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Asymmetric synthesis of Lactams mediated by Copper (I) complexes

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In the name of Allah, the Most Gracious and the Most Merciful

Say, "If the sea were ink for [writing] the words of my Lord, the sea would be exhausted before the words of my Lord were exhausted, even if We brought the like of it as a supplement."

Quran 18:109

All praise is due to Allah; we praise Him, seek His help, and ask for His forgiveness. Foremost, I am thankful to Allah, who supplied me with the courage, the guidance, and the love to complete this work.

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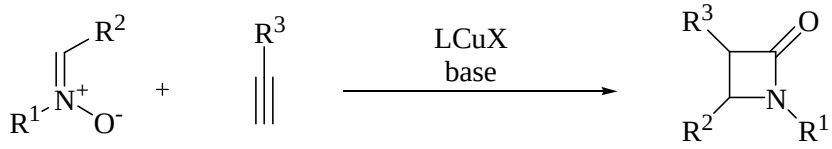
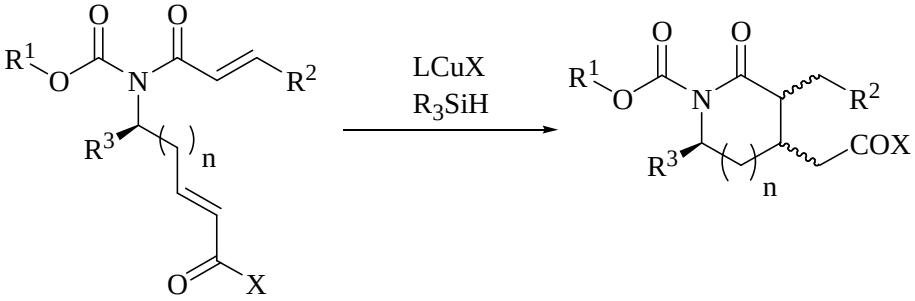
appreciation because it is so boundless. For being with me through this entire journey, it seems right that I dedicate this dissertation to you. I love you and you will always be in my heart.

ABSTRACT

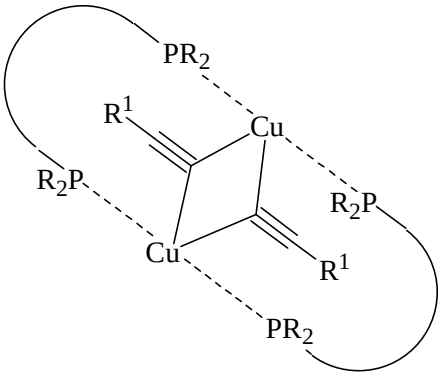
The asymmetric synthesis of β- and γ-lactams is a center of interest for chemists due to their biological and pharmaceutical applications. The asymmetric and diastereoselective synthesis of β-lactams through Kinugasa reaction, a (3+2) cycloaddtion reaction between a nitrone and a terminal alkyne and catalyzed by copper(I) complexes is studied.



Furthermore, a double Michael domino cyclization process catalyzed by a copper(I) catalyst is examined. This methodology allows the formation of γ- and δ-lactams in one step.

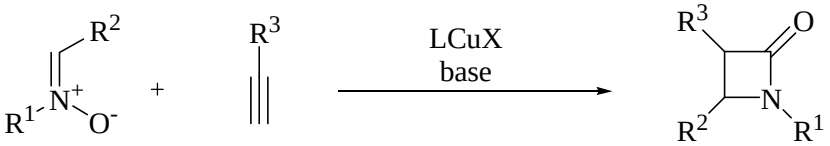


Besides, an illustration of a synthetic pathway to produce unprecedented dinuclear copper acetylide diphosphine complexes is demonstrated. These complexes are present with one phosphine of a given ligand bridging to one copper atom while the other phosphine bridges to the other copper atom.

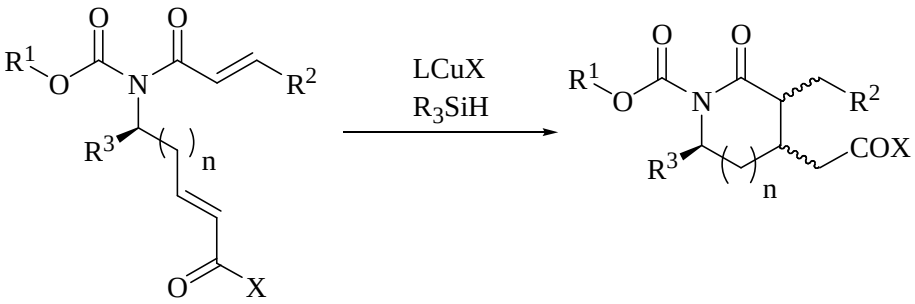

PR2
R1
Cu
R2P
R2P
Cu
R1
PR2

RÉSUMÉ

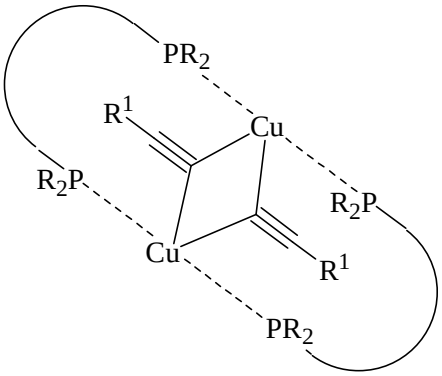
La synthèse asymétrique des β- et γ-lactames constitue une voie de recherche essentielle due à leurs propriétés biologiques et pharmaceutiques. Pour la synthèse de β-lactames de façons diastéréosélective et enantiosélective, l'étude de la réaction Kinugasa, une réaction de cycloaddtion (3 +2) entre un nitrone et un alcyne terminal catalysée par des complexes de cuivre(I), est effectué.



Un processus domino double Michael catalysé par un complexe de cuivre(I) est aussi discuter. Cette nouvelle méthodologie nous permet de former favorablement, en une seule étape, des γ-et δ-lactames de façon asymétrique.



Egalement une voie de synthèse pour produire des nouveaux complexes de diphosphine acetylenure cuivre dinucléaire est montrée. Dans ces complexes, une phosphine de la même molécule de ligand pont à un atome de cuivre, tandis que l'autre phosphine pont à l'autre atome de cuivre.


PR2
R1
Cu
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R2P
Cu
R1
PR2

“Verily in the creation of the heavens and the earth, and the alternation of night and day - there are indeed signs for men of understanding; Men who remember Allah, standing, sitting, and lying down on their sides, and contemplate the creation of the heavens and the earth (with the thought) "Our Lord! Not for nothing have You created (all) this. Glory to You! Give us salvation from the suffering of the Fire."

Quran 3:190-191

“When you're afraid of something, dive straight into it, because the intensity of abstaining from it is greater than what you're afraid of”

Imam Ali (AS)

“The Zahed desired the wine of Kousar; and Hafez, the cup:
Let us see between these two, the choice of the Omnipotent is what?”

Hafez

إلى صاحب الزمان

من روحي لتراب مقدمه الفداء...

وإلى نصف روحي التي حلقت

إلى محمد علي...

To Mohammad Ali

ABBREVIATIONS

Å	:	Angström
AcOEt	:	Ethyl acetate
AcOH	:	Acetic acid
Aq.	:	Aqueous
Ar	:	Aryl
atm.	:	Atmosphere
BAIB	:	Bis(acetoxy)iodobenzene
BINAP	:	2,2'-(diphenylphosphino)-1,1'-binaphtalene
Bn	:	Benzyl
Boc	:	*Di-tert-butyl dicarbonate*
n-Bu	:	Butyl
t-Bu	:	Tert-butyl
Cat.	:	catalytic
Cp	:	Cyclopentadienyl
CuAAc		Cu catalyzed alkyne azide cycloaddition
Cy	:	cyclohexyl
DBU	:	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	:	Dichloroethane
DCM	:	Dichloromethane
DMAP	:	4-Dimethylaminopyridine
DMF	:	*N*,*N*-dimethylformamide
DMPU	:	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	:	Dimethylsulfoxide

dpm	:	dipivaloylmethane
DPPBz	:	Diphenylphosphinobenzene
DPPE	:	Diphenylphosphinoethane
DPPF	:	Diphenylphosphinoferrocene
DPPM	:	Diphenylphosphinomethane
DtBPF		Ditertbutylphosphinoferrocene
E	:	Electrophile
d.e.	:	Diastereomeric excess
d.r.	:	Enantiomeric ratio
e.e.	:	Enantiomeric excess
Equiv.	:	Equivalent
Et	:	Ethyl
EWG	:	Electron withdrawing group
FMO		Frontier molecular orbital
GC	:	Gas chromatography
h	:	Hour
HRMS	:	High resolution mass spectroscopy
Hz	:	Hertz
i-Pr	:	Isopropyl
IR	:	Infra-red
KOAc	:	Potassium acetate
L	:	Ligand
LDA	:	Lithium diisopropylamide
LICA	:	Lithium isopropylcyclohexylamide

Me	:	Methyl
$MePh_2SiH$	:	Methyldiphenylsilane
$Me(EtO)_2SiH$	:	Methyldiethoxysilane
mmol	:	Millimole
n.d.	:	Non determined
n-BuLi	:	*n*-butyllithium
NAG	:	*N*-acetylglucosamine
NAM	:	*N*-acetylmuramic acid
NHC	:	*N*-heterocyclic carbene
NMR	:	Nuclear magnetic resonance
Nu	:	Nucleophile
PBP	:	Penicillin binding protein
PCC	:	Pyridinium chlorochromate
Ph	:	Phenyl
$PhSiH_3$	:	Phenylsilane
PMHS	:	Polyméthylhydrosilyloxane
PPTS	:	Pyridinium p-toluenesulfonate
pTSA	:	para-Toluenesulfonic acid
n-Pr	:	*n*-Propyl
ppm	:	Part per million
r.t.	:	Room temperature
TEMPO	:	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TFA	:	Trifluoroacetate
THF	:	Tetrahydrofuran

TLC	:	Thin layer chromatography
TMDS	:	1,1,3,3-tétraméthylhydrosiloxane
TMEDA	:	Tetramethylethylenediamine
TMG	:	Tetramethylguanidine
TMS	:	Trimethylsilyl
Tol.	:	Toluene
Ts	:	Tosyl

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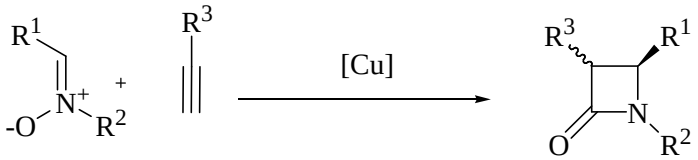
GENERAL OBJECTIVES

In the past few years, great attention has been dedicated to catalytic synthetic methods, especially transition metal catalyzed processes. Our group is particularily specialized in the development of copper(I) catalyzed processes. The general objective of the thesis was to develop efficient catalytic methods for the asymmetric synthesis of β- and γ-lactams in view of their utility as building blocks for total syntheses, or their biological and pharmaceutical properties.

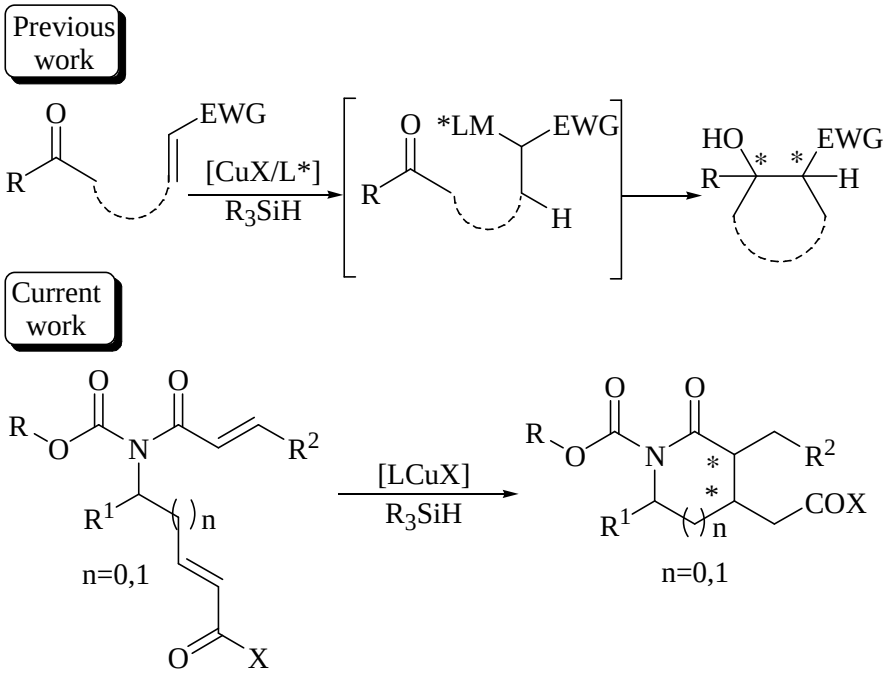
The first aim of this thesis was the development of a diastereoselective Kinugasa reaction for the synthesis of β-lactams using *N*-heterocyclic carbene (NHC) copper catalysts. The choice of such ligands was due to the fact that they are more likely to form stable complexes or intermediates compared to amine or diphopsphine ligands. These complexes or intermediates could provide some mechanistic information during our investigation. The valorization of the developed systems was also established through determining the scope of the reaction using different substrates. In addition, the use of chiral diphosphine ligands to induce asymmetry in the Kinugasa reaction was a second goal of this study. We aimed at optimizing the conditions necessary for this reaction to obtain high enantioselectivities.



Scheme 1. Kinugasa reaction catalyzed by copper(I)

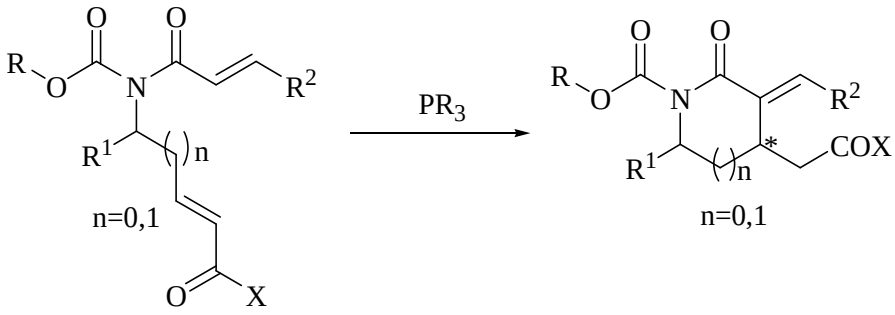
Moreover, due to our group's history in the development of new methodologies for copper(I) catalyzed domino reaction, our second objective was the development of a new methodology for the synthesis of γ-lactams from substrates containing two Michael acceptors. Initially, we envisaged to

report the reaction catalyzed by copper(I) complexes, and proposed a double reductive Michael cycloaddition mechanism that was initiated by the formation of a copper(I) hydride by the action of a silane.



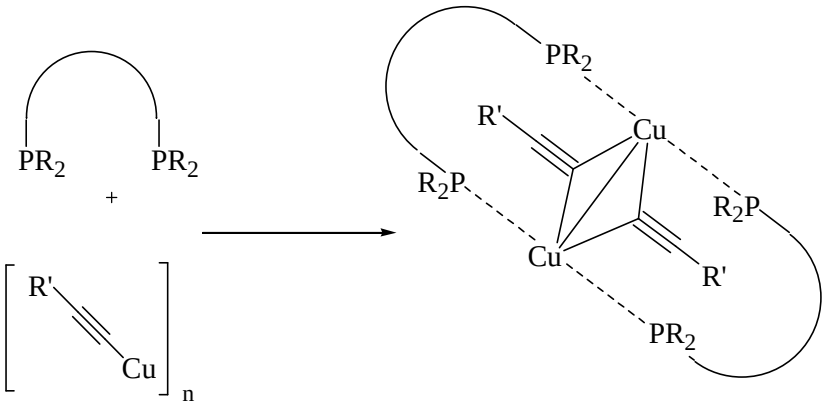
Scheme 2. Past and current studies of domino reactions catalyzed by copper(I)

Then, the formation of α-methylene-γ-lactams catalyzed by the action of trialkylphosphines on the same substrates containing two Michael acceptors, in an approach similar to Morita-Baylis-Hillman (MBH) reaction gained our interest.



Scheme 3. Vinologous MBH reaction catalyzed by trialkylphosphines

Finally, we looked at the synthesis and characterization of new airstable dinuclear copper complexes that were synthesized by a simple strategy starting from copper acetylide polymers and diphosphine ligands. These complexes could have some interesting physical properties.



Scheme 1. Synthesis of dinuclear copper acetylene diphosphine complexes

GENERAL INTRODUCTION

I. β- and γ-lactams

Lactams are one of the most perceived classes of naturally occurring compounds. The presence of lactam moiety in biologically active molecules of both natural and unnatural origin demonstrates the importance of this class of compounds. A reason for the great attention paid by chemists to these motifs is that, besides being present in immense number of natural and synthetic compounds that exhibit specific biological properties, its presence is much imperative for these properties to be displayed. In addition to having a diversified structure varying from 3-membered ring up to very big rings[1], these structures are versatile so that they can be devised for potential usage as interesting building blocks, especially in their chiral form, in both organic and medicinal fields. Although the synthesis and the organic chemistry of these moieties have been broadly studied, the development of new synthetic pathways for the access of such fundamental structures is still crucial especially for its enormous applications in pharmaceutical industry. Numerous classes of drugs for the treatment of inflammation, cancer, and other diseases contain the lactam motif in their structure such as β- and γ-lactams.

I.1 β-lactams

The term «antibiotic» (from Greek anti : « against », and bios : « life ») is defined as a natural substance that inhibits the growth of certain bacteria or destroys them by altering the chemical activity inside the bacteria or the chemical substances that are responsible for the formation of the bacterial

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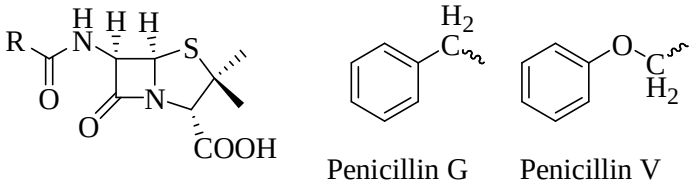
[1] Nubbemeyer, U., Synthesis of Medium-Sized Ring Lactams. In *Stereoselective Heterocyclic Synthesis III*, Metz, P., Ed. Springer Berlin Heidelberg2001; Vol. 216, pp 125.

cell wall[2]. β-Lactam antibiotics act through inhibiting the synthesis of the bacterial cell wall.

β-Lactams were first synthesized and characterized by Staudinger in 1907[3]. However, their function as antibiotics was not established before the discovery of penicillin in 1928 by Sir Alexander Fleming who remarked the antibacterial nature of the mold *Penicillium notatum* against *Staphylococcus aureus* cultures (Figure 1). Although it was proposed that penicillin contained a β-lactam ring, conventional understanding could not agree to the presence of such strained and reactive component within a naturally occurring substance. World war II brought forward an enormous effort to reveal the real structure of penicillin and to develop a means for a massive production of this compound. The chemical structure remained undetermined until 1945 when Hodgkin et al. proposed a molecular model and verified the structure by X-ray crystallography. This molecule was used for the first time as a remedy on a patient suffering from septicemia in 1941 in Oxford.



Penicillin G Penicillin V

Figure 1. Penicillin structure

Penicillins, recognized as the prime of the β-lactam family of antibiotics, were the first naturally occurring antibiotics to be characterized and employed in treatment of bacterial infections. The presence of the four

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[2] Fernandes, R.; Amador, P.; Prudêncio, C., *Reviews in Medical Microbiology* **2013,** *24*, 7.

[3] Tidwell, T. T., *Angewandte Chemie International Edition* **2008,** *47*, 1016.

membered β-lactam ring turned out to be responsible for the lethal action of the drug against bacteria. This antibiotic activity is directly related to the conformation adopted by penicillin where the nonplanar bridgehead bicyclic system, imposes the orthogonal orientation of the nitrogen lone pair and the carbonyl π-bond in a way that the normal amide conjugation exhibited by traditional amides is hindered[4]. This feature, in addition to the intrinsic strain of the four-membered ring, creates a situation where the β-lactam is more reactive than open chain amides, and the carbonyl functionality of the β-lactam ring turns out to be strongly electrophilic, thus acting as a highly effective acylating agent.

Afterwards, there has been an outbreak in studies concerning β-lactam antibiotics for reasons such as the constant need for new antibiotics due to the resistance developed by bacteria against common penicillins, in addition to the search for antibiotics with wide-ranging and/or different antibacterial activity[5]. For better results, new compounds had to possess low toxicity and good absorption, distribution, and metabolic characteristics a combination of properties often difficult to achieve. These studies have shown the feasibility of other lactam bearing structures in antibacterial treatment. Antibiotics bearing a β-lactam ring are responsible for the treatment of almost 55% of bacterial infections due to their high efficiency and limited secondary effects[6,7]. The β-lactam antibiotic family, all featuring a highly strained and reactive cyclic amide, can be classified into several groups according to their structure (Figure 2):

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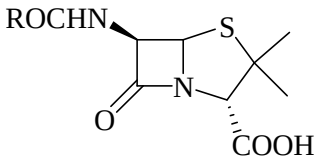
[4] http://www.scripps.edu/nicolaou/pdfs/Sample_Chapter13.pdf

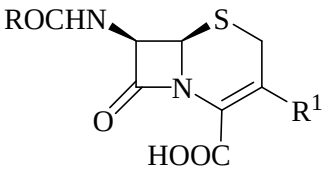
[5] Sammes, P. G., *Chemical Reviews* **1976,** *76*, 113.

[6] Matagne, A.; Dubus, A.; Galleni, M.; Frere, J.-M., *Natural Product Reports* **1999,** *16*, 1.

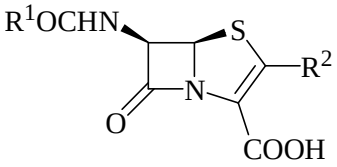
[7] Fisher, J. F.; Meroueh, S. O.; Mobashery, S., *Chemical Reviews* **2005,** *105*, 395.



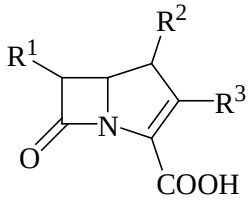
Penicillins (penams)



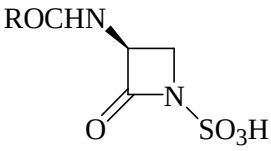
Cephalosporins (cephems)



Penems



Carbapenems



Monobactams

Figure 2. β-lactam antibiotic classes

Most antibiotics employed currently originate from natural sources, and are elaborated by microbes (bacteria or fungi) to serve as a chemical weapon against other surrounding microbes. β-lactams are produced by eukaryotic fungi, actinomycetes and even bacteria.

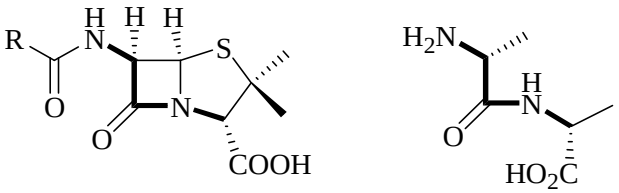
I.1.1 Mechanism of action of β-lactams

β-lactams deactivate the DD-transpeptidases, also called PBP (Penicillin Binding Protein), the enzymes responsible for the biosynthesis and remodeling of peptidoglycan ,a major component of the bacterial cell wall present in all bacteria[8]. Peptidoglycan forms a three dimensional network that surround the cell and protects it from osmotic pressure, providing it its shape and what's necessary for its growth and division. Peptidoglycan is a

[8] Matagne, A.; Lamotte-Brasseur, J.; Frère, J. M., *Biochem. J.* **1998,** *330,* 581.

polymer formed from linear repeating unit of alternating disaccharide containing N-acetylglucosamine (NAG) and N-acetylmuramic acid (NAM). The latter sugar in this disaccharide always terminates with two D-alanine residues. The final assembly of these unites, the transpeptidation, is a process catalyzed by the PBPs in which a peptide bond is formed between the D-alanine on one chain and the free amine in the other chain and which ends by the cleavage of the terminal D-alanine residue[9].

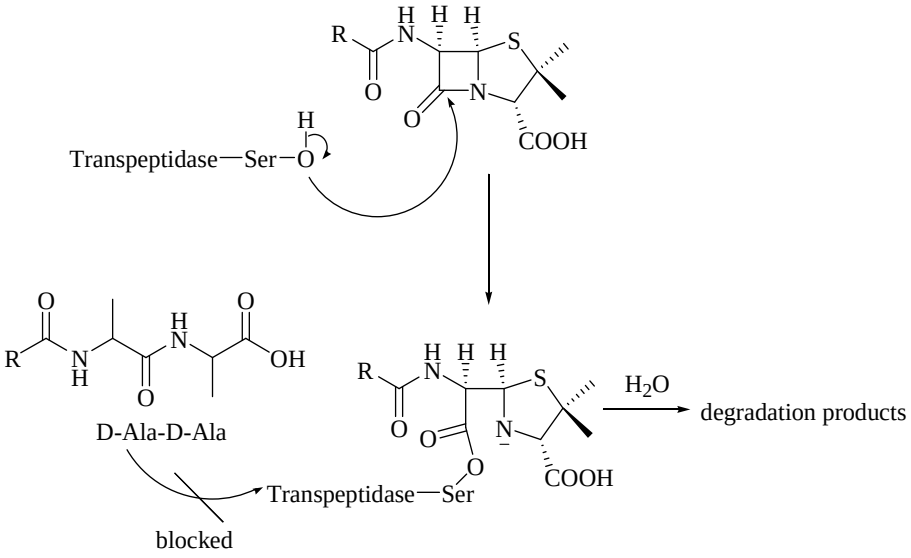
PBPs are active site serine enzymes which effectuate their catalytic cycle by an acylation/deacylation mechanism implying the formation of an acyl enzyme intermediate. Similarily, β-lactam antibiotics, owing to the high structural similarity of the β-lactam moiety with the D-alanine–D-alanine substrate (Figure 3), accomplish their action by acylating the active site serine residue of PBPs, forming a covalent non-catalytic acyl-enzyme complex[5,6], leading eventually to the inhibition of the PBPs and their unability to carry out transpeptidation which ultimately causes the cell membrane to rupture and leads to lysis and cell death (Scheme 1).



Penicillin D-Ala-D-Ala

Figure 3. Resemblance between penicillin and D-Ala–D-Ala moiety

[9] Wilke, M. S.; Lovering, A. L.; Strynadka, N. C. J., *Current Opinion in Microbiology* **2005,** *8,* 525.



Scheme 1. Reaction of penicillin with transpeptidase

I.1.2. Antibacterial resistance to β-lactams

Since the discovery of the first antibiotic, penicillin, the use of this wonder drug and its progeny has been a medical revolution empowering the rescue of millions of lives from fatal infections. Nevertheless, soon after the introduction of penicillin G, a report of a great number of bacteria showing resistance was observed, resulting in inefficient treatments. Today, over 90% of staphylococci infections show resistance to penicillin[10].

Bacteria are microorganism with wide variety that adapt to changes in their environment for the sake of survival. Antibacterial resistance existed way before the penicillins were discovered. Unfortunately, the significance of this concept was not fully perceived and they were often misused, sometimes abusively, resulting in a rigorous situation of bacterial resistance. An increase in the selection of the resistant bacteria led to a decrease in the

[10] www.who.int/en

activity of the β-lactam antibiotics. Soon after the emergence of bacterial resistance, many researches were conducted and several antibacterial drugs which competed with the bacterial resistance were put on the market. However, since the bacterial resistance is a natural biological phenomenon, it is just a matter of time before the bacteria will develop new mechanisms of resistance against the new drugs suggesting the continuous need to create new antibiotics that contest the bacterial resistance.

Notwithstanding, a status of abandon in the research for new drugs by pharmaceuticals is noticed. In the last 30 years there has been a void in the discovery of new potential antibiotics as reported by WHO (World Health Organization)[10] (Figure 4). An estimate of the burden of antibacterial resistance in the European union shows that overall society costs overpasses 1.5 billion euros each year, resulting in a reduced consumer income, employment, and savings, and an increase in national investment, spending, and healthcare delivery. These consequences ultimately cause a reduction in the gross domestic product (GDP): 1.4% to 1.6%.

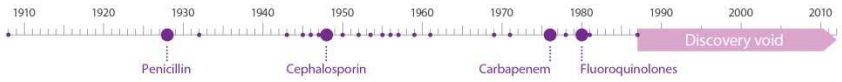


Figure 4. Timeline of antibiotics discovery

In their global report on surveillance of antimicrobial resistance 2014, WHO made a clear case, that resistance to common bacteria has reached alarming levels in many parts of the world. It calls attention to the need of surveillance as the basis for effectiveness of treatments and detection of new trends and threats. In a wider context, it considers antimicrobial resistance a global problem requiring a global solution that includes Surveillance as a key to inform public health actions and strategies. But as explained the resistance to

drugs found on the market is just a matter of time, such a research must be conducted for new antimicrobial drugs[10].

Generally speaking, there are four basic mechanisms of resistance to antimicrobial drugs that may take place in bacteria; decrease in the permeability due to porin mutation which results in a drop in the amount of the antimicrobial that reaches the target, an increase in pumping out of these antimicrobials by an efflux transporter; an enzymatic mechanism that destroys the antimicrobial molecules; the establishment of an unconventional metabolic pathway that does not require the use of precursors that non resistant bacteria need[11,12].

In general, the basic mechanism by which resistance to β-lactam antibiotics may occur in bacteria proceeds by the alteration of the antimicrobial activity in the presence of an enzyme that totally or partially destroys the antimicrobial molecules[13]. The expression of β-lactamases that hydrolyze the antibiotic is probably the most extensive case of resistance (Scheme 2). They hydrolyze the β-lactam ring in penicillin, cephalosporin and carbapenem series deactivating the chemical property of the antibacterial drug by destroying the β-lactam moiety. Some classes of β-lactamases are active site serine enzymes with structural and mechanistic resemblance to the PBPs.

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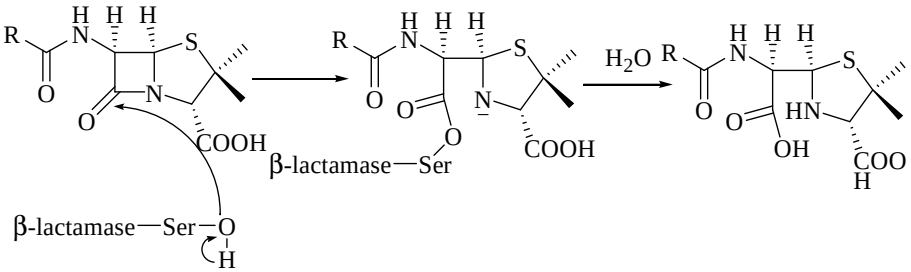
[11] Harbottle, H.; Thakur, S.; Zhao, S.; White, D. G., *Animal Biotechnology* **2006,** *17*, 111.

[12] Livermore, D. M., *Clinical Microbiology Reviews* **1995,** *8*, 557.

[13] Fernandes, R.; Amador, P.; Prudêncio, C., *Reviews in Medical Microbiology* **2013,** *24*, 7.



Scheme 2. Hydrolysis of β-lactams by β-lactamases

In case of the transpeptidase, the rate constant of the hydrolysis of the acyl-enzyme complex is very low, and thus an accumulation of this complex causes the deactivation of the enzymes. However, with β-lactamases the rate constant of hydrolysis is very high and leads to an inactive penicilloic acid products and the release of the active β-lactamase with high turnovers[14].

Another type of β-lactamases uses zinc to activate a water molecule and catalyzes its addition to the β-lactam ring in order to deactivate it.[5]

I.1.3 Synthesis of β-lactams

The stereoselective synthesis of the β-lactam unit has been a point of interest for many researchers for its biological and structural significance, and since it represents an important class of vastly useful synthons for natural product synthesis. Considerable effort has been devoted to refurbish already present methodologies, or to elaborate new methodologies necessary for the formation of these rings. Efficient methods for the synthesis of these 2-azetidinone rings have been the subject of several reviews and book chapters (Scheme 3)[15,16]. It is not until the last decade that real efforts for the direct

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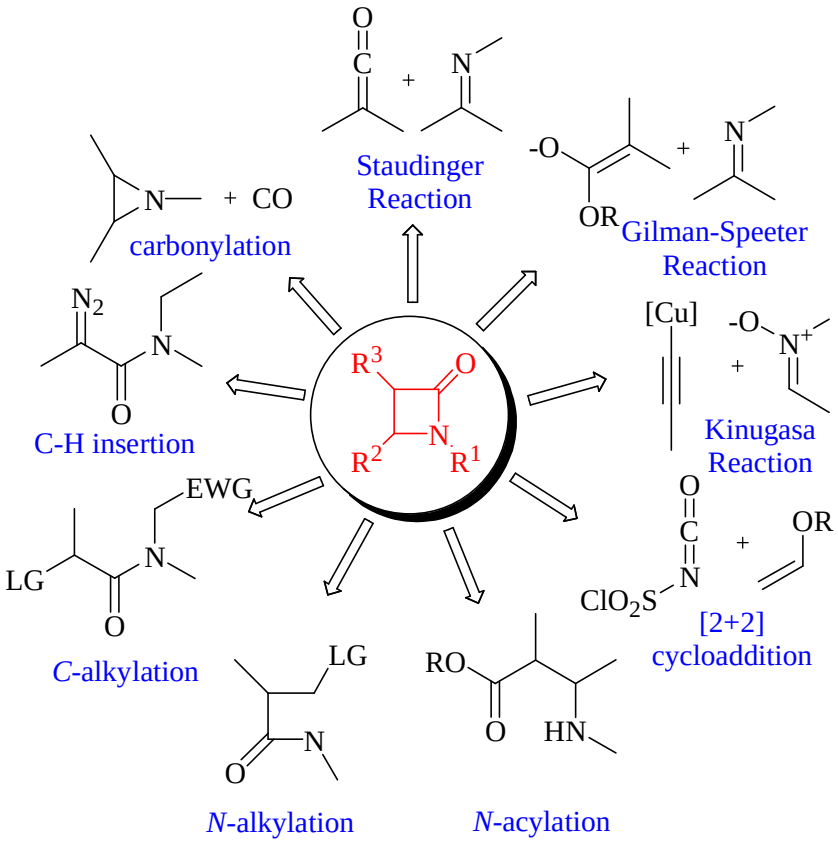
[14] Ghuysen, J. M., *Annu Rev Microbiol* **1991,** *45,* 37.

[15] France, S.; Weatherwax A.; Taggi, A. E.; Leckta T., *Accounts of Chemical Research* **2004**, *37,* 592-600.

[16] Georg, G. I., *The Organic chemistry of b [beta]-lactams.* VCH Publishers: New York, N.Y., 1992.

catalytic enantioselective or diastereoselective methods for the formation of these rings have been established. This does not hold back the presence of certain limitations for each of the methods developed.



Scheme 3. Important methods for β-lactam synthesis

Up until recently, the state of the art in this endeavor consisted mainly either of the Staudinger reaction[16,17,18], a ketene-imine cycloaddition approach, or

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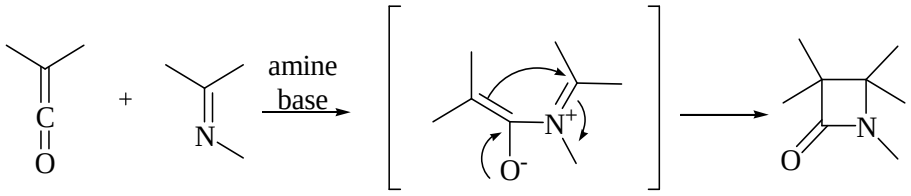
[17] Banik, B. K.; Subbaraju, G. V.; Manhas, M. S.; Bose, A. K., *Tetrahedron Letters* **1996,** *37*, 1363; Banik, B. K.; Manhas, M. S.; Bose, A. K., *The Journal of Organic Chemistry* **1994,** *59*, 4714; Kaluza, Z.; Manhas, M. S.; Barakat, K. J.; Bose, A. K., *Bioorganic & Medicinal Chemistry Letters* **1993,** *3*, 2357; Bose, A. K.; Manhas, M. S.; van der Veen, J. M.; Bari, S. S.; Wagle, D. R., *Tetrahedron* **1992,** *48*, 4831;

the Gilman-Speeter reaction[19], the condensation between ester enolates and imines.

I.1.3.1 Staudinger reaction

The Staudinger reaction is one of the most versatile routes to β-lactams. It was introduced as a reaction between a ketene and an imine that proceeds without the presence of a catalyst. The reaction mechanism proceeds by a nucleophilic attack of the imine on the central carbon of the ketene, resulting in a β-zwitterionic intermediate. The formation of the β-lactam product is achieved by a conrotatory electrocyclic ring closure (Scheme 4).



Scheme 4. Staudinger reaction

Two stereogenic centers are formed during this stepwise reaction, whose formation can be completely stereocontrolled (Scheme 5). These

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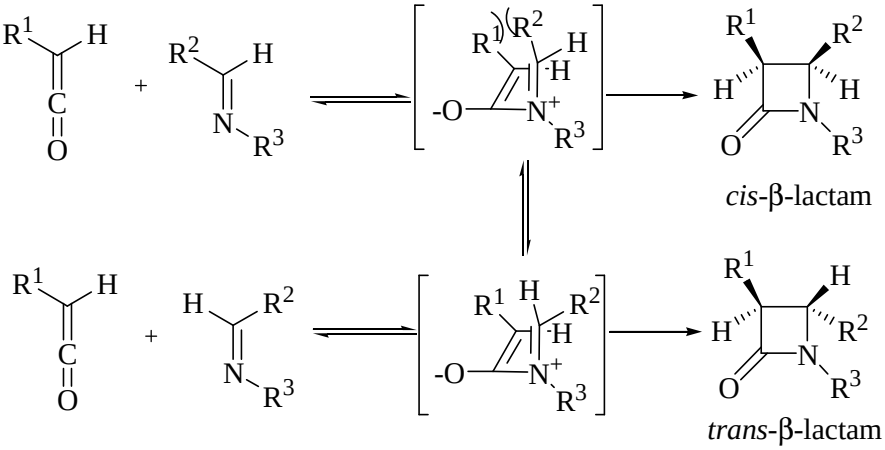
Manhas, M. S.; Ghosh, M.; Bose, A. K., *The Journal of Organic Chemistry* **1990,** *55*, 575; Van der Veen, J. M.; Bari, S. S.; Krishnan, L.; Manhas, M. S.; Bose, A. K., *The Journal of Organic Chemistry* **1989,** *54*, 5758; Wagle, D. R.; Garai, C.; Monteleone, M. G.; Bose, A. K., *Tetrahedron Letters* **1988,** *29*, 1649; Wagle, D. R.; Garai, C.; Chiang, J.; Monteleone, M. G.; Kurys, B. E.; Strohmeyer, T. W.; Hegde, V. R.; Manhas, M. S.; Bose, A. K., *The Journal of Organic Chemistry* **1988,** *53*, 4227; Sahu, D. P.; Mashawa, P.; Manhas, M. S.; Bose, A. K., *The Journal of Organic Chemistry* **1983,** *48*, 1142.

[18] R. D. G. Cooper, B. W. D., D. B. Boyd, *Pure and Applied Chemistry* **1987,** *59*, 485; Xu, J., *Arkivoc* **2009,** *ix*, 21.

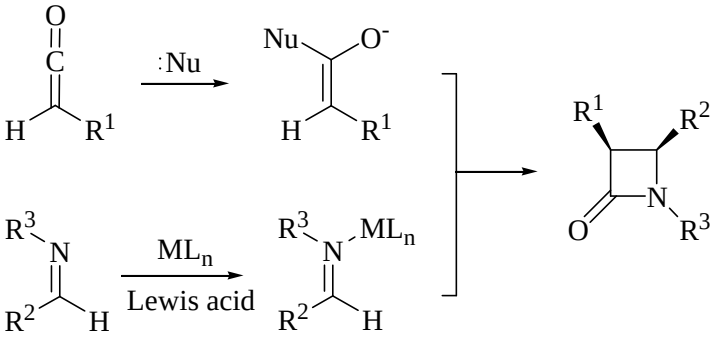
[19] Gilman, H.; Speeter, M., *Journal of the American Chemical Society* **1943,** *65*, 2255.

methodologies mostly rely on the presence of chiral auxiliaries or enantiomerically pure starting materials for the control of stereoselectivity.



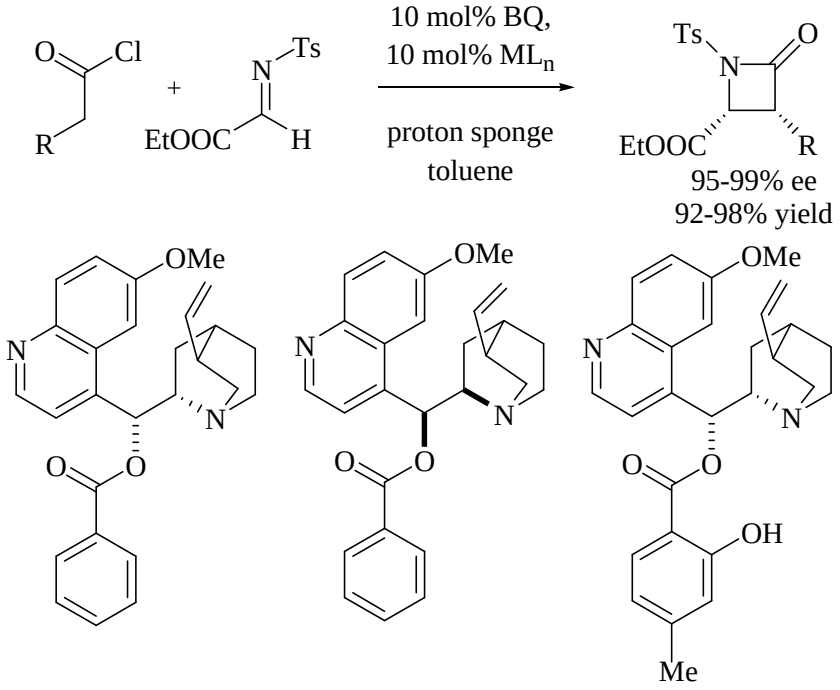
Scheme 5. Formation of *cis* and *trans* β-lactams by Staudinger reaction

To execute this reaction in a catalytic mode, we need to reverse the electronic properties of the substrates (umpolung); i.e. the imine would act as the electrophile and the ketene as the nucleophile. To achieve this with high selectivity, the imine could be activated by the use of a Lewis acid and the ketene by a nucleophile (Scheme 6).



Scheme 6. Umpolung effect

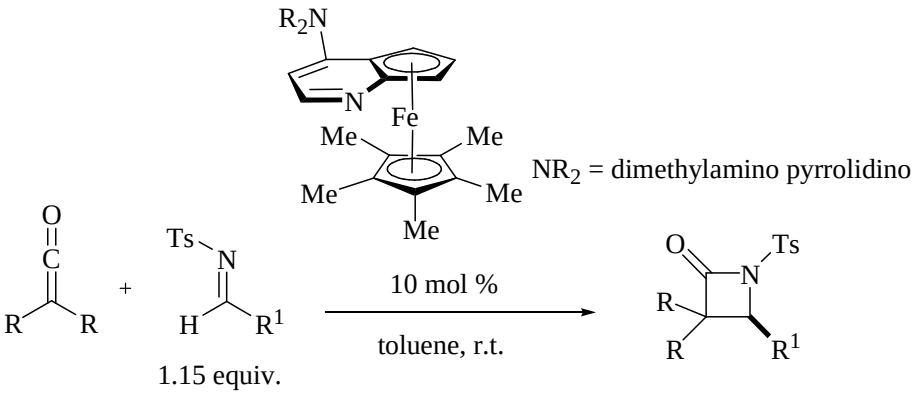
The first example of this methodology was reported by Lectka in 2000[20]. They described a highly enantioselective reaction between electron deficient ketenes and imines engaging a bifunctional catalytic system consisting of chiral amines such as benzoylquinines (BQ) and an achiral metal salt (ML_n) or Lewis acid such as $In(OTf)_3$ as catalysts. This bifunctional catalytic system provided optically enriched β-lactams (95-99% ee) in excellent yields (92-98%), and diastereomeric ratios ranging from 9:1 to 60:1 favoring the *cis* isomer (Scheme 7).



Scheme 7. Lectka's first catalytic Staudinger reaction

[20] France, S.; Wack, H.; Hafez, A. M.; Taggi, A. E.; Witsil, D. R.; Lectka, T., *Organic Letters* **2002,** *4*, 1603; Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Drury, W. J.; Lectka, T., *Journal of the American Chemical Society* **2000,** *122*, 7831.

Following Lectka's first example of the asymmetric synthesis of β-lactams, Fu *et al.* stated that a planar-chiral nucleophile catalyst is a very efficient catalyst for the Staudinger reaction, resulting in the *cis* isomer as the major product. Excellent yields (82-98%) and selectivities (81-98% ee, and 8:1 to 15:1 d.r.) are obtained, in addition to the broad scope of this reaction[21] (Scheme 8).



Scheme 8. Fu's planar nucleophile catalyst in Staudinger reaction

Fu and coworkers also showed the dependence of the diastereoselectivity on the protecting group of the nitrogen substituent[22] proposing that the mechanism is different in each case: in the case of triflyl (Tf), the reaction proceeds through an "imine first" mechanism leading to the *trans* product, while in the case of tosyl (Ts), the reaction proceeds through a "ketene first" mechanism leading to the *cis* product. They described the first example of a catalytic enantioselective Staudinger reaction leading to *trans*-β-lactams (Scheme 9).

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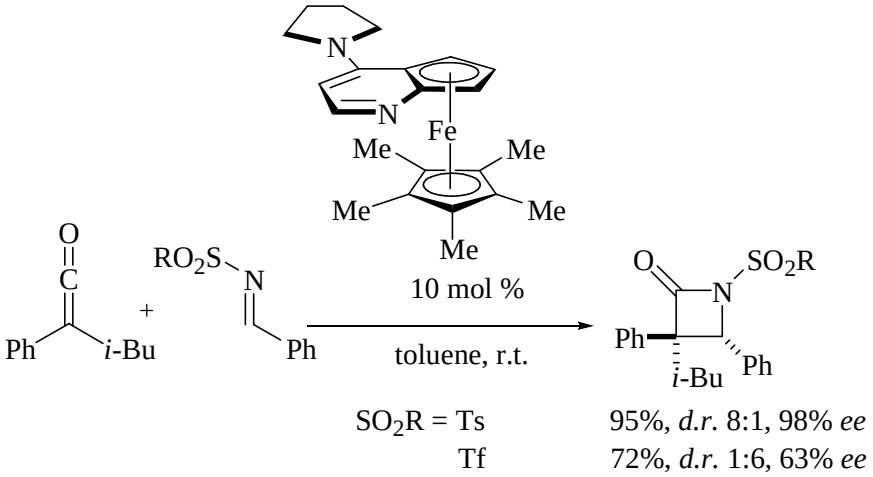
[21] Hodous, B. L.; Fu, G. C., *Journal of the American Chemical Society* **2002,** *124*, 1578.

[22] Lee, E. C.; Hodous, B. L.; Bergin, E.; Shih, C.; Fu, G. C., *Journal of the American Chemical Society* **2005,** *127*, 11586.

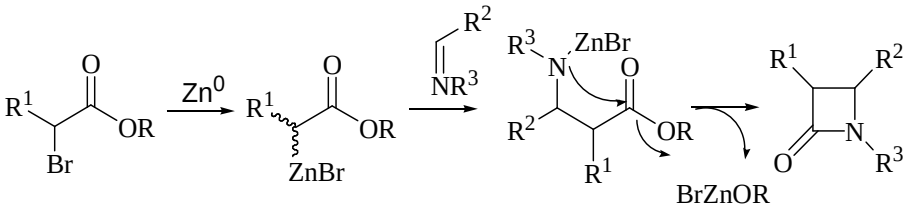


Scheme 9. Fu's enantioselective Staudinger reaction leading to *trans*-β-lactams

I.1.3.2 Gilman-Speeter reaction

The enolate-imine Condensation known as the Gilman-Speeter reaction is the first example of an enolate-imine condensation approach to β-lactams using a Reformatsky reagent. Upon the addition of zinc metal to a mixture of α-bromoester and imine, a zinc bromide enolate is formed. This enolate then adds to the imine to form an intermediate β-amino ester adduct. Subsequently, the ring closure via the attack of the N atom at the carbonyl of the ester group gives the final product releasing a zinc alkoxide[23] (Scheme 10).

[23] Gilman, H.; Speeter, M., *Journal of the American Chemical Society* **1943,** *65*, 2255.



Scheme 10. Gilman-Speeter reaction

Later, other types of enolates were introduced in this reaction, such as lithium, lithium thioesters, titanium, boron, tin[24]… The asymmetric version of this reaction was limited to the presence of enantiomerically pure starting materials or chiral auxiliaries. The first catalytic example was reported by Tomioka and coworkers in 1997[25]. They employed a chiral diether ligand and a lithium amide base that form a ternary complex reagent in solution. This complex is thought to induce asymmetry in the final product. Although the exact structure and the mechanism of this complex are not well understood, the presence of one or both the chiral ether ligand and the lithium amide bases are essential for higher rates of the reaction. The best results were obtained when symmetrically α-disubstituted ester enolates are used to exclude any problem of diastereoselectivity. The best lithium amide bases employed in this reaction were lithium isopropylcyclohexylamide (LICA) and lithium dicyclohexyl amide. The reaction in the presence of 0.2 equivalents of the ligand and LICA provides the β-lactam in 85% yield and 90% ee after 4 hours (Scheme 11).

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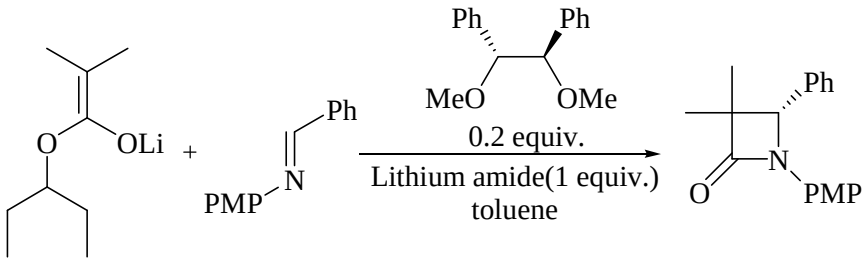
[24] Benaglia, M.; Cinquini, M.; Cozzi, F., *European Journal of Organic Chemistry* **2000,** *2000*, 563; Hart, D. J.; Ha, D. C., *Chemical Reviews* **1989,** *89*, 1447.

[25] Fujieda, H.; Kanai, M.; Kambara, T.; Iida, A.; Tomioka, K., *Journal of the American Chemical Society* **1997,** *119*, 2060.



Scheme 11. First catalytic example reported by Tomioka

When the lithium amide base and the chiral ether ligand are replaced by a chiral tridentate ligand (Figure 5), in order to avoid the addition of a lithium base that may cause some side product formation in certain cases, higher yields are obtained (99%) and *ee* between 65% and 90%[26].

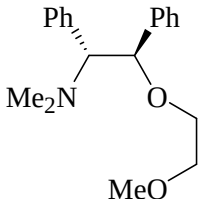


Figure 5. Chiral tridentate ligand used by Tomioka

I.1.3.3 Direct catalytic asymmetric approaches

The formation of β-lactams can be mediated by nucleophilic transition metal catalysis, which present an appealing alternative to the classical methodologies mentioned above. They contribute in providing a general route for more diverse structures of β-lactams. One example is the metal-catalyzed carbonylation and ring expansion of aziridines. The carbonylation process could be affected using Rh, Co… as metal catalysts. The general mechanism for the carbonylation of aziridines is shown in scheme 12.

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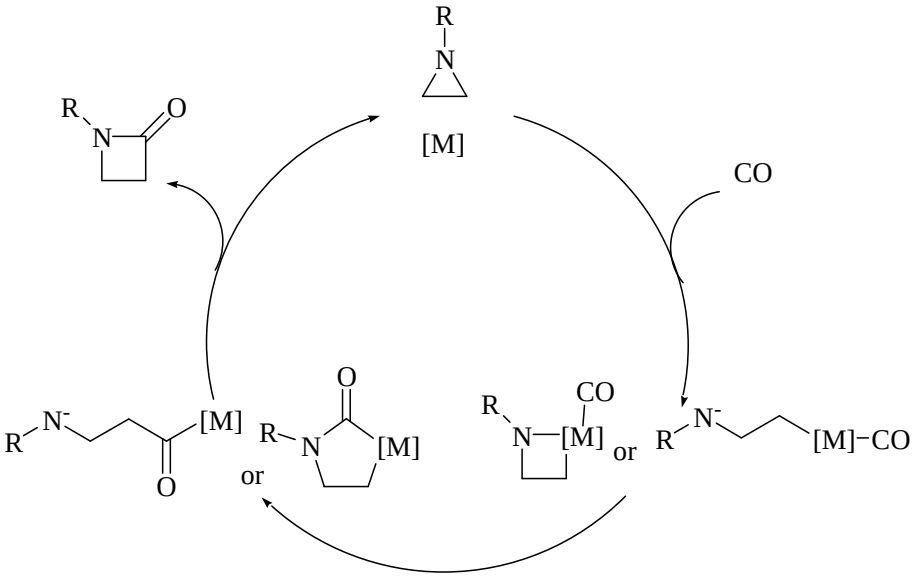
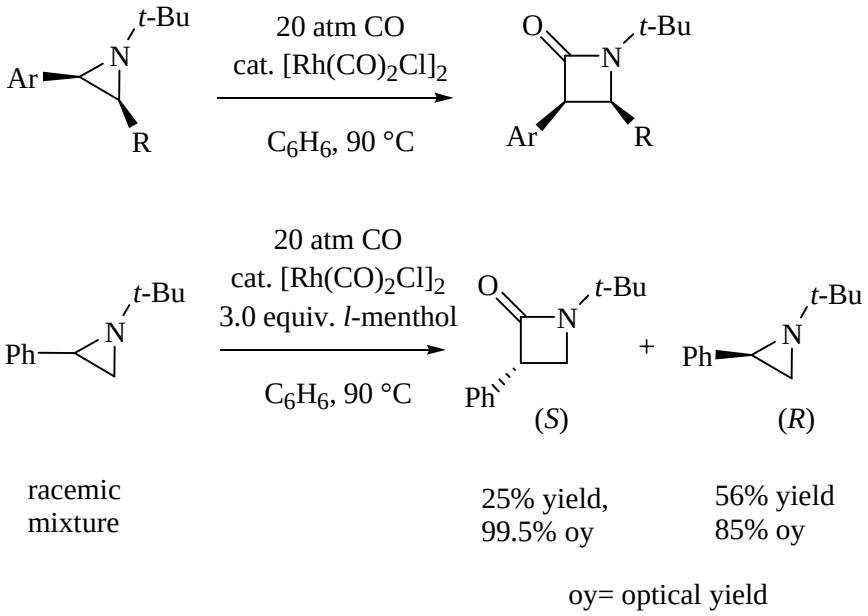
[26] Tomioka, K.; Ahmed Hussein, M.; Kambara, T.; Fujieda, H.; Hayashi, S.; Nomura, Y.; Kanai, M.; Koga, K., *Chemical Communications* **1999**, 715.



Scheme 12. Mechanism of metal catalyzed carbonylation

The pioneers in the development of this method were the Alper group whose approach promoted the use of $[Rh(CO)_2Cl]_2$ to carbonylate aryl substituted aziridines selectively at the benzylic position[27] (Scheme 13).

[27] Calet, S.; Urso, F.; Alper, H., *Journal of the American Chemical Society* **1989,** *111*, 931; Lu, S.-M.; Alper, H., *The Journal of Organic Chemistry* **2004,** *69*, 3558.



Scheme 2. Alper's aziridine carbonylation

More recently, the groups of Alper[28] and Coates[29] developed cobalt catalyzed carbonylations of aziridines. According to Alper *et al.*, and unlike their Rh catalyzed system, the cobalt system was effective in the transformation of simple alkyl aziridines to β-lactams (Scheme 14a). *Trans*-β-lactams were obtained from a *cis*-aziridine in quantitative yields, and *cis*-β-lactams were obtained when using a *trans*-aziridine. Aziridines bearing different N-substituents, as well as mono and disubstituted aziridines fit as suitable substrates under these conditions. Conversely, when an *N*-benzoyl aziridine was used, they obtained a mixture of regioisomers. This result led

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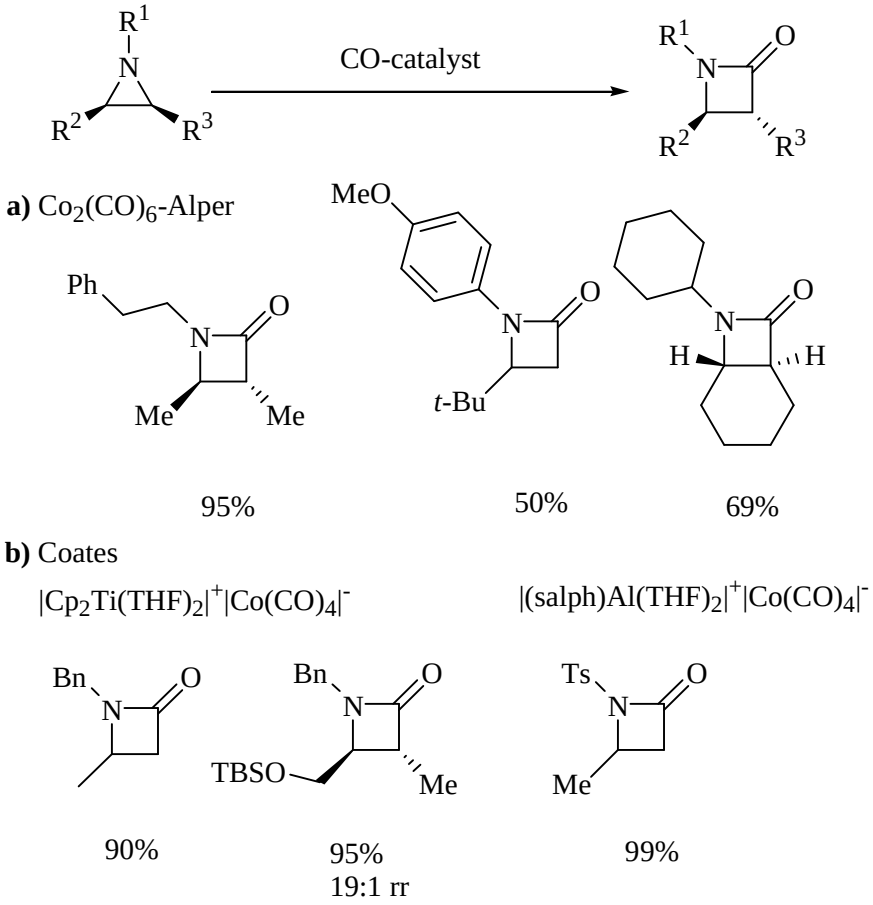
[28] Davoli, P.; Moretti, I.; Prati, F.; Alper, H., *The Journal of Organic Chemistry* **1999,** *64*, 518; Davoli, P.; Forni, A.; Moretti, I.; Prati, F.; Torre, G., *Tetrahedron* **2001,** *57*, 1801.

[29] Mahadevan, V.; Getzler, Y. D. Y. L.; Coates, G. W., *Angewandte Chemie International Edition* **2002,** *41*, 2781.

the researchers to propose an alternative single electron transfer (SET) oxidative addition mechanism that explains the regioselectivity of this system.



Scheme 14. Alper's and Coates cobalt carbonylations of aziridines

Later, Coates et al. showed that two of their developed Lewis acid–cobalt catalysts, $[Cp_2Ti\text{-}(THF)_2][Co(CO)_4]$ and $[(salph)Al(THF)_2][Co(CO)_4]$, could catalyze the ring expansion of aziridines to β-lactams[29] (Scheme 14b). The reaction initiates by the nucleophilic attack of the $Co(CO)_4^-$ on the aziridine ring resulting in an inversion of configuration at the electrophilic carbon, and

ring opening. The CO insertion takes place into the Co–C bond. The acyl transfer to the nitrogen results in the β-lactam ring.

Another important reaction for the synthesis of β-lactams is the catalytic asymmetric C–H insertion of diazoamides using rhodium catalysts: $Rh_2(OAc)_4$. The reaction proceeds through the formation of a metallocarbenoid (Scheme 15). A stable dirhodium tetracarboxylate carbenoid was isolated and was proven to catalyze the β-lactam formation from diazoacetamide[30]. Metallocarbenoids provide control over regio- and stereoselectivity in C–H insertions. When R^2 is an alkyl group, chances of formation of γ-lactam rings are high. The formation of 4-membered rings is favored in the cases of α-diazoacetamides depending on the methylene group adjacent to the amide nitrogen as reported by Doyle *et al*.[31]

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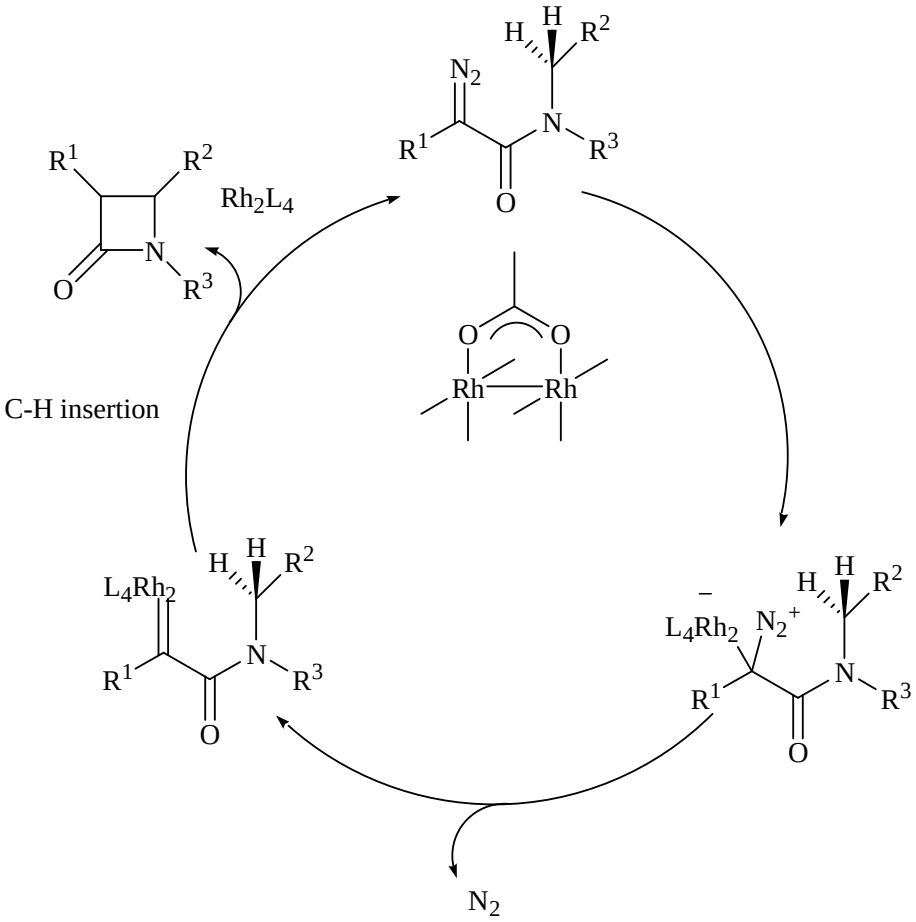
[30] Snyder, J. P.; Padwa, A.; Stengel, T.; Arduengo, A. J.; Jockisch, A.; Kim, H.-J., *Journal of the American Chemical Society* **2001,** *123*, 11318.

[31] Doyle, M. P.; Protopopova, M. N.; Winchester, W. R.; Daniel, K. L., *Tetrahedron Letters* **1992,** *33*, 7819.



Scheme 3. Mechanism of Rh catalyzed C–H insertion of diazoamides

In parallel, the research group of Hashimoto developed enantioselective methods that contributed to the understanding of the full capacity of this methodology. They replaced the acetate ligands on the rhodium metal with four *N*-phthaloyl-(*S*)-phenylalinate ligands (Figure 6).

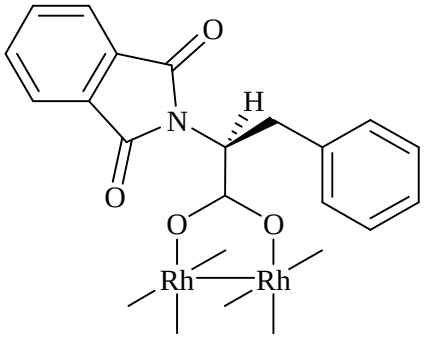


Figure 6. Hashimoto's catalyst

In order to promote the formation of the four-membered over five-membered lactam rings, Hashimoto placed a *t*-butyl group on the amide nitrogen and obtained high yields (97%) and moderate enantioselectivities (74% *ee*)[32]. In 1998 Hashimoto reported a highly enantioselective synthesis of a key azetidin-2-one necessary for the construction of carbapanem antibiotics using variants of his chiral Rh-catalyst. He ended with excellent yields (85-94%) and high enantioselectivities (84-96% *ee*)[33].

I.1.3.3.1 Kinugasa reaction

The Kinugasa reaction was first reported in 1972 by Kinugasa and Hashimoto, providing a convergent route to access β-lactam moieties in one step[34]. The reaction was carried out in anhydrous pyridine at r.t. and under inert atmosphere, between phenyl copper (I) acetylide and *α,N*-diphenyl nitrone (scheme 16). This reaction yielded exclusively the *cis*-1,3,4-triphenyl-2-azetidinone in 50-60% yield within 30 min.

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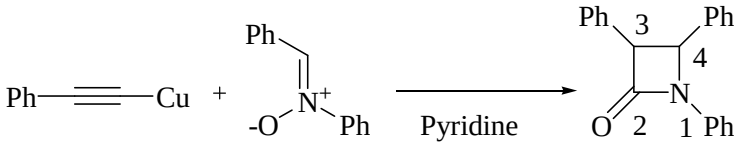
[32] Watanabe, N.; Anada, M.; Hashimoto, S.-i.; Ikegami, S., *Synlett* **1994,** *1994*, 1031.

[33] Anada, M.; Watanabe, N., *Chemical Communications* **1998**, 1517.

[34] Kinugasa, M.; Hashimoto, S., *Journal of the Chemical Society, Chemical Communications* **1972**, 466.



Scheme 16. Kinugasa reaction

The availability and relative stability of the starting materials are amongst the most tempting features of this reaction, as well as the mild reaction conditions and tolerance towards a variety of functional groups (alcohols, halides, amines, esters…). A great number of terminal alkynes variously substituted are commercially available or easily prepared from readily available precursors. These terminal alkynes are highly susceptible to being incorporated in useful transformations due the facile manipulation of their reactivity using transition metals[35]. Similarly, nitrones present a functional group that has been extensively employed in organic synthesis due to its reactivity, as well as its relative stability and easy access and handling. Another advantage of this reaction is the high atom economy that it provides. Furthermore, when the two main functionalities of this reaction are found on the same molecule, an intramolecular reaction is allowed to happen comparatively easier than in the Staudinger reaction which requires the use of an acyl halide, a more reactive functionality[35]. Furthermore, metal catalyzed processes provide a simpler pathway for the induction of asymmetry through the use of chiral catalytic systems.

The detailed mechanism and developments of this reaction will be discussed in chapter 1.

[35] Stecko, S.; Furman, B.; Chmielewski, M., *Tetrahedron* **2014,** *70*, 7817.

Other significant syntheses of β-lactams include the cyclization of activated hydroxyl amides using the Mitsunobu protocol, *N*-acylation of β-amino acids, *N*-alkylation of amides or hydroxamic acids by a β-leaving group[36]…

I.1.3 Conclusion

Due to the increasing difficulty in the use of β-lactams as antibiotics, and despite the outgrowing resistance from microbes and the lack of interest in research in this domain, β-lactams outpace these difficulties in non-antibiotic uses that were developed recently. Some of the most distinguished applications that were demonstrated concern the use of β-lactams as inhibitors of cytomegalovirus protease[37], thrombin[38], prostate specific antigen[39], β-lactamase[40], and cholesterol absorption[41].

Evidently, β-lactams preserve their significance in synthetic organic chemistry and represent a valuable target for chemists. This monocyclic system presents a significant synthon in organic chemistry, mainly in peptide

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[36] Brandi, A.; Cicchi, S.; Cordero, F. M., *Chemical Reviews* **2008,** *108*, 3988.

[37] Ogilvie, W. W.; Yoakim, C.; Dô, F.; Haché, B.; Lagacé, L.; Naud, J.; O'Meara, J. A.; Déziel, R., *Bioorganic & Medicinal Chemistry* **1999,** *7*, 1521.

[38] Han, W. T.; Trehan, A. K.; Kim Wright, J. J.; Federici, M. E.; Seiler, S. M.; Meanwell, N. A., *Bioorganic & Medicinal Chemistry* **1995,** *3*, 1123.

[39] Adlington, R. M.; Baldwin, J. E.; Chen, B.; Cooper, S. L.; McCoull, W.; Pritchard, G. J.; Howe, T. J.; Becker, G. W.; Hermann, R. B.; McNulty, A. M.; Neubauer, B. L., *Bioorganic & Medicinal Chemistry Letters* **1997,** *7*, 1689.

[40] Danelon, G. O.; Mata, E. G.; Mascaretti, O. A.; Girardini, J.; Marro, M.; Roveri, O. A., *Bioorganic & Medicinal Chemistry Letters* **1995,** *5*, 2037.

[41] Dugar, S.; Yumibe, N.; Clader, J. W.; Vizziano, M.; Huie, K.; Van Heek, M.; Compton, D. S.; Davis Jr, H. R., *Bioorganic & Medicinal Chemistry Letters* **1996,** *6*, 1271.

synthesis (synthesis of α- and β-amino acids …), and in stereocontrolled synthesis in general (amino acids and their optically pure derivatives, alkaloids …)[42,43,44]. In particular, the stereocontrolled synthesis of chiral and achiral β-lactams has gained much attention. A better understanding of the chemical structure (structure-activity relationship) would allow the development of more efficient drugs to defeat the continuous resistance of microbes. Enormous effort should be devoted to prepare new compounds bearing a 2-azetidinone ring.

I.2 γ-Lactams

γ-lactams are naturally occurring motifs in a large number of biologically active natural and unnatural substances[45] (Figure 7). They have been used as intermediates for the synthesis of a number of complex molecules[46] probably

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[42] Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M., *Synlett* **2001,** *2001*, 1813.

[43] Alcaide, B.; Almendros, P., *Synlett* **2002,** *2002*, 0381.

[44] Ojima, I.; Delaloge, F., *Chemical Society Reviews* **1997,** *26*, 377.

[45] For references citing the presence of γ-lactam moieties in biologically active substances see : Nacci, V.; Campiani, G.; Garofalo, A., *Journal of Heterocyclic Chemistry* **1990,** *27*, 1329. Mandal, S. B.; Achari, B.; Chattopadhyay, S., *Tetrahedron Letters* **1992,** *33*, 1647. Fishwick, C. W. G.; Foster, R. J.; Carr, R. E., *Tetrahedron Letters* **1996,** *37*, 3915. Fu, T.-h.; McElroy, W. T.; Shamszad, M.; Martin, S. F., *Organic Letters* **2012,** *14*, 3834. Shenvi, R. A.; Corey, E. J., *Journal of the American Chemical Society* **2009,** *131*, 5746. Barrett, A. G. M.; Head, J.; Smith, M. L.; Stock, N. S.; White, A. J. P.; Williams, D. J., *The Journal of Organic Chemistry* **1999,** *64*, 6005. Takahata, H.; Wang, E.-C.; Yatnazaki, T., *Synthetic Communications* **1988,** *18*, 1159. Kar, G. K.; Chatterjee, B. G.; Ray, J. K., *Synthetic Communications* **1993,** *23*, 1953.

[46] For examples of the use of γ-lactams as building blocks see : Kimmel, K. L.; Weaver, J. D.; Lee, M.; Ellman, J. A., *Journal of the American Chemical Society*

because of their controlled reactivity, structural diversity, and capability of controlling stereoselectivity during transformations[47]. They are of considerable importance in areas such as drug discovery, as key intermediates in the preparation of biologically and pharmaceutically relevant molecules, and polymer synthesis. These heterocycles are present in compounds that have direct applications in the treatment of cancer, fungal infections, epilepsy, HIV, neurodegenerative diseases, and depression[48]. This

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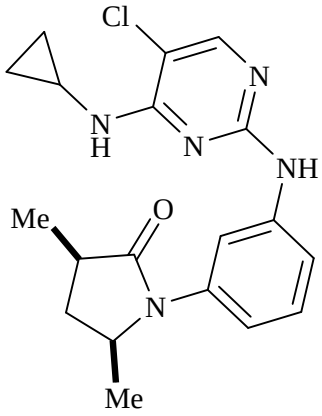
2012, *134*, 9058. Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y., *Journal of the American Chemical Society* **2004,** *127*, 119. Armanino, N.; Carreira, E. M., *Journal of the American Chemical Society* **2013,** *135*, 6814. Satoh, N.; Yokoshima, S.; Fukuyama, T., *Organic Letters* **2011,** *13*, 3028. Shao, C.; Yu, H.-J.; Wu, N.-Y.; Tian, P.; Wang, R.; Feng, C.-G.; Lin, G.-Q., *Organic Letters* **2011,** *13*, 788. Agosti, A.; Britto, S.; Renaud, P., *Organic Letters* **2008,** *10*, 1417. Chouhan, G.; Alper, H., *Organic Letters* **2008,** *10*, 4987. Ma, G.; Nguyen, H.; Romo, D., *Organic Letters* **2007,** *9*, 2143. Fustero, S.; García de la Torre, M.; Sanz-Cervera, J. F.; Ramírez de Arellano, C.; Piera, J.; Simón, A., *Organic Letters* **2002,** *4*, 3651. Chauhan, D.; Catley, L.; Li, G.; Podar, K.; Hideshima, T.; Velankar, M.; Mitsiades, C.; Mitsiades, N.; Yasui, H.; Letai, A.; Ovaa, H.; Berkers, C.; Nicholson, B.; Chao, T.-H.; Neuteboom, S. T. C.; Richardson, P.; Palladino, M. A.; Anderson, K. C., *Cancer Cell 8*, 407.

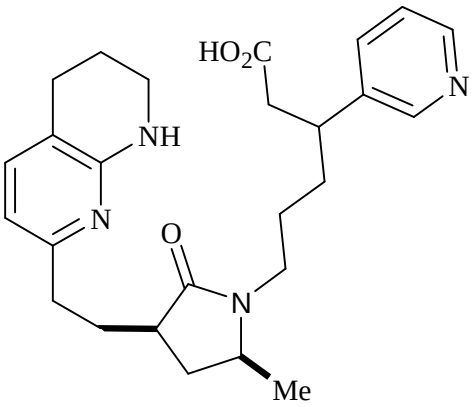
[47] Gomez, C.; Gicquel, M.; Carry, J.-C.; Schio, L.; Retailleau, P.; Voituriez, A.; Marinetti, A., *The Journal of Organic Chemistry* **2013,** *78*, 1488. Xiao, K.-J.; Luo, J.-M.; Ye, K.-Y.; Wang, Y.; Huang, P.-Q., *Angewandte Chemie International Edition* **2010,** *49*, 3037. Gheorghe, A.; Schulte, M.; Reiser, O., *The Journal of Organic Chemistry* **2006,** *71*, 2173. Madan, S.; Milano, P.; Eddings, D. B.; Gawley, R. E., *The Journal of Organic Chemistry* **2005,** *70*, 3066.

[48] Lettan, R. B.; Galliford, C. V.; Woodward, C. C.; Scheidt, K. A., *Journal of the American Chemical Society* **2009,** *131*, 8805.

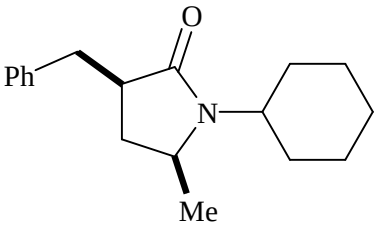
shows the significance of the employment of such moieties in organic synthesis.



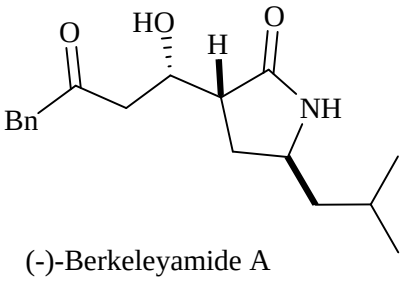
Agrochemical fungicide



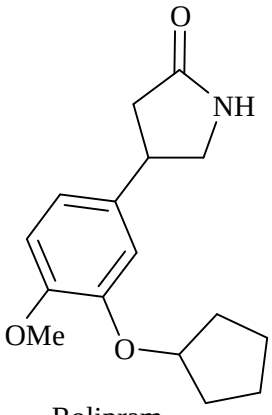
avb3/avb5 integrin receptor antagonist



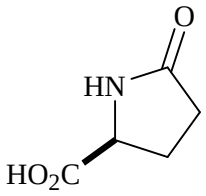
11b-hydroxysteroid dehydrogenase inhibitor



(-)-Berkeleyamide A



Rolipram antidepressant



pyroglutamic acid

Figure 7. Structures of γ-lactams from natural and synthetic sources

I.2.1 Synthesis of γ-lactams

A number of strategies for γ-lactam skeletons synthesis have been developed; this includes i) metal (Rh-Ru) carbenoid intramolecular C-H insertions by decomposition of R-diazocarbonyl compounds[49], ii) ring expansion of β-lactam derivatives[50], iii) formal annulations[23,51], iv) Lewis

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[49] Zhang, B.; Wee, A. G. H., *Organic Letters* **2010,** *12*, 5386. Grohmann, M.; Buck, S.; Schäffler, L.; Maas, G., *Advanced Synthesis & Catalysis* **2006,** *348*, 2203. Candeias, N. R.; Gois, P. M. P.; Afonso, C. A. M., *The Journal of Organic Chemistry* **2006,** *71*, 5489. Wee, A. G. H.; Duncan, S. C.; Fan, G.-j., *Tetrahedron: Asymmetry* **2006,** *17*, 297. Choi, M. K.-W.; Yu, W.-Y.; Che, C.-M., *Organic Letters* **2005,** *7*, 1081. Yoon, C. H.; Nagle, A.; Chen, C.; Gandhi, D.; Jung, K. W., *Organic Letters* **2003,** *5*, 2259.

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[51] Comesse, S.; Sanselme, M.; Daïch, A., *The Journal of Organic Chemistry* **2008,** *73*, 5566. Romero, A.; Woerpel, K. A., *Organic Letters* **2006,** *8*, 2127. Sun, P.-P.; Chang, M.-Y.; Chiang, M. Y.; Chang, N.-C., *Organic Letters* **2003,** *5*, 1761. Roberson, C. W.; Woerpel, K. A., *The Journal of Organic Chemistry* **1999,** *64*, 1434.

acid catalyzed tandem reactions[52], v) the cyclization of nitrogen radicals onto unsaturated systems from N-haloamides[53], vi) the cycloaddition reaction between imines and cyclic anhydrides[54], vii) the thermal reactions of π-allyltricarbonyliron lactam complexes obtained from oxazines and diiron nonacarbonyl[55], viii) Au(I)-catalyzed intramolecular addition of β-ketoamides to unactivated alkenes[56], and ix) palladium catalyzed cyclization reactions[57,58,59] (Scheme 17). Perhaps the currently most interesting methods of construction of such molecules are metal catalyzed processes that allow

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[52] Ghorai, M. K.; Tiwari, D. P., *The Journal of Organic Chemistry* **2010,** *75*, 6173. Blay, G.; Hernández-Olmos, V. c.; Pedro, J. R., *Organic Letters* **2010,** *12*, 3058. Wiedemann, S. H.; Noda, H.; Harada, S.; Matsunaga, S.; Shibasaki, M., *Organic Letters* **2008,** *10*, 1661. Tellitu, I.; Serna, S.; Herrero, M. T.; Moreno, I.; Domínguez, E.; SanMartin, R., *The Journal of Organic Chemistry* **2007,** *72*, 1526. Pohmakotr, M.; Yotapan, N.; Tuchinda, P.; Kuhakarn, C.; Reutrakul, V., *The Journal of Organic Chemistry* **2007,** *72*, 5016. Scott, M. E.; Schwarz, C. A.; Lautens, M., *Organic Letters* **2006,** *8*, 5521.

[53] Fallis, A. G.; Brinza, I. M., *Tetrahedron* **1997,** *53*, 17543.

[54] Ng, P. Y.; Masse, C. E.; Shaw, J. T., *Organic Letters* **2006,** *8*, 3999. Wei, J.; Shaw, J. T., *Organic Letters* **2007,** *9*, 4077.

[55] Ley, S. V.; Cox, L. R.; Meek, G., *Chemical Reviews* **1996,** *96*, 423.

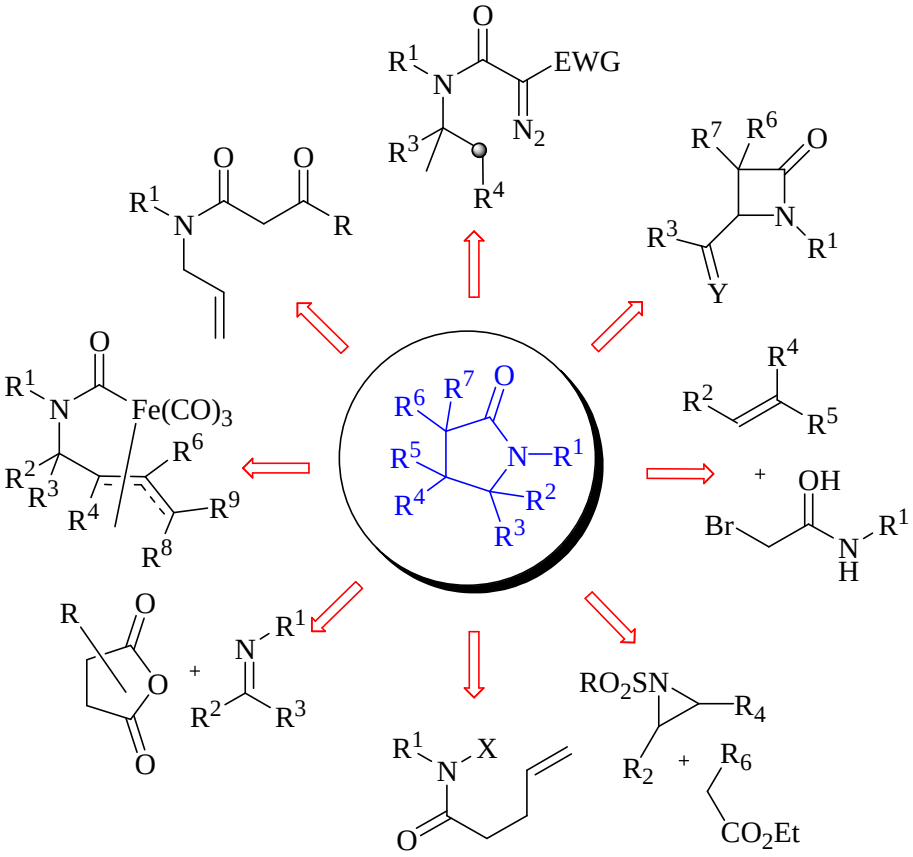
[56] Zhou, C.-Y.; Che, C.-M., *Journal of the American Chemical Society* **2007,** *129*, 5828.

[57] Yip, K.-T.; Zhu, N.-Y.; Yang, D., *Organic Letters* **2009,** *11*, 1911; Luan, X.; Mariz, R.; Robert, C.; Gatti, M.; Blumentritt, S.; Linden, A.; Dorta, R., *Organic Letters* **2008,** *10*, 5569.

[58] Xie, X.; Lu, X.; Liu, Y.; Xu, W., *The Journal of Organic Chemistry* **2001,** *66*, 6545.

[59] Kammerer, C.; Prestat, G.; Madec, D.; Poli, G., *Chemistry – A European Journal* **2009,** *15*, 4224.

access to asymmetric synthesis of substituted γ-lactams. The use of Rh, Ru, Pd, Au among other metals have been widely reported.

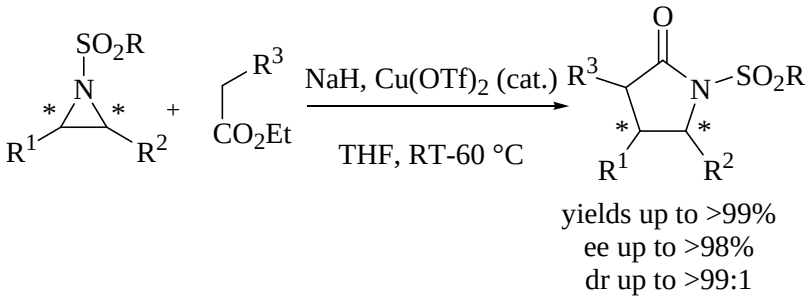


Scheme 17. Strategies for the synthesis of γ-lactams

The catalytic C–H insertion reaction of diazoacetamide compounds was discussed in the previous section and we mentioned the possibility of obtaining 4- and 5-membered ring lactam structures.

The development of a simple highly enantio- and diastereoselective synthesis of functionalized chiral γ-lactams catalyzed by Lewis acid S_N2-type ring opening of aziridines followed by cyclization with active methylene carbon nucleophiles in a domino fashion was carried out by

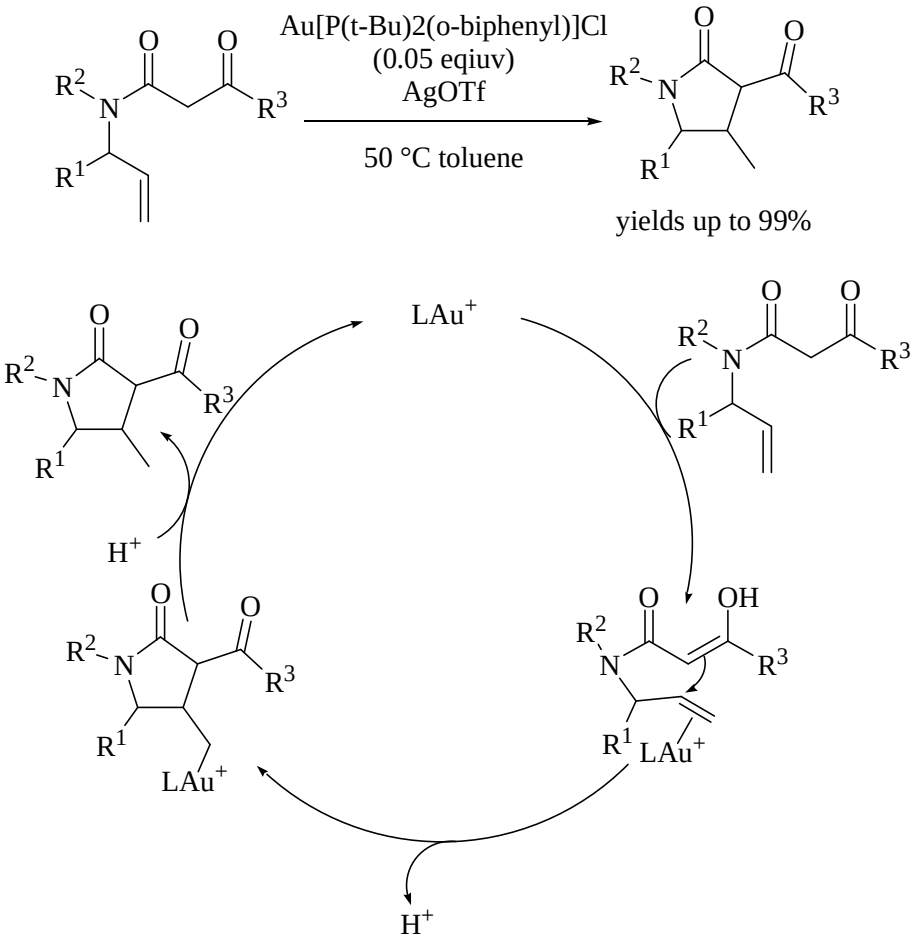
Ghorai *et al*. They obtained yields up to 99%, enantiomeric excess up to 98% and a diastereoisomeric ratio of 99:1[52] (Scheme 18).



Scheme 4. Lewis acid catalyzed cyclization

Other diastereoselective cyclization reactions using Lewis acid (LA) catalysts such as Mg, Sc, Zn and Cu were reported by several groups[52].

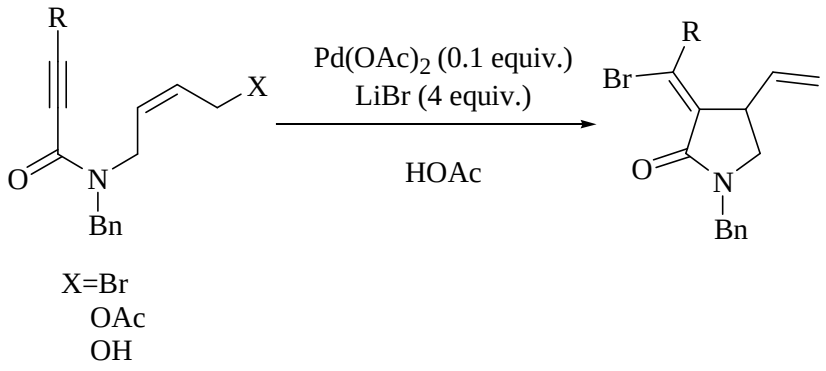
The use of a Au(I) complex can also efficiently catalyze the intramolecular addition of β-ketoamide to unactivated alkenes producing highly substituted lactams with excellent yields and regioselectivities. This result was demonstrated by the group of Che[56] and they carried out several reactions that were consistent with mechanism that they propose for this transformation (Scheme 19).



Scheme 19. Gold catalyzed intramolecular addition of β-ketoamide to unactivated alkenes

Besides, the use of palladium catalysts for the synthesis of γ-lactams starting from different substrates has been the subject of several articles. The intramolecular cyclization of *N*-allylic-2-alkynamides to form α-alkylidene-γ-butyrolactams via a palladium (II) catalyst has been developed by Xie *et al.*[58] The mechanism proceeds through halopalladation of the carbon triple bond in the presence of LiX, then intramolecular olefin insertion into the

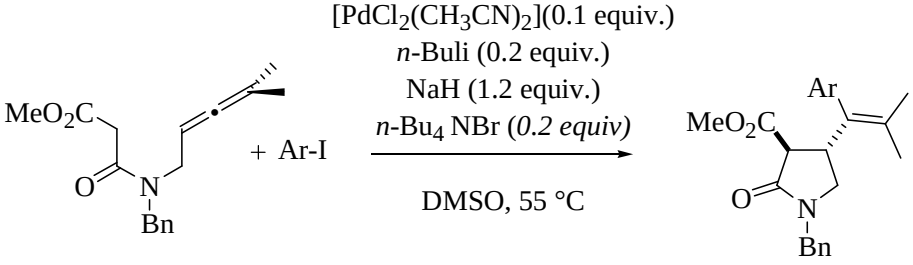
carbon–palladium bond, and ends by β-heteroatom elimination to produce the γ-butyrolactams and regenerate the Pd(II) species (Scheme 20).



Scheme 20. Intramolecular cyclization of N-allylic-2-alkynamides catalyzed by Pd

They obtained yields up to 98% and preferentially the *Z* isomer over the *E*-isomer with ratios up to 100:0.

Another example of the literature was described by the group of Poli[59] who used a phosphine free palladium catalyst for the allene carbopalladation/allylic alkylation domino sequence that produces 4-(α-styryl) γ-lactams (Scheme 21).



Scheme 21. Allene carbopalladation/allylic alkylation domino reaction

High yields were obtained for electron-rich as well as electron-poor aryl iodides (61-88%). The reaction is completely regio- and stereoselective in

favor of the 5-exo *trans* product. They have also applied this methodology for the synthesis of a new aza analogue of oxo-parabenzlactone (Figure 8).

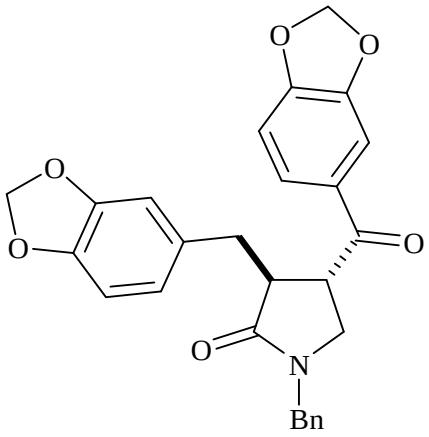


Figure 8. Aza analogue of oxo-parabenzlactone

Chapter 1: Synthesis of β-Lactams by Kinugasa Reaction

I. Bibliographic Introduction

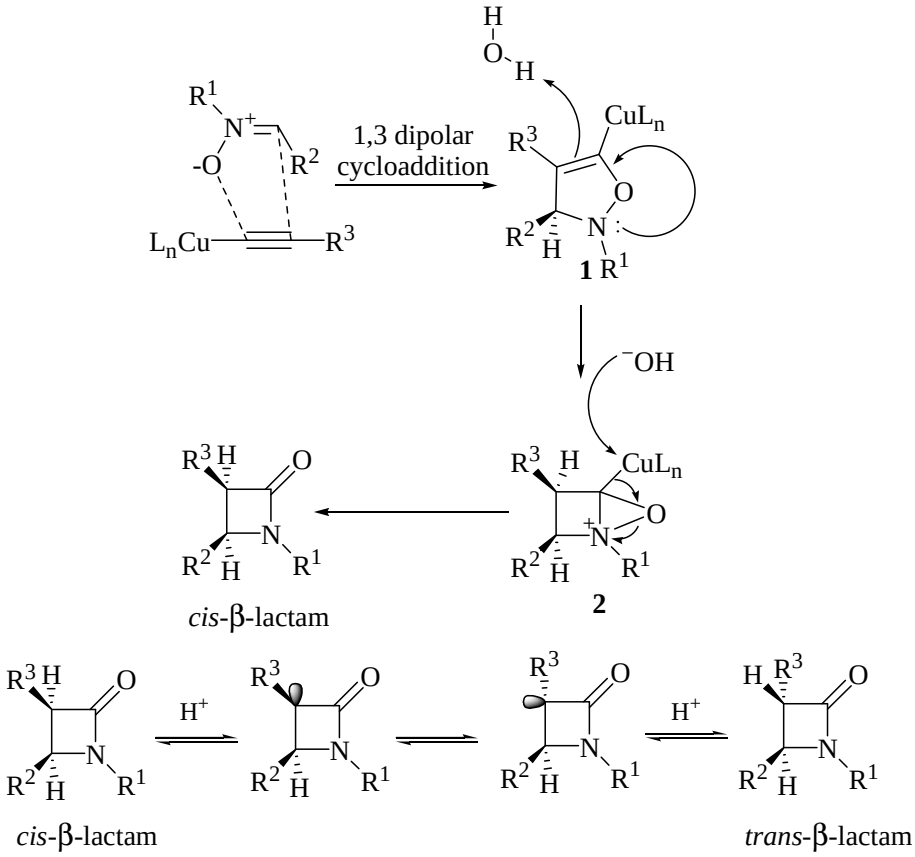
Direct, catalytic approaches for the construction of β-lactams serve as tempting alternatives to the classical strategies, providing general routes toward distinct β-lactam structures. The reaction between a terminal alkyne and a nitrone is very slow and unlikely to occur in the absence of a metal catalyst. The Kinugasa reaction is classified as a metal catalyzed 1,3-dipolar cycloaddition reaction; where a nitrone, the dipole, and an alkyne, the dipolarophile, react in a 1,3-dipolar cycloaddition fashion, in the presence of copper (I) as a catalyst, to produce a β-lactam ring. The relative stability and availability, or accessibility, of the starting materials are some of the attractive features of this reaction. In addition to that, is the high atom economy related to this process.

I.1 Mechanism of Kinugasa reaction

In 1976, Ding and Irwin published a full paper on the scope and limitations of the Kinugasa reaction[1]. They found that both *cis*- as well as *trans*-β-lactams can be obtained through this method, usually leading to mixtures of different ratios depending on the experimental conditions. They proposed the first mechanism (scheme 1) and suggested that the formation of the β-lactam ring passes through a highly strained oxaziridinium **2** intermediate where the formation of the *cis* isomer is attained by the protonation of the less hindered face of the isoxazoline **1** intermediate. The *cis* isomer, the supposed kinetic product, forms the major isomer in most cases; the *trans* isomer is believed to be the thermodynamic product, as it results from the easy isomerization at the C-3 position of the *cis* product

[1] Ding, L. K.; Irwin, W. J., *Journal of the Chemical Society, Perkin Transactions 1* **1976**, 2382.

under basic conditions, although this might alter according to the type of substituent at this position.



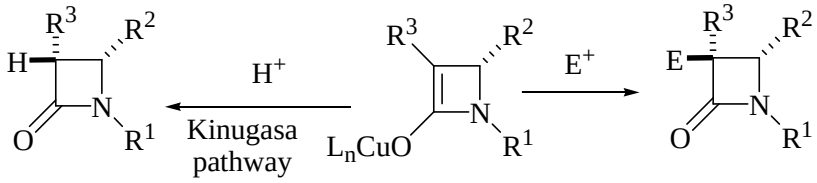
Scheme 1. Mechanism proposed by Ding and Irwin and the isomerization of the *cis*-β-lactam into *trans*-β-lactam

Support to this mechanism was provided by Miura who reported a modification of the original protocol using terminal alkynes in the reaction rather than copper (I) acetylides[2]. They proved that the reaction does not take

[2] Okuro, K.; Enna, M.; Miura, M.; Nomura, M., *Journal of the Chemical Society, Chemical Communications* **1993**, 1107.

place in the abscence of a CuX catalyst suggesting that the key intermediate for the transformation is the copper acetylide coordinating with the ligand.

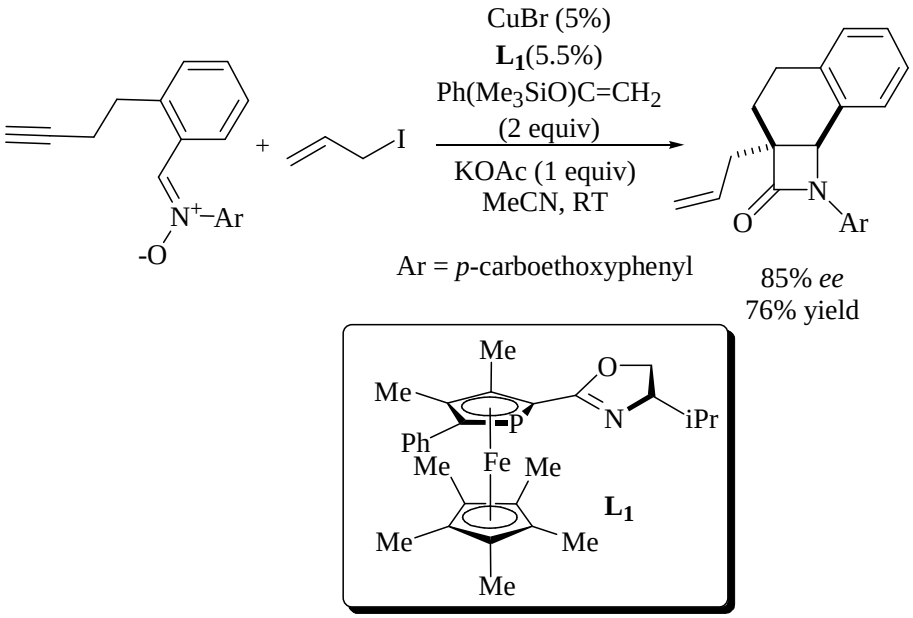
Later Fu *et al.* suggested the intermediacy of a copper enolate in the Kinugasa reaction mechanism[3]. They proposed that the isoxazoline **1** ring rearranges to afford the conjugate base of the lactam, the copper enolate, which, after protonation, delivers the desired product and releases the copper catalyst (Scheme 2).



Scheme 2. Generation on quaternary center by enolate trapping with an electrophile

They attempted to prove the presence of this copper enolate intermediate by trapping it with an electrophile thus creating a quaternary stereocenter. After several optimizations on intramolecular Kinugasa reaction models and the presence of a proton trap, they succeeded in determining the suitable conditions for the desired functionalization. The use of a mixture of silyl enol ether and KOAc as the base and in the presence of allyl iodide, the alkyne-nitrone substrate underwent cyclization followed by an alkylation to afford the product in good yield (76%) and high selectivity (85%) thus forming two new rings and a quaternary center in one single sequence (Scheme 3).

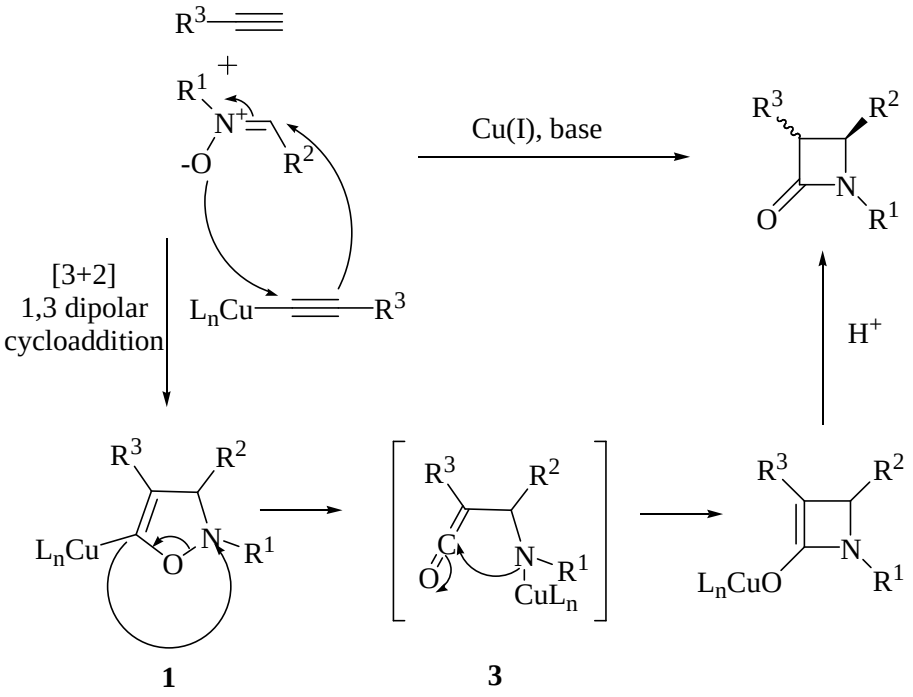
[3] Shintani, R.; Fu, G. C., *Angewandte Chemie International Edition* **2003,** *42*, 4082.



Scheme 3. Kinugasa reaction followed by alkylation

In view of the results of Fu *et al.* concerning the enolate trapping, Tang and coworkers proposed an alternate pathway whereby the isoxazoline **1**, common to both mechanisms, apparently undergoes a ring opening rearrangement to generate a ketene **3**, as in the Staudinger reaction[4]. This is followed by an intramolecular cyclization producing the copper enolate which in the presence of a proton provides the β-lactam (Scheme 4). They reinforced their suggestion by the fact that the imine derived from the nitrone was found as a byproduct and that nitrones with *N*-bound electron-withdrawing substituents gave better yields than those with *N*-bound electron-rich substituents. This is probably because of that stabilization that is provided by the *N*-bound electron-withdrawing group to the ketene intermediate preventing it from decomposition into the imine. However they were never capable of capturing the ketene intermediate.

[4] Ye, M.-C.; Zhou, J.; Tang, Y., *The Journal of Organic Chemistry* **2006,** *71*, 3576.

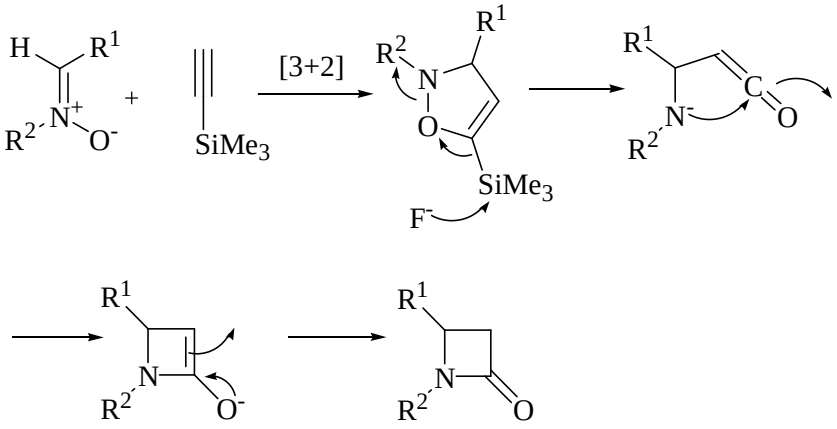


Scheme 4. Tang's plausible mechanism of Kinugasa reaction

Before the existence of any conclusive evidence to prove either of the two mechanisms (isolation or trapping of intermediates), De Shong obtained results that may have supported the mechanism with the ketene intermediate[5]. He showed that the reaction of a nitrone with a trimethylsilylacetylene resulted in the formation of β-lactams after treatment with fluoride for desilylation. The mechanism they proposed (Scheme 5) is very similar to the one proposed by Tang for the Kinugasa reaction (Scheme 4). It is noteworthy that in both mechanisms proposed, the enantioselectivity of the reaction is dependent on the first cycloaddition that generates the isoxazoline derivative **1**. The initial cycloaddition

[5] Ahn, C.; Kennington, J. W.; DeShong, P., *The Journal of Organic Chemistry* **1994,** *59*, 6282.

defines the configuration at C-4 position. The diastereoselectivity is determined in the protonation step at the C-3 position which is also influenced by the C-4 configuration. This is why in most cases; the *cis*-β-lactam is formed first. Still, the electronic properties of substituents on the adjacent stereogenic centers could influence the configuration of the C-3 position.



Scheme 5. Mechanism proposed by DeShong for the reaction of nitrones with trimethylsilylacetylenes

Of course, one cannot neglect the resemblance between the Kinugasa reaction and the well-known copper-catalyzed alkyne–azide cycloaddition, (CuAAC)[6]; where both reactions show similarities in terms of copper

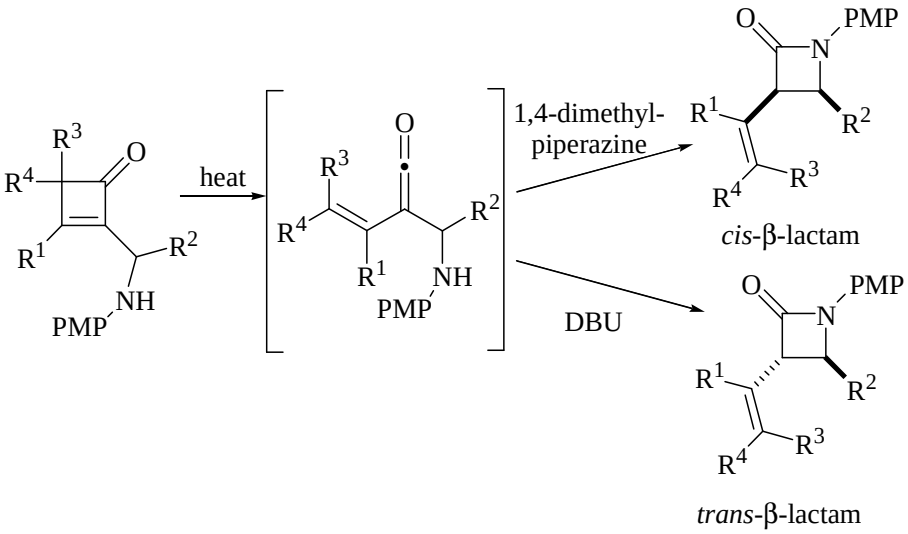
[6] Qin, A.; Lam, J. W. Y.; Tang, L.; Jim, C. K. W.; Zhao, H.; Sun, J.; Tang, B. Z., *Macromolecules* **2009,** *42*, 1421; Malkoch, M.; Schleicher, K.; Drockenmuller, E.; Hawker, C. J.; Russell, T. P.; Wu, P.; Fokin, V. V., *Macromolecules* **2005,** *38*, 3663; Tornøe, C. W.; Christensen, C.; Meldal, M., *The Journal of Organic Chemistry* **2002,** *67*, 3057; Ackermann, L.; Potukuchi, H. K.; Landsberg, D.; Vicente, R., *Organic Letters* **2008,** *10*, 3081; Orgueira, H. A.; Fokas, D.; Isome, Y.; Chan, P. C. M.; Baldino, C. M., *Tetrahedron Letters* **2005,** *46*, 2911; Rostovtsev, V. V.; Green,

acetylide intermediate. However, the nature of this reactive alkynyl copper species is not well recognized. The formation of polynuclear compounds from these copper species is highly probable. In addition to that is the easy ligand exchange at the copper center. Consequently, we could obtain mixtures of several species in the medium in equilibrium, for instance a dinuclear copper (I) species[7]. As a result, the real mechanism of this reaction could be a lot more complicated. However, the mechanism that proposes the involvement of a ketene intermediate seems more plausible because of the arguments provided by the groups of Fu and DeShong. Moreover, an indirect evidence of the likelihood of Tang's mechanism issues from the work of Shimizu *et al.*[8] They reported the formation of β-lactams by means of thermal rearrangement of aminocyclobutenones (Scheme 6). A plausible reaction mechanism for the thermal rearrangement includes the ring opening of the aminocyclobutenone to form an aminoketene which undergoes a cyclization to give the enol intermediate that after protonation provides the β-lactam.

L. G.; Fokin, V. V.; Sharpless, K. B., *Angewandte Chemie International Edition* **2002,** *41*, 2596.

[7] Buckley, B. R.; Dann, S. E.; Heaney, H., *Chemistry – A European Journal* **2010,** *16*, 6278.

[8] Hachiya, I.; Yoshitomi, T.; Yamaguchi, Y.; Shimizu, M., *Organic Letters* **2009,** *11*, 3266.



Scheme 6. Formation of β-lactams by the thermal rearrangement of aminocyclobutenones reported by Shimizu

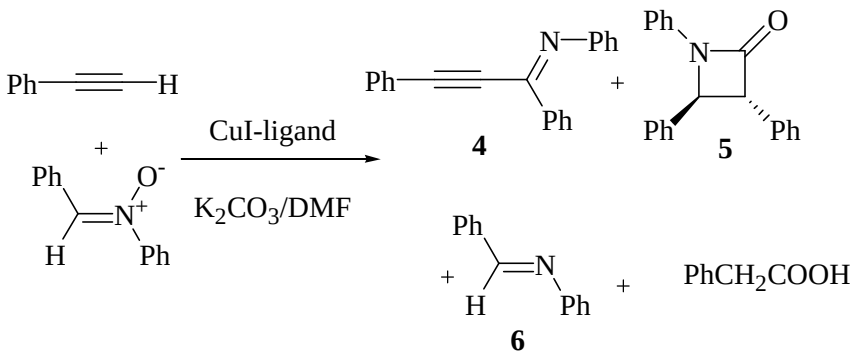
I.2 Selectivity in Kinugasa reaction

I.2.1 Diastereoselective Kinugasa reaction

I.2.1.1 Diastereoselectivity induced by the catalytic system

In a research they carried out, Miura and coworkers reported the catalytic coupling of *C,N*-diarylnitrones with alkynes in the presence of a catalytic amount of copper iodide and K_2CO_3 as a base resulting in a mixture of four compounds, where the yield of the target product could be increased by changing the ligand used[9] (Scheme 7).

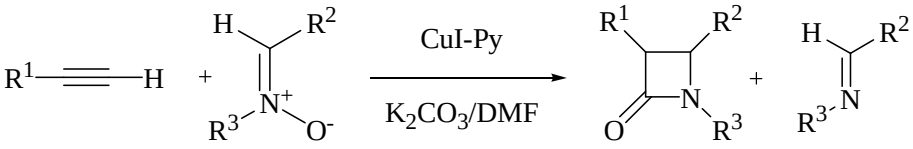
[9] Miura, M.; Enna, M.; Okuro, K.; Nomura, M., *The Journal of Organic Chemistry* **1995,** *60,* 4999.



Scheme 7. Catalytic Kinugasa reaction reported by Miura

Upon using DPPE as a ligand, they obtained the azenyne **4** selectively with a yield of 74%, while the use of pyridine at 0°C, afforded the azetidin-2-one **5** as the main product. Moreover, the employment of a para-substituted phenyl ring on the nitrone gave a mixture of **5** and **6** at room temperature. The ratio of the azetidin-2-one increased with the increase of the electron withdrawing nature of the substituent. The ratio of the *cis*:*trans* isomers of the azetidin-2-ones ranged from 1:1 to 3:1 (Table 1).

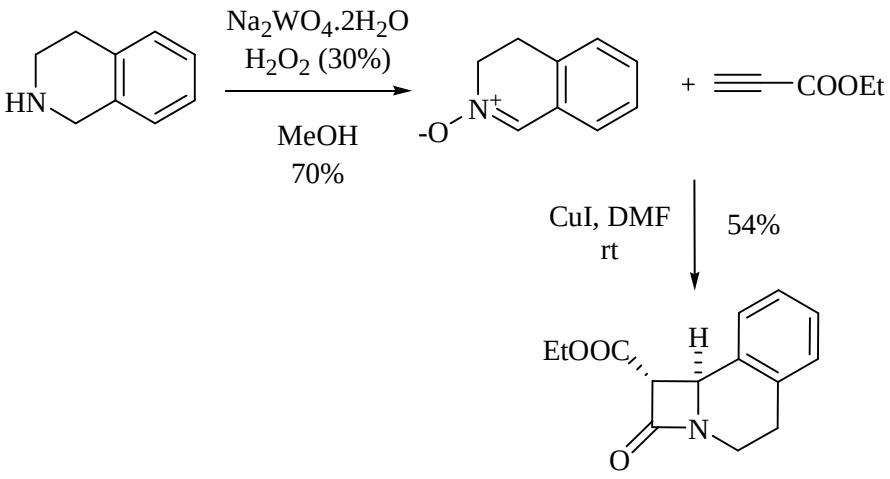
Table 1. Reaction of various alkynes with disubstituted nitrones



				Yield [%]	
R[1]	**R[2]**	**R[3]**	**time [h]**	2-azetidinone (*trans:cis*)	imine
Ph	Ph	Ph	3	**65** (34:66)	26
Ph	Ph	4-(MeOOC)C_6H_4	2	**82** (54:46)	11
Ph	Ph	4-ClC_6H_4	2	**73** (30:70)	25
Ph	Ph	4-MeC_6H_4	4	**54** (35:65)	35
Ph	Ph	4-MeOC_6H_4	5	**21** (40:60)	72
Ph	4-ClC_6H_4	Ph	3	**69** (38:62)	27
Ph	4-MeC_6H_4	Ph	3	**65** (34:66)	31
Ph	4-MeOC_6H_4	Ph	5	**32** (55:45)	58

Basak *et al.* demonstrated a general approach for the synthesis of tricyclic β-lactams by reacting a bicyclic nitrone that they synthesized with ethyl propiolate to obtain the *trans* form of the β-lactam in 54%[10] (Scheme 8).

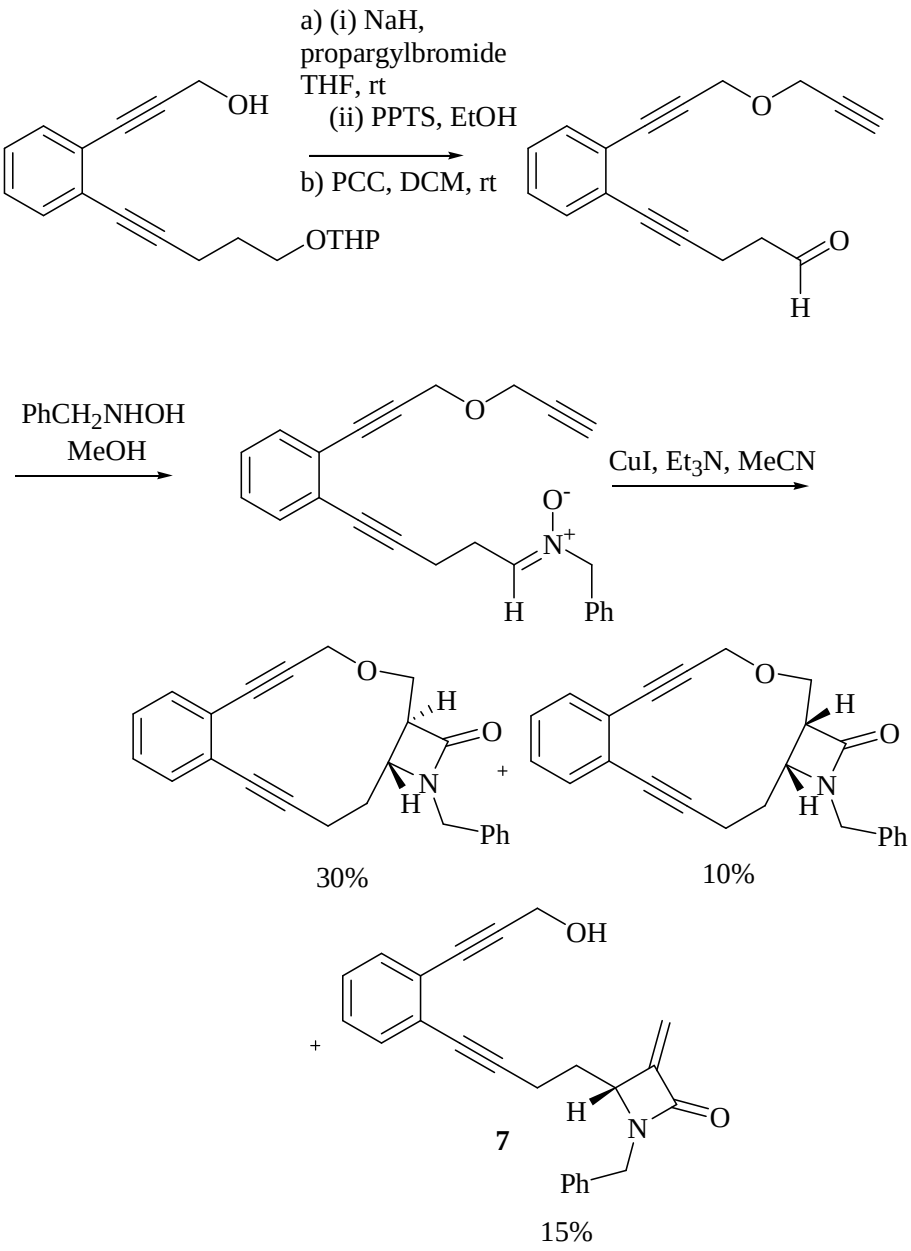
[10] Basak, A.; Rudra, K. R.; Bdour, H. M. M., *Indian Journal of Chemistry* **2003,** *42B,* 1508.



Scheme 8. Synthesis of tricyclic β-lactams by Kinugasa reaction

The intramolecular Kinugasa reaction was also studied by Basak *et al*. since they were interested in the synthesis of β-lactam fused enediynes[11]. These structures are interesting due to the aptitude of the β-lactam ring to act as a molecular lock inorder to stabilize the otherwise unstable enediyne moiety. They synthesized the desired enediynes first starting from the acyclic enediynes that were constructed by Sonogashira coupling, followed by O-propargylation and the generation of the nitrone moiety, and finally the intramolecular Kinugasa reaction (Scheme 9). They obtained a diastereoisomeric ratio *trans:cis* of 3:1 in addition to a lactam **7** resulting from the collapse of the isoxazoline intermediate formed in the initial cycloaddition.

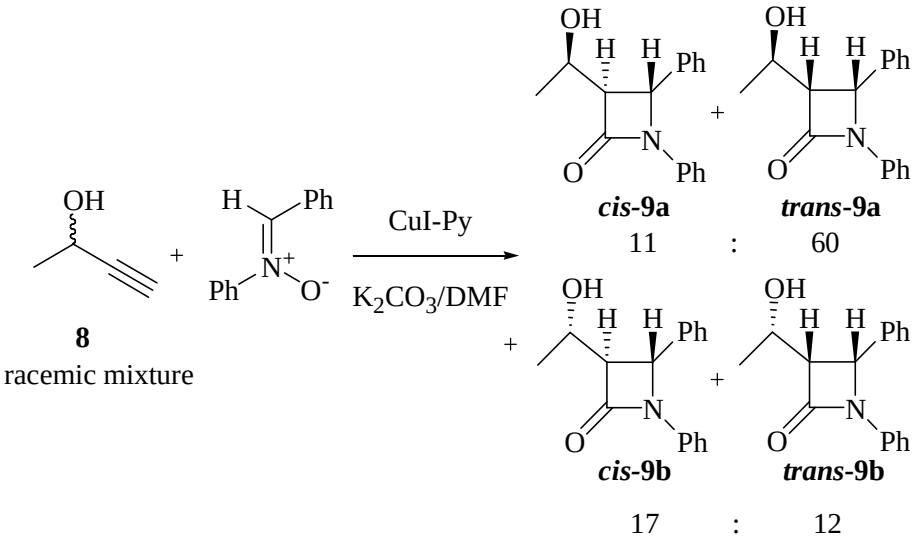
[11] Pal, R.; Basak, A., *Chemical Communications* **2006**, 2992.



Scheme 9. Intramolecular Kinugasa reaction for the synthesis of β-lactam fused enediynes

I.2.1.2 Diastereoselectivity induced by the presence of a chiral auxiliary on acetylenes

Miaura have described the reaction of a racemic mixture of alkyne **8** with the α,*N*-diphenylnitrone to produce four diastereomeric b-lactams *cis*-**9a**, *trans*-**9a**, *cis*-**9b** and *trans*-**9b** with respective ratios of 11:60:17:12 (Scheme 10)[9].



Scheme 10. Reaction of racemic mixture of an alkyne with a chiral center with diphenyl nitrone

They explained that the product ratio of (*trans*-**9a**+ *cis*-**9a**)/(*trans*-**9b**+ *cis*-**9b**) is determined in the cycloaddition step, and that the molecular models suggest a transition state where the methyl group of the alkyne **8** and the *C*-phenyl group of the nitrone are in anti-position due to sterical effect, driving the formation of the β-lactam **9a** (Figure 1).

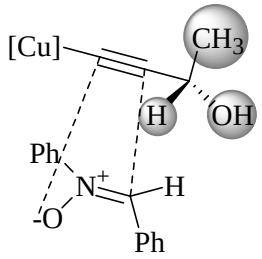


Figure 1. Cycloaddition approach

Basak and coworkers have also described an asymmetric approach based on the presence of a chiral auxiliary[12]. To induce asymmetry, they inserted a homochiral *N*-propargyl oxazolidinone ligand into the alkyne component of the Kinugasa reaction in a way that the ligand is chelated intramolecularly to the copper catalyst assuming that the side chain would control the approach of the nitrone. In the mechanism they propose (Scheme 11), the two substituents R and R^1 are on opposite sides in intermediate **10** giving access to two diastereoisomers, one from each enantiomer, with lower energy required than the intermediate **11.** Then the reaction between an alkyne, with the chiral oxazolidinone implanted on it, and a nitrone would give a mixture of two diastereoisomers, one enantiomer of the *cis* and one enantiomer of the *trans*. This mixture was separated easily by column chromatography, and they obtained the products with good yields (62-70%), moderate diastereoselectivity (*trans:cis* = 5:4 to 3:1) and greater than 95% asymmetric induction in both the *cis* and *trans* product. They showed that the *cis* isomers underwent epimerization to *trans* isomers when treated with *n*-BuLi at a low temperature.

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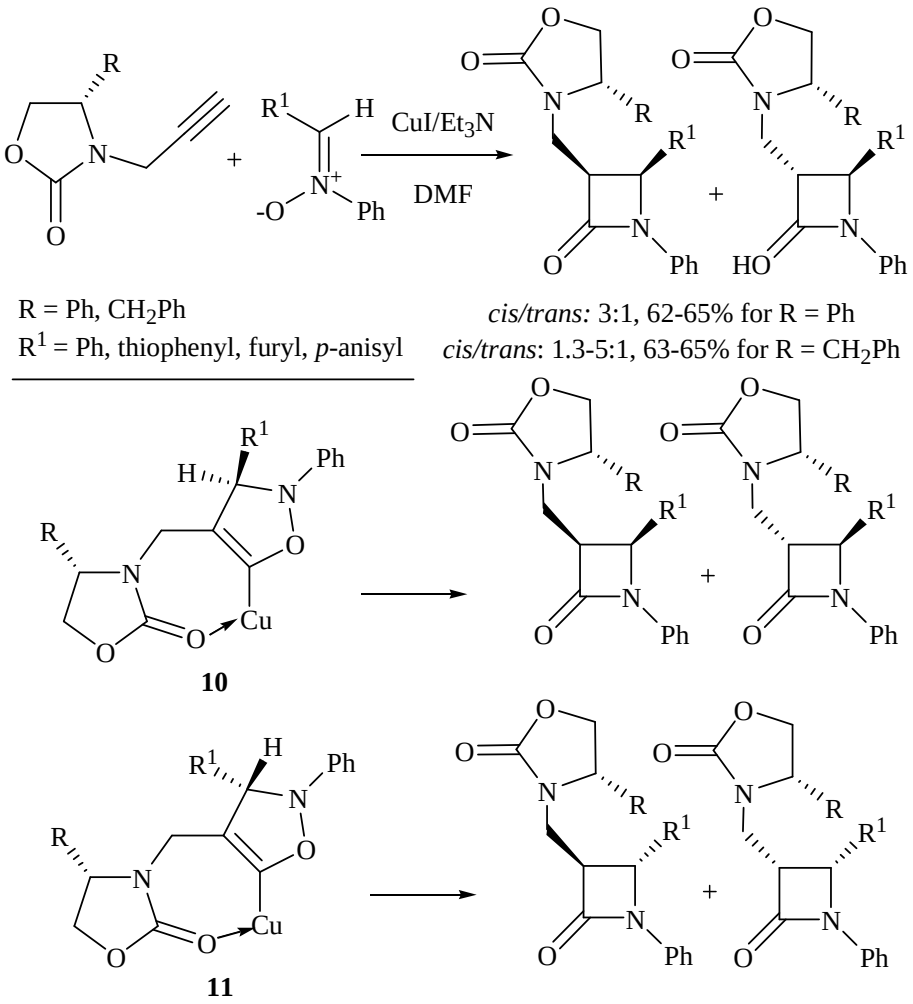
[12] Basak, A.; Ghosh, S. C.; Bhowmich, T.; Das, A. K.; Bertolasi, V., *Tetrahedron Letters* **2002,** *43*, 5499.

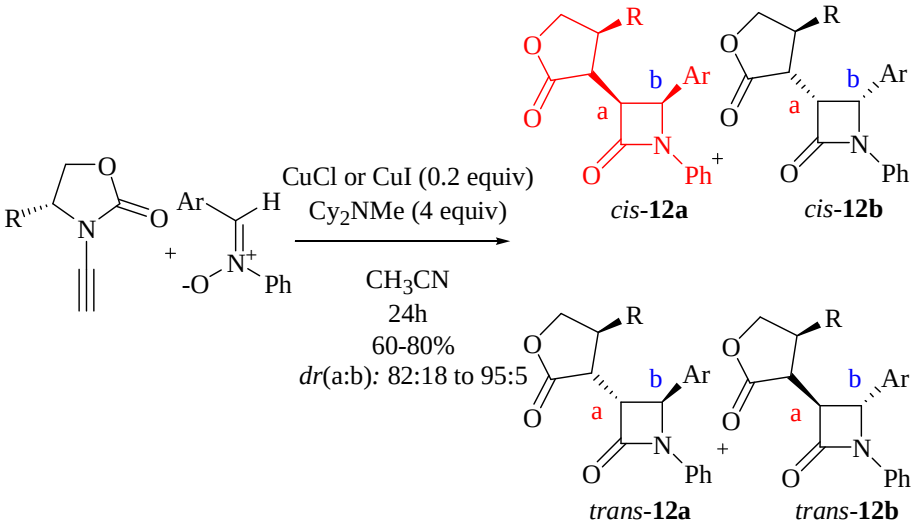


Scheme 11. Kinugasa reaction in the presence of a chiral auxiliary on the alkyne partner

In 2008, Hsung and coworkers[13] reported a highly stereoselective synthesis of chiral α-amino-β-lactam via the reaction of a chiral ynamide and a nitrone where they obtained high selectivities of 95:5 compared to the propynes used

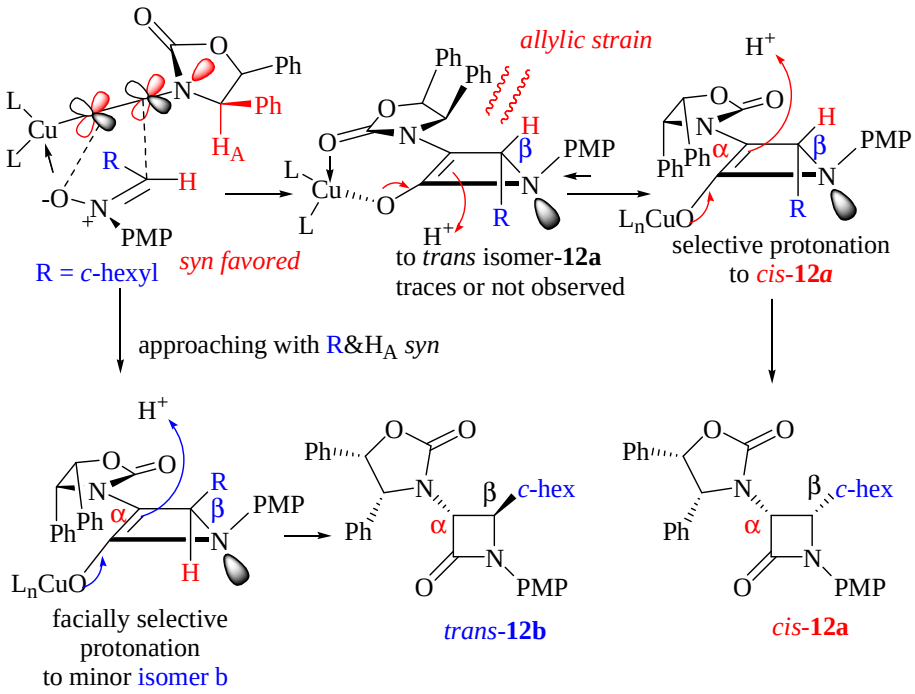
[13] Zhang, X.; Hsung, R. P.; Li, H.; Zhang, Y.; Johnson, W. L.; Figueroa, R., *Organic Letters* **2008,** *10*, 3477.

by *Basak et al.*[12] They found that the bulkier the substituent on the oxazolidinone auxiliary is, like in the case where R = *i*Pr, the lower is the reaction rate. A similar effect is observed when CuCl is used rather than CuI. Also, a substoichiometric amount of the copper catalyst (20%) was used rather than the stoichiometric amount that was employed in previously reported tests. The isomer *cis*-**12a** was obtained as the major product and was determined by X-ray analysis. The minor *trans*-**12b** isomer was determined based on proton coupling constants and then verified by NOE experiments (Scheme 12).



Scheme 12. Stereoselective synthesis of chiral α-amino-β-lactam

They also proposed a mechanistic model to clarify the observed high diastereoselectivity (Scheme 13). This model showed that the chiral auxiliary was responsible not only for the configuration of the first cycloaddtion step, but also of the protonation step that leads to the *cis* product.



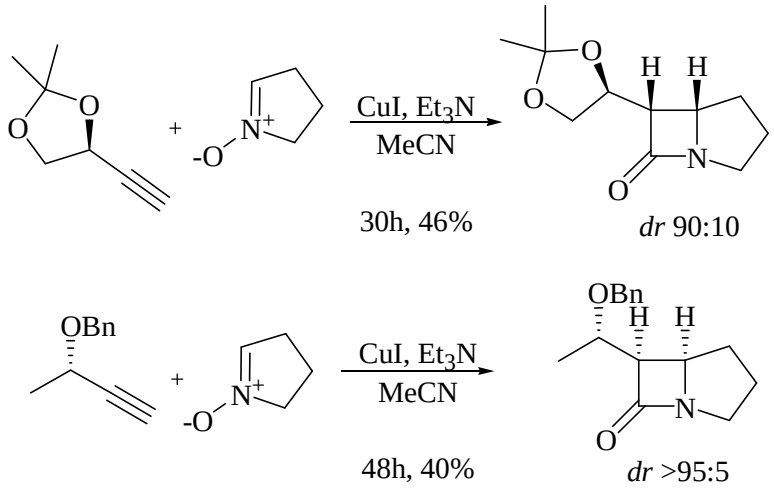
Scheme 13. Mechanistic model for the synthesis of α-amino-β-lactam

They have also described a direct application of this reaction where they remove the chiral auxiliary to obtain Boc-protected-α-amino-β-lactams. In addition to that they found that the treatment of *cis*-**12a** with DBU at high temperature promotes its epimerization into the *trans*-**12a**.

Afterwards, the Chmielewski group reported a series of Kinugasa reactions between chiral optically pure acetylenes and achiral five-membered ring nitrones, bearing a stereogenic center in a racemic mixture[14] (Scheme 14). The reactions provided β-lactams in moderate to good yield and high diastereoselectivity. Prior to this observation, they mentioned that yields of desired products vary from poor, for aliphatic acetylenes, to moderate and

[14] Stecko, S.; Mames, A.; Furman, B.; Chmielewski, M., *The Journal of Organic Chemistry* **2009,** *74*, 3094.

good for aryl acetylenes[15]. Surprisingly, oxygen bearing alipahatic acetylenes provided better yields than other aliphatic acetylenes. For example, the D-glyceraldehyde-derived compound acetylene and L-lactic acid-originating acetylene react with the achiral nitrone, pyrroline N-oxide, to afford the carbapenams with excellent diastereoselectivity and moderate yield (40-50%).



Scheme 14. Kinugasa reaction between optically pure acetylenes and achiral nitrones

In this case the observed diastereoselectivity was justified using a chemical model (Figure 2). It is the configuration of the nitrone that controls the cycloaddition step where it approaches the acetylene from the less hindered side between the oxygen and hydrogen atoms. The nitrone ring is directed towards the H atom. The protonation of the enolate intermediate is mostly governed by the configuration of the bridgehead carbon atom formed in the

[15] Stecko, S.; Mames, A.; Furman, B.; Chmielewski, M., *The Journal of Organic Chemistry* **2008,** *73,* 7402.

cycloaddition. The enolate protonation takes place from the convex side of the enolate intermediate.

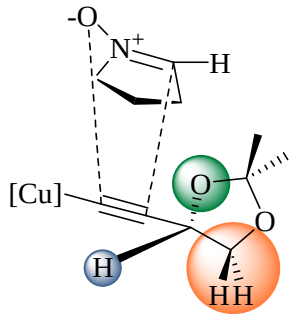


Figure 2. Model for the diastereoselectivity in the cycloaddition step

In cases where both substrates the nitrone and the acetylene are chiral, the result is different for matched and mismatched pairs. This *cis* product is obtained in the case of matched pairs, while in the case of mismatched pairs a mixture of the two stereoisomers the *cis* and the *trans* are obtained (Figure 3). It is the configuration of the chiral acetylene that could influence the selectivity in the protonation step leading to the formation of a mixture of the two diastereoisomers. This influence could be explained by the Felkin-Anh model.

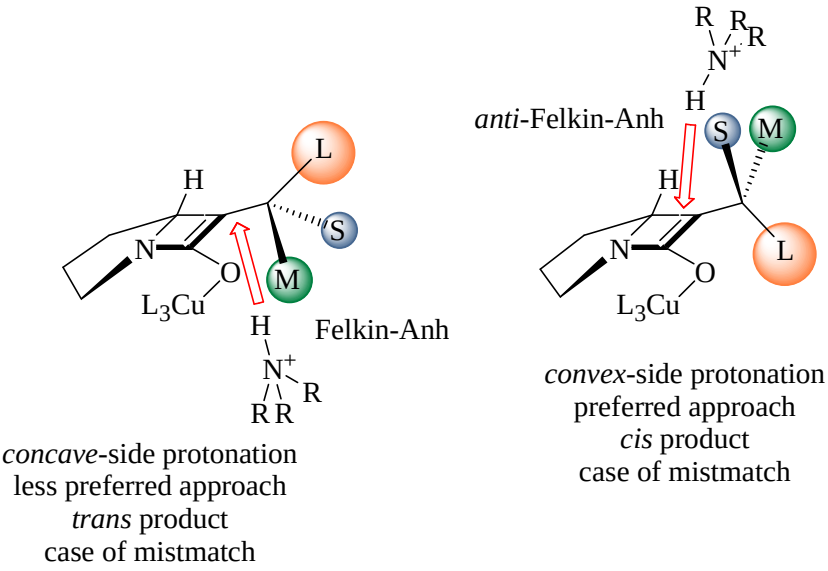
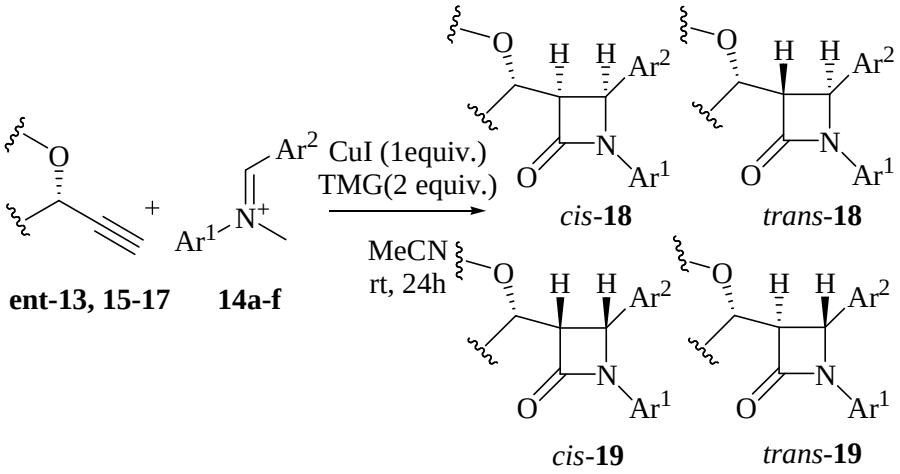


Figure 3. Possible approaches for mismatched pairs

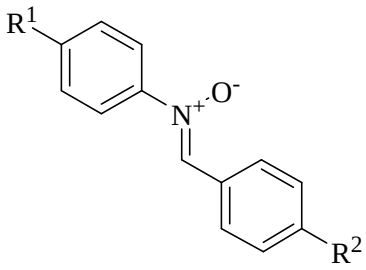
In a further report, the same group inspected the synthesis of *N*,4-diaryl substituted β-lactam framework by Kinugasa reaction[16]. A series of reactions of *C*,*N*-diarylnitrones with protected chiral propargyl alcohols were carried out to access highly functionalized β-lactams with moderate yields and a mixture of 4 diastereoisomers with high selectivity for the *cis* adduct (Table 2). The reaction is carried out in the presence of stoichiometric amount of CuI and 2 equiv. of tetramethylguanidine (TMG) that provided better yields and higher stereoselectivity than Et_3N.

[16] Michalak, M.; Stodulski, M.; Stecko, S.; Woźnica, M.; Staszewska-Krajewska, O.; Kalicki, P.; Furman, B.; Frelek, J.; Chmielewski, M., *Tetrahedron* **2012,** *68*, 10806.

Table 2. Reaction of *C,N*-diarylnitrones with protected chiral propargyl alcohols

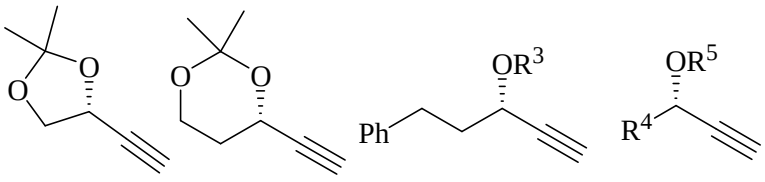


ent-13, 15-17 **14a-f** *cis*-**18** *trans*-**18** *cis*-**19** *trans*-**19**



14

14a R^1:F, R^2:OBn
14b R^1:H, R^2:OBn
14c R^1:F, R^2:H
14d R^1:F, R^2:OTs
14e R^1:H, R^2:H
14f R^1:F, R^2:OMs



***(R)*-13** **15**

16a R:H
16b R:TBS

17a R^1:Ph, R^2:H
17b R^1:Me, R^2:H
17c R^1:Ph, R^2:TBS

Entry	acetylene	Nitrone	*dr* (*cis*-**18**:*trans*-**18**):(*cis*-**19**:*trans*-**19**)	Yield of *cis*-**18** isomer (overall yield) [%]
1	***(R)*-13**	**14a**	(9.7:2.7):(1:1)	41 (61)
2	***(R)*-13**	**14b**	(4.1:1):(3.5:0)	62 (95)
3	***(R)*-13**	**14c**	(5.3:2.5):(1.3:1)	55 (62)
4	***(R)*-13**	**14e**	(4.8:1.2):(1.3:1.7)	48 (82)
5	**15**	**14a**	(4.8:1):(1.2:1.8)	41 (75)
6	**16a**	**14e**	(4.2:1):(2.6:2.2)	(62)
7	**16b**	**14e**	(4.5:2.6):(1.8:1.1)	(65)
8	**17a**	**14e**	(4.2:0.9):(2.6:2.3)	(57)

As observed, yields and selectivities are related to the electronic properties of the substituents present on the nitrone aryl groups. Regarding the reaction of nitrone **14c**, bearing a fluorophenyl substituent at the nitrogen atom of the nitrone, with acetylene ***(R)*-13**, higher selectivity of the *cis*-**18** product is observed. However, compared to **14e**, the overall yield is less. Conversely, when nitrone **14b**, bearing an electron rich substituent at the carbon of the nitrone, with acetylene ***(R)*-13**, provided a mixture of *cis* and *trans* products with no selectivity. In nitrone **14a**, both effects are present, so the product is obtained in high selectivity but moderate yield. The naturally occurring *N*,4-diaryl substituted β-lactams they were interested in synthesizing were all *trans* products. The epimerization of the *cis* products into the *trans* isomers was easily accessed through the oxidation of the hydroxyl group next β-lactam ring, followed by epimerization of the malonyl fragment using a base.

I.2.1.3 Diastereoselectivity induced by the presence of a chiral auxiliary on nitrone partner or both partners

Chmielewski *et al.* reported a Kinugasa reaction of cyclic nitrones and phenylacetylides for a facile approach to carbapenams[17]. They carried out the study of the reaction of non-racemic cyclic nitrones, derived from *S*-malic and *L*-tartaric acid, and terminal alkynes to afford 5,6-*cis*-penams. Different bases were tested in the reaction with Et_3N providing the best results. Various terminal alkynes were employed and the reaction proceeded smoothly with yields between 10 and 80%, *cis* selectivity ranging between 74:26 and >95:5, and an observed reaction time between 20 and 24 hours. They mentioned that the stereochemical outcome of the Kinugasa reaction is controlled by the initial cycloaddition step that leads to the formation of the isoxazoline intermediate, and that this cycloaddition governs the configuration at the bridgehead carbon. Two approaches are possible (Figure 5): the approach of the acetylide from the *si*-side, which is disfavored due to the steric interaction between the *t*-BuO and the phenyl group of the acetylide, and the *re*-side approach where there is no steric hindrance and thus is favored. Consequently, the cycloaddition takes place with high diastereoselectivity providing the *cis* product

[17] Stecko, S.; Mames, A.; Furman, B.; Chmielewski, M., *The Journal of Organic Chemistry* **2008,** *73,* 7402.

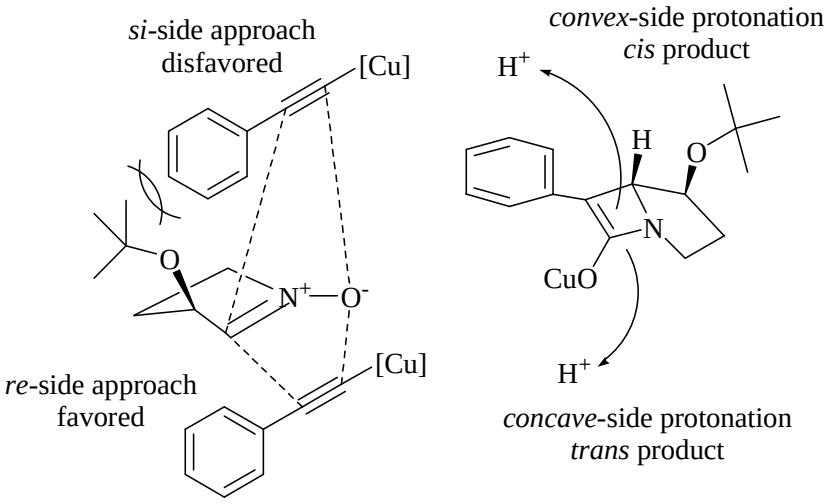
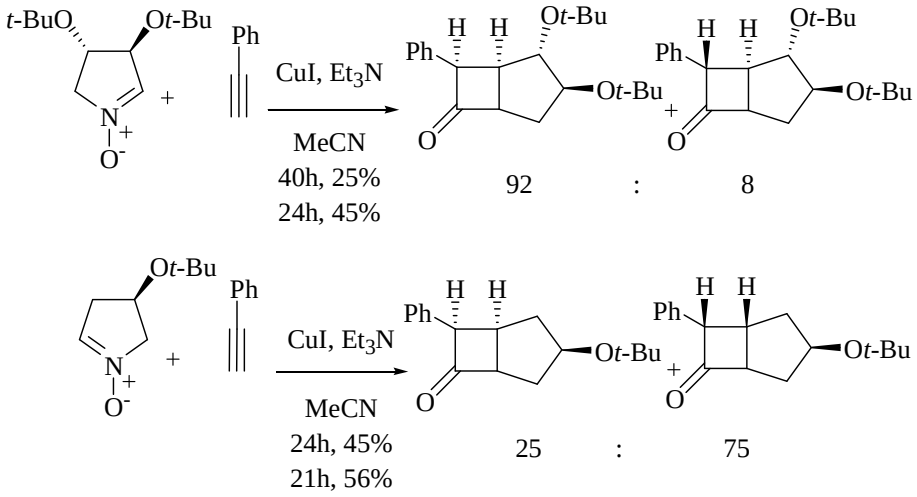


Figure 5. Possible approaches for cycloaddition and protonation steps

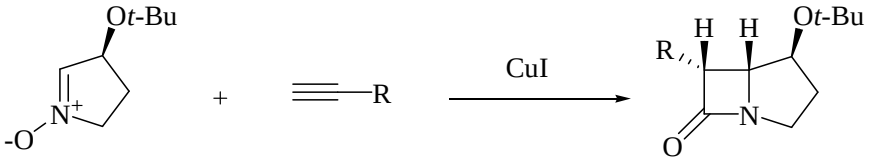
The authors also showed that the addition of a second *t*-BuO group to the nitrone did not interfere with the diastereoselectivity (Scheme 15). However, shifting the *t*-BuO group from C-3 to C-4 altered the stereochemical outcome dramatically.

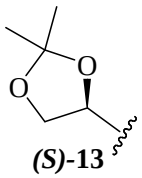
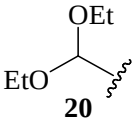


Scheme 15. Effect of the O*t*-Bu group on the diastereoselectivity

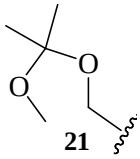
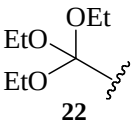
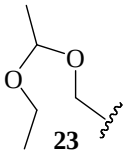
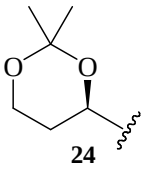
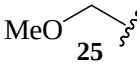
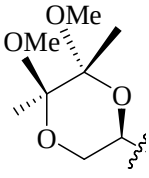
In a following report, Chmielewski *et al.* revealed the high reactivity of glyceraldehyde and propargyl aldehyde derived acetylenes which provide the product in higher yields and requiring less reaction time[18] (Table 3). For instance, the reaction of acetylene ***(S)*-13** provided 94% *cis* product with 1 equiv. of CuI. When the reaction is quenched after 2 hours, 80% yield is obtained. Similarily, when the loading of the CuI catalyst is decreased to 0.05 equiv., 80% yield is still obtained after 2 hours. A similar effect is observed with the acetylene **20**. 62% yield of the *cis* product is obtained after 2 hours with 1 equiv. of copper salt. And even when the amount of catalyst is decreased to 0.05 equiv., a comparable yield is obtained.

Table 3. Reaction of chiral nitrones with O-bearing acetylenes



R	CuI [mol%]	Time [h]	Yield [%]	R	CuI [mol%]	Time [h]	Yield [%]
	100	24	94 (60 [a])		100	24	72 (94 [a])
 ***(S)*-13**	100	2	80 (47 [a])	 **20**	100	2	62 (68 [a])
	5	24	78		5	24	58 (97 [a])
	5	2	80		5	2	60 [a]

[18] Mames, A.; Stecko, S.; Mikołajczyk, P.; Soluch, M.; Furman, B.; Chmielewski, M., *The Journal of Organic Chemistry* **2010,** *75*, 7580.

R	CuI [mol%]	Time [h]	Yield [%]	R	CuI [mol%]	Time [h]	Yield [%]
 **21**	100	24	75	 **22**	100	24	31 (36 [a])
	100	2	46		100	2	10
	5	24	30		5	24	n.d.
					5	2	n.d.
 **23**	100	24	41	 **24**	100	24	55 (55 [a])
	100	2	n.d.		100	2	55
	5	24	n.d.		5	24	35 (36 [a])
					5	2	36
 **25**	100	24	45 (55[a])	 **26**	100	24	56 (30 [a])
	100	2	12		100	2	57
	5	24	n.d.		5	24	49 (31[a])
	5	2	n.d		5	2	31

[a] in presence of 1,10-phenantroline.

To explain this reactivity, the authors suggested a structure-efficiency relationship in the copper acetylides formed by this type of acetylenes. They proposed that the improvement in yield and rate of the reaction for both acetylenes ***(S)*-13** and **20** originates from the formation of rigid dinuclear copper(I) complexes where the copper atom is coordinated to one or both oxygens in the acetylene and to both triple bonds (Figure 6). These rigid complexes are supposed to stabilize the conformation of the acetylide to optimize the interaction of the oxygen atoms with the copper atoms.

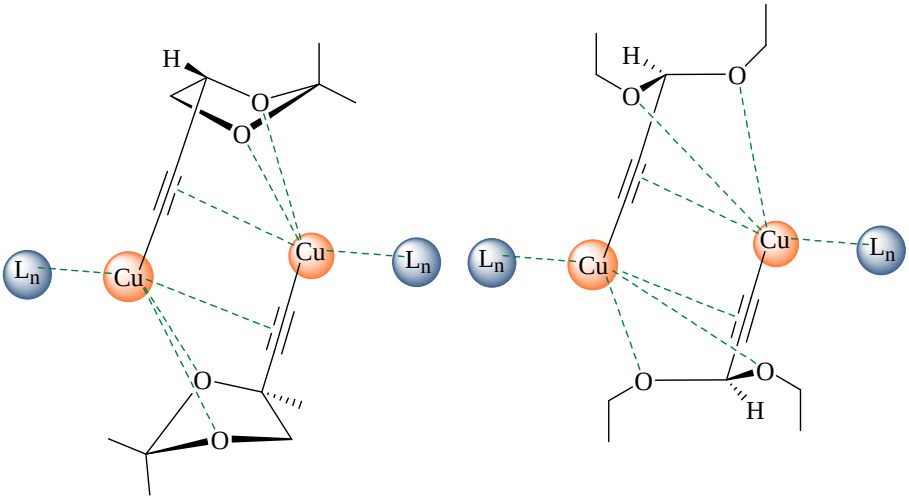


Figure 6. Dinuclear copper(I) complexes

In the case of acetylene **20**, a remarkable increase in the yield is observed when the 1,10-phenantroline is employed as a ligand. This seems to confirm a collaborative effect of the ligand and the oxygen atoms. On the other hand, with acetylenes **22** and **25**, only insignificant enhancement has been remarked upon the addition of 1,10-phenantroline. Contrarily, a decrease in yield is observed when the N,N-ligand is added to the reaction of acetylene ***(S)*-13**, which gives rise to propositions of competitive coordination of the copper ion with the ligand and the oxygen atoms of the corresponding acetylene. The same case of competitive coordination occurs when an

additional oxygen is present in the acetylene substrate (compare acetylenes **22** and **25** and acetylenes ***(S)*-13** and **26**).

Chmielewski and coworkers later reported similar reactions that were carried out this time with six-membered nitrones[19] (Scheme 16). These reactions provided very low yields very likely resulting from the lower stability of dipole components in larger rings. The reaction of nitrone **27** with different acetylenes under standard conditions resulted in β-lactams with low to moderate yields (28-65%). In the first example, the reaction with phenylacetylene provided only one cis product. The reaction with acetylene **20** gave a *cis* and a *trans* product in 2:1 ratio, both having the same configuration at the bridgehead carbon as a result of the *anti*-addition to the benzyloxy group of the nitrone. The formation of the *trans* isomer is probably the result of the epimerization at the carbon atom next to the carbonyl group.

Reaction of nitrone **27** with chiral acetylenes ***(S)*-13** and ***(R)*-13** resulted in a mixture of both diastereoisomers (Scheme 16). Earlier findings of the Chmielewski group depicted that compounds **27** and ***(S)*-13** are matched pairs and compounds **27** and ***(R)*-13** are mismatched pairs. Herein, in both cases a mixture of isomers was obtained with the *cis* isomer being the dominant isomer. In the first case, a ratio of about 2:1 is found. Both isomers had the same configuration at the bridgehead carbon atom, as a result of *anti*-addition to the benzyloxy group in the nitrone. In the other case, the *trans* product was produced in traces and could not be isolated in pure form. When the reaction was carried out in dichloromethane, a byproduct is formed resulting from the acid catalyzed deprotection of the diol moiety followed by elimination of a water molecule.

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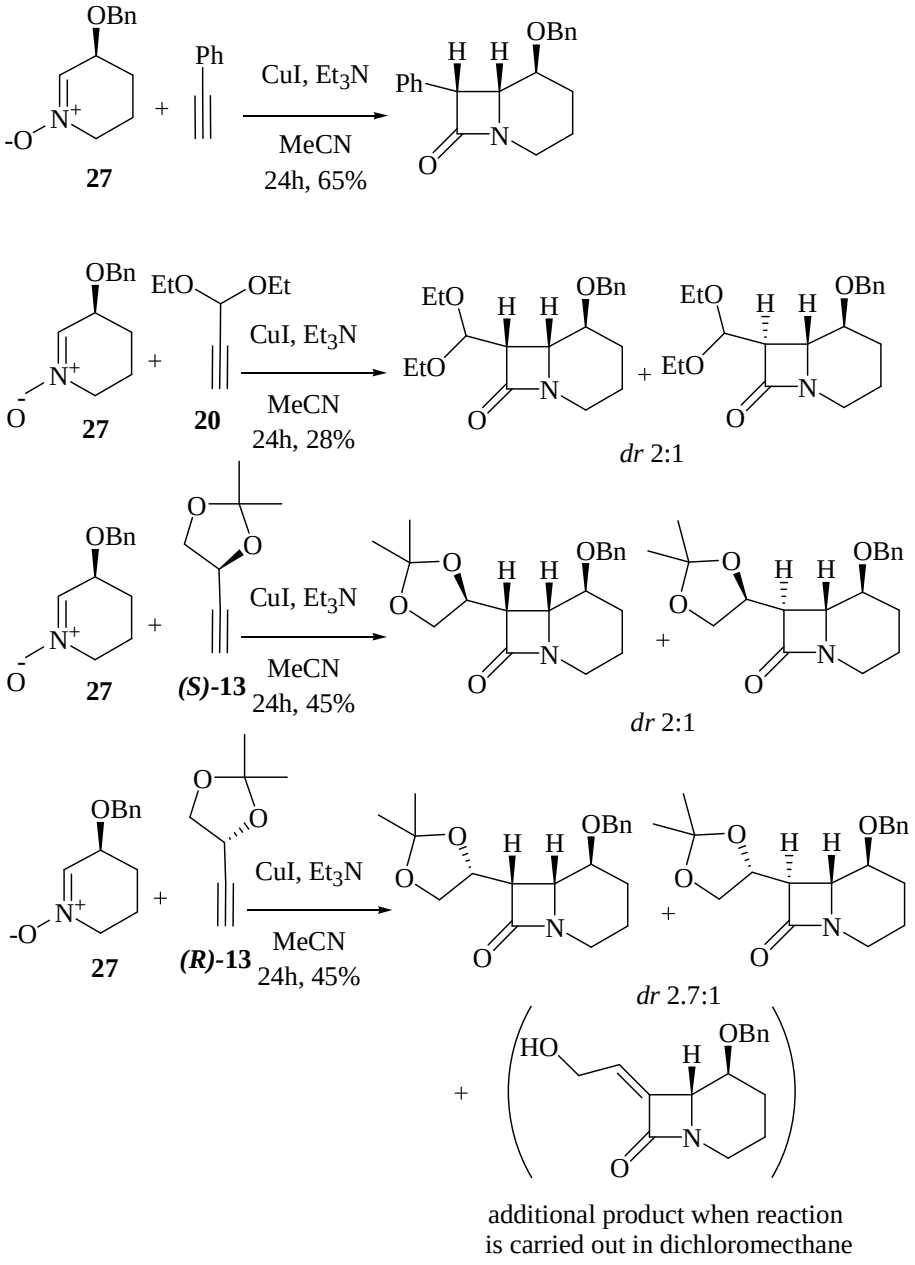
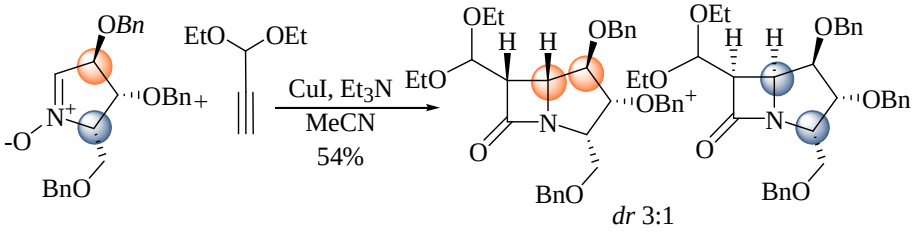
[19] Grzeszczyk, B.; Poławska, K.; Shaker, Y. M.; Stecko, S.; Mames, A.; Woźnica, M.; Chmielewski, M.; Furman, B., *Tetrahedron* **2012,** *68*, 10633.



Scheme 16. Reaction of 6-membered ring chiral nitrones with various acetylenes

Another report of Chmielewski *et al.*[20] described the reaction of five-membered nitrones derived from pentofuranoses and acetylenes (both chiral and non-chiral) to give mainly one *cis* product in moderate to high yields. When two stereogenic centers in the cyclic nitrone are present, the one closer to the double bond played the decisive role in the stereochemical outcome of the process. As reported previously, they confirmed that it is the structure of the nitrone that controls the stereochemical outcome in the cycloaddition step, and the effect of the chiral acetylene is negligible (Scheme 17).



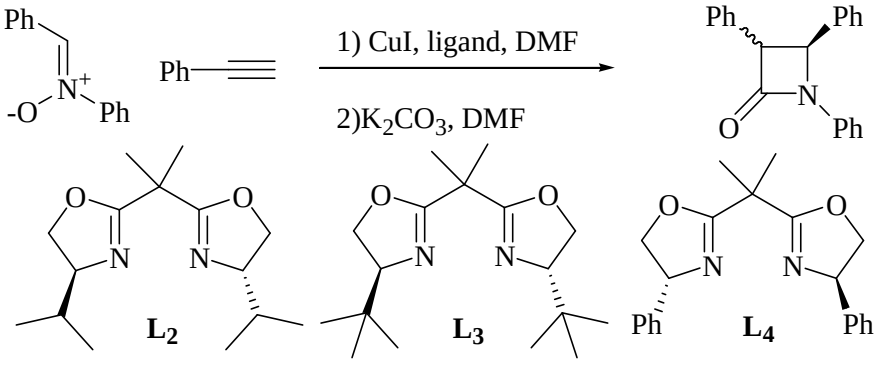
Scheme 17. Reaction of pentofuranose derives nitrones with acetylenes.

[20] Maciejko, M.; Stecko, S.; Staszewska-Krajewska, O.; Jurczak, M.; Furman, B.; Chmielewski, M., *Synthesis* **2012,** *44*, 2825.

I.2.2 Enantioselective Kinugasa reaction

Miura and coworkers extended their work to a chiral nitrogen containing ligands of the bis-oxazoline moiety[9] (Table 4). Their best result was obtained when they used a stoichiometric amount of CuI and diisopropyl-substituted bis-oxazoline $\mathbf{L_2}$ to give the β-lactam in 45% yield and a diastereoisomeric ratio *cis:trans* of 65:35. Using a chiral lanthanide shift reagent, they were able to determine a 40% *ee* for each of the isomers (Table 4, entry 2). After treatment with K_2CO_3 at 80 °C, they obtained exclusively the *trans* isomer in quantitative yield and 40% *ee*. In a modification of their technique, the slow addition of the alkyne over 10 mol % CuI and 20 mol% ligand $\mathbf{L_2}$ gave a *trans* β-lactam in 50% yield and 57% ee, after treatment with K_2CO_3 (Table 4, entry 4). They obtained higher *ee* when they used stoichiometric amounts of CuI and the chiral ligand $\mathbf{L_2}$ (68%) (Table 4, entry 3). The reactions using $\mathbf{L_3}$ and $\mathbf{L_4}$ afforded enantiomeric excesses of 67% and 45% respectively (Table 4, entries 5,6). This was a preliminary study of a catalytic asymmetric Kinugasa reaction; however, it presented a first example proving that a catalytic asymmetric version of this reaction was plausible.

Table 4. Miaura's first example of enantioselective Kinugasa reaction using bis-oxazoline ligands.



Entry	Ligand	Cu:ligand[a] [mmol]	Time [h]	Yield of *trans* [%][b]	*ee* [%]
1	**L_2**	0.1:0.2	5	5	n.d.
2	**L_2**	0.1:1.0	2	45	40
3	**L_2**	1.0: 1.0	1	54	68
4[c]	**L_2**	0.1:0.2	2	50	57
5	**L_3**	1.0: 1.0	2	40	67
6	**L_4**	1.0: 1.0	2	40	45
7	(–)- Sparteine	0.1–1.0	2	47	23

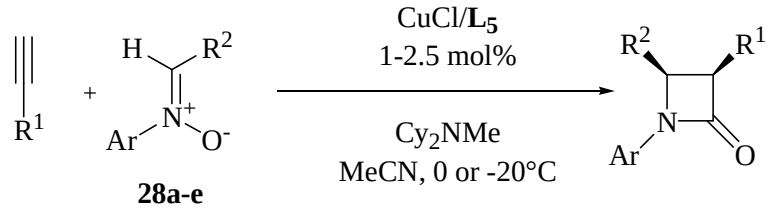
[a] reaction with 1 mmol *C,N*-dipheylnitrone and 1 mmol phenylacetylene.
[b] isomerization of mixture to *trans* isomer.
[c] addition of acetylene over 10 times.

A great deal of effort has been made since for the development of enantioselective examples using chiral ligands. In 2002, Lo and Fu focused on improving the selectivity of the reaction and reported the first asymmetric example by using CuCl and a new C_2-symmetric chiral planar

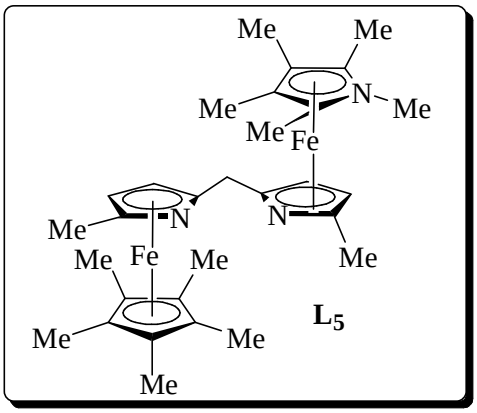
bis(azaferrocene) ligand **L_5** that produced selectively *cis*-β-lactams with broad scope and high *ee*[21]. They remarked that the yield and the *ee* of the reaction were dependent on the electronic properties of the nitrones used. The reaction of a nitrone with electron rich *N*-aryl substituent led to the formation of the *cis* β-lactam in moderate yield and high *ee* (Table 5 entry 1). Running the reaction at a lower temperature helps to improve the selectivity (Table 5, entry 4). On the other hand, an enhancement in the yield and a decrease in *ee* were observed when using nitrones bearing electron deficient *N*-aryl substituents (Table 5, entry 3).

[21] Lo, M. M. C.; Fu, G. C., *Journal of the American Chemical Society* **2002,** *124*, 4572.

Table 5. Fu's asymmetric Kinugasa reaction using CuCl and C_2-symmetric chiral planar bis(azaferrocene) ligand **L_5**



28a R^2 = Ph, Ar = Ph
28b R^2 = Ph, Ar = 4-(MeO)C_6H_4
28c R^2 = Ph, Ar = (EtO_2C)C_6H_4
28d R^2 = 4-(F_3C)C_6H_4, Ar = 4-(MeO)C_6H_4
28e R^2 = Cyclohexyl, Ar = 4-(MeO)C_6H_4

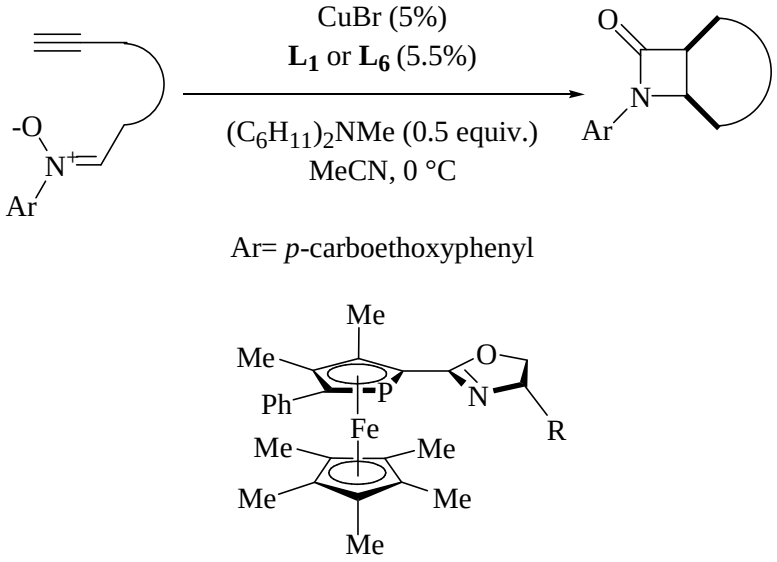


entry	R^1	nitrone	yield *cis* [%]	*cis:trans*	*ee cis* [%]
1	Ph	28b	53	95:5	85
2	Ph	28a	69	95:5	77
3	Ph	28c	79	96:4	67
4[a]	Ph	28c	71	95:5	91
5	Ph	28d	50	93:7	90
6	Ph	28e	57	93:7	89
7	4-(F_3C)C_6H_4	28e	57	>95:5	93
8	$PhCH_2$	28e	43	71:29	73

[a] Reaction at -20 °C

After the establishment of an enantioselective intermolecular methodology for the Kinugasa reaction, Shintani and Fu developed an intramolecular

variant of the Kinugasa reaction where they successfully prepared enantiomerically enriched polycyclic β-lactams[5]. The ligand used in their previous study showed low yield and selectivity when employed in this reaction. The replacement of this ligand with a phosphaferrocene–oxazoline ligand improved drastically the enantioselectivity of the reaction. The formation of tricyclic β-lactam derivatives with moderate to good yields and high enantioselectivites was achieved when they combined CuBr with ligands $\mathbf{L_1}$ and $\mathbf{L_6}$ (Scheme 18).



Scheme 18. Intramolecular Kinugasa reaction developed by Shintani and Fu

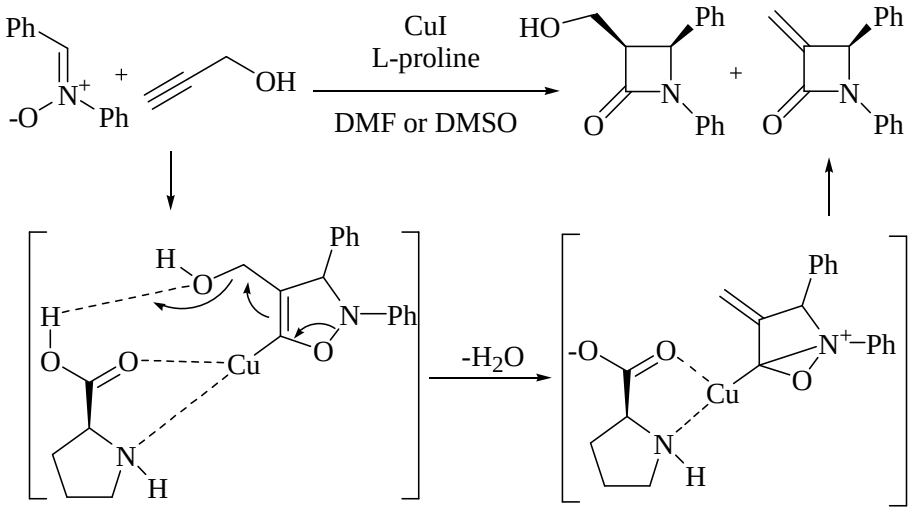
As mentioned above, their research aimed for the development of a protocol for the formation of a quaternary center in β-lactam cycles. They reported a highly diastereoselective α-allylation of the β-lactam ring supposing that it passes through a copper enolate intermediate as shown before in scheme 34. The optimization of the conditions used allowed access to α-allylated-β-lactams to be prepared with the same catalyst **L$_1$** in the presence of allyl iodide and a mixture of silyl enol ether and KOAc as the base. After some

optimization, silyl enol ether was recognized as the best irreversible proton trap that can disable the protonation step in the Kinugasa reaction. Several substrates underwent the Kinugasa/α-allylation sequence and the corresponding products were obtained in moderate to good yields (46-74%) and high *ee* (86-91%).

What's remarkable about this reaction is the one-pot formation of two carbon-carbon bonds, a carbon-nitrogen bond, a carbocyclic ring, a β-lactam, a carbonyl group, a tertiary stereocenter, and an all-carbon quaternary stereocenter.

Following Fu's enantioselective synthesis, Basak *et al.* developed a chiral amino acid mediated Kinugasa reaction between *C,N*-diarylnitrones and propargyl and homopropargyl alcohols for the synthesis of 3-exomethylene β-lactams[22]. In the presence of CuI and L-proline, both in 1 equiv., in DMF, *C,N*-diphenylnitrone and propargyl alcohol react to provide *cis*-β-lactam in 15% yield and 3-exomethylene β-lactam as the major product in 25% yield (Scheme 19). The use of DMSO as a solvent increases the yield of 3-exomethylene β-lactam to 70% along with 10% yield of *cis*-β-lactam. However, low enantiomeric excess was obtained (15%). The use of other L-amino acids (L-tyrosine, L-phenyl alanine) was not successful. The authors proposed a pathway to explain the formation of the 3-exomethylene β-lactam via the elimination of a water molecule from the isoxazoline intermediate before the formation of the β-lactam.

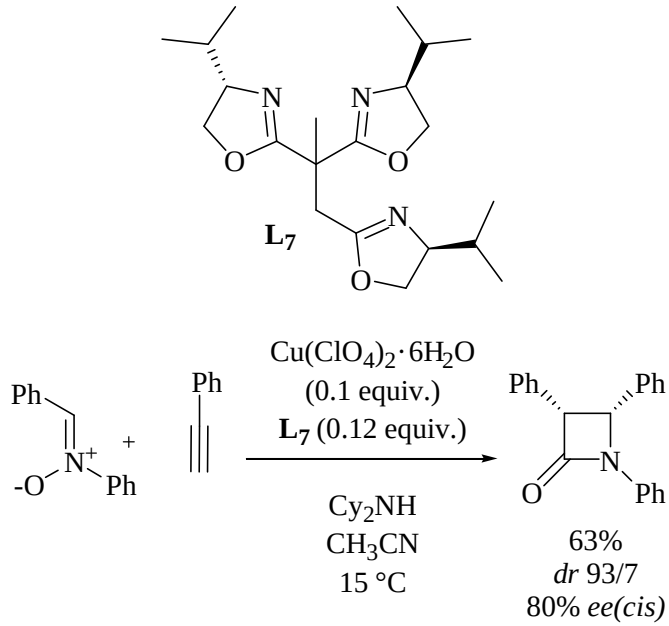
[22] Basak, A.; Ghosh, S. C., *Synlett* **2004,** *2004*, 1637.



Scheme 19. Amino acid mediated Kinugasa reaction

Tang and coworkers designed a new pseudo C_3-symmetric trisoxazoline ligand (TOX ligand) and tested it successfully in the Kinugasa reaction[23]. In their first report about this subject, they carried out reactions between alkynes and *C*,*N*-diarylnitrones using a catalytic amount of $Cu(ClO_4)_2 \cdot 6H_2O$ and the TOX ligand $\mathbf{L_7}$ to produce the desired β-lactams with moderate to good enantioselectivity (Scheme 20).

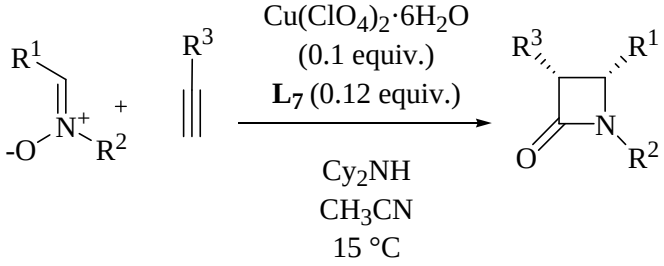
[23] Ye, M.-C.; Zhou, J.; Huang, Z.-Z.; Tang, Y., *Chemical Communications* **2003**, 2554.



Scheme 20. Kinugasa reaction catalyzed by copper salt and TOX ligand

They studied the scope of the reaction using different terminal alkynes and nitrones where they obtained moderate to excellent yields (36-98%), high diastereoselectivities (75/25-97/3) and good to very good enantiomeric excess (70-85%).

Table 6. Scope of the Kinugasa reaction catalyzed by copper salt and TOX ligand developed by Tang



Entry	Nitrone R^1, R^2	Alkyne R^3	*dr* [*cis/trans*]	*ee* (*cis*) [%]	Yield [%]
1	Ph, *p*-$MeOC_6H_4$	Ph	97/3	84	36
2	Ph, *p*-BrC_6H_4	Ph	93/7	74	70
3	Ph, *p*-$Et_2OCC_6H_4$	Ph	91/9	70	98
4	Ph, Ph	*p*-$CF_3C_6H_4$	75/25	73	65
5	Ph, Ph	1-cyclohexenyl	93/7	72	33

Electron rich substituents on the N-bound aromatic group of nitrones increased the enantioselectivity but decreased the reactivity (Table 6, entry 1). Electron deficient substituents slightly decreased the enantioselectivity and increased the reactivity (Table 6, entries 2-3). In addition, arylacetylenes (entry 4) and alkyl acetylenes (Table 6, entry 5) provided good enantioselectivities and diastereoselectivities.

In a subsequent full paper, they demonstrated an optimization of the reaction conditions as well as the scope and limitations[24]. After running several tests examining different copper (I) and copper (II) sources in combination with $\mathbf{L_7}$, they found that the copper salt, $Cu(ClO_4)_2 \cdot 6H_2O$, provided the best enantioselectivity. All the copper sources used provided the *cis*-β-lactam selectively in high diastereoisomeric ratios (>10:1). Further optimizations of the amine base used confirmed the amines influence on the diastereoselectivity, enantioselectivity, and rate of the reaction. With bulkier amines, better diastereoselectivities were obtained. However, secondary amines turn out to provide better enantioselectivities than the bulkier tertiary amines. A number of secondary amines were tested and they found that dicyclohexylamine gave the most fulfilling results in terms of both dia- and enantioselectivity. Likewise, the authors carried out a solvent optimization, and MeCN was found to be the optimal solvent. Furthermore, a number of oxazoline ligands were synthesized to study the effect of the ligand on the reaction. The best result was obtained using the TOX $\mathbf{L_7}$ ligand. It is worth mentioning that the reactions were carried out in air in contrast to other systems. Using optimal conditions, they carried out tests using a variety of alkynes and nitrones to study the scope of the reaction. They found that the electronic properties of substituents at the N-bound aromatic group of the nitrone had a negligible impact on the enantioselectivity. In both cases the enantio- and diastereoselectivity are satisfying. In fact it is the electronic properties of the C-bound aromatic groups that influenced both the yield and the stereoselectivity. Electron donating aromatic groups increased enantioselectivity but decreased the yield, while electron withdrawing ones marginally decreased enantioselectivity but increased the rate of the reaction.

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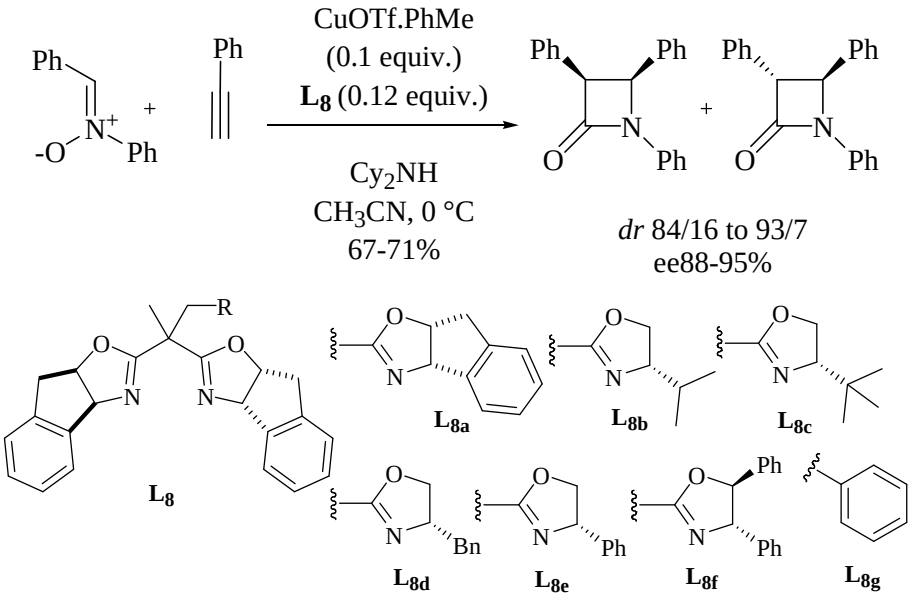
[24] Ye, M.-C.; Zhou, J.; Tang, Y., *The Journal of Organic Chemistry* **2006,** *71*, 3576.

C-alkyl and *N*-alkyl nitrones were unreactive. However, both aryl and alkyl alkynes provided the desired β-lactams. In most cases *cis*-β-lactams were formed predominately.

In a more recent report, Tang *et al.* reported novel pseudo C_3-symmetric IndaTOX ligands for the catalytic enantioselective Kinugasa reaction[25]. In this study, the CuOTf·PhMe complex was found to be the more efficient than the copper salt used in their previous studies leading to the formation of β-lactams with *ee* >90% and *dr* >90:10 (Scheme 21). Also the scope of the reaction was studied using a variety of structurally different diarylnitrones and alkynes providing the corresponding β-lactams with good yields and excellent diastereo- and enantioselectivity.

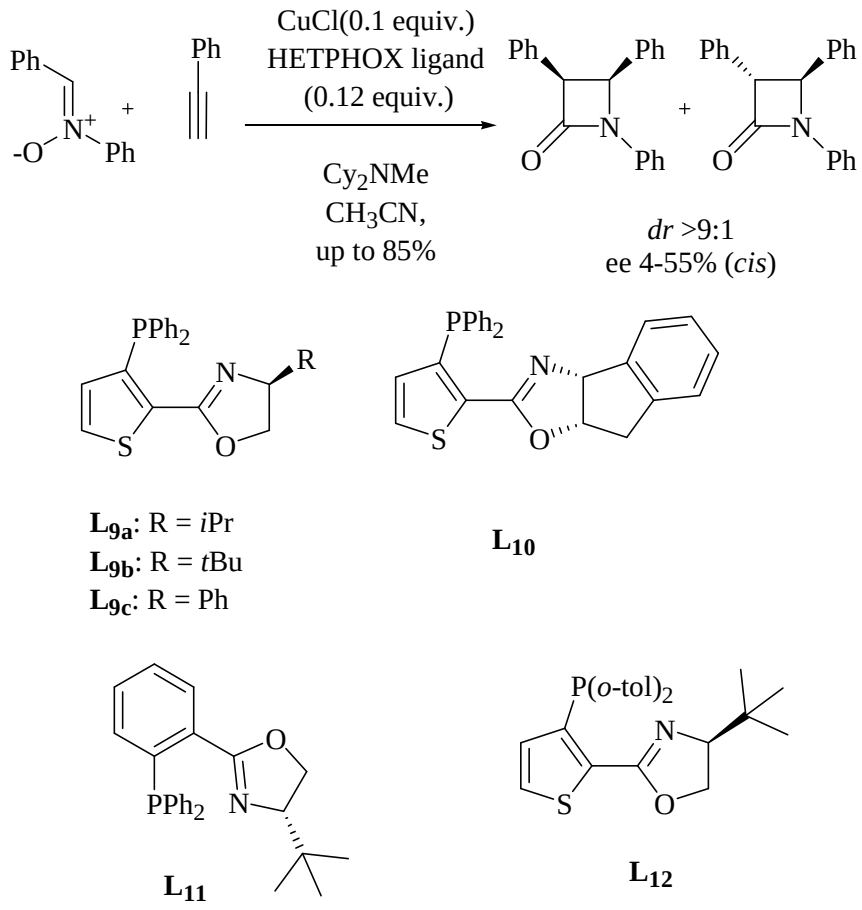


Scheme 21. IndaTOX ligands as ligands for the asymmetric Kinugasa reaction

[25] Chen, J.-H.; Liao, S.-H.; Sun, X.-L.; Shen, Q.; Tang, Y., *Tetrahedron* **2012,** *68*, 5042.

A catalytic enantioselective Kinugasa reaction was also studied by the Guiry group[26] who used a range of HETPHOX ligands in combination with CuCl and Cy_2NMe to afford β-lactams in moderate to good conversions with *ee*s up to 55% and a reaction time of 120 hours (Scheme 22). In the experiments they carried out later in their study, they observed the diastereoselectivity to depend on the alkyne. Phenyl acetylene afforded the product in >9:1 *dr*, whereas 3,5-trifluoromethyl phenylacetylene showed an inverse selectivity for the trans *isomer* with *dr* 1:9. The use of Cu(II) salts resulted in high diastereoselectivity, however the enantioselectivity and yield were poor. The reaction scope with structurally diverse nitrones and phenylacetylenes was also studied.

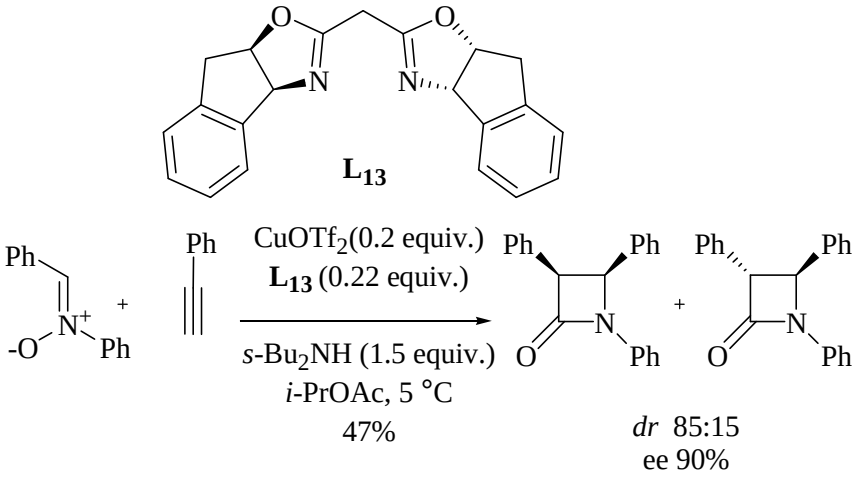
[26] Coyne, A. G.; Müller-Bunz, H.; Guiry, P. J., *Tetrahedron: Asymmetry* **2007,** *18*, 199.



Scheme 22. HETPHOX ligands used by Guiry in the enantioselective Kinugasa reaction

Saito *et al.* used copper (II) salts along with the C_2-symmetric IndaBOX ligands in 0.2 equiv. to catalyze the alkyne-nitrone enantioselective cyclization/rearrangement leading to the formation of β-lactams with high enantioselectivity. After optimization, *s*-Bu_2NH was found to be the most efficient amine and *i*-PrOAc the best solvent. The authors reported an enantioselectivity of 90% with a 85:15 *cis:trans* ratio and moderate yield (Scheme 23). They carried out a wide variety of reactions using both

aliphatic and aromatic terminal alkynes. The modification in the substituents at the nitrone also led to products with high enantioselectivity.



Scheme 23. Saito's Cu(II)/IndaBOX catalytic Kinugasa reaction

Also, Sierra and coworkers reported results that confirm the applicability of the Kinugasa reaction to access β-lactams containing different metal substituents at the C3-position. They used the ligand **L$_{13}$** in the synthesis of β-lactams starting from terminal alkynes substituted with metal fragments, including sandwich, half-sandwich, and arene-tethered metal-carbene complexes. However, the enantioselectivity did not exceed 35% *ee* (Figure 7).

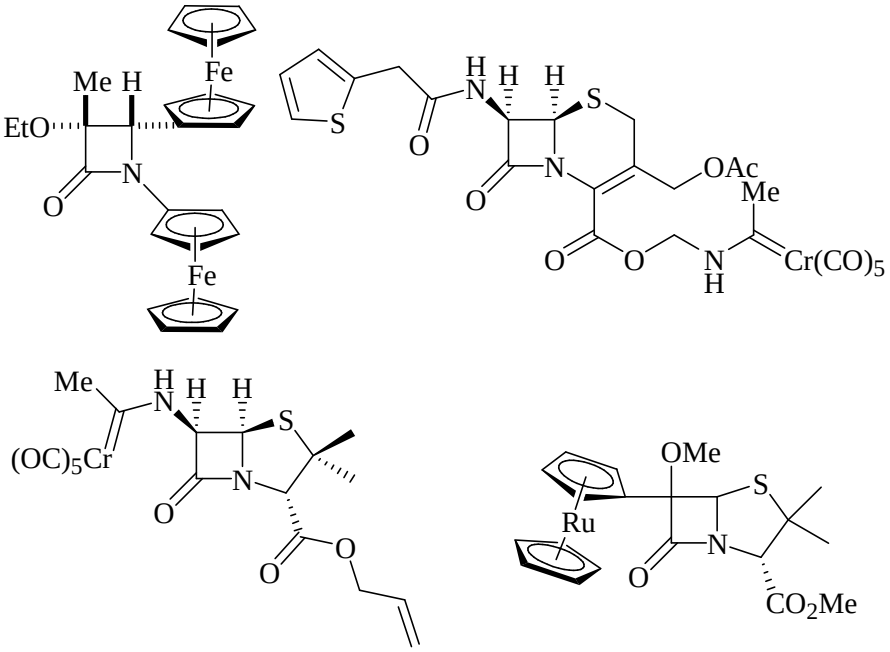
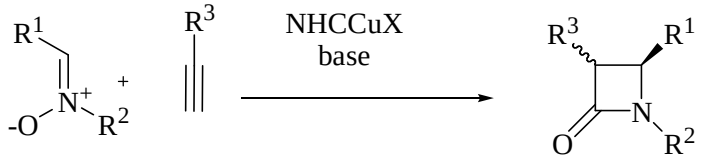


Figure 7. Metal containing β-lactams synthesized using IndaBOX ligands in Kinugasa reaction

II. Objectives

Our group is specialized in developing new methodologies for copper catalyzed processes. The Kinugasa reaction is a Cu(I) catalyzed cycloaddition that has not been well understood from a mechanistic point of view. First of all, this project aimed to identify a diastereoselective catalytic system, simple and stable enough for future kinetic studies of this reaction. Furthermore, we tried to identify possible ligands which influence the the diasterioselective outcome of this reaction, and are stable enough to permit mechanistic investigations. Within this context, and considering our recent successes with Cu(I) NHC complexes[27], we decided to test these latter within the scope of this reaction. Cu(I)NHC complexes, are known for their stability making them ideal candidates for future mechanistic studies (Scheme 24).



Scheme 24. Kinugasa reaction catalyzed by NHCCuX complexes

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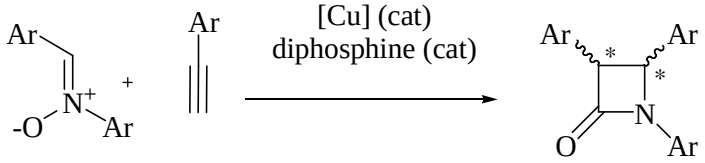
[27] Vergote, T.; Nahra, F.; Peeters, D.; Riant, O.; Leyssens, T., *Journal of Organometallic Chemistry* **2013,** *730*, 95; Vergote, T.; Nahra, F.; Welle, A.; Luhmer, M.; Wouters, J.; Mager, N.; Riant, O.; Leyssens, T., *Chemistry – A European Journal* **2012,** *18*, 793; Vergote, T.; Gathy, T.; Nahra, F.; Riant, O.; Peeters, D.; Leyssens, T., Mechanism of ketone hydrosilylation using NHC–Cu(I) catalysts: a computational study. In *Theoretical Chemistry in Belgium*, Champagne, B.; Deleuze, M. S.; De Proft, F.; Leyssens, T., Eds. Springer Berlin Heidelberg2014; Vol. 6, pp 135; Vergote, T.; Nahra, F.; Merschaert, A.; Riant, O.; Peeters, D.; Leyssens, T., *Organometallics* **2014,** *33*, 1953.

In order to identify an ideal ligand, a series of kinetic investigations of the Kinugasa reaction were performed allowing to establish the effect of the NHC ligand on the reactivity of the system. In addition, we endeavored to isolate some possible intermediates, copper(I) acetylides, for mechanistic investigations. As the mechanism proposed in the literature has not yet been fully proven, one of our goals was to gain some information to support/contradict this mechanism after optimization of the reaction parameters.

The second part of the project concerns the design of an asymmetric Kinugasa reaction for the synthesis of enantiomerically pure β-lactams. Asymmetric induction could be achieved using chiral ligands. Finding the right ligand is not an easy task. As our lab discloses a large library of chiral diphosphines, we intended to carry out screening tests of different families of chiral diphosphines to develop an efficient catalytic system and to obtain highly selective synthesis of β-lactams (Scheme 25). We expect to see a strong influence of the electronic properties of the ligand on the reactivity of the system. The literature shows that electron donating ligands (such as phenanthroline) are usually used with copper to accelerate the reaction and to induce enantioselectivity (such as bis-oxazoline ligands).



Scheme 25. Enantioselective Kinugasa reaction mediated by Cu(I)/chiral diphosphine ligands

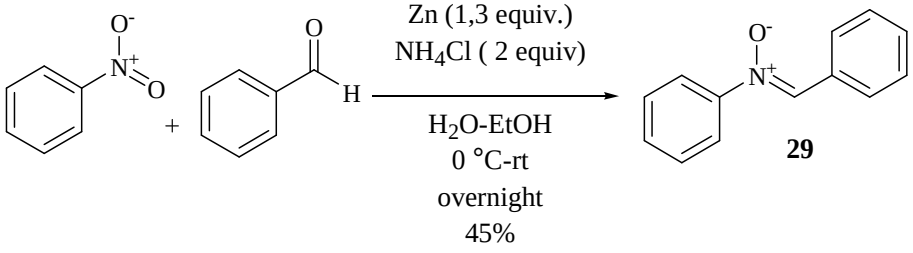
III. Results and discussion

III.1 Diastereoselective Kinugasa reaction

As stated above, we wanted to find a catalytic system simple and stable enough for future mechanistic studies. With this in mind, we decided to start with *C,N*-diphenylnitrone and phenylacetylene as our model system for the desired transformation. Phenylacetylene is commercially available, whereas, the *C,N*-diphenylnitrone had to be prepared as described in the following part.

III.1.1 C,N-diphenylnitrone synthesis

First of all, the nitrone was synthesized according to the literature[32]. The diphenylnitrone was prepared by reacting nitrobenzene with benzaldehyde in the presence of zinc and NH_4Cl in a 50-50 mixture of water and ethanol. The combination of Zn and NH_4Cl, leads to the reduction of the nitrobenzene into phenyl hydroxylamine, which then reacts with the aldehyde to form the nitrone (Scheme 26).



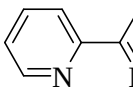
Scheme 26. Synthesis of *C,N*-diphenylnitrone

The *C,N*-diphenylnitrone **29** was obtained as fine white crystals in 45% yield after recrystallization, similar to literature. This product was used in the following catalytic tests. The product was recrystallized on a regular basis (every time a slight change in color was observed).

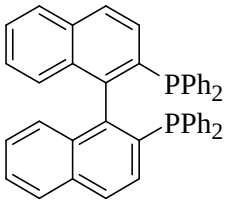
III.1.2 Catalytic tests

Our investigation started with screening a number of ligands to evaluate which type of ligands is suitable for the Kinugasa transformation. The reactions were carried out using 10 mol% CuI and 10 mol % of ligand in acetonitrile (Table 7). The base, followed by the reactants, were added at 0°C after which the temperature was increased and the reaction left at room temperature. The yields demonstrated from now on are isolated ones after chromatography on silica gel unless mentioned. The *cis/trans* ratios are calculated from NMR spectroscopy.

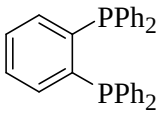
Table 7. Preliminary tests



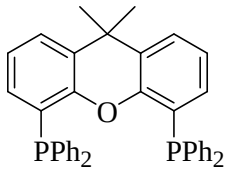
2,2'-bipyridyl



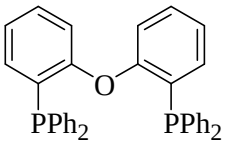
rac-BINAP



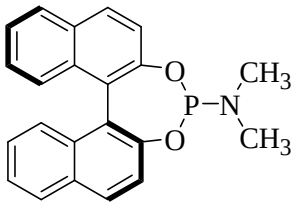
DPPBz



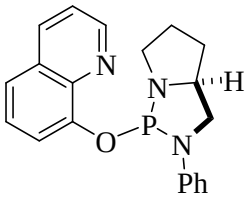
XantPhos



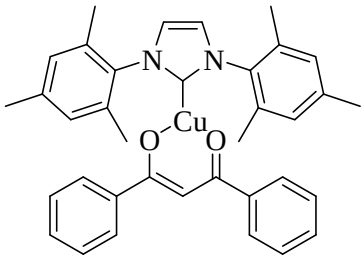
DpePhos



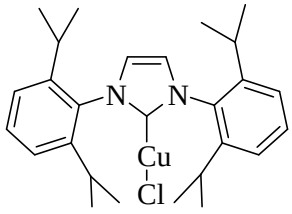
(*R*)-MonoPhos



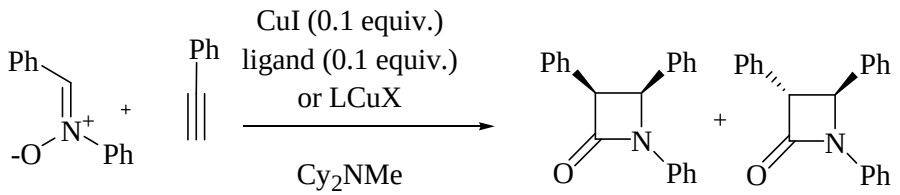
QUIPHOS



IMesCuDBM



IPrCuCl



29 ***cis*-5** ***trans*-5**

Entry	ligands	yield[a]	*cis-5/trans-5*
1[b]	2,2'-Bipyridyl	65%	91/9
2	*rac*-BINAP	-	-
3	Dppbz	-	-
4	XantPhos	-	-
5	dpePhos	-	-
6	MonoPhos (2equiv)	-	-
7	QuiPhos	Traces	-
8	IMesCudbm	44%	86/14
9	IPrCuCl	10%	76/24

[a] isolated yield. [b]reaction ended after 2 hours

As expected, the reaction with bipyridyl as a ligand ran smoothly with 65% yield and high diastereoselectivity (91/9) as shown in literature. Reactions including diphosphines as ligands did not show any transformation, instead the starting material was recovered (Table 7, entries 2-5). Ligands containing both phosphorus and nitrogen atoms were also tested. The reaction using the monodentate monoPhos gave no product (Table 7, entry 6). Traces of product were observed in the ^{1}H NMR spectrum when the bidentate QuiPhos ligand was tested (Table 7, entry 7). However, the use of *N*-heterocyclic

carbenes (NHC) copper complexes (Table 7, entries 8-9) showed promising results. For IMesCudbm, a diastereoisomeric ratio of 86/14 was obtained and a yield of 44%. A ratio of 76/24 was obtained when IPrCuCl for a 10% yield.

Previous reports on the Kinugasa reaction use highly basic ligands. This is the case for the bipyridyl ligand. Diamines are known for being good σ-donor ligands, but poor π-acceptors. On the other hand, diphosphines are good π-acceptors. The diphosphine σ-donating properties will depend on its substituents. In the cases studied, due to the electronegative substituents present on the phosphines, they show poor σ-donor properties. *N*-heterocyclic carbenes are electron-rich nucleophilic species in which the carbene center benefits from the stabilization associated to the orbital overlap of the nonbonding doublets of the nitrogen atoms with the empty p_z orbital of the carbine. NHCs are relatively weak backbonders even more so than phosphines. They pile electron density on the metal center through σ-donation[28]. The NHCs used in our case are good σ-donors and better π-acceptors than diamines, albeight less than phosphines. Due to their strong σ-electron-donating properties, NHC ligands form stronger bonds with metal centers than most classical ligands, such as phosphines, thus giving transition metal complexes that are generally resistant to decomposition and

[28] For reviews on properties of NHCs: Strassner, T., Electronic Structure and Reactivity of Metal Carbenes. In *Metal Carbenes in Organic Synthesis*, Springer Berlin Heidelberg2004; Vol. 13, pp 1; Cavallo, L.; Correa, A.; Costabile, C.; Jacobsen, H., *Journal of Organometallic Chemistry* **2005,** *690*, 5407; Díez-González, S.; Nolan, S. P., *Coordination Chemistry Reviews* **2007,** *251*, 874; Kühl, O., *Coordination Chemistry Reviews* **2009,** *253*, 2481; Dröge, T.; Glorius, F., *Angewandte Chemie International Edition* **2010,** *49*, 6940; Clavier, H.; Nolan, S. P., *Chemical Communications* **2010,** *46*, 841.

can therefore be used as precatalysts without an excess of ligand. This σ-donor property could play a role in determining the rate of the reaction. For the sake of homogeneity, the following nomenclature will be used throughout this work: NHCs with an unsaturated imidazoline ring are usually preceded with an I, while those with a saturated imidazoline ring are preceded with an S. The saturated NHCs are usually more basic and thus thought to be more reactive.

Since the Kinugasa reaction is thought to go through a 1,3-dipolar cycloaddition, and the HOMO of the phenylacetylene (since the alkyne is electron rich) is thought to react with the LUMO of the nitrone, the formation of the copper(I) acetylide complex with a good σ-donor ligand will render the acetylene more electron rich and stabilize the HOMO of copper(I) acetylide allowing the reaction to run faster.

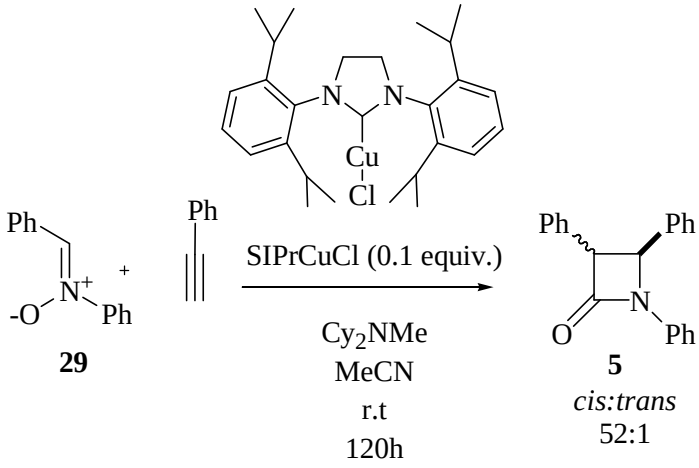
III.1.3 Kinetic monitoring

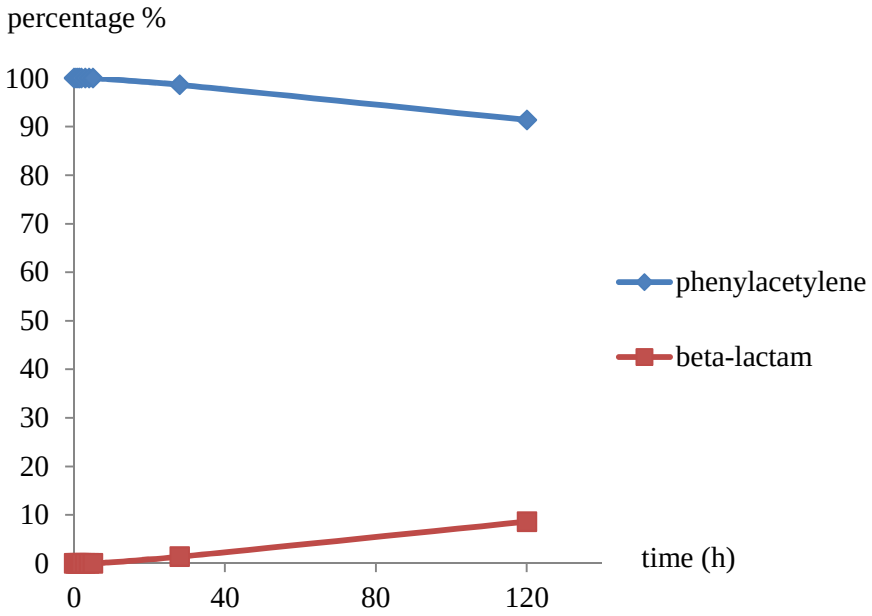
The results obtained using NHCCuX complexes are interesting. The long reaction time allows carrying out some kinetic monitoring experiments using different NHCCuX ligands to observe the rate of the formation of the product. Care should be taken with the interpretation of our results as the medium was not completely homogenous; the nitrone did not fully dissolve in the acetonitrile. We therefore measured the conversion based on the percentage of acetylene consumed. Of course, we were aware of the formation of side products, however, at the time we were interested in finding the optimal system that could provide the β-lactam in highest conversion. This monitoring was performed using reverse phase HPLC.

We screened a number of NHC copper complexes readily available in our lab. We used standard reaction conditions that were used in the previous tests. An internal standard sample of precise concentration for each of the

components of the reaction was already prepared (the acetylene, nitrone and the β-lactam). These internal standards were used to identify the peak of each of these components as well as to calculate their response factors in order to identify their real concentrations. Upon performing the reactions, a precise sample of 100 µL was withdrawn in specific time intervals depending on the rate of the reaction observed.

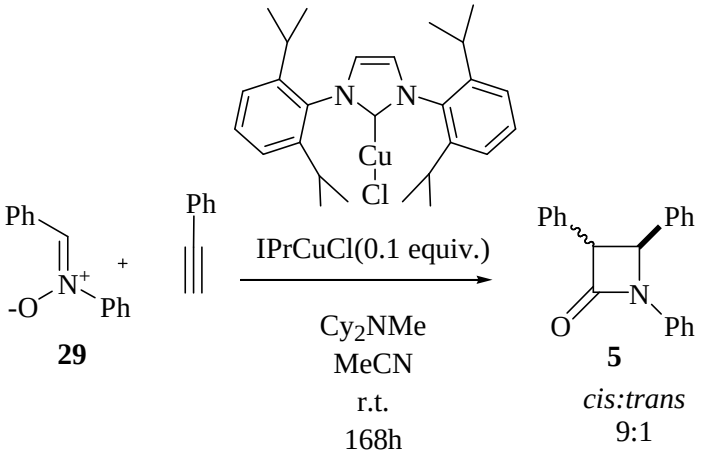
The first experiment involved SIPrCuCl. The reaction was found to be slow and only 9% conversion of the phenylacetylene was observed. However, we noticed that the diastereoselectivity obtained was high (52:1 for the *cis* product) (Scheme 27).

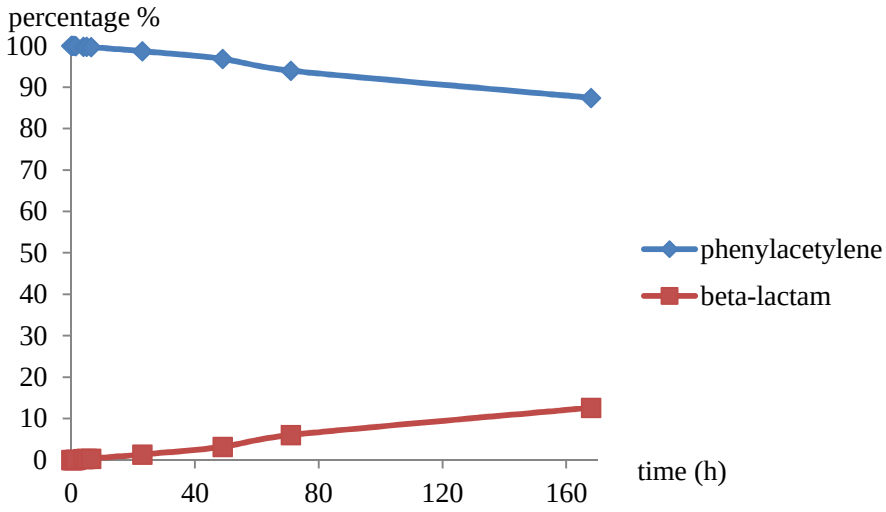




Scheme 27. Kinetic monitoring using SIPrCuCl

The use of IPrCuCl did not yield any improvement leading to a 13% observed conversion after 168 h (Scheme 28).



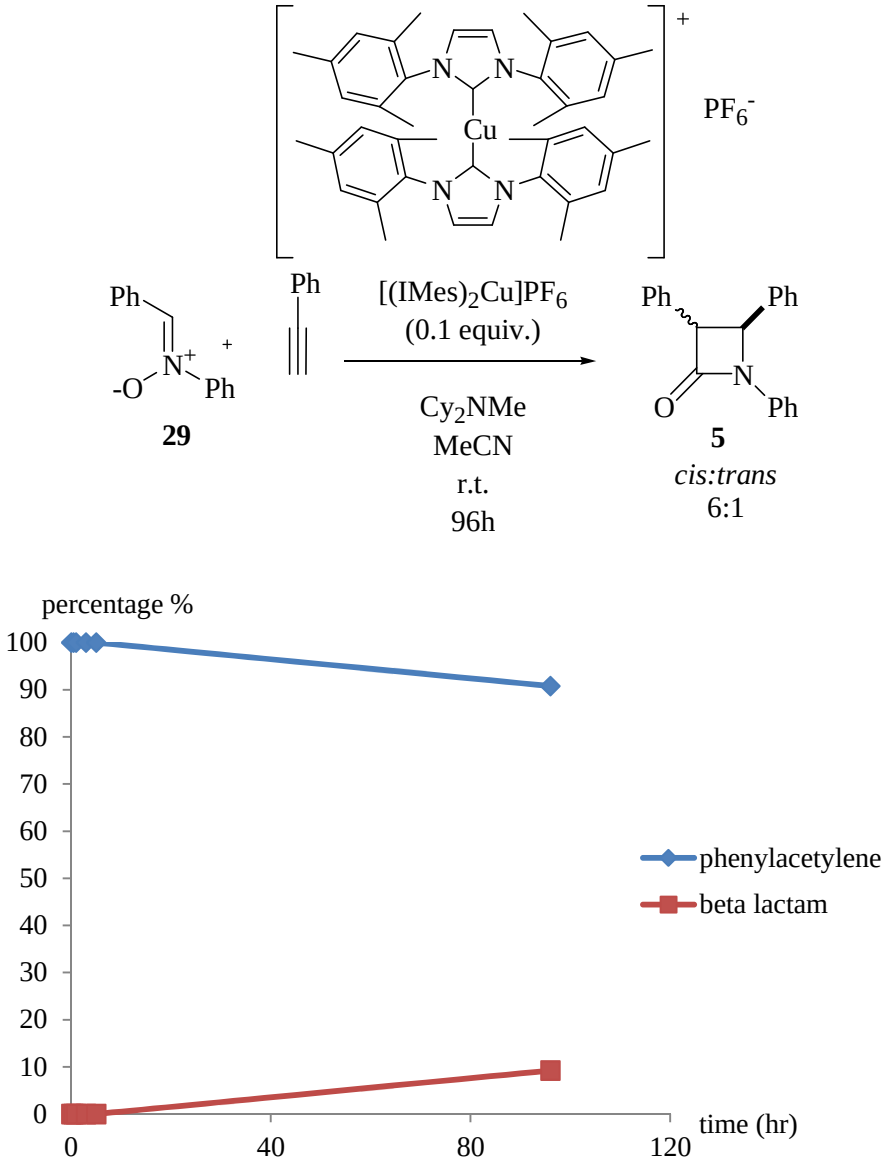


Scheme 28. Kinetic monitoring using IPrCuCl

The use of cationic NHC complexes, which have shown success in the Huisgen azide-alkyne cyclization[29], did not provide better results. After 96 h, the reaction of phenylacetylene with nitrone **29** using $[(IMes)_2Cu]PF_6$ as a

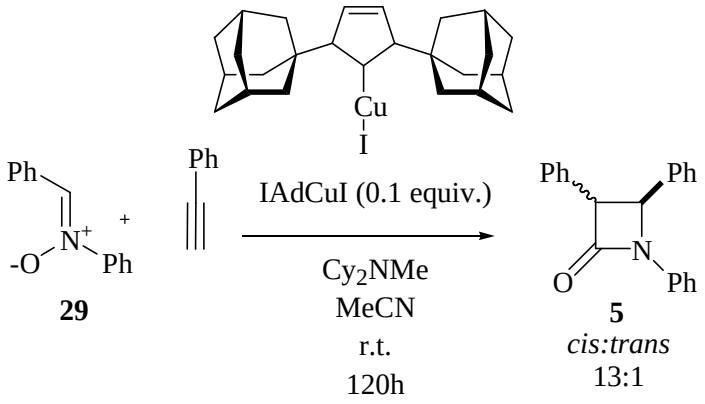
[29] Díez-González, S.; Nolan, S. P., *Angewandte Chemie International Edition* **2008,** *47*, 8881.

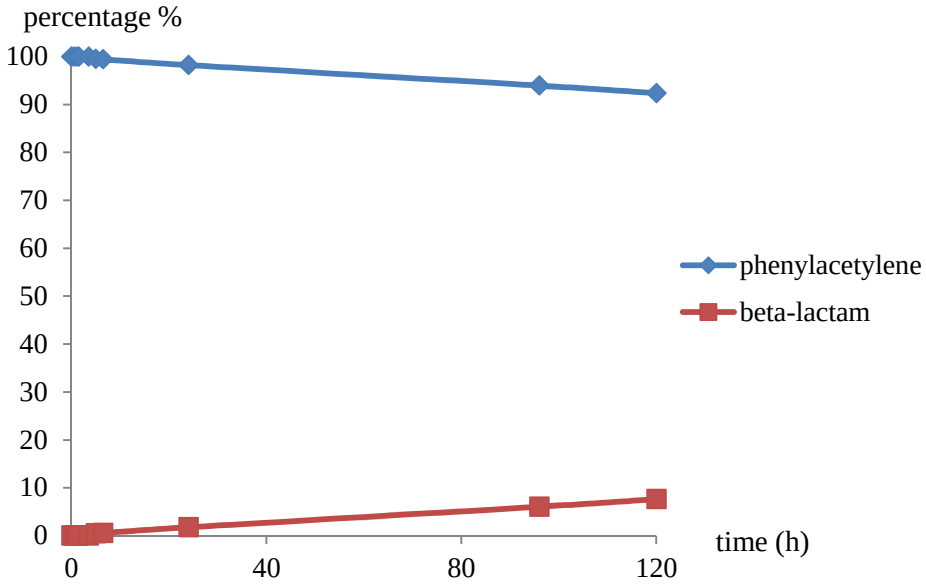
catalyst provided 10% conversion. The product was lost after 96h and we did not reproduce the reaction due to the low conversion that we observed (Scheme 29).



Scheme 29. Kinetic monitoring using $[(IMes)_2Cu]PF_6$

The use of the bulky IAdCuI catalyst did not improve the rate of the reaction. 8% conversion is detected after 120h of reaction (Scheme 30).

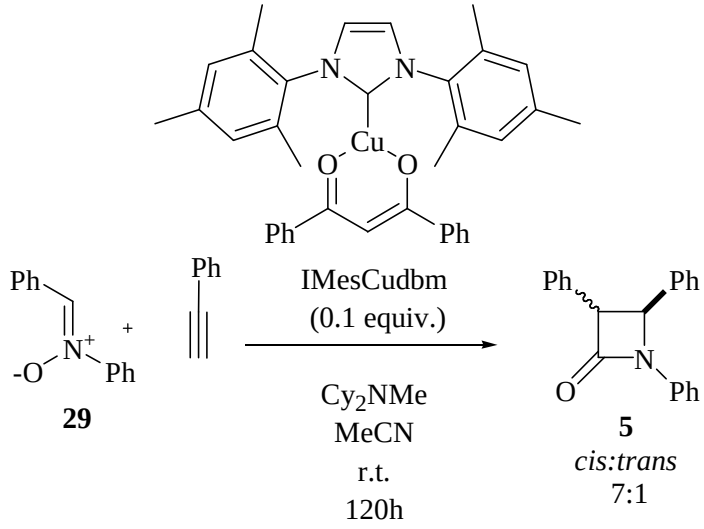


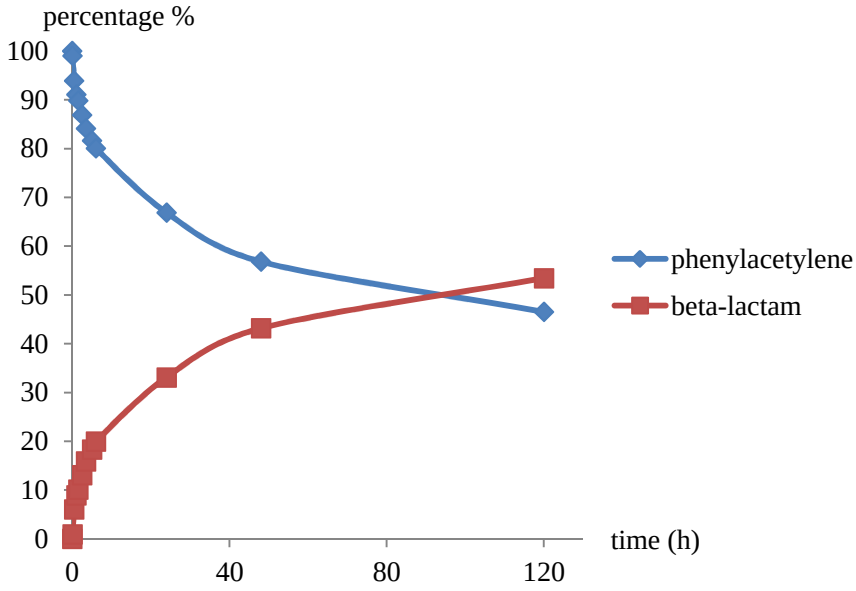


Scheme 30. Kinetic monitoring using IAdCuI

As expected, we observed higher reactivity from the IMesCudbm catalyst. According to the HPLC monitoring, a 54% conversion is noted after 120h (Scheme 31). The reaction was found to slow down with time. We remarked

that after 48h, the reaction no longer progresses although some initial reactants remain. This could be a result of the deactivation of the catalyst.

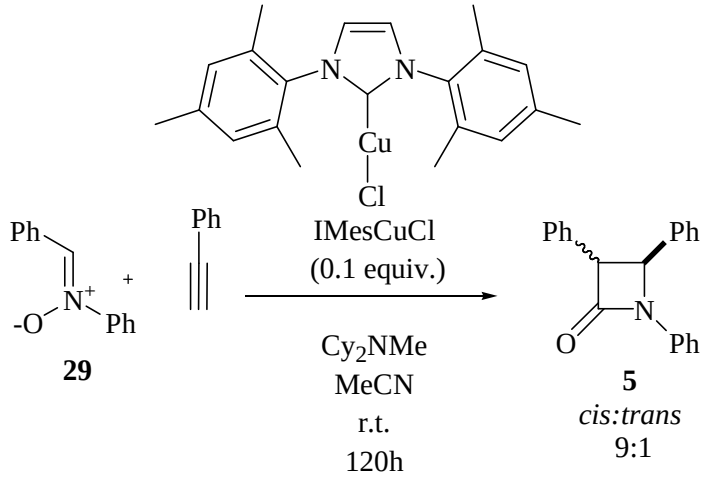


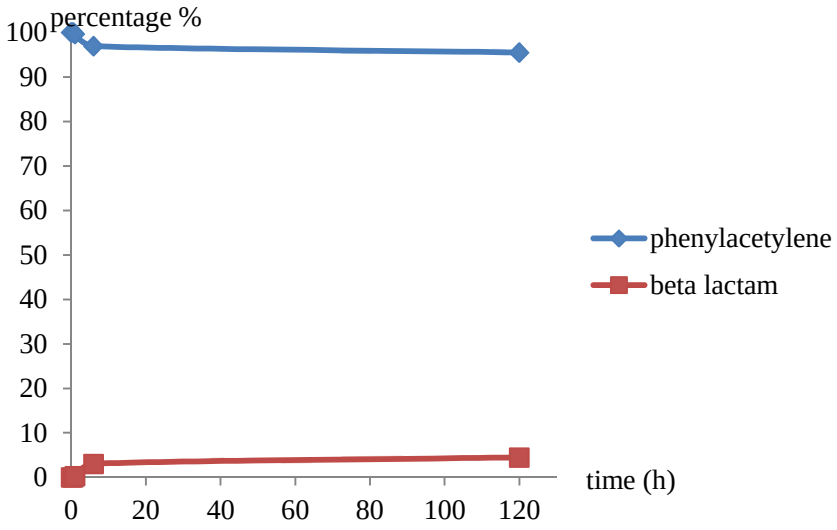


Scheme 31. Kinetic monitoring using IMesCudbm

We also carried out the reaction using IMesCuCl as the catalyst. However, the result was not satisfying. After 120h of reaction, a mere 5% conversion

of the acetylene was observed, clearly showing the importance of the nature of the catalyst (Scheme 32).



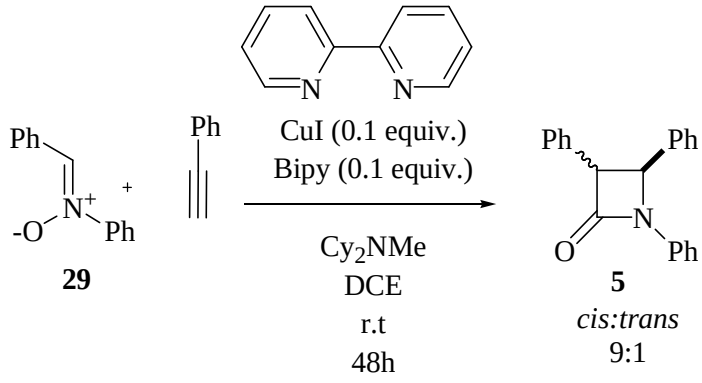


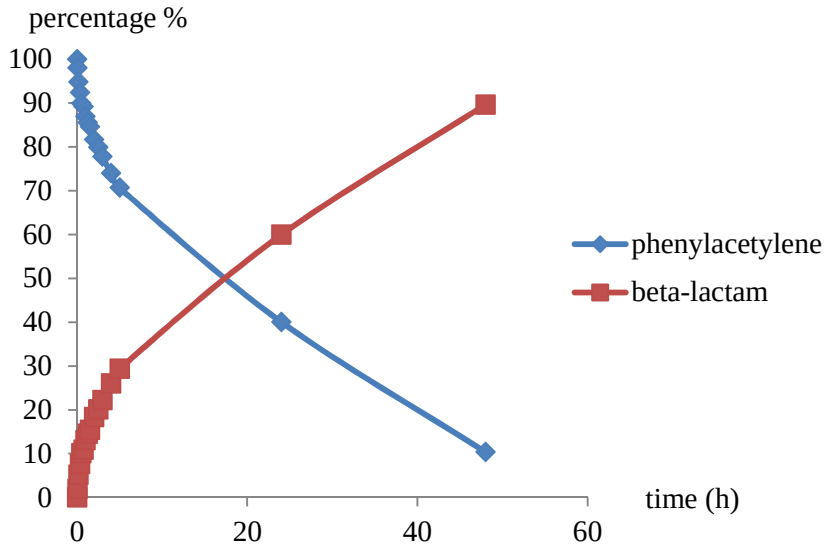
Scheme 32. Kinetic monitoring using IMesCuCl

As the reaction stops prior to all compound being transformed, and furthermore the reaction medium not being homogeneous (nitrone does not totally dissolve in MeCN), we decided to alter the reaction conditions. Initially we started by changing the nature of the solvent. We considered

using dichloroethane (DCE). The reactions were carried out in DCE and monitored for 48h by HPLC. All the reaction components are now soluble.

The first reaction was carried out using CuI (10 mol%) and bipy (10 mol%) as a reference catalytic system that functions well. A 90% conversion of the acetylene was obtained after 48h with a diastereoselectivity of 9:1 for the *cis* product (Scheme 33).

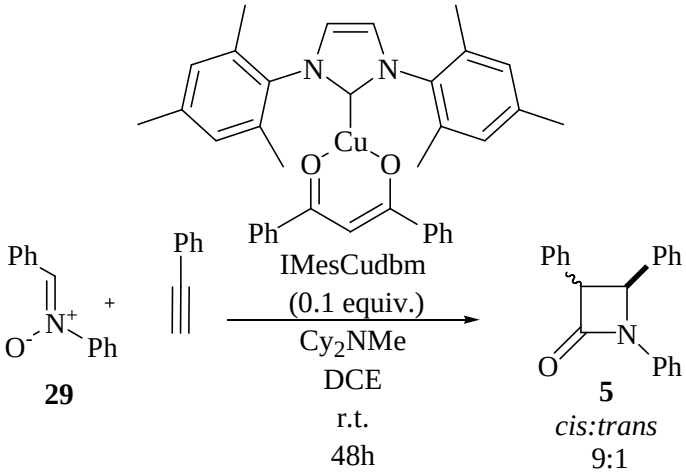


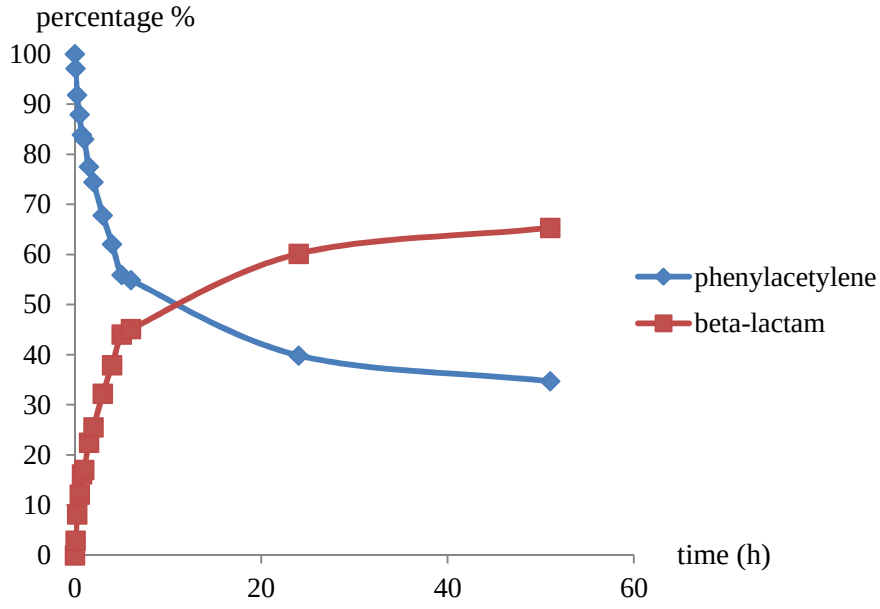


Scheme 33. Kinetic monitoring using CuI/Bipy

We then carried out the reaction using IMesCudbm as the catalyst since it provided the best result in the previous experiments. The observed

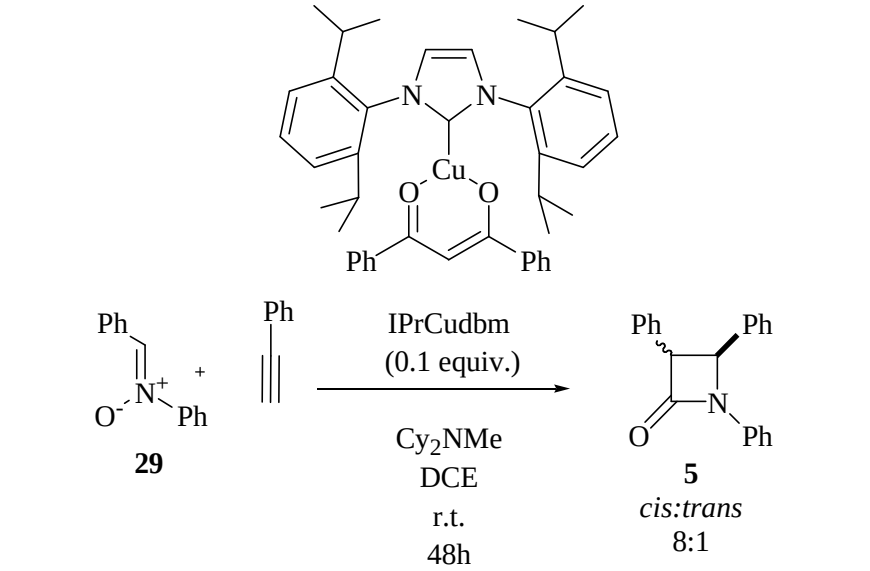
conversion was of 65% after 51h with an increase in the diastereoselectivity to 9:1 for the *cis* product and a higher initial rate (Scheme 34). This higher rate can possibly be explained as the reaction environment is now homogeneous. However the conversion levels off before complete conversion indicating a catalytic deactivation.

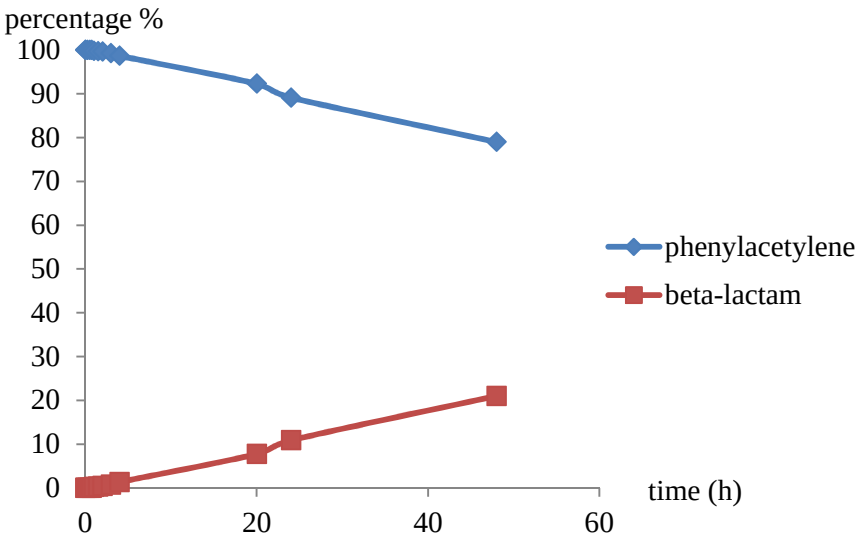




Scheme 34. Kinetic monitoring using IMesCudbm

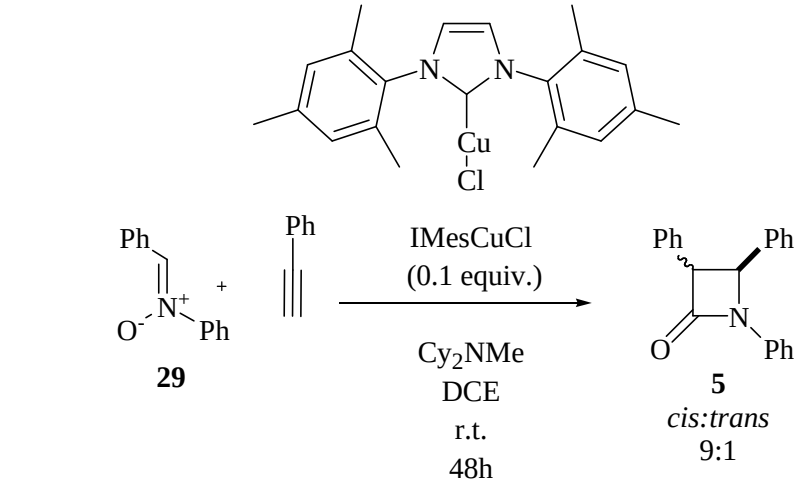
The use of IPrCudbm resulted in the formation of β-lactam in a conversion of 22% after 48h (Scheme 35). The steric hindrance caused by the isopropyl group on the NHC ring might play a role in blocking the reaction to proceed further.

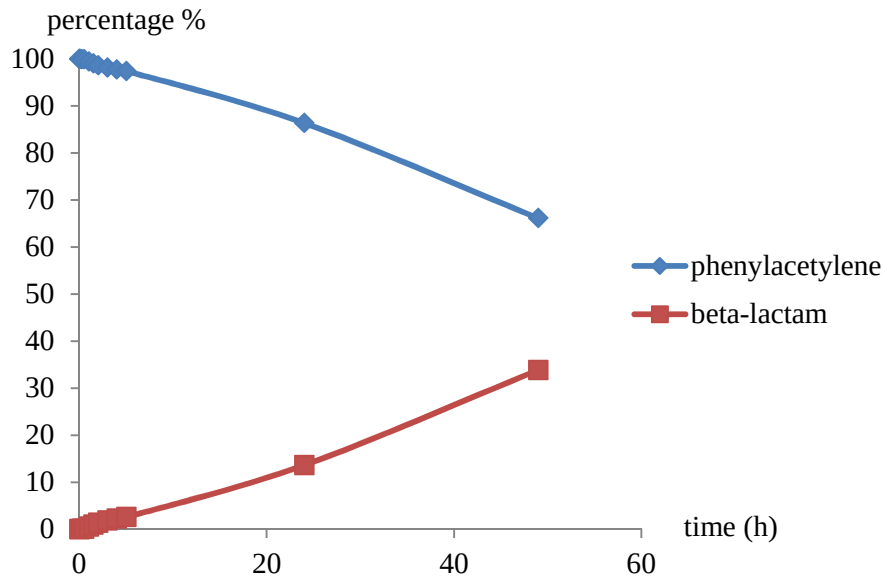




Scheme 35. Kinetic monitoring using IPrCudbm

Using IMesCuCl in DCE resulted in a better yield compared to MeCN. A conversion of 34% was observed after 48h (Scheme 36).

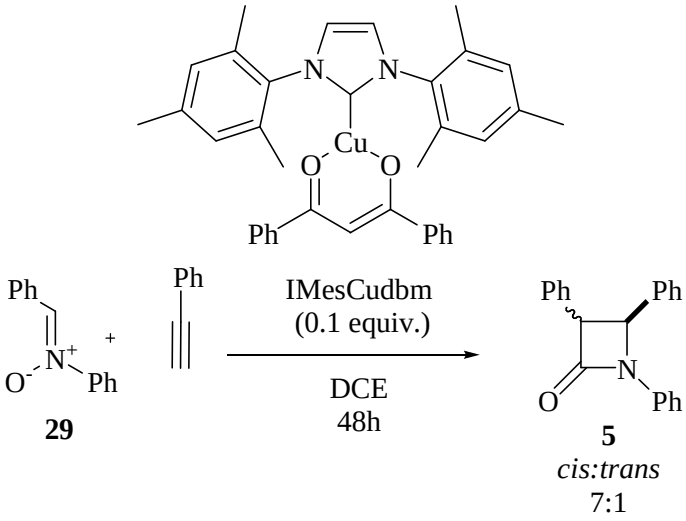


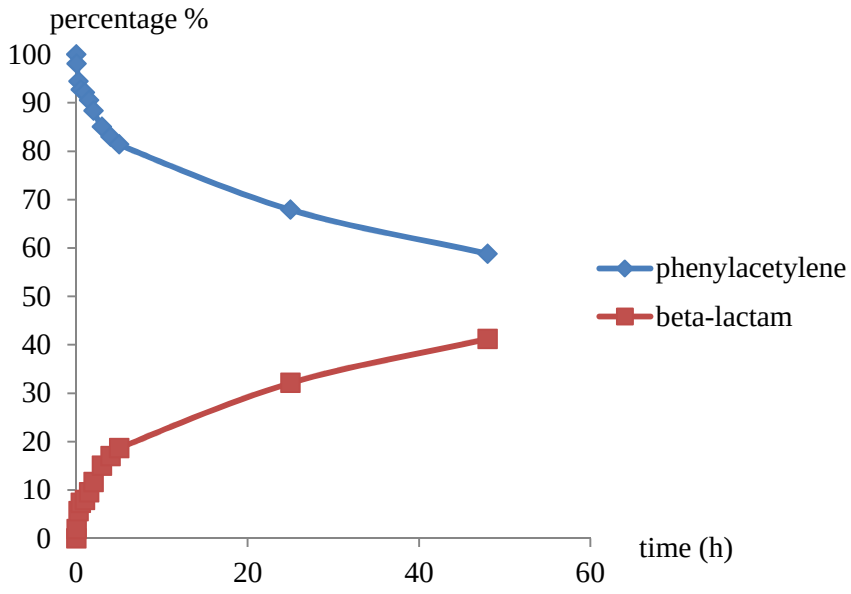


Scheme 36. Kinetic monitoring using IMesCuCl

We have also tested the use of IMesCudbm in the Kinugasa reaction without the use of a base. Remarkably, we obtained a 42% conversion after 48h (Scheme 37). We assume that dibenzoylmethane (dbm) acts as the base in

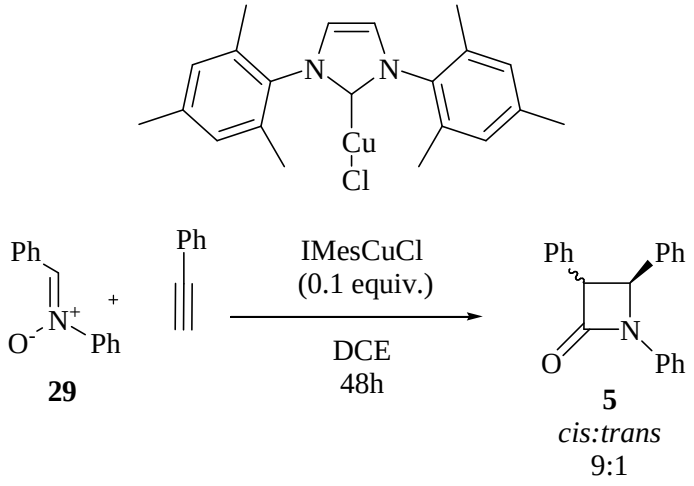
this reaction, thus compensating for the absence of the amine base. The yield obtained is less than that obtained when using an amine base, while the diastereoselectivity slightly decreases.

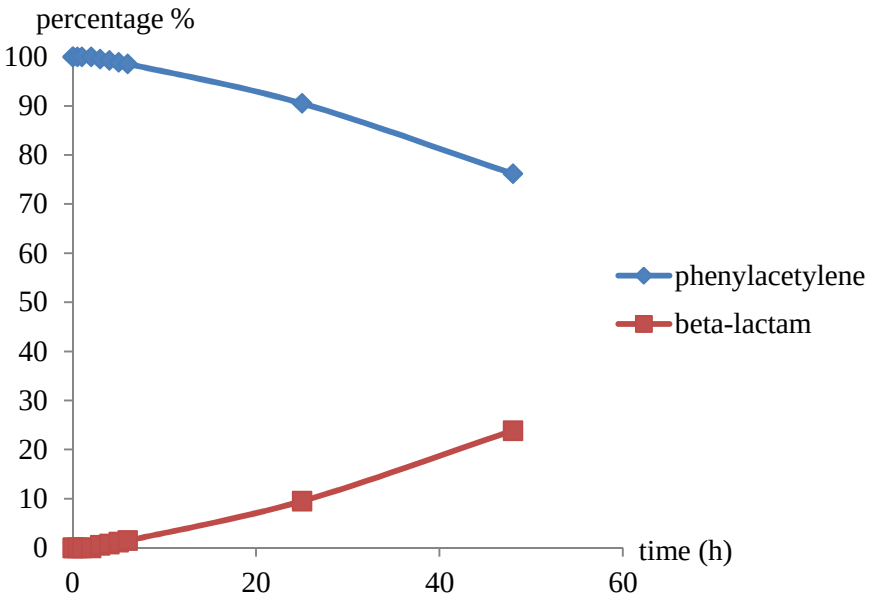




Scheme 37. Kinetic monitoring using IMesCudbm without base

We also attempted the same approach without base using IMesCuCl as a catalyst. After 48h, we obtain 24% conversion of the β-lactam (Scheme 38).



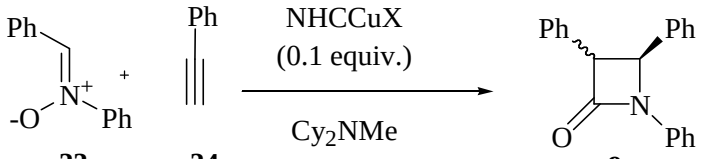


Scheme 38. Kinetic monitoring using IMesCuCl without base

A summary of the the results are shown in Table 8. In general increased conversions were detected comparing dichloroethane with acetonitrile (Table

8, entries 5 vs. 7 and 6 vs. 9). Comparing NHC ligands, an increased conversion is obtained using the IMes NHC ligand with respect to the IPr counterparts (Table 8, entries 7, 9 vs 8), showing how the reaction outcome can be modulated by changing the nature of NHC ligand which is of importance for the future optimization reactions. For a given NHC ligand, the dbm counterion seems most effective (Table 8, entries 5 vs. 6, 7 vs. 9, and 10 vs. 11). Based on these initial screening results, an optimal system so far combines, the IMes ligand with the dbm counterion and DCE as the solvent, leading to an observed conversion of 65% (Table 8, entry 7). Surprisingly, we noted the reaction occurred even without addition of one equivalent of the Cy_2NMe base. Although conversions were slightly lower under similar reaction conditions (Table 8, entries 7 vs. 10 and 9 vs. 11), this result was striking, as up to now the base is believed to intervene directly in the reaction mechanism. These results seem to indicate a more complex mechanism than that proposed in earlier publications, justifying the need for future mechanistic investigations.

Table 8. Summary of the kinetic monitoring results



33 **34** **9**

Entry	[Cu]	solvent	Time [h]	Conversion 9 [%][a]
1	S-IPrCuCl	MeCN	120	9
2	IPrCuCl	MeCN	168	13
3	[(IMes)2Cu]PF_6	MeCN	96	10
4	IAdCuI	MeCN	120	8
5	IMesCudbm	MeCN	120	54
6	IMesCuCl	MeCN	120	5
7	IMesCudbm	DCE	51	65
8	IPrCudbm	DCE	48	22
9	IMesCuCl	DCE	48	34
10	IMesCudbm[b]	DCE	48	42
11	IMesCuCl[b]	DCE	48	24

[a] Determined by HPLC using an internal standard, [b] without base.

III.1.4 Optimization of the reaction conditions

Taking the optimal system identified so far, IMesCudbm in DCE, an experimental plan was devised to optimize the reaction conditions. It should, however, be mentioned that such an optimization can in principle be performed for all of the systems studied in Table 8, which in some cases can lead to even higher yields than those presented here. In the context of this work, we decided to focus on a single system.

III.1.4.1 Temperature and concentration

The goal of the experimental design was to allow screening temperature and concentration effects, with a limited number of experiments, as presented in figure 8. The initial experimental plan did not include entries 1, 2 and 6 (Table 9) and allowed to estimate the main temperature and concentration effects, as well as their interaction. Linear regression using a first order model (aT+bCC+cT*CC) shows little to no effect of the concentration (b=≈0, c=≈0) on the yield nor on the selectivity. Temperature was clearly identified as a significant variable. Experiments performed at 12°C, using a cryostat, showed an increased yield with respect to temperatures of 0 and 25°C, leading us to expand the experimental plan with entries 1, 2 and 6, to be able to estimate a full quadratic temperature model (a'T+b'T2). Such a model explains 83% of the observed variability. The suggested model is statistically valid as shown by variance analysis, although the analysis also shows the model to be incomplete. An optimal temperature is expected at about 7 °C with a yield expected in a 95% confidence interval of [59%-75%]. The quadratic temperature effect is typically related to multiple reactions occurring simultaneously leading to a decreased yield at both lower and higher temperatures. When using NHC based systems for the Kinugasa reaction, control of reaction conditions will therefore be crucial.

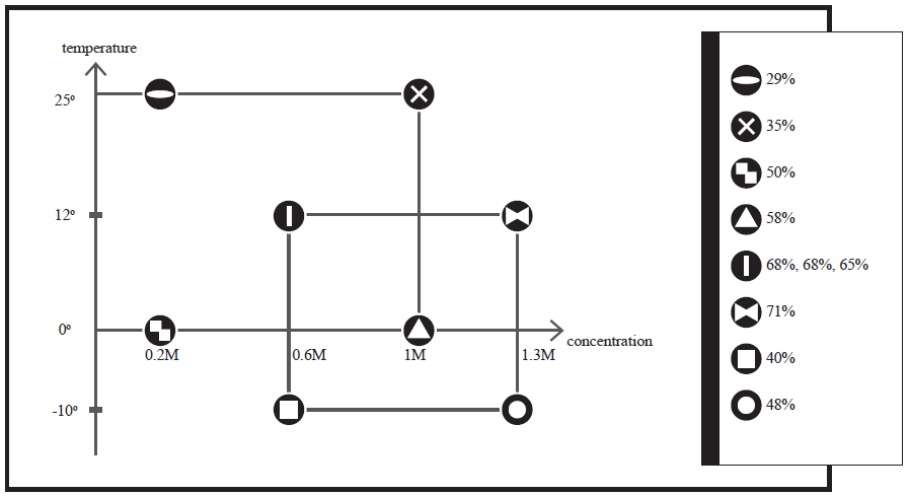
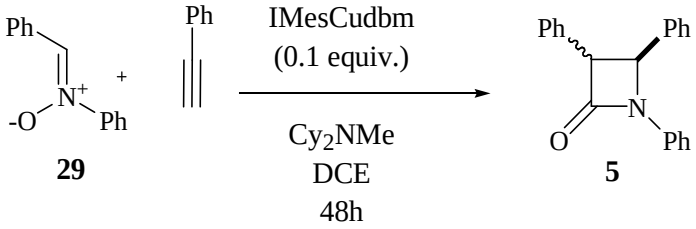


Figure 8. Experimental design

Table 9. Results of the experimental design



Entry	T °C	Conc. [M]	Yield 5[a] [%]	*cis/trans*[c]
1	-10	0.6	40	10:1
2	-10	1.3	48	10:1
3	0	0.2	50	10:3
4	0	1	58	10:4
5	12	0.6	68,68,65[b]	10:1
6	12	1.3	71	10:1
7	25	0.2	29	10:2
8	25	1	35	10:2

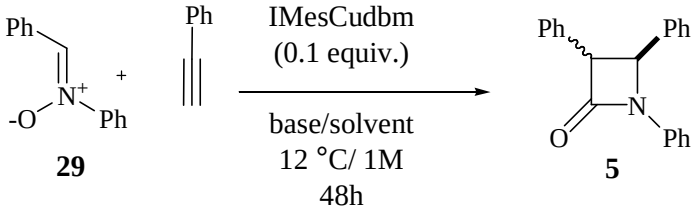
[a] Isolated yields [b] Repeated 3 times. [c] Ratios determined by NMR.

III.1.4.2 Base and solvent

Considering the strong solvent effect observed earlier, and the surprisingly strong reactivity, even in absence of a base, as a final part of our investigation, a screen was performed changing the nature of both these components. Keeping in mind, that a sterically hindered amine is imperative for achieving high yields and selectivity; we carried out several cross-experiments testing three different bases and 3 different solvents, keeping the temperature at 12°C and a concentration of 1M. As mentioned above, in

principle, a temperature and concentration optimization can be performed for every combination, but this goes beyond the scope of this work. As shown in table 10, THF leads to improved yields, which is particularly the case when using a DBU base. The nature of the base and the solvent are inter-linked, as shown by the increased yield when using DBU with THF as a solvent, but a lowered yield when switching to the DBU/DCE system. More striking however was the inversed selectivity obtained when using DBU (1:10), compared to Et_3N and DABCO bases. As mentioned before in the bibliographic data, DBU facilitates the epimerization of the *cis* isomer to the *trans* one at low temperature[13]. So, we propose that the reason why we obtain *trans* isomer as the major one could be this easy epimerization. Furthermore the use of DABCO leads to a significant decrease in selectivity (10:4). Based on these results, we show the feasibility of obtaining high-yield systems, for which the diastereoselectivity can be inverted, working on the nature of the base, once more illustrating the complexity of the underlying reaction mechanism.

Table 10. Base and solvent optimization



29 **5**

Entry	Base	Solvent	Yield [%]	*cis/trans*[a]
1	DBU	DCE	41	1:10
2	Et_3N	DCE	58	10:2
3	DABCO	DCE	50	10:2
4	DBU	THF	76	1:10
5	Et_3N	THF	61	10:2
6	DABCO	THF	65	10:4
7	DBU	AcOEt	61	1:10
8	Et_3N	AcOEt	55	10:2
9	DABCO	AcOEt	59	10:4

[a] ratios determined by NMR

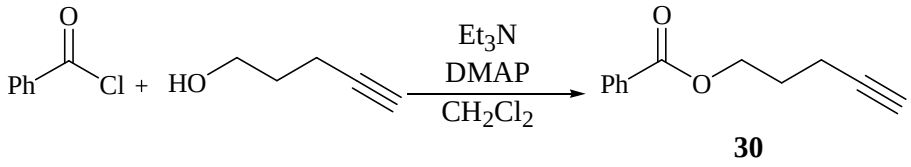
III.1.5 Scope of the reaction

With "optimal" conditions in hand, we decided to evaluate the scope of the catalytic systems by studying various acetylenes and nitrones.

Some substrates were commercially available, whereas others were prepared using previously reported procedures.

III.1.5.1 Synthesis of substrates

First, the acetylene **30** was prepared according to a procedure used in our lab. The reaction between the corresponding acyl chloride and 4-pentyn-1-ol in the presence of Et_3N and DMAP in dichloromethane provided the desired acetylene **30** in 94% yield (Scheme 39).

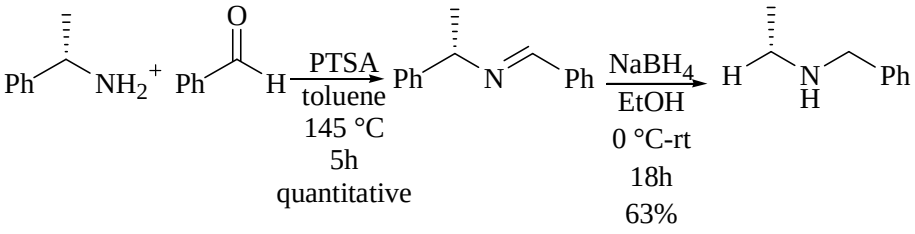


30

Scheme 39. Synthesis of acetylene **30**

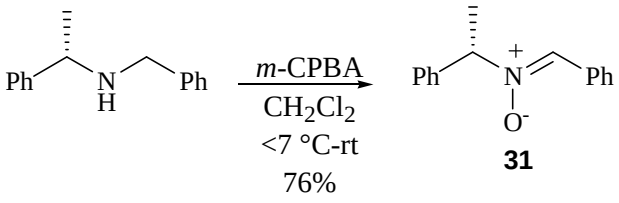
Other acetylenes were commercially available.

As for the nitrones, we prepared aliphatic and aromatic nitrones. Nitrone **31** was prepared according to a procedure from the literature[30]. (*S*)-phenylethylamine was reacted with benzaldehyde to provide the imine which in turn is reduced to the amine using $NaBH_4$ (Scheme 40).



Scheme 40. Synthesis of amine

This amine is then oxidized using *m*-CPBA to provide the corresponding nitrone **31** in 76% yield (Scheme 41).



31

Scheme 41. Oxidation of corresponding amine to nitrone **31**

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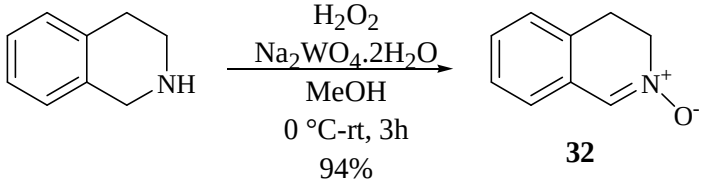
[30] Cheetham, C. A.; Massey, R. S.; Pira, S. L.; Pritchard, R. G.; Wallace, T. W., *Organic & Biomolecular Chemistry* **2011,** *9*, 1831.

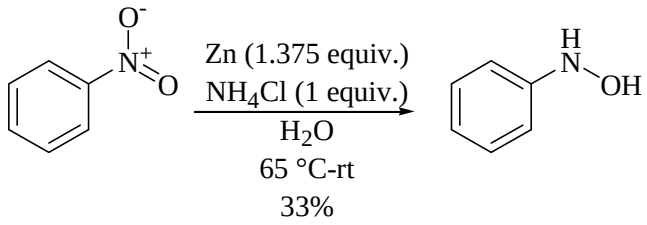
The synthesis of nitrone **32** was carried out according to a method from the literature[31]. 1,2,3,4-tetrahydroquinoline was oxidized into the corresponding nitrone in 94% yield, using hydrogen peroxide and sodium tungstate in methanol (Scheme 80).



32

Scheme 42. Synthesis of nitrone **32**

Other aryl nitrones were also prepared. Phenylhydroxylamine was synthesized following a procedure from literature[32]. The reduction of nitrobenzene using zinc metal leads to the formation of phenylhydroxylamine (Scheme 43).



Scheme 43. Preparation of phenylhydroxylamine

This amine was then employed in the synthesis of aryl nitrones **33-44**, which were obtained in good to excellent yields, by reaction with the corresponding aldehydes[33].

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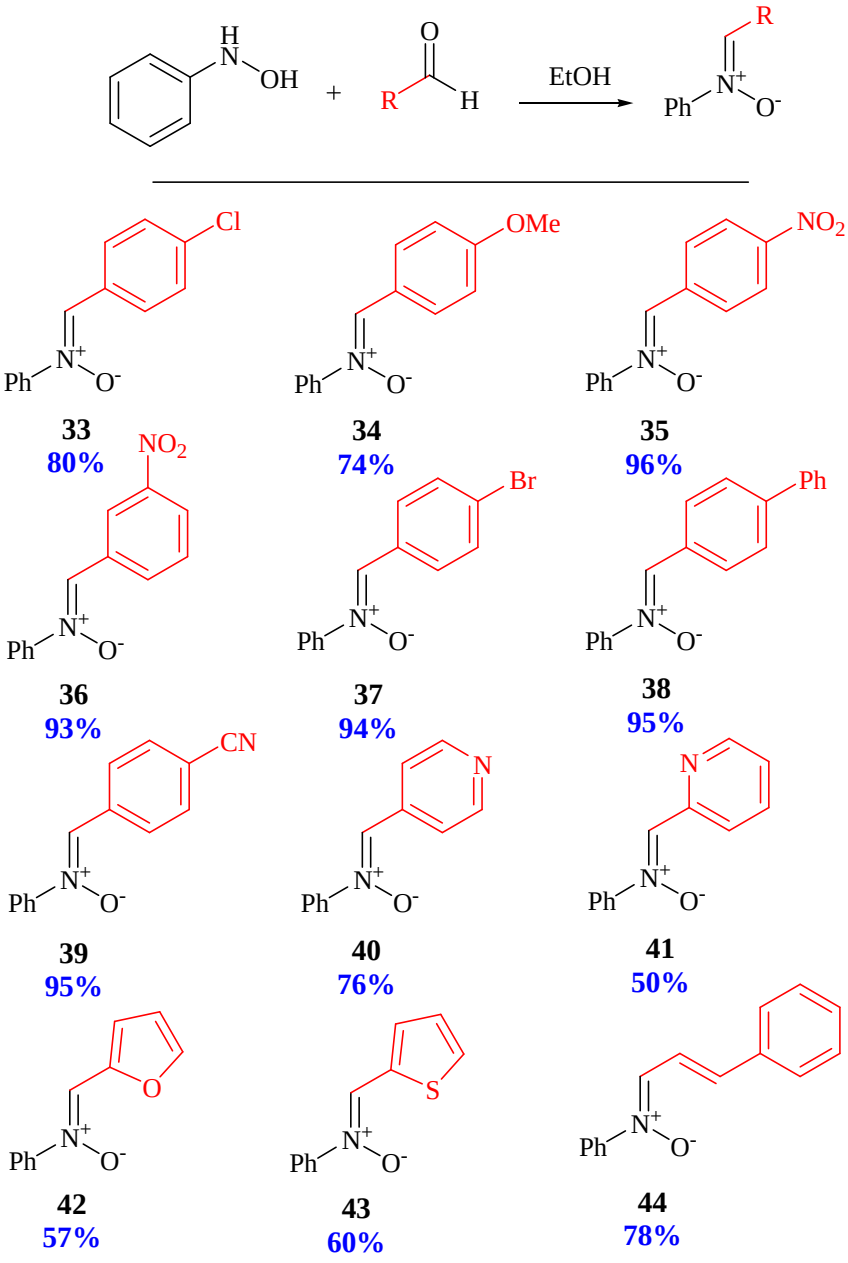
[31] Radivoy, G.; Radivoy, G.; Alonso, F.; Yus, M., *Synthesis* **2001,** *2001*, 0427.

[32] Wittstein, K.; García, A. B.; Schürmann, M.; Kumar, K., *Synlett* **2012,** *2012*, 227.

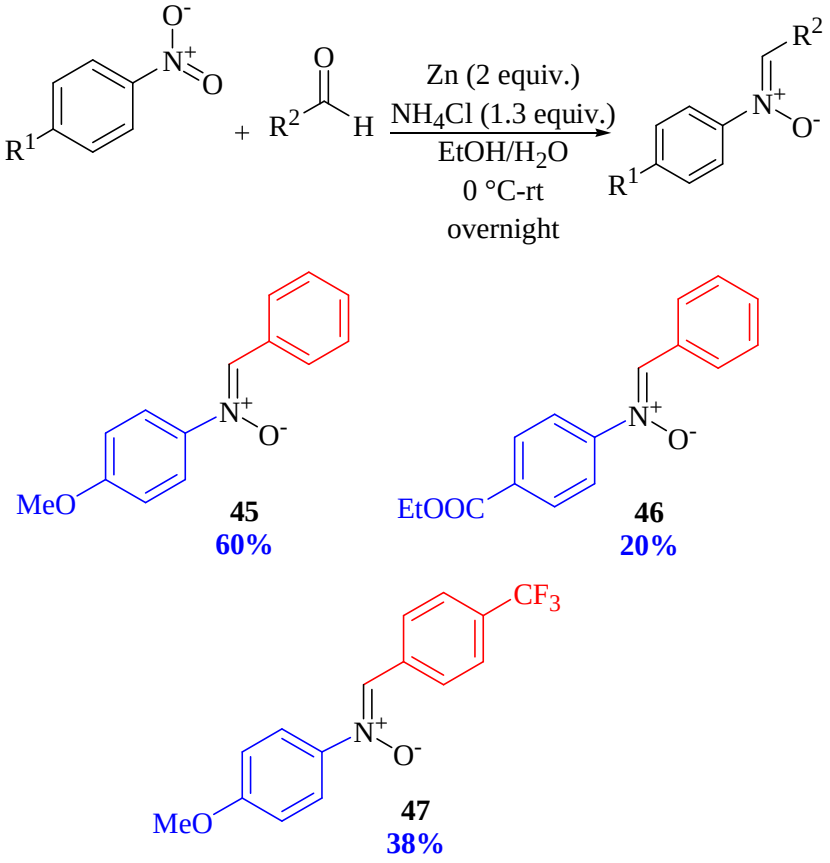
[33] Nelson, D. W.; Owens, J.; Hiraldo, D., *The Journal of Organic Chemistry* **2001,** *66*, 2572.



Scheme 44. General procedure for the preparation of nitrones **33-44**

Other aryl nitrones with substituted N-bound aryl groups were prepared following the same procedure, except that the corresponding aldehydes were

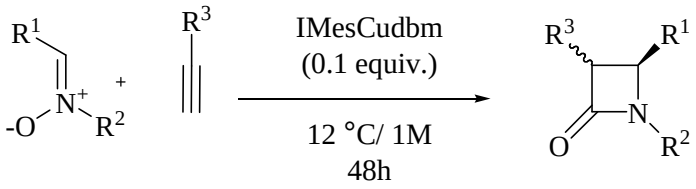
present directly with the nitroaryls, which are reduced *in situ* to the corresponding hydroxylamines in the presence of zinc. The nitrones were formed in moderate to good yields (Scheme 45).



Scheme 45. Synthesis of diarylnitrones with N-bound aryl groups

III.1.5.2 Catalytic tests

Following the synthesis of substrates, we envisaged to engage them, along with other commercially available substrates, in the two optimized catalytic systems we developed previously (Scheme 46).

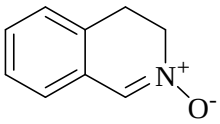


Method **A**: Cy_2NMe (1 equiv.) in DCE
Method **B**: DBU (1 equiv.) in THF

Scheme 46. Optimized systems for Kinugasa reaction catalyzed by IMesCudbm

The results obtained for method **A** are summarized in the following table.

Table 11. Kinugasa reaction method **A**

Entry	R^1, R^2	R^3	product	yield[a] [%]	*cis/trans*[b]
1	Ph, Ph	Ph	**5**	68	10:1
2	$CH(CH_3)Ph$, CHPh	Ph	**-**	-	-
3		Ph	**-**	-	-
4	4-ClC_6H_4, Ph	Ph	**48**	40	10:1.5
5	4-$MeOC_6H_4$, Ph	Ph	**49**	35	10:1
6	4-$NO_2C_6H_4$, Ph	Ph	**50**	27	10:3
7	3-$NO_2C_6H_4$, Ph	Ph	**51**	36	10:2.2
8	4-BrC_6H_4, Ph	Ph	**52**	33	10:1.6

Entry	R^1, R^2	R^3	product	yield[a] [%]	*cis/trans*[b]
9	4-PhC_6H_4, Ph	Ph	**53**	13	10:2
10	4-CNC_6H_4, Ph	Ph	**54**	40	10:3.5
11	4-pyridyl, Ph	Ph	-	n.d.	n.d.
12	3-pyridyl, Ph	Ph	-	n.d.	n.d.
13	2-furyl, Ph	Ph	**55**	20	10:3.4
14	2-thienyl, Ph	Ph	-	traces	-
15	*(E)*-styryl, Ph	Ph	-	-	-
16	Ph, 4-MeOC_6H_4	Ph	**56**	15	10:1
17	Ph, 4-COOEtC_6H_4	Ph	**57**	70	10:5
18	4-$CF_3C_6H_4$, 4-MeOC_6H_4	Ph	**58**	11	10:2
19	Ph	$(CH_2)_3$OCOPh	**59**	80	10:3
20	Ph	$CH(OCH_2CH_3)_2$	**60**	75	1:1

[a] isolated yield. [b] determined by NMR.

The analysis of the above results shows that with *C*-bound or *N*-bound alkyl groups, method **A** was not functional (entries **2-3**, **15**). In the case of electron withdrawing substituents on the *C*-bound phenyl ring of the nitrone (entries **4, 6-8, 10**), the yields are moderate (27-40%) and the diastereoselectivities were good (10:3 to 10:1). When electron donating substituents are present on *C*-bound phenyl ring of the nitrone (entries **5, 9**), low to moderate yields

were obtained (13-35%) and good diastereoselectivities (10:2-10:1). This result suggests the insignificance of the influence of *C*-substituents. In cases of *C*-bound heterocycles (entries **11-14**), it is only in the case of C-furyl that we obtained 20% yield with 10:3 diastereoselectivity. In the case of pyridyl groups the product was detected (NMR) but could not it be isolated. In the case of thienyl, only traces of product were obtained. Concerning *N*-bound substituted aryls, the presence of an electron withdrawing substituent increases the yield dramatically (entry **17**) obtaining up to 70% yield. However, the diastereoselectivity decreased to 10:5. In cases where the substituents are electron donating groups the yield decreases (entries **16, 18**) to values as low as 15 and 11% respectively, whereas the diastereoselectivity stays good (10:2-10:1). Using acetylenes **20** and **30** result in high conversion (75 and 80%) respectively (entries **19-20**), however, we observe lower selectivity.

The attribution of the *cis* and *trans* ratios was carried out using NMR. The peaks corresponding to the 2 protons that determine the configuration of the product show a coupling constant ranging between J=2-4 Hz for the *cis* product and J=5-7 Hz for the *trans* product. An example shown below presents two diastereoisomers of product **60** that were separated and attributed. In the case of the *cis* product, the $CH(OCH_2CH_3)_2$ moiety is partially blocked from rotation because of it being on the same side of the phenyl group.

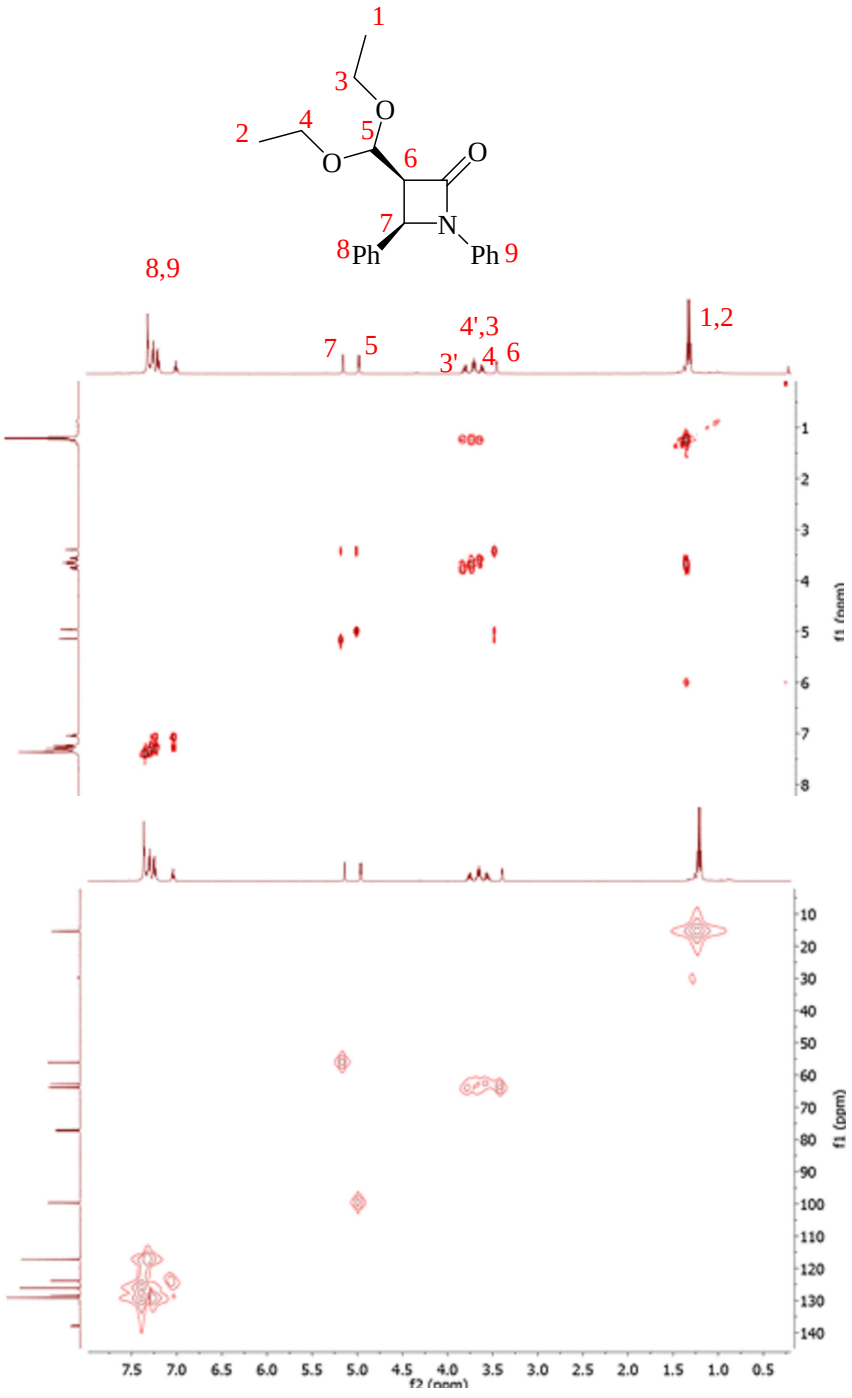


Figure 9. NMR experiments for the attribution of *cis*-**60**

In the case of the *trans* product, knowing that both CH_3 groups (OCH_2CH_3) are diastereotopic, they show different shifts.

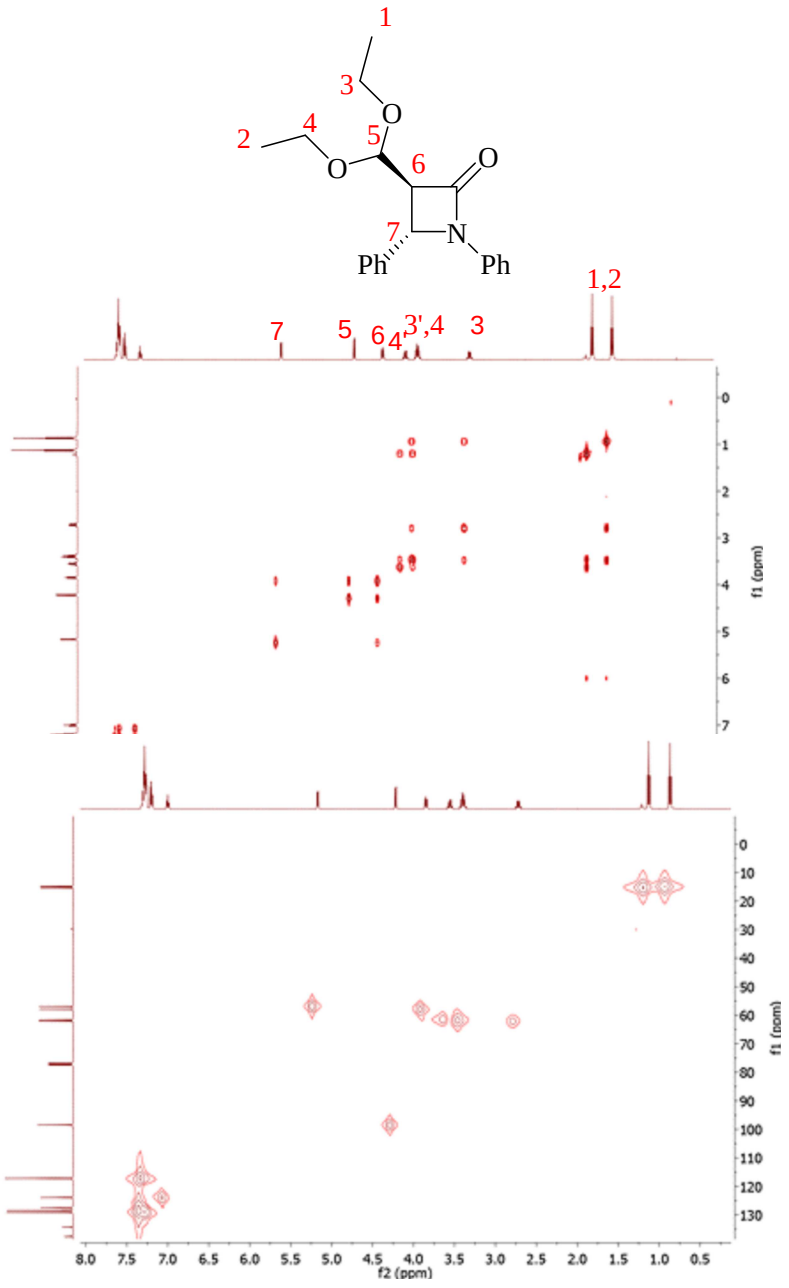
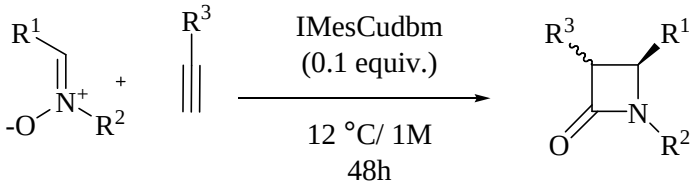


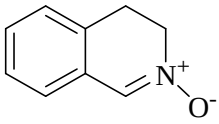
Figure 10. NMR experiments for the attribution of *trans*-**60**

We then carried out the exemplification of the NHC copper complex mediated Kinugasa reaction with method **B**. The results are presented in the following table.

Table 12. Kinugasa reaction method **B**



Method **A**: Cy_2NMe (1 equiv.) in DCE
Method **B**: DBU (1 equiv.) in THF

Entry	nitrone	alkyne	product	Yield [%][a]	*cis/ trans*[b]
1	Ph, Ph	Ph	**5**	76	1:10
2	$CH(CH_3)Ph$, CHPh	Ph	**-**	-	-
3		Ph	**-**	-	-
4	4-ClC_6H_4, Ph	Ph	**49**	45	1.5:10
5	4-$MeOC_6H_4$, Ph	Ph	**50**	32	1.2:10
6	4-$NO_2C_6H_4$, Ph	Ph	**51**	30	2.5:10
7	3-$NO_2C_6H_4$, Ph	Ph	**52**	35	2.4:10
8	4-BrC_6H_4, Ph	Ph	**53**	32	1.9:10
9	4-PhC_6H_4, Ph	Ph	**-**	traces	-

Entry	nitrone	alkyne	product	Yield [%][a]	*cis/ trans*[b]
10	4-CNC_6H_4, Ph	Ph	**54**	30	1.8:10
11	4-pyridyl, Ph	Ph	-	n.d.	n.d.
12	3-pyridyl, Ph	Ph	-	n.d.	n.d.
13	2-furyl, Ph	Ph	**55**	31	1:10
14	2-thienyl, Ph	Ph	-	-	-
15	*(E)*-styryl, Ph	Ph	-	-	-
16	Ph, 4-$MeOC_6H_4$	Ph	**56**	15	1:10
17	Ph, 4-$COOEtC_6H_4$	Ph	**57**	41	1.5:10
18	4-$CF_3C_6H_4$, 4-$MeOC_6H_4$	Ph	**58**	21	1.5:10
19	Ph	$(CH_2)_3OCOPh$	**59**	75	10:1
20	Ph	$CH(OCH_2CH_3)_2$	**60**	14	2:1

[a] isolated yield. [b] determined by NMR.

Almost the same analogy is presented here as in the previous method. Nitrones with *C*-bound and *N*-bound alkyl substituents do not provide any product using method **B** (entries **2-3, 15**). *C*-bound substituents with electron withdrawing groups (entries **4, 6-8, 10**) provide the *trans* product in moderate yield (30-45%) and good diastereoselectivity (2.5:10-1.5:10). For electron donating substituents, in case of OMe substituent (entry **5**), moderate yield (32%) is obtained together with high diastereoselectivity (1.2:10), whereas in case of Ph substituent (entry **9**), only traces of product were obtained. Similar to above results with respect to *C*-heterocycle

substituents, we obtain conversion only in the case of furyl (entry **13**) with 31% yield and 1:10 diastereoselectivity. Pyridyl substituents show some reactivity, however, the product could not be isolated (entries **11-12**), while thienyl group showed no reactivity (entry **14**). In the cases where substituents are found on the N-bound phenyl group, electron withdrawing groups (entry **17**, 41%) show better reactivity than electron donating groups (entries **16, 18**; 15 and 21% respectively). We also observed an enhanced selectivity for the *trans* isomer with respect to the results of method **A**. Acetylene **30** provide the product in high yield but also with high *cis* selectivity (entry **19**, 75%, 10:1) probably due to some steric effect; whereas acetylene **20** shows lower reactivity with 14% yield and a moderate selectivity for the *cis* product (entry **20**).

In comparing both methods we observe an inversion of diastereoselectivity in most cases using method **B**. It is only in the cases of entries **19** and **20** that this inversion is not observed. An explanation of this result could be the steric effect present by the groups present on the acetylene partner that would prevent the epimerization of the *cis* product to the *trans* one.

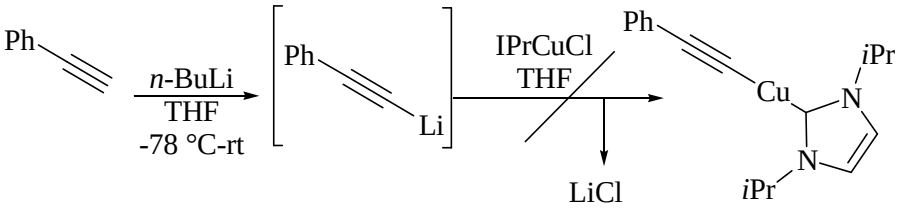
III.1.6 Mechanistic investigation

Considering the former results obtained with the NHC complexes, and due to their relative stability compared with other types of ligands, we decided to use these complexes to try to answer some of the mechanistic questions raised. In a first attempt, we tried to synthesize the first intermediate of the hypothetic mechanism of the Kinugasa reaction: the copper(I) acetylide.

Several experiments were carried out for the synthesis of this intermediate. Since we obtained good results with the IMesCudbm complex, we focused on the preparation of the IMesCu(I) acetylide. However, after several

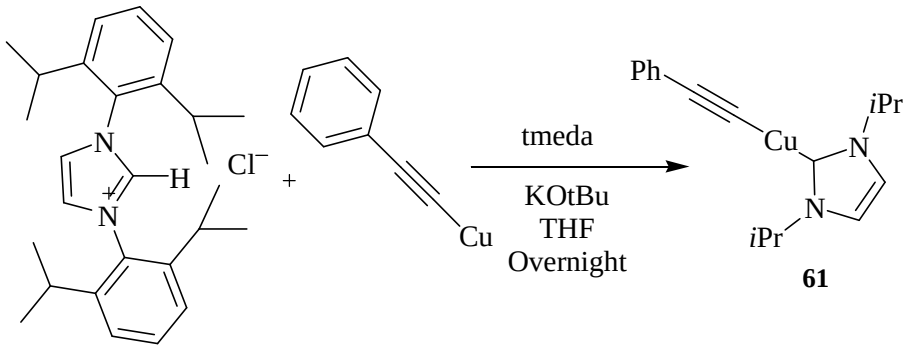
attempts we gave up this synthesis since this complex is apparently unstable. We then turned to the more stable IPr ligand.

First, we prepared lithium phenylacetylide, and tried to react this species *in situ* with IPrCuCl (Scheme 47). The reaction did not work and we recovered the starting material.



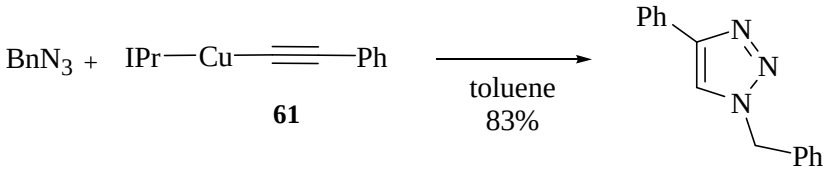
Scheme 47. Preparation of copper acetylide starting from acetylene and IPrCuCl in the presence of a strong base

Going the other way round, that is reacting a copper(I) acetylide with an NHC salt rather than trying to put an NHC copper on the acetylene was our next strategy. This strategy was successful, and we obtained the IPrCu(I) acetylide in a quantitative yield (Scheme 48). The obtained product is a yellow solid which is stable in air conditions. This solid has been characterized by NMR spectroscopy, and a carbine peak was detected in ^{13}C NMR. The spectrum was compared to the same product obtained by other literature methods and found to be identical.



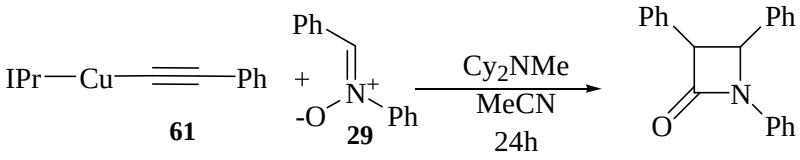
Scheme 48. Preparation of IPrCu phenylacetylide

We planned to carry out experiments using this complex to prove its intermediacy in the Kinugasa reaction. But first, due to its known intermediacy in the alkyne-azide cycloaddition, we ran a test reaction where this copper complex was used in stoichiometric amount with a benzylazide. The reaction proceeded successfully and provided the triazole, after work up, in very good yield (Scheme 49).



Scheme49. Alkyne-azide cycloaddition

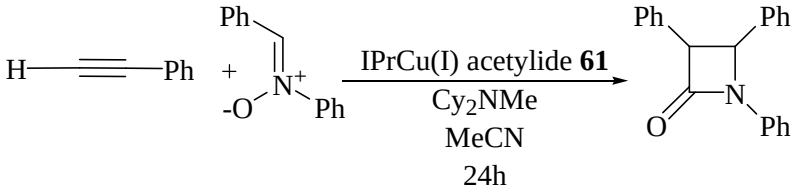
We then carried out some tests on the reaction of IPrCu(I) acetylide in the Kinugasa reaction. First, we tested the reaction between the acetylide and *C,N*-diphenylnitrone **29** in a stoichiometric amount under standard Kinugasa reaction conditions. After 24h hours of reaction, no product was detected by NMR, and the starting materials were recovered (Scheme 50).



Scheme 50. Kinugasa reaction using copper acetylide **61** in stoichiometric amount

The same reaction was carried out without the presence of a base, since as proposed by the mechanism, the base plays a role in the formation of the copper(I) acetylide. However no product was formed, instead the starting materials were recovered.

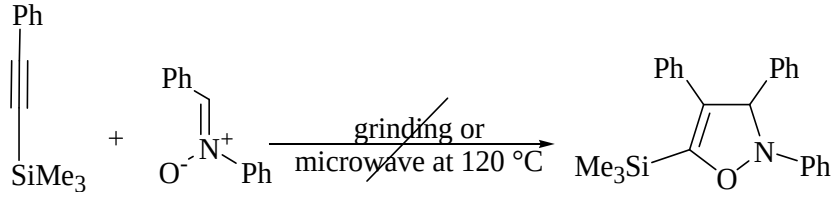
Another catalytic test was carried out, where the IPrCu(I) acetylide was used in catalytic amount to catalyze the reaction under standard conditions. However, with our without base the reaction did not proceed (Scheme 51).



Scheme 51. Kinugasa reaction using copper acetylide **66** in catalytic

Even under slow reaction kinetics (see case of IPrCuCl in kinetic monitoring), traces of the product should be detected (NMR). Having obtained no product in the four cases studied does not rule out the intermediacy of a copper acetylide, however, it could suggest a more complex reaction mechanism than the one proposed in literature.

Through our mechanistic investigation we were also interested in the synthesis of the oxazoline intermediate of the Kinugasa reaction. The report by DeShong *et al.*[5] showed the possibility of their formation under high pressure. Since we did not have access to equipment allowing high pressure, we attempted to prepare the oxazoline ring using microwave or grinding (Scheme 52). However none of these techniques work. We gave up on this synthesis since in the same report by Deshong, this oxazoline could never be detected since it degrades very fast and is very unstable.



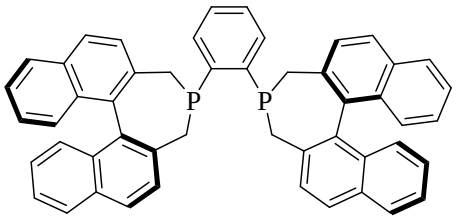
Scheme 52. Preparation of oxazoline ring using microwave or grinding

III.2 Enantioselective version

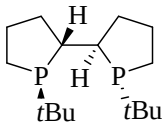
After the development of a diastereoselective version of the Kinugasa reaction, we intended to expand our work to the enantioselective version. We have access to a large library of chiral diphosphine ligands, and we aimed to use them in this context. One should take into account that electron rich ligands promote better the Kinugasa reaction.

We started by screening different families of chiral diphosphine ligands present (Table 13).

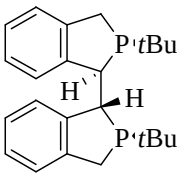
Table 13. Enantioselective Kinugasa reaction using chiral diphosphine ligands



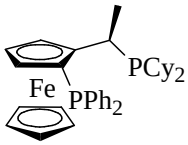
(*R*)-Binaphane
L_{14}



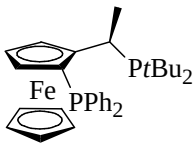
(*S*,*S*,*R*,*R*)-TangPhos
L_{15}



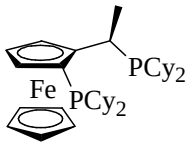
(R,R,S,S)-DuanPhos
L_{16}



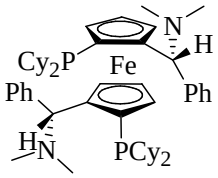
SL-J001-1
L_{17}



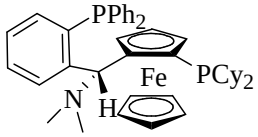
SL-J002-1
L_{18}



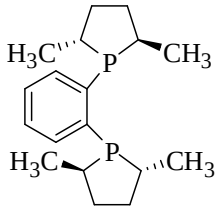
SL-J003-1
L_{19}



SL-M002-1
L_{20}

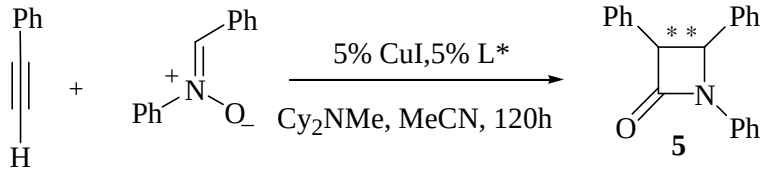


SL-T002-1
L_{21}



(-)-1,2-bis[(*2R*,*5R*)-2,5-dimethyl-phospholano]benzene
L_{22}

Table 13. Enantioselective Kinugasa reaction using chiral diphosphine ligands



Entry	Ligand	yield[a] [%]	*cis*/*trans*[b]	$ee_{cis(trans)}$ [%][b]
1	$\mathbf{L_{14}}$	25%	90/10	18%(21%)
2	$\mathbf{L_{15}}$	20%	88/12	0(4%)
3	$\mathbf{L_{16}}$	5%	82/18	14%(10%)
4	$\mathbf{L_{17}}$	35%	90/10	43%(40%)
5	$\mathbf{L_{18}}$	4%	80/20	31%(26%)
6	$\mathbf{L_{19}}$	35%	91/9	52%(46%)
7	$\mathbf{L_{20}}$	10%	83/17	10%(10%)
8	$\mathbf{L_{21}}$	19%	81/19	0(0)
9	$\mathbf{L_{22}}$	16%	81/19	6%(9%)

[a] isolated yields. [b] determined by HPLC of isolated product using Chiralpak IA column.

The HPLC chromatogram below shows the good separation of the four isomers presented as well defined peaks (Figure 11). The major product is the *cis* isomer.

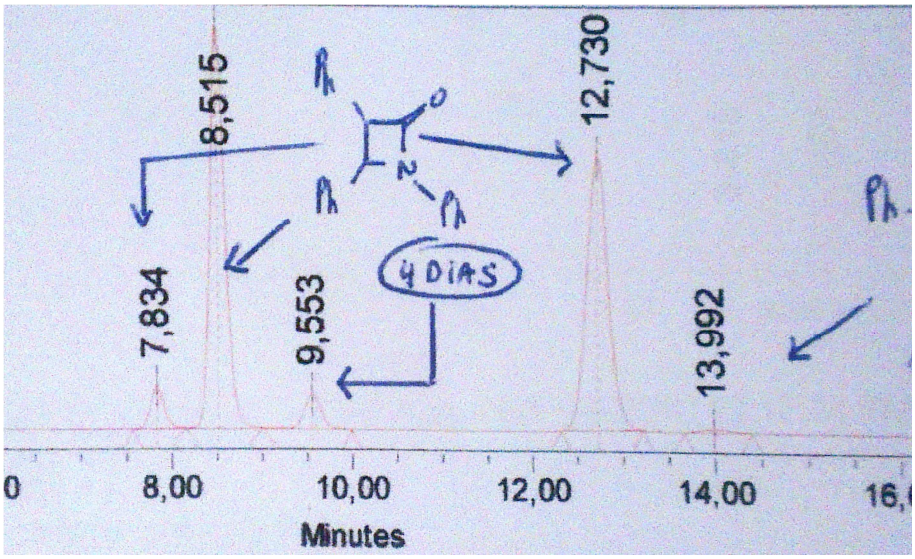
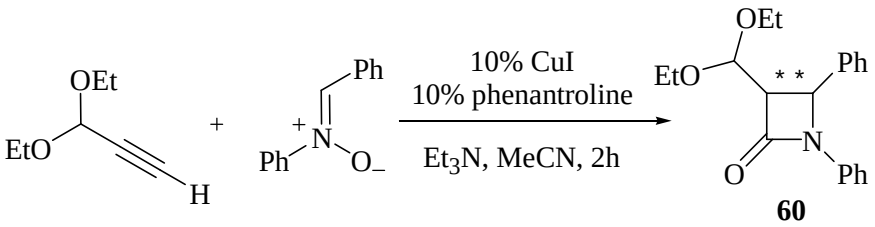


Figure 11. HPLC chromatogram of 1,2,3-triphenylazetidin-2-one

The study of the results obtained reveals that ligands of JosiPhos type were the most performant, both for reactivity as well as selectivity (entries **4,6**). Yields of 35% were obtained as well as an *ee* up to 52% and a diastereoselectivity ratio of 9:1. For the other ligand types, very good diastereoselectivities, low enantioselectivities, and yields were obtained. Moreover, we observed long reaction times. Chmielewski and coworkers[18], suggest oxygen bearing acetylenes to impact the reaction rate. We therefore decided to replace the phenyl acetylene substrate with the 3,3-diethoxy-propyne **20**. The consumption of the starting material was over in 2h (Scheme 53).

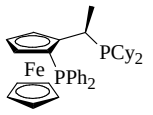


20 **60**

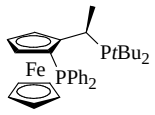
Scheme 53. Reaction of acetylene **20** with diphenylnitrone showing shorter reaction time in standard conditions

Furthermore, an extended set of ligands were tested under the following conditions (Table 14).

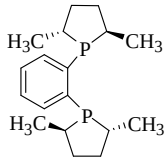
Table 14. Enantioselective Kinugasa reaction using chiral diphosphine ligands



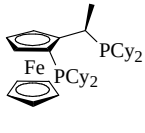
SL-J001-1
L$_{17}$



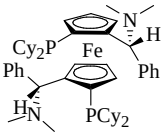
SL-J002-1
L$_{18}$



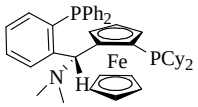
(-)-1,2-bis[(*2R*,*5R*)-2,5-dimethyl-phospholano]benzene
L$_{22}$



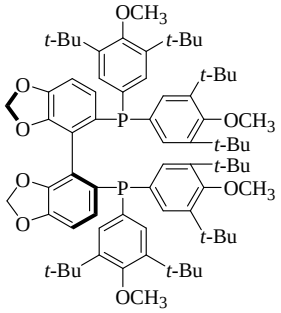
SL-J003-1
L$_{19}$



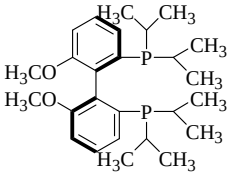
SL-M002-1
L$_{20}$



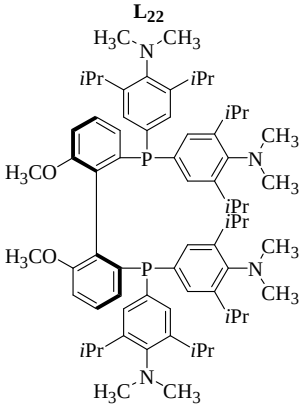
SL-T002-1
L$_{21}$



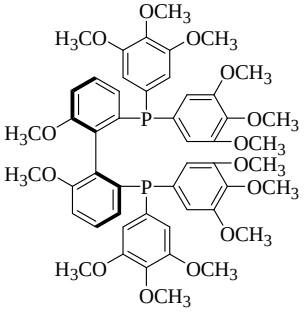
(*S*)-DTBM-SegPhos
L$_{23}$



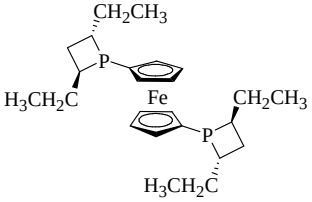
(*R*)-(6,6'-dimethoxybiphenyl-2,2'-diyl)-bis(diisopropylphosphine)
L$_{24}$



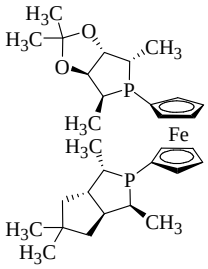
(*S*)-3,5-*i*Pr-4-NMe$_2$-MeOBIPHEP
L$_{25}$



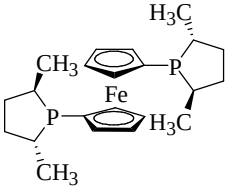
(*S*)-(6,6'-dimethoxybiphenyl-2,2'-diyl)bis-(bis(3,4,5-trimethoxyphenyl)phosphine)
L$_{26}$



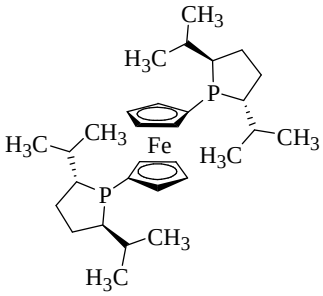
(*S*,*S*)-Et-ferroTANE
L$_{27}$



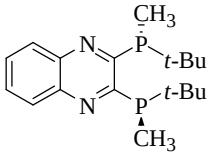
(*S*)-Me-f-KetalPhos
L$_{28}$



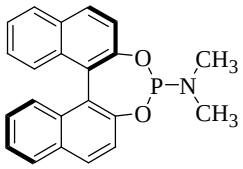
(*R*,*R*)-Me-Ferrocelane
L$_{29}$



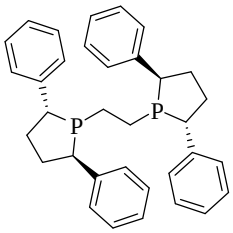
1,1'-Bis[(*2R*,*5R*)2,5-diisopropyl-phospholano]ferrocene
L$_{30}$



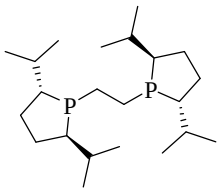
(*R*,*R*)-(-)-2,3-Bis (tert-butylmethyl-phosphino)quinoxaline
L$_{31}$



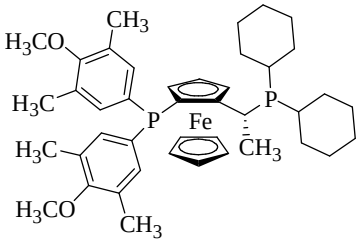
(S)-MonoPhos
L$_{32}$



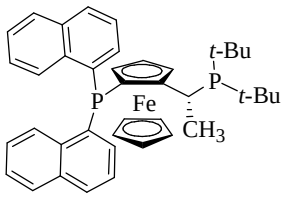
(*R*,*R*)-Ph-BPE
L$_{33}$



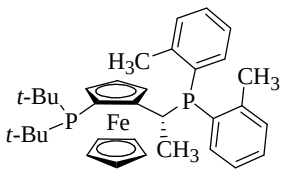
1,2-bis[(2*R*,5*R*)-2,5-diisopropyl-phospholano]ethane
L$_{34}$



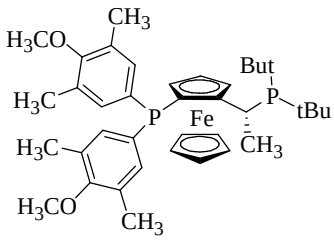
SL-J007-1
L$_{35}$



SL-J216-1
L$_{36}$

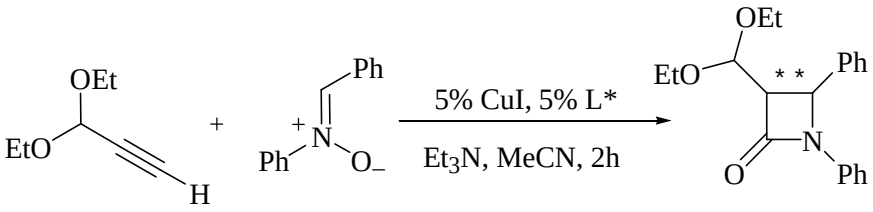


SL-J505-1
L$_{37}$



SL-J013-1
L$_{38}$

Table 14. Enantioselective Kinugasa reaction using chiral diphosphine ligands



20 **60**

Entry	Ligand	yield[a]	*cis*/*trans*[b]	*ee*$_{cis(trans)}$ (%)[b]
1	L_{17}	n.d	**79/21**	21%(20%)
2	L_{18}	-	-	-
3	L_{19}	41%	**82/18**	46%(47%)
4	L_{20}	35%	**75/25**	8%(14%)
5	L_{21}	56%	**79/21**	0(0)
6	L_{22}	57%	**79/21**	0(0)
7	L_{23}	48%	**82/18**	3%(3%)
8	L_{24}	52%	**78/22**	2%(1%)
9	L_{25}	54%	**78/22**	3%(3%)
10	L_{26}	35%	**76/24**	9%(7%)
11	L_{27}	46%	**71/29**	9%(12%)
12	L_{28}	13%	**74/26**	9%(10%)
13	L_{29}	-	-	-
14	L_{30}	-	-	-

Entry	Ligand	yield[a]	*cis*/*trans*[b]	$ee_{cis(trans)}$ (%)[b]
15	L_{31}	-	-	-
16	L_{32}	-	-	-
17	L_{33}	51%	**79/21**	67%(68%)
18	L_{34}	-	-	-
19	L_{35}	n.d.	**78/22**	13%(14%)
20	L_{36}	traces	-	-
21	L_{37}	-	-	-
22	L_{38}	n.d.	**75/25**	6%(10%)

[a] isolated yields. [b] determined by HPLC of the isolated product using Chiralpak IA column.

The HPLC chromatogram below shows the good separation of the four isomers presented as well defined peaks (Figure 12). The major product is the *cis* isomer.

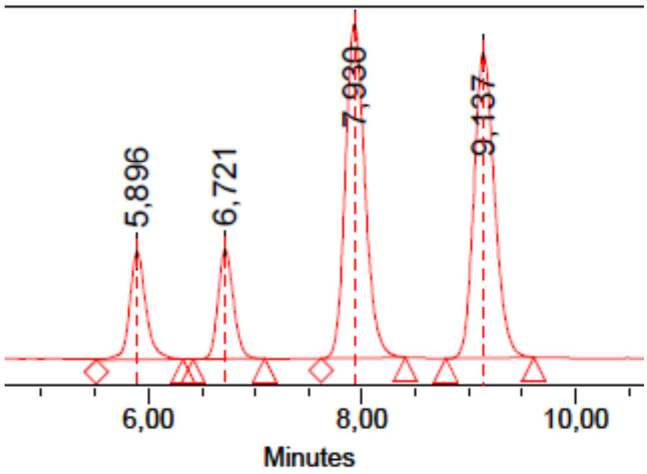


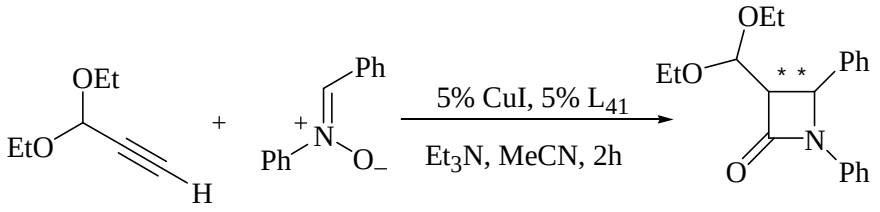
Figure 12. HPLC chromatogram of **65**

After analyzing the above results, we found out that ligand (R,R)-Ph-BPE **L_{33}** (entry **17**) provided the best enantioselectivity (68%) as well as the best yield (51%) and a good diastereoselectivity (79:21). Also the JosiPhos ligand **L_{19}** performed better than the other ligands and provided 46% *ee* with 41% yield and 82:18 diastereoselectivity. Some provided moderate yields but no *ee* (entries **4-12**), while others are not performant in this reaction (entries **13-16, 18, 20-21**). The very bulky ligands **L_{23}** and **L_{25}** afforded the product in good yields, however the enantioselectivities were negligible.

III.2.1 Optimization

With this system in hand, we decided to optimize the reaction conditions to develop a more performing system. First of all, we tried to enhance the enantioselectivity at lower temperatures (Table 15).

Table 15. Temperature optimization



20 **60**

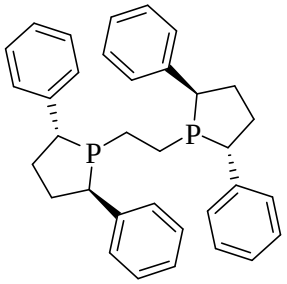
Entry	Ligand	temp.	yield[a]	*cis*/*trans*[b]	ee$_{cistrans)}$ (%)[b]
1	**L_{41}**	**rt**	51%	**79/21**	67%(68%)
2	**L_{41}**	**0°C**	40%	77/23	65%(68%)
3[c]	**L_{41}**	**-20°C**	35%	80/20	69%(68%)

[a] isolated yields. [b] determined by HPLC.[c] left overnight.

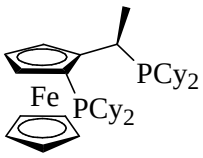
We noticed no substantial variation of the selectivity at lower temperatures, even after longer reaction times; the yield decreased (entries **2-3**). This might be explained by the lower reactivity of the catalytic species at low temperature.

Other tests were carried out varying the copper source (Table 16). We noticed that when using $Cu(CH_3CN)_4PF_6$ with the JosiPhos ligand **L_{19}**, we obtain good yields (65%) and moderate *ee* (52%) (entry **3**). However, the same copper source with the **L_{33}** ligand, provides low yield and low *ee* (entry **4**). With $CuBr.SMe_2$, **L_{33}** regains its selective character to provide 68% *ee*, however the yield decreased to 40% (entry **5**). Carrying out the reaction with the electron rich JosiPhos ligands **L_{39}** and **L_{40}** (entries **6-7**), results in moderate yields (26-35%) and moderate ee (46-56%).

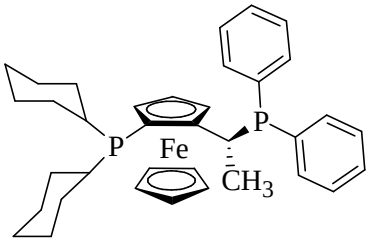
Table 16. Variation of copper source



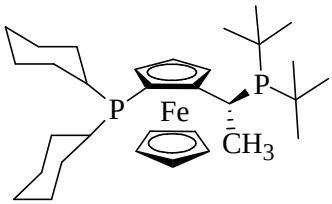
(*R*,*R*)-Ph-BPE
L_{33}



SL-J003-1
L_{19}

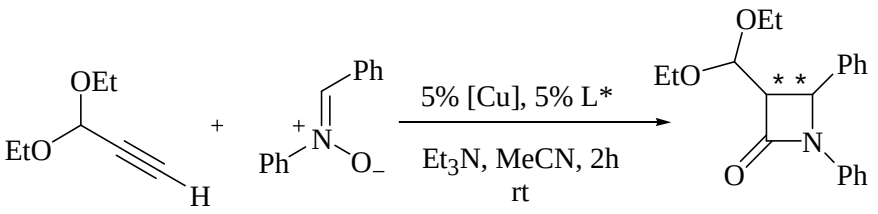


SL-J004-1
L_{39}



SL-J009-1
L_{40}

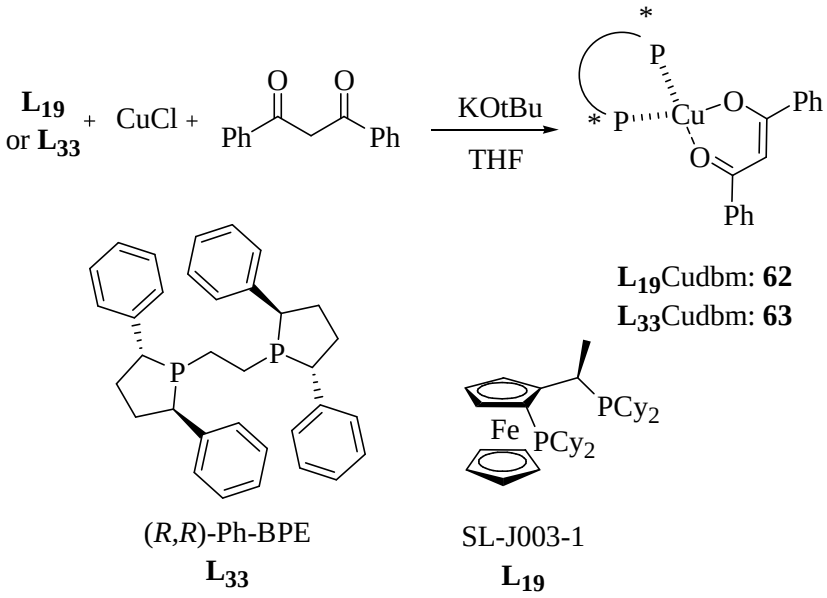
Table 16. Variation of copper source



20 **60**

Entry	Copper source	Ligand	Yield [%]	*cis*/*trans*	$ee_{cis(trans)}$ [%]
1	CuI	$\mathbf{L_{33}}$	41	82/18	46%(47%)
2	CuI	$\mathbf{L_{33}}$	51	79/21	67 (68)
3	$Cu(CH_3CN)_4PF_6$	$\mathbf{L_{19}}$	65	77/23	52(57)
4	$Cu(CH_3CN)_4PF_6$	$\mathbf{L_{33}}$	19	77/23	27 (27)
5	$CuBr.SMe_2$	$\mathbf{L_{33}}$	40	70/30	68(67)
6	$Cu(CH_3CN)_4PF_6$	$\mathbf{L_{39}}$	26	52/48	46(56)
7	$Cu(CH_3CN)_4PF_6$	$\mathbf{L_{40}}$	35	58/42	47(48)

Also, due to the effectiveness of the dibenzoylmethane (dbm) counterion observed in the previous part of this chapter, we decided to prepared chiral Cudbm complexes and test them in this reaction with anticipation that they would provide the product in high yield and selectivity. The complexes were prepared according to the following procedure and were obtained in quantitative yields (Scheme 54). These complexes were collected as red crystals and were noticed to be stable in air conditions.



Scheme 54. Preparation of chiral diphosphine Cu(I) dbm complexes

The structures of both complexes were confirmed by NMR and X-ray. A successful crystallization in THF-hexane at -20°C afforded X-ray quality crystals for analysis (Figures 13-14).

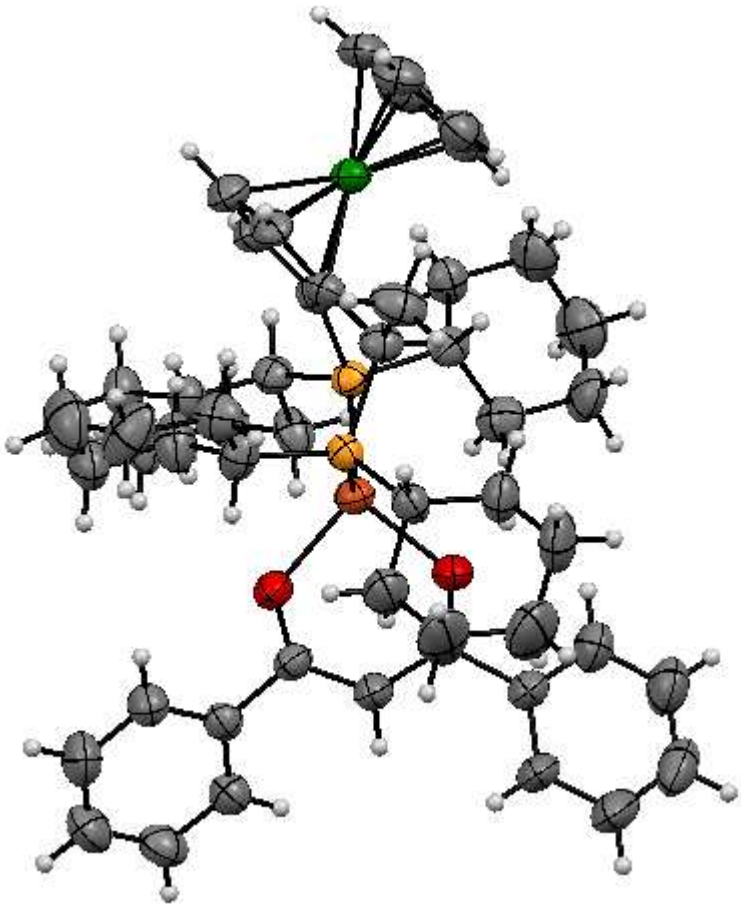


Figure 13. X-ray structure of complex $\mathbf{L_{19}}$Cudbm **62**

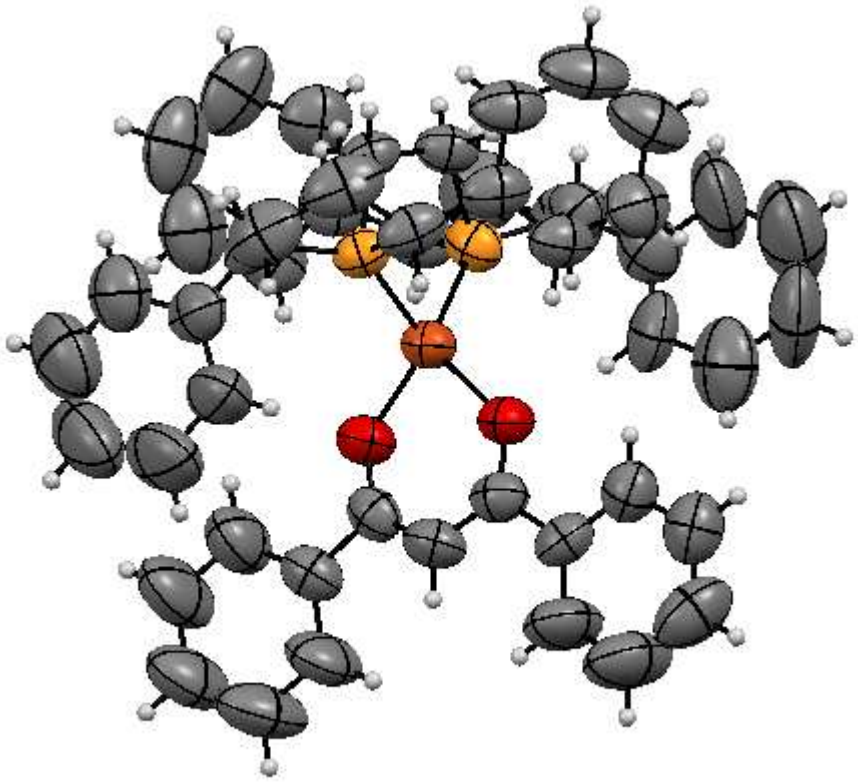
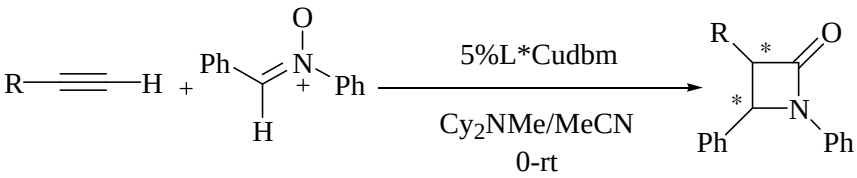


Figure 14. X-ray structure of complex $\mathbf{L_{33}}$Cudbm **63**

These complexes were then employed as catalysts for the Kinugasa reaction and tested with two different acetylenes (Table 17).

Table 17. Reaction of different acetylenes with diphenyl nitrone using complexes $\mathbf{L_{19}}$Cudbm and $\mathbf{L_{33}}$Cudbm as catalysts



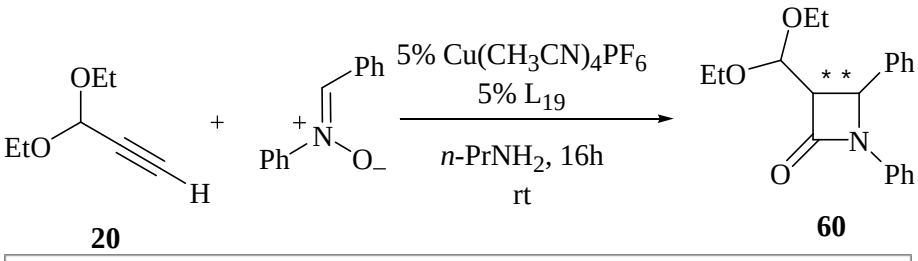
Entry	R	[Cu]	time	Yield [%]	*cis/trans*	$ee_{cis(trans)}$ *[%]*
1	Ph	$\mathbf{L_{19}}$Cudbm	120	50	88:12	54(56)
2	$CH(OCH_2CH_3)_2$	$\mathbf{L_{19}}$Cudbm	16	43	81:19	55(51)
3	Ph	$\mathbf{L_{33}}$Cudbm	120	25	89:11	0(19)
4	$CH(OCH_2CH_3)_2$	$\mathbf{L_{33}}$Cudbm	16	19	53:47	0(0)

The results were not too satisfying; entries **1-2** show moderate yields and *ee* similar to what was obtained before with the mixture CuX/ $\mathbf{L_{19}}$, with good diastereoselectivity, while entries **3-4** show almost no *ee* with low yields. This could be explained by the fact that $\mathbf{L_{19}}$ is a rigid ligand, thus leading in both cases, free ligand or complex, to the same complex ML. Whereas, $\mathbf{L_{33}}$ is a flexible ligand that could lead to a well-defined ML ligand that is not enantioselective at all. In the case of a mixture of CuX/ $\mathbf{L_{33}}$, more complex structures M_xL_y could be obtained, which could lead to higher selectivities. This actually explains the fact that the enantioselectivity varies in function of the copper source used.

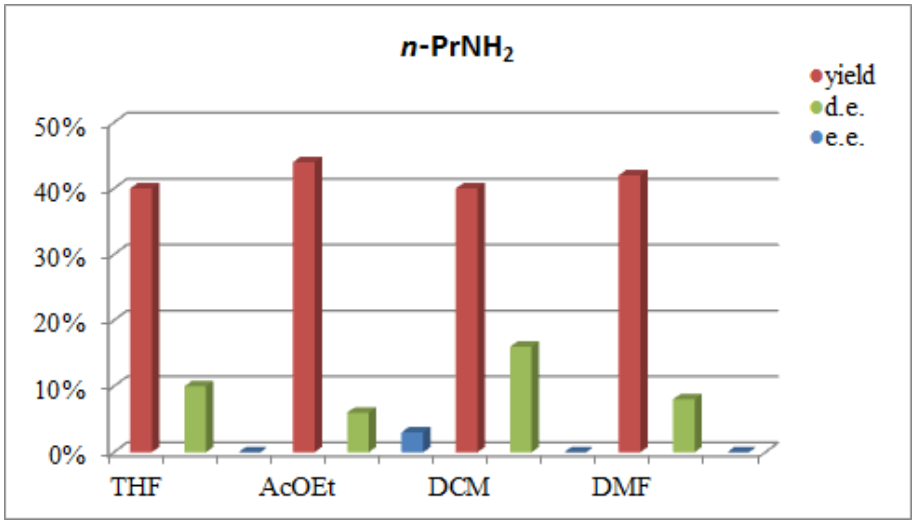
We then set out to look for improved base-solvent conditions. So we carried out cross tests of 4 different bases with 4 different solvents keeping the

conditions that provided the best yield until now which includes the use of $Cu(CH_3CN)_4PF_6$ and **L_{19}**.

The reaction using *n*-$PrNH_2$ resulted in moderate yields (40-44%) in all solvents, but very low diastereoisomeric excess for the *cis* isomer (6-16%) and no enantioselectivity (Scheme 55). The enantioselectivities presented from now on are those of the dominant isomer.



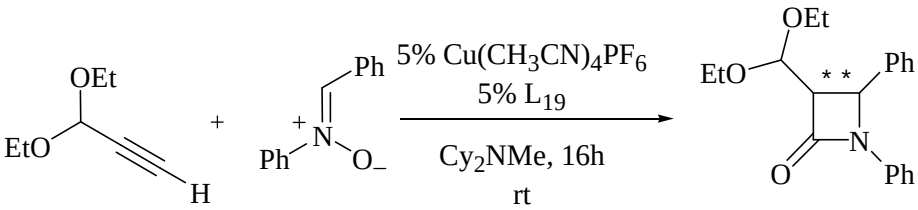
20 **60**



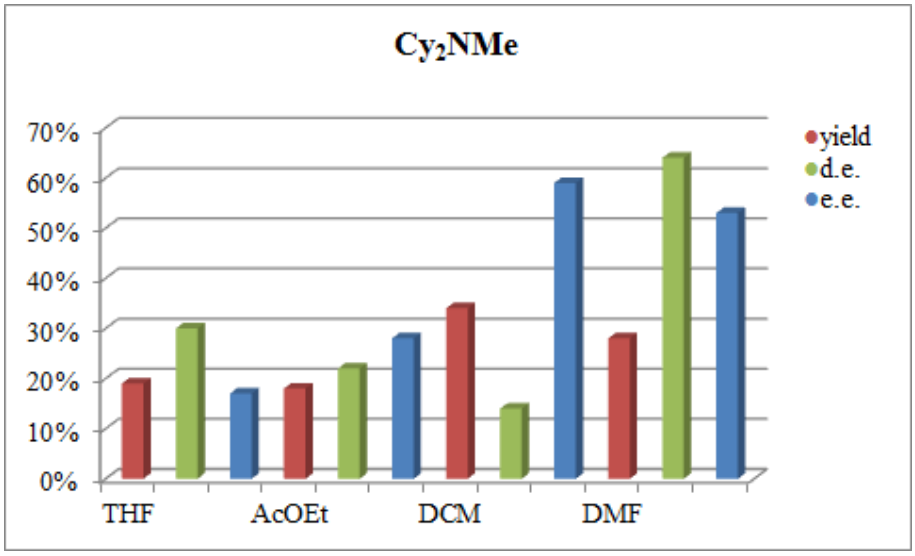
Scheme 55. Optimization of base-solvent factors using *n*-$PrNH_2$ as base

Using Cy_2NMe as the base resulted in low to moderate yields in general (18-34%). However, we remarked an increase in the diastereoselectivity for the *cis* isomer compared to the previous base used. (22-64% d.e.). Highest d.e. (64%) is obtained in DMF with an *ee* of 53% but a low yield of 28%; suggesting that polar solvents may improve the selectivity of the reaction, but not the yield. The highest *ee* is obtained in DCM (59%), however the

diastereoisomeric excess does not exceed 16% and the yield 34% (Scheme 56).

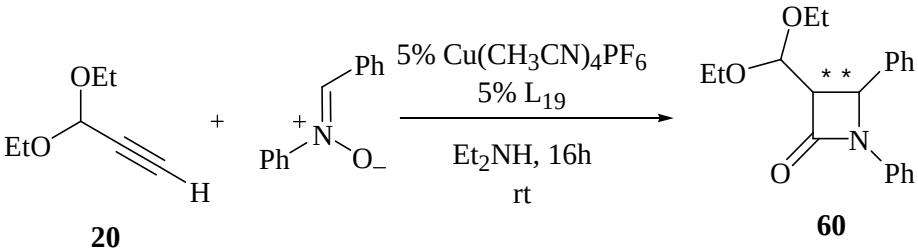


20 **60**

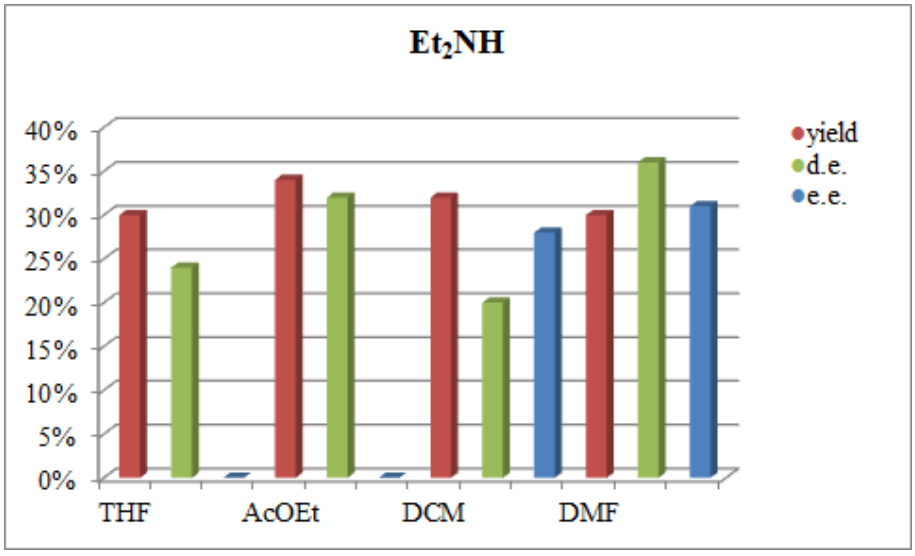


Scheme 56. Optimization of base-solvent factors using Cy_2NMe as base

The reaction using diethylamine as a base for the asymmetric Kinugasa reaction resulted in no *ee* when the reaction is carried out in THF and AcOEt. However, when the reaction is performed in DCM and DMF an *ee* of around 30% is obtained. The yields are almost constant in all solvents (30-34%), and the *d.e.* ranges from 20-36% for the *cis* isomer with highest *d.e*. in DMF (Scheme 57).

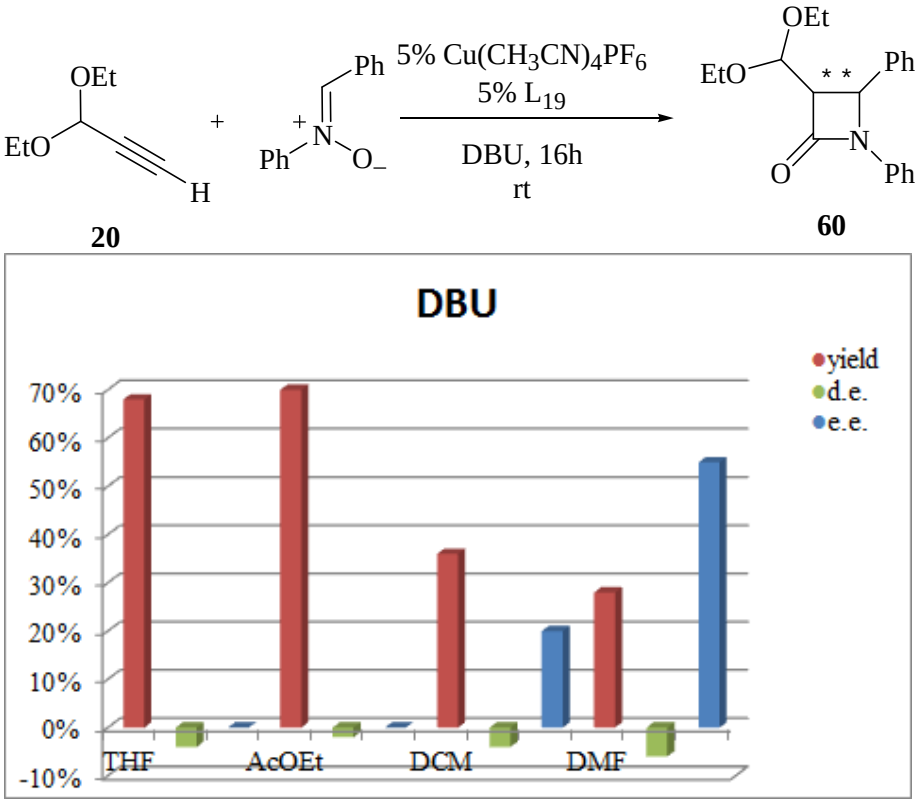


20 **60**



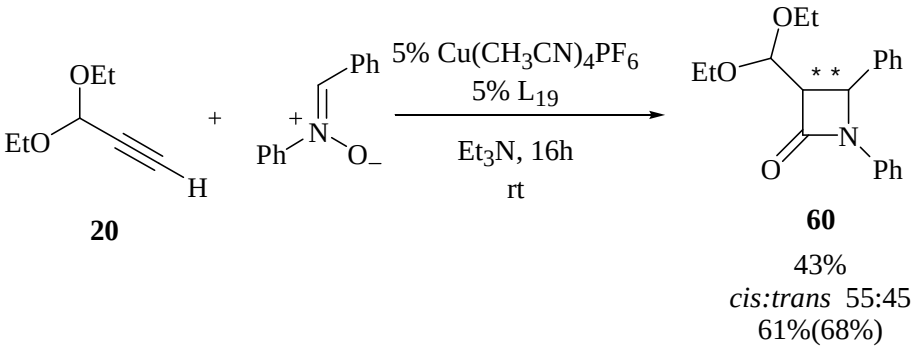
Scheme 57. Optimization of base-solvent factors using Et_2NH as base

Finally the use of DBU results as expected in a slightly reversed diastereoselectivity for the *trans* isomer in all the cases studied. However the numbers are insignificant. Similar to the previous base, no *ee* is detected when the reaction is carried out in THF or AcOEt. However, good yields are obtained in both cases (70%). When the reaction is run in DCM and DMF, lower yields are obtained (36 and 28% respectively), but a low to moderate enantiomeric excess is observed (20% in DCM, and 55% in DMF) (Scheme 58).



Scheme 58. Optimization of base-solvent factors using DBU as base

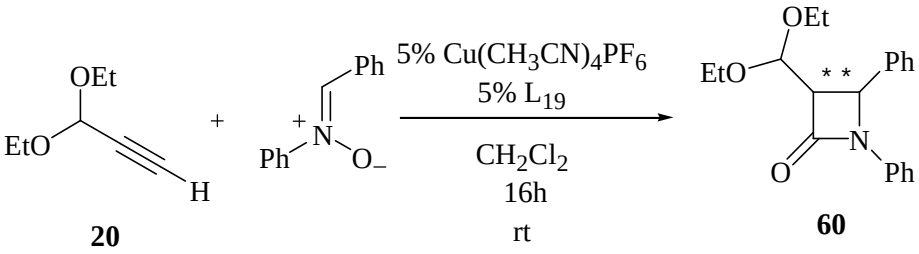
We also carried out one more reaction using Et_3N in DCM. This reaction provided the best combination of moderate yield and good enantioselectivity although the diastereoisomeric ratio was 55:45 for the *cis* isomer.



Scheme 59. Optimization of base-solvent factors using Et_3N in DCM

A last test concerning the use of a non-amine base revealed lower reactivity and selectivity in case of K_2CO_3, and no reactivity at all in the case of *t*-BuONa suggesting that amine bases are more convenient for this type of reaction which could implement a more important role of the base than that depicted in the proposed mechanisms. The use of an excess of triethyl amine lowers the yield and the enantioselectivity while slightly enhancing the diastereoselectivity (Table 18).

Table 18. Base optimizations



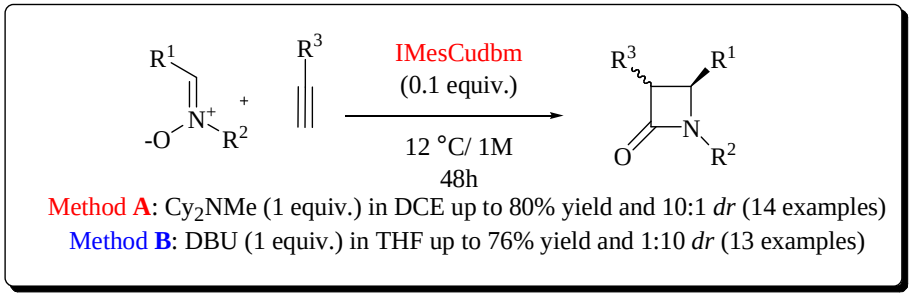
20 **60**

Entry	Base	Yield [%]	*cis/trans*	*ee cis(trans)* [%]
1	Et_3N	43%	55/45	61(68)
2	K_2CO_3	11%	60/40	57(53)
3	*t*-BuONa	-	-	-
4	3 equiv. Et_3N	10%	60/40	52(53)

IV. Conclusions and perspectives

In conclusion, we have successfully developed a new catalytic system capable of catalyzing the Kinugasa reaction. We are the first to report the use of NHC copper complexes for this reaction for selective synthesis of *cis* and *trans* β-lactams.

Two routes were developed, one for the diastereoisomeric synthesis of *cis* β-lactams in good yield and good diastereoselectivity, and the other for the diastereoisomeric synthesis of *trans* β-lactams also in good yield and good diastereoselectivity (Scheme 60). Exemplification of both systems was carried out with more complex structures of nitrones and acetylenes. Although in most cases, less reactive, the products were nevertheless often obtained with good selectivity. The results are comparable to what is found in the literature in terms of yields and selectivity. The main interest in this development is the stability of the catalytic complexes used. This means these systems could be employed in mechanistic studies.



Scheme 60. Optimized systems for the NHCCuX catalyzed Kinugasa reaction

These results encouraged us to carry out some mechanistic studies based on the isolation of reaction intermediates. We were capable of isolating a copper(I) acetylide and characterizing it (Figure 32). Unfortunately, the

catalytic tests we carried out did not provide enough information to yield valuable information on the reaction mechanism.

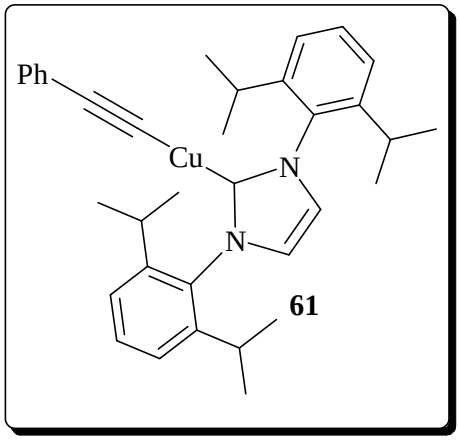


Figure 15. IPrCu(I) phenylacetylide

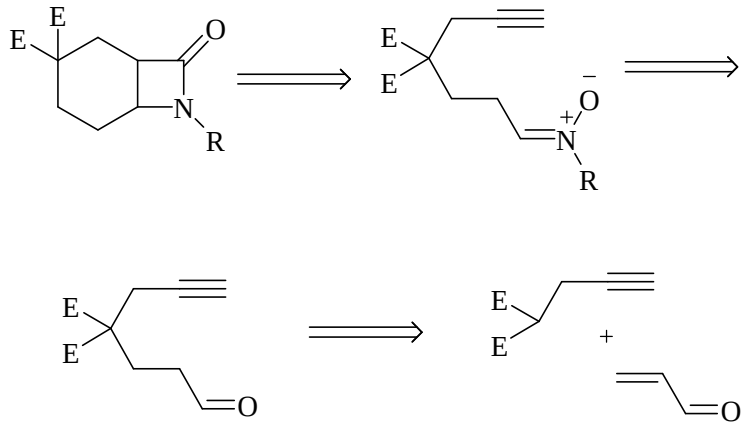
More intrinsic future experiments are planned to explore the mechanism.

Also the synthesis of other copper(I) acetylides will be shown in a following chapter following the methodology we adopted.

The enantioselective version of this reaction using chiral diphosphines as ligands is reported for the first time although the enantioselectivity did not exceed 68% with moderate yields. The optimizations carried out on this reaction did not critically improve the yields and selectivities.

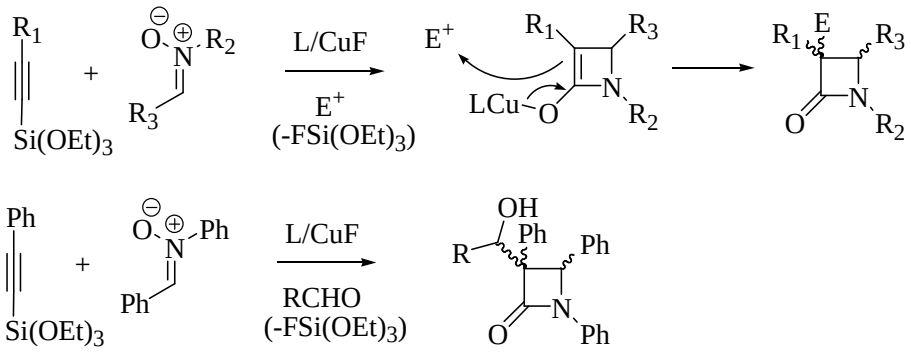
For the future it might be interesting to synthesize chiral NHC ligands and employ them in this reaction in the hope of improving results.

Also we suggest extending our study to intramolecular Kinugasa reaction, where the reaction should be easier. One pathway which has been envisaged for the synthesis of a substrate for this reaction, is shown in the following scheme 61.



Scheme 61. Retrosynthesis of intramolecular Kinugasa reaction

Another extension to this part of the work is the possibility to use the Kinugasa reaction for trapping the enolate intermediate by an electrophile, providing a quaternary carbon (Scheme 62). For this, we must avoid the presence of proton source in the reaction environment, implying a modification of the substrates and the catalytic system. To do so, the terminal alkyne will be replaced by a trialkoxysilane, which can react with the precatalyst LCuF to generate a copper(I) acetylide releasing one equivalent of fluorotriethoxysilane. The reaction will be conducted in the presence of an electrophile such as aldehyde that can be captured by the copper enolate to give β-lactam with a quaternary carbon.



Scheme 62. Enolate capturing using an electrophile

Chapter 2: Asymmetric Synthesis of γ-Lactams

I. Bibliographic introduction

I.1 1,4-Reductive Michael cyclization

Transition metal-catalyzed reductive couplings have been widely explored for their various applications in total syntheses of natural and non-natural biologically active compounds[1]. The catalyzed 1,4-reductive aldolization and 1,4-reductive Michael reactions constitute a part of the classical methods for stereogenic C–C bond formation[2,3]. Both reactions are classified as a domino type reaction whereby a latent enolate nucleophile is formed by the action of a metal hydride catalyst, formed *in situ*, from an α,β-unsaturated Michael acceptor. Then, this latent enolate undergoes addition to an electron-deficient π-unsaturated partner resulting in a stereocontrolled reductive C–C bond formation. In our case we study the Cu(I) catalyzed reactions.

Catalytic α,β-unsaturated carbonyl compounds hydrometallation using copper hydrides has been largely studied and developed during the past decade[4]. Taking advantage of the carbophilic nature of copper, the 1,4-addition is noticed to take place preferentially. This strategy is an alternative

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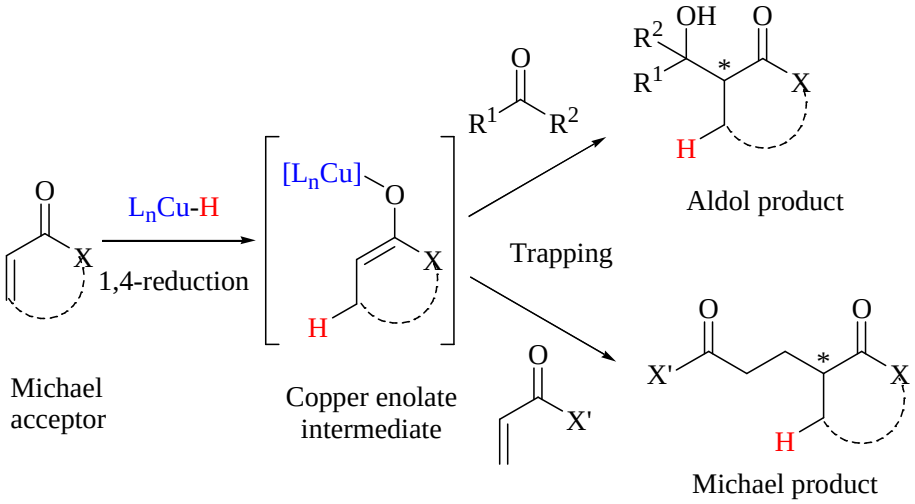
[1] Krische, M. J.; Breit, B., *Metal Catalyzed Reductive C-C Bond Formation: A Departure from Preformed Organometallic Reagents.* Springer: Heidelberg, 2007.

[2] Huddleston, R. R.; Krische, M. J., *Synlett* **2003,** *2003*, 0012.

[3] Chiu, P., *Synthesis* **2004**, 2210; Nishiyama, H.; Shiomi, T., Reductive Aldol, Michael, and Mannich Reactions. In *Metal Catalyzed Reductive C–C Bond Formation*, Krische, M., Ed. Springer Berlin Heidelberg 2007; Vol. 279, pp 105; Han, S. B.; Hassan, A.; Krische, M. J., *Synthesis* **2008,** *2008*, 2669.

[4] Rendler, S.; Oestreich, M., *Angewandte Chemie International Edition* **2007,** *46*, 498; Christoffers, J.; Koripelly, G.; Rosiak, A.; Rössle, M., *Synthesis* **2007,** *2007*, 1279; Deutsch, C.; Krause, N.; Lipshutz, B. H., *Chemical Reviews* **2008,** *108*, 2916.

toward catalytic stereoselective aldol and Michael processes involving the use of latent enolates rather than preformed enols. When 1,4-addition is carried out in the presence of an electrophile (aldehyde or ketone in case of aldolization process, or an unsaturated carbonyl function in the case of Michael addition), trapping of the copper enolate intermediate becomes possible, and the aldol or the Michael product is delivered in a domino process (Scheme 1). In seminal studies by Stork[5], the activation of enones via conjugate reduction results in regioselective enolate formation from chemically robust precursors in contrast to the problematic preparation of enol derivatives from unsymmetrical ketones using direct enantioselective catalytic aldol and Michael reactions.



Scheme 1. 1,4-reduction/ aldolization and 1,4-reduction/Michael processes

The first example of an enantioselective intermolecular reduction/aldolization reaction catalyzed by chiral Cu-H complexes was

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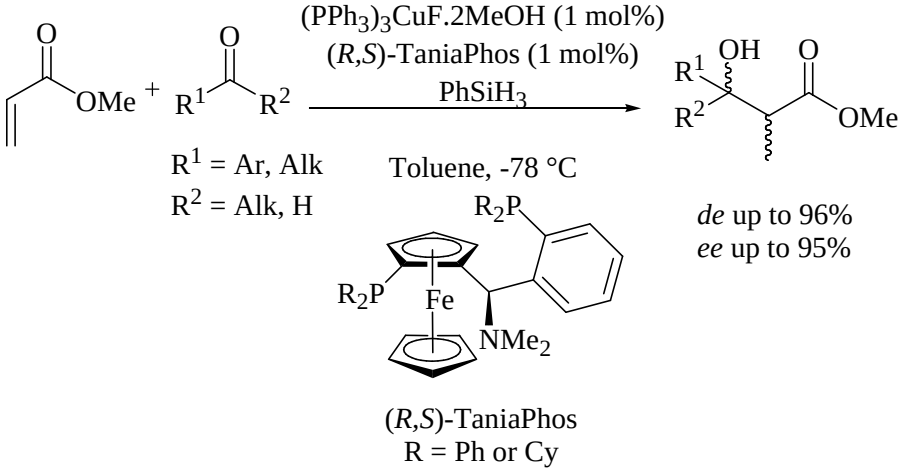
[5] Stork, G.; Rosen, P.; Goldman, N. L., *Journal of the American Chemical Society* **1961,** *83*, 2965; Stork, G.; Rosen, P.; Goldman, N.; Coombs, R. V.; Tsuji, J., *Journal of the American Chemical Society* **1965,** *87*, 275.

reported by our group in 2006[6]. Aromatic and aliphatic aldehydes and ketones react promptly with the copper enolate intermediate, formed by the 1,4 addition of the copper hydride complex to the acrylates, to provide the aldol product with high *syn*-selectivity and good to excellent *ee*'s (Scheme 2).



Scheme 2. Enantioselective 1,4-reduction/aldolisation of acrylates

Unlike 1,4-reductive aldolization, the metal catalyzed reductive Michael reaction has been reported very few times in literature and require further development. Moreover, despite a wealth of research on reductive aldol processes, transition metal catalyzed Michael cyclizations remain undeveloped.

I.1.1 Copper hydride complexes

The extensive progress in the use of copper hydride complexes promoted a growing popularity of the 1,4-reduction/aldolization domino reactions.

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[6] Chuzel, O.; Deschamp, J.; Chausteur, C.; Riant, O., *Organic Letters* **2006,** *8*, 5943; Deschamp, J.; Chuzel, O.; Hannedouche, J.; Riant, O., *Angewandte Chemie International Edition* **2006,** *45*, 1292.

Although they were first discovered around the middle of the 19th century, the real interest in their use was not exploited before the discovery of Stryker's reagent. This red crystalline solid was first prepared and characterized by Churchill and Osborn in 1971[7]; however, its utilization has not been widely explored before the work of Stryker and coworkers in 1988[8]. The mildness of reaction conditions it offers, as well as its wide functional group compatibility range and high efficiency, impelled the nomination of this compound as the "Reagent of the Year" in 1991[9]. The Stryker group remarked a tendency of the $[PPh_3CuH]_6$ hexamer to add in a 1,4 addition fashion to α,β-unsaturated ketones, esters and aldehydes, leading to regioselective 1,4-conjugate reductions. The state of the art in this domain showed that the addition of copper(I) hydride to electrophilic double bond in the presence of an electrophile leads to the formation of copper enolates that add to the electrophile allowing the formation of C-C bonds in a domino process.

Moreover, this complex was prepared starting from inexpensive starting materials that are commercially available (NaO*t*-Bu, CuCl, Ph_3P and H_2) and is produced along with environmentally benign byproducts (NaCl and *t*-BuOH). Stryker reported the following method for multi-gram scale preparation of this complex, which is still in use (Scheme 3).

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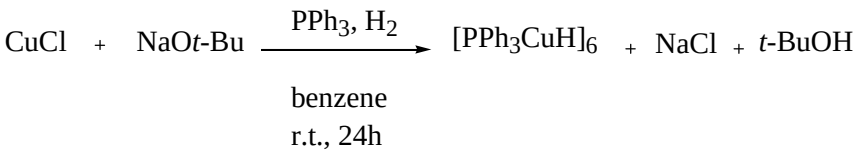
[7] Churchill, M. R.; Bezman, S. A.; Osborn, J. A.; Wormald, J., *Journal of the American Chemical Society* **1971,** *93*, 2063.

[8] Brestensky, D. M.; Huseland, D. E.; McGettigan, C.; Stryker, J. M., *Tetrahedron Letters* **1988,** *29*, 3749; Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M., *Journal of the American Chemical Society* **1988,** *110*, 291; Brestensky, D. M.; Stryker, J. M., *Tetrahedron Letters* **1989,** *30*, 5677; Koenig, T. M.; Daeuble, J. F.; Brestensky, D. M.; Stryker, J. M., *Tetrahedron Letters* **1990,** *31*, 3237.

[9] de Fátima, Â., *Synlett* **2005,** *2005*, 1805.



Scheme 3. Preparation of Stryker's complex

Reduction of CuCl to the copper hydride takes place in an inert atmosphere and under a hydrogen pressure of 1 atm. The use of molecular hydrogen puts restraints on this system. Some enhancements of this procedure were executed to avoid the use of this highly air-sensitive system. For instance; Chiu *et al.* reported the replacement of the hydrogen gas by dimethylphenylsilane as the reducing agent[10]. Also, Yun and Lee showed the usability of copper(II) salts for the synthesis of highly pure Stryker's reagent in high yield compared to the use of the highly unstable copper(I) alkoxide prepared *in situ*[11].

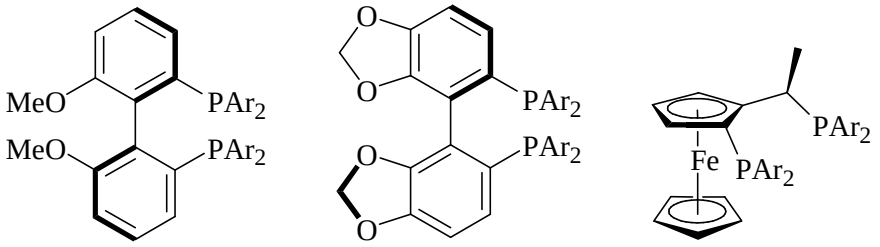
With exception of Stryker's reagent, Cu-H species are usually found highly reactive and therefore generated *in situ*. For their generation, silanes are commonly used as a stoichiometric source of hydride, for economic and environmental reasons. Examples of silanes used in the generation of copper hydride species are polymethylhydrosiloxane (PMHS), tetramethyldisiloxane (TMDS), Fleming's silane ($PhMe_2SiH$) and phenylsilane ($PhSiH_3$).

For the generation of chiral copper hydride species, nonracemic bis-phosphines ligands were used mostly such as biaryl and ferrocenyl bis-phosphine ligands. Remarkably, certain biaryl-diphosphines of the BiPheP,

[10] Chiu, P.; Li, Z.; Fung, K. C. M., *Tetrahedron Letters* **2003,** *44*, 455.

[11] Lee, D.-w.; Yun, J., *Tetrahedron Letters* **2005,** *46*, 2037.

SegPhos and JosiPhos series present high selectivity and high turnover numbers (TONs)[12] (Figure 1).



BiPheP ligands **SegPhos ligands** **JosiPhos ligands**

Figure 1. Chiral diphosphines used for the generation of copper hydride species

In addition to the Stryker's reagent, another stable form of Cu-H was identified by Lipshutz and coworkers in 2005[13]. They described the synthesis of a copper hydride complex bearing a chiral SegPhos ligand (Figure 2). They claimed that this complex was stable in solution if kept under argon.

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[12] Blaser, H.-U.; Brieden, W.; Pugin, B.; Spindler, F.; Studer, M.; Togni, A., *Topics in Catalysis* **2002,** *19*, 3; Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H., *Advanced Synthesis & Catalysis* **2001,** *343*, 264; Schmid, R.; Broger, E. A.; Cereghetti, M.; Crameri, Y.; Foricher, J.; Lalonde, M.; Müller, R. K.; Scalone, M.; Schoettel, G.; Zutter, U., *Pure and Applied Chemistry* **1996,** *68*, 131.

[13] Lipshutz, B. H.; Frieman, B. A., *Angewandte Chemie International Edition* **2005,** *44*, 6345.

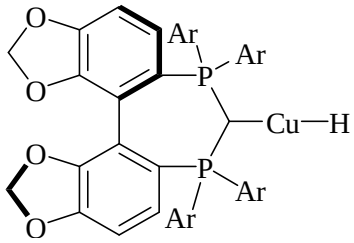
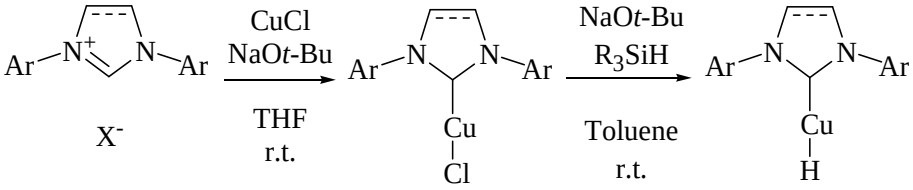


Figure 2. Lipshutz's stable chiral copper hydride complex

An interesting alternative to diphosphine ligands are the N-heterocyclic carbenes (NHCs). NHCs are both electronically and structurally different from biphosphines. The actual interest lies in the use of isolated, air stable coppercarbene complexes as an alternative of unstable biphosphine copper complexes[14]. The (NHC)Cu-H catalysts are usually prepared from the starting imidazolium salt which is treated with a base and CuCl, followed by the *in situ* generation of the copper hydride in the presence of a silane (Scheme 4).



Scheme 4. NHCCuH preparation

With robust methods for the generation of Cu-H in hand, we now turn to the usage of these complexes in catalytic asymmetric processes, with focus on 1,4-additions onto unsaturated electrophiles. For this important class of transformation the use of chiral catalytic complexes likely leads to enantioselective systems.

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[14] Díez-González, S.; Nolan, S. P., *Synlett* **2007,** *2007*, 2158; Díez-González, S.; Scott, N. M.; Nolan, S. P., *Organometallics* **2006,** *25*, 2355; Yun, J.; Kim, D.; Yun, H., *Chemical Communications* **2005**, 5181.

I.1.2 Previous reports on 1,4-reductive Michael cyclizations

Catalytic 1,4-additions of metal hydrides to a selection of unsaturated carbonyl compounds have been largely studied and developed during the past few years. In particular, copper(I) catalyzed processes have gained a lot of attention probably because of the carbophilic nature the copper atom which usually provides the 1,4 addition. In the presence of a second electrophile, this reaction could be further exploited to trap the nucleophilic metal enolate intermediate generated during the first addition. While the use of electrophiles such as aldehydes, ketones and esters for inducing aldol reactions has been widely studied using different metal hydride catalysts, especially copper, only few accounts discuss the analogous catalytic reductive Michael reaction of two α,β-unsaturated carbonyl compounds. Moreover, despite a wealth of research on catalytic Michael processes[15], intramolecular transition metal-catalyzed variants have only been meticulously approached in the last decade. In contrast to the reductive aldol reaction that provides the *cis* product as the major form, the double Michael addition cyclization leads majorly to the *trans* cyclized product[16].

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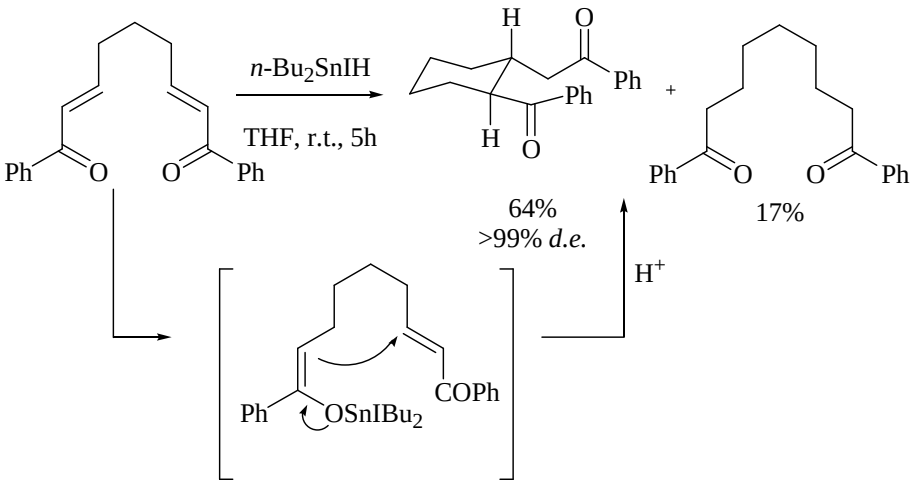
[15] Wei, M.-X.; Wang, C.-T.; Du, J.-Y.; Qu, H.; Yin, P.-R.; Bao, X.; Ma, X.-Y.; Zhao, X.-H.; Zhang, G.-B.; Fan, C.-A., *Chemistry – An Asian Journal* **2013,** *8*, 1966; Xie, C.; Lu, Z.; Zhou, W.; Han, J.; Pan, Y., *Tetrahedron Letters* **2012,** *53*, 6650; Lee, Y.-J.; Lee, J.; Kim, M.-J.; Jeong, B.-S.; Lee, J.-H.; Kim, T.-S.; Lee, J.; Ku, J.-M.; Jew, S.-s.; Park, H.-g., *Organic Letters* **2005,** *7*, 3207; Emori, E.; Arai, T.; Sasai, H.; Shibasaki, M., *Journal of the American Chemical Society* **1998,** *120*, 4043.

[16] Baik, T.-G.; Luis, A. L.; Wang, L.-C.; Krische, M. J., *Journal of the American Chemical Society* **2001,** *123*, 5112.

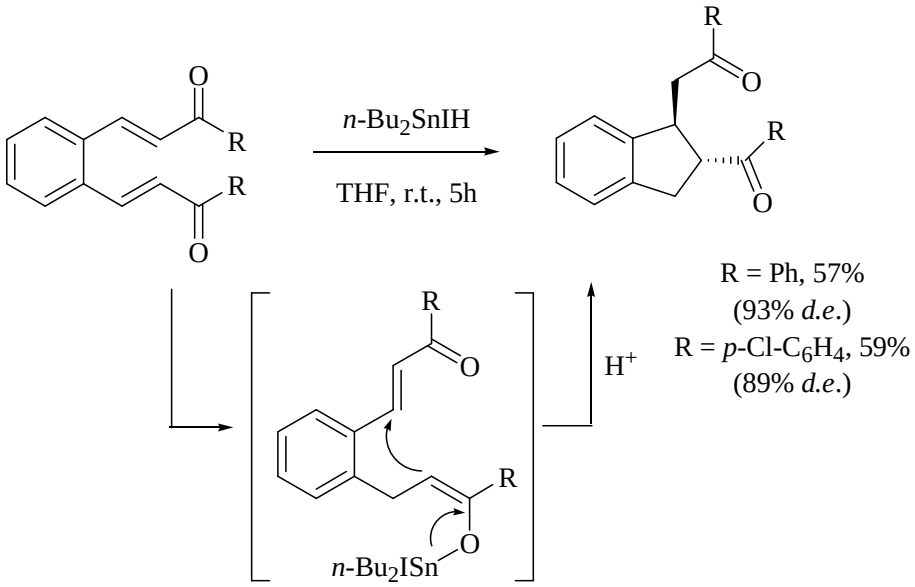
The first report of metal hydride reductive Michael cyclization was given by Baba and coworkers[17]. Their work focused on the intramolecular reductive aldol addition where they employed a stoichiometric amount of organoiodotin hydride which selectively reduces enones even in the presence of aldehydes. They stated that the reaction does not proceed in a radical manner since they noticed no decrease of the yield of the reductive aldol product in the presence of a radical inhibitor such as *p*-dinitorobenzene. In their survey, they carried out the double conjugate addition reaction of two carbocycles containing two α,β-unsaturated ketones. In the first example the reaction proceeded by the 1,4-reduction of one of the enones generating a tin enolate (Scheme 5). This latter in turn induces a Michael addition toward the other unreacted enone. The reaction resulted in the formation of a cyclic diketone as the major product with high *trans* selectivity. The minor product consisted of the saturated ketone derived from the 1,4-reduction of both enones.

[17] Suwa, T.; Nishino, K.; Miyatake, M.; Shibata, I.; Baba, A., *Tetrahedron Letters* **2000,** *41*, 3403.



Scheme 5. Intramolecular reductive cyclization using organoiodotin hydride in stoichiometric amount

In their second example, an *O*-Substituted aromatic dienone afforded the cyclic products in moderate yields under the same conditions. In this case the reaction proceeded with high diastereoselectivity, and no reduction product of both enones was detected (Scheme 6).

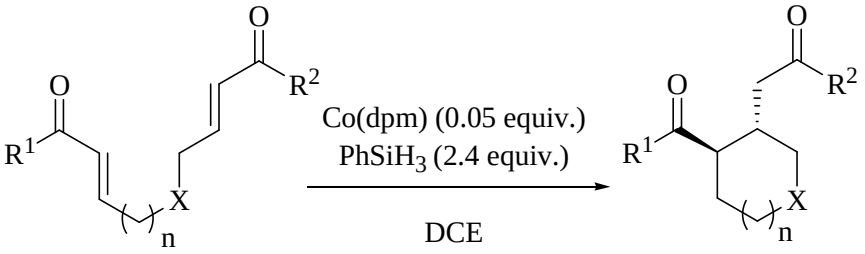


Scheme 105. Intramolecular reductive cyclization of *O*-substituted aromatic dienone using organoiodotin hydride in stoichiometric amount

The intramolecular reductive Michael reaction catalyzed by $Co(dpm)_2$ (dpm = dipivaloylmethane), which utilizes phenylsilane as the hydride source was investigated by Krische *et al*[14]. They described the first catalytic double Michael addition. Initially they examined the reductive Michael cyclization of symmetrical bis-enones (Table 1, entries **1-3**). When the bis-enone is exposed to the conditions mentioned above, they observed the formation of the reductive Michael cyclization product with exclusively *anti*-stereochemistry in good yields. They remarked that bis-enones bearing heteroatoms were tolerated (Table 1, entry **3**). Also, heteroatomic enones including 2-furyl substituted bis-enone (Table 1, entry **5**), underwent cycloreduction in moderate yield. Unsymmetrical bis-enones are subjected to Michael cycloreductions revealing the capability of the catalyst to distinguish electronic differences between both enones in the hydrometallation step (Table 1, entries **4-5**). The mixed bis-enone in entry 4

reveals a preference for the hydrometallation of the phenyl -substituted enone over the methyl-substituted enone resulting in a ratio of 3:1. While in entry 5, the bis-enone bearing both phenyl and 2-furyl substituents do not exhibit any preference and both isomers are obtained in 1:1 ratio.

Table 1. Krische's catalytic double Michael addition using Co catalyst



X=CH_2, O

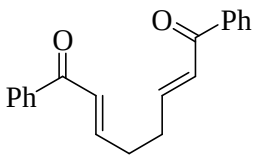
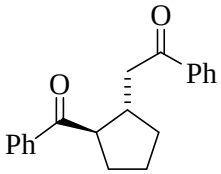
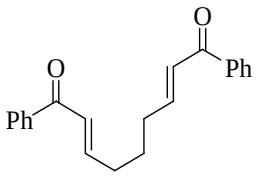
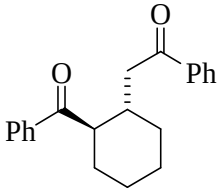
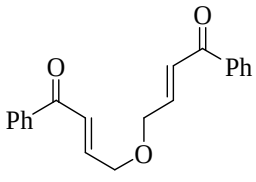
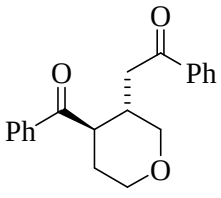
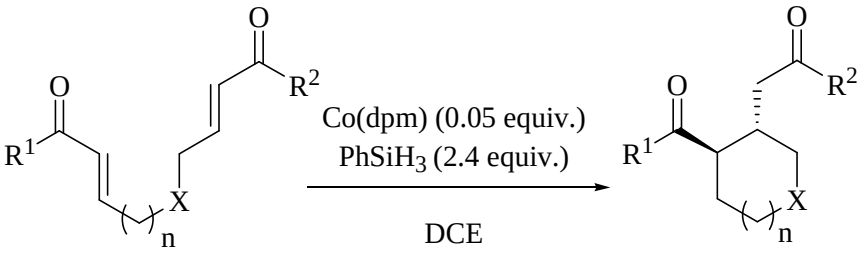
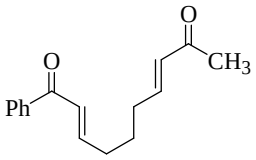
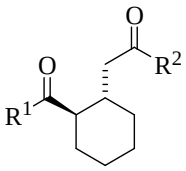
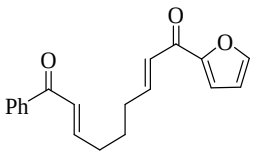
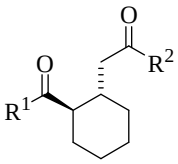
Entry	Substrate	Product	T [°C]	Yield [%]
1			50	62
2			50	73
3			50	63

Table 1. Krische's catalytic double Michael addition using Co catalyst

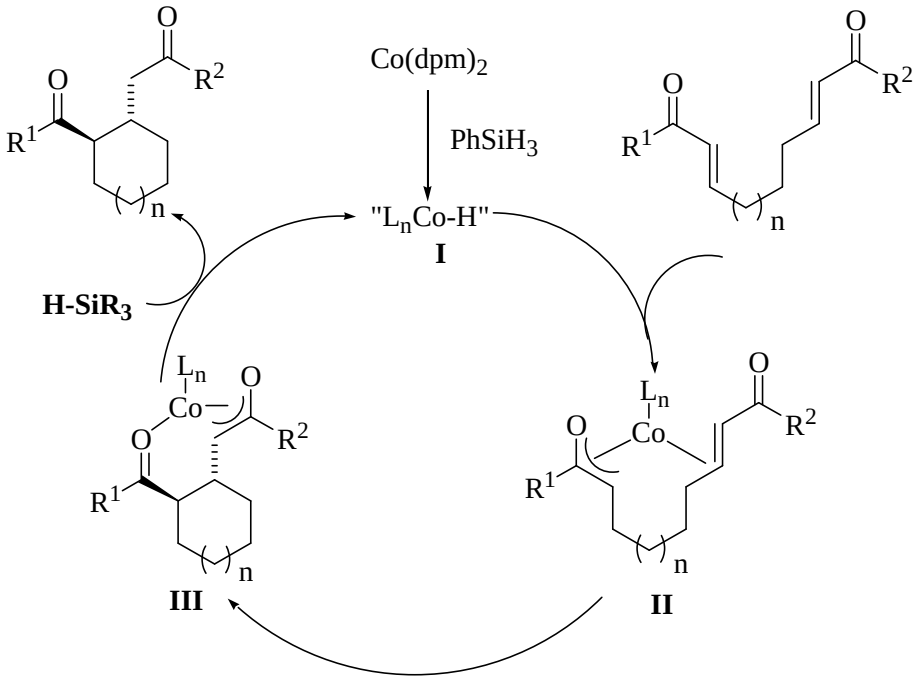


X=CH_2, O

Entry	Substrate	Product	T [°C]	Yield [%]
4		 a: R^1=Ph, R^2=CH_3 b: R^1=CH_3, R^2=Ph a:b (3:1)	70	62
5		 c: R^1=Ph, R^2=2-furyl d: R^1=2-furyl, R^2=Ph c:d (1:1)	50	54

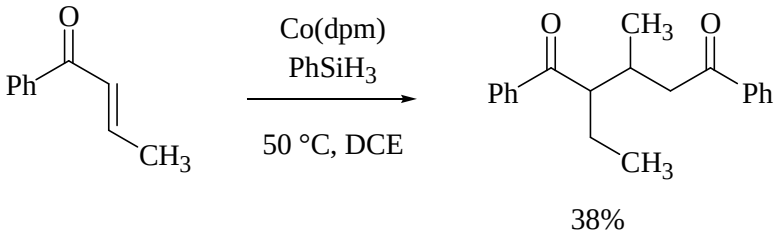
After they carried out some mechanistic studies, they demonstrated a plausible pathway for the catalytic Michael cycloreduction. The cobalt hydride species **I** generated upon the addition of the phenylsilane to the $Co(dpm)_2$ catalyst adds in a conjugate manner to the enone yielding a cobalt

enolate **II.** This enolate adds in a conjugate manner to the second enone thus leading to a cyclized cobalt enolate intermediate **III**, which then undergoes σ-bond metathesis liberating the product and regenerating the cobalt hydride **I** (Scheme 6).



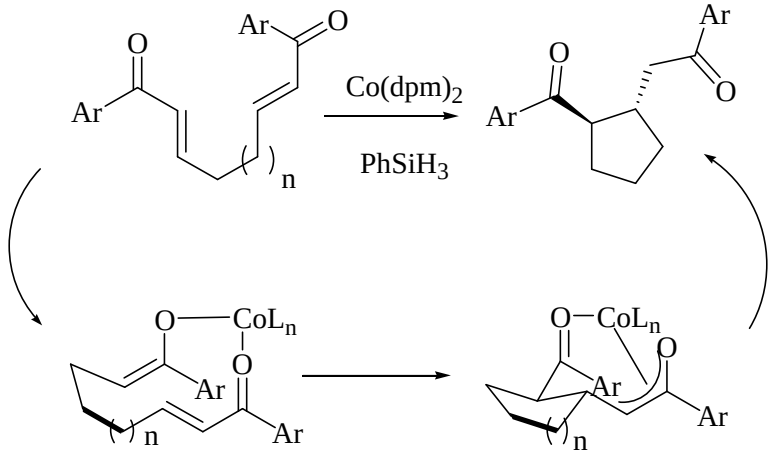
Scheme 6. Proposed mechanism for the double Michael addition developed by Krische

It is known for intermolecular Co catalyzed hydrodimerizations of α,β-unsaturated carbonyl compounds to exclusively afford the products of β,β-coupling upon the use of zinc as the hydride donor. However, when 1-phenylbutenone is exposed to the catalytic system: $Co(dpm)_2$-phenylsilane, the system provided the 'head-to-tail' hydrodimerization, that is the α,β-hydrodimerization, in 38% yield and as the single regioisomer (Scheme 7). This finding supports that the inversion in stereochemistry in intramolecular processes is due to the intermediacy of a nucleophilic cobalt enolate[2].



Scheme 7. 'head-to-tail' hydrodimerization

The Co-catalyzed Michael cycloreduction exibits high levels of *trans*-diastereoselectivity, which is explained on the basis of stereochemical model that proposes a chair-like transition state[2,18] (Scheme 8).

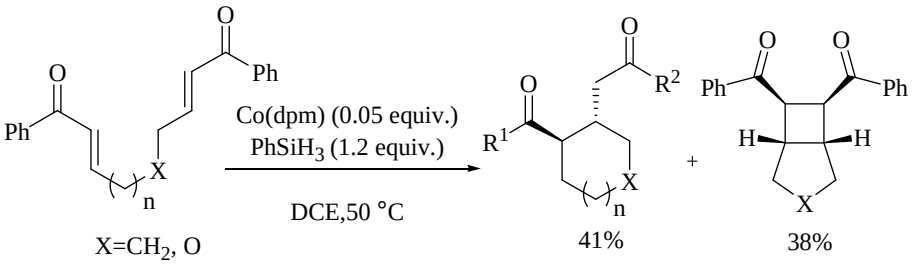


Scheme 8. Origin of *trans* selectivity of Co-catalyzed Michael cycloreduction

In a following report, they disclosed that when 2.4 equiv. of the silane are used, the Michael cycloreduction represents the exclusive reaction pathway. However, when the reactions were conducted in the presence of 1.2 equiv. of

[18] Wang, L.-C.; Jang, H.-Y.; Roh, Y.; Lynch, V.; Schultz, A. J.; Wang, X.; Krische, M. J., *Journal of the American Chemical Society* **2002,** *124*, 9448.

silane, comparable amounts of Michael cycloreduction and [2 + 2] cycloaddition products were observed[19] (Scheme 9).



Scheme 9. Michael cycloreduction and [2+2] cycloaddition products

They later explained that enone hydrometalation enables catalytic aldol and Michael cycloreduction pathways, that is, products derived from coupling at the β-position of the enone, while an electron-transfer-mediated enone reduction produces metallo-oxy-π-allyls leading to [2 + 2] cycloadducts[16].

Another system that was also applicable to both reductive aldol and Michael cyclizations was described by Hosomi and coworkers[20]. They employed an indium(III) acetate catalyst with phenylsilane to produce selectively the *trans*-cyclized products in good yields (Scheme 10).

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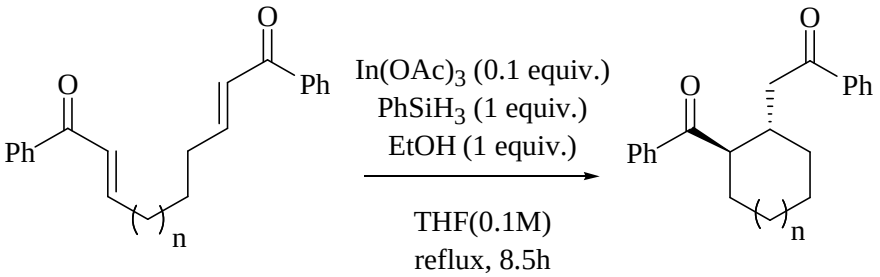
[19] Baik, T.-G.; Luis, A. L.; Wang, L.-C.; Krische, M. J., *Journal of the American Chemical Society* **2001,** *123*, 6716.

[20] Miura, K.; Yamada, Y.; Tomita, M.; Hosomi, A., *Synlett* **2004,** *2004*, 1985.



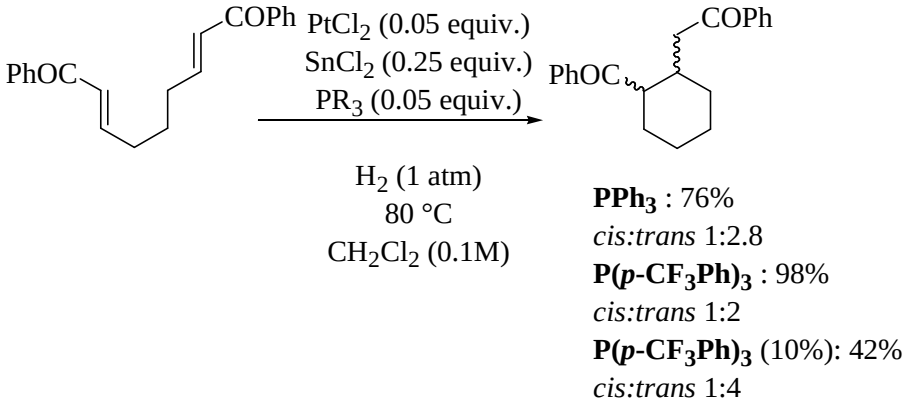
Scheme 10. In(III)-catalyzed reductive cycloaddition of bis-enones

Pt-catalyzed reductive cyclization of bis-enones in the presence of various phosphine ligands and H_2 or Et_3SiH, affording intra-molecular reaction was studied by Jang *et al.*[21] They presented the first account of hydrogen-mediated cyclization of bis-enones.

To introduce an optimal system, they initially performed the reductive cyclization reaction of (*2E,7E*)-1,9-diphenylnona-2,7-diene-1,9-dione using a platinum complex generated *in situ* by mixing $PtCl_2$ (5 mol %), PPh_3 (5 mol%), and $SnCl_2$ (25 mol %) in dichloroethane under 1 atm of H_2. While most reductive cyclizations of bis-enones provided the β,β-coupling product in the presence of reductants such as R_2Zn, as mentioned before, the hydrogen-mediated cyclization affords the α,β-coupling product similar to Co- and In-catalyzed reductive cyclizations of bis-enones using silane reported by Krische and Hosomi[19,20]. They obtained the cyclized product in a 76% yield and *cis:trans* ratio of 1:2.8. After ligand screening experiments, they found that P (*p*-$CF_3Ph)_3$ provided the cyclized product in highest conversion of 98% with *cis:trans* ratio of 1:2. However, adding 10 mol % of

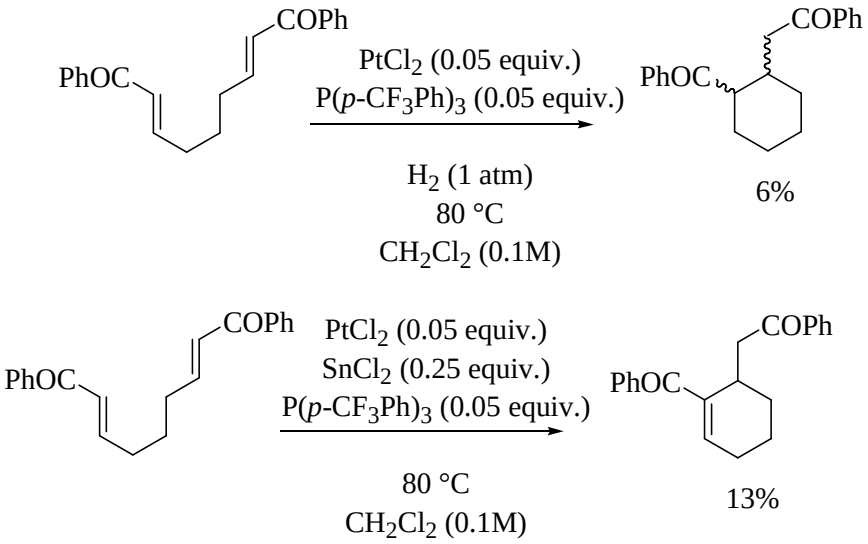
[21] Lee, H.; Jang, M.-S.; Hong, J.-T.; Jang, H.-Y., *Tetrahedron Letters* **2008,** *49*, 5785.

P(Ph–*p*CF_3)$_3$ to 5 mol % of $PtCl_2$ might hinder the reactivity (42% yield) of the catalyst while favoring the *trans* product formation (1:4) (Scheme 11).



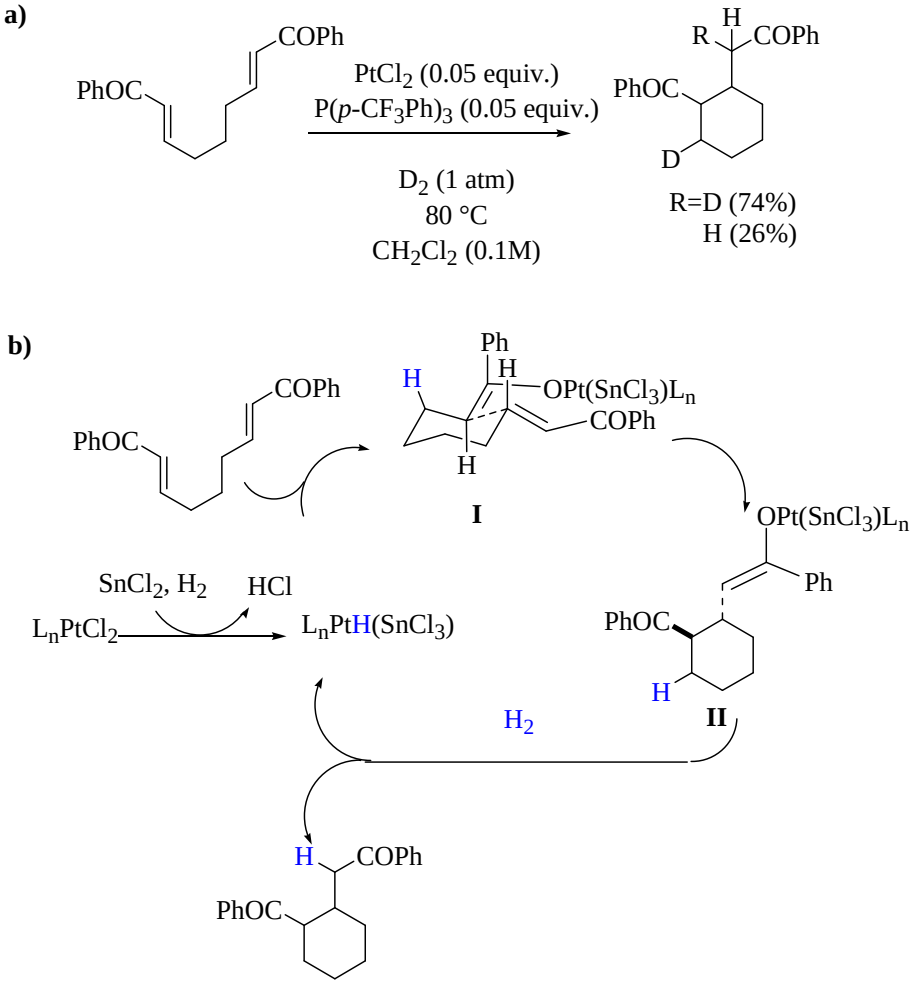
Scheme 11. Pt-catalyzed reductive cyclization of bis-enones developed by Jang

They also carried out some control experiments to identify the role of tin chloride ($SnCl_2$). In the absence of $SnCl_2$, the reaction system is poorly reactive and the product is formed with only 6% yield. Under the optimized conditions with the absence of the H_2 gas, the cycloisomerization product is provided in 13% yield, and no reductive cyclization product is detected (Scheme 12). These control experiments provided evidence that the role of $SnCl_2$ is that of a co-catalyst for the activation of $PtCl_2$ and not as a reductant.



Scheme 12. Control experiments for the verification of the role of $SnCl_2$

They have also performed a deuterium labeling experiment using the same bis-enone. The reaction provided the deuteriorated cyclized product in quantitave yield (Scheme 13.a). They determined the structure and the deuterium content by NMR. The deuteriums were found at the α-position of the ketone outside the ring, and so they proposed a mechanism that comprises the hydrometalation of the platinum-deuteride to the alkene. The Pt complex reacts with hydrogen and $SnCl_2$ to form $L_nPtH(SnCl_3)$. This complex hydrometallates the bis-enone to afford intermediate **I** where the coordination of the platinum metal ion is not strong enough toward the pendant alkene, which results in the formation of a mixture of *cis* and *trans* isomers of the cyclized intermediate **II**. Intermediate **II** undergoes oxidative addition with the hydrogen gas, followed by reductive elimination, establishing the cyclized product and the generation of $L_nPtH(SnCl_3)$ (Scheme 13.b).

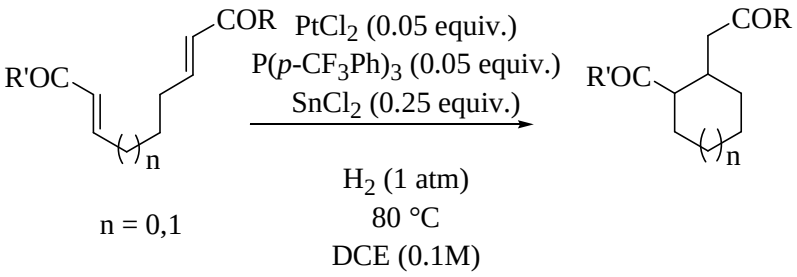


Scheme 13. a) Deuterium labeling experiment and b) proposed mechanism

To evaluate the scope of the reaction, they carried out the hydrogen-mediated reductive coupling of different bis-enones under the optimized conditions (Table 2). Good to excellent yields were obtained (59-98%). Aromatic bis-enones bearing electron-donating groups provide the cyclized product in 91% yield (entry 3). In the case of asymmetrical bis-enone (entry 4), hydride addition takes place at both the β-position with respect to the

phenyl ketone and the β-position with respect to the methyl ketone in a 4:1 ratio and with a total yield of 72% with a 1:1 *cis:trans* ratio.

Table 2. Scope of the reaction



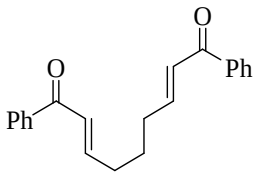
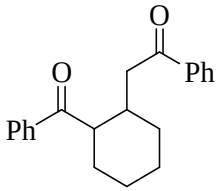
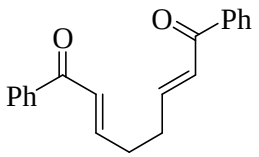
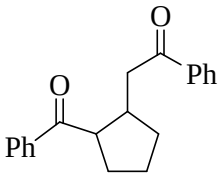
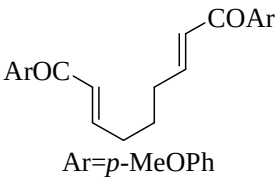
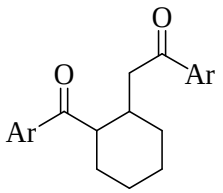
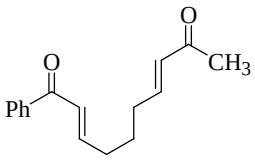
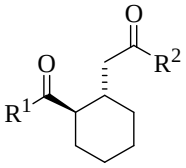
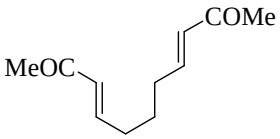
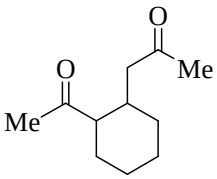
Entry	Substrate	Product	Yield [%] (*cis:trans*)
1			98 (1:2)
2			71 (1:1)
3	 Ar=*p*-MeOPh		91 (1:3.5)

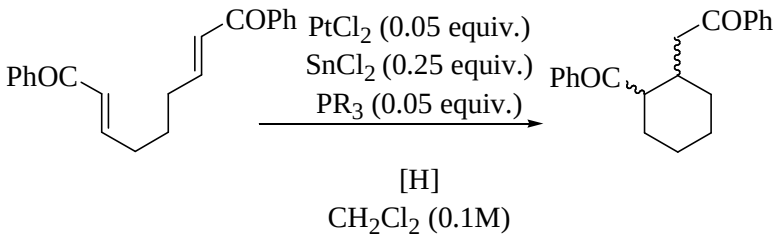
Table2. Scope of the reaction

Entry	Substrate	Product	Yield [%] (*cis:trans*)
4		 a: R^1=Ph, R^2=CH_3 b: R^1=CH_3, R^2=Ph	72 (1:1) a:b=4:1
5			59 (1:1)

In a subsequent report, Jang and coworkers discuss the Pt-catalyzed intramolecular reductive Michael reactions where Et_3SiH is used as a hydride source[22]. The outcome of the reaction showed that silanes were less performant than the hydrogen gas when used as reductants (Table 3).

[22] Lee, H.; Jang, M. S.; Song, Y. J.; Jang, H. Y., *Bulletin of the Korean Chemical Society* **2009,** *30*, 327.

Table 3. Pt-catalyzed reductive cyclization using Et_3SiH as a hydride source



Entry	Ligand	[H]	T °C	Yield [%] (*cis:trans*)
1	P(*p*-$CF_3C_6H_4$)$_3$	H_2	80	98 (33:76)
2	P(*p*-$OMeC_6H_4$)$_3$	H_2	80	66 (28:72)
3	P(*p*-$CF_3C_6H_4$)$_3$	Et_3SiH	50	71 (29:71)
4[a]	P(*p*-$CF_3C_6H_4$)$_3$	Et_3SiH	50	24 (50:50)
5	P(*p*-$OMeC_6H_4$)$_3$	Et_3SiH	50	52 (25:75)

[a] in the absence of $SnCl_2$

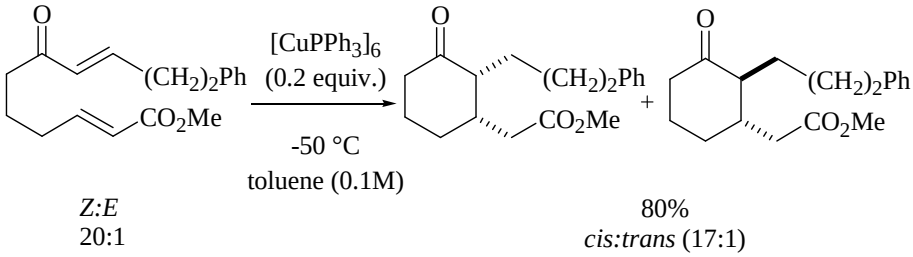
They also studied the scope of the reaction using a variety of bis-enones. Using silane as a reductant, the catalytic activity appears to be lower. The yields obtained using the same bis-enones studied above during the exemplification were less than those obtained when H_2 was used as the reductant.

The use of Cu-H for reductive Michael cyclization was first studied by Ly Sakata *et al.*[23] Although they employed the copper hydride in stoichiometric amount, it was one of the first examples for the reductive Michael cyclization. They employed the stable hexameric Stryker's reagent for the

[23] Kamenecka, T. M.; Overman, L. E.; Ly Sakata, S. K., *Organic Letters* **2001,** *4*, 79.

construction of substituted cyclohexanones by reductive cyclization of 7-oxo-2,8-alkadienyl esters.

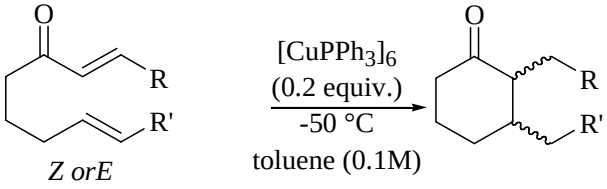
After several solvent and temperature optimizations they found that when the reaction was run with 1.2 equiv. of Cu-H, in toluene (0.1M) at -50 °C, they obtained 80% yield with a *cis:trans* ratio of 17:1 (Scheme 14).

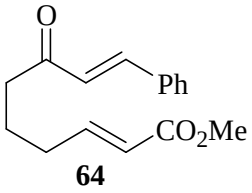
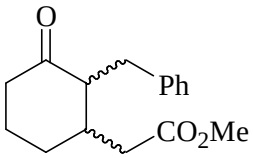
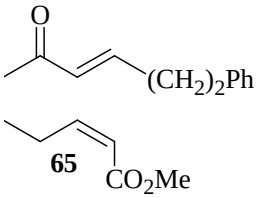
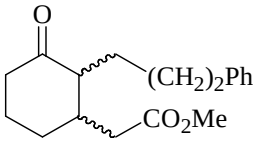
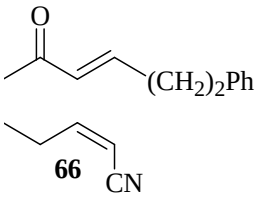
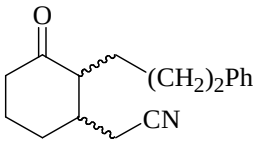
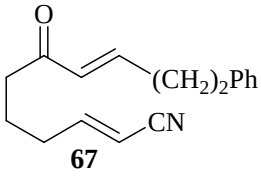
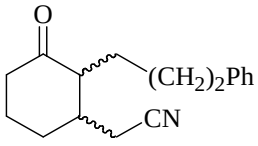


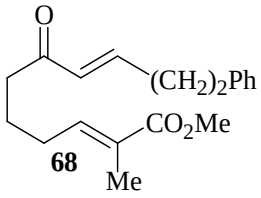
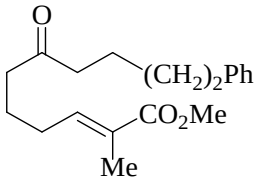
Scheme 14. Reductive cycloreduction using Stryker's reagent

The scope of the reaction was defined through subjecting different substrates to the optimized reaction conditions (Table 4). The substrate *(E)*-**64** undergoes reductive cyclization to provide the cis cyclized product as the major product. The *(Z)* enoate **65** cyclized under similar conditions with no stereoselectivity. *(Z)* and *(E)* enoates **66** and **67** undergo the cyclization reaction with low stereoselectivity, although **66** provides the *cis* product as a major isomer and **67** provides the *trans* one as the major product. The substitution on the double bond on the α-position of the enoate **68** inhibits the cyclization reaction (entry 5). Instead only the reduction product is obtained.

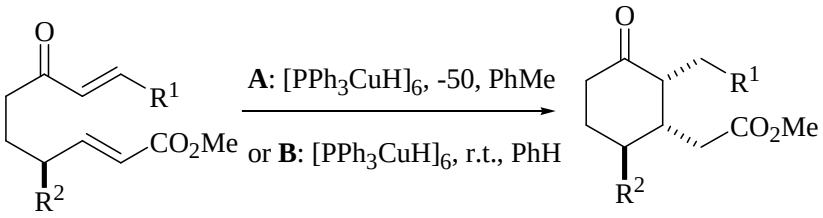
Table 4. Scope of the reaction

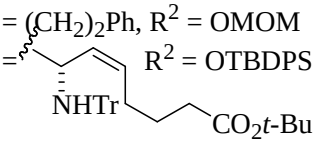


Entry	Substrate	Product	Yield [%] (*cis:trans*)
1	 **64**		50 (10:1)
2	 **65**		60 (1:1)
3	 **66**		55 (4:1)
4	 **67**		60 (1:3)

Entry	Substrate	Product	Yield [%] (*cis:trans*)
5	 **68**		59 (1:1)

Furthermore, Ly Sakata and coworkers executed the reductive cyclization reaction on a variety of enantiopure *(E)*-4-alkoxy- and *(E)*-4-siloxy-7-oxo-2,8-alkadienyl esters. These reactions provided a single cyclohexanone product in high yield (Scheme 15). Diastereoselection in the reaction of substrates **69-73** was found to be >20:1 in reactions carried out either at -50 °C or at room temperature. A variety of substituents were tolerated. The cyclization of enantiopure **73** provides the enantiopure product in high yield and validates the tolerance of highly bulky tritylamino groups at the γ-position of the enoate.



69 R^1 = Ph, R^2 = OTBDPS (**A**:88%, **B**: 96%)
70 R^1 = 2,4-$(MeO)_2C_6H_3$, R^2 = OMOM (**A**:75%)
71 R^1 = 2,4-$(MeO)_2C_6H_3$, R^2 = OTBDPS (**B**:87%)
72 R^1 = $(CH_2)_2Ph$, R^2 = OMOM (**A**:75%)
73 R^1 =  R^2 = OTBDPS (**B**:79%)

Scheme 15. Reductive cyclization using Stryker's reagent

To rationalize the formation of the less stable 2,3 *cis* isomer, they proposed a chair transition state in which the emerging C2 and C3 side chains adopt quasi-equatorial orientations. They suggested that the chelation between the copper of a (*Z*)-copper enolate intermediate and the enoate is responsible for the *cis* stereoselection observed.

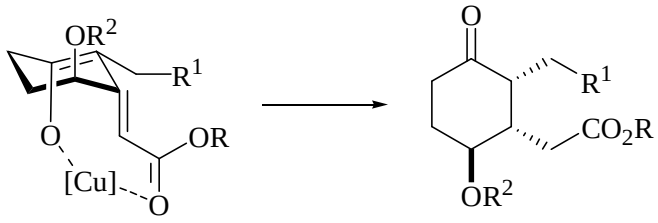


Figure 3. Transition state proposed responsible for the *cis* stereoselection

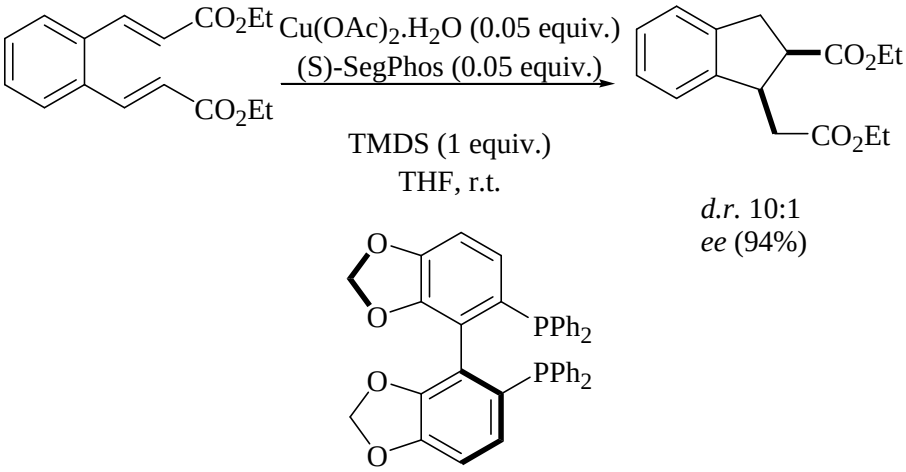
The use of chiral metal-ligand complexes usually provides an entry to enantiomerically enriched products. Many reports of catalytic asymmetric variants of reductive aldol and Mannich reactions have been described. Catalytic enantioselective reductive Michael reaction employing chiral secondary amines as a catalyst were reported on several occasions. The earliest and only report of metal catalyzed enantioselective reductive Michael reactions was disclosed by Lam *et al*[24].

Many studies were conducted for the enantioselective reductive aldol cyclizations using silanes as terminal reductant, and chiral copper-biphosphine complexes with high levels of enantioselectivity[4]. Lam and coworkers showed that these systems could also affect a reductive Michael cyclization of bis-enoates providing high enantioselectivities.

They initiated their study by investigating different biaryl-based chiral bisphosphines. Using 5 mol % of $Cu(OAc)_2 \cdot H_2O$, 5 mol % of ligand, and 1.0 equiv of TMDS in THF at room temperature, they found that the *(S)*-SegPhos ligand provided marginally superior levels of diastereo- and

[24] Oswald, C. L.; Peterson, J. A.; Lam, H. W., *Organic Letters* **2009,** *11*, 4504.

enantioselectivities with total consumption of the starting material (Scheme 16).

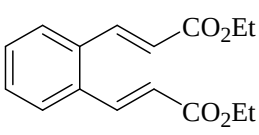
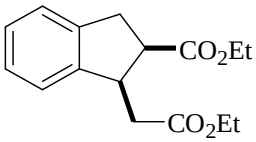
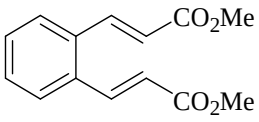
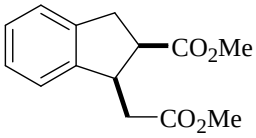
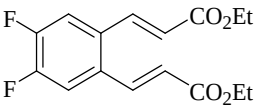
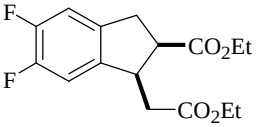
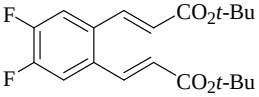
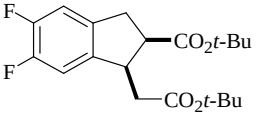
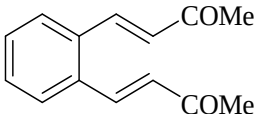
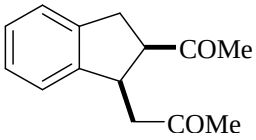
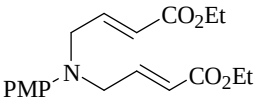
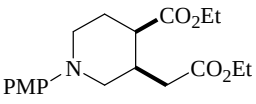


***(S)*-SegPhos**

Scheme 16. Enantioselective Cu-cataylyzed reductive Michael cyclization

To evaluate the scope of the reaction, a number of aromatic-tethered bis-α,β-unsaturated carbonyl compounds were subject to the previous reaction conditions. Modest yields of the cyclized products were obtained but with high diastereo- and enantioselectivities.

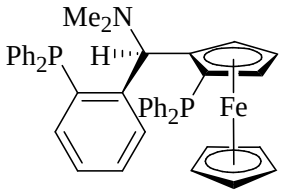
Table 5. Scope of the reaction

Entry	Substrate	Product	Yield [%]	dr	ee [%]
1			57	12:1	94(+)
2			41	6:1	93(+)
3			53	7:1	92(+)
4[a]			54	8:1	90(-)
5			41	6:1	97(+)
6[b]			41	4:1	91(-)

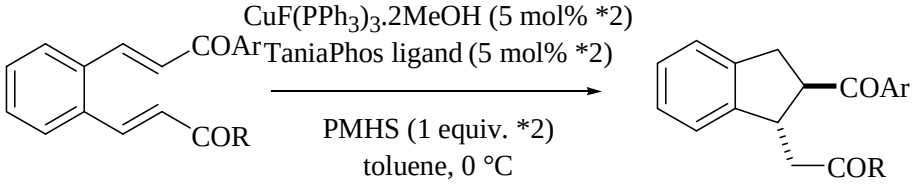
[a]Reaction conducted using (*R*)-BINAP (**L4**). [b]Reaction conducted using (*S*)-DM-SEGPHOS (**L2**).

The cyclization of the bis-ethyl ester analogue (entry 1) provided the cyclization product in 12:1 diasteriomeric mixture with 94% *ee* for the major isomer. However, the bis-methyl ester analogue resulted in lower diastereoselectivity but comparable enantioselectivity (entry 2). Fluorine substitution on the benzene ring was tolerated (entry 3), as was the use of methyl ketones (entry 5). Anilinetethered substrate (entry 6) underwent cyclization to provide the product in 4:1 *dr* and 91% *ee* using *(S)*-DM-SegPhos.

Similar conditions were used for the cyclization reaction of substrates containing aromatic ketones. However, the reaction did not take place. Upon using $CuF(PPh_3)_3.2MeOH$ (5 mol%) along with a TaniaPhos ligand (5 mol%) in toluene with 1 equiv of PMHS for 24 hours, followed by the addition of a second batch of catalyst (5 mol%) and 1 equiv of the silane for a further 24h, high conversions were ensured (Scheme 17). During these experiments *trans* products were obtained as the major products.



TaniaPhos ligand



Ar = Ph, R = Ph	46%, >19:1 dr, 83% *ee*
Ar = 4-ClC_6H_4, R = 4-ClC_6H_4 (-20°C)	41%, >19:1 dr, 90% *ee*

Scheme 17. Reductive cyclization of substrates containing aromatic ketones

In addition to the previous accounts of metal catalyzed reductive Michael cyclizations, an important number of accounts that describe the organocatalytic enantioselective reductive Michael reaction using chiral amines and NHCs was reported[25]. The discussion of these methods will not be carried out herein. Instead, we are interested in the vinologous Morita-Baylis-Hilman reaction which will be reviewed in the next section.

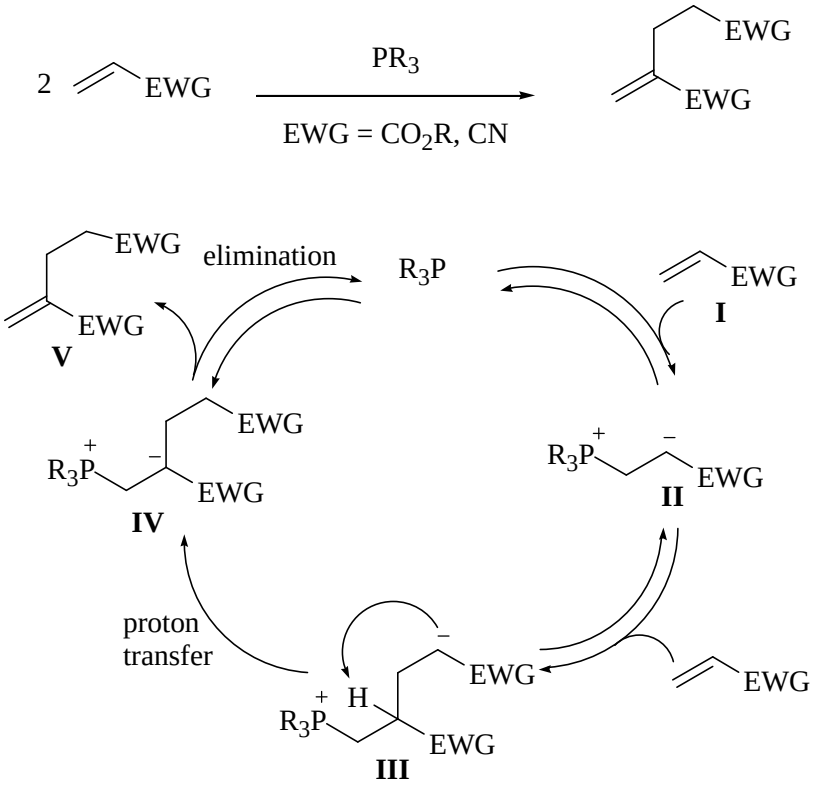
[25] Li, N.; Liu, G.-G.; Chen, J.; Pan, F.-F.; Wu, B.; Wang, X.-W., *European Journal of Organic Chemistry* **2014,** *2014*, 2677; Hong, B.-C.; Liao, W.-K.; Dange, N. S.; Liao, J.-H., *Organic Letters* **2013,** *15*, 468; Hong, B.-C.; Sadani, A. A.; Nimje, R. Y.; Dange, N. S.; Lee, G.-H., *Synthesis* **2011,** *2011*, 1887; Wang, X.-F.; An, J.; Zhang, X.-X.; Tan, F.; Chen, J.-R.; Xiao, W.-J., *Organic Letters* **2011,** *13*, 808; Michrowska, A.; List, B., *Nat Chem* **2009,** *1*, 225; Li, Y.; Wang, X.-Q.; Zheng, C.; You, S.-L., *Chemical Communications* **2009**, 5823; Tan, B.; Shi, Z.; Chua, P. J.; Zhong, G., *Organic Letters* **2008,** *10*, 3425; Phillips, E. M.; Wadamoto, M.; Chan, A.; Scheidt, K. A., *Angewandte Chemie International Edition* **2007,** *46*, 3107; Enders, D.; Grondal, C.; Hüttl, M. R. M., *Angewandte Chemie International Edition* **2007,** *46*, 1570; Yang, J. W.; Hechavarria Fonseca, M. T.; List, B., *Journal of the American Chemical Society* **2005,** *127*, 15036.

I.2 The Rauhut-Currier reaction

As mentioned previously, the use of enones as latent enolates provided a successful entry into reactions whose mechanisms are more commonly associated with enolates. Our interest was dedicated to a variant of Morita-Baylis-Hilman reaction (MBH), the vinologous MBH reaction or the Rauhut-Currier reaction (RC). The RC reaction is an organocatalyzed isomerization of electron-deficient alkenes which merges the concepts of conjugate addition and latent enolate generation and embraces the possibility to create a new C–C bond in an atom economical way. While the MBH reaction encompasses the C–C bond formation between an activated alkene (alkyne)/latent enolate with an electrophile (mostly aldehydes) under the influence of a nucleophilic catalyst (phosphines or amines), the RC reaction involves the C–C bond formation between the α-position of one active alkene/latent enolate and the β-position of a second Michael acceptor under the influence of a nucleophilic catalyst (generally trialkylphosphines).

The reaction was first reported by Rauhut and Currier in 1963[26]. They described the phosphine-catalyzed dimerization of electron-deficient alkenes, acrylonitrile and ethyl acrylate in a mechanism that is essentially that of the MBH reaction (Scheme 18). The transformation proceeds via a reversible conjugate addition of a nucleophilic catalyst (trialkylphosphine or triarylphosphine) to the activated alkene **I** generating a zwitterionic species **II**. This is followed by a Michael addition of the enolate to a second equivalent of activated alkene **I**, giving rise to intermediate **III**, which then undergoes a prototropic tautomerization followed by the elimination of the phosphine catalyst to generate the RC product **V**.

[26] Aroyan, C. E.; Dermenci, A.; Miller, S. J., *Tetrahedron* **2009,** *65*, 4069.



Scheme 18. Proposed mechanism

The RC reaction lacks substrate reactivity and reaction selectivity if compared to the MBH reaction. This is mostly observed in the intermolecular version of this reaction where the lack of selectivity in cross-coupling reactions involving different activated alkenes is common[25]. Later, several groups investigated a variant of this reaction using tertiary amines to catalyze the dimerization of several different activated alkenes. Unfortunately, when attempting the cross-coupling reaction they reported difficulty with the control of the cross-coupling[27].

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[27] Drewes, S. E.; Emslie, N. D.; Karodia, N., *Synthetic Communications* **1990,** *20*, 1915; Basavaiah, D.; Gowriswari, V. V. L.; Bharathi, T. K., *Tetrahedron Letters* **1987,** *28*, 4591; Amri, H.; Villieras, J., *Tetrahedron Letters* **1986,** *27*, 4307.

Despite the previous studies, little research was carried out on the phosphine catalyzed intermolecular Rauhut-Currier reaction that presents a potential for selective and more reactive counterpart of this reaction. It was until 2002, that groups of Krische[28] and Roush[29] carried out some methodology research in order to address selectivity issues in the RC reaction. Both groups demonstrated that trialkylphosphines were more efficient catalysts than amine based nucleophiles, used commonly in the MBH reaction. The cycloisomerization of five- and six-membered symmetrical and unsymmetrical bis(enones) catalyzed by trialkylphosphines proceeded with high efficiency. This efficiency of the trialkyl phosphines was related to their soft character, compared to amines, which is more compatible with the soft activated alkene substrates. Both groups also studied the solvents effect and found that polar protic solvents provided higher reaction rates. It is important to mention that they did not propose a single set of reaction conditions, since for some substrate classes, modification in the conditions were required to improve the results.

Krische *et al*. connected the reaction partners (activated alkenes) of different electrophilicity by a 2- or 3-atom chain resulting in the cycloisomerization of symmetrical and asymmetrical bis-enones using a catalytic amount of a tertiary alkylphosphine to provide five- and six-membered ring adducts in good overall yield[28]. For symmetrical bis-enones, Krische and co-workers used tributylphosphine (Bu_3P) in different solvents at temperatures ranging from 23 to 50 °C to provide aromatic cyclopentene products (86%-95%, Scheme 19) and aromatic and aliphatic cyclohexene products (61–90%).

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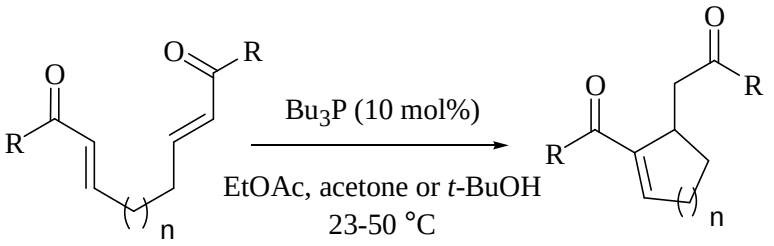
[28] Wang, L.-C.; Luis, A. L.; Agapiou, K.; Jang, H.-Y.; Krische, M. J., *Journal of the American Chemical Society* **2002,** *124*, 2402.

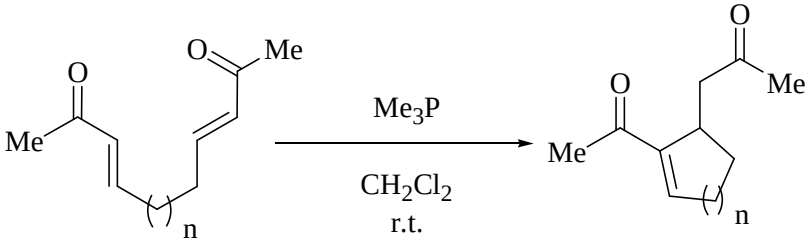
[29] Frank, S. A.; Mergott, D. J.; Roush, W. R., *Journal of the American Chemical Society* **2002,** *124*, 2404.



(n=1) R = Ph, 2-furyl (n=1) 86-95%
(n=2) R = 4-MeOPh, 4-CF_3Ph, (n=2) 61-90%
3-naphthyl, 2-furyl
2-thiophene
CH_3, $CH_2CH(CH_3)_2$

Scheme 19. PBu_3 catalyzed Rauhut Currier reaction

Simultaneously, Roush and co-workers reported similar trialkyl phosphine-mediated intramolecular RC reactions for diactivated 1,5-heptadienes, and 1,6-hexadienes to give the highly functionalized RC products[29]. They employed PMe_3 (Scheme 20) in CH_2Cl_2 at r.t. to provide cyclization products in 96 and 64% yield.

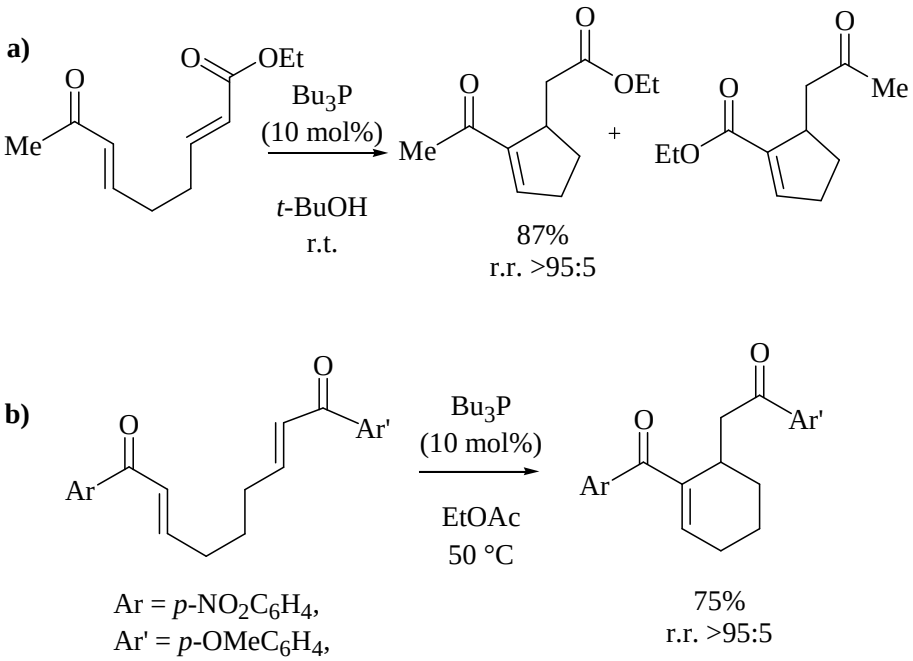


n=1 (10 mol% Me_3P) 96%
n=2 (25 mol% Me_3P) 64%

Scheme 20. PMe_3 catalyzed Rauhut Currier reaction

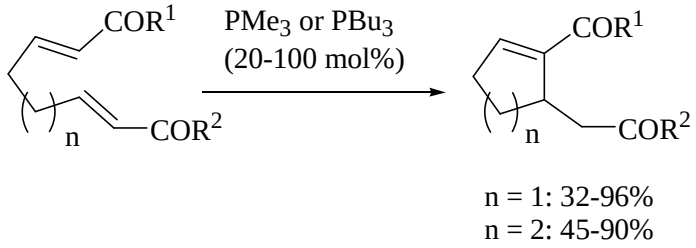
For unsymmetrical bis-enone substrates, both groups resolved the regioselectivity issues through variation in electronic and steric effects of both components. Krische and coworkers described highly regioselective systems for the formation of 5- and 6-membered rings. In the case of mono-enone mono-enoate (Scheme 21.a), they obtained selectively a single isomer

in >95:5 ratio. Also, in the case of distant para substituents, they have obtained one single isomer in a ratio >95:5 when the reaction is run at 50 °C in EtOAc (Scheme 21.b). This proves the ability to select cyclization manifolds based on the electronic effect of substituents even if they are distant.



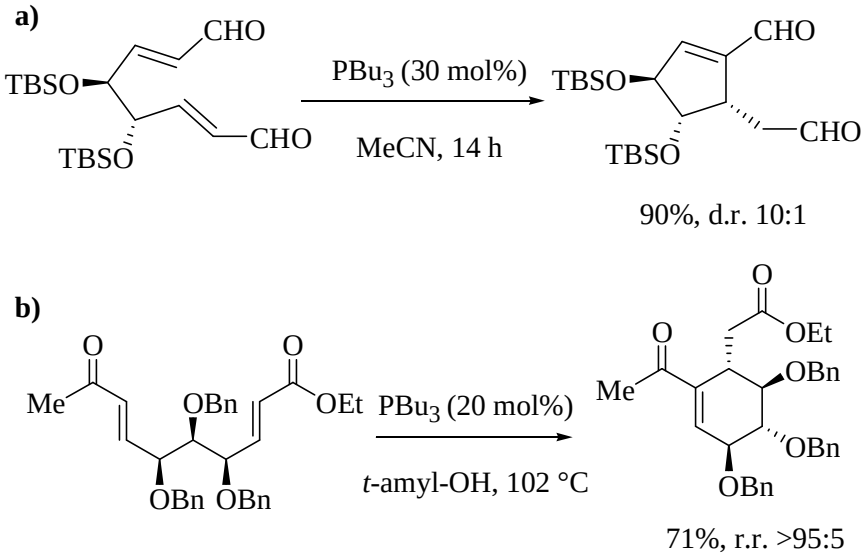
Scheme 21. Rauhut Currier reaction of a) unsymmetrical aliphatic bis-enones and b) unsymmetrical aromatic bis-enones

On the other hand, Roush *et al.* revealed similar electronic effects, where the major product originates from the nucleophilic addition of the phosphine catalyst to the more electrophilic enone followed by the cyclization on the less electrophilic Michael acceptor. Many substituted 5- and 6-membered products were obtained using PMe_3 or PBu_3 (20–100 mol %) in moderate to excellent yield (32–96%) with high selectivities for one isomer in most cases (Scheme 22).



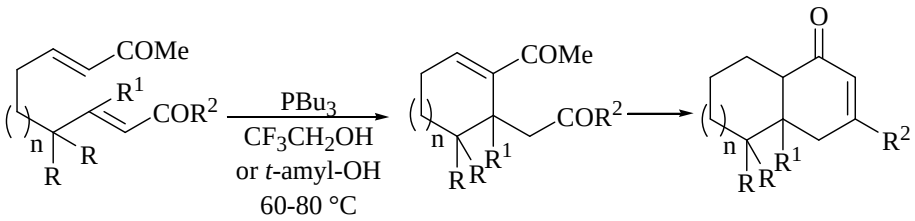
Scheme 22. Rauhut Currier reaction of unsymmetrical bis-enones

Optically pure substrates with multichiral centers were also studied by both groups. The cyclization of the bis-enal provided the cyclized product in 90% yield with diastereoselectivity of 10:1[29]. Also, the optically pure xylose-derived mono-enone mono-enoate provided the pentasubstituted cyclohexene as a single isomer in 71% yield[27].

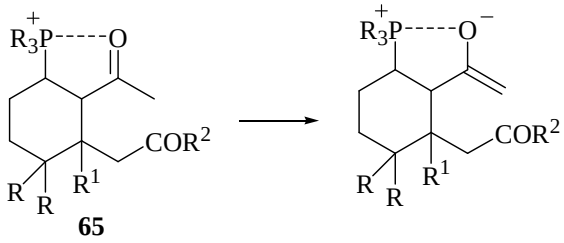


Scheme 23. Rauhut-Currier reaction starting from optically pure substrates

A couple of years later, Roush et al. demonstrated a tandem intramolecular RC/aldolization reaction[30]. While studying the RC reaction, they observed a by product resulting from the secondary aldol reaction. They carried out the optimization for this transformation, and obtained good yields and high regioselectivity. They referred this high level of regioselectivity to an interaction between the phosphonium unit and the adjacent carbonyl, leading to an increase in the acidity of the β-phosphonium-substituted methyl ketone, which consequently undergoes regioselective deprotonation by the action of the alkoxide (Scheme 24).



R = H, Me
R^1 = H, Me
R^2 = Me, $(CH_3)_2CH$, $(CH_3)_2CH_2CH$

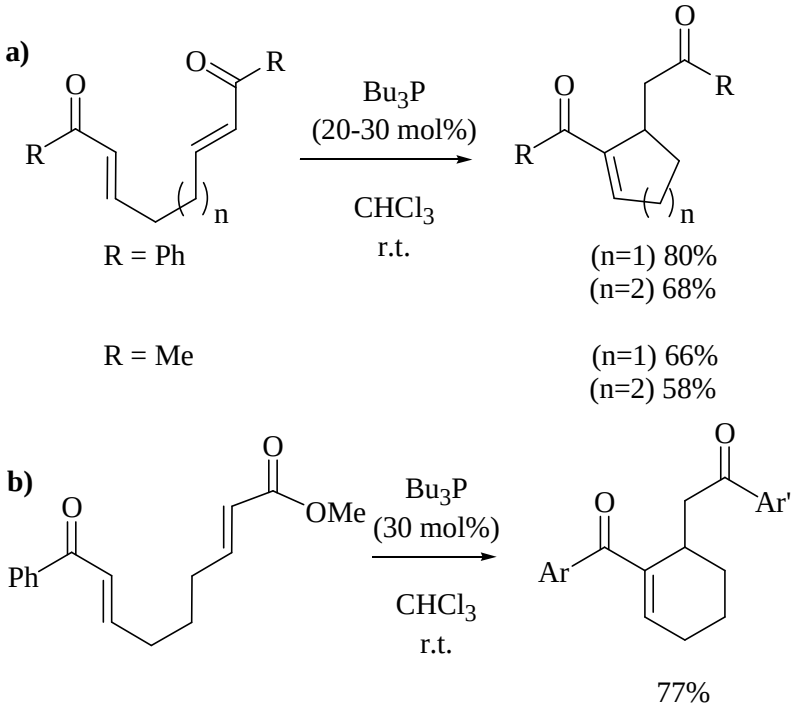


Scheme 24. Tandem intramolecular RC/aldolization reaction

Besides, Murphy *et al.* reported the effect of PBu_3 as a catalyst at room temperature for the RC cyclizations leading to the formation of

[30] Thalji, R. K.; Roush, W. R., *Journal of the American Chemical Society* **2005,** *127*, 16778.

cyclopentenes and cyclohexenes in good yields[31]. They carried out cyclization reactions of symmetrical bis-enones using PBu_3 (20-30 mol%) at r.t. affording the corresponding 5- or 6-membered ring in good yields (58-80%) (Scheme 25.a). An unsymmetrical enone-enoate substrate was found to provide a single isomer in good yield (77%) (Scheme 25.b).



Scheme 25. RC cyclizations for the formation of cyclopentenes and cyclohexenes

More recently, asymmetric induction in RC reaction has become an attractive subject. The group of Miller reported an early example of enantioselective RC reaction that provided high yields and enantioselectivity

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[31] Brown, P. M.; Käppel, N.; Murphy, P. J.; Coles, S. J.; Hursthouse, M. B., *Tetrahedron* **2007,** *63*, 1100; Brown, P. M.; Käppel, N.; Murphy, P. J., *Tetrahedron Letters* **2002,** *43*, 8707.

using simple cysteine (Cys) derivative as a chiral catalyst[32] (Table 6). The cycloisomerization of bis-enones catalyzed by a Cys-based amino acid (1 equiv.) in the presence of *t*-BuOK (6 equiv) and water (20 equiv) at -20 °C as optimal conditions afforded the product in 70% yield and 95% *ee*. The cyclization of the same bis-enone with a sub-stoichiometric catalyst loading (entry 2) resulted in comparable result with respect to the stoichiometric reaction (entry 1), however, when the loading is limited to 10% catalyst (entry 3), the enantioselectivity is preserved while the reaction rate seems to decrease. They extended their scope to symmetrical bis-enones bearing electron withdrawing substituents (entries 5,6) and electron donating substituents (entry 4), as well as aliphatic (entry 8) and heteroaromatic substituents (entry 7), and preserved high enantioselectivity and good reaction efficiency. The reaction of unsymmetrical keto-ester (entry 9) resulted in a diminished enantioselectivity and efficiency.

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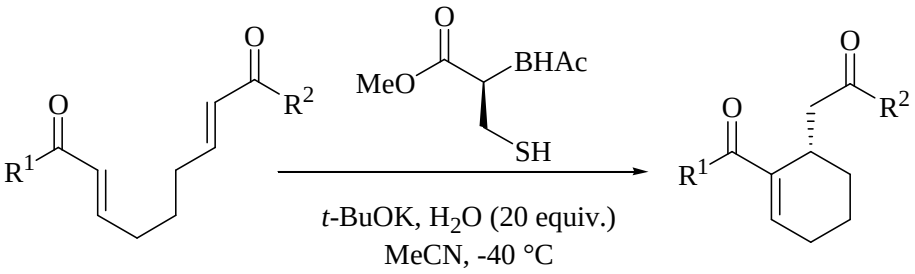
[32] Aroyan, C. E.; Miller, S. J., *Journal of the American Chemical Society* **2006,** *129*, 256.

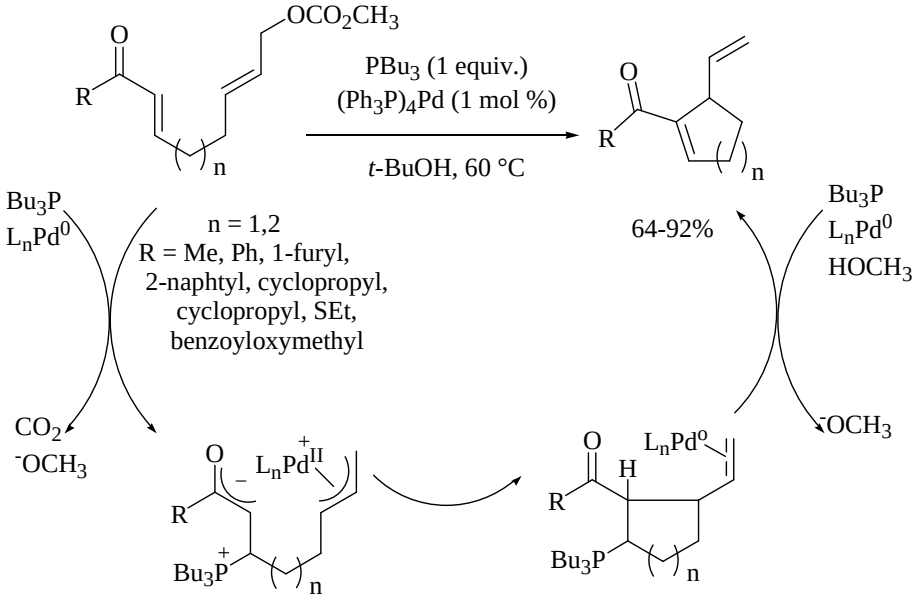
Table 6. Cysteine derivative catalyst for the Rauhut Currier reaction



Entry	R^1, R^2	Catalyst loading [%]	Yield [%]	ee [%]
1	Ph, Ph	100	70	95
2	Ph, Ph	20	75	92
3	Ph, Ph	10	41	91
4	4-$MeOC_6H_5$, 4-$MeOC_6H_5$	100	73	90
5	4-BrC_6H_5, 4-BrC_6H_5	100	70	94
6	4-$NO_2C_6H_5$, 4- $NO_2C_6H_5$	100	71	84
7	2-furyl, 2-furyl	100	54	92
8	Me, Me	100	55	90
9	Ph, CO_2Et	100	66	67

To extend the scope of the RC reaction, several attempts were carried out for the broadening of the repertoire of reacting partners including using non-classical electrophilic partners. Krische et al. described a catalytic enone cycloallylation where separate yet related actions of organic and metallic catalysts combine the nucleophilic features of the RC reaction with the

electrophilic features of the Tsuji-Trost reaction[33] (Scheme 26). In this modified RC example, the reaction of an allylic carbonate and an enone is catalyzed by the action of both stoichiometric amount of PBu_3 and catalytic amount of $(PPh_3)_4Pd$ (1 mol%), where the allyl carbonate is activated through the formation of a π-allyl-Pd complex, and the enone is activated by the conjugate addition of the phosphine, to afford the corresponding 5- and 6- membered ring cycloallylated products in good to excellent yields. They found out that enoates were not reactive under these conditions.



Scheme 26. Catalytic enone cycloallylation

In a following account, Krische and coworkers reported the use of *p*-nitrophenyl substituted vinyl sulfones as highly reactive electrophilic coupling partner with a range of enones and thioenoates[34]. Good to excellent

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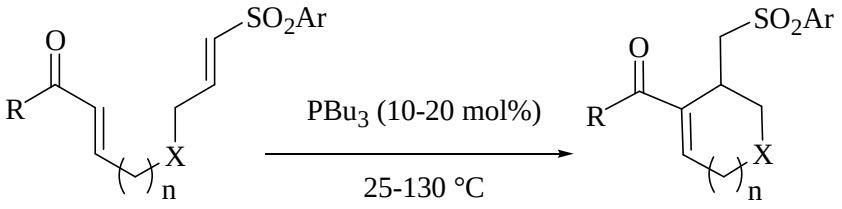
[33] Jellerichs, B. G.; Kong, J.-R.; Krische, M. J., *Journal of the American Chemical Society* **2003,** *125*, 7758.

[34] Luis, A. L.; Krische, M. J., *Synthesis* **2004,** *2004*, 2579.

yields were obtained in all cases using 10-20 mol% PBu_3; and high regioselectivity was observed where the vinyl sulfone unit plays the role of the Michael acceptor constantly (Scheme 27).



n = 0,1
Ar= *p*-$NO_2C_6H_4$
R = Me, Ph, SEt
X= CH_2, NTs

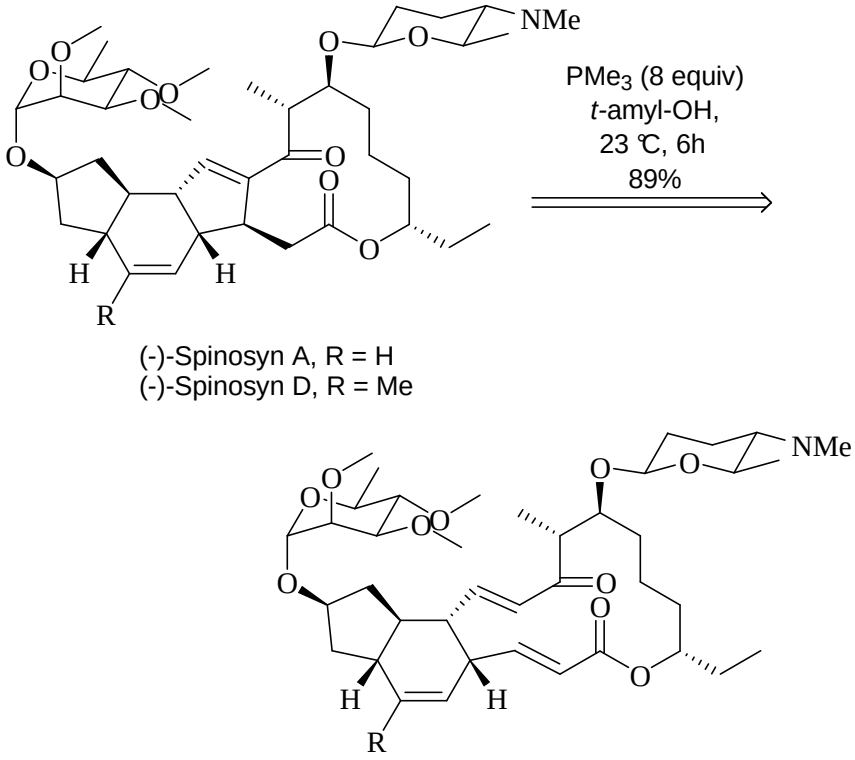
74-97%

Scheme 27. Reaction of *p*-nitrophenyl vinylsulfones as substrates in the Rauhut–Currier reaction

I.2.1 Applications of RC reaction

In view of the capability of the intramolecular RC reaction to provide complex cyclic systems with multiple stereogenic centers in a selective manner, it is now regarded as an interesting synthetic strategy for the assembly of natural products. Roush et al. targeted the synthesis of (-)-Spinosyn via tandem transannular intramolecular vinylogous RC cyclization sequence[35]. They obtained the desired diastereoisomer in high yield (89%) and excellent selectivity (Scheme 28).

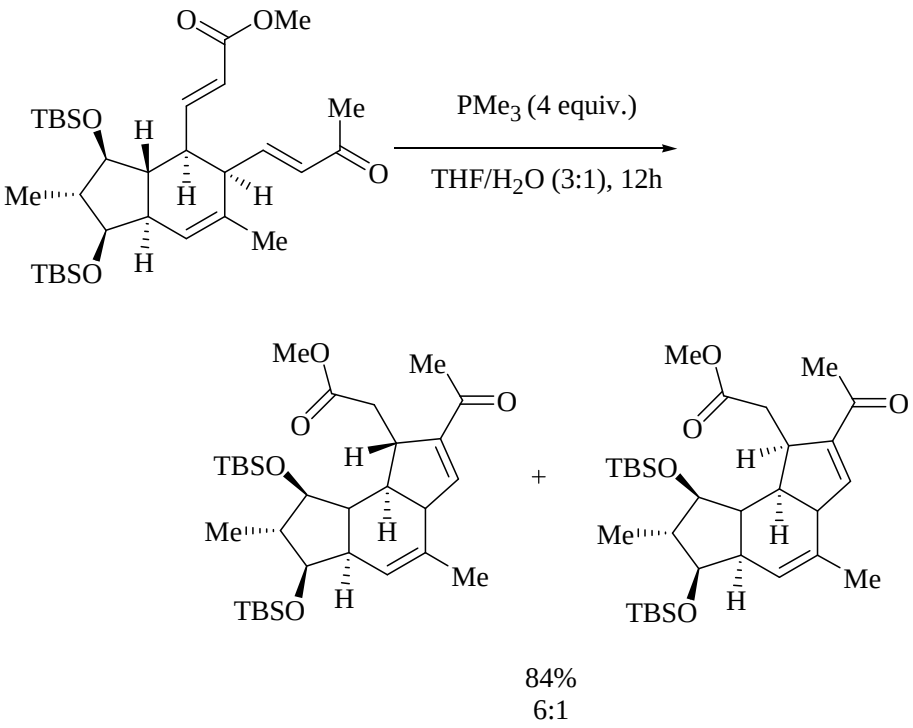
[35] Mergott, D. J.; Frank, S. A.; Roush, W. R., *Organic Letters* **2002,** *4*, 3157.



Scheme 28. Use of the Rauhut Currier reaction in the synthesis of (-)-Spinosyn

In a second report, Roush and coworkers exploited the intramolecular RC reaction to access the central cyclopentane ring of FR182877[36]. The reaction appeared to be solvent and substrate dependent. For the synthesis of the desired regioisomer, they optimized the conditions used and ended up obtaining this isomer as the major one (6:1) when using 4 equiv. of PMe_3 in a mixture of THF/H_2O (3:1) in 68% yield (Scheme 29).

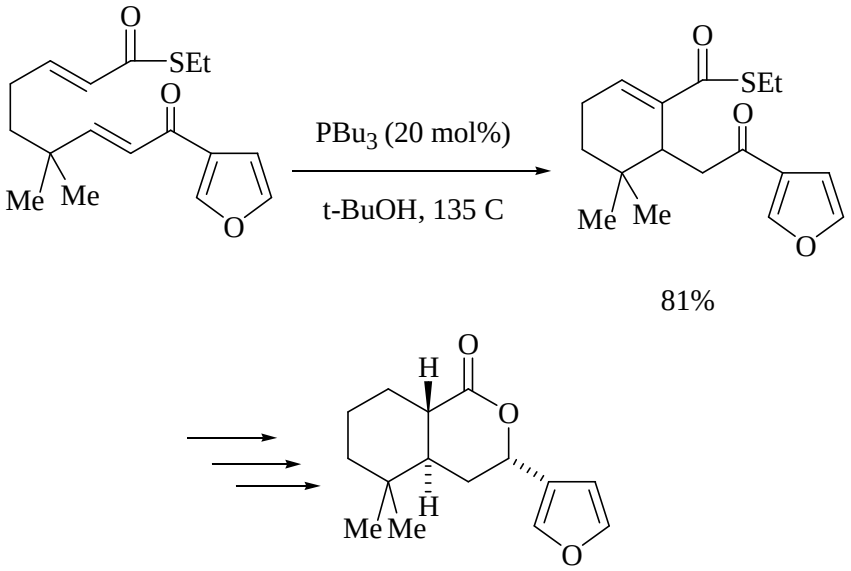
[36] Methot, J. L.; Roush, W. R., *Organic Letters* **2003,** *5*, 4223.



Scheme 29. Rauhut Currier reaction in the synthesis of FR182877

Krische *et al.* also revealed the use of thioenoate-enone substrates in the RC transformation for the synthesis of (±)-Ricciocarpin A[37]. This system showed high reactivity (81%) as well as high chemoselectivity in the production of the cyclized product which is then transformed to the (±)-Ricciocarpin A in 3 steps (Scheme 30).

[37] Agapiou, K.; Krische, M. J., *Organic Letters* **2003,** *5*, 1737.



(±)-Ricciocarpin A

Scheme 30. Use of thioenoate-enone in the Rauhut Currier transformation for the synthesis of (±)-Ricciocarpin A

II. Objectives

Multicomponent asymmetric reactions have shown large developments in the last few decades. The interest in these reactions lies in their ability to assemble a number of units in a single pot via a cascade of reactions. More important, is the selectivity control in such reactions giving access to the construction of a chiral library.

Our laboratory has a history in developing new and efficient catalytic systems using copper complexes for enantioselective tandem reactions[6,38,39]. For instance, the 1,4-reduction/aldolization domino reaction, that involves carbon-carbon bond formation between a Michael acceptor (acrylates, ynamides..) and an electrophile (ketone or aldehyde), has been developed. In the course of this project, our objective is to exploit the expertise we acquired during the development of the previous domino reactions to investigate a route towards polyfunctionalized N-heterocycles, lactams in particular. The importance of such nitrogen heterocycles for pharmaceutical and medicinal interests is well known. Our primary interest is in the construction of polyfunctionalized γ-lactams in a Michael/Michael domino process. The same methodology could be applied for the synthesis of δ-lactams also.

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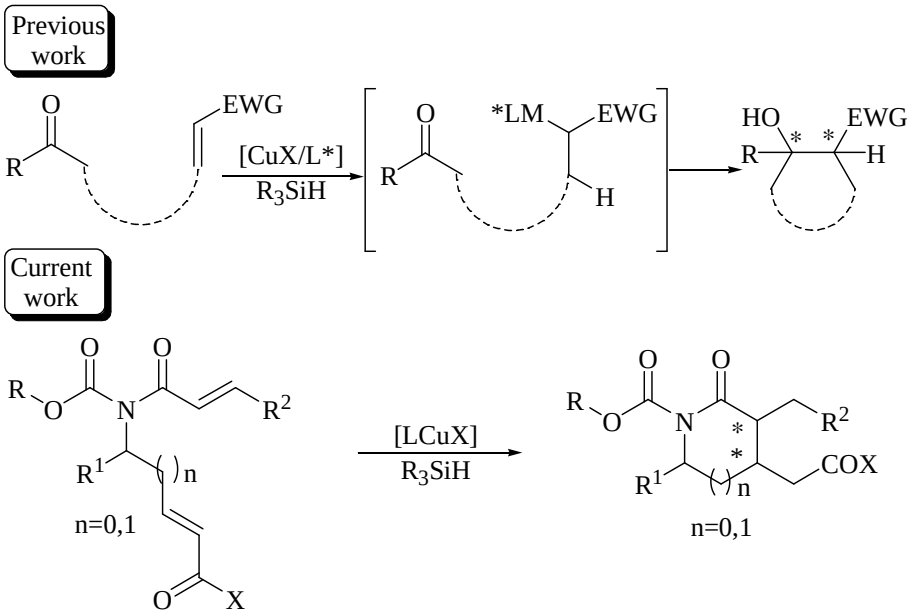
[38] Deschamp, J.; Hermant, T.; Riant, O., *Tetrahedron* **2012,** *68*, 3457; Deschamp, J.; Riant, O., *Organic Letters* **2009,** *11*, 1217.

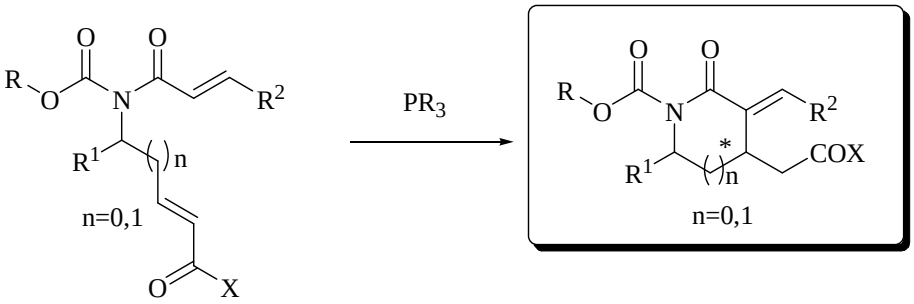
[39] Welle, A.; Díez-González, S.; Tinant, B.; Nolan, S. P.; Riant, O., *Organic Letters* **2006,** *8*, 6059.



Scheme 31. Development of new copper catalyzed tandem reaction

The main key to explore such catalytic systems is to find suitable substrates that could selectively undergo such transformation. Also, the definition of the right combination of ligand and metal complexes is a less easy task to handle. Furthermore, ideally chemoselectivity, regioselectivity, and diastereoselectivity are to be controlled.

On the other hand, these same substrates are susceptible to undergo an organocatalytic transformation, the Rauhut-Currier reaction (Scheme 32). This transformation contributes to the formation of α-methylene-γ-lactams. This type of γ-lactams are known for their interesting broad biological properties as antitumor, anti-inflammatory,...



Scheme 32. Rauhut Currier reaction

III. Results and discussion

III.1Copper catalyzed reductive Michael reaction

The work we discuss in the following section is related to previous studies conducted in our group.

We will therefore briefly explain the catalytic system that was developed and used in our group.

III.1.1 The copper catalytic system

Since the development of the 1,2-reduction of ketones, the use of the catalytic system developed became recurrent[40]. The same system was employed in the development of 1,4-reduction/aldolization reaction of Michael acceptors[6,39,40]. This system involved the use of a phosphine-bearing copper fluoride complex which was prepared according to a modified literature procedure by reacting Cu(II) fluoride with triphenylphosphine in methanol while refluxing.

$$\underset{(1.0\ \text{equiv.})}{CuF_2} + \underset{(3.5\ \text{equiv.})}{PPh_3} \xrightarrow{MeOH,\ \text{reflux, 3h}} \underset{\mathbf{74}}{[(PPh_3)_3CuF.2MeOH]} + Ph_3PO$$

Scheme 33. Preparation of copper catalyst

This complex is usually used in the presence of a diphosphine ligand. The most commonly used ligand in model reactions is BINAP probably because of its easy accessibility in racemic and enantiopure forms. The diphosphine replaces the monophosphine almost irreversibly while delivering a more stable complex that is more resistant to decomplexation/complexation phenomenon, usually witnessed with monophosphines (Scheme 34).

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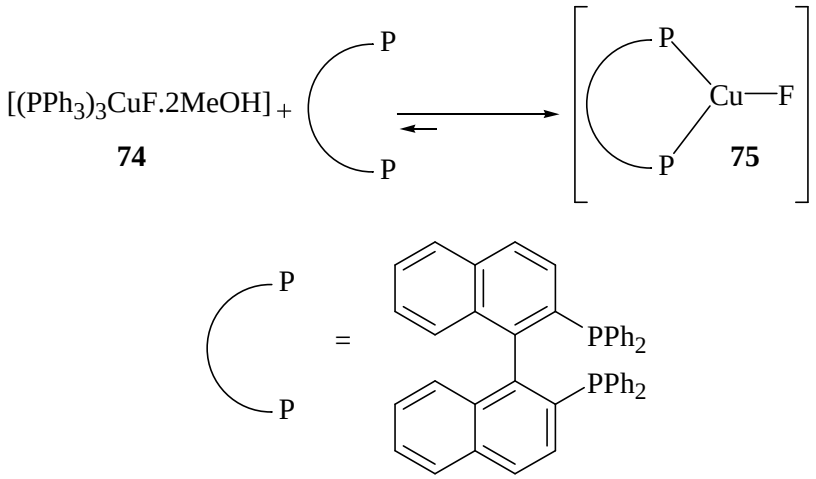
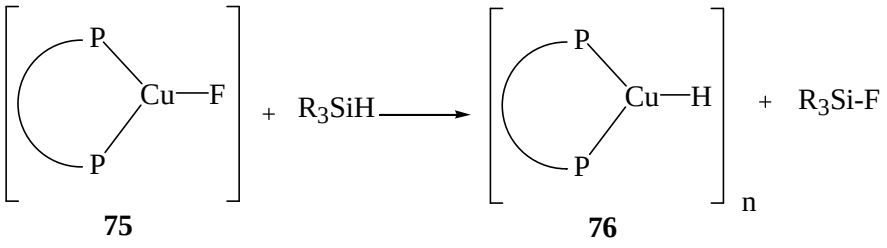
[40] Sirol, S.; Courmarcel, J.; Mostefai, N.; Riant, O., *Organic Letters* **2001,** *3*, 4111.



Scheme 34. Stability of BINAP ligand facing the decomplexation/complexation phenomenon

Without isolation, the diphosphine copper(I) complex **75** obtained *in situ* reacts easily with silanes to form the copper hydride complex **76** (Scheme 35). This complex will expectedly then catalyze the reductive Michael domino process.

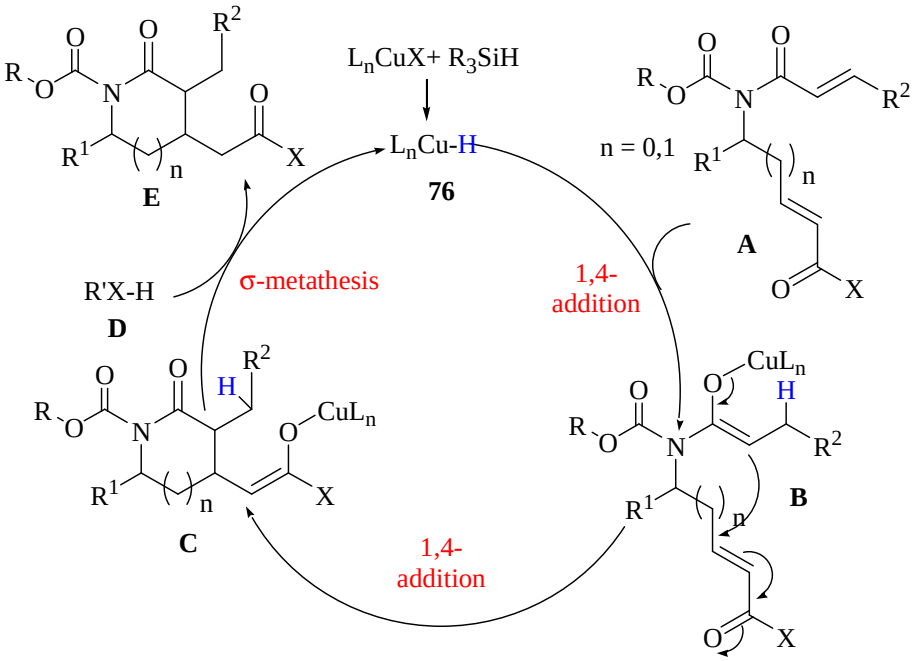


Scheme 35. Formation of copper hydride complexes

III.1.2 Proposed mechanism

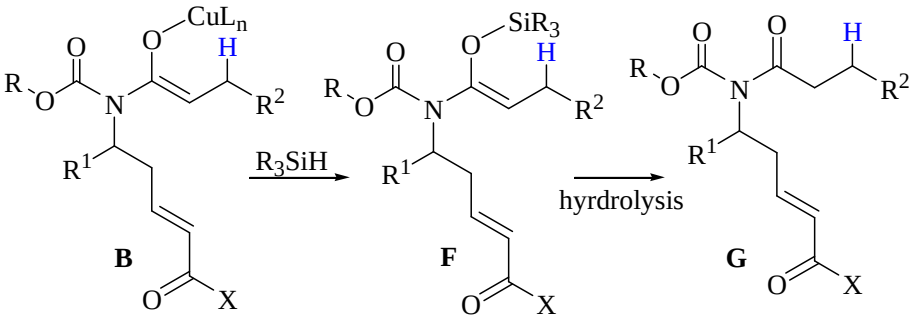
The proposed mechanism for the model reaction is illustrated in Scheme 135. The copper hydride complex **76** is formed *in situ* as mentioned before. Complex **76** will then add in a 1,4-addition fashion to the Michael acceptor **A** on the side closer to the carbamate to form the copper enolate intermediate

B. The copper enolate will subsequently attack intramolecularily the enone on the other terminal of the substrate **A** in a 1,4-addition fashion to form another copper enolate **C**. The quenching of the enolate in the presence of a proton source **D** will simultaneously form the cyclization adduct **E** and regenerate the copper hydride complex to close the catalytic cycle.



Scheme 36. Proposed mechanism

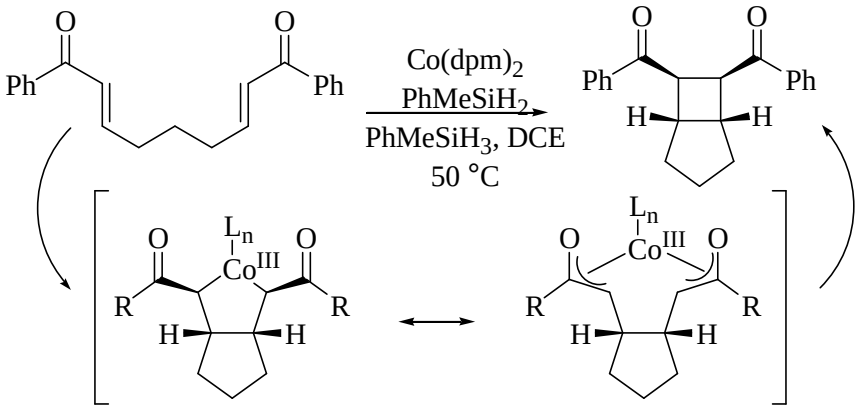
Although the mechanism proposed above is technically valid, the probability of some secondary reactions occuring, could influence the outcome of the reaction. For instance, if the reaction of the copper enolate **B** with the enone is not favored, **B** will prefer exchanging with the silane to form the silyl enol ether **F**. This silyl enolate could accumulate until the end of the reaction and after hydrolysis, it delivers the 1,4-reduction product **G** (Scheme 37).



Scheme 37. Hydrolysis of silyl enolate derivative

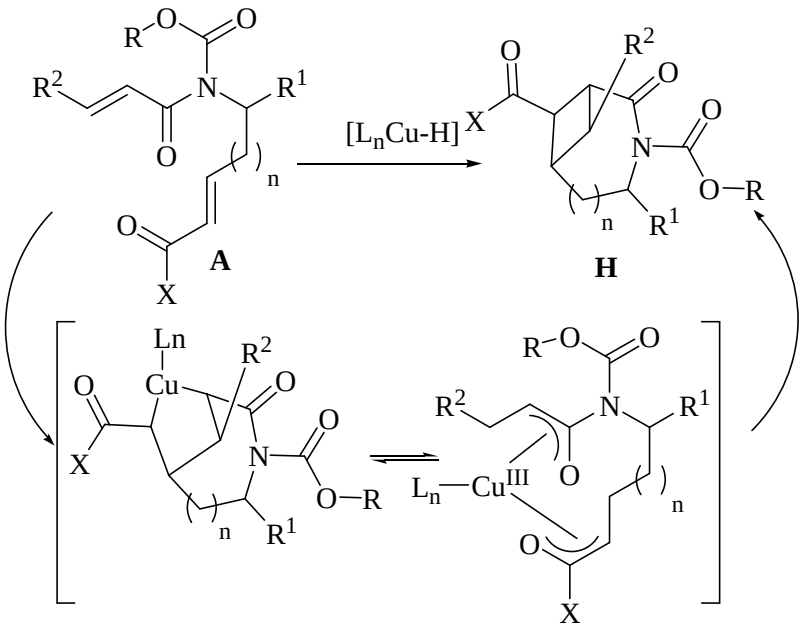
Another secondary reaction could occur as reported by Krische *et al.* [16,17] This side reaction was reported when using a cobalt catalyst for the cycloreduction of bis-enones. It provided the [2+2] cycloaddition product were the mechanism is no longer a hydrometallative one, but rather an anion radical mechanism (Scheme 38). Also, Krische later reported a mechanism with a copper catalyst.When using Me_2CuLi-LiI in sub catalytic amount (25 mol%), they obtained the [2+2] cycloaddition product, whereas the use of a stoichiometric amount of the catalyst provides the tandem alkyl conjugate addition-Michael cyclization product[41]. They concluded after carrying out electrochemically induced transformations and obtaining the same [2+2] cycloadducts, that the anion radical pathway is plausible. Thus, they considered the intermediacy of transition metal anion radicals in addition to metallo-oxy-π-allyls.

[41] Yang, J.; Cauble, D. F.; Berro, A. J.; Bauld, N. L.; Krische, M. J., *The Journal of Organic Chemistry* **2004,** *69*, 7979.



Scheme 38. [2+2] cycloaddition reaction

In the case of our substrate, we suppose the formation of a bridged cycle if possible following the same β-coupling mechanism (Scheme 39).

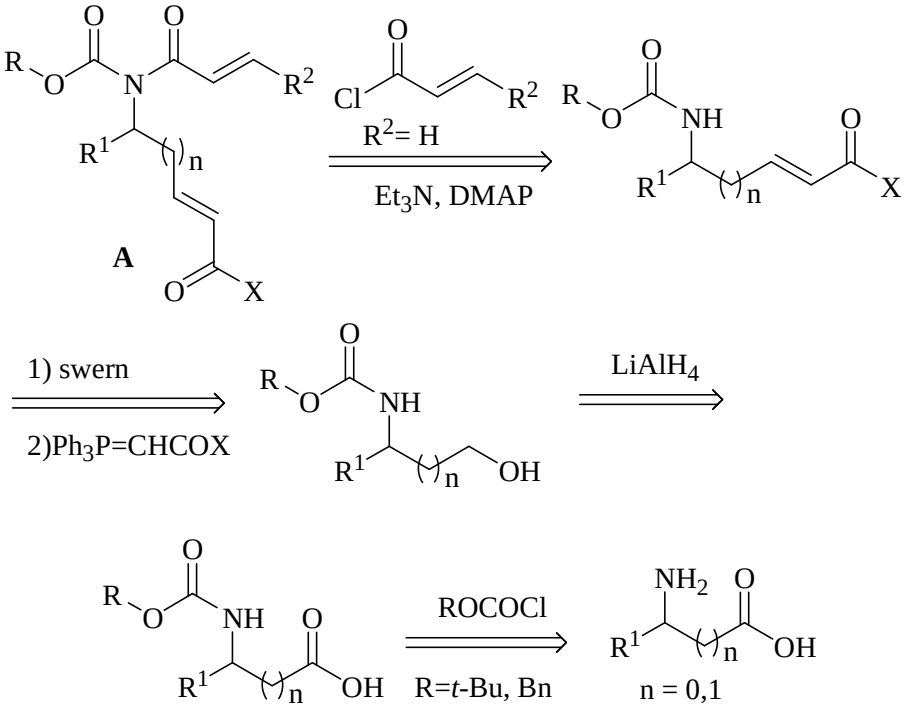


Scheme 39. Possible side reaction

III.1.3 Synthesis and Catalytic tests

III.1.3.1 Substrate synthesis

The substrates of structure similar to the model **A** are anticipated to be synthesized through a limited number of steps starting from α- or β-amino acids, or the corresponding amino alcohols, that are commercially available or easily accessible by simple synthesis steps (Scheme 40). The protecting group on the nitrogen atom would render the enone more electrophilic due to its withdrawing character. This would direct the first conjugate addition towards the enone next to the nitrogen atom and thus control the regioselectivity of the addition reaction and consequently deliver the desired products.



Scheme 40. Retrosynthesis of substrates for the reductive Michael cyclization

As a model substrate for the desired domino reaction, we launched the synthesis of substrate **77** (Figure 4). We believed this type of substrate to undergo the reductive Michael addition a provide the desired products selectively.

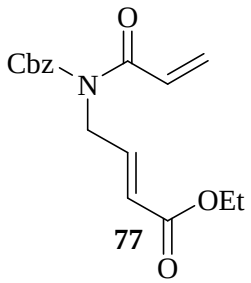
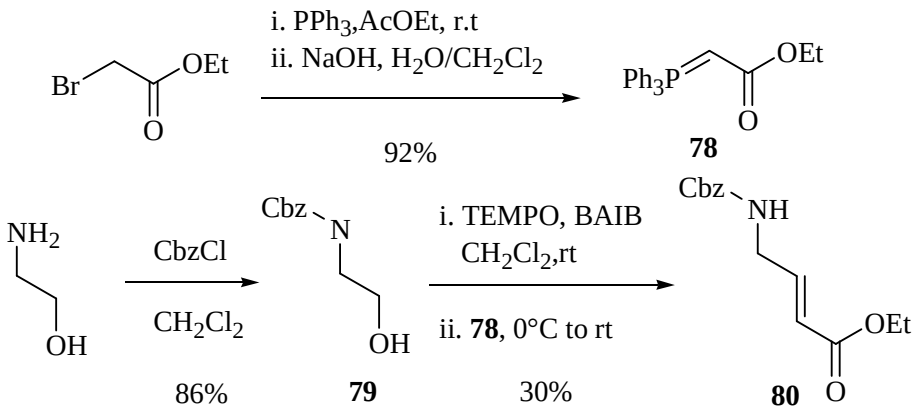


Figure 4. Model substrate for the reductive Michael addition

Starting from ethanol amine, and following some literature methods, the amine was first protected by a Cbz group, and product **79** was obtained in pure form in 86% yield. The protected aminoalcohol then underwent a mild oxidation using TEMPO and BAIB to what is believed is the corresponding aldehyde, which was not isolated. This latter was expected to react with the phosphorane **78** to provide the Wittig product: enoate **80** in 30% isolated yield.[42] (Scheme 41)

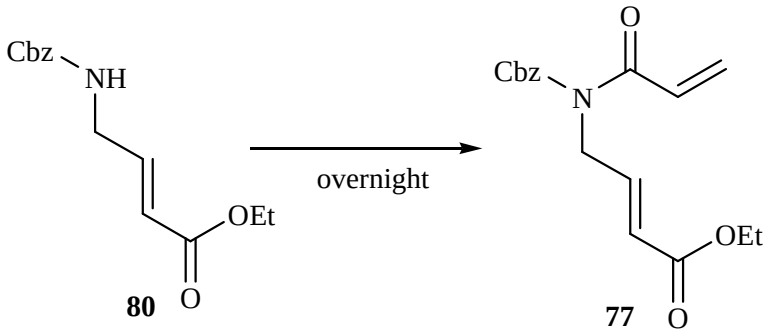
[42] Werkhoven, T. M.; van Nispen, R.; Lugtenburg, J., *European Journal of Organic Chemistry* **1999,** *1999*, 2909; Vatèle, J.-M., *Tetrahedron Letters* **2006,** *47*, 715; De Cola, C.; Manicardi, A.; Corradini, R.; Izzo, I.; De Riccardis, F., *Tetrahedron* **2012,** *68*, 499.



Scheme 41. Preparation of enoate **80**

At this stage several experiments were realized for the acryloylation of the protected amine group. However, no successful formation of the desired product occurred (Table 7).

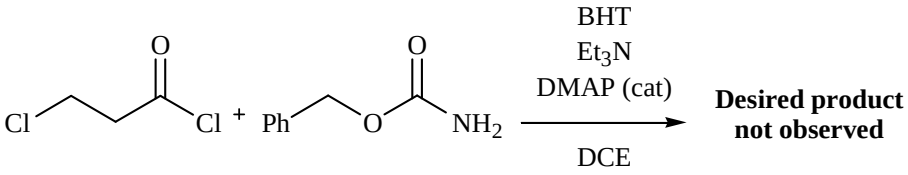
Table 7. Acryloylation of protected amine



Entry	Conditions	Product
1	**i.** NaH, THF, 0°C-r.t. **ii.** Acryloyl chloride, 0°C-r.t.	Degradation of starting material
2	**i.** DMAP, Et_3N, CH_2Cl_2, r.t. **ii.** Acryloyl chloride, 0°C-r.t.	Degradation of starting material
3	**i.** DMAP, DIPEA, CH_2Cl_2, r.t. **ii.** Acryloyl chloride, 0°C-r.t.	Recover starting material
4	**i.** DMAP, Et_3N, THF, r.t. **ii.** Acryloyl chloride, 60°C	Recover starting material
5	**i.** KHMDS, THF, -78°C-0°C **ii.** Acryloyl chloride, 0°C-r.t.	Degradation of starting material
6	**i.** n-BuLi, THF, , -78°C **ii.** Acryloyl chloride, -78°C-r.t.	Well defined unidentified product

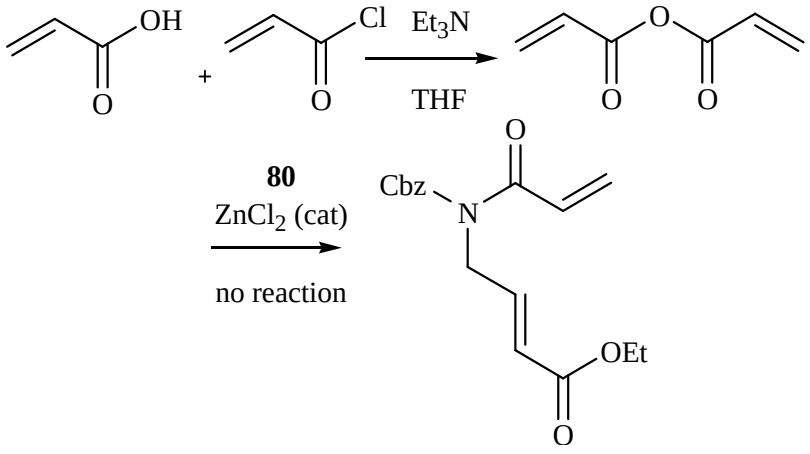
Other experiments were carried out for the acryloylation of the amine partner in earlier steps. The acryloylyation of benzoyl carbamate for

instance was reported in a patent. We reproduced the same conditions that were used, however, without any success.[43] (Scheme 42)



Scheme 42. Acryloylation of benzoyl carbamate

Another test was carried out for the acryloylation of the product **80** using the acryloyl anhydride synthesized *in situ* followed by adding the carbamate. This procedure was reported for the *N*-acylation of carbamates[44]. Also, no reaction took place and the starting material is recovered (Scheme 43).



Scheme 43. Zn(II) catalyzed acryloylation of **80**

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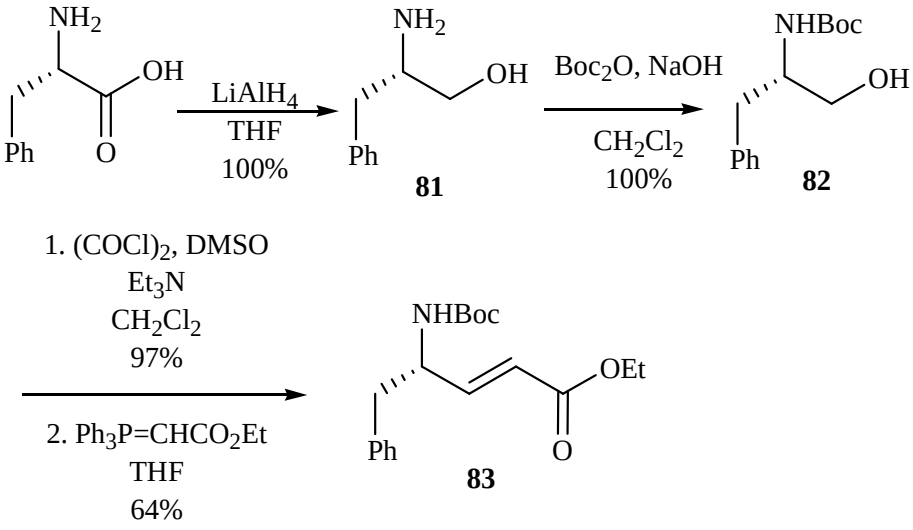
[43] Kaiube, G.; Arutaa, R.; Efu, G. G. PRODUCTION OF ACRYLOYL CARBAMATE OR ACRYLOYLUREA DE 19523169, C1 19.960.926, 1996.

[44] Raji, R. C.; Bodugam, M.; Rao, Y. S., *ARKIVOC* **2008,** *ii*, 250.

Taking into account the failure in all the acylation, the low yield for the oxidation-Wittig step, and the oily nature of intermediates, we decided to change the starting material.

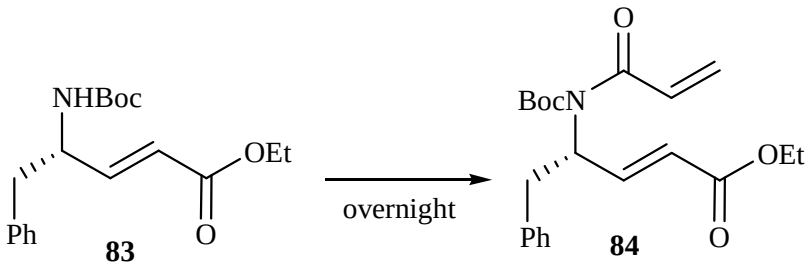
We chose to start with an amino acid substrate, L-phenylalanine, and chose a different protecting group on the nitrogen atom: tert-Butyloxycarbonyl protecting group (Boc) (Scheme 44). The amino acid is reduced to the corresponding amino alcohol **81** in total conversion. The amine group is protected with Boc group to give the Boc-amino alcohol **82** in total yield, which is oxidized using the swern oxidation to yield the corresponding aldehyde in quantitative yield. This aldehyde is further reacted with the phosphorane without any purification to yield the Wittig product **83** in 64% yield. . It is noteworthy to mention that no purification was conducted for all the products preceding the Wittig reaction step since all the products were obtained in pure form after the work ups required.



Scheme 44. Synthesis of substrate **83**

Similar to the previous methodology, several trials including the conditions used in the previous trials were conducted to acylate the protected amine group. However, the acylation of the protected amine could not be carried out using conventional amine acylation methods, likely due to the low reactivity due to the presence of the carbamate group rendering the nitrogen atom less nucleophilic. In all the tests carried out the starting material we recovered, and reaction only took place in the case of *n*-BuLi where we observe traces of the desired product (Table 8, entry 3).

Table 8. Acylation of Boc-amine **83**

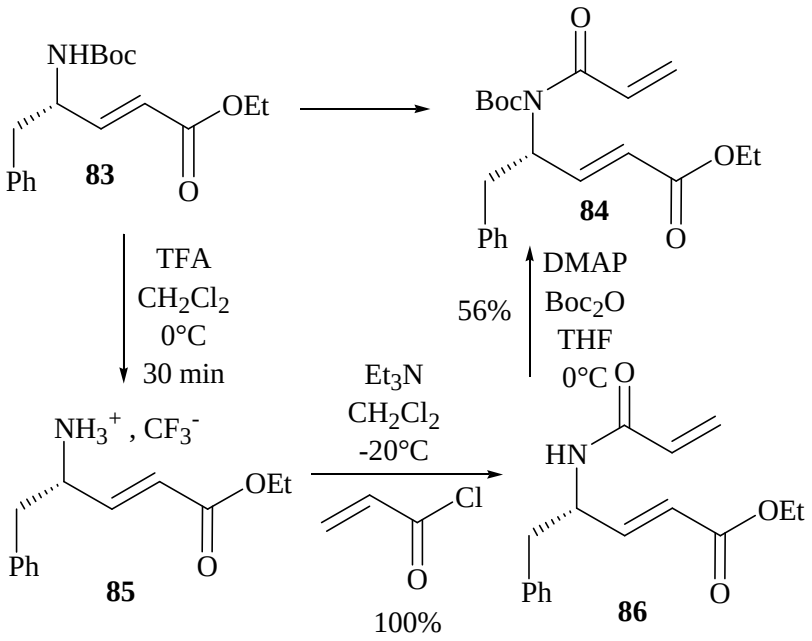


Entry	Conditions	Product
1	**i.** DMAP, Et_3N, CH_2Cl_2, r.t. **ii.** Acryloyl chloride, 0°C-r.t.	Recovered starting material
2	**i.** DMAP, DIPEA, CH_2Cl_2, r.t. **ii.** Acryloyl chloride, 0°C-r.t.	Recovered starting material
3	**i.** n-BuLi, THF, , -78°C **ii.** Acryloyl chloride, -78°C-r.t.	Traces of product + starting material

After these failures in acylating the protected amine group, an alternative strategy was adopted. Since the acylation of a carbamate group is difficult

because of its weak nucleophilicity, the deprotection of the amine group was believed to facilitate the acylation.

The deprotection was carried out using trifluoroacetic acid in dichloromethane at 0 °C. The crude product **85** was then directly acylated with acryloyl chloride at -20 °C in the presence of Et_3N and the product **86** was recovered in total conversion (Scheme 45). The protection of the acylated amine group was not an easy task. While working in small scales (1 mmol), up to 56% yield of the desired product **84** was obtained after purification (Table 9, entry 2). Upon increasing the scale to 10 mmol, the yield drops to 30% at best. So we decided to keep working on small scales in multiple reactions, assembling the crudes prior to purification. The structure of product **84** was verified by mass and NMR spectroscopies and found to be as anticipated.



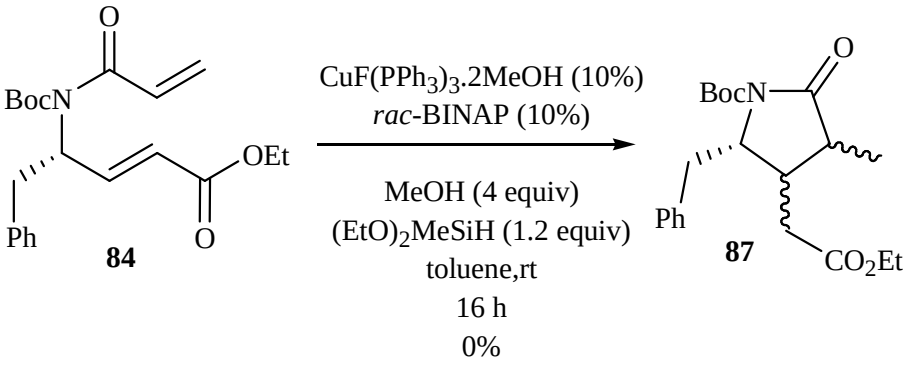
Scheme 45. Acryloylation of Boc-amine **83**

Table 9. Boc protection of amide **86**

Entry	Scale	Solvent	yield
1	0.47 mmol	THF	48-52%
2	1.17 mmol *10 times	THF	56%
3	10 mmol	THF	23%
4	0.5 mmol	MeCN	50%
5	10.2 mmol	MeCN	30%

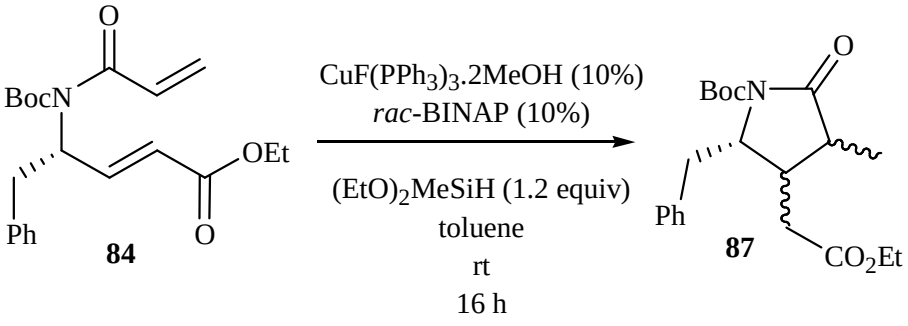
III.1.3.2 Catalytic tests

Taking into consideration the mechanism we proposed earlier for the double Michael addition reaction, we designed a catalytic test involving $CuF(PPh_3)_3.2MeOH$ as catalyst, *rac*-BINAP as the ligand, EtO_2MeSiH as a hydride source, and MeOH as proton donor (Scheme 46). Despite our efforts, the desired product **87** was not observed, and the substrate **84** was recovered. MeOH was suspected to 'poison' the catalyst, as in no example in the literature mentioned above, a proton source was used.



Scheme 46. Catalytic test for the cyclization of substrate **84**

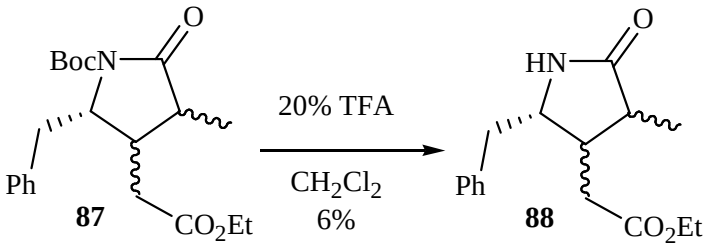
We therefore reproduced the same catalytic test without the use of MeOH, observing total consumption of the starting material and formation of a new product. Due to its weak revelation, the product was difficult to locate on a TLC plate, and we were unable to isolate the product in pure form (Scheme 47). The NMR of the crude product suggests the disappearance of both double bonds and the formation of a new product with well-defined peaks but also appearance of another product. A doublet at δ=1.03-1.05 ppm is thought to be the peak referring to the CH_3 α- to the lactam carbonyl.



Scheme 47. Catalytic reductive cyclization of substrate **84**

Due to difficulties in isolating the anticipated cyclization product **87**, we removed the Boc group using 20%TFA/CH_2Cl_2 on the crude product. The isolation of the deprotected lactam **88** was possible afterwards in 6% yield

(Scheme 48). The rest was the degradation of product **84** into the deprotected forms of substrates **83** and **86**.



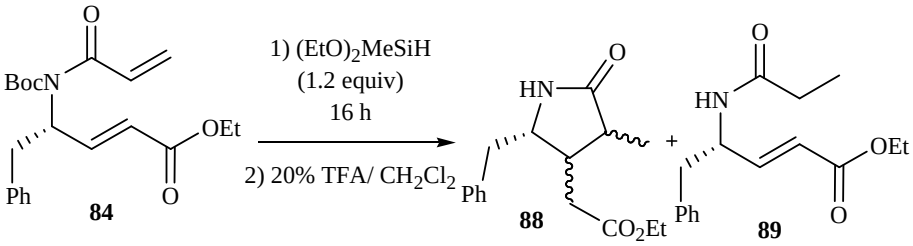
Scheme 48. Deprotection of the product **87**

The fact the MeOH has blocked the reaction before lead us to think that the original $CuF(PPh_3)_3.2MeOH$ catalyst may poison the reaction. Three other catalytic systems were therefore designed (Table 29). The first catalytic system comprises the same reaction conditions that Lipshutz used for the achiral conjugate reduction using a modified stryker reagent that is generated *in situ*[45]. The starting material has been totally consumed. Several portions of the chromatography column were separated but none was clear enough to suggest which product was obtained. However, The NMR spectrum is different than that of the previous one suggesting that we did not obtain the cyclization product **87**. The second catalytic system consisted of the use of an NHC copper complex as a catalyst. We noticed that the conversion was not total, however the NMR spectrum did not resemble that of the anticipated cyclized product **88**. The fractions obtained suggested the degradation of the starting material into products **86** and **83** without the Boc group in addition to an unidentified product. The third test was a reproduction of the $Cu(PPh_3)_3.2MeOH$ catalyst and the *rac*-BINAP ligand, but instead of adding the ligand in one portion of 10 mol%, two portions of 5

[45] Baker, B. A.; Bošković, Ž. V.; Lipshutz, B. H., *Organic Letters* **2007,** *10,* 289.

mol% catalyst/5 mol% ligand/silane (1.2 equiv.) were added. The consumption of the starting material was total and the cyclized product was isolated in 11% yield along with a side product **89** that is thought to be the 1,4-reduction of the enone **84**.

Table 10. Copper catalytic systems for the reductive cycloaddition reaction

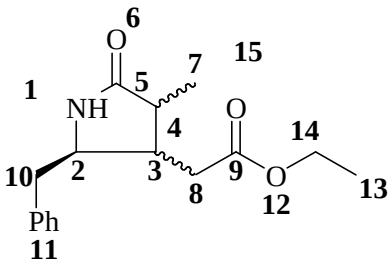


Entry	Copper	Ligand	solvent	Yield 85 [%][c]	Yield 86 [%][c]
1[a,b]	$Cu(OAc)_2.H_2O$ (5%)	DPPBz (2%)	*t*-BuOH	-	-
2	IMesCudbm (5%)	-	toluene	-	12
3	$CuF(PPh_3)_3.2MeOH$ (5% * 2)	*rac*-BINAP (5% * 2)	toluene	11	5

[a] 2 equiv. of silane was used.[b] no deprotection.[c] isolated yield.

Product **88** was characterized by NMR and mass spectroscopy. The peaks were attributed to their corresponding protons (Figure 5). We do not detect the presence of a second diastereoisomer. The NOE experiments carried out did not provide enough information for the identification of the exact

diasteriomeric nature of the isolated molecule. Trials to obtain single crystals were unsuccessfull.



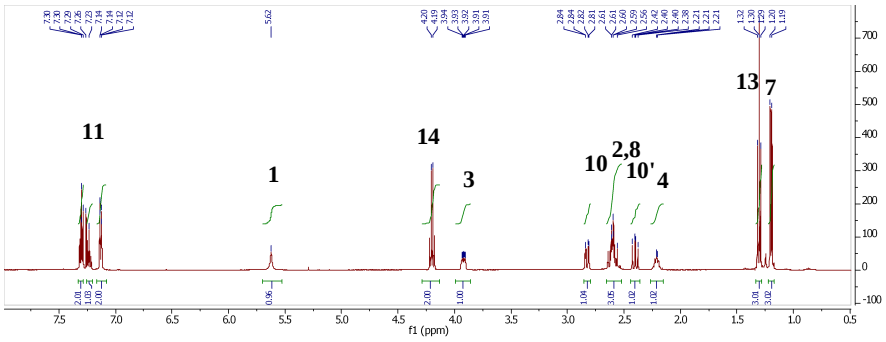
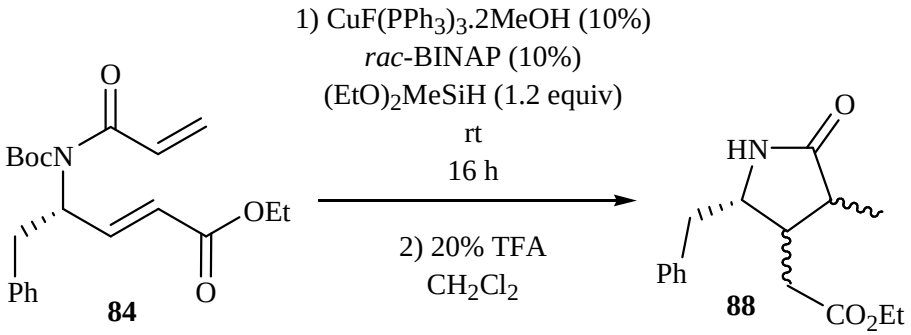


Figure 5. ^{1}H NMR of the product **88**

In order to improve the yield, we carried out some optimization tests to find the perfect combination of the conditions needed for an efficient reductive cyclization. To avoid the purification of all the experiments, an internal standard: 1,4-dinitrobenzene was used in a precise amount to quantify the yields. The product **88** peak δ= 3.9-3.95 was used as a reference for the quantification. Quantification of the remaining starting material is difficult since we deprotect the crude product before adding the internal standard. The starting material will therefore also be deprotected. However, before the deprotection of the crude product we examine the NMR to detect the degree of conversion of the starting material.

The first tests were carried out changing the nature of the solvent (Table 11). In both cases where toluene and THF were used, the substrate **84** was totally consumed, however, when CH_2Cl_2 was used as the solvent, the conversion was not total. However, the quantification of the remaining amount was not possible as explained before.

Table 11. Solvent effect

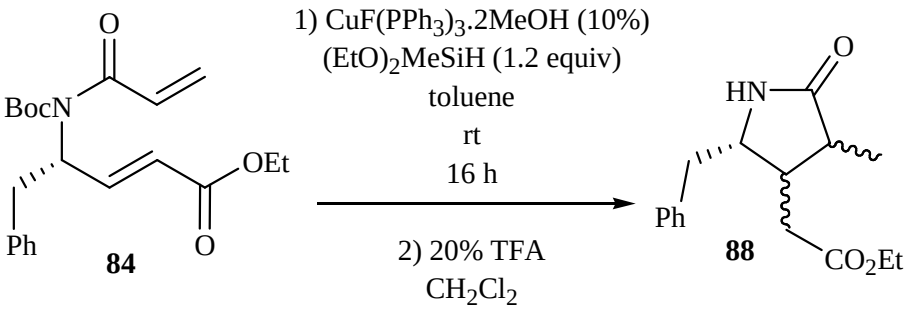


Entry	Solvent	NMR yield	Conversion 84
1	toluene	11%[a]	Total conversion
2	THF	12 %	total conversion
3	CH_2Cl_2	8%	conversion not total

[a] isolated yield

Variation of the ligand only showed a very small effect on the yield (Table 12). The use of D*t*BPF does not clearly show the formation of the desired product. Reaction without adding a specific ligand did also yield the product in 6%.

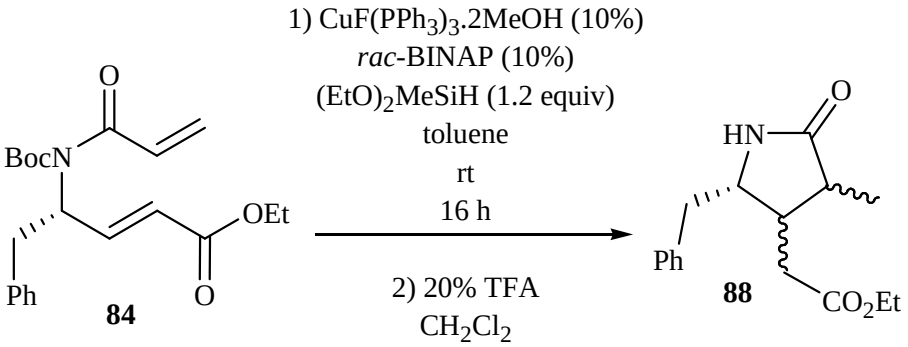
Table 12. Ligand effect



Entry	ligand	NMR yield	Conversion 84
1	dpePhos	6%	conversion not total
2	XantPhos	8%	total conversion
3	DPPF	8%	total conversion
4	D*t*BPF	?	conversion not total
5	-	6%	conversion not total

The addition of an additive for the activation of the copper catalyst does not affect the reaction (Table 13). In the case of KO*t*Bu, the product formation was unclear.

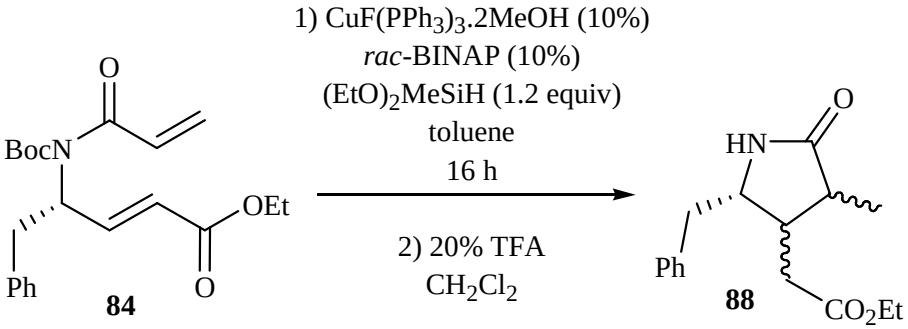
Table 13. Additive effect



Entry	20% additive	NMR yield	Conversion 84
1	KOtBu	?	total conversion
2	NaOtBu	8%	conversion not total

The effect of temperature, was studied conducting two reactions respectively at 0 °C and 45 °C. We noticed that the reaction at lower temperature (0 °C) slightly increased the yield. The conversion was not total in neither cases.

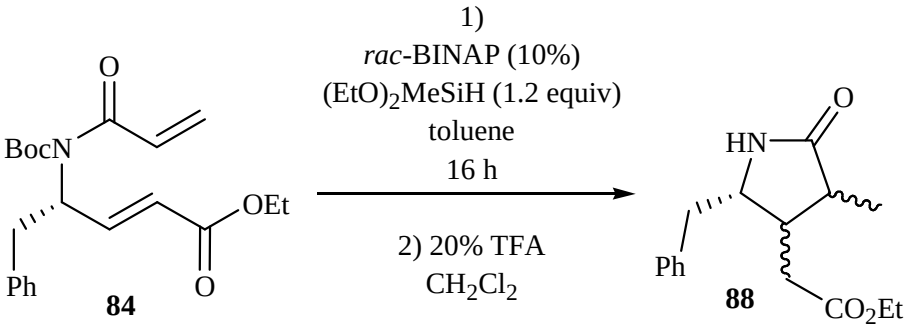
Table 14. Temperature effect



Entry	T °C	NMR yield	Conversion 84
1	0	9%	conversion not total
2	45	7%	conversion not total

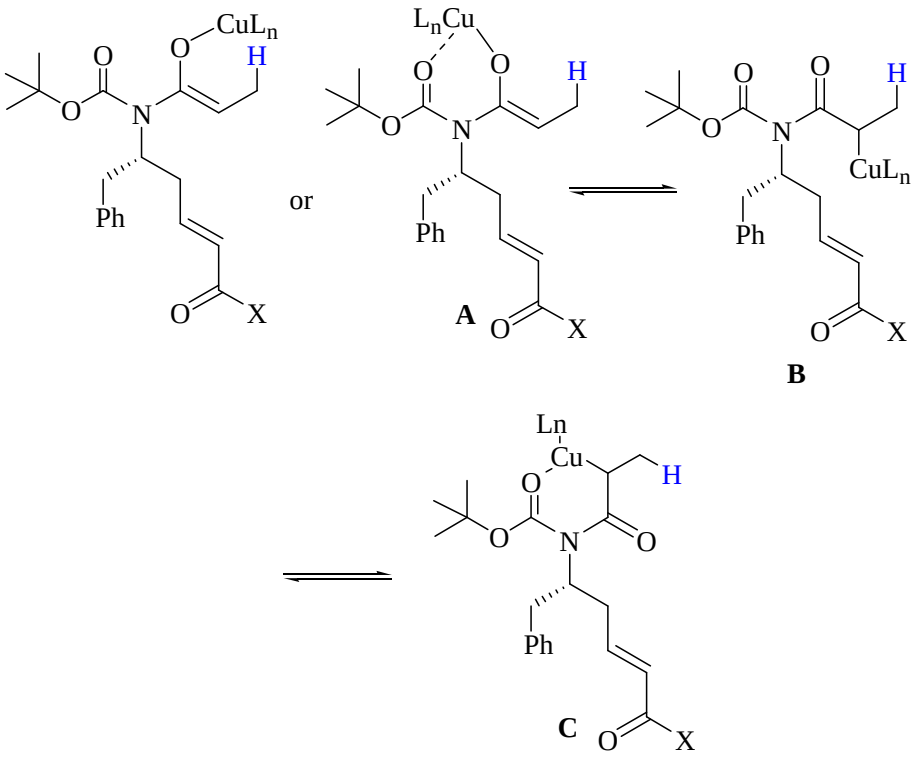
Finally the variation of the copper source was studied (Table 15). Several copper sources were studied along with the *rac*-BINAP ligand. The use of Stryker's complex as the copper source slightly increased the yield. The yield is also slighlty higher when we use Stryker's complex in stoichiometric amount. The NHC copper complex IMesCuDBM and the tetrakis copper complex $Cu(CH_3CN)_4PF_6$ did not provide product formation.

Table 15. Copper source effect



Entry	Copper Source (10%)	NMR yield	Conversion 84
1	$Cu(CH_3CN)_4PF_6$	no reaction	starting material
2	Stryker	8%	total conversion
3	Stryker (stoichiometric)	9 %	total conversion
4	$Cu(OAc)_2.H_2O$	6%	total conversion
5	IMesCudbm	no product	conversion not total

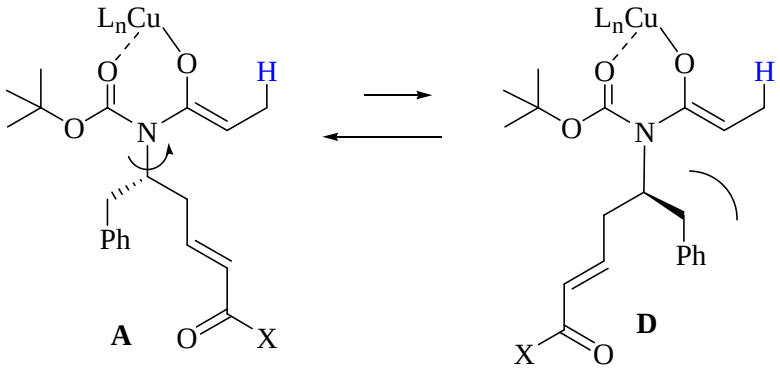
To suggest a reason for the low yield of the cyclization product, we proposed a model that may explain the formation of certain intermediates that blocks the cyclization process to take place (Scheme 49).



Scheme 49. Possible formation of intermediates during the first Michael addition

Proposing that after the addition of the copper hydride on the more electrophilic double bond, a C-enolate **B** may form. This C-enolate is capable of formaing a stable intermediate **C** that may turn out to be weakly reactive and highly stable and thus prevent the cyclization reaction. Instead, it is more likely that we might obtain the mono-reduction product, which is the case in table 29 upon the use of IMesCudbm as a catalyst. If the intermediate **C** is stable enough, its presence might be verified by NMR at low temperature, where the proton on the β-position should have different shifts in intermediates **B** and **C**. However, this does not rule out the presence of an O-enolate intermediate (Scheme 50). In case of the formation of

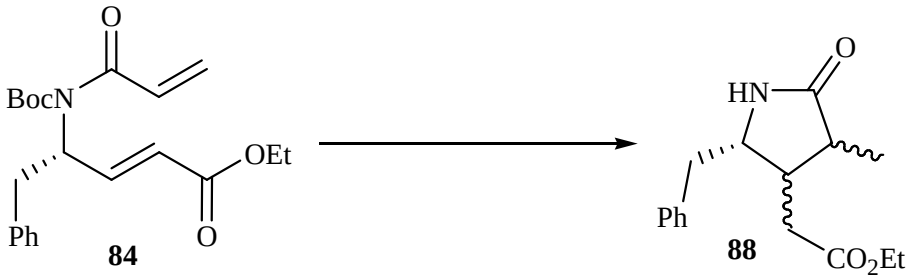
conformers **A** and **D**, and that the conformer **A** is disfavored due to steric effect of the Boc group, the equilibrium will shift towards the formation of intermediate **D**. The steric effect present on the right of the intermediate **D** might prevent the cyclization process and favor the monoreduction. To overcome this problem we could take into consideration the use of other protecting groups with smaller size.



Scheme 50. O-enolate conformers.

In addition to the previous tests that we performed, we decided to carry out some experiments with other metal complexes that were previously reported to induce a double Michael addition (Table 16). Co, Ni, and In catalysts were used for this goal. Unfortunately, in all the cases studied , we did not observe any formation of the product desired. In the cases of Co and In, the starting material was recovered and no product formation was detected. However, in the case of Ni, we observed the formation of a mixture of two products where one of them seems to be the product of the Michael addition of an ethyl group to the double bond. The mass spectroscopy favors this proposition although the NMR is not totally clear.

Table 16. Reductive cycloaddition using other metal complexes

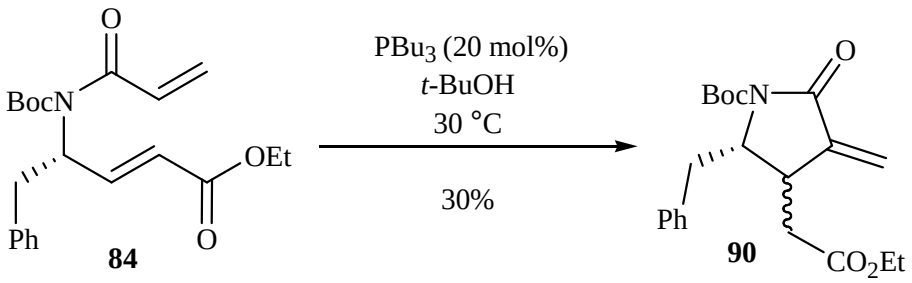


Entry	Conditions	Product
1	**1)** $In(OAc)_3$(10%), $PhSiH_3$ (1 equiv.), THF/EtOH, reflux 8.5h **2)** 20% TFA/CH_2Cl_2	Recovered starting material
2	**1)** $Co(dpm)_2$(5%), PhSiH3 (2.4 equiv.), DCE, rt, overnight **2)** 20% TFA/CH_2Cl_2	Recovered starting material
3	**1)** $Ni(acac)_2$(5%), Et_2Zn (2 equiv.), THF, 0°C-rt, 1h **2)** 20% TFA/CH_2Cl_2	Formation of 2 unidentified products

The results obtained until now are quite encouraging for the development of an efficient catalytic system that could provide the desired product. Meanwhile, the substrate used for this reaction is an interesting substrate for other types of reactions as will be shown below.

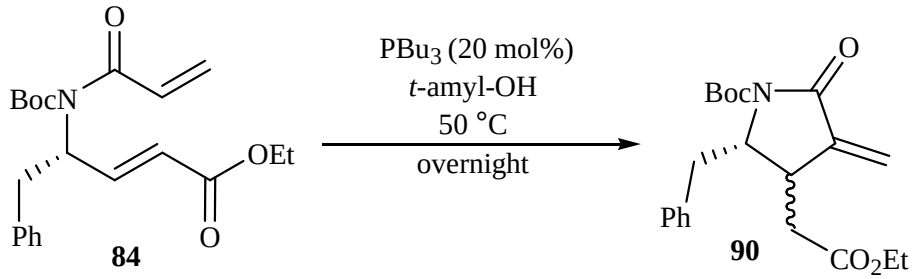
III.2 The Rauhut-Currier reaction

The substrate structure indicated the possibility of reaction under the Morita-Baylis-Hillman conditions. The Rauhut-Currier reaction, also known as vinylogous Morita–Baylis–Hillman reaction, is a reaction between two electron deficient alkenes under nucleophilic catalyst conditions. The first test we carried out utilized PBu_3 to catalyze this reaction in *t*-BuOH and the desired product **90** is obtained in 30% yield and verified by mass and NMR spectroscopy.



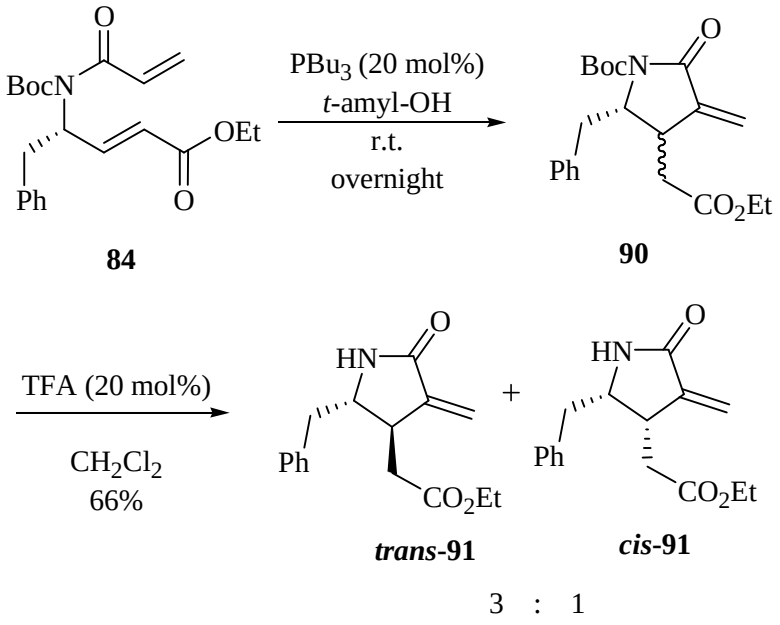
Scheme 51. Rauhut Currier reaction using PBu_3 in *t*-BuOH

The difficulty in handling *t*-BuOH, and the low yield lead us to changing the solvent used to the *t*-amyl alcohol which was frequently used in literature. We first reproduced the conditions used by Krische *et al.*[28], i.e. PBu_3 in *t*-amyl alcohol at 50°C, but we did not obtain any product after 16 h. The NMR spectrum of the crude product however showed total degradation of the starting material.



Scheme 52. Rauhut Currier reaction using PBu_3 in *t*-amyl-OH at 50°C

We then carried out the reaction at room temperature overnight, and after the deprotection of the crude product we obtained the desired 5-membered ring **91** in 66% yield with a trans:cis /3:1 diastereoselectivity (Scheme 53). The products are verified by NMR and mass spectroscopy.



Scheme 53. Rauhut Currier reaction using PBu_3 in *t*-amyl-OH

Using NOE-DIFF experiments we were able to attribute the stereoisomers and verify the structure. We can see that in the *trans* stereoisomer the

enhancement percentage between protons 10 and 12 is very small whilst in the *cis* isomer it is between 10-12%.

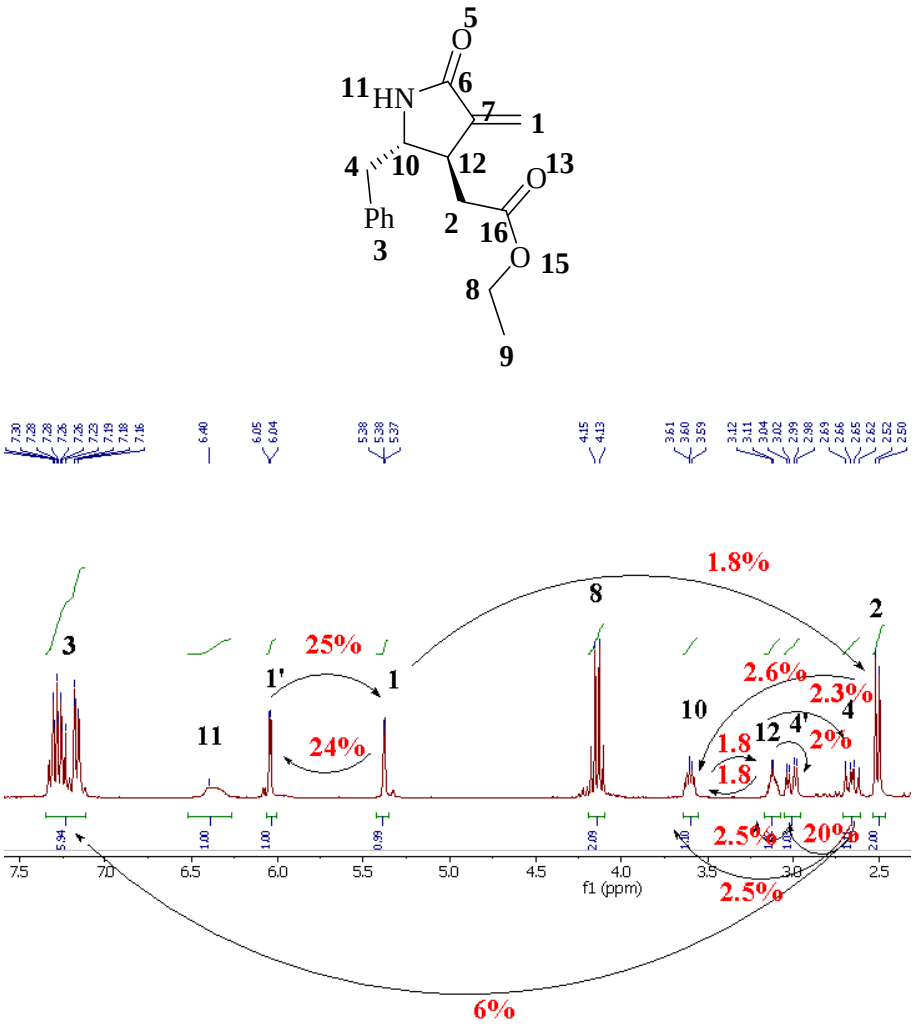


Figure 6. NOE-DIFF of *trans*-**91**

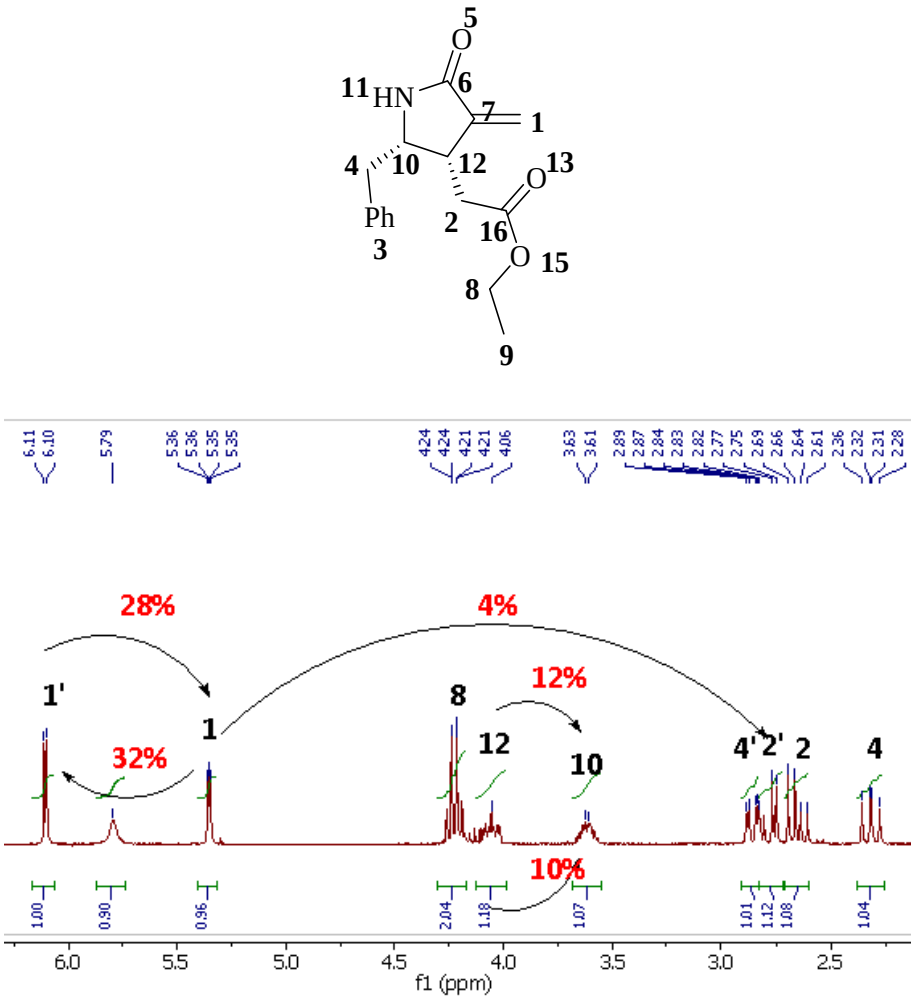
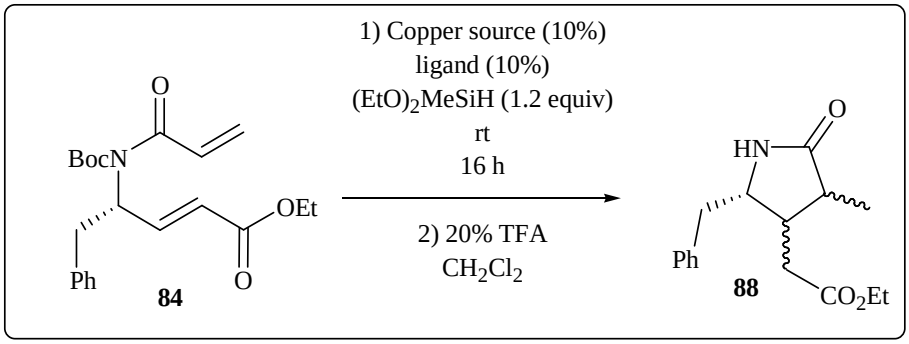


Figure 7. NOE-DIFF of *cis*-**91**

In view of these interesting results that permit the formation of α-methylene-γ-lactams, we are encouraged to pursue this project and study the different aspects for the optimization of this reaction.

IV. Conclusions and perspectives

As a conclusion, we were capable of synthesizing the model substrate in good yield. Unfortunately, for the catalytic reductive Michael cyclization tests, we were not capable of optimizing the efficiency (Scheme 152). A maximum of 13% yield was obtained in the best case. However, we were able to isolate and characterize the γ-lactam obtained although are not yet certain of the absolute configuration. We believe the reaction is stereoselective and that only one diastereoisomer is obtained. We believe the problem to lie with the choice of the starting material since the conversion is not total or does not occur at all using catalytic systems that proved to be efficient in similar domino reactions.

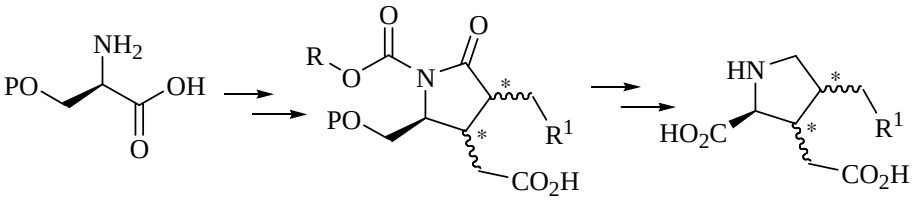


Scheme 54. Reductive Michael cyclization

In the future, we suggest synthesis of other substrates starting from amino acids and following the same synthetic sequence that we carried out before. A further challenge would be to characterize the unidentified products that were produced in several tests mentioned above.

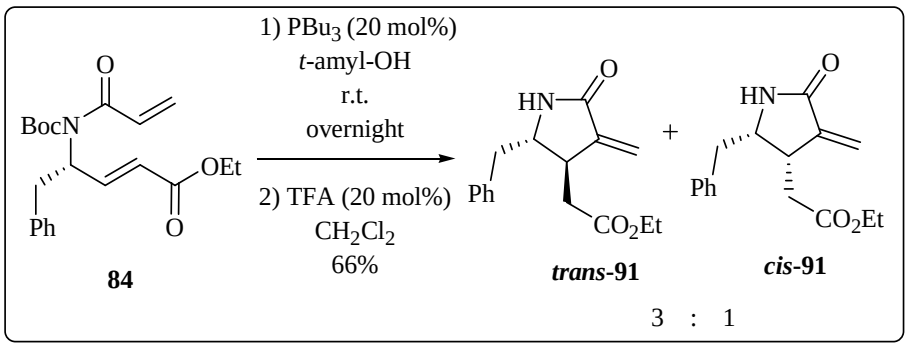
We also suggest further optimization of the reaction should be performed, as well as potential applications for this reaction, (eg. the use of serine as a building block for the heterocycles synthesis). The protected hydroxymethyl

group presents a masked precursor for a carboxylic acid function. Thus, we could obtain cyclic amino acid functionalized derivatives, such as proline, pipecolic acid,… bearing two complementary functions on the cycle. In the case of 5-membered ring, this method could lead to the formation of new compounds of the Kainoïde family.



Scheme 55. Possible synthesis of Kainoïdes

As for the Rauhut-Currier reaction, we were pleased with the good results that were obtained in the primary tests. A 66% yield with a *trans* selectivity of 3:1 was obtained. The products were also verified and characterized by NMR experiments.



Scheme 56. Rauhut Currier reaction

This reaction provides access to α-methylene-γ-lactams which are structures of great importance in medicinal chemistry. The exo-alkylidene moiety, conjugated to the carbonyl group, is thought to be essential for their biological activities including antitumor, anti-inflammatory, and other effects. Recent reviews briefly describe the synthesis of α-alkylidene γ-

lactams through Wittig or Horner–Wadsworth–Emmons olefination reactions and radical- and transition-metal-mediated cyclizations[46].

The synthesis of other substrates and the full optimization of the reaction will allow access to new structures in good yields (Figure 8). We have some collabroration with groups that carry out pharmaceutical studies, so structures with potential biological activities will be sent for biological tests.

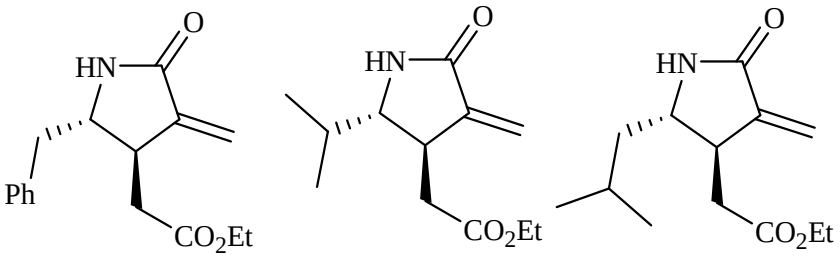


Figure 8. Possible structures of to α-methylene-γ-lactams

[46] Elford, T. G.; Ulaczyk-Lesanko, A.; De Pascale, G.; Wright, G. D.; Hall, D. G., *Journal of Combinatorial Chemistry* **2009,** *11*, 155; Albrecht, A.; Morana, F.; Fraile, A.; Jørgensen, K. A., *Chemistry – A European Journal* **2012,** *18*, 10348; Albrecht, A.; Albrecht, Ł.; Janecki, T., *European Journal of Organic Chemistry* **2011,** *2011*, 2747; Janecka, A.; Wyrębska, A.; Gach, K.; Fichna, J.; Janecki, T., *Drug Discovery Today* **2012,** *17*, 561; Tan, Y.; Yang, X.-D.; Liu, W.-J.; Sun, X.-W., *Tetrahedron Letters* **2014,** *55*, 6105; Companyó, X.; Geant, P.-Y.; Mazzanti, A.; Moyano, A.; Rios, R., *Tetrahedron* **2014,** *70*, 75.

Annex: Synthesis and Characterization of Dinuclear Cu(I)-Alkyne Complexes

I. Bibliographic introduction

Earlier in this manuscript (see chapter 1), we introduced the role of copper acetylide complexes in the Kinugasa reaction, as well as the generation of a NHC copper acetylide complex. In this section, we will focus on the synthesis of metal acetylide complexes. We describe in more detail the reporting of these complexes in literature, as well as their possible applications and properties.

I.1 Copper(I) acetylide complexes

Recent innovations in metal-catalyzed organic transformations have extensively reformed the face of modern organic synthesis. This area lies on the edge between organic and inorganic chemistry. In addition to their use as catalysts in organic reactions, a large number of metal complexes demonstrate physical properties that allow their usage in applied materials sciences.

Copper is a transition metal, which in the zero oxidation state has a $[Ar]4s^2 4p^6 3d^9$electron configuration. Copper is found in three different oxidation states: Cu(I), Cu(II), and Cu(III). Copper(I) atoms have 10 d electrons. Being d^{10} complexes, they have no Jahn-Teller distortion. Copper(I) demonstrates high versatility in terms of coordination for it may be di, tri, or tetra coordinated. This high lability allows copper(I) to be an efficient partner in several catalytic and stoichiometric processes[1]. The

[1] Markó, I. E.; Gautier, A.; Dumeunier, R.; Doda, K.; Philippart, F.; Brown, S. M.; Urch, C. J., *Angewandte Chemie International Edition* **2004,** *43*, 1588; Lewis, E. A.; Tolman, W. B., *Chemical Reviews* **2004,** *104*, 1047; Müller, P.; Fruit, C., *Chemical Reviews* **2003,** *103*, 2905; Caballero, A.; Díaz-Requejo, M. M.; Belderraín, T. R.; Nicasio, M. C.; Trofimenko, S.; Pérez, P. J., *Journal of the*

diversity of reactions susceptible to be catalyzed by copper is extensive. To develop new reactions and understand the mechanisms of some present transformations, the understanding and control of the coordination around this metal ion is crucial. Electronic and steric properties of the metal can be manipulated by the presence of ligands, which in turn influence the behavior and reactivity of the metal catalyst.

Copper acetylides are compounds containing a Cu–C≡CR substructure (R = H, alkyl, aryl, etc.), and are originally called alkynyl complexes. Cu(I) alkynyl complexes have been widely studied and are mainly synthesized from metal salts and terminal alkynes or alkali-metal reagents. They usually present a complex polymeric structure, eg. polymeric systems with alkyne units that are σ-bonded to one metal center and π-bound to another (Figure 1). They have been known for quite some time, but received less attention probably because of their poor solubility combined with a low reactivity.

American Chemical Society **2003,** *125*, 1446; Ley, S. V.; Thomas, A. W., *Angewandte Chemie International Edition* **2003,** *42*, 5400; Kirmse, W., *Angewandte Chemie International Edition* **2003,** *42*, 1088; Lipshutz, B. H.; Noson, K.; Chrisman, W.; Lower, A., *Journal of the American Chemical Society* **2003,** *125*, 8779; Mirica, L. M.; Vance, M.; Rudd, D. J.; Hedman, B.; Hodgson, K. O.; Solomon, E. I.; Stack, T. D. P., *Journal of the American Chemical Society* **2002,** *124*, 9332; Rovis, T.; Evans, D. A., Structural and Mechanistic Investigations in Asymmetric Copper(I) and Copper(II) Catalyzed Reactions. In *Progress in Inorganic Chemistry*, John Wiley & Sons, Inc.2002; pp 1.

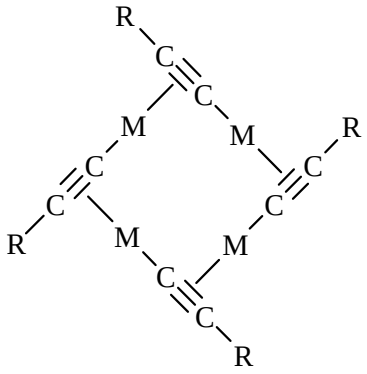


Figure 1. Metal alkyne polymeric system

The linear geometry of the alkynyl unit and its π-unsaturated character have led to metal alkynyls becoming attractive building blocks for molecular wires and polymeric organometallic materials, which can possess interesting properties, such as optical nonlinearity, luminescence, liquid crystallinity, and electrical conductivity[2].

The photophysical and photochemical properties of metal alkynyls of group 11 transition metals, were reviewed by Yam *et al.*[3] They remarked that trinuclear Cu(I) alkynyl complexes and $[Cu_3(\mu\text{-dppm})_3(\mu_3\text{–}\eta^1\text{-C}\equiv\text{C-R})_2]$ have long life time and intense luminescence in both the solid state and in solution, and the alkynyl groups seem to be involved in the formation of excited states in the complexes.

Acetylides are typical multisite bridging ligands in polymetallic complexes. Cu(I) alkynyls have provoked a lot of interest that originates from the high flexibility and ability of the acetylide groups to bond to transition metals forming a large number of mono- and polynuclear complexes with a variety of bonding modes including the $\mu_3\text{–}\eta^1$ type, of which the triangular Cu(I)

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[2] Long, N. J.; Williams, C. K., *Angewandte Chemie International Edition* **2003,** *42,* 2586.

[3] Yam, V. W.-W., *Accounts of Chemical Research* **2002,** *35,* 555.

alkynyls $[Cu_3(\mu\text{-dppm})_3(\mu_3\text{–}\eta^1\text{-C}\equiv\text{C-R})]^{2+}$ and $[Cu_3(\mu\text{-dppm})_3(\mu_3\text{–}\eta^1\text{-C}\equiv\text{C-R})_2]^+$ are known[4], as well as those complexes where the alkyne group bridges two copper ions, , the $Cu_2(\mu\text{-alkyne})$ unit[5-6] (Figure 2).

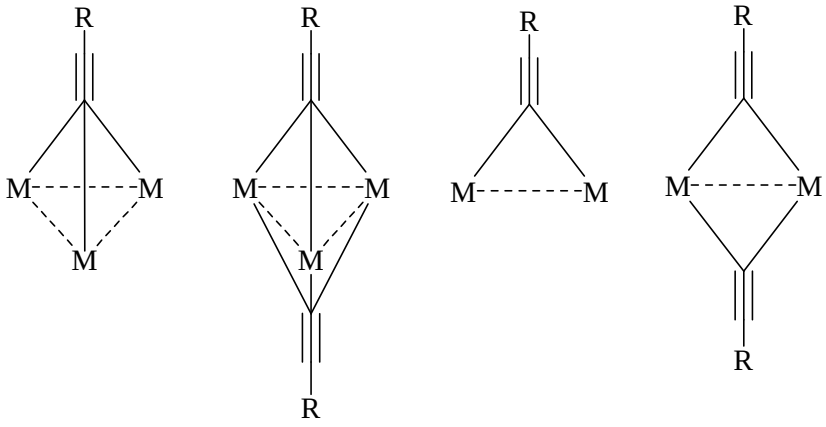

Figure 2. Mono and polynuclear alkyne complexes

Other tri- and dinuclear metal acetylides as well as heteronuclear complexes with metals such as Ni, Pt, Ru, Au, Ag… were reported[7]. These complexes

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[4] Yam, V. W. W.; Lee, W. K.; Lai, T. F., *Organometallics* **1993,** *12*, 2383; Diez, J.; Gamasa, M. P.; Gimeno, J.; Lastra, E.; Aguirre, A.; Garcia-Granda, S., *Organometallics* **1993,** *12*, 2213; Diez, J.; Gamasa, M. P.; Gimeno, J.; Aguirre, A.; Garcia-Granda, S., *Organometallics* **1991,** *10*, 380.

[5] Díez, J.; Gamasa, M. P.; Gimeno, J.; Aguirre, A.; García-Granda, S.; Holubova, J.; Falvello, L. R., *Organometallics* **1999,** *18*, 662.

[6] Bruce, M. I.; Zaitseva, N. N.; Skelton, B. W.; Somers, N.; White, A. H., *Inorganica Chimica Acta* **2007,** *360*, 681.

[7] Egler-Lucas, C.; Blacque, O.; Venkatesan, K.; López-Hernández, A.; Berke, H., *European Journal of Inorganic Chemistry* **2012,** *2012*, 1536; Wong, K. M.-C.; Lam, W. H.; Zhou, Z.-Y.; Yam, V. W.-W., *Chemistry – A European Journal* **2008,** *14*, 10928; Ying, J.-W.; Cordova, A.; Ren, T. Y.; Xu, G.-L.; Ren, T., *Chemistry – A European Journal* **2007,** *13*, 6874; Wei, Q.-H.; Yin, G.-Q.; Zhang, L.-Y.; Shi, L.-X.; Mao, Z.-W.; Chen, Z.-N., *Inorganic Chemistry* **2004,** *43*, 3484; Wing-Wah

usually show similar physical properties to the copper complexes including luminescence. In the following section, we focus on the synthesis of copper(I) alkynes and their possible applications.

I.1.1 Trinuclear complexes

García-Granda et *al.* reported the synthesis and characterization of the triangular Cu(I) complexes containing biphosphines: $[Cu_3(\mu\text{-dppm})_3(\mu_3\text{–}\eta^1\text{-C}\equiv\text{C-Ph})_2][BF_4]$ (Figure 3) and $[Cu_3(\mu\text{-dppm})_3(\mu^3\text{–}\eta^1\text{-C}\equiv\text{C-Ph})][BF_4]_2$[4]. The synthesis was carried out using a cationic copper complex in addition to the acetylene in the presence of a base. For instance the synthesis of $[Cu_3(\mu\text{-dppm})_3(\mu_3\text{–}\eta^1\text{-C}\equiv\text{C-Ph})_2][BF_4]$ was achieved upon the reaction of LiC≡CPh (5 equiv) to $[Cu_3(\mu_3\text{-Cl})_2(\mu\text{-dppm})_3][BF_4]$ (1 equiv) in THF.

Yam, V.; Cheung, K.-L.; Chung-Chin Cheng, E.; Zhu, N.; Cheung, K.-K., *Dalton Transactions* **2003**, 1830; Colbert, M. C. B.; Lewis, J.; Long, N. J.; Raithby, P. R.; Younus, M.; White, A. J. P.; Williams, D. J.; Payne, N. N.; Yellowlees, L.; Beljonne, D.; Chawdhury, N.; Friend, R. H., *Organometallics* **1998,** *17*, 3034; Maekawa, M.; Munakata, M.; Kuroda-Sowa, T.; Hachiya, K., *Inorganica Chimica Acta* **1995,** *233*, 1.

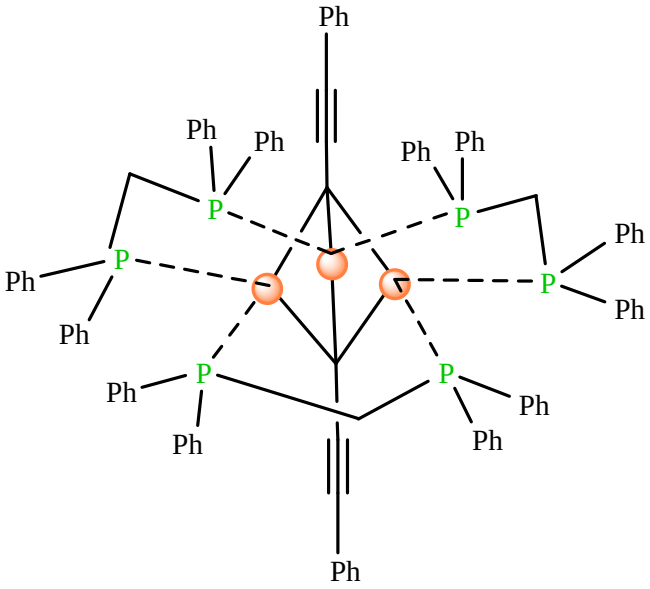

Figure 3. : $[Cu_3(\mu\text{-dppm})_3(\mu_3\text{–}\eta^1\text{-C}\equiv\text{C-Ph})_2][BF_4]$

Their work strongly suggested the special ability of the dppm ligand to stabilize the *triangulo*-Cu_3 frameworks, which can be used as an appropriate support of linear bridging alkynyl groups in organocopper chemistry. It is well-known that some diphosphine bidentate ligands show some coordination flexibility of its steric bite angle to respond to the geometric requirement of the metal. In addition to the chelating mode to the metal center to which they are attached, bidentate ligands are also present in bridging mode in polynuclear Cu(I) complexes, thus stabilizing these polynuclear complexes[8].

Structure determination by X-ray diffraction showed these cationic complexes consist of an isosceles triangle of copper atoms with a dppm ligand bridging each edge to form a roughly planar $[Cu_3P_6]$ core. The

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[8] Pilloni, G.; Graziani, R.; Longato, B.; Corain, B., *Inorganica Chimica Acta* **1991,** *190*, 165.

phenylethynyl ligands are *C*-bonded to the three copper atoms in an asymmetric μ_3–η^1-bridging (the copper to carbon distances are significantly different).

In a following report, García-Granda and coworkers described a new family of *triangulo* copper(I) complexes containing μ–η^1-isocyanide and μ_3–η^1-alkynyl or μ_3–chloride ligands: $[Cu_3(\mu_3\text{–}\eta^1\text{-}C{\equiv}CR^1)(\mu\text{–}\eta^1\text{-}C{\equiv}NR^2)(\mu\text{-dppm})_3][BF_4]_2$ and $[Cu_3(\mu_3\text{–Cl})(\mu\text{–}\eta^1\text{-}C{\equiv}NR)(\mu\text{-dppm})_3][BF_4]_2$. This was the first example of copper(I) complexes with isocyanide bridging ligands[9]. In complexes with group 10 metals, the isocyanide ligand adopts a μ_3–η^1-bonding mode, while with Cu(I) isocyanide complexes μ–η^1-bonding mode is observed.

The complex $[Cu_3(dppm)_3(\mu_3\text{–}\eta^1\text{-}C{\equiv}CFc)_2]\cdot PF_6$ (Figure 4) was synthesized and characterized using single-crystal X-ray diffraction, UV-vis spectroscopy, and voltammetry by the Vittal group[10]. The compound is composed of a trimetallic Cu_3 core bridged by three dppm and capped with two ferrocenylacetylides. It was synthesized by mixing 1 equiv. of $[Cu_2(dppm)_2(CH_3CN)_2]\cdot 2PF_6$ and 1.374 equiv. of ethynylferrocene in the presence of KOH as a base.

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[9] Díez, J.; Gamasa, M. P.; Gimeno, J.; Aguirre, A.; García-Granda, S., *Organometallics* **1997,** *16,* 3684.

[10] Yip, J. H. K.; Wu, J.; Wong, K.-Y.; Yeung, K.-W.; Vittal, J. J., *Organometallics* **2002,** *21,* 1612.

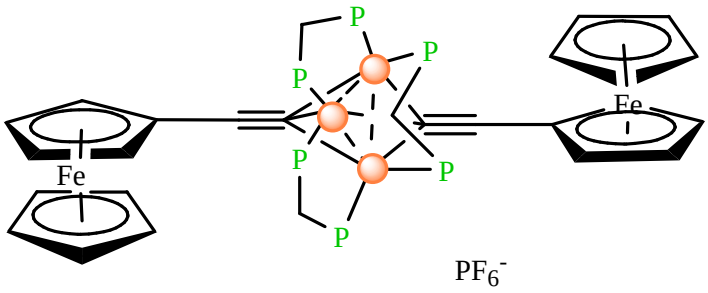

Figure 4. $[Cu_3(dppm)_3(\mu_3\text{–}\eta^1\text{-}C{\equiv}CFc)_2]\cdot PF6$

In this study they demonstrated that the redox-active ferrocenyl group could be readily attached to trinuclear Cu cluster. Their study showed that the trinuclear Cu_3 center does not provide efficient electron delocalization and should be regarded as a poor "conductor".

Halet and coworkers carried out the synthesis of trinuclear copper(I) and silver (I) complexes containing bicapped diynyl ligands of general formula $[M_3(\mu\text{-dppm})_3(\mu_3\text{–}\eta^1\text{-}C{\equiv}CC{\equiv}CR)_2]PF_6$ (R= H, Ph, 4-MeC_6H_4, 4-$OMeC_6H_4$, $^nC_6H_{13}$), and explored their electronic, photophysical, and electrochemical properties[11]. They envisaged that the presence of both diynyl ligands might serve to produce new luminescent metal-based carbon-rich materials for future applications in light-emitting oligomeric and polymeric materials in materials science. Using the classical methods for their synthesis, diphosphine Cu(I) or Ag(I) salt with acetylene and a base, they obtained the desired trinuclear complexes. They determined the X-ray crystal structures of $[Cu_3(\mu\text{-dppm})_3(\mu_3\text{–}\eta^1\text{-}C{\equiv}CC{\equiv}CPh)_2]PF_6$ and $[Cu_3(\mu\text{-dppm})_3(\mu_3\text{–}\eta^1\text{-}C{\equiv}CC{\equiv}CH)_2]PF_6$.

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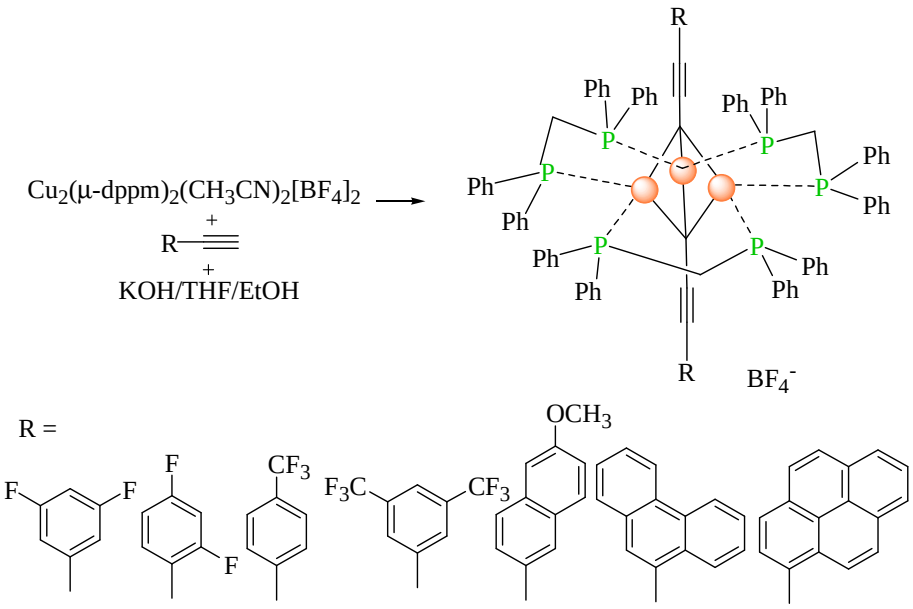
[11] Lo, W.-Y.; Lam, C.-H.; Yam, V. W.-W.; Zhu, N.; Cheung, K.-K.; Fathallah, S.; Messaoudi, S.; Le Guennic, B.; Kahlal, S.; Halet, J.-F., *Journal of the American Chemical Society* **2004,** *126,* 7300.

Later, Coppo *et al.* prepared phosphorescent Cu(I) trinuclear complexes carrying a range of alkynyl ligands with different electronic structure[12] (Scheme 1). They demonstrated high photoluminescence, and obtained a wide range of emission colours with the different alkynes. The energy, as well as the lifetime of the triplet state emission, can be tuned to a large extent by careful choice of the alkynyl ligand (higher lifetimes were obtained with more conjugated systems), making these complexes suitable candidates for application either in optoelectronic devices or in time-resolved and gated luminescence detection.

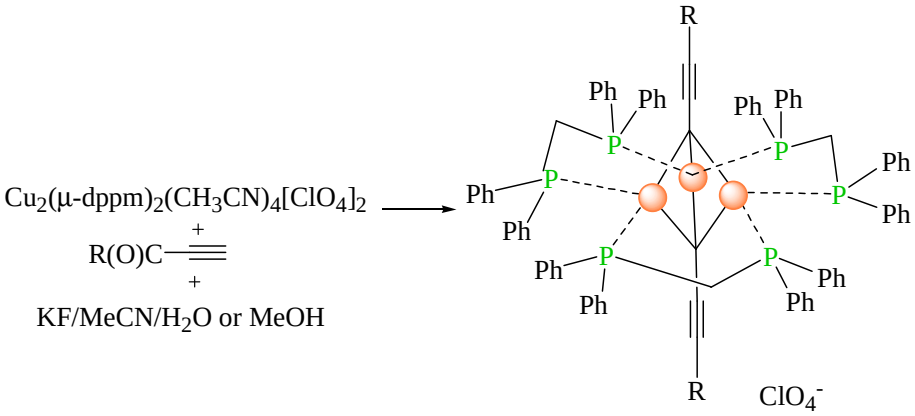


Scheme 1. Synthesis of trinuclear copper(I) acetylide complexes with different electronic properties

A series of trinuclear copper(I) acetylide complexes with carbonyl moiety, $[Cu_3(\mu\text{-dppm})_3(\mu_3\text{–}\eta^1\text{-C}\equiv\text{CC(O)R})_2](ClO_4)$ (R = H , CH_3 , OCH_3, NH_2, NEt_2)

[12] **!!! INVALID CITATION !!!**

have been synthesized and characterized by Chao and coworkers[13] (Scheme 2). They obtained the crystal structures of $[Cu_3(\mu\text{-dppm})_3(\mu_3\text{–}\eta^1\text{-}C{\equiv}CC(O)CH_3)_2](ClO_4)$ and $[Cu_3(\mu\text{-dppm})_3(\mu_3\text{–}\eta^1\text{-}C{\equiv}CC(O)NH_2)_2](ClO_4)$ by X-ray diffraction. The photophysical properties of the complexes have been studied, and luminescence was detected in both solid state and in solution.



R = H , CH_3 , OCH_3, NH_2, NEt_2

Scheme 2. Synthesis of trinuclear copper(I) acetylide complexes with carbonyl moiety

I.1.2 Dinuclear complexes

García-Granda *et al.* reported the synthesis of tetrabridged dicopper(I) alkyne complexes containing dppf as a chelate and bridging ligand: $[Cu_2(\mu\text{-}\eta1\text{-}C{\equiv}CR)_2(\mu\text{-dppf})_2]$ (R= 4-MeC_6H_4, Ph, CH_2OCH_3, $CH_2CH_2CH_3$, (η^5-C_5H_4)Fe(η^5-C_5H_5))[14]. For the preparation of such complexes, they first carried out the synthesis of the dinuclear copper(I) complex $[Cu_2(\mu\text{-Cl})_2(\kappa^2\text{-}$

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[13] Zhang, M.; Su, B.-C.; Li, C.-L.; Shen, Y.; Lam, C.-K.; Feng, X.-L.; Chao, H.-Y., *Journal of Organometallic Chemistry* **2011,** *696*, 2654.

[14] Díez, J.; Gamasa, M. P.; Gimeno, J.; Aguirre, A.; García-Granda, S.; Holubova, J.; Falvello, L. R., *Organometallics* **1999,** *18*, 662.

P,P-dppf)$_2$] by the reaction of equimolar amounts of CuCl, dppf, and TMEDA in THF. The complex obtained was further reacted with the corresponding lithium acetylides (LiC≡CR), prepared *in situ*, in THF to provide the complex [Cu$_2$(μ-η^1-C≡CR)$_2$(μ-dppf)$_2$] in 60-70% yields (Figure 5). Notably, upon the formation of the bridging alkynyl complexes, the dppf coordination mode transforms from chelating in the precursor [Cu$_2$(μ-Cl)$_2$(κ^2-P,P-dppf)$_2$] to bridging in the resulting novel products [Cu$_2$(μ-η^1-C≡CR)$_2$(μ-dppf)$_2$]. This shows the ability of the dppf ligand to adapt to the requirements of the dicopper(I) fragment Cu$_2$(μ-η^1-C≡CR)$_2$, thus stabilizing the complexes formed.

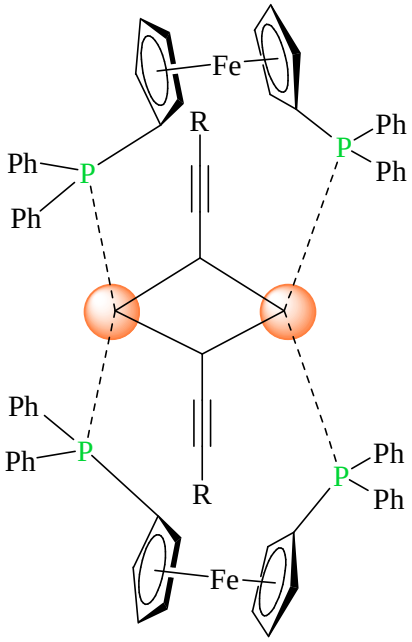

Figure 5. [Cu$_2$(μ-η^1-C≡CR)$_2$(μ-dppf)$_2$]

White and coworkers described the preparation of the binuclear complex [Cu(μ-C≡CPh)(triphos)]$_2$ [triphos = (PPh$_2$CH$_2$)$_3$CMe] (Figure 6) from a

reaction between $[Cu(C{\equiv}CPh)]_n$ and triphos[15]. The two copper atoms were found to be bridged unsymmetrically by two C≡CPh groups. Only two of the three phosphorus atoms in each ligand are coordinated to the copper atoms.

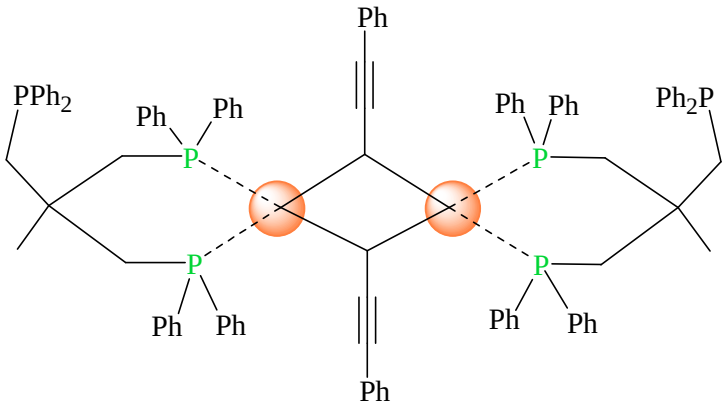

Figure 6. $[Cu(\mu\text{-}C{\equiv}CPh)(triphos)]_2$

Dinuclear Cu(I) alkynyl complexes have also been the subject of several studies concerning the mechanism for the alkyne-azide cycloaddition reaction. Experimental evidence for the involvement of such complexes in the mechanism of the click chemistry reaction has been demonstrated by the groups of Heaney[16] and Fokin[17]. Heany reported the preparation of polymeric dinuclear copper(I) alkynides (i.e., copper(I) phenylacetylide) involving the interaction of terminal alkynes with copper(II). These polymers act as heterogeneous catalysts for the azide−alkyne cycloaddition reactions. The appropriate copper(I) ladder polymers were prepared from

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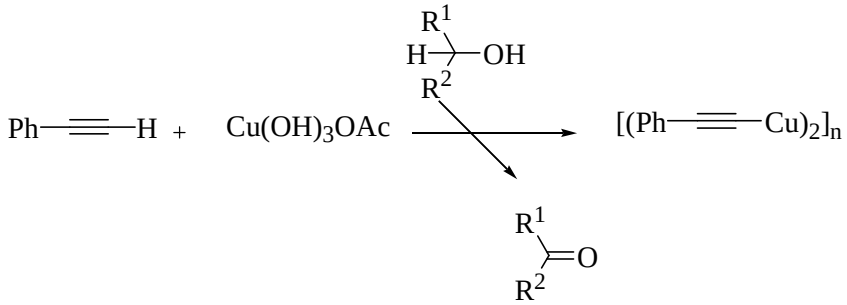
[15] Bruce, M. I.; Zaitseva, N. N.; Skelton, B. W.; Somers, N.; White, A. H., *Inorganica Chimica Acta* **2007,** *360*, 681.

[16] Buckley, B. R.; Dann, S. E.; Heaney, H., *Chemistry – A European Journal* **2010,** *16*, 6278.

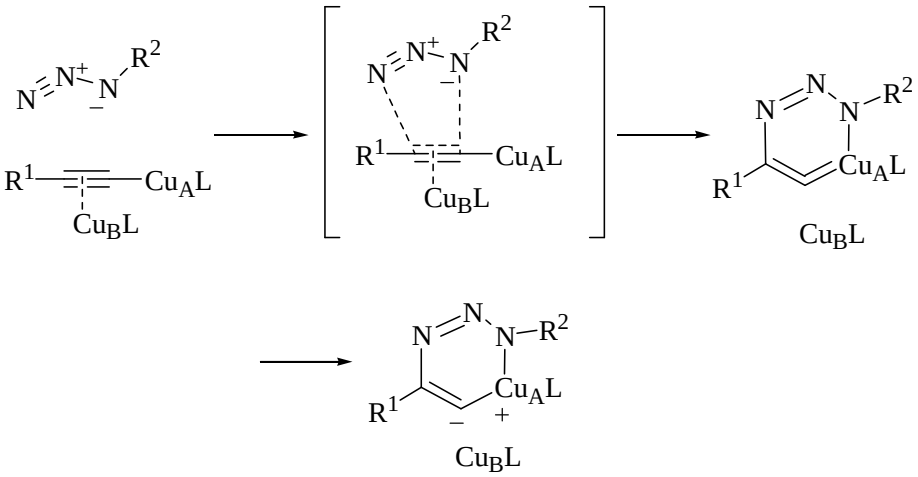
[17] Worrell, B. T.; Malik, J. A.; Fokin, V. V., *Science* **2013,** *340*, 457; Ahlquist, M.; Fokin, V. V., *Organometallics* **2007,** *26*, 4389.

the reduction of $[Cu(OAc)_2]$ or $[Cu(OH)_3(OAc)]$ by easily oxidizable alcohols in the presence of terminal alkynes (Scheme 3).



Scheme 3. Synthesis of Copper(I) ladder polymers

Fokin *et al.* proposed after some DFT calculations that the introduction of a second copper(I) atom may favorably influence the energetic profile of the CuAAc reaction. Real-time monitoring of a representative cycloaddition process via heat-flow reaction calorimetry revealed that monomeric copper acetylide complexes are not reactive toward organic azides unless an exogenous copper catalyst is added. The involvement of a second copper center in the catalysis shows better reactivity and may also explain the high activity of heterogeneous catalysts including the Cu(I) ladder polymers (Scheme 4).



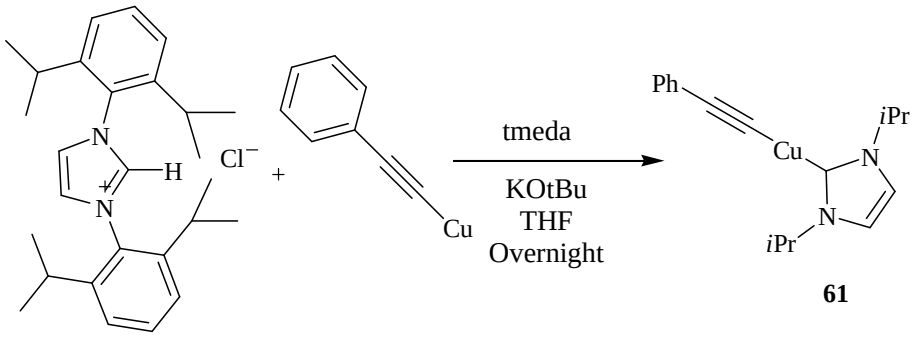
Scheme 4. Involvement of a second copper atom in the alkyne-azide cycloaddition reaction

II. Objectives

As shown previously, copper(I) acetylide complexes have proven to be an important arena that needs to be studied in detail. The possible intermediacy of such complexes in several reactions such as the Kinugasa reaction (discussed in chapter 1), CuAAc click chemistry reaction, and others, reveals the great interest given to such structures. Their importance surpasses the identification of the structures to the isolation of these complexes in stable forms in order to carry out some mechanistic and kinetic studies for unknown reaction mechanisms.

Also, the physical properties related to metal acetylide structures; in particular, their photophysical luminescent properties and conductivity present an important aspect in this domain for many possible applications.

In light of the result obtained in chapter 1 concerning the easy preparation of an NHC-Cu-acetylide complex **61**, we decided to carry out the synthesis of other copper acetylide complexes using the same technique (Scheme 5).



Scheme 5. Synthesis of NHC-Cu-acetylide **61**

In this section, we are going to describe only the synthesis part of this project, i.e the preparation of the diphosphine copper (I) acetylides and their structures.

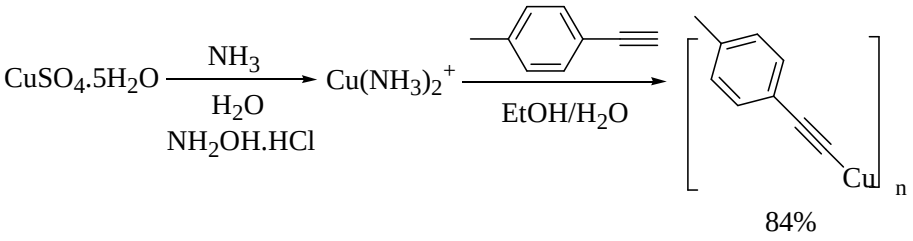
As we are going to see later on, we managed to synthesize a new class of diphosphine Cu(I) acetylide complexes opening the door to a whole new range of possibilities.

III. Results and discussion

The first step in this project was to establish a reliable method for the preparation of copper(I) acetylide polymeric structures starting from the corresponding terminal alkynes. Cu(I) phenylacetylide is commercially available.

III.1 Preparation of copper(I) acetylides

Copper(I) tolylacetylide was prepared according to a literature method[18] that requires mixing $CuSO_4.5H_2O$ with ammonia in the presence of ammonium chloride thus forming a $Cu(NH_3)_2^+$ which is then reacted with the acetylide in a mixture of ethanol and water to provide the desires copper(I) acetylide polymer in 84% yield (Scheme 6). However some oxidized product, appearing as a green color, was obtained along with the desired product, which could not be removed.



Scheme 6. Preparation of Copper(I) tolylacetylide

Two alternative methods for the synthesis of copper(I) acetylides were adopted[19]. These methods provided better quality complexes. Method A was used for more tolerant alkynes while method B was used for alkynes bearing less tolerant and reactive substituents (Scheme 7).

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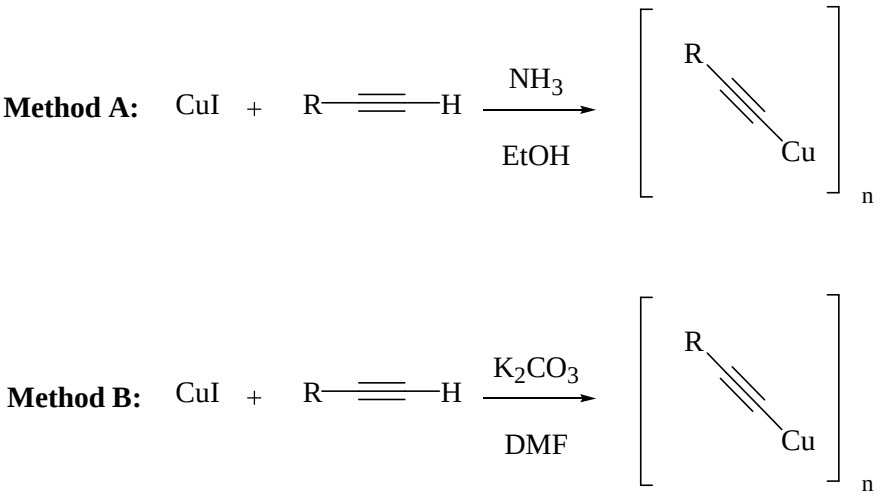
[18] Owsley, D. C.; Castro, C. E., *Organic Synthesis* **1972,** *52*, 128.

[19] Jouvin, K.; Heimburger, J.; Evano, G., *Chemical Science* **2012,** *3*, 756.



Scheme 7. Alternative methods for the preparation of Copper(I) acetylides

The synthesis of several alkynyl copper(I) complexes was carried out according to the previous methods. The results are summarized in table 1.

Table 1. Copper(I) acetylides

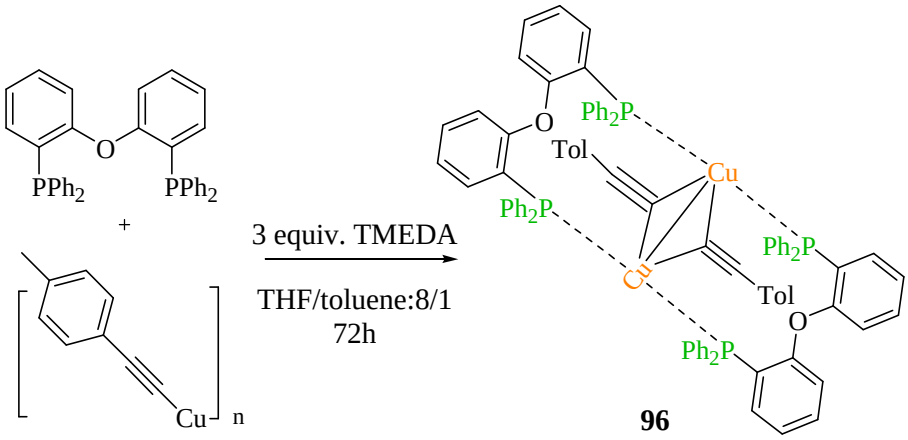
Entry	**R**	**Product**	**Isolated yield [%]**	**Method**
1	tolyl	**92**	65	**A**
2	$CH(OEt)_2$	**93**	30	**B**
3	$C(CH_3)_2OH$	**-**	degradation	**A**
4	$CH_3(CH_2)_4CH_2$	**94**	64	**A**
5	$BnO(CH_2)_3$	**95**	47	**A**
6	$PhCH_2N(Ts)CH_2$	-	degradation	**A**

III.2 Preparation of bridged diphosphine copper(I) alkynyl complexes

After having the copper(I) acetylide polymers in hand, the synthesis of the bridged diphosphine Cu(I) acetylide complexes was initiated following the procedure that was used for the synthesis of compound **66**.

Different diphosphines were used for this synthesis. To react the poorly soluble polymers with diphosphines, an excess of TMEDA aiming to break the polymer structure and facilitate the coordination of the diphosphine, was used.

As a first example, we mixed the copper(I) tolylacetylide with 1 equiv. of the large bite angle ligand: dpePhos and 3 equiv. of TMEDA in a mixture of toluene and THF (8:1). After 72 hours of reaction, filtering the reaction mixture provided a bridged binuclear complex **96** in quantitative yield (Scheme 8).



Scheme 8. Synthesis of binuclear complex **96**

This complex was found rather soluble in organic solvents in contrast to the copper(I) acetylide polymer. Its ^{31}P NMR spectrum suggests only one species is found in solution (one sharp peak δ = -19.5) (Figure 7).

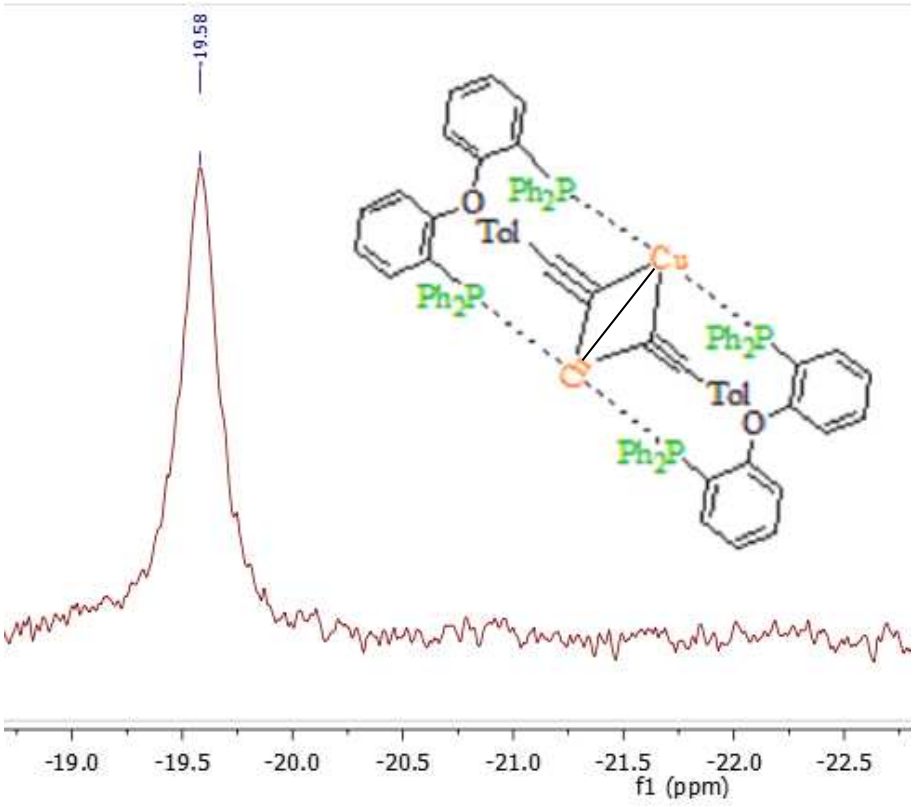


Figure 7. 31P NMR of binuclear complex **96**

This result was confirmed by a successful crystallization in diethyl ether at r.t. which afforded X-ray quality crystals for analysis. The structure confirmed the formation of a tetrabridged binuclear copper(I) tolylacetylide where two alkynyls are bridged to both copper atoms, and the two diphosphine ligands each bridged to both copper atoms. The structure of the complex obtained is to be written as: $[Cu_2(\mu\text{-dpePhos})_2(\mu\text{-}\eta^1\text{-C}\equiv\text{C-Tol})_2]$. Furthermore, we were delighted to find that this complex is very air and moisture stable both in the solid state and in solution.

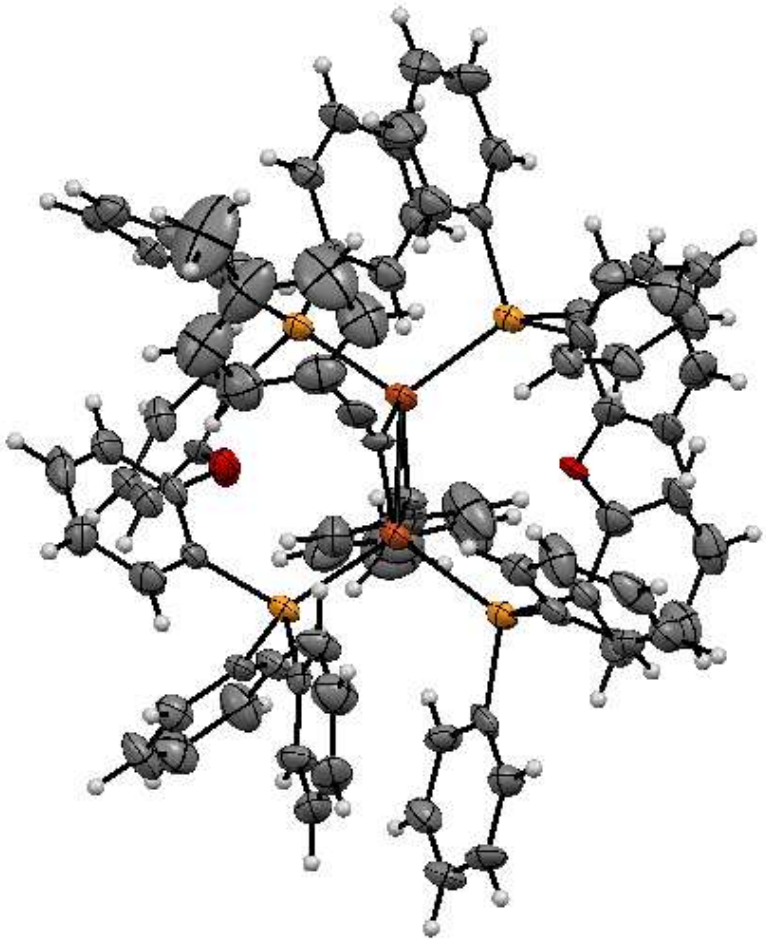
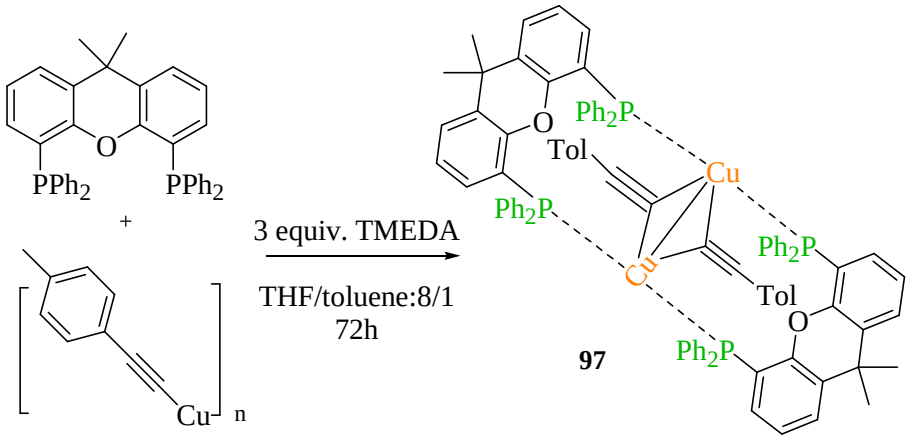


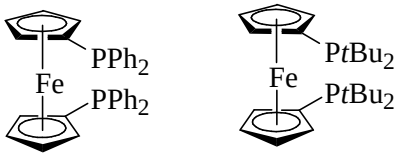
Figure 8. X-ray structure of binuclear complex **96**

When XantPhos is used as the ligand in the same synthetic procedure, a mixture of products was observed. We were not able to obtain a crystal structure; however, we assumed the formation of the desired complex **97** with another unidentified structure. The ^{31}P NMR spectrum reveals 2 peaks at δ = -13.1 and -17.6. Further filtration and recrystallization did not allow the separation of these two structures.



Scheme 9. Synthesis of binuclear complex **97**

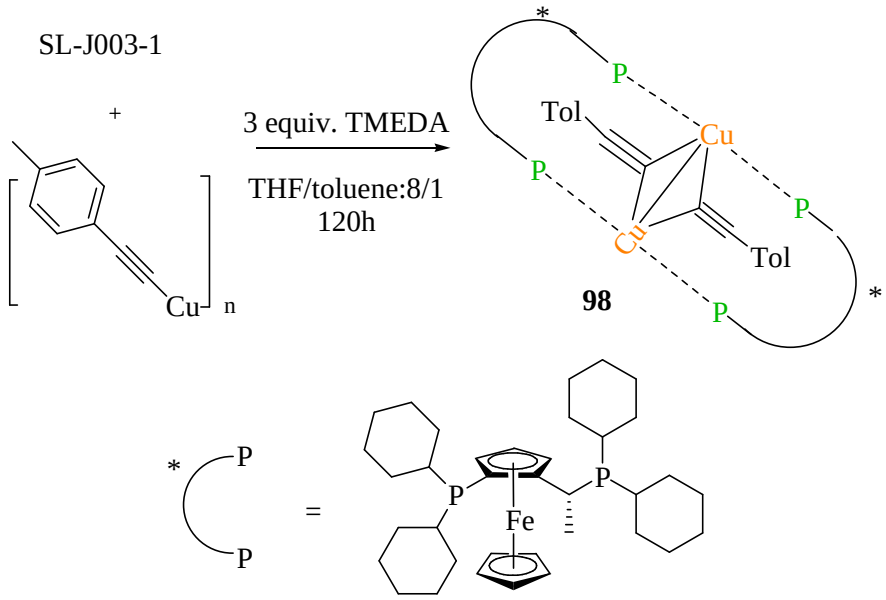
Similar result was obtained when DPPF (Figure 9) ligand was used. A mixture of several products was obtained. In case of the use of D*t*BPF (Figure 9), a single product was obtained according to the ^{31}P NMR spectrum. However, when trying to obtain a crystalline structure, the product degraded.



DPPF D*t*BPF

Figure 9. Structures of DPPF and D*t*BPF

The use of chiral diphosphine ligands was also considered. A JosiPhos ligand (SL-J003-1) was reacted with the copper(I) tolyl acetylide under the same conditions. Total dissolution of the reaction partners was observed after a few hours, and the reaction mixture was left for 72h (Scheme 10).



Scheme 10. Synthesis of binuclear complex **98**

The ^{31}P NMR spectrum suggests that only one species is found in solution (two doublets at δ= -2.6, -1.1 and -13.2, -14.7). Although we do not have in hand any proof of the formation of the desired molecule **98**, we suggest the formation of the anticipated product based on the ^{31}P NMR spectrum (Figure 10), in addition to the large bite angle of this ligand and its capability to adapt to the requirement of the structure. No single crystal large enough for single crystal analysis could be obtained.

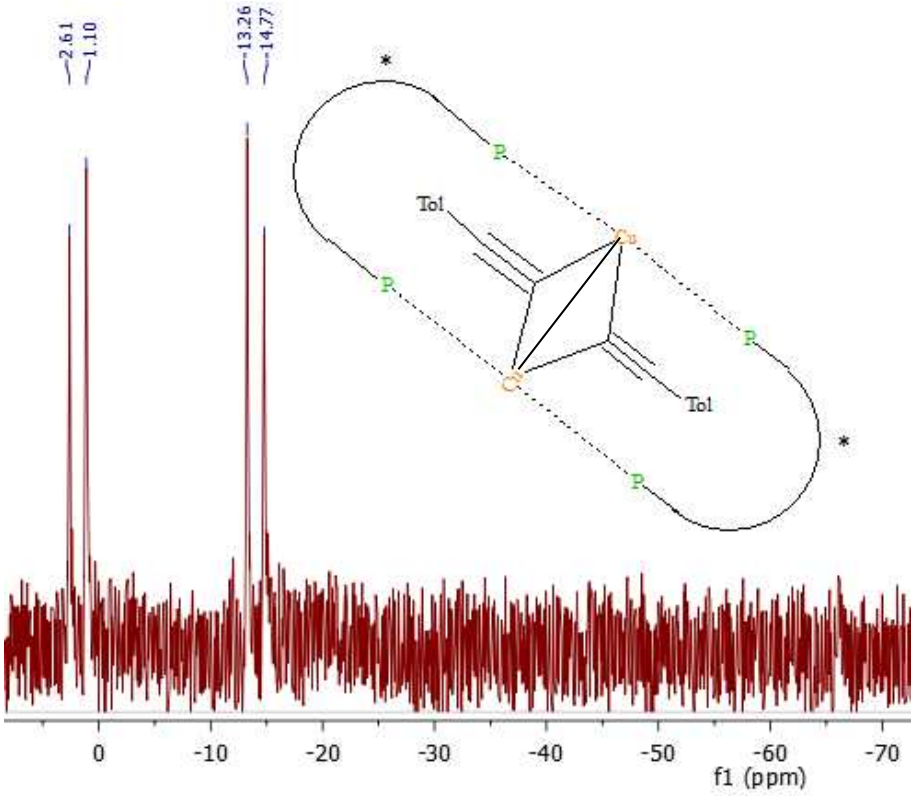
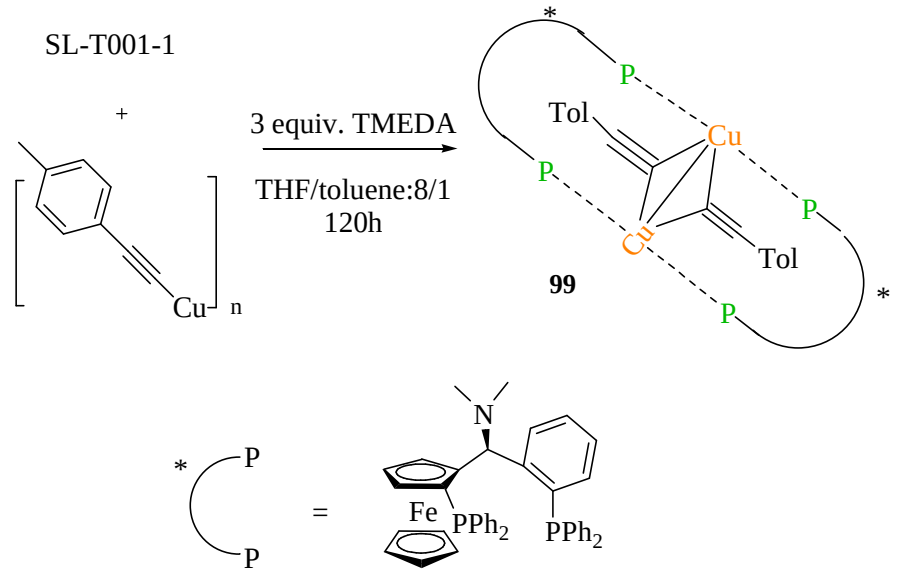


Figure 10. ^{31}P NMR of complex **98**

The use of the Taniaphos ligand (SL-T001-1) provided a single compound detected by ^{31}P NMR spectroscopy (Scheme 11).



Scheme 11. Synthesis of binuclear complex **99**

The ^{31}P NMR of the product is this time similar to what we have obtained with SL-J003-1. Two doublets at δ= -16.7,-16.8 and -23.2, -23.4 were observed (Figure 11). Trials for obtaining a single crystal for this product were not successful.

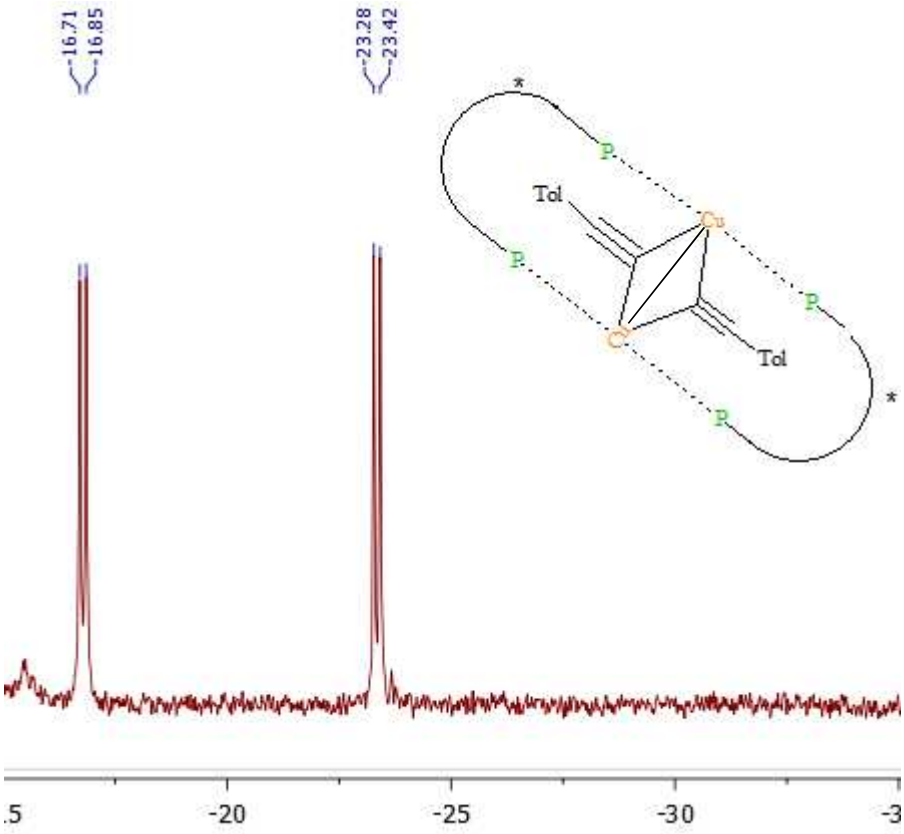
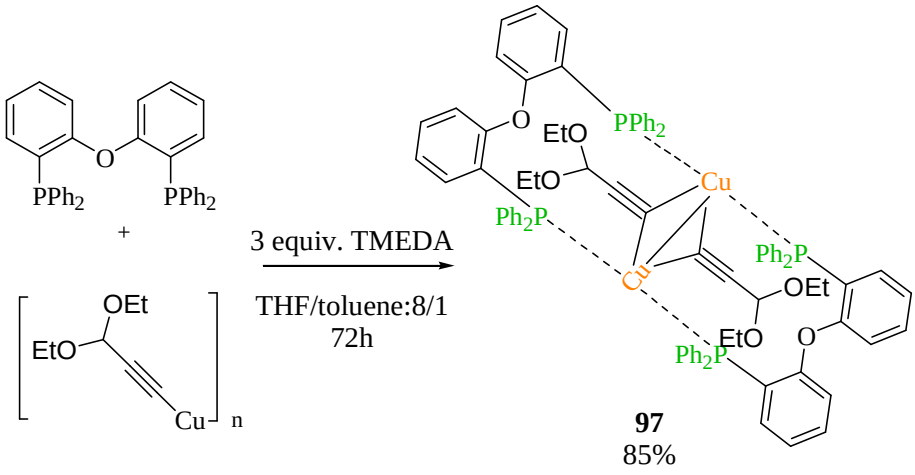


Figure 11. ^{31}P NMR of complex **99**

The use of other copper(I) acetylide polymers was also examined for the realization of binuclear structures. DpePhos was reacted with three different copper(I) acetylide polymers that were prepared previously. In the case of structure **100**, the reaction under conditions similar to the above reactions resulted in a single structure, after filtration, that was detected in NMR (Scheme 12).



Scheme 12. Synthesis of binuclear complex **100**

The ^{31}P NMR spectrum provided evidence for the formation of the anticipated product **100** (single sharp peak at δ=-17.6) (Figure 12).

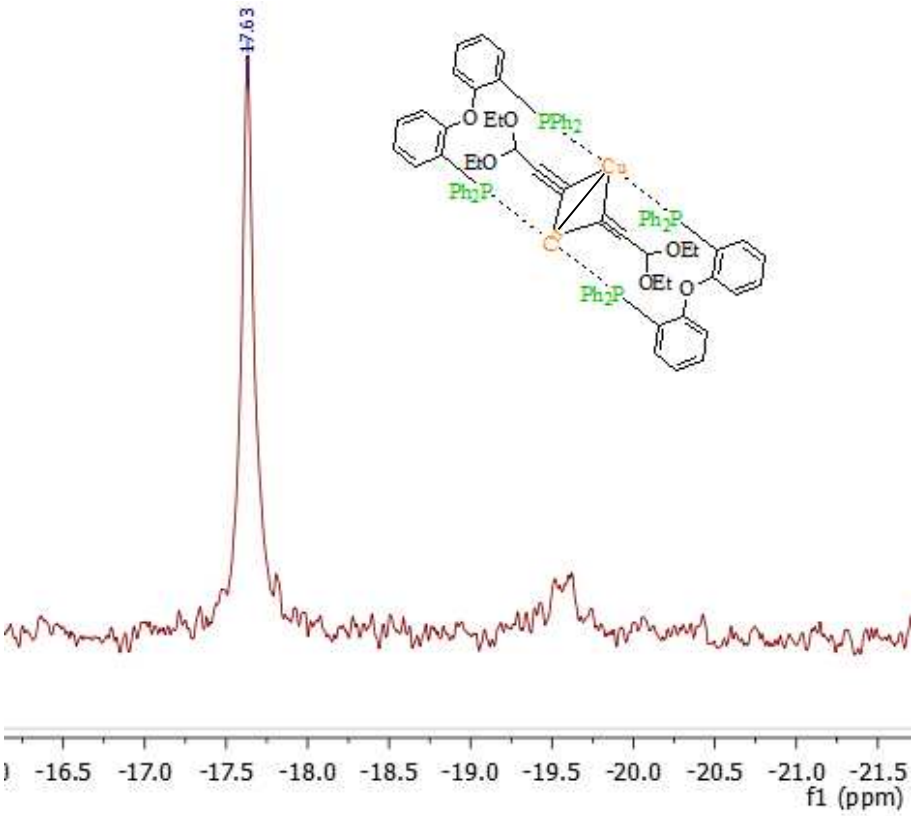


Figure 12. ^{31}P NMR of complex **100**

Furthermore, an X-ray determined structure confirmed the claims for the formation of such structure: $[Cu_2(\mu\text{-dpePhos})_2(\mu\text{-}\eta^1\text{-C}\equiv\text{C-CH(OEt)}_2)_2]$ (Figure 13).

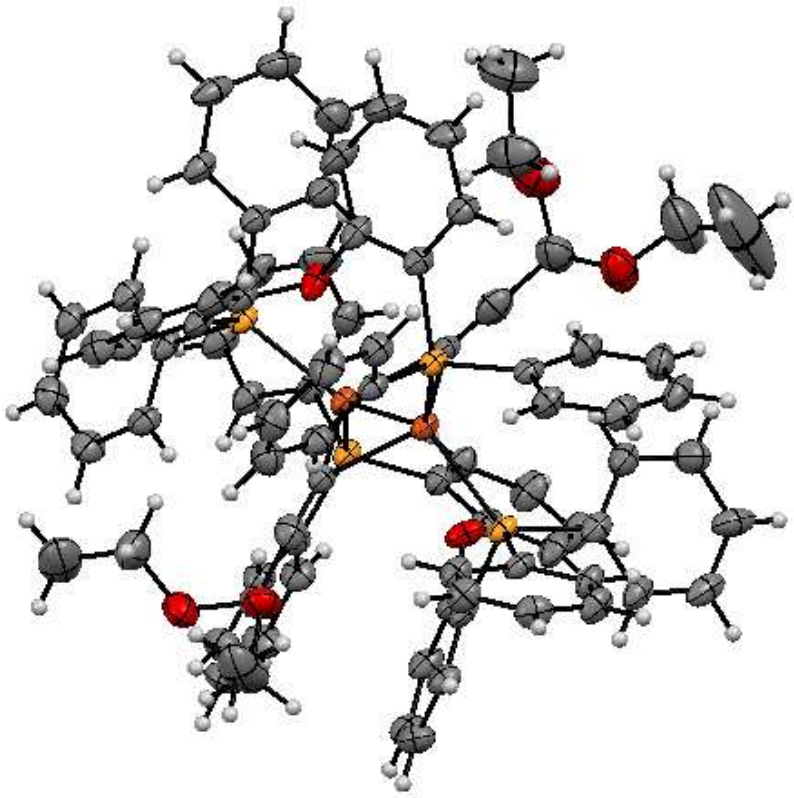


Figure 13. X-ray structure of binuclear complex **100**

Finally, the reaction of dpePhos with copper(I) acetylide polymers **94** and **95**, did not provide any product, instead, the ligand was recovered without coordinating to the copper complex.

IV. Conclusions and perspectives

In conclusion, we have developed the synthesis of bridged diphosphine binuclear copper(I) acetylides using a simple methodology that requires the easy preparation of copper(I) acetylide polymers according to methods present in the literature. These complexes were characterized by ^{1}H and ^{31}P NMR and X-ray diffraction whenever possible. Two X-ray structures were obtained for the complexes **93** and **97**. The spectroscopic data are in agreement with the structures obtained. The complexes obtained have a general formula of $[Cu_2(\mu\text{-dpePhos})_2(\mu\text{-}\eta^1\text{-}C{\equiv}C\text{-}R)_2]$ with two copper atoms linked by two bridging diphosphines and two bridging alkynyl units in a $\mu\text{-}\eta^1$ bonding arrangement.

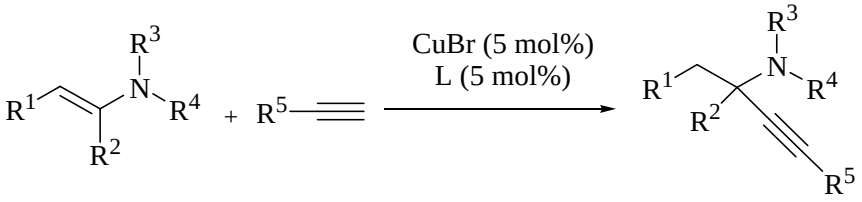
Unfortunately, we could not obtain the same type of bonding with all the diphosphine ligands that we used. This is likely explained by the fact that the dpePhos ligand has a large bite angle which could adapt to the structural and geometrical requirements in contrast to other types of ligands.

Also, in the case of the two chiral diphosphines, the products **95** and **96** that are obtained, no crystalline form has been obtained yet,. A future perspective could be to focus on other methods of crystallization and characterization of these complexes.

Furthermore it could be interesting in the future to test these complexes for luminescence properties.

Moreover, it would be interesting to study the potential of these complexes in reactions that postulate the intermediacy of copper(I) acetylides in the presence of large bite angle ligands. Some examples are present in the literature and are worth to be considered as potential systems for such

studies[20,21]. One example is the synthesis of propargylamines by copper-catalyzed addition of alkynes to enamines studied by Knochel[21] (Scheme 13).



Scheme 13. Synthesis of propargylamines catalyzed by copper salt and large bite angle diphosphine ligands

[20] Hattori, G.; Sakata, K.; Matsuzawa, H.; Tanabe, Y.; Miyake, Y.; Nishibayashi, Y., *Journal of the American Chemical Society* **2010,** *132,* 10592; Black, D. A.; Beveridge, R. E.; Arndtsen, B. A., *The Journal of Organic Chemistry* **2008,** *73,* 1906.

[21] Koradin, C.; Gommermann, N.; Polborn, K.; Knochel, P., *Chemistry – A European Journal* **2003,** *9*, 2797; Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P., *Angewandte Chemie International Edition* **2003,** *42,* 5763; Koradin, C.; Polborn, K.; Knochel, P., *Angewandte Chemie International Edition* **2002,** *41*, 2535.

Experimental Part

Apparatus, chemicals, and analyses

Unless otherwise noted, all experiments were performed under an argon atmosphere using standard Schlenk-type glassware. Solvents are of analytical grade or distilled before use. Toluene was distilled on sodium under an argon atmosphere. Diethyl ether and THF were distilled on sodium/benzophenone under an argon atmosphere. Dichloromethane, 1,2-dichloroethane, and acetonitrile were distilled on CaH_2 under an argon atmosphere. Solvents used for work-up were of technical grade. Commercial reagents were purchased from Acros, Sigma-Adrich, ABCR, TCI, STREM and Alfa, and used as received unless stated otherwise. 1H and 13C NMR spectra were recorded on Bruker-300 spectrometer or on a Bruker-500 spectrometer. 1H and 13C NMR chemical shifts are reported relative to $CDCl_3$ (7.26, 77.16 ppm), C_6D_6 (7.15 ppm, 128.06 ppm), CD_3CN (1.94 ppm, 118.26 ppm) and CD_2Cl_2 (5.32, 53.8 ppm). Spectral features were asigned as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad. 1,4-Dinitrobenzene was used as internal standard for 1H NMR. High resolution Mass Spectra were obtained from a Thermo Scientific QExactive, with accurate mass reported for the molecular ion [M+H]+ or suitable fragment ions. HPLC analyses were recorded on a Waters 600 apparatus with PDA 996 detector and 717 autosampler injector and columns Xbridge C18 2.5µm (4.6×50mm), and chiralpak IA 5µm (4.6×250mm). Products were diluted in isohexane/ethanol. Column chromatography was carried out on silica gel (ROCC 60, 40-63 µm). TLC analyses were performed on commercial aluminum plates bearing a 0.25 mm layer of Merck Silica gel 60F254, and revealed under UV at 254 nm and with a

solution of acidic or basic KMnO4. Stryker complex[1], IMesCuCl[2] and IMesCuDBM[3] were prepared by literature methods.

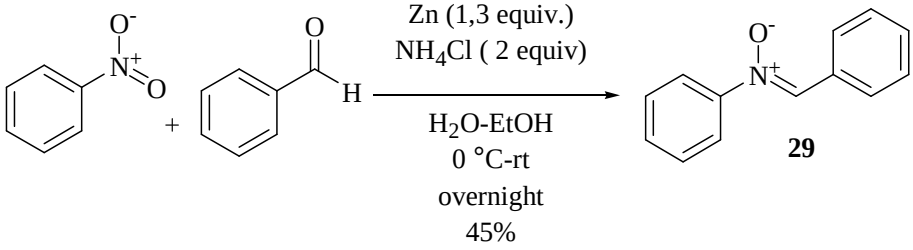
[1] Chiu, P.; Li, Z.; Fung, K. C. M., *Tetrahedron Letters* **2003,** *44*, 455.

[2] Citadelle, C. A.; Nouy, E. L.; Bisaro, F.; Slawin, A. M. Z.; Cazin, C. S. J., *Dalton Transactions* **2010,** *39*, 4489; Kaur, H.; Zinn, F. K.; Stevens, E. D.; Nolan, S. P., *Organometallics* **2004,** *23*, 1157; Jafarpour, L.; Stevens, E. D.; Nolan, S. P., *Journal of Organometallic Chemistry* **2000,** *606*, 49.

[3] Welle, A.; Díez-González, S.; Tinant, B.; Nolan, S. P.; Riant, O., *Organic Letters* **2006,** *8*, 6059.

I. Chapter 1: Synthesis of β-Lactams by Kinugasa Reaction

I.1 Synthesis of substrate 29[4]



Nitrobenzene (6.11 g, 50 mmol), benzaldehyde (6.08 mL, 50 mmol), NH_4Cl (3.47 g, 65 mmol), EtOH (100 mL) and water (100 mL) were added to a 500 mL round-bottomed flask. The reaction mixture was cooled to 0 °C, and zinc powder (6.53 g, 100 mmol) added slowly over 4 h. The mixture was then warmed to room temperature and stirred for 12 h. The reaction mixture was filtered through Celite and washed with CH_2Cl_2 (50 mL), and the filtrate extracted with CH_2Cl_2 (2 × 50 mL). The organic extracts were dried over $MgSO_4$ and concentrated to afford the crude product. This was purified by recrystallisation from dichloromethane and pentane. Off-white fine crystals were obtained with 45% yield.

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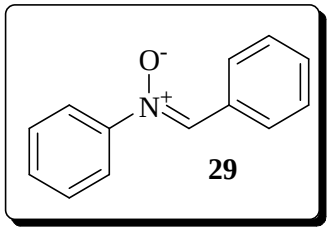
[4] Coyne, A. G.; Müller-Bunz, H.; Guiry, P. J., *Tetrahedron: Asymmetry* **2007,** *18*, 199.

- ***N*-Phenyl-*N*-(phenylmethylene)amine oxide 20**



29

Chemical Formula: $C_{13}H_{11}NO$
Molecular Weight: 197.08

^{1}H NMR (300 MHz, CDCl3) δ = 8.40 (dd, J = 6.8, 3.1 Hz, 2H), 7.94 (s, 1H), 7.83 – 7.73 (m, 1H), 7.49 (dd, J = 5.1, 2.4 Hz, 5H).

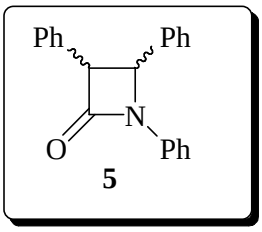
Spectral data are identical to those reported in the literature (CAS: 1137-96-8)[4].

I.2 Catalytic tests

I.2.1 General procedure for the preliminary catalytic tests of Kinugasa reaction using CuI as a catalyst

A flame-dried Schlenk tube under argon was charged with the copper iodide (0.066 mmol, 0.1 equiv.) and ligand (0.066 mmol, 0.1 equiv.) (Bipyridyl, rac-BINAP, DPPBz, XantPhos, dpePhos, MonoPhos (0.2 equiv.), QuiPhos). 2 mL of freshly distilled MeCN were introduced. After 2 hours the solution was cooled to 0°C and Cy_2NMe (0.66 mmol, 1 equiv.) was added. 10 min later, phenylacetylene (0.66 mmol, 1 equiv.) was added and the yellow solution was left to stir for a further 10 min. The nitrone (0.66 mmol, 1 equiv.) was finally added. The reaction mixture was stirred at r.t. for a further 120h. It was then poured into water, filtered over Celite. The celite bed was washed several times with AcOEt. The organic layers were washed by a saturated solution of NH_4Cl, water, and brine, and dried over Na_2SO_4 followed by the removal of solvents under reduced pressure. The final product was isolated by column chromatography with CH_2Cl_2 as the eluent.

- **1,3,4-triphenyl-azetidin-2-one 5**



5

Chemical Formula: $C_{21}H_{17}NO$
Molecular Weight: 299.37

Cis-3a: ^{1}H NMR: (300 MHz, CDCl3) δ = 7.35 (d, J = 35.0 Hz, 5H), 7.08 (dd, J = 7.3, 2.4 Hz, 10H), 5.47 (d, J = 6.1 Hz, 1H), 5.02 (d, J = 6.1 Hz, 1H). *Trans*-3a: ^{1}H NMR (300 MHz, CDCl3) δ 7.37 (dd, J = 9.5, 7.1 Hz, 13H), 7.08 (d, J = 7.4 Hz, 2H), 4.96 (d, J = 2.5 Hz, 1H), 4.28 (d, J = 2.5 Hz, 1H). ^{13}C NMR (75 MHz, CDCl3) δ = 165.78, 137.85, 134.51, 132.23, 129.24, 129.04, 128.37, 128.23, 128.02, 127.28, 124.21, 117.37, 60.50, 60.45.

The spectral data are identical to those reported in the literature (CAS: 7477-20-5)[5].

I.2.2 General procedure for the preliminary catalytic tests of Kinugasa reaction using a NHC catalyst

A flame-dried Schlenk tube under argon was charged with the NHC copper catalyst (0.066 mmol, 0.1 equiv.). 2 mL of the indicated solvent were introduced (freshly distilled MeCN, DCE). After 10 min the solution was cooled to 0°C and Cy_2NMe (0.66 mmol, 1 equiv.) was added. 10 min later, phenylacetylene (0.66 mmol, 1 equiv.) was added and the yellow solution was left to stir for a further 10 min. The nitrone (0.66 mmol, 1 equiv.) was finally added. The reaction mixture was stirred at r.t. for further 120h (or as precised). It was then poured into water, filtered over Celite. The celite bed was washed several times with AcOEt. The organic layers were washed by a saturated solution of NH_4Cl, water, and brine, and dried over Na_2SO_4

[5] McKay, C. S.; Kennedy, D. C.; Pezacki, J. P., *Tetrahedron Letters* **2009,** *50*, 1893.

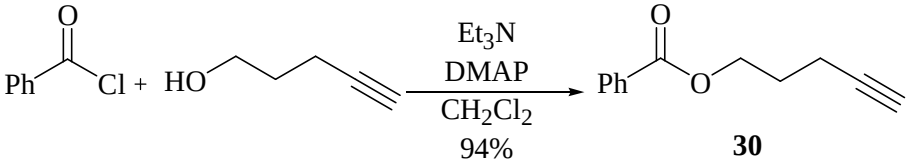
followed by the removal of solvents under reduced pressure. The final product was isolated by column chromatography with CH_2Cl_2 as the eluent.

I.2.3 General procedure for the optimization catalytic tests of Kinugasa reaction using IMesCuDBM

A flame-dried Schlenk tube under argon was charged with the NHC copper catalyst (1 mmol, 0.1 equiv.). The indicated solvent was introduced in the specified amount depending on the concentration (freshly distilled MeCN, DCE, THF, AcOEt). After 10 min the solution was cooled to 0°C and the indicated base (1 mmol, 1 equiv.) was added. 10 min later, phenylacetylene (1 mmol, 1 equiv.) was added and the yellow solution was left to stir for a further 10 min. The nitrone (1 mmol, 1 equiv.) was finally added. The reaction mixture was stirred at the indicated temperatures for further 48h. It was then poured into water, filtered over Celite. The celite bed was washed several times with AcOEt. The organic layers were washed by a saturated solution of NH_4Cl, water, and brine, and dried over Na_2SO_4 followed by the removal of solvents under reduced pressure. The final product was isolated by column chromatography with PE/CH_2Cl_2: 1/1 as the eluent.

I.2.4 Synthesis of substrates 30, 31, 32, 33-44, 45-47

I.2.4.1 Synthesis of substrate 30[6]

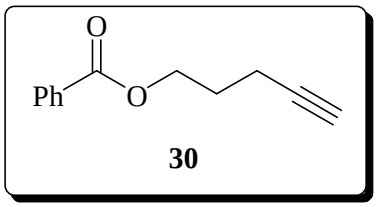


30

[6] Cornelissen, L.; Vercruysse, S.; Sanhadji, A.; Riant, O., *European Journal of Organic Chemistry* **2014,** *2014*, 35.

To a solution of 4-Pentyn-1-ol (6 mmol, 1 equiv.) in DCM (12 mL) was added 4-Dimethylaminopyridine (0.45 mmol, 0.075 equiv.) and Et_3N (7.2 mmol, 1.2 equiv.). The solution was cooled down to 0°C and benzoyl chloride (7.2 mmol, 1.2 equiv.) was added dropwise. The resulting solution was stirred at room temperature during 1h30, filtrated trough a short pad of silica and evaporated in vacuo. The residue was purified by flash chromatography PE/AcOEt : 97/3 to afford **30** in 90% yield as a colorless oil.

- **Pent-4-ynyl benzoate 30**



30

Chemical Formula: $C_{12}H_{12}O_2$
Molecular Weight: 188.22

^{1}H NMR (300 MHz, CDCl3) δ = 8.05 (d, J = 7.2 Hz, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.44 (t, J = 7.5 Hz, 2H), 4.43 (t, J = 6.2 Hz, 2H), 2.39 (td, J = 7.0, 2.6 Hz, 2H), 2.10 – 1.93 (m, 3H).

The spectral data are identical to those reported in the literature (CAS: 100330-28-7)[6].

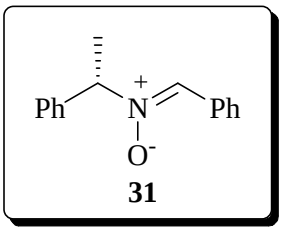
I.2.4.2 Synthesis of substrate 31

(*S*)-(−)-*N*-Benzyl-α-methylbenzylamine was prepared according to a literature method[7]. In a dry tricol equipped with a thermometer, under argon, (*S*)-(−)-N-Benzyl-α-methylbenzylamine (6.3 mmol, 1 equiv.) was introduced. 20 mL of CH_2Cl_2 are added. The solution wass cooled to 0°C in an ice bath. *m*-CPBA (14.9 mmol, 2.35 equiv.) was added in small portions over 30 min such that T< 7°C. The ice bath was removed and the reaction

[7] Cheetham, C. A.; Massey, R. S.; Pira, S. L.; Pritchard, R. G.; Wallace, T. W., *Organic & Biomolecular Chemistry* **2011,** *9*, 1831.

was stirred at r.t. for about 1h. The mixture was then cooled to 0°C, and aqueous $Na_2S_2O_3$ (12.9 mmol, 6 mL H_2O) and saturated $NaHCO_3$ (20 mL) were added. The reaction mixture was stirred vigorously for 15 min until dissolved. The phases were separated, and the organic layer is washed with brine (20 mL). The combined aqueous phases are extracted with 3x CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography PE/AcOEt : 9/1-7/3 to afford **31** in 76% yield.

- **(*S*)-*C*-phenyl-*N*-α-phenylethyl-N-oxide 36**



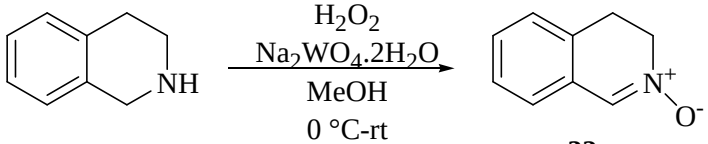
31

Chemical Formula: $C_{15}H_{15}NO$
Molecular Weight: 225.29

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.22 (dd, J = 6.7, 3.0 Hz, 2H), 7.58 – 7.34 (m, 9H), 5.22 (d, J = 6.9 Hz, 1H), 1.91 (d, J = 6.9 Hz, 3H).

The spectral data are identical to those reported in the literature (CAS: 64282-92-4)[8].

I.2.4.3 Synthesis of substrate 32[9]



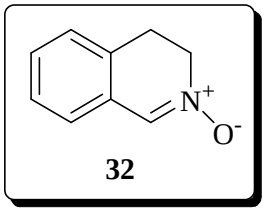
32

[8] Ballistreri, F. P.; Chiacchio, U.; Rescifina, A.; Tomaselli, G. A.; Toscano, R. M., *Tetrahedron* **1992,** *48*, 8677.

[9] Radivoy, G.; Radivoy, G.; Alonso, F.; Yus, M., *Synthesis* **2001,** *2001*, 0427.

In a 100 mL two-necked round bottom flask, equipped with a Teflon- coated magnetic stirring bar, were placed the corresponding secondary amine (10.0 mmol, 1 equiv.), $Na_2WO_4 \cdot 2H_2O$ (0.4 mmol, 0.04 equiv.), and MeOH (20 mL). To the stirred solution was added dropwise 30% aq H_2O_2 (30.0 mmol, 3 equiv.) with ice cooling. After the addition was complete, the reaction mixture was stirred at r.t. for 3 h. MeOH was removed under reduced pressure. To the resulting residue was added CH_2Cl_2 (80 mL) and brine (40 mL). The organic layer was separated, washed with brine (2 × 30 mL), dried (Na_2SO_4), filtered, and evaporated. Short column flash chromatography (silica gel packed in 9:1 EtOAc/MeOH, $CHCl_3$/ MeOH as eluent) gave the corresponding nitrone **32** in 94% yield.

- **3,4-Dihydroisoquinoline N-oxide 32**



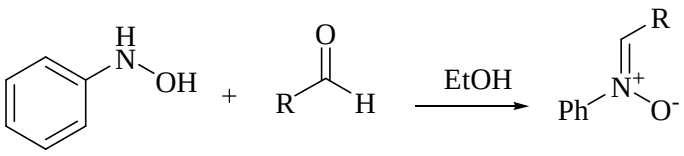
32

Chemical Formula: C_9H_9NO
Molecular Weight: 147.17

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.76 (s, 1H), 7.32 – 7.17 (m, 3H), 7.17 – 7.07 (m, 1H), 4.11 (td, J = 7.7, 1.1 Hz, 2H), 3.18 (t, J = 7.8 Hz, 2H).

The spectral data are identical to those reported in the literature (CAS: 24423-87-8)[9].

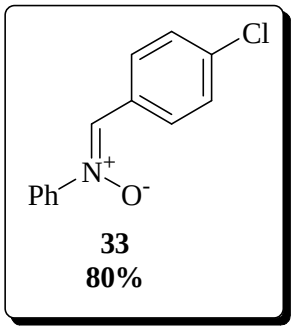
I.2.5. General procedure for the synthesis of nitrones 33-44



N-phenylhydroxylamine was synthesized according to a literature method[10].
To a 10 ml round flask containing a magnetic stirrer were added *N*-phenylhydroxylamine (5 mmol, 1 equiv.) and absolute ethanol (8 mL). The golden mixture was stirred until the hydroxylamine dissolved. The corresponding aldehyde (5mol, 1 equiv.) was added via a syringe. The flask was sealed with a rubber septum and stirred at r.t. for 4h. A white precipitate formed after about 30 min. Additional ethanol (1 mL) was added to facilitate stirring. The reaction flask was stored overnight in the refrigerator (5°C). The solid nitrone product was collected by vacuum filtration using a glass frit. In certain cases the nitrone products did not immediately precipitate from the ethanol solution, thus, small amounts (2-3 mL) of hexane were added to the hydroxylamine/aldehyde solution and/or the reaction mixtures were cooled to -20°C in a freezer until the product precipitated. The crude product was rinsed with hexane and dried under full vacuum to give crystalline solids. Additional product could be obtained by concentration of the mother liquor using a rotatory evaporator. The crude product was pure in all cases.

[10] Wittstein, K.; García, A. B.; Schürmann, M.; Kumar, K., *Synlett* **2012,** *2012*, 227.

➢ ***N*-[(4-Chlorophenyl)methylene]benzenamine *N*-oxide 33**



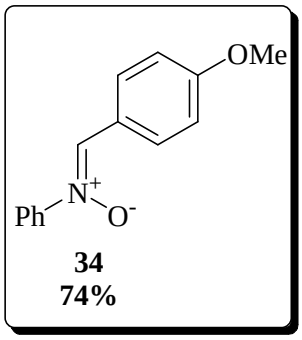
33
80%

The product was obtained as off-white crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.36 (d, J = 8.7 Hz, 2H), 7.91 (s, 1H), 7.82 – 7.72 (m, 2H), 7.52 – 7.40 (m, 5H).

The spectral data are identical to those reported in the literature (CAS: 5909-74-0)[11].

Chemical Formula:
$C_{13}H_{10}ClNO$
Molecular Weight: 231.68

➢ ***N*-[(4-methoxyphenyl)methylene]benzenamine *N*-oxide 34**



34
74%

The product was obtained as off-white crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.41 (d, J = 9.0 Hz, 2H), 7.86 (s, 1H), 7.82 – 7.72 (d, 2H), 7.46 (m, J = 7.1 Hz, 3H), 7.00 (d, J = 8.9 Hz, 2H), 3.88 (s, 3H).

The spectral data are identical to those reported in the literature (CAS: 3585-93-1)[11].

Chemical Formula:
$C_{14}H_{13}NO_2$
Molecular Weight: 227.26

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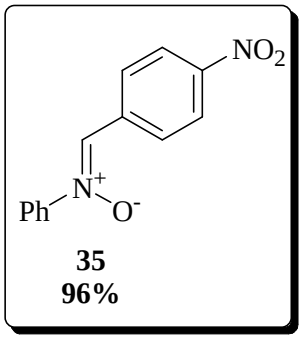
[11] Nelson, D. W.; Owens, J.; Hiraldo, D., *The Journal of Organic Chemistry* **2001,** *66*, 2572.

➢ ***N*-[(4-nitrophenyl)methylene]benzenamine *N*-oxide 35**



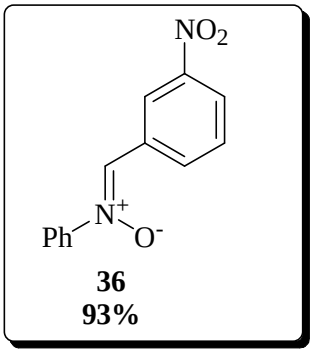
35
96%

The product was obtained as yellow crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.56 (d, J = 9.0 Hz, 2H), 8.32 (d, J = 9.1 Hz, 2H), 8.07 (s, 1H), 7.84 – 7.74 (m, 2H), 7.57 – 7.48 (m, 3H).

The spectral data are identical to those reported in the literature (CAS: 3585-90-8)[11].

Chemical Formula: $C_{13}H_{10}N_2O_3$
Molecular Weight: 242.23

➢ ***N*-[(3-nitrophenyl)methylene]benzenamine *N*-oxide 36**



36
93%

The product was obtained as yellow crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.18 (t, J = 2.0 Hz, 1H), 8.84 (d, J = 8.0 Hz, 1H), 8.36 – 8.25 (m, 1H), 8.07 (s, 1H), 7.84 – 7.74 (m, 2H), 7.67 (s, 1H), 7.57 – 7.48 (m, 3H).

The spectral data are identical to those reported in the literature (CAS: 19865-57-7)[12].

Chemical Formula: $C_{13}H_{10}N_2O_3$
Molecular Weight: 242.23

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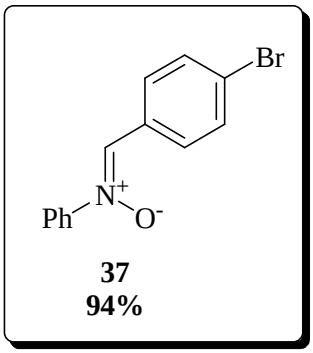
[12] Reyes, L.; Corona, S.; Arroyo, G.; Delgado, F.; Miranda, R., *International Journal of Molecular Sciences* **2010,** *11*, 2576.

- ***N*-[(4-Bromophenyl)methylene]benzenamine *N*-oxide 37**



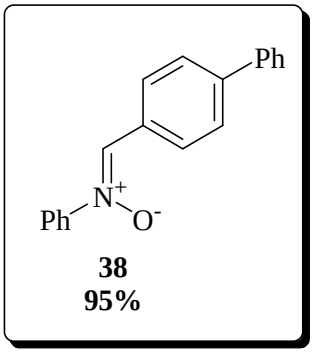
37
94%

Chemical Formula: $C_{13}H_{10}BrNO$
Molecular Weight: 276.13

The product was obtained as white crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.29 (d, J = 8.6 Hz, 2H), 7.90 (s, 1H), 7.80 – 7.72 (m, 2H), 7.61 (d, J = 8.7 Hz, 2H), 7.53 – 7.44 (m, 3H).

The spectral data are identical to those reported in the literature (CAS: 24720-81-8)[13].

- ***N*-[(1,1'-biphenyl)-4-ylmethylene]benzenamine *N*-oxide 38**



38
95%

Chemical Formula: $C_{19}H_{15}NO$
Molecular Weight: 273.12

The product was obtained as white crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.48 (d, J = 8.5 Hz, 2H), 7.97 (s, 1H), 7.86 – 7.62 (m, 6H), 7.54 – 7.35 (m, 6H).

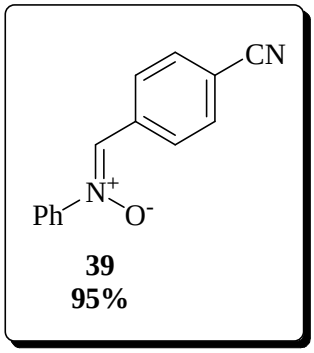
The spectral data are identical to those reported in the literature (CAS: 602332-30-9)[14].

---

[13] Duguet, N.; Slawin, A. M. Z.; Smith, A. D., *Organic Letters* **2009,** *11*, 3858.

[14] Ravi Kumar, K. R.; Mallesha, H.; Basappa; Rangappa, K. S., *European Journal of Medicinal Chemistry* **2003,** *38*, 613.

➢ **4-[(phenylimino)methyl]benzonitrile *N*-oxide 39**



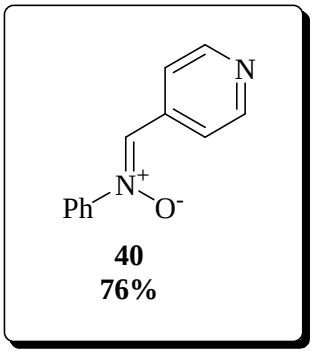
39
95%

Chemical Formula: $C_{14}H_{10}N_2O$
Molecular Weight: 222.24

The product was obtained as white crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.48 (d, J = 8.5 Hz, 2H), 8.00 (s, 1H), 7.75 (d, J = 8.5 Hz, 4H), 7.56 – 7.47 (m, 3H).

The spectral data are identical to those reported in the literature (CAS: 26447-78-9)[15].

➢ ***N*-(4-pyridinylmethylene)Benzenamine *N*-oxide 40**



40
76%

Chemical Formula: $C_{12}H_{10}N_2O$
Molecular Weight: 198.22

The product was obtained as white crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.76 (d, J = 6.2 Hz, 2H), 8.21 – 8.12 (m, 2H), 7.96 (s, 1H), 7.82 – 7.72 (m, 2H), 7.56 – 7.47 (m, 3H).

The spectral data are identical to those reported in the literature (CAS: 20147-42-6)[11].

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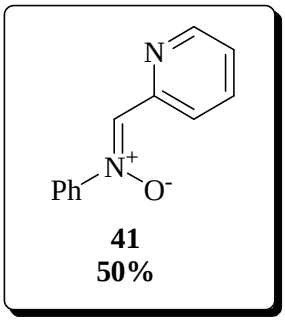
[15] Yijima, C.; Tsujimoto, T.; Suda, K.; Yamauchi, M., *Bulletin of the Chemical Society of Japan* **1986,** *59*, 2165.

- ***N*-(2-pyridinylmethylene)Benzenamine *N*-oxide 41**



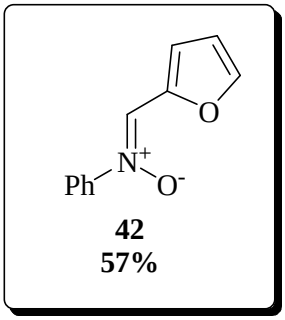
41
50%

Chemical Formula: $C_{12}H_{10}N_2O$
Molecular Weight: 198.22

The product was obtained as white crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.35 (d, J = 8.0 Hz, 1H), 8.70 (s, 1H), 8.29 (s, 1H), 7.89 – 7.77 (m, 3H), 7.50 (dd, J = 5.1, 1.9 Hz, 3H), 7.34 (ddd, J = 7.6, 4.8, 1.2 Hz, 1H).

The spectral data are identical to those reported in the literature (CAS: 20147-40-4)[11].

- ***N*-[(*α*-furyl)methylene]benzenamine *N*-oxide 42**



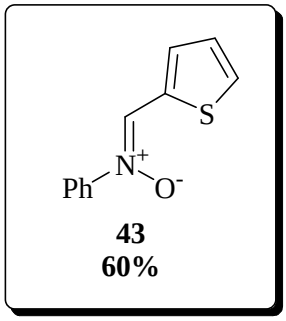
42
57%

Chemical Formula: $C_{11}H_9NO_2$
Molecular Weight: 187.19

The product was obtained as white crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.16 (s, 1H), 8.01 (d, J = 3.5 Hz, 1H), 7.85 – 7.75 (m, 2H), 7.59 (d, J = 1.6 Hz, 1H), 7.53 – 7.43 (m, 3H), 6.65 (dd, J = 3.7, 1.8 Hz, 1H).

The spectral data are identical to those reported in the literature (CAS: 35998-79-9)[11].

- ***N*-[(*α*-furyl)methylene]benzenamine *N*-oxide 43**

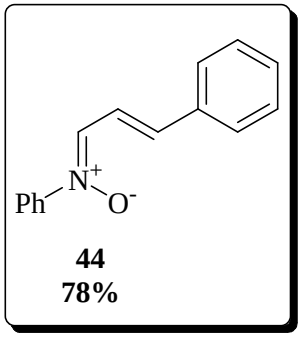


43
60%

Chemical Formula: $C_{11}H_9NOS$
Molecular Weight: 203.26

The product was obtained as white crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.49 (s, 1H), 7.83 (dd, J = 8.0, 1.9 Hz, 2H), 7.59 (dd, J = 14.7, 4.3 Hz, 1H), 7.56 (d, J = 5.1 Hz, 1H), 7.48 (d, J = 7.5 Hz, 3H), 7.22 (dd, J = 5.1, 3.8 Hz, 1H).
The spectral data are identical to those reported in the literature (CAS: 2780-52-1)[16].

- ***N*-(3-phenyl-2-propenylidene)benzenamine *N*-oxide 44**



44
78%

Chemical Formula: $C_{15}H_{13}NO$
Molecular Weight: 223.27

The product was obtained as white crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.86 (dd, J = 9.6 Hz, 1H), 7.83 (m, 3H), 7.59 (dd, J = 14.7, 4.3 Hz, 2H), 7.48 (m, 3H), 7.40 (m, 3H), 7.16 (d, J = 16.1 Hz, 1H).
The spectral data are identical to those reported in the literature (CAS: 37056-75-0)[11].

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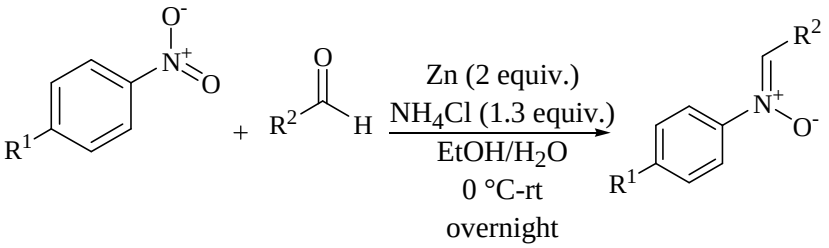
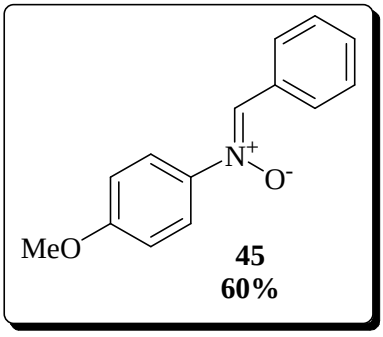
[16] Dooley, B. M.; Bowles, S. E.; Storr, T.; Frank, N. L., *Organic Letters* **2007,** *9*, 4781.

I.2.6 General procedure for the synthesis of nitrones 45-47[17]



The nitroarene (10 mmol, 1 equiv.), the aldehyde (10 mmol, 1 equiv.), NH_4Cl (13 mmol, 1.3 equiv.), EtOH (20 mL), and water (20 mL) were added to a 100-mL round-bottom flask. The reaction mixture was cooled to 0 °C, and zinc (20 mmol, 2 equiv.) was added slowly over 4 h. The mixture was then warmed to r.t. and stirred for 12 h. The reaction mixture was filtered through Celite (CH_2Cl_2 washings), and the filtrate was extracted (CH_2Cl_2). The organic extracts were dried ($MgSO_4$) and concentrated to afford the crude product, which was purified by recrystallization in CH_2Cl_2 and hexane.

- ***N*-(4-Methoxyphenyl)-α-phenylnitrone 45**



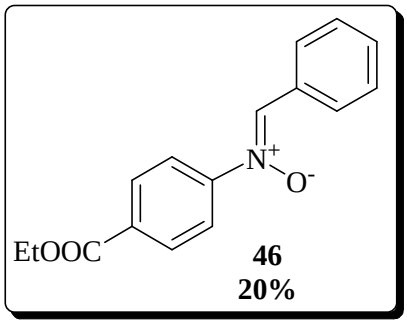
Chemical Formula $C_{14}H_{13}NO_2$
Molecular weight: 227.26

The product was obtained as white crystals. ^1H NMR (300 MHz, $CDCl_3$) δ = 8.43 – 8.33 (m, 2H), 7.88 (s, 1H), 7.73 (d, J = 9.0 Hz, 2H), 7.47 (dd, J = 5.3, 2.1 Hz, 3H), 6.96 (d, J = 9.0 Hz, 2H), 3.86 (s, 3H).

[17] Lo, M. M. C.; Fu, G. C., *Journal of the American Chemical Society* **2002,** *124*, 4572.

The spectral data are identical to those reported in the literature (CAS: 19064-76-7)[11].

- ***N*-(4-carboethoxyphenyl)-*α*-phenylnitrone 46**

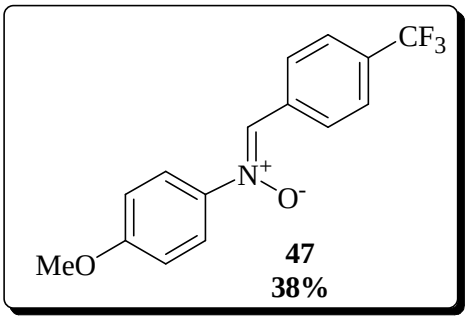


Chemical Formula $C_{16}H_{15}NO_3$
Molecular weight: 269.30

The product was obtained as white crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.41 (dd, J = 7.1, 2.5 Hz, 2H), 8.16 (d, J = 8.7 Hz, 2H), 8.08 (s, 1H), 7.95 – 7.77 (m, 2H), 7.51 (dd, J = 6.0, 1.7 Hz, 3H), 4.42 (q, J = 7.1 Hz, 2H), 1.42 (t, J = 7.2 Hz, 3H).

The spectral data are identical to those reported in the literature (CAS: 51911-71-8)[17].

- ***N*-(4-methoxyphenyl)-*α*-(4-trifluoromethylphenyl)nitrone 47**



Chemical Formula $C_{15}H_{12}F_3NO_2$
Molecular weight: 295.26

The product was obtained as white crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.47 (d, J = 8.3 Hz, 2H), 7.95 (s, 1H), 7.71 (dd, J = 9.0, 7.1 Hz, 4H), 6.96 (d, J = 9.1 Hz, 2H), 3.86 (s, 3H).

The spectral data are identical to those reported in the literature (CAS: 434283-62-2)[17].

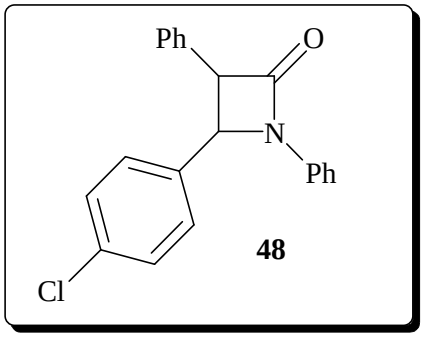
I.2.7 General procedure for the optimized Kinugasa reaction system for the synthesis of cis-β-lactams

In a flame dried schlenk, *N*,*N*-Dicyclohexylmethylamine (1mmol, 1equiv.) is added to a suspension of IMesCudbm (0.1 mmol, 0.1 equiv.) in dry dichloroethane (1 mL) at 0°C, under argon. 15 minutes later, the acetylene (1 mmol, 1equiv.) is added. The mixture was further stirred for 15 min, and then the nitrone (1mmol, 1equiv.) is added. After 15 minutes, the temperature is regulated to 12°C, and the reaction mixture is left for 48 h. The mixture is then filtered over celite, the solvent evaporated, a few ml of AcOEt added and the solution washed with HCl, water, and brine, and then purified by automated chromatography column using gradients of petroleum ether and ethyl acetate.

I.2.8 General procedure for the optimized Kinugasa reaction system for the synthesis of trans-β-lactams

In a flame dried schlenk, DBU (1mmol, 1equiv.) is added to a suspension of IMesCudbm (0.1 mmol, 0.1 equiv.) in dry THF (1 mL) at 0°C, under argon. 15 minutes later, the acetylene (1 mmol, 1equiv.) is added. The mixture was further stirred for 15 min, and then the nitrone (1mmol, 1equiv.) is added. After 15 minutes, the temperature is regulated to 12°C, and the reaction mixture is left for 48 h. The mixture is then filtered over celite, the solvent evaporated, a few ml of AcOEt added, the solution washed with HCl, water, and brine, and then purified by automated chromatography column using gradients of petroleum ether and ethyl acetate.

➢ **4-(4-chlorophenyl)-1,3-diphenylazetidin-2-one 48**



48

Chemical Formula $C_{21}H_{16}ClNO$
Molecular weight: 333.81

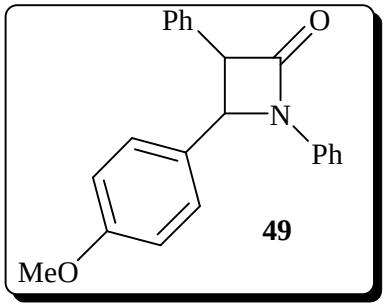
***Cis*-48**: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.39 (dd, J = 8.6, 1.1 Hz, 2H), 7.29 (dd, J = 13.4, 5.0 Hz, 2H), 7.19 – 6.92 (m, 10H), 5.44 (d, J = 6.1 Hz, 1H), 5.01 (d, J = 6.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 165.49 (s), 137.58 (s), 133.83 (s), 133.18 (s), 131.89 (s), 129.29 (s), 128.92 (s), 128.61 (s), 128.59 (s), 128.43 (s), 127.57 (s), 124.36 (s), 117.25 (s), 60.45 (s), 59.79 (s).

***Trans*-48**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.24 (m, 13H), 7.10 (dd, J = 11.3, 4.3 Hz, 1H), 4.94 (d, J = 2.5 Hz, 1H), 4.25 (d, J = 2.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 165.47 (s), 137.37 (s), 136.20 (s), 134.69 (s), 134.52 (s), 129.72 (s), 129.34 (s), 129.27 (s), 128.22 (s), 127.58 (s), 127.41 (s), 124.41 (s), 117.29 (s), 65.38 (s), 63.22 (s).

MS (ESI): m/z = 334.2 $[M + H]^+$. (CAS: 62500-55-4, 68271-51-2)[18]

[18] Miura, M.; Enna, M.; Okuro, K.; Nomura, M., *The Journal of Organic Chemistry* **1995,** *60*, 4999.

➢ **4-(4-methoxyphenyl)-1,3-diphenylazetidin-2-one 49**



49

Chemical Formula $C_{22}H_{19}NO_2$
Molecular weight: 329.39

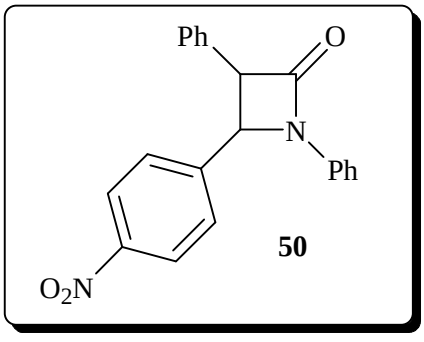
***Cis*-49:** ^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.46 – 7.40 (m, 2H), 7.28 (dd, J = 11.4, 4.5 Hz, 2H), 7.13 – 7.04 (m, 6H), 7.02 – 6.97 (m, 2H), 6.65 (d, J = 8.7 Hz, 2H), 5.43 (d, J = 6.0 Hz, 1H), 4.98 (d, J = 6.0 Hz, 1H), 3.67 (s, 3H).

***Trans*-49**: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.61 – 7.16 (m, 11H), 7.08 (dd, J = 4.9, 3.5 Hz, 1H), 6.99 – 6.89 (m, 2H), 4.91 (d, J = 2.5 Hz, 1H), 4.26 (d, J = 2.5 Hz, 1H), 3.81 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 165.90 (s), 159.26 (s), 137.85 (s), 132.42 (s), 129.17 (s), 128.96 (s), 128.49 (s), 128.25 (s), 127.24 (s), 126.37 (s), 124.09 (s), 117.36 (s), 113.78 (s), 60.36 (s), 60.06 (s), 55.18 (s).

MS (ESI): m/z = 330.3 $[M + H]^+$. (CAS: 62500-42-9)[18]

➢ **4-(4-nitrophenyl)-1,3-diphenylazetidin-2-one 50**



50

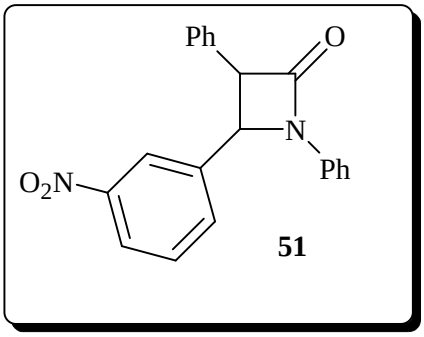
Chemical Formula $C_{21}H_{16}N_2O_3$
Molecular weight: 344.36

***Cis*-50**: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.98 (d, J = 8.8 Hz, 2H), 7.36-7.23 (m, 6H), 7.13-7.05 (m, 6H), 5.56 (d, J = 6.2 Hz, 1H), 5.11 (d, J = 6.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 164.96 (s), 147.46 (s), 142.34 (s), 137.24 (s), 129.41 (s), 128.80 (s), 128.58 (s), 128.08 (s), 127.90 (s), 124.66 (s), 123.55 (s), 117.09 (s), 60.76 (s), 59.57 (s).

***Trans*-50**: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.28 (d, J = 8.7 Hz, 2H), 7.58 (d, J = 8.7 Hz, 2H), 7.33 (dd, J = 11.6, 3.1 Hz, 9H), 7.12 (s, 1H), 5.06 (d, J = 2.6 Hz, 1H), 4.27 (d, J = 2.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 164.86 (s), 148.22 (s), 144.91 (s), 137.01 (s), 133.86 (s), 129.47 (s), 129.37 (s), 128.48 (s), 127.56 (s), 126.89 (s), 124.77 (s), 124.72 (s), 117.15 (s), 65.35 (s), 62.79 (s).

MS (ESI): m/z = 345.3 $[M + H]^+$ (CAS: 138714-67-7, 1150585-74-2)[19]

- **4-(3-nitrophenyl)-1,3-diphenylazetidin-2-one 51**



51

Chemical Formula $C_{21}H_{16}N_2O_3$
Molecular weight: 344.36

***Cis*-51**: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.96 (d, J = 1.1 Hz, 2H), 7.34 (dd, J = 13.3, 4.1 Hz, 6H), 7.15 – 7.03 (m, 6H), 5.56 (d, J = 6.1 Hz, 1H), 5.11 (d, J = 6.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 165.01 (s), 148.16 (s), 137.27 (s), 133.01 (s), 131.42 (s), 129.49 (s), 128.89 (s), 128.67 (s), 127.86 (s), 124.73 (s), 123.16 (s), 122.34 (s), 117.17 (s), 60.77 (s), 59.53 (s).

***Trans*-51**: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.32 – 8.19 (m, 2H), 7.79 – 7.72 (m, 1H), 7.62 (t, J = 7.9 Hz, 1H), 7.46 – 7.27 (m, 9H), 7.11 (ddd, J = 8.5, 6.1, 2.3 Hz, 1H), 5.08 (s, 1H), 4.30 (d, J = 2.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 165.02 (s), 149.07 (s), 140.07 (s), 137.03 (s), 133.95 (s), 131.76 (s), 130.77 (s), 129.51 (s), 129.41 (s), 128.50 (s), 127.58 (s), 124.73 (s), 123.93 (s), 121.35 (s), 117.21 (s), 65.46 (s), 62.85 (s).

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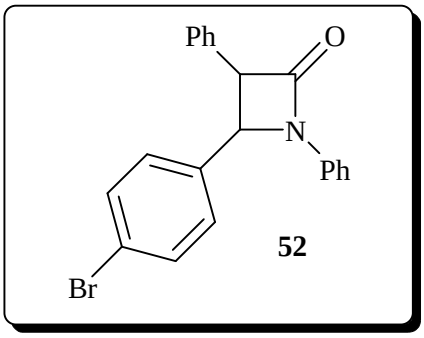
[19] McKay, C. S.; Kennedy, D. C.; Pezacki, J. P., *Tetrahedron Letters* **2009,** *50*, 1893.

MS (ESI): m/z = 345.2 $[M + H]^+$. (CAS: 918652-26-3, 1150585-73-1)[19]

- **4-(4-bromophenyl)-1,3-diphenylazetidin-2-one 52**



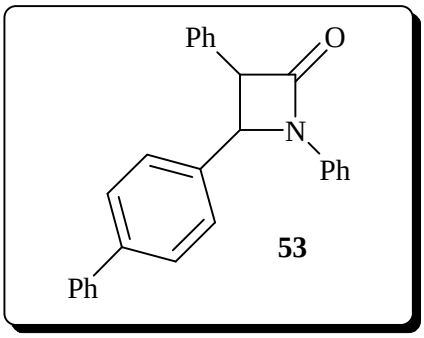
Chemical Formula $C_{21}H_{16}BrNO$
Molecular weight: 378.26

***Cis*-52**: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.33 (ddd, J = 17.6, 9.5, 1.5 Hz, 6H), 7.24 – 7.00 (m, 6H), 6.95 (d, J = 8.4 Hz, 2H), 5.42 (d, J = 6.1 Hz, 1H), 5.02 (d, J = 6.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 165.35 (s), 137.45 (s), 133.61 (s), 131.73 (s), 131.45 (s), 129.18 (s), 128.80 (s), 128.35 (s), 127.49 (s), 124.27 (s), 121.92 (s), 117.14 (s), 60.30 (s), 59.76 (s).

***Trans*-52**: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.54 (d, J = 8.4 Hz, 2H), 7.37 – 7.26 (m, 11H), 7.10 (d, J = 7.0 Hz, 1H), 4.92 (d, J = 2.5 Hz, 1H), 4.24 (d, J = 2.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 165.43 (s), 137.33 (s), 136.71 (s), 134.48 (s), 132.65 (s), 129.33 (s), 129.25 (s), 128.21 (s), 127.70 (s), 127.56 (s), 124.40 (s), 122.76 (s), 117.27 (s), 65.31 (s), 63.25 (s).

MS (ESI): m/z = 378.2 $[M + H]^+$. (CAS: 138714-66-6, 1150585-70-8)[19]

- **4-(biphenyl-4-yl)-1,3-diphenylazetidin-2-one 53**



Chemical Formula $C_{27}H_{21}NO$
Molecular weight: 375.46

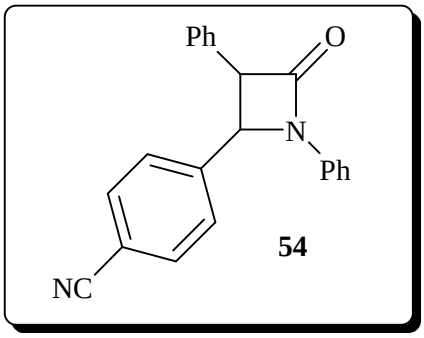
***Cis*-53**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 – 7.42 (m, 4H), 7.42 – 7.27 (m, 7H), 7.20 – 6.95 (m, 8H), 5.51 (d, J = 6.1 Hz, 1H), 5.04 (d, J = 6.1 Hz, 1H).

***Trans*-53**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (t, J = 9.8 Hz, 4H), 7.47 – 7.35 (m, 12H), 7.08 (s, 3H), 5.01 (d, J = 2.6 Hz, 1H), 4.33 (d, J = 2.5 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 165.81 (s), 140.71 (s), 140.42 (s), 137.87 (s), 133.59 (s), 132.20 (s), 129.28 (s), 129.04 (s), 128.85 (s), 128.31 (s), 127.75 (s), 127.53 (s), 127.41 (s), 127.01 (s), 124.26 (s), 117.40 (s), 60.56 (s), 60.28 (s).

HRMS-ESI (m/z) calcd. for $C_{27}H_{22}ON$ $[M + H]^+$ 376.16959; found 376.16959.

- **4-(4-oxo-1,3-diphenylazetidin-2-yl)benzonitrile 54**



54

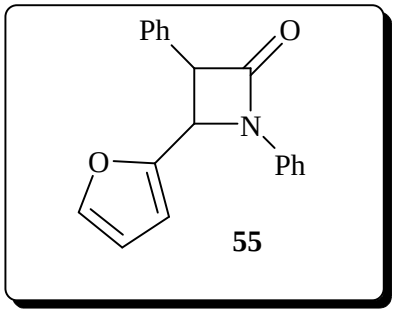
Chemical Formula $C_{22}H_{16}N_2O$
Molecular weight: 324.38

***Cis*-54**: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.42 – 7.30 (m, 7H), 7.15 – 7.01 (m, 7H), 5.50 (d, J = 6.2 Hz, 1H), 5.07 (d, J = 6.2 Hz, 1H).δ 7.43 – 7.06 (m, 14H), 5.01 (d, J = 2.6 Hz, 1H), 4.24 (d, J = 2.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 165.04 (s), 140.33 (s), 137.32 (s), 132.15 (s), 131.37 (s), 129.42 (s), 128.84 (s), 128.55 (s), 127.91 (s), 124.64 (s), 118.45 (s), 117.13 (s), 111.87 (s), 60.73 (s), 59.77 (s).

***Trans*-54**: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.75 – 7.68 (m, 2H), 7.55 – 7.48 (m, 2H), 7.45 – 7.27 (m, 9H), 7.12 (d, J = 4.2 Hz, 1H), 5.01 (d, J = 2.6 Hz, 1H), 4.25 (d, J = 2.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 164.87 (s), 142.92 (s), 136.98 (s), 133.93 (s), 133.22 (s), 129.36 (s), 129.25 (s), 128.33 (s), 127.47 (s), 126.65 (s), 124.56 (s), 118.30 (s), 117.08 (s), 112.68 (s), 77.55 (s), 77.12 (s), 76.70 (s), 65.20 (s), 62.96 (s).

MS (ESI): m/z = 325.2 $[M + H]^+$. (CAS: 1150585-72-0, 1150585-77-5)[19]

- **4-(furan-2-yl)-1,3-diphenylazetidin-2-one 55**



55

Chemical Formula $C_{19}H_{15}NO_2$
Molecular weight: 289.33

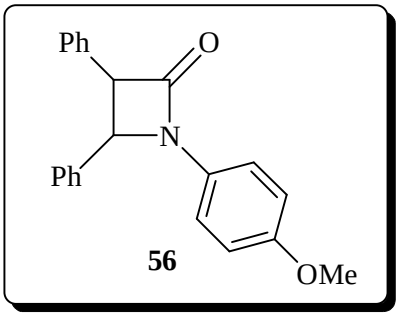
***Cis*-55**: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.52 – 7.00 (m, 11H), 6.12 (d, J = 1.8 Hz, 2H), 5.47 (d, J = 5.9 Hz, 1H), 4.97 (d, J = 5.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 165.34 (s), 148.38 (s), 142.99 (s), 137.70 (s), 132.36 (s), 129.22 (s), 128.64 (s), 128.31 (s), 127.61 (s), 124.34 (s), 117.14 (s), 110.45 (s), 109.85 (s), 59.81 (s), 54.53 (s).

***Trans*-55**:^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.48 – 7.27 (m, 10H), 7.09 (s, 1H), 6.49 (d, J = 3.2 Hz, 1H), 6.40 (dd, J = 3.3, 1.8 Hz, 1H), 5.01 (d, J = 2.7 Hz, 1H), 4.64 (d, J = 2.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 165.45 (s), 150.04 (s), 143.57 (s), 137.75 (s), 134.47 (s), 129.24 (s), 129.17 (s), 128.12 (s), 127.60 (s), 124.34 (s), 117.06 (s), 110.87 (s), 109.77 (s), 61.64 (s), 56.82 (s).

MS (ESI): m/z = 290.2 $[M + H]^+$. (CAS: 888735-49-7, 1380590-89-5)[20]

[20] Chen, J.-H.; Liao, S.-H.; Sun, X.-L.; Shen, Q.; Tang, Y., *Tetrahedron* **2012,** *68*, 5042.

➢ **1-(4-methoxyphenyl)-3,4-diphenylazetidin-2-one 56**



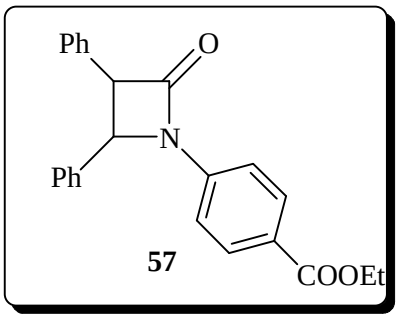
Chemical Formula $C_{22}H_{19}NO_2$
Molecular weight: 329.39

***Cis*-56**: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.36 (d, J = 9.1 Hz, 2H), 7.12 – 7.00 (m, 10H), 6.82 (d, J = 9.1 Hz, 2H), 5.43 (d, J = 6.0 Hz, 1H), 5.00 (d, J = 6.0 Hz, 1H), 3.76 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 165.16 (s), 156.23 (s), 134.63 (s), 132.37 (s), 131.46 (s), 129.03 (s), 128.33 (s), 128.20 (s), 127.98 (s), 127.30 (s), 127.25 (s), 118.63 (s), 114.45 (s), 60.49 (s), 55.59 (s).

***Trans*-56**:^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.28 (m, 12H), 6.81 (d, J = 9.0 Hz, 2H), 4.92 (d, J = 2.5 Hz, 1H), 4.27 (d, J = 2.4 Hz, 1H), 3.75 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 165.17 (s), 156.27 (s), 137.73 (s), 135.00 (s), 131.17 (s), 129.42 (s), 129.16 (s), 128.79 (s), 128.01 (s), 127.62 (s), 126.09 (s), 118.66 (s), 114.49 (s), 65.27 (s), 63.96 (s), 55.59 (s).

MS (ESI): m/z = 330.3 $[M + H]^+$. (CAS: 121389-27-3, 73308-41-5)[18]

➢ **ethyl 4-(2-oxo-3,4-diphenylazetidin-1-yl)benzoate 57**



Chemical Formula $C_{24}H_{21}NO_3$
Molecular weight: 371.43

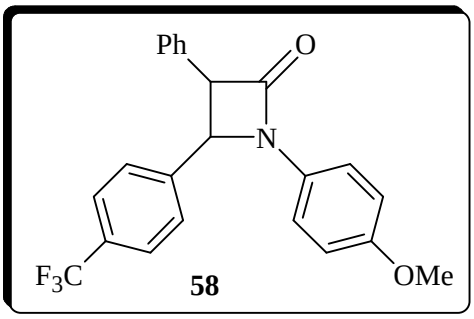
***Cis*-57**: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.98 (d, J = 8.8 Hz, 2H), 7.44 (d, J = 8.7 Hz, 2H), 7.14 – 6.99 (m, 10H), 5.51 (d, J = 6.2 Hz, 1H), 5.06 (d, J = 6.2 Hz, 1H), 4.33 (q, J = 7.1 Hz, 2H), 1.36 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.00 (s), 141.18 (s), 133.81 (s), 131.71 (s), 130.88 (s), 128.83 (s), 128.36 (s), 128.17 (s), 128.12 (s), 127.33 (s), 127.07

(s), 125.87 (s), 116.75 (s), 60.89 (s), 60.63 (s), 60.55 (s), 14.34 (s).

***Trans*-57**: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.96 (d, J = 8.8 Hz, 2H), 7.38 (dd, J = 6.5, 4.5 Hz, 12H), 5.01 (d, J = 2.7 Hz, 1H), 4.39 – 4.26 (m, 3H), 1.36 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.10 (s), 166.04 (s), 141.08 (s), 137.12 (s), 134.43 (s), 131.01 (s), 129.57 (s), 129.26 (s), 129.05 (s), 128.22 (s), 127.55 (s), 125.99 (s), 116.82 (s), 65.51 (s), 64.01 (s), 61.02 (s), 14.47 (s).

MS (ESI): m/z = 372.3 $[M + H]^+$. (CAS: 434283-72-4, 1380590-87-3)[19]

- **1-(4-methoxyphenyl)-3-phenyl-4-(4-(trifluoromethyl)phenyl)azetid in-2-one 58**



58

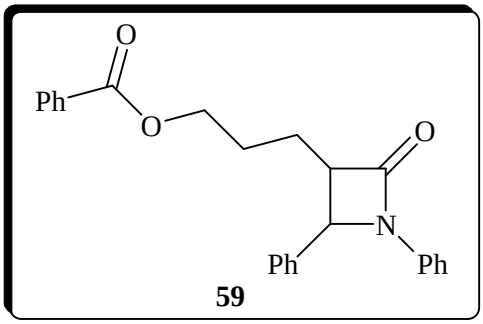
Chemical Formula $C_{23}H_{18}F_3NO_2$
Molecular weight: 397.39

***Cis*-58**: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.36 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 9.1 Hz, 2H), 7.17 (d, J = 8.3 Hz, 2H), 7.07 (t, J = 8.3 Hz, 5H), 6.84 (d, J = 9.1 Hz, 2H), 5.47 (d, J = 6.0 Hz, 1H), 5.05 (d, J = 6.1 Hz, 1H), 3.77 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 164.73, 156.47, 139.41, 139.02, 131.75, 131.09, 128.90 (q, $^{2}J_{C–F}$ = 33), 128.46, 127.66, 125.35 (q, $^{3}J_{C–F}$ = 3.9), 118.53, 114.60, 60.65, 59.96, 55.59.

***Trans*-58**: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.66 (s, 2H), 7.52 (s, 2H), 7.43 – 7.25 (m, 7H), 6.83 (d, J = 9.0 Hz, 2H), 4.98 (d, J = 2.4 Hz, 1H), 4.25 (d, J = 2.5 Hz, 1H), 3.76 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 164.52, 156.37, 141.73, 131.8, 129.16 (q, $^{2}J_{C–F}$ = 33), 128.15, 127.47, 126.41 (q, $^{3}J_{C–F}$ = 3.9), 124.0 (q, $^{1}J_{C–F}$ = 272), 118.45, 114.50, 65.86, 65.22, 63.17, 55.46.

MS (ESI): m/z = 398.2 $[M + H]^+$. (CAS: 434283-73-5, 1380590-79-3)[19]

➢ **3-(2-oxo-1,4-diphenylazetidin-3-yl)propyl 59**



59

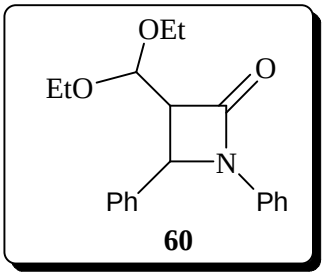
Chemical Formula $C_{25}H_{23}NO_3$
Molecular weight: 385.46

***Cis*-59**: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.03 (d, J = 7.0 Hz, 2H), 7.54 (dd, J = 5.0, 3.7 Hz, 1H), 7.43 (t, J = 7.5 Hz, 2H), 7.40 – 7.19 (m, 9H), 7.04 (t, J = 7.1 Hz, 1H), 4.70 (d, J = 2.4 Hz, 1H), 4.37 (t, J = 6.0 Hz, 2H), 3.17 (d, J = 2.2 Hz, 1H), 2.18 – 1.94 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.42 (s), 166.63 (s), 137.91 (s), 137.75 (s), 133.08 (s), 129.67 (s), 129.36 (s), 129.16 (s), 128.65 (s), 128.49 (s), 125.95 (s), 123.96 (s), 117.06 (s), 64.50 (s), 61.29 (s), 60.20 (s), 26.61 (s), 25.82 (s).

***Trans*-59**: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.99 – 7.89 (m, 2H), 7.58 – 7.50 (m, 1H), 7.41 (t, J = 7.6 Hz, 2H), 7.37 – 7.17 (m, 9H), 7.04 (dd, J = 10.1, 4.3 Hz, 1H), 5.22 (d, J = 5.8 Hz, 1H), 4.13 (m, 2H), 3.72 – 3.54 (m, 1H), 1.90 – 1.56 (m, 3H), 1.35 (dd, J = 9.5, 3.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.56 (s), 166.41 (s), 137.58 (s), 134.70 (s), 132.92 (s), 130.23 (s), 129.59 (s), 129.10 (s), 128.81 (s), 128.45 (s), 128.33 (s), 127.13 (s), 123.85 (s), 117.17 (s), 64.35 (s), 58.24 (s), 54.11 (s), 26.48 (s), 22.22 (s).

HRMS-ESI (m/z) calcd. for $C_{25}H_{23}O_3N$ $[M + H]^+$ 386.17502; found 386.17502

- **3-(diethoxymethyl)-1,4-diphenylazetidin-2-one 60**



60

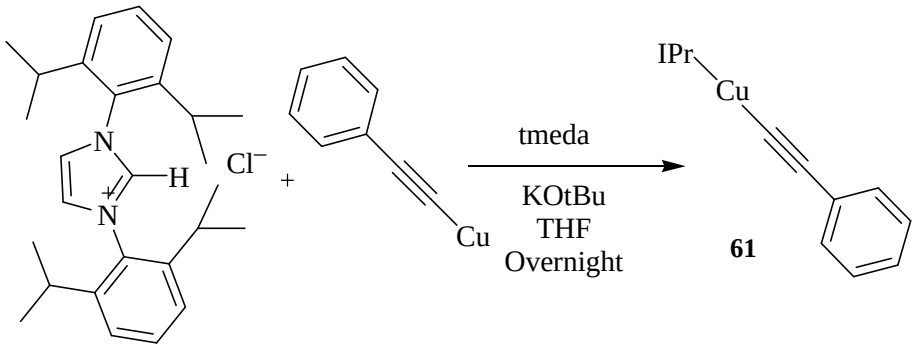
Chemical Formula $C_{20}H_{23}NO_3$
Molecular weight: 325.40

***Cis*-60**: ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.45 – 7.29 (m, 8H), 7.26 (dd, J = 11.1, 4.5 Hz, 2H), 7.05 (s, 1H), 5.15 (d, J = 2.4 Hz, 1H), 4.98 (d, J = 4.0 Hz, 1H), 3.76 (m, 1H), 3.70 – 3.63 (m, 2H), 3.58 (d, J = 7.0 Hz, 1H), 3.41 (dd, J = 3.9, 2.6 Hz, 1H), 1.22 (d, J = 7.5 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 164.12 (s), 137.94 (s), 137.74 (s), 129.12 (s), 129.10 (s), 128.33 (s), 126.16 (s), 123.89 (s), 117.16 (s), 99.63 (s), 63.96 (s), 63.76 (s), 62.80 (s), 56.04 (s), 15.38 (s), 15.32 (s).

***Trans*-60**: ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.33 – 7.25 (m, 7H), 7.21 (d, J = 7.3 Hz, 2H), 7.00 (s, 1H), 5.17 (d, J = 6.0 Hz, 1H), 4.22 (d, J = 7.4 Hz, 1H), 3.85 (d, J = 1.1 Hz, 1H), 3.56 (dd, J = 8.9, 7.0 Hz, 1H), 3.40 (m, 2H), 2.72 (dd, J = 9.2, 7.1 Hz, 1H), 1.13 (t, J = 7.0 Hz, 3H), 0.87 (t, J = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 163.41 (s), 137.61 (s), 134.36 (s), 129.14 (s), 128.48 (s), 128.38 (s), 127.50 (s), 123.96 (s), 117.23 (s), 98.52 (s), 62.13 (s), 61.66 (s), 57.92 (s), 56.92 (s), 15.31 (s), 14.89 (s).

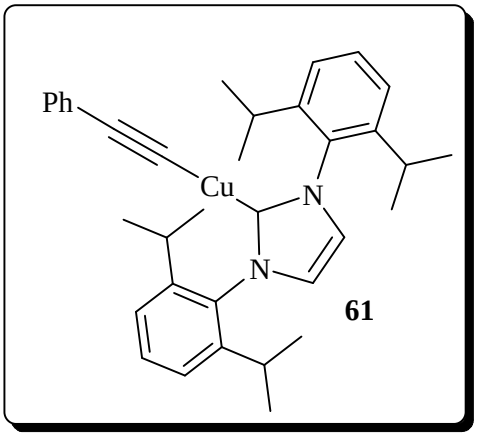
HRMS-ESI (m/z) calcd. for $C_{20}H_{24}O_3N$ $[M + H]^+$ 326.17; found 326.17507.

I.2.9 Synthesis of complex 61



IPrHCl (0.2 mmol, 1 equiv.) and KO*t*Bu (0.2 mmol, 1 equiv.) were introduced into a flame dried schlenk under argon. THF (5 mL) was added afterwards, and the mixture is left for agitation for 30 min. In a second dry schlenk, copper(I) phenylacetylide (0.2 mmol, 1 equiv.) and TMEDA (0.2 mmol, 1 equiv.) were introduced along with THF (5 mL). The first reaction mixture was transferred to the second schlenk. The reaction mixture was left overnight and then the solvent was removed under reduced pressure. The solid product was recrystallized in hexane. The product was obtained in total conversion as a yellow solid.

➢ **IPrCu(I) phenylacetylide 61**



61

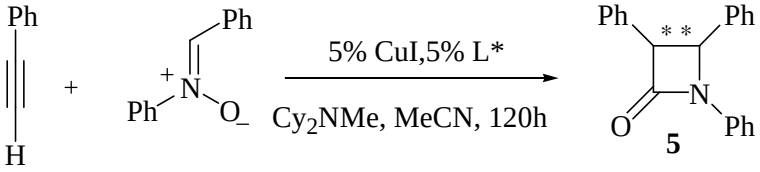
Chemical Formula $C_{35}H_{42}CuN_2$
Molecular weight: 554.27

^{1}H NMR (500 MHz, CD_2Cl_2) δ = 7.53 (dd, J = 13.8, 7.4 Hz, 2H), 7.34 (dd, J = 14.0, 7.8 Hz, 4H), 7.19 – 6.97 (m, 5H), 2.70 – 2.44 (m, 4H), 1.39 – 1.10 (m, 24H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ = 182.69 , 146.37 , 135.17 , 131.95 , 128.22 , 125.78 , 124.68 , 123.85 , 123.75, 122.12, 105.14 , 29.28, 25.26 , 25.07 , 24.12 , 24.04.

The spectral data are identical to those reported in the literature (CAS: 872034-79-2)[21].

I.3 Enantioselective version

I.3.1 General procedure for the enantioselective Kinugasa reaction for the synthesis of β-lactam 5



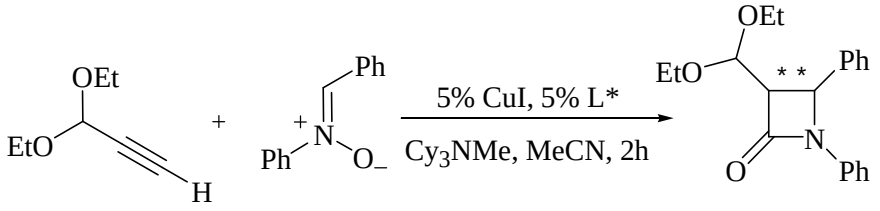
5

In a flame dried schlenk, under argon, the copper source (0.032 mmol, 0.05 equiv.) and the indicated chiral ligand L* (0.032 mmol, 0.05 equiv.) were introduced. MeCN (2 mL) was added, and the mixture was left for 2 hours to form the copper complex. The reaction mixture was then cooled to 0°C, and

[21] Goj, L. A.; Blue, E. D.; Munro-Leighton, C.; Gunnoe, T. B.; Petersen, J. L., *Inorganic Chemistry* **2005,** *44,* 8647.

Cy_2NMe (0.66 mmol, 1 equiv.) was added. 15 minutes later, the phenylacetylene (0.66 mmol, 1equiv.) was added. The mixture was further stirred for 15 min, and then the nitrone (0.66 mmol, 1equiv.) was added. After 15 minutes, the ice bath was removed, and the reaction mixture was left for 120 h. The mixture is then filtered over celite, the solvent is evaporated, then a few ml of AcOEt are added and the solution is washed with HCl, water, and brine, and then purified by automated chromatography column using CH_2Cl_2 as eluent. The enantiomeric ratio was determined by HPLC using CHIRALPAK IA column (Hexane/Isopropanol/EtOH: 85/10/5, 1 mL/min, 250 nm, t_R = 7.8 and 9.5 min (minor: *trans*), t_R = 8.5 and 12.7 min (major: *cis*)).

I.3.2 General procedure for the enantioselective Kinugasa reaction for the synthesis of β-lactam 60

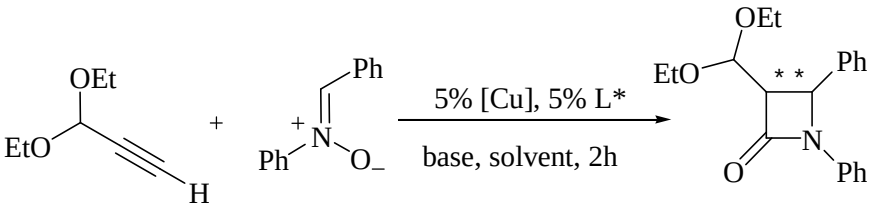


20 **60**

In a flame dried schlenk, under argon, the CuI (0.016 mmol, 0.05 equiv.) and the indicated chiral ligand L* (0.016 mmol, 0.05 equiv.) were introduced. MeCN (2 mL) was added, and the mixture was left for 2 hours to form the copper complex. The reaction mixture was then cooled to 0°C, and Cy_2NMe (0.33 mmol, 1 equiv.) was added. 15 minutes later, the acetylene **20** (0.33 mmol, 1equiv.) was added. The mixture was further stirred for 15 min, and then the nitrone (0.33 mmol, 1equiv.) was added. After 15 minutes, the ice bath was removed, and the reaction mixture was left for 2 h. The mixture is then filtered over celite, the solvent evaporated, a few ml of AcOEt added

and the solution washed with HCl, water, and brine, and then purified by automated chromatography column using PE and AcOEt (9:1) as eluent.
The enantiomeric ratio was determined by HPLC using CHIRALPAK IA column (isohexane/EtOH: 90/10, 1 mL/min, 248 nm, t_R = 5.8 and 6.7 min (minor: *trans*), t_R = 7.9 and 9.1 min (major: *cis*)).

I.3.3 General procedure for the enantioselective Kinugasa optimization reactions for the synthesis of β-lactam 60



20 **60**

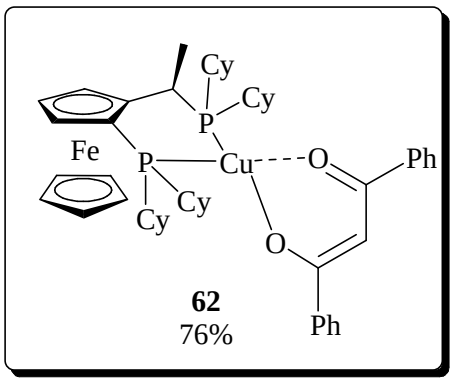
In a flame dried schlenk, under argon, the copper source (0.016 mmol, 0.05 equiv.) and the indicated chiral ligand L* (0.016 mmol, 0.05 equiv.) were introduced. The indicated solvent (2 mL) was added, and the mixture was left for 2 hours to form the copper complex. In cases where the catalyst is a readily available complex of the copper and the ligand (**62, 63**), the complex is only left to dissolve. The reaction mixture was then cooled to 0°C, and the base (0.33 mmol, 1 equiv.) was added. 15 minutes later, the acetylene **20** (0.33 mmol, 1equiv.) was added. The mixture was further stirred for 15 min, and then the nitrone (0.33 mmol, 1equiv.) added. After 15 minutes, the ice bath was removed, and the reaction mixture left for 2 h (unless specified). The mixture is then filtered over celite, the solvent evaporated, a few ml of AcOEt added and the solution washed with HCl, water, and brine, and then purified by automated chromatography column using PE and AcOEt (9:1) as eluent.

The enantiomeric ratio was determined by HPLC using CHIRALPAK IB column (isohexane/EtOH: 90/10, 1 mL/min, 248 nm, t_R = 5.8 and 6.7 min (minor: *trans*), t_R = 7.9 and 9.1 min (major: *cis*)).

I.3.4 Synthesis of complexes 62 and 63

CuCl (0.15 mmol, 1 equiv.) and the indicated ligand (Sl-J003-1 or SL-T001-1) (0.16 mmol, 1 equiv.) were left to stir in THF (3 mL), under argon, for 2 hours. KO*t*Bu (0.16 mmol, 1 equiv.) was added. 30 min later, dibenzoylmethane (DBMH) (0.24 mmol, 1,5 equiv.) was introduced. The reaction mixture was left to react for 1h. The resulting mixture was then filtered over Celite, the solvents evaporated, and the resulting solid crystallized in hexane at -20°C.

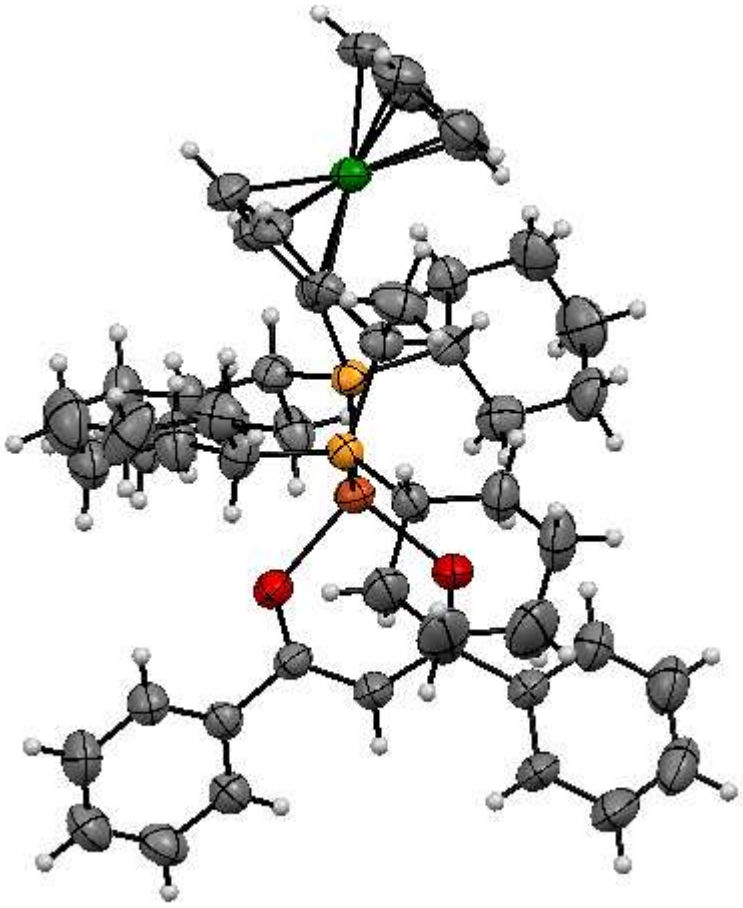
- **[(*R*)-1-[(S_P)-2-(Dicyclohexylphosphino)ferrocenyl]ethyl-dicyclohexylphosphine]copper(I) dibenzoylmethank (L_{19}Cudbm) 62**



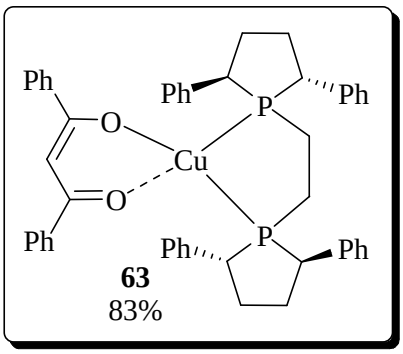
Chemical Formula: $Cu_{51}H_{67}CuFeO_2P_2$
Molecular Weight: 892.42

Complex 67 was obtained as dark orange crystals. ^{1}H NMR (300 MHz, CD_2Cl_2) δ = 7.90 (dd, J = 6.6, 3.0 Hz, 4H), 7.34 (dd, J = 5.2, 1.9 Hz, 6H), 6.41 (s, 1H), 4.43 (d, J = 2.9 Hz, 1H), 4.40 – 4.29 (m, 2H), 4.19 (s, 5H), 3.20 (d, J = 7.3 Hz, 1H), 2.04 – 0.78 (m, 47H). ^{31}P NMR (121 MHz, CD_2Cl_2) δ = 0.00, -13.22, -14.67.

The X-ray intensity data were collected at 283 K with a MAR345 image plate using MoKα (λ = 0.71073Å) radiation (Rigaku UltraX18). A crystal that was crystallized from THF-hexane at -20°C was chosen, mounted and transferred. The unit cell parameters were refined using all the collected spots after the integration process. Molecular formula = $C_{51}H_{67}CuFeO_2P_2$, Mr = 892, orthorhombic $P2_12_12_1$, a = 10.2494(4) Å, b = 11.7586(5) Å, c = 38.1712(16) Å, *V* = 4600.34 $Å^3$, Z = 4, Z' = 0, ρ_{calc} = 1.290 gcm^{-3}, T = 283 K, R = 5.51%.



- **1,2-Bis[(2*R*,5*R*)-2,5-diphenylphospholano]ethane(1,5-cyclooctadiene)copper(I) dibenzoylmethane (L_{33}Cudbm) 63**

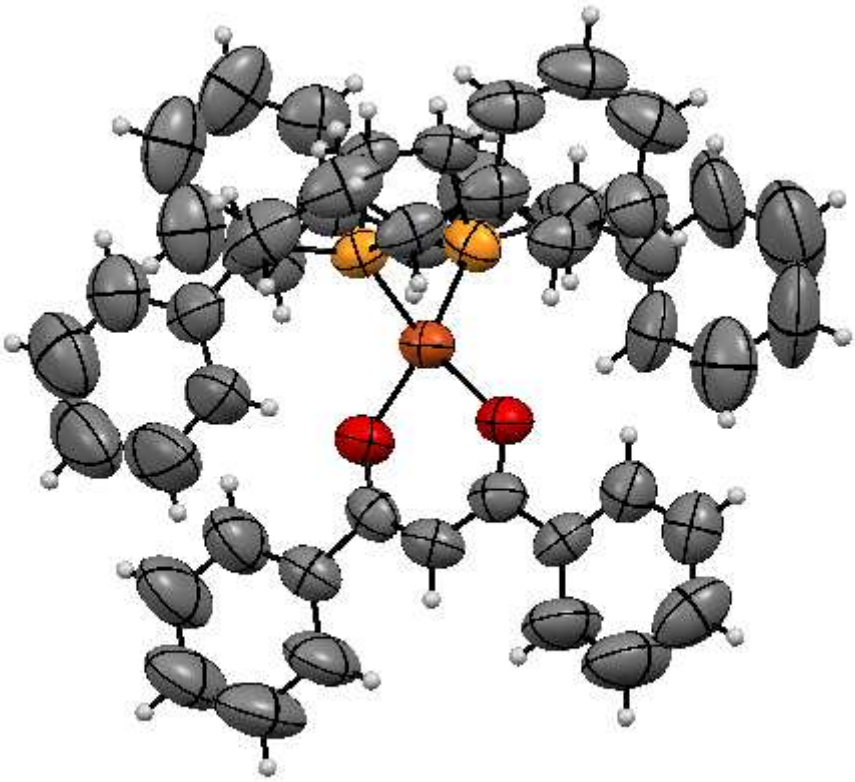


63
83%

Chemical Formula: $Cu_{49}H_{47}CuO_2P_2$
Molecular Weight: 793.39

^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.10 – 7.89 (m, 4H), 7.48 – 7.26 (m, 13H), 7.20 – 6.90 (m, 8H), 6.81 – 6.58 (m, 5H), 3.71 (dd, J = 12.7, 5.9 Hz, 2H), 3.41 (d, J = 7.0 Hz, 1H), 2.85 – 2.62 (m, 2H), 2.19 – 1.90 (m, 4H), 1.68 (s, 2H), 1.40 – 1.19 (m, 4H), 1.13 (t, J = 7.0 Hz, 1H), 0.86 (s, 1H). ^{31}P NMR (121 MHz, CD_2Cl_2) δ = 3.38.

The X-ray intensity data were collected at 283 K with a MAR345 image plate using MoKα (λ = 0.71073Å) radiation (Rigaku UltraX18). A crystal that was crystallized from THF-hexane at -20°C was chosen, mounted and transferred. The unit cell parameters were refined using all the collected spots after the integration process. Molecular formula = $C_{49}H_{47}CuO_2P_2$, Mr = 793, tetragonal $P4_3$, a = 18.2790 (4) Å, b = 18.2790 (4) Å, c = 13.9439 (7) Å, *V* = 4658.96 Å^3, Z = 4, Z' = 0, ρ_{calc} = 1.131 gcm^{-3}, T = 283 K, R = 4.55%.



II. Chapter 2: Asymmetric Synthesis of γ-Lactams

II.1 Synthesis of substrates

II.1.1 Synthesis of copper complex 74

$$\underset{(1.0\ \text{equiv.})}{CuF_2} + \underset{(3.5\ \text{equiv.})}{PPh_3} \xrightarrow{\text{MeOH, reflux, 3h}} \underset{\mathbf{74}}{[(PPh_3)_3CuF.2MeOH]} + Ph_3PO$$

A modified procedure from the literature was used[22]. A 50 mL round bottom flask was loaded with triphenylphosphine (7 mmol, 3.5 equiv.), copper(II) fluoride (2 mmol, 1 equiv.) and wet methanol (20 mL). The mixture was heated to reflux during 3 h. The solution was filtered and half of the solvent was removed under reduced pressure, the rest was then stored at 4 °C overnight. The white crystals formed, were then filtered and a second harvest of complex was obtained after a 50% concentration of the filtrate. The final product **74** was obtained as a white solid with 72% yield (1.36 g).

- **$[(Ph_3P)_3CuF.2MeOH]$ 74**

$[(PPh_3)_3CuF.2MeOH]$
74
72%

Chemical Formula: $C_{56}H_{53}CuFO_2P_3$
Molecular Weight: 933.48

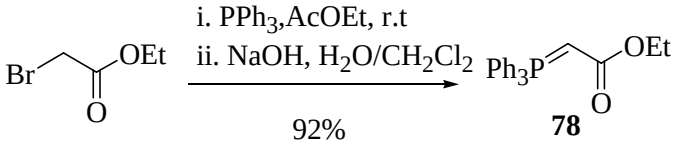
^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.30 (m, 45 H), 3.44 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 136.2 (d, J = 5.8 Hz), 134.1 (d, J = 18.7 Hz), 129.5 (s), 128.6 (d, J = 10.5 Hz), 50.8 (s).

[22] Gulliver, D. J.; Levason, W.; Webster, M., *Inorganica Chimica Acta* **1981,** *52*, 153.

^{19}F NMR (282 MHz, $CDCl_3$) δ = -204.8. ^{31}P NMR (202 MHz, $CDCl_3$) δ = -3.55.

II.1.2 Synthesis of 78, 79, and 80

II.1.2.1 Synthesis of 78[23]



A solution of ethyl bromoacetate (40 mmol, 1 equiv.), in 10 mL of AcOEt was added to a solution of triphenylphosphine (40 mmol, 1 equiv.) in 60 mL AcOEt. After stirring overnight, the white precipitate was filtered off, washed with diethyl ether and dried in vacuo at 40°C for 4h. The phosphonium bromide produced was dissolved in 150 mL in CH_2Cl_2 and NaOH (2M, 150 mL) was added. The reaction mixture was shaken vigorously in a separation funnel, after which the two layers were separated. The aqueous layer was washed twice with dichloromethane. The combined organic phases were dried over $MgSO_4$, and the solvent evaporated and dried under vacuum to provide **78** as a white solid in 92% yield.

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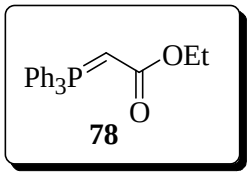
[23] Werkhoven, T. M.; van Nispen, R.; Lugtenburg, J., *European Journal of Organic Chemistry* **1999,** *1999*, 2909.

➢ **(2-Ethoxy-2-oxoethylidene)triphenylphosphorane 78**



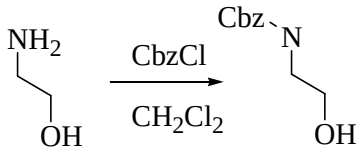
78

Chemical Formula: $C_{22}H_{21}O_2P$
Molecular Weight: 348.37

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.65 (ddd, J = 12.5, 8.3, 1.5 Hz, 6H), 7.59 – 7.50 (m, 3H), 7.50 – 7.38 (m, 6H), 3.96 (s, 2H), 2.87 (s, 1H), 1.16 (d, J = 45.0 Hz, 3H).

The spectral data are identical to those reported in the literature (CAS : 1099-45-2)[24]

II.1.2.2 Synthesis of 79



86% **79**

To a solution of ethanolamine (50 mmol, 1 equiv.) in dry CH_2Cl_2 (45 mL) at 0 °C, a solution CbzCl (55 mmol, 1.1 equiv) in dry CH_2Cl_2 (20 mL) was slowly added. The reaction mixture was stirred for 2 h at 0 °C and at room temperature for 18 h. The resulting mixture was washed with an aqueous saturated solution of $NaHCO_3$ and the aqueous phase extracted with CH_2Cl_2 (3×70 mL). The organic phase was dried over $MgSO_4$, filtered, and the solvent evaporated in vacuo to give crude **79** (86%, pale yellow oil), which was used in the next step without purification.

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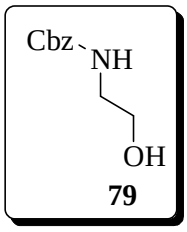
[24] Sadhukhan, S.; Han, Y.; Zhang, G.-F.; Brunengraber, H.; Tochtrop, G. P., *Journal of the American Chemical Society* **2010,** *132*, 6309.

➢ **Benzyl 2-hydroxyethylcarbamate 79[25]**



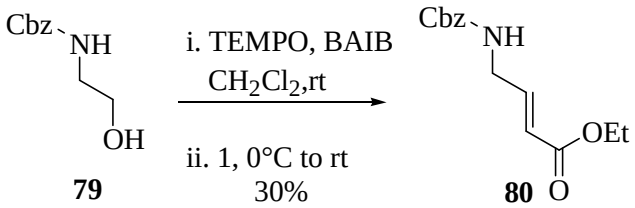
79

Chemical Formula: $C_{10}H_{13}NO_3$
Molecular Weight: 195.22

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.43 – 7.30 (m, 5H), 5.10 (s, 2H), 4.59 (s, 2H), 3.68 (t, J = 5.1 Hz, 2H), 3.33 (t, J = 5.1 Hz, 2H).

The spectral data are identical to those reported in the literature (CAS : 77987-49-6)[22].

II.1.2.3 Synthesis of 80[26]



79 **80**

To a stirred solution of benzyl 2-hydroxyethylcarbamate **79** (26 mmol, 1 equiv.) in CH_2Cl_2 (100 mL) were added bis(acetoxy)iodobenzene (29.9 mmol, 1.15 equiv) and 2,2,6,6-tetramethylpiperidinyloxy (2.6mmol, 0.1 equiv). The yellow solution was stirred for 150 min, cooled to 0 °C and (carboethoxymethylene)triphenylphosphorane (34 mmol, 1.3 equiv) was added. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. The solution was poured onto a column of silica gel and eluted with a mixture of ethyl acetate–petroleum ether (1:9 to 3:7) to give pure **80** (30% yield) as an oil.

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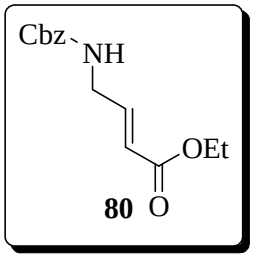
[25] De Cola, C.; Manicardi, A.; Corradini, R.; Izzo, I.; De Riccardis, F., *Tetrahedron* **2012,** *68*, 499.

[26] Vatèle, J.-M., *Tetrahedron Letters* **2006,** *47*, 715.

➢ **(*E*)-Ethyl 4-benzyloxycarbonylamino-but-2-enoate 80**



80

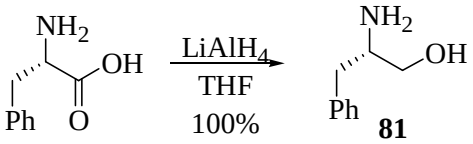
Chemical Formula: $C_{14}H_{17}NO_4$
Molecular Weight: 263.29

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.37 – 7.31 (m, 5H), 6.93 – 6.85 (m, 1H), 5.93 (dd, J = 15.7, 2.3 Hz, 1H), 5.10 (dd, J = 7.1, 2.4 Hz, 2H), 4.98 (br s, 1 H), 4.18 (dd, J = 7.2, 2.4 Hz, 2H), 3.96 (d, J = 5.7 Hz, 1H), 3.47 – 3.41 (m, 1H), 1.30 – 1.23 (m, 3H).

The spectral data are identical to those reported in the literature (CAS: 625457-45-6)[27].

II.1.3 Synthesis of 81, 82, and 83

II.1.3.1 Synthesis of 81[28]



81

L-phenylalanine (12 mmol, 1 equiv.) was added slowly, in small portions, to an ice cooled solution of lithium aluminum hydride (24 mmol, 2.0 equiv.) in dry THF (40 mL g−1 $LiAlH_4$). The mixture was allowed to react at 0°C for 1 h followed by reflux overnight. The solution was cooled to 0°C and the excess of $LiAlH_4$ quenched with aqueous sodium hydroxide (2.0 M). The precipitate was filtered off and extracted with boiling THF for an hour. The combined ethereal extract was concentrated under reduced pressure and the remaining mixture extracted with dichloromethane. The combined organic

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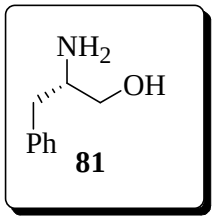
[27] Kinder, R. E.; Zhang, Z.; Widenhoefer, R. A., *Organic Letters* **2008,** *10*, 3157.

[28] Granander, J.; Sott, R.; Hilmersson, G., *Tetrahedron* **2002,** *58*, 4717.

extract was washed with brine, dried over sodium sulfate and the solvent evaporated under reduced pressure to give the known (*S*)-phenylalaninol in quantitative yield.

- **(*S*)-phenylalaninol 81**



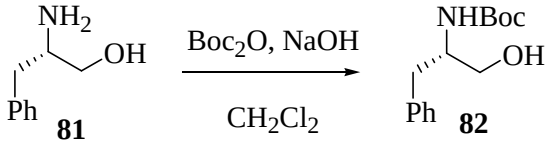
81

Chemical Formula: $C_9H_{13}NO$
Molecular Weight: 151.21

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.41 – 7.11 (m, 5H), 3.63 (dd, J = 10.7, 3.8 Hz, 1H), 3.39 (dd, J = 10.7, 7.2 Hz, 1H), 3.19 – 3.04 (m, 1H), 2.79 (dd, J = 13.5, 5.2 Hz, 1H), 2.52 (dd, J = 13.5, 8.7 Hz, 1H).

The spectral data are identical to those reported in the literature (CAS: 3182-95-4)[29].

II.1.3.2 Synthesis of 82[30]



81 100% **82**

.A solution of di-tert-butyl dicarbonate (12 mol, 1 equiv) in CH_2Cl_2 (48 mL) was added dropwise to a solution of (*S*)-phenylalaninol **81** (12 mol, 1 equiv.) in CH_2Cl_2 (48 mL) and 1 M NaOH (38 mL). The reaction mixture was then stirred at room temperature for 24 h, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (10 mL × 2). The combined organic layers were washed with water (10 mL × 2) and dried over Na_2SO_4.

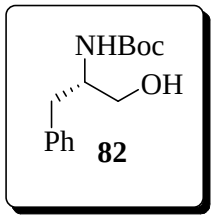
---

[29] Welch, J. T.; Seper, K. W., *The Journal of Organic Chemistry* **1988,** *53*, 2991.

[30] Ji, H.; Li, H.; Martásek, P.; Roman, L. J.; Poulos, T. L.; Silverman, R. B., *Journal of Medicinal Chemistry* **2009,** *52*, 779.

The solvent was evaporated in vacuo and the product was obtained as a white solid in quantitative yield.

➢ **(*S*)-tert-Butyl Benzyl(2-hydroxyethyl)carbamate 82**



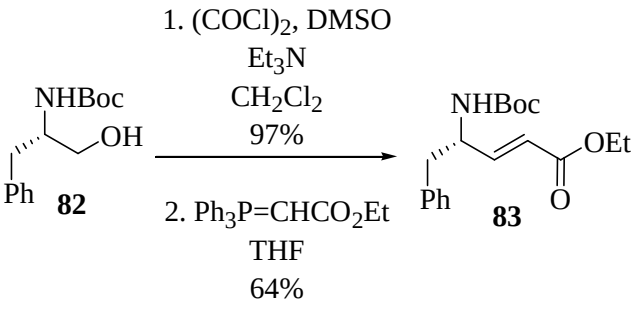
82

Chemical Formula: $C_{14}H_{21}NO_3$
Molecular Weight: 251.32

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.41 – 7.05 (m, 5H), 4.73 (s, 1H), 3.87 (s, 1H), 3.66 (td, J = 6.3, 5.8, 2.8 Hz, 1H), 3.63 – 3.47 (m, 1H), 2.84 (d, J = 7.2 Hz, 2H), 2.35 (s, 1H), 1.41 (s, 9H).

The spectral data are identical to those reported in the literature (CAS: 66605-57-0)[27].

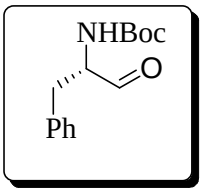
II.1.3.3 Synthesis of 83



A solution of DMSO (21 mmol, 1.75 equiv.) in anhydrous CH_2Cl_2 (9 mL) was added dropwise over 5 min to a solution of oxalyl chloride in anhydrous CH_2Cl_2 (2.0 M, 18 mmol, 1.5 equiv.) at –78 °C under argon. The mixture was stirred at –78 °C for 15 min, after which time a solution of (*S*)-2-(t-butoxycarbonylamino)-3-phenyl-1-propanol **82** (12 mmol, 1 equiv.) in anhydrous CH_2Cl_2 (9 mL) was added dropwise over 10 min. The mixture was stirred at –78 °C for 30 min, after which time a solution of Et_3N (48

mmol, 4 equiv.) in anhydrous CH_2Cl_2 (9 mL) was added dropwise over 10 min. The mixture was allowed to slowly warm to rt and stirred 1 h, after which time it was diluted with CH_2Cl_2 to about 150 mL and washed with 10% aq citric acid (75 mL), H_2O (75 mL), satd $NaHCO_3$ (75 mL) and dried over Na_2SO_4. The drying agent was filtered off and the solvent was removed in vacuo to give the aldehyde as an off-white solid in quantitative yield[31].

- **(*S*)-2-(t-Butoxycarbonylamino)-3-phenyl-1-propanal**



Chemical Formula: $C_{14}H_{19}NO_3$
Molecular Weight: 249.31

^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.62 (s, 1H), 7.34 – 7.23 (m, 3H), 7.21 – 7.12 (m, 2H), 5.09 (d, J = 6.7 Hz, 1H), 4.41 (d, J = 6.8 Hz, 1H), 3.11 (d, J = 6.7 Hz, 2H), 1.42 (s, 9H).

The spectral data are identical to those reported in the literature (CAS: 72155-45-4)[28].

The (S)-2-(t-Butoxycarbonylamino)-3-phenyl-1-propanal was dissolved in THF without any purification. Phosphorane **78** was added, and the reaction mixture was left to react overnight. The organic solvents were evaporated and the crude product was purified through a column of silica gel and eluted with a mixture of ethyl acetate–petroleum ether (1:9) to produce the enoate **83** in 64% yield[32].

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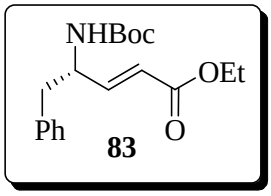
[31] Flentge, C. A.; Randolph, J. T.; Huang, P. P.; Klein, L. L.; Marsh, K. C.; Harlan, J. E.; Kempf, D. J., *Bioorganic & Medicinal Chemistry Letters* **2009,** *19,* 5444.

[32] Ganesh Kumar, M.; Mali, S. M.; Gopi, H. N., *Organic & Biomolecular Chemistry* **2013,** *11,* 803.

➢ **(*S*,*E*)-Ethyl 4-(tert-butoxycarbonylamino)-5-phenylpent-2-enoate 83**



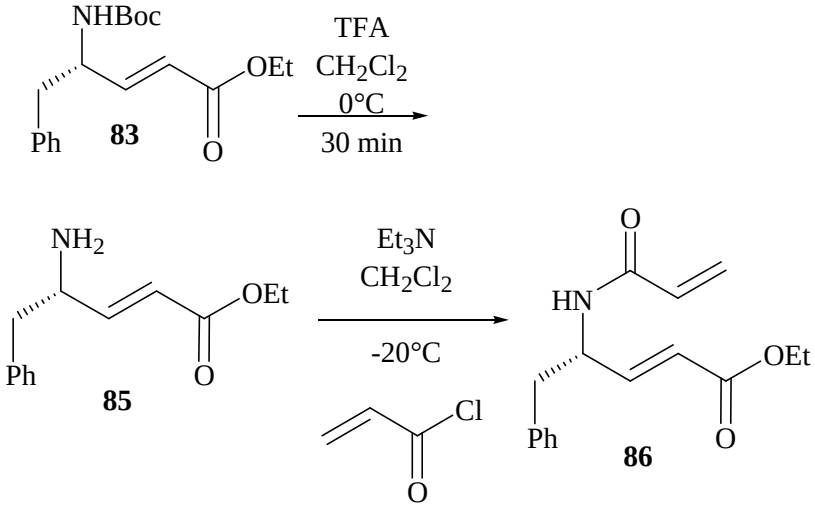
83

Chemical Formula: $C_{18}H_{25}NO_4$
Molecular Weight: 319.40

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.23 (m, 4H), 7.18 (s, 1H), 6.91 (dd, J = 15.6, 5.0 Hz, 1H), 5.86 (dd, J = 15.6, 1.7 Hz, 1H), 4.61 (s, 1H), 4.51 (s, 1H), 4.18 (d, J = 7.1 Hz, 2H), 2.89 (s, 2H), 1.39 (s, 9H), 1.27 (t, J = 7.1 Hz, 3H).

The spectral data are identical to those reported in the literature (CAS: 124818-94-6)[29].

II.1.4 Synthesis of 86

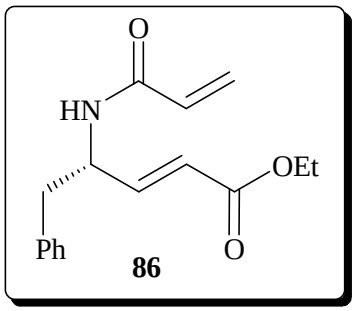


100%

In a dry schlenck, under argon, at 0°C, enoate **83** (10 mmol, 1 equiv) was introduced. 10ml of CH_2Cl_2 was added. When the solution became homogeneous TFA (0.2 equiv.) was added. The reaction was left for 30 min at 0°C. Excess CH_2Cl_2 and TFA were evaporated. The product **85** was directly transferred to a second dry schlenk in CH_2Cl_2 under argon.

Triethylamine (40 mmol, 4 equiv.) was added dropwise at -20°C. The reaction mixture was left to react for 10 min. Acryloylchloride (12 mmol, 1.2 equiv) was added dropwise. The reaction mixture was left for 1.5 hours at 0°C. Few ml of sat. $NaHCO_3$ were added. The phases were separated and the aqueous phase was extracted with AcOEt (2x20 mL). The combined organic layers were washed with sat. $NaHCO_3$ and brine, and dried over Na_2SO_4. The solvents were evaporated and dried under vacuum. The product **86** was obtained as a solid in quantitative yield.

- **4-Acryloylamino-5-phenyl-pent-2-enoic acid ethyl ester 86**



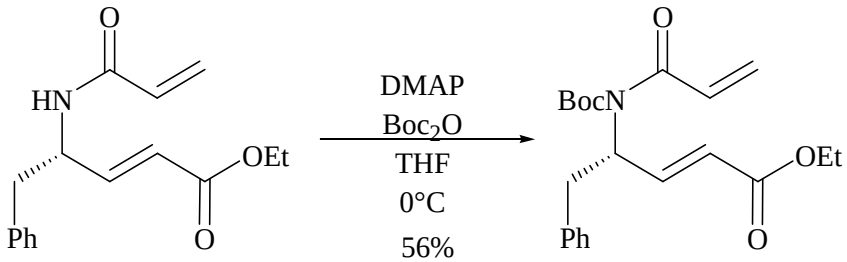
86

Chemical Formula: $C_{16}H_{19}NO_3$
Molecular Weight: 273.33

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.37 – 7.07 (m, 5H), 6.91 (dd, J = 15.6, 5.3 Hz, 1H), 6.46 – 6.30 (m, 1H), 6.30 – 6.03 (m, 2H), 5.84 (dd, J = 15.6, 1.7 Hz, 1H), 5.60 (dt, J = 9.9, 1.3 Hz, 1H), 5.09 – 4.91 (m, 1H), 4.11 (m, 2H), 2.93 (d, J = 7.0 Hz, 2H), 1.23 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 171.21 , 166.13 , 165.11 , 146.87 , 136.46 , 130.51 , 129.22 , 128.55 , 126.86 , 121.39 , 60.45, 51.08 , 40.24 .

HRMS-ESI (m/z) calcd. for $C_{16}H_{20}O_3N$ $[M + H]^+$ 274.14; found 274.14607.

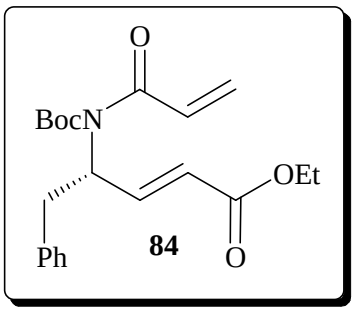
II.1.5 Synthesis of 84



86 **84**

In a dry schlenck, under argon, at 0°C, acryloyl amine **86** (1 mmol, 1 equiv) was introduced with DMAP (0.1 mmol, 0.1 equiv.) in THF (10 ml). The reaction mixture was left to stir for 15 min, then Boc_2O (1.2 mmol, 1.2 equiv.). The reaction was left overnight at 0°C. Excess solvents were then evaporated. The crude product was purified through a column of silica gel and eluted with a mixture of ethyl acetate–petroleum ether to produce **84** in 56% yield.

➢ **4-(Acryloyl-*tert*-butoxycarbonyl-amino)-5-phenyl-pent-2-enoic acid ethyl ester 84**



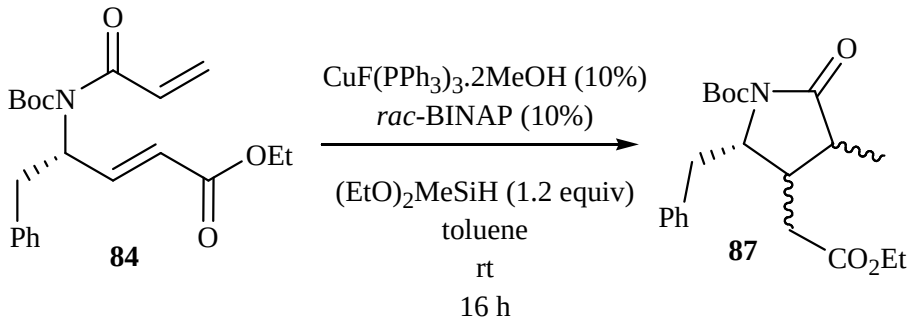
Chemical Formula: $C_{21}H_{27}NO_5$
Molecular Weight: 373.44

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.36 – 7.10 (m, 5H), 7.08 (d, J = 5.1 Hz, 1H), 6.57 (dd, J = 16.9, 10.4 Hz, 1H), 6.15 (dd, J = 17.0, 1.7 Hz, 1H), 5.88 (dd, J = 15.8, 1.9 Hz, 1H), 5.59 – 5.40 (m, 2H), 4.26 – 4.04 (m, 2H), 3.37 – 3.07 (m, 2H), 1.43 (s, 9H), 1.26 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 168.47, 165.98, 152.46, 146.82, 137.16, 131.4, 129.2, 128.44, 127.37, 126.70, 121.77, 84.03, 60.39, 56.61, 38.19, 27.84.

HRMS-ESI (m/z) calcd. for $C_{16}H_{20}O_3N$ $[M - Boc + H]^+$ 274.14; found 274.14616

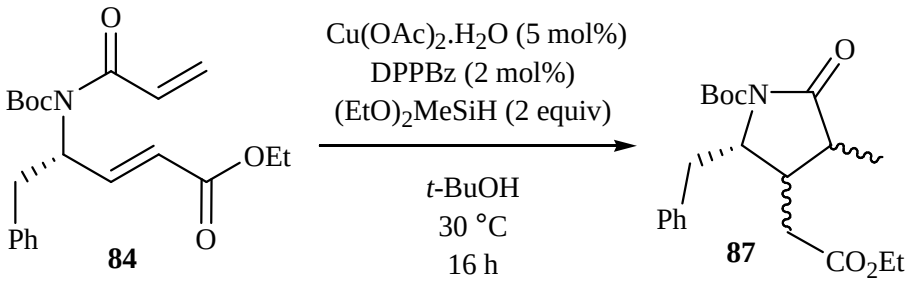
II.2 Catalytic tests

II.2.1 General procedure for the catalytic reductive Michael cyclization with $CuF(PPh_3)_3.2MeOH$



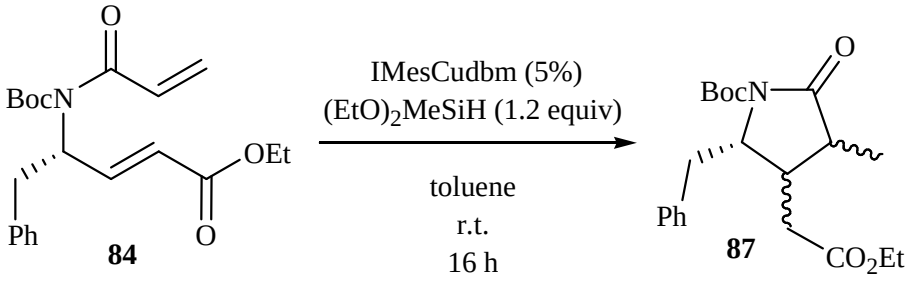
A solution of $CuF(PPh_3)_3.2MeOH$ (0.04 mmol, 0.1 equiv.) and *rac*-BINAP (0.04 mmol, 0.1 equiv.) in toluene (1 mL) was stirred for 15 min before $(EtO)_2MeSiH$ (0.48 mmol, 1.2 equiv.) was added. The solution was stirred until it became yellow (ca. 5 min), after which a solution of the substrate **84** (0.4 mmol, 1 equiv.) in toluene (1 mL) was added rapidly via cannula. The mixture was stirred at room temperature for 18 h, quenched carefully with 1 M HCl (1 mL), diluted with H_2O (15 mL) and then extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with NH_4Cl and brine and dried ($MgSO_4$) and concentrated in vacuo. The purification of the residue by column chromatography did not afford the pure product.

II.2.2 General procedure for the catalytic reductive Michael cyclization with $Cu(OAc)_2.H_2O$



A solution of $Cu(OAc)_2.H_2O$ (0.02 mmol, 0.05 equiv.) and DPPBz (0.008 mmol, 0.02 equiv.) in *t*-BuOH (0.8 mmol, 2 equiv., degassed) was stirred for 20 min before $(EtO)_2MeSiH$ (0.8 mmol, 2 equiv.) was added. The solution was stirred until it became yellow (ca. 5 min), after which a solution of the substrate **84** (0.1 mmol, 1 equiv.) in toluene (1 mL) was then added rapidly via cannula. The mixture was stirred at room temperature for 18 h, diluted in EtOAc (1mL) and washed with KOH (1N, 2 mL), HCl (1N, 2 mL), and brine. The aqueous layers extracted with EtOAc (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo.

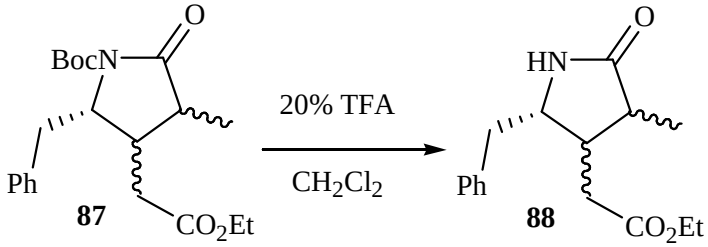
II.2.3 General procedure for the catalytic reductive Michael cyclization with IMesCudbm



A solution of the IMesCudbm (0.04 mmol, 0.1 equiv in toluene (1 mL) was stirred for 5 min before $(EtO)_2MeSiH$ (0.48 mmol, 1.2 equiv.) was added.

The solution was stirred for. 5 min, after which a solution of the substrate **84** (0.1 mmol, 1 equiv.) in toluene (1 mL) was then added rapidly via cannula. The mixture was stirred at room temperature for 18 h, quenched carefully with 1 M HCl (1 mL), diluted with H_2O (15 mL) and then extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with NH_4Cl and brine and dried ($MgSO_4$) and concentrated in vacuo. The purification of the residue by column chromatography did not afford the pure product.

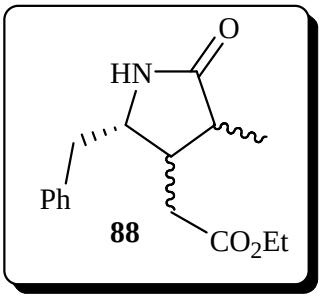
II.2.3 General procedure for the deprotection of the crude product 84



87 **88**

A solution of the crude product **87** (1 equiv.) was dissolved in CH_2Cl_2 (1.5ml/1 mmol of substrate). The reaction mixture was cooled to 0°C, and TFA (0.2 equiv) was added. The reaction mixture was left for 30 min. The excess TFA salts and dichloromethane were then evaporated with the help of toluene. The product was passed through a silica gel chromatography column using PE:AcOEt as eluent (4:6).

➢ **(*S*)- (2-Benzyl-4-methyl-5-oxo-pyrrolidin-3-yl)-acetic acid ethyl ester 88**

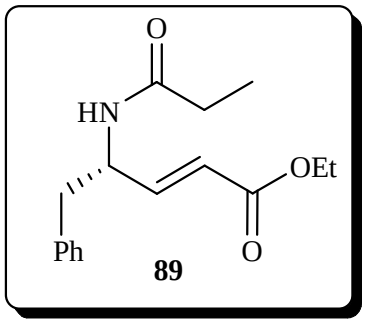


Chemical Formula: $C_{16}H_{21}NO_3$
Molecular Weight: 275.37

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.34 – 7.23 (m, 3H), 7.18 – 7.08 (m, 2H), 5.70 (s, 1H), 4.27-4.14 (m, 2H), 3.98 – 3.86 (m, 1H), 2.82 (dd, J = 13.1, 3.1 Hz, 1H), 2.60 (m, 3H), 2.40 (dd, J = 12.9, 11.3 Hz, 1H), 2.18 (s, 1H), 1.30 (t, J = 7.1 Hz, 3H), 1.19 (d, J = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.34 , 172.01 , 137.64 , 129.02, 129.21, 127.00 , 60.99 , 56.03 , 42.79 , 39.80 , 37.23 , 33.84 , 14.39 , 13.88.

HRMS-ESI (m/z) calcd. for $C_{16}H_{22}O_3N$ $[M + H]^+$ 276.16; found 274.16367

➢ **(*S*)-5-Phenyl-4-propionylamino-pent-2-enoic acid ethyl ester 89**

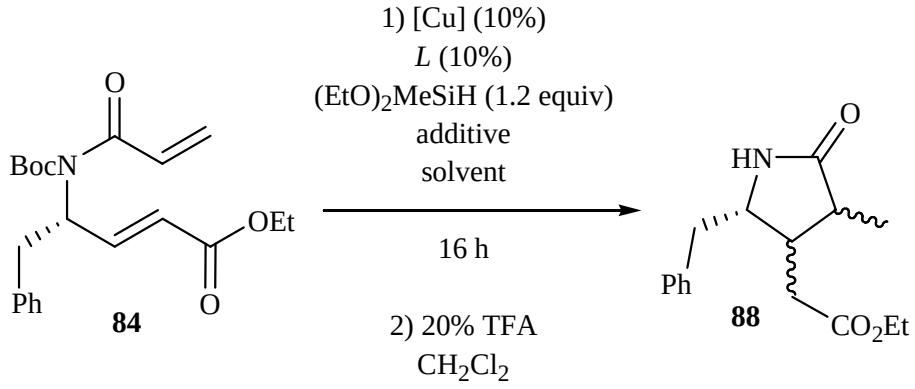


Chemical Formula: $C_{16}H_{21}NO_3$
Molecular Weight: 275.34

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.22 (m, 3H), 7.19 – 7.09 (m, 2H), 6.97 – 6.81 (m, 1H), 5.82 (dd, J = 15.7, 1.6 Hz, 1H), 5.43 (d, J = 8.3 Hz, 1H), 4.98 (t, J = 7.3 Hz, 1H), 4.18 (d, J = 7.1 Hz, 2H), 2.92 (m, 2H), 2.17 (q, J = 7.6 Hz, 2H), 1.27 (t, J = 7.1 Hz, 3H), 1.09 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.37 , 166.19 , 147.05 , 136.27 , 129.44 , 128.79 , 127.15 , 121.53 , 60.68 , 50.63 , 40.47 , 29.80 , 14.35 , 9.86 .

HRMS-ESI (m/z) calcd. for $C_{16}H_{22}O_3N$ $[M + H]^+$ 276.16; found 276.16563

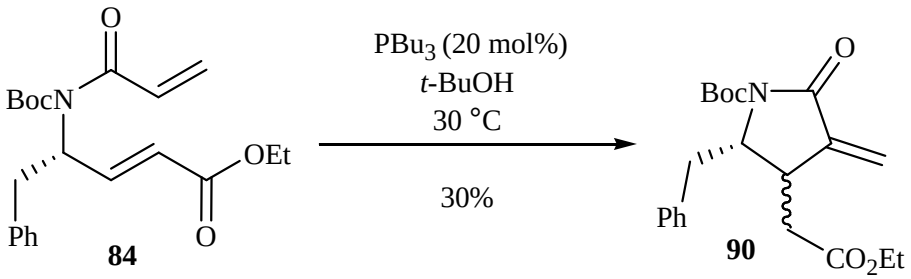
II.2.3 General procedure for the optimization reaction of the reductive Michael cyclizations



A solution of copper salt (0.05 mmol, 0.1 equiv.) and indicated ligand (0.05 mmol, 0.1 equiv.) in toluene (1 mL) was stirred for 15 min before $(EtO)_2MeSiH$ (0.6 mmol, 1.2 equiv.) was added. The solution was stirred until it became yellow (ca. 5 min), after which a solution of the substrate **84** (0.5 mmol, 1 equiv.) in toluene (1 mL) was added rapidly via cannula. The mixture was stirred at room temperature for 18 h, quenched carefully with 1 M HCl (1 mL), diluted with H_2O (15 mL) and then extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with NH_4Cl and brine and dried (MgSO4) and concentrated in vacuo. A precise amount of 1,4-dinitrobenzene (0.1 mmol, 0.2 equiv.) was added to the crude mixture and dissolved in $CDCl_3$ until the solution was homogeneous. A sample was taken for NMR experiments for the calculation of the NMR yield.

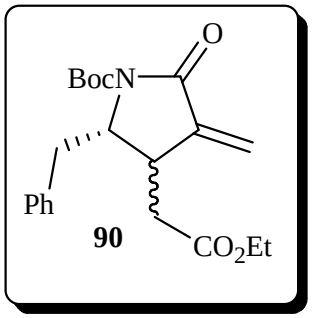
III.3 The Rauhut-Currier reaction

III.3.1 General procedure for the RC reaction in ^{t}BuOH.



A solution of **84** (0.16 mmol, 1 equiv.) and *t*BuOH (1.24g), such that the reaction concentration is 0.1M, was stirred at 30°C, under argon, in a flame dried schlenck. $(n\text{-}Bu)_3P$ (0.033 mmol, 0.2 equiv.) was added. The reaction mixture was left overnight. The organic solvents were evaporated and the crude product poured onto a silica gel column and eluted with a mixture of PE:AcOEt (1:1) to provide the pure product **90** in 30% yield.

➢ **2-Benzyl-3-ethoxycarbonylmethyl-4-methylene-5-oxo-pyrrolidine-1-carboxylic acid tert-butyl ester 90**



Chemical Formula: $C_{21}H_{27}NO_5$
Molecular Weight: 373.44

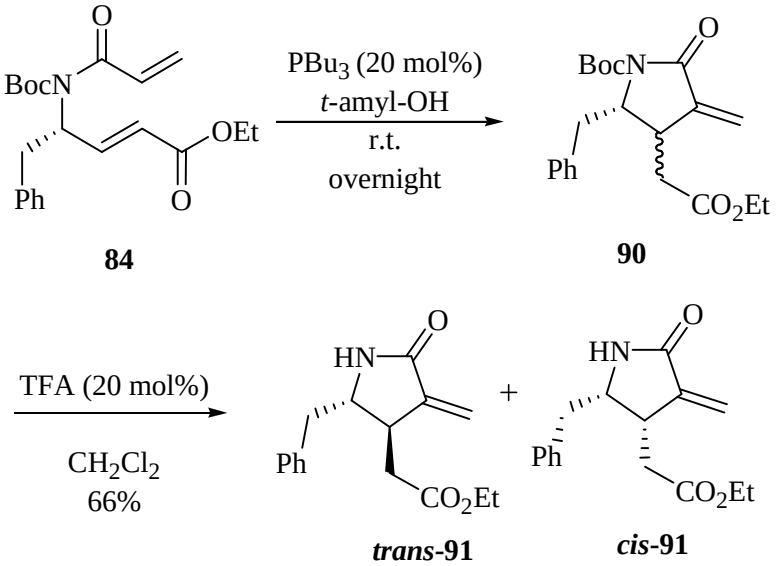
The product was obtained as a clear oil. The mixture of diastereoisomers in a mixture of trans:cis (3:1) was not separated.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.34 – 7.22 (m, 3H), 7.20 – 7.09 (m, 2H), 6.14 (dd, J = 4.4, 1.8 Hz, 1H), 5.47 (dd, J = 4.3, 1.5 Hz, 1H), 4.12 (ddd, J = 8.7, 3.6, 1.3 Hz, 1H), 3.97 (dd, J = 8.9, 7.1 Hz, 2H), 3.16 (dd, J = 13.3, 3.5 Hz, 1H), 3.08 (s, 1H), 2.69 (d, J = 8.7 Hz, 1H), 2.33 (dd, J = 10.2, 7.4 Hz, 2H), 1.59 (s,

9H), 1.16 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.71 , 165.52 , 150.50 , 141.98 , 136.25 , 129.73 , 128.80 , 127.05 , 122.27 , 83.55 , 61.59 , 60.90 , 40.48, 40.44, 36.95 , 28.24 , 14.22 .

MS (ESI): m/z = 274.24 $[M - Boc + H]^+$.

III.3.2 General procedure for the RC reaction in ^{t}amyl-OH



84 **90**

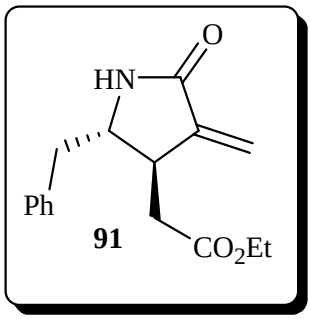
***trans*-91** ***cis*-91**

3 : 1

A solution of **84** (1 mmol, 1 equiv.) and *t*-amyl-OH (10 ml), such that the reaction concentration is 0.1M, was stirred at r.t., under argon, in a flame dried schlenck. $(n\text{-}Bu)_3P$ (0.2 mmol, 0.2 equiv.) was added. The reaction mixture was left overnight. The organic solvents were evaporated and the crude product was directly dissolved in CH_2Cl_2 (12 mL) and cooled to 0°C. TFA (0.2 mmol, 0.2 equiv.) was added and the reaction mixture was stirred for 30 min. Excess solvents and TFA salts were removed with the aid of toluene. The crude material was poured onto a silica gel column and eluted with a mixture of PE:AcOEt (4:6 to 3:7) to provide the pure product **91** in

66% yield in the form of two diastereoisomers with the ratio of 3:1 (*trans:cis*).

➢ **(*S,S*)-(2-Benzyl-4-methylene-5-oxo-pyrrolidin-3-yl)-acetic acid ethyl ester *trans*-91**

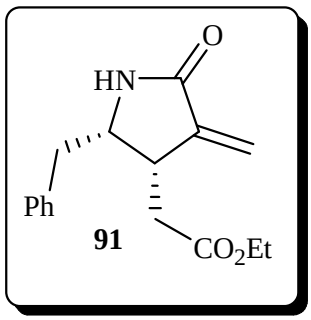


Chemical Formula: $C_{16}H_{19}NO_3$
Molecular Weight: 273.33

The product was obtained as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.38 – 7.23 (m, 3H), 7.23 – 7.08 (m, 2H), 6.40 (s, 1H), 6.04 (d, J = 2.4 Hz, 1H), 5.38 (dd, J = 1.9, 1.0 Hz, 1H), 4.14 (q, J = 7.1 Hz, 2H), 3.60 (t, J = 4.4 Hz, 1H), 3.12 (d, J = 2.7 Hz, 1H), 3.07 – 2.96 (m,1H), 2.73 – 2.62 (m, 1H), 2.51 (d, J = 7.2 Hz, 2H), 1.26 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 171.39 , 169.43 , 142.54 , 136.90 , 129.32 , 127.05 , 117.76 , 60.93 , 58.98 , 42.90 , 40.39 , 39.45 , 14.29 .

HRMS-ESI (m/z) calcd. for $C_{16}H_{20}O_3N$ $[M + H]^+$ 274.14; found 274.14506

➢ **(*S,R*)-(2-Benzyl-4-methylene-5-oxo-pyrrolidin-3-yl)-acetic acid ethyl ester *cis*-91**



Chemical Formula: $C_{16}H_{19}NO_3$
Molecular Weight: 273.33

The product was obtained as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.38 – 7.21 (m, 3H), 7.19 – 7.09 (m, 2H), 6.11 (d, J = 3.1 Hz, 1H), 5.79 (s, 1H), 5.35 (dd, J = 2.7, 0.9 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 4.05 (td, J = 7.7, 3.8 Hz, 1H), 3.61 (dd, J = 5.0, 2.4 Hz, 1H), 2.92 – 2.80 (m, 1H), 2.80 – 2.58 (m, 2H), 2.32 (dd, J =

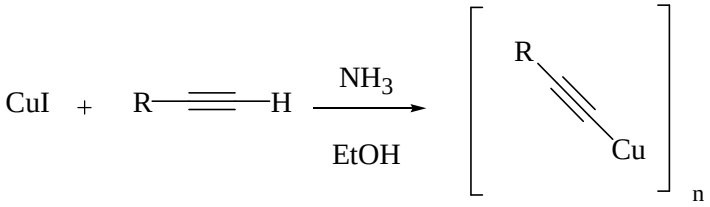
13.0, 11.4 Hz, 1H), 1.31 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.79 , 169.51 , 141.91 , 137.06 , 129.20 , 129.16 , 127.20 , 116.63 , 61.19 , 55.99 , 38.93 , 38.26 , 33.54 , 14.40 .

HRMS-ESI (m/z) calcd. for $C_{16}H_{20}O_3N$ $[M + H]^+$ 274.14; found 274.14506

III. Annex: Synthesis and Characterization of Dinuclear Cu(I)-Alkyne Complexes

III.1 Preparation of copper(I) acetylides

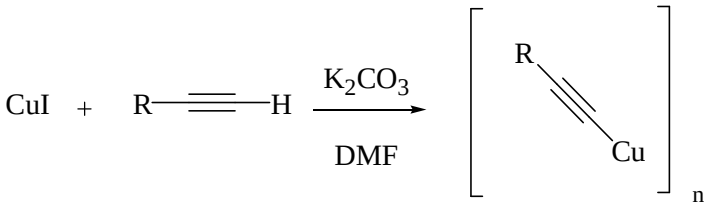
III.1.1 General method A for the preparation of copper(I) acetylides[33]



To a solution of well dissolved copper iodide (4 mmol, 2 equiv.) in a mixture of ammonium hydroxide (28% NH_3 solution, 10 mL) and ethanol (6 mL) was added the alkyne (2 mmol, 1 equiv.) dropwise. The deep blue reaction mixture was stirred overnight at room temperature under argon and the yellow precipitate was collected by filtration and successively washed in a centrifuge with ammonium hydroxide (10% NH_3 solution, 3x50 mL), water (3x50 mL), ethanol (3x50 mL), and diethyl ether (3x50 mL). The bright yellow solid was then dried under high vacuum overnight to afford the desired polymeric alkynylcopper reagent which was used without further purification.

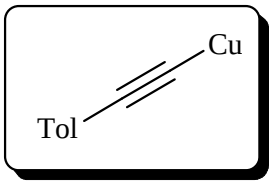
[33] Jouvin, K.; Heimburger, J.; Evano, G., *Chemical Science* **2012,** *3*, 756.

III.1.2 General method B for the preparation of copper(I) acetylides[30]



To a suspension of copper iodide (4.0 mmol, 1 equiv.) in DMF (15 mL) was added a solution of the alkyne (4 mmol, 1 equiv) in DMF (5 mL) via cannula and under argon. Finely powdered potassium carbonate (8.0 mmol, 2 equiv.) was then added at rt and the resulting slurry was stirred under argon for 2 hours, slowly turning into a bright yellow and thick suspension of copper acetylide which was then collected by filtration and successively washed with ammonium hydroxide (10% NH_3 solution, 2x10 mL), water (2x10 mL), absolute ethanol (2x10 mL), and diethyl ether (2x10 mL). The bright yellow solid was then dried under high vacuum overnight to afford the desired polymeric alkynylcopper reagent.

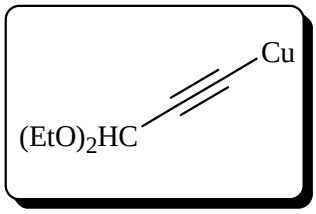
- **Copper(I) tolylacetylide 92**



CAS :31638-66-1

Chemical Formula: C_9H_7Cu
Molecular Weight: 178.7

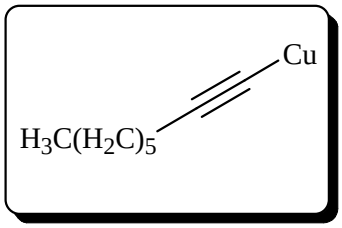
- **Copper(I) 3,3-diethoxy-1-propynyl 93**



Chemical Formula: $C_7H_{11}CuO_2$
Molecular Weight: 190.7

Analysis Calculated. for $C_7H_{11}CuO_2$ C, 44.09; H, 5.81; Cu, 33.32. Found: C, 42.26; H, 5.38; Cu, 33.18.

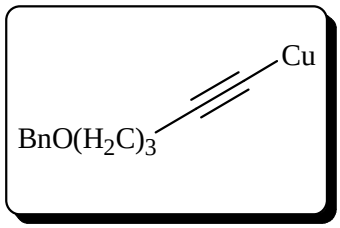
- **Copper(I) oct-1-ynyl 94**



Chemical Formula: $C_8H_{13}Cu$
Molecular Weight: 172.7

CAS: 54502-24-8

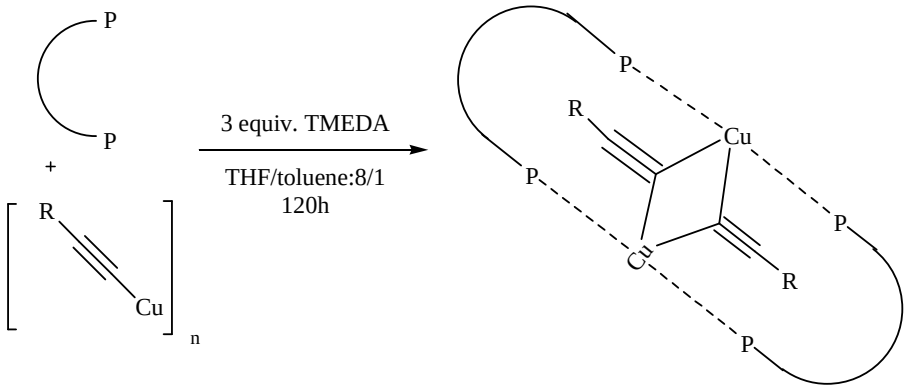
- **Copper(I) Pent-4-ynyloxymethyl-benzene 95**



Chemical Formula: $C_{12}H_{13}CuO$
Molecular Weight: 236.7

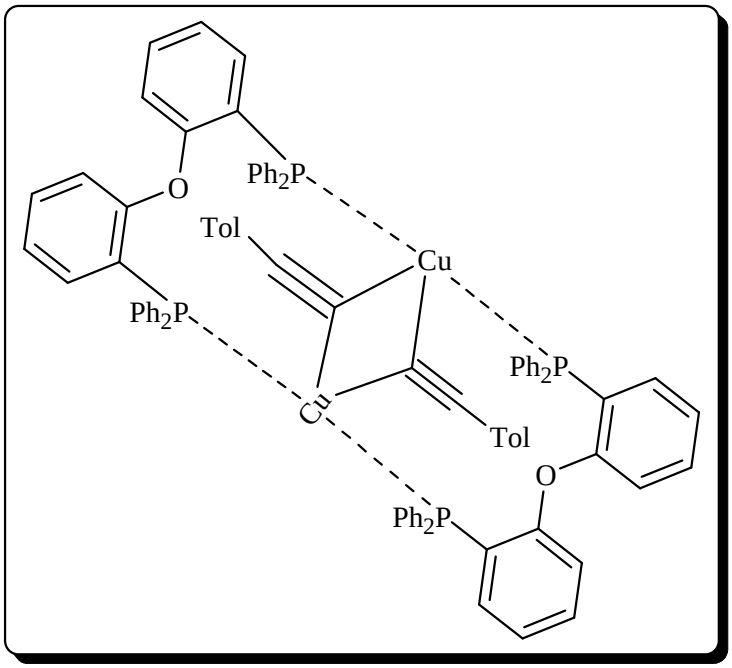
Analysis Calculated. for $C_{12}H_{13}CuO_2$ C, 60.87; H, 5.53; Cu, 26.84. Found: C, 59.17; H, 5.22; Cu, 27.01.

III.2 General procedure for the preparation of bridged diphosphine copper(I) alkynyl complexes



A solution of copper(I) acetylide (0.2 mmol, 1 equiv.) and diphosphine ligand (0.2 mmol, 1 equiv.) in a mixture of THF and toluene (8:1) was stirred under argon in a dry schlenk. TMEDA (0.6 mmol, 3 equiv.) was added. The reaction mixture was left for 72 hours or in some cases until all the solid particles pass into solution. The reaction mixture was then filtered over Celite. The organic solvents were evaporated.

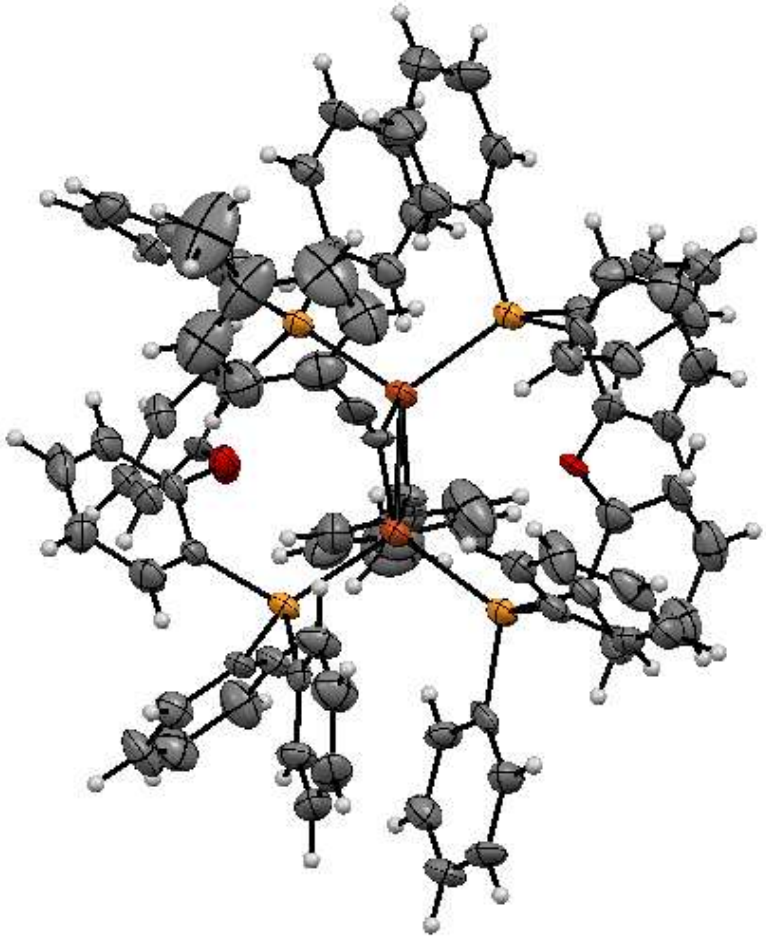
➢ **[Cu_2(μ-dpePhos)$_2$(μ-η^1-C≡C-Tol)] 96**



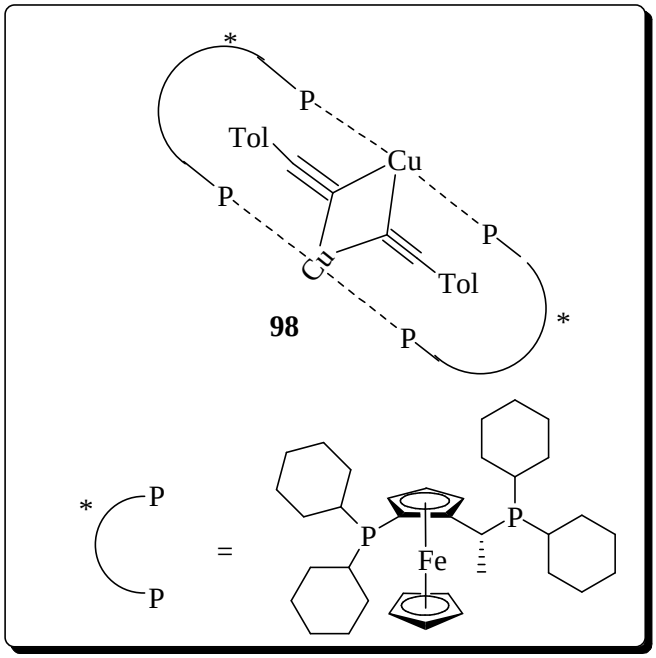
Chemical Formula: $C_{90}H_{70}Cu_2O_2P_4$
Molecular Weight: 1434.5

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.67 – 7.06 (m, 54H), 6.92 (t, J = 7.6 Hz, 6H), 6.76 (d, J = 6.5 Hz, 4H), 2.35 (s, 6H). ^{31}P NMR (121 MHz, $CDCl_3$) δ = -19.58.

The X-ray intensity data were collected at 160 K with a MAR345 image plate using MoKα (λ = 0.71073Å) radiation (Rigaku UltraX18). A crystal that was crystallized from CH_2Cl_2-pentane at r.t. was chosen, mounted and transferred. The unit cell parameters were refined using all the collected spots after the integration process. Molecular formula = $C_{90}H_{70}Cu_2O_2P_4$, Mr = 1434, triclinic $P\bar{1}$, a = 14.1787(14) Å, b = 15.0914(17) Å, c = 23.228(2) Å, *V* = 4412.3 Å^3, Z = 2, Z' = 0, ρ_{calc} = 1.247 gcm^{-3}, T = 160 K, R = 10.44%.



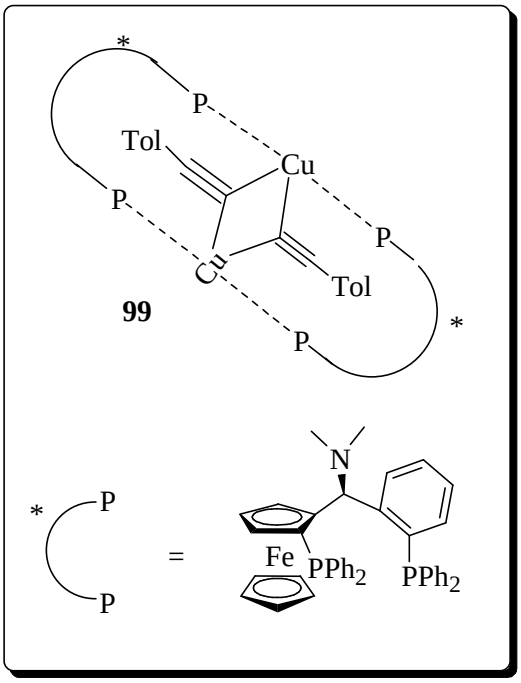
➢ **$[Cu_2(\mu\text{-SL-J003-1})_2(\mu\text{-}\eta^1\text{-C}\equiv\text{C-Tol})]$ 98**



Chemical Formula: $C_{76}H_{108}Cu_2Fe_2P_4$
Molecular Weight: 1384.35

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.38 (d, J = 8.0 Hz, 4H), 7.13 (d, J = 7.9 Hz, 4H), 4.37 (d, 2H), 4.20 (s, 6H), 2.35 (s, 6H), 1.94 – 1.13 (m, 88H). ^{31}P NMR (121 MHz, $CDCl_3$) δ = 2.61 , 1.10 , -13.26 , -14.77 .

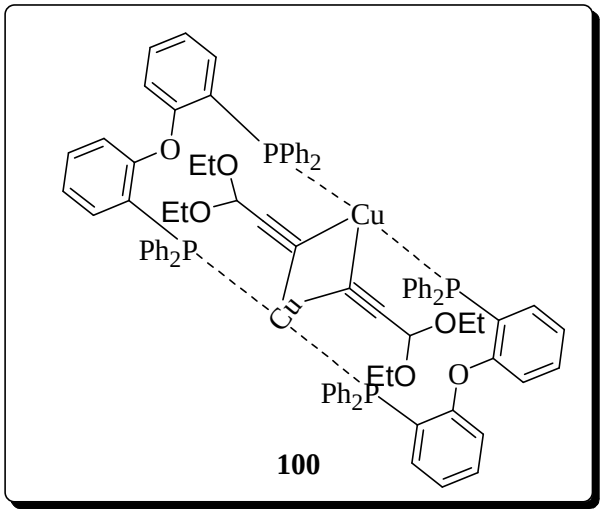
➢ **[Cu_2(*μ*-SL-T001-1)$_2$(*μ*-*η*^{1}-C≡C-Tol)] 99**



Chemical Formula: $C_{90}H_{78}Cu_2Fe_2N_2P_4$
Molecular Weight: 1550.27

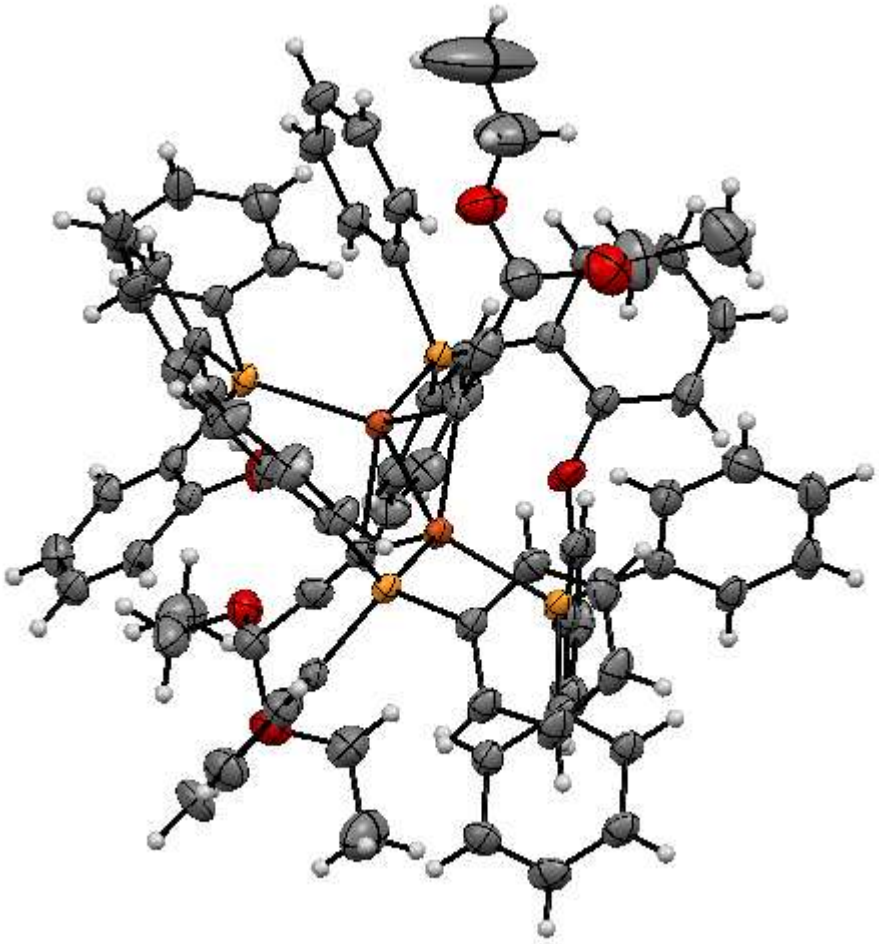
^{1}H NMR (30 MHz, C_6D_6) δ = 8.13 – 7.36 (m, 12H), 7.24 – 6.34 (m, 44H), 4.36 (d, J = 9.7 Hz, 12H), 4.13 (t, J = 1.8 Hz, 2H), 4.06 (s, 6H), 3.77 – 3.58 (m, 10H), 2.33 (s, 6H). ^{31P} NMR (121 MHz, C_6D_6) δ -16.78 (d, J = 17.2 Hz), -23.35 (d, J = 17.1 Hz).

➢ **$[Cu_2(\mu\text{-dpePhos})_2(\mu\text{-}\eta^1\text{-C}\equiv\text{C-CH(OEt)}_2)_2]$ 100**



100

Chemical Formula: $C_{86}H_{78}Cu_2O_6P_4$
Molecular Weight: 1458.52

1H NMR (300 MHz, $CDCl_3$) δ = 7.47 (m, 16H), 7.26 (m, 24H), 6.90 (d, J = 7.7 Hz, 16H), 3.95 – 3.80 (m, 2H), 3.83 – 3.67 (m, 8H), 1.24 (d, J = 5.1 Hz, 12H). ^{31}P NMR (121 MHz, $CDCl_3$) δ = -17.63.

The X-ray intensity data were collected at 150 K with a MAR345 image plate using MoKα (λ = 0.71073Å) radiation (Rigaku UltraX18). A crystal that was crystallized from CH_2Cl_2-pentane at r.t. was chosen, mounted and transferred. The unit cell parameters were refined using all the collected spots after the integration process. Molecular formula = $C_{86}H_{78}Cu_2O_6P_4$, Mr = 1458, monoclinic $P2_1/n$, a = 14.2884(2) Å, b = 23.7174(4) Å, c = 23.2343(3) Å, *V* = 7778.86 Å^3, T = 150 K.