Synthetic studies on novel anionic and transition metal catalyzed reactions. Synthesis of 3-Silapiperidines and cyclizations of 1,5- and 1,4-enynes

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Synthesis of 3-Silapiperidines and cyclizations of 1,5- and 1,4-enynes

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みんなをいつもおぼえている。やくそくだ！
おなかちゃんはおかしを食べすぎる。時々いっしょに食べた。そましはいつも《ｍａｚｉ で 》といいった。　ひちゃんはせんとくんが好きだった。けど私はきもいと思う。時々石井さんとしょくどうでいっしょに食べた。いっぱい男の話をした。じじはいつもおかしかった。おたくだから！きっぽくんはビデオゲームが大好きだった。やすみの時、かれは（オビワン）きのぴとゆうちゃんといっしょにあそんでた。。。あみちゃん（I know, I know ！）元気でね！たくくんとくうこうに来てくれてありがとう。M-研くんはいい人です。ホワイトデーのチョコカキをありがとう。
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Abbreviation list

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Reagents

BMDMS	bromomethyldimethylsilyl
CAN	cerium ammonium nitrate
DMAP	4-dimethylaminopyridine
LDA	lithium diisopropylamide
PTSA	*para*-toluenesulfonyl acid
TMEDA	tetramethylethylenediamine
TPPTS	sodium triphenylphosphine trisulfonate $P(C_6H_4SO_3Na)_3$

Solvents

DCM	dichloromethane
DCE	dichloroethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
PE	petroleum ether
pyr.	pyridine
TEA	triethylamine
tol.	toluene

Chemical groups

Ac	acetyl
Ar	aryle (RMN)
Bn	benzyl
Boc	*tert*-butoxycarbonyl
*i*Pr	isopropyl
n-Bu	linear-butyl
MEM	methoxyethoxymethyl ether
Piv	pivaloyl
PMP	*para*-methoxyphenyl
PNB	*para*-nitrobenzoate
Tr	trityl
t-Bu	*tert*-butyl
Sec-Bu	*sec*-butyl
TBS	*tert*-butyldimethylsilyl
TIPS	tri*iso*-propylsilyl
TMS	trimethylsilyl
Ts	tosyl

Chromatography and spectroscopy

bs	broad singlet
CI	chemical ionisation (MS)
COSY	Correlated spectroscopy Y
δ	chemical shift (NMR)
HRMS	high resolution mass spectrometry
IR	infrared
J	coupling constant
m	multiplet
M	molecular mass (MS)
NOESY	nuclear Overhauser experiment spectroscopy Y
NMR	nuclear magnetic resonance
q	quadriplet
Rf	retention factor
s	singlet
t	triplet
TLC	thin layer chromatography

Others

cat.	catalytic
conv.	conversion
DFT	density functional theory
dias.	diastereomer
Δ	heating at reflux
ee	enantiomeric excess
eq.	equivalent
quant.	quantitative
M	metal
m. p.	melting point
MW	micro-wave
r.t.	room temperature
UV	ultraviolet

Peptides

L	leucine
P	proline
R	arginine
V	valine

General Introduction

General Introduction

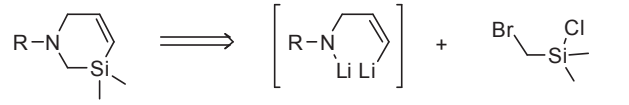
This manuscript consists of three chapters. Each of them deals with one research area developed during this thesis. In the third chapter, the results of the collaboration between Université Pierre et Marie Curie and Osaka Prefecture university are presented.

These three chapters are developed as follows:

- Dianionic chemistry is described as a tool for the synthesis of 3-silapiperidines (**Chapter I**).
- A new series of experiments were undertaken to get mechanistic insight into the [3.1.0]-bicyclic compounds formation under $PtCl_2$ catalysis (**Chapter II**).
- A new rhodium-catalyzed carbonylation of 1,4-enynes which allows the formation of resorcinol derivatives is detailed (**Chapter III**).

Chapter I

The reactivity of (bromomethyl)dimethylsilyl chloride (BMDMSCl) as a dielectrophile received relatively little attention these past few years. We had the idea to take advantage from the reactivity of this compound in concomitance with the dianionic chemistry of allylamine derivatives for the preparation of 3-silapiperidines (Scheme 1).



3-silapiperidine dianion Dielectrophile

Scheme 1

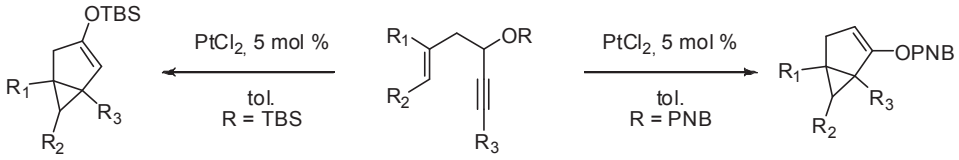
A brief bibliographic summary of the importance of synthesizing sila analogs of bioactive molecules, and a description of the interesting proprieties of *cis*-vinylic dianion derived from *N*-monoprotected allylamines will be presented. On the other hand, after the presentation of our

reaction conditions for the preparation of 3-silapiperidines and their subsequent functionalization, the scope and limitations of these synthetic transformations will be outlined. The reactivity of several allylamines (with different protecting groups) will be examined, then our attempts for the synthesis of a sila analog of a natural product (pipecolic acid) will be detailed.

Chapter II

Enynes skeletal rearrangements have been in full rise since the seminal reports by Trost in the early 1980's. In particular, transition metal-catalyzed cycloisomerizations of 1,4- to 1,7-enynes have given facile access to a broad variety of cyclic structures. Our laboratory has contributed in the blossoming of this field, in particular thanks to our work on 1,6- and 1,5-enyne platinum-catalyzed cyclizations. Our group was interested in the reactivity of platinum and gold salts and the possibility of these catalysts to promote novel cycloisomerization reactions. For this purpose, dienyne systems and later 1,5-enynes were studied. These substrates led to cycloadducts possessing a cyclopropane moiety and highlighted the importance of the substitution at the propargylic position.

Depending on the substitution at the propargylic position (esters or ethers), 1,2-migration may occur or not (Scheme 2). The purpose of the study presented in this chapter, is to clearly understand the mechanisms of these skeletal rearrangements so that we can extend the scope of this cyclisation by preparing products bearing more functionalities.

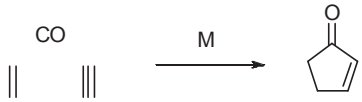


Scheme 2

The state of art of metal-catalyzed skeletal rearrangements of 1,6 and 1,5-enynes will be briefly presented, followed by a rapid summary of the mechanistic studies on these reactions. Besides, after the presentation of the scope of 1,5-enyne cyclopropanation reactions catalyzed by $PtCl_2$, the strategies we considered for the study of this reaction will be detailed. To date, a definitive conclusion about the mechanism pathways seems difficult, nevertheless the purpose of this chapter is to present our preliminary results about this delicate question and to show how some of the previous mechanistic hypotheses can be excluded.

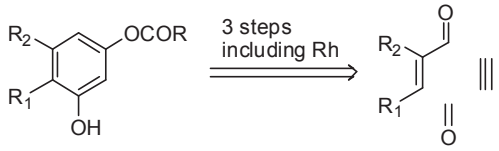
Chapter III

Metal-mediated reactions play an important role in the ongoing search for improved ways of building complex molecules. Reports about metal-catalyzed carbonylation have been numerous since the discovery in the early 1970's by Pauson and Khand of a coupling reaction between an alkyne, an alkene and carbon monoxide which affords cyclopentenones (Scheme 3). Thanks to the Pauson-Khand reaction, [2 + 2 +1]-cycloadditions have been widely employed and studied, moreover cycloadditions of higher order became a powerful tool for ring extension.



Scheme 3

The purpose of our work is to prepare resorcinol derivatives by combining our knowledge about enyne cycloisomerization (taking advantage of the Rautenstrauch rearrangement, see chapter II) and carbonylative cycloadditions (Scheme 4).



Scheme 4

A brief summary of the structure and properties of resorcinolic frameworks, in addition to a quick illustration of cycloadditions reactions will be outlined. Then, after the presentation of the diversely substituted resorcinols we prepared, the limitations of this reaction will be presented. We will particularly focus on the reaction conditions, show how the yields are influenced by these conditions, and also discuss about alternative mechanistic pathways.

I. Towards the synthesis of 3-silapiperidines

I. 1. Background

I. 1. 1. Challenges of pharmaceutical industries

I. 1. 1. a. Bioisosteric substitution

Drug discovery and design are complex processes that pharmaceutical industries have to handle.[1] Nowadays, the discovery process often starts by the synthesis of compound libraries and their evaluation. Optimization of the potential candidates goes through the determination of the best molecule design by a structure-activity survey. These new molecules in hands, *in vivo* suitability has to be proven before any further utilization on human being and subsequently commercialization as a new drug. However, these new compounds often have undesirable characteristics that limit their bioavailability, and possess unwanted effects or display toxicity.

Consequently, to remedy these side effects, it is necessary to convert these molecules into efficient drugs with desired pharmaceutical and suitable *in vivo* properties. One existing tool that allows this conversion into efficient drugs is the **bioisosteric substitution**.[2] A compound is called bioisostere when one atom of a molecule is replaced from the original structure by another atom with similar steric and electronic effects. Generally, a molecule and its bioisostere have the same number of atoms (classical bioisostere), but sometimes, they are known as non-classical bioisosteres because they only have in common similar distributions of electrons (Scheme I-1).[3]

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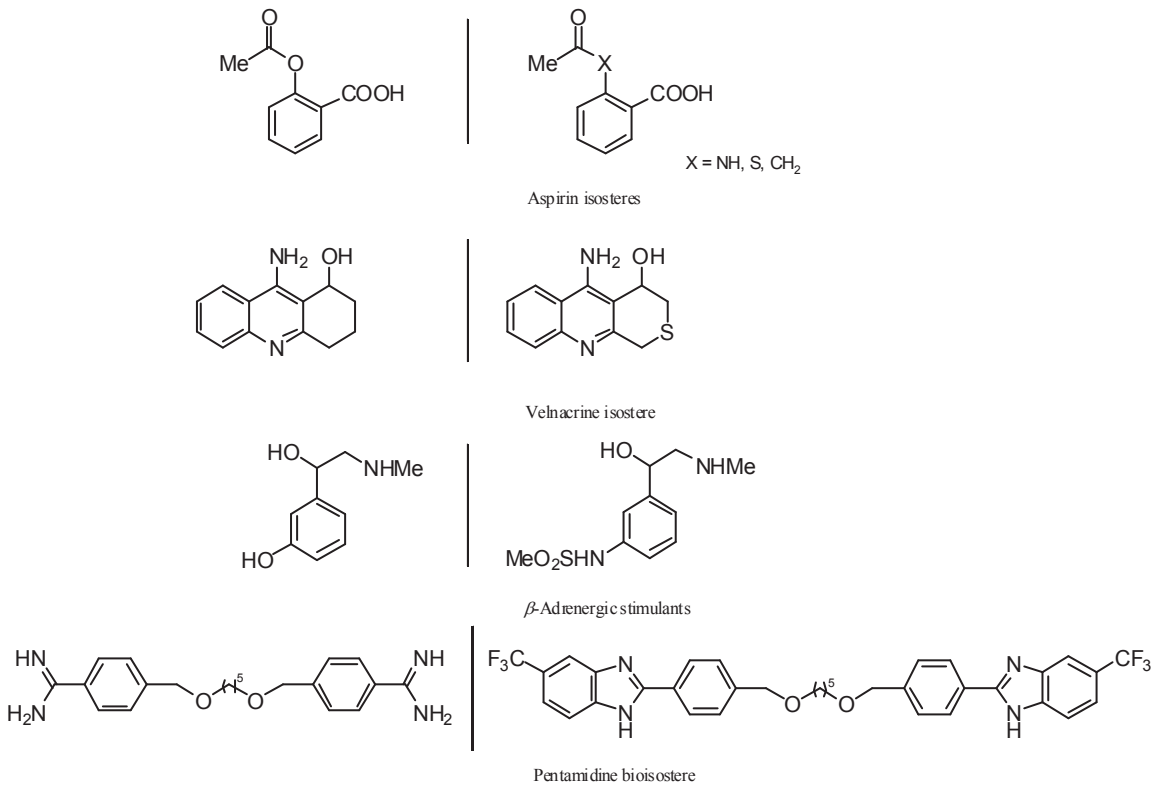
[1] Mills, J. S.; Showell, G. A. *Drug. Discov.Today* **2003**, *8*, 551.
[2] Thornber, C. W. *Chem. Soc. Rev*. **1979**, *4*, 563.
[3] (a) Thompkins, L.; Lee, K. H. *J. Pharm. Sci*. **1975**, *64*, 760 (b) Tabarrini, O.; Cecchetti, V.; Temperini, A.; Filipponi, E.; Lamperti, G. M.; Fravolini, A. *Bioorg. Med. Chem*. **2001**, *2*, 2921 (c) Larson, A. A.; Lish, P. M. *Nature* **1964**, *203*, 1283 (d) Torres-Gómez, H.; Hernández-Núñez, E.; León-Rivera, I.; Guerrero-Alvarez, J.; Chan-Bacab, M. J.; Navarrete-Vásquez, G. *Bioorg. Med. Chem*. **2008**, *18*, 3147.

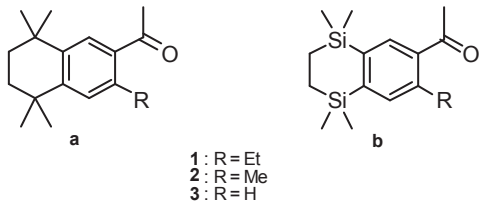


Scheme I-1: bioisosteric substitution

I. 1. 1. b. Sila substitution

Among classical bioisosteres, carbonyl, sulfoxyde and silyl groups are used to replace methylene and gem-dimethyl moiety, as for fluorine replace hydrogen. Since the 1970s, thanks to the work of Tacke and co-workers, sila substitution (C/Si exchange) has gained more attention.[4] Indeed, sila analogs can exhibit chemical and/or physical properties that are slightly modified compared to carbon analogs. A recent application of this modification was recently reported about the odorant properties of a sila analog of Versalide **1a** (Scheme I-2).[5] Versalide **1a** is a powerful musk odorant and compounds **2-3a** and **1-3b** are non natural derivatives. The muskiness of sila analogs **1-3b** was generally lower than their parent carbon analog, but allowed a wider odoriferous range.

[4] For recent synthesis of sila analogs, see:
[5] Büttner, M. W.; Penka, M. ; Doszczak, L.; Kraft, P.; Tacke, R. *Organometallics* **2007**, *26*, 1295.



Scheme I-2: Versalide and derivatives

Silicon chemistry appears to be a source of chemical diversity in the design of odorants, but other major applications exist in medicine, particularly in the field of drug delivery. One of the best potential benefits of sila substitutions is the improvement of lipophilicity of the analogs. Thanks to greater lipophilic character than its carbon derivative, tissue penetration would be enhanced and the distribution of the molecule would increase. It is also expected that sila analog would be less prone to liver metabolism. Adversely, the solubility of the molecule in water decreases along with increased lipophilicities.[1]

I. 1. 2. Applications of sila analogs in cell delivery and activity

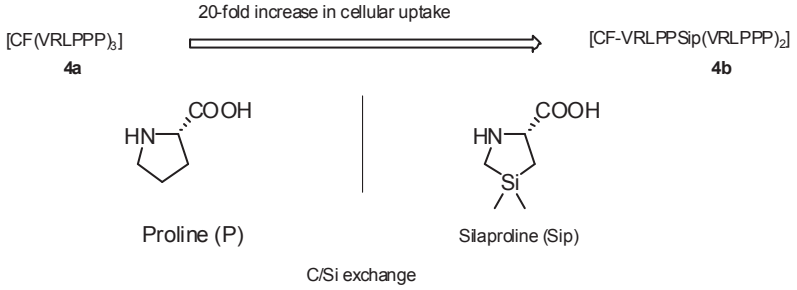
I. 1. 2. a. Silaproline unit in cell penetrating peptides (CPP)

When drug targets are located inside the cell, it is crucial to have a satisfactory delivery of active molecules. However, these molecules are generally unable to cross the cyctoplasmic membranes alone. In the middle of the 1990's, peptide sequences were reported to enter the cell membranes. These potential vectors of active drugs are named cell-penetrating peptides (CPP).[6]

Proline rich peptides are an interesting class of CPP thanks to the unique character of this natural amino acid compared to the other ones (that are acyclic). Indeed, proline confers rigidity to the peptide because of its strained structure and generates steric hindrance around the peptidic backbones. In 2004, Giralt and co-workers described the synthesis of an efficient proline rich CPP (**4a**), which sequence is: CF-(Val-Arg-Leu-Pro-Pro-Pro)$_3$. A polyaromatic chromophore (CF) was attached to CPP **4a** for the cell uptake monitoring.[7] Two years later, the same group published the results of the study upon cellular uptake of a sila bioisostere of CPP **4a**, where one proline unit was

[6] Pujals, S.; Giralt, E. *Adv. Drug Deliv. Rev*. **2007**, *60*, 473.
[7] Fernández-Carneado, J.; Kogan, M. J.; Castel, S.; Giralt, E. *Angew. Chem. Int. Ed*. **2004**, *43*, 1811.

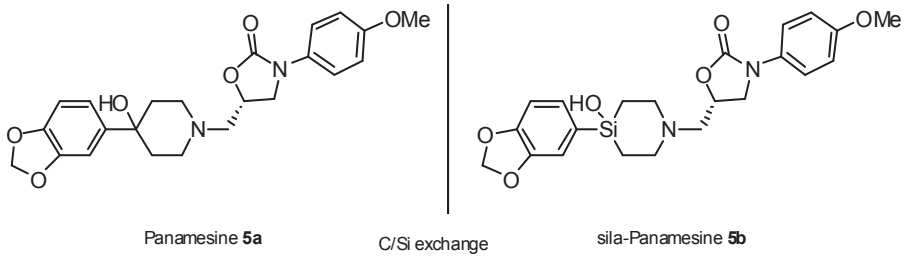
replaced by a silaproline (Sip).[8] The peptidique sequence of this bioisostere **4b** is CF-Val-Arg-Leu-Pro-Pro-Sip-(Val-Arg-Leu-Pro-Pro-Pro)$_2$. The modified peptid **4b** exhibit the same structural properties plus a 20-fold increase in the cellular uptake (Scheme I-3).



Scheme I-3: increased cellular uptake of a CPP bioisostere

I. 1. 2. b. A silapiperidine ligand for dopamine receptors

Another benefit of bioisosteric substitution is the potential modification of biological activity. In 2006, an impressive example of such action was reported. Tacke and co-workers prepared a sila analog of panamesine (EMD 57445) which is a ligand for dopamine receptors (Scheme I-4).[9] These receptors may be involved in the pathogenesis of schizophrenia and/or in the mechanism of action of antipsychotic drugs. The structure of panamesine **5a** has a central piperidine moiety. One carbon of this heterocycle was replaced by a silicon atom to form the 4-silapiperidine derivative **5b**. Subsequent pharmacological studies showed that analog **5b** exhibits 3-fold enhancement of affinity for dopamine receptors.



Scheme I-4: Panamesine

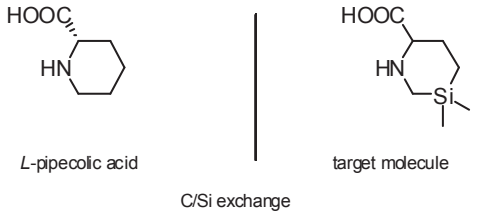
[8](a) Pujals, S.; Fernándes-Carnaedo, J.; Kogan, M. J.; Martinez, J.; Cavelier, F.; Giralt, E. *J. Am. Chem. Soc*., **2006**, *128*, 8479. For the influence of silaproline in peptid, see (b) Cavelier, F.; Vivet, B.; Martinez, J.; Aubry, A.; Didierjean, C.; Vicherat, A.; Marraud, M. *J. Am. Chem. Soc*. **2002**, *124*, 2917.
[9] Ilg, R.; Burschka, C.; Schepmann, D.; Wünsch, B.; Tacke, R. *Organometallics* **2006**, *25*, 5396.

I. 1. 3. Silapiperidines and (±)-pipecolic acid

I. 1. 3. a. Sila bioisostere of pipecolic acid (PA)

In our group, we set out to define a new method to synthesize sila analogs of piperidine ring and more particularly, 3-silapiperidine derivatives. Interestingly, such method may be used as a tool for the access to sila analogs of pipecolic acid (PA).

L-pipecolic acid is generally issued from plant,[10] whereas both *L*- and *D*-pipecolic acid are present in human physiological fluids (Scheme I-5).[11] *L*-PA is biosynthesized inter alia by the metabolism of *L*-lysine initiated by an enzyme issued from streptomyces bacteria.[12]



Scheme I-5: (-)-pipecolic acid and racemic sila bioisostere

I. 1. 3. b. Pipecolic acid as a precursor for a natural product synthesis

Pipecolic acid is a useful synthetic starting material for the total synthesis of natural products. For example, (+)-epiquinamide is a quinolizidine alkaloid extracted from an Ecuadorian poisonous frog. This natural product was found to be selective toward nicotinic acetylcholine receptors (nAChRs), and could be used for the development of therapeutic agents.[13]

Barker and co-worker reported the synthesis of (+)-epiquinamide in 12 steps from *L*-PA with an overall yield of 13 % (Scheme I-6). The key step involved a diastereoselective addition of a propargyl alcohol to a chiral aldehyde. This synthesis also allowed the confirmation of the absolute stereochemistry of the chiral centers of the isolated natural product.

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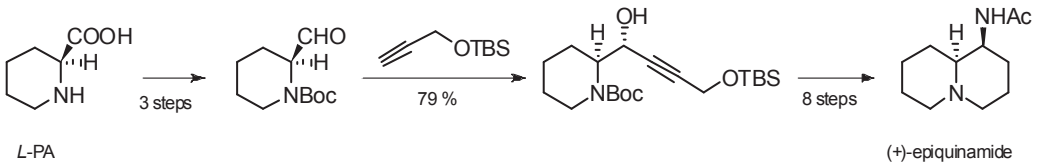
[10] (a) From fresh green beans, see: Zacharius, M.; Thompson, J. F.; Steward, F. C. *J. Am. Chem. Soc.* **1952**, *74*, 2949, (b) from mushrooms, see: Kiyoto, M.; Saito, S.; Hattori, K.; Cho, N.-S.; Hara, T.; Yagi, Y.; Aoyama, M.; *J. Wood. Sci.* **2008**, *54*, 179.
[11] Armstrong, D. W.; Gasper, M.; Haing Lee, S.; Zukowski, J.; Ercal, N. *Chirality.* **1993**, *5*, 375. Giacobini, E.; Nomura, Y.; Schmidt-Glenewinkle, T. *Cell. Mol. Biol.* **1980**, *26*, 135.
[12] Moulin, M.; Deleu, C.; Larher, F.; Bouchereau, A. *Plant Physiol. Biochem.* **2006**, *44*, 474.
[13] Barker, D.; Tong, S. T. *Tetrahedron Lett*. **2006**, *47*, 5010.



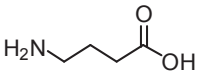
Scheme I-6: synthesis of (+)-epiquinamide

The use of a sila bioisostere of *L*-PA would be interesting here because the same synthetic route may allow the preparation of the sila bioisostere of (+)-epiquinamide (Scheme I-7). This potential new molecule may present an interest in the study of nAChRs activity in comparison to its carbon analog.

Scheme I-7: potential silylated agonist or nAChRs

I. 1. 3. c. Role of pipecolic acid in mammalian brain

The presence of pipecolic acid was reported in brains of dogs, rats and mice.[14] The role of this amino acid was not clearly established, but diverse studies point out the influence of PA in the regulation of γ-aminobutyric acid (GABA) which is a brain neurotransmitter (Scheme I-8).[15] The latter was demonstrated to have an inhibitory effect on synaptic activity.



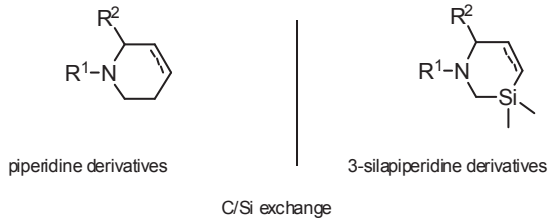
Scheme I-8: GABA

To compare PA and GABA activity, *in vivo* experiments were performed *via* their injections in mice brains. [16] In 1985, a survey has compared the effects of coadministration of picrotoxin (a convulsing agent) and GABA, with coadministration of picrotoxin and PA. While injections of picrotoxin alone provoked convulsions to the mice, its coadministration with GABA and PA

[14] For brain of dog, see (a): Kase, Y. K.; Kataoka, M.; Miyata, T.; Okano, Y. *Life Sci.*, **1973**, *13*, 867. For brain of rats, see (b): Giacobini, E.; Normura, Y.; Schmidt-Glenewinkel, T. *Cell. Mol. Biol*., **1980**, *26*, 135. For brain of mice, see (c): Nishio, H.; Segawa, T. *Anal. Biochem*., **1983**, *135*, 312.
[15] Guttierez, M. C.; Delgado-Coello, B. A. *Neurochem. Res.* **1989**, *14*, 405.
[16] Beitz, A. J.; Larson, A. A. *Eur. J. Pharma*. **1985**, *114*, 181.

inhibited these convulsions. In this experiment, synergic behaviours were observed for GABA and PA. On the other hand, when picrotoxin was injected before GABA, the latter failed to stop the convulsions. On the contrary, PA was efficient to diminish the duration of the convulsions. The sila bioisostere of PA may have a modified bioactivity that would be interesting to investigate for the study of the GABA receptors.

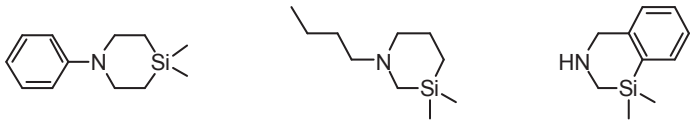
The two previous examples demonstrate the interest of the synthesis of sila bioisosteres of PA. We were not only interested in PA, but more generally in a simple synthetic method that would allow the access to diversly functionalized 3-silapiperidines (Scheme I-9).



Scheme I-9: piperidine bioisostere

I. 1. 3. d. Silapiperidine in the literature

To the best of our knowledge, silapiperidine frameworks are poorly reported in the literature. Few saturated silapiperidines, with various alkylation at the nitrogen have been synthesized. On the other hand, when it comes to silapiperidines with unsaturated carbons, bicyclic structures (with a phenyl group) are mainly encountered. (see below, selected silapiperidine frameworks, Scheme I-10).[17]

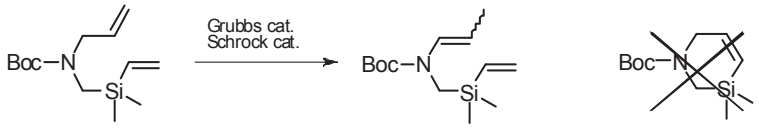


Scheme I-10: 3- and 4-silapiperidines

Encouraged by the results of Tacke and co-workers about the sila-panamesime,[9] we set out to study two approaches for the preparation of 3-piperidines: **metathesis** and **dianionic chemistry**.

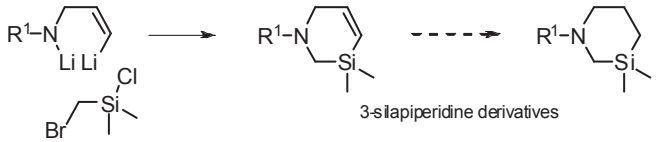
[17] (a) Fesseden, R. J.; Coon, M. D. *J. Org. Chem*. **1964**, *29*, 1607 (b) Aoyama, T.; Sato, Y.; Suzuki, T.; Shirai, H. *J. Organomet. Chem*. **1978**, *153*, 193 (c) Sato, Y.; Fukami, Y.; Shirai, H. *J. Organomet. Chem*. **1974**, *78*, 75.

This work was initiated in the laboratory by Christophe Blaszykowski[18] who has already discussed the metathesis approach in his thesis: attempts for the ring closing metathesis of a *N*-linked diene did not afford the desired silylated heterocyle (Scheme I-11).



Scheme I-11: metathesis approach

Only the dianionic chemistry approach will be detailed in the following paragraph. We were inspired by the dianionic chemistry of *N*-monoprotected allylamines that can form *cis*-vinylic dianions in the presence of two equivalents of lithiated base. Our idea was to take advantage of these regioselectively formed dianions to carry out nucleophilic substitution upon a silylated dielectrophile (Scheme I-12). The anion at the *cis*-vinylic position would be highly reactive and would attack first the more electrophilic site of the dielectrophile (silyl chloride position), then the less electrophilic site (methylbromide moiety) would be substituted by the nitrogen.



Scheme I-12: strategy using *cis*-vinylic dianion

Before the presentation of our results, a brief overall view of literature about anionic species derived from allylamines will be presented.

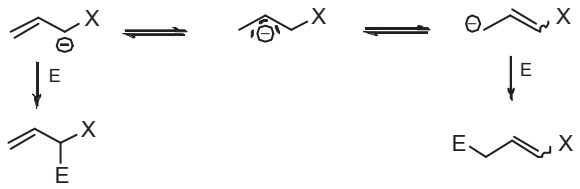
I. 1. 4. Anions derived from allylamines

I. 1. 4. a. Reactivity of allyl anions

Allyl anions chemistry is of major interest in organic chemistry because they give access to a wide variety of functionnalized products. Treatment of allylic halides with a strong base gives rise

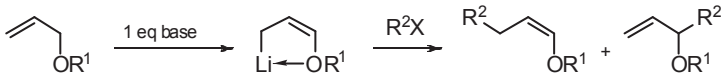
[18] Metathesis approach was fully detailed in the thesis of Dr. Blaszykowski: Réactivités radicalaire et dianionique d'amines β,γ-insaturées. Synthèse de γ-amino-alcools et de 3-silapipéridines (Thèse de l'université Pierre et Marie Curie, **2005**).

to synthetically useful allyl anions. These allyl anions are stabilized by resonance, and can react with electrophiles at two sites (Scheme I-13).



Scheme I-13: ambident anion

It should be noted that allyl anions are more stable than alkane anions, and that further stabilization can be brought by the heterosubstituent (Scheme I-14). For example, 1-alkoxy-2-propenes are lithiated with *sec*-butyllithium at -65°C to afford "O-linked products", due to the coordination of the oxygen to the lithium atom. Treatment of these allyl anions with alkyl halides gives rise to α- or γ-substituted allyl ethers. For this reason, they are called **ambident nucleophile**. The deprotonation must be carefully performed at low temperature, otherwise 1,2-Wittig rearrangement occurs[19].



Scheme I-14: stabilization of a lithiated allyl anion

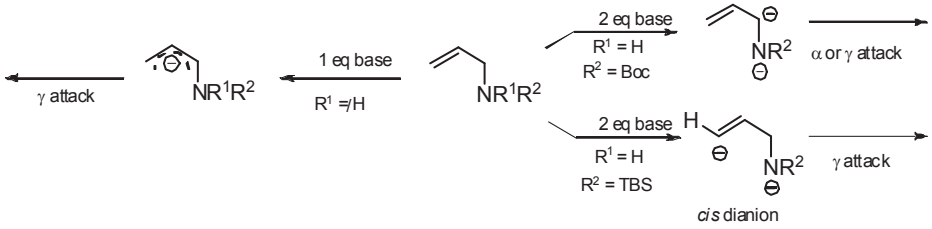
In this study, we will focus our attention on allylamine derivatives. The formation of anionic species and their reactivity will be briefly described here.

The treatment of *N*-dialkylated allylamine derivatives with one equivalent of strong base (organolithium reagents, like *n*-BuLi) yields anions that are not stabilized by the nitrogen atom. A subsequent quench with electrophiles affords enamines, in accordance with previous studies which showed that 1-amino-allylithiums usually give rise to γ-substitution.[20]

On the other hand, dianionic species derived from *N*-monoalkylated allylamines can also be generated by organolithiums under mild conditions. These dianions can be prepared by addition of two equivalents of *n*-butyllithium at room temperature after 24 h of stirring.[21] The first equivalent of the base deprotonates the hydrogen at the nitrogen atom, then the second equivalent either

[19] Nakai, T.; Mikami, K. *Chem. Rev*. **1986**, *86*, 885.
[20] Eish, J. J.; Shah, J. H. *J. Org. Chem*. **1991**, *56*, 2955.
[21] Burns, S. A.; Corriu, R. J. P.; Huynh, V.; Moreau, J. J. E. *J. Organomet. Chem*. **1987**, *333*, 281.

deprotonates at **allylic** or **vinylic** position depending on the substituent on the nitrogen atom (Scheme I-15). More precisely, allylcarbamate derivatives undergo allylic deprotonation whereas *N*-silyl or *N*-alkyl allylamine derivatives undergo vinylic deprotonation. This will be illustrated in the following paragraph with *N*-Boc allylamine and *N*-TMS allylamine.

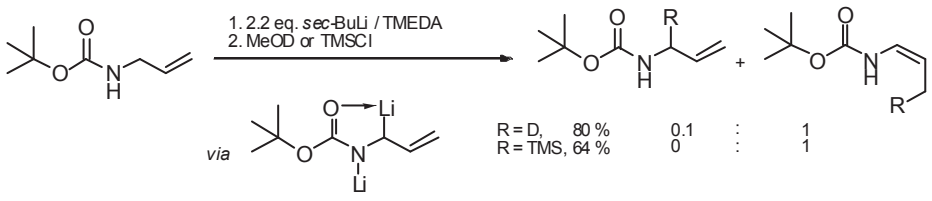


Scheme I-15: allylic versus vinylic dianion

I. 1. 4. b. Dianion derived from *N*-Boc-allylamines

The dianion derived from *N*-Boc-allylamine is generated by the use of 2.2 equivalents of *sec*-butyllithium. The formation of this dianion is proved by the two deuterated products obtained after quench with MeOD. Even though γ-substitution was largely favored in this deuteration reaction, these dianions still have an ambident character. Surprisingly, using trimethysilyl chloride as the electrophile exclusively led to the enamine (Scheme I-16).[22] The favored γ-attack observed by Beak and co-workers is in accordance with literature,[20] but it is surprising to obtain the *cis*-enamine. Beak and co-workers suggest that the *Z*-enamine is preferentially formed because it results from the kinetic pathway.[23]

Boc group is used here as a directing metalation group: the coordination between the carboxy- group and the lithium would explain the favored allylic lithiation.

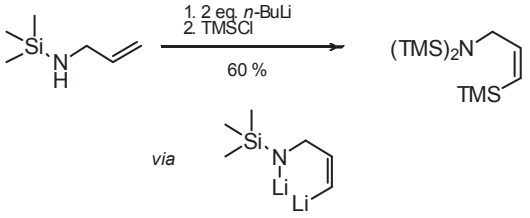


Scheme I-16: allylic deprotonation

[22] Resek, J. E.; Beak, P. *Tetrahedron lett*. **1993**, *34*, 3043.
[23] Pippel, D. J.; Weisenburger, G. A.; Faibish, N. C.; Beak, P. *J. Am. Chem. Soc*. **2001**, *123*, 4919.

I. 1. 4. c. Selective *cis*-vinylic deprotonation of *N*-TBS-allylamines

Contrary to *N*-Boc allylamines, the treatment of *N*-TMS allylamine (and *N*-mono alkylated allylamines) with two equivalents of strong base (alkyllithium reagents exclusively) affords a selective *cis*-vinylic deprotonation. This reactivity was reported for the first time by Corriu and co-workers (Scheme I-17).[21] The *cis*-vinylic deprotonation was demonstrated by the treatment of the generated dianionic species with trimethylsilyl chloride that yielded a silylated *Z*-allylamine derivative.

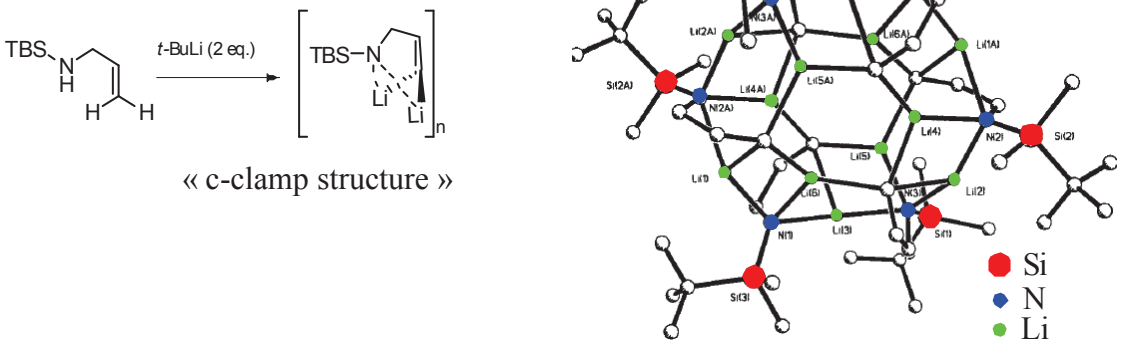


Scheme I-17: formation of *Z*-allylamine

The mechanism for the formation of this dianion is still not clear. Such a highly selective *cis*-vinylic deprotonation was unexpected and gave rise to various studies for the comprehension of this phenomenon. Crystallographic, DFT calculations and NMR studies will be briefly described here.

X-rays study:[24] In 2000, Williard and co-workers reported the crystallographic structure of lithiated *N*-TMS, *N*-TBS, and *N*-TIPS-allylamine. These *N*-monosilylated allylamine were dissolved in diethyl ether with 2 equivalents of *n*-BuLi and were allowed to stand for an extended period up to several days at -20°C until crystalline material was ready for X-ray diffraction analysis. The collected X-ray data revealed highly organized aggregate state for this dianionic species. In all case, it was demonstrated that the dianions form a "c-clamp" structure that would *a priori* explains the *cis* selectivity. Further studies that will be presented later will modify this reasoning. Otherwise, in each case dianionic aggregates were obtained in a unique but different aggregation state from one another. The dianion resulting from *N*-TBS-allylamine adopts a hexameric aggregate state where the vinyl carbon is linked to more than two lithium atoms (Scheme I-18). In summary, this crystallographic study clearly proves the *cis*-vinylic deprotonation of *N*-silyl allylamines, but also raises the question of the surprising number of lithium atoms at the vinylic position.

[24] Williard, P. G.; Jacobson, M. A. *Org. Lett*. **2000**, *2*, 2753.



Scheme I-18: crystallographic data of *N*-TBS allylamine dianion

DFT calculations:[25] The *cis*-vinylic deprotonation does not happen in hydrocarbon solvents but in such solvent, even small addition of THF or ether allowed the deprotonation to occur. Thus, DFT study was carried out taking into account the importance of the solvent that was represented by molecules of Me_2O in the calculations (Table I-1).

The mechanism controlling the regiospecific *cis*-vinylic deprotonation versus allylic deprotonation of lithiated silyl-allylamines was investigated by density functional theory (B3LYP/6-31+G*). First, it was demonstrated that the allylic dianion of *N*-TMS allylamine was favored compared to the vinylic dianion with a difference of 8 kcal/mol energy. This suggests that the deprotonation can not be under thermodynamic control.

On the other hand, the computed activation barrier was estimated lower for vinylic deprotonation than for allylic deprotonation, regardless to solvated or non solvated model. According to the calculations, this means that less enegy is required to generate the anion at the vinylic position than at the allylic dianion. It should also be noted that the activation barrier of the *cis*-vinylic dianion is almost the same, whether the dianion is solvated or not (24.3 *versus* 24.9 kcal/mol). To explain why the reaction can only occur in solvent like THF or diethyl ether, the authors suggest that THF may facilitate the formation of the "c-clamp" aggregate, contrary to hydrocarbon solvents. In summary, DFT calculations determined that a *cis*-vinylic deprotonation is favored compared to an allylic one, and that the deprotonation of lithiated *N*-TMS allylamines was kinetically controlled. Thus, the computed results are in accordance with the experimental data.

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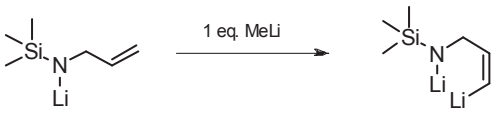
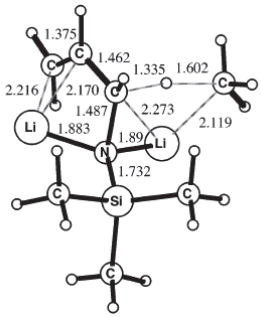
[25] Haeffner, F.; Jacobson, M. A.; Keresztes, I.; Williard, P. G. *J. Am. Chem. Soc*. **2004**, *126*, 17032.

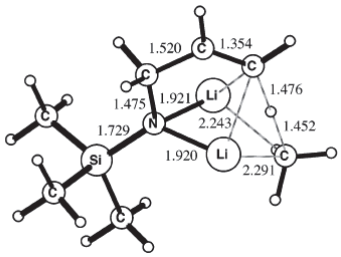


Allylic deprotonation | Vinylic deprotonation

Non solvated

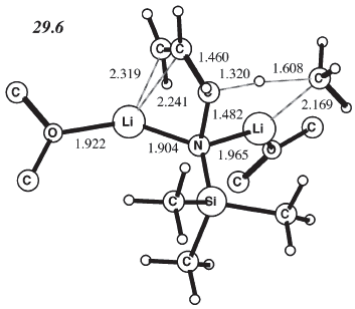


31.4 kcal/mol

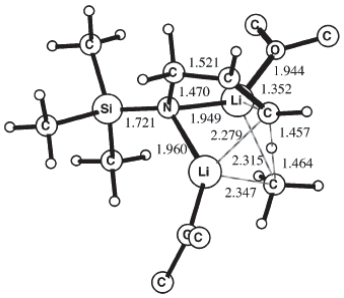


24.9 kcal/mol

solvated



29.6 kcal/mol



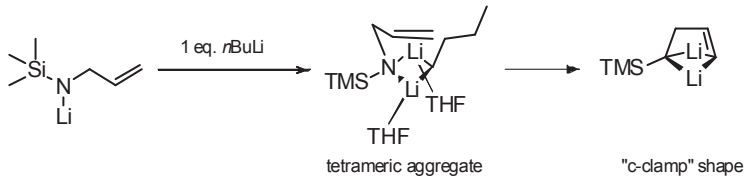
24.3 kcal/mol

Table I-1: transition state of allylic and vinylic dianion

NMR study:[26] an investigation of the structure-reactivity relationships of dilithiated anion aggregates was monitored by NMR. For this study, NMR sample was flame-dried, and 1 equivalent of *n*-BuLi in hexanes was added. Hexanes was removed, then *N*-lithio-*N*-(tert-butyldimethylsilyl) allylamine **8** and THF-d^8 were added. The sample was then allowed to stand at -40°C for 1 week before NMR measurement. A total of five aggregates were identified by NMR studies (COSY, NOESY, ^{7}Li NMR…), including two mixed aggregates. It was ascertained though that individual dianionic molecules adopt the same "c-clamp" shape conformation in monomeric and higher order states. However, as explained before with DFT calculations, the "c-clamp" shape is thermodynamically disfavoured compared to the allylic dianion, and does not explain the *cis*-vinylic regioselectivity. The authors argued for the formation of a particular four-membered ring mixed aggregate of allylamine with *n*-BuLi promoted by THF to explain the regioselectivity of this reaction (Scheme I-19). First, it appears that *n*-BuLi is away from the allylic hydrogens, which prevents from allylic deprotonation. In this intermediate, the steric hindrance is reduced to allow the

[26] Jacoson, M. A.; Keresztes, I.; Williard, P. G. *J. Am. Chem. Soc*. **2005**, *127*, 4965.

olefin interacting with the base, so that the "c-clamp" conformation could be form at the same time that lithiation occurs. Hence, this THF-induced particular aggregate would explain the formation of the *cis*-vinylic dianion.



Scheme I-19: mechanism of the *cis*-vinylic dianion

In our case, we took advantage of the *cis*-vinylic dianion formed from *N*-phenylallylamine to prepare 3-silapiperidine derivatives. Our results have been the corpus of a recent publication that is exhaustively developed in the next paragraph.

I. 2. Published results

Published in *Eur. J. Org. Chem*. **2009**, *11*, 1674.

I. 2. 1. Abstract

A straightforward and unprecedented method towards the synthesis of 3-silapiperidines is described. The key-step involves a formal double nucleophilic substitution reaction between the (bromomethyl)-dimethylsilyl chloride and *N*,*C*-sp^2-1,4-dianionic species generated from *N*-monoprotected-allylamines. Subsequent functionalizations are also presented.

Key Words: 3-silapiperidine, dianion, 1,2-dielectrophile

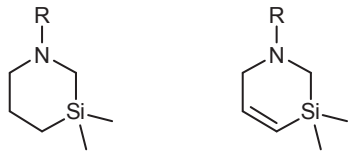
I. 2. 2. Introduction

Over the last two decades, silacycles have received a particular attention.[27] Their preparation has often been the occasion to study the reactivity and to prove the existence, even transient, of highly reactive and hardly characterizable species such as silenes ($R_2Si{=}CH_2$, alkene sila analogs) or silylenes (R_2Si, carbene sila analogs).

---

[27] For reviews, see: a) J. Dubac, A. Laporterie, G. Manuel, *Chem. Rev.* **1990**, *90*, 215-263. b) B. J. Aylett, A. C. Sullivan, In *The Comprehensive Organometallic Chemistry*; E. W. Abel, F. G. A. Stone, G. Wilkinson, Eds.; Pergamon, Oxford, **1995**, *2*, p 45. c) L. Fensterbank, M. Malacria, S. M. Sieburth, *Synthesis* **1997**, 813-854. d) J. Hermanns, B. Schmidt, *J. Chem. Soc., Perkin Trans. 1* **1998**, *14*, 2209-2230. e) J. Hermanns, B. Schmidt, *J. Chem. Soc., Perkin Trans. 1* **1999**, *2*, 81-102. f) G. Rousseau, L. Blanco, *Tetrahedron* **2006**, *62*, 7951-7993. For recent contributions: g) M. Leconte, S. Pagano, A. Mutch, F. Lefebvre, J. M. Basset, *Bull. Soc. Chim. Fr.* **1995**, *132*, 1069-1071. h) I. Ahmad, I. M. L. Falck-Pedersen, K. Undheim, *J. Organomet. Chem.* **2001**, *625*, 160-172. i) Y. Landais, C. Mahieux, K. Schenk, K., S.S. Surange, *J. Org. Chem.* **2003**, *68*, 2779-2789. j) S. Diez-Gonzalez, L. Blanco, *J. Organometal. Chem.* **2006**, *691*, 5531-5539. k) N. Agenet, J.-H. Mirebeau, M. Petit, R. Thouvenot, V. Gandon, M. Malacria, C. Aubert, *Organometallics* **2007**, *26*, 819-830. l) S. Sen, M. Purushotham, Y. Qi, S. M. Sieburth, *Org. Lett.* **2007**, *9*, 4963-4965. m) T. Sudo, N. Asao, Y. Yamamoto, *J. Org. Chem.* **2000**, *65*, 8919-8923. n) S. Diez-Gonzalez, R. Paugam, L. Blanco, *Eur. J. Org. Chem.* **2008**, 3298-3307.

Further motivation was the desire to obtain sila derivatives possessing interesting and possibly original chemical,[27] physical,[28] or biological[29] properties, relative to their carbon-analogs.[30] This synthetic effort provided a large variety of silacycles but, quite surprisingly, only a limited number of 3-silapiperidines **A** and **B** (Scheme I-20) have been reported in the literature over the last half-century.[31] Herein, we report a new first synthesis of a 3-silapiperidine of type **B** and its subsequent functionalization.



A **B**

Scheme I-20

I. 2. 3. Results and Discussion

We first investigated the formation of 3-silapiperidine **1** from allyl-vinylsilane **2** using a Ring Closing Metathesis (RCM) reaction as the key-step (Scheme I-21).

1 **2**

Scheme I-21

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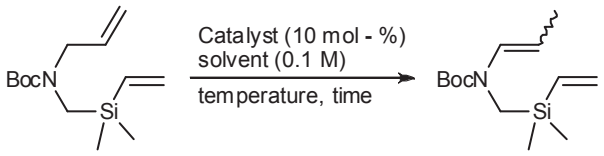
[28] J. Guay, A. Diaz, R. Wu, J. M. Tour, *J. Am. Chem. Soc.* **1993**, *115*, 1869-1874.

[29] For an account on bioactive organosilanes, see: a) S. M. Sieburth, C.-A. Chen, *Eur. J. Org. Chem.* **2006**, 311-322. See also: b) P. Ghosh, D. Shabat, S. Kumar, S. C. Sinha, F. Grynszpan, J. Li, L. Noodleman, E. Keinan, *Nature* **1996**, *382*, 339. For reviews on pharmacologically active sila-species: d) R. Tacke, U. Wannagat, *Top. Curr. Chem.* **1979**, *84*, 1. e) W. Bains, R. Tacke, *Current Opinion in Drug Discovery & Development* **2003**, *6*, 526-543.

[30] a) H. Alper, M. S. Wolin, *J. Org. Chem.* **1975**, *40*, 437-438. b) H. Alper, M. S. Wolin, *J. Organomet. Chem.* **1975**, *99*, 385-389. c) P. Heinonen, H. Sipilä, K. Neuvonen, H. Lönnberg, V. B. Cockroft, S. Wurster, R. Virtanen, M. K. T. Savola, J. S. Salonen, J. M. Savola, *Eur. J. Med. Chem.* **1996**, *31*, 725. d) U. Wannagat, R. Münstedt, U. Harder, *Liebigs Ann. Chem.* **1985**, 950-958. e) M. W. Buettner, C. Burschka, J. O. Daiss, D. Ivanova, N. Rochel, S. Kammerer, C. Peluso-Iltis, A. Bindler, C. Gaudon, P. Germain, D. Moras, H. Gronemeyer, R. Tacke, *ChemBioChem* **2007**, 1688-1699 and references therein. f) H. Tilman, C. Burschka, J. Warneck, R. Tacke, *Organometallics* **2004**, *23*, 361-366. g) B. Vivet, F. Cavelier, J. Martinez, *Eur. J. Org. Chem.* **2000**, 807-811. h) F. Cavelier, B. Vivet, J. Martinez, A. Aubry, C. Didierjean, A. Vicherat, M. Marraud, *J. Am. Chem. Soc.* **2002**, *124*, 2917-2923.

[31] a) see ref 18(a) b) E. D. Babich, V. N. Karel'skii, V. M. Vdovin, N. S. Nametkin, *Bull. Acad. Sc. USSR, Div. Chem. Sc.* **1968**, 1312. c) R. Dedeyne, M. J. O. Anteunis, *Bull. Soc. Chim. Belg.* **1976**, *85*, 319-331. d) M. J. O. Anteunis, R. Dedeyne, *Org. Magn. Reson.* **1977**, *9*, 127-132. e) S. V. Kirpichenko, A. T. Abrosimova, A. I. Albanov, M. G. Voronkov, *Russ. J. Gen. Chem.* **2001**, *71,* 1874-1878. f) S. Wendeborn, C. Lamberth, K. Nebel, P. J. Crowley, H. Nussbaumer, PCT WO 2006/066872 A1, **2006**. See also: g) Y. Sato, Y. Fukami, H. Shirai, *J. Organomet. Chem.* **1974**, *78*, 75-81. h) E. Lukevics, S. Germane, I. Segal, A. Zablotskaya, *Chemistry of Heterocyclic Compounds* **1997**, *33*, 234-238. i) R. Sanz, J. M. Ignacio, M. Pilar Castroviejo, F. Fañanas, *Arkivoc* **2007**, 84-91.

Allyl-vinylsilane **2** unfortunately did not undergo the expected RCM at any extent under any attempted conditions of catalyst, solvent or temperature. In the best case, the only generated products were diastereomeric enamines (***Z***)-**3** and (***E***)-**3**, along with unreacted precursor **2** (Table 1). The reported relative percentages, calculated from the crude ^{1}H NMR spectra (entries 1-2 and 4-6), correspond to the conversion of precursor **2** into enamines (***Z***)-**3** and (***E***)-**3** as well as to its unreacted form. Gratifyingly, both enamines could be isolated separately (entry 3), and their respective configuration undoubtedly determined.



2 ***Z*- and *E*-3**

Entry	Catalyst	Solvent	Temp., time	Relative % ***Z*-3** / ***E*-3** / **2**
1	Grubbs I	CH_2Cl_2	r.t., 22 h	18 / - / 82
2	Grubbs I	PhH	r.t., 24 h	3 / - / 97
3	Grubbs I	PhH	rfx, 1 h	75 / 10 / -[a]
4	Grubbs I	PhH	rfx, 18 h	25 / 75 / -
5	Grubbs II	CH_2Cl_2	rfx, 18 h	5 / 25 / 70
6	Schrock	PhH	r.t., 24 h	<1 / - / >99

[a] isolated yields

Table 1

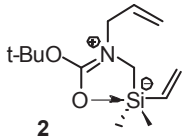
The generated enamines (***Z***)-**3** and (***E***)-**3** resulted from the isomerization of the allyl moiety of precursor **2**, its vinylsilane part remaining apparently untouched during the process. Interestingly, this isomerization process proved to be diastereoselective towards enamine (***Z***)-**3** as shown by the characteristic double bond coupling constant (J_{cis} = 8.3 Hz) obtained for this major diastereomer (a J_{trans} coupling constant of 20.2 Hz was measured for the minor diastereomer (***E***)-**3**). In all these reactions, it is believed that a ruthenium-hydride species, generated from the catalyst and compound **2**, triggers the isomerization process with high *Z*-diastereoselectivity.[32, 33, 34] On the other hand,

[32] The isomerization of *N*-Boc allylamines in the presence of first generation Grubbs' catalyst has been reported: a) J. F. Reichwein, R. M. J. Liskamp, *Eur. J. Org. Chem.* **2000**, 2335-2344. b) T. R. Hoye, H. Zhao, *Org. Lett.* **1999**, *1*, 169-171. c) For an account on this, see: B. Alcaide, P. Almendros, *Chem. Eur. J.* **2003**, *9*, 1259-1262 and references therein.

refluxing conditions and prolonged reactions times would promote the formation of the *E* isomer (entries 3 and 4).

In order to explain the observed reactivity and to rationalize why the expected RCM did not or could not occur, we first hypothesized that the (dimethyl)vinylsilane moiety was too sterically demanding for the RCM to take place. Unfortunately, although (methyl)vinylsilanes have indeed been reported on several occasions to remain inert towards first generation Grubbs' catalyst,[35] they have also been shown to efficiently react in RCM with both second generation Grubbs'[35] and Schrock's[35] catalysts under mild conditions.

We then hypothesized that the unability of allyl-vinylsilane **2** to undergo the RCM simply reflects the physical impossibility for the metathesis partners to interact and we proposed the existence of intramolecular coordination phenomena occuring within precursor **2** (Scheme I-22). These would be responsible for the formation of rigid conformations, in which both metathesis partners are too far apart to react together. As a consequence, the isomerization of the pendant allyl moiety would then have become the beneficiary process.



2

Scheme I-22

The proposed intramolecular coordination phenomena involves the silicon and the carbonyl oxygen atoms (Scheme I-22). This type of interaction has already been established thanks to X-ray analyses.[36] This spatial disposition is indeed favoured since it simultaneously involves a 5-membered chelate, a strong oxygen-silicon interaction,[37] and a pentavalent silicon atom, a situation that is particularly favourable.[38]

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[33] First generation Grubbs' catalyst has been shown to form ruthenium-hydride species above 60°C: B. Marciniec, M. Kujawa, C. Pietraszuk, *New J. Chem.* **2000**, *24*, 671-675 and references therein.

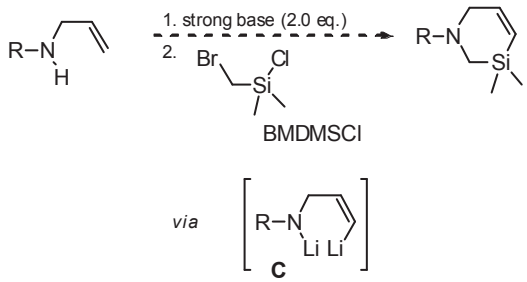
[34] Ruthenium-hydride species are known to be excellent catalysts for the migration of terminal olefins: a) T. Naota, H. Takaya, S.-I. Murahashi, *Chem. Rev.* **1998**, *98*, 2599-2660 and references therein. For applications, see: b) B. Alcaide, P. Almendros, J. M. Alonso, M. F. Aly, *Org. Lett.* **2001**, *3*, 3781-3784. c) C. Bressy, C. Menant, O. Piva, *Synlett* **2005**, 577-582 and references therein.

[35] a) A. G. M. Barrett, J. C. Beall, D. C. Braddock, K. Flack, V. C. Gibson, M. M. Salter, *J. Org. Chem.* **2000**, *65*, 6508-6514 and references therein. b) S. E. Denmark, S.-M. Yang, *Org. Lett.* **2001**, *3*, 1749-1752. c) M. Schuman, V. Gouverneur, *Tetrahedron Lett.* **2002**, *43*, 3513-3516. See also: d) C. Pietraszuk, B. Marciniec, H. Fisher, *Organometallics* **2000**, *19*, 913-917.

[36] a) K. D. Onan, A. T. McPhail, C. H. Yoder, R. W. Hillyard, *J. Chem. Soc., Chem. Commun.* **1978**, 209-210. b) A. A. Macharashvili, V. E. Shklover, Y. T. Struchkov, G. I. Oleneva, E. P. Kramarova, A. G. Shipov, Y. I. Baukov, *J. Chem. Soc., Chem. Commun.* **1988**, 683-685.

[37] See also: a) M. G. Voronkov, Y. L. Frolov, V. M. D'Yakov, N. N. Chipanina, L. I. Gubanova, G. A. Gavrilova, L. V. Klyba, T. N. Aksamentova, *J. Organomet. Chem.* **1980**, *201*, 165-177. b) M. G. Voronkov, E. A. Zel'bst, A. A.

At this point, we then decided to turn our attention to an alternative strategy. The latter was inspired by the dianionic chemistry[39] recently developed on *N*-monoprotected allylamines and by the reported reactivity of (BromoMethyl)-DiMethylSilyl Chloride (BMDMSCl) as a 1,2-dielectrophile (Scheme I-23).[40]



Scheme I-23

Indeed, under the action of 2 equiv. of a strong base,[41] *N*-monoprotected allylamines (*N*-alkyl, -silyl or -phenyl) have been shown to form dianionic species of type **C**.[42] While the first deprotonation occurs at the nitrogen (most acidic) site, the second one occurs regioselectively at the terminal position of the double bond (see background, I. 1. 4. c).

More importantly, this second deprotonation has been shown, thanks to X-ray analysis[42] to be completely stereoselective since only the *Z*-terminal proton is abstracted.[41a, 41d, 42, 43] Additionally, these dianionic species have proven to efficiently react with electrophiles to form a large variety of heterocycles.[41, 43, 44] BMDMSCl, on the other hand, has been shown to be an

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Kashaev, Y. V. Katkevich, V. A. Bruskov, N. F. Lazareva, A. I. Albanov, V. A. Pestunov, *Dod. Akad. Nauk.* **2002**, *386*, 628-631.

[38] C. Chuit, R. J. P. Corriu, C. Reye, J. C. Young, *Chem. Rev.* **1993**, *93*, 1371-1448 and references therein.

[39] For a description of a variety of dianionic species and their use in synthesis, see: a) C. M. Thompson, D. L. Green, *Tetrahedron* **1991**, *47*, 4223-4285 and references therein. For pioneering works, see: b) G. T. Morgan, T. M. Harris, *J. Am. Chem. Soc.* **1958**, *80*, 6360-6363. c) See also: C. Jorand-Lebrun, L. Fensterbank, M. Malacria, *Tetrahedron Lett.* **1995**, *36*, 6447-6648.

[40] BMDMSCl has been widely used in radical chemistry as a precursor to α-silyl radicals. See for instance: a) L. Fensterbank, M. Malacria, S. M. Sieburth, *Synthesis* **1997**, *8*, 813-854 and references therein. For some contribution, see: b) C. Blaszykowski, A.-L. Dhimane, L. Fensterbank, M. Malacria, *Org. Lett.* **2003**, *5*, 1341-1344. c) S. Bogen, L. Fensterbank, M. Malacria, *J. Am. Chem. Soc.* **1997**, *119*, 5037-38. d) For a review on the broader use of BMDMSCl, see: M. Koreeda, A.-L. Dhimane, L. Fensterbank, J.-P. Goddard, E. Lacôte, M. Malacria, *Electronic Encyclopedia of Reagents for Organic Synthesis* (Ed.: E. Crich), Wiley, **2007**, DOI: 10.1002/047084289X.rb304.pub2.

[41] a) S. A. Burns, R. J. P. Corriu, V. Huynh, J. J. E. Moreau, *J. Organomet. Chem.* **1987**, *333*, 281-290. See also: b) J. Barluenga, F. Foubelo, F. J. Fañanás, M. Yus, *J. Chem. Res. (S)* **1989**, 200-201; Barluenga, F. Foubelo, F. J. Fañanás, M. Yus, *J. Chem. Res. (M)* 1524-1552 **1989,** c) J. Barluenga, F. J. Fañanás, F. Foubelo, M. Yus, *J. Chem. Soc., Chem. Commun.* **1988**, 1135-1136. d) M. Yus, F. Foubelo, L. R. Falvello, *Tetrahedron : Asymmetry* **1995**, *6*, 2081-2092 and references therein.

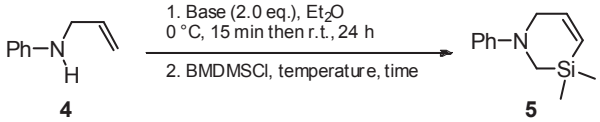
[42] P. G. Williard, M. A. Jacobson, *Org. Lett.* **2000**, *2*, 2753-2755 and references therein.

[43] For a rationalization of the *Z*-stereoselectivity of the second deprotonation, see: a) J. Barluenga, *Pure & Appl. Chem.* **1990**, *62*, 595-604. See also: b) B. M. Trost, D. M. T. Chan, *J. Am. Chem. Soc.* **1983**, *105*, 2315-2325. c) Refs 16a and 16d.

[44] a) J. Barluenga, F. J. Fañanás, F. Foubelo, M. Yus, *Tetrahedron Lett.* **1988**, *29*, 4859-4862. b) J. Schulze, G. Schmid, *J. Organomet. Chem.* **1980**, *193,* 83-91. c) J. Schulze, R. Boese, G. Schmid, *Chem. Ber.* **1981**, *114*, 1297-1305. d) D.

excellent 1,2-dielectrophilic partner for the formation of sila heterocycles, although reports in the literature remained sporadic.[45, 30a,b] We therefore anticipated that combination of both the dianionic chemistry of *N*-monoprotected allylamines and the 1,2-dielectrophilic property of BMDMSCl would constitute a powerful synthetic tool for the preparation of 3-silapiperidines.

We initially tested our strategy on *N*-phenyl-allylamine **4**. Gratifyingly, upon treatment with 2.0 equivalents of *n*-BuLi at room temperature for 24h[41] after trapping of the generated dianion[46] with BMDMSCl at -78°C, we were effectively able to isolate the targeted 3-silapiperidine **5** with an encouraging yield of 30% (Table 2, entry 1). We also recovered 30% of starting amine **4**. Interestingly, when BMDMSCl was added at 0°C, the yield reached 52% and the starting material was only 18% (entry 2). Finally, addition of BMDSMCl at room temperature, with *t*-Buli as a base, allowed us to even further improve the yield to 70% (entry 3).[47] Unfortunately, no other tested *N*-monoprotected allylamines was as successful since, either lower yields (*N*-*p*-methoxy-phenyl) or side-products (*N*-TBDMS, *N*-(*S*)-α-methyl-benzyl or *N*-tosyl) were obtained or did not react (*N*-Me or *N*-trityl) (see unpublished results, I. 3. 1).



4 **5**

Entry	Base	Temperature, time	Yield in **5** (%)	Recovery of **4** (%)
1	*n*-BuLi	-78 °C then r.t., 12 h	30	30
2	*n*-BuLi	0 °C then r.t., 2 h	52	18
3	*t*-BuLi	r.t., 30 min	**70**[a]	-

Table 2.

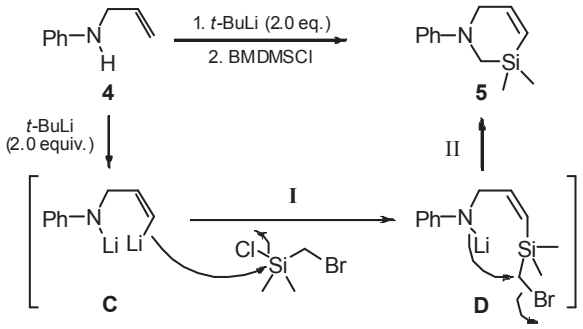
Hänssgen, E. Odenhausen, *Chem. Ber.* **1979**, *112*, 2389-2393. e) R. J. P. Corriu, B. Geng, J. J. E. Moreau, *J. Org. Chem.* **1993**, *58*, 1443-1448. f) M. A. Jacobson, P. G. Williard, *J. Org. Chem.* **2002**, *67*, 32-37.

[45] a) W. Simmler, *Chem. Ber.* **1963**, *96*, 349-356. b) D. Kummer, S. C. Chaudhry, J. Seifert, B. Deppisch, G. Mattern, *J. Organomet, Chem.* **1990**, *382*, 345-359. See also: c) D. E. Jr. Kaelin, S. M. Sparks, H. R. Plake, S. F. Martin, *J. Am. Chem. Soc.* **2003**, *125*, 12994-12995. For BMDMSCl-related derivatives, see: d) G. Märkl, P. L. Merz, *Tetrahedron Lett.* **1971**, *12*, 1303-1306. e) W. Simmler, *Chem. Ber.* **1961**, *94*, 1585-1591. f) H. Niederprüm, W. Simmler, *Chem. Ber.* **1963**, *96*, 965-975.

[46] A deuteration (99.9% D_2O) test reaction run in parallel under the same double deprotonation conditions unambiguously led to the formation of 3-(*Z*)-deutero-*N*-phenyl-allylamine as the unique product. The deuterium incorporation reached 91% and was totally regio- and *Z*-stereoselective.

[47] ***N*-phenyl-3,3-dimethyl-1-aza-3-sila-cyclohex-4-ene 5**. described in experimental part.

The proposed mechanism relies on a formal double nucleophilic substitution reaction (Scheme I-24). In a first step (**I**), the vinylic anion, the most nucleophilic part of dianion **C**, reacts with the most electrophilic BMDMSCl site (the silicon atom[30]) to give intermediary **D**. Final intramolecular nucleophilic substitution (**II**) ultimately gives rise to **5**.

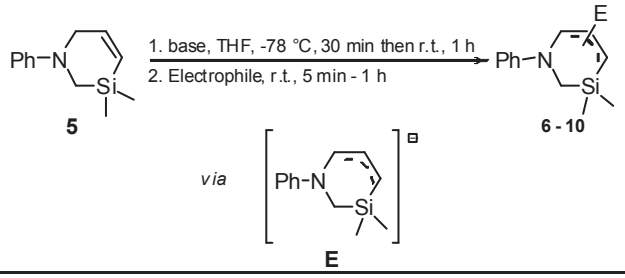


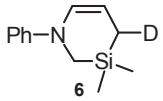
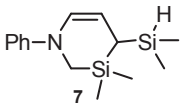
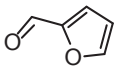
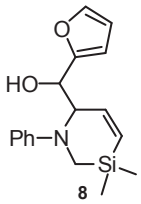
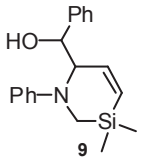
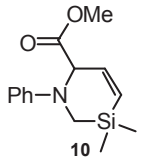
Scheme I-24

Finally we turned our attention to the functionalization of 3-silapiperidine **5**. Besides preparing derivatives, we incidentally wanted to develop access to sila analogs of biological interest. Our strategy consisted in treating **5** with one equivalent of base then intercepting the resulting expected delocalized anion **E**[48,49] with an electrophilic species (Table 3).

Upon treatment with one equivalent of *t*-BuLi followed by hydrolysis with D_2O, 3-silapiperidine **5** regioselectively led to its 4-deuterated enamine derivative **6** (entry 1). The same regioselectivity is observed for compound **7** when **5** is successively treated with t-BuLi followed by chlorodimethyl-silane (entry 2). 2-Furaldehyde and benzaldehyde also efficiently undergo reaction to providing β-amino-alcohols **8** and **9** in 60% and 75% yields and as 7:3 and 6:4 mixtures of diastereomers, respectively (entries 3 and 4).

[48] For a review on heteroatom stabilized allyl anions, see: A. R. Katritzky, M. Piffl, H. Lang, E. Anders, *Chem. Rev.* **1999**, *99*, 665-772.
[49] The deprotonation was anticipated to occur regioselectively at the allylic position and to give birth to anion **E**. For a study on the regioselectivity of the deprotonation of similar systems, see: S. M. Sieburth, J. J. Somers, *Tetrahedron* **1996**, *52*, 5683-5690.



Entry	Base	Electrophile	Product	Yield (%)
1	*t*-BuLi	D_2O	 **6**	88[a,b]
2	*t*-BuLi	Me_2SiHCl	 **7**	79[b]
3	*t*-BuLi		 **8**	60 *dr*: 7/3[c]
4	*n*-BuLi	PhCHO	 **9**	75 *dr:* 6/4[c]
5	*n*-BuLi	$ClCO_2Me$	 **10**	16[d]

[a] Deuterium regioselective incorporation determined by NMR, [b] NMR yield. [c] Undetermined stereochemistries, [d] The reverse addition of anion E onto $ClCO_2Me$ was necessary.[50]

Table 3.

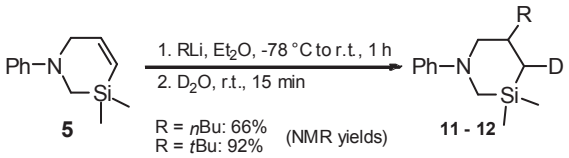
In these cases, proximal regioselectivity (α to the nitrogen atom) was observed. Unfortunately, methyl chloroformate only afforded α-amino-ester **10** in a low yield of 16% (entry 5). Nevertheless, this compound constitutes an interesting candidate for the preparation of sila analogs of pipecolic acid, a molecule of biological interest.[51]

[50] The direct dropwise addition of methyl chloroformate onto anion **E** resulted in a complex mixture wherein neither starting material **5** nor expected α-amino-ester **9** were to be found. Undesired subsequent side-reactions involving compound **9** and anion **E** are suspected to have occurred.

[51] Pipecolic acid is present in certain human physiologic fluids. It does not possess a well-defined biological activity but would play a role in the central nervous system: a) M. C. Gutierrez, B. A. Delgado-Coello, *Neurochem. Res.* **1989**, *14*,

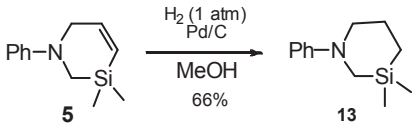
At this stage, it is difficult to rationalize the observed regioselectivities, as well as to correlate them with the few closely reported studies. Indeed, studies on α-silyl anions suggest that the regioselectivity is dependent from the size of the silyl substituents, the size of the electrophile or its nature.[52] Moreover, the alkylation of 3-silyl enamines gives only α-silyl alkylated products.[53]

Interestingly, when THF is replaced by ethyl ether for the anion formation step, *t*-BuLi or *n*-BuLi do not act as bases but as nucleophiles, giving rise to alkylated products **11** and **12** (Scheme I-25).



Scheme I-25

Finally, the saturated silapiperidine **13** was generated upon hydrogenation of 3-silapiperidine **5** with palladium on charcoal (Scheme I-26).



Scheme I-26

I. 2. 4. Conclusion

In conclusion, we have reported an interesting and straightforward method towards the synthesis of unprecedented 3-silapiperidines. Our strategy relied on a formal double nucleophilic substitution reaction involving *N*,*C*-sp^2-1,4-dianionic species generated from *N*-monoprotected allylamines and takes advantage of the remarkable but yet underexploited 1,2-dielectrophilic properties of (bromomethyl)dimethylsilyl chloride. Subsequent functionalizations proved to be successful and, while providing a variety of new siladerivatives, also opened new and promising opportunities towards the synthesis of sila analogs of biological interest.

405-408. b) T. Fujita, M. Fujita, T. Kodama, T. Hada, K. Higashino, *Annals of Nutrition & Metabolism* **2003**, *47*, 165-169. See also: c) F. P. J. T. Rutjes, J. J. N. Veerman, W. J. N. Meester, H. Hiemstra, H. E. Schoemaker, *Eur. J. Org. Chem.* **1999**, 1127-1135 and references therein.

[52] a) R. J. P. Corriu, J. Masse, D. Samate *J. Organometal. Chem.* **1975**, 71-80. b) R. F. Horvath, T. H. Chan J., *J. Org. Chem.* **1987**, *52*, 4489-4494. See also: c) B. M. Trost, A. Brandi, *J. Org. Chem.* **1984**, *49*, 4811-4816. d) See also ref. 1i for transmetallation with titanium (IV) and references therein.

[53] H. Ahlbrecht, C. S. Sudheendranath, *Synthesis* **1982**, 717-719.

I. 3. Unpublished results

We were pleased to implement a new and efficient method for the preparation and functionalization of *N*-phenyl silapiperidines. On the other hand, we were also interested in the preparation of non-protected 3-silapiperidines and sila bioisosteres of pipecolic acid (Scheme I-5). Unfortunately, the development of our dianionic strategy did not afford the excepted results, this will be discussed here.

I. 3. 1. Behaviour of diversly *N*-monoprotected allylamines

In order to utilize the best labile group for the deprotection of silapiperidines, the behaviour of several protecting groups was instigated (Scheme I-27).

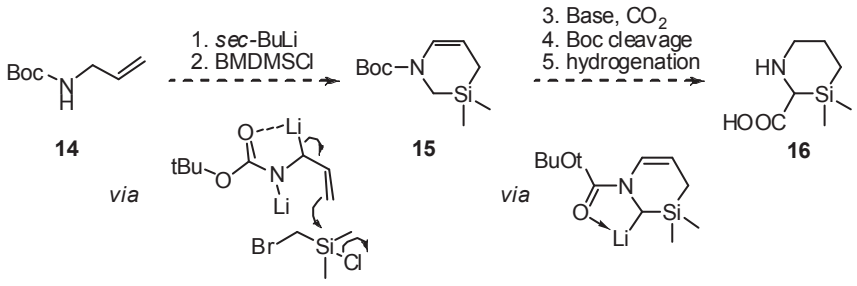
Scheme I-27: general equation

I. 3. 1. a. R = *tert*-Butyl carbamate (Boc)

First, we decided to examine the reactivity of the dianion resulting from *N*-Boc-allylamine with our dielectrophile. As presented in the beginning of this chapter, such allylamine **14** undergo allylic deprotonation and form enamimes in the presence of electrophiles (Scheme I-16). Taking advantage of this reactivity, we expected to synthesize silapiperidine **15** (Scheme I-28). We anticipated that submitting the latter to one equivalent of lithium reagent would lead to a single anion due to the stabilizing effect of the *tert*-butylcarbamate.[54] Then, alkylation at this position, deprotection of the secondary amine and hydrogenation of the olefin would lead to the regiosiomer **16** of our desired pipecolic acid sila bioiostere.

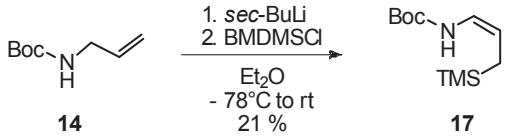
---

[54] Sieburth, S. McN. ; Somers, J. J. ; O'Hare, H. K. *Tetrahedron*, **1996**, *52*, 5669.



Scheme I-28

N-Boc-allylamine was submitted to deprotonation with 2 equivalents of *sec*-BuLi. Unfortunately, a subsequent quench with BMDMSCl did not afford the cyclic enamine **15.** Instead, the acyclic *cis*-enamine **17** (J = 8.8 Hz) was prepared (Scheme I-29). It is still unclear why the dianionic species did not react with both electrophilic sites of BMDMSCl, but as we will see in the next example, this is not an isolated case.

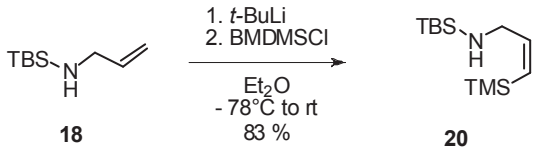


Scheme I-29

Finally, we decided to further investigate other protecting groups that are susceptible to generate the "c-clamp" conformation of the dianionic species.

I. 3. 1. b. R = trialkylsilyl- (SiR_3)

It is known that the dianionic species formed from *N*-TBS-allylamine **18** has a "c-clamp" conformation (see background: I. 1. 4. c). A deuteration experiment was carried out and as expected, led to a *cis*-vinylic deuterated allylamine. On the other hand, the generated dianion of *N*-TBS-allylamine **18** was quenched with BMDMSCl and afforded the acyclic *Z*-allylamine **20** in 83 % yield (Scheme I-30). Neither the expected cyclized compound nor an acyclic brominated compound were obtained. Unfortunately to date, there is no clear explaination that allow to rationalize this reduction.

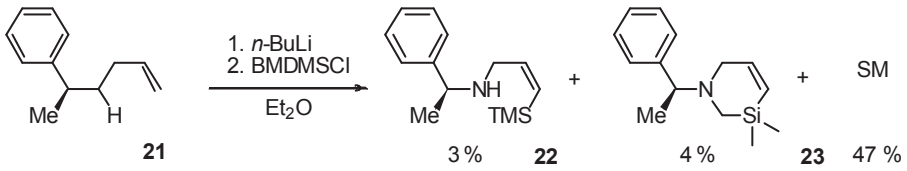


Scheme I-30

I. 3. 1. c. R = "Benzyl-type"

The case of a substitutent derived from benzyl has already been discussed in the thesis of Christophe Blaszykowski, more particularly with an enantioenriched methyl-benzyl labile group (**21**).[18]

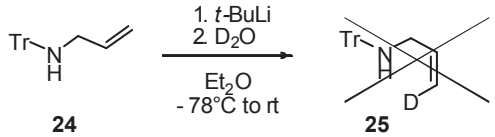
Reaction conditions for the dianion generation followed by a quench with BMDMSCl afforded acyclic product **22**. Starting material was mainly recovered but an increased dilution of the reaction mixture allowed to prepare the desired silapiperidine **23** in a low yield of 4 % (**Scheme I-31**). C-sp^3-*N*-allylamine structures were thus not suitable for this reaction, but this case underlined the question of the importance of the dilution.



Scheme I-31

I. 3. 1. d. R = Trityl- (Tr)

Our previous success employing phenyl group led up to turn our attention on the trityl protecting group. This labile group, commonly utilized in protein synthesis, is easily cleavable in acidic conditions. Unfortunately, whatever the base used for this transformation (*norm*-, *sec*-, or *tert*-BuLi), the allylamine **24** was not consumed and therefore no traces of deuterated product **25** was revealed by ^{1}H NMR (Scheme I-32). As lithiation did not occur, it was not worth engaging the product for the synthesis of silapiperidine. We suggest here that the deprotonation did not occur due to the steric hindrance generated by the bulky trityl group that prevent the approach of the base.

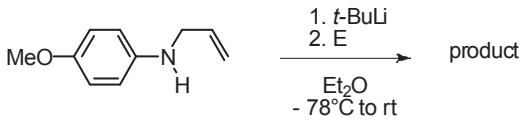


Scheme I-32

I. 3. 1. e. R = *p*-methoxyphenyl- (PMP)

Upon the action of organolithium reagents, anisoles undergo *ortho*-lithiation[55] whereas *N*-aromatic allylamines form cis-vinylic dianionic species respectively by the use of 1 and 2 equivalents of base. In our case, there should be competition between the desired deuterated product **28** and the mono-deuterated aromatic compound **27.** Our results are summarized in Table I-2.

N-para-methoxyphenyl-allylamine **26** was submitted to deprotonation with 2 equivalents of *tert*-BuLi. A quench with D_2O afforded deuterated allylamine **28** as a single product. The conversion of this reaction was not complete (allylamine **28** was synthesized in 52% by ^1H NMR yield) nevertheless, it was not possible to distinguish deuteration of the aromatic ring **27** (entries 1-2). On the other hand, a quench with BMDMSCl gave rise to silapiperidine **29** in 32 % yield.



26

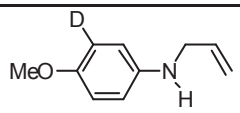
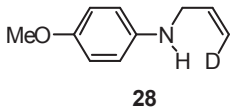
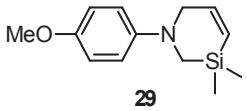
entry	base	electrophile (E)	product	yield
1	*t*BuLi	D_2O	 **27**	-
2	*t*BuLi	D_2O	 **28**	52 %
3	*n*BuLi	BMDMSCl	 **29**	32 %

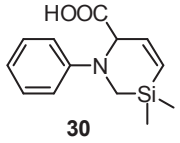
Table I-2

To determine the interest of this molecule before any further functionalizations, we examined the possibility of PMP cleavage. In order to do so, we used cerium ammonium nitrate as cleaving agent. The reaction was performed according to a procedure of Royer and co-workers[56] but we were not able to isolate neither the desired secondary amine, nor the starting material.

[55] For a review about direct ortho metalation, see: Snieckus, V. *Chem. Rev*. **1990**, *90*, 879.
[56] Lamo Marin, S.; Martens, T.; Mioskowski, C.; Royer, J. *J. Org. Chem*. **2005**, *70*, 10592.

I. 3. 2. Reactivity of phenylazasiline

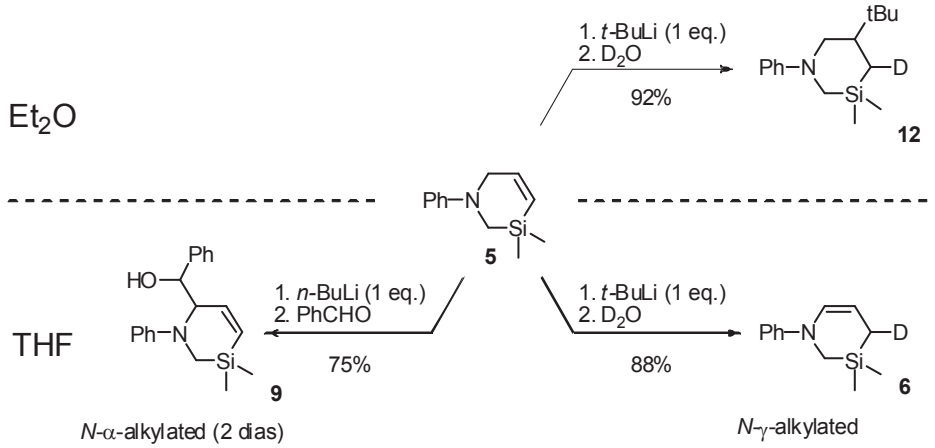
Despite our efforts to find an ideal labile group for amine functionality, phenyl moiety remained so far the most convenient group for the synthesis of 3-silapiperidines *via* dianionic chemistry. We then decided to extent the study of this compound by the investigation of reaction conditions that allow the preparation of a functionalized sila pipecolic acid (**30**, Scheme I-33).



30

Scheme I-33

First of all, the rationalization of the reactivity of the anion derived from *N*-phenyl-allylamine was necessary. Indeed, as described in the published results, this formation was solvent-dependent. On one hand, carbolithiation occurred; on the other hand allylic deprotonation afforded an ambident anion that gave rise to *N*-α- or *N*-γ-alkylated products (Scheme I-34). In this part, our preliminary study for the understanding of diversely alkylated products and our attempts to optimize the carboxylative alkylation of 3-silapiperidine **5** will be described.



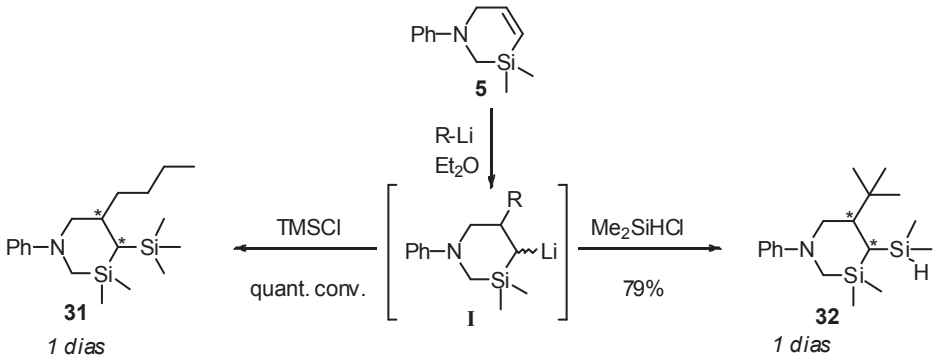
Scheme I-34

I. 3. 2. a. Solvatation effects and conjugate addition in diethyl ether

Organolithium compounds have been demonstrated to exist in different aggregate states depending on solvents. In particular, *tert*-butyllithium was established to exist as a tetrameric aggregate in hydrocarbon solvents (like pentane) and gas phase, while existing in lower order

aggregates in Et_2O and THF.[57] Here, the optimum solvatation of *tert*-butyllithium in THF explains its basic behavior, whereas in Et_2O, carbolithiation occurred (*tert*-butyl anion played the role of a nucleophile).

Conjugate addition of *t*-BuLi and *n*-BuLi to silapiperidine **5**, followed by nucleophilic substitution upon chlorosilane derivatives afforded respectively silanes **31** and **32** (Scheme I-35). In both cases, a single diastereoisomer was observed. As reported in literature, alkyl groups were added exclusively to the double bond such as the most stabilized organolithium **I** is formed.[58] Here, alkyl group reacted at the 3-position to form anion **I** that could benefit from the stabilizing effect of the silicon atom at the α-position.



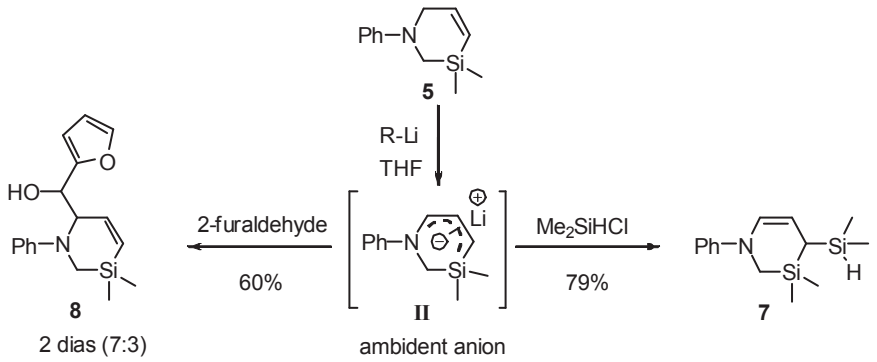
Scheme I-35

I. 3. 2. b. Alkylation of *N*-phenyl-silapiperidine in tetrahydrofuran

In THF, there was no competition between deprotonation and conjugate addition of the organolithium. The regioselectivity of this allylic anion could not be fully explained. We simply noticed that regioselectivity was in conformity with what was observed with acyclic allylsilanes (see below, Scheme I-36 and Scheme I-37). Indeed, depending on the electrophile, the regioselectivity of the nucleophilic attack was different: α–attack occurred for carbonylated electrophiles, whearas γ-attack occurred for alkyl halides.

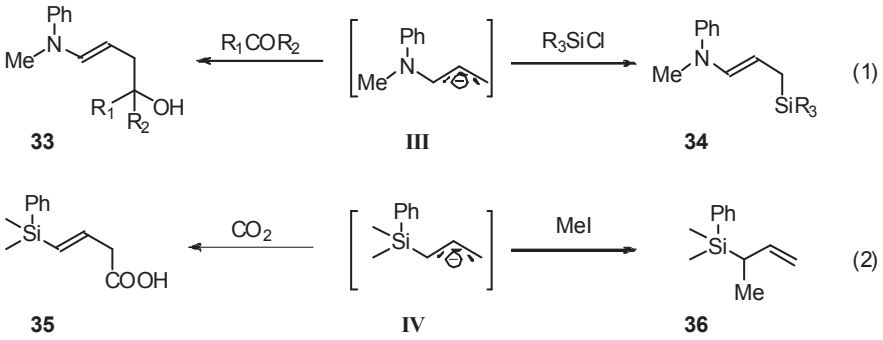
[57] Bauer, W.; Winchester, W. R.; Rague Schleyer, P. *Organometallics* **1987**, *6*, 2379.

[58] Hogan, A.-M. L.; O'Shea, D. F. *Chem. Commun*., **2008**, 3839.



Scheme I-36

According to the literature, when anionic species **III** (derived from allylamine) is submitted to a ketone or silane treatment, enamines **33** and **34** are formed.[59] This means that *N*-γ-alkylated compounds are obtained regarless the electrophile used. On the contrary, silyl-substituted allyllithiums are ambidentate nucleophiles and treatment of anionic species **IV** with ketone and methyliodide affords respectively vinylsilane **35** and allylsilane **36** (Scheme I-37).[60] We then assumed that our ambident anion **II** adopted the nucleophilic behaviour of the silyl alkylithium.

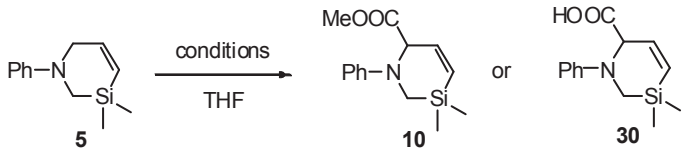


Scheme I-37

I. 3. 2. c. Attempts for the preparation of pipecolic acid analog

We tried to synthesize the sila analog of PA (**10** and **30**) in one or two steps, either by direct addition of an electrophile or *via* the corresponding ester. The experiments were carried out are summarized in the following table.

[59] Corriu, R. J. P.; Bolin, G.; Moreau, J. J. E. *Bull. Soc. Chim. Fr*. **1993**, *130*, 273.
[60] Uno, H.; *Bull. Chem. Soc. Jpn*. **1986**, *59*, 2471.

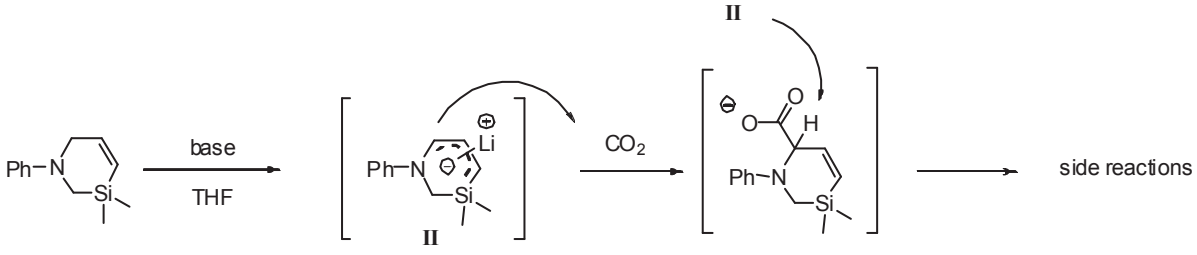


Entry	R	Base	Electrophile	Product	Yield (%)	comments
1	H	*n*-BuLi	CO_2	**10**	-	saturated solution of CO_2
2	H	*n*-BuLi	dry ice	**10**	-	anion in THF was added on dry ice *via canula*
3	Me	*t*-BuLi	CNCOOMe	**30**	-	direct addition
4	Me	*t*-BuLi	ClCOOMe	**30**	16	reverse addition

Table I-3 : attempts for the synthesis of pipecolic acid analog

The lithiated anion **II** was added *via* canula to a saturated solution of CO_2 in THF, or directly on a piece of dry ice (entries 1-2 The formation of the anion of **5** in THF results on orange-red colored mixture that generally becomes colourless following the addition of an electrophile.). The discoloration of the mixture was obvious, but there was no formation of **10**. Then, we turned our attention to Mander's reagent[61] that may be a better electrophile than carbon dioxide. Unfortunately, direct addition of this electrophile in the anionic mixture of **II** in THF did not yield sila analog **30** (entry 3). We were then pleased to discover that compound **30** could be prepared in a moderate yield by a slow reverse addition of anion **I** in a mixture of methyl chloroformate in THF (entry 4).

The acidic nature of the intermediate made difficult yield improvements. Indeed, anionic intermediate **II** is also a basic species that may deprotonate the acidic proton (Scheme I-38).



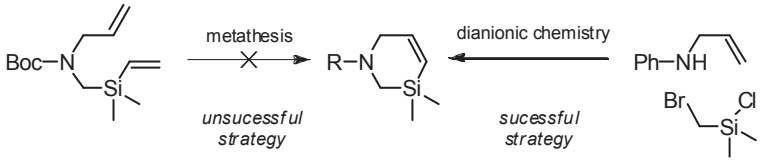
Scheme I-38

[61] Bissember, A. C. *Synlett* **2008**, *4*, 681.

I. 4. General conclusion

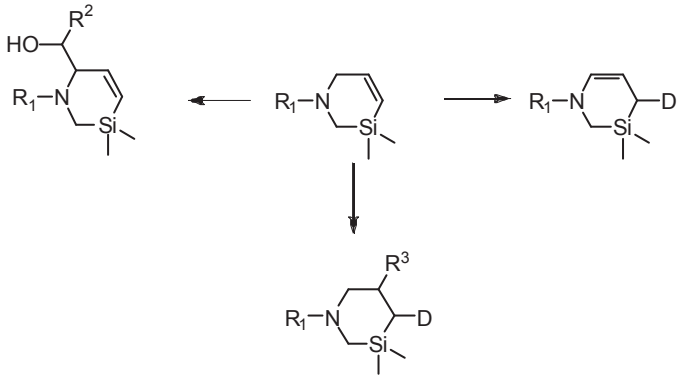
In this chapter, we aimed at developing a facile access to 3-silapiperidine derivatives that have received relatively little attention these past few years. Nevertheless, the interest of such molecules is of major order because they are potential precursors for pharmaceutical industry that could lead to bioisosteres of active carbon analog molecules.

As metathesis-based approach did not afford the desired products, we called upon dianionic chemistry to achieve the preparation of 3-silapiperidines (Scheme I-39). The reactions were easy to carry out. The reaction times were short and the molecules were synthesized in good yields.



Scheme I-39

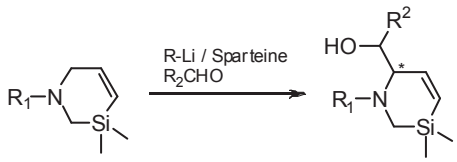
Functionalization of *N*-phenyl-allylamine gave birth to several products by taking advantage of the reaction solvent. Unfortunately, further deprotection of amine moiety was not possible (Scheme I-40). It would have been interesting to evaluate the reactivity of other *N*-alkyl-allylamines, but carbamate, silyl and trityl groups did not give rise to the expected silapiperidines.



Scheme I-40

Unfortunately, this chemistry has not yet permitted to synthesize a pipecolic acid sila analog. Such compound would have greatly valorized our research efforts and could have been a molecule ready for biological tests.

Experiments with *N*-phenyl-allylamine will not be given up in our laboratory. Particularly, experiments for the synthesis of enantio-enriched silapiperidine derivatives will be engaged (Scheme I-41).



Scheme I-41

I. 5. Experimental section

^{1}H NMR were recorded using Bruker instruments at 200, or 400 MHz, and ^{13}C NMR were recorded using Bruker instruments at 50, or 100 MHz. NMR shifts are reported relative to the residual solvent signal (7.26 ppm for $CDCl_3$, and 7.16 for C_6D_6) for proton NMR and relative the residual solvent central peak for carbon spectra (77.0 ppm for $CDCl_3$ and 128.0 ppm for C_6D_6). IR spectra were obtained using a Tensor 27 ATR diamond PKE Bruker instrument. Mass spectra (MS) were obtained on a GC-MS Hewlett-Packard HP 5971 apparatus and on a NERMAG R 30-10 apparatus in the Laboratoire de Chimie Structurale Organique et Biologique, Universite Pierre et Marie Curie.

Tetrahydrofuran (THF) and ether were distilled from sodium-benzophenone. CH_2Cl_2, benzene and toluene were distilled from calcium hydride or used as ACS reagents if noted. All reactions were performed under an atmosphere of argon in flame dried glassware using standard syringe-septum techniques unless otherwise noted.

Specific remarks

PhCHO, furfuraldehyde and Mander's reagent were freshly distilled before use. BMDMSCl and other silanes were commercially available. Deuteration experiments were run with 99.9 % D_2O purchased as 0.75 mL sealed phials.

Dianion generation

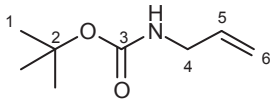
All dianionic species were generated following the procedure reported by R.J.P. Corriu: to a stirred solution of appropriate allylamine (1.0 eq.) in freshly distilled Et_2O (0.2 M) was added dropwise freshly titrated *t*-BuLi (2.0 eq.) at – 78°C. After addition, the reaction was allowed to warm to 0°C. Resulting dianions were then quenched by appropriate (di)-electrophiles.

Dianion treatments

For allylamines derivatives, deuteration and BMDMSCl treatments were run simultaneously, namely in strictly same conditions.

I. 5. 1. Allylamines derivatives:

Structure 1: *N*-(*tert*-butoxycarbonyl)-allylamine (14)



14

$C_8H_{15}NO_2$

Mol. Wt.: 157.2102

***N*-(*tert*-butoxycarbonyl)-allylamine (14)** was synthesized according literature in a quantitative yield.[62]

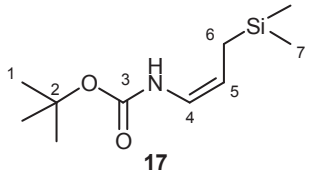
white solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.88-5.79 (m, 1H, H_5), 5.19-5.08 (m, 2H, H_6), 4.60 (bs, 1H, H_{NH}), 3.75-3.73 (m, 2H, H_4), 1.44 (s, 9H, H_1).

These spectroscopic data were consistent with those reported in the literature.[22]

CAS: 78888-18-3

Structure 2: *N*-butoxycarbamate -(3-(*Z*)-(trimethylsilyl)prop-1-enyl)-allylamine (17)



17

$C_{11}H_{23}NO_2Si$

Mol. Wt.: 243.5364

To a solution of freshly generated dianion issued from ***N*-(*tert*-butoxycarbonyl)-allylamine** (**14**, 1.9 mmol) was added BMDMSCl (0.28 mL, 4.3 mmol) at 0°C. After stirring at r.t. for 30 min, the reaction mixture was quenched with NH_4Cl sat. and the resulting solution was submitted to a Et_2O/H_2O extraction. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo* to give the crude ***N*-butoxycarbamate -(3-(*Z*)-(trimethylsilyl)prop-1-enyl)-allylamine (17)** as a crude yellow oil.

Purification was achieved by flash column chromatography on silica gel (10 % Et_2O/PE) to give a pale yellow oil (51 mg, 21 %).

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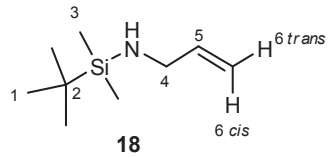
[62] Bischofberger, N.; Waldmann, H.; Saito, T.; Simon, E. S.; Lees, W.; Bednarski, M. D.; Whitesides, G. M. *J. Org. Chem*. **1988**, *53*, 3457.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.35 (d, ^3J = 8.8 Hz, 1H, H_4), 6.06 (bs, 1H, H_{NH}), 4.59 (dd, ^3J = 8.8, 8.6 Hz, 1H, H_5), 1.47 (s, 9H, H_1), 2.65 (dd, ^3J = 8.6 Hz, ^4J = 1.0 Hz, 2H, H_6), 0.02 (s, 6H, H_7).
CAS:

Structure 3: *N*-(*tert*-butyl)dimethylsilyl-allylamine (18)



18

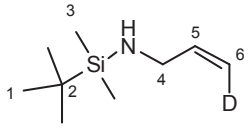
$C_9H_{21}NSi$

Mol. Wt.: 171.3552

***N*-(*tert*-butyl)dimethylsilyl-allylamine (18)** was synthesized according literature in 70 % yield.[63]
colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.95-5.86 (m, 1H, H_5), 5.14 (ddd, ^2J= 1.8 Hz, ^3J= 17.1 Hz, ^4J= 3.8 Hz, 1H, $H_{6\ cis}$), 4.96 (ddd, ^2J= 1.8 Hz, ^3J= 10.1 Hz, ^4J= 3.3 Hz, 1H, $H_{6\ trans}$), 3.39-3.36 (m, 2H, H_4), 0.88 (s, 9H, H_1), 0.00 (s, 6H, H_3).
These spectroscopic data were consistent with those reported in the literature.[63]
CAS: 120420-05-5

Structure 4: *N*-(*tert*-butyl)dimethylsilyl-3-(*Z*)-deutero –allylamine (19)



19

$C_9H_{20}DNSi$

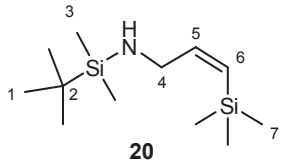
Mol. Wt.: 172.3614

To a solution of freshly generated dianion issued from ***N*-(*tert*-butyl)dimethylsilyl-allylamine** (**18**, 2.4 mmol) was added 99.9 % D_2O (0.75 mL, 41.4 mmol) at 0°C. After vigourous stirring at r.t. for 10 min, the resulting solution was submitted to a Et_2O/H_2O extraction. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo* to give the crude ***N*-(*tert*-butyl)dimethylsilyl-3-(*Z*)-deutero –allylamines (19)** as a colourless oil (350 mg, 87 % NMR yield).

[63] Colvin, E. W.; McGarry, D.; Nugent, M. J. *Tetrahedron*, **1988**, *44*, 4157.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.93-5.86 (m, 1H, H_6), 4.97-4.94 (m, 1H, H_5), 3.39-3.36 (m, 2H, H_4), 0.88 (s, 9H, H_1), 0.00 (s, 6H, H_3).

Structure 5: *N*-(*tert*-butyl)dimethylsilyl-3-trimethylsilyl-allylamine (20)



20

$C_{12}H_{29}NSi_2$

Mol. Wt.: 243.5364

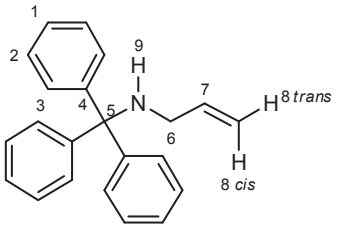
To a solution of freshly generated dianion issued from **N-(*tert*-butyl)dimethylsilyl -allylamine** (**18**, 4.1 mmol) was added BMDMSCl (0.61 mL, 4.1 mmol) at 0°C. After stirring at r.t. for 30 min, the resulting solution was submitted to a Et_2O/H_2O extraction. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo* to give the crude ***N*-(*tert*-butyl)dimethylsilyl-3-trimethylsilyl-allylamine (20)** as a yellow oil (830 mg, 83 % NMR yield).

^{1}H NMR (C_6D_6, 400 MHz): δ = 6.66 (dt, ^3J = 10.4, 2.2 Hz, 1H, H_5), 5.97 (dt, ^3J = 10.4, 2.4 Hz, 1H, H_1), 3.74 (t, ^3J = 2.2, 2H, H_3), 0.94 (s, 9H, H_1), 0.27 (s, 9H, H_7), 0.12 (s, 6H, H_3).

^{13}C NMR (C_6D_6, 100 MHz): δ = 149.5 (C_5), 128.2 (C_6), 56.5 (C_4), 28.2 (C_2), 20.2 (C_1), 4.1 (C_7), -3.4 (C_3).

IR (neat) 3425-3375 (br), 3035, 3005, 1640, 1470, 1463, 1388, 1360, 1249, 1047, 993, 827, 799, 769 cm^{-1}

Structure 6: *N*-tritylprop-2-en-1-amine (24)



24

$C_{22}H_{21}N$

Mol. Wt.: 299.4088

Tritylamine (437 mg, 1.7 mmol) and allyl bromide (0.73 mL, 8.4 mmol) in 2 mL of a 1 : 1 mixture of CH_3CN/DMF were added in a 2 – 5 ml microwave vial. The mixture was then stirred under μ-wave radiation at 120°C during 10 min. Solvents were evaporated *in vacuo* to give a crude brown

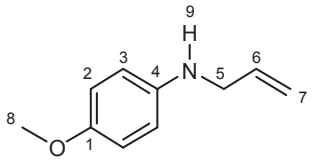
oil. Purification was achieved by flash column chromatography on silica gel (3 % Et_2O/PE) to give ***N*-tritylprop-2-en-1-amine (24)** as a white solid (140 mg, 28 %).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.51-7.49 (m, 6H, H_3), 7.31-7.27 (m, 6H, H_2), 7.22-7.18 (m, 3H, H_1), 6.02-5.93 (m, 1H, H_7), 5.28 (ddd, 1H, ^2J= 1.8 Hz, ^3J = 17.3 Hz, ^4J= 3.5 Hz, $H_{8\ cis}$), 5.08 (ddd, 1H, ^2J= 1.8 Hz, ^3J= 10.3 Hz, ^4J= 3.1 Hz, $H_{8\ trans}$), 2.79-2.77 (m, 2H, H_6), 1.66 (bs, 1H, H_9).

This spectroscopic data were consistent with those reported in the literature.[64]

CAS: 20020-75-1

Structure 7: *N-para*-methoxyphenyl-allylamine (26)



26

$C_{10}H_{13}NO$

Mol. Wt.: 163.2163

A solution of LDA was prepared by slow addition of *n*-BuLi in hexanes (c = 2.3M, 1.7 mL, 21 mmol) in a solution of freshly distilled DIPA (3 mL, 21 mmol) in 20 mL of THF at 0°C. This freshly prepared solution was slowly added *via canula* to a solution of anisole (25 g, 20 mmol) in 20 mL of THF at 0°C. The reaction mixture was then allowed to heat up to r.t. and was quenched with NH_4Cl sat. and the resulting solution was submitted to a Et_2O/H_2O extraction. The combined organic layers were washed with NaCl sat. and dried over Na_2SO_4, filtered and evaporated *in vacuo* to give ***N-para*-methoxyphenyl-allylamine (26)** as a crude yellow oil.

Purification was achieved by flash column chromatography on silica gel (20 % Et_2O/PE) to give a pale yellow oil (2.3 g, 68 %).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.81 (A of AB, d, 2H, ^3J= 8.8 Hz, H_2), 6.62 (B of AB, d, 2H, ^3J= 8.8 Hz, H_3), 6.04-5.94 (m, 1H, H_6), 5.34-5.28 (m, 1H, H_7), 5.21-5.17 (m, 1H, $H_{7'}$), 3.78 (s, 3H, H_8), 3.76-3.74 (m, 2H, H_5), 3.58 (bs, 1H, H_9).

These spectroscopic data were consistent with those reported in the literature.[65]

CAS: 71954-46-6

Structure 8: *N-para*-methoxyphenyl-3-(*Z*)-deutero-allylamine (28)

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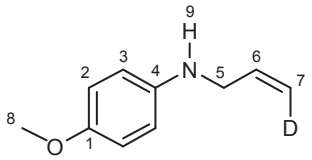
[64] Pepito, A. S.; Dittmer, D. C.; *J. Org. Chem*. **1997**, *62*, 7920.
[65] Yip, K.-T., Yang, M.; Laus, K.-L.; Zhu, N.-Y.; Yang, D.; *J. Am. Chem. Soc.* **2006**, *128*, 3130.



28

$C_{10}H_{12}DNO$

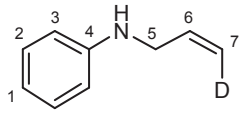
Mol. Wt.: 164.2225

To a solution of freshly generated dianion issued from ***N*-*para*-methoxyphenyl-allylamine** (**26**, 0.6 mmol) was added 99.9 % D_2O (0.50 mL, 27.6 mmol) at 0°C. After vigourous stirring at r.t. for 10 min, the resulting solution was submitted to a Et_2O/H_2O extraction. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo* to give 93 mg of the crude ***N*-*para*-methoxyphenyl-3-(*Z*)-deutero-allylamine (28)** as a yellow oil.

Isolated weigth represents 99 % of the expected weight for complete conversion. ^{1}H NMR spectrum exhibited 52 % starting material conversion into the expected deuterated product. Combinaison of both values finally gives a formation yield of 51 % for ***N*-*para*-methoxyphenyl-3-(*Z*)-deutero-allylamine (28)**.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.79 (A of AB, d, ^3J= 8.8 Hz, 2H, H_2), 6.60 (B of AB, d, ^3J= 8.8 Hz, 2H, H_3), 6.02 - 5.92 (m, 1H, H_6), 5.18 - 5.13 (m, 1H, H_7), 3.75 (s, 3H, H_8), 3.73 (d, ^3J= 5.5 Hz, 2H, H_5), 3.51 (bs, 1H, H_9).

Structure 9: *N*-phenyl-3-(*Z*)-deutero-allylamine (38).



38

$C_9H_{10}DN$

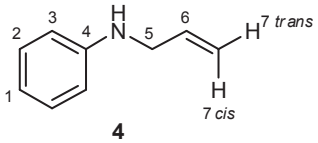
Mol. Wt.: 134.1965

To a solution of freshly generated dianion issued from ***N*-allylamine** (**4**, 6.0 mmol) was added 99.9 % D_2O (0.75 mL, 41.4 mmol) at 0°C. After 5 min of vigourous stirring at r.t., the resulting solution was submitted to a Et_2O/H_2O extraction. The combined organic layers were washed with NaCl sat. and dried over Na_2SO_4, filtered and evaporated *in vacuo* to give ***N*-phenyl-3-(*Z*)-deutero-allylamine (38)** as a pale yellow oil (922 mg, 74 % NMR yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.21-7.17 (m, 2H, H_2), 6.74-6.71 (m, 1H, H_1), 6.65-6.63 (m, 2H, H_3), 5.99-5.95 (m, 1H, H_6), 5.18-5.15 (m, 1H, H_7), 3.79-3.78 (m, 2H, H_5).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 148.2 (C_4), 135.5 (C_6), 129.3 (C_2), 117.6 (C_1), 116.0 (t, J= 24.0 Hz, C_7), 113.1 (C_3), 46.7 (C_5).

Structure 10: *N*-phenyl-allylamine (4)



4

$C_9H_{11}N$

Mol. Wt.: 133.1903

For comparison, commercially available ***N*-phenyl-allylamine (4)** was measured by NMR.

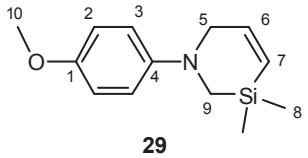
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.23-7.19 (m, 2H, H_2), 6.76-6.72 (m, 1H, H_1), 6.67-6.64 (m, 2H, H_3), 6.04-5.94 (m, 1H, H_6), 5.32 (dd, ^2J= 1.5 Hz, ^3J= 17.1 Hz, 1H, $H_{7\ cis}$), 5.20 (dd, J_{gem} = 1.5 Hz, ^3J= 10.1 Hz, 1H, $H_{7\ trans}$), 3.81-3.79 (m, 2H, H_5)

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 148.2 (C_4), 135.5 (C_6), 129.3 (C_2), 117.6 (C_1), 116.3 (C_7), 113.1 (C_3), 46.7 (C_5).

CAS: 589-9-3

I. 5. 2. Aza-3-sila-cyclohex-4-ene derivatives

Structure 11: *N-para*-methoxyphenyl-3,3-dimethyl-1-aza-3-sila-cyclohex-4-ene (29)



29

$C_{13}H_{19}NOSi$

Mol. Wt.: 233.3816

To a solution of freshly generated dianion issued from ***N-para*-methoxyphenyl-allylamine** (**26**, 4.7 mmol) was added BMDMSCl (0.80 mL, 5.6 mmol) at 0°C. After stirring at r.t. for 30 min, the resulting solution was submitted to a Et_2O/H_2O extraction. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo* to give 1,6 g of the crude ***N-para*-methoxyphenyl-3,3-dimethyl-1-aza-3-sila-cyclohex-4-ene (29)**.

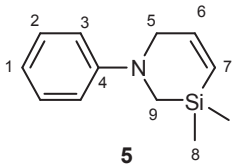
Purification was achieved by flash column chromatography on silica gel (20 % Et_2O/PE) to give a pale yellow oil (351 mg, 32 %).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.05 (A of AB, d, ^3J= 9.2 Hz, 2H, H_2), 6.92 (B of AB, d, ^3J= 9.2 Hz, 2H, H_3), 6.79 (dt, ^3J= 14.3, 3.6 Hz, 1H, H_6), 5.98 (dt, ^3J= 14.3, ^2J=2.3 Hz, 1H, H_7), 3.83 (s, 3H, H_{10}), 3.73-3.72 (m, 2H, H_5), 2.72 (s, 2H, H_9), 0.27 (s, 6H, H_8).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 153.5 (C_1), 148.7 (C_4), 146.1 (C_6), 125.0 (C_7), 119.2 (C_3), 114.2 (C_2), 55.4 (C_{10}), 55.3 (C_5), 41.7 (C_9), -2.6 (C_8).

IR (neat) 2952, 2767, 1507, 1242, 1039, 847 cm^{-1}.

Structure 12: *N*-phenyl-3,3-dimethyl-1-aza-3-sila-cyclohex-4-ene (5)



5

$C_{12}H_{17}NSi$

Mol. Wt.: 203.3556

To a solution of freshly generated dianion issued from ***N*-phenyl-allylamine** (**4**, 20 mmol) was added 99.9 % BMDMSCl (3.4 mL, 24 mmol) at 0°C. After 5 min of stirring at r.t., the resulting solution was submitted to a Et_2O/H_2O extraction. The combined organic layers were washed with NaCl sat. and dried over Na_2SO_4, filtered and evaporated *in vacuo* to give a crude orange oil.

Purification was achieved by flash column chromatography on silica gel (3 % Et_2O/PE) to give ***N*-phenyl-3,3-dimethyl-1-aza-3-sila-cyclohex-4-ene (5)** as a pale yellow oil (2.89 g, 70 %).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.24-7.22 (m, 2H, H_2), 6.96-6.94 (m, 2H, H_3), 6.81-6.77 (m, 1H, H_1), 6.75-6.69 (m, 1H, H_6), 5.91-5.86 (m, 1H, H_7), 3.79-3.78 (m, 2H, H_5), 2.78 (s, 2H, H_9), 0.15 (s, 6H, H_8).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 153.7 (C_4), 145.9 (C_6), 129.1 (C_2), 125.6 (C_7), 115.8 (C_1), 116.6 (C_3), 53.2 (C_5), 40.3 (C_9), -2.5 (C_8).

IR (neat) 3080, 3060, 3022, 1596, 1245, 1208, 845 cm^{-1}.

HRMS(ES^+): calcd for $C_{12}H_{18}NSi$ (MH^+) = 204.12030; found 204.12021.

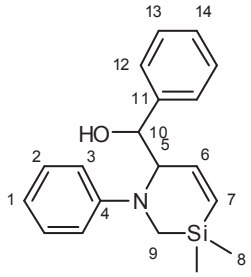
I. 5. 3. Reactivity of *N*-phenyl-3,3-dimethyl-1-aza-3-sila-cyclohex-4-ene

Anion generation

Anionic species were generated as follow: To a stirred solution of ***N*-phenyl-3,3-dimethyl-1-aza-3-sila-cyclohex-4-ene** (1 eq.) in Et_2O or THF (1 M) was added dropwise *t*-BuLi or *n*-BuLi (1.1 eq.) at -78°C. After addition, the reaction was allowed to warm to 0°C. Resulting anion was then quenched by the appropriate electrophile.

I. 5. 3. a. *n*-BuLi, THF

Structure 13: *N*-phenyl-6-hydroxybenzyl-3,3-dimethyl-1-aza-3-sila-cyclohex-4-ene (9)



9

$C_{19}H_{23}NOSi$

Mol. Wt.: 309.4775

To a solution of freshly generated anion issued from ***N*-phenyl-3,3-dimethyl-1-aza-3-sila-cyclohex-4-ene** (**5**, 199 mg, 0.98 mmol) was added was added dropwise freshly distilled benzaldehyde (0.10 mL, 0.98 mmol, 1.0 eq.) at r.t. The mixture was stirred 60 min then quenched with NH_4Cl sat., and allowed to heat up at r.t. The aqueous layer was extracted with ether, washed with NaCl sat., dried over Na_2SO_4, then filtered and evaporated *in vacuo* to give 390 mg of ***N*-phenyl-6-hydroxybenzyl-3,3-dimethyl-1-aza-3-sila-cyclohex-4-ene (9)** as a 6 / 4 mixture of two hardly separable diastereomers and as an orange-red oil.

Purification was achieved by flash column chromatography on silica gel (3 % Et_2O/PE) to give:

a pale yellow oil (147 mg, 48 %)

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.35-7.30 (m, 7H, H_{Ar}), 7.09-7.06 (m, 2H, H_{Ar}), 6.85-6.82 (m, 1H, H_{Ar}), 6.60-6.50 (m, 1H, H_6), 6.17 (d, ^3J= 14.8 Hz, 1H, H_7), 4.96 (bs, 1H, H_{10}), 4.67 (bs, 1H,

H_5), 3.04 (A of AB, d, ^2J= 14.3 Hz, 1H, H_9), 2.87 (B of AB, d, ^2J= 14.3 Hz, 1H, $H_{9'}$), 2.25 (bs, 1H, H_{11}), 0.22 (s, 3H, H_8), 0.12 (s, 3H, $H_{8'}$).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 152.8 (C_{Ar}), 144.0 (C_{Ar}), 142.7 (C_{Ar}), 130.2 (C_{Ar}), 129.3 (C_{Ar}), 128.4 (C_{Ar}), 127.3 (C_6), 125.4 (C_{Ar}), 119.3 (C_7), 118.0 (C_{Ar}), 74.8 (C_{10}), 66.4 (C_5), 35.6 (C_9), -1.8 (C_8), -2.5 ($C_{8'}$).

a pale yellow oil (84 mg, 27 %)

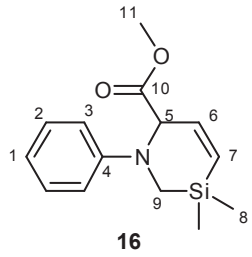
^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.45-7.24 (m, 7H, H_{Ar}), 7.02-7.08 (m, 2H, H_{Ar}), 6.81-6.89 (m, 1H, H_{Ar}), 6.29 (dd, ^3J= 14.8, 4.4 Hz, 1H, H_6), 5.93 (d, ^3J= 14.8 Hz, 1H, H_7), 4.75 (d, 1H, ^3J= 9.4 Hz, H_{10}), 4.25 (dd, ^3J= 9.4 Hz, 1H, H_5), 3.34 (A of AB, d, ^2J= 16.2 Hz, 1H, H_9), 3.09 (B of AB, d, ^2J= 16.2 Hz, 1H, $H_{9'}$), 2.30 (m, 1H, H_{11}), 0.17 (s, 3H, H_8), -0.10 (s, 3H, $H_{8'}$).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 151.9 (C_{Ar}), 145.9 (C_{Ar}), 141.1 (C_{Ar}), 129.3 (C_{Ar}), 128.9 (C_{Ar}), 128.6 (C_{Ar}), 128.3 (C_6), 127.6 (C_{Ar}), 119.5 (C_7), 117.8 (C_{Ar}), 74.8 (C_{10}), 65.8 (C_5), 35.5 (C_9), -1.2 (C_8), -2.5 ($C_{8'}$).

IR (neat) 3550 - 3100, 3080, 3062, 3031, 1664, 1599, 835 cm^{-1}.

MS(CI NH_3, *m/z*) 310 (MH^+), 204 (MH^+ - PhCHO).

Structure 14: methyl 3,3-dimethyl-1-phenyl-1,2,3,6-tetrahydro-1,3-azasiline-6-carboxylate (16)



16

$C_{14}H_{19}NO_2Si$

Mol. Wt.: 261.3917

A solution of freshly generated anion issued from ***N*-phenyl-3,3-dimethyl-1-aza-3-sila-cyclohex-4-ene** (**5**, 404 mg, 1.99 mmol) was added slowly via canula to a solution of freshly distilled ClCOOMe (0.17 mL, 2.20 mmol, 1.1 eq.) in THF (7 mL) at -20°C. The mixture was stirred 30 min then quenched with brine at this temperature, and allowed to heat up at r.t. The organic layer was extracted with ether, washed with NaCl sat., dried over Na_2SO_4, then filtered and evaporated *in vacuo* to give 0.53 g of **methyl 3,3-dimethyl-1-phenyl-1,2,3,6-tetrahydro-1,3-azasiline-6-carboxylate (16)** as a crude brown oil.

Purification was achieved by flash column chromatography on silica gel (1 % Et_2O/PE) to give a pale yellow oil (82 mg, 16 %).

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.30-7.23 (m, 2H, H_2), 6.97-6.93 (m, 2H, H_3), 6.88-6.76 (m, 2H, $H_{1,6}$), 6.08 (dd, ^3J= 14.3 Hz, ^4J= 2.0 Hz, 1H, H_7), 5.03 (dd, ^3J= 4.9 Hz, ^4J= 2.0 Hz, 1H, H_5), 3.69 (s, 3H, H_{11}), 3.09 (s, 2H, H_9), 0.20 (s, 3H, H_8), 0.18 (s, 3H, $H_{8'}$).

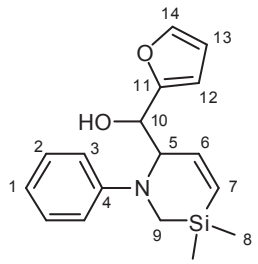
^{13}C NMR ($CDCl_3$, 50 MHz): δ = 171.9 (C_{10}), 143.1 (C_4), 142.9 (CH), 129.2 (C_2), 128.6 (CH), 118.9 (CH), 116.2 (C_3), 63.2 (C_5), 52.0 (C_9), 35.0 (C_{11}), -2.4 (C_8), -3.2 ($C_{8'}$).

IR (neat) 3089, 3061, 3037, 1732 (br), 1597, 837, 796 cm^{-1}.

MS(CI NH_3, *m/z*) 262 (MH^+).

I. 5. 3. b. *t*-BuLi, THF

Structure 15: (3,3-dimethyl-1-phenyl-1,2,3,6-tetrahydro-1,3-azasilin-6-yl)(furan-2-yl)methanol (8)



8

$C_{17}H_{21}NO_2Si$

Mol. Wt.: 299.4396

To a solution of freshly generated anion issued from ***N*-phenyl-3,3-dimethyl-1-aza-3-sila-cyclohex-4-ene** (**5**, 199 mg, 0.98 mmol) was added was added dropwise freshly distilled furfuraldehyde (85 µL, 1.03 mmol, 1.05 eq.) in THF (2 mL) at 0°C. The mixture was then allowed to heat up at r.t. After 10 min at r.t., the reaction mixture was quenched with H_2O. The organic layer was extracted with ether, washed with NaCl sat., dried over Na_2SO_4, then filtered and evaporated *in vacuo* to give **(3,3-dimethyl-1-phenyl-1,2,3,6-tetrahydro-1,3-azasilin-6-yl)(furan-2-yl)methanol (8)** as orange oil.

Purification was achieved by flash column chromatography on silica gel (10 % AcOEt/PE) to give a pale yellow oil (176 mg, 60 %) as a 7 / 3mixture of two non separable diastereomers of undetermined absolute configuration.

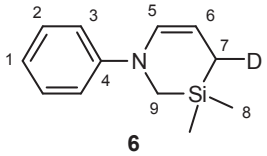
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.20-7.11 (m, 3H, H_{Ar}), 6.98-6.90 (m, 4H, H_{Ar}), 6.78-6.73 (m, 2H, H_{Ar}), 6.70 (dd, ^3J= 14.5, 4.8 Hz, 1H, H_{6maj}), 6.43 (dd, ^3J= 14.5, 4.6 Hz, 0.5H, H_{6min}), 6.20-6.19 (m, 0.5H, H_{Ar}), 6.09-6.07 (m, 0.5H, H_{Ar}), 6.02-5.99 (m, 3H, $H_{5maj, Ar}$), 5.75 (dt, ^3J= 14.5 Hz, ^4J= 2.6 Hz, 0.5H, H_{Ar}), 4.95 (d, ^3J= 3.6 Hz, 1H, H_{10maj}), 4.89-4.86 (m, 1H, H_{5maj}), 4.8 (d, ^3J= 8.8 Hz, 0.5H, H_{10min}), 4.73-4.70 (m, 0.5H, H_{5min}), 2.98 (A of Ab, d, ^2J= 14.6 Hz, 1H, H_{9maj}), 2.92 (A of AB, d, ^2J= 15.9 Hz, 0.5H, H_{9min}), 2.84 (B of AB, d, ^2J= 14.6 Hz, 1H, $H_{9'maj}$), 2.66 (B of AB, d, ^2J= 15.9 Hz, 0.5H, $H_{9'min}$), 0.06 (s, 3H, H_{8maj}), 0.01 (s, 3H, $H_{8'maj}$), -0.10 (s, 1.4H, H_{8min}), -0.21 (s, 1.4H, $H_{8'min}$).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 156.7, 155.1, 153.0, 152.6, 146.6, 145.9, 142.8, 142.2, 130.0, 129.9, 129.8, 129.1, 119.9, 119.2, 118.1, 117.6, 111.2, 111.1, 109.1, 106.8, 70.7, 68.6, 63.9 (C_{9maj}), 68.8 (C_{9min}), 36.0 ($C_{9'maj}$), 35.1 ($C_{9'min}$), -1.0 (C_{8maj}), -1.3 ($C_{8'maj}$), -2.2 (C_{8min}), -2.4 ($C_{8'min}$).

IR (neat) 3400-3200 (br), 2952, 1594, 1494, 1248, 839 cm^{-1}.

HRMS(ES^+): calcd for $C_{17}H_{22}NO_2Si$ (MH^+) = 300.14143; found 300.14153.

Structure 16: 4-deutero-3,3-dimethyl-1-phenyl-1,2,3,4-tetahydro-1,3-azasiline (6)



6

$C_{12}H_{16}DNSi$

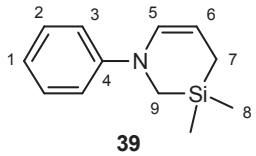
Mol. Wt.: 204.3617

A solution of *t*-BuLi in pentane (c = 1.5 M, 0.40 mL, 0.60 mmol) was added to a solution of ***N*-phenyl-3,3-dimethyl-1-aza-3-sila-cyclohex-4-ene** (**5**, 121 mg, 0.60 mmol) in THF (2 mL) at -78°C. The mixture was then allowed to slowly heat up at 0°C. After 10 min at 0°C, the reaction mixture was quenched with 99.9 % D2O. The organic layer was extracted with ether, washed with NaCl sat., dried over Na_2SO_4, then filtered and evaporated *in vacuo* to give **4-deutero-3,3-dimethyl-1-phenyl-1,2,3,4-tetahydro-1,3-azasiline (6)** as a crude yellow pale oil (104 mg, 86 % NMR yield) which was not purified due to its high sensitivity towards air moisture.

^{1}H NMR (C_6D_6, 400 MHz): δ = 7.20-7.16 (m, 2H, H_2), 6.89-6.86 (m, 2H, H_3), 6.83-6.80 (m, 1H, H_1), 6.38 (dd, ^3J= 8.5 Hz, ^4J= 0.9 Hz, 1H, H_5), 4.71 (dd, ^3J= 8.5, 5.5 Hz, 1H, H_6), 2.52 (s, ^3J= 5.5 Hz, ^4J= 0.9 Hz, 2H, H_9), 1.16-1.14 (m, ^3J= 5.5 Hz, ^4J= 0.9 Hz, 1H, H_7), -0.04 (s, 6H, H_8).

^{13}C NMR (C_6D_6, 100 MHz): δ = 146.9 (C_4), 133.1 (C_5), 129.9 (C_2), 120.1 (C_1), 116.0 (C_3), 99.9 (C_6), 36.4 (C_9), 9.6 (t, J = 18,9 Hz, C_7), -2.5 (C_8).

Structure 17: 5-*tert*-butyl-3,3-dimethyl-1-phenyl-1,3-azasilinane (39)



39

$C_{12}H_{17}NSi$

Mol. Wt.: 203.3556

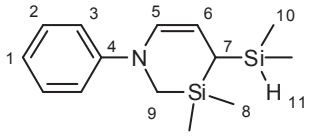
For comparison, a similar reaction was carried out in parallel using strictly the same conditions: a quench with H_2O was performed instead and afforded **5-*tert*-butyl-3,3-dimethyl-1-phenyl-1,3-azasilinane (39)** as a crude pale yellow oil in 88 % yield.

^{1}H NMR (C_6D_6, 400 MHz): δ = 7.24-7.20 (m, 2H, H_2), 6.93-6.91 (m, 2H, H_3), 6.88-6.84 (m, 1H, H_1), 6.42 (dt, ^3J = 8.5 Hz, ^4J= 0.9 Hz, 1H, H_5), 4.75 (dt, ^3J = 8.5, 5.5 Hz, 1H, H_6), 2.56 (s, 2H, H_9), 1.20 (dt, ^3J= 5.5 Hz, ^4J= 0.9 Hz, 2H, H_7), 0.00 (s, 6H, H_8).

^{13}C NMR (C_6D_6, 100 MHz): δ = 150.4 (C_4), 133.0 (C_5), 129.8 (C_2), 120.1 (C_1), 116.0 (C_3), 99.9 (C_6), 36.4 (C_9), 9.9 (C_7), -2.5 (C_8).

IR (neat) 2973, 2865, 1671, 1597, 1495, 1252 cm^{-1}.

Structure 18: 4-(dimethylsilyl)-3,3-dimethyl-1-phenyl-1,2,3,4-tetrahydro-1,3-azasiline (7)



7

$C_{14}H_{23}NSi_2$

Mol. Wt.: 261.5101

A solution of *t*-BuLi (c = 1.6 M, 0.47 mL, 0.75 mmol) was added to a solution of ***N*-phenyl-3,3-dimethyl-1-aza-3-sila-cyclohex-4-ene** (**5**, 153 mg, 0.8 mmol) in THF (2 mL) at -78°C. The mixture was allowed to stir for 60 min at -78°C then slowly allowed to heat up at 0°C. Chlorodimethylsilane (0.09 mL, 0.75 mmol) was then added and after 10 min at 0°C, the reaction mixture was quenched with H_2O. The organic layer was extracted with ether, washed with NaCl sat., dried over Na_2SO_4, then filtered and evaporated *in vacuo* to give **4-(dimethylsilyl)-3,3-dimethyl-1-phenyl-1,2,3,4-tetrahydro-1,3-azasiline (7)** as a crude oil (155mg, 79 % NMR yield) which was not purified due to its high sensitivity towards air moisture.

^{1}H NMR (C_6D_6, 400 MHz): δ = 7.20-7.16 (m, 2H, H_2), 6.88-6.80 (m, 3H, $H_{1,3}$), 6.38 (dd, ^3J= 8.6 Hz, ^4J= 0.6 Hz, 1H, H_5), 4.61 (dt, ^3J= 8.6, 7.0 Hz, 1H, H_6), 4.10-4.12 (m, 1H, H_{11}), 2.69-2.54 (m,

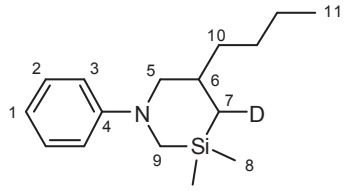
2H, H_9), 0.71-0.68 (m, 1H, H_7), 0.10 (s, 3H, H_8), 0.09 (s, 3H, $H_{8'}$), 0.08 (d, ^3J= 0.9 Hz, 3H, H_{10}), 0.07 (d, ^3J= 0.6 Hz, 3H, $H_{10'}$).

^{13}C NMR (C_6D_6, 100 MHz): δ = 149.9 (C_4), 131.4 (C_5), 130.1 (C_3), 120.0 (C_1), 115.6 (C_2), 100.9 (C_6), 36.7 (C_9), 10.8 (C_7), -1.0 (C_8), -2.0 ($C_{8'}$), -2.9 (C_{10}), -3.5 ($C_{10'}$).

IR (neat) 2955, 2103, 1595, 1497, 1249, 833 cm^{-1}.

I. 5. 3. c. *n*-BuLi, Et_2O

Structure 19: *N*-phenyl-4-deutero-3,3-dimethyl-5-*n*-butyl-1-aza-3-sila-cyclohexane (11)



11

$C_{16}H_{26}DNSi$

Mol. Wt.: 262.4839

A solution of *n*-BuLi in hexanes (0.47 mL, c = 2.2 M, 1.0 mmol) was added to a solution of ***N*-phenyl-3,3-dimethyl-1-aza-3-sila-cyclohex-4-ene** (**5**, 204 mg, 1.0 mmol) in Et_2O (2 mL) at -78°C. The mixture was then allowed to slowly heat up at 0°C. After 10 min at 0°C, the reaction mixture was quenched with 99.9 % D2O. The organic layer was extracted with ether, washed with NaCl sat., dried over Na_2SO_4, then filtered and evaporated *in vacuo* to give a crude colourless oil (173 mg, 66 %) as a single diastereomer.

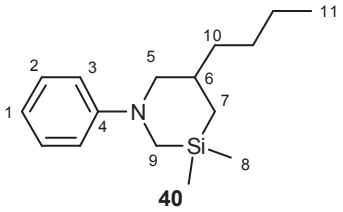
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.22-7.18 (m, 2H, H_2), 6.86-6.84 (m, 2H, H_3), 6.70-6.67 (m, 1H, H_1), 3.59 (A of AB, dt, ^2J= 13.6 Hz, ^4J= 2.2 Hz, 1H, H_5), 2.97 (A of AB, dd, ^2J = 14.7 Hz, ^4J= 2.2 Hz, 1H, H_9), 2.49 (B of AB, dd, ^2J = 13.6 Hz, ^3J= 10.3 Hz, 1H, $H_{5'}$), 2.37 (B of AB, d, J_{gem} = 14.7 Hz, 1H, $H_{9'}$), 1.83-1.80 (m, 1H, H_6), 1.36-1.33 (m, 6H, H_{10}), 0.93 (t, ^3J= 7.2 Hz, 3H, H_{11}), 0.30 (d, ^3J= 12.7 Hz, 1H, H_7), 0.08 (s, 3H, H_8), 0.05 (s, 3H, $H_{8'}$).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 153.1 (C_4), 129.1 (C_2), 117.1 (C_1), 114.9 (C_3), 59.4 (C_9), 40.3 (C_5), 37.6 (CH_2), 34.3 (C_6), 29.2 (CH_2), 23.1 (CH_2), 19.4 (t, J= 18.0 Hz, C_7),14.3 (C_{11}), -2.5 (C_8), -3.3 ($C_{8'}$).

IR (neat) 2954, 2923, 1597, 1501, 1248, 839 cm^{-1}.

HRMS(ES$^+$): calcd for $C_{16}H_{27}DNSi$ (MH^+) = 263.20483; found 263.20473; deuteration 99 %.

Structure 20: *N*-phenyl-3,3-dimethyl-5-*n*-butyl-1-aza-3-sila-cyclohexane (40)



40

$C_{16}H_{27}NSi$

Mol. Wt.: 261.4778

For comparison, a similar reaction was carried out in parallel using the same conditions on a smaller scale: starting with ***N*-phenyl-3,3-dimethyl-1-aza-3-sila-cyclohex-4-ene** (**5**, 0.87 mg, 177 mmol), a quench with H_2O was performed and afforded ***N*-phenyl-3,3-dimethyl-5-*n*-butyl-1-aza-3-sila-cyclohexane (40)** as a crude pale yellow oil (190 mg, 83 %).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.23-7.19 (m, 2H, H_2), 6.87-6.84 (m, 2H, H_3), 6.70-6.67 (m, 1H, H_1), 3.62-3.57 (m, 1H, H_5), 2.97 (A of AB, dt, ^2J= 14.5 Hz, ^4J= 1.6 Hz, 1H, H_9), 2.49 (A of AB, dd, ^2J= 13.6 Hz, ^3J= 10.1 Hz, 1H, $H_{5'}$), 2.38 (B of AB, d, ^2J= 14.5 Hz, 1H, $H_{9'}$), 1.82-1.84 (m, 1H, H_6), 1.37-1.32 (m, 6H, H_{10}), 0.92 (t, ^3J= 7.4 Hz, 3H, H_{11}), 0.34 (d, ^3J= 12.0 Hz, 1H, H_7), 0.30 (d, ^3J= 12.3 Hz, 1H, $H_{7'}$), 0.08 (s, 3H, H_8), 0.06 (s, 3H, $H_{8'}$).

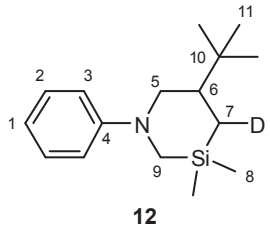
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 153.0 (C_4), 129.1 (C_2), 117.1 (C_1), 114.9 (C_3), 59.5 (C_9), 40.3 (C_5), 37.6 (CH_2), 34.9 (C_6), 29.2 (CH_2), 23.1 (CH_2), 19.8 (C_7), 14.3 (C_{11}), -2.6 (C_8), -3.2 ($C_{8'}$).

IR (neat) 2954, 2921, 1597, 1500, 1248, 840 cm^{-1}.

HRMS(ES^+): calcd for $C_{18}H_{34}NSi_2$ (MH^+) = 262.19855; found 262.19846.

I. 5. 3. d. *t*-BuLi, Et_2O

Structure 21: *N*-phenyl-4-deutero-3,3-dimethyl-5-*tert*-butyl-1-aza-3-sila-cyclohexane (12)



12

$C_{16}H_{26}DNSi$

Mol. Wt.: 262.4839

A solution of *t*-BuLi in pentane (0.40 mL, c = 1.5 M) was added to a solution of ***N*-phenyl-3,3-dimethyl-1-aza-3-sila-cyclohex-4-ene** (**5**, 123 mg, 0.6 mmol) in Et_2O (2 mL) at -78°C. The mixture was then allowed to slowly heat up at 0°C. After 10 min at 0°C, the reaction mixture was

quenched with 99.9 % D2O. The organic layer was extracted with ether, washed with NaCl sat., dried over Na_2SO_4, then filtered and evaporated *in vacuo* to give ***N*-phenyl-4-deutero-3,3-dimethyl-5-*tert*-butyl-1-aza-3-sila-cyclohexane (12)** as a crude colourless oil (131 mg, 86 %) as a single diastereomer.

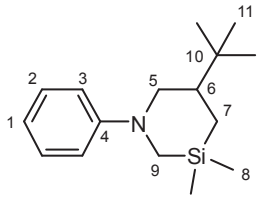
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.32-7.28 (m, 2H, H_2), 6.94-6.92 (m, 2H, H_3), 6.79-6.75 (m, 1H, H_1), 3.97 (A of AB, d, ^2J= 13.6 Hz, 1H, H_5), 3.31 (A of AB, d, ^2J= 14.5 Hz, 1H, H_9), 2.57 (B of AB, dd, ^2J= 13.6 Hz, ^3J= 10.7 Hz, 1H, $H_{5'}$), 2.45 (B of AB, d, ^2J= 14.5 Hz, 1H, $H_{9'}$), 1.68-1.74 (m, 1H, H_6), 1.04 (s, 9H, H_{11}), 0.53 (d, ^3J= 13.2 Hz, 1H, H_7), 0.20 (s, 3H, H_8), 0.15 (s, 3H, $H_{8'}$).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 152.5 (C_4), 129.1 (C_2), 116.5 (C_1), 114.2 (C_3), 55.6 (C_5), 44.3 (C_6), 39.9 (C_9), 33.6 (C_{10}), 27.3 (C_{11}), 13.9 (t, J = 18.3 Hz, C_7), -2.5 (C_8), -3.2 ($C_{8'}$).

IR (neat) 2954, 1667, 1597, 1502, 1248, 840 cm^{-1}.

HRMS(ES^+): calcd for $C_{16}H_{27}NDSi$ (MH^+) = 263.20483; found 263.20476; deuteration 98 %.

Structure 22: *N*-phenyl-3,3-dimethyl-5-*tert*-butyl-1-aza-3-sila-cyclohexane (41)



41

$C_{16}H_{27}NSi$

Mol. Wt.: 261.4778

For comparison, a similar reaction was carried out in parallel using the same conditions on a smaller scale: starting with ***N*-phenyl-3,3-dimethyl-1-aza-3-sila-cyclohex-4-ene** (**5**, 123 mg, 0.61 mmol), a quench with H_2O was performed and afforded ***N*-phenyl-3,3-dimethyl-5-*tert*-butyl-1-aza-3-sila-cyclohexane (41)** as a crude pale yellow oil (146 mg, 92 %).

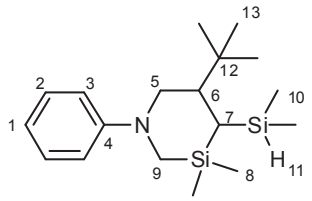
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.22-7.18 (m, 2H, H_2), 6.84-6.81 (m, 2H, H_3), 6.68-6.64 (m, 1H, H_1), 3.86 (A of AB, dd, ^2J= 13.6 Hz, ^3J= 2.2 Hz, 1H, H_5), 3.03 (A of AB, dd, ^2J= 14.5 Hz, ^4J= 1.6 Hz, 1H, H_9), 2.47 (B of AB, dd, ^2J= 13.6 Hz, ^3J= 10.5 Hz, 1H, $H_{5'}$), 2.35 (B of AB, ^2J= 14.5 Hz, 1H, $H_{9'}$), 1.64-1.53 (m, 1H, H_6), 0.94 (s, 9H, H_{11}), 0.90-0.85 (m, 1H, H_7), 0.45 (t, ^3J= 13.6 Hz, 1H, $H_{7'}$), 0.10 (s, 3H, H_8), 0.04 (s, 3H, $H_{8'}$).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 152.6 (C_4), 129.1 (C_2), 116.6 (C_1), 114.3 (C_3), 55.7 (C_5), 44.5 (C_6), 39.9 (C_9), 33.7 (C_{10}), 27.3 (C_{11}), 14.3 (C_7), -2.5 (C_8), -3.2 ($C_{8'}$).

IR (neat) 2954, 1598, 1502, 1248, 840 cm^{-1}.

HRMS(ES^+): calcd for $C_{16}H_{27}NSi$ (MH^+) = 262.19855; found 262.19850.

Structure 23: 5-*tert*-butyl-4-(dimethylsilyl)-3,3-dimethyl-1-phenyl-1,3-azasilane (32)



32

$C_{18}H_{33}NSi_2$

Mol. Wt.: 319.6323

A solution of *t*-BuLi (c = 1.6 M, 0.31 mL, 0.19 mmol) was added to a solution of ***N*-phenyl-3,3-dimethyl-1-aza-3-sila-cyclohex-4-ene** (**5**, 101 mg, 0.5 mmol) in Et_2O (2 mL) at -78°C. The mixture was allowed to stir for 60 min at -78C then slowly allowed to heat up at 0°C. Chlorodimethylsilane (0.06 mL, 0.5 mmol) was then added. After 10 min, the reaction mixture was quenched with H_2O and the organic layer was extracted with ether, washed with NaCl sat., dried over Na_2SO_4 and filtered and evaporated *in vacuo* to give **5-*tert*-butyl-4-(dimethylsilyl)-3,3-dimethyl-1-phenyl-1,3-azasilane (32)** as a pure colourless oil (126 mg, 79 % NMR yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.22-7.18 (m, 2H, H_2), 6.74-6.72 (m, 2H, H_3), 6.64-6.60 (m, 1H, H_1), 3.95-3.90 (m, 1H, H_{11}), 3.54-3.41 (m, 2H, H_5), 2.68 (A of AB, J_{gem}= 13.6 Hz, 1H, H_9), 2.54 (B of AB, J_{gem}= 13.6 Hz, 1H, $H_{9'}$), 1.97-1.93 (m, 1H, H_6), 0.93 (s, 9H, H_{13}), 0.27-0.25 (m, 1H, H_7), 0.25 (s, 3H, H_8), 0.22 (s, 3H, $H_{8'}$), 0.09 (d, 3H, ^3J= 3.7 Hz, H_{10}), 0.05 (d, ^3J= 3.7 Hz, 3H, $H_{10'}$).

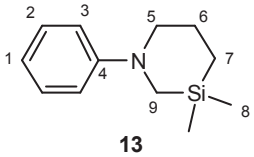
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 151.9 (C_4), 129.2 (C_2), 115.5 (C_1), 111.8 (C_3), 49.6 (C_5), 46.8 (C_6), 38.9 (C_9), 34.5 (C_{12}), 28.3 (C_{13}), 7.4 (C_7), 2.7 (C_8), 0.9 ($C_{8'}$), -2.7 (C_{10}), -3.3 ($C_{10'}$).

IR (neat) 2955, 2108, 1598, 1502, 1252, 838 cm^{-1}.

HRMS(ES^+): calcd for $C_{18}H_{34}NSi_2$ (MH^+) = 320.22243; found 320.22246.

I. 5. 4. Hydrogenation

Structure 24: *N*-phenyl-3,3-dimethyl-1-aza-3-sila-cyclohexane (13)



13

$C_{12}H_{19}NSi$

Mol. Wt.: 205.3715

***N*-phenyl-3,3-dimethyl-1-aza-3-sila-cyclohex-4-ene** (**5**, 425 mg, 2.1 mmol) was dissolved in MeOH (20 mL) and placed in the presence of Pd/C (43 mg, 10 %). 1 atm of H_2 pressure was applied and the resulting mixture was stirred at r.t. for 30 min. The residue was then filtered over a pad of Celite® and carefully rinsed with ether. Solvents were evaporated *in vacuo* to give 488 mg a colourless crude oil.

Purification was achieved by flash chromatography (2 % Et_2O/Pent) to afford ***N*-phenyl-3,3-dimethyl-1-aza-3-sila-cyclohexane (13)** as a colourless oil (287 mg, 66 %).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.23-7.19 (m, 1H, H_2), 6.90-6.87 (m, 1H, H_3), 6.73-6.69 (m, 1H, H_1), 3.23-3.20 (m, 2H, H_5), 2.68 (s, 2H, H_9), 1.95-1.89 (m, 2H, H_6), 0.74 (t, ^3J= 6.8 Hz, 2H, H_7), 0.09 (s, 6H, H_8).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 153.4 (C_4), 129.1 (C_2), 117.4 (C_1), 112.8 (C_3), 53.9 (C_5), 40.7 (C_9), 24.1 (C_6), 12.5 (C_7), -3.2 (C_8).

IR (neat) 2954, 2917, 1598, 1502, 1248 cm^{-1}.

HRMS(ES^+): calcd for $C_{12}H_{20}NSi$ (MH^+) = 206.13595; found 206.13588.

II. Platinum(II)chloride-catalyzed cycloisomerizations of 1,5-enynes

II. 1. Background

In the early 1980's, electrophilic transition-metal complexes or halides have found application in **skeletal rearrangement reactions** and since then, these transformations have been largely studied and reviewed.[66] These processes are generally initiated by a metal-promoted electrophilic activation of the alkyne moiety (metals are said alkynophilic when there is a selective activation of the alkyne moiety over the alkene) and involve concomitant carbon-carbon bond cleavages and formations. Such reactions are very attractive because they proceed with total mass transfer from substrates to products (cycloisomerizations) and give rise to a myriad of molecular structures.

After a brief historical summary of skeletal rearrangement reactions, an overall view of some reports about mechanistic investigations will be presented.

II. 1. 1. History

II. 1. 1. a. "Formal" metathesis-type products

For the first time in 1988, enyne skeletal rearrangement was mentioned in the literature (Scheme II-1).[67] Trost and co-worker reported the palladium(II)-catalyzed cycloisomerization of a 1,6-enyne in the presence of dimethyl acetylenedicarboxylate (DMAD), which yielded a [2+2+2]-cyclotrimerization product (expected by the authors) in a mixture with a vinylcyclopentene type of product. The latter is expected from the reactions of enyne metathesis initiated by carbenic complexes, hence the vinylcyclopentene is described as a "formal" metathesis product. Surprinsingly, a carbon-labeled experiment that afforded two isomers of the vinylcyclopentenic structure, suggests a very distinct mechanistic course for this reaction. We will deal with mechanism hypotheses later.

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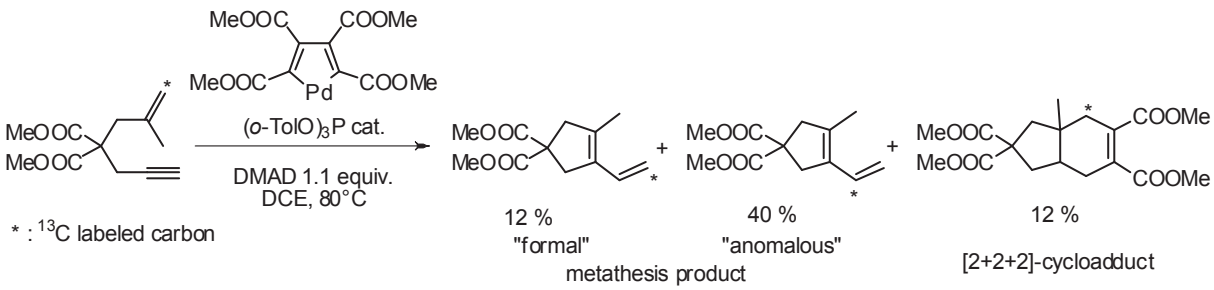
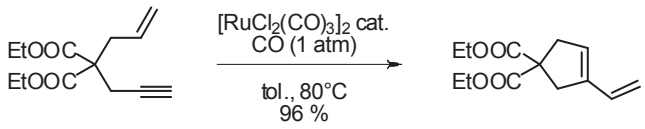
[66] (a) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333. (b) Ma, S.; Yu, S.; Gu, Z. *Angew. Chem. Int. Ed.* **2006**, *45*, 200. (c) Hashmi, A. S. K. *Gold Bull. (London)* **2004**, *37*, 51. (d) Bruneau, C. *Angew. Chem. Int. Ed.* **2005**, *44*, 2328.

[67] Trost, B. M.; Tanoury, G. J. *J. Am. Chem. Soc*. **1988**, *110*, 1636.



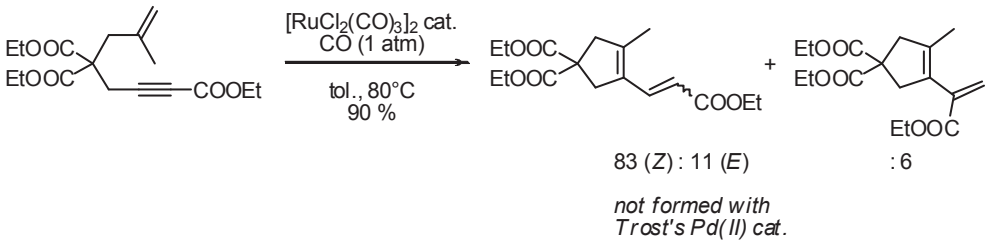
Scheme II-1 : palladium-catalyzed rearrangement

In 1994, Murai and co-workers reported a highly selective ruthenium dimer catalytic system for the conversion of 1,6-enynes into vinylcyclopentenes (Scheme II-2).[68] In this report, the authors also mentionned for the first time that the platinum salt $PtCl_2$ could catalyze this reaction, as well as $[RhCl(CO)_2]_2$, $ReCl(CO)_5$, $[IrCl(CO)_2]_n$ and $AuCl_3$ cause similar rearrangements.



Scheme II-2 : ruthenium-catalyzed rearrangement

Moreover, the formation of an unusual vinylcyclopentene (described as an "anomalous" metathesis-type product) was observed, starting from an electron deficient alkyne (Scheme II-3). The authors did not observe this anomalous metathesis product using Pd(II)-Trost's catalyst.



Scheme II-3 : mixture of "formal" and "anomalous" metathesis-type product

In 1996, Murai and co-workers reported their complementary results of the work presented above. [68] Among the previously cited catalysts (Rh, Ir, Pt, Re, Au), $PtCl_2$ was the most versatile and effective for the cyclization of various enynes.[69] An interesting example is the Pt(II)-catalyzed cycloisomerization of a *Z*-alkene that selectively afforded the expected diene in high yield, in contrast to ruthenium catalyst (Scheme II-4).

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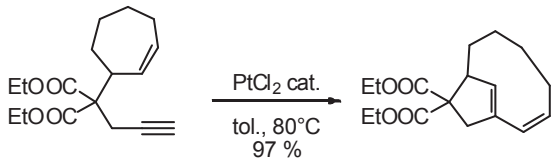
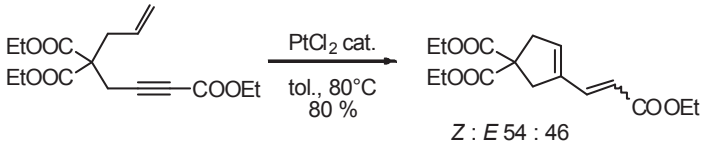
[68] Chatani, N.; Morimoto, T.; Muto, T.; Murai, S. *J. Am. Chem. Soc*. **1994**, *116*, 6049.
[69] Chatani, N.; Furukawa, N.; Sakurai, H.; Murai, S. *Organometallics*, **1996**, *15*, 901.



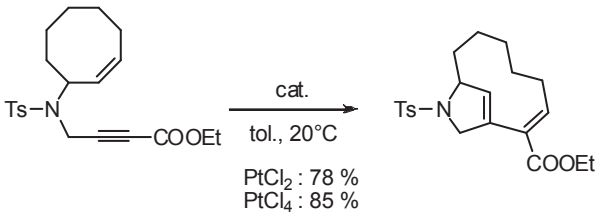
Scheme II-1 : platinum-catalyzed rearrangement

In addition, the authors reported that electron-deficient internal alkynes gave rise to a single product under Pt(II)-catalysis (Scheme II-5). This product of anomalous C-C bond formation was also observed in a deuterium-labelled experiment: the terminal position of the alkene was deuterated and led to a mixture "formal" and "anomalous" metathesis products.



Scheme II-5 : selective preparation of "anormal" metathesis-type product

In 1998, the versatility of platinum salt catalysts was confirmed by Fürstner and co-workers by their utilization for the synthesis of streptorubin B.[70] The "low-tech" $PtCl_2$, $PtCl_4$, $PtBr_4$ systems, as named by Fürstner, allowed the synthetic transformation of electron-deficient enynes into ring-expanded bicyclic products (Scheme II-6). These commercially available catalytic systems were proven to be more efficient than Trost's Pd(II) non commercial catalyst, and interestingly these reactions could directly be performed on a multi-gram scale.



Scheme II-6 : Pt(II)-catalyzed ring expansion

More recently, in 2004, Echavarren and co-workers reported that cationic gold(I) complexes were very reactive catalysts for the cyclization of enynes, particularly through skeletal rearrangements.[71] Gold(I)-catalyzed skeletal rearrangements were carried out at room temperature, in less than one hour and afforded vinylcyclopentenes in high yields (Scheme II-7). Moreover, these

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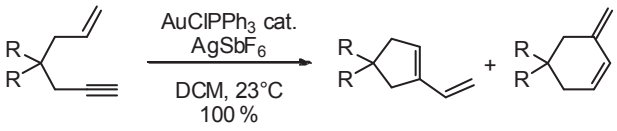
[70] Fürstner, A.; Szillat, H.; Gabor, B.; Mynott, R. *J. Am. Chem. Soc*. **1998**, *120*, 8305.
[71] Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. Angew. *Chem. Int. Ed*. **2004**, *43*, 2402.

reactions were selective towards the "formal" metathesis products. Nevertheless, some precursors underwent an unprecedented observed skeletal rearrangements that yielded to vinylcyclohexadienes.



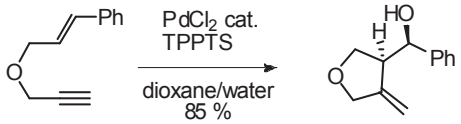
R = SO_2Ph	100 %	1	:	0
R = COOMe	77 %	1	:	7

Scheme II-7 : gold-catalyzed enyne rearrangement

II. 1. 1. b. Reactions of 1,6-enynes carried out in alcoholic media

Other studies brought new elements for the comprehension of the mechanism pathways that occur lead to these transformations. In particular, when the skeletal rearrangements presented above are carried out in alcoholic media, the solvent can play the role of an external nucleophile and can interfere with the reaction course. Such reactivity gives rise to a novel class of products, where carbon-carbon and carbon-oxygen bonds are simultaneously formed in a stereoselective fashion. These transformations are known as **alkoxy- and hydroxycyclizations**.

In 1997, Genêt and co-workers reported the first example of carbohydroxypalladation (so-named by the authors) of 1,6-enyne in aqueous media (scheme II-8).[72] Various propargyl ethers were subjected to a catalytic mixture of $PdCl_2$ and TPPTS in a homogeneous solution of dioxane and water. After few hours, the secondary alcohol was formed as a single diastereomer.

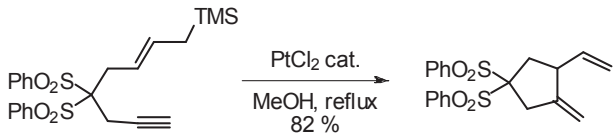


scheme II-8: carbohydroxypalladation

While enynes bearing an allylsilane moiety undergo the classical skeletal rearrangement in toluene under Ru-catalysis,[69] these substrates can give rise to 1,4-dienes if the reaction is carried out in methanol. Several catalytic systems, based on Ru(II), Pd(II), Ag(I) and Pt(II) complexes were efficient to promote this reaction. In that sense, Echavarren and co-workers reported in 2000 the cyclization of several enynes with the use of $PtCl_2$, depicted as the most efficient catalyst (Scheme

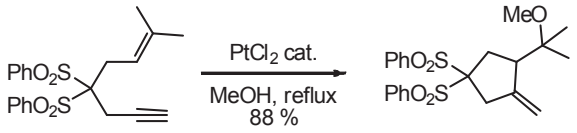
[72] Galland, J.-C.; Savignac, M.; Genêt, J.-P. *Tetrahedron lett*. **1997**, *38*, 8695.

II-9).[73] This reaction selectively affords 1,4-dienes without competition of the "formal" metathesis product.



Scheme II-9 : solvent-induced nucleophilic attack of the silane moiety

If a trimethylsilyl moiety is not a part of the alkene moiety, the same group reported that the electrophilic species generated by the coordination of the metal can be intercepted by the methanol, similarly to the hydroxycyclization already observed by Genêt and co-workers (Scheme II-10).[74]



Scheme II-10 : $PtCl_2$-catalyzed alkoxycyclization

Later, Genêt and co-workers reported an impressive asymmetric version of this reaction. $PtCl_2$-catalyzed cyclization afforded vinylcyclopentenes with a diastereoselective control, in the presence of atropoisomeric phoshine ligands.[75]

II. 1. 1. c. Cyclopropanation reactions

Cyclopentadiene frameworks are the most encountered cycloadducts in 1,6-enyne skeletal rearrangement, but other possibilities of rearrangement exist: just after the reported results of Murai and co-workers mentioning for the first time the reactivity of platinum salts, Blum and co-workers described a novel platinum-catalyzed skeletal rearrangement.[76] Indeed, $PtCl_4$.-catalyzed cycloisomerization of 1,6-propargyl ethers led to the formation of 3-oxabicylo[4.1.0]heptenes (Scheme II-11). Despite the relatively few number of examples and moderate yields of the products, this work was of big interest: concomitant formation of cyclopropanes with cyclization thanks to enynes rearrangements had never been reported before.

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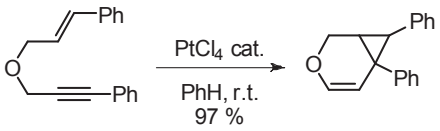
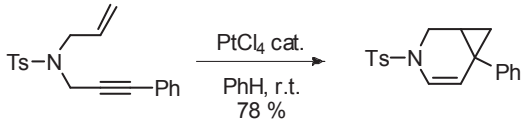
[73] Fernández-Rivas, C.; Méndez, M.; Echavarren, A. M. *J. Am. Chem. Soc*. **2000**, *122*, 1221.
[74] Méndez, M.; Muñoz, M. P.; Echavarren, A. M. *J. Am. Chem. Soc*. **2000**, *122*, 11549.
[75] Charruault, L.; Michelet, V.; Taras, R.; Gladiali, S.; Genêt, J.-P. *Chem. Commun*. **2004**, 850.
[76] Blum, J.; Beer-Kraft, H.; Badriech, Y. *J. Org. Chem*. **1995**, *60*, 5567.



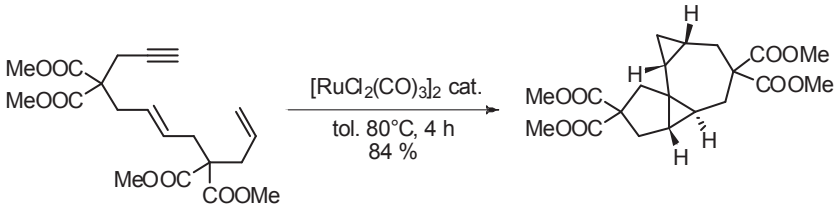
Scheme II-11: cyclopropanation resulting from enyne rearrangement

Later, Fürstner and co-workers discovered that tosylamine-linked 1,6-enynes in some case underwent cyclopropanation in addition to the expected enyne bond metathesis (Scheme II-12). $PtCl_4$-catalyzed cylopropanation proceeded for both internal and terminal alkynes, as well as internal and external substituted alkenes. This reaction demonstrated that subtle factors induce cyclopropanation, as cyclooctenyl-substituted compound exclusively gave rise to the metathesis product (Scheme II-6).



Scheme II-12: $PtCl_2$-catalyzed cyclopropanation of tosylamines

Shortly after Blum's report, Murai and co-workers reported in 1998 the construction of fused tetracycles by Ru(II)-catalyzed cycloisomerization of dodeca-6,11-dienynes (Scheme II-13).[77] This reaction constitutes the first example of bis-cyclopropanation induced by metal-catalyzed enyne rearrangement and is all the more impressive because of the following facts: four carbon-carbon bonds were formed at a time, the reaction was applicable to several dienyne systems without competition of metathesis products, and finally the polycyclic compounds were synthesized in a diastereoselective fashion. This time again, $PtCl_2$ as well as a rhodium catalyst were efficient to catalyse this reaction.

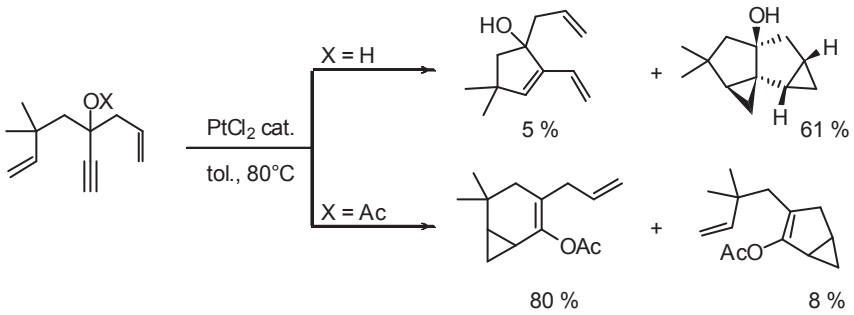


Scheme II-13: reactivity of a dienyne

This reaction of bis-cyclopropanation has also been observed in our laboratory with a dienyne substrate bearing a free alcohol, a silylated ether or an ether at the propargylic position (X

[77] Chatani, N.; Kataoka, K.; Murai, S.; Furukawa, N.; Seki, Y. *J. Am. Chem. Soc*. **1998**, *120*, 9104.

= H, Scheme II-14). [78] It should be noted that the "formal" enyne metathesis product was observed as a minor product. Moreover, this reaction demonstrated the importance of the substitution at the propargylic position. When a *para*-nitrobenzoate or an acetate is present at the propargylic position, the Pt(II)-catalyzed cycloisomerization resulted in the formation of a bicyclo[4.1.0]heptene as the major product of a mixture with a bicyclo[3.1.0]hexane (X = Ac). The main event here is the 1,2-migration of the ester moiety, known as the Ohloff-Rautenstrauch rearrangement, followed by cyclopropanation with one of the two olefins. We will deal with this ester migration later.



Scheme II-11: bis-cyclopropanation of a dienyne

Thereafter, our laboratory extended this reaction to 1,5-enynes. Indeed, we have focused our attention on $PtCl_2$-catalyzed bond rearrangements of 1,5-enynols as well as their ethers and esters derivatives. Such reactions allowed the preparation of bicyclo[3.1.0]hexenes, through a cyclopropanation reaction. These results have been the corpus of several publications,[79] one of them will be presented later.

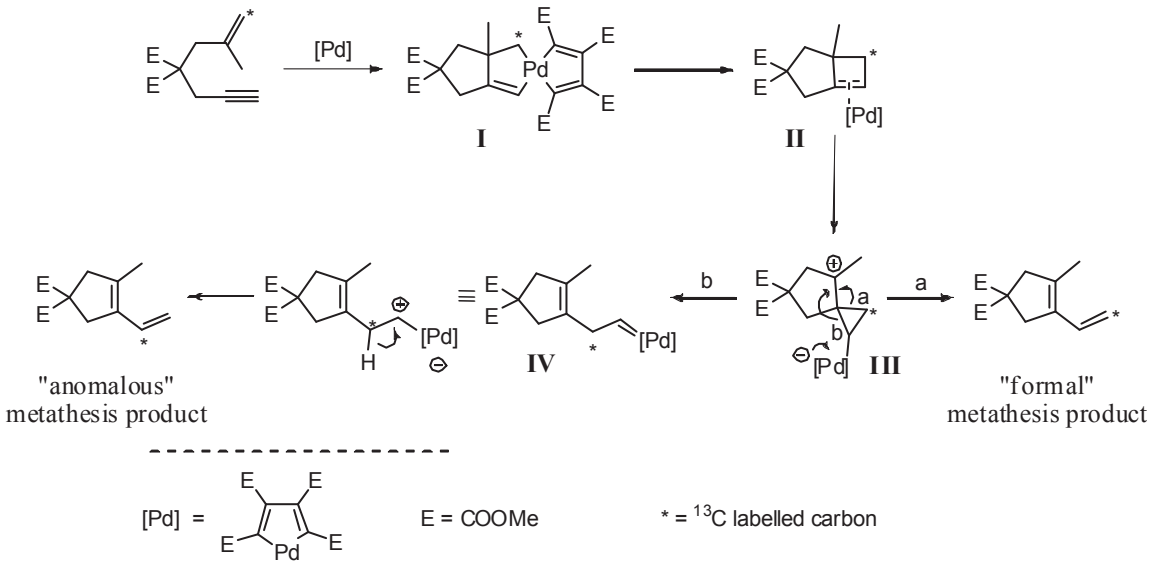
II. 1. 2. Mechanism of 1,6-enynes skeletal rearrangements

II. 1. 2. a. Pd(II)-catalyzed reactions

For Pd(II)-catalyzed bond rearrangement of 1,6-enynes, Trost and co-worker reported that the use of a ^{13}C-labeled substrate brought the evidence of some scrambling in the carbon position (Scheme II-1).[67] The catalyst would coordinate both the alkene and alkyne moiety to form the palladocyclopentene **I**, which would undergo reductive elimination to afford a π-coordinated

[78] Mainetti, E.; Mouriès, V.; Fensterbank, L.; Malacria, M.; Marco-contelles, J. *Angew. Chem. Int. Ed*. **2002**, *41*, 2132.
[79] (a) Harrak, Y.; Blaszykowski, C.; Bernard, M.; Cariou, K.; Mainetti, E.; Mouriès, V.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **2004**, *126*, 8656 (b) Cariou, K.; Mainetti, E.; Fensterbank, L.; Malacria, M. *Tetrahedron* **2004**, *60*, 9745 (c) Blaszykowski, C.; Harrak, Y.; Gonçalves, M.-H.; Cloarec, J.-M.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *Org. Lett*. **2004**, *6*, 3771.

palladium cyclobutene **II**. The latter can evolve into the zwitterionic spirocycle **III**. This species would then lead to the normal metathesis product, through the cleavage of bond **a**, alternatively, the cyclopropane ring opening process can go through the cleavage of bond **b** to form the vinylpalladium **IV**. A following hydride migration and metal elimination would form the rearranged product.



Scheme II-15 : proposed mechanism for palladium enyne bonds rearrangement

II. 1. 2. b. Au(I) and Pt(II)-catalyzed reactions

In case of gold salts, tetracoordinated metallacycles (like **I**, Scheme II-15) are never observed. Contrary to palladium complexes, gold salts are highly alkynophilic, which means the triple bond is selectively η^2-coordinated (**V**, Scheme II-16). Platinum salts, as for them, are evoked to form both type of complexes: Pt(II) can be coordinated to the triple bond like complex **V**, or form a platinocyclopentene like complex **I**. According to DFT calculations of Fensterbank and Gimbert, the tetracoordinated complex is the more stable, but the activation barrier to form **V** is lower.[80] Therefore, the reaction would follow the kinetic pathway through this η^2-coordinated complex.

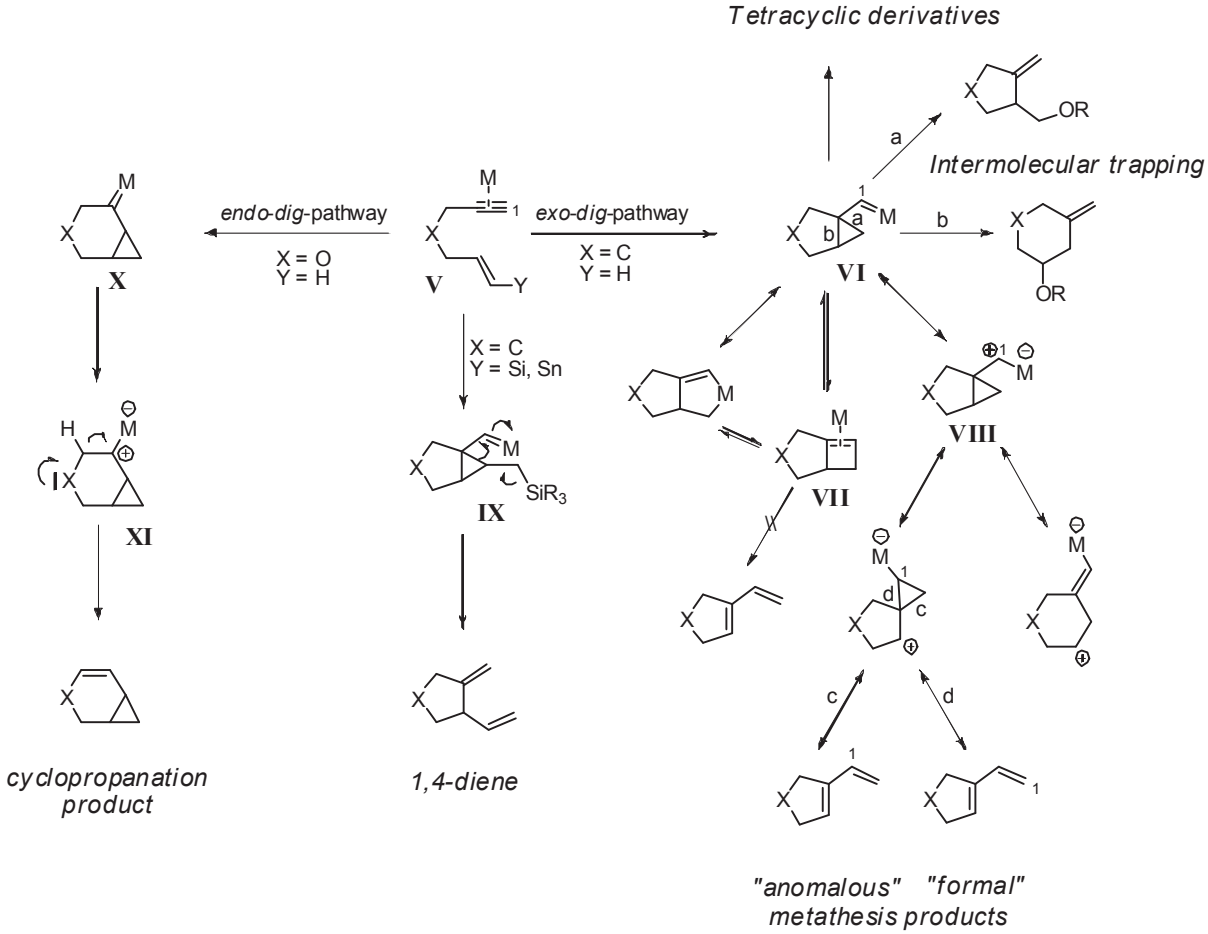
Once the electrophilic activation of the alkyne occurs, a 6-*endo-dig* or a 5-*exo-dig* nucleophilic attack can be envisaged. DFT calculations supports a kinetically favored 5-*exo-dig*

[80] Baumgarten, S. B.; Lesage, D.; Gandon, V.; Goddard; J.-P.; Malacria, M.; Tabet, J.-C.; Gimbert, Y.; Fensterbank, L. *ChemCatChem* **2009**, *1*, 138.

attack when X = CH_2.[81] Moreover, these calculations support the direct formation in a single step of the bicyclic carbenic species **VI**. This carbene can evolve through a second cyclopropanation to afford frameworks tetracycles derivatives, or can undergo nucleophilic attack of an alcohol to yield exomethylene cyclopentane or cyclohexane frameworks. This cyclopropylcarbene **VI** can also evolve to form the strained π-coordinated cyclobutene species **VII**. However, the ring-opening of the latter for the formation of the metathesis product, is not supported by DFT calculations. In contrast, the zwitterionic species **VIII** which is in equilibrium with the metallated spirocycle, is proposed to account for the formation of the metathesis products. Similarly, silylated and stannylated substrates, that lead to cyclopropylcarbene **IX** can be reopened to form 1,4-dienes. When X = O, the 6-*endo-dig* route becomes the kinetic pathway to form carbene **X**. The resulting zwitterionic bicyclic species **XI** can then undergo a 1,2-hydride shift that generates the endocyclic double bond.

It should be noted that despite the variety of cycloadducts encountered in 1,6-enynes skeletal rearrangements, the single metallacarbene cyclopropyl **I** would trigger the formation of most cycloadducts. Thus, some efforts were made to trap this species with external nucleophiles.

[81] (a) Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Chem Eur Joc*, **2003**, *9*, 2627 (b) Soriano, E.; Ballesteros, P.; Marco-Contelles, J. *Organometallics*, **2005**, *24*, 3172 (c) Soriano, E.; Ballesteros, P.; Marco-Contelles, J. *Organometallics*, **2005**, *24*, 3182.

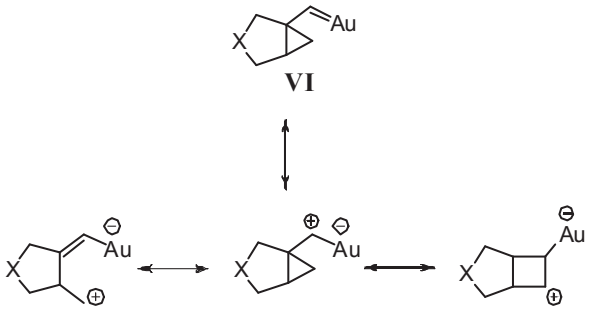


Scheme II-16: proposed mechanism for platinum and gold enyne bonds rearrangement

II. 1. 2. c. Experimental evidences of postulated intermediates

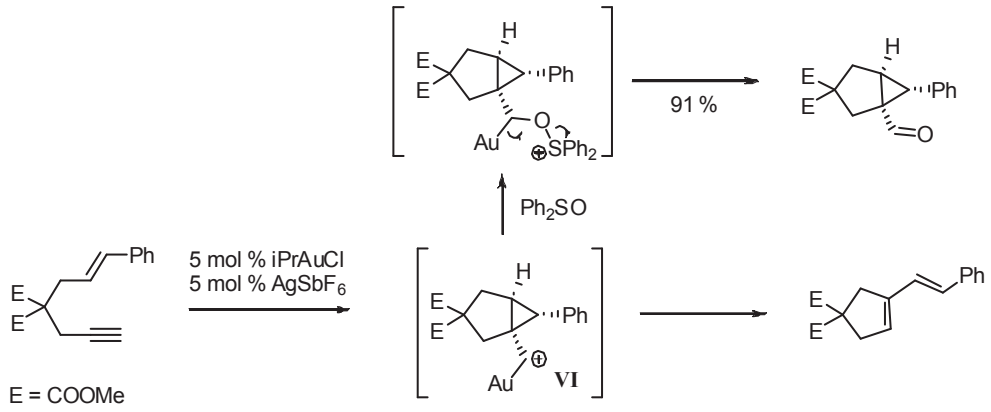
These past few years, introduction of intermolecular events gave a boost to the chemistry of skeletal rearrangements by both expanding the range of the cycloadducts that can be formed and by bringing mechanistic evidence for the suggested cyclopropylcarbene intermediates. On the other hand, Fürstner and co-worker recently proposed that gold intermediates would be more appropriately described as gold-stabilized carbocations than "gold carbene", and that these cationic species would better explain the reactivity of skeletal rearrangements than the gold cyclopropylcarbene **VI**.[82] The cationic rendition, as named by the authors can be described by the following mesomeric structures (Scheme II-17).

[82] Fürstner, A.; Morency, L. *Angew. Chem. Int. Ed*. **2008**, *47*, 5030.



Scheme II-17: carbocation-like intermediates

Recently, Toste and co-workers used dialkylsulfoxides as nucleophiles in order to bring evidence of gold intermediates of 1,6 enyne skeletal rearrangements (Scheme II-18).[83] The intermediate **VI** would have a carbocationic nature and would undergo the nucleophilic attack of these reagents. Consequently, instead of the expected metathesis-type product, the reaction gave rise to a [3.1.0]-bicyclohexene with an aldehyde entity.

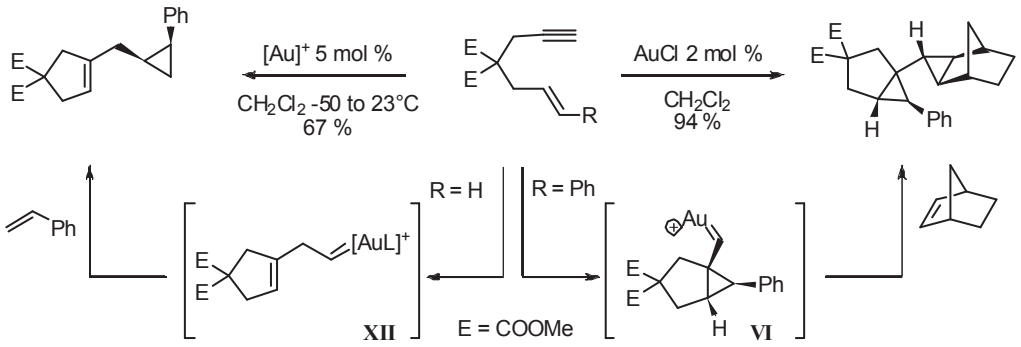


Scheme II-18: oxidation of a carbenic species

In contrast, Echavarren and co-workers recently reported the intermolecular trapping of gold carbenes with various external olefin (R = Ph, Scheme II-19).[84] This experiment, as well as the formation of the tetracycles presented before,[77,78] is rather in favour of a gold cyclopropylcarbene than a carbocationic intermediate. Besides, the intermediate **XII** proposed to account for the formation of the anomalous metathesis product, which was proven by DFT calculations to result from rearrangement of gold cyclopropylcarbene **VI** was also trapped..[85] Evidence about such

[83] Witham, C. A.; Mauleón, P.; Shapiro, N. D.; Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 5839.
[84] López, S.; Herrero-Gómez, E.; Pérez-Galán, P.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 6029.
[85] Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Cárdenas, D.J.; Buñuel, E.; Nevado, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6146.

species were highlighted in the same way, by the intermolecular interception with external olefins (R = H, Scheme II-19).



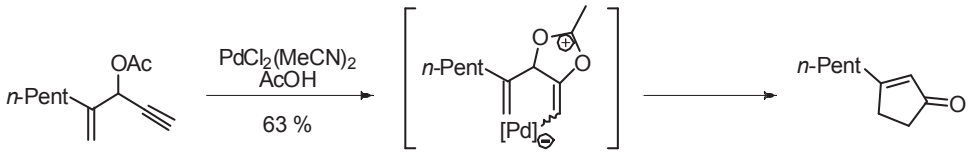
Scheme II-19: interception of a carbenic species

In our study, attempts for the trapping of similar intermediate that occurs with 1,5 enyne skeletal rearrangements were carried out and will be presented in the unpublished results part.

II. 1. 3. Mechanism of 1,5-enynes cyclopropanation

II. 1. 3. a. Ohloff-Rautenstrauch rearrangement

In case of metal-catalyzed cycloisomerizations of 1,5-enynes, the substitution at the propargylic position was demonstrated to influence the course of the reaction (Scheme II-14). Ohloff and Rautenstrauch have studied the reactivity propargylic esters in the presence of Zn(II) and Pd(II) complex respectively (Scheme II-20).[86] They demonstrated that the electrophilic activation of triple bond involves the 1,2-shift of the ester moiety. Thus, the preparation of cyclopentenones can be achieved by the cycloisomerization of 1,4-enyne acetates.[87] In this reaction, the ketone moiety results from the hydrolysis of the acetate functionality.



Scheme II-20: Ohloff-Rautenstrauch rearrangement

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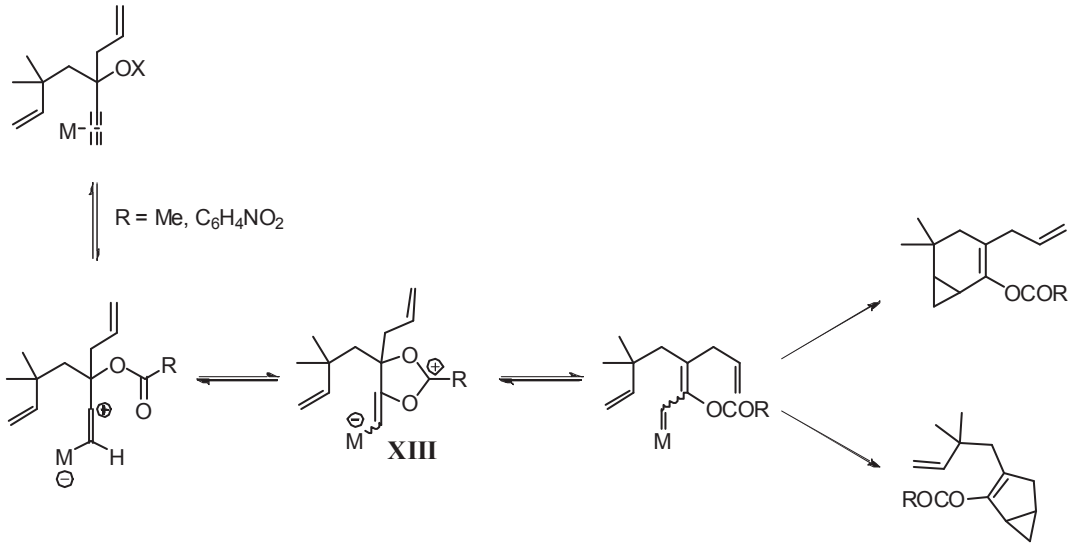
[86] (a) Stricker, H.; Davis, J. B.; Ohloff, G. *Helv. Chim. Acta.* **1976**, *59*, 1328 (b) Rautenstrauch, V. *J. Org. Chem* **1984**, *49*, 950.
[87] See also Shi, X.; Gorin, D. J.; Toste, F. D. *J. Am. Chem. Soc*. **2005**, *127*, 5802.

This methodology was applied to prepare bicyclo[4.1.0]heptenes (Scheme II-21). When an acetate or a *p*-nitrobenzoate is present at the propargylic position, a mixture of bicyclic structures **C** and **D** that exhibit a 1,2-ester shift of the ester group, is observed. The dienyne that undergo a π-Electrophilic activation of the alkyne, can be in equilibrium with the zwitterionic species **II**. A carbene species would then be generated after the complete migration of the ester, and afford preferentially the 6-membered ring cycloadduct.



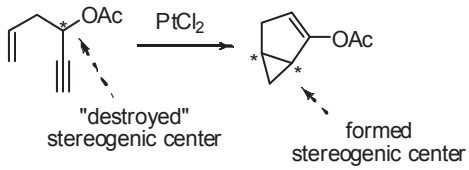
Scheme II-21: mechanism of dienyne bonds rearrangement

II. 1. 3. b. Chirality transfert study for the cyclization of 1,5-enynes esters

The reactivity of 1,5-enyne esters, as precursors for bicyclo[3.1.0]hexanes was applied to the preparation of a natural sesquiterpene, the (-)-cubebol.[88] Independantly, Fürstner and Fehr reported the total synthesis of this molecule, in addition to the study of the conservation (or not) of the enantiomeric excess in the metal-catalyzed cyclopropanation process (Scheme II-22). If a reaction involves the shifting of the chirality from one stereogenic center that is destroyed to another one that is formed, the reaction is said to occur with **chirality transfer**. Interstingly, it has been demonstrated that Rautenstrauch rearrangement can occur with chirality transfer. Indeed, Toste and co-workers reported the gold(I)-catalyzed synthesis of enantioenriched cyclopentenones from enantioenriched propargyl alcohols with high degree of chirality transfer.[87] Moreover, based on

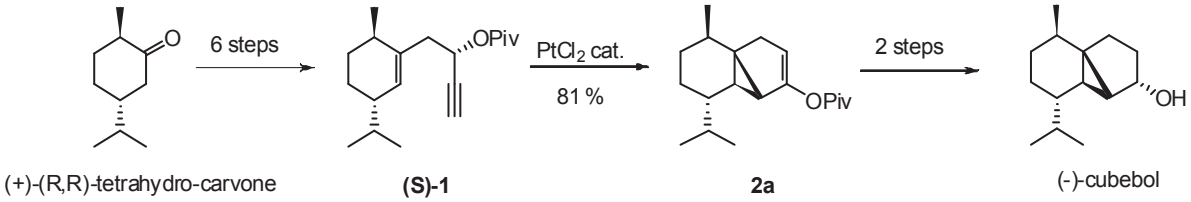
[88] (a) Fürstner, A.; Hannen, P. *Chem. Eur. J.* **2006**, *12*, 3006 (b) Fehr, C.; Galindo, J. *Angew. Chem*. **2006**, *118*, 2967.

DFT calculations, Lera and co-workers suggests that the Rautenstrauch rearrangement would go through a pentadienyl cation with the imprint of the chiral information.[89]



Scheme II-22: chirality transfer for 1,5-enyne acetates cycloisomerization

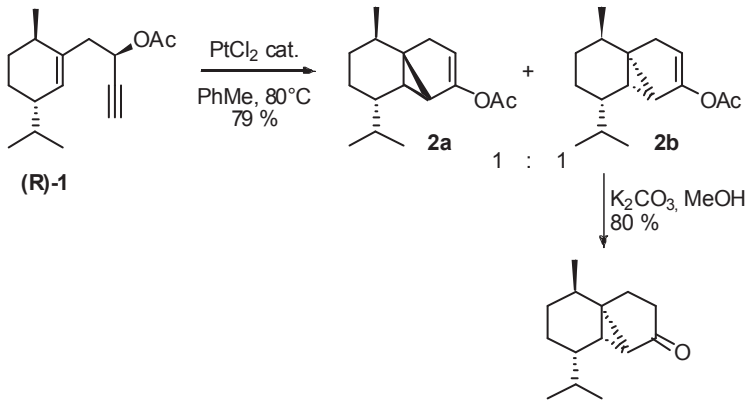
Starting from the (+)-(*R*,*R*)-tetrahydrocarvone, Fehr and co-worker prepared in a diastereoselective manner in six steps, the propargylic pivalate **(*S*)-1** (Scheme II-23). The key step of the total synthesis of (-)-cubebol is the cyclopropanation reaction which occurs in the presence of Pt(II), Cu(I) and Ag(I) in chlorinated solvents. $PtCl_2$-catalyzed cyclopropanation afforded **2a** in 81 % yield as the major diastereomer. For the same reaction performed in toluene, Fürstner obtained the tricyclic molecule in 92 %. Fehr described the synthesis (-)-cubebol in two more steps from tricycle **2a**.



Scheme II-23: total synthesis of (-)-cubebol

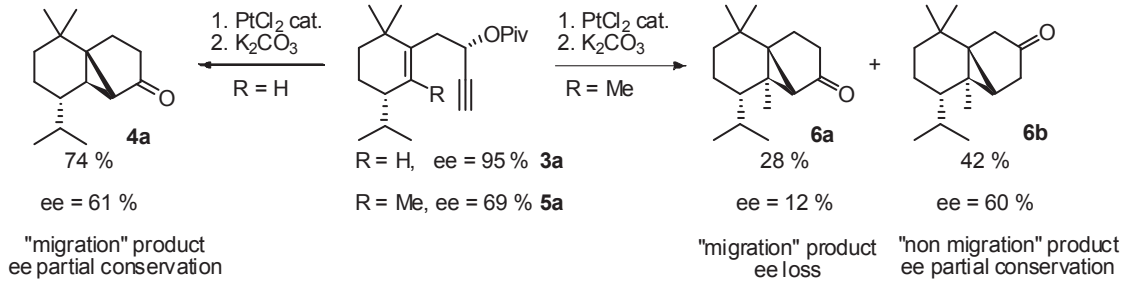
While the propargylic acetate **(*S*)-1** affords a single diastereomer in the presence of $PtCl_2$, Fürstner reported that the propargylic acetate **(*R*)-1** led to a 1 : 1 ratio of diastereomers in 79 % yield (Scheme II-24).

[89] Nieto Faza, O.; Silva Lopez, C.; Alvarez, R.; Lera, A. R. *J. Am. Chem. Soc*. **2006**, *128*, 2434.



Scheme II-24 : reactivity of (R)-propargylic acetate

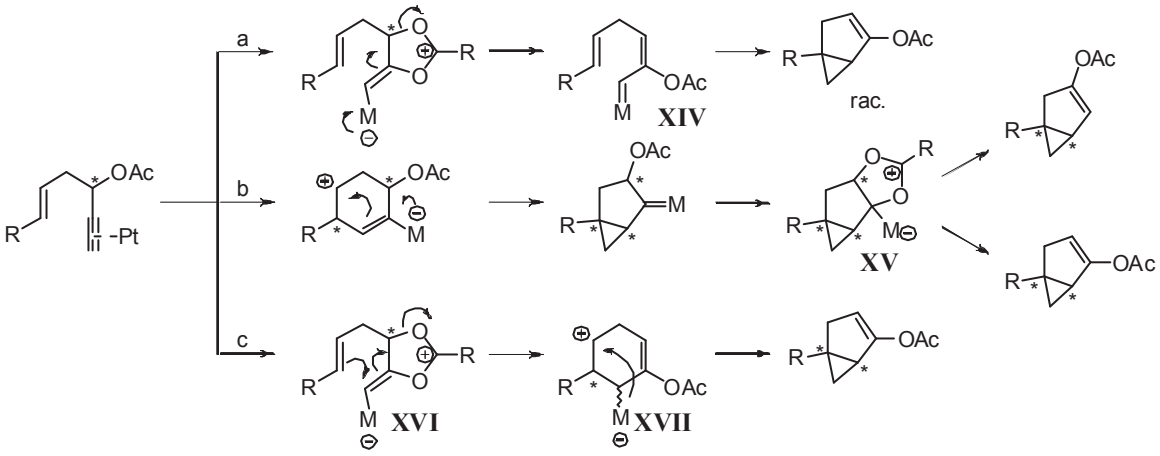
Further study revealed interesting cycloadducts. For a substrate with a *totally* substituted alkene, Fehr observed a surprising behaviour in the cyclization: the expected product **6a** was obtained in a mixture with the "non-migration" product **6b** (Scheme II-25). While propargylic ester **3a** affords the "migration product" **1a** with a partial conservation of the enantiomeric excess, it is noteworthy that the enantiomeric excess was not conserved from **5a** to the "migration product" **6a** in contrast to the "non migration product" **6a** (that is to say that a hydride shift occurs instead of the expected OAc migration). The enantiomeric excesses were determined after hydrolysis of the enol ester.



Scheme II-25 : chirality transfer for $PtCl_2$-catalyzed cyclopropanation

According to these findings, it was possible to advance new mechanistic hypotheses for the metal-catalyzed cyclopropanation of 1,5-enyne esters (Scheme II-26). Along **pathway a**, the chirality transfer from propargylic carbon to the cyclopropane cannot be justified by the achiral plannarized vinyl carbene **XIV**. This mechanistic route would then afford racemic mixture of bicyclic compounds. Therefore, Fürstner preferentially assumed an initial cyclopropanation (before the 1,2-acyloxy shift) that would be dependent of the absolute configuration of the precursor's propargylic center, to form an enantiomeric-enriched cyclopropyl metallacarbene (**pathway b**). Such mechanistic pathway would go through zwitterionic species **XV** that would afford both the "non migration" product and the "migration" product. Consequently, these compounds should be

observed with the same enantiomeric excess, which is not coherent with the experimental data of Fehr. For the above reasons, Fehr proposed another mechanistic route (**pathway c**). Basically, he suggests that the cyclopropanation would occur on a "half-rearranged" species **XVI**: after the intramolecular addition of the ester carbonyl to the metal-complexed acetylene to afford **XVI** with imprint chiral information, the nucleophilic attack of the double bond would lead to enriched-cyclohexene **XVII.** A following cyclopropanation would afford the bicyclic compound.



Scheme II-26: mechanistic pathways to account for chirality transfer

Thanks to diversely substituted 1,5-enynes and their resulting cyclized molecules, it was possible to advance mechanistic hypotheses for these synthetic transformations. However, predicting certain cycloadducts was not so instinctive. Thus, despite the hard task it is, evidences to account for a general mechanistic pathway are necessary. For this purpose, this work also deals with trapping experiments and chirality transfer study that will be detailed right after the presentation of the scope and limitation of the preparation of the bicyclo[3.1.0]hexane structures.

II. 2. Published results

Published in *Synthesis* **2007**, *13*, 2037

II. 2. 1. Abstract

1,5-enynes are highly reactive under $PtCl_2$ catalysis to give various bicyclo [3.1.0] skeletons. Scope and limitations of the process are presented. Regioisomeric keto derivatives can be obtained depending upon the nature of the oxygenated substituent at the propargylic position of the starting substrate.

Key words: enynes, platinum, bicyclic compounds, carbenes, cycloisomerizations

II. 2. 2. Introduction

Since the seminal report by Trost and Lautens in 1985,[90] enyne substrates particularly 1,6-enynes, have become some of the most studied substrates in the field of transition metal catalysis, especially regarding cycloisomerization reactions.[91] An interesting variant has emerged with the use of highly electrophilic metal species,[92] notably $PtCl_2$[93] and, more recently gold(I) or (III) salts,[94] which have given birth to a myriad of new reactions including skeletal rearrangements.[95] Because of distinct mechanisms that do not generally rely on a metallacyclopentene species, other enyne types are worth investigating since they should bring structural diversity a new mechanistic insights. In fact, these processes generally transit via charged intermediates so that heteroatomic functions can

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[90] Trost, B. M.; Lautens, M. *J. Am. Chem. Soc.* **1985**, *107*, 1781.

[91] (a) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813-834. (b) Malacria, M.; Goddard, J. P.; Fensterbank, L. in *Comprehensive Organometallic Chemistry III*, 2006, Crabtree, R.; Mingos, M. Edts, vol 10.07, Ojima, I. Ed. pp. 299-368.

[92] For a pioneering report, with Pd(II): (a) see ref 67. See also: (b) Trost, B. M.; Hashmi, A. S. K. *Angew. Chem. Int. Ed.* **1993**, *32*, 1085.

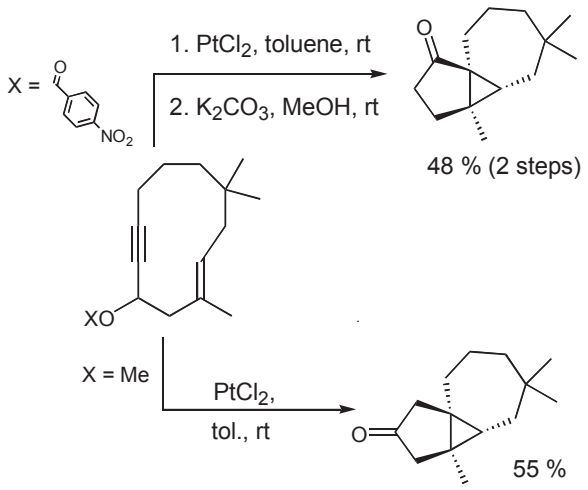
[93] For a pioneering report, with $PtCl_2$: see, ref 68. (b) See also: Fürstner, A.; Stelzer, F.; Szillat, H. *J. Am. Chem. Soc.* **2001**, *123*, 11863 (c) Méndez, M.; Muñoz, M. P.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2001**, *123*, 10511. (d) Méndez, M.; Mamane, V.; Fürstner, A. *Chemtracts-Organic Chemistry* **2003**, *16*, 397 (e) Fensterbank, L. "$PtCl_2$" in *e-Eros*. (f) First report of asymmetric synthesis: ref 75.

[94] For reviews: ref 66.

[95] (a) Oi, S.; Tsukamoto, I.; Miyano, S.; Inoue, Y. *Organometallics* **2001**, *20*, 3704. (b) For a review: Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317. (c) Theoretical treatment : see ref 85

also participate.[96] For instance, we[97] and others[98,99,100] have shown that an acetate group at a propargylic position upon electrophilic activation by $PtCl_2$ can undergo a 1,2-migration with concomitant cyclopropanation. This transformation, also known as Rautenstrauch rearrangement,[98b] has lent itself to higher sophistication with applications in natural products synthesis[101] as well as the formation of medium-sized rings.[97a] A further incentive in this investigation has stemmed from a desire to better understand our findings on the more elaborated transannular systems.[102] As shown in Scheme 1, different regiosiomeric keto-tricyclic derivatives are obtained depending upon the nature of the functional group at the propargylic position.

The *O*-acyl precursor generates the expected migration adduct, isolated as a ketone after saponification, whereas the O-methylated substrate gave a hydrogen migration product.



Scheme II-27

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[96] An illustration of this is the use of ynamides: (a) Marion, F.; Coulomb, J.; Courillon, C.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2004**, *6*, 1509. (b) Gold catalysis, see: Couty, S.; Meyer, C.; Cossy, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 6726.

[97] (a) see ref 78 (b) see ref 79a, 79b (d) Marco-Contelles, J.; Arroyo, N.; Anjum, S.; Mainetti, E.; Marion, N.; Cariou, K.; Lemière, G.; Mouriès, V.; Fensterbank, L.; Malacria, M. *Eur. J. Org. Chem.* **2006**, 4618. (e) Cariou, K.; Ronan, B.; Mignani, S.; Fensterbank, L.; Malacria, M. *Angew. Chem. Int. Ed.* **2007**, *46*, 1881.

[98] For earlier reports: (a) see ref 86.

[99] For platinum-catalyzed 1,2-migration (a) Mamane, V.; Gress, T.; Krause, H.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654. (b) Anjum, S.; Marco-Contelles, J. *Tetrahedron* **2005**, *61*, 4793. (c) Pujanauski, B. G.; Prasad, B. A. B.; Sarpong, R. *J. Am. Chem. Soc.* **2006**, *128*, 6786. (d) For a review: Marco-Contelles, J.; Soriano, E. *Chem. Eur. J.* **2007**, *13*, 1350.

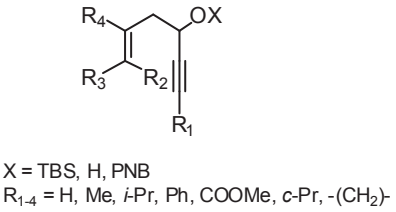
[100] For gold-catalyzed 1,2-migration: (a) For a review: Marion, N.; Nolan, S. P. *Angew. Chem. Int. Ed.* **2007**, *46*, early view. See also: (b) Marion, N.; de Frémont, P.; Lemière, G.; Stevens, E. D.; Fensterbank, L.; Malacria, M.; Nolan, S. P. *Chem. Commun.* **2006**, 2048. Asymmetric transformations: (c) see ref 87. (d) Johansson, M. J.; Gorin, D. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 18002. (e) Ru catalysis: K. Miki, K. Ohe, S. Uemura, *J. Org. Chem.* **2003**, *68*, 8505. (f) Tenaglia, A.; Marc, S. *J. Org. Chem.* **2006**, *71*, 3569.

[101] (a) Fürstner, A.; Hannen, P. *Chem. Commun.* **2004**, 2546. (b) See also ref. 88(a), 88(b), 99(b).

[102] see ref 79c.

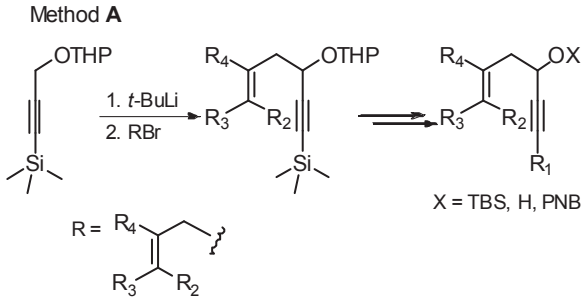
II. 2. 3. Results and discussion

Thus, in this study, we have focused on simple 1,5-enynes[97c,103] **I** bearing an oxygenated function at the 3-propargylic position, and we have prepared a broad variety of precursors diversely substituted not only at the unsaturated positions, but also at the oxygenated function (Scheme II-28).



Scheme II-28

The synthesis of these different precursors has been accomplished following two main routes. The first method (method **A**) involves as a key-step the alkylation of brominated allylic derivatives (RBr), by the suitably O-protected lithiated anion of the propargylic alcohol.[104] Classical functionalization steps then allowed access to the desired precursors (Scheme II-29).



Scheme II-29

The second method (method **B**) involved, as the key-step, a [2,3]-Wittig rearrangement of allylic and propargylic ethers,[105] prepared from the C-trimethylsilylated propargylic alcohol (Scheme II-30). Subsequent *O*-silylation or acylation furnished the desired precursors. These two methods together provided a simple and efficient access to a broad variety of substituted precursors.

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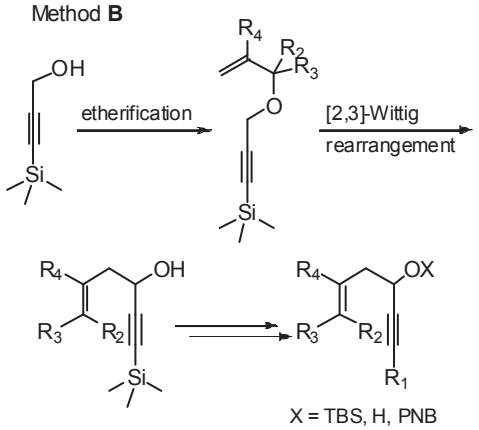
[103] See refs.: 99(a), 101(b) and 101(c). For gold-catalyzed studies on 1,5-enynes subtrates, see for intance: (d) Sun, J.; Conley, M. P.; Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2006**, *128*, 9705. (e) Luzung, M. R.; Markham, J. P.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 10858. (f) Gagosz, F. *Org. Lett.* **2005**, *7*, 4129. Copper catalysis: (g) Fehr, C.; Farris, I.; Sommer, H. *Org. Lett.* **2006**, *8*, 1839.

[104] Parsons, P. J.; Willis, P. J.; Eyley, S. C. *Tetrahedron* **1992**, *48*, 9461.

[105] (a) Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, *86*, 885. (b) Journet, M.; Malacria, M. *J. Org. Chem.* **1992**, *57*, 3085.

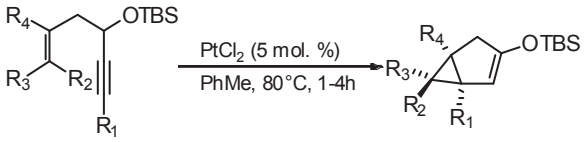


Scheme II-30

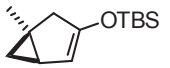
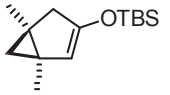
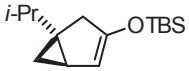
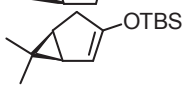
Cycloisomerization reactions were first conducted with OTBS-precursors **1a-c**. Because of a putative highly strained intermediate (incorporating a cyclobutane moiety), we anticipated that the competitive metathesis-type pathway should be disfavored, and by analogy with our findings in the transannular series,[102] only a hydride migration process would be possible.

Indeed, when OTBS-precursors **1a-d** were submitted to 5 mol. % $PtCl_2$ in PhMe at 80°C, [3.1.0]-bicyclic enol ethers **2a-d** were obtained in high yields (Table II-1).

Table II-1



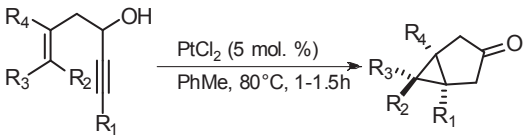
1a-c **2a-c**

Entry	Precursor	R_{1-4}	Product		yield
1	**1a**	R_1=R_2=R_3=H R_4=Me		**2a**	68%
2	**1b**	R_1= R_4=Me R_2=R_3=H		**2b**	84%
3	**1c**	R_1=R_2=R_3=H R_4=*i*-Pr		**2c**	83%
4	**1d**	R_1=R_4=H R_2=R_3=Me		**2d**	82%

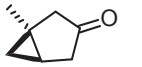
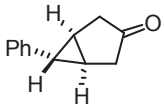
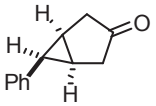
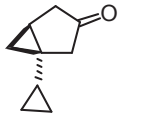
We then studied the cycloisomerization of alcohols **3a-e** and found that, upon exposure to the same reaction conditions as described for **1a-d** above, bicycle[3.1.0]hexanones **1a-e** were obtained in excellent yields and complete diastereoselectivity (Table II-2). The free alcohol

corresponding to precursor **1d** was also converted to the corresponding ketone **7f** which was only isolated in 28 % yield because of its volatility.

Table II-2

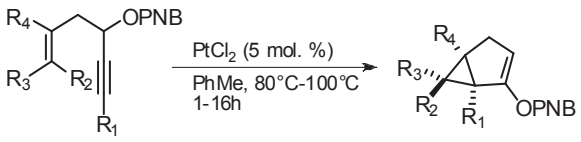


3a-e **4a-e**

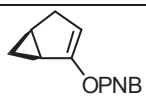
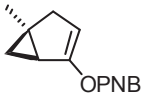
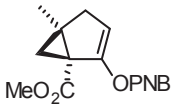
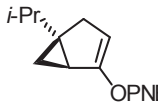
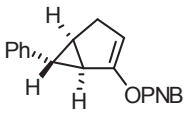
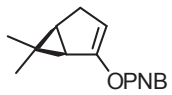
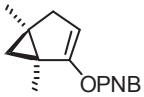
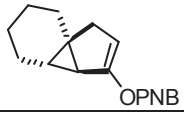
Entry	Precursor	R_{1-4}	Product		yield
1	**3a**	R_1=R_2=R_3=H R_4=Me		**1a**	50%
2	**3b**	R_1=R_2=R_4=H R_3=Ph		**1b**	96%
3	**3c**	R_1=R_3=R_4=H R_2=Ph		**1c**	83%
4	**3d**	R_2=R_3=R_4=H R_1=*c*-Pr		**1d**	88%
5	**3e**	R_1=R_2=H R_{3-4}=-$(CH_2)_2$-		**1e**	90%

Several important facts have to be highlighted. First, silyl ethers **1a-c** and free alcohols **3a-e** exhibit the same reactivity towards $PtCl_2$ and both allow the formation [3.1.0]-bicyclic compounds in high yields. In the case of silyl ethers, the products were isolated as silyl enol ethers (**2a-d**) while free alcohols led to the corresponding ketones (**1a-e**). It is also particularly worth noting that a broad variety of groups can be placed anywhere on the alkene moiety and that even particularly hindered unsaturations compounds (trisubstituted olefin **3e**) are able to efficiently undergo the reaction. Moreover, the stability of the cyclopropyl moiety (located on the triple bond) in the **3d→4d** transformation is particularly remarkable, as are the complete diastereoselectivities observed for **4b** and **4c** (according to the crude ^{1}H NMR spectra). The relative stereochemistries for **1b** and **1c** could be unambiguously assigned using NOe experiments. Interestingly, a TMS-substituted analog of **3c** proved to be poorly reactive and gave after prolonged heating only degradation product (see also Lemiere et al.[96c]). We further turned our attention towards the reactivity of *O*-PNB precursors **5a-h** (Table II-3).

Table II-3



5a-h **6a-h**

Entry	Precursor	R_{1-4}	Product		yield
1	**5a**	R_1=R_2=R_3=R_4=H		**6a**	85%
2	**5b**	R_1=R_2=R_3= H R_4=Me		**6b**	80%
3	**5c**	R_1=CO_2Me R_2=R_3=H R_4=Me		**6c**	50%[a]
4	**5d**	R_1=R_2=R_3=H R_1=*i*-Pr		**6d**	83%
5	**5e**	R_1=R_2=R_4=H R_3=Ph		**6e**	86%
6	**5f**	R_1=R_4=H R_2=R_3=Me		**6f**	39%[a]
7	**5g**	R_1=R_4=Me R_2=R_3=H		**6g**	10%[a]
8	**5h**	R_1=R_2=H R_{3-4}=-$(CH_2)_2$-		**6h**	85%

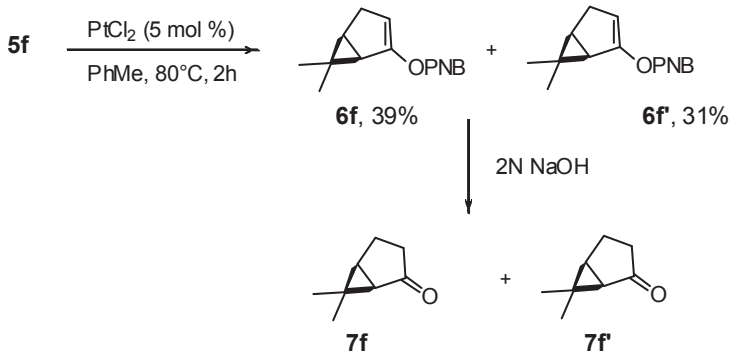
[a] others products were also isolated.

These substrates effectively underwent the cycloisomerization to give [3.1.0]-bicyclic structures, as described for the silyl ethers (**1a-c**) and the free alcohols (**3a-e**). However, in this case, the alkoxy moiety (*i.e.* OPNB) was located on the neighboring sp^2 carbon and thus, must have undergone a 1,2-migration during the cycloisomerization. This result is in perfect agreement with previous observations reported in the literature.[97,99,100] Yields were generally very good except in for few particular cases (entries 3, 6 and 7), see below. Interestingly, the transformation **5b→6b** could be realized with a lower catalyst loading (5% to 2%) without altering the yield, required reaction time, however, increased from 3h to 6h. It is also interesting to note that the benzyl carbonate analog of **5b** has been shown to give a good yield (79%) of migration product (see ref. 8c). These

reactions were also found to be totally diastereoselective (entry 5, **6e**). It is significant that the cycloisomerization of hindered unsaturated substrates, such as trisubstituted olefin **5h** was efficient.

An interesting exception, however, is the reaction of substrates possessing a substituent at the R_2 position. For instance, the reaction of the *Z* isomer of **5e** was very sluggish, giving a mixture of cycloisomerization products in poor yield (< 30%).[106]

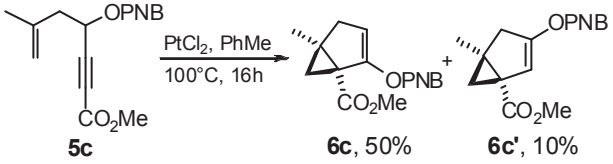
Similarly, the prenyl precursor **5f** (Scheme II-31) led to close competition between migration and non-migration of the *O*-PNB group during catalysis.



Scheme II-31

The isolation of ketones **7f** and **7f'**, after basic hydrolysis of a mixture of compounds **6f** and **6f'**, allowed us to confirm the regioisomeric relationship existing between those two cycloisomerization products (Scheme 5). Such competition between migration and non-migration of the *O*-acyl group has already been observed by Fehr[101c] on a substrate bearing a methyl group was at the R_2 position.

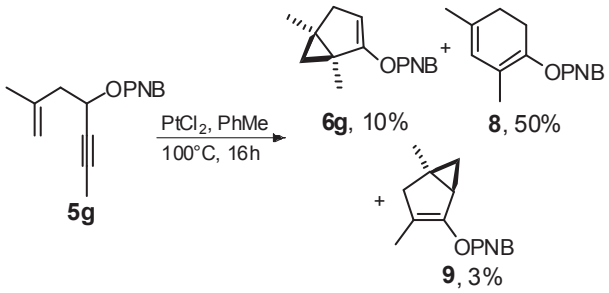
The introduction of a substituant at the triple bond, resulted in reaction manifolds. In the case of the substitution with an ester moiety (**5c**), it was possible to isolate, along with the expected compound **6c** resulting from the 1,2-migration of the *O*-PNB group, the regioisomer **6c'** in 10% yield (Scheme II-32).



Scheme II-32

[106] This is reminiscent of a result by Toste with a Z-precursor, see ref. 100(c).

In the case of the substitution of the triple bond with a methyl group, the major isolated product was not the expected one **6g**, resulting from the 1,2-migration of the *O*-PNB group, but cyclohexa-1,3-diene derivative **8**. Regioisomer **9** could also be isolated but only in a trace amounts (Scheme II-33).



Scheme II-33

The mechanism of the cycloisomerization of 1,5-enynes **I**, especially propargyl esters substrates is still a matter of debate.[107,101b,101c] Presumably, the preliminary electrophilic complexation of the alkyne triggers an attack of a pendant nucleophile. If the nucleophile is the alkene moiety, a direct 5-*endo-dig* cyclization would provide a carbene intermediate (**10**) that can undergo a 1,2-hydride shift when X = H or Me to give products **2a-d** and **1a-e** (Scheme II-34). Alternatively, for X = *O*-acyl, a 1,2-migration of the ester group would take place to give regioisomeric products **6a-h**, as proposed by Fürstner and Soriano. Another mechanistic pathway has been proposed by Fehr and consists in a nucleophilic attack of the *O*-acyl moiety followed by a cyclization of the alkene moiety on the vinylmetal species of **13** to generate **11**. Subsequent cyclopropanation leads to products **6a-h**.

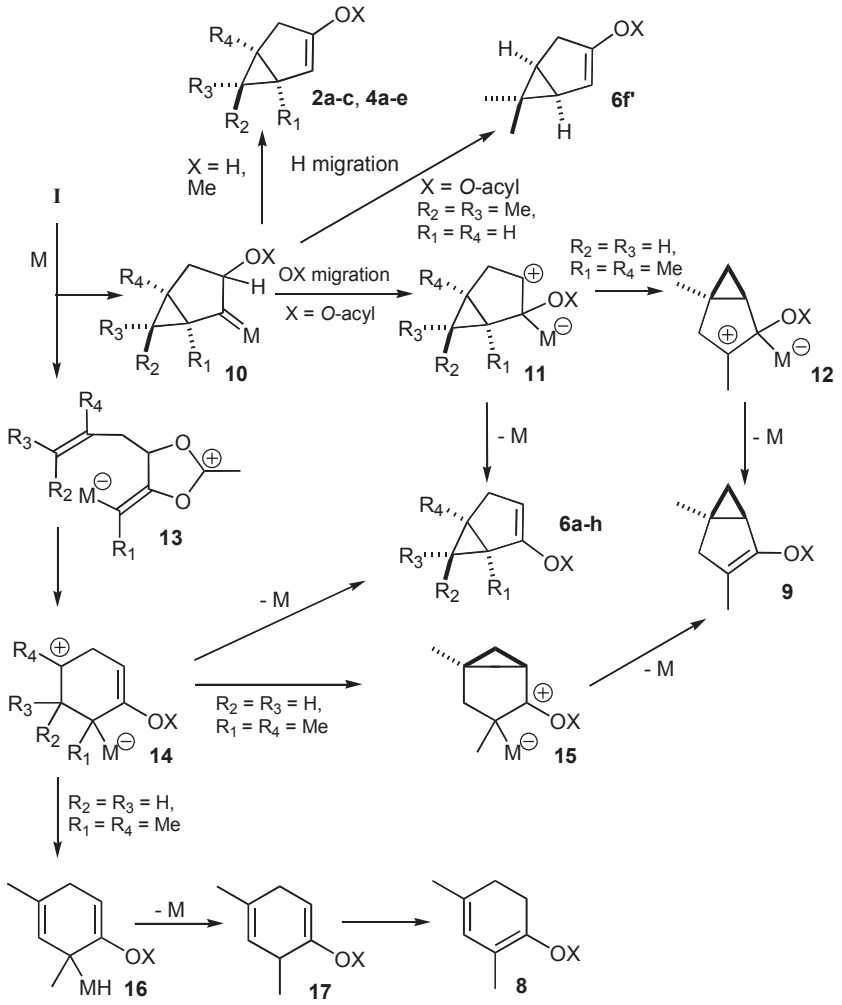
The proposal of these two pathways is based on the observation that a chirality transfer occurs during the cycloisomerization process. However, the fact that these chirality transfers are not complete suggests that the cycloproponation steps are not completely diastereoselective. Possibly, competitive mechanisms occur, such as the intervention of the previously proposed opened carbene intermediate which annihilates the influence of stereogenic center at the propargylic stereogenic center. Previous theoretical studies on 1,6-enynes have shown that very similar activation energy barriers exist between a direct *6-endo-dig* pathway and the open carbene pathway. [99e]

The question arise, how can the formation of unexpected products be rationalized? Regioisomeric products of type **9** have already been reported with gold catalysis on dienyne

[107] Soriano, E.; Marco-Contelles, J. *J. Org. Chem.* **2007**, *72*, 2651.

substrates, and, in this case, a carbocationic pathway has been proposed. Product **9** could originate from a rearrangement of **11** into **12**, followed by metal elimination.

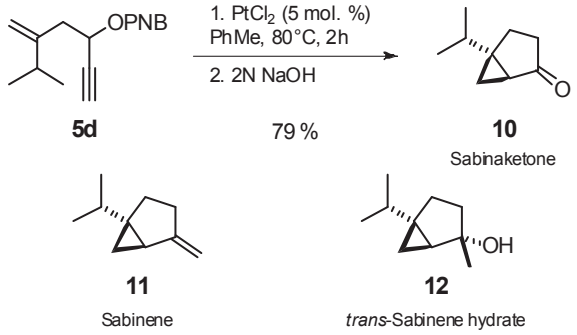
Fehr's pathway can also lead to **9** via **15**. Moreover, intermediate **11** could also evolve to **16** which, after reductive elimination and isomerization, would lead to the conjugate cyclohexadiene **8**. Other mechanistic pathways, including a platinum(II)-catalyzed opening of the cyclopropyl ring of **6g**,[108] are possible and we are now studying this reaction from a theoretical point of view. The formation of both products **6f** and **6f'** is an intriguing occurence, especially when compared to the selective formation of **2d** from **1d**. A tentative rationalization would be that the formation of enol ethers and enol esters do not transit via the same intermediate (i.e. **10**), and that enol esters are formed via a pathway that is presumably similar to that proposed by Fehr, an *endo* cyclization on a half rearranged species that is sensitive to the presence of R^2 substituent of the alkene. We are now investigating this issue in detail.



Scheme II-31

[108] Hours, A. E.; Snyder, J. K. *Tetrahedron Lett.* **2006**, *47*, 675.

In order to promote our method of preparation of [3.1.0]-bicyclic structures, we developed a rapid and efficient synthesis of sabinaketone through precursor **5d** (Scheme II-35)[109]. Sabinaketone is a key intermediate in the synthesis of important monoterpenes such as Sabinene or *trans*-Sabinene hydrate[110]. In fact, the latter is an important flavor chemical[11121] found in a variety of essential oils from mint and herbs.[112]



Scheme II-35

We also examined the possibility of applying the transannular *O*-acyl migration toward the synthesis of euphanginol[113] (Scheme II-36). Unfortunately, the reaction of precursor **19** in the presence of $PtCl_2$ gave only intractable material and no evidence of the product **18** resulting from the highly challenging simultaneous assembly of an eight-, three- and four-membered rings was found. In order to gain more insight, we decided to test simpler acyclic substrates bearing an oxygenated function at the external propargylic position of the enyne system.

Thus, precursor **20** provided **21** in good yield, as a 1 : 1 mixture of diastereomers that resulted from a 5-*endo* cyclization followed by a 1,2-H migration with no intervention of the OPNB group. This was in part confirmed by the cycloisomerization of alcohol **22** and methylether **23** similar to **21**. We attempted to inhibit the 1,2-H transfer by introducing a *gem*-dimethyl group at the propargylic position. Interestingly but logically, in that case, a moderate yield of product **25**, resulting from a migration of a methyl group, was observed.

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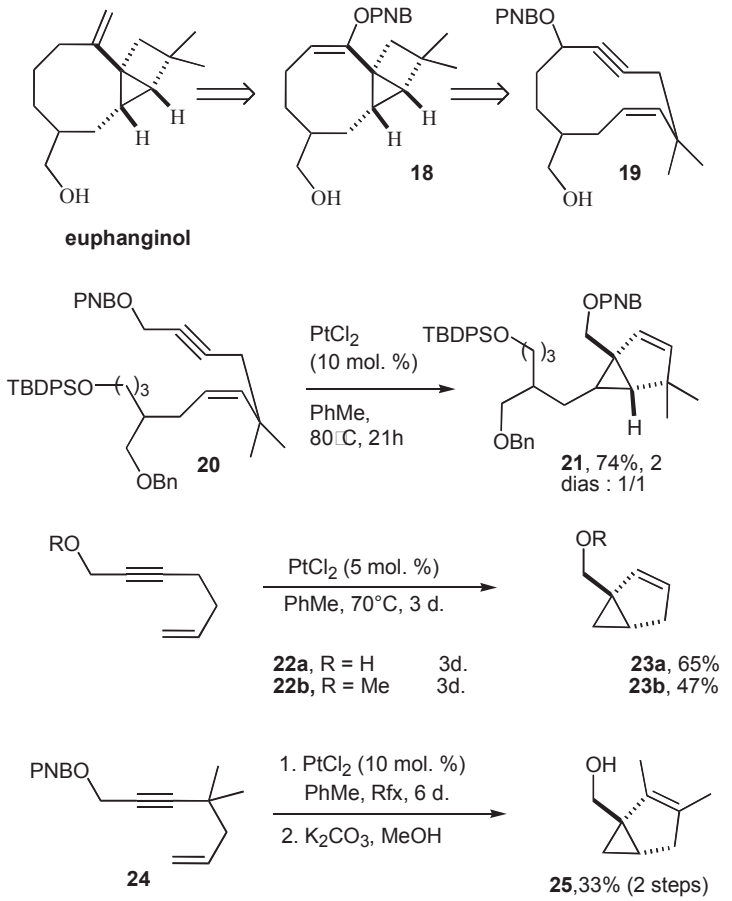
[109] For another recent synthesis of sabinaketone, see: Hodgson, D. M.; Chung, Y. K.; Paris, J.-M. *J. Am. Chem. Soc.* **2004**, *126*, 8664.
[110] Barberis, M.; Pérez-Prieto, J. *Tetrahedron Lett.* **2003**, *44*, 6683 and references therein.
[111] Galopin, C. C. *Tetrahedron Lett.* **2001**, *42*, 5589 and references therein.
[112] Shi, J.-G. ; Shi, Y.-P. ; Jia, Z.-J. *Phytochemistry* **1997**, *45*, 343.
[113] Le Bideau, F.; Gilloir, F.; Nillson, Y.; Aubert, C.; Malacria, M. *Tetrahedron* **1996**, *52*, 7487-7510.



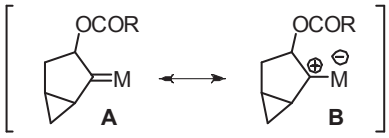
Scheme II-36

II. 2. 4. Conclusion

The cycloisomerization of a variety of 1,5-enyne systems (**1a-c**, **3a-e** and **5a-h**) has allowed us to develop a rapid and efficient access to highly functionalized [3.1.0]-bicyclic structures (**2a-c**, **1a-e** and **6a-h**).[79] In the course of this study, the role of the hydroxyl substitution (X = H, TBS or OPNB) on the cycloisomerization mechanism and on the isolated products has been shown. Further mechanistic determinations and synthetic applications will be reported in due course.

II. 3. Unpublished results

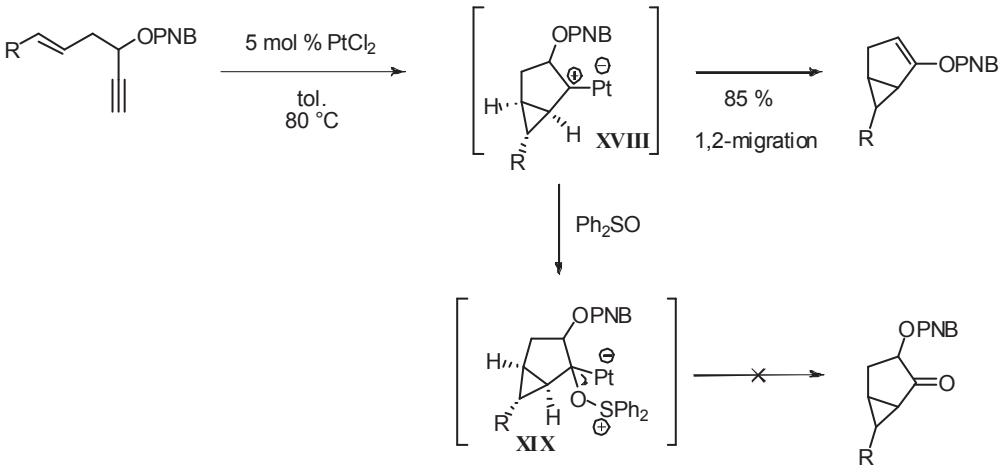
In this part, we will focus on the study of the mechanistic pathway. As we have seen before in case of 1,5-enyne esters, one possible mechanistic pathway is the direct formation of a cyclopropylcarbene, followed by the migration of an ester or hydride. We aimed at highlighting the pathway that would go through the cyclopropylcarbene **A** or the bicyclic zwitterionic species **B** (Scheme II-37). Moreover, we studied whether the 1,2-shift could occur before the cyclopropanation without chirality transfer experiments.



Scheme II-37

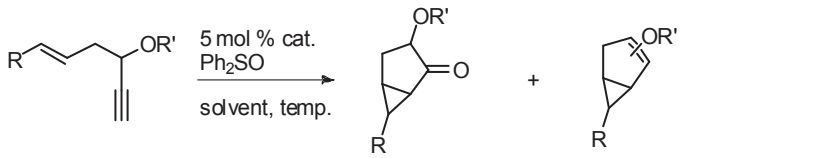
II. 3. 1. Trapping of the metalated bicycle intermediate

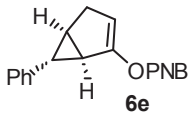
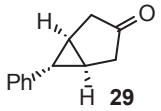
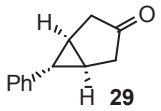
We have no evidence whether the mechanistic pathway would go through intermediate A and B. Similarly to Toste and co-workers experiment, platinum(II)-catalyzed cyclization of our propargyl ester substrates would go through the zwitterionic species **XVIII**. In this case, the intermediate should undergo nucleophilic attack of diphenylsulfoxide in the reaction mixture to form **XIX**.[83] Experimentally, the $PtCl_2$-catalyzed cycloisomerization of 1,5-enynes in the presence of diphenylsulfoxide would lead to bicyclo[3.1.0]hexanone (Scheme II-38).



Scheme II-38

The reactivity of propargyl ester **5e** was examined (entry 1). If two equivalents of diphenylsulfoxide are added, the carbene could be trapped before 1,2-shift of the *p*-nitrobenzoate, to form ketone **27**. However, the known [3.1.0] bicycle **6e** was obtained in a low yield of 23 %. Gold catalysis did not afford the ketone **27** either (entry 2). At this stage, we turned our attention to propargyl ethers. Without additive, enyne **26** afforded compound **29** in quantitative yield, but when two equivalents of diphenylsulfoxide are added in the reaction mixture, the yield decreased to 29 % and the putative reaction intermediate **28** was not trapped.



entry	molecule	cat.	Ph_2SO	solvent	temp	product	yield
1	**5a**	$PtCl_2$	2 eq.	toluene	80°C	 **6e**	23 %
2	**5e**	[Au][a]	2 eq.	DCM	r.t.	degradation	-
3	**31**	[Au]	0 eq.	DCM	r.t.	 **29**	quant.[b]
1	**31**	[Au]	2 eq.	DCM	- 78°C	 **29**	29 %

[a] [Au] = $AuClPPh_3/AgSbF_6$, [b] based on crude product NMR.

As intermolecular trapping have not brought evidence of the proposed type of intermediate, we turned our attention to the study of chirality transfer in the platinum-catalyzed cycloisomerization of 1,5-enynes.

II. 3. 2. Cycloisomerization of enantioenriched precursors

In comparison with the results of Fürstner and Fehr groups about chirality transfer during the synthesis of the enantiopure (-)-cubebol,[88] we set out to investigate the chirality transfer in the the $PtCl_2$-catalyzed rearrangement of 1,5-enynes. Enantioenriched substrates (with a chiral center at the propargylic position) were engaged in cyclization reactions, and the enantiomeric excesses of the cycloadducts were determined. A part of this work was realized by Dr Xavier Moreau.

II. 3. 2. a. Synthesis of enantioenriched 1,5-enyne ethers and esters

In the literature, there are two main strategies described for the synthesis of secondary enantioenriched propargylic alcohols. They can be prepared by enantioselective reduction of ketones[114] or by addition of metalled substrate on aldehydes.[115] Recently, Carreira and co-workers proposed a synthetic route that does not require prior preparation of the latter. Aliphatic aldehydes and terminal alkynes are directly submitted to a mixture of *N*-methylephedrine and zinc triflate, doing so, alkynes undergo *in situ* metallation (to form a zinc alkynide species).[116] This elegant strategy was unfortunately limited to saturated aldehydes.

We decided to prepare enantioenriched secondary alcohols by enzymatic resolution, using a lipase that generally gives the products with high enantiomeric excess.[117] Lipases from the bacteria *Pseudomonas sp* are selective toward secondary hydroxyl functions. By submitting our racemic alcohols to such lipase in transesterification conditions (that is to say, in the presence of vinylacetate and molecular sieve to prevent hydrolysis), we would be able to generate an enantioenriched alcohol starting from a secondary propargyl alcohol.[118]

Secondary racemic enynol **30** was submitted to a mixture of *Pseudomonas Amano AK*[119] and vinyl acetate in hexane. (*R*)-enynol underwent esterification to afford **32** in 41 % yield, whereas (*S*)-enynol **31** remained unreacted (Scheme II-39). It was not possible to obtain suitable GC and HPLC conditions for the separation of the racemic mixture of (*R*)- and (*S*)-enynols **30**. In contrast, enyne

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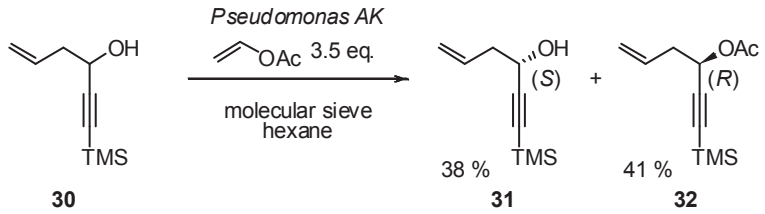
[114] Bogliotti, N.; Dalko, P. I.; Cossy, J. *Tetrahedron Lett*. **2005**, *46*, 6915.
[115] Beckmann, E.; Desai, V.; Hoppe, D. *Synlett* **2004**, *13*, 2275.
[116] Frantz, E. D.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806.
[117] Andersch, P.; Berger, M.; Hermann, J.; Laumen, K.; Lobell, M.; Seemayer, R.; Waldinger, C.; Schneider, M. P. *Meth. Enzymol*. **1997**, *286*, 406.
[118] Degueil-Castaing, M.; De Jeso, B.; Drouillard, S.; Maillard, B. *Tetrahedron Lett*. **1987**, *28*, 953.
[119] Burova, S. A.; Mac Donald, F. E. *J. Am. Chem. Soc.* **2002**, *124*, 8188.

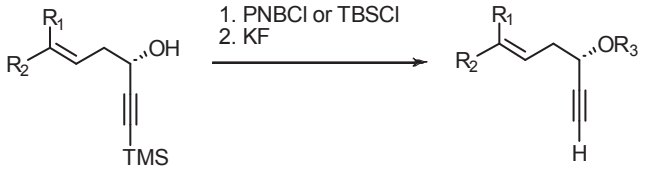
esters were more easily separable and were synthesized for the determination of enantiomeric excess.



Scheme II-39

Our precursors (1,5-enyne ethers and esters) were prepared in two steps from enantioenriched 1,5-enynols: esterification (or etherification) followed by terminal alkyne deprotection. These reactions do not involve racemizing steps, and therefore enantiopurity of the starting enynol would not be modified (in theory, enantiomeric excess for 1,5-enyne esters would be equal to enantiomeric excess of starting 1,5-enynols). Moreover, enzymatic resolution directly allowed the preparation of enriched 1,5-enyne acetates, then a simple deprotection of terminal alkyne is necessary before engaging this product in cycloisomerization (Table II-4).

Allylic and prenylic alcohols were submitted to esterification with *para*-nitrobenzoate followed by deprotection of the alkyne to give rise to **5a (*S*)** and **5f (*S*)** in 78 and 81 % yield respectively (entries 1-2). Prenylic and crotylic alcohols were submitted to etherification with *tert*-butyldimethylsilylchloride, followed by deprotection of terminal alkyne to afford **1d (*S*)** and **1e (*S*)** in 41 and 80 % yield respectively (entries 3-4). All precursors were synthesized with enantiomeric excesses over 90 %.



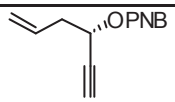
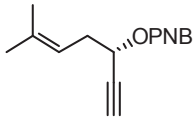
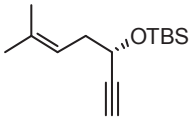
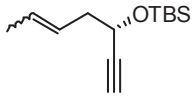
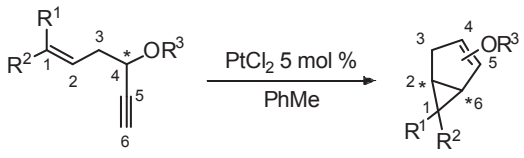
Entry	R_1	R_2	R_3	substrate	yield	ee
1	H	H	PNB	 **5a (*S*)**	78 %	99 %
2	Me	Me	PNB	 **5f (*S*)**	81 %	95 %
3	Me	Me	TBS	 **1d (*S*)**	41 %	92 %
1	H	Me	TBS	 **1e (*S*)**, *E* / *Z* 80 : 20	80 %	99 %

Table II-1 : enantioenriched precursors

II. 3. 2. b. Cyclization

With several enantioenriched enynes in our hands, we could start our study of the chirality transfer in $PtCl_2$-catalyzed cycloisomerization. Presumably, if the reaction goes through racemic intermediates, chiral information embedded at C_4 of enynes would not be transferred into the newly formed stereogenic carbons C_2 and C_6 (Scheme II-40).

The purpose of this study is to answer two questions: what is the most probable mechanistic pathway? And in case of 1,5-enyne *para*-nitrobenzoates, does 1,2-ester shift occur before (Fehr-like pathway) or after cyclization (Fürstner-like, Scheme II-26) ?



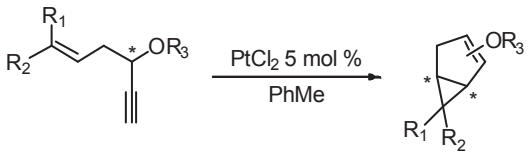
Scheme II-10

First of all, a careful interpretation of our determined enantiomeric excess for bicyclo[3.1.0]hexenes is necessary (Table II-5). In fact, moderate enantiomeric excess were determined, and the results does not seem to highlight an exclusive mechanistic pathway.

We started our study with 1,5-enynes bearing *O*-acyl migrating group (entries 1-3). Enantiopure (*R*)-propargylic acetate **33** and (*S*)- propargylic *para*-nitrobenzoate **5a (*S*)** yielded bicycles **35** and **6a** in respectively 19 and 50 % enantiomeric excess. The cyclization of the prenyl ester **5f (*S*)** lead to two products with very different enantiomeric excesses (entry 3). In contrast to the bicycle **6f** resulting from ester migration, the cyclized compound **6f'** resulting from hydride migration was prepared in a high enantiomeric excess of 93 %. The big difference of enantiomeric excesses between these products excludes the mechanistic pathway proposed by Fürstner. As presented earlier (Scheme II-26), they should result from a common intermediate, and exhibit the same enantiomeric excess, but they do not.

Then we turned our attention to 1,5-enyne ethers. Starting from enantiopure propargyl ethers **1d (*S*)** and **1e (*S*)** with 92 % and 99 % respectively, [3.1.0]-bicycles were formed with poor enantiomeric excess (entries 4-5). The ratio syn / anti of the bicycles was equivalent to the ratio E / Z of their parent enantiopure enyne **2e** (entry 5).

In view of these results, a conclusion towards a preferred intermediate was not possible. However, we suggest a favor Fehr-type pathway in case of 1,2-shift of the ester. Indeed, the ester 1,2-migration occurs with chirality transfer, but the subsequent cyclopropanation reaction occurs with a partial loss of the chiral information. Indeed, the enantiomeric excesses of the cycloadducts depend on the propargylic moiety: between **34** and **6a**, it is better for the bulky ester (entries 1-2). This would mean that the size of the propargylic substituent influences the transfer of the chiral information to the newly formed stereogenic centers. Similarly, the compounds **2d** and **2e,** resulting from hydride migration, were prepared with low enantiomeric excesses. On the other hand, in the case of the cycloadducts **6f**, **6f'** and **2d**, we suggest that the surprising observed enantiomeric excesses are related to the methyl substituent at the (*Z*) position of the olefin (entries 3-4). However, to date it is hard to understand why the enantiomeric excesses of **6f'** and **2d** that both result from hydride migration, are so different.



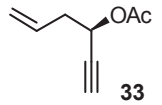
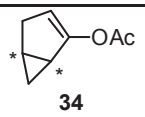
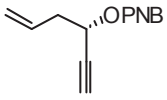
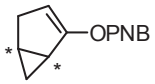
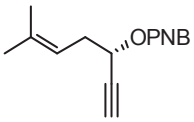
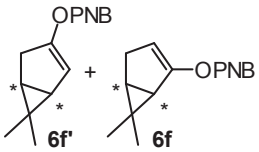
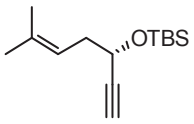
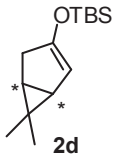
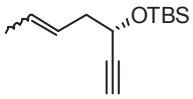
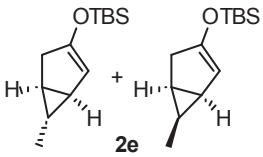
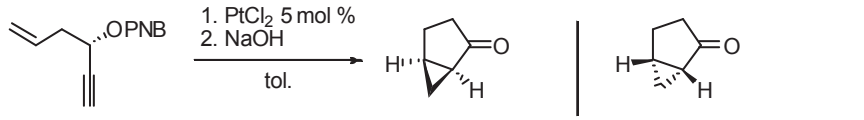
Entry	substrate	ee (%)	product	ee (%)	Yield (%)
1	 **33**	99	 **34**	19	82
2	 **5a (*S*)**	99	 **6a**	50	90
3	 **5f (*S*)**	95	 **6f'** **6f**	93 / 31	81
1	 **1d (*S*)**	92	 **2d**	7	77
5	 **1e (*S*)**, *E* / *Z* 80 : 20	99	 **2e** syn / anti 84 : 16	6 / 17	80

Table II-5 : chirality transfer for $PtCl_2$-catalyzed 1,5-enynes cycloisomerization

Finally, it was possible to determine the absolute configuration of the cyclopropane in the case of the cyclization of enantiopure allylic enyne ester **5a (*S*)** (Scheme II-41). After cyclization, the resulting [3.1.0]-bicycle was submitted to saponification to afford ketone **35**. The ketone **36** was fully described in the literature, its optical rotation value was measured negative.[120] On the contrary, the optical rotation value of our enantioenriched ketone **35** was positive.[121] We were then able to deduce the absolute configuration of our cyclopropane.

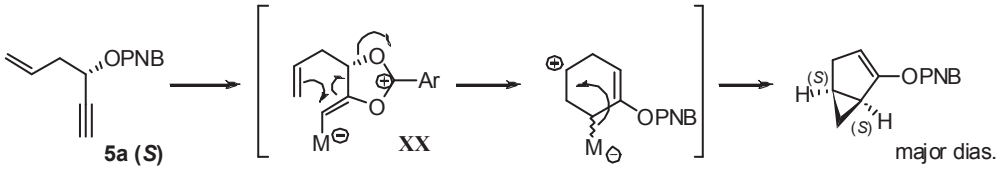
[120] Bergson, J. A. *J. Am. Chem. Soc*. **1991**, *113*, 4595.
[121] The optical rotation value was measured two times, but it was not possible to determine a precise value.



5a (*S*) **35** **36**

Scheme II-11

A Fehr-type mechanism with enyne **5a (*S*)** would lead to the "half-rearranged" intermediate **XX** that would undergo cyclopropanation with loss of chiral information. Despite the poor stereocontrol of this cyclopropanation, the reaction would favor the diastereomer resulting from the attack of the double bond on the opposite face of the ester (Scheme II-42).



5a (*S*)

Scheme II-12

II. 1. General conclusion

Skeletal rearrangement of 1,6- and 1,5-enynes have given birth to a myriad of cycloadducts, and are still studied nowadays demonstrating their importance in organic synthesis. Our group has particularly turned our attention to 1,5-enynes propargyl esters and ethers and has showed that Pt(II)-catalyzed cycloisomerization of these substrates afforded bicycle[3.1.0]hexenes in good yield.

A cyclopropylcarbene is generally assumed as the main mechanistic intermediate of this reaction. We consider the possibility of trapping the zwitterionic equivalent of this carbene, but the desired ketone was not obtained. We then turned our attention to the study of the chirality transfer of this reaction. We therefore synthesized a series of enantioenriched propargyl alcohols. These substrate were submitted to Pt(II) catalysis and the cycloadducts were obtained with poor to very good enantiomeric excesses. These results hardly led to a conclusion concerning the possible intermediate of the reaction, however, we suggest that the 1,2-migration occurs first with an imprint of the chiral information, which means that the loss of the latter occurs during the cyclopropanation.

II. 5. Experimental section

All reactions were run under an argon or nitrogen atmosphere in anhydrous solvents and flame-dried flask. $PtCl_2$ (99.9%) was purchased from Strem. $PtCl_2$-catalyzed cycloisomerizations were performed in freshly degassed (2-3 freeze-pump-thaw cycles or 30 min argon bubbling) anhydrous toluene. Thin layer chromatography (TLC) was performed on Merck silica gel 60 F 254 and and visualized under UV irradiation (λ=254 nm) and/or by dipping in *p*-anisaldehyde, phosphomolybdic acid or Ninhydrin solutions then heating. Column chromatography was performed using Silica gel Merck Geduran SI (40-63 nm). Solvents were systematically distilled prior to use. IR spectra were recorded on a Nicolet AVATAR 320 FT-IR, a Philips PYE UNICAM SP3-100 or a Bruker Tensor 27 (ATR diamond) spectrometers. IR is reported as characteristic bands (cm^{-1}) in their maximal intensity. ^{1}H and ^{13}C NMRspectra were recorded at room temperature, either at 200 MHz and 50 MHz, respectively on a AC200 Bruker spectrometer, or at 400 MHz and 100 MHz on an ARX400 and an AVANCE 400 Bruker spectrometers. Shifts are given in ppm and referenced from the solvent residual signal (7.27 ppm for $CDCl_3$, 7.16 ppm for C_6D_6) for proton NMR. For carbon NMR, shifts are referenced from the solvent central peak (77.23 ppm for $CDCl_3$, 128.62 ppm for C_6D_6). Coupling constants (*J*) are given in Hertz (Hz). Elemental analyses were performed by the Service Régional de Microanalyse de l'Université Pierre et Marie Curie or the Service de Microanalyse de l'Institut de Chimie des Substances Naturelles (ICSN, Gif-sur-Yvette, France). Mass spectra were obtained on a GS-MS Hewlett-Packard HP 5971 apparatus and on a NERMAG R 30-10 apparatus in the Laboratoire de Chimie Structurale Organique et Biologique, UPMC. High Resolution Mass Spectra were obtained on a Jeol MS 700 apparatus in the Département de Chimie, Ecole Normale Supérieure. Melting points were measured on a Reichert or a SMP3 Stuart Scientific melting point apparatuses and are uncorrected. Chiral GC was run using a column CP-Chirasil-DEX CB (25 m), FID and nitrogen as carrier gas.

II. 5. 1. Precursors synthesis

General procedure for the precursors synthesis: method A

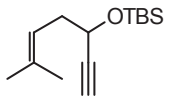
Alkylation at the propargylic position:[104] to a stirred solution of 3-(tetrahydropyran-2-yloxy)-1-trimethylsilyl-prop-1-yne[113] (1.0 eq.) in THF (0.5 M) was added dropwise *t*-BuLi (1.7M in pentane, 1.1 eq.) at -78 °C. After 1h, appropriate allylic halide (1.2 eq.) was added. The resulting solution was stirred for 1h at -78 °C then allowed to warm to r.t., with stirring, over further 1h of stirring. The reaction was then quenched with aqueous NH_4Cl sat. (10 mL/mmol) and the resulting aqueous layer was extracted with Et_2O (3 x 10 mL/mmol). The combined organic layers were washed with brine (10 mL/mmol), dried over anhydrous Na_2SO_4, filtered and evaporated *in vacuo* to afford corresponding crude THP-protected alcohol, which was used in the next step without further purification.

THP deprotection: to a stirred solution of crude THP-protected alcohol in MeOH (1.0 M) at r.t., was added PTSA (0.02 eq.). After the reaction was complete, the solvent was evaporated *in vacuo* and the product was purified by flash column chromatography on silica gel (PE/Et_2O gradient) to afford corresponding C-trimethylsilylated propargylic alcohol.

TBS substitution: to a stirred solution of the C-TMS alcohol (1.0 eq.) in DMSO (0.2 M) at r.t., was added KF (4.0 eq.) and water (4.0 eq.). After the reaction was complete, the reaction was quenched with water (10 mL/mmol) and the resulting aqueous layer was extracted with Et_2O (3 x 10 mL/mmol). The combined organic layers were washed with brine (10 mL/mmol), dried over anhydrous Na_2SO_4, filtered and evaporated *in vacuo*. Purification by flash column chromatography on silica gel (PE/Et_2O gradient) afforded corresponding C-desilylated propargylic alcohol. To a stirred solution of C-desilylated propargylic alcohol (1.0 eq.) in CH_2Cl_2 (1.0 M) at r.t., were successively added Et_3N (5.0 eq.), 4-DMAP (0.1 eq.) and *t*-butyldimethylsilyl chloride (1.5 eq.). The resulting solution was refluxed overnight then quenched with NH_4Cl sat. (10 mL/mmol) and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL/mmol). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated *in vacuo*. Purification by flash column chromatography on silica gel (PE/Et_2O gradient) afforded the corresponding O-TBS propargylic silyl-ether.

PNB substitution: to a stirred solution of C-silylated propargylic alcohol (1.0 eq.) in CH_2Cl_2 (0.5 M) at r.t., were successively added Et_3N (5.0 eq.) and 4-nitrobenzoyl chloride (1.2 eq.). After the reaction was complete, the reaction was quenched with NH_4Cl sat. (10 mL/mmol) and the resulting aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL/mmol). The combined organic layers were washed with brine (10 mL/mmol), dried over anhydrous Na_2SO_4, filtered and evaporated *in vacuo*. Purification by flash column chromatography on silica gel (PE/Et_2O gradient) to afford corresponding C-silylated O-PNB propargylic ester. The C-desilylation reaction described above (method A) was then performed on the resulting compound.

Structure 25 : 3-*tert*-Butyldimethylsilyloxy-6-methyl-hept-5-en-1-yne (1d)



$C_{14}H_{26}OSi$

Mol. Wt.: 238.4411

Synthesized following method A using commercially available prenyl bromide for the alkylation step. Alkylation and THP-deprotection were run on a 10.0 mmol scale (40% overall yield). C-Desylilation and subsequent O-silylation were run on a 1.5 mmol scale (46% overall yield)

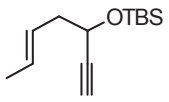
Pale-yellow oil

IR (neat): 3112, 2929, 2857, 1251, 1083 cm-[1]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.21-5.17 (m, 1H, C*H*H=), 4.29 (td, *J* = 6.4, 2 Hz, 1H, CHOSi), 2.42-2.84 (m, 2H, CH_2), 2.38 (d, *J* = 4 Hz, 1H, CH-acetyl), 1.72 (s, 3H, CH_3), 1.63 (s, 3H, CH_3), 0.90 [s, 9H, $C(CH_3)_3$], 0.12 (s, 3H, CH_3Si), 0.10 (s, 3H, CH_3Si),

^{1}H NMR (50 MHz, $CDCl_3$): δ = 134.8, 119.5, 85.7, 72.0, 63.1, 37.6, 26.0, 25.9, 18.4, 18.2, -4.6, -4.0.

Structure 26 : (*E*)-*tert*-butyl(hept-5-en-yn-3-yloxy)dimethylsilane (1e)

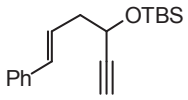


$C_{13}H_{24}OSi$

Mol. Wt.: 224.4146

Synthesized following method A using commercially available crotyl bromide for the alkylation step. C-Desylilation and subsequent O-silylation were run on a 1.5 mmol scale (46% overall yield)
Pale yellow oil (80% overall yield).
IR (neat) 2928, 2857, 1464, 1252, 1093 cm^{-1};
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.65 (m, 1H, C*H*H=), 4.29 (m, 1H, CH*H*=), 2.38 (bs, 1H, CHO), 2.35 (m, 2H, CH_2), 1.68 (d, *J* = 1.0 Hz, 3H, Me), 0.90 (s, 9H, CMe_3), 0.12 (s, 3H, SiMe), 0.10 (s, 3H, SiMe);
^{13}C NMR (400 MHz, $CDCl_3$) δ 128.7, 126.3, 85.4, 79.3, 63.2, 42.1, 25.9, 18.2, -4.50, -4. 92

Structure 27 : (E)-tert-butyldimethyl(6-phenylhex-5-en-1-yn-3-yloxy)silane (26)

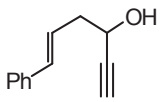


$C_{18}H_{26}OSi$

Mol. Wt.: 286.4839

Synthesized following method A using commercially available (*E*)-cinnamyl bromide for the alkylation step. C-Desylilation and subsequent O-silylation were run on a 3.48 mmol scale (85% overall yield)
Pale yellow oil (80% overall yield).
IR (neat) 2928, 2857, 1464, 1252, 1093 cm^{-1};
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-6.24 (m, 5H, Ar), 6.50 (d, *J* = 16.0 Hz, PhC*H*=), 6.31-6.24 (m, 1H, C*H*=), 4.48-4.44 (m, 1H, CHO), 2.64-2.61 (m, 2H, CH_2), 2.45 (d, *J* = 1.3 Hz, C-H), 0.95 (s, 9H, CMe_3), 0.18 (s, 3H, SiMe), 0.15 (s, 3H, SiMe);
^{13}C NMR (400 MHz, $CDCl_3$) δ 137.6, 133.1, 128.6, 127.3, 126.3, 125.5, 85.2, 72.7, 63.0, 42.4, 25.9, 18.4, -4.4, -4.9

Structure 28 : (*E*)-6-phenyl-hex-5-en-1-yn-3-ol (3b)



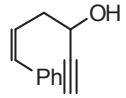
$C_{12}H_{12}O$

Mol. Wt.: 172.2231

Synthesized following method A using commercially available (*E*)-cinnamyl bromide for alkylation step. Spectral data were consistent with those previously reported as compound previously named (*E*)-**22**.[79b]

Anal. calcd. for $C_{12}H_{12}O$: C, 83.69; H, 7.02; Found: C, 83.51; H, 7.04.

Structure 29 : (*Z*)-6-phenyl-hex-5-en-1-yn-3-ol (3c)



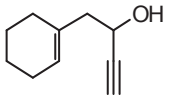
$C_{12}H_{12}O$

Mol. Wt.: 172.2231

Synthesized as its (*E*)-diastereomer **3b** following method A and using (*Z*)-cinnamyl bromide[122] for alkylation step. Spectral data were consistent with those previously reported as compound previously named (*Z*)-**22**.[79b]

Anal. calcd. for $C_{12}H_{12}O$: C, 83.69; H, 7.02; Found : C, 83.58; H, 7.01.

Structure 30 : 1-(cyclohex-1-en-1-yl)-but-1-yn-3-ol (3e)



$C_{10}H_{14}O$

Mol. Wt.: 150.2176

Synthesized following method A using 1-bromomethyl-cyclohex-1-ene[123] for alkylation step. Alkylation and THP deprotection run on a 14.9 mmol scale afforded a 2 steps 26% overall yield. *C*-desilylation run on a 1.7 mmol scale (86% yield).

colorless oil.

IR (neat) 3600-3100 (bs), 2114, 1665 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.55 (m, 1H, C*H*=), 4.41 (dt, *J* = 6.8, 2.0 Hz, 1H, C*H*OH), 2.42 (d, *J* = 2.0 Hz, 1H, C-H), 2.35 (bs, 1H, OH), 2.34 (d, *J* = 6.8 Hz, 2H, CH_2CHOH), 1.97 (m, 4H, CH_2=CHCH_2), 1.62 (m, 4H, $CH_2CH_2CH_2CH_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 132.8, 125.8, 84.8, 72.6, 60.1, 46.2, 28.3, 25.2, 22.6, 22.0; Anal. calcd. for $C_{10}H_{14}O$: C, 79.96; H, 9.39; Found: C, 79.22; H, 9.52.

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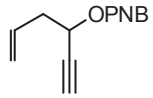
[122] (*Z*)-cinnamyl bromide was synthesized in a 3 steps 59% overall yield starting from commercially available phenylacetylene by: 1. *C*-hydroxymethylation (*n*-BuLi / $(CHO)_n$, 70%), 2. hydrogenolysis (H_2 / Pd / $CaCO_3$, 94%), 3. bromination (PBr_3 / pyridine, 90%).

[123] 1-bromomethyl-cyclohex-1-ene was synthesized in a 2 steps 74% overall yield starting from commercially available cyclohex-1-ene-1-carboxaldehyde by: 1. reduction ($NaBH_4$, no purification), 2. bromination (PBr_3 / pyridine, 74% overall yield).

Structure 31 : (hex-5-en-1-yn-3-yl) *para*-nitrobenzoate (5a)



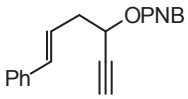
$C_{13}H_{11}NO_4$

Mol. Wt.: 245.2307

Synthesized following method A using allyl bromide for alkylation step. Alkylation and THP deprotection run on a 5.0 mmol scale (41% overall yield). PNB esterification and *C*-desilylation (directly realized on the crude material) were run on a 2.1 mmol scale (88% overall yield). Spectral data were consistent with those previously reported as compound previously named **9**.[79b]

Anal. calcd. for $C_{13}H_{11}NO_4$: C, 63.67; H, 4.52; N, 5.71; Found: C, 63.66; H, 4.55; N, 5.75.

Structure 32 : [(*E*)-6-phenyl-hex-5-en-1-yn-3-yl] *para*-nitrobenzoate (5e)



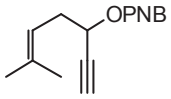
$C_{19}H_{15}NO_4$

Mol. Wt.: 321.3267

Synthesized following method A. Alkylation and THP deprotection run on a 15.0 mmol scale (43% overall yield). PNB esterification and *C*-desilylation (directly realized on the crude material) were run on a 1.0 mmol scale and afforded a 2 steps 94% overall yield. Spectral data were consistent with those previously reported as compound previously named **13**.[79b]

Anal. calcd. for $C_{19}H_{15}NO_4$: C, 71.02; H, 4.71; N, 4.36; Found: C, 71.06; H, 4.52; N, 4.31.

Structure 33 : (6-methyl-hept-5-en-1-yn-3-yl)*para*-nitrobenzoate (5f)



$C_{15}H_{15}NO_4$

Mol. Wt.: 273.2839

Synthesized following method A using commercially available prenyl bromide for alkylation step. Alkylation and THP deprotection run on a 10.0 mmol scale (40% overall yield). PNB esterification and *C*-desilylation (directly realized on the crude material) were run on a 1.0 mmol scale (73% overall yield).

yellow solid; m.p. 132-134°C.

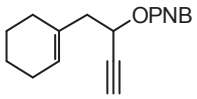
IR (neat) 3287, 3110, 2125, 1719, 1606, 1527 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 8.8 Hz, 2H, arom.), 8.22 (d, *J* = 8.8 Hz, 2H, arom.), 5.56 (td, *J* = 6.6, 2.2 Hz, 1H, CHO), 5.23 (m, 1H, CH=), 2.65 (m, 2H, CH_2), 2.52 (d, *J* = 2.2 Hz, 1H, C-H), 1.73 (s, 3H, Me), 1.67 (s, 3H, Me).

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 150.6, 136.5, 135.2, 130.9, 123.5, 117.1, 80.5, 74.3, 65.2, 33.5, 25.8, 18.1.

Anal. calcd. for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13; Found: C, 65.87; H, 5.39; N, 4.85.

Structure 31 : [1-(cyclohex-1-en-1-yl)-but-1-yn-3-yl)]*para*-nitrobenz-oate (5h)



$C_{17}H_{17}NO_4$

Mol. Wt.: 299.3212

Synthesized from alcohol **3e** (1.0 mmol scale) in a 97% yield following PNB esterification procedure described in method A.

colorless oil;

IR (neat) 3289, 3310, 3075, 3050, 2150, 1725, 1607, 1525 cm^{-1};

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.30 (d, *J* = 8.3 Hz, 2H, arom.), 8.21 (d, *J* = 8.3 Hz, 2H, arom.), 5.71 (m, 1H, CHO) 5.57 (m, 1H, CH=), 2.59 (m, 2H, C*H*$_2$CH), 2.53 (d, *J* = 2.3 Hz, 1H, C-H), 1.99 (m, 4H, C*H*$_2$C=CHC*H*$_2$), 1.60-1.50 (m, 4H, C*H*$_2$CH$_2$CH$_2$C*H*$_2$);

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 150.6, 135.2, 131.8, 130.8, 126.3, 123.5, 80.7, 74.3, 63.9, 43.5, 28.4, 25.3, 22.7, 22.0;

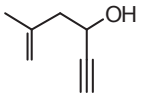
Anal. calcd. for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.72; N, 4.68; Found: C, 68.42; H, 5.67; N, 4.45.

General procedure for the precursors synthesis: method B

Ether formation: to a stirred solution of 3-trimethylsilyl-prop-2-yn-1-ol[124] (1.0 eq.), 1,10-phenanthroline (cat.) and HMPA (4.0 eq.) in THF (0.2 M) was added dropwise, EtMgBr (1.0 eq.) at 0 °C until a deep-red color persists. Appropriate allylic halide (1.5 eq.) was added and the resulting solution was refluxed for 4h. The reaction was allowed to cool to r.t. then quenched with brine (10mL/mmol). The resulting aqueous layer was extracted with Et_2O (3 x 10mL/mmol). The combined organic layers were washed with brine (10mL/mmol), dried over anhydrous Na_2SO_4, filtered and evaporated *in vacuo*. Purification by flash column chromatography on silica gel (PE/Et_2O gradient) afforded the corresponding allylic ether.

[2,3]-Wittig rearrangement: to a stirred solution of the allylic ether (1.0 eq.) in THF (0.2 M) was added dropwise freshly titrated *n*-BuLi (2.5 M in hexanes, 1.0 eq.) at 78 °C. After addition was complete, the reaction was quenched with NH_4CL sat. (10mL/mmol) and the aqueous layer was extracted with Et_2O (3 x 10mL/mmol). The combined organic layers were washed with brine (10mL/mmol), dried over anhydrous Na_2SO_4, filtered and evaporated *in vacuo*. Purification by flash column chromatography on silica gel (PE/Et_2O gradient) to afford corresponding *C*-trimethylsilylated propargylic alcohol. *C*-desilylation reaction was then performed according to procedure described in method A and the resultant *C*-desilylated propargylic alcohols were then derivatized by either a TBS or a PNB substituent according to procedures described in method A.

Structure 35 : 5-methyl-hex-5-en-1-yn-3-ol (3a)



$C_7H_{10}O$

Mol. Wt.: 110.1537

Prepared as previously described.[105b]

IR (neat) 3350 (br), 3300, 3080, 2120, 1650 cm^{-1};

^1H NMR (200 MHz, $CDCl_3$) δ 4.87 (bs, 1H, C*H*H=), 4.82 (bs, 1H, CH*H*=), 4.47 (td, *J* = 6.8, 2.0 Hz, 1H, C*H*OH), 2.44 (d, *J* = 2.0 Hz, 1H, C-H), 2.42 (d, *J* = 6.8 Hz, 2H, CH_2), 1.76 (s, 3H, Me).

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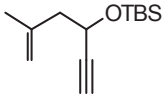
[124] This compound was synthezised according to literature procedure: Velcicky, J.; Lex, J.; Schmalz, H.-G. *Org. Lett.* **2002**, *4*, 565-568 and references cited therein.

^{13}C NMR (50 MHz, $CDCl_3$) δ 140.8, 114.2, 84.6, 72.9, 60.3, 45.9, 22.5.

Anal. calcd. for $C_7H_{10}O$: C, 76.33; H, 9.15; Found: C, 76.29; H, 9.12.

Structure 36 : 3-(*tert*-butyl)dimethylsilyloxy-5-methyl-hex-5-en-1-yne (1a)



$C_{13}H_{24}OSi$

Mol. Wt.: 224.4146

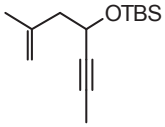
Synthesized in a quantitative yield from alcohol **3a** following TBS silylation described in method A.[125]

IR (neat) 3300, 3080, 2100, 1650 cm^{-1};

^{1}H NMR (200 MHz, $CDCl_3$) δ 4.82 (m, 1H, C*H*H=), 4.78 (m, 1H, CH*H*=), 4.46 (td, *J* = 6.7, 2.0 Hz, 1H, CHO), 2.39 (m, 3H, C-H and CH_2), 1.76 (s, 3H, Me), 0.89 (s, 9H, CMe_3), 0.13 (s, 3H, SiMe), 0.10 (s, 3H, SiMe);

^{13}C NMR (50 MHz, $CDCl_3$) δ 141.0, 113.3, 85.2, 72.0, 61.7, 46.6, 22.8, 22.6, 18.0, -4.8, -5.3.

Structure 37 : 1-(*tert*-butyl)dimethylsilyloxy-6-methyl-hept-6-en-2-yne (1b)



$C_{14}H_{26}OSi$

Mol. Wt.: 238.4411

Synthesized from silyl-ether **1a** (8.9 mmol scale) as follows: to a stirred solution of silyl-ether **1a** (2.0 g, 8.9 mmol, 1.0 eq.) in THF (20 mL) was added dropwise freshly titrated *n*-BuLi (2.3 M, 4.3 mL, 9.9 mmol, 1.1 eq.) at 78 °C. After 1h, MeI (2.2 mL, 35.3 mmol, 4.0 eq.) was added dropwise. The reaction was stirred for 2h at -78 °C then at rt overnight. The reaction was then quenched with brine (50 mL) and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and evaporated *in vacuo*. Purification by flash column chromatography on silica gel (PE/Et_2O gradient) gave pure **1b**. Spectral data were consistent with those previously reported as compound previously named **18b**.[79b]

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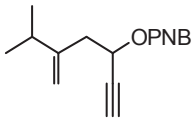
[125] Journet, M.; Lacôte, E.; Malacria, M. *J. Chem. Soc., Chem. Commun.* **1994**, *4*, 461-462.

Structure 38 : 3-(*tert*-butyl)dimethylsilyloxy-5-(*iso*-propyl)-hex-5-en-1-yne (1c)



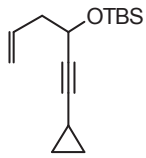
$C_{15}H_{28}OSi$

Mol. Wt.: 252.4677

Synthesized, from previously described corresponding *C*-trimethylsilylated alcohol, according to *C*-desilylation / O-TBS derivatization sequence described in method A. Reactions run on a 4.75 mmol scale (88% overall yield).

Spectral data were consistent with those previously reported as compound previously named **18c**.[79b]

Structure 39 : 1-cyclopropyl-hex-5-en-1-yn-3-ol (3d)



$C_{15}H_{26}OSi$

Mol. Wt.: 250.4518

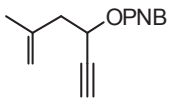
Synthesized as previously described.[126]

IR (neat) 3380 (br), 3080, 2240, 1640, 1430 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ 5.88 (m, 1H, C*H*=CH_2), 5.18 (dd, *J* = 17.3, 1.0 Hz, 1H, C$H_{trans}H_{cis}$=CH), 5.17 (dd, *J* = 10.7, 1.0 Hz, 1H, $CH_{trans}H_{cis}$=CH), 4.37 (td, *J* = 6.0, 1.0 Hz, 1H, C*H*OH_4), 2.43 (t, *J* = 6.0 Hz, 2H, CH_2), 1.25 (m, 1H, C*H*(CH_2CH_2)), 0.77 (m, 2H, CH(CH_2CH_2)), 0.68 (m, 2H, CH(CH_2CH_2));

^{13}C NMR (100 MHz, $CDCl_3$) δ 133.4, 118.8, 89.1, 75.9, 61.8, 42.6, 8.4 (2 ^{13}C), -0.5.

Structure 10 : (5-methyl-hex-5-en-1-yn-3-yl) *para*-nitrobenzoate (5b)



$C_{14}H_{13}NO_4$

Mol. Wt.: 259.2573

Synthesized from alcohol **3a** following PNB esterification described in method A.

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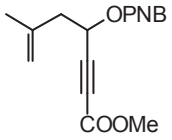
[126] Mainetti, E.; Fensterbank, L.; Malacria, M. *Synlett* **2002**, 923.

Spectral data were consistent with those previously reported as compound previously named **11a**.[79b]
Anal. calcd. for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40; Found: C, 64.87; H, 5.03; N, 5.62.

Structure 11 : (1-carbomethoxy-5-methyl-hex-5-en-1-yn-3-yl) *para*-nitrobenzoate (5c)

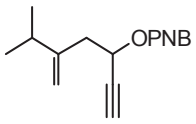


$C_{16}H_{15}NO_6$

Mol. Wt.: 317.2934

Synthesized in a 3 steps sequence (*C*-carbomethoxylation / THP deprotection / PNB esterification) starting from previously described O-THP protected alcohol.[105b] To a stirred solution of O-THP protected alcohol (0.20 g, 0.95 mmol, 1.0 eq.) in THF (8 mL) was added dropwise freshly titrated *n*-BuLi (2.3 M, 0.45 mL, 1.05 mmol, 1.1 eq.) at 78 °C. After 1h, $ClCO_2Me$ (0.11 mL, 1.40 mmol, 1.5 eq.) was added dropwise. The reaction was stirred for 1h at -78 °C then at r.t. for 1h. The reaction was then quenched with water and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated *in vacuo*. The resulting crude was then used without further purification. To a stirred solution of the latter in MeOH (10 mL) was added PTSA (0.02 eq.) at r.t.. After completion, the reaction was evaporated *in vacuo*. Purification was then achieved by flash column chromatography on silica gel (PE/Et_2O gradient) to afford corresponding propargylic alcohol (0.11 g, 69%). The latter was then submitted to PNB esterification described in method A to give **5c.**
Spectral data were consistent with those previously reported as compound previously named **11b**.[79b]
pale yellow oil (0.18 g, 87%);
Anal. calcd. for $C_{16}H_{15}NO_6$: C, 60.57; H, 4.77; N, 4.41; Found: C, 60.67; H, 4.73; N, 4.37.

Structure 12 : [5-(iso-propyl)-hex-5-en-1-yn-3-yl]*para*-nitrobenzoate (5d)



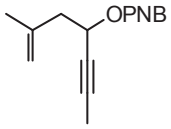
$C_{16}H_{17}NO_4$

Mol. Wt.: 287.3105

PNB esterification of the corresponding alcohol (see ref 79b) was run prior to *C*-desilylation by KF/DMSO. This latter step was realized on the resulting esterification crude ester. Reactions run on a 7.1 mmol scale (88% overall yield).

Spectral data were consistent with those previously reported as compound previously named **22**.[79b] Anal. calcd. for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88; Found: C, 66.99; H, 5.93; N, 4.78.

Structure 13 : (6-methyl-hept-6-en-2-yn-4-yl)*para*-nitrobenzoate (5g)



$C_{15}H_{15}NO_4$

Mol. Wt.: 273.2839

Synthesized from silyl-ether **1b** (on a 6.3 mmol scale) using, first, TBAF for O-desilylation (79%) then PNB esterification procedure (85%) described in method A to give **5g** as a yellow oil.

IR (neat) 3291, 3120, 3090, 3060, 2245, 1724, 1650, 1526 cm^{-1};

^1H NMR ($CDCl_3$, 200 MHz) δ 8.27 (d, *J* = 9.1 Hz, 2H, arom.), 8.20 (d, *J* = 9.1 Hz, 2H, arom.), 5.72 (m, 1H, CHO), 4.84 (m, 2H, CH_2=), 2.70-2.54 (m, 2H, CH_2), 1.85 (d, *J* = 2.0, 3H, C-Me), 1.80 (s, 3H, =CMe);

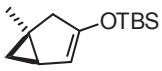
^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 150.5, 140.0, 135.4, 130.8, 123.5, 114.4, 82.8, 76.0, 64.4, 43.5, 22.4, 3.6.

II. 5. 2. Cycloadducts synthesis

General procedure for $PtCl_2$-catalyzed cycloisomerization:

To a stirred solution of appropriate acyclic precursor (1.0 eq.) in anhydrous degassed PhMe (0.02-0.20 M) was added $PtCl_2$ (0.05 eq.) at r.t.. The resulting solution was then heated at mentioned temperature (80 °C or reflux). After reaction completion, the solvent was evaporated *in vacuo*. The residue was then submitted to ^1H NMR analysis before being purified by flash column chromatography on silica gel (PE/Et_2O gradient).

Structure 11 : 3-(*tert*-butyl)dimethylsilyloxy-5-methyl-bicyclo[3.1.0] hex-2-ene (2a)



$C_{13}H_{24}OSi$

Mol. Wt.: 224.4146

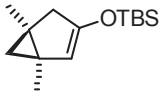
pale yellow oil (68%).

Spectral data were consistent with those previously reported as compound previously named **19a**.[79b]

IR (neat) 3070, 3040, 1628, 1252, 863 cm^{-1}.

Anal. calcd. for $C_{13}H_{24}OSi$: C, 69.58; H, 10.78; Found: C, 69.53; H, 10.74.

Structure 15 : 3-(*tert*-butyl)dimethylsilyloxy-1,5-dimethyl-bicyclo [3.1.0]hex-2-ene (2b)



$C_{14}H_{26}OSi$

Mol. Wt.: 228.4411

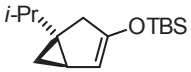
pale yellow oil (84%);

IR (neat) 3048, 1634, 1252, 831 (br) cm^{-1}.

Spectral data were consistent with those previously reported as compound previously named **19b**.[79b]

Anal. calcd. for $C_{14}H_{26}OSi$: C, 70.52; H, 10.99; Found: C, 69.82; H, 10.94.

Structure 16 : 3-(*tert*-butyl)dimethylsilyloxy-5-(*iso*-propyl)-bicyclo-[3.1.0]hex-2-ene (2c)



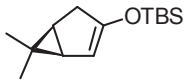
$C_{15}H_{28}OSi$

Mol. Wt.: 252.4677

pale yellow oil (83%).

Spectral data were consistent with those previously reported as compound previously named **19c**.[79b]

Structure 17 : 3-(*tert*-butyl)dimethylsilyloxy-5-(*iso*-propyl)-bicyclo-[3.1.0]hex-2-ene (2c)



$C_{14}H_{26}OSi$

Mol. Wt.: 238.4411

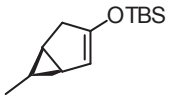
Brow oil.

IR (neat) 2930, 2901, 1629, 1226, 833 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz) δ 4.63-4.61 (m, 1H, C*H*=), 2.48-2.42 (dd, J = 17.6, 8 Hz, 1 H, C*H*HC=), 1.99-1.93 (m, 1H, CH*H*C=), 1.45-1.42 (m, 1H, C*H*CH), 1.00-0.98 (m, 1H, C*H*CH_2), 0.99 (s, 3H, CCH_3), 0.90 [s, 9H, $C(CH_3)_3$], 0.87 (s, 3H, CCH_3), 0.14 (s, 3H, $SiCH_3$), 0.12 (s, 3H, $SiCH_3$).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.8, 102.7, 33.8, 32.3, 26.4, 25.8, 23.7, 21.0, 18.2, 13.3, -4.4, -4.7.

Structure 18 : tert-butyldimethyl-6-methylbicyclo[3.1.0]hex-2-en-3-yloxysilane (2e)



$C_{13}H_{24}OSi$

Mol. Wt.: 224.4146

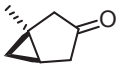
Pale yellow oil (75%)

IR (neat) 2930, 2858, 1630, 1228, 835 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.85 (bs, 1H, C*H*=), 2.57 (m, 1 H, C*H*HC=), 1.99-1.93 (m, 1H, CH*H*C=), 1.24-1.25 (m, 1H, C*H*CH), 0.95 (d, *J* = 6.4Hz, 3H, CHC*H*$_3$), 0.89 [s, 9H, C(CH$_3$)$_3$], 0.31-0.40 (m, 1H, C*H*CH$_2$)0.12 (s, 3H, SiCH$_3$), 0.10 (s, 3H, SiCH$_3$).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.9, 106.6, 37.1, 32.7, 23.4, 19.7, 17.2, 15.0, -4.4, -4.7.

Structure 19 : 1-methyl-bicyclo[3.1.0]hexan-3-one (1a)



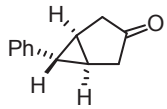
$C_7H_{10}O$

Mol. Wt.: 110.1537

yellow oil (50%).

Spectral data were consistent with those previously reported as compound previously named **21**.[79b]

Structure 50 : 6-phenyl-bicyclo[3.1.0]hexan-3-one (1b)



$C_{12}H_{12}O$

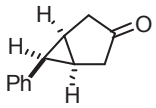
Mol. Wt.: 172.2231

beige solid (96%); m.p. 65-67°C.

Spectral data were consistent with those previously reported as compound previously named **23**.[79b]

Anal. calcd. for $C_{12}H_{12}O$: C, 83.69; H, 7.02; Found: C, 83.41; H, 7.01.

Structure 51 : 6-phenyl-bicyclo[3.1.0]hexan-3-one (1c)



$C_{12}H_{12}O$

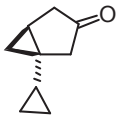
Mol. Wt.: 172.2231

beige solid (83%); m.p. 61-63°C.

Spectral data were consistent with those previously reported as compound previously named **24**.[79b]

Anal. calcd. for $C_{12}H_{12}O$: C, 83.69; H, 7.02; Found: C, 83.62; H, 7.09.

Structure 52 : 1-cyclopropyl-bicyclo[3.1.0]hexan-3-one (1d)



$C_9H_{12}O$

Mol. Wt.: 136.1910

Colorless oil (88%);

IR (neat) 1744 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.52 (m, 2H, CHC*H*$_2$C(O)), 2.26 (d, *J* = 19.0 Hz, 1H, CC*H*HC(O)), 2.11 (d, *J* = 19.0 Hz, 1H, CCH*H*C(O)), 1.17 (m, 1H, C*H*CH$_2$C(O)), 1.12 (m, 1H, C*H*(CH$_2$CH$_2$)), 0.66 (m, 1H, C*H*HCHCH$_2$C(O)), 0.37 (m, 2H, CH(C*H*HCH$_2$) and CH(CH$_2$C*H*H)), 0.03 (m, 2H, CH(CH*H*CH$_2$) and CH(CH$_2$CH*H*)), -0.01 [m, 1H, CH*H*CHCH$_2$C(O)].

^{13}C NMR (100 MHz, $CDCl_3$) δ 218.1, 46.3, 42.3, 26.0, 17.3, 16.6, 14.1, 2.9, 2.7.

Anal. calcd. for $C_9H_{12}O$: C, 79.37; H, 8.88; Found: C, 79.02; H, 9.02.

Structure 53 : Cis-anti-cis-tricyclo[1.1.0.0.^{1,7}]decan-9-one (1e)

$C_{10}H_{14}O$

Mol. Wt.: 150.2176

Colorless oil (90%);

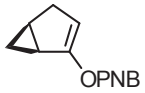
IR (neat) 1741 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.60 (dddd, *J* = 19.0, 5.8, 2.3, 1.0 Hz, 1H, CHC*H*$_{2\alpha}$HC(O)), 2.43 (m, 1H, C*H*$_{3\alpha}$HC(O)), 2.24 (d, *J* = 19.0 Hz, 1H, CH*H*$_{3\beta}$C(O)), 2.20 (d, *J* = 19.0 Hz, 1H, CHCH*H*$_{2\beta}$C(O)), 1.95 (m, 2H, C*H*HCCH$_2$C(O) and C*H*HCHCHCH$_2$C(O)), 1.81 (m, 1H, CH*H*CCH$_2$C(O)), 1.55 (m, 1H, CH*H*CHCHCH$_2$C(O)), 1.47 (m, 1H, C*H*HCH$_2$C), 1.28 (m, 1H,

CH*H*CH_2C), 1.17 (m, 3H, C*H*CH_2C(O) and C*H*$_2CH_2$CHCH), 0.48 (ddd, *J* = 8.0, 3.5, 2.3 Hz, 1H, C*H*CHCH_2C(O));

^{13}C NMR (100 MHz, $CDCl_3$) δ 218.7, 48.0, 42.6, 27.1, 24.6, 24.0, 23.9, 23.7, 21.6, 21.5; Anal. calcd. for $C_{10}H_{14}O$: C, 79.96; H, 9.39; Found: C, 79.07; H, 9.46.

Structure 54 : (bicyclo[3.1.0]hex-2-en-2-yl) *para*-nitro-benzoate (6a)



$C_{13}H_{11}NO_4$

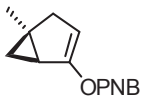
Mol. Wt.: 245.2307

beige solid (85%); m.p. 78-80°C.

Spectral data were consistent with those previously reported as compound previously named **10**.[79b]

Anal. calcd. for $C_{13}H_{11}NO_4$: C, 63.67; H, 4.52; N, 5.71; Found: C, 63.78; H, 4.41; N, 5.78.

Structure 55 : (5-methyl-bicyclo[3.1.0]hex-2-en-2-yl)*para*-nitrobenz- oate (6b)



$C_{14}H_{13}NO_4$

Mol. Wt.: 259.2573

beige solid (80%); m.p. 71-73°C.

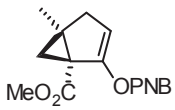
Spectral data were consistent with those previously reported as compound previously named **12a**.[79b]

Anal. calcd. for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40; Found: C, 64.79; H, 5.08; N, 5.39. Reaction run with 2% mol. $PtCl_2$ loading afforded the same yield after, nevertheless, extended reaction time.

Cycloisomerization of 1-carbomethoxy-5-methyl-hex-5-en-1-yn-3-yl) *para*-nitrobenzoate 5c:

$PtCl_2$-catalyzed cycloisomerization of precursor **5c** afforded two hardly separable regioisomeric bicyclic derivatives **6c** and **6c'**.

Structure 56 : (1-carbomethoxy-5-methyl-bicyclo[3.1.0]hex-2-en-2-yl) *para*-nitro-benzoate (6c)



$C_{16}H_{15}NO_4$

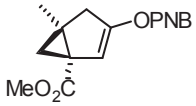
Mol. Wt.: 317.2934

beige solid (50%); M.p. 83-85°C.

Spectral data were consistent with those previously reported as compound previously named **12b**.[79b]

Anal. calcd. for $C_{16}H_{15}NO_6$: C, 60.57; H, 4.77; N, 4.41; Found: C, 60.56; H, 4.77; N, 4.21.

Structure 57 : (1-carbomethoxy-5-methyl-bicyclo[3.1.0]hex-2-en-3-yl) *para*-nitro-benzoate (6c')



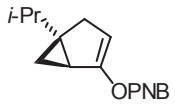
$C_{16}H_{15}NO_4$

Mol. Wt.: 317.2934

beige oil (10%):

^{1}H NMR (200 MHz, $CDCl_3$) δ 8.24 (m, 4H, arom.), 6.08 (m, 1H, CH=), 3.73 (s, 3H, OMe), 2.81 (m, 2H, CH_2C=), 1.75 (d, *J* = 4.2 Hz, 1H, C*H*H), 1.46 (s, 3H, Me), 1.01 (d, *J* = 4.2 Hz, 1H, CH*H*).

Structure 58 : [5-(iso-propyl)-bicyclo[3.1.0]hex-2-en-2-yl]*para*-nitro-benzoate (6d)



$C_{16}H_{17}NO_4$

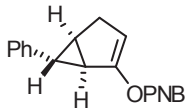
Mol. Wt.: 287.3105

yellow solid (83%).

Spectral data were consistent with those previously reported as compound previously named **A1**.[79b]

Anal. calcd. for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88; Found: C, 66.79; H, 6.01; N, 4.91.

Structure 59 : (6-phenyl-bicyclo[3.1.0]hex-2-en-2-yl)*para*-nitro-ben-zoate (6e)



$C_{19}H_{15}NO_4$

Mol. Wt.: 321.3267

beige solid (86%); m.p. 95-97°C.

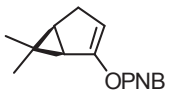
IR (neat) 3120, 3090, 3070, 3030, 1737, 1647, 1604, 1525, 1251 cm^{-1}.

Spectral data were consistent with those previously reported as compound previously named **11**.[79b]

Anal. calcd. for $C_{19}H_{15}NO_4$: C, 71.02; H, 4.71; N, 4.36; Found: C, 71.19; H, 4.53; N, 4.26.

Cycloisomerization of (6-methyl-hept-5-en-1-yn-3-yl) *para*-nitrobenzoate 5f: $PtCl_2$-catalyzed cycloisomerization of precursor **5f** afforded two inseparable regioisomeric bicyclic derivatives **6f** and **6f'**. Reaction run at 80 °C for 2h gave a **6f**/**6f'** 10/8 ratio in 70% overall yield. Reaction run at 40 °C for 30h gave a 10/3 ratio in 60% overall yield.

Structure 60 : (6,6-di-methyl-bicyclo [3.1.0]hex-2-en-2-yl) *para*-nitro-benzoate (6f)



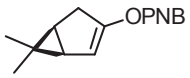
$C_{15}H_{15}NO_4$

Mol. Wt.: 273.2839

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (m, 4H, arom.), 5.37 (m, 1H, CH=), 2.56 (ddd, *J* = 16.3, 7.8, 2.2 Hz, 1H, C*H*HCH=), 2.16 (m, 1H, CH*H*CH=), 1.88 (dd, *J* = 6.8, 3.3 Hz, 1H, CH-C=), 1.45 (m, 1H, C*H*CH_2), 1.14 (s, 3H, Me), 1.01 (s, 3H, Me).

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 151.0, 150.3, 135.3, 131.2, 123.8, 112.6, 34.6, 28.1, 27.7, 26.4, 21.5, 13.3.

Structure 61 : (6,6-di-methyl-bicyclo [3.1.0]hex-2-en-3-yl) *para*-nitro-benzoate (6f')



$C_{15}H_{15}NO_4$

Mol. Wt.: 273.2839

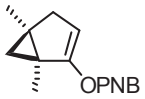
^{1}H NMR (400MHz, $CDCl_3$) δ 8.34 (m, 4H, arom.), 5.61 (m, 1H, CH=), 2.82 (dd, *J* = 17.6, 8.3 Hz, 1H, C*H*H-C=), 2.35 (m, 1H, CH*H*-C=), 1.66 (m, 1H, CH-C=), 1.27 (m, 1H, C*H*CH_2), 1.13 (s, 3H, Me), 0.99 (s, 3H, Me).

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 150.9, 150.8, 135.2, 131.2, 123.8, 115.3, 32.1, 31.6, 26.0, 24.8, 20.0, 13.3.

IR (mixture of both regioisomers) (neat) 3120, 3090, 3070, 1694 (br), 1605, 1526, 1265 cm^{-1}.

Cycloisomerization of (6-methyl-hept-6-en-2-yn-4-yl) *para*-nitrobenzoate 5g: $PtCl_2$-catalyzed cycloisomerization of precursor **5g** afforded three products: regioisomers **6g** (10%) and **9** (3%), and cyclohexa-1,3-diene **8** (50%).

Structure 62 : (1,5-di-methyl-bicyclo[3.1.0]hex-2-en-2-yl)*para* nitro-benzoate (6g)



$C_{15}H_{15}NO_4$

Mol. Wt.: 273.2839

yellow solid (10 %); m.p. 111-113°C.

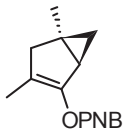
IR (neat) 3112, 3090, 3060, 1733, 1606, 1524, 1264 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 8.30 (m, 4H, arom.), 5.29 (t, *J* = 2.4 Hz, 1H, CH=), 2.49 (dd, *J* = 17.1, 2.4 Hz, 1H, C*H*HCH=), 2.38 (dd, *J* = 17.1, 2.4 Hz, 1H, CH*H*CH=), 1.25 (s, 3H, Me), 1.18 (s, 3H, Me), 0.62 (d, *J* = 3.8 Hz, 1H, C*H*HC), 0.55 (d, *J* = 3.8 Hz, 1H, CH*H*C).

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 155.2, 150.7, 135.1, 131.0, 123.6, 108.3, 38.2, 30.6, 28.0, 24.6, 18.4, 12.2.

Anal. calcd. for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13; Found: C, 65.73; H, 5.56; N, 4.74.

Structure 63 : (3,5-di-methyl-bicyclo[3.1.0]hex-2-en-2-yl) *para*-nitro-benzoate (9)



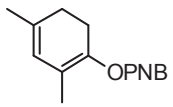
$C_{15}H_{15}NO_4$

Mol. Wt.: 273.2839

(3%):

^1H NMR (200 MHz, $CDCl_3$) δ 8.30 (m, 4H, arom.), 2.38 (m, 2H, CH_2C(Me)=), 1.70 (m, 1H, CH), 1.53 (s, 3H, C(Me)=), 1.31 (s, 3H, CMe), 0.82 (m, 1H, C*H*HCH), 0.56 (m, 1H, CH*H*CH).

Structure 64 : (2,4-di-methyl-cyclohexa-1,3-dien-1-yl)*para*-nitrobenzoate (8)



$C_{15}H_{15}NO_4$

Mol. Wt.: 273.2839

yellow solid (50%); m.p. 113-115°C.

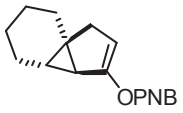
IR (neat) 3120, 3077, 1721, 1609, 1608, 1529 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 9.1 Hz, 2H, arom.), 8.25 (d, *J* = 9.1 Hz, 2H, arom.), 5.54 (m, 1H, CH=), 2.84 (bs, 4H, CH_2CH_2), 1.67 (s, 6H, Me and Me); ^{1}H NMR (400MHz, C_6D_6) δ 7.77 (d, *J* = 8.8 Hz, 2H, arom.), 7.69 (d, *J* = 8.8 Hz, 2H, arom.), 5.41 (m, 1H, CH=), 2.77 (m, 2H, C*H*$_2$CH$_2$), 2.54 (m, 2H, CH$_2$C*H*$_2$), 1.44 (s, 6H, Me and Me).

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 150.6, 145.7, 135.3, 130.9, 123.5, 122.7, 122.0, 112.2, 33.7, 33.1, 18.4, 17.9; ^{13}C NMR (100 MHz, C_6D_6) δ 162.9, 150.7, 146.4, 135.2, 130.9, 123.5, 122.8, 122.3, 112.3, 34.0, 33.4, 18.4, 17.9.

Anal. calcd. for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13; Found: C, 65.75; H, 5.39; N, 4.88.

Structure 65 : Cis-anti-cis-tricyclo[1.1.0.0.^{1,7}]decan-9-one (6h)



$C_{17}H_{17}NO_4$

Mol. Wt.: 299.3212

yellow solid (85 %); m.p. 161-163°C.

IR (neat) 3120, 3090, 3070, 1730, 1649, 1605, 1268, 1253 cm^{-1}.

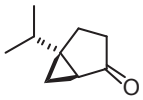
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (m, 4H, arom.), 5.16 (m, 1H, CH=), 2.48 (dt, *J* = 17.2, 2.8 Hz, 1H, C*H*$_{3\beta}$HCH=), 2.40 (d, *J* = 17.2 Hz, 1H, CH*H*$_{3\alpha}$CH=), 1.97 (m, 2H, C*H*HCCH$_2$ and C*H*HCHCH), 1.83 (m, 1H, CH*H*CCH$_2$), 1.60 (m, 2H, CHC= and CH*H*CHCH), 1.44 (m, 1H, C*H*HCH$_2$CHCH), 1.25 (m, 2H, C*H*$_2$CH$_2$C), 1.13 (m, 1H, CH*H*CH$_2$CHCH), 0.90 (dt, *J* = 7.6, 2.3 Hz, 1H, CH2C*H*CH).

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 153.9, 150.6, 135.1, 131.0, 123.6, 108.8, 39.0, 31.9, 28.2, 28.1, 26.3, 24.2, 22.2, 21.9.

Anal. calcd. for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.72; N, 4.68; Found: C, 68.52; H, 5.69; N, 4.46.

Sabinaketone 10 synthesis: basic hydrolysis. 20 mL of a 2N NaOH was poured on compound **6d** (200 mg, 0.70 mmol, 1.0 eq.) and the resulting mixture was vigorously stirred at r.t.. After completion, the reaction was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated *in vacuo*. Purification was achieved by flash chromatography on silica gel (PE/Et_2O gradient) to afford pure **Sabinaketone 10**.

Structure 66 : Sabinaketone (10)



$C_9H_{14}O$

Mol. Wt.: 138.2069

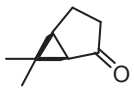
Spectroscopic data were consistent with those reported in the literature.[127]

91 mg, 95%.

IR (neat) 1725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.07 (m, 2H), 1.93 (m, 2H), 1.62 (dd, *J* = 9.2 ,3.2 Hz, 1H), 1.53 (hept, *J* = 6.8 Hz, $1H_4$), 1.15 (dd, *J* = 9.2, 4.5 Hz, 1H), 1.03 (dd, *J* = 4.5, 3.2 Hz, 1H), 0.94 (d, *J* = 6.8 Hz, $3H_5$), 0.90 (d, *J* = 6.8 Hz, $3H_5$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.3, 39.7, 33.9, 33.3, 32.4, 23.7, 19.7, 19.5, 19.3. Calculated yield from 1,5-enyne **5d** is 79% for two steps.

Basic hydrolysis of regioisomers 6f/6f': basic hydrolysis (2N NaOH, see procedure used for the synthesis of **Sabinaketone**) of a 10/8 ratio **6f/6f'** mixture afforded previously described ketones **7f**[126] and **7f'**[127] in the same 10/8 previous ratio.

Structure 67 : 6,6-di-methyl-bicyclo[3.1.0]hexan-2-one (7f)

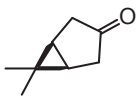


$C_8H_{14}O$

Mol. Wt.: 124.1804

^1H NMR (200 MHz, $CDCl_3$) δ 2.26-1.86 (m, 5H), 1.63 (m, 1H), 1.14 (s, 3H, Me), 1.10 (s, 3H, Me). Spectroscopic data were consistent with those reported in the literature.[126]

Structure 68 : 6,6-di-methyl-bicyclo[3.1.0]hexan-3-one (7f')



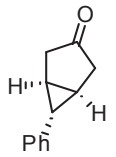
$C_8H_{14}O$

Mol. Wt.: 124.1804

[127] Mash, E. A.; Nelson, K. A. *Tetrahedron* **1987**, *43*, 679-692 and references cited therein.

^{1}H NMR (200MHz, $CDCl_3$) δ 2.57-1.86 (m, 4H), 1.28 (m, 2H), 1.06 (s, 3H, Me), 0.85 (s, 3H, Me). Spectroscopic data were consistent with those reported in the literature.[127]

Structure 69 : (1R,5S,6r)-6-phenylbicyclo[3.1.0]hexan-3-one



$C_{12}H_{12}O$

Mol. Wt.: 172.2231

A solution of (*E*)-tert-butyldimethyl(6-phenylhex-5-en-1-yn-3-yloxy)silane (**26**, 137mg, 0.47 mmol) in 1 mL of DCM was added to a mixture of preformed gold catalyst (6.3 mg, 3 mol %) and $AgSbF_6$ (4.5 mg, 3 mol %).After completion, the solvent was evaporated *in vacuo*. Purification was achieved by flash chromatography on silica gel (PE/Et_2O gradient) to afford:

Colorless oil, (29%)

^{1}H NMR (400MHz, $CDCl_3$) δ 7.30-7.04 (m, 5H), 2.75-2.35 (m, 2H), 1.91-1.89 (m, 2H), 1.48-1.44 (m, 1H).

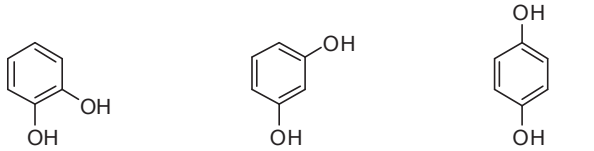
^{13}C NMR (100 MHz, $CDCl_3$) δ 210.0, 141.2, 128.6, 126.1, 125.6, 41.4, 31.7, 24.3.

III. Synthesis of functionalized resorcinols from 1,4-enyne esters by rhodium-catalyzed [5+1] cycloadditions reaction

III. 1. Background

III. 1. 1. Importance of the resorcinol skeleton

Polyphenols derivatives are of particular importance in medicinal chemistry as they are known for their antioxidant and antitumor preventive effects.[128] Diol derivatives constitute a particular class of polyphenols. In the case of non functionalized diols, three types of substitutions are possible where the hydroxyl groups can be in the *ortho*-, *meta*- or *para*- position (Scheme III-1). The corresponding structures are respectively 1,2-dihydroxybenzene (also named catechol), 1,3-dihydroxybenzene (also named resorcinol) and 1,4-dihydroxybenzene (also named hydroquinone). In our study, we focused our attention to resorcinol derivatives.



Scheme III-1: dihydroxybenzenes

III. 1. 1. a. Resorcinolic lipids

Most natural resorcinols are substituted in the 5-position (Scheme III-2). For example, Moracin M was extracted from an African tree named Iroko.[129] Interestingly, parts of its wood are directly employed as curative drug and fungicide in ethnomedicine. 5-Alkylresorcinols known as

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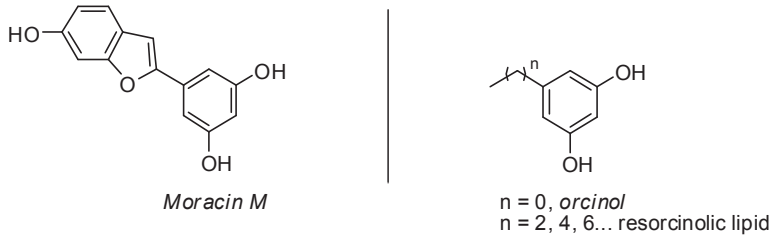
[128] For selected recent examples, see: Chen, K.-C.; Hsieh, C.-L.; Huang, K.-D.; Ker, Y.-B.; Chyau, C.-C.; Peng, R. Y. *J. Agric. Food Chem*. **2009**, *57*, 6114. Chew, Y.-L.; Goh, J.-K.; Lim, Y.-Y. *Food Chem*. **2009**, *116*, 13. Castillo-Pichardo, L.; Martínez-Montemayor, M. M.; Martínez, J. E.; Wall, K. M.; Cubano, L. A.; Dharmawardhane, S. *Clin. Exp. Metastasis* **2009**, *26*, 505.

[129] Kapche, G. D.; Watto-teguo, P.; Massip, S.; Guillon, J.; Vitrac, C.; Krisa, S.; Ngadjui, B.; Merillon, J.-M. *Anal. Sci.* **2007**, *23*, 59.

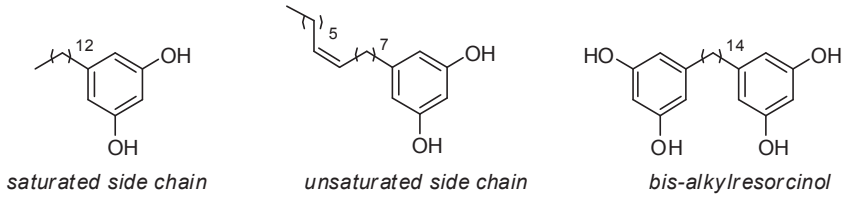
resorcinolic lipids are also commonly isolated from plants (like cereal grains or fruits)[130] but rarely isolated from microbial or animal organisms.[131]



Scheme III-2: 5-substituted resorcinols

III. 1. 1. b. Biosynthesis of resorcinols

5-Alkylresorcinols with various side chains can be isolated from one plant (Scheme III-3). Several compounds were isolated from a western Australia shrub: *Hakea trifurcate*. The hydrophobic chain of the resorcinol derivatives can be constituted of one or several insaturations, and the saturated alkyl chains generally possess an odd-numbered amount of carbons. All these observations were taken into consideration for the discussion of biosynthetic pathway.



Scheme III-3: lipid resorcinols issued from *Hakea trifurcate*

The biosynthesis of resorcinolic lipids is postulated to occur in the cells *via* the polyketide pathway. The mechanism would involve the cyclization of an acyclic precursor, the elongation of the side chain (two carbons at a time) and a final decarboxylation that would give odd-numbered carbonated side chains.

III. 1. 1. c. Organic synthesis of resorcinols

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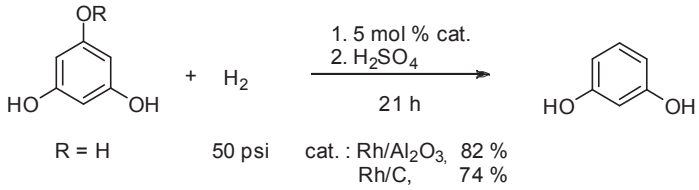
[130] Resorcinols in: (a) **cereals**, see: Seitz, L. M. *J. Agric. Food Chem.* **1992**, *40*, 1541, Ross, A. B.; Shepherd, M. J.; Schupphaus, M.; Sinclair, V.; Alfaro, B.; Kamal-Eldin, A.; Aman, P. *J. Agric. Food Chem.* **2003**, *51*, 4111 (b) **mango** peels, see: Knödler, M.; Reisenhauer, K.; Schieber, A.; Carle, R. *J. Agric. Food Chem.* **2009**, *57*, 3639 (c) **mushrooms**, see: Jin, W.; Zjawiony, J. K. *J. Nat. Prod.* **2006**, *69*, 704.

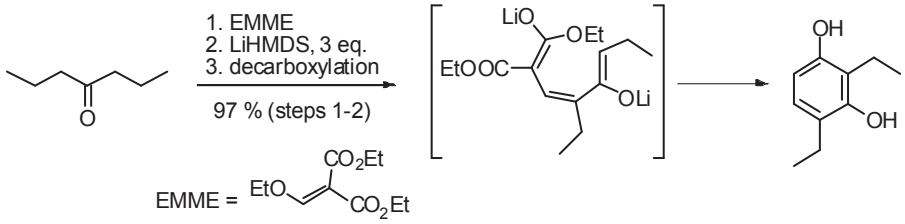
[131] Nowak-Thompson, B.; Hammer, P. E.; Hill, D. S.; Stafford, J.; Torkewitz, N.; Gaffney, T. D.; Lam, S. T.; Molnar, I.; Ligon, J. M. *J. Bacteriol.* **2003**, *185*, 860.

Synthetically, resorcinols are often prepared from a precursor with an aromatic skeleton, by hydroxylation of phenols.[132] In 2002, a deoxygenation approach was also proposed by Frost and co-worker where concomittant catalyzed-hydrogenation and acidic treatment of polyhydroxybenzenes led to hydroquinones and resorcinols.[133] It should be noted that phloroglucinol methyl ether (R = Me) is biosynthesized from glucose and also afforded resorcinol in 80 % yield. (Scheme III-4).



Scheme III-4: Preparation of resorcinols by deoxyganation approach

Synthesis of symmetric 2,4-dialkyl resorcinols was achieved by Ceglia and co-workers starting from acyclic material (malonates and ketones). In this reaction, a sequential addition of an excess of base (a total of 3 equivalents at least) would provide a dianion that would directly cyclized onto the corresponding aromatic via C-acylation (Scheme III-5).[134]



Scheme III-5: Preparation of resorcinols by aldolic condensation

III. 1. 2. Metal-catalyzed double carbonylation: a tool for the synthesis of aromatic compounds

Our interest was the development of an easy-to-handle method for the preparation of resorcinols. We aimed to obtain a general method for the synthesis of non-symmetric and diversely substituted resorcinols using acyclic molecules as precursors. We then started to investigate transition-metal-catalyzed carbonylations reactions, some of which have already been reported to afford catechols and dihydroquinones.

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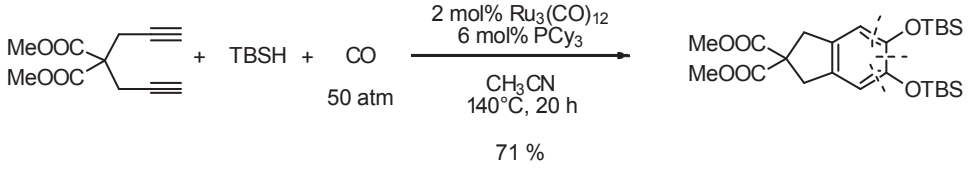
[132] (a) Gesson, J.-P.; Jacquesy, J.-C.; Jouannetaud, M.-P. *J. Chem. Soc., Chem. Commun.* **1980**, 1129 (b) Green, K. *J. Org. Chem.* **1991**, *56*, 4326 (c) Kim, A.; Powers, J. D.; Toczko, J. F. *J. Org. Chem.* **2006**, *71*, 2170.
[133] Hansen, C. A.; Frost, J. W. *J. Am. Chem. Soc*. **2002**, *124*, 5926.
[134] Ceglia, S. S.; Kress, M. H.; Nelson, T. D.; McNamara, J. M. *Tetrahedron lett.* **2005**, *46*, 1731.

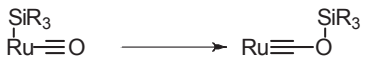
III. 1. 2. a. Synthesis of catechols derivatives

Murai and co-workers reported that ruthenium-catalyzed carbonylation of diynes with hydrosilanes yielded catechols derivatives (Scheme III-6).[135] An excess of hydrosilane was placed in the presence of 1,6-diynes and ruthenium catalyst under 50 atm of CO. A double carbonylation reaction gave rise to various catechol derivatives in good yields.



Scheme III-6: preparation of ring-fused catechol derivatives

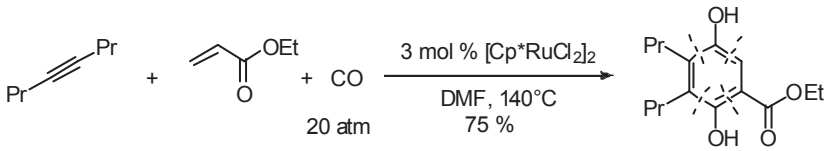
In order to explain the position of the silyl group in the final product, the authors postulated a new way for the incorporation of CO which implies an oxycarbyne complex (Scheme III-7).



Scheme III-7: non-classical CO incorporation

III. 1. 2. b. Synthesis of hydroquinone derivatives

Recently Mitsudo, Ryu and co-workers reported a ruthenium-catalyzed carbonylation (Scheme III-8). Cycloaddition of alkynes and alkenes with incorporation of two molecules of CO afforded hydroquinones (Scheme III-8).[136] Several electron-deficient alkenes were cyclized with octyne and gave rise to diversely substituted hydroquinones in good yield.



Scheme III-8: preparation of functionalized hydroquinones

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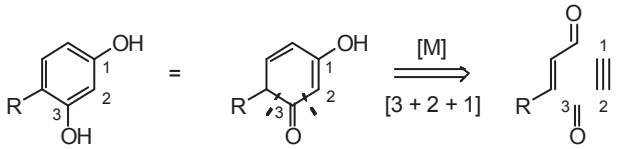
[135] Chatani, N.; Fukumoto, Y.; Ida, T.; Murai, S. *J. Am. Chem. Soc*. **1993**, *115*, 11614.
[136] Fukuyama, T.; Yamaura, R.; Higashibeppu, Y.; Okamura, T.; Ryu, I.; Kondo, T.; Mitsudo, T.-A. *Org. Lett*. **2005**, *7*, 5781.

III. 1. 2. c. What about the synthesis of resorcinol derivatives?

We set out to investigate a new method for the preparation of resorcinols based on metal-catalyzed carbonylation that has, to the best of our knowledge, never been reported so far for the preparation of these compounds. In our approach, we envisaged the resorcinolic skeleton in an enolic form, so we aimed at the synthesis of a cyclohexadienone (Scheme III-9). In our multicomponent strategy, we hypothesized a [3 + 2 + 1] cocyclization with an alkyne, an alkene and carbon monoxide that would imply the 1,2-migration of the "oxygen".



Scheme III-9: [3 + 2 + 1]-multicomponent reacion

Before going into details, selected reports of metal-assisted mutlicomponents reactions that involve carbon monoxide will be outlined. All the synthetic transformations presented below, deal with rhodium catalysts. Indeed, this is an efficient metal for [5 + 2], [6 + 2] or [5 + 2 + 1] cycloadditions,[137] and as presented later, $[RhCl(CO)_2]_2$ is the rhodium dimer that we used for the preparation of resorcinols.

III. 1. 3. Cycloaddition reactions

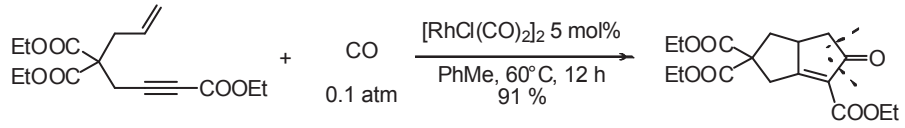
Metal-assisted multicomponent reactions are a powerful and useful tool in synthetic chemistry. They enable the rapid elaboration of complex structures, and several transformations in a single manipulation. Carbonylative cycloadditions represent an important class of these reactions for the synthesis of hetero- and polycyclic compounds.

---

[137] See: (a) Wender, P. A.; Croatt,, M. P.; Deschamps, M. *J. Am. Chem. Soc*. **2004**, *126*, 5946 (b) Wender, P. A.; Gamber, G. G.; Hubbard, R. D.; Pham, S. M.; Zhang, L. *J. Am. Chem. Soc*. **2005**, *127*, 2836 (c) Wender, P.A.; Takahashi, H.; Witulski, B. *J. Am. Chem. Soc*. **1995**, *117*, 4270.

III. 1. 3. a. Catalyzed Pauson-Khand reaction

Alkynes, olefins and carbon monoxide are maybe the more used components in metal-mediated organic synthesis.[138] The most famous example is probably the Pauson-Khand reaction which involves the coupling of these entities to give a cyclopentenone framework. Since the discovery of this cobalt-mediated cyclization in the early 1970s, other transition-metal reagents were demonstrated efficient for this transformation, and more particularly, in a catalytic fashion. For example, Narasaka and co-workers revealed that electron deficient alkenes and alkynes in the presence of 5 mol% of rhodium catalyst yielded [3.3.0]-cyclooctenones (Scheme III-10).[139]



Scheme III-10: Rhodium-catalyzed Pauson-Khand reaction

Except the notorious [2 + 2 + 1] cycloadditions for the synthesis of cyclopentenones (alkene an alkyne partners) and cyclopentadienones (two alkenes partners)[140], [m + n +….+ 1] processes with carbon monoxide are poorly reported in the literature. The following paragraph will briefly deal with selected original reports for these reactions.

III. 1. 3. b. Tandem ring expansion and cycloaddition

In 2002, Wender and co-workers reported the first transition metal-catalyzed [5 + 2 + 1] cycloadditions which consists in a three components reaction between vinylcyclopropanes, electron-deficient alkyne and carbon monoxide (Scheme III-11).[141] Bicyclo[3.3.0]octenones were obtained in good to high yields. Wender's group has developed in the middle of the 1990s the [5 + 2] cycloadditions with vinylcyclopropanes.[137c] Based on this previous work, the authors postulated that an intermediate of [5 + 2] cycloadditions can be intercepted by carbon monoxide to give rise to

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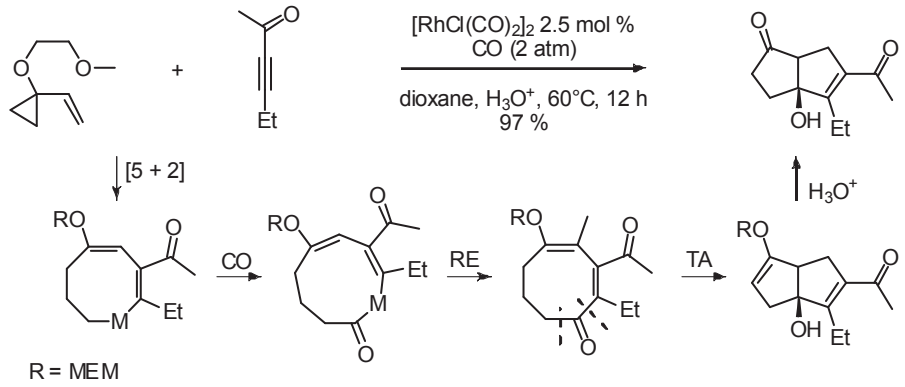
[138] For recent reviews, see: (a) Gibson, S. E.; Stevenazzi, A. *Angew. Chem. Int. Ed*. **2003**, *42*, 1800 (b) Gibson, S. E.; Mainolfi, N. *Angew. Chem. Int. Ed*. **2005**, *44*, 3022.
[139] Kobayashi, T.; Koga, Y.; Narasaka, K. *J. Organomet. Chem*. **2001**, *624*, 73.
[140] Schore, N. E. *Chem. Rev*. **1988**, *88*, 1081.
[141] Wender, P. A.; Gamber, G. G.; Hubbard, R. D.; Zhang, L. *J. Am. Chem. Soc*. **2002**, *124*, 2876.

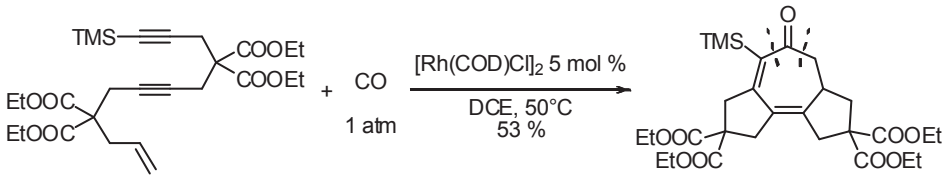
a cyclooctadienone after reductive elimination (RE) of the metal. A subsequent transannular closure (TA) of the eight-membered ring intermediate would lead to the bicyclo[3.3.0]octenones.



Scheme III-11: [5 + 2 + 1] cycloadditions with mechanistic hypothesis

III. 1. 3. c. Dienyne cyclization

When a substrate possesses several insaturations, there is the possibility to initiate a tandem cyclization.[142] In 2005, Ojima and co-workers discovered a novel intramolecular [2 + 2 + 2 + 1]-carbonylative cycloaddition reaction of polyunsaturated compounds catalyzed by rhodium complex.[143] This process was reported to afford 5-7-5 fused tricyclic compounds starting from enediynes (Scheme III-12). A side-product which corresponds to the non incorporation of carbon monoxide was sometimes formed as minor compound. This interesting rhodium-catalyzed tandem cyclization provided a broad range of functionalized tricylic compounds.

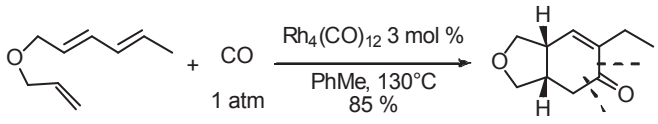


Scheme III-12: cascade reaction for the synthesis of 5-7-5 fused tricyclic skeleton

III. 1. 3. d. Triene cyclization

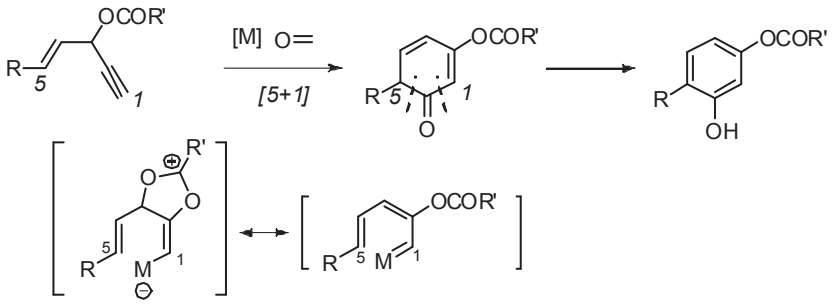
[142] For recent reviews about trimerization, see: (a) Saito, S.; Yamamoto, Y. *Chem. Rev*. **2000**, *100*, 2901 (b) Shibata, T.; Tsuchikama, K. Org. Biomol. Chem. 2008, 6, 1317.
[143] Bennacer, B.; Fujiwara, M.; Lee, S.-Y.; Ojima, I. *J. Am. Chem. Soc*. **2005**, *127*, 17763.

In 2004, Chung and co-workers reported the first transition metal-catalyzed carbonylative cycloadditions of triene (Scheme III-13).[144] This rhodium-catalyzed [3 + 2 + 1] reaction of trienes afforded bicyclic cyclohexenones in good yields. It is noteworthy that with optimized conditions, there was no competition between the non-carbonylated products and the bicyclic cyclohexenones.



Scheme III-13: preparation of bicyclic cyclohexenones

In the same manner, we envisaged to intercept the cyclization course of 1,4-enyne esters with carbon monoxide. Indeed, palladium or gold-catalyzed cyclization of 1,4-enyne esters involves the 1,2-acetate migration (known as Rautenstrauch rearrangement, already detailed in chapter II). In our approach, we challenged to intercept a putative carbenic species with carbon monoxide (Scheme III-14). We also envisaged to take advantage of the Rautenstrauch rearrangement of the enyne ester to prepare 1,3-hydroxypivalate resorcinols. With such substrate, a single incorporation of CO would allow the synthesis of the desired resorcinols.



Scheme III-14: synthetic strategy

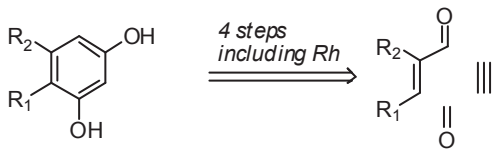
The work presented here results from collaboration between Malacria and Ryu groups.

[144] Lee, S. I.; Park, J. H.; Chung, Y. K.; Lee, S. G. *J. Am. Chem. Soc*. **2004**, *126*, 2714.

III. 2. Submitted article

III. 2. 1. Abstract

An unprecedented method towards the synthesis of resorcinol derivatives is described. The key-step involves a [5+1] rhodium-cycloaddition of carbon monoxide and 1,4-enyne pivalate, featuring an Ohloff-Rautenstrauch rearrangement of a pivalate moiety. This straightforward synthesis of resorcinol is formally a multicomponent cycloaddition between an enal, an acetylene and carbon monoxide (Scheme III-15). Subsequent saponification gives rise to potentially bioactive lipid resorcinols.



Scheme III-15

Key Words: resorcinol derivatives, [3+2+1] rhodium-cycloaddition, lipid resorcinols.

III. 2. 2. Introduction

For the past two decades, metal-catalyzed 1,*n*-enyne rearrangements have proven to be an exquisite method for access to a wide variety of carbo- and heterocyclic systems.[145] While the parent cycloisomerization mode of reactivity has thoroughly demonstrated its synthetic potential, the introduction of intermolecular events such as carbonylation,[146] and other

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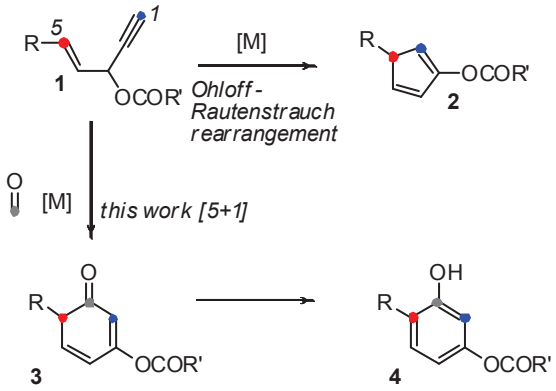
[145] For recent reviews see: (a) C. Aubert, O. Buisine, M. Malacria *Chem. Rev.* **2002**, *102*, 813. (b) Michelet, V.; Toullec, P. Y.; Genêt, J.-P. *Angew. Chem. Int. Ed.* **2008**, *47*, 4268.

[146] (a) *Modern Carbonylation Method,* Kollár, L. Ed., Wiley-VCH, Weinheim, 2008. (b) Fukuyama, T.; Ryu, I. Carbon Monoxide, *e-eros, Encyclopedia of Reagents for Organic Synthesis,* John Wiley & Sons. DOI: 10.1002/047084289X.rc013.pub2

incorporations,[147] in the process greatly expand the scope and the value of these reactions, as demonstrated by recent examples of the higher order variants of the intramolecular Pausond-Khand reaction.[148] In this context, we focused our attention on the known Ohloff-Rautenstrauch rearrangement,[149] which originally consisted of the Pd(II)- or the Pt(II)-catalyzed rearrangement of 1-ethynyl-2-propenyl acetates **1** to give cyclopentadienyl acetates **2** (Scheme III-16, eq 1). We anticipated that under carbonylation conditions with the proper metal complex, CO might be intercepted to give transient **3,** which would eventually lead to the aromatic system of resorcinols **4** (Scheme III-16, eq 2).



Scheme III-16

To the best of our knowledge, this transformation of enyne acetates into aromatics based on a metal-catalyzed [5+1] carbonylative sequence has no precedent.[150] In addition, resorcinols are valuable compounds with important bioactivity,[151] demonstrating, for instance, efficient DNA cleavage properties under oxidative conditions, as well as antibacterial activities.[152] We initiated our study with precursor **1a** in the hope of obtaining 4-phenyl substituted resorcinol derivative **4a**.

---

[147]Selected examples with butadiene: (a) Baik, M.-H.; Baum, E. W.; Burland, M. C.; Evans, P. A. *J. Am. Chem. Soc.* **2005**, *127*, 1602. (b) Gilbertson, S. R.; DeBoef, B. *J. Am. Chem. Soc.* **2002**, *124*, 8784. With carbenes: (c) Ni, Y.; Montgomery, J. *J. Am. Chem. Soc.* **2006**, *128*, 2609. (d) Monnier, F.; Vovard-Le Bray, C.; Castillo, D.; Aubert, C.; Dérien, S.; Dixneuf, P. H.; Toupet, L.; Ienco, A.; Meali, C. *J. Am. Chem. Soc.* **2007**, *129*, 6037.

[148] (a) see ref. 137(b) and (b) see ref .143.

[149] (a) Strickler, H.; Davis, J. B.; Ohloff, G. *Helv. Chim. Acta* **1976**, *59*, 1328. (b) Rautenstrauch, V. *J. Org. Chem.* **1984**, *49*, 950. (c) Mainetti, E.; Mouriès, V.; Fensterbank, L.; Malacria, M.; Marco-Contelles, J. *Angew. Chem. Int. Ed.* **2002**, *41*, 2132. (d) Shi, X.; Gorin, D. J.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 5802. Also see a review: (e) Marion, N.; Nolan, S. P. *Angew. Chem. Int. Ed.* **2007**, *46*, 2750.

[150] For Pd-catalyzed cyclocarbonylation of enynols leading to 6-membered ring lactones, see: Cao, H.; Xiao, W. J.; Alper, H. *J. Org. Chem.* **2007**, *72*, 8562.

[151] For a recent review, see: Kozubek, A. *Chem. Rev.* **1999**, *99*, 1.

[152] For DNA cleavage, see: (a) Lytollis, W.; Scannel, R. T.; An, H.; Murty, V. S.; Sambi Reddy, K.; Barr, J. R.; Hecht, S. M. *J. Am. Chem. Soc.* **1995**, *117*, 12683. For antibacterial properties, see: (b) Himejima, M.; Kubo, I. *J. Agric. Food Chem.* **1991**, *39*, 418.

III. 2. 3. Results and discussion

Incorporation of carbon monoxide was examined in the presence of a variety of transition metal catalysts for the envisaged [5 + 1]-type cycloaddition reaction. By using gold and platinum salts, 1,4-enyne pivalate **1a** was respectively recovered or converted to cyclopentone **5a**[5d] (Table 1, entries 1-2).[153,154] We were then pleased to find that rhodium catalysis[155] could lead to the desired carbonylated compound (entries 3-4). However, in these cases, either conversion was not sufficient (entry 3) or cyclopentenone **5a** was formed as a byproduct (entry 4).[156] The yield was slightly increased with $[RhCl(CO)_2]_2$ catalyst (entry 5) and the reaction was selective towards biphenyl adduct **4a** in 76% yield when replacing toluene with dichloromethane (entry 6).

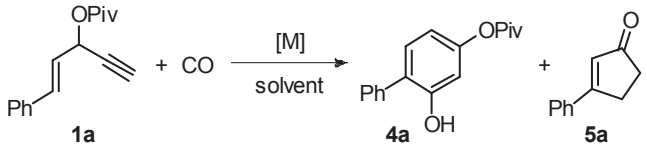
[153] Although insertion of CO in Pt-alkyl bonds has been reported: (a) Sivaramakrishna, A.; Makhubela, B. C. E.; Zheng, F.; Su, H.; Smith, G. S.; Moss, J. R. *Polyhedron* **2008**, *27*, 44. It has also been proposed as a ligand of $PtCl_2$ that increases the electrophilic character of the metal center, see: (b) Fürstner, A.; Davies, P. W.; Gress, T. *J. Am. Chem. Soc.* **2005**, *127*, 8244.

[154] For Pd(II)-catalyzed oxidative carbonylation, see: (a) Bacchi, A.; Costa, M.; Gabriele, B.; Pelizzi, G.; Salerno, G. *J. Org. Chem.* **2002**, *67*, 4450. (b) Kato, H.; Teraguchi, R.; Yamamura, S.; Mochida, T.; Akita, H.; Peganova, T. A.; Vologdin, N. V.; Gusev, O. V. *Synlett* **2007**, 638.

[155] Modern Rhodium-Catalyzed Organic Reactions, Ed. Evans, P. A. Wiley-VCH, Weinheim, 2005.

[156] Cyclopentenone **5a** results from an isomerized cyclopentadienyl pivaloate already observed by Toste and co-workers (see ref. 5d).

Table III-1. Optimization of the catalysts for [5+1] cycloaddition[a]



1a **4a** **5a**

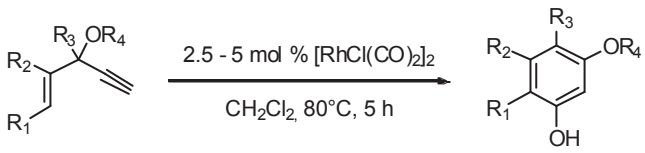
entry	cat.	solvent	CO (atm)	products[b]
1	AuCl (2 mol%)	PhMe	45	NR
2	$PtCl_2$ (5 mol%)	PhMe	50	**5a** 70%
3	$[Rh(CH_3COO)_2]_2$ (2.5 mol%)	PhMe	50	**4a** 30%[c]
4	$[RhCl_2Cp^*]_2$ (2.5 mol%)	PhMe	50	**4a** 40% + **5a** 30%
5	$[RhCl(CO)_2]_2$ (2.5 mol%)	PhMe	50	**4a** 45% + **5a** traces
6	$[RhCl(CO)_2]_2$ (2.5 mol%)	DCM	80	**4a** 76%

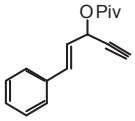
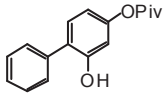
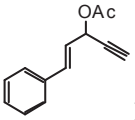
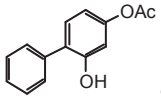
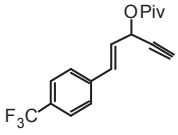
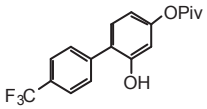
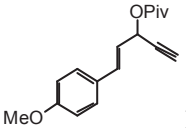
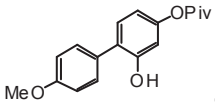
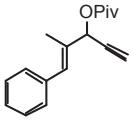
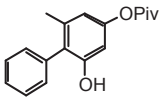
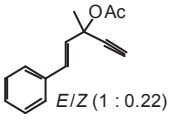
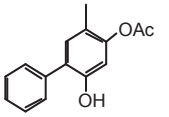
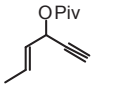
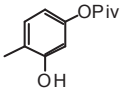
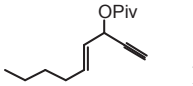
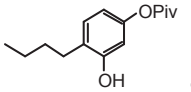
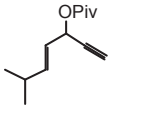
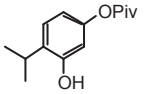
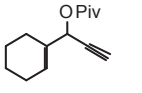
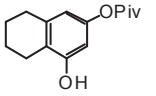
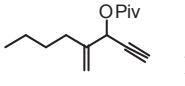
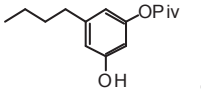
[a]Reactions were performed on a 0.5 mmol scale with 0.05M of substrate concentration for 5 h at 80 °C. [b]Yields refer to isolated yields. [c] Recovery of **1a**: 53%.

With the optimal reaction conditions in hand, we set out to define the scope of the present biaryl synthesis (Table 2). The cyclization was also successful when an ester group was changed from pivalate to acetate (entry 2). The reaction was compatible with the varying electronic effects of substituants on the aromatic ring; thus, functional groups such as trifluoromethyl (entry 3) and methoxy groups (entry 4) could be implemented. Enyne **1e**, having a 4-methyl group, also worked well to give 3-methyl-4-phenyl substituted resorcinol derivative **4e** (entry 5). Enyne **1f**, having a tertiary acetoxy unit, gave **4f** (entry 6). In this case we used **1f** as a mixture of *E/Z* (1 : 0.22). However, it turned out that the *Z* isomer was not reactive towards the carbonylative cyclization. Overall, this [5+1] type transformation could also be considered to be a highly versatile alternative method for the preparation of functionalized biaryl systems.[157] The scope and generality of this catalytic system towards the utilization of diversely alkylated enyne esters were also investigated. The results are shown in Table 2. The present catalytic system was tolerant and comparable in reactivity of 1-ethynyl-2-propenyl pivalates bearing alkyl chains. Me, *n*-Bu, and *i*-Pr substitution of alkene allowed the formation of the desired products in 54 to 64% yield (entries 7-9). Interestingly, **4h** was saponified and provided the corresponding resorcinol that has been reported to inhibit tyrosinase activity.[158] Product **4k** suggests a straightforward access to valuable lipid resorcinols[7,8] and analogues of the natural product olivetol (*n*-pentyl chain at position 5).[159]

[157] Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.
[158] Kim, D.-S.; Kim, S.-Y.; Park, S.-H.; Choi, Y.-G.; Kwon, S.-B.; Kim, M.-K.; Na, J.-I.; Youn, S.-W.; Park, K.-C. *Biol. Pharm. Bull.* **2005**, *28*, 2216.
[159] Raharjo, T. R.; Chang, W.-T.; Choi, Y. H.; Peltenburg-Looman, A. M. G.; Verpoorte, R. *Plant. Sci.* **2004**, *166*, 381.

Table III-2. $[RhCl(CO)_2]_2$-Catalyzed Synthesis of Functionalized Resorcinol Derivatives by [5+1] Cycloaddition[a]

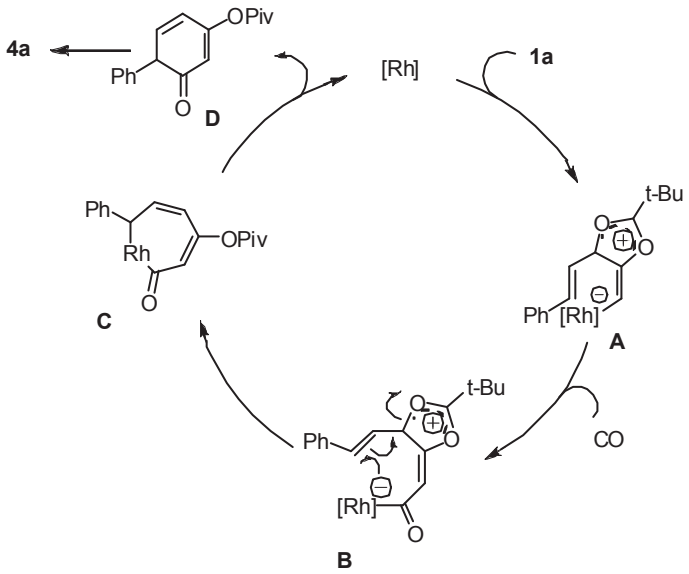


entry	Substrate **1**	CO (atm)	product **4**	yield (%)[b]
1	 **1a**	80	 **4a**	76
2	 **1b**	80	 **4b**	67
3	 **1c**	80	 **4c**	47
4	 **1d**	80	 **4d**	56
5	 **1e**	80	 **4e**	50
6	 *E*/*Z* (1 : 0.22) **1f**	50	 **4f**	68[c]
7	 **1g**	80	 **4g**	58
8	 **1h**	80	 **4h**	64
9	 **1i**	50	 **4i**	54
10	 **1j**	80	 **4j**	47
11[d]	 **1k**	70	 **4k**	37

[a]Reactions were performed on a 0.5 mmol scale in 0.05-0.016 M of dichloromethane. [b]Isolated yields by silica gel chromatography. [c]NMR yield from E isomer. [c] Reaction time: 15 h.

While a detailed mechanism awaits further study, based on our observed results we suggest a plausible reaction pathway to account for the formation of resorcinols (Scheme III-17).

We postulate that the formation of **4a** is initiated by electrophilic activation of the alkyne moiety of **1a** by the rhodium catalyst. Successive 1,2-migration of pivalate would generate the zwitterionic vinyl-rhodium species **A** that undergoes carbon monoxide insertion to afford rhoda-acyl **B**. The latter evolves into a rhodacycloheptadienone **C**,[160] then reductive elimination liberates the transient intermediate **D** and regenerates the Rh catalyst.



Scheme III-17. **Proposed Mechanistic Pathway**

III. 2. 4. conclusion

In summary, we have developped a new synthetic procedure for the efficient preparation of functionalized aromatics (resorcinols), including biaryl derivatives from readily available 1,4-enyne pivalates and CO. Further elaborations of the reaction toward target-oriented synthesis and asymmetric synthesis of biaryl derivatives are underway in our labs.

[160] It is not clear that cyclization occurs before or after carbon monoxide insertion, see also ref. 4b. Further mechanistic studies are underway.

III. 3. Further studies

We have developed a new method for the synthesis of diversely alkylated resorcinols. Although our catalytic system did not afford side-products, this method based on [5+1] rhodium-catalyzed cycloaddition yielded the products in non quantitative yields. After the presentation of the encountered limitations, in yields improvement and non-reactive precursors, the mechanism hypothesis will be discussed again.

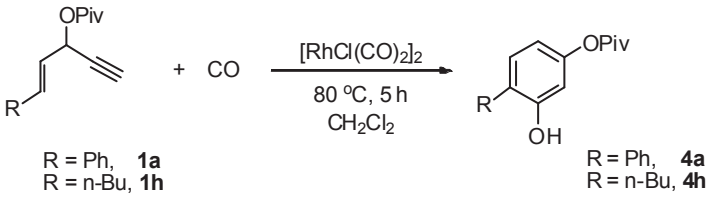
III. 3. 1. Reactions conditions and other cyclized substrate

III. 3. 1. a. Carbon monoxide pressure and catalyst load influence

Transition metal-catalyzed carbonylation are generally carried out under low carbon monoxide pressures.[161] Nevertheless, minimum pressure of 50 atm was required here to synthesize resorcinols (Table III-3).

Enyne ester **1h** was cyclized in presence of 2.5 mol % of rhodium catalyst, under 50 and 80 atm of carbon monoxide (entries 1-2). Resorcinol **4h** was respectively formed in 50 and 54 % yield. For a given amount of catalyst, yields were slightly increased by a pressure above 50 atm. On the other hand, the cyclization of enyne ester **1a** was carried out with 2.5 mol % of catalyst and 20 atm of carbon monoxide during 5 hours at 80°C (entry 3). Resorcinol **4a** was identified by NMR as the main product, but was not purified, and 5 % of non-carbonylated product **5a** was detected by GC monitoring. Below 50 atm, cyclopentenones could be formed as side-products, thus, these pressures are not recommended for this reaction.

Most reactions were carried out with 2.5 mol % of $[RhCl(CO)_2]_2$. However, sometimes yields improvements were observed with a larger amount of catalyst (entries 4-5). At 80 atm of carbon monoxide with 5 mol % of rhodium catalyst, resorcinol **4h** was prepared in 64 % yield (instead of 54 % with 2.5 mol % of catalyst). The yield augmentation was not exceptionally high but the tendency was general for all 1,4-enyne esters.



entry	R	substrate	CO	cat.	product	yield
1	*n*-Bu	**1h**	50 atm	2.5 mol %	**4h**	50 %
2	*n*-Bu	**1h**	80 atm	2.5 mol %	**4h**	54 %
3	Ph	**1a**	20 atm	2.5 mol %	**4a**	71 % [a]
4	*n*-Bu	**1h**	80 atm	2.5 mol %	**4h**	54 %
5	*n*-Bu	**1h**	80 atm	5 mol %	**4h**	64 %

[a] GC yield

Table III-3

As demonstrated above, it is not easy to increase the reaction yields. High carbon monoxide pressure and important catalyst load are necessary. We then wondered if it was possible to understand why the yields were limited, and what would be the correlation with our mechanistic hypothesis.

III. 3. 1. b. Propargylic ester and olefin substitution influences

Some precursors did not react as well as expected. In this part, these substrates and a few comments about their reactivity will be presented.

In the case of gold-catalyzed Rautenstrauch rearrangement of 1,4-enyne ester, Toste and co-workers demonstrated that for a given precursor, yield was increased by changing the ester moiety from acetate to pivalate.[149d] Although an acetate group at the propargylic position provided a good

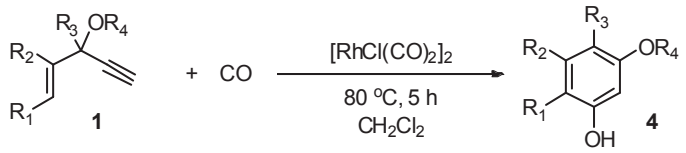
migration, we decided to mainly study the cyclization of 1,4-enyne pivalate.[162] The following table summarizes our results on the effects of the propargylic moiety and substituted olefins (Table III-4).

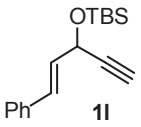
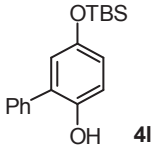
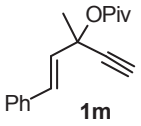
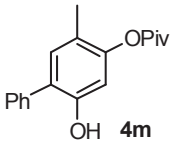
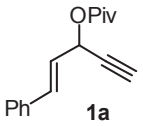
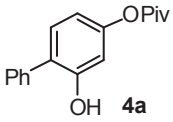
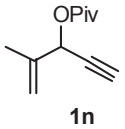
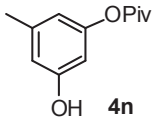
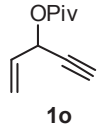
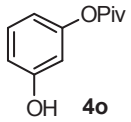
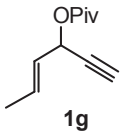
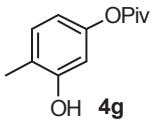
Silylated ethers are not able to undergo 1,2-shift (by comparison, 1,5-enyne ether afford [3.1.0]-bicycle *via* a hydride migration)[163], we then wondered what would happen if silylated enyne ether **1l** was submitted to [5+1]-cycloaddition conditions. When enyne **1l** was engaged with rhodium catalyst under 50 atm of CO, starting material was not consumed (entry 1). In the same way, when the reaction was carried out without carbon monoxide pressure, it did not give rise to the expected cyclopentenone. This would mean in this case that the migration of the hydrogen does not occur for 1,4-enyne ethers that remain unreacted,with rhodium catalyst.

Enyne pivalate **1m** which resulted from esterification of a tertiary enynol was, as expected, difficult to prepare. The whole amount of precursor was engaged for one experiment of cycloaddition and afforded resorcinol **4m** in 62 % yield (entry 2). The oxocarbenium (**A**, Scheme III-17) would be stabilized by the methyl group, and yield **4m** in mild conditions.[164] For comparison, secondary ester **1a** yielded resorcinol **4a** in 59 % yield in strictly same conditions (entry 3). Consequently, 1,2-migration of the ester moiety plays an important role in the completion of this reaction.

The substitution of the double bond and its subsequent role in the course of the reaction were studied. In fact, yields of this transformation greatly depended on the substitution of the vinyl pivalate moiety (entries 4 – 5). High temperature and long reaction time were necessary to afford resorcinol **4n** and **4o** in 23 and 38 % yield respectively. In these cases, starting material was poorly converted into resorcinol. For comparison, after 5 hours of reaction, resorcinol **4g** was isolated in 53 % yield (entry 6), whereas in strictly same conditions resorcinols **4n** and **4o** were observed as traces.

[162] Published results, Table III-2 entries 1-2
[163] Chapter II, published results, table 1



Entry	substrate	CO (atm)	cat. (mol %)	product	yield
1	 **1l**	50	2.5	 **4l**	n. r.
2	 **1m**	50	2.5	 **4m**	62 %
3	 **1a**	50	2.5	 **4a**	59 %
4	 **1n**	80	5	 **4n**	23 % [a,b]
5	 **1o**	80	10	 **4o**	38 % [a,c]
6	 **1g**	80	2.5	 **4g**	53 %

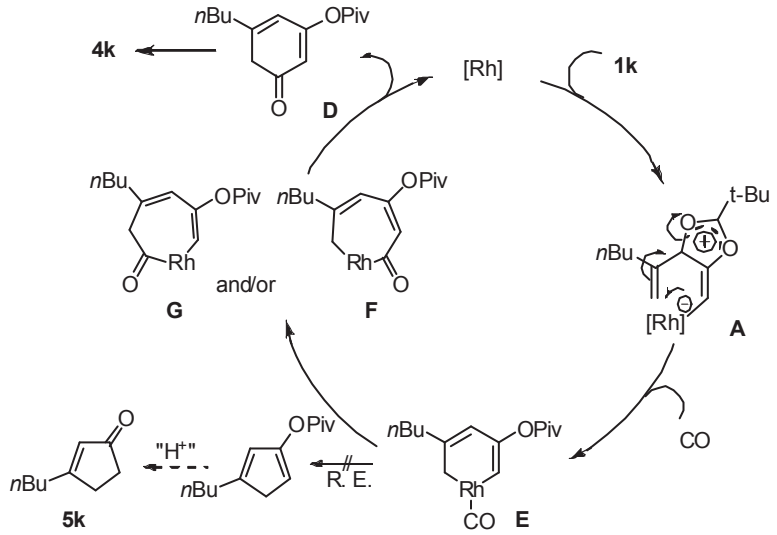
[a] 100°C, [b] 14 h, [c] 24 h

Table III-4

III. 3. 2. Mechanistic study

The most difficult task we encountered while studying the mechanistic pathway, was to determine whether the cyclization occurred before or after carbon monoxide insertion. We tend to think that the mechanistic pathway which would better explain the course of the reaction brings into play carbon monoxide insertion before cyclization (submitted results, Scheme III-17).

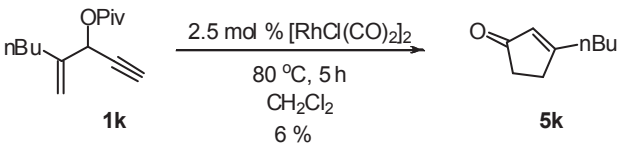
We wondered what would be the mechanistic pathway for a prior cyclization before carbon monoxide insertion. Such catalytic cycle can be represented as follows (scheme III-18). We postulated that the formation of **4k** would be initiated by electrophilic activation of the alkyne moiety of **1k** by the rhodium catalyst. Successive 1,2-migration of pivalate would generate the zwitterionic vinyl-rhodium species **A** that would have evolved into rhodacyclohexadiene **E**.[160] Instead of reductive elimination to afford **5k,** insertion of CO could possibly lead to **F** and/or **G**. Finally, reductive elimination would liberate the transient intermediate **D** and regenerated the rhodium catalyst.



scheme III-18

As a first observation, it should be noted that this catalytic cycle does not bring any obvious reasons which would explain why the cycloadduct **4k** (and similar 5-alkylresorcinols) were prepared in low yield compared to 4-alkylresorcinols.

Then, it should be observed that this reaction carried out without carbon monoxide pressure would lead to cyclopentenone **5k**. However, when 1,4-enyne pivalate **1k** was engaged with 2.5 mol % of rhodium catalyst in dichloromethane for 5 hours at 80°C, cyclopentenone **5k** was formed in a low yield of 6 % (scheme III-19). This experimental evidence allowed us to partially exclude the previous mechanism.

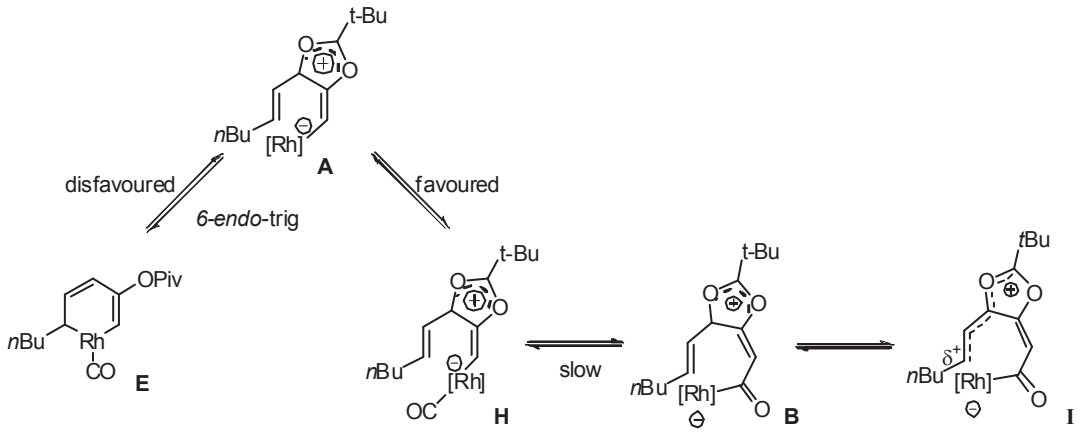


scheme III-19

In order to argue in favor of our preferential mechanistic pathway (where carbon monoxide insertion happens prior to cyclization), we had to interprete the observations:

- The functional group at the propargylic position is important
- Non substituted olefin is a less reactive substrate with our catalytic system
- Substitution at the terminal position of the olefin afforded resorcinols in good yields.

To account for theses observation, mechanistic hypothesis must be detailed again (Scheme III-20). Vinyl rhodium **A** is the same intermediate in our two mechanistic hypotheses. We have postulated above that the formation of cyclopentenone would be disfavored *via 6-endo*-trig cyclization. Instead, carbon monoxide would coordinate the metal and form **H**, before insertion into C-metal bond (**B**). We assumed here that an alkyl substituent at 3-position would stabilize the native δ^+ charge formed during the cyclization process represented by intermediate **I**.



Scheme III-20

III. 4. General conclusion

To our best knowledge, we have developed the first synthesis of non-symmetric substituted resorcinols based on a rhodium-catalyzed carbonylation of 1,4-enyne pivalates. This method is a major alternative of previously known methods. This is a benzene-free synthesis that can lead to diversely substituted biphenyls as well as lipid resorcinols that are naturally occurring molecules with potential bioactivity.

Although few mechanistic evidences were obtained, we could preferentially advance the hypothesis of a prior carbon monoxide insertion before cyclization. Doing so, we highlighted the importance of the migrant propargylic group and the substitution of the olefin.

Further studies are still underway in our laboratories, in particular for the cyclization of internal propargyl alkynes. Preliminary cyclization of such precursors afforded a ketone-type product that needs to be fully analyzed to bring conclusion of the structure.

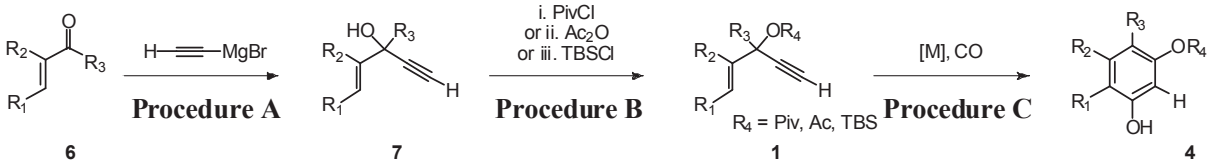
III. 5. Chapter III: Experimental part

^{1}H NMR spectra were recorded using JEOL JMN-500 or JMN-400 instruments respectively at 500, or 400 MHz. ^{13}C NMR spectra were recorded using JEOL JMN ECP-500 (125 MHz) spectrometer or JMN-400 (100 MHz) specrtrometer. NMR shifts are reported relative to the residual solvent signal (7.27 ppm for $CDCl_3$, and 7.15 for C_6D_6) for proton NMR and relative the residual solvent central peak for carbon spectra (77.0 ppm for $CDCl_3$ and 128.0 ppm for C_6D_6). Chemical shifts are given in part per millions (δ). Infrared spectra were obtained using a JASCO FT-IR 4100 spectrometer; absorptions are reported in reciprocal centimetres. Both conventional and high resolution mass spectra were recoded with JEOL JMS700 spectometer. The products were purified by flash chromatography on silica gel (Nacalai Tesque Inc., Silica Gel 60, 230-400 mesh). All commercially available reagents were used without further purification unless precised. Known products were identified by ^{1}H NMR and comparison with literature data.

Specific remarks

Prior to use, aldehydes were freshly distilled and Grignard reagents were freshly titrated. Pivaloyl chloride, acetic anhydride and rhodium catalyst were commercially available, and used without further purification.

General Procedure:

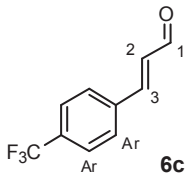


6 7 1 4

III. 5. 1. Synthesis of the precursors:

III. 5. 1. a. Enals

Structure 70: (*E*)-3-(4-(trifluoromethyl)phenyl)acrylaldehyde (6c)



6c

$C_{10}H_7OF_3$

Mol. Wt.: 200.1572

(Triphenylphosphinephosphoranylidene)-acetaldehyde (3 g, 10 mmol) was added to a solution of **4-(trifluoromethyl)benzaldehyde** (1.83 g, 10.5 mmol) in 10 mL of DCM. The mixture was allowed to stir at room temperature for 2 days. The solvent of the reaction mixture was then removed under reduced pressure. 20 mL of hexanes was then added, and the resulting solid was filtered over büchner. The filtrate was evaporated to give 2.5 g of a crude orange oil.

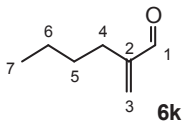
Purification was achieved by flash chromatography on silica gel (10% AcOEt/Hex) to give **(*E*)-3-(4-(trifluoromethyl)phenyl)acrylaldehyde (6c)** as a yellow solid (1.13 g, 54%)

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.76 (d, ^3J= 7.5 Hz, 1H, H_1), 7.69 (s, 4H, H_{Ar}), 7.50 (d, J_t= 16.2 Hz, 1H, H_3), 6.77 (dd, J_t= 16.1 Hz, ^3J= 7.5 Hz, 1H, H_2).

Spectroscopic data were consistent with those reported in the literature.[1]

CAS: 95123-61-8

Structure 71: 2-methylenehexanal (6k)



6k

$C_7H_{12}O$

Mol. Wt.: 112.1696

2-methylenehexanal (6k) was synthesized according literature.[165]

Colorless oil

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[165] Oppolzer, W.; Swenson, R. E.; Pachinger, W.; *Helvetica Chimica Acta* **1989**, *72*, 14.

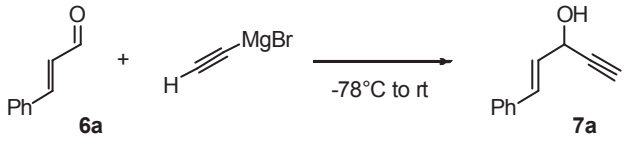
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.54 (s, 1H, H_1), 6.24 (s, 1H, H_3), 5.98 (s, 1H, H_3), 2.24 (t, ^3J= 7.8 Hz, 2H, H_4), 1.44-1.31 (m, 4H, $H_{5,6}$), 0.91 (t, ^3J= 7.4 Hz, 3H, H_7).

Spectroscopic data were consistent with those reported in the literature.[165]

CAS: 1070-66-2

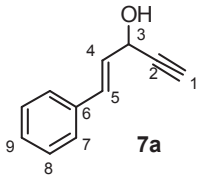
III. 5. 1. b. Enynols

Typical procedure A for enynols preparation:



Commercial ***trans*-cinnamaldehyde** (2.5 mL, 20 mmol) was slowly added to a solution of freshly titrated **ethynylmagnesiumbromide in THF** (c = 0.44 M, 45 mL, 20 mmol) at -78°C. The reaction mixture was allowed to warm to rt. After completion, the reaction was quenched with aqueous NH_4Cl sat.. The resulting solution was extracted with Et_2O. The combined organic layers were washed with NaCl sat., dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 3.1 g of the crude **(*E*)-1-phenylpent-1-en-4-yn-3-ol (7a)**. The yellow solid was engaged in the next step without further purification.

Structure 72: (*E*)-1-phenylpent-1-en-4-yn-3-ol (7a)



$C_{11}H_{10}O$

Mol. Wt.: 158.1965

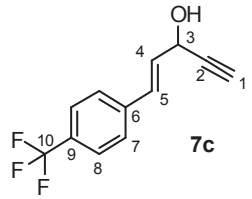
Yellows solid.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.43-7.40 (m, 2H, H_7), 7.36-7.32 (m, 2H, H_8), 7.30-6.29 (m, 1H, H_9), 6.81 (d, J_t= 15.9 Hz, 1H, H_5), 6.32 (dd, J_t= 15.9 Hz, ^3J= 5.9 Hz, 1H, H_4), 5.08 (bs, 1H, H_3), 2.66 (d, ^4J= 2.2 Hz, 1H, H_1), 2.08 (bs, 1H, H_{OH}).

Spectroscopic data were consistent with those reported in the literature.[166]

CAS: 31450-17-6

Structure 73: (*E*)-2-methyl-1-phenylpent-1-en-4-yn-3-ol (7c)



$C_{12}H_9OF_3$

Mol. Wt.: 226.1945

The typical procedure A was applied with freshy prepared **(*E*)-3-(4-(trifluoromethyl)phenyl)acrylaldehyde** (879 mg, 4 mmol) and **ethynylmagnesiumbromide in THF** (c = 0.50 M, 10 mL, 5 mmol). After treatment, 848 mg of crude **(*E*)-2-methyl-1-phenylpent-1-en-4-yn-3-ol (7c)** was obtained. The white solid was then engaged in the next step without further purification.

m. p. = 68 – 70°C.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.55-7.53 (d, ^3J= 7.8 Hz, 2H, H_8), 7.45-7.44 (d, ^3J= 7.8 Hz, 2H, H_7), 6.81 (d, ^3J= 16.1 Hz, 1H, H_5), 6.38 (dd, ^3J= 15.6, 5.5 Hz, 1H, H_4), 5.10 (s, 1H, H_3), 3.02 (bs, 1H, H_{OH}), 2.66 (s, 1H, H_1).

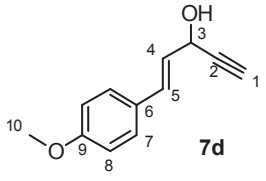
^{13}C NMR ($CDCl_3$, 125 MHz): δ = 139.3, 130.6, 130.0, 129.4, 126.9, 125.5, 122.9, 82.3 (C_2), 74.9 (C_1), 62.2 (C_3).

IR (KBr) 3400-3100 (br), 2924, 2854, 2117, 1616, 1327.

EIMS *m/z* (relative intensity) 226 (M^+, 100), 157 (71), 129 (61), 128 (54).

HRMS (EI) *m/z* calcd for $C_9H_{24}OF_3$: 226.0605, found: 226.0611.

Structure 74: (*E*)-1-(4-methoxyphenyl)pent-1-en-4-yn-3-ol (7d)



$C_{12}H_{12}O_2$

Mol. Wt.: 188.2225

[166] Touchard, D.; Haquette, P.; Daridor, A.; Romero, A.; Dixneuf, P. H.; *Organometallics* **1998**, *17*, 3844.

The typical procedure A was applied with commercial **4-methoxycinnamaldehyde** (649 mg, 4 mmol) and ethynylmagnesiumbromide in THF (c = 0.20 M, 20 mL, 4 mmol). After treatment, 736 mg of crude **(*E*)-1-(4-methoxyphenyl)pent-1-en-4-yn-3-ol (7d)** was obtained. The pale yellow oil was then engaged in the next step without further purification.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.35 (d, ^3J= 8.7 Hz, 2H, H_7), 6.86 (d, ^3J= 9.2 Hz, 2H, H_8), 6.75 (d, ^3J= 15.6 Hz, 1H, H_5), 6.18 (dd, ^3J= 15.6 Hz, ^4J= 6.0 Hz, 1H, H_4), 3.82 (s, 3H, H_{10}), 2.63 (d, ^4J= 2.3 Hz, 1H, H_1), 1.56 (s, 1H, H_{OH}).

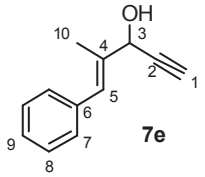
^{13}C NMR ($CDCl_3$, 125 MHz): δ = 159.7 (C_9), 132.0 (C_4), 128.8 (C_6), 128.2 (C_7), 125.4 (C_5), 114.2 (C_8), 83.1 (C_2), 74.6 (C_1), 69.9 (C_3), 55.4 (C_{10})

IR (KBr) 3500-3100 (br), 3032, 2962, 2881, 2114, 1608 cm^{-1}.

EIMS *m/z* (relative intensity) 188 (M^+, 56), 128 (19), 121 (100).

HRMS (EI) *m/z* calcd for $C_{12}H_{12}O_2$: 188.0837, found: 188.0837.

Structure 75: (*E*)-2-methyl-1-phenylpent-1-en-4-yn-3-ol (7e)



$C_{12}H_{12}O$

Mol. Wt.: 172.2231

The typical procedure A was applied with commercial **α-methylcinnamaldehyde** (1.5 mL, 10 mmol) and **ethynylmagnesiumbromide in THF** (c = 0.45 M, 22 mL, 10 mmol). After treatment, 1.8 g of crude **(*E*)-2-methyl-1-phenylpent-1-en-4-yn-3-ol (7e)** was obtained. The colourless crude oil was then engaged in the next step without further purification.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.37-7.33 (m, 2H, H_8), 7.31-7.29 (m, 2H, H_7), 7.26-7.23 (m, 1H, H_9), 6.72 (s, 1H, H_5), 4.95-4.94 (m, 1H, H_3), 2.61 (d, ^4J= 2.3 Hz, 1H, H_1), 2.01 (s, 3H, H_{10}), 1.96 (bs, 1H, H_{OH}).

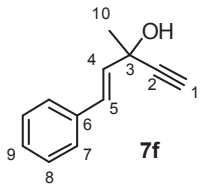
^{13}C NMR ($CDCl_3$, 125 MHz): δ = 137.1 (C_4), 136.5 (C_6), 129.1 (C_7), 128.3 (C_8), 127.5 (C_5), 127.0 (C_9), 83.1 (C_2), 74.4 (C_1), 68.1 (C_3), 14.1 (C_{10}).

IR (neat) 3600-3100 (br), 3293, 2980, 2918, 2859, 2116, 1600, 1444 cm^{-1}.

EIMS *m/z* (relative intensity) 172 (M^+, 20), 170 (78), 169 (100), 115 (67).

HRMS (EI) *m/z* calcd for $C_{12}H_{12}O$: 172.0888, found: 172.0886.

Structure 76: (*E*)-3-methyl-1-phenylpent-1-en-4-yn-3-ol (7f)



$C_{12}H_{12}O$

Mol. Wt.: 172.2231

The typical procedure A was applied with commercial **4-phenyl-3-butene-2-ol** (4.4 mL, 30 mmol) and **ethynylmagnesiumbromide in THF** (c = 0.50 M, 60 mL, 30 mmol). After treatment, 6.5 g of crude **(*E*)-3-methyl-1-phenylpent-1-en-4-yn-3-ol (7f)** was obtained.

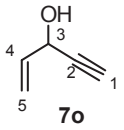
Purification was achieved by flash chromatography on silica gel (17% AcOEt/Hex) to give a white solid (3.68 g, 71%)

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.42-7.40 (m, 2H, H_7), 7.34-7.32 (m, 2H, H_8), 7.28-7.25 (m, 1H, H_9), 6.90 (d, J_t= 16.1 Hz, 1H, H_5), 6.30 (d, J_t= 15.6 Hz, 1H, H_4), 2.65 (s, 1H, H_1), 2.22 (bs, 1H, H_{OH}), 1.67 (s, 3H, H_{10}).

Spectroscopic data were consistent with those reported in the literature.[1]

CAS: 56188-07-9

Structure 77: pent-1-en-4-yn-3-ol (7o)



C_5H_6O

Mol. Wt.: 82.1005

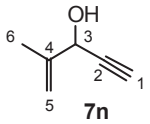
The typical procedure A was applied with freshly distilled **acrolein** (2 mL, 30 mmol) and **ethynylmagnesiumbromide in THF** (c = 0.3 M, 100 mL, 30 mmol). After treatment, 2.4 g of crude **pent-1-en-4-yn-3-ol (7o)** was obtained. The colourless crude oil was then engaged in the next step without further purification.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 6.02-5.95 (m, 1H, H_4), 5.50 (d, ^3J= 17.0 Hz, 1H, H_{5trans}), 5.25 (d, ^3J= 10.1 Hz, 1H, H_{5cis}), 4.89 (bs, 1H, H_3), 2.58 (d, ^4J= 2.3 Hz, 1H, H_1).

Spectroscopic data were consistent with those reported in the literature.[167]

CAS: 14304-27-9

Structure 78: 2-methylpent-1-en-4-yn-3-ol (7n)



7n

C_6H_8O

Mol. Wt.: 96.1271

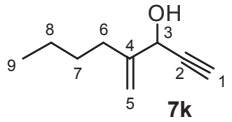
The typical procedure A was applied with freshly distilled **methacryladehyde** (852 mg, 12.2 mmol) and **ethynylmagnesiumbromide in THF** (c = 0.40 M, 30.5 mL, 12.2 mmol). After treatment, 1.2 g of crude **2-methylpent-1-en-4-yn-3-ol (7n)** was obtained. The colourless crude oil was then engaged in the next step without further purification.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.20 (s, 1H, H_5), 4.95 (s, 1H, H_5), 4.79 (bs, 1H, H_3), 2.54 (d, ^4J= 2.2 Hz, 1H, H_1), 2.06 (bs, 1H, H_{OH}), 1.87 (s, 3H, H_6).

Spectroscopic data were consistent with those reported in the literature.[168]

CAS: 1572-63-0

Structure 79: 4-methyleneoct-1-yn-3-ol (7k)



7k

$C_9H_{14}O$

Mol. Wt.: 138.2069

The typical procedure A was applied with freshly prepared **2-methylenehexanal 67 %** (1.3 g, 7.8 mmol) and **ethynylmagnesiumbromide in THF** (c = 0.20 M, 39 mL, 7.7 mmol). After treatment, 1.5 g of crude **4-methyleneoct-1-yn-3-ol (7k)** was obtained.

Purification was achieved by flash chromatography on silica gel (2 % Et_2O/Hex) to give a colourless oil (649 mg, 61 %)

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 5.30 (s, 1H, H_5), 4.97 (s, 1H, $H_{5'}$), 4.83 (bs, 1H, H_3), 2.54 (d, ^4J= 2.3 Hz, 1H, H_1), 2.20 (t, ^3J= 7.8 Hz, 2H, H_6), 1.91 (bs, 1H, H_{OH}), 1.52-1.46 (m, 2H, H_7), 1.40-1.32 (m, 2H, H_8), 0.92 (t, ^3J= 7.4 Hz, 3H, H_9).

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[167] Cosset, C.; Rio, I.; Bozec, H.; *Organometallics*; **1995**, *14*, 1938.

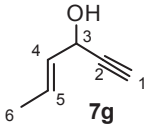
[168] Crombie, L.; Horsham, M. A.; Jarrett, S. R. M. ; *J. Chem. Soc., Perkin Trans. 1* **1991**, *6*, 1511.

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 147.9 (C_4), 111.5 (C_5), 83.2 (C_2), 74.1 (C_1), 65.5 (C_3), 31.5 (C_6), 30.0 (C_7), 22.6 (C_8), 14.1 (C_9).

IR (neat) 3500 – 3100 (br), 3305, 2958, 2931, 2866, 2118 cm^{-1}.

HRMS (EI) *m/z* calcd for $C_9H_{14}O$: 138.1045, found: 137.0956.

Structure 80: (*E*)-hex-4-en-1-yn-3-ol (7g)



7g

C_6H_8O

Mol. Wt.: 96.1271

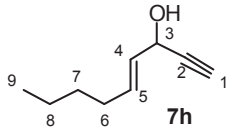
The typical procedure A was applied with commercial **but-2-enal** (2.45 mL, 30 mmol) and **ethynylmagnesiumbromide in THF** (c = 0.40 M, 75 mL, 30 mmol). After treatment, 2.3 g of crude **(*E*)-hex-4-en-1-yn-3-ol (7g)** was obtained. The colourless crude oil was then engaged in the next step without further purification.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.03-5.82 (m, 1H, H_5), 5.71-5.55 (m, 1H, H_4), 4.82 (s, 1H, H_3), 2.55 (d, ^4J= 2.2 Hz, 1H, H_1), 2.06 (bs, 1H, H_{OH}), 1.73 (d, ^3J= 6.6 Hz, 3H, H_6).

Spectroscopic data were consistent with those reported in the literature.[169]

CAS: 59095-52-2

Structure 81: (*E*)-non-4-en-1-yn-3-ol (7h)



7h

$C_9H_{14}O$

Mol. Wt.: 138.2069

The typical procedure A was applied with commercial ***trans*-2-hepten-1-al** (3.5 mL, 26 mmol) and **ethynylmagnesiumbromide in THF** (c = 0.40 M, 65 mL, 26 mmol). After treatment, 3.6 g of crude **(*E*)-non-4-en-1-yn-3-ol (7h)** was obtained. The orange crude oil was then engaged in the next step without further purification.

[169] Pilette, D.; Ouzzine, K.; Le Bozec, H.; Dixneuf, P. H.; Rickard, C. E. F.; Roper, W. R.; *Organometallics* **1992**, *11*, 809.

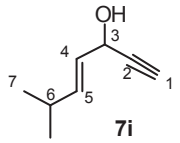
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.95-5.89 (m, 1H, H_5), 5.64-5.59 (m, 1H, H_4), 5.84 (bs, 1H, H_3), 2.56 (d, ^4J= 2.3 Hz, 1H, H_1), 2.09-2.04 (m, 2H, H_6), 2.01 (bs, 1H, H_{OH}), 1.39-1.32 (m, 4H, $H_{7,8}$), 0.92-0.89 (m, 3H, H_9).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 134.6 (C_5), 128.5 (C_4), 83.5 (C_2), 74.1 (C_1), 68.9 (C_3), 31.7 (C_6), 31.1 (C_7), 22.3 (C_8), 14.0 (C_9).

IR (neat) 3500-3100, 2957, 2928, 2872, 2859, 2117, 1466 cm^{-1}.

HRMS (EI) *m/z* calcd for $C_9H_{14}O$: 138.1045, found: 137.0956.

Structure 82: (*E*)-6-methylhept-4-en-1-yn-3-ol (7i)



7i

$C_8H_{12}O$

Mol. Wt.: 124.1803

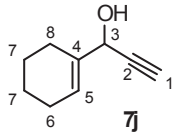
The typical procedure A was applied with commercial ***trans*-4-methyl-2-pentenal 95 %** (1.2 mL, 9.7 mmol) and **ethynylmagnesiumbromide in THF** (c = 0.44 M, 22 mL, 9.7 mmol). After treatment, 1.1 g of crude **(*E*)-6-methylhept-4-en-1-yn-3-ol (7i)** was obtained. The colourless crude oil was then engaged in the next step without further purification.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 5.88 (dd, J_t= 15.6 Hz, ^3J= 6.5 Hz, 1H, H_5), 5.58-5.53 (m, 1H, H_4), 4.83 (bs, 1H, H_3), 2.56 (d, ^4J= 2.3 Hz, 1H, H_1), 2.36-2.30 (m, 1H, H_6), 2.01 (bs, 1H, H_{OH}), 1.01 (d, ^3J= 6.4 Hz, 6H, H_7).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 141.3 (C_5), 125.8 (C_4), 83.6 (C_2), 74.1 (C_1), 63.0 (C_3), 30.6 (C_6), 22.1 (C_7).

IR (neat) 3600-3100, 3310, 2964, 2934, 2872, 2099, 1466 cm^{-1}.

Structure 83: cyclohexenylprop-2-yn-1-ol (7j)



7j

$C_9H_{12}O$

Mol. Wt.: 136.1910

The typical procedure A was applied with commercial **1-cyclohexene-1-carboxaldehyde 98 %** (1 g, 8.9 mmol) and **ethynylmagnesiumbromide in THF** (c = 0.44 M, 20 mL, 8.9 mmol). After

treatment, 1.2 g of crude **1-cyclohexenylprop-2-yn-1-ol (7j)** was obtained. The colourless crude oil was then engaged in the next step without further purification.

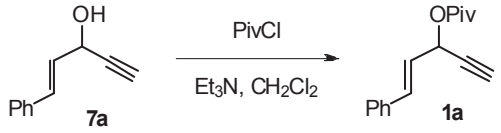
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.90 (bs, 1H, H_5), 4.71 (s, 1H, H_3), 2.50 (d, ^4J= 2.4 Hz, 1H, H_1), 2.17-2.04 (m, 4H, H_6), 1.67-1.62 (m, 2H, H_7), 1.60-1.57 (m, 2H, H_7).

Spectroscopic data were consistent with those reported in the literature.[170]

CAS: 7014-99-5

III. 5. 1. c. Propynylesters

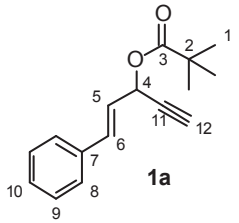
Typical procedure B for enyne esters preparation:



Pivaloyl chloride (0.7 mL, 5.5 mmol) was added to a solution of **1- (*E*)-1-phenylpent-1-en-4-yn-3-ol** (**7a**, 796 mg, 5 mmol) and **triethylamine** (0.8 mL, 5.5 mmol) and 17 mL of DCM. The reaction mixture was allowed to stir at room temperature for 24 hours and was then quenched with aqueous NH_4Cl sat.. The resulting solution was submitted to a DCM extraction. The combined organic layers were washed with NaCl sat. and dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 1.23 g of the crude.

Purification was achieved by flash chromatography on silica gel (5% AcOEt/Hex) to give **(*E*)-1-phenylpent-1-en-4-yn-3-yl pivalate (1a)** as a yellow oil (1.03 g, 84 %)

Structure 84: (*E*)-1-phenylpent-1-en-4-yn-3-yl pivalate (1a)



$C_{16}H_{18}O_2$

Mol. Wt.: 242.3129

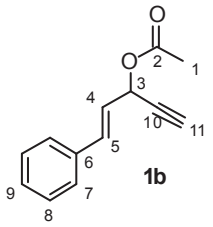
[170] Pujanauski, B. G.; Prasad, B. A. B.; Sarpong, R. *J. Am. Chem. Soc.* **2006**, *128*, 6786.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.44-7.40 (m, 2H, H_8), 7.33-7.36 (m, 2H, H_9), 7.30-7.29 (m, 1H, H_{10}), 6.89 (d, J_t= 16.0 Hz, 1H, H_6), 6.24 (dd, J_t= 15.6 Hz, ^3J= 6.5 Hz, 1H, H_5), 6.06-6.04 (m, 1H, H_4), 2.62 (d, ^4J= 2.3 Hz, 1H, H_{12}), 1.25 (s, 9H, H_1).

Spectroscopic data were consistent with those reported in the literature.[171]

CAS: 852449-30-0

Structure 85: (*E*)-1-phenylpent-1-en-4-yn-3-yl acetate (1b)



$C_{13}H_{12}O_2$

Mol. Wt.: 200.2332

The typical procedure B was applied with **(*E*)-1-phenylpent-1-en-4-yn-3-ol** (**7a**, 1.26 mg, 8 mmol), **acetic anhydride** (1.09 g, 10 mmol), **DMAP** (19 mg, 0.16 mmol) and **triethylamine** (1.3 mL, 17 mmol) in 30 mL of DCM. After treatment, 1.7 g of crude yellow oil was obtained.

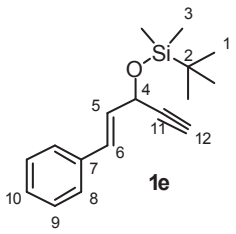
Purification was achieved by flash chromatography on silica gel (3 % Et_2O/Hex) to give **(*E*)-1-phenylpent-1-en-4-yn-3-yl acetate (1b)** as a yellow pale oil (1.5 g, 93 %)

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.42-7.40 (m, 2H, H_7), 7.35-7.26 (m, 3H, $H_{8,9}$), 6.89 (d, J_t= 15.6 Hz, 1H, H_5), 6.23 (dd, J_t= 16.1 Hz, ^3J= 6.5 Hz, 1H, H_4), 6.04 (d, ^3J= 9.5 Hz, 1H, H_3), 2.64 (d, ^4J= 2.3 Hz, 1H, H_{11}), 2.11 (s, 3H, H_1).

Spectroscopic data were consistent with those reported in the literature.[172]

CAS: 63399-81-5

Structure 86: (*E*)-*tert*-butyldimethyl(1-phenylpent-1-en-4-yn-3-yloxy)silane (1e)



$C_{17}H_{24}OSi$

Mol. Wt.: 272.4574

[171] Shi, X.; Gorin, D. J.; Toste, F. D.; *J. Am. Chem. Soc.* **2005**, *127*, 5802.
[172] Detz, R. J.; Delville, M. M. E.; Hiemstra, H.; van Marrseveen, J. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 3777.

The typical procedure B was applied with **(*E*)-1-phenylpent-1-en-4-yn-3-ol** (**7a**, 1.44 g, 9.1 mmol), ***tert*-Butyldimethylsilyl chloride** (1.5 g, 10 mmol), **triethylamine** (1.4 mL, 10 mmol) and **DMAP** (22 mg, 0.18). After treatment, 2.1 g of crude yellow oil was obtained.

Purification was achieved by flash chromatography on silica gel (5% AcOEt/Hex) to give **(*E*)-tert-butyldimethyl(1-phenylpent-1-en-4-yn-3-yloxy)silane (1e)** as a yellow pale oil (1.41 g, 57 % yield over 2 steps)

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.43-7.42 (m, 2H, H_8), 7.36-7.33 (m, 2H, H_9), 7.29-7.27 (m, 1H, H_{10}), 6.75 (d, ^2J= 15.6 Hz, 1H, H_6), 6.27 (dd, ^2J= 15.6 Hz, ^3J= 5.5 Hz, 1H, H_5), 5.11-5.09 (m, 1H, H_4), 2.58 (d, ^4J= 1.8 Hz, 1H, H_{12}), 0.97 (s, 9H, H_1), 0.21 (s, 3H, H_3), 0.20 (s, 3H, $H_{3'}$).

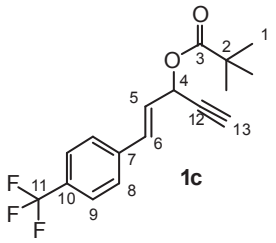
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 136.5 (C_7), 130.6 (C_6), 128.9 (C_5), 128.7 (C_9), 128.0 (C_{10}), 126.9 (C_8), 84.7 (C_{11}), 73.7 (C_{12}), 63.5 (C_4), 25.9 (C_1), 18.5 (C_2), -4.4 (C_3), -4.6 ($C_{3'}$).

IR (neat) 2955, 2930, 2886, 2857, 1602, 1253, 1064 cm^{-1}.

EIMS *m/z* (relative intensity) 272 (M^+, 9), 215 (54), 141 (100), 85 (56), 83 (87), 75 (71).

HRMS (EI) *m/z* calcd for $C_{17}H_{24}OSi$: 272.1596, found: 272.1592.

Structure 87: (*E*)-1-(4-(trifluoromethyl)phenyl)pent-1-en-4-yn-3-yl pivalate (1c)



1c

$C_{17}H_{17}O_2F_3$

Mol. Wt.: 310.3109

The typical procedure B was applied with **(*E*)-1-(4-(trifluoromethyl)phenyl)pent-1-en-4-yn-3-ol** (**7c**, 317 mg, 1.4 mmol), **pivaloyl chloride** (0.3 mL, 1.8 mmol) and **triethylamine** (0.3 mL, 1.8 mmol) in 5 mL of DCM. After treatment, 386 mg of crude yellow oil was obtained.

Purification was achieved by filtration over a pad of silica gel (product was rinsed with Et_2O) to give **(*E*)-1-(4-(trifluoromethyl)phenyl)pent-1-en-4-yn-3-yl pivalate (1c)** as a yellow solid (364 mg, 84 %).

M. p. = 39 – 41°C

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.59 (d, 2H, H_9), 7.51 (d, ^3J= 8.3 Hz, 2H, H_8), 6.91 (d, ^3J= 8.3 Hz, 1H, H_6), 6.31 (dd, ^3J= 16.0 Hz, 1H, H_5), 6.06 (d, ^3J= 16.0, 6.4 Hz, 1H, H_4), 2.63 (bs, 1H, H_{13}), 1.25 (s, ^4J= 2.3 Hz, 9H, H_1).

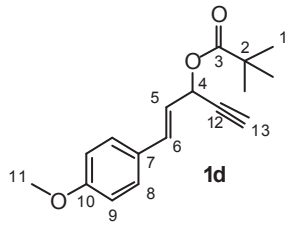
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 177.3 (C_3), 139.3 (C_7), 133.0 (C_6), 127.3 (C_8), 126.4 (C_5), 125.7 (C_9), 79.3 (C_{12}), 75.5 (C_{13}), 63.6 (C_4), 39.0 (C_2), 27.2 (C_1).

IR (KBr) 3309, 2977, 2936, 2875, 2126, 1735, 1617, 1326, 1131 cm^{-1}.

EIMS *m/z* (relative intensity) 310 (M^+, 19), 209 (74), 208 (68), 139 (36), 57 (100).

HRMS (EI) *m/z* calcd for $C_{17}H_{17}O_2F_3$: 310.1181, found: 310.1182.

Structure 88: (*E*)-1-(4-methoxyphenyl)pent-1-en-4-yn-3-yl pivalate (1d)



$C_{17}H_{20}O_3$

Mol. Wt.: 272.3389

The typical procedure B was applied with **(*E*)-1-(4-methoxyphenyl)pent-1-en-4-yn-3-ol** (617 mg, 3.3 mmol), **pivaloyl chloride** (**7d**, 0.4 mL, 3.6 mmol) and **triethylamine** (0.5 mL, 3.6 mmol) in 11 mL of DCM. After treatment, 880 mg of crude yellow oil was obtained.

Purification was achieved by filtration over a pad of silica gel with Et_2O to give **(*E*)-1-(4-methoxyphenyl)pent-1-en-4-yn-3-yl pivalate (1d)** as a yellow pale oil (820 mg, 92 %).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.35 (d, ^3J= 8.7 Hz, 2H, H_8), 6.87 (d, ^3J= 8.7 Hz, 2H, H_9), 6.81 (d, J_t= 16.0 Hz, 1H, H_6), 6.09 (dd, J_t= 15.6 Hz, ^3J= 6.5 Hz, 1H, H_5), 6.01 (d, ^3J= 5.5 Hz, 1H, H_4), 3.81 (s, 3H, H_{11}), 2.60 (d, ^4J= 1.8 Hz, 1H, H_{13}), 1.24 (s, 9H, H_1).

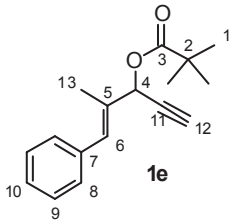
^{13}C NMR ($CDCl_3$, 125 MHz): δ = 177.3 (C_3), 160.0 (C_{10}), 134.2 (C_5), 128.5 (C_7), 128.3 (C_8), 121.4 (C_6), 114.2 (C_9), 79.9 (C_{12}), 74.9 (C_{13}), 64.2 (C_4), 55.4 (C_{11}), 38.9 (C_2), 27.1 (C_1).

IR (neat) 3293, 2972, 2916, 2838, 2124, 1730, 1607, 1513, 1143 cm^{-1}.

EIMS *m/z* (relative intensity) 272 (M^+, 19), 171 (100), 170 (77), 155 (35), 128 (61), 57 (65).

HRMS (EI) *m/z* calcd for $C_{17}H_{20}O_3$: 272.1412, found: 272.1411.

Structure 89: (*E*)-2-methyl-1-phenylpent-1-en-4-yn-3-yl pivalate (1e)



$C_{17}H_{20}O_2$

Mol. Wt.: 256.3395

The typical procedure B was applied with **(E)-2-methyl-1-phenylpent-1-en-4-yn-3-ol** (**7e**, 1.8 g, 10 mmol), **pivaloyl chloride** (1.5 mL, 12 mmol) and **triethylamine** (1.7 mL, 12 mmol) in 34 mL of DCM. After treatment, 2.1 g of crude yellow oil was obtained.

Purification was achieved by flash chromatography on silica gel (10 % AcOEt/Hex) to give **(*E*)-2-methyl-1-phenylpent-1-en-4-yn-3-yl pivalate (1e)** as a yellow pale oil (1.2 g, 57 % over 2 steps).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.37-7.34 (m, 2H, H_9), 7.31-7.29 (m, 2H, H_8), 7.27-7.24 (m, 1H, H_{10}), 6.76 (s, 1H, H_6), 5.93 (bs, 1H, H_4), 2.56 (d, ^4J= 2.3 Hz, 1H, H_{12}), 1.98 (s, 3H, H_{13}), 1.25 (s, 9H, H_1).

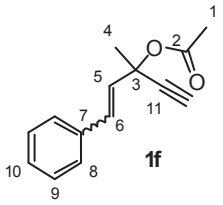
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 177.2 (C_3), 136.8 (C_5), 132.9 (C_7), 129.6 (C_6), 129.2 (C_8), 128.3 (C_9), 127.2 (C_{10}), 79.9 (C_{11}), 74.8 (C_{12}), 68.9 (C_4), 39.0 (C_2), 27.2 (C_1), 14.3 (C_{13}).

IR (neat) 3292, 2975, 2933, 2872, 2123, 1732, 1600, 1142 cm^{-1}.

EIMS *m/z* (relative intensity) 256 (M^+, 25), 155 (59), 154 (82), 153 (100), 57 (60).

HRMS (EI) *m/z* calcd for $C_{17}H_{20}O_2$: 272.1596, found: 272.1592.

Structure 90: 3-methyl-1-phenylpent-1-en-4-yn-3-yl acetate (1f)



$C_{14}H_{14}O_2$

Mol. Wt.: 214.2598

The typical procedure B was applied with **(*E*)-1-phenylpent-1-en-4-yn-3-ol** (**7f**, 816 mg, 4.7 mmol), **anhydridre acetic** (603 mg, 5.9 mmol), **DMAP** (13 mg, 0.11 mmol) and **triethylamine** (0.8 mL, 5.2 mmol) in 30 mL of DCM. After treatment, a crude pale yellow oil of **(*E*)-3-methyl-1-phenylpent-1-en-4-yn-3-yl acetate (1f)** was obtained as a mixture of stereoisomers E/Z 1: 0.24 (1.08 g, quantitative yield). The crude oil was then engaged in the next step without further purification.

(*E*)-3-methyl-1-phenylpent-1-en-4-yn-3-yl acetate :

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.43-7.25 (m, 5H, H_{Ar}), 6.93 (d, ^3J= 15.6 Hz, 1H, H_6), 6.34 (d, ^3J= 16.0 Hz, 1H, H_5), 2.77 (s, 1H, H_{12}), 2.07 (s, 3H, H_1), 1.82 (s, 3H, H_4).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 168.8 (C_2), 139.0 (C_{Ar}), 135.7 (C_{Ar}), 131.1 (C_{Ar}), 128.4 (C_5), 126.7 (C_6), 126.2 (C_{Ar}), 82.2 (C_{11}), 75.0 (C_{12}), 28.6 (C_1), 21.7 (C_4).

(*Z*)-3-methyl-1-phenylpent-1-en-4-yn-3-yl acetate :

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.43-7.26 (m, 1.21H, H_{Ar}), 6.73 (d, ^3J= 9.2 Hz, 0.24H, H_6), 5.94 (d, ^3J= 9.2 Hz, 0.25H, H_5), 3.28 (s, 0.23H, H_{12}), 2.10 (s, 0.66H, H_1), 1.90 (s, 0.73H, H_4).

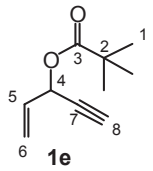
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 169.6 (C_2), 139.6 (C_{Ar}), 129.3 (C_{Ar}), 128.0 (C_{Ar}), 127.9 (C_5), 126.6 (C_6), 120.6 (C_{Ar}), 83.3 (C_{11}), 73.9 (C_{12}), 22.8 (C_1), 21.0 (C_4).

IR (neat) 3286, 3031, 2981, 2927, 1743, 1234 cm^{-1}.

EIMS *m/z* (relative intensity) 214 (M^+, 21), 171 (60), 154 (65), 153 (68), 85 (97), 83 (100).

HRMS (EI) *m/z* calcd for $C_{14}H_{14}O_2$: 214.0994, found: 214.0980.

Structure 91: pent-1-en-4-yn-3-yl pivalate (1e)



$C_{10}H_{14}O_2$

Mol. Wt.: 166.2170

The typical procedure B was applied with **pent-1-en-4-yn-3-ol** (**7e**, 3.9 g, 47 mmol), **pivaloyl choride** (6.2 g, 52 mmol) and **triethylamine** (7.5 mL, 54 mmol) in 20 mL of DCM. After treatment, 6.8 g of crude yellow oil was obtained.

Purification was achieved by flash chromatography on silica gel (2 % Et_2O/Hex) to give **(E)-3pent-1-en-4-yn-3-yl pivalate (1e)** as a yellow pale oil (1.1 g, 23 % over 2 steps).

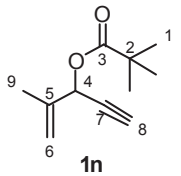
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.93-5.83 (m, 2H, $H_{4,5}$), 5.57 (d, ^3J= 16.1 Hz, 1H, H_{6trans}), 5.32 (d, ^3J= 9.6 Hz, 1H, H_{6cis}), 2.55 (d, ^4J= 2.3 Hz, 1H, H_8), 1.23 (s, 9H, H_1).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 177.0 (C_3), 132.6 (C_5), 118.7 (C_6), 79.2 (C_7), 74.8 (C_8), 63.7 (C_4), 38.7 (C_2), 26.9 (C_1).

IR (neat) 3600-3300, 3299, 2976, 2936, 2910, 2874, 2127, 1732, 1145 cm^{-1}.

HRMS (EI) *m/z* calcd for $C_{10}H_{14}O_2$: 166.0994, found: 166.0996.

Structure 92: 2-methylpent-1-en-4-yn-3-yl pivalate (1n)



1n

$C_{11}H_{16}O_2$

Mol. Wt.: 180.2435

The typical procedure B was applied with **2-methylpent-1-en-4-yn-3-ol** (**7n**, 1.17 g, 12.2 mmol), **pivaloyl chloride** (1.8 mL, 14.6 mmol) and **triethylamine** (2.1 mL, 14.6 mmol) in 25 mL of DCM. After treatment, 2.0 g of crude yellow oil was obtained.

Purification was achieved by flash chromatography on silica gel (10 % Et_2O/Pent) to give **2-methylpent-1-en-4-yn-3-yl pivalate (1n)** as a colorless oil (1.16 g, 53 % over 2 steps).

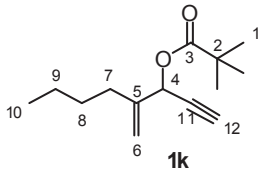
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.78 (s, 1H, H_4), 5.23 (s, 1H, H_6), 5.01 (s, 1H, H_6), 2.49 (d, ^4J= 2.2 Hz, 1H, H_8), 1.84 (s, 3H, H_9), 1.23 (s, 9H, H_1).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 177.1 (C_3), 140.2 (C_5), 114.9 (C_6), 79.8 (C_7), 74.3 (C_8), 66.7 (C_4), 38.9 (C_2), 27.1 (C_1), 18.3 (C_9).

IR (neat) 3296, 2976, 2124, 1733, 1138 cm^{-1}.

HRMS (EI) *m/z* calcd for $C_{11}H_{16}O_2$: 180.1150, found: 180.1144.

Structure 93: 4-methyleneoct-1-yn-3-yl pivalate (1k)



1k

$C_{14}H_{22}O_2$

Mol. Wt.: 222.3233

The typical procedure B was applied with **2-methylpent-1-en-4-yn-3-ol** (**7k**, 308 mg, 2.2 mmol), **pivaloyl chloride** (0.3 g, 2.7 mmol) and **triethylamine** (0.4 mL, 2.7 mmol) in 7 mL of DCM. After treatment, 554 mg of crude yellow oil was obtained.

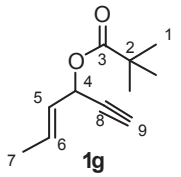
The crude oil was filtered over a pad of silica and washed with ether to give **4-methyleneoct-1-yn-3-yl pivalate (1k)** as a colorless oil (438 mg, 88 %).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.81 (s, 1H, H_4), 5.32 (s, 1H, H_6), 5.03 (s, 1H, H_6), 2.50 (d, ^4J= 1.9 Hz, 1H, H_{12}), 2.18-2.14 (m, 2H, H_7), 1.50-1.45 (m, 2H, H_8), 1.38-1.32 (m, 2H, H_9), 1.23 (s, 9H, H_1), 0.91 (t, 3H, H_{10}).

Spectroscopic data were consistent with those reported in the literature.[171]

CAS: 852449-26-4

Structure 94: (*E*)-hex-4-en-1-yn-3-yl pivalate (1g)



$C_{11}H_{16}O_2$

Mol. Wt.: 180.2435

The typical procedure B was applied with **(E)-hex-4-en-1-yn-3-ol** (**7g**, 2.88 g, 30 mmol), **pivaloyl chloride** (4.4 mL, 36 mmol) and **triethylamine** (5.2 mL, 36 mmol) in 60 mL of DCM. After treatment, 3.7 g of crude yellow oil was obtained.

Purification was achieved by flash chromatography on silica gel (10 % Et_2O/Pent) to give **(E)-hex-4-en-1-yn-3-yl pivalate (1g)** as a colorless oil (2.8 g, 52 % over 2 steps).

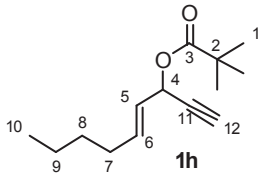
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.03-5.93 (m, 1H, H_6), 5.79-5.77 (m, 1H, H_4), 5.56-5.51 (m, 1H, H_5), 2.50 (appbs, 1H, H_9), 1.73 (d, 1H, ^3J= 6.6 Hz, H_7), 1.20 (s, 9H, H_1).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 177.2 (C_3), 131.4 (C_6), 126.0 (C_5), 80.2 (C_8), 74.4 (C_9), 63.9 (C_4), 38.8 (C_2), 27.1 (C_1), 17.7 (C_7).

IR (neat) 3296, 2972, 2147, 1732, 1140 cm^{-1}.

HRMS (EI) *m/z* calcd for $C_{11}H_{16}O_2$: 180.1150, found: 180.1148.

Structure 95: (*E*)-non-4-en-1-yn-3-yl pivalate (1h)



$C_{14}H_{22}O_2$

Mol. Wt.: 222.3233

The typical procedure B was applied with **(*E*)-non-4-en-1-yn-3-ol** (**7h**, 3.6 g, 26 mmol), **pivaloyl chloride** (4.4 g, 36 mmol) and **triethylamine** (4.6 mL, 33 mmol) in 30 mL of DCM. After treatment, 6.6 g of crude yellow oil was obtained.

Purification was achieved by flash chromatography on silica gel (2 % Et_2O/Pent) to give **(*E*)-non-4-en-1-yn-3-yl pivalate (1h)** as a pale yellow oil (2.99 g, 52 % over 2 steps).

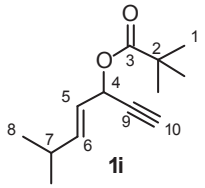
^{1}H NMR ($CDCl_3$, 500 MHz): δ = 6.01-5.95 (m, 1H, H_6), 5.80 (d, ^3J= 6.0 Hz, 1H, H_4), 5.52 (dd, J_t= 14.7 Hz, ^3J= 6.4 Hz, 1H, H_5), 2.52 (d, ^4J= 1.4 Hz, 1H, H_{12}), 2.09-2.05 (m, 2H, H_7), 1.41-1.35 (m, 2H, H_8), 1.35-1.28 (m, 2H, H_9), 1.21 (s, 9H, H_1), 0.89 (t, ^3J= 7.4 Hz, 3H, H_{10}).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 177.3 (C_3), 136.7 (C_6), 124.7 (C_5), 80.3 (C_{11}), 74.4 (C_{12}), 64.0 (C_4), 38.8 (C_2), 31.8 (C_7), 31.0 (C_8), 27.1 (C_1), 22.3 (C_9), 14.0 (C_{10}).

IR (neat) 3500-3100 (br), 3310, 2957, 2928, 2872, 2859, 2117, 1466 cm^{-1}.

HRMS (EI) *m/z* calcd for $C_{14}H_{22}O_2$: 222.1620, found: 222.1624.

Structure 96: (*E*)-6-methylhept-4-en-1-yn-3-yl pivalate (1i)



1i

$C_{13}H_{20}O_2$

Mol. Wt.: 208.2967

The typical procedure B was applied with **(*E*)-6-methylhept-4-en-1-yn-3-ol** (**7i**, 1.1 g, 8.8 mmol), **pivaloyl chloride** (1.3 mL, 10.6 mmol) and **triethylamine** (1.5 mL, 10.6 mmol) in 30 mL of DCM. After treatment, 2.04 g of crude yellow oil was obtained.

Purification was achieved by flash chromatography on silica gel (5 % Et_2O/Pent) to give **(*E*)-hex-4-en-1-yn-3-yl pivalate (1i)** as a pale yellow oil (1.17 g, 63 % over 2 steps).

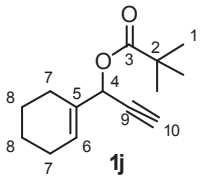
^{1}H NMR ($CDCl_3$, 500 MHz): δ = 5.96 (ddd, J_t= 15.6 Hz, ^3J= 6.9 Hz, ^4J= 1.4 Hz, 1H, H_6), 5.81 (d, ^3J= 6.4 Hz, 1H, H_4), 5.47 (ddd, J_t= 15.5 Hz, ^3J= 6.4 Hz, ^4J= 1.4 Hz, 1H, H_5), 2.52 (d, ^4J= 2.3 Hz, 1H, H_{10}), 2.31-2.37 (m, 1H, H_7), 1.20 (s, 9H, H_1), 1.01 (dd, ^3J= 6.9 Hz, ^4J= 1.4 Hz, 6H, H_8).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 177.3 (C_3), 143.2 (C_6), 122.0 (C_5), 80.3 (C_9), 74.4 (C_{10}), 64.0 (C_4), 38.8 (C_2), 30.7 (C_7), 27.1 (C_1), 22.0 (C_8).

IR (neat) 3313, 2872, 2934, 2963, 2125, 1735, 1145 cm^{-1}.

HRMS (EI) *m/z* calcd for $C_{13}H_{20}O_2$: 208.2967, found: 208.1457.

Structure 97: 1-cyclohexenylprop-2-ynyl pivalate (1j)



$C_{14}H_{20}O_2$

Mol. Wt.: 220.3074

The typical procedure B was applied with **1-cyclohexenylprop-2-yn-1-ol** (**7j**, 1.2 g, 8.9 mmol), **pivaloyl chloride** (1.6 mL, 10.9 mmol) and **triethylamine** (1.6 mL, 10.9 mmol) in 30 mL of DCM. After treatment, 1.8 g of crude yellow oil was obtained.

Purification was achieved by flash chromatography on silica gel (5 % Et_2O/Pent) to give **1-cyclohexenylprop-2-yny1-pivalate (1j)** as a pale yellow oil (1.45 g, 74 % over 2 steps).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 5.98 (bs, 1H, H_6), 5.73 (s, 1H, H_4), 2.48 (d, ^3J= 1.9 Hz, 1H, H_{10}), 2.22-1.98 (m, 4H, H_7), 1.64-1.68 (m, 2H, H_8), 1.57-1.61 (m, 2H, H_8), 1.22 (s, 9H, H_1).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 177.3 (C_3), 133.2 (C_5), 127.3 (C_6), 80.1 (C_9), 74.1 (C_{10}), 67.4 (C_4), 38.9 (C_2), 27.1 (C_1), 25.1 (C_7), 24.4 (C_7), 22.5 (C_8), 22.1 (C_8).

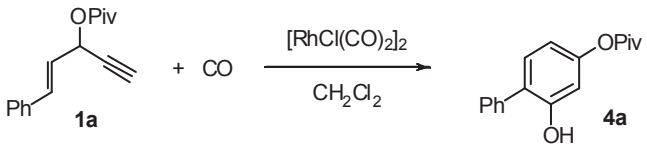
IR (neat) 3290, 2973, 2932, 2861, 2840, 2122, 1735, 1146 cm^{-1}.

EIMS *m/z* (relative intensity) 220 (M^+, 4), 117 (34), 91 (23), 83 (22), 57 (100).

HRMS (EI) *m/z* calcd for $C_{14}H_{20}O_2$: 220.1463, found: 220.1468.

III. 5. 2. Synthesis of the resorcinol derivatives

Typical procedure C for phenol derivatives preparation:

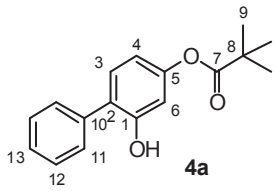


A magnetic stir bar, **(*E*)-1-phenylpent-1-en-4-yn-3-yl pivalate** (**1a**, 128.5 mg, 0.53 mmol, 1 eq), **tetracarbonyl-dichlorodirhodium** (4.9 mg, 0.013 mmol, 2.5 mol %) and 10 mL of DCM were placed in a 50 mL stainless steel autoclave. The autoclave was closed, purged three times with carbon monoxide, pressurized with 80 atm of **carbon monoxide** and then heated at 80°C for 5

hours. Excess of CO was discharged at room temperature. The autoclave was washed with ether and solvents were removed under reduced pressure to give 135 mg of a crude brown oil.

The residue was then purified by flash chromatography (29 % Et_2O/hexanes) to give a yellow solid (109 mg, 76 %)

Structure 98: 2-hydroxybiphenyl-4-yl pivalate (4a)



4a

$C_{17}H_{18}O_3$

Mol. Wt.: 270.3230

m. p. = 97 – 99°C

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.49-7.44 (m, 4H, $H_{11,12}$), 7.40-7.38 (m, 1H, H_{13}), 7.25-7.23 (m, 1H, H_3), 6.73-6.71 (m, 2H, $H_{4,6}$), 5.57 (bs, 1H, H_{OH}), 1.39 (s, 9H, H_9).

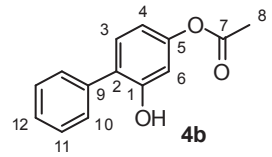
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 177.2 (C_7), 153.2 (C_1), 151.4 (C_5), 136.5 (C_{10}), 130.6 (C_{13}), 129.1 ($C_{11,12}$), 127.7 (C_3), 125.8 (C_2), 113.8 (C_4), 109.3 (C_6), 39.1 (C_8), 27.1 (C_9).

IR (KBr) 3600-3100 (br), 3052, 2965, 2872, 2933, 1744, 1732, 1610, 1591, 1129, 1150 cm^{-1}.

EIMS *m/z* (relative intensity) 270 (M^+, 32), 187 (20), 186 (100), 185 (21), 69 (24), 57 (49).

HRMS (EI) *m/z* calcd for $C_{17}H_{18}O_3$: 270.1256, found: 270.1252.

Structure 99: 2-hydroxybiphenyl-4-yl acetate (4b)



4b

$C_{14}H_{12}O_3$

Mol. Wt.: 228.2433

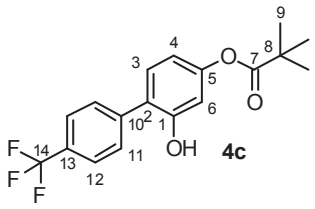
The typical procedure C was applied with **(*E*)-1-phenylpent-1-en-4-yn-3-yl acetate** (**1a**, 102 mg, 0.51 mmol), **tetracarbonyl-dichlorodirhodium** (9.7 mg, 0.025 mmol, 4.9 mol %) in 30 mL of DCM. The autoclave was pressurized with 80 atm of CO. After 5 hours, 123 mg of crude brown oil was obtained.

Purification was achieved by flash chromatography on silica gel (44 % Et_2O/Hex) to give **2-hydroxybiphenyl-4-yl acetate (4b)** as an orange solid (78.6 mg, 67 %).

m. p. = 109 - 111°C

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.49-7.46 (m, 2H, H_{11}), 7.45-7.43 (m, 2H, H_{10}), 7.41-7.38 (m, 1H, H_{12}), 7.23 (d, ^3J= 8.8 Hz, 1H, H_3), 6.74-6.73 (m, 2H, $H_{4,6}$), 5.36 (bs, 1H, H_{OH}), 2.31 (s, 3H, H_8).
^{13}C NMR ($CDCl_3$, 125 MHz): δ = 169.5 (C_7), 153.2 (C_1), 151.0 (C_5), 136.4 (C_9), 130.7 (C_{12}), 129.2 ($C_{10,11}$), 127.9 (C_3), 126.0 (C_2), 113.9 (C_4), 109.3 (C_6), 21.1 (C_8).
IR (KBr) 3500-3100 (br), 3070, 2924, 1732, 1604, 1227, 1196 cm^{-1}.
EIMS *m/z* (relative intensity) 228 (M^+, 37), 187 (34), 187 (34), 186 (100), 185 (62), 128 (21).
HRMS (EI) *m/z* calcd for $C_{14}H_{12}O_3$: 228.0786, found: 228.0782.

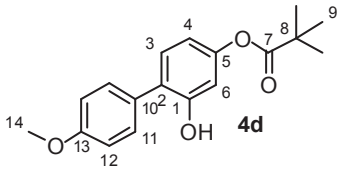
Structure 100: 2-hydroxy-4'-(trifluoromethyl)biphenyl-4-yl pivalate (4c)



$C_{18}H_{17}O_3F_3$
Mol. Wt.: 338.3210

The typical procedure C was applied with **(*E*)-1-(4-(trifluoromethyl)phenyl)pent-1-en-4-yn-3-yl pivalate** (**1c**, 156 mg, 0.5 mmol), **tetracarbonyl-dichlorodirhodium** (9.7 mg, 0.025 mmol, 5 mol %) in 30 mL of DCM. The autoclave was pressurized with 80 atm of CO. After 5 hours, 158 mg of crude brown oil was obtained.
Purification was achieved by flash chromatography on silica gel (23 % AcOEt/hex) to give **2-hydroxy-4'-(trifluoromethyl)biphenyl-4-yl pivalate (4c)** as a yellow solid (95 mg, 56 %).
m. p. = 170 – 172°C
^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.71 (d, ^3J= 8.3 Hz, 2H, H_{12}), 7.59 (d, ^3J= 7.8 Hz, 2H, H_{11}), 7.25 (d, ^3J= 8.3 Hz, 1H, H_3), 6.74 (dd, ^3J= 8.3 Hz, ^4J= 1.8 Hz, 1H, H_4), 6.70 (d, ^4J= 2.3 Hz, 1H, H_6), 5.27 (bs, 1H, H_{OH}), 1.40 (s, 9H, H_9).
^{13}C NMR ($CDCl_3$, 125 MHz): δ = 177.6 (C_7), 153.4 (C_1), 151.7 (C_5), 140.7 (C_{10}), 130.9 (C_q), 129.5 ($C_{11,12}$), 125.6 (C_3), 124.7 (C_q), 123.0 (C_q), 114.0 (C_4), 109.8 (C_6), 39.2 (C_8), 27.1 (C_9).
IR (KBr) 3600-3200, 2982, 2942, 2879, 1724, 1605, 1328, 1161, 1069 cm^{-1}.
EIMS *m/z* (relative intensity) 338 (M^+, 31), 254 (100), 205 (17), 177 (22), 57 (37).
HRMS (EI) *m/z* calcd for $C_{17}H_{18}O_3F_3$: 338.1130, found: 338.1143.

Structure 101: 2-hydroxy-4'-methoxybiphenyl-4-yl pivalate (4d)



$C_{18}H_{20}O_4$

Mol. Wt.: 300.3490

The typical procedure C was applied with **(*E*)-1-(4-methoxyphenyl)pent-1-en-4-yn-3-yl pivalate** (**1d**, 139.5 mg, 0.51 mmol), **tetracarbonyl-dichlorodirhodium** (5.0 mg, 0.013 mmol, 2.5 mol %) in 10 mL of DCM. The autoclave was pressurized with 80 atm of CO. After 5 hours, 162 mg of crude brown oil was obtained.

Purification was achieved by flash chromatography on silica gel (29 % Et_2O/Hex) to give **2-hydroxy-4'-methoxybiphenyl-4-yl pivalate (4d)** as a yellow solid (72.7 mg, 47 %).

m. p. = 112 – 114°C

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.37 (d, ^3J= 8.7 Hz, 2H, H_{11}), 7.19 (d, ^3J= 8.4 Hz, 1H, H_3), 7.02 (d, ^3J= 8.3 Hz, 2H, H_{12}), 6.70-6.68 (m, 2H, $H_{4,6}$), 5.22 (bs, 1H, H_{OH}), 3.86 (s, 3H, H_{14}), 1.37 (s, 9H, H_9).

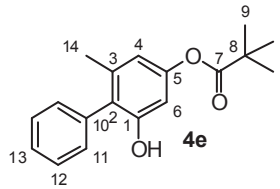
^{13}C NMR ($CDCl_3$, 125 MHz): δ = 177.1 (C_7), 159.3 (C_{13}), 153.2 (C_1), 151.2 (C_5), 130.5 (C_3), 130.3 (C_{11}), 128.6 (C_2), 125.4 (C_{10}), 114.7 (C_{12}), 113.7 (C_4), 109.1 (C_6), 55.3 (C_{14}), 39.1 (C_8), 27.1 (C_9).

IR (KBr) 3500-3300, 2974, 2935, 1732, 1604, 1500, 1246, 11579 cm^{-1}.

EIMS *m/z* (relative intensity) 300 (M^+, 25), 216 (63), 73 (100), 60 (67), 57 (89), 55 (67).

HRMS (EI) *m/z* calcd for $C_{18}H_{20}O_4$: 300.1362, found: 300.1363.

Structure 102: 2-hydroxy-6-methylbiphenyl-4-yl pivalate (4e)



$C_{18}H_{20}O_3$

Mol. Wt.: 284.3496

The typical procedure C was applied with **(E)-2-methyl-1-phenylpent-1-en-4-yn-3-yl pivalate** (**1e**, 115 mg, 0.45 mmol), **tetracarbonyl-dichlorodirhodium** (8.7 mg, 0.022 mmol, 5 mol %) in 9

mL of DCM. The autoclave was pressurized with 75 atm of CO. After 5 hours, 131 mg of crude brown oil was obtained.

Purification was achieved by flash chromatography on silica gel (20 % AcOEt/hexanes) to give **2-hydroxy-6-methylbiphenyl-4-yl pivalate (4e)** as a yellow solid (65 mg, 50 %).

M. p. = 93 – 95°C

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.52-7.49 (m, 2H, H_{12}), 7.44-7.41 (m, 1H, H_{13}), 7.29-7.26 (m, 2H, H_{11}), 6.37 (s, 2H, $H_{4,6}$), 4.83 (bs, 1H, H_{OH}), 2.06 (s, 3H, H_{14}), 1.36 (s, 9H, H_9).

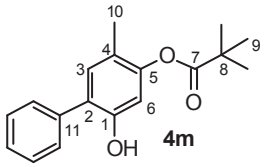
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 177.3 (C_7), 153.7 (C_1), 151.1 (C_5), 138.3 (C_3), 134.8 (C_{10}), 130.5 (C_{11}), 129.6 (C_{12}), 128.4 (C_{13}), 125.7 (C_2), 115.1 (C_4), 106.4 (C_6), 39.2 (C_8), 27.3 (C_9), 20.6 (C_{14}).

IR (KBr) 3600-3100, 2973, 2933, 2872, 1752, 1616, 1137 cm^{-1}.

EIMS *m/z* (relative intensity) 284 (M^+, 33), 200 (100), 83 (17), 57 (34).

HRMS (EI) *m/z* calcd for $C_{18}H_{20}O_3$: 284.1412, found: 284.1414.

Structure 103: 2-hydroxy-5-methylbiphenyl-4-yl pivalate (4m)



$C_{18}H_{20}O_3$

Mol. Wt.: 284.3496

The typical procedure C was applied with **(*E*)-3-methyl-1-phenylpent-1-en-4-yn-3-yl pivalate 84 %** (**1m**, 139 mg, 0.46 mmol), **tetracarbonyl-dichlorodirhodium** (4.6 mg, 0.012 mmol, 2.6 mol %) in 10 mL of DCM. The autoclave was pressurized with 50 atm of CO. After 5 hours, 157 mg of crude brown oil was obtained.

Purification was achieved by flash chromatography on silica gel (6 % AcOEt/hexanes) to give **2-hydroxy-5-methylbiphenyl-4-yl pivalate (4m)** as a pale yellow solid (81 mg, 62 %).

M. p. = 107 – 109°C

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.48-7.41 (m, 5H, H_{Ar}), 7.07 (s, 1H, H_3), 6.64 (s, 1H, H_6), 5.17 (bs, 1H, H_{OH}), 2.12 (s, 3H, H_{10}), 1.39 (s, 9H, H_9).

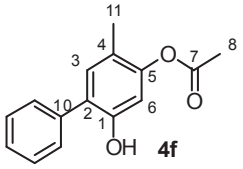
^{13}C NMR ($CDCl_3$, 125 MHz): δ = 176.7 (C_7), 151.1 (C_1), 149.4 (C_5), 136.7 (C_{11}), 132.1 (C_{Ar}), 129.1 (C_{Ar}), 127.7 (C_{Ar}), 125.8 (C_2), 122.0 (C_4), 109.5 (C_6), 39.2 (C_8), 27.2 (C_9), 15.3 (C_{10}).

IR (KBr) 3600-3300, 2974, 2931, 2873, 1728, 1616, 1122 cm^{-1}.

EIMS *m/z* (relative intensity) 284 (M^+, 33), 200 (100), 199 (16), 85 (11), 57 (40).

HRMS (EI) *m/z* calcd for $C_{18}H_{20}O_3$: 284.1412, found: 284.1418.

Structure 104: 2-hydroxy-5-methylbiphenyl-4-yl acetate (4f)



$C_{15}H_{14}O_3$

Mol. Wt.: 242.2699

The typical procedure C was applied with **(*E*)-3-methyl-1-phenylpent-1-en-4-yn-3-yl acetate 66%** (**1f**, 162 mg, 0.5 mmol), **tetracarbonyl-dichlorodirhodium** (4.9 mg, 0.012 mmol, 2.5 mol %) in 10 mL of DCM. The autoclave was pressurized with 50 atm of CO. After 5 hours, 174 mg of crude brown oil was obtained.

Purification was achieved by flash chromatography on silica gel (10 % AcOEt/hexanes) to give **2-hydroxy-5-methylbiphenyl-4-yl acetate (4f)** as a pale yellow solid (82 mg, 68 %) and **(*Z*)-3-methyl-1-phenylpent-1-en-4-yn-3-yl acetate** (9 mg, 8 %).

M. p. = 111 – 113°C

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.49-7.37 (m, 5H, H_{Ar}), 7.09 (s, 1H, H_3), 6.68 (s, 1H, H_6), 5.18 (bs, 1H, H_{OH}), 2.34 (s, 3H, H_8), 2.13 (s, 3H, H_9).

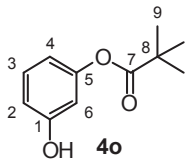
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 169.2 (C_7), 151.1 (C_1), 149.3 (C_q), 136.5 (C_q), 132.2 (C_q), 129.2 (C_{Ar}), 129.1 (C_{Ar}), 127.9 (C_3), 126.1 (C_q), 122.0 (C_q), 109.6 (C_6), 20.8 (C_8), 15.3 (C_9).

IR (KBr) 3500-3200 (br), 3028, 2931, 1720, 1612, 1038 cm^{-1}.

EIMS *m/z* (relative intensity) 242 (M^+, 16), 200 (100), 199 (22), 69 (19).

HRMS (EI) *m/z* calcd for $C_{15}H_{14}O_3$: 242.0943, found: 242.0943.

Structure 105: 3-hydroxyphenyl pivalate (4o)



$C_{11}H_{14}O_3$

Mol. Wt.: 194.2271

The typical procedure C was applied with **pent-1-en-4-yn-3-yl pivalate** (**1o**, 83 mg, 0.5 mmol), **tetracarbonyl-dichlorodirhodium** (19 mg, 0.05 mmol, 10 mol %) in 30 mL of DCM. The

autoclave was pressurized with 80 atm of CO. After 24 hours, 100 mg of crude brown oil was obtained.

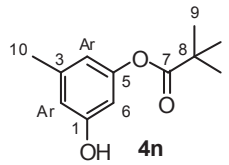
Purification was achieved by flash chromatography on silica gel (23 % Et_2O/hexanes) to give **3-hydroxyphenyl pivalate (4o)** as a pale yellow solid (37 mg, 38 %).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.16 (t, 1H, ^3J= 8.3,7.8 Hz, H_3), 6.61-6.57 (m, 2H, $H_{2,4}$), 6.49 (s, 1H, H_6), 6.28 (bs, 1H, H_{OH}), 1.36 (s, 9H, H_9).

Spectroscopic data were consistent with those reported in the literature.[173]

CAS: 214895-80-4

Structure 106: 3-hydroxy-5-methylphenyl pivalate (4n)



4n

$C_{12}H_{16}O_3$

Mol. Wt.: 208.2536

The typical procedure C was applied with **2-methylpent-1-en-4-yn-3-yl pivalate** (**1n**, 90.4 mg, 0.50 mmol), **tetracarbonyl-dichlorodirhodium** (9.7 mg, 0.025 mmol, 5 mol %) in 30 mL of DCM. The autoclave was pressurized with 80 atm of CO. After 14 hours at 100°C, 101 mg of crude brown oil was obtained.

Purification was achieved by flash chromatography on silica gel (29 % Et_2O/hexanes) to give **3-hydroxy-5-methylphenyl pivalate (4n)** as a pale yellow oil (23.7 mg, 23 %).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 6.47 (s, 1H, H_{Ar}), 6.43 (s, 1H, H_{Ar}), 6.34 (s, 1H, H_6), 5.45 (bs, 1H, H_{OH}), 2.26 (s, 3H, H_{10}), 1.33 (s, 9H, H_9).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 177.6 (C_7), 156.4 (C_1), 151.7 (C_5), 140.5 (C_3), 114.2 (C_{Ar}), 113.7 (C_{Ar}), 106.1 (C_6), 39.1 (C_8), 27.1 (C_9), 21.3 (C_{12}).

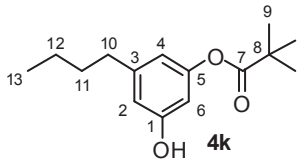
IR (neat) 3600-3100, 2975, 2934, 2873, 1728, 1595, 1134 cm^{-1}.

EIMS *m/z* (relative intensity) 208 (M^+, 23), 124 (100), 57 (33).

HRMS (EI) *m/z* calcd for $C_{12}H_{16}O_3$: 208.1099, found: 208.1090.

[173] Yamaguchi, M.; Arisawa, M.; Omata, K.; Kabuto, K.; Hirama, M.; Uchimaru, T. *J. Org. Chem.* **1998**, *63*, 7298.

Structure 107: 3-butyl-5-hydroxyphenyl pivalate (4k)



$C_{15}H_{22}O_3$

Mol. Wt.: 250.3334

The typical procedure C was applied with **4-methyleneoct-1-yn-3-yl pivalate** (**1k**, 104.5 mg, 0.47 mmol), **tetracarbonyl-dichlorodirhodium** (9.1 mg, 0.024 mmol, 5 mol %) in 10 mL of DCM. The autoclave was pressurized with 70 atm of CO. After 10 hours, 125 mg of crude brown oil was obtained.

Purification was achieved by flash chromatography on silica gel (10 % AcOEt/hexanes) to give **3-butyl-5-hydroxyphenyl pivalate (4k)** as a pale yellow oil (43 mg, 37 %).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.48 (s, 1H, H_{Ar}), 6.43 (s, 1H, H_{Ar}), 6.35 (t, 1H, ^4J= 2.3 Hz, H_6), 2.52 (t, 2H, ^3J= 7.8 Hz, H_{10}), 1.59-1.53 (m, 2H, H_{11}), 1.37-1.24 (m, 2H, H_{12}), 1.34 (s, 9H, H_9), 0.91 (t, 3H, ^3J= 7.4 Hz, H_{13}).

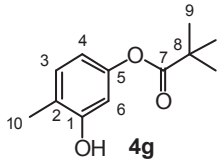
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 177.7 (C_7), 156.5 (C_1), 151.8 (C_5), 145.8 (C_3), 113.6 (C_{Ar}), 113.2 (C_{Ar}), 106.5 (C_6), 39.2 (C_8), 35.6 (C_{10}), 33.3 (C_{11}), 27.2 (C_9), 22.5 (C_{12}), 14.1 (C_{13}).

IR (neat) 3500-3100 (br), 2958, 2931, 2866, 1728, 1608, 1146 cm^{-1}.

EIMS *m/z* (relative intensity) 250 (M^+, 33), 166 (42), 124 (100), 83 (24), 57 (69).

HRMS (EI) *m/z* calcd for $C_{15}H_{22}O_3$: 250.1569, found: 250.1560.

Structure 108: 3-hydroxy-4-methylphenyl pivalate (4g)



$C_{12}H_{16}O_3$

Mol. Wt.: 208.2536

The typical procedure C was applied with **(*E*)-hex-4-en-1-yn-3-yl pivalate** (**1g**, 100 mg, 0.56 mmol), **tetracarbonyl-dichlorodirhodium** (5.4 mg, 0.014 mmol, 2.5 mol %) in 11 mL of DCM. The autoclave was pressurized with 80 atm of CO. After 5 hours, 126 mg of crude brown oil was obtained.

Purification was achieved by flash chromatography on silica gel (20 % AcOEt/hexanes) to give **3-hydroxy-4-methylphenyl pivalate (4g)** as a yellow solid (67 mg, 58 %).

m. p. = 70 - 72°C

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.05 (d, 1H, ^{3}J= 7.9 Hz, H_3), 6.49 (dd, 1H, ^{3}J= 7.9 Hz, ^{4}J= 1.8 Hz, H_4), 6.39 (d, 1H, ^{4}J= 1.8 Hz, H_6), 5.87 (bs, 1H, H_{OH}), 2.13 (s, 3H, H_{10}), 1.36 (s, 9H, H_9).

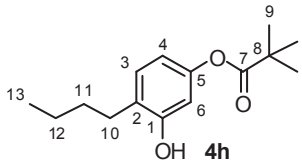
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 178.4 (C_7), 154.8 (C_1), 149.6 (C_5), 131.2 (C_3), 122.0 (C_2), 112.9 (C_4), 108.7 (C_6), 39.2 (C_8), 27.2 (C_9), 15.5 (C_{10}).

IR (KBr) 3600-3100 (br), 2975, 2933, 2873, 1727, 1608, 1153 cm^{-1}.

EIMS *m/z* (relative intensity) 208 (M^+, 24), 124 (100), 57 (37).

HRMS (EI) *m/z* calcd for $C_{12}H_{16}O_3$: 208.1099, found: 208.1104.

Structure 109: 4-butyl-3-hydroxyphenyl pivalate (4h)



4h

$C_{15}H_{22}O_3$

Mol. Wt.: 250.3334

The typical procedure C was applied with **(*E*)-non-4-en-1-yn-3-yl pivalate** (**1h**, 111.1 mg, 0.50 mmol), **tetracarbonyl-dichlorodirhodium** (9.9 mg, 0.025 mmol, 5.1 mol %) in 10 mL of DCM. The autoclave was pressurized with 80 atm of CO. After 5 hours, 146 mg of crude brown oil was obtained.

Purification was achieved by flash chromatography on silica gel (17 % Et_2O/hexanes) to give **4-butyl-3-hydroxyphenyl pivalate (4h)** as a pale yellow oil (81 mg, 64 %).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.07-7.05 (m, 1H, H_3), 6.56 (dd, ^{3}J= 8.3 Hz, ^{4}J= 2.3 Hz, 1H, H_4), 6.49 (d, ^{4}J= 1.9 Hz, 1H, H_6), 4.94 (bs, 1H, H_{OH}), 2.55 (t, ^{3}J= 15.1 Hz, 2H, H_{10}), 1.59-1.53 (m, 2H, H_{11}), 1.41-1.33 (m, 2H, H_{12}), 1.34 (s, 9H, H_9), 0.93 (t, ^{3}J= 7.3 Hz, 3H, H_{13}).

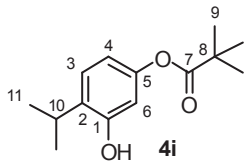
^{13}C NMR ($CDCl_3$, 125 MHz): δ = 177.6 (C_7), 154.1 (C_1), 149.5 (C_5), 130.2 (C_3), 126.3 (C_2), 113.0 (C_4), 108.7 (C_6), 39.1 (C_8), 31.8 (C_{10}), 29.2 (C_{11}), 27.1 (C_9), 22.5 (C_{12}), 13.9 (C_{13}).

IR (neat) 3600-3100 (br), 2958, 2932, 2872, 2861, 1728, 1606, 1156, 1124 cm^{-1}.

EIMS *m/z* (relative intensity) 250 (M^+, 29), 166 (62), 123 (100), 57 (59).

HRMS (EI) *m/z* calcd for $C_{15}H_{22}O_3$: 250.1569, found: 250.1560.

Structure 110: 3-hydroxy-4-isopropylphenyl pivalate (4i)



4i

$C_{14}H_{20}O_3$

Mol. Wt.: 236.3068

The typical procedure C was applied with **(E)-6-methylhept-4-en-1-yn-3-yl pivalate** (**1i**, 109 mg, 0.52 mmol), **tetracarbonyl-dichlorodirhodium** (5.1 mg, 0.013 mmol, 2.5 mol %) in 11 mL of DCM. The autoclave was pressurized with 50 atm of CO. After 5 hours, 124 mg of crude brown oil was obtained.

Purification was achieved by flash chromatography on silica gel (5 % AcOEt/hexanes) to give **3-hydroxy-4-isopropylphenyl pivalate (4i)** as a yellow solid (67 mg, 54 %).

m. p. = 52 – 54°C

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.16 (d, ^3J= 8.7 Hz, 1H, H_3), 6.61 (dd, ^3J= 8.3 Hz, ^4J= 2.3 Hz, 1H, H_4), 6.50 (d, ^4J= 2.4 Hz, 1H, H_6), 4.73 (bs, 1H, H_{OH}), 3.13-3.18 (m, 1H, H_{10}), 1.34 (s, 9H, H_9), 1.24 (d, ^3J= 6.9 Hz, 6H, H_{11}).

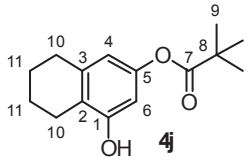
^{13}C NMR ($CDCl_3$, 125 MHz): δ = 178.3 (C_7), 153.8 (C_1), 149.2 (C_5), 132.5 (C_2), 126.8 (C_3), 112.9 (C_4), 108.8 (C_6), 39.2 (C_8), 27.2 (C_9), 26.8 (C_{10}), 22.6 (C_{11}).

IR (KBr) 3600-3300 (br), 2960, 2931, 2871, 1720, 1606, 1164 cm^{-1}.

EIMS *m/z* (relative intensity) 236 (M^+, 55), 152 (80), 137 (100), 57 (70).

HRMS (EI) *m/z* calcd for $C_{14}H_{20}O_3$: 236.1412, found: 236.1422.

Structure 111: 4-hydroxy-5,6,7,8-tetrahydronaphthalen-2-yl pivalate (4j)



4j

$C_{15}H_{20}O_3$

Mol. Wt.: 248.3175

The typical procedure C was applied with **1-cyclohexenylprop-2-ynyl pivalate** (**1j**, 113 mg, 0.51 mmol), **tetracarbonyl-dichlorodirhodium** (9.9 mg, 0.026 mmol, 5 mol %) in 10 mL of DCM. The autoclave was pressurized with 80 atm of CO. After 5 hours, 130 mg of crude brown oil was obtained.

Purification was achieved by flash chromatography on silica gel (10 % AcOEt/hexanes) to give **4-hydroxy-5,6,7,8-tetrahydronaphthalen-2-yl pivalate (4j)** as a yellow solid (58 mg, 47 %).

M. p. = 99 - 101°C

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 6.35 (s, 1H, H_4), 6.28 (d, ^{3}J= 2.5 Hz, 1H, H_6), 2.71-2.52 (m, 4H, H_{10}), 1.81-1.72 (m, 4H, H_{11}), 1.34 (m, 2H, H_9).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 178.0 (C_7), 154.3 (C_1), 149.0 (C_5), 139.7 (C_3), 121.1 (C_2), 113.7 (C_4), 105.8 (C_6), 39.2 (C_8), 29.8 (C_{10}), 27.3 (C_9), 22.8 (C_{11}), 22.7 (C_{11}), 22.6 (C_{10}).

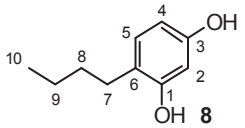
IR (KBr) 3600-3300, 3424, 2940, 2842, 1720, 1598, 1154 cm^{-1}.

EIMS *m/z* (relative intensity) 248 (M^+, 25), 164 (100), 136 (30), 85 (25), 83 (39), 57 (44).

HRMS (EI) *m/z* calcd for $C_{15}H_{20}O_3$: 248.1412, found: 248.1402.

III. 5. 3. Synthesis of a bioactive resorcinol

Structure 112: 4-butylbenzene-1,3-diol (8)



8

$C_{10}H_{14}O_2$

Mol. Wt.: 166.2170

4-butyl-3-hydroxyphenyl pivalate (4h, 67 mg, 0.26 mmol**)** was stirred in 8 mL of a 2N NaOH solution. The mixture was vigorously stirred at rt. After 7h, HCl 37% was added until pH = 1. The resulting solution was then was submitted to a EtOAc extraction. The combined organic layers were washed with NaCl sat., dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 50 mg of a crude brown oil.

Purification was achieved by flash chromatography on silica gel (20 % AcOEt/hexanes) to give **4-buthylbenzene-1,3-diol** as a pale yellow oil (32 mg, 73 %).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.95 (d, ^{3}J= 8.9 Hz, 1H, H_5), 6.35 (dd, ^{3}J= 8.3 Hz, ^{4}J= 2.3 Hz, 1H, H_4), 6.32 (d, ^{4}J= 2.3 Hz, 1H, H_2), 4.80 (bs, 2H, H_{OH}), 2.52 (t, ^{4}J= 7.8 Hz, 2H, H_7), 1.57-1.54 (m, 2H, H_8), 1.39-1.35 (m, 2H, H_9), 0.93 (t, ^{4}J= 7.5 Hz, 3H, H_{10}).

Spectroscopic data were in consistent with those reported in the literature.[1]

CAS: 18979-61-8

Etudes synthétiques de nouvelles réactions par voie anionique ou catalysées par des métaux de transition.

RESUME

Ce mémoire est articulé autour de trois chapitres. En premier lieu, nos nouveaux résultats concernant la synthèse de 3-silapiperidines par voie dianionique sont présentés. Le chapitre suivant traite de nos premières études sur les mécanismes mis en jeu, au cours de la cycloisomérisation d'enynes-1,5 catalysée par $PtCl_2$, lors de la formation de systèmes [3.1.0]-bicycliques. Enfin, le dernier chapitre concerne nos travaux en collaboration avec l'université préfectorale d'Osaka, sur la formation de résorcinols fonctionnalisés, à partir de pivalate vinylpropargyliques par carbonylation catalytique au $[RhCl(CO)_2]_2$.

MOTS-CLES : dianions ; diélectrophiles ; 3-silapipéridines ; énynes-1,5 ; $PtCl_2$–cycloisomerisation ; $[RhCl(CO)_2]_2$-carbonylation ; résorcinols.

アニオン種および遷移金属錯体種を活用した合成反応に関する研究

要旨

本論文は３つの章によって構成されている。まず第一章にはジアニオン種を活用した3−シラピペリジン類の新規合成法について述べられている。第二章では塩化白金触媒を用いた1, 5−エンイン類の
[3,1,0]−双環性化合物への環化異性化反応の反応機構に関する研究について述べられている。第三章では大阪府立大学との共同研究として行なった、$[RhCl(CO)_2]_2$触媒によるビニルプロパルギルピバレート類の新規カルボニル化反応に関して述べられている。

キーワード：ジアニオン、求電子剤、3−シラピペリジン、1,5-エンイン、
塩化白金、環化異性化、$[RhCl(CO)_2]_2$，カルボニル化、レゾルシノール

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