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Development of the (4+1) annulation reaction between 1,3-dienes and sulfonium ylides

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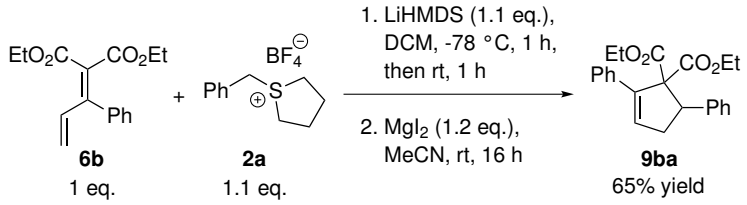
Abstract

Five-membered carbocycles are important features in organic chemistry since this motif is present in a wide range of biologically active molecules. The development of methodologies for the construction of these systems is thus a fundamental and important issue in synthetic organic chemistry, especially since the isolation of many cyclopentanoids terpenes in the mid seventies.

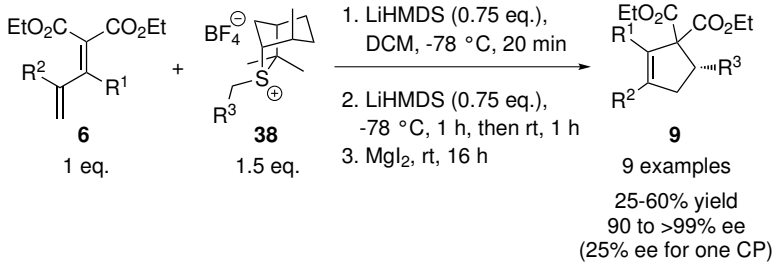
Our laboratory envisioned the (4+1) annulation reaction between 1,3-diene and sulfonium ylide. Unfortunately, preliminary researches showed that reaction between these two partners leads exclusively to vinylcyclopropanes (VCP) formation resulting from a (2+1) annulation reaction, with no traces of the desired cyclopentenes (CP). Dr. Thierry Delaunay, during his post-doctoral stay in our laboratory, discovered however that the bis-activation of the diene promotes the VCP/CP rearrangement, allowing to smoothly rearrange the VCP into the corresponding CP. Finally, he successfully carried out a one-pot procedure, leading to a formal (4+1) annulation methodology.



The first objective of our thesis was to investigate the scope of this (4+1) annulation methodology, using various 1,3-dienes and sulfonium ylides. It is noteworthy that a significant part of this thesis was dedicated to 1,3-dienes synthesis. After optimisation of the reaction conditions, all synthesized dienes were then engaged in (4+1) annulation reactions with various sulfonium ylides, giving access to fifteen cyclopentenes in moderates yields.

These promising results allowed us to envision an asymmetric version of our methodology, using chiral sulfonium salts **38**. We succeeded in synthesising nine enantioenriched cyclopentenes, in moderate yields, but with excellent enantiomeric excesses.

ABSTRACT



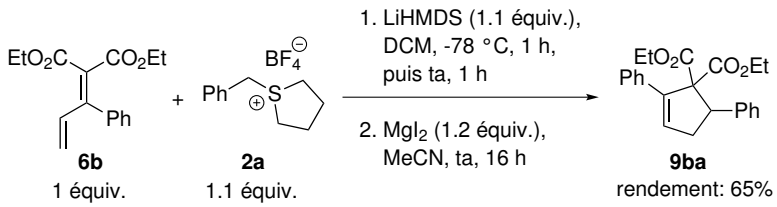
The versatility of our methodology was next highlighted by carrying out various derivatization reactions on one model cyclopentene. We successfully performed an ozonolysis reaction, a selective ester reduction, a hydrogenation of the double bond, a Krapcho decarboxylation, and a hydroboration reaction, although the isolated yield of this latter reaction was only 9 %.

Finally, we investigated the mechanism of the VCP/CP rearrangement process, and based on Aggarwal studies, we proposed a mechanistic explanation for the excellent enantiomeric excesses observed when using chiral sulfonium ylides.

Résumé

Les carbocycles à cinq chaînons sont des motifs important en chimie organique étant donné la présence de ces structures dans de nombreuses molécules biologiquement actives. Le développement de voies d'accès vers ces motifs structuraux est donc un sujet d'intense efforts en synthèse organique, en particulier depuis l'isolation, durant les années septante, de nombreux dérivés terpéniques comportant un carbocycle à cinq chaînons.

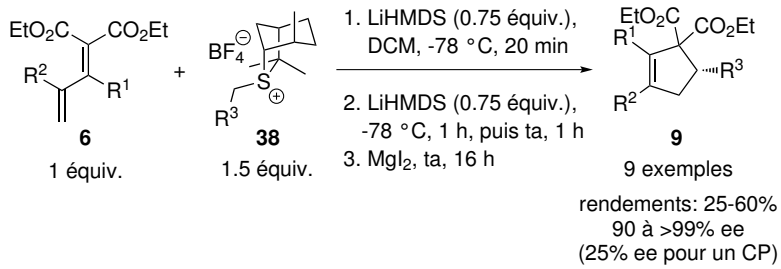
Notre laboratoire a envisagé la réaction d'annulation (4+1) entre un diène 1,3 et un ylure de sulfonium. Des recherches préliminaires dans ce domaine ont montré que la réaction entre ces deux partenaires conduit exclusivement aux vinylcyclopropanes (VCP) issus de la réaction d'annulation (2+1), sans aucune trace des cyclopentènes (CP) désirés. Le Dr. Thierry Delaunay, durant son stage postdoctoral dans notre laboratoire, a cependant mis en évidence que la bis-activation du diène facilite le réarrangement VCP/CP, permettant de ce fait la transformation du VCP en CP correspondant, en utilisant des conditions de réaction douces. Finalement, Dr. Delaunay a développé avec succès une procédure "one-pot", permettant d'accéder à une méthodologie de réaction d'annulation (4+1) formelle.



Le premier objectif de notre thèse était d'examiner le champ d'application de notre méthodologie d'annulation (4+1), en utilisant divers dièenes 1,3 et une série d'ylures de sulfonium. Il est à noter qu'une partie importante de cette thèse a été dédiée à la synthèse de dièenes 1,3. Après une optimisation des conditions de réactions, tous les dièenes synthétisés ont été engagés dans des réactions d'annulation (4+1) avec une gamme d'ylures de sulfonium, permettant d'accéder à quinze cyclopentènes différents, avec des rendements modérés.

Ces résultats prometteurs nous ont poussés à envisager une version asymétrique de notre méthodologie, en utilisant des sels de sulfonium chiraux (**38**).

Nous avons de la sorte pu accéder à neuf cyclopentènes énantio-enrichis, avec des rendements modérés mais avec d'excellents excès énantiomériques.



L'intérêt de notre méthodologie a ensuite été illustré en réalisant différentes réactions de dérivatisations sur un cyclopentène modèle. Nous avons pu réaliser avec succès une réaction d'ozonolyze, une réduction sélective d'un des deux esters, une réaction d'hydrogénation de la double liaison, une décarboxylation de Krapcho, ainsi qu'une réaction d'hydroboration, bien que le rendement isolé de cette dernière réaction était seulement de 9 %.

Finalement, nous avons étudié le mécanisme du réarrangement VCP/CP et, basé sur des études du groupe du Pr. Aggarwal, nous avons proposé une explication mécanistique des excellents excès énantiomériques observés avec les ylures de sulfonium chiraux.

Foreword

This Ph.D. thesis is part of the research carried out previously in our laboratory. The interested reader may consult the following references:

- R. Robiette, J. Marchand-Brynaert, *Synlett* **2008**, 517–520.
- C. Joie, *Développement de la cycloaddition (4+1) entre diènes et ylures*, Master thesis, **2010**, Université catholique de Louvain.
- O. Rousseau, *Synthèse de diènes pauvres en électrons et leur utilisation en cycloaddition (4+1)*, Master thesis, **2011**, Université catholique de Louvain.

In addition, this Ph.D. thesis allowed the publication of two articles:

- O. Rousseau, T. Delaunay, R. Robiette, *Synlett* **2014**, *25*, 519–522.
- O. Rousseau, T. Delaunay, G. Dequirez, T. Trieu-Van, K. Robeyns, R. Robiette, *Chem. Eur. J.* **2015**, *21*, 12899–12902.

Contents

Abbreviations

$[\alpha]_D^T$	specific rotation (at T temperature and at sodium D line wavelenght)
Å	ångström
Ac	acetyl
acac	acetylacetonate
ald.	aldehyde
APCI	atmospheric pressure chemical ionization
API	active pharmaceutical ingredient
Ar	aryl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
bs	broad singlet (NMR)
Bt	benzotriazole
Bu	butyl
c	concentration
calcd.	calculated
cat	catalyst
cod	1,5-cyclooctadiene
comp	complex (signals overlapping - NMR)
COSY	correlation spectroscopy
CP	cyclopentene
cy	cyclohexyl or cyclohexane
d	doublet (NMR)
d_x	deuterated (x deuterium)
d.r.	diastereoisomeric ratio
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane

DCM	dichloromethane
DEPT	distortionless enhancement by polarization transfer
DIMCARB	dimethylammonium dimethylcarbamate
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
E	electrophile
ee	enantiomeric excess
eq.	equivalent
équiv.	équivalent (french)
ESI	electrospray ionization
Et	ethyl
EWG	electron withdrawing group
FT-IR	Fourier transform infrared spectroscopy
gem	geminal
hν	electromagnetic radiation
Hex	hexane
HMBC	heteronuclear multiple bond coherence
HMDS	bis(trimethylsilyl)amide
HMPA	hexamethylphosphorictriamide (solvent)
HMPT	hexamethylphosphorictriamide (cosolvent)
HMQC	heteronuclear multiple quantum coherence
HPLC	high performance liquid chromatography
i	*iso*
IPA	isopropanol
J	coupling constant
L	ligand
L*	chiral ligand
LDA	lithium diisopropylamide
LG	leaving group
Lys	lysine
M	molarity
M	molecular mass (mass spectrometry)
m/z	mass-to-charge ratio
mal.	malonate

MBH	Morita-Baylis-Hillman
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
(*R*,*R*)-Me-DuPHOS	(+)-1,2-bis[(2*R*,5*R*)-2,5-diisopropylphospholano]-benzene
min.	minimum
mol	mole
mol%	mole percent
Mol.	molecular
MS	molecular sieve
Ms	mesyl
n	*normal*
NBS	N-bromosuccinimide
NCS	N-chlorosuccinimide
NGP	neighbouring group participation
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
num.	number
o	*ortho*
obs.	observation
p	*para*
Pd/C	palladium on carbon
PG	protecting group
Ph	phenyl
Piv	pivalate
(*R*,*S*)-PPF-P(*t*-Bu)$_2$	(2*R*)-1-[(1*R*)-1-[bis(1,1-dimethylethyl)phosphino]-ethyl]-2-(diphenylphosphino)ferrocene
ppm	part per million
Pr	propyl
Py	pyridine
q	quartet (NMR)
quant.	quantitative
R_f	retardation factor
ref.	reference
rt	room temperature
s	singlet (NMR)

(*R*)-SEGPHOS	(*R*)-(+)-5,5'-bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole
sep	septet (NMR)
SM	starting material
S_N2	second-order nucleophilic substitution
t	triplet (NMR)
t	*tert*
ta	température ambiante (french)
TAS	trialkylsilyl
TBS	*tert*-butyldimethylsilyl
Tf	triflate
THF	tetrahydrofurane
THT	tetrahydrothiophene
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMP	tetramethylpiperidine
TMS	trimethylsilyl
Ts	tosyl
USP	unidentified side product
VCP	vinylcyclopropane
wt.	weight
wt.%	weight percent

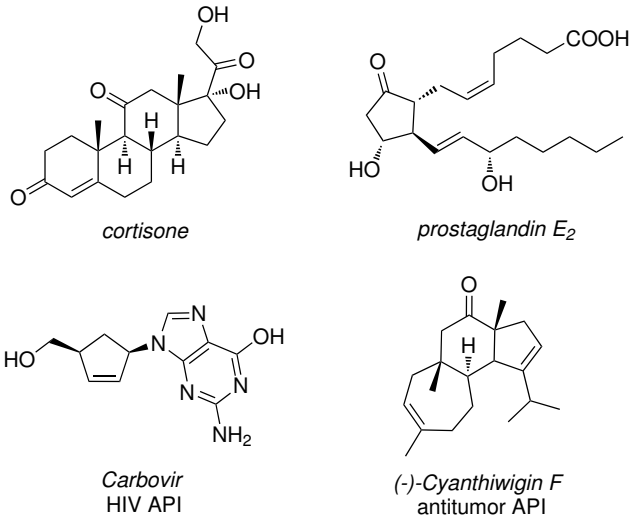
Chapter 1

Introduction

1.1 Five-membered carbocycles

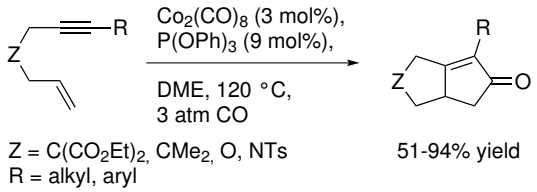
The ring moiety has an essential role in nature. It is found in many natural compounds as well as biologically active molecules.[6,7] The ring can be carbocyclic or heterocyclic, saturated or unsaturated, monocyclic or fused to one or multiple other cycles, and the size starts from three to more than ten or even more.

Among the most encountered cycles (three to eight-membered rings), the five-membered carbocycle occupies an important place. The isolation, in the mid-seventies, of many cyclopentanoids terpenes increased the research towards the synthesis of this structural motif.[8] Besides terpenes, a tremendous variety of natural and non-natural biologically active molecules includes this motif, such as steroids (for example cholesterol and cortisone) and prostaglandin molecules. Few examples are represented below (scheme 1.1). The development of methodologies for the construction of these systems is thus a fundamental and important issue in synthetic organic chemistry.



Scheme 1.1

One can envision two main strategies in order to reach 5-membered carbocycles: cyclisation reactions and cycloaddition/annulation reactions[1]. Because of convergent synthesis, the latter are more interesting to use than the cyclisation reactions. Among them, the (2+2+1), the (3+2), and the (4+1) cycloaddition/annulation reactions afford this scaffold. Nevertheless, the first one, or the so-called Pauson-Khand cycloaddition reaction, suffers from a poor regioselectivity in its intermolecular version.[10] Thereby, 5-membered carbocycles synthesis using this methodology mostly involves intramolecular (2+2+1) cycloadditions of enynes (scheme 1.2).[11,12]

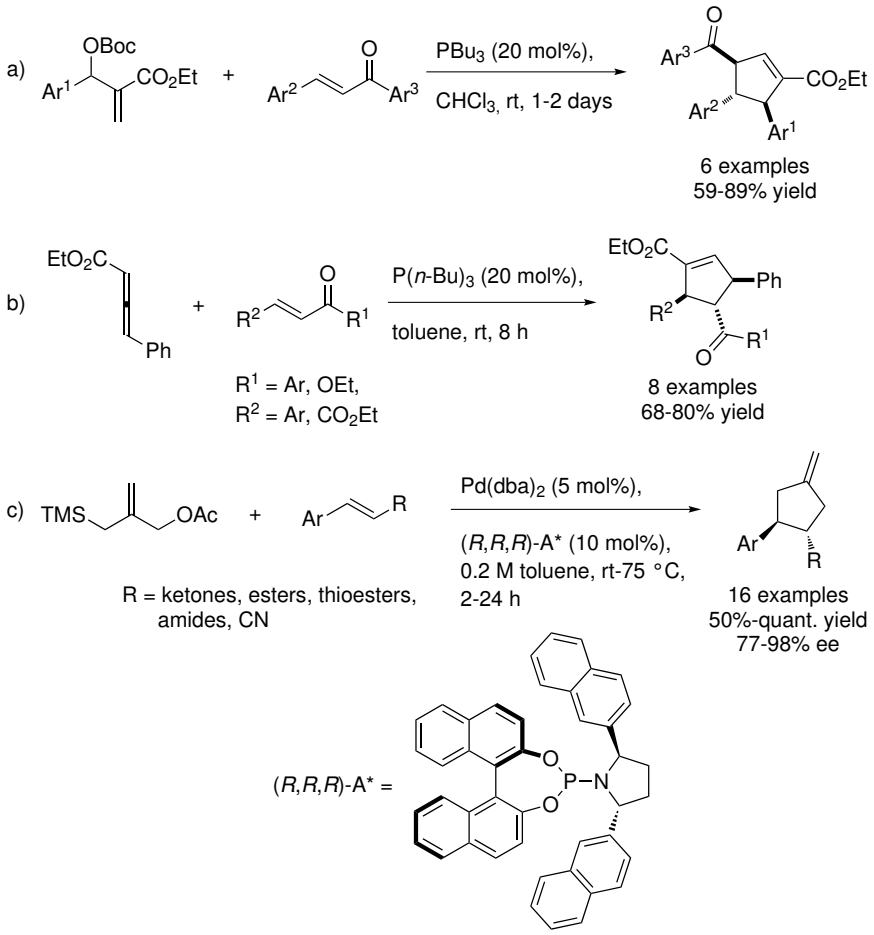


Scheme 1.2

The (3+2) cycloaddition/annulation reaction (or the 1,3-dipolar cycloaddition/annulation reaction) is however the most encountered strategy for 5-

[1]Strictly speaking, a cycloaddition reaction between molecular entities A and B implies no loss of atoms, within A and B, in the adduct C. An annulation reaction, on the contrary, does not require that specificity, as it is simply defined by a ring synthesis *via* two new bonds.[9] Thereby, depending on the reaction, one or the other of these denominations will be appropriately used.

membered carbocycles synthesis. It involves a 1,3-dipole and a dipolarophile, and can be considered as complementary to the (4+1) cycloaddition/annulation reaction although it is noteworthy that an all-carbon 1,3-dipole unit has to be employed, like MBH carbonates (a),[13] allenes (b),[14] or 2-((trimethylsilyl)-methyl)allyl acetate (c)[15] (scheme 1.3).[13–24]



Scheme 1.3

Regarding the third strategy, namely the (4+1) cycloaddition/annulation reaction, it implies the connection between a four-atoms unit and an one-atom unit. Scientists have been developed numerous four- and one-atom units so far.[25] Indeed, this strategy allows a high flexibility in the development of the two partners, as we will discover in the next section, allowing access to a large variety of five-membered rings *via* numerous reaction pathways.

The next section summarizes the research in this field,[2] and in a second part is reviewing the preliminary results obtained in our laboratory.

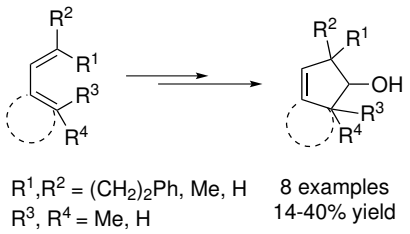
1.2 The (4+1) cycloaddition/annulation reaction

Since the discovery of the (4+1) cycloaddition/annulation reaction, numerous four- and one-carbon units have been elaborated and successfully engaged in this reaction. The reaction between 1,3-dienes and carbenes[3] will be first considered. The other carbenoid[4] reagents will then be discussed, and finally we will examine more specific four-carbons units.

1.2.1 Reaction between 1,3-diene and carbene

1.2.1.1 Two-step procedure

The reaction of carbene with 1,3-diene could be viewed as the Diels-Alder equivalent for the synthesis of five-membered rings.[5] In 1981, Danheiser and coworkers succeeded to synthesize rapidly eight cyclopentenes, in 14-40 % overall yields using a two-step procedure (scheme 1.4).[27] This procedure is depicted, for one substrate, in scheme 1.5.[6]



Scheme 1.4

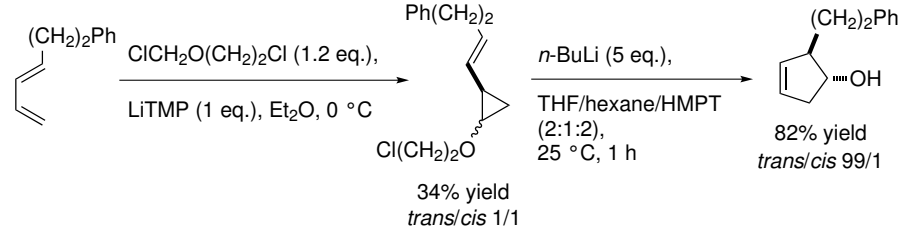
[2]We focus our attention, in this manuscript, on carbocycle synthesis. For heterocycles, the interested reader can consult a review recently published.[25]

[3]A carbene is defined by :CR_2, in which the carbon is covalently bonded to two univalent groups of any kind or a divalent group and bears two nonbonding electrons, which may be spin-paired (singlet state) or spin-non-paired (triplet state).[9]

[4]Carbenoids are complexed carbene-like entities that display the reactivity characteristics of carbenes, either directly or by acting as sources of carbenes.[9]

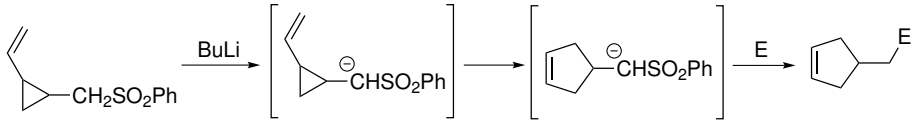
[5]The very first isolation of a (4+1) annulation adduct was carried out by Volker Franzen in 1961, by reacting 1,3-butadiene with methylene radical.[26] The vinylcyclopropane (VCP) side-product was also generated.

[6]For the nine other substrates, the cyclopentenes were generated by stirring vinylcyclopropanes for 1-2 h at 50 °C.



Scheme 1.5

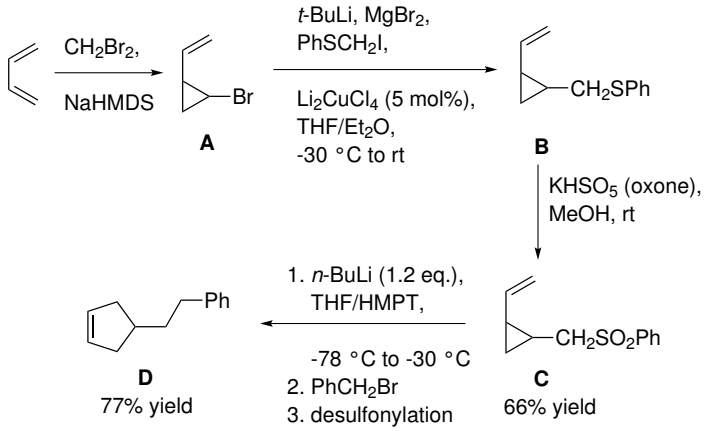
In 1985, Danheiser reported a second generation of his rearrangement. This new methodology involves a carbanion-accelerated VCP-CP rearrangement. The resulting cyclopentenylmethyl sulfone anions can be trapped *in situ* with numerous electrophiles which, after desulfonylation, allows access to a variety of substituted cycloadducts (scheme 1.6).[28]



Scheme 1.6

The rearrangement proceeds at lower temperature and more rapidly as compared to the alkoxy-rearrangement.[7] The scheme 1.7 shows an example of this strategy. Requisite [(phenylsulfonyl)methyl]-2-vinylcyclopropanes (**C**) are obtained from the cyclopropanation of 1,3-dienes, using dibromomethane as carbene precursor, leading to brominated vinylcyclopropanes in 19-71 % (**A**). In a subsequent step, the alkylation with $PhSCH_2I$ (**B**), followed by the oxidation using oxone, *m*-CPBA, or $MoO_5.HMPT.H_2O$, furnishes the sulfonyl vinylcyclopropanes in 56-74 % yields (**C**). Exposure of these intermediates to *n*-BuLi in a mixture of THF-HMPT from −78 °C to −30 °C (slow warming), followed by the *in-situ* trapping with various electrophiles, and subsequent desulfonylation provides the cyclopentenes in 46-88 % yields (**D**).

[7] The slow warming from −78 °C to −30 °C is enough to complete the rearrangement.



Scheme 1.7

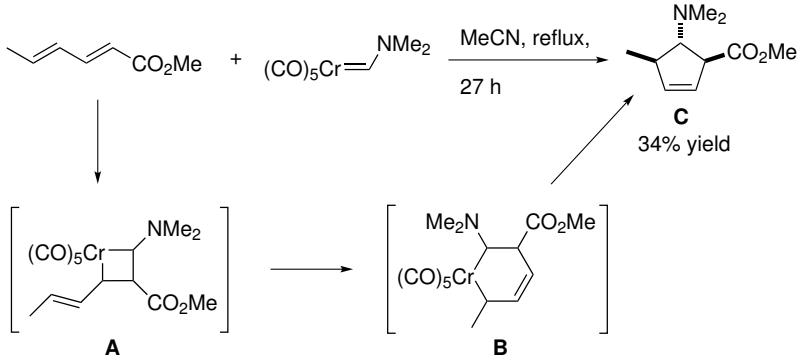
It is interesting to note that, although low reaction temperatures are employed, these strategies involve the use of highly reactive agents, such as *n*-BuLi, *t*-BuLi, and oxone, decreasing the interest for these reactions.

In addition, this strategy involves two distinctive steps, whereas it would be more interesting to perform cyclopentenes using a one-step procedure starting from 1,3-dienes, allowing access to a formal (4+1) cycloaddition/annulation reaction.

1.2.1.2 One-step procedure

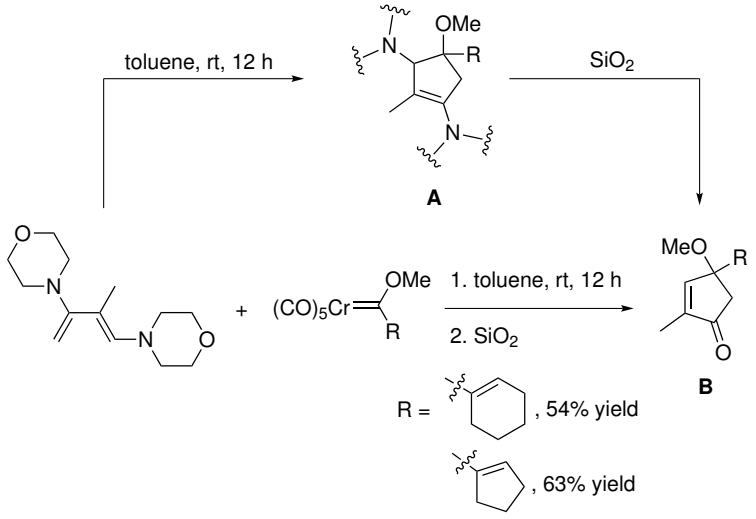
Later, in 1993, Hegedus succeeded to synthesize, in one synthetic step, a cyclopentene in 34 % yield using methyl sorbate and a Fischer carbene (scheme 1.8).[29] Indeed, as compared to nucleophilic carbenes, Fischer carbenes are stable versatile reagents, and have been used, for a long time in annulation reactions.[30,31] The cyclopentene is obtained after a (2+2) cycloaddition, leading to the metallacyclobutane intermediate **A**. The subsequent ring enlargement (**B**) and reductive elimination generates product **C**. It should be emphasized that harsh reaction conditions have to be employed to generate the cyclopentene (27 h in refluxing acetonitrile).[8]

[8]The acetonitrile boiling point is 82 °C.



Scheme 1.8

The use of aminocarbene is the reason of such a reactivity. Indeed, usually, the more common (2+1) annulation reaction takes place with a 1,3-diene and an alkoxycarbene chromium complex, affording a vinylcyclopropane.[32–34] The nature of the Fischer carbene is thus crucial for the reaction pattern. In 1997, Barluenga's group however disclosed a smooth cyclopentene synthesis using alkoxycarbene chromium complex (scheme 1.9).[35] The substitution effect on the carbene seems to be the explanation of the observed regioselectivity. The final crude product **B** is isolated after the filtration of compound **A** on a pad of silica gel. It should be noticed that the diene is easily prepared, in one step, from 2-methyl-1-ethoxy-l-buten-3-yne and morpholine.[36]



Scheme 1.9

Barluenga and Aznar also employed alkoxy(alkenyl) carbene complexes to form cyclopentenes (figure 1.1), with respectively 2-substituted butenes and 1-amino-1,3-dienes.[37,38]

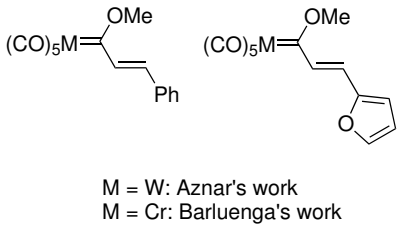
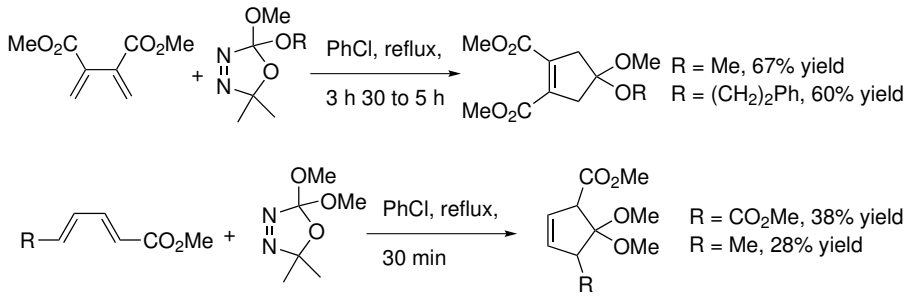


Figure 1.1

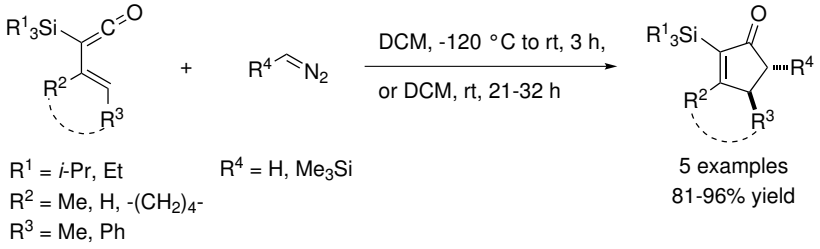
Beyond the use of Fischer carbenes, Spino and co-workers have managed, in 2004, to form cyclopentenes in one step from dialkoxycarbenes and electron-poor 1,3-dienes (scheme 1.10).[39] The thermal decomposition of oxadiazolines is giving the free dialkoxycarbenes. Whereas the reaction time is reduced compared to Hegedus and Barluenga, the required temperature is higher (chlorobenzene reflux[9]). The intramolecular version was also designed, giving bicyclic adducts in good yields and excellent diastereoselectivities.[40,41]



Scheme 1.10

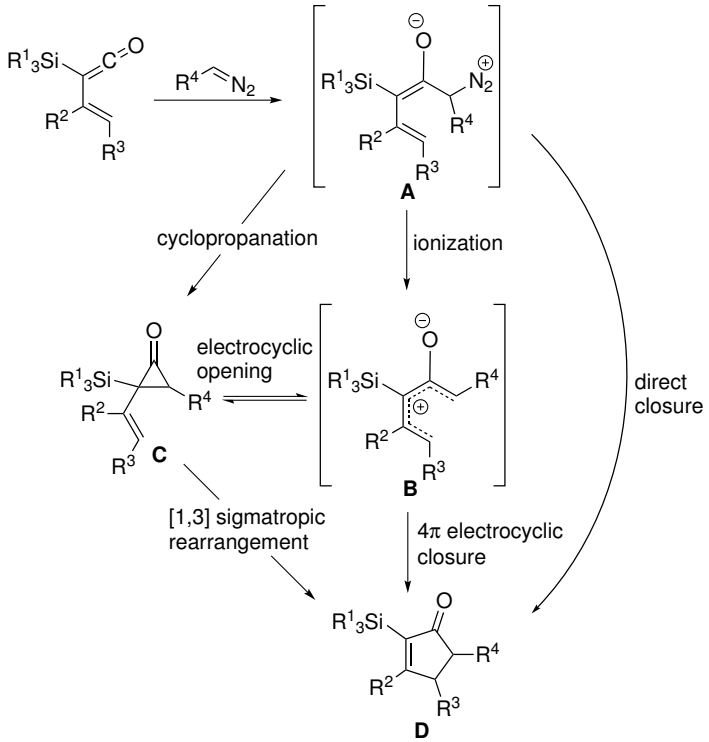
Conversely to Spino, Danheiser's group succeeded, in 1998, to form cyclopentenes in mild reaction conditions, in one-single step procedure, using diazo reagents as C1 unit, the other partner being (trialkylsilyl)vinylketenes (TAS-vinylketenes).[42] These latter are indeed well known to be versatile four-carbons fragments in annulation reactions.[43–46] For stability purpose, the vinylketene is flanked by a trialkylsilyl group. Using these two reagents, an efficient and very smooth diastereoselective (4+1) annulation reaction was disclosed, allowing access to a variety of cyclopentenones (scheme 1.11).

[9]The chlorobenzene boiling point is 132 °C.



Scheme 1.11

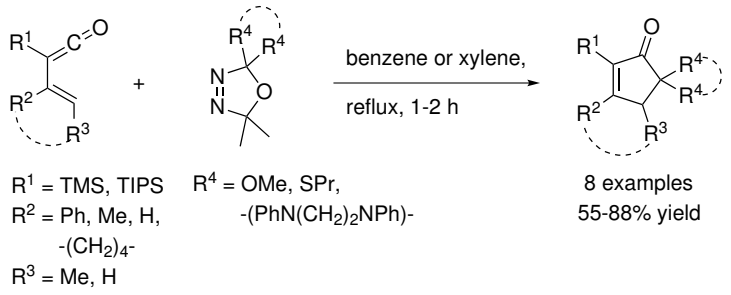
Three different pathways were proposed for this transformation (scheme 1.12). The first intermediate **A** is the same for all, resulting from the diazo compound addition. After dinitrogen extrusion, ionic intermediate **B** undergoes a 4π electrocyclic closure giving cyclopentene **D**. Another possible mechanism is the direct ring closure, giving the product without any intermediate. Finally, the vinylcyclopropanol **C** could be obtained, followed by either a [1,3]-sigmatropic rearrangement leading to the product, or an electrocyclic opening, generating ionic compound **B**.



Scheme 1.12

A few years later, Danheiser further demonstrated the feasibility of this reaction using TAS-arylketenes and diazo reagents, affording 2-indanones.[47] In 2006, Moser and co-workers disclosed a similar procedure, using highly substituted TAS-vinylketene chromium complexes.[48]

While efforts were undertaken towards the (4+1) annulation reaction between ketenes and diazo reagents, Rigby demonstrated, in 2003, an effective (4+1) annulation reaction strategy using nucleophilic carbenes (derived from the thermal decomposition of oxadiazolines), the other partner being silyl ketenes. Several cyclopentenones could be obtained, in 55-88 % yields (scheme 1.13).[49] To carry out the reaction, more drastic conditions have to be used, as the reaction mixture has to be heated for 1-2 h at reflux of benzene or xylene.[10] Though the reaction required harsh reaction conditions, various substitution patterns were tolerated.



Scheme 1.13

The use of nucleophilic carbenes in (4+1) cycloaddition/annulation reactions is not an easy task. The handling of such compounds is challenging, due to their high reactivity and the risk of carbene degradation. Moreover they exhibit a poor chemoselectivity. The Fischer carbenes solves the handling problem, but the scope remains limited and does not offer a general method. The disclosure of another carbene-like C1 unit, namely diazo compounds, increases the interest in this transformation, as more sensitive adducts could be obtained due to the very soft reaction conditions. However, the encountered chemoselectivities with those reagents are relatively low. In addition, another drawback, and not the least, comes with the use of such reagents, the threat of explosion if all precautions are not taken while handling.[11] Accordingly, alternatives to carbenes have been explored in recent years.

[10] The benzene and xylene boiling points are, respectively, 80 °C and approximately 140 °C.
[11] The propensity of dinitrogen extrusion is significant.

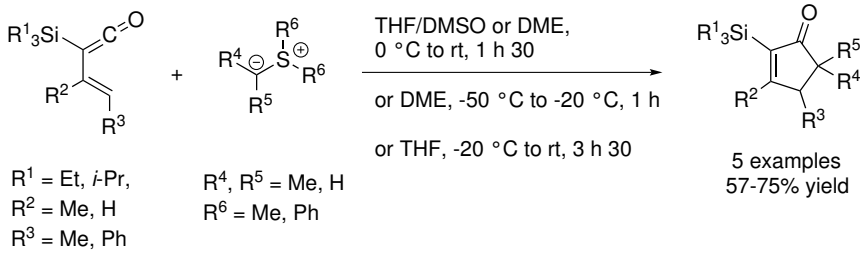
1.2.2 Other carbenoid reagents

As previously mentioned, the use of carbenes has many drawbacks. Accordingly, scientists have developed (4+1) cycloaddition/annulation reactions using other carbenoid reagents, such as ylide, α-benzotriazolyl lithium derivatives, isocyanide, or carbon monoxide.

1.2.2.1 Ylides

The ylide-mediated (4+1) cycloaddition/annulation reaction of 1,3-dienes may be another powerful strategy for the synthesis of cyclopentanoids, and a good alternative to carbenes. Furthermore, they are easy to handle and could provide good chemoselectivities. The most encountered ylides are phosphonium, ammonium, and sulfonium ylides. They have been extensively used, especially in (2+1) cycloaddition/annulation reactions in order to access aziridines, epoxides, and cyclopropanes.[50]

In his research towards an efficient (4+1) annulation reaction using TAS-vinylketenes, Danheiser's group reported that sulfonium ylides can efficiently be used as one-carbon units (scheme 1.14).[42] One must note however that only five examples were reported, with poor substitution diversity. Furthermore, depending on the substituents, various reaction conditions had to be employed.

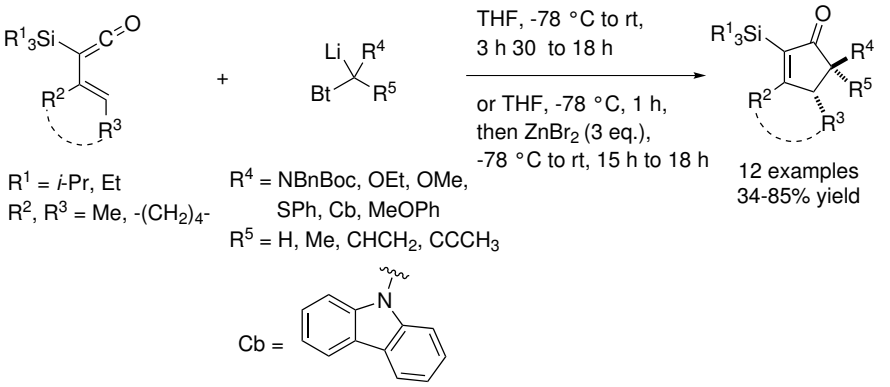


Scheme 1.14

The ylide generation is carried out by deprotonation of the corresponding iodide or tetrafluoroborate sulfonium salts, using *n*-BuLi or *t*-BuLi. Cyclopentenes formation could be explained by the same three possible mechanistic pathways as for diazo reagents (scheme 1.12 page 9), i.e. the direct cyclopentene synthesis, the ionization followed by a 4π electrocyclic closure, or the vinylcyclopropanol intermediate that can subsequently undergo a [1,3] sigmatropic rearrangement.

In 2005, Danheiser showed that benzotriazole (Bt) can also be employed, very efficiently, as a leaving group. Numerous highly substituted cyclopenten-

ones were generated very smoothly, in good yields and excellent diastereoselectivities (scheme 1.15).[51]

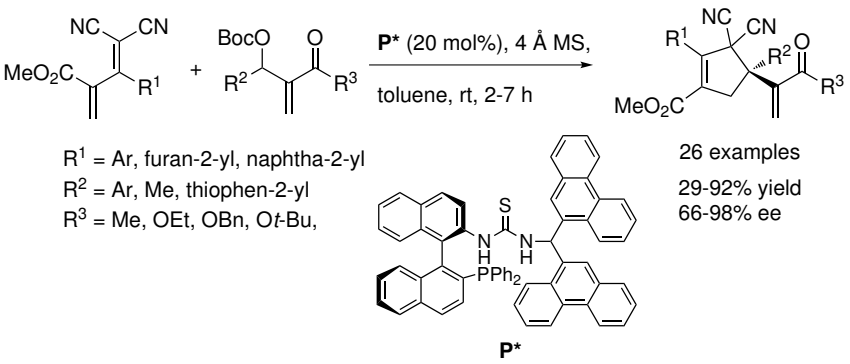


Scheme 1.15

He used *n*-BuLi as a base for the lithium salts generation. It is emphasized that this C1 unit allows a greater substitution diversity. Besides, Danheiser explained the cycloadducts formation by the same previously-mentioned mechanistic pathways as for ylide and diazo reagents.

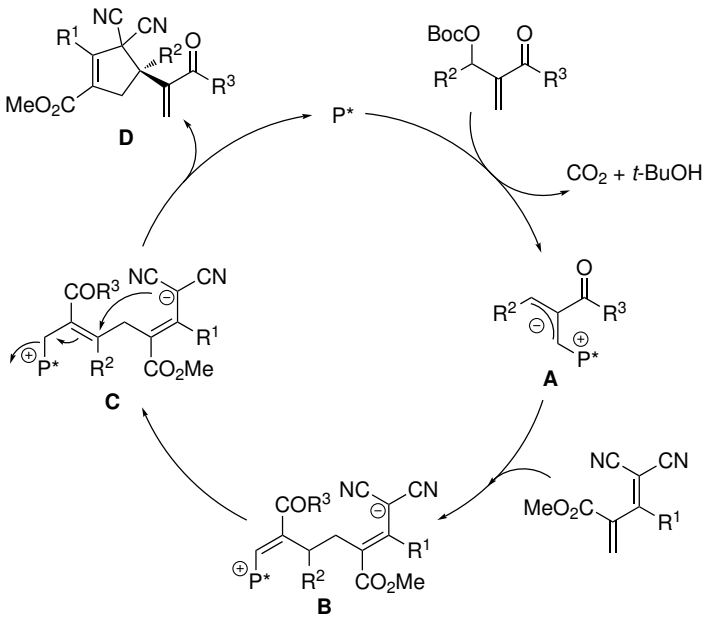
Very few phosphonium ylides are encountered in the field of annulation, probably due to the poor leaving group ability of the phosphonium moiety.[52,53] However, they also were successfully employed in (4+1) annulation reactions involving 1,1-dicyano 1,3-dienes. Indeed, Shi and co-workers used, in 2012, Morita-Baylis-Hillman (MBH) carbonates as C1 unit[12] and a chiral phosphine. He disclosed the first enantioselective (4+1) annulation reaction with MBH-carbonates (scheme 1.16).[56]

[12]Whereas such compounds are best known for their 1,3-dipole reactivity.[54,55]



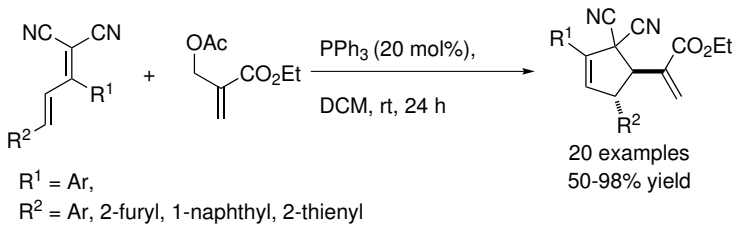
Scheme 1.16

This procedure gives highly functionalized cyclopentenes, smoothly, in relatively good yields with moderate to excellent enantiomeric excesses (ee). The chiral phosphine is obtained in eight steps from (*R*)-Binol and an isothiocyanate derivative,[57–59] whereas 1,1-dicyano-1,3-dienes are easily prepared in two steps from malononitrile, methyl propiolate, and various aldehydes.[60] Mechanistically speaking, it was postulated that the cyclopentene formation is initiated by the *in situ* ylide generation (**A**), followed by the 1,6-addition of the latter to the electron-deficient diene (**B**). The subsequent isomerization and cyclisation give the desired product **D** (scheme 1.17).



Scheme 1.17

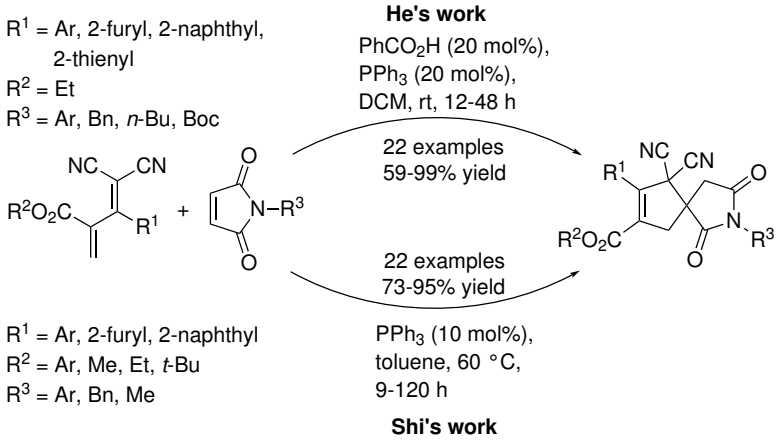
In a similar manner, He's group used other 1,1-dicyano 1,3-dienes, and a plethora of cyclopentenes were obtained at room temperature, using 20 mol% of PPh_3 (scheme 1.18).[61]



Scheme 1.18

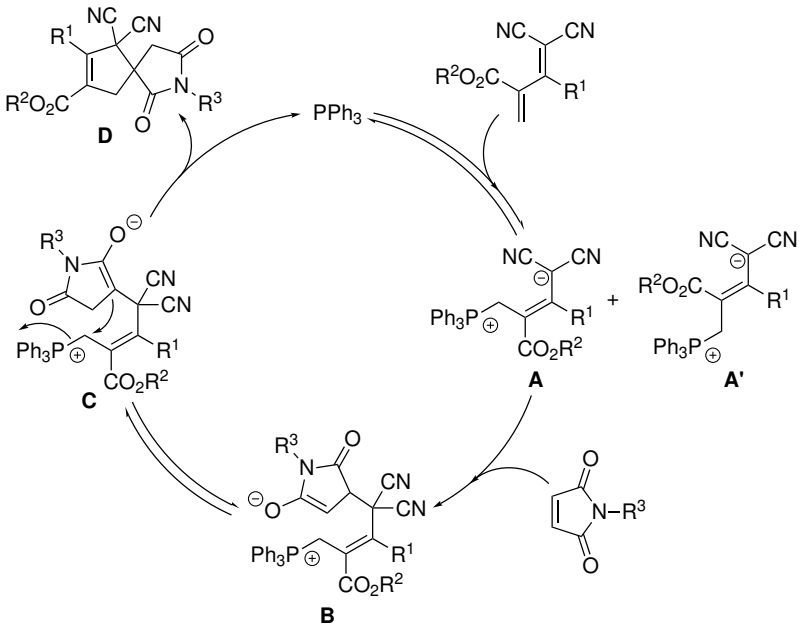
The two same groups developed in 2014 a (4+1) cycloaddition reaction strategy with maleimides as 1,1-dipole.[62,63] These latter are indeed frequently found in cycloaddition/annulation reactions, but commonly as C2 unit.[64,65] In the study in question, however, an azaspiro[4.4]nonene scaffold is reached. As it occurs in many biologically active compounds, the facile access to this structure is attractive.[66–68] Stirring for usually 12 h at a minimum of 60 °C is suitable for the Shi's reaction.[62] On the contrary, a lower temperature is employed for He and co-workers,[63] but the reaction time is longer (scheme 1.19). A large

variety of cyclopentenes could be obtained by both methods.



Scheme 1.19

They proposed a different mechanistic pathway for the formation of the aza-spiro[4.4]nonene. However, unlike He, Shi did deuterium-labeling experiments in order to support his proposed mechanism (scheme 1.20).[62] Let's remember that in the case of MBH acetates and carbonates it is postulated that the ylide is generated from the MBH adduct. However, when maleimides are used, the ylide is coming from the diene rather than the maleimide. Indeed, according to Shi, the phosphine adds to the diene, leading to ylides **A** and **A'**. Intermediate **A'** cannot be cyclised, and thus only **A** is involved in the catalytic cycle. After a nucleophilic addition on the maleimide (**B**) and an isomerization *via* proton transfer (**C**), the phosphine elimination generates spirocyclic product **D**.



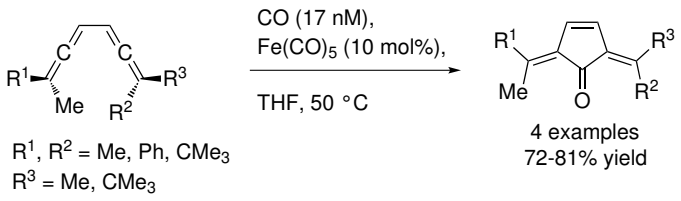
Scheme 1.20

The use of ylides in (4+1) annulation reactions with 1,3-dienes is well described, as highly functionalized silylated cyclopentenones,[42,51] allyl-substituted cyclopentenes,[56,61] or azaspiro[4.4]nonenes[62,63] could be easily and smoothly obtained, generally in good to excellent yields. In addition, the use of a chiral phosphine allows access to enantioenriched cyclopentenes.

1.2.2.2 Carbon monoxide

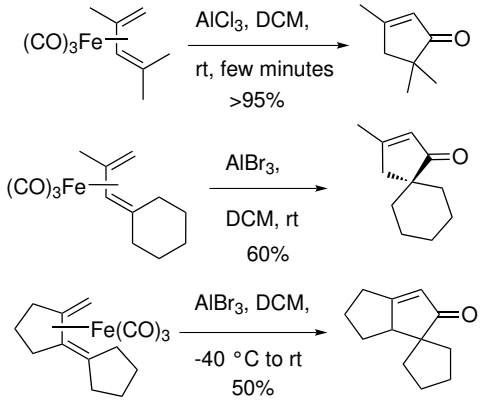
Carbon monoxide as one atom unit is another strategy to afford cyclopentenes. This reagent has been used for a long time in cycloaddition reactions.[69,70] It represents a cheap, readily available, and important C1 feedstock.

Eaton, in 1992, reported the first transition metal-catalyzed (4+1) cycloaddition reaction, using $Fe(CO)_5$ as a catalyst and diallenes as four-carbons unit, allowing access to 2,5-bis(methylene) cyclopentenones, in good yields (scheme 1.21).[71]



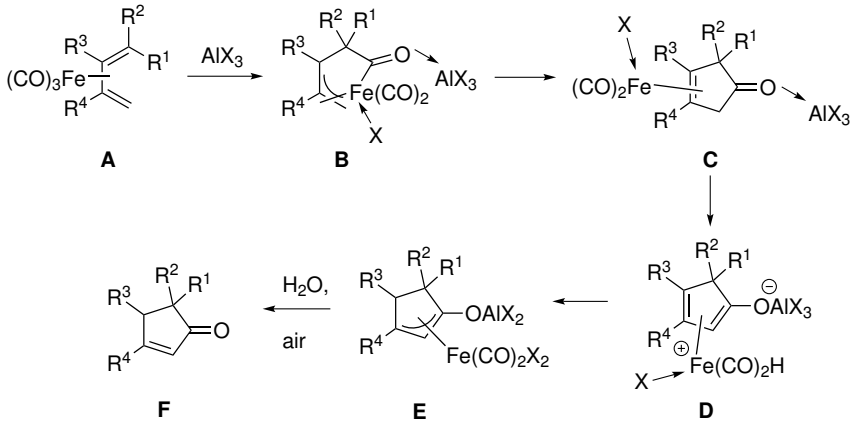
Scheme 1.21

On the other hand, Thompson described, in 1974, the decomplexation of iron complexes using aluminium chloride.[72] Inspired by this discovery, Frank-Neumann synthesized, in 1992, a cyclopentenone in mild conditions, in good yields, and in the absence of CO atmosphere. He then further explored this area of research with differently-substituted dienes, leading to spirocyclic or fused cycloadducts (scheme 1.22.[73,74] However, the functional groups tolerance was not tested. It is noteworthy that the diene must not be substituted at the C4 position.



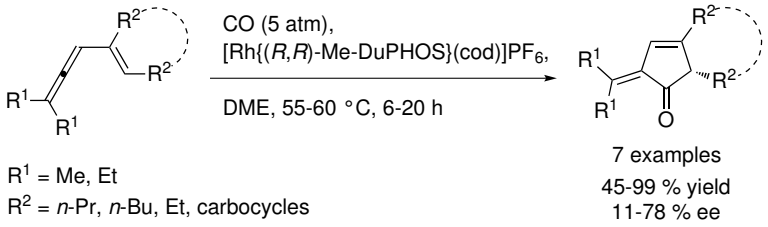
Scheme 1.22

The mechanism was postulated to proceed *via* an intermediate acyl π-allyl complex **B** (scheme 1.23), followed by a cyclisation to give compound **C**. A subsequent CH insertion leads to **D**, and then the formation of a π-allyl aluminium alcoholate iron halide **E**. The final decomplexation provides product **F**.[73]



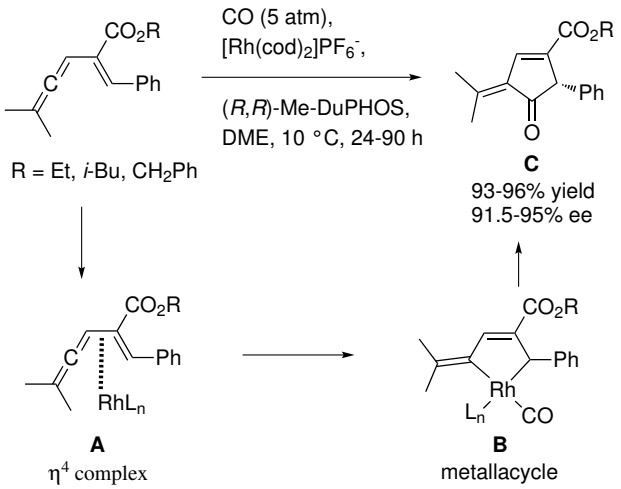
Scheme 1.23

Besides iron, Ito obtained, in the late 90's, various cyclopentenones using a rhodium catalyzed asymmetric (4+1) cycloaddition reaction, with cyclic and non-cyclic vinylallenes, in very good yields but poor enantiomeric excesses (scheme 1.24).[75,76]



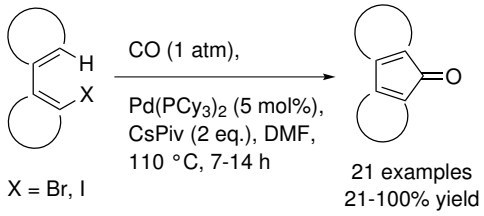
Scheme 1.24

Interestingly, the change of rhodium to platinum gives the opposite configuration, with a slight increase of enantioselectivity. He noticed however that an ester group on the vinyl moiety increases drastically the ee, and allows smoother reaction conditions (scheme 1.25). Mechanistically speaking, he highlights the η^4-coordination of the vinylallene in a *cis* conformation to rhodium (**A**) before the CO insertion. As compared to the two previous examples from Eaton and Neumann, a more general, high yielding, and enantioselective (4+1) cycloaddition reaction was discovered.



Scheme 1.25

In early 2000's, Larock and co-workers disclosed a palladium-catalyzed (4+1) annulation reaction using *o*-haloaryl compounds, allowing access to a plethora of fluorenones in moderate to excellent yields (scheme 1.26).[77,78] Although twenty-one cyclopentenones were successfully synthesized, almost no functionalized substrates were tested. In addition, drastic reaction conditions were employed (7-14 h at 110 °C). The cyclopentene's synthesis was postulated to proceed through a palladium-catalyzed carbon monoxide insertion, followed by a subsequent CH activation and finally a reductive elimination. In 2003, he applied this strategy to numerous styrenes derivatives using different reaction conditions.[79]



Scheme 1.26

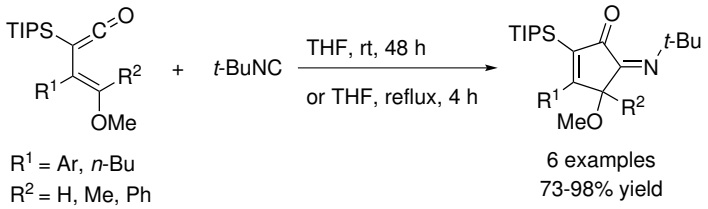
The cyclopentenones synthesis *via* carbonylative (4+1) cycloaddition reactions between 1,3-dienes and carbon monoxide generated only little interest, even if more general methods appeared in late 90's[75,76] and early 2000's.[77–79] A possible explanation for this observation is the Danheiser discovery, over the same period, of ylides- and diazo-mediated (4+1) annulation reactions,[42] al-

lowing to easily access cyclopentenones, in good to excellent yields, using a metal-free procedure and very smooth reaction conditions. However, more recently, numerous 2-methylene cyclopentenones syntheses by a Rh-catalyzed carbonylative (4+1) annulation reaction were reported, but using enyne esters as C4 units (see further, pages 25-27).

1.2.2.3 Isocyanides

Carbon monoxide could be substituted by isocyanide as a C1 unit. Indeed, this latter has a similar structure and an analogous reactivity profile as compared to carbon monoxide, with the benefits over this latter to be non-gaseous.[13] As a consequence, numerous examples of isocyanide-based (4+1) cycloaddition/annulation reactions are found in the literature, but mostly to perform heterocycles.[25]

Moser and co-workers reported, in 2007, a (4+1) cycloaddition reaction strategy using *tert*-butyl isocyanide as 1,1 dipole, and TAS-vinylketenes as four carbons unit, without any catalyst, allowing access to various highly substituted cyclopentenones, in good to excellent yields (scheme 1.27).[80] The isocyanide nucleophilic addition onto the ketene, followed by a cyclisation process, leads to the cyclopentenone.

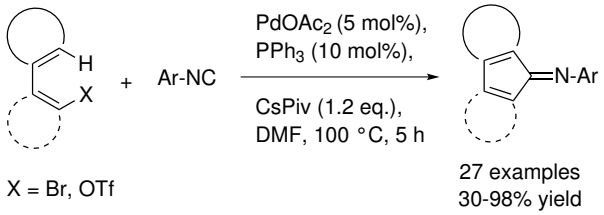


Scheme 1.27

Three years later, in the extension of the Larock carbonylative (4+1) cycloaddition reactions (see page 19),[77–79] Chatani's group reported a (4+1) cycloaddition reaction between numerous biaryls and aryl-substituted isocyanides (scheme 1.28).[81] The protocol also supports arylstyrenes and heterobiaryls as four-carbons unit, as well as various functional groups. The mechanistic explanation is similar to that of Larock's work.[14]

[13] The horrible smell of isocyanides, added to their high toxicity, are however negative aspects of using such compounds.

[14] A palladium-catalyzed isocyanide insertion, followed by a subsequent CH activation and finally a reductive elimination.



Scheme 1.28

In summary, although very few reports of isocyanide-based cyclopentanoids syntheses *via* (4+1) cycloaddition/annulation reactions with 1,3-dienes are found in the literature, the procedure of Moser[80] furnishes highly substituted and structurally interesting cyclopentenones, in good to excellent yields. Regarding the Chatani's strategy,[81] its high similarity to the Larock carbonylative (4+1) annulation reaction[77–79] (see page 19) makes both procedures very interesting methods to obtain indene derivatives, fluorenones, and 9-fluorenone Schiff base derivatives (despite the harsh required reaction conditions). In addition, the discovery, during the same period, of cyclopenteneimine synthesis *via* a palladium-catalyzed (4+1) annulation reaction strategy of various 5-methylene δ-valerolactones and isocyanides[82] (see further, page 28) increases the importance of this C1 feedstock in (4+1) cycloaddition/annulation reactions.

The use of 1,3-dienes in (4+1) cycloaddition/annulation reactions draws the scientists attention since the 80's, where Danheiser disclosed the two-step procedure of cyclopentenes synthesis by vinylcyclopropanes rearrangement (see page 5).[27] Since then, huge efforts have been undertaken to carry out facile and general cyclopentanoid syntheses in one step, smoothly, in high chemical yields, such as the Danheiser benzotriazole-mediated (4+1) annulation reaction strategy with vinylketenes,[51] accessing silylated cyclopentenones, as well as the He and Shi's works on allyl-substituted 1,1-dicyano cyclopentenes[56,61] and azaspiro[4.4]nonenes[62,63] syntheses starting from 1,1-dicyano 1,3-dienes and phosphonium ylides. Finally, the Moser isocyanide-mediated (4+1) cycloaddition reaction strategy has to be mentioned, despite the limited scope of the reaction, allowing access to structurally interesting silylated cyclopentenones in good to excellent yields.[80]

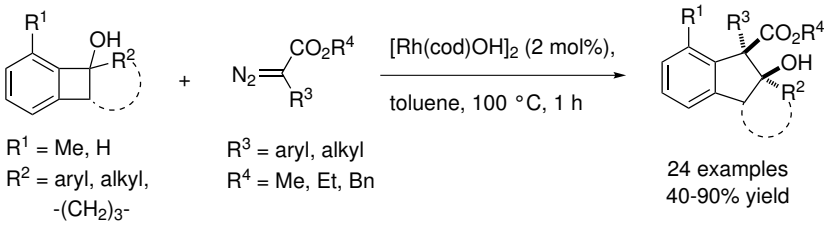
After reviewing the 1,3-dienes, we are now focusing our attention on other C4 units scaffolds.

1.2.3 Other four-carbon units

Although the use of other C4 skeletons than 1,3-dienes for (4+1) cycloaddition/annulation reactions appeared in the mid 80's,[83,84] the research in this specific area increased only a few years ago. A large variety of C4 structures are involved, such as enyne esters, cyclobutenes, and allenoates derivatives.

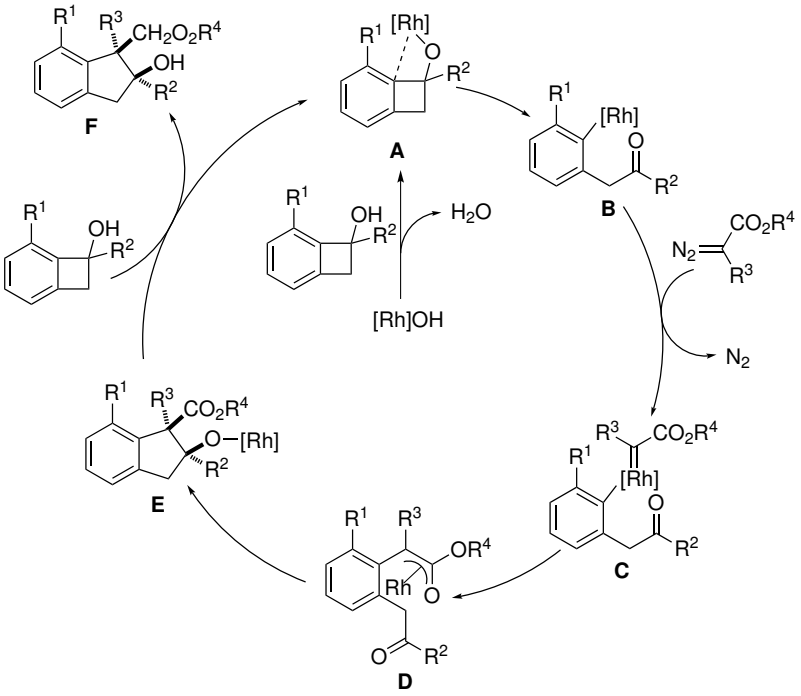
1.2.3.1 Four-membered ring expansions

In 2014, Wang and his co-workers envisioned a C-C bond insertion onto benzocyclobutenols, using diazo compounds as C1 unit, leading diastereoselectively to numerous indanols, in moderate to excellent yields (scheme 1.29).[85] The required benzocyclobutenols are obtained from Grignard addition onto corresponding benzocyclobutenones. It is emphasized that diazo compounds have to be manipulated at high temperature (100 °C), making this strategy less interesting for accessing these structures.



Scheme 1.29

The C-C bond cleavage and the rhodium carbene migratory insertion are the key steps of this (4+1) annulation reaction (formation of **B** and **D** respectively in the catalytic cycle represented below, scheme 1.30). After the initial arylrhodium specie **B** formation, this latter reacts with the diazo compound, generating carbene **C**. The subsequent migratory insertion affords the oxa-π-allyl Rh(I) intermediate **D**, followed by a diastereoselective intramolecular aldol reaction to furnish *cis* isomer **E**. Finally, the final product **F** is obtained after a protonation by the starting material.



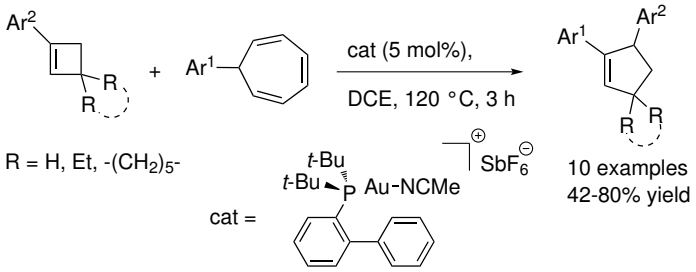
Scheme 1.30

A few months later, Murakami's group disclosed an enantioselective version of this reaction, by means of the same rhodium complex as Wang, and a chiral ligand.[86] It is emphasized that the two diastereoisomers are accessible through the use of (*R*)-SEGPHOS or (*R*,*S*)-PPF-P(*t*-Bu)$_2$ ligands. Very high enantioselectivities could be reached with this methodology (>92 % ee). Moreover, softer reaction conditions were employed.[15]

In a totally different manner, Echavarren reported, the same year, a gold(I) rearrangement of bicyclo[2.1.0]pentanes (synthesized from cyclobutenes[16] and gold(I) carbenes), to their corresponding cyclopentenes (scheme 1.31).[87] The gold(I) carbenes are generated from retro-Buchner reaction of 1,3,5-cycloheptatrienes. Therefore, the metal plays a double catalytic role, as it allows the generation of the carbene as well as carries out the rearrangement process.

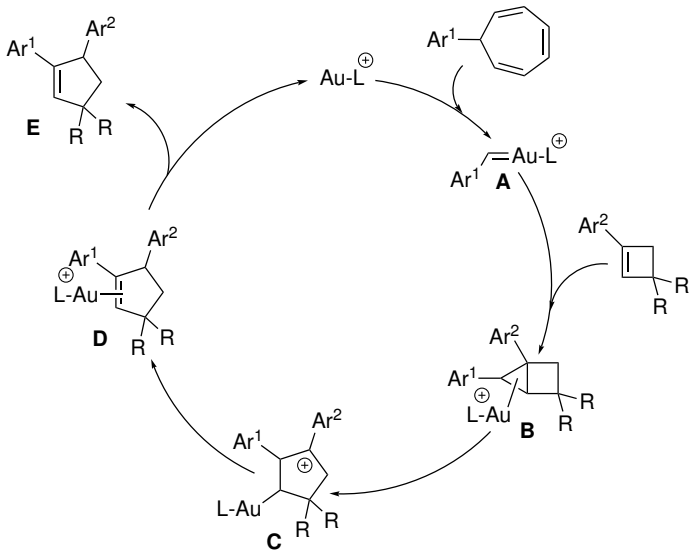
[15] 24-48 h of stirring at 50 °C.

[16] Interestingly, the C4 skeleton could be replaced by methylenecyclopropanes.[87]



Scheme 1.31

From a mechanistic point of view, as depicted in scheme 1.32, in a first step, a ligand exchange followed by the retro-Buchner reaction gives the gold(I) carbene complex **A**, which reacts with the cyclobutene in order to form the bicyclo gold(I) complex **B**. In a subsequent step, cationic intermediate **C** is formed after opening of the gold(I)-catalyzed cyclopropane. In the last steps, a [1,2]-H shift gives the complex **D** which, after decomplexation, affords product **E**.

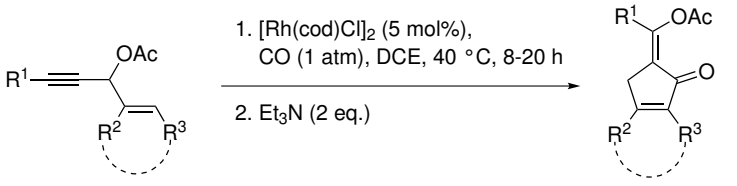


Scheme 1.32

The low functionalized cyclopentenes, as well as the required harsh reaction conditions, make this strategy not very powerful.

1.2.3.2 Rhodium-mediated carbonylation with enyne esters

In the field of metal-catalyzed cycloaddition reactions, Tang's group disclosed, in 2012, that 1,4-enynes could be successfully used as C4 units in carbonylative (4+1) cycloaddition reactions, affording highly substituted and structurally interesting methylene cyclopentenones, with a preferred *Z* selectivity (scheme 1.33).[88] To do so, chloro(1,5-cyclooctadiene)rhodium(I) complex is used as a catalyst, under 1 atm of CO at 40 °C. It is noteworthy that, conversely to the other carbonylative strategies generating similar structures,[71,75,76] 2-cyclopentenones are obtained in this case, whereas 3-cyclopentenone derivatives are generated with the other methods.

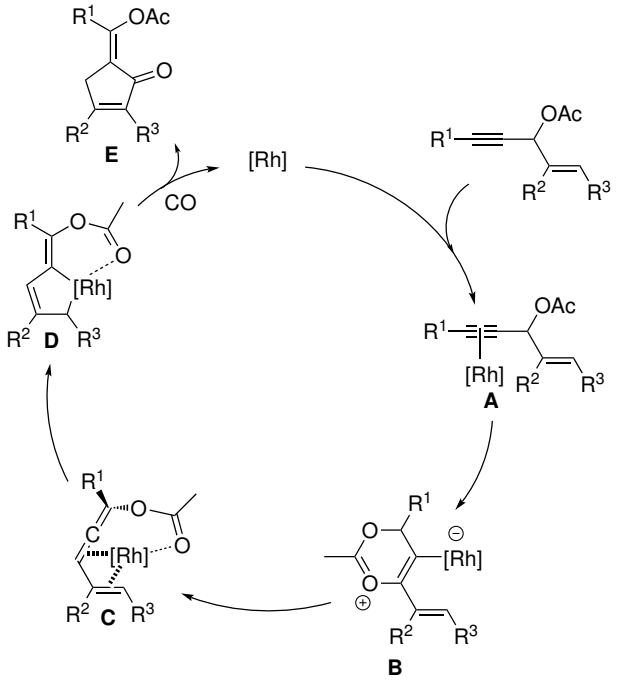


R^1 = $Ph(CH_2)_2$, *n*-Pent, $BnO(CH_2)_2$, $TBSO(CH_2)_2$
R^2 = Me, Et, Ph; R^3 = Me, *n*-Bu, Ph
or R^2,R^3 = $(CH_2)_n$, n = 3, 4, 5

13 examples
48-86% yield
Z/*E*: 3/1 to 17/1

Scheme 1.33

They explained the cyclopentenone synthesis by a Rh-catalyzed 1,3-acyloxy migration to form allene **C** (scheme 1.34). The more-favored metallocyclopentene **D** is then obtained, which, after CO insertion, reductive elimination and isomerization, affords the *Z*-isomer of cyclopentenone **E**.

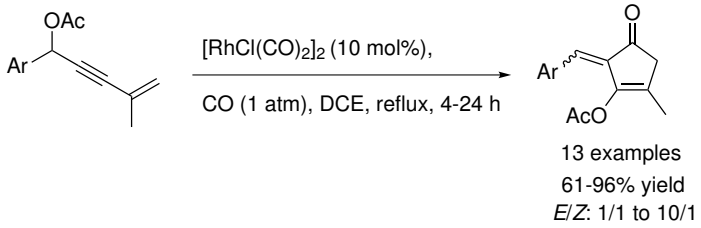


Scheme 1.34

In a similar manner, Malacria, Fensterbank, Fukuyama, Ryu and their coworkers worked with less substituted enynes, using the same catalyst, in harsher conditions, to obtain a mixture of *E* and *Z* cyclopentenones.[89]

Interestingly, the strategy could be extended to 1,3-enynes, using the catalyst $[RhCl(CO)_2]_2$ in refluxing 1,2-dichloroethane,[17] as described by Yu and Pu (scheme 1.35).[90] However, the minimal substitution pattern as well as the higher required temperature are not positive aspects of this strategy. Indeed, similar structures could be obtained using the Ito's carbonylative (4+1) cycloaddition strategy,[75,76] in softer reaction conditions (see page 18), but without the acetate functional group substitution, which could however be interesting for further transformations.

[17] The 1,2-dichloroethane boiling point is 83 °C.

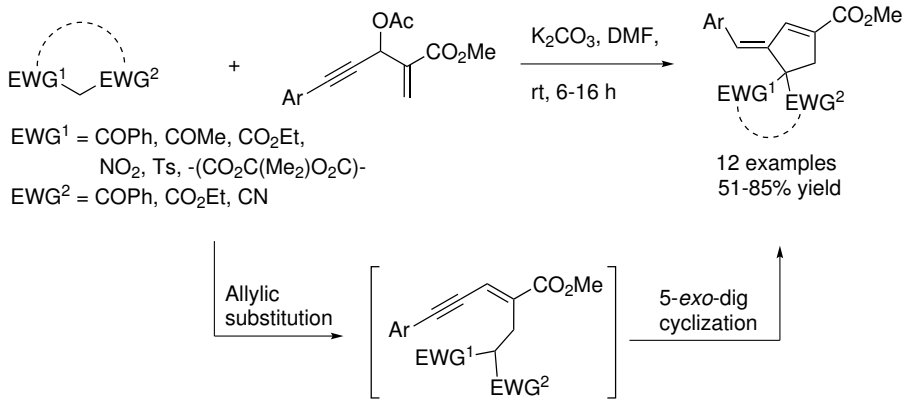


Scheme 1.35

1.2.3.3 MBH acetates

In line with the previously mentioned method where 1,4-enynes are used (see page 25),[88] Reddy and co-workers employed, in 2012, MBH acetates as C4 units, and different 1,1'-bis-nucleophiles, in a mild base-mediated metal-free (4+1) annulation reaction, affording arylidene cyclopentenes in good to high yields (scheme 1.36).[91] A variety of 1,1-bis-activated C1 units were well tolerated, as well as electron-donating and electron-withdrawing aryl moieties on the C4 unit. In addition, the ready availability of starting materials has to be mentioned.

Interestingly, the reaction was postulated to proceed *via* a 5-*exo*-dig rearrangement, after an allylic substitution.



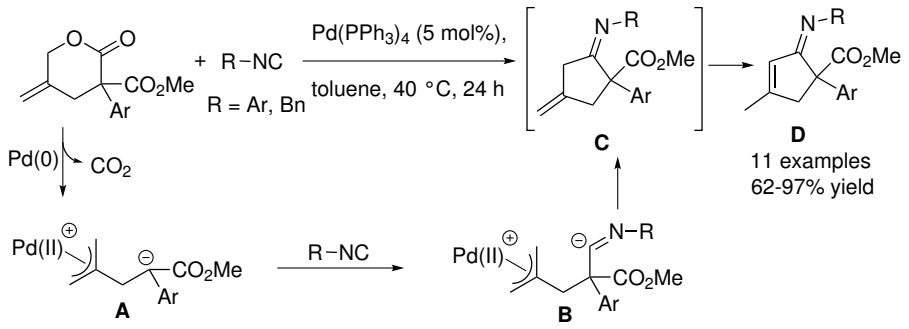
Scheme 1.36

1.2.3.4 5-methylene δ-valerolactones

Conversely to the previous examples on isocyanide-based (4+1) cycloaddition/annulation reactions (pages 20-21),[80,81] Hayashi and Shintani highlighted, in 2009, a mild procedure to access cyclopenteneimines. Indeed, this strategy

involves more reactive 1,4-zwitterionic compounds (generated from δ-valerolactones) and isocyanides (scheme 1.37).[82] This palladium-catalyzed (4+1) annulation reaction affords cyclopenteneimines in good to excellent yields, despite the low functional variation (only aromatics).

It was postulated that the reaction goes through the initial palladium-assisted lactone decarboxylation to obtain zwitterionic specie **A**, followed by the addition on the isocyanide (**B**). Subsequent ring closure and reductive elimination afford cyclopenteneimine intermediate **C**, that undergoes an olefin isomerization to yield conjugated isomer **D**.



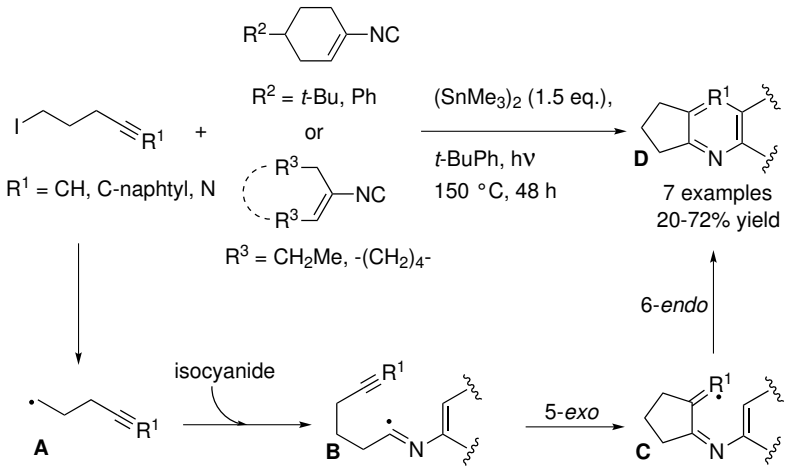
Scheme 1.37

1.2.3.5 Iodoalkynes

Besides cyclopentenimines synthesis previously mentioned in this manuscript, where isocyanides are employed as nucleophiles and electrophiles, these latter also could undergo radical processes. Indeed, Curran and Nanni employed them, in the 90's, as one-carbon units, respectively in tandem radical (4+1) annulation/intermolecular cyclisation reactions with iodoalkynes[92] and iodonitriles,[93] leading to cyclopenta-fused quinolines and quinoxalines in moderate to good yields. The reaction was initiated by $(SnMe_3)_2$ and sunlamp irradiation. Tricyclic structures could be easily synthesized using this methodology. It is interesting to note that the enantioselective synthesis of the antitumoral compound (20S)-camptothecin and its analogues could be successfully achieved using this strategy.[94] However, only aromatic isocyanides were involved in these reactions.

In 2000, Smith and Lenoir extended the scope of this methodology to vinyl isocyanides, using similar reaction conditions (scheme 1.38).[95] From a mechanistic point of view, alkyl radical **A** is obtained after the reaction with the initiator, followed by the nucleophilic addition on the isonitrile carbon to lead

intermediate **B**. The subsequent 5-*exo*-dig and 6-*endo*-trig cyclisations generates the final product **D**.



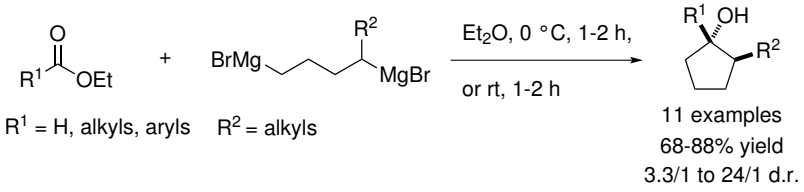
Scheme 1.38

However, the harsh reaction conditions (irradiation for 36 h or 48 h at 150 °C, which should impact the functional groups tolerance[18]), added to the relatively moderate chemical yields, limit the interest in this methodology. Nevertheless, it is noteworthy that complex fused-carbocyclic structures are easily synthesized by these methods.

1.2.3.6 1,4-bis-Grignard reagents

Most of the mentioned strategies involves 1,4-dipole synthons as C4 units, but other reaction schemes could be envisioned. Accordingly, in the late 80's, Cannonne and co-workers disclosed an efficient diastereoselective (4+1) annulation reaction between 1,4-bis Grignard reagents (prepared from the corresponding dibromides derivatives) and various ethyl ester compounds as one carbon units, leading smoothly and diastereoselectively to cyclopentanols (rather than the more encountered unsaturated 5-membered cycles), in good yields (scheme 1.39).[96,97] The observed stereoselectivities are determined at the cyclisation step, i.e. the second Grignard nucleophilic addition.

[18]Smith and Lenoir employed unsubstituted substrates, whereas only halides- and methoxy-substituted substrates were used by Curran and Nanni.



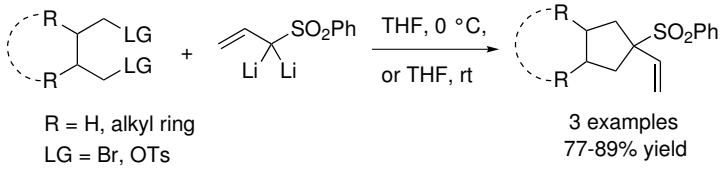
Scheme 1.39

Although efficient, this is the only (4+1) annulation reaction strategy involving 1,4-bis-nucleophiles as four-carbons units. The handling of Grignard substrates, limiting the functional groups tolerance, as well as the discovery of other more powerful strategies in the subsequent years are probably the reasons for the lack of interest in this methodology. It is however emphasized that the handling of highly reactive molecules allows soft reactions conditions, as a stirring for 1-2 h at 0 °C or room temperature generates the products in the indicated yields.

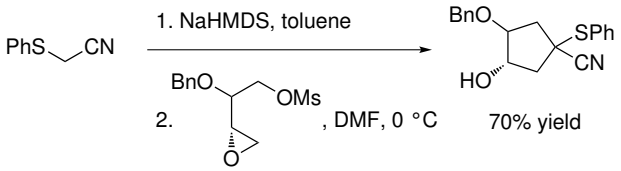
1.2.3.7 1,4-bis-electrophiles

In contrast to the previous strategy where 1,4-bis-nucleophiles reagents were employed, one can envision the opposite reactivity profile, where 1,4-bis-electrophiles C4 units are reacting with 1,1-bis-nucleophiles one-carbon units. The research in this specific area has been fruitful, and one can divide it in three main strategies, that we are going to discuss.

Gais, Lukas and co-workers designed, in 1985, C4 units that are 1,4-disubstituted by leaving groups. By means of 1,1-dilithioallyl phenyl sulfone (prepared from allyl phenyl sulfone and *n*-BuLi), an effective (4+1) annulation reaction could be achieved (scheme 1.40a).[83] The same year, Géro highlighted the use of an epoxide as a leaving group. Derived from (*R*,*R*)-(+)-tartaric acid, this chiral epoxide lead to an optically pure cyclopentanoid, using (phenylthio)acetonitrile as C1 feedstock, and NaHMDS as a base (scheme 1.40b).[84]



(a) Gais' work

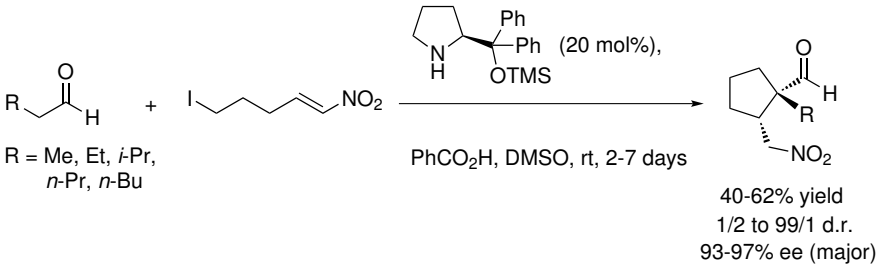


(b) Géro's work

Scheme 1.40

Although the substrate scope of these two reactions schemes are notably low, they represent an easy way to smoothly synthesize cyclopentanes. An interesting feature is the presence of a vinyl or a hydroxy functional group, that allows further chemical modifications. The highly basic reaction conditions are a clear weakness for these two types of reaction.

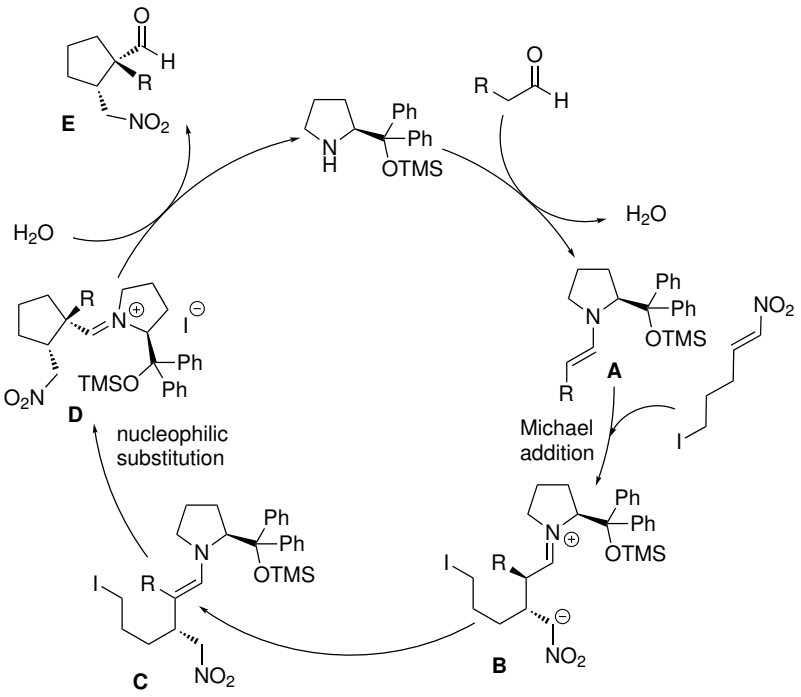
In the extension of these works, one can envision a second strategy, resulting from a Michael addition/nucleophilic substitution sequence. In this perspective, Enders explored, in 2008, an enamine-catalyzed enantioselective (4+1) annulation reaction between aliphatic aldehydes and (1*E*)-5-iodo-1-nitropent-1-ene, affording cycloadducts in moderate yields and excellent enantiomeric excesses (scheme 1.41).[98] It is noteworthy that the reaction times were especially long.



Scheme 1.41

As outlined in scheme 1.42, the initial formation of the chiral enamine **A** enables the Michael addition step (*via* the *Si* face at Cα of the enamine),

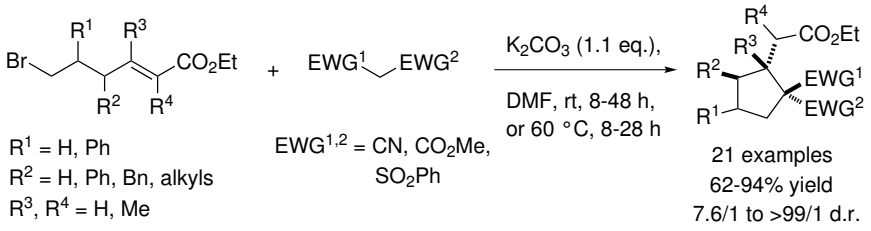
giving the chiral iminium **B**. Subsequent proton transfer yields the requisite intermediate **C** for the nucleophilic substitution step (also occurring from the *Si* face at Cα of the enamine), affording chiral iminium **D**. Finally, hydrolysis of the latter leads to the (4+1) annulation product **E** and the release of the amine catalyst.



Scheme 1.42

The presence, in the product, of a nitro and an aldehyde group is interesting as it allows further functional modifications. The highly enantioselective character, as well as the readily available chiral inducer are also positive aspects of this transformation. However, this strategy has some limitations such as reaction times, the moderates chemical yields and a limited substrates scope.

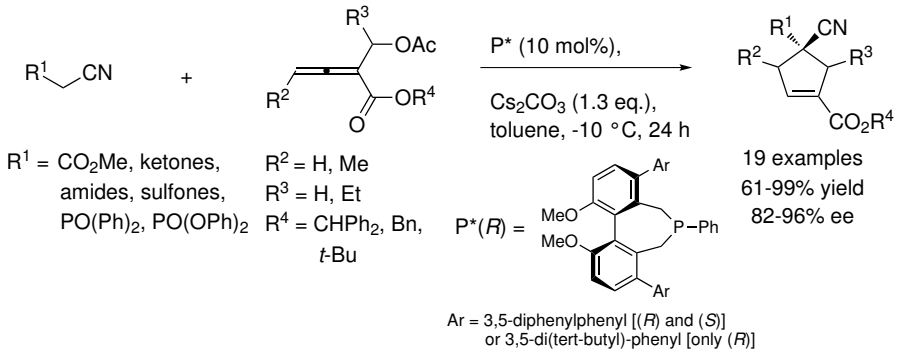
But four years later, Chiba's group reported the synthesis of highly-substituted cyclopentanes from several ethyl (2*E*)-6-bromohex-2-enoate derivatives and various 1,1-bis-nucleophiles (scheme 1.43).[99]



Scheme 1.43

Although non-enantioselective, the large scope of this reaction has to be emphasized, and the usually high diastereoselectivities encountered. Moreover, the reaction proceeds smoothly,[19] and furnishes the products in good to excellent yields,[20] making this reaction a very interesting method for cyclopentanoids synthesis.

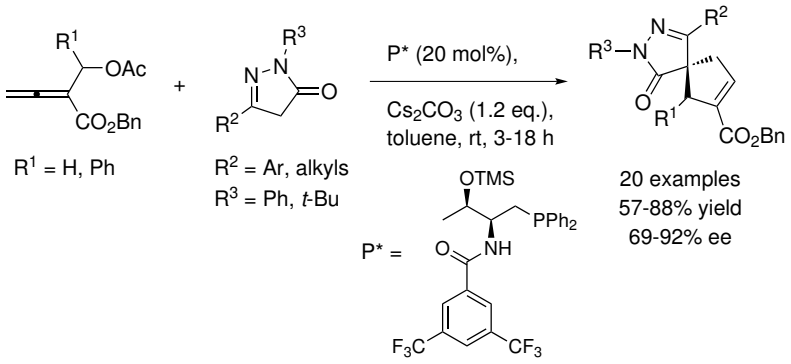
The third and last strategy using 1,4-bis-electrophiles as C4 units involves allenoate-derived MBH acetates derivatives and a phosphine catalyst. This strategy was for the first time reported by Tong and co-workers, in 2010.[100] More recently, Fu highlighted an enantioselective version of this reaction, in very smooth conditions, using 2-substituted acetonitriles and bisphenyl phosphine chiral ligands, affording numerous cyclopentenes, in 61-99 % yield and good to high enantioselectivities (scheme 1.44).[101]



Scheme 1.44

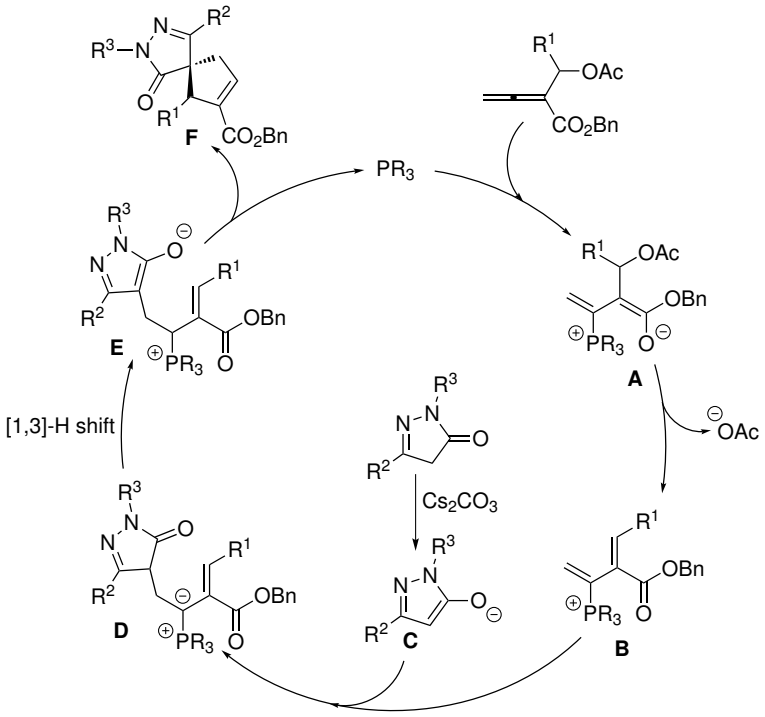
Lu used a similar procedure to easily and smoothly access enantioenriched spiropyrazolones in 57-88 % yield and relatively high enantioselectivities, starting from various pyrazolones as C1 units (scheme 1.45).[102]

[19] Except for three substrates where an eating at 60 °C is required.
[20] For one substrate, the product is isolated in only 13 % yield.



Scheme 1.45

The mechanistic explanation of this phosphine-catalyzed (4+1) annulation reaction is depicted in scheme 1.46. The allenoate is first subjected to the phosphine nucleophilic addition, affording intermediate **A**. The subsequent acetate elimination gives 1,3-diene **B**, followed by the anion-derived pyrazolone (**C**) addition, leading to phosphonium ylide **D**. In last steps, a hydrogen shift and a Michael addition generate the spirocycloadduct **F**, and the release of the chiral phosphine catalyst.



Scheme 1.46

Although on these two reaction schemes the chemical variations on the allenoate-derived MBH acetates is weak, the functional groups tolerance on the C1 feedstock is to emphasize, as various cyclic and non-cyclic activated compound can be successfully employed. In addition, the good to excellent yields and the observed enantioselectivities make this strategy a highly efficient method for the preparation of 4,4-bis-substituted cyclopent-1-ene-1-carboxylates derivatives (figure 1.2).

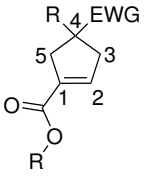


Figure 1.2

The substitution variation is however much lower on the 3 and 5 positions. Using MBH acetates, the previously mentioned procedure of Reddy allows access to 3-arylidene-substituted scaffolds, in similar reaction conditions

(page 27), but in a non-enantioselective manner. Also mentioned, the procedure of Shi generates softly highly 3 and 5 substituted similar structures (with the double bond displacement), enantioselectively, *via* a phosphonium ylide-mediated (4+1) annulation reaction (page 13). One then has access to a multitude of procedures to generate, enantioselectively or not, this important scaffold.

In summary, since the early 80's when Danheiser discovered a two-step formal (4+1) annulation reaction leading to 3-cyclopenten-1-ol derivatives from nucleophilic carbenes C1 units and 1,3-dienes,[27] scientists have made huge efforts in the development of a mild, general, and facile (4+1) cycloaddition/annulation procedure allowing the synthesis of cyclopentanoids. Thereby, numerous four and one carbon units have been elaborated and successfully engaged in the reaction. In the 90's, several one-step procedures have been discovered, starting from 1,3-dienes and more stable Fischer carbenes,[29,35] but a major breakthrough appeared in 1998 when Danheiser and co-workers disclosed an efficient diazo-, and ylide-based (4+1) annulation reaction, leading very smoothly, in good yields, to 2-(silylated)cyclopent-2-en-1-one derivatives, starting from vinylketenes (**A**, figure 1.3).[42] A few years latter, he further improved this strategy using benzotriazole lithium reagents as C1 unit.[51] In late 90's and during the 2000's, a plethora of (4+1) cycloaddition/annulation reactions strategies were discovered, leading to a large variety of cyclopentanoid scaffolds. However, most of them present strong limitations such as a low functional groups tolerance, a high substrate complexity, and/or harsh reaction conditions. But since 2010, more interesting strategies appeared. Indeed, Tang and co-workers could access numerous 2-oxocyclopent-3-en-1-ylidene methyl acetate derivatives *via* a rhodium-mediated carbonylation of enyne esters (**B**, figure 1.3).[88] The other strategies all involved 1,1-bis-activated C1 units. Thereby, 4,4-bis-substituted cyclopent-1-ene-1-carboxylates derivatives (**C**, figure 1.3) were obtained by Reddy,[91] Tong,[100] Fu,[101] and Lu (generating **C** spirocyclic similar structures),[102] from MBH acetates and allenoate-derived MBH acetates as 1,4-bis-electrophile units, using cesium or potassium carbonate as a base. Interestingly, enantioselective versions are reachable.[101,102] Chiba, meanwhile, employed several ethyl (2*E*)-6-bromohex-2-enoate derivatives as bis-electrophile units, leading to various 1,1-bis-activated cyclopentanes of type **D** (figure 1.3).[99] Finally, *via* a phosphonium ylide (4+1) annulation reaction strategy, Shi and He obtained a plethora of 3,3-dicyanocyclopent-1-ene-1-carboxylate derivatives (**E**, figure 1.3), structurally similar to **C**,[56,62,63] with

various 1,1-dicyano-1,3-dienes. It is noteworthy that enantioenriched products could be obtained using a chiral phosphine.[56]

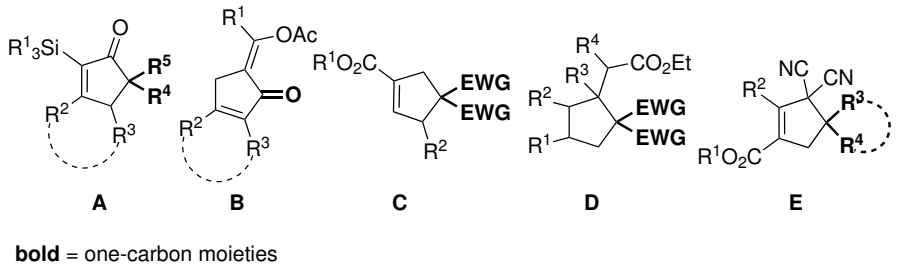


Figure 1.3

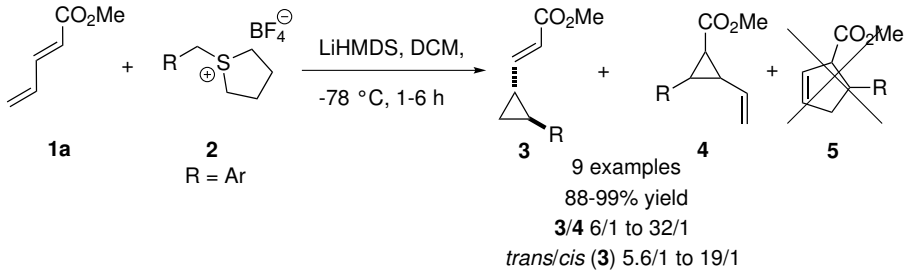
Despite impressive advances in this area of research, there are still many challenges to solve. Being usually the active substrate in the reaction (mostly as carbene, ylide, and bis-nucleophiles), the choice in the C1 unit scaffold is a key point of either the reaction pattern, the functional groups tolerance, the required reaction conditions, or the easy achievement of an enantioselective version. It is still challenging to develop a (4+1) cycloaddition/annulation reaction strategy involving versatile C1 units, in mild reaction conditions, and allowing facile asymmetric syntheses. Indeed, except for the Danheiser ylide-mediated (4+1) annulation reaction strategy (**A**, figure 1.3), which does not allow enantioselective syntheses, only bis-activated and carbon-monoxide C1 units are employed for all the other major breakthroughs (figure 1.3, **B**-**E**). This prompted our laboratory to address these challenges, in order to carry out (4+1) annulation reaction smoothly and easily, with versatile C1 units, allowing the facile access to optically-enriched cyclopentanoids.

1.3 Preliminary results of the laboratory

With the previously mentioned challenges in mind, our laboratory envisioned the use of sulfur ylides as C1 unit for developing (4+1) annulation reactions. Indeed, sulfur ylides have been reported to be effective in epoxidation,[103–106] cyclopropanation,[53,103,107] and aziridination reactions.[104,108] Moreover, they exhibit some benefits over carbenes, such as their interesting chemoselectivities, their easy handling and generation from the corresponding salts, and the facile accessibility to chiral sulfur ylides, allowing to carry out asymmetric syntheses.[108–110]

Our laboratory first investigated the (4+1) annulation reactions between

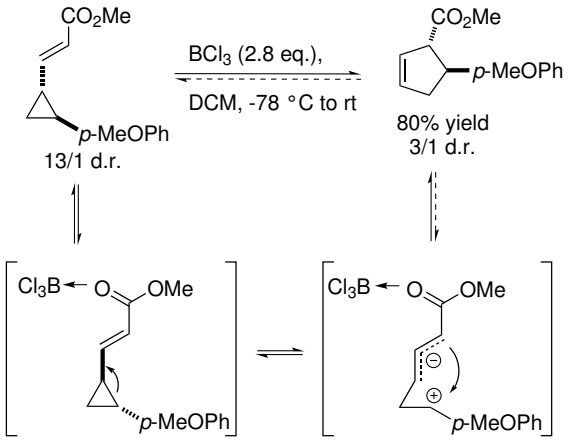
readily available methyl (2*E*)-penta-2,4-dienoate **1a** and various sulfur ylides (generated from the corresponding tetrafluoroborate salts). However, instead of cyclopentenes **5**, only (2+1) annulation products (vinylcyclopropanes) were obtained, stemming from the 1,6 and the 1,4 ylide addition (scheme 1.47, **3** and **4** respectively).[1] All attempts to obtain cyclopentenes, by varying the reaction conditions, failed. It should be emphasized that the reaction proceeds very smoothly, in nearly quantitative yield. Good regioselectivities were observed towards the 1,6-addition, affording mainly the *trans* diastereoisomer. In addition, the aryl electronic properties did not influence the yields, regio- and diastereoselectivities.



Scheme 1.47

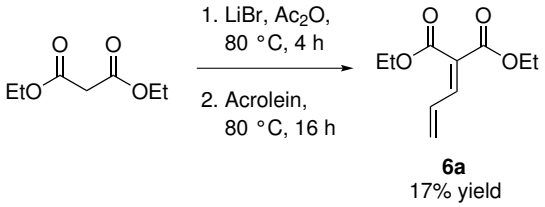
As the goal is to have five-membered carbocycles in hand, our laboratory searched for reaction conditions allowing vinylcyclopropanes rearrangement. A series of Lewis acids were screened in order to promote the rearrangement. Only one VCP could be rearranged to the corresponding cyclopentene (when Ar = *p*-MeOPh), requiring the addition of 2.8 equivalents of boron trichloride.[21] Despite the harsh conditions and the very limited scope of the reaction, the chemical yield was promising (scheme 1.48). However, the diastereoselectivity was impacted during the reaction. It was postulated that the rearrangement goes through a Lewis acid-assisted zwitterionic mechanism.

[21] Unpublished results. Prof. Raphaël Robiette.



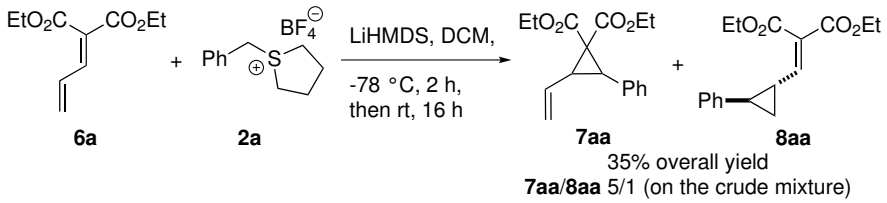
Scheme 1.48

In order to favor the rearrangement, Dr. Thierry Delaunay, during his post-doctoral stay in our research group, envisioned the elaboration of a new 1,3-diene structural motif, easily obtained from diethyl malonate and acrolein, using the Dumas' procedure[111] (scheme 1.49).



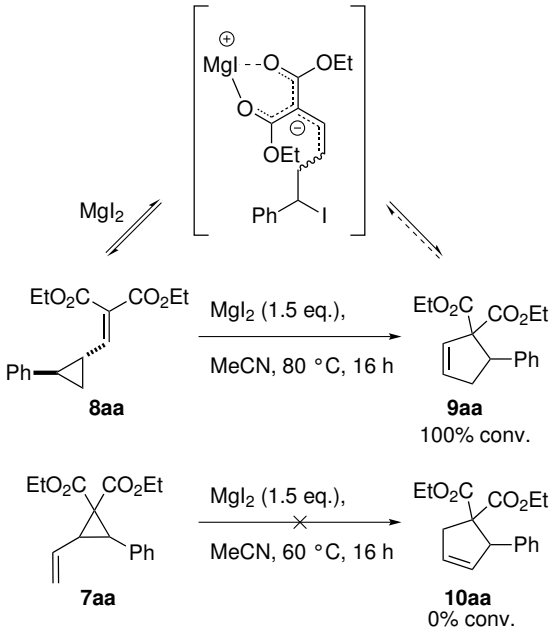
Scheme 1.49

With diene **6a** in hand and under the previously mentioned conditions, Dr. Delaunay proceeded to the cyclopropanation step. Unlike mono-activated dienes, a selectivity towards the 1,4-addition was observed, leading mainly to gem-bis-activated cyclopropane **7aa** (scheme 1.50).



Scheme 1.50

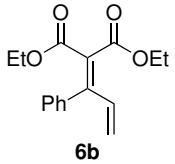
The rearrangement of these two VCP was then attempted. In the event, it was found that the VCP derived from the 1,6-addition (**8aa**) could be quantitatively converted to the corresponding cyclopentene **9aa**, at 80 °C, in the presence of 1.5 equivalents of MgI_2. However, under similar reaction conditions, vinylcyclopropane **7aa** did not rearrange (scheme 1.51).[22] Based on previous studies by Lambert, we postulated a mechanism involving an iodide-assisted cyclopropane opening *via* S_N2 reaction, followed by a S_N2 ring closure, generating the desired product and the release of the iodide leaving group.[112]



Scheme 1.51

With this promising outcome, and considering that the gem-bis-activated cyclopropane **7aa** does not rearrange under the previously-mentioned reaction conditions, our laboratory thought to substitute the diene at the C2 position, in order to minimise the 1,4-addition propensity. The synthesis of 2-substituted 1,1-dicarbonyl ester 1,3-diene **6b** was thus undertaken (figure 1.4).

[22] Carried out by Dr. Thierry Delaunay.

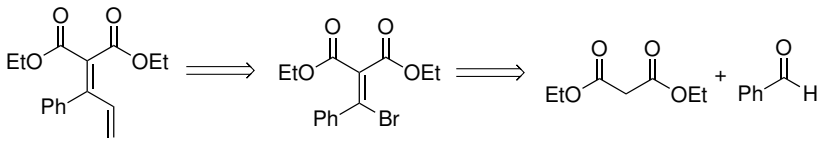


6b

Figure 1.4

Though the preparation of dienyl ester scaffolds are well documented,[113–115] there are, however, fewer reports on the synthesis of their bis-activated analogues,[111,113,116–118] especially those not substituted at the C4 position.[23]

The strategy of our laboratory towards the synthesis of this diene consists in a Suzuki-Miyaura cross coupling with compound **11b** (scheme 1.52), that could be prepared from the commercially available diethyl malonate and benzaldehyde.

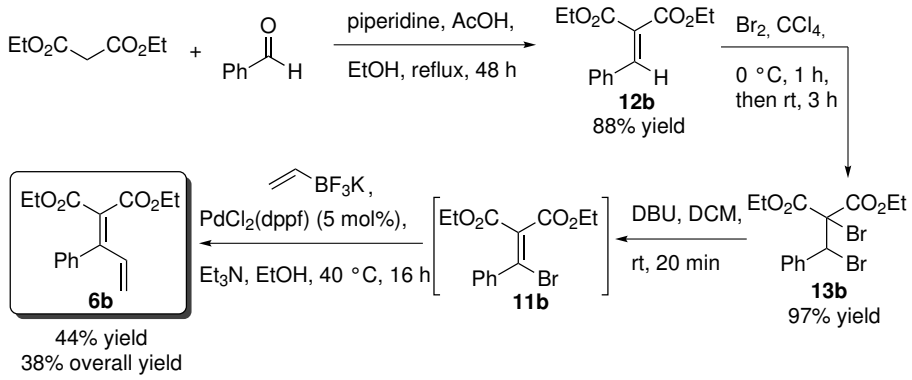


6b **11b**

Scheme 1.52

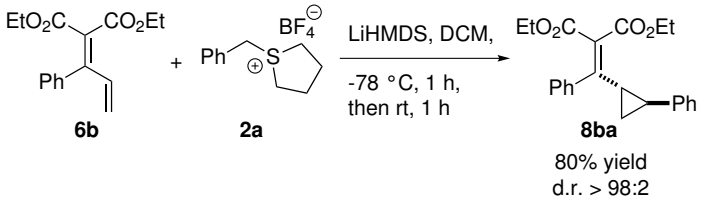
Dr. Delaunay succeeded in synthesising this diene, using a four steps procedure (scheme 1.53). The first step is a Knoevenagel condensation between diethyl malonate and benzaldehyde, leading to diethyl benzylidenemalonate **12b** in 88 % yield. Afterwards, the double bond bromination is successfully achieved, in almost quantitative yield (**13b**). The subsequent elimination (**11b**) and Suzuki-Miyaura cross coupling reaction affords diene **6b** in 38 % overall yield.

[23] To the best of our knowledge, no example of 2-substituted 1,1-dicarbonyl ester 1,3-dienes syntheses can be found in the literature.



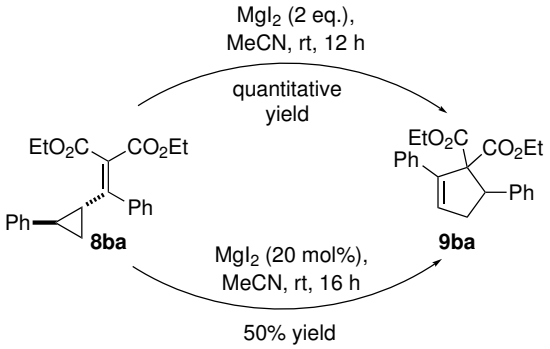
Scheme 1.53

With the diene in hand, Dr. Delaunay attempted the vinylcyclopropanation reaction and the following rearrangement. He was pleased to observe a total regioselectivity towards the 1,6-addition, leading to the desired vinylcyclopropane in 80 % yield, and a total diastereoselectivity (scheme 1.54).



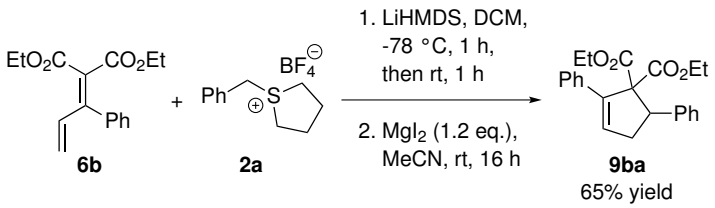
Scheme 1.54

Much to his surprise, Dr. Delaunay successfully rearranged the vinylcyclopropane under milder conditions, in quantitative yield, after 12 h at room temperature (scheme 1.55). It is noteworthy that the rearrangement also proceeds with a catalytic amount of MgI_2, but with a lower isolated yield.



Scheme 1.55

Dr. Delaunay next developed a one-pot procedure, where the vinylcyclopropanation reaction is immediately followed by the rearrangement process, allowing access to a formal (4+1) annulation reaction strategy. The cyclopentene could be isolated in 65 % yield, using 1.2 equivalents of magnesium iodide, at room temperature (scheme 1.56).



Scheme 1.56

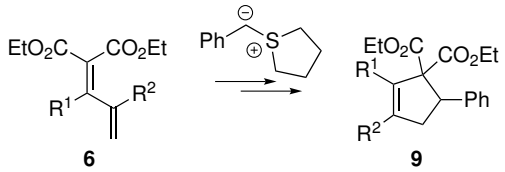
From these results, one highlighted that the substitution of the diene in position 2 is required in order to avoid 1,4-ylide addition. As a consequence, only desired VCP coming from 1,6-ylide addition is obtained. Furthermore, the diene bis-activation by two ester groups promotes the next VCP/CP rearrangement, allowing the use of soft reaction conditions. Finally, Dr. Delaunay succeeded in a formal (4+1) annulation methodology by carrying out these two reaction steps in a one-pot procedure.

Chapter 2

Objectives and strategies

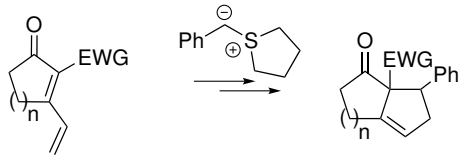
In order to further develop the (4+1) annulation strategy between sulfur ylide and 1,3-diene, we set ourselves four objectives.

1) Studying how general is our (4+1) annulation reaction methodology. To do so, we envisioned the synthesis of other 1,1-dicarbonyl ester 1,3-dienes, differently substituted in position 2 and 3 (scheme 2.1). We may that way also investigate the chemo- and regioselectivity of the reaction.



Scheme 2.1

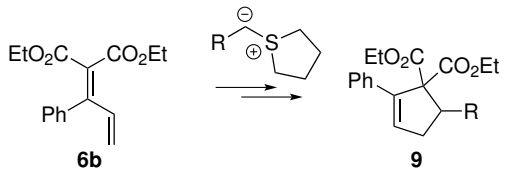
In order to test the robustness of our methodology, we also plan to explore the synthesis of a cyclic 1,3-diene, which would lead to a bicyclic adduct (scheme 2.2).



Scheme 2.2

The substitution pattern on the sulfonium ylide also has to be varied, with electron withdrawing and donating groups (scheme 2.3). Together with the

results obtained with the various 1,3-dienes, we could generalise the impact of the diene- and ylide electronic properties on our (4+1) annulation reaction methodology.



Scheme 2.3

2) The development of an asymmetric version. Aggarwal and other groups have indeed elaborated several chiral sulfonium ylides, such as those reported below (figure 2.1), which were effective in enantioselective cyclopropanation, epoxidation, and aziridination reactions.[109,110,119] We thus envision an asymmetric version of our methodology using an appropriate chiral ylide.

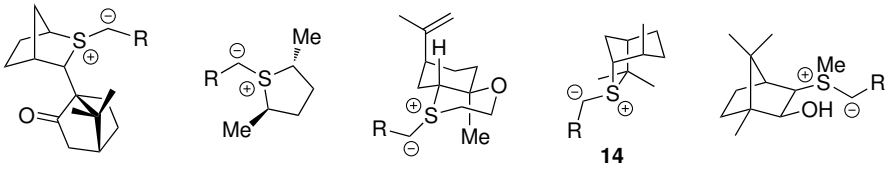
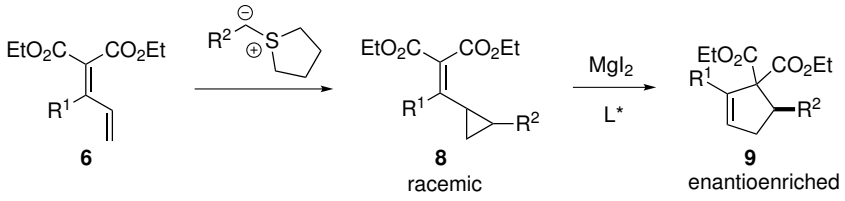
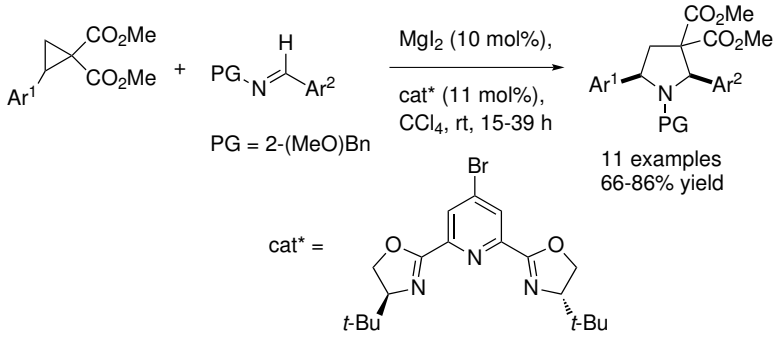


Figure 2.1

It has to be emphasized that in order to obtain enantioenriched cyclopentenes, the rearrangement process has to be stereospecific. If it is not the case, another strategy towards an enantioselective (4+1) annulation reaction methodology is to employ a chiral catalyst, such as bisoxazoline metal complexes, in order to carry out the rearrangement process in an enantioselective manner (scheme 2.4). Bisoxazoline metal complexes were indeed shown to be effective in asymmetric (3+2) cycloaddition/annulation reactions.[120,121] An example is represented in scheme 2.5.[121]



Scheme 2.4



Scheme 2.5

3) We were also interested in getting answers to a series of questions:

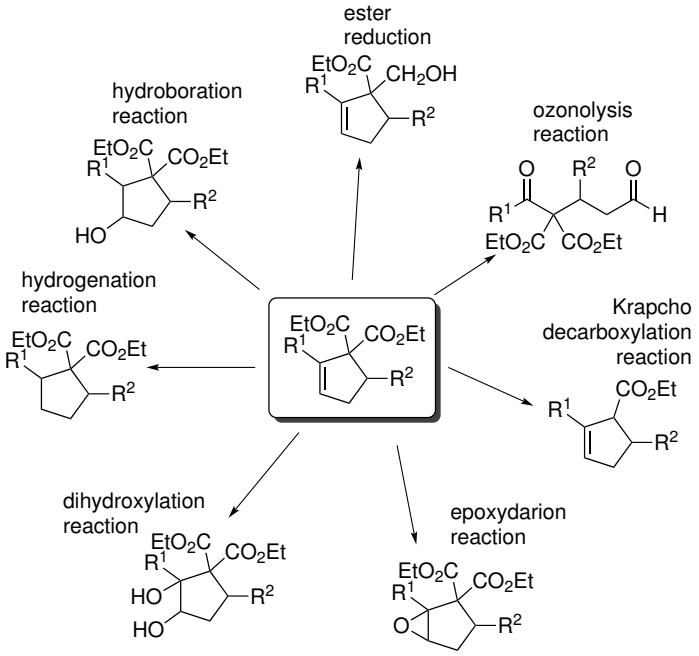
– Do the magnesium cation and the iodide anion are involved in the rearrangement process?

– Does the MgI_2 promoted rearrangement process is stereospecific?

A mechanistic study was envisioned in order to deal with these questions.

In addition to this study, we also planned to identify the key parameters that could influence the enantioselectivity of our (4+1) annulation product when using a chiral ylide.

4) Finally, we planned to subject our cyclopentenes to various chemical transformations, as an illustration of the potential applications of our methodology. Carrying two esters groups and an internal double bond, several reactions can be attempted on our cyclopentenes, such as a hydroboration, an ozonolysis, a dihydroxylation, an epoxidation, a double-bond reduction, a Krapcho decarboxylation, and an ester reduction (scheme 2.6).


ester
reduction
hydroboration
reaction
ozonolysis
reaction
hydrogenation
reaction
Krapcho
decarboxylation
reaction
dihydroxylation
reaction
epoxydarion
reaction

Scheme 2.6

Chapter 3

Substrate syntheses

We will, in the next following pages, focus our attention on the results obtained for the syntheses of substrates. In a second chapter, (4+1) annulation reactions will be discussed.

A major part of time and effort were dedicated to substrates preparation required for (4+1) annulation reactions, namely 1,3-dienes and sulfonium salts. Herein we are going to detail the developments that have allowed the syntheses of various 1,3-dienes, non-chiral and chiral sulfonium salts (ylides precursors).

3.1 Mono-activated 1,3-dienes

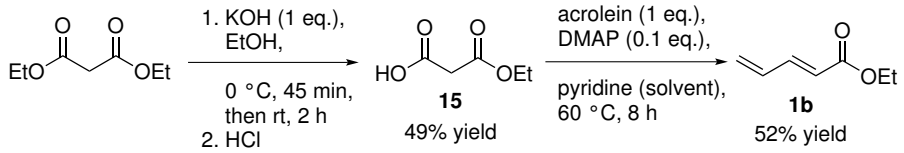
Although previous attempts of (4+1) annulation reactions carried out in our laboratory using mono-activated 1,3-dienes were unsuccessful (see introduction, scheme 1.47 page 38), we achieved some studies using these dienes. Three mono-activated dienes were envisioned, and two of them were successfully synthesized.

Ethyl (2*E*)-penta-2,4-dienoate (1b)

At the time of preliminary studies described in the introduction (see page 38), methyl (2*E*)-penta-2,4-dienoate (**1a**) was commercially available. When we started our studies, this was however no longer the case. We thus had to devise a synthesis for this diene. Having diethyl malonate at our disposal in the laboratory, we started our synthesis from this latter and thus prepared ethyl (2*E*)-penta-2,4-dienoate **1b** rather than the methyl derivative **1a** (scheme 3.1).

First of all, one of the two esters undergoes a saponification reaction, yielding 3-ethoxy-3-oxopropanoic acid **15** in 49 % yield. Afterwards, using a liter-

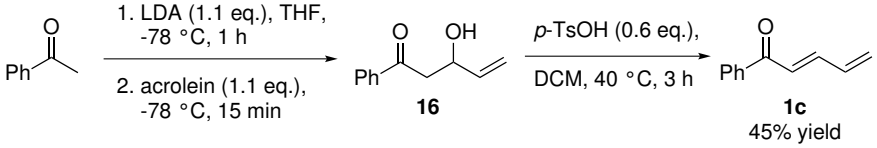
ature protocol,[122] an aldol reaction and subsequent dehydration is performed on acrolein. Despite the relative harsh reaction conditions and the high reactivity of compound **1b**, pure 1,3-diene could be obtained, on gram scale, in 52 % yield, without any further purification.



Scheme 3.1

(2*E*)-1-Phenylpenta-2,4-dien-1-one (1c)
Activated by a ketone (rather than an ester), this diene is particularly interesting. The influence of the activating group on the annulation reaction and on the subsequent rearrangement may therefore be examined.

Described in the literature,[123] the synthesis strategy is similar to that of diene **1b**, where a dehydration occurs after an aldol reaction. Involving acetophenone, acrolein, and LDA as a base, aldol adduct **16** is isolated after only 15 min at −78 °C. The crude aldol product is then immediately subjected to the elimination step using *p*-TsOH, at reflux of DCM. Pure diene **1c** is isolated in 45 % yield after purification by flash chromatography on silica gel.



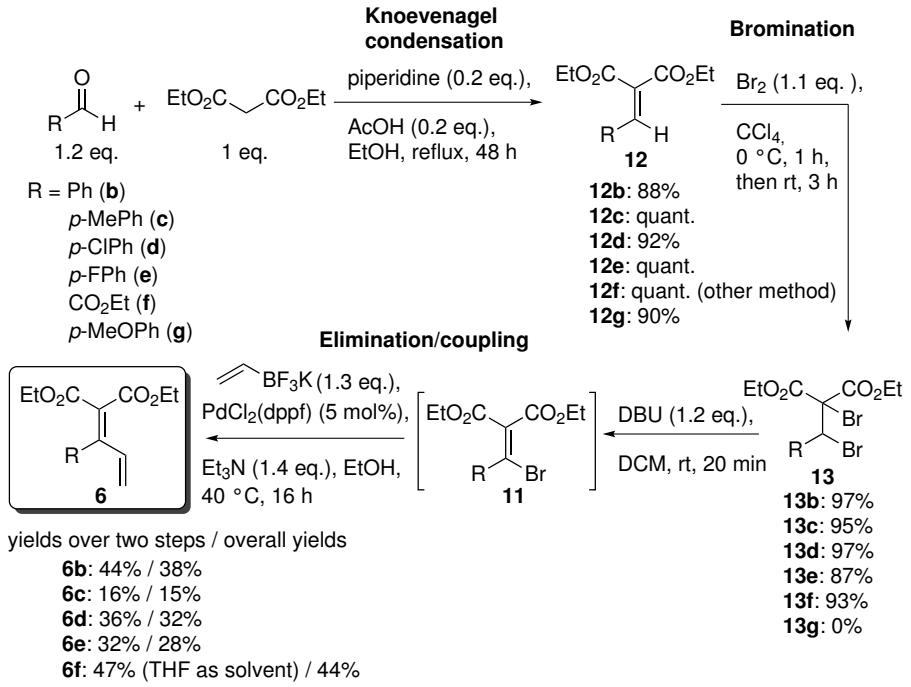
Scheme 3.2

3.2 Bis-activated 1,3-dienes

As explained in the preliminary results part (see page 37), this scaffold is a highly promising C4 unit for our (4+1) annulation reaction methodology. A multitude of bis-activated 1,3-dienes were successfully obtained during our studies, despite many failures and unsuccessful attempts.

3.2.1 Suzuki-Miyaura cross-coupling strategy

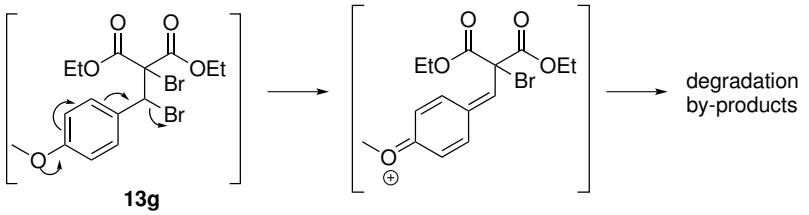
Using the same procedure as for compound **6b** (page 42), we were able to obtain four other similar dienes (scheme 3.3).[1]



Scheme 3.3

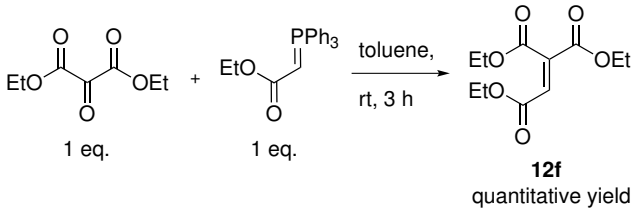
Regarding the first two steps, namely the Knoevenagel condensation and the bromination reaction, about ten grams of product could be synthesized, in very good yields (min. 88 % and 87 % yield respectively), independently of the substitution pattern, except for *p*-MeOPh substituent (**g**) where only degradation products were observed after the bromination step. This observation could be accounted for by a low stability of **13g** due to the strong electron-donating character of the *p*-MeOPh group (scheme 3.4).

[1] Compounds **12b**, **12d**, **12g**, **13d**, **11d**/**6d** were synthesized by Dr. Thierry Delaunay. The attempt to synthesize **13g** was also carried out by Dr. Delaunay.



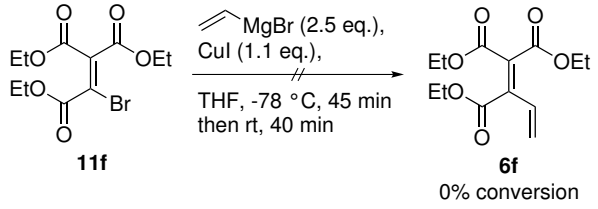
Scheme 3.4

It has to be noted that compound **12f** was obtained by a Wittig reaction between diethyl ketomalonate and (carbethoxymethylene)triphenyl-phosphorane, using a literature protocol (scheme 3.5).[124] Pure adduct was isolated in quantitative yield after purification by flash chromatography on silica gel.



Scheme 3.5

Focusing our attention on the next two steps, i.e. the elimination/Suzuki-Miyaura cross-coupling, electron-withdrawing groups (**d** and **e**) were well tolerated, as well as aliphatic ester (**f**). On the contrary, the electron-donating group *p*-MePh (**c**) was problematic, as the diene was isolated in only 16 % yield. It is noteworthy that these two last steps can be carried out on gram scale. In the case of the ester derivative (**f**, R = CO_2Et), the general procedure furnishes a mixture of diene **6f** and monobrominated compound **11f** in a 0.3/1 ratio (**6f**/**11f**). Inspired by a described procedure,[125] we first thought to carry out vinylmagnesium bromide addition onto compound **11f**, which could successively undergo a bromide elimination to give diene **6f** (scheme 3.6). Unfortunately, no conversion was observed.



Scheme 3.6

We then tried to improve cross-coupling reaction conditions. A multitude of trials were thus carried out:

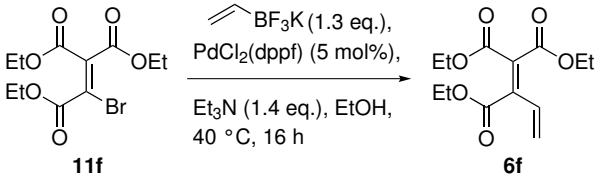


Table 3.1

Entry	Variation from mentioned reaction conditions	**6f**/**11f** ratio[a]
1	/	0.3/1
2	10 mol% $PdCl_2$(dppf)	/[b]
3	10 mol% $Pd(PPh_3)_4$	0.1/1
4	10 mol% $Pd(PPh_3)_4$ without triethylamine	no conversion
5	1,4-dioxane as a solvent	1.4/1
6	toluene as a solvent	0.3/1
7	**THF as a solvent**	**2/1**[c]

[a] Calculated on the ^{1}H NMR spectrum of the crude mixture.

[b] Could not be calculated due to overlapping with signals of side products. A lower conversion as compared to entry 1 is supposed based on the analysis of the ^{1}H NMR spectrum of the crude mixture.

[c] 47 % isolated yield after purification by flash chromatography on silica gel.

Observations are the following:

– A lower conversion is observed using 10 mol% of catalyst, for $PdCl_2$(dppf) and for $Pd(PPh_3)_4$ (entries 2 and 3 respectively).

– An approximately same conversion is observed using toluene rather than ethanol (entry 6).

– No conversion is observed using $Pd(PPh_3)_4$ in the absence of triethylamine (entry 4).

– On the contrary, an increased conversion is reported using 1,4-dioxane as a solvent (entry 5), and even more with THF, where a 2/1 ratio (**6f**/**11f**) is observed (entry 7). Subsequent purification by flash chromatography on silica gel of this crude mixture lead to the desired diene in 47 % isolated yield. In order to further improve the conversion when THF is used as a solvent, we increased boron derivative and catalyst quantities (2 equivalents and 0.1 equivalent respectively), but without any improvement of the results.

Besides these four new dienes (**6c-f**), other non-aromatic substituents were considered, but problems occurred for all of them during the elimination/coupling reactions steps (table 3.2).

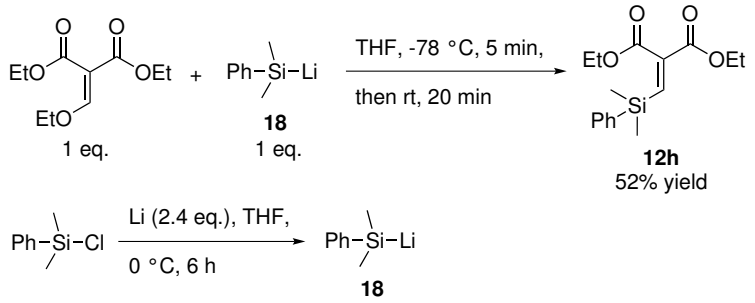
Table 3.2

Subst.	Knoevenagel (**12**)	Bromination (**13**)	Elim./coupling (**6**)
$SiMe_2Ph$ (**h**)	/	91 %	0 %
Me (**i**)	/	89 %	0 %
i-Pr (**j**)	/	91 %	0 %[a]

[a] For the elimination step, the reaction conditions are 0 °C, 20 min, then rt, 40 min.

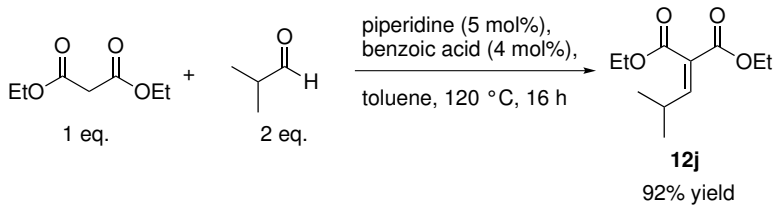
It is noted that **12i** is commercially available. For compounds **12h** and **12j**, other procedures were employed, as described below.

The silylated diethyl methylenemalonate **12h** was synthesized according to a described procedure,[126] consisting of an addition/elimination process of [dimethyl(phenyl)silyl]lithium reagent **18** on diethyl (ethoxymethylene)malonate, leading to the product in 52 % yield (scheme 3.7). It should be noted that organolithium reagent **18** was obtained by activating chlorodimethyl(phenyl)silane with lithium, in THF.[127]



Scheme 3.7

Concerning the *i*-Pr substitution (**12j**), a described procedure was also used (scheme 3.8).[128] Similar to the general procedure leading to **12**, this Knoevenagel condensation however employs benzoic acid rather than acetic acid.[2] Using a Dean-Stark apparatus, the adduct could be isolated in 92 % yield without any purification.



Scheme 3.8

Focusing our attention on bromination reactions, it is noteworthy that all three adducts were isolated in similar yields to that of previously mentioned compounds **13b-f** (89-91 %).

We are now going to focus our attention on the subsequent bromide elimination/Suzuki-Miyaura cross-coupling reactions. Table 3.2 page 54 clearly shows that this procedure was totally inefficient for the three concerned substituents (Me, *i*-Pr, and Me_2PhSi). ^1H NMR studies revealed that the problem is coming from the elimination step, as a mixture of starting brominated material **13** and retro-bromination (giving back the Knoevenagel adduct **12**), were generally obtained after this step (table 3.3). Concerning the methyl-substituted substrate **13i**, the only observed compound was the methylenemalonate **12i**. Elimination reaction on *i*-Pr-substituted brominated product **13j** gave a 2.6/1 **13j**/**12j**

[2]Indeed, **12j** is a known compound and these reaction conditions were applied. We nevertheless could assume that our standard reaction conditions should successfully furnish the desired product.

mixture. Interestingly, the Suzuki-Miyaura cross-coupling reaction on this mixture completely converted **13j** to the Knoevenagel adduct **12j**. Finally, with silylated compound **13h**, a mixture of **13h**, **12h**, and the desired monobrominated compound **11h** was observed, in a 1/0.5/1 ratio (**13h**/**11h**/**12h**). Although the subsequent cross-coupling reaction gave a small amount of diene **6h**, as seen on the ^{1}H NMR spectrum of the crude mixture, the purification by flash chromatography failed, possibly due to diene degradation on silica gel.

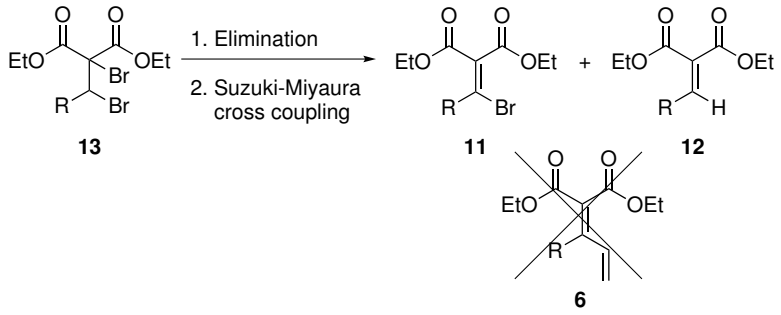


Table 3.3

Substituent	Observation[a]
$SiMe_2Ph$ (**h**)	1/0.5/1 **13h**/**11h**/**12h**
Me (**i**)	**12i**
i-Pr (**j**)	2.6/1 **13j**/**12j**

[a] On the ^{1}H NMR spectrum of the crude mixture.

With the aim of synthesising these three dienes *via* the Suzuki-Miyaura strategy, a variation of reaction conditions was envisioned in order to optimize the problematic bromide elimination step.

The methyl-substituted substrate **13i** was subjected to four elimination reactions, by varying the amine base (table 3.4). However, for all these attempts, only starting material was recovered.

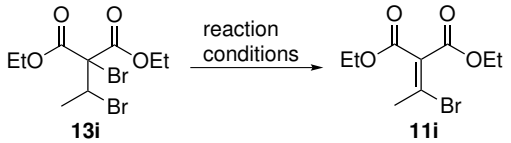


Table 3.4

Entry	Base (eq.)	Solvent	Temperature, time	Obs.
1	propylamine (1.2)	DCM	rt, 30 min	SM
2	DTBMP (1.2)	DCM	0 °C, 50 min, then rt, 10 min	SM
3	DTBMP (1.2)	DCM	rt, 1 h	SM
4[a]	2,4,6-collidine (3)	DCM	rt, 1 h 30	SM

[a] Reaction conditions from: G. Grossmann, M. Poncioni, M. Bornand, B. Jolivet, M. Neuburger, U. Séquin, *Tetrahedron* **2003**, *59*, 3237–3251.

Because the chemoselectivity could be problematic,[3] we focused our efforts on the *i*-Pr substituted brominated substrate **13j**, for which a plethora of reaction conditions were tested, as depicted in table 3.5 (entry 1 refers to standard reaction conditions).

[3]The base could reacts with methyl protons rather than the gem-bromo proton.

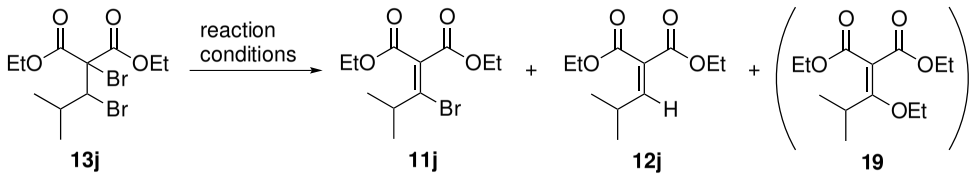


Table 3.5

Entry	Base (eq.)	Additive (eq.)	Solvent	Temperature, time	Results (**13j**/**11j**/**12j**)[a]
1	DBU (1.2)	/	DCM	0 °C, 20 min, then rt, 40 min	1/0/0.4
2	DBU (1.2)	$AgBF_4$ (excess)	DCM	0 °C, 20 min, then rt, 40 min	1/0/0
3	DBU (1.2)[b]	$Pb(NO_3)_2$ (1.3)	EtOH	rt, 40 min	1/0/0.02 + USP (a)[c]
4	DBU (3)[b]	$Pb(NO_3)_2$ (1.3)	EtOH	rt, 40 min	1/0/0.6 + USP (a)[c]
5	DBU (1.2)	/	DMSO	rt, 40 min	1/0/1
6	EtONa (1.7)[d]	/	EtOH	0 °C, 20 min, then rt, 20 min	0/0/0 + **19**[e]
7	*t*-BuONa (1.1)[d]	/	THF	0 °C, 20 min, then rt, 30 min	1/0/0.1 + USP (a)[c]
8	*t*-BuONa (1.1)[f]	/	THF	0 °C, 20 min, then rt, 30 min	1/0/0.1 + USP (a)[c]

[a] Calculated on the ^{1}H NMR spectrum of the crude mixture.

[b] Added at 0 °C.

[c] Unidentified side-products (a: small amounts; A: large amounts).

[d] Added in solution (solvent of reaction) to the reaction mixture.

[e] A full conversion towards **19** is observed on the ^{1}H NMR spectrum of the crude mixture, and isolated in 49 % yield.

[f] Added in one fraction to the reaction mixture, at −10 °C.

Entry	Base (eq.)	Solvent	Temperature, time	Results (**13j**/**11j**/**12j**)[a]
9	*t*-BuONa (1.1)[d]	toluene	0 °C, 20 min, then rt, 30 min	1/0/0.05 + USP (a)[c]
10	K_2CO_3 (1.5)[g]	THF	0 °C, 20 min, then rt, 45 min	1/0/0
11	K_2CO_3 (1.5)[g]	DMF	0 °C, 20 min, then rt, 45 min	1/0/0
12	Na_2CO_3 (1.4)[g]	THF	0 °C, 20 min, then rt, 45 min	1/0/0
13	Na_2CO_3 (1.4)[g]	DMF	0 °C, 20 min, then rt, 45 min	1/0/0
14	Et_3N (1.1)[b]	CCl_4	rt, 2 h 30	1/0/0
15	Cs_2CO_3 (1.2)[g]	EtOH	0 °C, 20 min, then rt, 40 min	1/11/1.2 + USP (A)[c]
16	Cs_2CO_3 (1.2)[g]	Et_2O	0 °C, 20 min, then rt, 40 min	1/0/0
17	Cs_2CO_3 (1.2)[g]	MeCN	0 °C, 20 min, then rt, 40 min	1/0/0
18	Cs_2CO_3 (1.2)[g]	DMSO	0 °C, 20 min, then rt, 40 min	1/0/0
19	Cs_2CO_3 (1.2)[g]	THF	0 °C, 20 min, then rt, 40 min	1/0/0
20	**Cs_2CO_3 (2)**[g]	**EtOH**	**0 °C, 30 min, then rt, 2 h**	**0/1/0 + USP (A)**[c]
21	Cs_2CO_3 (2)[g]	EtOH	0 °C, 30 min, then rt, 2 h	degradation[h]
22	Cs_2CO_3 (2)[g]	EtOH	0 °C, 1 h, then rt, 2 h	0/1/0.1 + USP (A)[c]

[a] Calculated on the ^{1}H NMR spectrum of the crude mixture.

[b] Added at 0 °C.

[c] Unidentified side-products (a: small amounts; A: large amounts).

[d] Added in solution (solvent of reaction) to the reaction mixture.

[g] Added in one fraction to the reaction mixture.

[h] After filtration on silica gel, using EtOAc as eluent.

In a nutshell, observations are the following:

- For all entries (except 15, 20, 22), no desired product is formed.
- For most of entries (except 1, 4-6, 15, 20-22), the conversion is very low.
- Much to our surprise, for entries 1, 3-5, 7-9, 15, and 22, retro-bromination reaction compound **12j** (the Knoevenagel adduct) is observed.
- Attempts to precipitate the bromide (*via* AgBr or $PbBr_2$, entries 2 and 3 respectively) in order to push forward the reaction were not efficient, neither with increasing the amount of base, where even more retro-bromination product **12j** is formed (entry 4).
- Base screening reveals that Cs_2CO_3 (entry 15) effectively generates a large amount of monobrominated compound **11j**, but together with similar amounts of an undesired side-product. Nevertheless, only a small amount of Knoevenagel adduct **12j** is detected on the crude mixture. On the contrary, *t*-BuONa, K_2CO_3, Na_2CO_3, and Et_3N are ineffective, as only starting material is recovered (entries 7, 10, 12, and 14 respectively). Regarding EtONa, only substitution product **19** is observed (entry 6).
- Using *t*-BuONa as a base, addition of the latter in one fraction does not influence the reaction (entry 8).
- Solvent screening (with various bases) does not lead to better results (entry 9 for *t*-BuONa, 11 for K_2CO_3, 13 for Na_2CO_3, and entries 16-19 for Cs_2CO_3). However, using DBU as a base, DMSO is pushing the conversion towards the Knoevenagel adduct **12j**, without any desired **11j** synthesis (entry 5).
- Best reaction conditions are the entry 20 as they allow a complete conversion of the starting material, with no Knoevenagel adduct **12j** formation.[4]
- Based on these optimized reaction conditions, a rapid filtration on silica gel (in order to remove polar compounds) shows that monobrominated compound **11j** apparently decomposes on silica gel (entry 21). Furthermore, stirring 1 h at 0 °C rather than 30 min is inefficient (entry 22).

Using optimized reaction conditions for the elimination step (entry 20), the Suzuki-Miyaura cross-coupling could be envisioned. Unfortunately, a complex

[4]The yield could not be calculated, due to the large amounts of by-products in the crude mixture, and to the absence of the internal standard for the ^{1}H NMR analysis.

mixture was observed on the ^{1}H NMR spectrum of the crude mixture, with no trace of diene **6j**, neither any vinylic signals. The change of solvent to THF did not improve the results. Finally, regular addition of palladium catalyst (5 mol% after 45 min and 1 h 30), together with addition, after 1 h 30, of potassium vinyltrifluoroborate (1.3 eq.) and Et_3N (1.4 eq.) did not allow the formation of the desired diene, a complex mixture being observed.

In the meantime, a series of reaction conditions for the elimination step was carried out on the silyl-substituted brominated compound **13h** (table 3.6).

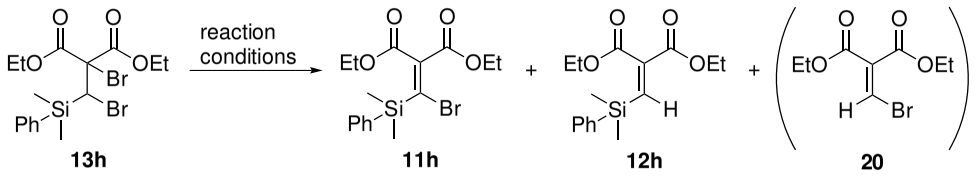


Table 3.6

Entry	Base (eq.)	Additive (eq.)	Solvent	Temperature, time	Results (**13h**/**11h**/**12h**)[a]
1	**DBU (1.2)**[b]	/	**DCM**	**rt, 20 min**	**1/0.5/1**
2	DBU (1.2)	$AgPF_6$ (1.2)	DCM	0 °C, 20 min, then rt, 30 min	0/0/0 + **20**[c]
3	DBU (1.2)	$AgBF_4$ (1.4)	THF	0 °C, 20 min, then rt, 30 min	1/0.1/0.1
4	DBU (1.2)	$AgBF_4$ (excess)	THF	0 °C, 20 min, then rt, 30 min	0/0/0 + **20**[c]
5	DBU (1.2)	/	DCM	0 °C, 1 h	1/0.2/1
6	DBU (1.2)	/	DCM	reflux (40 °C), 1 h	1/0.1/1 + USP (A)[d]
7	DBU (1.2)[b]	/	Cy	rt, 20 min	1/0/0.3 + USP (a)[d]
8	DBU (1.2)[b]	/	EtOAc	rt, 1 h	1/1/4
9	DBU (1.2)	/	EtOAc	0 °C, 1 h	1/0.4/0.8

[a] Calculated on the ^{1}H NMR spectrum of the crude mixture.

[b] Added at 0 °C, or 6.5 °C for cyclohexane (melting point temperature).

[c] A full conversion towards the desilylated compound **20** is observed.

[d] Unidentified side-products (a: small amounts; A: large amounts).

Entry	Base (eq.)	Additive (eq.)	Solvent	Temperature, time	Results (**13h**/**11h**/**12h**)[a]
10	DBU (1.2)[b]	/	CCl_4	rt, 1 h	1/0/0.5
11	DBU (1.8)[b]	/	Et_2O	rt, 15 min	1/0.2/0.7
12	DBU (1.8)[b]	/	Et_2O	rt, 40 min	1/0.2/1.4
13	Cs_2CO_3 (2)[e]	/	EtOH	0 °C, 30 min, then rt, 2 h	0/0.3/1 + USP (A)[d]
14	DBN (1.2)[b]	/	DCM	rt, 20 min	1/0/5
15	Et_2NH (1.4)[b]	/	DCM	rt, 20 min	1/0/0
16[f]	Et_2NH (as a solvent)	/	/	rt, 5 h	1/0.3/1.3
17	EtONa (1.6)[g]	/	EtOH	0 °C, 20 min, then rt, 30 min	1/0.4/1.6 + USP (a)[d]
18	*p*-(O_2N)PhOLi (1.0)	/	DCM	0 °C, 15 min, then rt, 15 min	1/0/0.1
19	H_2C=CH-MgBr (1.2)	/	THF	−78 °C, 10 min, then rt, 10 min	1/0/2 + USP (A)[d]
20	H_2C=CH-MgBr (1.2)	$AgBF_4$(1.8)	THF	−78 °C, 20 min, then rt, 10 min	1/0/0.6 + USP (a)[d,h]
21	NaH (2)[i]	/	THF	0 °C, 20 min, then rt, 15 min	1/0/0.2 + USP (a)[d]

[a] Calculated on the ^{1}H NMR spectrum of the crude mixture.

[b] Added at 0 °C.

[d] Unidentified side-products (a: small amounts; A: large amounts).

[e] Added in one fraction to the reaction mixture.

[f] Procedure from: A. Ottolenghi, M. Fridkin, A. Zilkha, *Can. J. Chem.* **1963**, *41*, 2977–2982.

[g] EtONa is added in solution (EtOH) to the reaction mixture.

[h] Vinyl signals are detected on the ^{1}H NMR spectrum of the crude mixture, indicating Grignard 1,2-addition.

[i] A THF solution of starting material **13h** is added, dropwise, to a THF solution of NaH.

From this table the observations are the following:

- The best reaction conditions remain the standard procedure (entry 1), where a 33 % conversion towards the monobrominated compound **11h** is observed.[5]
- No desired product is obtained for entries 2, 4, 7, 10, 14, 15, and 18-21.
- As for the *i*-Pr substituted substrate, Knoevenagel adduct **12h** is also observed, for all entries except 2, 4, and 15.
- Using the best reaction conditions for the *i*-Pr-substituted substrate (entry 13) decreases the conversion towards the desired compound **11h**, together with a significant amount of an unidentified side-product (and the Knoevenagel adduct **12h**).
- Reaction conditions using $AgPF_6$ (1.2 eq.) and excess of $AgBF_4$ (entries 2 and 4 respectively) in order to precipitate the bromide are totally ineffective, a full conversion towards the desilylated compound **20** being observed. One can explain this observation by a tandem fluoride-assisted silyl deprotection/bromide elimination. Using less $AgBF_4$ (1.4 eq), no deprotection occurs, but almost no conversion either (entry 3).
- Carrying out the reaction for 1 h at 0 °C or for 1 h at 40 °C decreases the conversion towards the desired compound **11h** (entries 5 and 6 respectively).
- Using cyclohexane and CCl_4 in place of DCM (entries 7 and 10) decreases the conversion, with no desired compound **11h**, and additional unidentified side-product for entry 7 (cyclohexane). Carrying out the reaction in more polar solvents Et_2O (entry 11) effectively generates monobrominated compound **11h**, but in lower conversion as compared to the standard procedure. Stirring for 40 min at room temperature (rather than 15 min; entry 12), increases only the conversion towards retro-brominated compound **12h**. Finally, the more polar solvent EtOAc pushes forward the conversion towards undesired Knoevenagel adduct **12h** (entry 8), and using smoother reaction conditions (1 h at 0 °C; entry 9) generates better **13h**/**11h**/**12h** ratios, but similar to that of the standard procedure.

[5] The absence of by-products allows us to calculate a yield of 20 % based on the ratio of **13h**, **11h**, and **12h**.

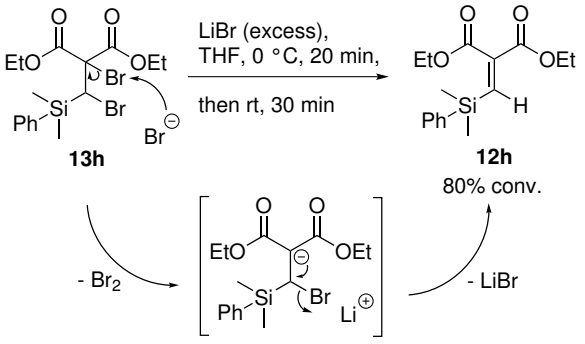
– Change DBU to DBN, Et_2NH, *p*-(O_2N)PhOLi,[6] H_2C=CH-MgBr, and NaH (entries 14, 15, 18, 19, and 21 respectively) do not generate the desired compound **11h**. No or very low conversion is observed for Et_2NH, *p*-(O_2N)PhOLi and NaH (entries 15, 18, and 21), whereas only Knoevenagel adduct **12h** and starting material are observed for DBN (entry 14). Using Et_2NH as a solvent (entry 16) effectively generates desired compound **11h**, but in lower proportion as compared to **12h**. Furthermore, a low conversion is observed. The Grignard reagent gives rise to the synthesis of **12h** together with a large amount of an unidentified side-product (entry 19), and the use of $AgBF_4$ in order to favor the bromide elimination, using the same base (entry 20) does not allow the desired compound synthesis. In addition, vinyl signals are detected on the ^{1}H NMR spectrum of the crude mixture, indicating Grignard 1,2-addition.

  Eventually, changing DBU to EtONa (entry 17) effectively generates compound **11h**, but the conversion and the **11h**/**12h** ratio are not interesting as compared to the standard reaction conditions.

Observation of **12h** whenever a conversion is observed (except for entries 2 and 4 where desilylated compound **20** is obtained) can be explained by a plausible bromide-catalyzed debromination reaction. This hypothesis was examined by stirring a mixture of starting material **13h** and excess of LiBr in THF,[7] but no conversion was observed. However, when a large excess of LiBr is used, a 80 % conversion towards Knoevenagel adduct **12h** was observed, with no other side-products (scheme 3.9). We thereby cannot exclude bromide anion involvement in the formation of Knoevenagel adducts **12h** and **12j**.

[6] A solution of the organolithium reagent *p*-(O_2N)PhOLi (1 M) is obtained by stirring a solution of *n*-BuLi (2.5 M in *n*-hexane; 1.0 eq.) and paranitrophenol (1 mmol) in THF (1 mL), for 1 h, at −78 °C.[127]

[7] At 0 °C for 20 min and then at room temperature for 30 min.



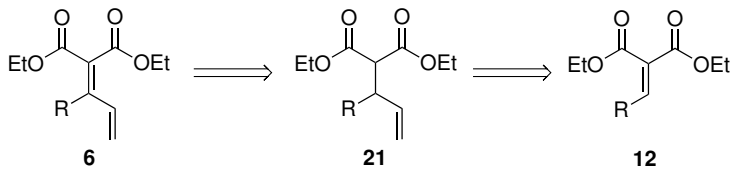
Scheme 3.9

This observation can also explain why no or much less conversion towards Knoevenagel adducts **12h** and **12j** is observed when $AgBF_4$ or $Pb(NO_3)_2$ are employed (entries 2 and 3, table 3.5 and entries 2-4, 20 table 3.6), the bromide ion may be captured by silver and lead, generating AgBr and $PbBr_2$.

The various elimination reactions carried out on the two brominated compounds **13h** (Me_2PhSi) and **13i** (Me) being unsuccessful, added to the impossibility to succeed in the Suzuki-Miyaura cross-coupling reaction on the monobrominated compound **11j** (*i*-Pr), prompted us to investigate another strategy to access to these dienes.

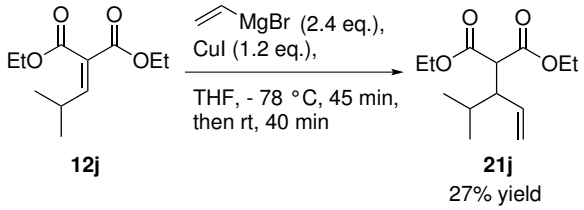
3.2.2 Selenium-mediated oxidation

As it seems that the bromide is problematic for the elimination step, we envisioned a bromine-free strategy to reach these dienes. Indeed, 1,3-diene **6** scaffold could be obtained *via* a selenium mediated oxidation of vinyl compound **21** (scheme 3.10). Interestingly, this latter could be synthesized by a Michael addition of organocuprate reagent onto Knoevenagel adducts **12**, making this strategy very interesting as this intermediate is in common with the Suzuki-Miyaura strategy.



Scheme 3.10

Using a Shia modified procedure,[125] organocuprate addition was thus carried out with *i*-Pr substituted Knoevenagel adduct **12j** (100 mg scale; scheme 3.11).[8]



Scheme 3.11

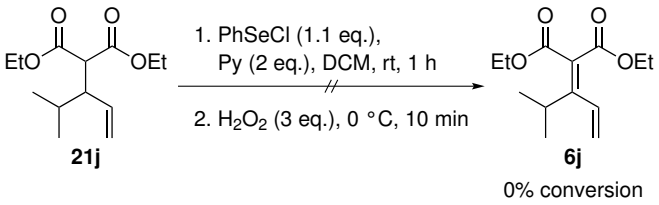
Although the reaction effectively furnishes Michael adduct **21j**, the isolated yield is quite low (27 %),[9] and starting material is still observed on the ^{1}H NMR spectrum of the crude mixture (1/0.28 **21j**/**12j**), added to large amounts of other by-products. We thus considered to extend the reaction time at −78 °C to 2 h (rather than 45 min). We were pleased to observe an improved ratio towards the desired product **21j** (1/0.04 **21j**/**12j**), and an isolated yield of 35 %,[9] despite by-products still being observed in the crude mixture. In order to further improve the conversion, we allowed the cooling bath to warm slowly to room temperature overnight after Knoevenagel adduct addition. Compound **21j** could be obtained in 65 % isolated yield,[9] starting from 500 mg of Knoevenagel adduct **12j**.

Michael adduct **21j** in hand, we investigated the oxidation reaction, allowing access to the desired 1,3-diene, using a described procedure (scheme 3.12).[125] It is noteworthy that phenylselenylchloride was first of all activated by pyridine, for 20 min at 0 °C in DCM.[10] Unfortunately, only starting material and unidentified by-products were observed on the ^{1}H NMR spectrum of the crude mixture.

[8] The organocuprate reagent is firstly generated by stirring the Grignard reagent (2.4 equivalents) and copper iodide (1.2 equivalents) for 45 min at 0 °C in THF, before dropwise addition of the starting material solution at −78 °C.

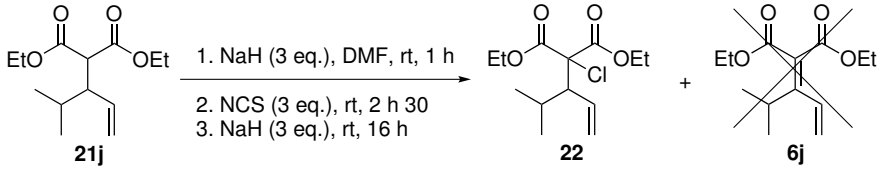
[9] After purification by flash chromatography on silica gel.

[10] In order to remove pyridine, an acidic treatment with HCl (1 M) was carried out prior to selenium oxidation.



Scheme 3.12

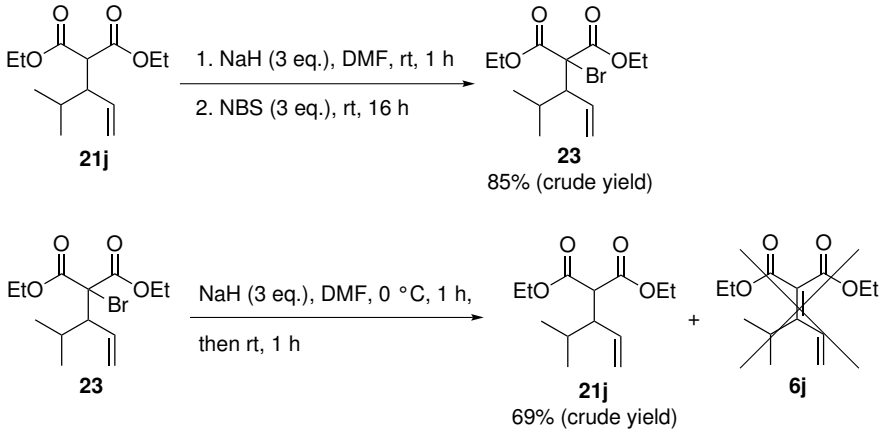
In line with this strategy, we next envisioned to replace PhSeCl by N-chlorosuccinimide (NCS) and, *via* a treatment with sodium hydride, a double-bond reformation could occur (scheme 3.13). Using NaH as a base[11] and NCS as an electrophile, a chloride substituent could be added that way on the starting material, leading to intermediate **22**. Unfortunately, the subsequent chloride elimination, by means of NaH, failed, as only chlorinated intermediate **22** was observed in the crude mixture. Using more drastic reaction conditions for the elimination step (40 °C for 5 h) led to a total degradation of compound **22**.



Scheme 3.13

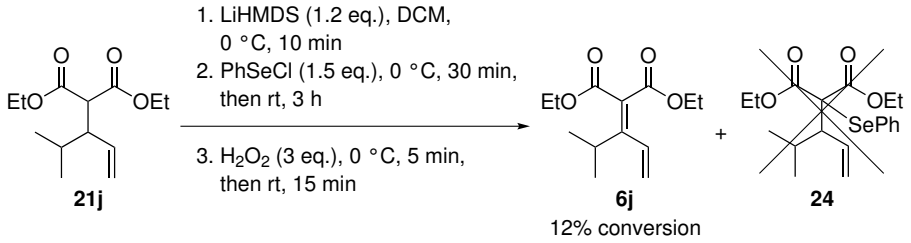
Using N-bromosuccinimide (NBS) rather than NCS, ^{1}H NMR spectrum of the crude mixture revealed large amounts of compound **23**, together with few by-products (scheme 3.14). Unfortunately, the elimination step failed. Surprisingly, a full conversion of the brominated compound towards Michael adduct **21j** was observed. A plausible explanation for this observation is a hydride addition onto bromide, astonishingly highlighting a nucleophilic property of NaH. Bromide being a better leaving group than chloride, that could explain why this retro-halogenation reaction did not occurs with chlorinated compound **22**.

[11] NaH addition onto the starting material was carried out at 0 °C.



Scheme 3.14

This strategy being ineffective, we envisioned to optimize reaction conditions using the selenium-mediated oxidation method. Indeed, according to us, the tandem selenium oxidation/elimination step should not be problematic, phenylselenyl addition onto the starting material being the key stage. In this context, inspired by a procedure described in the same article as scheme 3.12 page 68,[125] base-mediated malonate activation was considered, rather than phenylselenyl chloride activation (scheme 3.15). After stirring a DCM solution of starting material **21j** with LiHMDS for 10 min at 0 °C,[12] PhSeCl was then added, in one fraction, to the reaction mixture.

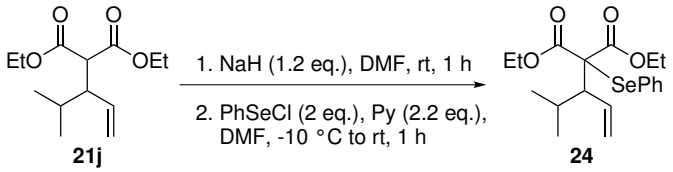


Scheme 3.15

Analysis of the ^{1}H NMR spectrum of the crude mixture revealed a 12 % conversion towards desired diene **6j**, with no trace of intermediate **24**. As a large amount of starting material was recovered, our hypothesis of an effective compound **24** oxidation is confirmed, the difficulty residing in the phenylselenyl addition onto the substrate.

[12] LiHMDS addition on the malonate solution was carried out at −78 °C.

These results prompted us to use the more convenient sodium hydride as a base, in place of LiHMDS. Indeed, being a small hard base, one can predict an effective malonate deprotonation. In addition, the only generated by-product is dihydrogen, which escapes from the reaction mixture, allowing a displacement of the equilibrium towards the product (scheme 3.16).[13] The ^{1}H NMR spectrum of the crude mixture however revealed only a small increase of the conversion towards compound **24**.



Scheme 3.16

From these results various reaction conditions were screened, starting from 25-50 mg of the Michael adduct, as depicted in table 3.7.[14] Results are explained on next pages.

[13]The hydride mediated malonate activation is firstly carried out using 1.2 equivalents of NaH. This mixture is then added, dropwise, to a DMF solution of activated PhSeCl at −10 °C (in order to promote the reaction, phenylselenyl chloride was also previously activated, stirring PhSeCl and pyridine for 20 min at 0 °C, in DMF).

[14]NaH addition onto the starting material was achieved at 0 °C. It is also to emphasize that for entries 2, 4 and 5, hydrogen peroxide promoted oxidation was not carried out.

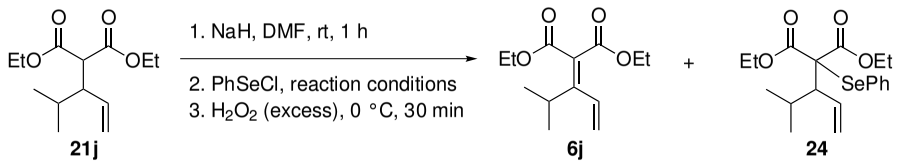


Table 3.7

Entry	NaH; PhSeCl (eq.)	Temperature, time (PhSeCl)	Selenation step results (**24**/**21j**)[a]	Oxidation/elimination step results (**21j**/**6j**/**24**)[a]
1	3.0; 3.0[b]	rt, 4 h	1/1	3/1/2 + USP (a)[c]
2	3.0; 3.0	40 °C, 40 min	1/1	not carried out
3	1.2; 2.0[b]	rt, 1 h, then 40 °C, 2 h	1/0 + USP (A)[c]	0/1/0 + USP (A)[c]
4	1.2; 2.0[b]	rt, 24 h	degradation	not carried out
5	1.2; 2.0[b]	rt, 30 min	1/1.3	not carried out
6	1.2; 2.0[d]	−10 °C, 20 min, then 0 °C, 2 h	not determined	0.7/1/0 + USP (A)[c]
7	1.5; 2.0[d]	−10 °C, 2 h 30, then 0 °C, 1 h30	not determined	0.5/1/0 + USP (a)[c]
8[e]	**1.5; 2.0**[d,f]	**−10 °C, 2 h, then 0 °C, 2 h**	**not determined**	**0.3/1/0**

[a] Calculated on the ^{1}H NMR spectrum of the reaction/crude mixture (for selenation step and oxidation/elimination step respectively).

[b] Addition of PhSeCl at 0 °C for entries 1 and 3, at −78 °C for entry 4, and at −10 °C for entry 5.

[c] Unidentified side-products (a: small amounts; A: large amounts).

[d] The activated malonate solution was added dropwise to the DMF solution of PhSeCl.

[e] The reaction was carried out on a larger scale (150 mg of starting material).

[f] Very slow addition of the activated malonate solution (50 µL min^{-1}).

Based on the previous scheme procedure, and in order to promote the activated substrate nucleophilic addition to phenylselenyl chloride, the reaction mixture was stirred for 4 h at room temperature using 3 equivalents of NaH and PhSeCl (entry 1). We were pleased to observe a 50 % conversion towards intermediate **24**. In order to improve the nucleophilic addition to substrate **21j**, harsher reaction conditions were used (40 °C), but the same 50 % conversion was observed (entry 2). We then tried stirring for 1 h at room temperature before heating (using less NaH and PhSeCl), but by-products were mainly observed (entry 3). Considering that a 50 % conversion towards **24** was already observed after only stirring 30 min at room temperature, a prolonged reaction at this temperature was carried out, but, surprisingly, only degradation products were observed (entry 4). Quenching the reaction after only 30 min at room temperature (entry 5) led us to consider even smoother reaction conditions (−10 °C; entry 6). As large amounts of side products were observed, a prolonged reaction at −10 °C was envisioned, and led to much less by-products (entry 7).[15] Finally, a very slow addition of the activated substrate solution to the phenylselenyl chloride reaction mixture led to no observed by-products (entry 8). The purification by flash chromatography on silica gel allowed isolation of diene **6j** in 36 % yield.[16]

Using our best reaction conditions (entry 8), we applied this strategy to other dienes where the Suzuki-Miyaura methodology was inefficient (see table 3.2 page 54), i.e. *p*-MeOPh substituted diene **6g** and silylated diene **6h**. As methyl-substituted diene **6i** includes potential acidic protons, which may be problematic in basic conditions of our (4+1) annulation reaction methodology, we thought to employ the less acidic *n*-Bu substituent in order to have a *n*-alkyl-substituted diene.[17]

The vinyl organocuprate Michael addition and the subsequent selenium-mediated oxidation was performed on Knoevenagel products **12g,h,k** (table 3.8).

[15] It is noted that the use of 1.2 equivalents of NaH (rather than 1.5) does not have an impact on the isolated yield.

[16] The loss of product on silica gel seems to be responsible of this low isolated yield.

[17] Adduct **12k** was synthesized in 43 % yield using a modified Knoevenagel procedure.

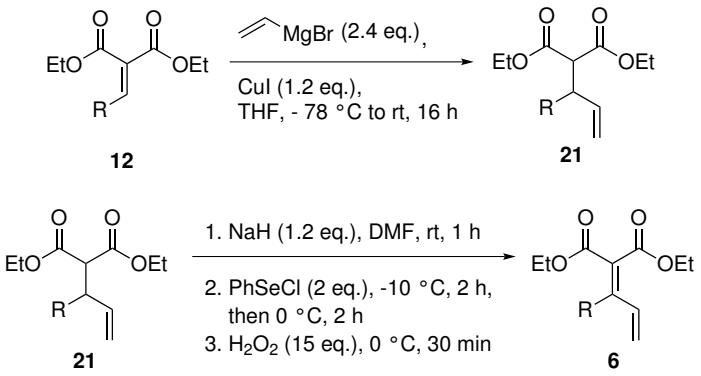


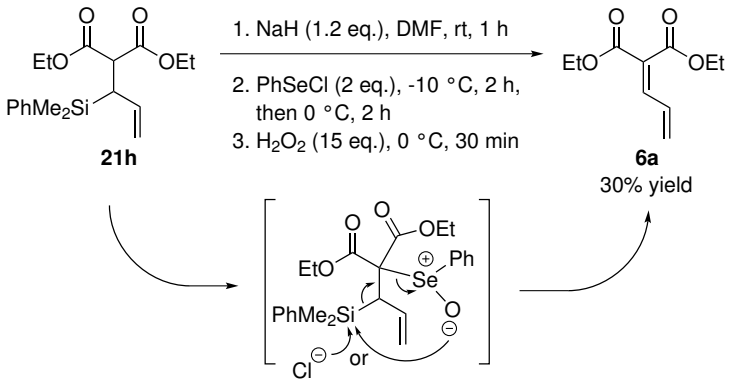
Table 3.8

Substituent	Organocuprate addition (**21**)	Selenium-mediated oxidation (**6**)
i-Pr (**j**)	65 %	36 %[a]
p-MeOPh (**g**)	48 %	47 %
$SiMe_2Ph$ (**h**)	61 %	30 % **6a**
n-Bu (**k**)	96 %	35 %[a]

[a] Carried out with 1.5 equivalents of NaH.

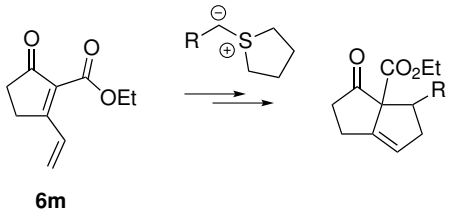
Michael addition reactions occurred in moderate yields, except for *n*-Bu substituted product **21k** where an excellent isolated yield of 96 % was observed. Subsequent oxidation reactions, on the other hand, took place in moderate yields for **6g** and **6k**,[18] whereas, surprisingly, only diene **6a** was synthesized in the case of $SiMe_2Ph$ substitution (scheme 3.17). One could explain diene **6a** isolation by a selenoxide-mediated deprotection of the silyl moiety.

[18]Low isolated yields of **6g** and **6k** are explained by loss of product on silica gel for the former, and by side-reactions for the latter.



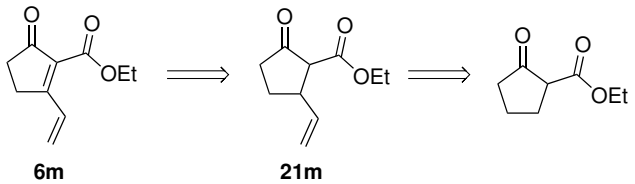
Scheme 3.17

We were also interested in the synthesis of bis-activated diene **6m**. Structurally slightly different from the others, the presence of a cyclic core is particularly interesting as it allows access to a bicyclic scaffold after the (4+1) annulation reaction (scheme 3.18).



Scheme 3.18

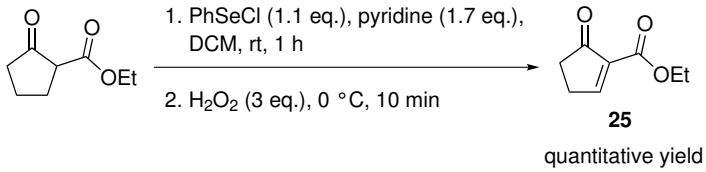
The proposed retrosynthetic pathway is outlined in scheme 3.19. Highly similar to the selenium-mediated oxidation methodology, starting material is however not diethyl malonate as before, but the commercially available ethyl 2-oxocyclopentanecarboxylate.



Scheme 3.19

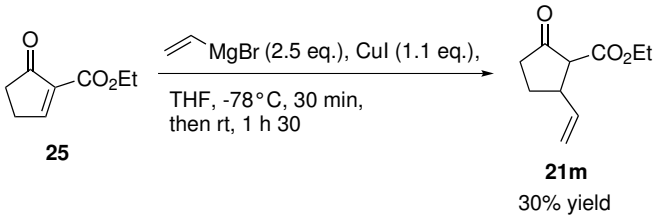
The synthesis of intermediate **21m** requires substrate oxidation before or-

ganocuprate Michael addition reaction. The previously mentioned procedure from Shia (scheme 3.12 page 68) actually describes oxidation reactions on similar substrates.[125] We thus thought to access compound **25** using this procedure (scheme 3.20). The desired product could be obtained in quantitative yield without any further purification.



Scheme 3.20

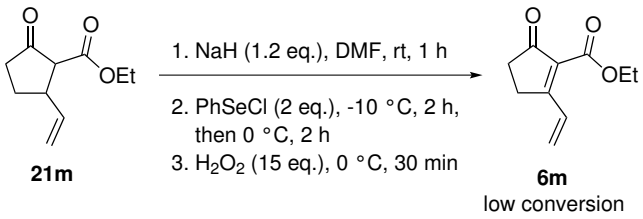
Ethyl 5-oxocyclopent-1-ene-1-carboxylate **25** in hand, Michael addition reaction was next attempted, *via* the same procedure as for previous dienes[19] (scheme 3.21).[125] Pure product **21m** could be isolated in 30 % yield.



Scheme 3.21

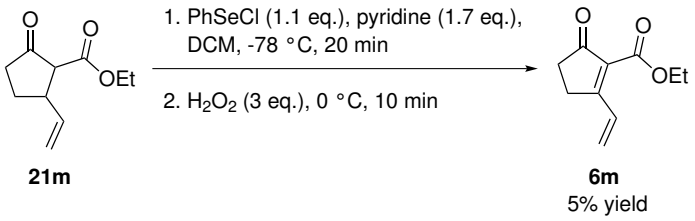
The last step was similar to the synthesis of intermediate **25**, involving selenium-mediated oxidation reaction. We used the procedure developed for the other dienes, involving sodium hydride (scheme 3.22). Although the ^{1}H NMR spectrum of the crude mixture showed small amounts of diene **6m** (together with by-products), no desired product was isolated after the purification by flash chromatography on silica gel.

[19]The reaction mixture was stirred for 1 h 30 at room temperature, rather than 16 h previously.



Scheme 3.22

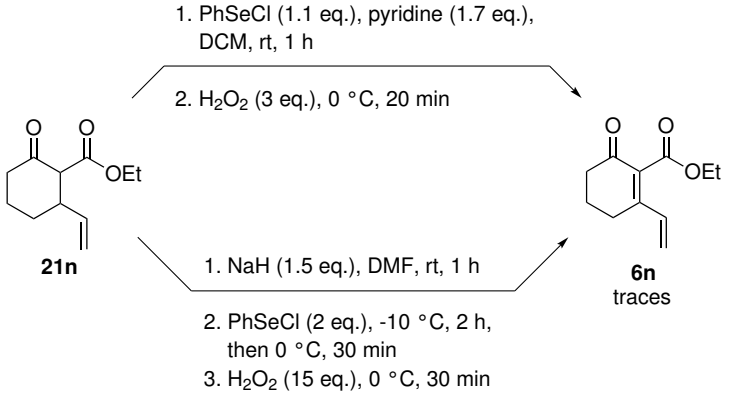
We next applied the reaction conditions involving pyridine, as described in the literature (scheme 3.23).[125] It is noted that the first step was carried out at −78 °C in order to prevent substrate **21m** degradation under the mentioned reaction conditions. Although various by-products were seen on the ^{1}H NMR spectrum of the crude mixture, diene **6m** was observed in significant amount. Subsequent purification by flash chromatography on silica gel allowed however to isolate the desired product in only 5 % yield.



Scheme 3.23

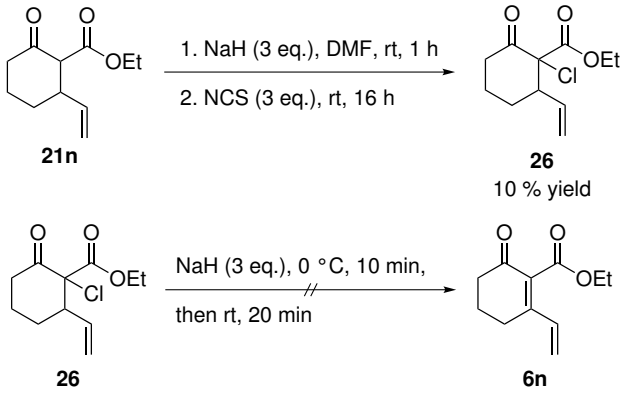
These two last reactions indicate that diene **6m** is unstable on silica gel. Meanwhile, they were applied to similar starting material **21n**, but only traces of diene **6n** was obtained, together with large amounts of by-products (scheme 3.24).[20]

[20]Syntheses of intermediate **21n**, as well as both oxidation reactions were carried out by Alexandre Begasse during his internship.



Scheme 3.24

As these two procedures did not lead to the diene, chlorination[21] and subsequent hydride-mediated elimination reactions were performed on intermediate **21n**, as previously attempted for *i*-Pr substituted diene **6j** page 68 (scheme 3.25).[22] Although chlorinated compound **26** was isolated in 10 % yield, the further hydride-mediated elimination generated degradation products.



Scheme 3.25

We did not further explore strategies in order to reach dienes **6m,n**, focusing our synthetic effort towards the synthesis of other 1,3-dienes.

We could then access, *via* Suzuki-Miyaura and selenium-mediated strategies, numerous 1,1-bis-activated 1,3-dienes. However, all these dienes are substituted

[21] *Via* N-chlorosuccinimide.

[22] Synthesis of **26** and subsequent elimination reaction were carried out by Alexandre Begasse during his internship.

at the second position of the diene moiety. We envisioned to also study our (4+1) annulation reaction strategy with 3-substituted 1,3-dienes.[23]

3.2.3 Synthesis of 3-substituted dienes by a Knoevenagel condensation

In order to have 3-substituted 1,3-dienes in hand, we applied the Knoevenagel procedure of diene **6a**[111] to methacrolein and dimethyl malonate substrates (table 3.9, entry 1). However, only dimethyl malonate was recovered.

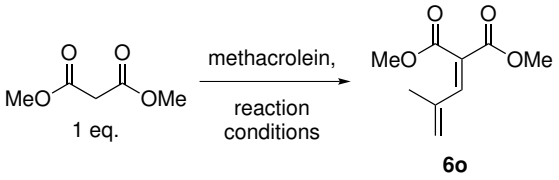


Table 3.9

Entry	Reaction conditions
1	1. LiBr (0.2 eq.), Ac_2O (1.7 eq.), 80 °C, 2 h
	2. methacrolein (3 eq.), 80 °C, 1 h
2	methacrolein (1 eq.), $Me_2NH.HO_2CNMe_2$ (0.5 eq.), rt, 16 h
3	methacrolein (1.2 eq.), $NbCl_5$ (0.2 eq.), rt, 16 h
4	1. methacrolein (1 eq.), $TiCl_4$ (2 eq.), CCl_4/THF, 0 °C, 20 min
	2. pyridine (4 eq.), rt, 16 h

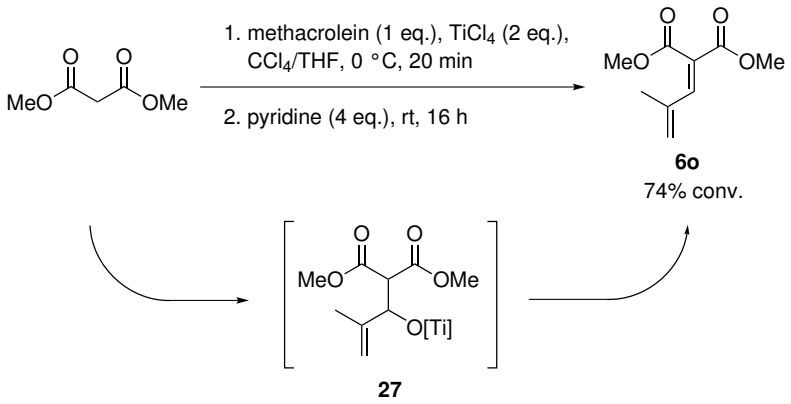
As we suspected that the problem was coming from methacrolein degradation due to the high temperature, we searched for a softer procedure. In 2013, Mase and co-workers described a Knoevenagel condensation reaction between malonate derivatives and aromatic aldehydes in mild solvent-free reaction conditions.[131] It is noted that they used dimethylammonium dimethylcarbamate (DIMCARB) as a catalyst.[24] We thus envisioned applying this procedure to our substrates (table 3.9, entry 2). However, a 0 % conversion was observed on the ^{1}H NMR spectrum of the crude mixture.

[23] We envisioned that the use of such dienes as substrates for our (4+1) annulation reaction methodology implies regioselectivity problems, as 1,4-ylide addition can now competes with 1,6-addition. Such results were indeed already obtained with non-substituted diene **6a** (scheme 1.50 page 39).

[24] The aldehyde is reacting with this latter to lead the iminium activated substrate, that subsequently undergoes a nucleophilic addition from the malonate derivative, to furnish the product and the release of the amine catalyst.

Another procedure was then attempted (table 3.9, entry 3).[132] This latter was indeed employed to carry out Knoevenagel condensation reactions between various malonate derivatives and aromatic/aliphatic aldehydes.[132] It involves $NbCl_5$ as a Lewis acid, in solvent-free conditions, but, unfortunately, the ^1H NMR spectrum of the crude mixture showed only by-products.

Eventually, titanium tetrachloride was employed as a Lewis acid (table 3.9, entry 4).[25] Indeed, Sosnovskikh and co-workers successfully performed, using this activating reagent, Knoevenagel condensation reactions with 2-trifluoromethylchromone and compounds bearing an active methylene group.[133] Titanium (IV) alkoxide complex **27** was first generated, followed by pyridine-mediated elimination reaction, giving diene **6o** (scheme 3.26).



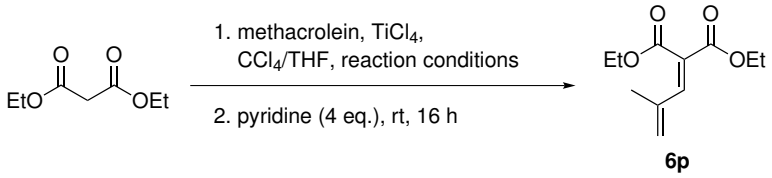
Scheme 3.26

We were pleased to observe a 74 % conversion towards the desired diene, without any other by-products. The use of 6 equivalents of $TiCl_4$ led to only malonate and by-products. Finally, the change of dimethyl to diethyl malonate gave a lower conversion (57 %), but no side-products were observed.

In order to further improve the conversion, various reaction conditions were screened, using diethyl malonate because of similarity to previous dienes, as depicted in table 3.10 (entry 1 refers to standard reaction conditions.).[26] The table is discussed afterwards.

[25] Titanium tetrachloride THF complex is first generated, stirring a CCl_4 solution of $TiCl_4$ in THF for 10 min at 0 °C. Methacrolein and dimethyl malonate were then added to this mixture.

[26] For all entries, $TiCl_4(THF)_2$ complex was generated by stirring a CCl_4 solution of $TiCl_4$ for 10 min at 0 °C in THF.



6p

Table 3.10

Entry	ald.; malonate (eq.)	$TiCl_4$ (eq.)	Reaction conditions	Conversion to **6p**[a]
1	1.0; 1.0	2.0	0 °C, 20 min	57 %
2	1.0; 1.0	2.0	0 °C, 1 h	59 %
3	1.0; 1.0	2.0	0 °C, 20 min, then rt, 45 min	56 %
4	1.0; 1.0	2.0	0 °C, 1 h, then rt, 45 min	57 %
5	1.5; 1.0	2.0	0 °C, 20 min	48 %
6	1.0; 1.0	3.0	0 °C, 20 min[b]	65 %
7[c,e]	**2.0**[d]**; 1.0**[d]	**4.0**	**0 °C, 20 min**	**88 %**

[a] Calculated on the ^{1}H NMR spectrum of the crude mixture.

[b] In order to generate $TiCl_4.(THF)_2$ in similar conditions, THF and CCl_4 volumes were consequently increased by a 1.5 factor.

[c] Pyridine was added very slowly (60 µL min^{-1}).

[d] Methacrolein and diethyl malonate were added very slowly (30 µL min^{-1}).

[e] Using 8 eq. of pyridine in order to have the same ratios as compared to methacrolein and $TiCl_4$.

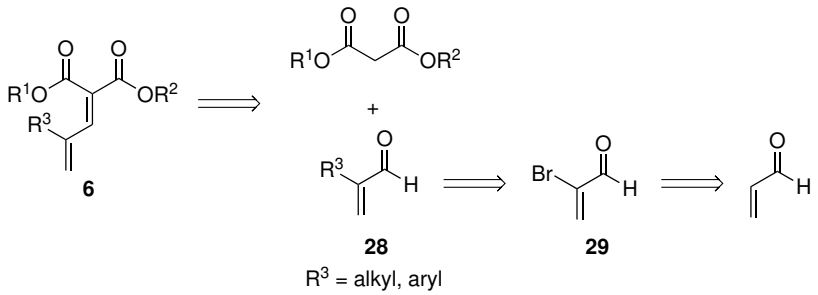
We found that the use of less diethyl malonate gives the best conversion towards diene **6p** (88 %) (entry 7).

Purification of the diene by flash chromatography on silica gel led however to a dramatic decrease in the yield (43 %). Accordingly, the crude mixture, being only a mixture of diene **6p** and diethyl malonate in 7/1 ratio, was used in (4+1) annulation reactions with no further purification (a 88 % crude yield is calculated).

Application of best reaction conditions to dimethyl malonate substrate generated diene **6o** in a slightly lower 77 % crude yield.[27]

In order to develop a general strategy leading to 3-substituted 1,1-dicarbonyl 1,3-dienes, the following retrosynthesis pathway was proposed (scheme 3.27).

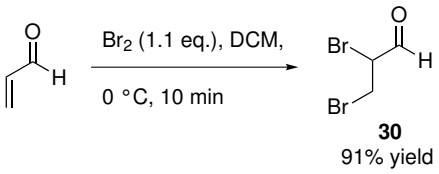
[27] The remaining dimethyl malonate could be removed in the workup *via* a basic treatment.



Scheme 3.27

From acrolein, 2-bromoacrylaldehyde **29** can be synthesized from conjugate bromination/elimination reactions. Afterwards, a Suzuki-Miyaura cross-coupling reaction furnishes the aldehyde substrate **28**, which is used for the Knoevenagel condensation reaction with various malonate derivatives, leading to diene **6**.

The bromination reaction was performed on acrolein, yielding to 2,3-dibromopropanal **30** in 91 % yield (scheme 3.28).[134]

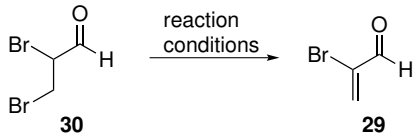


Scheme 3.28

The synthesis of desired geminally-substituted vinyl derivative **29** is described by Li and co-workers, by simply stirring a DMSO solution of compound **30** for 2 h at 60 °C (scheme 3.29).[134] Whereas desired product was observed in the crude mixture ^{1}H NMR spectrum, the presence of additional by-products prompted us to reduce the reaction time to 1 h. Unfortunately, less product **29** was observed, together with starting material and side-products. Furthermore, the mass loss is significant, starting from 1 g of compound **30** only 300 mg of crude was obtained.

Scheme 3.29

As it seems that substrate **30** and/or product **29** are unstable under the mentioned reaction conditions, various milder procedures were performed in order to successfully have 2-bromoacrylaldehyde **29** in hand (table 3.11).



30 **29**

Table 3.11

Entry	Reaction conditions	Results
1	DBU (1.5 eq.), DCM, rt, 20 min	degradation products
2	pyridine (5 eq.), THF, 50 °C, 5 min	1/4 **29**/**30**[a] + USP[b]
3	**Et_3N (1.2 eq.), THF, −78 °C to rt**[c]	**74 % yield**
4	DBU (1.1 eq.), THF, 0 °C, 15 min	57 % yield
5	DBU (1.1 eq.), Et_2O, 0 °C, 15 min	58 % yield

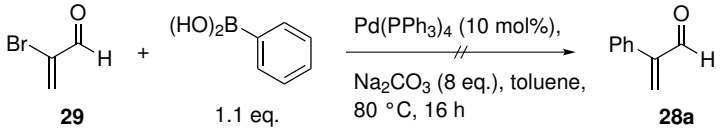
[a] Calculated on the ^{1}H NMR spectrum of the crude mixture.

[b] Unidentified side-products.

[c] Stirring for 5 h.

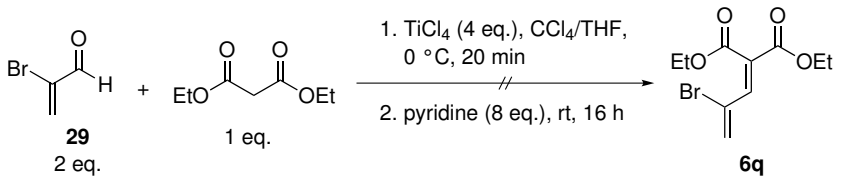
We first tested the reaction conditions derived from the Suzuki-Miyaura strategy previously mentioned in the manuscript (entry 1). However, only degradation products were observed. Exposure of substrate to pyridine, under harsher reaction conditions (50 °C), but only for 5 min (entry 2) generated desired product **29** but together with by-products and remaining starting material. As a smaller conversion was observed for entry 2, a stronger base was then used, under very mild reaction conditions (entry 3). A good yield of 74 % must be noted, with no remaining substrate. The use of a stronger base (DBU), at 0 °C for 15 min (entry 4), furnished a lower isolated yield, although no starting material was observed. The change of THF to Et_2O, in order to ensure that a potential loss of product, due to partial transfer to the aqueous phase during the workup, did not take place (entry 5), gave the same yield. This latter hypothesis is thus excluded.

Having compound **29** in hand, the Suzuki-Miyaura cross-coupling reaction was then attempted, leading to atropaldehyde **28a** (scheme 3.30).[135] Analyses of the ^{1}H NMR spectrum of the crude mixture however showed only large amounts of aromatics signals, without any desired compound **28a**.



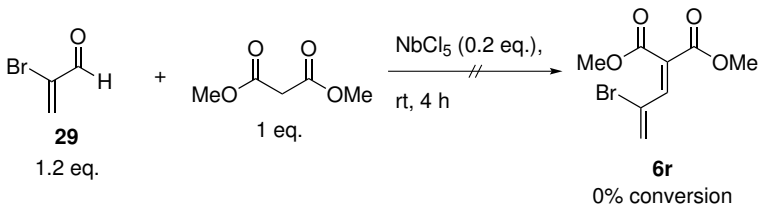
Scheme 3.30

This observation could be explained by substrate/product degradation under these harsh reaction conditions (80 °C for 16 h). We thus thought to perform the Knoevenagel condensation before the Suzuki-Miyaura cross-coupling reaction, as the first occurs in milder reaction conditions (see entry 7 table 3.10 page 80), affording diene **6q** (scheme 3.31). Unfortunately, only large amounts of malonate starting material, together with side-products, were observed on the ^{1}H NMR spectrum of the crude mixture.



Scheme 3.31

Another procedure was then attempted, using $NbCl_5$ as a Lewis acid, and dimethyl malonate, in solvent-free reaction conditions (scheme 3.32). Let's remembered that this procedure was already tested for the synthesis of 3-methyl substituted diene **6o** (see table 3.9 entry 3, page 78). Only dimethyl malonate substrate was recovered.

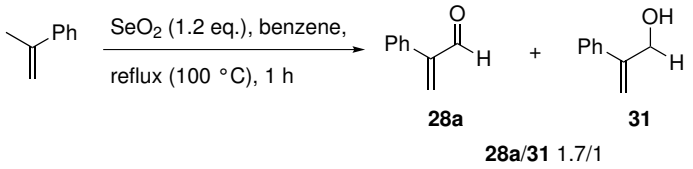


Scheme 3.32

These unsuccessful attempts prompted us to reconsider our retrosynthetic pathway, by firstly focusing our attention on the main reaction, namely the Knoevenagel condensation, using atropaldehyde **28a**, this latter being obtained *via* another method. Depending upon the results, a more general procedure to

synthesize scaffold **28** will be envisioned afterwards.

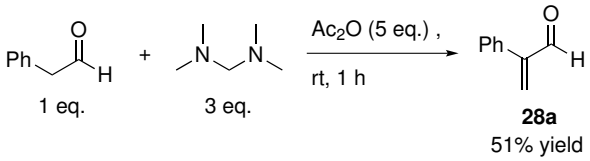
Atropaldehyde can indeed be generated by α-methylstyrene oxidation, refluxing a benzene solution of this latter and selenium dioxide for 1 h, as described by Davies (scheme 3.33).[136] The crude mixture showed desired product **28a** together with corresponding alcohol **31** and large amounts of aromatic by-products. Unfortunately a purification by flash chromatography on silica gel did not allow isolation of the product.



Scheme 3.33

Performing the reaction for 1 h at 90 °C or for 45 min at 85 °C did not decrease the amount of by-products and alcohol derivative **31**, and using toluene as a solvent generated a slow conversion, together with side-products.[28]

As the problem is certainly coming from harsh reaction conditions, another method was envisioned (scheme 3.34).[137] It implies methylene group addition onto phenylacetaldehyde, in the form of an iminium moiety.



Scheme 3.34

The desired product could be obtained in 51 % yield, smoothly, without any by-product or any purification.

Eventually, the Knoevenagel condensation was carried out with dimethyl malonate (table 3.12, entry 1). Large amounts of atropaldehyde and dimethyl malonate starting materials were recovered, together with aromatic by-products. A tiny amount of desired diene **6s** was, however, observed on the ^{1}H NMR spectrum of the crude mixture (0.07/1 **6s**/malonate).

[28] Stirring for 1 h at 120 °C allowed a complete conversion but, again, together with large amounts of aromatic by-products.

We thus improved our previous best reaction conditions developed for 3-methyl substituted dienes **6o,p** (entries 2-7).[29] Results are discussed afterwards.

[29]For all entries, $TiCl_4(THF)_2$ complex was generated as previously, stirring a CCl_4 solution of $TiCl_4$ for 10 min at 0 °C in THF.

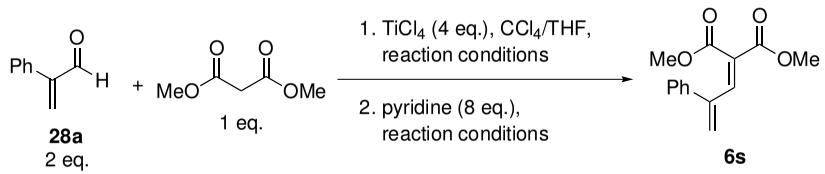


Table 3.12

Entry	Reaction conditions (1.)	Reaction conditions (2.)	Results (**6s**/malonate)[a]
1	0 °C, 20 min	rt, 16 h	substrates + **6s** (0.07/1) + USP (A)[b]
2	0 °C, 20 min	40 °C, 3 h 30	substrates + **6s** (0.14/1) + USP (A)[b]
3	0 °C, 20 min	rt, 15 min[c], then reflux,[d] 1 h 15	substrates + **6s** (0.7/1) + USP (A)[b]
4	0 °C, 20 min	rt, 15 min[c], then reflux,[d] 2 h 30	substrates[e] + **6s** (1.8/1) + USP (A)[b]
5	0 °C, 20 min	rt, 15 min[c], then reflux,[d] 3 h 30	almost no substrates + **6s** (3.8/1) + USP (A)[b]
6	0 °C, 20 min[f]	rt, 15 min[c], then reflux,[d] 1 h	substrates + **6s** (1/1) + USP (A)[b]
7	**−78 °C, 40 min**	**rt, 30 min[c], then reflux,[d] 2 h**	**almost no substrates + 6s + USP (A)[b]**

[a] Calculated on the ^{1}H NMR spectrum of the crude mixture.

[b] Unidentified aromatics side-products (a: small amounts; A: large amounts).

[c] Addition at 0 °C (entries 3-6) or −78 °C (entry 7).

[d] THF boiling point is 66 °C.

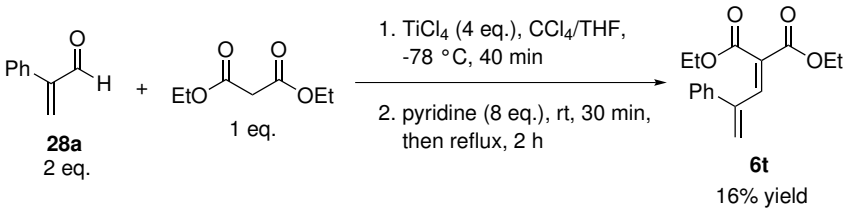
[e] In lower amounts than for entries 1-3.

[f] Addition at −78 °C.

We first focused our attention on the elimination step (conditions 2.), using harsher reaction conditions (40 °C; entry 2). We observed a better **6s**/malonate ratio. Entries 3-5 indicate that using even harsher reaction conditions is beneficial for the conversion, this latter increasing from entry 3 to 5, with almost no remaining substrates for entry 5.

As large amounts of aromatic signals were observed for all previous entries (1-5), we thought to improve the reaction conditions of the first step (the titanium-promoted malonate addition onto atropaldehyde), using smooth reaction conditions (entry 6).[30] The better ratio (as compared to entry 3) allowed us to use even milder reaction conditions (entry 7). We observed mainly diene **6s** (together with large quantities of aromatics by-products), which could be isolated in 34 % yield.

We did not envision to further improve these reaction conditions. Using diethyl malonate, diene **6t** was isolated in 16 % yield (scheme 3.35). Indeed, the crude mixture showed an incomplete conversion, with more by-products than previously.



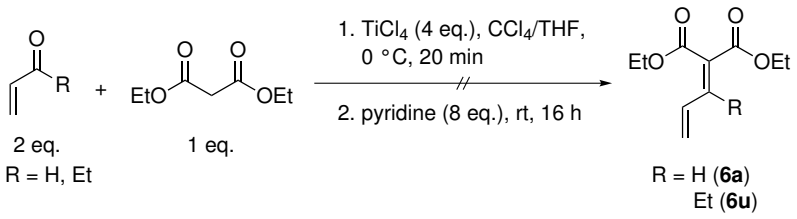
Scheme 3.35

We next considered the development of a general and straightforward methodology for non- and 2-substituted dienes synthesis, using the Knoevenagel condensation reaction.

3.2.4 Knoevenagel condensation for non- and 2-substituted dienes synthesis

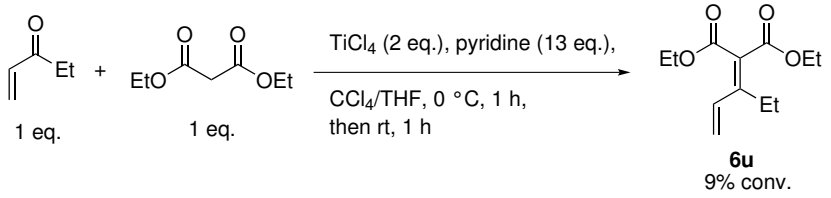
We first applied our titanium-mediated Knoevenagel condensation reaction to acrolein and ethyl vinyl ketone, to obtain diene **6a** and 2-substituted diene **6u** respectively (scheme 3.36). Unfortunately, only diethyl malonate starting material was observed on the ^{1}H NMR spectra of both crude mixtures.

[30] Atropaldehyde can indeed be unstable in the presence of $TiCl_4$.



Scheme 3.36

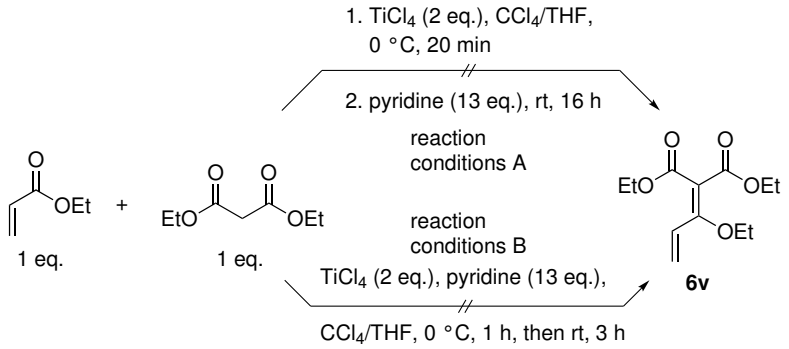
Using ethyl vinyl ketone, a similar procedure was then performed, with a double quantity of malonate and more pyridine (scheme 3.37).[138] It is noted that $TiCl_4$, starting materials and pyridine were successively added in the reaction mixture. We were pleased to observe diene **6u**, but only in small amounts (9 % conversion). Unfortunately, after purification by flash chromatography on silica gel, no desired diene was isolated.[31] An increased reaction time at room temperature (3 h) gave the same conversion, whereas only stirring 2 h at 0 °C, followed by the workup, resulted in no conversion at all.



Scheme 3.37

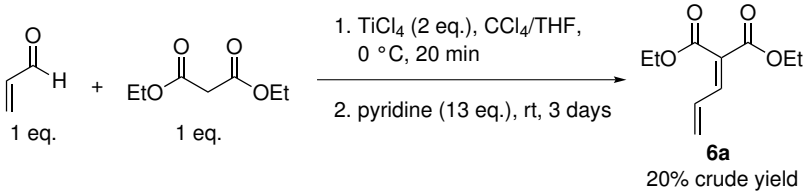
As the ketone moiety (instead of an aldehyde) may be problematic, this latter scaffold was replaced by an ester (ethyl acrylate). Using the same ratio of reagents as the previous scheme, the two mentioned procedures were employed (scheme 3.38).[133,138] It is important to note that procedure A involves $TiCl_4(THF)_2$ complex generation for 10 min at 0 °C before starting materials addition. Analyses of the crudes mixtures by ^{1}H NMR indicated 0 % yield in product **6v**, as only diethyl malonate was observed for both reactions.

[31] Mixtures of diene and large amounts of diethyl malonate starting material were retrieved.



Scheme 3.38

Application of reaction conditions A using acrolein generated, on the contrary, 20 % conversion towards diene **6a** (scheme 3.39). Compared to scheme 3.36 (page 88), where no diene was observed, the quantity of malonate was doubled, using more pyridine. It is emphasized that reaction monitoring by ^{1}H NMR indicated no further increase of conversion after 16 h of reaction at room temperature. In order to push the equilibrium towards desired diene, 5 equivalents of acrolein were employed. Unfortunately, no conversion was observed. Using harsher conditions (4 equivalents of titanium tetrachloride),[32] led to no reaction neither, even with increased reaction time (monitoring up to two days).



Scheme 3.39

As best results were encountered with acrolein, we decided to improve the conversion using this starting material. We first investigated a lithium bromide catalyzed Knoevenagel condensation (table 3.13, entry 1).[111] Indeed, this procedure was applied to have diene **6a** in hand (see scheme 1.49 page 39).

[32] With 2 equivalents of acrolein.

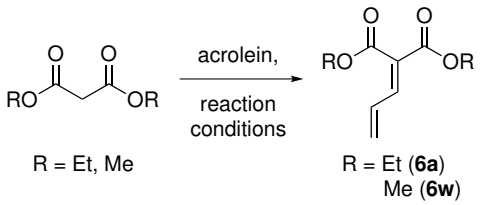
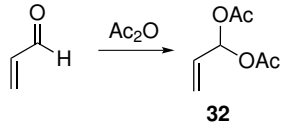


Table 3.13

Entry	R	Reaction conditions
1	Me	1. LiBr (0.2 eq.), Ac_2O (2 eq.), 80 °C, 2 h 2. acrolein (3 eq.), 80 °C, 7 h
2	Et	acrolein (1.2 eq.), $NbCl_5$ (0.2 eq.), rt, 3 h
3	Me, Et	acrolein (1 eq.), L-lys.HCl (0.2 eq.), Et_3N (0.2 eq.), DMSO, rt, 16 h
4	Me, Et	acrolein (5 eq.), piperidine (4 drops), DCM, rt, 1 h

Surprisingly, product **6w** could be isolated in only 25 % yield after purification by flash chromatography on silica gel, together with large amounts of by-products, whereas Dumas and co-workers highlighted an excellent isolated yield of 87 % for the synthesis of this specific diene.[111] In addition, ^{1}H NMR analyse of the crude mixture revealed the presence of a vinylic by-product in a significant amount, in agreement with the structure **32** represented below (in 1.8/1 **6w**/**32** ratio; scheme 3.40).



Scheme 3.40

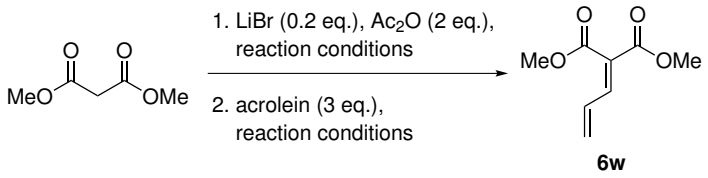
We then explored other methods in order to increase the conversion. We first investigated a $NbCl_5$ catalyzed Knoevenagel condensation, as previously attempted for 3-substituted 1,3-dienes (table 3.13, entry 2).[132] However, diethyl malonate substrate was the only observed compound. Using 5 equivalents of acrolein and stirring for 7 h at 50 °C gave the same 0 % conversion.

In 2011, Guan and co-workers disclosed an efficient L-lysine mediated Knoevenagel condensation between various α,β unsaturated aldehydes and 1,3-dicarbonyl compounds.[139] The application of this procedure to diethyl malon-

ate and dimethyl malonate did however not generate desired dienes, as only starting material and degradation products were observed (table 3.13, entry 3).

We then attempted another procedure, involving piperidine as a catalyst (table 3.13, entry 4).[140] These mild reaction conditions were indeed employed to perform a Knoevenagel product starting from cinnamaldehyde and dimethyl malonate. However, only degradation products were observed after only 1 h of reaction, with no trace of any remaining starting materials.

As the best way to synthesize dienes **6a,w** is the LiBr-catalyzed Knoevenagel condensation so far,[33] we envisioned optimizing the reaction conditions using this methodology (table 3.14). It is noted that entry 1 refers to the reaction conditions from the previous table.



6w

Table 3.14

Entry	Reaction conditions (1.)	Reaction conditions (2.)	Results
1	80 °C, 2 h	80 °C, 7 h	**6w** (25 %)[a] + **32**[b] + USP (A)[c]
2[d]	80 °C, 2 h	80 °C, 5 h	**6w** + USP (A)[c]
3	80 °C, 2 h	80 °C, 1 h 30	**6w** (23 %)[a] + USP (A)[c]
4	80 °C, 2 h	50 °C, 16 h	**6w** + USP (A)[c]
5	80 °C, 1 h	50 °C, 16 h	**6w** + USP (A)[c]
6	60 °C, 2 h	50 °C, 16 h	**6w** + USP (A)[c]
7[e]	**80 °C, 1 h**	**50 °C, 16 h**	**6w (37 %)[a] + USP (A)[c]**
8[e]	60 °C, 2 h	50 °C, 16 h	**6w** + USP (A)[c]
9[f]	80 °C, 1 h	50 °C, 16 h	**6w** + USP (A)[c]

[a] Isolated yield after purification by flash chromatography on silica gel.

[b] A mixture of **6w** and **32** in 1.8/1 ratio was observed on the ^{1}H NMR spectrum of the crude mixture.

[c] Unidentified side-products (a: small amounts; A: large amounts).

[d] A large excess of acrolein was used.

[e] Addition of Ac_2O just before acrolein.

[f] Using $(CF_3CO)_2O$ (1 eq.) instead of Ac_2O (2 eq.), added just before acrolein.

[33] See scheme 1.49 page 39 for **6a**, and entry 1 of previous table for **6w**.

In order to improve the conversion, a large excess of acrolein was employed (entry 2). More by-products were observed, without improving the conversion. Reaction monitoring by ^{1}H NMR revealed a complete conversion after only 1 h 30 of reaction (entry 3). The purification of this last crude mixture by flash chromatography on silica gel allowed isolation of **6w** in similar yield as entry 1 (23 %). Interestingly, no compound **32** was observed on the crude ^{1}H NMR spectrum, but major other by-products were still detected.

Since the reaction is over after only 1 h 30 at 80 °C, a milder procedure was performed (heating at 50 °C; entry 4). Reaction monitoring by ^{1}H NMR informed us that malonate was still present in the reaction mixture after 4 h 30 of reaction, but a full conversion was observed after 16 h. The ^{1}H NMR spectrum of the crude mixture indicated less by-products.[34]

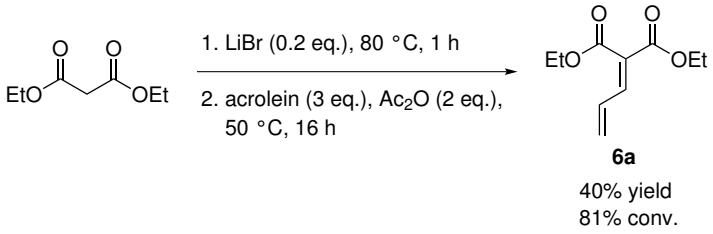
As the observed side-products could come from the first 2 h at 80 °C (malonate degradation), a decrease to 1 h was carried out (entry 5). Unfortunately, these less drastic reaction conditions did not allow a reduction of side-products. It should be emphasized that no impact on **6w** amount was observed either. A milder procedure, involving a stirring for 2 h at 60 °C (entry 6), interestingly gave similar results.

Because acetic anhydride could be the reason of the poor results (by promoting the degradation of malonate starting material during the first step), we envisioned to add this reagent at the end of this step, just before the addition of acrolein, but similar results were observed (entry 7). Subsequent purification by flash chromatography on silica gel allowed isolation of diene **6w** in 37 % yield. It is noteworthy, like entries 5-6, that decreasing the temperature for the first step (from 80 °C to 60 °C) gave similar results (entry 8). Finally, changing Ac_2O to the more active trifluoroacetic anhydride generated only a little amount of the desired diene (entry 9).

The slightly better results observed for entry 7 (associated with a shorter first step) led us to consider these reaction conditions for the further attempts.

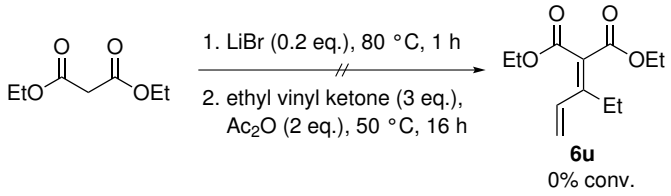
These reaction conditions were first applied to diethyl malonate. We were pleased to observe an isolated yield of 40 % towards diene **6a** after purification by flash chromatography on silica gel (scheme 3.41). Contrary to dimethyl malonate, starting material was recovered.[35] Let's remember that using standard reaction conditions, diene **6a** was isolated in only 17 % yield (see scheme 1.49, page 39).

[34] Whereas still in significant amounts.
[35] An approximately 81 % conversion was calculated.



Scheme 3.41

Encouraged by these results, ethyl vinyl ketone was used as a substrate, in order to synthesize a 2-substituted 1,3-diene (scheme 3.42). Unfortunately, only starting material was retrieved. The use of harsher reaction conditions did not allow to push forward the conversion, as a mixture of malonate starting material and degradation products were observed.[36]



Scheme 3.42

Whereas we improved the methodology for the synthesis of dienes **6a,w**, application of these reaction conditions to other substrates in order to have 2-substituted dienes did not allow to successfully have these products in hand. As we realised that the amount of work to develop a general Knoevenagel condensation procedure for 1,1-dicarbonylester 1,3-dienes synthesis is tremendous, we did not further spend time and energy optimizing reaction conditions.

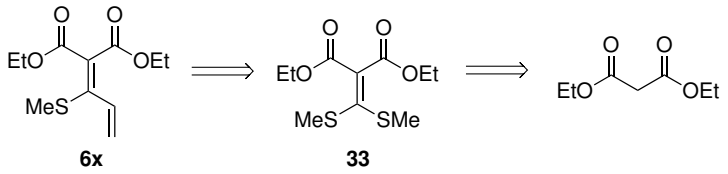
A last strategy was envisioned in the synthesis of 2-substituted 1,3-dienes, in order to access ether and thioether functional groups.

3.2.5 Tandem Michael addition/elimination reactions

This strategy was already applied, unsuccessfully, for the synthesis of diene **6f** *via* vinyl organocuprate Michael addition onto monobrominated precursor **11f** (see scheme 3.6 page 53). Inspired by this methodology, a retrosynthesis

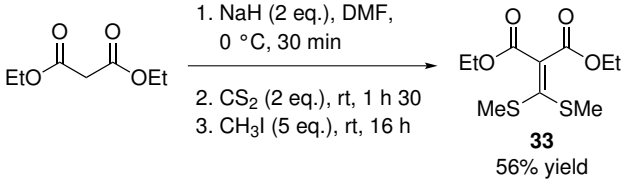
[36] Dimethyl malonate was used as starting material for this latter attempt.

pathway was envisioned in order to have structurally interesting 2-substituted diene **6x** (scheme 3.43)



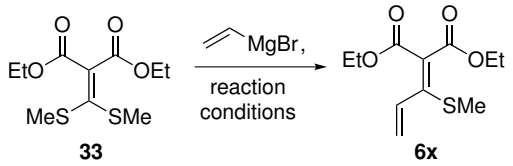
Scheme 3.43

The synthesis of diethyl [bis(methylthio)methylene]malonate **33** was described by Wiles, starting from diethyl malonate, carbon disulfide and methyl iodide (scheme 3.44).[141] The desired compound was obtained in 56 %. A few grams could be synthesized that way.



Scheme 3.44

The requisite intermediate **33** in hand, we then attempted the tandem vinyl organocuprate addition/elimination reactions (table 3.15, entry 1). The ^{1}H NMR spectrum of the crude mixture unfortunately showed only degradation products.



33 **6x**

Table 3.15

Entry	Reaction conditions
1	H_2C=CH-MgBr (1.2 eq.), THF, −78 °C, 1 h 20, then rt, 1 h
2	H_2C=CH-MgBr (1.2 eq.), CuCl (0.4 eq.), THF, −78 °C, 1 h 20, then rt, 16 h
3	H_2C=CH-MgBr (2.5 eq.), Me_2S (5 eq.), CuI (1.1 eq.), THF, 0 °C, 1 h

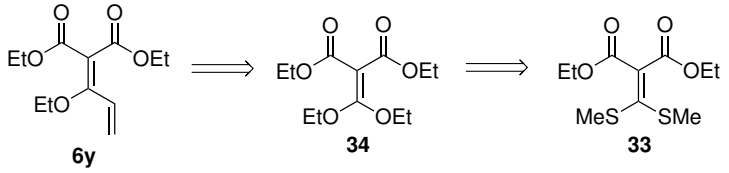
As vinyl Grignard was employed directly, without preliminary cuprate generation, more side reactions can occur. The use of CuCl however did not solve the problem, the crude mixture revealing only degradation compounds (table 3.15, entry 2).[37]

It is to note that previous reaction conditions may be problematic for copper salt solubility (in a −78 °C THF solution). In order to improve the solubility, complexation of copper by dimethyl sulfide was carried out (table 3.15, entry 3).[125] Analyses of ^{1}H NMR spectrum of the crude mixture revealed vinylic signals, but the purification by flash chromatography on silica gel confirmed the absence of diene **6x**.[38]

In line with scheme 3.7 on page 55, where an addition/elimination process of an organolithium reagent on diethyl (ethoxymethylene)malonate furnished the desired substitution product in 52 % yield, we attempted a similar procedure using vinyl Grignard and compound **34**, to lead 2-ethoxy-substituted 1,3-diene **6y** (scheme 3.45).

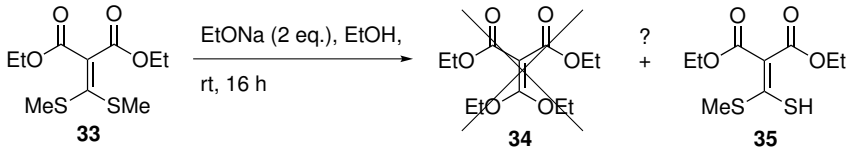
[37] The reaction mixture was stirred for 16 h at room temperature, rather than 1 h previously.

[38] (a) The cuprate reagent was first generated by stirring a mixture of vinyl Grignard, CuI and Me_2S for 30 min at −78 °C, in THF. (b) The exact structure of the vinylic compound by-product could not be determined.



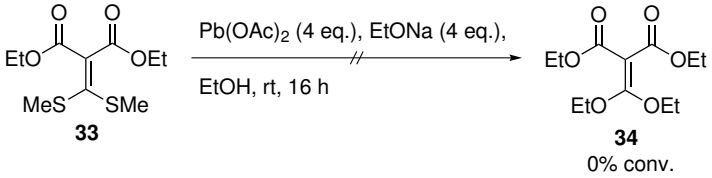
Scheme 3.45

Synthesis of requisite compound **34** was carried out by reacting **33** with sodium ethoxide (scheme 3.46). However, analyses of the ^{1}H NMR spectrum of the crude mixture revealed an almost full conversion into compound **35**.[39]



Scheme 3.46

In 2004, Wang and co-workers disclosed a transformation of dithioacetals to acetals, including synthesis of **34** from a structurally similar compound to that of **33**.[142] Involving lead acetate to catch the released sulfide, compound **34** was isolated in limited 20 % yield. We attempted this procedure on substrate **33**, but, unfortunately, only starting material was observed (scheme 3.47).



Scheme 3.47

As numerous 2- and 3-substituted 1,1-dicarbonyl ester 1,3-dienes were successfully obtained *via* previously mentioned strategies, added to time and effort spent for their synthesis, we did not further explore other methods accessing such scaffold.

[39] It is noteworthy that order of addition of **33** and sodium ethoxide did not influence observations.

The following table lists all the bis-activated 1,3-dienes that were successfully synthesized (table 3.16).[40] The synthetic strategy, as well as the overall yield, are mentioned for each diene. These works led to the publication of an article in 2014.[41]

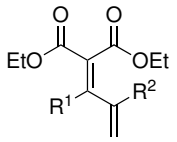


Table 3.16

R^1	R^2	Ref. num.	Synthetic strategy	Overall yield
H	H	**6a**	Knoevenagel condensation (LiBr)	40 %
H	H	**6w**[a]	Knoevenagel condensation (LiBr)	37 %
Ph	H	**6b**	Suzuki-Miyaura cross-coupling	38 %
Ph	H	**6l**[b]	Selenium-mediated olefination	5 %
p-MeOPh	H	**6g**	Selenium-mediated olefination	20 %
p-MePh	H	**6c**	Suzuki-Miyaura cross-coupling	15 %
p-ClPh	H	**6d**	Suzuki-Miyaura cross-coupling	32 %
p-FPh	H	**6e**	Suzuki-Miyaura cross-coupling	28 %
EtO_2C	H	**6f**	Suzuki-Miyaura cross-coupling	44 %
i-Pr	H	**6j**	Selenium-mediated olefination	22 %
n-Bu	H	**6k**	Selenium-mediated olefination	14 %
H	Me	**6o**[a]	Knoevenagel condensation ($TiCl_4$)	77 %
H	Me	**6p**	Knoevenagel condensation ($TiCl_4$)	43 %
H	Ph	**6s**[a]	Knoevenagel condensation ($TiCl_4$)	34 %
H	Ph	**6t**	Knoevenagel condensation ($TiCl_4$)	16 %

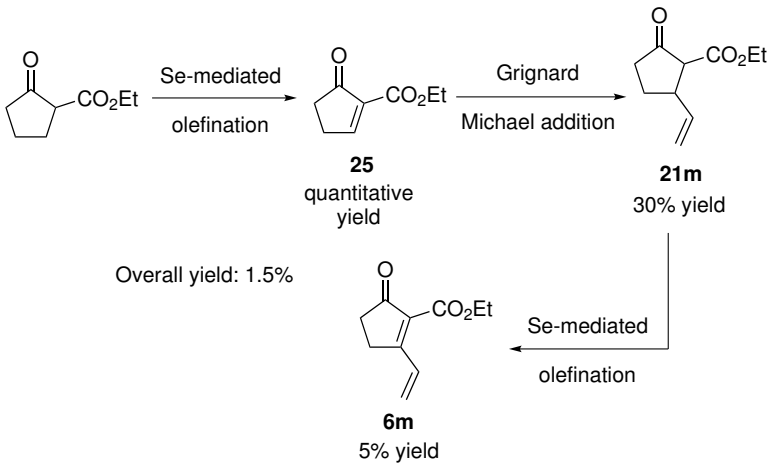
[a] CO_2Me as electron withdrawing groups.

[b] Non symmetric diene: CO_2Me/CO_2Bn as electron withdrawing groups (see the next section, page 98).

In addition, cyclic diene **6m** could be isolated, despite a particularly high loss of diene during the purification on silica gel. Indeed, a 5 % isolated yield must be noted for the last synthetic step (scheme 3.48). As a result, an overall yield of 1.5 % was calculated.

[40] Except diene **6l**; see page 98.

[41] O. Rousseau, T. Delaunay, R. Robiette, *Synlett* **2014**, *25*, 519–522.

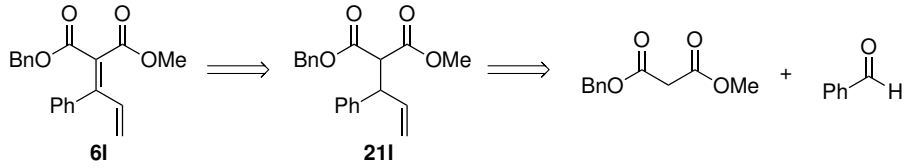


Scheme 3.48

Finally, a last bis-activated 1,3-diene was synthesized, bearing two different electron-withdrawing groups.

3.3 Synthesis and stereochemical studies of diene 6l[42]

This compound is very similar to previous dienes, except that it bears two different electron-withdrawing groups. It was synthesized *via* the Michael addition/selenium-mediated oxidation strategy (scheme 3.49).

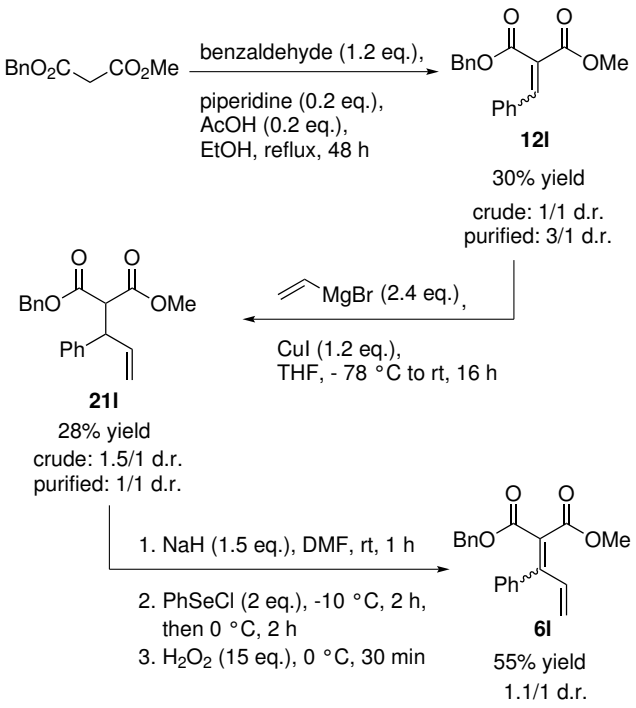


Scheme 3.49

The first step was thus the Knoevenagel condensation between benzylmethyl malonate and benzaldehyde (scheme 3.50). A 1/1 d.r. was observed on the ^{1}H NMR spectrum of the crude mixture. The purification by flash chromatography on silica gel allowed to isolate the product **12l** in 30 % yield as a mixture of

[42] All nOe difference experiments mentioned in this section were carried out by Dr. Cécile Le Duff, using a 500 MHz spectrometer. The irradiation time was set to 0.6 sec, and 8 scans were carried out.

isomers in 3/1 ratio.[43] The low yield is explained by the formation of side-products. The subsequent organocuprate Michael addition led to a mixture of isomers of **21l** (in 1.5/1 ratio). Subsequent purification by flash chromatography on silica gel gave a 28 % isolated yield of isomers mixture (in 1/1 ratio). Although significant amounts of side-products were observed on the ^{1}H NMR spectrum of the crude mixture, this especially low yield is explained by an additional loss of product on silica gel. Finally, the selenium-mediated oxidation reaction was carried out,[44] resulting in diene **6l** as a mixture of E/Z isomers (in 1.1/1 ratio). Subsequent purification by flash chromatography on silica gel allowed isolation of the desired diene in 55 % yield as a mixture of isomers (in 1/1 ratio). Indeed, the presence of two different electron withdrawing groups implies a stereochemical information on diene **6l**, as E and Z isomers can be synthesized.

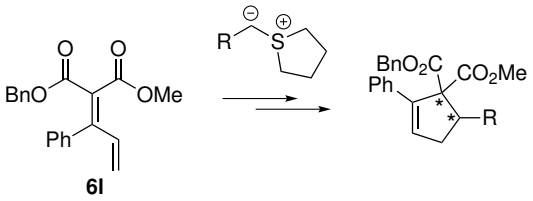


Scheme 3.50

As explained further in this manuscript (see page 129), this diene is especially interesting as it should allow the creation of a new chiral center in the

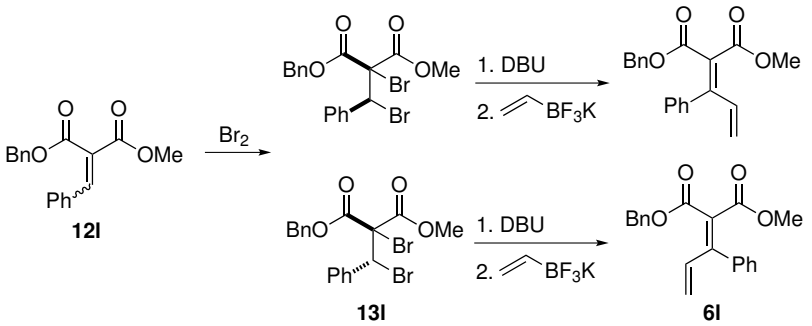
[43] The horizontal distillation being unsuccessful.
[44] Using 1.5 equivalents of NaH.

(4+1) annulation product (scheme 5.1).



Scheme 3.51

The encountered difficulties to isolate intermediates and diene isomers *via* the selenium-mediated olefination strategy (see page 98), added to the non stereoselective character of the synthesis prompted us to consider another strategy to synthesize diene **6l** in a stereoselective manner. We thought to use the Suzuki-Miyaura cross-coupling methodology. Indeed, assuming the stereospecificity of the tandem elimination/cross-coupling reactions, one diastereoisomer of brominated compound **13l** should provide one isomer of diene **6l** (scheme 3.52).



Scheme 3.52

Using general procedure for bromination reaction, large amounts of by-products were observed in the crude mixture by ^{1}H NMR. A mixture of both **13l** isomers, in a 1.3/1 ratio, was however observed, starting from a substrate sample having a 3/1 d.r. Pure compound **13l** could be isolated (as a mixture of isomers) in 33 % yield after purification by flash chromatography on silica gel.[45]

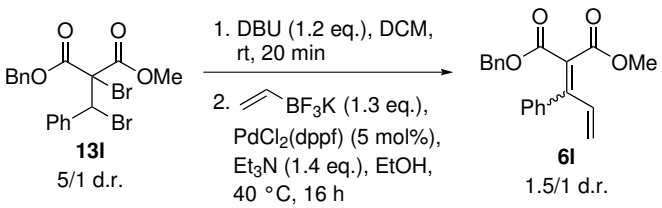
Despite close R_f, a much better ratio could be obtained after multiple attempts.[46] Starting from a crude mixture with a 3/1 d.r., subsequent puri-

[45] The very close R_f did not allow to separate isomers.
[46] Using each time a new batch of the crude mixture.

fication by flash chromatography on silica gel allowed to increase this ratio to 5/1, but together with by-products.[47]

Purification by flash chromatography being especially complicated, we envisioned to use High Pressure Liquid Chromatography (HPLC) method in order to separate both isomers. Using normal phase analytical HPLC, these isomers could be separated, having retention times of 614 s and 663 s,[48] but together with by-products. The change to reverse phase analytical HPLC did not separate the isomers, despite an especially long retention time (1821 s).[49]

Before using our best conditions for preparative HPLC, elimination/Suzuki cross-coupling reactions were first performed on our 5/1 d.r. **13l** sample, in order to confirm the stereospecificity of these two steps (scheme 3.53). Unfortunately, a decrease to 1.5/1 d.r. (for diene **6l**) was observed on the ^{1}H NMR spectrum of the crude mixture.



Scheme 3.53

As conjugate elimination/Suzuki-Miyaura cross-coupling reactions decrease the d.r., we planned to separate directly E/Z diene **6l** isomers by preparative HPLC. After finding the best conditions on a purified[50] isomer mixture,[51] a preparative separation attempt was carried out.[52] Retention times being much higher than for the analytical analysis,[53] an improved condition was used,[54] by injecting directly the crude mixture (having a 1/1 d.r.), allowing to have the best isolated yield as possible. This technique was however problematic, as E and Z isomers were not any longer separated after few automated injections.[55]

[47] Syntheses and purification attempts were performed by Trieu-Van Tran.
[48] CHIRALPAK IB; isohexane/EtOH 98/02 0.8 mL min^{-1}.
[49] Waters Symmetry C_{18}; H_2O/MeCN 45/55 1 mL min^{-1}.
[50] Carried out by flash chromatography on silica gel.
[51] Reverse phase HPLC (retention times of 438 s and 469 s); Waters XBridge C_{18}; H_2O/MeCN 50/50 1 mL min^{-1}.
[52] The sample was automatically injected every 15 min (900 s), in order to have a continuous system allowing to isolate larger amounts of pure products (the collector being calibrated on signals intensity). Besides, the flow was setted up to 4.5 mL min^{-1}.
[53] 1303 s and 1442 s.
[54] Automated injection every 30 min (1800 s), H_2O/MeCN ratio of 60/40.
[55] Observed on the monitoring screen.

We were pleased to observe that simple crude filtration on silica gel solved this problem. Using 46 mg of filtrated crude compound, diluted in 2 mL of acetonitrile, twenty automated injections gave 17.1 mg of one isomer and 10.5 mg of the other.[56] The total amount of *E* and *Z* isomers (27.6 mg) gave rise to an isolated yield of 2 %, but considering the amount of crude mixture that was used (46 mg), a calculated yield of 38 % is highlighted.

Both isomers in hand, nOe difference experiments were then carried out, with both fractions. It is emphasized that to determine absolute configuration, a nOe must be observed between the malonate moiety and the bottom part of the molecule (figure 3.1).

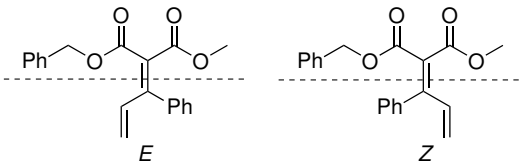


Figure 3.1

Figure 3.2 depicts the first isomer ^{1}H NMR spectrum, and the subsequent table 3.17 sums up nOe results.

[56] In 47/1 d.r. and 1/53 d.r. respectively.

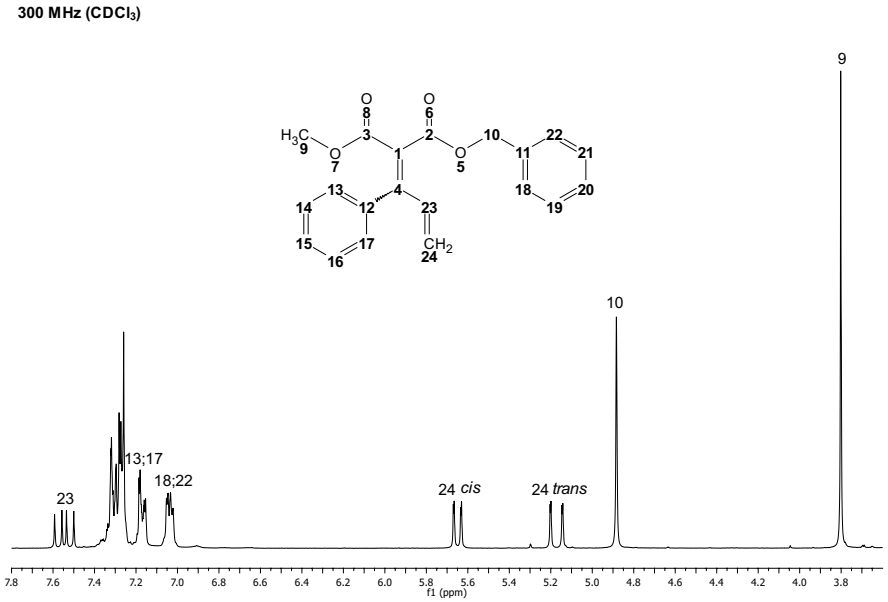


Figure 3.2

Table 3.17

Entry	Signal irradiation	nOe
1	9	no observed nOe
2	24*trans*	24*cis* (28.4 %), 13 and 17 (2.8 %)
3	24*cis*	24*trans* (30.6 %), 23 (13.6 %)
4	23[a]	24*cis* (7.0 %)
5	10	18 and 22 (4.4 %)

[a] Aromatic signals were irradiated together with signal 23.

Entries 1 to 4 enable to determine the structure represented on figure 3.3, whereas entry 5 confirms the presence of the benzyl moiety. Unfortunately, no nOe was observed between the malonate moiety and the bottom part of the molecule represented below. As a consequence, the absolute configuration of this isomer cannot be elucidated using nOe experiments.

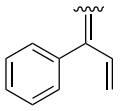


Figure 3.3

Having the other isomer in hand, the same methodology was applied. Figure 3.4 depicts the ^{1}H NMR spectrum, and table 3.18 represents nOe experiments.

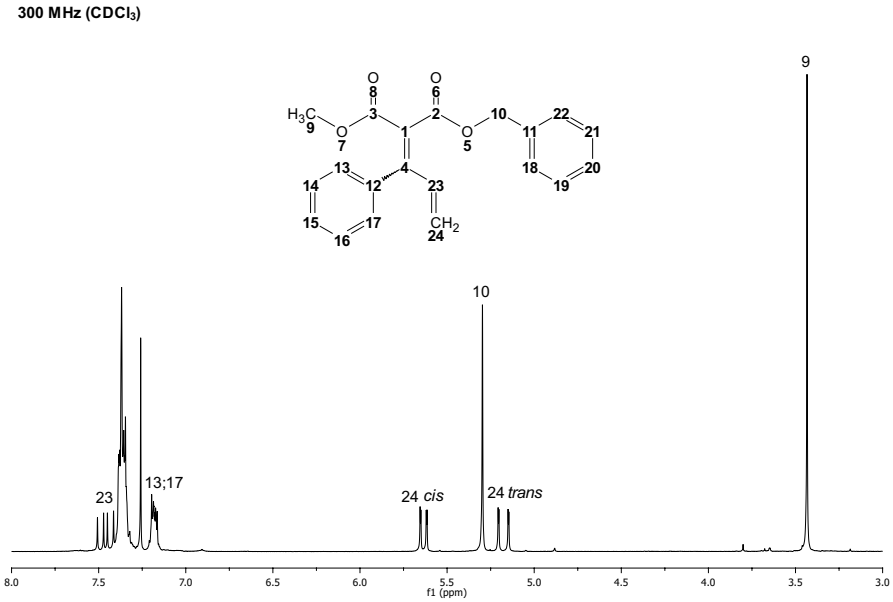


Figure 3.4

Table 3.18

Entry	Signal irradiation	nOe
1	9	no observed nOe
2	10[a]	no observed nOe
3	24*trans*[b]	24*cis* (27.6 %), 13 and 17 (2.4 %)
4	24*cis*	24*trans* (30.5 %), 23 (12.6 %)
5	13 and 17	24*trans* (2.4 %)
6	23[c]	24*cis* (6.6 %)

[a] Signal 10 was irradiated together with signal 24*trans*.
[b] Signal 24*trans* was irradiated together with signal 10.
[c] Aromatic signals were irradiated together with signal 23. Irradiation at slighly higher frequency (in order to avoid aromatic signals irradiation), did not allow to totally irradiate signal 23.

We observed that irradiation of signals 9 and 10 did not give nOe (entries 1 and 2), whereas entries 3 to 6 allowed the same conclusion as previously (bottom part structural elucidation). Unfortunately, no nOe between the malonate part and the bottom part was observed, making impossible the elucidation of the absolute configuration.

These observations could probably be accounted for by conformational issue. Indeed, as depicted in figure 3.5, the esters moieties may be in *s-cis/s-cis* conformation, rather than *s-trans/s-trans* as previously drawn. Such a conformation places Bn/Me ester groups far away from the diene moiety, which would explain the non-observation of nOe.

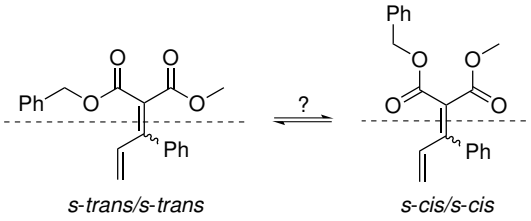


Figure 3.5

As a solvent effects could influence a change of conformation, various deuterated solvents were then screened on crude isomers mixture of diene **6l**,[57] not-

[57] After filtration on silica gel.

ably focusing on significant changes of chemical shifts.[58] We screened DMF-d_7, acetonitrile-d_3, acetone-d_6, methanol-d_4, and benzene-d_6. Except for deuterated benzene, ^{1}H NMR spectra were highly similar as compared to $CDCl_3$. In addition, signal of proton 23 was mixed with aromatic signals in DMF-d_7 and acetonitrile-d_3, making impossible nOe experiments involving this proton. More interesting results were however obtained in deuterated benzene, where signals of protons 23 and 9 were especially shifted as compared to chloroform-d (figure 3.6).

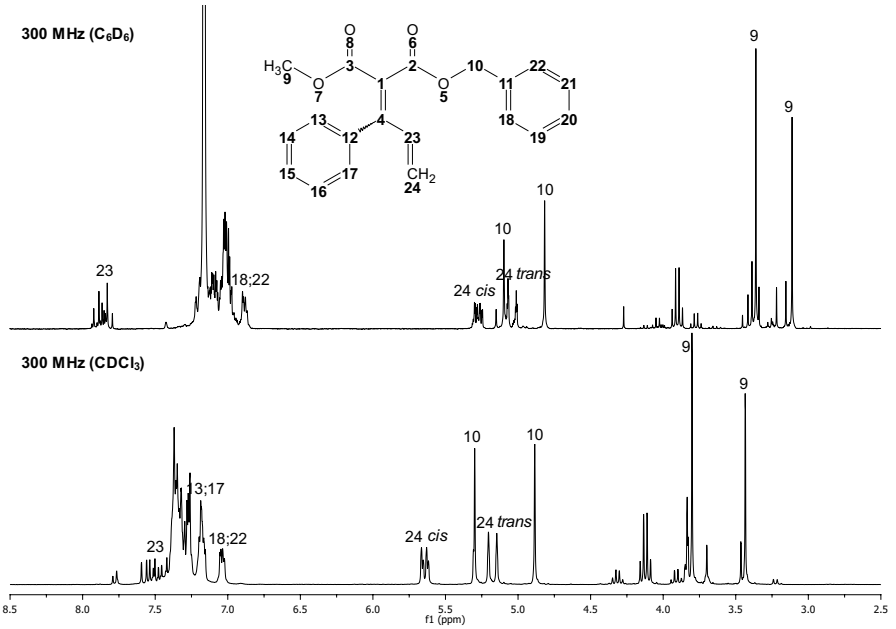


Figure 3.6

A NOESY experiment in C_6D_6[59] unfortunately only confirmed the same bottom scaffold like previous nOe difference experiments (see figure 3.3 page 104). We did not further explored deuterated benzene as a solvent to find the absolute configuration of both isomer fractions.

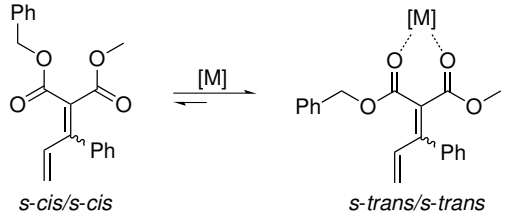
Although the ^{1}H NMR using methanol-d_4 and chloroform-d were highly similar, possible ester rotation due to hydrogen bonding in MeOD led us to nevertheless carry out nOe difference experiments in this solvent, with both pure isomers. Same results were unfortunately obtained. We next thought to perform those experiments at a higher temperature (50 °C) in order to promote

[58] A change of chemical shift may indicate a conformational modification.

[59] Using a 300 MHz spectrometer. The mixing time was set to 0.9 sec, and 32 scans were carried out.

bonds rotation, but again nuclear Overhauser effects between the malonate scaffold and the bottom part of diene **6l** were not observed.

In order to effectively observe nOe to allow us to establish the absolute configuration of each isomer, and in line with our hypothesis, we planned to favor the *s-trans/s-trans* conformation *via* generation of a metal complex (scheme 3.54).



Scheme 3.54

Because the complexation should involve a change of signals chemical shifts, effects of metal addition were observed on the ^{1}H NMR spectra, using two symmetric dienes (**6c** (*p*-MePh) and **6d** (*p*-ClPh)).[60] Ten metals were screened: $MgCl_2$, $NiCl_2.6H_2O$, $Cu(acac)_2$, $Cu(OTf)_2$, $MoO_2(acac)_2$, $Cr(acac)_3$, $TiCl_4$, $Sm(OTf)_3$, $CoCl_2.6H_2O$, and $AlMe_2Cl$.[61] General procedure is the following: metal complex (1.5 eq.)[62] is added to a solution of diene **6** (10 mg; 1.0 eq.) in $CDCl_3$ (1 mL), at room temperature.[63] After stirring for 1 h,[64] the reaction mixture is diluted with water (0.5 mL). The organic layer is dried over $MgSO_4$, and finally filtered. The ^{1}H NMR analysis is carried out on this organic layer.

For all complexes, except titanium tetrachloride, ^{1}H NMR spectra were highly similar to the ones in the absence of Lewis acid, with slightly broader signals (due to remaining metal) for Cu(II). Concerning Cr(III), large broads signals were observed, making analysis impossible. On the contrary, the ^{1}H NMR spectrum with $TiCl_4$ was interesting, as significant changes of chemical shifts were observed (figure 3.7).

[60] These dienes were chosen without any scientific arguments, their presence in the laboratory being the only reason.

[61] Diene **6c** was used for $AlMe_2Cl$, and diene **6d** for the nine other metals, for no scientific reasons.

[62] (a) For chloroform solubility purposes, $MgCl_2$, $NiCl_2.6H_2O$, $Cu(OTf)_2$, and $CoCl_2.6H_2O$ were diluted in MeCN (0.5 mL). This solution was then added in the reaction mixture. (b) 1 equivalent for $TiCl_4$ and $AlMe_2Cl$.

[63] At 0 °C for $AlMe_2Cl$.

[64] The stirring was not carried out for $TiCl_4$ and $AlMe_2Cl$. The ^{1}H NMR analysis was directly carried out after metal addition, without any workup.

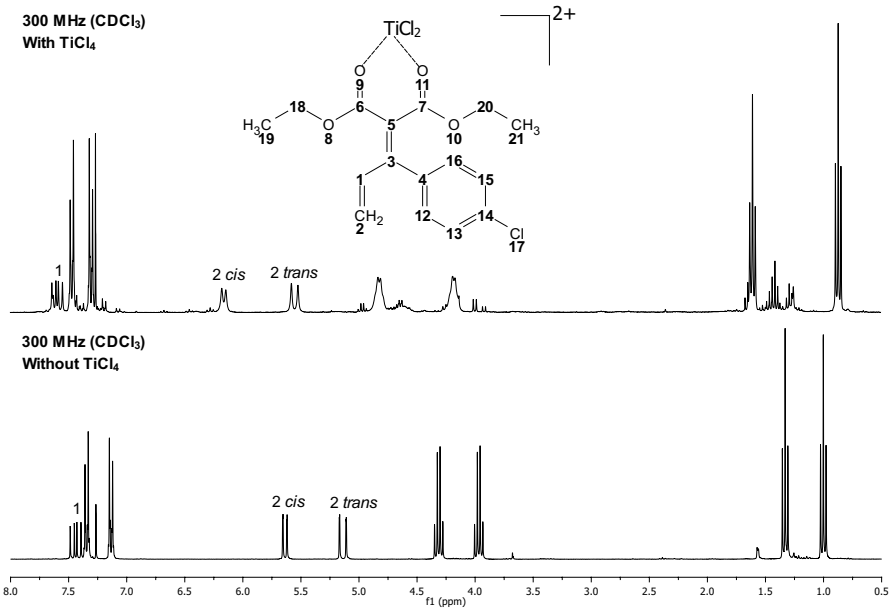


Figure 3.7

Despite the high reactivity of titanium tetrachloride, almost no side-products were observed on the spectrum. Furthermore, a good resolution was obtained, except for CH_2 ester groups, where the quadruplet multiplicity could not be observed. It is noted that all signals have a higher chemical shift, except for one of the two methyl. A ^{1}H NMR analysis after 1 h however showed large amounts of degradation products.

We then envisioned the complexation reaction using crude isomers mixture of our asymmetric diene **6l**. In order to decrease the formation of by-products, various reaction conditions were tested, and best results were found using 1.5 equivalents of a 0.2 M $TiCl_4$ solution, at 0 °C, although large amounts of side-products were still observed (figure 3.8).

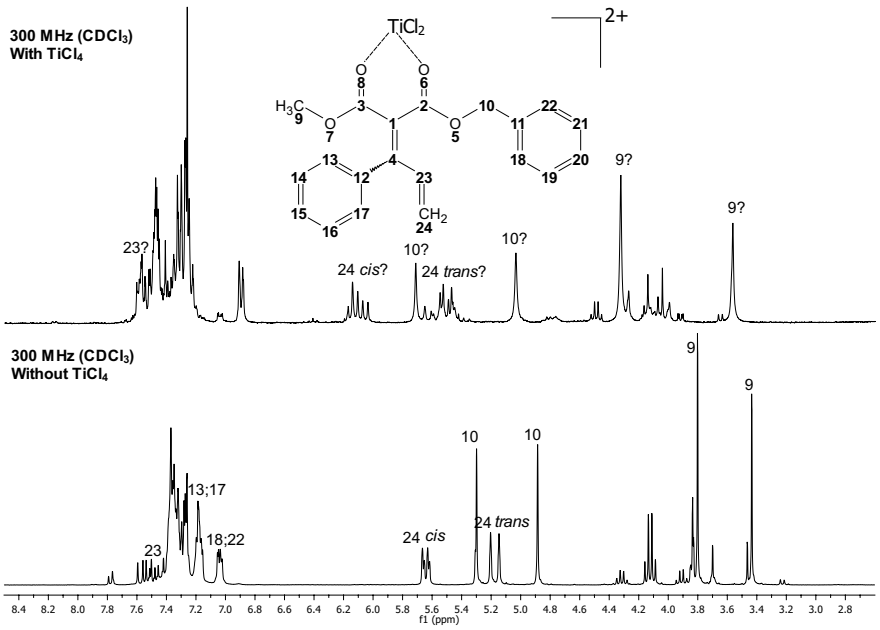


Figure 3.8

As signal 23 appears to be contaminated by aromatic signals, a complexation was attempted in benzene-d_6. Indeed, as previously mentioned, signal 23 in C_6D_6 has a higher chemical shift, well separated from aromatic signals (see figure 3.6 page 106). The ^{1}H NMR spectrum however revealed degradation products. A 1/1 solvent mixture of $CDCl_3/C_6D_6$ avoided degradation, but signal 23 was still stacked with aromatic signals.

We nevertheless planned to perform nOe difference experiments using our previous best reaction conditions. Because of setting requirements inherent to such an NMR experiment, reference nOe ^{1}H NMR spectrum[65] already revealed partial degradation, signals 9 and 10 having far too small integrations. Despite this observation, impulsions on signals 24*cis* and 24*trans* were carried out. Unfortunately, nOe were only observed between the three vinyl signals 23, 24*cis*, and 24*trans*.

As our efforts to determine isomers absolute configuration of diene **6l** were unsuccessful, we decided to stop using this diene for this purpose. Indeed, another substitution patterns can better promote nOe observations than benzyl and methoxy groups in the present case. Furthermore, the use of two distinctive aromatic moieties should help aromatic signals discrimination, which is highly

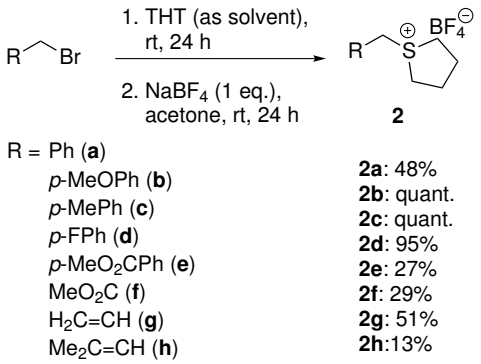
[65]The reference nOe spectrum was performed *via* an impulsion at 12 ppm.

interesting to determine absolute configuration, as analyses of potential nOe with aromatic signals would be facilitated.

At this point, we turned our attention to (4+1) annulation reactions, but, first of all, a variety of non-chiral and chiral sulfonium salts have to be synthesized.

3.4 Sulfonium salts

Based on a described procedure involving tetrahydrothiophene (THT) and bromide derivatives,[143] eight sulfonium salts (ylides precursors) were synthesized (scheme 3.55).[66] It is noted that for solubility and hygroscopic reasons, an ion exchange is carried out, from bromide to tetrafluoroborate anion. Indeed, bromide salts are generally less soluble in organic solvents and more hygroscopic than tetrafluoroborate salts. Electron-rich (**2b**, **2c**) and electron-poor aromatic salts (**2d**, **2e**) were successfully synthesized. In addition, methyl ester and allyl substituted sulfonium salts (**2f** and **2g,h** respectively) were also obtained that way. Isolated yields were generally good to excellent, except for **2e**, **2f**, and **2h**.[67] It is noteworthy that these salts can be obtained in very large quantities, and could be stored for years in anhydrous environment.



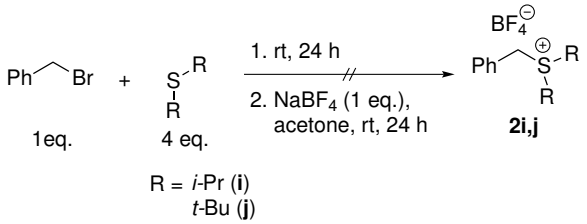
Scheme 3.55

We also envisioned the synthesis of salts **2i,j** (scheme 3.56). Indeed, their higher steric hindrance is particularly interesting for regiocontrol (see scheme 4.5 page 128), but only starting materials were observed on ^{1}H NMR spectra

[66] Sulfonium salts **2b-d** were synthesized by Prof. Raphaël Robiette.

[67] Because salts **2g,h** are liquid, standard purification (precipitation *via* MeOH/Et_2O) cannot be applied. Salt **2g** was purified by washing the crude mixture with DCM, then EtOAc, followed by concentration under reduced pressure, whereas salt **2h** purification was performed *via* freeze-drying of the aqueous layer after dilution with DCM and water.

of crude mixtures in both cases. Using more drastic reaction conditions did not allow any conversion towards desired products.[68]



Scheme 3.56

As mentioned in our thesis objectives (page 45), we were also interested in the access to chiral sulfonium ylides, in order to develop an asymmetric version of the (4+1) annulation strategy. For this purpose, we were inspired by works of Aggarwal and other groups, who developed chiral sulfide compounds represented on figure 3.9.[108,119,144–149]

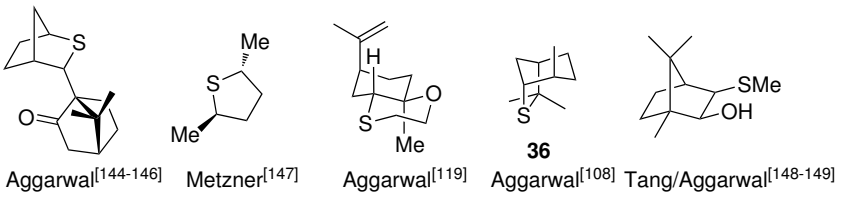
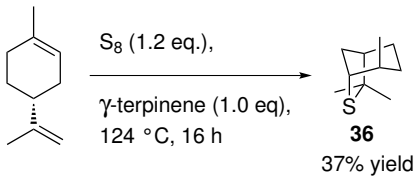


Figure 3.9

We especially focused our attention on sulfide **36**, isothiocineole. Indeed, this chiral skeleton was shown to be effective in asymmetric epoxidation and aziridination reactions with various aromatic, aliphatic, and α,β-unsaturated aldehydes and imines.[109] The facile access to isothiocineole is another positive aspect in favor of this chiral scaffold. Indeed, although obtained in moderate yields, isothiocineole is readily synthesized in one single step, from (*R*)-(+)-limonene and elemental sulfur (scheme 3.57).[108]

[68] Stirring 16 h at 40 °C, then 3 h at 70 °C for **2i**; Stirring 16 h at 100 °C for **2j**.



Scheme 3.57

It is noted that the γ-terpinene reagent prevents formation of side-product **37** (figure 3.10).

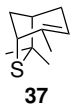
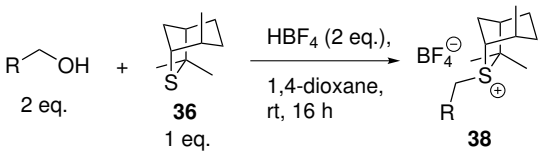


Figure 3.10

With isothiocineole in hand, various chiral sulfonium salts were synthesized (using the same substitution patterns as the non-chiral salts), based on a described procedure (scheme 3.58).[109]



R = Ph (**a**)	**38a**: 81%
p-MeOPh (**b**)	**38b**: 41%
p-MePh (**c**)	**38c**: 60%
p-FPh (**d**)	**38d**: 72%
p-MeO_2CPh (**e**)	**38e**: 68%
MeO_2C (**f**)	**38f**: 0%
H_2C=CH (**g**)	**38g**: 52%

Scheme 3.58

Various salts were obtained in moderate to good yields,[69] except for ester salt **38f**, where sulfonium salt **38h** was the only observed compound, this latter being isolated in 24 % yield (figure 3.11).

[69]The general workup, involving salt washing with EtOAc, is inefficient for salts **38b,e,g**, which are soluble in this solvent. Salt **38b** was isolated by freeze-drying of the aqueous layer after dilution with EtOAc (20 mL) and water (50 mL), **38e** by precipitation *via* MeOH/Et_2O, and **38g** *via* freeze-drying of the aqueous layer after dilution with EtOAc (20 mL) and water (50 mL), followed by precipitation of the resulting solid *via* MeOH/Et_2O.

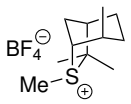


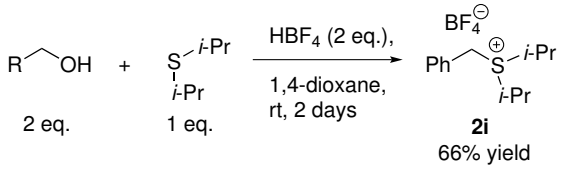
Figure 3.11

The formation of **38h** is explained by an acid-promoted methylation reaction (scheme 3.59).

Scheme 3.59

Using the reaction conditions from non chiral sulfonium salts (methyl bromoacetate as substrate) did unfortunately not allow isolation of the desired salt **38f**.[70]

Finally, non-chiral sulfonium salt **2i**, which cannot be synthesized *via* the previous-mentioned methodology, could be isolated *via* this acid-promoted nucleophilic substitution reaction, in good yield, as a white powder (scheme 3.60).



Scheme 3.60

A variety of sulfonium salts and 1,3-dienes in hand, annulation reactions may be carried out.

[70]The reaction was performed in DCM with 1 equivalent of isothiocineole (instead of using it as a solvent).

Chapter 4

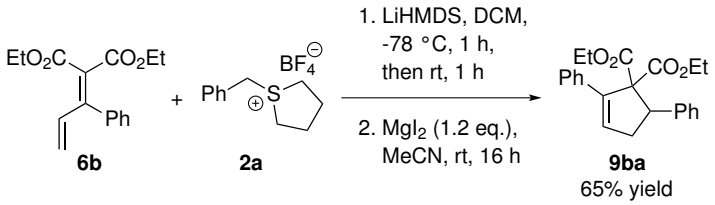
(4+1) annulation reactions

4.1 Racemic version

The following pages describe the development of our (4+1) annulation methodology, and its application to various 1,3-dienes and sulfonium ylides.

4.1.1 Application of standard reaction conditions

As mentioned in the preliminary results of the laboratory, an effective (4+1) annulation reaction was previously performed with diene **6b** and sulfonium salt **2a**, in a tandem (2+1) annulation reaction/MgI_2 promoted vinylcyclopropane-cyclopentene rearrangement (scheme 4.1).



Scheme 4.1

Using these standard reaction conditions, various (4+1) annulation reactions were carried out, with various dienes (**6**) and sulfonium salts (**2**) (table 4.1).[1]

[1] (a) On 50 mg of diene **6**. (b) As previously, ylide generation was carried out prior to diene addition, by stirring a mixture of sulfonium salt and LiHMDS for 20 min, at −78 °C, in DCM.

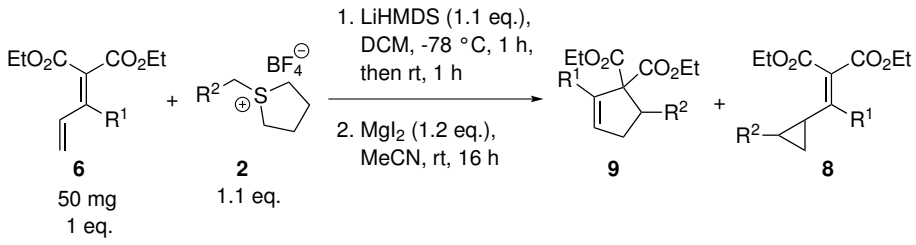


Table 4.1

Entry	R^1 (**6**)	R^2 (**2**)	Observations[a]	**9**[b]
1	Ph (**6b**)	MeO_2C (**2f**)	**8bf**, **6b** + USP (A)[c]	/
2[d]	Ph (**6b**)	H_2C=CH (**2g**)	**9bg**, **6b** + USP (A)[c]	/[e]
3	*p*-MeOPh (**6g**)	Ph (**2a**)	**9ga** + USP (a)[c]	29 %
4	*p*-FPh (**6e**)	Ph (**2a**)	**9ea** + USP (a)[c]	58 %
5	EtO_2C (**6f**)	Ph (**2a**)	**9fa**, **8fa** + USP (A)[c]	13 %
6	*i*-Pr (**6j**)	Ph (**2a**)	**9ja** + USP (A)[c]	24 %
7	*n*-Bu (**6k**)[f]	Ph (**2a**)	**9ka** + USP (a)[c]	39 %

[a] on the ^{1}H NMR spectrum of the crude mixture.

[b] Isolated yield after purification by flash chromatography on silica gel.

[c] Unidentified side-products (a: small amounts; A: large amounts).

[d] 2 h at room temperature, rather than 1 h.

[e] The purification was not carried out.

[f] With 100 mg of diene.

Electron-donating and electron-withdrawing substituted dienes were screened (entries 3 and 4-5 respectively), as well as alkyl groups (entries 6-7). Finally, ester and allyl substituted sulfonium salts were also employed (entries 1-2). In all cases poor isolated yields were observed (13-39 %), except for entry 4 (R^1= *p*-FPh, 58 %). In addition, except for entries 3, 4 and 7, large amounts of unidentified by-products were observed on ^{1}H NMR spectra of crude mixtures.

A non-complete conversion was observed with allyl-substituted ylide (entry 2), where a 0.7/1 **9bg**/**6b** ratio was observed. Regarding ester-substituted ylide **2f** (entry 1), the cyclopentene was not observed on the ^{1}H NMR spectrum of the crude mixture, vinylcyclopropane **8bf** (resulting from 1,6-ylide addition) and significant side-products being the only observed compounds, together with diene **6b**.[2] Besides, VCP **8bf** was isolated in 24 % yield. It seems that the activating ester group is problematic for the rearrangement process.

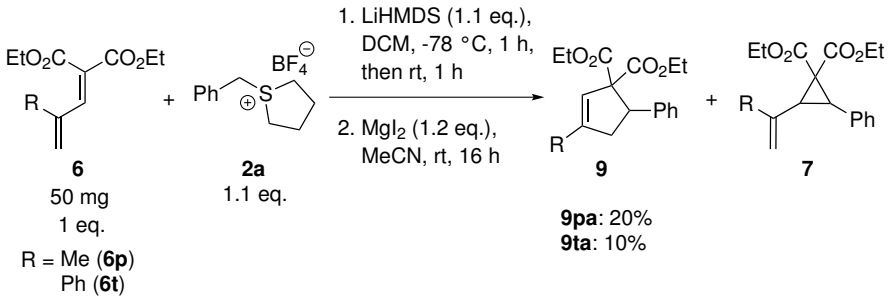
[2] In 1.3/1 **8bf**/**6b** ratio.

Concerning electron-withdrawing substituted diene **6f** (entry 5), a mixture of cyclopentene **9fa** and vinylcyclopropane **8fa** (resulting from 1.6-ylide addition) was observed.[3] The ester group seems to reduce the efficiency of the MgI_2 promoted VCP/CP rearrangement. Subsequent purification by flash chromatography on silica gel allowed isolation of **9fa** in 13 % yield. The observed large amounts of by-products explains this particularly low yield.

With *p*-MeOPh, *p*-FPh, and *n*-Bu substituted dienes (entries 3, 4 and 7), the desired (4+1) annulation reaction product was prevalent, as observed on the ^{1}H NMR spectrum of the crude mixture. The corresponding isolated yields were only of 29 %, 58 %, and 39 % respectively. Loss of product during the purification by flash chromatography on silica gel seems to be the explanation of these poor isolated yields.

The last reaction, involving another alkyl substitution (*i*-Pr, entry 6), gave the desired product **9ja** in 24 % isolated yield. Analysis of the ^{1}H NMR spectrum of the crude mixture indicated significant amounts of by-products.[4] Interestingly, *n*-Bu alkyl substituent (entry 7) seemed more effective than *i*-Pr, as a better isolated yield, but also a cleaner ^{1}H NMR spectrum of the crude mixture, are to highlight.

We also applied our methodology to 3-substituted dienes **6p** and **6t** (scheme 4.2).



Scheme 4.2

With diene **6p**, a mixture of cyclopentene **9pa** and vinylcyclopropane **7pa** (resulting from 1,4-ylide addition) was observed, in a 1.4/1 ratio (**9pa**/**7pa**), together with large amounts of unidentified by-products. Indeed, as this diene

[3] In 1.4/1 ratio (**9fa**/**8fa**).

[4] A vinylic side-product was especially obtained, in 60 % proportion as compared to the desired cyclopentene. This product may come from a possible reaction of diene with magnesium iodide.

is not substituted in position 2, the 1,4 and 1,6 ylide-additions are in competition. Furthermore, we previously mentioned in the preliminary results of our laboratory that VCP resulting from the 1,4-ylide addition does not rearrange with magnesium iodide (see page 40), contrary to the VCP resulting from the 1,6-ylide addition. As a consequence, the reaction generates a mixture of cyclopentene **9pa** and vinylcyclopropane **7pa**. Subsequent purification by flash chromatography on silica gel allowed isolation of a mixture of compounds **9pa** and **7pa**.[5]. An estimation on this purified mixture revealed a 20 % yield towards **9pa**. We then envisioned purifying this mixture by preparative TLC, but the desired cyclopentene could not be isolated.[6]

Interestingly, the use of 3-phenyl substituted diene **6t** did not lead to 1.4-ylide addition, but a non complete conversion was observed,[7] together with large amounts of side-products. The steric hindrance of the phenyl moiety is the likely explanation of this regioselectivity. Subsequent purification by flash chromatography on silica gel gave pure cyclopentene **9ta** in 10 % isolated yield. The encountered difficulties to isolate the product, together with large quantities of by-products, seem to be responsible for this poor yield.

As large amounts of side products were observed in most cases, efforts were made in order to find better reaction conditions. Adjustments could be realised by varying substrates/reagents proportions, orders of addition, the base, the presence of an additive, the temperature, the time, the solvent, and finally the reaction scale. The use of stabilised ylide (entry 1 of table 4.1 page 116) is examined in a separated section, page 129.

4.1.2 Development of a general (4+1) reaction procedure

As so far almost all attempts were carried out on 50 mg scale of diene, we first envisioned a scale up with three dienes and sulfonium salt **2a**, using previous reaction conditions (table 4.2).

[5]Because **9pa** and **7pa** have similar R_f, the desired product cannot be isolated.

[6]Preparative TLC technical informations: *Analtech Uniplate* Silica Gel GF (1000 µm), 20 cm x 20 cm plate.

[7]A 1.8/1 **9ta**/**6t** ratio was calculated.

Table 4.2

Diene	Isolated yield (50 mg)[a]	Isolated yield (100 mg)
p-MeOPh (**6g**)	29 %	45 %[b]
p-FPh (**6e**)	58 %	57 %[b]
i-Pr (**6j**)	24 %	32 %

[a] Results from table 4.1 page 116.

[b] The reaction mixture was stirred for 2 h at −78 °C and then for 2 h at room temperature (rather than 1 h for both of these temperatures).

Based on isolated yields, it seems that our methodology was improved when the reaction was performed on a larger scale. It is however noticed that a similar yield was obtained for the electron-withdrawing *p*-FPh substituent. Furthermore, 50 mg scale crudes ^{1}H NMR spectra were similar to that of 100 mg scale.

From these results one can suppose that:

– 50 mg scale poor isolated yields are due to a loss of product during the purification by flash chromatography on silica gel.

– Prolonged reactions times do not influence the outcome of the reaction.

The full conversion of vinylcyclopropane **8ba** to the corresponding cyclopentene **9ba** (see preliminary results of the laboratory, scheme 1.55 page 43), as well as the absence of VCP on previous ^{1}H NMR spectra of crude mixtures indicates that the development must focus on the vinylcyclopropanation step. Next reactions were thus quenched after the (2+1) annulation process, using 50 mg of diene.

Because we had a large batch of pure *i*-Pr diene **6j**,[8] this latter was employed for the development process. It is noteworthy that this substrate includes a potential acidic proton (figure 4.1). Ylide basicity versus nucleophilicity properties can therefore be studied, allowing to reach the most general procedure.

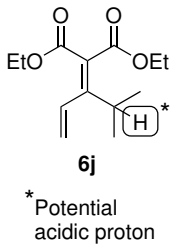
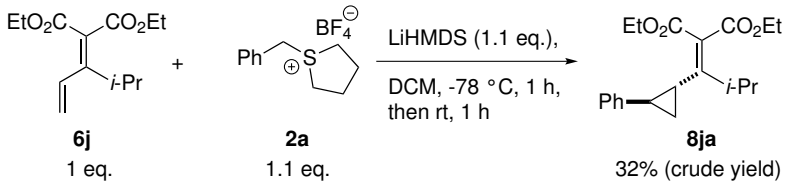


Figure 4.1

[8] About 500 mg.

The application of standard reaction conditions indicated a 32 % crude yield towards VCP **8ja** (scheme 4.3).[9] It is noteworthy that sulfonium ylide was first generated by mixing salt **2a** and LiHMDS for 20 min at −78 °C, in DCM. Interestingly, the previous results (see table 4.2) indicate an identical cyclopentene isolated yield, supporting our hypothesis of an effective MgI_2 promoted rearrangement. The ^{1}H NMR spectrum of the crude mixture also revealed remaining diene substrate in 1/1 **6j**/**8ja** ratio, indicating an incomplete conversion.



Scheme 4.3

We next carried out direct addition of LiHMDS in a mixture of sulfonium salt and diene, giving a more simple procedure. So, the reactivity of diene **6j** towards LiHMDS can also be studied as well as sulfonium ylide stability and reactivity towards the diene, as sulfonium ylide can react with diene as soon as it is generated. The analysis of the ^{1}H NMR spectrum of the crude mixture indicated the same 32 % crude yield, and a slightly better **6j**/**8ja** ratio (0.8/1). In order to favor the reaction, an excess of diene was then employed (1.5 equivalents), giving a better crude yield of 37 %. The effect of the concentration was also investigated, by performing the reaction in a three times higher concentration.[10] Surprisingly, only diene starting material was observed in the crude mixture.

The effect of the ylide substituent was also studied, using *p*-MeOPh and *p*-FPh substituted sulfonium salts (**2b** and **2d** respectively). Similar results were obtained with **2d** (29 % crude yield, and a 1/1 **6j**/**8jd** ratio), whereas a large amounts of diene was observed with salt **2b**, without any traces of VCP, independently of the order of addition of the reactants. The higher reactivity of this ylide, due to the *p*-MeO substituent, may be the reason of such observation, as it could react with the potential acidic proton of diene **6j**.

After all these developments, we ran out of diene **6j**. As all attempts of

[9] Crude yield was determined by ^{1}H NMR analysis using an internal standard (Ph_2MeSiH). Indeed, the particularly low methyl chemical shift (0.67 ppm) reduces potential overlapping with another signals. NMR experiments were performed after mixing 50 µL of internal standard with crude compound diluted in $CDCl_3$.

[10] 1 mL of DCM rather than 3 mL.

improving the (4+1) annulation using diene **6j** were unsuccessful until now, we planned to carry out a more exhaustive development. The required amount of diene **6j** for the development process was unfortunately a restricting aspect. Indeed, given the overall yield of diene **6j** synthesis (22 %), having large amounts of pure diene in hand was complicated. We thus turned our attention to 3-methyl-substituted diene **6p** (figure 4.2), as this latter was synthesized in one single synthetic step, without requiring any further purification. A batch of several grams of pure diene **6p** could be obtained in only 24 h.

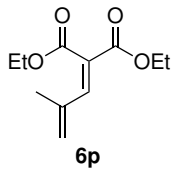


Figure 4.2

We thus planned to use 3-substituted diene **6p** for our development process. With this diene came however significant 1,4-ylide addition. Inspired by results obtained in our laboratory, we first changed DCM to THF. Indeed, a reaction carried out in the laboratory revealed that this solvent drastically improved the regioselectivity towards 1,6-ylide addition using non-substituted diene **6a**.[11] However, the application of these reaction conditions to diene **6p** gave the same regioselectivity ratio as previously.

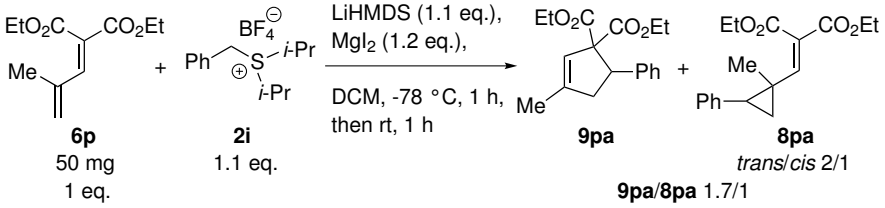
We then used sulfonium salt **2i**, taking the advantage of its steric hindrance to improve the regioselectivity towards 1,6-ylide addition. As previous results with this salt indicated no reactivity towards *i*-Pr diene **6j**, we envisioned an additional diene activation in order to promote ylide addition. In this perspective magnesium iodide and diene were together added to the reaction mixture (scheme 4.4).[12] Analysis of the ^{1}H NMR spectrum of the crude mixture revealed a mixture of diene, cyclopentene **9pa**, VCP **8pa**,[13] as well as large amounts of by-products, in 1.7/1/2 **9pa**/**8pa**/**6p** ratios. Due to side-products and VCP **7pa** signals overlapping,[14] the presence of this latter VCP could not be claimed. From these results non-complete (2+1) annulation and rearrangement processes must be noted, as remaining diene and VCP **8pa** were observed in the crude mixture. A **8pa** *trans*/*cis* ratio of 2/1 is finally observed.

[11] Annulation reaction in THF with diene **6a** was performed by Trieu-Van Tran.

[12] (a) Ylide generation was carried out prior to diene addition. (b) This procedure also allowed the synthesis of desired cyclopentene in one single step.

[13] **8pa** = vinylcyclopropane resulting from 1,6-ylide addition.

[14] **7pa** = vinylcyclopropane resulting from 1,4-ylide addition.



Scheme 4.4

We next investigated VCP formation step by performing the same reaction, but without diene activation by magnesium iodide, quenching the reaction after the vinylcyclopropanation step. We were pleased to observe a complete conversion and small amounts of by-products, added to a better regioselectivity (3.3/1 **8pa**/**7pa**).[15] A calculated yield of 30 % towards **9pa** was also highlighted. Based on this process, various reaction conditions were tested (table 4.3). The table is explained hereafter (it is noted that the first entry refers to standard reaction conditions).

[15]By comparison, using salt **2a**, a 1.4/1 ratio was highlighted. See page 117.

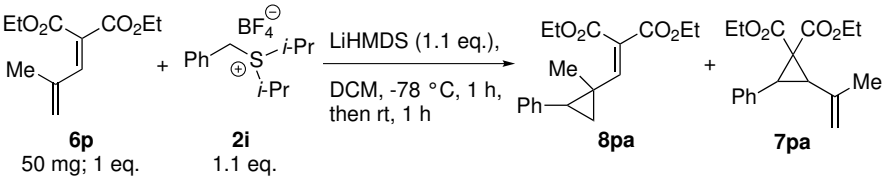


Table 4.3

Entry	Variation from mentioned reaction conditions	Yield[a]	**8pa**/**7pa** ratio[b]
1	/	30 %	3.3/1
2	1 h 30 at −78 °C	32 %	3.6/1
3	30 min at −78 °C	31 %	2.9/1
4	2 h 30 at room temperature after diene addition	19 %	2.4/1
5	1.5 eq. of sulfonium salt and LiHMDS	/[c]	2/1
6	1.5 eq. of diene	26 %	4.5/1
7	ylide addition on diene DCM solution	0 %	/
8	**no ylide generation prior to diene addition**	**34 %**	**3.8/1**
9	more concentrated reaction mixture (2 mL)[d]	28 %	2.6/1
10	more polar solvent (DMF)[e]	19 %	1/0

[a] Calculated on the ^{1}H NMR spectrum of the crude mixture using Ph_2MeSiH as an internal standard.

[b] Calculated on the ^{1}H NMR spectrum of the crude mixture; **8pa** refers to 1,6-ylide addition; **7pa** refers to 1,4-ylide addition.

[c] Due to internal standard and side-products signals overlapping, the yield could not be calculated.

[d] Instead of 4 mL.

[e] The reaction was performed at ca. −60 °C, due to DMF melting point (−61 °C).

First of all, although not mentioned in the table, it is emphasized that complete conversion was observed for all reactions, except for entries 4 and 6, where small amounts of remaining diene was observed in 1/10 **6p**/**8pa** ratio, as well as for entry 10 where a 1/1 ratio was obtained, and finally for entry 7 where no conversion was observed.

Secondly, a generally 3/1-4/1 regioselectivity ratio towards 1,6-ylide addition was observed on the ^{1}H NMR spectrum of the crude mixture. Removing the cooling bath after diene addition (entry 4) gave a lower ratio, as well as

using a more concentrated reaction mixture. The reaction with 1.5 equivalents of sulfonium salt and LiHMDS (entries 9 and 5 respectively) led also to a poor ratio, whereas 1.5 equivalents of diene (entry 6) generated a good ratio (4.5/1). In this latter case the calculated yield was however impacted. An improved ratio was also observed without prior ylide generation (entry 8). Finally, a total regioselectivity towards the 1,6 addition was obtained when DMF was used as a solvent (entry 10). Unfortunately, a particularly low calculated yield made this latter method not interesting.

Observed d.r. for desired product were about 12/1, except for entries 5 and 9 where only one isomer was observed, for entries 1, 2 and 3 where observed d.r. were higher (25/1, 33/1 and 50/1 respectively), and finally a lower 7/1 d.r. was observed for entry 10.

It is emphasized that for most of entries (except entry 7), significant by-products were formed, especially for entries 4 and 5. A higher concentration (entry 9) did not influence results, nor performing the reaction for longer or shorter time at −78 °C (entries 2 and 3 respectively). Finally, the only better yield, together with an improved **8pa**/**7pa** ratio, was encountered when LiHMDS was added directly to a mixture of diene and sulfonium salt (i.e. no prior ylide generation; entry 8).

In addition to this screening, we planned to study diene **6p** stability towards LiHMDS, by mixing the diene and 0.5 equivalent of LiHMDS in DCM, for 30 min at −78 °C then 1 h at room temperature. The calculated yield *via* the internal standard highlighted only 26 % of recovered diene. It thus seems that diene **6p** did not tolerate these basic reaction conditions. Indeed, one can assume a relative unstable diene given its structural motif. In the presence of a nucleophile, a polymerisation reaction may for example occur. One can extend this reactivity profile to other synthesized 1,3-dienes **2**, as the free fourth position, added to a bis-activation, generate particular actives dienes towards 1,6-addition, and so to polymerisation reactions (figure 4.3).

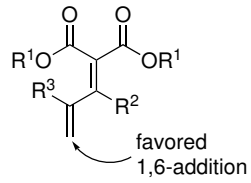


Figure 4.3

One can predict a better sulfonium salt reactivity towards LiHMDS than for 1,3-diene **2**, but these results indicate that an excess of LiHMDS regarding sulfonium salt should be detrimental. Also, the nucleophilicity vs basicity reactivity of ylide must be an important factor when *i*-Pr and *n*-Bu 2-substituted 1,3-dienes are engaged in annulation reactions, as they possess potential acidic proton(s).

Two last stability studies were carried out. In order to simplify further reaction conditions, we planned a procedure where MgI_2 and the diene were added at the same time to the reaction mixture, allowing the synthesis of the desired cyclopentene in a one single step methodology. This approach was already unsuccessfully carried out with 3-substituted diene **6p** (see scheme 4.4 page 122). An assay, where diene **6p** and magnesium iodide (1.2 equivalents) were stirred in DCM for 1 h at room temperature, confirmed that this method was inappropriate, as diene was no longer observed on the ^{1}H NMR spectrum of the crude mixture, indicating diene degradation under these reaction conditions.

Eventually, as adding LiHMDS to a mixture of diene and sulfonium salt was more effective than prior generation of the ylide, we were interested in testing the sulfonium ylide stability. We chose sulfonium salt **2a** for tests, as the majority of (4+1) annulation reactions were performed with this scaffold. Stirring this salt and LiHMDS (1 equivalent) in DCM at −78 °C revealed that the corresponding ylide is stable under these conditions, for at least 2 h.[16] These results suggest that ylide stability is not the reason of the observed better yield when LiHMDS is added directly to a mixture of diene and sulfonium salt.

4.1.3 Scope of our (4+1) annulation methodology

With optimized reaction conditions in hand, a series of (4+1) annulation reactions were carried out, between various 1,3-dienes and sulfonium salts (table 4.4). It has to be mentioned that each reaction was performed on 100 mg scale of diene.

[16](a) The monitoring was performed by ^{1}H NMR. (b) Carry out the same procedure at room temperature indicated ylide degradation already after 30 min.

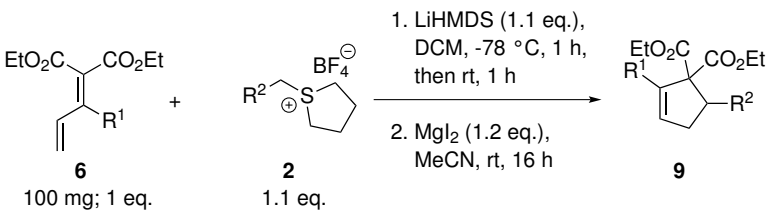


Table 4.4

Entry	R^1	R^2	Isolated yield (**9**)[a]
1[b]	Ph	Ph	65 % (**9ba**)
2	*p*-MeOPh	Ph	55 % (**9ga**)
3	*p*-MePh	Ph	45 % (**9ca**)
4	*p*-FPh	Ph	57 % (**9ea**)
5[b]	*p*-BrPh	Ph	40 % (**9za**)
6	EtO_2C	Ph	32 % (**9fa**)
7	*i*-Pr	Ph	41 % (**9ja**)
8	*n*-Bu	Ph	39 % (**9ka**)
9	Ph	*p*-MeOPh	58 % (**9bb**)
10	Ph	*p*-MePh	50 % (**9bc**)
11	Ph	*p*-FPh	57 % (**9bd**)
12	Ph	*p*-MeO_2CPh	55 % (**9be**)
13	Ph	H_2C=CH	0 % (**9bg**)[c]
14	Ph	Me_2C=CH	57 % (**9bh**)

[a] After purification by flash chromatography on silica gel.
[b] Performed by Trieu-Van Tran.
[c] No purification was carried out, due to the observed large amount of by-products.

We first observed that crudes ^{1}H NMR spectra were not contaminated by large amounts of side-products, except for dienes EtO_2C, *i*-Pr, and *n*-Bu (entries 6-8), as well as with allyl sulfonium salt **2g** (entry 13). In this latter case, no purification was carried out, due to the presence of a large amount of by-products in the crude mixture.

We also noticed that isolated yields were generally around 55 % (from 32 % to 65 %). These moderate yields can, according to us, be explained by partial degradation of diene under mentioned basic reaction conditions, namely the

vinylcyclopropanation step.[17] Table 4.5 compares our best reaction conditions with previous standard conditions (i.e. table 4.2 page 119).

Table 4.5

Diene substituent	Std. cond.[a,b]	Best cond.[a,c]
p-MeOPh	45 %	55 %
p-FPh	57 %	57 %
i-Pr	32 %	41 %
n-Bu	39 %	39 %

[a] Isolated yield after purification by flash chromatography on silica gel.
[b] 100 mg scale of diene; With prior ylide generation.
[c] 100 mg scale of diene; No prior ylide generation.

Except for *p*-FPh and *n*-Bu substituents where identical isolated yields were obtained, all yields were improved from standard reaction conditions to the optimized conditions. Two conclusions can be drawn from these results:

- It is recommended to avoid ylide generation prior to diene addition.
- Diene and intermediates stability in mentioned reaction conditions seems to be the key factor of the final isolated yield.

Regarding functional groups tolerance, electron-withdrawing and electron-donating groups were well tolerated, and did not influence the yield. Similar results were also observed independently of the substituent position (diene or sulfonium salt). Interestingly, *p*-MeO_2CPh diene substitution (entry 12) was well tolerated, contrary to simple EtO_2C functional group (entry 6). Alkyl substitution (entries 7 and 8) was detrimental for the reaction, as well as the *p*-BrPh substituent (entry 5). Finally, allyl sulfonium salt **2g** (entry 13) generated large amounts of by-products.[18] The presence of two nucleophilic centers was the most likely explanation of such results, as probability of side reactions was increased that way (figure 4.4).

[17] The use of internal standard revealed that there is no or few loss of product during the purification by flash chromatography on silica gel, eliminating this potential explanation for the moderate isolated yield.

[18] In order to favor allyl ylide 1,6-addition, a stirring for 1 h at room temperature after only stirring 20 min at −78 °C was further performed, but only by-products were observed on the ^{1}H NMR spectrum of the crude mixture.

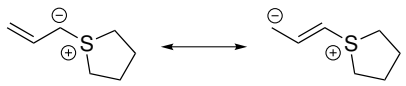


Figure 4.4

We were pleased to observe better results with the similar $Me_2C{=}CH$ allyl salt (entry 14), in which one of the nucleophilic center is much more hindered (figure 4.5).

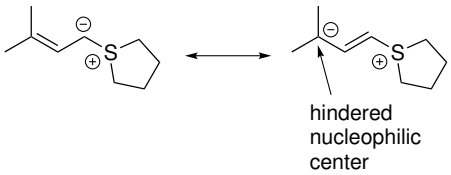
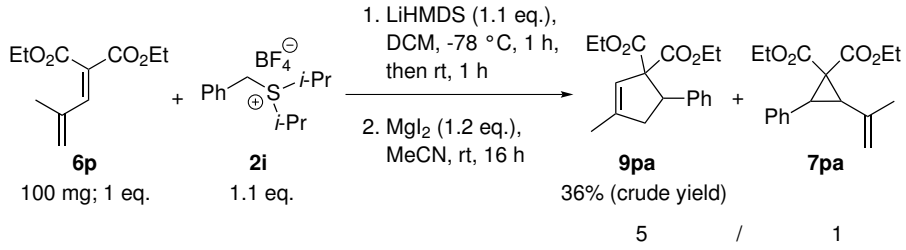


Figure 4.5

These best reaction conditions were also applied to 3-methyl substituted diene **6p**, using *i*-Pr salt **2i** (scheme 4.5).



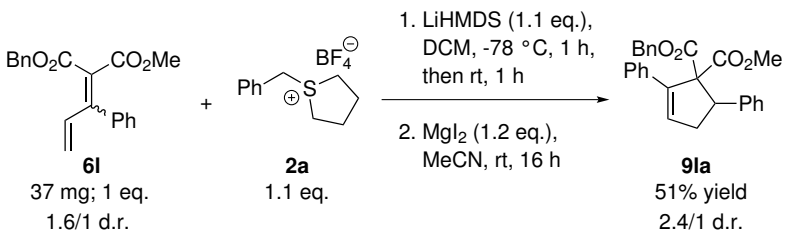
Scheme 4.5

Unfortunately, the presence of various side-products did not allow cyclopentene **9pa** isolation. Furthermore, the purest fraction (after purification by flash chromatography on silica gel) was contaminated with vinylcyclopropane **7pa**.[19] Besides, it is noteworthy a good regioselectivity of 5/1 towards the desired product.[20] Besides, the use of Ph_2MeSiH internal standard revealed a 36 % yield towards cyclopentene **9pa**.

Finally, we used these best reaction conditions on non-symmetric diene **6l** (scheme 4.6). It is noteworthy that the use of this diene allows the formation of a second chiral center.

[19] VCP stemming from 1,4-ylide addition.

[20] Calculated using another signal of the VCP **7pa**, due to the overlapping with by-products signals on the ^{1}H NMR spectrum of the crude mixture.



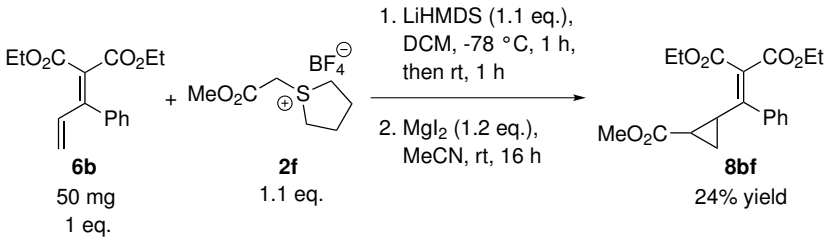
Scheme 4.6

Starting from a diene sample with a 1.6/1 d.r, a 2.4/1 d.r. was observed on the ^{1}H NMR spectrum of the crude mixture. A mixture of diastereoisomers was isolated in 51 % yield after purification by flash chromatography on silica gel. This yield is consistent with previous examples.

Unfortunately, we did not succeed in identifying the stereochemistry of diastereoisomeric cyclopentenes by NOESY experiments on the purified **9la** isomers mixture.[21]

4.1.4 Stabilised ylides, the tuning of reactivity

We previously mentioned in table 4.1, page 116 that the application of our methodology to ester-substituted sulfonium salt **2f** did not allow to obtain the corresponding cyclopentene **9bf**. Only VCP **8bf** was isolated in relatively poor yield (scheme 4.7 *infra*).



Scheme 4.7

It is emphasized that salt **2f** generates a stabilised and thus less reactive ylide, which could explain the presence of remaining diene. In order to favor the ylide addition, the solution was stirred at room temperature for 2 h after diene addition.[22] And to know if the vinylcyclopropanation step was problematic,

[21] Using a 300 MHz spectrometer. The mixing time was set to 0.9 sec, and 32 scans were carried out. The NOESY spectrum is represented in the appendix, page 289.

[22] Instead of 1 h at −78 °C followed by 1 h at room temperature.

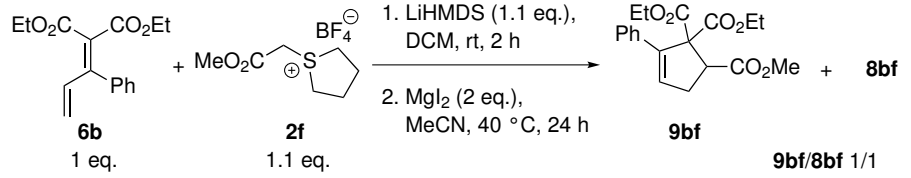
a workup after this latter was carried out. We were pleased to observe a good conversion into cyclopropane **8bf** (4.5/1 **8bf**/**6b** ratio), but together with large amounts of by-products. The desired VCP **8bf** was isolated in 32 % yield. Inspired by a procedure describing a (2+1) annulation reaction between an enone and an ester sulfonium ylide as C1 unit,[150] NaH was employed as a base, in a mixture of THF and hexamethylphosphorictriamide (HMPA). Unfortunately, this reaction yielded a complex mixture (^{1}H NMR), with no trace of any desired vinylcyclopropane. The same reaction in THF did not give the VCP neither.

These last attempts to improve the yield in VCP being unsuccessful, the VCP/CP rearrangement was next investigated, on pure vinylcyclopropane **8bf**:

- No conversion was observed with 2 equivalents of MgI_2 (rather than 1.2), at room temperature, for 24 h.
- Another Lewis acid was then envisioned, known for its efficiency in the opening of gem bis-activated cyclopropanes: $Sc(OTf)_3$.[151] Addition of a large excess of this latter to **8bf**, at room temperature, and a stirring for 16 h, however led to no conversion.
- 1.2 equivalents of MgI_2 at 40 °C, for 2 h, gave the same results (no conversion).
- A palladium catalyzed rearrangement, using $Pd(PPh_3)_4$ (1 equivalent), at reflux of THF,[23] for 3 h, was totally inefficient, as no conversion was observed.
- We then tried MgI_2 promoted rearrangement at 40 °C, but with 2 equivalents of MgI_2. We were pleased to observe a low conversion towards the desired cyclopentene after 24 h. Using the same reaction conditions, a large excess of magnesium iodide (a tip of spatula) allowed the complete VCP conversion towards cyclopentene **9bf** after 16 h at 40 °C, which could however be isolated in only 25 % yield after purification by flash chromatography on silica gel.

The one-pot procedure was then applied, with 2 equivalents of MgI_2, at 40 °C. Although an almost complete conversion was observed on the ^{1}H NMR spectrum of the crude mixture, only very few amount of the desired cyclopentene was obtained, together with similar quantity of VCP and large amounts of side-products (scheme 4.8).

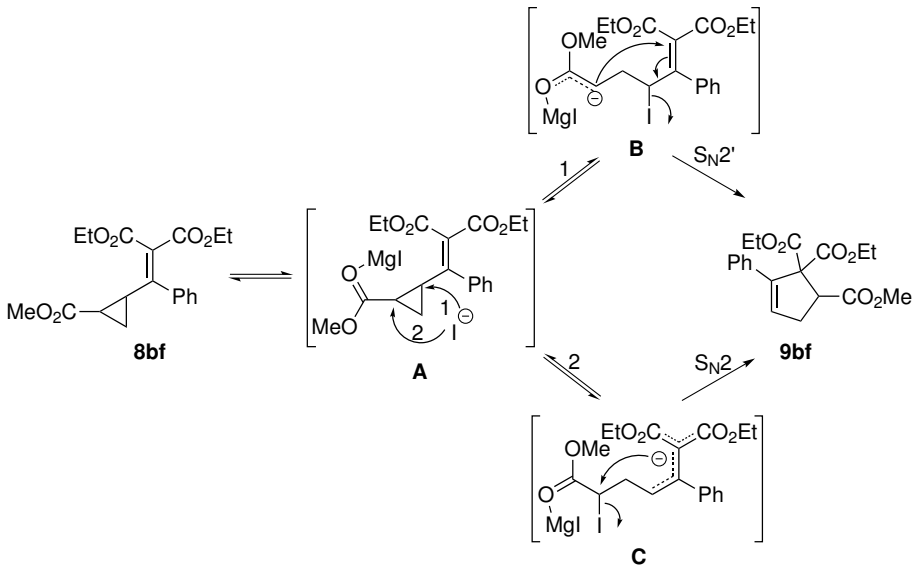
[23] THF boiling point is 66 °C.



Scheme 4.8

To sum up, more drastic reaction conditions had to be used for both vinylcyclopropanation and rearrangement steps. The first one was improved when the solution was stirred at room temperature for 2 h, giving a 32 % isolated yield. The further rearrangement proceeded with a full conversion when a large excess of magnesium iodide was employed at 40 °C, for 24 h, giving desired cyclopentene in 25 % isolated yield. The overall calculated yield was thus only 8 %. Unfortunately, the one-pot procedure was inefficient, as very large amounts of side-products were observed on the crude.

Two possible phenomena may explain the lower reactivity of VCP **8bf** towards the rearrangement process. The first one implies a complexation of the ester substituent by MgI_2, that could result in the opening of the VCP in a different way, leading to **B** (scheme 4.9). From this latter, the access to CP **9bf** requires an S_N2' process, and one could suppose a more complicated S_N2' process onto a sterically hindered position.



Scheme 4.9

The other phenomenon is a deactivation of the ring opening by iodide through a S_N2 processes (**A** to **C**, scheme 4.9, *vide supra*), by the ester substituent. Indeed, Robiette and Aggarwal showed that in the case of delocalized anionic nucleophiles such as iodide, conversely to the received textbook wisdom, alpha substitution by an electron-withrawing π system deactivates the S_N2 reaction.[152]

With all promising results observed concerning our (4+1) annulation reaction methodology, an enantioselective version was next envisioned.

4.2 Development of an enantioselective methodology[24]

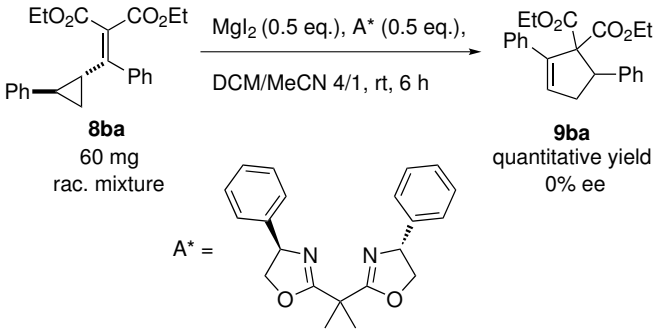
As mentioned in *Objectives and strategies* section (see page 45), two strategies are conceivable to synthesize enantioenriched cyclopentenes. The first one involves asymmetric catalysis of the VCP rearrangement, allowing the conversion of a racemic vinylcyclopropane mixture to an optically active cyclopentene mixture. The chiral information is thus introduced during the rearrangement process. The second strategy employs a chiral sulfonium ylide, in order to obtain an optically active vinylcyclopropane. It is noteworthy that this last strategy requires a stereospecific rearrangement process in order to obtain an enantioenriched cyclopentene.

4.2.1 Discovery of a stereospecific process

Dr. Thierry Delaunay, during his post-doctoral stay in our research group, investigated the use of a chiral catalyst for carrying out the VCP rearrangement. This strategy is indeed more interesting, as a racemic cyclopentene mixture or an enantioenriched one could be obtained easily starting from the same substrates, by adding, or not, in the reaction mixture, the chiral molecule. This methodology also suppresses the risk of a non-stereospecific rearrangement process at the C1 unit, or enantiomeric excess degradation during this process, as chiral information is introduced during the last step, i.e. the MgI_2 promoted rearrangement. Finally, this methodology allows the use of a catalytic amount of the chiral inducer. Dr. Delaunay employed a bisoxazoline magnesium complex as a chiral catalyst for his reactions, as this scaffold was

[24] All enantiomeric excesses mentioned in this section were measured after enantiomers separation by analytical chiral HPLC.

shown to be effective in asymmetric (3+2) cycloaddition/annulation reactions (scheme 4.10).[120,121] The reaction monitoring revealed complete conversion after 6 h. He was pleased to observe a quantitative yield towards desired cyclopentene **9ba**. Unfortunately, chiral HPLC showed no enantiomeric excess on purified product. A one-pot procedure was next envisioned, but analyses of the ^{1}H NMR spectrum of the crude mixture indicated only cyclopropane product together with diene starting material.[25]



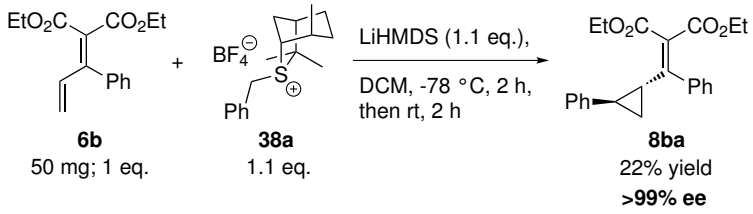
Scheme 4.10

We thus turned our attention to the use of a chiral sulfonium ylide. As mentioned in *Substrate syntheses* section (see page 111), isothiocineole was chosen as sulfide to access chiral sulfonium salts, for its readily accessibility and its effectiveness in asymmetric epoxidation and aziridination reactions.[108,109]

A (2+1) annulation process was first performed, quenching the reaction after the vinylcyclopropanation step. The rearrangement stereospecificity was then studied by performing VCP rearrangement and comparing enantiomeric excesses of VCP and corresponding CP products.

Diene **6b** and sulfonium salt **38a** were chosen for this first reaction (scheme 4.11).[26] The reaction mixture was stirred for 2 h at −78 °C and then 2 h at room temperature in order to reach the reaction completion, as the higher steric hindrance of this ylide scaffold as compared to non-chiral sulfonium ylide suggests a lower reactivity of the ylide towards nucleophilic addition.

[25] Carried out by Dr. Thierry Delaunay.
[26] No prior ylide generation before diene addition.

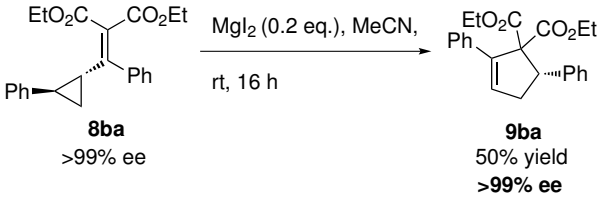


Scheme 4.11

The ^{1}H NMR spectrum of the crude mixture revealed remaining diene in 1/7 **6b**/**8ba** ratio. The closed **8ba** and isothiocineole R_f allowed the isolation of the desired vinylcyclopropane in only 22 %. We were however pleased to observe an enantiomeric excess of >99 %.[27]

In order to favor the ylide nucleophilic addition, we planned a diene activation. Using the same procedure as in scheme 4.4 page 122, MgI_2 (1.2 eq.) and diene was added together to the reaction mixture.[28] Unfortunately, only diene starting material was recovered. As the iodide anion may be detrimental for the vinylcyclopropanation step, magnesium iodide was replaced by $Mg(ClO_4)_2$ (1.2 eq.). Indeed, the perchlorate anion is expected to be less reactive than iodide anion. The same results were nevertheless observed, independently of prior ylide generation.

Reaction conditions improvements being unsuccessful, MgI_2 promoted rearrangement was next carried out (scheme 4.12).[29] Using 0.2 equivalent of magnesium iodide, the desired cyclopentene was isolated in 50 % yield. Chiral HPLC analysis reveals a >99 % ee, indicating a fully stereospecific rearrangement at this stereogenic center.



Scheme 4.12

The mechanistic study of our rearrangement process is discussed in section 4.5.1 page 152.

[27] The absolute stereochemistry is studied later in the manuscript - see section 4.5.2 page 154.

[28] The ylide was generated prior to diene addition.

[29] Carried out by Trieu-Van Tran.

These highly promising results prompted us to apply the one-pot procedure using sulfonium salt **38a**, to develop an asymmetric (4+1) annulation methodology.

4.2.2 Application of standard reaction conditions

The standard one-pot procedure (first ylide formation[30] and then addition of the diene) was first applied with various dienes and sulfonium salts (table 4.6).

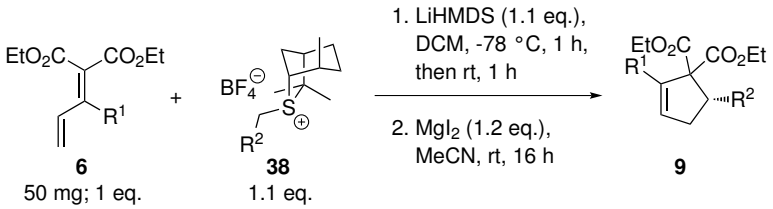


Table 4.6

Entry	R^1 (**6**)	R^2 (**38**)	Observations (**9**/**6** ratio)[a]
1[b]	*p*-MeOPh (**6g**)	Ph (**38a**)	**9ga**, **6g** (1/1), + USP (A)[c]
2	*p*-MePh (**6c**)	Ph (**38a**)	**9ca**, **6c** (1/23)
3[d]	*p*-FPh (**6e**)	Ph (**38a**)	**9ea**, **6e** (1/2)
4	EtO_2C (**6f**)	Ph (**38a**)	**6f** + USP (A)[c]
5[e]	*i*-Pr (**6j**)	Ph (**38a**)	**6j** + USP (A)[c]
6	Ph (**6b**)	*p*-MeOPh (**38b**)	**9bb**, **6b** (1/1.7)
7[e]	Ph (**6b**)	*p*-FPh (**38d**)	**9bd** + USP (A)[c]

[a] on the ^{1}H NMR spectrum of the crude mixture.
[b] Stirring 4 h at room temperature before MgI_2 addition.
[c] Unidentified side-products (a: small amounts; A: large amounts).
[d] Stirring 16 h at room temperature before MgI_2 addition.
[e] Carried out on 100 mg scale of diene.

Cyclopentene **9** was obtained in all cases except for diene **6f** and **6j** (entries 4 and 5). However, remaining diene was observed for all entries except 7, indicating a non complete conversion. The total diene **6b** conversion for *p*-FPh substituted ylide **38d** and the low conversion towards **9ga** in the case of *p*-MeOPh ylide **38b** suggested that our observations result from a low stability of sulfur ylides **38**. A low reactivity of ylides **38**, due to high steric hindrance of this chiral sulfonium ylide scaffold, is another explanation of these observations.

[30] For 20 min at −78 °C in DCM.

In addition, this procedure was carried out on 3-methyl substituted diene **6p** (scheme 4.13). The ^{1}H NMR spectrum of the crude mixture revealed large amounts of by-products, together with cyclopentene and vinylcyclopropane **7pa**.[31] We were pleased to observe a good 4.5/1 **9pa**/**7pa** ratio. The steric hindrance of chiral sulfonium ylide is probably the reason of such regioselectivity towards 1,6 ylide addition. Unfortunately, as previously, subsequent purification by flash chromatography on silica gel did not allow separation of the desired product from VCP **7pa**.

Scheme 4.13

4.2.3 Approach to an improved asymmetric procedure

In order to favor ylide nucleophilic addition, other reaction conditions were employed, removing the cooling bath immediately after diene addition (MgI_2 was added after stirring 2 h at room temperature). It is noted that the ylide was generated prior to diene addition. The application of these conditions with *p*-MeOPh sulfonium salt **38b** (and diene **6b**) provided better results (56 % conversion - 37 % previously[32]), with no additional by-products. Unfortunately, this procedure was detrimental for electron-poor *p*-FPh sulfonium salt **38d**. We indeed observed only 27 % conversion, whereas a full conversion must be noted for the standard procedure. It is however noteworthy that much less by-products were formed. We finally applied this procedure to *n*-Bu substituted diene. Unfortunately, only reactants, together with small amounts of side-products, were observed. In order to study if the sulfonium ylide substitution may influence the result,[33] the reaction was performed with *p*-MeOPh salt and *n*-Bu substituted diene **6k**, but similar results were obtained.[34] Carrying out the reaction in milder conditions (−41 °C for 1 h and then 2 h at room

[31] **7pa** refers to vinylcyclopropane resulting from 1,4-ylide nucleophilic addition.

[32] Corresponding to a ratio of 1/1.7 **9bb**/**6b**. See the entry 6 of the previous table.

[33] Indeed, a withdrawing group or a donating group may influence nucleophilicity/basicity ylide properties.

[34] A withdrawing salt (*p*-MeO_2CPh, **38e**) was also employed, with *i*-Pr diene **6j**, but the cyclopentene was not observed on the crude mixture.

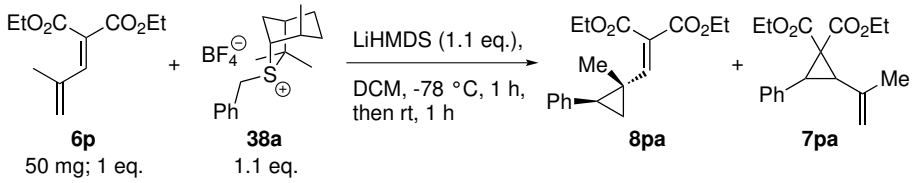
temperature before MgI_2 addition) gave the same observations.

All previous reactions indicate that the ylide stability/reactivity ratio is the key factor to favor the conversion towards the desired cyclopentene. Indeed, the use of harsher reaction conditions can favor or be detrimental to the annulation process, depending on the substrates. In the latter case, the sulfonium ylide degradation is probably the reason of the poor observed conversion. So, it seems that chiral sulfonium ylides are quite unstable (contrary to non-chiral salts **2**). In order to study the sulfonium ylide stability, sulfonium salt **38a** was stirred for 2 h at −78 °C in the presence of LiHMDS (1.1 eq.), in DCM. The reaction monitoring revealed an incipient ylide degradation after 1 h, and large amounts of by-products were observed after 2 h at −78 °C. These results support our hypothesis of a low stability of the chiral ylide at −78 °C. As a consequence, the reaction conditions for the (4+1) annulation reactions must be soft enough to avoid ylide degradation, but also hard enough to favor ylide nucleophilic addition (due to ylide steric hindrance).

This particularity required exhaustive reaction conditions development. This screening was carried out with the same 3-Me substituted diene **6p** as previously, for the same reasons (its readily availability).

Given the poor ylide stability, we first envisioned to add LiHMDS in a mixture of chiral sulfonium salt and diene, in order to minimise potential ylide degradation before diene addition (same reaction conditions than for non-chiral ylides). Indeed, these reaction conditions allowed the ylide nucleophilic addition immediately after its formation and hence avoided ylide accumulation.

All further development reactions were thus carried out without ylide generation prior to diene addition (table 4.7).



6p 50 mg; 1 eq. **38a** 1.1 eq. **8pa** **7pa**

Table 4.7

Entry	Variation from mentioned reaction conditions	Crude yield[a]	**8pa**/**7pa** ratio[b]
1	/	24 %	1.7/1
2	30 min at −78 °C	24 %	1.8/1
3	entry 1 conditions, with half LiHMDS quantity (0.55 eq.)	13 %	1.7/1
4	1 h 30 at −78 °C	25 %	1.9/1
5	only 30 min at −78 °C (then quench)	14 %	3/1
6	only 2 min at −78 °C (then quench)	9 %	3/1
7	2 h 30 at −96 °C[c]	4 %	/[d]
8	30 min at −63 °C[e]	23 %	1.8/1
9	1.5 eq. of LiHMDS	26 %	1.9/1
10	**1.5 eq. of sulfonium salts and LiHMDS**[f]	**28 %**	**1.9/1**
11	very slow LiHMDS addition (100 µL min^{-1})	21 %	2/1
12	fast LiHMDS addition (1.5 mL min^{-1})	25 %	2/1
13	diene activation with $Mg(ClO_4)_2$ (1.2 eq.)	6 %	3/1
14	entry 13 conditions, with prior ylide generation	0 %	/

[a] Calculated on the ^{1}H NMR spectrum of the crude mixture using Ph_2MeSiH as internal standard.

[b] Calculated on the ^{1}H NMR spectrum of the crude mixture; **8pa** refers to 1,6-ylide addition; **7pa** refers to 1,4-ylide addition.

[c] Carried out *via* DCM/liquid nitrogen bath.

[d] Due to especially small amounts of products **8pa** and **7pa**, the ratio could not be calculated.

[e] Carried out *via* $CHCl_3$/dry ice bath.

[f] LiHMDS was added in two portions of 0.75 eq., separated by 20 min.

It is first noteworthy that large amounts of by-products were observed for all attempts. A full conversion was also observed for most of entries, except 5-7 and

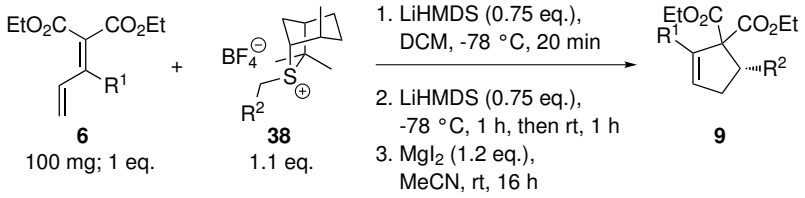
13-14 where no or almost no product was found, and for entry 3 where a poor 1.6/1 **8pa**/**6p** ratio is highlighted. Good **8pa** *trans*/*cis* ratios were observed (about 12/1), except for entries 3, 6 and 13 where better 20/1 to 33/1 ratios are highlighted.[35] Finally, poor regioselectivities towards 1,6-ylide addition were observed (approximately 1.8/1 **8pa**/**7pa**), except for entries 5, 6 and 13, where a better 3/1 ratio was observed, but poor yields were unfortunately calculated in those cases.

To go a little further into details„ decreasing or increasing the reaction time at −78 °C did not influence the reaction (entries 2 and 4). We next envisioned to investigate the reaction behaviour during the −78 °C reaction time. Thereby, the reaction was quenched after stirring 30 min at this temperature (entry 5), as well as after only 2 min of reaction (entry 6). Compared to entries 2 and 4, lower yields indicated that the room temperature stirring is beneficial for the reaction, even with a prolonged reaction time at −78 °C. Carrying out the annulation process in milder conditions (entry 7) was detrimental for the reaction, as well as at a slightly higher temperature than −78 °C (entry 8). A LiHMDS slow addition gave a slightly lower yield (entry 11), whereas a fast addition yielded same results as the entry 1 (entry 12). The diene activation by $Mg(ClO_4)_2$ gave very poor results (entries 13-14). Finally, 1.5 equivalents of LiHMDS (entry 9) seemed to slightly improve the yield. Inspired by this last result we thought to use 1.5 equivalents of sulfonium salt (in addition to 1.5 equivalents of LiHMDS). Besides, the base was added in two fractions of 0.75 equivalent, separated by 20 min (entry 10). Thereby, after 20 min of reaction, a freshly batch of ylide was generated, allowing to overcome ylide poor stability, and favoring diene consumption. We were pleased to observe a slightly better yield of 28 %, together with a good regioselectivity towards 1,6-ylide addition.

4.2.4 Scope of the asymmetric version

Using our best reaction conditions (entry 10), numerous (4+1) annulation reactions were carried out with various dienes and chiral sulfonium salts (table 4.8). All these reactions were performed on 100 mg scale of diene.

[35] It is however emphasized that for these entries, particularly low **8pa** amounts generate imprecise ratios.



6
100 mg; 1 eq.

38
1.1 eq.

9

Table 4.8

Entry	R^1	R^2	Isolated yield (**9**)[a]	ee
1[b]	Ph	Ph	47 % (**9ba**)	>99 %
2	*p*-MeOPh	Ph	47 % (**9ga**)	94 %
3	*p*-MePh	Ph	38 % (**9ca**)	90 %
4	*p*-FPh	Ph	47 % (**9ea**)	94 %
5[c]	*p*-BrPh	Ph	60 % (**9za**)	>99 %
6	EtO_2C	Ph	35 % (**9fa**)	25 %
7	*i*-Pr	Ph	0 %[d] (**9ja**)	/
8	*n*-Bu	Ph	0 %[e] (**9ka**)	/
9	Ph	*p*-MeOPh	55 % (**9bb**)	91 %
10	Ph	*p*-FPh	50 % (**9bd**)	90 %

[a] After purification by flash chromatography on silica gel.
[b] Carried out on 300 mg scale of diene.
[c] Performed by Dr. Geoffroy Dequirez.
[d] Only diene and large amounts of side products were observed on the crude mixture.
[e] No purification was carried out, due to especially low diene conversion (0.2/1 cycloptentene/diene ratio).

It is first noted that significant amounts of by-products were observed in all cases, contrary to previous racemic reaction. Also, the desired cyclopentene was isolated for all entries, except for *i*-Pr and *n*-Bu dienes (entries 7 and 8 respectively).

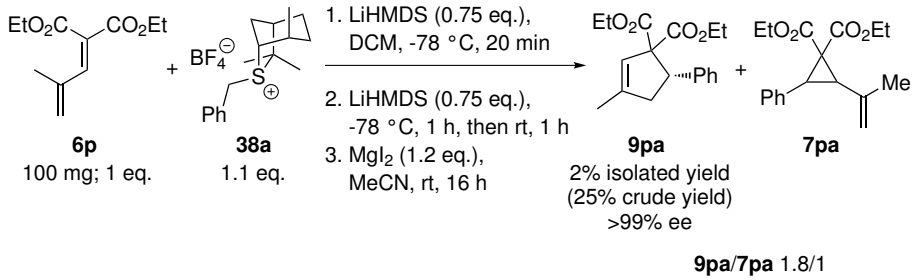
As compared to racemic version, where isolated yields were around 55 %, our asymmetric methodology generated slightly lower yields (approximately 50 %; variation from 35 % to 60 %), expect for *p*-MePh and EtO_2C substituents where similar isolated yields are highlighted (entries 3 and 6 respectively), as well as with *p*-BrPh substituted diene (entry 5), where a better yield of 60 % is obtained (40 % for the racemic version). These moderate yields are explained by partial diene degradation under mentioned reaction conditions, together with

fast ylide degradation.[36] It is noted that a scale-up was successfully carried out, starting from 300 mg of diene **2b** (rather than 100 mg), without any impact on the isolated yield (entry 1).

Regarding functional groups tolerance, as for previous racemic reactions, electron-withdrawing and electron-donating groups were well tolerated, and did not influence the yield. Similar results were also observed independently of the substitution position (diene or sulfonium salt). A lower yield was however obtained for *p*-MePh substituted diene (entry 3), as well as with the ester substitution (entry 6). Besides, the particular better yield with the *p*-Br substituted diene (as compared to the racemic (4+1) annulation reaction) is explained by the lower reactivity of the chiral ylide.

Eventually, we were pleased to observe particularly excellent enantiomeric excesses, as they vary from 90 % to >99 %, except for the ester substituted diene (entry 6), where a limited 25 % ee was observed. Explanations of this especially high enantiocontrol and the limited ee for entry 6 are explained in section 4.5.2 page 154.

These optimized reaction conditions were also applied to 3-methyl substituted diene **6p** (scheme 4.14).



Scheme 4.14

Analyses of the ^{1}H NMR spectrum of the crude mixture revealed large amounts of by-products, together with vinylcyclopropane resulting from the 1,4-ylide addition. The regioselectivity of 1.8/1 towards 1,6-addition is consistent with previous reactions between this diene and chiral sulfonium salt **38a**. Besides, the internal standard allowed to highlight a limited crude yield of 25 %. Subsequent purification by flash chromatography on silica gel gave the desired product **9pa** in only 2 % yield, due to very closed cyclopentene and

[36] The use of Ph_2MeSiH internal standard indeed revealed similar crude and isolated yields, indicating almost no loss of product during subsequent purification by flash chromatography on silica gel.

VCP **7pa** R_f. Despite this, analytical chiral HPLC analysis revealed a total enantiocontrol (>99 % ee).

4.2.5 Determination of absolute stereochemistry

Enantioenriched cyclopentenes **9** in hand, we were next interested in determining their absolute stereochemistry.

The best way to unambiguously establish the absolute configuration is to carry out X-ray diffraction analysis. This requires however to have a crystal. A series of crystallisation processes were thus attempted, with all chiral cyclopentenes in our possession. We were pleased to succeed in obtaining a pure **9pa** crystal.[37] The further X-ray diffraction analysis revealed a *S* absolute configuration (figure 4.6; for technical details, see section 6.3.1 page 285). In order to ensure that the specific crystal employed for X-ray analysis contains only major isomer molecules, a chiral HPLC was performed on this latter. We were pleased to observe a >99 % ee towards the desired isomer.

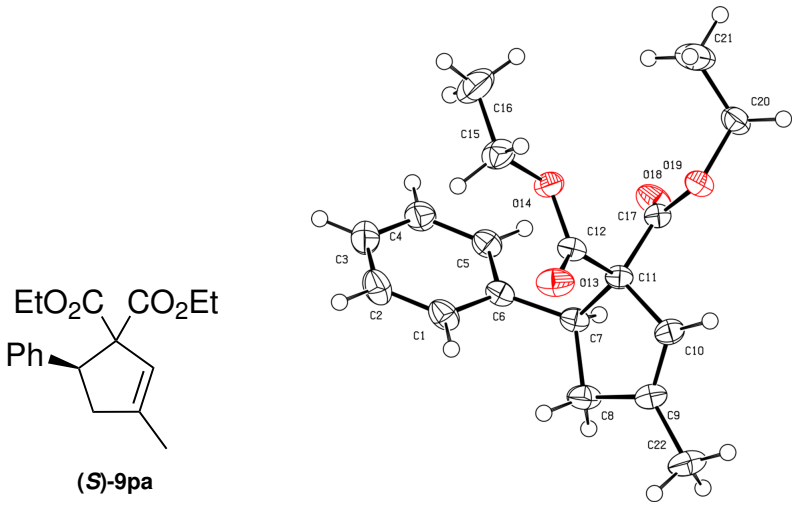


Figure 4.6

The enantiocontrol of our asymmetric (4+1) annulation reaction methodology is discussed in section 4.5.2 page 154.

In summary, a general method was developed and applied to various electron-withdrawing and electron-donating 2-substituted dienes, as well as to 3-methyl

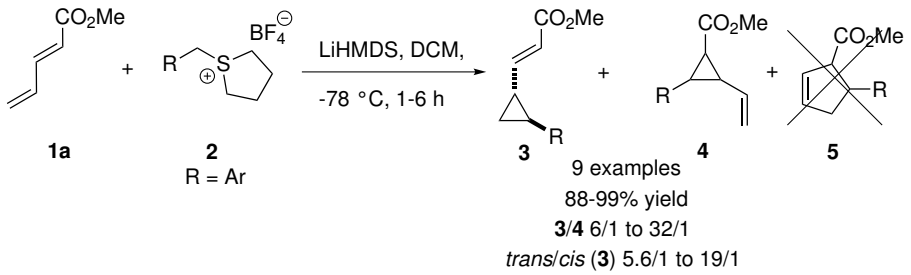
[37] Crystallisation process was carried out with a Et_2O solution of pure chiral cyclopentene **9pa** sample, allowing the solvent to slowly evaporate, at room temperature (in a vial).

substituted diene **6p**, with various sulfonium ylide, in moderate yields. A subsequent development allowed the discovery of an asymmetric version of our methodology. This latter was also applied to various dienes and sulfonium salts, in moderates yields. An especially high enantiocontrol for this asymmetric procedure must be emphasized.

We are now going to focus on non-substituted mono-activated dienes, to study how general are the vinylcyclopropanation step and the subsequent rearrangement process.

4.3 The use of mono-activated dienes[38]

We previously mentioned in the preliminary results of our laboratory that the reaction of diene **1a** with various non-chiral sulfonium ylides does not give any cyclopentene, only VCP resulting from 1,4 and 1,6 ylide addition being isolated (scheme 4.15).[1]



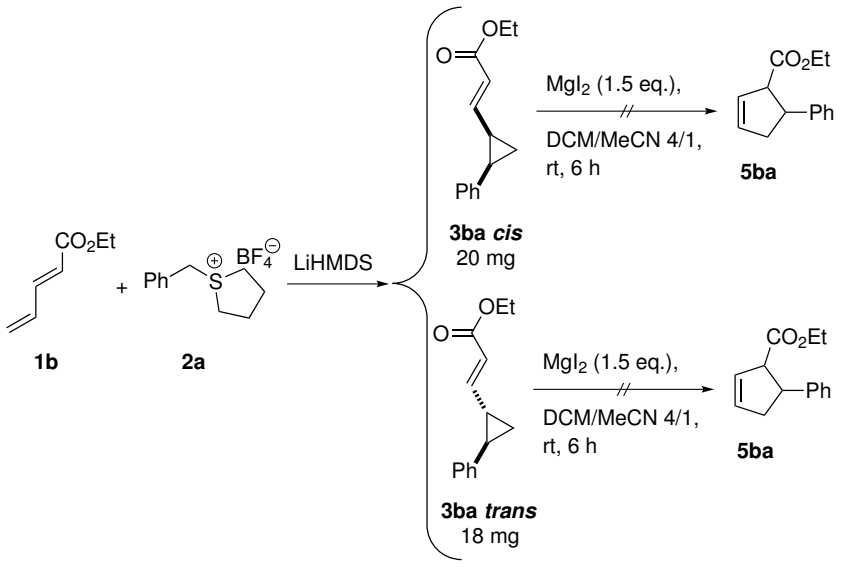
Scheme 4.15

Using similar diene **1b**, we then tried to rearrange VCP **3ba**[39] with MgI_2, but any conversion was observed towards desired cyclopentene **5ba** (scheme 4.16).[40]

[38]It is noteworthy that all reactions in this section were carried out before previously mentioned developments processes (racemic and asymmetric versions). All annulation reactions were thus performed using unoptimized procedures.

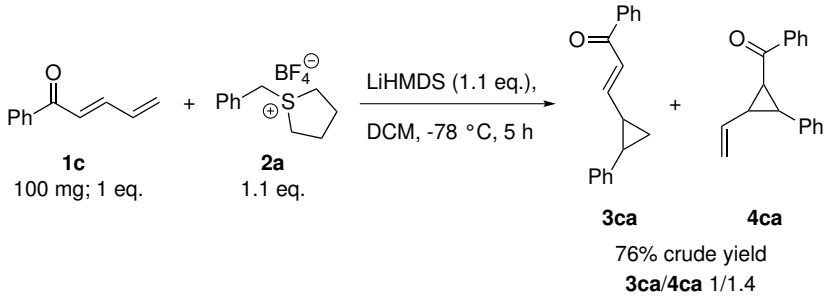
[39]The synthesis of VCP **3ba** is detailed in the experimental part, page 233. Besides, traces of VCP **4ba** was also observed in the crude mixture.

[40]The rearrangement of VCP **3ba** ***trans*** was performed on an impure sample.



Scheme 4.16

We next envisioned using diene **1c** as substrate. It is noted that this diene gave unfortunately mainly VCP coming from 1,4-ylide addition (scheme 4.17).[3]



Scheme 4.17

We can thus conclude that a more activated diene favor 1,4-ylide addition (diene **1c**), whereas the 1,6-ylide addition is favored with dienes **1a,b**, activated by weaker withdrawing ester groups. This conclusion is also supported by the preferred 1,4-ylide addition with bis-activated diene **6a** (see page 39), as the presence of two activating ester groups generates a more activated diene as compared to **1a,b** (figure 4.7).

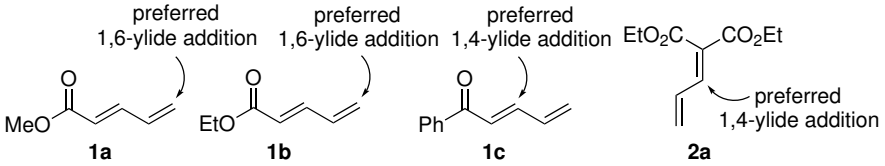
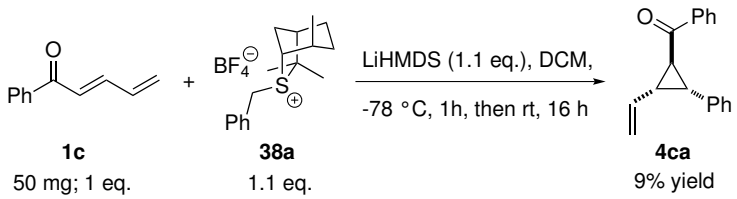


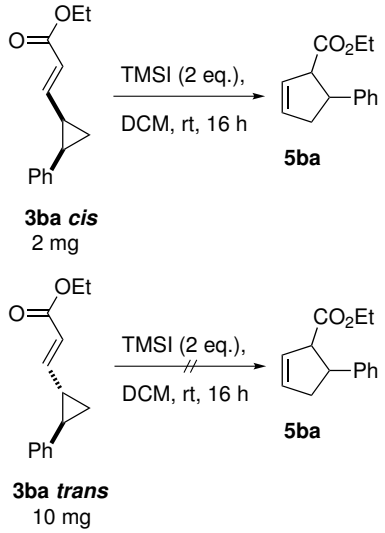
Figure 4.7

We thus investigated the asymmetric vinylcyclopropanation reaction with diene **1c**. Indeed, we envisioned that the use of the bulkier chiral sulfonium salt should reverse the regioselectivity towards 1,6-ylide addition (scheme 4.18). Surprisingly, only vinylcyclopropane resulting from 1,4-ylide addition was observed on the ^{1}H NMR spectrum of the crude mixture, together with large amounts of diene and by-products (1/3.5 **4ca**/**1c**). Subsequent purification by flash chromatography on silica gel gave a limited 9 % yield of **4ca**.



Scheme 4.18

As diene **1c** mainly furnished VCP **4ca**, we next attempted a last rearrangement on VCP **3ba**, using TMSI, as silicon coordinates well oxygen atom and so could promote VCP activation. Although the *trans* isomer was totally recovered, it seems that the *cis* isomer was converted to cyclopentene **5ba** under the mentioned reaction conditions (scheme 4.19). The especially strained **3ba** ***cis*** vinylcyclopropane is probably the explanation of such observations. Subsequent purification was not carried out, due to especially low crude mass (2 mg).



Scheme 4.19

A further attempt on another crude isomers mixture (200 mg) gave identical results.[41] Subsequent purification by flash chromatography on silica gel did unfortunately not allow us to isolate the desired product, as fractions were contaminated by large amounts of by-products. We did not spend further time and energy in order to rearrange such vinylcyclopropane, focusing our attention instead on the bis-activated diene synthesis and annulation reaction with the latter.

A plethora of racemic cyclopentenes, as well as enantioenriched one, were successfully synthesized, using bis-activated dienes **2**. We tried to extend our strategy to mono-activated dienes **1b** and **1c**, unsuccessfully.

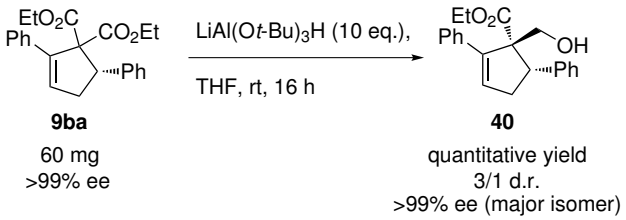
In order to illustrate the potential applications of our methodology, we subsequently envisioned to perform various transformation reactions on cyclopentenes.

[41] VCP **5ba** ***trans*** was recovered, conversely to the other isomer, which was apparently converted to corresponding cyclopentene.

4.4 Diversity oriented functionalization of cyclopentenes[42]

As all 5-membered carbocycles resulting from our (4+1) annulation reaction methodology bear functional groups, derivatization reactions were attempted. Indeed, the double bond allows for example an ozonolysis reaction, as well as hydroboration or hydrogenation reactions. On the other hand, a diastereoselective ester reduction can be envisioned, as one of the two ester activating groups is less accessible due to the substitution pattern at the C1 unit.

Using enantiopure cyclopentene **9ba**, selective reduction of one ester group was first performed. Using sterically hindered $LiAl(O\mathit{t}\text{-}Bu)_3H$, a diastereoselective ester reduction was expected (scheme 4.20). We were pleased to observe a quantitative yield towards desired product **40** after purification by flash chromatography on silica gel. Furthermore, a satisfying 3/1 diastereoselectivity was observed on the crude mixture,[43] without alteration of the enantiomeric excess. It is noted that the hydroxy group should allow further interesting functionalization reactions.

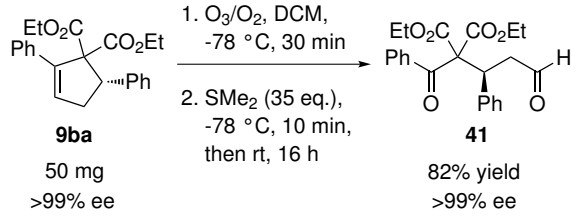


Scheme 4.20

We next planned an ozonolysis reaction on the same chiral cyclopentene **9ba** (scheme 4.21). Pure non cyclic compound **41** was isolated in 82 % yield after purification, with a preservation of the enantiomeric excess. This interesting chiral compound could be further functionalized, especially on the ketone and aldehyde moieties.

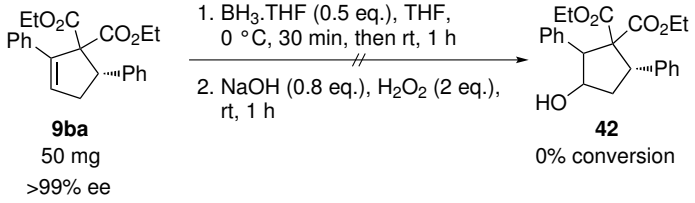
[42] All enantiomeric excesses mentioned in this section were calculated after enantiomers separation by analytical chiral HPLC. Besides, isomers retention times were determined on the racemic mixture.

[43] Relative stereochemistry was attributed assuming that the less hindered ester group undergoes reduction faster.



Scheme 4.21

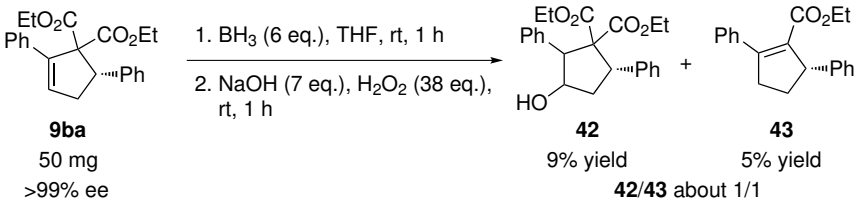
A hydroboration reaction was subsequently carried out, on the chiral cyclopentene **9ba** (scheme 4.22). The crude however revealed a 0 % conversion.



Scheme 4.22

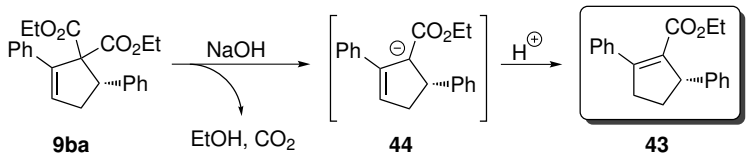
As the total amount of starting material was retrieved, we thus thought to employ more drastic reaction conditions: double quantities of reagents, together with a direct warming up at room temperature for 1 h after borane addition. The crude mixture revealed a tiny amount of desired product **42**, together with cyclopentene substrate. Quantities of reagents were next drastically increased (scheme 4.23). The crude mixture revealed remaining substrate, together with desired product and large amounts of side-products (in 0.8/1/1 **9ba**/**42**/**43** ratios). Subsequent purification by flash chromatography on silica gel allowed isolation of the hydroboration adduct **42** only in a 9 % yield. Analysis of the ^{1}H NMR spectrum of the crude mixture indicated a good diastereoselectivity for **42**. Unfortunately, this latter could not be calculated precisely, due to large amounts of by-products observed in the crude mixture.[44]

[44]The enantiomeric excess was not determined. Indeed, since the racemic compound has not been synthesized, enantiomers retention times were not known. Thereby, no chiral HPLC of enantioenriched product **42** was carried out.



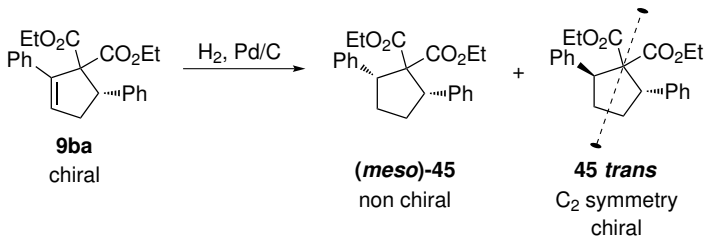
Scheme 4.23

As mentioned in the scheme, side-product **43** was notably obtained. Formation of **43** can be explained by partial saponification reaction of substrate **9ba** followed by a decarboxylation during the oxidation step (scheme 4.24). The driving force of this decarboxylation reaction may be explained by the stabilisation of the intermediate anion **44** by the ester and allyl moieties. This by-product **43** was isolated in 5 % yield. As mentioned before, the crude showed identical amounts of product **42** and by-product **43**.[45] We did not try to improve the conversion towards the desired product.



Scheme 4.24

A double bond hydrogenation was also performed. It must be noted that the reaction gives, depending on the facial selectivity, the *meso* or the C_2 symmetry adducts (scheme 4.25).



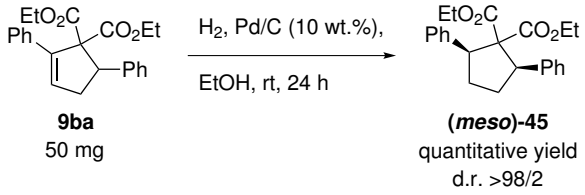
Scheme 4.25

Given that non-chiral product ***(meso)*-45** should be formed,[46] the reaction

[45]The enantiomeric excess was not calculated, as the racemic compound was not synthesized.

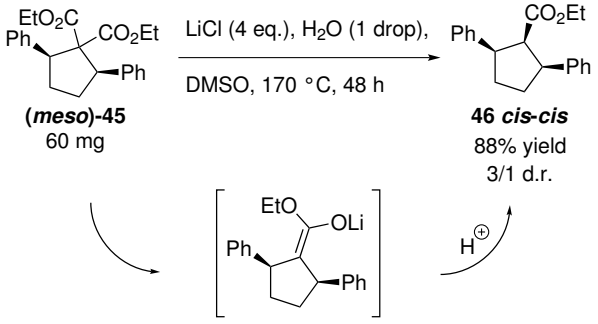
[46]The hydrogenation reaction occurring from the less hindered face of the molecule.

was carried out using racemic mixture of cyclopentene **9ba** (scheme 4.26). The reaction proceeded smoothly, and desired product **45** (*meso*) was obtained in quantitative isolated yield.[47] A total diastereoselectivity towards the more hindered *cis* product has to be highlighted.



Scheme 4.26

Finally, using this last product **45**, diastereoselectivity of the Krapcho decarboxylation reaction was studied (scheme 4.27).[48] The ^{1}H NMR spectrum of the crude mixture revealed a mixture of both diastereoisomers in a 3/1 ratio. Subsequent purification by flash chromatography on silica gel gave a mixture of isomers in 88 % yield. Unfortunately, relative stereochemistry of each isomer could not be determined from the NOESY experiment performed on this mixture.[49] However, one can assume that the observed product is the kinetic one (see below) and that this latter is the one involving the lower steric interactions during the protonation step (protonation from the opposite side of phenyls), i.e. the isomer **46** ***cis-cis***.



Scheme 4.27

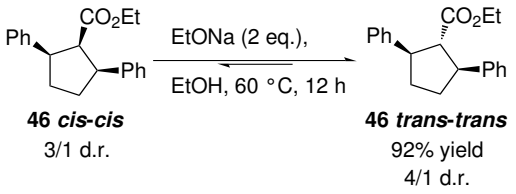
In order to have the most stable *trans-trans* isomer, EtONa promoted iso-

[47]The adduct was attributed to the *meso* isomer by the analysis of the ^{1}H NMR spectrum. Indeed, because of symmetry purposes, two different signals are expected for the ester groups in the case of the *meso* isomer, whereas one signal is expected in the case of the *trans* isomer.

[48]Carried out by Dr. Thierry Delaunay.

[49]In $CDCl_3$, using a 300 MHz spectrometer. The mixing time was set to 0.9 sec, and 32 scans were carried out.

merisation reaction was then performed on this last purified mixture (scheme 4.28).[50] We were pleased to observe mainly the desired thermodynamically most stable *trans-trans* isomer.[51] Furthermore, the d.r. was improved (3/1 to 1/4). One highlighted a 92 % isolated yield after purification by flash chromatography on silica gel.



Scheme 4.28

All these successful derivatization reactions illustrate the versatility of our methodology. Indeed, cyclopentene **9ba** is stable under various reaction conditions, especially basic conditions and elevated temperature. Partial side-reactions with sodium hydroxide (in THF solvent) to produce by-product **43** was however observed. Also, ^{1}H NMR analysis confirms cyclopentene **9ba** stability up to four years.[52]

The development of our (4+1) annulation reaction methodology, the subsequent enantioselective strategy, as well as the various derivatization reactions led to the publication of an article in 2015.[53]

The last section is focusing on the stereospecificity of the MgI_2 promoted rearrangement, as well as the origin of observed enantiocontrol with sulfonium salts **38**.

[50] Performed by Dr. Thierry Delaunay.

[51] Computational studies, carried out by Prof. Raphaël Robiette, supports that **46** ***trans-trans*** is more stable that the other isomer **46** ***cis-cis***. See section 6.3.2 page 288.

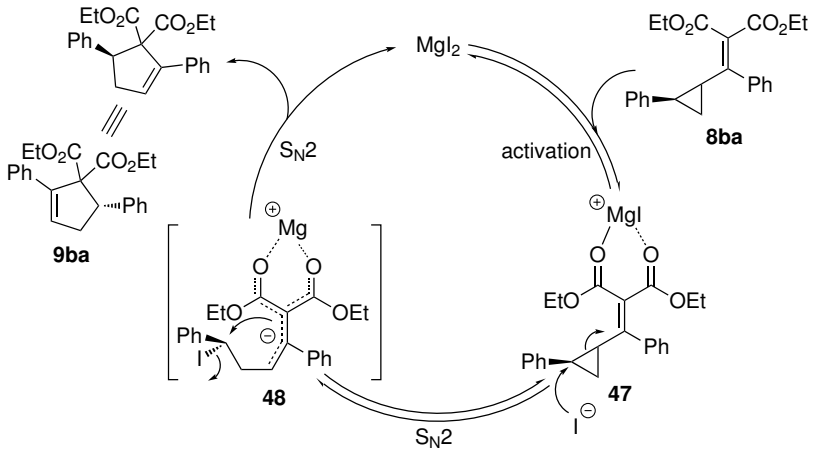
[52] In pure phase, under inert atmosphere, at −20 °C.

[53] O. Rousseau, T. Delaunay, G. Dequirez, T. Trieu-Van, K. Robeyns, R. Robiette, *Chem. Eur. J.* **2015**, *21*, 12899–12902.

4.5 Mechanistic studies

4.5.1 MgI_2 mediated stereospecific rearrangement[54]

We previously mentioned that the non-alteration of the enantioselectivity during the rearrangement reaction involves a stereospecific process (see scheme 4.12 page 134). These observations allowed us to propose a mechanism for the rearrangement process (scheme 4.29). According to this mechanism, vinylcyclopropane **8ba** is first activated by magnesium cation, leading to compound **47**. An iodide promoted vinylcyclopropane opening is then taking place, *via* a S_N2 process, giving intermediate **48**. After electrons delocalization and subsequently ring closure by another S_N2 process, desired cyclopentene **9ba** is obtained, with release of the iodide anion. The reaction stereospecificity resides in this double S_N2 processes, as absolute configuration of the stereogenic center bearing the phenyl moiety is inverted during both ring opening and ring closure processes.

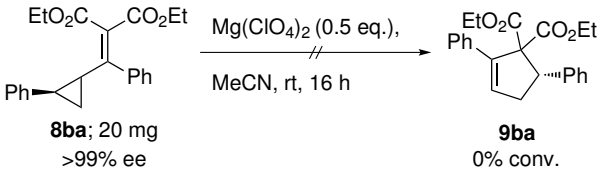


Scheme 4.29

In order to study if both magnesium cation and iodide anion are required for the conversion of vinylcyclopropane to the corresponding cyclopentene, two rearrangement reactions were planned on enantiopure vinylcyclopropane **8ba**. The first reaction involves a $Mg(ClO_4)_2$ promoted VCP/CP rearrangement (scheme 4.30). This reaction should allow us to investigate the role of the iodide anion, the perchlorate anion being non-nucleophilic. Using 0.5 equivalent of $Mg(ClO_4)_2$, we observed no conversion to cyclopentene **9ba**, even after 16 h

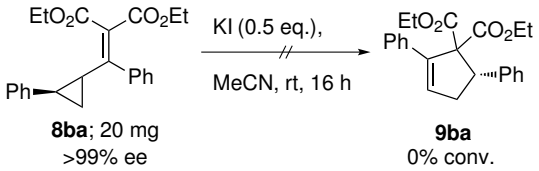
[54] All reactions mentioned in this section were performed by Trieu-Van Tran.

of reaction.



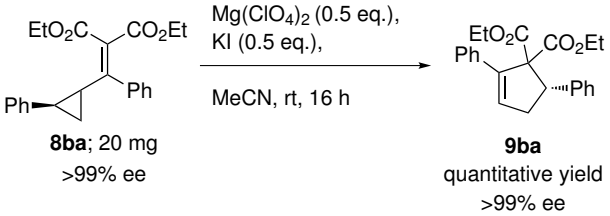
Scheme 4.30

Another rearrangement was also performed, using KI as a reagent, in order to investigate the magnesium cation influence on the reaction (scheme 4.31). Analyses of ^{1}H NMR spectrum of the crude mixture revealed only vinylcyclopropane starting material.



Scheme 4.31

Finally, we tested the use of both magnesium perchlorate and potassium iodide (scheme 4.32). We were pleased to observe a full conversion towards desired product **9ba**, this latter being isolated in quantitative yield. Furthermore, chiral HPLC showed a total conservation of the enantiomeric excess.



Scheme 4.32

These results confirm that both magnesium cation and iodide anion are required for the VCP/CP rearrangement and give credence to our proposed mechanism.

4.5.2 Enantiocontrol with chiral sulfonium ylides

We previously observed especially high enantiomeric excesses using chiral sulfonium salts **38** (page 140), ranging from 90 % to >99 %. Aggarwal and coworkers also noticed high enantiocontrol in epoxidation and aziridination reactions with such structures.[109]

They notably highlighted that the enantioselectivity is controlled by the two following aspects:[109]

1. the ylide conformation
2. the facial selectivity of ylide addition

Conformations **49a** and **49b** are both accessible (figure 4.8). The **b** conformation is however less probable, due to steric interactions with the phenyl group.

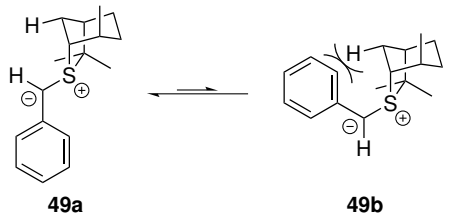


Figure 4.8

Secondly, they mentioned that one face is totally blocked, because of steric interactions with the gem-methyl groups. One can thus assume that the diene is coming from the front face (figure 4.9).

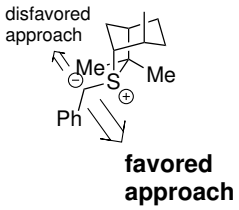
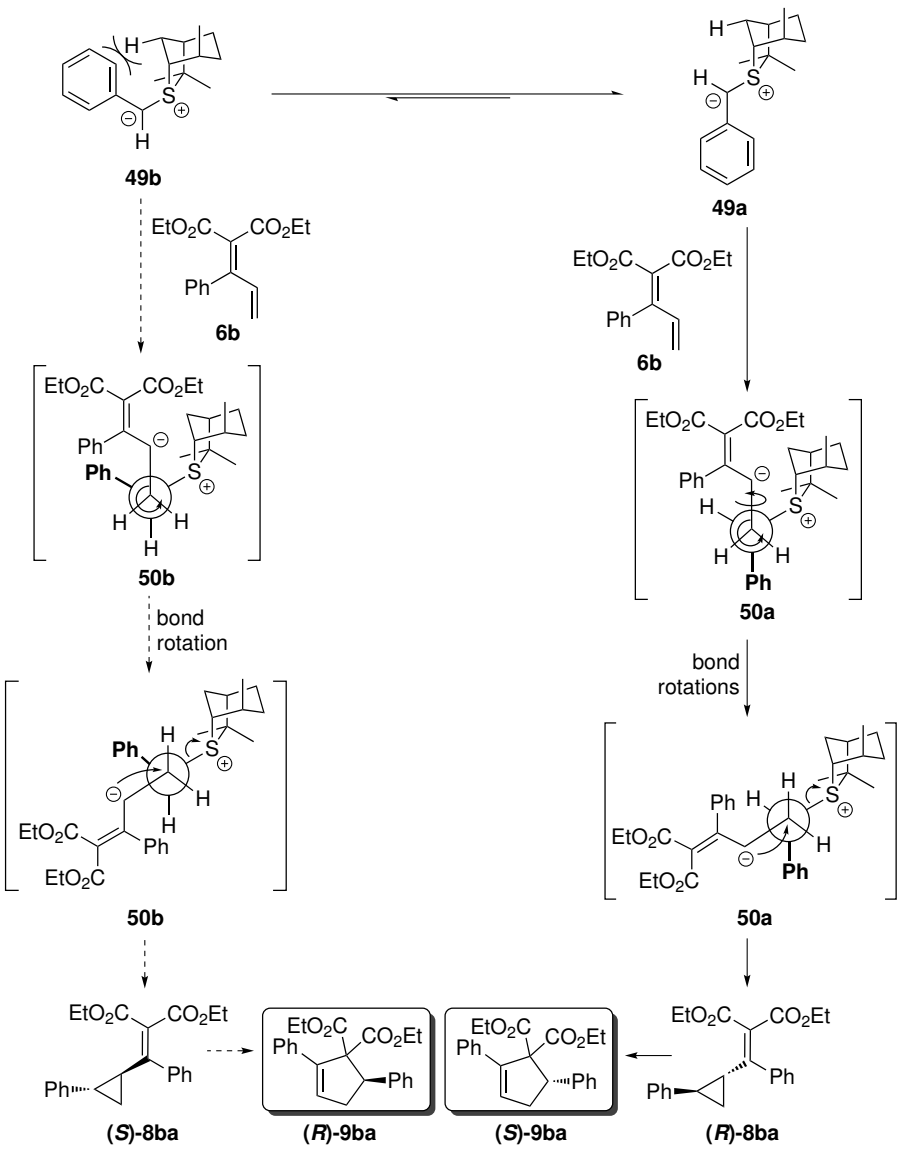


Figure 4.9

Accordingly, the following mechanism is proposed (scheme 4.33): ylide **49a** is giving betaine **50a**, which allowed, after bonds rotation and then the release of isothiocineole, to obtain vinylcyclopropane **(*R*)-8ba**. On the contrary, the other ylide conformer **49b** would have generated VCP **(*S*)-8ba**.

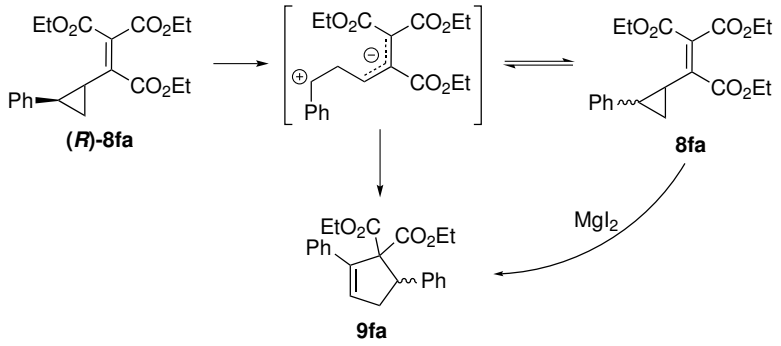


Scheme 4.33

The higher population of **49a** as compared to **49b**, together with the very high facial selectivity are likely explanations of the observed enantioselectivities on the vinylcyclopropane product. Also, the stereospecific MgI_2 promoted rearrangement, involving two S_N2 processes, allows the retention of the benzylic carbon configuration from the VCP to the CP product.

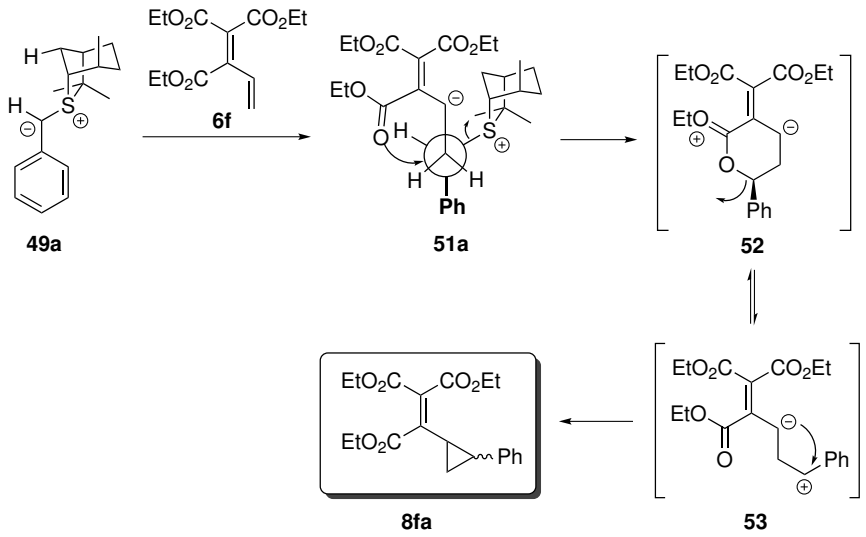
We nevertheless observed a limited 25 % ee with the ester-substituted diene **6f** (see page 140). Three possible explanations are proposed:

First, a rearrangement process, involving a heterolytic VCP opening favored by the inductive effect of the electron-withdrawing ester substituent, generates cyclopentene **9fa** in a less or a non stereospecific manner (scheme 4.34). Indeed, the sp^2 positively charged carbon on the intermediate would result in a loss of the chiral information, thus lowering the final enantiomeric excess.



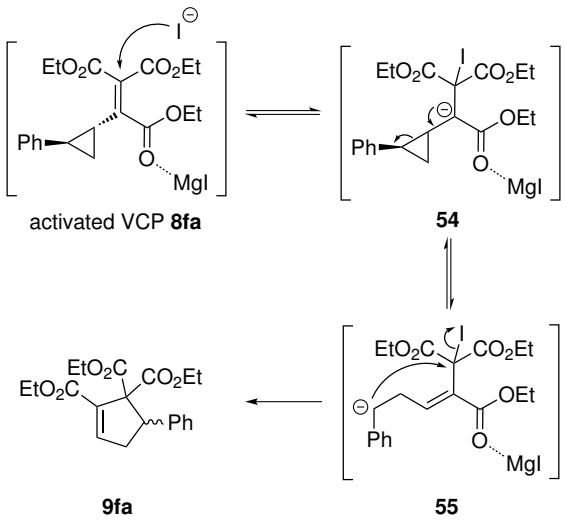
Scheme 4.34

A second possible explanation of the observed low enantiomeric excess involves Neighbouring Group Participation (NGP) of the ester moiety (scheme 4.35). Ylide addition is giving betaine **51a**, which could lead to the lactone-derived zwitterionic intermediate **52** *via* a NGP process. Subsequent ring opening is the key step, as chiral information is lost on intermediate **53**, and thus generates desired VCP **8fa** with deterioration of the enantiomeric excess.



Scheme 4.35

Finally, the rearrangement process could take place in a different way, due to the presence of the ester substituent (scheme 4.36). Indeed, the iodide anion could add on the gem-bis-activated carbon of the activated VCP **8fa**, giving the intermediate **54**. The next step, involving the cyclopropane opening, is crucial, as the chiral information is lost during the process (**55**). Finally, ring closure on intermediate **55** could give the desired cyclopentene **9fa**.



Scheme 4.36

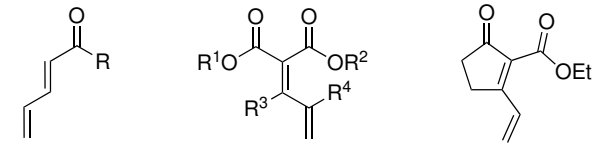
Chapter 5

Conclusion and perspectives

In order to develop an effective (4+1) annulation reaction methodology, allowing access to five-membered carbocycles, we decided to employ 1,3-dienes and sulfonium ylides as substrates (as C4 and C1 units respectively).

5.1 Substrates synthesis

In this perspective, two mono-activated 1,3-dienes were synthesized, as well as fifteen bis-activated ones, generally in moderate yields. Finally, a cyclic diene was isolated, although in a limited yield (figure 5.1).



1
R = OEt, Ph
2 examples
25-45 % yield

6
R^1 = R^2 = Me, Et
or R^1 = Bn, R^2 = Me
R^3 = H, alkyl, aryl, ester
R^4 = H, Me, Ph
15 examples
5-77 % yield

6m
1.5% yield

Figure 5.1

Depending on the nature of the diene (and substitution pattern), various synthetic strategies have been used, involving, as the key step:

– Aldol/dehydratation conjugated reactions

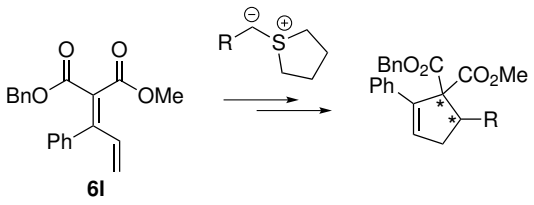
– a Suzuki-Miyaura cross-coupling reaction

– a selenium-mediated olefination reaction

– a $TiCl_4$ promoted Knoevenagel condensation

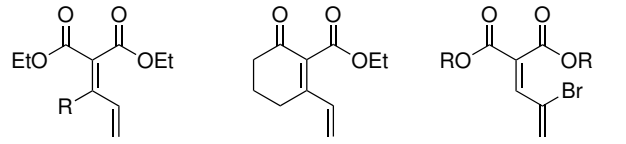
– a LiBr mediated Knoevenagel condensation

It has to be noted that the structural specificity of diene **6l** allows formation of an additional chiral center on the (4+1) annulation product (scheme 5.1). This diene is thus especially interesting. It also allows studying the stereospecificity of our methodology. This study requires however to determine previously the absolute configuration of the diene. Numerous attempts were carried out to determine this latter configuration, but without success.



Scheme 5.1

In addition to these dienes, some other dienes were envisioned, but could not be isolated (figure 5.2).



R = $SiMe_2Ph$ (**6h**), Et (**6u**), OEt (**6v**), SMe (**6x**)

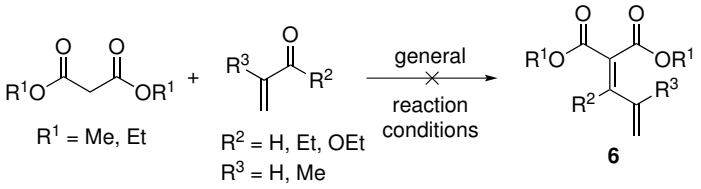
6n

R = Et (**6q**), Me (**6r**)

Figure 5.2

Finally, we were interested in the development of a general method for dienes **6** synthesis, *via* a one-step procedure involving a Knoevenagel condensation

between malonate derivatives and vinylic aldehyde, ketone, and ester (scheme 5.2). Unfortunately we did not succeed in the development of such a general methodology.



Scheme 5.2

These works led to the publication of an article in 2014.[1] 1,3-Dienes in hand, we next turned our attention to the synthesis of various sulfonium salts (precursor of ylides). Inspired by described protocols,[109,143] nine sulfonium salts **2** were successfully synthesized, in generally good yields (figure 5.3).

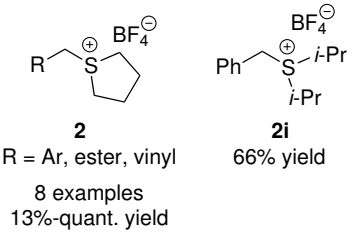
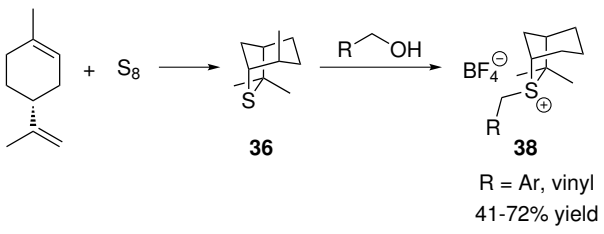


Figure 5.3

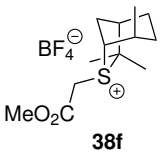
We also were interested in chiral sulfonium salts synthesis, as they should allow us to obtain enantioenriched (4+1) annulation products. Inspired by a described procedure,[109] six chiral salts **38** were obtained, from isothiocineole **36** and various alcohol derivatives, in good yields (scheme 5.3).



Scheme 5.3

[1] O. Rousseau, T. Delaunay, R. Robiette, *Synlett* **2014**, *25*, 519–522.

Unfortunately, structurally interesting ester-substituted chiral salt **38f** could not be isolated (figure 5.4).

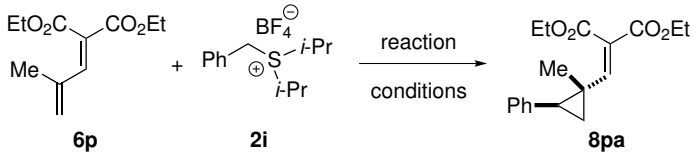


38f

Figure 5.4

5.2 (4+1) Annulation reactions

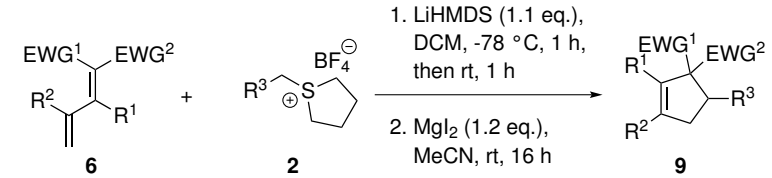
The application of reaction conditions developed in our laboratory by Dr. Thierry Delaunay to other dienes substrates giving poor results, we started to improve our methodology. Using 3-methyl-substituted diene **6p**, a series of reaction conditions were tested for the vinylcyclopropanation step (scheme 5.4).



6p **2i** **8pa**

Scheme 5.4

The best reaction conditions were then applied to various dienes and sulfonium salts, allowing us to obtain cyclopentenes products in generally moderate yields after the MgI_2 mediated rearrangement (scheme 5.5).



6
100 mg; 1 eq.
(37 mg for diene **6l**)

2
1.1 eq.

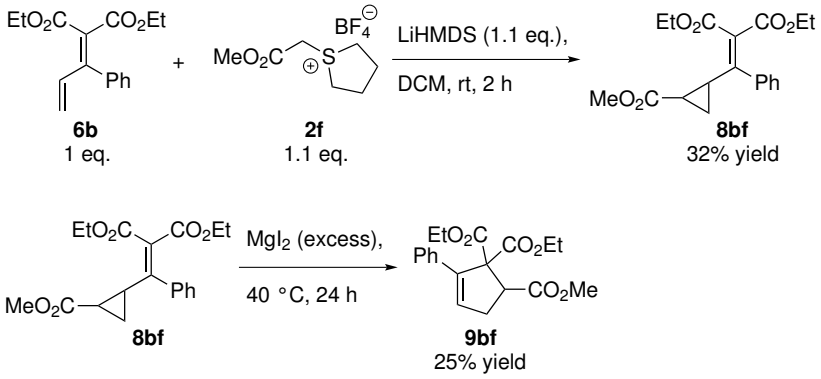
9
15 examples
32-65% yield

Scheme 5.5

The addition of LiHMDS to a mixture of diene and sulfonium salt (rather than the prior generation of the ylide before diene addition) improved isolated

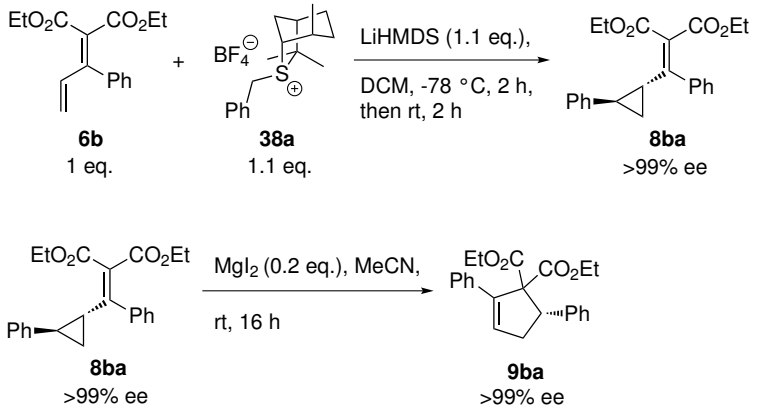
yields. In addition, diene and intermediate stability seems to be additional keys factors in determining the isolated yield.

Concerning ester-stabilised ylide (from ester salt **2f**), a two-step procedure was required to have CP **9bf** in hand, requiring harsher reaction conditions for the vinylcyclopropanation step as well as for the rearrangement process (scheme 5.6).



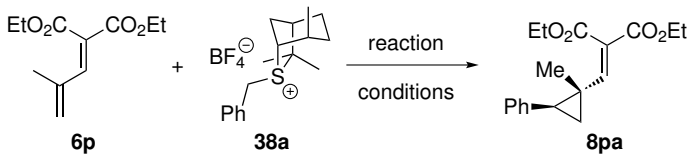
Scheme 5.6

We then turned our attention to the development of an enantioselective version of our methodology. The use of a bisoxazoline ligand being ineffective to obtain an enantioenriched cyclopentene, chiral ylide was thus envisioned, allowing us to obtain enantioenriched vinylcyclopropane **8ba** in >99 % ee (scheme 5.7). We subsequently found that the MgI_2 promoted rearrangement is a stereospecific process, as no ee deterioration was observed from VCP to CP.



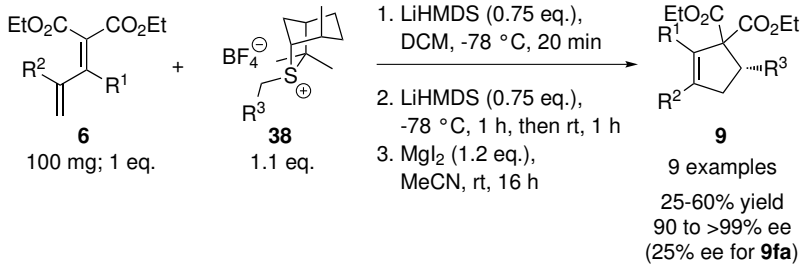
Scheme 5.7

The application of the standard one-pot procedure being ineffective, various reaction conditions were screened on the vinylcyclopropanation step, using diene **6p** (scheme 5.8).



Scheme 5.8

Using our best reaction conditions, nine cyclopentenes were obtained in moderate yields and excellent enantiomeric excesses after the MgI_2 promoted rearrangement (except for ester-substituted CP **9fa** - scheme 5.9).



Scheme 5.9

Unfortunately, alkyl-substituted cyclopentenes **9ja** and **9ka** could not be isolated (figure 5.5).

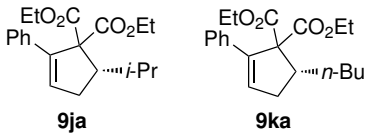


Figure 5.5

It is noteworthy that the absolute configuration of enantioenriched cyclopentenes were attributed to *S*, by analogy with X-ray diffraction analyses of **9pa** where a *S* configuration was determined.

We finally were interested in the use of mono-activated dienes **1b,c** as substrate for our (4+1) annulation reaction methodology (figure 5.6).

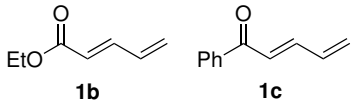


Figure 5.6

Although a total regioselectivity towards 1,6-ylide addition is mentioned with diene **1b**, the MgI_2 promoted rearrangement failed to furnish desired cyclopentene. It is noteworthy that changing MgI_2 to TMSI allowed to observe a rearrangement for one of the two VCP diastereoisomers (*cis*), but subsequent purification did not allow us to isolate the desired compound.

On the other hand, a regioselectivity towards 1,4-ylide addition was observed with diene **1c** and non-chiral ylide.[3] The use of the bulkier chiral ylide did unfortunately not allow to improve the regioselectivity towards 1,6-ylide addition.

We previously mentioned that the choice in the C1 unit is crucial to develop a general (4+1) annulation methodology, allowing to carry out easily an asymmetric version. For that purpose we choose sulfur ylides as C1 unit, and bis-activated 1,3-dienes as C4 unit, giving gem-bis-activated cyclopentenes. But other groups employed bis-activated 1,3-dienes as C4 unit,[2] furnishing highly similar cyclopentenes as compared to our methodology (regarding the position of the double bond, the chemical substitution and functional groups tolerance).[56,61–63] Highly substituted cyclopentenes could be obtained, in a phosphine-catalyzed (4+1) annulation strategy (figure 5.7). It is noteworthy that a quaternary carbon could be introduced at the C1 unit, in an enantioselective manner, using a chiral phosphine. Furthermore, spirocyclic compounds are reachable. The difficulty to carry out the asymmetric version is however a limiting aspect of this strategy as compared to our methodology (regarding the synthesis of the chiral phosphine versus our chiral sulfonium salts).

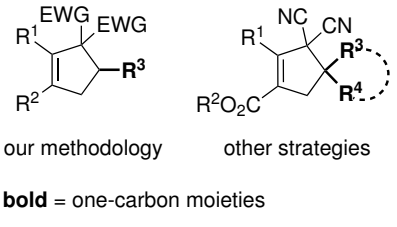


Figure 5.7

[2]With MBH carbonates, maleimides, and ethyl 2-(acetoxymethyl)acrylate as C1 unit.

In all other strategies allowing to synthesize similar structures as compared to our methodology, the bis-activated carbon of the 5-membered ring moiety comes from the C1 unit under the form of a malonate derivative,[3] the other partner being an allene,[100–102] a MBH acetate,[91] or an α,β-unsaturated ester (figure 5.8).[99] Although numerous malonate derivatives could be used as C1 unit, the functional groups tolerance is however low for the other partner, conversely to our methodology. These strategies provide cyclopentanes, or cyclopentenes with a migration of the double bond as compared to our methodology, with other substitution patterns. It is noted that enantioenriched products could be obtained at the gem-bis-activated carbon, using chiral phosphines.[101,102]

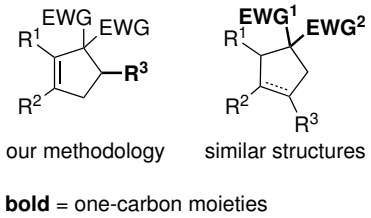


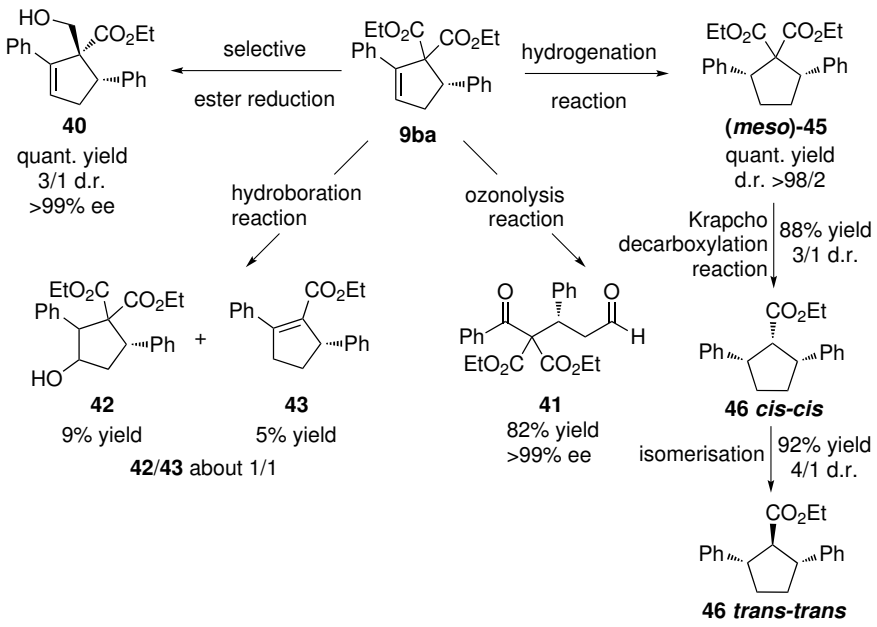
Figure 5.8

It is noteworthy that our methodology generates only gem-bis-activated 5-membered rings, but other structures could be envisioned using other strategies, such as cyclopenteneimines[82] and cyclopentenones.[42,51,75,76,88]

5.3 Diversity oriented functionalization of cyclopentenes

As an illustration of the potential applications of our methodology, various transformation reactions were carried out, involving ester functional group as well as the double-bond of CP **9ba** (scheme 5.10). In this perspective, a selective ester reduction, an ozonolysis reaction, a hydrogenation of the double bond, as well as a Krapcho reaction were successfully carried out. We also performed a hydroboration reaction but the isolated yield was particularly low.

[3] Rather than from the diene in our methodology.



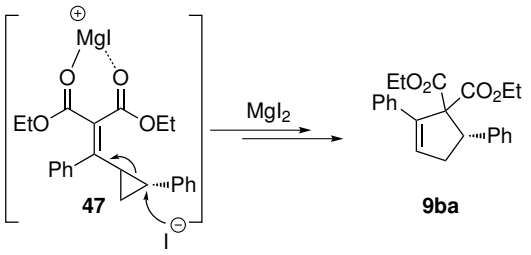
Scheme 5.10

The development of our (4+1) annulation reaction methodology, the subsequent enantioselective strategy, as well as the various derivatization reactions led to the publication of an article in 2015.[4]

5.4 Mechanistic studies

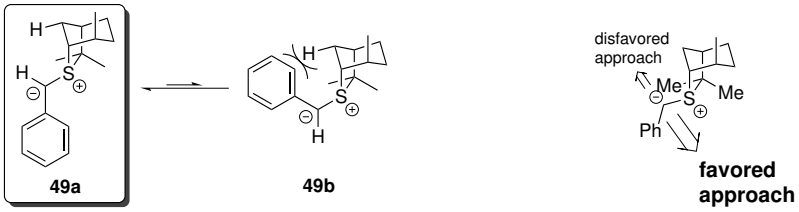
In a last section we were interested in the mechanism of the MgI_2 promoted VCP/CP rearrangement, as well as the enantiocontrol provided by the chiral ylide **49**. Various experiments enabled us to establish that both magnesium and iodide ions are required for the rearrangement. Indeed, the magnesium cation activates the VCP, whereas the iodide anion performs a VCP ring opening/ring closure conjugated reactions *via* S_N2 processes, allowing us to obtain the desired cyclopentene with retention of the absolute configuration (scheme 5.11).

[4] O. Rousseau, T. Delaunay, G. Dequirez, T. Trieu-Van, K. Robeyns, R. Robiette, *Chem. Eur. J.* **2015**, *21*, 12899–12902.



Scheme 5.11

On the other hand, inspired by Aggarwal studies,[109] a mechanistic explanation of the observed high enantiocontrol on the cyclopentenes using chiral salts **38** was carried out. We concluded that the equilibrium between the two conformers of the chiral ylide as well as the facial selectivity are the key-factors of the observed enantiocontrol.



(a) Conformers equilibrium (b) Facial selectivity

Figure 5.9

5.5 Perspectives

It is noteworthy that most of dienes **6** were synthesized either by the Suzuki-Miyaura cross-coupling and the selenium-mediated olefination strategies, involving four and three steps respectively. Because of moderates (around 30-40 %) overall yields and relatively low stability of this structure (requiring to regularly carry out a new batch of diene), it could be interesting and challenging to find another way accessing these dienes, *via* a one-step procedure, thus saving time and energy to synthesize these dienes substrates. Although our attempts to apply a Knoevenagel reaction strategy (developed for non-substituted dienes **6a**/**6w** and 3-substituted dienes) failed, further efforts should be done to develop such a methodology. The possible access to other 2- and 3-substituted dienes is another aspect in favor of this development.

Synthesis of cyclic dienes **6m,n**, as well as other cyclic dienes, are very

interesting as they would allow to synthesize bicyclic (4+1) annulation products (very common in natural/synthetic biologically active compounds; figure 5.10). Although they could not be isolated in the required amount to perform an annulation reaction attempt, efforts must be carried out to have them in hand, for example using the Suzuki-Miyaura strategy.

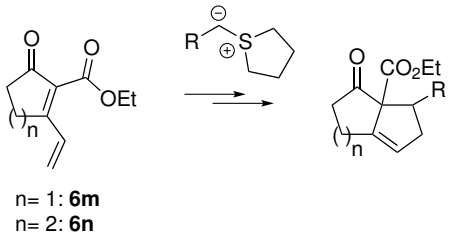


Figure 5.10

Due to the bis-activation and its free fourth position, diene **6** is especially interesting starting material, which may have utility in numerous other reactions than our (4+1) annulation methodology, such as the Diels-Alder reaction, the (3+2) cycloaddition/annnulation reaction, various metal-catalyzed reactions, etc.

Concerning our (4+1) annulation reaction methodology, we observed moderate yields for both non-chiral and chiral ylides. It seems that diene and intermediates stability are key factors of the observed isolated yields (together with ylide stability in the case of chiral ylide). It could be interesting to study the influence of diene stability/reactivity on our (4+1) annulation strategy, in order to improve the yields using our optimized reaction conditions (for example using additives, etc.). In addition, isolated yields of enantioenriched cyclopentenes being poor to moderate, optimization is suitable. To do so, improving chiral sulfonium ylides stability (for example using another base or another solvent) could be envisioned. The use of other chiral scaffolds is also possible, but the observed excellent enantiomeric excesses and the ease to synthesize chiral salts **38** are determining aspects to use this last scaffold as substrate.

During our thesis, we were only interested in using ester-activated dienes in our (4+1) annulation strategy. It could however be very interesting to test the robustness of our methodology towards other activated dienes, such as nitro, amide, cyano, and ketone groups (figure 5.11).

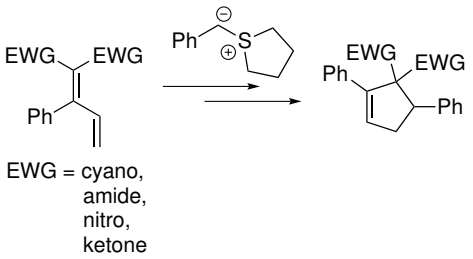
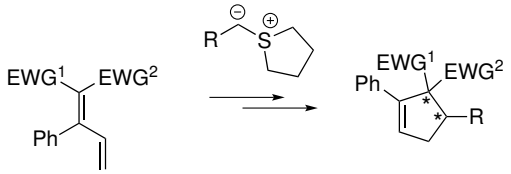


Figure 5.11

In order to further investigate the mechanism of our methodology (on the vinylcyclopropanation step as well as the rearrangement process), we could use the Hammett equation. Indeed, the relative reactivity of differently substituted substrates as compared to a reference substrate should give information on the mechanism of the reaction.

As mentioned previously, the use of two different electron-withdrawing groups is attractive, as it allows the formation of two new stereogenic centers on the (4+1) annulation product, in a one step procedure (scheme 5.12). It would facilitate also selective functionalization reactions on one specific EWG.

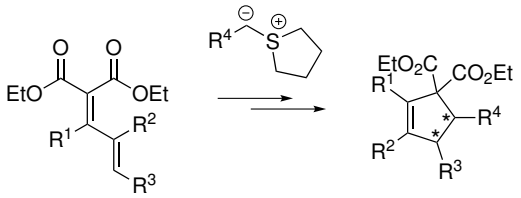


Scheme 5.12

In these perspectives, we used non-symmetrical diene **6l**, but, as mentioned before, nOe experiments did not allow to determine the absolute configuration of the new chiral center. For the above-mentioned reasons, efforts must be carried out to successfully determine the absolute configuration of this chiral center, using for example two distinctive aromatic moieties (the first one substituted by an electron-withdrawing substituent and the other one by an electron-donating group), that should help aromatic signals discrimination and thus facilitate nOe analyses. One could also use other substitution patterns than benzyl and methoxy groups in the present case to promote nOe observations, such as esters substituted by a *tert*-butyl or a trimethylsilyl group.

It could also be interesting to investigate how general is our (4+1) annulation methodology using bis-substituted dienes. Indeed, we only used dienes

that are mono-substituted in 2 and 3 position. The use of dienes substituted either in 2 and 4 positions or in 2 and 3 positions could however be employed (scheme 5.13).[5] It is noteworthy that such dienes would also allow the formation of an additional stereogenic center on the (4+1) annulation product.



Scheme 5.13

Our methodology could also be applied to other ylides, using ammonium or phosphonium ylides (figure 5.12).

Figure 5.12

Although various derivatization reactions were successfully performed, the yield of the hydroboration reaction must be improved, using less basic reaction conditions. Besides, other reactions could be carried out, for example a transesterification reaction, or an epoxydation reaction on the double bond.

Finally, our methodology could have a significant importance in total organic synthesis, given:

- the high functional groups tolerance for both partners (diene and sulfonium ylide).
- the interesting substitution pattern on the cyclopentene (for example the double bond or the ester group), allowing further functionalization.
- the ease to obtain enantioenriched cyclopentene (>90 % ee).

We could reach for example the active pharmaceutical ingredient (API) represented below, which is a ligand of the melanocortin receptor. This compound may have utility over a broad range of therapeutic applications, like

[5]The use of dienes substituted in both 3 and 4 positions are not envisioned, due to the predicted regioselectivity only towards 1,4-ylide addition.

the treatment of obesity, inflammation, pain, and sexual dysfunction (figure 5.13).[153]

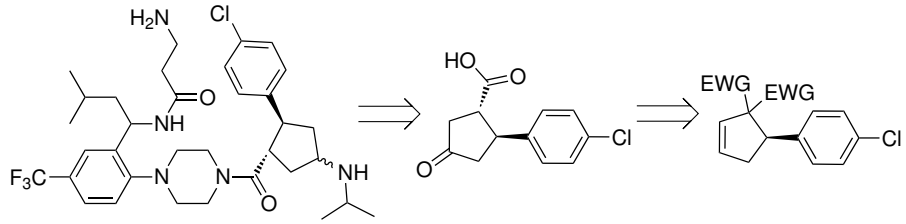


Figure 5.13

Another biologically-active molecule that could be envisioned is Elisabethin C, which has a potential antituberculosis activity (figure 5.14).[154,155] The use of a cyclic diene in our (4+1) annulation reaction methodology would allow to access to this structural motif.

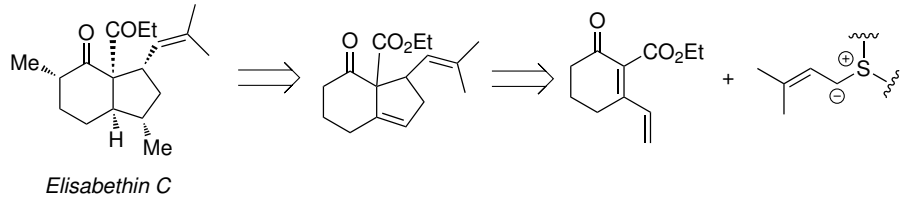


Figure 5.14

Chapter 6

Experimental Part

6.1 Generalities

6.1.1 Equipment

– NMR spectra were recorded either on a 300 MHz *Bruker avance II 300* or a 500 MHz *Bruker avance 500* spectrometer in the indicated solvent. Chemical shifts are given in ppm relative to the reference (TMS) and coupling constants are given in Hz. For some molecules, the ^{1}H and ^{13}C signals attributions required additional analyses (COSY, HMQC, HMBC, ^{13}C DEPT-Q and ^{13}C DEPT-135).

– Mass spectra and high resolution mass spectra were obtained on a *Thermo Orbitrap Exactive* device. The masses are given in Dalton.

– Analytical high Performance Liquid Chromatographies (HPLCs), using *CHIRALPAK IC* and *CHIRALPAK IB* columns were carried out on a quaternary pump *Waters 600* Controller equipped with a *Waters 996* Photodiode Array Detector and a *Waters 717 plus* Autosampler. The two columns were purchased from *Daicel chemical industries* (4.6 x 250 mm; 5 µm particles size).

  Analytical HPLCs using *Waters XBridge C18* and *Waters Symmetry C18* columns were carried out on a quaternary pump *Waters Alliance 2695* Separations Module equipped with a *Waters 2998* Photodiode Array Detector. *Waters XBridge C18* column specifications: 4.6 x 50 mm; 2.5 µm particles size. *Waters Symmetry C18* column specifications: 4.6 x 250 mm; 5 µm particles size.

Preparative HPLCs were carried out using *Waters XBridge Prep C18* column on a quaternary pump *Waters 600* Controller equipped with a *Waters 486* Tunable Absorbance Detector. Column specifications: 10 x 100 mm; 5 µm particles size.

- Infra-red spectra were recorded on a *Shimadzu FTIR-8400S* device. Absorption frequencies are given in cm^{-1}.
- Melting points were determined on a *Büchi B-540* device.
- Optical rotations were obtained on an *Atago Polax-2L* semi-automatic polarimeter device equipped with a 1 mL cell (1 dm length).
- Freeze-drying conditionings were carried out on a *Alpha 2-4 LD plus* device.
- Ozonolysis reactions were performed using an ozone generator device (*Triogen LAB2B*).
- X-ray data collection was performed on a Mar345 image plate detector using Mo-K_α radiation (Rigaku UltraX18S generator, Xenocs Fox3d mirrors) at 150(2) K. Fore more informations, see section 6.3.1 page 285.

6.1.2 Laboratory practice

- All reactions were carried out under magnetic stirring.
- Commercially available reactants and reagents were used as purchased.
- Unless mentioned otherwise, all solvents (for reactions, extractions and purification by flash chromatography) were used without further purifications. An exception is made for technical grade ethyl acetate and technical grade cyclohexane (extractions and purification by flash chromatography), which were used after distillation under reduced pressure.
- Reactions requiring anhydrous conditions were carried out using glassware previously heated *via* bunsen burner under reduced pressure.
- Reactions requiring inert atmosphere were carried out using argon as inert gaz.
- Reactions requiring a temperature of −78 °C were carried out using a bath of $CO_{2(s)}$ and isopropanol, those requiring a temperature of −10 °C were carried out using a bath of ice and brine, those requiring a temperature

of 0 °C were carried out using a bath of ice, and those requiring a temperature >25 °C were carried out using a silicon oil bath (with a magnetic stirring bar), installed on a heating plate equipped with a temperature probe.

– Thin Layer chromatographies (TLCs) were carried out on Merck Silica gel 60 F_{254} aluminium backed plates using UV light, potassium permanganate, iodine, or *p*-anisaldehyde solution for revelation.

– Flash chromatographies were performed using Merck Silica gel 60Å (40-63 µm).

6.2 Procedures and compounds characterisation

6.2.1 Non-chiral sulfonium salts

Reference: O. Rousseau, T. Delaunay, G. Dequirez, T. Trieu-Van, K. Robeyns, R. Robiette, *Chem. Eur. J.* **2015**, *21*, 12899–12902.

General procedure:[1] in a round-bottom flask are added the bromide derivative (10 mmol; 1 eq.) and tetrahydrothiophene (10 mL; 11 eq.). After stirring for 24 h at room temperature, the resulting solid is washed with cyclohexane in order to remove the excess of tetrahydrothiophene.[2] The crude bromide derivative is then diluted with acetone (20 mL), followed by the addition of $NaBF_4$ (10 mmol; 1 eq.). After stirring for 24 h at room temperature, the reaction mixture is filtered in order to remove NaBr. The solution is then concentrated under reduced pressure. The crude powder is purified by precipitation ($MeOH/Et_2O$)[3] giving sulfonium salt **2** in a moderate to excellent yield.

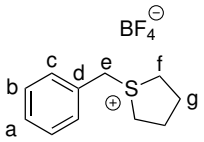
[1] Based on a described procedure; see: V. K. Aggarwal, G. Y. Fang, A. T. Schmidt, *J. Am. Chem. Soc.* **2005**, *127*, 1642–1643.

[2] The bromide salt is not soluble in cyclohexane.

[3] (a) For compound **2g**, the purification is performed by washing the crude with DCM (10 mL), then EtOAc (10 mL), followed by concentration under reduced pressure. (b) The purification of compound **2h** is carried out *via* freeze-drying of the aqueous layer after dilution with DCM (50 mL) and water (100 mL).

1-Benzyltetrahydrothiophenium tetrafluoroborate
CAS Reg No. 1478-78-0

Isolated yield: 48 %
Aspect: white powder
Chemical formula: $C_{11}H_{15}SBF_4$
Mol. wt.: 266.11 g/mol



2a

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49-7.37 (comp, 5H, a, b and c), 4.61 (s, 2H, e), 3.62-3.40 (comp, 4H, f), 2.37-2.22 (comp, 4H, g).

^{13}C NMR (75 MHz, $CDCl_3$): δ 130.7 (b or c), 130.3 (a), 130.0 (c or b), 128.2 (d), 46.0 (e), 42.4 (f), 28.6 (g).

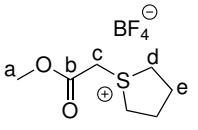
HRMS (APCI): m/z= 179.088 89; calcd. for $[M - BF_4]^+$ ($C_{11}H_{15}{}^{32}S$): 179.088 90

FT-IR (cm^{-1}): 3011, 2959, 1497 (C=C Ar), 1458, 1423, 1286, 1265, 1049, 1032 ($BF_4{}^-$), 951, 775, 700.

Melting point: 79 °C

1-(2-Methoxy-2-oxoethyl)tetrahydrothiophenium tetrafluoroborate

Isolated yield: 29 %
Aspect: white powder
Chemical formula: $C_7H_{13}O_2SBF_4$
Mol. wt.: 248.05 g/mol



2f

^{1}H NMR (300 MHz, CD_2Cl_2): δ 4.31 (s, 2H, c), 3.87 (s, 3H, a), 3.74-3.54 (comp, 4H, d), 2.53-2.27 (comp, 4H, e).

^{13}C NMR (125 MHz, CD_2Cl_2): δ 165.2 (b), 54.6 (a), 44.31 (c or d), 44.29 (d or c), 29.0 (e).

HRMS (APCI): m/z= 161.063 08; calcd. for $[M - BF_4]^+$ ($C_7H_{13}O_2{}^{32}S$): 161.063 08

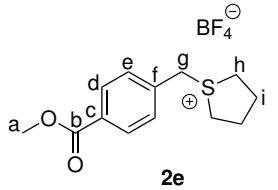
FT-IR (cm^{-1}): 3647, 3007, 2959, 2926, 2854, 1736 (C=O), 1439, 1385, 1329, 1286, 1261 (C-O), 1205, 1182, 1053, 1028 ($BF_4{}^-$), 916, 887.

Melting point: 69 °C

1-[4-(Methoxycarbonyl)benzyl]tetrahydrothiophenium tetrafluoroborate

CAS Reg No. 1028192-21-3

Isolated yield: 27 %
Aspect: white powder
Chemical formula: $C_{13}H_{17}O_2SBF_4$
Mol. wt.: 324.14 g/mol



2e

^{1}H NMR (300 MHz, CD_2Cl_2): δ 8.08 (d, $J_{d,e}$ = 8.4 Hz, 2H, d), 7.58 (d, $J_{e,d}$ = 8.4 Hz, 2H, e), 4.59 (s, 2H, g), 3.91 (s, 3H, a), 3.64-3.38 (comp, 4H, h), 2.48-2.22 (comp, 4H, i).

^{13}C NMR (75 MHz, CD_2Cl_2): δ 166.2 (b), 132.9 (c or f), 132.5 (f or c), 131.2 (d), 131.0 (e), 52.7 (a), 46.2 (g), 43.3 (h), 29.0 (i).

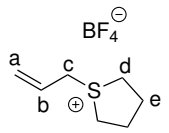
HRMS (ESI): m/z= 237.094 34; calcd. for $[M - BF_4]^+$ ($C_{13}H_{17}O_2{}^{32}S$): 237.094 38

FT-IR (cm^{-1}): 3005, 2955, 2363, 2355, 1722 (C=O), 1433, 1418, 1275, 1188, 1105, 1055, 1041 (BF_4^-), 1011, 712.

Melting point: 121 °C

1-Allyltetrahydrothiophenium tetrafluoroborate
CAS Reg No. 88926-99-2

Isolated yield: 51 %
Aspect: pale yellow oil
Chemical formula: $C_7H_{13}SBF_4$
Mol. wt.: 216.05 g/mol



2g

^{1}H NMR (300 MHz, CD_2Cl_2): δ 5.96-5.80 (comp, 1H, b), 5.75-5.62 (comp, 2H, a), 3.93 (d, $J_{c,b}$ = 7.2 Hz, 2H, c), 3.65-3.33 (comp, 4H, d), 2.47-2.24 (comp, 4H, e).

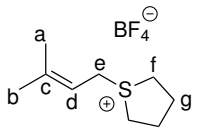
^{13}C NMR (75 MHz, CD_2Cl_2): δ 128.4 (a), 124.5 (b), 45.2 (c), 42.6 (d), 29.2 (e).

HRMS (ESI): m/z= 129.073 42; calcd. for [M - BF_4]$^+$ ($C_7H_{13}{}^{32}S$): 129.073 25

FT-IR (cm^{-1}): 3641, 3015, 2986, 2959, 1637 (C=C), 1450, 1425, 1408, 1285, 1263, 1030 (BF_4^-), 951, 883, 735.

1-(3-Methylbut-2-en-1-yl)tetrahydrothiophenium tetrafluoroborate

Isolated yield: 13 %
Aspect: brown oil
Chemical formula: $C_9H_{17}SBF_4$
Mol. wt.: 244.10 g/mol



2h

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.26 (t, $J_{d,e}$ = 8.1 Hz, 1H, d), 3.95 (d, $J_{e,d}$ = 8.1 Hz, 2H, e), 3.64-3.27 (comp, 4H, f), 2.48-2.19 (comp, 4H, g), 1.85 (s, 3H, a or b), 1.81 (s, 3H, b or a).

^{13}C NMR (75 MHz, $CDCl_3$): δ 147.9 (c), 110.1 (d), 41.9 (f), 40.4 (e), 28.8 (g), 26.3 (a or b), 18.8 (b or a).

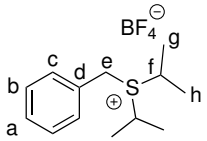
HRMS (ESI): m/z= 157.104 55; calcd. for [M - BF_4]$^+$ ($C_9H_{17}{}^{32}S$): 157.104 58

FT-IR (cm^{-1}): 3649, 3556, 2955, 1662 (C=C), 1450, 1427, 1383, 1055, 1036 ($BF_4{}^-$).

Benzyl(diisopropyl)sulfonium tetrafluoroborate

This salt is synthesized using the general procedure for chiral sulfonium salt (diisopropylsulfide instead of isothiocineole). See page 180.

Isolated yield: 66 %
Aspect: white powder
Chemical formula: $C_{13}H_{21}SBF_4$
Mol. wt.: 296.18 g/mol



2i

^{1}H NMR (300 MHz, CD_2Cl_2): δ 7.52-7.42 (comp, 5H, Ar), 4.58 (s, 2H, e), 3.84 (qq, $J_{f,g}$ = 6.8 Hz, $J_{f,h}$ = 6.8 Hz, 2H, f), 1.55 (d, $J_{g,f}$ = 6.8 Hz, 6H, g), 1.51 (d, $J_{h,f}$ = 6.9 Hz, 6H, h).

^{13}C NMR (75 MHz, CD_2Cl_2): δ 130.3,130.2 (three signals: a, b and c), 128.7 (d), 45.5 (f), 40.2 (e), 19.3 (h), 18.8 (g).

HRMS (ESI): m/z= 209.136 01; calcd. for $[M - BF_4]^+$ ($C_{13}H_{21}{}^{32}S$): 209.135 85

FT-IR (cm^{-1}): 2991, 2937, 1499, 1460, 1425, 1394, 1381, 1285, 1269, 1248, 1163, 1153, 1051, 1038 ($BF_4{}^-$), 777, 712, 704.

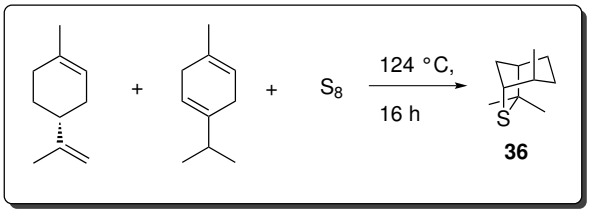
Melting point: 89 °C

6.2.2 Chiral sulfonium salts

Reference: O. Rousseau, T. Delaunay, G. Dequirez, T. Trieu-Van, K. Robeyns, R. Robiette, *Chem. Eur. J.* **2015**, *21*, 12899–12902.

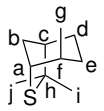
Isothiocineole
CAS Reg No. 5718-75-2

Reference: O. Illa, M. Arshad, A. Ros, E. M. McGarrigle, V. K. Aggarwal, *J. Am. Chem. Soc.* **2010**, *132*, 1828–1830.



Procedure: in a round-bottom flask are added limonene (8.2 g; 60 mmol; 1 eq.), γ-terpinene (60 mmol; 1 eq.), and elemental sulfur (70 mmol; 1.2 eq.). After stirring for 16 h at 120 °C, pure isothiocineole **36** is isolated by fractional distillation under reduced pressure (50-60 °C; 1.5 mbar).

Isolated yield: 37 %
Aspect: colourless liquid
Chemical formula: $C_{10}H_{18}S$
Mol. wt.: 170.31 g/mol

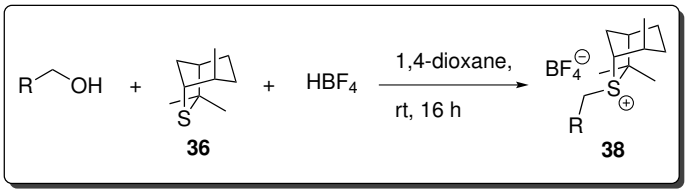


36

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.32 (m, 1H, a), 2.32 (m, 1H), 2.11-1.99 (comp, 2H), 1.90 (m, 1H), 1.82 (m, 1H), 1.69-1.55 (comp, 2H), 1.50 (s, 3H, i or j), 1.38 (s, 3H, j or i), 1.15 (dd, J = 14.0, 5.3 Hz, 1H), 1.06 (d, $J_{g,f}$ = 7.2 Hz, 3H, g).

HRMS (APCI): m/z= 171.120 28; calcd. for $[M + H]^+$ ($C_{19}H_{19}{}^{32}S$): 171.120 20

^{1}H NMR and mass spectra are in agreement with literature; see: O. Illa, M. Arshad, A. Ros, E. M. McGarrigle, V. K. Aggarwal, *J. Am. Chem. Soc.* **2010**, *132*, 1828–1830.



36 **38**

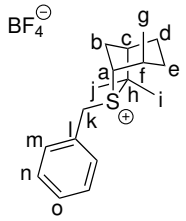
General procedure:[4] in a dried round-bottom flask, under inert atmosphere, isothiocineole **36** (0.68 g; 4.0 mmol; 1 eq.), the alcohol derivative (8.0 mmol; 2.0 eq.) and $HBF_4.Et_2O$ (54 wt.% in Et_2O; 8.0 mmol; 2.0 eq.) are added in 1,4-dioxane (10 mL). After stirring for 16 h at room temperature, the mixture is concentrated under reduced pressure. The sulfonium salt **38** is isolated by filtration, after dilution with EtOAc (20 mL), in a moderate to good yield.[5]

[4]Based on a described procedure; see: O. Illa, M. Namutebi, C. Saha, M. Ostovar, C. C. Chen, M. F. Haddow, S. Nocquet-Thibault, M. Lusi, E. M. McGarrigle, V. K. Aggarwal, *J. Am. Chem. Soc.* **2013**, *135*, 11951–11966.

[5](a) Because of compound **38b** solubility in EtOAc, this salt is isolated by freeze-drying of the aqueous layer after dilution with EtOAc (20 mL) and water (50 mL). (b) Because of compound **38e** solubility in EtOAc, this salt is isolated by precipitation *via* $MeOH/Et_2O$. (c) Because compound **38g** does not precipitate in EtOAc, this salt is isolated by freeze-drying of the aqueous layer after dilution with EtOAc (20 mL) and water (50 mL), followed by precipitation of the resulting solid *via* $MeOH/Et_2O$.

(1*R*,4*R*,5*R*)-6-Benzyl-4,7,7-trimethyl-6-thioniabicyclo[3.2.1]octane tetrafluoroborate

Isolated yield: 81 %
Aspect: white powder
Chemical formula: $C_{17}H_{25}SBF_4$
Mol. wt.: 348.25 g/mol



38a

^{1}H NMR (300 MHz, CD_2Cl_2): δ 7.57-7.41 (comp, 5H, m, n and o), 4.74 (d, $J_{k,k'}$ = 12.9 Hz, 1H, k), 4.31 (d, $J_{k',k}$ = 12.9 Hz, 1H, k'), 3.86 (m, 1H, a), 2.64-2.52 (m, 1H, b), 2.51-2.40 (comp, 2H, b and c), 2.11 (m, 1H, f), 1.81 (s, 3H, i or j), 1.79-1.54 (comp, 4H, d and e), 1.76 (s, 3H, j or i), 1.12 (d, $J_{g,f}$ = 7.1 Hz, 3H, g).

^{13}C NMR (75 MHz, CD_2Cl_2): δ 130.6 (m or n), 130.3 (o), 130.2 (n or m), 129.0 (l), 73.1 (h), 64.7 (a), 50.9 (c), 42.7 (k), 32.6 (f), 32.2 (b), 25.8 (i or j), 25.5 (e), 23.5 (j or i), 22.4 (d), 17.9 (g).

HRMS (APCI): *m/z*= 261.167 00; calcd. for [M - BF_4]$^+$ ($C_{17}H_{25}{}^{32}S$): 261.167 15

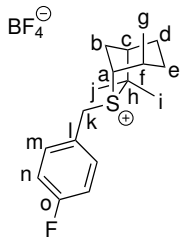
FT-IR (cm^{-1}): 3015, 2972, 2932, 2922, 2365, 2338, 1499, 1472, 1456, 1427, 1396, 1377, 1284, 1159, 1134, 1082, 1049, 1032 ($BF_4{}^-$), 1001, 980, 777, 716, 708.

Melting point: 173 °C (degradation)

Specific rotation: $[\alpha]_D^{21} = -235°$ (c = 1.04, CH_2Cl_2)

(1*R*,4*R*,5*R*)-6-(4-Fluorobenzyl)-4,7,7-trimethyl-6-thioniabicyclo [3.2.1]octane tetrafluoroborate

Isolated yield: 72 %
Aspect: white powder
Chemical formula: $C_{17}H_{24}SBF_5$
Mol. wt.: 366.24 g/mol



38d

^{1}H NMR (300 MHz, CD_2Cl_2): δ 7.55 (m, 2H, m), 7.14 (m, 2H, n), 4.74 (d, $J_{k,k'}$ = 12.9 Hz, 1H, k), 4.32 (d, $J_{k',k}$ = 12.9 Hz, 1H, k'), 3.83 (m, 1H, a), 2.66-2.54 (m, 1H, b), 2.50-2.40 (comp, 2H, b and c), 2.11 (m, 1H, f), 1.81 (s, 3H, i or j), 1.78-1.52 (comp, 4H, d and e), 1.76 (s, 3H, j or i), 1.12 (d, $J_{g,f}$ = 7.1 Hz, 3H, g).

^{13}C NMR (75 MHz, CD_2Cl_2): δ 163.9 (d, J = 249.7 Hz, o), 132.9 (d, J = 8.8 Hz, m), 125.0 (d, J = 3.1 Hz, l), 117.2 (d, J = 22.0 Hz, n), 73.3 (h), 64.6 (a), 50.9 (c), 41.9 (k), 32.6 (f), 32.1 (b), 25.7,25.5,23.4 (e, i and j), 22.4 (d), 17.9 (g).

HRMS (ESI): m/z= 279.157 84; calcd. for $[M - BF_4]^+$ ($C_{17}H_{24}F^{32}S$): 279.157 73

FT-IR (cm^{-1}): 2999, 2976, 2934, 2883, 2872, 1603, 1512 (C=C Ar), 1464, 1421, 1398, 1285, 1230, 1163, 1136, 1053, 1036 (BF_4^-), 984, 970, 849, 833, 762, 733.

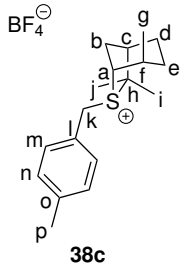
Melting point: 156 °C (degradation)

Specific rotation: $[\alpha]_D^{21} = -237°$ (c = 1.07, CH_2Cl_2)

(1*R*,4*R*,5*R*)-4,7,7-Trimethyl-6-(4-methylbenzyl)-6-thioniabicyclo [3.2.1]octane tetrafluoroborate

Isolated yield: 60 %

Aspect: white powder
Chemical formula: $C_{18}H_{27}SBF_4$
Mol. wt.: 362.28 g/mol



38c

^{1}H NMR (300 MHz, CD_2Cl_2): δ 7.39 (d, $J_{m,n}$ = 7.9 Hz, 2H, m), 7.24 (d, $J_{n,m}$ = 7.9 Hz, 2H, n), 4.70 (d, $J_{k,k'}$ = 12.8 Hz, 1H, k), 4.26 (d, $J_{k',k}$ = 12.8 Hz, 1H, k'), 3.83 (m, 1H, a), 2.64-2.52 (m, 1H, b), 2.51-2.39 (comp, 2H, b and c), 2.36 (s, 3H, p) 2.09 (m, 1H, f), 1.80 (s, 3H, i or j), 1.78-1.51 (comp, 4H, d and e), 1.75 (s, 3H, j or i), 1.11 (d, $J_{g,f}$ = 7.1 Hz, 3H, g).

^{13}C NMR (75 MHz, CD_2Cl_2): δ 140.7 (o), 130.8 (n), 130.5 (m) 125.7 (l), 72.8 (h), 64.5 (a), 50.9 (c), 42.6 (k), 32.6 (f), 32.1 (b), 25.7,25.5 (e and [i or j]), 23.4 (j or i), 22.4 (d), 21.4 (p), 17.9 (g).

HRMS (ESI): m/z= 275.183 36; calcd. for [M - BF_4]$^+$ ($C_{18}H_{27}{}^{32}S$): 275.182 80

FT-IR (cm^{-1}): 2951, 2928, 2876, 1514 (C=C Ar), 1464, 1423, 1398, 1379, 1284, 1136, 1053, 1036 ($BF_4{}^-$), 824, 725.

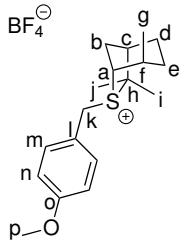
Melting point: 144-147 °C (degradation)

Specific rotation: $[\alpha]_D^{21} = -229°$ (c = 1.03, CH_2Cl_2)

(1*R*,4*R*,5*R*)-6-(4-Methoxybenzyl)-4,7,7-trimethyl-6-thioniabicyclo[3.2.1]octane tetrafluoroborate

Isolated yield: 41 %
Aspect: white powder
Chemical formula: $C_{18}H_{27}SOBF_4$

Mol. wt.: 378.28 g/mol



38b

^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.44 (d, $J_{m,n}$ = 8.7 Hz, 2H, m), 6.95 (d, $J_{n,m}$ = 8.7 Hz, 2H, n), 4.70 (d, $J_{k,k'}$ = 12.8 Hz, 1H, k), 4.25 (d, $J_{k',k}$ = 12.8 Hz, 1H, k'), 3.85-3.78 (comp, 4H, a and p), 2.61-2.52 (m, 1H, b), 2.48-2.40 (comp, 2H, b and c), 2.08 (m, 1H, f), 1.81 (s, 3H, i or j), 1.79-1.53 (comp, 4H, d and e), 1.75 (s, 3H, j or i), 1.12 (d, $J_{g,f}$ = 7.1 Hz, 3H, g).

^{13}C NMR (125 MHz, CD_2Cl_2): δ 161.3 (o), 132.2 (m), 120.2 (l), 115.6 (n), 72.6 (h), 64.2 (a), 55.8 (p), 50.9 (c), 42.7 (k), 32.6 (f), 32.1 (b), 25.7 (i or j), 25.5 (e), 23.4 (j or i), 22.5 (d), 17.9 (g).

HRMS (ESI): *m/z*= 291.177 57; calcd. for [M - BF_4]$^+$ ($C_{18}H_{27}O^{32}S$): 291.177 71

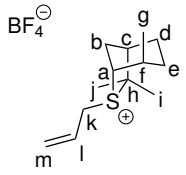
FT-IR (cm^{-1}): 2961, 2953, 2932, 1609, 1514, 1466, 1250, 1182, 1136, 1055, 1034 (BF_4^-).

Melting point: 81 °C

Specific rotation: $[\alpha]_D^{21} = -265°$ (c = 1.13, CH_2Cl_2)

(1*R*,4*R*,5*R*)-6-Allyl-4,7,7-trimethyl-6-thioniabicyclo[3.2.1]octane tetrafluoroborate

Isolated yield: 52 %
Aspect: white powder
Chemical formula: $C_{13}H_{23}SBF_4$
Mol. wt.: 298.19 g/mol



38g

^{1}H NMR (500 MHz, CD_2Cl_2): δ 5.95 (dddd, $J_{l,m}$ = 16.1 Hz, $J_{l,m'}$ = 10.0 Hz, $J_{l,k'}$ = 8.4 Hz, $J_{l,k}$ = 6.0 Hz, 1H, l), 5.72 (d, $J_{m,l}$ = 17.0 Hz, 1H, m), 5.60 (d, $J_{m',l}$ = 10.1 Hz, 1H, m'), 4.12 (dd, $J_{k,k'}$ = 12.9 Hz, $J_{k,l}$ = 5.9 Hz, 1H, k), 3.94 (m, 1H, a), 3.81 (dd, $J_{k',k}$ = 12.9 Hz, $J_{k',l}$ = 8.4 Hz, 1H, k'), 2.48-2.38 (comp, 3H, b and c), 2.34 (m, 1H, f), 1.83-1.53 (comp, 4H, d and e), 1.80 (s, 3H, i or j), 1.69 (s, 3H, j or i), 1.20 (d, $J_{g,f}$ = 7.1 Hz, 3H, g).

^{13}C NMR (75 MHz, CD_2Cl_2): δ 127.2 (m), 126.1 (l), 72.3 (h), 64.8 (a), 50.7 (c), 41.3 (k), 32.5 (b or f), 32.3 (f or b), 25.64,25.59 (e and [i or j]), 23.5 (j or i), 22.5 (d), 17.9 (g).

HRMS (ESI): *m/z*= 211.151 55; calcd. for [M - BF_4]$^+$ ($C_{13}H_{23}{}^{32}S$): 211.151 50

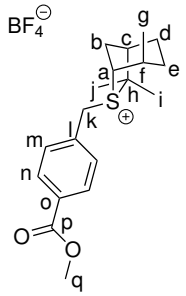
FT-IR (cm^{-1}): 2932, 1639 (C=C), 1472, 1466, 1429, 1408, 1400, 1379, 1286, 1140, 1109, 1092, 1049, 1034 ($BF_4{}^-$), 991, 949, 735.

Melting point: 150 °C

Specific rotation: $[\alpha]_D^{21} = -181°$ (c = 1.02, CH_2Cl_2)

(1*R*,4*R*,5*R*)-6-[4-(Methoxycarbonyl)benzyl]-4,7,7-trimethyl-6-thioniabicyclo[3.2.1]octane tetrafluoroborate

Isolated yield: 68 %
Aspect: white powder
Chemical formula: $C_{19}H_{27}O_2SBF_4$
Mol. wt.: 406.29 g/mol



38e

^{1}H NMR (300 MHz, CD_2Cl_2): δ 8.04 (d, $J_{n,m}$ = 8.4 Hz, 2H, n), 7.62 (d, $J_{m,n}$ = 8.3 Hz, 2H, m), 4.79 (d, $J_{k,k'}$ = 12.9 Hz, 1H, k), 4.39 (d, $J_{k',k}$ = 12.9 Hz, 1H, k'), 3.90 (s, 3H, q), 3.84 (m, 1H, a), 2.67-2.54 (m, 1H, b), 2.50-2.38 (comp, 2H, b and c), 2.10 (m, 1H, f), 1.81 (s, 3H, i or j), 1.67-1.49 (comp, 4H, d and e), 1.76 (s, 3H, j or i), 1.10 (d, $J_{g,f}$ = 7.1 Hz, 3H, g).

^{13}C NMR (75 MHz, CD_2Cl_2): δ 166.1 (p), 133.8 (o), 131.7 (l), 130.7 (n), 130.5 (m), 73.4 (h), 64.7 (a), 52.3 (q), 50.6 (c), 41.6 (k), 32.2 (f), 31.9 (b), 25.4 (i or j), 23.1 (j or i), 25.1 (e), 22.1 (d), 17.5 (g).

HRMS (ESI): m/z= 319.172 44; calcd. for $[M - BF_4]^+$ ($C_{19}H_{27}O_2{}^{32}S$): 319.172 63

FT-IR (cm^{-1}): 2932, 1720 (C=O), 1466, 1437, 1285 (C-O), 1136, 1105, 1055, 1036 ($BF_4{}^-$).

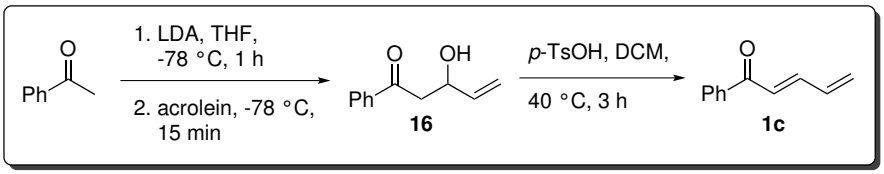
Melting point: 120-123 °C (degradation)

Specific rotation: $[\alpha]_D^{24} = -155°$ (c = 1.03, CH_2Cl_2)

6.2.3 Non-substituted 1,3-dienes

(2*E*)-1-Phenylpenta-2,4-dien-1-one
CAS Reg No. 148408-52-0

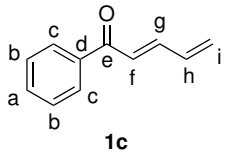
Reference: L. Bernardi, J. López-Cantarero, B. Niess, K. A. Jørgensen, *J. Am. Chem. Soc.* **2007**, *129*, 5772–5778.



Procedure: in a dried round-bottom flask, under inert atmosphere, LDA (2 M solution in THF/n-heptane/ethylbenzene; 19 mmol; 1.1 eq.) is added in THF (20 mL), at −78 °C. Acetophenone (2 mL; 17 mmol; 1 eq.) is then added, dropwise, and the reaction mixture is stirred for 1 h at the same temperature, before dropwise addition of acrolein (19 mmol; 1.1 eq.). After stirring for 15 min at −78 °C, the reaction is quenched with a saturated aqueous solution of NH_4Cl (5 mL) and extracted with Et_2O (20 mL). The organic layer is washed with a 1 M aqueous solution of HCl (5 mL), brine (5 mL), dried over $MgSO_4$, and then concentrated under reduced pressure.

Next, *p*-TsOH (10 mmol; 0.6 eq.) is added in a solution of the crude aldol adduct **16** in DCM (15 mL). After stirring in refluxing DCM for 3 h, the mixture is diluted with water (5 mL). The aqueous layer is washed with DCM (5 mL), the combined organic layers are dried over $MgSO_4$ and then concentrated under reduced pressure. Pure diene **1c** is isolated in 45 % yield after purification by flash chromatography on silica gel (04/96 EtOAc/cyclohexane).

Isolated yield: 45 %
Aspect: fluorescent yellow liquid
Chemical formula: $C_{11}H_{10}O$
Mol. wt.: 158.20 g/mol



1c

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96 (d, $J_{c,b}$ = 8.4 Hz, 2H, c), 7.60-7.37 (comp, 4H, a, b and g), 7.01 (d, $J_{f,g}$ = 15.3 Hz, 1H, f), 6.61 (ddd, $J_{h,i}$ = 17.0 Hz, $J_{h,i' \ or \ h,g}$ = 10.6 Hz, $J_{h,g \ or \ h,i'}$ = 10.2 Hz, 1H, h), 5.73 (dd, $J_{i,h}$ = 17.0 Hz, $J_{i,i'}$ = 0.4 Hz, 1H, i), 5.60 (dd, $J_{i',h}$ = 10.0 Hz, $J_{i',i}$ = 0.4 Hz, 1H, i').

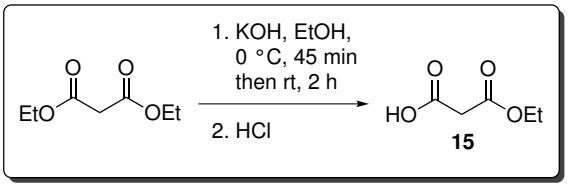
HRMS (APCI): *m/z*= 159.080 45; calcd. for $[M + H]^+$ ($C_{11}H_{11}O$): 159.080 44

^{1}H NMR and mass spectra are in agreement with literature; see: L. Bernardi, J. López-Cantarero, B. Niess, K. A. Jørgensen, *J. Am. Chem. Soc.* **2007**, *129*, 5772–5778.

3-Ethoxy-3-oxopropanoic acid

CAS Reg No. 1071-46-1

Reference: D. S. Breslow, E. Baumgarten, C. R. Hauser, *J. Am. Chem. Soc.* **1944**, *66*, 1286–1288.

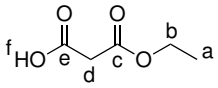


15

Procedure: in a round-bottom flask, equipped with an addition funnel, diethyl malonate (5 mL; 30 mmol; 1 eq.) is added in EtOH (50 mL), at 0 °C. A solution of KOH (30 mmol; 1 eq.) in EtOH (50 mL) is next added, dropwise, *via* the addition funnel. After stirring for 45 min at the same temperature and then 2 h at room temperature, the crude is concentrated under reduced pressure. The residue is diluted with water (50 mL) and washed with Et_2O (25 mL). The aqueous layer is next acidified (pH 1) with a 1 M aqueous solution of HCl, then extracted with Et_2O (50 mL). The organic layer is dried over $MgSO_4$ and concentrated under reduced pressure. Compound **15** is used without further

purification.

Isolated yield: 49 %
Aspect: colourless liquid
Chemical formula: $C_5H_8O_4$
Mol. wt.: 132.11 g/mol



15

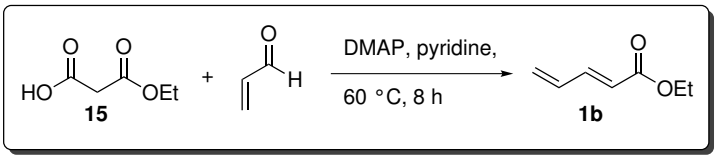
^{1}H NMR (300 MHz, $CDCl_3$): δ 11.09 (bs, 1H, f), 4.19 (q, $J_{b,a} = 7.1$ Hz, 2H, b), 3.4 (s, 2H, d), 1.26 (t, $J_{a,b} = 7.1$ Hz, 3H, a).

^{13}C NMR (75 MHz, $CDCl_3$): δ 171.9 (c or e), 166.8 (e or c), 62.0 (b), 41.1 (d), 14.0 (a).

The ^{1}H and ^{13}C NMR spectra are in agreement with literature; see: M. E. Hediger, *Bioorg. Med. Chem.* **2004**, *12*, 4995–5010.

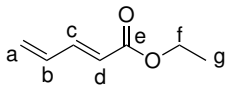
Ethyl (2*E*)-penta-2,4-dienoate
CAS Reg No. 13369-23-8

Reference: J. Rodriguez, B. Waegel, *Synthesis* **1988**, *7*, 534–535.



Procedure: in a round-bottom flask, 3-ethoxy-3-oxopropanoic acid **15** (6.6 g; 50 mmol; 1 eq.) is added in pyridine (40 mL). Acrolein (50 mmol; 1 eq.) and DMAP (5 mmol; 0.1 eq.) are then added to this solution. After stirring for 8 h at 60 °C, the reaction mixture is diluted with water (10 mL) and extracted with Et_2O (2 x 30 mL). The organic layer is washed with a 1 M aqueous solution of HCl (4 x 5 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Pure diene **1b** is isolated without further purification.

Isolated yield: 52 %
Aspect: fluorescent yellow liquid
Chemical formula: $C_7H_{10}O_2$
Mol. wt.: 126.15 g/mol



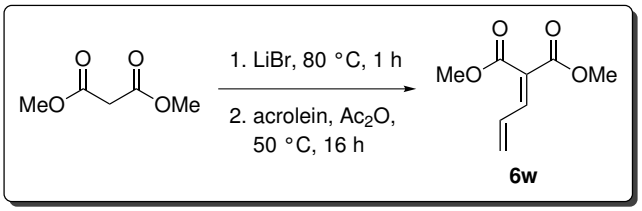
1b

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.16 (dd, $J_{c,d} = 15.4$ Hz, $J_{c,b} = 11.0$ Hz, 1H, c), 6.35 (ddd, $J_{b,a'} = 17.0$ Hz, $J_{b,a} = 10.5$ Hz, $J_{b,c} = 10.5$ Hz, 1H, b), 5.80 (d, $J_{d,c} = 15.4$ Hz, 1H, d), 5.49 (d, $J_{a',b} = 17.0$ Hz, 1H, a'), 5.37 (d, $J_{a,b} = 10.0$ Hz, 1H, a), 4.10 (q, $J_{f,g} = 7.2$ Hz, 2H, f), 1.18 (t, $J_{g,f} = 7.2$ Hz, 3H, g).

^{13}C NMR (75 MHz, $CDCl_3$): δ 166.6 (e), 144.5,134.7,125.2,122.2 (a, b, c and d), 60.2 (f), 14.1 (g).

The ^{1}H and ^{13}C NMR spectra are in agreement with literature; see: J. Rodriguez, B. Waegel, *Synthesis* **1988**, *7*, 534–535.

Dimethyl prop-2-en-1-ylidenemalonate
CAS Reg No. 84740-82-9



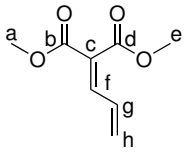
6w

Procedure:[6] in a dried round-bottom flask, under inert atmosphere, are added dimethyl malonate (1.1 mL; 10 mmol, 1 eq.) and LiBr (2 mmol; 0.2 eq.). After stirring for 1 h at 80 °C, Ac_2O (20 mmol; 2 eq.) and acrolein (30 mmol; 3 eq.) are added, at 50 °C. After stirring for 16 h at the same temperature, a saturated aqueous solution of Na_2CO_3 (25 mL) is added, dropwise, at 0 °C, and the solution is extracted with Et_2O (2 x 15 mL). The combined organic layers are washed with brine (5 mL), dried over Na_2SO_4, and concentrated under

[6]Based on a described procedure; see: M. Sylla, D. Joseph, E. Chevallier, C. Camara, F. Dumas, *Synthesis* **2006**, 1045–1049.

reduced pressure. Pure diene **6w** is isolated after purification by flash chromatography on silica gel (10/90 to 20/80 EtOAc/cyclohexane).

Isolated yield: 37 %
Aspect: colourless liquid
Chemical formula: $C_8H_{10}O_4$
Mol. wt.: 170.16 g/mol



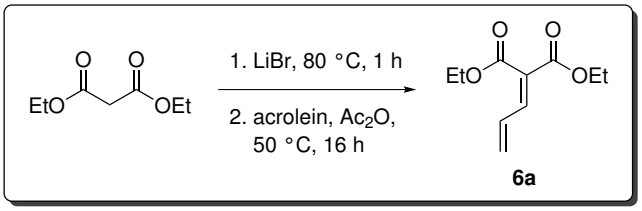
6w

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 (d, $J_{f,g}$ = 11.6 Hz, 1H, f), 6.75 (ddd, $J_{g,h}$ = 16.8 Hz, $J_{g,f}$ = 11.6 Hz, $J_{g,h'}$ = 10.0 Hz, 1H, g), 5.78 (d, $J_{h,g}$ = 16.8 Hz, 1H, h), 5.68 (d, $J_{h',g}$ = 10.0 Hz, 1H, h'), 3.85 (s, 3H, a or e), 3.80 (s, 3H, e or a).

^{13}C NMR (125 MHz, $CDCl_3$): δ 165.2 (b or d), 164.6 (d or b), 145.0 (f), 131.7 (g), 129.9 (h), 125.9 (c), 52.4 (a or e), 52.3 (e or a).

The ^{1}H and ^{13}C NMR spectra are in agreement with literature; see: M. Sylla, D. Joseph, E. Chevallier, C. Camara, F. Dumas, *Synthesis* **2006**, 1045–1049.

Diethyl prop-2-en-1-ylidenemalonate
CAS Reg No. 13654-26-7

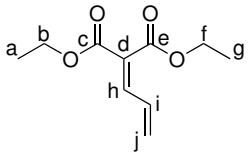


6a

Procedure: using the same procedure than for dimethyl prop-2-en-1-ylidenemalonate **6w**, pure diene **6a** is isolated after purification by flash chro-

matography on silica gel (05/95 to 20/80 EtOAc/cyclohexane) in 40 % yield.

Isolated yield: 40 %
Aspect: colourless liquid
Chemical formula: $C_{10}H_{14}O_4$
Mol. wt.: 198.22 g/mol



6a

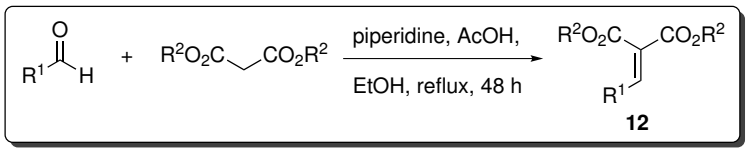
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 (d, $J_{h,i}$ = 11.6 Hz, 1H, h), 6.74 (ddd, $J_{i,j}$ = 16.8 Hz, $J_{i,h}$ = 11.5 Hz, $J_{i,j'}$ = 10.0 Hz, 1H, i), 5.74 (d, $J_{j,i}$ = 16.8 Hz, 1H, j), 5.63 (d, $J_{j',i}$ = 10.0 Hz, 1H, j'), 4.30 (q, J = 7.1 Hz, 2H, b or f), 4.23 (q, J = 7.1 Hz, 2H, f or b), 1.31 (t, J = 7.1 Hz, 3H, a or g), 1.28 (t, J = 7.1 Hz, 3H, g or a).

The ^{1}H NMR spectrum is in agreement with the proposed structure. No further analyses were however carried out.

6.2.4 2-Substituted bis-activated 1,3-dienes

6.2.4.1 Knoevenagel condensation

Reference: O. Rousseau, T. Delaunay, R. Robiette, *Synlett* **2014**, *25*, 519–522.



12

General procedure: in a round-bottom flask, AcOH (8 mmol; 0.2 eq.) and piperidine (8 mmol; 0.2 eq.) are added in a solution of malonate derivative (40 mmol; 1 eq.) and aldehyde (48 mmol; 1.2 eq.) in EtOH (20 mL). After refluxing for 48 h,[7] by products are distilled *via* a Kugelrohr apparatus, under

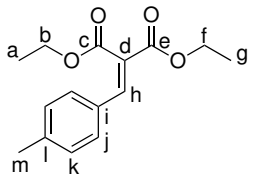
[7]For compound **12k**, the mixture is stirred for 16 h at room temperature and then concentrated under reduced pressure. The residue is diluted with EtOAc (50 mL), water (20 mL),

reduced pressure (120 °C; 1.5 mbar).[8] The desired compound **12** is obtained with an excellent yield.

For compound **12j**, another procedure is applied:[9] using a Dean-Stark apparatus, diethyl malonate (7 mL; 40 mmol; 1 eq.), 2-methylpropanal (80 mmol; 2 eq.), piperidine (2 mmol; 0.05 eq.), and benzoic acid (2 mmol; 0.05 eq.) are added in toluene (10 mL). After refluxing for 16 h at 120 °C, the reaction mixture is washed with water (2 x 5 mL), then a 1 M aqueous solution of HCl (2 x 5 mL), followed by a saturated aqueous solution of Na_2CO_3 (5 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The product is isolated without further purification.

Diethyl (4-methylbenzylidene)malonate
CAS Reg No. 14111-33-2

Isolated yield: quantitative
Aspect: yellow oil
Chemical formula: $C_{15}H_{18}O_4$
Mol. wt.: 262.30 g/mol



12c

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70 (s, 1H, h), 7.35 (d, J = 8.1 Hz, 2H, j or k), 7.18 (d, J = 8.1 Hz, 2H, k or j), 4.34 (q, J = 7.2 Hz, 2H, b or f), 4.30 (q, J = 7.2 Hz, 2H, f or b), 2.36 (s, 3H, m), 1.33 (t, J = 7.2 Hz, 3H, a or g), 1.30 (t, J = 7.2 Hz, 3H, g or a).

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and a 1 M aqueous solution of HCl (10 mL), then the aqueous layer is extracted with EtOAc (2 x 20 mL). The combined organic layers are washed with brine (20 mL), dried over $MgSO_4$ and then concentrated under reduced pressure. The residue is purified by flash chromatography on silica gel (04/96 => 10/90 EtOAc/cyclohexane) to give the desired compound in 43 % yield.

[8] The ^{1}H NMR spectrum of the crude mixture of compound **12l** reveals a 1.3/1 d.r. Besides, a further purification by flash chromatography on silica gel (10/90 EtOAc/cyclohexane) is required in order to isolate the product.

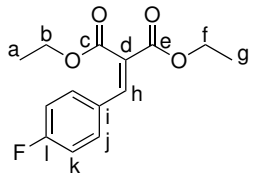
[9] W. Fraser, C. J. Suckling, H. C. S. Wood, *J. Chem. Soc. Perkin Trans. 1* **1990**, 3137–3144.

^{13}C NMR (75 MHz, $CDCl_3$): δ 167.1 (c or e), 164.4 (e or c), 142.3 (h), 141.3 (i), 130.2 (l), 129.71 (j or k), 129.68 (k or j), 125.3 (d), 61.8 (b or f), 61.7 (f or b), 21.6 (m), 14.3 (a or g), 14.0 (g or a).

The ^{1}H and ^{13}C NMR spectra are in agreement with literature; see: J.-K. Kim, P.-S. Kwon, T.-W. Kwon, S.-K. Chung, J.-W. Lee, *Synth. Commun.* **1996**, *26*, 535–542.

Diethyl (4-fluorobenzylidene)malonate
CAS Reg No. 790-53-4

Isolated yield: quantitative
Aspect: yellow oil
Chemical formula: $C_{14}H_{15}FO_4$
Mol. wt.: 266.26 g/mol



12e

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69 (s, 1H, h), 7.46 (m, 2H, j or k), 7.07 (m, 2H, k or j), 4.34 (q, J = 7.2 Hz, 2H, b or f), 4.31 (q, J = 7.2 Hz, 2H, f or b), 1.33 (t, J = 7.2 Hz, 3H, a or g), 1.30 (t, J = 7.2 Hz, 3H, g or a).

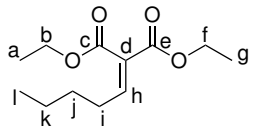
^{13}C NMR (75 MHz, $CDCl_3$): δ 166.7 (c or e), 164.0 (d, J = 251.2 Hz, l), 164.1 (e or c), 140.9 (h), 131.7 (d, J = 8.6 Hz, j), 129.2 (d, J = 3.2 Hz, i), 126.2 (d), 116.1 (d, J = 21.7 Hz, k), 61.9 (b or f), 61.8 (f or b), 14.2 (a or g), 14.0 (g or a).

HRMS (APCI): m/z= 267.102 68; calcd. for $[M + H]^+$ ($C_{14}H_{16}FO_4$): 267.102 71. **Fragment**: m/z= 221 $[M - OEt]^+$

FT-IR (cm^{-1}): 1724 (C=O), 1634, 160, 1510 (Ar), 1259, 1238, 1223, 1213, 1196, 1163, 1065, 835.

Diethyl pentylidenemalonate
CAS Reg No. 18795-86-3

Isolated yield: 43 %
Aspect: pale yellow turbid liquid
Chemical formula: $C_{12}H_{20}O_4$
Mol. wt.: 228.28 g/mol



12k

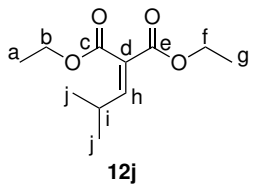
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.99 (t, $J_{h,i}$ = 7.9 Hz, 1H, h), 4.30 (q, J = 7.1 Hz, 2H, b or f), 4.23 (q, J = 7.1 Hz, 2H, f or b), 2.29 (td, $J_{i,j}$ = 7.5 Hz, $J_{i,h}$ = 7.5 Hz, 2H, i), 1.52-1.24 (comp, 4H, j and k), 1.32 (t, J = 7.1 Hz, 3H, a or g), 1.29 (t, J = 7.1 Hz, 3H, g or a), 0.90 (t, $J_{l,k}$ = 7.2 Hz, 3H, l).

HRMS (APCI): *m/z*= 229.144 24; calcd. for $[M + H]^+$ ($C_{12}H_{21}O_4$): 229.143 44

^{1}H NMR and Mass spectra are in agreement with literature; see: G. Cahiez, M. Alami, *Tetrahedron* **1989**, *45*, 4163–4176.

Diethyl (2-methylpropylidene)malonate
CAS Reg No. 5652-68-6

Isolated yield: 92 %
Aspect: yellow oil
Chemical formula: $C_{11}H_{18}O_4$
Mol. wt.: 214.26 g/mol



12j

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.77 (d, $J_{h,i}$ = 10.6 Hz, 1H, h), 4.29 (q,

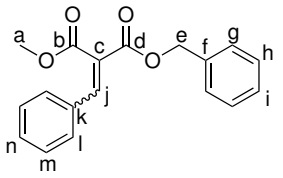
J = 7.1 Hz, 2H, b or f), 4.22 (q, J = 7.1 Hz, 2H, f or b), 2.68 (m, 1H, i), 1.32 (t, J = 7.1 Hz, 3H, a or g), 1.28 (t, J = 7.1 Hz, 3H, g or a), 1.06 (d, $J_{j,i}$ = 6.6 Hz, 6H, j).

HRMS (APCI): m/z= 215.127 83; calcd. for $[M + H]^+$ ($C_{11}H_{19}O_4$): 215.127 79

^{1}H NMR and Mass spectra are in agreement with literature; see: W. Fraser, C. J. Suckling, H. C. S. Wood, *J. Chem. Soc. Perkin Trans. 1* **1990**, 3137–3144.

Benzyl methyl 2-benzylidenemalonate
CAS Reg No. 88926-99-2

d.r.: 1/1 (A/B)[10]
Isolated yield: 30 % (mixture of isomers)
Aspect: colourless oil
Chemical formula: $C_{18}H_{16}O_4$
Mol. wt.: 296.32 g/mol



12l

The analyses below refer to the B diastereoisomer.[11]

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81 (s, 1H, j), 7.49-7.28 (comp, 10H, Ar), 5.30 (s, 2H, e), 3.83 (s, 3H, a).

^{13}C NMR (75 MHz, $CDCl_3$): δ 166.9 (b), 163.7 (d), 142.9 (j), 135.5 (f), 132.6 (k), 130.7 (i or n), 129.4 (l), 128.8,128.5,127.8 (g, h and m), 128.2 (n or i), 125.5 (c), 67.0 (e), 52.5 (a).

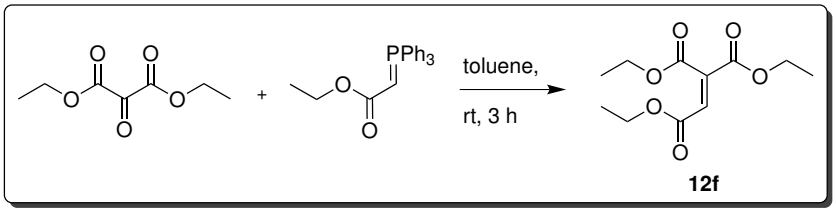
[10] Calculated on the ^{1}H NMR spectrum of the crude mixture.
[11] The A isomer being not isolated, no analyses were carried out.

HRMS (APCI): m/z= 297.112 24; calcd. for $[M + H]^+$ ($C_{18}H_{17}O_4$): 297.112 14. **Fragments**: m/z= 265 $[M - OMe]^+$, 189 $[M - OBn]^+$

FT-IR (cm^{-1}): 3032, 2951, 1728 (C=O), 1706 (C=O), 1628 (C=C), 1497, 1450, 1435, 1373, 1321, 1292, 1256 (C-O), 1217 (C-O), 1198, 1082, 1059, 768, 750, 694.

6.2.4.2 Wittig olefination

Reference: K. Okuro, H. Alper, *J. Org. Chem.* **2012**, *77*, 4420–4424.

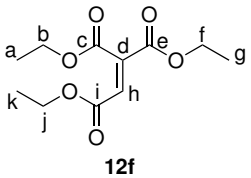


Procedure: in a dried round-bottom flask, under inert atmosphere, diethyl ketomalonate 95 % (0.64 mL; 4 mmol; 1 eq.) and (carbethoxymethylene)-triphenyl-phosphorane (4 mmol; 1 eq.) are added in toluene (5 mL), at 0 °C. After stirring for 3 h at room temperature, the crude is concentrated under reduced pressure. The residue is purified by flash chromatography on silica gel (20/80 EtOAc/cyclohexane).

Diethyl ethoxycarbonylbutendienoate

CAS Reg No. 13049-86-0

Isolated yield: quantitative
Aspect: colourless liquid
Chemical formula: $C_{11}H_{16}O_6$
Mol. wt.: 244.24 g/mol



^{1}H NMR (500 MHz, $CDCl_3$): δ 6.87 (s, 1H, h), 4.38 (q, J = 7.2 Hz, 2H, b, f or j), 4.30 (q, J = 7.2 Hz, 2H, f, j or b), 4.25 (q, J = 7.2 Hz, 2H, j, b or f),

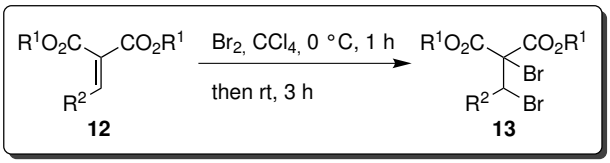
1.36 (t, $J = 7.0$ Hz, 3H, a, g or k), 1.34-1.29 (comp, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 164.4,163.7,162.4 (c, e and i), 139.0 (d), 130.2 (h), 62.6,62.2,61.9 (b, f and j), 14.12,14.10,14.06 (a, g and k).

The ^{1}H and ^{13}C NMR spectra are in agreement with literature; see: K. Okuro, H. Alper, *J. Org. Chem.* **2012**, *77*, 4420–4424.

6.2.4.3 Bromination

Reference: O. Rousseau, T. Delaunay, R. Robiette, *Synlett* **2014**, *25*, 519–522.

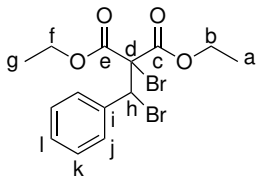


General procedure: in a round-bottom flask Knoevenagel adduct **12**[12] (7 mmol; 1 eq.) and bromine (8 mmol; 1.1 eq.) are added in CC_4 (4 mL), at 0 °C. After stirring for 1 h at the same temperature and then 3 h at room temperature, the solution is diluted with water (5 mL) and extracted with DCM (20 mL). The organic layer is washed with an aqueous solution of NaOH (10 wt.%; 10 mL), brine (10 mL), dried over $MgSO_4$, and then concentrated under reduced pressure. The desired brominated compound **13** is used in the next step without further purification.[13]

Diethyl bromo[bromo(phenyl)methyl]malonate
CAS Reg No. 77752-84-2

Isolated yield: 97 %
Aspect: yellow oil
Chemical formula: $C_{14}H_{16}Br_2O_4$
Mol. wt.: 408.08 g/mol

[12]Compound **13h** is synthesized *via* an addition/elimination reaction of [dimethyl(phenyl)silyl]lithium on diethyl (ethoxymethylene)malonate. See page 283.
[13]For compound **13l**, the product is isolated after purification by flash chromatography on silica gel (05/95 to 10/90 EtOAc/cyclohexane).



13b

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 (m, 2H, j and k), 7.34–7.25 (comp, 3H, Ar), 5.77 (s, 1H, h), 4.36 (m, 2H, b), 4.16 (q, $J_{f,g} = 7.2$ Hz, 2H, f), 1.34 (t, $J = 7.2$ Hz, 3H, a or g), 1.19 (t, $J = 7.2$ Hz, 3H, g or a).

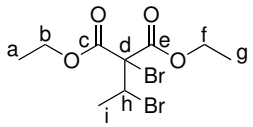
^{13}C NMR (75 MHz, $CDCl_3$): δ 164.5 (c or e), 164.5 (e or c), 136.4 (i), 130.0 (j or k), 129.4 (l), 128.1 (k or j), 68.7 (d), 63.9 (b or f), 63.8 (f or b), 53.3 (h), 14.0 (a or g), 13.8 (g or a).

HRMS (APCI): m/z= 406.949 01; calcd. for $[M + H]^+$ ($C_{14}H_{17}O_4{}^{79}Br_2$): 406.948 81. **Fragments**: m/z= 249 [M - Br_2 + H]$^+$, 203 [M - Br_2 - OEt]$^+$

FT-IR (cm^{-1}): 2992, 1743 (C=O), 1465, 1451, 1367, 1237 (C-O), 1190, 1095 (C-O), 1016, 992, 861, 756, 698, 671.

Diethyl bromo(1-bromoethyl)malonate

Isolated yield: 89 %
Aspect: colourless liquid
Chemical formula: $C_9H_{14}Br_2O_4$
Mol. wt.: 346.01 g/mol



13i

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.73 (q, $J_{h,i} = 6.6$ Hz, 1H, h), 4.32 (q, $J_{b,a} = 7.1$ Hz, 2H, b), 4.29 (q, $J_{f,g} = 7.1$ Hz, 1H, h), 1.94 (d, $J_{i,h} = 6.6$ Hz, 3H, i), 1.32 (t, $J_{a,b} = 7.1$ Hz, 3H, a), 1.30 (t, $J_{g,f} = 7.1$ Hz, 3H, g).

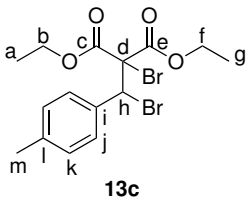
^{13}C NMR (75 MHz, $CDCl_3$): δ 165.2 (e), 164.4 (c), 69.0 (d), 63.9 (b or f), 63.5 (f or b), 49.5 (h), 23.7 (i), 14.0 (a or g), 13.9 (g or a).

HRMS (APCI): m/z= 344.933 17; calcd. for [M ($^{79}Br_2$) + H]$^+$ ($C_9H_{15}O_4{}^{79}Br_2$): 344.933 16. **Fragment**: m/z= 187 [M - Br_2 + H]$^+$

FT-IR (cm^{-1}): 2982, 1771, 1742 (C=O), 1447, 1367, 1298, 1246 (C-O), 1202, 1090, 1036.

Diethyl bromo[bromo(4-methylphenyl)methyl]malonate

Isolated yield: 95 %
Aspect: orange liquid
Chemical formula: $C_{15}H_{18}Br_2O_4$
Mol. wt.: 422.11 g/mol



13c

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46 (d, J = 8.2 Hz, 2H, j or k), 7.11 (d, J = 8.0 Hz, 2H, k or j), 5.75 (s, 1H, h), 4.35 (m, 2H, b or f), 4.17 (q, J = 7.1 Hz, 2H, f or b), 2.33 (s, 3H, m), 1.34 (t, J = 7.1 Hz, 3H, a or g), 1.20 (t, J = 7.1 Hz, 3H, g or a).

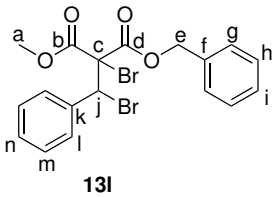
^{13}C NMR (75 MHz, $CDCl_3$): δ 164.58 (c or e), 164.56 (e or c), 139.5 (l), 133.5 (i), 129.8 (k), 128.8 (j), 68.9 (d), 63.8 (b or f), 63.7 (f or b), 53.3 (h), 21.3 (m), 14.0 (a or g), 13.8 (g or a).

HRMS (APCI): m/z= 420.964 45; calcd. for [M + H]$^+$ ($C_{15}H_{19}O_4{}^{79}Br_2$): 420.964 46. **Fragments**: m/z= 263 [M - Br_2 + H]$^+$, 217 [M - Br_2 - OEt]$^+$

FT-IR (cm^{-1}): 1747 (C=O), 1514 (C=C Ar), 1464, 1298, 1240 (C-O), 1199, 1030, 1020.

Methyl phenyl bromo[bromo(phenyl)methyl]malonate

d.r.: 1.3/1 (A/B)[14]
Isolated yield: 33 % (mixture of isomers)
Aspect: colourless oil
Chemical formula: $C_{18}H_{16}Br_2O_4$
Mol. wt.: 456.13 g/mol



13l

The analyses below were carried out on a 0.4/1 d.r. (A/B) sample.

^{1}H NMR A isomer (500 MHz, $CDCl_3$): δ 7.65-7.24 (comp, 10H, Ar), 5.83-5.80 (comp, 1H, j), 5.37 (d, $J_{e,e'} = 12.2$ Hz, 1H, e), 5.34 (d, $J_{e',e} = 12.2$ Hz, 1H, e'), 3.66 (s, 3H, a).

^{13}C NMR A isomer (125 MHz, $CDCl_3$): δ 164.4 (b), 163.9 (d), 135.6 (k), 134.4 (f), 130.1,130.0,129.9,129.6,129.4,128.9,128.8,128.7,128.6,128.4,128.2, 128.1 (Ar from A and B isomers), 69.3 (e), 67.5 (c), 54.1 (a), 53.1 (j).

^{1}H NMR B isomer (500 MHz, $CDCl_3$): δ 7.65-7.24 (comp, 10H, Ar), 5.83-5.80 (comp, 1H, j), 5.18 (d, $J_{e,e'} = 12.2$ Hz, 1H, e), 5.15 (d, $J_{e',e} = 12.2$ Hz, 1H, e'), 3.84 (s, 3H, a).

^{13}C NMR B isomer (125 MHz, $CDCl_3$): δ 164.8 (b), 164.1 (d), 136.0 (k), 134.2 (f), 130.1,130.0,129.9,129.6,129.4,128.9,128.8,128.7,128.6,128.4,128.2, 128.1 (Ar from A and B isomers), 69.1 (e), 68.3 (c), 54.3 (a), 53.1 (j).

HRMS (APCI): m/z= 454.948 87; calcd. for [M ($^{79}Br_2$) + H]$^+$ ($C_{18}H_{17}O_4{}^{79}Br_2$): 454.948 81. **Fragment**: m/z= 297 [M - Br_2 + H]$^+$

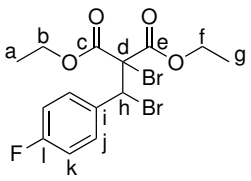
FT-IR (cm^{-1}): 3063, 3032, 3007, 2984, 2953, 1747 (C=O), 1497, 1454, 1435, 1306, 1244 (C-O), 1229 (C-O), 1209, 1178, 1080, 1026, 1003, 991, 972,

[14](a) Calculated on the ^{1}H NMR spectrum of the crude mixture. (b) Starting from a sample having a 3/1 d.r.

935, 752, 696, 654.

Diethyl bromo[bromo(4-fluorophenyl)methyl]malonate

Isolated yield: 87 %
Aspect: orange oil
Chemical formula: $C_{14}H_{15}Br_2FO_4$
Mol. wt.: 426.07 g/mol



13e

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 (m, 2H, j or k), 7.00 (m, 2H, k or j), 5.75 (s, 1H, h), 4.36 (m, 2H, b or f), 4.17 (q, J = 7.1 Hz, 2H, f or b), 1.34 (t, J = 7.1 Hz, 3H, a or g), 1.21 (t, J = 7.1 Hz, 3H, g or a).

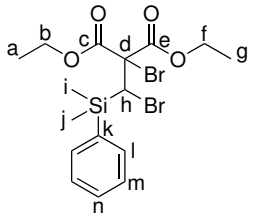
^{13}C NMR (75 MHz, $CDCl_3$): δ 164.4 (c or e), 164.3 (e or c), 163.0 (d, J = 248.2 Hz, l), 132.3 (d, J = 3.2 Hz, i), 132.0 (d, J = 8.3 Hz, j), 114.9 (d, J = 21.7 Hz, k), 68.6 (d), 63.9 (b or f), 63.7 (f or b), 52.3 (h), 13.9 (a or g), 13.7 (g or a).

HRMS (APCI): m/z= 424.939 37; calcd. for $[M + H]^+$ ($C_{14}H_{16}FO_4{}^{79}Br_2$): 424.939 39. **Fragments**: m/z= 267 [M - Br_2 + H]$^+$, 221 [M - Br_2 - OEt]$^+$

FT-IR (cm^{-1}): 1743 (C=O), 1605, 1508 (C=C Ar), 1466, 1445, 1367, 1300, 1238 (C-O), 1227, 1207, 1194, 1163, 1099, 1026, 1016, 839.

Diethyl bromobromo[dimethyl(phenyl)silyl]methylmalonate

Isolated yield: 91 %
Aspect: colourless liquid
Chemical formula: $C_{16}H_{22}O_4Br_2Si$
Mol. wt.: 466.24 g/mol



13h

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68-7.65 (comp, 2H, Ar), 7.41-7.35 (comp, 3H, Ar), 4.38-4.26 (comp, 2H, b or f), 4.23 (s, 1H, h), 4.15-4.07 (comp, 2H, f or b), 1.31 (t, J = 7.0 Hz, 3H, a or g), 1.25 (t, J = 7.2 Hz, 3H, g or a), 0.62 (s, 3H, i), 0.53 (s, 3H, j).

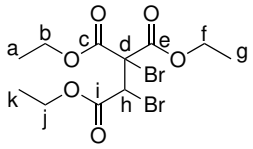
^{13}C NMR (125 MHz, $CDCl_3$): δ 165.4 (two signals: c and e), 136.7 (k), 134.6 (l or m), 129.8 (n), 127.8 (m or l), 67.8 (d), 63.9 (b or f), 63.7 (f or b), 45.9 (h), 14.0 (a or g), 13.8 (g or a), -1.4 (two signals: i and j).

HRMS (ESI): m/z= 486.954 81; calcd. for $[M + Na]^+$ ($C_{16}H_{22}O_4{}^{79}Br_2SiNa$): 486.954 63. **Fragment**: m/z= 389 [M ($^{79}Br^{81}Br$) - Ph]$^+$

FT-IR (cm^{-1}): 3584, 3070, 3049, 2982, 2964, 2937, 2905, 2361, 1767, 1728 (C=O), 1698, 1590 (C=C Ar), 1485, 1464, 1445, 1427, 1391, 1367, 1300, 1246 (C-O), 1221, 1213, 1190, 1113 (C-O), 1092 (C-O), 1028, 932, 910, 839, 820, 785, 731, 698.

Triethyl 1,2-dibromoethane-1,1,2-tricarboxylate

Isolated yield: 93 %
Aspect: colourless liquid
Chemical formula: $C_{11}H_{16}O_6Br_2$
Mol. wt.: 404.05 g/mol



13f

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.14 (s, 1H, h), 4.41-4.24 (comp, 6H, b, f and j), 1.38-1.30 (comp, 9H, a, g and k).

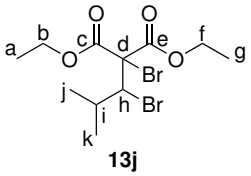
^{13}C NMR (75 MHz, $CDCl_3$): δ 165.8,164.5,163.5 (c, e and i), 64.0,63.9, 62.9 (b, f and j), 62.0 (d), 46.4 (h), 13.8,13.8,13.7 (a, g and k).

HRMS (APCI): m/z= 402.938 92; calcd. for [M ($^{79}Br_2$) + H]$^+$ ($C_{11}H_{17}O_6{}^{79}Br_2$): 402.938 64

FT-IR (cm^{-1}): 2984, 2939, 2907, 1740 (C=O), 1466, 1445; 1393, 1367, 1327, 1296, 1244 (C-O), 1192, 1155 (C-O), 1111 (C-O), 1096, 1020, 914, 856, 731.

Diethyl bromo(1-bromo-2-methylpropyl)malonate

Isolated yield: 91 %
Aspect: yellow oil
Chemical formula: $C_{11}H_{18}O_4Br_2$
Mol. wt.: 374.07 g/mol



13j

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.70 (d, $J_{h,i}$ = 3.0 Hz, 1H, h), 4.30 (q, J = 7.1 Hz, 4H, b and f), 2.32 (qqd, $J_{i,j}$ = 6.6 Hz, $J_{i,k}$ = 6.6 Hz, $J_{i,h}$ = 3.0 Hz, 1H, i), 1.32 (t, J = 7.1 Hz, 3H, a or g), 1.31 (t, J = 7.1 Hz, 3H, g or a), 1.07 (d, J = 6.7 Hz, 3H, j or k), 1.06 (d, J = 6.4 Hz, 3H, k or j).

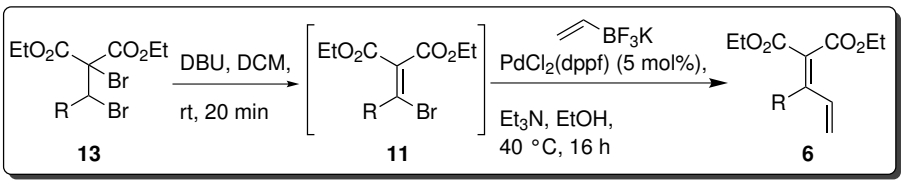
^{13}C NMR (125 MHz, $CDCl_3$): δ 165.5 (c or e), 164.5 (e or c), 68.5 (d), 63.9 (b or f), 63.6 (f or b), 62.7 (h), 32.0 (i), 23.3 (j or k), 19.9 (k or j), 14.0 (a or g), 13.9 (g or a).

HRMS (APCI): m/z= 372.964 96; calcd. for [M ($^{79}Br_2$) + H]$^+$ ($C_{11}H_{19}O_4{}^{79}Br_2$): 372.964 46. **Fragment**: m/z= 329 [M ($^{79}Br^{81}Br$) - OEt]$^+$

FT-IR (cm^{-1}): 2980, 2937, 2908, 2878, 1740 (C=O), 1464, 1445, 1389, 1367, 1337, 1327, 1298, 1238 (C-O), 1192, 1121, 1096, 1068, 1020, 991, 858.

6.2.4.4 Elimination/Suzuki-Miyaura cross coupling

Reference: O. Rousseau, T. Delaunay, R. Robiette, *Synlett* **2014**, *25*, 519–522.



General procedure: in a dried round-bottom flask, under inert atmosphere, brominated compound **13** (3 mmol; 1 eq.) is added in DCM (20 mL). DBU (3.6 mmol; 1.2 eq.) is next added, dropwise, at 0 °C. After stirring for 20 min at room temperature, the solution is diluted with water (10 mL). The organic layer is washed with a 1 M aqueous solution of HCl (10 mL), dried over $MgSO_4$, and then concentrated under reduced pressure.

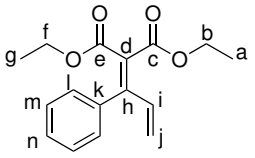
In a dried round-bottom flask, under inert atmosphere, the residue (com-

pound **11**) is diluted in EtOH (15 mL)[15]. Potassium vinyltrifluoroborate (3.9 mmol; 1.3 eq.), $PdCl_2$(dppf) (0.15 mmol; 5 mol%) and triethylamine (4.2 mmol; 1.4 eq.) are then added. After stirring for 16 h at 40 °C, the crude is concentrated under reduced pressure.[16] The residue is then diluted with EtOAc (25 mL), washed with water (10 mL), a saturated aqueous solution of NH_4Cl (10 mL), and finally brine (10 mL). The organic layer is dried over $MgSO_4$ and concentrated under reduced pressure. Pure diene **6** is obtained after purification by flash chromatography on silica gel with the appropriate mixture of cyclohexane and EtOAc (*vide infra* for ratios).

Diethyl (1-phenylprop-2-en-1-ylidene)malonate

Procedure: using the general procedure, diene **6b** is isolated after purification by flash chromatography on silica gel (02/98 EtOAc/cyclohexane).

Isolated yield: 44 %
Aspect: yellow oil
Chemical formula: $C_{16}H_{18}O_4$
Mol. wt.: 274.31 g/mol



6b

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (dd, $J_{i,j'} = 17.2$ Hz, $J_{i,j} = 10.8$ Hz, 1H, i), 7.36–7.27 (comp, 3H, Ar), 7.16 (m, 2H, l or m), 5.60 (dd, $J_{j,i} = 10.5$ Hz, $J_{j,j'} = 1.5$ Hz, 1H, j), 5.13 (dd, $J_{j',i} = 17.3$ Hz, $J_{j',j} = 1.3$ Hz, 1H, j'), 4.28 (q, $J = 7.2$ Hz, 2H, b or f), 3.89 (q, $J = 7.2$ Hz, 2H, f or b), 1.29 (t, $J = 7.0$ Hz, 3H, a or g), 0.89 (t, $J = 7.0$ Hz, 3H, g or a).

^{13}C NMR (125 MHz, $CDCl_3$): δ 165.7 (c or e), 164.2 (e or c), 153.0 (h), 136.4 (k), 134.8 (i), 128.9 (l), 128.4 (n), 127.9 (m), 127.6 (j), 125.7 (d), 61.3 (b or f), 61.0 (f or b), 14.1 (a or g), 13.6 (g or a).

[15]For compound **6f**, THF is used instead of EtOH.
[16]For compound **6f**, the crude is diluted with water (10 mL) and extracted with Et_2O (3 x 15 mL). The combined organic layers are washed with brine (10 mL), dried over $MgSO_4$, and then concentrated under reduced pressure.

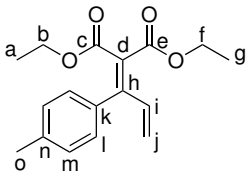
HRMS (APCI): m/z= 275.127 73; calcd. for $[M + H]^+$ ($C_{16}H_{19}O_4$): 275.127 79. **Fragment**: m/z= 229 $[M - OEt]^+$

FT-IR (cm^{-1}): 1728 (C=O), 1252 (C-O), 1224 (C-O), 1095, 1065, 1023, 701.

Diethyl [1-(4-methylphenyl)prop-2-en-1-ylidene]malonate

Procedure: using the general procedure, diene **6c** is isolated after purification by flash chromatography on silica gel (10/90 EtOAc/cyclohexane).

Isolated yield: 16 %
Aspect: colourless liquid
Chemical formula: $C_{17}H_{20}O_4$
Mol. wt.: 288.34 g/mol



6c

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 (dd, $J_{i,j} = 17.2$ Hz, $J_{i,j'} = 10.6$ Hz, 1H, i), 7.14 (d, $J = 8.1$ Hz, 2H, l or m), 7.06 (d, $J = 8.1$ Hz, 2H, m or l), 5.60 (dd, $J_{j',i} = 10.6$ Hz, $J_{j',j} = 1.0$ Hz, 1H, j'), 5.17 (dd, $J_{j,i} = 17.1$ Hz, $J_{j,j'} = 0.9$ Hz, 1H, j), 4.28 (q, $J = 7.1$ Hz, 2H, b or f), 3.93 (q, $J = 7.1$ Hz, 2H, f or b), 2.34 (s, 3H, o), 1.30 (t, $J = 7.2$ Hz, 3H, a or g), 0.95 (t, $J = 7.0$ Hz, 3H, g or a).

^{13}C NMR (75 MHz, $CDCl_3$): δ 166.0 (c or e), 164.5 (e or c), 153.4 (h), 138.4 (n), 135.1 (i), 133.6 (k), 129.0 (l or m), 128.7 (m or l), 127.6 (j), 125.6 (d), 61.4 (b or f), 61.1 (f or b), 21.4 (o), 14.2 (a or g), 13.8 (g or a).

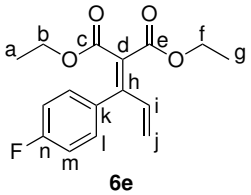
HRMS (ESI): m/z= 289.143 76; calcd. for $[M + H]^+$ ($C_{17}H_{21}O_4$): 289.143 44. **Fragment**: m/z= 243 $[M - OEt]^+$

FT-IR (cm^{-1}): 2986, 1713 (C=O), 1614, 1578, 1510 (C=C Ar), 1464, 1446, 1367, 1325, 1227 (C-O), 1184, 1122, 1096, 1063, 1032, 820.

Diethyl [1-(4-fluorophenyl)prop-2-en-1-ylidene]malonate

Procedure: using the general procedure, diene **6e** is isolated after purification by flash chromatography on silica gel (05/95 to 10/90 EtOAc/cyclohexane).

Isolated yield: 32 %
Aspect: colourless liquid
Chemical formula: $C_{16}H_{17}FO_4$
Mol. wt.: 292.30 g/mol



6e

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44 (dd, $J_{i,j} = 17.2$ Hz, $J_{i,j'} = 10.6$ Hz, 1H, i), 7.16-7.11 (comp, 2H, l), 7.04-6.98 (comp, 2H, m), 5.59 (dd, $J_{j',i} = 10.5$ Hz, $J_{j',j} = 1.2$ Hz, 1H, j'), 5.10 (dd, $J_{j,i} = 17.1$ Hz, $J_{j,j'} = 1.2$ Hz, 1H, j), 4.26 (q, $J = 7.1$ Hz, 2H, b or f), 3.92 (q, $J = 7.1$ Hz, 2H, f or b), 1.28 (t, $J = 7.2$ Hz, 3H, a or g), 0.95 (t, $J = 7.0$ Hz, 3H, g or a).

^{13}C NMR (75 MHz, $CDCl_3$): δ 165.6 (c or e), 164.2 (e or c), 162.8 (d, $J = 246.4$ Hz, n), 151.9 (h), 134.9 (i), 132.3 (d, $J = 3.2$ Hz, k), 130.8 (d, $J = 8.1$ Hz, l), 127.6 (j), 126.2 (d), 115.1 (d, $J = 21.5$ Hz, m), 61.5 (b or f), 61.1 (f or b), 14.1 (a or g), 13.7 (g or a).

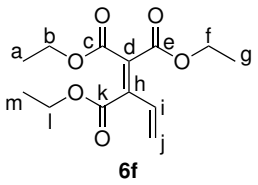
HRMS (APCI): m/z= 293.118 32; calcd. for $[M + H]^+$ ($C_{16}H_{18}FO_4$): 293.118 36. **Fragment**: m/z= 247 $[M - OEt]^+$

FT-IR (cm^{-1}): 1716 (C=O), 1614 (C=C Ar), 1603 (C=C Ar), 1576, 1504 (C=C Ar), 1466, 1446, 1367, 1323, 1250, 1228 (C-O), 1200, 1159, 1122, 1095, 1059, 1030, 1014, 937, 864, 839, 820, 791.

Triethyl buta-1,3-diene-1,1,2-tricarboxylate

Procedure: using the general procedure (THF is used instead of EtOH)[17], diene **6f** is isolated after purification by flash chromatography on silica gel (10/90 EtOAc/cyclohexane).

Isolated yield: 47 %
Aspect: colourless liquid
Chemical formula: $C_{13}H_{18}O_6$
Mol. wt.: 270.28 g/mol



6f

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.65 (dd, $J_{i,j} = 17.5$ Hz, $J_{i,j'} = 11.0$ Hz, 1H, i), 5.68 (d, $J_{j',i} = 11.0$ Hz, 1H, j'), 5.65 (d, $J_{j,i} = 17.5$ Hz, 1H, j), 4.36 (q, $J = 7.0$ Hz, 2H, b, f or l), 4.33 (q, $J = 7.0$ Hz, 2H, f, l or b), 4.24 (q, $J = 7.0$ Hz, 2H, l, b or f), 1.35 (t, $J = 7.0$ Hz, 3H, a, g or m), 1.33 (t, $J = 7.0$ Hz, 3H, g, m or a), 1.28 (t, $J = 7.0$ Hz, 3H, m, a or g).

^{13}C NMR (75 MHz, $CDCl_3$): δ 166.1,164.4,163.1 (c, e and k), 145.1 (h), 129.7 (i), 126.8 (j), 125.4 (d), 62.11,62.06,62.04 (b, f and l), 14.19,14.11,14.09 (a, g and m).

HRMS (APCI): m/z= 271.117 34; calcd. for $[M + H]^+$ ($C_{13}H_{19}O_6$): 271.117 61. **Fragment**: m/z= 215 $[M - OEt]^+$

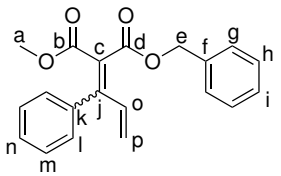
FT-IR (cm^{-1}): 2984, 2962, 2926, 2905, 2872, 2853, 1724 (C=O), 1620, 1595, 1466, 1447, 1391, 1367, 1319, 1298, 1244 (C-O), 1182, 1163, 1096, 1068, 1024, 943, 862, 800, 779, 719.

[17]For the workup, the crude is diluted with water (10 mL) and extracted with Et_2O (3 x 15 mL). The combined organic layers are washed with brine (10 mL), dried over $MgSO_4$, and then concentrated under reduced pressure.

Benzyl methyl (1-phenylprop-2-en-1-ylidene)malonate

Procedure: using the general procedure, a 1/1 d.r. is observed on the ^{1}H NMR spectrum of the crude mixture.[18] Pure diene **6l** is isolated as 1/1 isomers mixture after purification by flash chromatography on silica gel (10/90 EtOAc/cyclohexane).

Isolated yield: 14 % (1/1 d.r. isomers mixture)
Aspect: colourless liquid
Chemical formula: $C_{20}H_{18}O_4$
Mol. wt.: 322.35 g/mol

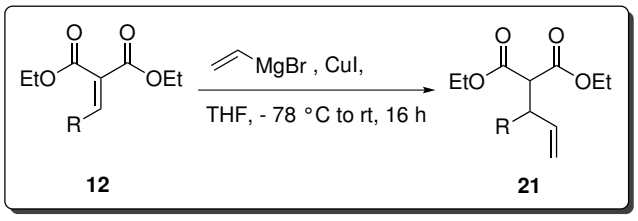


6l

For descriptions of ^{1}H NMR, ^{13}C NMR, Mass, and IR spectra, see page 221).

6.2.4.5 Michael addition

Reference: O. Rousseau, T. Delaunay, R. Robiette, *Synlett* **2014**, *25*, 519–522.



12 **21**

General procedure: in a dried round-bottom flask, under inert atmosphere, a solution of vinylmagnesiumbromide (1 M in THF; 7.2 mmol; 2.4 eq.) is added, dropwise, to a suspension of CuI (3.6 mmol; 1.2 eq.) in THF (20 mL), at 0 °C. After stirring for 45 min at this temperature, a solution of Knoevenagel adduct **12** (3 mmol; 1 eq.) in THF (20 mL) is next added, dropwise, at −78 °C. After stirring 16 h (the cooling bath recovering slowly to room temperature),

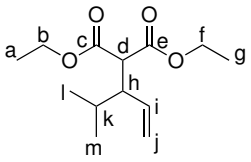
[18] Starting from the crude brominated substrate, having a 1.8/1 d.r.

the reaction is quenched with a saturated aqueous solution of NH_4Cl (5 mL), then diluted with water (10 mL) and extracted with Et_2O (3 x 40 mL). The combined organic layers are washed with brine (10 mL), dried over $MgSO_4$, and then concentrated under reduced pressure. The residue is purified by flash chromatography on silica gel with the appropriate mixture of cyclohexane and EtOAc (*vide infra* for ratios).

Diethyl (1-isopropylprop-2-en-1-yl)malonate

Procedure: using the general procedure, Michael adduct **21j** is isolated after purification by flash chromatography on silica gel (10/90 EtOAc/cyclohexane).

Isolated yield: 65 %
Aspect: pale yellow liquid
Chemical formula: $C_{13}H_{22}O_4$
Mol. wt.: 242.31 g/mol



21j

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.69 (ddd, $J_{i,j}$ = 17.0 Hz, $J_{i,j'}$ = 10.1 Hz, $J_{i,h}$ = 10.1 Hz, 1H, i), 5.10 (dd, $J_{j',i}$ = 10.3 Hz, $J_{j',j}$ = 2.0 Hz, 1H, j'), 5.06 (dd, $J_{j,i}$ = 17.0 Hz, $J_{j,j'}$ = 1.9 Hz, 1H, j), 4.22-4.12 (comp, 4H, b and f), 3.53 (d, $J_{d,h}$ = 9.7 Hz, 1H, d), 2.65 (ddd, $J_{h,d}$ = 9.7 Hz, $J_{h,i}$ = 9.7 Hz, $J_{h,k}$ = 4.9 Hz, 1H, h), 1.75 (m, 1H, k), 1.26 (t, J = 7.2 Hz, 3H, a or g), 1.24 (t, J = 7.2 Hz, 3H, g or a), 0.91 (d, J = 6.8 Hz, 3H, l or m), 0.84 (d, J = 6.9 Hz, 3H, m or l).

^{13}C NMR (125 MHz, $CDCl_3$): δ 168.8 (c or e), 168.5 (e or c), 135.0 (i), 118.8 (j), 61.5 (b or f), 61.3 (f or b), 55.1 (d), 50.4 (h), 29.1 (k), 21.4 (l or m), 17.7 (m or l), 14.2 (two signals: a and g).

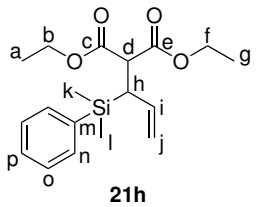
HRMS (APCI): m/z= 243.158 93; calcd. for $[M + H]^+$ ($C_{13}H_{23}O_4$): 243.159 09. **Fragment**: m/z= 197 $[M - OEt]^+$

FT-IR (cm^{-1}): 2974, 2961, 2934, 2905, 2874, 1755 (C=O), 1732 (C=O), 1639 (C=C), 1466, 1447, 1389, 1369, 1323, 1300, 1259, 1242, 1227, 1178, 1144, 1132, 1096, 1034, 1003, 920.

Diethyl 1-[dimethyl(phenyl)silyl]prop-2-en-1-ylmalonate

Procedure: using the general procedure, Michael adduct **21h** is isolated after purification by flash chromatography on silica gel (10/90 EtOAc/cyclohexane).

Isolated yield: 61 %
Aspect: colourless liquid
Chemical formula: $C_{18}H_{26}O_4Si$
Mol. wt.: 334.48 g/mol



21h

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51-7.48 (comp, 2H, n or o), 7.36-7.34 (comp, 3H, p and (o or n)), 5.80 (ddd, $J_{i,j}$ = 17.0 Hz, $J_{i,j'}$ = 10.1 Hz, $J_{i,h}$ = 10.1 Hz, 1H, i), 4.96 (dd, $J_{j',i}$ = 10.2 Hz, $J_{j',j}$ = 1.6 Hz, 1H, j'), 4.88 (dd, $J_{j,i}$ = 17.0 Hz, $J_{j,j'}$ = 1.5 Hz, 1H, j), 4.08 (q, J = 7.2 Hz, 2H, b or f), 3.92 (q, J = 7.2 Hz, 2H, f or b), 3.46 (d, $J_{d,h}$ = 9.0 Hz, 1H, d), 2.60 (dd, $J_{h,d}$ = 9.5 Hz, $J_{h,i}$ = 9.5 Hz, 1H, h), 1.19 (t, J = 7.2 Hz, 3H, a or g), 1.16 (t, J = 7.2 Hz, 3H, g or a), 0.33 (s, 3H, k or l), 0.32 (s, 3H, l or k).

^{13}C NMR (75 MHz, $CDCl_3$): δ 169.1 (c or e), 169.0 (e or c), 136.7 (m), 135.8 (i), 134.3 (n or o), 129.3 (p), 127.8 (o or n), 115.0 (j), 61.4 (b or f), 61.3 (f or b), 52.8 (d), 34.5 (h), 14.2 (a or g), 14.1 (g or a), -3.6 (k or l), -4.3 (l or k).

HRMS (APCI): m/z= 335.167 27; calcd. for $[M + H]^+$ ($C_{18}H_{27}O_4Si$): 335.167 31. **Fragment**: m/z= 257 $[M - Ph]^+$

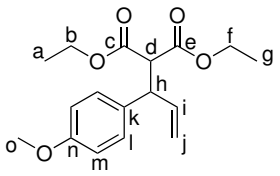
FT-IR (cm^{-1}): 2978, 2961, 2937, 2905, 1758 (C=O), 1728 (C=O), 1628

(C=C), 1464, 1447, 1427, 1367, 1339, 1300, 1248 (C-O), 1229 (C-O), 1176, 1148, 1113 (Si-Ar), 1097, 1032, 999, 906, 837 (Si-C), 814 (Si-C), 779, 735, 702.

Diethyl [1-(4-methoxyphenyl)prop-2-en-1-yl]malonate
CAS Reg No. 1127889-64-8

Procedure: using the general procedure, Michael adduct **21g** isisolated after purification by flash chromatography on silica gel (10/90 EtOAc/cyclohexane).

Isolated yield: 48 %
Aspect: pale yellow liquid
Chemical formula: $C_{17}H_{22}O_5$
Mol. wt.: 306.35 g/mol



21g

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15 (m, 2H, l), 6.83 (m, 2H, m), 5.97 (ddd, $J_{i,j}$ = 17.1 Hz, $J_{i,j'}$ = 10.2 Hz, $J_{i,h}$ = 8.0 Hz, 1H, i), 5.09 (dd, $J_{j,i}$ = 17.1 Hz, $J_{j,j'}$ = 1.2 Hz, 1H, j), 5.05 (dd, $J_{j',i}$ = 10.2 Hz, $J_{j',j}$ = 1.0 Hz, 1H, j'), 4.20 (q, J = 7.1 Hz, 2H, b or f), 4.06 (dd, $J_{h,d}$ = 11.1 Hz, $J_{h,i}$ = 8.1 Hz, 1H, h), 3.95 (m, 2H, f or b), 3.78 (d, $J_{d,h}$ = 11.1 Hz, 1H, d), 3.77 (s, 3H, o), 1.27 (t, J = 7.1 Hz, 3H, a or g), 1.02 (t, J = 7.1 Hz, 3H, g or a).

^{13}C NMR (125 MHz, $CDCl_3$): δ 168.0 (c or e), 167.7 (e or c), 158.7 (n), 138.4 (i), 132.2 (k), 129.2 (l), 116.2 (j), 114.1 (m), 61.6 (b or f), 61.4 (f or b), 57.7 (d or o), 55.4 (o or d), 49.0 (h), 14.2 (a or g), 14.0 (g or a).

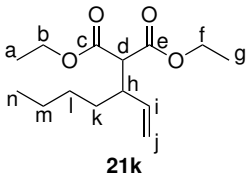
HRMS (APCI): m/z= 307.153 91; calcd. for $[M + H]^+$ ($C_{17}H_{23}O_5$): 307.154 00

FT-IR (cm^{-1}): 2982, 2935, 2907, 2361, 2338, 1753 (C=O), 1730 (C=O), 1637, 1610, 1583, 1512, 1464, 1445, 1391, 1367, 1302, 1246 (C-O), 1176, 1157, 1144, 1124, 1095, 1034, 993, 922, 829, 658.

Diethyl (1-butylprop-2-en-1-yl)malonate
CAS Reg No. 117749-06-1

Procedure: using the general procedure, Michael adduct **21k** is isolated after purification by flash chromatography on silica gel (10/90 EtOAc/cyclohexane).

Isolated yield: 96 %
Aspect: orange liquid
Chemical formula: $C_{14}H_{24}O_4$
Mol. wt.: 256.34 g/mol



21k

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.64 (ddd, $J_{i,j}$ = 17.0 Hz, $J_{i,j'}$ = 10.2 Hz, $J_{i,h}$ = 9.4 Hz, 1H, i), 5.10-5.04 (comp, 2H, j), 4.19 (q, J = 7.1 Hz, 2H, b or f), 4.14 (q, J = 7.1 Hz, 2H, f or b), 3.33 (d, $J_{d,h}$ = 8.9 Hz, 1H, d), 2.75 (tdd, $J_{h,i}$ = 9.1 Hz, $J_{h,d}$ = 9.1 Hz, $J_{h,k}$ = 3.4 Hz, 1H, h), 1.37-1.14 (comp, 6H, k, l and m), 1.26 (t, J = 7.1 Hz, 3H, a or g), 1.24 (t, J = 7.1 Hz, 3H, g or a), 0.87 (t, $J_{n,m}$ = 6.7 Hz, 3H, n).

^{13}C NMR (125 MHz, $CDCl_3$): δ 168.6 (c or e), 168.4 (e or c), 138.4 (i), 117.4 (j), 61.4 (b or f), 61.3 (f or b), 57.2 (d), 44.2 (h), 32.1 (k), 29.3 (k or l), 22.6 (l or k), 14.3,14.1 (three signals: a, g and n).

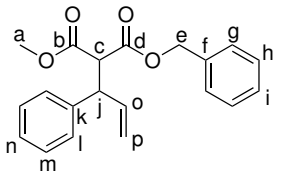
HRMS (APCI): m/z= 257.174 64; calcd. for $[M + H]^+$ ($C_{14}H_{25}O_4$): 257.174 74. **Fragment**: m/z= 211 $[M - OEt]^+$

FT-IR (cm^{-1}): 2982, 2957, 2934, 2907, 2874, 2860, 2365, 2341, 2316, 1751 (C=O), 1732 (C=O), 1641 (C=C), 1466, 1447, 1391, 1369, 1300, 1263, 1242 (C-O), 1223, 1176, 1144, 1095, 1034, 918.

Benzyl methyl (1-phenylprop-2-en-1-yl)malonate

Procedure: using the general procedure, a 1.5/1 d.r. is observed on the ^{1}H NMR spectrum of the crude mixture.[19] Michael adduct **21l** is isolated as 1/1 isomers mixture after purification by flash chromatography on silica gel (15/85 EtOAc/cyclohexane), in 28 % yield.

Isolated yield: 28 % (mixture of isomers)
Aspect: colourless oil
Chemical formula: $C_{20}H_{20}O_4$
Mol. wt.: 324.37 g/mol



21l

The analyses below were carried out on a 1/1 d.r. sample.

^{1}H NMR A isomer (300 MHz, $CDCl_3$): δ 7.41-7.03 (comp, 10H, Ar), 6.13-5.94 (comp, 1H, o), 5.19-5.01 (comp, 2H, p), 4.94 (s, 2H, e), 4.24-4.11 (comp, 1H, j), 3.98 (d, $J_{c,j}$ = 4.0 Hz, 1H, c), 3.73 (s, 3H, a).

^{13}C NMR A isomer (75 MHz, $CDCl_3$): δ 168.0 (b), 167.2 (d), 139.8 (k), 137.9 (o), 135.1 (f), 128.65,128.61,128.55,128.52,128.39,128.35,128.2,128.03, 127.99,127.9,127.12,127.09 (Ar from A and B isomers), 116.6 (p), 67.0 (e), 57.3 (c), 52.5 (a), 49.7 (j).

^{1}H NMR B isomer (300 MHz, $CDCl_3$): δ 7.41-7.03 (comp, 10H, Ar), 6.13-5.94 (comp, 1H, o), 5.21 (s, 1H, e), 5.20 (s, 1H, e'), 5.19-5.01 (comp, 2H, p), 4.24-4.11 (comp, 1H, j), 3.95 (d, $J_{c,j}$ = 3.8 Hz, 1H, c), 3.48 (s, 3H, a).

^{13}C NMR B isomer (75 MHz, $CDCl_3$): δ 167.7 (b), 167.6 (d), 140.0 (k), 137.6 (o), 135.3 (f), 128.65,128.61,128.55,128.52,128.39,128.35,128.2,128.03, 127.99,127.9,127.12,127.09 (Ar from A and B isomers), 117.0 (p), 67.2 (e), 57.3

[19] Starting from a sample having a 3/1 d.r.

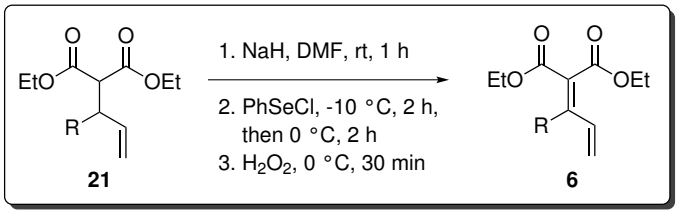
(c), 52.3 (a), 49.7 (j).

HRMS (APCI): m/z= 325.143 33; calcd. for $[M + H]^+$ ($C_{20}H_{21}O_4$): 325.143 44. **Fragments**: m/z= 293 $[M - OMe]^+$, 217 $[M - OBn]^+$

FT-IR (cm^{-1}): 3082, 3063, 3032, 3009, 2982, 2953, 1757 (C=O), 1736 (C=O), 1637 (C=C) 1495 (C=C Ar), 1454, 1435, 1377, 1350, 1313, 1259 (C-O), 1217, 1196, 1155, 1142 (C-O), 1028, 1001, 991, 924, 761, 752, 700.

6.2.4.6 Selenium-mediated olefination

Reference: O. Rousseau, T. Delaunay, R. Robiette, *Synlett* **2014**, *25*, 519–522.



General procedure: in a dried round-bottom flask, under inert atmosphere, NaH (60 % dispersion in mineral oil; 0.72 mmol; 1.2 eq.) is added to a solution of Michael adduct **21** (0.6 mmol; 1 eq.) in DMF (4 mL), at 0 °C. After stirring 1 h at room temperature, this reaction mixture is added, very slowly,[20], to a solution of PhSeCl (1.2 mmol; 2.0 eq.) in DMF (4 mL), −10 °C.[21]. After stirring 2 h at the same temperature, and then for 2 h at 0 °C, H_2O_2 (30 wt.% in water; 9 mmol; 15 eq.) is added, dropwise, at 0 °C. The solution is stirred for 30 min at this temperature, then quenched with a saturated aqueous solution of $NaHCO_3$ (3 mL), diluted with water (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layers are washed with water (10 mL), brine (5 mL), dried over $MgSO_4$, and then concentrated under reduced pressure. The residue is purified by flash chromatography on silica gel with the appropriate mixture of EtOAc and cyclohexane (*vide infra* for ratios).

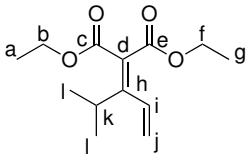
[20] carried out *via* a syringe pump (50 µL min^{-1}).

[21] The round-bottom flask containing phenylselenyl chloride in DMF is also previously dried, then filled with inert gas.

Diethyl (1-isopropylprop-2-en-1-ylidene)malonate

Procedure: using the general procedure,[22] diene **6j** is isolated after purification by flash chromatography on silica gel (05/95 EtOAc/cyclohexane).

Isolated yield: 36 %
Aspect: pale yellow liquid
Chemical formula: $C_{13}H_{20}O_4$
Mol. wt.: 240.30 g/mol



6j

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.42 (dd, $J_{i,j} = 17.7$ Hz, $J_{i,j'} = 11.7$ Hz, 1H, i), 5.31 (dd, $J_{j,i} = 17.7$ Hz, $J_{j,j'} = 1.5$ Hz, 1H, j), 5.27 (dd, $J_{j',i} = 11.7$ Hz, $J_{j',j} = 1.5$ Hz, 1H, j'), 4.17 (q, $J = 7.2$ Hz, 2H, b or f), 4.12 (q, $J = 7.2$ Hz, 2H, f or b), 3.32 (sep, $J_{k,l} = 6.9$ Hz, 1H, k), 1.22 (t, $J = 7.3$ Hz, 3H, a or g), 1.20 (t, $J = 7.3$ Hz, 3H, g or a), 1.03 (d, $J_{l,k} = 6.9$ Hz, 6H, l).

^{13}C NMR (75 MHz, $CDCl_3$): δ 166.2 (c or e), 165.0 (e or c), 161.3 (h), 132.6 (i), 124.2 (d), 120.9 (j), 61.1 (2 signals, b and f), 30.9 (k), 20.9 (l), 14.1 (a or g), 14.0 (g or a).

HRMS (APCI): m/z= 241.143 22; calcd. for $[M + H]^+$ ($C_{13}H_{21}O_4$): 241.143 44. **Fragment**: m/z= 195 $[M - OEt]^+$

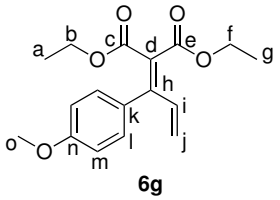
FT-IR (cm^{-1}): 2980, 2936, 2907, 2874, 1721 (C=O), 1615, 1580, 1466, 1447, 1418, 1387, 1366, 1337, 1298, 1285, 1269, 1219 (C-O), 1204 (C-O), 1160, 1096, 1061, 1025, 934, 868, 791, 733.

[22] Using 1.5 equivalents of NaH.

Diethyl [1-(4-methoxyphenyl)prop-2-en-1-ylidene]malonate

Procedure: using the general procedure, diene **6g** is isolated after purification by flash chromatography on silica gel (10/90 EtOAc/cyclohexane).

Isolated yield: 47 %
Aspect: pale yellow liquid
Chemical formula: $C_{17}H_{20}O_5$
Mol. wt.: 304.34 g/mol



6g

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 (dd, $J_{i,j} = 17.2$ Hz, $J_{i,j'} = 10.5$ Hz, 1H, i), 7.12 (m, 2H, l), 6.87 (m, 2H, m), 5.62 (dd, $J_{j',i} = 10.5$ Hz, $J_{j',j} = 1.4$ Hz, 1H, j'), 5.21 (dd, $J_{j,i} = 17.2$ Hz, $J_{j,j'} = 1.4$ Hz, 1H, j), 4.29 (q, $J = 7.1$ Hz, 2H, b or f), 3.96 (q, $J = 7.1$ Hz, 2H, f or b), 3.81 (s, 3H, o), 1.31 (t, $J = 7.1$ Hz, 3H, a or g), 0.99 (t, $J = 7.1$ Hz, 3H, g or a).

^{13}C NMR (125 MHz, $CDCl_3$): δ 166.2 (c or e), 164.5 (e or c), 159.9 (n), 153.2 (h), 135.4 (i), 130.5 (l), 128.8 (k), 127.5 (j), 125.5 (d), 113.5 (m), 61.4 (b or f), 61.1 (f or b), 55.4 (o), 14.2 (a or g), 13.8 (g or a).

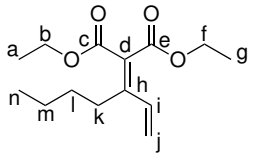
HRMS (APCI): m/z= 305.138 27; calcd. for $[M + H]^+$ ($C_{17}H_{21}O_5$): 305.138 35. **Fragment**: m/z= 259 $[M - OEt]^+$

FT-IR (cm^{-1}): 2980, 2964, 2937, 2907, 2837, 1717 (C=O), 1609, 1578, 1510, 1464, 1445, 1404, 1391, 1367, 1327, 1306, 1292, 1248 (C-O), 1215 (C-O), 1176, 1124, 1113, 1095, 1063, 1030, 939, 862, 835, 812, 797, 783.

Diethyl (1-butylprop-2-en-1-ylidene)malonate

Procedure: using the general procedure,[23] diene **6k** is isolated after purification by flash chromatography on silica gel (05/95 EtOAc/cyclohexane).

Isolated yield: 35 %
Aspect: yellow liquid
Chemical formula: $C_{14}H_{22}O_4$
Mol. wt.: 254.32 g/mol



6k

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.93 (dd, $J_{i,j} = 17.4$ Hz, $J_{i,j'} = 11.0$ Hz, 1H, i), 5.70 (d, $J_{j,i} = 17.4$ Hz, 1H, j), 5.50 (d, $J_{j',i} = 11.0$ Hz, 1H, j'), 4.23 (q, $J = 7.1$ Hz, 4H, b and f), 2.55 (m, 2H, k), 1.53-1.20 (comp, 4H, l and m), 1.28 (t, $J = 7.1$ Hz, 6H, a and g), 0.90 (t, $J_{n,m} = 7.1$ Hz, 3H, n).

^{13}C NMR (75 MHz, $CDCl_3$): δ 165.6 (c or e), 165.5 (e or c), 153.7 (h), 133.8 (i), 125.3 (d), 122.2 (j), 61.3 (b or f), 61.1 (f or b), 31.9 (l or m), 29.2 (k), 23.2 (m or l), 14.2,13.9 (three signals: a, g and n).

HRMS (APCI): m/z= 255.158 82; calcd. for $[M + H]^+$ ($C_{14}H_{23}O_4$): 255.159 09. **Fragment**: m/z= 209 $[M - OEt]^+$

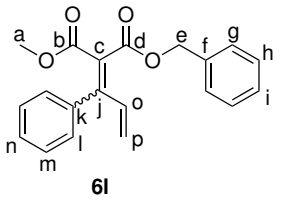
FT-IR (cm^{-1}): 2978, 2959, 2933, 2907, 2872, 1717 (C=O), 1620 (C=C), 1583, 1464, 1447, 1389, 1366, 1300, 1279, 1223 (C-O), 1198, 1115, 1096, 1061, 1030, 932, 868, 791, 733.

[23] Using 1.5 equivalents of NaH.

Benzyl methyl (1-phenylprop-2-en-1-ylidene)malonate

Procedure: using the general procedure,[24] a 1.1/1 d.r. is observed on the ^{1}H NMR spectrum of the crude mixture.[25] Pure diene **6l** is isolated as isomers mixture after purification by flash chromatography on silica gel (10/90 EtOAc/cyclohexane).

Isolated yield: 55 % (mixture of isomers)
Aspect: colourless liquid
Chemical formula: $C_{20}H_{18}O_4$
Mol. wt.: 322.35 g/mol



6l

^{1}H NMR and ^{13}C NMR spectra were obtained on pure isomers samples (separated by HPLC). Mass and IR spectra were recorded using a 1.1/1 d.r. sample.

^{1}H NMR A isomer (500 MHz, $CDCl_3$): δ 7.55 (dd, $J_{o,p}$ = 17.2 Hz, $J_{o,p'}$ = 10.6 Hz, 1H, o), 7.36-7.23 (comp, 6H, Ar), 7.17 (m, 2H, Ar), 7.04 (m, 2H, Ar) 5.65 (dd, $J_{p',o}$ = 10.6 Hz, $J_{p',p}$ = 1.3 Hz, 1H, p'), 5.17 (dd, $J_{p,o}$ = 17.2 Hz, $J_{p,p'}$ = 1.3 Hz, 1H, p), 4.88 (s, 2H, e), 3.80 (s, 3H, a).

^{13}C NMR A isomer (125 MHz, $CDCl_3$): δ 165.9 (d), 164.6 (b), 154.0 (j), 136.3 (k), 135.2 (f), 134.9 (o), 129.0,128.7,128.48,128.47,128.3,128.2,128.1 (p and Ar), 125.0 (c), 67.15 (e), 52.4 (a).

^{1}H NMR B isomer (500 MHz, $CDCl_3$): δ 7.46 (dd, $J_{o,p}$ = 17.1 Hz, $J_{o,p'}$ = 10.6 Hz, 1H, o), 7.40-7.30 (comp, 8H, Ar), 7.20-7.15 (comp, 2H, Ar), 7.09-6.99 (comp, 2H, Ar) 5.64 (dd, $J_{p',o}$ = 10.6 Hz, $J_{p',p}$ = 1.3 Hz, 1H, p'), 5.30 (s, 2H, e), 5.18 (dd, $J_{p,o}$ = 17.1 Hz, $J_{p,p'}$ = 1.3 Hz, 1H, p), 3.43 (s, 3H, a).

[24] Using 1.5 equivalents of NaH.
[25] Starting from a sample having a 1/1 d.r.

^{13}C NMR B isomer (125 MHz, $CDCl_3$): δ 166.1 (b), 164.2 (d), 154.2 (j), 136.4 (k), 135.7 (f), 134.9 (o), 128.9,128.7,128.6,128.4,128.3,128.14,128.09 (p and Ar), 67.09 (e), 52.1 (a). The carbon "c" could not be observed.

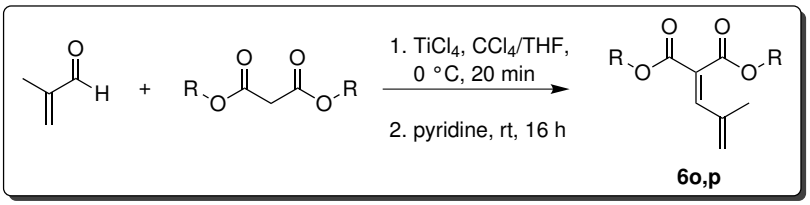
HRMS (APCI): m/z= 323.127 66; calcd. for $[M + H]^+$ ($C_{20}H_{19}O_4$): 323.127 79. **Fragments**: m/z= 291 $[M - OMe]^+$, 215 $[M - OBn]^+$

FT-IR (cm^{-1}): 3065, 3034, 2951, 1724 (C=O), 1612, 1580, 1574, 1493 (C=C Ar), 1454, 1443, 1435, 1325, 1283, 1270 (C-O), 1219 (C-O), 1188, 1159, 1124 (C-O), 1097, 1065, 1015, 1002, 750, 698.

6.2.5 3-Substituted bis-activated 1,3-dienes

6.2.5.1 3-Methyl bis-activated 1,3-dienes

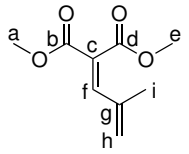
Reference: O. Rousseau, T. Delaunay, R. Robiette, *Synlett* **2014**, *25*, 519–522.



General procedure: in a dried round-bottom flask, under inert atmosphere, a solution of $TiCl_4$ (6 mmol; 4 eq.) in CCl_4 (1.5 mL) is added, dropwise, at 0 °C, in THF (12 mL). After stirring for 10 min at 0 °C, methacrolein (3 mmol; 2 eq.) and malonate (1.5 mmol; 1 eq.) are added, dropwise. After stirring for 20 min at 0 °C, pyridine (12 mmol; 8 eq.) is added, dropwise, at the same temperature. After stirring for 16 h at room temperature, the reaction mixture is diluted with water (10 mL) and extracted with Et_2O (3 x 10 mL). The combined organic layers are washed with an aqueous saturated solution of $NaHCO_3$ (10 mL), brine (5 mL), dried over Na_2SO_4, and then concentrated under reduced pressure.

Dimethyl (2-methylprop-2-en-1-ylidene)malonate
CAS Reg No. 63646-70-8

Isolated yield: 77 %[26]
Aspect: colourless liquid
Chemical formula: $C_9H_{12}O_4$
Mol. wt.: 184.19 g/mol



6o

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (s, 1H, f), 5.38 (s, 1H, h), 5.33 (s, 1H, h'), 3.76 (s, 3H, a or e), 3.72 (s, 3H, e or a), 1.80 (s, 3H, i).

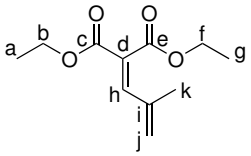
^{13}C NMR (125 MHz, $CDCl_3$): δ 167.0 (b or d), 164.8 (d or b), 144.5 (f), 139.3 (g), 127.9 (h), 124.6 (c), 52.6 (a or e), 52.5 (e or a), 18.8 (i).

The ^{1}H and ^{13}C NMR spectra are in agreement with literature; see: T. Matsuki, N. X. Hu, Y. Aso, T. Otsubo, F. Ogura, *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2105–2107.

Diethyl (2-methylprop-2-en-1-ylidene)malonate
CAS Reg No. 13654-27-8

Yield: 88 %[27]
Aspect: colourless liquid
Chemical formula: $C_{11}H_{16}O_4$
Mol. wt.: 212.24 g/mol

[26] In order to remove the remaining dimethyl malonate, a NaOH (10 wt.% aqueous solution) treatment is achieved during the workup.
[27] Calculated on the ^{1}H NMR spectrum of the crude mixture. Indeed, it remains 12 % of diethyl malonate on the crude.



6p

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 (s, 1H, h), 5.44 (m, 1H, j), 5.38 (m, 1H, j'), 4.29 (q, J = 7.2 Hz, 2H, b or f), 4.24 (q, J = 7.2 Hz, 2H, f or b), 1.90 (s, 3H, k) 1.34 (t, J = 7.0 Hz, 3H, a or g), 1.30 (t, J = 7.0 Hz, 3H, g or a).

^{13}C NMR (75 MHz, $CDCl_3$): δ 166.6 (c or e), 164.4 (e or c), 143.6 (h), 139.4 (i), 127.3 (j), 125.4 (d), 61.5 (b or f), 61.5 (f or b), 19.0 (k), 14.0 (a or g), 13.9 (g or a).

HRMS (APCI): m/z= 213.111 98; calcd. for $[M + H]^+$ ($C_{11}H_{17}O_4$): 213.112 14. **Fragment**: m/z= 167 $[M - OEt]^+$

FT-IR (cm^{-1}): 2991, 2982, 2966, 2935, 1726 (C=O), 1713 (C=O), 1622, 1601, 1445, 1369, 1234, 1205, 1067, 1030.

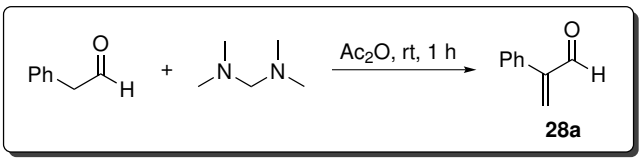
6.2.5.2 3-phenyl bis-activated 1,3-dienes

Reference: O. Rousseau, T. Delaunay, R. Robiette, *Synlett* **2014**, *25*, 519–522.

Atropaldehyde

CAS Reg No. 4432-63-7

Reference: C. Nsanzumuhire, J.-L. Clément, O. Ouari, H. Karoui, J.-P. Finet, P. Tordo, *Tetrahedron Letters* **2004**, *45*, 6385–6389.

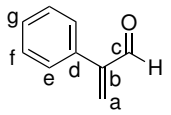


28a

Procedure: in a dried round-bottom flask, under inert atmosphere, Ac_2O (15 mmol; 5.0 eq.) is added, dropwise, to a mixture of phenylacetaldehyde (3 mmol; 1 eq.) and N,N,N',N'-tetramethyldiaminomethane (9 mmol; 3.0 eq.),

at 0 °C. After stirring for 1 h at room temperature, the mixture is diluted, at 0 °C, with ice water (4 mL), and extracted with Et_2O (3 x 4 mL). The combined organic layers are washed vigorously with a 1 M aqueous solution of HCl (5 mL), a saturated aqueous solution of $NaHCO_3$ (5 mL), brine (5 mL), dried over $MgSO_4$, and then concentrated under reduced pressure.

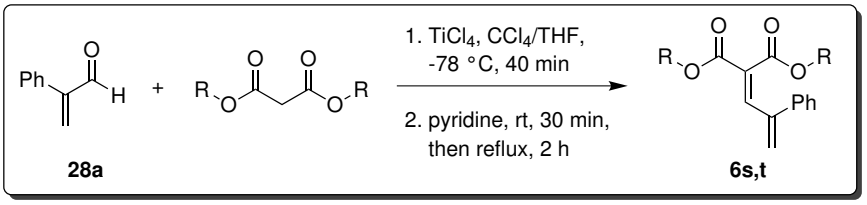
Isolated yield: 51 %
Aspect: colourless liquid
Chemical formula: C_9H_8O
Mol. wt.: 132.16 g/mol



28a

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.83 (s, 1H, c), 7.51-7.35 (comp, 5H, Ar), 6.65 (s, 1H, a), 6.20 (s, 1H, a').

The ^{1}H NMR spectrum is in agreement with literature; see: C. Nsanzumuhire, J.-L. Clément, O. Ouari, H. Karoui, J.-P. Finet, P. Tordo, *Tetrahedron Letters* **2004**, *45*, 6385–6389.



28a **6s,t**

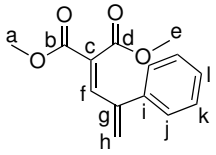
General procedure: in a dried round-bottom flask, under inert atmosphere, a solution of $TiCl_4$ (3 mmol; 4 eq.) in CCl_4 (1.0 mL) is added, dropwise, at 0 °C, in THF (6 mL). After stirring for 10 min at 0 °C, a solution of atropaldehyde **28a** (*vide infra*; 1.5 mmol; 2.0 eq.) in THF (0.2 mL), as well as malonate derivative (0.8 mmol; 1 eq.) are added, dropwise, at −78 °C. After stirring 40 min at the same temperature, pyridine (7 mmol; 8 eq.) is added, dropwise, at −78 °C. The cooling bath is then removed. When the reaction mixture reached room temperature, it is heated at reflux for 2 h. After cooling, the reaction mixture is diluted with water (5 mL) and extracted with Et_2O (3 x 5 mL). The combined organic layers are washed with a saturated aqueous

solution of $NaHCO_3$ (5 mL), brine (5 mL), dried over Na_2SO_4, and then concentrated under reduced pressure. The residue is purified by flash chromatography on silica gel with the appropriate mixture of EtOAc and cyclohexane (*vide infra* for ratios).

Dimethyl (2-phenylprop-2-en-1-ylidene)malonate

Procedure: using the general procedure, diene **6s** is isolated after purification by flash chromatography on silica gel (05/95 to 10/90 EtOAc/cyclohexane).

Isolated yield: 34 %
Aspect: colourless liquid
Chemical formula: $C_{14}H_{14}O_4$
Mol. wt.: 246.26 g/mol



6s

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (s, 1H, f), 7.38-7.27 (comp, 5H, Ar), 5.65 (s, 2H, h), 3.82 (s, 3H, a or e), 3.34 (s, 3H, e or a).

^{13}C NMR (125 MHz, $CDCl_3$): δ 165.8 (b or d), 164.6 (d or b), 144.25 (g), 144.19 (f), 138.2 (i), 128.5 (j or k), 128.4 (l), 127.8 (c), 127.5 (k or j), 123.8 (h), 52.8 (a or e), 52.2 (e or a).

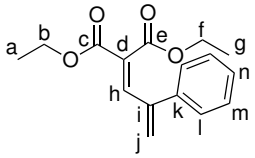
HRMS (APCI): *m/z*= 247.096 80; calcd. for $[M + H]^+$ ($C_{14}H_{15}O_4$): 247.096 49. **Fragment**: *m/z*= 216 $[M - OMe]^+$

FT-IR (cm^{-1}): 3028, 2951, 1728 (C=O), 1713 (C=O), 1620, 1603, 1495, 1435, 1364, 1315, 1300, 1244 (C-O), 1213 (C-O), 1184, 1067, 1005, 916, 843, 777, 752, 704.

Diethyl (2-phenylprop-2-en-1-ylidene)malonate

Procedure: using the general procedure, diene **6t** is isolated after purification by flash chromatography on silica gel (02/98 to 10/90 EtOAc/cyclohexane).

Isolated yield: 16 %
Aspect: colourless liquid
Chemical formula: $C_{16}H_{18}O_4$
Mol. wt.: 274.31 g/mol



6t

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 (s, 1H, h), 7.37-7.28 (comp, 5H, Ar), 5.63 (s, 2H, j), 4.28 (q, J = 7.1 Hz, 2H, b or f), 3.81 (q, J = 7.1 Hz, 2H, f or b), 1.31 (t, J = 7.1 Hz, 3H, a or g), 1.12 (t, J = 7.1 Hz, 3H, g or a).

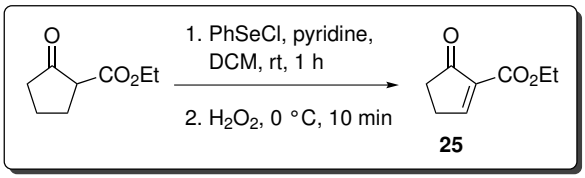
^{13}C NMR (125 MHz, $CDCl_3$): δ 165.4 (c or e), 164.2 (e or c), 144.2 (i), 143.2 (h), 138.3 (k), 128.41 (l or m), 128.36 (n), 128.2 (d), 127.5 (m or l), 122.8 (j), 61.8 (b or f), 61.4 (f or b), 14.3 (a or g), 13.8 (g or a).

HRMS (APCI): m/z= 275.127 41; calcd. for $[M + H]^+$ ($C_{16}H_{19}O_4$): 275.127 79. **Fragment**: m/z= 229 $[M - OEt]^+$

FT-IR (cm^{-1}): 2982, 2937, 2903, 1732 (C=O), 1724 (C=O) 1622, 1495, 1464, 1445, 1393, 1375, 1350, 1298, 1277, 1240 (C-O), 1215 (C-O), 1171, 1159, 1113, 1096, 1065, 1026, 916, 864, 777, 700.

6.2.6 Cyclic diene

Ethyl 5-oxocyclopent-1-ene-1-carboxylate
CAS Reg No. 57020-97-0

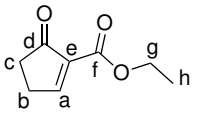


25

Procedure:[28] in a dried round-bottom flask, under inert atmosphere, pyridine (5 mmol; 1.7 eq.) is added, dropwise, to a solution of PhSeCl (3.3 mmol; 1.1 eq.) in DCM (15 mL), at 0 °C. After stirring for 15 min at the same temperature, a solution of ethyl 2-oxocyclopentanecarboxylate (0.44 mL; 3 mmol; 1 eq.) in DCM (8 mL) is added, dropwise, at 0 °C. After stirring for 1 h at room temperature, the reaction mixture is washed with a 1 M aqueous solution of HCl (5 mL). The organic layer is next treated with H_2O_2 (30 wt.%; 9 mmol; 3.0 eq.), at 0 °C. After stirring vigorously for 10 min at the same temperature, the mixture is washed with a saturated aqueous solution of $NaHCO_3$ (10 mL). The aqueous layer is extracted with DCM (2 x 10 mL). The combined organic layers are washed with brine (10 mL), dried over Na_2SO_4, and then concentrated under reduced pressure.

Because of instability purposes, the crude compound **25** is stored in the freezer and rapidly used in the next step (within 16 h).

Isolated yield: quantitative
Aspect: pale yellow liquid
Chemical formula: $C_8H_{10}O_3$
Mol. wt.: 154.16 g/mol



25

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.39 (dd, $J_{a,b}$ = 2.7, 2.7 Hz, 1H, a),

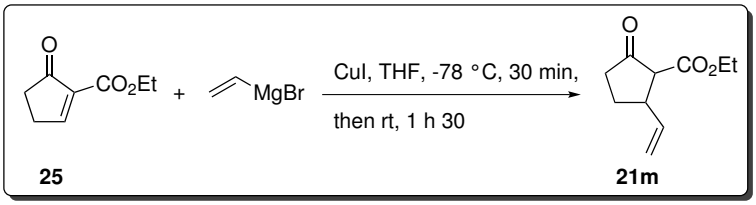
[28] From: M.-T. Hsieh, H.-J. Liu, T. W. Ly, K.-S. Shia, *Org. Biomol. Chem.* **2009**, *7*, 3285–3290.

4.29 (q, $J_{g,h}$ = 7.1 Hz, 2H, g), 2.75-2.71 (comp, 2H, b or c), 2.56-2.53 (comp, 2H, c or b), 1.33 (t, $J_{h,g}$ = 7.1 Hz, 3H, h).

Because of the compound instability, no further analyses were carried out. Whereas, the ^{1}H NMR spectrum is in agreement with the literature; see: S. Piovesana, D. M. S. Schietroma, L. G. Tulli, M. R. Monaco, M. Bella, *Chem. Commun.* **2010**, *46*, 5160–5162.

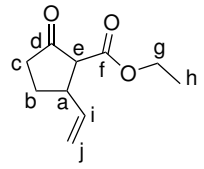
Ethyl 2-oxo-5-vinylcyclopentanecarboxylate

CAS Reg No. 67695-10-7



Procedure: in a dried round-bottom flask, under inert atmosphere, vinylmagnesiumbromide (7.5 mmol; 2.5 eq.) is added, dropwise, to a suspension of CuI (3.3 mmol; 1.1 eq.) in THF (15 mL), at 0 °C. After stirring for 45 min at the same temperature, a solution of compound **25** (0.46 g; 3 mmol; 1 eq.) in THF (10 mL) is added, dropwise, at −78 °C. After stirring for 30 min at the same temperature and then 1 h 30 at room temperature, the reaction is quenched with a saturated aqueous solution of NH_4Cl (10 mL). The aqueous layer is then extracted with Et_2O (3 x 10 mL). The combined organic layers are washed with brine (10 mL), dried over $MgSO_4$, and then concentrated under reduced pressure. Pure Michael adduct **21m** is isolated after purification by flash chromatography on silica gel (07/93 EtOAc/cyclohexane).

Isolated yield: 30 %
Aspect: colourless liquid
Chemical formula: $C_{10}H_{14}O_3$
Mol. wt.: 182.22 g/mol



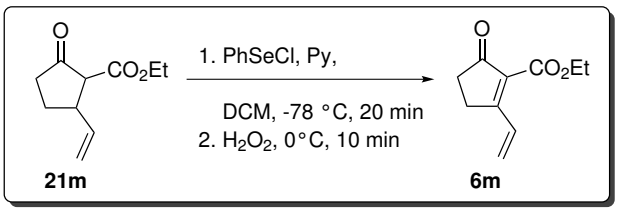
21m

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.83 (ddd, $J_{i,j}$ = 17.1 Hz, $J_{i,j'}$ = 10.3 Hz, $J_{i,a}$ = 6.8 Hz, 1H, i), 5.15 (d, $J_{j,i}$ = 17.2 Hz, 1H, j), 5.09 (d, $J_{j',i}$ = 10.4 Hz, 1H, j'), 4.21 (q, $J_{g,h}$ = 7.1 Hz, 2H, g), 3.21 (m, 1H, a), 2.99 (d, $J_{e,a}$ = 11.5 Hz, 1H, e), 2.56-2.13 (comp, 3H, b and c), 1.69 (m, 1H, b'), 1.27 (t, $J_{h,g}$ = 7.1 Hz, 3H, h).

HRMS (APCI): m/z= 183.101 56; calcd. for $[M + H]^+$ ($C_{10}H_{15}O_3$): 183.101 57

^{1}H NMR and mass spectra are in agreement with literature; see: B. B. Snider, J. J. Patricia, S. A. Kates, *J. Org. Chem.* **1988**, *53*, 2137–2143.

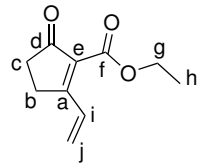
Ethyl 5-oxo-2-vinylcyclopent-1-ene-1-carboxylate
CAS Reg No. 918150-71-7



Procedure: in a dried round-bottom flask, under inert atmosphere, pyridine (1.49 mmol; 1.7 eq.) is added to a solution of PhSeCl (0.96 mmol; 1.1 eq.) in DCM (5 mL), at 0 °C. After stirring 20 min at the same temperature, a solution of compound **21m** (0.16 g; 0.88 mmol; 1.0 eq.) in DCM (3 mL) is added, dropwise, at −78 °C. After stirring 20 min at the same temperature, the reaction is quenched with an aqueous solution of HCl 1 M. The organic layer is then treated with H_2O_2 (2.64 mmol; 3 eq.), for 10 min at 0 °C. The reaction mixture is then quenched with a saturated aqueous solution of $NaHCO_3$ (2 mL). The aqueous layer is extracted with DCM (2 x 5 mL). The combined organic layers are washed with brine (5 mL), dried over Na_2SO_4, and then concentrated

under reduced pressure. Pure diene **6m** is isolated after purification by flash chromatography on silica gel (15/85 EtOAc/cyclohexane).

Isolated yield: 5 %
Aspect: colourless liquid
Chemical formula: $C_{10}H_{12}O_3$
Mol. wt.: 180.20 g/mol



6m

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43 (dd, $J_{i,j} = 17.6$ Hz, $J_{i,j'} = 10.7$ Hz, 1H, i), 6.00 (d, $J_{j,i} = 17.6$ Hz, 1H, j), 5.75 (d, $J_{j',i} = 10.8$ Hz, 1H, j'), 4.34 (q, $J_{g,h} = 7.1$ Hz, 2H, g), 2.83 (m, 2H, b), 2.54 (m, 2H, c), 1.35 (t, $J_{h,g} = 7.1$ Hz, 3H, h).

^{13}C NMR (75 MHz, $CDCl_3$): δ 203.7 (d), 173.5 (a), 163.0 (f), 131.7 (i), 126.2 (j), 61.3 (g), 34.5 (c), 25.6 (b), 14.4 (h). The carbon "e" could not be observed.

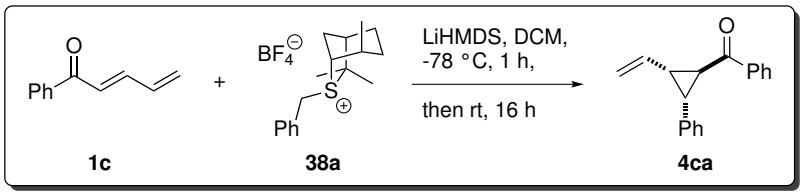
HRMS (APCI): m/z= 181.085 85; calcd. for $[M + H]^+$ ($C_{10}H_{13}O_3$): 181.085 92

FT-IR (cm^{-1}): 1734 (C=O), 1709 (C=O), 1628, 1576, 1437, 1373, 1350, 1298, 1256, 1232, 1175, 1032.

6.2.7 Vinylcyclopropanes syntheses

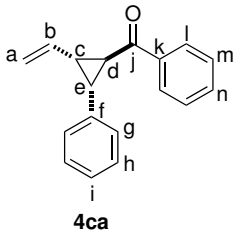
6.2.7.1 Mono-activated 1,3-diene

Phenyl[(1*R,2*R**,3*S**)-2-phenyl-3-vinylcyclopropyl]methanone**
CAS Reg No. 27557-57-9



Procedure: in a dried round-bottom flask, under inert atmosphere, LiHMDS (1 M in THF; 0.33 mmol; 1.1 eq.) is added, dropwise, to a suspension of sulfonium salt **38a** (0.33 mmol; 1.1 eq.) in DCM (2 mL), at −78 °C. After stirring for 15 min at the same temperature, a solution of diene **1c** (47 mg; 0.30 mmol; 1 eq.) in DCM (1 mL) is added, dropwise. After stirring for 1 h at −78 °C and then 16 h at room temperature, the reaction is quenched with a 1 M aqueous solution of HCl (2 mL). The aqueous layer is then extracted with DCM (2 mL). The combined organic layers are washed with water (2 mL), brine (2 mL), dried over $MgSO_4$, and then concentrated under reduced pressure. Vinylcyclopropane **4ca** is isolated after purification by flash chromatography on silica gel (10/90 EtOAc/cyclohexane).

Isolated yield: 9 %
Aspect: colourless liquid
Chemical formula: $C_{18}H_{16}O$
Mol. wt.: 248.32 g/mol



^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (m, 2H, l), 7.61 (m, 1H, n), 7.55 (m, 2H, Ar), 7.41-7.16 (comp, 5H, Ar), 5.36-5.27 (comp, 2H, a and b), 5.04 (m,

1H, a'), 3.24 (dd, $J_{e,c} = 8.3\,\text{Hz}$, $J_{e,d} = 5.5\,\text{Hz}$, 1H, e), 3.23 (d, $J_{d,e} = 5.5\,\text{Hz}$, 1H, d), 2.67 (dd, $J_{c,b} = 14.0\,\text{Hz}$, $J_{c,e} = 8.2\,\text{Hz}$, 1H, c).

^{13}C NMR (75 MHz, $CDCl_3$): δ 198.2 (j), 137.9 (f or k), 136.6 (k or f), 134.8 (b), 133.2 (n), 129.2,128.8,128.5 (g, h and m), 128.3 (l), 127.0 (i), 117.3 (a), 36.0 (c), 34.8 (e), 32.0 (d).

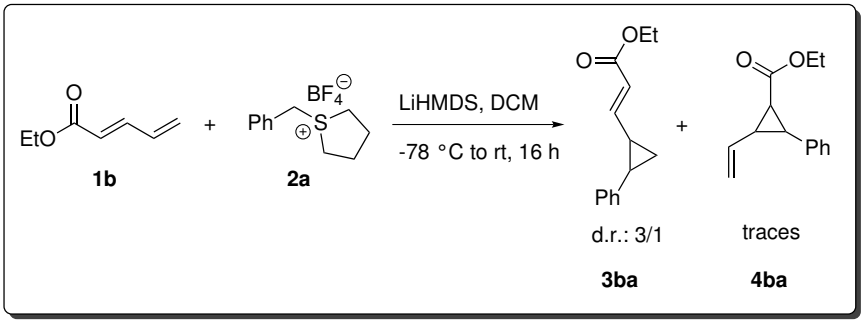
HRMS (APCI): m/z= 249.127 19; calcd. for $[M + H]^+$ ($C_{18}H_{17}O$): 249.127 39

FT-IR (cm^{-1}): 3057, 2924, 1666 (C=O), 1636 (C=C), 1597, 1580, 1448, 1404, 1279, 1217, 1034, 1016, 737, 698.

Specific rotation: $[\alpha]_D^{26} = -152°$ (c = 0.33, CH_2Cl_2)

Enantiomeric excess: not calculated[29]

Ethyl (2*E*)-3-(2-phenylcyclopropyl)acrylate

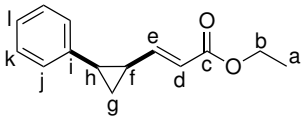


Procedure: in a dried round-bottom flask, under inert atmosphere, LiHMDS (1 M in THF; 3.3 mmol; 1.1 eq.) is added, dropwise, to a suspension of sulfonium salt **2a** (3.3 mmol; 1.1 eq.) in DCM (10 mL), at −78 °C. After stirring for 15 min at the same temperature, a solution of diene **1b** (0.38 g; 3.0 mmol; 1 eq.) in DCM (4 mL) is added, dropwise. After stirring 16 h (the cooling bath recovering slowly to room temperature), the reaction is quenched with a 1 M aqueous solution of HCl (2 mL). The organic layer is washed with water (5 mL), brine (5 mL), dried over $MgSO_4$, and then concentrated

[29]The racemic compound have not been synthesized, the two enantiomers retention times are not know. Thereby, no chiral HPLC of the enantioenriched product was performed.

under reduced pressure. A 3/1 d.r. of vinylcyclopropane **3ba** is observed on the ^{1}H NMR spectrum of the crude mixture. The **3ba** minor diastereoisomer is isolated after purification by flash chromatography on silica gel (04/96 EtOAc/cyclohexane) in 12 % yield.

Isolated yield: 12 % of minor diastereoisomer (contains impurities)
Aspect: colourless liquid
Chemical formula: $C_{14}H_{16}O_2$
Mol. wt.: 216.28 g/mol



3ba *cis*

The analyses below relate to the minor diastereoisomer (assuming *cis*).[30]

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.00 (comp, 5H, Ar), 6.60 (dd, $J_{e,d}$ = 15.4 Hz, $J_{e,f}$ = 9.9 Hz, 1H, e), 5.90 (d, $J_{d,e}$ = 15.4 Hz, 1H, d), 4.20 (q, $J_{b,a}$ = 7.1 Hz, 2H, b), 1.86 (m, 1H, f), 1.46 (m, 1H, g), 1.32 (m, 1H, g'), 1.30 (t, $J_{a,b}$ = 7.1 Hz, 3H, a), 0.94 (m, 1H, h).

^{13}C NMR (75 MHz, $CDCl_3$): δ 166.8 (c), 151.7 (e), 142.7 (i), 119.0 (d), 60.3 (b), 21.9 (f), 17.9 (g), 14.4 (a), 14.1 (h). Because of the compound purity, aromatic carbons j, k and l could not be attributed to their corresponding signals.

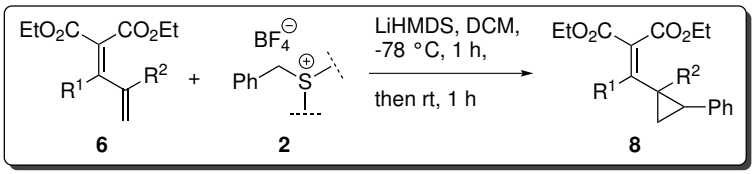
HRMS (APCI): *m/z*= 217.122 35; calcd. for $[M + H]^+$ ($C_{14}H_{17}O_2$): 217.122 31. **Fragment**: *m/z*= 171 $[M - OEt]^+$

d.r.: 3/1

Because of the compound purity, the infrared absorption is not carried out.

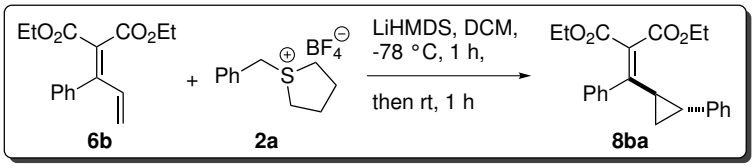
[30]The purity of isomer **3ba *trans*** did not allow to describe this isomer.

6.2.7.2 Bis-activated 1,3-dienes



General procedure:[31] in a dried round-bottom flask, under inert atmosphere, LiHMDS (1 M in THF; 0.33 mmol; 1.1 eq.) is added, dropwise, to a mixture of sulfonium salt **2** (0.33 mmol; 1.1 eq.) and diene **6** (0.3 mmol; 1 eq.), in DCM (3 mL), at −78 °C. After stirring for 1 h at the same temperature and then 1 h at room temperature, the reaction is quenched with a 1 M aqueous solution of HCl (1 mL) after dilution with DCM (2 mL) and water (2 mL). The aqueous layer is extracted with DCM (2 x 2 mL). The combined organic layers are washed with water (2 mL), brine (2 mL), dried over $MgSO_4$, and then concentrated under reduced pressure. Vinylcyclopropane **8** is isolated after purification by flash chromatography on silica gel with the appropriate mixture of EtOAc and cyclohexane (*vide infra* for ratios).[32]

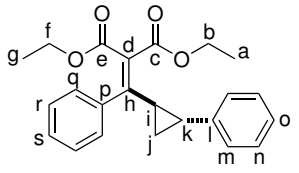
Diethyl phenyl[(1*R,2*R**)-2-phenylcyclopropyl]methylenemalonate**



Procedure: using the general procedure (0.6 mmol of diene **6b**), vinylcyclopropane **8ba** is isolated after purification by flash chromatography on silica gel (05/95 EtOAc/cyclohexane).

Isolated yield: 26 %
Aspect: colourless liquid
Chemical formula: $C_{23}H_{24}O_4$
Mol. wt.: 364.43 g/mol

[31] For compound **8ba**, the reaction is performed on double scale (0.6 mmol of diene).
[32] For compound **8pa**, the yield is determined on the crude using Ph_2MeSiH as an internal standard. No further purification is carried out.



8ba
(+/-)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39-7.32 (comp, 3H, Ar), 7.26 (m, 2H, Ar), 7.17 (t, J = 7.4 Hz, 1H, o or s), 7.15-7.09 (comp, 4H, Ar), 4.26-4.18 (comp, 2H, b or f), 3.86 (q, J = 7.1 Hz, 2H, f or b), 3.09 (ddd, $J_{i,j}$ = 8.7 Hz, $J_{i,j'}$ = 5.8 Hz, $J_{i,k}$ = 4.7 Hz, 1H, i), 2.00 (ddd, $J_{k,j'}$ = 9.1 Hz, $J_{k,j}$ = 6.0 Hz, $J_{k,i}$ = 4.8 Hz, 1H, k), 1.32 (ddd, $J_{j,i}$ = 8.7 Hz, $J_{j,k}$ = 6.2 Hz, $J_{j,j'}$ = 5.0 Hz, 1H, j), 1.22 (t, J = 7.1 Hz, 3H, a or g), 1.10 (ddd, $J_{j',k}$ = 9.1 Hz, $J_{j',i}$ = 5.8 Hz, $J_{j',j}$ = 5.1 Hz, 1H, j'), 0.91 (t, J = 7.1 Hz, 3H, g or a).

^{13}C NMR (125 MHz, $CDCl_3$): δ 165.6 (c or e), 165.3 (e or c), 159.3 (h), 140.9 (l), 135.3 (p), 128.6,128.5,127.9,126.5 (m, n, q and r), 128.2 (o or s), 126.3 (s or o), 61.3 (b or f), 60.9 (f or b), 26.6 (i), 24.8 (k), 16.1 (j), 14.2 (a or g), 13.8 (g or a). The carbon "d" could not be observed.

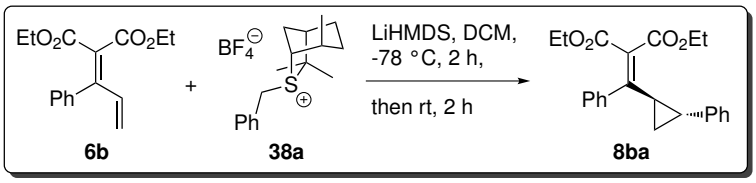
HRMS (APCI): m/z= 365.174 70; calcd. for $[M + H]^+$ ($C_{23}H_{25}O_4$): 365.174 74. **Fragment**: m/z= 319 $[M - OEt]^+$

FT-IR (cm^{-1}): 2978, 1718 (C=O), 1608, 1593, 1495, 1459, 1444, 1368, 1322, 1223 (C-O), 1178, 1099, 1074, 1054, 1028, 766, 750, 700.

d.r.: >98/2

Enantiomeric excess: racemic mixture (retention times: 1324 sec and 1416 sec | CHIRALPAK IC; IPA/*i*-Hex 05/95; 1 mL min^{-1})

Diethyl phenyl[(1*R*,2*R*)-2-phenylcyclopropyl]methylenemalonate



Procedure: using the general procedure, vinylcyclopropane **8ba** is isolated after purification by flash chromatography on silica gel (05/95 EtOAc/cyclohexane).

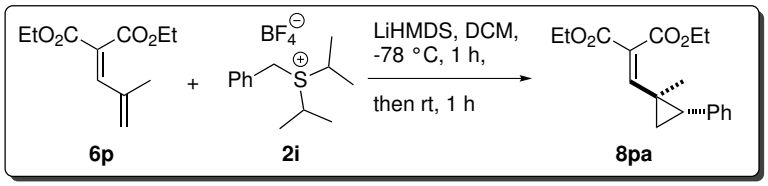
Isolated yield: 22 %
Aspect: colourless liquid
Chemical formula: $C_{23}H_{24}O_4$
Mol. wt.: 364.43 g/mol

For descriptions of ^{1}H NMR, ^{13}C NMR, Mass, and IR spectra, see the racemic compound (page 235).

d.r.: >98/2

Enantiomeric excess: >99 % (retention time: 1479 sec | CHIRALPAK IC; IPA/*i*-Hex 05/95; 1 mL min^{-1})

Diethyl [(1*S*,2*R*)-1-methyl-2-phenylcyclopropyl]methylenemalonate[33]

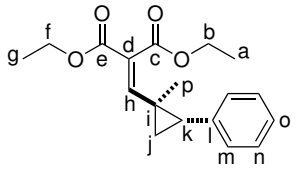


Procedure: using the general procedure, vinylcyclopropane **8pa** is isolated after purification by flash chromatography on silica gel (05/95 EtOAc/cyclohex-

[33]The stereochemistry is determined by correlation with compound **8ba**.

ane). A 14/1 d.r. is noted. [34]

Isolated yield: 31 %
Aspect: colourless liquid
Chemical formula: $C_{18}H_{22}O_4$
Mol. wt.: 302.36 g/mol



8pa
(+/-)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.14 (comp, 5H, Ar), 6.66 (s, 1H, h), 4.27 (q, J = 7.1 Hz, 2H, b or f), 4.24 (q, J = 7.1 Hz, 2H, f or b), 2.49 (m, 1H, k), 1.39 (m, 1H, j), 1.32 (t, J = 7.1 Hz, 3H, a or g), 1.31 (m, 1H, j'), 1.29 (t, J = 7.1 Hz, 3H, g or a), 0.90 (s, 3H, p).

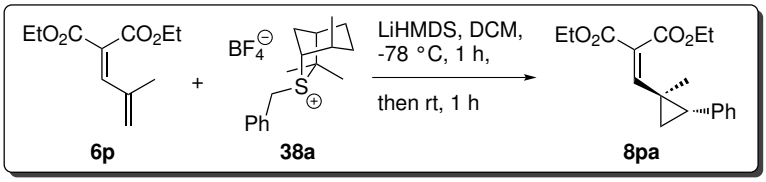
^{13}C NMR (75 MHz, $CDCl_3$): δ 167.0 (c or e), 164.6 (e or c), 154.0 (h), 136.9 (l), 129.5 (m), 128.3 (n), 126.8 (o), 125.4 (d), 61.53 (b or f), 61.48 (f or b), 32.8 (k), 24.9 (i), 21.7 (j), 16.1 (p), 14.3 (a or g), 14.1 (g or a).

HRMS (APCI): m/z= 303.159 00; calcd. for $[M + H]^+$ ($C_{18}H_{23}O_4$): 303.159 09. **Fragment**: m/z= 257 $[M - OEt]^+$

FT-IR (cm^{-1}): 1724 (C=O), 1630, 1497, 1462, 1448, 1393, 1381, 1367, 1296, 1261 (C-O), 1215 (C-O), 1200, 1094, 1072, 1051, 1028, 951, 700.

[34] Calculated on the ^{1}H NMR spectrum of the crude mixture.

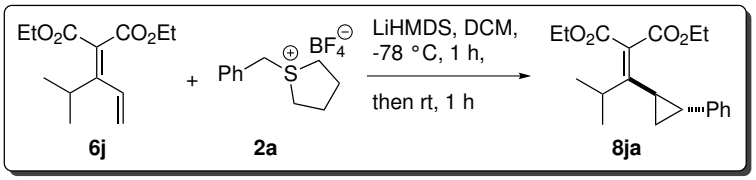
Diethyl [(1S,2R)-1-methyl-2-phenylcyclopropyl]methylenemalonate[35]



Yield: 24 %[36]
Aspect: colourless liquid
Chemical formula: $C_{18}H_{22}O_4$
Mol. wt.: 302.36 g/mol

For descriptions of ^{1}H NMR, ^{13}C NMR, Mass, and IR spectra, see the racemic compound (page 237).

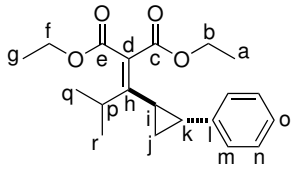
Diethyl 2-methyl-1-[(1*R,2*R**)-2-phenylcyclopropyl]propylidene malonate**



Procedure: using the general procedure (0.4 mmol of diene **6j**), vinylcyclopropane **8ja** is isolated as mixture with diene starting material after purification by flash chromatography on silica gel (05/95 EtOAc/cyclohexane).

Yield: 16 % (mixture with diene starting material)
Aspect: colourless liquid (mixture with diene starting material)
Chemical formula: $C_{20}H_{26}O_4$
Mol. wt.: 330.42 g/mol

[35]The stereochemistry is determined by correlation with compound **8ba**.
[36]The yield is determined on the ^{1}H NMR spectrum of the crude mixture using Ph_2MeSiH as an internal standard. No further purification is carried out.



8ja
(+/-)

Analyses below were carried out on mixture of desired product and diene starting material.

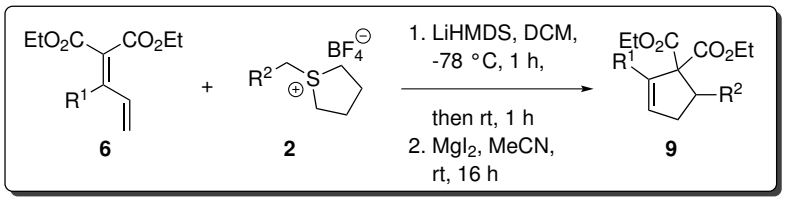
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27 (m, 2H, Ar), 7.16 (m, 1H, Ar), 7.07 (m, 2H, Ar), 4.27-4.13 (comp, 4H, b and f) 4.13-4.01 (comp, 1H, i or j or j' or k), 3.24 (qq, $J_{p,q} = 6.9$ Hz, $J_{p,r} = 6.9$ Hz 1H, p), 2.08 (m, 1H, j or j' or k or i), 1.96 (m, 1H, j' or k or i or j), 1.32-1.16 (comp, 7H, a, g and [k or i or j or j']), 1.13-1.06 (comp, 6H, q and r).

HRMS (APCI): m/z= 331.190 19; calcd. for $[M + H]^+$ ($C_{20}H_{27}O_4$): 331.190 39

Because of the compound purity, no further analyses were carried out.

6.2.8 Formal (4+1) annulation reactions[37]

Reference: O. Rousseau, T. Delaunay, G. Dequirez, T. Trieu-Van, K. Robeyns, R. Robiette, *Chem. Eur. J.* **2015**, *21*, 12899–12902.



General procedure: in a dried round-bottom flask, under inert atmosphere, LiHMDS (1 M in THF; 1.1 eq.) is added, dropwise, to a mixture of diene **6** (100 mg; 1 eq.) and sulfonium salt **2** (1.1 eq.), in DCM (4 mL), at −78 °C. After stirring for 1 h at the same temperature and then 1 h at room

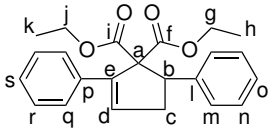
[37]The yield was also calculated for most of cyclopentenes by analyses of the ^{1}H NMR spectrum of the crude mixture, using Ph_2MeSiH as an internal standard. Being very closed of the isolated yield, they are not mentioned, excepted for **9pa** where no purification was carried out.

temperature, a solution of MgI_2 (1.2 eq.)[38] in MeCN (1 mL) is added, at room temperature. After stirring for 16 h at the same temperature, the reaction mixture is quenched with a 1 M aqueous solution of HCl (1 mL) after dilution with DCM (2 mL) and water (2 mL). The aqueous layer is washed with DCM (2 x 5 mL). The combined organic layers are washed with an aqueous solution of NaOH (10 wt.%; 5 mL), water (5 mL), brine (5 mL), dried over $MgSO_4$, and then concentrated under reduced pressure. The residue is purified by flash chromatography on silica gel with the appropriate mixture of EtOAc and cyclohexane (*vide infra* for ratios) to give racemic mixture of cyclopentene **9** in a moderate to good yield.

Diethyl 2,5-diphenylcyclopent-2-ene-1,1-dicarboxylate[39]

Procedure: using the general procedure, cyclopentene **9ba** is isolated after purification by flash chromatography on silica gel (05/95 EtOAc/*n*-hexane).

Isolated yield: 65 %
Aspect: colourless liquid
Chemical formula: $C_{23}H_{24}O_4$
Mol. wt.: 364.43 g/mol



9ba

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.17 (comp, 10H, Ar), 6.34 (dd, $J_{d,c} = 2.6$ Hz, $J_{d,c'} = 2.6$ Hz, 1H, d), 4.61 (dd, $J_{b,c} = 7.9$ Hz, $J_{b,c'} = 7.9$ Hz, 1H, b), 4.11-3.97 (comp, 2H, g), 3.75 (dq, $J_{j,j'} = 10.7$ Hz, $J_{j,k} = 7.1$ Hz, 1H, j), 3.54 (dq, $J_{j',j} = 10.7$ Hz, $J_{j',k} = 7.2$ Hz, 1H, j'), 3.00 (ddd, $J_{c,c'} = 17.2$ Hz, $J_{c,b} = 8.1$ Hz, $J_{c,d} = 2.7$ Hz, 1H, c), 2.92 (ddd, $J_{c',c} = 17.2$ Hz, $J_{c',b} = 7.7$ Hz, $J_{c',d} = 2.6$ Hz, 1H, c'), 0.96 (t, $J_{h,g} = 7.1$ Hz, 3H, h), 0.80 (t, $J_{k,j} = 7.2$ Hz, 3H, k).

^{13}C NMR (75 MHz, $CDCl_3$): δ 170.5 (f), 169.1 (i), 142.1 (e), 140.3 (l), 136.3 (p), 134.4 (d), 128.9 (m), 128.14,128.05,127.8 (n, q and r), 127.4 (o or

[38] In order to have a homogeneous solution, MgI_2 is dissolved *via* ultrasonic agitation for few seconds.
[39] Carried out by Trieu-Van Tran.

s), 127.3 (s or o), 73.7 (a), 61.6 (g), 61.1 (j), 52.3 (b), 37.8 (c), 13.8 (h), 13.6 (k).

HRMS (APCI): m/z= 365.174 59; calcd. for $[M + H]^+$ ($C_{23}H_{25}O_4$): 365.174 74. **Fragment**: m/z= 319 $[M - OEt]^+$

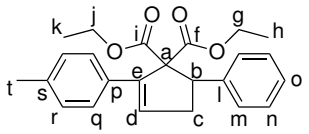
FT-IR (cm^{-1}): 3053, 3028, 2982, 2961, 2924, 2901, 1720 (C=O), 1603, 1495 (C=C Ar), 1454, 1445, 1366, 1300, 1259 (C-O), 1213, 1200, 1159, 1095, 1080, 1047, 700.

Enantiomeric excess: racemic mixture (retention times: 409 sec and 436 sec | CHIRALPAK IB; EtOH/*i*-Hex 05/95; 0.7 mL min^{-1})

Diethyl 2-(4-methylphenyl)-5-phenylcyclopent-2-ene-1,1-dicarboxylate

Procedure: using the general procedure, cyclopentene **9ca** is isolated after purification by flash chromatography on silica gel (04/96 EtOAc/cyclohexane).

Isolated yield: 45 %
Aspect: colourless liquid
Chemical formula: $C_{24}H_{26}O_4$
Mol. wt.: 378.46 g/mol



9ca

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 (m, 2H, m), 7.28-7.16 (comp, 5H, Ar), 7.05 (d, J = 8.0 Hz, 2H, r), 6.29 (dd, $J_{d,c}$ = 2.5 Hz, $J_{d,c'}$ = 2.5 Hz, 1H, d), 4.57 (dd, $J_{b,c}$ = 7.8 Hz, $J_{b,c'}$ = 7.8 Hz, 1H, b) 4.11-4.00 (comp, 2H, g), 3.73 (dq, $J_{j,j'}$ = 10.7 Hz, $J_{j,k}$ = 7.1 Hz, 1H, j), 3.53 (dq, $J_{j',j}$ = 10.7 Hz, $J_{j',k}$ = 7.1 Hz, 1H, j'), 2.98 (ddd, $J_{c,c'}$ = 17.2 Hz, $J_{c,b}$ = 8.2 Hz, $J_{c,d}$ = 2.5 Hz, 1H, c), 2.89 (ddd, $J_{c',c}$ = 17.2 Hz, $J_{c',b}$ = 7.2 Hz, $J_{c',d}$ = 2.5 Hz, 1H, c'), 2.30 (s, 3H, t) 0.99 (t, $J_{h,g}$ = 7.0 Hz, 3H, h), 0.79 (t, $J_{k,j}$ = 7.2 Hz, 3H, k).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5 (f), 169.1 (i), 142.0 (e), 140.5 (l), 137.0 (s), 133.6 (d), 133.3 (p), 128.8,128.4,128.1,127.9 (m, n, q and r), 127.2

(o), 73.6 (a), 61.5 (g), 61.0 (j), 52.4 (b), 37.8 (c), 21.3 (t), 13.8 (h), 13.6 (k).

HRMS (APCI): m/z= 379.190 38; calcd. for $[M + H]^+$ ($C_{24}H_{27}O_4$): 379.190 39. **Fragment**: m/z= 333 $[M - OEt]^+$

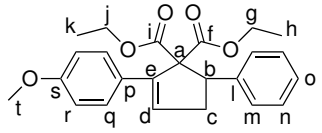
FT-IR (cm^{-1}): 2978, 1717 (C=O), 1514 (C=C Ar), 1495, 1454, 1445, 1366, 1300, 1250 (C-O), 1198, 1159, 1096, 1078, 1047, 814, 700.

Enantiomeric excess: racemic mixture (retention times: 350 sec and 517 sec | CHIRALPAK IC; EtOH/*i*-Hex 05/95; 1.0 mL min^{-1})

Diethyl 2-(4-methoxyphenyl)-5-phenylcyclopent-2-ene-1,1-dicarboxylate

Procedure: using the general procedure, cyclopentene **9ga** is isolated after purification by flash chromatography on silica gel (07/93 EtOAc/cyclohexane).

Isolated yield: 55 %
Aspect: colourless liquid
Chemical formula: $C_{24}H_{26}O_5$
Mol. wt.: 394.46 g/mol



9ga

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34-7.21 (comp, 7H, Ar), 6.80 (d, J = 8.8 Hz, 2H, Ar), 6.27 (dd, $J_{d,c}$ = 2.5 Hz, $J_{d,c'}$ = 2.5 Hz, 1H, d), 4.59 (dd, $J_{b,c}$ = 7.7 Hz, $J_{b,c'}$ = 7.7 Hz, 1H, b) 4.13-4.02 (comp, 2H, g), 3.79 (s, 3H, t), 3.75 (dq, $J_{j,j'}$ = 10.7 Hz, $J_{j,k}$ = 7.2 Hz, 1H, j), 3.54 (dq, $J_{j',j}$ = 10.7 Hz, $J_{j',k}$ = 7.2 Hz, 1H, j'), 3.00 (ddd, $J_{c,c'}$ = 17.3 Hz, $J_{c,b}$ = 8.1 Hz, $J_{c,d}$ = 2.7 Hz, 1H, c), 2.90 (ddd, $J_{c',c}$ = 17.2 Hz, $J_{c',b}$ = 7.4 Hz, $J_{c',d}$ = 2.5 Hz, 1H, c'), 1.02 (t, $J_{h,g}$ = 7.1 Hz, 3H, h), 0.81 (t, $J_{k,j}$ = 7.1 Hz, 3H, k).

^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6 (f), 169.2 (i), 159.0 (s), 141.6 (e), 140.5 (l), 133.0 (d), 129.2,128.8,128.1,113.1 (m, n, q and r), 128.7 (p), 127.2

(o), 73.6 (a), 61.5 (g), 61.0 (j), 55.4 (t), 52.4 (b), 37.8 (c), 13.9 (h), 13.6 (k).

HRMS (APCI): m/z= 395.185 25; calcd. for $[M + H]^+$ ($C_{24}H_{27}O_5$): 395.185 30. **Fragment**: m/z= 209 $[M - OEt]^+$

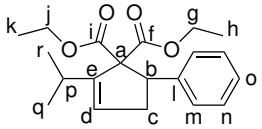
FT-IR (cm^{-1}): 2980, 2959, 2934, 2903, 1720 (C=O), 1607 (C=C cyclopentene), 1512 (C=C Ar), 1497, 1464, 1456, 1445, 1298, 1252 (C-O), 1198, 1182, 1096, 1080, 1036, 837, 825, 700.

Enantiomeric excess: racemic mixture (retention times: 367 sec and 566 sec | CHIRALPAK IC; EtOH/*i*-Hex 10/90; 1.0 mL min^{-1})

Diethyl 2-isopropyl-5-phenylcyclopent-2-ene-1,1-dicarboxylate

Procedure: using the general procedure, cyclopentene **9ja** is isolated after purification by flash chromatography on silica gel (04/96 EtOAc/cyclohexane).

Isolated yield: 41 %
Aspect: colourless liquid
Chemical formula: $C_{20}H_{26}O_4$
Mol. wt.: 330.42 g/mol



9ja

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29-7.10 (comp, 5H, Ar), 5.91 (dd, $J_{d,c}$ = 2.4 Hz, $J_{d,c'}$ = 2.4 Hz, 1H, d), 4.36 (dd, $J_{b,c}$ = 8.2 Hz, $J_{b,c'}$ = 5.5 Hz, 1H, b) 4.33-4.12 (comp, 2H, g), 3.68 (dq, $J_{j,j'}$ = 10.7 Hz, $J_{j,k}$ = 7.2 Hz, 1H, j), 3.50 (dq, $J_{j',j}$ = 10.7 Hz, $J_{j',k}$ = 7.2 Hz, 1H, j'), 2.90 (ddd, $J_{c,c'}$ = 16.6 Hz, $J_{c,b}$ = 8.2 Hz, $J_{c,d}$ = 2.1 Hz, 1H, c), 2.64 (ddd, $J_{c',c}$ = 16.6 Hz, $J_{c',b}$ = 5.5 Hz, $J_{c',d}$ = 2.5 Hz, 1H, c'), 2.54 (qq, $J_{p,q}$ = 6.7 Hz, $J_{p,r}$ = 6.7 Hz, 1H, p), 1.28 (t, $J_{h,g}$ = 7.1 Hz, 3H, h), 1.21 (d, $J_{q,p}$ = 6.8 Hz, 3H, q), 1.04 (d, $J_{r,p}$ = 6.8 Hz, 3H, r), 0.83 (t, $J_{k,j}$ = 7.2 Hz, 3H, k).

^{13}C NMR (75 MHz, $CDCl_3$): δ 170.7 (f), 169.5 (i), 149.0 (e), 141.7 (l), 128.9 (d), 128.7 (m or n), 128.0 (n or m), 127.0 (o), 74.3 (a), 61.6 (g), 60.7 (j),

50.7 (b), 38.4 (c), 28.0 (p), 24.3 (r), 24.0 (q), 14.2 (h), 13.6 (k).

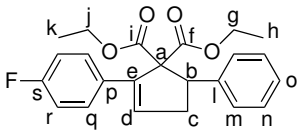
HRMS (APCI): m/z= 331.190 15; calcd. for $[M + H]^+$ ($C_{20}H_{27}O_4$): 331.190 39. **Fragments**: m/z= 285 $[M - OEt]^+$, 257 $[M - CO_2Et]^+$

FT-IR (cm^{-1}): 3030, 2976, 2962, 2930, 2907, 2868, 1724 (C=O), 1497, 1456, 1447, 1389, 1381, 1366, 1298, 1248, 1209, 1182, 1161, 1136, 1094, 1078, 1045, 1005, 864, 824, 777, 760, 700.

Diethyl 2-(4-fluorophenyl)-5-phenylcyclopent-2-ene-1,1-dicarboxylate

Procedure: using the general procedure, cyclopentene **9ea** is isolated after purification by flash chromatography on silica gel (05/95 EtOAc/cyclohexane).

Isolated yield: 57 %
Aspect: colourless liquid
Chemical formula: $C_{23}H_{23}FO_4$
Mol. wt.: 382.42 g/mol



9ea

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41-7.18 (comp, 7H, Ar), 6.95 (m, 2H, Ar), 6.30 (dd, $J_{d,c}$ = 2.5 Hz, $J_{d,c'}$ = 2.5 Hz, 1H, d), 4.61 (dd, $J_{b,c}$ = 7.8 Hz, $J_{b,c'}$ = 7.8 Hz, 1H, b) 4.14-3.98 (comp, 2H, g), 3.76 (dq, $J_{j,j'}$ = 10.7 Hz, $J_{j,k}$ = 7.2 Hz, 1H, j), 3.52 (dq, $J_{j',j}$ = 10.7 Hz, $J_{j',k}$ = 7.2 Hz, 1H, j'), 3.00 (ddd, $J_{c,c'}$ = 17.2 Hz, $J_{c,b}$ = 8.2 Hz, $J_{c,d}$ = 2.7 Hz, 1H, c), 2.91 (ddd, $J_{c',c}$ = 17.2 Hz, $J_{c',b}$ = 7.5 Hz, $J_{c',d}$ = 2.5 Hz, 1H, c'), 1.00 (t, $J_{h,g}$ = 7.1 Hz, 3H, h), 0.80 (t, $J_{k,j}$ = 7.1 Hz, 3H, k).

^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3 (f), 169.1 (i), 162.3 (d, J = 246.1 Hz, s), 141.0 (e), 140.3 (l), 134.7 (d), 132.4 (d, J = 3.2 Hz, p), 129.8 (d, J = 8.0 Hz, q), 128.8 (m or n), 128.2 (n or m), 127.3 (o), 114.6 (d, J = 21.3 Hz, r), 73.8 (a), 61.6 (g), 61.2 (j), 52.2 (b), 37.8 (c), 13.8 (h), 13.6 (k).

HRMS (APCI): *m/z*= 383.165 19; calcd. for $[M + H]^+$ ($C_{23}H_{24}FO_4$): 383.165 31

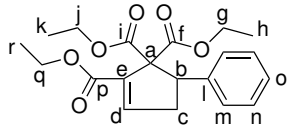
FT-IR (cm^{-1}): 2982, 2961, 2930, 2905, 2854, 1720 (C=O), 1601 (C=C cyclopentene), 1508 (C=C Ar), 1456, 1445, 1366, 1300, 1258, 1234, 1221, 1200, 1159, 1096, 1080, 1047, 843, 827, 700.

Enantiomeric excess: racemic mixture (retention times: 629 sec and 691 sec | CHIRALPAK IC; IPA/*i*-Hex 02/98; 0.7 mL min^{-1})

Triethyl 5-phenylcyclopent-2-ene-1,1,2-tricarboxylate

Procedure: using the general procedure, cyclopentene **9fa** is isolated after purification by flash chromatography on silica gel (10/90 EtOAc/cyclohexane).

Isolated yield: 32 %
Aspect: yellow liquid
Chemical formula: $C_{20}H_{24}O_6$
Mol. wt.: 360.40 g/mol



9fa

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26-7.19 (comp, 5H, Ar), 7.11 (dd, $J_{d,c}$ = 2.6 Hz, $J_{d,c'}$ = 2.6 Hz, 1H, d), 4.32-4.15 (comp, 5H, b, g and q), 3.71-3.61 (comp, 2H, j), 3.09 (ddd, $J_{c,c'}$ = 18.6 Hz, $J_{c,b}$ = 8.4 Hz, $J_{c,d}$ = 2.5 Hz, 1H, c) 2.90 (ddd, $J_{c',c}$ = 18.6 Hz, $J_{c',b}$ = 5.5 Hz, $J_{c',d}$ = 2.7 Hz, 1H, c'), 1.29-1.25 (comp, 6H, h and r), 0.86 (t, $J_{k,j}$ = 7.1 Hz, 3H, k).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6 (f), 167.9 (i), 164.1 (p), 146.3 (d), 140.1 (l), 135.8 (e), 128.8 (m or n), 128.2 (n or m), 127.5 (o), 71.2 (a), 61.9 (g or q), 61.2 (j), 60.7 (q or g), 52.4 (b), 39.1 (c), 14.3 (h or r), 14.1 (r or h), 13.6 (k).

HRMS (APCI): *m/z*= 361.164 45; calcd. for $[M + H]^+$ ($C_{20}H_{25}O_6$):

361.164 56. **Fragment**: m/z= 315 $[M - OEt]^+$

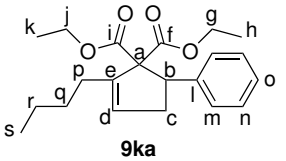
FT-IR (cm^{-1}): 2980, 2959, 2926, 2907, 2870, 2853, 2363, 1720 (C=O), 1637, 1497, 1454, 1445, 1391, 1367 (C=C cyclopentene), 1331, 1265, 1238 (C-O), 1213 (C-O), 1171, 1159, 1128, 1096, 1074, 1051, 1032, 864, 773, 752, 700.

Enantiomeric excess: racemic mixture (retention times: 1112 sec and 1179 sec | CHIRALPAK IC; EtOH/*i*-Hex 05/95; 1.0 mL min^{-1})

Diethyl 2-butyl-5-phenylcyclopent-2-ene-1,1-dicarboxylate

Procedure: using the general procedure, cyclopentene **9ka** is isolated after purification by flash chromatography on silica gel (03/97 EtOAc/cyclohexane).

Isolated yield: 39 %
Aspect: colourless liquid
Chemical formula: $C_{21}H_{28}O_4$
Mol. wt.: 344.44 g/mol



9ka

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28-7.14 (comp, 5H, Ar), 5.84 (m, 1H, d), 4.37 (dd, $J_{b,c}$ = 8.2 Hz, $J_{b,c'}$ = 4.9 Hz, 1H, b), 4.29-4.15 (comp, 2H, g), 3.69 (dq, $J_{j,j'}$ = 10.7 Hz, $J_{j,k}$ = 7.1 Hz, 1H, j), 3.48 (dq, $J_{j',j}$ = 10.7 Hz, $J_{j',k}$ = 7.1 Hz, 1H, j'), 2.93 (m, 1H, c), 2.62 (m, 1H, c'), 2.41-2.24 (comp, 1H, p), 2.20-2.04 (comp, 1H, p'), 1.70-1.33 (comp, 4H, q and r), 1.27 (t, $J_{h,g}$ = 7.1 Hz, 3H, h), 0.93 (t, $J_{s,r}$ = 7.2 Hz, 3H, s), 0.83 (t, $J_{k,j}$ = 7.2 Hz, 3H, k).

^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4 (f), 169.2 (i), 141.89 (e or l), 141.86 (l or e), 129.5 (d), 128.7 (m or n), 128.0 (n or m), 127.0 (o), 74.2 (a), 61.5 (g), 60.7 (j), 50.6 (b), 38.7 (c), 30.5 (q or r), 28.5 (p), 22.9 (r or q), 14.2 (two signals: h and s), 13.6 (k).

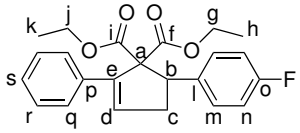
HRMS (APCI): m/z= 345.205 81; calcd. for $[M + H]^+$ ($C_{21}H_{29}O_4$): 345.206 04. **Fragment**: m/z= 299 $[M - OEt]^+$

FT-IR (cm^{-1}): 3061, 3030, 2980, 2957, 2930, 2858, 1724 (C=O), 1603 (C=C cyclopentene), 1495 (C=C Ar), 1456, 1445, 1389, 1366 (C=C cyclopentene), 1298, 1250 (C-O), 1205, 1161, 1078, 1045, 1007, 864, 824, 773, 762, 700.

Diethyl 5-(4-fluorophenyl)-2-phenylcyclopent-2-ene-1,1-dicarboxylate

Procedure: using the general procedure, cyclopentene **9bd** is isolated after purification by flash chromatography on silica gel (05/95 EtOAc/cyclohexane).

Isolated yield: 57 %
Aspect: colourless liquid
Chemical formula: $C_{23}H_{23}FO_4$
Mol. wt.: 382.42 g/mol



9bd

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-7.28 (comp, 4H, Ar), 7.27-7.20 (comp, 3H, Ar), 6.94 (m, 2H, Ar), 6.32 (dd, $J_{d,c} = 2.6$ Hz, $J_{d,c'} = 2.6$ Hz, 1H, d), 4.58 (dd, $J_{b,c} = 7.9$ Hz, $J_{b,c'} = 7.9$ Hz, 1H, b) 4.08-3.98 (comp, 2H, g), 3.79 (dq, $J_{j,j'} = 10.8$ Hz, $J_{j,k} = 7.2$ Hz, 1H, j), 3.59 (dq, $J_{j',j} = 10.8$ Hz, $J_{j',k} = 7.2$ Hz, 1H, j'), 2.97 (ddd, $J_{c,c'} = 17.1$ Hz, $J_{c,b} = 8.2$ Hz, $J_{c,d} = 2.7$ Hz, 1H, c), 2.87 (ddd, $J_{c',c} = 17.1$ Hz, $J_{c',b} = 7.6$ Hz, $J_{c',d} = 2.4$ Hz, 1H, c'), 0.94 (t, $J_{h,g} = 7.1$ Hz, 3H, h), 0.85 (t, $J_{k,j} = 7.2$ Hz, 3H, k).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4 (f), 169.0 (i), 162.1 (d, $J = 245.5$ Hz, o), 142.2 (e), 136.2 (p), 136.0 (d, $J = 3.1$ Hz, l), 134.3 (d), 130.4 (d, $J = 7.8$ Hz, m), 128.0 (q or r), 127.8 (r or q), 127.4 (s), 114.9 (d, $J = 21.1$ Hz, n), 73.6 (a), 61.6 (g), 61.2 (j), 51.5 (b), 37.9 (c), 13.72 (h or k), 13.66 (k or h).

HRMS (APCI): m/z= 383.1654; calcd. for $[M + H]^+$ ($C_{23}H_{24}FO_4$): 383.1653

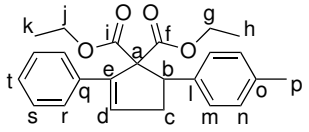
FT-IR (cm^{-1}): 2986, 2921, 1720 (C=O), 1606 (C=C cyclopentene), 1507 (C=C Ar), 1449, 1395, 1302, 1255 (C-O), 1200, 1162, 1092 (C-O), 1042, 838, 761, 697.

Enantiomeric excess: racemic mixture (retention times: 419 sec and 451 sec | CHIRALPAK IB; EtOH/*i*-Hex 05/95; 0.7 mL min^{-1})

Diethyl 5-(4-methylphenyl)-2-phenylcyclopent-2-ene-1,1-dicarboxylate

Procedure: using the general procedure, cyclopentene **9bc** is isolated after purification by flash chromatography on silica gel (05/95 EtOAc/cyclohexane).

Isolated yield: 50 %
Aspect: colourless liquid
Chemical formula: $C_{24}H_{26}O_4$
Mol. wt.: 378.46 g/mol



9bc

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40-7.35 (m, 2H, m, r or s), 7.30-7.20 (comp, 5H, Ar), 7.08 (d, $J_{n,m}$ = 7.9 Hz, 2H, n), 6.34 (dd, $J_{d,c}$ = 2.5 Hz, $J_{d,c'}$ = 2.5 Hz, 1H, d), 4.58 (dd, $J_{b,c}$ = 7.9 Hz, $J_{b,c'}$ = 7.9 Hz, 1H, b) 4.10-4.00 (comp, 2H, g), 3.79 (dq, $J_{j,j'}$ = 10.7 Hz, $J_{j,k}$ = 7.1 Hz, 1H, j), 3.61 (dq, $J_{j',j}$ = 10.7 Hz, $J_{j',k}$ = 7.1 Hz, 1H, j'), 2.98 (ddd, $J_{c,c'}$ = 17.1 Hz, $J_{c,b}$ = 8.1 Hz, $J_{c,d}$ = 2.7 Hz, 1H, c), 2.92 (ddd, $J_{c',c}$ = 17.1 Hz, $J_{c',b}$ = 7.7 Hz, $J_{c',d}$ = 2.7 Hz, 1H, c'), 2.31 (s, 3H, p), 0.97 (t, $J_{h,g}$ = 7.1 Hz, 3H, h), 0.85 (t, $J_{k,j}$ = 7.1 Hz, 3H, k).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5 (f), 169.1 (i), 142.1 (e), 137.1 (l), 136.8 (o), 136.4 (q), 134.5 (d), 128.8,128.7,128.0,127.7 (m, n, r and s), 127.3 (t), 73.6 (a), 61.5 (g), 61.0 (j), 52.1 (b), 37.8 (c), 21.1 (p), 13.7 (h), 13.6 (k).

HRMS (APCI): *m/z*= 279.1903; calcd. for $[M + H]^+$ ($C_{24}H_{27}O_4$): 279.1904

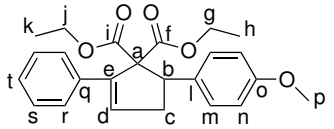
FT-IR (cm^{-1}): 3051, 3022, 2980, 2928, 2858, 1720 (C=O), 1514 (C=C Ar), 1493, 1464, 1445, 1366, 1300, 1256 (C-O), 1198, 1159, 1111, 1096, 1049, 1036, 1022, 820, 770, 750, 696.

Enantiomeric excess: racemic mixture (retention times: 373 sec and 488 sec | CHIRALPAK IC; EtOH/*i*-Hex 05/95; 1.0 mL min^{-1})

Diethyl 5-(4-methoxyphenyl)-2-phenylcyclopent-2-ene-1,1-dicarboxylate

Procedure: using the general procedure, cyclopentene **9bb** is isolated after purification by flash chromatography on silica gel (07/93 EtOAc/cyclohexane).

Isolated yield: 58 %
Aspect: pale yellow liquid
Chemical formula: $C_{24}H_{26}O_5$
Mol. wt.: 394.46 g/mol



9bb

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41-7.32 (comp, 2H, Ar), 7.31-7.26 (comp, 5H, Ar), 6.81 (m, 2H, Ar), 6.34 (dd, $J_{d,c}$ = 2.5 Hz, $J_{d,c'}$ = 2.5 Hz, 1H, d), 4.56 (dd, $J_{b,c}$ = 7.9 Hz, $J_{b,c'}$ = 7.9 Hz, 1H, b) 4.13-3.97 (comp, 2H, g), 3.81 (dq, $J_{j,j'}$ = 10.8 Hz, $J_{j,k}$ = 7.2 Hz, 1H, j), 3.78 (s, 3H, p), 3.62 (dq, $J_{j',j}$ = 10.8 Hz, $J_{j',k}$ = 7.2 Hz, 1H, j'), 2.99 (ddd, $J_{c,c'}$ = 17.1 Hz, $J_{c,b}$ = 8.2 Hz, $J_{c,d}$ = 2.7 Hz, 1H, c), 2.89 (ddd, $J_{c',c}$ = 17.1 Hz, $J_{c',b}$ = 7.6 Hz, $J_{c',d}$ = 2.5 Hz, 1H, c'), 0.97 (t, $J_{h,g}$ = 7.1 Hz, 3H, h), 0.88 (t, $J_{k,j}$ = 7.1 Hz, 3H, k).

^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4 (f), 169.1 (i), 158.7 (o), 142.0 (e), 136.3 (q), 134.3 (d), 132.1 (l), 129.8 (m), 127.9 (r or s), 127.6 (s or r), 127.2 (t), 113.3 (n), 73.5 (a), 61.4 (g), 61.0 (j), 55.3 (p), 51.6 (b), 37.8 (c), 13.63 (h or k), 13.57 (k or h).

HRMS (APCI): *m/z*= 395.185 22; calcd. for $[M + H]^+$ ($C_{24}H_{27}O_5$): 395.185 30. **Fragment**: *m/z*= 349 $[M - OEt]^+$

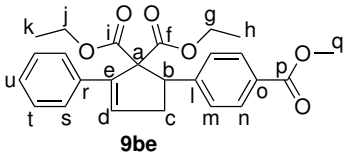
FT-IR (cm^{-1}): 2982, 2955, 2934, 2922, 2905, 1718 (C=O), 1610 (C=C cyclopentene), 1514 (C=C Ar), 1464 (O-CH_3), 1443 (O-CH_3), 1304, 1248 (C-O), 1213, 1200, 1182, 1094, 1038, 831.

Enantiomeric excess: racemic mixture (retention times: 448 sec and 581 sec | CHIRALPAK IC; EtOH/*i*-Hex 05/95; 1.0 mL min^{-1})

Diethyl 5-[4-(methoxycarbonyl)phenyl]-2-phenylcyclopent-2-ene-1,1-dicarboxylate

Procedure: using the general procedure, cyclopentene **9be** is isolated after purification by flash chromatography on silica gel (10/90 EtOAc/cyclohexane).

Isolated yield: 55 %
Aspect: colourless liquid
Chemical formula: $C_{25}H_{26}O_6$
Mol. wt.: 422.47 g/mol



9be

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94 (d, $J_{n,m}$ = 8.4 Hz, 2H, n), 7.46-7.19 (comp, 7H, Ar), 6.33 (dd, $J_{d,c}$ = 2.5 Hz, $J_{d,c'}$ = 2.5 Hz, 1H, d), 4.66 (dd, $J_{b,c}$ = 7.8 Hz, $J_{b,c'}$ = 7.8 Hz, 1H, b) 4.12-3.98 (comp, 2H, g), 3.89 (s, 3H, q), 3.77 (dq, $J_{j,j'}$ = 10.8 Hz, $J_{j,k}$ = 7.1 Hz, 1H, j), 3.55 (dq, $J_{j',j}$ = 10.8 Hz, $J_{j',k}$ = 7.2 Hz, 1H, j'), 3.01 (ddd, $J_{c,c'}$ = 17.2 Hz, $J_{c,b}$ = 8.1 Hz, $J_{c,d}$ = 2.7 Hz, 1H, c), 2.92 (ddd, $J_{c',c}$ = 17.1 Hz, $J_{c',b}$ = 7.6 Hz, $J_{c',d}$ = 2.4 Hz, 1H, c'), 0.96 (t, $J_{h,g}$ = 7.1 Hz, 3H, h), 0.81 (t, $J_{k,j}$ = 7.2 Hz, 3H, k).

^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1 (f), 168.8 (i), 167.0 (p), 145.7 (l), 142.1 (e), 136.0 (r), 134.1 (d), 129.3 (n), 129.0 (o), 128.9,128.0,127.7 (m, s and t), 127.4 (u), 73.6 (a), 61.6 (g), 61.1 (j), 52.1 (b or q), 52.0 (q or b), 37.5 (c), 13.7 (h or k), 13.6 (k or h).

HRMS (APCI): *m/z*= 423.179 52; calcd. for $[M + H]^+$ ($C_{25}H_{27}O_6$):

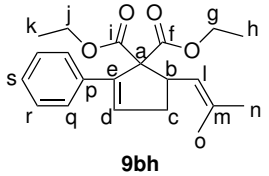
423.180 22

FT-IR (cm^{-1}): 2982, 2953, 2939, 2930, 2905, 1713 (C=O), 1610 (C=C cyclopentene), 1493, 1435, 1418, 1391, 1366, 1304, 1277, 1252 (C-O), 1194, 1159, 1103, 1047, 1036, 1020, 860, 771, 750, 696.

Diethyl 5-(2-methylprop-1-en-1-yl)-2-phenylcyclopent-2-ene-1,1-dicarboxylate

Procedure: using the general procedure, cyclopentene **9bh** is isolated after purification by flash chromatography on silica gel (03/97 EtOAc/cyclohexane).

Isolated yield: 57 %
Aspect: colourless liquid
Chemical formula: $C_{21}H_{26}O_4$
Mol. wt.: 342.43 g/mol



9bh

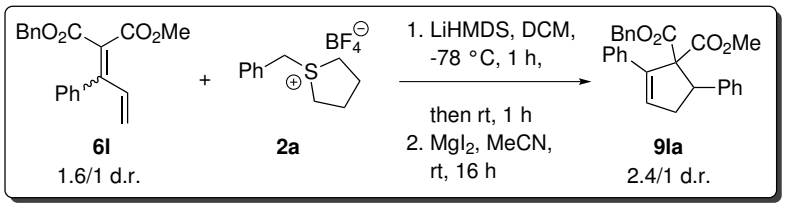
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42-7.34 (comp, 2H, q), 7.30-7.16 (comp, 3H, r and s), 6.27 (dd, $J_{d,c}$ = 2.5 Hz, $J_{d,c'}$ = 2.5 Hz, 1H, d), 5.16 (d, $J_{l,b}$ = 10.4 Hz, 1H, l), 4.26-3.98 (comp, 5H, b, g and j), 2.80 (ddd, $J_{c,c'}$ = 16.9 Hz, $J_{c,b}$ = 7.8 Hz, $J_{c,d}$ = 2.6 Hz, 1H, c), 2.36 (ddd, $J_{c',c}$ = 16.9 Hz, $J_{c',b}$ = 6.3 Hz, $J_{c',d}$ = 2.5 Hz, 1H, c'), 1.70 (s, 6H, n and o), 1.21 (t, $J_{h,g}$ = 7.1 Hz, 3H, h), 1.04 (t, $J_{k,j}$ = 7.1 Hz, 3H, h).

^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6 (i), 169.7 (f), 142.1 (e), 136.2 (p), 134.7 (m), 133.7 (d), 127.8 (r), 127.5 (q), 127.2 (s), 124.1 (l), 71.5 (a), 61.3 (j), 61.1 (g), 46.8 (b), 38.8 (c), 26.1 (n or o), 18.3 (o or n), 14.2 (h), 13.9 (k).

HRMS (APCI): m/z= 343.190 26; calcd. for $[M + H]^+$ ($C_{21}H_{27}O_4$): 343.190 39. **Fragment**: m/z= 297 $[M - OEt]^+$

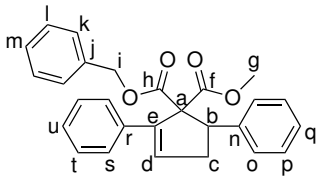
FT-IR (cm^{-1}): 2980, 2928, 2910, 2870, 2849, 1724 (C=O), 1445, 1366, 1296, 1242, 1221, 1192, 1095, 1082, 1055, 1034, 696.

1-Benzyl 1-methyl 2,5-diphenylcyclopent-2-ene-1,1-dicarboxylate



Procedure: using the general procedure (on 40 mg diene **6l**), a 2.4/1 d.r. (A/B) is observed on the ^{1}H NMR spectrum of the crude mixture.[40] Pure cyclopentene **9la** is isolated as isomers mixture after purification by flash chromatography on silica gel (05/95 EtOAc/cyclohexane).

Isolated yield: 51 % (mixture of isomers)
Aspect: colourless liquid
Chemical formula: $C_{27}H_{24}O_4$
Mol. wt.: 412.48 g/mol



9la

The analyses below were carried out on a 3.5/1 d.r. (A/B) sample.

^{1}H NMR A isomer (300 MHz, $CDCl_3$): δ 7.41-7.14 (comp, 14H, Ar), 6.91 (m, 1H, Ar), 6.38 (dd, $J_{d,c} = 2.7$ Hz, $J_{d,c'} = 2.7$ Hz, 1H, d), 4.69 (d, $J_{i,i'} = 12.5$ Hz, 1H, i), 4.58 (dd, $J_{b,c} = 7.6$ Hz, $J_{b,c'} = 7.6$ Hz, 1H, b), 4.46 (d, $J_{i',i} = 12.5$ Hz, 1H, i'), 3.57 (s, 3H, g), 3.11-2.85 (comp, 2H, c).

^{13}C NMR A isomer (125 MHz, $CDCl_3$): δ 171.0 (f), 168.8 (h), 141.8 (e), 140.1 (n), 136.0 (r), 135.3 (j), 134.5 (d), 128.8,128.4,128.3,128.25,128.19, 128.16,128.15,128.12,128.01,127.98,127.91,127.85,127.8,127.7,127.45,127.42, 127.39,127.36 (Ar from A and B isomers), 73.7 (a), 66.9 (i), 52.8 (b), 52.5 (g),

[40] Starting from a sample having a 1.6/1 d.r.

38.0 (c).

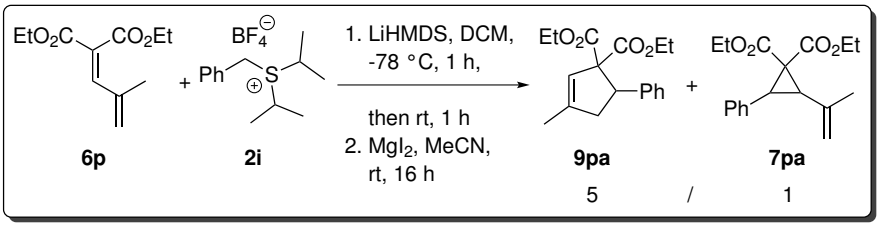
^{1}H NMR B isomer (300 MHz, $CDCl_3$): δ 7.41-7.14 (comp, 14H, Ar), 6.98 (m, 1H, Ar), 6.36 (m, 1H, d), 5.07 (d, $J_{i,i'}$ = 12.4 Hz, 1H, i), 4.99 (d, $J_{i',i}$ = 12.3 Hz, 1H, i'), 4.58 (dd, $J_{b,c}$ = 7.6 Hz, $J_{b,c'}$ = 7.6 Hz, 1H, b), 3.19 (s, 3H, g), 3.11-2.85 (comp, 2H, c).

^{13}C NMR B isomer (125 MHz, $CDCl_3$): δ 170.3 (h), 169.4 (f), 141.7 (e), 140.0 (n), 136.0 (r), 135.3 (j), 134.4 (d), 128.8,128.4,128.3,128.25,128.19, 128.16,128.15,128.12,128.01,127.98,127.91,127.85,127.8,127.7,127.45,127.42, 127.39,127.36 (Ar from A and B isomers), 73.8 (a), 67.5 (i), 52.7 (b), 51.9 (g), 37.8 (c).

HRMS (APCI): m/z= 413.174 61; calcd. for $[M + H]^+$ ($C_{27}H_{25}O_4$): 413.174 74

FT-IR (cm^{-1}): 3057, 3032, 2947, 2928, 1724 (C=O), 1495, 1454, 1443, 1433, 1310, 1259, 1215, 1200, 1159, 1080, 1045, 779, 746, 698.

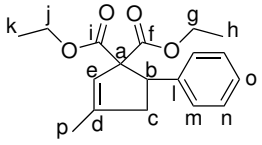
Diethyl 3-methyl-5-phenylcyclopent-2-ene-1,1-dicarboxylate



Procedure: using the general procedure (benzyl(diisopropyl)sulfonium tetrafluoroborate **2i** is used instead of 1-benzyltetrahydrothiophenium tetrafluoroborate **2a**; the sulfonium salt and the diene are diluted in 2.5 mL of DCM instead of 4 mL), a 5/1 mixture of cyclopentene **9pa** and vinylcyclopropane **7pa** (resulting from the ylide 1,4 addition) is observed on the ^{1}H NMR spectrum of the crude mixture. Subsequent purification by flash chromatography on silica gel (07/93 EtOAc/cyclohexane) does not allowed to separate these compounds, a 6/1 mixture **9pa**/**7pa** being obtained.[41]

[41] Vinylcyclopropane **7pa** being not isolated, analyses of this compound could not be per-

Yield: 36 %[42]
Aspect: colourless liquid
Chemical formula: $C_{18}H_{22}O_4$
Mol. wt.: 302.36 g/mol



9pa

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30-7.12 (comp, 5H, Ar), 5.50 (s, 1H, e), 4.34 (dd, $J_{b,c} = 8.4$ Hz, $J_{b,c'} = 4.1$ Hz, 1H, b), 4.30-4.09 (comp, 2H, g), 3.70 (dq, $J_{j,j'} = 10.7$ Hz, $J_{j,k} = 7.1$ Hz, 1H, j), 3.50 (dq, $J_{j',j} = 10.7$ Hz, $J_{j',k} = 7.2$ Hz, 1H, j'), 2.96 (dd, $J_{c,c'} = 16.3$ Hz, $J_{c,b} = 8.3$ Hz, 1H, c), 2.55 (dd, $J_{c',c} = 16.7$ Hz, $J_{c',b} = 4.1$ Hz, 1H, c'), 1.88 (s, 3H, p), 1.24 (t, $J_{h,g} = 7.1$ Hz, 3H, h), 0.80 (t, $J_{k,j} = 7.1$ Hz, 3H, k).

^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9 (f), 170.0 (i), 146.2 (d), 142.2 (l), 128.5 (m or n), 128.1 (n or m), 127.0 (o), 123.0 (e), 72.6 (a), 61.6 (g), 60.9 (j), 49.3 (b), 44.8 (c), 16.8 (p), 14.2 (h), 13.6 (k).

HRMS (APCI): *m/z*= 303.1592; calcd. for $[M + H]^+$ ($C_{18}H_{23}O_4$): 303.1591. **Fragment**: *m/z*= 257 $[M - OEt]^+$

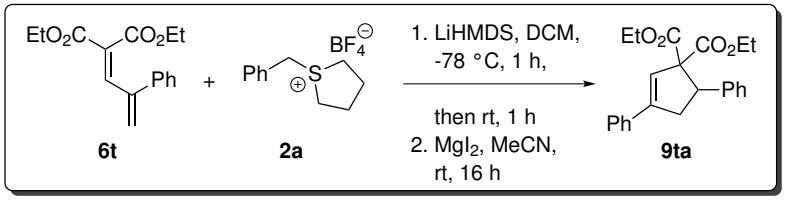
FT-IR (cm^{-1}): 2979, 2926, 1729, 1447, 1388, 1370, 1273, 1244 (C=O), 1203, 1116, 1056, 1038, 863, 834, 757, 701.

Enantiomeric excess: racemic mixture (retention times: 442 sec and 456 sec | CHIRALPAK IC; IPA/*i*-Hex 02/98; 1.0 mL min^{-1})

formed. Besides, analyses of **9pa** below were carried out on a pure **9pa** sample, obtained *via* MgI_2 mediated rearrangement of purified vinylcyclopropane **8pa**, carried out by Dr. Thierry Delaunay.

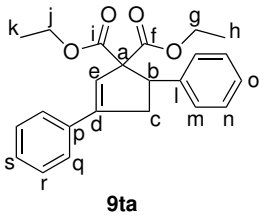
[42]The yield is calculated on the ^{1}H NMR spectrum of the crude mixture using Ph_2MeSiH as an internal standard.

Diethyl 3,5-diphenylcyclopent-2-ene-1,1-dicarboxylate



Procedure: in a dried round-bottom flask, under inert atmosphere, LiHMDS (1 M in THF; 0.22 mmol; 1.1 eq.) is added, dropwise, to a suspension of sulfonium salt **2a** (0.22 mmol; 1.1 eq.) in DCM (3 mL), at −78 °C. After stirring for 20 min at the same temperature, a solution diene **6t** (0.20 mmol; 1 eq.) in DCM (1 mL) is added, dropwise. After stirring for 1 h at −78 °C and then 2 h at room temperature, a solution of MgI_2 (0.24 mmol; 1.2 eq.)[43] in MeCN (1 mL) is added, at room temperature. After stirring for 16 h at the same temperature, the reaction mixture is quenched with a 1 M aqueous solution of HCl (1 mL) after dilution with DCM (2 mL) and water (2 mL). The aqueous layer is then washed with DCM (2 x 5 mL). The combined organic layers are washed with an aqueous solution of NaOH (10 wt.%; 5 mL), water (5 mL), brine (5 mL), dried over $MgSO_4$, and then concentrated under reduced pressure. The residue is purified by flash chromatography on silica gel (03/97 to 10/90 EtOAc/cyclohexane) to give the desired product **9ta** in 10 % yield.

Isolated yield: 10 %
Aspect: colourless liquid
Chemical formula: $C_{23}H_{24}O_4$
Mol. wt.: 364.43 g/mol



9ta

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (m, 2H, Ar), 7.42-7.11 (comp, 8H,

[43] In order to have a homogeneous solution, MgI_2 is dissolved *via* ultrasonic agitation for few seconds.

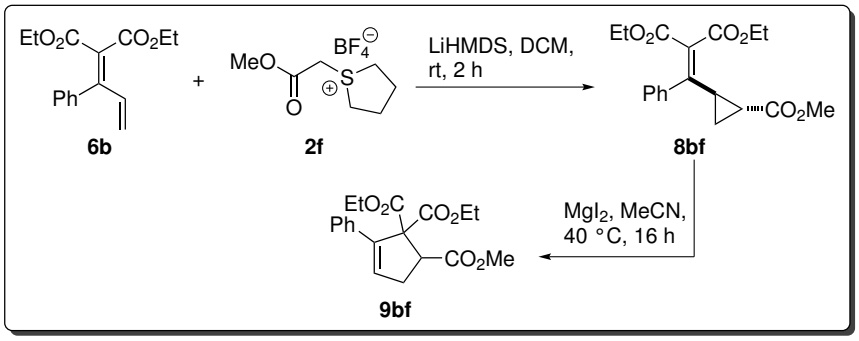
Ar), 6.29 (dd, $J_{e,c} = 2.1\,\text{Hz}$, $J_{e,c'} = 1.4\,\text{Hz}$, 1H, e), 4.48 (dd, $J_{b,c} = 8.2\,\text{Hz}$, $J_{b,c'} = 3.6\,\text{Hz}$, 1H, b), 4.28 (dq, $J_{g,g'} = 10.9\,\text{Hz}$, $J_{g,h} = 7.1\,\text{Hz}$, 1H, g), 4.16 (dq, $J_{g',g} = 10.7\,\text{Hz}$, $J_{g',h} = 7.1\,\text{Hz}$, 1H, g'), 3.75 (dq, $J_{j,j'} = 10.7\,\text{Hz}$, $J_{j,k} = 7.1\,\text{Hz}$, 1H, j), 3.58 (dq, $J_{j',j} = 10.7\,\text{Hz}$, $J_{j',k} = 7.1\,\text{Hz}$, 1H, j'), 3.45 (ddd, $J_{c,c'} = 16.3\,\text{Hz}$, $J_{c,b} = 8.2\,\text{Hz}$, $J_{c,e} = 2.3\,\text{Hz}$, 1H, c), 3.05 (ddd, $J_{c',c} = 16.3\,\text{Hz}$, $J_{c',b} = 3.6\,\text{Hz}$, $J_{c',e} = 1.3\,\text{Hz}$, 1H, c), 1.26 (t, $J_{h,g} = 7.1\,\text{Hz}$, 3H, h), 0.84 (t, $J_{k,j} = 7.1\,\text{Hz}$, 3H, k).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.3 (f or i), 169.6 (i or f), 146.7 (d), 142.0 (l), 135.0 (p), 128.6,128.5,128.2,127.2,126.4 (six signals: m, n, o, q, r and s), 123.0 (e), 72.7 (a), 61.9 (g), 61.1 (j), 48.8 (b), 41.2 (c), 14.2 (h), 13.7 (k).

HRMS (APCI): m/z= 365.174 76; calcd. for $[M + H]^+$ ($C_{23}H_{25}O_4$): 365.174 74. **Fragment**: m/z= 319 $[M - OEt]^+$

FT-IR (cm^{-1}): 2926, 1728 (C=O), 1495, 1456, 1447, 1298, 1285, 1256, 1236, 1200, 1094, 1080, 1041, 750, 700.

1,1-Diethyl 2-methyl 5-phenylcyclopent-4-ene-1,1,2-tricarboxylate

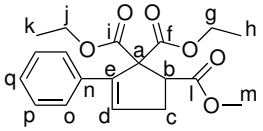


Procedure: in a dried round-bottom flask, under inert atmosphere, LiHMDS (1 M in THF; 0.22 mmol; 1.1 eq.) is added, dropwise, to a suspension of sulfonium salt **2f** (0.22 mmol; 1.1 eq.) in DCM (3 mL), at −78 °C. After stirring for 20 min at the same temperature, a solution diene **6b** (0.20 mmol; 1 eq.) in DCM (1 mL) is added, dropwise, at −78 °C. After stirring for 2 h at room temperature, the reaction is quenched with a 1 M aqueous solution of HCl (1 mL) after dilution with DCM (2 mL) and water (2 mL). The aqueous layer is washed with DCM (2 x 5 mL). The combined organic layers are washed with

water (5 mL), brine (5 mL), dried over $MgSO_4$, and then concentrated under reduced pressure. Pure vinylcyclopropane **8bf** is obtained after purification by flash chromatography on silica gel (05/95 to 10/90 EtOAc/cyclohexane) in 32 % yield (20.2 mg).[44]

In a dried bottomed flask, under inert atmosphere, a suspension of MgI_2 (large excess) in MeCN (2 mL)[45] is added to a solution of vinylcyclopropane **8bf** (12.9 mg) in MeCN (3 mL). After stirring for 16 h at 40 °C,[46] the reaction is quenched with an aqueous solution of NaOH (10 wt.%; 2 mL). The organic layer is washed with brine (5 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Pure cyclopentene **9bf** is obtained after purification by flash chromatography on silica gel (10/90 to 20/80 EtOAc/cyclohexane) in 25 % yield.

Isolated yield: 8 % (over two steps)
Aspect: colourless liquid
Chemical formula: $C_{19}H_{22}O_6$
Mol. wt.: 346.37 g/mol



8bf

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (dd, $J_{o,p}$ = 7.9 Hz, $J_{o,q}$ = 1.7 Hz, 2H, o), 7.30-7.22 (comp, 3H, p and q), 6.29 (d, $J_{d,b}$ = 2.6 Hz, 1H, d), 4.22-4.11 (comp, 4H, g and j), 3.82 (ddd, $J_{b,c}$ = 8.2 Hz, $J_{b,c'}$ = 6.7 Hz, $J_{b,d}$ = 2.6 Hz, 1H, b), 3.73 (s, 3H, m), 3.02 (dd, $J_{c,c'}$ = 13.4 Hz, $J_{c,b}$ = 8.1 Hz, 1H, c), 2.94 (dd, $J_{c',c}$ = 13.4 Hz, $J_{c',b}$ = 6.7 Hz, 1H, c'), 1.15 (t, $J_{h,g}$ = 7.1 Hz, 3H, h), 1.14 (t, $J_{k,j}$ = 7.1 Hz, 3H, k).

^{13}C NMR (125 MHz, $CDCl_3$): δ 173.0 (two signals: f and i), 170.9 (l), 130.8 (d), 128.0 (two signals: p and q), 127.9 (o), 67.5 (a), 62.0 (g or j), 61.8 (j

[44]The ^{1}H NMR spectrum analyses reveals pure vinylcyclopropane **8bf**. No analyses were however carried out.
[45]In order to have a homogeneous solution, MgI_2 is dissolved *via* ultrasonic agitation for few seconds.
[46]The rearrangement by stirring the reaction mixture for 16 h at room temperature, using 1.2 equivalents of magnesium iodide, is unsuccessful, as only starting material being recovered.

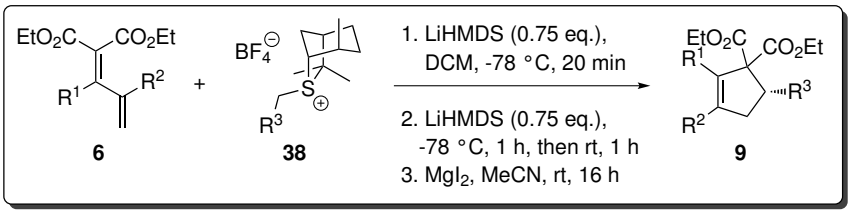
or g), 52.4 (m), 48.7 (b), 38.6 (c), 14.01 (h or k), 13.98 (k or h). Two carbons could not be observed (e and n).

HRMS (APCI): *m/z*= 347.148 66; calcd. for $[M + H]^+$ ($C_{19}H_{23}O_6$): 347.148 91

FT-IR (cm^{-1}): 2955, 2922, 2856, 1730 (C=O), 1445, 1259 (C-O), 1198, 1188, 1180, 1097, 1080.

6.2.9 Formal asymmetric (4+1) annulation reactions[47]

Reference: O. Rousseau, T. Delaunay, G. Dequirez, T. Trieu-Van, K. Robeyns, R. Robiette, *Chem. Eur. J.* **2015**, *21*, 12899–12902.



General procedure: in a dried round-bottom flask, under inert atmosphere, LiHMDS (1 M in THF; 0.75 eq.) is added, dropwise, to a mixture of diene **6** (100 mg; 1 eq.) and sulfonium salt **38** (1.5 eq.), in DCM (4 mL), at −78 °C. After stirring for 20 min at the same temperature, additional LiHMDS (1 M in THF; 0.75 eq.) is then added, dropwise. After stirring 1 h at −78 °C and then 1 h at room temperature, a solution of MgI_2 (1.2 eq.)[48] in MeCN (1 mL) is added, at room temperature. After stirring for 16 h at the same temperature, the reaction mixture is quenched with a 1 M aqueous solution of HCl (1 mL) after dilution with DCM (2 mL) and water (2 mL). The aqueous layer is washed with DCM (2 x 5 mL). The combined organic layers are washed with an aqueous solution of NaOH (10 wt.%; 5 mL), water (5 mL), brine (5 mL), dried over $MgSO_4$, and then concentrated under reduced pressure. The residue is purified by flash chromatography on silica gel with the

[47]The yield was also calculated for most of cyclopentenes by analyses of the ^{1}H NMR spectrum of the crude mixture, using Ph_2MeSiH as an internal standard. Being very closed of the isolated yield, they are not mentioned, excepted for **9pa** where the purification by flash chromatography was especially complicated.

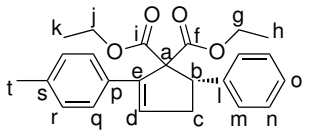
[48]In order to have a homogeneous solution, MgI_2 is dissolved *via* ultrasonic agitation for few seconds.

appropriate mixture of EtOAc and cyclohexane (*vide infra* for ratios) to give enantioenriched cyclopentene **9** in a moderate to good yield.

Diethyl (5*S*)-2-(4-methylphenyl)-5-phenylcyclopent-2-ene-1,1-dicarboxylate

Procedure: using the general procedure, cyclopentene **9ca** is isolated after purification by flash chromatography on silica gel (04/96 EtOAc/cyclohexane).

Isolated yield: 38 %
Aspect: colourless liquid
Chemical formula: $C_{24}H_{26}O_4$
Mol. wt.: 378.46 g/mol



9ca

For descriptions of ^{1}H NMR, ^{13}C NMR, Mass, and IR spectra, see the racemic compound (page 242).

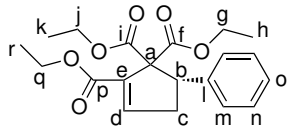
Specific rotation: $[\alpha]_D^{25} = -43°$ (c = 4.09, CH_2Cl_2)

Enantiomeric excess: 90 % (retention times: 349 sec (minor) and 515 sec (major) | CHIRALPAK IC; EtOH/*i*-Hex 05/95; 1.0 mL min^{-1})

Triethyl (5*S*)-5-phenylcyclopent-2-ene-1,1,2-tricarboxylate

Procedure: using the general procedure, cyclopentene **9fa** is isolated after purification by flash chromatography on silica gel (10/90 EtOAc/cyclohexane).

Isolated yield: 35 %
Aspect: yellow liquid
Chemical formula: $C_{20}H_{24}O_6$
Mol. wt.: 360.40 g/mol



9fa

For descriptions of ^{1}H NMR, ^{13}C NMR, Mass, and IR spectra, see the racemic compound (page 246).

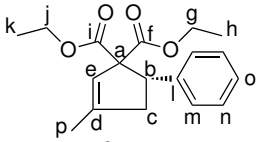
Specific rotation: $[\alpha]_D^{26} = +25°$ (c = 1.38, CH_2Cl_2)

Enantiomeric excess: 25 % (retention times: 851 sec (major) and 898 sec (minor) | CHIRALPAK IC; EtOH/*i*-Hex 05/95; 1.0 mL min^{-1})

Diethyl (5*S*)-3-methyl-5-phenylcyclopent-2-ene-1,1-dicarboxylate

Procedure: using the general procedure, cyclopentene **9pa** is isolated after purification by flash chromatography on silica gel (07/93 EtOAc/cyclohexane).[49]

Yield: 25 %[50]
Isolated yield: 2 %
Aspect: colourless liquid
Chemical formula: $C_{18}H_{22}O_4$
Mol. wt.: 302.36 g/mol



9pa

For descriptions of ^{1}H NMR, ^{13}C NMR, Mass, and IR spectra, see the racemic compound (page 254).

Specific rotation: $[\alpha]_D^{26} = -250°$ (c = 0.20, CH_2Cl_2)

[49] Vinylcyclopropane **7pa** could not be isolated.
[50] Calculated on the ^{1}H NMR spectrum of the crude mixture using Ph_2MeSiH as an internal standard.

Enantiomeric excess: >99 % (retention time: 4569 sec | CHIRALPAK IC; IPA/*i*-Hex 02/98; 1.0 mL min^{-1})

X-ray diffraction

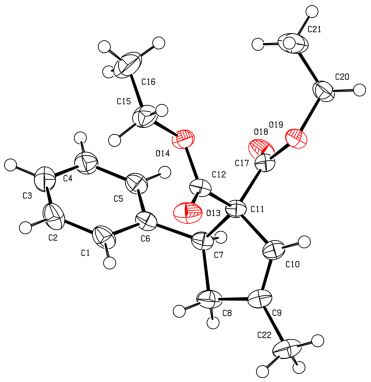


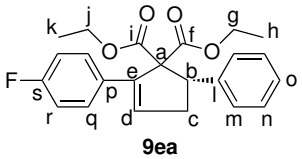
Figure 6.1: Ortep representation of compound **9pa** with thermal ellipsoids drawn at the 50 % probability level. For good order the hydrogen on carbon C7 is pointing down, the absolute configuration can thus be assigned as *S*.

For technical details, see section 6.3.1 page 285.

Diethyl (5*S*)-2-(4-fluorophenyl)-5-phenylcyclopent-2-ene-1,1-dicarboxylate

Procedure: using the general procedure, cyclopentene **9ea** is isolated after purification by flash chromatography on silica gel (04/96 EtOAc/cyclohexane).

Isolated yield: 47 %
Aspect: colourless liquid
Chemical formula: $C_{23}H_{23}FO_4$
Mol. wt.: 382.42 g/mol



9ea

For descriptions of ^{1}H NMR, ^{13}C NMR, Mass, and IR spectra, see the racemic compound (page 245).

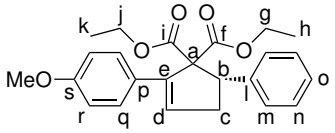
Specific rotation: $[\alpha]_D^{21} = -90°$ (c = 0.83, CH_2Cl_2)

Enantiomeric excess: 94 % (retention times: 700 sec (minor) and 754 sec (major) | CHIRALPAK IC; IPA/*i*-Hex 02/98; 0.7 mL min^{-1})

Diethyl (5*S*)-2-(4-methoxyphenyl)-5-phenylcyclopent-2-ene-1,1-dicarboxylate

Procedure: using the general procedure, cyclopentene **9ga** is isolated after purification by flash chromatography on silica gel (07/93 EtOAc/cyclohexane).

Isolated yield: 47 %
Aspect: colourless liquid
Chemical formula: $C_{24}H_{26}O_5$
Mol. wt.: 394.46 g/mol



9ga

For descriptions of ^{1}H NMR, ^{13}C NMR, Mass, and IR spectra, see the racemic compound (page 243).

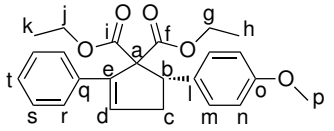
Specific rotation: $[\alpha]_D^{26} = -4°$ (c = 4.81, CH_2Cl_2)

Enantiomeric excess: 94 % (retention times: 368 sec (minor) and 571 sec (major) | CHIRALPAK IC; EtOH/*i*-Hex 10/90; 1.0 mL min^{-1})

Diethyl (5*S*)-5-(4-methoxyphenyl)-2-phenylcyclopent-2-ene-1,1-dicarboxylate

Procedure: using the general procedure, cyclopentene **9bb** is isolated after purification by flash chromatography on silica gel (07/93 EtOAc/cyclohexane).

Isolated yield: 55 %
Aspect: colourless liquid
Chemical formula: $C_{24}H_{26}O_5$
Mol. wt.: 394.46 g/mol



9bb

For descriptions of ^{1}H NMR, ^{13}C NMR, Mass, and IR spectra, see the racemic compound (page 250).

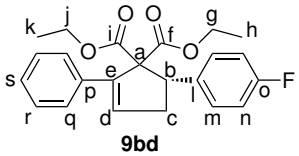
Specific rotation: $[\alpha]_D^{21} = -109°$ (c = 1.01, CH_2Cl_2)

Enantiomeric excess: 91 % (retention times: 449 sec (major) and 581 sec (minor) | CHIRALPAK IC; EtOH/*i*-Hex 05/95; 1.0 mL min^{-1})

Diethyl (5*S*)-5-(4-fluorophenyl)-2-phenylcyclopent-2-ene-1,1-dicarboxylate

Procedure: using the general procedure, cyclopentene **9bd** is isolated after purification by flash chromatography on silica gel (05/95 EtOAc/cyclohexane).

Isolated yield: 50 %
Aspect: colourless liquid
Chemical formula: $C_{23}H_{23}FO_4$
Mol. wt.: 382.42 g/mol



9bd

For descriptions of ^{1}H NMR, ^{13}C NMR, Mass, and IR spectra, see the racemic compound (page 248).

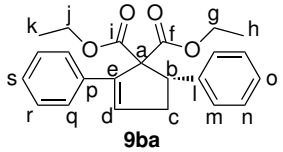
Specific rotation: $[\alpha]_D^{25} = -38°$ (c = 5.27, CH_2Cl_2)

Enantiomeric excess: 90 % (retention times: 414 sec (major) and 448 sec (minor) | CHIRALPAK IB; EtOH/*i*-Hex 05/95; 0.7 mL min^{-1})

Diethyl (5*S*)-2,5-diphenylcyclopent-2-ene-1,1-dicarboxylate

Procedure: using the general procedure, cyclopentene **9ba** is isolated after purification by flash chromatography on silica gel (05/95 EtOAc/cyclohexane).

Isolated yield: 47 %
Aspect: colourless liquid
Chemical formula: $C_{23}H_{24}O_4$
Mol. wt.: 364.43 g/mol



9ba

For descriptions of ^{1}H NMR, ^{13}C NMR, Mass, and IR spectra, see the racemic compound (page 241).

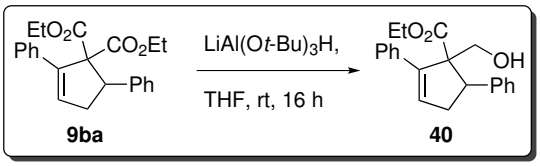
Specific rotation: $[\alpha]_D^{26} = +31°$ (c = 0.65, CH_2Cl_2)

Enantiomeric excess: >99 % (retention time: 397 sec | CHIRALPAK IB; EtOH/*i*-Hex 05/95; 0.7 mL min^{-1})

6.2.10 Versatility of our methodology

6.2.10.1 Diastereoselective ester reduction

Reference: O. Rousseau, T. Delaunay, G. Dequirez, T. Trieu-Van, K. Robeyns, R. Robiette, *Chem. Eur. J.* **2015**, *21*, 12899–12902.

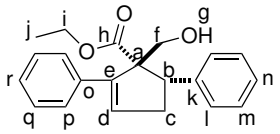


General procedure: in a dried round-bottom flask, under inert atmosphere, $LiAl(O\textit{t}\text{-}Bu)_3H$ (1 M in THF; 10 eq.) is added, dropwise, to a solution of cyclopentene **9ba** (6 mg to 60 mg; 0.016 mmol to 0.16 mmol; 1 eq.) in THF (1 mL), at 0 °C. After stirring for 16 h at room temperature, the reaction mixture is diluted with Et_2O (1 mL), then a saturated aqueous solution of "Rochelle salt" (potassium sodium tartrate; 2 mL) is added, dropwise. After stirring for 5 h at room temperature, the reaction mixture is diluted with water (2 mL) and extracted with Et_2O (1 mL). The organic layer is washed with water (2 x 2 mL), dried over $MgSO_4$, and then concentrated under reduced pressure, giving pure product **40** without further purification.

Ethyl 1-(hydroxymethyl)-2,5-diphenylcyclopent-2-ene-1-carboxylate (racemic mixture)

Procedure: using the general procedure (6.3 mg of racemic cyclopentene **9ba**), pure 3/1 diastereoisomers mixture of **40** is obtained in 56 % yield.

Isolated yield: 56 % (diastereoisomers mixture)
Aspect: colourless liquid
Chemical formula: $C_{21}H_{22}O_3$
Mol. wt.: 322.40 g/mol



40
d.r. 3/1

The analyses below relate to the major isomer (assuming [1*R**,5*S**]).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.19 (comp, 10H, Ar), 6.43 (dd, $J_{d,c}$ = 2.5 Hz, $J_{d,c'}$ = 2.5 Hz, 1H, d), 4.15 (dd, $J_{b,c}$ = 8.5 Hz, $J_{b,c'}$ = 8.5 Hz, 1H, b), 4.11 (dd, $J_{f,f'}$ = 11.8 Hz, $J_{f,g}$ = 6.6 Hz, 1H, f), 3.91-3.77 (comp, 2H, f' and i), 3.70 (dq, $J_{i',i}$ = 10.8 Hz, $J_{i',j}$ = 7.1 Hz, 1H, i'), 3.09 (ddd, $J_{c,c'}$ = 17.3 Hz, $J_{c,b}$ = 8.3 Hz, $J_{c,d}$ = 2.4 Hz, 1H, c), 2.90 (ddd, $J_{c',c}$ = 17.3 Hz, $J_{c',b}$ = 8.5 Hz, $J_{c',d}$ = 2.8 Hz, 1H, c'), 2.08 (t, $J_{g,f}$ = 6.7 Hz, 1H, g), 0.95 (t, $J_{j,i}$ = 7.2 Hz, 3H, j).

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.8 (h), 142.0 (e), 140.2 (k), 135.7 (o), 133.0 (d), 129.1 (l), 128.7,128.2,126.4 (m, p and q), 127.6 (n or r), 127.2 (r or n), 66.9 (a), 63.8 (f), 60.8 (i), 50.8 (b), 37.4 (c), 13.8 (j).

HRMS (APCI): *m/z*= 323.164 21; calcd. for $[M + H]^+$ ($C_{21}H_{23}O_3$): 323.164 17. **Fragment**: *m/z*= 277 $[M - OEt]^+$

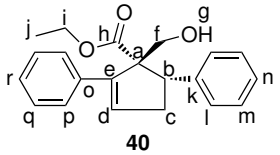
FT-IR (cm^{-1}): 3487, 2982;2953;2924;2901;2891;2853 (OH), 1720 (C=O), 1601 (C=C cyclopentene), 1497 (C=C Ar), 1464, 1454, 1445, 1259, 1221 (C-O), 1202, 1080, 1030, 758, 700.

Enantiomeric excess: racemic mixture (retention times: 722 sec and 779 sec | CHIRALPAK IC; EtOH/*i*-Hex 05/95; 1.0 mL min^{-1})

Ethyl (2*S*)-1-(hydroxymethyl)-2,5-diphenylcyclopent-2-ene-1-carboxylate

Procedure: using the general procedure (60 mg of enantioenriched cyclopentene **9ba**), pure 3/1 diastereoisomers mixture of **40** is obtained in quantitative yield.

Isolated yield: quantitative
Aspect: colourless liquid
Chemical formula: $C_{21}H_{22}O_3$
Mol. wt.: 322.40 g/mol



40
d.r. 3/1

For descriptions of ^{1}H NMR, ^{13}C NMR, Mass, and IR spectra, see the racemic compound above (page 267).

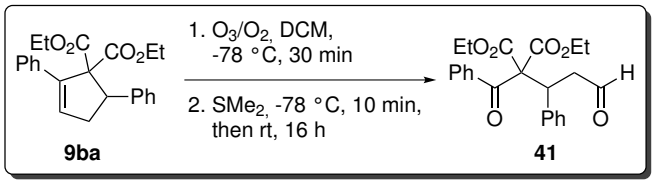
The analyses below relate to the major diastereoisomer (assuming [1*R*,5*S*]).

Specific rotation: $[\alpha]_D^{26} = +94°$ (c = 1.01, CH_2Cl_2)

Enantiomeric excess: >99 % (retention time: 727 sec | CHIRALPAK IC; EtOH/*i*-Hex 05/95; 1.0 mL min^{-1})

6.2.10.2 Ozonolysis reactions

Reference: O. Rousseau, T. Delaunay, G. Dequirez, T. Trieu-Van, K. Robeyns, R. Robiette, *Chem. Eur. J.* **2015**, *21*, 12899–12902.

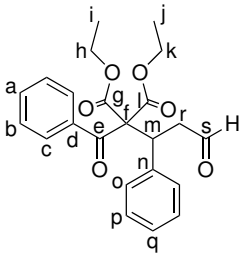


General procedure: in a round-bottom flask cyclopentene **9ba** (6 mg to 50 mg; 0.016 mmol to 0.14 mmol; 1 eq.) is added in DCM (10 mL). The reaction mixture is stirring for 30 min at −78 °C after 1 min of ozone injection at the same temperature. Dimethylsulfide (35 eq.) is next added, dropwise, at −78 °C. After stirring for 10 min at the same temperature and then for 16 h at room temperature, the reaction mixture is concentrated under reduced pressure.

Diethyl benzoyl(3-oxo-1-phenylpropyl)malonate (racemic mixture)

Procedure: using the general procedure (6.3 mg of racemic cyclopentene **9ba**), ozonolysis product **41** is obtained in quantitative yield without further purification.

Isolated yield: quantitative
Aspect: colourless liquid
Chemical formula: $C_{23}H_{24}O_6$
Mol. wt.: 396.43 g/mol



41

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.60 (s, 1H, s), 7.75 (m, 2H, c), 7.50 (t, $J_{a,b}$ = 7.4 Hz, 1H, a), 7.43-7.32 (comp, 4H, b and p), 7.29-7.15 (comp, 3H, o and q), 4.61 (dd, $J_{m,r}$ = 9.3 Hz, $J_{m,r'}$ = 5.0 Hz, 1H, m), 4.29-4.08 (comp, 2H, h), 4.02-3.76 (comp, 2H, k), 3.12-3.03 (comp, 2H, r), 1.08 (t, $J_{i,h}$ = 7.1 Hz, 3H, i), 0.89 (t, $J_{j,k}$ = 7.1 Hz, 3H, j).

^{13}C NMR (75 MHz, $CDCl_3$): δ 200.0 (s), 190.8 (e), 166.8 (g), 166.3 (l), 138.1 (n), 136.3 (d), 133.0 (a), 130.3 (o), 128.5,128.4,128.3 (b, c and p), 127.9 (q), 71.0 (f), 62.2 (h), 62.1 (k), 47.1 (r), 43.5 (m), 13.8 (i), 13.5 (j).

HRMS (APCI): *m/z*= 397.164 64; calcd. for $[M + H]^+$ ($C_{23}H_{25}O_6$): 397.164 56

FT-IR (cm^{-1}): 3065, 3032, 2982, 2937, 2905, 2849, 2829, 2735, 2725, 1771 (C=O ester), 1751 (C=O ester), 1724 (C=O), 1691 (C=O), 1597, 1582, 1495, 1464, 1447, 1389, 1367, 1296, 1245, 1230, 1213, 1186, 1095, 1074, 1053, 1038, 1024, 926, 899, 858, 756, 743, 700, 692.

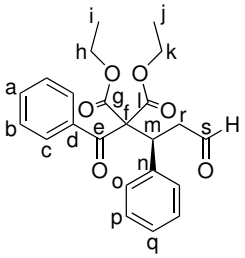
Enantiomeric excess: racemic mixture (retention times: 589 sec and 1054 sec (first enantiomer); 716 sec and 770 sec (second enantiomer)[51] | CHIRALPAK IC; EtOH/*i*-Hex 10/90; 1.0 mL min^{-1})

[51]Because ethanol is used as solvent for chiral HPLC, racemic ozonolysis product **41** is in equilibrium with the corresponding acetal, giving four retention times (589 sec, 716 sec, 770 sec, and 1054 sec).

Diethyl benzoyl[(1*S*)-3-oxo-1-phenylpropyl]malonate

Procedure: using the general procedure (50 mg of enantioenriched cyclopentene **9ba**), ozonolysis product **41** is obtained after purification by flash chromatography on silica gel (15/85 EtOAc/cyclohexane).

Isolated yield: 82 %
Aspect: colourless liquid
Chemical formula: $C_{23}H_{24}O_6$
Mol. wt.: 396.43 g/mol



41

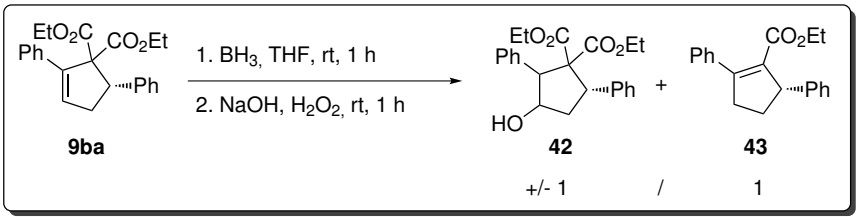
For descriptions of ^{1}H NMR, ^{13}C NMR, Mass, and IR spectra, see the racemic compound (page 270).

Specific rotation: $[\alpha]_D^{26} = -13°$ (c = 2.70, CH_2Cl_2)

Enantiomeric excess: >99 % (retention times: 771 sec and 831 sec[52] | CHIRALPAK IC; EtOH/*i*-Hex 10/90; 1.0 mL min^{-1})

[52]Because ethanol is used as solvent for chiral HPLC, enantioenriched ozonolysis product **41** is in equilibrium with the corresponding acetal, giving two retention times (771 sec and 831 sec). This particularity does not affect the enantiomeric excess calculation.

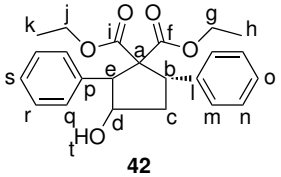
6.2.10.3 Hydroboration reaction



Procedure: in a dried round-bottom flask, a solution of BH_3.THF (1 M in THF; 0.75 mmol; 6.0 eq.) is added, dropwise, under inert atmosphere, to a solution of enantioenriched cyclopentene **9ba** (48 mg; 0.13 mmol; 1 eq.) in THF (2 mL), at 0 °C. After stirring for 1 h at room temperature, ice is added in the reaction mixture. A 1 M aqueous solution of NaOH (0.9 mmol; 7.0 eq.), followed by H_2O_2 (30 wt.%; 4.9 mmol; 38 eq.) are added, dropwise, at 0 °C. After stirring for 1 h at room temperature, the reaction mixture is diluted with water (2 mL) and extracted with Et_2O (3 x 2 mL). The combined organic layers are dried over $MgSO_4$ and concentrated under reduced pressure. An approximate 1/1 mixture of desired hydroboration adduct **42** and side product **43** is observed on the ^{1}H NMR spectrum of the crude mixture. Subsequent purification by flash chromatography allows to isolate these two products (20/80 to 60/40 EtOAC/cyclohexane).

Ethyl 3-hydroxy-2,5-diphenylcyclopentanecarboxylate

Isolated yield: 9 %
Aspect: colourless liquid
Chemical formula: $C_{23}H_{26}O_5$
Mol. wt.: 382.45 g/mol



42

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45-7.17 (comp, 10H, Ar), 5.24 (ddd, $J_{d,c} = 8.4$ Hz, $J_{d,e} = 8.4$ Hz, $J_{d,c'} = 4.1$ Hz, 1H, d), 4.28 (dd, $J_{b,c} = 10.2$ Hz, $J_{b,c'} = 10.2$ Hz, 1H, b), 4.09 (m, 2H, g), 3.75-3.66 (m, 1H, j), 3.63-3.53 (comp,

2H, e and j'), 2.97 (ddd, $J_{c,c'} = 13.9\,\text{Hz}$, $J_{c,b} = 10.6\,\text{Hz}$, $J_{c,d} = 8.8\,\text{Hz}$, 1H, c), 2.23 (ddd, $J_{c',c} = 13.9\,\text{Hz}$, $J_{c',b} = 9.8\,\text{Hz}$, $J_{c',d} = 4.1\,\text{Hz}$, 1H, c'), 1.03 (t, $J_{h,g} = 7.1\,\text{Hz}$, 3H, h), 0.72 (t, $J_{k,j} = 7.2\,\text{Hz}$, 3H, k). Proton "t" could not be observed.

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.0 (f or i), 169.5 (i or f), 139.1 (l), 137.2 (p), 130.1,129.7,128.1,127.9 (m, n, q and r), 127.6 (o or s), 127.2 (s or o), 75.7 (d), 71.0 (a), 63.1 (e), 61.2 (j), 60.8 (g), 50.0 (b), 38.6 (c), 13.9 (h), 13.5 (k).

HRMS (APCI): m/z= 383.185 06; calcd. for $[M + H]^+$ ($C_{23}H_{27}O_5$): 383.185 30. **Fragment**: m/z= 337 $[M - OEt]^+$

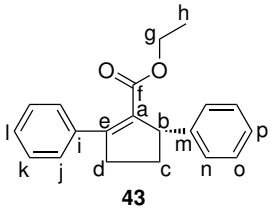
FT-IR (cm^{-1}): 3433, 2932, 2363, 1718 (C=O), 1497, 1456, 1445, 1367, 1269 (O-H), 1234, 1203, 1176, 1113, 1095, 1082, 1065, 1038, 700.

Specific rotation: because of the limited amount of isolated compound, the optical rotation was not carried out.

Enantiomeric excess: not calculated[53]

Ethyl 2,5-diphenylcyclopent-1-ene-1-carboxylate

Isolated yield: 5 %
Aspect: colourless liquid
Chemical formula: $C_{20}H_{20}O_2$
Mol. wt.: 292.37 g/mol



43

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 (m, 2H, j), 7.42 (d, $J_{n,o} = 7.3\,\text{Hz}$, 2H, n), 7.34 (dd, $J_{k,j} = 7.6\,\text{Hz}$, $J_{k,l} = 7.6\,\text{Hz}$, 2H, k), 7.30-7.24 (comp, 3H, o and [l or p]), 7.19 (t, $J = 7.3\,\text{Hz}$, 1H, l or p), 4.26 (dd, $J_{b,c} = 9.8\,\text{Hz}$, $J_{b,c'} =$

[53]The racemic compound have not been synthesized, enantiomers retention times were not known. Thereby, no chiral HPLC of enantioenriched product **42** was carried out.

9.8 Hz, 1H, b), 3.56 (q, $J_{g,h}$ = 7.2 Hz, 2H, g), 3.31 (ddd, $J_{d,d'}$ = 14.0 Hz, $J_{d,c}$ = 11.0 Hz, $J_{d,c'}$ = 5.7 Hz, 1H, d), 2.76 (dddd, $J_{c,c'}$ = 12.9 Hz, $J_{c,b}$ = 10.9 Hz, $J_{c,d}$ = 10.9 Hz, $J_{c,d'}$ = 4.8 Hz, 1H, c), 2.42 (dddd, $J_{c',c}$ = 12.9 Hz, $J_{c',b}$ = 9.2 Hz, $J_{c',d'}$ = 9.2 Hz, $J_{c',d}$ = 5.7 Hz, 1H, c'), 2.04 (ddd, $J_{d',d}$ = 13.9 Hz, $J_{d',c'}$ = 8.9 Hz, $J_{d',c}$ = 4.8 Hz, 1H, d'), 0.81 (t, $J_{h,g}$ = 7.2 Hz, 3H, h).

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.3 (f), 142.5 (i), 139.7 (m), 129.2 (n), 128.2 (two signals: l and p), 127.8 (k or o), 126.8 (o or k), 126.5 (j), 89.6 (e), 67.1 (a), 60.3 (g), 47.2 (b), 39.9 (d), 27.2 (c), 13.6 (h).

HRMS (APCI): *m/z*= 293.153 37; calcd. for $[M + H]^+$ ($C_{20}H_{21}O_2$): 293.153 61. **Fragment**: *m/z*= 247 $[M - OEt]^+$

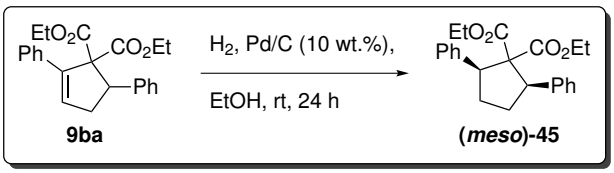
FT-IR (cm^{-1}): 3443, 3323, 3232, 2939, 1722 (C=O), 1707, 1495, 1460, 1445, 1225 (C-O), 1034, 702.

Specific rotation: because of the limited amount of isolated compound, the optical rotation was not carried out.

Enantiomeric excess: not calculated[54]

6.2.10.4 Double bond hydrogenation

Reference: O. Rousseau, T. Delaunay, G. Dequirez, T. Trieu-Van, K. Robeyns, R. Robiette, *Chem. Eur. J.* **2015**, *21*, 12899–12902.



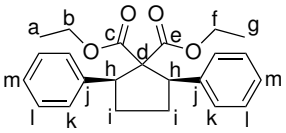
Procedure: in a dried round-bottom flask, under inert atmosphere, Pd/C (10 wt.%; 0.015 mmol; 0.1 eq.) is added to a solution of racemic cyclopentene **9ba** (50 mg; 0.14 mmol; 1 eq.) in degassed EtOH (1 mL). The reaction mixture is stirring for 24 h at room temperature under atmosphere of H_2 after 5 min of H_2 injection at the same temperature. The reaction mixture is next filtered on celite. The ^{1}H NMR spectrum of the crude mixture shows a d.r.

[54]The racemic compound have not been synthesized, the two enantiomers retention times are not know. Thereby, no chiral HPLC of the enantioenriched product was performed.

>98/2. Pure *meso* cyclopentane **45** is obtained after purification by flash chromatography on silica gel (04/96 EtOAc/cyclohexane).

(*Meso*)-diethyl 2,5-diphenylcyclopentane-1,1-dicarboxylate
CAS Reg No. 929721-54-0

Isolated yield: quantitative
Aspect: colourless liquid
Chemical formula: $C_{23}H_{26}O_4$
Mol. wt.: 366.45 g/mol



(*meso*)-45

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48-7.37 (comp, 4H, Ar), 7.34-7.19 (comp, 6H, Ar), 4.13 (q, $J_{b,a}$ = 7.1 Hz, 2H, b), 3.92 (m, 2H, h), 3.67 (q, $J_{f,g}$ = 7.1 Hz, 2H, f), 2.69 (m, 2H, i), 2.30 (m, 2H, i'), 1.07 (d, $J_{a,b}$ = 7.1 Hz, 3H, a), 0.75 (d, $J_{g,f}$ = 7.2 Hz, 3H, g).

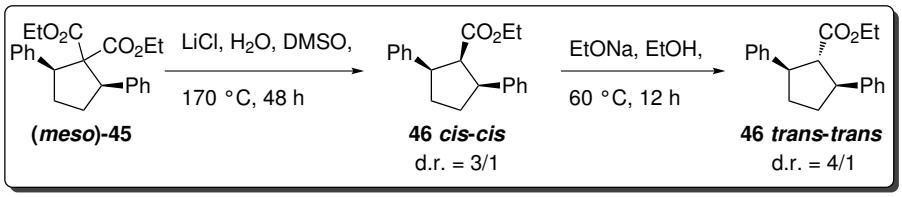
^{13}C NMR (75 MHz, $CDCl_3$): δ 171.7 (c), 168.6 (e), 139.7 (j), 129.4 (k), 127.8 (l), 127.0 (m), 70.4 (d), 61.0 (b), 60.3 (f), 54.2 (h), 29.6 (i), 13.9 (a), 13.5 (g).

HRMS (APCI): *m/z*= 367.190 21; calcd. for $[M + H]^+$ ($C_{23}H_{27}O_4$): 367.190 39. **Fragment**: *m/z*= 321 $[M - OEt]^+$

FT-IR (cm^{-1}): 3063, 3030, 2982, 2957, 2937, 2918, 2876, 2849, 1717 (C=O), 1603, 1497 (C=O), 1464, 1454, 1447, 1366, 1294, 1265 (C-O), 1227, 1202, 1159, 1105, 1074, 1043, 1028, 764, 746, 698.

6.2.10.5 Krapcho decarboxylation[55]

Reference: O. Rousseau, T. Delaunay, G. Dequirez, T. Trieu-Van, K. Robeyns, R. Robiette, *Chem. Eur. J.* **2015**, *21*, 12899–12902.



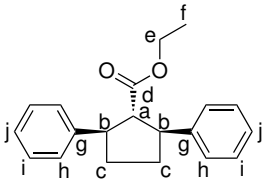
Procedure: in a round-bottom flask, equipped with a reflux condenser, *meso* cyclopentane **45** (60 mg; 0.16 mmol; 1 eq.), LiCl (0.64 mmol, 4 eq.), and one drop of water are added, in DMSO (2 mL). After stirring for 48 h at 170 °C, the reaction mixture is diluted with EtOAc (2 mL) and water (1 mL). The organic layer is washed with water (1 mL), brine (1 mL), dried over $MgSO_4$, and then concentrated under reduced pressure. The ^{1}H NMR spectrum of the crude mixture shows a 3/1 d.r of compound **46** (*cis-cis*/*trans-trans*). This diastereoisomeric mixture could be isolated after purification by flash chromatography on silica gel (04/96 EtOAc/cyclohexane) as a colorless liquid, in 88 % yield.

In order to have the most sterically-favored compound **46** *trans-trans* (see section 6.3.2, page 288), EtONa (0.32 mmol, 2 eq.) is added to the purified mixture of **46** *cis-cis* and **46** *trans-trans*, in EtOH (1 mL). After stirring for 12 h at 60 °C, the reaction mixture is concentrated under reduced pressure, and then diluted with EtOAc (2 mL) and water (1 mL). The organic layer is washed with brine (1 mL), dried over $MgSO_4$ and then concentrated under reduced pressure. A 4/1 diastereoisomeric mixture in which **46** *trans-trans* is the major isomer is obtained as a colorless liquid in 92 % yield without further purification.

[55]The two reactions were carried out by Dr. Thierry Delaunay.

(1*R*)-ethyl (2*R*,5*S*)-2,5-diphenylcyclopentanecarboxylate

Isolated yield: 81 % (over two steps)
Aspect: colourless liquid
Chemical formula: $C_{20}H_{22}O_2$
Mol. wt.: 294.39 g/mol



46 *trans-trans*

The analyses below relate to the major diastereoisomer (assuming [2*R*,5*S*]).[56]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34-7.25 (comp, 8H, Ar), 7.21 (m, 2H, Ar), 3.94 (q, $J_{e,f}$ = 7.1 Hz, 2H, e), 3.52 (m, 2H, b), 2.96 (t, $J_{a,b}$ = 10.6 Hz, 1H, a), 2.35 (m, 2H, c), 2.04 (m, 2H, c'), 0.95 (t, $J_{f,e}$ = 7.1 Hz, 1H, f).

^{13}C NMR (125 MHz, $CDCl_3$): δ 174.7 (d), 143.5 (g), 128.6 (i), 127.3 (h), 126.6 (j), 60.7 (e), 60.3 (a), 50.7 (b), 33.8 (c), 14.2 (f).

HRMS (APCI): *m/z*= 295.169 14; calcd. for $[M + H]^+$ ($C_{20}H_{23}O_2$): 295.169 26. **Fragment**: *m/z*= 249 $[M - OEt]^+$

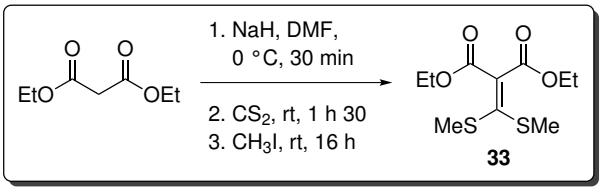
FT-IR (cm^{-1}): 2972, 2955, 2918, 2903, 2872, 1728 (C=O), 1603, 1495 (C=C Ar), 1464, 1454, 1377, 1296, 1263, 1215, 1178, 1028, 754, 698.

[56]The analyses on the other isomer *cis-cis* were not carried out, its percentage in the diastereoisomers mixture being too small.

6.2.11 Miscellaneous reactions

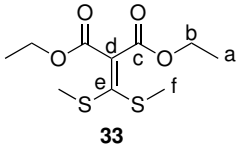
Diethyl [bis(methylthio)methylene]malonate
CAS Reg No. 55084-15-6

Reference: J. A. Wiles, A. Hashimoto, J. A. Thanassi, J. Cheng, C. D. Incarvito, M. Deshpande, M. J. Pucci, B. J. Bradbury, *J. Med. Chem.* **2006**, *49*, 39–42.



Procedure: in a dried round-bottom flask, under inert atmosphere, a solution of diethyl malonate (2.9 mL; 19 mmol; 1 eq.) in DMF (10 mL) is added, dropwise, to a solution of NaH (60 % dispersion in mineral oil; 38 mmol; 2.0 eq.) in DMF (20 mL), at −5 °C. After stirring for 30 min at 0 °C, carbon disulfide (38 mmol; 2.0 eq.) is added, dropwise, at the same temperature. After stirring for 1 h 30 at room temperature, methyl iodide (95 mmol; 5 eq.) is added, dropwise, at 0 °C. The reaction mixture is stirred for 16 h at room temperature, then diluted with water (50 mL) and extracted with EtOAc (5 x 25 mL). The combined organic layers are washed with water (3 x 25 mL), brine (20 mL), dried over $MgSO_4$, and then concentrated under reduced pressure. The product **33** is isolated after purification by flash chromatography on silica gel (10/90 EtOAc/cyclohexane).

Isolated yield: 56 %
Aspect: dark orange oil
Chemical formula: $C_{10}H_{16}O_4S_2$
Mol. wt.: 264.36 g/mol



^{1}H NMR (300 MHz, $CDCl_3$): δ 4.25 (q, $J_{b,a}$ = 7.1 Hz, 4H, b), 2.43 (s,

6H, f), 1.29 (t, $J_{a,b}$ = 7.1 Hz, 6H, a).

^{13}C NMR (75 MHz, $CDCl_3$): δ 164.0 (c), 158.7 (e), 127.4 (d), 61.4 (b), 18.5 (f), 14.0 (a).

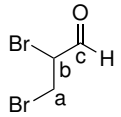
The ^{1}H and ^{13}C NMR spectra are in agreement with literature; see: J. A. Wiles, A. Hashimoto, J. A. Thanassi, J. Cheng, C. D. Incarvito, M. Deshpande, M. J. Pucci, B. J. Bradbury, *J. Med. Chem.* **2006**, *49*, 39–42.

2,3-Dibromopropanal
CAS Reg No. 5221-17-0

Reference: W. Li, J. Li, Z.-K. Wan, J. Wu, W. Massefski, *Org. Lett.* **2007**, *9*, 4607–4610.

Procedure: in a dried round-bottom flask, under inert atmosphere, bromine (11 mmol; 1.1 eq.) is added, dropwise, to a solution of acrolein (0.7 mL; 10 mmol; 1 eq.) in DCM (20 mL), at 0 °C. After stirring for 10 min at the same temperature, a saturated aqueous solution of $Na_2S_2O_3$ (20 mL) is added, at 0 °C, in order to remove the excess of bromine. The reaction mixture is stirred for 15 min at room temperature, then layers are separated. The aqueous layer is extracted with DCM (2 x 10 mL), the combined organic layers are washed with water (10 mL), brine (10 mL), dried over $MgSO_4$, and then concentrated under reduced pressure.

Isolated yield: 91 %
Aspect: pale yellow liquid
Chemical formula: $C_3H_4Br_2O$
Mol. wt.: 215.87 g/mol



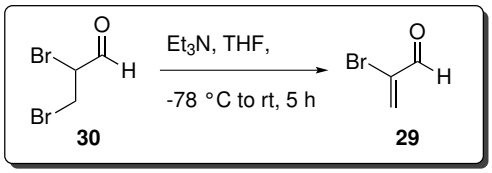
30

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.36 (d, $J_{c,b} = 2.8$ Hz, 1H, c), 4.53 (ddd, $J_{b,a} = 10.1$ Hz, $J_{b,a'} = 4.7$ Hz, $J_{b,c} = 2.8$ Hz, 1H, b), 3.86 (dd, $J_{a,b} = 10.4$ Hz, $J_{a,a'} = 10.4$ Hz, 1H, a), 3.71 (dd, $J_{a',a} = 10.6$ Hz, $J_{a',b} = 4.7$ Hz, 1H, a').

^{13}C NMR (75 MHz, $CDCl_3$): δ 189.1 (c), 49.0 (b), 27.0 (a).

2-Bromoacrylaldehyde

CAS Reg No. 14925-39-4

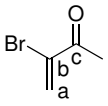


30 **29**

Procedure: in a bottomed flask, Et_3N (1 mmol; 1.2 eq.) is added, dropwise, to a solution of brominated compound **30** (0.2 g; 0.9 mmol; 1 eq.) in THF (10 mL), at −78 °C. After stirring for 5 h at room temperature (the cooling bath recovering slowly to room temperature), the reaction mixture is diluted with water (10 mL) and extracted with Et_2O (10 mL). The organic layer is washed with water (2 x 10 mL), brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure.[57]

Isolated yield: 74 %
Aspect: colourless liquid
Chemical formula: C_3H_3BrO
Mol. wt.: 134.96 g/mol

[57]The rotary evaporator bath is set to 0 °C to avoid desired product **29** degradation and evaporation.

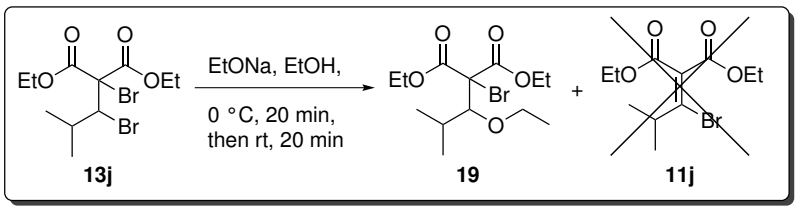


29

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.20 (s, 1H, c), 6.88 (d, $J_{a,a'} = 2.3$ Hz, 1H, a), 6.86 (d, $J_{a',a} = 2.3$ Hz, 1H, a').

The ^{1}H NMR spectrum is in agreement with literature; see: M. Hatano, T. Mizuno, A. Izumiseki, R. Usami, T. Asai, M. Akakura, K. Ishihara, *Angew. Chem. Int. Ed.* **2011**, *50*, 12189–12192.

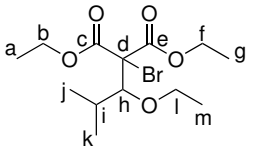
Diethyl bromo(1-ethoxy-2-methylpropyl)malonate



13j **19** **11j**

Procedure: in a dried round-bottom flask, under inert atmosphere, a solution of EtONa (0.2 mmol; 1.7 eq.) in EtOH (0.5 mL) is added, dropwise, to a solution of compound **13j** (44 mg; 0.12 mmol; 1 eq.) in EtOH (0.5 mL), at 0 °C. After stirring for 20 min at the same temperature and then 20 min at room temperature, the reaction mixture is concentrated under reduced pressure, then diluted with water (3 mL) and extracted with DCM (2 x 4 mL). The combined organic layers are washed with brine (4 mL), dried over $MgSO_4$, and then concentrated under reduced pressure. Pure S_N2 product **19** is isolated without further purification in 49 % yield.

Isolated yield: 49 %
Aspect: pale yellow liquid
Chemical formula: $C_{13}H_{23}O_5Br$
Mol. wt.: 339.22 g/mol



19

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.32-4.22 (comp, 4H, b and f), 3.92 (d, $J_{h,i}$ = 3.6 Hz, 1H, h), 3.66 (m, 2H, l), 2.15 (m, 1H, i), 1.31 (t, J = 7.0 Hz, 3H, a or g), 1.29 (t, J = 7.0 Hz, 3H, g or a), 1.15 (t, $J_{m,l}$ = 6.9 Hz, 3H, m), 1.08 (d, J = 6.9 Hz, 3H, j or k), 1.03 (d, J = 6.9 Hz, 3H, k or j).

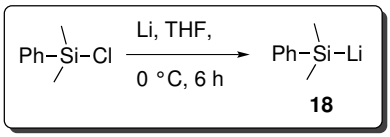
^{13}C NMR (75 MHz, $CDCl_3$): δ 166.4 (c or e), 165.8 (e or c), 85.9 (h), 69.4 (l), 69.0 (d), 63.2 (b or f), 63.0 (f or b), 32.6 (i), 23.4 (j or k), 18.0 (k or j), 15.6 (m), 14.0 (a or g), 13.9 (g or a).

HRMS (APCI): m/z= 339.080 16; calcd. for [M (^{79}Br) + H]$^+$ ($C_{13}H_{24}O_5{}^{79}Br$): 339.080 16. **Fragment**: m/z= 293 [M (^{79}Br) - OEt]$^+$

FT-IR (cm^{-1}): 2976, 2934, 2907, 2876, 1767, 1738 (C=O), 1466, 1445, 1389, 1367, 1298, 1244 (C-O), 1198, 1134, 1092, 1020, 947, 860.

[Dimethyl(phenyl)silyl]lithium
CAS Reg No. 3839-31-4

Reference: I. Fleming, R. S. Roberts, S. C. Smith, *J. Chem. Soc. Perkin Trans. 1* **1998**, 1209–1214.



18

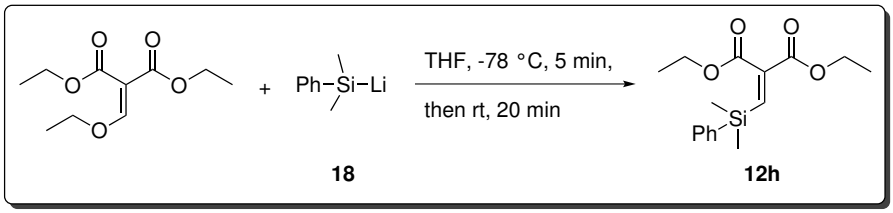
Procedure: in a dried round-bottom flask, under inert atmosphere, chloro-(dimethyl)phenylsilane (5 mL; 30 mmol; 1 eq.) is added, dropwise, to a solution of lithium wires (72 mmol; 2.4 eq.) in THF (20 mL), at 0 °C. After stirring vigorously fo 6 h at the same temperature, a THF solution of the organolithium reagent **18** is ready to use for the next step.[58]

[58] According to the literature, a 1 M solution of the organolithium reagent **18** is obtained that way.

Aspect: dark red liquid (solution in THF)
Chemical formula: $C_8H_{11}SiLi$
Mol. wt.: 142.20 g/mol

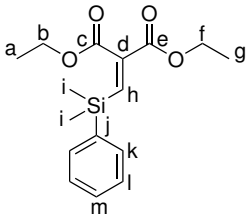
Diethyl [dimethyl(phenyl)silyl]methylenemalonate
CAS Reg No. 130247-53-9

Reference: S. M. Date, P. Iyer, S. K. Ghosh, *Synth. Commun.* **2004**, *34*, 405–411.



Procedure: in a dried round-bottom flask, under inert atmosphere, organolithium reagent **18** (1 M in THF; 1 mmol; 1 eq.) is added to a solution of diethyl (ethoxymethylene)malonate (0.2 mL; 1.0 mmol; 1 eq.) in THF (2 mL), at −78 °C. After stirring for 5 min at the same temperature and then for 20 min at room temperature, the reaction is quenched with a saturated aqueous solution of NH_4Cl (2 mL) and then extracted with Et_2O (2 x 4 mL). The combined organic layers are washed with water (2 mL), brine (2 mL), dried over $MgSO_4$, and then concentrated under reduced pressure. The product **12h** is isolated after purification by flash chromatography on silica gel (02/98 to 05/95 EtOAc/cyclohexane).

Isolated yield: 52 %
Aspect: colourless liquid
Chemical formula: $C_{16}H_{22}O_4Si$
Mol. wt.: 306.43 g/mol



12h

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54-7.51 (comp, 2H, Ar), 7.39-7.33 (comp, 3H, Ar), 7.32 (s, 1H, h), 4.24 (q, J = 7.2 Hz, 2H, b or f), 4.00 (q, J = 7.2 Hz, 2H, f or b), 1.28 (t, J = 7.0 Hz, 3H, a or g), 1.19 (t, J = 7.2 Hz, 3H, g or a), 0.45 (s, 6H, i).

^{13}C NMR (125 MHz, $CDCl_3$): δ 166.2 (c or e), 163.8 (e or c), 147.6 (h), 141.7 (d), 136.3 (j), 134.0,129.5,127.9 (k, l and m), 61.6 (b or f), 61.3 (f or b), 14.1 (a or g), 13.9 (g or a), -2.5 (i).

The ^{1}H and ^{13}C NMR spectra are in agreement with literature; see: S. M. Date, P. Iyer, S. K. Ghosh, *Synth. Commun.* **2004**, *34*, 405–411.

6.3 Appendices

6.3.1 X-ray diffraction analysis of 9pa[59]

X-ray data collection was performed on a Mar345 image plate detector using Mo-K_α radiation (Rigaku UltraX18S generator, Xenocs Fox3d mirrors) at 150(2) K. The data were integrated with the crysAlisPro software[60]. The implemented empirical absorption correction was applied. The structures were solved by direct methods using the SHELXS-97 program[61] and refined by full-matrix least squares on $|F^2|$ using SHELXL-2014/7[61]. Non-hydrogen atoms were anisotropically refined and the hydrogen atoms were placed on calculated positions in riding mode with temperature factors fixed at 1.2 times U_{eq} of the parent atoms (1.5 for methyl hydrogens). Figures were generated using the program PLATON[62]

The absolute configuration of **9pa** was finally determined using the anomalous signal from the 4 oxygen atoms in the molecule.[63] High resolution data (Mo radiation, highest resolution: 0.77 Å) were collected (a total of 344 images, corresponding to a total of 516°) with an average redundancy of 8; although the standard deviation on the parsons z value (0.0(2)) is high, the absolute structure determination using likelihood analysis on Bijvoet differences (t-distribution)[64] as implemented in PLATON[62] indicates that the absolute structure had been correctly assigned. The probability that the structure is inverted is less than 6.110×10^{-7}, the configuration around C7 can thus be assigned as S.

HPLC analysis on the crystal itself an on the crystal combined with the bulk also confirmed that the synthesis was enantiomeric pure (ee >99 %). See page 261.

[59] Carried out by Dr. Koen Robeyns.
[60] Oxford Diffraction Data collection and Data reduction, version 1.171.37.31.
[61] G.M. Sheldrick, *Acta Cryst.* **2008**, A**64**, 112-122.
[62] A.L. Spek. PLATON, A Multipurpose Crystallographic Tool; Utrecht University, Utrecht, The Netherlands, 2014.
[63] The use of Mo Kα radiation in the assignment of the absolute configuration of light-atom molecules; the importance of high-resolution data E. C. Escudero-Adán, J. Benet-Buchholz, P. Ballester, *Acta Cryst. B* **2014**, *70*, 660-668.
[64] R.W.W. Hooft, L.H. Straver, A.L. Spek, *J. Appl. Cryst.* **2010**, *43*, 665-668. *Using the t-distribution to improve the absolute structure assignment with likelihood calculations.*

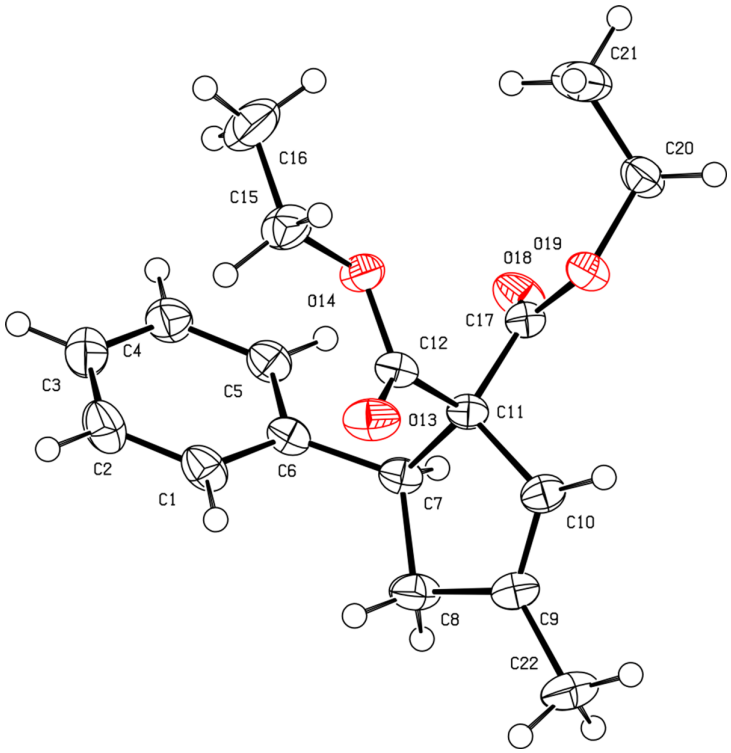


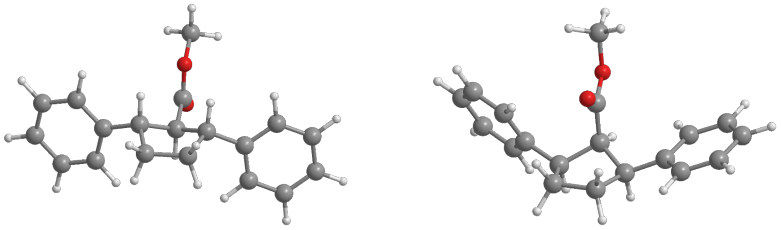
Figure 6.2: Ortep representation of compound **9pa** with thermal ellipsoids drawn at the 50 % probability level. For good order the hydrogen on carbon C7 is pointing down, the absolute configuration can thus be assigned as *S*.

Table 6.1: Crystal data and structure refinement statistics for **9pa**

Empirical formula	$C_{18}H_{22}O_4$
CCDC deposition number	1405787
Formula weight	302.35
Temperature	150(2) K
Wavelenght	0.710 73 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 8.221 05(11) Å ; $\alpha = 90°$
	b = 12.466 93(14) Å ; $\beta = 90°$
	c = 16.261 58(20) Å ; $\gamma = 90°$
Volume	1666.67(3) $Å^3$
Z	4
Density (calculated)	1.205 Mg/m^3
Absorption coefficient	0.084 mm^{-1}
F(000)	648
Crystal size	0.50 x 0.20 x 0.05 mm^3
Theta range for data collection	3.222 to 27.431°
Index ranges	$-10 \leq h \leq 10$
	$-16 \leq k \leq 16$
	$-21 \leq l \leq 20$
Reflections collected	30389
Independent reflections	3758 [$R_{(int)} = 0.0427$]
Completeness to theta = 25.242°	98.5 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.91397
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3758 / 0 / 202
Goodness-of-fit on F^2	1.069
Final R indices [I>2sigma(I)]	$R_1 = 0.0337$, $wR_2 = 0.0909$
R indices (all data)	$R_1 = 0.0349$, $wR_2 = 0.0918$
Absolute struct. param. (Parsons)	0.0(2)
Largest diff. peak and hole	0.191 and -0.132 e/$Å^3$

6.3.2 Stability studies of 46[65]

The relative stability of the two diastereoisomers of **46** was investigated by computational means. Optimization calculations were performed at the B3LYP-D3/6-31+G(d) level of theory using Jaguar 8.0. Energies were obtained by single point calculations at the B3LYP-D3/6-311+G(d,p) level of theory using the fine DFT grid. Solvation effects were included at both the optimization and single point level using the polarizable continuum–Poisson method as incorporated in Jaguar 8.0 and the parameters for EtOH.



(a) **46** ***trans-trans***
ΔE_{rel} = 0.0 kcal/mol

(b) **46** ***cis-cis***
ΔE_{rel} = 4.7 kcal/mol

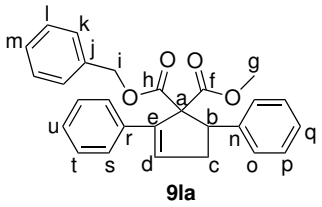
Figure 6.3: Relative stability of the two diastereoisomers of **46**.

[65]Carried out by Prof. Raphaël Robiette.

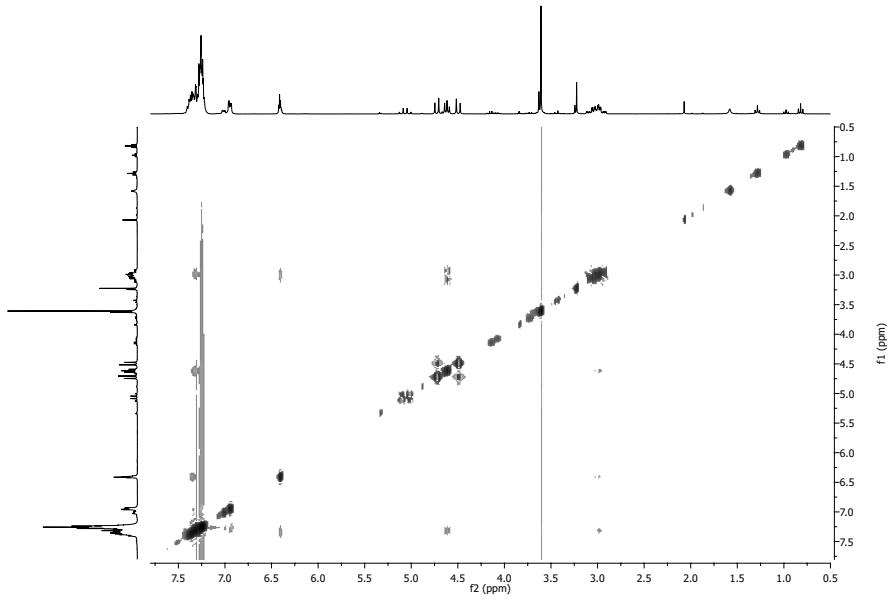
6.3.3 NOESY experiment on cyclopentene 9la

A NOESY experiment was carried out on non-symmetric cyclopentene **9la** in order to determine its absolute configuration. However, this latter could not be elucidated from this spectrum.

NOESY (300 MHz, $CDCl_3$):[66]



9la



[66]The mixing time was set to 0.9 sec, and 32 scans were carried out.

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