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Marllon Nascimento De Oliveira

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Université Pierre et Marie Curie

École doctorale : Chimie Moléculaire (ED 406)

Laboratoire de Chimie Organique / ESPCI Paris

Palladium-Catalyzed Asymmetric Allylic Alkylations: Control of All-Carbon Quaternary Centers

Par M. Marllon NASCIMENTO DE OLIVEIRA

Thèse de doctorat de Chimie Organique

Dirigée par Pr. Janine Cossy et Dr. Stellios Arseniyadis

Présentée et soutenue publiquement le 30 Novembre 2017

Devant un jury composé de :

Pr. Janine Cossy	Professeur	Directrice de thèse
Dr. Stellios Arseniyadis	Directeur de Recherche	Co-Directeur de thèse
Pr. Guillaume Prestat	Professeur	Rapporteur
Pr. Laurent El Kaïm	Professeur	Rapporteur
Pr. Serge Thorimbert	Professeur	Examinateur
Pr. Christine Greck	Professeur	Examinatrice

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To my family

for their unconditional love and constant support

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Abbreviation List

$[\alpha]_D$	specific rotation at wavelength of sodium D line
Å	Ångström
AAA	asymmetric allylic alkylation
Ac	acetyl
acac	acetylacetonate

Ad	1-adamantyl
App	apparent
Ar	Aryl
ATR	attenuated total reflectance
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthlene
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
br	broad signal
BSA	*N*,*O*-bis(trimethylsilyl)acetamide
Bu	butyl
bz	benzoyl
c	concentration for specific rotation measurements
calcd	calculated
Cbz	carboxybenzyl
cod	1,5-cyclooctadiene
Cy	cyclohexyl
d	doublet
dba	dibenzylideneacetone
DBU	1,8-diazobicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DFT	density functional theory
DIOP	2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)-butane
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	dimethylsulfoxyde
Dr	diastereomeric ratio
dtpf	1,1'-bis(di-*tert*-butylphosphino)ferrocene
ee	enantiomeric excess
ent	opposite enantiomer

eq	equation
equiv	equivalent
ESI	electron spray ionization
Et	ethyl
FBIP-Cl	bis(di-μ-((bis-η^5-(*4'R*,*5'R*)-(S_p)-2-(2'-4',5'-dihydro-4',5'-diphenyl-1'-tosyl-imidazolyl)cyclopendienyl))iron(II) 1-*C*, 3'-*N*) dipalladium (II))
GABA	γ-aminobutyric acid
GC-MS	gas chromatography-mass spectrometry
GH-II	second generation Hoveyda-Grubbs catalyst
HRMS	high resolution mass spectrometry
IR	infrared
*i*Pr	isopropyl
J	Spin coupling constant
JOSIPHOS	(*R*)-1-[(S_P)-(dyphenylphosphino)ferrocenyl] ethylbis(3,5-dimethyl--phenyl)phosphine
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
m	*meta*
m	multiplet or overlap of non-equivalent resonances
Me	methyl
MOM	methoxymethyl
Mp	meting point
MS	mass spectrometry or molecular sieves
MTBE	methyl *tert*-butyl ether
NaHMDS	sodium bis(trimethylsilyl)amide
ND	non-determined
NIS	*N*-iodosuccinimide
NMP	*N*-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
o	*ortho*
p	*para*
PE	petroleum ether

Ph	phenyl
PHANEPHOS	4,12-bis(diphenylphosphino)-[2,2]-paracyclophane
PHOX	phosphinoxazoline
p*K*a	p*K* for association of an acid
PPY	4-pyrrolidinopyridine
PTC	phase-transfer catalysis
q	quadruplet
R	non-defined group or alkyl
rac	racemic
R_f	retention factor
rt	room temperature
s	singlet
sc	super critic
SDP	7,7'-bis(diphenylphosphino)-2,2',3,3'-tetrahydro-1,1'-spirobiindene
SEGPHOS	5,5'-bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole
SFC	supercritical fluid chromatography
S_N2	second-order nucleophilic substitution
T	temperature
t	*tert* or triplet
t-Bu	*tert*-butyl
Tipp	1-(2,4,6-triisopropyl)phenyl
Tf	triflate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
TMS	trimethylsilyl
t_R	retention time
TRAP	2,2''-bis[1-(diphenylphosphino)ethyl]-1,1'-biferrocene
Ts	tosyl
TS	transition state

Résumé en Français

Introduction Générale

Le développement de méthodes catalytiques énantiosélectives permettant la synthèse des produits naturels ou pharmaceutiques, possédant un ou plusieurs centres quaternaires, représente un objectif majeur dans le domaine de la synthèse organique. Dans ce contexte, l'alkylation allylique asymétrique décarboxylante pallado-catalysée est apparue comme l'une des méthodes les plus efficaces pour former des centres stéréogènes quaternaires. L'intérêt d'utiliser l'allylation asymétrique catalysée au palladium comme étape clé pour la formation de la liaison C–C dans la synthèse de molécules structurellement complexes a été largement démontré depuis sa mise au point. Cette réaction tolère une large gamme de groupes fonctionnels et permet d'accéder à des produits hautement énantioenrichis.

Le premier chapitre de cette thèse est consacré à l'application de la réaction d'alkylation allylique asymétrique décarboxylante catalysée au palladium à une large gamme d'énols carbonates allyliques cycliques et exocycliques, permettant d'accéder à des γ-butyrolactones énantioenrichies possédant un centre stéréogénique quaternaire en position α (Schéma I). La présence du motif γ-butyrolactones dans de nombreux produits bioactifs explique l'intérêt croissant des chimistes pour réaliser la synthèse de ces motifs de manière simple et efficace. Ces lactones chirales possédant un centre quaternaire ont été reconnues comme briques moléculaires extrêmement flexibles qui peuvent être transformées en motifs structurellement plus complexes particulièrement utiles en synthèse totale de produits naturels.

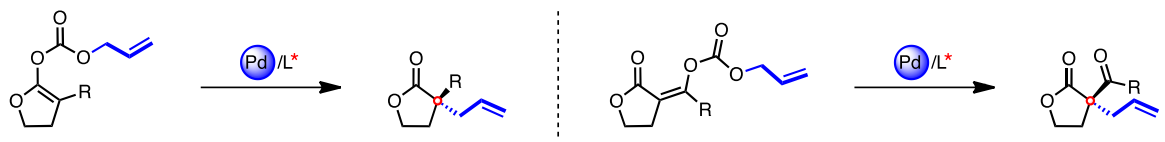


Schéma I. L'application de la Pd-DAAA aux énols carbonates allyliques cycliques et exocycliques.

Le second chapitre est dévolu à la synthèse asymétrique des isoxazolidin-5-ones possédant un centre quaternaire en position α à travers une réaction d'alkylation allylique asymétrique pallado-catalysée. Cette méthode nous a permis d'accéder à des acides $\beta^{2,2}$-aminés après coupure réductrice de la liaison N–O (Schéma II). Malgré le nombre de méthodes qui ont été développées pour la synthèse asymétrique de précurseurs d'acides aminés, une stratégie plus générale permettant de préparer de tels motifs de manière catalytique et énantiosélective représente encore aujourd'hui un défi. Dans ce contexte, l'allylation asymétrique catalysée au palladium des isoxazolidin-5-ones substituées en position 4 est apparue comme une méthode particulièrement intéressante pour répondre à ce défi. Elle permet notamment d'accéder à des précurseurs d'acides aminés dans des conditions douces et opérationnellement simple.

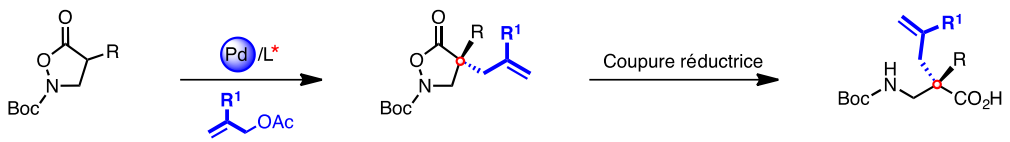


Schéma II. Synthèse d'acides $\beta^{2,2}$-aminés en utilisant la Pd-AAA comme étape clé.

Chapitre 1

Synthèse de γ-butyrolactones α-quaternaires par alkylation allylique asymétrique décarboxylante pallado-catalysée

1. Principales méthodes de synthèse des γ-butyrolactones possédant un centre quaternaire en α

Les lactones sont considérées comme une classe importante de produits naturels en raison d'une vaste gamme d'activités biologiques présentées par ces composés. C'est aussi

que les γ-butyrolactones représentent environ 10% de tous les produits naturels décrits dans la littérature.[1] Parmi eux, on trouve aussi un grand nombre de γ-butyrolactones possédant un centre stéréogène quaternaire en α. Ce motif par exemple a été identifié dans le (+)-hopeahainol A (Figure 1), qui possède une activité inhibitrice de l'acétylcholinestérase, une enzyme liée à la maladie d'Alzheimer.[10] Un autre exemple de γ-butyrolactone bioactive possédant un centre stéréogène quaternaire en α est le rosmanol (Figure 1), qui a montré un effet cytotoxique remarquable.[11] Un grand nombre de composés synthétiques ont également été identifiés comme ayant des activités biologiques intéressantes. L'évaluation de deux énantiomères de **L.1** a par exemple montré que ces composés exerçaient un effet à la fois inhibiteur et stimulant sur le récepteur $GABA_A$ (acide γ-aminobutyrique A) selon l'énantiomère (Figure 1).[12]

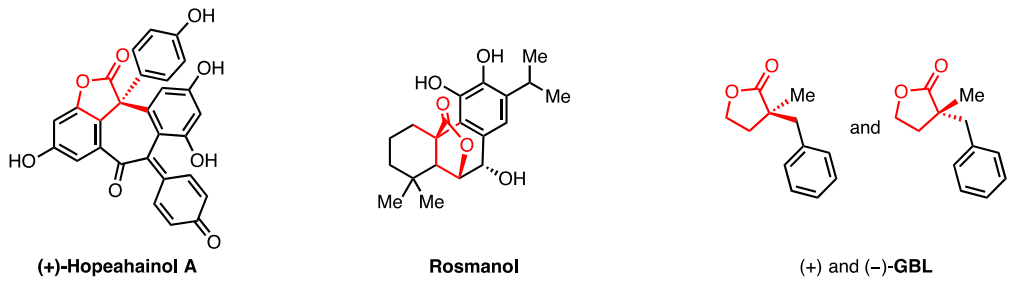


Figure 1. Structures du (+)-hopeahainol A, du rosmanol et du **GBL**.

En conséquence, l'intérêt pour le développement de nouvelles méthodes vers la construction énantiosélective de γ-butyrolactones possédant un centre stéréogène quaternaire en α s'est trouvé être le centre d'intérêt de plusieurs groupes de recherche dont le nôtre. Malgré l'avancement significatif dans le domaine de la synthèse asymétrique, les approches catalytiques et énantiosélectives restent relativement limitées.

Petersen et Wilent ont décrit l'utilisation d'acides de Brønsted chiraux pour réaliser la désymétrisation de différents esters prochiraux. Cette stratégie s'est révélée extrêmement efficace pour préparer des γ-butyrolactones énantioenrichies avec de bons rendements et d'excellentes énantiosélectivités (ees supérieurs à 98%) (Schéma 1).[23]

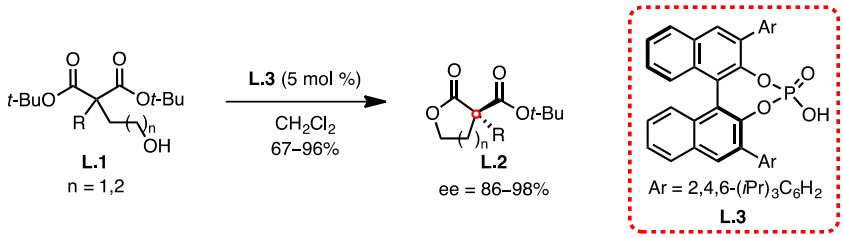


Schéma 1. Désymétrisation des esters prochiraux réalisée par Petersen et Wilent.

Inspiré par les travaux de Buchwald *et al*. sur des réactions de couplage-croisé asymétrique d'halogénures d'aryle avec différentes cétones, catalysé au palladium, Zhang *et al*. ont étendu la méthode d'α-arylation asymétrique aux α-méthyl γ-butyrolactones (Schéma 2, éq 1). Ce système catalytique a permis d'obtenir les lactones désirées avec des rendements modérés (55-65%) et de faibles énantiosélectivités (ee = 15-65%).[33] Surpris par les faibles sélectivités obtenues lors de l'α-arylation de γ-butyrolactones, Buchwald et Spielvogel ont développé une méthode alternative utilisant une catalyse au nickel (Schéma 2, éq 2).[34] Le système catalytique Ni/(S)-BINAP a fourni une variété de γ-butyrolactones possédant un centre stéréogène quaternaire en α à partir de précurseurs α-substitués et de chlorures d'aryle avec d'excellents excès énantiomériques compris entre 83% et 97%.

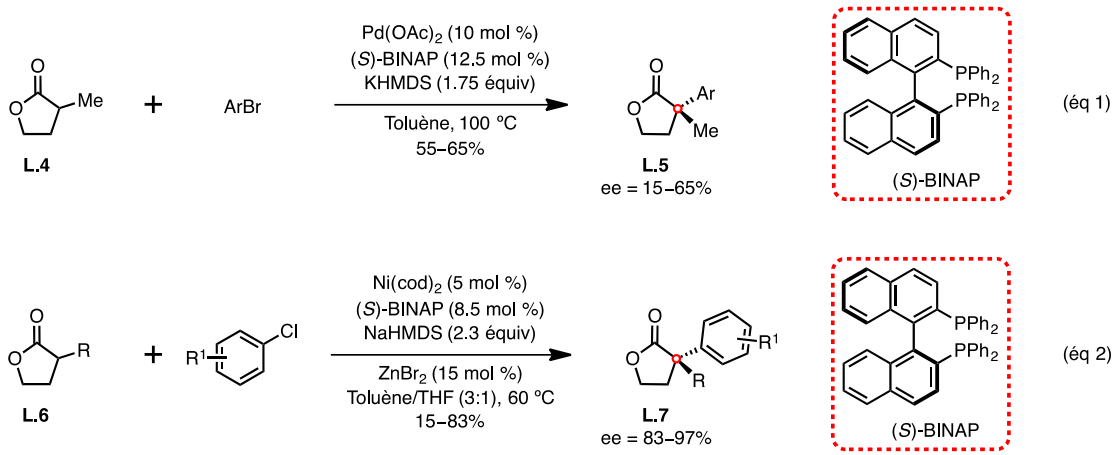


Schéma 2. α-Arylation de γ-butyrolactones par couplage-croisé asymétrique catalysé au palladium et nickel.

Maruoka *et al*. ont développé des conditions de transfert de phase permettant d'accéder à des β-céto esters possédant un centre quaternaire en α en utilisant une nouvelle

classe de sels d'ammonium *N*-spirocycliques. Plus récemment, ces mêmes auteurs ont étendu l'utilisation de ces catalyseurs à des α-acyle γ-butyrolactones, donnant un accès direct à un certain nombre de γ-butyrolactones α-alkylées chirales **L.11** avec de très bons rendements et d'excellentes énantiosélectivités (Schéma 3).[37]

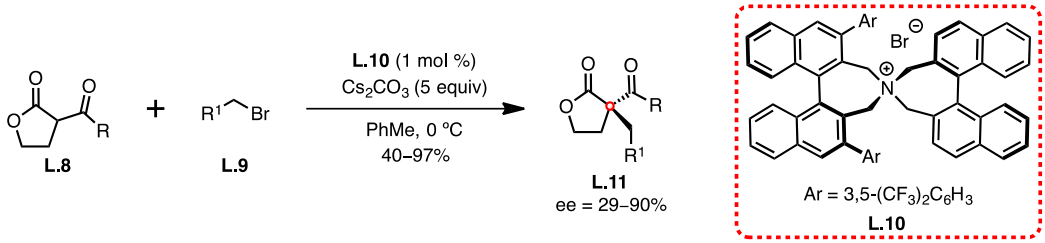


Schéma 3. Synthèse d'α-acyle α-alkyle γ-butyrolactones réalisée par Maruoka *et al*.

Une stratégie alternative a été rapportée par Fu *et a*l. Ces auteurs ont réalisé une réaction de *C*-acylation asymétrique directe d'acétals de cétènes silylés organocatalysée (Schéma 4). Cette méthode fait intervenir des catalyseurs à chiralité planaire de type 4-pyrrolidinopyridine (PPY) **L.13** et a permis d'ouvrir une voie d'accès aux γ-butyrolactones α-acylées possédant un centre stéréogène quaternaire en α.

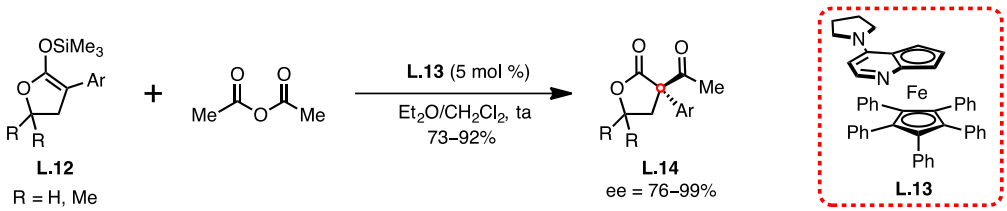


Schéma 4. *C*-Acylation asymétrique d'acétals de cétènes silylés réalisée par Fu *et al*.

2. Alkylation allylique asymétrique décarboxylante pallado-catalysée

L'avènement de l'alkylation allylique asymétrique décarboxylante catalysée par des complexes de palladium (Pd-DAAA) a permis de faire un énorme bon en avant dans le domaine de la catalyse asymétrique. Cette méthode, à la fois robuste et efficace, a permis le contrôle de centres stéréogènes dans la synthèse d'un grand nombre de produits naturels et de composés pharmaceutiques. Ce processus énantiosélectif, également connu sous le nom de

réaction de Tsuji-Trost, est devenu au cours de ces dernières années un outil très performant en raison de sa capacité de coupler des allyles électrophiles avec des nucléophiles de manière chimio-, régio- et stéréosélective, dans des conditions douces et neutres.[46, 47]

3. Contexte de l'étude et objectifs

Comme nous l'avons vu, la synthèse stéréosélective des γ-butyrolactones possédant un centre stéréogène quaternaire en α a entraîné le développement de nouvelles méthodes catalytiques et énantiosélectives. Cependant, dans la plupart des cas, les résultats obtenus lors de la formation du centre stéréogène quaternaire se sont révélés insatisfaisants. La réaction d'alkylation allylique asymétrique décarboxylante catalysée par des complexes de palladium nous a paru être une alternative intéressante.

En effet, précédemment au laboratoire, le contrôle de centres quaternaires stéréodefinis a été réalisé en appliquant la Pd-DAAA aux diénols carbonates allyliques **L.15**. Cette réaction a permis d'accéder à des buténolides **L.16** énantiomériquement enrichies (Schéma 5, éq 1).[63] Par analogie, nous avons envisagé d'appliquer cette réaction aux énols carbonates d'allyle cycliques et exocycliques, **L.17** et **L.19** respectivement. Ces derniers pourraient subir une allylation asymétrique décarboxylante en présence d'un précurseur de palladium et un ligand chiral, et fournir les γ-butyrolactones correspondantes **L.18** et **L.20** possédant un centre quaternaire en position α (Schéma 5, éq 2 et 3).

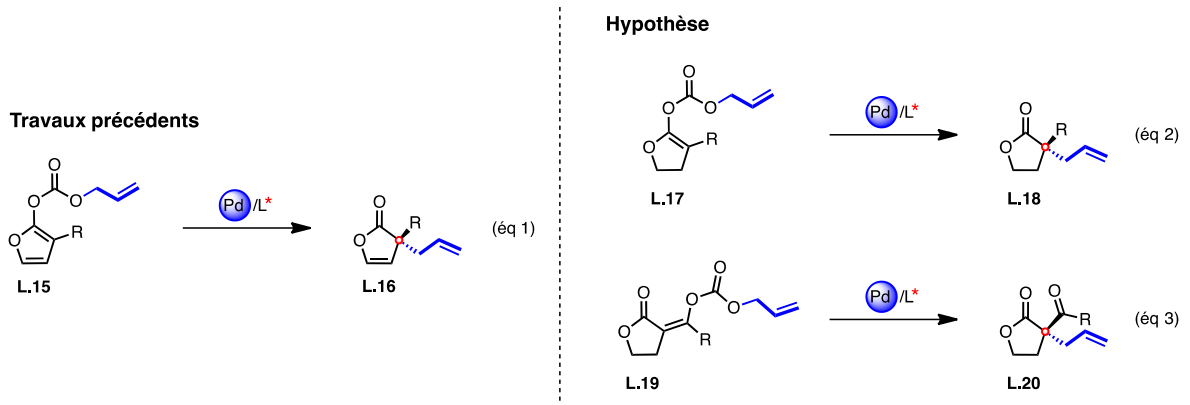


Schéma 5. Application de la Pd-DAAA aux énols carbonates allyliques cycliques et exocycliques.

4. Résultats et discussion

4.1. Synthèse des substrats

Nous avons commencé notre étude en développant deux stratégies générales d'accès aux énols carbonates allyliques **L.23**. Dans un premier temps, les précurseurs portant un substituant aryle en α ont été préparés à partir de l'α-bromofuranone **II.21** grâce à un couplage de type Suzuki suivi d'une réaction d'hydrogénation et d'une réaction de *O*-acylation. Les énols carbonates **L.23** ont ainsi pu être obtenus avec des rendements qui varient entre 10% et 94% (Schéma 6).

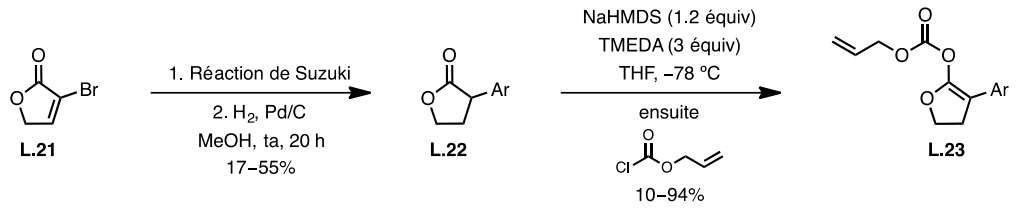


Schéma 6. Synthèse des énols carbonates allyliques α-arylés.

Afin d'apporter plus de diversité structurale, une seconde méthode de synthèse des énols carbonates a été envisagée. Celle-ci consiste à former l'enolate de lithium à partir de la γ-butyrolactone **L.24** et à effectuer une réaction de substitution nucléophile à l'aide d'halogénures d'alkyles afin d'accéder aux lactones α-alkylés **L.25**. Ces dernières ont ensuite été transformées en carbonates allyliques en utilisant la méthode décrite dans le Schéma 6 (NaHMDS, TMEDA, THF, –78 °C, chloroformate d'allyle) avec des rendements allant de 33% à 44% (Schéma 7).

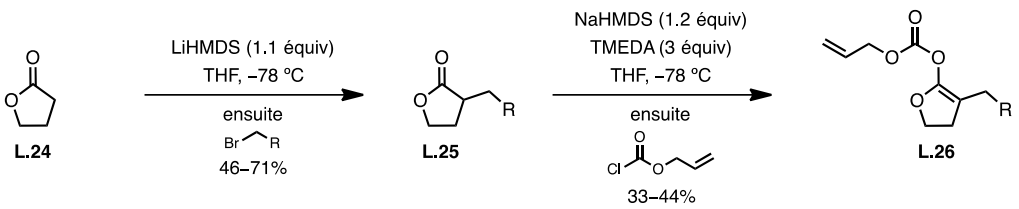
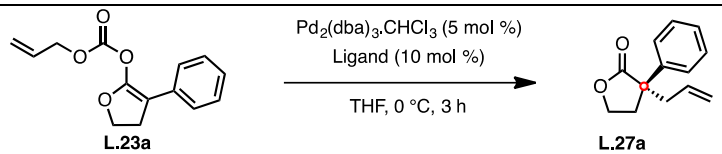


Schéma 7. Synthèse des énols carbonates allyliques α-alkylés.

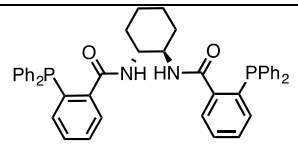
4.2. Optimisation des conditions réactionnelles

Dans le but de valider notre hypothèse devant conduire à des γ-butyrolactones possédant un centre quaternaire en α, nous avons testé la réaction Pd-DAAA sur l'énol carbonate **L.23a**. Celui-ci a été mis en réaction avec 5 mol % de $Pd_2(dba)_3.CHCl_3$ et 10 mol % d'un ligand chiral (**L1-L11**, Tableau 1) dans le THF à 0 ºC. Les résultats sont résumés dans le Tableau 1. Dans tous les cas, les réactions ont fourni la γ-butyrolactone allylée **L.27a** avec de bons rendements allant de 83% à 99% (Tableau 1, entrées 1 à 11). L'utilisation de diphosphines chirales (Tableau 1, entrées 6 et 11) et des ligands de type PHOX (Tableau 1, entrées 4 et 5) a donné les produits désirés avec des excès énantiomériques inférieurs à ceux obtenus avec les phosphines chirales **L1-L3** développées par Trost *et al.* (Tableau 1, entrées 1-3). Ces dernières se sont révélées particulièrement efficaces. En effet, l'utilisation de ligand de Trost (*R*,*R*)-DACH phényle (**L1**) a fourni la butyrolactone **L.27a** avec un rendement de 98% et un excès de 77% (Table 1, entrée 1).

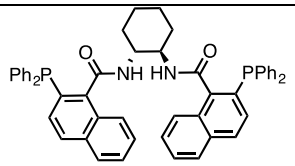
Tableau 1. Influence du ligand.



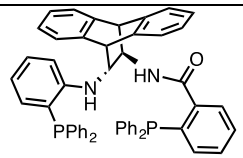
Entrée	Ligand	Rdt (%)	ee (%)
1	(*R*,*R*)-**L1**	98	77
2	(*R*,*R*)-**L2**	85	64
3	(*R*,*R*)-**L3**	99	55
4	(*S*)-**L4**	83	12
5	(*S*)-**L5**	95	7
6	(*R*)-**L6**	80	10
7	(*R*,*R*)-**L7**	98	4
8	(*R*)-**L8**	92	-2
9	(*R*)-**L9**	95	-9
10	(p*S*,*R*)-**L10**	92	0



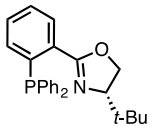
(*R*,*R*)-**L1**



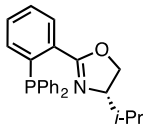
(*R*,*R*)-**L2**



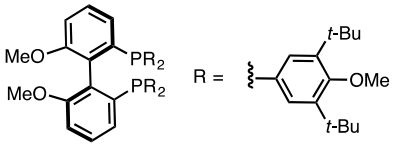
(*R*,*R*)-**L3**



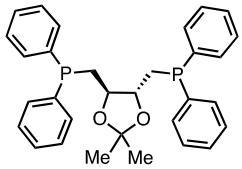
(*S*)-**L4**



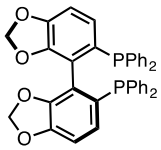
(*S*)-**L5**



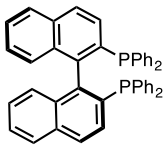
(*R*)-**L6**



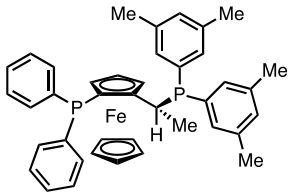
(*R*,*R*)-**L7**



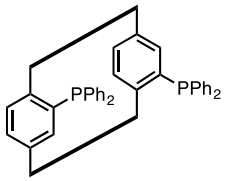
(*S*)-**L8**



(*S*)-**L9**



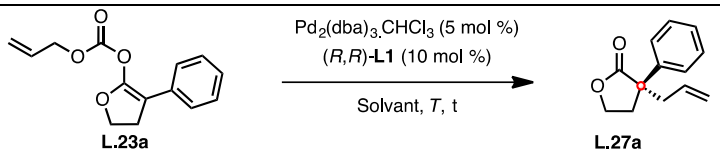
(p*S*,*R*)-**L10**



(p*R*)-**L11**

Encouragés par ces résultats préliminaires, nous avons examiné l'influence du solvant. Curieusement, lorsque la réaction est réalisée dans l'hexane, le rendement et l'ee de **L.27a** ont diminué de manière très considérable (35% et 29%, respectivement) (Tableau 2, entrée 2). L'utilisation d'autres solvants tels que MeCN, toluène, Et_2O, AcOMe, DMF et CH_2Cl_2 a conduit à de bonnes conversions mais à des excès faibles (Tableau 1, entrées 3-8). Enfin, la réaction effectuée dans le THF à −78 ºC a permis d'améliorer la sélectivité et d'obtenir la butyrolactone **L.27a** avec un ee de 80% (Tableau 1, entrée 9). Le THF a donc été utilisé dans la suite de l'étude.

Tableau 2. Influence du solvant.



Entrée	Solvant	*T* (ºC)	t (h)	Rdt (%)	ee (%)

1	THF	0	3	98	77
2	Hexane	0	24	35	29
3	MeCN	0	1	94	56
4	PhMe	0	3	87	64
5	Et_2O	0	1	97	65
6	MeOAc	0	3	97	67
7	DMF	0	3	87	69
8	CH_2Cl_2	0	3	72	70
9	THF	−78 ºC	3	89	80

4.3. Généralisation de la réaction

Après avoir déterminé les conditions optimales d'allylation asymétrique [5 mol % de $Pd_2(dba)_3.CHCl_3$ et 10 mol % du ligand de Trost (**L1**) dans le THF à −78 ºC], celles-ci ont été appliquées aux divers énols carbonates qui ont été synthétisés précédemment (Schéma 8). En général, les γ-butyrolactones α,α-disubstituées correspondantes ont été obtenues avec d'excellents rendements compris entre 76% et 99% et des énantiosélectivités pouvant atteindre 90%. Cependant, les substrats portant un substituant aromatique riche en électron ou un groupe alkyle, en particulier, ont été isolés avec des sélectivités inférieures aux substrats substitués par un groupement aromatique possédant un effet électronique modéré.

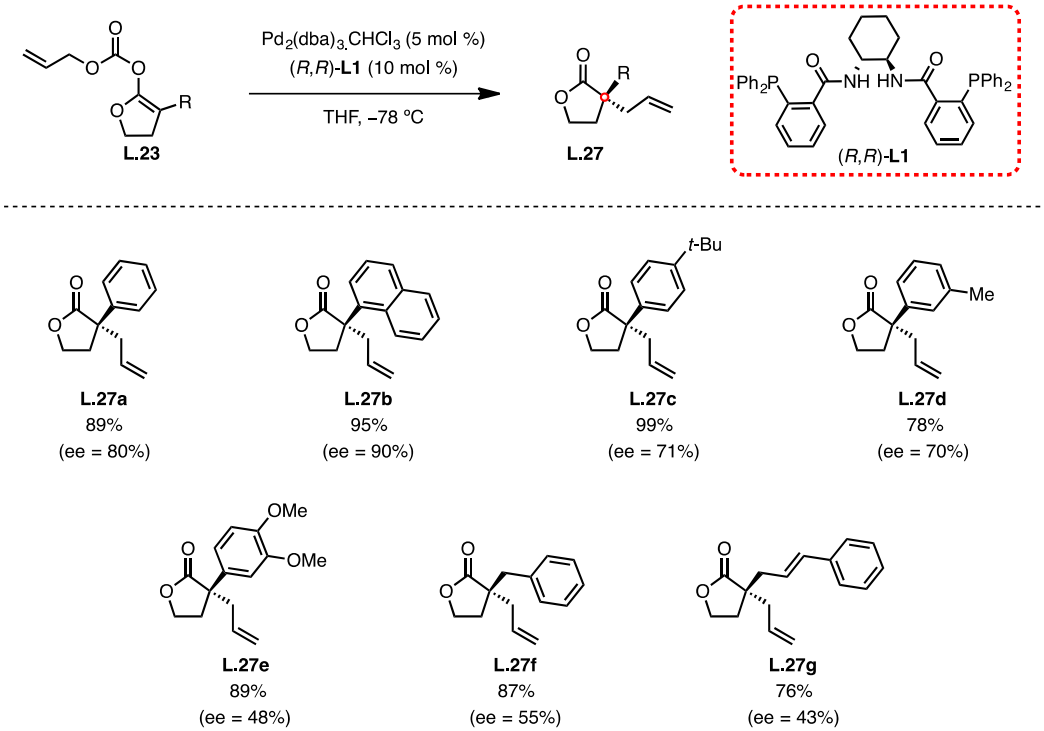


Schéma 8. Scope de la réaction avec les énols carbonates allyliques cycliques.

Afin d'élargir le champ d'application de la réaction, nous l'avons également étendue aux énols carbonates d'allyle exocycliques. Ces derniers ont été préparés en deux étapes à partir de la γ-butyrolactone **L.24** en réalisant une *C*-acylation suivie d'une *O*-acylation (Schéma 9).

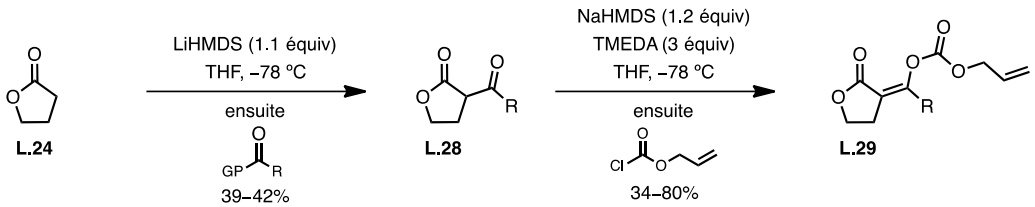


Schéma 9. Synthèse des énols carbonates allyliques exocycliques.

Lors de l'application des conditions optimisées d'allylation décarboxylante, un changement drastique de la réactivité a été observé. En effet, ces énols carbonates exocycliques semblaient être moins réactifs, ce qui, en toute, n'est pas surprenant vu que lors du processus de décarboxylation la charge négative générée est délocalisée sur les deux carbonyles. En conséquence, toutes les réactions ont été effectuées à –20 ºC étant donné

qu'aucune conversion n'a été observée à −78 ºC. Néanmoins, les γ-butyrolactones α,α-disubstituées désirées ont été obtenues avec de bons rendements allant de 83% à 98% et de bonnes énantiosélectivités (Schéma 10) ; les meilleurs résultats ont été obtenus avec l'énol carbonate dérivé de l'α-formyle γ-butyrolactone (ee = 94%).

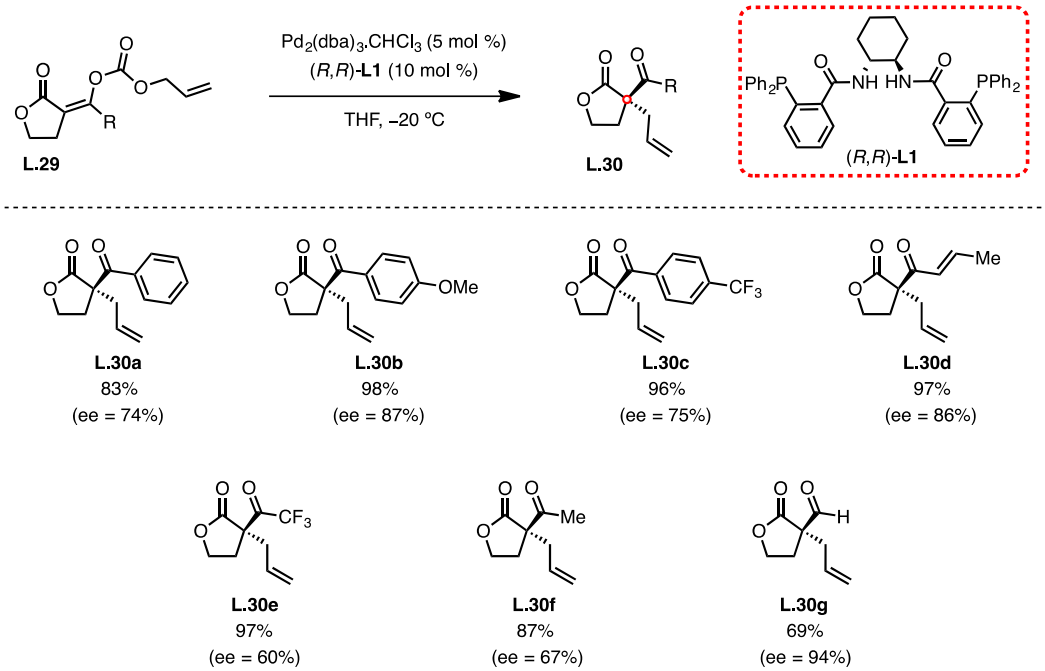


Schéma 10. Scope de la réaction avec les énols carbonates allyliques exocycliques.

4.4. Post-fonctionnalisation

Prenant en compte l'importance du motif spirocyclique qui est présent dans un certain nombre de produits naturels et pharmaceutiques, nous avons ensuite décidé d'appliquer la réaction Pd-DAAA à la synthèse des spirocycles dérivés de γ-butyrolactones. Notre première stratégie fait intervenir une réaction d'allylation asymétrique décarboxylante suivie d'une réaction de métathèse cyclisante, ce qui nous a permis d'obtenir la spirolactone désirée **L.31** avec un rendement global de 88% sans érosion de l'ee (Schéma 11, éq 1). La seconde stratégie implique une réduction de Luche appliquée à la γ-butyrolactone α,α-disubstituée **L.30b** suivie d'une iodocyclisation. Dans ces conditions, le composé spirocyclique **L.33** a été obtenu avec un rendement global de 85% et un rapport diastéréomérique de 3,5:1 en faveur de l'isomère *trans* (Schéma 11, éq 2).

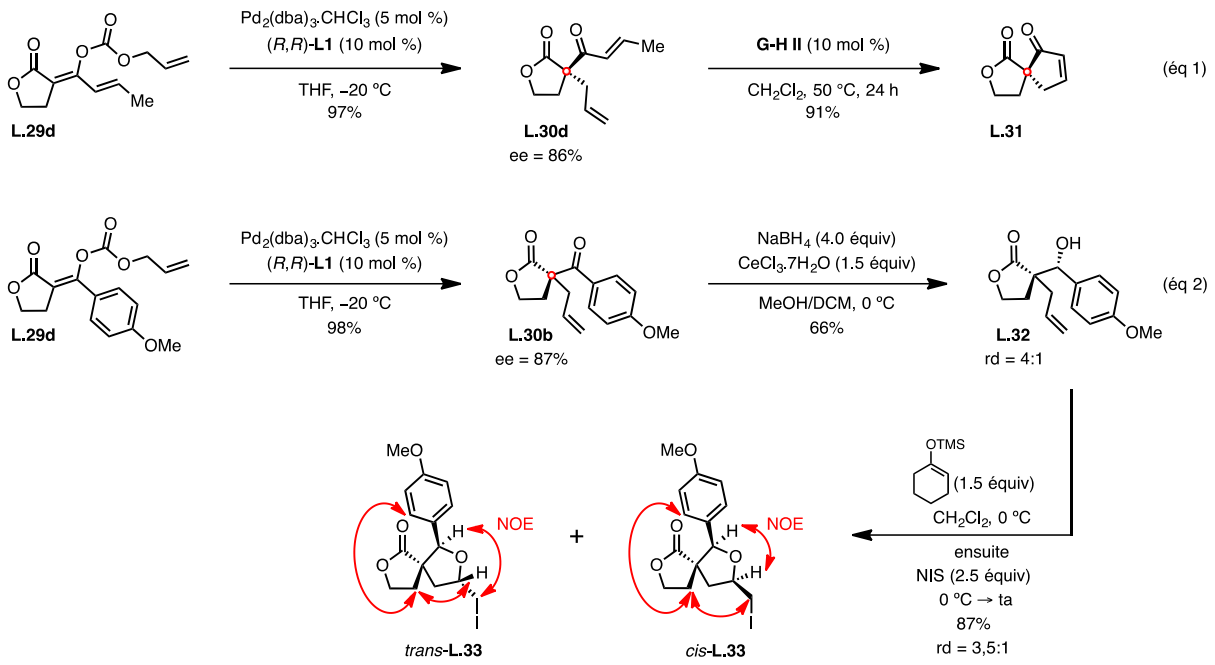


Schéma 11. Application de la Pd-DAAA à la synthèse des spirocycles.

5. Résumé

Nous avons développé une méthode extrêmement douce et particulièrement efficace d'accès à des γ-butyrolactones possédant un centre stéréogène quaternaire en α à partir d'énols carbonates d'allyle cycliques et exocycliques. Cette réaction a été utilisée comme étape clé dans la synthèse des spirolactones chirales.

Chapitre 2

Alkylation allylique asymétrique pallado-catalysée de 4-isoxazolidin-5-ones vers la synthèse d'acides $\beta^{2,2}$-aminés

1. Principales méthodes de synthèse des précurseurs d'acides $\beta^{2,2}$-aminés

La synthèse stéréosélective d'acides aminés est devenue un sujet d'intérêt croissant ces dernières années, en raison de l'utilité de ces composés comme précurseurs de protéines, de β-peptides, et de β-lactames ou encore pour réaliser la synthèse de produits naturels, tels comme la cryptophycine 1 et le jasplakinolide qui possèdent des propriétés biologiques intéressantes (Figure 2).

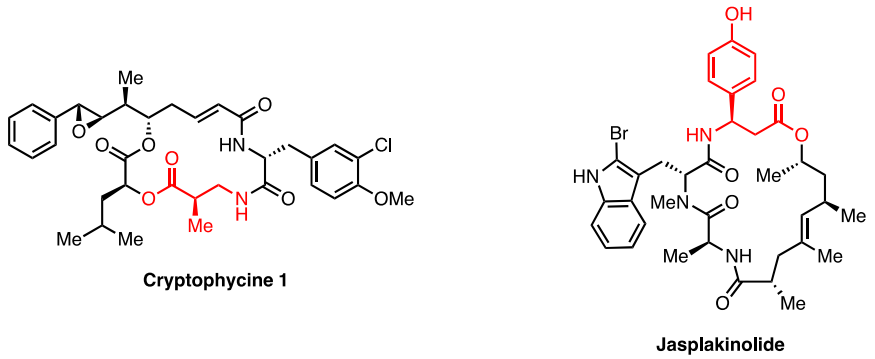


Figure 2. Structure de la cryptophycine 1 et du jasplakinolide.

Vu l'importance des acides β-aminés, un certain nombre de méthodes permettant d'accéder à ce type de motif ont été décrites dans la littérature. Cependant, parmi toutes ces méthodes, seules quelques-unes permettent d'accéder à ces acides aminés possédant un centre stéréogène quaternaire en α. La première partie de ce chapitre sera donc consacrée à ces méthodes.

De nombreuses équipes se sont intéressées à la mise au point de réactions d'alkylation diastéréosélective d'α-cyanoesters racémiques pour accéder à des précurseurs des acides $\beta^{2,2}$-aminés. C'est ainsi que l'introduction diastéréosélective d'une variété de groupements alkyles en position α du carbonyle a fourni les produits d'alkylation correspondant avec d'excellents rapports diastéréomériques (dr = 98:2) (Schéma 12).[101]

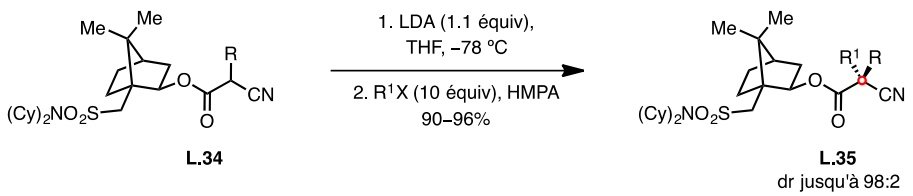


Schéma 12. Synthèse diastéréosélective des précurseurs des acides $\beta^{2,2}$-aminés.

Cependant, l'utilisation d'α-cyanoesters comme précurseurs d'acides aminés possédant un centre quartenaire α ne se cantonne pas aux approches diastéréosélectives. En effet, plusieurs versions catalytiques énantiosélectives ont été mises au point depuis le début des années 90.

L'addition conjuguée d'α-cyanoesters α-substitués sur des oléfines activées constitue une méthode de choix pour la construction des liaisons C–C en raison du nombre de partenaires commercialement disponibles.

La première réaction de Michael catalytique énantiosélective a été décrite par Ito *et al*. en 1992 et permet l'addition conjuguée d'α-méthyle α-cyanoesters **L.36** sur des enones **L.37** avec de bons rendements et d'excellentes énantiosélectivités en utilisant des complexes de Rh(I) en présence de la diphosphine chiral TRAP, **L.38** (Schéma 13, éq 1).[106] Des procédures alternatives inspirées par ce travail ont ensuite été rapportées notamment par les équipes de Takaya, Nozaki et Motoyama.[107, 108] Ces équipes ont étendu cette réaction à la méthylevinylecétone et à l'acroléine (Schéma 13, éq 2 et 3, respectivement), conduisant à la formation des adduits de Michael correspondants avec de bons rendements, malgré les excès énantiomériques modestes.

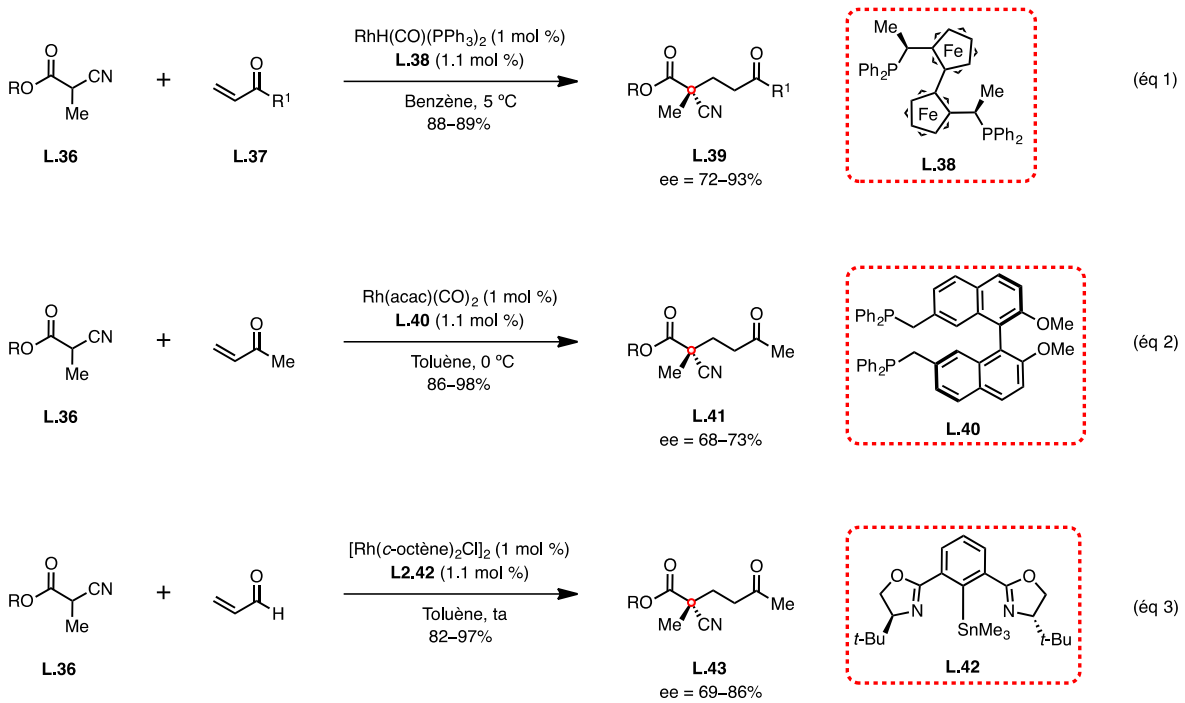


Schéma 13. Addition de Michael d'α-méthyle α-cyanoesters catalysée au rhodium.

Malgré les bons résultats obtenus au cours de cette réaction d'addition de Michael d'α-méthyle α-cyanoesters, catalysée au rhodium, celle s'est montrée incapable de fournir des niveaux d'énantiosélectivité satisfaisants pour l'addition conjuguée d'α-cyanoesters possédant des substituants plus encombrants que le méthyle. Par conséquent, Peters et Jautze ont décrit l'application d'un système catalytique alternatif basé sur l'utilisation de complexes de palladium.[112] L'utilisation de complexes bimétalliques capables d'activer simultanément l'accepteur du Michael et l'α-cyanoénolate s'est révélée particulièrement intéressante pour surmonter les limites observées avec la catalyse au rhodium (Schéma 14).

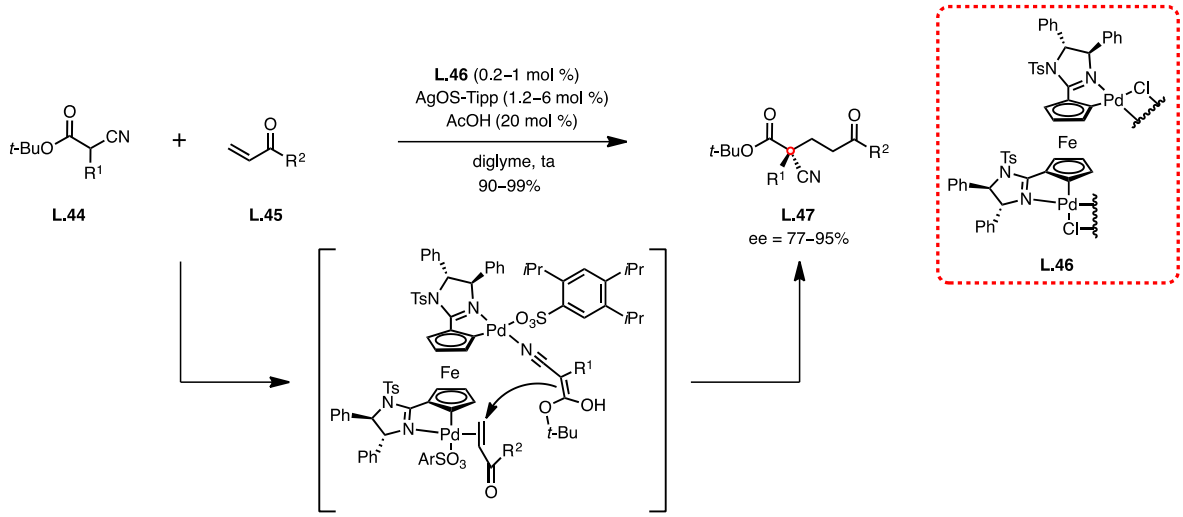


Schéma 14. Addition d'α-cyanoesters sur vinyles cétones catalysée au palladium.

Des approches organocatalytiques ont également été mises au point. C'est ainsi qu'en 2005, un dérivé d'alcaloïde cinchona **L.50** a été utilisé comme catalyseur pour réaliser l'addition conjuguée asymétrique d'α-cyanoesters **L.48**, structurellement diversifiés, sur vinyles sulfones **L.49**. Les produits d'addition **L.51** ont pu être obtenus avec de très bon rendements et d'excellentes énantiosélectivités (Schéma 15).[114]

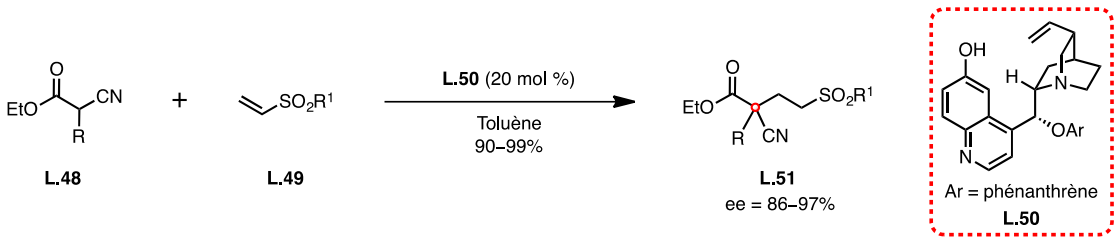


Schéma 15. Addition de Michael d'α-alkyle cyanoesters sur vinyle sulfones par organocatalyse.

2. Alkylation allylique asymétrique pallado-catalysée

La construction énantiosélective de centres tertiaires et quartenaires par addition de différents types de nucléophile sur des complexes π-allyliques de palladium chiraux représente une méthode de choix pour la formation de liaisons C–C. Cette approche a été très largement utilisée pour la synthèse d'intermédiaires clés dans le cadre de la synthèse de

différents produits naturels et autres composés bioactifs. La réaction d'alkylation allylique asymétrique catalysée au palladium (Pd-AAA) a permis d'accéder à des structures très variées avec de bons rendements et d'excellentes régio- et énantiosélectivités.[144, 145]

3. Contexte de l'étude et objectifs

Comme nous l'avons déjà souligné, les méthodes asymétriques permettant un accès direct aux acides β-aminés ont fait l'objet d'efforts considérables par de nombreux groupes de recherche dû à l'importance de ce motif. Les acides β-aminés sont devenus des précurseurs potentiels de β-lactames, de β-peptides résistants aux protéases et de peptides hybrides de type α/β. Malgré les méthodes établies pour la synthèse d'acides β^2- et β^3-aminés, le développement d'une stratégie plus générale de production énantiosélective d'acides $\beta^{2,2}$-aminés reste un défi. L'alkylation allylique asymétrique catalysée au palladium d'isoxazolidin-5-ones substituées en position 4 est apparue comme une approche particulièrement intéressante pour résoudre ce problème.

En effet, suite aux résultats préliminaires que nous avions obtenu sur la Pd-AAA de γ-butyrolactones (Chapitre 1, Section 4.9), nous avons envisagé une approche basée sur une réaction d'alkylation allylique énantiosélective pallado-catalysée d'isoxazolidin-5-ones **L.52**. Cette stratégie devait nous permettre d'accéder aux acides $\beta^{2,2}$-aminés souhaités **L.54** après une coupure réductrice de la liaison N–O (Schéma 16).

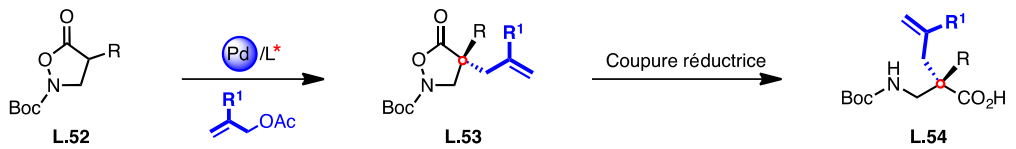


Schéma 16. Synthèse d'acides $\beta^{2,2}$-aminés en utilisant la Pd-AAA comme étape clé.

4. Résultats et discussion

4.1. Synthèse des substrats

Cette étude a débuté par le développement de deux stratégies générales de préparation des isoxazolidin-5-ones substituées en position 4. Les isoxazolidinones α-arylées ont été synthétisées à partir du malonate de diéthyle grâce à une séquence réactionnelle comprenant l'introduction du groupement aromatique par une réaction de couplage-croisé, saponification, une étape de formation de l'acide de Meldrum correspondant et une cycloaddition formelle [3+2] (Schéma 17).[120-124]

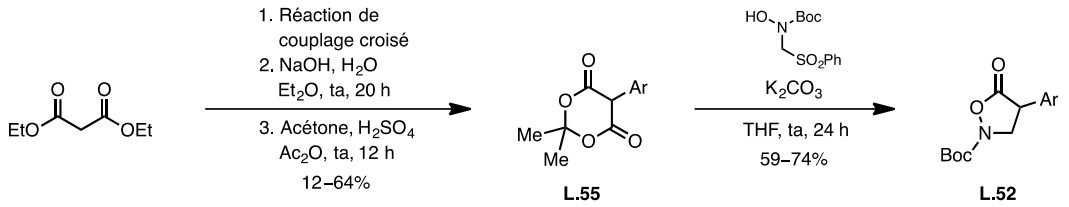


Schéma 17. Synthèse des isoxazolidinones α-arylées.

Les substrats portant un substituant alkyle ont été synthétisés en suivant le protocole développé par Rachamary *et al*. Dans cette approche, une réaction de condensation de Knoevenagel entre l'acide de Meldrum et des aldéhydes permet de former les produits d'homologation qui ont ensuite été réduits par l'ester de Hantzsch pour produire les acides de Meldrum alkylés correspondants. Ces derniers ont ensuite été engagés dans une réaction de cycloaddition [3+2] pour donner les isoxazolidinones désirées avec de bons rendements (Schéma 18).

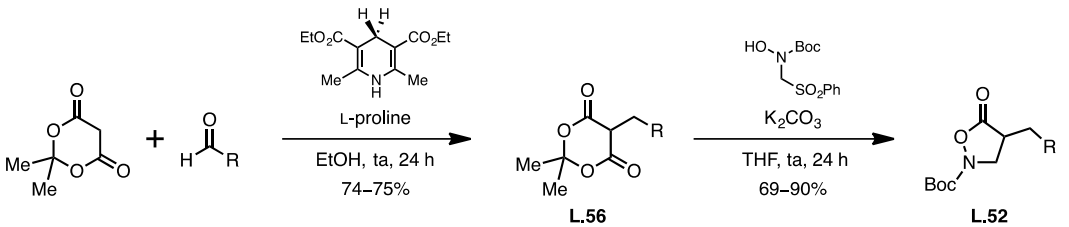


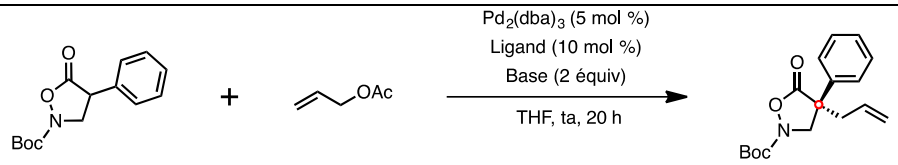
Schéma 18. Synthèse des isoxazolidinones α-alkylées.

4.2. Optimisation de conditions réactionnelles

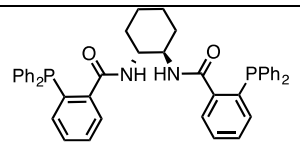
Nous avons décidé d'évaluer dans un premier temps l'influence du ligand sur l'allylation asymétrique de l'isoxazolidin-5-one **L.52a**. Les réactions ont été menées dans le THF à température ambiante en présence de 5 mol % de $Pd_2(dba)_3$, 2 équivalents de Na_2CO_3, 1 équivalent d'acétate d'allyle et 10 mol % d'un ligand chiral. Les résultats sont résumés dans le Tableau 3. Le produit désiré **L.57a** a été obtenu avec de bons rendements allant de 85% à 95%, indépendamment du ligand utilisé. Cependant, comme nous avons pu le voir dans notre étude précédente, la nature du ligand a un impact important sur la énantiosélectivité et, encore une fois, les diphosphines développées par Trost *et al*. (**L1**-**L3**) ont fourni les excès énantiomériques les plus élevés allant jusqu'à 90%, les meilleurs résultats étant obtenus avec **L1** (Tableau 3, entrée 1).

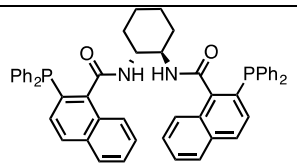
Suite à ces résultats, nous avons évalué l'influence de la base, mais aucune influence significative n'a pu être observée puisque les excès énantiomériques sont tous compris entre 80% et 90% (Tableau 3, entrées 8-12). Néanmoins, alors que la plupart des bases ont donné le produit allylé avec de bons rendements (83-95%), l'utilisation de DBU a eu un impact négatif sur le rendement en **L.57a** (14%) (Tableau 3, entrée 12).

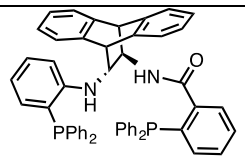
Tableau 3. Influence du ligand et de la base.

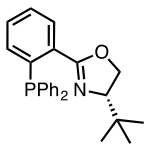


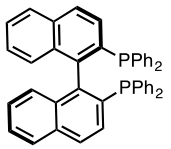
Entrée	Ligand	Base	Rdt (%)	ee (%)
1	(*R*,*R*)-**L1**	Na_2CO_3	95	90
2	(*R*,*R*)-**L2**	Na_2CO_3	81	82
3	(*R*,*R*)-**L3**	Na_2CO_3	93	26
4	(*S*)-**L4**	Na_2CO_3	92	4
5	(*R*)-**L5**	Na_2CO_3	94	22
6	(*S,R,R*)-**L6**	Na_2CO_3	85	8
7	(*S*)-**L7**	Na_2CO_3	90	3
8	(*R*,*R*)-**L1**	Li_2CO_3	90	87
9	(*R*,*R*)-**L1**	K_2CO_3	83	82
10	(*R*,*R*)-**L1**	NaH	96	87
11	(*R*,*R*)-**L1**	BSA	85	80
12	(*R*,*R*)-**L1**	DBU	14	86

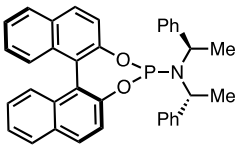

(*R*,*R*)-**L1**

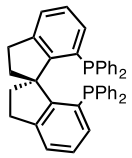

(*R*,*R*)-**L2**


(*R*,*R*)-**L3**


(*S*)-**L4**


(*R*)-**L5**

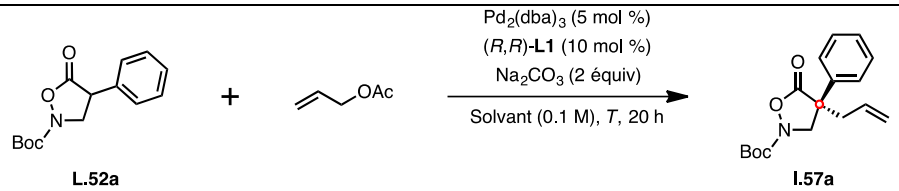

(*S,R,R*)-**L6**


(*S*)-**L7**

Nous avons également étudié l'effet du solvant sur l'énantiosélectivité. En général, les solvants éthérés comme le THF (Tableau 4, entrée 1), le MTBE (Tableau 4, entrée 5) et le

1,4-dioxane (Tableau 4, entrée 6) ou encore un solvant plus polaire telle que la NMP (Tableau 4, entrée 4) ont donné les meilleures énantiosélectivités (ee = 82-90%). Les solvants tels que le toluène (Tableau 4, entrée 2) et le MeCN (Tableau 4, entrée 3) ont donné le produit allylé avec des rendements quasiment quantitatifs, mais avec des énantiosélectivités beaucoup plus faibles (66% et 42% respectivement). Finalement, les ees ont pu être légèrement améliorés en réalisant la réaction à une température plus basse, telle que 0 ºC ou −10 ºC (Tableau 4, entrées 7 et 8). Cependant, pour de raisons pratiques, nous avons choisi de mener nos réactions à 0 ºC.

Tableau 4. Influence du solvant.



Entrée	Solvant	*T*	Rdt (%)	ee (%)
1	THF	ta	95	90
2	PhMe	ta	99	66
3	MeCN	ta	92	42
4	NMP	ta	78	82
5	MTBE	ta	99	89
6	1,4-dioxane	ta	85	83
7	THF	0 ºC	95	91
8	THF	−10 ºC	94	92

4.3. Généralisation de la réaction

Après avoir optimisé les conditions réactionnelles, nous avons examiné le champ d'application de la Pd-AAA en appliquant les conditions optimisées, à savoir $Pd_2(dba)_3$ (5 mol %), Na_2CO_3 (2 équiv), THF à 0 ºC, à divers isoxazolidin-5-ones substituées en position 4 (Schéma 19). Ces conditions se sont révélées être applicables à une large gamme d'isoxazolidinones portant un groupe α-aryle/hétéroaryle, confirmés par les bons rendements (86-97%) et les excellentes énantiosélectivités (85-92%) obtenus. Les substrats contenant un fragment aryle substitué par un groupe électrodonneur, tel qu'un groupement méthoxy

(86%, ee = 87%) ou un méthyle (91%, ee = 90%), ainsi que des noyaux aromatiques substitués par un groupement électroattracteur, tel qu'un atome de fluor (97%, ee = 92%) or un CF_3 (92%, ee = 91%) semblaient être tolérés. Cependant, cette méthode s'est montrée moins performante sur les composés α-alkylés qui ont fournis à la fois de faibles rendements et des mauvaises sélectivités en **L.57**.

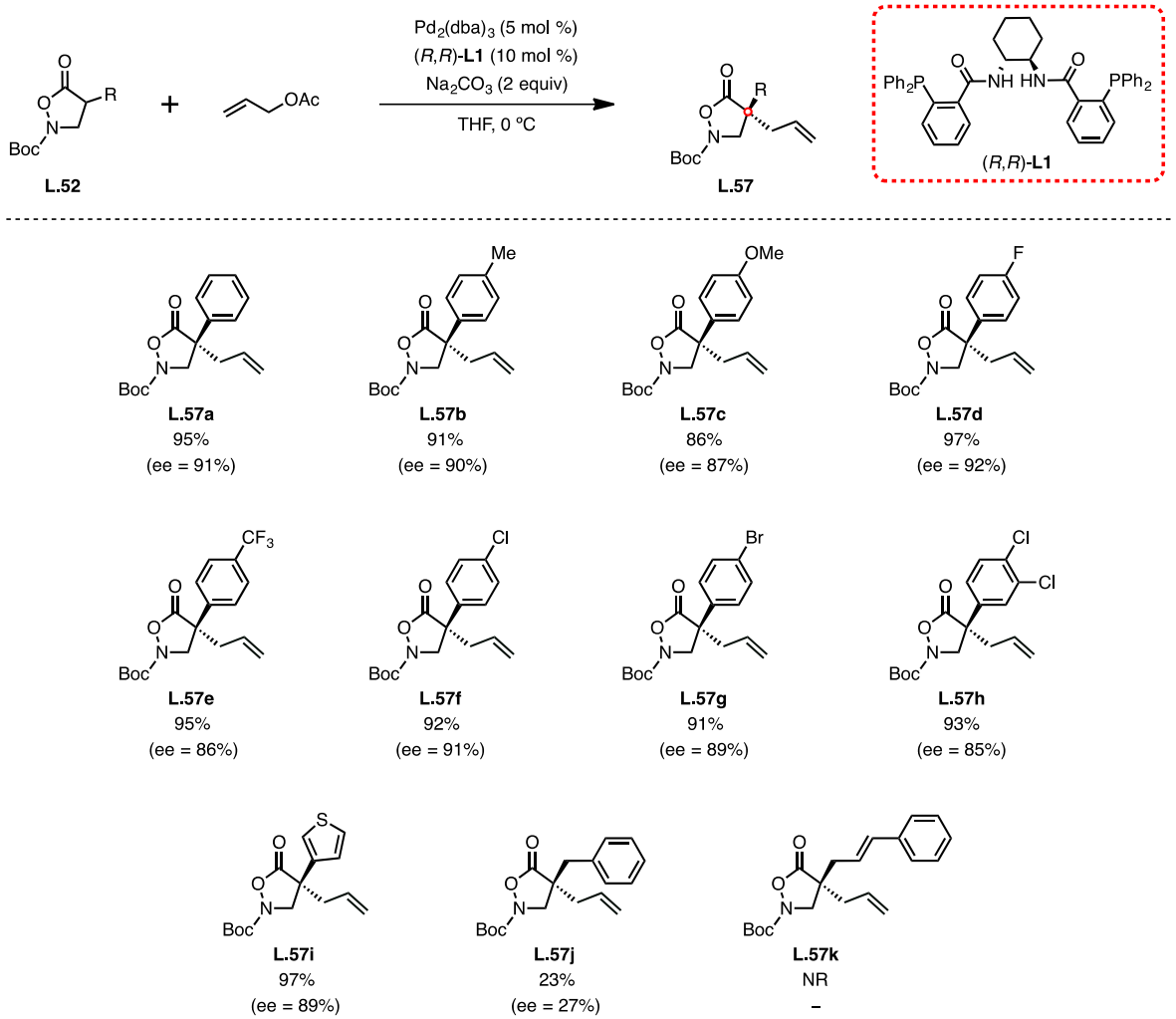
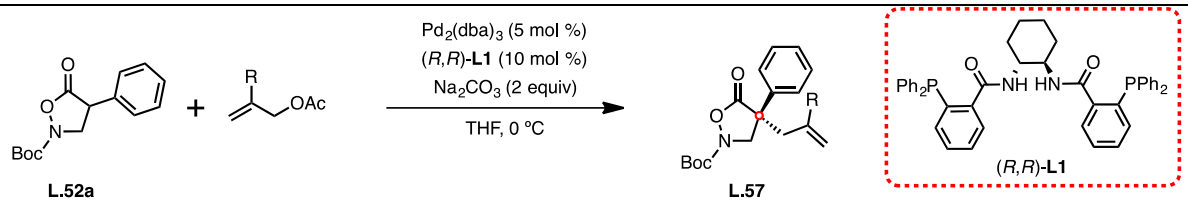


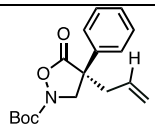
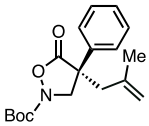
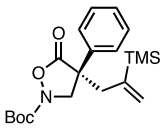
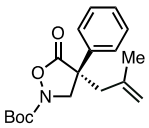
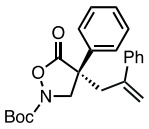
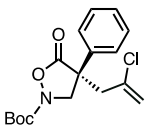
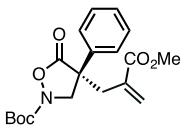
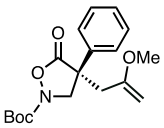
Schéma19. Scope de la réaction avec les isoxazolidin-5-ones substituées en position 4.

Afin d'élargir le champ d'application de la réaction, l'utilisation des acétates d'allyle substitués en positon 2 a ensuite été réalisée. Les résultats sont présentés dans le Tableau 5. D'une manière générale, lorsque l'isoxazolidinone **L.52a** a été engagée dans la réaction d'alkylation allylique avec différents acétates allyliques substitués en position 2, nous avons pu isoler les produits α-allylés correspondants avec d'excellentes énantiosélectivités (jusqu'à ee = 95%). En général, les effets électroniques semblaient avoir un impact beaucoup plus

important sur l'énantiosélectivité que les effets stériques. En effet, lorsque l'encombrement stérique devient plus significatif, aucune amélioration de la sélectivité n'a été observée. C'est ainsi que le remplacement de l'atome d'hydrogène (Table 5, entrée 1) par un groupement triméthylsilyle (Table 5, entrée 3) permet d'obtenir l'excès énantiomérique de 93% au lieu de 91% pour **L.57**. En revanche, le remplacement de l'hydrogène par un atome de chlore (ee = 74%) (Table 5, entrée 6) ou un groupe ester méthylique (ee = 25%) (Table 5, entrée 7) a eu un effet négatif à la fois sur l'énantiosélectivité et sur les rendements. Une disparition totale de réactivité a même été observée avec l'acétate d'allyle substitué en position 2 par un groupement méthoxy (Table 5, entrée 8).

Tableau 5 Scope de la réaction avec les acétates d'allyle substituées en position 2.



Entrée	R	Produit	Rdt (%)	ee (%)
1	H	 L.57a	95	91
2	Me	 L.57l	88	95
3	TMS	 L.57m	76	93
4	CH_2TMS	 L.57l	94	90
5	Ph	 L.57n	71	95
6	Cl	 L.57o	22	74
7	CO_2Me	 L.57p	25	25
8	OMe	 L.57q	NR	–

4.4. Post-fonctionnalisation

Après avoir établi une voie pratique et hautement énantiosélective permettant d'accéder aux isoxazolidinones α,α-disubstituées **L.57**, nous avons décidé d'en démontrer son utilité synthétique en développant des conditions permettant de convertir ces composés en acides $\beta^{2,2}$-aminés et en β-lactames (Schéma 20).

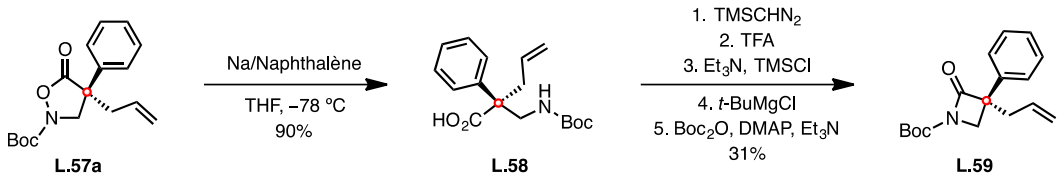


Schéma 20. Synthèse d'acide $\beta^{2,2}$-aminé et de β-lactame.

Pour effectuer la coupure de la liaison N–O, nous avons testé différentes conditions réactionnelles ($Na_2S_2O_4$/EtOH/H_2O, SmI_2/THF et Zn/AcOH). Cependant, aucune n'a menée à l'acide aminé désiré. En revanche, l'utilisation du naphthalénure de sodium dans le THF à −78 ºC a donné le produit **L.58** avec un rendement de 90%. Ce dernier a par la suite été engagé dans une estérification de l'acide carboxylique par le $TMSCHN_2$, suivi d'une déprotection de l'azote avec du TFA (coupure du *N*-Boc) et, finalement, l'utilisation de TMSCl/Et_3N/*t*-BuMgCl a conduit au β-lactame **L.59** correspondant avec un rendement global de 31%.

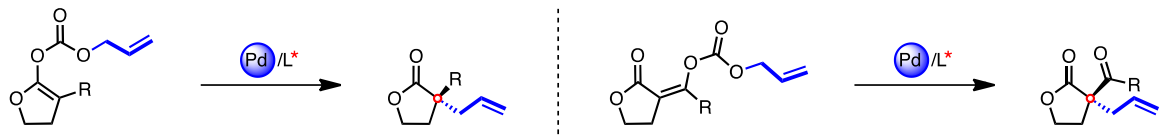
5. Résumé

Nous avons développé une nouvelle méthode catalytique robuste et hautement énantiosélective permettant d'accéder aux isoxazolidinones α,α-disubstituées. Ce protocole repose sur une alkylation allylique asymétrique catalysée par des complexes de palladium chiraux et amène aux produits désirés avec de bons rendements et d'excellents excès énantiomériques (jusqu'à 95%). Par ailleurs, nous avons également mis au point des conditions permettant de convertir ces isoxazolidinones α,α-disubstituées en acides $\beta^{2,2}$-aminés et en β-lactames.

Abstract

Structural units containing an all-carbon quaternary stereogenic center are found in a plethora of bioactive natural products and pharmaceuticals. However, due to the steric hindrance enforced by the four distinct carbon substituents, the construction of such frameworks remains a particularly challenging task in organic synthesis. The development of catalytic enantioselective methods enabling the preparation of such compounds has been a major concern in the last decades. In this regard, the palladium-catalyzed asymmetric allylic alkylation has appeared as the utmost relevance method for the assembly of all-carbon quaternary stereogenic centers. Indeed, since its introduction by Trost *et al*. in the late 70s, the fundamental role of this key transformation has been extensively demonstrated as showcased by number of applications reported in the literature.

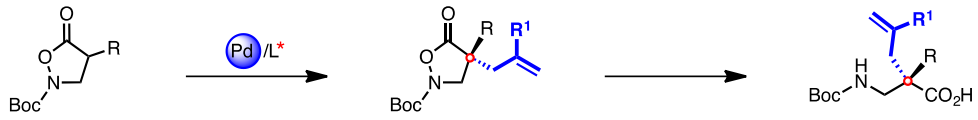
In the first chapter of this thesis, we will describe how we have applied the palladium-catalyzed asymmetric decarboxylative allylic alkylation (Pd-DAAA) to a range of cyclic and exocyclic allyl enol carbonates providing a straightforward access to enantiomerically enriched γ-butyrolactones bearing an α-quaternary stereogenic center (Scheme I). The interest of accessing such motifs has been growing in both academia and industry, due to the ubiquity and importance of lactones in natural products and bioactive compounds. Furthermore, these enantioenriched α-quaternary lactones have been shown to be particularly versatile building blocks that can be further converted to more complex structural motifs.



Scheme I. Pd-DAAA of cyclic and exocyclic allyl enol carbonates.

In the second chapter of this thesis, we will present our efforts towards the asymmetric synthesis of α-quaternary isoxazolidin-5-ones using our key palladium-catalyzed asymmetric allylic alkylation (Pd-AAA). This culminated in the development of a highly enantioselective route to $\beta^{2,2}$-amino acids (Scheme II). Despite the number of methods that have been developed for the asymmetric synthesis of β-amino acids over the last two decades, a general strategy to produce such motifs in a highly enantioselective fashion remained a challenge,

particularly for $\beta^{2,2}$-amino acids bearing an all-carbon quaternary stereogenic centers. The palladium-catalyzed asymmetric allylic alkylation of 4-substituted isoxazolidin-5-ones appeared as a particularly attractive approach to successfully address this issue.



Scheme II. Synthesis of $\beta^{2,2}$-amino acids *via* a key Pd-AAA.

Chapter

1

Palladium-Catalyzed Asymmetric Decarboxylative Allylic Alkylation: Synthesis of All-Carbon α-Quaternary γ-Butyrolactones

1. Occurrence of the γ-butyrolactone motif in natural and/or bioactive compounds

1.1. Natural products and biological activity

Lactones are considered to be one of the most significant class of natural products due to their occurrence in a variety of compounds exhibiting a broad range of biological activities. Organic chemists have shown considerable interest to their potential synthetic use as key building blocks since they displayed a vast structural diversity including ring size. Among them, naturally occurring γ-butyrolactones represent about 10% of all known natural products of which few representative examples are shown below (Figure 1).[1]

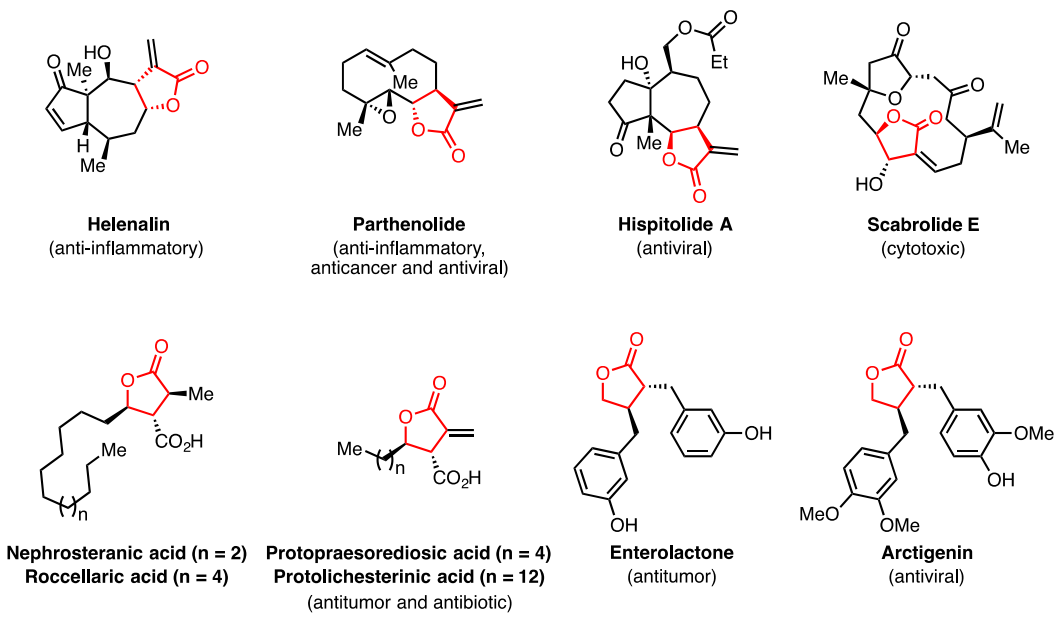


Figure 1. Structures of various γ-butyrolactone-containing natural products.

The γ-butyrolactone ring is a prevalent structural motif in natural products, usually found as part of a more complex framework, such as bicyclic or tricyclic systems.

1 (a) Janecki, T., *Natural Lactones and Lactams*. 1st ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, **2013**; (b) Ogliaruso, M.; Wolfe, J., *Synthesis of lactone and lactamas*. John Wiley & Sons: New York, **1993**; (c) Koch, S.; Chamberlin, R. *Stud. Nat. Prod. Chem.* **1995**, *16*, 687.

A multitude of biological profiles have been discovered for this class of molecules including antibiotic, antitumor, antifungal, antiviral and anti-inflammatory properties, to name a few.[2]

Natural products bearing a γ-butyrolactone motif are so abundant that it would be impossible to describe all of them in this chapter. We therefore decided to present the three major classes of γ-butyrolactones.

1.1.1. α-Alkylidene-γ-butyrolactones

α-Alkylidene-γ-butyrolactones represent the largest group of naturally occurring γ-butyrolactones, many of which are biologically active species. The conjugated exocyclic double bond of these lactones is believed to be a key element for their biological properties.[3] The first representative compound of this class, the α-methylene-γ-butyrolactone named pyrethrosin, was isolated at the end of 19th century (Figure 2). Since then, numerous other members of this family have been reported. According to Kitson's review, published in 2009,[4] approximately 5000 natural α-alkylidene-γ-butyrolactones have been reported.

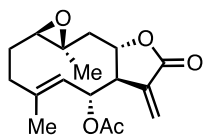


Figure 2. Structure of pyrethrosin.

Naturally occurring α-alkylidene-γ-butyrolactones can be further classified into two main categories. The first one is the sesquiterpenic lactones (terpenoids possessing 15 carbons), which represent the largest and the most diversified category, usually isolated from plants belonging to the families of *Compositae*, *Acanthaceae*, *Lauraceae*, *Magnoliaceae* and *Rutaceae*. These sesquiterpenic lactones can be further classified according to the carbocyclic scaffold attached to the lactone ring e.g. germacranolides, guaianolides, eudesmanolides and pseudoguaianolides (Figure 3).

2 (a) Dong, D.; Zhang, R.; Zhang, D.; Liang, Y. *Synthesis* **2012**, *44*, 1679; (b) Seitz, M.; Reiser, O. *Curr. Opin. Chem. Biol.* **2005**, *9*, 285.
3 Hoffmann, H. M. R.; Rabe, J. *Angew. Chem. Int. Ed.* **1985**, *24*, 94.
4 Kitson, R. R.; Millemaggi, A.; Taylor, R. J. *Angew. Chem. Int. Ed.* **2009**, *48*, 9426.

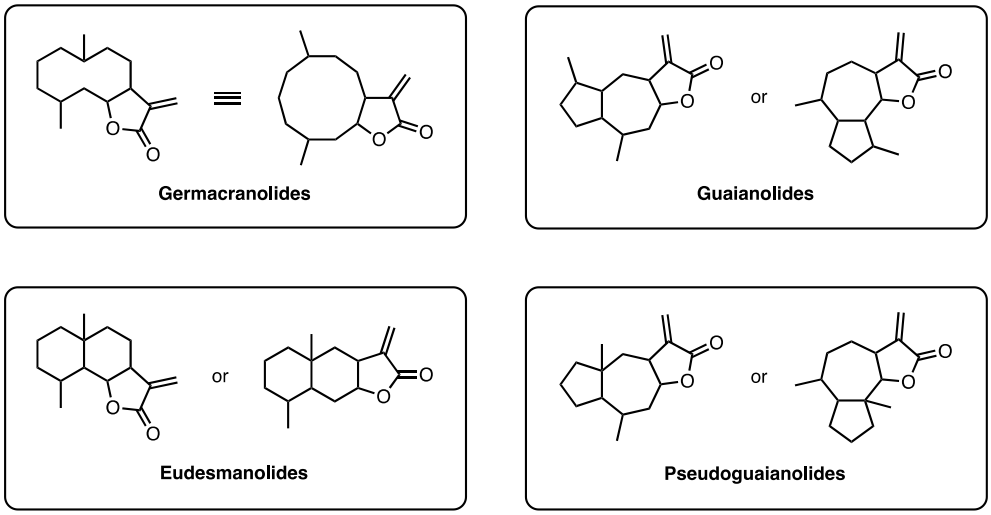


Figure 3. General structures of sesquiterpene lactones.

The second category is constituted by the α-alkylidene-γ-butyrolactone diterpenes that have a 14-membred ring attached to the lactone skeleton (Figure 4). These diterpenic lactones, also referred to as *Cembranolides*, have been predominantly found in marine soft corals of the genus *lobophytum*, *Sinularia*, and *Sacrophyton* and in gorgonian octocorals of the genus *Eunicea*. Crassocolide A (Figure 4), isolated from *Sarcophyton crassocaule*, bearing a *trans*-fused lactone ring to the carbocyclic scaffold, is a representative example. This α-methylene-γ-butyrolactone diterpene exhibits cytotoxic activity against breast, liver and lung cancer cell lines.

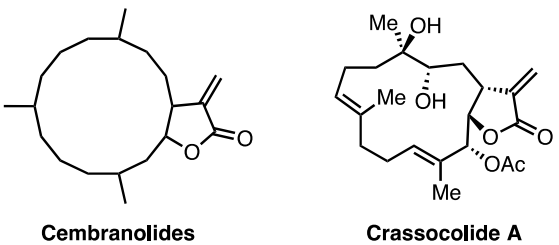
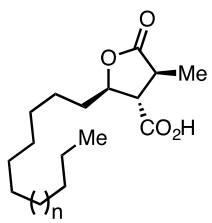


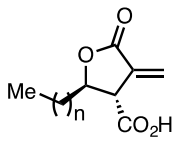
Figure 4. General structure of cembranolides and structure of crassocolide A.

1.1.2. Paraconic acids

Paraconic acids are naturally occurring trisubstituted γ-butyrolactones bearing a 3-carboxylic acid group, and these lactones are mainly isolated from lichens. The carboxylic functionality at the C-4 position and the pendent alkyl chain at the C-5 position are characteristic features of this class of lactones, while the α-methylene/methyl group on the lactone moiety seems to be crucial for its antibiotic and antitumor activities.[5] The well-known protolichesterinic acid, found in *Parmelia* species (lichens indigenous to India), is probably the best representative example of this class of molecules, which includes nephrosterinic, roccellaric, protopraesorediosic and protolichesterinic acids (Figure 5).[6]



Nephrosteranic acid (n = 2)
Roccellaric acid (n = 4)



Protopraesorediosic (n = 4)
Protolichesterinic acid (n = 12)

Figure 5. Structures of nephrosteranic, roccellaric, protopraesorediosic and protolichesterinic acids.

1.1.3. Lignan lactones

Lignans are naturally occurring secondary metabolites extensively encountered in many plant species. Structurally, they are dimeric propyl phenols linked by a β,β'-bond (Figure 6), which is the result from the union of two cinnamic acid residues *via* oxidative coupling. The lignan lactones is an important family among the eight different categories of lignans, due to their variety of biological properties.[7] Within the lignan lactone class, the dibenzyl-γ-butyrolactone and aryltetralin-γ-butyrolactone lignans have been recognized as particularly important natural products, due to their remarkable biological activities.

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5 (a) Bandichhor, R.; Nosse, B.; Reiser, O. *Top. Curr. Chem.* **2005**, *243*, 43; (b) Blanc, D.; Madec, J.; Popowyck, F.; Ayad, T.; Phansavath, P.; Ratovelomanana-Vidal, V.; Genêt, J.-P. *Adv. Synth. Catal.* **2007**, *349*, 943.

6 Murta, M. M.; Azevedo, M. B. M. d.; Greene, A. E. *J. Org. Chem.* **1993**, *58*, 7537.

7 Ward, R. S. *Chem. Soc. Rev.* **1982**, *11*, 75.

The (+)-5'-methoxyyatein (Figure 6), a dibenzyl-γ-butyrolactone, isolated from *Peperomia duclouxii* (a whole plant), has shown to possess potent cytotoxicity toward several cancer types.[8] The aryltetralin-γ-butyrolactone lignan, podophyllotoxin, is the most prominent example of its class (Figure 6). They can be found in plants belonging to the *Berberidaceae* family (*Podophyllum peltatum* and *Podophyllum emodi*) and it has been recognized to possess potent anti-mitotic activity.[9]

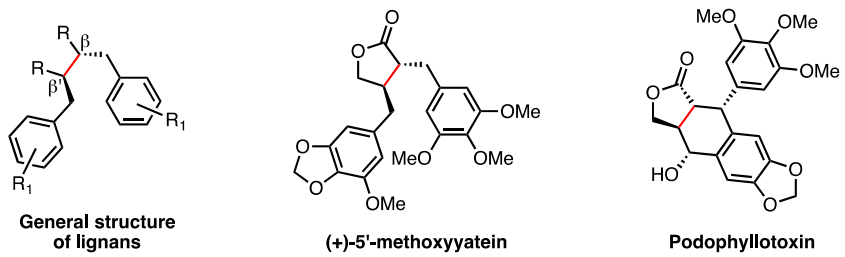


Figure 6. General structure of lignans and structures of (+)-5'-methoxyyatein and podophyllotoxin.

2. Stereoselective synthesis of all-carbon α-quaternary carbonyl derivatives

The ubiquitousness of the γ-butyrolactone motif in naturally occurring molecules, many of them being recognized for their biological properties, has been briefly described in the previous section. The occurrence of biologically active γ-butyrolactones bearing an all-carbon α-quaternary stereocenter is also common, albeit to a lesser extent. Such scaffold has been identified, for example in (+)-hopeahainol A (Figure 7), which possesses inhibitory activity against acetylcholinesterase, an enzyme related to the Alzheimer's disease.[10] Another example of γ-butyrolactone with a stereochemically defined all-carbon α-quaternary center of particular biological importance is rosmanol (Figure 7). The latter is found in the culinary and medicinal herbal rosemary (*Rosmarinus officinalis*), and exhibits marked cytotoxic effects.[11] Alongside natural products, the synthetic α-quaternary γ-butyrolactones have also

8 Amancha, P. K.; Liu, H.-J.; Ly, T. W.; Shia, K.-S. *Eur. J. Org. Chem.* **2010**, *18*, 3473.
9 Sellars, J. D.; Steel, P. G. *Eur. J. Org. Chem.* **2007**, *23*, 3815.
10 (a) Snyder, S. A.; Thomas, S. B.; Mayer, A. C.; Breazzano, S. P. *Angew. Chem. Int. Ed.* **2012**, *51*, 4080; (b) Nicolaou, K. C.; Wu, T. R.; Kang, Q.; Chen, D. Y. *Angew. Chem. Int. Ed.* **2009**, *48*, 3440.
11 (a) Cheng, A. C.; Lee, M. F.; Tsai, M. L.; Lai, C. S.; Lee, J. H.; Ho, C. T.; Pan, M. H. *Food Chem. Toxicol.* **2011**, *49*, 485; (b) Zhang, Y.; Smuts, J. P.; Dodbiba, E.; Rangarajan, R.; Lang, J. C.; Armstrong, D. W. *J. Agric. Food Chem.* **2012**, *60*, 9305.

demonstrated interesting biological activities. The biological evaluation of (−)- and (+)-**L1.1** has shown that these compounds have both inhibitory and stimulatory effects on the $GABA_A$ (γ-aminobutyric $acid_A$) receptor, depending on the enantiomer.[12]

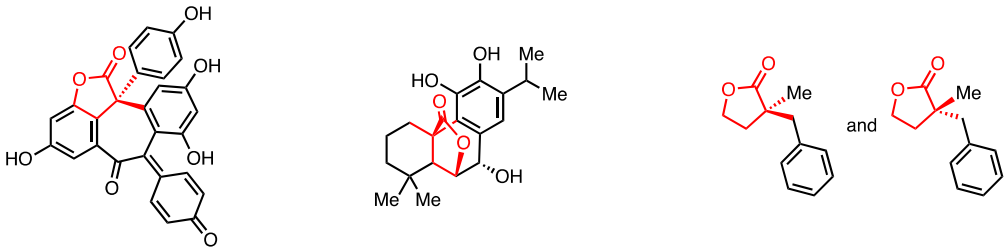


Figure 7. Structures of (+)-hopeahainol A, rosmanol and (−)- and (+)-**L1.1**.

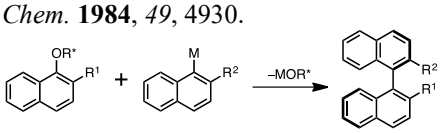
Consequently, the interest in developing new methods toward the enantioselective construction of all-carbon α-quaternary γ-butyrolactones has been the focus of intensive efforts. Despite the significant advances in asymmetric synthesis, the stereoselective approaches allowing the access to such chiral compounds remains limited.

The main goal of this section is to provide and outline a detailed coverage of the most recent available methods applied to the asymmetric synthesis of all-carbon α-quaternary γ-butyrolactones, in particular the ones involving catalytic enantioselective methods.

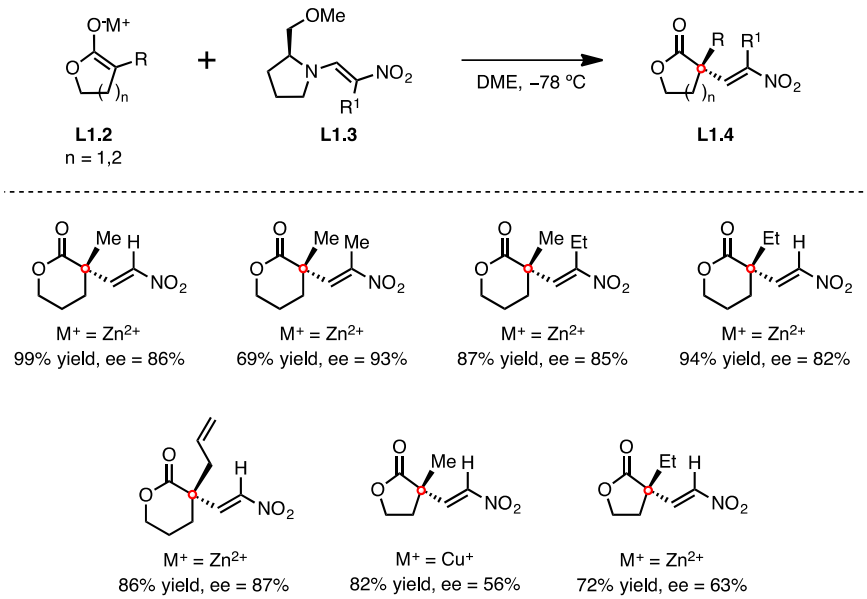
2.1. Diastereoselective method

The indirect asymmetric synthesis involving the transfer of asymmetry from a chiral auxiliary have been extensively used to control the formation of stereogenic centers. On the other hand, the asymmetric induction by chiral leaving groups in the straightforward construction of all-carbon quaternary stereocenters remains relatively less explored.[13] The first successful chiral induction through this approach was reported by Cram and Wilson,[14] and involves a one-pot addition/elimination sequence in the synthesis of chiral binaphthyls.

12 Gonzales, E. B.; Bell-Horner, C. L.; de la Cruz, M. A.; Ferrendelli, J. A.; Covey, D. F.; Dillon, G. H. *J. Pharmacol. Exp. Ther.* **2004**, *309*, 677.
13 Roos, G., *Key Chiral Auxiliary Applications*. 2nd ed.; Academic Press: Oxford, **2014**.
14 (a) Wilson, J. M.; Cram, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 881; (b) Wilson, J. M.; Cram, D. J. *J. Org. Chem.* **1984**, *49*, 4930.



Inspired by this work, Fuji *et al.*[15] described the diastereoselective synthesis of chiral all-carbon α-quaternary lactones **L1.4** using a similar strategy, as shown in the Scheme 1.



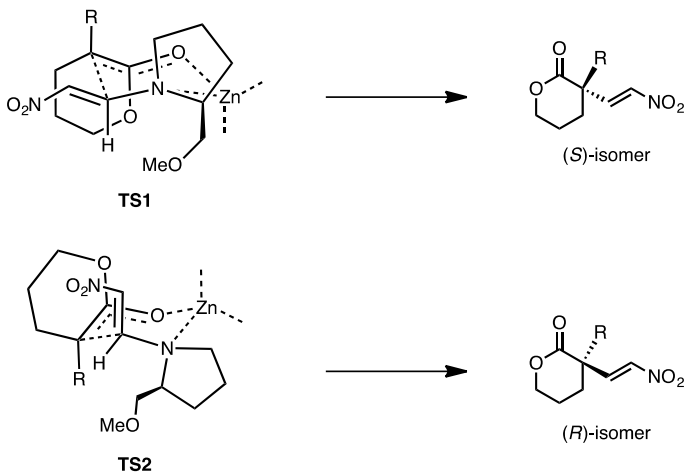
Scheme 1. Fuji's diastereoselective synthesis of chiral α-quaternary lactones.

Fuji *et al*. described the reaction of enolates of α-substituted δ- and γ-lactones **L1.2** with optically active nitro enamines **L1.3** through a Michael-type addition/elimination process (Scheme 1). This method allowed the access to α-quaternary δ-lactones in high yields and excellent enantioselectivities ranging from 82% to 93% ee. Although, the extension of this process to γ-butyrolactones led to less satisfactory results with ee values comprised between 56% and 63%, revealing the limit of this approach.

During the investigation of this reaction, the authors realized that the enantiomeric excess could be dramatically affected by the choice of the cation, thus showcasing the importance of the chelation in the transition state. A cyclic transition model was proposed to rationalize the stereoselectivity, as depicted in Scheme 2. Considering the two possible transition states, **TS1** and **TS2**, the Michael-type addition of the enolate onto the enamine governs the absolute stereochemistry of the formed α-quaternary lactone. The chair like transition state **TS1** resulting from the combination of the *re*-face of both the enolate and the nitro enamine is preferred rather than **TS2** since the nitroalkyl group is disposed equatorially

15 Fuji, K.; Node, M.; Nagasawa, H.; Naniwa, Y.; Taga, T.; Machida, K.; Snatzke, G. *J. Am. Chem. Soc.* **1989**, *111*, 7921.

in the transition state **TS1**, avoiding an additional 1,3-diaxial interaction and thus providing the observed (*S*)-isomer preferentially (Scheme 2).



Scheme 2. Understanding the stereoselectivity outcome.

2.2. Enantioselective methods

2.2.1. Kinetic resolution

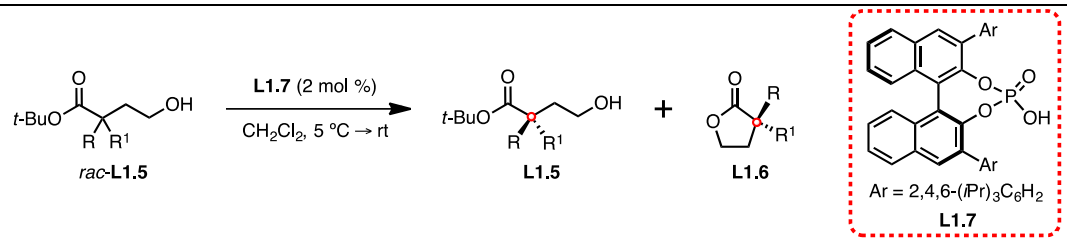
Since the seminal work of Akiyama *et al.*,[16] Uraguchi and Terada[17], chiral Brønsted acid catalysis has been widely used to achieve a plethora of enantioselective transformations.[18] List *et al.*, for example, used chiral phosphoric acids to catalyze the kinetic resolution of homoaldols *via* a transacetalization.[19] This approach was eventually applied to γ-hydroxy esters *rac*-**L1.5** to obtain to enantioenriched α-substituted γ-butyrolactones **L1.6** (Table 1).[20]

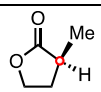
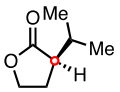
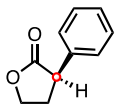
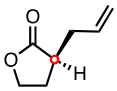
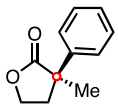
The strategy for the synthesis of stereochemically defined lactones **L1.6** was based on the separation of the enantiomers of *rac*-**L1.5** *via* selective lactonization of one enantiomer over the other in the presence of the chiral BINOL-derived phosphoric acid catalyst **L1.7**. The separation of the two enantiomers was possible due to the different intramolecular transesterification rates of the two enantiomers. Unfortunately, the substrate scope revealed

16 Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem. Int. Ed.* **2004**, *43*, 1566.
17 Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356.
18 (a) Rueping, M.; Kuenkel, A.; Atodiresei, I. *Chem. Soc. Rev.* **2011**, *40*, 4539; (b) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999.
19 Coric, I.; Muller, S.; List, B. *J. Am. Chem. Soc.* **2010**, *132*, 17370.
20 Qabaja, G.; Wilent, J. E.; Benavides, A. R.; Bullard, G. E.; Petersen, K. S. *Org. Lett.* **2013**, *15*, 1266.

that the α-substituted hydroxy esters underwent a very modest kinetic resolution. In most cases, the transacetalization proceeded with poor to moderate enantioselectivities. However, a remarkable result came along when an α-quaternary hydroxy ester was subjected to the kinetic resolution, leading to the formation of the all-carbon α-quaternary γ-butyrolactone **L1.6e** (Table 1, entry 6) with the best selectivity factor (s = 16.7).[21] Thus, this kinetic resolution offers a potentially complementary tool for the chiral Brønsted acid-catalyzed construction of all-carbon α-quaternary γ-butyrolactone.

Table 1. Kinetic resolution of homoaldols *via* catalytic asymmetric transacetalization.



Entry	Product	**L1.6**	Conversion (%)	**L1.5** ee%	**L1.6** ee%	s
1		**L1.6a**	68	21	24	1.4
2[a]		**L1.6b**	56	52	37	3.9
3[b]		**L1.6c**	71	50	26	2.3
4		**L1.6d**	63	86	50	7.9
5		**L1.6e**	53	83	66	16.7

[a]Hexane was used as solvent. [b]Toluene was used as solvent.

2.2.1.1. Desymmetrization

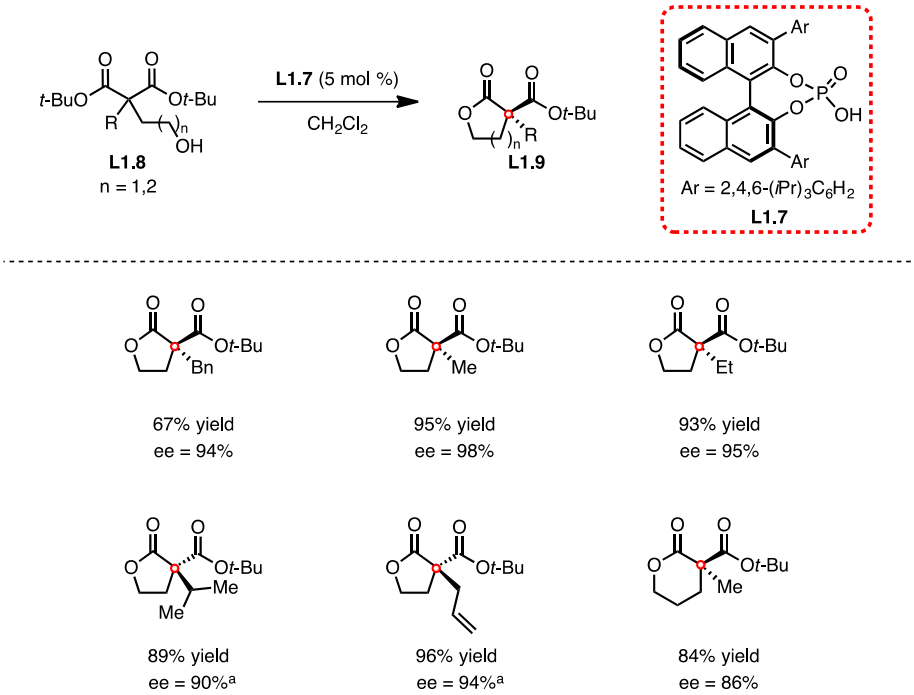
21 (a) The selectivity factor (s) was determined using the Kagan's equation: $s = k_{rel(fast/slow)} = \ln[(1-c)(1-ee_s)]/\ln[(1-c)(1+ee_s)]$, where c = conversion and ee_s the ee of the recovered starting material. (b) Eliel, E. L., *Topics in Stereochemistry*; Wiley & Sons: New York, **1988**; Vol. 18.

The desymmetrization of *meso* and prochiral compounds consists of a modification of the substrate that results in the removal of one or more elements of symmetry, making attainable the introduction of chirality. Such transformation represents an important variant of the standard kinetic resolution process as it prevented the intrinsic limitation related to the traditional kinetic resolution. The desymmetrization differs from the latter in a very practical reason; In kinetic resolution, the two enantiomers of a racemic mixture react with different reaction rates in a chemical transformation, which allows their separation through the transformation of one enantiomer into product and recovery of the other. While in a desymmetrization process, the reaction proceeds faster at one of the two enantiotopic groups or faces of the substrate, affording only one enantiomer of the product, preferentially, with possible 100% yield. For this advantage, more attention has been recently paid on the desymmetrization of *meso* and prochiral molecules which represents a powerful tool in asymmetric synthesis.[22]

Chiral Brønsted acids have been recognized to be highly efficient in the desymmetrization of different prochiral esters, compounds that can be easily synthesized from inexpensive starting materials as showcased by Petersen and Wilent in their elegant desymmetrization of *meso* hydroxy diesters **L1.8** into all-carbon α-quaternary lactones **L1.9** (Scheme 3).[23]

The successful synthesis of chiral lactones **L1.9** by means of desymmetrization of *meso* hydroxy diesters **L1.8** in the presence of the chiral Brønsted acid **L1.7** have been accomplished through an enantioselective activation of one ester functionality by the chiral phosphoric acid, promoting an intramolecular transesterification (Scheme 3). This method proved to be an extremely effective synthetic route for the enantioselective preparation of lactones bearing the challenging all-carbon α-quaternary stereogenic center, particularly α-quaternary γ-butyrolactones but also α-quaternary δ-lactones, which could be obtained in good yields and excellent enantioselectivities (ee up to 98%).

22 (a) Willis, M. C. *J. Chem. Soc., Perkin Trans. 1* **1999**; (b) García-Urdiales, E.; Alfonso, I.; Gotor, V. *Chem. Rev.* **2005**, *105*, 313.
23 Wilent, J.; Petersen, K. S. *J. Org. Chem.* **2014**, *79*, 2303.



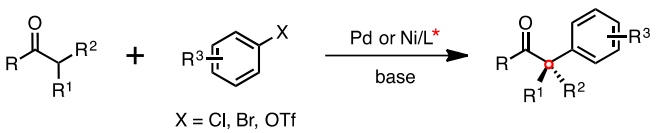
[a] The opposite enantiomer of **L1.7** was used.

Scheme 3. Petersen and Wilent desymmetrization of *meso* hydroxy diesters.

2.2.2. Metal-mediated α-arylation

Cross-coupling reactions, mediated by transition metals, represent one of the most versatile methods for the formation of C–C bonds.[24] Since their introduction, the number of metal-based protocols published has increased considerably. In this vein, the asymmetric metal-catalyzed α-arylation of enolates has received great attention, not only for the possibility of broadening the reaction scope and generality, but also for the potential construction of quaternary stereogenic centers α to the carbonyl moiety.[25] Palladium- and nickel-based systems are typically used to catalyze the reaction between aryl halides or pseudohalides and enolates formed *in situ* from different carbonyl-containing compounds such as aldehydes, ketones, esters and amides (Scheme 4).

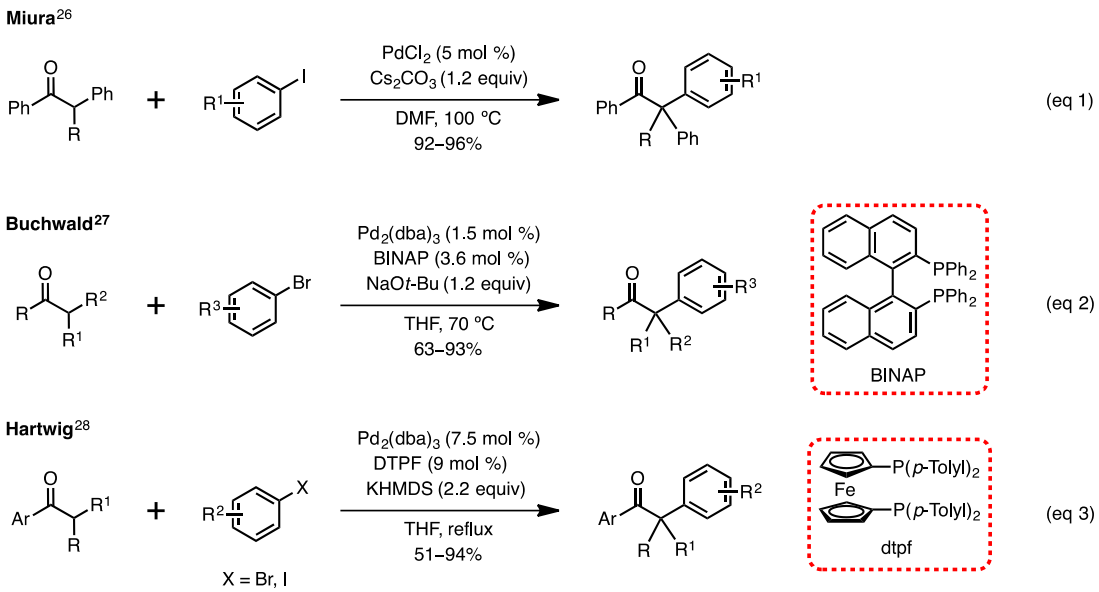
24 Meijere, A. d.; Diederich, F., *Metal-Catalyzed Cross-Coupling Reactions*. 2nd ed.; WILEY-VCH Verlag GmbH & Co. KGaA: Weinheim, **2004**.
25 Johansson, C. C.; Colacot, T. J. *Angew. Chem. Int. Ed.* **2010**, *49*, 676.



Scheme 4. Palladium- and nickel-catalyzed α-arylation of enolates formed *in situ*.

2.2.2.1. Palladium-catalyzed α-arylation

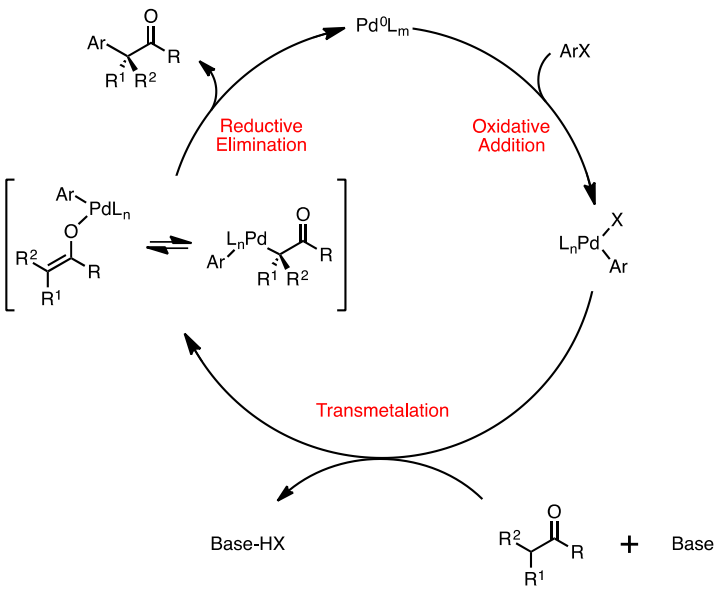
The first examples of palladium-catalyzed direct α-arylation of ketones were reported by Miura *et al.*,[26] Buchwald and Palucki,[27] and Hartwig and Hamman,[28] almost simultaneously in the late 1990s. In this series of publications, the coupling of aryl bromides and iodides with a variety of ketones is described (Scheme 5). These contributions have allowed the direct access to aryl ketones starting from the readily available and cheap starting materials, offering an excellent alternative to the toxic bismuth and lead reagents typically employed in this kind of transformation.



Scheme 5. Miura's, Buchwald's and Hartwig's Pd-catalyzed α-arylation of enolates.

26 Satoh, T.; Inoh, J.-i.; Kawamura, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2239.
27 Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108.
28 Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382.

Mechanistic investigations revealed that the palladium-catalyzed α-arylation of ketones tend to follow the same reaction pathway than cross-coupling processes in which the enolates behave as the nucleophilic organometallic reagents. Hence, the catalytic cycle involves the oxidative addition of the aryl halide onto an active Pd(0) species, followed by a subsequent transmetalation step. In the case of ketone enolates, both *C*- and *O*-palladium bound species can be formed depending on the catalytic system used. The reductive elimination eventually takes place to afford the α-arylated ketone and regenerate Pd(0) as shown in Scheme 6.[29]



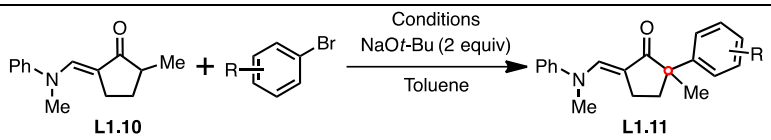
Scheme 6. Proposed mechanism for the Pd-catalyzed α-arylation of enolates.

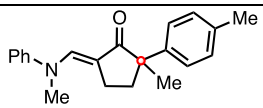
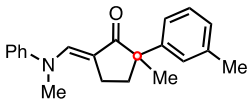
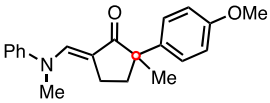
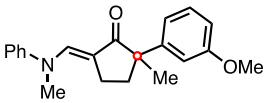
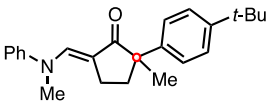
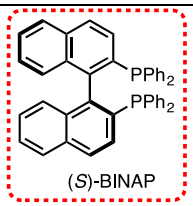
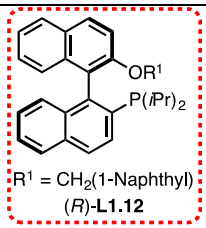
Encouraged by the successful development of the palladium-catalyzed coupling protocols of aryl halides and ketones, Buchwald *et al.* reported the first version of the asymmetric arylation method of enolates to afford all-carbon quaternary stereogenic centers. In this asymmetric variant, the initial Pd/*rac*-BINAP based catalytic system was then replaced by the Pd/(*S*)-BINAP.[30] However, to achieve high yields and enantioselectivities, harsh conditions and elevated catalytic loading were necessary. Therefore, an improvement in the catalytic system by changing the ligand allowed the asymmetric arylation of ketone enolates to proceed under mild reaction conditions and with a considerable decrease in the catalyst

29 Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360.
30 Ahman, J.; Wolfe, J. P.; Troutman, M. V.; Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 1918.

amount, as depicted in the Table 2.[31] The improved conditions were $Pd_2(dba)_3$ (1 mol %) and the binaphthyl ligand (*R*)-**L1.12** (1.5 mol %) at rt.

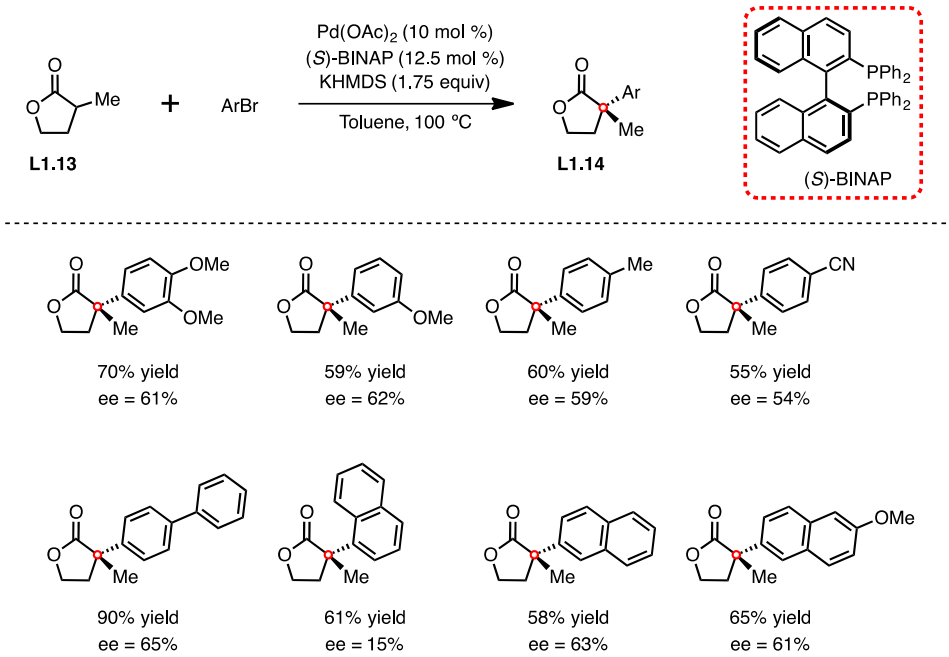
Table 2. Asymmetric arylation of ketone enolates.



			Conditions	
			$Pd_2(dba)_3$ (5 mol %) (*S*)-BINAP (7.5 mol %) 100 ºC	$Pd_2(dba)_3$ (1 mol %) (*R*)-**L1.12** (1.5 mol %) rt
Entry	Product	**L1.11**	Yield, ee, (conf)	Yield, ee, (conf)
1		**L1.11a**	65%, ee = 63%, (*S*)	84%, ee = 93%, (*R*)
2		**L1.11b**	70%, ee = 80%, (*S*)	85%, ee = 94%, (*R*)
3		**L1.11c**	74%, ee = 57%, (*S*)	80%, ee = 94%, (*R*)
4		**L1.11d**	87%, ee = 85%, (*S*)	80%, ee = 89%, (*R*)
5		**L1.11e**	65%, ee = 88%, (*S*)	84%, ee = 93%, (*R*)
			 (*S*)-BINAP	 $R^1 = CH_2$(1-Naphthyl) (*R*)-**L1.12**

31 Hamada, T.; Chieffi, A.; Ahman, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1261.

The abovementioned process has proved to be an attractive approach to prepare enantioenriched α-aryl cyclic ketones. In contrast, there are only a few available arylation methods to access α-aryl cyclic esters and amides.[32] The enantioselective arylation of lactones remains a challenge owing to their inherent reactivity under basic conditions combined with the fact that esters can undergo a Claisen condensation. In 2003, Zhang *et al*. extended the palladium-catalyzed asymmetric α-arylation method developed by Buchwald *et al*. to produce optically active α-methyl γ-butyrolactones, as shown in the Scheme 7.[33] However, Buchwald's catalytic system proved inefficient to enantioselectively access α-quaternary γ-butyrolactones. The coupling of α-methyl γ-butyrolactones with aryl bromides proceeded with moderate yields (55-65%) and enantioselectivities (ee = 15-65%).



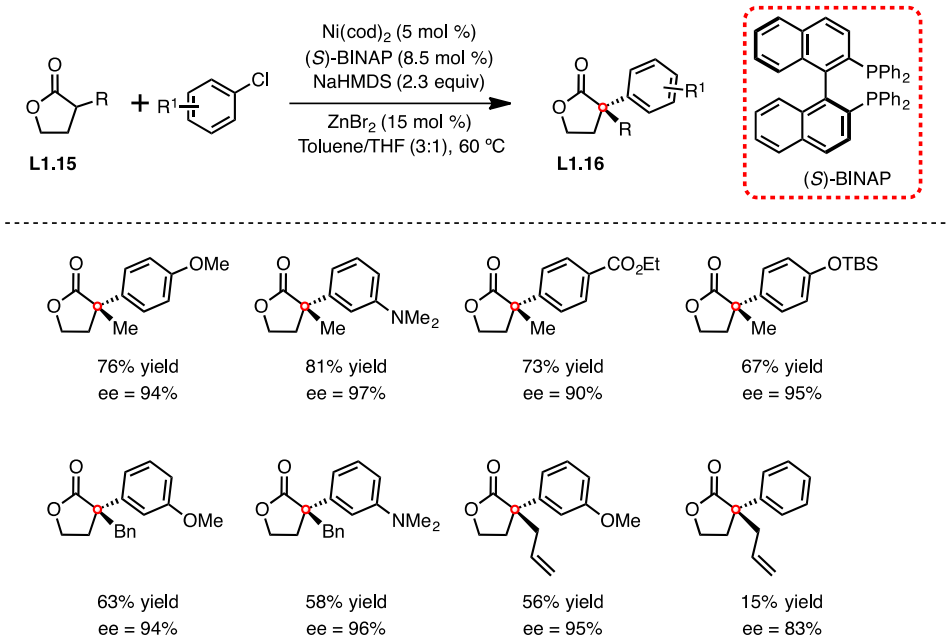
Scheme 7. Asymmetric α-arylation of α-methyl γ-butyrolactones by Zhang *et al*.

32 (a) de Filippis, A.; Gomez Pardo, D.; Cossy, J., *Tetrahedron* **2004**, *60*, 9757; (b) Cossy, J.; de Filippis, A.; Gomez Pardo, D., *Synthesis* **2004**, *17*, 2930.

33 Proctor, C. S.; Zhang, H.; Zhang, T. Y. *Enantioselective process for preparing arylated lactones and derivatives*. US World Patent WO2001072731, Jan 16, **2003**.

2.2.2.2. Nickel-catalyzed α-arylation

Although the palladium-based catalytic systems were widely used in α-arylation of carbonyl compounds, they proved to be problematic in the context of γ-butyrolactones in delivering acceptable levels of enantioselectivity. To circumvent this issue, Buchwald and Spielvogel disclosed an alternative approach relying on nickel-based catalyst. The replacement of palladium by nickel, which is much cheaper than palladium, appeared to be crucial for the formation of enantioenriched α-arylated products (Scheme 8). The authors argued that such enhancement in the enantioselectivity could be justified by a tighter chiral environment around the metallic center.[34]



Scheme 8. Nickel-catalyzed α-arylation of γ-butyrolactones by Buchwald and Spielvogel.

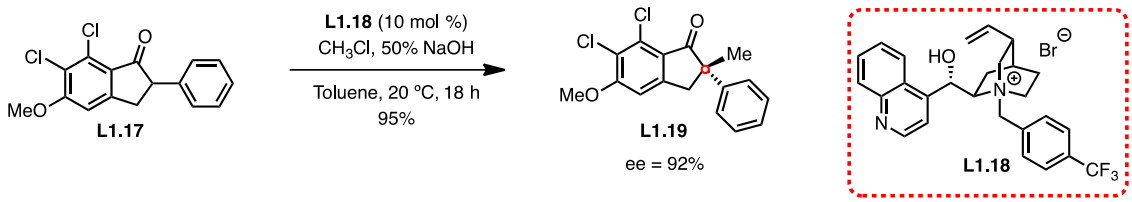
The use of a Ni/(*S*)-BINAP catalytic system allowed the asymmetric synthesis of α-quaternary γ-butyrolactones with excellent ee ranging from 83% to 97% albeit with moderate yields starting from α-substituted γ-butyrolactones and aryl chlorides. Interestingly, the addition of $ZnBr_2$ to the reaction mixture considerably improved the yield, suggesting that this additive acted as a Lewis acid to facilitate the bromide abstraction from

34 Spielvogel, D. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 3500.

[(BINAP)Ni(Ar)(Br)] to generate the cationic [(BINAP)Ni(Ar)]$^+$ species, which subsequently undergoes a transmetalation more rapidly.

2.2.3. Phase-transfer catalyzed α-alkylation

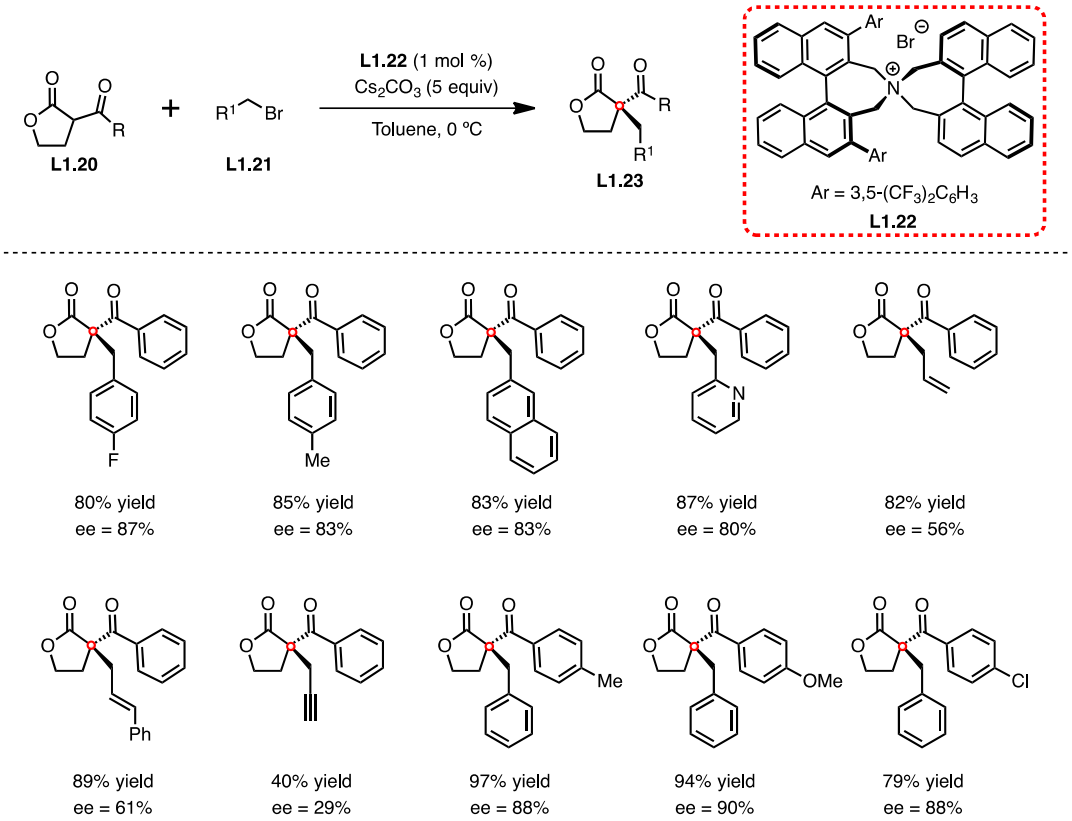
Since the seminal work of Starks *et al.*, numerous chiral phase-transfer catalysts have been developed and successfully used to achieve a range of asymmetric transformations.[35] The application of a phase-transfer catalysis (PTC) to asymmetric alkylation was initially introduced, in 1984 by Grabowski *et al.*, a Merck research group,[36] which used the cinchona-based quaternary ammonium salt **L1.18** to catalyze the methylation of phenylindanone **L1.17** (Scheme 9).



Scheme 9. Asymmetric phase-transfer catalyzed alkylation of phenylindanone.

In 2007, Maruoka *et al.* unveiled a new class of *N*-spiro C_2-symmetric chiral ammonium salts, which were used to catalyze the stereoselective alkylation of β-ketoesters under phase-transfer conditions. The use of this conditions provided a straightforward access to a number of enantioenriched α-alkylated γ-butyrolactones **L1.23** in both excellent yields and enantioselectivities (Scheme 10).[37]

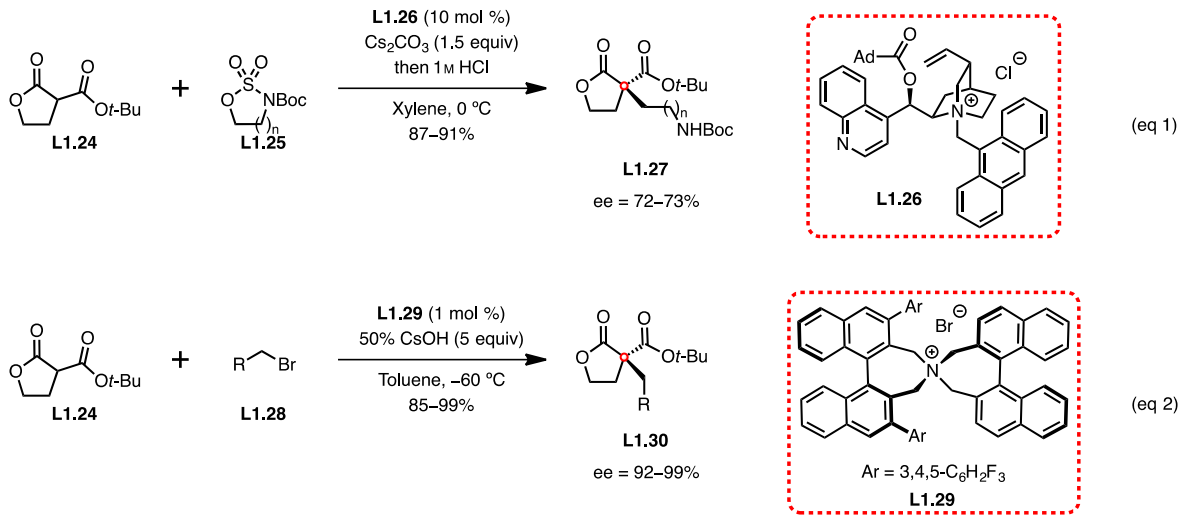
35 Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2007**, *107*, 5656.
36 Dolling, U.-H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446.
37 Ooi, T.; Miki, T.; Fukumoto, K.; Maruoka, K. *Adv. Synth. Catal.* **2006**, *348*, 1539.



Scheme 10. Synthesis of α-acyl α-alkyl γ-butyrolactones by Maruoka *et al*.

Two similar applications were independently reported by Dixon *et al.*[38] and Park *et al.*[39] on the synthesis of α-quaternary γ-butyrolactones. Dixon *et al.* conducted the enantioselective α-alkylation of α-carboxy γ-butyrolactones using the cinchona-derived phase-transfer catalyst **L1.26**, to promote the ring-opening of five-membered cyclic sulfamidates (Scheme 11, eq 1). Park *et al*. used a *N*-spiro chiral ammonium salt **L1.29** to catalyze the alkylation of α-carboxy γ-butyrolactones with improved selectivities, compared to the selectivities obtained by Maruoka *et al*. (Scheme 11. eq 2).

38 Moss, T. A.; Alonso, B.; Fenwick, D. R.; Dixon, D. J. *Angew. Chem. Int. Ed.* **2010**, *49*, 568.
39 Ha, M. W.; Lee, H.; Yi, H. Y.; Park, Y.; Kim, S.; Hong, S.; Lee, M.; Kim, M.-h.; Kim, T.-S.; Park, H.-g. *Adv. Synth. Catal.* **2013**, *355*, 637.



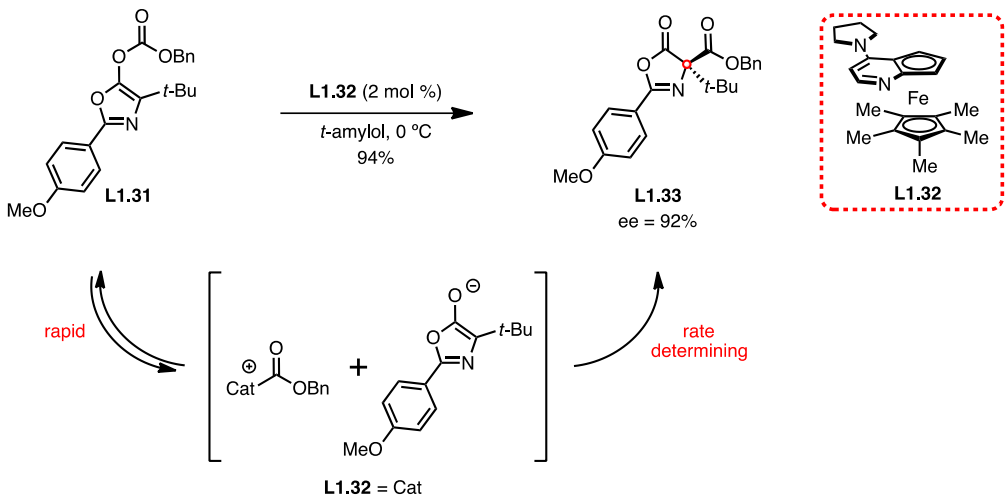
Scheme 11. Stereoselective alkylation of γ-butyrolactones under phase-transfer catalysis.

2.2.4. Organocatalyzed α-acylation

Alternative strategies for the enantioselective construction of all-carbon quaternary centers of carbonyl derivatives, such as the straightforward asymmetric *C*-acylation of enolates, have remained elusive. Over the years, the asymmetric Steglich, *O*- to *C*-rearrangement have been the principal synthetic route to *C*-acylated derivatives, usually mediated by Lewis base chiral catalysts.[40] As a matter of fact, among all the chiral catalysts employed in this asymmetric acyl transfer process, planar-chiral DMAP (4-(*N*,*N*-dimethylamino)pyridine) and PPY (4-pyrrolidinopyridine) scaffolds have been long recognized as being the most remarkable and powerful catalysts for the enantioselective assembly of quaternary stereocenters.[41] This was illustrated in the Steglich rearrangement of *O*-acylated azlactone **L1.31** (Scheme 12).[42]

According to kinetic studies, the formation of the ion pair, issued from the reaction of the catalyst **L1.32** with the *O*-acylated azlactone led to an "acyl-pyridinium" ion along with an enolate counterion, and this step is believed to be reversible, while the *C*-acylation step is not (Scheme 12).

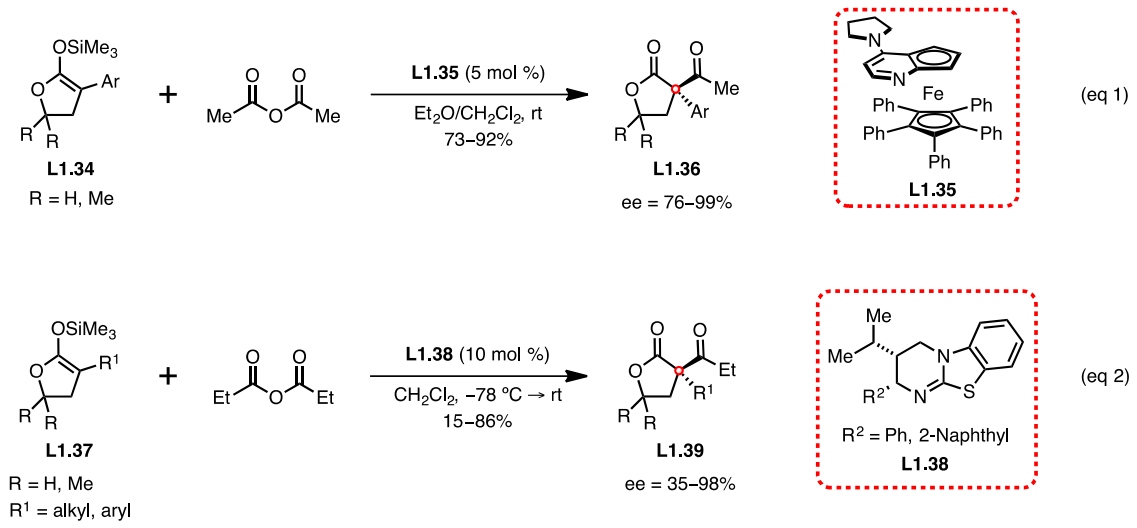
40 Furuta, T.; Kawabata, T. *Science of Synthesis: Asymmetric Organocatalysis*; List, B.; Maruoka, K., Ed. Thieme: Stuttgart, **2012**; Vol. 1, pp 497.
41 Wurz, R. P. *Chem. Rev.* **2007**, *107*, 5570.
42 Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 11532.



Scheme 12. Steglich rearrangement pathway of *O*-acylated azlactones.

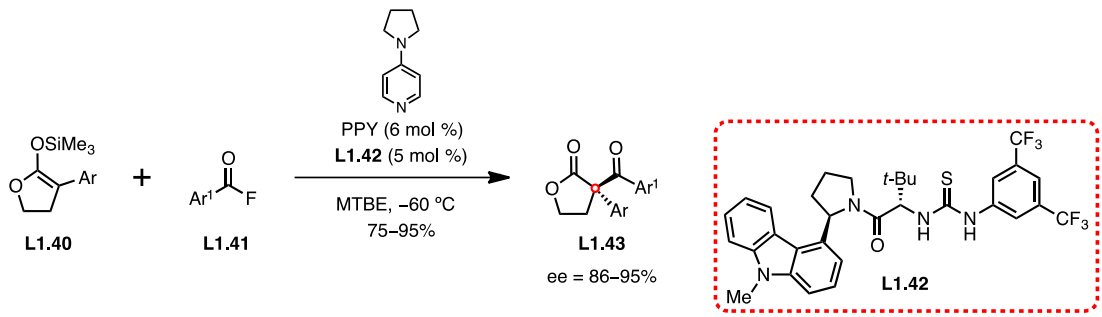
Fu and Mermerian also reported a challenging intermolecular version of this reaction. The authors described the asymmetric *C*-acetylation of ketene silyl acetals with acetic anhydride catalyzed by planar-chiral PPY **L1.35** (Scheme 13, eq 1).[43] The catalytic enantioselective α-acetylation of α-substituted γ-butyrolactones **L1.34** afforded lactones bearing an all-carbon quaternary stereogenic center and the acylated lactones were isolated with good enantioselectivities from a variety of aryl- and heteroaryl-substituted silyl ketene acetals. Inspired by these results, Smith *et al.* successively applied a chiral isothiourea catalyst to the asymmetric *C*-acylation of ketene silyl acetals with propionic anhydride (Scheme 13, eq 2).[44] The chiral isothiourea **L1.38** promoted the direct enantioselective *C*-acylation in good yields, however in slightly reduced levels of enantioselectivity compared to the PPY catalyst **L1.35**.

43 Mermerian, A. H.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 4050.
44 Woods, P. A.; Morrill, L. C.; Bragg, R. A.; Smith, A. D. *Chemistry* **2011**, *17*, 11060.



Scheme 13. Fu and Mermerian, and Smith *et al*. asymmetric *C*-acylation of ketene silyl acetals.

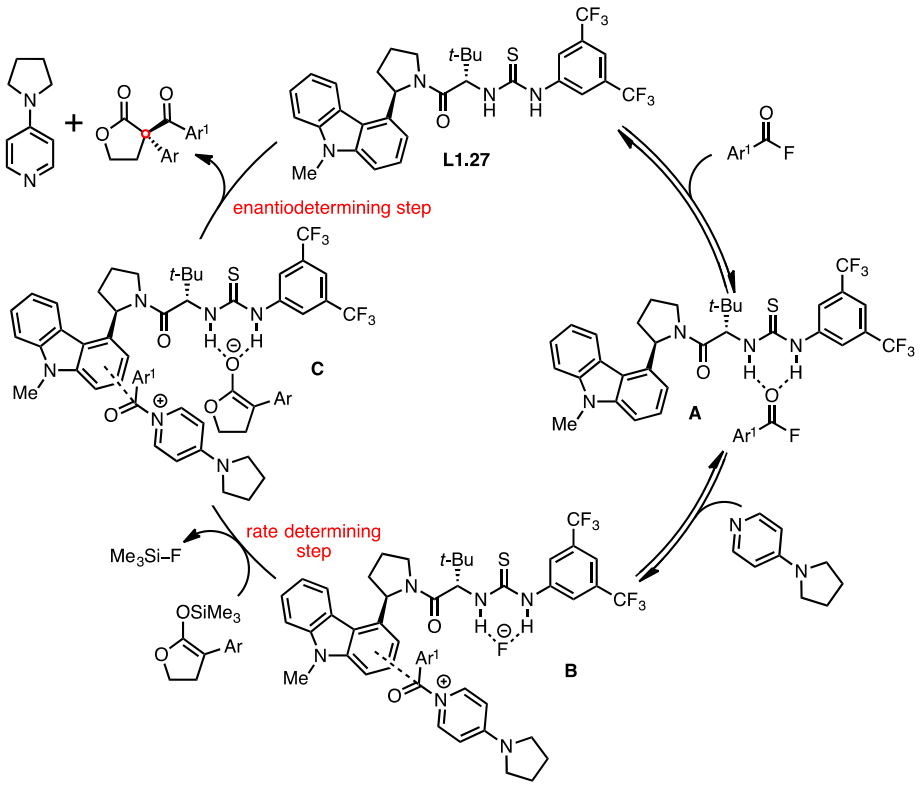
More recently, Jacobsen *et al.* disclosed a fundamentally innovative approach to the field of asymmetric acyl transfer.[45] Indeed, they introduced the first successful dual catalysis anion-binding process involving a chiral thiourea and PPY for the enantioselective *C*-acylation (Scheme 14). The reaction involved the *C*-acylation of ketene silyl acetals **L1.40** with acyl fluorides **L1.41** promoted by the thiourea catalyst **L1.42** and PPY (4-pyrrolidinopyridine). The use of dual catalysis provided a useful route to α-quaternary γ-butyrolactones **L1.43**, which could thus be obtained with excellent enantioselectivities. Interestingly, the use of acyl fluorides played a crucial role not only for the achievement of high enantioselectivities but also to improve the reactivity — as no reaction was observed using acyl chlorides.



Scheme 14. Jacobsen *et al.* enantioselective *C*-acylation of ketene silyl acetals.

45 Birrell, J. A.; Desrosiers, J. N.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2011**, *133*, 13872.

A proposed catalytic cycle is shown in Scheme 15. Accordingly, the thiourea catalyst activates the acyl fluoride *via* complexation with the carbonyl moiety to give intermediate **A**. The latter is eventually converted to the corresponding thiourea-bound acylpyridinium/fluoride intermediate **B**, in which the thiourea is associated to the fluoride anion and the catalyst aryl substituent is engaged in the stabilizing interaction with the acylpyridinium cation. The reaction of **B** with silyl ketene acetal is believed to be rate-determining on the basis of the observed dependence of the overall rate on the identity of the silyl group, while *C*-acylation of the thiourea-bound enolate in **C** is assumed to be the enantiodetermining step as the enantioselectivity is independent of the nature of the silyl group.



Scheme 15. Mechanism of the enantioselective *C*-acylation of ketene silyl acetals.

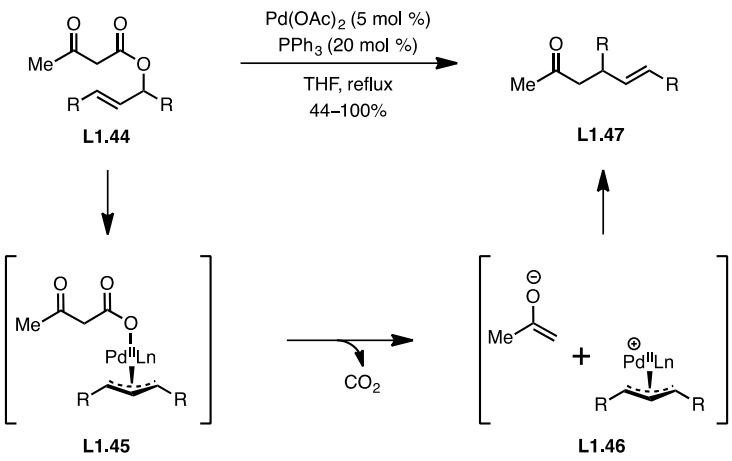
3. Palladium-catalyzed asymmetric decarboxylative allylic alkylation (Pd-DAAA)

The **P**alladium-catalyzed **A**symmetric **D**ecarboxylative **A**llylic **A**lkylation (Pd-DAAA) has emerged as a particularly appealing tool for the construction of quaternary stereogenic centers. This powerful method has enabled the direct asymmetric construction of C–C bonds in several pharmaceuticals and biologically relevant natural products.[46] Over the past two decades, this enantioselective process, also referred to the Tsuji-Trost reaction, has been the subject of ever-growing interest owing to its ability to couple allylic electrophiles with a variety of nucleophiles in a chemo-, regio- and stereoselective fashion,[47] taking advantage of the formation of CO_2 as a driving force for the site-specific generation of nucleophiles under mild and formally neutral conditions. This section will focus on the subclass of the Tsuji-Trost reactions relying on the *in situ* generation of pro-chiral enolates after an initial decarboxylative step.

3.1. Decarboxylative allylic alkylation of enolates

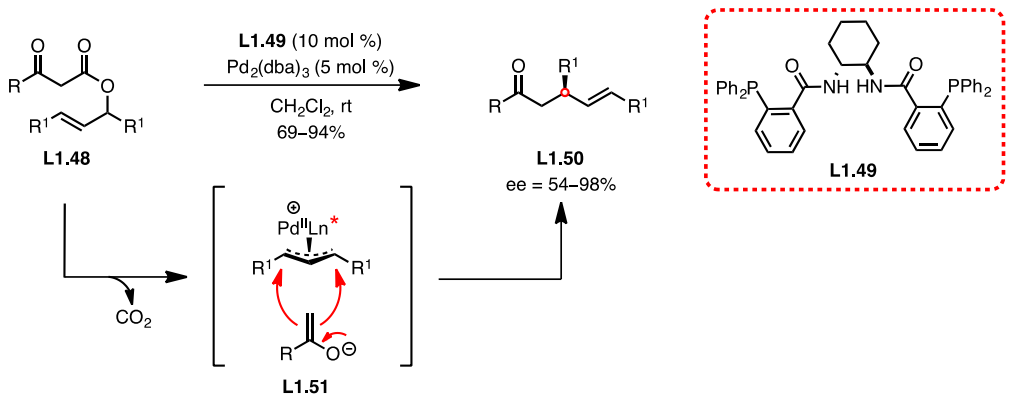
After the advent of the palladium-mediated allylic alkylation,[48] Tsuji *et al.* attempted an intramolecular allylic alkylation of an acetoacetic acid-derived allylic ester (**L1.44**) and observed the formation of the corresponding decarboxylative alkylated product (Scheme 16).[49] According to the proposed mechanism, allyl ketoester **L1.44** underwent a facile oxidative addition in the presence of palladium(0) to afford the palladium(II) π-allyl complex **L1.45**, which subsequently underwent a decarboxylation. Finally, upon reductive elimination of **L1.46**, the allylated product **L1.47** was isolated.

46 Hong, A. Y.; Stoltz, B. M. *European J Org Chem* **2013**, *14*, 2745.
47 (a) Mohr, J. T.; Stoltz, B. M. *Chem Asian J* **2007**, *2*, 1476; (b) Weaver, J. D.; Recio, A., 3rd; Grenning, A. J.; Tunge, J. A. *Chem. Rev.* **2011**, *111*, 1846.
48 Tsuji, J.; Takahashi, H.; Morikawa, M. *Tetrahedron Lett.* **1965**, *49*, 4387.
49 Shimizu, I.; Yamada, T.; Tsuji, J. *Tetrahedron Lett.* **1980**, *21*, 3199.



Scheme 16. Pioneering work on the palladium-catalyzed allylic alkylation by Tsuji *et al.*

Despite the increasing number of reports published in the field of palladium-catalyzed decarboxylative allylic alkylation since its introduction, it was only in 2004 that the first example of an enantioselective version of this reaction was reported.[50] Hence, by introducing a chiral environment around the metal, Tunge and Burger were able to favor the nucleophilic attack of the enolate to proceed selectively at one of the prochiral allylic termini (Scheme 17). Under their optimized reaction conditions, a number of homoallylic ketones **L1.50** bearing a tertiary stereogenic center at the β-position were prepared in high yields and excellent stereoselectivity.

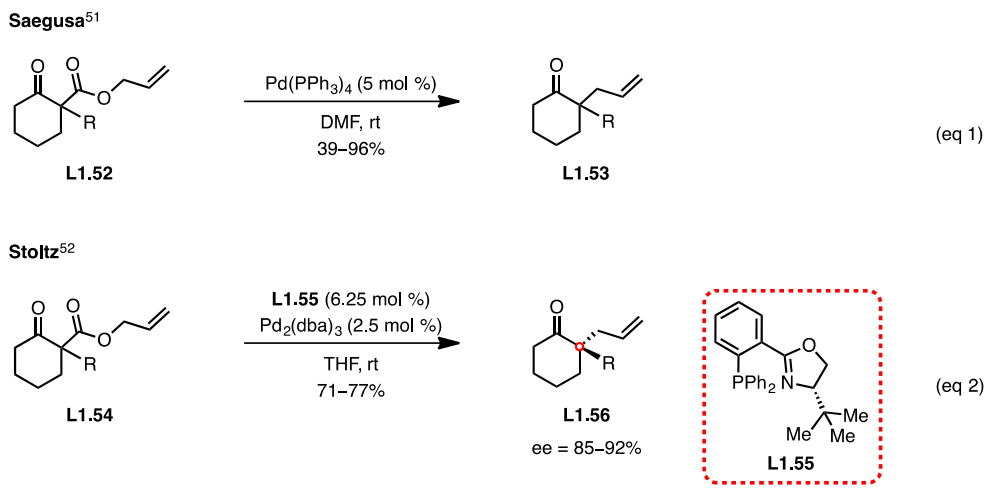


Scheme 17. Asymmetric palladium-catalyzed allylic alkylation by Tunge and Burger.

50 Burger, E. C.; Tunge, J. A. *Org. Lett.* **2004**, *6*, 4113.

Following an earlier account by Saegusa *et al*. who had shown that cyclic β-ketoesters **L1.52** could undergo decarboxylative coupling (Scheme 18, eq 1),[51] Stoltz *et al*. demonstrated that the use of a chiral ligand on the palladium-catalyzed asymmetric decarboxylative allylic alkylation (Pd-DAAA) of such β-ketoesters **L1.54** could lead to the formation of all-carbon quaternary center at the α-position of ketones **L1.56** in high enantioselectivities (Scheme 18, eq 2), [52] while in Tunge and Burger's approach only tertiary stereogenic centers at the β-position of ketones could be achieved through the Pd-DAAA.

This stereoablative enantioconvergent process, pioneered by Stoltz *et al*. relied on the use of a racemic starting material (allylic β-ketoester), which would undergo the destruction of its stereochemical information to produce a prochiral enolate intermediate which, upon interaction with a chiral allyl-palladium complex could lead to the selective formation of one enantiomer of the α-allylated ketone.

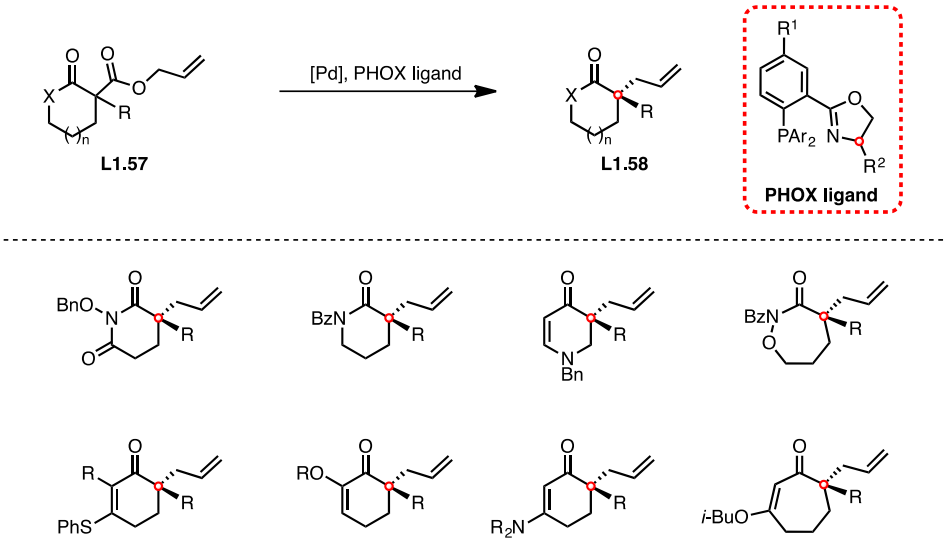


Scheme 18. Palladium-catalyzed asymmetric decarboxylative allylic alkylation of allyl β-ketoesters.

Ultimately, it was found that the treatment of allyl β-ketoesters with the *N*,*P* chelating chiral phosphinoxazoline ligand (PHOX ligand) in conjunction with a palladium complex could promote high asymmetric induction on non-stabilized unbiased enolates providing high degrees of enantioenrichment of α-quaternary ketones. Thus, this process represented a considerable advance in the construction of α-quaternary centers of carbonyl compounds.

51 Tsuda, T.; Chujo, Y.; Nishi, S.-i.; Tawara, K.; Saegusa, T. *J. Am. Chem. Soc.* **1980**, *102*, 6381.
52 Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6924.

Since this seminal work, many research groups, particularly Stoltz's group, have significantly contributed to broaden the scope of this transformation. Notably, by performing the Pd-DAAA on oxygen- and/or nitrogen-based heterocyclic substrates offering a facile entry to useful chiral building blocks (Scheme 19).[53]

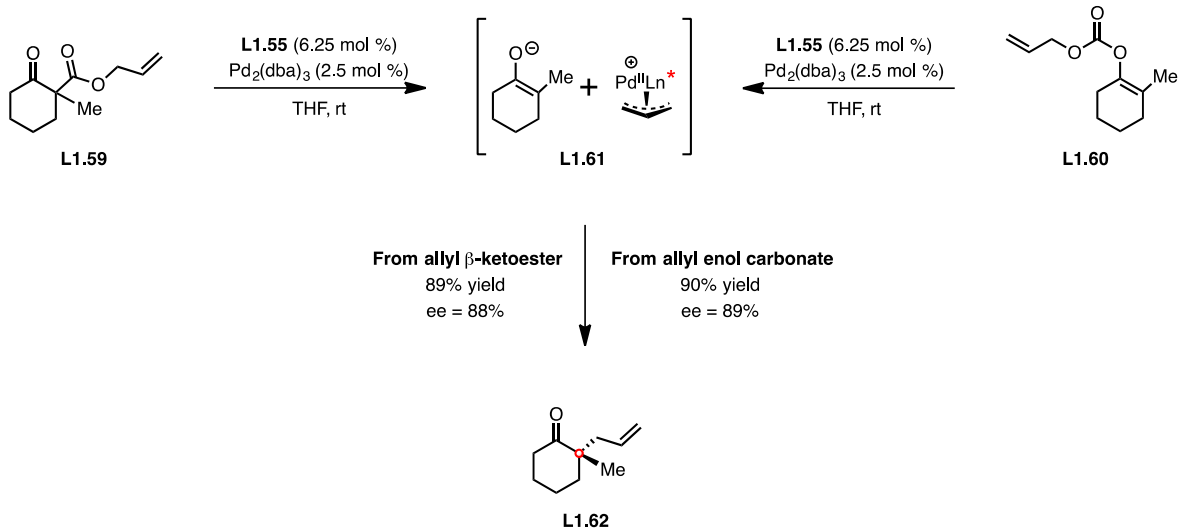


Scheme 19. Pd-DAAA of allyl β-ketoesters by Stoltz *et al*.

Stoltz and Behenna were able to show that their palladium/PHOX-based catalytic system was also highly effective for the enantioselective intramolecular allylic alkylation by the use of allyl β-ketoesters **L1.59** or allyl enol carbonates **L1.60** (Scheme 20).[54] The *in situ* formation of both the allyl electrophile and the enolate nucleophile, initiated by a Pd(0) catalyst and starting from allyl enol carbonates or isomeric allyl β-ketoesters, lends credence to the proposal of a common intermediate. Most importantly, each of these palladium-catalyzed decarboxylative reactions from both substrate types affords the alkylated products bearing an all-carbon α-quaternary center with a high level of enantioselectivity and regiochemical fidelity. As a general trend, allylic β-ketoesters have practical advantages over allyl enol carbonates such as the easier introduction of various α-substituents under relatively mild conditions and their typically higher thermal and chemical stability. All the disadvantages associated with allyl enol carbonates are mitigated by their ability to form highly enantioenriched compounds and by the fact that the Pd-DAAA is more facile to take

53 Bhat, V.; Welin, E. R.; Guo, X.; Stoltz, B. M. *Chem. Rev.* **2017**, *117*, 4528.
54 Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044.

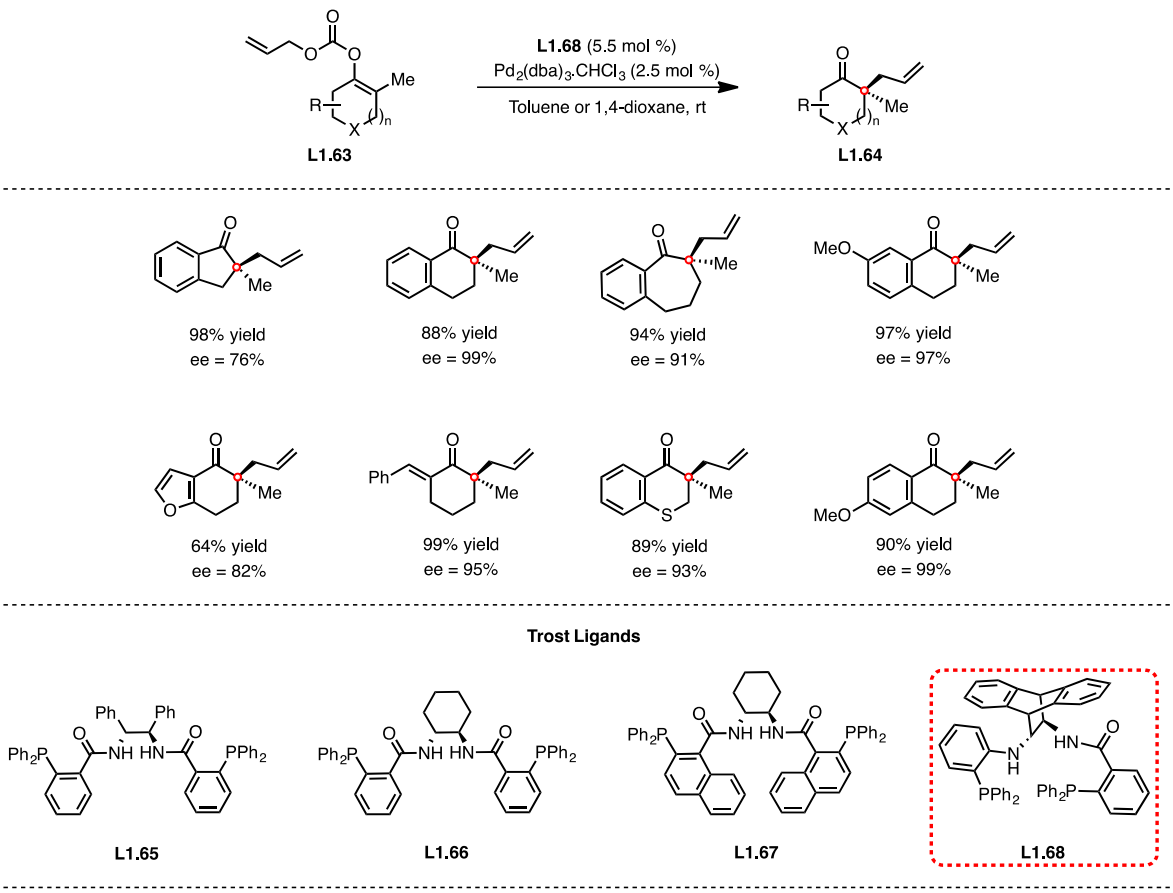
place with allyl enol carbonates compared to allylic β-ketoesters, presumably due to the faster decarboxylation of enol carbonates.



Scheme 20. Convergent Pd-DAAA of allyl β-ketoesters and allyl enol carbonates.

Shortly afterward, Trost and Xu disclosed a study involving the development of a different catalytic system for the enantioselective decarboxylative allylic alkylation of allyl enol carbonate substrates (Scheme 21).[55] As a result of a screening of various C_2-symmetric ligands with modified diamine backbones (Scheme 21), the *P*,*P* chelating Trost ligand **L1.68** in conjunction with $Pd_2(dba)_3.CHCl_3$ provided an effective catalyst for the synthesis of chiral all-carbon α-quaternary ketones. The extension of this result to more complex systems proved to be rewarding. The mild reaction conditions were tolerant to a variety of substituents and functional groups. Furthermore, cyclic allyl enol carbonates of various ring sizes, including benzoannulated and non-benzoannulated substrates, could undergo asymmetric decarboxylative allylation to afford products in high enantioselectivities. Notably, several heterocyclic ketones could also be prepared.

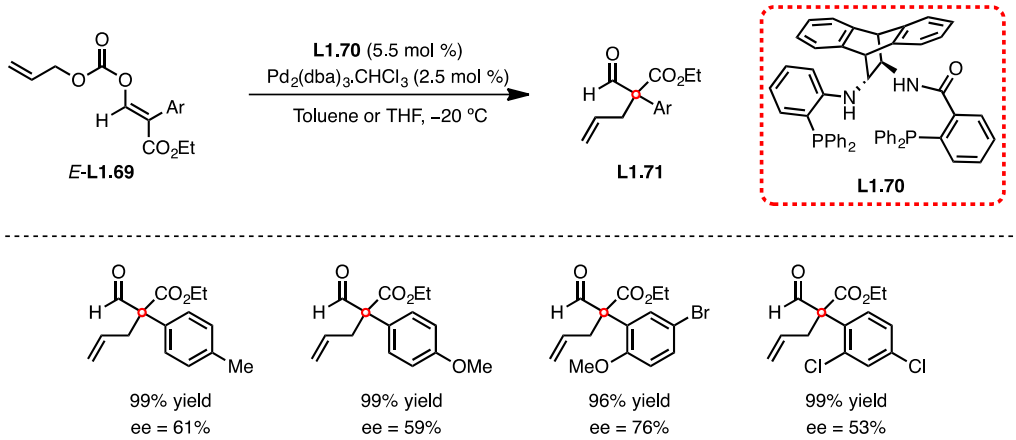
55 Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 2846.



Scheme 21. Pd-DAAA of cyclic allyl enol carbonates by Trost *et al*.

Despite the successful Trost's approach in the formation of α-tertiary stereocenters with acyclic allyl enol carbonates (cf Appendix 1), the extension of this chemistry in creating all-carbon quaternary centers at the α-position of acyclic carbonyl compounds has remained elusive. To date, Hossain *et al*. described few examples of the synthesis of α-quaternary aldehydes by applying the palladium-catalyzed asymmetric decarboxylative allylic alkyl process to allyl enol carbonates **L1.69** (Scheme 22).[56] Considering that the double bond geometry of the enol carbonate turned out to have different reactivities and furnished the product with different degrees of enantiodifferentiation (cf Appendix 1), both stereoisomers were investigated. Unfortunately, neither the *Z*- nor *E*-allyl enol carbonate afforded high levels of enantioselectivity. The Pd-DAAA of the *E*-allyl enol carbonate substrates proceeded smoothly, giving rise to α-quaternary aldehydes **L1.71** in excellent yield (99% average), albeit moderate enantioselectivities varying between 53% and 76% ee.

56 Hossain, M.; Alberch, E.; Brook, C.; Asad, S.; Shevyrev, M.; Ulicki, J. *Synlett* **2015**, *26*, 388.



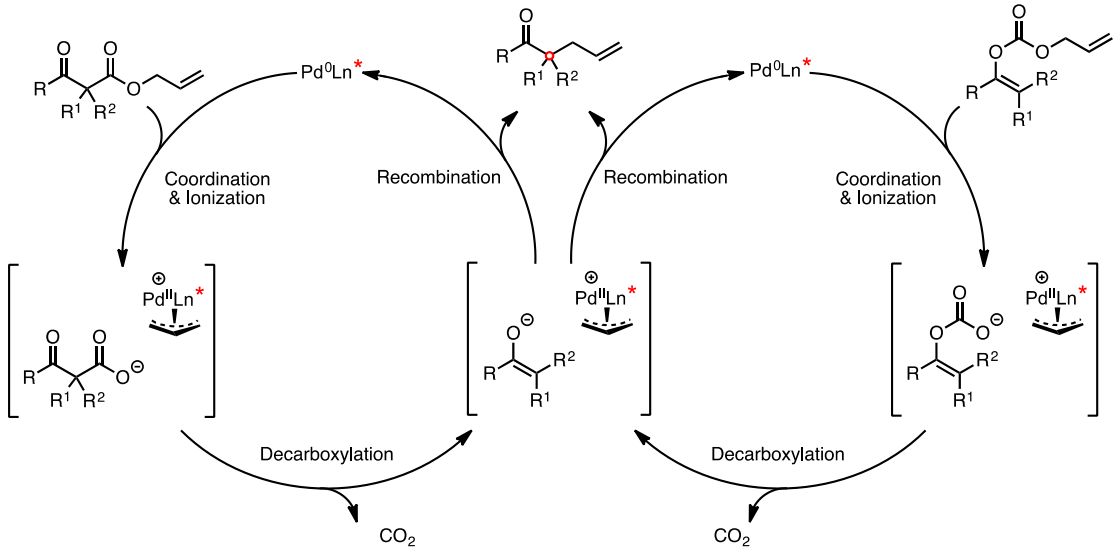
Scheme 22. Pd-DAAA of the *E*-allyl enol carbonate by Hossain *et al*.

3.2. Mechanistic considerations in the decarboxylative allylic alkylation of enol carbonates and allyl β-ketoesters

Along with the advances made in the palladium-catalyzed asymmetric decarboxylative allylic alkylation protocols, several mechanistic proposals have emerged. Despite some differences among the proposed mechanisms, a simplified mechanism can be presented to roughly outline the convergence of the various propositions. This generic mechanism relies on the following common steps: first the coordination of the Pd(0)Ln* to the allyl moiety, second the ionization of the ester or the carbonate, followed by the Pd-promoted decarboxylation to generate the corresponding enolate *in situ* and a final recombination of the enolate with the π-allyl complex to afford the allylated product and regeneration of the catalyst (Scheme 23).[57] It is worth mentioning that a change in the ligand or in the reaction conditions, for instance, may result in a significant modification in the reaction mechanism.

Stoltz *et al*. suggested a convergent mechanism for the palladium-catalyzed decarboxylative allylic alkylation of both allyl enol carbonates and allylic β-ketoesters. Kinetic studies determined that both were first order in the catalyst and zero order in the substrate, indicating that the reaction rate is linearly dependent on the concentration of the catalyst, and not on the concentration of the substrate.[58]

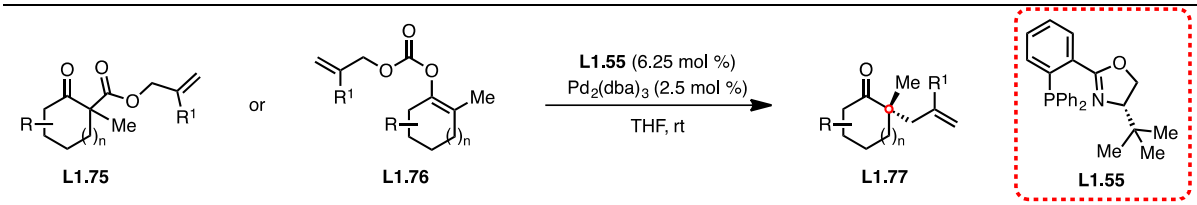
57 Trost, B. M.; Xu, J.; Schmidt, T. *J. Am. Chem. Soc.* **2009**, *131*, 18343.
58 Keith, J. A.; Behenna, D. C.; Mohr, J. T.; Ma, S.; Marinescu, S. C.; Oxgaard, J.; Stoltz, B. M.; Goddard, III, W. A. *J. Am. Chem. Soc.* **2007**, *129*, 11876.

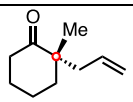
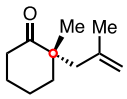
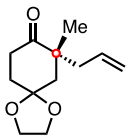
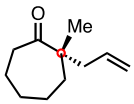


Scheme 23. Accepted mechanisms for the Pd-DAAA.

Notably, these two classes of substrates afford the allylated product in similar yields and practically identical enantioselectivity (Table 3).[52, 54] These results strongly supported a single underlying mechanism that must converge at or before the formation of the ketone enolate intermediate.

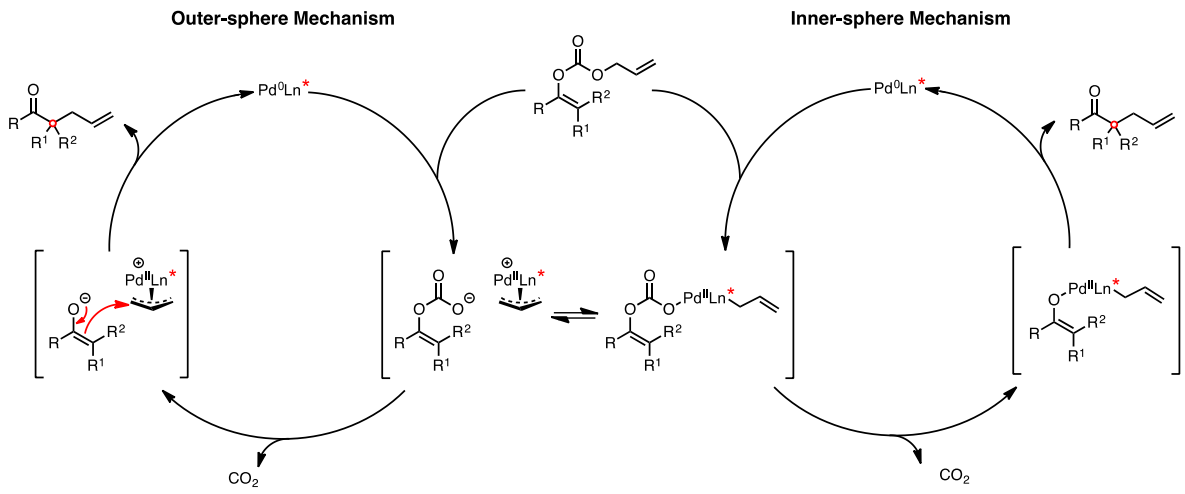
Table 3. Pd-DAAA of allyl β-ketoesters and allyl enol carbonate.



	From allyl β-ketoester		From allyl enol carbonate	
Product	Yield (%)	ee (%)	Yield (%)	ee (%)
	85	88	85	87
	87	92	89	92
	94	85	87	86
	83	87	81	87

The mechanism of the palladium-catalyzed allylic alkylation of stabilized nucleophiles has been extensively investigated and is now well understood.[59] According to these studies, the C–C bond formation is believed to occur through the direct nucleophilic attack on the allyl moiety of the π-allyl complex, generally referred as an outer-sphere mechanism. However, there is still a debate over whether non-stabilized palladium enolates proceed *via* an outer-sphere mechanism where the free enolate directly attacks the allyl termini (Scheme 24, left) or through an inner-sphere mechanism where the enolate is bound to the palladium prior to the reductive elimination (Scheme 24, right).

59 Trost, B. M. *Chem. Rev.* **1996**, *96*, 395.



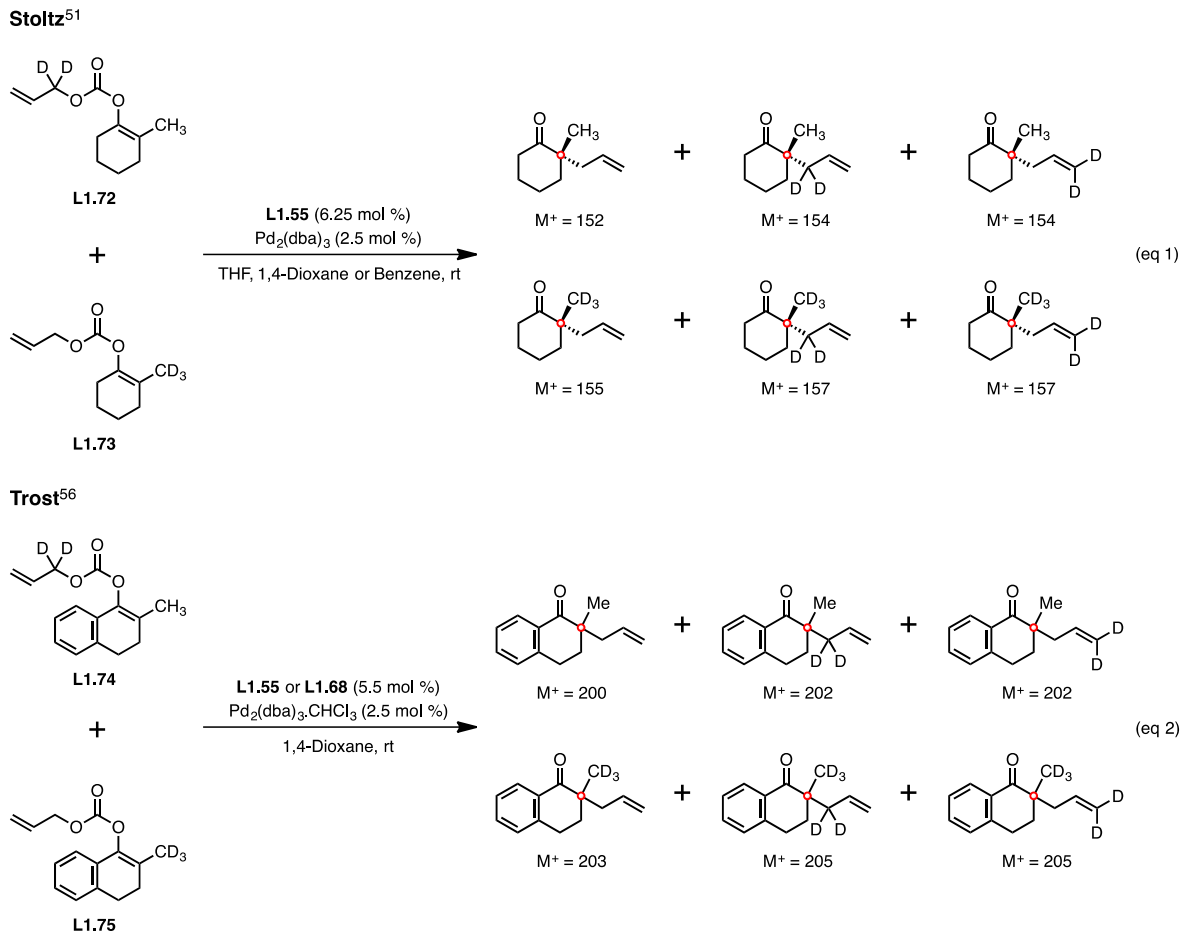
Scheme 24. Inner-sphere *versus* outer-sphere mechanism.

For the allylic alkylation of non-stabilized ketone enolates, an outer-sphere mechanism would imply the formation of a free enolate species, at least transiently, during the course of the reaction. However, a number of non-stabilized enolate precursors — allyl enol carbonates and allyl β-oxo esters — bearing multiple acid sites sensitive to such free enolates has been synthesized and subjected to the palladium-catalyzed asymmetric allylic alkylation, undergoing the decarboxylative allylation with no more than traces of side products, as depicted throughout this section. Even the introduction of up to 33.3 equivalents of H_2O into the reaction failed to quench the putative intermediate enolate and had only moderate effect on the yield of the allylated product.[60] This observed H_2O tolerance contrasts with the typical behavior of enolates, which are readily quenched by H_2O, and suggests that once decarboxylation takes place, the enolate intermediate is tightly associated with or covalently bound to the palladium counterion for most of its lifetime. Together these results raised serious questions about the possible nonexistence of a free enolate intermediate and thus the nature of the mechanism itself.

Substantial efforts have been done by Stoltz *et al*. and Trost *et al*. in order to fate the allyl and enolate fragments in the course of the reaction. They have all performed similar crossover experiments using equimolar amounts of deuterium labeled allyl enol carbonates under decarboxylative allylation conditions (Scheme 25).[52, 57] Mass spectral analysis of the products from each reaction showed a complete scrambling of the allyl and ketone moieties,

60 Behenna, D. C.; Mohr, J. T.; Sherden, N. H.; Marinescu, S. C.; Harned, A. M.; Tani, K.; Seto, M.; Ma, S.; Novak, Z.; Krout, M. R.; McFadden, R. M.; Roizen, J. L.; Enquist, J. A., Jr.; White, D. E.; Levine, S. R.; Petrova, K. V.; Iwashita, A.; Virgil, S. C.; Stoltz, B. M. *Chemistry* **2011**, *17*, 14199.

with an almost perfect statistical distribution of all six possible products for each case, which is a clear indication of complete crossover.



Scheme 25. Mechanistic investigation.

Although it is important to shine some light on the fact that the initial ionization of the allyl enol carbonate *via* oxidative addition likely creates ion pairs that are also capable of complete crossover prior to the decarboxylation, the observation of crossover products leads to an ambiguous or even a misinterpretation of the evidence as an apparent proof of an outer-sphere mechanism. In this context, Stoltz *et al*. succeeded to isolate and characterize a (σ-allyl)palladium-β-ketoester intermediate which was found to be the resting state for the catalytic cycle mediated by the Pd/PHOX complex.[61] Consequently, they concluded that the

61 Sherden, N. H.; Behenna, D. C.; Virgil, S. C.; Stoltz, B. M. *Angew. Chem. Int. Ed. Engl.* **2009**, *48*, 6840. These outcomes are in line with the previous mentioned kinetic data for the overall reaction which showed a first order dependence on the catalyst concentration and a zero-order dependence on the substrate concentration.

decarboxylation was the rate-determining step and that rapid C–C bond-forming reductive elimination was the enantiodetermining step for the allylic alkylation of allyl β-ketoesters. This implies that any ion-pair scrambling might undergo ion exchange prior to the decarboxylation — preceding to the palladium enolate stage — lending credence to an inner-sphere mechanism.

In search of a better mechanistic understanding, Stoltz *et al*. used the density functional theory (DFT) calculations to investigate the possible reaction pathway for the palladium enolate intermediate **L1.76** (Figure 8).[58] Considering a traditional outer-sphere allylic alkylation pathway, the DFT simulation predicted a favored nucleophilic attack at the π-allyl terminus *trans* to the phosphorus (**L1.77**). Although, practically no energy difference between the two facial approaches of the prochiral enolate nucleophile was identified. Therefore, such outer-sphere mechanism would imply the formation of a racemic allylated product, which is totally inconsistent with the highly enantioenriched allylated ketone experimentally observed.

Following the unsatisfactory results obtained for the outer-sphere pathway, an alternative inner-sphere allylic alkylation mechanism was investigated using DFT calculations. From the palladium allyl enolate **L1.80**, the *O*- to *C*-bond rearrangement and subsequent traditional three-centered reductive elimination (**L1.81**) was calculated to have prohibitively high kinetic barrier. However, a seven-centered doubly vinylogous reductive elimination (**L1.82**) directly from the palladium allyl enolate **L1.80** was determined to have a smaller kinetic barrier and thus a viable mechanism for the formation of the ketone **L1.62**. Furthermore, in the lowest-energy seven-membered pathway for the C–C bond formation, similar to a Claisen-like transition state originally proposed by Echavarren *et al*., accounts for a higher facial selectivity of the ligand in the allylic alkylation.[62]

62 Méndez, M.; Cuerva, J. M.; Gómez-Bengoa, E.; Cárdenas, D. J.; Echavarren, A. M. *Chem. Eur. J.* **2002**, *8*, 3620.

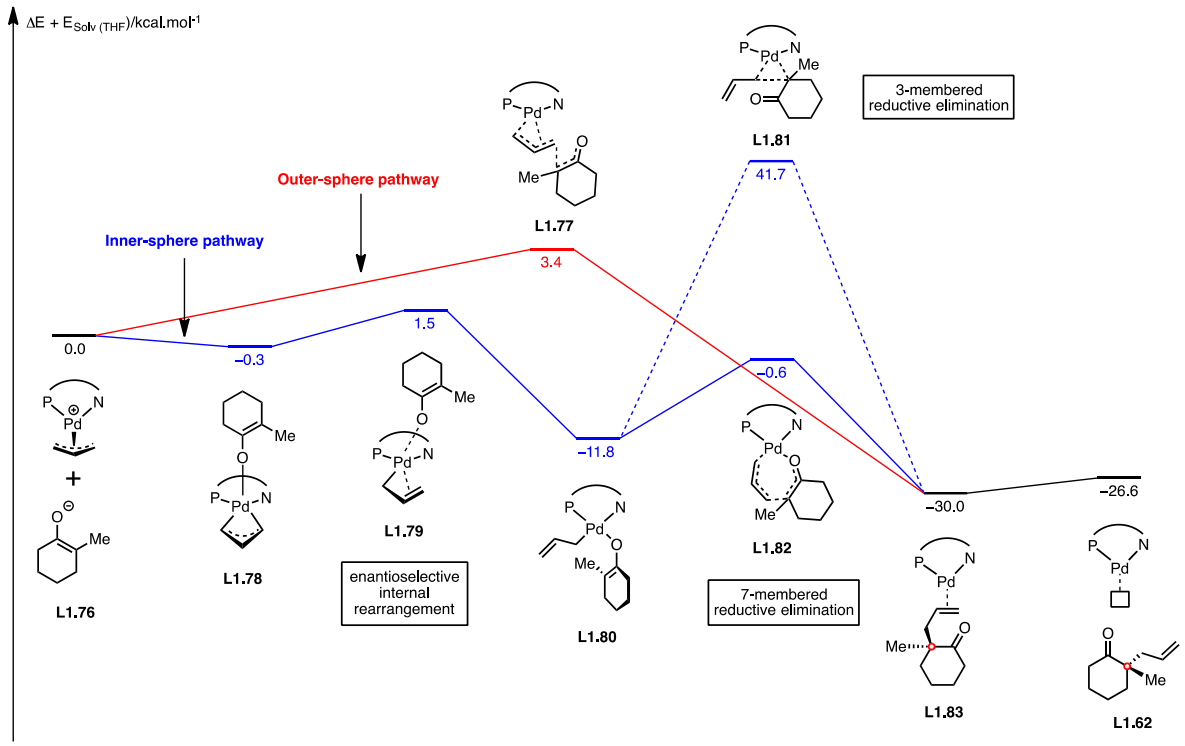


Figure 8. Reaction pathway according to DFT calculations.

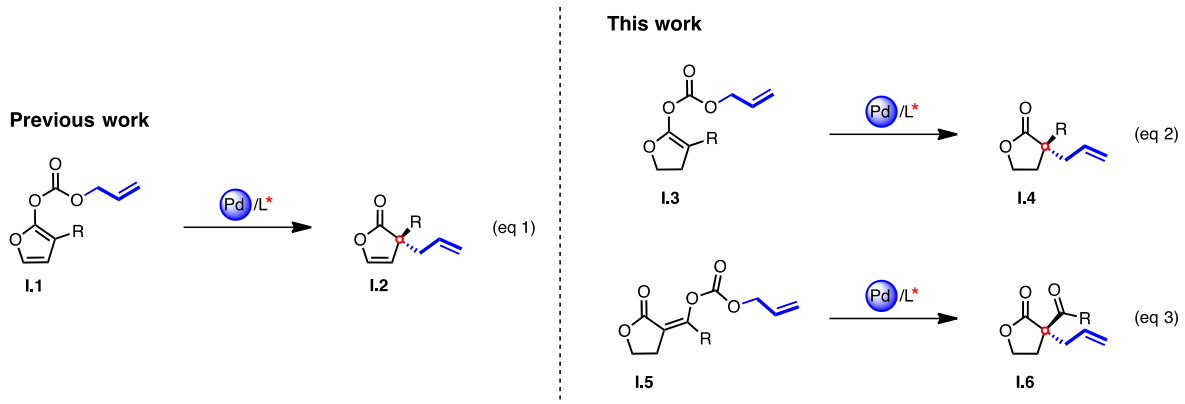
Overall, these results contradict the usual results for the allylic alkylation of stabilized nucleophiles which have been determined to proceed through an outer-sphere mechanism. However, the remarkable H_2O and functional group tolerance, and the high regioselectivity obtained with allyl enol carbonates and allyl β-ketoesters, along with the support of the crossover experiments and DFT calculations **strongly suggested an inner-sphere mechanism.**

4. Results and discussion

4.1. Context and objective

As shown throughout this chapter, the stereoselective synthesis of all-carbon α-quaternary γ-butyrolactones has been the focus of various research groups around the world, resulting in the development of new catalytic enantioselective methods. However, most of these methods were far less effective when generating of all-carbon quaternary stereocenters. In this context, the palladium-catalyzed decarboxylative asymmetric allylic alkylation has appeared as an interesting alternative.

Our group has previously reported the formation of stereochemically defined α-quaternary centers by applying the Pd-DAAA to cyclic dienol carbonates **I.1**, providing a straightforward access to enantiomerically enriched butenolides (Scheme 26, eq 1).[63] By analogy, we have envisioned to apply the Pd-DAAA process to cyclic and exocyclic allyl enol carbonates **I.3** and **I.5**, respectively, which might undergo asymmetric decarboxylative allylation in the presence of a chiral Pd(0) complex, allowing the synthesis of a range of chiral γ-butyrolactones **I.4** and **I.6** bearing an α-quaternary stereocenter (Scheme 26, eq 2 and 3).

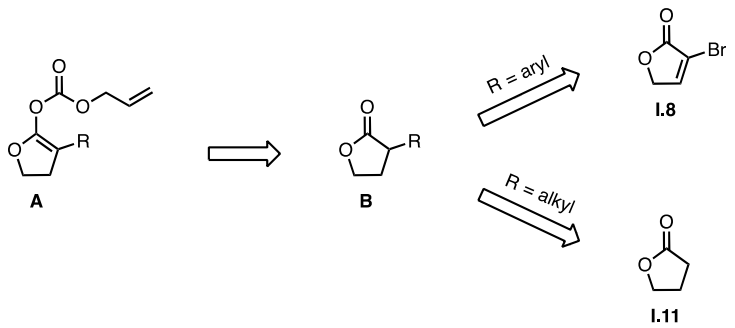


Scheme 26. Pd-DAAA of cyclic and exocyclic allyl enol carbonates.

63 Fournier, J.; Lozano, O.; Menozzi, C.; Arseniyadis, S.; Cossy, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 1257.

4.2. Synthesis of the cyclic allyl enol carbonates

We initiated our study by synthesizing the cyclic allyl carbonates **A** from α-substituted lactones **B**. Depending on the substituent at the α-position, lactones **B** can be obtained by either a Suzuki cross-coupling reaction applied to **I.8** if R = aryl, or by an alkylation of γ-butyrolactone **I.11** if R = alkyl (Scheme 27).



Scheme 27. Strategies for the synthesis of allyl enol carbonates.

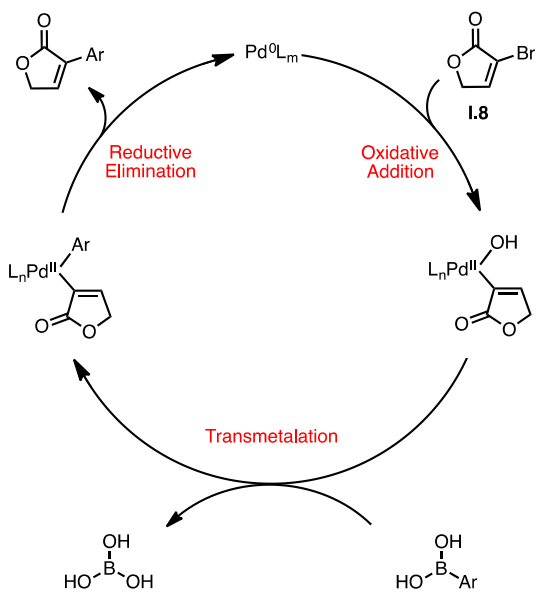
4.2.1. Synthesis of aryl lactones

The synthesis of the aryl substituted lactones **I.10** started from the commercially available 2-(*5H*)-furanone **I.7**, which was transformed to the α-bromofuranone **I.8** by treatment with Br_2 in CCl_4 at reflux. After 3 h, Et_3N was added to the reaction media (1 h, 0 ºC) to produce **I.8** in 89% yield. Then, the introduction of the aryl group was achieved by using two different Suzuki cross-coupling protocols depending on the aryl group, as shown in the Table 4.[63, 64] For the placement of the phenyl and 4-*tert*-butylphenyl groups, the arylation was performed by treatment of **I.8** (1 equiv) with $Pd(PPh_3)_4$ (0.05 equiv) and Na_2CO_3 (2 equiv) in the presence of the corresponding boronic acid $ArB(OH)_2$ (1.5 equiv) in a solvent mixture of benzene/H_2O (3:1) under microwave irradiation at 100 ºC for 30 min. Under these conditions the arylated lactones **I.9a** and **I.9c** were obtained in modest to good yields, 57% and 68%, respectively (Table 4, entries 1 and 3). On the other hand, for the introduction of 1-naphthyl, 3-methylphenyl, 3,4-dimethoxyphenyl, 3,5-difluorophenyl and 3,5-bis(trifluoromethyl)phenyl groups, the Suzuki cross-coupling was conducted using

64 Banwell, M. G.; Jones, M. T.; Loong, D. T. J.; Lupton, D. W.; Pinkerton, D. M.; Ray, J. K.; Willis, A. C. *Tetrahedron* **2010**, *66*, 9252.

I.8 (1 equiv), $PdCl_2(PPh_3)_2$ (0.05 equiv), KF (3 equiv) and Aliquat^{TM} 336 (0.05 equiv) in the presence of the corresponding boronic acid $ArB(OH)_2$ (2 equiv) in a solvent mixture of toluene/H_2O (1:1) under microwave irradiation at 110 ºC for 30 min. The coupling products were formed in yields varying between 23% and 70% (Table 4, entries 2, 4-7). It is worth mentioning that the presence of strong electron-donating groups (Table 4, entry 5) or strong electron-withdrawing groups (Table 4, entry 7) on the aryl moiety led to slightly lower yields than aryl groups bearing substituents with moderate electronic effects, except for the case of the difluoro substituted arene, which furnished the lowest yield of 23% (Table 4, entry 6). We have to point out as well that, in the case of the heteroaryl-containing boronic acids such as 2-furyl and 2-thiophenyl, only traces of the desired products were obtained, independently of the method used (Table 4, entries 8 and 9).

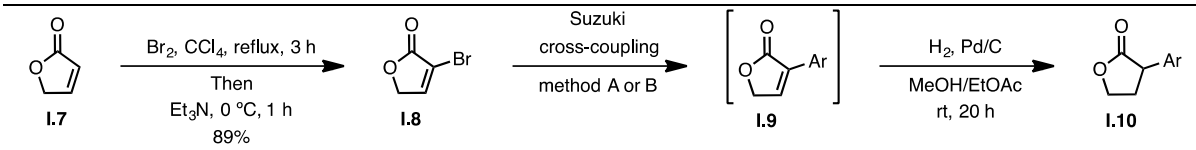
It is well-known that the mechanism of the Suzuki cross-coupling is analogous to the catalytic cycle for the other cross-coupling reactions (as briefly shown in Section 2.2.2), involving the oxidative addition of the α-bromofuranone **I.8** to the Pd(0) species to form the Pd(II), transmetalation between Pd(II) and the borate — organo boronic acids do not transmetalate to the Pd(II) complexes, although the corresponding ate-complex readily undergoes transmetalation — and reductive elimination to form the C-C bond (Scheme 28).[24]

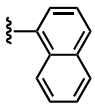
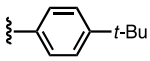
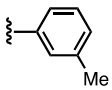
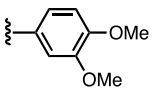
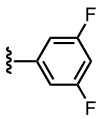
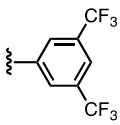


Scheme 28. Synthesis of α-aryl substituted furanones.

To access the α-aryl γ-butyrolactones **I.10**, the hydrogenation of the crude Suzuki cross-coupling products **I.9** was accomplished in a mixture of MeOH/EtOAc (3:2) at rt using Pd/C 10% as catalyst under 1 atm of H_2 (Table 4). In most cases, the desired products were isolated in good yields, however it is worth pointing out that in some cases, after "long" reaction times (15 h), some of the butyrolactones were converted to the corresponding ring-opening products (ω-hydroxymethyl ester).

Table 4. Synthesis of α-aryl substituted γ-butyrolactones.



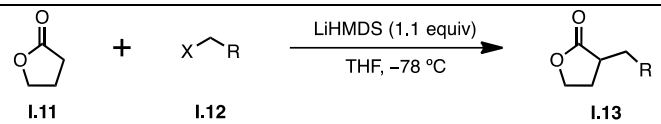
Entry	Method	Ar	**I.9** (yield[a])	**I.10** (yield[b])
1	A		**I.9a** (57%)	**I.10a** (41%)
2	B		**I.9b** (54%)	**I.10b** (29%)
3	A		**I.9c** (68%)	**I.10c** (48%)
4	B		**I.9d** (70%)	**I.10d** (55%)
5	B		**I.9e** (30%)	**I.10e** (29%)
6	B		**I.9f** (23%)	**I.10f** (17%)
7	B		**I.9g** (46%)	**I.10g** (34%)
8	A or B		**I.9h** (0%)	–
9	A or B		**I.9i** (0%)	–

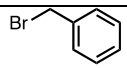
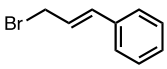
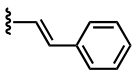
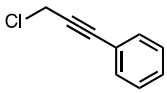
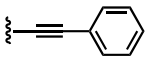
Method A: **I.8** (1 equiv), $Pd(PPh_3)_4$ (0.05 equiv), $ArB(OH)_2$ (1.5 equiv), Na_2CO_3 (2 equiv), benzene/H_2O (3:1), 30 min (μW), 100 °C. **Method B**: **I.8** (1 equiv), $PdCl_2(PPh_3)_2$ (0.05 equiv), $ArB(OH)_2$ (2 equiv), KF (3 equiv), Aliquat™ 336 (0.05 equiv), toluene/H_2O (1:1), 30 min (μW), 110 °C. [a] Determined by NMR. [b] Isolated yield.

4.2.2. Synthesis of alkyl lactones

Once we have accomplished the synthesis of the α-aryl γ-butyrolactones, the access to α-alkyl substituted γ-butyrolactones **I.13** was achieved by alkylation of the commercially available γ-butyrolactone **I.11**. After initial formation of the lithium enolate of **I.11** by treatment with LiHMDS (1.1 equiv) in THF at −78 ºC, the resulting enolate was quenched with an alkyl halide, e.g. benzyl and cinnamyl bromide, leading to the formation of the corresponding alkylated products **I.13a** and **I.13b** in 46% and 71%, respectively (Table 5, entries 1 and 2).[44] However, this approach seemed to be unsuccessful with propargyl chloride (Table 5, entry 3). Indeed, even after adding 1 equivalent of NaI to the reaction mixture or raising the reaction temperature, we were not able to isolate any of the desired product. The yields are summarized in the Table 5.

Table 5. Alkylation of γ-butyrolactone.



Entry	I.12	I.13	R	Yield[a] (%)
1		**I.13a**		46
2		**I.13b**		71
3		**I.13c**		0

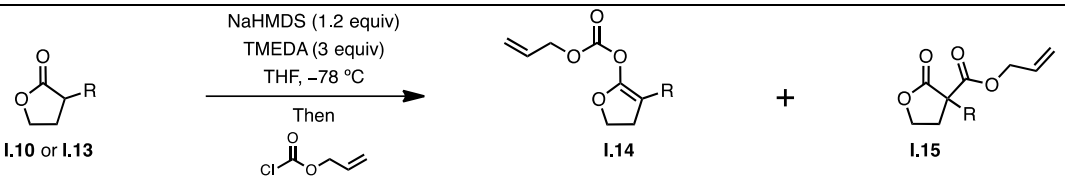
[a] Isolated yield.

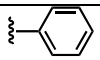
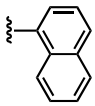
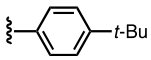
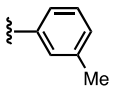
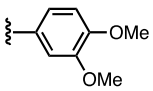
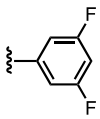
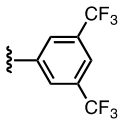
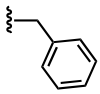
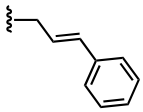
4.2.3. Formation of cyclic allyl enol carbonates

Having the α-substituted γ-butyrolactones in hands, they were transformed into their corresponding allyl enol carbonates using the method developed by Trost *et al.*[57] After treatment of **I.10** and **I.13** by NaHMDS (1.2 equiv), TMEDA (3 equiv) in THF at −78 ºC, the sodium enolate was generated and quenched with allyl chloroformate at low temperature (−78 ºC). As listed in the Table 6, a variety of allyl enol carbonates were synthesized in modest to excellent yields.

The major inconvenience in the synthesis of allyl enol carbonates is the competition between the *O*- and the *C*-acylation process. As a matter of fact, the generation of the allyl carboxylate byproduct was observed in a few reactions in a lesser or greater extent, depending on the substrate. Curiously, in the case of the lactones substituted by aryl groups bearing electron-withdrawing groups (Table 6, entries 6 and 7), the *C*-acylated products **I.15f**, and **I.15g** were exclusively obtained in 58% and 47% yield, respectively, even by performing the reaction in a coordinating solvent such as THF in the presence of TMEDA, which should stabilize the charge separated ion-pairs and favor the formation of the *O*-acylated product. On the other hand, it is comprehensible that the *C*-acylation might take place more easily than the *O*-acylation for these substrates, since there is a better stabilization of the negative charge at C2 due to the presence of the aromatic ring containing electron-withdrawing groups.

Table 6. Synthesis of the Pd-DAAA precursors.



Entry	R	**I.14** (yield[a])	**I.15** (yield[a])
1		**I.14a** (94%)	**I.15a** (0%)
2		**I.14b** (62%)	**I.15b** (0%)
3		**I.14c** (70%)	**I.15c** (0%)
4		**I.14d** (10%)	**I.15d** (0%)
5		**I.14e** (32%)	**I.15e** (0%)
6		**I.14f** (0%)	**I.15f** (58%)
7		**I.14g** (0%)	**I.15g** (47%)
8		**I.14h** (33%)	**I.15h** (0%)
9		**I.14i** (44%)	**I.15i** (0%)

[a] Isolated yield.

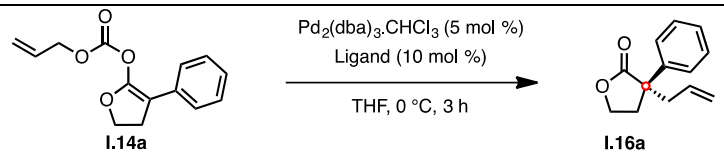
4.3. Optimization of the Pd-DAAA conditions for cyclic allyl enol carbonates

To test our hypothesis and to access enantioenriched all-carbon α-quaternary γ-butyrolactones, we decided to initiate our study by engaging the allyl enol carbonate **I.14a** in a reactivity and enantioselectivity screening through an array of chiral ligands, solvents, temperatures and palladium sources.

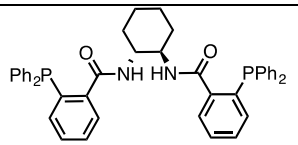
The influence of the ligand was initially investigated by subjecting the model allyl enol carbonate **I.14a** to the palladium-catalyzed decarboxylative asymmetric allylic alkylation conditions using $Pd_2(dba)_3.CHCl_3$ (5 mol %) as the source of palladium and a variety of chiral ligands (Table 7, entries 1-11) in THF at 0 ºC.

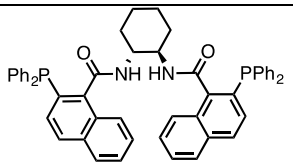
All the reactions afforded the corresponding α,α-disubstituted γ-butyrolactone **I.16a** in good to excellent yields ranging from 80% to 99%, independently of the ligand used. Interestingly, the ligands commonly used in this type of transformation, including the *N*,*P* chelating chiral phosphinoxazoline ligands (PHOX) such as *t*-Bu-PHOX (*S*)-**L4** and *i*Pr-PHOX (*S*)-**L5**, the axially dissymmetric C_2-chiral diphosphine ligands such as (*R*)-**L6**, DIOP (*R*,*R*)-**L7**, SEGPHOS (*S*)-**L8**, and BINAP (*S*)-**L9**, and the diphosphines exhibiting either central, and planar or only planar chirality such as PHANEPHOS (p*R*)-**L11** and JOSIPHOS (p*S*,*R*)-**L10** (Table 7, entries 4-11) induced lower levels of selectivity compared to the C_2-symmetric chiral ligands, derived from 2-diphenylphosphinobenzoic or 1-naphthoic acid and scalemic diamines developed by Trost, (*R*,*R*)-**L1**, (*R*,*R*)-**L2**, and (*R*,*R*)-**L3**, (Table 7, entries 1-3). Among the eleven chiral ligands tested, the DACH phenyl Trost ligand (*R*,*R*)-**L1** led to the best results, affording the allylated γ-butyrolactone **I.16a** in 98% yield and 77% ee (Table 7, entry 1).

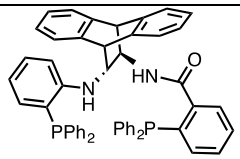
Table 7. Influence of the ligand.[a]

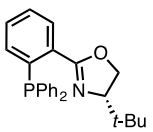


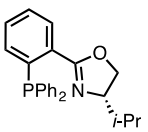
Entry	Ligand	Yield[b] (%)	ee[c] (%)
1	(*R*,*R*)-**L1**	98	77
2	(*R*,*R*)-**L2**	85	64
3	(*R*,*R*)-**L3**	99	55
4	(*S*)-**L4**	83	12
5	(*S*)-**L5**	95	7
6	(*R*)-**L6**	80	10
7	(*R*,*R*)-**L7**	98	4
8	(*R*)-**L8**	92	-2
9	(*R*)-**L9**	95	-9
10	(p*S*,*R*)-**L10**	92	0
11	(p*R*)-**L11**	94	0

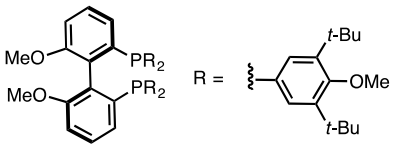

(*R*,*R*)-**L1**

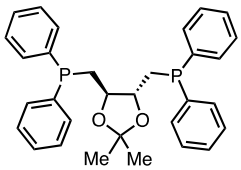

(*R*,*R*)-**L2**

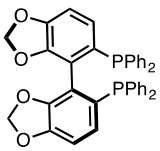

(*R*,*R*)-**L3**

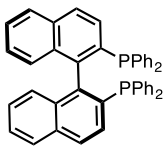

(*S*)-**L4**

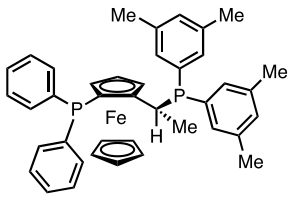

(*S*)-**L5**

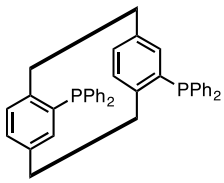

(*R*)-**L6**


(*R*,*R*)-**L7**


(*S*)-**L8**


(*S*)-**L9**

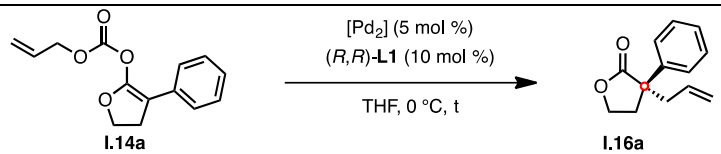

(p*S*,*R*)-**L10**


(p*R*)-**L11**

[a] All the reactions were performed on 0.1 mmol. [b] Isolated yield. [c] Determined by SFC analysis.

As reported in Table 7, the choice of the ligand appeared to be crucial for achieving high selectivities. However, besides the ligand, other parameters, such as the palladium catalyst, may be equally important to ensure the success of this reaction. Therefore, the influence of the source of palladium in the overall efficacy of the reaction was evaluated (Table 8).

Table 8. Influence of the source of palladium.[a]



Entry	[Pd_2]	t (h)	Yield[b] (%)	ee[c] (%)
1	$Pd(OAc)_2$	24	91	77
2	$Pd_2(dba)_3.CHCl_3$	3	98	77

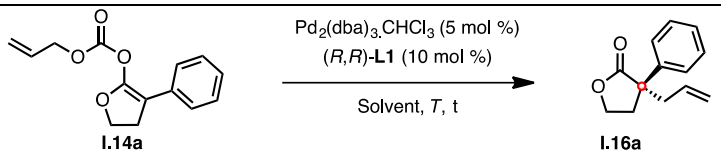
[a] All the reactions were performed on 0.1 mmol. [b] Isolated yield. [c] Determined by SFC analysis.

Interestingly, the treatment of the allyl carbonate with $Pd(OAc)_2$ (Table 8, entry 1) afforded the same enantioselectivity (ee = 77%) and a comparable reaction yield of 91% (Table 8, entry 2). However, the $Pd_2(dba)_3.CHCl_3$ appeared to be more efficient as a complete conversion of **I.14a** was observed after only 3 h *versus* 24 h when the $Pd(OAc)_2$ was utilized. The longer reaction time with $Pd(OAc)_2$ precursor can be explained by the fact that the latter needs to get to be reduced *in situ* into a Pd(0), which is the active species able to promote the Pd-DAAA process. According to Amatore, Jutand *et al.*,[65] a mixture of $Pd(OAc)_2$ and a phosphine spontaneously evolves in the formation of the Pd(0) complex. Ozawa, Hayashi *et al*. proved that the presence of H_2O was essential for the quantitative formation of the Pd(0), as the use of water-free solvents results in lower conversions.[66] It is worth pointing out that in our case, all the reactions were performed in the absence of purposely added H_2O, however residual H_2O in the carefully distilled THF may be responsible for the formation of the active Pd(0) species and, consequently allowing the formation of the allylated γ-butyrolactone **I.16a**.

65 Amatore, C.; Carré, E.; Jutand, A.; M'Barki, M. A. *Organometallics* **1995**, *14*, 1818.
66 Ozawa, F.; Kubo, A.; Hayashi, T. *Chem. Lett.* **1992**, *21*, 2177.

After screening the sources of palladium, we systematically investigated the Pd-DAAA by varying the solvent under otherwise identical conditions (Table 9). We could notice that the solvent had a significant impact on both the enantiomeric excess and the yield. As a matter of fact, by performing the reaction in THF resulted in the formation of the allylated product **I.16a** in 98% yield and 77% ee (Table 9, entry 1), while running the reaction in hexane led to a decrease in both the yield (35%) and the ee (29%) (Table 9, entry 2). Otherwise, the reaction proceeded with comparable good yields and enantioselectivities in solvents of a wide polarity range, such as toluene, Et_2O and DMF (Table 9, entries 4, 5 and 7, respectively). However, we were not able to improve the enantioselectivities. Ultimately, among all the solvents examined, THF appeared to be the one that offered the highest enantioselectivity. Decreasing the reaction temperature from 0 ºC to –78 ºC, under otherwise identical conditions, allowed a slight improvement of the ee, which reached 80% (Table 9, entry 9).

Table 9. Solvent and temperature effect.[a]

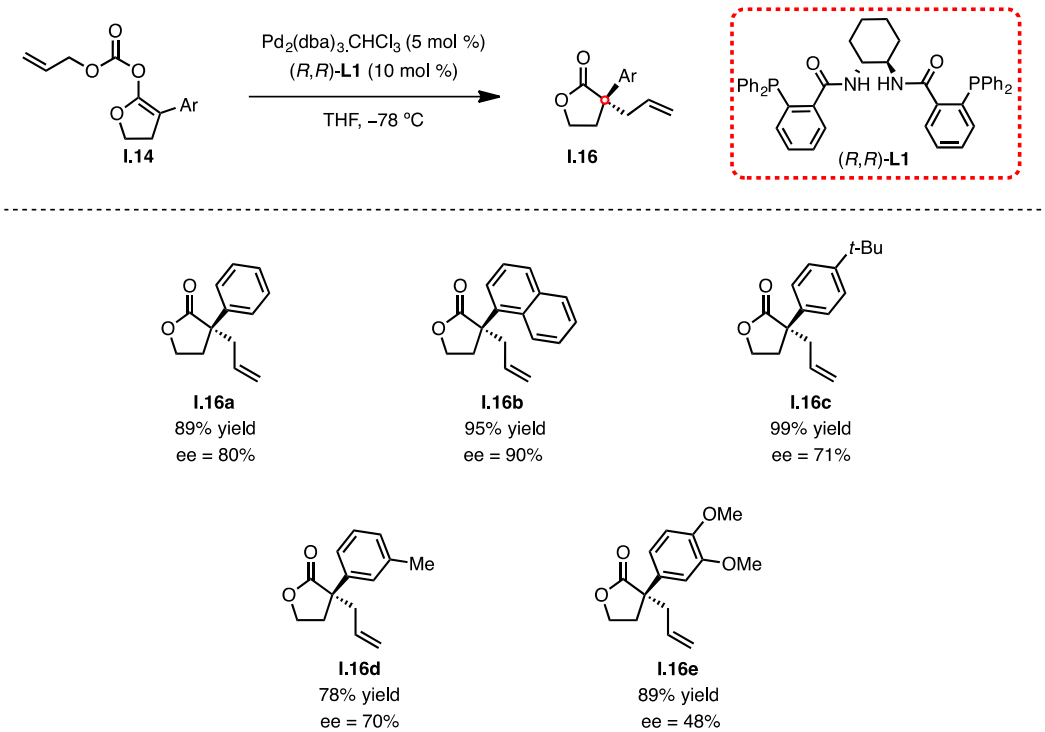


Entry	Solvent	*T* (ºC)	t (h)	Yield[b] (%)	ee[c] (%)
1	THF	0	3	98	77
2	Hexane	0	24	35	29
3	MeCN	0	1	94	56
4	PhMe	0	3	87	64
5	Et_2O	0	1	97	65
6	MeOAc	0	3	97	67
7	DMF	0	3	87	69
8	CH_2Cl_2	0	3	72	70
9	THF	–78 ºC	3	89	80

[a] All the reactions were performed on 0.1 mmol. [b] Isolated yield. [c] Determined by SFC analysis.

4.4. Reaction scope of the cyclic allyl enol carbonates

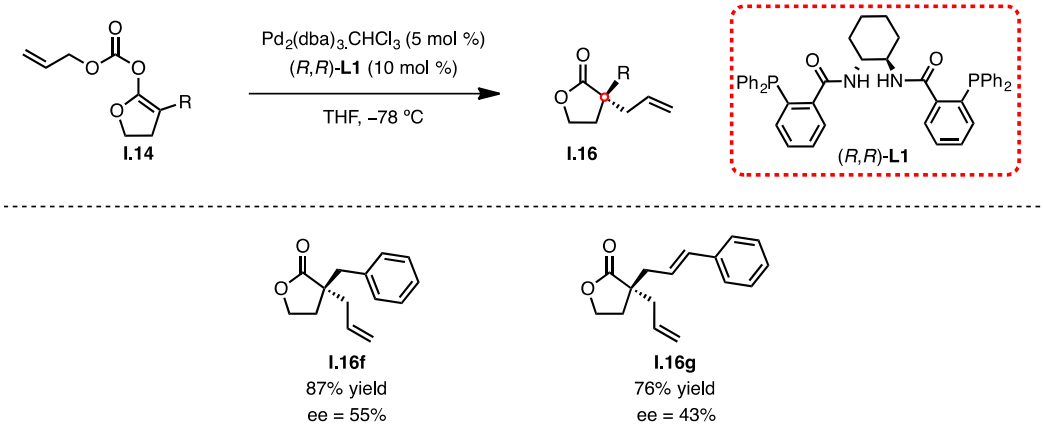
After the identification of the best set of reaction conditions (5 mol % of $Pd_2(dba)_3.CHCl_3$ and 10 mol % of (*R*,*R*)-**L1** in THF at −78 ºC), the reaction scope was examined by applying these optimized reaction conditions to various α-aryl (**I.14a-e**) substituted allyl enol carbonates (Scheme 29). In all cases, the total conversion of the starting materials to the corresponding α-quaternary γ-butyrolactone **I.16** was observed. These butyrolactones were isolated in excellent yields ranging from 78% to 99%, and good to excellent enantioselectivities (up to 90%). Interestingly, the allyl enol carbonates bearing an aryl group containing strong electron-donating substituents such as two methoxy groups (**I.14e**) furnished a lower ee value (48%) than substrates possessing an aryl group substituted by an alkyl group (**I.14c-d**), which afforded an average ee of 70%.



Scheme 29. Scope of the reaction with aryl containing allyl enol carbonate.

The synthesized α-alkyl substituted allyl enol carbonates **I.14i-h** were equally engaged in the asymmetric allylation process (Scheme 30). The corresponding α-alkyl

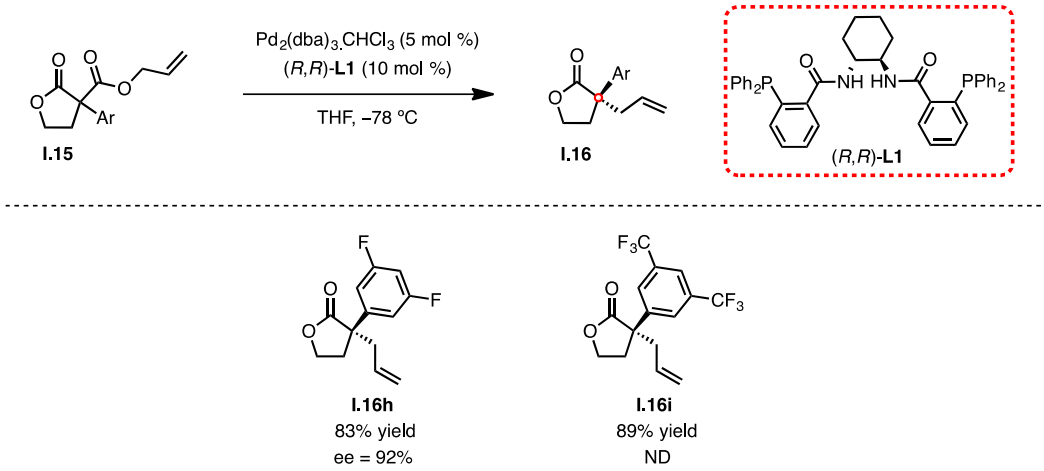
γ-butyrolactones **I.16f-g** could be isolated in good yields of 87% (**I.16f**) and 76%(**I.16g**). However, in general, the α-alkyl substituted allyl enol carbonates **I.14i-h** gave lower ee values than the α-aryl substituted ones (**I.14a-e**), which varied between 43% and 55%.



Scheme 30. Scope of the reaction with alkyl containing allyl enol carbonate.

4.5. Reaction scope of the allyl carboxylates

As mentioned in Section 3.2, allyl enol carbonates and allyl carboxylates have a similar underlying mechanism. Therefore, we comforted the idea that our optimized reaction conditions would also be applicable to the ally carboxylates into the formation of α-quaternary γ-butyrolactones. To check this hypothesis, we subjected the various allyl carboxylates **I.15.f-g** to the identical Pd-DAAA conditions (Scheme 31). As expected, each substrate smoothly underwent decarboxylative asymmetric allylation to form the corresponding α-quaternary-γ-butyrolactones **I.16h-i** in good yields. While **I.16h** was obtained with a high enantiomeric excess (92%), we were not able to determine the ee of **I.14i** by SFC analysis. Most importantly, these results revealed a plausible alternative route to access the valuable chiral γ-butyrolactones using our optimized catalytic system, since the allyl carboxylates can be readily synthesized.



Scheme 31. Scope of the reaction with allyl carboxylates.

These results could lend credence that a more stable transient enolate may have a better degree of enantiodifferentiation, by trivial comparison of substrates bearing electron-rich aromatic substituents or alkyl groups *versus* substrates bearing electron-withdrawing groups. However, this is a simple extrapolation without any further experimental support since we have not compared both allyl enol carbonates and allyl carboxylates bearing the same α-substituent group.

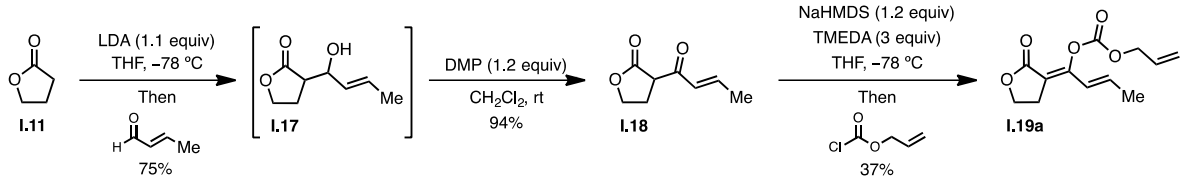
4.6. Exocyclic allyl enol carbonates

To broaden the scope, we envisaged to perform the first palladium-catalyzed decarboxylative asymmetric allylic alkylation of exocyclic allyl enol carbonates derived from α-acyl γ-butyrolactones, synthesized using three different strategies.

4.6.1. Synthesis of exocyclic allyl enol carbonates

The exocyclic allyl enol carbonates were prepared starting from the commercially available γ-butyrolactone **I.11** using three different strategies. At first, the γ-butyrolactone **I.11** was treated with LDA (THF, −78 ºC), followed by the addition of the crotonaldehyde to the enolate to form the hydroxylactone **I.17** (75%). After an oxidation step using the Dess-Martin periodinane reagent (DMP) in CH_2Cl_2 at rt, the corresponding ketolactone **I.18** was isolated in 94% yield. The latter was transformed into the desired allyl

enol carbonate **I.19a** (37%), after treatment with NaHMDS in the presence of TMEDA, followed by the addition of allyl chloroformate, in 26% overall yield (Scheme 32).[67]



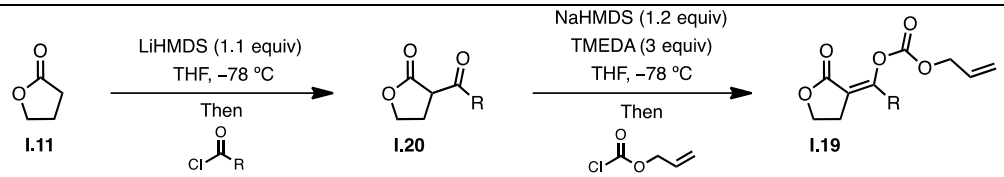
Scheme 32. Synthesis of allyl enol carbonates derived from α-acyl γ-butyrolactones.

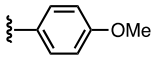
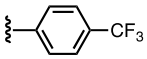
In an effort to improve the synthetic route to α-acyl γ-butyrolactones, a more straightforward strategy was envisioned. This approach relies on the direct *C*-acylation of the γ-butyrolactone **I.11** with an acyl chloride, followed by the transformation of the resulting β-ketolactone **I.20** into the allyl enol carbonate **I.19** by using the usual *O*-acylation conditions (NaHMDS, TMEDA, allyl chloroformate, THF, −78 ºC) (Table 10).[68] In this second approach, the desired allyl enol carbonates **I.19b-d** were obtained, albeit disappointingly lower overall yields ranging from 13% to 24%, with the *Z*-isomer as the major product. The *C*-acylation step, contradictory to the results reported in the literature, revealed inefficient in the generation of the desired β-ketolactone. Actually, in most cases, the major product revealed to be the di-*C*-acylated products.

67 (a) Petrovic, D.; Bruckner, R. *Org. Lett.* **2011**, *13*, 6524; (b) Sai, H.; Ogiku, T.; Ohmizu, H. *Tetrahedron* **2007**, *63*, 10345.

68 Jiang, X.; Fu, D.; Zhang, G.; Cao, Y.; Liu, L.; Song, J.; Wang, R. *Chem Commun.* **2010**, *46*, 4294.

Table 10. Synthesis of allyl enol carbonates derived from α-acyl γ-butyrolactones.

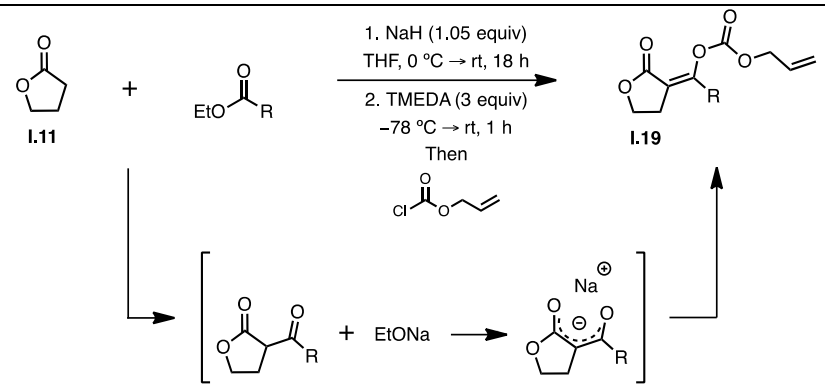


Entry	R	**I.20** (Yield[a])	**I.19** (Yield[a])	*Z*/*E*[b]
1		**I.20a** (39%)	**I.19b** (34%)	95:5
2		**I.20b** (42%)	**I.19c** (58%)	96:4
3		**I.20c** (18%)	**I.19d** (80%)	66:34

[a] Isolated yield. [b] Determined by ^{1}H NMR analysis.

Since the desired allyl enol carbonates were obtained in low yields, a third approach was envisioned. The third strategy relied on a sequential one-pot *C*-acylation/*O*-acylation (Table 11). The synthesis of **I.19** began with the generation of the sodium enolate (NaH, THF) of the γ-butyrolactone **I.11** which was engaged in a Claisen condensation with an ethyl ester. The resulting β-ketoester intermediate was subsequently deprotonate by the sodium ethoxide which is generated *in situ* as a result of the Claisen condensation. The resulting β-ketoester anion was quenched with allyl chloroformate in the presence of TMEDA at −78 ºC to promote the *O*-acylation resulting in the formation of the allyl enol carbonate **I.19e-f** in moderate overall yields of 38% and 43%. Even if the yields were slightly better than the ones previously obtained, it appeared that this method was the most convenient and straightforward pathway to access the desired allyl enol carbonates.

Table 11. One-pot synthesis of allyl enol carbonates.



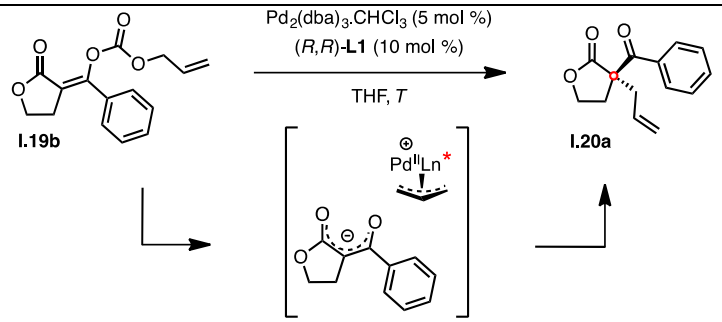
Entry	R	**I.19**	Yield[a] (%)
1	H	**I.19e**	38
2	CF_3	**I.19f**	42

[a] Isolated yield.

4.7. Optimization of the Pd-DAAA conditions for exocyclic allyl enol carbonates

By subjecting the newly synthesized exocyclic allyl enol carbonates to our previously optimized Pd-DAAA conditions (5 mol % of $Pd_2(dba)_3.CHCl_3$ and 10 mol % of (*R*,*R*)-**L1** in THF at −78 ºC), a change in the reactivity was observed — comparing to cyclic allyl enol carbonates **I.14** — as these allyl enol carbonates **II.19** appeared to be unreactive under such conditions. This lack of reactivity is not surprising considering that the transient enolate, generated *in situ* during the Pd-DAAA process, is a stabilized nucleophile with the negative charge delocalized on both carbonyl groups, thus turning this latter less reactive than its non-stabilized counterpart. Consequently, in order to find the best set of reaction conditions, a brief screening of the reaction conditions was carried out, using the exocyclic allyl enol carbonate **I.19b** as a model substrate. This substrate was treated with 5 mol % of $Pd_2(dba)_3.CHCl_3$ and 10 mol % (*R*,*R*)-**L1** in THF at different temperatures (Table 12). This investigation revealed that raising the temperature from −78 ºC to −20 ºC allowed the allyl enol carbonate **I.19b** to undergo the decarboxylative asymmetric allylation in good yield and enantioselectivity (83% yield and ee = 74%) (Table 12, entry 2). However, by increasing the reaction temperature to 0 ºC led to a slightly lower enantioselectivity (ee = 72%) and, curiously, also decreased reaction yield to 75% *versus* 83% (Table 12, entry 3). As a consequence, we have established the best reaction conditions to transform **I.19b** into **I.20a**, e.g. by using 5 mol % of $Pd_2(dba)_3.CHCl_3$ and 10 mol % (*R*,*R*)-**L1** in THF at −20 ºC.

Table 12. Influence of the temperature.

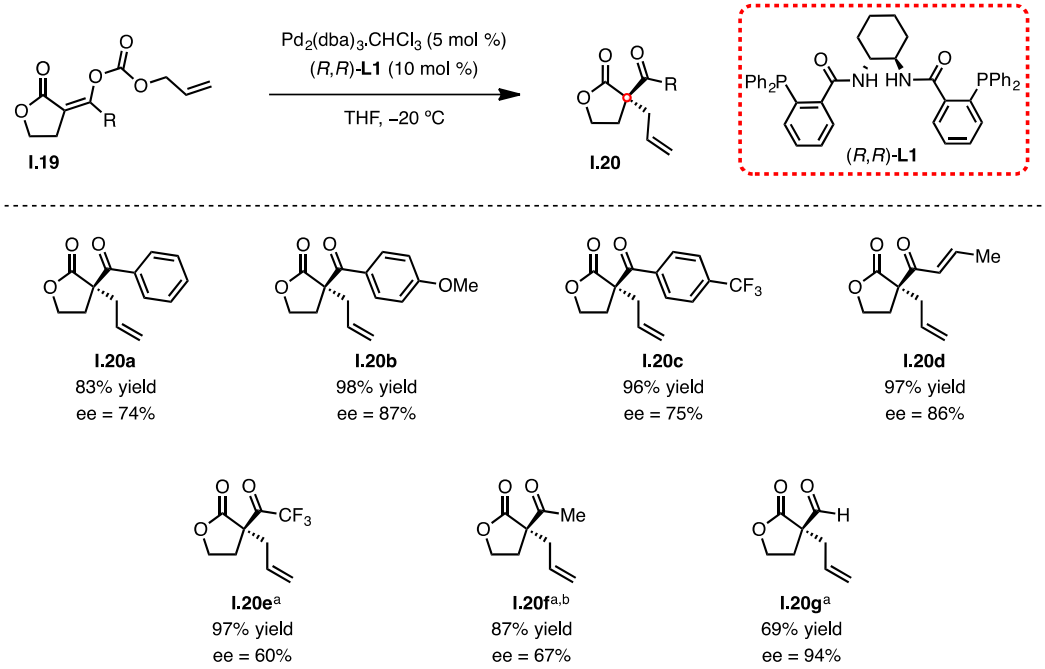


Entry	*T* (ºC)	Yield[a] (%)	ee[b] (%)
1	–78	NR	-
2	–20	83	74
3	0	75	72

[a] Isolated yield. [b] Determined by SFC analysis.

4.8. Reaction scope of exocyclic allyl enol carbonates

The use of our optimal Pd-DAAA conditions to the exocyclic allyl enol carbonates **I.19** gave rise to the desired α-quaternary γ-butyrolactones in high yields ranging from 83% and 98%, and good to excellent enantioselectivities, superior to 60% and up to ee = 94% (Scheme 33). The structural diversity and heterogeneity in the obtained results made the rationalization slightly challenging. Both steric and electronic effects induced by the α-substituent to the carbonate appeared to have a significant impact not only on the enantioselectivity but also on the overall reactivity.



[a] Enantiomeric excess determined after chemical derivatization. [b] The allyl enol substrate was synthesized from the commercially available α-acetyl γ-butyrolactone following the usual procedure.

Scheme 33. Scope of the reaction with exocyclic allyl enol carbonates.

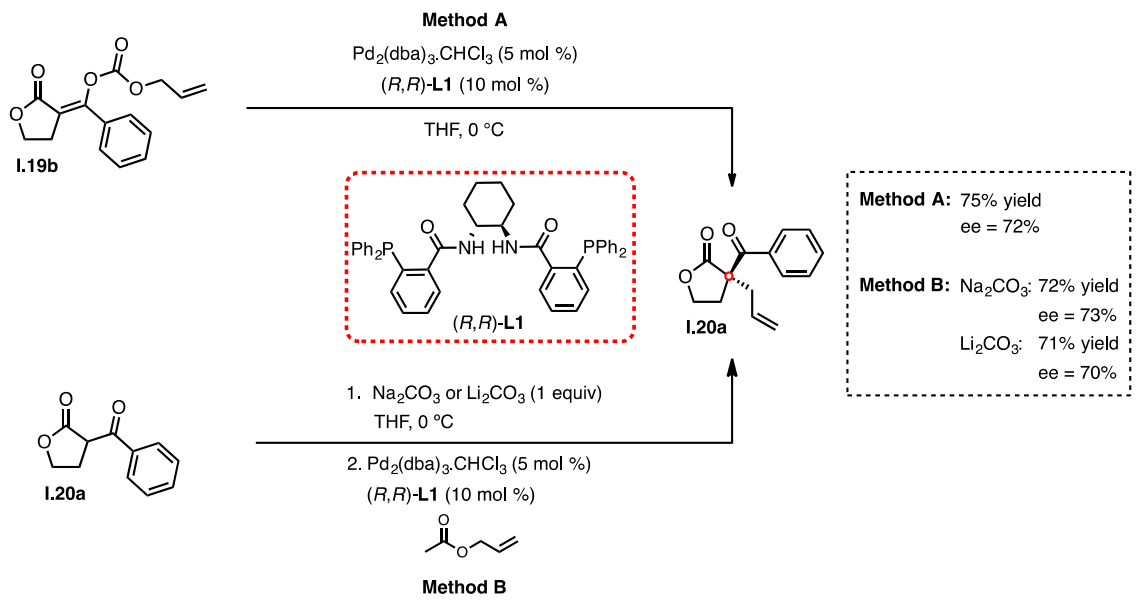
In the case of benzoyl-containing substrates such as **I.19b-d**, a better enantioselectivity was observed with electron-rich aromatic substituents (**I.19c**) than with electron-deficient ones (**I.19d**). Nonetheless, this comparison is not absolutely accurate since the *E*/*Z* ratios of the allyl enol carbonates **I.19c** (*Z*/*E* = 96:4) and **I.19d** (*Z*/*E* = 66:34) are totally different. As the geometry of the preformed enolate intermediate can also influence the selectivity and the reactivity (cf Appendix 1). So, it is difficult to have a clear understanding of which parameter is contributing the most to the enantioselectivity enhancement.

Steric effects seemed to play a more important than the electronic effects. This is, particularly, the case for substrates bearing an alkyl side chain (**I.19f-g**). Indeed, a slightly increase in the enantiomeric excess was observed as the size of the acyl chain became sterically less demanding. As a matter of fact, the allyl enol carbonate **I.19f** bearing a CF_3 group afforded the corresponding allylated γ-butytolactone in lower ee value (ee = 60%) than the allyl enol carbonate **I.19g** containing a smaller CH_3 group (ee = 67%). Replacing the alkyl chain by an even less hindering group, such as a hydrogen (**I.19e**), led to a sharp improvement in the enantiomeric excess, as the product was obtained in up to 94% ee.

4.9. Intramolecular *versus* intermolecular asymmetric allylation

In an effort to further improve the asymmetric allylation method, we next evaluated whether a change in the enantioselectivity would be observed by running the asymmetric allylation of a preformed enolate in an intermolecular fashion, using an external source of allyl, instead of using an allyl enol carbonate (Scheme 34).[59, 69]

Interestingly, both the yield and the ee remained roughly unchanged whether the reaction was performed on the allyl enol carbonate (Scheme 34, Method A) or on the α-acyl γ-butyrolactone using allyl acetate as the allyl donor (Scheme 34, Method B). In addition, it is worth pointing out that the nature of the base did not have an impact on the enantioselectivity, as both Na_2CO_3 and Li_2CO_3 led to similar ee values. Nonetheless, this intermolecular approach seemed much more appealing, since it does not require the synthesis of the allyl enol carbonate and can afford diversely substituted α-quaternary γ-butyrolactones by simply changing the allyl donor.



Scheme 34. Intramolecular *versus* intermolecular asymmetric allylation.

69 Trost, B. M. *Tetrahedron* **2015**, *71*, 5708.

4.10. Origin of enantioselectivity

A great deal of work has been devoted in developing a mechanistic understanding of the diphenylphosphino benzoic acid (DPPBA) based palladium-catalyzed asymmetric allylic alkylation. In particular, Trost's group has coupled mechanistic insights with a working model for predicting the stereochemical outcome of the allylations.[70]

Given the mechanism (discussed in Section 3.2), the seven-membered reductive elimination step was identified as the enantiodetermining step which will, thus, define the resulting stereochemistry outcome of the product. Using a ground state minimized conformation and assuming a 1:1 ratio of Pd/Trost ligand (*R*,*R*)-**L1**, a simplified cartoon model of the chiral pocket was developed (Figure 9).[71] In this conformation, two phenyl "walls" are approximately perpendicular to the other two phenyl "flaps". As illustrated in this model, this creates a chiral environment where the back right and front left are effectively blocked, allowing the quadrants to be differentiated on steric basis.

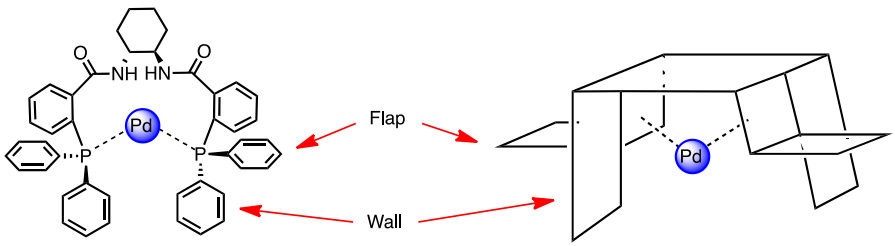


Figure 9. Cartoon model representation.

Considering the allylation of the corresponding enolate of **I.14a** following this model, we can assume that the preferred transition state will place the sterically "bulky" aryl ring under the flap rather than close to the wall (Figure 10). Then, minimizing the steric interactions between the enolate and the ligand differentiates the two enantiotopic faces of the enolate. Hence, this analysis predicts the (*R*) stereochemistry which was further confirmed by comparison of the optical rotation of its two enantiomers. Since the $[\alpha]_D$ value obtained for compound **I.16a**, the $[\alpha]^{20}_D$ = +120 (*c* 0.21, CH_3Cl, ee = 80%), has the opposite sign to the

70 (a) Lloyd-Jones, G. C.; Stephen, S. C.; Fairlamb, I. J. S.; Aina Martorell, B. D.; Tomlin, P. M.; Murray, M.; Fernandez, J. M.; Jeffery, J. C.; Riis-Johannessen, T.; Guerziz, T. *Pure Appl. Chem.* **2004**, *76*, 589; (b) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545; (c) Trost, B. M.; Vranken, D. L. V.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327.

71 Trost, B. M.; Machacek, M. R.; Aponick, A. *Acc. Chem. Res.* **2006**, *39*, 747.

(*S*)-**I.16a** assigned by Buchwald and Spielvogel,[34] $[\alpha]^{20}_{D} = -7.6$ (*c* 1.6, CH_3Cl, ee = 83%), we concluded that the absolute configuration for **I.16a** synthesized through our method is (*R*), which is in line with the prediction of the cartoon model.

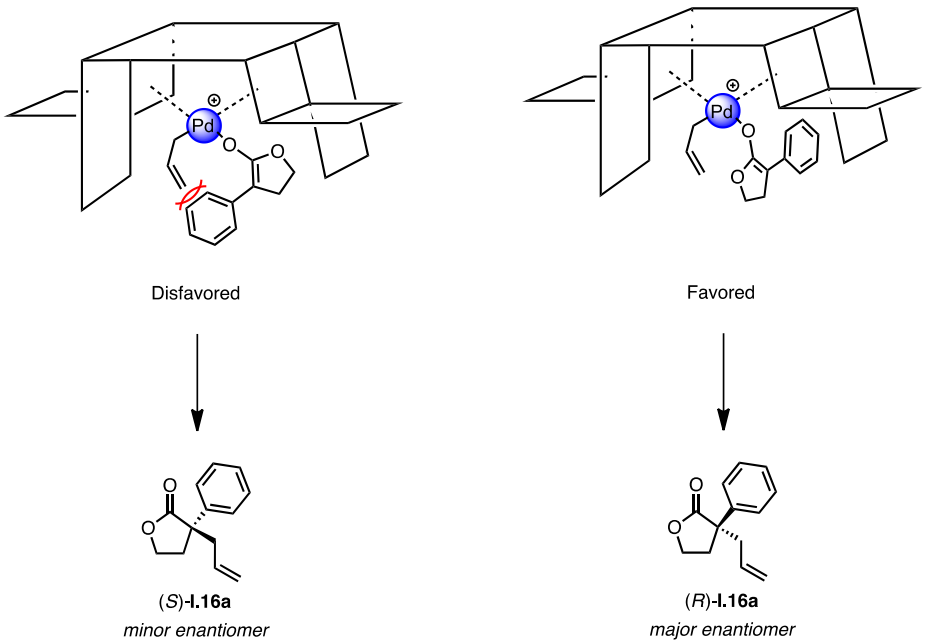
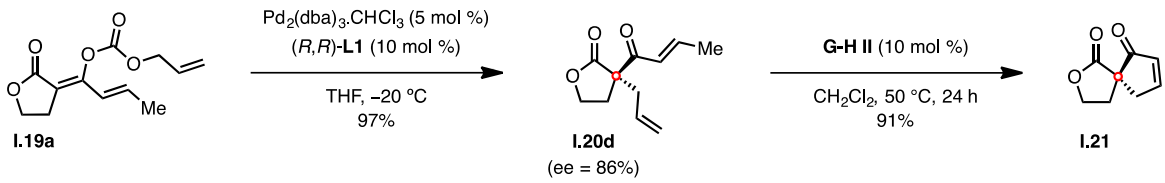


Figure 10. Stereochemistry prediction of **I.16a**.

4.11. Post-functionalization: the synthesis of spirocyclic compounds

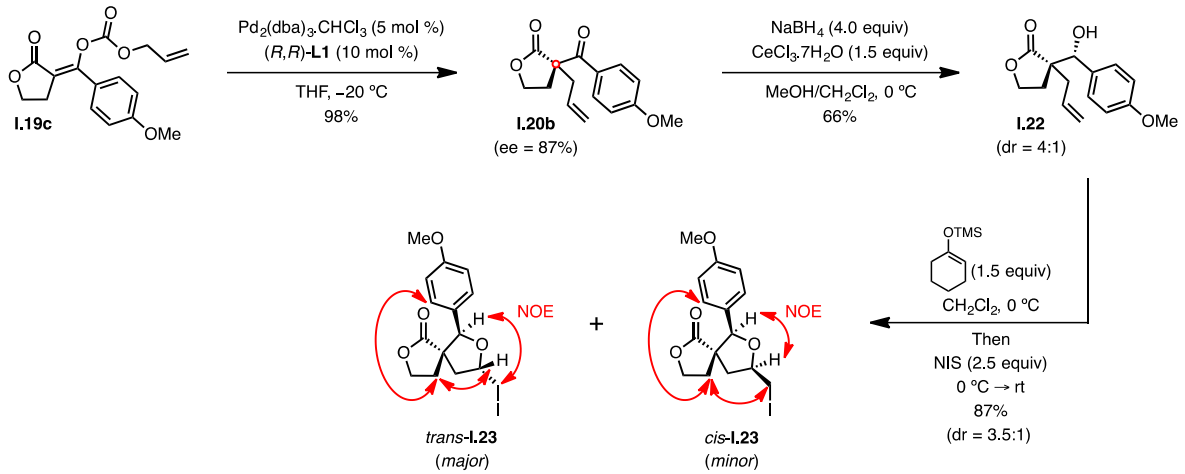
The spirocyclic motif is found in a variety of natural products and it has become more prevalent as a template in drug candidates. The synthesis of spirocyclic compounds have been the focus of many chemists, due to their biological activities, but also to the challenge of generating spiro quaternary centers and/or multiple chiral centers.[72] In this context, we decided to demonstrate the synthetic utility of the compounds that we have obtained through the Pd-DAAA process. Our first strategy to access such spirocyclic scaffolds relied on a Pd-DAAA applied to the allyl enol carbonate **I.19a** followed by a ring-closing metathesis in the presence of the second generation Hoveyda-Grubbs catalyst (**G-H II**), affording the desired spirolactone **I.21** in 88% overall yield without any erosion of the enantiomeric excess (Scheme 35).[73]

72 (a) Smith, L. K.; Baxendale, I. R. *Org Biomol Chem* **2015**, *13*, 9907; (b) Singh, G. S.; Desta, Z. Y. *Chem. Rev.* **2012**, *112*, 6104; (c) Hong, L.; Wang, R. *Adv. Synth. Catal.* **2013**, *355*, 1023.
73 Lafaye, K.; Nicolas, L.; Guerinot, A.; Reymond, S.; Cossy, J., *Org. Lett.* **2014,** *16*, 4972.



Scheme 35. Application of the Pd-DAAA to the synthesis of spirocyclic compound.

The second method utilized to prepare spirocycles allowed the access to spirocyclic tetrahydrofuran. This strategy started with the formation of compound **I.20b** through a decarboxylative asymmetric allylation, followed by a Luche reduction by using $NaBH_4$ and $CeCl_3.7H_2O$ in a 1:1 mixture of CH_2Cl_2/MeOH, providing a 4:1 diastereomeric mixture of the hydroxy γ-butyrolactone **I.22** in 66% yield (Scheme 36).[74] The resulting alcohol **I.22** was, subsequently, engaged in a diastereoselective iodocyclization with *N*-iodosuccinimide (NIS) in the presence of a silyl enol ether.[75] The stereoselective cyclization proceeded smoothly affording two spirocyclic compounds *trans*-**I.23** and *cis*-**I.23** in 87% yield isolated from a mixture of *trans*/*cis*-**I.22** (dr = 3.5:1); the dr was determined by ^{1}H NMR analysis of the crude. The relative configuration of the two newly formed stereocenters was assigned by a chemical correlation established by NMR spectroscopy (NOESY).

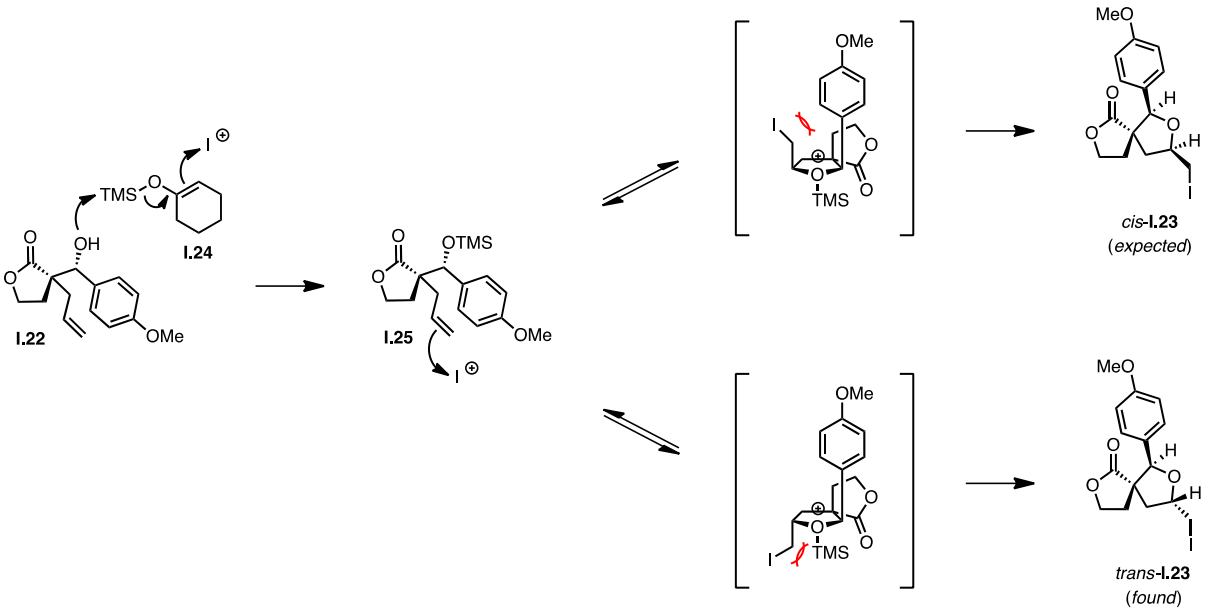


Scheme 36. Application of the Pd-DAAA to the synthesis of spirocyclic tetrahydrofuran.

74 Pohmakotr, M.; Pinsa, A.; Mophuang, T.; Tuchinda, P.; Prabpai, S.; Kongsaeree, P.; Reutrakul, V. *J. Org. Chem.* **2006**, *71*, 386.

75 Fujioka, H.; Maehata, R.; Wakamatsu, S.; Nakahara, K.; Hayashi, T.; Oki, T. *Org. Lett.* **2012**, *14*, 1054.

A plausible explanation for the reaction mechanism has been proposed by Bartlett and Rychnovsky (Scheme 37).[76] Initially, the silyl enol ether **I.24** gets activated by NIS ("I^+") and reacts with the alcohol **I.22** to give the intermediate **I.25**. According to this mechanistic proposal, the minor product *trans*-**I.23** should be generated through a high-energy transition state due to the unfavorable 1,2-steric interactions. On the other hand, the *cis*-**I.23** should be obtained favorably as a result of a lower energy barrier. However, considering the moderate selectivity obtained in this process, two hypotheses can be raised: either the silyl enol ether is not bulky enough or the 1,2-steric interaction between the aryl ring and the iodomethylenic moiety is higher in energy than the 1,2-interaction between the TMS and the iodomethylene. Consequently, the diastereomeric ratio observed through this approach is similar to any traditional halocyclization without the silyl enol ether, producing the thermodynamically more stable *trans*-2,5-THF derivative as the major product.



Scheme 37. Iodocyclization mechanism proposed by Bartlett and Rychnovsky.

76 Rychnovsky, S. D.; Bartlett, P. A., *J. Am. Chem. Soc.* **1981,** *103*, 3964.

5. Conclusion

The development of a palladium-catalyzed decarboxylative allylic alkylation protocol applied to allyl enol carbonates has allowed a highly enantioselective access to a range of γ-butyrolactones bearing an all-carbon α-quaternary stereogenic center. Remarkably, the use of the cyclic and exocyclic allyl enol carbonates appeared to be sensitive to stereoelectronic considerations. However, despite the drawbacks, this approach allowed the extension of the Pd-DAAA to substrates with no precedent in the literature, such as the exocyclic allyl enol carbonates. Alternatively, we have demonstrated that all-carbon α-quaternary γ-butyrolactones could also be achieved without erosion of the enantioselectivity and in a straightforward fashion *via* the intermolecular asymmetric Tsuji-Trost reaction, since this approach does not require the preparation of the challenging allyl enol carbonates. In addition, a greater structural diversity can be introduced by the use of different allyl donors. The Pd-DAAA process was eventually used for the synthesis of chiral spirolactones, which were readily obtained in high yields and in high optical purity.[77]

77 Nascimento de Oliveira, M.; Fournier, J.; Arseniyadis, S.; Cossy, J. *Org. Lett.* **2017**, *19*, 14.

Chapter

1

Experimental Section

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1. General experimental methods

All reactions were run under an argon atmosphere in oven-dried glassware unless otherwise specified. All commercially available compounds were purchased from Aldrich Chemical Co. and used as received. Dichloromethane ($CHCl_2$) was distilled from calcium hydride. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium/benzophenone. *N*,*N*-dimethylformamide (DMF) was distilled under vacuum over anhydrous $MgSO_4$.

Analytical thin layer chromatography (TLC) was performed on silica gel plates (Merck $60F_{254}$) visualized either with a UV lamp (254 nm) or by using solutions of *p*-anisaldehyde/sulfuric acid/acetic acid in ethanol or $KMnO_4/K_2CO_3$ in water followed by heating. Flash chromatography was performed on silica gel (230-400 mesh).

The experiences under microwave irradiation were performed in an Initiator Biotage TM EXP (0-400 W, 2.45 GHz) apparatus.

Melting points (Mp) were recorded using a Wagner & Munz Kofler bench.

Infrared spectra (IR) were recorded on a Bruker TENSOR™ 27 (IR-FT) with attenuated total reflectance (ATR) and wavenumbers are indicated in cm^{-1}.

^1H NMR spectra were recorded on a Bruker AVANCE 400 at 400 MHz in $CDCl_3$ (unless otherwise specified) and the observed signals are reported as follows: chemical shift in parts per million from tetramethylsilane with the solvent as an internal indicator ($CDCl_3$ δ 7.26 ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or overlap of non-equivalent resonances), integration. ^{13}C NMR spectra were recorded at 100 MHz in $CDCl_3$ (unless otherwise specified) and the observed signals were reported as follows: chemical shift in parts per million from tetramethylsilane with the solvent as an internal indicator ($CDCl_3$ δ 77.16 ppm), multiplicity on respect to proton (deduced from DEPT experiments, s = quaternary C, d = CH, t = CH_2, q = CH_3). Coupling constants (*J*) are reported in Hertz (Hz). All NMR spectra were obtained at room temperature unless otherwise specified.

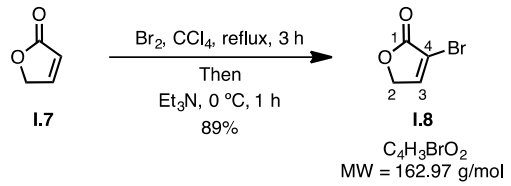
Mass spectra with electronic impact (EI–MS) were recorded with a Shimadzu GCM-QP 2010S gas chromatography-mass spectrometer. High-resolution mass spectra (HRMS) were performed by "Groupe de Spectrométrie de masse de l'Université Pierre et Marie Curie (Paris)".

Optical rotations were determined using a Perkin Elmer 343 polarimeter. The enantiomeric excesses were determined by supercritical fluid chromatography (SFC) analysis

on a chiral stationary phase using a Minigram Berger SFC-Mettler Toledo apparatus. The sign before the ees values is arbitrary.

2. Synthesis of α-aryl butyrolactones

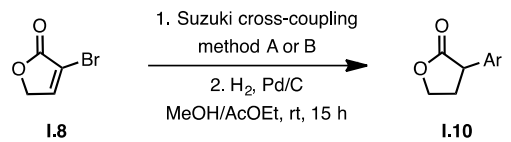
2.1. Synthesis of 3-bromofuran-2(5*H*)-one (I.8)



To a stirred solution of furan-2(5*H*)-one **I.7** (3.00 g, 35.7 mmol, 1.0 equiv) in CCl_4 (60 mL) was slowly added a solution of bromine (4.20 mL, 82.1 mmol, 2.3 equiv) in CCl_4 (40 mL). The resulting reaction mixture was heated at reflux and after 4 h, the excess of bromine was removed by bubbling argon in the reaction mixture for 10 min. The resulting solution was cooled to 0 °C and treated, dropwise over 10 min, with Et_3N (11.4 mL, 82.1 mmol, 2.3 equiv). Stirring was continued for one additional hour, and then the temperature was allowed to reach rt. The mixture was then washed with H_2O (3 x 40 mL) and brine (40 mL), dried over anhydrous $MgSO_4$, filtered and concentrated, under reduced pressure. The crude residue was finally purified by flash column chromatography over silica gel (PE/EtOAc = 7:3) to afford the desired product **I.8** as light brown crystals (5.18 g, 89%). The spectroscopic and physical data of the product were identical to those reported in the literature.[64]

IR (ATR): 3101, 1783, 1704, 1604, 1453, 1346, 1279, 1155, 1040, 988, 828 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (t, J = 1.9 Hz, 1H, H_3), 4.86 (d, J = 1.9 Hz, 2H, H_2).
^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0 (s, C_1), 149.4 (d, C_3), 113.1 (s, C_4), 71.6 (t, C_2).

2.2. General procedures for the synthesis of α-arylbutyrolactones (I.10a-g)

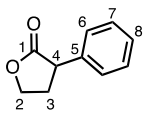


Method A: To a solution of vinyl bromide **I.8** (3.0 mmol, 1.0 equiv) in benzene (9 mL) was added the boronic acid (4.5 mmol, 1.5 equiv), $Pd(PPh_3)_4$ (0.15 mmol, 0.05 equiv) and a solution of Na_2CO_3 (6.0 mmol, 2.0 equiv) in 3 mL of distilled H_2O. The reaction mixture was heated at 100 °C for 15 min under microwave irradiation (400 W). Then a saturated solution of brine was added and the aqueous phase was extracted with EtOAc (3 x 10 mL). The

combined organic layers were finally dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was then dissolved in anhydrous MeOH/EtOAc 3:2 (30 mL) at rt and Pd/C 10% (0.30 mmol, 0.10 equiv) was added. The reaction mixture was stirred, under 1 atm of H_2 for 15 h at rt. The mixture was finally filtered on Celite® (EtOAc) and the residue was purified by flash column chromatography over silica gel to afford the desired lactone **I.10**.

Method B: To a solution of vinyl bromide **I.8** (3.0 mmol, 1.0 equiv) in a 1:1 mixture of toluene/H_2O (12 mL) was added boronic acid (6.0 mmol, 2.0 equiv), $PdCl_2(PPh_3)_2$ (0.15 mmol, 0.05 equiv), KF (9.0 mmol, 3.0 equiv) and Aliquat® 336 (0.015 mmol, 0.005 equiv). The reaction mixture was heated at 110 °C for 30 min under microwave irradiation (400 W). A saturated solution of brine was then added and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic layers were finally dried over $MgSO_4$, filtered and concentrated under reduced pressure.[2] The crude residue was then dissolved in anhydrous MeOH/EtOAc 3:2 (30 mL) at rt and Pd/C 10% (0.30 mmol, 0.10 equiv) was added. The reaction mixture was stirred, under 1 atm of H_2 for 15 h at rt. The mixture was finally filtered over Celite® (EtOAc) and the residue was purified by flash column chromatography on silica gel to afford the desired lactone **I.10**.[63]

α-Phenyl-γ-butyrolactone (I.10a)[78]



I.10a

$C_{10}H_{10}O_2$
MW = 162.19 g/mol

Synthesized according to Method A.

The titled compound was obtained after flash column chromatography on silica gel (PE/EtOAc = 8:2) as a clear oil (199 mg, 41%).

R_f: 0.41 (PE/EtOAc = 8:2)

IR (ATR): 2917, 1767, 1497, 1453, 1374, 1151, 1024 cm^{-1}.

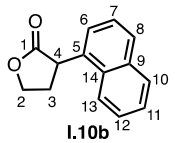
78 McElvian, S. M.; Laughton, P. M., *J. Am. Chem. Soc.* **1951,** *73*, 448.

^{1}H NMR (400 MHz, $CDCl_3$)**:** δ 7.40-7.27 (m, 5H, H_{Ar}), 4.48 (td, *J* = 8.7, 3.3 Hz, 1H, H_2), 4.35 (td, *J* = 9.2, 6.7 Hz, 1H, $H_{2'}$), 3.81 (dd, *J* = 10.2, 9.1 Hz, 1H, H_4), 2.79-2.66 (m, 1H, H_3), 2.52-2.36 (m, 1H, $H_{3'}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 177.5 (s, C_1), 136.8 (s, C_5), 129.0 (d, 2C, C_7), 128.0 (d, 2C, C_6), 127.8 (d, C_8), 66.6 (t, C_2), 45.6 (d, C_4), 31.7 (t, C_3).

HRMS (ESI) *m/z*: calcd for $C_{10}H_{10}O_2$ $[M+H]^+$: 163.0754, found: 163.0754.

α-(1-Naphthyl)-γ-butyrolactone (I.10b)



I.10b

$C_{14}H_{12}O_2$
MW = 212.25 g/mol

Synthesized according to Method B.

The titled compound was obtained after flash column chromatography on silica gel (PE/EtOAc = 8:2) as a clear oil (185 mg, 29%).

R$_f$: 0.33 (PE/EtOAc = 8:2)

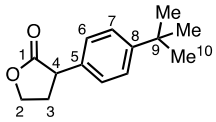
IR (ATR): 3049, 2911, 1766, 1598, 1511, 1373, 1211, 1153, 1025, 991, 952, 909 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (dd, *J* = 7.7, 2.0 Hz, 2H, H_{Ar}), 7.83 (dt, *J* = 8.2, 1.0 Hz, 1H, H_{Ar}), 7.60-7.40 (m, 4H, H_{Ar}), 4.56-4.44 (m, 3H, H_3 and H_4), 2.89 (m, 1H, H_3), 2.47 (m, 1H, $H_{3'}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 177.9 (s, C_1), 134.3 (s, C_5), 133.3 (s, C_9 or C_{14}), 131.4 (s, C_9 or C_{14}), 129.3 (d, C_{Ar}), 128.6 (d, C_{Ar}), 126.7 (d, C_{Ar}), 126.1 (d, C_{Ar}), 125.6 (d, C_{Ar}), 125.4 (d, C_{Ar}), 123.0 (d, C_{Ar}), 66.9 (t, C_2), 43.0 (d, C_4), 31.8 (t, C_3).

HRMS (ESI) *m/z*: calcd for $C_{14}H_{13}O_2$ $[M+H]^+$: 213.0910, found: 213.0910.

α-(4-*t*-Butylphenyl)-γ-butyrolactone (I.10c)



I.10c

$C_{14}H_{18}O_2$
MW = 218.30 g/mol

Synthesized according to Method A.

The titled compound was obtained after flash column chromatography on silica gel (PE/EtOAc = 9:1) as a clear oil (314 mg, 48%).

R_f: 0.56 (PE/EtOAc = 8:2)

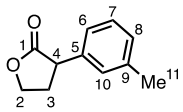
IR (ATR): 2962, 2869, 1769, 1515, 1461, 1371, 1268, 1215, 1150, 1025 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d_{app}, J = 8.1 Hz, 2H, H_7), 7.23 (d_{app}, J = 8.1 Hz, 2H, H_6), 4.48 (td, J = 8.8, 3.3 Hz, 1H, H_2), 4.35 (td, J = 8.8, 6.8 Hz, 1H, $H_{2'}$), 3.80 (dd, J = 9.2, 9.0 Hz, 1H, H_4), 2.70 (m, 1H, H_3), 2.46 (m, 1H, $H_{3'}$), 1.32 (s, 9H, H_{10}).

^{13}C NMR (100 MHz, $CDCl_3$): δ 177.8 (s, C_1), 150.7 (s, C_8), 133.6 (s, C_5), 127.7 (d, 2C, C_6), 126.0 (d, 2C, C_7), 66.7 (t, C_2), 45.2 (d, C_4), 34.7 (s, C_9), 31.7 (t, C_3), 31.4 (q, 3C, C_{10}).

HRMS (ESI) *m/z*: calcd for $C_{14}H_9O_2$ $[M+H]^+$: 219.1377, found: 219.1380.

α-(*m*-Tolyl)-γ-butyrolactone (I.10d)



I.10d

$C_{11}H_{12}O_2$
MW = 176.22 g/mol

Synthesized according to Method B.

The titled compound was obtained after flash column chromatography on silica gel (PE/EtOAc = 9:1) as a clear oil (290 mg, 55%).

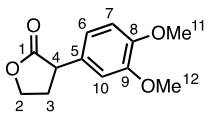
R_f: 0.51 (PE/EtOAc = 8:2)

IR (ATR)**:** 2915, 1765, 1608, 1491, 1456, 1372, 1213, 1148, 1025, 950 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.23 (m, 2H, H_{Ar}), 7.15-7.05 (m, 3H, H_{Ar}), 4.47 (td, J = 8.2, 3.3 Hz, 1H, H_2), 4.35 (td, J = 9.6, 7.2 Hz, 1H, $H_{2'}$), 3.78 (t_{app}, J = 10.1, 9.0 Hz, 1H, H_4), 2.71 (m, 1H, H_3), 2.44 (m, 1H, $H_{3'}$), 2.36 (s, 3H, H_{11}).

^{13}C NMR (100 MHz, $CDCl_3$): δ 177.7 (s, C_1), 138.8 (s, C_5), 136.7 (s, C_9), 129.0 (d, C_6), 128.8 (d, C_{10}), 128.6 (d, C_8), 125.0 (d, C_7), 66.7 (t, C_2), 45.6 (d, C_4), 31.8 (t, C_3), 21.6 (q, C_{11}).
HRMS (ESI) *m/z*: calcd for $C_{11}H_{13}O_2$ $[M+H]^+$: 177.0911, found: 177.0910.

α-(3,4-Dimethoxyphenyl)-γ-butyrolactone (I.10e)[79]



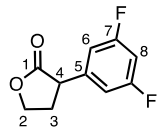
I.10e
$C_{12}H_{14}O_4$
MW = 222.24 g/mol

Synthesized according to Method B.
The titled compound was obtained after flash column chromatography on silica gel (PE/EtOAc = 7:3) as a clear oil (191 mg, 29%).

R_f: 0.47 (PE/EtOAc = 6:4)
IR (ATR): 2937, 2838, 1755, 1592, 1470, 1463, 1420, 1373, 1253, 1235, 1150, 1010, 950 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.88-6.80 (m, 3H, H_{Ar}), 4.47 (td, *J* = 8.6, 3.3 Hz, 1H, H_2), 4.34 (td, *J* = 9.2, 6.6 Hz, 1H, $H_{2'}$), 3.89 (s, 3H, H_{11} or H_{12}), 3.87 (s, 3H, H_{11} or H_{12}), 3.76 (dd, *J* = 9.9, 8.9 Hz, 1H, H_4), 2.71 (m, 1H, H_3), 2.44 (m, 1H, $H_{3'}$).
^{13}C NMR (100 MHz, $CDCl_3$): δ 177.7 (s, C_1), 149.4 (s, C_9), 148.7 (s, C_8), 129.1 (s, C_5), 120.1 (d, C_6), 111.5 (d, C_{10}), 111.2 (d, C_7), 66.6 (t, C_2), 56.1 (q, C_{11} or C_{12}), 56.0 (q, C_{11} or C_{12}), 45.2 (d, C_4), 31.8 (t, C_3).
MS *m/z* (relative intensity): 222 ($M^{+\cdot}$,100), 178 (20), 163 (50), 147 (48), 135 (20), 115 (17), 107 (67), 91 (60), 77 (40), 65 (21), 51 (51).

α-(3,5-difluorophenyl)-γ-butyrolactone (I.10f)

79 Gu, J. X.; Holland, H. L. *Synth. Commun.* **1998**, *28*, 3305.



I.10f

$C_{10}H_8F_2O_2$
MW = 198.17 g/mol

Synthesized according to Method B.

The titled compound was obtained after flash column chromatography on silica gel (PE/EtOAc = 8:2) as clear oil (101 mg, 17%).

R$_f$: 0.38 (PE/EtOAc = 7:3)

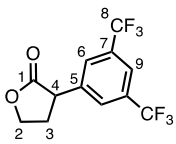
IR (ATR): 3090, 2919, 1769, 1626, 1595, 1460, 1375, 1212, 1150, 1095, 1021, 855, 684 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.90-6.82 (m, 2H, H_6), 6.76 (tt, J = 8.8, 2.3 Hz, 1H, H_8), 4.50 (td, J = 8.9, 2.9 Hz, 1H, H_2), 4.36 (td, J = 8.9, 2.9 Hz, 1H, $H_{2'}$), 3.80 (dd, J = 10.8, 8.9 Hz, 1H, H_4), 2.74 (m, 1H, H_3), 2.43 (m, 1H, $H_{3'}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.1 (s, C_1), 163.3 (s, $^1J_{C\text{-}F}$ = 236, 13.8 Hz, 2C, C_7), 140.1 (s, $^3J_{C\text{-}F}$ = 9.2 Hz, C_5), 111.2 (d, $^2J_{C\text{-}F}$ = 12.2, 7.3 Hz, 2C, C_6), 103.4 (d, $^2J_{C\text{-}F}$ = 25.9 Hz, C_8), 66.5 (t, C_2), 45.0 (d, C_4), 31.1 (t, C_3).

HRMS (ESI) *m/z*: calcd for $C_{10}H_8F_2O_2Na$ $[M+Na]^+$: 221.0385, found: 221.0385.

α-(3,5-bis(trifluoromethyl)phenyl)-γ-butyrolactone (I.10g)



I.10g

$C_{12}H_8F_6O_2$
MW = 298.18 g/mol

Synthesized according to Method B.

The titled compound was obtained after flash column chromatography on silica gel (PE/EtOAc = 8:2) as clear oil (302 mg, 34%).

R$_f$: 0.35 (PE/EtOAc = 8:2)

IR (ATR): 2915, 1766, 1598, 1459, 1420, 1371, 1211, 1150, 1025, 952, 855, 681 cm^{-1}.

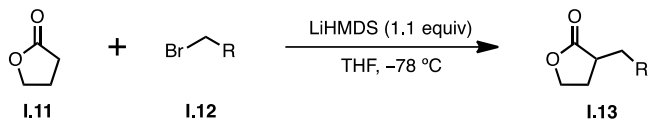
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92-7.76 (m, 3H, H_{Ar}), 4.56 (td, J = 8.4, 2.2 Hz, 1H, H_2), 4.41 (ddd, J = 10.9, 9.2, 6.3 Hz, 1H, $H_{2'}$), 3.96 (dd, J = 11.5, 8.8 Hz, 1H, H_4), 2.82 (m, 1H, H_3), 2.51 (m, 1H, $H_{3'}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.7 (s, C_1), 138.9 (s, C_5), 132.4 (s, $^2J_{C\text{-}F}$ = 33.5 Hz, 2C, C_7), 128.5 (d, $^3J_{C\text{-}F}$ = 3.2 Hz, 2C, C_6), 123.3 (s, $^1J_{C\text{-}F}$ = 273 Hz, 2C, C_8), 122.0 (d, C_9), 66.5 (t, C_2), 45.1 (d, C_4), 31.2 (t, C_3).

HRMS (ESI) *m/z*: calcd for $C_{12}H_8F_6O_2Na$ $[M+Na]^+$: 321.0321, found: 321.0323.

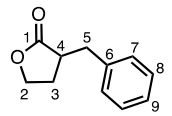
3. Synthesis of α-alkyl butyrolactones

General procedures for the synthesis of α-alkyl butyrolactones (I.13a-b)[44]



To a solution of LiHMDS (12.8 mL, 1.0 M in THF, 12.8 mmol, 1.1 equiv) in THF (103 mL) at −78 °C was added γ-butyrolactone (1.00 g, 11.6 mmol, 1.0 equiv) dropwise followed by the addition of alkyl bromide (13.9 mmol, 1.2 equiv). After 1 h, stirring was continued at −78 °C, the reaction was quenched with a saturated aqueous solution of NH_4Cl, extracted with Et_2O, dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel to afford the desired lactone.

α-Benzyl-γ-butyrolactone (I.13a)



I.13a
$C_{11}H_{12}O_2$
MW = 176.22 g/mol

I.13a was synthesized according to the method aforementioned from γ-butyrolactone (1.00 g, 11.6 mmol, 1.0 equiv) and benzyl bromide (1.67 mL, 13.9 mmol, 1.2 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/EtOAc = 8:2) as a colorless oil (940 mg, 46%).

R$_f$: 0.35 (PE/EtOAc = 8:2)

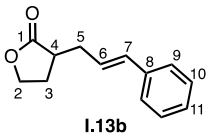
IR (ATR): 2914, 1770, 1603, 1495, 1454, 1374, 1203, 1184, 1145, 1049, 1020, 958, 915 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.20 (m, 2H, H_{Ar}), 7.21-7.11 (m, 3H, H_{Ar}), 4.16 (td, *J* = 8.8, 3.0 Hz, 1H, H_2), 4.08 (td, *J* = 9.3, 6.7 Hz, 1H, $H_{2'}$), 3.19 (dd, *J* = 13.6, 4.0 Hz, 1H, H_5), 2.78 (m, 1H, H_4), 2.69 (dd, *J* = 13.6, 9.4 Hz, 1H, $H_{5'}$), 2.18 (m, 1H, H_3), 1.93 (m, 1H, $H_{3'}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 178.9 (s, C_1), 138.5 (s, C_6), 129.0 (d, 2C, C_8), 128.8 (d, 2C, C_7), 126.9 (d, C_9), 66.7 (t, C_2), 41.2 (d, C_4), 36.2 (d, C_5), 28.2 (t, C_3).

MS *m/z* (relative intensity): 176 ($M^{+\cdot}$,42), 148 (47), 147 (54), 131 (16), 117 (12), 104 (32), 91 (100), 78 (9), 77 (8), 65 (21), 51 (10).

α-Cinnamyl-γ-butyrolactone (I.13b)



I.13b

$C_{13}H_{14}O_2$
MW = 202.25 g/mol

I.13b was synthesized according to the method aforementioned from γ-butyrolactone (1.00 g, 11.6 mmol, 1.0 equiv) and cinnamyl bromide (2.06 mL, 13.9 mmol, 1.2 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/EtOAc = 9:1) as a colorless oil (1.658 g, 71%).

R$_f$: 0.45 (PE/EtOAc = 9:1)

IR (ATR): 3025, 2985, 2909, 1775, 1598, 1495, 1449, 1374, 1183, 1149, 1021, 967 cm^{-1}.

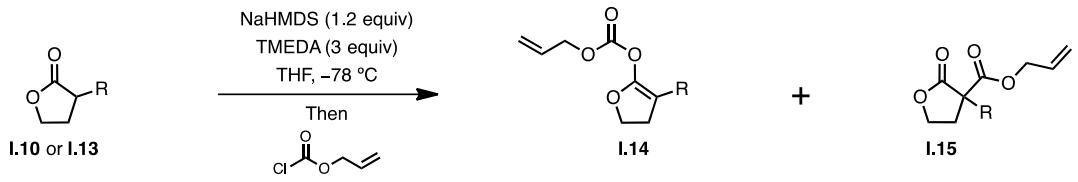
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.28 (m, 4H, H_{Ar}), 7.23 (m, 1H, H_{Ar}), 6.49 (d_{app}, *J* = 15.7 Hz, H_7), 6.17 (dt, *J* = 15.7, 7.2 Hz, 1H, H_6), 4.35 (td, *J* = 8.9, 3.2 Hz, 1H, H_2), 4.21 (td, *J* = 9.4, 6.8 Hz, 1H, $H_{2'}$), 2.80-2.68 (m, 2H, H_4 and H_5), 2.52-2.33 (m, 2H, $H_{5'}$ and H_3), 2.06 (m, 1H, $H_{3'}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 178.9 (s, C_1), 137.0 (s, C_8), 133.1 (d, C_7), 128.7 (d, 2C, C_{10}), 127.6 (d, C_{11}), 126.3 (d, 2C, C_9), 125.9 (d, C_6), 66.7 (t, C_2), 39.4 (d, C_4), 33.7 (t, C_5), 27.9 (t, C_3).

MS *m/z* (relative intensity): 202 ($M^{+\cdot}$,50), 184 (2), 174 (12), 156 (6), 141 (4), 129 (71), 117 (100), 104 (13), 91 (42), 77 (10), 65 (10), 51 (10).

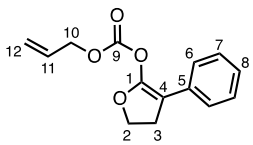
4. Synthesis of cyclic allyl enol carbonates

General procedures for the synthesis of allyl enol carbonates (I.14a-e/h-i and I.15f-g) (Representative procedure)



To a solution of NaHMDS (1.20 mL, 1.0 M in THF, 1.2 mmol, 1.2 equiv) in THF (9 mL) at −78 °C was added TMEDA (0.45 mL, 3.0 mmol, 3.0 equiv). A solution of lactone (1.0 mmol, 1.0 equiv) in THF (1 mL) was added dropwise. After 1 h at −78 °C, allyl chloroformate (0.32 mL, 3.0 mmol, 3.0 equiv) was added, after 15 min, a saturated aqueous solution of NH_4Cl was then added and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and evaporated under reduced pressure to afford a crude residue, which was purified by flash column chromatography on silica gel to afford the corresponding allyl enol carbonate **I.14** or, eventually, the allyl carboxylate **I.15**.

Allyl (3-phenyl-4,5-dihydrofuran-2-yl) carbonate (I.14a)



I.14a

$C_{14}H_{14}O_4$
MW = 246.26 g/mol

I.14a was synthesized according to the method aforementioned from α-phenyl-γ-butyrolactone **I.10a** (445 mg, 2.74 mmol, 1.0 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/EtOAc = 95:5) as colorless oil (634 mg, 94%).

R$_f$: 0.58 (PE/EtOAc = 9:1)

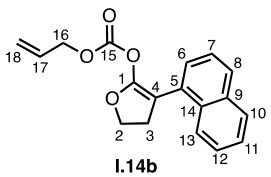
IR (ATR): 2922, 1784, 1679, 1617, 1247, 1209, 1103, 1021, 946, 843, 692 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.27 (m, 4H, H_7 and H_6), 7.19-7.12 (m, 1H, H_8), 5.97 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 1H, H_{11}), 5.42 (dq, *J* = 17.2, 1.4 Hz, 1H, H_{12}), 5.34 (dq, *J* = 10.4, 1.2 Hz, 1H, $H_{12'}$), 4.75 (dt, *J* = 5.9, 1.3 Hz, 2H, H_{10}), 4.56 (dd, *J* = 9.6, 8.8 Hz, 2H, H_2), 3.14 (dd, *J* = 9.6, 8.8 Hz, 2H, H_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.9 (s, C_1), 149.9 (s, C_9), 132.7 (s, C_5), 130.7 (d, C_{11}), 128.6 (d, 2C, C_7), 125.7 (d, C_8), 125.2 (d, 2C, C_6), 120.1 (t, C_{12}), 94.2 (s, C_4), 70.1 (t, C_2), 67.7 (t, C_{10}), 30.8 (t, C_3).

HRMS (ESI) *m/z*: calcd for $C_{14}H_{14}O_4Na$ $[M+Na]^+$: 269.0784, found: 269.0790.

Allyl (3-(naphthalen-1-yl)-4,5-dihydrofuran-2-yl) carbonate (14.b)



I.14b

$C_{18}H_{16}O_4$
MW = 296.32 g/mol

I.14b was synthesized according to the method aforementioned from α-(1-naphthyl)-γ-butyrolactone **I.10b** (170 mg, 0.80 mmol, 1.0 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/EtOAc = 95:5) as a colorless oil (147 mg, 62%).

R$_f$: 0.71 (PE/EtOAc = 8:2)

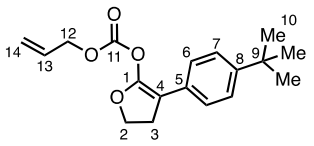
IR (ATR): 2970, 1775, 1710, 1509, 1453, 1370, 1246, 1205, 1088, 1028, 933, 802 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04-7.98 (m, 1H, H_{13}), 7.89-7.81 (m, 1H, H_{10}), 7.77 (m, 1H, H_8), 7.37 (m, 4H, H_6 and H_7 and H_{11} and H_{12}), 5.77 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 1H, H_{17}), 5.26-5.17 (m, 2H, H_{18}), 4.69 (dd, *J* = 9.4, 8.8 Hz, 2H, H_2), 4.55 (dt, *J* = 5.8, 1.3 Hz, 2H, H_{16}), 3.25 (dd, *J* = 9.4, 8.9 Hz, 2H, H_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 151.1 (s, C_1), 150.1 (s, C_{15}), 133.9 (s, 2C, C_9 and C_{14}), 131.8 (s, C_5), 130.6 (d, C_{17}), 128.5 (d, C_{10}), 127.8 (d, C_8), 126.7 (d, C_{Ar}), 126.1 (d, C_{Ar}), 125.9 (d, C_{Ar}), 125.7 (d, C_{Ar}), 125.6 (d, C_{Ar}), 119.5 (t, C_{18}), 93.5(s, C_4), 69.7 (t, C_2), 68.3 (t, C_{16}), 34.4 (t, C_3).

HRMS (ESI) *m/z*: calcd for $C_{18}H_{16}O_4Na$ $[M+Na]^+$: 319.0941, found: 319.0940.

Allyl (3-(4-(*tert*-butyl)phenyl)-4,5-dihydrofuran-2-yl) carbonate (I.14c)



I.14c

$C_{18}H_{22}O_4$
MW = 302.37 g/mol

I.14c was synthesized according to the method aforementioned from α-(4-*t*-butylphenyl)-γ-butyrolactone **I.10c** (73 mg, 0.33 mmol, 1.0 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/EtOAc = 95:5) as a colorless oil (70 mg, 70%).

R$_f$: 0.58 (PE/EtOAc = 9:1)

IR (ATR): 2963, 2869, 1773, 1607, 1514, 1461, 1368, 1250, 1206, 1153, 1024, 957, 829 cm^{-1}.

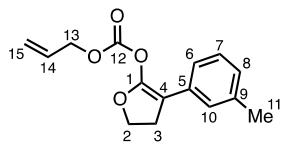
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.31 (m, 2H, H_7), 7.28-7.21 (m, 2H, H_6), 5.97 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 1H, H_{13}), 5.43 (dq, *J* = 17.2, 1.4 Hz, 1H, H_{14}), 5.34 (dq, *J* = 10.4, 1.2 Hz, 1H, $H_{14'}$), 4.74 (dt, *J* = 5.8, 1.4 Hz, 2H, H_{12}), 4.54 (dd, *J* = 9.5, 8.8 Hz, 2H, H_2), 3.13 (dd, *J* = 9.6, 8.8 Hz, 2H, H_3), 1.32 (s, 9H, H_{10}).

^{13}C NMR (100 MHz, $CDCl_3$): δ 130.8 (d, C_{13}), 129.8 (s, C_5), 125.5 (d, 2C, C_6), 125.0 (d, 2C, C_7), 94.1 (s, C_4), 70.0 (t, C_2), 67.6 (t, C_{12}), 34.6 (s, C_9), 31.4 (q, 3C, C_{10}), 30.8 (t, C_3).

Note: The C_1, C_8 and C_{11} signals were not observed.

HRMS (ESI) *m/z*: calcd for $C_{18}H_{22}O_4Na$ $[M+Na]^+$: 325.1410, found: 325.1410.

Allyl (3-(*m*-tolyl)-4,5-dihydrofuran-2-yl) carbonate (I.14d)



I.14d

$C_{15}H_{16}O_4$
MW = 260.29 g/mol

I.14d was synthesized according to the method aforementioned from α-(*m*-tolyl)-γ-butyrolactone **I.10d** (190 mg, 1.1 mmol, 1.0 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/EtOAc = 95:5) as colorless oil (28 mg, 10%).

R_f: 0.53 (PE/EtOAc = 9:1)

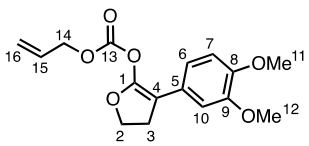
IR (ATR): 2925, 1779, 1685, 1606, 1454, 1371, 1252, 1206, 1113, 1025, 942, 840, 784, 696 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (t, *J* = 7.6 Hz, 1H, H_7), 7.14-7.06 (m, 2H, H_6 and H_{10}), 6.97 (m, 1H, H_8), 5.96 (ddt, *J* = 17.1, 10.3, 5.8 Hz, 1H, H_{14}), 5.42 (dq, *J* = 17.2, 1.5 Hz, 1H, H_{13}), 5.33 (dq, *J* = 10.5, 1.2 Hz, 1H, $H_{13'}$), 4.74 (dt, *J* = 5.8, 1.4 Hz, 2H, H_{15}), 4.54 (dd, *J* = 9.6, 8.8 Hz, 2H, H_2), 3.13 (dd, *J* = 9.6, 8.8 Hz, 2H, H_3), 2.33 (d_{app}, *J* = 0.7 Hz, 3H, H_{11}).

^{13}C NMR (100 MHz, $CDCl_3$): δ 151.0 (s, C_1), 149.8 (s, C_{12}), 138.1 (s, C_9), 132.7 (s, C_5), 130.7 (d, C_{14}), 128.5 (d, C_8), 126.6 (d, C_{10}), 125.9 (d, C_6), 122.4 (d, C_7), 120.0 (t, C_{15}), 94.23 (s, C_4), 70.0 (t, C_2), 67.6 (t, C_{13}), 30.9 (t, C_3), 21.7 (q, H_{11}).

HRMS (ESI) *m/z*: calcd for $C_{15}H_{16}O_4Na$ $[M+Na]^+$: 283.0941, found: 283.0943.

Allyl (3-(3,4-dimethoxyphenyl)-4,5-dihydrofuran-2-yl) carbonate (I.14e)



I.14e

$C_{16}H_{18}O_6$

MW = 306.31 g/mol

I.14e was synthesized according to the method aforementioned from α-(3,4-dimethoxyphenyl)-γ-butyrolactone **I.10e** (183 mg, 0.82 mmol, 1.0 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/EtOAc = 8:2) as a colorless oil (80 mg, 32%).

R_f: 0.22 (PE/EtOAc = 8:2)

IR (ATR): 2936, 1771, 1688, 1519, 1464, 1367, 1251, 1206, 1147,1103, 1026, 941, 858, 765 cm^{-1}.

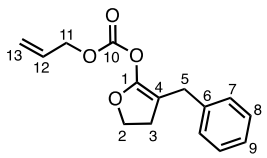
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.92 (d, *J* = 2.0 Hz, 1H, H_{10}), 6.84-6.75 (m, 2H, H_6 and H_7), 5.94 (ddt, *J* = 17.2, 10.4, 5.9 Hz, 1H, H_{15}), 5.40 (dq, *J* = 17.2, 1.4 Hz, 1H, H_{16}), 5.32 (dq, *J* =

10.4, 1.1 Hz, 1H, $H_{16'}$), 4.72 (dt, J = 5.9, 1.3 Hz, 2H, H_{14}), 4.53 (dd, J = 9.5, 8.8 Hz, 2H, H_2), 3.85 (s, 3H, H_{11} or H_{12}), 3.86 (s, 3H, H_{11} or H_{12}), 3.11 (dd, J = 9.6, 8.8 Hz, 2H, H_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 151.1 (s, C_1), 149.0 (s, C_8 or C_9), 148.9 (s, C_8 or C_9), 147.3 (s, C_{13}), 130.6 (d, C_{15}), 125.7 (s, C_5), 120.2 (t, C_{16}), 117.8 (d, C_7), 111.3 (d, C_6), 108.5 (d, C_{10}), 94.0 (s, C_4), 70.0 (t, C_{14}), 67.5 (t, C_2), 56.0 (q, C_{11} or C_{12}), 55.8 (q, C_{11} or C_{12}), 31.0 (t, C_3).

HRMS (ESI) *m/z*: calcd for $C_{16}H_{18}O_6Na$ $[M+Na]^+$: 329.0996, found: 329.0995.

Allyl (3-benzyl-4,5-dihydrofuran-2-yl) carbonate (I.14h)



I.14h

$C_{15}H_{16}O_4$

MW = 260.29 g/mol

I.14h was synthesized according to the method aforementioned from α-benzyl-γ-butyrolactone **I.13a** (300 mg, 1.70 mmol, 1.0 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/EtOAc = 95:5 to 8:2) as a colorless oil (145 mg, 33%).

R_f: 0.71 (PE/EtOAc = 8:2)

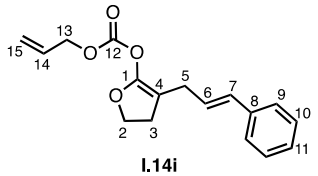
IR (ATR): 3063, 3028, 2901, 2863, 1774, 1728, 1494, 1453, 1365, 1256, 1204, 1085, 1028, 995, 941, 701 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.16 (m, 5H, H_{Ar}), 5.95 (ddt, J = 17.1, 10.3, 5.7 Hz, 1H, H_{12}), 5.40 (dq, J = 17.2, 1.3 Hz, 1H, H_{13}), 5.32 (dq, J = 10.5, 1.2 Hz, 1H, $H_{13'}$), 4.71 (dt, J = 5.9, 1.3 Hz, 2H, H_{11}), 4.40 (dd, J = 9.5, 8.8 Hz, 2H, H_2), 3.34 (s, 2H, H_5), 2.58 (ddd, J = 9.9, 8.7, 1.0 Hz, 2H, H_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 151.8 (s, C_1), 149.3 (s, C_{10}), 139.0 (s, C_6), 130.8 (d, C_{12}), 128.6 (d, 2C, C_7 or C_8), 128.4 (d, 2C, C_7 or C_8), 126.4 (d, C_9), 120.0 (t, C_{13}), 92.8 (s, C_4), 69.8 (t, C_{11}), 67.8 (t, C_2), 31.2 (t, C_5), 30.9 (t, C_3).

HRMS (ESI) *m/z*: calcd for $C_{15}H_{16}O_4Na$ $[M+Na]^+$: 283.0941, found: 283.0941.

Allyl (3-cinnamyl-4,5-dihydrofuran-2-yl) carbonate (I.14i)



I.14i

$C_{17}H_{18}O_4$
MW = 286.33 g/mol

I.14i was synthesized according to the method aforementioned from α-cinnamyl-γ-butyrolactone **I.13b** (300 mg, 1.48 mmol, 1.0 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/EtOAc = 95:5) as a colorless oil (185 mg, 44%).

R_f: 0.40 (PE/EtOAc = 9:1)

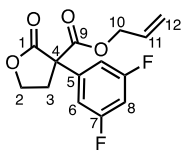
IR (ATR): 3026, 2900, 2861, 1775, 1728, 1449, 1366, 1251, 1203, 1089, 1028, 967, 941, 750, 694 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.26 (m, 4H, H_{Ar}), 7.21 (m, 1H, H_{11}), 6.47-6.39 (m, 1H, H_7), 6.15 (dt, *J* = 15.8, 6.8 Hz, 1H, H_6), 5.89 (ddt, *J* = 17.2, 10.3, 5.7 Hz, 1H, H_{14}), 5.37 (dq, *J* = 17.2, 1.5 Hz, 1H, H_{15}), 5.29 (dq, *J* = 10.5, 1.2 Hz, 1H, $H_{15'}$), 4.64 (dt, *J* = 5.9, 1.3 Hz, 2H, H_{13}), 4.42 (dd, *J* = 9.5, 8.8 Hz, 2H, H_2), 2.90 (dt, *J* = 6.8, 1.3 Hz, 2H, H_5), 2.72 (t_{app}, *J* = 9.2 Hz, 2H, H_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 151.7 (s, C_1), 149.1 (s, C_{12}), 137.5 (s, C_8), 131.3 (d, C_7), 130.8 (d, C_{14}), 128.6 (d, 2C, C_9 or C_{10}), 127.3 (d, C_{11}), 126.9 (d, C_6), 126.2 (d, 2C, C_9 or C_{10}), 119.9 (t, C_{15}), 91.7 (s, C_4), 69.8 (t, C_{13}), 67.8 (t, C_2), 31.3 (t, C_3), 28.5 (t, C_5).

HRMS (ESI) *m/z*: calcd for $C_{17}H_{18}O_4Na$ $[M+Na]^+$: 309.1097, found: 309.1095.

Allyl 3-(3,5-difluorophenyl)-2-oxotetrahydrofuran-3-carboxylate (I.15f)



I.15f

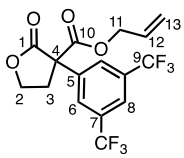
$C_{14}H_{12}F_2O_4$
MW = 282.07 g/mol

I.15f was synthesized according to the method aforementioned from α-(3,5-difluorophenyl)-γ-butyrolactone **I.10f** (84 mg, 0.42 mmol, 1.0 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/EtOAc = 9:1) as colorless oil (69 mg, 58%).

Note: Only for this case, the allyl carboxylate was obtained exclusively, even using otherwise identical conditions.

R_f: 0.11 (PE/EtOAc = 9:1)
IR (ATR): 3091, 2957, 2924, 2854, 1770, 1686, 1626, 1600, 1439, 1375, 1248, 1213, 1155, 1027, 938, 858, 795, 681 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17-7.06 (m, 2H, H_6), 6.81 (tt, J = 8.7, 2.3 Hz, 1H, H_8), 5.84 (ddt, J = 17.2, 10.5, 5.6 Hz, 1H, H_{11}), 5.33-5.21 (m, 2H, H_{12}), 4.73-4.61 (m, 2H, H_{10}), 4.46-4.24 (m, 2H, H_2), 3.24 (ddd, J = 13.0, 6.7, 4.6 Hz, 1H, H_3), 2.68 (dt, J = 13.0, 7.7 Hz, 1H, $H_{3'}$).
^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9 (s, C_1), 167.6 (s, C_9), 163.2 (s, $^1J_{C-F}$ = 236, 14 Hz, 2C, C_7), 138.8 (s, C_5), 130.7 (d, C_{11}), 119.6 (t, C_{12}), 110.9 (d, $^2J_{C-F}$ = 20.1, 7.0 Hz, 2C, C_6), 103.4 (d, $^2J_{C-F}$ = 25.9 Hz, C_8), 67.5 (t, C_{10}), 65.8 (t, C_2), 58.2 (s, C_4), 34.9 (t, C_3).
HRMS (ESI) *m/z*: calcd for $C_{14}H_{12}F_2O_4Na$ $[M+Na]^+$: 305.0596, found: 305.0596.

Allyl 3-(3,5-bis(trifluoromethyl)phenyl)-2-oxotetrahydrofuran-3-carboxylate (I.15g)



I.15g
$C_{16}H_{12}F_6O_4$
MW = 382.26 g/mol

I.15g was synthesized according to the method aforementioned from α-(3,5-bis(trifluoromethyl)phenyl)-γ-butyrolactone **I.10g** (200 mg, 0.67 mmol, 1.0 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/EtOAc = 9:1) as colorless oil (122 mg, 47%).

Note: Only for this case, the allyl carboxylate was obtained exclusively, even using otherwise identical conditions.

Rf: 0.27 (PE/EtOAc = 8:2)

IR (ATR): 2927, 1778, 1738, 1456, 1374, 1277, 1168, 1129, 1029, 938, 900, 844, 704, 682 cm^{-1}.

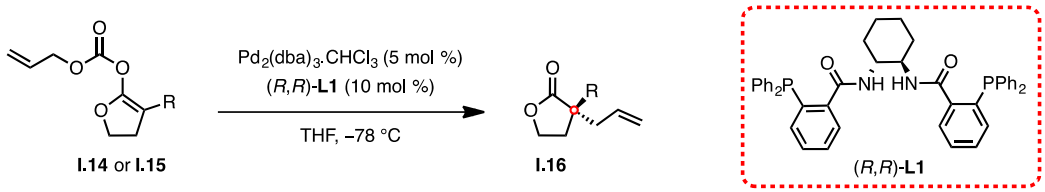
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11-8.06 (m, 2H, H_6), 7.89 (m, 1H, H_8), 5.84 (ddt, J = 17.1, 10.4, 5.8 Hz, 1H, H_{12}), 5.29 (dq, J = 17.2, 1.5 Hz, 1H, H_{13}), 5.26 (m, 1H, $H_{13'}$) 4.77-4.62 (m, 2H, H_{11}), 4.53-4.37 (m, 2H, H_2), 3.32 (ddd, J = 13.0, 6.4, 3.7 Hz, 1H, H_3), 2.77 (ddd, J = 13.0, 8.7, 8.0 Hz, 1H, $H_{3'}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7 (s, C_1), 167.3 (s, C_{10}), 137.9 (s, C_5), 132.2 (s, $^2J_{C\text{-}F}$ = 33.6 Hz, 2C, C_7), 130.4 (d, C_{12}), 127.9 (d, $^3J_{C\text{-}F}$ = 3.6 Hz, 2C, C_6), 123.2 (s, $^1J_{C\text{-}F}$ = 273 Hz, 2C, C_9), 122.6 (d, C_8), 120.1 (t, C_{13}), 67.8 (t, C_{11}), 66.0 (t, C_2), 58.1 (s, C_4), 34.7 (t, C_3).

HRMS (ESI) *m/z*: calcd for $C_{16}H_{12}F_6O_4Na$ $[M+Na]^+$: 405.0532, found: 405.0535.

5. General Procedures for the Pd-DAAA of cyclic allyl enol carbonate

synthesis of α-allyl-α-aryl and α-alkyl butyrolactones (I.16a-g)
(Representative procedure)



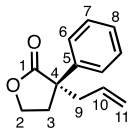
To a solution of $Pd_2(dba)_3.CHCl_3$ (0.01 mmol, 0.05 equiv) in THF (1 mL) at room temperature was added (*R*,*R*)-DACH phenyl Trost ligand (0.02 mmol, 0.1 equiv) and the mixture was stirred for 30 min. This solution was then cooled to −78 °C and transferred via cannula to a flask containing a cooled solution (−78 °C) of allyl enol carbonate (0.2 mmol, 1 equiv) in THF (1 mL). The reaction mixture was then stirred at the same temperature until complete consumption of the starting material (confirmed by TLC). A saturated solution of brine was then added and the aqueous phase was extracted with EtOAc (3 x 2 mL). The combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure to afford a crude residue, which was purified by flash column chromatography on silica gel to afford the corresponding allylated butyrolactone.

General procedure for the synthesis of racemic compounds

(Representative procedure)

To a solution of allyl enol carbonate (0.1 mmol, 1 equiv) in THF (1 mL) at room temperature was added $Pd(PPh_3)_4$ (0.005 mmol, 0.05 equiv). The reaction mixture was then stirred at the same temperature for 10 min as the complete consumption of the starting material (confirmed by TLC). The solvent was then evaporated under reduced pressure to afford a crude residue, which was purified following the same procedure described for the corresponding enantioenriched compound.

(*R*)-3-Allyl-3-phenyldihydrofuran-2(3*H*)-one (I.16a)



I.16a

$C_{13}H_{14}O_2$

MW = 202.25 g/mol

I.16a was synthesized according to the method aforementioned from allyl (3-phenyl-4,5-dihydrofuran-2-yl) carbonate **I.14a** (25 mg, 0.1 mmol, 1.0 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/EtOAc = 95:5) as a colorless oil (18 mg, 89%).

R$_f$: 0.52 (PE/EtOAc = 9:1)

[α]^{20} D = +120 (*c* 0.21, $CHCl_3$)

ee = 80% (determined by SFC)

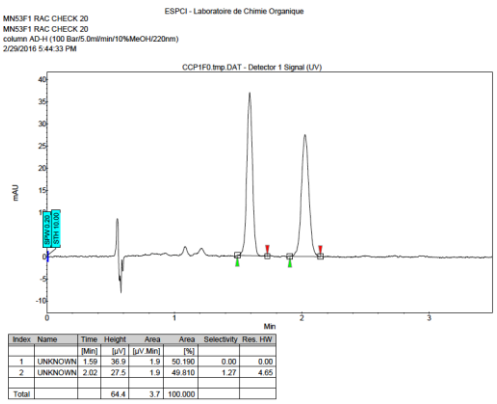
SFC: AD-H column, Pressure = 100 bar, eluent = sc CO_2/MeOH = 90:10, Flow rate = 5 mL/min, detection wavelength = 220 nm. t_R = 1.60 min (minor) and t_R = 1.89 min (major).

IR (ATR): 2981, 2914, 1766, 1600, 1495, 1447, 1372, 1164, 1081, 1025, 925, 769 cm^{-1}.

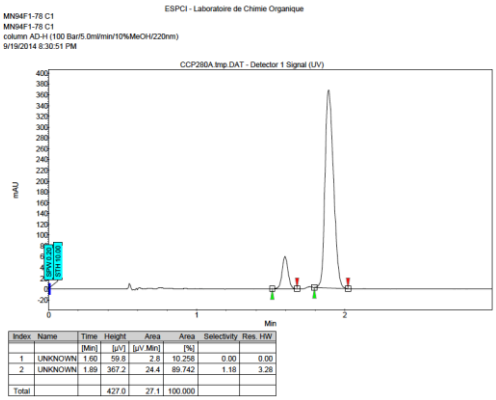
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49-7.41 (m, 2H, H_6), 7.41-7.33 (m, 2H, H_7), 7.33-7.26 (m, 1H, H_8), 5.64 (m, 1H, H_{10}), 5.16-5.07 (m, 2H, H_{11}), 4.31 (ddd, *J* = 9.0, 8.0, 3.3 Hz, 1H, H_2), 4.11 (td$_{app}$, *J* = 9.2, 6.5 Hz, 1H, $H_{2'}$), 2.68 (dt, *J* = 7.3, 1.1 Hz, 2H, H_9), 2.63 (ddd, *J* = 13.1, 6.5, 3.3 Hz, 1H, H_3), 2.54 (ddd, *J* = 13.1, 9.4, 8.0 Hz, 1H, $H_{3'}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 178.8 (s, C_1), 139.1 (s, C_5), 133.0 (d, C_{10}), 128.9 (d, 2C, C_7), 127.7 (d, C_8), 126.4 (d, 2C, C_6), 119.6 (t, C_{11}), 65.4 (t, C_2), 51.1 (s, C_4), 43.6 (t, C_9), 33.4 (t, C_3).

HRMS (ESI) *m/z*: calcd for $C_{13}H_{15}O_2$ $[M+H]^+$: 203.1067, found: 203.1068.

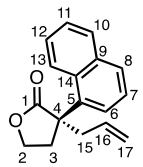


Index	Name	Time [Min]	Height [µV]	Area [µV.Min]	Area [%]	Selectivity	Res. HW
1	UNKNOWN	1.59	36.9	1.9	50.190	0.00	0.00
2	UNKNOWN	2.02	27.5	1.9	49.810	1.27	4.65
Total			64.4	3.7	100.000		



Index	Name	Time [Min]	Height [µV]	Area [µV.Min]	Area [%]	Selectivity	Res. HW
1	UNKNOWN	1.60	59.8	2.8	10.258	0.00	0.00
2	UNKNOWN	1.89	367.2	24.4	89.742	1.18	3.28
Total			427.0	27.1	100.000		

(*R*)-3-Allyl-3-(naphthalen-1-yl)dihydrofuran-2(3*H*)-one (I.16b)



I.16b

$C_{17}H_{16}O_2$

MW = 252.31 g/mol

I.16b was synthesized according to the method aforementioned from allyl (3-(naphthalen-1-yl)-4,5-dihydrofuran-2-yl) carbonate **I.14b** (27 mg, 0.09 mmol, 1.0 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/EtOAc = 95:5 to 9:1) as a colorless oil (22 mg, 95%).

R$_f$: 0.47 (PE/EtOAc = 9:1)

[α]^{20} $_D$ = +119 (*c* 0.43, $CHCl_3$)

ee = 90% (determined by SFC)

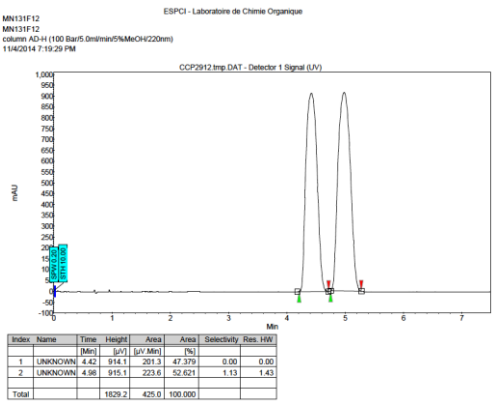
SFC: AD-H column, Pressure = 100 bar, eluent = sc CO_2/MeOH = 95:5, Flow rate = 5 mL/min, detection wavelength = 220 nm. t_R = 4.42 min (major) and t_R = 4.97 min (minor).

IR (ATR): 3051, 2918, 2850, 1768, 1639, 1599, 1510, 1375, 1219, 1176, 1030, 925, 804, 778 cm^{-1}.

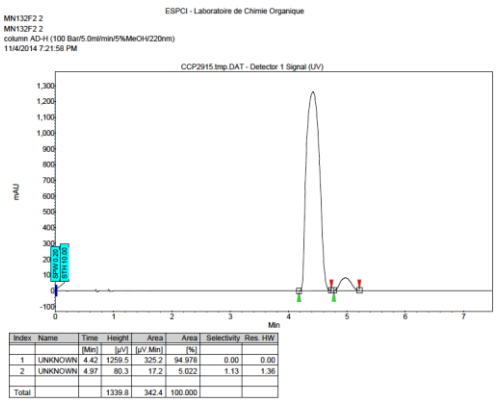
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02(dd, J = 8.1, 1.6 Hz, 1H, H_{13}), 7.92 (dd, J = 8.0, 1.6 Hz, 1H, H_{10}), 7.81 (dt, J = 8.2, 1.1 Hz, 1H, H_8), 7.59-7.46 (m, 3H, H_6 and H_7 and H_{12}), 7.40 (dd, J = 8.2, 7.3 Hz, 1H, H_{11}), 5.88 (m, 1H, H_{16}), 5.33-5.18 (m, 2H, H_{17}), 4.35 (td, J = 8.8, 3.4 Hz, 1H, H_2), 4.12 (td, J = 9.0, 7.1 Hz, 1H, $H_{2'}$), 3.18 (m, 1H, H_{15}), 3.11-2.90 (m, 2H, $H_{15'}$ and H_3), 2.79 (dt, J = 13.0, 8.9 Hz, 1H, H_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 179.8 (s, C_1), 135.6 (s, C_9 or C_{14}), 135.4 (s, C_9 or C_{14}), 133.4 (d, C_{16}), 130.2 (d, C_{10}), 130.1 (s, C_5), 129.3 (d, C_8), 126.1 (d, C_{Ar}), 125.6 (d, C_{Ar}), 125.5 (d, C_{Ar}), 125.3 (d, C_{Ar}), 124.7 (d, C_{13}), 120.1 (t, C_{17}), 65.8 (t, C_2), 53.0 (s, C_4), 41.5 (t, C_{15}), 33.9 (t, C_3).

HRMS (ESI) *m/z*: calcd for $C_{17}H_{16}O_2Na$ $[M+Na]^+$: 275.1043, found: 275.1044.

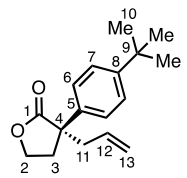


Index	Name	Time [Min]	Height [µV]	Area [µV.Min]	Area [%]	Selectivity	Res. HW
1	UNKNOWN	4.42	914.1	201.3	47.379	0.00	0.00
2	UNKNOWN	4.98	915.1	223.6	52.621	1.13	1.43
Total			1829.2	425.0	100.000		



Index	Name	Time [Min]	Height [µV]	Area [µV.Min]	Area [%]	Selectivity	Res. HW
1	UNKNOWN	4.42	1259.5	325.2	94.978	0.00	0.00
2	UNKNOWN	4.97	80.3	17.2	5.022	1.13	1.36
Total			1339.8	342.4	100.000		

(*R*)-3-Allyl-3-(4-(*tert*-butyl)phenyl)dihydrofuran-2(3*H*)-one (I.16c)



I.16c

$C_{17}H_{22}O_2$

MW = 258.36 g/mol

I.16c was synthesized according to the method aforementioned from allyl (3-(4-(*tert*-butyl)phenyl)-4,5-dihydrofuran-2-yl) carbonate **I.14c** (31 mg, 0.1 mmol, 1.0 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/EtOAc = 95:5 to 9:1) as a colorless oil (26 mg, 98%).

R_f: 0.28 (PE/EtOAc = 9:1)

$[\alpha]^{20}_{D}$ = +30.2 (*c* 1.23, $CHCl_3$)

ee = 71% (determined by SFC)

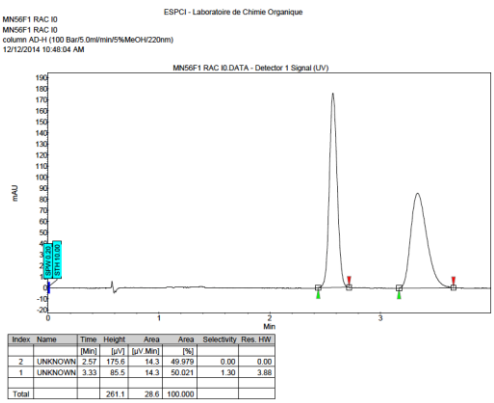
SFC: AD-H column, Pressure = 100 bar, eluent = sc CO_2/MeOH = 95:5, Flow rate = 5 mL/min, detection wavelength = 220 nm. t_R = 2.58 min (minor) and t_R = 3.38 min (major).

IR (ATR): 2961, 2925, 2853, 1768, 1640, 1512, 1461, 1370, 1216, 1165, 1119, 1026, 923, 832 cm^{-1}.

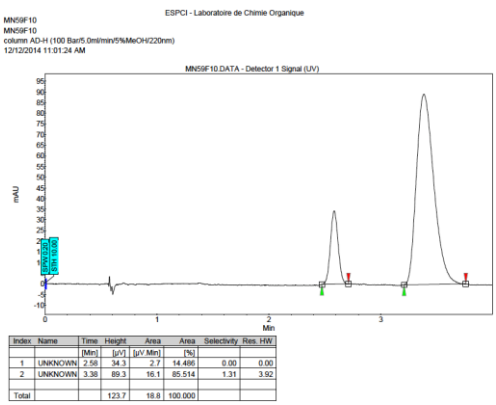
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (s, 4H, H_{Ar}), 5.65 (m, 1H, H_{12}), 5.16-5.08 (m, 2H, H_{13}), 4.30 (ddd, *J* = 9.0, 8.0, 3.2 Hz, 1H, H_2), 4.12 (ddd, *J* = 9.5, 8.9, 6.5 Hz, 1H, $H_{2'}$), 2.67 (m, 2H, H_{11}), 2.61 (ddd, *J* = 13.1, 6.5, 3.1 Hz, 1H, H_3), 2.52 (ddd, *J* = 13.1, 9.5, 8.1 Hz, 1H, $H_{3'}$), 1.30 (s, 9H, H_{10}).

^{13}C NMR (100 MHz, $CDCl_3$): δ 179.0 (s, C_1), 150.6 (s, C_8), 136.0 (s, C_5), 133.3 (d, C_{12}), 126.1 (d, 2C, C_6 or C_7), 125.9 (d, 2C, C_6 or C_7), 119.5 (t, C_{13}), 65.4 (t, C_2), 50.7 (s, C_4), 43.5 (t, C_{11}), 34.6 (s, C_9), 33.4 (t, C_3), 31.4 (q, 3C, C_{10}).

HRMS (ESI) *m/z*: calcd for $C_{17}H_{22}O_2Na$ $[M+Na]^+$: 281.1512, found: 281.1512.

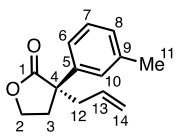


Index	Name	Time	Height	Area	Area	Selectivity	Res. HW
		[Min]	[µV]	[µV.Min]	[%]		
2	UNKNOWN	2.57	175.6	14.3	49.979	0.00	0.00
1	UNKNOWN	3.33	85.5	14.3	50.021	1.30	3.88
Total			261.1	28.6	100.000		



Index	Name	Time	Height	Area	Area	Selectivity	Res. HW
		[Min]	[µV]	[µV.Min]	[%]		
1	UNKNOWN	2.58	34.3	2.7	14.486	0.00	0.00
2	UNKNOWN	3.38	89.3	16.1	85.514	1.31	3.92
Total			123.7	18.8	100.000		

(*R*)-3-Allyl-3-(*m*-tolyl)dihydrofuran-2(3*H*)-one (I.16d)



I.16d

$C_{14}H_{16}O_2$

MW = 216.28 g/mol

I.16d was synthesized according to the method aforementioned from allyl (3-(*m*-tolyl)-4,5-dihydrofuran-2-yl) carbonate **I.14d** (8 mg, 0.03 mmol, 1.0 equiv). The titled compound was

obtained after flash column chromatography on silica gel (PE/EtOAc = from 95:5 to 9:1) as a colorless oil (5.2 mg, 78%).

R_f: 0.37 (9:1 PE/EtOAc)

$[\alpha]^{20}_{D}$ = +57.0 (*c* 0.12, $CHCl_3$)

ee = 70% (determined by SFC)

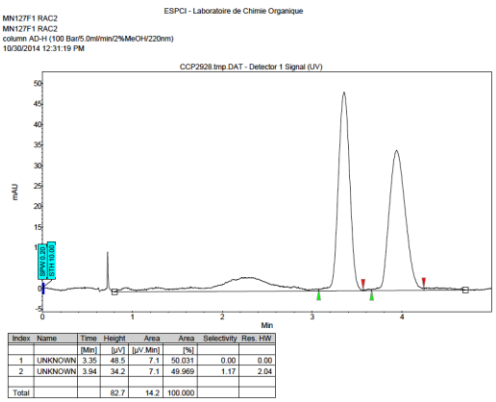
SFC: AD-H column, Pressure = 100 bar, eluent = sc CO_2/MeOH = 98:2, Flow rate = 5 mL/min, detection wavelength = 220 nm. t_R = 3.36 min (minor) and t_R = 3.97 min (major).

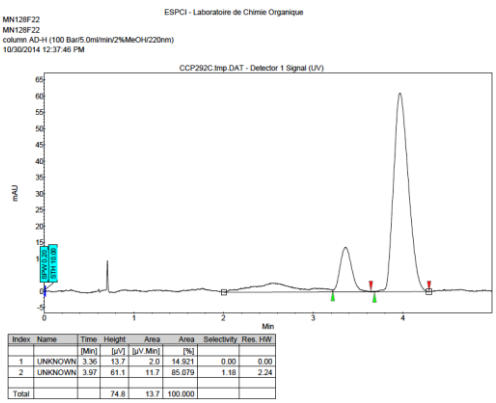
IR (ATR): 2917, 2925, 1768, 1640, 1606, 1488, 1372, 1213, 1173, 1026, 923, 787, 705, 670 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.20 (m, 3H, H_{Ar}), 7.11 (m, 1H, H_{Ar}), 5.66 (m, 1H, H_{13}), 5.16-5.08 (m, 2H, H_{14}), 4.30 (ddd, *J* = 9.0, 8.0, 3.0 Hz, 1H, H_2), 4.10 (ddd, *J* = 9.6, 8.9, 6.4 Hz, 1H, $H_{2'}$), 2.71-2.47 (m, 4H, H_{12} and H_3), 2.36 (s, 3H, H_{11}).

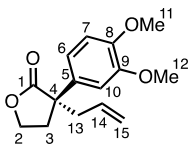
^{13}C NMR (100 MHz, $CDCl_3$): δ 178.9 (s, C_1), 139.1 (s, C_5 or C_9), 138.7 (s, C_5 or C_9), 133.2 (d, C_{13}), 128.8 (d, C_{Ar}), 128.5 (d, C_{Ar}), 127.2 (d, C_{Ar}), 123.4 (d, C_{Ar}), 119.5 (t, C_{14}), 65.4 (t, C_2), 51.1 (s, C_4), 43.5 (t, C_{12}), 33.6 (t, C_3), 21.8 (q, C_{11}).

HRMS (ESI) *m/z*: calcd for $C_{14}H_{16}O_2Na$ $[M+Na]^+$: 239.1043, found: 239.1041.





(*R*)-3-Allyl-3-(3,4-dimethoxyphenyl)dihydrofuran-2(3*H*)-one (I.16e)



I.16e

$C_{15}H_{18}O_4$
MW = 262.31 g/mol

I.16e was synthesized according to the method aforementioned from allyl (3-(3,4-dimethoxyphenyl)-4,5-dihydrofuran-2-yl) carbonate **I.14e** (19 mg, 0.08 mmol, 1.0 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/EtOAc = 9:1 to 8:2) as a colorless oil (19 mg, 95%).

R$_f$: 0.20 (PE/EtOAc = 8:2)

[α]^{20} $_D$ = +30.0 (*c* 0.48, $CHCl_3$)

ee = 48% (determined by SFC)

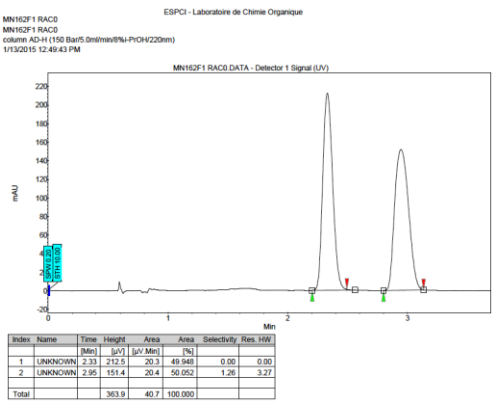
SFC: AD-H column, Pressure = 150 bar, eluent = sc CO_2/*i*-PrOH = 92:8, Flow rate = 5 mL/min, detection wavelength = 220 nm. t_R = 2.35 min (major) and t_R = 2.91 min (minor).

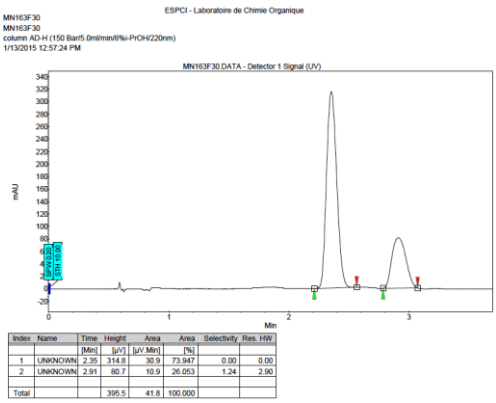
IR (ATR): 2923, 2853, 1768, 1604, 1588, 1513, 1412, 1373, 1227, 1165, 1030, 926, 867, 767, 688 cm^{-1}.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ 7.05 (d, *J* = 2.3 Hz, 1H, H_{10}), 6.93 (dd, *J* = 8.4, 2.3 Hz, 1H, H_6), 6.83 (d, *J* = 8.4 Hz, 1H, H_7), 5.64 (m, 1H, H_{14}), 5.14-5.07 (m, 2H, H_{15}), 4.31 (ddd, *J* = 8.9, 8.0, 3.1 Hz, 1H, H_2), 4.13 (ddd, *J* = 9.4, 8.9, 6.4 Hz, 1H, $H_{2'}$), 3.89 (s, 3H, H_{11} or H_{12}), 3.88 (s, 3H, H_{11} or H_{12}), 2.67-2.57 (m, 3H, H_{13} and H_3), 2.50 (ddd, *J* = 13.1, 9.4, 8.0 Hz, 1H, $H_{3'}$).

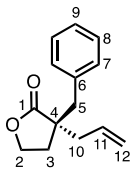
^{13}**C NMR** (100 MHz, $CDCl_3$): δ 179.1 (s, C_1), 149.3 (s, C_8 or C_9), 148.6 (s, C_8 or C_9), 133.1 (d, C_{14}), 131.2 (s, C_5), 119.5 (t, C_{15}), 118.5 (d, C_6), 111.0 (d, C_{10}), 110.0 (d, C_7), 65.4 (t, C_2), 56.1 (q, C_{11} or C_{12}), 56.0 (q, C_{11} or C_{12}), 50.6 (s, C_4), 43.8 (t, C_{13}), 33.5 (t, C_3).

MS *m/z* (relative intensity): 262 ($M^{+\cdot}$,21), 221 (100), 175 (4), 163 (17), 146 (5), 131 (3), 115 (4), 103 (3),91 (5), 77 (5), 65 (3), 51 (3).





(*S*)-3-Allyl-3-benzyldihydrofuran-2(3*H*)-one (I.16f)



I.16f

$C_{14}H_{16}O_2$
MW = 216.28 g/mol

I.16f was synthesized according to the method aforementioned from allyl (3-benzyl-4,5-dihydrofuran-2-yl) carbonate **I.14h** (26 mg, 0.1 mmol, 1.0 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/EtOAc = 9:1 to8:2) as a colorless oil (19 mg, 87%).

R$_f$: 0.33 (PE/EtOAc = 9:1)

[α]^{20} **D** = +1.88 (*c* 0.43, $CHCl_3$)

ee = 55% (determined by SFC)

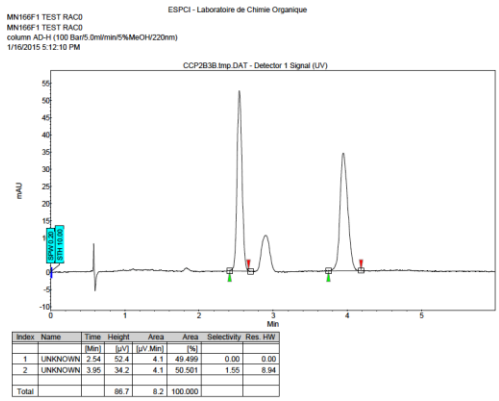
SFC: AD-H column, Pressure = 100 bar, eluent = sc CO_2/MeOH = 95:5, Flow rate = 5 mL/min, detection wavelength = 220 nm. t_R = 2.53 min (major) and t_R = 3.92 min (minor).

IR (ATR): 2918, 2850, 1768, 1640, 1495, 1378, 1216, 1170, 1029, 921, 772, 702 cm^{-1}.

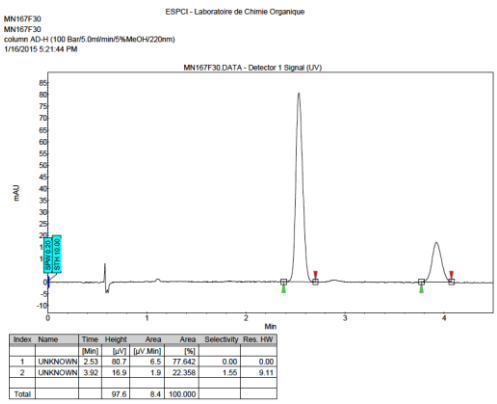
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.23 (m, 3H, H_8 and H_9), 7.23-7.17 (m, 2H, H_7), 5.79 (m, 1H, H_{11}), 5.23-5.15 (m, 2H, H_{12}), 4.02 (ddd, *J* = 8.9, 7.8, 6.2 Hz, 1H, H_2), 3.46 (ddd, *J* = 9.0, 7.8, 6.5 Hz, 1H, $H_{2'}$), 3.07 (d, *J* = 13.4 Hz, 1H, H_5), 2.74 (d, *J* = 13.5 Hz, 1H, $H_{5'}$), 2.51 (ddt, *J* = 13.8, 6.4, 1.4 Hz, 1H, H_{10}), 2.33 (ddt, *J* = 13.8, 8.4, 1.0 Hz, 1H, $H_{10'}$), 2.19-2.12 (m, 2H, H_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 181.0 (s, C_1), 136.6 (s, C_6), 132.8 (d, C_{11}), 130.1 (d, 2C, C_7), 128.7 (d, 2C, C_8), 127.3 (d, C_9), 120.0 (t, C_{12}), 65.5 (t, C_2), 48.1 (s, C_4), 42.9 (t, C_5), 42.2 (t, C_{10}), 29.9 (t, C_3).

MS *m/z* (relative intensity): 216 ($M^{+\cdot}$,2), 198 (2), 188 (15), 175 (7), 156 (3), 143 (7), 129 (9), 125 (17), 115 (6), 91 (100), 79 (5), 77 (3), 65 (11), 53 (3).

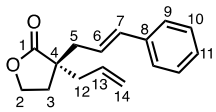


Index	Name	Time	Height	Area	Area	Selectivity	Res. HW
		[Min]	[µV]	[µV.Min]	[%]		
1	UNKNOWN	2.54	52.4	4.1	49.499	0.00	0.00
2	UNKNOWN	3.95	34.2	4.1	50.501	1.55	8.94
Total			86.7	8.2	100.000		



Index	Name	Time	Height	Area	Area	Selectivity	Res. HW
		[Min]	[µV]	[µV.Min]	[%]		
1	UNKNOWN	2.53	80.7	6.5	77.642	0.00	0.00
2	UNKNOWN	3.92	16.9	1.9	22.358	1.55	9.11
Total			97.6	8.4	100.000		

(*S*)-3-Allyl-3-cinnamyldihydrofuran-2(3*H*)-one (I.16g)



I.16g

$C_{16}H_{18}O_2$
MW = 242.32 g/mol

I.16g was synthesized according to the method aforementioned from allyl (3-cinnamyl-4,5-dihydrofuran-2-yl) carbonate **I.14i** (29 mg, 0.1 mmol, 1.0 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/EtOAc = 9:1) as a colorless oil (18 mg, 75%).

R$_f$: 0.25 (PE/EtOAc = 9:1)

[α]^{20} $_D$ = +1.65 (*c* 0.43, $CHCl_3$)

ee = 43% (determined by SFC)

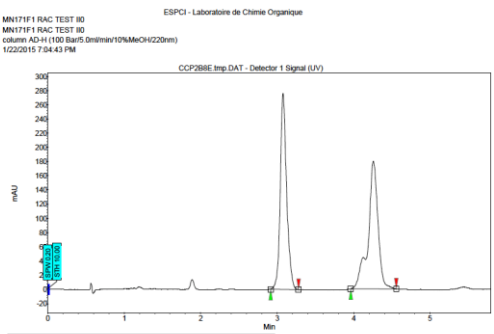
SFC: AD-H column, Pressure = 100 bar, eluent = sc CO_2/MeOH = 90:10, Flow rate = 5 mL/min, detection wavelength = 220 nm. t_R = 3.08 min (major) and t_R = 4.29 min (minor).

IR (ATR): 2918, 1768, 1640, 1598, 1494, 1449, 1437, 1376, 1214, 1174, 1028, 969, 922, 747 cm^{-1}.

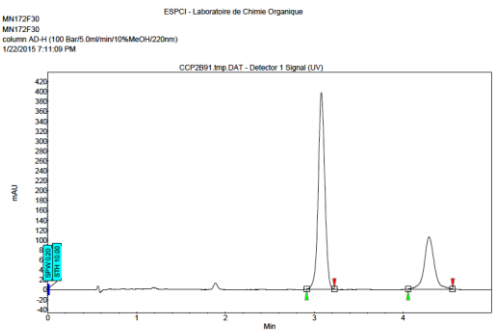
^{1}**H NMR** (400 MHz, $CDCl_3$): δ 7.31-7.10 (m, 5H, H_{Ar}), 6.41 (dd, *J* = 15.7, 1.5 Hz, 1H, H_7), 6.14 (m, 1H, H_6), 5.70 (m, 1H, H_{13}), 5.14-5.05 (m, 2H, H_{14}), 4.12 (td, *J* = 8.5, 1.8 Hz, 2H, H_2), 2.48 (m, 1H, H_5), 2.42-2.31 (m, 2H, H_{12}), 2.26 (m, 1H, $H_{5'}$), 2.21 (td, *J* = 8.7, 3.5 Hz, 2H, H_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 180.7 (s, C_1), 137.0 (s, C_8), 134.6 (d, C_7), 132.7 (d, C_{13}), 128.7 (d, 2C, C_{10}), 127.7 (d, C_{11}), 126.4 (d, 2C, C_9), 124.1 (d, C_6), 119.9 (t, C_{14}), 65.5 (t, C_2), 46.7 (s, C_4), 41.2 (t, C_5), 40.3 (t, C_{12}), 30.7 (t, C_3).

MS *m/z* (relative intensity): 242 ($M^{+\cdot}$,8), 214 (3), 201 (11), 169 (3), 155 (6), 144 (14), 129 (12), 117 (100), 104 (36), 91 (28), 77 (6), 65 (5), 50 (2).



Index	Name	Time	Height	Area	Area	Selectivity	Res. HW
		[Min]	[µV]	[µV.Min]	[%]		
1	UNKNOWN	3.08	276.0	26.6	49.600	0.00	0.00
2	UNKNOWN	4.26	179.9	27.0	50.400	1.38	7.01
Total			455.9	53.6	100.000		

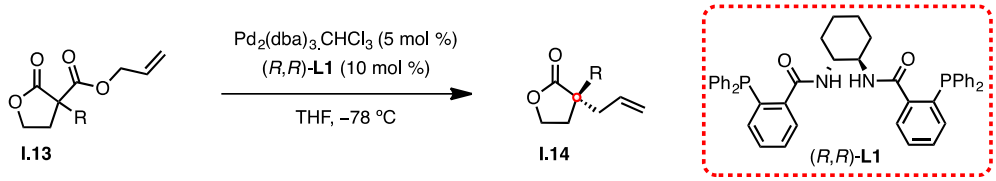


Index	Name	Time	Height	Area	Area	Selectivity	Res. HW
		[Min]	[µV]	[µV.Min]	[%]		
1	UNKNOWN	3.08	396.9	34.1	71.420	0.00	0.00
2	UNKNOWN	4.29	105.5	13.6	28.580	1.39	7.55
Total			502.4	47.7	100.000		

6. General Procedures for the Pd-AAA of allyl carboxylates

synthesis of α-allyl-α-aryl butyrolactones (I.16h-i)

(Representative procedure)



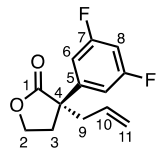
To a solution of $Pd_2(dba)_3.CHCl_3$ (0.01 mmol, 0.05 equiv) in THF (1 mL) at room temperature was added (*R*,*R*)-DACH phenyl Trost ligand (0.02 mmol, 0.1 equiv) and the mixture was stirred for 30 min. This solution was then cooled to −78 °C and transferred via cannula to a flask containing a cooled solution (−78 °C) of allyl carboxylate (0.2 mmol, 1 equiv) in THF (1 mL). The reaction mixture was then stirred at the same temperature until complete consumption of the starting material (confirmed by TLC). A saturated solution of brine was then added and the aqueous phase was extracted with EtOAc (3 x 2 mL). The combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, filtered and

evaporated under reduced pressure to afford a crude residue, which was purified by flash column chromatography on silica gel to afford the corresponding allylated butyrolactone.

General procedure for the synthesis of racemic compounds
(Representative procedure)

To a solution of allyl carboxylate (0.1 mmol, 1 equiv) in THF (1 mL) at room temperature was added $Pd(PPh_3)_4$ (0.005 mmol, 0.05 equiv). The reaction mixture was then stirred at the same temperature for 10 min as the complete consumption of the starting material (confirmed by TLC). The solvent was then evaporated under reduced pressure to afford a crude residue, which was purified following the same procedure described for the corresponding enantioenriched compound.

(*R*)-3-allyl-3-(3,5-difluorophenyl)dihydrofuran-2(3*H*)-one (I.16h)



I.16h
$C_{13}H_{12}F_2O_2$
MW = 238.23 g/mol

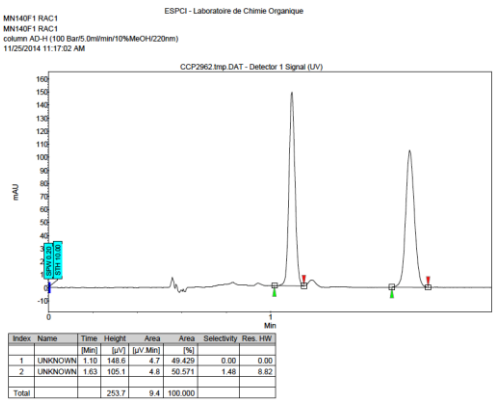
I.16h was synthesized according to the method aforementioned from allyl 3-(3,5-difluorophenyl)-2-oxotetrahydrofuran-3-carboxylate **I.15f** (19 mg, 0.067 mmol, 1.0 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/EtOAc = 9:1) as colorless oil (13 mg, 81%).

Rf: 0.52 (PE/EtOAc = 8:2)
$[\alpha]^{20}_{D}$ = +54.6 (*c* 0.23, $CHCl_3$)
ee = 92% (determined by SFC)
SFC: AD-H column, Pressure = 100 bar, eluent = sc CO_2/MeOH = 90:10, Flow rate = 5 mL/min, detection wavelength = 220 nm. t_R = 1.09 min (minor) and t_R = 1.62 min (major).
IR (ATR): 3084, 2923, 2854, 1765, 1624, 1436, 1374, 1321, 1175, 1080, 1028, 928, 857, 693 cm^{-1}.

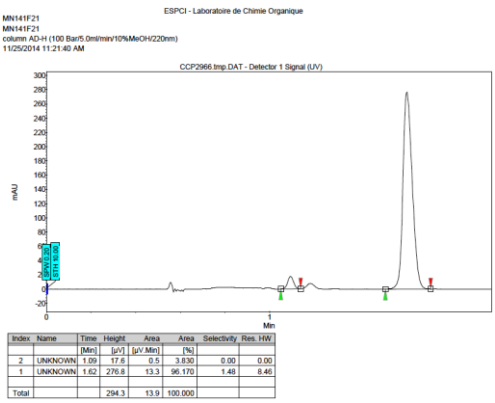
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09-6.97 (m, 2H, H_6), 6.81-6.70 (m, 1H, H_8), 5.68-5.52 (m, 1H, H_{10}), 5.19-5.04 (m, 2H, H_{11}), 4.34 (m, 1H, H_2), 4.17 (m, 1H, $H_{2'}$), 2.68-2.60 (m, 2H, H_9), 2.60-2.48 (m, 2H, H_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 177.8 (s, C_1), 163.3 (s, $^{1}J_{C\text{-}F}$ = 248, 13 Hz, 2C, C_7), 143.2 (s, C_5), 132.0 (d, C_{10}), 120.5 (t, C_{11}), 110.9 (d, $^{2}J_{C\text{-}F}$ = 25.0, 7.3 Hz, 2C, C_6), 103.4 (d, $^{2}J_{C\text{-}F}$ = 25.1 Hz, C_8), 65.3 (t, C_2), 50.8 (s, C_4), 43.6 (t, C_9), 33.3 (t, C_3).

HRMS (ESI) *m/z*: calcd for $C_{13}H_{12}F_2O_2Na$ $[M+Na]^+$: 261.0698, found: 261.0700.

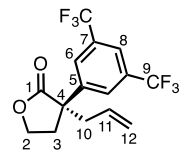


Index	Name	Time [Min]	Height [µV]	Area [µV.Min]	Area [%]	Selectivity	Res. HW
1	UNKNOWN	1.10	148.6	4.7	49.429	0.00	0.00
2	UNKNOWN	1.63	105.1	4.8	50.571	1.48	8.82
Total			253.7	9.4	100.000		



Index	Name	Time [Min]	Height [µV]	Area [µV.Min]	Area [%]	Selectivity	Res. HW
2	UNKNOWN	1.09	17.6	0.5	3.830	0.00	0.00
1	UNKNOWN	1.62	276.8	13.3	96.170	1.48	8.46
Total			294.3	13.9	100.000		

(*R*)-3-allyl-3-(3,5-(trifluoromethyl)phenyl)dihydrofuran-2(3*H*)-one (I.16i)



I.16i

$C_{15}H_{12}F_6O_2$

MW = 338.25 g/mol

I.16i was synthesized according to the method aforementioned from allyl 3-(3,5-difluorophenyl)-2-oxotetrahydrofuran-3-carboxylate **I.15g** (22 mg, 0.058 mmol, 1.0 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/EtOAc = 9:1) as colorless oil (18 mg, 89%).

R$_f$: 0.51 (PE/EtOAc = 8:2)

[α]^{20} D = +54.2 (*c* 0.22, $CHCl_3$)

ee = Not determined

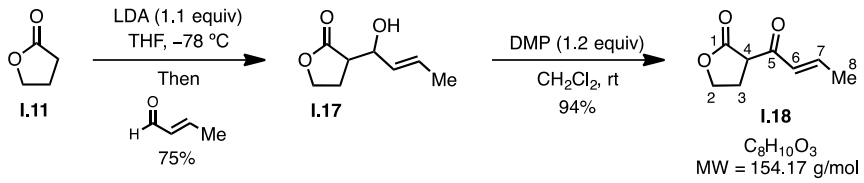
SFC: The enantiomers could not be separated using any SFC conditions.

IR (ATR): 2922, 1768, 1471, 1374, 1277, 1169, 1129, 1030, 928, 897, 846, 706, 683 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99-7.94 (m, 2H, H_6), 7.84 (m, 1H, H_8), 5.59 (m, 1H, H_{11}), 5.18 (ddt, J = 10.1, 1.6, 0.8 Hz, 2H, H_{12}), 5.13 (dq, J = 16.9, 1.4 Hz, 1H, $H_{12'}$), 4.40 (ddd, J = 9.3, 6.9, 6.2 Hz, 1H, H_2), 4.23 (dt, J = 9.3, 7.2 Hz, 1H, $H_{2'}$), 2.77-2.60 (m, 4H, H_3 and H_9).
^{13}C NMR (100 MHz, $CDCl_3$): δ 177.4 (s, C_1), 142.3 (s, C_5), 132.2 (s, $^2J_{C\text{-}F}$ = 33.4 Hz, 2C, C_7), 131.4 (d, C_{11}), 127.0 (d, $^3J_{C\text{-}F}$ = 3.6 Hz, 2C, C_6), 123.3 (s, $^1J_{C\text{-}F}$ = 273 Hz, 2C, C_9), 121.9 (d, C_8), 121.2 (t, C_{12}), 65.2 (t, C_2), 50.8 (s, C_4), 43.8 (t, C_{10}), 33.2 (t, C_3).
HRMS (ESI) *m/z*: calcd for $C_{15}H_{12}F_6O_2H$ $[M+H]^+$: 339.0814, found: 339.0818.

7. Synthesis of α-acyl butyrolactones

(*E*)-3-(But-2-enoyl)dihydrofuran-2(3*H*)-one (I.18)[67a]



At −78 °C, *n*-BuLi (5.92 mL, 2.16 M in hexanes, 12.8 mmol, 1.1 equiv) was added to a solution of diisopropylamine (1.08 mL, 12.8 mmol, 1.1 equiv) in THF (25 mL) and the reaction mixture was stirred for 1 h. Then, a solution of γ-butyrolactone (1.00 g, 11.6 mmol, 1.0 equiv) in THF (2.5 mL) was added dropwise within 10 min and after stirring 1 h, a solution of crotonaldehyde (1.04 mL, 12.8 mmol, 1.1 equiv) in THF (5 mL) was added dropwise during 60 min. The temperature was raised to rt within 30 min. The mixture was cooled to 0 °C and the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl and CH_2Cl_2 (15 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (4 x 10 mL). The combined organic extracts were washed with a saturated aqueous brine solution (10 mL), dried over $MgSO_4$ and concentrated under vacuum. The crude residue was finally purified by flash column chromatography on silica gel (PE/EtOAc = 75:25) to afford **I.17** (1.35 g, 75%) as a mixture of two diastereomeres (*syn*:*anti* = 50:50) as a viscous oil. This mixture was engaged without purification in the oxidation step. To a solution of alcohol **I.17** (350 mg, 2.24 mmol, 1.0 equiv) in CH_2Cl_2 (18 mL) at rt was added Dess-Martin periodinane (1.175 g, 2.69 mmol, 1.2 equiv) in one portion. The reaction mixture was stirred for 24 h at rt. Then the solvent was removed under vacuum and the

residue was purified by flash chromatography on silica gel (PE/EtOAc = 7:3) to give **I.18** (323 mg, 94%) as viscous oil.

R_f: 0.36 (PE/EtOAc = 7:3)

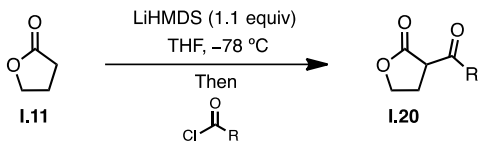
IR (ATR)**:** 2918, 2360, 1765, 1693, 1656, 1629, 1442, 1375, 1340, 1294, 1227, 1156, 1016, 966, 910 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) mixture of *enol*-**I.18**/*keto*-**I.18** = 1:2: δ 10.78 (d, *J* = 1.7 Hz, 0.33H, (OH)H_5 of *enol*-**I.18**), 7.07 (dq, *J* = 15.7, 6.9 Hz, 0.66H, H_7 of *keto*-**I.18**), 6.71 (m, 0.33H, H_7 of *enol*-**I.18**), 6.47-6.39 (dq, *J* = 15.8, 1.5 Hz, 0.66H, H_6 of *keto*-**I.18**), 5.89 (dt, *J* = 15.5, 1.6 Hz, 0.33H, H_6 of *enol*-**I.18**), 4.43-4.29 (m, 1.98H, H_2 of *enol*-**I.18** and H_2 of *keto*-**I.18**), 3.89 (dd, *J* = 9.2, 5.8 Hz, 0.66H, H_4 of *keto*-**I.18**), 2.93 (t, *J* = 7.8 Hz, 0.66H, H_3 of *enol*-**I.18**), 2.76 (m, 0.66H, H_3 of *keto*-**I.18**), 2.35 (m, 0.66H, $H_{3'}$ of *keto*-**I.18**), 1.96 (ddd, *J* = 6.9, 1.7, 0.5 Hz, 1.98H, H_8 of *keto*-**I.18**), 1.91 (ddt, *J* = 7.0, 1.6, 0.7 Hz, 0.99H, H_8 of *enol*-**I.18**).

^{13}C NMR (400 MHz, $CDCl_3$) mixture of *enol*-**I.18**/*keto*-**I.18** = 1:2: δ 191.4 (s, C_5 of *keto*-**I.18**), 177.1 (s, C_5 of *enol*-**I.18**), 173.2 (s, C_1 of *keto*-**I.18**), 161.9 (s, C_1 of *enol*-**I.18**), 147.0 (d, C_6 of *keto*-**I.18**), 138.0 (d, C_6 of *enol*-**I.18**), 129.8 (d, C_7 of *keto*-**I.18**), 123.2 (d, C_7 of *enol*-**I.18**), 94.3 (s, C_4 of *enol*-**I.18**), 67.8 (t, C_2 of *keto*-**I.18**), 66.9 (t, C_2 of *enol*-**I.18**), 50.2 (d, C_4 of *keto*-**I.18**), 24.7 (t, C_3 of *keto*-**I.18**), 24.0 (t, C_3 of *enol*-**I.18**), 18.8 (q, C_8 of *enol*-**I.18**), 18.7 (q, C_8 of *keto*-**I.18**).

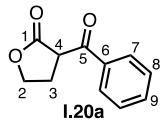
MS *m/z* (relative intensity): 154 ($M^{+\cdot}$,3), 139 (3), 126 (5), 70 (5), 69 (100), 55 (3).

General procedures for the synthesis of α-acylbutyrolactones (I.20a-c)[68]



To a solution of γ-butyrolactone (1.00 g, 11.6 mmol, 1.0 equiv) in THF (103 mL) at −78 °C was added LiHMDS (12.8 mL, 1.0 M in THF, 12.8 mmol, 1.1 equiv). After 1 h at −78 °C, benzoyl chloride (11.6 mmol, 1.0 equiv) was added over a period of 30 min. After 15 min at −78 °C, the reaction mixture was diluted with HCl (1 M) and then extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel to afford the desired lactone.

α-Benzoyl-γ-butyrolactone (I.20a)



I.20a

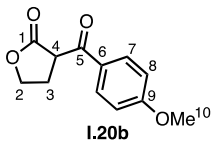
$C_{11}H_{10}O_3$
MW = 190.20 g/mol

I.20a was synthesized according to the method aforementioned from γ-butyrolactone (1.00 g, 11.6 mmol, 1.0 equiv) and benzoyl chloride (1.35 mL, 11.6 mmol, 1.0 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/EtOAc = 7:3 to 6:4) as a colorless oil (862 mg, 39%).

Note: Only the ketone is reported.

R_f: 0.26 (PE/EtOAc = 7:3)
IR (ATR): 3063, 2981, 2918, 1760, 1680, 1596, 1579, 1448, 1374, 1343, 1294, 1243, 1213, 1151, 1070, 1019 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$) mixture of *enol*-**I.20a**/*keto*-**I.20a** = 1:18: δ 8.13-8.05 (d_{app}, J = 8.1 Hz, 2H, H_7), 7.63 (m, 1H, H_9), 7.57-7.48 (t_{app}, J = 7.5 Hz, 2H, H_8), 4.62-4.49 (m, 2H, H_2), 4.48-4.39 (m, 1H, H_4), 2.87 (m, 1H, H_3), 2.52 (m, 1H, $H_{3'}$).
^{13}C NMR (100 MHz, $CDCl_3$) mixture of *enol*-**I.20a**/*keto*-**I.20a** = 1:18: δ 193.1 (s, C_5), 172.9 (s, C_1), 135.4 (s, C_6), 134.2 (d, C_9), 129.6 (d, 2C, C_8), 128.9 (d, 2C, C_7), 68.0 (t, C_2), 48.2 (d, C_4), 26.2 (t, C_3).
MS *m/z* (relative intensity): 190 ($M^{+\cdot}$,4), 162 (6), 133 (2), 115 (1), 105 (100), 85 (2), 77 (45), 51 (13).

α-(4-Methoxybenzoyl)-γ-butyrolactone (I.20b)[80]



I.20b

$C_{12}H_{12}O_4$
MW = 220.22 g/mol

80 Yamamoto, Y.; Yamada, K.-i.; Tomioka, K. *Tetrahedron Lett.* **2004**, *45*, 795.

I.20b was synthesized according to the method aforementioned from γ-butyrolactone (1.00 g, 11.6 mmol, 1.0 equiv) and 4-methoxybenzoyl chloride (1.57 mL, 11.6 mmol, 1.0 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/EtOAc = 7:3) as a colorless oil (1.081 g, 42%).

Note: Only the ketone is reported.

R_f: 0.17 (PE/EtOAc = 7:3)

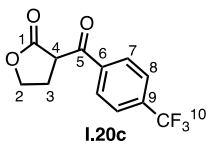
IR (ATR): 2920, 1760, 1668, 1597, 1573, 1510, 1458, 1421, 1375, 1249, 1149, 1021, 844 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) mixture of *enol*-**I.20b**/*keto*-**I.20b** = 1:33: δ 8.09-8.00 (m, 2H, H_7), 6.96 (dq, *J* = 9.1, 2.4, 1.9 Hz, 2H, H_8), 4.55-4.45 (m, 2H, H_2), 4.41 (td, *J* = 8.4, 5.3 Hz, 1H, H_4), 3.87 (s, 3H, H_{10}), 2.85 (ddt, *J* = 13.1, 7.8, 5.3 Hz, 1H, H_3), 2.48 (m, 1H, $H_{3'}$).

^{13}C NMR (100 MHz, $CDCl_3$) mixture of *enol*-**I.20b**/*keto*-**I.20b** = 1:33: δ 193.1 (s, C_5), 173.3 (s, C_1), 164.4 (s, C_9), 132.5 (d, 2C, C_7), 128.3 (s, C_6), 114.1 (d, 2C, C_8), 68.0 (t, C_2), 55.7 (q, C_{10}), 47.8 (d, C_4), 26.1 (t, C_3).

MS *m/z* (relative intensity): 220 ($M^{+\cdot}$,16), 192 (3), 163 (2), 135 (100), 107 (17), 92 (20), 77 (22), 64 (7), 50 (3).

α-(4-Bis(trifluoromethyl)benzoyl)-γ-butyrolactone (I.20c)



I.20c

$C_{12}H_9F_3O_3$
MW = 258.20 g/mol

I.20c was synthesized according to the method aforementioned from γ-butyrolactone (1.00 g, 11.6 mmol, 1.0 equiv) and 4-bis(trifluoromethyl)benzoyl chloride (1.73 mL ,11.6 mmol, 1.0 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/EtOAc = 8:2 to 7:3) as a colorless oil (545 mg, 18%).

Note: Only the ketone is reported.

R_f: 0.18 (PE/EtOAc = 8:2)

IR (ATR): 2924, 2854, 1764, 1692, 1579, 1410, 1377, 1327, 1164, 1113, 1068, 1026 cm^{-1}.

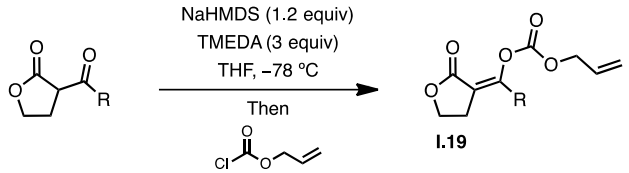
^{1}H NMR (400 MHz, $CDCl_3$) mixture of *enol*-**I.20c**/*keto*-**I.20c** = 1:100: δ 8.20 (d_{app}, J = 7.7 Hz, 2H, H_7), 7.81-7.74 (m, 2H, H_8), 4.62-4.48 (m, 2H, H_4 and H_2), 4.44 (ddd, J = 8.8, 8.0, 5.8 Hz, 1H, $H_{2'}$), 2.92 (ddt, J = 13.1, 8.0, 5.9 Hz, 1H, H_3), 2.52 (m, 1H, $H_{3'}$).

^{13}C NMR (100 MHz, $CDCl_3$) mixture of *enol*-**I.20c**/*keto*-**I.20c** = 1:100: δ 192.1 (s, C_5), 172.4 (s, C_1), 138.0 (s, C_6), 135.6 (s, $^2J_{C\text{-}F}$ = 32.2 Hz, C_9), 130.0 (d, 2C, C_7), 125.9 (d, $^3J_{C\text{-}F}$ = 3.8 Hz, 2C, C_8), 123.5 (s, $^1J_{C\text{-}F}$ = 272 Hz, C_{10}), 68.0 (t, C_2), 48.6 (d, C_4), 26.7 (t, C_3).

HRMS (ESI) *m/z*: calcd for $C_{12}H_9F_3O_3Na$ $[M+Na]^+$: 281.0396, found: 281.0399.

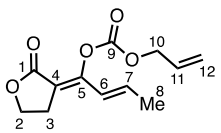
8. Synthesis of exocyclic allyl enol carbonates

8.1. General procedures for the synthesis of allyl enol carbonates (I.19) (Representative procedure)



To a solution of NaHMDS (1.20 mL, 1.0 M in THF, 1.2 mmol, 1.2 equiv) in THF (9 mL) at −78 °C was added TMEDA (0.45 mL, 3.0 mmol, 3.0 equiv). A solution of lactone (1.0 mmol, 1.0 equiv) in THF (1 mL) was added dropwise. After 1 h at −78 °C, allyl chloroformate (0.32 mL, 3.0 mmol, 3.0 equiv) was added, after 15 min, a saturated aqueous solution of NH_4Cl was then added and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and evaporated under reduced pressure to afford a crude residue, which was purified by flash column chromatography on silica gel to afford the corresponding allyl enol carbonate **I.19**.

Allyl ((1*Z*,2*E*)-1-(2-oxodihydrofuran-3(2*H*)-ylidene)but-2-en-1-yl) carbonate (I.19a)



I.19a

$C_{12}H_{14}O_5$
MW = 238.24 g/mol

I.19a was synthesized according to the method aforementioned from (*E*)-3-(but-2-enoyl)dihydrofuran-2(3*H*)-one **I.18** (300 mg, 1.95 mmol, 1.0 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/EtOAc = 9:1 to 8:2) as a colorless oil (171 mg, 37%).

R$_f$: 0.22 (PE/EtOAc = 8:2)

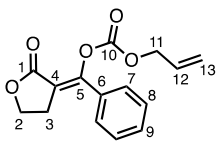
IR (ATR)**:** 2918, 1761, 1659, 1627, 1442, 1375, 1295, 1206, 1116, 1078, 1031, 958, 909, 774, 676 cm^{-1}.

^{1}**H NMR (**400 MHz, $CDCl_3$): δ 7.38-7.30 (m, 1H, H_6), 6.26 (m, 1H, H_7), 6.02-5.89 (m, 1H, H_{11}), 5.42-5.31 (m, 2H, H_{12}), 4.72 (dq, *J* = 5.8, 1.1 Hz, 2H, H_{10}), 4.35 (td, *J* = 7.5, 0.8 Hz, 2H, H_2), 2.94 (t, *J* = 7.5 Hz, 2H, H_3), 1.91 (ddt, *J* = 7.0, 2.1, 1.1 Hz, 3H, H_8).

^{13}**C NMR** (100 MHz, $CDCl_3$): δ 169.7 (s, C_1), 153.7 (s, C_9), 151.2 (s, C_5), 134.7 (d, C_7), 130.8 (d, C_{11}), 121.8 (d, C_6), 120.1 (t, C_{12}), 112.8 (s, C_4), 69.7 (t, C_{10}), 64.9 (t, C_2), 26.2 (t, C_3), 18.7 (q, C_8).

HRMS (ESI) *m/z*: calcd for $C_{12}H_{15}O_5$ $[M+H]^+$: 239.0914, found: 239.0914.

(*Z*)-Allyl ((2-oxodihydrofuran-3(2*H*)-ylidene)(phenyl)methyl) carbonate (I.19b)



I.19b
$C_{15}H_{14}O_5$
MW = 274.27 g/mol

I.19b was synthesized according to the method aforementioned from α-benzoyl-γ-butyrolactone **I.20a** (300 mg, 1.58 mmol, 1.0 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/EtOAc = 9:1 to 8:2) as a colorless oil (147 mg, 34%).

R$_f$: 0.26 (PE/EtOAc = 8:2)

IR (ATR): 2988, 2901, 1761, 1672, 1447, 1377, 1212, 1135, 1067, 976, 774, 746, 696 cm^{-1}.

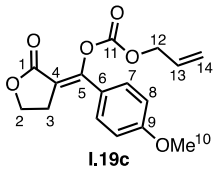
^{1}**H NMR** (400 MHz, $CDCl_3$) mixture of *(E)*-**I.19b**/*(Z)*-**I.19b** = 5:95: δ 7.63-7.57 (m, 2H, H_7), 7.42 (m, 3H, H_8 and H_9), 5.87 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 1H, H_{12}), 5.37-5.26 (m, 2H, H_{13}),

4.62 (dt, J = 5.8, 1.4 Hz, 2H, H_{11}), 4.40 (t_{app}, J = 7.6, 7.1 Hz, 2H, H_2), 3.13 (t, J = 7.4 Hz, 2H, H_3).

^{13}C NMR (100 MHz, $CDCl_3$) mixture of *(E)*-**I.19b**/*(Z)*-**I.19b** = 5:95: δ 168.5 (s, C_1), 155.7 (s, C_{10}), 151.3 (s, C_5), 131.2 (s, C_6), 130.9 (d, C_{12}), 130.7 (d, C_9), 129.2 (d, 2C, C_8), 128.1 (d, 2C, C_7), 120.0 (t, C_{13}), 114.8 (s, C_4), 69.7 (t, C_{11}), 64.6 (t, C_2), 27.2 (t, C_3).

HRMS (ESI) *m/z*: calcd for $C_{15}H_{14}O_5Na$ $[M+Na]^+$: 297.0733, found: 297.0731.

(*Z*)-Allyl ((4-methoxyphenyl)(2-oxodihydrofuran-3(2*H*)-ylidene)methyl) carbonate (I.19c)



I.19c
$C_{16}H_{16}O_6$
MW = 304.30 g/mol

I.19c was synthesized according to the method aforementioned from α-(4-methoxybenzoyl)-γ-butyrolactone **I.20b** (300 mg, 1.36 mmol, 1.0 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/EtOAc = 8:2 to 7:3) as a colorless oil (241 mg, 58%).

R$_f$: 0.26 (PE/EtOAc = 6:4)

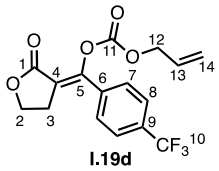
IR (ATR): 2934, 1752, 1650, 1604, 1512, 1442, 1365, 1231, 1214, 1117, 1082, 1031, 906, 725 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) mixture of *(E)*-**I.19c**/*(Z)*-**I.19c** = 4:96: δ 7.58-7.47 (m, 2H, H_7), 7.01-6.89 (m, 2H, H_8), 5.99 (m, 1H, H_{13}), 5.47-5.35 (m, 1H, H_{14}), 5.29 (m, 1H, $H_{14'}$), 4.73 (dq, J = 5.8, 1.2 Hz, 2H, H_{12}), 4.33 (t_{app}, J = 7.2 Hz, 2H, H_2), 3.84 (s, 3H, H_{10}), 3.24 (t_{app}, J = 7.2 Hz, 2H, H_3).

^{13}C NMR (100 MHz, $CDCl_3$) mixture of *(E)*-**I.19c**/*(Z)*-**I.19c** = 4:96: δ 168.7 (s, C_1), 161.6 (s, C_9), 152.2 (s, C_{11}), 151.7 (s, C_5), 131.3 (d, C_{13}), 129.5 (d, 2C, C_7), 125.6 (s, C_6), 119.3 (t, C_{14}), 114.3 (d, 2C, C_8), 111.8 (s, C_4), 69.6 (t, C_{12}), 64.9 (t, C_2), 55.6 (q, C_{10}), 28.6 (t, C_3).

HRMS (ESI) *m/z*: calcd for $C_{16}H_{16}O_6Na$ $[M+Na]^+$: 327.0839, found: 327.0838.

(*Z*)-allyl ((2-oxodihydrofuran-3(2*H*)-ylidene)(4-(trifluoromethyl)phenyl)methyl) carbonate (I.19d)



I.19d

$C_{16}H_{13}F_3O_5$
MW = 342.27 g/mol

I.19d was synthesized according to the method aforementioned from α-(4-bis(trifluoromethyl)benzoyl)-γ-butyrolactone **I.20c** (300 mg, 1.16 mmol, 1.0 equiv). The titled compound was obtained after flash column chromatography o silica gel (PE/EtOAc = 7:3 to 1:1) as a colorless oil (319 mg, 80%).

R$_f$: 0.55 (PE/EtOAc = 1:1)

IR (ATR): 2929, 1775, 1665, 1410, 1367, 1326, 1231, 1214, 1169, 1127, 1067, 1014, 850 cm^{-1}.

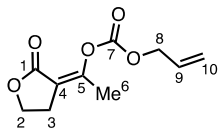
^{1}H NMR (400 MHz, $CDCl_3$) mixture of (*E*)-**I.19d**/(*Z*)-**I.19d** = 1:2: δ 7.75-7.64 (m, 3.96H, $H_{Ar\ of\ (E)\text{-}\mathbf{I.19d}}$ and $H_{Ar\ of\ (Z)\text{-}\mathbf{I.19d}}$), 5.99 (m, 0.66H, $H_{13\ of\ (Z)\text{-}\mathbf{I.19d}}$), 5.87 (m, 0.33H, $H_{13\ of\ (E)\text{-}\mathbf{I.19d}}$), 5.43 (dq, *J* = 17.2, 1.5 Hz, 0.66H, $H_{14\ of\ (E)\text{-}\mathbf{I.19d}}$), 5.39-5.28 (m, 1.32H, $H_{14\ of\ (Z)\text{-}\mathbf{I.19d}}$), 4.74 (dt, *J* = 5.8, 1.4 Hz, 1.32H, $H_{12\ of\ (Z)\text{-}\mathbf{I.19d}}$), 4.63 (dt, *J* = 5.9, 1.3 Hz, 0.66H, $H_{12\ of\ (E)\text{-}\mathbf{I.19d}}$), 4.43 (t, *J* = 7.3 Hz, 0.66H, $H_{2\ of\ (E)\text{-}\mathbf{I.19d}}$), 4.39 (t, *J* = 7.2 Hz, 1.32H, $H_{2\ of\ (Z)\text{-}\mathbf{I.19d}}$), 3.26 (t, *J* = 7.1 Hz, 1.32H, $H_{3\ of\ (Z)\text{-}\mathbf{I.19d}}$), 3.16 (t, *J* = 7.3 Hz, 0.66H, $H_{3\ of\ (E)\text{-}\mathbf{I.19d}}$).

^{13}C NMR (100 MHz, $CDCl_3$) mixture of (*E*)-**I.19d**/(*Z*)-**I.19d** = 1:2: δ 168.2 (s, $C_{1\ of\ (Z)\text{-}\mathbf{I.19d}}$), 167.8 (s, $C_{1\ of\ (E)\text{-}\mathbf{I.19d}}$), 153.8 (s, $C_{11\ of\ (E)\text{-}\mathbf{I.19d}}$), 152.1 (s, $C_{11\ of\ (Z)\text{-}\mathbf{I.19d}}$), 151.2 (s, $C_{5\ of\ (E)\text{-}\mathbf{I.19d}}$), 150.2 (s, $C_{5\ of\ (Z)\text{-}\mathbf{I.19d}}$), 136.9 (s, $C_{6\ of\ (Z)\text{-}\mathbf{I.19d}}$), 134.7 (s, $C_{6\ of\ (E)\text{-}\mathbf{I.19d}}$), 132.5 (s, $^2J_{C\text{-}F}$ = 33 Hz, $C_{9\ of\ (Z)\text{-}\mathbf{I.19d}}$), 131.0 (t, $C_{13\ of\ (Z)\text{-}\mathbf{I.19d}}$), 130.5 (t, $C_{13\ of\ (E)\text{-}\mathbf{I.19d}}$), 129.7 (d, 2C, $C_{7\ of\ (E)\text{-}\mathbf{I.19d}}$), 128.2 (d, 2C, $C_{7\ of\ (Z)\text{-}\mathbf{I.19d}}$), 125.9 (d, $^3J_{C\text{-}F}$ = 3.9 Hz, 2C, $C_{8\ of\ (Z)\text{-}\mathbf{I.19d}}$), 125.2 (d, $^3J_{C\text{-}F}$ = 3.9 Hz, 2C, $C_{8\ of\ (E)\text{-}\mathbf{I.19d}}$), 123.6 (s, $^1J_{C\text{-}F}$ = 272 Hz, $C_{10\ of\ (Z)\text{-}\mathbf{I.19d}}$), 120.3 (t, $C_{14\ of\ (E)\text{-}\mathbf{I.19d}}$), 119.7 (t, $C_{14\ of\ (Z)\text{-}\mathbf{I.19d}}$), 116.7 (s, $C_{4\ of\ (E)\text{-}\mathbf{I.19d}}$), 116.1 (s, $C_{4\ of\ (Z)\text{-}\mathbf{I.19d}}$), 70.1 (t, $C_{12\ of\ (Z)\text{-}\mathbf{I.19d}}$), 70.0 (t, $C_{12\ of\ (E)\text{-}\mathbf{I.19d}}$), 65.0 (t, $C_{2\ of\ (Z)\text{-}\mathbf{I.19d}}$), 64.8 (t, $C_{2\ of\ (E)\text{-}\mathbf{I.19d}}$), 28.4 (t, $C_{3\ of\ (Z)\text{-}\mathbf{I.19d}}$), 27.1 (t, $C_{3\ of\ (E)\text{-}\mathbf{I.19d}}$).

Note: The C_9 and C_{10} signals of (*E*)-**I.19d** were not observed.

HRMS (ESI) *m/z*: calcd for $C_{16}H_{13}F_3O_5Na$ $[M+Na]^+$: 365.0607, found: 365.0610.

(*Z*)-Allyl (1-(2-oxodihydrofuran-3(2*H*)-ylidene)ethyl) carbonate (I.19g)



I.19g

$C_{10}H_{12}O_5$

MW = 212.20 g/mol

I.19g was synthesized according to the method aforementioned from the commercially available α-acetyl-γ-butyrolactone (1.00 g, 7.81 mmol, 1.0 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/EtOAc = 9:1) as a colorless oil (976 mg, 59%).

R$_f$: 0.31 (PE/EtOAc = 8:2)

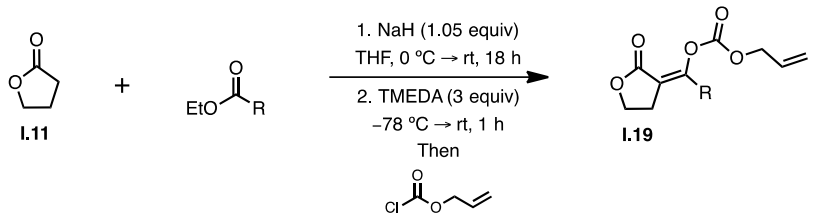
IR (ATR): 2924, 1754, 1696, 1443, 1377, 1277, 1185, 1116, 1021, 946, 903, 779, 750 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.01-5.88 (m, 1H, H_9), 5.45-5.36 (m, 1H, H_{10}), 5.33 (m, 1H, $H_{10'}$), 4.69 (dq, *J* = 5.8, 1.1 Hz, 2H, H_8), 4.30 (t_{app}, *J* = 8.4 Hz, 2H, H_2), 2.96-2.87 (m, 2H, H_3), 2.43 (td, *J* = 2.4, 0.8 Hz, 3H, H_6).

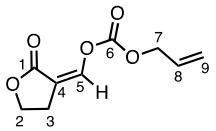
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2 (s, C_1), 157.5 (s, C_7), 151.1 (s, C_5), 130.8 (d, C_9), 120.0 (t, C_{10}), 114.1 (s, C_4), 69.6 (t, C_8), 64.8 (t, C_2), 25.7 (t, C_3), 16.3 (q, C_6).

HRMS (ESI) *m/z*: calcd for $C_{10}H_{13}O_5$ $[M+H]^+$: 213.0758, found: 213.0760.

8.2. General procedures for the synthesis of allyl enol carbonates *via* one-pot reaction (I.19e-f)



(*Z*)-Allyl ((2-oxodihydrofuran-3(2*H*)-ylidene)methyl) carbonate (I.19e)



I.19e

$C_9H_{10}O_5$
MW = 198.17 g/mol

A dispersion of NaH (2.44 g, 60% in mineral oil, 61.0 mmol, 1.05 equiv) was washed with hexanes and suspended in THF (120 mL) then cooled to 0 °C. A solution of γ-butyrolactone (5.00 g, 58.1 mmol, 1.0 equiv) and ethyl formate (4.69 mL, 58.1 mmol, 1.0 equiv) in THF (5.00 mL) was added dropwise over a period of 30 min. The reaction temperature was kept at 0 °C and after 1 h, the temperature was raised to rt. After 16 h, the reaction mixture was cooled to −78 °C, TMEDA (26.0 mL, 174 mmol, 3.0 equiv) and allyl chloroformate (18.6 mL, 174 mmol, 3.0 equiv) were added successively. The reaction mixture was stirred for an additional 15 min. A saturated aqueous solution of NH_4Cl was then added and the aqueous phase was extracted with Et_2O. The combined organic phases were dried over $MgSO_4$, filtered and evaporated under reduced pressure to afford a crude residue, which was recrystallized from ether/hexane to afford the corresponding allyl enol carbonate as a white solid (4.33 g, 38%).

Note: Due to the presence of ethanol in the media, a mixture (**I.19e**/(*Z*)-ethyl ((2-oxodihydrofuran-3(2*H*)-ylidene)methyl) carbonate = 10:1) was observed. Only **I.19e** is reported.

Mp = 69-72 °C

R$_f$: 0.31 (PE/EtOAc = 7:3)

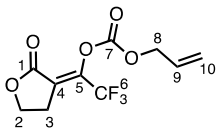
IR (ATR): 2925, 1770, 1699, 1452, 1369, 1216, 1166, 1074, 1025, 944, 777, 734 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) mixture of ethyl-**I.19e**/**I.19e** = 1:10: δ 8.07 (t_{app}, *J* = 3.0 Hz, 1H, H_5), 5.90 (m, 1H, H_8), 5.42 (dq, *J* = 17.2, 1.4 Hz, 1H, H_9), 5.34 (dq, *J* = 10.4, 1.1 Hz, 1H, $H_{9'}$), 4.76-4.71 (m, 2H, H_{10}), 4.43-4.47 (m, 2H, H_2), 3.04-2.93 (m, 2H, H_3).

^{13}C NMR (100 MHz, $CDCl_3$) mixture of ethyl-**I.19e**/**I.19e** = 1:10: δ 171.0 (s, C_1), 151.4 (s, C_6), 144.2 (s, C_5), 130.4 (d, C_8), 120.7 (t, C_9), 110.7 (s, C_4), 70.2 (t, C_7), 66.0 (t, C_2), 24.2 (t, C_3).

HRMS (ESI) *m/z*: calcd for $C_9H_{11}O_5$ $[M+H]^+$: 199.0601, found: 199.0602.

(*Z*)-Allyl (2,2,2-trifluoro-1-(2-oxodihydrofuran-3(2*H*)-ylidene)ethyl) carbonate (I.19f)



I.19f

$C_{10}H_9F_3O_5$
MW = 266.17 g/mol

A dispersion of NaH (975 mg, 60% in mineral oil, 24.4 mmol, 1.05 equiv) was washed with hexanes and suspended in THF (48 mL) then cooled to 0°C. A solution of γ-butyrolactone (2.00 g, 23.2 mmol, 1.0 equiv) and ethyl trifluoracetate (2.75 mL, 23.2 mmol, 1.0 equiv) in THF (5.00 mL) was added dropwise over a period of 30 min. The reaction temperature was kept at 0 °C and after 1 h, the temperature was raised to rt. After 16 h, the reaction mixture was cooled to −78 °C, TMEDA (10.5 mL, 69.7 mmol, 3.0 equiv) and allyl chloroformate (7.45 mL, 69.7 mmol, 3.0 equiv) were added successively. The reaction mixture was stirred for an additional 15 min. A saturated aqueous solution of NH_4Cl was then added and the aqueous phase was extracted with Et_2O. The combined organic phases were dried over $MgSO_4$, filtered and evaporated under reduced pressure to afford a crude residue, which was recrystallized from ether/hexane to afford the corresponding allyl enol carbonate as a white solid (2.60 g, 42%).

Note: Due to the presence of ethanol in the media, a mixture (**I.19f**/(*Z*)-ethyl (2,2,2-trifluoro-1-(2-oxodihydrofuran-3(2*H*)-ylidene)ethyl) carbonate = 10:1) was observed. Only **I.19f** is reported.

Mp = 39-41 °C

Rf: 0.68 (PE/EtOAc = 7:3)

IR (ATR)**:** 2998, 2928, 2853, 1766, 1695, 1486, 1345, 1195, 1140, 1103, 1022, 990, 938, 890 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) mixture of ethyl-**I.19f/I.19f** = 1:10: δ 5.97 (m, 1H, H_9), 5.43 (dq, J = 17.2, 1.4 Hz, 1H, H_{10}), 5.33 (dq, J = 10.4, 1.2 Hz, 1H, $H_{10'}$), 4.76 (dt_{app}, J = 5.8, 1.4 Hz, 2H, H_8), 4.44 (t, J = 7.2 Hz, 2H, H_2), 3.29 (m, 2H, H_3).

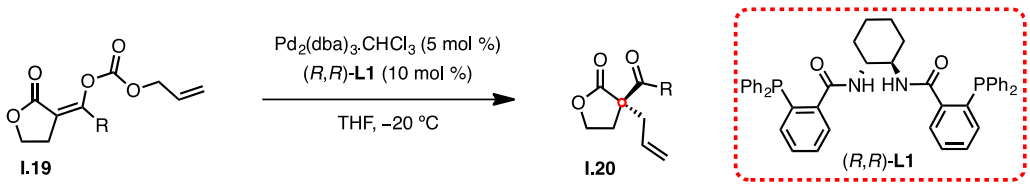
^{13}C NMR (100 MHz, $CDCl_3$) mixture of ethyl-**I.19f/I.19f** = 1:10: δ 166.3 (s, C_1), 150.9 (s, C_7), 139.6 (s, $^2J_{C\text{-}F}$ = 38.5 Hz, C_5), 130.6 (d, C_9), 121.7 (s, $^3J_{C\text{-}F}$ = 2.1 Hz, C_4), 120.1 (t, C_{10}), 119.3 (s, $^1J_{C\text{-}F}$ = 274 Hz, C_6), 70.7 (t, C_8), 65.3 (t, C_2), 25.7 (t, $^4J_{C\text{-}F}$ = 2.7 Hz, C_3).

HRMS (ESI) *m/z*: calcd for $C_{10}H_9F_3O_5Na$ $[M+Na]^+$: 289.0294, found: 289.0296.

9. General Procedures for the Pd-DAAA of exocyclic allyl enol carbonate

synthesis of α-allyl-α-acyl butyrolactones (I.20a-g)

(Representative procedure)

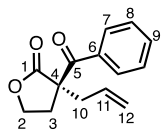


To a solution of $Pd_2(dba)_3.CHCl_3$ (0.01 mmol, 0.05 equiv) in THF (1 mL) at room temperature was added (*R*,*R*)-DACH phenyl Trost ligand (0.02 mmol, 0.1 equiv) and the mixture was stirred for 30 min. This solution was then cooled to −20 °C and transferred via cannula to a flask containing a cooled solution (−20 °C) of allyl enol carbonate (0.2 mmol, 1 equiv) in THF (1 mL). The reaction mixture was then stirred at the same temperature until complete consumption of the starting material (confirmed by TLC). A saturated solution of brine was then added and the aqueous phase was extracted with EtOAc (3 x 2 mL). The combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure to afford a crude residue, which was purified by flash column chromatography on silica gel to afford the corresponding allylated butyrolactone.

General procedure for the synthesis of racemic compounds
(Representative procedure)

To a solution of allyl enol carbonate (0.1 mmol, 1 equiv) in THF (1 mL) at room temperature was added $Pd(PPh_3)_4$ (0.005 mmol, 0.05 equiv). The reaction mixture was then stirred at the same temperature for 10 min as the complete consumption of the starting material (confirmed by TLC). The solvent was then evaporated under reduced pressure to afford a crude residue, which was purified following the same procedure described for the corresponding enantioenriched compound.

(*R*)-3-Allyl-3-benzoyldihydrofuran-2(3*H*)-one (I.20a)



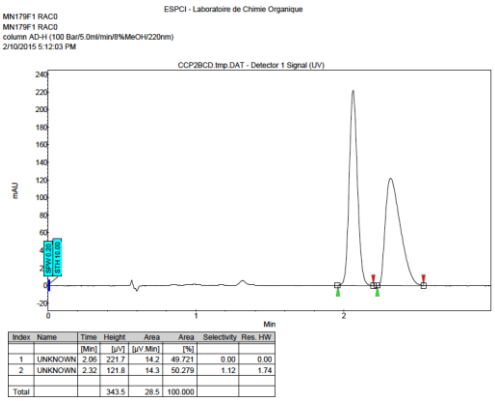
I.20a
$C_{14}H_{14}O_3$
MW = 230.26 g/mol

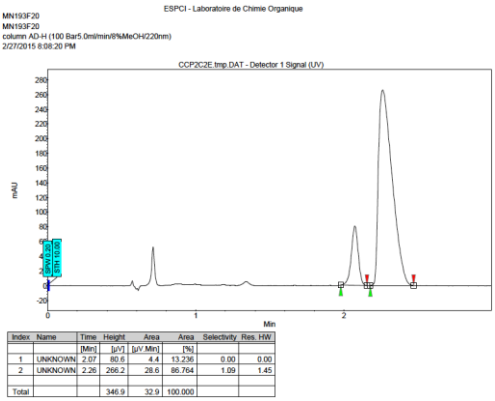
I.20a was synthesized according to the method aforementioned from (*Z*)-allyl ((2-oxodihydrofuran-3(2*H*)-ylidene)(phenyl)methyl) carbonate **I.19b** (27 mg, 0.1 mmol, 1.0 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/EtOAc = 9:1 to 8:2) as a colorless oil (19 mg, 83%).

R$_f$: 0.38 (PE/EtOAc = 8:2)
[α]^{20} D = –7.89 (*c* 0.19, $CHCl_3$)
ee = 74% (determined by SFC)
SFC: AD-H column, Pressure = 100 bar, eluent = sc CO_2/MeOH = 92:8, Flow rate = 5 mL/min, detection wavelength = 220 nm. t_R = 2.07 min (minor) and t_R = 2.26 min (major).
IR (ATR): 3077, 2924, 2853, 1761, 1678, 1597, 1578, 1447, 1375, 1245, 1213, 1172, 1028, 1000, 928, 788, 752 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06-8.00 (m, 2H, H_7), 7.60-7.52 (m, 1H, H_9), 7.50-7.41 (m, 2H, H_8), 5.66 (m, 1H, H_{11}), 5.17-5.05 (m, 2H, H_{12}), 4.45-4.33 (m, 2H, H_2), 3.02-2.92 (m, 2H, H_3 and H_{10}), 2.79 (m, 1H, $H_{10'}$), 2.33 (ddd, *J* = 13.1, 8.5, 8.0 Hz, 1H, $H_{3'}$).

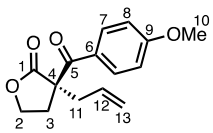
^{13}C NMR (100 MHz, $CDCl_3$): δ 195.6 (s, C_5), 175.9 (s, C_1), 135.6 (s, C_6), 133.2 (d, C_9), 131.7 (d, C_{11}), 129.2 (d, 2C, C_7), 128.7 (d, 2C, C_8), 120.5 (t, C_{12}), 66.7 (t, C_2), 59.5 (s, C_4), 40.1 (t, C_{10}), 32.2 (t, C_3).

HRMS (ESI) *m/z*: calcd for $C_{14}H_{14}O_3Na$ $[M+Na]^+$: 253.0835, found: 253.0833.





(*R*)-3-Allyl-3-(4-methoxybenzoyl)dihydrofuran-2(3*H*)-one (I.20b)



I.20b

$C_{15}H_{16}O_4$

MW = 260.29 g/mol

I.20b was synthesized according to the method aforementioned from (*Z*)-allyl ((4-methoxyphenyl)(2-oxodihydrofuran-3(2*H*)-ylidene)methyl) carbonate **I.19c** (31 mg, 0.1 mmol, 1.0 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/EtOAc = 8:2) as a colorless oil (26 mg, 93%).

R$_f$: 0.39 (PE/EtOAc = 7:3)

[α]^{20} $_D$ = –22.3 (*c* 0.22, $CHCl_3$)

ee = 87% (determined by SFC)

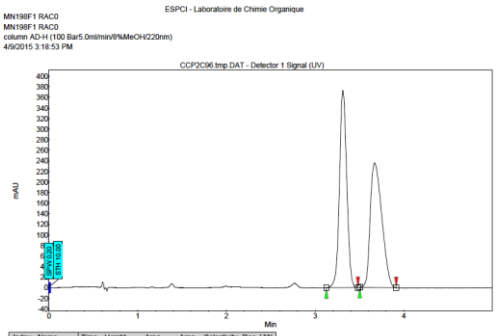
SFC: AD-H column, Pressure = 100 bar, eluent = sc CO_2/MeOH = 92:8, Flow rate = 5 mL/min, detection wavelength = 220 nm. t_R = 3.31 min (minor) and t_R = 3.63 min (major).

IR (ATR): 3079, 2921, 2843, 1763, 1667, 1600, 1510, 1374, 1251, 1172, 1027, 930, 845, 612 cm^{-1}.

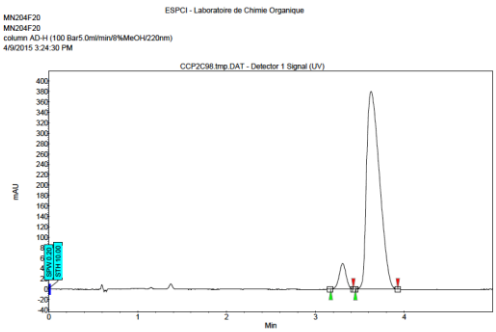
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13-8.07 (m, 2H, H_7), 6.95-6.89 (m, 2H, H_8), 5.66 (m, 1H, H_{12}), 5.14-5.05 (m, 2H, H_{13}), 4.39-4.32 (m, 2H, H_2), 3.86 (s, 3H, H_{10}), 3.05-2.96 (m, 2H, H_3 and H_{11}), 2.82-2.74 (m, 1H, $H_{11'}$), 2.30 (dt, J = 13.1, 8.4 Hz, 1H, $H_{3'}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.2 (s, C_5), 176.3 (s, C_1), 163.6 (s, C_9), 132.0 (d, 2C, C_7), 131.8 (d, C_{12}), 127.9 (s, C_6), 120.3 (t, C_{13}), 113.9 (d, 2C, C_8), 66.7 (t, C_2), 59.3 (s, C_4), 55.6 (q, C_{10}), 40.3 (t, C_{11}), 32.4 (t, C_3).

HRMS (ESI) *m/z*: calcd for $C_{15}H_{16}O_4Na$ $[M+Na]^+$: 283.0941, found: 283.0940.

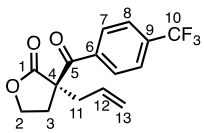


Index	Name	Time	Height	Area	Area	Selectivity	Res. HW
		[Min]	[µV]	[µV Min]	[%]		
1	UNKNOWN	3.31	372.9	35.4	49.878	0.00	0.00
2	UNKNOWN	3.67	235.2	35.6	50.122	1.11	1.80
Total			608.1	71.0	100.000		



Index	Name	Time	Height	Area	Area	Selectivity	Res. HW
		[Min]	[µV]	[µV Min]	[%]		
1	UNKNOWN	3.31	49.3	4.5	6.500	0.00	0.00
2	UNKNOWN	3.63	380.1	64.1	93.500	1.10	1.53
Total			429.4	68.5	100.000		

(*R*)-3-Allyl-3-(4-(trifluoromethyl)benzoyl)dihydrofuran-2(3*H*)-one (I.20c)



I.20c

$C_{15}H_{13}F_3O_3$
MW = 298.26 g/mol

I.20c was synthesized according to the method aforementioned (*Z*)-allyl ((2-oxodihydrofuran-3(2*H*)-ylidene)(4-(trifluoromethyl)phenyl)methyl) carbonate **I.19d** (44 mg, 0.13 mmol, 1.0 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/EtOAc = 8:2) as a colorless oil (37 mg, 96%).

R$_f$: 0.55 (PE/EtOAc = 7:3)

$[\alpha]^{20}_{D}$ = –2.62 (*c* 0.65, $CHCl_3$)

ee = 75% (determined by SFC)

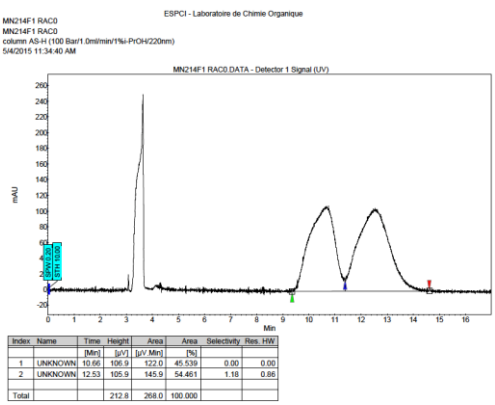
SFC: AS-H column, Pressure = 100 bar, eluent = sc CO_2/*i*-PrOH = 99:1, Flow rate = 1 mL/min, detection wavelength = 220 nm. t_R = 10.64 min (minor) and t_R = 12.25 min (major).

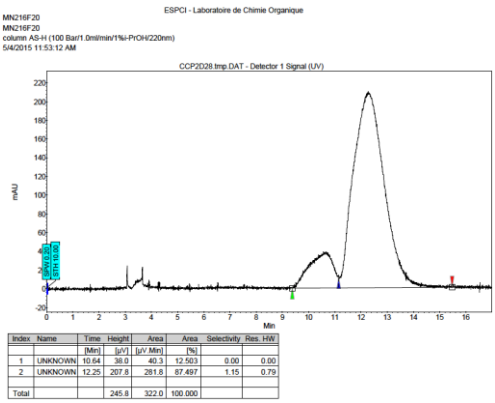
IR (ATR): 3082, 2924, 2853, 1764, 1683, 1408, 1375, 1326, 1167, 1127, 1067, 1029, 996, 930, 855 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22-8.07 (d_{app}, J = 8.3 Hz, 2H, H_7), 7.72 (d_{app}, J = 8.5 Hz, 2H, H_8), 5.61 (m, 1H, H_{12}), 5.15-5.00 (m, 2H, H_{13}), 4.44-4.34 (m, 2H, H_2), 3.04-2.91 (m, 2H, H_3 and H_{11}), 2.77 (ddt, J = 14.3, 6.7, 1.4 Hz, 1H, $H_{11'}$), 2.33 (dt, J = 13.2, 8.4 Hz, 1H, $H_{3'}$).

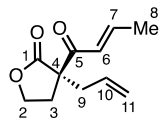
^{13}C NMR (100 MHz, $CDCl_3$): δ 195.1 (s, C_5), 175.3 (s, C_1), 138.8 (s, C_6), 134.3 (s, $^2J_{C-F}$ = 33.1 Hz, C_9), 131.1 (d, C_{12}), 129.6 (d, 2C, C_7), 125.7 (d, $^3J_{C-F}$ = 3.8 Hz, 2C, C_8), 123.5 (s, $^1J_{C-F}$ = 274 Hz, C_8), 120.8 (t, C_{13}), 66.9 (t, C_2), 59.9 (s, C_4), 40.0 (t, C_{11}), 32.0 (t, C_3).

HRMS (ESI) *m/z*: calcd for $C_{15}H_{13}F_3O_3Na$ $[M+Na]^+$: 321.0709, found: 321.0711.





(*R*,*E*)-3-Allyl-3-(but-2-enoyl)dihydrofuran-2(3*H*)-one (I.20d)



I.20d

$C_{11}H_{14}O_3$

MW = 194.23 g/mol

I.20d was synthesized according to the method aforementioned from allyl ((1*Z*,2*E*)-1-(2-oxodihydrofuran-3(2*H*)-ylidene)but-2-en-1-yl) carbonate **I.19a** (125 mg, 0.53 mmol, 1.0 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/EtOAc = 9:1 to 8:2) as a colorless oil (99 mg, 97%).

R$_f$: 0.50 (PE/EtOAc = 8:2)

[α]^{20} $_D$ = +14.0 (*c* 1.25, $CHCl_3$)

ee = 86% (determined by SFC)

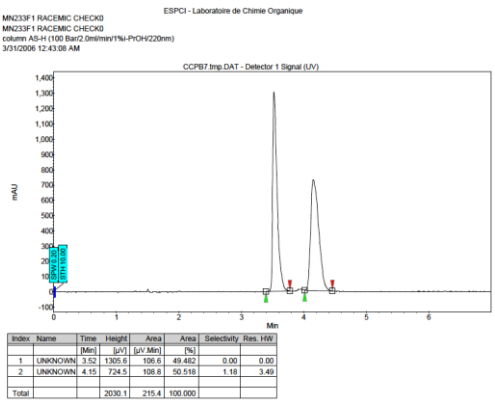
SFC: AS-H column, Pressure = 100 bar, eluent = sc CO_2/*i*-PrOH = 99:1, Flow rate = 2 mL/min, detection wavelength = 220 nm. t_R = 3.69 min (minor) and t_R = 4.25 min (major).

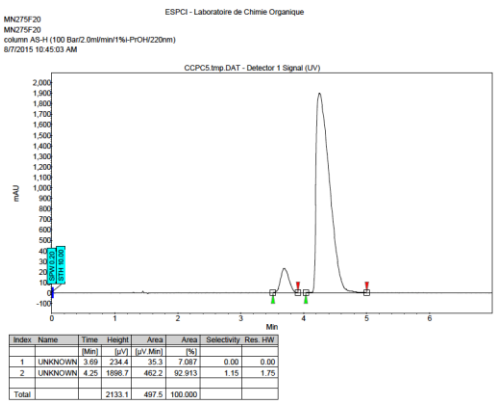
IR (ATR): 2981, 2917, 1764, 1690, 1627, 1441, 1374, 1291, 1218, 1163, 1067, 1026, 970, 930, 811 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09 (dq, *J* = 15.2, 7.0 Hz, 1H, H_7), 6.77 (dq, *J* = 15.2, 1.6 Hz, 1H, H_6), 5.56 (m, 1H, H_{10}), 5.18-5.09 (m, 2H, H_{11}), 4.28 (td, *J* = 8.9, 3.0 Hz, 1H, H_2), 4.14 (td, *J* = 9.2, 7.1 Hz, 1H, $H_{2'}$), 2.93 (ddd, *J* = 13.0, 7.1, 3.0 Hz, 1H, H_3), 2.73 (m, 1H, H_9), 2.62 (ddt, *J* = 14.3, 6.9, 1.3 Hz, 1H, $H_{9'}$), 2.11 (ddd, *J* = 13.1, 9.3, 8.8 Hz, 1H, $H_{3'}$), 1.93 (dd, *J* = 7.0, 1.6 Hz, 3H, H_8).

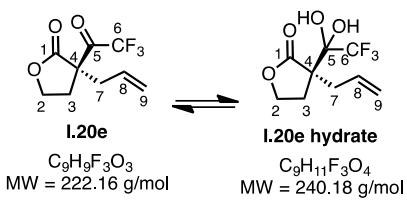
^{13}C NMR (100 MHz, $CDCl_3$): δ 191.9 (s, C_5), 175.7 (s, C_1), 146.8 (d, C_7), 131.4 (d, C_{10}), 125.4 (d, C_6), 120.2 (t, C_{11}), 66.5 (t, C_2), 59.6 (s, C_4), 39.0 (t, C_9), 28.8 (t, C_3), 18.7 (q, C_6).

HRMS (ESI) *m/z*: calcd for $C_{11}H_{14}O_3Na$ $[M+Na]^+$: 217.0835, found: 217.0834.





(*R*)-3-Allyl-3-(2,2,2-trifluoroacetyl)dihydrofuran-2(3*H*)-one (I.20e)



I.20e was synthesized according to the method aforementioned from (*Z*)-allyl (2,2,2-trifluoro-1-(2-oxodihydrofuran-3(2*H*)-ylidene)ethyl) carbonate **I.19f** (130 mg, 0.49 mmol, 1.0 equiv). Compounds **I.20e** and **I.20e hydrate** were obtained as an inseparable mixture (3:7) after flash column chromatography on silica gel (PE/EtOAc = 9:1 to 8:2) as a colorless oil (105 mg, 90%).

R$_f$: 0.70 (PE/EtOAc = 8:2)

[α]^{20} D = –13.5 (*c* 0.73, $CHCl_3$)

ee = 60% (determined by SFC)

Note: The **I.20e** compound could not be detected at 220 nm by SFC analysis. The *ee* was therefore determined after subjecting **I.20e** to further derivatization (see description of compound **I.20e-deriv**).

IR (ATR): 3410, 2990, 2931, 1742, 1644, 1488, 1443, 1390, 1263, 1184, 1165, 1103, 1061, 1031, 989, 934, 898, 866, 741 cm^{-1}.

Mixture of **I.20e**/**I.20e hydrate** = 3:7

^{1}H NMR (400 MHz, $CDCl_3$) – compound **I.20e**: δ 5.77-5.63 (m, 1H, H_8), 5.35-5.19 (m, 2H, H_9), 4.47-4.31 (m, 2H, H_2), 2.88-2.70 (m, 2H, H_3 and H_7), 2.46-2.34 (m, 1H, $H_{7'}$), 2.25-2.13 (m, 1H, $H_{3'}$).

^{1}H NMR (400 MHz, $CDCl_3$) – compound **I.20e hydrate**: δ 6.42-6.34 (m, 1H, H_5), 5.77-5.63 (m, 1H, H_8), 5.35-5.19 (m, 2H, H_9), 4.47-4.31 (m, 1H, H_2), 4.22 (q, *J* = 8.6 Hz, 1H, $H_{2'}$), 3.44 (d, *J* = 9.5 Hz, 1H, $H_{5'}$), 2.94 (m, 1H, H_3), 2.88-2.70 (m, 2H, H_7), 2.46-2.34 (m, 1H, $H_{3'}$).

^{13}C NMR (100 MHz, $CDCl_3$) – compound **I.20e**: δ 186.8 (s, $^2J_{C\text{-}F}$ = 35 Hz, C_5), 172.6 (s, C_1), 130.2 (d, C_8), 122.2 (t, C_9), 66.2 (t, C_2), 57.3 (s, C_4), 37.4 (t, C_7), 28.9 (t, C_3).

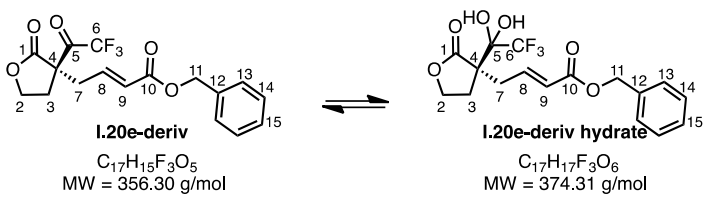
Note: The C_6 signal was not observed.

^{13}C NMR (100 MHz, $CDCl_3$) – compound **I.20e hydrate**: δ 180.7 (s, C_1), 131.3 (d, C_8), 122.4 (s, $^1J_{C\text{-}F}$ = 286 Hz, C_6), 121.5 (t, C_9), 95.2 (s, $^2J_{C\text{-}F}$ = 35 Hz, C_5), 67.5 (t, C_2), 52.0 (s, C_4), 37.7 (t, $^4J_{C\text{-}F}$ = 2.3 Hz, C_7), 28.7 (t, $^4J_{C\text{-}F}$ = 2.7 Hz, C_3).

HRMS (ESI) *m/z*: compound **I.20e** is not stable under ESI (see HRMS of compound **I.20e-deriv**, compound **I.20e** after derivatization).

Derivatization for enantiomeric excess determination through Cross-metathesis[73]

Benzyl (*R*,*E*)-4-(2-oxo-3-(2,2,2-trifluoroacetyl)tetrahydrofuran-3-yl)but-2-enoate (I.20e-deriv)



To a microvial containing (*R*)-3-allyl-3-(2,2,2-trifluoroacetyl)dihydrofuran-2(3*H*)-one **I.20e** (50 mg, 0.21 mmol, 1.0 equiv), benzyl acrylate (99 µL, 0.63 mmol, 3.0 equiv) and Grubbs-Hoveyda second generation catalyst (13 mg, 0.021 mmol, 0.1 equiv) was added CH_2Cl_2 (2 mL). The vial was sealed and heated at 50 °C for 24 h. Concentration under reduced pressure afforded a crude residue, which was purified by flash chromatography on silica gel. Compounds **I.20e-deriv** and **I.20e-deriv hydrate** were obtained as an inseparable mixture (1:4) after flash column chromatography on silica gel (PE/EtOAc = 8:2) as colorless oil (60 mg, 77%).

R_f: 0.27 (PE/EtOAc = 8:2)

$[\alpha]^{20}_{D}$ = –31.4 (*c* 0.69, $CHCl_3$)

ee = 60% (determined by SFC)

SFC: AS-H column, Pressure = 100 bar, eluent = sc CO_2/MeOH = 90:10, Flow rate = 4 mL/min, detection wavelength = 220 nm. t_R = 2.08 min (major) and t_R = 2.42 min (minor).

IR (ATR): 3390, 2925, 1719, 1656, 1456, 1382, 1327, 1260, 1161, 1060, 1028, 982, 741, 697 cm^{-1}.

Mixture of **I.20e-deriv**/**I.20e-deriv hydrate** = 1:4

^{1}H NMR (400 MHz, $CDCl_3$) – compound **I.20e-deriv**: δ 7.42-7.30 (m, 5H, H_{Ar}), 6.89-6.76 (m, 1H, H_8), 6.06 (ddt, *J* = 15.4, 4.3, 1.4 Hz, 1H, H_9), 5.21-5.13 (m, 2H, H_{11}), 4.50-4.33 (m, 2H, H_2), 3.04-2.90 (m, 1H, H_7), 2.90-2.79 (m, 2H, H_3), 2.40-2.30 (m, 1H, $H_{7'}$).

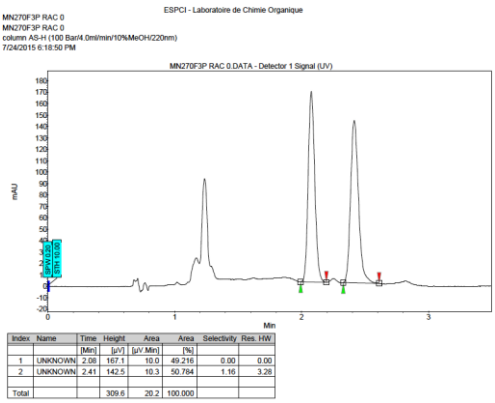
^{1}H NMR (400 MHz, $CDCl_3$) – compound **I.20e-deriv hydrate**: δ 7.42-7.30 (m, 5H, H_{Ar}), 6.89-6.76 (m, 1H, H_8), 6.24 (q, *J* = 1.1 Hz, 1H, H_5), 6.06 (ddt, *J* = 15.4, 4.3, 1.4 Hz, 1H, H_9), 5.21-5.13 (m, 2H, H_{11}), 4.50-4.33 (m, 1H, H_2), 4.17 (td, *J* = 8.9, 8.2 Hz, 1H, $H_{2'}$), 3.77 (d_{app}, *J* = 5.1 Hz, 1H, $H_{5'}$), 3.04-2.90 (m, 2H, H_3 and H_7), 2.58 (m, 1H, $H_{7'}$), 2.17 (ddd, *J* = 13.8, 8.0, 3.4 Hz, 1H, $H_{3'}$).

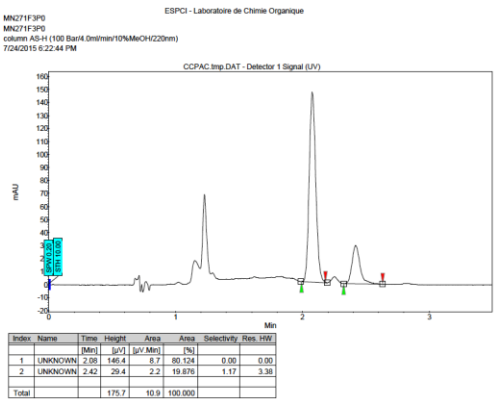
^{13}C NMR (100 MHz, $CDCl_3$) – compound **I.20e-deriv**: δ 171.9 (s, C_1), 165.3 (s, C_{10}), 140.0 (d, C_8), 135.6 (s, C_{12}), 128.8 (d, 2C, C_{13} or C_{14}), 128.6 (d, C_{15}), 127.4 (d, C_9), 66.8 (t, C_2), 66.2 (t, C_{11}), 56.9 (s, C_4), 35.4 (t, C_7), 29.8 (t, C_3).

Note: The C_5, C_6 and C_{13}/C_{14} signals were not observed.

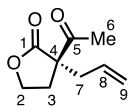
^{13}C NMR (100 MHz, $CDCl_3$) – compound **I.20e-deriv hydrate**: δ 179.8 (s, C_1), 165.4 (s, C_{10}), 141.1 (d, C_8), 135.7 (s, C_{12}), 128.7 (d, 2C, C_{13} or C_{14}), 128.5 (d, C_{15}), 128.4 (d, 2C, C_{13} or C_{14}), 126.8 (d, C_9), 122.4 (s, $^1J_{C\text{-}F}$ = 289 Hz, C_6), 95.1 (s, $^2J_{C\text{-}F}$ = 33 Hz, C_5), 67.2 (t, C_2), 66.7 (t, C_{11}), 51.8 (s, C_4), 35.6 (t, $^4J_{C\text{-}F}$ = 2.4 Hz, C_7), 28.9 (t, $^4J_{C\text{-}F}$ = 2.4 Hz, C_3).

HRMS (ESI) *m/z*: calcd for $C_{17}H_{18}F_3O_6$ $[M+H]^+$: 375.1050, found: 375.1052.





(*R*)-3-Acetyl-3-allyldihydrofuran-2(3*H*)-one (I.20f)[81]



I.20f

$C_9H_{12}O_3$

MW = 168.19 g/mol

I.20f was synthesized according to the method aforementioned from (*Z*)-allyl (1-(2-oxodihydrofuran-3(2*H*)-ylidene)ethyl) carbonate **I.19g** (120 mg, 0.57 mmol, 1.0 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/EtOAc = 9:1 to 8:2) as a colorless oil (91 mg, 96%).

R$_f$: 0.40 (PE/EtOAc = 8:2)

$[\alpha]^{20}_{D}$ = +58.1 (*c* 0.87, $CHCl_3$)

ee = 67% (determined by SFC)

Note: The **I.20f** compound could not be detected at 220 nm by SFC analysis. The *ee* was therefore determined after subjecting **I.20f** to further derivatization (see description of compound **I.20f-deriv**).

IR (ATR): 3082, 2982, 2920, 1761, 1711, 1641, 1485, 1437, 1360, 1373, 1219, 1276, 1167, 1025, 999, 926 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.65-5.52 (m, 1H, H_8), 5.22-5.12 (m, 2H, H_9), 4.27 (td, *J* = 8.9, 3.5 Hz, 1H, H_2), 4.16 (td, *J* = 8.9, 7.3 Hz, 1H, $H_{2'}$), 2.85 (ddd, *J* = 13.1, 7.4, 3.5 Hz, 1H,

81 Molander, G. A.; Kenny, C. *Tetrahedron Lett.* **1987**, *28*, 4367.

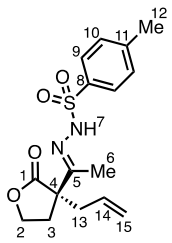
H_3), 2.75 (ddt, J = 14.5, 8.0, 1.0 Hz, 1H, H_7), 2.62 (ddt, J = 14.4, 6.5, 1.4 Hz, 1H, $H_{7'}$), 2.32 (s, 3H, H_6), 2.10 (dt, J = 13.1, 8.8 Hz, 1H, $H_{3'}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 202.2 (s, C_5), 175.2 (s, C_1), 131.4 (d, C_8), 120.3 (t, C_9), 66.5 (t, C_2), 61.1 (s, C_4), 39.1 (t, C_7), 28.8 (t, C_3), 25.8 (q, C_6).

MS *m/z* (relative intensity): 167 (M^+-H, 1), 126 (100), 125 (34), 111 (18), 97 (11), 81 (34), 92 (20), 67 (40), 53 (13).

Derivatization for enantiomeric excess determination through hydrazone derivatives formation

(*R*,*E*)-*N*'-(1-(3-allyl-2-oxotetrahydrofuran-3-yl)ethylidene)-4-methylbenzenesulfono-hydrazide (I.20f-deriv)



I.20f-deriv
$C_{16}H_{20}N_2O_4S$
MW = 336.41 g/mol

To a solution of (*R*)-3-acetyl-3-allyldihydrofuran-2(3*H*)-one **I.20f** (50 mg, 0.3 mmol, 1.0 equiv) in THF (1.25 mL) was added tosyl hydrazide (0.30 mmol, 1.0 equiv) at rt. The resulting reaction mixture was heated at reflux for 18 h, and then concentrated under reduced pressure to afford a crude residue. The titled compound was obtained after flash column chromatography on silica gel (PE/EtOAc = 7:3) as a yellow oil (73 mg, 73%).

R_f: 0.36 (PE/EtOAc = 6:4)

$[\alpha]^{20}_D$ = +30.2 (*c* 0.33, $CHCl_3$)

ee = 67% (determined by SFC)

SFC: AS-H column, Pressure = 100 bar, eluent = sc CO_2/MeOH = 90:10, Flow rate = 5 mL/min, detection wavelength = 220 nm. t_R = 3.85 min (minor) and t_R = 6.30 min (major).

IR (ATR): 3535, 3217, 2923, 1751, 1642, 1597, 1439, 1376, 1167, 1091, 1022, 922, 815, 730, 667 cm^{-1}.

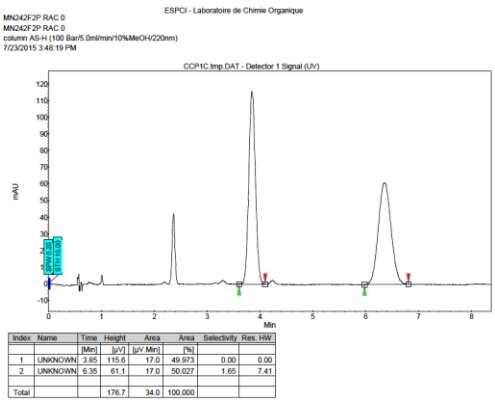
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85-7.72 (m, 3H, H_7 and H_9), 7.31 (d, J = 8.1 Hz, 2H, H_{10}), 5.37 (m, 1H, H_{14}), 5.08-4.94 (m, 2H, H_{15}), 4.17 (td, J = 8.6, 2.8 Hz, 1H, H_2), 3.93 (tdd, J = 9.1, 6.7, 2.9 Hz, 1H, $H_{2'}$), 2.84 (ddd, J = 12.9, 6.7, 2.9 Hz, 1H, H_3), 2.57 (m, 1H, H_{13}), 2.47-2.33 (m, 4H, H_{12} and $H_{13'}$), 2.06 (m, 1H, $H_{3'}$), 1.86 (s, 3H, H_6).

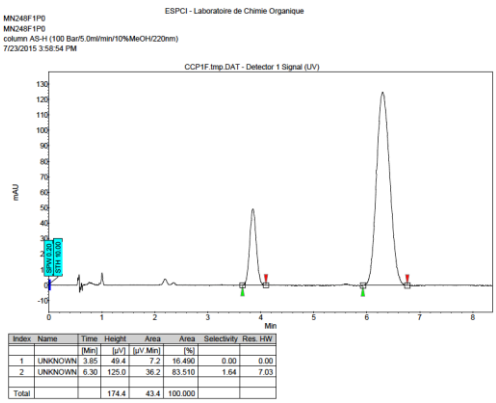
Note: During the ^{13}C NMR analysis a complex mixture of **(*E*)-I.20f-deriv**, **(*Z*)-I.20f-deriv**, **I.20f** and tosyl hydrazide was observed.

^{13}C NMR (100 MHz, $CDCl_3$) – compound **(*E*)-I.20f-deriv**: δ 176.5 (s, C_1), 151.6 (s, C_5), 144.6 (s, C_{11}), 135.1 (s, C_8), 131.8 (d, C_{14}), 129.7 (d, 2C, C_{10}), 128.2 (d, 2C, C_9), 119.6 (t, C_{15}), 66.3 (t, C_2), 54.0 (s, C_4), 38.9 (t, C_{13}), 30.1 (t, C_3), 21.8 (q, C_{12}), 12.3 (q, C_6).

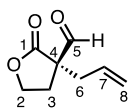
^{13}C NMR (100 MHz, $CDCl_3$) – compound **(*Z*)-I.20f-deriv**: δ 175.3 (s, C_1), 164.1 (s, C_5), 145.6 (s, C_{11}), 134.9 (s, C_8), 129.8 (d, 2C, C_{10}), 129.4 (d, C_{14}), 128.4 (d, 2C, C_9), 120.4 (t, C_{15}), 58.6 (t, C_2), 57.5 (s, C_4), 40.0 (t, C_{13}), 37.3 (t, C_3), 21.9 (q, C_{12}), 14.7 (q, C_6).

HRMS (ESI) *m/z*: calcd for $C_{16}H_{21}N_2O_4S$ $[M+H]^+$: 337.1217, found: 337.1217.





(*R*)-3-Allyl-2-oxotetrahydrofuran-3-carbaldehyde (I.20g)



I.20g

$C_8H_{10}O_3$

MW = 154.17 g/mol

I.20g was synthesized according to the method aforementioned (*Z*)-allyl ((2-oxodihydrofuran-3(2*H*)-ylidene)methyl) carbonate **I.19e** (100 mg, 0.51 mmol, 1.0 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/EtOAc = 8:2 to 7:3) as a colorless oil (54 mg, 69%).

Rf: 0.27 (PE/EtOAc = 7:3)

[α]^{20} D = +4.31 (*c* 0.33, $CHCl_3$)

ee = 94% (determined by SFC)

Note: The **I.20g** compound could not be detected at 220 nm by SFC analysis. The *ee* was therefore determined after subjecting **I.20g** to further derivatization (see description of compound **I.20g-deriv**).

IR (ATR): 2986, 2920, 2850, 1763, 1721, 1641, 1486, 1439, 1373, 1218, 1170, 1023, 928, 884, 682 cm^{-1}.

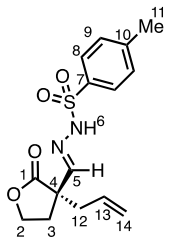
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.57 (d, *J* = 0.9 Hz, 1H, H_5), 5.71-5.57 (m, 1H, H_7), 5.27-5.18 (m, 2H, H_8), 4.35-4.21 (m, 2H, H_2), 2.77 (ddd, *J* = 13.3, 8.0, 5.3 Hz, 1H, H_3), 2.72-2.61 (m, 2H, H_{11}), 2.15 (m, 1H, $H_{3'}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 196.0 (s, C_5), 174.1 (s, C_1), 130.4 (d, C_7), 121.1 (t, C_8), 66.3 (t, C_2), 59.3 (s, C_4), 36.9 (t, C_6), 26.2 (t, C_3).

HRMS (ESI) *m/z*: calcd for $C_8H_{10}O_3Na$ $[M+Na]^+$: 177.0522, found: 177.0523.

Derivatization for enantiomeric excess determination through hydrazone derivatives formation

(*R*,*E*)-*N*'-((3-allyl-2-oxotetrahydrofuran-3-yl)methylene)-4-methylbenzenesulfono-hydrazide (I.20g-deriv)



I.20g-deriv
$C_{15}H_{18}N_2O_4S$
MW = 322.38 g/mol

To a solution of (*R*)-3-allyl-2-oxotetrahydrofuran-3-carbaldehyde **I.20g** (30 mg, 0.2 mmol, 1.0 equiv) in THF (1.25 mL) was added tosyl hydrazide (0.30 mmol, 1.0 equiv) at rt. The resulting reaction mixture was heated at reflux for 18 h, and then concentrated under reduced pressure to afford a crude residue. The titled compound was obtained after flash column chromatography on silica gel (PE/EtOAc = 7:3) as a yellow oil (57 mg, 91%).

R$_f$: 0.36 (PE/EtOAc = 6:4)

[α]^{20} D = +2.46 (*c* 0.69, $CHCl_3$)

ee = 94% (determined by SFC)

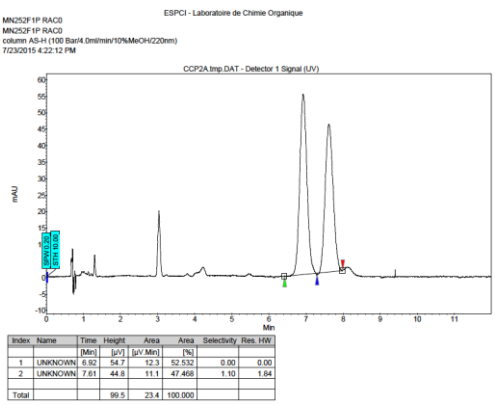
SFC: AS-H column, Pressure = 100 bar, eluent = sc CO_2/MeOH = 90:10, Flow rate = 4 mL/min, detection wavelength = 220 nm. t_R = 6.91 min (major) and t_R = 7.65 min (minor).

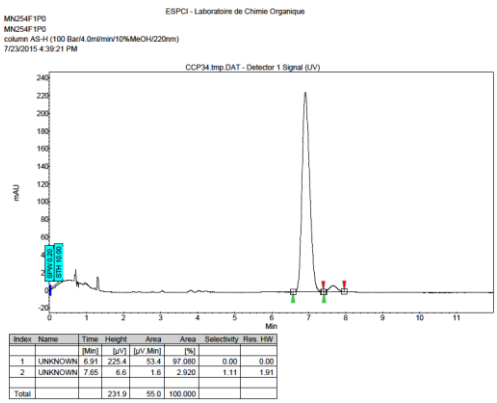
IR (ATR): 3195, 2889, 2852, 1760, 1597, 1440, 1361, 1218, 1166, 1092, 1025, 926, 815, 669 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (s, 1H, H_5), 7.79-7.72 (m, 2H, H_8), 7.33-7.27 (m, 2H, H_9), 7.12 (s, 1H, H_6), 5.47 (ddt, *J* = 17.4, 10.1, 7.3 Hz, 1H, H_{11}), 5.12-5.03 (m, 2H, H_{14}), 4.23 (ddd, *J* = 9.0, 8.3, 4.8 Hz, 1H, H_2), 4.11 (dt, *J* = 8.9, 7.6 Hz, 1H, $H_{2'}$), 2.66 (ddd, *J* = 13.2, 7.6, 4.8 Hz, 1H, H_3), 2.50-2.39 (m, 5H, H_{11} and H_{12}), 2.14 (dt, *J* = 13.2, 7.9 Hz, 1H, $H_{3'}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.9 (s, C_1), 147.7 (d, C_5), 144.7 (s, C_{10}), 135.0 (s, C_7), 131.2 (d, C_{13}), 129.8 (d, 2C, C_9), 128.0 (d, 2C, C_8), 120.5 (t, C_{14}), 66.4 (t, C_2), 50.4 (s, C_4), 39.2 (t, C_{12}), 29.2 (t, C_3), 21.8 (q, C_{11}).

HRMS (ESI) *m/z*: calcd for $C_{15}H_{18}N_2O_4SNa$ $[M+Na]^+$: 345.0880, found: 345.0877.

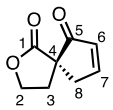




10. Synthesis of spirocyclic compounds

10.1. Synthesis of spirocycle through ring-closing metathesis

(*R*)-2-Oxaspiro[4.4]non-7-ene-1,6-dione (I.21)

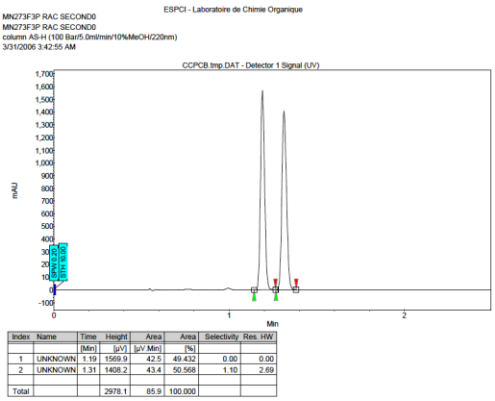


I.21

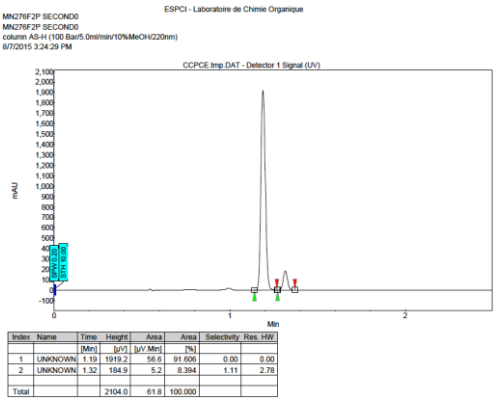
$C_8H_8O_3$
MW = 152.15 g/mol

To a vial containing (*R*,*E*)-3-allyl-3-(but-2-enoyl)dihydrofuran-2(3*H*)-one **I.20d** (28 mg, 0.14 mmol, 1.0 equiv) and Grubbs-Hoveyda second generation catalyst (9 mg, 0.014 mmol, 0.1 equiv) was added CH_2Cl_2 (0.7 mL). The vial was sealed and heated at 50 °C for 24 h. Concentration under reduced pressure afforded a crude residue, which was purified by flash column chromatography over silica gel. The titled compound was obtained after flash column chromatography on silica gel (PE/EtOAc = 6:4) as a colorless oil (20 mg, 91%).

R$_f$: 0.32 (PE/EtOAc = 1:1)
[α]^{20} D = –67.7 (*c* 0.53, $CHCl_3$)
ee = 83% (determined by SFC)
SFC: AS-H column, Pressure = 100 bar, eluent = sc CO_2/MeOH = 90:10, Flow rate = 5 mL/min, detection wavelength = 220 nm. t_R = 1.19 min (major) and t_R = 1.32 min (minor).
IR (ATR): 2923, 2853, 1760, 1700, 1589, 1422, 1376, 1343, 1312, 1219, 1175, 1134, 1107, 1082, 1023, 952, 814, 766, 725 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (dt, *J* = 5.5, 2.7 Hz, 1H, H_7), 6.16 (dt, *J* = 5.8, 2.2 Hz, 1H, H_6), 4.65 (ddd, *J* = 9.3, 8.7, 7.2 Hz, 1H, H_2), 4.39 (td, *J* = 8.7, 3.1 Hz, 1H, $H_{2'}$), 3.27 (dt, *J* = 19.1, 2.5 Hz, 1H, H_8), 2.67 (dt, *J* = 19.1, 2.4 Hz, 1H, $H_{8'}$), 2.60 (m, 1H, H_3), 2.35 (dt, *J* = 12.8, 9.0 Hz, 1H, $H_{3'}$).
^{13}C NMR (100 MHz, $CDCl_3$): δ 204.9 (s, C_5), 175.3 (s, C_1), 164.7 (d, C_7), 131.6 (d, C_6), 66.5 (t, C_2), 54.2 (s, C_4), 40.4 (t, C_8), 32.9 (t, C_3).
HRMS (ESI) *m/z*: calcd for $C_8H_9O_3$ $[M+H]^+$: 153.0546, found: 153.0545.

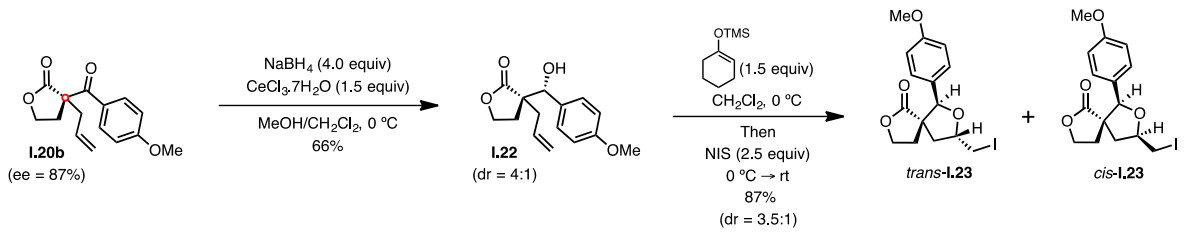


Index	Name	Time	Height	Area	Area	Selectivity	Res. HW
		[Min]	[µV]	[µV.Min]	[%]		
1	UNKNOWN	1.19	1569.9	42.5	49.432	0.00	0.00
2	UNKNOWN	1.31	1408.2	43.4	50.568	1.10	2.69
Total			2978.1	85.9	100.000		

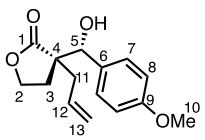


Index	Name	Time	Height	Area	Area	Selectivity	Res. HW
		[Min]	[µV]	[µV.Min]	[%]		
1	UNKNOWN	1.19	1919.2	56.6	91.606	0.00	0.00
2	UNKNOWN	1.32	184.9	5.2	8.394	1.11	2.78
Total			2104.0	61.8	100.000		

10.2. Synthesis of spirocycle through iodocyclization



(*R)-3-allyl-3-((*R**)-hydroxy(4-methoxyphenyl)methyl)dihydrofuran-2(3*H*)-one (I.22)**[74]



I.22

$C_{15}H_{18}O_4$
MW = 262.31 g/mol

A solution of $CeCl_3.7H_2O$ (120 µL, 1.0 M in MeOH, 0.12 mmol, 1.5 equiv) was added to a solution of (*R*)-3-allyl-3-(4-methoxybenzoyl)dihydrofuran-2(3*H*)-one **I.20b** (21 mg, 0.081 mmol, 1 equiv) in a mixture of methanol (0.8 mL) and CH_2Cl_2 (0.8 mL). $NaBH_4$ (12 mg, 0.32 mmol, 4 equiv) was then slowly added at 0 °C under an argon atmosphere. After stirring for 2 h at the same temperature, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (4 mL), diluted with water (8 mL), and a 2 M HCl solution was added until the reaction mixture became clear. The mixture was extracted with EtOAc (3 x 8 mL). The combined organic layers were washed with H_2O, brine and dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to afford a crude residue, which was purified by flash column chromatography on silica gel (PE/EtOAc = 8:2 to 7:3) to afford a colorless

oil of **I.22** (14 mg, 66%) as single diastereoisomer, isolated from a mixture 4:1 dr determined by ^{1}H NMR analysis of crude.

R_f: 0.18 (PE/EtOAc = 8:2)

$[\alpha]^{20}_D$ = –27.0 (*c* 0.46, $CHCl_3$)

IR (ATR): 3458, 3077, 2920, 2851, 1746, 1612, 1513, 1458, 1441, 1381, 1249, 1178, 1031, 925, 840 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.30 (m, 2H, H_7), 6.90-6.85 (m, 2H, H_8), 5.77 (m, 1H, H_{12}), 5.22-5.13 (m, 2H, H_{13}), 4.90 (s, 1H, H_5), 4.04 (td, *J* = 8.9, 6.0 Hz, 1H, H_2), 3.80 (s, 3H, H_{10}), 3.68 (td, *J* = 8.9, 6.2 Hz, 1H, H_3), 2.99 (s, 1H, H_5(OH)), 2.73 (ddt, *J* = 13.7, 6.2, 1.4 Hz, 1H, H_{11}), 2.47-2.33 (m, 2H, H_3 and $H_{11'}$), 2.01 (ddd, *J* = 13.4, 8.9, 6.2 Hz, 1H, $H_{3'}$).

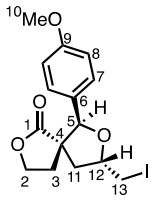
^{13}C NMR (100 MHz, $CDCl_3$): δ 180.4 (s, C_1), 159.7 (s, C_9), 133.2 (d, C_{12}), 131.3 (s, C_6), 128.3 (d, 2C, C_7), 120.0 (t, C_{13}), 113.8 (d, 2C, C_8), 76.5 (d, C_5), 66.4 (t, C_2), 55. 4 (q, C_{10}), 52.5 (s, C_4), 38.6 (t, C_{11}), 28.1 (t, C_3).

HRMS (ESI) *m/z*: calcd for $C_{15}H_{18}O_4Na$ $[M+Na]^+$: 285.1097, found: 285.1098.

Iodocyclization (general procedure)[75]

Under argon atmosphere, 1-cyclohexenyloxytrimethylsilane (9 µL, 0.045 mmol, 1.5 equiv) was added to a solution of (*R**)-3-allyl-3-((*R**)-hydroxy(4-methoxyphenyl)methyl)-dihydrofuran-2(3*H*)-one **I.22** (8.0 mg, 0.030 mmol, 1.0 equiv) in CH_2Cl_2 at 0 °C. The reaction was stirred for 10 min at 0 °C and NIS (17 mg, 0.075 mmol, 2.5 equiv) was added to the mixture at 0 °C. The reaction mixture was stirred for 20 min at 0 °C and then stirred at rt for 16 h. After checking the complete consumption of the starting material by TLC, a saturated solution of brine was added and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to afford a crude residue, which was purified by flash column chromatography on silica gel (PE/EtOAc = 8:2) to afford a colorless oil of *trans*-**I.23** (10 mg) and *cis*-**I.23** (3 mg) in 87% yield isolated from a mixture of *trans*-**I.23**/*cis*-**I.23** (dr = 3.5:1) determined by ^{1}H NMR analysis of crude.

(5*S,6*R**,8*S**)-8-(Iodomethyl)-6-(4-methoxyphenyl)-2,7-dioxaspiro[4.4]nonan-1-one (*trans*-I.23)**



trans-**I.23**

$C_{15}H_{17}IO_4$

MW = 388.20 g/mol

(10 mg, 67%)

R_f: 0.33 (PE/EtOAc = 8:2)

$[\alpha]^{20}_D$ = –6.60 (*c* 0.50, $CHCl_3$)

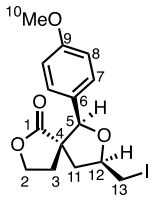
IR (ATR): 2923, 2853, 1761, 1613, 1514, 1454, 1376, 1303, 1250, 1215, 1174, 1026, 837, 787 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25-7.20 (m, 2H, H_7), 6.90-6.84 (m, 2H, H_8), 5.32 (s, 1H, H_5), 4.43 (tdd, *J* = 8.6, 6.5, 4.7 Hz, 1H, H_{12}), 4.04 (ddd, *J* = 9.1, 8.3, 5.4 Hz, 1H, H_2), 3.80 (s, 3H, H_{10}), 3.45 (dd, *J* = 9.8, 4.7 Hz, 1H, H_{13}), 3.38-3.29 (m, 2H, $H_{13'}$ and $H_{2'}$), 2.49-2.37 (m, 2H, H_{11}), 2.17 (ddd, *J* = 13.3, 8.0, 5.4 Hz, 1H, H_3), 1.91 (ddd, *J* = 13.2, 8.4, 6.9 Hz, 1H, $H_{3'}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 178.2 (s, C_1), 159.8 (s, C_9), 128.5 (s, C_6), 127.1 (d, 2C, C_7), 114.1 (d, 2C, C_8), 84.9 (d, C_5), 78.2 (d, C_{12}), 65.8 (t, C_2), 55. 4 (q, C_{10}), 55.1 (s, C_4), 45.1 (t, C_{11}), 29.9 (t, C_3), 9.1 (t, C_{13}).

HRMS (ESI) *m/z*: calcd for $C_{15}H_7IO_4Na$ $[M+Na]^+$: 411.0064, found: 411.0065.

(5*S,6*R**,8*R**)-8-(Iodomethyl)-6-(4-methoxyphenyl)-2,7-dioxaspiro[4.4]nonan-1-one (*cis*-I.23)**



cis-**I.23**

$C_{15}H_{17}IO_4$
MW = 388.20 g/mol

(3 mg, 20%)

R_f: 0.29 (PE/EtOAc = 8:2)

$[\alpha]^{20}_{D}$ = +12.0 (*c* 0.20, $CHCl_3$)

IR (ATR): 2924, 2853, 1764, 1614, 1515, 1462, 1375, 1304, 1251, 1216, 1174, 1028, 839 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) mixture of *trans*-**I.23**/*cis*-**I.23** = 1:20: δ 7.32-7.27 (m, 2H, H_7), 6.93-6.85 (m, 2H, H_6), 5.12 (s, 1H, H_5), 4.19 (dtd, *J* = 8.2, 6.0, 4.1 Hz, 1H, H_{12}), 4.01 (ddd, *J* = 9.0, 8.3, 5.0 Hz, 1H, H_2), 3.81 (s, 3H, H_{10}), 3.48 (dd, *J* = 10.5, 5.7 Hz, 1H, H_{13}), 3.39 (dd, *J* = 10.5, 4.1 Hz, 1H, $H_{13'}$), 3.32 (dt, *J* = 9.0, 7.6 Hz, 1H, $H_{2'}$), 2.81 (dd, *J* = 13.2, 8.2 Hz, 1H, H_{11}), 2.21 (ddd, *J* = 12.9, 7.7, 5.0 Hz, 1H, H_3), 1.99 (dt, *J* = 13.4, 7.8 Hz, 1H, $H_{3'}$), 1.92 (dd, *J* = 13.2, 6.2 Hz, 1H, $H_{11'}$).

^{13}C NMR (100 MHz, $CDCl_3$) mixture of *trans*-**I.23**/*cis*-**I.23** = 1:20: δ 179.8 (s, C_1), 159.9 (s, C_9), 128.4 (s, C_6), 127.6 (d, 2C, C_7), 114.1 (d, 2C, C_8), 86.1 (d, C_5), 76.1 (d, C_{12}), 66.2 (t, C_2), 55. 4 (q, C_{10}), 53.7 (s, C_4), 44.7 (t, C_{11}), 32.8 (t, C_3), 9.8 (t, C_{13}).

HRMS (ESI) *m/z*: calcd for $C_{15}H_7IO_4Na$ $[M+Na]^+$: 411.0064, found: 411.0069.

Chapter

2

Palladium-Catalyzed Asymmetric Allylic Alkylation of 4-Substituted Isoxazolidin-5-ones Toward the Synthesis of $\beta^{2,2}$-Amino Acids

1. Occurrence of β-amino acid motif in natural products and/or bioactive compounds

1.1. β-Amino acids

β-Amino acids occur in Nature in the form of the free amino acids or as substructures of peptides and alkaloids. Although less abundant than their α-analogues, β-amino acids have been found in a number of biologically relevant natural products.[82] Due to their unique pharmacological properties and the synthetic challenge they represent, the preparation of such compounds has emerged as a particularly important and stimulating endeavor.[83]

β-Amino acids can be associated with different designations, depending on which carbon the substitution takes place. Seebach *et al*. introduced a very effective nomenclature, using the term β^x-amino acid where x indicates the position of the side chain on the carbon backbone to distinguish positional isomers (Figure 11).[84]

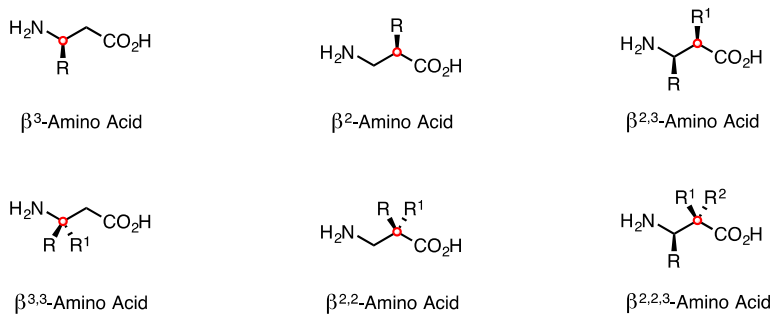


Figure 11. Various types of β-amino acids.

1.2. Naturally occurring β-amino acids

In contrast to proteinogenic α-amino acids, which are the primary constituents of all enzymes which in turn control the metabolism in living organisms, most β-amino acids only

82 Juaristi, E.; Soloshonok, V. A., *Enantioselective synhtesis of beta-amino acids*. 2nd ed.; John Wiley & Sons: Hoboken NJ, **2005**.
83 Windholz, M.; Budavari, S.; Stroumtsos, L. Y.; Fertig, M. N., *The Merck Index: An Encyclopedia of Chemicals and Drugs*. 9th ed.; Merck: Rahway, NJ, **1976**.
84 (a) Hintermann, T.; Seebach, D. *Synlett* **1997**, 437; (b) Seebach, D.; Gademann, K.; Schreiber, J. V.; Matthews, J. L.; Hintermann, T.; Jaun, B., *Helv. Chim. Acta* **1997**, *80*, 2033.

occur as constituents of distinct natural products such as peptides, cyclopeptides, depsipeptides, glycopeptides, alkaloids, or terpenoids of which selected representative examples are depicted in Figure 12.[85]

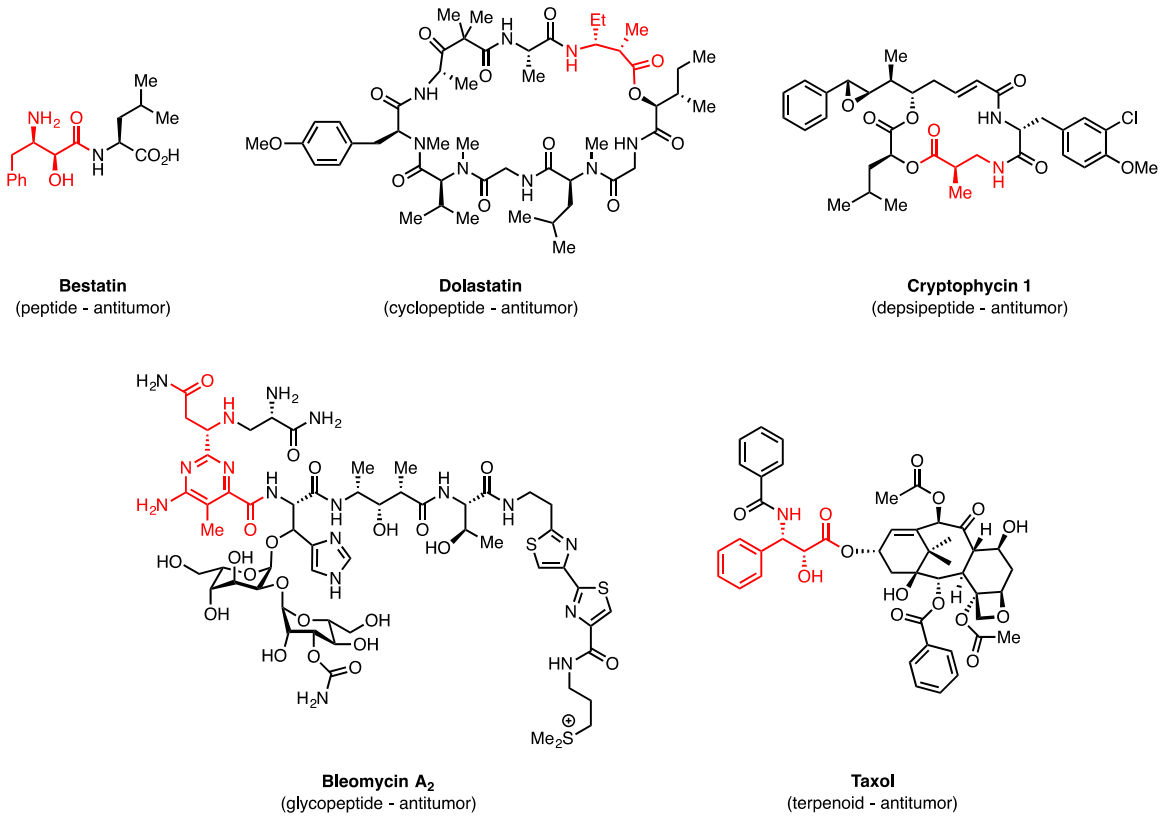


Figure 12. Structures of various β-amino acid-containing natural products.

These compounds are often characterized by potent biological activities that are often crucially dependent on the β-amino acid subunit such as, for example, bestatin, dolastatin, cryptophycin 1, bleomycin A_2 and taxol (Figure 12). As a consequence, these naturally occurring molecules containing a β-amino acid motif have inspired the development of new drug candidates.[86]

Moreover, the incorporation of β-amino acids into peptides instead of α-amino acids increases their stability against degradation by mammalian peptidases. This enhanced stability is caused by the lack of enzymes capable of cleaving the peptide bonds between α-amino

85 Schmuck, C.; Wennemers, H. *β-Amino Acids in Nature in Highlights in Bioorganic Chemistry: Methods and Applications*. Wiley-VCH: Weinheim, **2004**.

86 (a) Ballard, C. E.; Wang, H. Y. a. B. *Curr. Med. Chem.* **2002**, *9*, 471; (b) Steer, D. L.; Lew, R. A.; Perlmutter, P.; Smith, A. I.; Aguilar, M.-I. *Curr. Med. Chem.* **2002**, *9*, 811.

acids and β-amino acids.[87] Therefore, β-amino acids are an important tool in the development of drugs capable of withstanding hydrolytic degradation.

To date, there is no evidence that animals are able to produce any β-amino acids, except β-alanine **L2.1** and β-aminoisobutyric acid **L2.2** which are present in all living organisms, since they are directly involved in primary metabolism (Figure 13, a). The reported occurrence of β-amino acids in natural products, isolated from animals such as sponges and mollusks, are not contradictory to that hypothesis since it has been demonstrated that the cyanobacteria, which live in a symbiotic relationship with sponges or serving as nutrition for mollusks, are the real producers of the β-amino acids in question.[88] On the other hand, many β-amino acids are formed by 2,3-aminomutase, which catalyzes the α,β-shift of the amino group. These enzymes are present in bacteria, plants and fungi.[85] A few other β-amino acids that are directly derived from the corresponding proteinogenic α-amino acids has been discovered in Nature in their free form or as part of larger molecules (Figure 13, b).

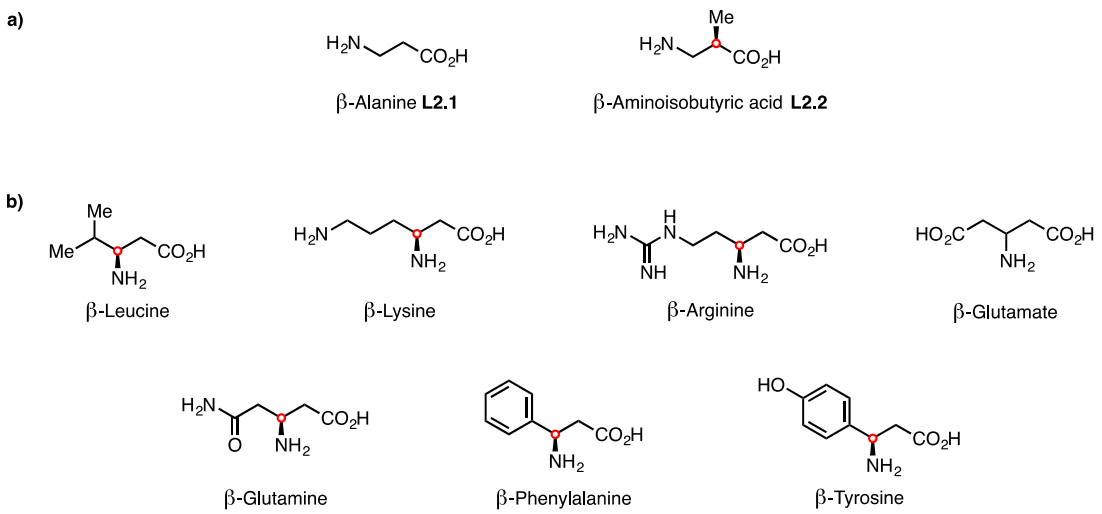


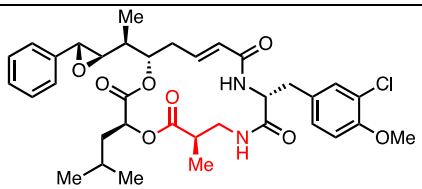
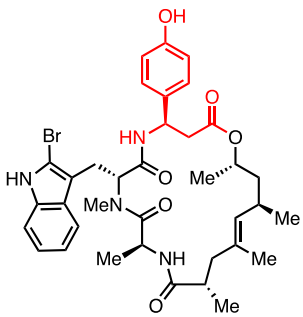
Figure 13. β-Amino acids found in Nature.

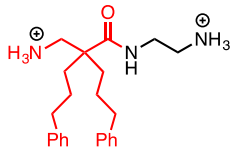
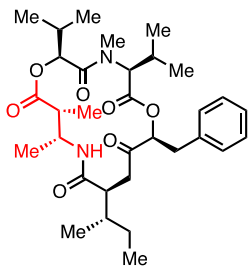
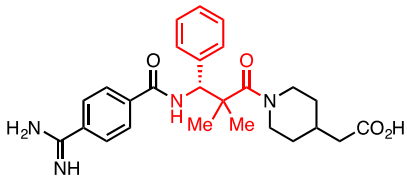
A considerable number of reviews covering the synthesis, biosynthesis and biological activities inherent to β-amino acid-containing natural products are available.[82, 85, 89]

87 Pegova, A.; Abe, H.; Boldyrev, A. *Comp. Biochem. Physiol. B: Biochem. Mol. Biol.* **2000**, *127*, 443.
88 Bewley, C. A.; Faulkner, D. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 2162.
89 Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, *25*, 117.

Therefore, a brief overview of examples of natural and synthetic products bearing a β-amino acid moiety with interesting biological properties are reported in Table 12 and classified according to their substitution pattern.

Table 12. Representative examples of bioactive β-amino acid-containing molecules.

β-Amino acid Type	Representative example	Biological activity
β^2	 **Cryptophycin 1**	antitumor (depsipeptide)
β^3	 **Jasplakinolide**	anthelminthic insecticidal antifungal (polyketide-depsipeptide)

$\beta^{2,2}$	 LTX-401	antitumor (non-natural peptide)
$\beta^{2,3}$	 Dolastatin D	antitumor (cyclodepsipeptide)
$\beta^{2,2,3}$	 NSL-95301	antithrombotic agent (non-natural peptide)

1.3. The use of β-amino acids as precursors

1.3.1. β-Amino acids in β-lactams

β-Lactam antibiotics, such as penicillins **L2.3** and cephalosporins **L2.4** (Figure 14), are still the most prominent class of therapeutic antibacterial agents. They are clearly the most important group of naturally occurring molecules used as drugs that contain a β-amino acid substructure.[90] Nowadays, they represent more than 60% of all clinically administrated antibiotics.[91] Due to the occurrence of resistant bacterial strains that possess β-lactamases, which are thus able to deactivate β-lactam antibiotics by hydrolytic ring-opening, the

90 Schofield, C. J.; Walter, M. W. *Amino-acids, Peptides, and Proteins* Royal Society of Chemistry: Cambridge, **1999**; Vol. 30.
91 Lee, W.; McDonough, M. A.; Kotra, L. P.; Li, Z.-H.; Silvaggi, N. R.; Takeda, Y.; Kelly, J. A.; Mobashery, S. *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 1427.

development of new types of synthetic β-lactam antibiotics to overcome these problems remains still today an important challenge.[92]

Figure 14. Structures of β-lactam-containing antibiotics.

The access to the β-lactam skeleton has been appealing to organic chemists because of its medicinal significance. There are a few synthetic approaches to construct the β-lactam ring. Among them, the cyclization of β-amino acids or β-amino esters is the most obvious pathway to construct the β-lactam ring.[93] In this approach, the design of new compounds involving structural modifications of the β-amino acid substrate through the introduction of substituents onto the less explored α-position — forming new $\beta^{2,2}$-amino acids — has led to the discovery of a few compounds with promising antibacterial activities, as shown below Figure 15.[94]

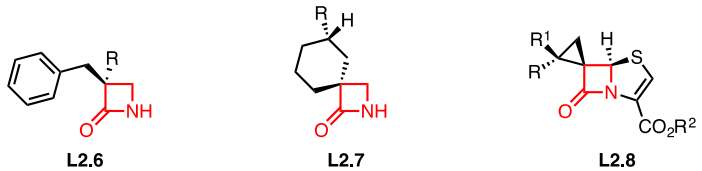


Figure 15. Structures of various β-lactams.

1.3.2. β-Amino acids in β- and α/β-peptides and peptidomimetics

Exciting discoveries in the field of β-peptides have provided an ever-growing interest in recent years for the development of synthetic routes to β-amino acids. While individual

92 (a) Matagne, A.; Dubus, A.; Galleni, M.; Frère, J.-M. *Natural Product Reports* **1999**, *16*, 1; (b) Kelly, J. A.; Dideberg, O.; Charlier, P.; Wery, J. P.; M. Libert; Moews, P. C.; Knox, J. R.; Duez, C.; Fraipont, C.; B. Joris; Dusart, J.; Frère, J. M.; Ghuysen, J. M. *Science* **1986**, *231*, 1429.
93 Singh, G. S. *Tetrahedron* **2003**, *59*, 7631.
94 (a) Avenoza, A.; Cativiela, C.; París, M.; Peregrina, J. M. *Tetrahedron: Asymmetry* **1995**, *6*, 1409; (b) Cativiela, C.; Diaz-de-Villegas, M. D.; Gálvez, J. A. *J. Org. Chem.* **1994**, *59*, 2497.

β-amino acids and closely related compounds, most notably the β-lactams, have long held a prominent position in medicinal chemistry, the study of β-peptides has been very limited until the past two decades. Research on β-peptides has undergone a tremendous development ever since and has revealed that peptides, derived from proteinogenic amino acids, form more stable secondary structures — helix, turn and sheet — than their natural counterpart.[95] Furthermore, β-peptides and the hybrid α/β-peptides generally exhibit increased proteolytic and metabolic stability (Figure 16). Consequently, many strategies have been unveiled to develop molecules that mimic natural peptides. These approaches rely on the strategical replacement of specific α-amino acids within a given peptide sequence by suitable β-amino acids.[96]

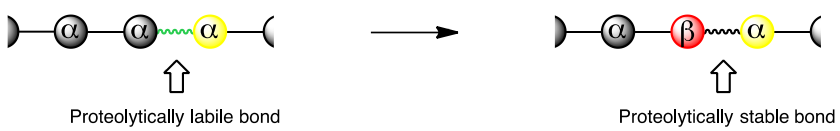


Figure 16. The achievement of a proteolically stable bond after replacement of α-amino acid fragment by an β-amino acid in a peptide.

The field of peptidomimetics has been revolutionized due to the remarkable structure and the proteolytic stability of these unnatural peptides. Hence, researchers have been presented with significant opportunities to provide new chemical therapies for a range of human diseases. Indeed, a number of examples of potent anticancer peptides containing a β-amino acid unit, more specifically, a $\beta^{2,2}$-amino acid unit, have been recently disclosed by medicinal chemists. These peptides include linear heptapeptides and cyclic tetrapeptides bearing a lipophilic $\beta^{2,2}$-amino acid and a series of short peptidomimetics consisting of a

95 (a) Seebach, D.; Beck, A. K.; Capone, S.; Deniau, G.; Grošelj, U.; Zass, E. *Synthesis* **2009**, *1*, 1; (b) Seebach, D.; Abele, S.; Gademann, K.; Jaun, B. *Angew. Chem. Int. Ed.* **1999**, *38*, 1595; (c) Seebach, D.; Matthews, J. L. *Chem. Commun.* **1991**, 2015; (d) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F., *Chem. Rev.* **2001**, *101*, 3219.

96 (a) Aguilar, M. I.; Purcell, A. W.; Devi, R.; Lew, R.; Rossjohn, J.; Smith, A. I.; Perlmutter, P. *Org Biomol Chem* **2007**, *5*, 2884; (b) Seebach, D.; Gardiner, J. *Acc. Chem. Res.* **2008**, *41*, 1366.

single $\beta^{2,2}$-amino acid, displaying antimicrobial and anticancer activities (Figure 17).[97] These anticancer peptides have a unique mode of action by selectively interfering with cancer cells *via* a charge-triggered membrane disruption. This has led to the development of anticancer peptide-chemotherapeutic drugs.

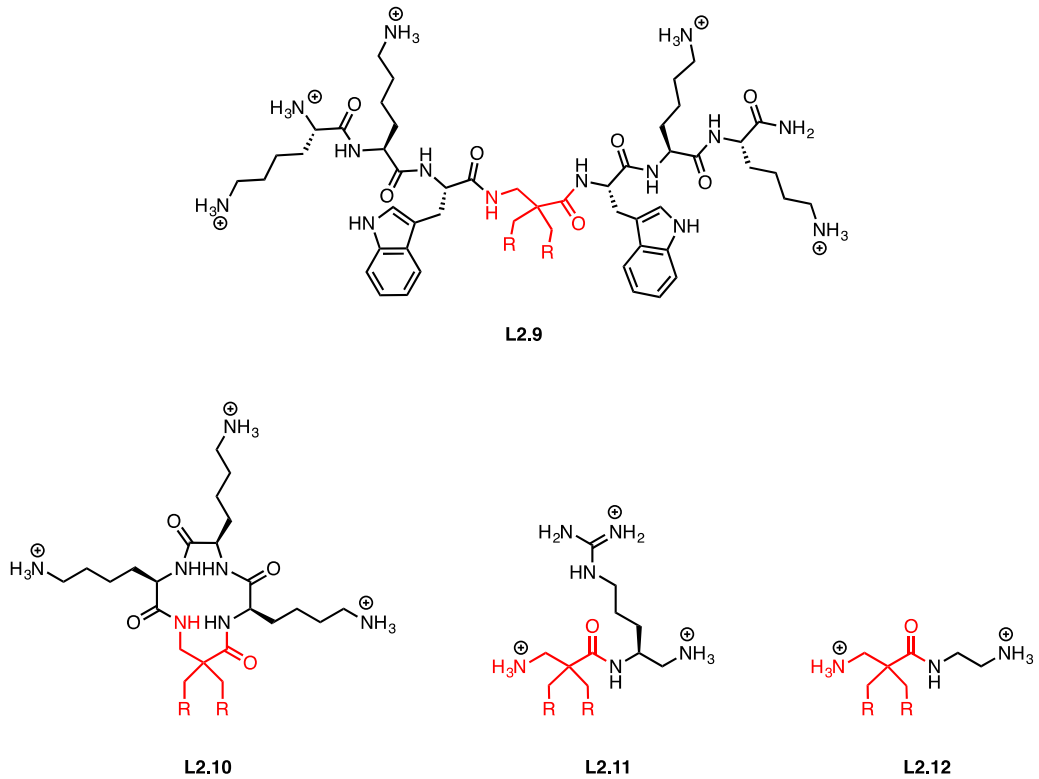


Figure 17. Representative examples of potent antimicrobial and anticancer peptides containing a $\beta^{2,2}$-amino acid unit.

2. Stereoselective syntheses of $\beta^{2,2}$-amino acid precursors

97 (a) Hansen, T.; Ausbacher, D.; Flaten, G. E.; Havelkova, M.; Strom, M. B. *J. Med. Chem.* **2011**, *54* , 858; (b) Hansen, T.; Alst, T.; Havelkova, M.; Strom, M. B. *J. Med. Chem.* **2010,** *53* , 595; (c) Ausbacher, D.; Svineng, G.; Hansen, T.; Strom, M. B. *Biochim. Biophys. Acta* **2012**, *1818* , 2917; (d) Hansen, T.; Ausbacher, D.; Zachariassen, Z. G.; Anderssen, T.; Havelkova, M.; Strom, M. B. *Eur. J. Med. Chem.* **2012,** *58*, 22; (e) Sivertsen, A.; Torfoss, V.; Isaksson, J.; Ausbacher, D.; Anderssen, T.; Brandsdal, B. O.; Havelkova, M.; Skjorholm, A. E.; Strom, M. B. *J. Pept. Sci.* **2014**, *20* , 279; (f) Cabrele, C.; Martinek, T. A.; Reiser, O.; Berlicki, L. *J. Med. Chem.* **2014,** *57* , 9718; (g) Sharma, G. V. M.; Reddy, P. S.; Chatterjee, D.; Kunwar, A. C. *Tetrahedron* **2012**, *68* , 4390; (h) Torfoss, V.; Isaksson, J.; Ausbacher, D.; Brandsdal, B. O.; Flaten, G. E.; Anderssen, T.; Cavalcanti-Jacobsen C de, A.; Havelkova, M.; Nguyen, L. T.; Vogel, H. J.; Strom, M. B. *J. Pept. Sci.* **2012**, *18* , 609; (i) Torfoss, V.; Ausbacher, D.; Cavalcanti-Jacobsen C de, A.; Hansen, T.; Brandsdal, B. O.; Havelkova, M.; Strom, M. B. *J. Pept. Sci.* **2012**, *18* , 170.

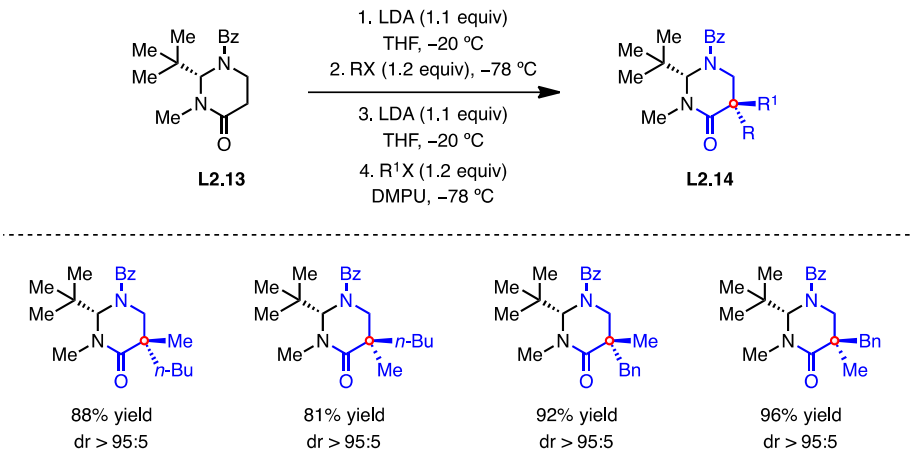
The stereoselective synthesis of β-amino acids has become a subject of growing interest in recent years, due to the wide utility of such compounds as components of proteins, peptides, and β-lactams and, as well as, starting materials for the synthesis of naturally occurring biologically active compounds. Given the importance of β-amino acids, a number of methods allowing the access to β-amino acids with various substitution patterns have been described in the literature. However, among all the available methods for the preparation of β-amino acids, only a few approaches provided the generation of β-amino acids bearing an all-carbon α-quaternary stereocenter.[98] In the following section, the stereoselective preparation of $\beta^{2,2}$-amino acid precursors will be presented.

2.1. Diastereoselective alkylation using chiral auxiliaries

2.1.1. Pyrimidinone derivative

The diastereoselective introduction of two alkyl substituents at the α-position of (*S*)-1-benzoyl-2-*tert*-butyl-3methylperhydropyrimidin-4-one **L2.13** has been reported by Juaristi *et al*. as a particular efficient way to access enantioenriched $\beta^{2,2}$-amino acid precursors (Scheme 38).[99] The successive alkylations of the enolates derived of **L2.13** by two different alkyl halides gave rise to α-quaternary products **L2.14** in high yields and diastereoselectivities (up to dr = 95:5). In both alkylation steps, only one single diastereoisomer was observed. This approach did not seem to be very efficient, since the authors pointed out that drastic conditions had to be used to achieve the hydrolysis of compounds **L2.14** toward the formation of their corresponding $\beta^{2,2}$-amino acid, such as long reaction time and high temperature (HCl 8 M, 100-140 ºC, 48-72 h).

98 Abele, S.; Seebach, D. *Eur. J. Org. Chem.* **2000**, *1*, 1.
99 Juaristi, E.; Balderas, M.; Ramírez-Quirós, Y. *Tetrahedron: Asymmetry* **1998**, *9*, 3881.

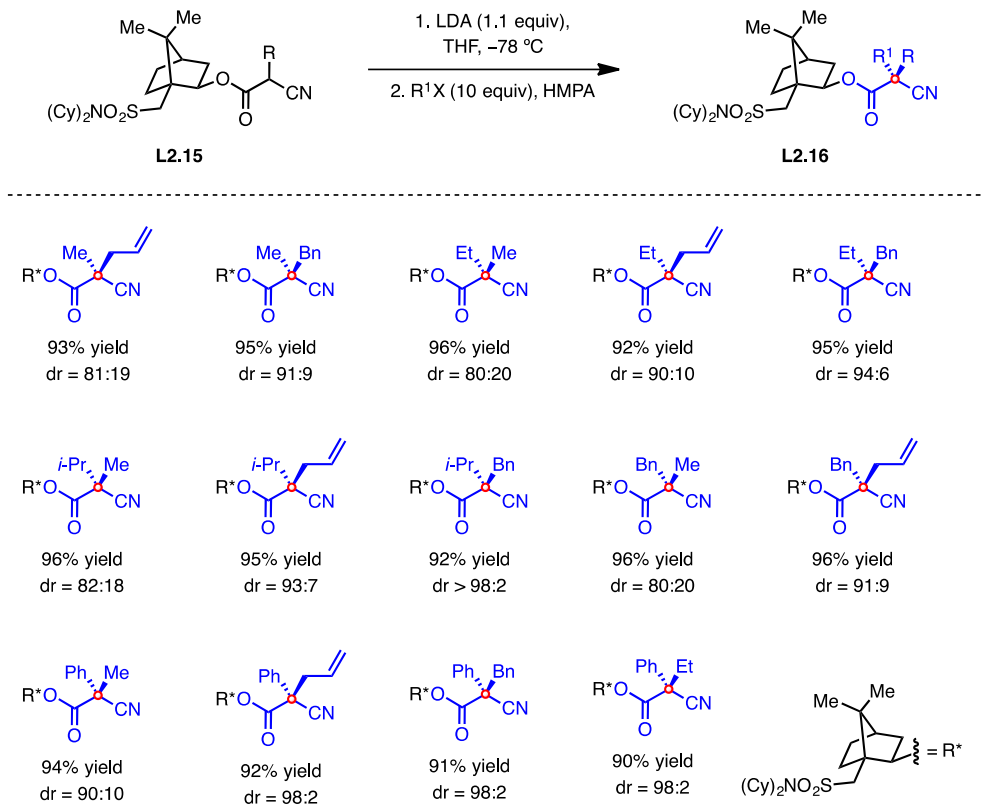


Scheme 38. Diastereoselective double alkylation strategy by Juaristi *et al*.

2.1.2. Oppolzer's sultam analogue

In a conceptually related system, Cativiela *et al*. reported the diastereoselective alkylation of the corresponding lithium enolate of **L2.15** in the preparation of α-quaternary cyanoesters derivatives **L2.16** (Scheme 39).[100] Hence, the alkylation of an epimeric mixture of α-cyanoester **L2.15** containing Oppolzer's sultam chiral auxiliary revealed to be compatible with a range of α-substituents in **L2.15**, affording the desired products **L2.16** in high yields and diastereoselectivities. One advantage of this procedure is that the chiral auxiliary can be easily removed under mild alkaline conditions (KOH, MeOH, reflux, 6 h).[101]

100 Cativiela, C.; Diaz-de-Villegas, M. D.; Gálvez, J. A. *J. Org. Chem.* **1994**, *59*, 2497.
101 (a) Cativiela, C.; Diaz-de-Villegas, M. D.; Gálvez, J. A. *Tetrahedron: Asymmetry* **1993**, *4*, 1445; (b) Ramón Badorrey, C. C., Maria D. Dias-de-Villegas, José A. Gálvez and; Lapeña, Y. *Tetrahedron: Asymmetry* **1997**, *8*, 311.

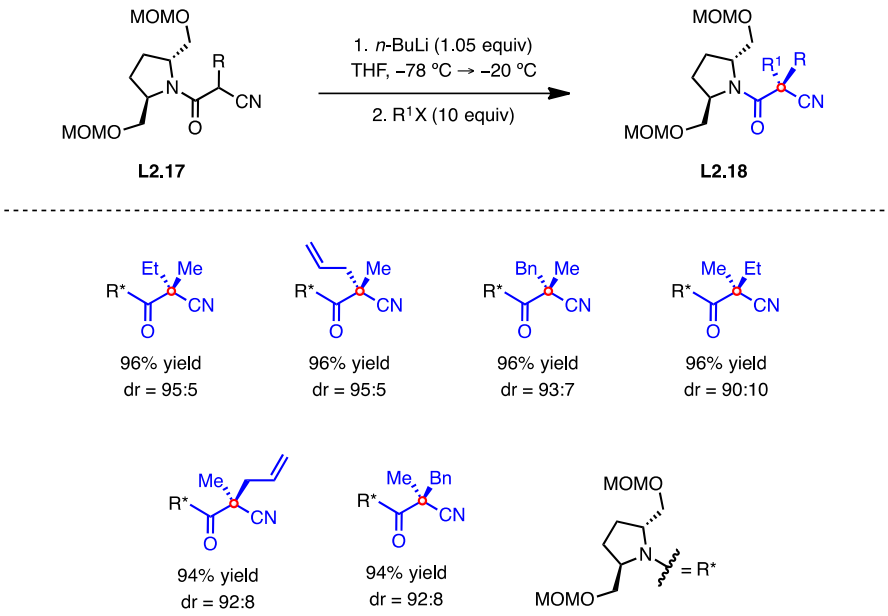


Scheme 39. Diastereoselective alkylation of chiral α-cyanoesters by Cativiela *et al*.

2.1.3. Pyrrolidine derivative

Similarly, Katsuki *et al*. have disclosed a diastereoselective synthesis of all-carbon α-quaternary cyanoacetamides **L2.18** by alkylation of the lithium amide enolate of **L2.17** using *trans*-2,5-bis(methoxymethoxymethyl)pyrrolidine as chiral auxiliary (Scheme 40).[102] The disubstituted pyrrolidine used by the authors accounted for a highly diastereoselective alkylation, leading to the formation of the desired $\beta^{2,2}$-amino acid precursors in high diastereomeric ratios and almost quantitative yields. Furthermore, the chiral auxiliary could be cleaved under mild acid media (HCl 6 M, rt, 12 h).

102 Hanamoto, T.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 2463.



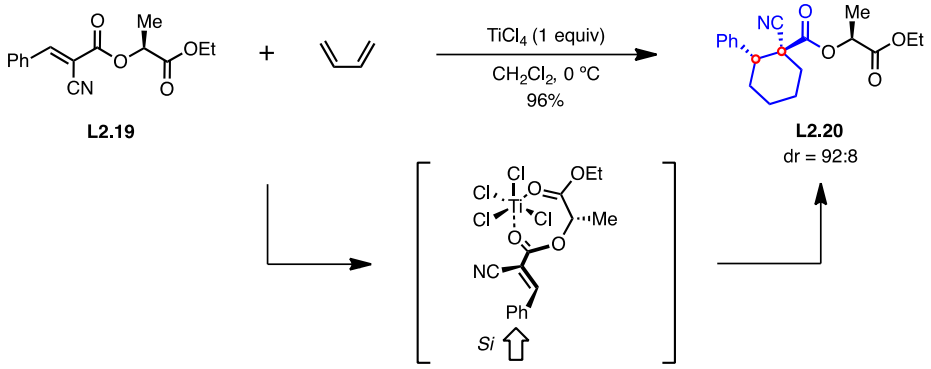
Scheme 40. Diastereoselective synthesis of α-quaternary cyanoacetamides by Katsuki *et al*.

2.1.4. Lactic acid derivative

For the preparation of $\beta^{2,2}$-amino acid precursors, Cativiela *et al*. explored a totally different approach (Scheme 41).[103] They used (*E*)-α-cyanocinnamate **L2.19** containing the (*S*)-ethyl lactate as the chiral auxiliary in a diastereoselective Diels-Alder reaction with 1,3-butadiene as the key step to produce the all-carbon α-quaternary center. The asymmetric Diels-Alder reaction of this chiral dienophile **L2.19** in the presence of equimolar amounts of $TiCl_4$ allowed the synthesis of the cycloadduct **L2.20** in good yield and diastereoselectivity. The asymmetric induction was in line with the seven-membered $TiCl_4$-dienophile chelate complex model, favoring the approach of the diene from the *Si* face. The hydrolysis and

103 Avenoza, A.; París, M.; Peregrina, J. M. *J. Org. Chem.* **1994**, *59*, 7774.

subsequent hydrogenations afforded the corresponding $\beta^{2,2}$-amino acid methyl ester in enantioenriched form.[104]



Scheme 41. Diastereoselective Diels-Alder approach by Cativiela *et al*.

2.2. Enantioselective Michael addition

Enantioenriched α-cyanoesters bearing all-carbon quaternary centers have been recognized as attractive precursors for the synthesis of all-carbon α-quaternary amino acid precursors and more specifically, $\beta^{2,2}$-amino acids, and other biologically relevant compounds. In this context, several catalytic enantioselective Michael addition approaches toward the synthesis of these stereodefined compounds have been reported since the early 1990's.[105]

2.2.1. Transition metal catalysis

104 Avenoza, A.; Cativiela, C.; París, M.; Peregrina, J. M. *Tetrahedron: Asymmetry* **1995**, *6*, 1409.
105 Peters, R.; Jautze, S. *Synthesis* **2010**, *3*, 365.

2.2.1.1. Rhodium catalysts

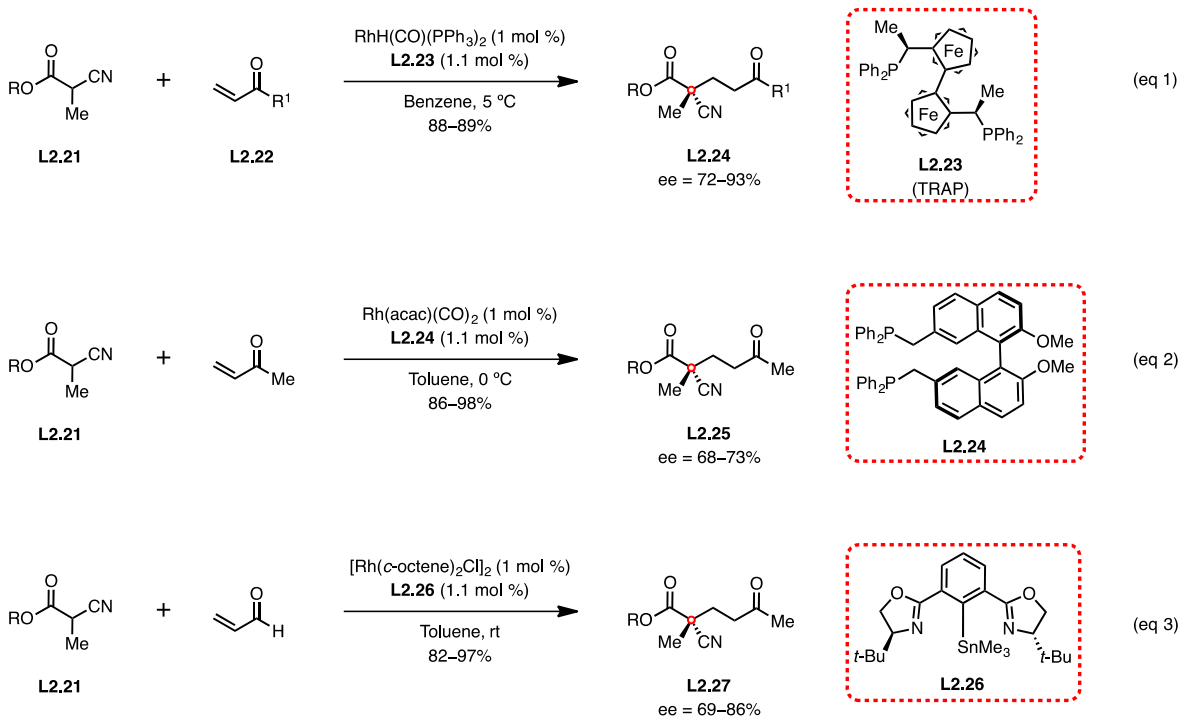
The direct enantioselective conjugate addition of α-substituted α-cyanoesters to activated olefins is among the most established and attractive method for C–C bond construction, due to their ideal atom economy and the availability of the required starting materials.

The first enantioselective catalytic Michael addition was disclosed by Ito *et al*. in 1992, enabling the conjugate addition of α-methyl α-cyanoesters **L2.21** to enones **L2.22** in good yields and enantioselectivities by using a Rh(I) complex in conjunction with a chiral diphosphine (TRAP **L2.23**) (Scheme 42, eq 1). [106] The authors argued that the *trans*-coordinating mode of the TRAP ligand was crucial to obtain high enantioselectivities, since the usual *cis*-coordinating ligands, such as BINAP or DIOP, led to racemic products. Moreover, the proposed mechanistic model suggests a rhodium complex *via* the coordination of the cyano moiety to the metal, whereas the concave chiral environment created by the TRAP ligand allows an efficient differentiation of both enantiotopic faces of the cyanoester enolate.

Inspired by the pioneering work of Ito *et al*., Takaya, Nozaki *et al*. later extended the Michael addition of α-methyl α-cyanoesters **L2.21** to the methyl vinyl ketone employing the binaphthol-derived ligand **L2.24** in combination with $Rh(acac)(CO)_2$, thus, obtaining Michael adducts in good yields but modest enantioselectivities (Scheme 42, eq 2).[107]

An alternative procedure was later reported by Motoyama *et al*. where a positive influence in the enantioselectivity was observed by using the pre-catalyst $[(Phebox)SnMe_3)]$ **L2.26** in combination with a Rh(I) source which undergoes an oxidative addition into the carbon-tin bond to provide the catalytic active Rh(III) species, leading to the formation of the Michael adduct in good yields but still with modest ee values (Scheme 42, eq 3).[108]

106 Sawamura, M.; Hamashima, H.; Ito, Y. *J. Am. Chem. Soc.* **1992**, *114*, 8295
107 Inagaki, K.; Nozaki, K.; Takaya, H. *Synlett* **1997**, 119.
108 Motoyama, Y.; Koga, Y.; Kobayashi, K.; Aoki, K.; Nishiyama, H. *Chem. Eur. J.* **2002**, 2968.



Scheme 42. Rh-catalyzed Michael addition of α-methyl α-cyanoesters.

As shown above, three different elements of chirality — planar, axial and central — have been used with rhodium catalysts, however, the planar-chiral complex reported by Ito *et al*. provided the best results in terms of enantioselectivity in the Michael addition of α-methyl α-cyanoesters.

2.2.1.2. Palladium catalysts

Although good results were obtained using the rhodium catalysis to realize Michael addition involving α-methyl α-cyanoesters, this method revealed unable to afford satisfactory levels of enantioselectivity for α-substituents larger than methyl. Therefore, alternative catalytic systems, such as palladium-based ones, were evaluated in an effort to address this issue.

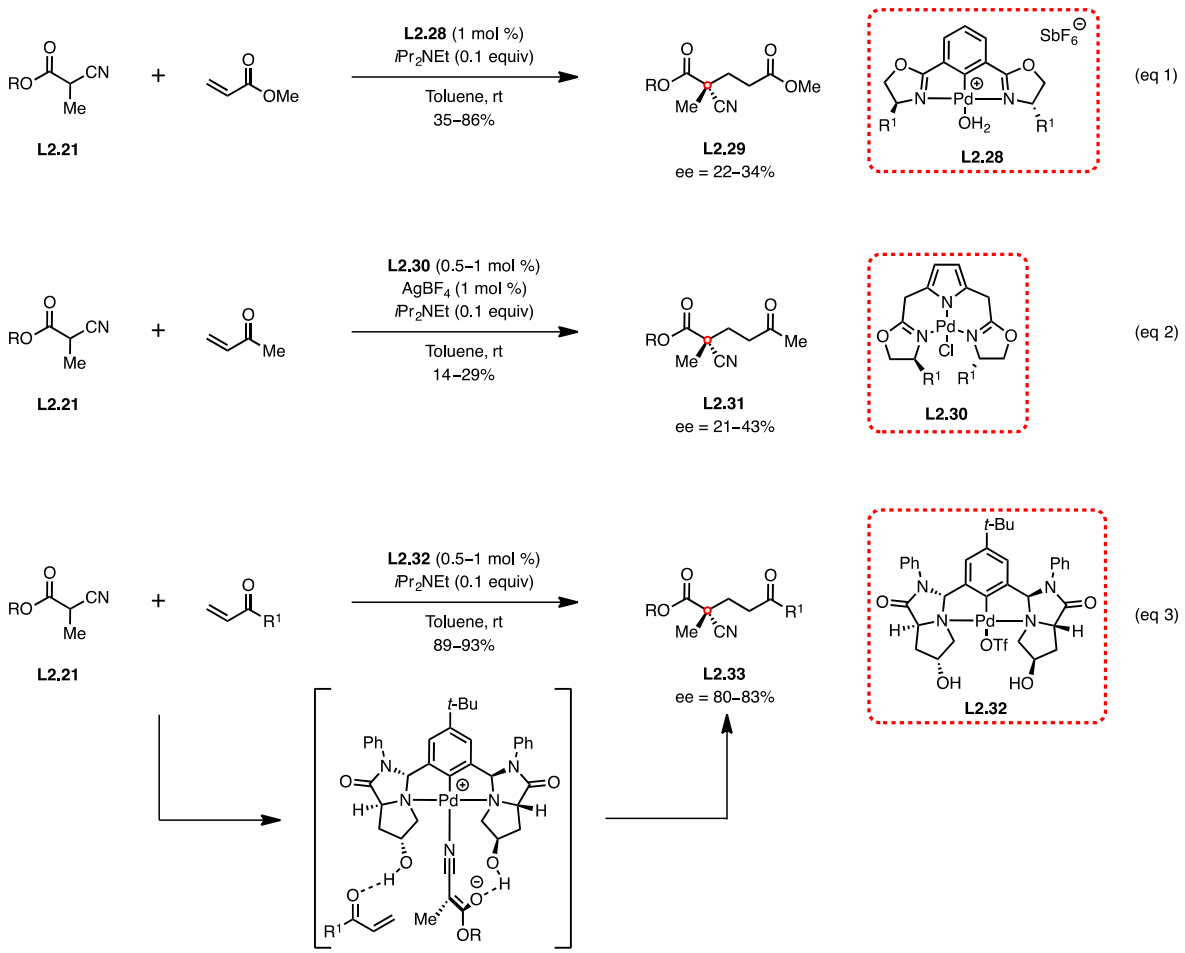
Richard *et al*. reported the first example of a palladium-catalyzed asymmetric Michael addition of α-methyl α-cyanoesters **L2.21** (Scheme 43, eq 1). In contrast to the rhodium-catalyzed Michael addition, a base was required to enable the reaction to take place.

Despite the series of different bisoxazoline palladium pincer complexes **L2.28** examined, these palladium catalysts were not able to afford better selectivities.[109]

An alternative palladium-based system was later developed by Mazet and Gade involving an asymmetric Michael addition of α-cyanoesters **L2.21** to methyl vinyl ketone (Scheme 43, eq 2).[110] Although slightly higher enantioselectivities were attained with the C_2-symetric *N*,*N*,*N*-palladium complex **L2.30**, yields remained poor due to low reactivity of the palladium catalyst, even after activating it with a silver salt.

Uozimi *et al*. introduced a very interesting new type of ligand to improve the enantioselectivity with palladium catalysts. Indeed, the use of NCN pincer palladium complex **L2.32** in combination with the Hünig's base as a co-catalyst afforded up to 83% ee (Scheme 43, eq 3).[111] The free hydroxyl groups revealed to be a key structural element for delivering high levels of enantioselectivity, since the selectivity dropped if the hydroxyl groups were protected or replaced by other substituents. These results lend credence to a possible higher organized transition state *via* hydrogen bonding of the hydroxyl groups to the α-cyanoenolate and the Michael acceptor. Unfortunately, like all the other transition metal catalysts evaluated, this system seemed to be limited to α-methyl substituted α-cyanoesters, as no α-substituents bulkier than methyl were reported.

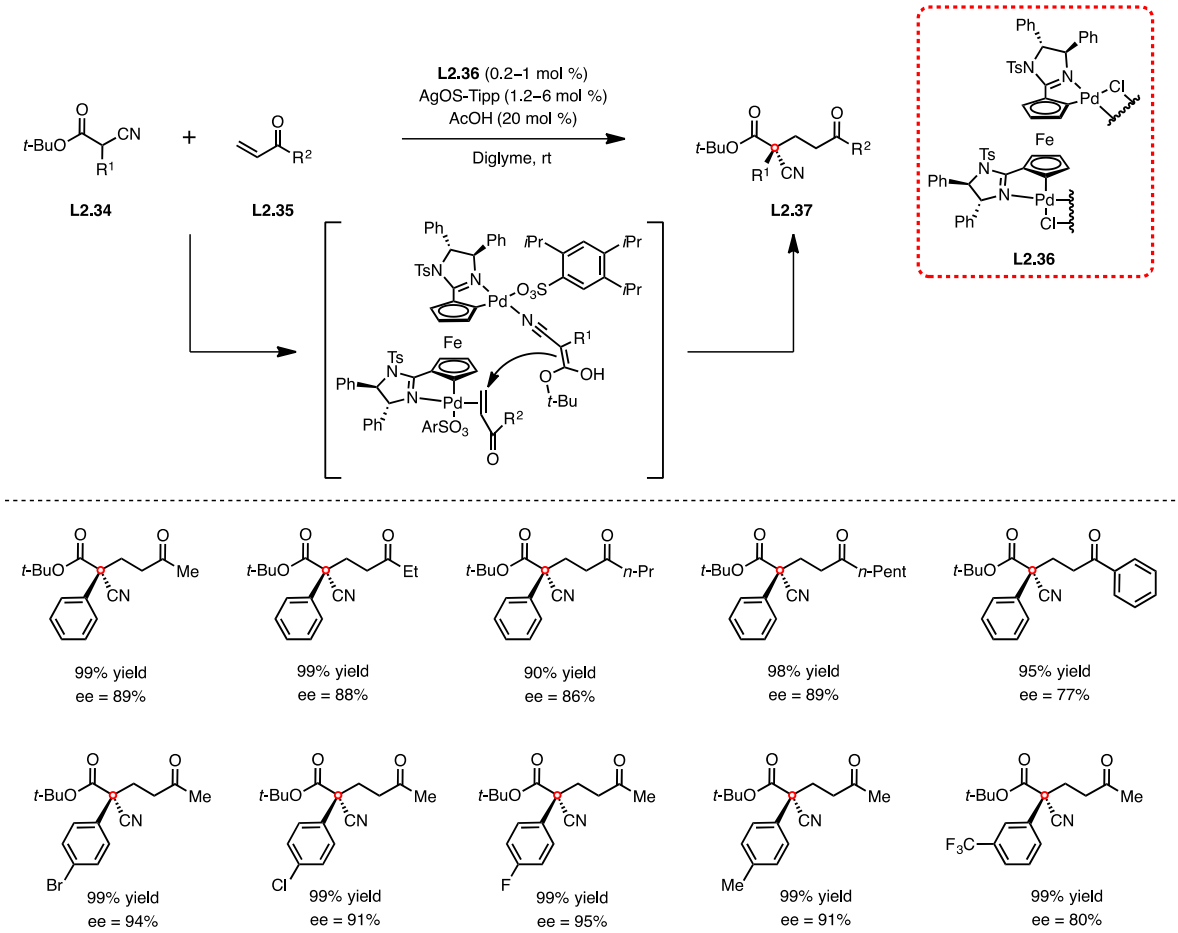
109 Stark, M. A.; Jones, G.; Richards, C. J. *Organometallics* **2000**, *19*, 1282.
110 Mazet, C.; Gade, L. H. *Chem. Eur. J.* **2003**, *9*, 1759.
111 Takenaka, K.; Minakawa, M.; Uozumi, Y. *J. Am. Chem. Soc.* **2005**, *127*, 12273.



Scheme 43. Pd-catalyzed Michael addition of α-methyl α-cyanoesters.

Based on the idea that an enhancement in the level of stereocontrol would be achieved with a highly-organized transition state, Peters and Jautze reported the application of a soft bimetallic complex capable of simultaneously activating both the Michael acceptor and the α-cyanoenolate (Scheme 44).[112] According to this hypothesis, an α-cyanoacetate such as **L2.34** should be activated by enolization promoted by coordination of the nitrile moiety to one Pd(II) center of the bispalladacycle complex FBIP-Cl **L2.36**, while the enone **L2.35** should be activated as an electrophile by coordination to the carbophilic Lewis acid. As a matter of fact, the use of the bimetallic catalyst **L2.36** induced high levels of enantioselectivity for the addition of different α-aryl α-cyanoacetate donors to Michael acceptors, revealing to be a successful alternative to overcome the limitations of the other transition metals based catalytic system had in the formation of bulkier α,α-disubstituted cyanoesters.

112 Jautze, S.; Peters, R. *Angew. Chem. Int. Ed.* **2008**, *47*, 9284.



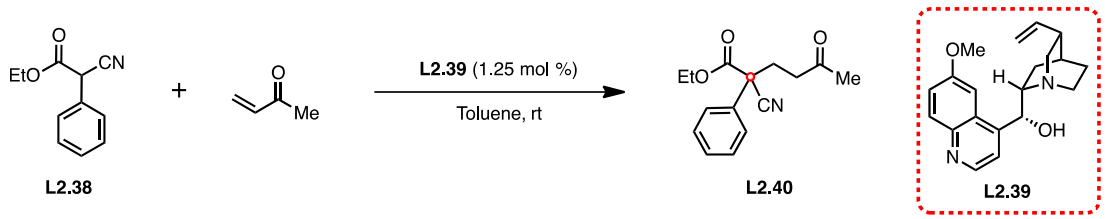
Scheme 44. Addition of α-cyanoesters to vinyl ketone by Jautze and Peters.

2.2.2. Organocatalysis

2.2.2.1. Cinchona catalysts

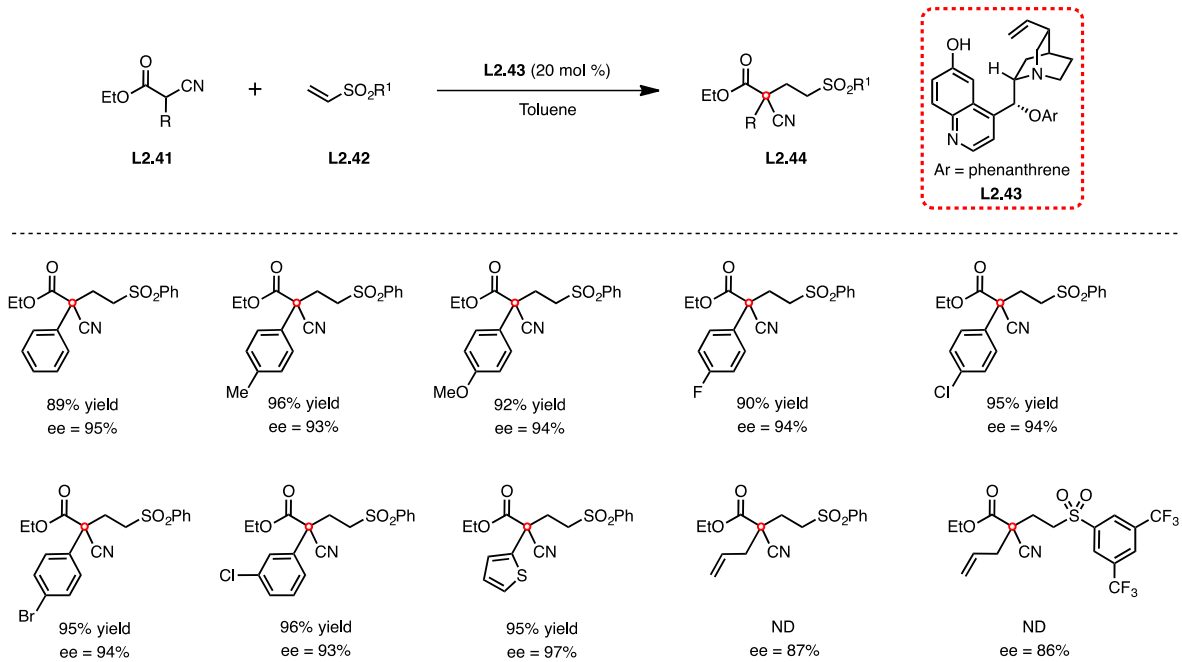
The use of organocatalysts in the enantioselective Michael addition of α-cyanoesters has been reported since 1975, when the first example of quinine **L2.39** catalyzed Michael addition of the α-cyanoester **L2.38** to methyl vinyl ketone was described by Wynberg and Helder (Scheme 45).[113] Unfortunately, neither the yields and enantiomeric excess were reported by the authors in this seminal work.

113 Wynberg, H.; Helder, R. *Tetrahedron Lett.* **1975**, *16*, 4057.



Scheme 45. Addition of α-cyanoester to methyl vinyl ketone by Wynberg and Helder.

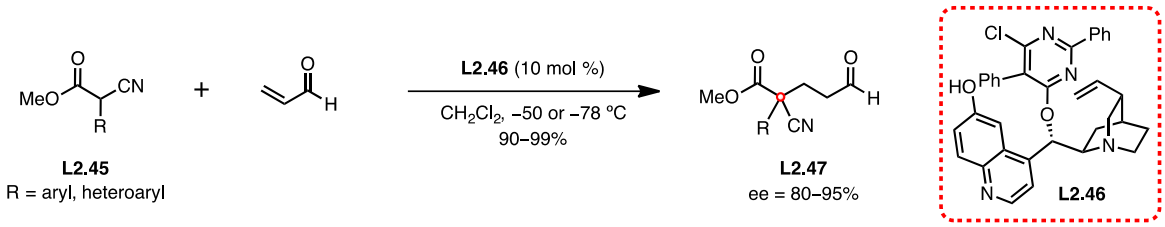
Nonetheless it was only in 2005 that the use of cinchona alkaloid derivatives was reported in the asymmetric Michael addition of α-cyanoesters. Deng *et al*. employed the quinine derivative **L2.43** in the conjugate addition of a range of structurally diverse α-cyanoesters **L2.41** onto vinyl sulfones **L2.42**. The addition products **L2.44** were obtained in both good yields and enantioselectivities (Scheme 46).[114] In the case of α-alkyl cyanoesters, the sulfonyl group was needed to exert a stronger electron-withdrawing effect to have a useful reactivity, due their lower enolization tendency. The observation of a slower reactivity of α-aryl cyanoesters, in which the aryl moiety was substituted by electron-rich groups, is in line with this assumption.



Scheme 46. Enantioselective addition of α-alkyl cyanoesters onto vinyl sulfones.

114 Li, H.; Song, J.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2005**, *127*, 8948.

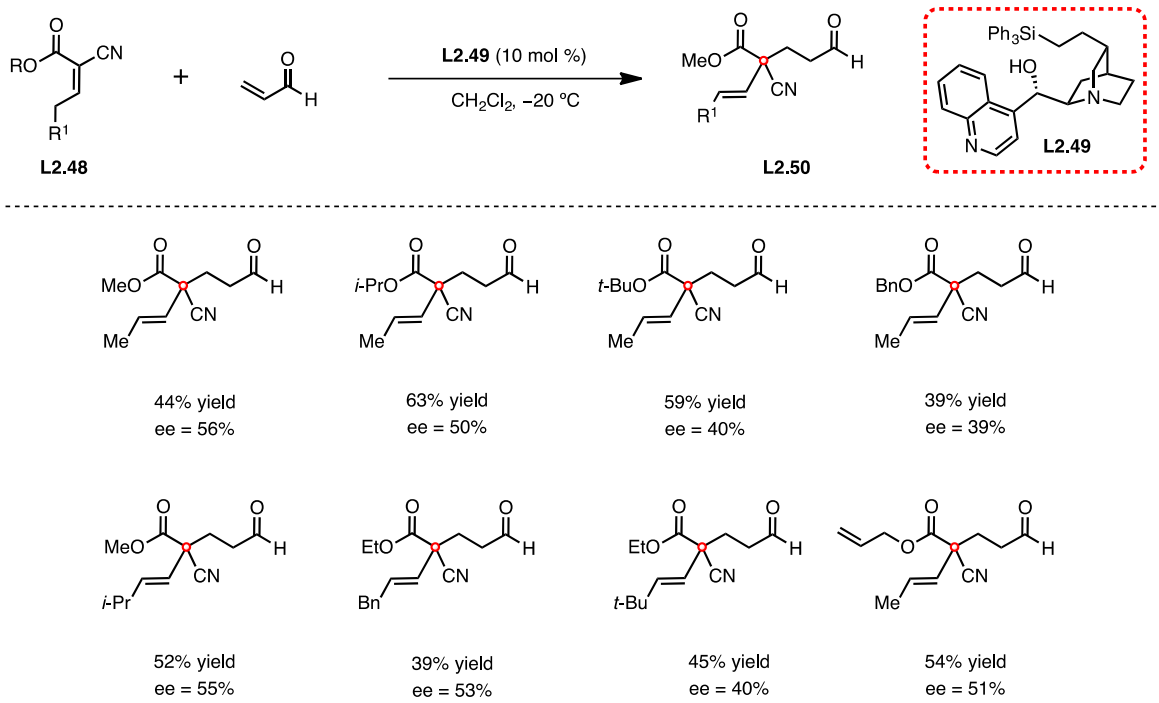
The broad applicability of alkaloid derivatives was even further extended by Deng *et al*. They disclosed the synthesis of a series of enantioenriched aldehydes **L2.47** through an asymmetric Michael reaction, using the catalyst **L2.46**, which plays a dual role of Brønsted acid-base catalyst. However, despite the good results, this procedure revealed to be limited to α-aryl and α-heteroaryl substituted cyano esters (Scheme 47).[115]



Scheme 47. Asymmetric Michael addition of α-cyanoesters onto acrolein by Deng *et al*.

A totally new approach was introduced by Jørgensen *et al*. in the formation of chiral quaternary aldehydes by Michael addition.[116] This conceptually different approach relied on the deprotonation of α,β-unsaturated α-cyanoesters **L2.48** at the γ-position by using cinchona alkaloid derivative **L2.49**. The resulting allylic anion intermediate subsequently underwent a conjugate addition, reacting preferentially at the α-position over to the γ-position. Despite the fact that this method relies on the use of readily available starting materials prepared by a simple Knoevenagel condensation, the enantioselectivities and yields remained moderate, ee = 39-56% and yield = 34-68% (Scheme 48).

115 Wu, F.; Hong, R.; Khan, J.; Liu, X.; Deng, L. *Angew. Chem. Int. Ed.* **2006**, *45*, 4301.
116 Bell, M.; Frisch, K.; Jørgensen, K. A. *J. Org. Chem.* **2006**, *71*, 5407.

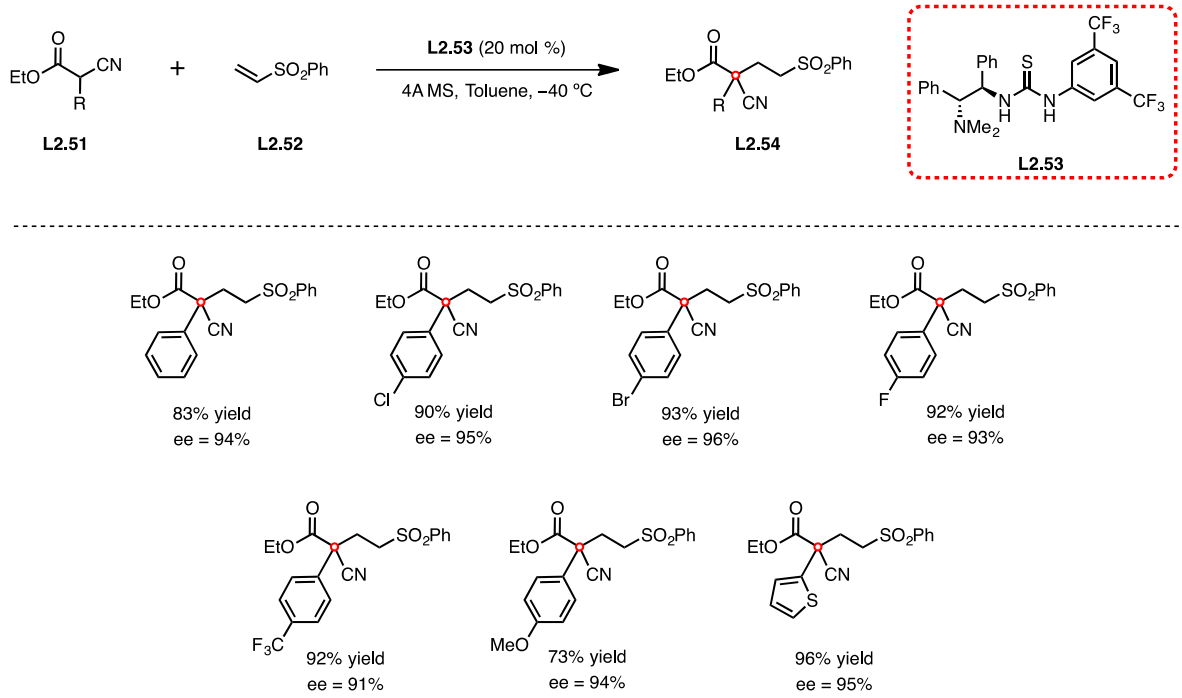


Scheme 48. Addition of α,β-unsaturated α-cyanoesters onto acrolein by Jørgensen *et al*.

2.2.2.2. Thiourea-derived catalysts

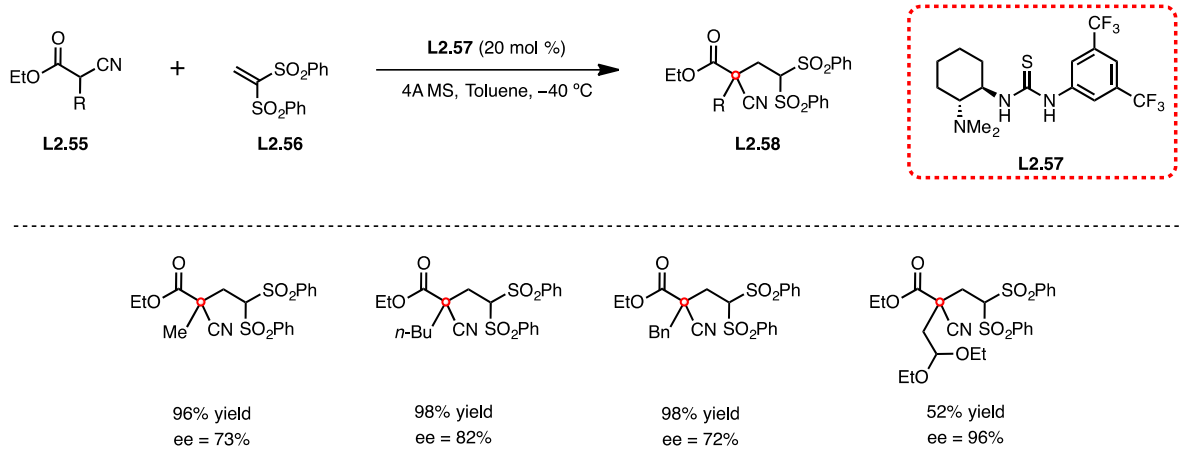
Chen *et al*. have showed that thiourea functionalized with a scalemic diamine moiety could also be used as catalyst in the enantioselective Michael addition of α-aryl substituted α-cyanoesters **L2.51** to vinyl sulfones **L2.52** (Scheme 49).[117] The thiourea-based catalyst **L2.53** allowed the access to Michael products bearing α-quaternary center in both high yields and enantioselectivities. It is worth pointing out that the sulfone group in the Michael acceptor has a fundamental role in this reaction.

117 Liu, T. Y.; Long, J.; Li, B. J.; Jiang, L.; Li, R.; Wu, Y.; Ding, L. S.; Chen, Y. C. *Org. Biomol. Chem.* **2006**, *4*, 2097.



Scheme 49. Enantioselective Michael addition of α-aryl substituted α-cyanoesters onto vinyl sulfones.

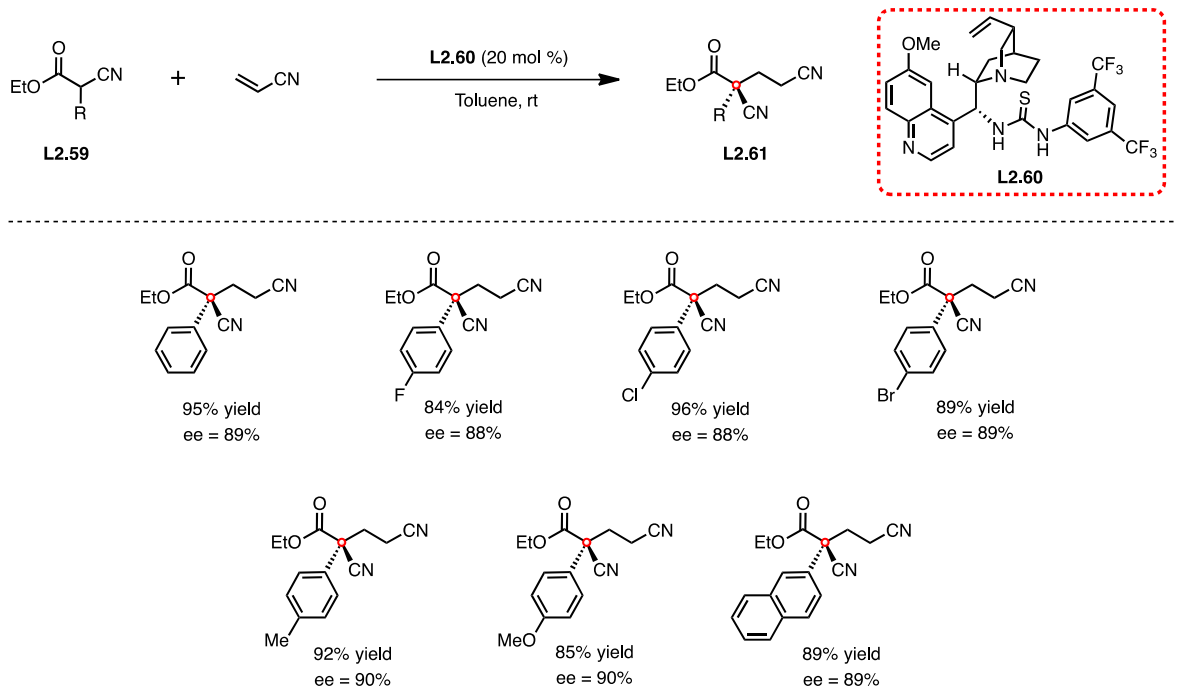
Nonetheless, the abovementioned catalytic system revealed to be inefficient for α-alkyl substituted α-cyanoesters **L2.55**, requiring longer reaction times and higher catalyst loadings. In order to overcome the low reactivity and selectivity, the same authors used a thiourea-based catalyst **L2.57** containing a different chiral amine scaffold and a more electron-deficient Michael acceptor **L2.56** to afford the Michael products **L2.58** in good selectivities and yields (Scheme 50).[117]



Scheme 50. Enantioselective Michael addition of α-substituted α-cyanoesters onto vinyl disulfones.

The remarkable catalytic efficiency demonstrated by cinchona alkaloids and thiourea-derived catalysts for the asymmetric Michael reaction of α-cyanoesters with a variety of Michael acceptors prompted Deng *et al*. to explore their ability to promote the enantioselective conjugate addition onto acrylonitrile, which had no precedent in the literature.[118] Partially due to its weak activity as Michael acceptor, the acrylonitrile appears to be particularly challenging for catalytic asymmetric conjugate additions. While both cinchona and thiourea catalysts failed to afford useful levels of enantioselectivity, the hybrid cinchona-thiourea catalyst **L2.60** was found to afford dramatically enhanced enantioselectivities in the formation of the Michael adducts **L2.61** (Scheme 51). Constituting the first highly enantioselective catalytic conjugate addition of α-cyanoesters onto acrylonitiles.

118 Wang, B.; Wu, F.; Wang, Y.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2007**, *129*, 768.



Scheme 51. First highly enantioselective catalytic conjugate addition onto acrylonitiles.

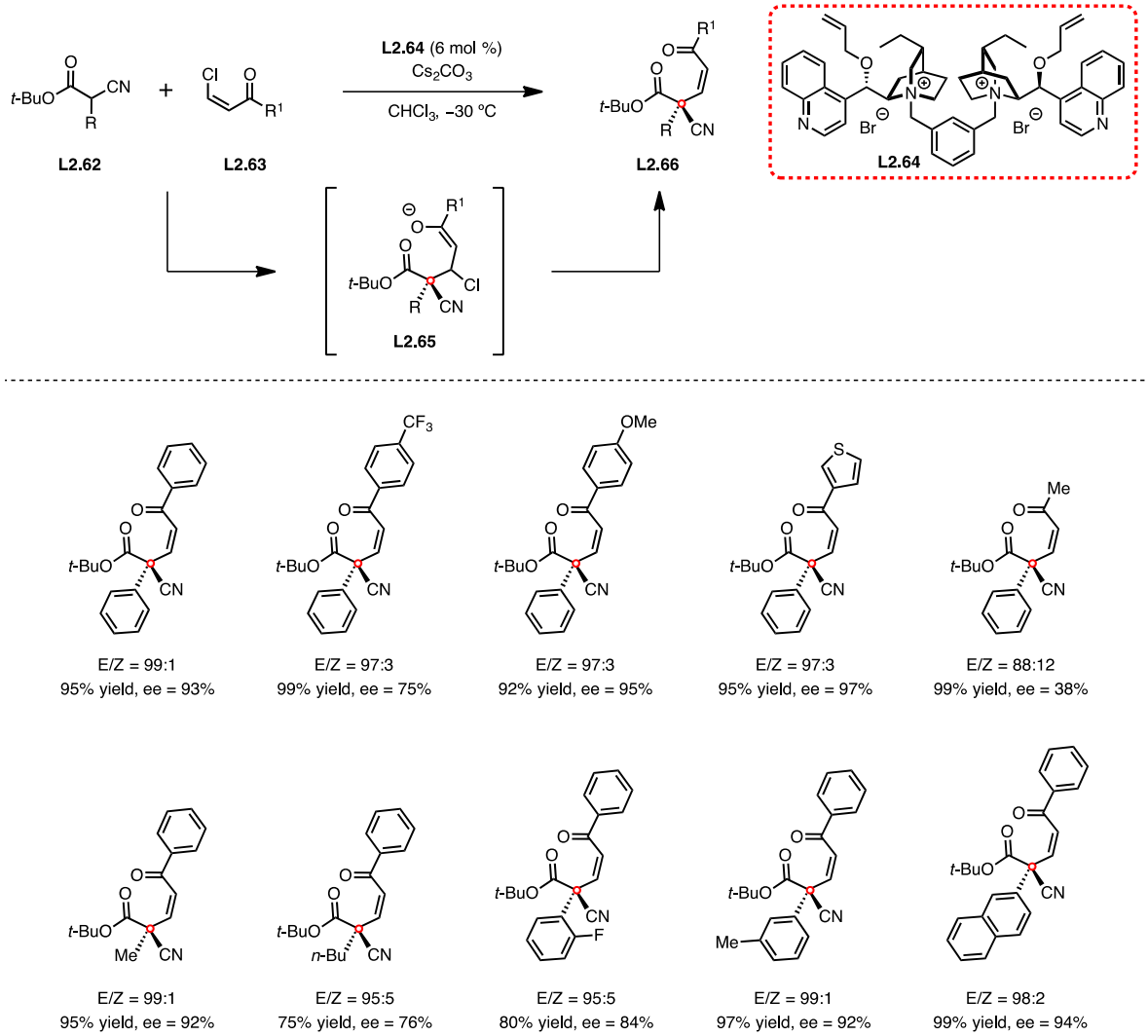
2.2.2.3. Phase-transfer catalysts

As shown throughout this Section, several research groups have developed chiral metal complexes and chiral secondary amines that are capable of catalyzing the Michael addition of α-cyanoesters in a highly enantioselectivity fashion. Ultimately, Jørgensen *et al*. disclosed a powerful catalytic system relying on the chiral phase-transfer catalyst **L2.64** derived from cinchonine (Scheme 52).[119] They described a synthetic method based on the asymmetric conjugated addition of α-substituted α-cyanoesters **L2.62** to β-chloro α,β-unsaturated carbonyl compounds **L2.63**, leading to the stereoselective construction of all-carbon α-quaternary centers in good yields, high ees and excellent control of the double bond geometry.

The vinylic substitution occurs through an initial conjugate addition of the α-cyano cesium enolate onto the Michael acceptor, resulting in the formation of a β-chloro substituted enolate **L2.65** which undergoes rapid elimination of the halide to form the double bond. More importantly, this type of addition/elimination sequence takes place with retention of the

119 Bell, M.; Poulsen, T. B.; Jørgensen, K. A. *J. Org. Chem.* **2007**, *72*, 3053.

configuration of the double bond due to the stereoelectronic properties of the β-chloro enolate intermediate **L2.65**.

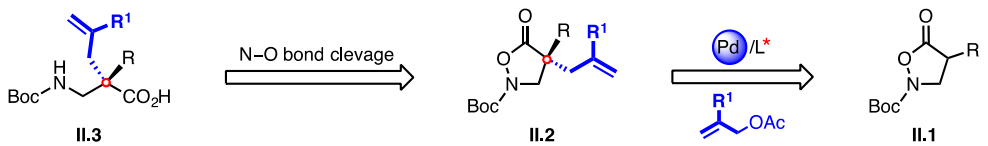


Scheme 52. Phase-transfer catalyzed enantioselective Michael addition of α-cyanoesters.

3. Results and discussion

3.1. Context and objective

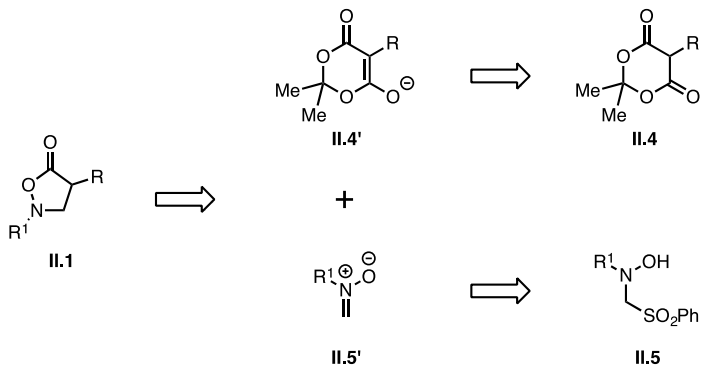
As mentioned previously, asymmetric methods allowing a straightforward access to β-amino acids have been the focus of tremendous efforts over the past decade. Based on our previous results obtained in the synthesis of α-quaternary γ-butyrolactones *via* an intermolecular palladium-catalyzed asymmetric allylation (Chapter 1 - Section 4.9),[77] we envisioned that the $\beta^{2,2}$-amino acids **II.3** could be prepared from all-carbon α-quaternary isoxazolidin-5-ones **II.2**, after reductive cleavage of N–O bond, which will be obtained, in turn, by the enantioselective allylic alkylation of 4-substituted isoxazolidin-5-ones **II.1** (Scheme 53).



Scheme 53. Synthesis of $\beta^{2,2}$-amino acids *via* a key Pd-AAA.

3.2. Synthesis of 4-substituted isoxazolidin-5-ones

This investigation began with the development of two general strategies toward the preparation of 4-substituted isoxazolidin-5-ones required for this study. The synthesis of the substrates **II.1** bearing different substituents at the 4-position should be accomplished through an anionic formal [3+2] cycloaddition between the enolate of Meldrum's acid **II.4'** and the nitrone **II.5'**, which will be respectively issued from the Meldrum's acid **II.4** and the *N*-hydroxyamine sulfone **II.5** (Scheme 54).[120]



Scheme 54. General strategy for the synthesis of 4-substituted isoxazolidin-5-ones **II.1**.

3.2.1. Synthesis of substituted Meldrum's acid

3.2.1.1. From diethyl malonate by using cross-coupling

The Meldrum's acids **II.4** containing an aromatic substituent were prepared from the commercially available diethyl malonate **II.6** in three steps. The first step consisted of the arylation of **II.6** catalyzed by either Pd and Cu catalysts. The palladium-catalyzed arylation was performed according to the procedure reported by Hartwig and Beare,[121] by preparing the enolate of diethyl malonate **II.6** (NaH 1.1 equiv) and treatment with ArBr (1 equiv) in the presence of Pd(*t*-$Bu_3P)_2$ (4 mol %) in THF at 70 ºC for 48 h. In the case of copper-catalyzed arylation, the reaction was performed following Ma *et al*. procedure,[122] e.g. by using Cs_2CO_3 (4 equiv) and ArI (1 equiv) in the presence of CuI (10 mol %) and L-proline (20 mol %) in

120 (a) Tite, T.; Sabbah, M.; Levacher, V.; Briere, J. F. *Chem Commun* **2013**, *49*, 11569; (b) Postikova, S.; Tite, T.; Levacher, V.; Brière, J.-F. *Adv. Synth. Catal.* **2013**, *355*, 2513.
121 Beare, N. A.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 541.
122 Xie, X.; Cai, G.; Ma, D. *Org. Lett.* **2005**, *7*, 4693.

DMSO at 40 ºC for 48 h. A second copper-based protocol was also used to realize the arylation of **II.6**, by utilizing Cs_2CO_3 (3 equiv), CuI (10 mol %), 2-picolinic acid (10 mol %) and ArI (1 equiv) in 1,4-dioxane at rt for 48 h (Table 13).[123]

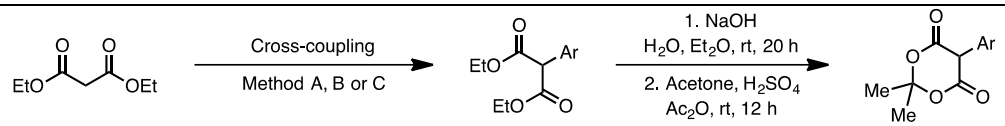
The palladium-catalyzed arylation protocol (**Method A**) reported by Hartwig and Beare generally afforded inferior results compared to the copper-based protocols (**Method B** and **C**), which afforded the cross-coupling products in yields ranging between 44% and 50%. The moderate electron-rich aryl bromide (Table 13, entry 3) furnished a slightly higher yield than the electron-deficient one (Table 13, entry 7). The milder copper-based systems reported by Ma *et al*. and Kwong *et al*. allowed the synthesis of the arylated malonates in good yields. The catalytic system developed by Ma (**Method B**: CuI (10 mol %), L-proline (20 mol %) in DMSO at 40 ºC) appeared to be efficient in coupling aryl iodides with diethyl malonate (Table 13, entry 4), although the improved Kwong's system (**Method C**), which could be carried out at room temperature and with a lower catalytic loading of 5 mol % of CuI and 10 mol % of 2-picolinic acid, proved to be even more efficient in delivering the cross-coupled product in up to 81% yield (Table 13, entry 6). Interestingly, neither the palladium- nor the copper-catalytic systems were able to realize the coupling of aryl halides bearing strong electron-withdrawing groups with the enolate of diethyl malonate **II.6**, and resulted in the recovery of the corresponding dehalogenated arenes.

With the aryl group in place, compounds **II.7** were transformed to **II.4** in two steps. After saponification using NaOH (4 equiv) in a mixture of Et_2O/H_2O (3:1) at rt, the corresponding malonic acids were isolated in good to excellent yields (see experimental section for further details). Ultimately, the synthesis of Meldrum's acid could be accomplished after treatment of the dicarboxylic acids with acetone under acidic conditions (H_2SO_4, Ac_2O, rt, 12 h). The Meldrum's acids formation seemed to be substrate dependent, with yields varying between 31% and 82% (Table 13). Besides the modest to good yields obtained in the Meldrum's acid formation step, the latter revealed to be incompatible to functionalities possessing alkaline sites, since this reaction is performed in acidic media.[124]

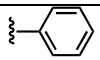
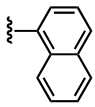
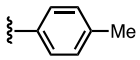
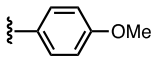
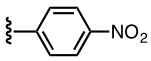
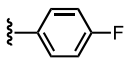
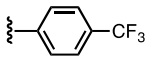
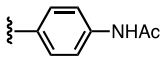
123 Yip, S. F.; Cheung, H. Y.; Zhou, Z.; Kwong, F. Y. *Org. Lett.* **2007**, *9*, 3469.

124 (a) Crooy, P.; Neys, R. d.; Eliaers, J.; Liveyns, R.; Simonet, G.; Vandevelde, J. *Bull. Soc. Chim. Belg.* **1977**, *86*, 991; (b) Dandala, R. S., M. S. P.; Chaudhary, H.; Sivakumaran, M. *An improved process for the preparation of penicillin derivatives*. Indian Pat. Appl. IN 2004CH01095, **2006**.

Table 13. Synthesis of aryl-containing Meldrum's acids from diethyl malonate.



II.6 **II.7** **II.4**

Entry	Catalyst / Method	**II.7** (yield[a])	Ar	**II.4** (yield[a])
1	–[b]	**II.7a** (–%)		**II.4a** (64%)
2	Pd / A	**II.7b** (50%)		**II.4b** (15%)
3	Pd / A	**II.7c** (49%)		**II.4c** (24%)
4	Cu / B	**II.7d** (59%)		**II.4d** (47%)
5	Pd or Cu / A or B	– (0%)		–
6	Cu / C	**II.7e** (81%)		**II.4e** (41%)
7	Pd / A	**II.7f** (44%)		**II.4f** (52%)
8	Pd or Cu / A or B	– (0%)		–
9	–[b]	**II.7g** (–%)		**II.4g** (79%)

Method A: **II.6** (1.1 equiv), ArBr (1 equiv), Pd(*t*-Bu_3P)$_2$ (4 mol %), NaH (1.1 equiv), THF, 70 ºC, 48h. **Method B**: **II.6** (1.2 equiv), ArI (1 equiv), CuI (10 mol %), L-proline (20 mol %), Cs_2CO_3 (4 equiv), DMSO, 40 ºC, 48h. **Method C**: **II.6** (2 equiv), ArI (1 equiv), CuI (5 mol %), 2-picolinic acid (10 mol %), Cs_2CO_3 (3 equiv), 1,4-dioxane, rt, 48h. [a] Isolated yield over two steps. [b] The corresponding α-aryl malonic acid is commercially available.

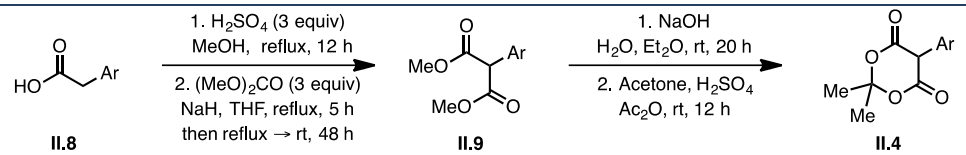
3.2.1.2. From α-aryl acetic acids by using *C*-acylation

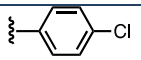
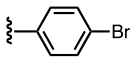
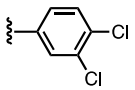
In order to broaden the set of synthesized Meldrum's acids **II.4**, we next decided to prepare various substrates bearing halide-substituted aromatic rings. Since the transition metal-catalyzed cross-coupling approaches could not be used, an alternative strategy was envisioned. This strategy relied on the use of commercially available α-aryl acetic acids **II.8** and featured an esterification reaction by using H_2SO_4 (3 equiv) in refluxing MeOH,[125] followed by a *C*-acylation. This *C*-acylation was achieved by the treatment of the corresponding methyl ester of **II.8** with NaH (2.4 equiv) in THF, and then by trapping the

125 Ringstrand, B.; Oltmanns, M.; Batt, J. A.; Jankowiak, A.; Denicola, R. P.; Kaszynski, P. *Beilstein J Org Chem* **2011**, *7*, 386.

resulting sodium enolate with dimethyl carbonate.[126] The corresponding dimethyl malonates **II.9** were then subjected to the same above-mentioned saponification conditions (NaOH, Et_2O, H_2O), followed by treatment with acetone under acidic conditions (H_2SO_4, Ac_2O, rt, 12 h) toward the Meldrum's acid formation as previously. The desired products **II.4**, bearing the desired halide-substituted aromatic rings, were obtained in much better overall yields compared to the previous approach, ranging from 51% to 67%, as depicted in Table 14.

Table 14. Synthesis of aryl-containing Meldrum's acids from α-aryl acetic acids.



Entry	Ar	**II.4**	Yield[a] (%)
1		**II.4h**	63
2		**II.4i**	67
3		**II.4j**	51

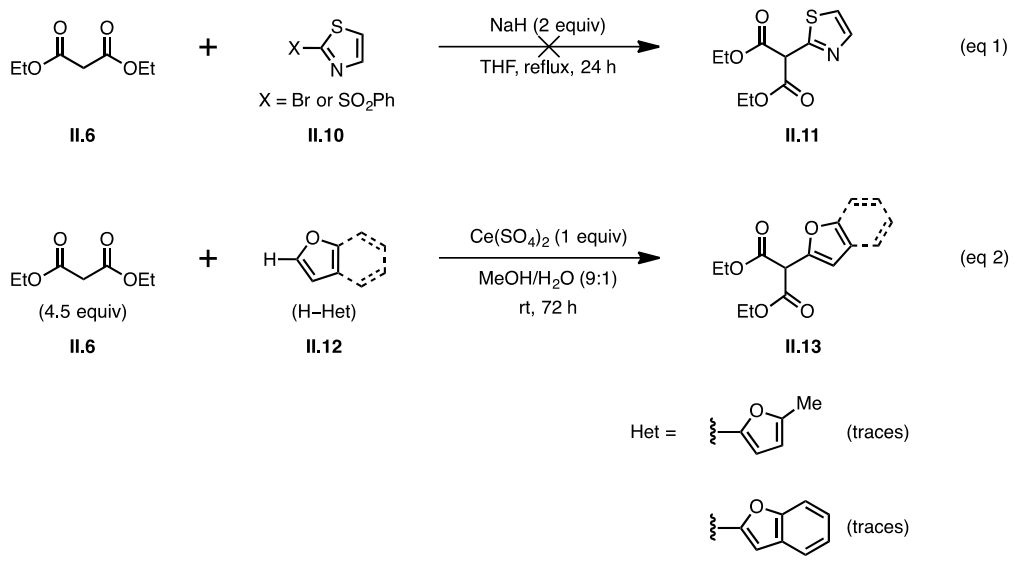
[a] Isolated yield over four steps.

3.2.1.3. From diethyl malonates by using SNAr and a radical heteroarylation

Two other strategies have been used to access the malonic ester-containing heteroaromatic moieties. The first one, consisting of an aromatic substitution reaction between diethyl malonic ester sodium enolate, generated from diethyl malonic ester **II.6** in the presence of NaH (2 equiv) in THF, and 2-substituted thiazoles (Scheme 55, eq 1).[127] Unfortunately, neither the 2-bromo nor the 2-phenylsulfonyl thiazoles appeared to be reactive enough to lead to the desired product, even when running the reaction at higher temperature, resulting in complete recovery of the starting material. The second approach, based on a Ce(IV)-promoted reaction between the malonyl radical issued from **II.6** and electron-rich heteroaromatic molecules such as 2-methylfuran and benzofuran, proved unsuccessful for

126 Zi, W.; Toste, F. D. *Angew. Chem. Int. Ed.* **2015**, *54*, 14447.
127 (a) Yamanaka, H.; Ohba, S.; Sakamoto, T. *Heterocycles* **1990**, *31*, 1115; (b) Liang, S.; Zhang, R. Y.; Xi, L. Y.; Chen, S. Y.; Yu, X. Q. *J. Org. Chem.* **2013**, *78*, 11874.

delivering the heteroarylated malonates, as only traces of the product were detected (Scheme 55, eq 2).[128]



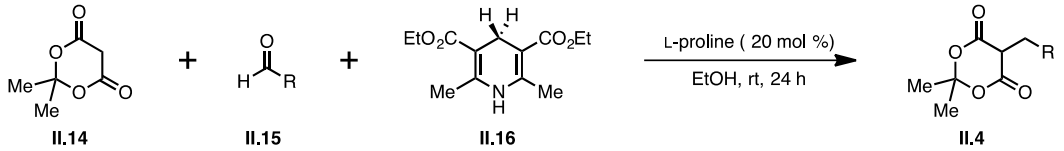
Scheme 55. Attempts for the preparation of heteroaryl-containing diethyl malonates toward the synthesis of Meldrum's acids.

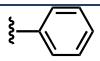
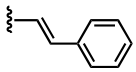
3.2.1.4. From the Meldrum's acid by using a Tandem Knoevenagel/Reduction

In the case of alkyl substituted Meldrum's acid **II.4**, we considered the protocol developed by Ramachary *et al.*[129] involving a tandem Knoevenagel condensation of the native Meldrum's acid **II.14** with aldehydes **II.15** in the presence of a catalytic amount of L-proline (20 mol %) in EtOH. The reactions afforded the homologated products, which subsequently underwent the double bond reduction in the presence of Hantzsch ester **II.16** to produce the substituted Meldrum's acid **II.4** (Table 15).

128 Weinstock, L. M.; Corley, E.; Abramson, N. L.; King, A. O.; Karady, S. *Heterocycles* **1988**, *27*, 2726.
129 (a) Ramachary, D. B.; Kishor, M.; Reddy, Y. V. *Eur. J. Org. Chem.* **2008**, *2008*, 975; (b) Ramachary, D. B.; Kishor, M.; Ramakumar, K. *Tetrahedron Lett.* **2006**, *47*, 651.

Table 15. Synthesis of alkyl-containing Meldrum's acids.



Entry	R	**II.4**	Yield[a] (%)
1		**II.4k**	74
2		**II.4l**	75

[a] Isolated yield.

The products **II.4k** and **II.4l**, resulting from the tandem reaction, were isolated in 74% and 75% yield, respectively, albeit the total conversion of the starting material. The biggest disadvantage of this method relied on the though purification process due to the co-elution of the corresponding byproduct of the Hantzsch ester and the Meldrum's acid **II.4**.

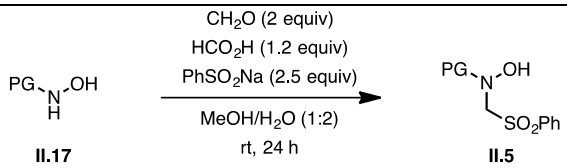
3.2.2. Synthesis of the nitrone precursors: *N*-hydroxyamine sulfones

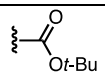
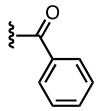
The synthesis of the first example of *N*-hydroxyamine sulfones **II.5**, which are the nitrone precursors required in the synthesis of isoxazolidinones **II.1**, was easily realized following the procedure described in the pioneering work of Denis *et al.*[130] Hence, starting from formaldehyde and *t*-butyl *N*-hydroxycarbamate in a mixture of MeOH/H_2O (1:2) in the presence of sodium benzene sulfonate and formic acid at rt, the sulfone **II.5a** was isolated in an excellent yield of 92% after simple filtration of the reaction mixture, followed by recrystallization from a mixture of hexane/AcOEt (3:1) (Table 16, entry 1).

With this procedure in hands, we then aimed at preparing various *N*-hydroxyamine sulfones bearing a protecting group with different electronic and steric features imbedded within alkyl, aryl and acyl groups (Table 16, entries 2-6). Unfortunately, all our attempts to prepare these compounds failed. It seems that the reactivity of these *N*-hydroxyamines **II.17** toward the formation of nitrone precursors is strongly dependent on the nature of the substituent directly attached to the nitrogen atom, as only the Boc protected nitrogen-containing substrate afforded the desired sulfone **II.5**.[131]

130 Guinchard, X.; Vallée, Y.; Denis, J.-N. *Org. Lett.* **2005**, *7*, 5147.
131 Gioia, C.; Fini, F.; Mazzanti, A.; Bernardi, L.; Ricci, A. *J. Am. Chem. Soc.* **2009**, *131*, 9614.

Table 16. Synthesis of nitrone precursors.



Entry	PG	**II.5**	Yield[a] (%)
1		**II.5a**	92
2		–	0
3		–	0
4		–	0
5		–	0
6		–	0

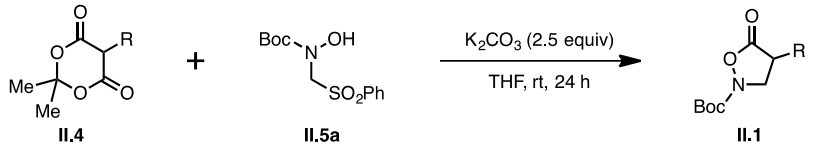
[a] Isolated yield.

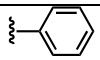
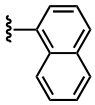
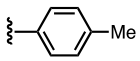
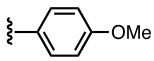
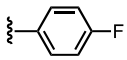
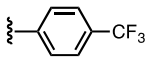
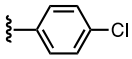
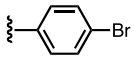
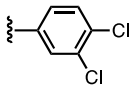
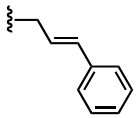
3.2.3. Formation of 4-substituted isoxazolidin-5-ones

Once we had accomplished the synthesis of the Meldrum's acids **II.4** and nitrone precursor **II.5a**, these compounds were engaged into the formation of the corresponding isoxazolidin-5-ones **II.1**, following the method previously mentioned, e.g. by using basic conditions such as K_2CO_3 (2.5 equiv) in THF at rt for 24 h. The results are depicted in Table17.[120]

As shown in Table 17, a variety of 4-substituted isoxazolidin-5-ones was prepared in this manner in good to excellent yields. In contrast to the observation made by Brière *et al*. for non-formation of isoxazolidin-5-ones bearing an aryl substituent at the 4-position, we were able to successfully synthesize these compounds, albeit in slightly reduced yields compared to the alkylated compounds. However, we have noticed one exception, 5-naphthyl Meldrum's acid **II.4b**, which demonstrated to be unreactive and did not lead to the formation of the corresponding isoxazolidinone (Table 17, entry 2). In the case of isoxazolidinone **II.1h**, containing a dichloro-substituted aryl group, the observed low yield of 41% is most probably the result of a low solubility of the Meldrum's acid precursor (Table 17, entry 9).

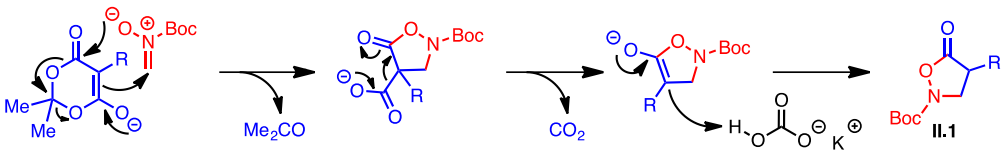
Table 17. Synthesis of 4-substituted isoxazolidin-5-ones.



Entry	R	II.1	Yield[a] (%)
1		**II.1a**	70
2		–	NR
3		**II.1b**	63
4		**II.1c**	59
5		**II.1d**	74
6		**II.1e**	75
7		**II.1f**	69
8		**II.1g**	65
9		**II.1h**	41
10		**II.1i**	79
11		**II.1j**	90
12		**II.1k**	69

[a] Isolated yield.

In the presence of the Meldrum's acid enolate, the nitrone, generated *in situ* from **II.5a** under basic conditions (K_2CO_3, THF, rt), underwent an anionic domino formal [3+2] cycloaddition, triggering the domino fragmentation-decarboxylation-protonation sequence in the formation of the corresponding isoxazolidinone derivatives **II.1** (Scheme 56).



Scheme 56. Reaction pathway toward the formation of the isoxazolidinones.

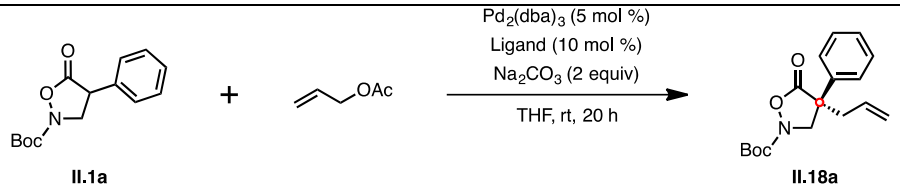
3.3. Optimization study to access all-carbon α-quaternary isoxazolidinones

Once the syntheses were completed, each 4-substituted isoxazolidin-5-ones **II.1** were engaged in the palladium-catalyzed allylic alkylation reaction (Pd-AAA) to evaluate their reactivity and determine any eventual selectivity.

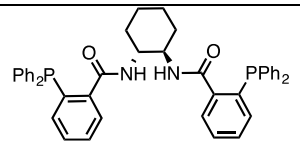
The study started with the 4-phenyl isoxazolidin-5-one **II.1a** as the model substrate and the allyl acetate as the allyl donor. These two compounds were subjected to an array of conditions including different bases, solvents, additives, reaction temperatures, palladium sources and chiral ligands. The results are summarized in Table 18.

The asymmetric allylic alkylation of isoxazolidin-5-one **II.1a** was first examined using $Pd_2(dba)_3$ (5 mol %) and a variety of chiral ligands (Table 18, entries 1-7). As a general trend, the reaction afforded the corresponding allylated isoxazolidinone **II.18a** in good yields ranging from 85% to 95%, independently of the ligand used. The investigation revealed that neither the *t*-Bu-PHOX ligand (*S*)-**L4**, nor the axially chiral diphosphine-type ligands such as BINAP (*R*)-**L5**, and the spirocyclic SDP (*R*)-**L7**, or the phosphoramidite-type ligand (*S*,*R*,*R*)-**L6** could induce high levels of enantioselectivity (Table 18, entries 4-7). As observed in Chapter 1 – Section 4.3, the C_2-symmetric diphosphines developed by Trost (*R*,*R*)-**L1**, (*R*,*R*)-**L2**, and (*R*,*R*)-**L3**, again led to useful level of selectivity. Interestingly, the DACH phenyl Trost ligand (*R*,*R*)-**L1** was once again the best ligand, affording the best results for α,α-disubstituted isoxazolidinone **II.18a**, which was isolated in 95% yield and 90% ee (Table 18, entry 1).

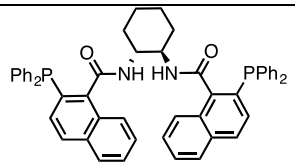
Table 18. Influence of the ligand[a]



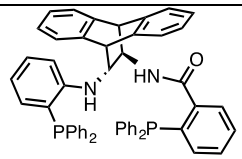
Entry	Ligand	Yield[b] (%)	ee[c] (%)
1	(*R*,*R*)-**L1**	95	90
2	(*R*,*R*)-**L2**	81	82
3	(*R*,*R*)-**L3**	93	26
4	(*S*)-**L4**	92	4
5	(*R*)-**L5**	94	22
6	(*S*,*R*,*R*)-**L6**	85	8
7	(*S*)-**L7**	90	3



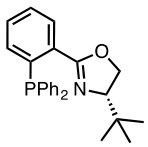
(*R*,*R*)-**L1**



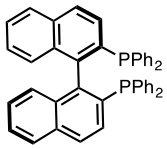
(*R*,*R*)-**L2**



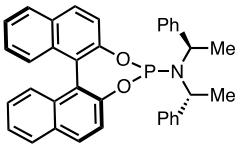
(*R*,*R*)-**L3**



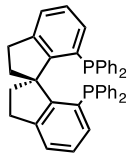
(*S*)-**L4**



(*R*)-**L5**



(*S*,*R*,*R*)-**L6**

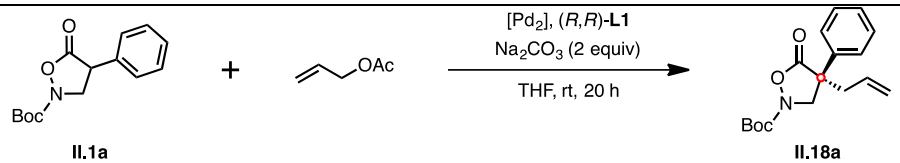


(*S*)-**L7**

[a] All the reactions were performed on 0.2 mmol. [b] Isolated yield. [c] Determined by SFC analysis.

Encouraged by these preliminary results, the effect of the palladium catalyst precursor on the enantioselectivity was then evaluated. In general, changing the palladium source drastically influenced both the yield and the enantiomeric excess. Indeed, $[Pd(allyl)Cl]_2$ (Table 19, entry 3) and $[Pd(cinnamyl)Cl]_2$ (Table 19, entry 4) both afforded the allylated product in similar yields but with a significant difference in the ee values, 70% and 80%, respectively. The use of $Pd(OAc)_2$ (Table 19, entry 5), on the other hand, provided the poorest yield, albeit with a comparable enantioselectivity to $[Pd(cinnamyl)Cl]_2$ (ee = 78%) (Table 19, entry 4). The use $Pd_2(dba)_3$ (5 mol %) in conjunction with the Trost ligand (*R*,*R*)-**L1** (10 mol %), led to the best results in terms of yield and ee (95% yield and ee = 90%) (Table 19, entry 2). Surprisingly, decreasing the amount of $Pd_2(dba)_3$ from 5 mol % to 1.25 mol % led to a considerable erosion of the ee from 90% to 79% (Table 19, entry 1).

Table 19. Influence of palladium.[a]



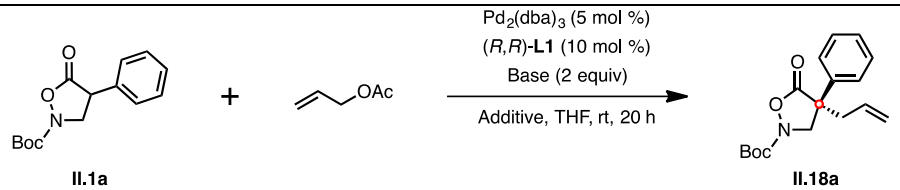
Entry	[Pd$_2$]	(mol %)	(R,R)-L1 (mol%)	Yield[b] (%)	ee[c] (%)
1	$Pd_2(dba)_3$	(1.25)	10	83	79
2	$Pd_2(dba)_3$	(5)	10	95	90
3	$[Pd(allyl)Cl]_2$	(5)	10	43	70
4	$[Pd(cinnamyl)Cl]_2$	(5)	10	40	80
5	$Pd(OAc)_2$	(5)	20	10	78

[a] All the reactions were performed on 0.2 mmol. [b] Isolated yield. [c] Determined by SFC analysis.

After screening the source of palladium, we systematically investigated the aforementioned Pd-AAA by varying the nature of the base under otherwise identical conditions. The results are summarized in Table 20.

Interestingly, the nature of the base appeared to have a tremendous impact on the reactivity as exemplified by the use of NaH (Table 20, entry 4) and DBU (Table 20, entry 6), which induced similar enantioselectivities but totally different yields. Indeed, the use of NaH afforded the desired isoxazolidinone **II.18a** in an excellent 96% yield, while switching the base to DBU led to only 14% yield. Employing another organic base such as BSA in the presence of a catalytic amount of KOAc disclosed a complete different scenario in comparison to DBU, affording **II.18a** in 85% yield (Table 20, entry 5). A brief investigation of mineral bases such as Li_2CO_3, Na_2CO_3 and K_2CO_3 (Table 20, entries 1-3) revealed that good results could be obtained, independent of the base used, albeit a slightly variation of both the reactivity and the enantioselectivity. The best results were achieved with Na_2CO_3 as **II.18a** was isolated in 95% yield and a ee of 90% (Table 20, entry 2).

Table 20. Base and additive influence.[a]



Entry	Base (pK_a)	Additive (equiv)	Yield[b] (%)	ee[c] (%)
1	Li_2CO_3 (10)	–	90	87
2	Na_2CO_3 (10)	–	95	90
3	K_2CO_3 (10)	–	83	82
4	NaH (30)	–	96	87
5	BSA[d] (18)	–	85	80
6	DBU (12)	–	14	86
7	Na_2CO_3 (10)	LiCl (1)	NR	–
8	Na_2CO_3 (10)	15-Crown-5 (2)	90	88

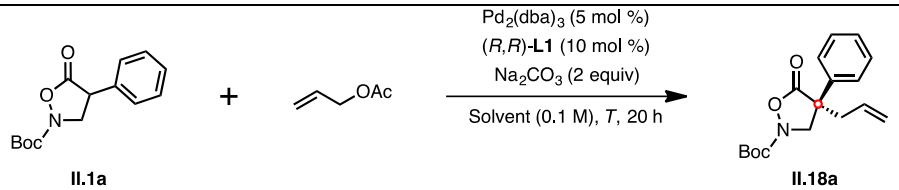
[a] All the reactions were performed on 0.2 mmol. [b] Isolated yield. [c] Determined by SFC analysis. [d] 20 mol % of KOAc were used. pK_a source: Scifinder.

As additives can have an influence on the enantioselectivity outcome, we then performed the Pd-AAA process along with some additives. Interestingly, a lack of reactivity was observed by adding stoichiometric amounts of LiCl (Table 20, entry 7). As a matter of fact, the starting material was entirely recovered after 20 h. In another experiment, we envisioned that the use of a 15-crown-5 (Table 20, entry 8) would render the enolate less associated to the cation and perhaps will lead to a better level of selectivity.[156] However, the addition of the crown ether provided a comparable enantioselectivity and a lower yield.

In order to improve the enantioselectivity, one last important parameter on the Pd-AAA reaction was explored: the solvent. As depicted in Table 21, we noticed, in a brief screening of different solvents, a pronounced impact of the solvent on the enantiomeric excess was observed depending, but in a less extent on the yield. The reaction proceeded with good to excellent selectivity and yield in ethereal solvents (Table 21, entries 1, 5 and 6). Among them, THF (ee = 90%) (Table 21, entry 1) and MTBE (ee = 89%) (Table 21, entry 5) provided the best results. Curiously, by switching to a polar solvent such as MeCN (Table 21, entry 3), we were able to isolate isoxazolidin-5-one **II.18a** in an excellent 92% yield, however the enantioselectivity was dramatically decreased from 90% to 42%. Running the reaction in either polar or non-polar solvents, such as NMP (ee = 82%) (Table 21, entry 4) and toluene (ee = 66%) (Table 21, entry 2), did not improve the selectivity. Hence, THF appeared to be

the solvent of choice offering the best compromise between yield and enantioselectivity (95% yield, ee = 90%) (Table 21, entry 1). Diluting the reaction (Table 21, entry 7) did not improve the selectivity, however by reducing the temperature, first to 0 ºC (ee = 91%) (Table 21, entry 8) and then to −10 ºC (ee = 92%) (Table 21, entry 9) led to a slight increase in the ee. Performing the reaction at 0 ºC however appeared to be the best compromise between practicality, reactivity and selectivity.

Table 21. Influence of the solvent.[a]



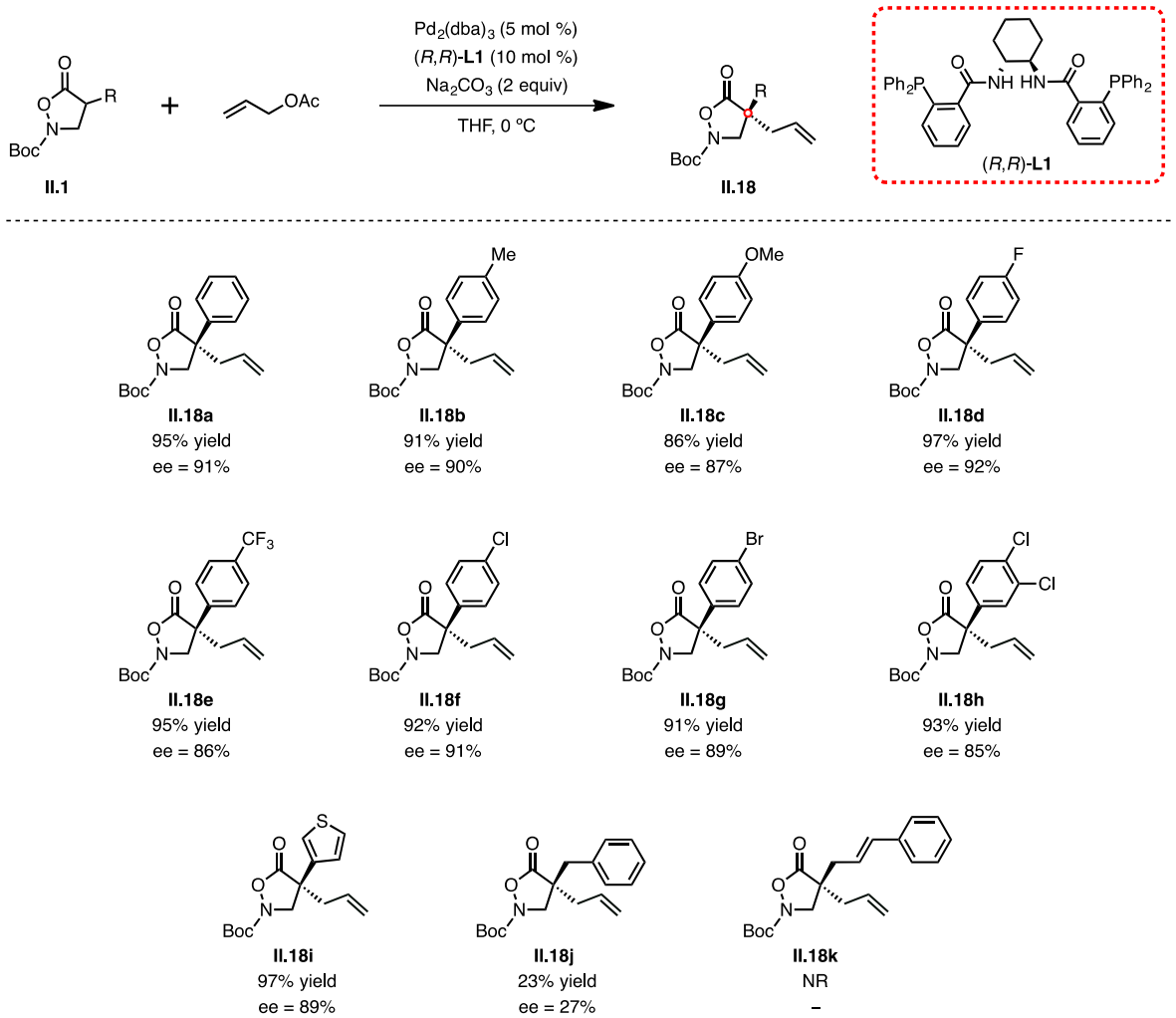
Entry	Solvent	*T*	Yield[b] (%)	ee[c] (%)
1	THF	rt	95	90
2	PhMe	rt	99	66
3	MeCN	rt	92	42
4	NMP	rt	78	82
5	MTBE	rt	99	89
6	1,4-dioxane	rt	85	83
7	THF (0.033 M)	rt	90	89
8	THF	0 ºC	95	91
9	THF	−10 ºC	94	92

[a] All the reactions were performed on 0.2 mmol. [b] Isolated yield. [c] Determined by SFC analysis.

3.4. Reaction scope of the 4-substituted isoxazolidin-5-ones

Having identified the best set of reaction conditions (5 mol % of $Pd_2(dba)_3$, 10 mol % of (*R*,*R*)-**L1** and 2 equivalents of Na_2CO_3 in THF at 0 ºC), we next examined the reaction scope by applying the optimized Pd-AAA reaction conditions to various 4-substituted isoxazolidin-5-ones (**II.1**). These conditions appeared to be tolerant to a wide range of functionalities as a variety of 4-aryl/heteroaryl isoxazolidin-5-ones (**II.1**) were converted to the corresponding allylated products in both excellent yields ranging from 86% to 97% and enatioselectivies (up to 92%) (Scheme 57). As a general trend, substrates bearing strong electron-donating or electron-withdrawing groups on the aryl ring, such as OMe (**II.18c**,

ee = 87%) and CF_3 (**II.18e**, ee = 86%), led to slightly lower selectivities than substrates bearing substituents with moderate electronic effects, such as Me (**II.18b**, ee = 90%), F (**II.18d**, ee = 92%), Cl (**II.18f**, ee = 91%) and Br (**II.18g**, ee = 89%). In addition, the optical purity of the products could be further improved after recrystallization from a mixture of pentane/Et_2O (7:3). This was the case for **II.18a** which was obtained in a highly enantioenriched form (ee > 99%). Unfortunately, the method appeared to be less efficient for 4-alkyl substituted isoxazolidin-5-ones, where both low yield and enantioselectivity were observed for **II.1j** (23% yield and ee = 27%), and a complete lack of reactivity was noticed for **II.1k**.

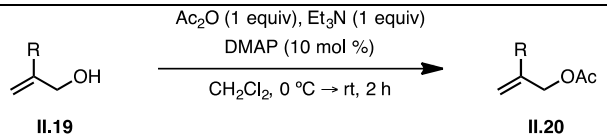


Scheme 57. Scope of the reaction of 4-substituted isoxazolidin-5-ones.

3.5. Synthesis of 2-substituted allyl acetates

In an effort to broaden the scope of the reaction, we subsequently turned our attention to introducing more structural diversity to the chiral isoxazolidinones, using substituted allyl acetates, more specifically 2-substituted allyl acetates. Hence, the allyl acetates were prepared, mainly starting from commercially available allylic alcohols and by implementing a classical acetylation protocol (Ac_2O, DMAP and Et_3N in CH_2Cl_2 at 0 ºC), as showcased in Table 22.[132] Hence, the desired allyl acetates were isolated in good yields varying from 67% to 97% (Table 22, entries 1-3).

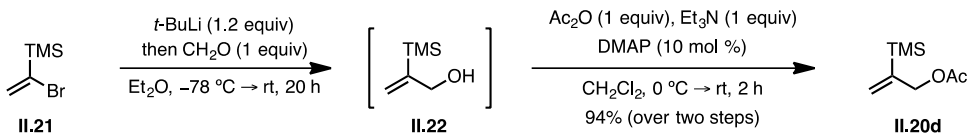
Table 22. Synthesis of allyl acetates from commercially available allyl alcohols.



Entry	R	**II.20**	Yield[a] (%)
1	Me	**II.20a**	97
2	Cl	**II.20b**	90
3	CO_2Me	**II.20c**	67

[a] Isolated yield.

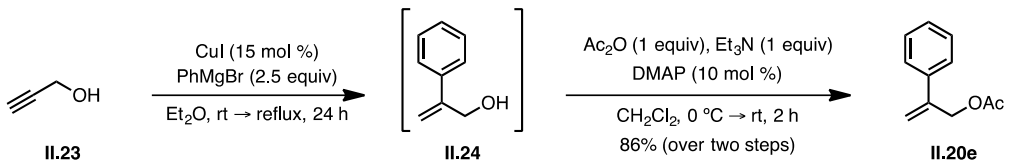
To access the allyl acetate **II.20d**, the vinyl bromide **II.21** was subjected to a three-step sequence featuring a lithium-halogen exchange process, followed by a nucleophilic addition of the organolithium intermediate on paraformaldehyde to give rise to its corresponding allylic alcohol **II.22**, which was subsequently engaged in the acetylation using the same method described above (Ac_2O, DMAP and Et_3N in CH_2Cl_2 at 0 ºC). The desired product was thus obtained in 94% over the two steps (Scheme 58).[133]



Scheme 58. Synthesis of TMS-modified allyl acetate **II.20d**.

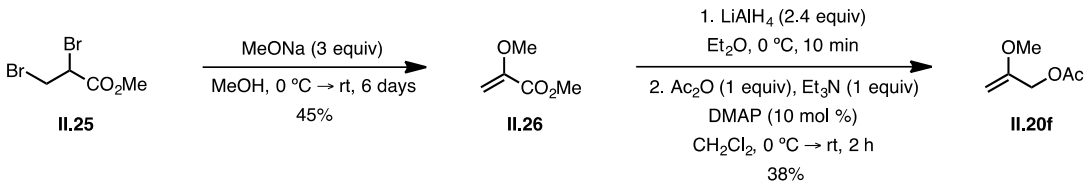
132 Blaisdell, T. P.; Caya, T. C.; Zhang, L.; Sanz-Marco, A.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 9264.
133 Amat, M.; Arioli, F.; Pérez, M.; Molins, E.; Bosh, J. *Org. Lett.* **2013**, *15*, 2470.

In a different approach, 2-phenyl allyl acetate **II.20e** was prepared from propargyl alcohol **II.23** through a simple and particularly versatile strategy depicted in Scheme 59. Hence, propargyl alcohol **II.23** was subjected to a regioselective Grignard addition in the presence of CuI (15 mol %) to yield the corresponding allylic alcohol **II.24**. The latter was eventually subjected to the acetylation conditions to afford the target allyl reagent **II.20e** in a 86% overall yield.[134]



Scheme 59. Synthesis of the phenyl-modified allyl acetate **II.20e**.

In contrast to the excellent results obtained previously for the synthesis of the allyl acetates, compound **II.20f** was isolated in a very low overall yield of 17% following the sequence depicted in Scheme 60. The first step smoothly provided the methyl 2-methoxy acrylate **II.26** in a moderate yield of 45%, after the reduction of the ester with $LiAlH_4$ followed by an acetylation, the desired allyl compound **II.20f** was isolated in a modest 38% yield.



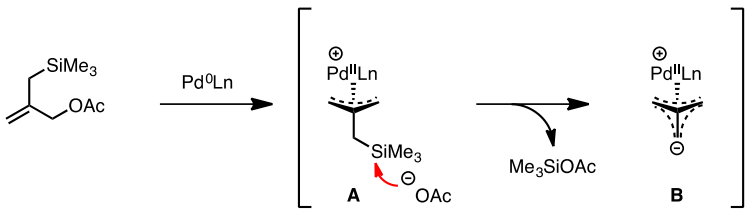
Scheme 60. Synthesis of methoxy-modified allyl acetate **II.20e**.

3.6. Reaction scope with 2-substituted allyl acetates

4-Phenyl isoxazolidin-5-one **II.1a** was subjected to an array of 2-substituted allyl acetates under our previously optimized Tsuji-Trost reaction conditions. Interestingly, electronic effects demonstrated a more pronounced impact on the enantioselectivity than the

134 Duan, Z. C.; Hu, X. P.; Zhang, C.; Wang, D. Y.; Yu, S. B.; Zheng, Z. *J. Org. Chem.* **2009**, *74*, 9191.

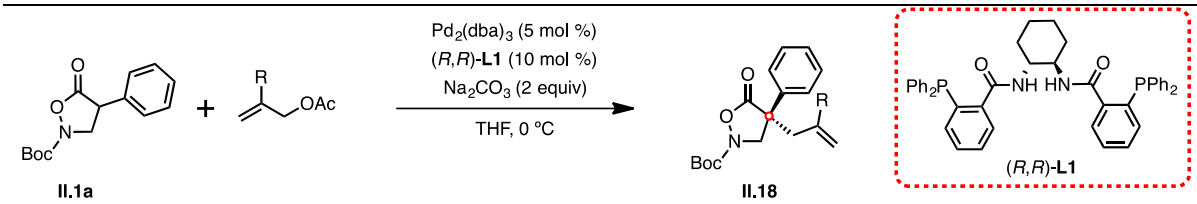
steric effects as shown in Table 23. The desired allylated products were isolated in good yields and excellent enantioselectivities when treated with allyl acetates bearing substituents having a moderate electronic effect such as a Me (**II.18l**, ee = 91%), a TMS (**II.18m**, ee = 93%) or a Ph (**II.18o**, ee = 95%). The replacement of the hydrogen atom on the allyl acetate by a more sterically hindered group such as a Me or a TMS group did not induce an erosion of the enantioselectivity, it did lead to a slightly loss of reactivity though. On the other hand, replacing the hydrogen atom by moderate or strong electron deficient groups such as a Cl (**II.18p**, ee = 74%) or a CO_2Me (**II.18q**, ee = 25%) had a crucial impact on both the reactivity and the enantioselectivity. It is worth pointing out that no evident reason was found to explain the astonishing result obtained with the 2-chloro allyl acetate (Table 23, entry 6), which usually behaves as an excellent partner for Pd-AAA. Besides, a complete lack of reactivity was even observed when using a 2-methoxy substituted allyl reagent (Table 23, entry 8). Interestingly, the reaction between **II.1a** and the commercially available 2-[(TMS)methyl] allyl acetate furnished the same compound that the 2-methyl allyl acetate **II.20a** (Table 23, entry 4). The loss of the TMS group might have taken place after the formation of the π-allyl palladium complex **A**, when the C–Si bond got weakened by the proximal positive charge and subsequent attack of acetate anion on the silicon atom resulted in the formation of palladium complex of TMM (trimethylmethane) **B** (Scheme 61), which eventually evolved to produce the isoxazolidinone **II.18n**.[135]

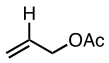
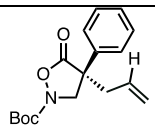
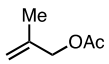
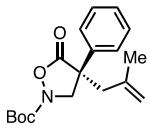
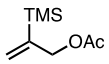
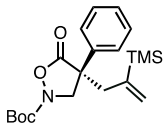
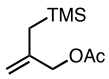
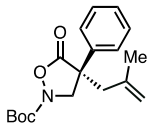
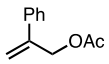
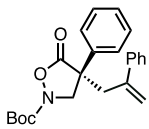
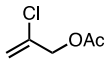
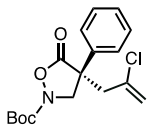
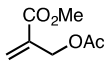
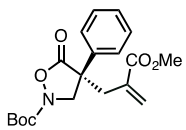
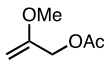
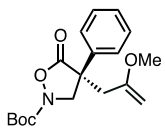


Scheme 61. Formation of TMM-palladium complex.

135 Trost, B. M. *Angew. Chem. Int. Ed.* **1986**, *25*, 1.

Table 23. Scope of the reaction with 2-substituted allyl acetates.



Entry	Allyl acetate	**II.18**	Yield[a] (%)	ee[b] (%)
1		 **II.18a**	95	91
2		 **II.18l**	88	95
3		 **II.18m**	76	93
4		 **II.18n**	94	90
5		 **II.18o**	71	95
6		 **II.18p**	22	74
7		 **II.18q**	25	25
8		 **II.18r**	NR	–

[a] Isolated yield. [b] Determined by SFC analysis.

3.7. Origin of the enantioselectivity

The sense of asymmetric induction using the Trost 'standard ligand' (*R*,*R*)-**L1** could be explained by the cartoon model presented in Chapter 1 – Section 4.9 and in the Appendix 2 – Section 1.3. Indeed, according to the model, the enolate approaches the π-allyl palladium complex by its *Re* face to avoid any disfavored interaction between the 'wall' of the ligand and the Boc group of the substrate, delivering the product with the (*S*) configuration. This explanation is in line with the model improved by Lloyd-Jones *et al*. and Norrby *et al*., which predicts a facilitated approach of the stabilized nucleophile — pro-*S* approach — by hydrogen bonding with one amide N–H. In **II.18a**, the absolute configuration of the formed stereocenter was later confirmed by a single crystal X-Ray analysis (Figure 18).

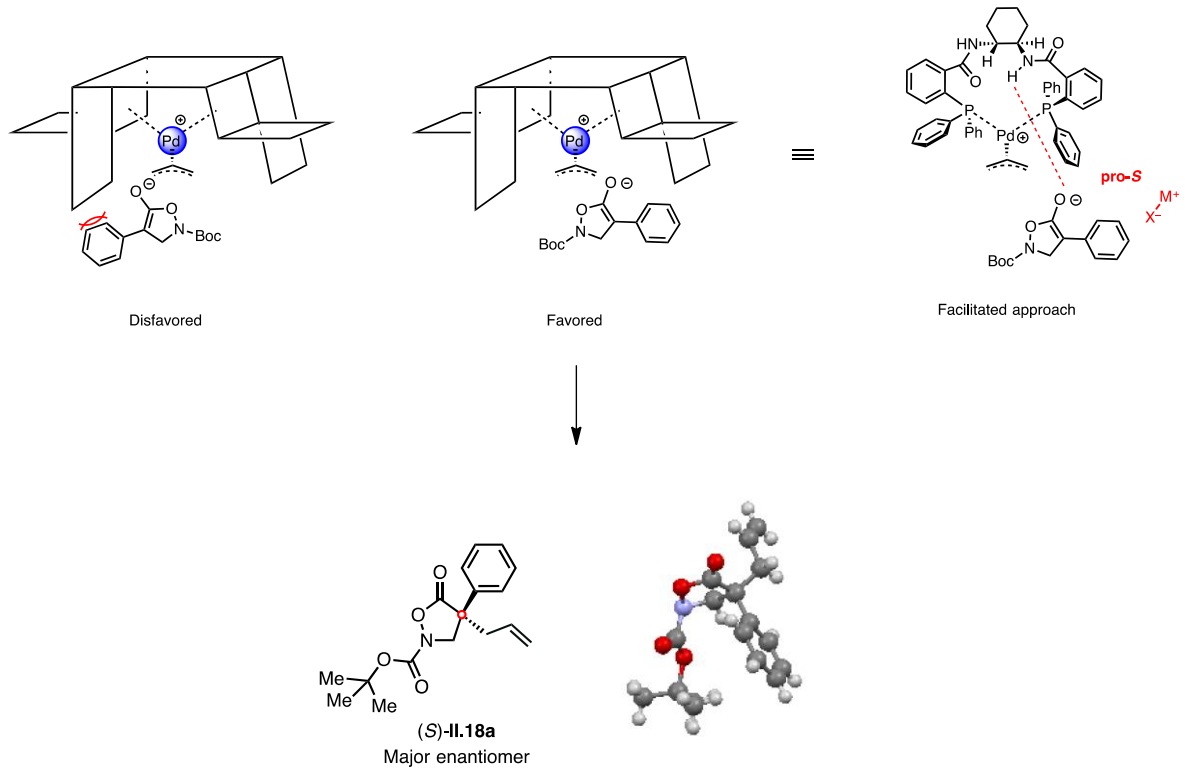


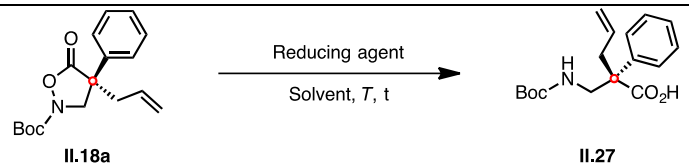
Figure 18. Stereochemistry prediction of **II.18a**.

3.8. Post-functionalization: the synthesis of $\beta^{2,2}$-amino acid and β-lactam

Finally, after having established a practical and highly enantioselective route to enantioenriched α,α-disubstituted isoxazolidinones **II.18**, we decided to demonstrate the synthetic utility of the method by developing a straightforward sequence which would allow to convert the isoxazolidinones to the corresponding $\beta^{2,2}$-amino acids **II.27** and β-lactam **II.28**.

To access the enantioenriched $\beta^{2,2}$-amino acids bearing an all-carbon α-quaternary stereogenic center, we carried out a brief screen of reagents to cleave the N–O bond using the isoxazolidinone **II.18a** as model substrate. As shown in Table 24,[136] none of the reducing agents used such as $Na_2S_2O_4$, SmI_2 or Zn, led to the desired amino acid. Luckily, the use of sodium naphthalenide in THF at –78 ºC afforded the $\beta^{2,2}$-amino acid **II.27** in 90% isolated yield.

Table 24. Screening of reducing reagents toward the formation of $\beta^{2,2}$-amino acid.



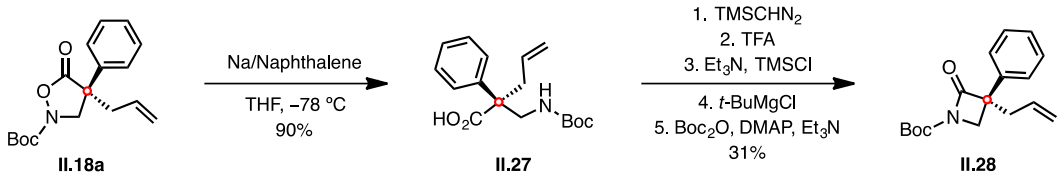
Entry	Reducing agent	Solvent	*T*	t	Yield[a] (%)
1	$Na_2S_2O_4$	EtOH/H_2O	78 ºC	24 h	NR
2	SmI_2	THF	rt	24 h	NR
3	Zn	AcOH	rt	24 h	NR
4	Na/Naphthalene	THF	–78 ºC	10 min	90

[a] Isolated yield.

Once we had accomplished the synthesis of the $\beta^{2,2}$-amino acid **II.27**, we directly engaged the amino acid in an esterification of the carboxylic acid using $TMSCHN_2$ and a Boc-deprotection using TFA. The resulting *N*-Boc methyl β-amino ester was treated with TMSCl and Et_3N followed by the addition of *t*-BuMgCl at 0 ºC, leading to the formation of

136 (a) Jones, A. L.; Snider, J. K. *Org. Lett.* **2010**, *12*, 1592; (b) Pearson, C.; Rinehart, K. L.; Sugano, M.; Costerison, J. R. *Org. Lett.* **2000**, *2*, 2901; (c) Bergmeier, S. C.; Seth, P. P. *Tetrahedron Lett.* **1999**, *40*, 6181; (d) Adam, W.; Degen, H.-G.; Krebs, O.; Saha-Moller, C. R. *J. Am. Chem. Soc.* **2002**, *124*, 12938.

the corresponding β-lactam **II.28** which was *N*-Boc re-protected for purification purposes (Scheme 62).[137]



Scheme 62. Synthesis of β-lactam **II.28**.

4. Conclusion

137 Gianelli, C.; Sambri, L.; Carlone, A.; Bartoli, G.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2008,** *47*, 8700.

We have developed a palladium-catalyzed asymmetric allylic alkylation of 4-substituted isoxazolidin-5-ones with an array of 2-substituted allyl acetates to produce isoxazolidin-5-ones bearing highly stereodefined all-carbon α-quaternary center. The reaction proceeded in both excellent enantioselectivity and yield with 4-substituted isoxazolidin-5-ones containing an α-aryl substituents or an α-heteroaryl moieties, such as thiophene. Unfortunately, α-alkyl substituents revealed to be not suitable for this approach. Nonetheless, this robust and highly enantioselective method allowed the access to valuable $\beta^{2,2}$-amino acids and β-lactams.

Chapter

2

Experimental Section

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4. Synthesis of 4-substituted isoxazolidin-5-ones
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6. Synthesis of allyl acetates
7. General procedures for the Pd-AAA of 2-substituted allyl reagents
8. Product derivatizations
    8.1. Synthesis of $\beta^{2,2}$-amino acid
    8.2. Synthesis of β-lactam

1. General experimental methods

All reactions were run under an argon atmosphere in oven-dried glassware unless otherwise specified. All commercially available compounds were purchased from Aldrich Chemical Co. and used as received. Dichloromethane ($CHCl_2$) was distilled from calcium hydride. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium/benzophenone. *N*,*N*-dimethylformamide (DMF) was distilled under vacuum over anhydrous $MgSO_4$.

Analytical thin layer chromatography (TLC) was performed on silica gel plates (Merck $60F_{254}$) visualized either with a UV lamp (254 nm) or by using solutions of *p*-anisaldehyde/sulfuric acid/acetic acid in ethanol or $KMnO_4/K_2CO_3$ in H_2O followed by heating. Flash chromatography was performed on silica gel (230-400 mesh).

Melting points (Mp) were recorded using a Wagner & Munz Kofler bench.

Infrared spectra (IR) were recorded on a Bruker TENSOR™ 27 (IR-FT) with attenuated total reflectance (ATR) and wavenumbers are indicated in cm^{-1}.

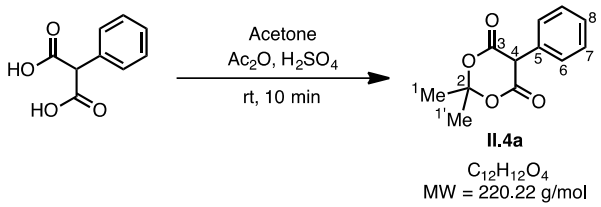
^1H NMR spectra were recorded on a Bruker AVANCE 400 at 400 MHz in $CDCl_3$ (unless otherwise specified) and the observed signals are reported as follows: chemical shift in parts per million from tetramethylsilane with the solvent as an internal indicator ($CDCl_3$ δ 7.26 ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or overlap of non-equivalent resonances), integration. ^{13}C NMR spectra were recorded at 100 MHz in $CDCl_3$ (unless otherwise specified) and the observed signals were reported as follows: chemical shift in parts per million from tetramethylsilane with the solvent as an internal indicator ($CDCl_3$ δ 77.16 ppm), multiplicity on respect to proton (deduced from DEPT experiments, s = quaternary C, d = CH, t = CH_2, q = CH_3). Coupling constants (*J*) are reported in Hertz (Hz). All NMR spectra were obtained at room temperature unless otherwise specified.

Mass spectra with electronic impact (EI–MS) were recorded with a Shimadzu GCM-QP 2010S gas chromatography-mass spectrometer. High-resolution mass spectra (HRMS) were performed by "Groupe de Spectrométrie de masse de l'Université Pierre et Marie Curie (Paris)".

Optical rotations were determined using a Perkin Elmer 343 polarimeter. The enantiomeric excesses were determined by supercritical fluid chromatography (SFC) analysis on a chiral stationary phase using a Minigram Berger SFC-Mettler Toledo apparatus. The sign before the ees values is arbitrary.

2. Synthesis of Meldrum's acids (II.4a-l)

2,2-Dimethyl-5-phenyl-1,3-dioxane-4,6-dione (II.4a)[124a]



To a suspension of phenylmalonic acid (9.00 g, 50.0 mmol, 1.00 equiv) in Ac_2O (24 mL) was added concentrated H_2SO_4 (1.0 mL, 18 mmol, 0.4 equiv) dropwise, which caused complete dissolution. After 1 minute of the addition of acetone (6.00 mL, 81.6 mmol, 1.60 equiv), the product began to precipitate. The reaction mixture was stirred for 10 min, cooled, and filtered. The precipitate was washed thoroughly with ice-cold H_2O and then dissolved in CH_2Cl_2 (200 mL). The resulting solution was washed with a saturated brine solution, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude solid was purified by trituration in hexane/EtOAc = 7:3 to give **II.4a** as a white solid (7.07 g, 64%).

Mp = 143-145 °C

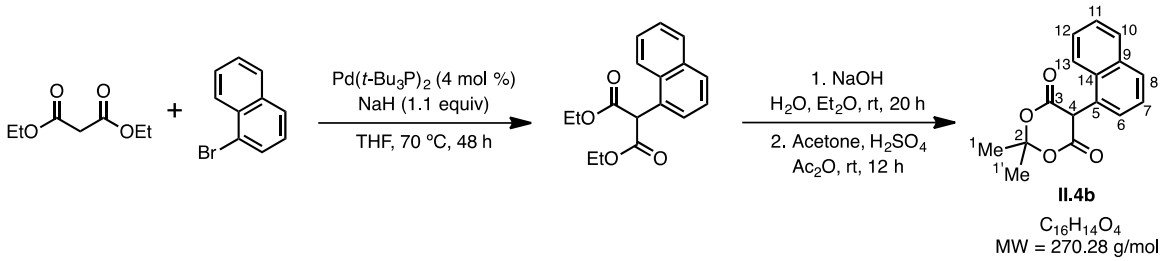
IR (ATR): 2884, 1780, 1735, 1503, 1457, 1387, 1349, 1319, 1284, 1261, 1217, 1068, 1014, 886 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46-7.35 (m, 3H, H_7 and H_8), 7.33-7.25 (m, 2H, H_6), 4.79 (s, 1H, H_4), 1.84 (s, 3H, H_1), 1.74 (s, 3H, $H_{1'}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9 (s, 2C, C_3), 130.7 (s, C_5), 129.3 (d, 2C, C_6 or C_7), 129.2 (d, 2C, C_6 or C_7), 128.9 (d, C_8), 105.8 (s, C_2), 52.9 (d, C_4), 28.6 (q, $C_{1'}$), 27.5 (q, C_1).

HRMS (ESI) *m/z*: calcd for $C_{12}H_{12}O_4Na$ $[M+Na]^+$: 243.0628, found: 243.0627.

2,2-Dimethyl-5-(naphthalen-1-yl)-1,3-dioxane-4,6-dione (II.4b)



Method Pd: to a flame-dried flask containing a dispersion of NaH (750 mg, 60% in mineral oil, 19 mmol, 1.1 equiv) in THF (17 mL) was added diethyl malonate (2.85 mL, 18.8 mmol, 1.10 equiv) dropwise. Upon evolution of hydrogen (approximately 2 min), 1-bromonaphthalene (2.44 mL, 17.0 mmol, 1.00 equiv), Pd(t-Bu_3P)$_2$ (174 mg, 0.340 mmol, 0.020 equiv) and THF (34 mL) were added. The reaction mixture was stirred at 70 °C. After 48 h, the reaction was cooled to rt and an aqueous solution of HCl (1 M) was added. The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic extracts were washed with a saturated aqueous brine solution (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (PE/EtOAc = 9:1) to afford a clear oil (2.43 g, 50%) which was engaged in the saponification step without further purification or characterization.

The 1,3-diethyl 2-(naphthalene-1-yl)propanedioate (2.00 g, 7.00 mmol, 1.00 equiv) was dissolved in Et_2O (7.0 mL) and then added to a flask containing a solution of NaOH (1.12 g, 28.0 mmol, 4.00 equiv) in H_2O (23 mL) at 0 °C over a period of 10 min. The resulting mixture was stirred at rt for 20 h. The aqueous layer was separated and washed with EtOAc (2 x 100 mL), acidified to pH 2 with an aqueous solution of HCl (6 M), and extracted with EtOAc (2 x 200 mL). The combined organic extracts were washed with a saturated aqueous brine solution (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to result in a white solid (1.30 g, 81%) that was used in the next step without further purification or characterization.

To a suspension of 2-(naphthalen-1-yl)propanedioic acid (1.00 g, 4.34 mmol, 1.00 equiv) in Ac_2O (2.0 mL) was added concentrated H_2SO_4 (95 µL, 1.7 mmol, 0.4 equiv) dropwise, which caused complete dissolution. After 1 minute of the addition of acetone (0.50 mL, 6.94 mmol, 1.60 equiv), the product began to precipitate. The reaction mixture was stirred for 12 h,

cooled, and filtered. The precipitate was washed thoroughly with ice-cold H_2O and then dissolved in CH_2Cl_2 (20 mL). The resulting solution was washed with a saturated brine solution, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude solid was purified by trituration in hexane/EtOAc = 7:3 to give **II.4b** as a white solid (188 mg, 16%).

Mp = 138-139 °C

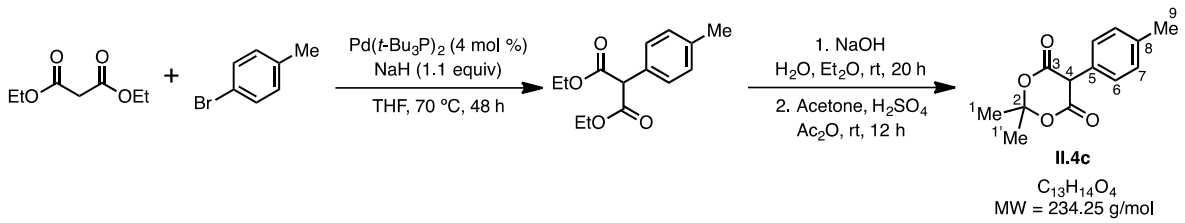
IR (ATR): 2999, 1784, 1739, 1513, 1455, 1395, 1384, 1311, 1270, 1236, 1201, 1185, 1069, 1009, 894, 862, 804, 780 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96-7.87 (m, 2H, H_{Ar}), 7.56-7.41 (m, 5H, H_{Ar}), 5.09 (s, 1H, H_4), 1.97 (s, 6H, H_1 and $H_{1'}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9 (s, 2C, C_3), 134.4 (s, C_5), 130.5 (s, C_9 or C_{14}), 130.4 (d, C_{Ar}), 130.3 (d, C_{Ar}), 129.6 (d, C_{Ar}), 128.0 (s, C_9 or C_{14}), 127.3 (d, C_{Ar}), 126.3 (d, C_{Ar}), 125.3 (d, C_{Ar}), 122.9 (d, C_{Ar}), 105.7 (s, C_2), 52.2 (d, C_4), 28.6 (q, C_1 or $C_{1'}$), 27.4 (q, C_1 or $C_{1'}$).

HRMS (ESI) *m/z*: calcd for $C_{16}H_{14}O_4Na[M+Na]^+$: 293.0784, found: 293.0786.

2,2-Dimethyl-5-(4-methylphenyl)-1,3-dioxane-4,6-dione (II.4c)



Method Pd: to a flame-dried flask containing a dispersion of NaH (751 mg, 60% in mineral oil, 19 mmol, 1.1 equiv) in THF (17 mL) was added diethyl malonate (2.85 mL, 18.8 mmol, 1.10 equiv) dropwise. Upon evolution of hydrogen (approximately 2 min), 4-bromotoluene (2.10 mL, 17.1 mmol, 1.00 equiv), Pd(*t*-$Bu_3P)_2$ (174 mg, 0.340 mmol, 0.020 equiv) and THF (34 mL) were added. The reaction mixture was stirred at 70 °C. After 48 h, the reaction was cooled to rt and an aqueous solution of HCl (1 M) was added. The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic extracts were washed with a saturated aqueous brine solution (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column

chromatography on silica gel (PE/EtOAc = 9:1) to afford a clear oil (2.10 g, 49%) which was engaged in the saponification step without further purification or characterization.[121]

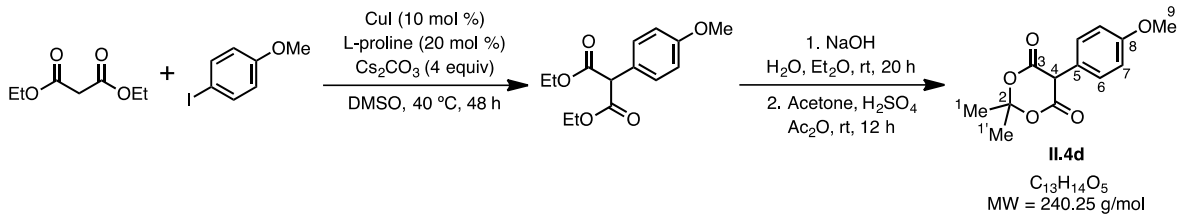
The 1,3-diethyl 2-(4-methylphenyl)propanedioate (2.00 g, 8.00 mmol, 1.00 equiv) was dissolved in Et_2O (8.0 mL) and then added to a flask containing a solution of NaOH (1.28 g, 32.0 mmol, 4.00 equiv) in H_2O (26 mL) at 0 °C over a period of 10 min. The resulting mixture was stirred at rt for 20 h. The aqueous layer was separated and washed with EtOAc (2 x 100 mL), acidified to pH 2 with an aqueous solution of HCl (6 M), and extracted with EtOAc (2 x 200 mL). The combined organic extracts were washed with a saturated aqueous brine solution (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to result in a white solid (1.21 g, 77%) that was used in the next step without further purification or characterization.[138]

To a suspension of 2-(4-methylphenyl)propanedioic acid (1.00 g, 5.20 mmol, 1.00 equiv) in Ac_2O (2.5 mL) was added concentrated H_2SO_4 (120 µmL, 2.1 mmol, 0.4 equiv) dropwise, which caused complete dissolution. After 1 minute of the addition of acetone (0.60 mL, 8.3 mmol, 1.60 equiv), the product began to precipitate. The reaction mixture was stirred for 12 h, cooled, and filtered. The precipitate was washed thoroughly with ice-cold H_2O and then dissolved in CH_2Cl_2 (20 mL). The crude solid was purified by trituration in hexane/EtOAc = 7:3 to give **II.4c** as a white solid (374 mg, 31%).

Mp = 141-143 °C
IR (ATR): 2892, 1773, 1735, 1707, 1519, 1430, 1385, 1346, 1319, 1288, 1260, 1223, 1210, 1064, 1014, 895, 806 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25-7.15 (m, 4H, H_6 and H_7), 4.73 (s, 1H, H_4), 2.36 (s, 3H, H_9), 1.87 (s, 3H, H_1), 1.75 (s, 3H, $H_{1'}$).
^{13}C NMR (100 MHz, $CDCl_3$): δ 165.0 (s, 2C, C_3), 138.9 (s, C_5), 130.0 (d, 2C, C_6), 129.0 (d, 2C, C_7), 127.6 (s, C_8), 105.8 (s, C_2), 52.6 (d, C_4), 28.7 (q, $C_{1'}$), 27.7 (q, C_1), 21.3 (q, C_9).
HRMS (ESI) *m/z*: calcd for $C_{13}H_{14}O_4Na[M+Na]^+$: 257.0784, found: 257.0784.

2,2-Dimethyl-5-(4-methoxyphenyl)-1,3-dioxane-4,6-dione (II.4d)

138 Reddy Chidipudi, S.; Khan, I.; Lam, H. W. *Angew. Chem. Int. Ed.* **2012,** *51*, 12115.



Method Cu A: a flame-dried flask was charged with 4-iodoanisole (5.00 g, 21.3 mmol, 1.00 equiv), CuI (407 mg, 2.10 mmol, 0.100 equiv), L-proline (492 mg, 4.20 mmol, 0.200 equiv) and Cs_2CO_3 (27.8 g, 85.2 mmol, 4.00 equiv), evacuated and backfilled with argon. Then diethyl malonate (3.90 mL, 26.0 mmol, 1.20 equiv) and DMSO (42.5 mL) were added under argon. The reaction mixture was stirred at 40 °C. After 48 h, the cooled mixture was partitioned between EtOAc and a saturated aqueous solution of NH_4Cl, the organic layer was washed with a saturated aqueous brine solution, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 9:1) to provide a clear oil (3.34 g, 59%) which was engaged in the saponification step without further purification or characterization.the desired product.[122]

The 1,3-diethyl 2-(4-methoxyphenyl)propanedioate (3.00 g, 11.3 mmol, 1.00 equiv) was dissolved in Et_2O (11.0 mL) and then added to a flask containing a solution of NaOH (1.81 g, 45.2 mmol, 4.00 equiv) in H_2O (36 mL) at 0 °C over a period of 10 min. The resulting mixture was stirred at rt for 20 h. The aqueous layer was separated and washed with EtOAc (2 x 150 mL), acidified to pH 2 with an aqueous solution of HCl (6 M), and extracted with EtOAc (2 x 200 mL). The combined organic extracts were washed with a saturated aqueous brine solution (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a white solid (1.70 g, 72%) that was used in the next step without further purification or characterization.

To a suspension of 2-(4-methoxyphenyl)propanedioic acid (1.50 g, 7.10 mmol, 1.00 equiv) in Ac_2O (3.4 mL) was added concentrated H_2SO_4 (156 μL, 2.8 mmol, 0.4 equiv) dropwise, which caused complete dissolution. After 1 minute of the addition of acetone (0.85 mL, 11.4 mmol, 1.60 equiv), the product began to precipitate. The reaction mixture was stirred for 12 h, cooled, and filtered. The precipitate was washed thoroughly with ice-cold H_2O and then dissolved in CH_2Cl_2 (30 mL). The resulting solution was washed with a saturated brine

solution, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude solid was purified by trituration in hexane/EtOAc = 7:3 to give **II.4d** as an off-white solid (1.16 g, 65%).

Mp = 129-130 °C

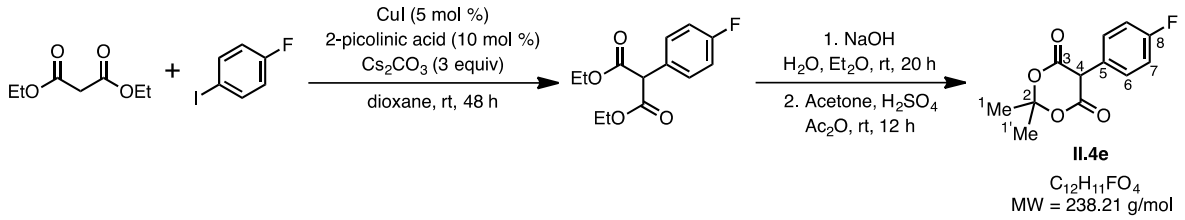
IR (ATR): 1737, 1615, 1518, 1430, 1299, 1251, 1217, 1179, 1066, 1013, 893, 820, 757, 652 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23-7.16 (m, 2H, H_6), 6.97-6.89 (m, 2H, H_7), 4.74 (s, 1H, H_4), 3.81 (s, 3H, H_9), 1.85 (s, 3H, H_1), 1.75 (s, 3H, $H_{1'}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2 (s, 2C, C_3), 159.9 (s, C_8), 130.4 (s, 2C, C_6), 122.5 (s, C_5), 114.7 (d, 2C, C_7), 105.7 (s, C_2), 55.4 (q, C_9), 52.2 (d, C_4), 28.6 (q, $C_{1'}$), 27.5 (q, C_1).

HRMS (ESI) *m/z*: calcd for $C_{13}H_{15}O_5$ $[M+H]^+$: 251.0914, found: 251.0914.

2,2-Dimethyl-5-(4-fluorophenyl)-1,3-dioxane-4,6-dione (II.4e)



<u>Method Cu B</u>: a flame-dried flask was charged with CuI (132 mg, 0.690 mmol, 0.050 equiv), 2-picolinic acid (171 mg, 1.39 mmol, 0.100 equiv) and Cs_2CO_3 (13.6 g, 41.7 mmol, 3.00 equiv), evacuated and backfilled with argon. Then 1,4-dioxane (14 mL), diethyl malonate (4.20 mL, 28.0 mmol, 2.00 equiv) and 1-fluoro-4-iodobenzene (1.60 mL, 14.0 mmol, 1.00 equiv) were added under argon. The reaction mixture was stirred at rt. After 48 h, the cooled mixture was partitioned between EtOAc and a saturated aqueous solution of NH_4Cl, the organic layer was washed with a saturated aqueous brine solution, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 9:1) to provide a yellow oil (2.84 g, 81%) which was engaged in the saponification step without further purification or characterization.the desired product.[123]

The 1,3-diethyl 2-(4-fluorophenyl)propanedioate (2.70 g, 10.6 mmol, 1.00 equiv) was dissolved in Et_2O (11.0 mL) and then added to a flask containing a solution of NaOH (1.70 g, 42.4 mmol, 4.00 equiv) in H_2O (36 mL) at 0 °C over a period of 10 min. The resulting mixture was stirred at rt for 20 h. The aqueous layer was separated and washed with EtOAc (2 x 100 mL), acidified to pH 2 with an aqueous solution of HCl (6 M), and extracted with EtOAc (2 x 200 mL). The combined organic extracts were washed with a saturated aqueous brine solution (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a white solid (2.05 g, 97%) that was used in the next step without further purification or characterization.

To a suspension of 2-(4-fluorophenyl)propanedioic acid (1.80 g, 9.10 mmol, 1.00 equiv) in Ac_2O (4.4 mL) was added concentrated H_2SO_4 (200 µL, 3.6 mmol, 0.4 equiv) dropwise, which caused complete dissolution. After 1 minute of the addition of acetone (1.00 mL, 14.6 mmol, 1.60 equiv), the product began to precipitate. The reaction mixture was stirred for 12 h, cooled, and filtered. The precipitate was washed thoroughly with ice-cold H_2O and then dissolved in CH_2Cl_2 (40 mL). The resulting solution was washed with a saturated brine solution, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude solid was purified by trituration in hexane/EtOAc = 7:3 to give **II.4e** as a beige solid (909 mg, 42%).

Mp = 143-144 °C

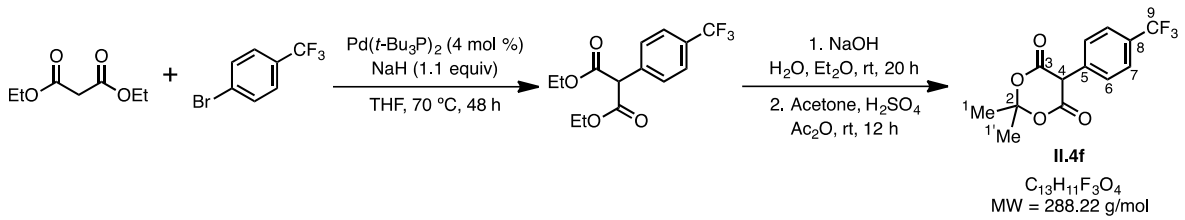
IR (ATR): 1737, 1606, 1515, 1393, 1347, 1310, 1294, 1218, 1159, 1072, 1017, 898, 823, 733, 651 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.23 (m, 2H, H_6), 7.15-7.07 (m, 2H, H_7), 4.75 (s, 1H, H_4), 1.88 (s, 3H, H_1), 1.78 (s, 3H, $H_{1'}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7 (s, 2C, C_3), 163.0 (s, $^1J_{C-F}$ = 247 Hz, C_8), 131.3 (d, $^3J_{C-F}$ = 8.1 Hz, 2C, C_6), 126.4 (s, $^4J_{C-F}$ = 3.6 Hz, C_5), 116.4 (d, $^2J_{C-F}$ = 21.9 Hz, 2C, C_7), 105.9 (s, C_2), 52.3 (d, C_4), 28.7 (q, $C_{1'}$), 27.5 (q, C_1).

HRMS (ESI) *m/z*: calcd for $C_{12}H_{12}FO_4$ $[M+H]^+$: 239.0714, found: 239.0713.

2,2-Dimethyl-5-(4-(trifluoromethyl)phenyl)-1,3-dioxane-4,6-dione (II.4f)



Method Pd: to a flame-dried flask containing a dispersion of NaH (375 mg, 60% in mineral oil, 9.4 mmol, 1.1 equiv) in THF (8.5 mL) was added diethyl malonate (1.40 mL, 9.39 mmol, 1.10 equiv) dropwise. Upon evolution of hydrogen (approximately 2 min), 4-bromobenzotrifluoride (1.20 mL, 8.53 mmol, 1.00 equiv), Pd(t-Bu_3P)$_2$ (87 mg, 0.17 mmol, 0.020 equiv) and THF (17 mL) were added. The reaction mixture was stirred at 70 °C. After 48 h, the reaction was cooled to rt and an aqueous solution of HCl (1 M) was added. The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic extracts were washed with a saturated aqueous brine solution (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (PE/EtOAc = 95:5) to afford a colorless oil (1.15 g, 44%) which was engaged in the saponification step without further purification or characterization.

The 1,3-diethyl 2-(4-(trifluoromethyl)phenyl)propanedioate (1.00 g, 3.29 mmol, 1.00 equiv) was dissolved in Et_2O (3.5 mL) and then added to a flask containing a solution of NaOH (528 mg, 13.2 mmol, 4.00 equiv) in H_2O (11 mL) at 0 °C over a period of 10 min. The resulting mixture was stirred at rt for 20 h. The aqueous layer was separated and washed with EtOAc (2 x 50 mL), acidified to pH 2 with an aqueous solution of HCl (6 M), and extracted with EtOAc (2 x 100 mL). The combined organic extracts were washed with a saturated aqueous brine solution (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a white solid (792 mg, 97%) that was used in the next step without further purification or characterization.

To a suspension of 2-(4-(trifluoromethyl)phenyl)propanedioic acid (750 mg, 3.00 mmol, 1.00 equiv) in Ac_2O (1.4 mL) was added concentrated H_2SO_4 (10 µL, 1.2 mmol, 0.4 equiv) dropwise, which caused complete dissolution. After 1 minute of the addition of acetone (0.4

mL, 4.8 mmol, 1.60 equiv), the product began to precipitate. The reaction mixture was stirred for 12 h, cooled, and filtered. The precipitate was washed thoroughly with ice-cold H_2O and then dissolved in CH_2Cl_2 (15 mL). The resulting solution was washed with a saturated brine solution, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude solid was purified by trituration in hexane/EtOAc = 7:3 to give **II.4f** as a beige solid (472 mg, 54%).

Mp = 155-156 °C

IR (ATR): 2891, 1701, 1619, 1414, 1326, 1295, 1238, 1227, 1164, 1123, 1068, 1020, 917, 833, 685 cm^{-1}.

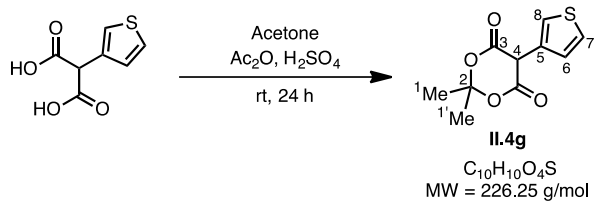
Note: A mixture of the corresponding malonic acid/ **II.4f** = 1:4 was observed during NMR acquisition. Only **II.4f** is reported.

^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 7.79-7.71 (m, 2H, H_7), 7.65-7.59 (m, 2H, H_6), 5.72 (s, 1H, H_4), 2.02 (s, 3H, H_1), 1.80 (s, 3H, $H_{1'}$).

^{13}C NMR (100 MHz, $(CD_3)_2CO$): δ 165.1 (s, 2C, C_3), 137.9 (s, C_5), 132.4 (d, 2C, C_6), 130.5 (s, $^2J_{C\text{-}F}$ = 32.4 Hz, C_8), 125.3 (s, $^1J_{C\text{-}F}$ = 272 Hz, C_9), 125.0 (d, $^3J_{C\text{-}F}$ = 3.9 Hz, 2C, C_7), 106.3 (s, C_2), 53.6 (d, C_4), 28.8 (q, $C_{1'}$), 26.5 (q, C_1).

HRMS (ESI) *m/z*: calcd for $C_{13}H_{12}F_3O_4$ $[M+H]^+$: 289.0682, found: 289.0683.

2,2-Dimethyl-5-(thiophen-3-yl)-1,3-dioxane-4,6-dione (II.4g)[124b]



To a suspension of 3-thiophenemalonic acid (1.00 g, 5.37 mmol, 1.00 equiv) in Ac_2O (1.0 mL) was added concentrated H_2SO_4 (22 µL, 0.4 mmol, 0.08 equiv) dropwise. The resulting suspension was stirred for 30 min and then diluted with acetone (1.0 mL, 14 mmol, 2.5 equiv). The reaction mass was quenched by the addition of cold H_2O (20 mL), the precipitate was filtered and washed with cold water (3 x 15 mL). The resulting solid was suspended in $(i\text{-}Pr)_2O$ (4 mL) and stirred for 30 min. Then filtered to furnish **II.4g** as an off-white (beige) solid (962 mg, 79%).

Mp = 129-130 °C

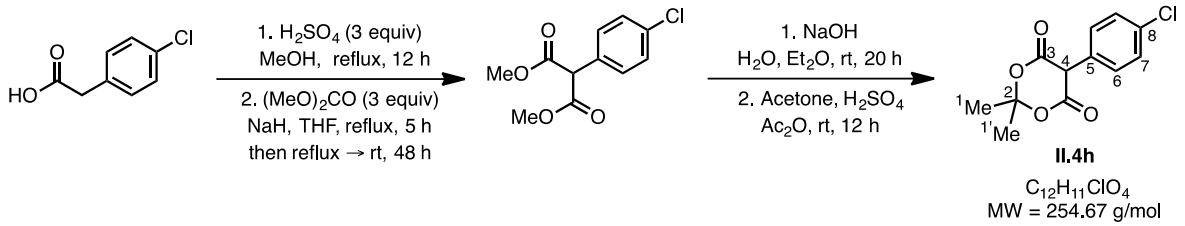
IR (ATR): 1781, 1739, 1392, 1341, 1268, 1216, 1075, 1022, 900, 840, 786, 696, 664, 644, 600 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (dd, J = 5.1, 3.0 Hz, 1H, H_7), 7.34 (m, 1H, H_8), 7.09 (dd, J = 5.0, 1.4 Hz, 1H, H_6), 4.91 (s, 1H, H_4), 1.84 (s, 3H, H_1), 1.67 (s, 3H, $H_{1'}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5 (s, 2C, C_3), 129.1 (s, C_5), 127.3 (d, C_6 or C_7), 127.2 (d, C_6 or C_7), 125.0 (d, C_8), 106.2 (s, C_2), 48.2 (d, C_4), 28.6 (q, $C_{1'}$), 27.7 (q, C_1).

HRMS (ESI) *m/z*: calcd for $C_{10}H_{10}O_4SNa$ $[M+Na]^+$: 249.0192, found: 249.0193.

2,2-Dimethyl-5-(4-chlorophenyl)-1,3-dioxane-4,6-dione (II.4h)



A flame-dried flask was charged with 4-chlorophenylacetic acid (3.00 g, 17.6 mmol, 1.00 equiv), MeOH (30.0 mL) and H_2SO_4 (3.0 mL, 55 mmol, 3.1 equiv) and the reaction mixture was heated at reflux for 12 h. Then, the reaction mixture was cooled to rt and concentrated under reduced pressure. The resulting residue was partitioned between H_2O (30 mL) and Et_2O (30 mL), and the aqueous phase was extracted with Et_2O (3 × 30 mL). The organic layers were combined, washed with a saturated aqueous solution of $NaHCO_3$ (3 × 30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the methyl 4-chlorophenylacetate as a slight yellow oil (2.78 g, 86%) which was engaged in the next step without further purification or characterization.[125]

To a solution of methyl 4-chlorophenylacetate (2.78 g, 15.1 mmol, 1.00 equiv) in THF (75 mL) was added NaH (1.45 g, 60% in mineral oil, 36 mmol, 2.4 equiv), followed by dimethyl carbonate (3.8 mL, 45 mmol, 3.0 equiv). The mixture was heated at reflux for 5 h and then cooled to rt, stirring was kept for additional 48 h. Then a saturated aqueous solution of NH_4Cl was carefully added to quench the reaction. The organic layer was extracted with EtOAc (3 x 30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the corresponding dimethyl malonate as a yellow solid (3.50 g, 96%) which was engaged in the saponification step without further purification or characterization.[126]

The 1,3-dimethyl 2-(4-chlorophenyl)propanedioate (3.50 g, 14.4 mmol, 1.00 equiv) was dissolved in Et_2O (15 mL) and then added to a flask containing a solution of NaOH (2.30 g, 57.6 mmol, 4.00 equiv) in H_2O (50 mL) at 0 °C over a period of 10 min. The resulting mixture was stirred at rt for 20 h. The aqueous layer was separated and washed with EtOAc (2 x 200 mL), acidified to pH 2 with an aqueous solution of HCl (6 M), and extracted with EtOAc (2 x 200 mL). The combined organic extracts were washed with a saturated aqueous brine solution (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a slightly yellow solid (2.87 g, 93%) that was used in the next step without further purification or characterization.

To a suspension of 2-(4-chlorophenyl)propanedioic acid (2.80 g, 13.1 mmol, 1.00 equiv) in Ac_2O (6.3 mL) was added concentrated H_2SO_4 (290 µL, 5.2 mmol, 0.4 equiv) dropwise, which caused complete dissolution. After 1 minute of the addition of acetone (2.50 mL, 34.1 mmol, 1.60 equiv), the product began to precipitate. The reaction mixture was stirred for 12 h, cooled, and filtered. The precipitate was washed thoroughly with ice-cold H_2O and then dissolved in CH_2Cl_2 (200 mL). The resulting solution was washed with a saturated brine solution, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude solid was purified by trituration in hexane/EtOAc = 7:3 to give **II.4h** as a white pale solid (2.71 g, 82%).

Mp = 145-147 °C

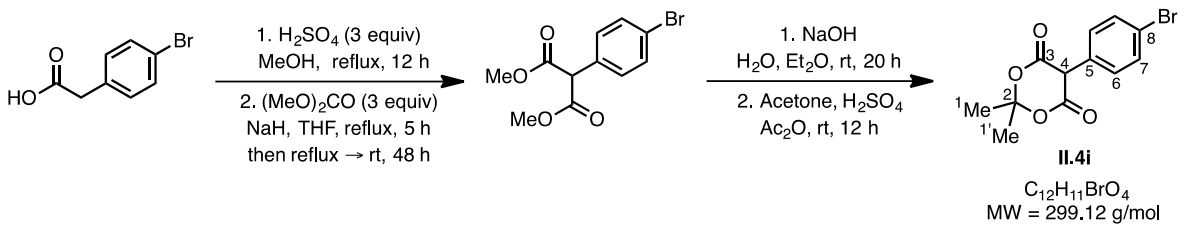
IR (ATR): 1739, 1496, 1393, 1344, 1311, 1282, 1260, 1222, 1090, 1072, 1015, 895, 815, 728, 647 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d_{app}, J = 8.5 Hz, 2H, H_7), 7.22 (d_{app}, J = 8.6 Hz, 2H, H_6), 4.74 (s, 1H, H_4), 1.87 (s, 3H, H_1), 1.78 (s, 3H, $H_{1'}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5 (s, 2C, C_3), 135.2 (s, C_5), 130.8 (d, 2C, C_6), 129.5 (d, 2C, C_7), 129.1 (s, C_8), 105.9 (s, C_2), 52.4 (d, C_4), 28.7 (q, $C_{1'}$), 27.5 (q, C_1).

HRMS (ESI) *m/z*: calcd for $C_{12}H_{11}ClO_4Na$ $[M+Na]^+$: 277.0238, found: 277.0240.

2,2-Dimethyl-5-(4-bromophenyl)-1,3-dioxane-4,6-dione (II.4i)



A flame-dried flask was charged with 4-bromophenylacetic acid (3.00 g, 14.0 mmol, 1.00 equiv), MeOH (24.0 mL) and H_2SO_4 (2.4 mL, 43 mmol, 3.1 equiv) and the reaction mixture was heated at reflux for 12 h. Then, the reaction mixture was cooled to rt and concentrated under reduced pressure. The resulting residue was partitioned between H_2O (30 mL) and Et_2O (30 mL), and the aqueous phase was extracted with Et_2O (3 × 30 mL). The organic layers were combined, washed with a saturated aqueous solution of $NaHCO_3$ (3 × 30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the methyl 4-bromophenylacetate as a clear oil (3.07 g, 96%) which was engaged in the next step without further purification or characterization.

To a solution of methyl 4-bromophenylacetate (3.00 g, 13.1 mmol, 1.00 equiv) in THF (66 mL) was added NaH (1.26 g, 60% in mineral oil, 31 mmol, 2.4 equiv), followed by dimethyl carbonate (3.3 mL, 39 mmol, 3.0 equiv). The mixture was heated at reflux for 5 h and then cooled to rt, stirring was kept for additional 48 h. Then a saturated aqueous solution of NH_4Cl was carefully added to quench the reaction. The organic layer was extracted with EtOAc (3 x 30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the corresponding dimethyl malonate as a yellow solid (3.74 g, 99%) which was engaged in the saponification step without further purification or characterization.

The 1,3-dimethyl 2-(4-bromophenyl)propanedioate (3.74 g, 13.0 mmol, 1.00 equiv) was dissolved in Et_2O (13.0 mL) and then added to a flask containing a solution of NaOH (2.08 g, 52.0 mmol, 4.00 equiv) in H_2O (42 mL) at 0 °C over a period of 10 min. The resulting mixture was stirred at rt for 20 h. The aqueous layer was separated and washed with EtOAc (2 x 100 mL), acidified to pH 2 with an aqueous solution of HCl (6 M), and extracted with EtOAc (2 x 200 mL). The combined organic extracts were washed with a saturated aqueous brine solution (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford an off-white solid (3.32 g, 98%) that was used in the next step without further purification or characterization.

To a suspension of using 2-(4-bromophenyl)propanedioic acid (3.32 g, 12.8 mmol, 1.00 equiv) in Ac_2O (6.1 mL) was added concentrated H_2SO_4 (280 μL, 5.1 mmol, 0.4 equiv) dropwise, which caused complete dissolution. After 1 minute of the addition of acetone (1.50 mL, 20.5 mmol, 1.60 equiv), the product began to precipitate. The reaction mixture was stirred for 12 h, cooled, and filtered. The precipitate was washed thoroughly with ice-cold H_2O and then dissolved in CH_2Cl_2 (200 mL). The resulting solution was washed with a saturated brine solution, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude solid was purified by trituration in hexane/EtOAc = 7:3 to give **II.4i** as a white solid (2.76 g, 72%).

Mp = 137-139 °C

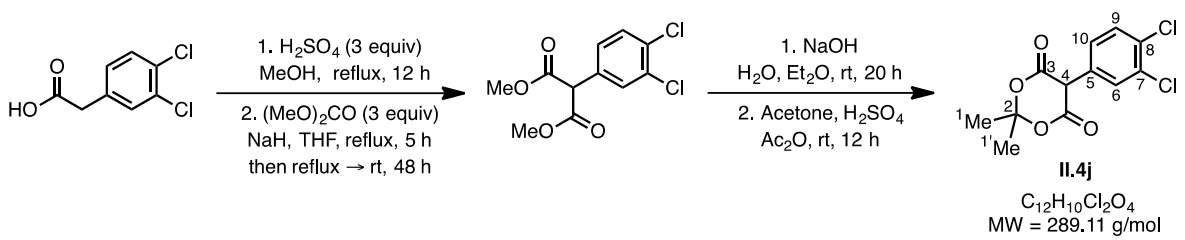
IR (ATR): 1786, 1745, 1494, 1394, 1384, 1340, 1312, 1280, 1259, 1216, 1074, 1055, 1008, 894, 813, 649 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59-7.53 (m, 2H, H_7), 7.20-7.13 (m, 2H, H_6), 4.72 (s, 1H, H_4), 1.88 (s, 3H, H_1), 1.78 (s, 3H, $H_{1'}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4 (s, 2C, C_3), 132.5 (d, 2C, C_7), 131.1 (d, 2C, C_6), 129.6 (s, C_5), 123.4 (s, C_8), 105.9 (s, C_2), 52.5 (d, C_4), 28.7 (q, $C_{1'}$), 27.5 (q, C_1).

HRMS (ESI) *m/z*: calcd for $C_{12}H_{11}BrO_4Na$ $[M+Na]^+$: 320.9733, found: 320.9736.

2,2-Dimethyl-5-(3,4-dichlorophenyl)-1,3-dioxane-4,6-dione (II.4j)



A flame-dried flask was charged with 3,4-dichlorophenylacetic acid (3.00 g, 14.6 mmol, 1.00 equiv), MeOH (25.0 mL) and H_2SO_4 (2.5 mL, 45 mmol, 3.1 equiv) and the reaction mixture was heated at reflux for 12 h. Then, the reaction mixture was cooled to rt and concentrated under reduced pressure. The resulting residue was partitioned between H_2O (30 mL) and Et_2O (30 mL), and the aqueous phase was extracted with Et_2O (3 × 30 mL). The organic layers were combined, washed with a saturated aqueous solution of $NaHCO_3$ (3 × 30 mL), dried

over $MgSO_4$, filtered and concentrated under reduced pressure to afford the methyl 3,4-dichlorophenylacetate as a clear oil (3.20 g, 99%) which was engaged in the next step without further purification or characterization.

To a solution of methyl 3,4-dichlorophenylacetate (3.20 g, 14.5 mmol, 1.00 equiv) in THF (73 mL) was added NaH (1.40 g, 60% in mineral oil, 35 mmol, 2.4 equiv), followed by dimethyl carbonate (3.7 mL, 44 mmol, 3.0 equiv). The mixture was heated at reflux for 5 h and then cooled to rt, stirring was kept for additional 48 h. Then a saturated aqueous solution of NH_4Cl was carefully added to quench the reaction. The organic layer was extracted with EtOAc (3 x 30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the corresponding dimethyl malonate as a yellow solid (4.00 g, 99%) which was engaged in the saponification step without further purification or characterization.

The 1,3-dimethyl 2-(3,4-dichlorophenyl)propanedioate (4.00 g, 14.4 mmol, 1.00 equiv) was dissolved in Et_2O (15 mL) and then added to a flask containing a solution of NaOH (2.30 g, 57.6 mmol, 4.00 equiv) in H_2O (50 mL) at 0 °C over a period of 10 min. The resulting mixture was stirred at rt for 20 h. The aqueous layer was separated and washed with EtOAc (2 x 100 mL), acidified to pH 2 with an aqueous solution of HCl (6 M), and extracted with EtOAc (2 x 200 mL). The combined organic extracts were washed with a saturated aqueous brine solution (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a beige solid (3.20 g, 89%) that was used in the next step without further purification or characterization.

To a suspension of 2-(3,4-dichlorophenyl)propanedioic acid (3.20 g, 12.8 mmol, 1.00 equiv) in Ac_2O (6.1 mL) was added concentrated H_2SO_4 (280 µL, 5.1 mmol, 0.4 equiv) dropwise, which caused complete dissolution. After 1 minute of the addition of acetone (1.50 mL, 20.5 mmol, 1.60 equiv), the product began to precipitate. The reaction mixture was stirred for 12 h, cooled, and filtered. The precipitate was washed thoroughly with ice-cold H_2O and then dissolved in CH_2Cl_2 (200 mL). The resulting solution was washed with a saturated brine solution, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude solid was purified by trituration in hexane/EtOAc = 7:3 to give **II.4j** as a white solid (2.20 g, 59%).

Mp = 157-158 °C

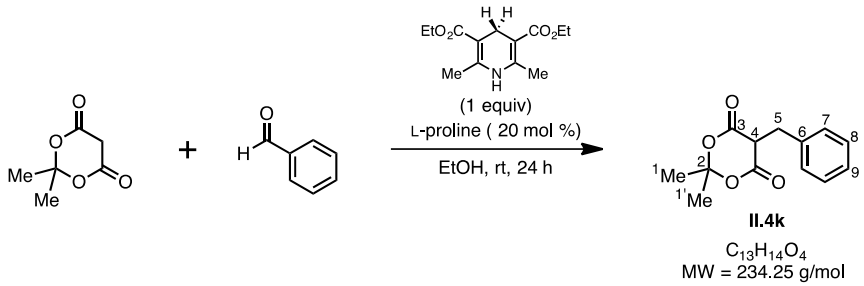
IR (ATR): 2891, 1785, 1743, 1732, 1475, 1395, 1384, 1344, 1284, 1258, 1227, 1077, 1022, 910, 873, 821, 773, 679, 639 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, *J* = 8.3 Hz, 1H, H_9), 7.40 (d, *J* = 2.3 Hz, 1H, H_6), 7.12 (dd, *J* = 8.3, 2.2 Hz, 1H, H_{10}), 4.71 (s, 1H, H_4), 1.90 (s, 3H, H_1), 1.81 (s, 3H, $H_{1'}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9 (s, 2C, C_3), 133.7 (s, C_8), 133.5 (s, C_7), 131.8 (d, C_6), 131.2 (d, C_9), 130.5 (s, C_5), 128.9 (d, C_{10}), 106.1 (s, C_2), 52.1 (d, C_4), 28.8 (q, $C_{1'}$), 27.4 (q, C_1).

HRMS (ESI) *m/z*: calcd for $C_{12}H_{10}Cl_2O_4Na$ $[M+Na]^+$: 310.9848, found: 310.9851.

2,2-Dimethyl-5-benzyl-1,3-dioxane-4,6-dione (II.4k)



To a solution of the native Meldrum's acid — 2,2-dimethyl-1,3-dioxane-4,6-dione — (569 mg, 3.95 mmol, 1.00 equiv) in EtOH (13 mL) was added benzaldehyde (400 µL, 3.95 mmol, 1.00 equiv), followed by L-proline (91 mg, 1.6 mmol, 0.20 equiv) and the Hantzsch ester (1.00 g, 3.95 mmol, 1.00 equiv). The reaction mixture was stirred at rt for 24h. EtOAc (50 mL) was added and, then, H_2O (50 mL). The layers were separated, and the aqueous layer extracted with EtOAc (2 x 25 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography on silica gel (PE/EtOAc from 95:5 to 9:1) to afford the cascade product **II.4k** as viscous oil (684mg, 74%).[129]

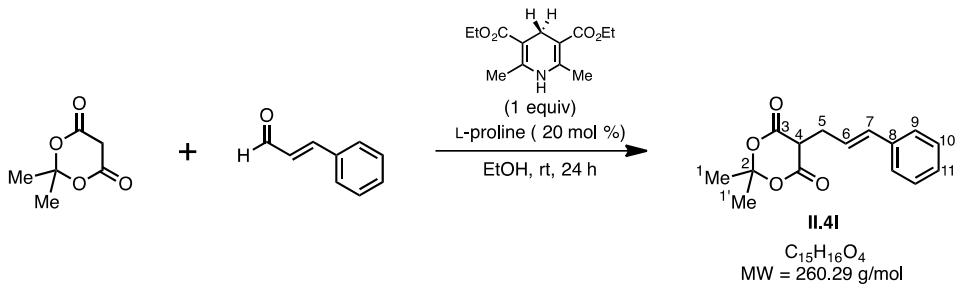
R_f: 0.70 (PE/EtOAc = 7:3)

IR (ATR): 2985, 2934, 1719, 1689, 1593, 1443, 1374, 1292, 1043, 1227, 852, 773 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.19 (m, 5H, H_{Ar}), 3.76 (t, *J* = 5.0 Hz, 1H, H_4), 3.49 (d, *J* = 5.0 Hz, 2H, H_5), 1.73 (s, 3H, H_1), 1.49 (s, 3H, $H_{1'}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7 (s, 2C, C_3), 136.9 (s, C_6), 129.5 (d, 2C, C_7 or C_8), 128.4 (d, 2C, C_7 or C_8), 127.0 (d, C_9), 105.0 (s, C_2), 48.1 (d, C_4), 32.1 (t, C_5), 28.2 (q, $C_{1'}$), 27.0 (q, C_1).

2,2-Dimethyl-5-cinnamyl-1,3-dioxane-4,6-dione (II.4l)



To a solution of the native Meldrum's acid — 2,2-dimethyl-1,3-dioxane-4,6-dione — (569 mg, 3.95 mmol, 1.00 equiv) in MeCN (13 mL) was added *trans*-cinnamaldehyde (500 µL, 3.95 mmol, 1.00 equiv), followed by L-proline (91 mg, 1.6 mmol, 0.20 equiv) and the Hantzsch ester (1.00 g, 3.95 mmol, 1.00 equiv). The reaction mixture was stirred at rt for 24h. EtOAc (50 mL) was added and, then, H_2O (50 mL). The layers were separated, and the aqueous layer extracted with EtOAc (2 x 25 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography on silica gel (PE/EtOAc from 95:5 to 9:1) to afford the cascade product **II.4l** as viscous oil (769mg, 75%).

R$_f$: 0.73 (PE/EtOAc = 7:3)

IR (ATR): 1776, 1737, 1598, 1494, 1450, 1384, 1289, 1202, 1167, 1070, 970, 944, 751, 696 cm^{-1}.

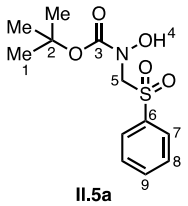
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.19 (m, 5H, H_{Ar}), 6.62 (d_{app}, J = 15.8 Hz, 1H, H_7), 6.28 (dt, J = 15.8, 7.3 Hz, 1H, H_6), 3.68 (t, J = 5.1 Hz, 1H, H_4), 3.05 (ddd, J = 7.4, 5.0, 1.3 Hz, 2H, H_5), 1.81 (s, 3H, H_1), 1.76 (s, 3H, $H_{1'}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1 (s, 2C, C_3), 136.9 (s, C_8), 134.9 (d, C_7), 128.7 (d, 2C, C_9 or C_{10}), 127.7 (d, C_{11}), 126.5 (d, 2C, C_9 or C_{10}), 124.0 (d, C_6), 105.2 (s, C_2), 46.8 (d, C_4), 29.8 (t, C_5), 28.6 (q, $C_{1'}$), 27.1 (q, C_1).

HRMS (ESI) *m/z*: calcd for $C_{15}H_{16}O_4Na$ $[M+Na]^+$: 283.0941, found: 283.0941.

3. Preparation of *N*-Boc Nitrone precursor

***tert*-Butyl ((phenylsulfonyl)methyl)-*N*-hydroxycarbamate (II.5a)**[130]



II.5a

$C_{12}H_{17}NO_5S$
MW = 287.33 g/mol

Sodium benzenesulfinate (15.5 g, 93.9 mmol, 2.50 equiv) was dissolved in H_2O/MeOH 2:1 (111 mL). To this solution was added sequentially *tert*-butyl-*N*-hydroxycarbamate (5.00 g, 37.6 mmol, 1.00 equiv), formaldehyde (5.6 mL, 37% wt in H_2O, 75 mmol, 2.0 equiv) and formic acid 95% (1.8 mL, 45 mmol, 1.2 equiv). This mixture was stirred for 24 h at rt. The resulting precipitate was collected by filtration, washed with H_2O and pentane, and then purified by trituration in hexane/EtOAc = 3:1. The sulfone was obtained as a white solid (9.90 g, 92%).

Mp = 138-139 °C

IR (ATR): 3362, 3009, 2985, 2931, 1707, 1476, 1448, 1394, 1368, 1309, 1287, 1223, 1140, 1094, 1082, 905 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97-7.92 (m, 2H, H_7), 7.68 (m, 1H, H_9), 7.60-7.54 (m, 2H, H_8), 4.90 (s, 2H, H_5), 1.32 (s, 9H, H_1).

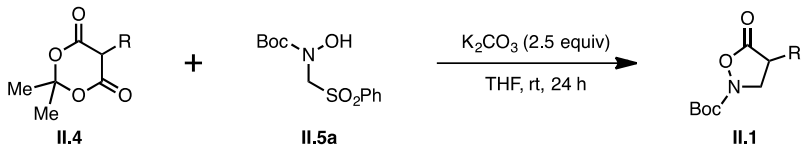
Note: The signal corresponding to the OH moiety was not observed.

^{13}C NMR (100 MHz, $CDCl_3$): δ 154.3 (s, C_3), 138.3 (s, C_6), 134.3 (d, C_9), 129.5 (d, 2C, C_8), 128.9 (d, 2C, C_7), 83.9 (s, C_2), 71.2 (t, C_5), 28.0 (q, 3C, C_1).

HRMS (ESI) *m/z*: calcd for $C_{12}H_{17}NO_5SNa$ $[M+Na]^+$: 310.0720, found: 310.0720.

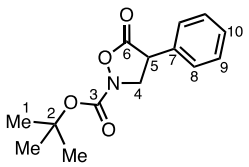
4. Synthesis of 4-substituted isoxazolidin-5-ones (II.1a-k)

General procedure for the synthesis of 4-aryl isoxazolidin-5-ones



To a mixture of meldrum's acid **II.4** (1.1 equiv), nitrone precursor **II.5a** (1.0 equiv) and K_2CO_3 (2.5 equiv) was added THF (0.1 M) at rt. The reaction mixture was stirred for 24 h and filtrated. The solid was washed with Et_2O and the filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel using Et_2O/PE as eluent to afford the desired isoxazolidin-5-one **II.1**.[120]

***tert*-Butyl 5-oxo-4-phenylisoxazolidine-2-carboxylate (II.1a)**[120]



II.1a

$C_{14}H_{17}NO_4$
MW = 263.29 g/mol

II.1a was synthesized according to the method aforementioned from *tert*-butyl ((phenylsulfonyl)methyl)-*N*-hydroxycarbamate **II.5a** (1.19 g, 4.13 mmol, 1.00 equiv) and 2,2-dimethyl-5-phenyl-1,3-dioxane-4,6-dione **II.4a** (1.00 g, 4.54 mmol, 1.10 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/Et_2O = 9:1) as a colorless viscous oil (755 mg, 70%).

R$_f$: 0.16 (PE/Et_2O = 8:2)

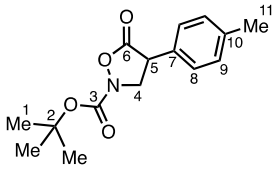
IR (ATR): 2981, 1798, 1745, 1718, 1456, 1369, 1318, 1258, 1216, 1137, 975, 897, 846 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.27 (m, 5H, H_{Ar}), 4.56 (m, 1H, H_4), 4.14-4.06 (m, 2H, $H_{4'}$ and H_5), 1.52 (s, 9H, H_1).

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.5 (s, C_6), 156.1 (s, C_3), 133.4 (s, C_7), 129.4 (d, 2C, C_8 or C_9), 128.6 (d, C_{10}), 128.0 (d, 2C, C_8 or C_9), 84.5 (s, C_2), 55.8 (t, C_4) 46.5 (d, C_5), 28.2 (q, 3C, C_1).

MS *m/z* (relative intensity): 264 ($[M+H]^{+\cdot}$,1), 248 (1), 204 (3), 163 (10), 135 (8), 118 (6), 104 (9), 91 (4), 77 (3), 57 (100).

***tert*-Butyl 5-oxo-4-(*p*-tolyl)isoxazolidine-2-carboxylate (II.1b)**



II.1b

$C_{15}H_{19}NO_4$
MW = 277.32 g/mol

II.1b was synthesized according to the method aforementioned from *tert*-butyl ((phenylsulfonyl)methyl)-*N*-hydroxycarbamate **II.5a** (279 mg, 0.970 mmol, 1.00 equiv) and 2,2-dimethyl-5-(4-methylphenyl)-1,3-dioxane-4,6-dione **II.4c** (250 mg, 1.07 mmol, 1.10 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/Et_2O = 9:1) as a colorless oil (169 mg, 63%).

R$_f$: 0.26 (PE/Et_2O = 8:2)

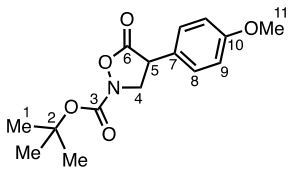
IR (ATR): 2980, 2919, 1796, 1745, 1718, 1517, 1458, 1370, 1316, 1258, 1217, 1138, 975, 904, 847, 773 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22-7.16 (m, 4H, H_{Ar}), 4.54 (dd, *J* = 12.3, 2.6 Hz, 1H, H_4), 4.10-4.02 (m, 2H, $H_{4'}$ and H_5), 2.35 (s, 3H, H_{11}), 1.52 (s, 9H, H_1).

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.6 (s, C_6), 156.1 (s, C_3), 138.5 (s, C_7), 130.4 (s, C_{10}), 130.0 (d, 2C, C_8 or C_9), 127.9 (d, 2C, C_8 or C_9), 84.5 (s, C_2), 55.8 (t, C_4), 46.2 (d, C_5), 28.2 (q, 3C, C_1), 21.2 (q, C_{11}).

HRMS (ESI) *m/z*: calcd for $C_{15}H_{19}NO_4Na$ $[M+Na]^+$: 300.1206, found: 300.1208.

***tert*-Butyl 4-(4-methoxyphenyl)-5-oxoisoxazolidine-2-carboxylate (II.1c)**



II.1c

$C_{15}H_{19}NO_5$
MW = 293.32 g/mol

II.1c was synthesized according to the method aforementioned from *tert*-butyl ((phenylsulfonyl)methyl)-*N*-hydroxycarbamate **II.5a** (1.04 g, 3.63 mmol, 1.00 equiv) and 2,2-

dimethyl-5-(4-methoxyphenyl)-1,3-dioxane-4,6-dione **II.4d** (1.00 g, 4.00 mmol, 1.10 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/Et_2O = 7:3) as a colorless oil (628 mg, 59%).

R_f: 0.51 (PE/Et_2O = 1:1)

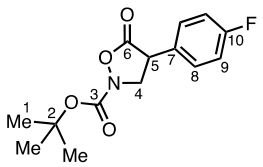
IR (ATR): 1796, 1719, 1613, 1515, 1369, 1250, 1138, 1031, 905, 834, 776 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (m, 2H, H_8), 6.91 (m, 2H, H_9), 4.53 (m, 1H, H_4), 4.10-3.99 (m, 2H, $H_{4'}$ and H_5), 3.80 (s, 3H, H_{11}), 1.52 (s, 9H, H_1).

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.8 (s, C_6), 159.7 (s, C_{10}), 156.1 (s, C_3), 129.2 (d, 2C, C_8), 125.3 (s, C_7), 114.8 (d, 2C, C_9), 84.5 (s, C_2), 55.9 (t, C_4), 55.5 (q, C_{11}), 45.8 (d, C_5), 28.2 (q, 3C, C_1).

HRMS (ESI) *m/z*: calcd for $C_{15}H_{19}NO_5Na$ $[M+Na]^+$: 316.1155, found: 316.1156.

***tert*-Butyl 4-(4-fluorophenyl)-5-oxoisoxazolidine-2-carboxylate (II.1d)**



II.1d
$C_{14}H_{16}FNO_4$
MW = 281.28 g/mol

II.1d was synthesized according to the method aforementioned from *tert*-butyl ((phenylsulfonyl)methyl)-*N*-hydroxycarbamate **II.5a** (548 mg, 1.91 mmol, 1.00 equiv) and 2,2-dimethyl-5-(4-fluorphenyl)-1,3-dioxane-4,6-dione **II.4e** (500 mg, 2.10 mmol, 1.10 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/Et_2O = 8:2) as a colorless oil (398 mg, 74%).

R_f: 0.16 (PE/Et_2O = 8:2)

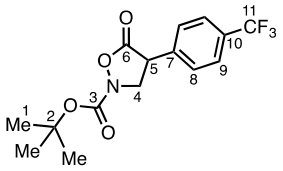
IR (ATR): 2982, 1718, 1607, 1512, 1459, 1395, 1370, 1320, 1227, 1137, 1016, 977, 907, 840, 780, 735, 685 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.26 (m, 2H, H_8), 7.12-7.05 (m, 2H, H_9), 4.56 (dd, J = 10.4, 7.8 Hz, 1H, H_4), 4.14-4.00 (m, 2H, $H_{4'}$ and H_5), 1.52 (s, 9H, H_1).

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.2 (s, C_6), 162.8 (s, $^1J_{C\text{-}F}$ = 249 Hz, C_{10}), 156.0 (s, C_3), 129.8 (d, $^3J_{C\text{-}F}$ = 8.3 Hz, 2C, C_8), 129.1 (s, $^4J_{C\text{-}F}$ = 3.4 Hz, C_7), 116.4 (d, $^2J_{C\text{-}F}$ = 21.8 Hz, 2C, C_9), 84.7 (s, C_2), 55.7 (t, C_4), 45.8 (d, C_5), 28.2 (q, 3C, C_1).

HRMS (ESI) *m/z*: calcd for $C_{14}H_{16}FNO_4Na$ $[M+Na]^+$: 304.0956, found: 304.0959.

***tert*-Butyl 5-oxo-4-(4-(trifluoromethyl)phenyl)isoxazolidine-2-carboxylate (II.1e)**



II.1e

$C_{15}H_{16}F_3NO_4$
MW = 331.29 g/mol

II.1e was synthesized according to the method aforementioned from *tert*-butyl ((phenylsulfonyl)methyl)-*N*-hydroxycarbamate **II.5a** (287 mg, 0.552 mmol, 1.00 equiv) and 2,2-dimethyl-5-(4-(trifluoromethyl)phenyl)-1,3-dioxane-4,6-dione **II.4f** (175 mg, 0.607 mmol, 1.10 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/Et_2O = 9:1) as a colorless oil (141 mg, 75%).

R$_f$: 0.33 (PE/Et_2O = 8:2)

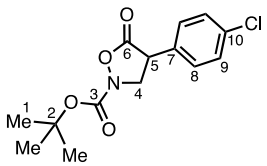
IR (ATR): 2983, 1798, 1720, 1622, 1459, 1422, 1396, 1371, 1325, 1260, 1126, 1069, 1019, 909, 845, 767, 694, 607 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d_{app}, *J* = 8.1 Hz, 2H, H_9), 7.46 (d_{app}, *J* = 8.3 Hz, 2H, H_8), 4.61 (dd, *J* = 11.0, 8.3 Hz, 1H, H_4), 4.19 (t_{app}, *J* = 8.7 Hz, 1H, H_5), 4.09 (dd, *J* = 11.0, 9.1 Hz, 1H, $H_{4'}$), 1.53 (s, 9H, H_1).

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.6 (s, C_6), 155.9 (s, C_3), 137.2 (s, C_7), 131.1 (s, $^2J_{C\text{-}F}$ = 32.9 Hz, C_{10}), 128.6 (d, 2C, C_8), 126.4 (d, $^3J_{C\text{-}F}$ = 3.7 Hz, 2C, C_9), 123.9 (s, $^1J_{C\text{-}F}$ = 273 Hz, C_{11}), 84.9 (s, C_2), 55.4 (t, C_4), 46.2 (d, C_5), 28.2 (q, 3C, C_1).

HRMS (ESI) *m/z*: calcd for $C_{15}H_{16}F_3NO_4Na$ $[M+Na]^+$: 354.0924, found: 354.0926.

***tert*-Butyl 5-oxo-4-(4-chlorophenyl)isoxazolidine-2-carboxylate (II.1f)**

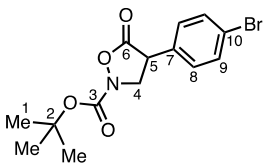


II.1f
$C_{14}H_{16}ClNO_4$
MW = 297.74 g/mol

II.1f was synthesized according to the method aforementioned from *tert*-butyl ((phenylsulfonyl)methyl)-*N*-hydroxycarbamate **II.5a** (1.03 g, 3.57 mmol, 1.00 equiv) and 2,2-dimethyl-5-(4-chlorophenyl)-1,3-dioxane-4,6-dione **II.4h** (1.00 g, 3.93 mmol, 1.10 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/Et_2O = 8:2) as an off-white solid (736 mg, 69%).

Mp = 87-89 °C
R$_f$: 0.21 (PE/Et_2O = 8:2)
IR (ATR): 2981, 1796, 1716, 1599, 1494, 1477, 1459, 1395, 1370, 1321, 1258, 1217, 1138, 1090, 1016, 906, 844, 768, 731, 649 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.34 (m, 2H, H_8), 7.27-7.22 (m, 2H, H_9), 4.56 (dd, *J* = 10.3, 7.6 Hz, 1H, H_4), 4.14-3.99 (m, 2H, $H_{4'}$ and H_5), 1.52 (s, 9H, H_1).
^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0 (s, C_6), 155.9 (s, C_3), 134.8 (s, C_7), 131.7 (s, C_{10}), 129.6 (d, 2C, C_8), 129.4 (d, 2C, C_9), 84.7 (s, C_2), 55.5 (t, C_4), 45.9 (d, C_5), 28.2 (q, 3C, C_1).
HRMS (ESI) *m/z*: calcd for $C_{14}H_{16}ClNO_4Na$ $[M+Na]^+$: 320.0660, found: 320.0663.

***tert*-Butyl 5-oxo-4-(4-bromophenyl)isoxazolidine-2-carboxylate (II.1g)**



II.1g
$C_{14}H_{16}BrNO_4$
MW = 342.19 g/mol

II.1g was synthesized according to the method aforementioned from *tert*-butyl ((phenylsulfonyl)methyl)-*N*-hydroxycarbamate **II.5a** (500 mg, 1.74 mmol, 1.00 equiv) and

2,2-dimethyl-5-(4-bromophenyl)-1,3-dioxane-4,6-dione **II.4i** (573 mg, 1.91 mmol, 1.10 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/Et_2O = 8:2) as a white solid (386 mg, 65%).

Mp = 88-89 °C

R$_f$: 0.20 (PE/Et_2O = 8:2)

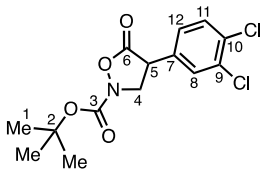
IR (ATR): 2980, 1795, 1718, 1491, 1370, 1320, 1258, 1139, 1073, 1012, 905, 845, 778 cm^{-1}.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ 7.55-7.50 (m, 2H, H_9), 7.21-7.16 (m, 2H, H_8), 4.57 (m, 1H, H_4), 4.11-3.99 (m, 2H, $H_{4'}$ and H_5), 1.52 (s, 9H, H_1).

^{13}**C NMR** (100 MHz, $CDCl_3$): δ 172.9 (s, C_6), 155.9 (s, C_3), 132.5 (d, 2C, C_9), 132.3 (s, C_7), 129.7 (d, 2C, C_8), 122.9 (s, C_{10}), 84.7 (s, C_2), 55.4 (t, C_4), 45.9 (d, C_5), 28.2 (q, 3C, C_1).

HRMS (ESI) *m/z*: calcd for $C_{14}H_{16}BrNO_4Na$ $[M+Na]^+$: 364.0155, found: 364.0157.

***tert*-Butyl 5-oxo-4-(3,4-dichlorophenyl)isoxazolidine-2-carboxylate (II.1h)**



II.1h

$C_{14}H_{15}Cl_2NO_4$

MW = 332.18 g/mol

II.1h was synthesized according to the method aforementioned from *tert*-butyl ((phenylsulfonyl)methyl)-*N*-hydroxycarbamate **II.5a** (500 mg, 1.74 mmol, 1.00 equiv) and 2,2-dimethyl-5-(3,4-dichlorophenyl)-1,3-dioxane-4,6-dione **II.4j** (553 mg, 1.91 mmol, 1.10 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/Et_2O = 8:2) as a white solid (236 mg, 41%).

Mp = 113-114 °C

R$_f$: 0.15 (PE/Et_2O = 8:2)

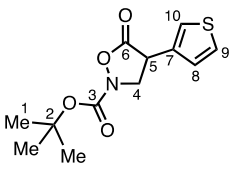
IR (ATR): 2981, 1797, 1719, 1475, 1395, 1370, 1319, 1258, 1136, 1033, 936, 846, 771, 678 cm^{-1}.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ 7.48 (d, *J* = 8.3 Hz, 1H, H_{11}), 7.42 (d, *J* = 2.2 Hz, 1H, H_8), 7.17 (ddd, *J* = 8.4, 2.2, 0.4 Hz, 1H, H_{12}), 4.56 (m, 1H, H_4), 4.11-4.00 (m, 2H, $H_{4'}$ and H_5), 1.53 (s, 9H, H_1).

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.4 (s, C_6), 155.9 (s, C_3), 133.6 (s, C_{10}), 133.3 (s, C_7), 133.2 (s, C_9), 131.3 (d, C_{11}), 130.1 (d, C_8), 127.4 (d, C_{12}), 85.0 (s, C_2), 55.2 (t, C_4), 45.5 (d, C_5), 28.2 (q, 3C, C_1).

HRMS (ESI) *m/z*: calcd for $C_{14}H_{15}Cl_2NO_4Na$ $[M+Na]^+$: 354.0270, found: 354.0273.

***tert*-Butyl 5-oxo-4-(thiophen-3-yl)isoxazolidine-2-carboxylate (II.1i)**



II.1i

$C_{12}H_{15}NO_4S$
MW = 269.32 g/mol

II.1i was synthesized according to the method aforementioned from *tert*-butyl ((phenylsulfonyl)methyl)-*N*-hydroxycarbamate **II.5a** (693 mg, 2.41 mmol, 1.00 equiv) and 2,2-dimethyl-5-(thiophen-3-yl)-1,3-dioxane-4,6-dione **II.4g** (600 mg, 2.65 mmol, 1.10 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/Et_2O = 8:2) as a yellowish oil (515 mg, 79%).

R_f: 0.25 (PE/Et_2O = 8:2)

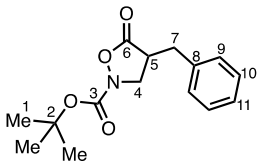
IR (ATR): 2980, 1798, 1715, 1458, 1394, 1370, 1319, 1259, 1220, 1136, 985, 958, 844, 786, 641 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (dd, *J* = 5.0, 2.9 Hz, 1H, H_9), 7.30 (m, 1H, H_{10}), 7.08 (dd, *J* = 5.1, 1.4 Hz, 1H, H_8), 4.53 (dd, *J* = 10.3, 7.6 Hz, 1H, H_4), 4.22-4.08 (m, 2H, $H_{4'}$ and H_5), 1.50 (s, 9H, H_1).

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0 (s, C_6), 156.1 (s, C_3), 132.7 (s, C_7), 127.4 (d, C_9), 126.6 (d, C_8), 123.5 (d, C_{10}), 84.6 (s, C_2), 55.1 (t, C_4), 41.9 (d, C_5), 28.1 (q, 3C, C_1).

HRMS (ESI) *m/z*: calcd for $C_{12}H_{15}NO_4SNa$ $[M+Na]^+$: 292.0614, found: 292.0617.

***tert*-Butyl 5-oxo-4-benzylisoxazolidine-2-carboxylate (II.1j)**[120]



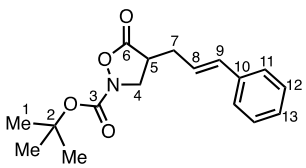
II.1j

$C_{15}H_{19}NO_4$
MW = 277.32 g/mol

II.1j was synthesized according to the method aforementioned from *tert*-butyl ((phenylsulfonyl)methyl)-*N*-hydroxycarbamate **II.5a** (703 mg, 2.45 mmol, 1.00 equiv) and 2,2-dimethyl-5-benzyl-1,3-dioxane-4,6-dione **II.4k** (630 mg, 2.69 mmol, 1.10 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/Et_2O = from 95:5 to 8:2) as a viscous oil (612 mg, 90%).

R_f: 0.40 (PE/Et_2O = 8:2)
IR (ATR): 2982, 1790, 1710, 1454, 1357, 1319, 1263, 1145, 1029, 994, 846, 747, 705 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.15 (m, 5H, H_{Ar}), 4.14 (dd, *J* = 11.1, 8.4 Hz, 1H, H_4), 3.71 (dd, *J* = 11.1, 9.2 Hz, 1H, $H_{4'}$), 3.26 (dd, *J* = 14.0, 4.5 Hz, 1H, H_7), 3.17 (m, 1H, H_5), 2.80 (dd, *J* = 14.0, 9.9 Hz, 1H, $H_{7'}$), 1.51 (s, 9H, H_1).
^{13}C NMR (100 MHz, $CDCl_3$): δ 174.1 (s, C_6), 155.9 (s, C_3), 136.8 (s, C_8), 128.9 (d, 2C, C_9 or C_{10}), 128.7 (d, 2C, C_9 or C_{10}), 127.3 (d, C_{11}), 84.0 (s, C_2), 52.9 (t, C_4), 42.1 (d, C_5), 34.3 (t, C_7), 28.0 (q, 3C, C_1).

***tert*-Butyl 5-oxo-4-cinnamylisoxazolidine-2-carboxylate (II.1k)**



II.1k

$C_{17}H_{21}NO_4$
MW = 303.36 g/mol

II.1k was synthesized according to the method aforementioned from *tert*-butyl ((phenylsulfonyl)methyl)-*N*-hydroxycarbamate **II.5a** (251 mg, 0.87 mmol, 1.00 equiv) and 2,2-dimethyl-5-cinnamyl-1,3-dioxane-4,6-dione **II.4l** (230 mg, 0.96 mmol, 1.10 equiv). The

titled compound was obtained after flash column chromatography on silica gel (PE/Et_2O = 9:1) as a viscous oil (183 mg, 69%).

R_f: 0.37 (PE/Et_2O = 7:3)

IR (ATR): 2980, 2917, 1796, 1743, 1726, 1451, 1369, 1329, 1254, 1212, 1138, 966, 846, 746, 693 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.20 (m, 5H, H_{Ar}), 6.51 (dt_{app}, J = 15.7, 1.4 Hz, 1H, H_9), 6.13 (ddd, *J* = 15.7, 7.7, 6.8 Hz, 1H, H_8), 4.29 (dd, *J* = 11.0, 8.7 Hz, 1H, H_4), 3.75 (dd, *J* = 11.1, 9.3 Hz, 1H, $H_{4'}$), 3.06 (m, 1H, H_5), 2.77 (m, 1H, H_7), 2.50 (m, 1H, $H_{7'}$), 1.51 (s, 9H, H_1).

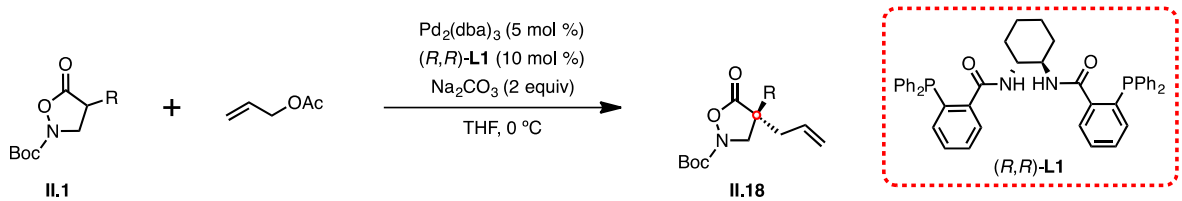
^{13}C NMR (100 MHz, $CDCl_3$): δ 174.2 (s, C_6), 155.9 (s, C_3), 136.5 (s, C_{10}), 133.1 (d, C_{13}), 128.6 (d, 2C, C_{11} or C_{12}), 127.8 (d, C_9), 126.3 (d, 2C, C_{11} or C_{12}), 124.1 (d, C_8), 84.2 (s, C_2), 52.9 (t, C_4), 40.4 (d, C_5), 31.9 (t, C_7), 28.1 (q, 3C, C_1).

HRMS (ESI) *m/z*: calcd for $C_{17}H_{21}NO_4Na$ $[M+Na]^+$: 326.1363, found: 326.1363.

5. General procedures for the Pd-AAA of 4-substituted isoxazolidin-5-ones

Synthesis of isoxazolidin-5-ones (II.18a-j)

(Representative procedure)



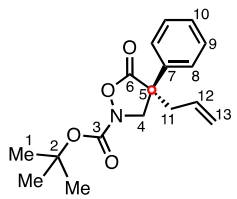
To a solution of $Pd_2(dba)_3$ (0.01 mmol, 0.05 equiv) in THF (2.0 mL) at rt was added (*R*,*R*)-DACH phenyl Trost ligand (0.02 mmol, 0.10 equiv) and the mixture was stirred for 30 min. This solution was then cooled to 0 °C and transferred via cannula to a flask containing 4-substituted isoxazolidin-5-one (0.2 mmol, 1 equiv) and Na_2CO_3 (0.4 mmol, 2 equiv). Followed by the addition of allyl acetate (0.2 mmol, 1 equiv) and stirring was continued at the same temperature until complete consumption of the starting material (confirmed by TLC). The reaction mixture was filtered through a plug of Celite® and concentrated under reduced pressure to afford a crude residue, which was purified by flash column chromatography on silica gel to afford the corresponding allylated isoxalidin-5-one.

General procedure for the synthesis of the racemic compounds

(Representative procedure)

To a flask containing 4-substituted isoxazolidin-5-one (0.2 mmol, 1 equiv) and Na_2CO_3 (0.4 mmol, 2 equiv) in THF (2 mL) at rt was added $Pd(PPh_3)_4$ (0.01 mmol, 0.05 equiv). Followed by the addition of allyl acetate (0.2 mmol, 1 equiv) and stirring was continued at the same temperature until complete consumption of the starting material (confirmed by TLC). The reaction mixture was filtered through a plug of Celite® and concentrated under reduced pressure to afford a crude residue, which was purified following the same procedure described for the corresponding enantioenriched compound.

***tert*-Butyl (*S*)-4-allyl-5-oxo-4-phenylisoxazolidine-2-carboxylate (II.18a)**



II.18a

$C_{17}H_{21}NO_4$
MW = 303.36 g/mol

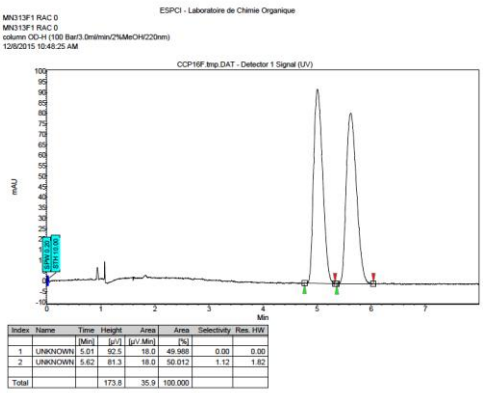
II.18a was synthesized according to the method aforementioned from *tert*-butyl 5-oxo-4-phenylisoxazolidine-2-carboxylate **II.1a** (55 mg, 0.21 mmol, 1.0 equiv) and allyl acetate (23 µL, 0.21 mmol, 1.0 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/Et_2O = 95:5) as a white solid (60 mg, 95%).

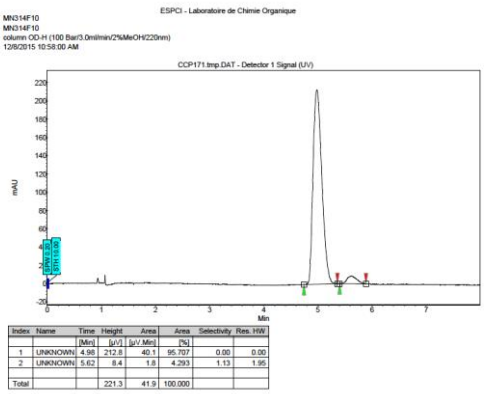
Mp = 94-95 °C
R$_f$: 0.49 (PE/Et_2O = 8:2)
[α]^{20} D = + 118 (*c* 0.50, $CHCl_3$)
ee = 91% (determined by SFC)
SFC: AD-H column, Pressure = 100 bar, eluent = sc CO_2/MeOH = 98:2, Flow rate = 3 mL/min, detection wavelength = 220 nm. t_R = 4.98 min (major) and t_R = 5.62 min (minor).
IR (ATR): 2981, 2933, 1796, 1747, 1721, 1497, 1450, 1370, 1342, 1258, 1145, 1080, 1033, 994, 929, 848 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47-7.29 (m, 5H, H_{Ar}), 5.61 (m, 1H, H_{12}), 5.19-5.09 (m, 2H, H_{13}), 4.61 (d, *J* = 11.8 Hz, 1H, H_4), 4.16 (d, *J* = 11.7 Hz, 1H, $H_{4'}$), 2.75-2.64 (m, 2H, H_{11}), 1.33 (s, 9H, H_1).

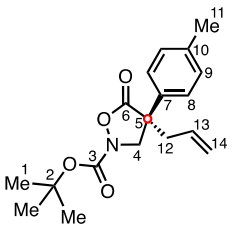
^{13}C NMR (100 MHz, $CDCl_3$): δ 175.7 (s, C_6), 156.1 (s, C_3), 136.5 (s, C_7), 131.5, (d, C_{12}), 129.1 (d, 2C, C_8 or C_9), 128.4 (d, C_{10}), 126.6 (d, 2C, C_8 or C_9), 120.8 (t, C_{13}), 84.1 (s, C_2), 57.6 (t, C_4), 52.2 (s, C_5), 41.9 (t, C_{11}), 27.9 (q, 3C, C_1).

HRMS (ESI) *m/z*: calcd for $C_{17}H_{21}NO_4Na$ $[M+Na]^+$: 326.1363, found: 326.1362.





***tert*-Butyl (*S*)-4-allyl-5-oxo-4-(*p*-tolyl)isoxazolidine-2-carboxylate (II.18b)**



II.18b

$C_{18}H_{23}NO_4$
MW = 317.39 g/mol

II.18b was synthesized according to the method aforementioned from *tert*-butyl 5-oxo-4-(*p*-tolyl)isoxazolidine-2-carboxylate **II.1b** (50 mg, 0.18 mmol, 1.0 equiv) and allyl acetate (20 µL, 0.19 mmol, 1.0 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/Et_2O = 9:1) as a colorless oil (52 mg, 91%).

R$_f$: 0.45 (PE/Et_2O = 8:2)

$[\alpha]^{20}_D$ = +65.2 (*c* 0.65, $CHCl_3$)

ee = 90% (determined by SFC)

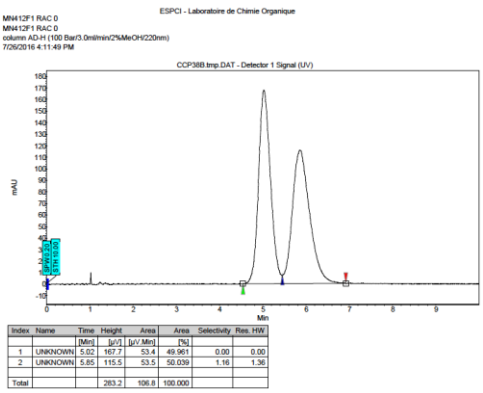
SFC: AD-H column, Pressure = 100 bar, eluent = sc CO_2/MeOH = 98:2, Flow rate = 3 mL/min, detection wavelength = 220 nm. t_R = 4.93 min (major) and t_R = 5.86 min (minor).

IR (ATR): 2980, 2918, 2850, 1795, 1746, 1719, 1641, 1515, 1458, 1370, 1144, 995, 928, 848, 815, 782, 766 cm^{-1}.

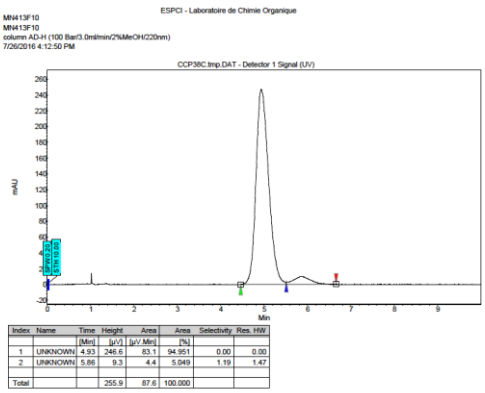
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.28 (m, 2H, H_8), 7.21-7.15 (m, 2H, H_9), 5.61 (ddt, *J* = 16.5, 10.7, 7.3 Hz, 1H, H_{13}), 5.18-5.08 (m, 2H, H_{14}), 4.57 (d, *J* = 11.7 Hz, 1H, H_4), 4.14 (d, *J* = 11.7 Hz, 1H, $H_{4'}$), 2.74-2.61 (m, 2H, H_{12}), 2.33 (s, 3H, H_{11}), 1.34 (s, 9H, H_1).

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.5 (s, C_6), 156.1 (s, C_3), 138.2 (s, C_7), 133.4 (s, C_{10}), 131.6 (d, C_{13}), 129.7 (d, 2C, C_9), 126.5 (d, 2C, C_8), 120.6 (t, C_{14}), 84.0 (s, C_2), 57.7 (t, C_4), 51.9 (s, C_5), 41.8 (t, C_{12}), 27.9 (q, 3C, C_1), 21.0 (q, C_{11}).

HRMS (ESI) *m/z*: calcd for $C_{18}H_{23}NO_4Na$ $[M+Na]^+$: 340.1519, found: 340.1520.

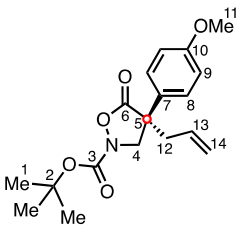


Index	Name	Time [Min]	Height [µV]	Area [µV.Min]	Area [%]	Selectivity	Res. HW
1	UNKNOWN	5.02	167.7	53.4	49.961	0.00	0.00
2	UNKNOWN	5.85	115.5	53.5	50.039	1.16	1.36
Total			283.2	106.8	100.000		



Index	Name	Time [Min]	Height [µV]	Area [µV.Min]	Area [%]	Selectivity	Res. HW
1	UNKNOWN	4.93	246.6	83.1	94.951	0.00	0.00
2	UNKNOWN	5.86	9.3	4.4	5.049	1.19	1.47
Total			255.9	87.6	100.000		

***tert*-Butyl (*S*)-4-allyl-4-(4-methoxyphenyl)-5-oxoisoxazolidine-2-carboxylate (II.18c)**



II.18c

$C_{18}H_{23}NO_5$
MW = 333.38 g/mol

II.18c was synthesized according to the method aforementioned from *tert*-butyl 4-(4-methoxyphenyl)-5-oxoisoxazolidine-2-carboxylate **II.1c** (50 mg, 0.17 mmol, 1.0 equiv) and allyl acetate (18 µL, 0.17 mmol, 1.0 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/Et_2O = 8:2) as a colorless oil (49 mg, 86%).

R$_f$: 0.26 (PE/Et_2O = 8:2)

[α]^{20} D = +35.5 (*c* 0.22, $CHCl_3$)

ee = 87% (determined by SFC)

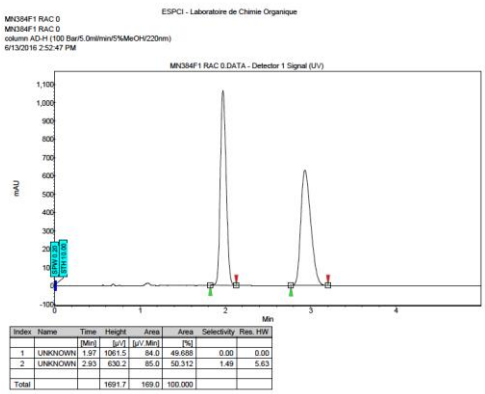
SFC: AD-H column, Pressure = 100 bar, eluent = sc CO_2/MeOH = 95:5, Flow rate = 5 mL/min, detection wavelength = 220 nm. t_R = 1.96 min (major) and t_R = 2.95 min (minor).

IR (ATR): 2980, 1794, 1745, 1719, 1610, 1515, 1459, 1370, 1300, 1253, 1142, 1031, 994, 928, 830, 783, 685 cm^{-1}.

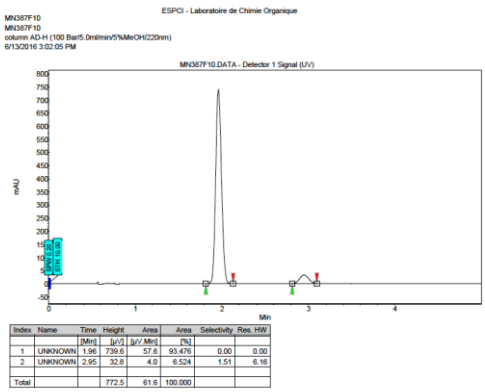
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.31 (m, 2H, H_8), 6.92-6.86 (m, 2H, H_9), 5.60 (ddt, *J* = 16.6, 10.4, 7.3 Hz, 1H, H_{13}), 5.20-5.08 (m, 2H, H_{14}), 4.56 (d, *J* = 11.8 Hz, 1H, H_4), 4.12 (d, *J* = 11.7 Hz, 1H, $H_{4'}$), 3.79 (s, 3H, H_{11}), 2.73-2.59 (m, 2H, H_{12}), 1.35 (s, 9H, H_1).

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.6 (s, C_6), 159.6 (s, C_{10}), 156.1 (s, C_3), 131.6 (d, C_{13}), 128.2 (s, C_7), 127.8 (d, 2C, C_8), 120.6 (t, C_{14}), 114.4 (d, 2C, C_9), 84.0 (s, C_2), 57.6 (t, C_4), 55.5 (q, C_{11}), 51.6 (s, C_5), 41.9 (t, C_{12}), 27.9 (q, 3C, C_1).

HRMS (ESI) *m/z*: calcd for $C_{18}H_{23}NO_5Na$ $[M+Na]^+$: 356.1468, found: 356.1470.

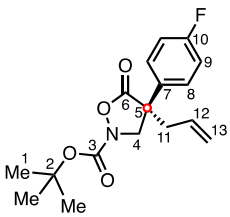


Index	Name	Time [Min]	Height [µV]	Area [µV.Min]	Area [%]	Selectivity	Res. HW
1	UNKNOWN	1.97	1061.5	84.0	49.688	0.00	0.00
2	UNKNOWN	2.93	630.2	85.0	50.312	1.49	5.63
Total			1691.7	169.0	100.000		



Index	Name	Time [Min]	Height [µV]	Area [µV.Min]	Area [%]	Selectivity	Res. HW
1	UNKNOWN	1.96	739.8	57.6	93.476	0.00	0.00
2	UNKNOWN	2.95	32.8	4.0	6.524	1.51	6.16
Total			772.5	61.6	100.000		

***tert*-Butyl (*S*)-4-allyl-4-(4-fluorophenyl)-5-oxoisoxazolidine-2-carboxylate (II.18d)**



II.18d

$C_{17}H_{20}FNO_4$
MW = 321.35 g/mol

II.18d was synthesized according to the method aforementioned from *tert*-butyl 4-(4-fluorophenyl)-5-oxoisoxazolidine-2-carboxylate **II.1d** (50 mg, 0.18 mmol, 1.0 equiv) and allyl acetate (20 µL, 0.19 mmol, 1.0 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/Et_2O = 8:2) as a colorless oil (56 mg, 97%).

R$_f$: 0.41 (PE/Et_2O = 8:2)

[α]^{20} D = +41.5 (*c* 0.20, $CHCl_3$)

ee = 92% (determined by SFC)

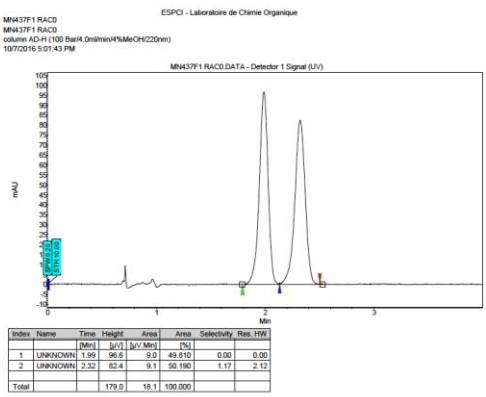
SFC: AD-H column, Pressure = 100 bar, eluent = sc CO_2/MeOH = 96:4, Flow rate = 4 mL/min, detection wavelength = 220 nm. t_R = 1.98 min (minor) and t_R = 2.30 min (major).

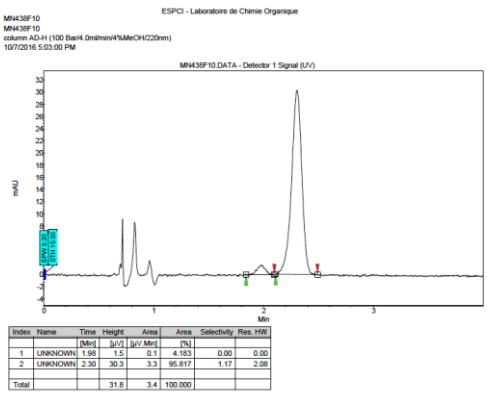
IR (ATR): 2981, 1794, 1719, 1606, 1511, 1459, 1370, 1236, 1143, 1035, 995, 929, 836, 783, 684 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46-7.39 (m, 2H, H_8), 7.11-7.03 (m, 2H, H_9), 5.57 (ddt, *J* = 16.8, 10.2, 7.3 Hz, 1H, H_{12}), 5.19-5.09 (m, 2H, H_{13}), 4.56 (d, *J* = 11.8 Hz, 1H, H_4), 4.17 (d, *J* = 11.8 Hz, 1H, $H_{4'}$), 2.73-2.60 (m, 2H, H_{11}), 1.36 (s, 9H, H_1).

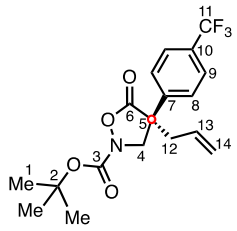
^{13}C NMR (100 MHz, $CDCl_3$): δ 175.2 (s, C_6), 162.6 (s, $^1J_{C\text{-}F}$ = 248 Hz, C_{10}), 156.1 (s, C_3), 132.1 (s, $^4J_{C\text{-}F}$ = 3.5 Hz, C_7), 131.1 (d, C_{12}), 128.5 (d, $^3J_{C\text{-}F}$ = 8.1 Hz, 2C, C_8), 121.0 (t, C_{13}), 116.0 (d, $^2J_{C\text{-}F}$ = 21.6 Hz, 2C, C_9), 84.3 (s, C_2), 57.5 (t, C_4), 51.7 (s, C_5), 42.0 (t, C_{11}), 28.0 (q, 3C, C_1).

HRMS (ESI) *m/z*: calcd for $C_{17}H_{20}FNO_4Na$ $[M+Na]^+$: 344.1269, found: 344.1268.





***tert*-Butyl (*S*)-4-allyl-5-oxo-4-(4-(trifluoromethyl)phenyl)isoxazolidine-2-carboxylate (II.18e)**



II.18e

$C_{18}H_{20}F_3NO_4$
MW = 371.36 g/mol

II.18e was synthesized according to the method aforementioned from *tert*-butyl 4-(4-(trifluoromethyl)phenyl)-5-oxoisoxazolidine-2-carboxylate **II.1e** (50 mg, 0.15 mmol, 1.0 equiv) and allyl acetate (16 µL, 0.15 mmol, 1.0 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/Et_2O = 8:2) as a colorless oil (53 mg, 95%).

R_f: 0.48 (PE/Et_2O = 8:2)

$[\alpha]^{20}_D$ = +57.0 (*c* 0.68, $CHCl_3$)

ee = 86% (determined by SFC)

SFC: OD-H column, Pressure = 100 bar, eluent = sc CO_2/MeOH = 98:2, Flow rate = 3 mL/min, detection wavelength = 220 nm. t_R = 3.28 min (minor) and t_R = 3.52 min (major).

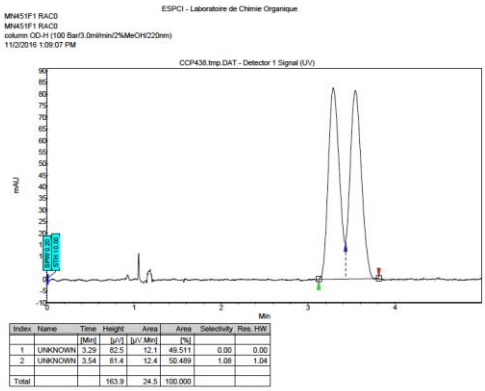
IR (ATR): 2918, 2850, 1798, 1722, 1371, 1328, 1168, 1146, 1129, 1073, 1017, 931, 845, 705 cm^{-1}.

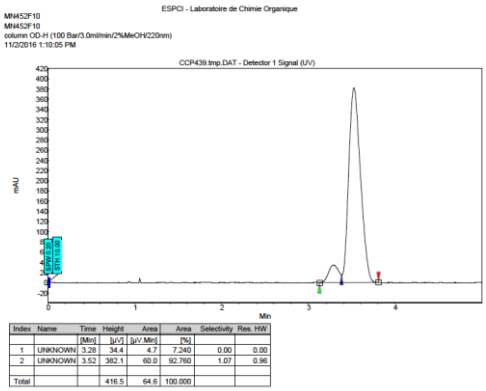
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68-7.62 (m, 2H, H_9), 7.61-7.55 (m, 2H, H_8), 5.57 (ddt, *J* = 16.8, 10.2, 7.3 Hz, 1H, H_{13}), 5.23-5.10 (m, 2H, H_{14}), 4.58 (d, *J* = 11.8 Hz, 1H, H_4), 4.22 (d, *J* = 11.8 Hz, 1H, $H_{4'}$), 2.76-2.65 (m, 2H, H_{12}), 1.35 (s, 9H, H_1).

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.7 (s, C_6), 156.0 (s, C_3), 140.5 (s, C_7), 130.8 (s, $^2J_{C-F}$ = 32.5 Hz, C_{10}), 130.7 (d, C_{13}), 127.2 (d, 2C, C_8), 126.0 (d, $^3J_{C-F}$ = 3.7 Hz, 2C, C_9), 123.9 (s, $^1J_{C-F}$ = 273 Hz, C_{11}), 121.4 (t, C_{14}), 84.5 (s, C_2), 57.3 (t, C_4), 52.3 (s, C_5), 41.8 (t, C_{12}), 27.9 (q, 3C, C_1).

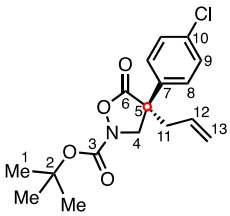
Note: Two signals corresponding to C_{10} quadruplet were not observed.

HRMS (ESI) *m/z*: calcd for $C_{18}H_{20}F_3NO_4Na$ $[M+Na]^+$: 394.1237, found: 394.1238.





***tert*-Butyl (*S*)-4-allyl-4-(4-chlorophenyl)-5-oxoisoxazolidine-2-carboxylate (II.18f)**



II.18f

$C_{17}H_{20}ClNO_4$
MW = 337.80 g/mol

II.18f was synthesized according to the method aforementioned from *tert*-butyl 4-(4-chlorophenyl)-5-oxoisoxazolidine-2-carboxylate **II.1f** (50 mg, 0.17 mmol, 1.0 equiv) and allyl acetate (18 µL, 0.17 mmol, 1.0 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/Et_2O = 8:2) as a white solid (52 mg, 92%).

Mp = 58-60 °C

R$_f$: 0.42 (PE/Et_2O = 8:2)

[α]^{20} D = +88.9 (*c* 1.40, $CHCl_3$)

ee = 91% (determined by SFC)

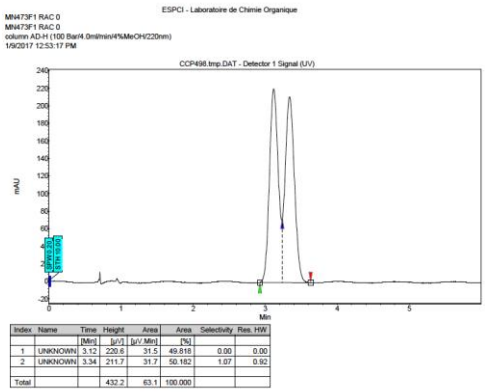
SFC: AD-H column, Pressure = 100 bar, eluent = sc CO_2/MeOH = 96:4, Flow rate = 4 mL/min, detection wavelength = 220 nm. t_R = 3.13 min (minor) and t_R = 3.34 min (major).

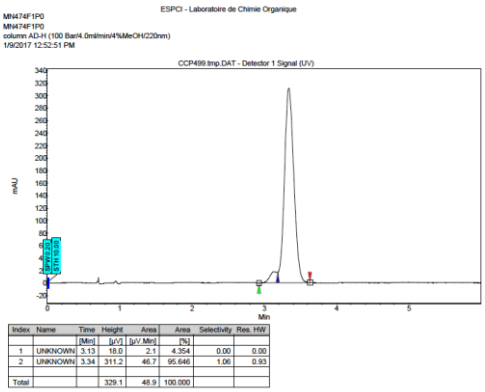
IR (ATR): 2981, 1794, 1746, 1720, 1496, 1458, 1370, 1324, 1258, 1144, 1096, 1014, 994, 929, 847, 828, 741, 683 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.33 (m, 4H, H_{Ar}), 5.57 (ddt, *J* = 16.8, 10.2, 7.3 Hz, 1H, H_{12}), 5.21-5.08 (m, 2H, H_{13}), 4.54 (d, *J* = 11.8 Hz, 1H, H_4), 4.17 (d, *J* = 11.8 Hz, 1H, $H_{4'}$), 2.74-2.59 (m, 2H, H_{11}), 1.37 (s, 9H, H_1).

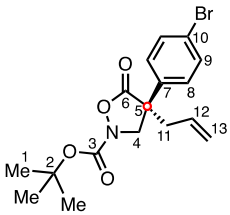
^{13}C NMR (100 MHz, $CDCl_3$): δ 174.9 (s, C_6), 156.0 (s, C_3), 134.9 (s, C_7), 134.6 (s, C_{10}), 131.0 (d, C_{12}), 129.2 (d, 2C, C_8 or C_9), 128.1 (d, 2C, C_8 or C_9), 121.2 (t, C_{13}), 84.4 (s, C_2), 57.3 (t, C_4), 51.8 (s, C_5), 41.8 (t, C_{11}), 27.9 (q, 3C, C_1).

HRMS (ESI) *m/z*: calcd for $C_{17}H_{20}ClNO_4Na$ $[M+Na]^+$: 360.0973, found: 360.0975.





***tert*-Butyl (*S*)-4-allyl-4-(4-bromophenyl)-5-oxoisoxazolidine-2-carboxylate (II.18g)**



II.18g

$C_{17}H_{20}BrNO_4$

MW = 382.25 g/mol

II.18g was synthesized according to the method aforementioned from *tert*-butyl 4-(4-bromophenyl)-5-oxoisoxazolidine-2-carboxylate **II.1g** (50 mg, 0.15 mmol, 1.0 equiv) and allyl acetate (16 µL, 0.15 mmol, 1.0 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/Et_2O = 8:2) as a clear solid (51 mg, 91%).

R_f: 0.42 (PE/Et_2O = 8:2)

$[\alpha]^{20}_D$ = +24.7 (*c* 1.84, $CHCl_3$)

ee = 89% (determined by SFC)

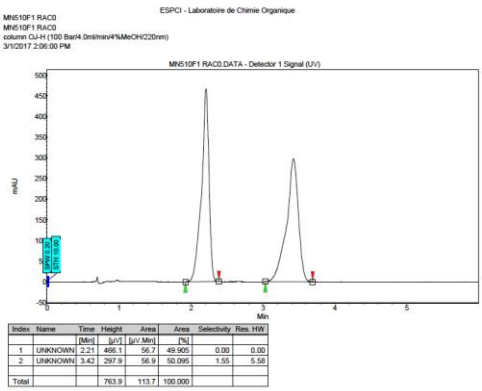
SFC: OJ-H column, Pressure = 100 bar, eluent = sc CO_2/MeOH = 96:4, Flow rate = 4 mL/min, detection wavelength = 220 nm. t_R = 2.20 min (major) and t_R = 3.44 min (minor).

IR (ATR): 2981, 1795, 1746, 1720, 1493, 1397, 1370, 1324, 1145, 1079, 1010, 929, 847, 823, 768, 726 cm^{-1}.

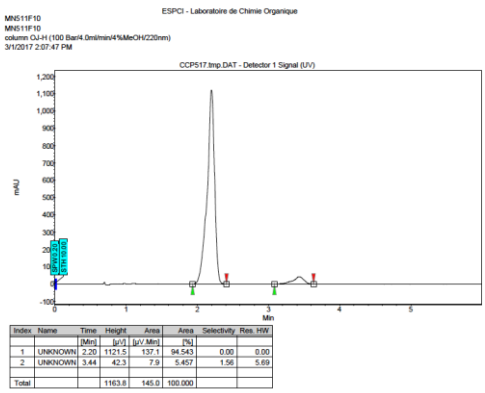
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54-7.48 (m, 2H, H_9), 7.35-7.28 (m, 2H, H_8), 5.57 (ddt, *J* = 16.8, 10.2, 7.3 Hz, 1H, H_{12}), 5.21-5.08 (m, 2H, H_{13}), 4.53 (d, *J* = 11.8 Hz, 1H, H_4), 4.16 (d, *J* = 11.8 Hz, 1H, $H_{4'}$), 2.72-2.61 (m, 2H, H_{11}), 1.37 (s, 9H, H_1).

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.9 (s, C_6), 156.0 (s, C_3), 135.5 (s, C_7), 132.2 (d, 2C, C_9), 131.0 (d, C_{12}), 128.4 (d, 2C, C_8), 122.7 (s, C_{10}), 121.2 (t, C_{13}), 84.4 (s, C_2), 57.3 (t, C_4), 51.9 (s, C_5), 41.8 (t, C_{11}), 28.0 (q, 3C, C_1).

HRMS (ESI) *m/z*: calcd for $C_{17}H_{20}BrNO_4Na$ $[M+Na]^+$: 404.0468, found: 404.0468.

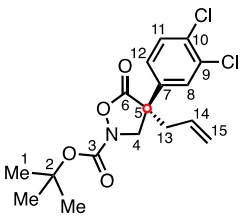


Index	Name	Time [Min]	Height [µV]	Area [µV.Min]	Area [%]	Selectivity	Res. HW
1	UNKNOWN	2.21	466.1	56.7	49.905	0.00	0.00
2	UNKNOWN	3.42	297.9	56.9	50.095	1.55	5.58
Total			763.9	113.7	100.000		



Index	Name	Time [Min]	Height [µV]	Area [µV.Min]	Area [%]	Selectivity	Res. HW
1	UNKNOWN	2.20	1121.5	137.1	94.543	0.00	0.00
2	UNKNOWN	3.44	42.3	7.9	5.457	1.56	5.69
Total			1163.8	145.0	100.000		

***tert*-Butyl (*S*)-4-allyl-4-(3,4-dichlorophenyl)-5-oxoisoxazolidine-2-carboxylate (II.18h)**



II.18h

$C_{17}H_{19}Cl_2NO_4$

MW = 372.24 g/mol

II.18h was synthesized according to the method aforementioned from *tert*-butyl 4-(4-chlorophenyl)-5-oxoisoxazolidine-2-carboxylate **II.1h** (50 mg, 0.15 mmol, 1.0 equiv) and allyl acetate (16 µL, 0.15 mmol, 1.0 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/Et_2O = 8:2) as a white solid (52 mg, 93%).

Mp = 114-115 °C

R$_f$: 0.28 (PE/Et_2O = 8:2)

[α]^{20} D = +22.5 (*c* 0.08, $CHCl_3$)

ee = 85% (determined by SFC)

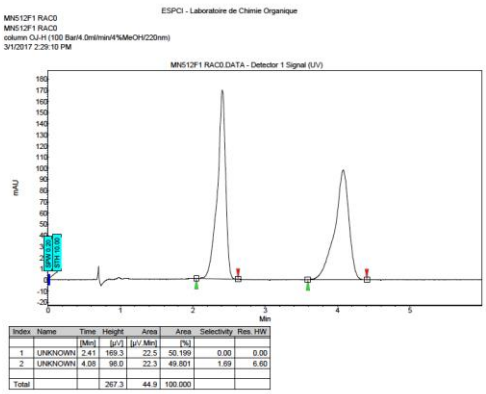
SFC: OJ-H column, Pressure = 100 bar, eluent = sc CO_2/MeOH = 96:4, Flow rate = 4 mL/min, detection wavelength = 220 nm. t_R = 2.41 min (major) and t_R = 4.09 min (minor).

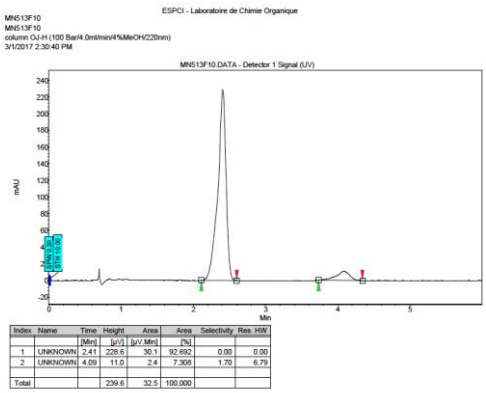
IR (ATR): 1796, 1722, 1476, 1371, 1340, 1259, 1144, 1031, 995, 930, 847, 768, 678 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, *J* = 2.4 Hz, 1H, H_8), 7.46 (d, *J* = 8.5 Hz, 1H, H_{11}), 7.30 (dd, *J* = 8.5, 2.4 Hz, 1H, H_{12}), 5.56 (ddt, *J* = 16.9, 10.2, 7.3 Hz, 1H, H_{14}), 5.22-5.10 (m, 2H, H_{15}), 4.50 (d, *J* = 11.9 Hz, 1H, H_4), 4.18 (d, *J* = 11.9 Hz, 1H, $H_{4'}$), 2.71-2.61 (m, 2H, H_{13}), 1.40 (s, 9H, H_1).

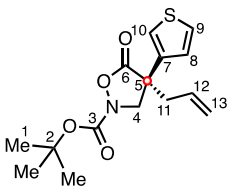
^{13}C NMR (100 MHz, $CDCl_3$): δ 174.4 (s, C_6), 155.9 (s, C_3), 136.6 (s, C_7), 133.4 (s, C_{10}), 132.9 (s, C_9), 131.0 (d, C_{11}), 130.6 (d, C_{14}), 128.8 (d, C_8), 126.2 (d, C_{12}), 121.5 (t, C_{15}), 84.6 (s, C_2), 57.1 (t, C_4), 51.7 (s, C_5), 41.7 (t, C_{13}), 28.0 (q, 3C, C_1).

HRMS (ESI) *m/z*: calcd for $C_{17}H_{19}Cl_2NO_4Na$ $[M+Na]^+$: 394.0583, found: 394.0586.





***tert*-Butyl (*S*)-4-allyl-5-oxo-4-(thiophen-3-yl)isoxazolidine-2-carboxylate (II.18i)**



II.18i

$C_{15}H_{19}NO_4S$

MW = 309.38 g/mol

II.18i was synthesized according to the method aforementioned from *tert*-butyl 5-oxo-4-(thiophen-3-yl)isoxazolidine-2-carboxylate **II.1i** (50 mg, 0.19 mmol, 1.0 equiv) and allyl

acetate (20 µL, 0.19 mmol, 1.0 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/Et_2O = 9:1) as an off-white solid (57 mg, 97%).

Mp = 75-77 °C

R_f: 0.47 (PE/Et_2O = 8:2)

$[\alpha]^{20}_D$ = +86.9 (*c* 1.76, $CHCl_3$)

ee = 89% (determined by SFC)

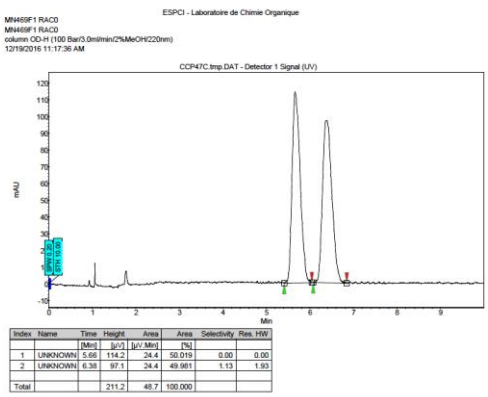
SFC: OD-H column, Pressure = 100 bar, eluent = sc CO_2/MeOH = 98:2, Flow rate = 3 mL/min, detection wavelength = 220 nm. t_R = 5.62 min (major) and t_R = 6.36 min (minor).

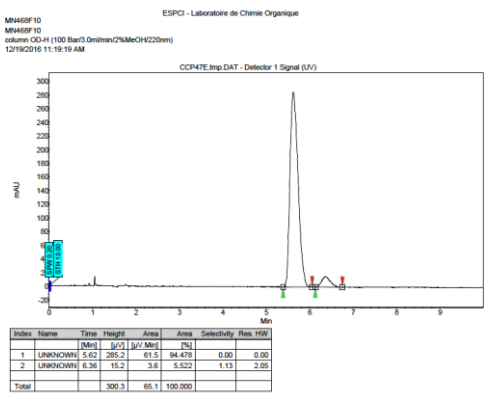
IR (ATR): 2918, 2850, 1795, 1718, 1458, 1370, 1322, 1142, 995, 925, 847, 789, 690 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (dd, *J* = 5.1, 3.0 Hz, 1H, H_9), 7.28 (dd, *J* = 3.0, 1.5 Hz, 1H, H_{10}), 7.13 (dd, *J* = 5.1, 1.5 Hz, 1H, H_8), 5.61 (ddt, *J* = 16.7, 10.5, 7.3 Hz, 1H, H_{12}), 5.20-5.10 (m, 2H, H_{13}), 4.53 (d, *J* = 11.7 Hz, 1H, H_4), 4.14 (d, *J* = 11.7 Hz, 1H, $H_{4'}$), 2.75-2.60 (m, 2H, H_{11}), 1.39 (s, 9H, H_1).

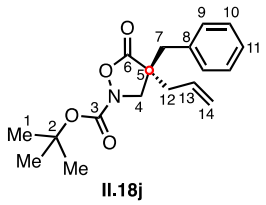
^{13}C NMR (100 MHz, $CDCl_3$): δ 175.1 (s, C_6), 156.2 (s, C_3), 136.9 (s, C_7), 131.3 (d, C_{12}), 127.2 (d, C_9), 126.0 (d, C_8), 122.9 (d, C_{10}), 120.7 (t, C_{13}), 84.2 (s, C_2), 57.7 (t, C_4), 49.8 (s, C_5), 41.4 (t, C_{11}), 28.0 (q, 3C, C_1).

HRMS (ESI) *m/z*: calcd for $C_{15}H_{19}NO_4SNa$ $[M+Na]^+$: 332.0927, found: 332.0930.





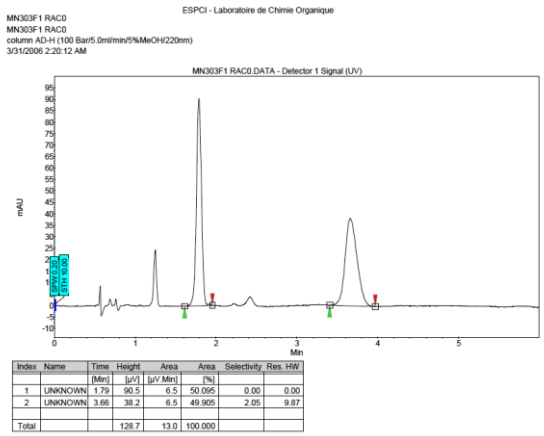
***tert*-Butyl (*S*)-4-allyl-5-oxo-4-benzylisoxazolidine-2-carboxylate (II.18j)**

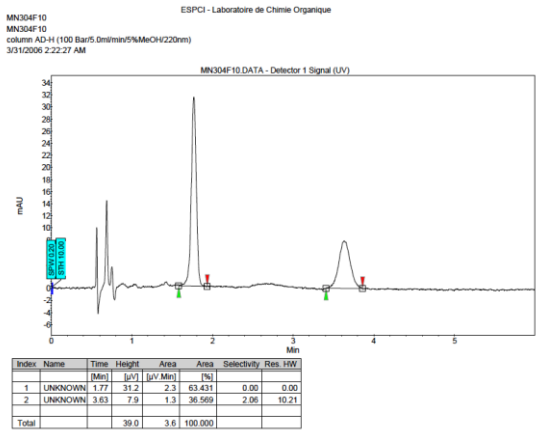


II.18j
$C_{18}H_{23}NO_4$
MW = 317.39 g/mol

II.18j was synthesized according to the method aforementioned with minor modifications, from *tert*-butyl 5-oxo-4-phenylisoxazolidine-2-carboxylate **II.1j** (50 mg, 0.18 mmol, 1.0 equiv), allyl acetate (20 µL, 0.18 mmol, 1.0 equiv), BSA (45 µL, 0.18 mmol, 1.0 equiv) and KOAc (1.8 mg, 0.18 mmol, 0.1 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/Et_2O = from 95:5 to 9:1) as a colorless oil (13 mg, 23%).

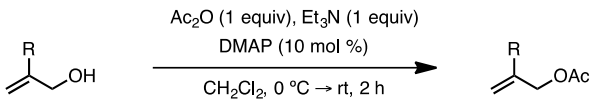
R$_f$: 0.33 (PE/Et_2O = 9:1)
[α]^{20} $_D$ = + 2.80 (*c* 0.20, $CHCl_3$)
ee = 27% (determined by SFC)
SFC: AD-H column, Pressure = 100 bar, eluent = sc CO_2/MeOH = 95:5, Flow rate = 5 mL/min, detection wavelength = 220 nm. t_R = 1.77 min (major) and t_R = 3.63 min (minor).
IR (ATR): 2924, 1790, 1715, 1456, 1369, 1329, 1277, 1136, 1024, 967, 845, 744 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.06 (m, 5H, H_{Ar}), 5.68 (m, 1H, H_{13}), 5.20-5.07 (m, 2H, H_{14}), 3.88 (d, *J* = 11.2 Hz, 1H, H_4), 3.81 (d, *J* = 11.2 Hz, 1H, $H_{4'}$), 2.99 (d, *J* = 13.9 Hz, 1H, H_7), 2.77 (d, *J* = 13.9 Hz, 1H, $H_{7'}$), 2.42 (ddt, *J* = 14.1, 6.8, 2.3 Hz, 1H, H_{12}), 2.24 (ddt, *J* = 14.0, 7.9, 1.0 Hz, 1H, $H_{12'}$), 1.41 (s, 9H, H_1).
^{13}C NMR (100 MHz, $CDCl_3$): δ 176.0 (s, C_6), 155.7 (s, C_3), 135.0 (s, C_8), 131.5, (d, C_{13}), 130.3 (d, 2C, C_9 or C_{10}), 129.9 (d, 2C, C_9 or C_{10}), 127.6 (d, C_{11}), 121.2 (t, C_{14}), 84.0 (s, C_2), 54.4 (t, C_4), 49.5 (s, C_5), 40.2 (t, C_7), 39.3 (t, C_{12}), 28.2 (q, 3C, C_1).





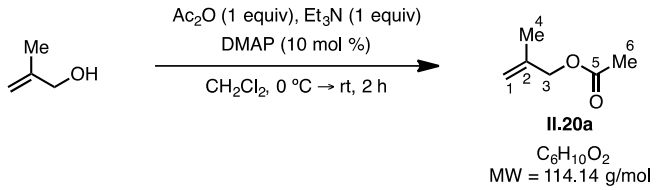
6. Synthesis of allyl acetates (II.20a-f)

Representative acetylation procedure



To a flame-dried round bottom flask equipped with a magnetic stirring bar was added the 2-substituted allyl alcohol (88 mmol, 1.0 equiv) and Ac_2O (8.3 mL, 88 mmol, 1.0 equiv) under argon atmosphere. The flask was cooled to 0 °C and DMAP (108 mg, 0.880 mmol, 0.010 equiv) was quickly added. A solution of Et_3N (12.2 mL, 88.0 mmol, 1.00 equiv) in CH_2Cl_2 (7.0 mL) was prepared in a separate flame-dried flask, then added dropwise to the first flask. The reaction mixture was allowed to stir while warming to rt for 2 h. The reaction mixture was poured into a flask containing an aqueous solution of HCl (2 M) and ice. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2(2 x 10 mL). The combined organic extracts were washed with a saturated aqueous solution of $NaHCO_3$ and then with a saturated aqueous brine solution, dried over $MgSO_4$, filtered and carefully concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (PE/Et_2O) to afford the 2-substituted allyl acetate.

2-Methylallyl acetate (II.20a)[132]



The tittle compound was synthesized according to the aforementioned procedure using 2-methallyl alcohol (7.4 mL, 88 mmol, 1.0 equiv). The desired allyl acetate **II.20a** was obtained after flash column chromatography on silica gel (PE/Et_2O = 95:5) as a clear oil (9.74 g, 97%).[139]

R$_f$: 0.18 (PE/Et_2O = 95:5)

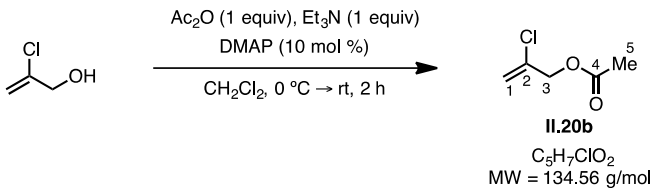
IR (ATR): 2978, 2942, 1738, 1660, 1450, 1373, 1224, 1053, 1026, 957, 904, 844 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.96 (m, 1H, H_1), 4.91 (m, 1H, $H_{1'}$), 4.47 (s, 2H, H_3), 2.08 (s, 3H, H_6), 1.75 (s, 3H, H_4).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8 (s, C_5), 140.0 (s, C_2), 113.0 (t, C_1), 67.8 (t, C_3), 21.0 (q, C_6), 19.6 (q, C_4).

HRMS (ESI) *m/z*: calcd for $C_6H_{10}O_2Na$ $[M+Na]^+$: 137.0573, found: 137.0573.

2-Chloroallyl acetate (II.20b)



The tittle compound was synthesized according to the aforementioned procedure using 2-chloroallyl alcohol (1.00 mL, 11.3 mmol, 1.00 equiv). The desired allyl acetate **II.20b** was obtained, without further purification, as a clear oil (1.37 g, 90%).

IR (ATR): 1744, 1640, 1371, 1218, 1038, 895, 758, 665 cm^{-1}.

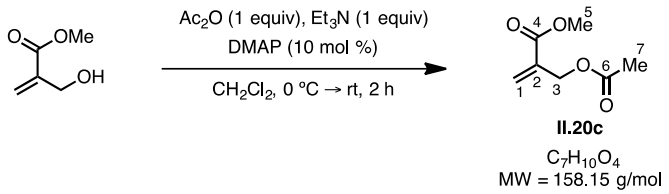
139 Xi, Z.; Hao, W.; Wang, P.; Cai, M., *Molecules* **2009,** *14*, 3528.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.47 (m, 1H, H_1), 5.41 (m, 1H, $H_{1'}$), 4.65 (s, 2H, H_3), 2.13 (s, 3H, H_5).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2 (s, C_4), 136.0 (s, C_2), 115.1 (t, C_1), 66.2 (t, C_3), 20.9 (q, C_5).

HRMS (ESI) *m/z*: calcd for $C_5H_7ClO_2Na$ $[M+Na]^+$: 157.0027, found: 157.0835.

Methyl 2-(acetoxymethyl)acrylate (II.20c)



The tittle compound was synthesized according to the aforementioned procedure using methyl 2-(hydroxymethyl)acrylate (1.00 g, 8.61 mmol, 1.00 equiv). The desired allyl acetate **II.20c** was obtained, without further purification, as a clear oil (912 mg, 67%).

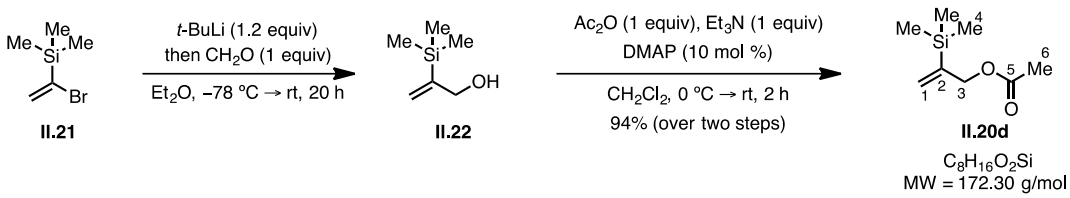
IR (ATR): 1720, 1641, 1369, 1309, 1273, 1227, 1197, 1153, 1049, 990, 951, 913, 834, 816, 732, 647, 602 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.36 (dd, J = 2.0, 1.1 Hz, 1H, H_1), 5.85 (dd, J = 2.7, 1.4 Hz, 1H, $H_{1'}$), 4.80 (t, J = 1.2 Hz, 2H, H_3), 3.79 (s, 3H, H_5), 2.10 (s, 3H, H_7).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5 (s, C_6), 165.8 (s, C_4), 135.4 (s, C_2), 127.7 (t, C_1), 62.6 (t, C_3), 52.2 (q, C_5), 21.0 (q, C_7).

HRMS (ESI) *m/z*: calcd for $C_7H_{10}O_4Na$ $[M+Na]^+$: 181.0471, found: 181.0470.

2-(Trimethylsilyl)allyl acetate (II.20d)

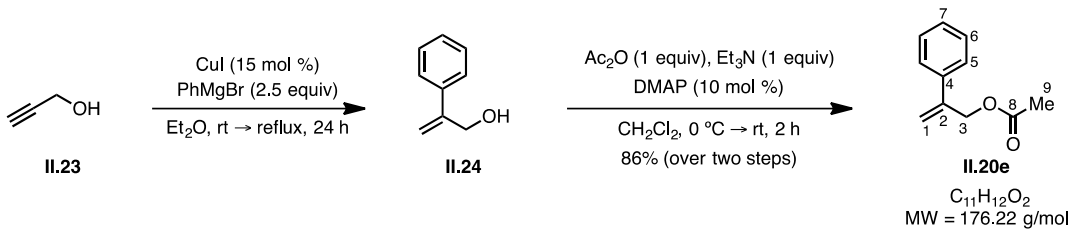


To a solution of (1-bromovinyl)trimethylsilane **II.21** (1.00 g, 5.58 mmol, 1.00 equiv) in Et_2O (56 mL) at −78 °C and under argon atmosphere was added *t*-BuLi (3.95 mL, 1.7 M in

pentane, 6.7 mmol, 1.2 equiv). The resulting mixture was stirred at −78 °C for 3 h. Dry paraformaldehyde (168 mg, 1.86 mmol, 0.33 equiv) was then added, and the mixture was allowed to warm slowly to rt. After 18 h, H_2O was carefully added and the organic layer was separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting allyl alcohol **II.22** was engaged in the formation of its corresponding acetate following the aforementioned general acetylation procedure; in order to afford the 2-(trimethylsilyl)allyl acetate **II.20d**, without further purification, as a clear oil (903 mg, 94%).[133]

IR (ATR): 1741, 1372, 1232, 1147, 1031, 839, 759 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.77 (dt, J = 2.8, 1.8 Hz, 1H, H_1), 5.46 (dt, J = 2.7, 1.4 Hz, 1H, $H_{1'}$), 4.69 (t_{app}, J = 1.6 Hz, 2H, H_3), 2.09 (s, 3H, H_6), 0.13 (s, 9H, H_4).
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9 (s, C_5), 146.6 (s, C_2), 125.7 (t, C_1), 68.2 (t, C_3), 21.1 (q, C_6), −1.51 (q, 3C, C_4).
HRMS (ESI) *m/z*: calcd for $C_8H_{16}O_2SiNa[M+Na]^+$: 195.0812, found: 195.0813.

2-Phenylallyl acetate (II.20e)

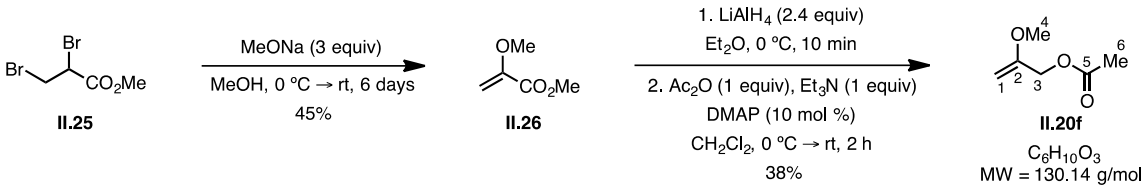


To a solution of PhMgBr (50 mL, 1.0 M in THF, 50 mmol, 2.5 equiv) in Et_2O (120 mL) was added CuI (571 mg, 3.00 mmol, 0.150 equiv). The mixture was stirred at rt for 30 min, and then a solution of propargyl alcohol **II.23** (1.20 mL, 20.0 mmol, 1.00 equiv) in Et_2O (20 mL) was added dropwise. Once the addition was done, the reaction mixture was heated at reflux for 24 h. After cooling to rt, a saturated aqueous solution of NH_4Cl was added slowly. The organic layer was separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure.[134] The resulting allylic alcohol **II.24** was engaged in the formation of its corresponding acetate following aforementioned general acetylation procedure. The crude residue was purified by

flash column chromatography on silica gel (PE/Et_2O = 95:5) to afford the 2-phenylallyl acetate **II.20e** as a yellow oil (3.02 g, 86%).[140]

R_f: 0.35 (PE/Et_2O = 9:1)
IR (ATR): 1736, 1634, 1575, 1496, 1444, 1373, 1222, 1027, 979, 907, 843 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47-7.28 (m, 5H, H_{Ar}), 5.56 (m, 1H, H_1), 5.37 (m, 1H, $H_{1'}$), 4.99-4.97 (m, 2H, H_3), 2.08 (s, 3H, H_9).
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9 (s, C_8), 142.6 (s, C_2), 138.1 (s, C_4), 128.6 (d, 2C, C_6 or C_5), 128.2 (d, C_7), 126.1 (d, 2C, C_6 or C_5), 115.4 (t, C_1), 65.9 (t, C_3), 21.1 (q, C_9).
HRMS (ESI) *m/z*: calcd for $C_{11}H_{12}O_2Na$ $[M+Na]^+$: 199.0730, found: 199.0731.

2-(Methoxy)allyl acetate (II.20f)



NaOMe (15.3 g, 268 mmol, 3.0 equiv) was dissolved in MeOH (120 mL) at 0 °C. Then, methyl 2,3-dibromopropanoate **II.25** (11.7 mL, 89.5 mmol, 1.00 equiv) was added dropwise and reaction mixture was allowed to stir at rt for 6 days. Afterward the reaction mixture was quenched by the addition of dry-ice until reaching pH 7. The resulting white suspension was diluted with CH_2Cl_2 (100 mL) and washed with H_2O (2 x 120 mL). The organic layer was dried over Na_2SO_4, filtered and carefully concentrated under reduced pressure. The remaining product was purified by distillation under reduced pressure (30 mbar, 50 °C) to give the ester **II.26** (4.67 g, 45%) as a colorless liquid which was engaged in the next step without further purification or characterization.[141]

The methyl 2-methoxy acrylate **II.26** (1.00 g, 8.61 mmol, 1.00 equiv) was added dropwise to a solution of $LiAlH_4$ (785 mg, 20.7 mmol, 2.4 equiv) in Et_2O (18 mL) at 0 °C over 10 min. The reaction was quenched carefully by dropwise addition of H_2O (0.35 mL), an aqueous solution of NaOH (15%, 0.35 mL), and H_2O (1.0 mL). The white precipitate was filtered and

140 Ruan, J.; Li, X.; Saidi, O.; Xiao, J., *J. Am. Chem. Soc.* **2008,** *130*, 2424.
141 Marti, C.; Carreira, E. M., *J. Am. Chem. Soc.* **2005,** *127*, 11505.

washed with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and filtered.[142] This resulting solution was cooled to 0 °C and then treated with Ac_2O (0.80 mL, 8.6 mmol, 1.0 equiv), DMAP (11 mg, 0.86 mmol, 0.010 equiv) and a solution of Et_3N (1.3 mL, 8.6 mmol, 1.0 equiv) in CH_2Cl_2 (7.0 mL), prepared in a separate flame-dried flask. The reaction mixture was allowed to stir while warming to rt for 2 h. The reaction mixture was poured into a flask containing an aqueous solution of HCl (2 M) and ice. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were washed with a saturated aqueous solution of $NaHCO_3$ and then with a saturated aqueous brine solution, dried over $MgSO_4$, filtered and carefully concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (PE/Et_2O = 95:5) to afford the 2-methoxyallyl acetate **II.20f** as a clear oil (425 mg, 38%).

R_f: 0.32 (PE/Et_2O = 95:5)

IR (ATR): 1738, 1669, 1638, 1452, 1373, 1304, 1221, 1080, 1032, 977, 947, 916, 825, 733, 605 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.50 (s, 2H, H_3), 4.21 (d_{app}, J = 2.5 Hz, 1H, H_1), 4.12 (d, J = 2.6 Hz, 1H, $H_{1'}$), 3.59 (s, 3H, H_4), 2.10 (s, 3H, H_6).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7 (s, C_5), 158.3 (s, C_2), 84.7 (t, C_1), 64.7 (t, C_3), 55.3 (q, C_4), 21.1 (q, C_6).

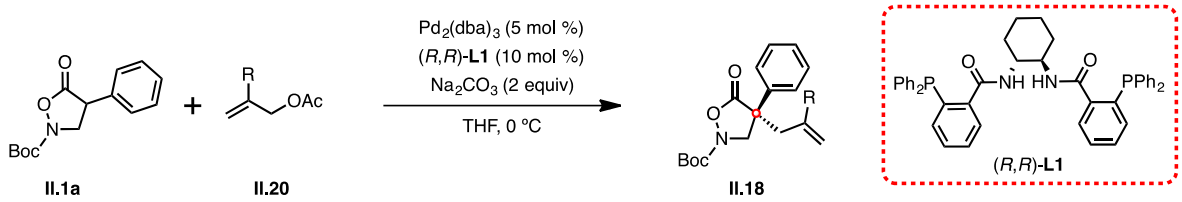
HRMS (ESI) *m/z*: calcd for $C_3H_{10}O_3Na$ $[M+Na]^+$: 153.0522, found: 153.0522.

142 Coates, R. M.; Rogers, B. D.; Hobbs, S. J.; Peck, D. R.; Curran, D. P. *J. Am. Chem. Soc.* **1987**, *109*, 1160.

7. General procedures for the Pd-AAA of 2-substituted allyl reagents

Synthesis of isoxazolidin-5-ones (II.18l-q)

(Representative procedure)



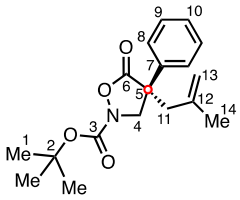
To a solution of $Pd_2(dba)_3$ (0.01 mmol, 0.05 equiv) in THF (2.0 mL) at rt was added (*R*,*R*)-DACH phenyl Trost ligand (0.02 mmol, 0.10 equiv) and the mixture was stirred for 30 min. This solution was then cooled to 0 °C and transferred via cannula to a flask containing *tert*-butyl 5-oxo-4-phenylisoxazolidine-2-carboxylate **II.1a** (0.2 mmol, 1 equiv) and Na_2CO_3 (0.4 mmol, 2 equiv). Followed by the addition of 2-substituted allyl acetate **II.20** (0.2 mmol, 1 equiv) and stirring was continued at the same temperature until complete consumption of the starting material (confirmed by TLC). The reaction mixture was filtered through a plug of Celite® and concentrated under reduced pressure to afford a crude residue, which was purified by flash column chromatography on silica gel to afford the corresponding allylated isoxalidin-5-one.

General procedure for the synthesis of the racemic compounds

(Representative procedure)

To a flask containing *tert*-butyl 5-oxo-4-phenylisoxazolidine-2-carboxylate **II.1a** (0.2 mmol, 1 equiv) and Na_2CO_3 (0.4 mmol, 2 equiv) in THF (2 mL) at rt was added $Pd(PPh_3)_4$ (0.01 mmol, 0.05 equiv). Followed by the addition of 2-substituted allyl acetate **II.20** (0.2 mmol, 1 equiv) and stirring was continued at the same temperature until complete consumption of the starting material (confirmed by TLC). The reaction mixture was filtered through a plug of Celite® and concentrated under reduced pressure to afford a crude residue, which was purified following the same procedure described for the corresponding enantioenriched compound.

***tert*-Butyl (*S*)-4-(2-methylallyl)-5-oxo-4-phenylisoxazolidine-2-carboxylate (II.18l)**



II.18l

$C_{18}H_{23}NO_4$
MW = 317.39 g/mol

II.18l was synthesized according to the method aforementioned from *tert*-butyl 5-oxo-4-phenylisoxazolidine-2-carboxylate **II.1a** (50 mg, 0.19 mmol, 1.0 equiv) and 2-methylallyl acetate **II.20a** (190 µL, 1.0 M in THF, 0.19 mmol, 1.0 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/Et_2O = 9:1) as a white solid (53 mg, 88%).

Mp = 91-92 °C

R$_f$: 0.24 (PE/Et_2O = 9:1)

[α]^{20} $_D$ = +110 (*c* 0.29, $CHCl_3$)

ee = 95% (determined by SFC)

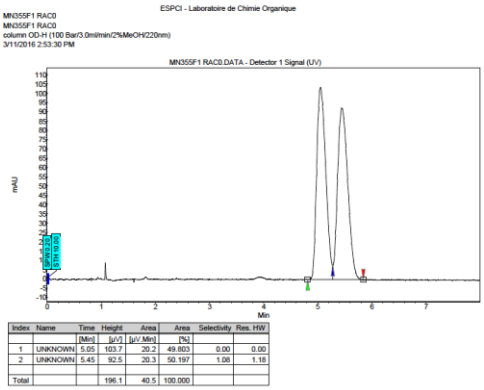
SFC: OD-H column, Pressure = 100 bar, eluent = sc CO_2/MeOH = 98:2, Flow rate = 3 mL/min, detection wavelength = 220 nm. t_R = 5.04 min (major) and t_R = 5.46 min (minor).

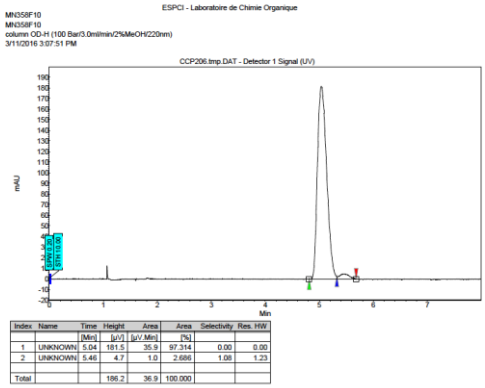
IR (ATR): 2980, 2934, 1795, 1748, 1719, 1449, 1370, 1341, 1255, 1230, 1142, 1082, 1050, 967, 904, 848 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50-7.44 (m, 2H, H_8), 7.40-7.28 (m, 3H, H_9 and H_{10}), 4.89 (quint, *J* = 1.5 Hz, 1H, H_{13}), 4.77-4.69 (m, 2H, H_4 and $H_{13'}$), 4.19 (d, *J* = 11.9 Hz, 1H, $H_{4'}$), 2.74 (d_{app}, *J* = 14.1 Hz, 1H, H_{11}), 2.69 (d_{app}, *J* = 14.1 Hz, 1H, $H_{11'}$), 1.49 (br s, 3H, H_{14}), 1.33 (s, 9H, H_1).

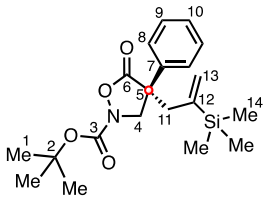
^{13}C NMR (100 MHz, $CDCl_3$): δ 175.7 (s, C_6), 156.1 (s, C_3), 140.1 (s, C_{12}), 136.3 (s, C_7), 129.0 (d, 2C, C_9), 128.4 (d, C_{10}), 126.7 (d, 2C, C_8), 116.9 (t, C_{13}), 84.1 (s, C_2), 57.1 (t, C_4), 52.1 (s, C_5), 45.6 (t, C_{11}), 27.9 (q, 3C, C_1), 23.8 (q, C_{14}).

HRMS (ESI) *m/z*: calcd for $C_{18}H_{23}NO_4Na$ $[M+Na]^+$: 340.1519, found: 340.1518.





***tert*-Butyl (*S*)-5-oxo-4-phenyl-4-(2-(trimethylsilyl)allyl)isoxazolidine-2-carboxylate (II.18m)**



II.18m

$C_{20}H_{29}NO_4Si$
MW = 375.54 g/mol

II.18m was synthesized according to the method aforementioned from *tert*-butyl 5-oxo-4-phenylisoxazolidine-2-carboxylate **II.1a** (50 mg, 0.19 mmol, 1.0 equiv) and 2-(trimethylsilyl)allyl acetate **II.20d** (190 µL, 1.0 M in THF, 0.19 mmol, 1.0 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/Et_2O = 95:5) as a white solid (54 mg, 76%).

Mp = 40-42 °C

R$_f$: 0.41 (PE/Et_2O = 9:1)

[α]^{20} D = +73.6 (*c* 1.12, $CHCl_3$)

ee = 93% (determined by SFC)

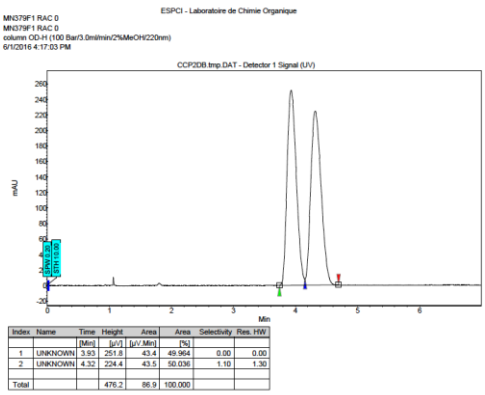
SFC: OD-H column, Pressure = 100 bar, eluent = sc CO_2/MeOH = 98:2, Flow rate = 3 mL/min, detection wavelength = 220 nm. t_R = 3.88 min (major) and t_R = 4.31 min (minor).

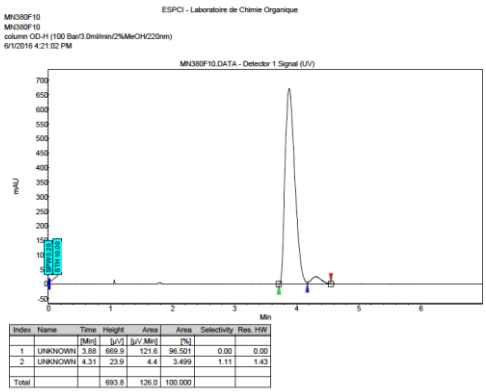
IR (ATR): 2955, 1794, 1751, 1719, 1449, 1370, 1248, 1142, 1034, 990, 943, 838, 760, 697 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48-7.25 (m, 5H, H_{Ar}), 5.54 (d_{app}, J = 13.2 Hz, 2H, H_{13}), 4.73 (d, J = 11.8 Hz, 1H, H_4), 4.16 (d, J = 11.8 Hz, 1H, $H_{4'}$), 2.84 (s, 2H, H_{11}), 1.32 (s, 9H, H_1), –0.01 (s, 9H, H_{14}).

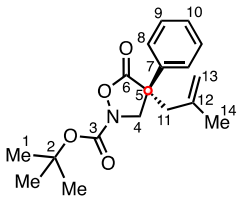
^{13}C NMR (100 MHz, $CDCl_3$): δ 175.8 (s, C_6), 156.1 (s, C_3), 146.4 (s, C_{12}), 136.6 (s, C_7), 130.2 (t, C_{13}), 129.1 (d, 2C, C_9), 128.4 (d, C_{10}), 126.8 (d, 2C, C_8), 84.0 (s, C_2), 57.4 (t, C_4), 53.0 (s, C_5), 41.3 (t, C_{11}), 27.9 (q, 3C, C_1), –1.52 (q, 3C, C_{14}).

HRMS (ESI) *m/z*: calcd for $C_{20}H_{29}NO_4SiNa$ $[M+Na]^+$: 398.1758, found: 398.1759.





***tert*-Butyl (*S*)-4-(2-methylallyl)-5-oxo-4-phenylisoxazolidine-2-carboxylate (II.18n)**



II.18n

$C_{18}H_{23}NO_4$

MW = 317.39 g/mol

II.18n was synthesized according to the method aforementioned from *tert*-butyl 5-oxo-4-phenylisoxazolidine-2-carboxylate **1a** (70 mg, 0.27 mmol, 1.0 equiv) and the commercially available 2-((trimethylsilyl)methyl)allyl acetate (57 µL, 0.27 mmol, 1.0 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/Et_2O = 9:1) as a white solid (81 mg, 94%).

Mp = 91-92 °C

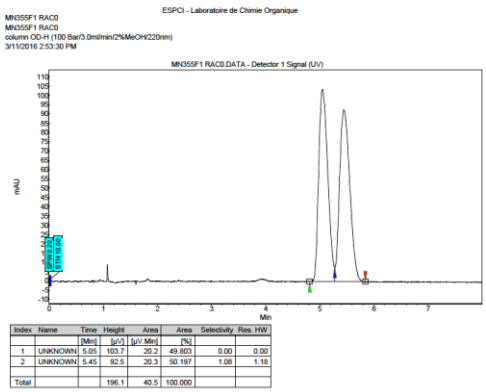
R_f: 0.24 (PE/Et_2O = 9:1)

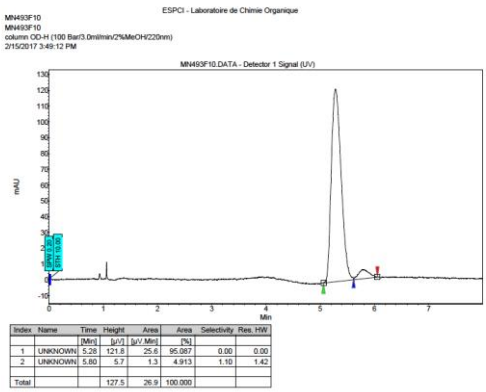
$[\alpha]^{20}_{D}$ = +109 (*c* 0.25, $CHCl_3$)

ee = 90% (determined by SFC)

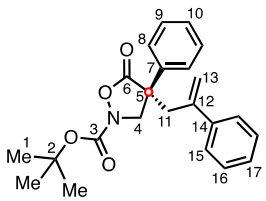
SFC: OD-H column, Pressure = 100 bar, eluent = sc CO_2/MeOH = 98:2, Flow rate = 3 mL/min, detection wavelength = 220 nm. t_R = 5.28 min (major) and t_R = 5.80 min (minor).

Note: for full characterization of **II.18n** check **II.18l**.





***tert*-Butyl (*S*)-5-oxo-4-phenyl-4-(2-phenylallyl)isoxazolidine-2-carboxylate (II.18o)**



II.18o

$C_{23}H_{25}NO_4$

MW = 379.46 g/mol

II.18o was synthesized according to the method aforementioned from *tert*-butyl 5-oxo-4-phenylisoxazolidine-2-carboxylate **1a** (50 mg, 0.19 mmol, 1.0 equiv) and 2-phenylallyl acetate **II.20e** (190 µL, 1.0 M in THF, 0.19 mmol, 1.0 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/Et_2O = 9:1) as a colorless oil (51 mg, 71%).

R$_f$: 0.38 (PE/Et_2O = 9:1)

$[\alpha]^{20}_{D}$ = +81.6 (*c* 0.17, $CHCl_3$)

ee = 95% (determined by SFC)

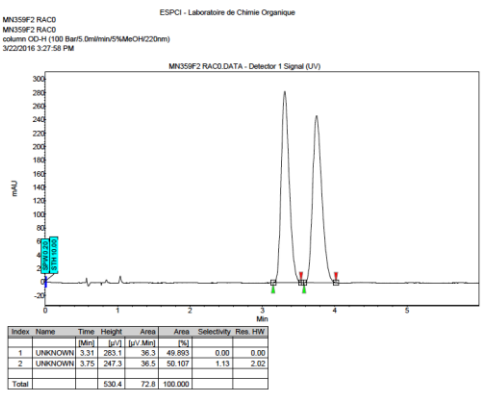
SFC: OD-H column, Pressure = 100 bar, eluent = sc CO_2/MeOH = 95:5, Flow rate = 5 mL/min, detection wavelength = 220 nm. t_R = 3.31 min (major) and t_R = 3.76 min (minor).

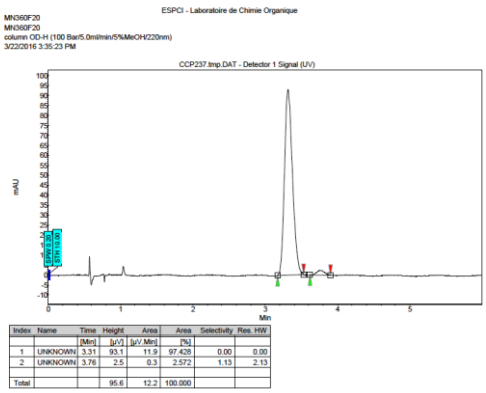
IR (ATR): 2980, 1794, 1748, 1718, 1448, 1370, 1344, 1311, 1257, 1232, 1142, 1079, 1030, 990, 908, 847, 777, 731, 695 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.20 (m, 10H, H_{Ar}), 5.25 (m, 1H, H_{13}), 4.94 (m, 1H, $H_{13'}$), 4.43 (d, J = 12.2 Hz, 1H, H_4), 3.87 (d, J = 12.2 Hz, 1H, $H_{4'}$), 3.26-3.13 (m, 2H, H_{11}), 1.22 (s, 9H, H_1).

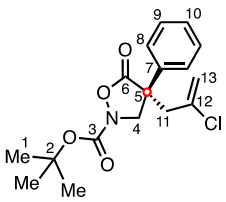
^{13}C NMR (100 MHz, $CDCl_3$): δ 175.7 (s, C_6), 156.0 (s, C_3), 143.0 (s, C_{12}), 141.0 (s, C_{14}), 135.4 (s, C_7), 128.8 (d, 2C, C_9 or C_{16}), 128.7 (d, 2C, C_9 or C_{16}), 128.4 (d, C_{10} or C_{17}), 128.0 (d, C_{10} or C_{17}), 126.9 (d, 2C, C_8 or C_{15}), 126.5 (d, 2C, C_8 or C_{15}), 119.1 (t, C_{13}), 83.9 (s, C_2), 57.1 (t, C_4), 53.1 (s, C_5), 43.0 (t, C_{11}), 27.8 (q, 3C, C_1).

HRMS (ESI) *m/z*: calcd for $C_{23}H_{25}NO_4Na$ $[M+Na]^+$: 402.1676, found: 402.1678.





***tert*-Butyl (*S*)-4-(2-chloroallyl)-5-oxo-4-phenylisoxazolidine-2-carboxylate (II.18p)**



II.18p

$C_{17}H_{20}ClNO_4$

MW = 337.80 g/mol

II.18p was synthesized according to the method aforementioned from *tert*-butyl 5-oxo-4-phenylisoxazolidine-2-carboxylate **1a** (50 mg, 0.19 mmol, 1.0 equiv) and 2-chloroallyl

acetate **II.20b** (18 µL, 0.19 mmol, 1.0 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/Et_2O = 9:1) as a colorless oil (14 mg, 22%).

R_f: 0.19 (PE/Et_2O = 9:1)

$[\alpha]^{20}_{D}$ = +10.7 (*c* 0.15, $CHCl_3$)

ee = 74% (determined by SFC)

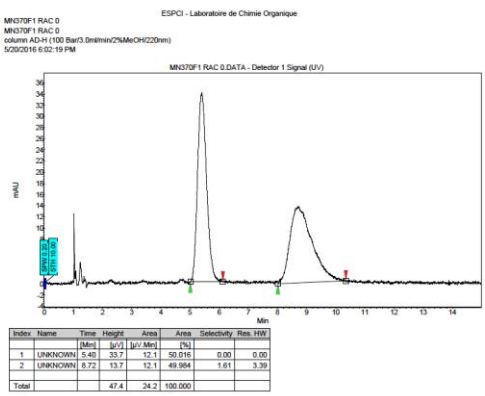
SFC: AD-H column, Pressure = 100 bar, eluent = sc CO_2/MeOH = 98:2, Flow rate = 3 mL/min, detection wavelength = 220 nm. t_R = 5.39 min (minor) and t_R = 8.41 min (major).

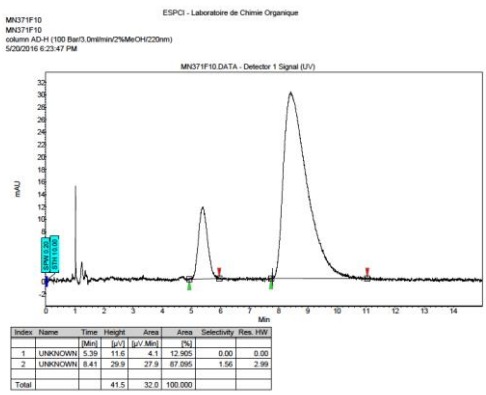
IR (ATR): 2919, 2850, 1795, 1749, 1720, 1634, 1458, 1371, 1145, 1034, 993, 900, 848, 767, 698 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48-7.29 (m, 5H, H_{Ar}), 5.19 (d, *J* = 1.6 Hz, 1H, H_{13}), 5.05 (d, *J* = 12.4 Hz, 1H, H_4), 4.97 (t, *J* = 1.3 Hz, 1H, $H_{13'}$), 4.26 (d, *J* = 12.4 Hz, 1H, $H_{4'}$), 3.05 (d, *J* = 14.7 Hz, 1H, H_{11}), 2.96 (dd, *J* = 14.7, 1.1 Hz, 1H, $H_{11'}$), 1.26 (s, 9H, H_1).

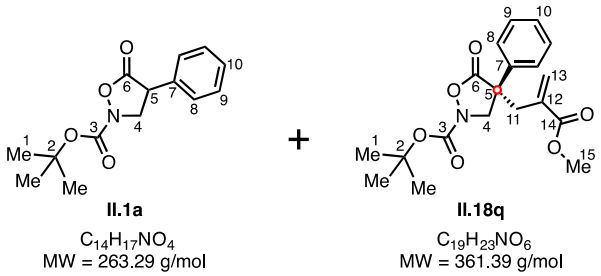
^{13}C NMR (100 MHz, $CDCl_3$): δ 175.2 (s, C_6), 155.9 (s, C_3), 135.7 (s, C_{12}), 134.3 (s, C_7), 129.0 (d, 2C, C_9), 128.6 (d, C_{10}), 126.7 (d, 2C, C_8), 118.4 (t, C_{13}), 84.0 (s, C_2), 57.7 (t, C_4), 52.3 (s, C_5), 46.8 (t, C_{11}), 27.7 (q, 3C, C_1).

HRMS (ESI) *m/z*: calcd for $C_{17}H_{20}ClNO_4Na$ $[M+Na]^+$: 360.0973, found: 360.0973.





***tert*-Butyl (*S*)-4-(2-(methoxycarbonyl)allyl)-5-oxo-4-phenylisoxazolidine-2-carboxylate (II.18q)**



II.18q was synthesized according to the method aforementioned from *tert*-butyl 5-oxo-4-phenylisoxazolidine-2-carboxylate **1a** (50 mg, 0.19 mmol, 1.0 equiv) and methyl 2-(acetoxymethyl)acrylate **II.20c** (190 µL, 1.0 M in THF, 0.19 mmol, 1.0 equiv). The titled compound was obtained after flash column chromatography on silica gel (PE/Et_2O = 9:1) in an inseparable mixture of **II.1a**/**II.18q** = 65:35 as a colorless viscous oil (48 mg, 25%).

R_f: 0.16 (PE/Et_2O = 8:2)

ee = 25% (determined by SFC)

SFC: AD-H column, Pressure = 100 bar, eluent = sc CO_2/MeOH = 95:5, Flow rate = 5 mL/min, detection wavelength = 220 nm. t_R = 1.65 min (minor) and t_R = 1.85 min (major).

IR (ATR): 2970, 2919, 2850, 1797, 1737, 1724, 1456, 1371, 1217, 1144, 909, 848, 766, 732, 700 cm^{-1}.

Note: the mixture of **II.1a**/**II.18q** = 65:35 is described separately.

^{1}H NMR (400 MHz, $CDCl_3$) mixture of **II.1a**/**II.18q** = 65:35:

Compound II.1a: δ 7.44-7.27 (m, 5H, H_{Ar}), 4.56 (m, 1H, H_4), 4.14-4.06 (m, 2H, $H_{4'}$ and H_5), 1.52 (s, 9H, H_1).

Compound II.18q: δ 7.44-7.27 (m, 5H, H_{Ar}), 6.24 (d, *J* = 1.1 Hz, 1H, H_{13}), 5.52 (q, *J* = 1.0 Hz, 1H, $H_{13'}$), 4.70 (d, *J* = 12.2 Hz, 1H, H_4), 4.14-4.06 (m, 1H, $H_{4'}$), 3.69 (s, 3H, H_{15}), 3.09 (d_{app}, *J* = 14.1 Hz, 1H, H_{11}), 2.90 (dd, *J* = 14.0, 0.9 Hz, 1H, $H_{11'}$), 1.26 (s, 9H, H_1).

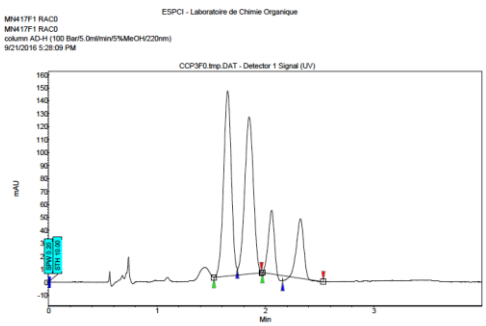
^{13}C NMR (100 MHz, $CDCl_3$) mixture of **1a**/**3f** = 65:35:

Compound II.1a: δ 173.5 (s, C_6), 156.1 (s, C_3), 133.4 (s, C_7), 129.4 (d, 2C, C_8 or C_9), 128.7 (d, C_{10}), 128.0 (d, 2C, C_8 or C_9), 84.5 (s, C_2), 55.8 (t, C_4) 46.5 (d, C_5), 28.2 (q, 3C, C_1).

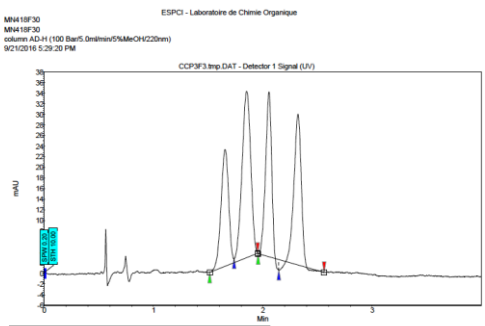
Compound II.18q: δ 175.4 (s, C_6), 167. 5 (s, C_{14}), 136.0 (s, C_{12}), 134.6 (s, C_7), 131.1 (t, C_{13}), 129.1 (d, 2C, C_8 or C_9), 128.6 (d, C_{10}), 126.9 (d, 2C, C_8 or C_9), 84.0 (s, C_2), 57.9 (t, C_4), 53.5 (s, C_5), 52.3 (q, C_{15}), 38.9 (t, C_{11}), 27.8 (q, 3C, C_1).

Note: the quaternary carbon corresponding to C_3 was not observed.

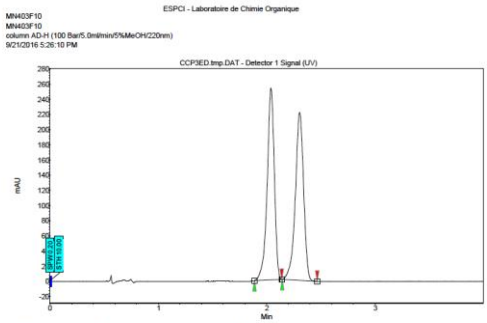
HRMS (ESI) *m/z*: calcd for $C_{19}H_{23}NO_6Na$ $[M+Na]^+$: 384.1418, found: 384.1417.



Index	Name	Time	Height	Area	Area	Selectivity	Res. HW
		[Min]	[µV]	[µV.Min]	[%]		
3	UNKNOWN	1.65	142.7	11.7	40.023	0.00	0.00
4	UNKNOWN	1.85	121.0	11.3	38.546	1.12	1.43
1	UNKNOWN	2.06	49.0	2.9	10.036	1.11	1.64
2	UNKNOWN	2.32	45.8	3.3	11.395	1.13	2.36
Total			358.4	29.3	100.000		

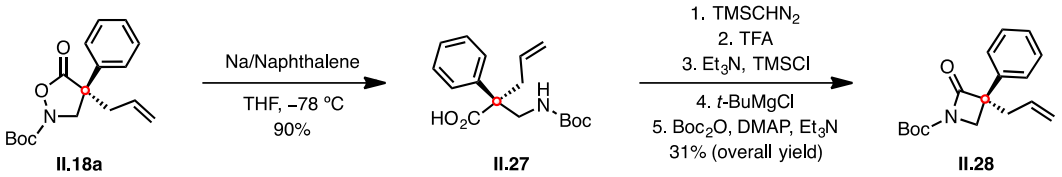


Index	Name	Time	Height	Area	Area	Selectivity	Res. HW
		[Min]	[µV]	[µV.Min]	[%]		
3	UNKNOWN	1.65	22.0	1.8	20.268	0.00	0.00
4	UNKNOWN	1.85	31.4	2.9	33.238	1.12	1.42
1	UNKNOWN	2.05	31.1	2.0	22.270	1.11	1.61
2	UNKNOWN	2.32	28.5	2.1	24.223	1.13	2.36
Total			113.0	8.8	100.000		



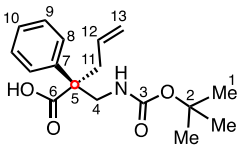
Index	Name	Time	Height	Area	Area	Selectivity	Res. HW
		[Min]	[µV]	[µV.Min]	[%]		
2	UNKNOWN	2.04	253.2	19.4	49.752	0.00	0.00
1	UNKNOWN	2.30	221.5	19.6	50.248	1.13	2.11
Total			474.6	39.0	100.000		

8. Product derivatizations



8.1. Synthesis of $\beta^{2,2}$-amino acid

(*S*)-2-(((*tert*-Butoxycarbonyl)amino)methyl)-2-phenylpent-4-enoic acid (II.27)



II.27

$C_{17}H_{23}NO_4$
MW = 305.37 g/mol

To a solution of recrystallized naphthalene (960 mg, 7.50 mmol, 1.00 equiv) in THF (15.0 mL) at rt was added finely chopped Na (190 mg, 8.25 mmol, 1.10 equiv) and the mixture was stirred for 2 h, to provide the dark green solution of sodium naphthalenide solution (0.5 M). Then to a second flask containing a solution of *tert*-butyl (*S*)-4-allyl-5-oxo-4-phenylisoxazolidine-2-carboxylate **II.18a** (100 mg, 0.33 mmol, 1.0 equiv) in THF (11.0 mL) at −78 °C was added dropwise, via syringe, the freshly prepared the sodium naphthalenide solution until the dark green color remained. The reaction was quenched, at −78 °C, by the addition of H_2O (10 mL) and the reaction mixture was warmed to rt. The pH was adjusted to 2 with an aqueous solution of HCl (1 M). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH = from 95:5 to 90:10) to afford the the amino acid **II.27** as a clear oil (91 mg, 90%).[136c]

R$_f$: 0.45 (CH_2Cl_2/MeOH = 9:1)

$[\alpha]^{20}_{D}$ = −2.65 (*c* 0.98, $CHCl_3$)

IR (ATR): 2978, 2929, 1703, 1653, 1507, 1448, 1404, 1368, 1248, 1167, 1075, 1029, 993, 921, 855, 773, 726, 699, 633 cm^{-1}.

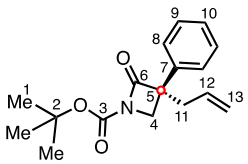
^{1}H NMR (400 MHz, DMSO-d_6): δ 12.62 (s, 1H, OH), 7.34-7.26 (m, 2H, H_{Ar}), 7.26-7.18 (m, 3H, H_{Ar}), 6.32 (t, J = 6.1 Hz, 1H, NH), 5.66 (ddt, J = 17.3, 10.1, 7.2 Hz, 1H, H_{12}), 5.12 (d_{app}, J = 17.2 Hz, 1H, H_{13}), 5.01 (d_{app}, J = 10.2 Hz, 1H, $H_{13'}$), 3.60 (dd, J = 13.8, 6.8 Hz, 1H, H_4), 3.48 (dd, J = 13.6, 5.7 Hz, 1H, $H_{4'}$), 2.76 (dd, J = 13.8, 7.5 Hz, 1H, H_{11}), 2.68 (dd, J = 13.8, 7.5 Hz, 1H, $H_{11'}$), 1.27 (s, 9H, H_1).

^{13}C NMR (100 MHz, DMSO-d_6): δ 175.2 (s, C_6), 155.5 (s, C_3), 140.6 (s, C_7), 134.0 (d, C_{12}), 128.0 (d, 2C, C_9), 126.7 (d, 2C, C_8), 126.6 (d, C_{10}), 118.7 (t, C_{13}), 77.7 (s, C_2), 54.1 (s, C_5), 43.7 (t, C_4), 37.5 (t, C_{11}), 28.1 (q, 3C, C_1).

HRMS (ESI) *m/z*: calcd for $C_{17}H_{23}NO_4Na$ $[M+Na]^+$: 328.1519, found: 328.1521.

8.2. Synthesis of β-lactam

***tert*-Butyl (*S*)-3-allyl-2-oxo-3-phenylazetidine-1-carboxylate (II.28)**



II.28
$C_{17}H_{21}NO_3$
MW = 287.36 g/mol

To a solution of (*S*)-2-(((*tert*-butoxycarbonyl)amino)methyl)-2-phenylpent-4-enoic acid **II.27** (174 mg, 0.57 mmol, 1.0 equiv) in toluene (3.0 mL) and MeOH (7.5 mL) at 0 °C was added dropwise $TMSCHN_2$ (2 M in Et_2O) until the yellow color persisted. The solution was stirred for an additional 20 min and quenched with a drop of acetic acid. The reaction mixture was concentrated under reduced pressure to afford the crude methyl ester (180 mg, 99%) as a clear oil which was engaged in the next step without further purification or characterization.[137]

The abovementioned methyl ester (180 mg, 0.56 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (5.6 mL). The resulting solution was cooled to 0 °C and TFA (840 µL, 11.3 mmol, 20.0 equiv) was added. The reaction mixture was stirred at rt for 2 h. Then, the mixture was cooled to 0 °C and a saturated aqueous solution of $NaHCO_3$ (20 mL) was added. The layers were separated and the aqueous layer was extracted CH_2Cl_2 (2 x 10 mL). The organic layers were

combined and washed with H_2O (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure, affording the crude β-amino ester (120 mg, 98%) as a brownish oil which was engaged in the next step without further purification or characterization.

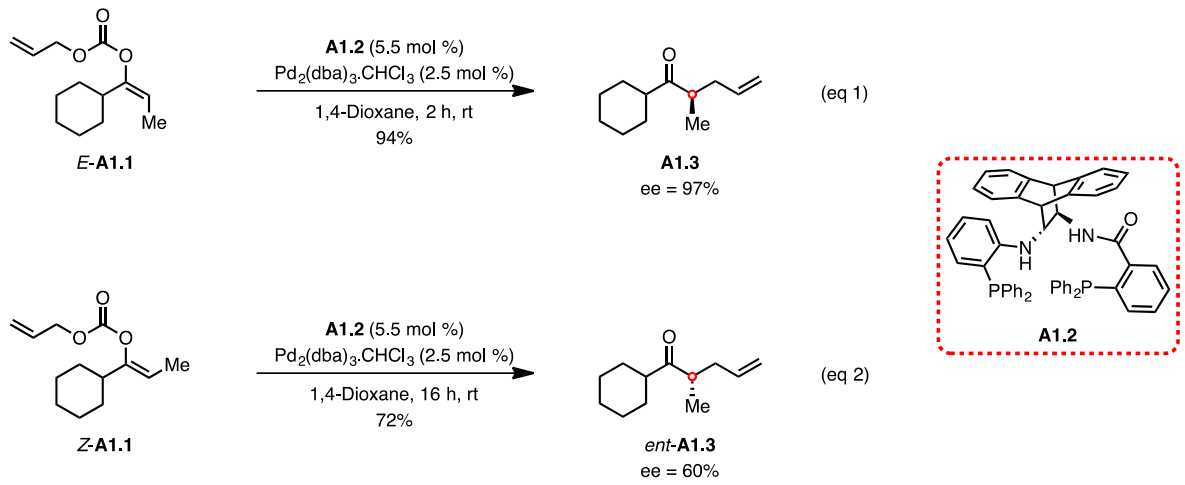
A solution of the aforementioned β-amino ester (50 mg, 0.23 mmol, 1.0 equi) in CH_2Cl_2 (1.2 mL) was cooled to 0 °C, and then treated with Et_3N (35 µL, 0.25 mmol, 1.1 equiv) and TMSCl (32 µL, 0.25 mmol, 1.1 equiv), stirring was continued at same temperature for 30 min. Then, *t*-BuMgCl (1.50 mL, 1 M in THF, 1.50 mmol, 6.6 equiv) was added dropwise. The reaction mixture was stirred at rt for 18 h, then H_2O (2 mL) was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure.[19] The resulting residue was then dissolved in CH_2Cl_2 (1.0 mL), cooled to 0 °C and treated with Et_3N (38 µL, 0.27 mmol, 1.2 equiv), Boc_2O (128 mg, 0.60 mmol, 2.6 equiv) and DMAP (34 mg, 0.27 mmol, 1.2 equiv). The mixture was stirred overnight at rt. The reaction was acidified with an aqueous solution of HCl (1M), the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (PE/Et_2O = 9:1) to afford the desired β-lactam **II.28** as a clear oil (21 mg, 32%).

R_f: 0.36 (PE/Et_2O = 8:2)
$[\alpha]^{20}_D$ = +16.4 (*c* 0.32, $CHCl_3$)
IR (ATR): 2980, 2919, 1798, 1723, 1370, 1345, 1258, 1146, 1051, 993, 850, 771, 701 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.33 (m, 4H, H_{Ar}), 7.32-7.26 (m, 1H, H_{Ar}), 5.11 (m, 1H, H_{12}), 5.18-5.08 (m, 2H, H_{13}), 3.83 (d, *J* = 6.7 Hz, 1H, H_4), 3.77 (d, *J* = 6.7 Hz, 1H, $H_{4'}$), 2.76-2.62 (m, 2H, H_{11}), 1.52 (s, 9H, H_1).
^{13}C NMR (100 MHz, $CDCl_3$): δ 167.9 (s, C_6), 148.4 (s, C_3), 138.3 (s, C_7), 132.0 (d, C_{12}), 128.8 (d, 2C, C_8 or C_9), 127.7 (d, C_{10}), 126.7 (d, 2C, C_8 or C_9), 119.9 (t, C_{13}), 83.6 (s, C_2), 61.3 (s, C_5), 49.4 (t, C_4), 42.2 (t, C_{11}), 28.2 (q, 3C, C_1).
HRMS (ESI) *m/z*: calcd for $C_{17}H_{21}NO_3Na$ $[M+Na]^+$: 310.1414, found: 310.1416.

Appendix 1

1. Palladium-catalyzed asymmetric decarboxylative allylic alkylation of acyclic allyl enol carbonates

Controlling the stereochemistry in acyclic carbonyl compounds through palladium-catalyzed asymmetric decarboxylative allylic alkylation has proven difficult, generally affording low enantioselectivities. The appropriate positioning of functional groups to favor the formation of a single enolate geometry has emerged as the simplest solution to this problem. Indeed, Trost *et al*. showed that the use of preformed enol carbonates affected both the reaction rate and the absolute stereochemistry of the resulting stereogenic center (Scheme 1).[143]

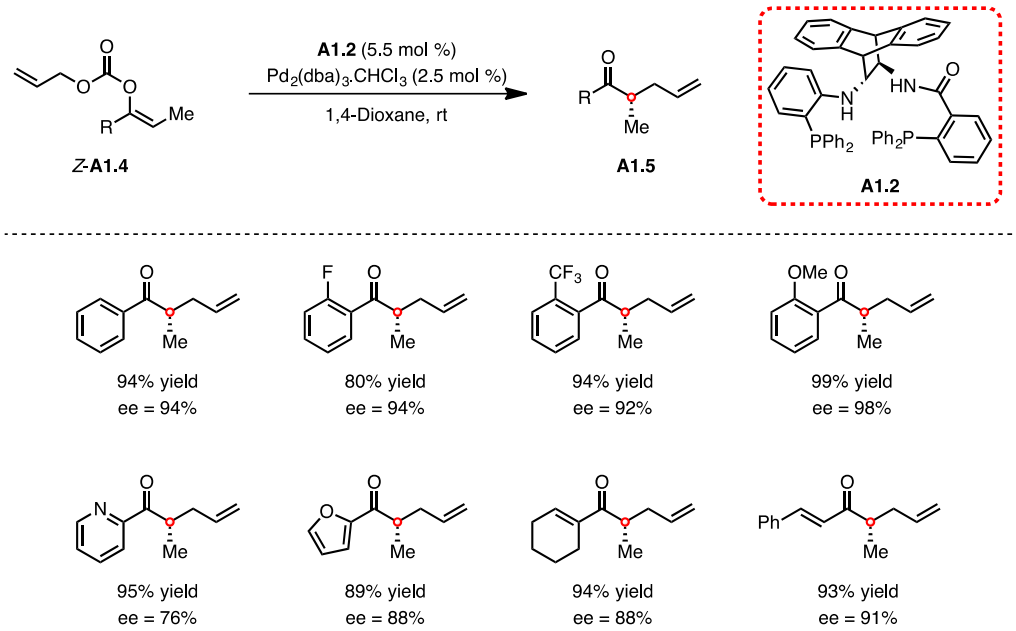


Scheme 1. Pd-DAAA of acyclic allyl enol carbonates by Trost and Xu.

As a matter of fact, the *E*-enol carbonate *E*-**A1.1** smoothly underwent decarboxylative allylation to afford the homoallylic ketone **A1.2** in high yield and enantioselectivity (Scheme 1, eq 1). In contrast, the opposite enantiomer (*ent*-**L1.70**) was obtained in both decreased yield and enantioselectivity, when the isomeric *Z*-enol *Z*-**L1.69** was allowed to react under otherwise identical conditions (Scheme 1, eq 2). These results indicated a clear match-mismatch effect where the *E*-isomer matched with the catalyst while the *Z*-isomer mismatched. More importantly, this investigation demonstrated that neither the enol carbonate nor the putative Pd-enolate underwent significant geometric isomerization.

143 Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 17180.

Interestingly, the reaction of *Z*-enol carbonates of acyclic aryl, heteroaryl and alkenyl ketones *Z*-**A1.4**, using the same Trost ligand (**A1.2**)/$Pd_2(dba)_3.CHCl_3$ catalytic system, provided the formation of a wide range of α-tertiary ketones **A1.5** in excellent yields and enantioselectivities (Scheme 23) thus demonstrating that the mismatch case observed with alkyl ketone **A1.1** was not general for all acyclic allyl enol carbonates.



Scheme 2. Pd-DAAA of acyclic allyl enol carbonates by Trost and Xu.

Appendix 2

1. Palladium-catalyzed asymmetric allylic alkylation (Pd-AAA)

The enantioselective construction of tertiary and quaternary stereocenters by reacting a chiral Pd(II)-π-allyl complex, generated from the oxidative addition of a Pd(0) species on an activated allylic substrates, represents another particularly appealing approach which is complementary with the Pd-DAAA strategy mentioned previously.[59, 69] Indeed, the reaction proceeds under extremely mild conditions, it is highly functional group tolerant and as such has allowed the access to structurally diverse and synthetically useful chiral compounds in high yields and excellent regioselectivities and enantioselectivities.[144]

A number of reviews and book chapters on the palladium-catalyzed asymmetric allylic alkylation have been published over the past years.[24, 145] hence, the aim here is just to briefly introduce a few key aspects of the Pd-AAA process considered important to fully comprehension of the following sections.

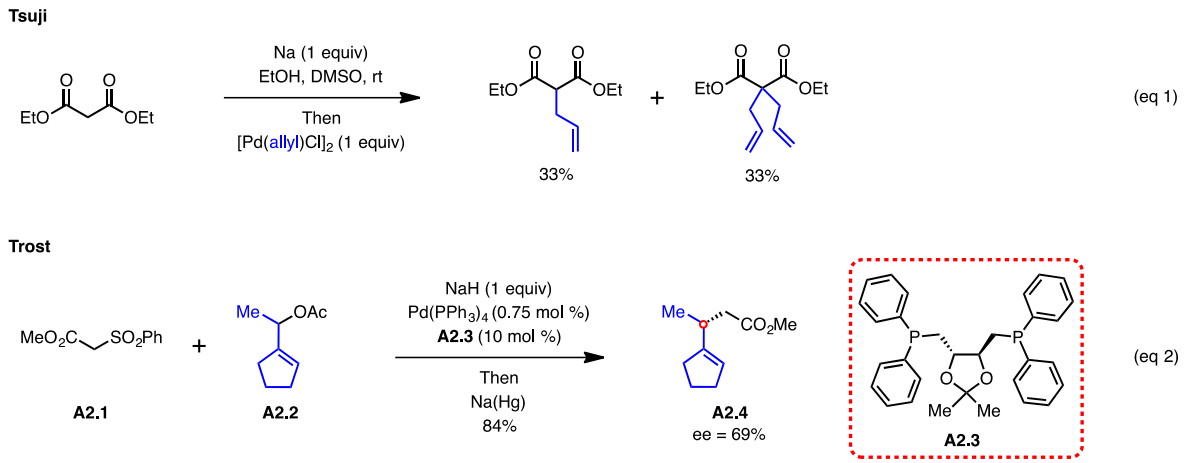
1.1. Introduction to Tsuji-Trost allylic alkylation reaction

The advent of the palladium-mediated allylic alkylation was first reported by Tsuji in 1965 by demonstrating that a stoichiometric amounts of a π-allyl palladium chloride dimer could react with nucleophiles such as anions derived from diethyl malonate and ethyl acetoacetate to afford the corresponding allylated products (Scheme 1, eq 1).[48] About a decade later, Trost described his first attempts at palladium-catalyzed asymmetric allylic alkylation of soft carbon nucleophiles in the presence of the chiral diphosphine ligand

144 (a) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921; (b) Trost, B. M.; Strege, P. E. *J. Am. Chem. Soc.* **1977**, *99*, 1649; (c) Graening, T.; Schmalz, H. G. *Angew. Chem. Int. Ed.* **2003**, *42* , 2580.

145 (a) Lu, Z.; Ma, S. *Angew. Chem. Int. Ed.* **2008**, *47* , 258; (b) Butt, N. A.; Zhang, W. *Chem. Soc. Rev.* **2015**, *44* , 7929; (c) Tsuji, J. *New J. Chem.* **2000**, *24*, 127; (d) Trost, B. M. *Chem. Pharm. Bull.* **2002**, *50*, 1; (e) Helmchen, G. *J. Organomet. Chem.* **1999**, *576*, 203; (f) Frost, C. G.; Howarth, J.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1992**, *3*, 1089; (g) Tsuji, J. *Pure Appl. Chem.* **1999**, *71*, 1539; (h) Moberg, C.; Bremberg, U.; Hallman, K.; Svensson, M.; Norrby, P.-O.; Hallberg, A.; Larhed, M.; Csoregh, I. *Pure Appl. Chem.* **1999**, *71*, 1477; (i) Leeuwen, P. W. N. M. V.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P. *Chem. Rev.* **2000**, *100*, 2741; (j) Heumann, A., Palladium-catalyzed allylic substitutions in *Transition Metals for Organic Synthesis*, Beller, M.; Bolm, C., Eds. WILEY-VCH Verlag GmbH: Weinheim, **1998**; pp 251; (k) Mandai, T., Palladium-Catalyzed Allylic, Propargylic, and Allenic Substitution with Nitrogen, Oxygen, and Other Groups 15–17 Heteroatom Nucleophiles in *Handbook of Organopalladium Chemistry for Organic Synthesis*, Negishi, E.-i., Ed. John Wiley & Sons, Inc: New York, **2002**; (l) Acemoglu, L.; Williams, J. M. J., Synthetic Scope of the Tsuji–Trost Reaction with Allylic Halides, Carboxylates, Ethers, and Related Oxygen Nucleophiles as Starting Compounds in *Handbook of Organopalladium Chemistry for Organic Synthesis*, Negishi, E.-i., Ed. John & Sons, Inc: New York, **2002**; (m) Kazmaier, U., *Transition Metal Catalyzed Enantioselective Allylic Substitution in Organic Synthesis*. Springer-Verlag: Berlin, **2002**. (n) Tsuji, J., *Palladium Reagents and Catalysts: New perspectives for the 21st centurey*. John Wiley & Sons, Ltd: Chichester, **2004**.

(*S*,*S*)-DIOP **A2.3**, resulting in the allylation of the nucleophile with excellent regioselectivity and promising level of enantioselectivity as exemplified in Scheme 1, eq 2.[144b]

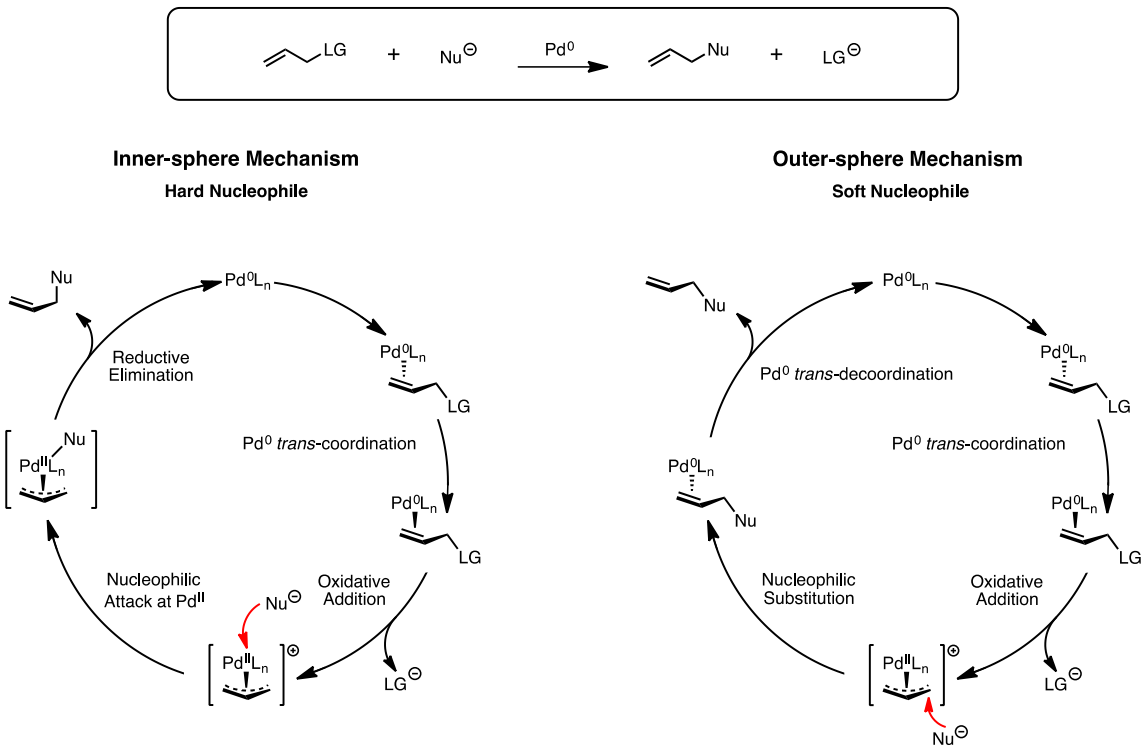


Scheme 1. Pioneering work by Tsuji and Trost.

Since these seminal studies, the field of Pd-AAA has been extensively investigated by different research groups including ours, resulting in a fine understanding of the parameters involved in achieving high enantioselectivities.

The typical mechanism for a Pd-AAA can be summed up in two distinctive pathways depending on the nature of the nucleophile involved (Scheme 2). As a general trend, the reaction begins by the π-coordination of the substrate to the Pd(0) complex which occurs *trans* with respect to the leaving group, thus affording a Pd(0)-coordinated substrate. Subsequent oxidative addition leads to the formation of the η^3-allyl Pd(II) complex, which is in equilibrium with the isomeric η^1-allyl Pd(II) complex. The actual C–C bond forming step then occurs by a trapping of the electrophilic π-allyl palladium intermediate with a carbon-nucleophile.[145m, 146]

146 Fiaud, J.-C.; Legros, J.-Y. *J. Org. Chem.* **1987**, *52*, 1907.



Scheme 2. Accepted mechanism.

For hard nucleophiles — defined as those whose conjugated acids have p*K*a > 25, such as "nonstabilized" carbanions: aryl and alkenylmetal reagents involving Al, B, Mg, Si, Sn, Zn and Zr — similarly to the mechanism presented in Chapter 1 – Section 4 for the palladium-catalyzed decarboxylative allylic alkylation reaction, an inner-sphere pathway may be envisaged allowing the π-allyl complex to be trapped by the hard nucleophiles as outlined in Scheme 2, left.[147] In this pathway, the attack occurs directly on the electrophilic palladium center, generating an allyl(organyl)palladium complex intermediate by *trans*-metalation. The latter subsequently evolves *via* reductive elimination to a Pd(0)-olefin complex, which eventually releases the allylated product along with an activate Pd(0) species.

On the other hand, the reaction with soft nucleophiles — defined as those whose conjugated acids have p*K*a < 25, such as stabilized carbanions of diesters, -amides, -nitriles, -aldehydes, -ketones, nitrones, sulfones, sulfoxides and phosphonates — normally follows a different course as outlined in Scheme 2, right.[69, 148] As soft nucleophiles approach the

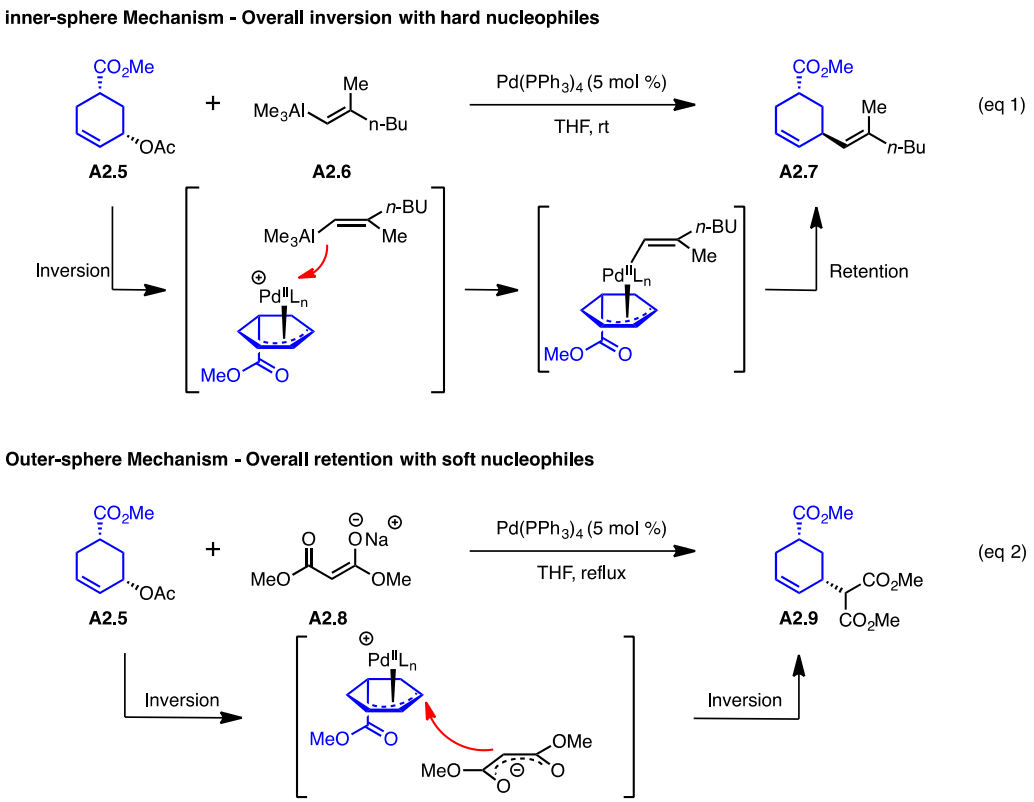
147 (a) Matsushita, H.; Negishi, E.-i. *J. Am. Chem. Soc.* **1981**, *103*, 2882; (b) Miyaura, N.; Yano, T.; Suzuki, A. *Tetrahedron Lett.* **1980**, *21*, 2865; (c) Hayashi, T.; Konishi, M.; Yokota, K.-I.; Kumada, M. *J. Chem. Soc., Chem. Commun.* **1981**, 313; (d) Yoshida, J.-I.; Tamao, K.; Takahashi, M.; Kumada, M. *Tetrahedron Lett.* **1978**, *19*, 2161; (e) Hayasi, Y.; Riediker, M.; Temple, J. S.; Schwartz, J. *Tetrahedron Lett.* **1981**, *22*, 2629.
148 Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1976**, *98*, 630.

electrophilic π-allyl complex on the face opposite of the metal, the bond forming event occurs out of the coordination sphere of the metal. This is referred as an outer sphere process and results in a η^3-to-η^2 reorganization to afford the Pd(0)-olefin complex, which evolves to the allylated product and regenerates an activate Pd(0) species.

Negishi *et al*. proved that Pd-AAA reactions involving hard nucleophiles proceeded through an inner-sphere mechanism. Indeed, by running the allylic substitution on a substrate which allows to track the stereochemistry of the intermediate such as *cis*-cyclohexenyl acetate **A2.5**, and using an alkenylalane such as **A2.6** as a nucleophile under Pd(0) catalysis, they were able to observe an overall inversion of the relative stereochemistry in the allylated product **A2.7** (Scheme 3, eq 1). Since the oxidative addition furnishes the transient π-allyl palladium complex *via* inversion and the direct attack of the hard nucleophile **A2.6** with subsequent reductive elimination proceeds *via* retention, this gave rise to the 1,3-disubstituted cyclohexene **A2.6** with a *trans* relative configuration.[149]

On the other hand, Trost *et al*. observed that the allylic substitution of **A2.5** with a soft nucleophile, under otherwise identical conditions, afforded the allylated product **A2.9** with net retention of the relative stereochemistry. In this study case, they showed that the reaction with *cis*-cyclohexenyl acetate **A2.5** and the carbon-nucleophile **A2.8** derived from dimethyl malonate under Pd(0) catalysis proceeded through an outer-sphere mechanism (Scheme 3, eq 2). As the oxidative addition furnishes the transient π-allyl palladium complex *via* inversion and the nucleophilic attack occurs *anti* to the palladium center, this results in the formation of the *cis* 1,3-disubstituted product **A2.9**.[150]

149 Matsushita, H.; Negishi, E.-i. *J. Chem. Soc., Chem. Commun.* **1982**, 160.
150 Trost, B. M.; Verhoeven, T. R. *J. Org. Chem.* **1976**, *41*, 3215.



Scheme 56. Pd-catalyzed allylation pathways involving hard and soft nucleophiles.

1.2. Mechanistic features of η^3-allyl palladium complex

1.2.1. Generation of η^3-allyl palladium complex

The oxidative addition of the allyl acetate to Pd(0) complex has been demonstrated by Yamamoto *et al*. in 1981, who isolated and characterized the corresponding η^3-allyl(acetato) palladium intermediate. [151] Ultimately, studies performed by Amatore and Jutand demonstrated that the oxidative addition, leading to the formation of η^3-allyl palladium complex from allyl acetate and Pd(0) is a reversible process and thermodynamically disfavored, of which equilibrium lies extensively in favor of the Pd(0) side.[152] In this case, the η^1-allyl palladium complex maybe the resting state of the catalytic cycle. On the other hand, it

151 Yamamoto, T.; Saito, O.; Yamamoto, A. *J. Am. Chem. Soc.* **1981**, *103*, 5600.
152 Amatore, C.; Gamez, S.; Jutand, A.; Meyer, G.; Moreno-Mañas, M.; Morral, L.; Pleixats, R. *Chem. Eur. J.* **2000**, *6*, 3372

has been clearly demonstrated that the nature of the leaving group dramatically influences on the dislocation of the equilibrium and, therefore, on the entire substitution process.[153]

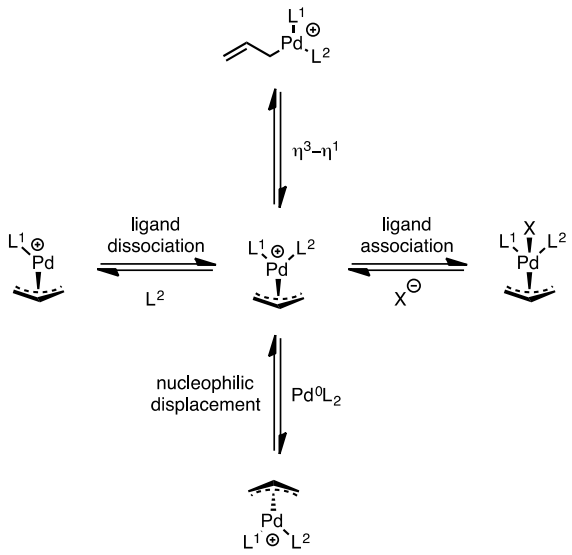
The rate-determining step can be either be the oxidative addition or the nucleophilic substitution, depending on the relative height of their respective transition state energy. Due to the irreversibility of the nucleophilic substitution by exogenous nucleophile, the global transformation can be usually entirely shifted toward the formation of the product.

1.2.2. Isomerization of η^3-allyl palladium complex

In the case of a cationic η^3-allyl palladium complex, two coordination sites are occupied by the allyl fragment. This complex features a square planar geometry around the metallic center, which can incorporate different stereogenic elements, depending on the substitution pattern of the allyl moiety and/or the nature of the ligands. Since the allyl metal complexes of this type exhibit a fluxional behavior, interconversion between these different isomeric forms is possible and can take place *via* different mechanisms.[145m]

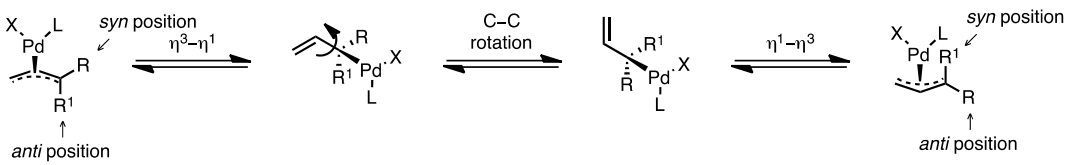
In the absence of a nucleophile, or if the nucleophilic attack step is slow enough, a generic η^3-allyl palladium complex may undergo the following four different equilibria: a) η^3–η^1 isomerization, b) ligand association, c) ligand dissociation, d) nucleophilic displacement by Pd(0) complex (Scheme 4).[154] The activation of these equilibria depends on the reaction conditions and can trigger the exchange of the allyl face complexed by the metal or the formal rotation of the allyl moiety with respect to the other coordinated ligands.

153 Vitagliano, A.; Akermark, B.; Hansson, S. *Organometallics* **1991**, *10*, 2592.
154 Pregosin, P. S.; Salzmann, R. *Coord. Chem. Rev.* **1996**, *155*, 35.



Scheme 4. η^3-Allyl palladium complex possible equilibria.

η^3–η^1 Isomerization followed by C–C bond rotation and η^1–η^3 equilibration leads to a global *syn-anti* exchange of the substituent pair concerned in the rotation, with concomitant exchange of the complexed allyl face (Scheme 5). This equilibrium is very facile when $R^1 = R^2 = H$, and is very fast in coordinating solvents, according to studies performed by Szabó.[155]

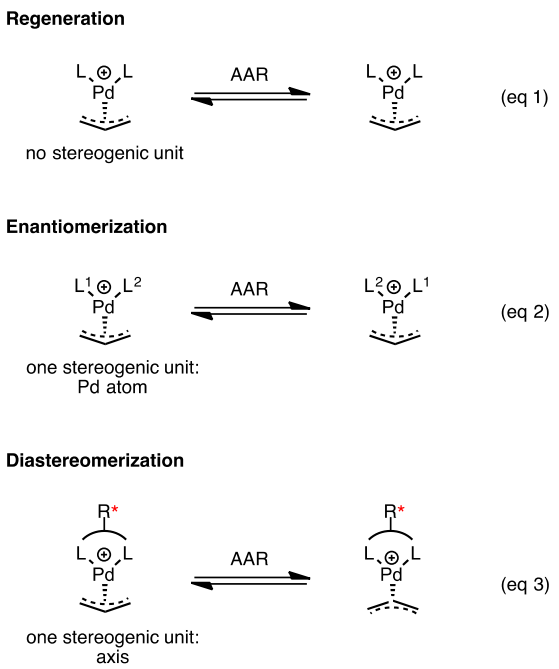


Scheme 5. η^1–η^3 Equilibration of allyl palladium complex.

1.2.2.1. Apparent allyl rotation

Apparent Allyl Rotation (AAR) implies the formal rotation of the allyl moiety around the imaginary Pd-allyl bond axis. Such movement can bring about inversion of the stereogenic palladium center or of the stereogenic axis. As a consequence, apparent allyl rotation can regenerate a structure identical to the starting one, or bring about enantiomerization or diastereomerization, depending on the starting complex (Scheme 6).

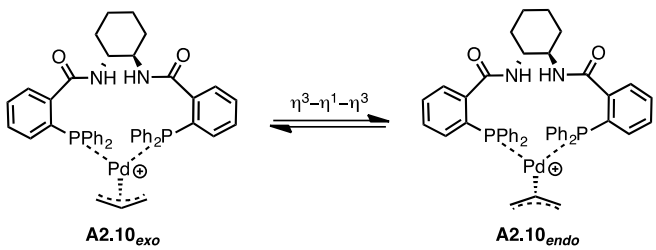
155 Solin, N.; Szabó, K. *Organometallics* **2001**, *20*, 5464.



Scheme 6. AAR of η^3 allyl palladium complex.

Importantly, an η^3-allyl palladium complex can show the presence of slowly interconverting rotamers once coordinated by *P*,*P* ligands. Thus, for example, the 13-membered η^3-allyl palladium complex ligated to Trost 'Standard Ligand' **A2.10**, admits two possible diastereoisomeric forms **A2.10***endo* and **A2.10***exo*, of which $^{31}P(^1H)$ NMR spectrum shows two distinct and equally populated rotamers (Scheme 7).[156] The different reactivity of *endo*/*exo* isomers of the corresponding **A2.10** is a very important issue. As a matter of fact, nucleophilic attack to one or the other isomer may determine the formation of one enantiomer preferentially over the other.

156 Butts, C. P.; Filali, E.; Lloyd-Jones, G. C.; Norrby, P.-O.; Sale, D. A.; Schramm, Y. *J. Am. Chem. Soc.* **2009**, *131*, 9945.



Scheme 7. Diastereoisomeric forms of Trost 'Standard Ligand'.

1.3. Enantiodiscriminating step using Trost 'Standard Ligand'

The Trost 'standard ligand' **A2.10** is undoubtedly the most successful chiral ligand used in asymmetric allylic alkylation substitution toward the natural product synthesis. Structural and computational studies have shown that the palladium atom is bonded through the phosphorus, while the nitrogen and the oxygen atoms are not involved in the chelation.[156, 157] Furthermore, the phenyl groups on the phosphorus atoms are used to transfer the chiral information to the substrate, as previously shown in the Chapter 1- Section 3 with the cartoon model.

This initial model to explain the sense of asymmetric induction has been improved as a result of the mechanistic studies performed by Lloyd-Jones and Norrby.[156] Two phenomena add to the steric interactions due to the phenyl groups: pro-*S* delivery of the nucleophile can be facilitated by hydrogen bonding with one amide N-H, and pro-*R* delivery can be facilitated by an escort ion M^+ binding to one amide carbonyl (Figure 1).

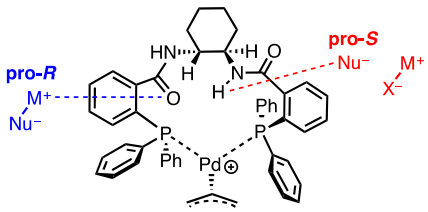


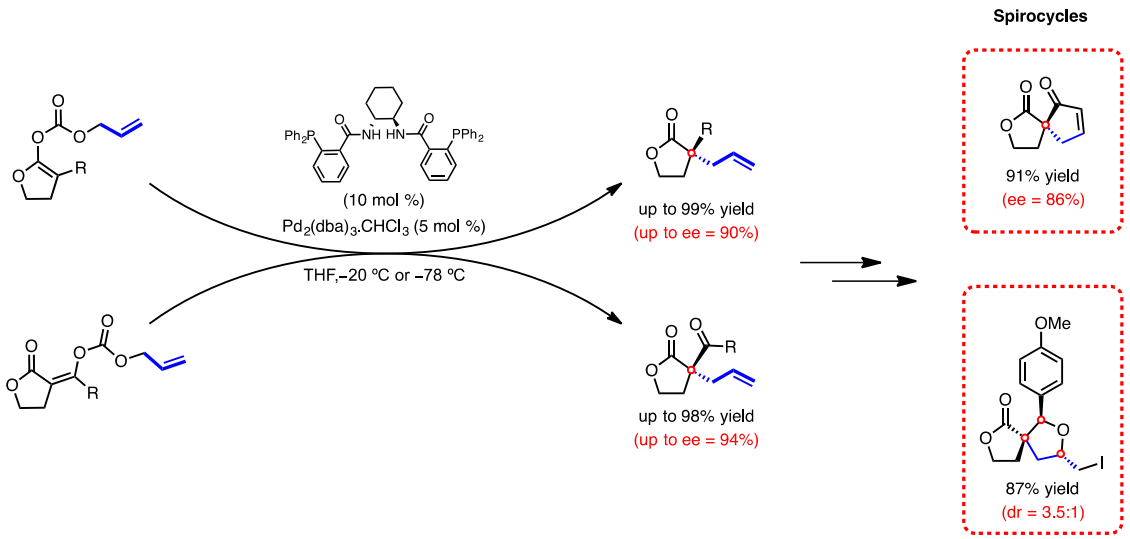
Figure 1. Lloyd-Jones and Norrby improved model.

157 Amatore, C.; Jutand, A.; Mensah, L.; Ricard, L. *J. Organomet. Chem.* **2007**, *692*, 1457.

General Conclusion

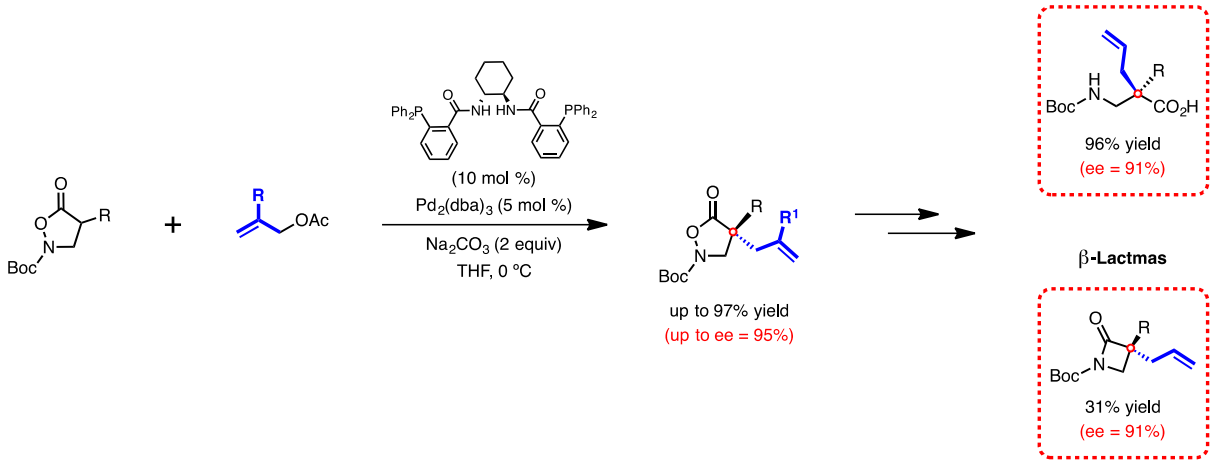
In summary, we have successfully developed two synthetic methods to access all-carbon α-quaternary functionalized heterocycles — the γ-butyrolactones and the isoxazolidin-5-ones — by palladium-catalyzed asymmetric allylic alkylations.

The development of a palladium-catalyzed decarboxylative allylic alkylation protocol (Pd-DAAA) applied to cyclic and exocyclic allyl enol carbonates has allowed a highly enantioselective access to a range of γ-butyrolactones bearing an all-carbon α-quaternary sterogenic center (Scheme I). Remarkably, despite the drawbacks, this approach allowed the extension of this reaction to substrates with no precedent in the literature, such as the exocyclic allyl enol carbonates. The Pd-DAAA process was eventually used for the synthesis of chiral spirolactones, which were readily obtained in high yields and in high optical purity.



Scheme I. Synthesis of all-carbon α-quaternary γ-butyrolactones by Pd-DAAA.

The synthesis of different isoxazolidin-5-ones bearing highly stereodefined all-carbon α-quaternary center was accomplished by palladium-catalyzed asymmetric allylic alkylation (Pd-AAA) of 4-substituted isoxazolidin-5-ones with an array of 2-substituted allyl acetates (Scheme II). The reaction proceeded in both excellent enantioselectivity and yield with isoxazolidin-5-ones containing an α-aryl substituents or an α-heteroaryl moieties, such as thiophene. Unfortunately, α-alkyl substituents revealed to be not suitable for this approach. Nonetheless, this robust and highly enantioselective method allowed the access to valuable $\beta^{2,2}$-amino acids and β-lactams.



Scheme II. Synthesis of all-carbon α-quaternary isoxazolidin-5-ones by Pd-AAA.

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Marllon NASCIMENTO DE OLIVEIRA

Palladium-Catalyzed Asymmetric Allylic Alkylations: Control of All-Carbon Quaternary Centers

Dans le cadre de nos travaux, nous avons développé une méthode extrêmement douce et particulièrement efficace d'accès à des γ-butyrolactones possédant un centre stéréogène quaternaire en α à partir d'énols carbonates d'allyle cycliques et exocycliques en utilisant la réaction d'alkylation allylique asymétrique décarboxylante pallado-catalysée (Pd-DAAA). Remarquablement, cette méthode a permis d'étendre l'utilisation de l'allylation asymétrique décarboxylante à des substrats sans précèdent dans la littérature, tels que les énols carbonates allyliques exocycliques. Cette réaction a été utilisée comme étape clé dans la synthèse des spirolactones chirales qui ont été obtenues avec de bons rendements et d'excellentes énantiosélectivités.

Une nouvelle méthode catalytique robuste et hautement énantiosélective permettant d'accéder à des isoxazolidinones possédant un centre stéréogène quaternaire en α a été développée. Ce protocole repose sur une alkylation allylique asymétrique catalysée par des complexes de palladium chiraux (Pd-AAA) et amène aux produits désirés avec de bons rendements et d'excellents excès énantiomériques. Par ailleurs, nous avons également mis au point des conditions permettant de convertir ces isoxazolidinones α,α-disubstituées en acides $\beta^{2,2}$-aminés et en β-lactames.

Mots-clés : catalyse asymétrique, centre quaternaire, palladium, alkylation allylique.

The development of a palladium-catalyzed decarboxylative allylic alkylation protocol (Pd-DAAA) applied to cyclic and exocyclic allyl enol carbonates has allowed a highly enantioselective access to a range of γ-butyrolactones bearing an all-carbon α-quaternary stereogenic center. Remarkably, this approach allowed the extension of this reaction to substrates with no precedent in the literature, such as the exocyclic allyl enol carbonates. The Pd-DAAA process was eventually used for the synthesis of chiral spirolactones, which were readily obtained in high yields and in high optical purity.

The synthesis of different isoxazolidin-5-ones bearing highly stereodefined all-carbon α-quaternary center was accomplished by palladium-catalyzed asymmetric allylic alkylation (Pd-AAA) of 4-substituted isoxazolidin-5-ones with an array of 2-substituted allyl acetates. The reaction proceeded in both excellent enantioselectivity and yield with isoxazolidin-5-ones containing an α-aryl substituents or an α-heteroaryl moieties. This robust and highly enantioselective method allowed the access to valuable $\beta^{2,2}$-amino acids and β-lactams.

Keywords: Asymmetric catalysis, all-carbon quaternary center, palladium, allylic alkylation.

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