from Garner's aldehyde.

Comparison of the HPLC traces for the racemic oxazolidinone **(±)-282** with compounds **(*S*,*S*)-282** and **(*S*,*S*)-282** from Garner's aldehyde proved that both products presented the same absolute configuration.

The results obtained from the kinetic resolution of both the *anti*- and the *syn*-substituted oxazolidinones reveal that it is the configuration of the carbon atom bearing the reactive amino group what determines the enantiomer being acylated for a specific catalyst whereas the adjacent stereocentre has little influence on the final outcome of the protocol. Moreover, we have demonstrated that the present organocatalysed kinetic resolution of racemic oxazolidinones via enantioselective *N*-

[139] D. Leonori, P. H. Seeberger, *Org. Lett.* **2012**, *14*, 4954–4957.
[140] J. L. Abad, I. Nieves, P. Rayo, J. Casas, G. Fabriàs, A. Delgado, *J. Org. Chem.* **2013**, *78*, 5858–5866.

acylation can be applied to a wider array of compounds than at first sight hypothesised.[136] Thus, substrates with an aliphatic chain directly attached to the oxazolidinone ring can be resolved as long as cation-π-interactions are stablished through the protection of the hydroxy moiety with Csp^2-containing functionalities.

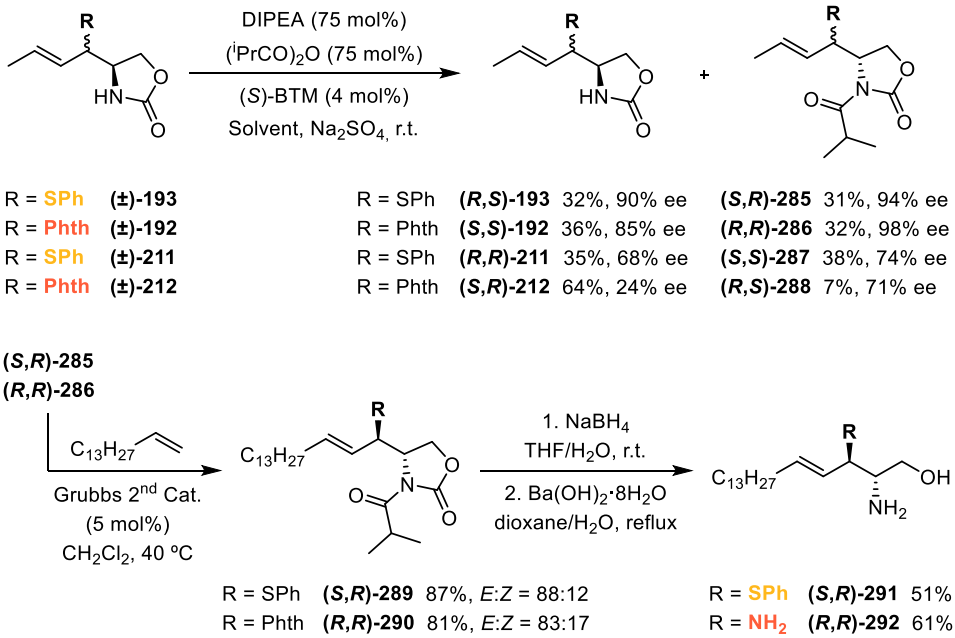
5.3.2. Organocatalysed kinetic resolution of *S*- and *N*-substituted oxazolidinones

Taking into account the already mentioned interactions at the reactive transition state between the carbonyl moiety from the protecting group in oxazolidinones **(±)-274** and the thiazolium cation resulting from the initial acylation of the BTM catalyst (**Figure 5.5**), we hypothesised that related *S*- and *N*-containing substrates could also be used as starting materials for the present kinetic resolution since the phenylsulfanyl group or the carbonyl moieties from phthalimide group could also stabilise the transition state in a similar way. Thus, *S*-substituted oxazolidinones, **(±)-193** and **(±)-211**, and *N*-substituted oxazolidinones, **(±)-192** and **(±)-212** obtained from PhIO mediated aziridination/ring-opening methodology were submitted to kinetic resolution conditions using (*S*)-BTM as catalyst since previously applied (*R*)-BTM enantiomer rendered the acylated precursor **(*R,S*)-275a** with the opposite configuration than that of the natural occurring sphingosine (**Scheme 5.7**).

To our delight, both *anti*-oxazolidinones **(±)-193** and **(±)-192** underwent kinetic resolution in good yields and remarkable enantioselectivities, 94% ee and 98% ee for the acylated products **(*S,R*)-285** and **(*R,R*)-286** and 90% ee and 85% ee for the recovered starting material **(*R,S*)-193** and **(*S,S*)-192**, respectively (**Scheme 5.7**). However, only moderate selectivities were observed for the *syn*-*S*-substituted oxazolidinone **(±)-211** whereas *syn*-*N*-containing derivative **(±)-212** proved to be rather unreactive under the kinetic resolution conditions probably due to its low solubility in the reaction medium (**Scheme 5.7**).

With the aim of exploiting this methodology in the synthesis of biologically relevant molecules such as sphingosine analogues, the enantioenriched acylated compounds were further elaborated via a cross-metathesis reaction to introduce the characteristic aliphatic chain of these natural products. Disappointingly, only *anti*-

substituted oxazolidinones **(*S,R*)-285** and **(*R,R*)-286** rendered the desired elongated products **(*S,R*)-289** and **(*R,R*)-290** when they were treated under previously optimised reaction conditions (**Scheme 5.7**). The reason for this lack of reactivity is not clear and has not been addressed but could be due to the steric clash between the ruthenium catalyst and the *syn*-substituted oxazolidinone.



Scheme 5.7. Kinetic resolution of intermediate *anti*-oxazolidinones **(±)-193**, **(±)-192** and *syn*-oxazolidinones **(±)-211**, **(±)-212** and final synthesis of heterosubstituted sphingosine analogues **(*S,R*)-291** and **(*R,R*)-292** via cross-metathesis and deprotection.

Deprotection of the terminal amino-alcohol moiety was accomplished in moderate yields to finally obtain two enantioenriched heterosubstituted sphingosine analogues with the same configuration than that of the natural occurring product bearing a thiophenol group **(*S,R*)-291** and a primary amine **(*R,R*)-292** at the 3-position respectively (**Scheme 5.7**).

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CHAPTER VI

SUPPORTING INFORMATION

UNIVERSITAT ROVIRA I VIRGILI
METAL-FREE REGIO- AND STEREOSELECTIVE VICINAL DIFUNCTIONALISATION OF DIENYL CARBAMATES
Irene Giménez Nueno

6.1. General methods

All chemicals used were reagent grade and used as supplied unless otherwise specified. Reagent grade dichloromethane (CH_2Cl_2), chloroform ($CHCl_3$), acetonitrile (CH_3CN), tetrahydrofuran (THF), toluene (Tol), benzene (C_6H_6) and triethyl amine (Et_3N) were purified using standard procedures.[141]

^1H and ^{13}C NMR spectra were recorded on a Varian Mercury VX400 or a Varian NMR System 400 spectrometers (400 MHz and 100 MHz respectively) in $CDCl_3$ and CD_3OD as solvents, with chemical shifts (δ) referenced to internal standards in $CDCl_3$ (7.26 ppm ^1H, 77.16 ppm ^{13}C) or CD_3OD (3.31 ppm ^1H, 49.00 ppm ^{13}C). 2D correlation spectra (gCOSY, NOESY, gHSQC, gHMBC) were visualized using VNMR program from Varian. ESI-TOF HRMS were recorded on an Agilent 1200 liquid chromatograph coupled to 6210 Time of Flight (TOF) mass spectrometer from Agilent Technologies with an ESI interface instrument. HPLC-DAD spectra were recorded on an Agilent 1200 liquid chromatograph coupled to G1315D Diode array Detector from Agilent Technologies. IR spectra were recorded on a JASCO FT/IR-680 plus Fourier Transform Infrared Spectrometer ATR Specac Golden Gate. Optical rotations were measured at room temperature in a Perkin-Elmer 241 MC polarimeter with 10 cm cells. Melting points were determined in an analogue Griffin melting point apparatus.

Reactions were monitored by TLC carried out on 0.25 mm Merck® silica gel 60 F_{254} aluminium plates. Developed TLC plates were visualized under a short-wave UV lamp (254 nm) and by heating plates that were dipped in a basic solution of potassium permanganate, a solution of *p*-anisaldehyde in ethanol/H_2SO_4/AcOH (90:3:1) or a solution of ninhydrin in butanol/AcOH (97:3). Flash column chromatography was carried out using forced flow of the indicated solvent on Merck® silica gel 60 (0.040-0.063 mm).

[141] D. D. Perrin, W. L. F. Armarego, *Purification of Laboratory Chemicals*; 3rd Ed.; Pergamon Press plc.: Oxford, England, **1988**.

6.2. General procedures

General procedure for the conversion of allylic dienols to carbamates (carbamoylation).[61] A solution of trichloroacetyl isocyanate (TAI) (1.05 mmol) in dry benzene (1 mL / mmol dienol) was added to a solution of dienol (1.00 mmol) in dry dichloromethane (2 mL / mmol dienol). The mixture was left at room temperature until TLC showed complete consumption of the starting dienol. Then a 20 mol% solution of K_2CO_3 in methanol (3 mL / mmol dienol) was added and the mixture was stirred at room temperature for 3 hours. After solvent evaporation, the residue was dissolved in a 1:1 mixture of dichloromethane and brine. The aqueous phase was extracted with dichloromethane and the combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure.

General procedure for *one-pot* PhIO mediated Aziridination/Ring-Opening. A flame dried Schlenk containing a magnetic stirring bar was charged with activated 4Å M.S. (100 mg / 0.1 mmol carbamate) in distilled CH_2Cl_2 (0.04 M) under argon atmosphere. Dienyl carbamate (0.1 mmol) and PhIO (0.2 mmol) were added and the heterogeneous mixture was stirred at 35ºC unless stated in the specific procedure until TLC showed complete consumption of the starting material. Nucleophile was then added and the reaction mixture was stirred overnight. The crude solution was filtered over celite, abundantly washed with CH_2Cl_2 and concentrated under reduced pressure. The yield over the two steps was determined by ^{1}H-NMR spectroscopy, using 1,3-dinitrobenzene as internal standard. The reaction crude was initially purified through a short column chromatography (2-3 cm) in order to avoid product decomposition under prolonged contact with silicagel.

General procedure for *one-pot* ArI(OAc)$_2$ mediated Aziridination/Ring-Opening. A flame dried Schlenk containing a magnetic stirring bar was charged with oven dried K_2CO_3 (0.4 mmol), activated 4Å M.S. (100 mg / 0.1 mmol carbamate) and carbamate (0.1 mmol) in deoxygenated CH_2Cl_2 (0.04 M) under argon atmosphere. After overnight stirring, ArI(OAc)$_2$ (0.2 mmol) was added and the crude mixture was left at room temperature until TLC showed complete consumption of the carbamate (c.a. 72 hours). The ring-opening step was then performed using a mixture of H_2O in CH_3CN and the reaction was finally quenched with MeOH overnight. The crude mixture was directly purified by column chromatography.

General procedure for the preparation of lactate-based chiral aryliodide precursors.[108a,142] To a solution 2-iodobenzene-1,3-diol or 2-iodo-5-methylbenzene-1,3-diol (8.0 mmol), Ph_3P (18.4 mmol) and chiral lactate derivative (16.8 mmol) in THF (80 mL) at 0ºC, diisopropyl azodicarboxylate (DIAD) (18.4 mmol) was added dropwise. The mixture was allowed to warm up to room temperature and stirred overnight. After complete consumption of starting material, the solvent was removed under reduced pressure and the residue was purified by column chromatography.

General procedure for the BTM-catalysed kinetic resolution of oxazolidinones with isobutyric anhydride.[137] The reactions were set at the globe box. The catalyst was used within a solution which was prepared by dissolving the corresponding BTM reagent (10.1 mg, 0.04 mmol) and DIPEA (131 μL, 0.75 mmol) in $CHCl_3$ (4.9 mL). One dram vial was charged with the oxazolidinone substrate (0.10 mmol) and 0.5 mL of the catalyst solution. Then 100 mg of Na_2SO_4 were added and the reaction mixture was magnetically stirred for 5 min before being treated with isobutyric anhydride (0.075 mmol). The reaction mixture was kept under stirring and followed by ^1H NMR. Methanol was finally added to quench the reaction.

General procedure for the *N*-acylation of racemic oxazolidinones with isobutyric anhydride.[143] Oxazolidinone (0.10 mmol) was dissolved in CH_2Cl_2 (0.1 M) at room temperature under argon atmosphere. Et_3N (0.10 mmol) was then added and the solution was cooled to 0ºC. Stirring was continued for approximately 20 min and DMAP (2.5 mol%) and ($^iPrCO_2$)O (0.11 mmol) were subsequently added. The resulting mixture was kept at 0ºC for one hour and then warmed to room temperature. After completion, the crude was concentrated under reduced pressure.

General procedure for the cross metathesis of alkenyl oxazolidinones with terminal olefins.[137] A two-neck round-bottom flask fitted with a reflux condenser was charged with a solution of alkenyl oxazolidinone (0.10 mmol) in dry dichloromethane (0.05 M). Terminal olefin (0.12 mmol) and Grubbs catalyst 2nd generation (5 mol%) were then added and the reaction mixture was stirred at 40ºC for 24 h. After completion, the crude was concentrated under reduced pressure.

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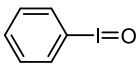
142 S. Tsujiyama, K. Suzuki, *Org. Synth.* **2007**, *84*, 272–284; **2009**, *Coll. Vol. 11*, 488–497.

143 C. S. Schindler, P. M. Forster, E. M. Carreira, *Org. Lett.* **2010**, *12*, 4102–4105.

6.3. Compound characterisation

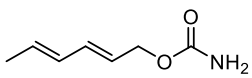
Iodosylbenzene (PhIO).[91]



PhIO

A sodium hydroxide solution (3*N*, 20 mL) was added over a 10-minutes period to finely ground recrystallised (5*M* AcOH) (diacetoxyiodo)benzene (4.0 g, 12.4 mmol) in a 100 mL beaker under vigorous stirring. The reaction mixture was left at room temperature until completion (c.a. 45 minutes); then, H_2O (15 mL) was added and the crude, solid iodosylbenzene, was filtered on a Büchner funnel. The wet solid was returned to the beaker, triturated with H_2O (25 mL), collected again on a Büchner funnel, washed with water and dried overnight under vacuum. Final purification was effected by triturating the dried solid with chloroform (10 mL) in a beaker, separating it by filtration and drying under vacuum to afford 2.0 g (75% yield) of iodosylbenzene as a yellow powder.

(2*E*,4*E*)-hexa-2,4-dien-1-yl carbamate (172).



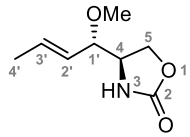
172

The title compound was synthesised following the general carbamoylation procedure starting from commercially available (2*E*,4*E*)-hexa-2,4-dien-1-ol (1.1 mL, 10.0 mmol) and TAI (0.8 mL, 10.5 mmol). The crude was purified by column chromatography (30:70 to 50:50 AcOEt/hexanes). Compound **172** was recrystallised by slow diffusion of pentane into a solution of the carbamate in THF to afford 1.3 g (93% yield) of pure carbamate **172** as a white powder.

R_f = 0.20 (30:70 AcOEt/Hexanes). **M.p.** = 93-95 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 6.24 (dd, *J* = 15.2, 10.5 Hz, 1H, H-3), 6.04 (ddd, *J* = 14.2, 10.5, 1.3 Hz, 1H, H-4), 5.74 (dq, *J* = 14.2, 6.7 Hz, 1H, H-5), 5.62 (dt, *J* = 15.2, 6.6 Hz, 1H, H-2), 4.85 (brs, 2H, NH_2), 4.55 (d, *J* = 6.6 Hz, 2H, H-1), 1.75 (dd, *J* = 6.7, 1.3 Hz, 3H, H-6). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 157.0 (C=O), 134.7 (C-3), 131.3 (C-5), 130.5 (C-4), 124.1 (C-2), 65.7 (C-1), 18.3 (C-6). **ESI-TOF**

[M+Na]$^+$ calc for $C_7H_{11}NNaO_2$: 164.0682, found: 164.0682. **FT-IR (ATR)** ν in cm^{-1}: 3426, 3296, 3213, 2911, 2851, 1652, 1616, 1429, 1344, 1314, 1108, 1054, 990.

***u*-4-[(*E*)-1-methoxybut-2-en-1-yl]-oxazolidin-2-one ((±)-174).**

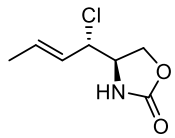


(±)-174

The title compound was synthesised following PhIO mediated aziridination/ring-opening procedure starting from carbamate **172** (70.6 mg, 0.5 mmol), PhIO (220.1 mg, 1.0 mmol) and using MeOH (10.0 mL) as nucleophile. NMR-yield: 95%. The crude was purified by column chromatography (40:60 AcOEt/hexanes) to afford 59.6 mg (70% yield) of oxazolidinone **(±)-174** as a white solid.

R$_f$ = 0.68 (AcOEt). **M.p.** = 46-49 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 5.84 (dq, *J* = 15.3, 6.5 Hz, 1H, H-3'), 5.55 (brs, 1H, NH), 5.24 (ddq, *J* = 15.3, 8.6, 1.7 Hz, 1H, H-2'), 4.43 (t, *J* = 8.8 Hz, 1H, H-5$_a$), 4.25 (dd, *J* = 9.0, 4.8 Hz, 1H, H-5$_b$), 3.76 (ddd, *J* = 8.5, 6.9, 4.8 Hz, 1H, H-4), 3.43 (dd, *J* = 8.6, 6.9 Hz, 1H, H-1'), 3.25 (s, 3H, OMe), 1.77 (dd, *J* = 6.5, 1.7 Hz, 3H, H-4'). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 159.6 (C=O), 134.4 (C-3'), 126.6 (C-2'), 84.0 (C-1'), 67.7 (C-5), 56.4 (OMe), 55.2 (C-4), 18.1 (C-4'). **ESI-TOF** [M+Na]$^+$ calc for $C_8H_{13}NNaO_3$: 194.0788, found: 194.0784. **FT-IR (ATR)** ν in cm^{-1}: 3228, 3146, 2916, 2824, 1747, 1483, 1446, 1403, 1246, 1119, 1091.

***u*-4-[(*E*)-1-chlorobut-2-en-1-yl]-oxazolidin-2-one ((±)-177).**



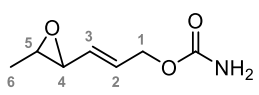
(±)-177

The title compound was synthesised following PhIO mediated aziridination/ring-opening procedure starting from carbamate **172** (14.1 mg, 0.1

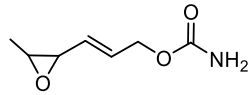
mmol), PhIO (44.0 mg, 0.2 mmol) and using solid $Bu_4N^+Cl^-$ (139.0 mg, 0.5 mmol) as nucleophile. The crude was purified by column chromatography (40:60 AcOEt/hexanes) to afford 2.9 mg (17% yield) of oxazolidinone **(±)-177** as a white solid.

R_f = 0.72 (AcOEt). **M.p.** = 92-96 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 5.91 (dq, *J* = 15.1, 6.6 Hz, 1H, H-3'), 5.52 (brs, 1H, NH), 5.46 (ddq, *J* = 15.1, 9.2, 1.7 Hz, 1H, H-2'), 4.51 (dd, *J* = 9.3, 8.4 Hz, 1H, H-5_a), 4.32 (dd, *J* = 9.3, 4.7 Hz, 1H, H-5_b), 4.22 (dd, *J* = 9.2, 7.8 Hz, 1H, H-1'), 4.02-3.96 (m, 1H, H-4), 1.78 (dd, *J* = 6.6, 1.7 Hz, 3H, H-4'). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 158.7 (C=O), 134.1 (C-3'), 126.5 (C-2'), 68.0 (C-5), 63.5 (C-1'), 57.1 (C-4), 18.0 (C-4'). **ESI-TOF** $[M+Na]^+$ calc for $C_7H_{10}ClNNaO_2$: 198.0292, found: 198.0290. **FT-IR (ATR)** ν in cm^{-1}: 3232, 2923, 2852, 1765, 1402, 1234, 966.

(*trans*/*cis*,2*E*)-4,5-epoxihexa-2-ene-1-yl carbamate ((±)-176*trans*/(±)-176*cis*).



(±)-176*trans*



(±)-176*cis*

Epoxides **(±)-176*trans*** and **(±)-176*cis*** were obtained as side products of PhIO mediated aziridination/ring-opening procedures in yields up to 20% depending on reaction conditions. For characterisation proposes, combined crude mixtures were purified by column chromatography (30:70 to 40:60 AcOEt/hexanes) to afford an inseparable mixture of 9:1 *trans*/*cis*-epoxides. Spectroscopy data for epoxide **(±)-176*trans*** were in agreement with those available at the literature,[144] whereas epoxide **(±)-176*cis*** was not described.

R_f = 0.70 (AcOEt). **M.p.** = 72-76 ºC.

Compound **(±)-176*trans***: **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 5.99 (dt, *J* = 15.6, 5.8 Hz, 1H, H-2), 5.50 (ddt, *J* = 15.6, 7.8, 1.5 Hz, 1H, H-3), 4.64 (brs, 2H,

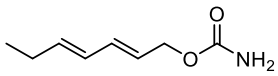
[144] a) M. O. Lederer, *J. Agric. Food Chem.* **1996**, *44*, 2531–2537. b) J.-J. Feng, J. Zhang, *J. Am. Chem. Soc.* **2011**, *133*, 7304–7307.

NH_2), 4.57 (dd, *J* = 5.8, 1.5 Hz, 2H, H-1), 3.08 (dd, *J* = 7.8, 2.1 Hz, 1H, H-4), 2.92 (qd, *J* = 5.2, 2.1 Hz, 1H, H-5), 1.34 (d, *J* = 5.2 Hz, 3H, H-6). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 156.4 (C=O), 131.6 (C-3), 129.2 (C-2), 64.6 (C-1), 58.7 (C-4), 56.7 (C-5), 17.6 (C-6).

Compound **(±)-176*cis***: **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 6.01 (dt, *J* = 15.6, 5.8 Hz, 1H, H-2), 5.64 (ddt, *J* = 15.6, 7.3, 1.5 Hz, 1H, H-3), 4.64 (brs, 2H, NH_2), 4.61 (dd, *J* = 5.8, 1.5 Hz, 2H, H-1), 3.41 (dd, *J* = 7.3, 4.3 Hz, 1H, H-4), 3.22 (qd, *J* = 5.5, 4.3 Hz, 1H, H-5), 1.28 (d, *J* = 5.5 Hz, 3H, H-6). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 156.4 (C=O), 130.7 (C-2/C-3), 128.3 (C-2/C-3), 64.8 (C-1), 56.4 (C-4/C-5), 54.7 (C-4/C-5), 13.5 (C-6).

ESI-TOF $[M+Na]^+$ calc for $C_7H_{11}NNaO_3$: 180.0631, found: 180.0632. **FT-IR (ATR)** ν in cm^{-1}: 3387, 1708, 1618, 1401, 1321, 1102, 1053, 1007, 973, 932.

(2*E*,4*E*)-hepta-2,4-dien-1-yl carbamate (180).



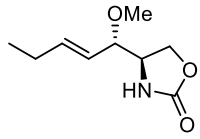
180

The title compound was synthesised following the general carbamoylation procedure starting from commercially available (2*E*,4*E*)-hepta-2,4-dien-1-ol (1.0 g, 8.9 mmol) and TAI (0.7 mL, 9.3 mmol). The crude was purified by column chromatography (10:90 to 20:80 AcOEt/hexanes). Compound **180** was recrystallised by slow diffusion of pentane into a solution of the carbamate in THF to afford 1.0 g (76% yield) of pure carbamate **180** as a white powder.

R_f = 0.20 (30:70 AcOEt/Hexanes). **M.p.** = 59-64 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 6.23 (dd, *J* = 14.5, 10.4 Hz, 1H, H-3), 6.01 (dd, *J* = 15.1, 10.4 Hz, 1H, H-4), 5.76 (dt, *J* = 15,1, 6.5 Hz, 1H, H-5), 5.62 (dt, *J* = 14.5, 6.5 Hz, 1H, H-2), 5.05 (brs, 2H, NH_2), 4.54 (d, *J* = 6.5 Hz, 2H, H-1), 2.08 (p, *J* = 6.9 Hz, 2H, H-6), 0.98 (t, *J* = 7.5 Hz, 3H, H-7). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 157.2 (C=O), 138.2 (C-5), 134.8 (C-3), 128.2 (C-4), 124.3 (C-2), 65.6 (C-1), 25.7 (C-6), 13.4 (C-7). **ESI-TOF** $[M+Na]^+$ calc for $C_8H_{13}NNaO_2$: 178.0838, found: 178.0840. **FT-**

IR (ATR) ν in cm-1: 3424, 3271, 3212, 2967, 1688, 1608, 1463, 1412, 1324, 1094, 1048, 984.

***u*-4-[(*E*)-1-methoxypent-2-en-1-yl]-oxazolidin-2-one ((±)-181).**

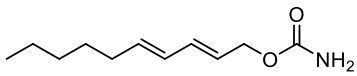


(±)-181

The title compound was synthesised following PhIO mediated aziridination/ring-opening procedure starting from carbamate **180** (15.5 mg, 0.1 mmol), PhIO (44.0 mg, 0.2 mmol) and using MeOH (2.0 mL) as nucleophile. NMR-yield: 95%. The crude was purified by column chromatography (40:60 AcOEt/hexanes) to afford 13.1 mg (71% yield) of oxazolidinone **(±)-181** as a colourless oil.

R_f = 0.71 (AcOEt). **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 5.90 (dt, *J* = 15.5, 6.3 Hz, 1H, H-3'), 5.23 (ddt, *J* = 15.5, 8.6, 1.6 Hz, 1H, H-2'), 4.92 (brs, 1H, NH), 4.46 (t, *J* = 8.7 Hz, 1H, H-5_a), 4.26 (dd, *J* = 9.0, 4.8 Hz, 1H, H-5_b), 3.78 (ddd, *J* = 8.4, 7.0, 4.8 Hz, 1H, H-4), 3.45 (dd, *J* = 8.6, 7.0 Hz, 1H, H-1'), 3.26 (s, 3H, OMe), 2.13 (pd, *J* = 7.4, 1.6 Hz, 2H, H-4'), 1.03 (t, *J* = 7.5 Hz, 3H, H-5'). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 159.5 (C=O), 141.3 (C-3'), 124.2 (C-2'), 84.1 (C-1'), 67.7 (C-5), 56.3 (OMe), 55.3 (C-4), 25.5 (C-4'), 13.5 (C-5'). **ESI-TOF** $[M+Na]^+$ calc for $C_9H_{15}NNaO_3$: 208.0944, found: 208.0943. **FT-IR (ATR)** ν in cm^{-1}: 3275, 2964, 1745, 1405, 1234, 1100, 1024.

(2*E*,4*E*)-deca-2,4-dien-1-yl carbamate (182).



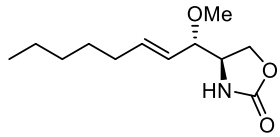
182

The title compound was synthesised following the general carbamoylation procedure starting from commercially available (2*E*,4*E*)-deca-2,4-dien-1-ol (1.0 g, 6.5 mmol) and TAI (0.5 mL, 6.8 mmol). The crude was purified by column

chromatography (10:90 to 20:80 AcOEt/hexanes). Compound **182** was recrystallised by slow diffusion of pentane into a solution of the carbamate in THF to afford 0.9 g (72% yield) of pure carbamate **182** as a white powder.

R_f = 0.15 (30:70 AcOEt/Hexanes). **M.p.** = 56-59 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 6.26 (dd, *J* = 15.2, 10.5 Hz, 1H, H-3), 6.03 (dd, *J* = 15.1, 10.5 Hz, 1H, H-4), 5.74 (dt, *J* = 15.1, 7.0 Hz, 1H, H-5), 5.64 (dt, *J* = 15.2, 6.6 Hz, 1H, H-2), 4.67 (brs, 2H, NH_2), 4.57 (d, *J* = 6.6 Hz, 2H, H-1), 2.07 (q, *J* = 7.0 Hz, 2H, H-6), 1.41-1.34 (m, 2H, H-7-H-9), 1.32-1.25 (m, 4H, H-7-H-9), 0.88 (t, *J* = 6.9 Hz, 3H, H-10). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 157.1 (C=O), 136.9 (C-5), 134.8 (C-3), 129.1 (C-4), 124.3 (C-2), 65.6 (C-1), 32.7 (C-6), 31.5, 28.9, 22.6 (C-7-C-9), 14.1 (C-10). **ESI-TOF** $[M+Na]^+$ calc for $C_{11}H_{19}NNaO_2$: 220.1308, found: 220.1307. **FT-IR (ATR)** ν in cm^{-1}: 3431, 3257, 2953, 2925, 2853, 1689, 1606, 1466, 1415, 1320, 1107, 1051, 986.

***u*-4-[(*E*)-1-methoxyoct-2-en-1-yl]-oxazolidin-2-one ((±)-183).**



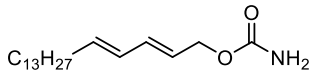
(±)-183

The title compound was synthesised following PhIO mediated aziridination/ring-opening procedure starting from carbamate **182** (19.7 mg, 0.1 mmol), PhIO (44.0 mg, 0.2 mmol) under reflux and using MeOH (2.0 mL) as nucleophile. NMR-yield: 86%. The crude was purified by column chromatography (35:75 AcOEt/hexanes) to afford 18.6 mg (82% yield) of oxazolidinone **(±)-183** as a colourless oil.

R_f = 0.75 (AcOEt). **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 5.83 (dt, *J* = 15.4, 6.8 Hz, 1H, H-3'), 5.24 (brs, 1H, NH), 5.22 (ddt, *J* = 15.4, 8.6, 1.4 Hz, 1H, H-2'), 4.44 (t, *J* = 8.7 Hz, 1H, H-5_a), 4.26 (dd, *J* = 9.0, 4.8 Hz, 1H, H-5_b), 3.78 (ddd, *J* = 8.5, 6.8, 4.8 Hz, 1H, H-4), 3.44 (dd, *J* = 8.6, 6.8 Hz, 1H, H-1'), 3.26 (s, 3H, OMe), 2.10 (qd, *J* = 6.8, 1.4 Hz, 2H, H-4'), 1.44-1.36 (m, 2H, H-5'-H-7'), 1.34-1.25 (m, 4H, H-5'-H-7'), 0.89 (t, *J* = 6.9 Hz, 3H, H-8'). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm):

δ = 159.7 (C=O), 139.8 (C-3'), 125.0 (C-2'), 84.0 (C-1'), 67.6 (C-5), 56.3 (OMe), 55.3 (C-4), 32.4 (C-4'), 31.5, 28.8, 22.5 (C-5'-C-7'), 14.1 (C-8'). **ESI-TOF** $[M+Na]^+$ calc for $C_{12}H_{21}NNaO_3$: 250.1414, found: 250.1412. **FT-IR (ATR)** ν in cm^{-1}: 3253, 3139, 2926, 2860, 2828, 1743, 1481, 1467, 1401, 1242, 1099.

(2*E*,4*E*)-octadeca-2,4-dien-1-yl carbamate (184).

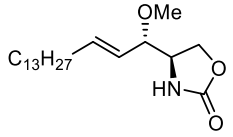


184

The title compound was synthesised following the general carbamoylation procedure starting from (2*E*,4*E*)-octadeca-2,4-dien-1-ol[73] (1.35 g, 5.1 mmol) and TAI (0.4 mL, 5.3 mmol). The crude was purified by column chromatography (10:90 to 30:70 AcOEt/hexanes). Compound **184** was recrystallised by slow diffusion of pentane into a solution of the carbamate in THF to afford 1.43 g (91% yield) of pure carbamate **184** as a white powder.

R_f = 0.11 (10:90 AcOEt/Hexanes). **M.p.** = 87 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 6.26 (dd, *J* = 15.2, 10.5 Hz, 1H, H-3), 6.03 (dd, *J* = 14.9, 10.5 Hz, 1H, H-4), 5.74 (dt, *J* = 14.9, 7.1 Hz, 1H, H-5), 5.64 (dt, *J* = 15.2, 6.6 Hz, 1H, H-2), 4.70 (brs, 2H, NH_2), 4.57 (d, *J* = 6.6 Hz, 2H, H-1), 2.07 (q, *J* = 7.1 Hz, 2H, H-6), 1.39-1.25 (m, 22H, H-7-H-17), 0.87 (t, *J* = 6.9 Hz, 3H, H-18). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 156.8 (C=O), 137.1 (C-5), 135.0 (C-3), 129.1 (C-4), 124.2 (C-2), 65.8 (C-1), 32.8 (C-6), 32.1, 29.8, 29.8, 29.8, 29.7, 29.6, 29.5, 29.3, 29.3, 22.8 (C-7-C-17), 14.3 (C-18). **ESI-TOF** $[M+Na]^+$ calc for $C_{19}H_{35}NNaO_2$: 332.2560, found: 332.2547. **FT-IR (ATR)** ν in cm^{-1}: 3435, 3289, 3018, 2954, 2917, 2848, 1691, 1606, 1472, 1461, 1438, 1073, 982.

***u*-4-[(*E*)-1-methoxyhexadeca-2-en-1-yl]-oxazolidin-2-one ((±)-185).**

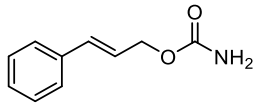


(±)-185

The title compound was synthesised following PhIO mediated aziridination/ring-opening procedure starting from carbamate **184** (21.0 mg, 0.07 mmol), PhIO (29.9 mg, 0.14 mmol) under reflux and using MeOH (2.0 mL) as nucleophile. NMR-yield: 73%. The crude was purified by column chromatography (20:80 AcOEt/hexanes) to afford 12.5 mg (54% yield) of oxazolidinone **(±)-185** as a yellowish solid.

R_f = 0.75 (AcOEt). **M.p.** = 51-55 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 5.83 (dt, *J* = 15.3, 6.7 Hz, 1H, H-3'), 5.22 (ddt, *J* = 15.3, 8.6, 1.3 Hz, 1H, H-2'), 5.07 (brs, 1H, NH), 4.45 (t, *J* = 8.7 Hz, 1H, H-5_a), 4.26 (dd, *J* = 9.0, 4.8 Hz, 1H, H-5_b), 3.78 (ddd, *J* = 8.5, 6.9, 4.8 Hz, 1H, H-4), 3.44 (dd, *J* = 8.6, 6.9 Hz, 1H, H-1'), 3.26 (s, 3H, OMe), 2.09 (qd, *J* = 6.7, 1.3 Hz, 2H, H-4'), 1.41-1.25 (m, 22H, H-5'-H-15'), 0.88 (t, *J* = 6.9 Hz, 3H, H-16'). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 159.3 (C=O), 140.1 (C-3'), 125.1 (C-2'), 84.1 (C-1'), 67.7 (C-5), 56.3 (OMe), 55.2 (C-4), 32.5 (C-4'), 32.1, 29.8, 29.8, 29.7, 29.6, 29.5, 29.3, 29.2, 22.8 (C-5'-C-15'), 14.3 (C-16'). **ESI-TOF** $[2M+Na]^+$ calc for $C_{40}H_{74}N_2NaO_6$: 701.5439, found: 701.5445. **FT-IR (ATR)** ν in cm^{-1}: 3229, 2920, 2851, 1738, 1469, 1401, 1249, 1101, 1011, 969.

(*E*)-3-phenyl-2-propen-1-yl carbamate (186).



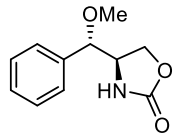
186

The title compound was synthesized following the general carbamoylation procedure starting from commercially available (2*E*)-3-phenyl-2-propen-1-ol (1.1 g, 7.9 mmol) and TAI (0.6 mL, 8.3 mmol). The crude was purified by column chromatography (20:80 AcOEt/hexanes). Compound **186** was recrystallised by slow

diffusion of pentane into a solution of the carbamate in THF to afford 1.2 g (83% yield) of pure carbamate **186** as a white powder.

R_f = 0.15 (30:70 AcOEt/Hexanes). **M.p.** = 120-126 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 7.40- 7.37 (m, 2H, Ar), 7.34-7.30 (m, 2H, Ar), 7.28-7.24 (m, 1H, Ar), 6.65 (d, *J* = 15.9 Hz, 1H, H-3), 6.29 (dt, *J* = 15.9, 6.4 Hz, 1H, H-2), 4.99 (brs, 2H, NH_2), 4.73 (dd, *J* = 6.4, 1.3 Hz, 2H, H-1). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 156.9 (C=O), 136.2 (Ar), 133.8 (C-3), 128.6, 128.0, 126.6 (Ar), 123.5 (C-2), 65.6 (C-1). **ESI-TOF** $[M+Na]^+$ calc for $C_{10}H_{11}NNaO_2$: 200.0682, found: 200.0680. **FT-IR (ATR)** ν in cm-1: 3409, 3328, 3264, 3055, 1679, 1626, 1602, 1409, 1341, 1115, 1048, 969.

***u*-4-[Methoxyphenylmethyl]oxazolidin-2-one ((±)-187).**

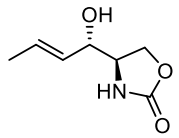


(±)-187

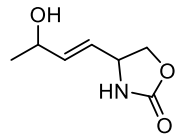
The title compound was synthesized following PhIO mediated aziridination/ring-opening procedure starting from carbamate **186** (177.2 mg, 1.0 mmol), PhIO (440.2 mg, 2.0 mmol) and using MeOH (20.0 mL) as nucleophile at 55ºC. NMR-yield: 83%. The crude was purified by column chromatography (AcOEt/hexanes from 30:70 to 50:50) to afford 102.7 mg (50% yield) of oxazolidinone **(±)-187** as a yellow solid.

R_f = 0.59 (AcOEt). **M.p.** = 84-88 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 7.42-7.28 (m, 5H, Ar), 5.39 (brs, 1H, NH), 4.45 (dd, *J* = 9.0, 8.1 Hz, 1H, H-5_a), 4.41 (dd, *J* = 9.0, 5.0 Hz, 1H, H-5_b), 4.09 (d, *J* = 7.4 Hz, 1H, H-1'), 3.90 (ddd, *J* = 8.1, 7.4, 5.0 Hz, 1H, H-4), 3.23 (s, 3H, OMe). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 159.4 (C=O), 137.0, 129.1, 129.0, 127.3 (Ar), 84.9 (C-1'), 68.0 (C-5), 57.1 (C-4), 57.1 (OMe). **ESI-TOF** $[M+Na]^+$ calc for $C_{11}H_{13}NNaO_3$: 230.0788, found: 230.0791. **FT-IR (ATR)** ν in cm-1: 3244, 3140, 2928, 2828, 1756, 1483, 1455, 1399, 1231, 1104, 1087, 1030, 924.

***u*-4-[(*E*)-1-hydroxybut-2-en-1-yl]-oxazolidin-2-one ((±)-188) and 4-[(*E*)-3-hydroxybut-1-en-1-yl]-oxazolidin-2-one (189).**



(±)-188



189

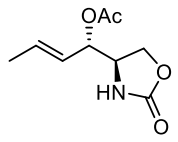
Procedure 1. The title compounds were synthesised following PhIO mediated aziridination/ring-opening procedure starting from carbamate **172** (14.1 mg, 0.1 mmol), PhIO (44.0 mg, 0.2 mmol) and using a mixture of 6 drops of H_2O in CH_3CN (1.5 mL) as nucleophile to afford a mixture of compounds **(±)-188** and **189**. The crude solution was filtered over celite, washed with MeOH and concentrated under reduced pressure. NMR-yield: 81% (ratio **(±)-188**:**189** = 86:14). The crude was purified by column chromatography (80:20 AcOEt/hexanes to AcOEt) to afford 11.0 mg (70% overall yield) of oxazolidinone **(±)-188** as a white solid and regioisomer **189** as a colourless oil.

Procedure 2. The title compounds were synthesized following $PhI(OAc)_2$ mediated aziridination/ring-opening procedure starting from carbamate **172** (14.1 mg, 0.1 mmol), K_2CO_3 (55.3 mg, 0.4 mmol), $PhI(OAc)_2$ (64.4 mg, 0.2 mmol) and using a mixture of 6 drops of H_2O in CH_3CN (1.5 mL) as nucleophile and 2 mL of MeOH as quenching agent to afford a mixture of compounds **(±)-188** along with other ring-opening products. The crude was directly purified by column chromatography (80:20 AcOEt/hexanes) to afford 11.2 mg (71% yield) of oxazolidinone **(±)-188** as a white solid.

Compound **(±)-188**: $\mathbf{R_f}$ = 0.46 (AcOEt). **M.p.** = 110-115 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 6.03 (brs, 1H, NH/OH), 5.85 (dq, *J* = 15.3, 6.5 Hz, 1H, H-3'), 5.40 (ddq, *J* = 15.3, 7.0, 1.6 Hz, 1H, H-2'), 4.40 (t, *J* = 8.8 Hz, 1H, H-5_a), 4.33 (dd, *J* = 8.9, 5.0 Hz, 1H, H-5_b), 4.13-4.09 (m, 1H, H-1'), 3.88-3.83 (m, 1H, H-4), 2.88 (brs, 1H, NH/OH), 1.73 (dd, *J* = 6.5, 1.6 Hz, 3H, H-4'). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 160.5 (C=O), 131.4 (C-3'), 128.0 (C-2'), 73.3 (C-1'), 66.5 (C-5), 56.4 (C-4), 18.1 (C-4'). **ESI-TOF** $[M+Na]^+$ calc for $C_7H_{11}NNaO_3$: 180.0631, found: 180.0627. **FT-IR (ATR)** ν in cm^{-1}: 3389, 2918, 1781, 1716, 1478, 1418, 1233, 1089, 1020, 966.

Compound **189**: $\mathbf{R}_f$ = 0.26 (AcOEt). **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 5.83 (ddd, *J* = 15.4, 5.5, 1.2 Hz, 1H, H-2'), 5.68 (ddd, *J* = 15.4, 7.6, 2.1 Hz, 1H, H-1'), 5.11 (brs, 1H, NH/OH), 4.54 (td, *J* = 8.5, 2.1 Hz, 1H, H-5_a), 4.43-4.33 (m, 2H, H-4, H-3'), 4.07 (ddd, *J* = 8.5, 6.7, 4.0 Hz, 1H, H-5_b), 1.29 (d, *J* = 6.5 Hz, 3H, H-4'). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 159.3 (C=O), 138.9 (C-2'), 127.0 (C-1'), 70.2 (C-5), 67.7 (C-3'), 54.5 (C-4), 23.5 (C-4'). **ESI-TOF** $[M+Na]^+$ calc for $C_7H_{11}NNaO_3$: 180.0631, found: 180.0628. **FT-IR (ATR)** ν in cm^{-1}: 3296, 2967, 2921, 2852, 1728, 1403, 1237, 1063, 1022, 971.

***u*-4-[(*E*)-1-acetoxybut-2-en-1-yl]-oxazolidin-2-one ((±)-190).**

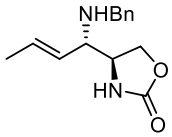


(±)-190

The title compound was synthesised following PhIO mediated aziridination/ring-opening procedure starting from carbamate **172** (70.6 mg, 0.5 mmol), PhIO (220.1 mg, 1.0 mmol) and using a mixture of solid sodium acetate (205.1 mg, 2.5 mmol) and 15-crown-5 (0.1 mL, 0.5 mmol) as nucleophile. NMR-yield: 50%. The crude was purified by column chromatography (60:40 AcOEt/hexanes) to afford 41.6 mg (42% yield) of oxazolidinone **(±)-190** as a colourless oil.

$\mathbf{R}_f$ = 0.66 (AcOEt). **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 5.91 (dq, *J* = 15.3, 6.6 Hz, 1H, H-3'), 5.68 (brs, 1H, NH), 5.37 (ddq, *J* = 15.3, 7.7, 1.7 Hz, 1H, H-2'), 5.23 (dd, *J* = 7.7, 4.7 Hz, 1H, H-1'), 4.43 (t, *J* = 8.9 Hz, 1H, H-5_a), 4.22 (dd, *J* = 9.0, 5.0 Hz, 1H, H-5_b), 3.99 (dt, *J* = 8.8, 4.9 Hz, 1H, H-4), 2.08 (s, 3H, OAc), 1.74 (dd, *J* = 6.6, 1.7 Hz, 3H, H-4'). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 170.1 (C=O OAc), 159.3 (C=O), 134.2 (C-3'), 123.6 (C-2'), 74.8 (C-1'), 66.3 (C-5), 54.7 (C-4), 21.2 (OAc), 18.1 (C-4'). **ESI-TOF** $[M+Na]^+$ calc for $C_9H_{13}NNaO_4$: 222.0737, found: 222.0738. **FT-IR (ATR)** ν in cm^{-1}: 3279, 2921, 1730, 1401, 1373, 1225, 1022, 967.

***u*-4-[(*E*)-1-benzylaminobut-2-en-1-yl]-oxazolidin-2-one ((±)-191).**

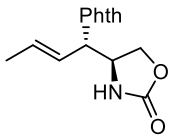


(±)-191

The title compound was synthesised following PhIO mediated aziridination/ring-opening procedure starting from carbamate **172** (14.1 mg, 0.1 mmol), PhIO (44.0 mg, 0.2 mmol) and using liquid NH_2Bn (0.1 mL, 1.0 mmol) as nucleophile. NMR-yield: 98%. The crude was purified by column chromatography (70:30 AcOEt/hexanes) to afford 12.0 mg (48% yield) of oxazolidinone **(±)-191** as an orange oil.

R_f = 0.51 (AcOEt). **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 7.35-7.23 (m, 5H, Bn), 5.72 (dq, *J* = 15.3, 6.5 Hz, 1H, H-3'), 5.34 (brs, 1H, NH), 5.22 (ddq, *J* = 15.3, 8.8, 1.7 Hz, 1H, H-2'), 4.43 (t, *J* = 8.7 Hz, 1H, H-5_a), 4.27 (dd, *J* = 8.9, 5.6 Hz, 1H, H-5_b), 3.84 (d, *J* = 13.2 Hz, 1H, Bn), 3.69 (ddd, *J* = 8.6, 6.8, 5.6 Hz, 1H, H-4), 3.62 (d, *J* = 13.2 Hz, 1H, Bn), 2.95 (dd, *J* = 8.8, 6.8 Hz, 1H, H-1'), 1.77 (dd, *J* = 6.5, 1.7 Hz, 3H, H-4'). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 159.5 (C=O), 140.0 (Bn), 132.3 (C-3'), 128.6 (Bn), 128.5 (C-2'), 128.3 (Bn), 127.3 (Bn), 68.1 (C-5), 63.4 (C-1'), 55.6 (C-4), 51.0 (Bn), 18.2 (C-4'). **ESI-TOF** $[M+Na]^+$ calc for $C_{14}H_{18}N_2NaO_2$: 269.1260, found: 269.1261. **FT-IR (ATR)** ν in cm-1: 3295, 2916, 2850, 1742, 1453, 1404, 1236, 1028, 971.

***u*-4-[(*E*)-1-phthalimidobut-2-en-1-yl]-oxazolidin-2-one ((±)-192).**



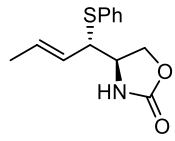
(±)-192

The title compound was synthesised following PhIO mediated aziridination/ring-opening procedure starting from carbamate **172** (14.1 mg, 0.1 mmol), PhIO (44.0 mg, 0.2 mmol) and using a mixture of solid potassium phthalimide (185.2 mg, 1.0 mmol) and 18-crown-6 (21.0 μL, 0.1 mmol) as nucleophile. NMR-yield: 52%. The crude was purified by column chromatography

(30:70 AcOEt/hexanes) to afford 11.5 mg (40% yield) of oxazolidinone **(±)-192** as a white solid.

R_f = 0.74 (AcOEt). **M.p.** = slowly melts >172 ºC with decomposition. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 7.88-7.83 (m, 2H, Phth), 7.78-7.73 (m, 2H, Phth), 5.95-5.81 (m, 3H, H-2', H-3', NH), 4.65 (dd, *J* = 8.1, 5.3 Hz, 1H, H-1'), 4.49 (t, *J* = 8.7 Hz, 1H, H-5_a), 4.37 (dt, *J* = 8.8, 5.3 Hz, 1H, H-4), 4.14 (dd, *J* = 8.8, 5.6 Hz, 1H, H-5_b), 1.73 (d, *J* = 5.1 Hz, 3H, H-4'). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 168.2 (C=O Phth), 158.8 (C=O), 134.8 (C-2'/C-3'), 134.6 (Phth), 131.6 (Phth), 123.8 (Phth), 122.3 (C-2'/C-3'), 67.7 (C-5), 56.7 (C-1'), 54.4 (C-4), 18.1 (C-4'). **ESI-TOF** $[M+H]^+$ calc for $C_{15}H_{15}N_2O_4$: 287.1026, found: 287.1028. **FT-IR (ATR)** ν in cm^{-1}: 3352, 2923, 1760, 1703, 1382, 1234, 1068, 973.

***u*-4-[(*E*)-1-phenylsulfanylbut-2-en-1-yl]-oxazolidin-2-one ((±)-193).**



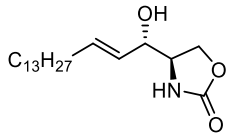
(±)-193

The title compound was synthesised following PhIO mediated aziridination/ring-opening procedure starting from carbamate **172** (141.2 mg, 1.0 mmol), PhIO (440.2 mg, 2.0 mmol) and using a suspension of preformed $PhSNHEt_3$ (2.1 g, 10.0 mmol) in CH_2Cl_2 (30.0 mL) as nucleophile. NMR-yield: 63%. The crude was purified by column chromatography (20:80 AcOEt/hexanes) to afford 99.3 mg (40% yield) of oxazolidinone **(±)-193** as a white solid.

R_f = 0.82 (AcOEt). **M.p.** = 64-67 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 7.42-7.37 (m, 2H, SPh), 7.34-7.28 (m, 3H, SPh), 5.57 (brs, 1H, NH), 5.56 (dq, *J* = 15.2, 6.5 Hz, 1H, H-3'), 5.33 (ddq, *J* = 15.2, 9.3, 1.6 Hz, 1H, H-2'), 4.48 (t, *J* = 8.8 Hz, 1H, H-5_a), 4.31 (dd, *J* = 9.1, 5.3 Hz, 1H, H-5_b), 3.86 (ddd, *J* = 8.3, 7.4, 5.3 Hz, 1H, H-4), 3.49 (dd, *J* = 9.3, 7.4 Hz, 1H, H-1'), 1.67 (dd, *J* = 6.5, 1.6 Hz, 3H, H-4'). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 159.2 (C=O), 134.1 (SPh), 132.1 (SPh), 132.0 (C-3'), 129.2 (SPh), 128.4 (SPh), 126.0 (C-2'), 68.5 (C-5), 55.8 (C-1'), 54.7 (C-4), 18.0 (C-4'). **ESI-TOF** $[M+Na]^+$ calc for $C_{13}H_{15}NNaO_2S$: 272.0716, found:

272.0714. **FT-IR (ATR)** ν in cm^{-1}: 3252, 2923, 2854, 2094, 1738, 1438, 1403, 1242, 1011, 956.

***u*-4-[(*E*)-1-hydroxyhexadeca-2-en-1-yl]-oxazolidin-2-one ((±)-196).**

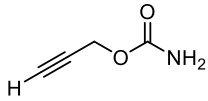


(±)-196

The title compound was synthesised following PhIO mediated aziridination/ring-opening procedure starting from carbamate **184** (154.8 mg, 0.5 mmol), PhIO (220.1 mg, 1.0 mmol) and using a mixture of 30 drops of H_2O in CH_3CN (7.5 mL) as nucleophile. The crude solution was filtered over celite, washed with MeOH and concentrated under reduced pressure. The crude was purified by column chromatography (70:30 AcOEt/hexanes) to afford 52.5 mg (32% yield) of oxazolidinone **(±)-196** as a white solid.

R_f = 0.24 (AcOEt). **M.p.** = 76-79 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 5.93 (brs, 1H, NH/OH), 5.84 (dt, *J* = 15.3, 6.9 Hz, 1H, H-3'), 5.37 (dd, *J* = 15.3, 6.9 Hz, 1H, H-2'), 4.40 (t, *J* = 8.8 Hz, 1H, H-5_a), 4.33 (dd, *J* = 8.9, 5.1 Hz, 1H, H-5_b), 4.14-4.10 (m, 1H, H-1'), 3.88-3.83 (m, 1H, H-4), 2.76 (d, *J* = 3.5 Hz, 1H, NH/OH), 2.04 (q, *J* = 6.9 Hz, 2H, H-4'), 1.38-1.25 (m, 22H, H-5'-H-15'), 0.87 (t, *J* = 6.9 Hz, 3H, H-16'). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 160.3 (C=O), 136.8 (C-3'), 126.6 (C-2'), 73.4 (C-1'), 66.5 (C-5), 56.3 (C-4), 32.5 (C-4'), 32.1, 29.8, 29.8, 29.8, 29.7, 29.6, 29.5, 29.4, 29.1, 22.8 (C-5'-C-15'), 14.3 (C-16'). **ESI-TOF** $[M+Na]^+$ calc for $C_{19}H_{35}NNaO_3$: 348.2509, found: 348.2520. **FT-IR (ATR)** ν in cm^{-1}: 3384, 2917, 2849, 1777, 1699, 1474, 1435, 1233, 1096, 1027, 977.

Prop-2-yn-1-yl carbamate (200).

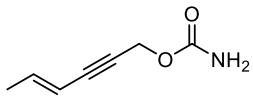


200

The title compound was synthesised following the general carbamoylation procedure starting from commercially available propargyl alcohol (0.2 mL, 3.6 mmol) and TAI (0.3 mL, 3.8 mmol). The crude was purified by column chromatography (30:70 AcOEt/hexanes) to afford 274.3 mg (78% yield) of carbamate **200** as a white solid.

R_f = 0.32 (50:50 AcOEt/Hexanes). **M.p.** = 54-58 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 5.13 (brs, 2H, NH_2), 4.66 (d, *J* = 2.5 Hz, 2H, H-1), 2.48 (t, *J* = 2.5 Hz, 1H, H-3). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 155.9 (C=O), 78.0 (C-3), 75.0 (C-2), 52.8 (C-1). **ESI-TOF** $[M+Na]^+$ calc for $C_4H_5NNaO_2$: 122.0212, found: 122.0210. **FT-IR (ATR)** ν in cm^{-1}: 3438, 3288, 3214, 2957, 1645, 1608, 1450, 1326, 1301, 1269, 1070.

(*E*)-hex-4-en-2-yn-1-yl carbamate (199).[73]



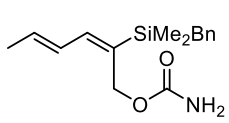
199

To a solution of *trans*-1-bromo-propene (0.2 mL, 1.7 mmol) and $Pd(PPh_3)_4$ (52.1 mg, 0.05 mmol) in dry THF (6 mL), carbamate **200** (111.7 mg, 1.1 mmol), copper iodide (4.3 mg, 0.02 mmol) and freshly distilled diisopropylamine (0.8 mL) were added dropwise. The mixture was stirred overnight at room temperature. After solvent evaporation, the crude was dissolved in CH_2Cl_2, washed with an aqueous solution of NH_4Cl, dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by column chromatography (5:95 to 30:70 AcOEt/hexanes) to afford 107.4 mg (68% yield) of carbamate **199** as a white solid.

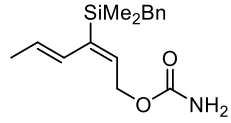
R_f = 0.44 (50:50 AcOEt/Hexanes). **M.p.** = 73-76 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 6.20 (dq, *J* = 15.8, 6.8 Hz, 1H, H-5), 5.49 (dsext, *J* = 15.8, 1.9

Hz, 1H, H-4), 4.95 (brs, 2H, NH_2), 4.77 (d, *J* = 1.9 Hz, 2H, H-1), 1.78 (dd, *J* = 6.8, 1.9 Hz, 3H, H-6). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 156.3 (C=O), 141.5 (C-5), 109.9 (C-4), 85.4 (C-2/C-3), 81.4 (C-2/C-3), 53.7 (C-1), 18.8 (C-6). **ESI-TOF** $[M+Na]^+$ calc for $C_7H_9NNaO_2$: 162.0525, found: 162.0527. **FT-IR (ATR)** ν in cm^{-1}: 3431, 3329, 3204, 2218, 1687, 1445, 1405, 1343, 1279, 1172, 1051, 1007, 950.

(2*E*,4*E*)-2-(benzyldimethylsilyl)hexa-2,4-dien-1-yl carbamate (203a) and (2*E*,4*E*)-3-(benzyldimethylsilyl)hexa-2,4-dien-1-yl carbamate (203b).[100]



203a



203b

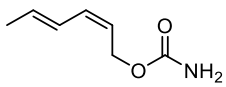
To a solution of alkyne **199** (401.9 mg, 2.9 mmol) and benzylchlorodimethylsilane (0.6 mL, 3.5 mmol) in CH_2Cl_2 (20 mL), 10 mol% of $PtCl_2$ catalyst (77.1 mg, 0.3 mmol) was added. The reaction mixture was stirred overnight at 25 ºC to obtain carbamates **203a** and **203b** as an 87:13 mixture of regioisomers. After solvent evaporation, the crude was purified by column chromatography (15:85 AcOEt/hexanes) to afford 576.1 mg (70% yield) of silanes **203a** and **203b** as a colourless oil.

Compound **203a**: $\mathbf{R}_f$ = 0.54 (50:50 AcOEt/Hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 7.21 (t, *J* = 7.7 Hz, 2H, Bn), 7.07 (t, *J* = 7.7 Hz, 1H, Bn), 7.00 (dd, *J* = 7.7, 1.2 Hz, 2H, Bn), 6.45 (ddq, *J* = 13.8, 10.9, 1.5 Hz, 1H, H-4), 6.36 (d, *J* = 10.9 Hz, 1H, H-3), 5.86 (dq, *J* = 13.8, 6.8 Hz, 1H, H-5), 4.83 (d, *J* = 0.7 Hz, 2H, H-1), 4.83 (brs, 2H, NH_2), 2.21 (s, 2H, Bn), 1.83 (dd, *J* = 6.8, 1.5 Hz, 3H, H-6), 0.10 (s, 6H, Me). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 157.1 (C=O), 142.5 (C-3), 140.0 (Bn), 134.4 (C-5), 132.5 (C-2), 128.4 (Bn), 128.2 (Bn), 127.1 (C-4), 124.1 (Bn), 63.6 (C-1), 26.0 (Bn), 18.6 (C-6), -3.3 (Me). **ESI-TOF** $[M+Na]^+$ calc for $C_{16}H_{23}NNaO_2Si$: 312.1390, found: 312.1393. **FT-IR (ATR)** ν in cm^{-1}: 3345, 3024, 2955, 1712, 1599, 1394, 1322, 1248, 1040.

Compound **203b**: $\mathbf{R}_f$ = 0.48 (50:50 AcOEt/Hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 7.19 (t, *J* = 7.7 Hz, 2H, Bn), 7.06 (t, *J* = 7.7 Hz, 1H, Bn), 6.97

(dd, *J* = 7.7, 1.2 Hz, 2H, Bn), 6.20 (d, *J* = 15.7 Hz, 1H, H-4), 5.70 (t, *J* = 6.0 Hz, 1H, H-3), 5.62 (dq, *J* = 15.7, 6.5 Hz, 1H, H-5), 4.76 (d, *J* = 6.0 Hz, 2H, H-1), 4.60 (brs, 2H, NH_2), 2.20 (s, 2H, Bn), 1.79 (dd, *J* = 6.5, 1.6 Hz, 3H, H-6), 0.09 (s, 6H, Me). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 157.0 (C=O), 141.7 (C-3), 139.9 (Bn), 134.2 (C-2), 130.0 (C-5), 129.0 (C-4), 128.4 (Bn), 128.2 (Bn), 124.2 (Bn), 62.7 (C-1), 25.7 (Bn), 19.1 (C-6), -2.9 (Me). **ESI-TOF** $[M+Na]^+$ calc for $C_{16}H_{23}NNaO_2Si$: 312.1390, found: 312.1393. **FT-IR (ATR)** ν in cm^{-1}: 3351, 3024, 2957, 1711, 1599, 1393, 1326, 1249, 1057.

(2*Z*,4*E*)-hexa-2,4-dien-1-yl carbamate (201).



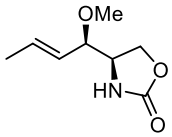
201

A solution of silanes **203a** and **203b** (1.05 g, 3.6 mmol) in anhydrous THF (60 mL) at 0 ºC was treated with commercially available TBAF solution (4.4 mL, 4.4 mmol, 1M in THF). The mixture was heated up to 40 ºC and stirred overnight. Then, a solution of TAI (0.3 mL, 3.8 mmol) in anhydrous benzene (4 mL) was added and the reaction mixture was left overnight at room temperature, according to the general carbamoylation procedure. After solvent evaporation, the residue was dissolved in a 1:1 mixture of dichloromethane and brine and the organic phase was separated. The aqueous phase was extracted with diethyl ether and the combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by column chromatography (15:85 AcOEt/hexanes) to afford 339.0 mg (67% yield) of carbamate **201** as a white solid. Finally, compound **201** was recrystallised by slow diffusion of pentane into a solution of the carbamate in THF.

R_f = 0.36 (50:50 AcOEt/Hexanes). **M.p.** = 50-53 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 6.34 (ddq, *J* = 14.2, 11.1, 1.1 Hz, 1H, H-4), 6.14 (t, *J* = 11.0 Hz, 1H, H-3), 5.80 (dq, *J* = 14.2, 6.8 Hz, 1H, H-5), 5.41 (dt, *J* = 10.9, 7.2 Hz, 1H, H-2), 4.72 (brs, 2H, NH_2), 4.71 (d, *J* = 7.2 Hz, 2H, H-1), 1.79 (dd, *J* = 6.8, 1.1 Hz, 3H, H-6). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 157.1 (C=O), 133.2 (C-3), 133.0 (C-5), 126.1 (C-4), 121.8 (C-2), 61.2 (C-1), 18.5 (C-6). **ESI-TOF** $[M+Na]^+$ calc for

$C_7H_{11}NNaO_2$: 164.0682, found: 164.0677. **FT-IR (ATR)** ν in cm^{-1}: 3371, 3207, 2963, 2908, 1688, 1614, 1447, 1387, 1354, 1051, 960.

***rac*-4-[(*E*)-1-methoxybut-2-en-1-yl]-oxazolidin-2-one ((±)-207).**

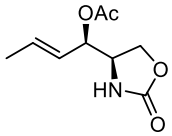


(±)-207

The title compound was synthesised following PhIO mediated aziridination/ring-opening procedure starting from carbamate **201** (14.1 mg, 0.1 mmol), PhIO (44.0 mg, 0.2 mmol) and using MeOH (2.0 mL) as nucleophile. NMR-yield: 79%. The crude was purified by column chromatography (40:60 AcOEt/hexanes) to afford 10.2 mg (60% yield) of oxazolidinone **(±)-207** as a white solid.

R_f = 0.58 (AcOEt). **M.p.** = 44-48 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 5.85 (dq, *J* = 15.4, 6.5 Hz, 1H, H-3'), 5.47 (brs, 1H, NH), 5.15 (ddq, *J* = 15.4, 8.7, 1.7 Hz, 1H, H-2'), 4.33 (t, *J* = 8.9 Hz, 1H, H-5_a), 4.05 (dd, *J* = 9.1, 5.2 Hz, 1H, H-5_b), 3.73 (td, *J* = 8.5, 5.2 Hz, 1H, H-4), 3.43 (t, *J* = 8.6 Hz, 1H, H-1'), 3.26 (s, 3H, OMe), 1.77 (dd, *J* = 6.5, 1.7 Hz, 3H, H-4'). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 159.2 (C=O), 134.5 (C-3'), 126.2 (C-2'), 84.9 (C-1'), 66.5 (C-5), 56.2 (OMe), 55.6 (C-4), 18.1 (C-4'). **ESI-TOF** $[M+H]^+$ calc for $C_8H_{14}NO_3$: 172.0968, found: 172.0971. **FT-IR (ATR)** ν in cm^{-1}: 3252, 2963, 2919, 2823, 1759, 1411, 1238, 1140, 1098, 1023, 982, 928.

***rac*-4-[(*E*)-1-acetoxybut-2-en-1-yl]-oxazolidin-2-one ((±)-208).**



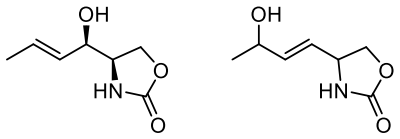
(±)-208

The title compound was synthesised following PhIO mediated aziridination/ring-opening procedure starting from carbamate **201** (14.1 mg, 0.1

mmol), PhIO (44.0 mg, 0.2 mmol) and using a solution of sodium acetate (41.0 mg, 0.5 mmol) and 15-crown-5 (19.8 μL, 0.1 mmol) in CH_2Cl_2 (2.5 mL) as nucleophile. NMR-yield: 13%. The crude was purified by column chromatography (60:40 AcOEt/hexanes) to afford 2.1 mg (11% yield) of oxazolidinone **(±)-208** as a colourless oil.

R_f = 0.58 (AcOEt). **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 5.92 (dq, *J* = 15.3, 6.6 Hz, 1H, H-3'), 5.66 (brs, 1H, NH), 5.31 (ddq, *J* = 15.3, 7.6, 1.7 Hz, 1H, H-2'), 5.16 (t, *J* = 7.2 Hz, 1H, H-1'), 4.41 (dd, *J* = 9.1, 8.7 Hz, 1H, H-5_a), 4.15 (dd, *J* = 9.1, 4.8 Hz, 1H, H-5_b), 3.95 (ddd, *J* = 8.7, 6.8, 4.8 Hz, 1H, H-4), 2.10 (s, 3H, OAc), 1.74 (dd, *J* = 6.6, 1.7 Hz, 3H, H-4'). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 170.1 (C=O OAc), 159.2 (C=O), 134.2 (C-3'), 124.0 (C-2'), 75.8 (C-1'), 66.5 (C-5), 54.6 (C-4), 21.2 (OAc), 18.2 (C-4'). **ESI-TOF** $[M+Na]^+$ calc for $C_9H_{13}NNaO_4$: 222.0737, found: 222.0742. **FT-IR (ATR)** ν in cm^{-1}: 3278, 2922, 2852, 1738, 1409, 1373, 1226, 1025, 967, 936.

***I*-4-[(*E*)-1-hydroxybut-2-en-1-yl]-oxazolidin-2-one ((±)-209) and 4-[(*E*)-3-hydroxybut-1-en-1-yl]-oxazolidin-2-one (189).**

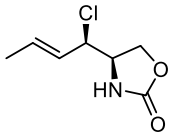


(±)-209 **189**

The title compounds were synthesised following PhIO mediated aziridination/ring-opening procedure starting from carbamate **201** (14.1 mg, 0.1 mmol), PhIO (44.0 mg, 0.2 mmol) and using a mixture of 6 drops of H_2O in CH_3CN (1.5 mL) as nucleophile to afford a mixture of compounds **(±)-209** and **189**. The crude solution was filtered over celite, washed with MeOH and concentrated under reduced pressure. NMR-yield: 74% (ratio **(±)-209**:**189** = 91:9). The crude was purified by column chromatography (80:20 AcOEt/hexanes to AcOEt) to afford 10.3 mg (66% yield) of oxazolidinone **(±)-209** as a colourless oil and regioisomer **189** as a colourless oil.

Compound **(±)-209**: $\mathbf{R_f}$ = 0.35 (AcOEt). **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 6.48 (brs, 1H, NH/OH), 5.82 (dq, *J* = 15.3, 6.5 Hz, 1H, H-3'), 5.37 (ddq, *J* = 15.3, 7.4, 1.6 Hz, 1H, H-2'), 4.36 (t, *J* = 8.9 Hz, 1H, H-5_a), 4.13 (dd, *J* = 9.0, 5.4 Hz, 1H, H-5_b), 3.99 (t, *J* = 7.3 Hz, 1H, H-1'), 3.78 (ddd, *J* = 8.7, 7.3, 5.4 Hz, 1H, H-4), 3.47 (brs, 1H, NH/OH), 1.72 (dd, *J* = 6.5, 1.6 Hz, 3H, H-4'). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 160.3 (C=O), 131.4 (C-3'), 128.6 (C-2'), 75.0 (C-1'), 67.0 (C-5), 56.9 (C-4), 18.0 (C-4'). **ESI-TOF** $[M+H]^+$ calc for $C_7H_{12}NO_3$: 158.0812, found: 158.0812. **FT-IR (ATR)** ν in cm^{-1}: 3295, 2919, 1739, 1412, 1242, 1092, 1034, 969.

***I*-4-[(*E*)-1-chlorobut-2-en-1-yl]-oxazolidin-2-one ((±)-210).**

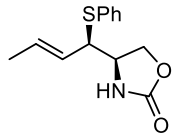


(±)-210

The title compound was synthesised following PhIO mediated aziridination/ring-opening procedure starting from carbamate **201** (14.1 mg, 0.1 mmol), PhIO (44.0 mg, 0.2 mmol) and using solid $Bu_4N^+Cl^-$ (277.9 mg, 1.0 mmol) as nucleophile. The crude was purified by column chromatography (40:60 AcOEt/hexanes) to afford 3.7 mg (21% yield) of oxazolidinone **(±)-210** as a white solid.

$\mathbf{R_f}$ = 0. 61 (AcOEt). **M.p.** = 82-90 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 6.28 (brs, 1H, NH), 5.91 (dq, *J* = 15.1, 6.6 Hz, 1H, H-3'), 5.44 (ddq, *J* = 15.1, 9.1, 1.7 Hz, 1H, H-2'), 4.41 (dd, *J* = 9.4, 8.5 Hz, 1H, H-5_a), 4.30 (dd, *J* = 9.1, 7.4 Hz, 1H, H-1'), 4.19 (dd, *J* = 9.4, 4.7 Hz, 1H, H-5_b), 4.01 (ddd, *J* = 8.5, 7.4, 4.7 Hz 1H, H-4), 1.76 (dd, *J* = 6.6, 1.7 Hz, 3H, H-4'). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 159.4 (C=O), 133.8 (C-3'), 125.7 (C-2'), 67.0 (C-5), 64.2 (C-1'), 57.4 (C-4), 17.9 (C-4'). **ESI-TOF** $[M+Na]^+$ calc for $C_7H_{10}ClNNaO_2$: 198.0292, found: 198.0292. **FT-IR (ATR)** ν in cm^{-1}: 3244, 3130, 2940, 1753, 1474, 1413, 1364, 1233, 1090, 1005, 970.

***rel*-4-[(*E*)-1-phenylsulfanylbut-2-en-1-yl]-oxazolidin-2-one ((±)-211).**

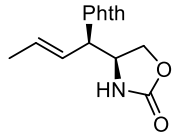


(±)-211

The title compound was synthesised following PhIO mediated aziridination/ring-opening procedure starting from carbamate **201** (14.1 mg, 0.1 mmol), PhIO (44.0 mg, 0.2 mmol) and using solid PhSNa (66.1 mg, 0.5 mmol) and 15-crown-5 (19.8 μL, 0.1 mmol) as nucleophile. NMR-yield: 21%. The crude was purified by column chromatography (40:60 AcOEt/hexanes) to afford 4.6 mg (18% yield) of oxazolidinone **(±)-211** as a colourless oil.

R_f = 0.77 (AcOEt). **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 7.42-7.37 (m, 2H, SPh), 7.33-7.27 (m, 3H, SPh), 6.14 (brs, 1H, NH), 5.51 (dq, *J* = 15.2, 6.4 Hz, 1H, H-3'), 5.27 (ddq, *J* = 15.2, 9.1, 1.6 Hz, 1H, H-2'), 4.37 (dd, *J* = 9.1, 8.5 Hz, 1H, H-5_a), 4.23 (dd, *J* = 9.1, 5.1 Hz, 1H, H-5_b), 3.85 (td, *J* = 8.2, 5.1 Hz, 1H, H-4), 3.54 (t, *J* = 8.5 Hz, 1H, H-1'), 1.65 (dd, *J* = 6.4, 1.6 Hz, 3H, H-4'). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 158.7 (C=O), 134.3 (SPh), 131.8 (SPh), 131.6 (C-3'), 129.2 (SPh), 128.6 (SPh), 125.8 (C-2'), 67.9 (C-5), 56.6 (C-1'), 54.7 (C-4), 18.1 (C-4'). **ESI-TOF** $[2M+Na]^+$ calc for $C_{26}H_{30}N_2NaO_4S_2$: 521.1539, found: 521.1556. **FT-IR (ATR)** ν in cm^{-1}: 3282, 2920, 2853, 1750, 1477, 1439, 1404, 1230, 1024, 967.

***rel*-4-[(*E*)-1-phthalimidobut-2-en-1-yl]-oxazolidin-2-one ((±)-212).**



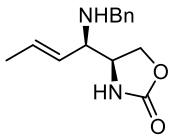
(±)-212

The title compound was synthesised following PhIO mediated aziridination/ring-opening procedure starting from carbamate **201** (14.1 mg, 0.1 mmol), PhIO (44.0 mg, 0.2 mmol) and using a mixture of solid potassium phthalimide (185.2 mg, 1.0 mmol) and 18-crown-6 (21.4 μL, 0.1 mmol) as nucleophile. NMR-yield: 33%. The crude was purified by column chromatography

(80:20 Et_2O/pentane) to afford 3.7 mg (13% yield) of oxazolidinone **(±)-212** as a white solid.

R_f = 0.78 (AcOEt). **M.p.** = 224-228ºC. **^{1}H NMR** (400 MHz, CD_2Cl_2, δ in ppm): δ = 7.84-7.80 (m, 2H, Phth), 7.76-7.72 (m, 2H, Phth), 5.89 (dq, *J* = 15.3, 6.3 Hz, 1H, H-3'), 5.75 (ddq, *J* = 15.3, 8.5, 1.5 Hz, 1H, H-2'), 5.25 (brs, 1H, NH), 4.66 (t, *J* = 8.6 Hz, 1H, H-1'), 4.57 (tdd, *J* = 8.7, 4.9, 1.3 Hz, 1H, H-4), 4.44 (dd, *J* = 9.1, 8.3 Hz, 1H, H-5_a), 4.21 (dd, *J* = 9.1, 4.9 Hz, 1H, H-5_b), 1.70 (dd, *J* = 6.3, 1.5 Hz, 3H, H-4'). **^{13}C NMR** (100 MHz, CD_2Cl_2, δ in ppm): δ = 168.1 (C=O Phth), 158.6 (C=O), 134.5 (Phth), 134.0 (C-3'), 131.9 (Phth), 123.5 (Phth), 123.4 (C-2'), 68.1 (C-5), 57.8 (C-1'), 53.0 (C-4), 17.7 (C-4'). **ESI-TOF** $[2M+Na]^+$ calc for $C_{30}H_{28}N_4NaO_8$: 595.1799, found: 595.1818. **FT-IR (ATR)** ν in cm^{-1}: 3138, 2921, 2852, 1747, 1703, 1384, 1241, 1085, 1016.

***I*-4-[(*E*)-1-benzylaminobut-2-en-1-yl]-oxazolidin-2-one ((±)-213).**



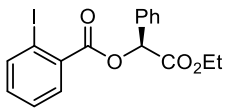
(±)-213

The title compound was synthesised following PhIO mediated aziridination/ring-opening procedure starting from carbamate **201** (14.1 mg, 0.1 mmol), PhIO (44.0 mg, 0.2 mmol) and using liquid NH_2Bn (0.1 mL, 1.0 mmol) as nucleophile. NMR-yield: 59%. The crude was purified by column chromatography (70:30 AcOEt/hexanes) to afford 5.5 mg (22% yield) of oxazolidinone **(±)-213** as an orange solid.

R_f = 0.49 (AcOEt). **M.p.** = 72-76 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 7.35-7.23 (m, 5H, Bn), 5.76 (brs, 1H, NH), 5.68 (dq, *J* = 15.2, 6.4 Hz, 1H, H-3'), 5.12 (ddq, *J* = 15.2, 8.7, 1.6 Hz, 1H, H-2'), 4.33 (t, *J* = 8.7 Hz, 1H, H-5_a), 4.14 (dd, *J* = 8.9, 5.4 Hz, 1H, H-5_b), 3.86 (d, *J* = 13.1 Hz, 1H, Bn), 3.63 (dt, *J* = 8.3, 5.4 Hz, 1H, H-4), 3.60 (d, *J* = 13.1 Hz, 1H, Bn), 2.91 (t, *J* = 8.4 Hz, 1H, H-1'), 1.76 (dd, *J* = 6.4, 1.6 Hz, 3H, H-4'). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 159.5 (C=O), 139.9 (Bn), 131.7 (C-3'), 128.6 (Bn), 128.4 (Bn), 128.3 (C-2'), 127.3 (Bn), 67.6 (C-5), 63.7

(C-1'), 56.1 (C-4), 50.8 (Bn), 18.2 (C-4'). **ESI-TOF** $[M+H]^+$ calc for $C_{14}H_{19}N_2O_2$: 247.1441, found: 247.1432. **FT-IR (ATR)** ν in cm^{-1}: 3252, 2919, 1762, 1732, 1404, 1231, 1102, 1011, 976.

(*S*)-2-Ethoxy-2-oxo-1-phenylethyl 2-iodobenzoate (256).

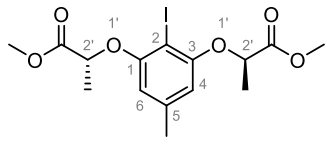


256

To a solution of 2-iodobenzoic acid (2.0 g, 8.1 mmol), Ph_3P (2.6 g, 10.1 mmol) and (*R*)-mandelic acid ethylester (1.8 g, 10.1 mmol) in THF (85 mL) at 0 ºC, diisopropyl azodicarboxylate (DIAD) (4.0 mL, 20.2 mmol) was added dropwise. The mixture was allowed to warm up to room temperature and stirred overnight. After complete consumption of starting material, the solvent was removed under reduced pressure and the residue was purified by column chromatography (2:98 to 5:95 AcOEt/hexanes) to afford 3.1 g (93% yield) of chiral aryliodide precursor **256** as a yellowish oil.

R_f = 0.27 (5:95 AcOEt/Hexanes). **$[\alpha]_D^{25}$** = +66.0 (c = 1.04, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 8.03-8.00 (m, 2H, Ar), 7.59-7.55 (m, 2H, Ar), 7.45-7.39 (m, 4H, Ar), 7.20-7.16 (m, 1H, Ar), 6.16 (s, 1H, H-3'), 4.30-4.16 (m, 2H, Et), 1.25 (t, *J* = 7.1 Hz, 3H, Et). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 168.7, 165.7 (C=O), 141.7, 134.0, 133.8, 133.3, 131.8, 129.4, 129.0, 128.1, 127.9, 94.6 (Ar), 75.6 (C-3'), 62.0 (Et), 14.2 (Et). **ESI-TOF** $[2M+Na]^+$ calc for $C_{34}H_{30}I_2NaO_8$: 842,9922, found: 842,9921. **FT-IR (ATR)** ν in cm^{-1}: 2980, 1730, 1583, 1465, 1369, 1242, 1210, 1180, 1094, 1015.

Dimethyl 2,2'-((2-iodo-5-methyl-1,3-phenylene)bis(oxy))-(2*R*,2'*R*)-dipropionate (263a).

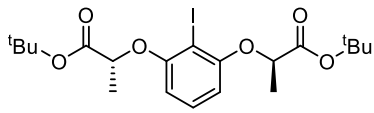


263a

The title compound was synthesised following the general procedure for chiral aryliodide preparation starting from 2-iodo-5-methylbenzene-1,3-diol (1.0 g, 4.0 mmol), Ph_3P (2.4 g, 9.2 mmol), methyl-(*S*)-lactate (0.8 mL, 8.4 mmol) and DIAD (1.8 mL, 9.2 mmol). The crude was purified by column chromatography (10:90 to 20:80 AcOEt/hexanes) to afford 1.2 g (74% yield) of chiral aryliodide precursor **263a** as a white solid.

R_f = 0.12 (10:90 AcOEt/Hexanes). **$[\alpha]_D^{25}$** = –3.0 (c = 1.07, $CHCl_3$). **M.p.** = 62-65 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 6.19 (s, 2H, H-4, H-6), 4.75 (q, *J* = 6.8 Hz, 2H, H-2'), 3.75 (s, 6H, Me), 2.25 (s, 3H, Me-5), 1.68 (d, *J* = 6.8 Hz, 6H, Me-2'). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 172.4 (C=O), 158.1 (C-1, C-3), 140.3 (C-5), 108.3 (C-4, C-6), 76.9 (C-2), 74.3 (C-2'), 52.5 (Me), 22.0 (Me-4), 18.8 (Me-2'). **ESI-TOF** $[2M+Na]^+$ calc for $C_{30}H_{38}I_2NaO_{12}$: 867,0345, found: 867,0347. **FT-IR (ATR)** ν in cm^{-1}: 2992, 2951, 1752, 1727, 1575, 1442, 1238, 1130, 1107, 1072.

Di-*tert*-butyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))-(2*R*,2'*R*)-dipropionate (264a).

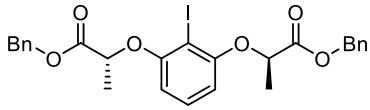


264a

The title compound was synthesised following the general procedure for chiral aryliodide preparation starting from 2-iodobenzene-1,3-diol (1.4 g, 6.1 mmol), Ph_3P (3.7 g, 13.9 mmol), *tert*-butyl-(*S*)-lactate (1.9 g, 12.7 mmol) and DIAD (2.7 mL, 13.9 mmol). The crude was purified by column chromatography (2:98 AcOEt/hexanes) to afford 1.2 g (41% yield) of chiral aryliodide precursor **264a** as a sticky colourless solid.

R_f = 0.60 (30:70 AcOEt/Hexanes). **$[\alpha]_D^{25}$** = –28.8 (c = 1.09, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 7.07 (t, *J* = 8.3 Hz, 1H, H-5), 6.31 (d, *J* = 8.3 Hz, 2H, H-4, H-6), 4.60 (q, *J* = 6.8 Hz, 2H, H-2'), 1.60 (d, *J* = 6.8 Hz, 6H, Me-2'), 1.37 (s, 18H, CH_3-^{t}Bu). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 170.7 (C=O), 158.2 (C-1, C-3), 129.2 (C-5), 106.4 (C-4, C-6), 81.8 (C-^{t}Bu), 80.3 (C-2), 74.3 (C-2'), 27.8 (CH_3-^{t}Bu), 18.4 (Me-2'). **ESI-TOF** $[2M+Na]^+$ calc for $C_{40}H_{58}I_2NaO_{12}$: 1007,1910, found: 1007,1912. **FT-IR (ATR)** ν in cm^{-1}: 2978, 2935, 1727, 1582, 1456, 1370, 1297, 1236, 1163, 1128, 1095, 1062, 1017.

Dibenzyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))-(2*R*,2'*R*)-dipropionate (265a).

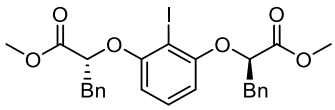


265a

The title compound was synthesised following the general procedure for chiral aryliodide preparation starting from 2-iodobenzene-1,3-diol (2.0 g, 8.5 mmol), Ph_3P (5.1 g, 19.5 mmol), benzyl-(*S*)-lactate (3.2 g, 17.8 mmol) and DIAD (3.8 mL, 19.5 mmol). The crude was purified by column chromatography (5:95 AcOEt/hexanes) to afford 4.4 g (93% yield) of chiral aryliodide precursor **265a** as a sticky colourless solid.

R_f = 0.22 (10:90 AcOEt/Hexanes). **$[\alpha]_D^{25}$** = –34.4 (c = 1.00, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 7.36-7.27 (m, 10H, Bn), 7.01 (t, *J* = 8.3 Hz, 1H, H-5), 6.31 (d, *J* = 8.3 Hz, 2H, H-4, H-6), 5.18 (d, *J* = 2.1 Hz, 4H, CH_2-Bn), 4.80 (q, *J* = 6.8 Hz, 2H, H-2'), 1.71 (d, *J* = 6.8 Hz, 6H, Me-2'). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 171.6 (C=O), 158.3 (C-1, C-3), 135.4 (Bn), 129.6 (C-5), 128.7, 128.5, 128.3 (Bn), 107.1 (C-4, C-6), 80.8 (C-2), 74.3 (C-2'), 67.0 (CH_2-Bn), 18.7 (Me-2'). **ESI-TOF** $[2M+Na]^+$ calc for $C_{52}H_{50}I_2NaO_{12}$: 1143,1284, found: 1143,1280. **FT-IR (ATR)** ν in cm^{-1}: 2945, 1732, 1585, 1456, 1383, 1270, 1253, 1180, 1130, 1106, 1065, 1019.

Dimethyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))-(2*R*,2'*R*)-bis(3-phenyl propanoate) (266a).

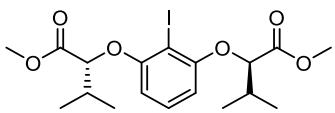


266a

The title compound was synthesised following the general procedure for chiral aryliodide preparation starting from 2-iodobenzene-1,3-diol (2.0 g, 8.5 mmol), Ph_3P (5.1 g, 19.5 mmol), methyl (2*S*)-2-hydroxy-3-phenylpropanoate (3.2 g, 17.8 mmol) and DIAD (3.8 mL, 19.5 mmol). The crude was purified by column chromatography (7:93 AcOEt/hexanes) to afford 2.2 g (46% yield) of chiral aryliodide precursor **266a** as a white solid.

R_f = 0.27 (20:80 AcOEt/Hexanes). **$[\alpha]_D^{25}$** = +66.4 (c = 1.09, $CHCl_3$). **M.p.** = 104-110 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 7.44-7.41 (m, 4H, Bn), 7.33-7.23 (m, 6H, Bn), 7.04 (t, *J* = 8.3 Hz, 1H, H-5), 6.22 (d, *J* = 8.3 Hz, 2H, H-4, H-6), 4.82 (dd, *J* = 8.0, 4.5 Hz, 2H, H-2'), 3.67 (s, 6H, Me), 3.36 (dd, *J* = 14.0, 8.0 Hz, 2H, $(CH_2)_a$-Bn), 3.29 (dd, *J* = 14.0, 4.5 Hz, 2H, $(CH_2)_b$-Bn). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 171.1 (C=O), 158.2 (C-1, C-3), 136.2, 130.0 (Bn), 129.6 (C-5), 128.5, 127.2 (Bn), 106.0 (C-4, C-6), 79.5 (C-2), 79.0 (C-2'), 52.5 (Me), 39.3 (CH_2-Bn). **ESI-TOF** $[2M+Na]^+$ calc for $C_{52}H_{50}I_2NaO_{12}$: 1143,1284, found: 1143,1279. **FT-IR (ATR)** ν in cm^{-1}: 2950, 1753, 1729, 1589, 1461, 1433, 1290, 1246, 1196, 1099, 1023, 1000.

Dimethyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))-(2*R*,2'*R*)-bis(3-methyl butanoate) (267a).



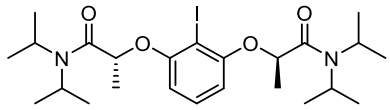
267a

The title compound was synthesised following the general procedure for chiral aryliodide preparation starting from 2-iodobenzene-1,3-diol (850.4 mg, 3.6 mmol), Ph_3P (2.2 g, 8.3 mmol), methyl (2*S*)-2-hydroxy-3-methylbutanoate (1.0 g, 7.6 mmol) and DIAD (1.6 mL, 8.3 mmol). The crude was purified by column chromatography

(5:95 to 6:94 AcOEt/hexanes) to afford 539.1 mg (32% yield) of chiral aryliodide precursor **267a** as a colourless oil.

R_f = 0.56 (20:80 AcOEt/Hexanes) **$[\alpha]_D^{25}$** = +6.9 (c = 1.03, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 7.11 (t, *J* = 8.3 Hz, 1H, H-5), 6.24 (d, *J* = 8.3 Hz, 2H, H-4, H-6), 4.44 (d, *J* = 4.8 Hz, 2H, H-2'), 3.73 (s, 6H, Me), 2.41-2.29 (m, 2H, CH-^{i}Pr), 1.17 (d, *J* = 6.9 Hz, 6H, CH_3-^{i}Pr), 1.13 (d, *J* = 6.9 Hz, 6H, CH_3-^{i}Pr). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 171.4 (C=O), 158.3 (C-1, C-3), 129.7 (C-5), 105.3 (C-4, C-6), 82.4 (C-2'), 79.1 (C-2), 52.2 (Me), 32.1 (CH-^{i}Pr), 19.2, 17.8 (CH_3-^{i}Pr). **ESI-TOF** $[2M+Na]^+$ calc for $C_{36}H_{50}I_2NaO_{12}$: 951,1284, found: 951,1281. **FT-IR (ATR)** ν in cm^{-1}: 2965, 1753, 1734, 1586, 1459, 1248, 1202, 1134, 1078, 1020.

(2*R*,2'*R*)-2,2'-((2-Iodo-1,3-phenylene)bis(oxy))-bis(*N*,*N*-diisopropyl propanamide) (268a).



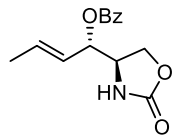
268a

According to a reported procedure,[108b] to a suspension of iodoarene (2*R*,2'*R*)-2,2'-(2-iodo-1,3-phenylene)bis(oxy)dipropanoic acid (165.0 mg, 0.4 mmol) in CH_2Cl_2 (1.9 mL) and catalytic amounts of DMF (1 drop) under argon atmosphere, oxalyl chloride (0.29 mL, 3.5 mmol) was added and the mixture was stirred overnight at room temperature. The solvent was next removed under reduced pressure and the residue was re-dissolved in CH_2Cl_2 (1.1 mL) at 0 ºC under argon atmosphere. Then, diisopropylamine (0.11 mL, 0.8 mmol) and triethylamine (0.22 mL, 1.6 mmol) were subsequently added and the final mixture was stirred overnight at room temperature. After completion, the reaction was poured into HCl aqueous solution (1M) and extracted with brine and CH_2Cl_2. The organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by column chromatography (20:80 AcOEt/hexanes) to afford 80.8 mg (34% yield) of chiral aryliodide precursor **268a** as a white solid.

R_f = 0.25 (20:80 AcOEt/Hexanes). **$[\alpha]_D^{25}$** = –136.2 (c = 1.03, $CHCl_3$). **M.p.** = 135-139 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 7.11 (t, *J* = 8.4 Hz, 1H, H-

5), 6.50 (d, *J* = 8.4 Hz, 2H, H-4, H-6), 4.81 (q, *J* = 6.9 Hz, 2H, H-2'), 4.52 (septet, *J* = 6.6 Hz, 2H, CH-^{i}Pr), 3.28 (septet, *J* = 6.8 Hz, 2H, CH-^{i}Pr), 1.65 (d, *J* = 6.9 Hz, 6H, Me-2'), 1.39 (d, *J* = 6.8 Hz, 6H, CH_3-^{i}Pr), 1.27 (d, *J* = 6.8 Hz, 6H, CH_3-^{i}Pr), 1.17 (d, *J* = 6.6 Hz, 6H, CH_3-^{i}Pr), 0.89 (d, *J* = 6.6 Hz, 6H, CH_3-^{i}Pr). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 169.6 (C=O), 157.8 (C-1, C-3), 130.0 (C-5), 106.0 (C-4, C-6), 78.6 (C-2), 78.0 (C-2'), 47.7, 46.5 (CH-^{i}Pr), 21.0, 20.7, 20.6, 20.0 (CH_3-^{i}Pr), 18.0 (Me-2'). **ESI-TOF** $[M+H]^+$ calc for $C_{24}H_{40}IN_2O_4$: 547,2027, found: 547,2038. **FT-IR (ATR)** ν in cm^{-1}: 2962, 1626, 1458, 1374, 1340, 1251, 1092.

***u*-4-[(*E*)-1-Benzoyloxybut-2-en-1-yl]-oxazolidin-2-one ((±)-274a).**

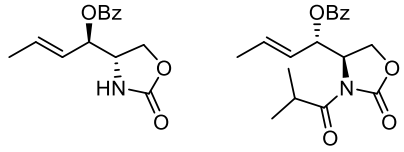


(±)-274a

To a solution of alcohol **(±)-188** (564.6 mg, 3.6 mmol) in anhydrous pyridine (10.6 ml) and dichloromethane (31.8 ml) at 0ºC, freshly distilled benzoyl chloride (0.75 ml, 6.5 mmol) was added. The reaction mixture was then allowed to warm to room temperature, stirred for 3 hours and poured into a saturated aqueous $CuSO_4$ solution. The organic layer was washed several times with the $CuSO_4$ solution. Finally, the combined organic phases were washed with brine and dried over Na_2SO_4. Purification was effected by column chromatography (30:70 to 50:50 AcOEt/hexanes) to afford 863.5 mg (92% yield) of benzoylated compound **(±)-274a** as a colourless syrup.

R_f = 0.20 (50:50 AcOEt/Hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 8.02 (dd, *J* = 8.4, 1.4 Hz, 2H, Ar), 7.56 (tt, *J* = 7.5, 1.4 Hz, 1H, Ar), 7.43 (t, *J* = 7.7 Hz, 2H, Ar), 6.37 (brs, 1H, NH), 6.02-5.91 (m, 1H, H-3'), 5.51-5.43 (m, 2H, H-2', H-1'), 4.47 (t, *J* = 8.9 Hz, 1H, H-5_a), 4.34 (dd, *J* = 9.0, 4.8 Hz, 1H, H-5_b), 4.11-4.07 (m, 1H, H-4), 1.74 (dd, *J* = 6.6, 1.1 Hz, 3H, H-4'). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 165.6 (C=O), 160.1 (C=O), 134.1 (C-3'), 133.5 (Ar), 129.8 (Ar), 128.6 (Ar), 128.5 (Ar), 123.5 (C-2'), 75.4 (C-1'), 66.4 (C-5), 54.9 (C-4), 18.1 (C-4'). **ESI-TOF** $[M+Na]^+$ calc for $C_{14}H_{15}NNaO_4$: 284.0893, found: 284. 0845. **FT-IR (ATR)** ν in cm^{-1}: 3292, 2922, 2853, 1754, 1720, 1267, 1109, 712.

(*S*)-4-[(1*R*,2*E*)-1-Benzoyloxybut-2-en-1-yl]-oxazolidin-2-one ((*S,R*)-274a) and (*R*)-4-[(1*S*,2*E*)-1-benzoyloxybut-2-en-1-yl]-3-isobutyryloxazolidin-2-one ((*R,S*)-275a).



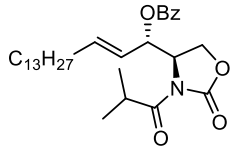
(*S*,*R*)-274a **(*R*,*S*)-275a**

Oxazolidinones **(*S,R*)-274a** and **(*R,S*)-275a** were synthesised from compound **(±)-274a** (52.3 mg, 0.2 mmol) following the general method for the (*R*)-BTM-catalysed kinetic resolution of oxazolidinones. The reaction mixture was stirred for 4 h and purified by column chromatography (30:70 to 50:50 AcOEt/Hexanes) to afford 25.5 mg (49% yield and 73% ee) of compound **(*S,R*)-274a** and 27.8 mg (42% yield and 96% ee) of compound **(*R,S*)-275a** as a colourless oils.

Compound (*S,R*)-274a: **HPLC** Chiralpak IC column (80:20 hexanes:ethanol, 1.0 mL/min, 220 nm); major enantiomer t_r = 16.83 min, minor enantiomer t_r = 15.12 min, 73% ee.

Compound (*R,S*)-275a: $\mathbf{R}_f$ = 0.20 (50:50 AcOEt/Hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 8.00 (dd, *J* = 8.4, 1.4 Hz, 2H, Ar), 7.58 (tt, *J* = 7.4, 1.4 Hz, 1H, Ar), 7.45 (t, *J* = 7.7 Hz, 2H, Ar), 5.99-5.89 (m, 2H, H-3', H-1'), 5.46 (ddq, *J* = 15.2, 6.2, 1.6 Hz, 1H, H-2'), 4.71 (ddd, *J* = 8.8, 2.9, 2.4 Hz, 1H, H-4), 4.61 (dd, *J* = 9.1, 2.9 Hz, 1H, H-5_a), 4.40 (t, *J* = 9.0 Hz, 1H, H-5_b), 3.66 (septet, *J* = 6.8 Hz, 1H, CH ^{i}Pr), 1.74 (dd, *J* = 6.6, 1.6 Hz, 3H, H-4'), 1.14 (d, *J* = 6.8 Hz, 3H, CH_3 ^{i}Pr), 1.08 (d, *J* = 6.8 Hz, 3H, CH_3 ^{i}Pr). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 177.6 (C=O), 165.4 (C=O), 153.1 (C=O), 133.6 (Ar), 132.1 (C-3'), 129.8 (Ar), 129.4 (Ar), 128.8 (Ar), 124.0 (C-2'), 72.1 (C-1'), 62.8 (C-5), 56.4 (C-4), 32.7 (CH ^{i}Pr), 19.4 (CH_3 ^{i}Pr), 18.4 (CH_3 ^{i}Pr), 18.1 (C-4'). **ESI-TOF** $[M+Na]^+$ calc for $C_{18}H_{21}NNaO_5$: 354.1312, found: 354.1321. **FT-IR (ATR)** ν in cm^{-1}: 2919, 1780, 1724, 1701, 1388, 1266, 1201, 1097. **HPLC** Chiralpak OD-H column (90:10 hexanes:ethanol, 1.0 mL/min, 220 nm); major enantiomer t_r = 10.14 min, minor enantiomer t_r = 8.81 min, 96% ee.

(*R*)-4-[(1*S*,2*E*)-1-benzoyloxyhexadeca-2-en-1-yl]-3-isobutyryloxazolidin-2-one ((*R,S*)-277).

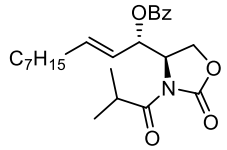


(*R*,*S*)-277

Compound **(*R,S*)-277** was synthesised following the cross metathesis general procedure starting from alkenyl oxazolidinone **(*R,S*)-275a** (36.3 mg, 0.11 mmol) and commercially available 1-pentadecene (35.7 μL, 0.13 mmol). The crude was purified by column chromatography (hexanes to 5:95 AcOEt/hexanes) to afford 50.9 mg (93% yield, *E*:*Z* = 89:11) of oxazolidinone **(*R,S*)-277** as a colourless oil.

R_f = 0.86 (25:75 AcOEt/Hexanes). **$[\alpha]_D^{25}$** = +67.4 (c = 1.15, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 8.00 (dd, *J* = 8.4, 1.4 Hz, 2H, Ar), 7.58 (tt, *J* = 7.5, 1.4 Hz, 1H, Ar), 7.45 (t, *J* = 7.6 Hz, 2H, Ar), 5.99 (ddd, *J* = 5.9, 2.2, 1.3 Hz, 1H, H-1'), 5.91 (dtd, *J* = 15.5, 6.9, 1.3 Hz, 1H, H-3'), 5.42 (ddt, *J* = 15.5, 5.9, 1.5 Hz, 1H, H-2'), 4.72 (ddd, *J* = 8.8, 2.9, 2.2 Hz, 1H, H-4), 4.61 (dd, *J* = 9.1, 2.9 Hz, 1H, H-5_a), 4.39 (t, *J* = 9.0 Hz, 1H, H-5_b), 3.66 (septet, *J* = 6.8 Hz, 1H, CH ^{i}Pr), 2.06 (q, *J* = 6.9 Hz, 2H, H-4'), 1.37-1.24 (m, 22H, H-5'-H-15'), 1.14 (d, *J* = 6.8 Hz, 3H, CH_3 ^{i}Pr), 1.08 (d, *J* = 6.8 Hz, 3H, CH_3 ^{i}Pr), 0.88 (t, *J* = 6.9 Hz, 3H, H-16'). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 177.6 (C=O), 165.4 (C=O), 153.1 (C=O), 137.4 (C-3'), 133.6 (Ar), 129.8 (Ar), 129.5 (Ar), 128.8 (Ar), 122.5 (C-2'), 72.1 (C-1'), 62.8 (C-5), 56.5 (C-4), 32.7 (C-5'-C-15'), 32.5 (CH ^{i}Pr), 32.1 (C-4'), 29.8, 29.8, 29.8, 29.8, 29.7, 29.5, 29.5, 29.3, 28.9, 22.8 (C-5'-C-15'), 19.4 (CH_3 ^{i}Pr), 18.4 (CH_3 ^{i}Pr), 14.3 (C-16'). **ESI-TOF** $[M+Na]^+$ calc for $C_{30}H_{45}NNaO_5$: 522.3190, found: 522.3190. **FT-IR (ATR)** ν in cm^{-1}: 2922, 2853, 1781, 1708, 1480, 1462, 1385, 1320, 1281, 1235, 1194, 1152, 1087, 969, 803, 759, 688, 666.

(*R*)-4-[(1*S*,2*E*)-1-benzoyloxydeca-2-en-1-yl]-3-isobutyryloxazolidin-2-one ((*R,S*)-278).

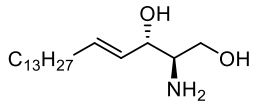


(*R,S*)-278

Compound **(*R,S*)-278** was synthesised following the cross metathesis general procedure starting from alkenyl oxazolidinone **(*R,S*)-275a** (8.0 mg, 0.024 mmol) and commercially available 1-nonene (5.0 μL, 0.029 mmol). After 24 h, TLC showed uncomplete consumption of the starting material. Then, additional amounts of 1-nonene (5.0 μL, 0.029 mmol) and Grubbs catalyst 2nd generation (1.0 mg, 0.001 mmol) were added and the reaction mixture was stirred for another 24 h. The crude was purified by column chromatography (hexanes to 8:92 AcOEt/hexanes) to afford 9.0 mg (90% yield, *E*:*Z* = 84:16) of oxazolidinone **(*R,S*)-278** as a colourless oil.

R*f* = 0.26 (10:90 AcOEt/Hexanes). **[α]D25** = +72.9 (c = 0.90, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 8.00 (dd, *J* = 8.4, 1.4 Hz, 2H, Ar), 7.58 (tt, *J* = 7.5, 1.4 Hz, 1H, Ar), 7.45 (t, *J* = 7.7 Hz, 2H, Ar), 5.99 (ddd, *J* = 5.9, 2.1, 1.2 Hz, 1H, H-1'), 5.91 (dtd, *J* = 15.4, 6.9, 1.2 Hz, 1H, H-3'), 5.42 (ddt, *J* = 15.4, 5.9, 1.5 Hz, 1H, H-2'), 4.72 (ddd, *J* = 8.9, 2.9, 2.1 Hz, 1H, H-4), 4.61 (dd, *J* = 9.1, 2.9 Hz, 1H, H-5_a), 4.39 (t, *J* = 9.0 Hz, 1H, H-5_b), 3.66 (septet, *J* = 6.8 Hz, 1H, CH ^{i}Pr), 2.06 (q, *J* = 6.9 Hz, 2H, H-4'), 1.39-1.21 (m, 10H, H-5'-H-9'), 1.14 (d, *J* = 6.8 Hz, 3H, CH_3 ^{i}Pr), 1.08 (d, *J* = 6.8 Hz, 3H, CH_3 ^{i}Pr), 0.86 (t, *J* = 6.9 Hz, 3H, H-10'). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 177.6 (C=O), 165.4 (C=O), 153.1 (C=O), 137.3 (C-3'), 133.6 (Ar), 129.8 (Ar), 129.5 (Ar), 128.8 (Ar), 122.6 (C-2'), 72.1 (C-1'), 62.8 (C-5), 56.5 (C-4), 32.7 (CH ^{i}Pr), 32.5 (C-4'), 31.9, 29.2, 29.2, 28.8, 22.8 (C-5'-C-9'), 19.4 (CH_3 ^{i}Pr), 18.4 (CH_3 ^{i}Pr), 14.2 (C-10'). **ESI-TOF** $[M+Na]^+$ calc for $C_{24}H_{33}NNaO_5$: 438.2251, found: 438.2242. **FT-IR (ATR)** ν in cm^{-1}: 2925, 2854, 1782, 1725, 1703, 1387, 1264, 1238, 1200, 1094, 1068, 1026, 982.

(2*R*,3*S*,4*E*)-2-aminooctadec-4-ene-1,3-diol ((*R*,*S*)-279).[80,145]



(*R*,*S*)-279

To a solution of acylated oxazolidinone **(*R*,*S*)-277** (22.5 mg, 0.05 mmol) in THF (130 μL) and H_2O (45 μL), solid $NaBH_4$ (6.8 mg, 0.18 mmol) was added at a rate that maintains the internal temperature between 20-25ºC. The resulting mixture was stirred at room temperature until complete consumption of the starting material was observed by TLC. Then, the reaction was quenched with a 2N HCl aqueous solution. The aqueous phase was extracted with AcOEt and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Crude was next dissolved in a mixture of dioxane (1.9 mL) and H_2O (1.2 mL), solid $Ba(OH)_2 \cdot 8H_2O$ (42.6 mg, 0.13 mmol) was subsequently added and the reaction was refluxed overnight. Then, the mixture was left to cool to room temperature, filtered and concentrated under vacuum. Finally, the crude was purified by column chromatography (94:6:1 $CH_2Cl_2/CH_3OH/NH_4OH$) to afford 6.9 mg (46% yield) of L-*erythro*-sphingosine **(*R*,*S*)-279** as a white solid. Spectroscopy data for compound **(*R*,*S*)-279** were in agreement with those available at the literature.[138d,146]

R_f = 0.11 (94:6:1 $CH_2Cl_2/CH_3OH/NH_4OH$). **$[\alpha]_D^{25}$** = +1.9 (c = 0.58, $CHCl_3$). **^{1}H NMR** (400 MHz, CD_3OD, δ in ppm): δ = 5.74 (dt, *J* = 15.2, 6.7 Hz, 1H, H-5), 5.49 (dd, *J* = 15.2, 7.4 Hz, 1H, H-4), 3.97 (t, *J* = 6.7 Hz, 1H, H-3), 3.68 (dd, *J* = 10.9, 4.5 Hz, 1H, H-1_a), 3.49 (dd, *J* = 10.9, 6.7 Hz, 1H, H-1_b), 2.75 (td, *J* = 6.7, 4.5 Hz, 1H, H-2), 2.09 (q, *J* = 6.7 Hz, 2H, H-6), 1.44-1.29 (m, 22H, H-7-H-17), 0.90 (t, *J* = 6.9 Hz, 3H, H-18). **^{13}C NMR** (100 MHz, CD_3OD, δ in ppm): δ = 135.3 (C-5), 130.8 (C-4), 75.1 (C-3), 64.3 (C-1), 58.0 (C-2), 33.5, 33.1, 30.8, 30.8, 30.8, 30.7, 30.5, 30.4, 30.4, 23.8 (C-6-C-17), 14.5 (C-18). **ESI-TOF** $[M+H]^+$ calc for $C_{18}H_{38}NO_2$: 300.2897, found: 300.2913.

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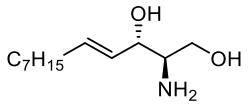
145 C. Palomo, M. Oiarbide, F. Dias, A. Ortiz, A. Linden, *J. Am. Chem. Soc.* **2001**, *123*, 5602–5603.

146 S. Kim, S. Lee, T. Lee, H. Ko, D. Kim, *J. Org. Chem.* **2006**, *71*, 8661–8664.

(2*R*,3*S*,4*E*)-2-aminododec-4-ene-1,3-diol ((*R,S*)-280).[80,145]



(*R,S*)-280

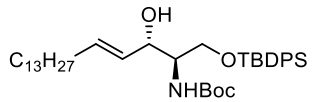
To a solution of acylated oxazolidinone **(*R,S*)-278** (8.6 mg, 0.021 mmol) in THF (70 μL) and H_2O (21 μL), solid $NaBH_4$ (3.1 mg, 0.083 mmol) was added at a rate that maintains the internal temperature between 20-25ºC. The resulting mixture was stirred at room temperature until complete consumption of the starting material was observed by TLC. Then, the reaction was quenched with a 2N HCl aqueous solution. The aqueous phase was extracted with AcOEt and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Crude was next dissolved in a mixture of dioxane (0.8 mL) and H_2O (0.6 mL), solid $Ba(OH)_2 \cdot 8H_2O$ (19.6 mg, 0.062 mmol) was subsequently added and the reaction was refluxed overnight. Then, the mixture was left to cool to room temperature, filtered and concentrated under vacuum. Finally, the crude was purified by column chromatography (94:6:1 $CH_2Cl_2/CH_3OH/NH_4OH$) to afford 2.7 mg (60% yield) of compound **(*R,S*)-280** as a colourless oil.

R_f = 0.09 (94:6:1 $CH_2Cl_2/CH_3OH/NH_4OH$). **$[\alpha]_D^{25}$** = +1.4 (c = 0.18, $CHCl_3$). **^{1}H NMR** (400 MHz, CD_3OD, δ in ppm): δ = 5.75 (dt, *J* = 15.2, 6.7 Hz, 1H, H-5), 5.49 (dd, *J* = 15.2, 7.4 Hz, 1H, H-4), 4.00 (t, *J* = 6.6 Hz, 1H, H-3), 3.68 (dd, *J* = 10.9, 4.4 Hz, 1H, H-1_a), 3.50 (dd, *J* = 10.9, 7.0 Hz, 1H, H-1_b), 2.79 (ddd, *J* = 7.0, 6.0, 4.4 Hz, 1H, H-2), 2.09 (q, *J* = 6.7 Hz, 2H, H-6), 1.44-1.28 (m, 10H, H-7-H-11), 0.90 (t, *J* = 7.0 Hz, 3H, H-12). **^{13}C NMR** (100 MHz, CD_3OD, δ in ppm): δ = 135.4 (C-5), 130.6 (C-4), 74.7 (C-3), 63.9 (C-1), 58.0 (C-2), 33.4, 33.0, 30.4, 30.3, 30.3, 23.7 (C-6-C11), 14.4 (C-12). **ESI-TOF** $[M+H]^+$ calc for $C_{12}H_{26}NO_2$: 216.1958, found: 216.1953. **FT-IR (ATR)** ν in cm^{-1}: 3355, 2924, 2858, 1457, 1020.

Determination of absolute configuration of compound (*R,S*)-279.

Absolute configuration of compound **(*R,S*)-279** was assigned by comparison of HPLC traces recorded under identical conditions of derivatives **(*R,S*)-281** and **(*S,R*)-281** obtained from **(*R,S*)-279** and natural D-*erythro*-sphingosine respectively.

(2*R*,3*S*,4*E*)-1-(*tert*-Butyldiphenylsilyloxy)-2-(*N*-*tert*-butyloxycarbonyl) amino-octadec-4-ene-3-ol ((*R*,*S*)-281).[147,148]



(*R*,*S*)-281

To a solution of L-*erythro*-sphingosine **(*R,S*)-279** (4.0 mg, 0.013 mmol) in a 9:1 mixture of dioxane/H_2O (0.2 mL) and Et_3N (2 μL), di-*tert*-butyl dicarbonate (4 μL, 0.016 mmol) was slowly added. After overnight stirring at room temperature, solvent was removed under vacuum and co-evaporated with Et_2O. The so obtained Boc-derivative was next dissolved in CH_2Cl_2 (0.4 mL) and imidazole (3.6 mg, 0.053 mmol) and TBDPSCl (7 μL, 0.027 mmol) were subsequently added. The reaction mixture was stirred at room temperature for 3 h and finally concentrated under reduced pressure. The crude was purified by column chromatography (5:95 AcOEt/Hexanes) to afford 4.2 mg (51% yield) of compound **(*R,S*)-281** as a colourless oil.

R_f = 0.36 (10:90 AcOEt/Hexanes). **$[\alpha]_D^{25}$** = –13.7 (c = 0.09, $CHCl_3$). **^{1}H NMR** (400 MHz, $CHCl_3$, δ in ppm): δ = 7.66-7.62 (m, 4H, Ar), 7.47-7.36 (m, 6H, Ar), 5.78 (dt, *J* = 15.3, 7.0 Hz, 1H, H-5), 5.48 (dd, *J* = 15.3, 5.9 Hz, 1H, H-4), 5.21 (d, *J* = 8.4 Hz, 1H, NH/OH), 4.24 (q, *J* = 5.9 Hz, 1H, H-3), 3.90 (dd, *J* = 10.5, 3.6 Hz, 1H, H-1_a), 3.75 (dd, *J* = 10.5, 3.2 Hz, 1H, H-1_b), 3.67-3.64 (m, 1H, H-2), 3.20 (d, *J* = 7.6 Hz, 1H, NH/OH), 2.03 (q, *J* = 7.0 Hz, 2H, H-6), 1.45 (s, 9H, CH_3 *t*Bu), 1.37-1.25 (m, 22H, H-7-H-17), 1.06 (s, 9H, CH_3 *t*Bu), 0.88 (t, *J* = 6.9 Hz, 3H, H-18). **^{13}C NMR** (100 MHz, $CHCl_3$, δ in ppm): δ = 156.0 (C=O), 135.7 (Ar), 133.5 (C-5), 132.7 (Ar), 130.1 (Ar), 129.2 (C-4), 128.0 (Ar), 79.6 (C *t*Bu), 77.4 (C *t*Bu), 74.5 (C-3), 64.3 (C-1), 55.1 (C-2), 32.5, 32.1, 29.9, 29.8, 29.8, 29.8, 29.7, 29.5, 29.4, 29.3 (C-6-C-17), 28.5 (CH_3 *t*Bu), 27.0 (CH_3 *t*Bu), 22.9, 19.3 (C-6-C-17), 14.3 (C-18). **ESI-TOF** $[M+Na]^+$ calc for $C_{39}H_{63}NNaO_4Si$: 660.4419, found: 660.4419. **FT-IR (ATR)** ν in cm^{-1}: 3442, 2925, 2854, 2361, 2341, 1717, 1112. **HPLC** Chiralpak OD-H column (90:10 hexanes:isopropanol, 0.6 mL/min, 220 nm); major enantiomer t_r = 5.27 min, minor enantiomer t_r = 6.63 min, 89% ee.

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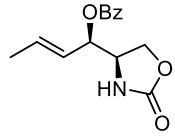
147 A. Tarnowski, O. Retz, T. Bär, R. R. Schmidt, *Eur. J. Org. Chem.* **2005**, 1129–1141.

148 R. S. Lankalapalli, A. Ouro, L. Arana, A. Gómez-Muñoz, R. Bittman, *J. Org. Chem.* **2009**, *74*, 8844–8847.

An identical synthetic strategy was carried out using racemic sphingosine and D-*erythro*-sphingosine as starting materials to generate **(±)-281** and **(*S*,*R*)-281** derivatives respectively. Comparison of HPLC traces of racemic derivate with compounds **(*R*,*S*)-281** and **(*S*,*R*)-281** proved that the application of tandem (*R*)-BTM catalysed kinetic resolution/cross-metathesis protocol to racemic oxazolidinone **(±)-274a** afforded synthetic sphingosine **(*R*,*S*)-279** with the opposite configuration than the natural occurring product.

***I*-4-[(*E*)-1-Benzoyloxybut-2-en-1-yl]-oxazolidin-2-one ((±)-282).**

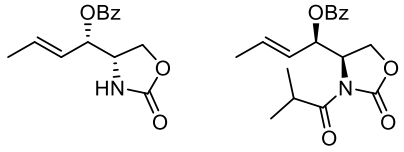


(±)-282

To a solution of alcohol **(±)-209** (27.2 mg, 0.17 mmol) in anhydrous pyridine (0.5 ml) and dichloromethane (1.5 ml) at 0ºC, freshly distilled benzoyl chloride (24.0 µl, 0.21 mmol) was added. The reaction mixture was then allowed to warm to room temperature, stirred for 3 hours and poured into a saturated aqueous $CuSO_4$ solution. The organic layer was washed several times with the $CuSO_4$ solution. Finally, the combined organic phases were washed with brine and dried over Na_2SO_4. Purification was effected by column chromatography (50:50 AcOEt/hexanes) to afford 18.9 mg (43% yield) of benzoylated compound **(±)-282** as a colourless syrup.

R_f = 0.75 (AcOEt). **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 8.02 (dd, *J* = 8.4, 1.4 Hz, 2H, Ar), 7.58 (tt, *J* = 7.5, 1.4 Hz, 1H, Ar), 7.44 (t, *J* = 7.7 Hz, 2H, Ar), 6.03-5.95 (m, 2H, NH, H-3'), 5.49-5.41 (m, 2H, H-2', H-1'), 4.46 (t, *J* = 8.9 Hz, 1H, H-5_a), 4.25 (dd, *J* = 9.1, 4.6 Hz, 1H, H-5_b), 4.12-4.08 (m, 1H, H-4), 1.74 (dd, *J* = 6.7, 1.1 Hz, 3H, H-4'). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 165.6 (C=O), 159.4 (C=O), 133.9 (C-3'), 133.6 (Ar), 129.8 (Ar), 129.6 (Ar), 128.7 (Ar), 123.9 (C-2'), 75.9 (C-1'), 66.6 (C-5), 54.8 (C-4), 18.2 (C-4'). **ESI-TOF** $[M+Na]^+$ calc for $C_{14}H_{15}NNaO_4$: 284.0893, found: 284.0882. **FT-IR (ATR)** ν in cm^{-1}: 3265, 2918, 1749, 1715, 1450, 1406, 1315, 1261, 1108, 1068, 1025.

(*S*)-4-[(1*S*,2*E*)-1-Benzoyloxybut-2-en-1-yl]-oxazolidin-2-one ((*S*,*S*)-282) and (*R*)-4-[(1*R*,2*E*)-1-benzoyloxybut-2-en-1-yl]-3-isobutyryloxazolidin-2-one ((*R*,*R*)-283).



(*S*,*S*)-282 **(*R*,*R*)-283**

Oxazolidinones **(*S*,*S*)-282** and **(*R*,*R*)-283** were synthesised from compound **(±)-282** (19.7 mg, 0.08 mmol) following the general method for the (*R*)-BTM-catalysed kinetic resolution of oxazolidinones. The reaction mixture was stirred for 10 h and purified by column chromatography (10:90 to 50:50 AcOEt/Hexanes) to afford 7.8 mg (40% yield and 61% ee) of compound **(*S*,*S*)-282** and 9.6 mg (39% yield and 85% ee) of compound **(*R*,*R*)-283** as a colourless oils.

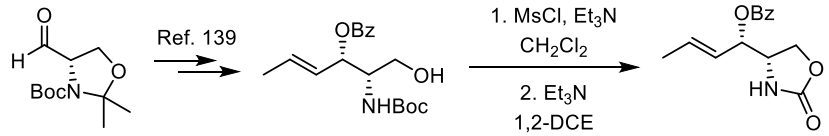
Compound (*S*,*S*)-282: $[\alpha]_D^{25}$ = +79.1 (c = 0.61, $CHCl_3$). **HPLC** Chiralpak OD-H column (75:25 hexanes:isopropanol, 1.0 mL/min, 230 nm); major enantiomer t_r = 8.47 min, minor enantiomer t_r = 12.77 min, 61% ee.

Compound (*R*,*R*)-283: R_f = 0.83 (50:50 AcOEt/Hexanes). $[\alpha]_D^{25}$ = +16.1 (c = 0.81, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 8.00 (dd, *J* = 8.4, 1.4 Hz, 2H, Ar), 7.58 (tt, *J* = 7.5, 1.4 Hz, 1H, Ar), 7.45 (t, *J* = 7.7 Hz, 2H, Ar), 5.93 (dq, *J* = 15.3, 6.6 Hz, 1H, H-3'), 5.87 (dd, *J* = 8.0, 4.8 Hz, 1H, H-1'), 5.49 (ddq, *J* = 15.3, 8.0, 1.6 Hz, 1H, H-2'), 4.85 (ddd, *J* = 8.2, 4.8, 2.6 Hz, 1H, H-4), 4.54 (dd, *J* = 9.4, 2.6 Hz, 1H, H-5_a), 4.40 (dd, *J* = 9.4, 8.2 Hz, 1H, H-5_b), 3.73 (septet, *J* = 6.8 Hz 1H, CH *i*Pr), 1.73 (dd, *J* = 6.6, 1.6 Hz, 3H, H-4'), 1.17 (d, *J* = 6.8 Hz, 3H, CH_3 *i*Pr), 1.16 (d, *J* = 6.8 Hz, 3H, CH_3 *i*Pr). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 177.3 (C=O), 165.0 (C=O), 153.2 (C=O), 135.0 (C-3'), 133.5 (Ar), 129.8 (Ar), 129.7 (Ar), 128.6 (Ar), 122.4 (C-2'), 72.9 (C-1'), 63.7 (C-5), 55.1 (C-4), 32.7 (CH *i*Pr), 19.7 (CH_3 *i*Pr), 18.4 (CH_3 *i*Pr), 18.2 (C-4'). **ESI-TOF** $[M+Na]^+$ calc for $C_{18}H_{21}NNaO_5$: 354.1312, found: 354.1324. **FT-IR (ATR)** ν in cm^{-1}: 2921, 1757, 1719, 1266, 1109, 1026. **HPLC** Chiralpak AD-H column (80:20 hexanes:isopropanol, 1.0 mL/min, 220 nm); major enantiomer t_r = 10.07 min, minor enantiomer t_r = 6.88 min, 85% ee.

Determination of absolute configuration of compound (*S,S*)-282.

Absolute configuration of compound **(*S,S*)-282** prepared by kinetic resolution of **(±)-282** was assigned by comparison of HPLC traces recorded under identical conditions with the product obtained from Garner's aldehyde, as shown below.

Synthesis of (*S*)-4-[(1*S*,2*E*)-1-Benzoyloxybut-2-en-1-yl]-oxazolidin-2-one ((*S,S*)-282) from Garner's Aldehyde.[139,140]

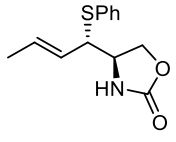


According to a reported procedure, to a solution of aminoalcohol **(*S,S*)-284** (6.0 mg, 0.018 mmol) in CH_2Cl_2 (0.2 mL) containing Et_3N (9 μL, 0.063 mmol), MsCl (2 μL, 0.027 mmol) was added dropwise. After stirring for 30 min at room temperature, the reaction mixture was quenched with H_2O and the organic phase was separated, dried over Na_2SO_4 and evaporated to dryness. The resulting crude was taken up in 1,2-DCE (0.2 mL), Et_3N (13 μL, 0.089 mmol) was next added dropwise and the reaction mixture was refluxed until TLC indicated the total formation of oxazolidinone **(*S,S*)-282**. Then, solvent was removed under reduced pressure and the crude was purified by column chromatography (30:70 AcOEt/Hexanes) to afford 3.7 mg (79% yield) of compound **(*S,S*)-282** as a colourless oil. Spectroscopy data for oxazolidinone **(*S,S*)-282** were in agreement with those previously reported in this experimental section.

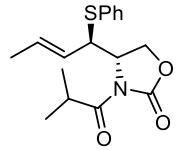
$[\alpha]_D^{25}$ = +0.9 (c = 0.21, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 8.03 (dd, *J* = 8.4, 1.4 Hz, 2H, Ar), 7.59 (tt, *J* = 7.5, 1.4 Hz, 1H, Ar), 7.46 (t, *J* = 7.7 Hz, 2H, Ar), 6.05-5.94 (m, 1H, H-3'), 5.48-5.41 (m, 2H, H-2', H-1'), 5.30 (brs, 1H, NH), 4.49 (t, *J* = 8.9 Hz, 1H, H-5_a), 4.26 (dd, *J* = 9.2, 4.6 Hz, 1H, H-5_b), 4.11 (dt, *J* = 8.8, 4.7 Hz, 1H, H-4), 1.76 (dd, *J* = 6.6, 1.0 Hz, 3H, H-4'). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 165.6 (C=O), 159.0 (C=O), 133.9 (C-3'), 133.7 (Ar), 129.9 (Ar), 129.5 (Ar), 128.7 (Ar), 123.9 (C-2'), 75.9 (C-1'), 66.6 (C-5), 54.7 (C-4), 18.2 (C-4'). **ESI-TOF** $[M+Na]^+$ calc for $C_{14}H_{15}NNaO_4$: 284.0893, found: 284.0900. **HPLC** Chiralpak OD-H column (75:25 hexanes:isopropanol, 1.0 mL/min, 230 nm); single enantiomer t_r = 8.48 min, >99% ee.

Comparison of HPLC traces of the racemic product with compounds **(*S,S*)-282** and **(*S,S*)-282** from Garner's aldehyde proved that both products present the same absolute configuration.

(*R*)-4-[(1*S*,2*E*)-1-phenylsulfanylbut-2-en-1-yl]-oxazolidin-2-one ((*R,S*)-193) and(*S*)-4-[(1*R*,2*E*)-1-phenylsulfanylbut-2-en-1-yl]-3-isobutyryloxazolidin-2-one ((*S,R*)-285).



(*R,S*)-193



(*S,R*)-285

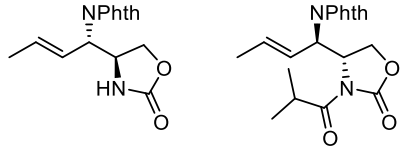
Oxazolidinones **(*R,S*)-193** and **(*S,R*)-285** were synthesised from compound **(±)-193** (28.9 mg, 0.11 mmol) following the general method for the (*S*)-BTM-catalysed kinetic resolution of oxazolidinones. The reaction mixture was stirred for 6 h and purified by column chromatography (10:90 to 40:60 AcOEt/Hexanes) to afford 8.9 mg (32% yield and 90% ee) of compound **(*R,S*)-193** and 10.9 mg (31% yield and 94% ee) of compound **(*S,R*)-285** as a white solids.

Compound (*R,S*)-193: $[\alpha]_D^{25}$ = –0.8 (c = 0.85, $CHCl_3$). **HPLC** Chiralpak IA column (90:10 hexanes:ethanol, 1.0 mL/min, 210 nm); major enantiomer t_r = 12.02 min, minor enantiomer t_r = 1.82 min, 90% ee.

Compound (*S,R*)-285: R_f = 0.59 (20:80 AcOEt/Hexanes). $[\alpha]_D^{25}$ = –90.6 (c = 0.98, $CHCl_3$). **M.p.** = 103-105 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 7.37-7.32 (m, 2H, SPh), 7.27-7.20 (m, 3H, SPh), 5.64 (dq, *J* = 15.2, 6.5 Hz, 1H, H-3'), 5.37 (ddq, *J* = 15.2, 8.0, 1.6 Hz, 1H, H-2'), 4.70 (ddd, *J* = 8.6, 4.2, 3.3 Hz, 1H, H-4), 4.43 (dd, *J* = 9.2, 3.3 Hz, 1H, H-5_a), 4.34 (t, *J* = 8.9 Hz, 1H, H-5_b), 4.31 (dd, *J* = 8.0, 4.2 Hz, 1H, H-1'), 3.45 (septet, *J* = 6.8 Hz, 1H, CH ^{i}Pr), 1.67 (dd, *J* = 6.5, 1.6 Hz, 3H, H-4'), 1.06 (d, *J* = 6.8 Hz, 3H, CH_3 ^{i}Pr), 0.91 (d, *J* = 6.8 Hz, 3H, CH_3 ^{i}Pr). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 177.8 (C=O ^{i}Pr), 153.2 (C=O), 133.6 (SPh), 132.9 (SPh), 130.6 (C-3'), 129.2 (SPh), 127.9 (SPh), 126.8 (C-2'), 64.4 (C-5), 57.5 (C-4), 53.6 (C-1'), 32.6 (CH ^{i}Pr), 18.9 (CH_3 ^{i}Pr), 18.8 (CH_3 ^{i}Pr), 18.1 (C-4'). **ESI-TOF** $[M+Na]^+$ calc for $C_{17}H_{21}NNaO_3S$: 342.1134, found: 342.1137. **FT-IR (ATR)** ν in cm^{-1}: 2973,

1761, 1699, 1397, 1385, 1360, 1220, 1117, 1092, 1050, 1025, 968. **HPLC** Chiralpak IC column (95:05 hexanes:ethanol, 1.0 mL/min, 220 nm); major enantiomer t_r = 7.27 min, minor enantiomer t_r = 8.31 min, 94% ee.

(*S*)-4-[(1*S*,2*E*)-1-phthalimidobut-2-en-1-yl]-oxazolidin-2-one ((*S*,*S*)-192) and (*R*)-4-[(1*R*,2*E*)-1-phthalimidobut-2-en-1-yl]-3-isobutyryloxazolidin-2-one ((*R*,*R*)-286).



(*S*,*S*)-192 **(*R*,*R*)-286**

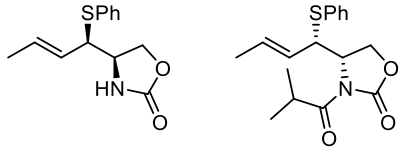
Oxazolidinones **(*S*,*S*)-192** and **(*R*,*R*)-286** were synthesised from compound **(±)-192** (28.6 mg, 0.10 mmol) following the general method for the (*S*)-BTM-catalysed kinetic resolution of oxazolidinones. The reaction mixture was stirred for 14 h and purified by column chromatography (20:80 to 70:30 AcOEt/Hexanes) to afford 10.3 mg (36% yield and 85% ee) of compound **(*S*,*S*)-192** and 11.3 mg (32% yield and 98% ee) of compound **(*R*,*R*)-286** as a white solids.

Compound (*S*,*S*)-192: $[\alpha]_D^{25}$ = –51.0 (c = 1.16, $CHCl_3$). **HPLC** Chiralpak OD-H column (85:15 hexanes:ethanol, 0.8 mL/min, 220 nm); major enantiomer t_r = 21.90 min, minor enantiomer t_r = 24.21 min, 85% ee.

Compound (*R*,*R*)-286: R_f = 0.62 (30:70 AcOEt/Hexanes). $[\alpha]_D^{25}$ = –59.4 (c = 1.13, $CHCl_3$). **M.p.** = 162-165 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 7.85-7.81 (m, 2H, Phth), 7.75-7.70 (m, 2H, Phth), 6.13 (ddq, *J* = 15.3, 9.0, 1.6 Hz, 1H, H-2'), 5.87 (dq, *J* = 15.3, 6.4 Hz, 1H, H-3'), 5.14 (dd, *J* = 9.0, 5.1 Hz, 1H, H-1'), 4.95 (ddd, *J* = 8.1, 5.1, 2.0 Hz, 1H, H-4), 4.80 (dd, *J* = 9.3, 2.0 Hz, 1H, H-5_a), 4.31 (dd, *J* = 9.3, 8.1 Hz, 1H, H-5_b), 3.62 (septet, *J* = 6.8 Hz, 1H, CH ^{i}Pr), 1.72 (dd, *J* = 6.4, 1.6 Hz, 3H, H-4'), 1.20 (d, *J* = 6.8 Hz, 3H, CH_3 ^{i}Pr), 1.14 (d, *J* = 6.8 Hz, 3H, CH_3 ^{i}Pr). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 177.4 (C=O ^{i}Pr), 168.4 (C=O Phth), 153.2 (C=O), 134.5 (Phth), 133.7 (C-3'), 131.6 (Phth), 123.7 (Phth), 122.9 (C-2'), 65.0 (C-5), 56.7 (C-4), 54.8 (C-1'), 32.7 (CH ^{i}Pr), 19.2 (CH_3 ^{i}Pr), 18.8 (CH_3 ^{i}Pr), 18.0 (C-4'). **ESI-TOF** $[M+Na]^+$ calc for $C_{19}H_{20}N_2NaO_5$: 379.1264, found: 379.1267. **FT-IR**

(ATR) ν in cm^{-1}: 2921, 2851, 1781, 1710, 1697, 1380, 1354, 1332, 1197, 1074, 714. **HPLC** Chiralpak IA column (90:10 hexanes:ethanol, 1.0 mL/min, 220 nm); major enantiomer t_r = 21.42 min, minor enantiomer t_r = 19.96 min, 98% ee.

(*R*)-4-[(1*R*,2*E*)-1-phenylsulfanylbut-2-en-1-yl]-oxazolidin-2-one ((*R,R*)-211) and (*S*)-4-[(1*S*,2*E*)-1-phenylsulfanylbut-2-en-1-yl]-3-isobutyryloxazolidin-2-one ((*S,S*)-287).



(*R*,*R*)-211 **(*S*,*S*)-287**

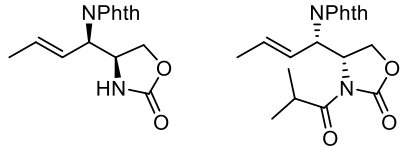
Oxazolidinones **(*R,R*)-211** and **(*S,S*)-287** were synthesised from compound **(±)-211** (12.1 mg, 0.048 mmol) following the general method for the (*S*)-BTM-catalysed kinetic resolution of oxazolidinones. The reaction mixture was stirred for 6 h and purified by column chromatography (10:90 to 50:50 AcOEt/Hexanes) to afford 4.2 mg (35% yield and 68% ee) of compound **(*R,R*)-211** and 5.9 mg (38% yield and 74% ee) of compound **(*S,S*)-287** as a colourless oils.

Compound (*R,R*)-211: $[\alpha]_D^{25}$ = –7.3 (c = 0.31, $CHCl_3$). **HPLC** Chiralpak IA column (80:20 hexanes:isopropanol, 1.0 mL/min, 230 nm); major enantiomer t_r = 6.62 min, minor enantiomer t_r = 8.50 min, 68% ee.

Compound (*S,S*)-287: R_f = 0.72 (20:80 AcOEt/Hexanes). $[\alpha]_D^{25}$ = +24.8 (c = 0.59, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 7.46-7.43 (m, 2H, SPh), 7.35-7.30 (m, 2H, SPh), 7.27-7.23 (m, 1H, SPh), 5.71 (dq, *J* = 14.3, 6.5 Hz, 1H, H-3'), 5.32 (ddq, *J* = 14.3, 9.9, 1.6 Hz, 1H, H-2'), 4.61-4.56 (m, 2H, H-4, H-5_a), 4.45 (dd, *J* = 9.9, 3.3 Hz, 1H, H-1'), 4.30-4.25 (m, 1H, H-5_b), 3.71 (septet, *J* = 6.8 Hz, 1H, CH ^{i}Pr), 1.69 (dd, *J* = 6.5, 1.6 Hz, 3H, H-4'), 1.16 (d, *J* = 6.8 Hz, 3H, CH_3 ^{i}Pr), 1.13 (d, *J* = 6.8 Hz, 3H, CH_3 ^{i}Pr). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 177.8 (C=O ^{i}Pr), 153.2 (C=O), 134.5 (C-3'), 132.7 (SPh), 131.4 (SPh), 129.4 (SPh), 127.6 (SPh), 122.0 (C-2'), 63.5 (C-5), 55.7 (C-4), 48.7 (C-1'), 32.7 (CH ^{i}Pr), 19.7 (CH_3 ^{i}Pr), 18.4 (CH_3 ^{i}Pr), 18.2 (C-4'). **ESI-TOF** $[2M+Na]^+$ calc for $C_{34}H_{42}N_2NaO_6S_2$: 661.2376, found: 661.2379. **FT-IR (ATR)** ν in cm^{-1}: 2971, 2920, 1781, 1698, 1384, 1238, 1209,

1089, 784. **HPLC** Chiralpak OD-H column (80:20 hexanes:isopropanol, 1.0 mL/min, 210 nm); major enantiomer t_r = 6.30 min, minor enantiomer t_r = 8.84 min, 74% ee.

(*S*)-4-[(1*R*,2*E*)-1-phthalimidobut-2-en-1-yl]-oxazolidin-2-one ((*S*,*R*)-212) and (*R*)-4-[(1*S*,2*E*)-1-phthalimidobut-2-en-1-yl]-3-isobutyryloxazolidin-2-one ((*R*,*S*)-288).



(*S*,*R*)-212 **(*R*,*S*)-288**

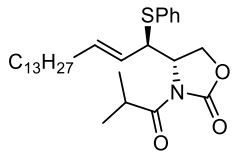
Oxazolidinones **(*S*,*R*)-212** and **(*R*,*S*)-288** were synthesised from compound **(±)-212** (10.3 mg, 0.036 mmol) following the general method for the (*S*)-BTM-catalysed kinetic resolution of oxazolidinones, using CH_2Cl_2 as solvent. The reaction mixture was stirred for 24 h under reflux and purified by column chromatography (20:80 to 50:50 AcOEt/Hexanes) to afford 6.6 mg (64% yield and 24% ee) of compound **(*S*,*R*)-212** and 0.9 mg (7% yield and 71% ee) of compound **(*R*,*S*)-288** as a white solids.

Compound (*S*,*R*)-212: $[\alpha]_D^{25}$ = 0.0 (c = 0.20, CH_2Cl_2). **HPLC** Chiralpak IA column (80:20 hexanes:isopropanol, 0.8 mL/min, 230 nm); major enantiomer t_r = 21.79 min, minor enantiomer t_r = 16.83 min, 24% ee.

Compound (*R*,*S*)-288: R_f = 0.47 (30:70 AcOEt/Hexanes). $[\alpha]_D^{25}$ = –43.8 (c = 0.15, $CHCl_3$). **M.p.** = 150-153 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 7.86-7.81 (m, 2H, Phth), 7.74-7.70 (m, 2H, Phth), 6.06 (ddq, *J* = 15.2, 9.1, 1.6 Hz, 1H, H-2'), 5.87 (dq, *J* = 15.2, 6.5 Hz, 1H, H-3'), 5.02 (ddd, *J* = 7.8, 6.9, 2.1 Hz, 1H, H-4), 4.91 (dd, *J* = 9.1, 6.9 Hz, 1H, H-1'), 4.65 (dd, *J* = 9.6, 2.1 Hz, 1H, H-5_a), 4.36 (dd, *J* = 9.6, 7.8 Hz, 1H, H-5_b), 3.66 (septet, *J* = 6.8 Hz, 1H, CH ^{i}Pr), 1.74 (dd, *J* = 6.5, 1.6 Hz, 3H, H-4'), 1.02 (d, *J* = 6.8 Hz, 3H, CH_3 ^{i}Pr), 1.00 (d, *J* = 6.8 Hz, 3H, CH_3 ^{i}Pr). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 177.7 (C=O ^{i}Pr), 168.0 (C=O Phth), 153.1 (C=O), 135.2 (C-3'), 134.3 (Phth), 131.9 (Phth), 123.5 (Phth), 122.6 (C-2'), 65.2 (C-5), 55.6 (C-4), 55.1 (C-1'), 32.6 (CH ^{i}Pr), 19.7 (CH_3 ^{i}Pr), 18.3 (CH_3 ^{i}Pr), 18.1 (C-

4'). **ESI-TOF** $[2M+Na]^+$ calc for $C_{38}H_{40}N_4NaO_{10}$: 735.2637, found: 735.2641. **FT-IR (ATR)** ν in cm^{-1}: 2964, 2920, 1783, 1711, 1378, 1237, 1196, 1087, 973, 716. **HPLC** Chiralpak IA column (70:30 hexanes:isopropanol, 1.0 mL/min, 220 nm); major enantiomer t_r = 26.47 min, minor enantiomer t_r = 13.79 min, 71% ee.

(*S*)-4-[(1*R*,2*E*)-1-phenylsulfanylhexadeca-2-en-1-yl]-3-isobutyryl oxazolidin-2-one ((*S*,*R*)-289).

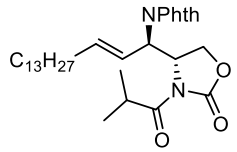


(*S*,*R*)-289

Compound **(*S*,*R*)-289** was synthesised following the cross metathesis general procedure starting from alkenyl oxazolidinone **(*S*,*R*)-285** (9.9 mg, 0.031 mmol) and commercially available 1-pentadecene (10.1 μL, 0.037 mmol). The crude was purified by column chromatography (5:95 AcOEt/hexanes) to afford 13.1 mg (87% yield, *E*:*Z* = 88:12) of oxazolidinone **(*S*,*R*)-289** as a colourless oil.

R_f = 0.80 (20:80 AcOEt/Hexanes). **$[\alpha]_D^{25}$** = –57.3 (c = 0.86, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 7.41-7.35 (m, 2H, SPh), 7.28-7.20 (m, 3H, SPh), 5.61 (dt, *J* = 14.9, 7.0 Hz, 1H, H-3'), 5.34 (dd, *J* = 14.9, 7.9 Hz, 1H, H-2'), 4.74-4.70 (m, 1H, H-4), 4.45 (dd, *J* = 9.2, 3.4 Hz, 1H, H-5_a), 4.38-4.33 (m, 2H, H-5_b, H-1'), 3.48 (septet, *J* = 6.8 Hz, 1H, CH ^{i}Pr), 1.98 (q, *J* = 7.0 Hz, 2H, H-4'), 1.32-1.26 (m, 22H, H-5'-H-15'), 1.08 (d, *J* = 6.8 Hz, 3H, CH_3 ^{i}Pr), 0.95 (d, *J* = 6.8 Hz, 3H, CH_3 ^{i}Pr), 0.88 (t, *J* = 6.8 Hz, 3H, H-16'). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 177.8 (C=O ^{i}Pr), 153.2 (C=O), 136.2 (C-3'), 133.3 (SPh), 133.0 (SPh), 129.2 (SPh), 127.8 (SPh), 125.4 (C-2'), 64.3 (C-5), 57.5 (C-4), 53.6 (C-1'), 32.6 (C-5'-C-15'), 32.5 (CH ^{i}Pr), 32.1 (C-4'), 29.8, 29.8, 29.8, 29.7, 29.6, 29.5, 29.2, 29.1, 22.8 (C-5'-C-15'), 19.0 (CH_3 ^{i}Pr), 18.8 (CH_3 ^{i}Pr), 14.3 (C-16'). **ESI-TOF** $[M+Na]^+$ calc for $C_{29}H_{45}NNaO_3S$: 510.3012, found: 510.3034. **FT-IR (ATR)** ν in cm^{-1}: 2922, 2852, 1783, 1700, 1466, 1386, 1232, 1091, 753.

(*R*)-4-[(1*R*,2*E*)-1-phthalimidohexadeca-2-en-1-yl]-3-isobutyryloxazolidin-2-one ((*R*,*R*)-290).

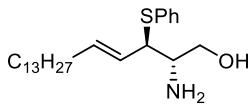


(*R*,*R*)-290

Compound **(*R*,*R*)-290** was synthesised following the cross metathesis general procedure starting from alkenyl oxazolidinone **(*R*,*R*)-286** (8.0 mg, 0.022 mmol) and commercially available 1-pentadecene (7.3 μL, 0.027 mmol). The crude was purified by column chromatography (15:85 AcOEt/hexanes) to afford 9.5 mg (81% yield, *E*:*Z* = 83:17) of oxazolidinone **(*R*,*R*)-290** as a colourless oil.

R*f* = 0.70 (40:60 AcOEt/Hexanes). **[α]$_D^{25}$** = –36.7 (c = 0.79, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 7.85-7.81 (m, 2H, Phth), 7.75-7.70 (m, 2H, Phth), 6.11 (dd, *J* = 15.3, 8.9 Hz, 1H, H-2'), 5.86 (dt, *J* = 15.3, 6.7 Hz, 1H, H-3'), 5.17 (dd, *J* = 8.9, 4.7 Hz, 1H, H-1'), 4.92 (ddd, *J* = 8.1, 4.7, 1.9 Hz, 1H, H-4), 4.85 (dd, *J* = 9.2, 1.9 Hz, 1H, H-5_a), 4.31 (dd, *J* = 9.2, 8.1 Hz, 1H, H-5_b), 3.62 (septet, *J* = 6.8 Hz, 1H, CH ^{i}Pr), 2.04 (q, *J* = 7.2 Hz, 2H, H-4'), 1.36-1.23 (m, 22H, H-5'-H-15'), 1.21 (d, *J* = 6.8 Hz, 3H, CH_3 ^{i}Pr), 1.14 (d, *J* = 6.8 Hz, 3H, CH_3 ^{i}Pr), 0.87 (t, *J* = 6.8 Hz, 3H, H-16'). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 177.5 (C=O ^{i}Pr), 168.5 (C=O Phth), 153.2 (C=O), 139.1 (C-3'), 134.5 (Phth), 131.7 (Phth), 123.7 (Phth), 121.3 (C-2'), 65.0 (C-5), 57.1 (C-4), 54.7 (C-1'), 32.7 (C-5'-C-15'), 32.5 (CH ^{i}Pr), 32.1 (C-4'), 29.9, 29.8, 29.8, 29.8, 29.7, 29.6, 29.5, 29.3, 28.9, 22.8 (C-5'-C-15'), 19.2 (CH_3 ^{i}Pr), 18.9 (CH_3 ^{i}Pr), 14.3 (C-16'). **ESI-TOF** $[M+Na]^+$ calc for $C_{31}H_{44}N_2NaO_5$: 547.3142, found: 547.3158. **FT-IR (ATR)** ν in cm^{-1}: 2922, 2851, 1783, 1715, 1386, 1198, 719.

(2*S*,3*R*,4*E*)-2-amino-3-phenylsulfanyloctadec-4-en-1-ol ((*S*,*R*)-291).[80,145]



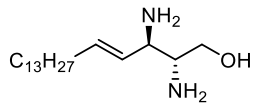
(*S*,*R*)-291

To a solution of acylated oxazolidinone **(*S*,*R*)-289** (9.0 mg, 0.018 mmol) in THF (50 μL) and H_2O (16 μL), solid $NaBH_4$ (2.8 mg, 0.074 mmol) was added at a rate that

maintains the internal temperature between 20-25ºC. The resulting mixture was stirred at room temperature until complete consumption of the starting material was observed by TLC. Then, the reaction was quenched with a 2N HCl aqueous solution. The aqueous phase was extracted with AcOEt and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Crude was next dissolved in a mixture of dioxane (0.7 mL) and H_2O (0.5 mL), solid $Ba(OH)_2 \cdot 8H_2O$ (17.5 mg, 0.055 mmol) was subsequently added and the reaction was refluxed overnight. Then, the mixture was left to cool to room temperature, filtered and concentrated under vacuum. Finally, the crude was purified by column chromatography (96:4 CH_2Cl_2/CH_3OH) to afford 3.6 mg (51% yield) of compound **(*S,R*)-291** as a colourless oil.

R_f = 0.17 (96:4 CH_2Cl_2/CH_3OH). **$[\alpha]_D^{25}$** = –19.4 (c = 0.24, $CHCl_3$). **^{1}H NMR** (400 MHz, CD_3OD, δ in ppm): δ = 7.42-7.39 (m, 2H, SPh), 7.31-7.21 (m, 3H, SPh), 5.46-5.33 (m, 2H, H-5, H-4), 3.80 (dd, *J* = 8.7, 5.7 Hz, 1H, H-3), 3.67 (dd, *J* = 10.9, 5.1 Hz, 1H, H-1_a), 3.54 (dd, *J* = 10.9, 6.6 Hz, 1H, H-1_b), 2.94 (q, *J* = 5.6 Hz, 1H, H-2), 1.99-1.90 (m, 2H, H-6), 1.35-1.17 (m, 22H, H-7-H-17), 0.90 (t, *J* = 6.9 Hz, 3H, H-18). **^{13}C NMR** (100 MHz, CD_3OD, δ in ppm): δ = 136.6 (C-5), 135.6 (SPh), 134.2 (SPh), 129.8 (SPh), 128.3 (SPh), 127.5 (C-4), 64.9 (C-1), 56.3 (C-2), 55.6 (C-3), 33.3, 33.1, 30.8, 30.8, 30.7, 30.6, 30.5, 30.3, 30.0, 23.8 (C-6-C-17), 14.5 (C-18). **ESI-TOF** $[M+H]^+$ calc for $C_{24}H_{42}NOS$: 392.2982, found: 392.3001. **FT-IR (ATR)** ν in cm^{-1}: 3357, 2923, 2852, 1466, 1026.

(2*R*,3*R*,4*E*)-2,3-diaminooctadec-4-en-1-ol ((*R,R*)-292).[80,145]



(*R*,*R*)-292

To a solution of acylated oxazolidinone **(*R,R*)-290** (15.8 mg, 0.030 mmol) in THF (83 μL) and H_2O (27 μL), solid $NaBH_4$ (4.6 mg, 0.120 mmol) was added at a rate that maintains the internal temperature between 20-25ºC. The resulting mixture was stirred at room temperature until complete consumption of the starting material was observed by TLC. Then, the reaction was quenched with a 2N HCl aqueous solution. The aqueous phase was extracted with AcOEt and the combined organic

layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Crude was next dissolved in a mixture of dioxane (1.2 mL) and H_2O (0.8 mL), solid $Ba(OH)_2 \cdot 8H_2O$ (28.5 mg, 0.090 mmol) was subsequently added and the reaction was refluxed overnight. Then, the mixture was left to cool to room temperature, filtered and concentrated under vacuum. Finally, the crude was purified by column chromatography (96:4:1 $CH_2Cl_2/CH_3OH/NH_4OH$) to afford 5.5 mg (61% yield) of compound **(*R,R*)-292** as a white solid.

R_f = 0.21 (95:5:1 $CH_2Cl_2/CH_3OH/NH_4OH$). **$[\alpha]_D^{25}$** = –7.1 (c = 0.26, $CHCl_3$). **M.p.** = 68-74 ºC. **^{1}H NMR** (400 MHz, CD_3OD, δ in ppm): δ = 5.73 (dt, *J* = 15.3, 6.9 Hz, 1H, H-5), 5.50 (dd, *J* = 15.3, 7.8 Hz, 1H, H-4), 4.31 (t, *J* = 8.2 Hz, 1H, H-3), 3.82 (ddd, *J* = 8.7, 7.8, 4.8 Hz, 1H, H-2), 3.56 (dd, *J* = 11.0, 4.8 Hz, 1H, H-1_a), 3.49 (dd, *J* = 11.0, 7.8 Hz, 1H, H-1_b), 2.08 (q, *J* = 6.9 Hz, 2H, H-6), 1.42-1.29 (m, 22H, H-7-H-17), 0.90 (t, *J* = 6.9 Hz, 3H, H-18). **^{13}C NMR** (100 MHz, CD_3OD, δ in ppm): δ = 135.7 (C-5), 126.8 (C-4), 62.9 (C-1), 59.0 (C-2), 58.1 (C-3), 33.2 , 33.1, 30.8, 30.8, 30.8, 30.7, 30.6, 30.5, 30.3, 30.3, 23.8 (C-6-C-17), 14.5 (C-18). **ESI-TOF** $[M+Na]^+$ calc for $C_{31}H_{44}N_2NaO_5$: 547.3142, found: 547.3158. **FT-IR (ATR)** ν in cm^{-1}: 3290, 2954, 2916, 2850, 1675, 1651, 1468, 1273, 1029.

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CHAPTER VII

TOWARDS THE TOTAL SYNTHESIS OF PHLEGHENRINE ALKALOIDS

UNIVERSITAT ROVIRA I VIRGILI
METAL-FREE REGIO- AND STEREOSELECTIVE VICINAL DIFUNCTIONALISATION OF DIENYL CARBAMATES
Irene Giménez Nueno

7.1. Introduction

7.1.1. Structure and biological properties of phleghenrine alkaloids

In 2016, Q.-S. Zhao and co-workers reported the first isolation and characterisation of five new *Lycopodium* alkaloids, phleghenrine A-D and neophleghenrine, from *Phlegmariurus henry* (Baker) Ching, a plant native to some regions of China and northern Vietnam (**Figure 7.1**).[36,149] A common structural feature among phleghenrine alkaloids is their bicyclo[3.2.2]nonane core flanked by two-nitrogen-containing heterocycles. In addition to this bridged framework, neophleghenrine displays an unprecedent 9-azaprotoadamantane skeleton arising from an additional N-C bond between the piperidine and 2-piperidone rings.

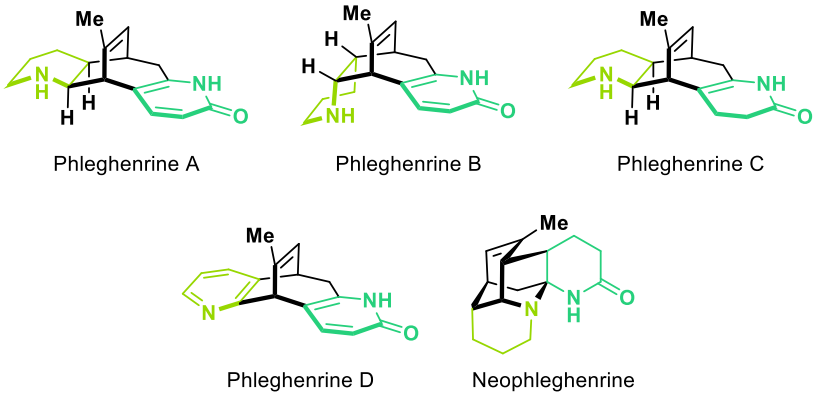

Figure 7.1. Phleghenrine family of natural products.

The proposed biogenetic pathway for the formation of phleghenrines A-D is depicted in **Scheme 7.1**.[36] Taking into account the large amount of huperzine B (HupB), a related *Lycopodium* alkaloid bearing two *N*-heterocycles and a bridged aliphatic core,[150] isolated from *Phlegmariurus henry* samples, this specie was envisaged as a plausible starting material for the biological preparation of phleghenrine family. Thus, initial Hup B enzymatic oxidation and subsequent aza-seminpinacol rearrangement of its carbon skeleton gave access to key intermediate **I** containing the observed 6/6/7/6 ring-system (**Scheme 7.1**).

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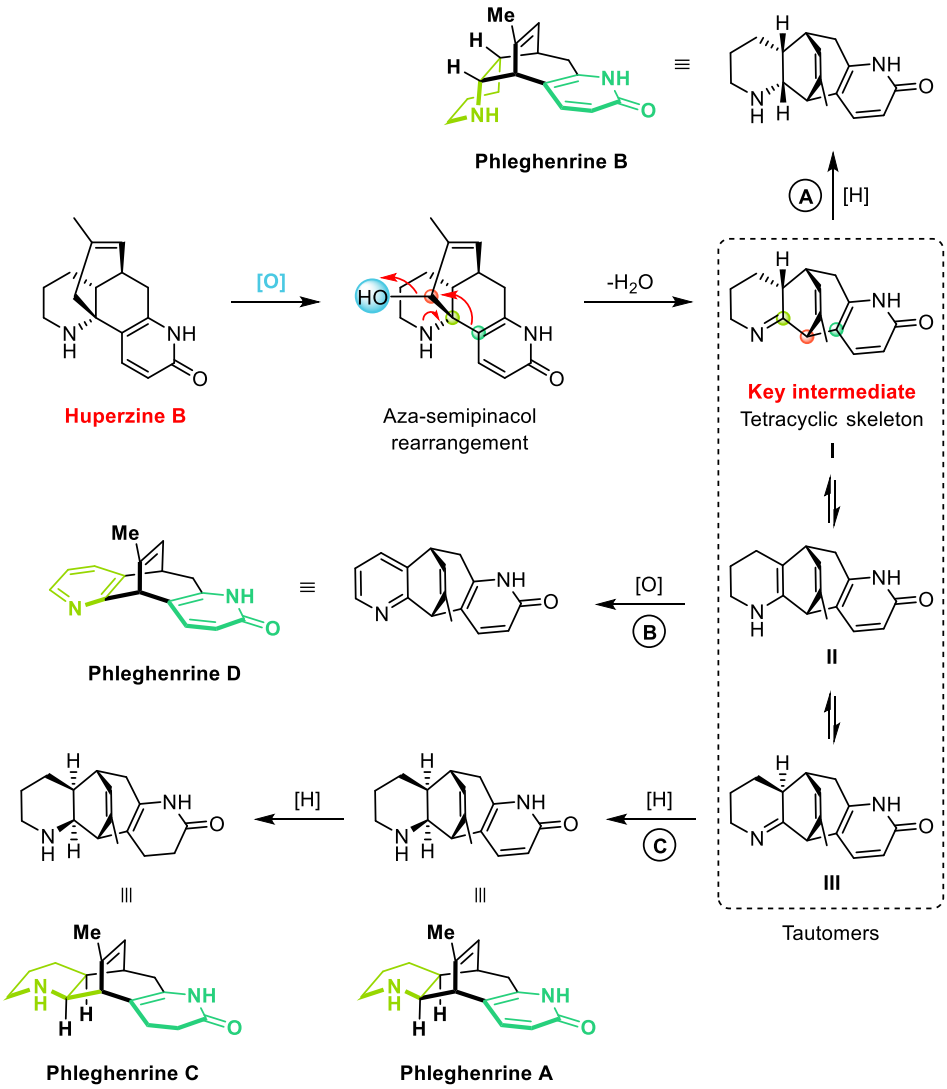
149 X. Ma, C. Tan, D. Zhu, D. R. Gang, *J. Ethnopharmacol.* **2006**, *104*, 54–67.

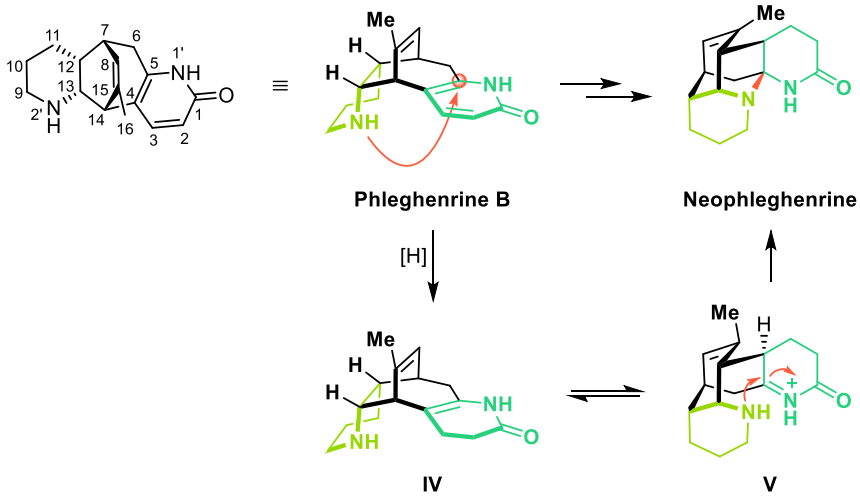
150 J.-S. Liu, Y.-L. Zhu, C.-M. Yu, Y.-Z. Zhou, Y.-Y. Han, F.-W. Wu, B.-F. Qi, *Can. J. Chem.* **1986**, *64*, 837–839.



Scheme 7.1. Proposed biogenetic pathway for phleghenrines A-D from huperzine B.

Then, selective reduction of C=N bond in compound **I** furnished phleghenrine B (**Scheme 7.1**, pathway A), whereas phleghenrine D was generated via oxidation of piperidine ring in tautomeric form **II** (**Scheme 7.1**, pathway B). Finally, the reverse stereoselectivity displayed by phleghenrines A and C has its origin in diastereomer **III** (**Scheme 7.1**, pathway C). Moreover, an alternative route involving a

phlegmarine-type precursor has also been published for the biological synthesis of a hydroxy-substituted tetracyclic product analogous to key intermediate **I**.[151]



Scheme 7.2. Proposed biogenetic formation of neophleghenrine via spontaneous intramolecular cyclisation of phleghenrine B.

In addition, neophleghenrine was proposed to stem from phleghenrine B based on the identical absolute configuration of C12 and C13 in both molecules (**Scheme 7.2**). Therefore, additional N2'-C5 bond was generated by initial reduction of pyridone ring in Phleghenrine B to furnish intermediate **IV** followed by spontaneous intramolecular cyclisation of iminium tautomer **V** via Mannich-type reaction.

Some members of the *Lycopodium* alkaloid family have been reported to exert biological activity against acetylcholinesterase (AChE), an enzyme that catalyses the breakdown of the neurotransmitter acetylcholine, hampering the synaptic transmission between neurons (**Figure 7.2**). Therefore, its inhibition has been widely studied for the treatment of the early effects of the Alzheimer's disease (AD),[152] a

[151] W.-J. Meng, J. Xiong, W.-X. Wang, H.-Y. Zhang, H. Zeng, J.-F. Hu, *Tetrahedron Lett.* **2016**, *57*, 3218–3221.

[152] M. Mehta, A. Adem, M. Sabbagh, *Int. J. Alzheimers Dis.* **2012**, *2012*, 1–8.

chronic and degenerative brain condition that affects around 50 million people worldwide, according to the World Health Organisation.[153]

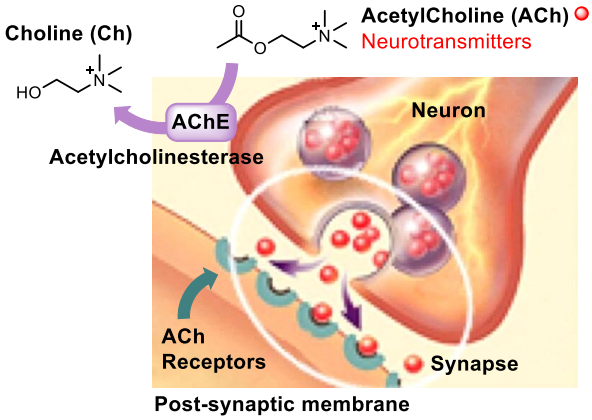


Figure 7.2. Cell signalling through synapse transmission and biological mode of action of acetylcholinesterase (AChE).[154]

Along these lines, phleghenrines A and D have shown promising inhibitory activity against AChE, with IC_{50} values of 4.91 and 4.32 μM respectively. Even though these results are far of being competitive with those reported for marketed drug tacrine (IC_{50} = 0.30 μM), the fact that phleghenrine D displays no biological interaction with butyrylcholinesterase (BuChE), whose inhibition has been related to hepatotoxic side effects, entails a valuable advance for the development of new treatments for Alzheimer's disease.

7.1.2. Methods for the direct preparation of bicyclo[3.2.2]nonane

Tropone (2,4,6-cycloheptatrien-2-one) is a nonbenzenoid aromatic compound belonging with the troponoid family that has been widely used as a precursor in the

[153] Alzheimer's Association. 2015. Alzheimer's disease facts and figures. Alzheimers Dement. *J. Alzheimers Assoc.* **2015**, *11*, 332–384.

[154] Figure adapted from Alzheimer's association website: https://www.alz.org/alzheimers-dementia/what-is-alzheimers/brain_tour.

synthesis of natural products.[155] Depending on the coupling reactant, its conjugated system can participate in different cycloaddition reactions as a 4π,[156] 6 π[157] or 8 π[158] structure. In particular, the [4+2] cycloaddition of tropone derivatives with a suitable dienophile partner has been described for the direct preparation of several bicyclo[3.2.2]nonanes.

Firstly reported in 1928,[159] the Diels-Alder (DA) reaction has become a versatile and powerful tool in organic synthesis for the stereoselective construction of carbon-carbon and carbon-heteroatom bonds via a concerted [4+2] cycloaddition of conjugated dienes with dienophiles.[160] According to the frontier electron theory, it

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155 a) P. L. Pauson, *Chem. Rev.* **1955**, *55*, 9–136. b) F. Pietra, *Chem. Rev.* **1973**, *73*, 293–364. c) F. Pietra, *Acc. Chem. Res.* **1979**, *12*, 132–138. d) G. Fischer, In *Advances in Heterocyclic Chemistry*; A. R. Katritzky, Ed.; Elsevier: New York, USA, **1995**; Vol *64*, pp. 81–157. e) G. Fischer, In *Advances in Heterocyclic Chemistry*; A. R. Katritzky, Ed.; Elsevier: New York, USA, **1996**; Vol *66*, pp. 285–403. f) N. Liu, W. Song, C. M. Schienebeck, M. Zhang, W. Tang, *Tetrahedron* **2014**, *70*, 9281–9305. g) A. Dastan, H. Kilic, N. Saracoglu, *Beilstein J. Org. Chem.* **2018**, *14*, 1120–1180.

156 a) K. N. Houk, L. J. Luskus, N. S. Bhacca, *J. Am. Chem. Soc.* **1970**, *92*, 6392–6394. b) P. Yu, T. Q. Chen, Z. Yang, C. Q. He, A. Patel, Y. Lam, C.-Y. Liu, K. N. Houk, *J. Am. Chem. Soc.* **2017**, *139*, 8251–8258.

157 a) R. Mose, G. Preegel, J. Larsen, S. Jakobsen, E. H. Iversen, K. A. Jørgensen, *Nat. Chem.* **2017**, *9*, 487–492. b) M. Bonadeo, C. De Micheli, R. Gandolfi, *J. Chem. Soc. Perkin Trans. 1* **1977**, 939–944. c) B. M. Trost, P. R. Seoane, *J. Am. Chem. Soc.* **1987**, *109*, 615–617. d) Y. Du, J. Feng, X. Lu, *Org. Lett.* **2005**, *7*, 1987–1989. e) B. M. Trost, P. J. McDougall, O. Hartmann, P. T. Wathen, *J. Am. Chem. Soc.* **2008**, *130*, 14960–14961. f) B. M. Trost, P. J. McDougall, *Org. Lett.* **2009**, *11*, 3782–3785. g) H. Liu, Y. Wu, Y. Zhao, Z. Li, L. Zhang, W. Yang, H. Jiang, C. Jing, H. Yu, B. Wang, Y. Xiao, H. Guo, *J. Am. Chem. Soc.* **2014**, *136*, 2625–2629. h) H.-L. Teng, L. Yao, C.-J. Wang, *J. Am. Chem. Soc.* **2014**, *136*, 4075–4080. i) L. Isakovic, J. A. Ashenhurst, J. L. Gleason, *Org. Lett.* **2001**, *3*, 4189–4192. j) J. H. Rigby, M. Fleming, *Tetrahedron Lett.* **2002**, *43*, 8643–8646.

158 a) M. Oda, M. Funamizu, Y. Kitahara, *J. Chem. Soc. D.* **1969**, 737–738. b) T. S. Cantrell, *J. Am. Chem. Soc.* **1971**, *93*, 2540–2541. c) K. Kumar, A. Kapur, M. P. S. Ishar, *Org. Lett.* **2000**, *2*, 787–789. d) J. Okamoto, S. Yamabe, T. Minato, T. Hasegawa, T. Machiguchi, *Helv. Chim. Acta* **2005**, *88*, 1519–1539. e) M. Xie, X. Liu, X. Wu, Y. Cai, L. Lin, X. Feng, *Angew. Chem. Int. Ed.* **2013**, *52*, 5604–5607.

159 O. Diels, K. Alder, *Justus Liebigs Ann. Chem.* **1928**, *460*, 98–122.

160 a) J. Sauer, *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 211–230. b) J. Sauer, *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 16–33. c) J. Sauer, R. Sustmann, *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 779–807.

can be classified as a normal-, neutral- or inverse-electron demand transformation depending on the relative energies of the frontier molecular orbitals for the coupling partners (**Figure 7.3**). Thus, for a normal Diels-Alder reaction, the cycloaddition of electron-rich dienes with electron-poor dienophiles is controlled by the highest occupied molecular orbital from the former reactant ($HOMO_{DIENE}$). On the contrary, inverse-electron demand Diels-Alder reaction (IEDDA) is dominated by the interactions between the $HOMO_{DIENOPHILE}$ from dienophiles bearing electron-donating groups and the $LUMO_{DIENE}$ from electron-withdrawing substituted dienes.[161] Nevertheless, both transformations are thermally allowed by the Woodward-Hoffman rules.[162]

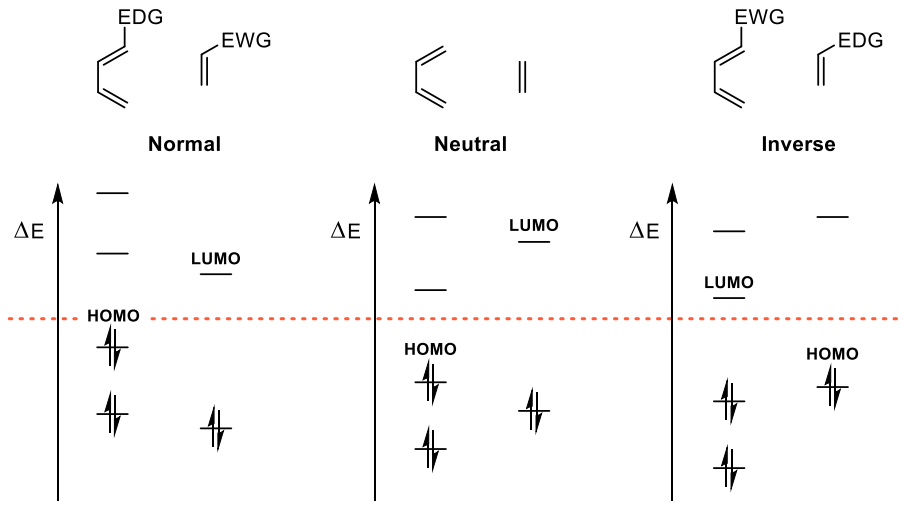


Figure 7.3. Classification of Diels-Alder reactions.

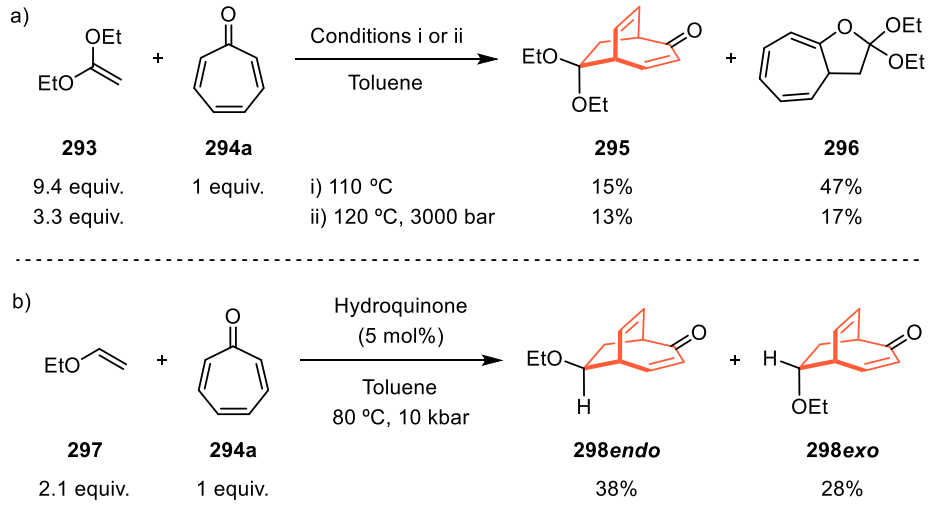
Along these lines, an early report by H. Takesita and co-workers described the formation [4+2] cycloadduct **295** and related [8+2] cycloadduct **296** from tropone **294a** and electron-rich diethoxyethene **293** under thermal and high-pressure conditions (**Scheme 7.3** a).[163] Interestingly, when the reaction was carried out at 3000

[161] a) J. Zhang, V. Shukla, D. L. Boger, *J. Org. Chem.* **2019**, DOI 10.1021/acs.joc.9b00834. b) E. Brachet, P. Belmont, *Curr. Org. Chem.* **2016**, *20*, 2136–2160. c) X. Jiang, R. Wang, *Chem. Rev.* **2013**, *113*, 5515–5546.

[162] R. B. Woodward, R. Hoffmann, In *The Conservation of Orbital Symmetry*; Verlag Chemine: Weinheim, Germany, **1970**.

[163] H. Takeshita, H. Nakashima, S. Sugiyama, A. Mori, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 573–574.

bar, cycloaddition compounds were obtained in a nearly 1:1 mixture along with a consistent recovery of unreacted starting material. Moreover, by increasing the reaction pressure up to 10 kbar, larger ratios of [4+2]/[8+2] cycloadducts were encountered for the reaction of tropone **294a** with ethyl vinyl ether **297**, yielding bicyclo[3.2.2]nonane diastereomers **298*endo*** and **298*exo*** as the major products (**Scheme 7.3** b).[164] This protocol was also applied to the cycloaddition of monosubstituted tropones with dienophile **297** leading to a complex combination of regio- and diastereomers.



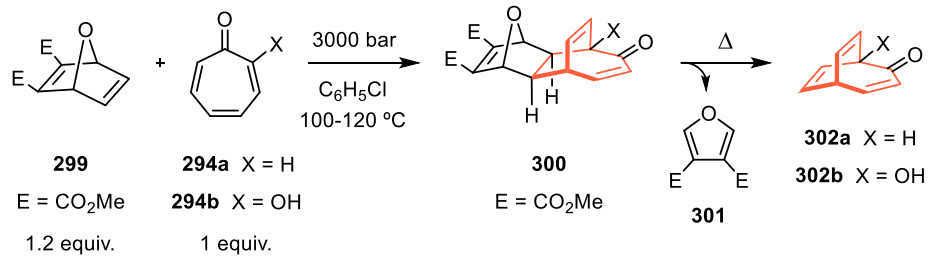
Scheme 7.3. High-pressure cycloaddition of tropone **294a** with electron-rich dienophiles.

The preparation of homobarrelenones **302** via high-pressure cycloaddition of tropone derivatives **294a** (X = H) and **294b** (X = OH) and subsequent cycloreversion of fused intermediates **300** under thermal conditions has also been published by the same group (**Scheme 7.4**).[165] Homobarrelenones **302a** (X = H) and **302b** (X = OH) contain a bicyclo[3.2.2]nonatrienone difficult to access via direct cycloaddition reaction due to the limited utility of acetylene as dienophile. Moreover, in the specific case of tropone **294a** (X = H) and tropolone **294b** (X = OH), *endo*-cycloadduct **300**

[164] A. Mori, Z.–H. Li, H. Takeshita, *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2257–2263.

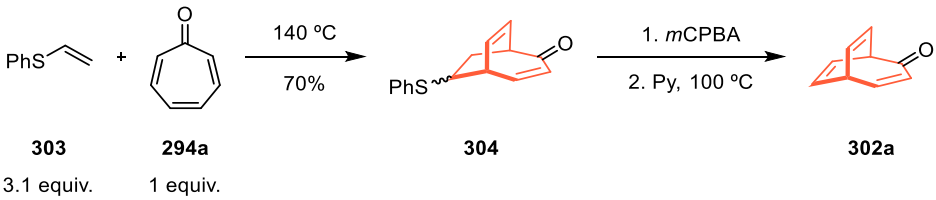
[165] a) G. R. Tian, S. Sugiyama, A. Mori, H .Takeshita, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2393–2399. b) G. R. Tian, S. Sugiyama, A. Mori, H .Takeshita, *Chem. Lett.* **1987**, *16*, 1557–1560.

was isolated in 88% and 67% yield respectively when the reaction was carried out at 3000 bar.



Scheme 7.4. Preparation of homobarrelenones **302a** (X = H) and **302b** (X = OH) via high-pressure cycloaddition of tropone derivatives **294a** (X = H) and **294b** (X = OH) and subsequent thermal cycloreversion.

An alternative preparation of homobarrelenones **302a** via a two-step sequence from tropone **294a** has also been reported (**Scheme 7.5**).[166] Thus, initial cycloaddition with phenyl vinyl sulphide **303** as acetylene surrogate gave access to bridged intermediate **304** that upon oxidation with *m*CPBA and subsequent elimination under basic conditions furnished desired bicyclo[3.2.2]nonatrienone **302a** in good yields.



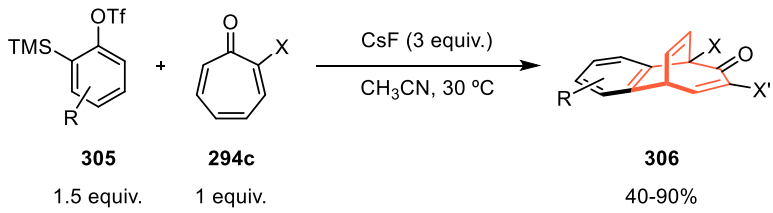
Scheme 7.5. Preparation of homobarrelenone **302a** via thermal cycloaddition of tropone **294a** with phenyl vinyl sulphide **303**.

Moreover, Diels-Alder reaction of tropone derivatives **294c** with *in situ* generated arynes via 1,2-elimination of 2-(trimethylsilyl)aryl triflates **305** yielded related benzobicyclo[3.2.2]nonatrienone **306** (**Scheme 7.6**).[167] During the study of the

[166] J. H. Rigby, J. M. Sage, *J. Org. Chem.* **1983**, *48*, 3591–3592.

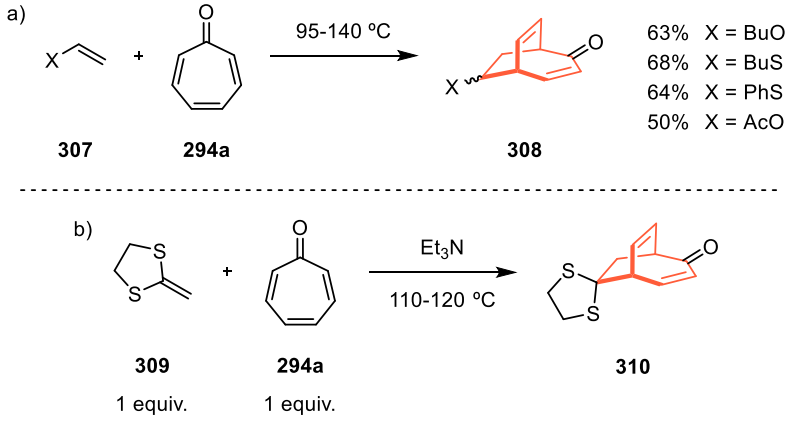
[167] a) M. Thangaraj, S. S. Bhojgude, R. H. Bisht, R. G. Gonnade, A. T. Biju, *J. Org. Chem.* **2014**, *79*, 4757–4762. b) Joseph. Ciabattoni, J. E. Crowley, A. S. Kende, *J. Am. Chem. Soc.* **1967**, *89*, 2778–2779.

reaction scope, complete regiocontrol over cycloadduct **306** (X or X' = OR) formation was observed for tropolone and other oxygen-containing tropone derivatives **294c** (X = OR) whereas aryl- and halogen-substituted starting materials **294c** (X = Ar or halogen) furnished variable mixtures of regioisomers **306** (X and X' = Ar or halogen).



Scheme 7.6. Diels-Alder reaction of tropone derivatives **294c** with *in situ* generated arynes.

In 1982, J. H. Rigby and co-workers described a thermal inverse-electron demand Diels-Alder reaction of tropone **294a** with different substituted electron-rich dienophiles **307** (**Scheme 7.7** a).[168] Interestingly, a single bicyclo[3.2.2]nonane regioisomer bearing the electron-donating group from the dienophile partner in *γ*-position with respect to the carbonyl group was formed in all the cases.

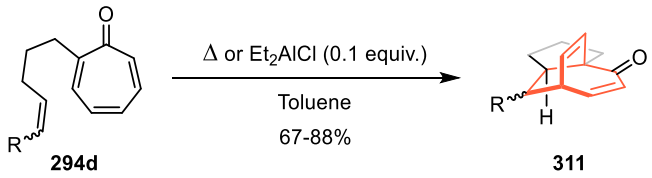


Scheme 7.7. Thermal inverse-electron demand Diels-Alder reaction of tropone **294a** with different substituted electron-rich dienophiles.

[168] J. H. Rigby, J. M. Sage, J. Raggon, *J. Org. Chem.* **1982**, *47*, 4815–4816.

Along these lines, symmetric dienophile **309** has also been employed for the thermal [4+2] cycloaddition reaction with electron deficient tropone **294a** using triethylamine as solvent as part of a program aiming at synthesising cyathins' skeleton (**Scheme 7.7** b).[169]

The intramolecular version of the [4+2] cycloaddition of tropone analogues was reported by R. L. Funk and co-workers. (**Scheme 7.8**)[170] Thus, under thermal conditions, terminal alkenes **294d** (R = H) were smoothly converted into desired bicyclo[3.2.2]nonane **311** (R = H) in remarkable yields whereas more substituted olefins **294d** displayed lower reaction rates. However, in the presence of catalytic amounts of Et_2AlCl as a Lewis acid, pre-activation of diene moiety from tropone ring rendered *endo*-cycloadducts **311** in a stereospecific manner with high yields.



Scheme 7.8. Thermal or Lewis acid catalysed intramolecular [4+2] cycloaddition of tethered olefinic tropones **294d**.

Likewise, a recent example of a Lewis acid catalysed inverse-electron demand Diels-Alder reaction of tropone **294a** with vinyl ethers **312** employed substoichiometric amounts of tris(pentafluoro)phenyl borane (**Scheme 7.9** a).[171] Moreover, the asymmetric version of this cycloaddition reaction was accomplished in the presence of a binuclear BINOL-aluminium complex with enantioselectivities up to 97% for ketene diethyl acetal **293** (**Scheme 7.9** b). Noteworthy, predominant formation of regioisomers **313** and **315** bearing electro-donating group from the dienophile partner in *γ*-position to carbonyl moiety was observed in both cases.

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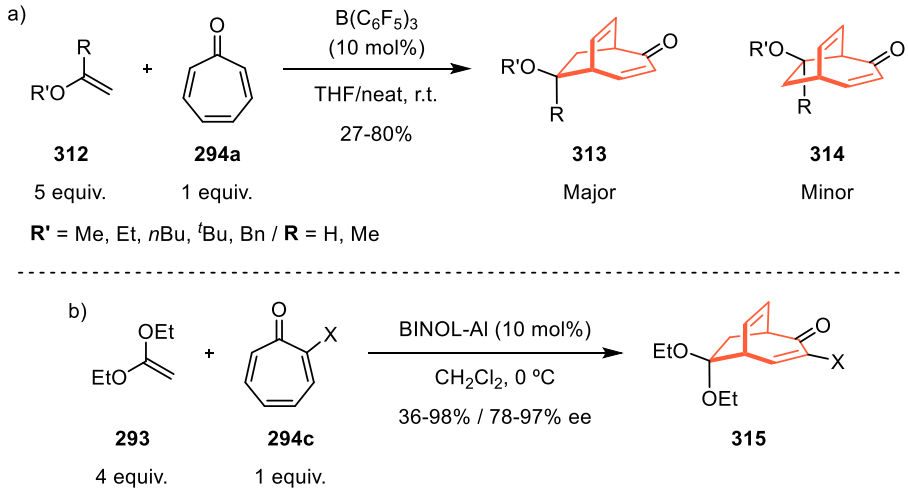
169 a) K. R. Dahnke, L. A. Paquette, *J. Org. Chem.* **1994**, *59*, 885–899. b) K. R. Dahnke, L. A. Paquette, *Org. Synth.* **1993**, *71*, 181–185.

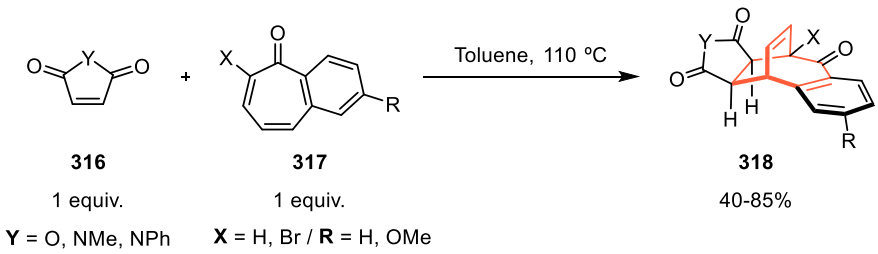
170 a) R. L. Funk, G. L. Bolton, *J. Am. Chem. Soc.* **1986**, *108*, 4655–4657. b) R. L. Funk, G. L. Bolton, *J. Org. Chem.* **1987**, *52*, 3173–3174.

171 a) P. Li, H. Yamamoto, *J. Am. Chem. Soc.* **2009**, *131*, 16628–16629. b) P. Li, H. Yamamoto, *Chem. Commun.* **2010**, *46*, 6294–6295.



Scheme 7.9. Lewis acid catalysed inverse-electron demand Diels-Alder reaction of tropone derivatives **294a** and **294c** with electron-rich dienophiles.

On the other hand, related 2,3-benzotropone derivatives **317** also underwent thermal [4+2] cycloaddition reactions in the presence of electro-deficient dienophiles such as maleic anhydride **316** (Y = O) or *N*-substituted maleimides **316** (Y = NMe or NPh) to furnish benzocycloheptenones **318** in moderate to good yields (**Scheme 7.10**).[172]

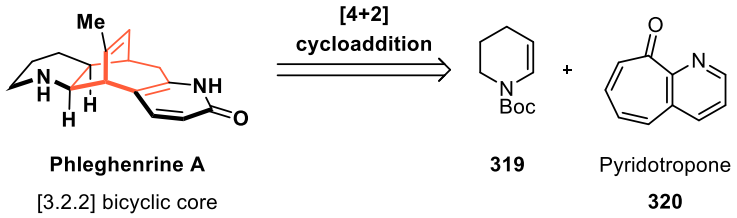


Scheme 7.10. Thermal [4+2] cycloaddition of 2,3-benzotropone derivatives **317** with electron-deficient dienophiles **316**.

[172] a) A. Hassner, D. Middlemiss, J. Murray-Rust, P. Murray-Rust, *Tetrahedron* **1982**, *38*, 2539–2546. b) S. Ebine, M. Hoshino, T. Machiguchi, *Bull. Chem. Soc. Jpn.* **1971**, *44*, 3480–3481.

7.2. Aims and objectives

As part of a program aiming at developing new synthetic methods for the total synthesis of phleghenrine alkaloids to test their biological activity as palliative drugs for Alzheimer's disease, an Inverse-Electron Demand Diels-Alder (IEDDA) reaction of pyridotropone **320** with a suitable electron-rich dienophile was envisioned for the preparation of the characteristic bicyclo[3.2.2]nonane scaffold present at these natural products (**Scheme 7.11**). Therefore, upon analysis of the structural features of the phleghenrine family, enecarbamate **319** was selected as the dienophile partner for [4+2] cycloaddition with pyridotropone **320** since it will give access to the desired bridged carbon framework together with the direct introduction of both nitrogen-containing heterocycles in a single step.



Scheme 7.11. Proposed retrosynthetic pathway for the preparation of phleghenrine [3.2.2] bicyclic core via Inverse-Electron Demand Diels-Alder reaction.

7.3. Results and discussion

The following optimisation of the [4+2] cycloaddition of pyridotropone **320** with electron-rich dienophiles and subsequent study of reaction scope has been carried out in collaboration with Dr. P. J. Gritsch.[173]

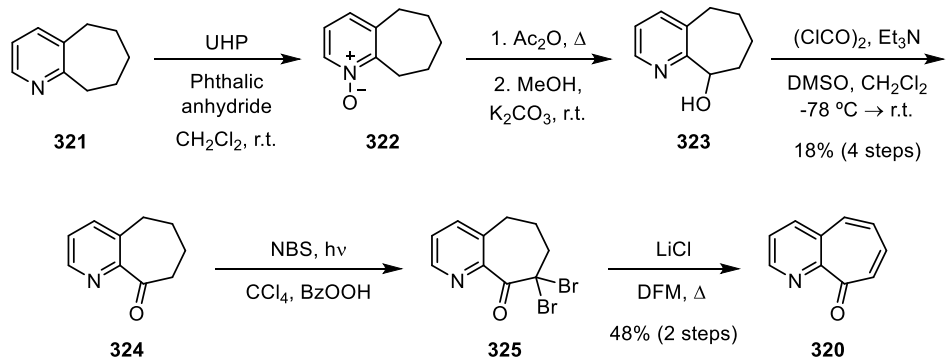
7.3.1. Synthesis of starting materials

In 1973, G. Jones and co-workers reported the preparation of pyridotropone **320** and other heterocyclic-substituted members of the troponoid family.[174] In the present

[173] P. J. Gritsch, I. Gimenez-Nueno, L. Wonilowicz, R. Sarpong, *J. Org. Chem.* **2019**, DOI 10.1021/acs.joc.9b00899.

[174] G. Jones, R. K. Jones, M. J. Robinson, *J. Chem. Soc. Perkin Trans. 1* **1973**, 968–972.

case, the synthesis of pyridotropone **320** was accomplished applying a slightly modified protocol based on previous synthetic experience from the group (**Scheme 7.12**).[175]



Scheme 7.12. Modified synthetic route for the preparation of pyridotropone **320**.

Thus, *N*-oxidation of commercially available 2,3-cycloheptenopyridine **321** in the presence urea-hydrogen peroxide (UHP) and phthalic anhydride afforded **322**. Then, a Boekelheide-type reaction was used for the regioselective installation of the alcohol moiety in compound **323** via [3,3]-sigmatropic rearrangement of the *N*-trifluoroacetoxy intermediate and subsequent deprotection. Oxidation under common Swern conditions gave access to ketone **324** in a 18% yield over the four steps. Final preparation of pyridotropone **320** was carried out upon geminal halogenation of **324** using *N*-bromosuccinimide under visible light irradiation to render **325** followed by LiCl-promoted dehydrobromination.

On the other hand, enecarbamate **319** was synthesised applying a reported protocol.[176] Thus, after *N*-protection, lactam carbamate **327** was treated with super hydride at low temperatures and trifluoroacetic anhydride in triethylamine to rendered enecarbamate **319** in moderate yields. One of the main drawbacks of present methodology was the difficulty to perform this reaction on large scale since final rates for product formation strongly depended on temperature control.

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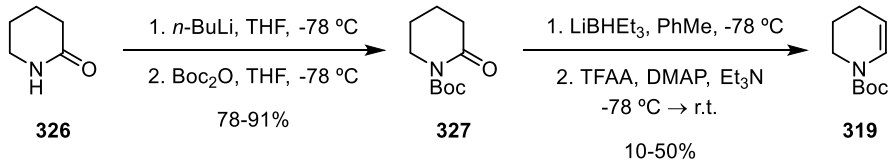
175 A. R. H. Narayan, R. Sarpong, *Org Biomol Chem* **2012**, *10*, 70–78.

176 a) J. Yu, V. Truc, P. Riebel, E. Hierl, B. Mudryk, *Tetrahedron Lett.* **2005**, *46*, 4011–4013. b) J. Yu, V. Truc, P. Riebel, E. Hierl, B. Mudryk, *Org. Synth.* **2008**, *85*, 64–71.

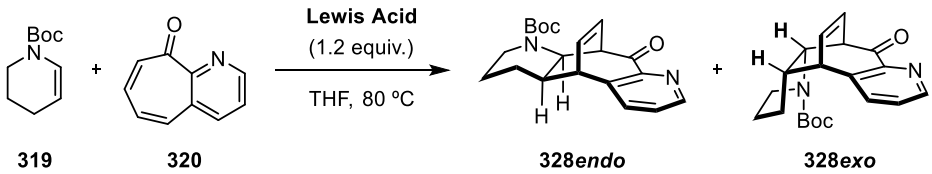


Scheme 7.13. Two step protocol for the preparation of enecarbamate **319**.

7.3.2. [4+2] cycloaddition reaction optimisation

Inspired by previous examples at the literature, the [4+2] cycloaddition of pyridotropone **320** with enecarbamate **319** was attempted under thermal conditions (THF, 80 ºC). However, only unreacted starting material was recovered after overnight stirring (**Table 7.1**, entry 1).

Table 7.1. Lewis acid screening for the [4+2] cycloaddition of pyridotropone **320** with enecarbamate **319**.



319 **320** **328*endo*** **328*exo***

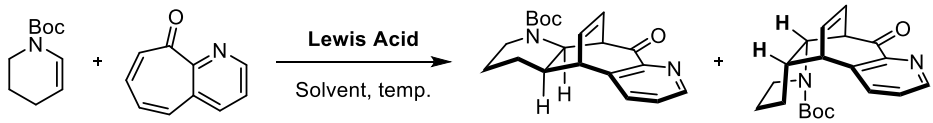
Entry	Lewis acid	Conv. 320 (%)	Yield (%)[b]	Entry	Lewis acid	Conv. 320 (%)	Yield (%)[b]
1	-	<5	NA[c]	**8**	$ZrCl_4$	<5	NA[c]
2	$B(C_6F_5)_3$	-[d]	NA[c]	**9**	$ZnCl_2$	24	10
3	$BF_3.EtO_2$	-[d]	NA[c]	**10**	$Zn(OAc)_2$	<5	NA[c]
4	$AlCl_3$	-[d]	NA[c]	**11**	ZnF_2	<5	NA[c]
5	$TiCl_4$	-[d]	NA[c]	**12**	$Zn(OTf)_2$	53	16
6	$SnCl_4$	-[d]	NA[c]	**13**	$ZnBr_2$	58	22
7	$Yb(OTf)_3$	-[d]	NA[c]	**14**[e]	$ZnBr_2$	14	13

[a] Pyridotropone **320** (1 equiv.), enecarbamate **319** (3 equiv.), Lewis acid (1.2 equiv.), THF (0.06 M), 80 ºC. [b] Combined yield (**328*endo*** + **328*exo***). Determined by ^{1}H NMR spectroscopy using 1,3-dinitrobenzene as internal standard. [c] Not applicable. [d] Starting material decomposition. [e] Open flask reaction.

A preliminary study of Lewis acids for diene **320** activation towards IEDDA reaction proved that commonly used boron, aluminium, titanium, tin and ytterbium

salts promoted substrate decomposition (**Table 7.1**, entries 2-7) whereas no reaction was observed for $ZrCl_4$ (**Table 7.1**, entry 8). To our delight, when $ZnCl_2$ was tested as a Lewis acid, a mixture of *endo*- and *exo*-isomers **328*endo*** and **328*exo*** was generated in modest yield (**Table 7.1**, entry 9). Moreover, upon screening of other zinc salts, $Zn(OTf)_2$ and $ZnBr_2$ were encountered to furnish compounds **328*endo*** and **328*exo*** (**Table 7.1**, entries 10-13). However, despite product formation, the differences between calculated conversions and yields were significantly high in all these cases (**Table 7.1**, entries 9, 12 and 13). Interestingly, when the cycloaddition reaction was performed under open flask conditions, an improved mass balance was observed, despite diminish yield (**Table 7.1**, entry 14).

Table 7.2. Optimisation of reaction conditions for the [4+2] cycloaddition of pyridotropone **320** with enecarbamate **319**.



319 **320** **328*endo*** **328*exo***

Entry	Lewis acid (equiv.)	Solvent (M), temperature	Conv. 320 (%)	Yield (%) (*dr*)[b]
1	$ZnBr_2$ (2.4)	THF (0.06), 80 ºC	19	18[c]
2[d]	$ZnBr_2$ (1.2)	THF (0.06), 80 ºC	44	39[c]
3[e]	$ZnBr_2$ (1.2)	THF (0.06), 80 ºC	63	51 (6.1:1)
4[e]	**$ZnBr_2$ (1.2)**	**THF (0.12), 80 ºC**	**100**	**89 (4.9:1)**
5[e]	$ZnBr_2$ (1.2)	THF/H_2O 10:1 (0.12), 80 ºC	87	56 (5.3:1)
6[e]	$ZnBr_2$ (1.2)	CH_3CN (0.12), 80 ºC	100	73 (2.7:1)
7[e]	$ZnBr_2$ (1.2)	MeOH (0.12), 80 ºC	100	59 (3.5:1)
8[e]	$ZnBr_2$ (1.2)	1,2-DCE (0.12), 80 ºC	91	55 (4:1)
9[e]	$ZnBr_2$ (1.2)	Toluene (0.12), 80 ºC	<5	NA
10[e]	$ZnBr_2$ (1.2)	THF (0.12), 40 ºC	<5	NA
11[e]	$ZnBr_2$ (0.1)	THF (0.12), 80 ºC	<5	NA
12[e,f]	**CuCl (0.1)**	**1,2-DCE (0.12), 80 ºC**	**100**	**73 (2.7:1)**
13[e,f]	CuCl (0.1)	THF (0.12), 80 ºC	26	15[c]
14[e,f]	CuCl (0.1)	1,2-DCE (0.12), 40 ºC	<5	NA

[a] Open flask reaction, pyridotropone **320** (1 equiv.), enecarbamate **319** (3 equiv.). [b] *dr*: **328*endo*:328*exo***. [c] Combined yield (**328*endo*** + **328*exo***). Determined by ^1H NMR spectroscopy using 1,3-dinitrobenzene as internal standard. [d] Enecarbamate **319** (5 equiv.). [e] Enecarbamate **319** (10 equiv.). [f] Inert reaction conditions.

With the optimised Lewis acid in hand, the effect of different experimental parameters was studied. Thus, similar yields were encountered when the equivalents of $ZnBr_2$ were doubled (**Table 7.2**, entry 1) whereas increased amounts of dienophile **319** proved to be beneficial for the final reaction outcome (**Table 7.2**, entries 2 and 3). Eventually, the [4+2] cycloaddition of pyridotropone **320** with 10 equivalents of enecarbamate **319** under more concentrated conditions rendered the desired bicyclo[3.2.2]nonanes **328*endo*** and **328*exo*** in 89% yield and 4.9:1 *dr*, with the *endo*-isomer as the major product (**Table 7.2**, entry 4).

In addition, solvent screening revealed that wet THF, polar protic solvents or chlorinated solvents were also tolerated for the present inverse-electron demand Diels-Alder reaction, albeit in lower yields and variable *dr* (**Table 7.2**, entries 5-8). On the contrary, unreacted starting material was recovered when non-polar toluene was used, probably due to the low solubility of the zinc salt in the reaction medium, (**Table 7.2**, entry 9). Likewise, cycloaddition strategy did not proceed under decreased temperatures (**Table 7.2**, entry 10).

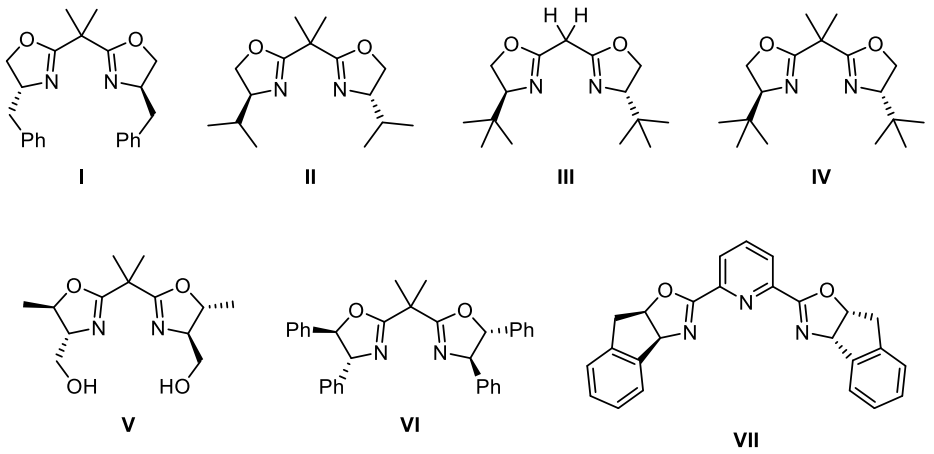


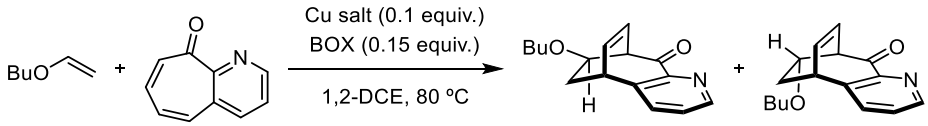
Figure 7.4. Chiral bisoxazoline ligands **I**-**VII**.

Preliminary attempts to render IEDDA protocol catalytic were unsuccessful (**Table 7.2**, entry 11). To our delight, by switching from substoichiometric amounts of $ZnBr_2$ to CuCl, pyridotropone **320** smoothly underwent cycloaddition reaction to furnish desired bicyclo[3.2.2]nonanes **328*endo*** and **328*exo*** in 73% yield and 2.7:1 *dr* (**Table 7.2**, entry 12). However, different solvents or decreased reaction

temperatures proved to be detrimental for the final outcome of the methodology (**Table 7.2**, entries 13 and 14).

The use of catalytic amounts copper salts for the [4+2] cycloaddition reaction of pyridotropone **320** with enecarbamate **319** opens up the possibility of an asymmetric version in the presence of chiral bisoxazoline ligands **I-VII** (**Figure 7.4**). Disappointingly, only racemic products were obtained under optimised conditions for dienophile **319**.

Table 7.3. Study of the enantiomeric [4+2] cycloaddition of pyridotropone **320** with butyl vinyl ether **329** in the presence of bisoxazoline ligands.



329 **320** **330*endo*** **330*exo***

Entry	Lewis acid	BOX Ligand	Conv. 320 (%)	Yield (%) (*dr*)[b]	330*endo* ee (%)
1	CuCl	I	100	80 (5.3:1)	-
2	CuCl	II	95	68 (5.3:1)	-
3	CuCl	III	38	21 (8.1:1)	-
4	CuCl	IV	100	66 (4.6:1)	-
5	**CuCl**	**V**	**86**	**78 (6.7:1)**	**16**
6	CuCl	VI	100	47 (4.6:1)	-
7	CuCl	VII	88	81 (5.3:1)	-
8[c]	**CuCl**	**V**	**10**	**9 (15.7:1)**	**27**
9[d]	CuCl	V	<5	NA	-
10	$Cu(OTf)_2$	V	18	14 (20:1)	-
11[e]	$Cu(OTf)_2$	V	39	31 (20:1)	-
12	$CuBr_2$	V	12	10 (6.7:1)	-
13[f]	$CuBr_2$	V	94	45 (3.3:1)	-

[a] Inert reaction conditions, pyridotropone **320** (1 equiv.), butyl vinyl ether **329** (10 equiv.), Cu salt (0.1 equiv.), BOX ligand (0.15 equiv.), 1,2-DCE (0.12 M), 80 ºC. [b] *dr*: **330*endo*:330*exo***. [c] Temp. = 60 ºC. [d] Temp. = 40 ºC. [e] MeOH (10 mol%). [f] $AgSbF_6$ (10 mol%).

Alternatively, a less sterically demanding dienophile, commercially available butyl vinyl ether **329**, was selected for the optimisation of the cooper-catalysed asymmetric

cycloaddition of pyridotropone **320** (**Table 7.3**). Thus, upon screening of different substituted bisoxazoline ligands **I-VII**, *endo*-isomer **330*endo*** was formed in moderate to good yields and increased selectivities (**Table 7.3**, entries 1-7). However, only a modest 16% ee was achieved for alcohol-containing ligand **V** (**Table 7.3**, entry 5). Attempts to lowering reaction temperature resulted in a slightly better enantioselectivity with notorious shrinkage of the final yield (**Table 7.3**, entry 8) whereas further temperature decrease rendered unreacted starting material after overnight stirring (**Table 7.3**, entry 9).

Interestingly, [4+2] cycloaddition reaction of pyridotropone **320** with butyl vinyl ether **329** was also catalysed by copper-(II) salts. In particular, $Cu(OTf)_2$ or a mixture of $Cu(OTf)_2$ with MeOH in the presence of BOX ligand **V** furnished bicyclo[3.2.2] nonane as essentially *endo*-isomer **330*endo***, albeit with no enantiocontrol (**Table 7.3**, entries 10 and 11).[177] Likewise, the use of $CuBr_2$ or a reported mixture of $CuBr_2$ with 10 mol% of $AgSbF_6$ was unsuccessful (**Table 7.3**, entries 12 and 13).[178] At this point, due to time constrains, we abandoned the asymmetric route and focussed on the study of the CuCl-catalysed cycloaddition of pyridotropone **320** with different electron-rich dienophiles .

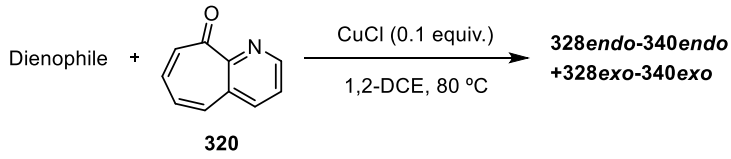
7.3.3. Copper-catalysed [4+2] cycloaddition of pyridotropone with different substituted electron-rich dienophiles

With the optimised conditions for the cycloaddition reaction of enecarbamate **319** in hand (0.1 equiv. of CuCl, 10.0 equiv. of dienophile, 0.12 M in 1,2-DCE) (**Table 7.4**, entry 1), other electron-rich dienophiles were tested. Thus, terminal vinyl ethers **329** and **297** effectively formed the corresponding bicyclo[3.2.2]nonanes **330*endo*** and **331*endo*** in high yields and good *endo*-selectivities (**Table 7.4**, entries 2 and 3). However, disubstituted olefin **293** proved to be a more challenging substrate, rendering the corresponding cycloadduct **332** in lower yields (**Table 7.4**, entry 4) whereas unreacted starting material was recovered when sterically hindered dihydropyran **333** was used as dienophile, even under increased reaction temperatures (**Table 7.4**, entry 5). On the other hand, highly reactive enamine

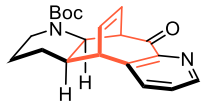
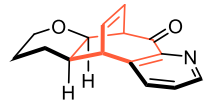
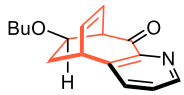
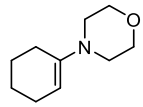
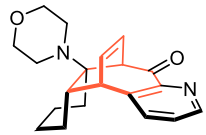
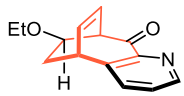
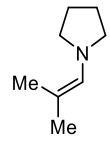
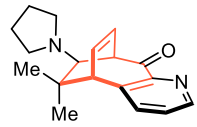
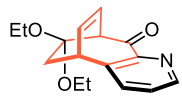
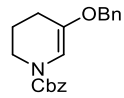
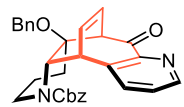
[177] V. N. G. Lindsay, R. A. Murphy, R. Sarpong, *Chem. Commun.* **2017**, *53*, 10291–10294.
[178] V. K. Aggarwal, D. E. Jones, A. M. Martin-Castro, *Eur. J. Org. Chem.* **2000**, 2939–2945.

derivatives **335** and **337** smoothly underwent inverse-electron demand Diels-Alder reaction with pyridotropone **320** at room temperature (**Table 7.4**, entries 6 and 7).

Table 7.4. Reaction scope for the [4+2] cycloaddition of pyridotropone **320** with different substituted electron-rich dienophiles.



320

Entry	Dienophile	Major product[b]	Entry	Dienophile	Major product[b]
1	 **319**	 **328*endo*** 73%, 2.7:1 *dr*	5	 **333**	 **334*endo*** n.p.[c]
2	 **329**	 **330*endo*** 80%, 5.6:1 *dr*	6[d]	 **335**	 **336*endo*** 53%, 2.5:1 *dr*
3	 **297**	 **331*endo*** 79%, 5.0:1 *dr*	7[d,e]	 **337**	 **338*endo*** 75%, >95:1 *dr*
4	 **293**	 **332** 48%	8	 **339**	 **340*endo*** n.p.[c]

[a] Inert reaction conditions, pyridotropone **320** (1 equiv.), dienophile (10 equiv.), CuCl (0.1 equiv.), 1,2-DCE (0.12 M), 80 °C. [b] *dr*: **328*endo*-340*endo*:328*exo*-340*exo***. [c] No product formation observed. [d] Temp. = 25 °C. [e] *In situ* formation of enamine.

To our surprise, the study of the IEDDA reaction scope for pyridotropone **320** rendered in all the cases cycloadducts **328endo-340endo** where the electron-

donating group from the corresponding dienophile partner took up a β-position with respect to the carbonylic function, despite an anticipated γ-regioselectivity based on the previously mentioned literature examples for tropone derivatives **294** (**Scheme 7.9**). In fact, experimental results would be in agreement with the electronic bias imposed by both the pyridotropone **320** and the electron-rich dienophiles. Therefore, the unexpected reaction outcome prevented the direct application of this methodology to the synthesis of phleghenrine alkaloids. In an attempt to reverse the observed regioselectivity, enecarbamate **339** containing an electron-donating moiety at C-β was used as a dienophile, however the [4+2] cycloaddition reaction did not proceed probably due to the high steric hinderance of this starting material (**Table 7.4**, entry 8).

7.4. Supporting Information

Unless otherwise noted, all reactions were performed in flame- or oven-dried glassware fitted with rubber septa under a positive pressure of nitrogen using standard Schlenk techniques. Air- and moisture-sensitive liquids were transferred via syringe or stainless-steel cannula through rubber septa. Solids were added under inert gas or were dissolved in the appropriate solvents. Reaction temperatures above 23 ºC were conducted in an oil or sand bath. Reactions were magnetically stirred and monitored by NMR spectroscopy or analytical thin-layer chromatography (TLC), using glass plates precoated with silica gel (Silicycle Siliaplates, glass backed, extra hard layer, 60 Å, 250 μm thickness, F254 indicator). TLC plates were visualized by exposure to ultraviolet light (254 nm), were stained by submersion in aqueous potassium permanganate solution ($KMnO_4$) or phosphomolybdic acid solution (PMA) and were developed by heating with a heat gun. Flash column chromatography was performed employing silica gel (Silicycle silica gel, 40–63 μm particle size). Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) pure material. Unless noted below, commercial reagents were purchased from MilliporeSigma, Acros Organics, Chem Impex, Oakwood Chemical, Combi Blocks, TCI, and/or Alfa Aesar and used without additional purification. Solvents were purchased from Fisher Scientific, Acros Organics, Alfa Aesar, and Sigma-Aldrich. Tetrahydrofuran (THF), diethyl ether (Et_2O), acetonitrile (CH_3CN), benzene, toluene, methanol (MeOH), and triethylamine (Et_3N) were sparged with argon and

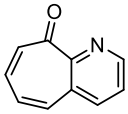
dried by passing through alumina columns using argon in a Glass Contour solvent purification system. Dichloromethane (CH_2Cl_2) was freshly distilled over calcium hydride under a N_2 atmosphere prior to each use. NMR spectral data were obtained using deuterated solvents, obtained from Cambridge Isotope Laboratories, Inc. ^1H NMR and ^{13}C NMR data were recorded on Bruker AV-600 or AV-700 spectrometers (operating at 600 and 700 MHz for proton nuclei and 150 and 175 MHz for carbon nuclei), respectively. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to residual protium in the NMR solvent ($CHCl_3$: δ 7.26). Carbon chemical shifts are expressed in parts per million (δ scale, assigned carbon atom) and are referenced to the carbon resonance of the NMR solvent ($CDCl_3$: δ 77.16). All raw FID files were processed and the spectra analyzed using the program MestReNova v12.0.4-22023. Note that the AV-600 instrument was partially supported by NIH grants SRR023679A, RR02424A-01, S10RR03353-01 and 1S10RR016634-01 and NSF grants CHE-9633007, CHE-8208992, CHE-0130862, and CHE-8703048. The AV-700 instrument was supported by the Berkeley College of Chemistry NMR facility. Mass spectral data were obtained from the Mass Spectral Facility at the University of California, Berkeley, on a Finnigan/Thermo LTQ-FT instrument (ESI). Data acquisition and processing were performed using the XcaliburTM software. IR spectroscopic data were recorded on a Bruker ALPHA FT-IR spectrophotometer using a diamond attenuated total reflectance (ATR) accessory. Melting points were recorded using a Mel-Temp II by Laboratory Devices, Inc. Preparative HPLC was performed on an Agilent System using an Agilent Prepstar solvent delivery system, Agilent Prostar UV-detector and an Agilent Technologies 440-LC Fraction collector. A Phenomex Luna, 5 μm silica (2) 100 Å, AXIA packed 250 x 21.2 mm column was used. Data acquisition and processing were performed using Agilent OpenLAB CDS C.01.03[37]. Compounds **319**,[176] **293**,[179] **335**,[180] and **339**[181] were prepared following literature procedures.

[179] P. C. Venneri, J. Warkentin, *Can. J. Chem.* **2000**, *78*, 1194–1203.

[180] I. S. Darwish, C. Patel, M. J. Miller, *J. Org. Chem.* **1993**, *58*, 6072–6075.

[181] Y. Takeuchi, M. Hattori, H. Abe, T. Harayama, *Synthesis* **1999**, 1814–1818.

9*H*-Cyclohepta[*b*]pyridin-9-one (320).



320

Ketone **324** was obtained according to a published procedure.[175] The two subsequent steps are a modification of a published procedure.[174] To a round-bottomed flask were added a magnetic stir bar, **324** (1.00 g, 6.20 mmol, 1.0 equiv.), NBS (2.27 g, 12.7 mmol, 2.05 equiv.) and BzOOH (75.0 mg, 0.310 mmol, 0.05 equiv.). The flask was fitted with a reflux condenser, sealed with a septum and flushed with nitrogen. Finally CCl_4 (30 mL) was added to the flask and the mixture was heated and held at reflux and irradiated using a 300 W halogen sunlight lamp (EIKO ELH 300/120 V, AV/Photolamp). Full conversion of the starting material was observed after 20 min (TLC analysis) and the reaction mixture was cooled down to room temperature. Water was added and the resulting mixture was extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude dibromide **325** (1.47 g, 4.61 mmol, 1.0 equiv.) was dissolved in DMF (20 mL) and LiCl (1.95 g, 46.1 mmol, 10.0 equiv.) was added. This mixture was heated to 160 ºC and held at this temperature for 20 min at which point TLC analysis indicated complete consumption of the starting material. The reaction mixture was cooled to 23 ºC and the DMF was evaporated under vacuum. The resulting solid was taken up in water and filtered through a plug of Celite. The residue was triturated three times with CH_2Cl_2 and filtered through the same plug of Celite. The combined filtrates were partitioned and the aqueous phase was extracted four times with CH_2Cl_2 until TLC analysis showed complete removal of the product from the aqueous phase. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was subsequently purified with flash chromatography on silica gel (100 g, 1% Et_3N in EtOAc) to provide **320** (452 mg, 48%, 2 steps) as a brown solid. Compound **320** provided analytical data fully consistent with previously reported data from the literature.

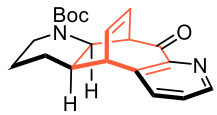
TLC (99% EtOAc, 1% Et_3N) $\mathbf{R_f}$ = 0.09 (UV, PMA). **M.p.** = 50–52 ºC. **^{1}H NMR** (600 MHz, $CDCl_3$, δ in ppm) δ = 9.02 (dd, *J* = 4.3 Hz, 1.7 Hz, 1H), 8.04 (dd, *J* = 8.2 Hz, 1.6 Hz, 1H), 7.62 (dd, *J* = 7.9 Hz, 4.5 Hz, 1H), 7.20 (d, *J* = 11.5 Hz, 1H), 7.13 (ddd, *J* = 12.3 Hz, 7.5 Hz, 0.8 Hz, 1H), 7.09 (d, *J* = 12.4 Hz, 1H), 6.83 (ddd, *J*

= 11.6 Hz, 7.44 Hz, 1.4 Hz, 1H). **^{13}C NMR** (150 MHz, $CDCl_3$, δ in ppm) δ = 187.1, 152.8, 152.2, 141.9, 136.7, 136.0, 135.2, 132.0, 128.6, 126.3. **HRMS (ESI$^+$)** $[M+H]^+$ calc for $C_{10}H_8NO$: 158.0600, found: 158.0605. **IR (Diamond ATR, neat)** ν in cm^{-1}: 3453 (b), 1642 (s), 1611 (s), 1586 (s), 1323 (m), 831 (s), 797 (m), 559 (w).

Representative procedure for the synthesis of [3.2.2] bicycles.

In a glovebox, a conical 2 mL microwave vial equipped with a magnetic stir bar was charged with CuCl (0.6 mg, 0.006 mmol, 0.1 equiv.), sealed shut and taken out of the glovebox. A solution of **320** (10 mg, 0.064 mmol, 1.0 equiv.) in 1,2-DCE (300 *μL*) was added followed by a solution of the dienophile (10 equiv.) in 1,2-DCE (200 *μL*). The resulting brown mixture was heated to 80 ºC and held at this temperature for 16 h or until TLC analysis indicated complete consumption of the starting material. The reaction mixture was then allowed to cool to 23 ºC and finally poured onto 2N NaOH. The resulting mixture was extracted three times with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Because the products tend to degrade under light and at temperatures higher than 25 ºC, the flasks containing the organic phase were covered with aluminium foil during removal of the solvent. The crude product was purified by flash column chromatography on silica gel (2.5 g SiO_2, 70% EtOAc, 1% Et_3N in hexanes → 1% Et_3N in EtOAc) to provide the cycloaddition product.

***tert*-Butyl 11-oxo-5,5a,6,7,8,9a,10,11-octahydro-9*H*-5,10-ethenocyclohepta[1,2-*b*:5,4-*b*']dipyridine-9-carboxylate (328*endo*).**



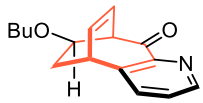
328*endo*

Following the representative procedure, [3.2.2] bicycle **328*endo*** was prepared using **319** (120 mg, 0.640 mmol, 10.0 equiv.) as the dienophile. The crude residue was purified by flash column chromatography on silica gel (2.5 g SiO_2, 1% Et_3N in EtOAc) to provide the cycloaddition product **328*endo*** (16.2 mg, 73% yield, 2.7:1 *dr*) as a colourless oil. The diastereomers were separated using preparative HPLC

(hexanes/*i*-PrOH = 70:30, flow rate = 20.0 mL/min, t_{minor} = 20.7 min, t_{major} = 25.1 min) to obtain the major diastereomer as an analytically pure sample.

TLC (10% acetone in $CHCl_3$) $\mathbf{R_f}$ = 0.36 (UV, PMA). **^{1}H NMR** (700 MHz, $CDCl_3$, δ in ppm) δ = 8.70 (d, *J* = 4.6 Hz, 1H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.31 (dd, *J* = 7.5 Hz, 4.9 Hz, 1H), 6.62 (dd *J* = 7.7 Hz, 7.7. Hz, 1H), 6.24 (dd, *J* = 7.9 Hz, 7.89 Hz, 1H), 4.47 (br s, 1H), 4.20 (br s, 1H), 3.90 (br s, 1H), 3.70 (t, *J* = 6.5 Hz, 1H), 2.71-2.64 (m, 1H), 2.31 (br s, 1H), 1.69-1.62 (br s, 1H), 1.49 (s, 9H) 1.24-1.18 (br m, 2H), 0.84-0.76 (m, 1H). **^{13}C NMR** (175 MHz, $CDCl_3$, δ in ppm) δ = 194.4, 155.3, 149.5, 148.9, 148.8, 144.6, 137.1, 136.8, 130.3, 126.0, 80.3, 48.0, 33.0, 29.8, 28.6 (3), 27.3, 25.5, 22.9. **HRMS (ESI$^+$)** $[M+Na]^+$ calc for $C_{20}H_{24}NaN_2O_3$: 363.1679, found: 363.1682. **IR (Diamond ATR, neat)** ν in cm^{-1}: 2969 (w), 2932 (m), 2866 (w), 1737 (w), 1686 (s), 1391 (m), 1289 (w) 1158 (s).

10-Butoxy-5,8-dihydro-9*H*-8,5-ethanocyclohepta[*b*]pyridin-9-one (330*endo*).



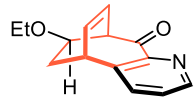
330*endo*

Following the representative procedure, [3.2.2] bicycle **330*endo*** was prepared using *n*-butyl vinyl ether (64.1 mg, 0.64 mmol, 10.0 equiv.) as the dienophile. The crude residue was purified by flash column chromatography on silica gel (2.5 g SiO_2, 1% Et_3N in EtOAc) to provide cycloadduct **330*endo*** (13.1 mg, 80% yield, 5.4:1 *dr*) as a colourless oil. The diastereomers were separated using preparative HPLC (hexanes/*i*-PrOH = 70:30, flow rate = 20.0 mL/min, t_{minor} = 14.7 min, t_{major} = 17.8 min) to obtain the major diastereomer as an analytically pure sample.

TLC (1% Et_3N in EtOAc) $\mathbf{R_f}$ = 0.18. **^{1}H NMR** (600 MHz, $CDCl_3$, δ in ppm) δ = 8.70 (br s, 1H), 7.57 (br s, 1H), 7.33 (dd, *J* = 6.5 Hz, 4.3 Hz, 1H), 6.84 (dd, *J* = 7.0 Hz, 7.0 Hz, 1H), 6.16 (dd, *J* = 6.7 Hz, 6.7 Hz, 1H), 4.10 (d, *J* = 4.9 Hz, 2H), 3.64 (br, 1H) 3.56-3.50 (m, 1H), 3.42-3.36 (m, 1H), 2.54 (dd, *J* = 13.5 Hz, 8.6 Hz, 1H), 1.92 (d, *J* = 13.5 Hz, 1H), 1.55-1.50 (m, 2H), 1.38-1.31 (m, 2H), 0.93-0.88 (m, 3H). **^{13}C NMR** (175 MHz, $CDCl_3$, δ in ppm) δ = 192.1, 149.2, 148.3, 144.9, 138.8, 136.6, 126.8, 124.9, 75.2, 69.4, 57.5, 40.8, 36.5, 32.0, 19.5, 14.0. **HRMS (ESI$^+$)** $[M+H]^+$ calc

for $C_{16}H_{20}NO_2$: 258.1489, found: 258.1495. **IR (Diamond ATR, neat)** ν in cm^{-1}: 2955 (m), 2923 (m), 2864 (m), 1692 (s) 1289 (w), 1098 (s), 767 (m), 715 (w).

10-Ethoxy-5,8-dihydro-9*H*-8,5-ethanocyclohepta[*b*]pyridin-9-one (331*endo*).

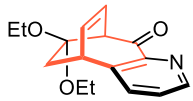


331*endo*

Following the representative procedure, [3.2.2] bicycle **331*endo*** was prepared using ethyl vinyl ether (46.1 mg, 0.640 mmol, 10.0 equiv.) as the dienophile. The crude residue was purified by flash column chromatography on silica gel (2.5 g SiO_2, 1% Et_3N in EtOAc) to provide cycloadduct **331*endo*** (11.6 mg, 79% yield, 5.0:1 *dr*) as a colourless oil. The diastereomers were separated using preparative HPLC (hexanes/*i*-PrOH = 80:20, flow rate = 20.0 mL/min, t_{minor} = 14.0 min, t_{major} = 15.8 min) to obtain the major diastereomer as an analytical pure sample.

TLC (1% Et_3N in EtOAc) $\mathbf{R_f}$ = 0.18 (UV, PMA). **^{1}H NMR** (700 MHz, $CDCl_3$, δ in ppm) δ = 8.70 (br s, 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.32 (dd, *J* = 6.2 Hz, 5.0 Hz, 1H), 6.84 (dd, *J* = 7.8 Hz, 7.8 Hz, 1H), 6.17 (dd, *J* = 7.6 Hz, 7.6 Hz, 1H), 4.15-4.12 (br s, 1H), 4.10 (dd, *J* = 16.3 Hz, 6.0 Hz, 1H), 3.64 (br s, 1H), 3.61 (dd, *J* = 7.5 Hz, 7.5 Hz, 1H), 3.46 (ddd, *J* = 14.7 Hz, 7.2 Hz, 7.2 Hz, 1H). 2.55 (dd, *J* = 12.7 Hz, 9.9 Hz, 1H) 1.95-1.90 (app m, 1H), 1.20 (t, *J* = 6.7 Hz, 3H). **^{13}C NMR** (175 MHz, $CDCl_3$, δ in ppm) δ = 192.1, 149.2, 148.2, 144.8, 138.9, 136.6, 126.8, 124.9, 75.0, 64.9, 57.5, 40.7, 36.5, 15.5. **HRMS (ESI$^+$)** $[M+H]^+$ calc for $C_{14}H_{16}NO_2$: 230.1176, found: 230.1172. **IR (Diamond ATR, neat)** ν in cm^{-1}: 2970 (m), 292z (b), 2864 (m), 1692 (s) 1099 (s), 766 (m).

10,10-Diethoxy-5,8-dihydro-9*H*-5,8-ethanocyclohepta[*b*]pyridin-9-one (332).

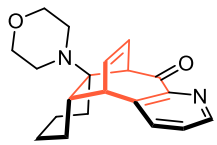


332

Following the representative procedure, [3.2.2] bicycle **332** was prepared using **293** (74.0 mg, 0.640 mmol, 10.0 equiv.) as the dienophile. The crude residue was purified by flash column chromatography on silica gel (2.5 g SiO_2, 1% Et_3N in 1:5 hexanes/EtOAc) to provide the cycloaddition product **332** (8.4 mg, 48% yield) as colourless oil.

TLC (1% Et_3N in 1:5 hexanes/EtOAc) $\mathbf{R_f}$ = 0.25 (UV, PMA). **^{1}H NMR** (600 MHz, $CDCl_3$, δ in ppm) δ = 8.69 (d, *J* = 4.2 Hz, 1H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.31 (ddd, *J* = 6.9 Hz, 5.3 Hz, 1.4 Hz, 1H), 6.79 (dd, *J* = 7.6 Hz, 7.6 Hz, 1H), 6.17 (dd, *J* = 7.8 Hz, 7.8 Hz, 1H), 4.21 (d, *J* = 7.3 Hz, 1H), 3.67 (br s, 1H), 3.54-3.49 (m, 3H), 3.49-3.44 (m, 1H), 2.27 (s, 2H), 1.19 (t, *J* = 6.9 Hz. 3H), 0.94 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$, δ in ppm) δ = 191.9, 149.1, 148.9, 141.8, 138.5, 136.9, 125.9, 68.1, 61.9, 56.6, 47.3, 38.6, 29.0, 27.2, 19.0, 17.6. **HRMS (ESI$^+$)** $[M+H]^+$ calc for $C_{16}H_{20}NO_3$: 274.1438, found: 274.1434. **IR (Diamond ATR, neat)** ν in cm^{-1}: 2973 (m), 2925 (m), 2897 (w), 2850 (w), 1693 (s), 1453 (w), 1119 (m), 1106 (m), 1084 (s), 1046 (s), 1021 (m), 427 (w), 416 (w).

9a-Morpholino-5,5a,6,7,8,9,9a,10-octahydro-11*H*-5,10-ethenobenzo[4,5] cyclohepta[1,2-*b*]pyridin-11-one (336*endo*).



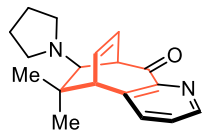
336*endo*

Following representative procedure at room temperature, [3.2.2] bicycle **336*endo*** was prepared using **335** (107 mg, 0.640 mmol, 10.0 equiv.) as the dienophile. The crude residue was purified by flash column chromatography on silica gel (2.5 g SiO_2, 1% Et_3N in EtOAc) to provide the cycloaddition product **336*endo*** (11 mg, 53% yield, 2.5:1 *dr*) as a colourless oil. A partial separation via flash

chromatography enabled us to obtain an analytical pure sample of the major diastereomer.

TLC (1% Et_3N in EtOAc) $\mathbf{R_f}$ = 0.12 (UV, PMA). **^{1}H NMR** (700 MHz, $CDCl_3$, limited rotation, δ in ppm) δ = 8.71 (d, *J* = 4.6 Hz, 1H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.30 (dd, *J* = 7.5 Hz, 4.6 Hz, 1H), 6.61 (dd, *J* = 7.8 Hz, 7.8 Hz, 1H), 6.06 (dd, *J* = 7.8 Hz, 7.8 Hz, 1H), 3.80 (d, *J* =7.4 Hz, 1H), 3.74-3.58 (br s, 4H), 3.42 (dd, *J* = 6.5 Hz, 5.0 Hz, 1H), 2.77-2.67 (br s, 2H), 2.43-2.31 (br s, 2H), 2.17-2.13 (m, 1H), 1.77 (dd, *J* = 15.0 Hz, 6.0 Hz, 1H), 1.74-1.68 (m, 1H), 1.63-1.58 (m, 1H), 1.47-1.39 (m, 1H), 1.25-1.21 (m, 2H), 0.94 (ddd, *J* = 14.0 Hz, 13.0 Hz, 7.4 Hz, 1H), 0.82 (dq, *J* = 12.9 Hz, 2.9 Hz, 1H). **^{13}C NMR** (175 MHz, $CDCl_3$, δ in ppm) δ = *1*91.9, 149.2, 149.0, 141.8, 138.5, 136.9, 125.9, 125.9, 68.1, 68.1, 62.0, 56.6, 48.8 (br), 48.7 (br), 47.3, 38.6, 29.0, 27.2, 19.0, 17.6. **HRMS (ESI$^+$)** $[M+Na]^+$ calc for $C_{20}H_{24}NaN_2O_2$: 347.1730, found: 347.1738. **IR (Diamond ATR, neat)** ν in cm^{-1}: 2969 (m), 2942 (br), 2855 (w), 1738 (s), 1686 (w), 1452 (w), 1434 (m), 1229 (m), 1216 (m) 1117 (w).

11,11-Dimethyl-10-(pyrrolidin-1-yl)-5,8-dihydro-9*H*-8,5-ethanocyclohepta [*b*]pyridin-9-one (338*endo*).



338*endo*

This compound was prepared using a variation of the representative procedure. In a glovebox, a conical 2 mL microwave vial containing a stir bar was charged with CuCl (0.6 mg, 0.006 mmol, 0.1 equiv.) and $MgSO_4$ (77.0 mg, 0.64 mmol, 10 equiv.), sealed shut and brought outside the glovebox. A solution of **320** (10 mg, 0.064 mmol, 1.0 equiv.) in 1,2-DCE (500 μL) was added followed by isobutyraldehyde (46.2 mg, 0.640 mmol, 10 equiv.) and subsequently pyrrolidine (23 mg, 0.320 mmol, 5.0 equiv.). The reaction mixture was stirred for 6 h at room temperature at which point TLC analysis showed complete conversion of the starting material. The mixture was subsequently poured onto 2N NaOH and extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. As the products seem to degrade under light and temperatures higher than 25 °C, the

flask containing the combined organic phase was covered with aluminium foil during removal of the solvent. The crude product was purified by flash column chromatography on silica gel (2.5 g SiO_2, 4% MeOH, 1% Et_3N in CH_2Cl_2) to provide the cycloaddition product **338*endo*** (13.5 mg, 75%) as a colourless oil and single diastereomer.

TLC (4% MeOH, 1%Et_3N in CH_2Cl_2) $\mathbf{R_f}$ = 0.25 (UV, PMA). **^{1}H NMR** (700 MHz, $CDCl_3$, δ in ppm) δ = 8.70 (d, *J* = 3.5 Hz, 1H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.33 (dd, *J* = 7.4 Hz, 4.7 Hz, 1H), 6.70-6.63 (br m, 1H), 6.17 (dd, *J* = 7.7 Hz, 7.7 Hz, 1H), 3.72 (d, *J* = 7.4 Hz, 1H), 3.25- 3.18 (m, 2H), 2.83-2.73 (br s, 2H), 2.66-2.56 (br s, 2H), 1.84-1.69-(br s, 4H), 1.22 (s, 3H), 0.92 (s, 3H). **^{13}C NMR** (175 MHz, $CDCl_3$, δ in ppm) δ = 193.1, 149.1, 148.2, 142.5, 139.3, 138.8, 126.4, 124.3, 66.2, 55.3 (2), 52.8, 51.8, 40.0, 30.8, 26.6, 24.7 (2). **HRMS (ESI$^+$)** $[M+H]^+$ calc for $C_{18}H_{23}N_2O$: 283.1805, found: 283.1807. **IR (Diamond ATR, neat)** ν in cm^{-1}: 2954 (s), 2924 (s), 2868 (m), 1690 (s), 1451 (w), 1115 (w), 806 (m).

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CHAPTER VIII

GENERAL CONCLUSIONS

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General conclusions

As previously stated in the objectives section of this thesis, the present PhD work aimed at developing new synthetic methodologies for the regio- and stereoselective preparation of unsaturated vicinal hetero-amino moieties related to relevant lipids occurring in nature. The proposed retrosynthetic strategy relied on the ring-opening of different vinylaziridine intermediate to get access to 1,2-difunctionalised products in a straightforward manner.

The results have been divided in three chapters dealing with the metal-free intramolecular aziridination/ring-opening of dienyl carbamates in the presence of iodosylbenzene to furnish racemic *anti*- and *syn*-oxazolidinones (chapter III), a related protocol for the asymmetric synthesis of vinylaziridines using chiral hypervalent iodine reagents (chapter IV) and an alternative approach for the preparation of enantioenriched vicinal hetero-amino moieties via organocatalysed kinetic resolution of racemic oxazolidinones (chapter V).

Regarding the *one-pot* intramolecular aziridination/ring-opening of dienyl carbamates, iodosylbenzene has proved to efficiently promote this transformation under metal-free conditions via transient iminoiodane formation. After extensive optimisation of reaction conditions, several dienyl carbamates bearing different side chains have been successfully converted into the desired *anti*-oxazolidinone products in high yields and complete stereoselectivities using 2 equivalents of PhIO and 4Å molecular sieves. Moreover, recrystallisation of the starting material was found to be crucial for the final outcome of the aziridination protocol.

Along these lines, the thermodynamic analysis carried out by Dr. I. Funes-Ardoiz and Prof. F. Maseras (ICIQ) highlighted the endergonic character of PhIO-mediated iminoiodane formation (0.8 kcal/mol nitrene). However, the addition of preactivated molecular sieves to the crude mixture enabled water by-product removal, favouring full conversion of the starting material into the iminoiodane intermediate. On the contrary, reaction of model dienyl carbamate with commercially available $PhI(OAc)_2$ did not proceed whereas $PhI(OCOCF_3)_2$ led to a complex mixture of products.

From a mechanistic point of view, a DFT study revealed that, after iminoiodane formation, the aziridination reaction proceeds through a concerted pathway with asynchronous C-N bond formation and a transition state stabilised by dispersion interactions between the phenyl ring from hypervalent iodine reagent and the distal double in dienyl carbamate. Then, according to the calculated free energy profile, final dissociation of iodobenzene yielded bicyclic vinylaziridine.

Several O-, X-, S- and N-nucleophiles have been tested for the ring-opening step rendering *anti*-substituted oxazolidinones in moderate to good yields and complete S_N2 regioselectivity. An important limitation of this strategy was the low solubility of some nucleophilic sources in dichloromethane, the solvent of choice. Therefore, in order to ensure full consumption of the vinylaziridine intermediate, it was necessary to increase nucleophile/substrate molar ratio. Moreover, a slightly acidic reaction medium was observed to hamper regiocontrol during ring-opening step, enhancing S_N2' product's formation.

Additionally, when related (2*Z*,4*E*)-hexa-2,4-dien-1-yl carbamate was treated with PhIO under the optimised aziridination conditions in the presence of the same set of heteroatomic nucleophiles, the corresponding *syn*-substituted oxazolidinones were obtained with complete S_N2 regioselectivity although in lower yields.

The development of a new asymmetric protocol for preparation of enantioenriched vinylaziridines started by the optimisation of the *one-pot* $PhI(OAc)_2$-mediated aziridination/ring-opening of model dienyl carbamate. Interestingly, among commonly used acidic and basic additives, only K_2CO_3 successfully promoted the formation of racemic *anti*-oxazolidinone.

Subsequent application of lactate-based (diacetoxyiodo)arenes to the asymmetric synthesis of vicinal difunctionalised products led to different results. Whereas amide-containing λ^3-iodanes rendered hydroxy-substituted oxazolidinones in low enantioselectivities, promising enantiocontrol was achieved for ester-containing analogues. Disappointingly, poor reaction yields were observed in all the cases probably due to the uncomplete oxidation of chiral iodine(I) precursor in the previous step. Therefore, current on-going studies are focussed on the *in situ* preparation of hypervalent iodine reagents to circumvent isolation problems.

Finally, the kinetic resolution of racemic oxazolidinones through an efficient organocatalysed *N*-acylation reaction was envisaged as an interesting alternative for the preparation of enantioenriched vicinal hetero-amino functionalities. Thus, racemic *anti*-substituted oxazolidinones bearing different *O*-, *S*- and *N*-groups successfully underwent kinetic resolution in the presence of BTM catalyst under optimised conditions rendering the acylated oxazolidinone up to 98% ee whereas the unreacted starting material was isolated in only slightly lower enantioselectivities. Moreover, the applicability of this methodology was further expanded to the resolution of analogous *syn*-substituted oxazolidinones, albeit with decreased selectivities. Interestingly, after kinetic resolution, both *syn*- and *anti*- acylated compounds displayed the same absolute configuration for the carbon stereocentre adjacent to the reactive nitrogen atom.

In addition, the formal syntheses of 3-heterosubstituted sphingosine analogues were accomplished via cross metathesis of enantioenriched *anti*-acyl-oxazolidinones with side chains of different length. Catalyst screening highlighted the outstanding performance of commercially available Grubbs 2nd generation reagent for the present coupling reaction. Finally, deprotection of the polar head under basic conditions led to *O*-, *S*- and *N*-substituted products.

On the other hand, as part of a project concerning the total synthesis of phleghenrine alkaloids for their biological evaluation as palliative drugs for Alzheimer's disease, the preparation of desired bicyclo[3.2.2]nonane via Lewis acid catalysed [4+2] cycloaddition of pyridotropone with different electron-rich dienophiles was achieved with complete selectivity. Both $ZnBr_2$ and CuCl additives led to full conversion of the starting material however only the copper salt allowed working under substoichiometric conditions. Unfortunately, attempts to develop the asymmetric version of the cycloaddition reaction in the presence of bisoxazoline ligands failed.

Moreover, the protocol was successfully applied to enecarbamate and enamine derivates as well as terminal vinyl ethers. However, more substituted olefins proved to be challenging substrates for the cycloaddition reaction. In all the cases, the electron-donating group from the dienophile partner took up β-position with respect to the carbonyl group from pyridotropone, leading to bicyclo[3.2.2]nonanes with an

incorrect disposition of the heteroatomic substituents for the final preparation of phleghenrine alkaloids. Disappointingly, efforts to reverse the observed regioselectivity for the cycloaddition reaction have been fruitless to date.

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ANNEX

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PUBLICATIONS

- J. Guasch, I. Giménez-Nueno, I. Funes-Ardoiz, M. Bernús, M. I. Matheu, F. Maseras, S. Castillón, Y. Díaz "**Enantioselective Synthesis of Aminodiols by Sequential Rhodium-Catalysed Oxyamination/Kinetic Resolution: Expanding the Substrate Scope of Amidine-Based Catalysis**" *Chem. Eur. J.* **2018**, *24*, 4635–4642.

- P. J. Gritsch, I. Giménez-Nueno, L. Wonilowicz, R. Sarpong "**Copper-Catalyzed [4+2] Cycloaddition of 9*H*-Cyclohepta[*b*]pyridine-9-one and Electron-Rich Alkenes**" *J. Org. Chem.* **2019**, DOI 10.1021/acs.joc.9b00899.

- I. Giménez-Nueno, J. Guasch, I. Funes-Ardoiz, M. I. Matheu, F. Maseras, S. Castillón, Y. Díaz "**Enantioselective Synthesis of 3-Heterosubstituted-2-amino-1-ols by Sequential Metal-free Diene Aziridination/Kinetic Resolution**". Submitted.

SCIENTIFIC MEETINGS

- **VII-French Catalan Meeting. Toulouse, France. 26-27th January 2016.** Oral presentation. *One-pot metal-free regioselective diene aziridination/ring-opening.* Irene Giménez, Joan Guasch, Yolanda Díaz, Maribel Matheu, Sergio Castillón.

- **XXVI Biennial Meeting of Organic Chemistry, Spanish Royal Society of Chemistry. Punta Umbría, Huelva, Spain. 14-17th June 2016.** Poster session. *One-pot metal-free regioselective diene aziridination/ring-opening. A general strategy for the synthesis of SphK1 inhibitors.* Irene Giménez, Yolanda Díaz, M. Isabel Matheu, Sergio Castillón.

- **XXXVI Biennial Meeting, Spanish Royal Society of Chemistry. Sitges, Barcelona, Spain. 25-29th June 2017.** Flash presentation. *Iodine-(III) mediated diene aziridination/ring-opening. A general strategy for the synthesis of SK1 inhibitors.* Irene Giménez, Joan Guasch, Omar Boutureira, M. Isabel Matheu, Yolanda Díaz, Sergio Castillón.

- **ICIQ-INTECAT School. Hotel Termes de Montbrió, Tarragona, Spain. 11-13th December 2018.** Oral communication. *Iodine-(III) mediated diene aziridination/ring-opening. A general strategy for the synthesis of SK1 inhibitors*. Irene Giménez, Joan Guasch, M. Isabel Matheu, Yolanda Díaz, Sergio Castillón.