NHC ligands as chiral catalysts for the copper-catalyzed asymmetric conjugate addition of Grignard reagents on trisubstituted cyclic enones: formation of quaternary chiral centers

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NHC ligands as chiral catalysts for the copper-catalyzed asymmetric conjugate addition of Grignard reagents on trisubstituted cyclic enones. Formation of quaternary chiral centers.

THÈSE

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par

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La Faculté des sciences, sur le préavis de Messieurs A. ALEXAKIS, professeur ordinaire et directeur de thèse (Département de chimie organique), C. MAZET, docteur (Département de chimie organique) et I. MARKO, professeur (Département de chimie, Université Catholique de Louvain, Louvain-la-Neuve, Belgique), autorise l'impression de la présente thèse, sans exprimer d'opinion sur les propositions qui y sont énoncées.

Genève, le 5 novembre 2009

Thèse - 4150 -

Le Doyen Jean-Marc TRISCONE

N.B.- La thèse doit porter la déclaration précédente et remplir les conditions énumérées dans les "Informations relatives aux thèses de doctorat à l'Université de Genève".

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Cette these a donné lieu aux publications suivantes:

(1) Martin, D.; Kehrli, S.; D'Augustin, M.; Clavier, H.; Mauduit, M.; Alexakis, A. *J. Am. Chem. Soc.* 2006, *128*, 8416-8417.

(2) Alexakis, A.; Vuagnoux-d'Augustin, M.; Martin, D.; Kehrli, S. *Latv. Kim. Z.* 2007, 373-377.

(3) Vuagnoux-d'Augustin, M.; Kehrli, S.; Alexakis, A. *Synlett* 2007, 2057-2060.

(4) Alexakis, A.; Vuagnoux-d'Augustin, M.; Martin, D.; Kehrli, S.; Palais, L.; Henon, H.; Hawner, C. *Chimia* 2008, *62*, 461-464.

(5) Wencel, J.; Mauduit, M.; Henon, H.; Kehrli, S.; Alexakis, A. *Aldrichimica Acta* 2009, *42*, 43-50.

(6) Kehrli, S.; Martin, D.; Mauduit, M.; Alexakis, A. *In preparation.*

To my daughter Mathilda.

Imagination is more important than knowledge, because if knowledge concerns everything that exists, imagination concerns everything what is to exist.

Albert Einstein

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RESUME

I. Introduction

I.1 Catalyse asymétrique

Les deux énantiomères d'une même molécule peuvent avoir des propriétés chimiques (toxicité, odeur...) très différentes. C'est pourquoi, les chimistes ont développé des techniques afin de synthétiser stéréosélectivement leurs produits cibles. L'idée générale est de gêner stériquement une face du substrat par rapport à l'autre, ce qui pousse le réactif à venir se lier par l'autre face.

Deux techniques principales ont été développées : d'une part, la fixation sur le substrat d'une copule chirale qui crée une gêne stérique sur une face de la molécule et influence donc l'approche du réactif sur l'autre face (Schéma 1).[1] D'autre part, l'ajout dans le système d'un catalyseur chiral qui se liera, de façon momentanée, avec le réactif et le substrat. Ces catalyseurs possèdent des groupements chiraux encombrants qui développent une gêne stérique sur une face du substrat favorisant l'approche du nucléophile par l'autre face.

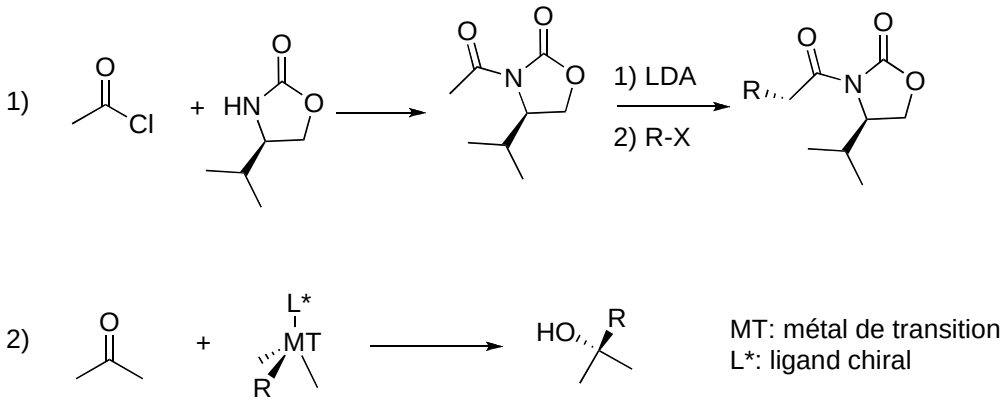


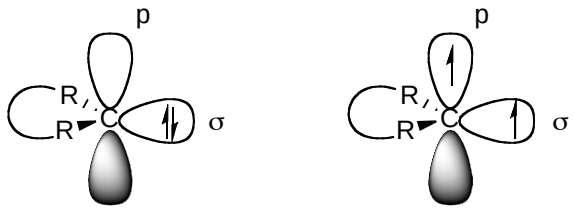
Schéma 1

Les copules chirales donnent d'excellents résultats, mais le gros désavantage est que celle-ci doit être utilisée en quantité stoechiométrique.

[1] Evans, D.A.; Ennis, M. D.; Marthe, D. J. *J. Am. Chem. Soc*. 1982, *104*, 1737-1739.

Dans le second cas, une quantité catalytique de complexe chiral est suffisante pour mener à terme une réaction avec de très bons rendements et excès énantiomériques. Les ligands phosphorés ont été largement utilisés à cet effet, et ont donné d'excellents résultats. Cependant, ces ligands sont souvent sensibles à l'oxygène. De plus, ces ligands étant souvent faiblement liés au métal de transition (MT), il est nécessaire de les utiliser en excès par rapport au MT. De nouveaux ligands ont donc été recherchés pour contrer ces lacunes.

À la fin des années 1960, Öfele[2] puis Wanzlick[3] publient leurs premières découvertes à propos d'une nouvelle sorte de molécule, les carbènes N-hétérocycliques (NHC). Ces NHC sont des composés divalents neutres possédant un carbone à six électrons de valence. Ils sont donc considérés comme étant électrophiles (orbitale p vide) et nucléophiles (paire libre dans l'orbitale atomique σ) (Schéma 2).



carbène singulet
2S+1 = 1
orbital *p* vide

carbène triplet
2S+1 = 3
"di-radical"

Schéma 2

Ce n'est qu'en 1991 qu'Arduengo[4] parvient à synthétiser le premier carbène stable sous forme cristalline.

Initialement qualifiés d'équivalents de ligands phosphines, les expériences théoriques et pratiques démontrent actuellement que les NHC ont un potentiel bien plus large que les phosphines. Tout d'abord, parce que les substituants chiraux entourent le centre réactionnel, ce qui permet une meilleure induction de chiralité sur le centre asymétrique à former. D'autre part, parce que les facteurs stériques et électroniques des NHC sont beaucoup plus complexes que ceux des phosphines. Ainsi, l'éventail des variations possibles des propriétés des

[2] K. Öfele *J. Organomet. Chem.*, 1968, 1*2,* P42.

[3] Wanzlick, H.W. *Angew. Chem., Int. Ed*. 1962, *1*, 75.

[4] Arduengo, A. J., III; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* 1991, *113*, 361-3.

NHC par un échange de substituant est énorme et reste encore à être découvert.[5]

I.2 Addition conjuguée asymétrique

L'addition conjuguée est une méthode de choix pour former des centres enantioenrichis à quatre carbones (Schéma 3).[6] Après avoir utilisé les organoaluminiques, notre groupe s'est penché sur l'addition conjuguée asymétrique (A.C.A.) d'organomagnésiens sur des énones cycliques pour former des centres chiraux.

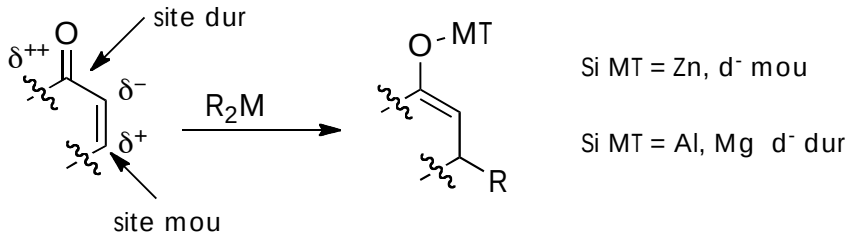


Schéma 3

Au cours de cette thèse, nous avons développé une méthodologie catalytique basée sur des complexes Cu:NHC pour former des centres chiraux quaternaires en utilisant des additions conjuguées de Grignards sur des énones cycliques trisubstituées.

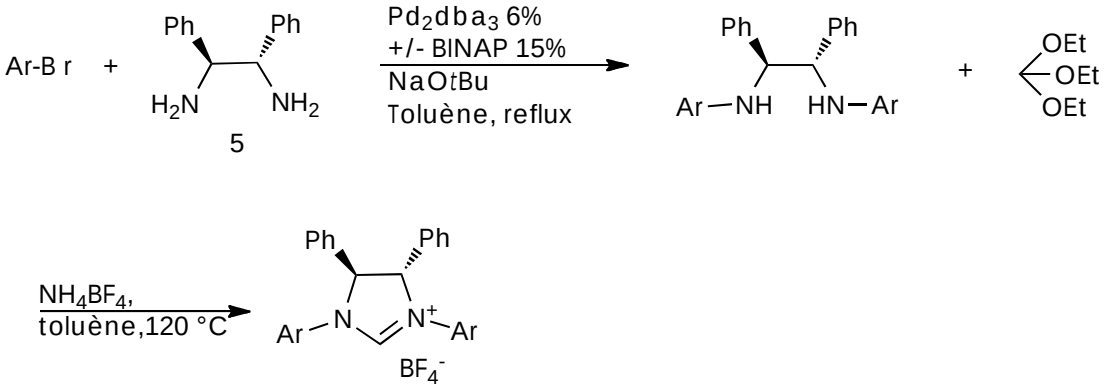
II. A.C.A. catalysées par des NHC C_2-symétriques

II.1 Synthèse de ligands C2-symétriques

Nous avons tout d'abord synthétisé différent NHC *C_2*-symétriques à partir de couplages de Buchwald-Hartwig entre la diphényle éthanediamine (DPEDA) et différents cycles aromatiques bromés (Schéma 4).

[5] Crabtree, R. H. *J. Organomet. Chem.* 2006, *691*, 3146-3150.

[6] a) Alexakis, A.; Backvall, J. E.; Krause, N.; Pamies, O.; Dieguez, M. *Chem. Rev. (Washington, DC, U. S.)* 2008, *108*, 2796-2823. b) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* 2002, 3221-3236. c) Bos, P. H.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* 2008, *10*, 4219-4222. d) Trost, B. M.; Jiang, C. *Synthesis* 2006, 369-396. e) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev. (Washington, DC, U. S.)* 2008, *108*, 2824-2852.



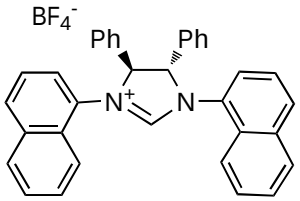
2a: Ar = 1-Naphthyl
2b: Ar = 2-Naphthyl
2c: Ar = 2-Me-C_6H_4 (fait par Dr Martin)
2d: Ar = 2-iPr-C_6H_4 (fait par Dr Martin)
2e: Ar = 1-OMe-8-Naphthyl

Schéma 4

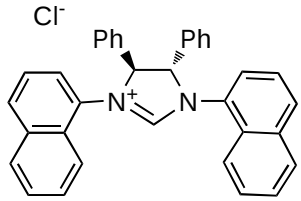
Le ligand 2e contenant deux fonctions -OMe chélatantes a été synthétisé dans le but d'observer une quelconque différence de réactivité avec ou sans chélation des substituants présents sur les atomes d'azote.

II.2 Variation des Grignards aliphatiques sur la méthyle cyclohexénone

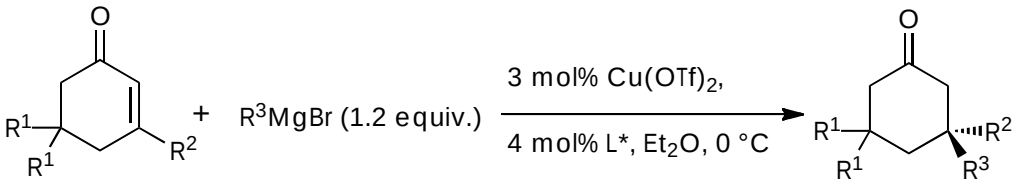
La mise au point des conditions réactionnelles a été réalisée pas A.C.A. d'EtMgBr sur la méthyle cyclohexénone. Les meilleurs résultats ont été obtenus avec le ligand 2a (73% *ee*). Celui-ci a ensuite été utilisé avec d'autres Grignards linéaires, ramifiés et cycliques afin d'évaluer l'étendue d'action de nos catalyseurs (Tableau 1).



2a



2i

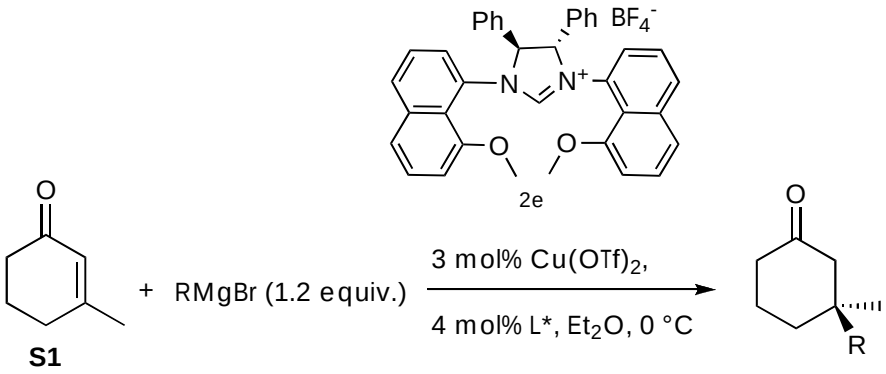


Entrée	R^1	R^2	R^3	ImH^+	Prod.	Conv.[a]	*ee* [b]
1	H	Me	Et	2a	21	92%	73% (-) *S*
2	H	Me	Et	2i	21	>99%	72% (-) *S*
3	H	Me	*n*-Bu	2a	22	99%	73% (-) *S*
4	H	Me	But-3-en	2a	23	81%	73% (+) *R*
5	H	Me	*c*-Pent	2a	24	97%	60% (-) *S*
6	H	Me	*c*-Pent	2i	24	>99%	60% (-) *S*
7	H	Me	*i*-Prop	2a	25	99%	39% (-) *S*
8	H	Me	*i*-Prop	2i	25	>99%	40% (-) *S*
9	H	Et	Me	2a	20	99%	21% (+) *R*
10	H	But-3-en	Et	2a	26	88%	50% (+) *S*
11	Me	Me	Et	2a	27	93%	71% (-) *S*

(a) conversion déterminée par GC-MS, après 30 min. ou 3 h. (T < 0 °C). (b) déterminée par GC chirale (Lipodex E).

Tableau 1

Les résultats obtenus sont très encourageants, avec des excès énantiomériques compris entre 60% et 70%. L'addition d'*i*-PropMgBr donne de moins bons résultats (40% *ee*). Le ligands tridentate 2e a été utilisé pour observer si la rigidification de l'induction chirale sur le complexe pouvait résoudre ce problème (Tableau 2).



Entrée	R	ImH^+	Prod.	Conv.[a]	*ee* [b]
1	Ethyl	2e	21	>99%	67% (-) *S*
2	*n*-Butyl	2e	22	>99%	72% (-) *S*
3	*c*-pentyl	2e	24	>99%	56% (-) *S*
4	*i*-propyl	2e	25	>99%	70% (-) *S*
5	*t*-butyl	2e	28	>99%	0%

(a) conversion déterminée par GC-MS, après 30 min. ou 3 h. (T < 0 °C). (b) déterminée par GC chirale (Lipodex E).

Tableau 2

Ce ligand permet de largement augmenter la stéréosélectivité de l'addition de l'*i*-PropMgBr encombré par rapport à son homologue 2a (cf Tableau 1, Entrée 7-8 ; Tableau 2, Entrée 4). En conclusion, ces ligands C_2-symétriques permettent de catalyser l'A.C.A. de différents Grignards linéaires et encombrés sur différentes cyclohexénones trisubtituées avec des *ee* compris entre 60% et 70%. De plus, l'addition d'un gros groupe *t*-Butyl est possible avec une conversion totale mais sans stéréosélectivité.

II.3 Résumé des résultats obtenus avec 2a et 2e

Résultats obtenus avec les NHC C2-symmétriques

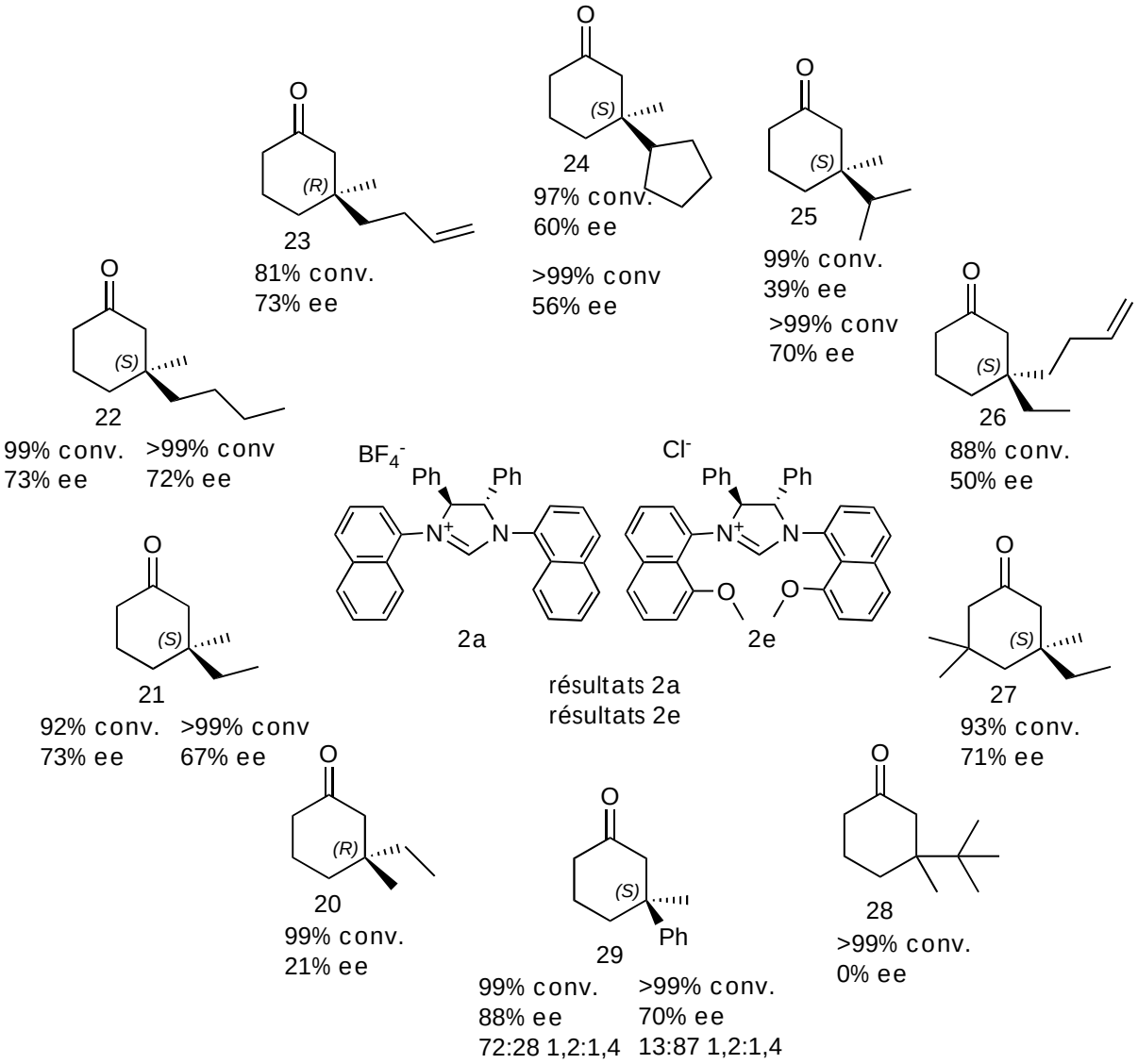


Schéma 5

III. A.C.A. catalysées par des alkoxy-NHC

III.1 Synthèse de ligands de type « Mauduit »

Comme la présence de groupements coordinants semble donner de bons résultats en A.C.A., une autre famille de ligand NHC contenant une fonction

alkoxy- a également été synthétisée. Ces ligands de type « Mauduit » sont facilement synthétisés selon la procédure donnée ci-dessous (Schéma 6).

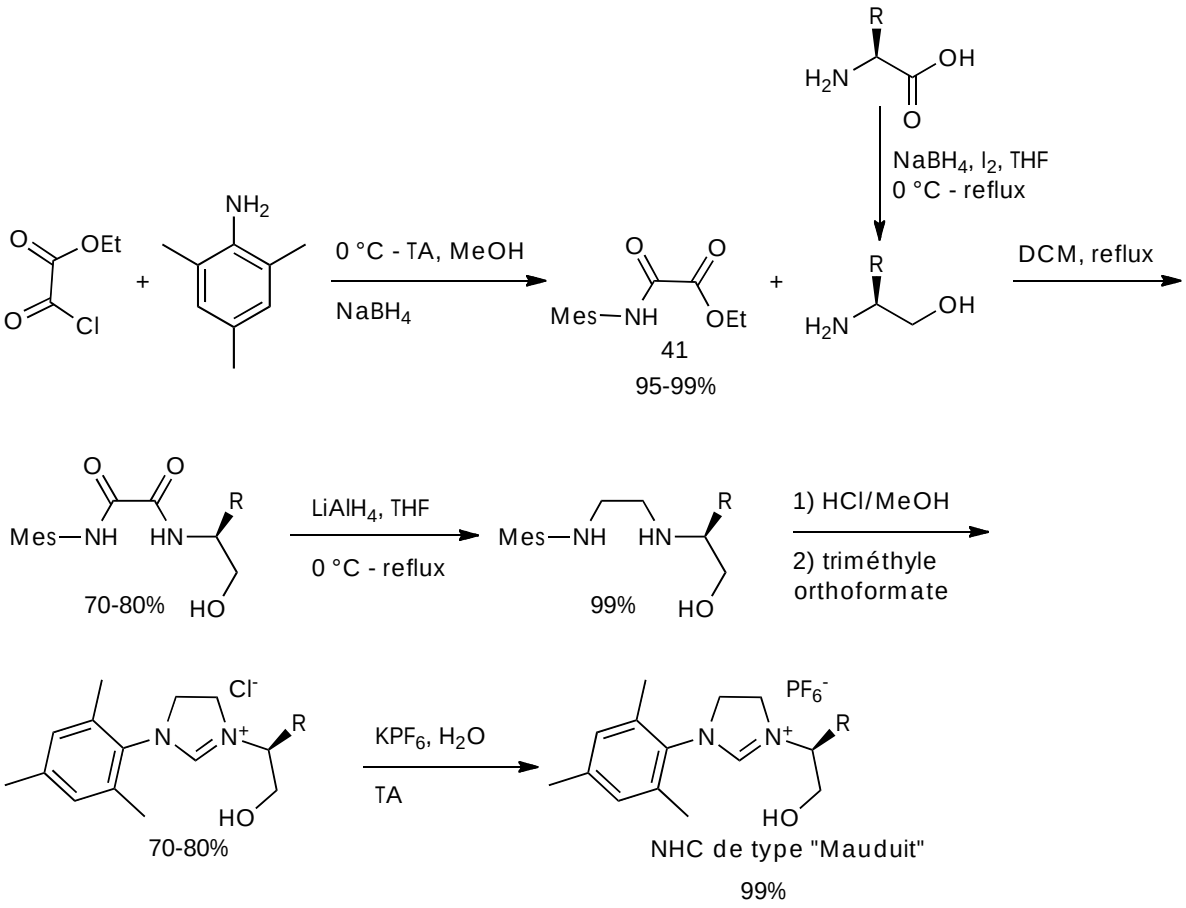
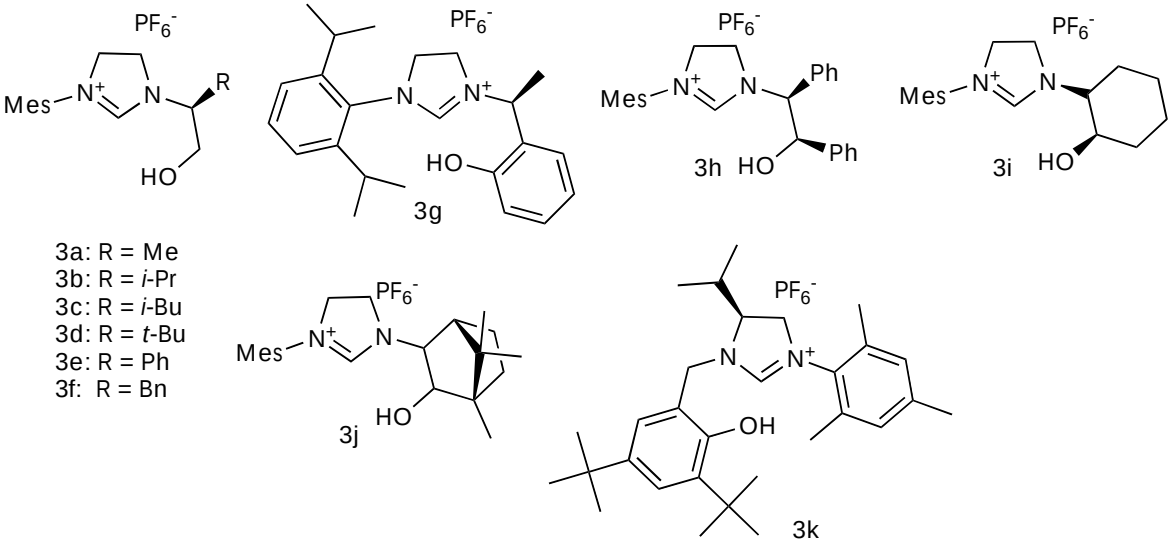


Schéma 6

Une série de ligands a été obtenue grâce à ce procédé (Schéma 7).

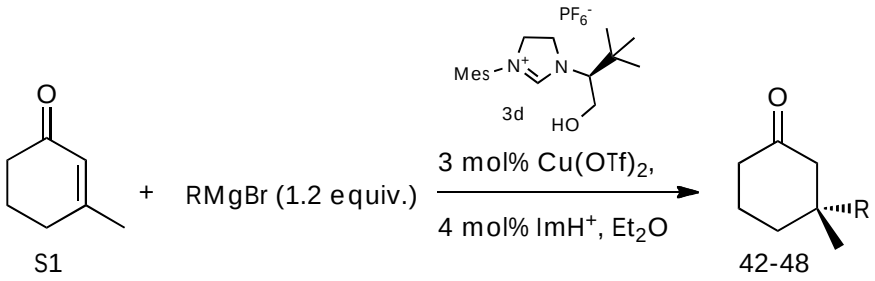


3a: R = Me
3b: R = *i*-Pr
3c: R = *i*-Bu
3d: R = *t*-Bu
3e: R = Ph
3f: R = Bn

Schéma 7

III.2 Variation des Grignards aliphatiques sur la méthyle cyclohexénone

Après avoir trouvé les meilleures conditions opératoires pour l'A.C.A. d'EtMgBr sur la méthyle cyclohexénone, le meilleur ligand 3d a été testé avec différents Grignards linéaires, ramifiés et cycliques (Tableau 3).



S1 42-48

Entry	Prod.	R^1	Temp	Temps addition substrat	Conv.[a]	η[c]	*ee*[b]
1	42	*n*-Bu	0 °C	60 min	100%	-	78% *R*
2	43	Butenyl	-30 °C	15 min	91%	80%	90% *S*
3	44	*i*-Bu	-30 °C	60 min	100%	72%	96% *S*
4	45	*i*-Pr	-18 °C	50 min	100%	77%	78% *R*
5	46	*c*-Pent	-30 °C	60 min	100%	80%	86% *R*
6	47	*c*-Hex	-30 °C	10 min	100%	77%	79% *R*
7	48	Me-TMS	-30 °C	30 min	99%	74%	6% *R*

(a) conversion déterminée par GC-MS, après 15-30 minutes. (b) déterminée par GC chirale (Lipodex E). *(c)* rendement isolé.

Tableau 3

Les résultats obtenus avec ces différents complexes sont très bons et donnent d'excellentes stéréosélectivités (80% - 96% d'*ee*).

III.3 Variation des substrats avec l'EtMgBr

Plusieurs substrats ont été synthétisés pour s'assurer que notre complexe n'était pas substrat-dépendant (Schéma 8).

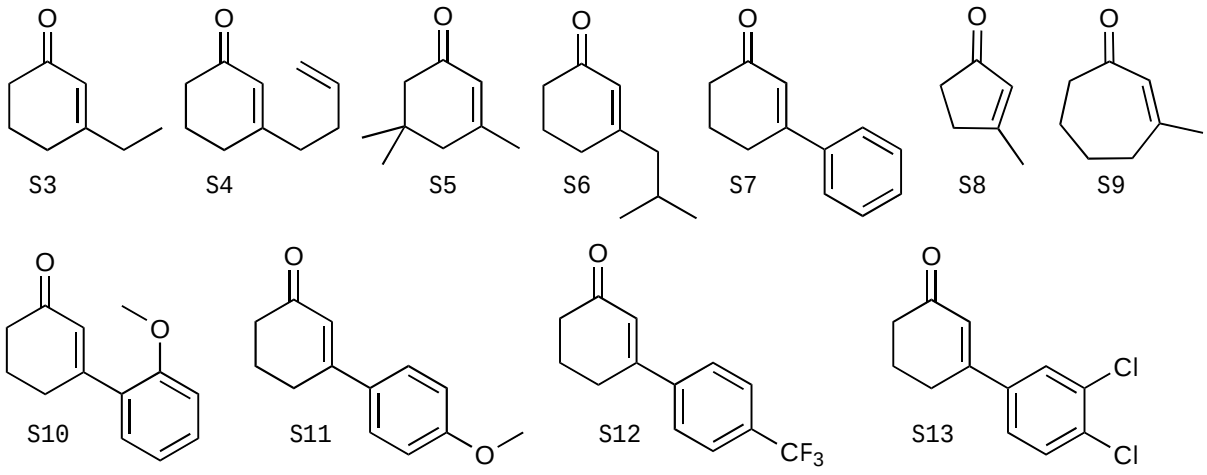
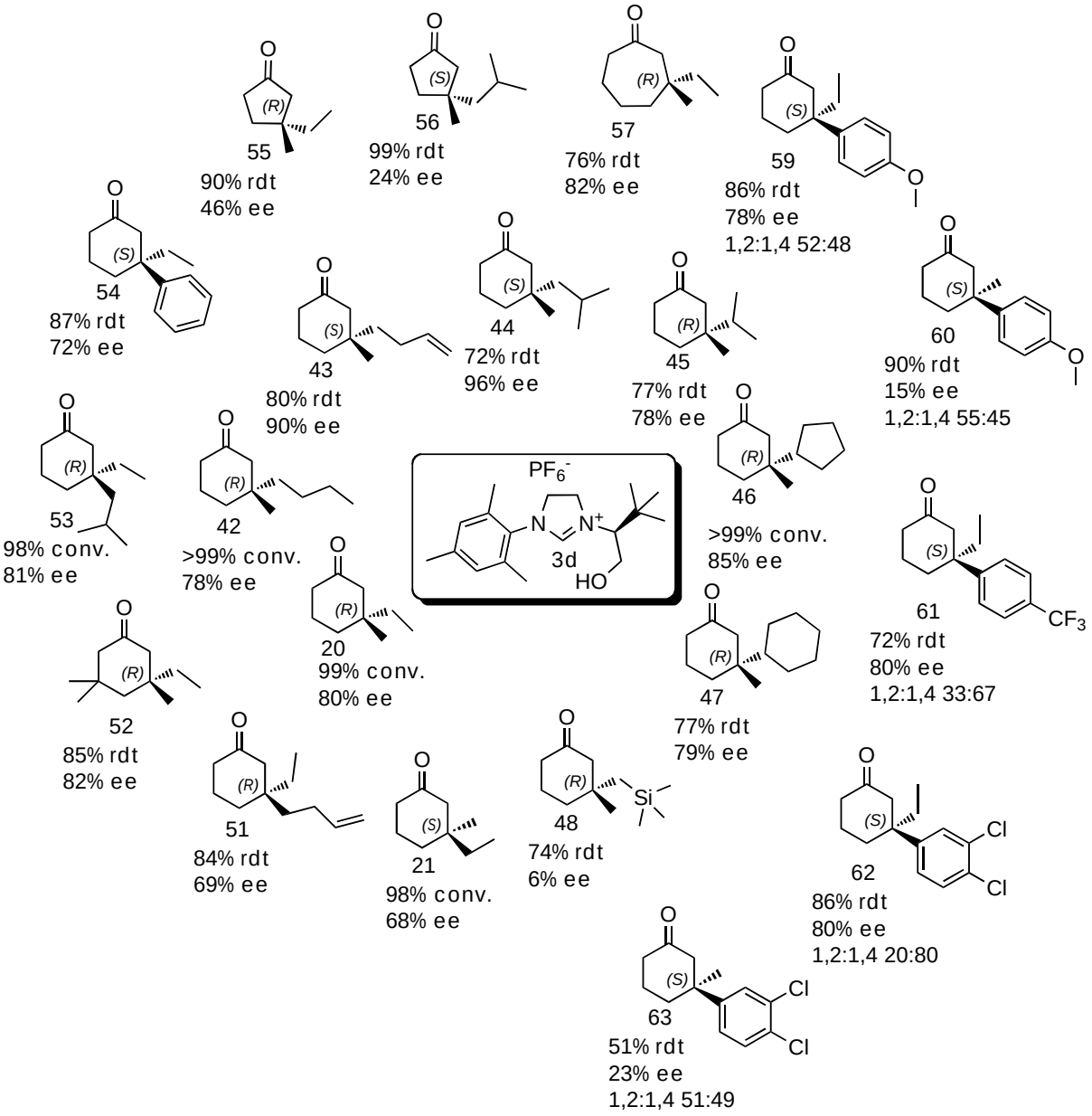


Schéma 8

L'EtMgBr et le MeMgBr ont été testés sur ces substrats avec également de très bons résultats (70% - 80% d'*ee*). L'utilisation du cycle à sept chaînons S9 donne des résultats similaires au cycle à six. Par contre, l'*ee* chute avec la méthyle cyclopentenone S8 (46%).

L'A.C.A. sur des substrats aromatiques donne de bons *ee* mais la régiosélectivité n'est plus totalement en faveur de l'addition 1,4. L'A.C.A. de Grignard aromatiques sur la méthyle cyclohexénone donne des résultats encore plus mauvais avec des régiosélectivités nettement en faveur de l'addition 1,2. Un résumé des résultats obtenus est retranscrit dans le Schéma 9.



Résultats avec le ligand 3d
addition de Grignards aromatiques

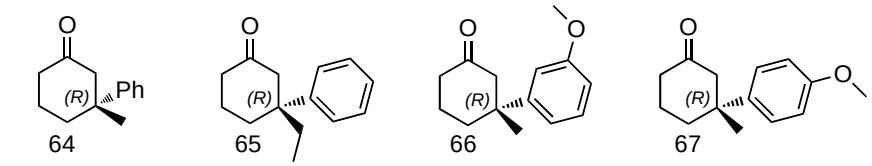


Schéma 9

IV. A.C.A. catalysées par des alkoxy-NHC homologués

IV.1 Synthèse de ligands de type triméthylebenzyle

Pour observer l'effet de l'augmentation du volume du centre réactionnel sur l'énantiosélectivité de l'A.C.A., une famille de ligands triméthyle benzylés a été synthétisé. En homologuant la chaîne du groupement mesityle, le volume de l'espace réactionnel est augmenté.

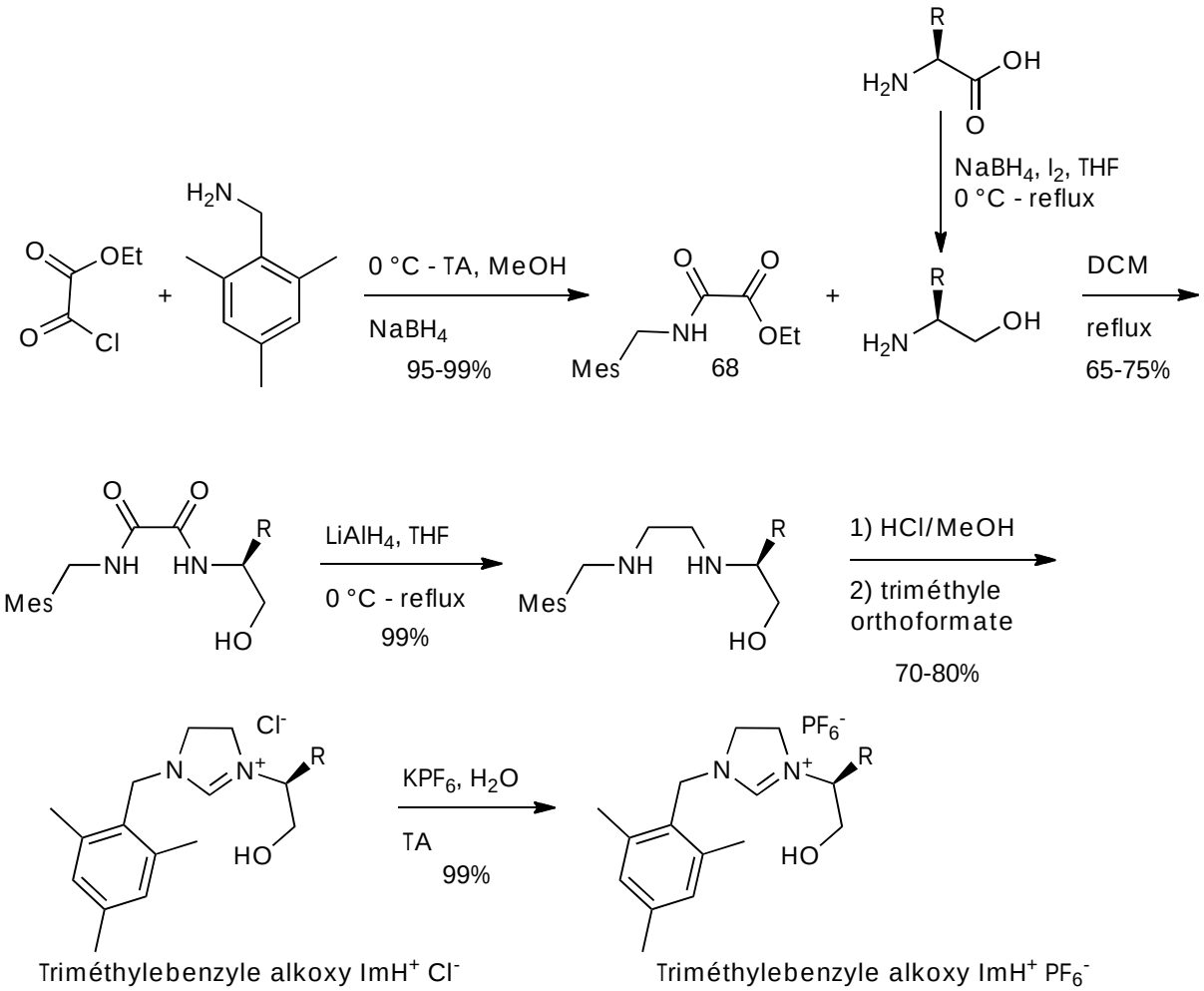


Schéma 10

Cette méthodologie nous a permis de synthétiser cinq ligands (3l, 3m, 3n, 3o, 3p), le Dr. Mauduit nous offrant généreusement les ligands 3q et 3r (Schéma 11).

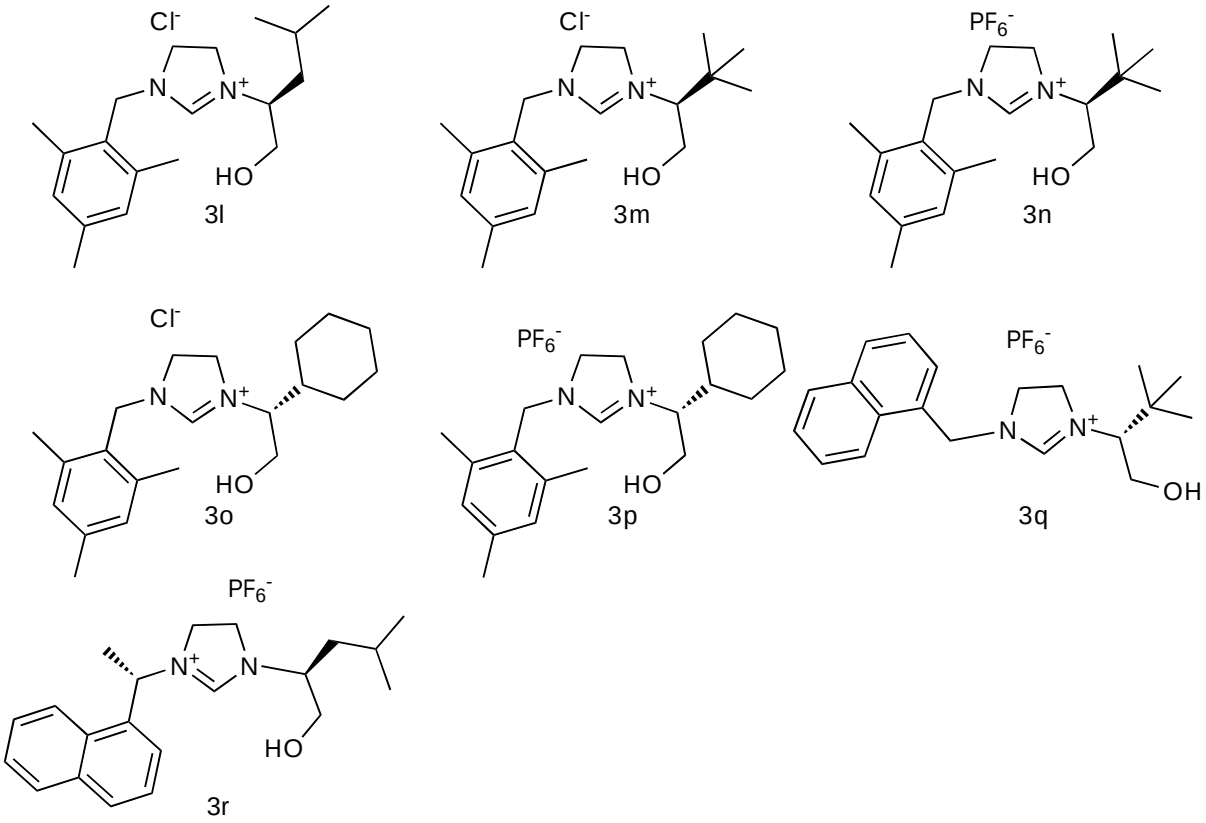


Schéma 11

IV.2 Variation des Grignards aliphatiques sur la méthyle cyclohexénone

Ces ligands ont été testés en A.C.A. de différents Grignards linéaires, ramifiés et cycliques sur la méthyle cyclohexénone dans les mêmes conditions opératoires que pour les NHC de type « Mauduit » (Schéma 12).

Les résultats obtenus avec les ligands homologués sont meilleurs que ceux obtenus avec leurs mésitylés correspondant dans les cas où le substrat utilisé est plus encombré que la triméthyle cyclohexénone (S3, S6). En effet, les *ee* augmentent d'environ 10% pour chaque résultat où le substrat utilisé possède un substituant en position β plus gros qu'un méthyle. L'A.C.A sur la méthyle cyclopentenone donne également de meilleurs résultats avec le nouveau ligand 3m.

encadré = résultats améliorés avec les ligands triméthylebenzyl par rapport au ligand 3d

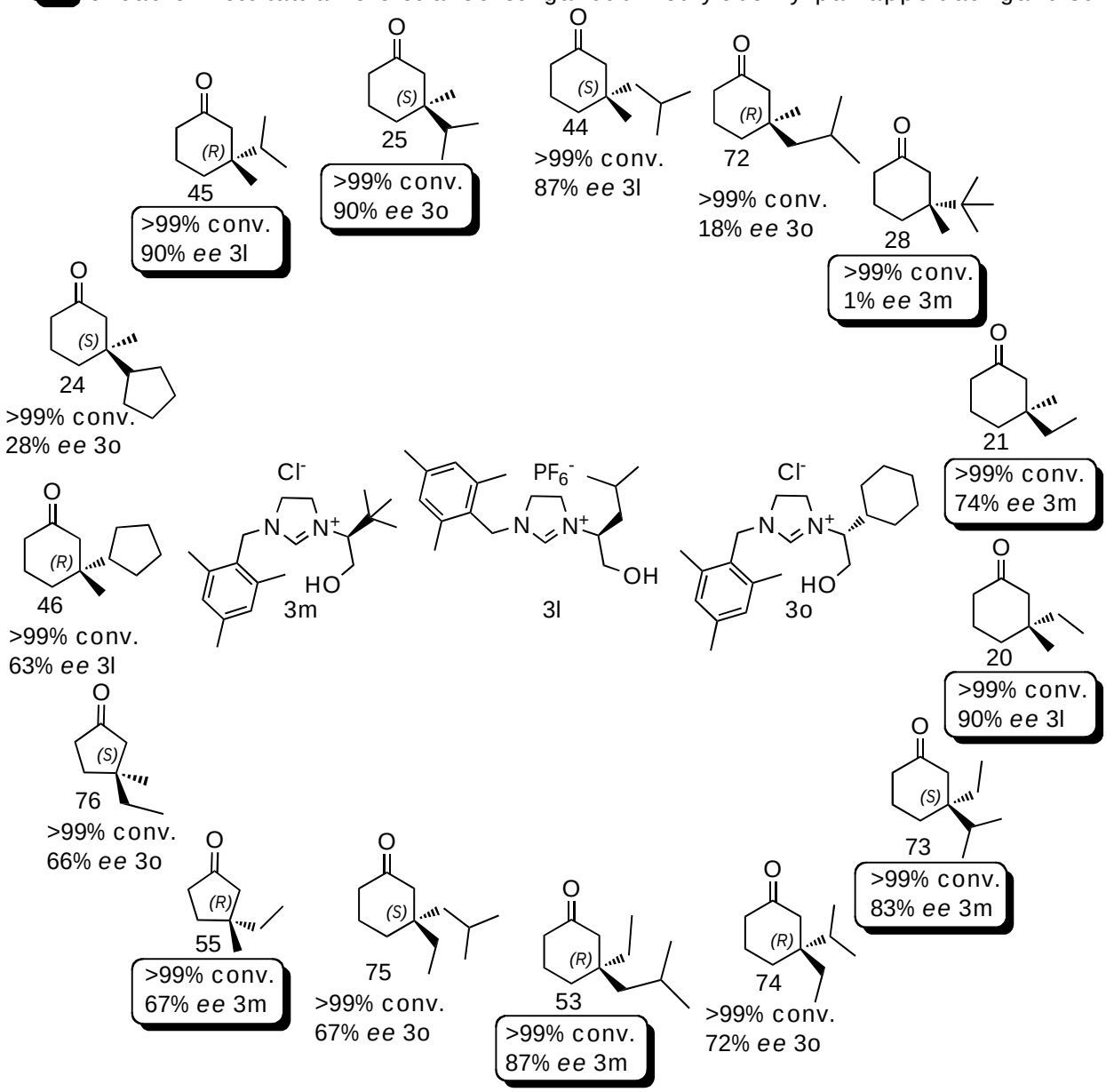
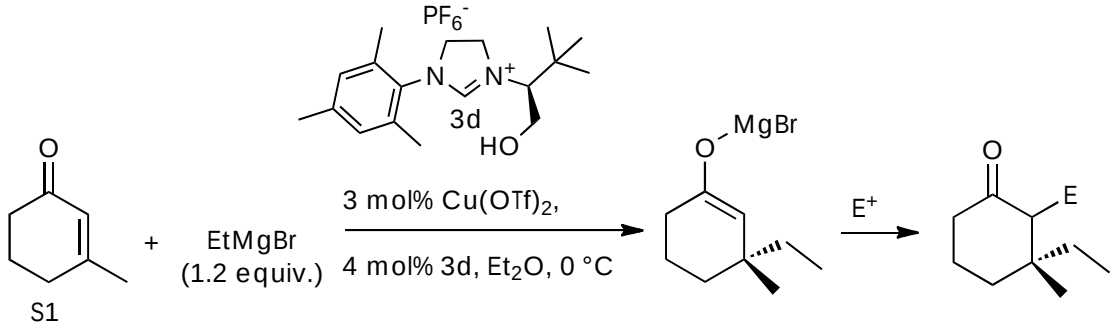


Schéma 12

V. Applications en synthèse

V.1 Piégeage d'énolate de magnésium

Pour augmenter la valeur de notre méthodologie en synthèse, nous avons piégé les énolates de magnésium obtenu après A.C.A. avec différents électrophiles (Tableau 4). Cette technique permet de fonctionnaliser facilement la position α des énones cycliques en « one-pot ».



Entrée	Prod.	E^+	Temps	Conv.[a]	η[b]	1er dia./2ème dia *ee*[c]	dia. Ratio
1[d]	79	Iodo allyl	25 h.	>99%	81%	76%[e]	70:30
2[d]	80	MeI	12 h.	99%	79%	76%[e]	59:41
3	82	Benzaldehyde[f]	30 min	>99%	72%	77%/68%	41:59
4	83	Br_2	30 min	>99%	78%	76%/78%	12:88

(a) conversion déterminée par GC-MS, après 30 minutes. (b) rendement isolé (c) déterminé par GC chiral. (d) HMPA: THF 1:1, 40 °C. (e) *ee* de la 1ère étape. (f) l'alcool obtenu est oxidé pour éliminer des diatéréoisomères.

Tableau 4

VI. Conclusion

En conclusion, nous avons montré que les trois familles de ligands NHC que nous avons synthétisé sont des ligands valables pour l'A.C.A. de réactifs de Grignard sur des enones cycliques trisubstituées. Nous avons atteint d'excellentes énantiosélectivités (jusqu'à 96%) avec l'addition de Grignards linéaires ou ramifiés sur des énones cycliques linéaires ou ramifiées. L'utilisation de substrats substitués par

des aromatiques a donné également des *ee* élevés jusqu'à 80%, bien que la régiosélectivité de la réaction ne soit pas parfaite.

L'énantiosélectivité des additions de nucléophiles aromatiques est élevée (jusqu'à 90%), mais la régiosélectivité doit être améliorée. Nos deux familles de ligands montrent également une sélectivité faciale parfaite. En effet, en inversant le substituant sur l'énone et celui du réactif de Grignard, nous obtenons toujours l'énantiomère majoritaire opposé. Nous avons également développé un moyen facile d'α-fonctionnaliser l'énolate de magnésium formé durant l'A.C.A. dans une méthode « one-pot » avec des électrophiles de type : alkyle, benzaldéhyde, halogénures et allyle. La rétention de configuration est parfaite. Cette méthodologie a permis d'agrandir le champ d'application de la réaction. Cette réaction d'A.C.A. n'est pas substrat-dépendante et utilise un des nucléophile les plus facilement modifiable : le réactif de Grignard.

Table of contents

Abbreviations

η : isolated yield

TEP : Tolman's electronic parameters

°C : degree Celsius

A.C.A. : asymmetric conjugate addition

bde : bond dissociation energy

BINAP : 2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene

br s : broad singlet

d : doublet

dba : dibenzylideneacetone

DCM : dichloromethane

DMAP : 4-dimethylaminopyridine

DMF : dimethylformamide

DPEDA : diphenylethylenediamine

ee : enantiomeric excess

EI-MS : electron impact mass spectrometry

equiv. : equivalent

GC : gas chromatography

h. : hour

HMPA : hexamethylphosphoric triamide

HOMO : highest occupied molecular orbital

ImH^+ : imidazolium salt

J : coupling constant in Hertz

LHMDS : lithium hexamethyldisilazide $LiN(SiMe_3)_2$

LUMO : lowest unoccupied molecular orbital

m : multiplet

m-CPBA : *meta*-chloroperbenzoic acid

Mes : mesityl (trimethylphenyl)

min. : minute

mL : milliliter

mmol : millimolar

MS : mass spectrometry

Ms : mesyl (methanesulfonyl)

MTBE : methyl *tert*-butylether

MW : microwave

NHC : N-heterocyclic carbene

-OAc : acetate

-OTf : trifluoromethanesulfonate

PCC : pyridinium chlorochromate

ppm : part per million

p-TsCl : *para*-toluenesulfonylchloride

q : quartet

quint. : quintet

ref. : reference

Rf : retention factor

RT : room temperature

s : singlet

TASF : tris(dimethylamino)sulfonium difluorotrimethylsilicate

TBDMS : tertbutyldimethylsilyl

Temp. : temperature

TEP : Tolman electronic parameters

TFA : trifluoroacetic acide

THF : tetrahydrofurane

THP : tetrahydropyrane

TMS : trimethylsilyl

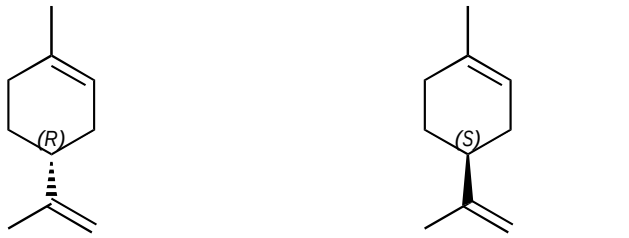
TM : transition metal

Yld : isolated yield

1. Introduction

1.1 Asymmetric catalysis

Early in the history of organic chemistry, scientists had observed that molecules containing a chiral position could exist in different configurations, called enantiomers. These enantiomers of an identical molecule possess the same chemical and physical properties except light polarization. However, they could be felt differently by the human body depending on the *R*- or *S*- configuration. It is the case for limonene, for instance, where the *R*-enantiomer has an orange smell whereas the *S*-enantiomer has a piney turpentine smell (Scheme 1).[1]



(*R*)-Limonen
citrus smell

(*S*)-Limonen
piney turpentine smell

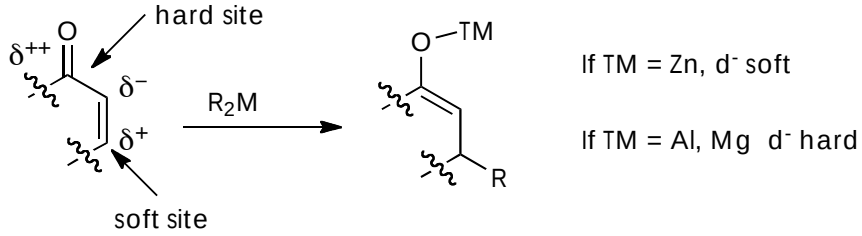
Scheme 1

Since this discovery, all the modern pharmaceutical chemistry had to deal with a new issue: the enantioselectivity of a given reaction. This was the beginning of the asymmetric catalyzed reactions. In the following thesis, there is one specific reaction we were interested in: the asymmetric conjugate addition.

1.2 Asymmetric conjugate addition (A.C.A.)

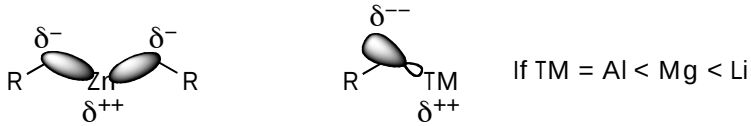
1.2.1 The conjugate addition

One of the most efficient reactions to create a C-C bond in a stereoselective way is the asymmetric conjugate addition.[2-5] It allows to easily functionalize the β-position of an α,β-unsaturated ketone, by adding a soft nucleophile to the soft β position of the substrate (Scheme 2).



Scheme 2

By using a soft organozinc reagents, the reaction rate is slow, but the nucleophile enters almost only in a 1,4 way. But by going to organoaluminum, organomagnesium or organolithium reagents, the hardness of the nucleophile is strongly increased and the 1,2-addition product is favored. In fact, the metal becomes less and less electronegative, and the partial charge is therefore more and more centered on the nucleophilic carbon (Scheme 3).



Pauling electronegativity scale
Zn = 1.65 > Al = 1.61 > Mg = 1.31 > Li = 0.98

Scheme 3

To circumvent that problem, Kharasch showed in 1941[6] that copper was the transition metal (TM) of choice for this reaction. Indeed, hard nucleophiles were easily transmetallated to the more electronegative copper, turning the hard nucleophile to a soft one. By doing so, Kharasch observed that by adding a catalytic amount of copper salt in the addition of MeMgBr onto isophorone, only the 1,4-addition product was obtained. That result led the way to the copper chemistry.

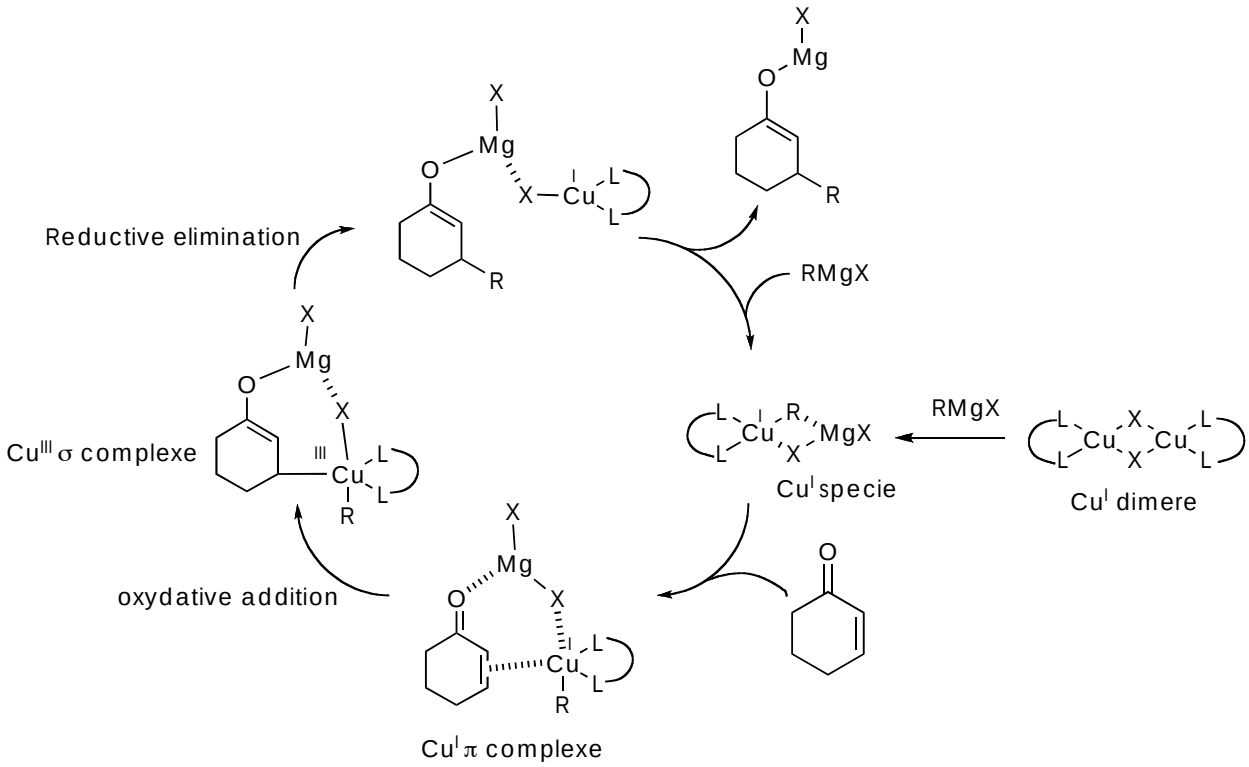
1.2.2 Copper-complexes chemistry

The copper chemistry possesses its own nomenclature, depending on the number and the variety of substituents surrounding the copper (Table 1).

Copper complex	Name	Example	Reactivity
RCu	organocopper	MeCu	Poorly soluble, poorly reactive, not basic
R_2CuLi	Homocuprate, Gilman's cuprate	Me_2CuLi	Soluble, reactive, basic
RCuR'Li	Mixed homocuprate	MeCuBuLi	
RCuZR'	Heterocuprate, Posner's cuprate	RCuSPhLi	
R_3CuLi_2	Higher order cuprate	Bu_3CuLi_2	
$R_2CuCNLi_2$	Cyanocuprate, Lipshutz cuprates	$Bu_2CuCNLi_2$	

Table 1

A lot of work was done to understand the mechanism of the copper-catalyzed conjugate addition, but it has still not been totally proven. The most accepted mechanistic pathway started with a dimeric Cu^{I} source. Cu^{II} species are often preferred in catalytic reactions because they are less hygroscopic, more stable and are simply reduced *in-situ* to Cu^{I} by the organometallic nucleophile. The mechanism described by Alexakis, Krause, Feringa and others[7-10] is based on a Cu^{I} salt and a Grignard reagent as nucleophile, but other classes of nucleophiles would give the same outcome. The Cu^{I} dimmer is first broken to a Cu^{I} monomer with transmetallation of the Grignard reagent substituent to form the active specie (Scheme 4). This forms a π-complex with the enone insaturation, while the magnesium coordinates the oxygen. An oxidative addition brings the Cu^{I} to a Cu^{III} complex. The following reductive elimination reduces the copper back to a Cu^{I} specie with liberation of the magnesium enolate. This was shown by Schrader[11] to be the rate-determining step of the reaction.



Scheme 4

1.2.3 Dialkylzinc nucleophile in Cu-catalyzed A.C.A.

Grignard reagents were historically the first to be used in copper-catalyzed conjugate additions. But organozinc nucleophiles became strongly preferred, after the pioneering work of Alexakis.[12] In 1993, he proposed the first Cu-catalyzed A.C.A. with a dialkyl zinc nucleophile. A large majority of the studies published since then, deals with organozinc species. The advantage of that family of nucleophiles is their poor reactivity, which permit to often obtain excellent enantioselectivities by moving slowly through the catalytic cycle. Furthermore, they are more tolerant than Grignard reagents on different sensitive functionalities.[13] But these nucleophiles have also strong drawbacks. Due to their poor reactivity, the reaction times are often long (around 24 hours), they required frequently a large excess of reagent to bring the reaction to completion, and finally, they are hard to synthesized and only few of them are commercially available. This explains why Et_2Zn is most often used.

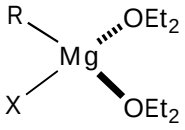
The most employed solvent with dialkylzinc reagents is toluene, but diethyl ether give often better enantioselectivities.[7] Dichloromethane can be used, but not tetrahydrofurane (THF), in which the organozinc species are too strongly coordinated and the reactions become really slow.

1.2.4 Trialkylaluminum nucleophile in Cu-catalyzed A.C.A.

To avoid the long reaction times and excess of nucleophile, trialkylaluminum species were then used. As they are more reactive than dialkyl zinc reagents, it is often sufficient to add only one equivalent of nucleophile to obtain a total conversion in less than twelve hours.[14,15] As they coordinate very efficiently to oxygen, they are widely used on problematic substrates like trisubstituted enones, to form quaternary chiral centers.[16] The main drawback of this family of nucleophile is the short panel of commercially available compounds. Indeed, only *n*-butyl, *i*-butyl, ethyl, methyl and propyl aluminum reagents are commonly used in diethyl ether. In this solvent, the monomeric complex is strongly favored compared to the dimeric one. Thus, the reactivity of the nucleophile is highly enhanced. In toluene, the opposite is observed, with an equilibrium in favor of the non reactive dimeric compound.[16,17]

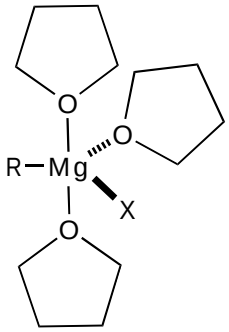
1.2.5 Organomagnesium nucleophile in Cu-catalyzed A.C.A.

Since 2004, Grignard reagents regain their popularity.[4] Those reagents counteract the deficiency of the two precedent nucleophiles, by being easily obtainable in a large variety of choice, and being strongly reactive, which increase drastically the reaction rate. This point is the main drawback of this family of nucleophiles. Indeed, it is not really compatible with sensitive functionalities and reacts easily in a 1,2-addition way. Grignard reagents are always prepared in ethereal solvents. These solvents allow to stabilize the complex by chelating the magnesium (Scheme 5).[18-20]



Distorted tetrahedrical complex in Et_2O.

Ehlers, A. W. *et al.* *J. Mol. Model.* 2000, *6*, 186-194.

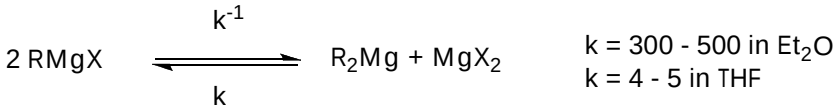


Bipyramidal trigonal complex in THF.

Yamaguchi, K. *et al. Org. Lett.* 2001, *3*, 1793-1795.

Scheme 5

In solution, Grignard reagents are in the so-called Schlenk equilibrium between the mono- and the bis-alkylated form (Scheme 6).[21] This equilibrium is largely controllable by changing the solvent of the reaction. Indeed, the use of diethylether (Et_2O) gives almost only RMgX as reagent and the dimeric complex is favored. In contrast, THF gives a mixture between RMgX and R_2Mg with a monomeric complex stabilization.[22] To push the equilibrium completely to the bis-alkylated magnesium form, one can use dioxane. Due to the insolubility of MgX_2 salts in that solvent, the equilibrium is therefore balanced on the R_2Mg side.



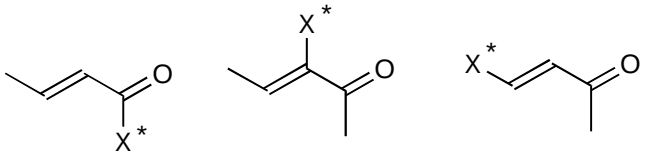
Scheme 6

When looking at the advantages of this type of nucleophiles (tunability, easy synthesizability and high reactivity), it is surprising that only few papers deal about copper-catalyzed A.C.A. with Grignard reagents.

1.3 Stereo-induction in copper-catalyzed A.C.A.

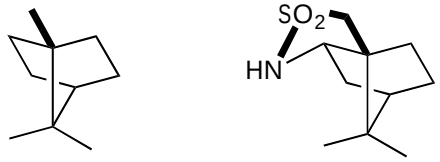
1.3.1 Stoichiometric chiral auxiliaries

There are different ways to induce a stereoselectivity in copper-catalyzed A.C.A. reactions. Chronologically, the first to be successfully tested was the use of a stoichiometric amount of a chiral auxiliary binded to the substrate (Scheme 7).



Scheme 7

Among the large number of different chiral auxiliaries reported between 1970 and 1980, one family stand out: camphor-based ligands[23] and particularly Oppolzer's sultams (Scheme 8).[24,25] Indeed, pure diastereoisomers of this sulfone-based chiral auxiliary are easily obtained by simple crystallization.



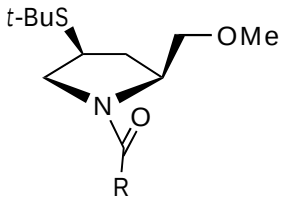
Scheme 8

This method is particularly interesting in some cases, when the chiral auxiliary is also used as a protecting group. In those cases, the chiral auxiliary acts both as a protecting and a chiral inducing group. Another point in favor of the diastereoisomeric pathways is the generally easy separation by chromatography or crystallization, which is not possible with enantiomers.[26] But the use of a stoichiometric amount of reagent and the difficulties encountered to remove the chiral auxiliary after the reaction render that approach too inconvenient. Although this type of A.C.A. reactions proved to be efficient, a catalytic version was preferred after the 1980's.[23]

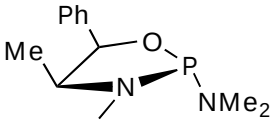
1.3.2 Enantioselective reactions catalyzed by chiral complexes

The use of chiral auxiliaries may decrease the reaction rate of a given reaction, by changing the functionality on the substrate. For instance, an acyl chloride treated with a chiral amine becomes an amide, which is less reactive than the starting carbonyl. That is why reactions in asymmetric catalysis have not only to be enantioselective but also accelerated to increase the rate of the product formation. A catalyst is an entity, often a TM complex, which has the ability to lower the energy of the transition state of a given reaction. By putting the two concepts together, the chemists proposed different chiral complexes bearing chiral ligands to induce a stereoselectivity and the TM core for accelerating the reaction.

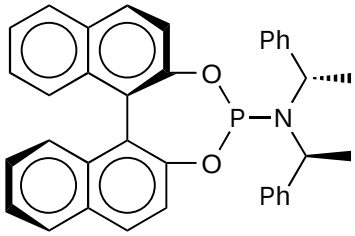
First examples using a stoichiometric amount of chiral ligand, reported by Leyendecker[27] with a proline derived ligand and Alexakis[28] with the first phosphorous-based ligand in copper-catalyzed A.C.A. (Scheme 9), opened the door to the synthesis of hundreds of chiral phosphorus ligands.[29] A general trend for these first generations of ligands is their strong reaction rate acceleration, by increasing the electronic density on the TM.[11,30] Moreover, all are monodentate with the phosphorous coordinating to the copper.



Proline derived ligand
Leyendecker 1985



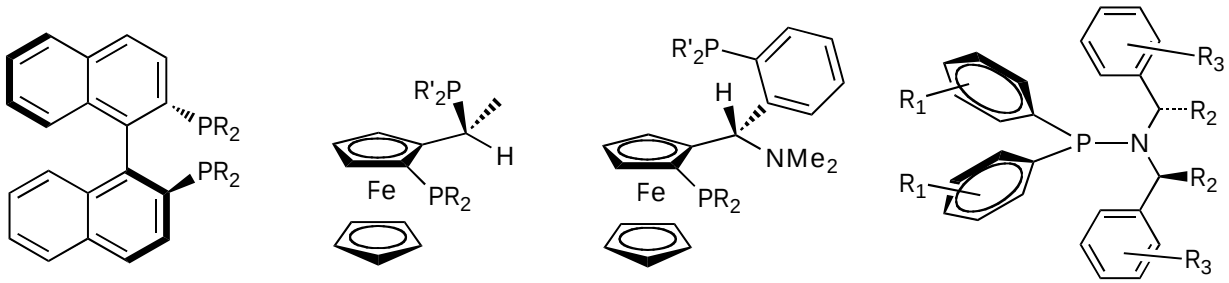
First phosphorus based ligand in Cu-catalyzed ACA
Alexakis 1991



Phosphoramidite ligand
Feringa 1997

Scheme 9

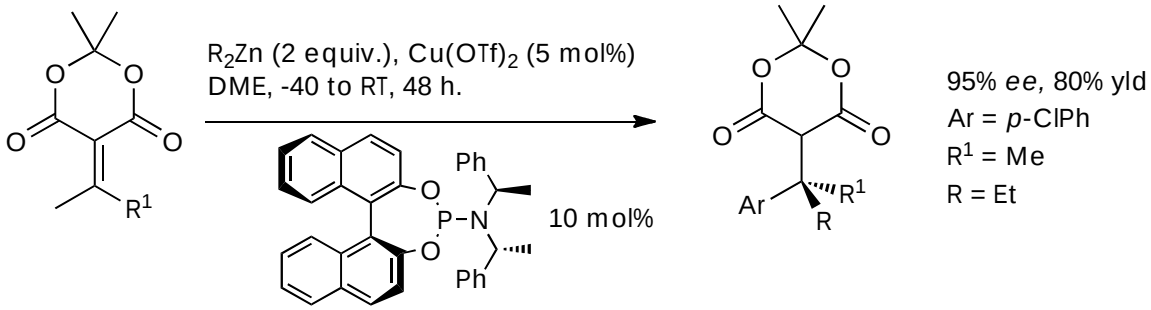
The stoichiometric procedure was then gradually abandoned in favor of a catalytic process, since the pioneering work of Alexakis[12] in 1993, followed by the efficient phosphoramidite ligand proposed by Feringa in 1997 (Scheme 9).[31] Other highly efficient families of ligands appeared, like BINAP,[32] Josiphos,[10] Taniaphos[33] and recently Simplephos (Scheme 10).[34]



BINAP family | Josiphos family | Taniaphos family | Simplephos family

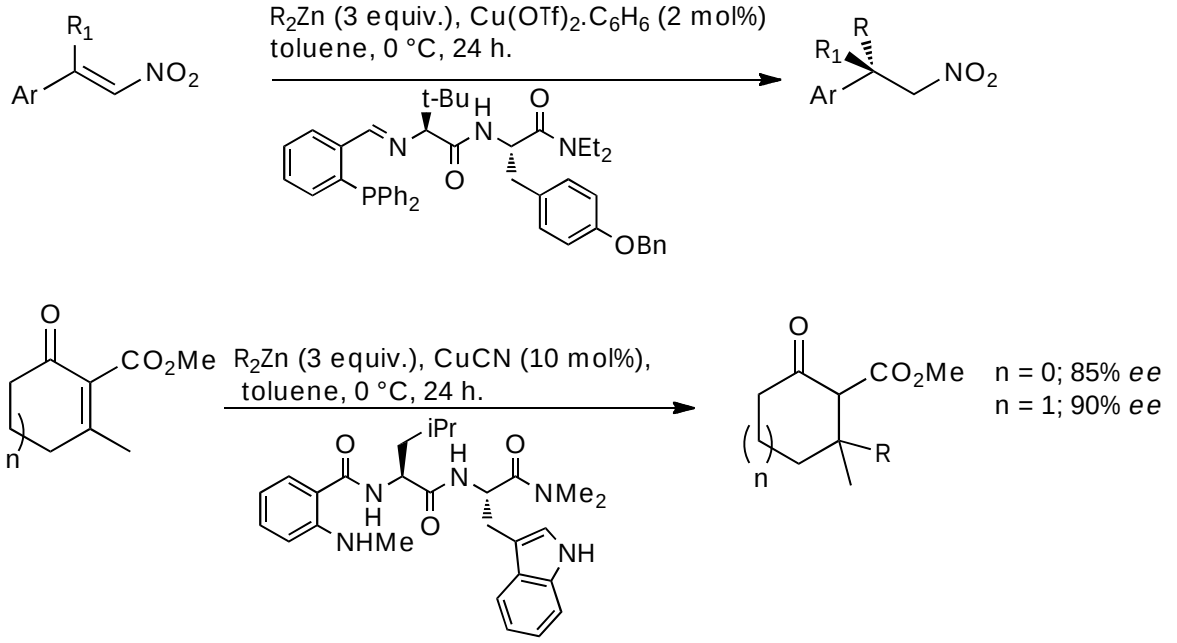
Scheme 10

The large majority of the previously mentioned ligands are mostly used for the A.C.A. on disubstituted enones. However, only few examples using trisubstituted analogs are reported.[3-5,35] The construction of quaternary chiral centers are tricky reactions, and most of the time, the employed substrates have to be activated.[36] For example, Fillion proposed an association between organozinc nucleophiles and phosphoramidite ligands with excellent enantioselectivities on doubly activated meldrum's acid derivative (Scheme 11).[37-39]



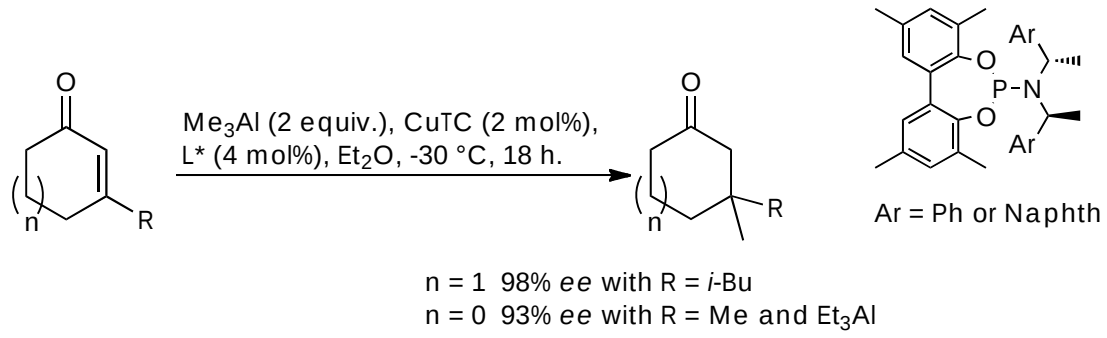
Scheme 11

The organozinc species were also associated with peptidic ligands either on nitroolefines[40] or doubly activated cyclic enones by Hoveyda in good yields and *ee*'s (Scheme 12).[41] In those cases, activated Michael acceptors were almost always needed to obtain good conversions. The low reactivity of the organozinc nucleophiles renders the reactions sluggish.



Scheme 12

To circumvent the poor reactivity of the nucleophile, Alexakis proposed an alternative by using organoaluminum reagents with phosphorus-based ligands. He was able to create quaternary chiral centers starting with non-activated cyclic enones (Scheme 13).[16,34,42-44]



Scheme 13

As told above, the main drawback of those approaches is the poor availability of the nucleophiles and the long reaction time. Furthermore, only few non phosphorous-based ligands were successfully used in copper-catalyzed A.C.A.. The goal of this work is to find a new way to build quaternary chiral centers through faster reactions with keeping a high enantiomeric excess (*ee*).

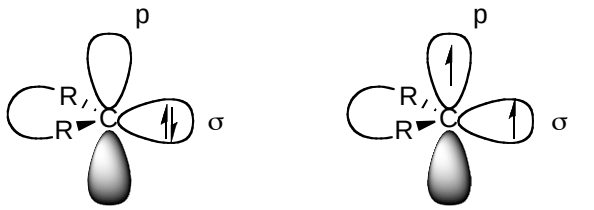
A promising new family of ligands emerged in early 2000, called N-heterocyclic carbene (NHC),[45-51] is the perfect challenger we have chosen to reach our goal.

They are believed to possess better electron-donor properties[52-54] and steric factors[53,55,56] than their phosphine counterparts.

2. *N-Heterocyclic carbenes (NHC)*

2.1 NHC's history

Since the beginning of the 20th century, carbene species were considered as transient very reactive entities, often present in transition states, but impossible to isolate.[57] Indeed, a carbene is a neutral carbon possessing only six electrons in his valence shell, and is therefore highly reactive. The electrons can be paired in the same orbital, which gives singlet state carbenes, or dispatched in two different orbitals to give triplet state carbenes. Those are considered as di-radical species and have there own chemistry that will not be detailed in this thesis (Scheme 14).[45]



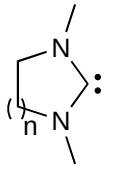
singlet state carbene
2S+1 = 1
empty p orbital

triplet state carbene
2S+1 = 3
"di-radical"

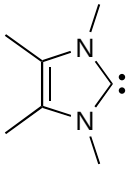
Scheme 14

Nowadays, a lot of different more or less stable carbenes were described in the literature. [45,58] These carbenes can be cyclic or acyclic but have always at least one heteroatom next to the carbenic carbon (Scheme 15).

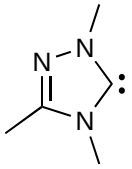
Examples of cyclic carbenes:



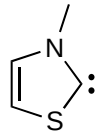
cyclic diaminocarbenes



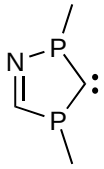
imidazol-2-ylidenes



1,2,4-triazol-3-ylidenes

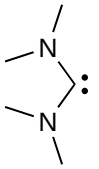


1,3-thiazol-2-ylidenes

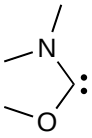


cyclic diphosphino-carbenes

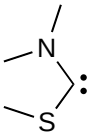
Examples of acyclic carbenes:



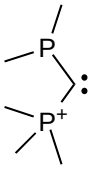
acyclic diamino-carbenes



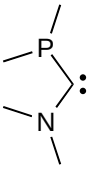
acyclic aminooxy-carbenes



acyclic aminothio-carbenes



phosphino-phosphonio-carbenes



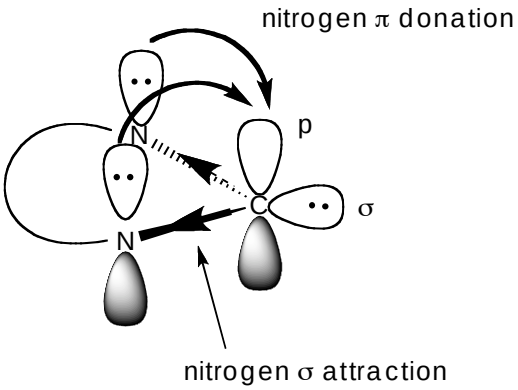
aminophosphino-carbenes

Scheme 15

Since a singlet carbene is a dual specie being electrophile (empty p orbital) and nucleophile (full σ orbital), the stabilization of such a compound is possible by surrounding it with opposite dual heteroatoms. Many different heteroatoms were used such as nitrogen, phosphorus, silicon, boron and others, but nitrogen seems to be the best choice. Its σ-attracting ability lowers the electronic density on the carbene filled orbital, and his π-donating property brings some electronic density in the empty carbene p orbital (Scheme 16).

The cyclic carbene ligands are more used in organic chemistry than their acyclic counterparts, due to their ability to form a stable complex with TM.

In the 60's, Wanzlick[59] and Öfele[60] studied the imidazolines chemistry and observed independently the formation of a dimeric compound when heating a chloroform C_2-substituted imidazoline. They concluded that the loss of chloroform allowed to obtain a free carbene specie, which undergo dimerization in the experimental conditions.

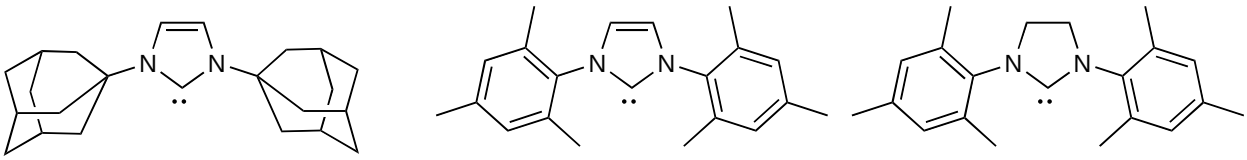


Scheme 16

In the 70's, the group of Lappert worked extensively on the stabilization of NHC-TM complexes. After his first publication in 1971[61] describing the formation of a stable Pt-NHC complex starting from a dimeric diphenylimidazolium treated with $(PtCl_2(PEt_3))_2$, he increased his library by using a wide range of TM like Cr, Mo, W, Mn, Fe, Ru, Co and others.[62] With these complexes in hand, he investigated the role of carbenes as reaction intermediates[63] but he never tried to obtain free stable carbenes.[64]

It was only in 1988 that Bertrand and coworkers obtained the first isolable and stable free phosphinosilylcarbene.[65] They continued to work on acyclic and cyclic phosphinocarbenes,[66] but these kinds of phosphorus-based ligands were not really used in the catalysis field (Scheme 15).

The carbene chemistry had to wait until 1991 to breakthrough when Arduengo synthesized the first stable NHC (Scheme 17).[67] To prevent dimerization by steric hindrance, he added two adamantyl groups on the nitrogens. Moreover, this NHC was unsaturated, which brings a supplementary aromatic stabilizing character to the heterocycle. Few years later, he proposed a stable NHC with two mesityl[68] groups instead of adamantyl, in a saturated and unsaturated heterocycle.



First stable NHC
Arduengo 1991

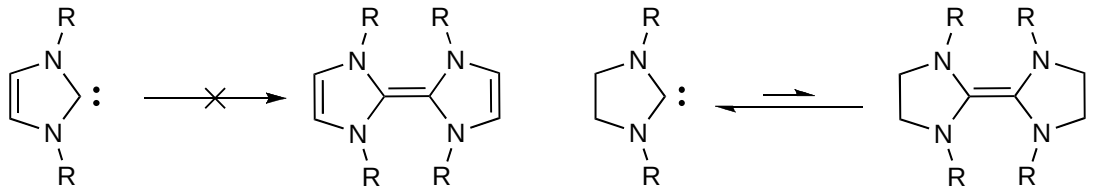
Arduengo 1995

Scheme 17

A lot of theories followed these researches, trying to explain the stabilization of the carbenes. Frenking (1996)[69] showed by computational studies, that the nitrogen π-donation in the carbene LUMO seemed to be the main stabilizing factor. Schwarz(1996),[70] followed by Denk (1999)[71] and Herrmann (2000),[72] suggested that the aromaticity helps to stabilize the NHC's. If there was not enough steric bulk on the nitrogen substituents of the saturated NHC's, they will dimerize. Recent works published by Nolan and Denk now reversed those theories. Indeed, Nolan[73] showed that the bonding dissociation energy (bde) difference between a saturated and an unsaturated NHC-Ru complex was around 4 KJ/mol. He concluded that nitrogens σ-attraction and π-donation were the key factors for stabilization. Steric bulk and aromaticity were only complementary factors but they were not necessary to obtain a stable NHC.[74]

Denk[75] combined DFT calculations and NMR studies and concluded that an unsaturated NHC could not dimerize. The saturated NHC counterpart is in the Wanzlick equilibrium but the dimerization is thermodynamically disadvantaged. In fact, it is not really the stability of the monomer, but the strong instability of the dimer, which favors the formation of the monomeric specie. If there is more than one carbon on the alkyl chain on the nitrogen, the dimerization will not be observed at RT (Scheme 18).

Wanzlick equilibrium, R = phenyl, anisyl



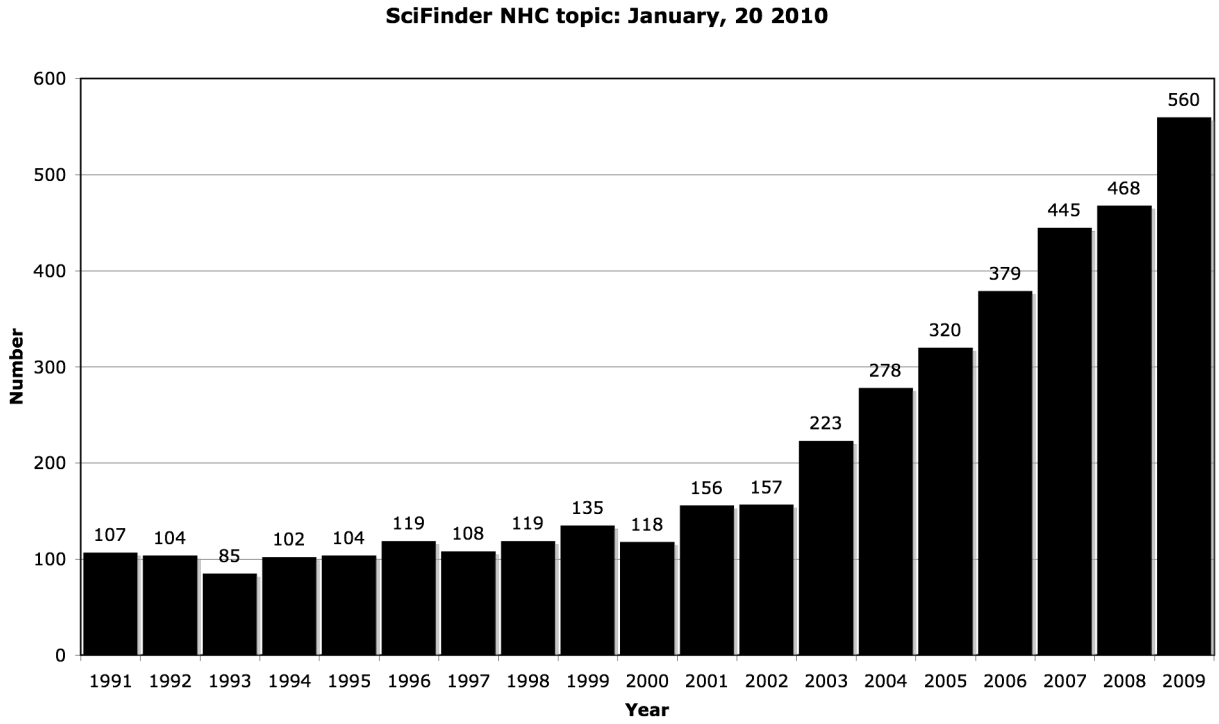
unsaturated NHC cannot dimerize

saturated NHC can dimerize, but with R = Me, Et. Dimeric form is thermodynamically disfavored.

Scheme 18

2.2 NHC structure and chirality

The interest in NHC's is growing more and more since the beginning of the 21th century (Graphic 1). The reason comes from the properties of NHC's. They are often very robust ligands with poor sensitivity to air and high temperatures (more than 200 °C).[45]



Graphic 1

Moreover, they form almost covalent bonds with TM, and become therefore very good chiral anchors. Contrary to phosphorous-based ligands with which often extra-ligand has to be added to favor the TM–ligand bonding, it is not necessary to add an excess of NHC. A lot of work was therefore done to design NHC's with the best chiral inducing properties.

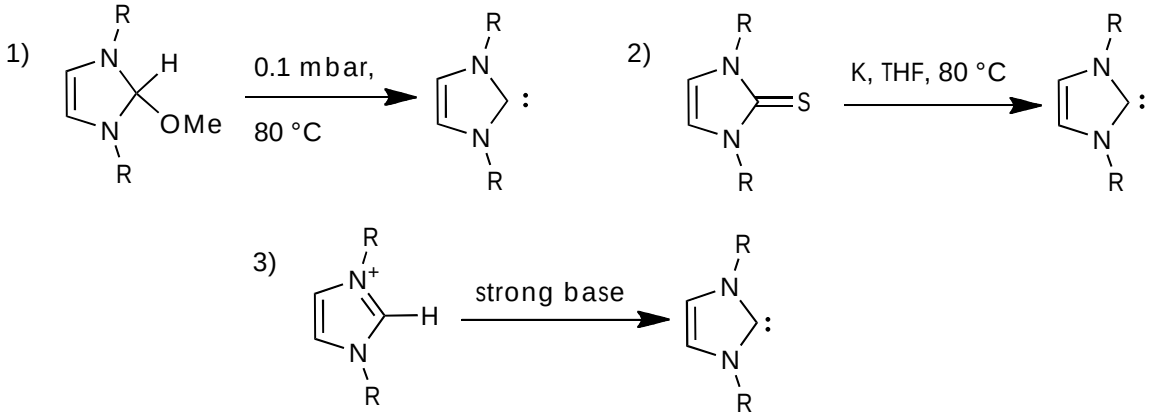
2.2.1 NHC structures

To simplify, the NHC family may be separated in four major classes, depending on their structure (Scheme 19).

imidazolinylidene or SIm (for saturated imidazolinylidene) | imidazolylidene Im | triazolylidene | pyrimidylidene

Scheme 19

These ligands are activated by three main ways (Scheme 20). The first way go through a thermal elimination of methanol or ethanol under low pressure. The second is the dethionylation with metallic potassium and warming. And the last, by far the most used one, is the deprotonation of the corresponding imidazolium salt (ImH^+) with a strong base (*n*-BuLi, KO*t*Bu).[45]

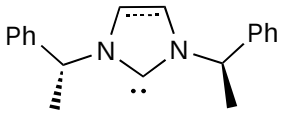


Scheme 20

2.2.2 Structural NHC chirality

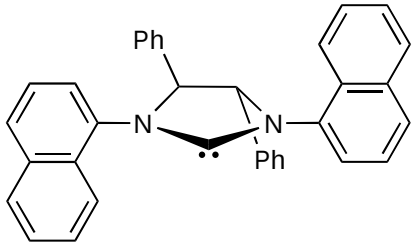
To induce chirality to the target molecule, a large variety of structures appeared since the first review of Burgess[76] on NHC in asymmetric catalysis. But all these structures may be resumed in five big subgroups (Scheme 21):

- NHC bearing a central chirality on the nitrogen atoms
- NHC bearing fixed chiral substituents on the heterocycle
- NHC showing an axial chirality
- NHC showing a planar chirality
- NHC bearing a chiral substituent with a chelating group on the nitrogen.



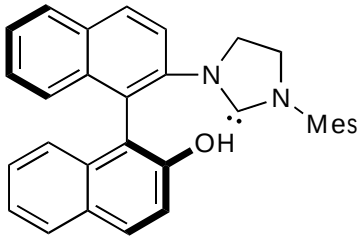
Herrmann's type NHC

Herrmann, W. A. *et al. Angew. Chem. Int. Ed.*1996, *35*, 2805.



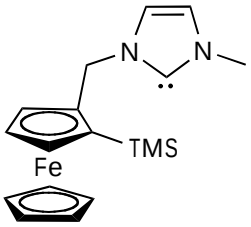
Chirality fixed in the back

Grubbs, R. *et al. Org. Lett.* 2001, 20, 3225.



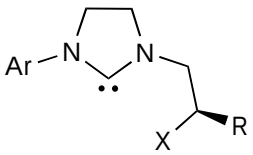
Axial chirality

Hoveyda, A. H. *et al. J. Am. Chem. Soc.* 2005,*127*, 6877.



Planar chirality

Bolm, C. *et al. Organometallics* 2002, *21*, 707.



Chiral substituent with a chelating heteroatom

Arnold, P. *et al. Chem. Commun.* 2001, 2340.

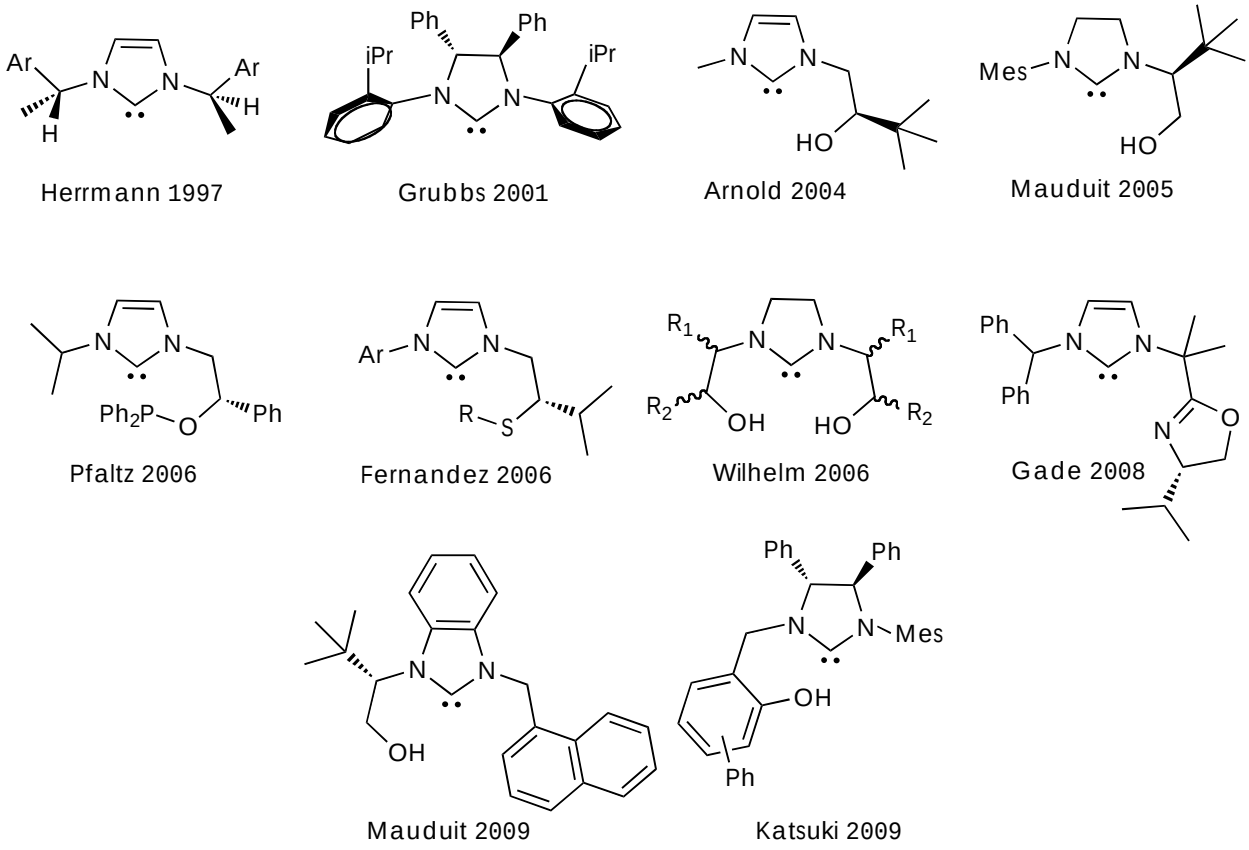
Scheme 21

The first family to be synthesized was the one bearing a central chirality on the nitrogen atoms.[77] They are C_2-symmetric, with the chiral inducing-substituent near the reacting center. These ligands induce often poor enantioselectivities on asymmetric reactions. Indeed, the rotation around the N-R* bond is not completely constrained; the chiral information is therefore less fixed.

The second family of NHC's possesses chiral bulky substituents on the back of the heterocycle. Those bulky groups induce chirality to the nitrogen achiral substituents, by pushing them opposite to the steric bulk. The chiral induction on the reacting center is improved because the movements of the substituents are prevented by the back bulkiness.[46]

The third and fourth families are based on axial and planar geometry of the nitrogen substituents. Those substituents have already proved their worth on phosphorous-based ligands, by Togni[78] and his Josiphos[79] or by Noyori and his BINAP.[80] That last one was used in the NHC-Cu chemistry with success by Hoveyda.[81]

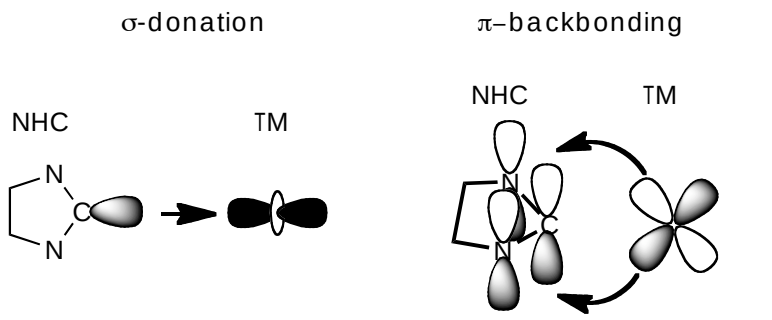
The last subgroup of NHC is now the most prolific one in asymmetric reactions. The chiral induction is optimized by the coordination of the chiral chain onto the TM. The steric bulk is frozen in the space, and there are therefore no possible movements from the chiral part, which could lower the enantioselectivity of a given reaction. In fact, by looking to the actual tendency in NHC design, there is no doubt that the bidentate non-symmetrical NHC's are now the most synthesized one in asymmetric catalysis (Scheme 22).[82-93]



Scheme 22

2.2.3 NHC electronic properties

Another point of debate, along with the NHC intrinsic stability, is the electronic propertie of an NHC toward a TM. At the beginning, NHC's were considered as tri-alkyls phosphine mimics. But rapidly, it became clear that this new family of non phosphorous-based ligands was better electron-donor than the phosphine ligands. From the first studies, Herrmann,[94,95] Frenking[96] and others believed that the NHC's were pure σ-donors, with negligible π-backbonding from the TM to the empty p orbital of the NHC. However, Frenking[97] had to reconsider his results in 2004 when he built models with the Group 11 atoms (Cu, Ag, Au). Indeed, he observed that the π-backbonding from the TM to the NHC lays around 10-15% of the total bonding energy. The same year, Meyer showed by X-ray structures and DFT calculations that the π-backbonding can reach 30% of the total bonding energy for copper (Scheme 23).

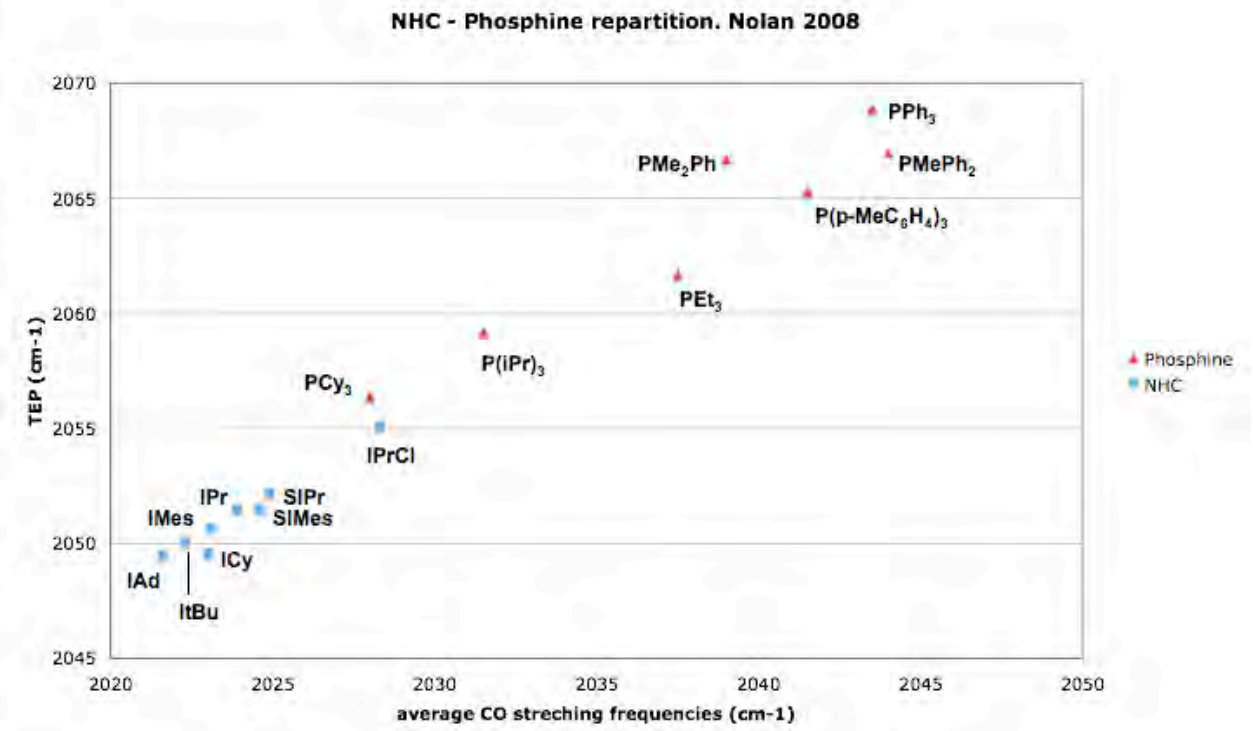


NHC are strong σ-donors

up to 30% of total bonding energy with TM = Cu

Scheme 23

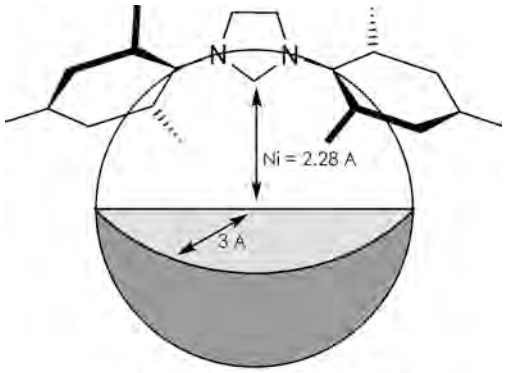
Jacobsen[98] confirmed by computational calculations that π-backbonding energies lay between 10% to 30%, depending on the TM electron-richness. This percentage is, of course, not negligible anymore but it seems that NHC's stay better electron-donor ligands than the phosphine family.[99] In fact, they are among the strongest neutral bases known (pKa's around 22-24).[100] To prove this theory, Nolan[101] measured the bond dissociation energy (bde) for different (NHC)Ni(CO)$_2$ complexes. He showed that the most electron-donor phosphine (PCy_3) is less donor than the less electron-donor NHC (IMes) tested. This was also shown by Canac,[102] who coordinated different bidentate phosphines, NHC's and mixed species on Rh(CO)$_2$ complexes. He concluded that di-NHC's are better electron-donors than di-phosphine ligands, but less than phosphorus ylides. Gusev[103] confirmed the results by comparing the infrared (IR) stretching frequencies of LNi(CO)$_2$ complexes. In conclusion, it seems without a doubt that NHC's are better σ-donor ligands than phosphines (Graphic 2).



Graphic 2

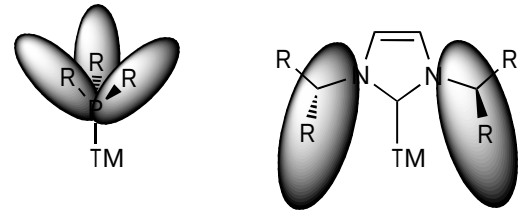
But what about the electron-donor variations? On Graphic 2, one can observe that for phosphorous ligands, the variability of the electron-donation between the weakest and the strongest donor, known as ΔTEP (for Tolman Electronic Parameter), is about 12 cm^{-1}. Sigman[53] showed in 2006 that the ΔTEP for different NHC's is about 3 cm^{-1}. This result is far away from the phosphine's one. It means that whatever the substituents are on the NHC, the electron-donor ability stays almost unchanged. But one year later, Plenio[104] showed by cyclic voltammetry that the ΔTEP of his panel of NHC's is about 7 cm^{-1}. He showed also that the value for a saturated NHC is higher than for its unsaturated counterpart (10-60 mV). This means that a saturated NHC is better electron-donor than an unsaturated one.

In 2008, Nolan[52] went one step further, with a ΔTEP of 8 cm^{-1}. In his studies, he also compared the buried volume of his NHC's on a sphere centered on a TM. He observed that the saturated NHC's are 1-3% more covering than their unsaturated equivalent (Scheme 24). He concluded that in organic reactions, the difference of reactivity between both NHC's groups have certainly more to do with steric hindrance than electronic differences.



Scheme 24

For now, it seems that the electron-donor ability of the NHC's family have a less extended panel than the one of the phosphine family, but the ΔTEP of 8 cm^{-1} is not a bad result. It shows that this new family of ligands can be somewhat tuned in terms of electronic properties. In any case, the recent development of NHC's family is of great interest for organic and organometallic chemists, due to their ability to catalyze symmetric and asymmetric reactions. Furthermore, the NHC's are expected to be better chiral inducing ligands than phosphines, because their substituents surround the reacting center, contrary to phosphines, were the bulky substituents are opposite to the TM (Scheme 25).



Scheme 25

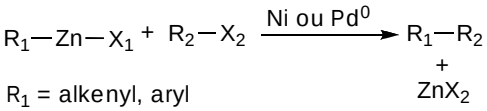
NHC's are not always bonded to TM by the C2 carbon, but some examples showed the formation of C5 bonded NHC-TM complexes (Scheme 26).[105-107] These ligands are called abnormql NHC's and are qualified as better electron-donor than their normal NHC's counterparts. However, the asymmetric induction is more difficult to control with that kind of ligands, as the C4 or the C5 can bind to the TM. That is why these abnormal NHC's are not used in asymmetric catalysis for now.

Scheme 26

2.3 NHC in copper-chemistry

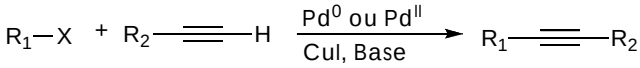
2.3.1 NHC-Cu complexes catalyzing racemic reactions

Nowadays, NHC's are combined with a lot of different standard TM, as Pd, Pt, Ru, Rh, Ni, Co, Os. Most often, the obtained complexes catalyze coupling reactions, like metathesis,[108-110] Negishi,[49,111,112] Sonogashira,[113] Suzuki-Miyaura,[49,112,114,115] Kumada-Tamao,[49,112] Heck-Mizoroki,[116-118] Stille[119,120] etc (Scheme 27). The NHC's are also described with more exotic metals like Ce, W, Yb, Re, Tc, Be, Hg. For the majority of the unusual cases, NHC's are used as ligands to stabilize complexes, but these exotic complexes are seldom used as catalysts.



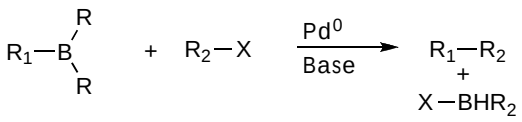
R_1 = alkenyl, aryl
R_2 = alkenyl, aryl
X_1 = Cl, Br, I, OTf
X_2 = Cl, Br, I

Negishi coupling



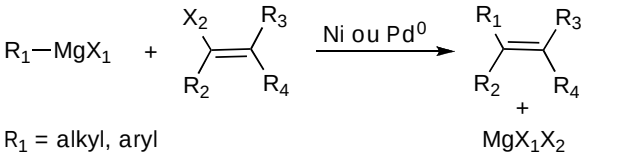
R_1 = alkenyl, aryl
R_2 = H, alkyl, aryl
X_1 = Cl, Br, I, OTf

Sonogashira coupling



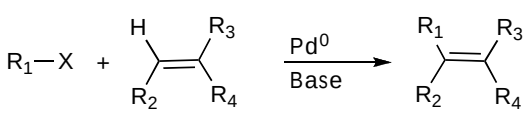
R_1 = alkyl, aryl
R_2 = alkyl, aryl
X = Cl, Br, I, OTf

Suzuki-Miyaura coupling



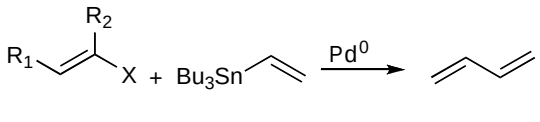
R_1 = alkyl, aryl
R_2, R_3, R_4 = H, alkyl, aryl
X_1 = Br, I
X_2 = F, Cl, Br, I, OTf

Kumada-Tamao coupling



R_1 = alkyl without β H, aryl
R_2, R_3, R_4 = alkyl, aryl
X = Cl, Br, I, OTf

Heck-Mizoroki coupling



R_1 = alkyl, aryl
R_2 = alkyl
X = Cl, Br, I, OTf

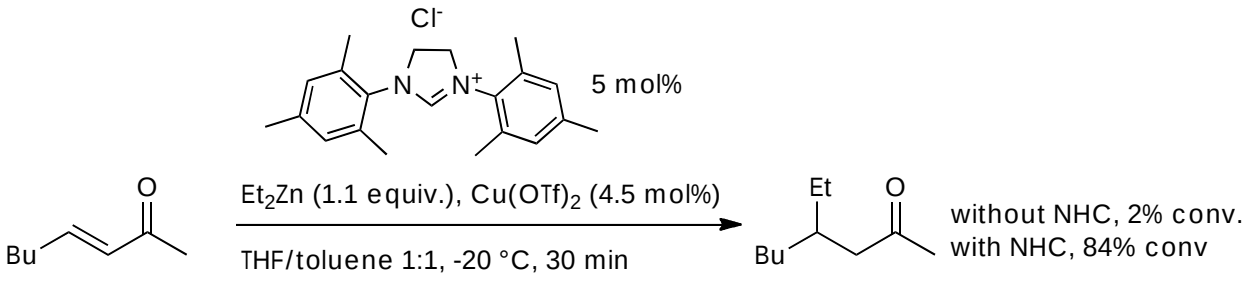
Stille coupling

Scheme 27

Copper is also used as TM in association with NHC's. In the symmetric reactions field, some reports about coupling-reactions are known. They are mostly Ullman-type reactions involving the coupling of a nitrogen and an aromatic ring.[121,122] The Sharpless-developped Click-chemistry[123,124] is also a remarkable Cu-catalyzed reaction, but Cu-NHC complexes are more often used in asymmetric catalytic reactions such as the asymmetric conjugate addition (A.C.A).

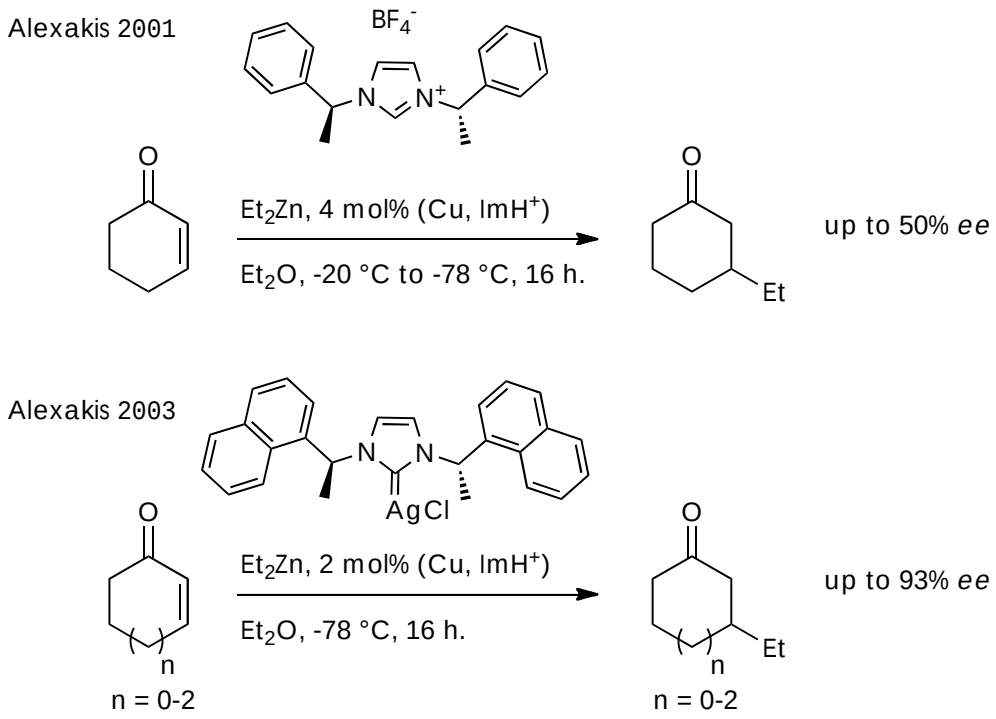
2.3.2 A.C.A. on disubstituted enones catalyzed by NHC-Cu complexes.

In 2001, Woodward[125] showed that the addition of an achiral NHC on copper accelerated drastically the conjugate addition of Et_2Zn to cyclohexenone (Scheme 28).



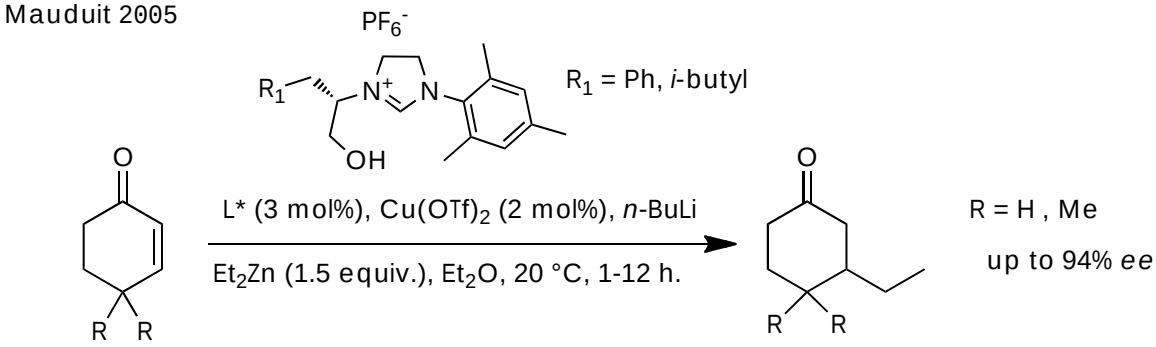
Scheme 28

That study was immediately followed by the first asymmetric version of the reaction by Alexakis in 2001.[126] He obtained up to 50% *ee* by adding Et_2Zn on the cyclohexenone catalyzed by a copper - diphenyl Herrmann-type NHC complex. That result was increased to 93% *ee* in 2003[127] by changing the biphenyl with a binaphthyl substituent.



Scheme 29

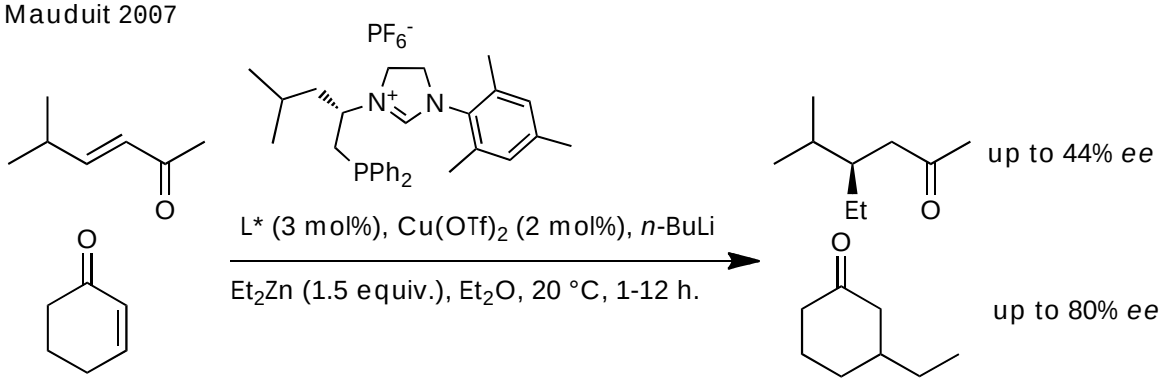
In 2005, Mauduit[128] proposed a new type of NHC, bearing a chiral substituent with a chelating group on the nitrogen. He tested his NHC in an A.C.A. of Et_2Zn on cyclohexenone at 20 °C with an NHC : Cu ratio of 1:1.3 to obtain up to 94% *ee* (Scheme 30).



Scheme 30

He then modified the chelating heteroatom, going from oxygen to phosphorous, and applied his new ligand on linear and cyclic substrates. In this case, a decrease of the *ee* was observed for the cyclohexenone.[129] These results were explained by a too hindering PPh_2 group near to the reacting center (Scheme 31).

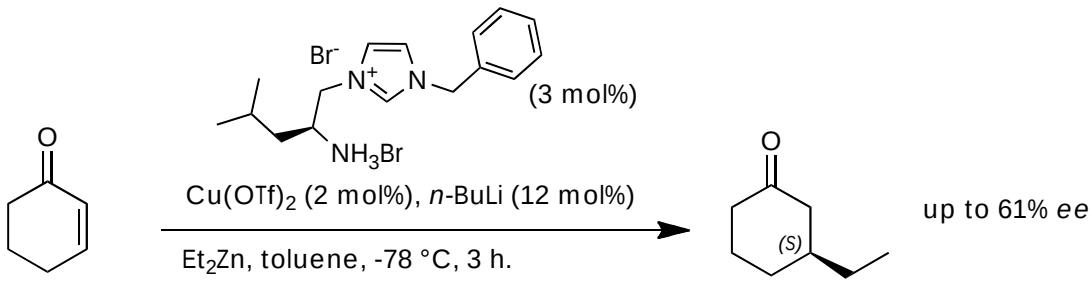
Mauduit 2007



Scheme 31

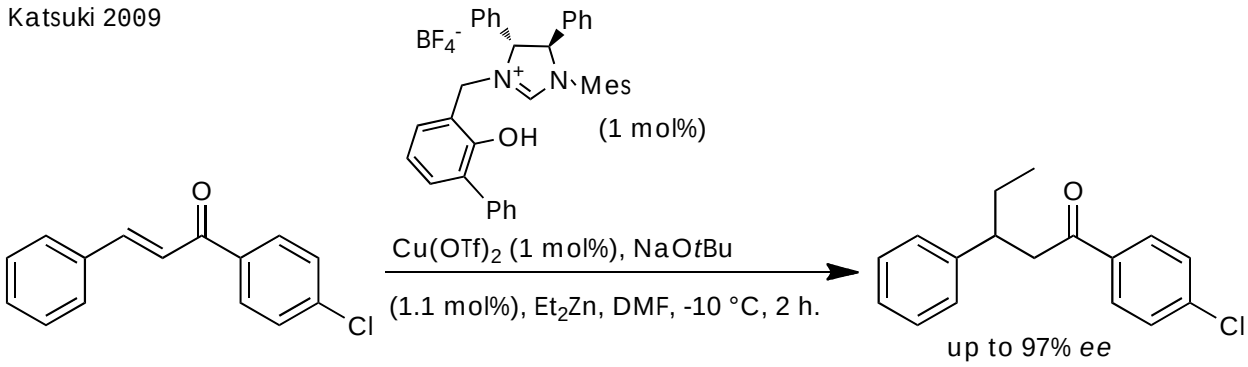
In 2008, Williams[130] proposed another Mauduit-like NHC, with a nitrogen as chelating atom. The steric bulk was displaced from the α to the β position of the alkyl substituent. He obtained up to 61% *ee* for the addition of Et_2Zn to the cyclohexenone at -78 °C in toluene. The reaction rate was faster than that obtained by Mauduit Mauduit, since it was done in 3 hours at -78 °C, but the steric bulkiness on the β-position, as shown by Mauduit, decreased the enantio-control of the complex (Scheme 32).

Williams 2008



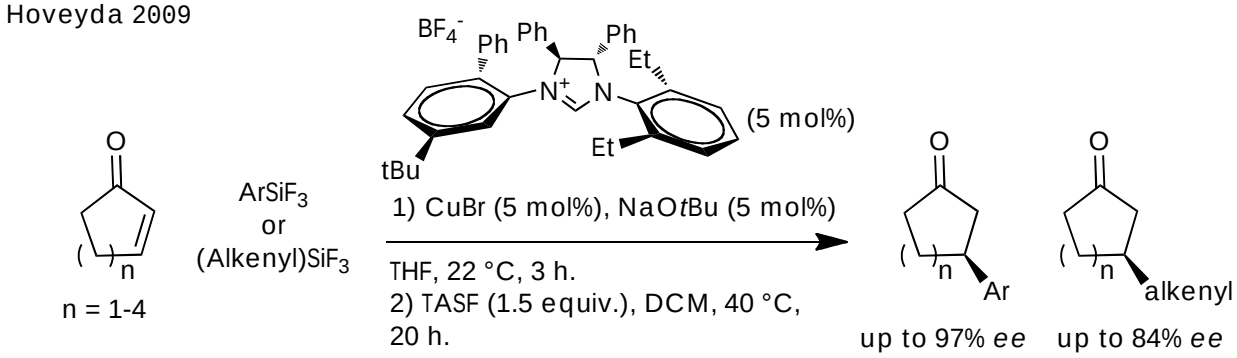
Scheme 32

In 2009, Katsuki[93] proposed a mixed NHC containing fixed chiral bulky groups in the back of the ring and a chelating group on one of the nitrogen substituents. He could obtain up to 97% *ee* for the addition of 1.5 equivalent of Et_2Zn to a *para*-activated chalcone.



Scheme 33

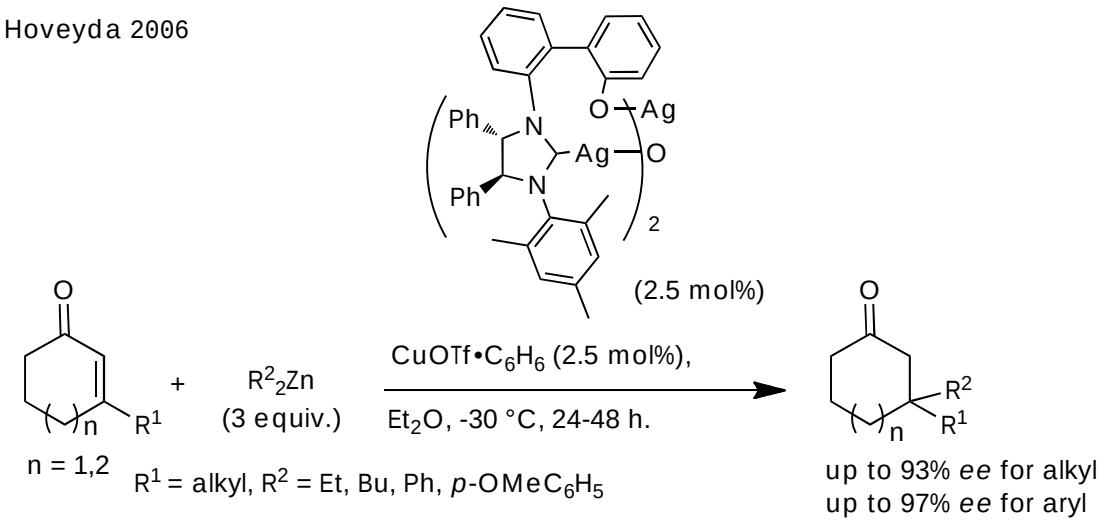
Finally, Hoveyda[131] proposed to use silicon-based reagents, which after treatment by tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF), were desyllilated and ready to coordinate on a Cu-NHC complex. His methodology allowed the addition of aryl and alkenyl substituents on cyclic enones, which resulted in high yield and *ee*'s between 70 and 97% (Scheme 34).



Scheme 34

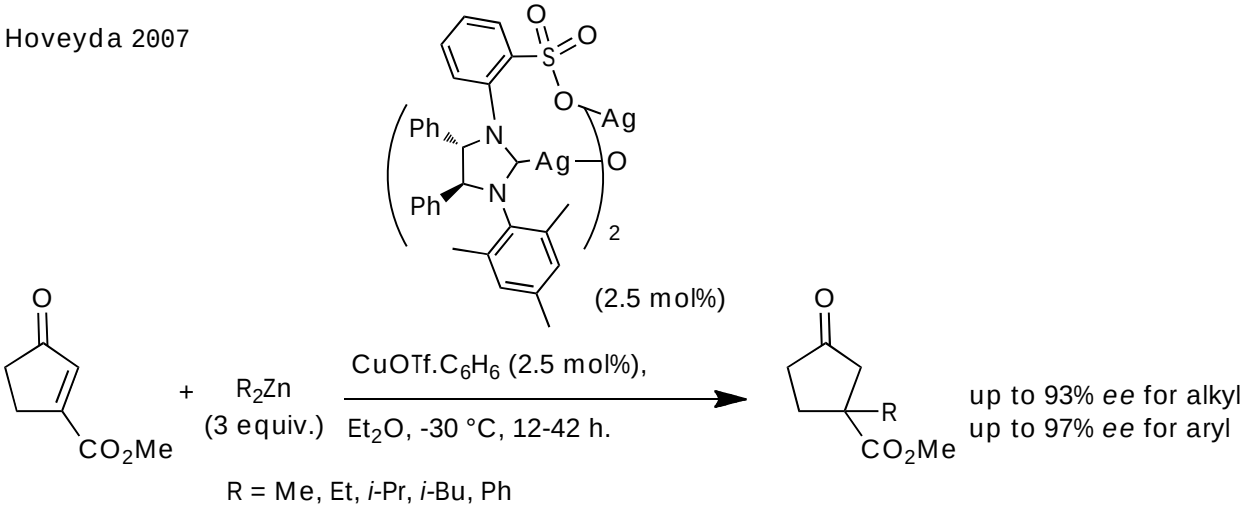
2.3.3 NHC-Cu's A.C.A. on trisubstituted enones, quaternary chiral centers.

All the pre-cited researches are based on disubstituted Michael acceptors. The use of trisubstituted enones to create quaternary chiral centers is more difficult due the steric hindrance of the β position. As a result, few documents report on the subject. In 2006, Alexakis[132] and Hoveyda[133] published separately the first papers about formation of quaternary chiral centers catalyzed by Cu-NHC complexes. Hoveyda used a large excess of organozinc nucleophiles with a Ag-NHC pre-catalyst (Scheme 35). The use of a 1:1 mixture of Cu(OTf)•C_6H_6 and NHC allowed to obtain *ee*'s up to 93% for the addition of Et_2Zn on 3-methylcyclohex-2-enone and up to 97% for the addition of Ph_2Zn on the same substrate.



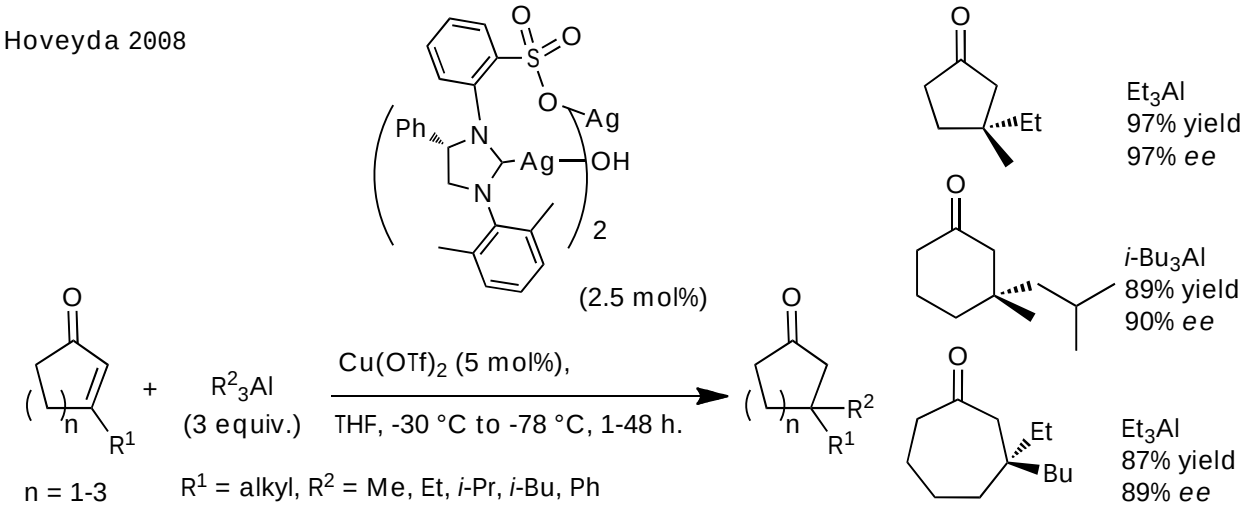
Scheme 35

The variation of the chelating group, from the phenol to sulfonyl, allowed Hoveyda[134] to add zinc nucleophiles to activated five-membered trisubstituted cyclic enones (Scheme 36). The difference of reactivity seem to come from the more strained metallacycle (seven-membered ring) and the lower basicity of the sulfonyl group compared to the phenol.



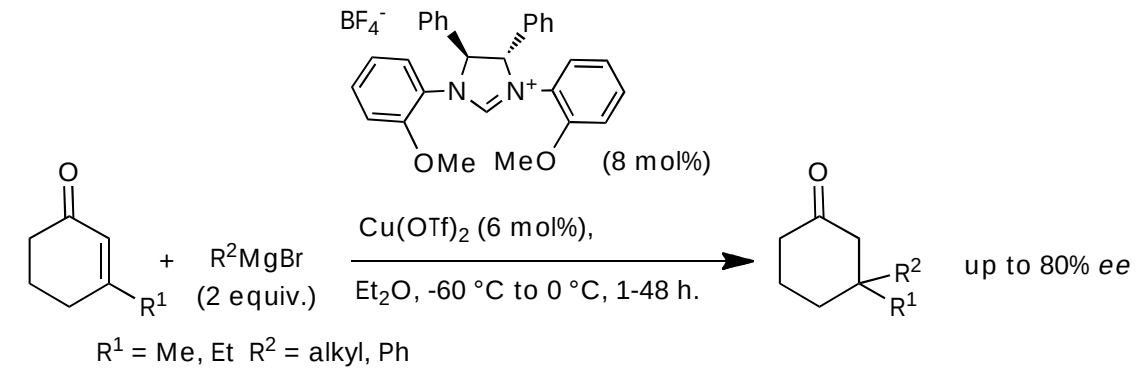
Scheme 36

To accelerate the reaction rate, Hoveyda also applied his methodology to the nucleophilic addition of organoaluminum reagents to five, six and seven membered cyclic enones (Scheme 37).[135,136] The alkyl nucleophiles, namely methyl, ethyl and *iso*-butyl are commercially available. The aryl ones were synthesized by mixing the corresponding aryl lithium reagent with $AlEt_2Cl$. That methodology allowed to obtain *ee*'s up to 97% for the addition of Et_3Al on 3-methylcyclopent-2-enone.



Scheme 37

Finally, Tomioka[137] in 2008, proposed a Grubbs-like NHC, with the chiral back-induction of two phenyls on methoxyphenol nitrogen substituent. He used Grignard reagents and a 1:1.3 Cu:NHC ratio to obtain up to 80% *ee* for the addition of EtMgBr to the 3-methylcyclohex-2-enone (Scheme 38).



Scheme 38

Nowadays, only six papers reported the use of NHC-Cu catalyzed A.C.A. to form quaternary chiral centers. High *ee*'s were obtained with poorly reactive organozinc nucleophiles, but the reaction rates were still low. When going to stronger organoaluminum species, the *ee*'s remained very good but the reaction times were still long and three equivalent of nucleophile were necessary. Finally, the reactions proceeded faster with organomagnesium nucleophiles but the *ee*'s dropped down.

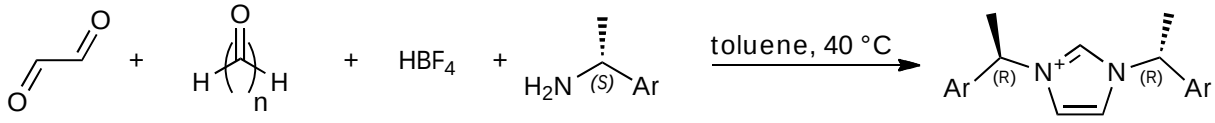
The purpose of the present thesis was to find an easy methodology to functionalize trisubstituted cyclic enones by combining high reaction rates and high *ee*'s, with a large scope of alkyl and aryl chains. The obtained results are detailed below.

3. *C_2-symmetric NHC's as chiral ligands for A.C.A.*

At the beginning of that PhD work, there was no example of NHC-Cu catalyzed A.C.A. on trisubstituted enones. We therefore applied our best conditions used for the A.C.A. on disubstituted substrates, namely a Herrmann-type ligand in presence of Et_2Zn, but we obtained no conversion after 16 hours. We therefore started to synthesize different Herrmann and Grubbs type ligands in order to reach our goal: the formation of quaternary chiral centers by the use of NHC-Cu complexes.

3.1 Synthesis of Herrmann's-like NHC

The first family, synthesized by Dr. David Martin, was obtained following Herrmann's procedure (Scheme 39).[138,139] A solution of glyoxal, tetrafluoroboric acid, paraformaldehyde and two equivalents of a chiral primary amine were heated at reflux. Multi gram scale of imidazolium salts were easy to obtain, to isolate and to purify by chromatography on silica gel.

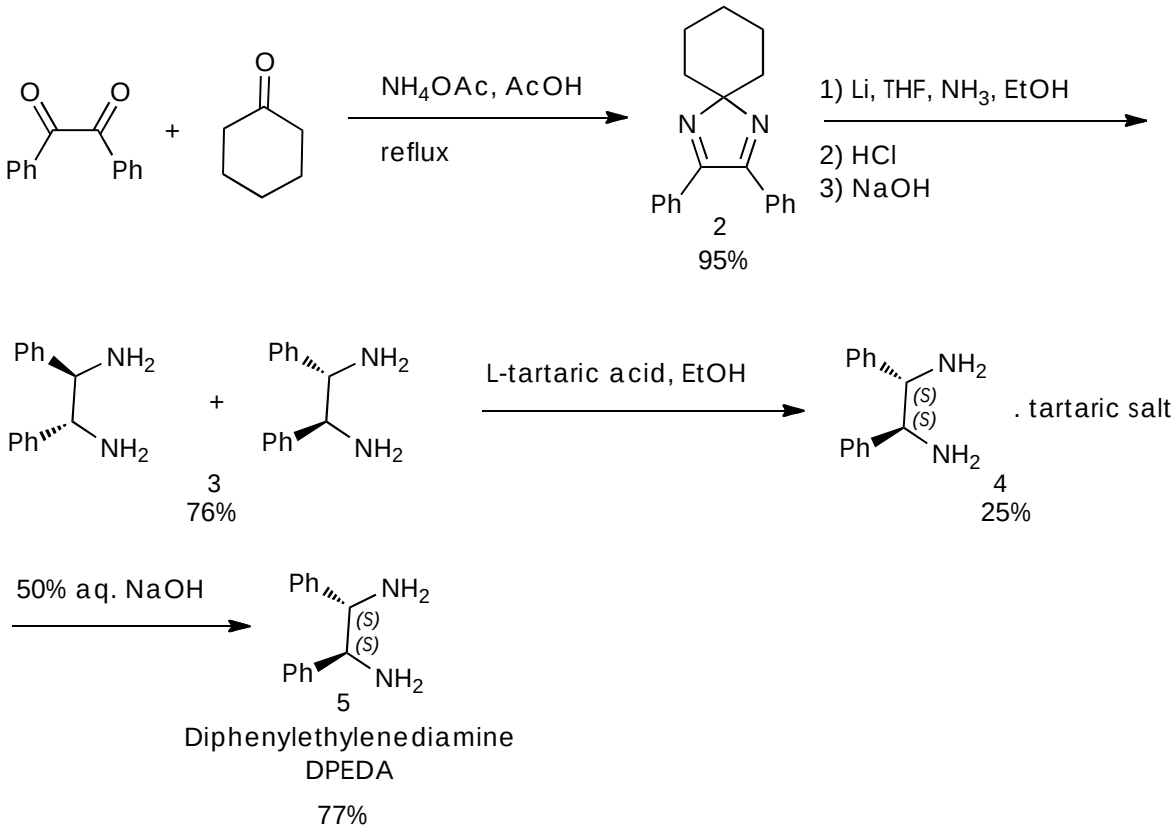


1a: Ar = Ph
1b: Ar = 1-Naphthyl
1c: Ar = 2-OMe-C_6H_4

Scheme 39

3.2 Synthesis of Grubbs'-like NHC

The Grubbs' like NHC ligands were more difficult to synthesize (Scheme 40). We first had to synthesize the diphenylethylenediamine (DPEDA) 5, following a procedure described by Corey,[140] starting from benzil. This was treated with cyclohexenone to form the aminal. A Birch reduction followed by an acidic hydrolysis cleaved the bicyclic compound. A final basic treatment led to a mixture of two enantiomers. The addition of an enantio-pure tartaric acid permited to crystallize the corresponding diastereoisomer. Finally, treatment with aqueous sodium hydroxide gave the pure enantiomer as white needles. The drawback of that reaction was the resolution step, where only 25% of the pure product was recovered. Indeed, four consecutive recrystallizations were needed to obtain the pure diastereoisomer on a 45 g scale.

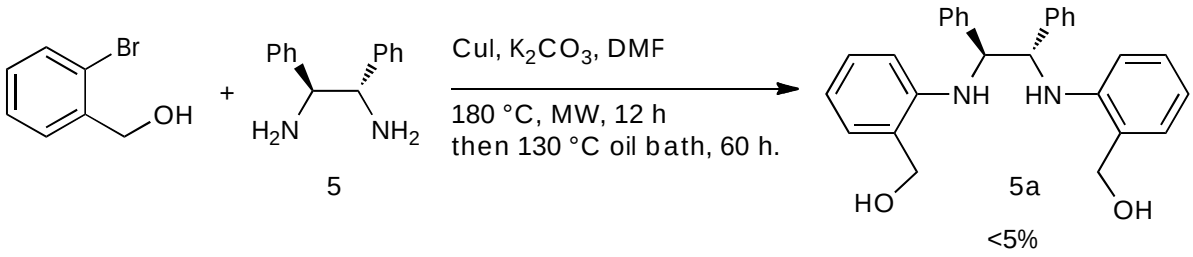


Scheme 40

Different techniques were then used to bis-arylate the DPEDA.

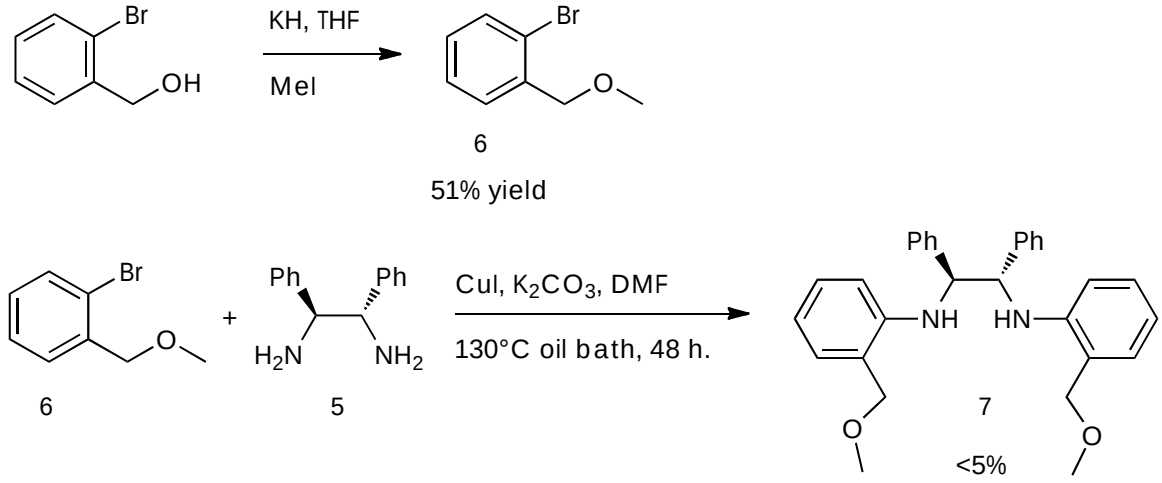
3.2.1 Ullmann's coupling

One of the oldest method to couple an aromatic halide with an aliphatic amine is a reaction promoted by copper, named Ullmann coupling.[141,142] A first trial was done by dissolving bromohydroxybenzyl, CuI, K_2CO_3 and the diamine in dimethylformamide (DMF) (Scheme 41). The reactor was heated to 180 °C for twelve hours under microwave irradiation. As there was no conversion, the reactor was warmed again to 130 °C for 60 hours in an oil bath with no effect. Only traces of the diamine 5a were observed.



Scheme 41

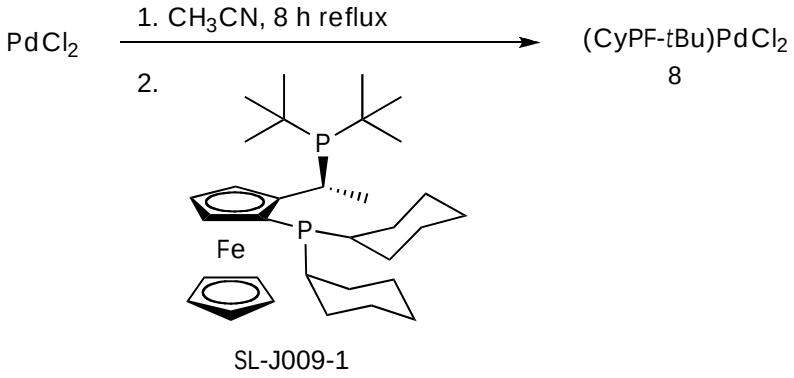
To ensure it was not the free hydroxy group that prevents the reaction, the bromohydroxybenzyl was first protected with a methoxy group (Scheme 42). The process was repeated in an oil bath at 130 °C for 48 hours. Once again, no conversion was observed. We therefore looked for another more efficient reaction.



Scheme 42

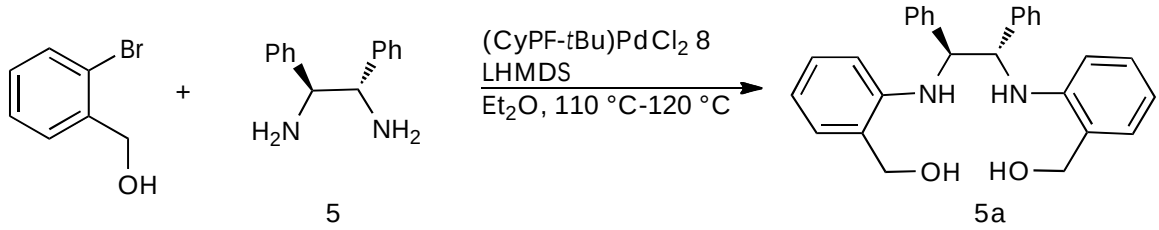
3.2.2 Hartwig's coupling

Hartwig[143] has recently published a method to couple primary or secondary amines with brominated aryl substituents using an air and moisture stable catalytic complex (CyPF-*t*Bu)$PdCl_2$. The methodology is easy to handle because it goes through a stock-solution of the catalyst in acetonitrile. We started with synthesizing the Josiphos-Pd complex by heating $PdCl_2$ to reflux in acetonitrile in order to solvate the palladium complex. Josiphos SL-J009-1 was then added and coordinated to the TM to form the catalyst 8 (Scheme 43).



Scheme 43

To observe the efficiency of that complex for our ligands synthesis, some coupling reactions between bromohydroxybenzyl and DPEDA 5 were attempted (Scheme 44).



Scheme 44

According to the work of Hartwig, the best conditions to perform his coupling reactions was to use the palladium complex 8 and NaO*t*Bu in Et_2O at 100 °C. But in presence of sensitive functionalities, as hydroxy-groups, the use of Lithium bis(trimethylsilyl)amide (LHMDS) was recommended. Moreover, polar solvents lower the reaction rate, but acetonitrile was needed to dissolve the palladium complex 8, because it was not soluble in Et_2O.

For our first attempt, a solution of LHMDS 1M in THF was added to a solution of diamine and bromoaryl in Et_2O. The reaction mixture was heated at 110 °C in a sealed Schlenk tube for 36 hours in an oil bath. Only traces of coupling product were observed (Table 2, Entry 1). To find out if microwave irradiations could help, a second attempt was done in a microwave reactor, and heated to 120 °C for 2.5 hours. The same outcome was observed (Table 2, Entry 2).

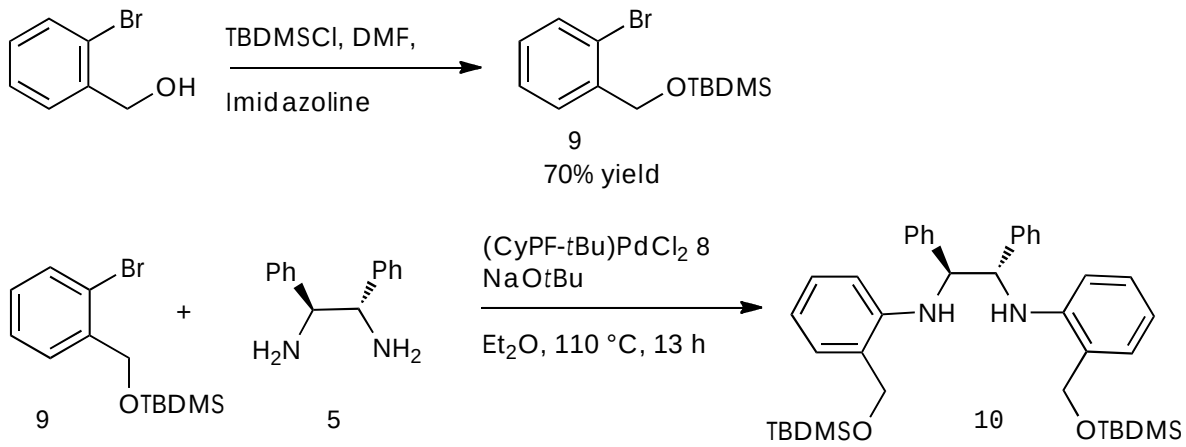
As reported by Hartwig , the reaction did not occur in polar solvents. That is why we dried the LHMDS solution at the high *vacuum* pump and tried the reaction again. Only 5% of coupling product were obtained (Table 2, Entry 3).

Entry	Base	Temperature	Time	Conv.
1	LHMDS in THF	110 °C oil bath	36 h	<5%
2	LHMDS in THF	120 °C MW	2.5 h	0%
3	LHMDS dry	110 °C oil bath	36 h	<5%
4[(a)]	NaO*t*Bu	110 °C	13 h	0%

a) reaction with TBDMS protected amine 9

Table 2

NaO*t*Bu was also tested in this reaction as LHMDS was thought to inhibit the reaction. This trial was done using the TBDMS protected compound 9 (Scheme 45). Once again, the conversion was below 5% (Table 2, Entry 4). It seemed therefore that it was not the solvent, but the steric hindrance of the catalyst relative to the diamine 5 that prevented the approach of the brominated aryl.

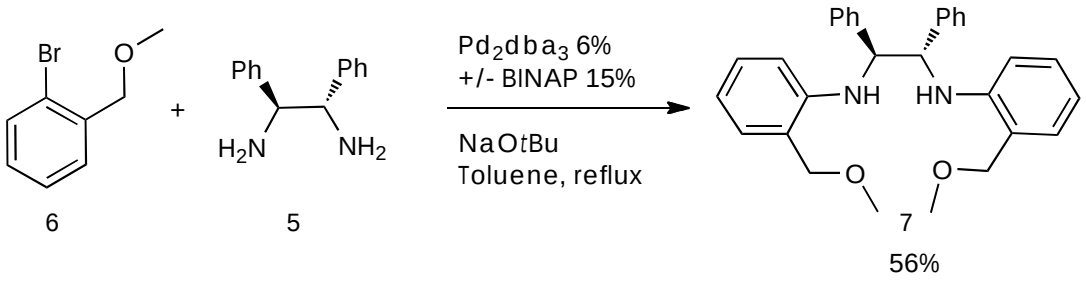


Scheme 45

3.2.3 Buchwald-Hartwig's coupling

The next reaction we tried was reported by Buchwald in 1998.[144] Mangeney[145] and Denmark[146] independently developed that reaction with a $Pd_2(dba)_3$ complex instead of $Pd(OAc)_2$. The differences lied in the procedure. Mangeney coupled aromatic brominated substituents on the DPEDA in toluene, while Denmark used iodo-naphthyls in dioxane.

We tried the Mangeney procedure by adding the methoxy-protected bromohydroxybenzyl 6 and the diamine 5 on the preformed catalyst BINAP-Pd catalyst. The mixture was heated to reflux for 12 hours in a sealed Schlenk-tube, to give the substituted diamine 5 with 56% yield (Scheme 46).



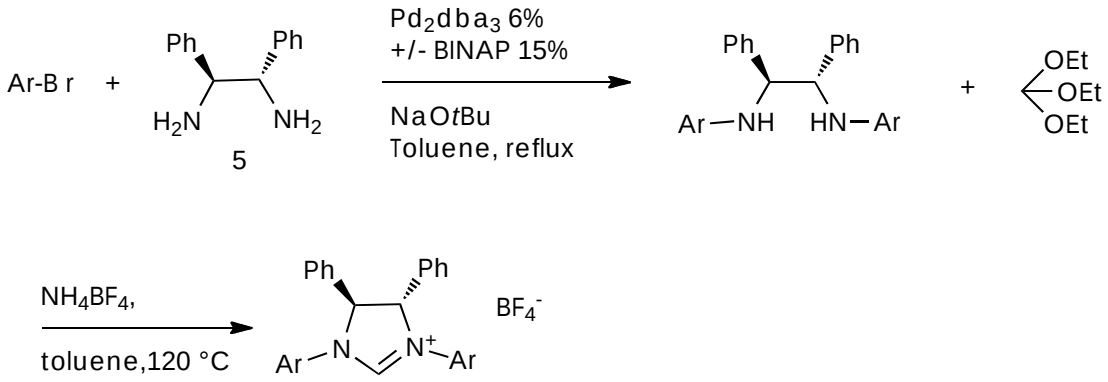
6 5 7

56%

Scheme 46

This reaction was very tricky and the first runs gave yields between 20-30%. We succeed to increase the yields by following highly important rules. Firstly, at least 30 minutes were needed to the palladium, BINAP and NaO*t*Bu mixture to form the active catalyst. Secondly, all the reagents had to be handled under a nitrogen atmosphere. Thirdly, the solvent has to be degassed by the freeze-vacuum technique, and not only with nitrogen bubbling in the aluminum oxide column. Finally, although NaO*t*Bu is much harder to sublimate than KO*t*Bu, it worked better for the reaction. Any steps missed during the reaction lowered the yield for about 10-20%.

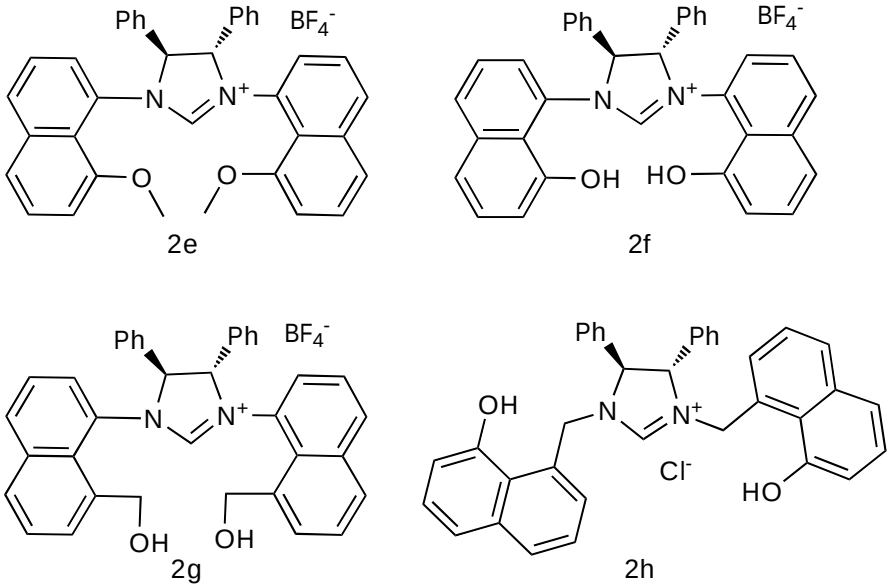
With those optimized conditions in hand, we synthesized different C_2-symmetric diamines, bearing aromatic rings on the nitrogen substituents. Those diamines were then cyclized by a Grubbs[83] described procedure, namely by adding triethylorthoformate in presence of NH_4BF_4 to give the corresponding NHC's (Scheme 47).



2a: Ar = 1-Naphthyl 81% yield
2b: Ar = 2-Naphthyl 76% yield
2c: Ar = 2-Me-C_6H_4 23% yield (done by Dr Martin)
2d: Ar = 2-*i*Pr-C_6H_4 31% yield (done by Dr Martin)

Scheme 47

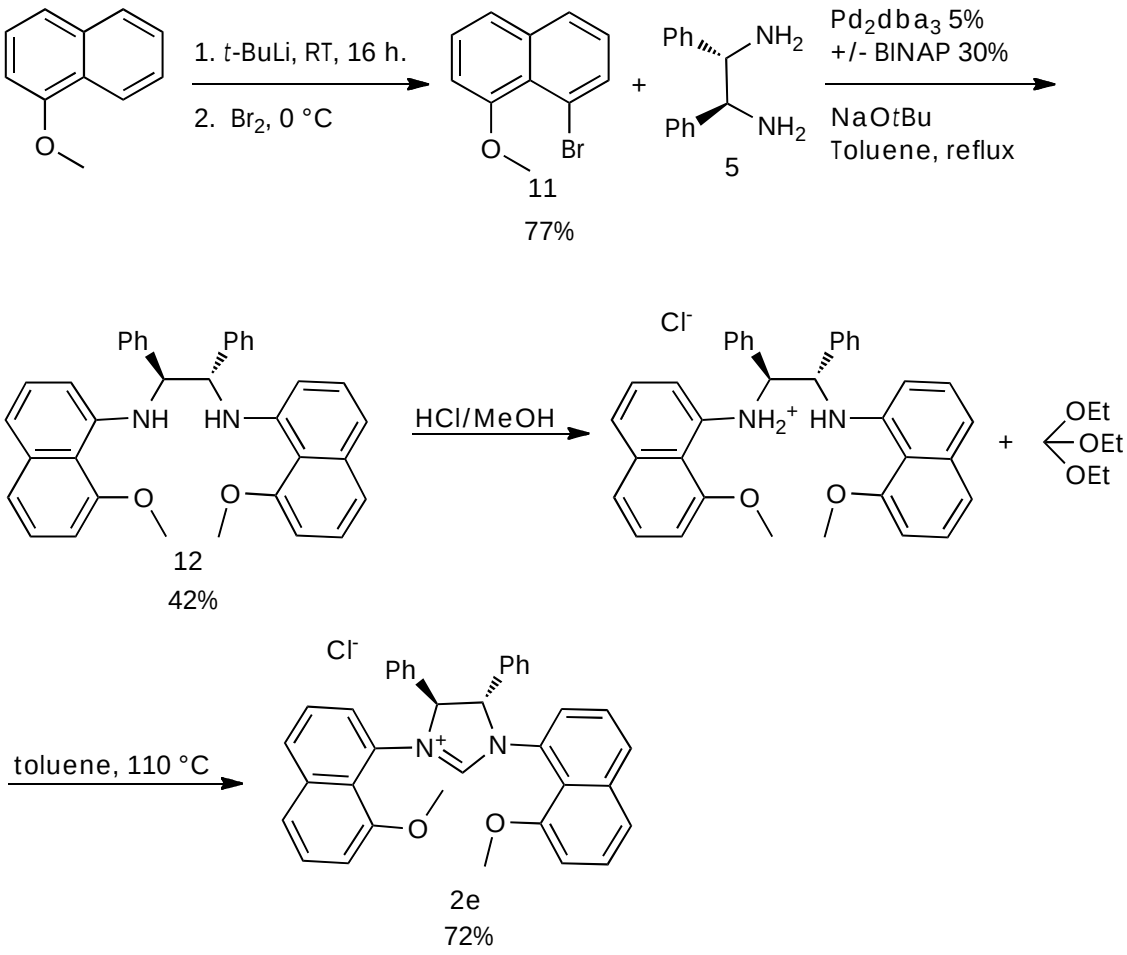
To observe the effect of chelating heteroatoms on the enantioselectivity of the A.C.A., we also decided to synthesize different C_2-symmetric NHC's bearing an atom of chelating oxygen on the nitrogen substituents (Scheme 48).



Scheme 48

The synthesis of the methoxy-NHC 2e based on the procedure described by Kirby,[147] started with the preparation of 1,8 bromomethoxy naphthalene (Scheme 49). The presence of the methoxy group coordinated the lithiated base and forced the deprotonation in the position 8. The obtained bromomethoxy naphthalene 11 was then coupled by Buchwald-Hartwig reaction to give the C_2-symmetric diamine.

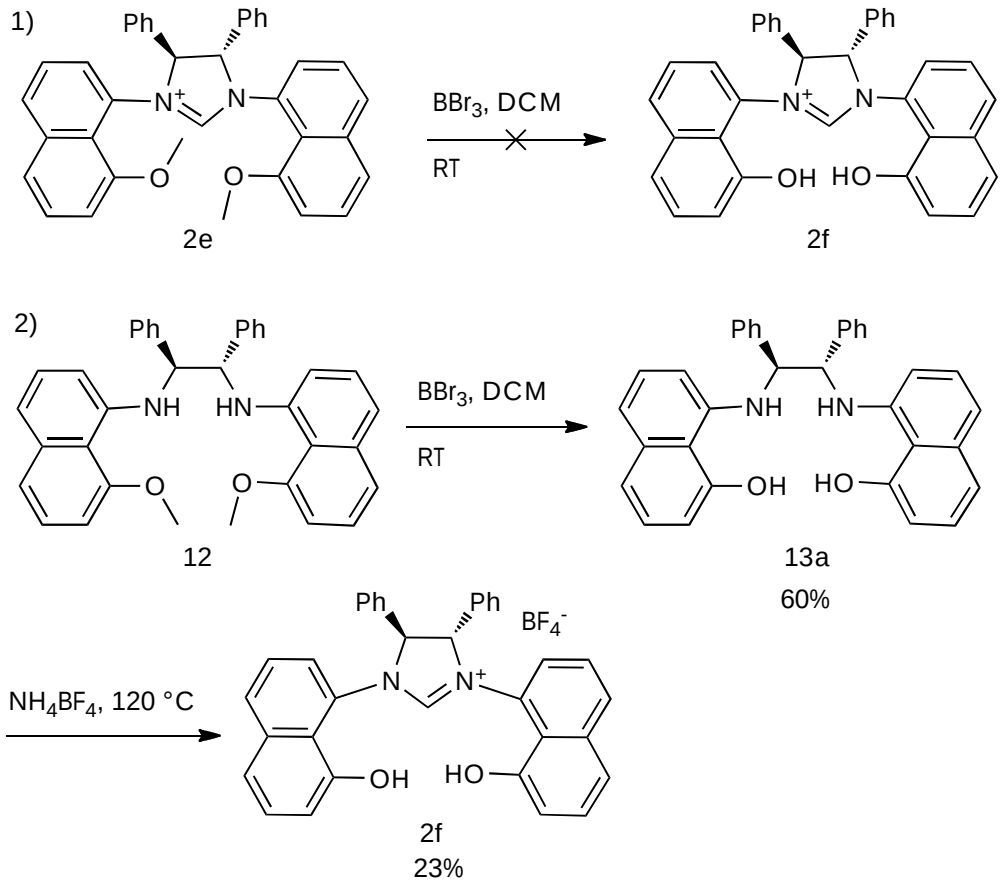
The yield of that product was low (42%), because three to four consecutive chromatographic columns were needed to obtain the pure diamine 12. Indeed, there is co-elution effect between the starting naphthalene and the diamine. The best technique is to filter the crude mixture through a plug of Celite®, followed by three consecutive purifications. The first one on silica gel (17 cm, 65 mm ∅ for 1,3 g of crude), the second one on basic alumina and the last one on silica. The diamine 12 was then treated with a solution of HCl in methanol and cyclized with triethylorthoformate to give the imidazolium salt 2e with 72% yield.



Scheme 49

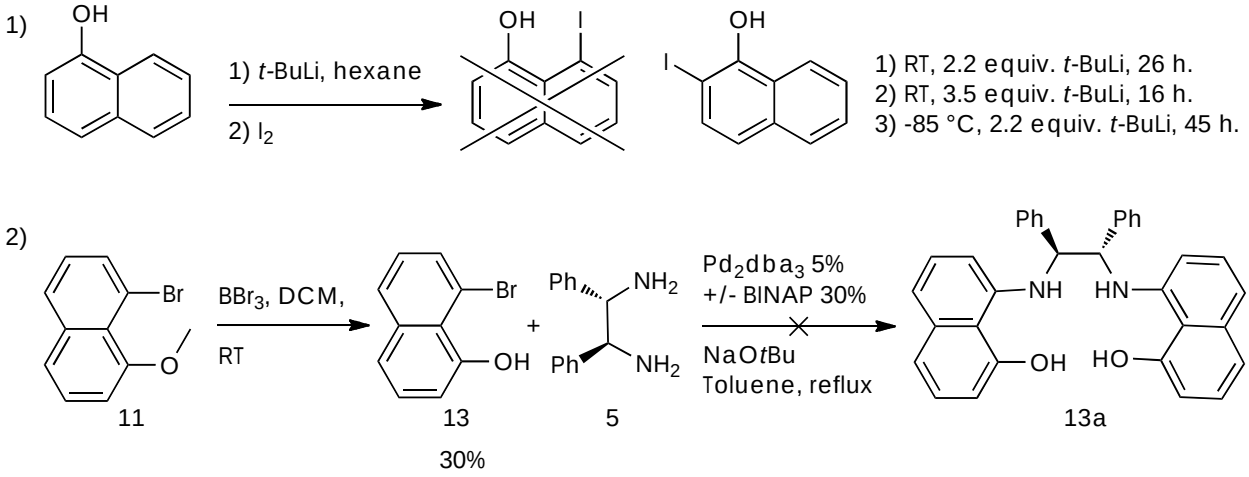
To synthesize the imidazolium salt 2f, we tried to deprotect the methoxy groups from 2e, using two equivalents of BBr_3 at room temperature in dichloromethane for two hours but it did not work (Scheme 50). Therefore, we tried the same approach on the diamine 12, and we succeeded to obtain the free hydroxy groups with moderate yield (60%). In fact, the purification on silica was difficult because of the high polarity

of the diamine and purification on basic alumina was not efficient. Finally, the cyclization step with NH_4BF_4 and triethylorthoformate gave only 23% yield.



Scheme 50

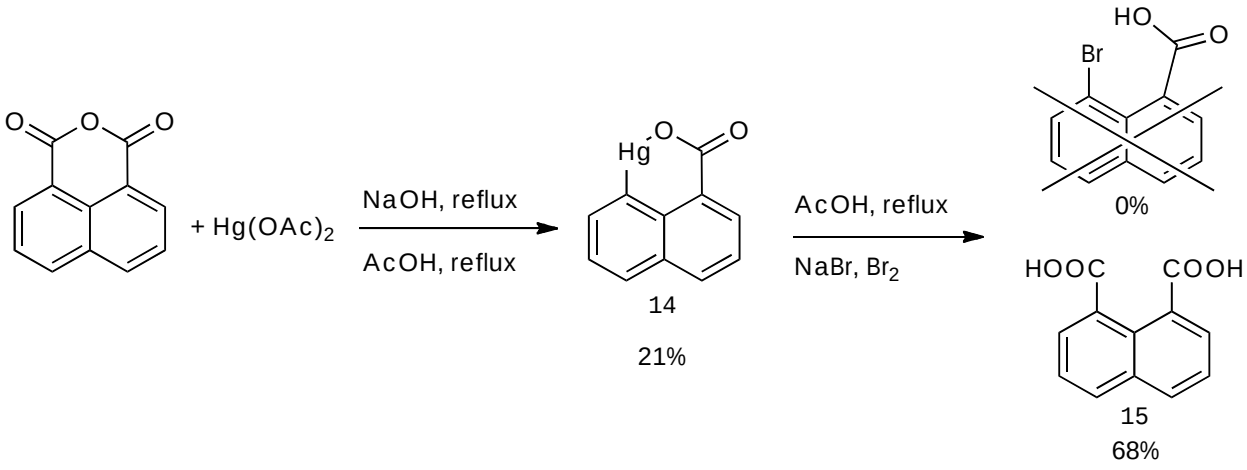
To improve the yield, we tried to change the reaction sequence by starting directly with 1-bromo-8-naphthol (Scheme 51). The Kirby's method was applied on 1-naphthol, but unfortunately, only 1-bromo-2-naphthol was obtained, whatever the reaction conditions were. Finally, we deprotected the naphthalene 11 with BBr_3, and tried to couple the obtained 1-bromo-8-naphthol with the DPEDA 5. Unfortunately, no conversion was obtained. The Buchwald-Hartwig reaction seems to be incompatible with the presence of free hydroxy groups.



Scheme 51

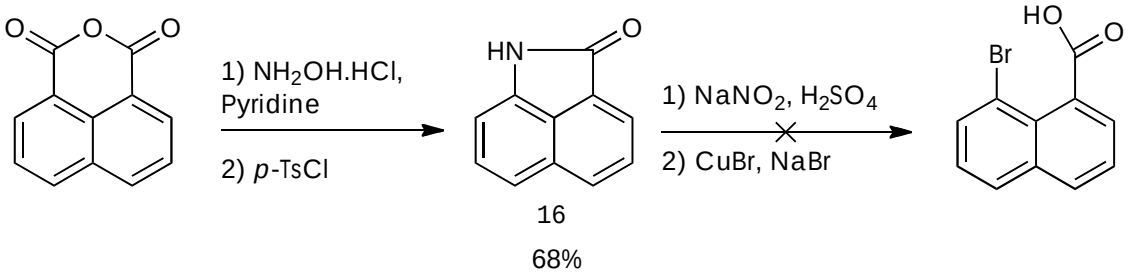
Although the yield was low, the best way to obtain the imidazolium salt 2f remains to deprotect the methoxy groups on diamine, and then to perform the cyclization with triethylorthoformate in presence of NH_4BF_4.

To obtain the imidazolium salt 2g, we tried to use the methodology developed by Schechter (Scheme 52).[148] Naphthalic anhydride was treated with mercuric acetate in order to form the metallacycle, which was then treated with boiling acetic acid and NaBr. Then, the obtained bromocarboxylic acid was reduced with $LiAlH_4$ to give the corresponding 1,8-bromonaphthalene methanol. In our case, electron impact mass spectrometry (EI-MS) showed only 21% of metallated naphthalene 14, instead of the Schechter's announced 100% conversion. This analysis method was the only one we could used because the obtained salt was insoluble in all the tested solvents (H_2O, DMSO, acetonitrile, dichloromethane (DCM), chloroform ($CHCl_3$), Acetone, MeOH). The opening of the metallacycle by boiling acetic acid gave 68% of the dicarboxylic acid 15.



Scheme 52

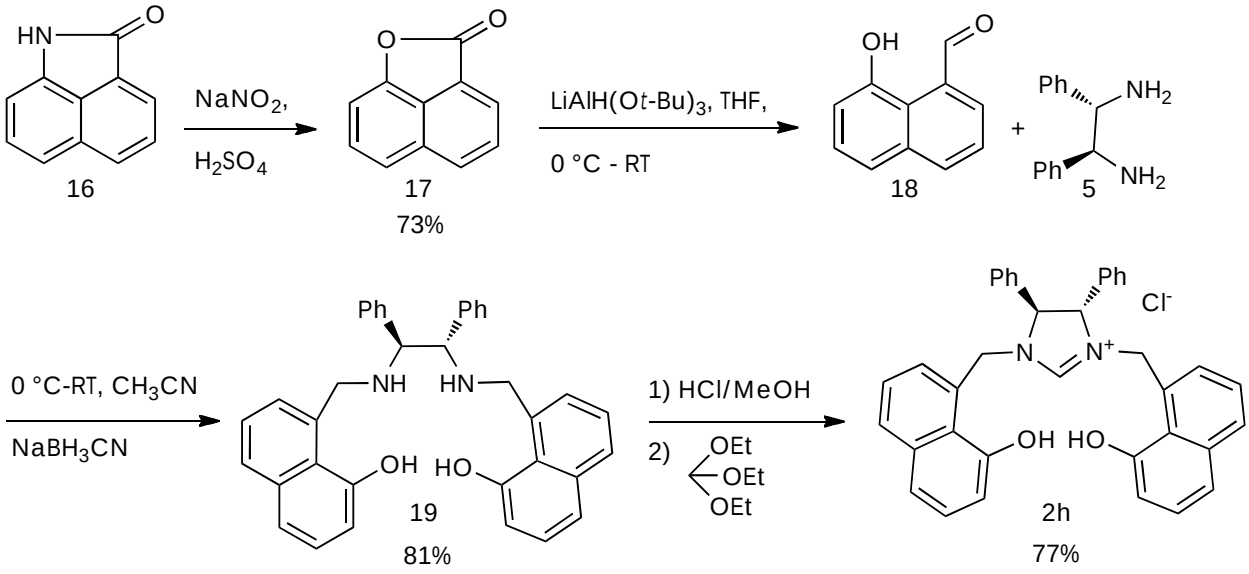
As that procedure did not give the expected product, we tried another approach proposed by Goldstein in 1932 (Scheme 53),[149] namely the copper-catalyzed opening of a naphthalic lactam by $NaNO_2$, followed by addition of NaBr. The lactam was first synthesized by treating naphthalic anhydride with hydroxylamine chlorhydrate and *p*-TsCl in good yield (68%).[150] Unfortunately, the opening of the lactam was not possible, and the starting material was recovered.



Scheme 53

Another synthetic route has to be found to obtain the NHC 2g. For now, the tested reactions gave no results.

The last imidazolium salt 2h, with one more carbon between the aromatic moiety and the nitrogen, was synthesized following a different approach (Scheme 54). The previously obtained lactam 16 was treated with $NaNO_2$ to form the lactone 17 with 73% yield. This was reduced by $LiAlH(OtBu)_3$ to give the corresponding 1-hydroxy-8-naphthaldehyde 18. This one was submitted to reductive amination with DPEDA 5, followed by cyclization with HCl/MeOH and triethylorthoformate to give the imidazolium salt 2h with 77% yield.

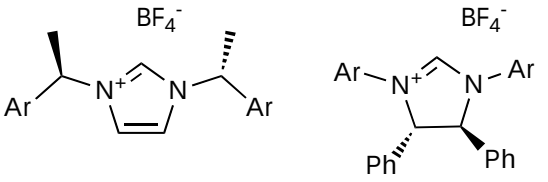


Scheme 54

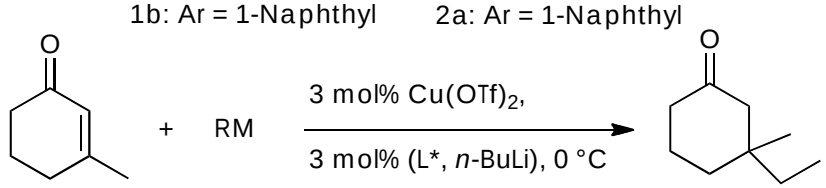
3.3 Optimization of the reaction conditions

With a panel of *C2*-symmetric NHC in hand, we tested them in the copper-catalyzed 1,4-addition on trisubstituted cyclic enones. As nothing was done on the subject at that time, we started our study with the *C2*-symmetric NHC's by a screening of nucleophiles (Table 3). The first observation we made was the total regioselectivity of the reactions in favor of the conjugate addition. As expected, the simplest NHC 1b, with no chelating functionality or fixed stereo-inducing groups, gave the worst results in terms of enantioselectivities and conversion. But it allowed to point out that organozinc nucleophiles were less reactive than the other ones, as there is no conversion after 16 hours (Table 3, Entry 1). Et_3Al and EtMgBr gave the best conversions but the enantioselectivities remained low (Table 3, Entry 2, 3). For the Grubbs-type NHC 2a, the rotation around the C-N axis was constrained, due to the stereo-induction from the back of the heterocycle. As a result, the stereo-information was better transmitted to the reacting center and it was not surprising to see an increase of the *ee*'s with those ligands. As the chiral information is not fixed on the TM by a heteroatom chelation, the main advantage of that kind of *C2*-symmetric NHC's is some possible adaptability of the reactive pocket size, depending on the nucleophile size. This is not possible when the substituent is bound to the TM.

For both families, the aluminum species gave worse results in terms of enantioselectivity than their organomagnesium counterparts (Table 3, Entry 2-3 and 4-5). Moreover, the Grignard reagents gave the shortest reaction times and we will see later that those nucleophiles were also basic enough to deprotonate the ImH^+, facilitating the procedure.



1b: Ar = 1-Naphthyl 2a: Ar = 1-Naphthyl



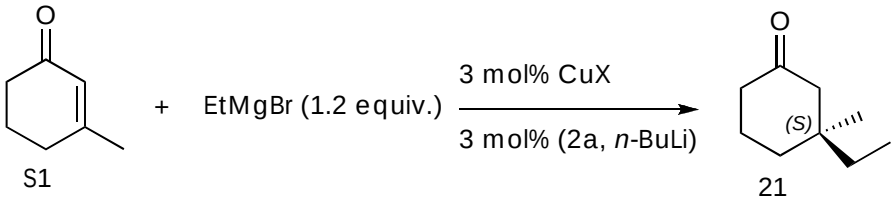
S1 20

Entry	ImH^+	RM	Time	Conv.[a]	Ratio 1,2:1,4	ee[b]
1	1b	Et_2Zn	16 h.	1%	-	-
2	1b	Et_3Al	16 h.	85%	0:100	9% (+) *R*
3	1b	EtMgBr	0.5 h.	86%	0:100	17% (+) *R*
4	2a	Et_3Al	16 h.	94%	0:100	54% (-) *S*
5	2a	EtMgBr	0.5 h.	92%	0:100	68% (-) *S*

a) after 16 h., determined by GC-MS. b) determined by chiral GC (Lipodex E)

Table 3

A screening of different copper sources, solvents and temperature were done to find the best reaction conditions for the 1,4-addition of EtMgBr to 3-methylcyclohex-2-enone (Table 4).



Entry	CuX	Solvent	Temp.	Conv.[a]	*ee*[b]
1	$Cu(OTf)_2$	THF	0 °C	> 99%	0%
2	$Cu(OTf)_2$	MTBE	0 °C	77%	57% (-)
3	$Cu(OTf)_2$	CH_2Cl_2	0 °C	80%	40% (-)
4	$Cu(OTf)_2$	Toluene	0°C	87%	38% (-)
5	$Cu(OTf)_2$	Dioxane	0 °C	32%	41% (-)
6	$Cu(OTf)_2$	Et_2O	RT	95%	60% (-)
7	$Cu(OTf)_2$	Et_2O	0 °C	92%	68% (-)
8	$Cu(OTf)_2$	Et_2O	-40 °C	85%	37% (-)
9	CuBr	Et_2O	0 °C	82%	38% (-)
10	CuTC	Et_2O	0 °C	73%	8% (-)
11	$Cu(CN)_4PF_6$	Et_2O	0 °C	98%	68% (-)
12	$Cu(CN)_4BF_4$	Et_2O	0 °C	98%	40% (-)

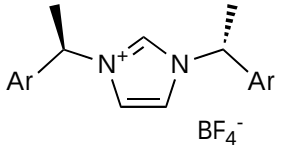
(a) conversion determined by GC-MS, after 30 min. or 3 h. (T < 0 °C).

(b) determined by chiral GC (Lipodex E).

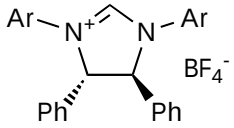
Table 4

The most important parameter seemed to be the solvent. With the same copper source, the variation of solvent changed dramatically the enantioselectivity of the reaction. Indeed, as Et_2O gave the best *ee* (68%; Table 4, Entry 7), the use of THF gave a racemate (Table 4, Entry 1). Methyl *tert*-butylether (MTBE), CH_2Cl_2 and toluene gave no improvement to our reaction (Table 4, Entry 2-4). Interestingly, dioxane in which the Schlenk equilibrium is shifted in favor of R_2Mg, since magnesium salt $MgBr_2$ precipitate in that solvent, gave still 41% *ee* with low conversion (Table 4, Entry 5). The best temperature for this reaction was 0 °C (Table 4, Entry 6-8) and $Cu(OTf)_2$ or $Cu(CN)_4PF_6$ appeared to be appropriate copper sources for the reaction.

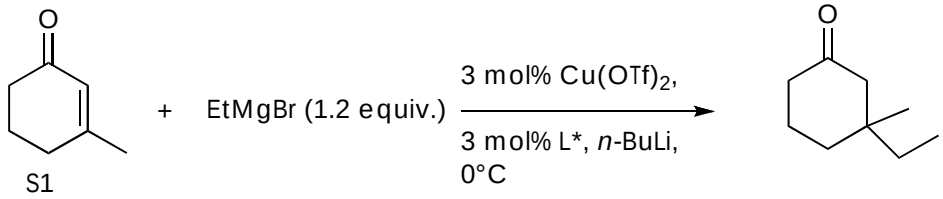
Using the previously optimized reaction conditions, the addition of EtMgBr on 3-methylcyclohex-2-enone was tested with the different imidazolium salts (ImH^+) (Table 5).



1a: Ar = Ph
1b: Ar = 1-Naphthyl
1c: Ar = 2-OMe-C_6H_4



2a: Ar = 1-Naphthyl
2b: Ar = 2-Naphthyl
2c: Ar = 2-Me-C_6H_4
2d: Ar = 2-iPr-C_6H_4



S1

Entry	ImH^+	Conv.[a]	*ee*[b]
1	1a	81%	9% (+) *R*
2	1b	86%	17% (+) *R*
3	1c	75%	42% (+) *R*
4	2a	92%	68% (-) *S*
5[c]	2a	89%	2% (-) *S*
6[d]	2a	94%	73% (-) *S*
7[e]	2a	96%	70% (-) *S*
8	2b	82%	17% (-) *S*
9	2c	87%	63% (-) *S*
10	2d	85%	10% (-) *S*

(a) conversion determined by GC-MS, after 30 min. or 3 h. ($T < 0$ °C). (b) determined by chiral GC (Lipodex E). (c) The substrate was added first, then the Grignard reagent was added dropwise (d) 3 mol% $Cu(OTf)_2$ 4 mol% ImH^+. (e) 3 mol% $Cu(OTf)_2$ 6 mol% ImH^+.

Table 5

For the Hermann's type ImH^+, the best result was obtained using ligand 1c with 42% *ee* (Table 5, Entry 3) as 1a gave only 9% *ee* (Table 5, Entry 1). With ligand 1b containing a 2-ethylnaphthyl group, the *ee* drops to 17% (Table 5, Entry 2).

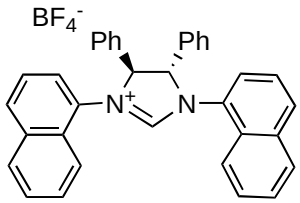
For the ImH^+ 2a-d, the results were more tricky: the enantioselectivity decreased with the following order: 2a (68%) > 2c (63%) >> 2b (17%) > 2d (10%) (Table 5, Entry 4, 8-10). The ligand 2d, which gave up to 90% *ee* for the desymmetrization of trienes by Grubbs metathesis,[83] led to a disappointing result in our experimental conditions. The difference between 2a and 2b was certainly due to the remoteness of the naphthyl group from the reacting center going from 1-naphthyl to 2-naphthyl. When the environment surrounding the copper was less hindered the *ee* decreased dramatically.

The order of addition was also highly important. Indeed, if the Grignard reagent was added on the substrate, the *ee* dropped to 2% (Table 5, Entry 5) using ImH^+ 2a. This observation could be explained if the active asymmetric specie was an "ate-complex" or a higher-order cuprate such as $[(NHC)CuEt_2]$. Indeed, when the Grignard reagent was added after the substrate, the Mg-Cu transmetallation time was shorter and only organocopper reagents were formed. When the Grignard reagent was added first, the transmetallation had time to occur twice to form the higher order cuprate, which could be the highly stereoselective asymmetric catalytic specie.

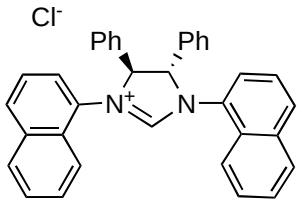
This contrasts with the copper-catalyzed asymmetric allylic substitution where the Grignard reagent is added very slowly to the substrate, in order to avoid the formation of cuprate species.[151,152] Finally, using a Cu:NHC ratio of 1:1.3 gave the best *ee*'s (Table 5, Entry 6) and a 1:2 ratio decreased the *ee*'s (Table 5, Entry 7).

3.4 Scope of the reaction: alkyl Grignard reagents

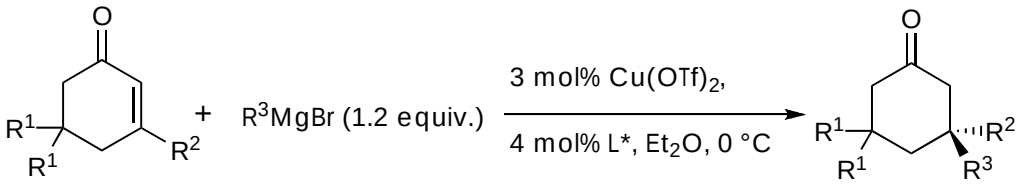
With our best structural NHC in hand, we first synthesized the analogue of 2a with a chloride instead of BF_4^- as counter-ion, in order to observe the counter-ion effect. The ImH^+ 2i was synthesized using the same method as 2a, but the ring closure was realized by MeOH/HCl hydrochlorination instead of NH_4BF_4 reaction pathway. The optimized conditions were applied to the addition of different alkyl organomagnesium reagents (Table 6).



2a



2i



Entry	R^1	R^2	R^3	ImH$^+$	Prod.	Conv.[a]	*ee* [b]
1	H	Me	Et	2a	21	92%	73% (-) *S*
2	H	Me	Et	2i	21	>99%	72% (-) *S*
3	H	Me	*n*-Bu	2a	22	99%	73% (-) *S*
4	H	Me	But-3-en	2a	23	81%	73% (+) *R*
5	H	Me	*c*-Pent	2a	24	97%	60% (-) *S*
6	H	Me	*c*-Pent	2i	24	>99%	60% (-) *S*
7	H	Me	*i*-Pr	2a	25	99%	39% (-) *S*
8	H	Me	*i*-Pr	2i	25	>99%	40% (-) *S*
9	H	Et	Me	2a	20	99%	21% (+) *R*
10	H	But-3-en	Et	2a	26	88%	50% (+) *S*
11	Me	Me	Et	2a	27	93%	71% (-) *S*

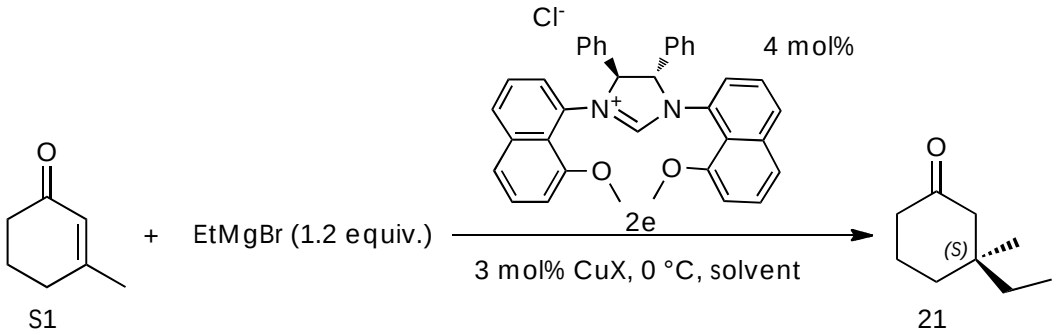
(a) conversion determined by GC-MS, after 30 min. or 3 h. (T < 0 °C). (b) determined by chiral GC (Lipodex E).

Table 6

One can observe the perfect facial selectivity of the nucleophilic approach. Indeed, the nucleophile entered always from the *Re* side of the cyclic enone when using ImH^+ 2a, which was proven by the opposite major enantiomer obtained when inverting the nucleophile and the substrate's substituent (Table 6, Entry 1, 9).

In accordance with Tomioka's work,[137] the variation of the counter-ion from BF_4^- to Cl^- has almost no effect on the *ee* of the conjugate addition (Table 6, Entry 1-2, 5-6, 7-8). The linear nucleophiles, except methyl, which react with poor enantioselectivity, gave good results with *ee*'s around 73% (Table 6, Entry 1-3). The addition of EtMgBr on the poorly reactive isophorone gave a promising 71% *ee* (Table 6, Entry 8).

Unfortunately, when the Grignard reagent was α-branched, the *ee* decreased (Table 6, Entry 4-5). As the NHC naphthyl substituents were not chelated to the copper, the steric bulk of the nucleophile may "push" that naphthyls away from the reacting center during the transmetallation step, and by doing so, leaves the copper with weaker chiral induction as observed with the 2-Naphthyl substituents. To prove that hypothesis, we used the C_2-symmetric NHC 2e, having the same structure than 2a, but with two extra chelating methoxy groups. We started by doing a solvent and copper salt screening, in order to control the reactivity of that tridentate ligand (Table 7).



Entry	CuX	Solvent	Conv.[a]	Ratio 1,2:1,4	*ee*[b]
1[c]	$Cu(OTf)_2$	Et_2O	92%	0:100	73% (-)
2	$Cu(OTf)_2$	Et_2O	>99%	0:100	67% (-)
3	$CuBr•Me_2S$	Et_2O	>99%	0:100	68% (-)
4	$[Cu(OTf)]_2•C_6H_6$	Et_2O	>99%	0:100	68% (-)
5	$Cu(OAc)_2•H_2O$	Et_2O	>99%	0:100	64% (-)
6	$CuBr•Me_2S$	Toluene	>99%	89:11	2%
7	$Cu(OTf)•C_6H_6$	Toluene	>99%	16:84	54% (-)
8	$Cu(OAc)_2•H_2O$	Toluene	>99%	25:75	54% (-)
9	$CuBr•Me_2S$	DCM	92%	71:29	6%
10	$[Cu(OTf)]_2•C_6H_6$	DCM	>99%	12:88	28% (-)
11	$Cu(OAc)_2•H_2O$	DCM	>99%	78:22	40% (-)

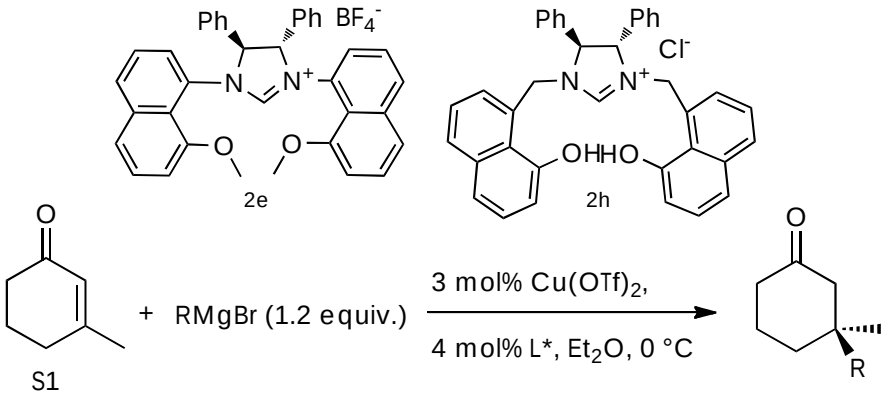
(a) conversion determined by GC-MS, after 60 minutes. (b) determined by chiral GC Lipodex E. (c) obtained with the ligand 2a.

Table 7

The ligand 2e gave similar *ee*'s than the 2a in the same conditions (Table 7, Entry 1, 2). In that case, there was also a high solvent dependency on the reaction. Indeed, the regioselectivity was lowered in toluene (Table 7, Entry 4, 7) and could be totally inverted when the reaction was done in DCM (Table 7, Entry 5, 11). Interestingly, $[Cu(OTf)]_2•C_6H_6$ seemed to be more active than $CuBr•Me_2S$ and $Cu(OAc)_2•H_2O$. The regioselectivity of that copper salt in DCM and toluene was always in favor of the

1,4-addition product, in opposite to the two other copper salts where the major product was the 1,2-addition product.

As the best reaction conditions were the same for 2a and 2e, a scope of the reaction was done with ImH+ 2e and 2h, bearing also two chelating substituents, with a series of linear and branched Grignard reagents (Table 8).



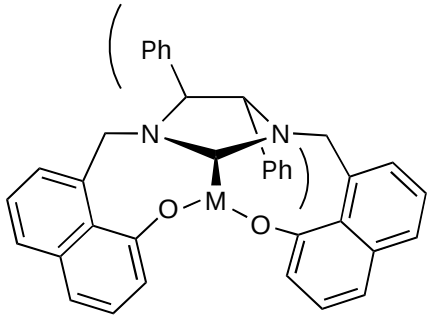
Entry	R	ImH+	Prod.	Conv.(a)	*ee* (b)
1	Et	2e	21	>99%	67% (-) *S*
2	Et	2h		>99%	0%
3	*n*-Bu	2e	22	>99%	72% (-) *S*
4	*c*- Pent	2e	24	>99%	56% (-) *S*
5	*c*-Pent	2h	24	>99%	0%
6	*i*-Pr	2e	25	>99%	70% (-) *S*
7	*i*-Pr	2h	25	>99%	0%
8	*t*-Bu	2e	28	>99%	0%

(a) conversion determined by GC-MS, after 30 min. or 3 h. (T < 0 °C). (b) determined by chiral GC (Lipodex E).

Table 8

The linear nucleophiles gave the same results than with ImH+ 2a. In contrast, for the α-branched Grignard reagents, the results were totally different. With *c*-pentyl, the *ee* decreased slightly (60% to 56% Table 8, Entry 4) but with *i*-propyl, the *ee* increased strongly from 39% to 70% (Table 8, Entry 6).

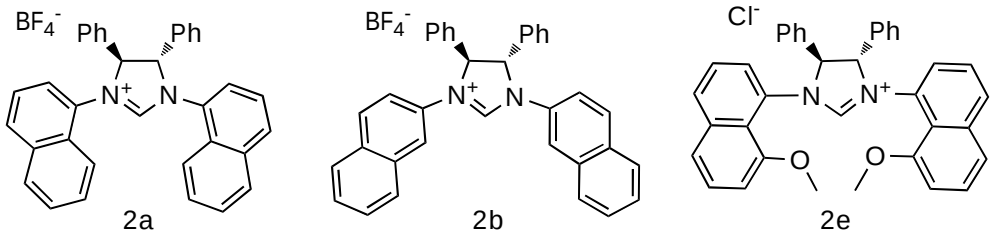
These results were in accordance with our previous hypothesis. Indeed, the presence of chelating substituents on the naphthyl group prevents the "opening" of the chiral reacting center and the result was an increasing *ee*. Moreover, the reaction pocket stayed big enough with the 2e ligand to allowed the addition of *t*-Butyl group on the 3-methylcyclohex-2-enone S1 (Table 8, Entry 5) but in a racemic way. On the other hand, the ImH^+ 2h gave no enantioselectivity. It was most likely due to the high distance between the naphthyl substituent and the chiral inducing group on the back of the cycle. Indeed, the steric hindrance of the phenyl group is too far away from the naphthyl because of an extra CH_2 bond, to push it opposite to itself. The result is a very flexible eight-membered metallacycle, which cannot induce any enantioselectivity (Scheme 55).

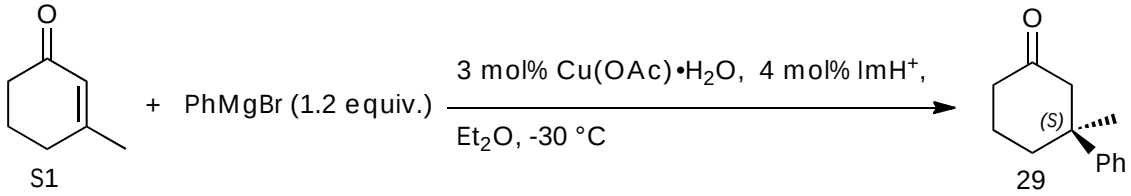


Scheme 55

3.5 Scope of the reaction: aryl Grignard reagents

With those encouraging results in hand, we wanted to extend the scope of our methodology by successfully adding aromatic nucleophiles on trisubstituted cyclic enones. As the two C_2-symmetric analogues react almost in the same way with linear Grignard reagents but differently with branched nucleophiles, we tested them in the addition of aromatic nucleophiles. Therefore, we started as usual, by finding the best reaction conditions for the addition of PhMgBr to the 3-methylcyclohex-2-enone (Table 9).



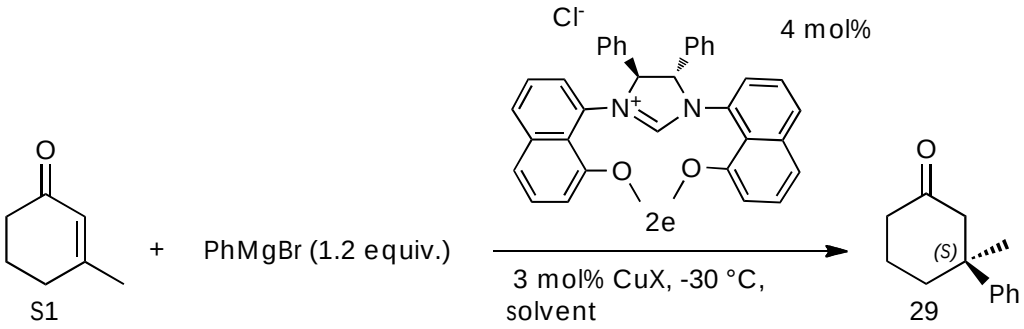


Entry	ImH^+	Add. Time	Conv.[a]	Ratio 1,2:1,4	*ee*[b]
1	1b	30 min	97%	97:3	4% (+)
2	2a	30 min	99%	72:28	88% (+)
3	2b	30 min	97%	49:51	10% (+)
4	2e	30 min	99%	16:84	48% (+)

(a) conversion determined by GC-MS, after 60 minutes. (b) determined by chiral GC Hydrodex-B-3P.

Table 9

As for the alkyl Grignard reagents, the Herrmann's family gave the worst results (Table 9, Entry 1). The ImH^+ 2a gave very good *ee* (88%), but the regioselectivity was bad (Table 9, Entry 2). As for the addition of aliphatic Grignard reagents, the ligand 2b gave poor *ee*, because of the remoteness of the naphthyl substituents from the reacting center. The main drawback of this reaction was the regioselectivity, largely in favor of the 1,2-addition. The use of ImH^+ 2e allowed a better regiocontrol, although the *ee* was disappointingly low (48%) (Table 9, Entry 4). Therefore, we made a short screening of different parameters to see if we could keep a high regioselectivity and increase the *ee* (Table 10).



Entry	CuX	Solvent	Conv.[a]	Ratio 1,2:1,4	*ee*[b]
1	$Cu(OAc)•H_2O$	Et_2O	>99%	16:84	48% (+)
2	$CuBr•Me_2S$	Et_2O	>99%	11:89	46% (+)
3	$[Cu(OTf)]_2•C_6H_6$	Et_2O	>99%	11:89	46% (+)
4	$[Cu(OTf)]_2•C_6H_6$	Toluene	>99%	17:83	64% (+)
5	$Cu(OAc)•H_2O$	Toluene	>99%	95:5	68% (+)
6	$CuBr•Me_2S$	DCM	>99%	13:87	70% (+)
7	$[Cu(OTf)]_2•C_6H_6$	DCM	>99%	28:72	72% (+)
8	$Cu(OAc)•H_2O$	DCM	>99%	20:80	70% (+)

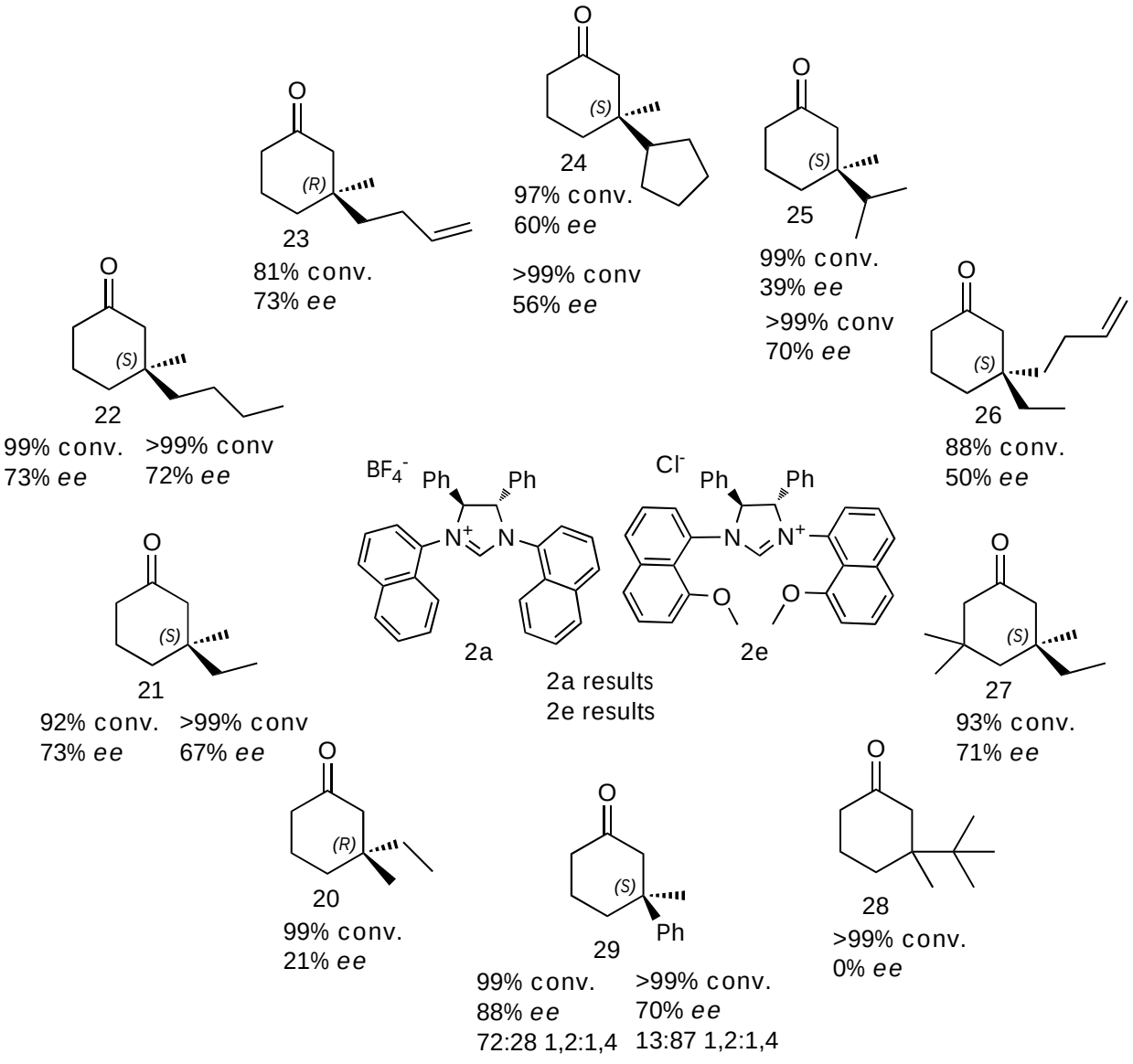
(a) conversion determined by GC-MS, after 60 minutes. (b) determined by chiral GC Lipodex E.

Table 10

Surprisingly, in that case, unlike the addition of an alkyl nucleophile, the best solvent was DCM with high regioselectivity and high *ee*'s (Table 10, Entry 6). The presence of the –OMe functionalities were also shown to be highly important, not for the enantioselectivity but for the regioselectivity of the reaction. In fact, almost all the reactions gave a highly better 1,4:1,2 ratio with 2e than with 2a. The temperature parameter was also investigated, but -30 °C stays the optimized temperature in terms of *ee* and regioselectivity. By lowering the temperature to -45 °C or warming it to 0 °C, the 1,2-addition was favored. Moreover, the phenyl copper complex seemed to become unstable at 0 °C, because the reaction was messy and the complex became black after 10 minutes.

In conclusion, the C_2-symmetric NHC were good ligands to catalyze regioselectively and enantioselectively the asymmetric conjugate addition of alkyl Grignard reagents, with *ee*'s up to 73% (Scheme 56). The presence of two methoxy chelating substituents on the NHC allowed to maintain the chiral information around the reactive center, and doing so, enhanced the *ee* for the addition of α-branched nucleophiles (*i*-propyl, 39% *ee* with 2a to 70% *ee* with 2e). The addition of an aromatic organomagnesium nucleophile gave an impressive 88% *ee* with 2a, but the regioselectivity drops down. The use of the methoxy ImH$^+$ 2e allowed to increase the regioselectivity in favor of the 1,4-addition by keeping a good *ee* (70%).

Scope of the reaction with C_2-symmetric NHC



Scheme 56

4. *Asymmetric NHC as chiral ligands for A.C.A.*

As mentioned previously, the NHC containing a chelating group on the chiral substituent should induce better enantioselectivity, due to their fixed steric hindrance. We therefore synthesize some NHC with different chelating heteroatom and tested them in the A.C.A..

4.1 Sulfonamide as chelating groups

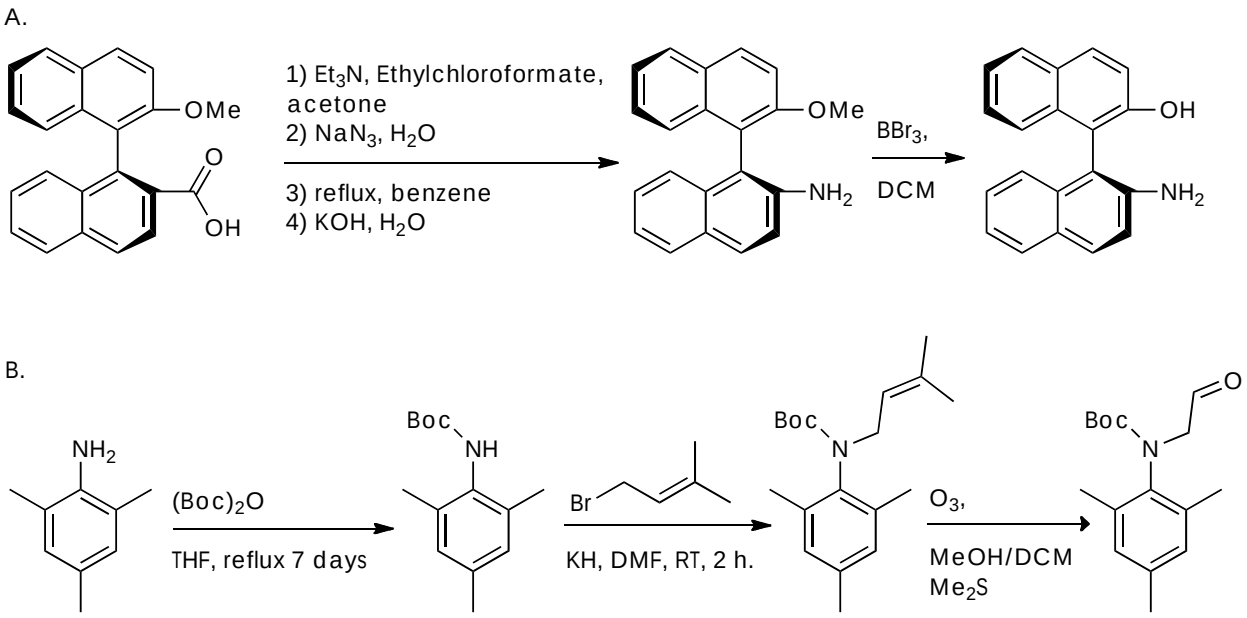
Many different chelating groups were used to rigidify the steric bulkiness, as alkoxides, amines, phosphates, thiols etc. Sulfonamides were less employed for that use, although they showed very good results in chemistry. Indeed, as the nitrogen proton becomes highly acidic because of the sulfone, the nitrogen is strongly attached to the TM. Many groups have designed ligands with sulfonamides, like Sewald[153] for the A.C.A. of Et_2Zn on cyclohexenone reaching 30% *ee*. Noyori[154] proposed also Cu-sulfonamide complexes catalyzing the racemic conjugate addition of Me_2Zn, Et_2Zn and Ph_2Zn on cyclohexenone. The sulfonamide group allowed to decrease the reaction time from 20 hours to 1 hour. It seems that the sulfonamide brings the copper and the zinc reagent close together, accelerating the transmetallation step. Yoshioka,[155] Knochel,[156] and others[157] used also sulfonamide-based ligands in titanium-catalyzed addition of Et_2Zn on different aldehydes with excellent 99% *ee*'s.

As this motif was never used on NHC's as chelating group, we tried to use it on a modified Hoveyda binaphthol-type ligand.

4.2 Sulfonamide based modified Hoveyda's binaphthol

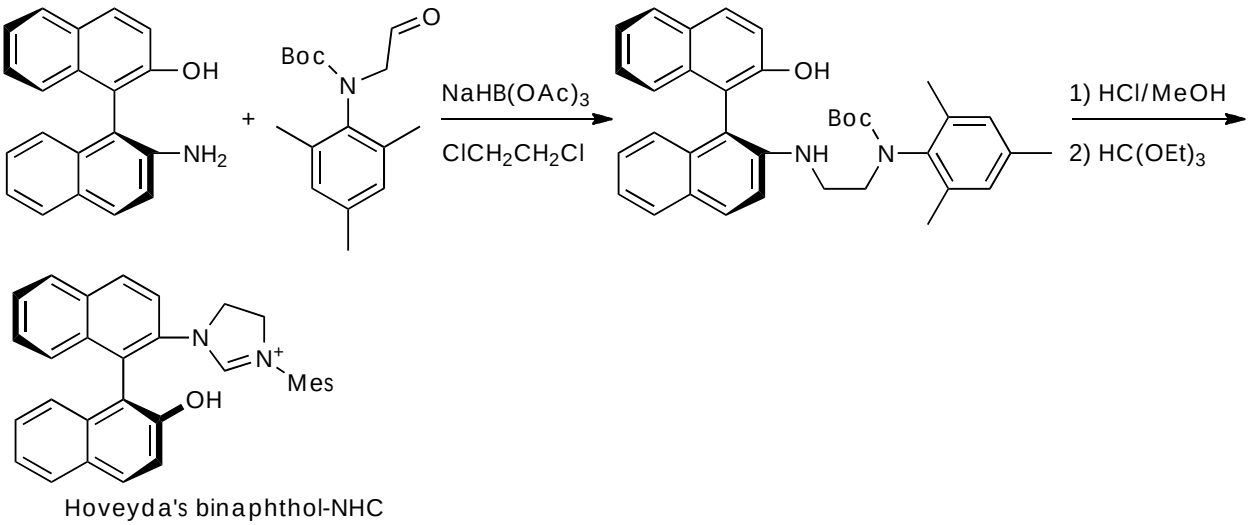
4.2.1 Hoveyda's ligand synthesis

Hoveyda's modified binaphthol ligand was synthesized adapting a described procedure, namely the convergent synthesis of the binaphthylhydroxylamine and the Boc-protected mesityl aldehyde (Scheme 57).



Scheme 57

These two synthons were then coupled by reductive amination and the obtained diamine was cyclized with HCl/MeOH followed by triethylorthoformate to give the binaphthol NHC (Scheme 58).



Hoveyda's binaphthol-NHC

Scheme 58

4.2.2 Optimization of the ligand synthesis

Hoveyda's procedure has one major drawback: the too long reaction time. The protection of mesitylamine by $(Boc)_2O$ takes seven days at reflux temperature. We started therefore our synthesis by optimizing the reaction conditions. For the first step of the way B (Scheme 57), we used the same reagents, while heating the system in a microwave reactor for two minutes at 180 °C followed by thirty minutes at 140 °C. The system had to be degassed after two minutes, to eliminate the gaseous CO_2. That procedure allowed to obtain pure protected aniline on a six-gram scale in thirty-five minutes.

The deprotection of the Boc group was also modified. Instead of using gaseous HCl in MeOH, we followed Barros[158] procedure using trifluoroacetic acid (TFA) in DCM at room temperature (RT). Since the tertiary protected amine is really hindered, only 58% conversion was obtained after twenty-eight hours at RT. Another attempt was therefore done in a microwave reactor, at 100 °C for 10 minutes to give total conversion and 83% of pure isolated product. The heating temperature had to be carefully monitored. If the system was warmed at 120 °C and above, degradation products were observed and only 46% of pure product was obtained after 18 minutes under microwave irradiations.

Finally, in the second step of the way B (Scheme 57), we used allyl bromide instead of the dimethylated one. It cost's approximately 100 times less and is cleaved as well as the other one by ozonolysis. In fact, Hoveyda obtain 90% yield with the dimethylated allyl and we achieve 82% yield on a 6 gram-scale with allyl bromide. A resume of the precedent optimization is reported in Table 11.

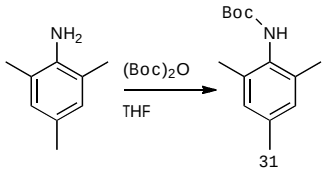
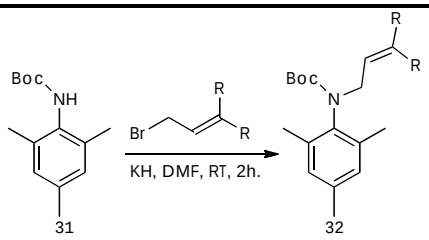
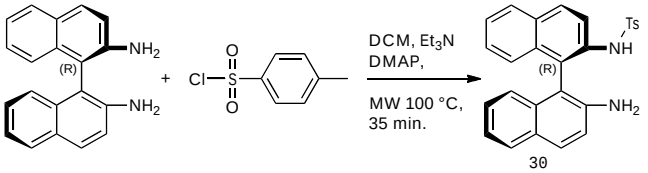
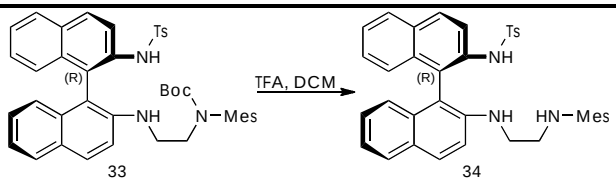
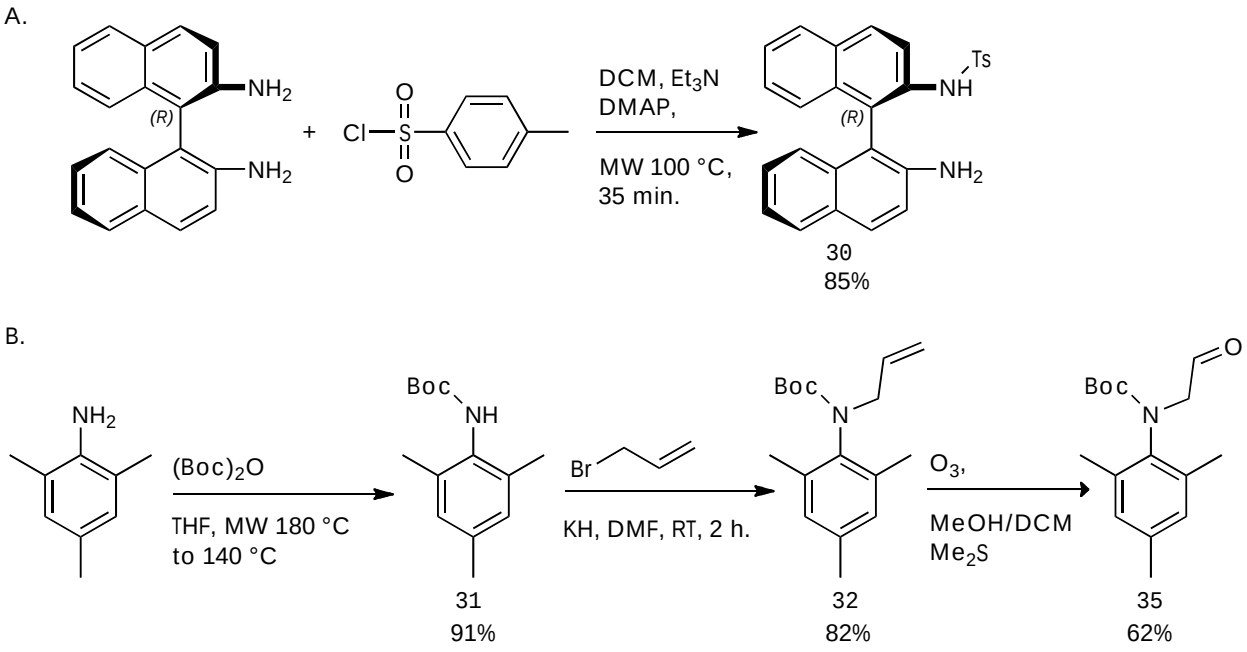
Reaction	React.	Temp	Time	Conv. (Yld)
	1 equiv. $(Boc)_2O$	Reflux	8 days	100% (>99%)
	1.01 equiv. $(Boc)_2O$	MW 180 °C then 140 °C	35 min	100% (91%)
	If R =Me	RT	2 h.	(90%)
	If R = H	RT	2 h.	95% (82%)
	1.3 equiv. TsCl	RT	5 days	70% (56%)
	1.8 equiv. TsCl	MW 100 °C	35 min	100% (97%)
	20 mol% TFA	RT	28 h.	58%
	4 equiv. TFA	MW 100 °C	10 min	97% (83%)

Table 11

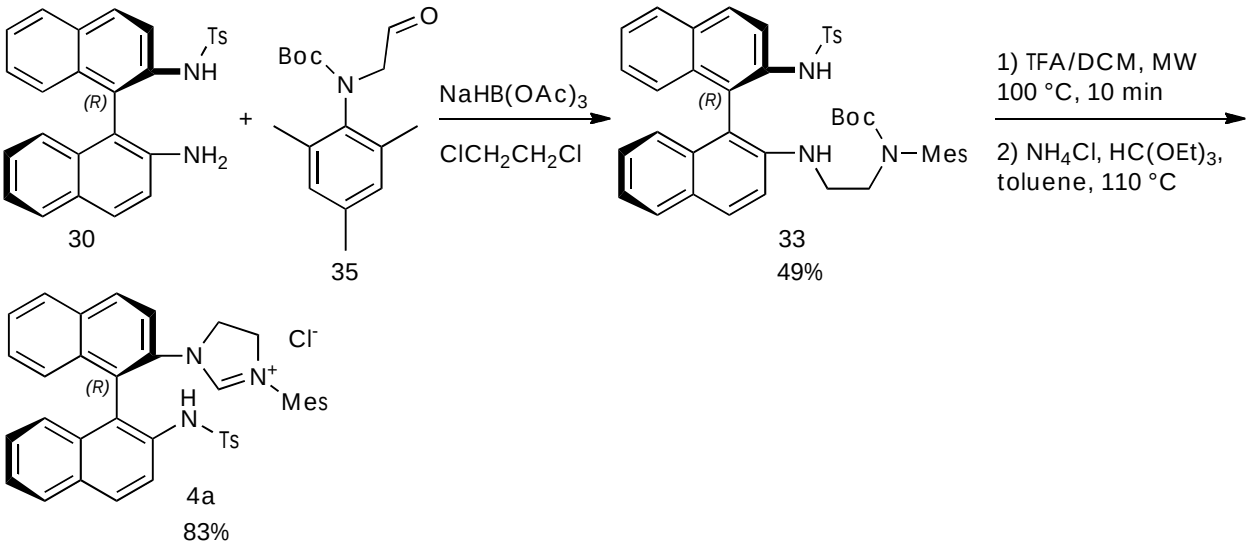
As the chirality of the binaphthylamine is effective because of the non-rotation around the C-C axis of the binaphthyl moiety, we heated some binaphthylamine at 100 °C in the microwave reactor to control if some racemization took place under our reaction conditions. After 35 minutes at 100 °C, the αD before and after irradiation was almost the same (-298.9 before, -302.8 after). There was therefore no racemization during the microwave heating.

With that optimized procedure in hand, we started the synthesis of our sulfonamide ligand with a protection step using *p*-TsCl on (*R*)-2,2-diaminobinaphtyl. Since the diamine was highly stericaly hindered, the reaction at RT took 5 days to give 56% conversion. The DCM, *p*-TsCl, NEt_3, 4-dimethylamino pyridine (DMAP) and the diamine were therefore mixed in a sealed reactor and heated to 100 °C for 35 minutes in a microwave reactor to give the pure product with 85% yield. The diamine was so hindered that the addition of two equivalents of *p*-TSCl gave only the mono-sulfonated amine. The reaction sequence was then performed following Hoveyda's optimized procedure (Scheme 59).



Scheme 59

The two synthons were coupled by reductive amination to give the corresponding diamine 33 (Scheme 60). A deprotection step with TFA in DCM under microwave irradiation followed by a cyclization with NH_4Cl and triethylorthoformate gave the pure ImH^+ 4a.

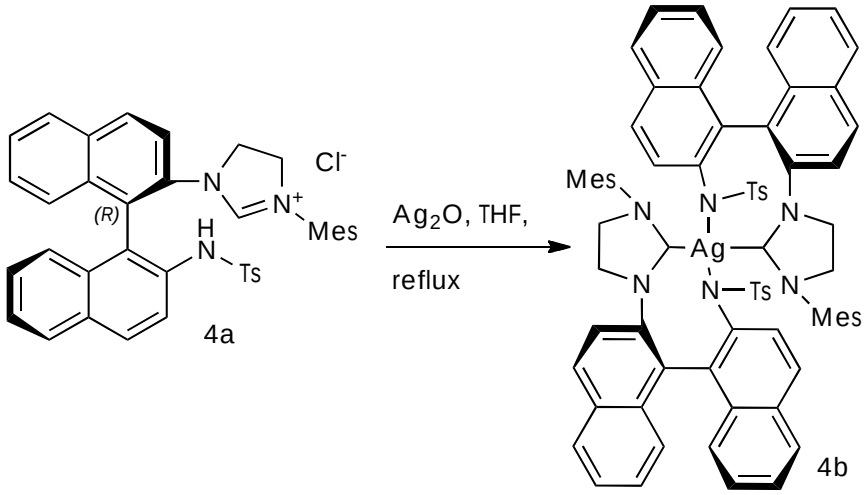


Scheme 60

A main drawback of that sequence was the reductive amination step. The binaphthyldiamine 30 was very bulky because of the tosyl group and seemed to prevent the approach of the aldehyde 35. As a result, we never succeeded in obtaining more than 89% conversion and 50% yield for that reaction, neither by warming nor by using $NaBH_3CN$ as hydride source.

4.2.3 Silver salt complex of 4a

Hoveyda always used preformed silver complexes of his NHC ligands to catalyze the reactions. To observe the difference of reactivity between a free ImH^+ and its corresponding silver complex, we synthesized one starting from 4a (Scheme 61) by adding one equivalent of freshly prepared Ag_2O, obtained by mixing $AgNO_3$ and aqueous NaOH.



Scheme 61

The obtained brown precipitate silver complex was analyzed by ESI-MS. Contrary to Hoveyda's X-ray, which showed the formation of a silver dimer composed by two silver atoms and two NHC ligands, the ESI-MS analysis showed that we have a monomer composed by one silver metal and two NHC ligands. Indeed, the isotopic distribution is different from a mono-silver atom complex and a di-silver atoms complex (Figure 1).

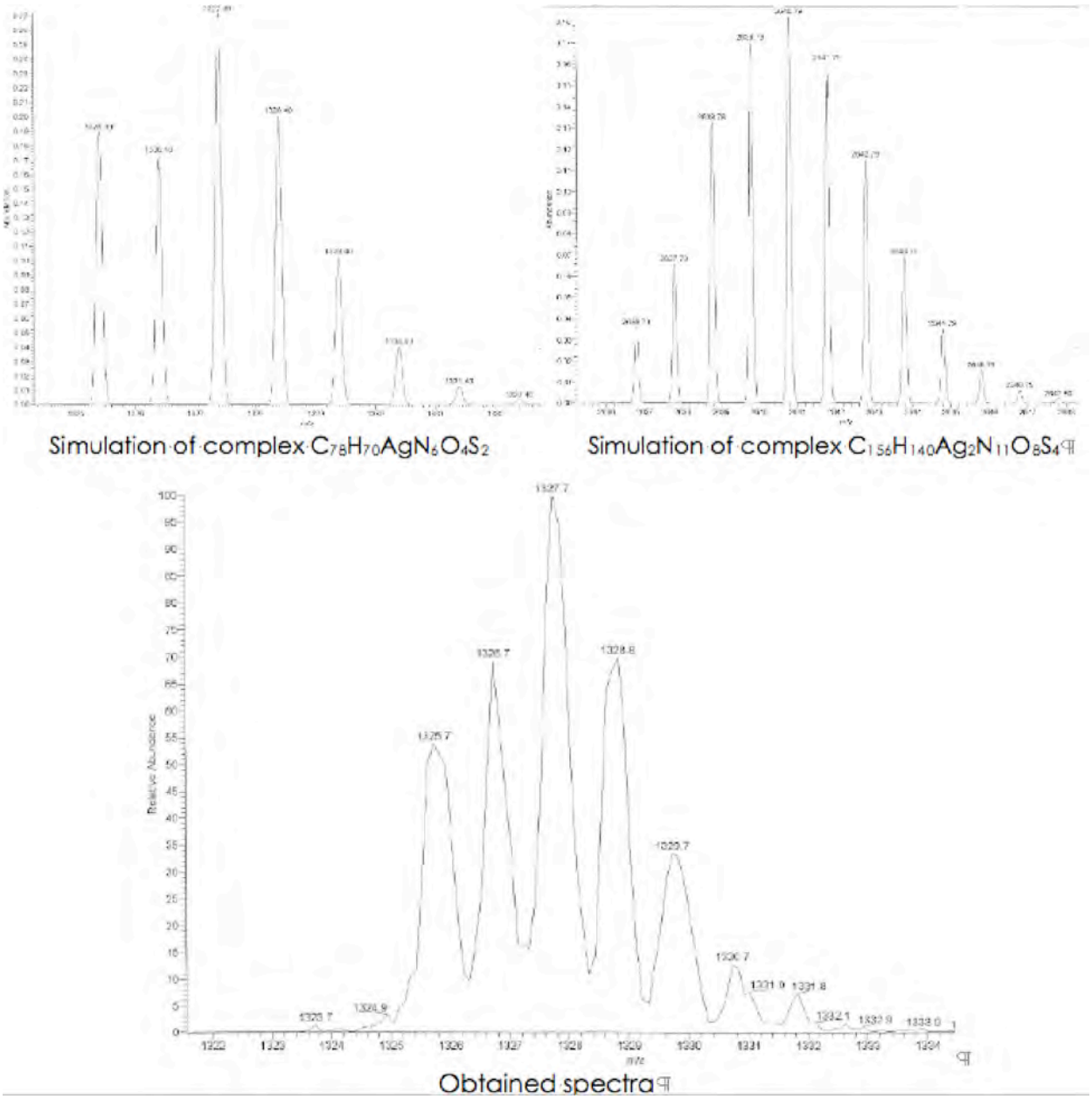
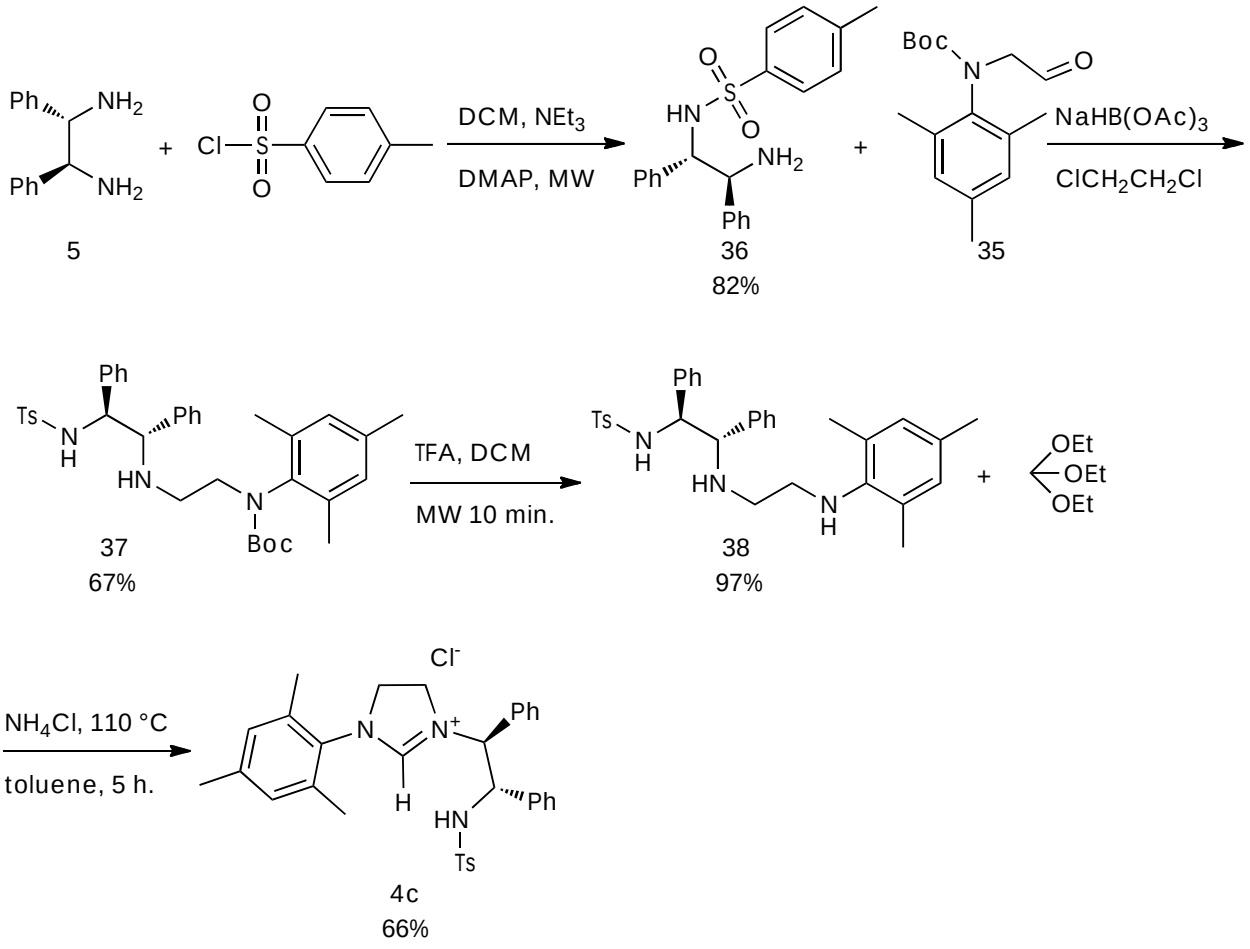


Figure 1

The obtained isotopic peaks correspond to a one-silver atom complex (Figure 1, upper left). An X-ray could prove definitively that the complex is monomeric, but deceptively, although the presence of a sulfone and the silver, we were not able to obtain a sufficiently good crystal to make the X-ray analysis.

4.3 NHC with DPEDA as chiral substituent

To increase the scope of sulfonamides NHC ligands, we synthesized another one bearing the DPEDA as chiral inducing substituent. The synthetic strategy was to use the optimized conditions for synthesizing Hoveyda's modified NHC. The mesitylaminealdehyde was used again. The inserted sulfonated diamine was obtained from DPEDA 5. To achieve this, the diamine 5 was mono-tosylated in the same conditions as previously, to form the protected diamine with 82% isolated yield. This last intermediate was coupled to the aldehyde 35 through reductive amination. The obtained Boc-protected diamine 37 was deprotected and cyclized with triethylorthoformate and NH_4Cl to give the pure ImH^+ 4c as a brown solid with 66% isolated yield (Scheme 62).



Scheme 62

The synthesis of NHC 4c allowed validating the viability of our process using microwave-irradiation for the insertion of a tosyl group and a Boc deprotection (Table 12).

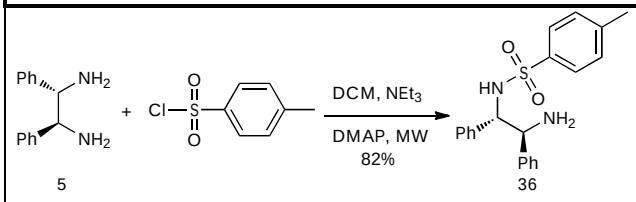
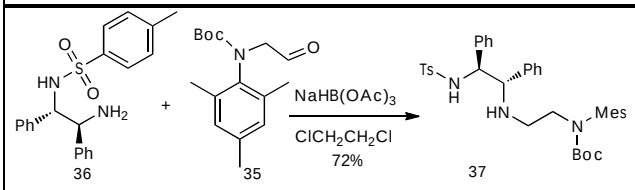
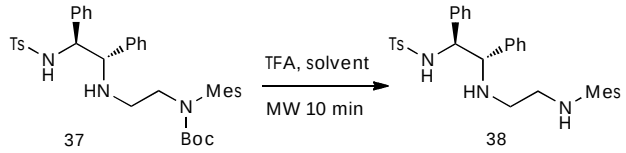
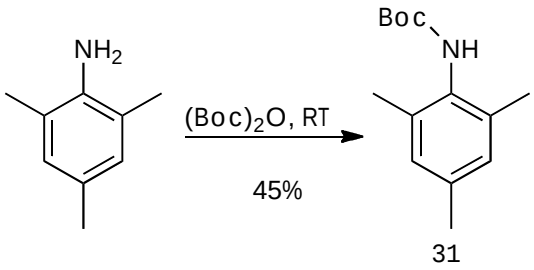
Reaction	React.	Batch	Temp.	Time	Conv. (Yld)
 5 36	1.05 equiv. TsCl	100 mg	MW 100 °C	50 min	>99% (82%)
	1.05 equiv. TsCl	500 mg	MW 100 °C	50 min	96% (94%)
 36 35 37	3 equiv. NaHB(OAc)3	120 mg	RT	18 h.	91% (72%)
	3 equiv. NaHB(OAc)3	860 mg	MW 100 °C	50 min	84% (67%)
 37 38	4 equiv. TFA	270 mg	MW 100 °C CHCl3	10 min	20%
	4 equiv. TFA	270 mg	MW 100 °C DCM	10 min	(97%)

Table 12

In that case, the reductive amination worked better, with 72% isolated yield after 18 hours at RT. By trying to accelerate the reaction in a microwave reactor, a lot of degradation products were observed and only 25% of the diamine 37 was recovered.

The Boc-protected mesitylamine was synthesized using another pathway, developed by Jia (Scheme 63).[159] The mesitylamine was diluted directly in pure $(Boc)_2O$ at RT for 3.5 hours to give the protected amine 31 with 95% conversion, but only 45% of isolated yield. The big advantage of that method was the absence of heating, which causes the liberation of gaseous CO_2. On the other hand, the yield was really low compared to the 91% obtained with the MW irradiation procedure.

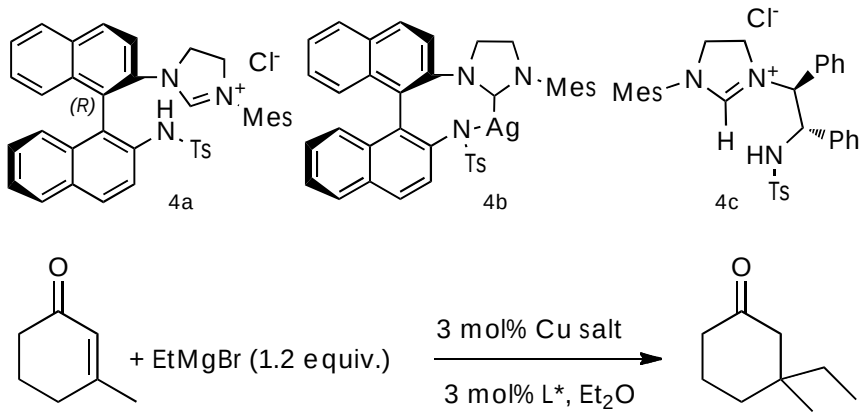


Scheme 63

Another interesting point was the high solvent dependency of the Boc deprotection. Indeed, the reaction done in chloroform gave only 20% conversion after 10 minutes, while the same reaction in DCM gave 97% conversion in the same time scale.

4.4 Application of NHC 4a, 4b and 4c in A.C.A.

The three sulfonamide-based NHC were tested in the A.C.A. of EtMgBr on 3-methylcyclohex-2-enone, in presence of different copper-salts (Table 13).



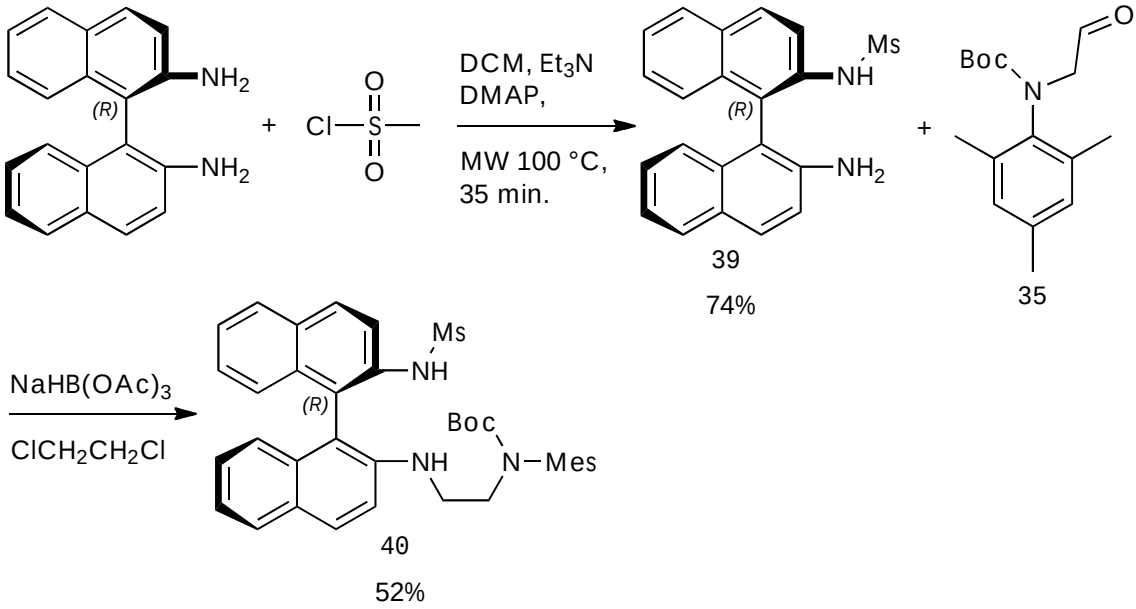
Entry	NHC	CuX	Temp	Add. time	Ratio 1,2:1,4	Conv. [a]	*ee*
1[b]	4a	$Cu(OTf)_2$	0°C	15 min.	25:75	82%	6%
2	4a	$[Cu(OTf)]_2 \bullet C_6H_6$	-10°C	60 min.	0:100	79%	1%
3[c]	4a	$[Cu(OTf)]_2 \bullet C_6H_6$	-20°C	30 min.	0:100	38%[d]	22%
4	4b	$[Cu(OTf)]_2 \bullet C_6H_6$	-20°C	10 min.	0:100	10%	8%
5	4a	$Cu(acac)_2$	-20°C	60 min.	0:100	75%	4%
6	4a	$CuBr_2$	-20°C	60 min.	0:100	80%	4%
7	4a	$Cu(OAc)_2 \bullet H_2O$	-20°C	60 min.	0:100	72%	2%
8	4a	$CuBr \bullet Me_2S$	-20°C	60 min.	0:100	94%	2%
9	4a	$Cu(CNCH_3)_4BF_4$	-20°C	60 min.	0:100	81%	4%
10	4a	CuI	-20°C	60 min.	0:100	77%	2%
11	4a	CuTC	-20°C	60 min.	0:100	81%	8%
12	4c	$CuBr_2$	0°C	30 min.	0:100	92%	13%
13	4c	$[Cu(OTf)]_2 \bullet C_6H_6$	0°C	30 min.	0:100	71%	18%
14	4c	$Cu(OAc)_2 \bullet H_2O$	0°C	60 min.	13:87	99%	12%

(a) conversion determined by GC-MS, after 60 minutes. (b) 3 mol% CuX, 4 mol% L*. (c) Hoveyda best conditions. (d) After 4 hours.

Table 13

The sulfonamide-based NHC gave disappointing results. The Hoveyda's best conditions gave also the best one in our case with 22% *ee*, but the conversion was really poor after four hours (Table 13, Entry 3). By trying to increase the temperature from -20 °C to -10 °C, the *ee* decreased dramatically to a racemate product (Table 13, Entry 2, 3). The use of silver complex 4b gave a really bad conversion of 10% after four hours, and the *ee* was largely worse than the free ImH^+ 4a obtained one (8% to 22% Table 13, Entry 3, 4). The DPEDA-substituted NHC 4c gave also bad *ee*'s around 12% and the regioselectivity was copper-salt dependant. Indeed, when using $Cu(acetate)_2 \bullet H_2O$ or $Cu(OTf)_2$, the regioselectivity was no more totally in favor of the 1,4-addition product (13:87 1,2:1,4 ratio Table 13, Entry 14).

For now, the sulfonamide group seems to be an ineffective chelating group due to the high bulkiness of the sulfone. Other attempts were therefore done with a mesyl instead of a tosyl group as chelating substituent, in order to decrease the steric bulk around the reacting center (Scheme 64). We started the synthesis of the mesylated diamine, using the same procedure as for the tosylated one, to obtain the mono-protected diamine with 74% yield. This was then coupled by reductive amination to give the Boc-protected diamine 40.



Scheme 64

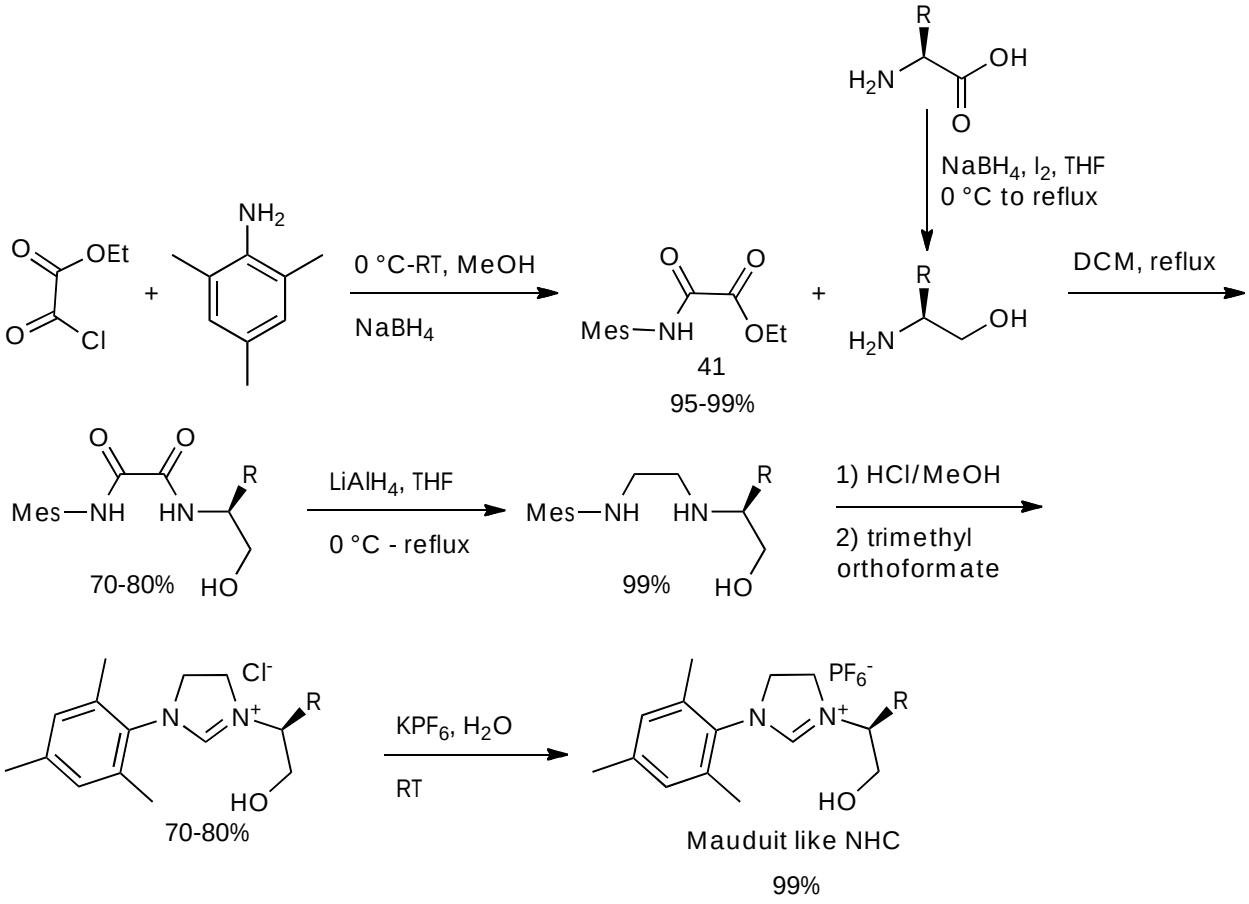
However, the high temperature and copper salt dependency of the ligands added to the poor enantioselectivity obtained since now led us to leave that investigations to find another more efficient coordinating group.

5. *Alkoxy-substituted NHC as chiral ligands for A.C.A.*

The last family of NHC we wanted to study contained an alkoxide as chelating group on the chiral substituent. The alkoxide have the advantage to be a little anchoring atom, compared to the sulfonamide. With its low steric hindrance, it should induce better enantioselectivities than the previous one. Moreover, as the steric hindrance is fixed in space, the corresponding NHC's should also be better stereo-inducing ligands than the C_2-symmetric ones. We started by synthesizing a panel of alkoxy-NHC, with the help of the group of Dr Mauduit in Rennes, France.

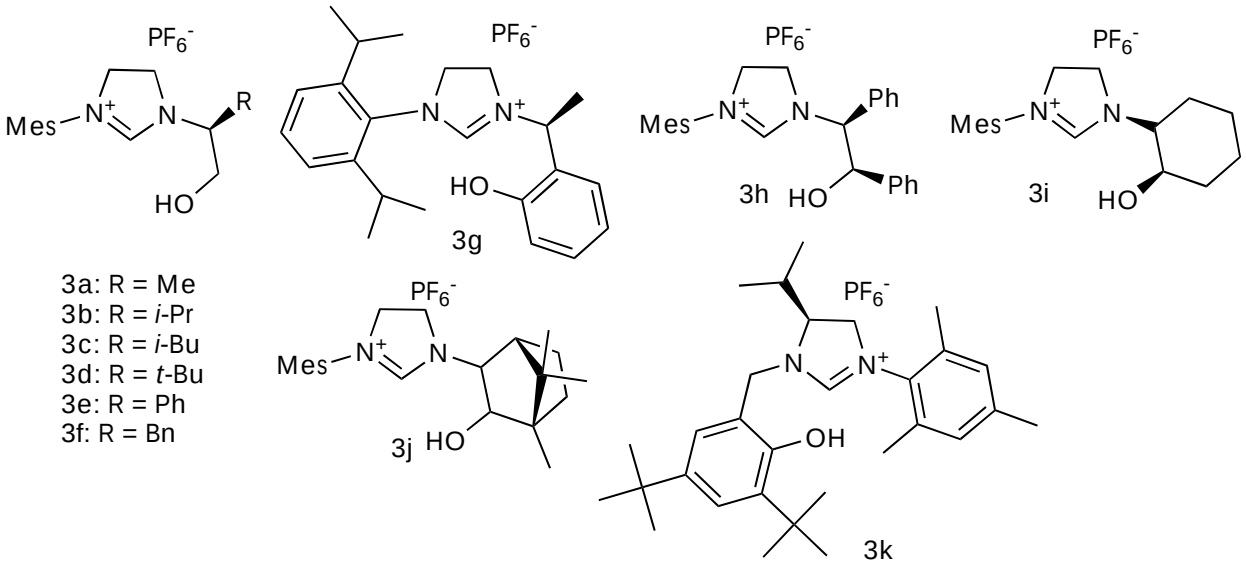
5.1 Synthesis of Mauduit-like NHC's

Most of the Mauduit-like alkoxy-NHC ligands were synthesized following an easy procedure (Scheme 65). The mesitylamine was first coupled to ethyl oxalyl chloride to give the mesityl ester amide. The ester functionality was then attacked by an optically pure amino alcohol in DCM at reflux temperature. This amino alcohol was obtained by reducing the corresponding amino acid with $NaBH_4 - I_2$. The diamide was then reduced to the diamine with $LiAlH_4$, followed by hydrochlorination – cyclization with trimethyl orthoformate to give the pure ImH^+ with around 55% overall yield.



Scheme 65

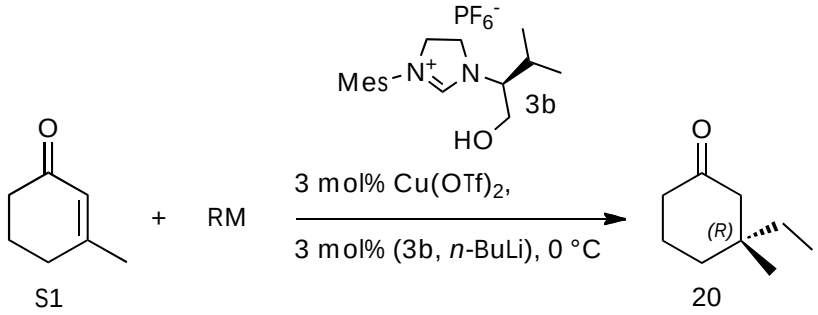
That procedure allowed us to obtain the six different ImH$^+$ 3a-f, Dr Mauduit giving us generously five other ImH$^+$ 3g-k to be tested (Scheme 66).



Scheme 66

5.2 Optimization of the reaction conditions

As for the C_2-symmetric NHC's, we started our study by looking for the most efficient nucleophile. The use of organozinc nucleophiles on the trisubstituted 3-methylcyclohex-2-enone S1 gave no conversion after twelve hours. We therefore decided to compare the nucleophilic addition Et_3Al and EtMgBr to the 3-methyl cyclohex-2-enone (Table 14).



S1 20

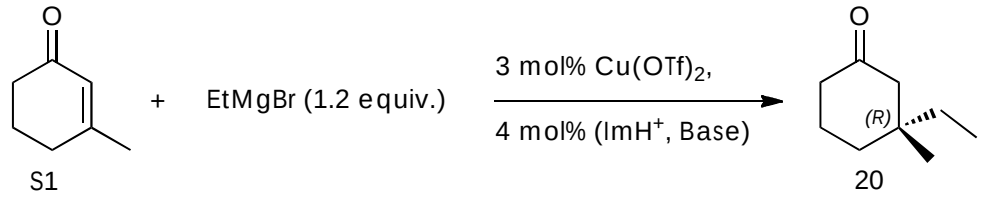
Entry	RM	Time	Conv.[a]	*ee*[b]
1	Et_3Al	16 h.	94%	0%
2	EtMgBr	0.5 h.	96%	61% (+)

(a) determined by GC-MS. (b) determined by chiral GC (Lipodex E).

Table 14

In that case, as for C_2-symmetric NHC, the organomagnesium reagent gave the best results in terms of reaction rate and enantiomeric excess (Table 14, Entry 1). Surprisingly, aluminum reagent, which is known to be an excellent nucleophile when used with phosphorous-based ligands, brings no enantioselectivity to that reaction with NHC's.

A screening of solvents and temperatures was done on the conjugate addition of EtMgBr to the 3-methylcyclohex-2-enone (Table 15).



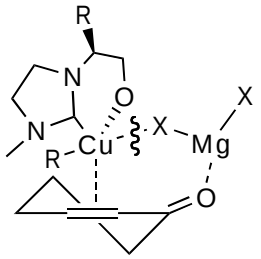
S1 20

Entry	Solvent	ImH+	Base	Temp	Conv.(a)	*ee*(b)
1	Et_2O	3b	*n*-BuLi	0 °C	>99%	69% (+)
2	Et_2O	3b	*n*-BuLi	-30 °C	85%	67% (+)
3	Et_2O	3d	*n*-BuLi	0 °C	>99%	80% (+)
4	Et_2O	3d	-	0 °C	>99%	80% (+)
5	THF	3b	*n*-BuLi	0 °C	92%	26% (+)
6	THF	3b	*n*-BuLi	-78 °C	71%	35% (+)
7	CH_2Cl_2	3b	DBU	0 °C	63%	46% (+)
8	CH_2Cl_2	3b	DBU	-30 °C	66%	44% (+)
9	MTBE	3b	*n*-BuLi	0 °C	47%	49% (+)
10	MTBE	3b	*n*-BuLi	-78 °C	66%	13% (+)

(a) after 30 min. determined by GC-MS; (b) determined by chiral GC (Lipodex E)

Table 15

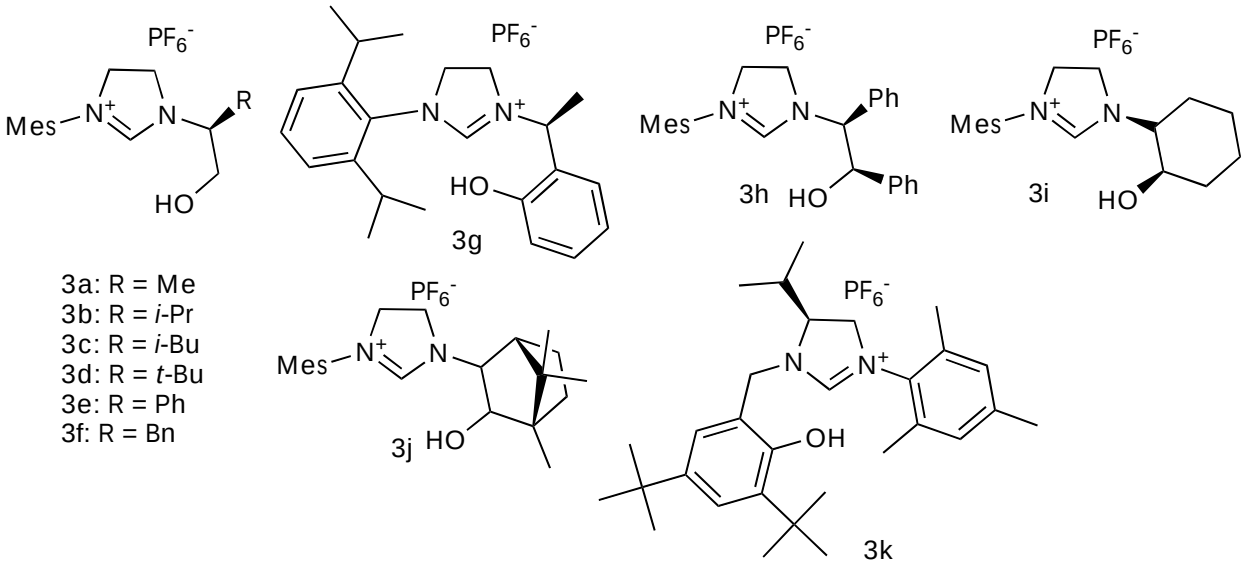
The best results were obtained in Et_2O at 0 °C (Table 15, Entry 1). MTBE, which often showed better enantioselectivities than Et_2O[32] gave worse results in our case (Table 15, Entry 9). The temperature is also an important parameter. Indeed, in all solvents tested (except THF), the *ee* decreased with the temperature. In THF, the opposite was observed (Table 15, Entry 5, 6), but the *ee* was by far the worst of all the solvents tested. That could be explained by the complete solvation of magnesium in THF, which breaks the Cu-Mg-O cluster (Scheme 67). The Cu π bond may be therefore less strongly coordinated to the double bond and the rotation around that bond would loose the stereo-inducing effect of the chiral bulky substituent on the NHC.



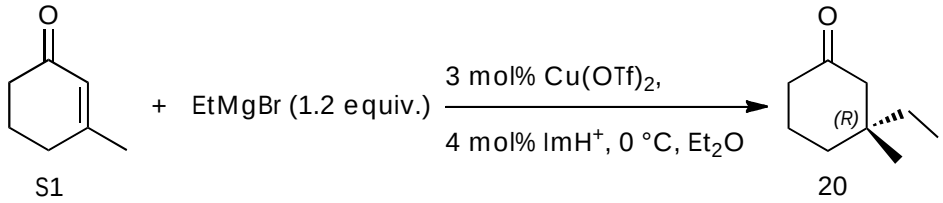
Scheme 67

Another advantage of using Grignard reagents, nearby the easy way to synthesize a broad range of different alkyl or aryl magnesium nucleophiles, is the strong basicity of the compound, which can deprotonate the ImH^+ *in situ*. Indeed, unlike aluminum and zinc nucleophiles, strong bases as *n*-BuLi were not required to activate the ImH^+. The absence of *n*-BuLi had no influence on conversion and *ee* (Table 15, Entry 3, 4). With that defined parameters in hand, we optimized the Cu:NHC ratio. The minimum ratio to obtain the highest *ee* (80%) was 1:1.3. Below that ratio, the *ee* decreased (70% *ee* for 1:1). Surprisingly, by increasing the ratio to 1:2, the *ee* stayed almost unchanged (78% *ee* for 1:2).

With the optimized conditions in hand, we tested the different alkoxy-NHC on the A.C.A. of EtMgBr on the 3-methylcyclohex-2-enone (Table 16).



3a: R = Me
3b: R = *i*-Pr
3c: R = *i*-Bu
3d: R = *t*-Bu
3e: R = Ph
3f: R = Bn



Entry	ImH+	1,2:1,4	Conv.(a)	*ee*(b)
1	3a	0:100	87%	68% (+) R
2	3b	0:100	91%	73% (+) *R*
3	3c	0:100	85%	74% (+) *R*
4	3d	0:100	98%	80% (+) *R*
5	3e	0:100	42%	37% (+) *R*
6	3f	0:100	78%	62% (+) *R*
7	3g	10:90	99%	0%
8	3h	0:100	99%	13% (+) *R*
9	3i	0:100	99%	0%
10	3j	45:55	99%	25% (+) *R*
11	3k	43:57	99%	6% (-) *S*

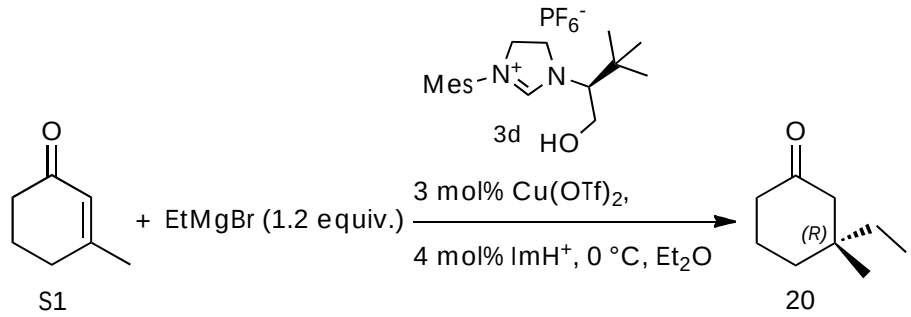
(a) conversion determined by GC-MS, after 30 min. or 3 h. (T < 0 °C). (b) determined by chiral GC (Lipodex E).

Table 16

The results showed clearly that the enantioselectivity of the reaction decreases with the steric hindrance on the nitrogen substituent. Indeed, the best *ee*'s were obtained with *t*-Bu ≈ *i*-Bu > *i*-Pr > Me > Bn >> Ph. As expected, the two aromatic ImH+ 3e and 3f did not bring a strong chiral induction on the reacting center. In fact, as there is no π interaction between the aliphatic Grignard reagent and the phenyl moiety, only the steric hindrance influenced the reaction. By increasing the steric bulk around the reacting center, modifying the chiral or achiral substituent, the regioselectivity of the reaction decreased. Indeed, with exotic ligands 3g, 3k and 3j, the regioselectivity of the reaction decreased dramatically to almost 50:50 for the 1,2:1,4 ratio (Table 16, Entry 7, 10, 11). The active species seemed to became too

hindered to favor the 1,4-addition. 3d gave the best enantioselectivity and led to almost total conversion (Table 16, Entry 4).

The impact of the substrate addition time on the *ee* of the reaction was investigated by using the best ImH^+ 3d in presence or in absence of an additional base (Table 17).



S1 20

Entry	ImH^+	*n*-BuLi	Substr. Add. Time	Conv.[a]	*ee*[b]
1[c]	3d	10 mol%	120 min.	99%	79%
2[c]	3d	-	20 min.	100%	80%
3[c]	3d	10 mol%	20 min.	99%	80%

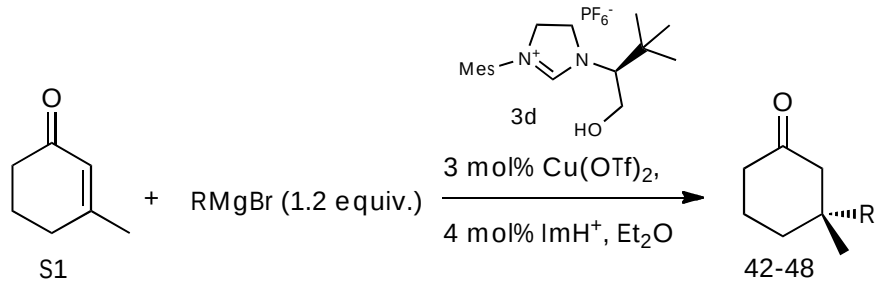
(a) conversion determined by GC-MS, after 15 minutes. (b) determined by chiral GC (Lipodex E). (c) Freshly prepared EtMgBr.

Table 17

The reactions performed with freshly prepared Grignard reagents gave highly reproducible results (Table 17, Entry 1-3). Those experiments allowed to confirm that the presence of an additional base was not necessary (Table 17, Entry 2, 3). Finally, the substrate addition time seemed to be a less important parameter. In fact, by adding the substrate on the preformed complex in 20 or 120 minutes had no impact on the outcome of the reaction (Table 17, Entry 1, 3). As soon as the dropwise addition of diluted substrate reach the ethereal solution, it reacts in a complete 1,4-addition way. The reaction time was therefore shortened. Of course, the addition of the substrate in less than 5 minutes favored the 1,2-addition pathway. Indeed, although the 1,4-addition reaction is largely faster than the 1,2-addition reaction at 0 °C, the presence of a large excess of free Grignard reagent with a large amount of unreacted substrate will promote some 1,2-addition product.

5.3 Scope of the reaction: alkyl Grignard reagents

For now we have reached the optimization of the copper-catalyzed A.C.A. of EtMgBr on 3-methylcyclohex-2-enone in the presence of ligand 3d. We then extended the scope of the reaction to other Grignard reagents on 3-methylcyclohex-2-enone (Table 18).



S1 42-48

Entry	Prod.	R[1]	Temp	Substr. Add. time	Conv.[(a)]	η[(c)]	*ee*[(b)]
1	42	*n*-Bu	0 °C	60 min.	100%	-	78% *R*
2	43	Butenyl	-30 °C	15 min.	91%	80%	90% *S*
3	44	*i*-Bu	-30 °C	60 min.	100%	72%	96% *S*
4		*i*-Pr	0 °C	10 min.	70%[(c)]	0%	nd
5	45	*i*-Pr	-18 °C	50 min.	100%	77%	78% *R*
6	46	*c*-Pent	-15 °C	10 min.	86%	-	84% *R*
7	46	*c*-Pent	-30 °C	15 min.	100%	-	85% *R*
8	46	*c*-Pent	-30 °C	60 min.	100%	80%	86% *R*
9	47	*c*-Hex	-30 °C	10 min.	100%	77%	79% *R*
10		*t*-Bu	-30 °C	10 min.	40%	0%	
11	48	Me-TMS	-30 °C	30 min.	99%	74%	6% *R*
12[(d)]	48	Me-TMS	-30 °C	30 min.	99%	-	0%
13[(e)]	48	Me-TMS	-30 °C	30 min.	99%	-	4% *R*

(a) conversion determined by GC-MS, after 15-30 minutes. (b) determined by chiral GC (Lipodex E). (c) isolated yield. (d) the Grignard reagent is synthesized in Me-THF and Me-THF is used as reaction solvent. (e) the Grignard reagent is synthesized in Me-THF and Et_2O is used as reaction solvent.

Table 18

The bidentate ligand 3d proved to catalyze the regio- and enantioselective A.C.A. of linear and branched Grignard reagents. Indeed, the addition of linear alkyl chains (ethyl, butyl and butenyl) led to *ee*'s around 80% to 90% (Table 17, Entry 4; Table 18, Entry 1, 2). For α-branched nucleophiles (*i*-propyl, *c*-pentyl and *c*-hexyl), the enantioselectivities staid close to the range obtained for linear ones with 78% to 86% *ee* (Table 18, Entry 5, 8, 9). The β-branched nucleophiles gave opposite results. *i*-butyl gave the best result with 96% *ee* (Table 18, Entry 3), but the trimethylsylil substituted nucleophile gave a poor 6% *ee* (Table 18, Entry 11). Knowing that this Grignard reagent was biphasic in Et_2O and the reaction gave almost only racemates in THF, we tried to make the same reaction with the Grignard reagent prepared in 2-methyltetrathydrofuran (Me-THF). Schmalz[160] and co-workers have reported that this solvent gave impressive high *ee*'s in the 1,4-addition of Grignard reagents to the cyclohexenone, whereas the THF gave racemates. Unfortunately, in our case, the obtained *ee* was smaller than 5% by using a Grignard reagent prepared in Me-THF and Et_2O as reaction solvent (Table 18, Entry 13), and 0% when using only Me-THF as Grignard and reaction solvent (Table 18, Entry 12).

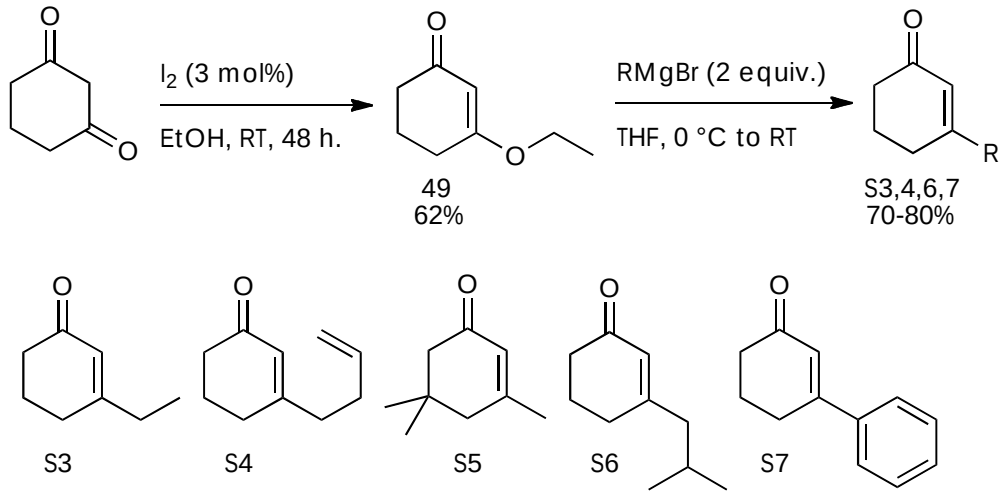
Finally, in contrast to the C_2-symmetric NHC 2e, where a *t*-Butyl group could be inserted in a racemic way (Table 8, Entry 8), the ImH^+ 3d gave 40% conversion of only 1,2-addition product and degradation products after 2 hours (Table 18, Entry 10). The lack of reactivity of the *t*-Butyl organomagnesium nucleophile was certainly due to the sterically hindered β-position, which prevented the approach of such a bulky group. Indeed, in the racemic way, without NHC, the 1,4-addition product was obtained with more than 99% conversion, but with the NHC, a lot of degradation products and 30% of 1,2-addition product were obtained.

The reaction temperature was an important factor. In all cases, the chiral R_2Cu specie seemed to be active between a range of temperatures. Above or below those temperatures, we observed competition in regioselectivity and by-product formations (Table 18, Entry 4-5). Surprisingly, we could expect that when slowing down the reaction rate by decreasing the temperature (-15 °C to -30 °C), the *ee* should increase but no variation was observed (Table 18, Entry 6-7). As the 1,4 and 1,2-additions were competitive, it seemed that when the temperature was below -

40 °C, the 1,4-addition rate decreased faster than the 1,2-addition and the direct addition was consequently promoted.

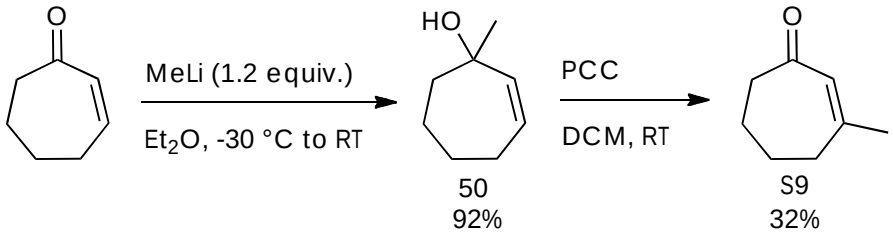
5.4 Scope of the reaction: substrate synthesis

Now that the methodology was well established for the A.C.A. on 3-methylcyclohex-2-enone, we wanted to extend the scope of our researches to different aliphatic substrates. That would confirm that our catalyst was not substrate dependant. We started therefore by synthesizing different linear and branched trisubstituted cyclic enones (Scheme 68). The six-membered rings were synthesized by treating cyclohexanedione with iodine, to form the cyclic ketoenol ether 49 with good yield on a 60-gram scale.[161] This intermediate was then treated with the corresponding Grignard reagent to give the desired substrate in good yield.[16] By this way, we obtained the two substrates S3-S4, one β-branched S6 and one aromatic substituted substrate S7. To test the activity of our complex on an inactivated cyclic enone, we used the commercially available isophorone S5.



Scheme 68

The seven-membered ring was synthesized by applying a procedure published by Dauben (Scheme 69).[162] Cycloheptenone was treated with methyl lithium to give the corresponding tertiary allylic alcohol 50 in good yield. This last product was mixed with pyridinium chlorochromate (PCC) to form an oxochromium complex, which after migration gave the desired methyl cycloheptenone in poor yield.



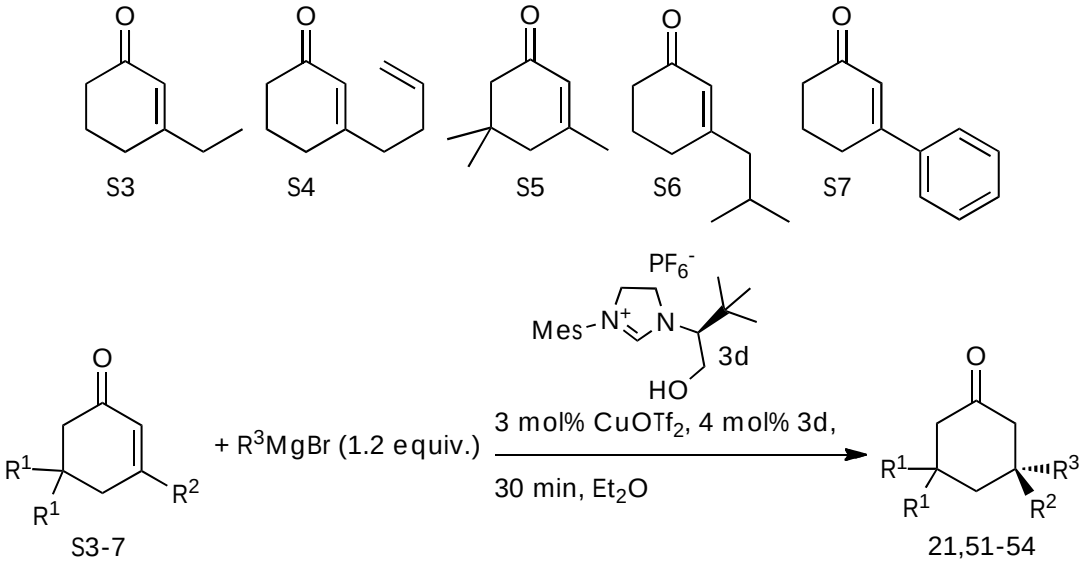
Scheme 69

Finally, we also used commercially available methylcyclopentenone S8 to observe the behavior of our catalyst on five-membered ring substrates.

5.5 Scope of the reaction: substrate variation with alkyl Grignard reagents

5.5.1 Six-membered cyclic substrates

We started first by investigating the scope of the reaction on different six-membered cycles (Table 19).



Entry	Substr.	Prod.	R^3	Temp	Conv.[a]	η[c]	ee[b]
1	S3	21	Me	0 °C	98%	67%	68 (-) *S*
2	S4	51	Et	0 °C	99%	84%	69 (+) *R*
3	S5	52	Et	0 °C	100%	85%	82 (+) *R*
4	S6	53	Et	0 °C	98%	69%	81 (+) *R*
5	S7	54	Et	0 °C	98%	87%	72 (+) *S*

(a) conversion determined by GC-MS, after 30 minutes. (b) determined by chiral GC (Lipodex E). (c) isolated yield.

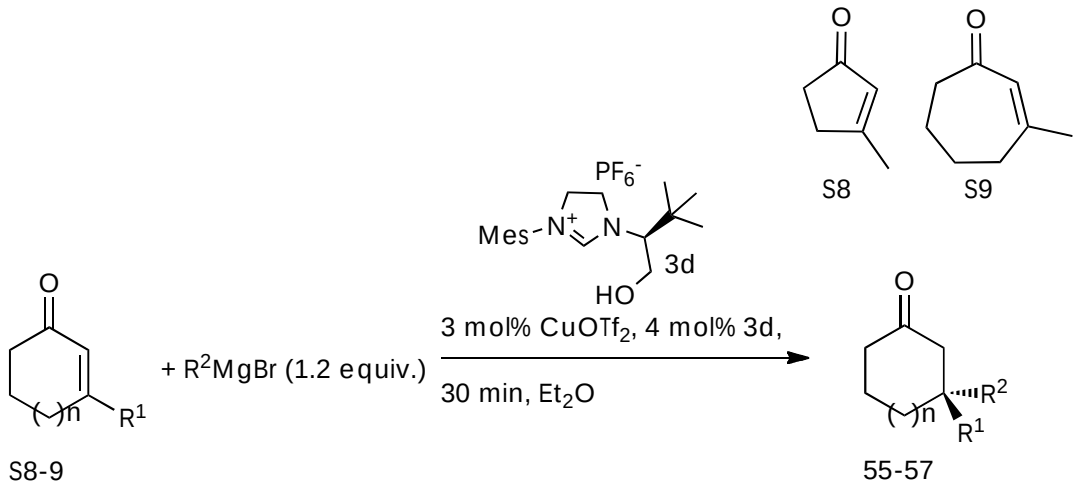
Table 19

The obtained results showed that the NHC*-Cu catalyzed 1,4-addition of Grignard reagents on substituted cyclohexenones is a valuable method to form a large variety of all-carbon quaternary chiral centers in high yield and good *ee*'s. The substrates containing a linear substituent (S3-S4) gave good *ee*'s around 70% (Table 19, Entry 1-2). This result was not surprising for the addition of MeMgBr. It is well known that methyl nucleophiles were poorly reactive and were difficult to add with good stereo-control. A motivating point was the good *ee* obtained with the low reactive isophorone S5 (Table 19, Entry 3). By going to a bulkier *i*-butyl substituent, the enantio-discrimination worked better and the *ee*'s rose up to 81% (Table 19, Entry 4). Another promising result was obtained with the addition of EtMgBr on the phenyl substituted substrate S7 (72% *ee*) (Table 19, Entry 5). A general trend, as for C_2-symmetric NHC's, is the total facial selectivity obtained with the NHC 3d. Indeed, we always obtained

the opposite major enantiomer by inverting the nucleophile and the substituent on the substrate. In contrast to the C_2-symmetric 2a ImH^+, the stereoselectivity for the ligand 3d is on the *Si*-face.

5.5.2 Five- and seven-membered cyclic substrates

The same trials were performed on five- and seven-membered rings S8 and S9 to observe possible variations in catalysis (Table 20).



Entry	Substr.	Prod.	R^3	Temp	Conv.[a]	η[c]	*ee* [b]
1	S8	55	Et	0 °C	98%	90%	38 (+) *R*
2	S8	55	Et	-10 °C	98%	90%	46 (+) *R*
3	S8	56	*i*-Bu	-30 °C	99%	-	24 *S*
4	S9	57	Et	0 °C	99%	76%	82 (+) *R*

(a) conversion determined by GC-MS, after 30 minutes. (b) determined by chiral GC (Lipodex E). (c) isolated yield.

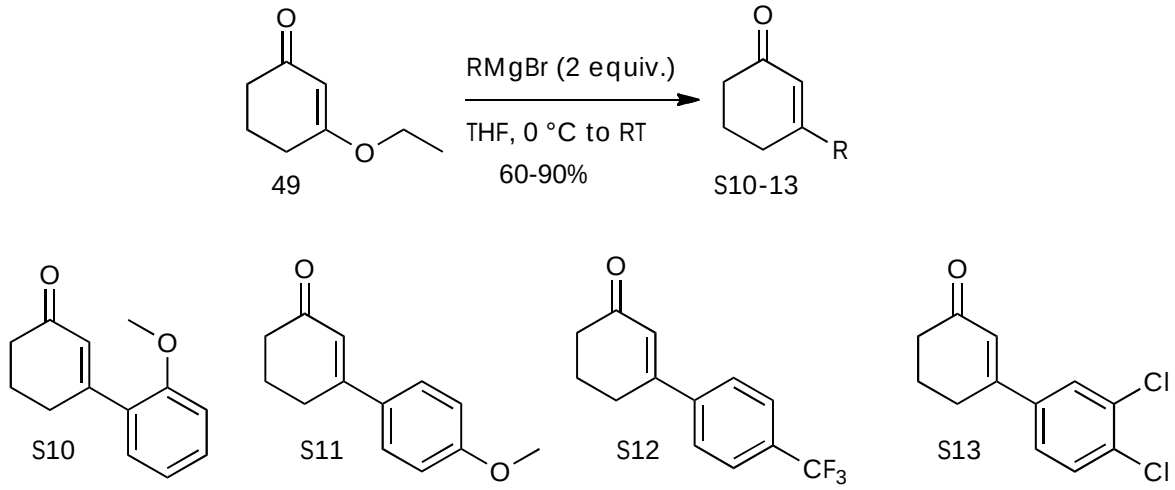
Table 20

The experiments realized on varying the ring size gave interesting results. In the case of S8, contrary to the six-membered ring, the temperature played an important role. Indeed, the *ee* rose up from 38% at 0 °C to 46% at -10 °C (Table 20, Entry 1, 2). The *i*-butyl nucleophile, which gave the best *ee* (96%) on the 3-methylcyclohex-2-enone, gave a disappointing 24% *ee* in the case of the five-membered analogue S8 (Table 20, Entry 3).

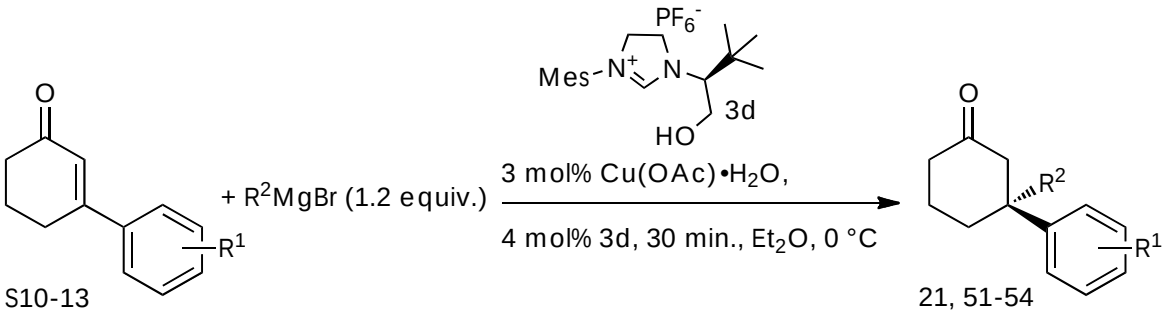
On the other hand, the seven-membered substrate S9 gave the same range of *ee* than those obtained with the six-membered rings (Table 20, Entry 4). It seems therefore that the five-membered ring is too small to permit a good approach of the catalyst, which led to a low enantio-control.

5.5.3 Substituted aromatic substrates

As the addition of EtMgBr on the phenylcyclohexenone S7 gave a promising 72% *ee* (Table 19, Entry 5), new aromatic substrates containing electro-attracting and withdrawing aryl groups were synthesized (Scheme 70). We used the same methodology developed previously to observe the electronic effects on the A.C.A. of different alkyl magnesium nucleophiles (Table 21).



Scheme 70



Entry	Substr.	Prod.	R	Cu mol%	ImH+ mol%	Conv.(a)	η(c)	Ratio 1,2:1,4	ee(b)
1	S10	58	Et	3	0	97%		23:77	0%
2	S10	58	Et	5	7.5	nd		nd(d)	
3	S10	58	Et	10	13	40%	nd	99:1	
4(e)	S10	58	Et	5	7.5	99%		98:2	
5	S11	59	Et	3	4	84%	86%	52:48	78% *S*
6	S11	60	Me	5	7	90%	nd	55:45	15% *S*
7(f)	S11		*i*-Bu	10	0	75%	nd	95:5	0%
8(f)	S11		*i*-Bu	5	7.5	60%	nd	99:1	
9(f)	S11		*i*-Bu	8	10	85%	nd	95:5	nd
10	S12	61	Et	3	0	95%	nd	95:5	0%
11	S12	61	Et	3	4	99%	72%	33:67	80% *S*
12	S13	62	Et	3	4	99%	86%	20:80	80% *S*
13	S13	63	Me	5	7	99%	51%	51:49	23% *S*

(a) conversion determined by GC-MS, after 60 minutes. (b) determined by chiral GC Hydrodex-B-3P. (c) isolated yield. (d) not possible to separate, decomposition products. (e) left at 0 °C for 16 hours. (f) reaction done at -30 °C.

Table 21

The obtained results were very interesting in term of regioselectivity. Indeed, the racemic addition of EtMgBr on the *ortho*-substituted aromatic substrate S10 gave a racemate with a 1,2:1,4 ratio of 23:77. But by adding the chiral complex, the regioselectivity was inversed and the 1,2-addition product became favored (Table 21, Entry 1-3). As the addition of more catalyst did not changed the outcome of the

reaction, we concluded that the *o*-OMe substituted substrate S10 is too stericaly hindered to allow the approach of the bigger NHC-Cu complex, in contrast to the free copper complex.

The *p*-OMe electron-donating substrate S11 gave 78% *ee* for the addition of EtMgBr, but the MeMgBr gave a poor 15% *ee* (Table 21, Entry 5, 6). The regioselectivity around 50:50 in the two cases was mediocre, but by increasing the bulkiness of the nucleophile to *i*-Butyl, the 1,2-addition was favored (95:5) (Table 21, Entry 8, 9). This observation was consistent with the bigger size of the nucleophile (Table 21, Entry 7). When going to electron-withdrawing substrates, the outcomes of the reaction change drastically. Indeed, the *p*-CF_3 substrate S12 gave a very good 80% *ee* with a regioselectivity of 33:67 in favor of the 1,4-addition product (Table 21, Entry 11). The regioselectivity was even better starting from the chloro-substituted adduct S13 (20:80) with keeping a high enantio-control (Table 21, Entry 12). In contrast, the racemic version of the reaction with S12 gave a very bad regioselectivity of 95:5 in favor of the 1,2-addition product (Table 21, Entry 10).

For these reactions, the regioselectivity depend on the electronic effects of the aromatic substituents. Indeed, by comparing S11, S12 and S13, one may observe that the electron-donating –OMe group (Table 21, Entry 5), by decreasing the reactivity of the β-position, gave worse regioselectivity than the electron-withdrawing –CF_3 (Table 21, Entry 11) and -Cl substituents (Table 21, Entry 12). These groups activate the β-position of the cyclic substrate by decreasing its electronic density, and doing so, increased the electrophilicity of that position. The 1,4-addition was therefore favored.

Another interesting point was the effect of the NHC on the regioselectivity of the reaction. For S12, when only copper was added without the ligand to catalyze the reaction, the regioselectivity was largely in favor of the direct addition (95:5) (Table 21, Entry 10). However, when the NHC 3d was added, the regioselectivity was inverted and the 1,4-addition was favored. The ligand effect could be explained by the NHC electron-donor ability to the copper center. As there is only little steric hindrance, the more electron-rich copper center reacts faster on the β-position of

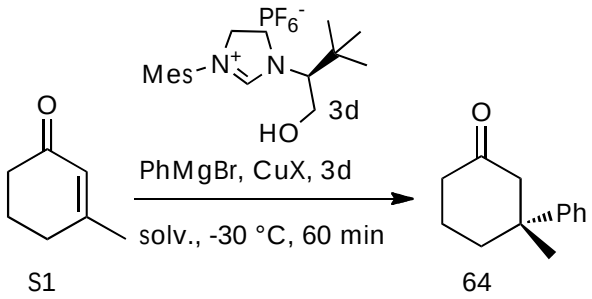
the -CF_3 substituted substrate than the less electron rich free copper, and by the way, renders the 1,4 –addition favored compared to the 1,2-addition.

5.6 Scope of the reaction: aryl Grignard reagents on alkyl-substituted cyclohexenone

As described previously, the conjugate addition on trisubstitued enones is a tricky reaction. But with the promising results obtained with aliphatic Grignard reagents, we increased the challenge and tried to insert aromatic Grignard reagents. These reactions were not only difficult in term of enantioselectivity, but also in term of regioselectivity. There were only few papers concerning A.C.A. describing the formation of quaternary carbon centers containing an aromatic cycle. Most of the time, the aromatic group was already on the substrate[34,44] or only phenyl and *p*-anisyl[132,133,137] were inserted. It was only recently, that our group proposed a viable method to insert a large panel of aromatic aluminum species.[163] Therefore, we tried to apply our methodology to the addition of aromatic organomagnesium reagents on aliphatic cyclohexenones.

5.6.4 Optimization of the reaction conditions: copper salts and solvents screening

To start the study, we tested the addition of a simple aromatic organomagnesium nucleophile, PhMgBr, on 3-methylcyclohex-2-enone. As the optimized conditions for the addition of alkyl Grignard reagents on alkyl-substituted cyclohexenone gave only 62% *ee* and an average regioselectivity of 35:65 (Table 22, Entry 1) we first screened the solvents and copper salts to find out the best conditions for this new reaction (Table 22).



S1 64

Entry	Solv.	CuX	Add. time	Conv.[a]	Ratio 1,2:1,4	*ee*[b]
1		$Cu(OTf)_2$		72%	35:65	62%
2		$Cu(acac)_2$		>99%	23:78	57%
3		$CuBr_2$		>99%	5:95	65%
4	Et_2O	$Cu(OAc)_2 \cdot H_2O$	20 min.	99%	12:88	70%
5[c]		$Cu(OAc)_2 \cdot H_2O$		99%	18:82	70%
6		$CuBr \cdot Me_2S$		45%	33:67	32%
7		$Cu(CNCH_3)_4BF_4$		>99%	15:85	51%
8		CuI		85%	63:37	70%
9		CuTC		>99%	28:72	66%
10		$Cu(acac)_2$		98%	22:78	50%
11		$CuBr_2$		>99%	29:71	53%
12		$Cu(OAc)_2 \cdot H_2O$		98%	99:1	nd
13	MTBE	$CuBr \cdot Me_2S$	20 min.	>99%	31:69	46%
14		$Cu(CNCH_3)_4BF_4$		>99%	25:75	38%
15		CuI		98%	99:1	nd
16		CuTC		99%	29:71	56%
17	DCM	$Cu(acac)_2$	20 min.	98%	16:84	58%
18		$CuBr_2$		>99%	21:79	48%
19		$Cu(OAc)_2 \cdot H_2O$		88%	30:70	44%
20		$CuBr \cdot Me_2S$		93%	19:81	44%
21		$Cu(CNCH_3)_4BF_4$		>99%	29:71	48%

22		CuI		97%	84:16	46%
23		CuTC		99%	25:75	56%
24		$Cu(acac)_2$		>99%	14:86	0%
25		$CuBr_2$		>99%	13:87	0%
26		$Cu(OAc)_2 \bullet H_2O$		>99%	7:93	3%
27	THF	$CuBr \bullet Me_2S$	20 min.	>99%	12:88	3%
28		$Cu(CNCH_3)_4BF_4$		>99%	23:77	2%
29		CuI		>99%	23:77	0%
30		CuTC		>99%	28:72	1%
31		$Cu(acac)_2$		86%	12:88	12%
32		$CuBr_2$		78%	29:71	5%
33		$Cu(OAc)_2 \bullet H_2O$		65%	33:67	8%
34	THP	$CuBr \bullet Me_2S$	20 min.	69%	23:77	15%
35		$Cu(CNCH_3)_4BF_4$		35%	54:46	11%
36		CuI		36%	73:27	4%
37		CuTC		77%	21:79	17%
38		$Cu(acac)_2$		>99%	52:48	54%
39		$CuBr_2$		>99%	44:56	54%
40		$Cu(OAc)_2 \bullet H_2O$		>99%	98:2	nd
41	Toluene	$CuBr \bullet Me_2S$	20 min.	>99%	45:55	54%
42		$Cu(CNCH_3)_4BF_4$		>99%	49:51	49%
43		CuI		>99%	97:3	nd
44		CuTC		>99%	48:52	52%

(a) conversion determined by GC-MS, after 30 minutes. (b) determined by chiral GC (Hydrodex-B-3P). (c) done with Cl^- instead of PF_6^- as counter-ion.

Table 22

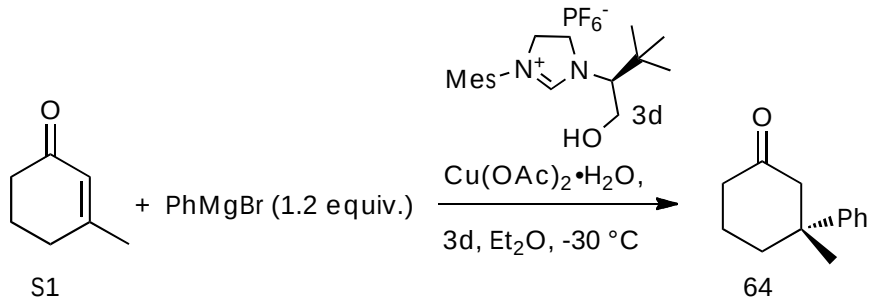
Compared to the methodology using alkylgrignard reagents, Et_2O remained the best solvent for the reaction, but $Cu(OAc)_2 \cdot H_2O$ gave the best results in terms of regio- and enantioselectivity. Interestingly, as for the *C_2*-symmetric ImH^+ 2e, the variation of the counter-ion had no effect on the enantioselectivity of the reaction (Table 22, Entry 4, 5). In that case, contrary to the work of Loh[32], MTBE gave worse results than Et_2O in both regio- and enantioselectivities (Table 22, Entry 3, 11; 4, 12; 6, 13).

DCM gave a lower regioselectivity, and the *ee*'s were about 20% lower than with their Et_2O counterparts, but that solvent was not bad for this reaction (Table 22, Entry 17-23). THF, which coordinates strongly to the magnesium, gave very good regioselectivities but almost only racemates (Table 22, Entry 24-30). By using THP (tetrahydropyrane) as solvent, the regioselectivity remained acceptable; the *ee*'s increased a little, but the reactivity of the complex drops down, with an average of 46% conversion after 1 hour (Table 22, Entry 31-37).

Finally, toluene, which was expected to bring some beneficial π-π interaction with the Grignard reagent, showed poor enantioselectivity and moderate regioselectivity around 50:50 for all the tested copper salts (Table 22, Entry 38-44).

5.6.5 Optimization of the reaction conditions: variation of copper / NHC ratio

A study of copper : NHC ratio was then done in order to improve the 1,2:1,4 ratio and the *ee*'s of the reaction.



S1 64

Entry	Cu :NHC	Cu (mol%)	Add. time	Conv.(a)	Ratio 1,2:1,4	*ee*(b)
1	1 : 1	3	7 min.	99%	41:59	60%
2	1 : 1.3	3	20 min.	99%	12:88	70%
3	1 : 1.3	10	7 min.	>99%	22:78	53%
4	1 : 1.5	3	7 min.	99%	37:63	71%
5	1 : 1.5	3	60 min.	>99%	28:72	70%
6	1 : 2	3	7 min.	98%	35:65	68%

(a) conversion determined by GC-MS, after 60 minutes. (b) determined by chiral GC Hydrodex-B-3P

Table 23

As for the alkyl Grignard reagents, the *ee* was not influenced by the addition time, but the regioselectivity was largely better when the addition was done slowly (Table 23, Entry 4, 5). By increasing the substrate addition time, the regioselectivity improved strongly, going from 22:78 to 12:88 (Table 23, Entry 3, 2). This would imply that the catalytic cycle of the aryl Cu-NHC complexe was slower than for its alkyl counterpart. Indeed, by using alkyl Cu-NHC complexes in the same range of addition time, only 1,4-addition product was observed. For aryl ones, if the substrate was added too quickly, the catalytic cycle was too slow to absorb it completely, and a part of the substrate was therefore consumed by the free Grignard reagent in excess in the reaction, giving 1,2-addition products. This hypothesis was supported by the addition of an increasing amount of copper to 10 mol%. Indeed, the reaction with three times more catalyst gave an improvement in the regioselectivity going from around 37:63 to 22:78 (Table 23, Entry 4, 3). In contrast, the *ee* decreased dramatically from 70% to 53% with formation of a brown aggregate. In fact, as the Cu-NHC complex was poorly soluble in Et_2O, the presence of a too high

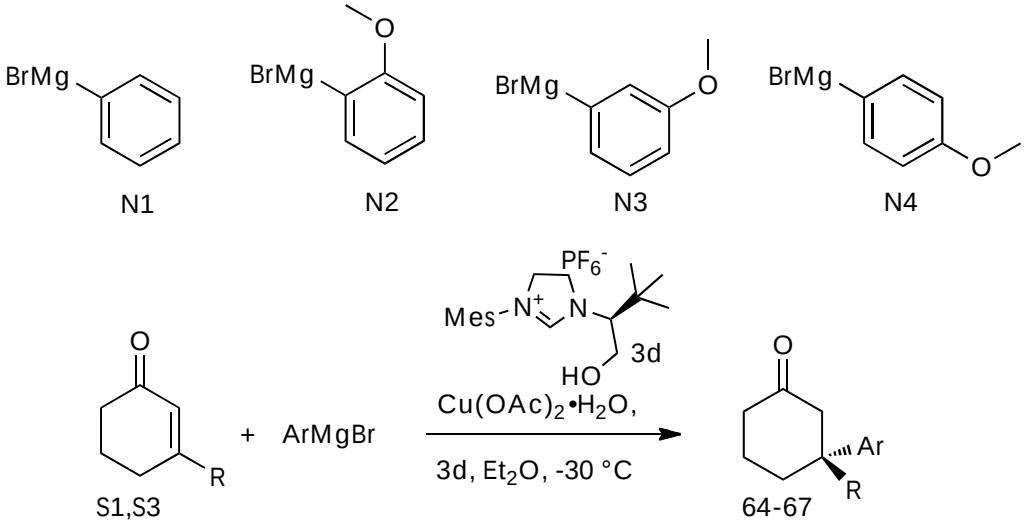
concentration of complex favors the aggregation of an insoluble NHC:Cu heap of unknown ratio. That could leave some free copper in solution, which by giving only racemic product, lowers the total enantioselectivity of the reaction but increase the regioselectivity.

The Cu:NHC ratio is also important. There is a maxima around 1:1.5. Below and above this ratio, the *ee* diminish (Table 23, Entry 1, 5, 6). Surprisingly, the regioselectivity in favor of the conjugate addition was better when the formed complex contains more than one NHC. Indeed, with a 1:1 ratio, the regioselectivity was worse than for a 1:1.5 or 1:2 ratio. This effect could be explained by the electron-donating effect of the NHC. Although the steric hindrance increases in the presence of more NHC, which should disadvantage the conjugate addition, the electron density brought by the extra NHC on the reacting center may accelerate the catalytic cycle, and by the way, favors the 1,4 addition.

These improvements attempts have not brought the expected results, because the 1,2:1,4 ratio could not be enhanced. We could lower the Cu:NHC ratio to 1:1,3 by keeping a high *ee* and good regioselectivity (Table 23, Entry 2), which means that the best ratio for alkyl additions was also the best for aryl ones and the optimized reaction conditions were: 3 mol% of $Cu(OAc)_2 \bullet H_2O$, 4 mol% ImH^+ 3d at -30 °C in Et_2O. The substrate had to be added in 30 minutes.

5.6.6 Conjugate addition of Aryl Grignard reagents on alkyl cyclohexenone

New aromatic Grignard reagents N1-N4 were freshly synthesized by adding dropwise an ethereal solution of aryl bromide onto magnesium turnings. We then used these aromatic Grignard regents on the two alkylcyclohexenone S1 and S3.



S1 R = Me
S2 R = Et

Entry	Prod.	R-	Ar-	Cu mol%	NHC mol%	Conv.(a)	Ratio 1,2:1,4	*ee*(b)
1(d)	64	Me	N1	3	4	99%	12:88	70% (-) *R*
2	65	Et	N1	3	4	98%		34% (-) *R*
3		Me	N2	3	4	>99%	100:0	nd
4		Me	N2	5	6.5	>99%	98:2	nd
5	66	Me	N3	5	6.5	67%	70:30	90% *R*
6		Me	N4	3	4	>99%	100:0	nd
7	67	Me	N4	5	6.5	>99%	77:23	70% *R*
8		Et	N4	3	4	97%	100:0	nd
9(c)		Et	N4	3	4	98%	100:0	nd

(a) conversion determined by GC-MS, after 60 minutes. (b) determined by SFC. (c) reaction done at -14 °C. (d) taken from Table 22, Entry 4.

Table 24

All the results were worse than for the PhMgBr, especially in term of regioselectivity. By increasing the substrate substituent alkyl chain from one carbon, namely going from S1 to S3, made the *ee* sinking from 70% to 34% for the addition of PhMgBr N1 (Table 24, Entry 1, 2). The *o*-anisol derivative N2 was the worst one. The reaction worked almost in a complete 1,2-addition way. No *ee* was obtained, even if the

copper amount was increased to 5 mol% (Table 24, Entry 4). The *m*-anisol N3 gave an excellent 90% *ee*, but the regioselectivity was strongly in favor of the 1,2-addition product, even if 5 mol% of catalyst were added (Table 24, Entry 5). Surprisingly, under the same conditions, although the *p*-anisol N4 should be less bulky than his *meta*-counterpart N3, it gave even worse enantio- and regioselectivity.

For N2, it is clear that the steric bulkiness issued from the *ortho*-methoxy group prevented the approach on the stericaly hindered β-position. But for the *meta*- and *para*-methoxy N3 and N4, it is less obvious. Electronic effects could explain the differences of regioselectivities. Indeed, the electron-donor methoxy group in *para*-position brings more electron density to the nucleophile, making it harder, and by doing so, making it more reactive. It means that the catalytic cycle becomes even less competitive against the free nucleophile, entering in a 1,2-addition way. The same electron-donor group in the *meta*-position brings no extra electronic density on the carbon nucleophile and the steric bulkiness is barely bigger than his *para*-counterpart. Thereby, as the steric hindrance is almost the same for N3 and N4, but the N4 is more nucleophilic, it could explain that there is more 1,2 product using *para*- then *meta*-methoxy substituted phenyl Grignard reagents.

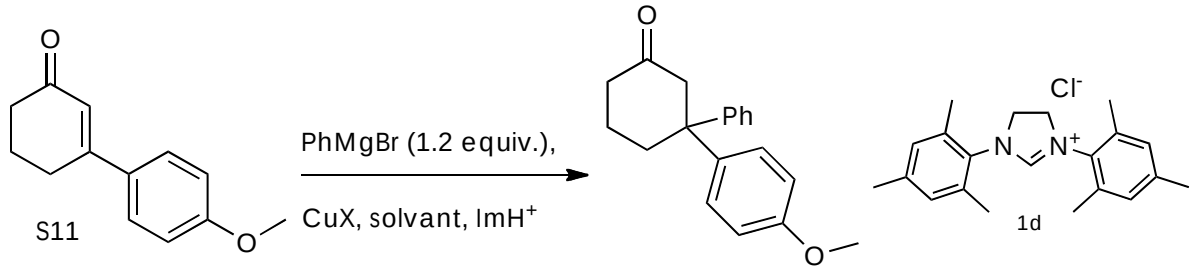
Other attempts with electron-withdrawing nucleophiles, like *para*-CF_3 phenyl Grignard reagents should be synthesized to confirm this results. But as N2, N3 and N4 were biphasic in Et_2O, the titration was almost impossible and the reactions were therefore qualified as not sufficiently user-friendly in contrast to the organoaluminum route developed in our group.[163] This explained why we stopped the investigations in that field.

5.7 Scope of the reaction: aryl Grignard reagents on aryl-substituted cyclohexenone

To see the limitations of our methodology, we went one step further and tried to form quaternary chiral centers containing two aromatic cycles. As the reaction was never reported before, we had first to determine the experimental conditions.

5.7.1 Optimization of the reaction conditions: racemic conjugate addition

We started by investigating the reactivity of a trisubstituted aromatic substrate by using PhMgBr and an achiral ImH^+, in order to look at the NHC effect (Table 25).



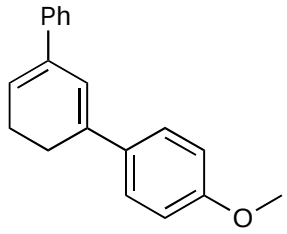
Entry	ImH^+	CuX in mol%	Temp	Add. Time	Conv.[a]	Ratio 1,2:1,4
1	-	$Cu(OTf)_2$ 5%	-20 °C	15 min	95%	100 :0
2	-	$Cu(OTf)_2$ 10%	-30 °C	15 min	93%	100 : 0
3[b]	-	CuCN 110%	0 °C	15 min	0%	
4[c]	-	CuBr•Me_2S 5% + TMSCl	-30 °C	8 min	98%	100 : 0
5	1d	$Cu(OTf)_2$ 5%	-25 °C	15 min	92%	100 : 0
6	1d	$Cu(OTf)_2$ 10%	-78 °C	15 min	0%	
7	1d	$Cu(OTf)_2$ 10%	RT	15 min	85%	100 : 0
8	1d	$Cu(OTf)_2$ 10% + TMSCl	-50 °C	60 min	0%	
9	1d	CuBr•Me_2S 5% + TMSCl + *n*-BuLi	-30 °C	9 min	99%	100 : 0
10	1d	CuBr•Me_2S 10%+TMSCl + *n*-BuLi	-40 °C	60 min	93%	100 : 0
11[c]	1d	CuBr•Me_2S 10%+TMSCl + *n*-BuLi	-30 °C	60 min	69%	100 : 0
12[d]	1d	CuBr•Me_2S 10%+TMSCl + *n*-BuLi	0 °C	60 min	>99%	100 : 0
13	3d	$Cu(OTf)_2$ 6%	-30 °C	16 min	92%	100 : 0
14	3d	$Cu(OTf)_2$ 6% + TMSCl	-30 °C	11 min	62%	100 : 0

(a) determined by GC-MS, after 30 minutes. (b) reaction done with LiCl (2 equiv,) CuCN (1.1 equiv.), PhLi (2 equiv.) in THF, 2 hours. (c) mixture of Cu, TMSCl and substrate was added dropwise on Grignard reagent. (d) TMSCl and substrate were added on the preformed cuprate.

Table 25

The obtained results were not encouraging. None of the tested system allowed to catalyze the addition of a second aromatic group on the β-position of the enone. The racemic pathway using free copper gave only 1,2-addition product (Table 25, Entry 1, 2). We tried to increase the reactivity of the copper specie, by forming a Lipshutz cyanocuprate synthesized with PhLi (2 equiv.), LiCl (2 equiv.) and CuCN (1.1 equiv.) in THF. Unfortunately, as the stoechiometric amount of copper left no free phenyls in solution, nor the 1,4 neither the 1,2-addition occurred and we obtained only starting material after 2 hours (Table 25, Entry 3). The application of Knochel's procedure,[164] which was used to add aryl Grignard reagents on cyclic enones, gave only the 1,2-addition product on the cyclic enone S11 (Table 25, Entry 4).

As NHC's brings more electron-density on the TM, we tried to add the racemic IMes 1d in the reaction in order to increase the nucleophilicity of the copper complex. Unfortunately, only the 1,2-addition product was recovered. We also tried to add TMSCl as β-activator. Indeed, the oxophilic silicon should bind the enone's oxygen and lower its electron-density. By doing so, the partial positive charge δ^+ of the β-position should increase and therefore becomes more electrophilic and reactive. But in that case as for the others, only 1,2-addition product was obtained (Table 25, Entry 8-12). Moreover, by lowering the temperature under -40 °C, no reaction occurred (Table 25, Entry 6, 8). It means that we could not vary the temperature range to favor the 1,4-addition versus the 1,2-addition. Finally, we tried to use the chiral 3d ImH^+, to see if the presence of an alkoxide on the NHC could changes the regioselectivity of the reaction. But as for the other cases, only the 1,2-addition product was obtained (Table 25, Entry 13, 14) (Scheme 71).



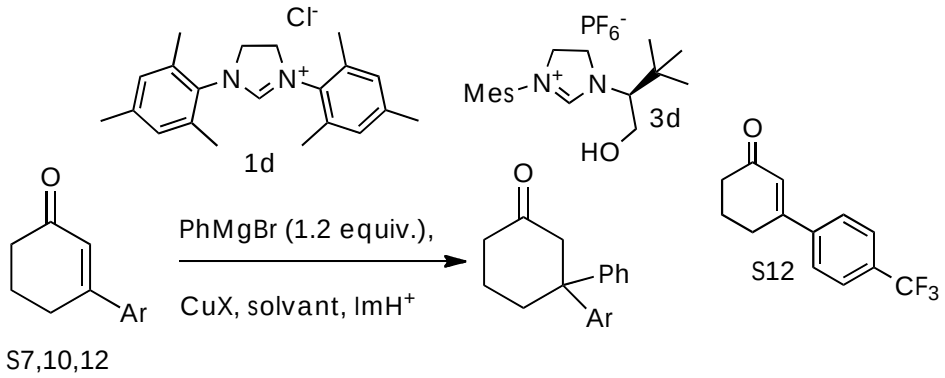
1,2 addition product

Scheme 71

5.7.2 Aromatic substrate variation

Before leaving this investigation field, we tried to do the same reaction on another electron-withdrawing substrate to ensure that the catalytic cycle inertia is not due to

electronic effects on substrate S11. Indeed, the *para*-methoxy electron-donating group brings some extra electron-density at the β-position of the enone, and by the way, lowers the electrophilicity of this position.



Entry	ImH+	Substr.	CuX (mol%)	Temp	Substr. Add. Time	Conv.(a)	Ratio 1,2:1,4
1	3d	S12	$Cu(OTf)_2$ (6)	0 °C	10 min	39%	100:0
2(b)	1d	S12	CuBr•Me_2S (10) + TMSCl + *n*-BuLi	-30 °C	8 min	95%	99:1

(a) conversion determined by GC-MS, after 30 minutes. (b) using Knochel's procedure.

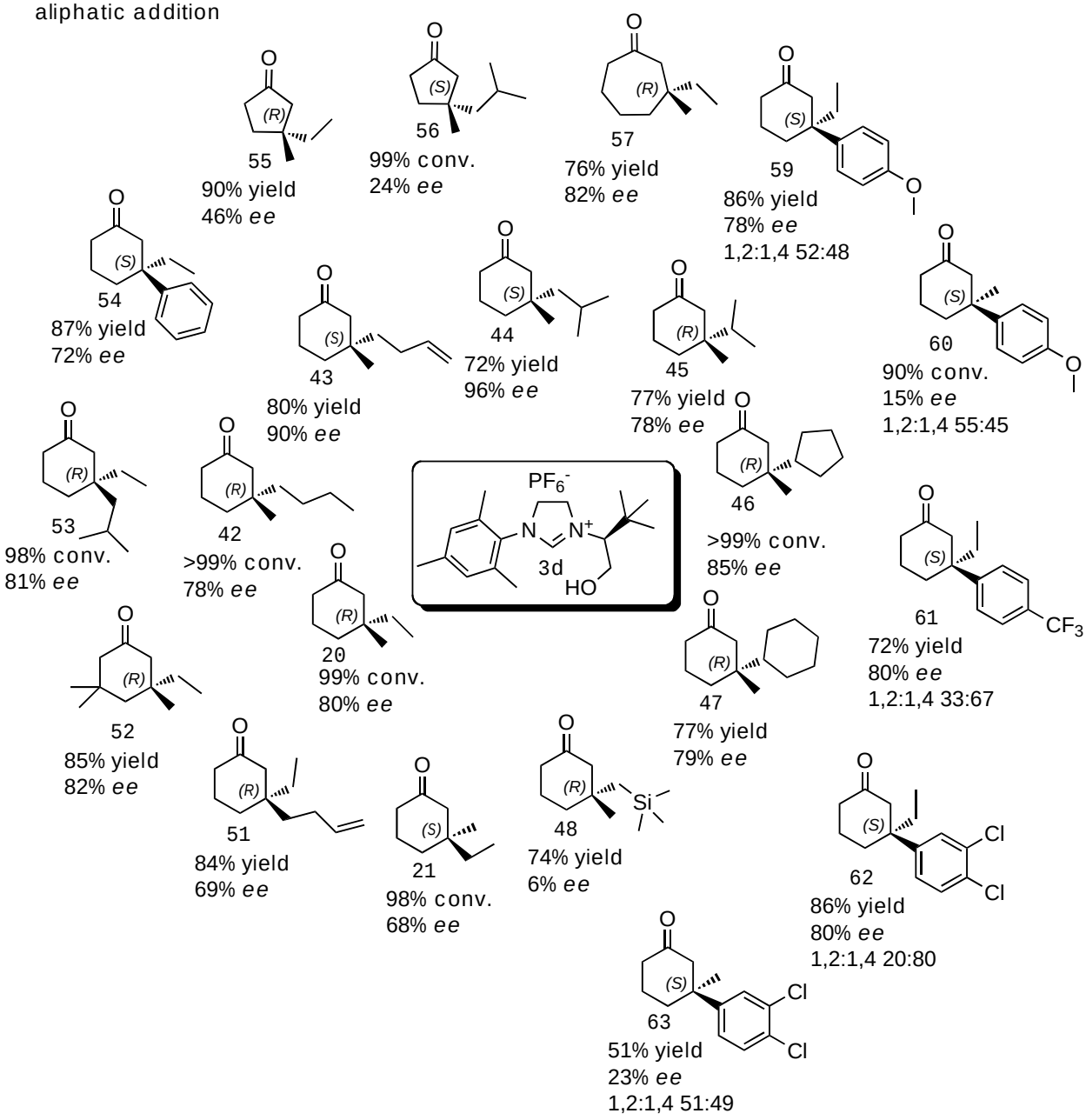
Table 26

Going from an electron-donating to an electron-withdrawing substituent did not change the regioselectivity of the reaction. By using the chiral alkoxy-NHC 3d or the achiral IMes 1d in Knochel's conditions, we obtained only the 1,2-addition product (Table 26, Entry 1, 2). We could therefore conclude that the limitation of our catalytic system lied on the regioselectivity of the aryl addition on alkyl- or aryl-substituted substrates.

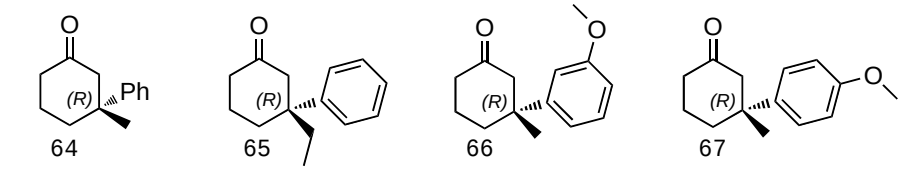
5.8 Scope of the reaction: results resume

For now, the alkoxy-ImH+ gave the best results in terms of conversions and enantiomeric excesses. With our catalytic system in hand, we were able to promote highly enantioselective A.C.A. by using alkyl or aryl Grignard reagents (Scheme 72). The regioselectivity for the aryl addition is the drawback of our methodology, but it will certainly be enhanced in the following researches.

Scope of the reaction with alkoxy- NHC
aliphatic addition



Scope of the reaction with alkoxy- NHC 3d
aromatic addition



Scheme 72

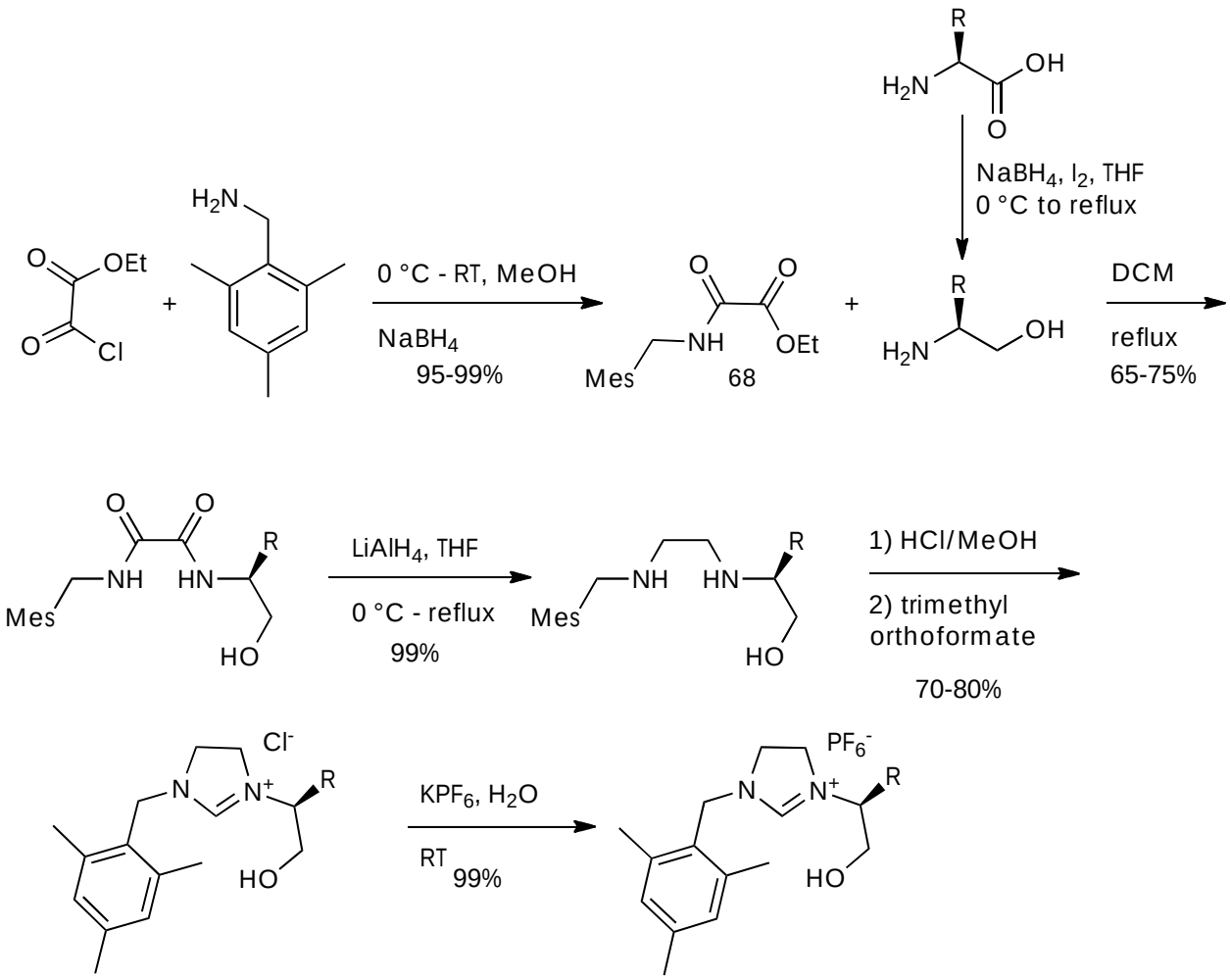
6. *Homologated alkoxy-substituted NHC as chiral ligands for A.C.A.*

When looking at the previous results, one can notice that the reacting center volume is highly important to control the enantio- and regioselectivity of the A.C.A.. Indeed, the C_2-symmetric ImH^+ have larger chiral reacting volumes than the alkoxy-ones. It allowed to catalyze the addition of a bulky *t*-butyl group with total regio- but no enantioselectivity. This reaction was not possible with the alkoxy-ImH^+ species where only 1,2-addition products were observed. On the other hand, the *ee*'s were almost always better using the alkoxy-ImH^+ 3d instead of the C_2-symmetric ligand family. One could therefore conclude that the adaptable reacting center volume of C_2-symmetric ImH^+ permitted to control the regioselectivity of the reaction, but the fixed reacting center volume of alkoxy-ImH^+ allowed a better enantio-control.

We therefore wanted to increase the adaptability of the reacting center volume of our alkoxy-substituted ImH^+ while keeping a high enantioselectivity by replacing the mesityl substituent with a trimethylbenzyl one. That achiral substituent would leave more flexibility to the reacting volume by allowing the homologated mesityl to rotate around the C-C bond but the fixed chirality on the other substituent should leave a high *ee*.

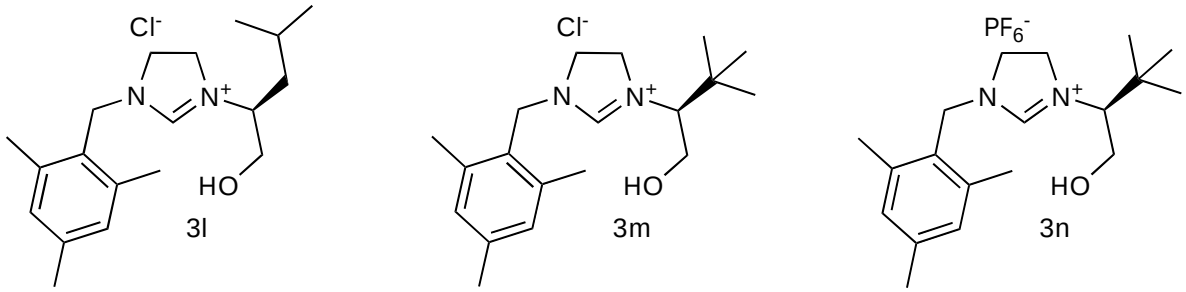
6.1 Synthesis of Mes- homologated Mauduit-like NHC

The desired ImH^+ were synthesized following the same procedure as the precedent alkoxy-NHC's, but using trimethylbenzyl amine instead of aniline (Scheme 73). The trimethylbenzyl amine was first coupled to ethyl oxalyl chloride, the resulting ester was then treated with an optically pure amino alcohol, obtained by reduction of the corresponding amino acid with $NaBH_4$ – I_2. The diamide was then reduced to diamine with $LiAlH_4$, followed by hydrochlorination – cyclization with trimethyl orthoformate to give the pure ImH^+ with 50% overall yield. An anionic transmetallation from Cl^- to PF_6^- was performed to observe any counter-ion effect.



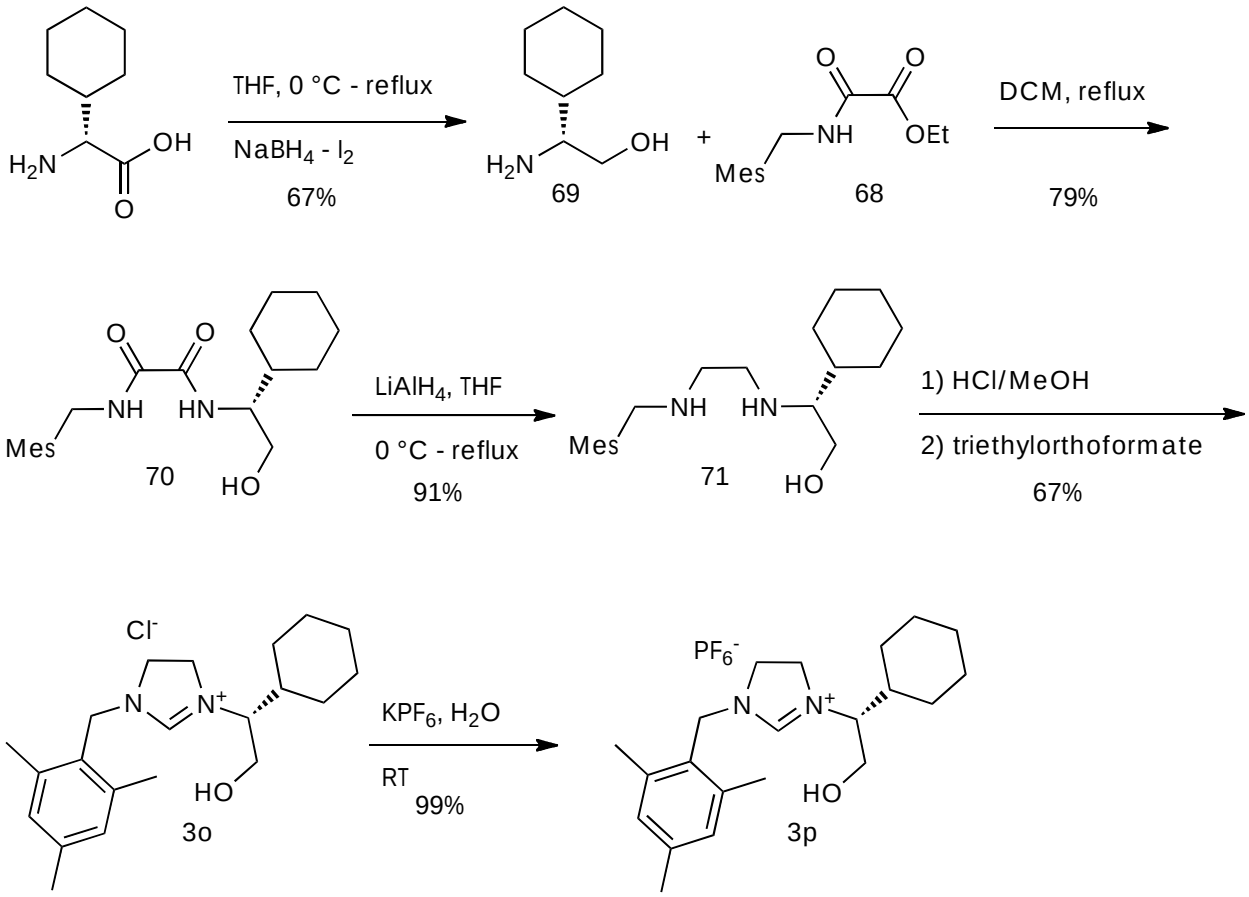
Scheme 73

Through this procedure, we synthesized 3l, 3m and 3n (Scheme 74), which are homologues of *i*-butyl 3c and *t*-butyl 3d based ImH$^+$.



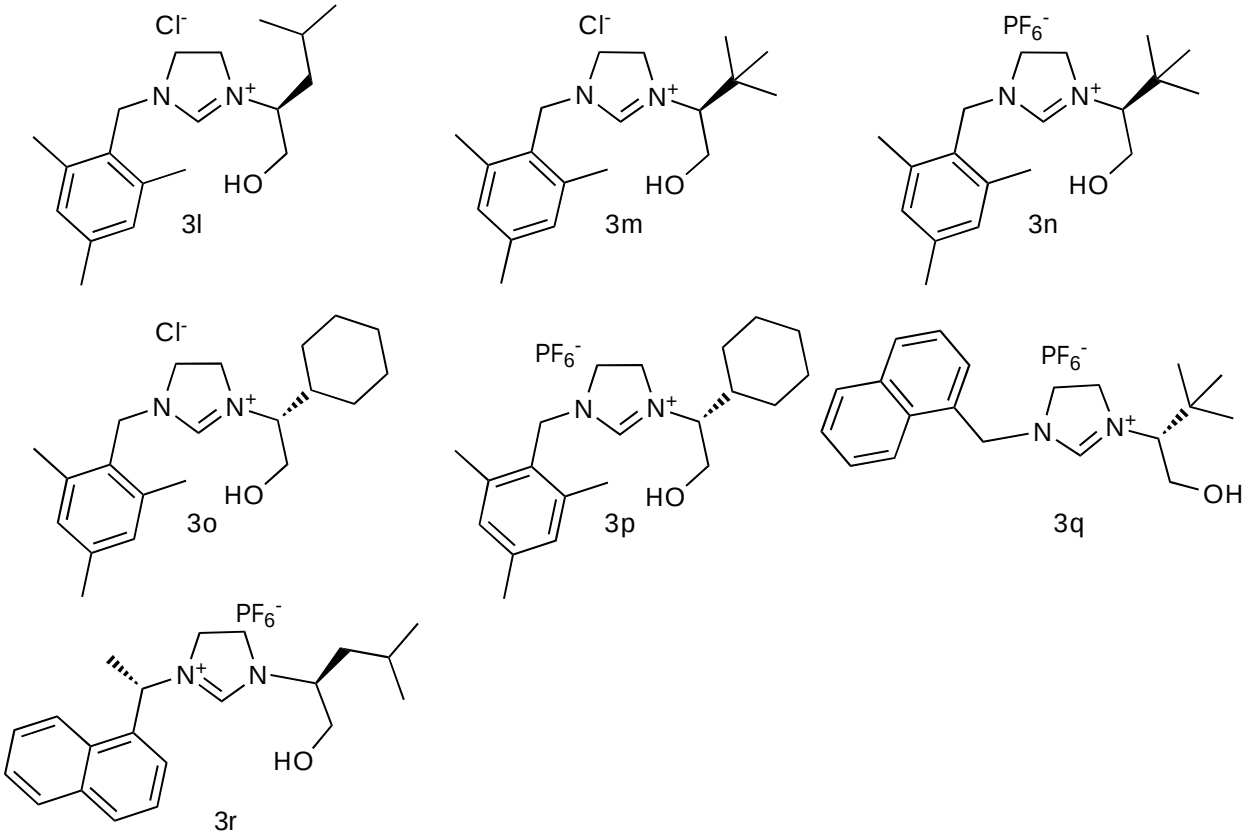
Scheme 74

To vary the steric hindrance, new ImH+ 3o and 3p containing a chiral *c*-hexyl moiety were also synthesized (Scheme 75).



Scheme 75

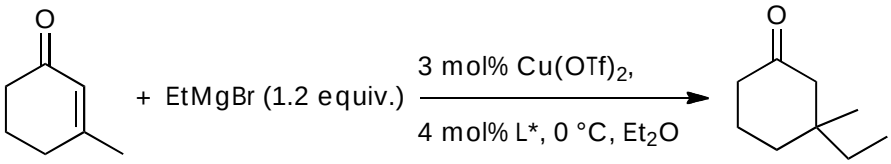
This short panel was completed by two naphthyl substituted ImH+ 3q and 3r, generously gifted by Dr Mauduit, in Rennes. To summarize, we possess now seven homologated aromatic substituted ImH+ to be tested in the copper-catalyzed A.C.A. (Scheme 76).

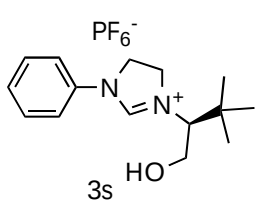


Scheme 76

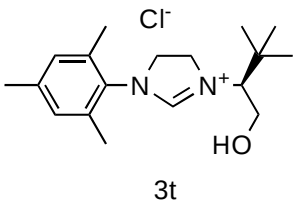
6.2 Homologated-alkoxy substituted ImH^+ in the A.C.A. of EtMgBr in standard conditions

We tested our new NHC's in the A.C.A. of EtMgBr to the 3-methylcyclohex-2-enone, in order to compare the effect of the achiral substituent homologation. For a better overview, the Scheme 77 shows the results obtained with the most efficient ligands previously tested, in order to compare the efficiency of the newly obtained benzyl-substituted ImH^+. The ligands are classified according to their chiral substituent, going from the smallest to the bulkiest of each family (Scheme 77).

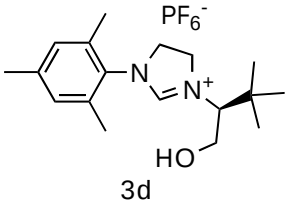




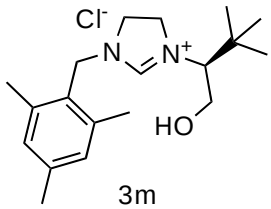
3s
Conv. 99%, 70% *ee*



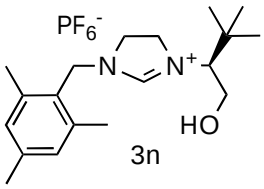
3t
Conv. 99%, 79% *ee*



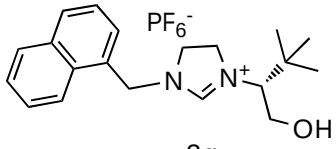
3d
Conv. 99%, 80% *ee*



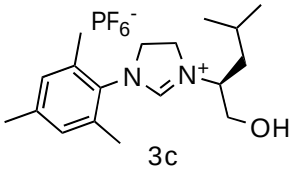
3m
Conv. 99%, 88% *ee*



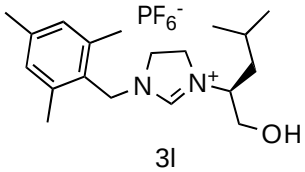
3n
Conv. 99%, 89% *ee*



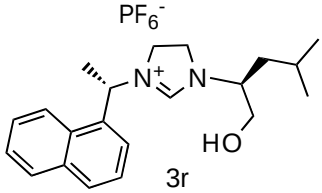
3q
Conv. 99%, 86% *ee*



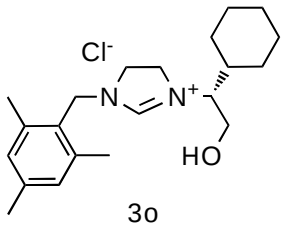
3c
Conv. 99%, 74% *ee*



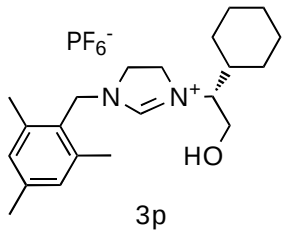
3l
Conv. 99%, 90% *ee*



3r
Conv. 99%, 84% *ee*



3o
Conv. 99%, 85% *ee*

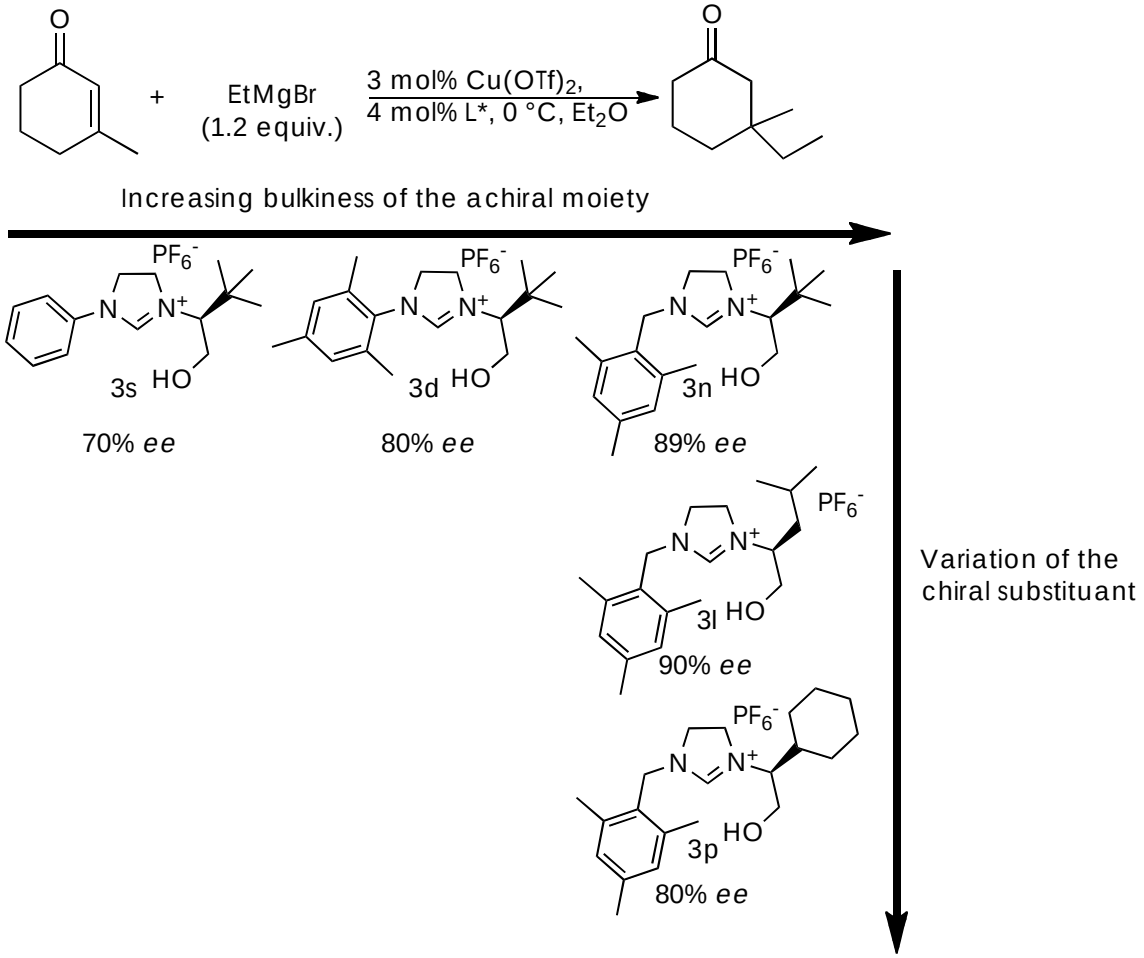


3p
Conv. 99%, 80% *ee*

Scheme 77

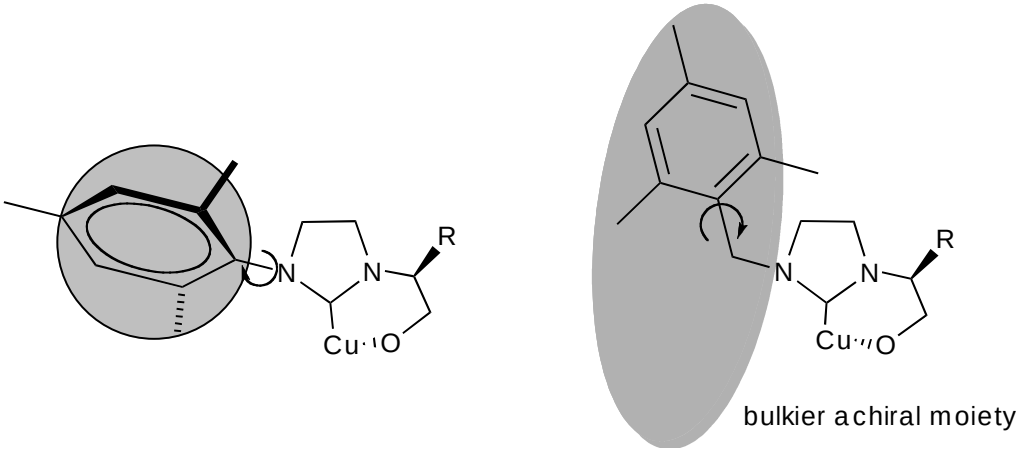
One can immediately notice that the presence of a bulky achiral moiety increased the enantioselectivity of the reaction. Indeed, with changing phenyl 3s to mesityl 3d, the *ee* rose from 70% to 80%. The new NHC 3n containing a homologated mesityl gave a better result than 3d (89% *ee*). By going from trimethylbenzyl 3n to methylnaphthyl 3q decreased the enantioselectivity (89% versus 86%).

In those cases, the variation of the counter-ion had again almost no effect on the enantioselectivity of the reaction. Indeed, the variation from Cl^- 3m to PF_6^- 3n gave the same *ee*. It is only in the case of *c*-hexyl substituted ImH^+ 3o and 3p that the *ee* difference reached 5% (Scheme 77). We preferred to use the PF_6^- ImH^+ because these ligands are less hygroscopic and easier to handle than their Cl^- counterparts. Surprisingly, the *i*-butyl substituent, which induced worse enantioselectivity than the *t*-butyl one for ImH^+ 3c and 3d, gave the best result with the trimethylbenzyl ligand 3l. In this family, increasing the steric bulkiness going to ethylnaphthyl ImH^+ 3r caused a decrease of the reaction enantioselectivity. Finally, the new *c*-hexyl substituted ImH^+ 3p gave also a very good 80% *ee* for the addition of EtMgBr on the methyl cyclohexenone. In summary, the increasing bulkiness of the achiral moiety promotes an increasing in the enantioselectivity of the A.C.A. of EtMgBr to the 3-methylcyclohex-2-enone (Scheme 78).



Scheme 78

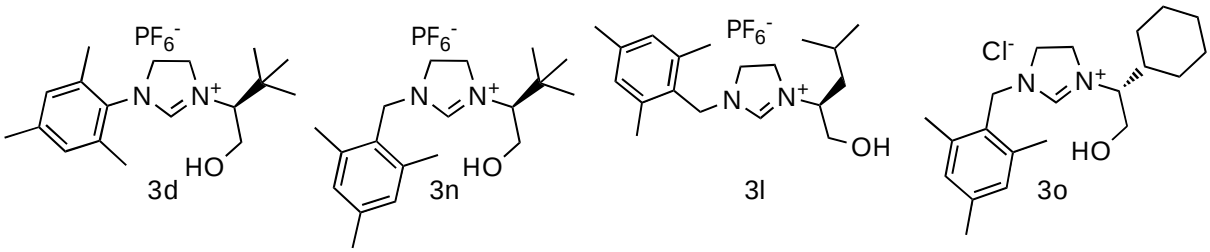
All the newly synthesized ImH$^+$ gave better results than their mesityl counterparts, increasing the *ee* for about 10%. It seems that the homologation of the achiral substituent facilitate the approach of the substrate by increasing the reacting center volume and increasing the bulkiness of the achiral part by allowing to the homologated mesityl to rotate around the C-C bond (Scheme 79). This promotes a better enantio-control of the reaction.

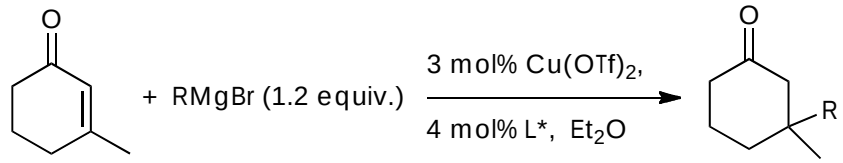


Scheme 79

6.3 Scope of the reaction: addition of Grignard reagents on 3-methylcyclohex-2-enone

We synthesized different branched Grignard reagents to observe the behavior of those new ImH$^+$ in the catalysis of stericaly hindered nucleophiles in the A.C.A. reaction (Table 27).





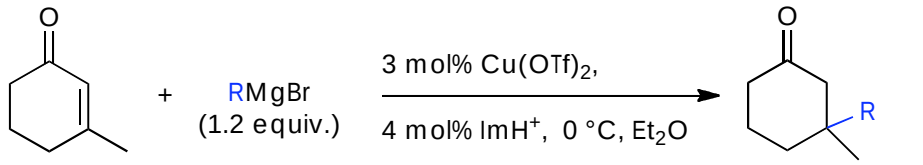
Entry	Prod.	R-	ImH$^+$	Temp	Conv.[a]	*ee*[b]
1[c]	46	*c*-Pent	3d	-30 °C	>99%	85% *R*
2	46	*c*-Pent	3n	-30 °C	>99%	28% *R*
3	46	*c*-Pent	3l	-30 °C	>99%	63% *R*
4	24	*c*-Pent	3o	-30 °C	>99%	28% *S*
5[c]	45	*i*-Pr	3d	-18 °C	>99%	78% *R*
6	45	*i*-Pr	3n	-30 °C	>99%	73% *R*
7	45	*i*-Pr	3l	-30 °C	>99%	90% *R*
8	25	*i*-Pr	3o	-30 °C	>99%	90% *S*
9[c]	44	*i*-Bu	3d	-30 °C	>99%	96% *S*
10	44	*i*-Bu	3n	-30 °C	>99%	62% *S*
11	44	*i*-Bu	3l	-30 °C	>99%	87% *S*
12	72	*i*-Bu	3o	-30 °C	>99%	18% *R*
13[c]		*t*-Bu	3d	0 °C	-	-
14	28	*t*-Bu	3n	0 °C	>99%	1%

(a) conversion determined by GC-MS, after 60 minutes. (b) determined by chiral GC (Lipodex E). (c) taken from Table 18.

Table 27

With comparing the results obtained previously with ImH$^+$ 3d and those obtained with the new ImH$^+$, we can conclude that both families were complementary. One can notice that for all the tested nucleophiles, the enantioselectivity of the reaction was better for the mesityl ImH$^+$ 3d than its homologated 3n counterpart (Table 27, Entry 1, 2; 5, 6; 9, 10). However, the other homologated derivatives 3l and 3o enhanced the results obtained with 3d, while this last was the most efficient ImH$^+$ salt of its family. For the trimethylbenzyl derivatives, the best ligand was the *i*-butyl substituted 3l. For the cyclic α-branched *c*-pentyl nucleophile, the bigger reacting

center was a disadvantage resulting in a dramatic decrease of the *ee*, from 85% to 63% (Table 27, Entry 1, 3). In contrast to that result, the addition of non-cyclic α-branched *i*-propyl nucleophile is largely better catalyzed with the new ImH$^+$ 3l than with the mesityl 3d ligand (78% to 90% *ee*) (Table 27, Entry 5, 7). The β-branched nucleophiles seemed to be better catalyzed by the mesityl based ImH$^+$. For example, where 3d gave 96% *ee* for the addition of *i*-butylMgBr on the 3-methylcyclohex-2-enone, the most efficient ligand 3l reached 87% *ee* (Table 27, Entry 9, 11). An interesting point is the addition of the bulky *t*-butyl substituent. Indeed, we saw previously that the ImH$^+$ 3d could not catalyze this reaction, and only 1,2-addition product was obtained (Table 18, Entry 10). By increasing the reacting volume, namely by homologating the mesityl, the 1,4-addition reaction was favored but as for the C_2-symmetric ImH$^+$ 2e, no enantio-control was obtained (Table 27, Entry 13, 14). The comparison of PF_6^- based ImH$^+$ 3d and 3n showed that the addition of bulkier nucleophiles than ethyl led to worse enantioselectivities for the new homologated 3n than for the normal 3d (Table 28).



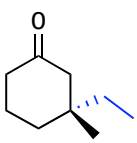
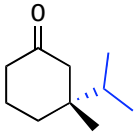
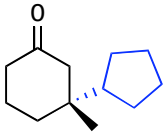
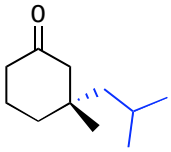
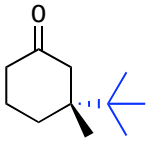
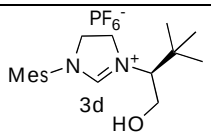
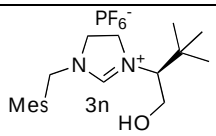
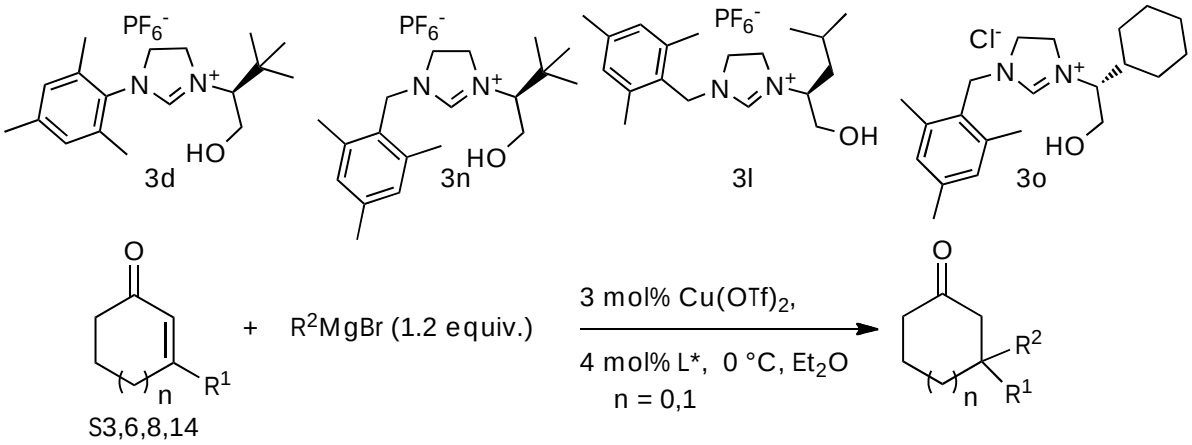
					
	80% *ee*	78% *ee*	85% *ee*	96% *ee*	Yield : 0% *ee* : nd
	88% *ee*	73% *ee*	28% *ee*	62% *ee*	Yield : 87% 1% *ee*

Table 28

6.4 Scope of the reaction: substrate variation, alkyl substituted substrates

As these new ligands were better catalysts for the addition of linear than for branched nucleophiles, they should increase the enantioselectivity for the A.C.A. of methyl and ethyl Grignard reagents on different bulkier substrates.

That is why we tested our new catalysts on some alkyl-substituted five- and six-membered cyclic enones (Table 29). These substrates were obtained in the same way as described previously in Scheme 68.



Entry	Subst.	R^1	R^2	Prod.	ImH^+	Conv.[a]	*ee*[b]
1[c]	S3	Et	Me	21	3d	98%	68% *S*
2	S3	Et	Me	21	3n	>99%	74% *S*
3	S3	Et	Me	21	3l	>99%	45% *S*
4	S3	Et	Me	20	3o	>99%	54% *R*
5	S14	*i*-Pr	Et	73	3n	>99%	83% *S*
6	S14	*i*-Pr	Et	73	3l	>99%	68% *S*
7	S14	*i*-Pr	Et	74	3o	>99%	72% *R*
8[c]	S6	*i*-Bu	Et	53	3d	98%	81% *R*
9	S6	*i*-Bu	Et	53	3n	>99%	87% *R*
10	S6	*i*-Bu	Et	53	3l	99%	50% *R*
11	S6	*i*-Bu	Et	75	3o	>99%	67% *S*
12[c]	S8	Me	Et	55	3d	98%	46% *R*
13	S8	Me	Et	55	3n	>99%	67% *R*
14	S8	Me	Et	76	3o	>99%	66% *S*

(a) conversion determined by GC-MS, after 60 minutes. (b) determined by chiral GC (Lipodex E). (c) taken from (Table 18).

Table 29

The results were really encouraging, with improved *ee*'s in all cases. The addition of methyl, known for its poor reactivity and enantioselectivity, rose from 68% to 74% by going from ligand 3d to its homologated counterpart 3n (Table 29, Entry 1, 2). Also by using α- and β-branched substituted substrates, the enantioselectivity was enhanced for the addition of an ethyl group. Indeed, the α-hindered *i*-propyl substrate S14 gave 83% *ee* (Table 29, Entry 5), whereas an increase of *ee* (81% to 87%) was obtained for the β-branched *i*-butyl trisubstituted center (Table 29, Entry 8, 9). The improvement was also observable for five-membered rings. Indeed, the addition of EtMgBr on methylcyclopentenone was better stereo-controlled by the new ImH^+ 3n compared to 3d (46% to 67%) (Table 29, Entry 12, 13). The ligand 3o containing the cyclohexyl glycinol gave poorer results in all cases. This was expected because this ligand gave worse enantioselectivity in the addition of EtMgBr on the 3-methylcyclohex-2-enone than analogue 3n.

However, it was surprising that the difference of *ee* between 3n and 3o was so important, while the difference for the aforementioned addition was only about 3% (Scheme 77, 3n, 3o). This could be explained by a larger steric hindrance of the catalytic complex toward the substrate. In the case of the addition of EtMgBr to the 3-methylcyclohex-2-enone, the little methyl substituent on the substrate S1 causes poor steric bulkiness, which did not much discriminate the approach of the larger 3n–based copper complex versus the smaller 3o-based one. In the other cases, the bulkier achiral substituent on the substrates increased also the total reacting volume bulkiness. By the way, the difference of bulkiness between a *t*-Bu and a *c*-hex is enhanced in term of *ee*.

6.5 Scope of the reaction: substrate variation, aryl substituted substrates

To conclude our study, we also applied our test reaction to the different electron-attracting and electron-withdrawing aromatic substituted substrates S7, S11 and S13. In the case of 3d-catalyzed A.C.A., we obtained good enantioselectivities but the regioselectivities were often problematic. That is why we wanted to observe the behavior of our new homologated 3n ImH^+ counterpart. The resume of the results we obtained is represented in Table 30.

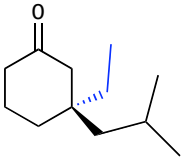
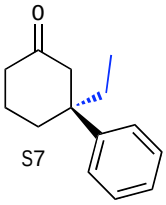
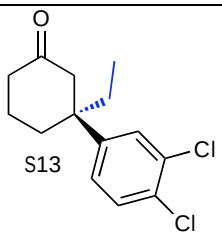
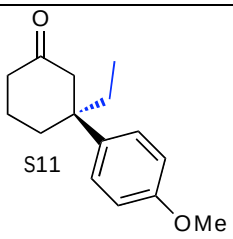
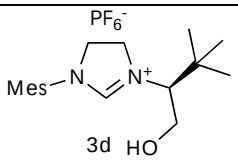
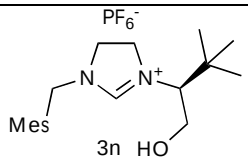
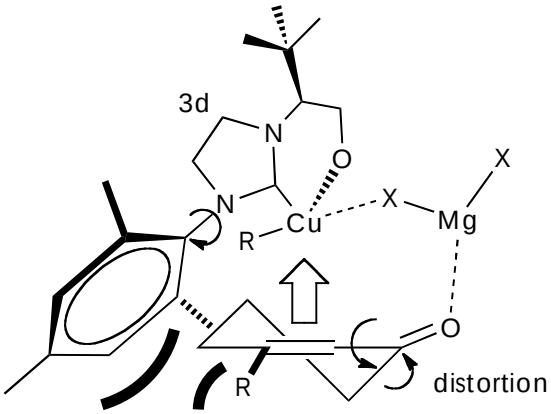
EtMgBr A.C.A. on different trisubstituted substrates		 S7	 S13	 S11
 3d	81% *ee*	72% *ee*	80% *ee* (20:80)	78% *ee* (52:48)
 3n	87% *ee*	82% *ee*	90% *ee* (13:87)	79% *ee* (36:64)

Table 30

All the substituents bigger than 3-methylcyclohex-2-enone we tested gave better results with EtMgBr as nucleophile. In the case of electron-withdrawing or free phenyl aromatic-based substrates, the ee's and regioselectivities were strongly increased with ImH$^+$ 3n compared to ImH$^+$ 3d. With electron-donating substrate S11, the enantioselectivity is the same with 3d or 3n, but the regioselectivity is by far better with the homologated ImH$^+$ 3n.

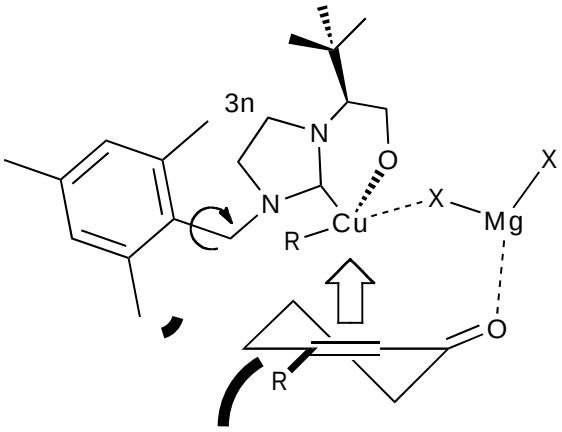
The differences of reactivity between ImH$^+$ 3d and 3n could be explained by the homologation of the achiral moiety. Indeed, as the volume of the catalytic reacting site of 3n is larger than the 3d one because of the extra carbon in the achiral substituent's 3n chain, it allows an easier approach of bulkier substrates. The reacting volume is therefore somewhat adaptable to the bulkiness of the substrate, as the previous C_2-symmetric ImH$^+$ were. In fact, the approach of a bulkier substrate may push the achiral part away making the approach easier. In the case of 3d, the mesityl is directly fixed to the nitrogen and can therefore do nothing else than turning on itself, which enhanced only poorly the reacting volume size. As a result, the enantioselectivity of reactions done on bigger substrates decreased, maybe because the cyclic substrate has to "twist" to enter the reacting center. In the case of 3n, the rotation of the achiral chain around the C-C bond allowed the cyclic substrate to enter without distortion. While by using smaller substrates and varying

the nucleophile, the bigger reacting volume becomes a disadvantage, because the substrate is less directed in the reacting volume (Scheme 80).



If R = Me => better chiral induction.

If R > Me => poor reactive volume adaptability. More steric hindrance, substrate distortion, less stereoselective.



If R = Me => less chiral induction due to less stable reactive volume.

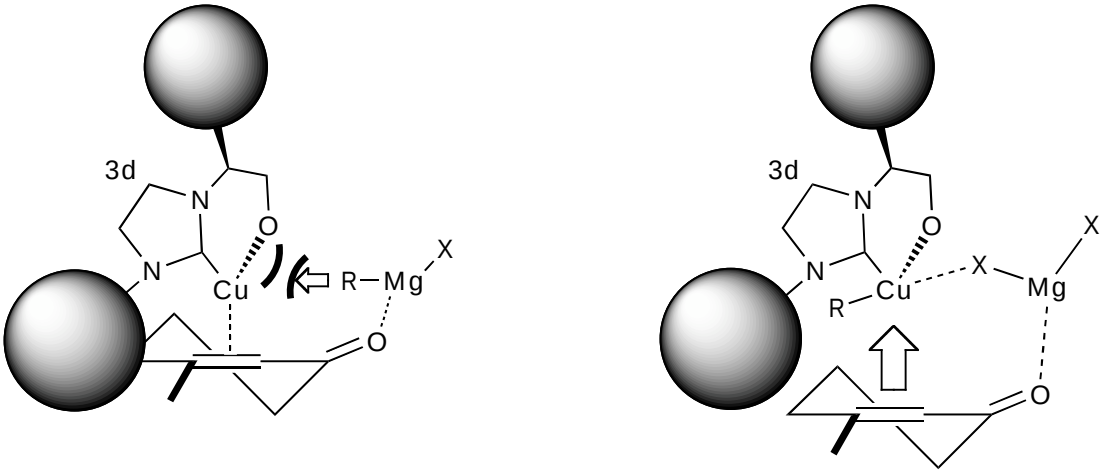
If R > Me => best stereoselectivity. Reactive volume adaptability increase stereoselectivity. No distortion.

Scheme 80

In the same idea, the better regioselectivity obtained for aromatic substrates with homologated ImH^+ 3n could be explained because of the less important steric hinderance between the substrate and the catalyst, which does not disadvantage the approach on the β-position compared to the direct addition.

The obtained results are in accordance with the proposed conjugate addition mechanistic cycle (Scheme 4). Indeed, following the proposed mechanism, the Grignard to copper transmetallation happens before the π-coordination of the substrate. In our case, if the nucleophile would make the opposite and bind after the substrate on the copper, there would be a high incidence on the variation of the nucleophile bulkiness for the 3d-based complex, but no one for the 3n-based complex. Indeed, if the nucleophile would arrive after the substrate, the bigger the substrate is and the worse the nucleophile could approach the bulky rigid 3d-based complex.

But as the achiral arm of 3n may move easily, the nucleophile could simply push the trimethylbenzyl group away and enter easily. As a result, the enantioselectivity of the reaction should decrease with the increasing bulkiness of the nucleophile for 3d, and be stable for 3n. But as we observe that the increasing nucleophile's bulk is better for the stereo-induction of the reaction with 3d, it means that the nucleophile's approach is done before the substrate, as proposed in the postulated mechanism (Scheme 81).



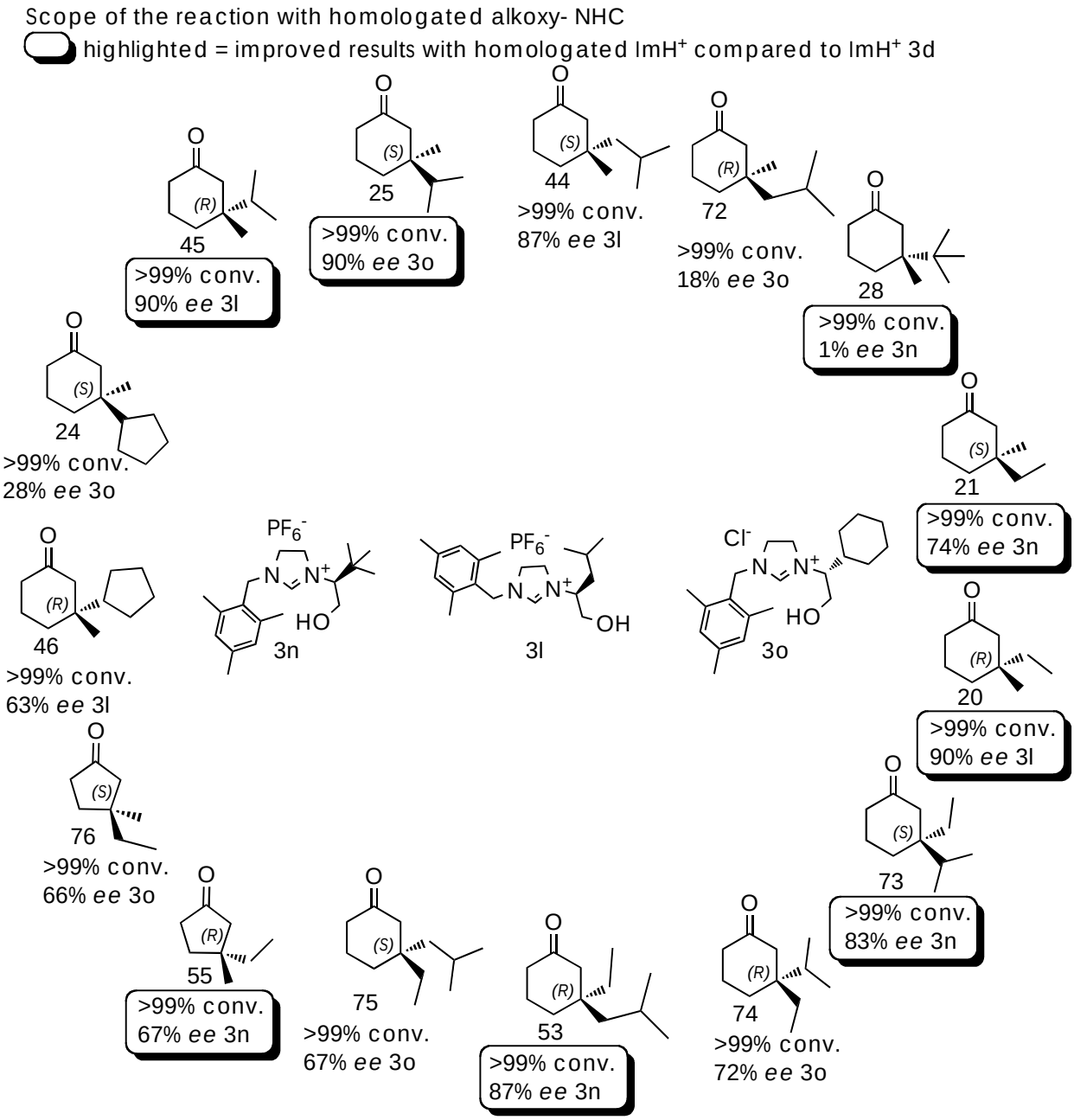
If substrate would comes before transmetallation
the more R is big => more steric hinderance and less enantioselectivity.

As substrate comes after transmetallation
the more R is big => more spatial constraint and better enantioselectivity.

Scheme 81

6.6 Scope of the reaction: results resume

As a resume, this new homologated alkoxy-ImH$^+$ gave even better results than their mesityl counterparts when the substrate became bulkier. In contrast, by using the small 3-methylcyclohex-2-enone S1 as substrate and varying the size of the nucleophiles, the homologated ImH$^+$ were less efficient than the mesityl 3d (Scheme 82).

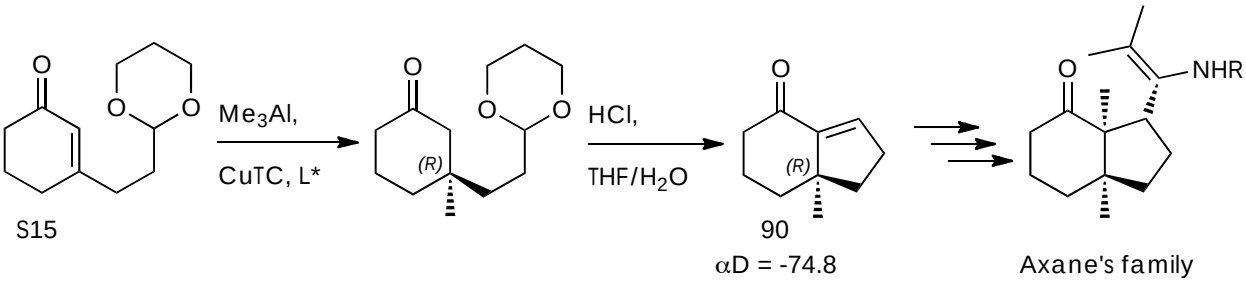


Scheme 82

6.7 Determination of the absolute configurations

As all the tested ligands showed a total facial selectivity, the absolute configuration of all the conjugate addition products were determined by analogy with the work of Dr Magali Vuagnoux-D'Augustin.[16] Indeed, she synthesized an Axane's family intermediate bearing a known absolute configuration, by doing an A.C.A. of Me_3Al

on 3-(2-(1,3-dioxan-2-yl)ethyl)cyclohex-2-enone S15 (Scheme 83). The obtained chiral acetal was hydrolyzed and trapped *in situ* to gave the 6,5-membered bicyclic (*R*)-7a-methyl-5,6,7,7a-tetrahydro-1*H*-inden-4(2*H*)-one 90. An optical rotation analysis showed a negative rotation (-74.8, c = 1.53, $CHCl_3$), which corresponds to the *R* configuration of the Axane's synthesis intermediate.[165]



Scheme 83

7. *Applications in synthesis*

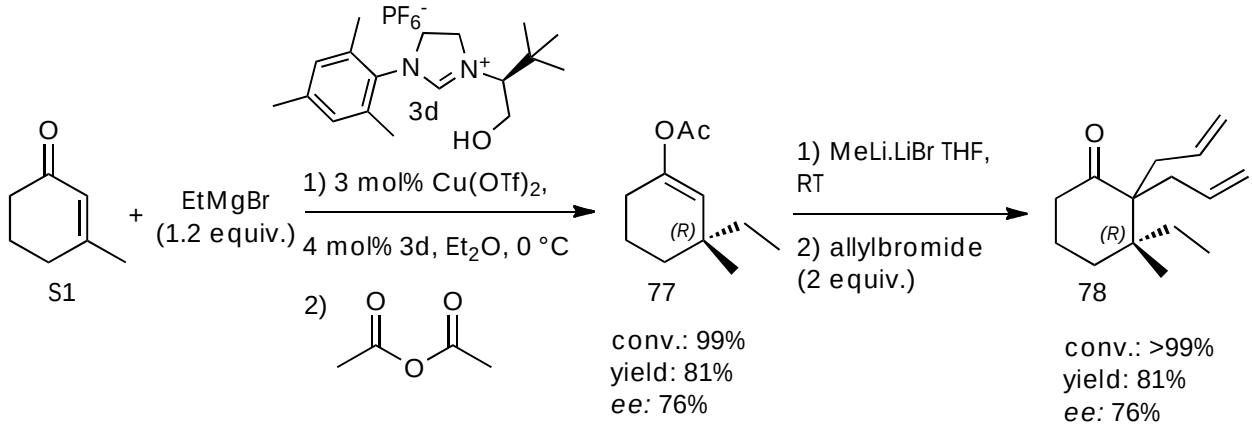
With our different ImH^+ in hand, we possess now a multi-tasked tool, capable to catalyze the A.C.A. of Grignard reagents to different aliphatic and aromatic trisubstituted cyclic enones. This processes allows to isolate functionalizable compounds with high yield and *ee*'s. That is why we focused on developing synthetical applications in order to increase the value of our methodology.

7.1 α-functionalization: enolate trapping

As the 1,4-addition reaction goes trough a magnesium enolate step, it should be possible to trap it with an electrophile in a one-pot procedure, in order to open the door to easy α-functionalization possibilities. The problem lies in the fact that magnesium enolates, compared to lithium enolates,[166] were much nucleophilic because more stabilized. They have generally to be trapped by an oxophilic

electrophile, as Ac_2O[167] or TMSOTf,[44] in a first step, and then be treated by MeLi.LiBr to form the lithium enolate, which becomes then highly reactive (Scheme 84).[168]

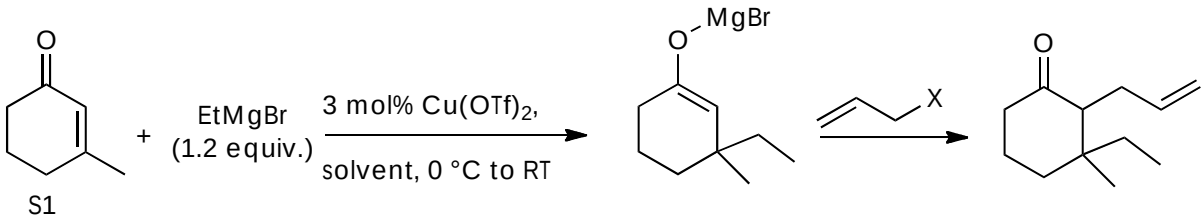
We started our investigations by trapping an enolate with allyl bromide, doing the common two-pots reaction. We trapped the formed enolate with acetic anhydride to give the stable enol-acetate 77 with high yield and retention of the absolute configuration. A treatment of 77 with MeLi.LiBr led to the formation of the highly reactive lithium enolate, which was finally trapped with two equivalents of allyl bromide to gave the *gem*-bis-allylated product 78 with high yield as the only product of the reaction (Scheme 84). No α-α'-allylation was observed. Indeed, since MeLi.LiBr was used at RT, it formed LiOtBu in the reaction conditions, which led to a thermodynamic control and gave only product 78.



Scheme 84

7.1.1 Optimization of the reaction conditions: racemic allyl trapping

As this reaction was done with no loss of enantioselectivity, we tried to perform the same reaction in a one-pot process by trapping directly the magnesium enolate with different allyl substituted electrophiles. We first tested the racemic version of the reaction, in order to find out the best conditions for the reaction (Table 31).



Entry	X	Solvant	$Pd(PPh_3)_4$	Time	Conv.[a]	Allyl:H
1	OAc	Et_2O	-	72 h.	99%	0:100
2	OAc	THF	-	48 h.	95%	0:100
3	OAc	THF:HMPA	-	48 h.	>99%	0:100
4	OAc	THF:HMPA	5 mol%	72 h.	95%	0:100
5	I	Et_2O	-	72 h.	99%	0:100
6	I	THF	-	48 h.	99%	0:100
7	I	THF:HMPA	-	72 h.	>99%	94:6
8	I	THF:HMPA	5 mol%	48 h.	98%	96:4
9	Br	THF	-	72 h.	58%	0:100
10	Br	THF:HMPA	-	48 h.	94%	77:23
11	Br	THF:HMPA	5 mol%	72 h.	95%	74:26

a) conversion determined by GC-MS.

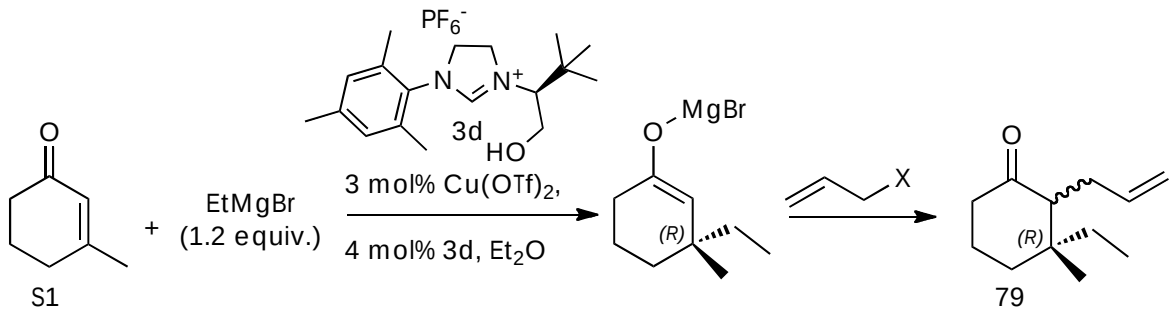
Table 31

The first thing we noticed was the high solvent dependency of the process. Indeed, the enolate trapping did not take place in Et_2O or THF, where only ethylmethylcyclohexanone 20 was obtained after work-up (Table 31, Entry 1, 2, 5, 6, 9). Enolate trapping happened only when a 1:1 mixture of HMPA and THF was added in the flask after total enolate formation. The HMPA is known to solvates selectively cations with its basic oxygen, letting the anion free and more reactive. Using Noyori's process,[154] we tried to modify the reactivity of the allyl specie, by adding *tetrakis*-(triphenylphosphine)palladium in order to form a more reactive π-allyl system, but with no improvements. Indeed, the presence of palladium in the cases where the reaction already works with HMPA:THF did not show any improvements with the presence of the TM (Table 31, Entry 7,8 and 10, 11). To confirm these results, we changed the palladium source by using palladium

acetate, but the same results were obtained. About the allyl electrophiles, only allyl acetate gave no enolate trapping at all, even in the presence of palladium (Table 31, Entry 4). By looking at the results, one can conclude that the allyl reactivity decreases following the order I > Br >> OAc (Table 31, Entry 7, 10, 3).

7.1.2 Chiral allylic trapping

With those optimized conditions in hand, we applied our methodology in the asymmetric version of the reaction (Table 32). As Glorius[169] and Campora[170] showed that the NHC-TM complex could stabilize and activate allyl acetates, we tried also to do some trapping attempts directly in Et_2O, with the chiral Cu-NHC complex supposed to act as a π-allyl activator.



Entry	X	Solvant	$Pd(PPh_3)_4$	Temp.	Time	Conv.[a]	Allyl:H
1	OAc	Et_2O	-	RT	72 h.	99%	42:58
2	OAc	Et_2O	5 mol%	RT	52 h.	99%	0:100
3	I	Et_2O	5 mol%	RT	55 h.	99%	0:100
4	I	THF:HMPA	-	40 °C	12 h.	99%	87:13
5	I	THF:HMPA	-	40 °C	25 h.	99%	>99:1

a) conversion determined by GC-MS.

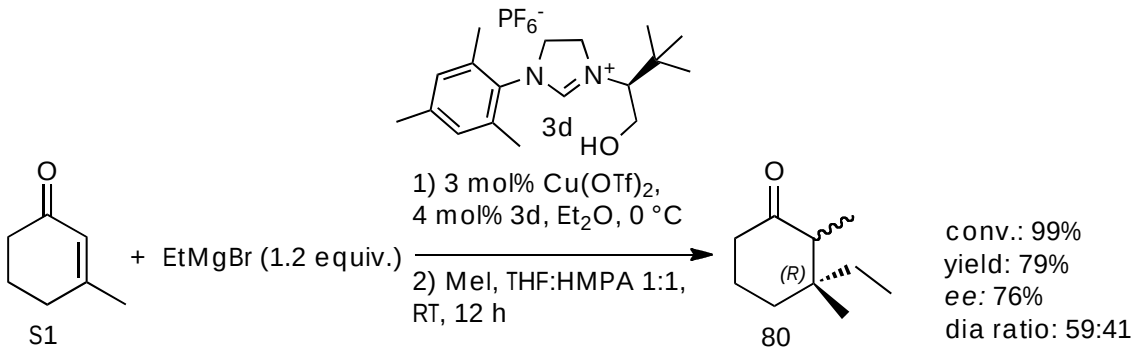
Table 32

By looking at the results, it seems that the presence of the NHC-Cu complex allowed to obtain 42% of allylated product (Table 32, Entry 1). Unfortunately, this result was not reproducible. We repeated this reaction twice and we always obtain no allylated product. In this case as for the racemic version, the addition of palladium did not improve the outcome of the reaction (Table 32, Entry 2). Finally, using the optimized conditions with THF:HMPA, the reaction worked perfectly well. The α-

allylated product 79 was obtained with 99% conversion and 70:30 diastereomeric ratio after 25 hours at 40 °C (Table 32, Entry 5). This methodology allows therefore to trap magnesium enolates with allyl electrophiles, without the presence of extra activating complex, in high yields and complete retention of stereo-selectivity, just by adding a 1:1 mixture of HMPA:THF in the media.

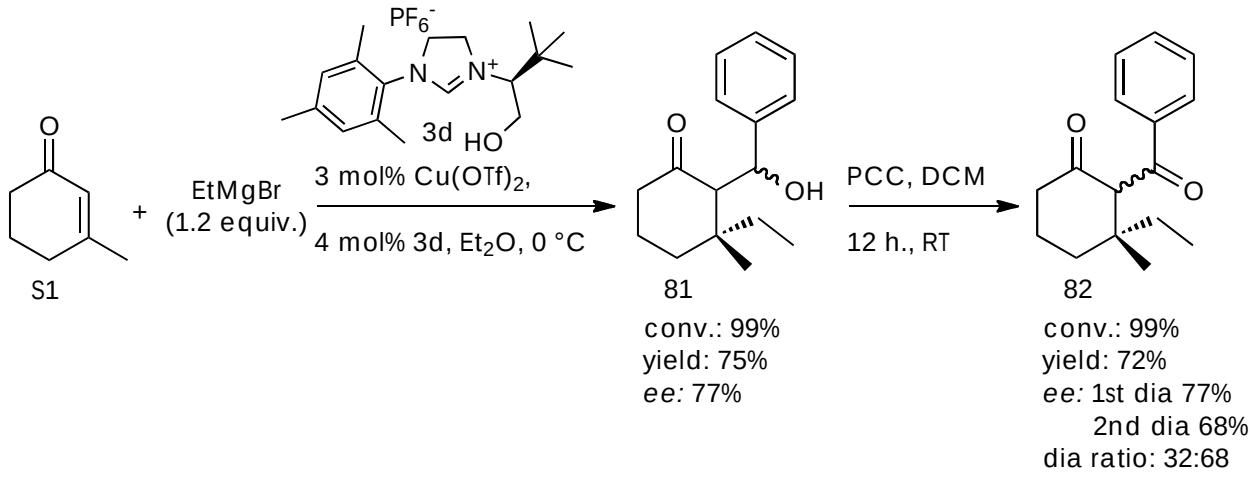
7.1.3 Scope of the reaction: other electrophiles used in enolate-trapping

To enhance the scope of this methodology, we tried to trap the magnesium enolates with other electrophiles, namely methyl iodide, benzaldehyde and a halide. The reaction with the alkyl was done in the same way as for the allyl iodide and allowed to obtain the expected 3-methyl-4,4-ethylmethylcyclohexanone 80 with 99% conversion and 59:41 diastereoisomeric ratio (Scheme 85).



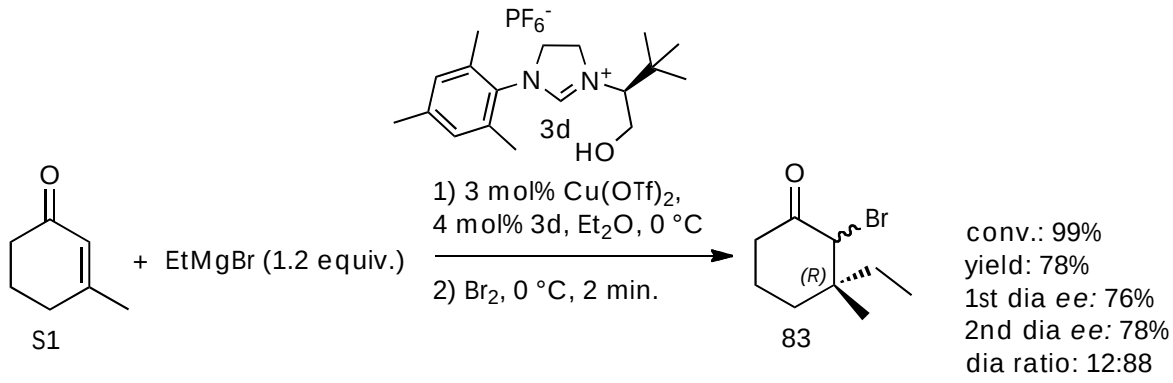
Scheme 85

The third trapping of our selected panel was done with benzaldehyde (Scheme 86). As this electrophile was very reactive, there was no need to add the HMPA:THF mixture. Indeed, it was sufficient to add directly the benzaldehyde onto the preformed magnesium enolate to obtain the desired product with high yield. As the product 81 was very difficult to analyze by NMR because of the obtained mixture of diastereoisomers, we oxidized the secondary alcohol to the ketone 82 in order to have only two diastereoisomers in a 32:68 mixture.



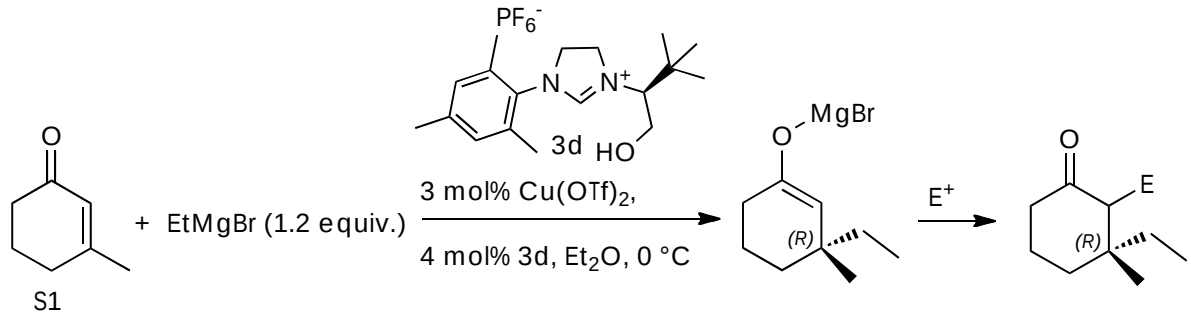
Scheme 86

The last electrophile tested in the one-pot trapping was bromine. Like benzaldehyde, bromine was reactive enough in Et_2O and was therefore added dropwise on the magnesium enolate. In that particular case, it was important to quench the reaction after 2 minutes to prevent the formation of multi-brominated species.[171]



Scheme 87

In summary, we were now able to easily α-functionalize our substrates in a one-pot process, by trapping many different classes of electrophiles directly by the preformed magnesium enolate. These reactions were done without racemization after the A.C.A. of EtMgBr on the 3-methylcyclohex-2-enone (Table 33).



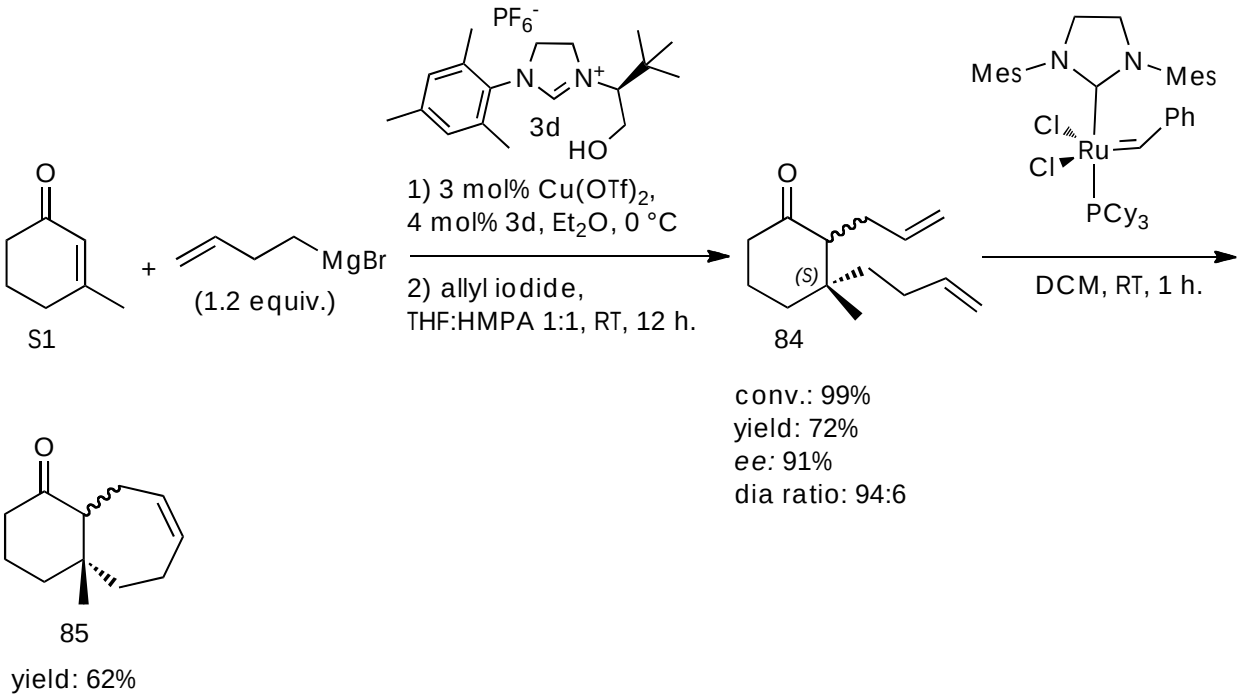
Entry	Prod.	E^+	Reaction time	Conv.[a]	η[b]	1st dia./2nd dia *ee*[c]	dia. Ratio
1[d]	79	Iodo allyl	25 h.	>99%	81%	76%[e]	70:30
2[d]	80	MeI	12 h.	99%	79%	76%[e]	59:41
3	82	Benzaldehyde[f]	30 min.	>99%	72%	77%/68%	32:68
4	83	Br_2	30 min.	>99%	78%	76%/78%	12:88

(a) conversion determined by GC-MS, after 30 minutes. (b) isolated yield (c) determined by chiral GC. (d) HMPA: THF 1:1, 40 °C. (e) *ee* of the first step. (f) the obtained alcohol is oxidized to eliminate some diastereoisomers.

Table 33

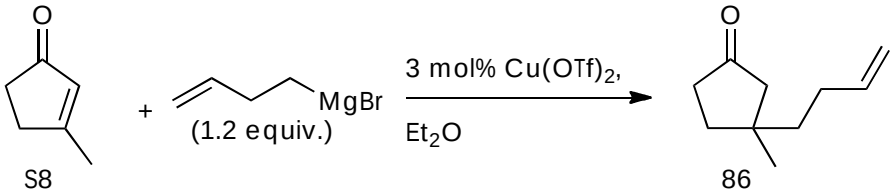
7.2 1,4-addition / α-functionalization / cyclization sequence

The opportunity to insert different functionalities as halide, alkyl, allyl or benzylic alcohol with good diastereoselectivity allowed to multiply the possibilities of our methodology. To improve the value of the addition / allylic trapping sequence, we thought to go one step further and try to synthesize a bicyclic compound using our methodology (Scheme 88). We started therefore by adding butenyl Grignard reagent on the 3-methylcyclohex-2-enone and trapped the formed magnesium enolate with allyl iodide. The obtained dialkene substrate was then cyclized by metathesis with Grubbs II catalyst to form a bicyclic six – seven membered rings with high *ee*'s and 45:55 E:Z diastereoselectivity.



Scheme 88

As the reaction works well for six-membered rings, we tried to do the same reaction on 3-methylcyclopent-2-enone S8. As we never used such a big alkyl chain for the A.C.A on this substrate, we first performed the racemic version of the simple conjugate addition reaction (Table 34).



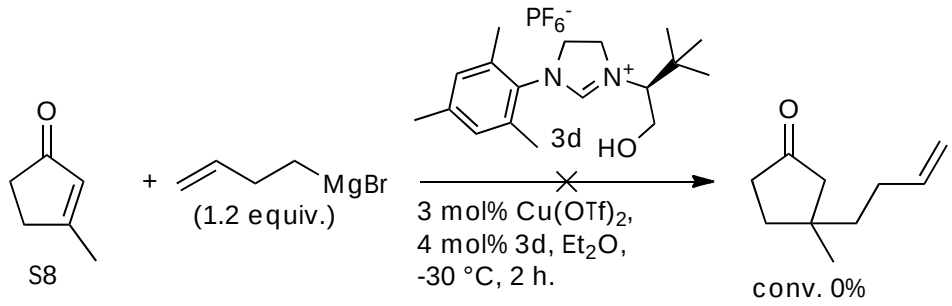
Entry	Reaction time	Temp.	Conv.[a]	η[b]	Ratio1,2:1,4
1	25 h.	0 °C	>99%	-	100:0
2	30 min.	-30 °C	>99%	85%	0:100

(a) conversion determined by GC-MS, after 30 minutes. (b) isolated yield

Table 34

Surprisingly, the reaction was highly temperature dependant. Indeed, doing the reaction at 0 °C gave only the 1,2-addition product (Table 34, Entry 1). In the same experimental conditions, but by lowering the temperature to -30 °C, the outcome of

the reaction was completely opposite and only the desired product 86 was obtained (Table 34, Entry 2). Having succeeded in the racemic way, we tried to apply the conditions to an asymmetric reaction way (Scheme 89). Unfortunately, in presence of ImH^+ 3d, no reaction was observed at -30 °C after 2 hours.

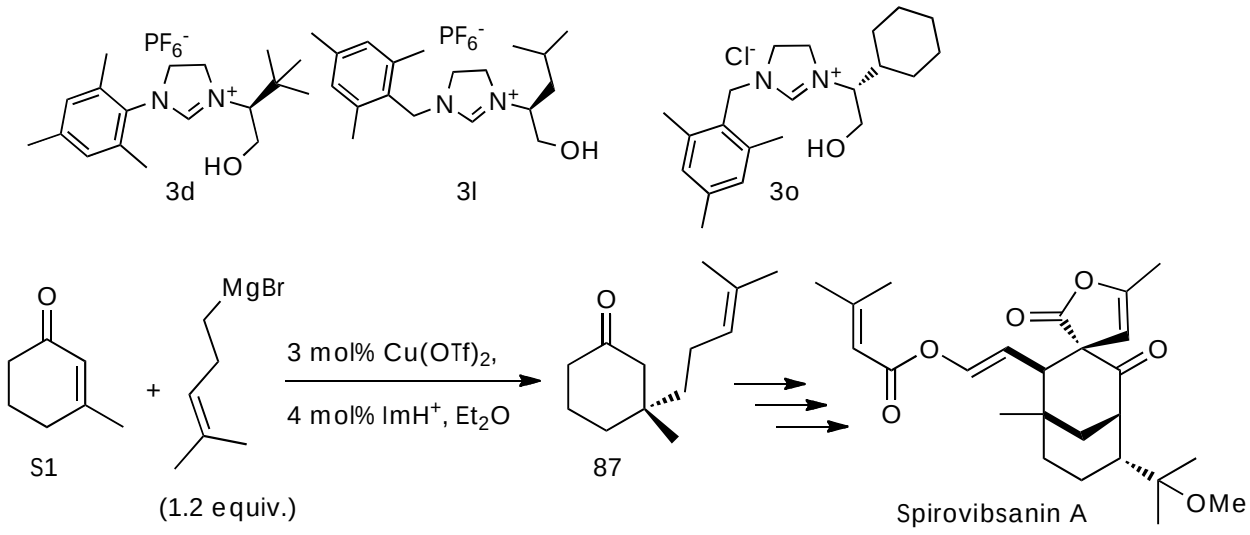


Scheme 89

7.3 Applications in total synthesis

7.3.1 Spirovibsanin A, first step synthesis

Recently, a paper by Williams described the synthesis of Spirovibsanin A.[172] The first step was the racemic conjugate addition of 2-methylpent-2-enyl Grignard reagent to 3-methylcyclohex-2-enone. As it was exactly the field we had investigated, we tried to reproduce the first step of this synthesis but with asymmetric induction (Table 35).



Entry	ImH^+	Temp.	Reaction time	Conv.[a]	η[b]	*ee*[c]
1	3d	-40 °C	30 min.	90%	-	86%
2	3d	-30 °C	30 min.	96%	72%	86%
3	3d	0 °C	30 min.	>99%	-	82%
4	3l	-30 °C	30 min.	>99%	-	62%
5	3o	-30 °C	30 min.	>99%	-	78%

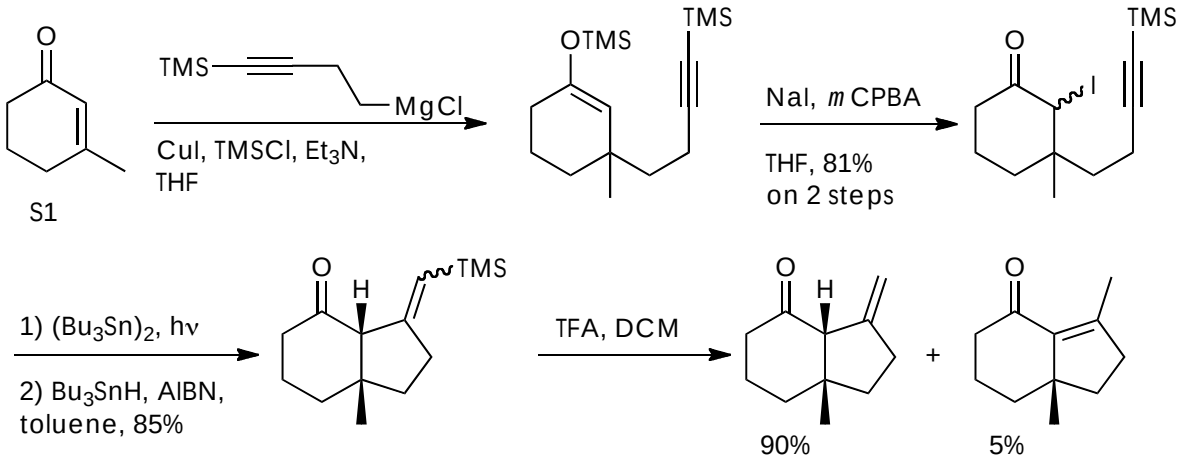
(a) conversion determined by GC-MS, after 30 minutes. (b) isolated yield (c) determined by chiral GC.

Table 35

We were pleased to see that our methodology allowed to reach 86% *ee* for the first step of the Spirovibsanin A synthesis (Table 35, Entry 2). As for the precedent results, the homologated ImH^+ analogue gave worse results than its mesityl 3d counterpart in the addition of longer and bulkier chains on a small substrate (Table 35, Entry 2, 4, 5).

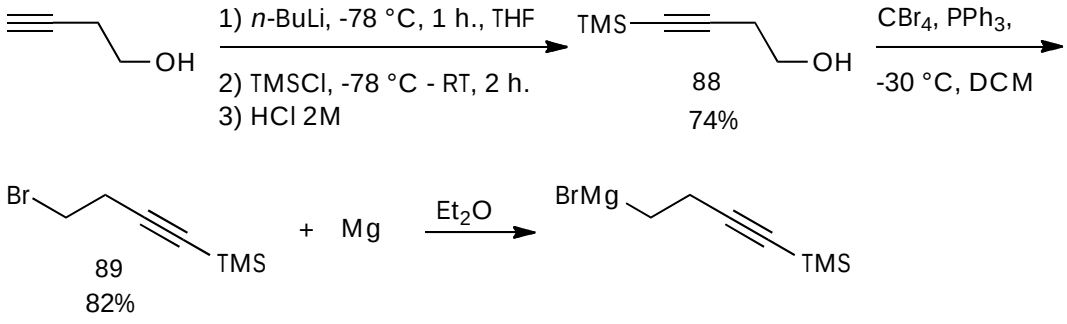
7.3.2 Axisonitrile, first step synthesis attempts

Sha reported recently the synthesis of axisonitrile (Scheme 90).[173] The first step was a racemic conjugate addition of a sylilated homopropargylic Grignard reagent to 3-methylcyclohex-2-enone, followed by the trapping of the magnesium enolate with TMSCl. The enolate was then liberated and an α-iodination occurred. The intermediate was then cyclized using a radical reaction pathway and the elimination of the sylilated group gave the title product.



Scheme 90

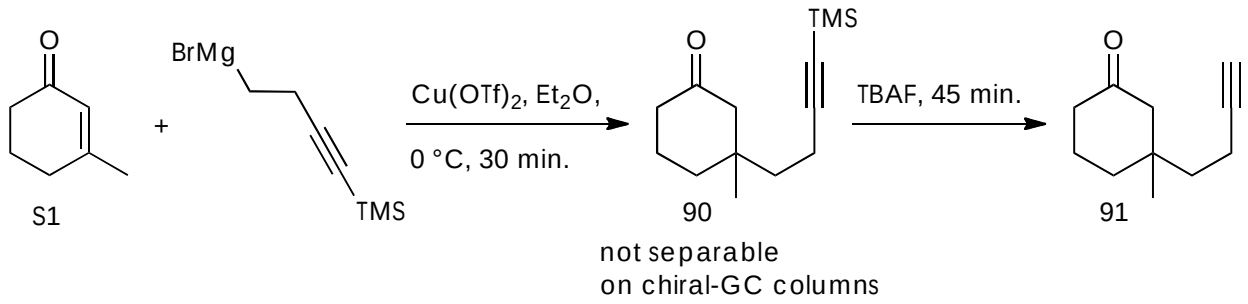
As the reaction reported by Sha was racemic, we tried to make the two first steps in an asymmetric one-pot process by applying our methodology. We therefore had to synthesize the Grignard reagent, by treating the commercially available homopropargylic alcohol with *n*-BuLi and trap the formed dianion with TMSCl to form the sylilated homopropargylic alcohol 88 (Scheme 91).[174] This intermediate was then brominated to give the analogue 89 with a good 82% yield.[175] This product was finally added on magnesium turnings to form the corresponding ethereal Grignard reagent. Unfortunately, this organomagnesium reagent was biphasic in diethyl ether and could not been titrated.



Scheme 91

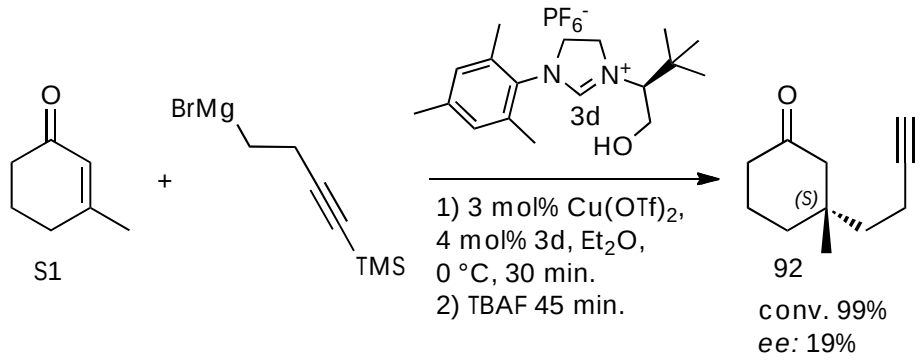
The one-pot procedure was nevertheless done with a calculated Grignard concentration. We started by doing the racemic conjugate addition of the Grignard reagent on the 3-methylcyclohex-2-enone. The desired product was obtained in a total 1,4 regioselectivity, but the problem was the separation of the enantiomers. Indeed, the 1,4-addition product was not separable on any of our chiral columns.

We had therefore to desylilate the product with TBAF in order to obtain a separable compound (Scheme 92).



Scheme 92

We the chiral separation conditions in hand, we made the asymmetric version of the reaction. The 3-methylcyclohex-2-enone S1 was added on a mixture of the sylilated Grignard reagent, $Cu(OTf)_2$ and the ImH^+ 3d. An aliquot of this intermediate was withdrawn and treated with TBAF to obtain a separable mixture of enantiomers. Unfortunately, we reached only 19% *ee* for that reaction (Scheme 93).



Scheme 93

This disappointing result will be certainly enhanced in further studies, for instance by increasing the bulkiness on the chiral part of the ImH^+.

8. *General conclusion*

These last years, the Alexakis group has reported efficient methods to do A.C.A. using organozinc, organoaluminum and organomagnesium nucleophiles in the presence of many chiral ligands leading to high yield and *ee*'s. However, NHC's described in the literature as powerful and stable chiral-inducing moieties had never been tested on the A.C.A.. The goal of our work has been to test the existing NHC's in the copper-catalyzed A.C.A. of Grignard reagents on cyclic enones and to design new families of NHC's. Those ligands have been tested in order to induce chirality on trisubstituted five-, six- and seven-membered cyclic enones to form quaternary stereogenic centers.

We therefore started our project with synthesizing four different families of NHC's reported in the literature. These families have different ways to induce a chirality on the reaction, with having free chiral substituents, with chiral induction on the back of the ring or possessing a chelating heteroatom on the chiral substituent. The first family, known as Herrmann's type NHC, gave disappointing results on the A.C.A. due to the rotation ability of the substituent's. Indeed, we never succeed to obtain results higher than 42% *ee* and 75% conversion for the A.C.A. of EtMgBr on the 3-mehylcyclohex-2-enone (Table 5, Entry 1).

The next step was to test a C_2-symmetric family of NHC ligands. Those DPEDA based carbenes allowed to obtain good results in terms of conversion and enantioselectivity. As these ligands had the possibility to adapt a little the size of the reacting volume to the size of the nucleophile, they could catalyze the 1,4-addition of a bulky t*ert*-butyl group on the 3-methylcyclohex-2-enone in a total 1,4 regioselectivity but with no enantioselectivity. Despite the fact that this kind of ligands were difficult to synthesize with good yield, they allowed the 1,4-addition of linear Grignard reagents to the 3-methylcyclohex-2-enone with high yields and good *ee*'s lying between 70-80% with a perfect regioselectivity. By switching to branched nucleophiles (*c*-pentyl, *i*-propyl), the *ee*'s dropped between 40% to 60% but kept perfect regioselectivities. The -OMe substituted ImH^+ 2e gave a little decrease of the *ee* for the addition of EtMgBr on the 3-methylcyclohex-2-enone but the addition of

the branched *i*-propyl nucleophile led to a strong increase of the *ee* from 40% to 70%. It seems that the -OMe groups acts as chelating moieties and improve the rigidity of the complex. By doing so, they also prevent the opening of the reactive site and bring therefore a better enantio-control. The addition of PhMgBr gave a promising 88% *ee* with ImH^+ 2a but with low regioselectivity (72:28 1,2:1,4). The use of ImH^+ 2e allowed to increase dramatically the regioselectivity (13:87 1,2:1,4) with keeping an acceptable 70% *ee*.

As the presence of chelating ligands seemed to bring better enantioselectivity, we synthesized Hoveyda's type ImH^+ containing a sulfonamide coordinating group. We were able to enhanced the Hoveyda's ligand synthesis efficiency by increasing the reaction rates using microwave irradiation and lower the cost by using cheaper reagents. The yields were always as good or better than those obtained by Hoveyda. Unfortunately, the synthesized ImH^+ gave not more than 20% *ee* and low conversions for our test reaction, namely the addition of EtMgBr on the 3-methylcyclohex-2-enone.

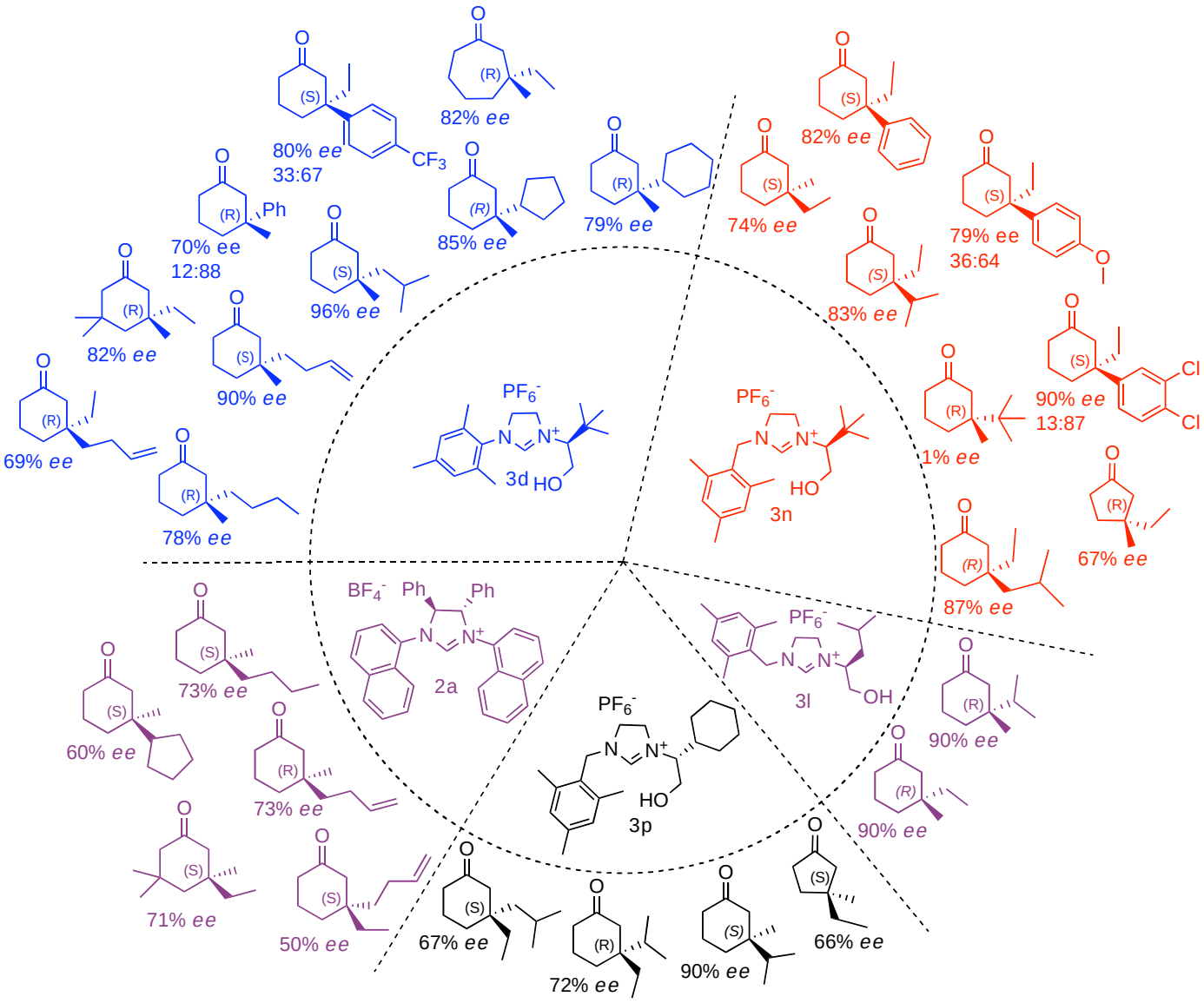
To circumvent this problem, we used alkoxy-substituted Mauduit-like ligands, which were easily synthesized through an amino alcohol nucleophilic substitution followed by a reductive amination and a standard cyclization in the presence of triethylorthoformate. These ImH^+ were obtained with high yields and gave excellent results for the 1,4-addition of linear Grignard reagents (ethyl, butyl, butenyl) to 3-methylcyclohex-2-enone with *ee*'s between 80% and 90%. The use of branched nucleophiles (*i*-butyl, *i*-propyl, *c*-hexyl, *c*-pentyl) gave also excellent results in term of enantioselectivities lying between 78% and 96% with perfect regioselectivities. We were pleased to see that our methodology was not substrate dependant. Indeed, the variation of the alkyl group on the cyclic substrate (ethyl, butenyl, isophorone, *i*-butyl, phenyl) gave very good results keeping the *ee*'s between 68% and 90%. By changing the ring size to a seven-membered ring, the *ee*'s were comparable to the six-membered ring ones, but by decreasing the ring size to five carbons, the *ee*'s droped to 40%. We also used aromatic substituted six-membered enones with very good *ee*'s around 80%. Unfortunately in those cases, the regioselectivity of the reaction decreased dramatically. The presence of an electron-withdrawing aromatic group gave better regiocontrol than an electron-donating substituent, but

the results were between 50:50 and 20:80 1,2:1,4. Finally, the addition of aromatic Grignard reagents on alkyl substituted cyclic enones gave very good *ee*'s up to 90% for the addition of *m*-OMe phenyl Grignard with often poor 1,4 regioselectivity.

In analogy with the DPEDA based ligands, we decided to increase the size of the reacting volume by homologating the mesityl group of Mauduit-like ligands. We observed that the enantioselectivities of the 1,4-addition reactions were highly increased (10% to 30%) when using substrates bulkier than 3-methylcyclohex-2-enone in presence of different Grignard reagents. We therefore had in hand a methodology that allowed to add quickly strong nucleophiles on trisubstituted cyclic enones with high yield, enantioselectivity and regioselectivity, by exchanging the mesityl with the methylmesityl substituted ligand depending on the substrate's bulkiness.

We finally developed synthetic applications with trapping the formed magnesium enolates with MeI, benzaldehyde, bromine and allyl iodide. These enolate trappings allowed to functionalize the cyclic substrates at the α-position with many different functionalities. Our methodology was also successfully applied in the first step of the total synthesis of Spirovibsanin A with 86% *ee* for the addition of 2-methylpent-2-enyl Grignard reagent to the 3-methylcyclohex-2-enone.

Best results scheme:



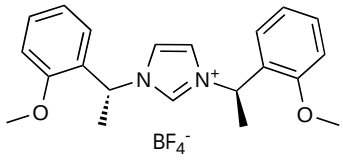
9. *Experimental part*

General Procedures :

All reactions were conducted under inert atmosphere. Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. All solvents employed in the reactions were dried on alumina columns and degassed prior to use. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded in $CDCl_3$, and chemical shift (δ) are given in ppm relative to residual $CHCl_3$. Evolution of reaction was followed by GC-MS Hewlett Packard (EI mode). Optical rotations were measured at 20 °C in a 1 cm cell in the stated solvent; $[\alpha]_D$ values are given in 10^{-1} deg·cm^2·g^{-1} (concentration c given as g / 100 mL). Enantiomeric excesses were determined by chiral-GC (capillary column, 10 psi H_2). Temperature programs are described as follows: initial temperature (°C) – initial time (min) – temperature gradient (°C / min) – final temperature (°C) ; retention time (R_T) are given in min.. Isophorone S5 and 3-methylcyclopent-2-enone S8 are commercially available (Aldrich) and were used without further purification. 3-methylcyclohept-2-enone was synthesized following a known procedure.[176] All Grignard reagents excepted ethyl and methyl magnesium bromide (Aldrich) were synthesized in Et_2O by addition of the corresponding bromide onto magnesium. Flash chromatography's were performed using silica gel 32-63 µm, 60 Å.

NHC spectral characterizations :

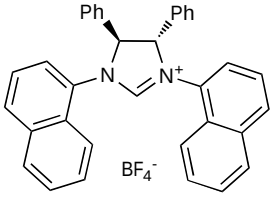
The NHC's 1a-b,[177] 2c-d,[83] 3a-f,[128] 3h[128] and 3j[128] were already described and their NMR are in accordance with the literature.



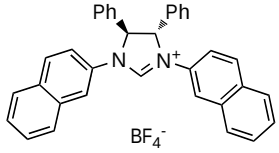
1,3-bis((R)-1-(2-methoxyphenyl)ethyl)-1H-imidazol-3-ium (1c): synthesized by Dr Martin

A flame-dried Schlenk tube was charged with paraformaldehyde (11 mmol) and dry toluene (10 mL). (*R*)-*o*-methoxy-α-methylbenzylamine (11 mmol) was added. The mixture was stirred and heated until dissolution of the solids. The obtained solution was then cooled to 0 °C and the other part of (R)-*o*-methoxy-α-methylbenzylamine (11 mmol) was added, followed by a 3 M

aqueous solution of NH_4BF_4 (11 mmol). The reaction was then stirred at 40 °C overnight. The solvents were discarded by high *vacuo* and the obtained crude solid was washed with Et_2O, filtered and dried in *vacuo* to give the pure product as a pale pink solid. (3.7 g, 76%) (3.7 g, 76%) ^{1}H NMR (400 MHz, $CDCl_3$) : 9.25 (s, 1 H), 7.40-7.33 (m, 4 H), 7.04-6.99 (m, 4 H), 6.88-6.86 (m, 2 H), 6.02-5.97 (q, 2 H, *J* = 7.1 Hz, 14.2 Hz), 3.76 (s, 6 H), 1.97-1.96 (d, 6 H, *J* = 7.1 Hz) ^{13}C NMR (125 MHz, $CDCl_3$) : 157.2, 135.9, 131.1, 127.4, 125.9, 121.4, 120.4, 111.4, 55.7, 55.1, 19.5 MS-ESI M^+ = 337.1 (calculated for $C_{21}H_{25}O_2N_2^+$: 337.2) $[\alpha]_D^{20}$ = -32.6 (c = 1.5; $CHCl_3$).

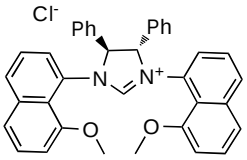


(4S,5S)-1,3-di(naphthalen-1-yl)-4,5-diphenylimidazolidine (2a): A flame dried Schlenk tube was charged with Pd_2dba_3 (915.70 g/mol, 0.12 mmol, 114 mg), +/- BINAP (622.69 g/mol, 0.24 mmol, 154 mg) and dry toluene (10 mL). The solution was stirred under N_2 for 1 hour at RT. Sublimed NaOtBu (96.10 g/mol, 7.1 mmol, 682 mg) and 1-bromonaphtalene (207.07 g/mol, 4.72 mmol, 977 mg) were then added and the mixture was stirred for 30 min at RT. DPEDA 5 (212.29 g/mol, 2.36 mmol, 499 mg) was finally added and the solution was stirred vigorously under reflux temperature (100 °C) for 20 hours. The obtained suspension was quenched with water (50 mL) and extracted with DCM (3 x 30 mL). The organic phase was dried on Na_2SO_4, filtered on a plug of Celite® and concentrated to give the crude product. This compound was purified by chromatography on a silica column with *c*-hexane : DCM 5:2 to give the pure product as a white solid. Rf = 0.11; MM = 425.25 g/mol (813 mg, 81%) ^{1}H NMR (400 MHz, $CDCl_3$) : 8.57 (s, 1 H), 8.09-8.07 (m, 2 H), 7.93-7.89 (m, 4 H), 7.86-7.84 (m, 2 H), 7.76-7.73 (m, 2 H), 7.60-7.57 (m, 2 H), 7.53-7.46 (m, 6 H), 7.35-7.30 (m, 6 H), 6.25 (s, 2 H) ^{13}C NMR (125 MHz, $CDCl_3$) : 158.6, 134.3, 132.7, 130.7, 130.4, 129.7, 129.3, 128.6, 127.2, 126.2, 125.9, 120.6 MS-ESI M^+ = 475.1 (calculated for $C_{35}H_{27}N_2^+$: 475.2) $[\alpha]_D^{20}$ = -393 (c = 0.3; $CHCl_3$).



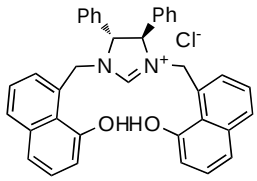
(4R,5R)-1,3-di(naphthalen-2-yl)-4,5-diphenylimidazolidine (2b) : synthesized by Dr Martin, same synthetic pathway as for 2a. (850 mg, 76%) ^{1}H NMR (400 MHz, $CDCl_3$) : 9.92 (s, 1 H), 7.99 (m, 2 H), 7.88-7.82 (m, 4 H), 7.76-7.74 (m, 2 H), 7.56-7.54 (m, 2 H), 7.49-7.42 (m, 14 H), 5.88 (s, 2 H) ^{13}C NMR (125 MHz, $CDCl_3$) : 153.8, 134.8, 133.3, 132.5, 131.8, 130.6, 130.4, 130.4,

128.6, 127.8, 127.6, 127.4, 126.9, 120.1, 118.5, 75.0 MS-ESI M^+ = 475.5 (calculated for $C_{35}H_{27}N_2^+$: 475.2)



(4*S*,5*S*)-1,3-bis(8-methoxynaphthalen-1-yl)-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-3-ium chloride (2e):

A flame dried 50 mL two-necked round-bottom flask surmounted by a condenser was charged with the diamine (975 mg, 1.8 mmol) in dry Et_2O. The solution was cooled to 0 °C and a solution of 2M HCl/MeOH (0.9 mL, 1 equiv.), prepared by adding acetyl chloride (1.42 mL, 20 mmol) in dry MeOH (10 mL) at 0°C, was added. The obtained chlorhydrate precipitate immediately from the ethereal solution, and the solvents were discarded by high vacuum. Dry toluene (30 mL) and trimethylorthoformate (0.32 mL, 1.9 mmol, 1.05 equiv.) were added and the obtained white suspension was placed in a 110°C prewarmed metal bath for 16 hours. The solvents were discarded by high vacuo and the obtained crude solid was washed with Et_2O, filtered and dried in vacuo to give the pure product as a pale pink solid. (735 mg, 72%) ^1H NMR ($CDCl_3$, 400 MHz) 9.05 (br s, 1 H), 8.41-8.39 (d, 2 H, J = 8.3 Hz), 8.28-8.26 (d, 2 H, *J* = 8.4 Hz), 7.98-7.96 (d, 2 H, *J* = 8.3 Hz), 7.70-7.64 (m, 6 H), 7.54-7.50 (m, 2 H), 7.29-7.27 (m, 6 H), 6.78-6.75 (d, 2 H, *J* = 7.7 Hz), 6.25 (s, 2 H), 3.92 (s, 6 H) ^{13}C ($CDCl_3$) 159.9, 156.5, 133.5, 130.0, 129.8, 129.5, 128.9, 128.4, 126.0, 125.9, 123.6, 122.6, 120.3, 103.8, 77.4, 55.9 HRMS (ESI-MS) : $[M]^+$ found, 535.2354 calculated for $C_{37}H_{31}N_2O_2$: 535.23800 Accuracy = -4.9. $[\alpha]_D^{20}$ = - 442.0 (c = 1.1; $CHCl_3$)

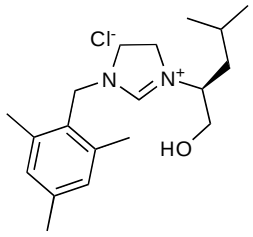


(4*R*,5*R*)-1,3-bis((8-hydroxynaphthalen-1-yl)methyl)-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-3-ium chloride (2h):

A 2M solution of HCl in MeOH was first prepared by adding acetyl chloride (1.42 mL, 20 mmol) in dry MeOH (10 mL) at 0 °C.

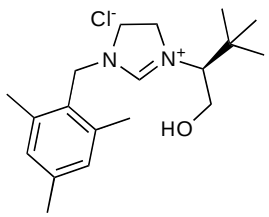
A flame dried 50 mL two-necked round-bottom flask surmounted by a condenser was charged with 8,8'-((1*R*,2*R*)-1,2-diphenylethane-1,2-diyl)bis(azanediyl)bis(methylene)dinaphthalen-1-ol 19 (524.65 g/mol, 1.9 mmol, 1.00 g) in dry Et_2O (15 mL). The solution was cooled to 0 °C and a solution of HCl/MeOH (0.95 mL) was added. A white precipitate was immediately formed. The solvents were discarded at the high *vacuum* pump for 15 minutes. Dry toluene (30 mL) and trimethyl orthoformate (106.12 g/mol, 2.0 mmol, 212 mg, 0.22 mL) were added and the obtained white suspension was placed in a 119 °C prewarmed metal bath for 20 hours. The formed ethanol and

the toluene were eliminated in *vacuo* to give a pale brown solid. This was dissolved in 2 mL of DCM and Et_2O was added to precipitate the product. This was filtered and dried at the high *vacuum* pump overnight to give the pure product as a pale brown solid. MM = 571.11 g/mol (544 mg, 77%) ^1H NMR ($CDCl_3$, 400 MHz) 9.23 (s, 1 H), 7.77 (d, 2 H, *J* = 7.6 Hz), 7.62 (d, 2 H, *J* = 8.1 Hz), 7.42 (t, 2 H, *J* = 7.8 Hz), 7.30-7.28 (m, 2 H), 7.24-7.21 (m, 2 H), 7.15-7.11 (m, 4 H), 7.07 (t, 2 H, *J* = 7.0 Hz), 6.85-6.84 (m, 4 H), 6.64 (br s, 2 H), 5.97-5.95 (m, 2 H), 4.65-4.62 (m, 2 H), 4.29 (s, 2 H), 1.31 (s, 2 H) ^{13}C ($CDCl_3$) 153.9, 136.4, 136.3, 130.3, 130.0, 129.4, 129.3, 127.8, 127.2, 126.5, 124.4, 122.7, 120.1, 112.3, 71.8, 53.2 HRMS (ESI-MS) : $[M]^+$ found, 535.2332 ; calculated for $C_{37}H_{31}N_2O_2$: 535.2385 Accuracy = -10 ppm. $[\alpha]_D^{20}$ = -27.2 (c = 0.8; $CHCl_3$).



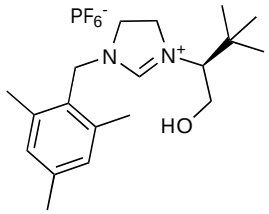
(*S*)-3-(1-hydroxy-4-methylpentan-2-yl)-1-(2,4,6-trimethyl benzyl) -4,5-dihydro-1*H*-imidazol-3-ium chloride (3l):

^1H NMR (400 MHz, $CDCl_3$) 8.48 (s, 1 H), 6.92 (s, 2 H), 6.08 (br s, 1 H), 4.86-4.82 (m, 1 H), 4.68-4.64 (m, 1 H), 4.21 (br s, 2 H), 3.89-3.87 (m, 1 H), 3.79-3.77 (m, 2 H), 3.64-3.59 (m, 2 H), 2.38 (s, 6 H), 2.29 (s, 3 H), 1.63-1.60 (m, 1 H), 1.50-1.45 (m, 1 H), 1.30-1.23 (m, 1 H), 0.94 (t, 6 H, *J* = 5.3 Hz) ^{13}C NMR (100 MHz, $CDCl_3$) : 157.9, 139.2, 138.1, 129.9, 125.6, 60.4, 59.8, 48.0, 46.4, 44.9, 37.7, 36.8, 25.0, 23.0, 22.1, 21.1, 20.1 $[\alpha]_D^{20}$ = +31.3 (c = 0.4; $CHCl_3$).



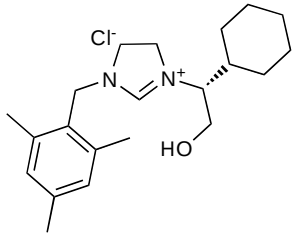
(*S*)-3-(1-hydroxy-3,3-dimethylbutan-2-yl)-1-(2,4,6-trimethyl benzyl)-4,5-dihydro-1*H*-imidazol-3-ium chloride (3m):

^{31}H NMR (400 MHz, $CDCl_3$) 8.68 (s, 1 H), 6.89 (s, 2 H), 4.91-4.88 (d, 1 H, J = 14.4 Hz), 4.75-4.72 (d, 1 H, J = 14,4 Hz)), 4.34-4.27 (m, 1 H), 4.10-4.03 (m, 1 H), 3.93-3.84 (m, 3 H), 3.76-3.68 (m, 1 H), 3.76-3.68 (m, 1 H), 3.62-3.59 (m, 1 H), 2.35 (s, 6 H), 2.27 (s, 3 H), 0.98 (s, 9 H) ^{13}C NMR (125 MHz, $CDCl_3$) : 159.2, 138.1, 129.9, 71.0, 56.9, 48.2, 46.5, 33.5, 27.6, 27.2, 21.1, 21.0, 20.1 HRMS (ESI-MS) : $[M]^+$ found, 303.2438; calculated for $C_{19}H_{31}N_2O$: 303.2430 Accuracy = +2.3 ppm.



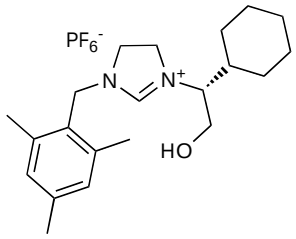
(*S)*-3-(1-hydroxy-3,3-dimethylbutan-2-yl)-1-(2,4,6-trimethyl benzyl)-4,5-dihydro-1*H*-imidazol-3-ium hexafluorophosphate (V) (3n):

(652 mg, 97%) ^{1}H NMR (300 MHz, $CDCl_3$) 8.68 (s, 1 H), 6.89 (s, 2 H), 4.91-4.88 (d, 1 H, J = 14.4 Hz), 4.75-4.72 (d, 1 H, J = 14,4 Hz)), 4.34-4.27 (m, 1 H), 4.10-4.03 (m, 1 H), 3.93-3.84 (m, 3 H), 3.76-3.68 (m, 1 H), 3.76-3.68 (m, 1 H), 3.62-3.59 (m, 1 H), 2.35 (s, 6 H), 2.27 (s, 3 H), 0.98 (s, 9 H) ^{31}P NMR (125 MHz, $CDCl_3$) : -144.68 (quint, *J* = 713 Hz) $[\alpha]_D^{20}$ = +14.4 (c = 1.1; $CHCl_3$).

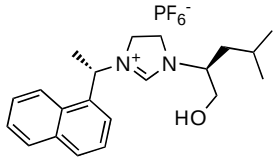


(*R*)-3-(1-cyclohexyl-2-hydroxyethyl)-1-(2,4,6-trimethyl benzyl)-4,5-dihydro-1*H*-imidazol-3-ium chloride (3o):

A 2M solution of HCl in MeOH was first prepared by adding acetyl chloride (1.42 mL, 20 mmol) in dry MeOH (10 mL) at 0 °C. A flame dried 50 mL two-necked round-bottom flask surmounted by a condenser was charged with (*R*)-2-cyclohexyl-2-(2-(2,4,6-trimethylbenzylamino)ethylamino) ethanol 71 (318.49 g/mol, 2.35 mmol, 750 mg) in dry Et_2O (10 mL). The solution was cooled to 0 °C and a solution of HCl/MeOH (1.2 mL) was added. A white precipitate was immediately formed. The solvents were discarded at the high *vacuum* pump for 2 hours. Dry toluene (30 mL) and triethyl orthoformate (148.20 g/mol, 2.47 mmol, 366 mg, 0.41 mL) were added and the obtained white suspension was placed in a 117 °C prewarmed metal bath for 20 hours. The formed ethanol and the toluene were eliminated in *vacuo* to give a pale brown solid. This was dissolved in 2 mL of DCM and Et_2O was added to precipitate the product. This was filtered and dried at the high *vacuum* pump overnight to give the pure product as a pale brown solid. MM = 364.95 g/mol (571 mg, 67%) ^{1}H NMR (400 MHz, $CDCl_3$) 8.64 (s, 1 H), 6.88 (s, 2 H), 4.85-4.82 (d, 1 H, *J* = 14.4 Hz), 4.67-4.64 (d, 1 H, *J* = 14.4 Hz), 4.22-4.05 (m, 2 H), 3.83-3.79 (m, 1 H), 3.70-3.62 (m, 3 H), 3.57-3.52 (m, 1 H), 2.34 (s, 6 H), 2.25 (s, 3 H), 1.74-1.66 (m, 4 H), 1.57-1.54 (m, 1 H), 1.46-1.40 (m, 1 H), 1.21-1.11 (m, 4 H), 1.03-0.94 (m, 2 H) ^{13}C NMR (125 MHz, $CDCl_3$) : 159.2, 138.1, 129.9, 71.0, 56.9, 48.2, 46.5, 33.5, 27.6, 27.2, 21.1, 21.0, 20.1 HRMS (ESI-MS) : $[M]^+$ found, 329.2583; calculated for $C_{21}H_{32}N_2O$: 329.2587 Accuracy = -1.3 ppm $[\alpha]_D^{20}$ = -20.3 (c = 0.6; $CHCl_3$).

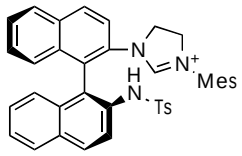


(*R*)-3-(1-cyclohexyl-2-hydroxyethyl)-1-(2,4,6-trimethylbenzyl)-4,5-dihydro-1*H*-imidazol-3-ium hexafluorophosphate(V) (3p): The imidazolium chloride 3o (364.95 g/mol, 0.55 mmol, 200 mg) was dissolved in distilled water (20 mL). The aqueous layer was washed with EtOAc, then KPF_6 (184.06 g/mol, 1.1 mmol, 203 mg) was added and the solution was stirred at RT for 4 hours. The imidazolium salt was extracted with DCM (3 x 50 mL), the organic phases were then washed with brine, dried over $MgSO_4$ and concentrated in *vacuo* to give the pure sticky product. This was dissolved twice in DCM (2 mL) and toluene (3 mL) and it was dried in *vacuo* to give a white solid. MM = 474.46 g/mol (258 mg, 99%) ^{1}H NMR (400 MHz, $CDCl_3$) 8.64 (s, 1 H), 6.88 (s, 2 H), 4.85-4.82 (d, 1 H, *J* = 14.4 Hz), 4.67-4.64 (d, 1 H, *J* = 14.4 Hz), 4.22-4.05 (m, 2 H), 3.83-3.79 (m, 1 H), 3.70-3.62 (m, 3 H), 3.57-3.52 (m, 1 H), 2.34 (s, 6 H), 2.25 (s, 3 H), 1.74-1.66 (m, 4 H), 1.57-1.54 (m, 1 H), 1.46-1.40 (m, 1 H), 1.21-1.11 (m, 4 H), 1.03-0.94 (m, 2 H) ^{31}P (162 MHz, $CDCl_3$) -135.5, -139.9, -144.3, -148.7, -153.1.



1-((*S*)-1-hydroxy-4-methylpentan-2-yl)-3-((*S*)-1-(naphthalene-1-yl)ethyl)-4,5-dihydro-1*H*-imidazol-3-ium hexafluorophosphate (V) (3r): synthesized by Dr Mauduit

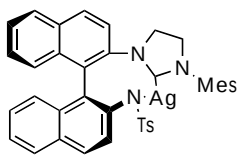
^{1}H NMR (400 MHz, $CDCl_3$) 7.99 (s, 1 H), 7.96-7.94 (m, 1 H), 7.89-7.85 (m, 2 H), 7.61-7.58 (m, 1 H), 7.54-7.49 (m, 2 H), 7.47-7.45 (m, 1 H), 5.59-5.54 (m, 1 H), 3.93-3.83 (m, 5 H), 3.68-3.66 (m, 1 H), 3.54-3.50 (m, 1 H), 2.93 (s, 1 H), 1.86 (d, 3 H, *J* = 6.8 Hz), 1.52-1.43 (m, 2 H), 1.31-1.25 (m, 1 H), 0.91 (d, 3 H, J=6.3 Hz), 0.86 (t, 3 H, *J* = 6.3 Hz) ^{13}C NMR (100 MHz, $CDCl_3$): 156.4, 134.2, 132.7, 130.5, 130.0, 129.5, 127.6, 126.5, 125.7, 124.2, 121.9, 61.3, 59.4, 54.5, 47.2, 44.8, 36.7, 24.8, 22.7, 22.0, 19.3 $[\alpha]_D^{20}$ = -9.2 (c = 0.4; $CHCl_3$).



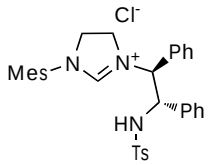
(*S*)-3-mesityl-1-(2'-(4-methylphenylsulfonamido)-1,1'-binaphthyl-2-yl)-4,5-dihydro-1*H*-imidazol-3-ium chloride (4a):

(808 mg, 83%) ^{1}H NMR (400 MHz, DMSO-*d*) 9.92 (br s, 1 H), 8.61 (br s, 1 H), 8.42-8.40 (m, 1 H), 8.21-8.19 (m, 1 H), 8.12-8.10 (m, 1 H), 8.06-8.04 (m, 2 H), 7.67 (br s, 2 H), 7.52-7.50 (m, 2 H), 7.37-7.34 (m, 4 H), 6.95 (m, 4 H), 4.37-4.35 (m, 1 H), 4.24-4.22 (m, 1 H), 4.11-4.09 (m, 1 H), 4.04-4.01 (m, 1 H), 2.41 (s, 3 H), 2.24 (s, 3 H), 2.00 (br s, 3 H), 1.49 (br s, 3 H) ^{13}C NMR (100 MHz, $CDCl_3$) : 158.2, 139.6, 135.2, 134.6, 133.7, 133.0, 132.3,

130.7, 130.4, 129.8, 129.2, 128.4, 128.3, 128.0, 127.7, 127.2, 126.4, 126.0, 124.8, 123.2, 121.1, 51.2, 50.7, 21.1, 20.5 $[\alpha]_D^{20}$ = -53.3 (c = 0.5; $CHCl_3$).



(*S*)-3-mesityl-1-(2'-(4-methylphenylsulfonamido)-1,1'-binapht hyl-2-yl)-4,5-dihydro-1*H*-imidazol-3-ium silver complex (4b):
(808 mg, 83%) MS (ESI) : 1332.9, 1331.0, 1330.7, 1329.7, 1328.8, 1327.7, 1326.7, 1325.7.

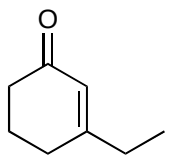


1-mesityl-3-((1*S*,2*S*)-2-(4-methylphenylsulfonamido)-1,2-diphenylethyl)-4,5-dihydro-1*H*-imidazol-3-ium chloride (4c):
(54 mg, 66%) HRMS (ESI-MS) : $[M]^+$ found, 538.2521; calculated for $C_{37}H_{31}N_2O_2$: 538.2522 Accuracy = -0.3 ppm.

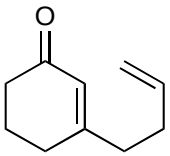
Substrates spectral characterizations:

Typical procedure for 3-substituted cyclohex-2-enone synthesis.

A flame-dried flask was charged with Grignard reagent (2.0 eq.) and cooled to 0 °C. The ethoxycyclohex-2-en-1-one 49 (50 mmol) in THF (40 mL) was added dropwise. Once the addition was complete the reaction mixture was left at room temperature until complete disappearance of the starting material. The reaction was hydrolyzed by addition of aqueous sulfuric acid (5% w/w). Diethyl ether (50 mL) was added and the aqueous phase was separated and extracted further with diethyl ether (3 x 20 mL). The combined organic layers were washed with $NaHCO_3$, brine and water, dried over sodium sulfate, filtered and concentrated in *vacuo*. The oily residue was purified by Kugelrohr distillation under reduced pressure.

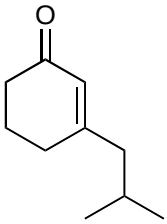


3-ethylcyclohex-2-enone (S3):[178]
(800 mg, 73% yield) ^1H NMR (500 MHz, $CDCl_3$) : 5.87 (t, 1 H, *J* = 1.4 Hz), 2.36 (t, 2 H, *J* = 3.3 Hz), 2.29 (t, 2 H, *J* = 5.7 Hz), 2.27-2.22 (m, 2 H), 1.99 (m, 2 H), 1,1 (t, 3 H, *J* = 7.4 Hz) ^{13}C NMR (125 MHz, $CDCl_3$) : 200.0, 167.8, 124.5, 37.4, 30.8, 29.7, 22.7, 11.2.



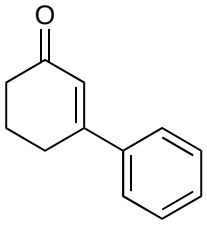
3-(3-butenyl)cyclohex-2-enone (S4):[16,179]

(1.2 g, 92% yield) ^{1}H NMR (500 MHz, $CDCl_3$) : 5.80 (s, 1 H), 5.75-5.67 (m, 1 H), 4.98 (dd, 1 H, J_1 = 17.1 Hz, J_2 = 1.5 Hz), 4.92 (dd, 1 H, J_1 = 9.4 Hz, J_2 = 1.6 Hz), 2.29-2.19 (m, 8 H), 1.94-1.89 (m, 2 H) ^{13}C NMR (125 MHz, $CDCl_3$) : 199.9, 165.6, 137.1, 126.1, 115.7, 37.5, 37.4, 31.1, 29.9, 22.8.



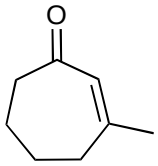
3-*isobutyl*-butylcyclohex-2-enone (S6):[180]

(5.4 g, 71% yield). ^{1}H NMR (400 MHz, $CDCl_3$) : 5.83 (s, 1 H), 2.35 (t, 2 H, *J* = 6.7 Hz), 2.26 (t, 2 H, *J* = 5.9 Hz), 2.08 (d, 2 H, *J* = 7.3 Hz), 2.00 (quint., 2 H), 1.92 (sept., 1 H, *J* = 6.4 Hz), 0.90 (d, 6 H, *J* = 6.6 Hz) ^{13}C NMR (100 MHz, $CDCl_3$) : 200.0, 165.7, 127.0, 47.8, 37.5, 29.8, 26.5, 22.9, 22.6.



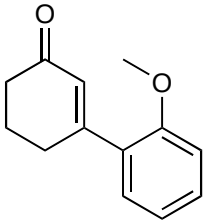
3-phenylcyclohex-2-enone (S7):[181,182]

(5.8 g, 67% yield) ^{1}H NMR (400 MHz, $CDCl_3$) : 7.55 (m, 2 H), 7.42 (m, 3 H), 6.42 (s, 1 H), 2.79 (m, 2 H), 2.51 (t, 2 H, *J* = 6.3 Hz), 2.19 (quint., 2 H, *J* = 6.3 Hz) ^{13}C NMR (100 MHz, $CDCl_3$) : 200.2, 160.0, 130.2, 129.0, 126.3, 125.7, 37.5, 28.4, 23.1.



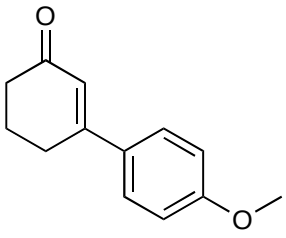
3-methylcyclohept-2-enone (S9):[44]

(91 mg, 20% yield) ^{1}H NMR (500 MHz, $CDCl_3$) : 5.89 (s, 1 H), 2.56-2.53 (m, 2 H), 2.39-2.37 (m, 2 H), 1.93 (s, 3 H), 1.81-1.72 (m, 4 H) ^{13}C NMR (125 MHz, $CDCl_3$) : 203.6, 158.3, 129.7, 42.1, 34.4, 27.5, 25.0, 21.4 MS (EI) : 124 (41), 109 (24), 96 (21), 95 (100), 82 (93), 81 (49), 80 (23), 69 (10), 68 (20), 67 (56), 59 (11), 55 (20), 54 (21), 53 (26) HRMS (ESI-MS) : $[M]^+$ found, 124.08898 calculated for $C_8H_{12}O$: 124.08882.



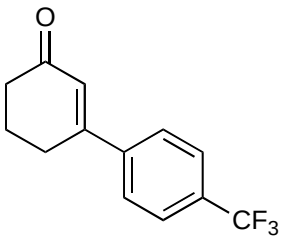
3-(2-methoxyphenyl)cyclohex-2-enone (S10):[44]

(1.9 g, 57% yield) ^{1}H NMR (400 MHz, $CDCl_3$) : 7.36-7.32 (t, 1 H, *J* = 10.1 Hz), 7.21-7.19 (d, 1 H, *J* = 9.3 Hz), 6.99-6.92 (m, 2 H), 6.20 (s, 1 H), 3.84 (s, 3 H), 2.75-2.72 (t, 2 H, *J* = 5.8 Hz), 2.50-2.47 (t, 2 H, *J* = 6.3 Hz), 2.14-2.07 (q, 2 H, *J* = 5.8 Hz) ^{13}C NMR (100 MHz, $CDCl_3$) : 200.3, 161.8, 156.7, 130.5, 129.2, 128.9, 128.3, 120.9, 111.3, 55.6, 37.7, 30.2, 23.4.



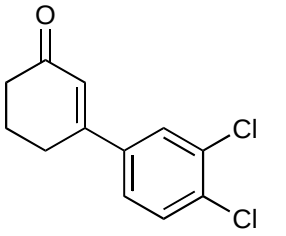
3-(4-methoxyphenyl)cyclohex-2-enone (S11):[44]

(2.8 g, 98% yield) ^{1}H NMR (400 MHz, $CDCl_3$) : 7.53-7.51 (d, 2 H), 6.94-6.92 (d, 2 H), 6.40 (s, 1 H), 3.84 (s, 3 H), 2.77-2.73 (m, 2 H), 2.49-2.45 (t, 2 H, *J* = 6.3 Hz), 2.17-2.11 (quint, 2 H, *J* = 6.3 Hz) ^{13}C NMR (100 MHz, $CDCl_3$) : 200.2, 161.4, 159.4, 130.9, 127.8, 123.8, 114.3, 55.5, 37.3, 28.0, 22.9 MS (EI): 202, 174*, 159, 146, 131, 115, 103, 89, 77, 63, 51.



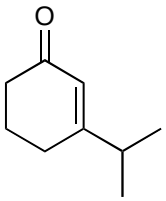
3-(4-(trifluoromethyl)phenyl)cyclohex-2-enone (S12):[44]

(810 mg, 84% yield) ^{1}H NMR (400 MHz, $CDCl_3$) : 7.69-7.61 (m, 4 H), 6.43 (s, 1 H), 2.79-2.76 (t, 2 H, *J* = 5.80 Hz), 2.53-2.50 (t, 2 H, *J* = 6.8 Hz), 2.22-2.16 (quint., 2 H, *J* = 6.3 Hz) ^{13}C NMR (100 MHz, $CDCl_3$) : 199.6, 158.2, 127.1, 126.6, 125.9, 125.9, 125.9, 125.7, 37.3, 28.3, 22.9 MS (EI): 240, 221, 212, 171, 151, 143, 133, 115*, 75, 63, 51.



3-(3,4-dichlorophenyl)cyclohex-2-enone (S13):

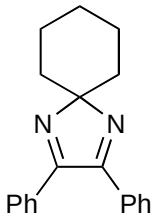
(1.6 g, 96% yield) ^{1}H NMR (400 MHz, $CDCl_3$) : 7.61-7.60 (m, 1 H), 7.50-7.47 (m, 1 H), 7.37-7.35 (m, 1 H), 6.38 (s, 1 H), 2.73-2.70 (t, 2 H, *J* = 6.1 Hz), 2.51-2.48 (t, 2 H, *J* = 6.6 Hz), 2.20-2.13 (q, 2 H, *J* = 6.3 Hz) MS (EI): 242, 240, 214, 212, 205, 184, 149, 114, 99, 74, 63, 51.



3-isopropylcyclohex-2-enone (S14):[183]

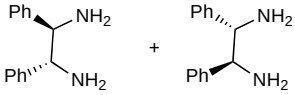
^{1}H NMR (400 MHz, $CDCl_3$) : 5.85 (s, 1 H), 3.20-3.17 (t, 2 H, *J* = 6.8 Hz) 2.55-2.52 (m, 1 H), 2.10-2.07 (t, 2 H, *J* = 6.8 Hz), 1.69-1.66 (m, 2 H), 1.06-1.04 (d, 6 H, *J* = 7.1 Hz) ^{13}C NMR (100 MHz, $CDCl_3$) : 200.1, 172.2, 123.7, 37.7, 36.0, 27.7, 23.3, 21.6.

Products spectral characterizations :



2,3-diphenyl-1,4-diazaspiro[4.5]deca-1,3-diene (2):[140]

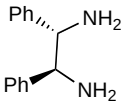
A round-bottomed flask equipped with a reflux condenser was charged with glacial AcOH (500 mL), benzil (210.23 g/mol, 376 mmol, 79.0 g), NH_4OAc (77.08 g/mol, 2.59 mol, 200.0 g) and *c*-hexanone (98.14 g/mol, 387 mmol, 38.0 g, 40.0 mL). The yellow suspension was heated to reflux for 1.5 hour. It was then poured warm in stirred water (1.5 L) The pale yellow suspension was left without stirring at RT overnight. The crystals were then filtered, washed with water and dried in *vacuo* at 60 °C over the weekend. MM = 288.39 g/mol (103 g, 95%) ^1H NMR (400 MHz, $CDCl_3$) : 7.51 (s, 2 H), 7.49 (s, 2 H), 7.44-7.42 (m, 1 H), 7.41-7.40 (m, 1 H), 7.37 (s, 1 H), 7.35 (s, 2 H), 7.34 (s, 1 H), 1.98-1.95 (m, 4 H), 1.82-1.80 (m, 4 H), 1.74-1.72 (m, 2 H) ^{13}C NMR (100 MHz, $CDCl_3$) : 164.1, 133.2, 130.1, 129.0, 128.4, 104.2, 34.8, 25.8, 24.2.



(1*S*,2*S*)-(1R,2R)-1,2-diphenylethane-1,2-diamine (3):[140]

A tri-necked round-bottomed flask equipped with a thermometer was charged with 2,3-diphenyl-1,4-diazaspiro[4.5]deca-1,3-diene 2 (288.39 g/mol, 0.25 mol, 72.0 g). Dry THF (400 mL) was added and the suspension was stirred until the entire solid was dissolved. Then, the solution was cooled to -78 °C and gaseous NH_3 (≈400 mL) was added (it takes 1.5 h) The temperature was maintained under -65 °C (bp NH_3 = -33 °C) Lithium (6.94 g/mol, 1.0 mol, 6.9 g, 153 cm) was then added in little pieces. The temperature was maintained below -65 °C. The solution was then stirred for 50 minutes. After 30 minutes, it becomes dark violet. EtOH (30 mL) was then added dropwise and the mixture was stirred for additional 30 minutes. NH_4Cl (53.49 g/mol, 1.31 mmol, 70 g) was then added in three portions and the cold bath was removed to allow the suspension to warm to RT overnight. The suspension was warmed 2 hours at -30 °C to evaporate NH_3. H_2O (400 mL) was carefully added and the phases were separated. The aqueous layer was extracted with ether (3 x 300 mL) and the combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated to about 200 mL. The solution was poured at RT on a solution of HCl 2M (300 mL) The biphasic mixture was vigorously stirred at RT for 1 hour, then H_2O (500 mL) was added and the layers were separated. The organic phase was extracted with H_2O and the combined aqueous phases were washed with DCM

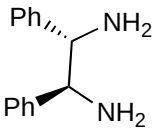
(300 mL) The aqueous phase was then carefully treated with NaOH 2M and extracted with DCM (4 x 150 mL) The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated to give a yellow solid. MM = 212.29 g/mol (40.33 g, 76%) ^1H NMR (400 MHz, $CDCl_3$) : 7.3-7.2 (m, 10 H), 4.13 (s, 2 H), 1.59 (s, 4 H).



. tartaric salt

(1*S*,2*S*)-1,2-diphenylethane-1,2-diamine tartaric salt (4):[140]

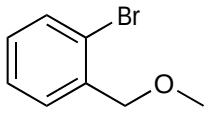
A round-bottomed flask was charged with (1*S*,2*S*)-(1R,2R)-1,2-diphenylethane-1,2-diamine 3 (212.29 g/mol, 0.19 mol, 40.33 g) and EtOH (230 mL) The solid was dissolved by heating the mixture at 70 °C. A 70 °C homogenous solution of tartaric acid in EtOH (230 mL) was then added. The tartrate salt precipitate immediately. The suspension was allowed to come back to RT and the crystals were filtrated. The solid was fixed on the bottom of the flask and it was not possible to take it off. It was dried in *vacuo* to give a pale yellow solid. This was dissolved in boiling water (310 mL), then EtOH (310 mL) was added and the solution was allowed to come back slowly to RT. The solution was left at RT for 15 hours (important, otherwise, there was only poor recristallized product). The pale yellow solid was filtered and washed with EtOH (50 mL) The solid was dried in *vacuo*, and then recristallized in water (260 mL) followed by EtOH (260 mL) The obtained pale yellow crystals were filtered and washed with EtOH. The crystals were a third time recristallized in the same manner as before, with 230 mL of H_2O and EtOH. The obtained transparent crystals were dried under high *vacuo*. MM = 326.35 g/mol (18.61 g, 25%).



(1*S*,2*S*)-1,2-diphenylethane-1,2-diamine (DPEDA) (5):[140]

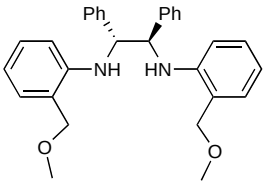
A round-bottomed flask was charged with the diamine tartaric acid salt 4 (326.35 g/mol, 57.0 mmol, 18.61g) and H_2O (300 mL) The solid was dissolved by stirring it at RT. NaOH 50% (25 mL) was then added, followed by DCM (150 mL) The biphasic solution was stirred at RT overnight. The two phases were then separated. The aqueous layer was extracted with DCM (4 x 150 mL) The combined organic phases were washed with brine, dried on Na_2SO_4, filtered and concentrated to give a pale yellow solid. This was recristallized in hexane to give the pure product as pale yellow needles.

MM = 212.29 g/mol (9.30 g, 77%) ^{1}H NMR (400 MHz, $CDCl_3$) : 7.34-7.33 (m, 8 H), 7.29-7.27 (m, 2 H), 4.16 (s, 2 H), 1.65 (br s, 4 H) ^{13}C NMR (100 MHz, $CDCl_3$) : 143.5, 128.4, 127.1, 127.0, 62.0 MS (ESI-Neg) : 235.1 (+Na) $[\alpha]_D$: -104 (MeOH, c = 1.4).



1-bromo-2-(methoxymethyl)benzene (6):[184, commercially available]

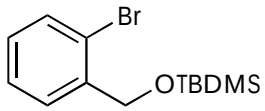
A 50 mL flame dried round-bottomed flask was charged with KH 20% in oil (40.11 g/mol, 3.32 mmol, 532 mg) and dry THF (10 mL) The suspension was warmed to 50 °C and MeI (141.94 g/mol, 4.0 mmol, 0.24 mL) was added. A solution of Bromohydroxybenzil (187.03 g/mol, 2.66 mmol, 500 mg) methanol in THF (15 mL) was then added dropwise in 30 minutes to the warm suspension. The suspension was then heated for 60 more minutes. The system was allowed to come back to RT and was stirred over the weekend. It became a yellow white suspension. H_2O (1 mL) was added to hydrolyze excess of KH. The solvents were evaporated to discard THF. EtOAc (30 mL) was added and the product was extracted with EtOAc (5 x 30 mL) The organic layer was washed with NaCl aq., dried on $MgSO_4$, filtered and concentrated to give a transparent oil. There was still some product in the aqueous layer. The crude was purified on silica with *c*-hexane to give the pure product as a pale pink oil. Rf = 0.41; MM = 201.06 g/mol (270 mg, 51%) ^{1}H NMR (400 MHz, $CDCl_3$) : 7.54 (d, 1 H, *J* = 7.9 Hz), 7.45 (d, 1 H, *J* = 9.2 Hz), 7.33 (t, 1 H, *J* = 6.2 Hz), 7.15 (t, 1 H, *J* = 6.1 Hz), 4.53 (s, 2 H), 3.47 (s, 3 H) ^{13}C NMR (100 MHz, $CDCl_3$) : 137.7, 132.7, 129.1, 129.0, 127.5, 122.8, 74.0, 58.8 MS (EI): 202, 200, 171, 169, 121*, 91, 77, 63, 51.



(1*R*,2*R*)-*N*^{1},*N*^{2}-bis(2-(methoxymethyl)phenyl)-1,2-diphenyl ethane -1,2-diamine (7): [137]

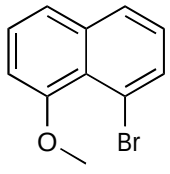
A flame-dried high-pressure Schlenk tube was charged with dry toluene (5 mL) The mixture was degassed by freeze-*vacuum* (Schlenk technique) (3x). +/- BINAP (622.69 g/mol, 0.04 mmol, 25 mg), Pd_2dba_3 (915.70 g/mol, 0.014 mmol, 13.2 mg) and NaO*t*Bu (96.10 g/mol, 0.67 mmol, 65 mg) were then added and the suspension was stirred at RT for 60 minutes. (1*S*,2*S*)-1,2-diphenylethane-1,2-diamine 5 (212.29 g/mol, 0.24 mmol, 51 mg) was then added, followed by 1-bromo-2-(methoxymethyl)benzene 6 (201.06 g/mol, 0.5 mmol, 100 mg). The mixture was then heated to 130 °C for 60 hours in the sealed Schlenk tube under N_2 in a prewarmed oil bath. The system was allowed to come back to RT and the

solvent was discarded at the high *vacuum* pump. EtOAc was added and the suspension was filtered on a plug of Celite®. The Celite® was washed with EtOAc and the mother liquor was concentrated in *vacuo* to give a dark solid. This was purified by chromatography on silica with *c*-hexane : EtOAc 10:1 to give the pure product as a red semi-solid. Rf = 0.25; MM = 452.59 g/mol (61 mg, 56%) ^{1}H NMR (400 MHz, $CDCl_3$) 7.35-7.33 (m, 4 H), 7.31-7.29 (m, 3 H), 7.27-7.24 (m, 3 H), 7.06-7.04 (m, 2 H), 7.03-6.99 (m, 2 H), 6.61 (t, 2 H, *J* = 7.3 Hz), 6.31 (d, 2 H, *J* = 8.1 Hz), 5.86 (br s, 2 H), 4.79-4.78 (m, 2 H), 4.61-4.58 (m, 2 H), 4.51-4.49 (m, 2 H), 3.27 (s, 6 H) ^{13}C NMR (100 MHz, $CDCl_3$) : 146.5, 140.1, 129.8, 129.2, 128.4, 127.4, 127.3, 122.5, 116.6, 112.2, 74.2, 63.1, 57.2.



(2-bromobenzyloxy)(*tert*-butyl)dimethylsilane (9):

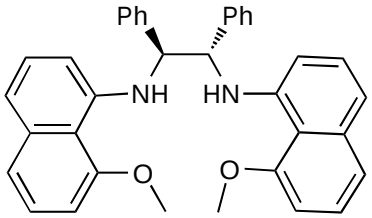
A 50 mL flame dried round-bottomed flask was charged with bromohydroxybenzil (187.03 g/mol, 1.33 mmol, 250 mg) DMF (15 mL), TBDMSCl (150.72 g/mol, 5.32 mmol, 802 mg) and imidazoline (68.08 g/mol, 10.64 mmol, 724 mg). The suspension was warmed to 60 °C over the weekend. The system was allowed to come back to RT. A solution of sat. $NaHCO_3$, H_2O and Et_2O (1 : 1 : 2) was added. The product was extracted with Et_2O (4 x 30 mL) The organic layer was washed with NaCl aq., dried on Na_2SO_4, filtered and concentrated to give a transparent oil. This was purified on silica with pure c-hexane to give the pure product as a transparent oil. Rf = 0.38; MM = 301.30 g/mol (279 mg, 70%) ^{1}H NMR (400 MHz, $CDCl_3$) 7.56 (d, 1 H, *J* = 7.6 Hz), 7.49 (d, 1 H, *J* = 7.6 Hz), 7.33 (t, 1 H, *J* = 7.3 Hz), 7.12 (t, 1 H, *J* = 7.8 Hz), 4.74 (s, 2 H), 0.97 (s, 9 H), 0.14 (s, 6 H) ^{13}C NMR (100 MHz, $CDCl_3$) : 140.5, 132.1, 128.3, 127.7, 127.5, 121.1, 64.7, 26.1, 18.6, -5.2.



1-bromo-8-methoxynaphtalene (11):[185]

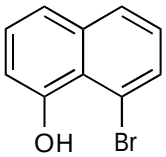
A 250 mL flame-dried two-neck round-bottomed flask was charged with 1-methoxynaphtalene (31.6 mmol, 4.57 mL) and dry hexane (60 mL). The transparent solution was stirred under N_2 at RT while *t*-BuLi (1.5 M, 38 mmol, 25.3 mL) was added dropwise. After 10 minutes, the solution became yellow and cloudy. The solution was stirred for 26 hours at RT. A solution of Br_2 (1.95 mL, 38 mmol, 1.2 eq.) in dry hexane (15 mL) was added dropwise to the dark yellow suspension. After addition, the dark solution was stirred for 12 hours. A saturated aqueous solution of $Na_2S_2O_3$ (30 mL) was added and the suspension was stirred for 10 minutes. H_2SO_4 5% (3 mL) was then added and the aqueous layer was extracted with

EtOAc (3 x 15 mL). The combined organic layers were dried on Na_2SO_4, filtered on a plug of silica with EtOAc and concentrated to give a dark brown liquid. This was purified by chromatography on silica with pure hexane to give a mixture of product and starting material (3:1). ^{1}H NMR (400 MHz, $CDCl_3$) : 8.32-8.30 (m, 1 H), 8.21-8.19 (m, 1 H), 7.70-7.68 (m, 1 H), 7.66-7.62 (m, 1 H), 7.57-7.54 (m, 1 H), 6.71-6.69 (m, 1 H), 4.01 (s, 3 H) ^{13}C NMR (125 MHz, $CDCl_3$) : 155.4, 132.5, 129.6, 127.9, 126.9, 126.1, 122.5, 120.3, 113.4,104.6, 55.8.



Synthesis of C2 symmetric diamines (12):

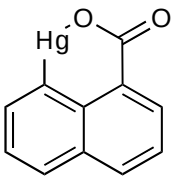
A flame-dried high-pressure Schlenk tube was charged with dry toluene (20 mL). This was 3 times degassed by "freeze-*vacuum* technique", and put under N_2. +/- BINAP (1.65 mmol, 997 mg), Pd_2dba_3 (0.286 mmol, 262 mg) and NaO*t*Bu (15.4 mmol, 1.48 g) were weighted under a cone of N_2 and added to the solvent. The suspension was stirred at RT for 60 minutes under N_2. *S,S*-DPEDA 5 (5.5 mmol, 1.17 g) was then added, followed by 1-bromo-8-methoxynaphthalene 2e' (3.50 g, 11 mmol, 2.1 eq.) The sealed Schlenk was then heated in a prewarmed 130 °C oil bath for 15 hours. The dark mixture was cooled to RT, filtered on a plug of Celite® and washed with THF. The filtrate was concentrated in *vacuo*. It was then deposit on silica and filtrated on silica chromatography with EtOAc : hexane 1:10. The obtained mixture was then purified on basic alumina chromatography (65 mm, 17 cm alumina) with EtOAc:hexane 1:10 to give the pure product 2e' as a lemon yellow solid. It was highly important to degass the solvent, give the time to the complexe formation and weight the reagents under an inert atmosphere. (1.95 g, 42%) ^{1}H NMR ($CDCl_3$, 400 MHz) 8.25-8.23 (m, 2 H), 7.95-7.94 (m, 2 H), 7.51-7.48 (m, 4 H), 7.34-7.32 (m, 4 H), 7.23-7.20 (m, 6 H), 6.55-6.53 (m, 2 H), 6.33-6.31 (m, 2 H), 5.19 (br s, 2 H), 4.85 (s, 2 H), 3.86 (s, 6 H) ^{13}C ($CDCl_3$) 128.7, 127.8, 127.5, 126.3, 126.0, 125.8, 125.4, 122.8, 120.3, 104.4, 65.0, 55.8 EI-MS: 524, 262*.



1-bromo-8-hydroxynaphthalene (13):[186]

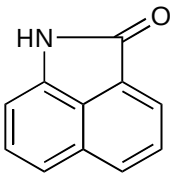
A 250 mL flame-dried two-neck round-bottomed flask was charged with 1-bromo-8-methoxynaphtalene 11 (237.09 g/mol, 23.6 mmol, 5.6 g) and dry DCM (20 mL) The transparent solution was cooled to -78 °C under N_2. The flask was protected with aluminum, then BBr_3 in DCM (0.7 mol/L, 28.3 mmol, 40.4 mL)

was added dropwise with a plastic syringe. The brown solution was allowed to come back to RT over 3 hours. It was then stirred in the dark for 20 hours. NaOH 1M (100 mL) was then carefully added and the mixture was extracted with DCM (3 x 10 mL) The combined organic layers were washed with brine, water, dried on $MgSO_4$, filtered and concentrated in *vacuo* to give a brown solid. The crude was purified by chromatography on silica with EtOAc : *c*-hexane 1:30 to give a dark solid. MM = 223.07 g/mol (1.58 g, 30%) ^{1}H NMR (400 MHz, $CDCl_3$) 8.04-8.02 (d, 1 H, *J* = 7.3 Hz), 7.81-7.79 (d, 1 H, *J* = 8.1 Hz), 7.47-7.45 (m, 1 H), 7.41-7.37 (m, 1 H), 7.17 (s, 1 H), 7.08-7.06 (m, 1 H), 7.05-7.02 (m, 1 H) ^{13}C NMR (100 MHz, $CDCl_3$) : 151.7, 140.2, 136.5, 130.1, 127.1, 126.8, 122.6, 122.1, 113.0, 85.3.



1-bromo-8-methoxynaphthalene (14):

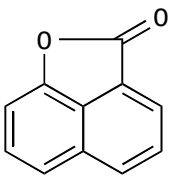
1,8-naphtalic anhydride (198.18 g/mol, 50.5 mmol, 10 g) was suspended in aqueous NaOH (0.9M, 200 mL, 7.08 g), to form a pale brown suspension, and refluxed until the solid material dissolved to form a dark brown solution (10 minutes at 115 °C). The excess base was neutralized with glacial acetic acid (5 mL) at 115 °C. A pale brown precipitate was formed. A solution of mercuric acetate (318.68 g/mol, 51.5 mmol, 16.4 g) in glacial acetic acid (30 mL) and water (50 mL) was added in one portion to the hot suspension and the slurry was refluxed for 47 hours. The pale brown solid was filtered and washed with water. The solid was dried in a dessicator charged with P_2O_5 for 4 days. No NMR was possible; <u>insoluble</u> in H_2O, DMSO, Acetonitrile, DCM, $CHCl_3$, Acetone, MeOH.
Conv. = 21% per MS MM = 370.75 g/mol MS-ESI: 202 (Hg^+ septuplet 196, 198, 199, 200, 201, 202, 204) ; 172 (without Hg) ; 199 (starting material).



benzo[*cd*]indol-2(1*H*)-one (16):[150, commercially available]

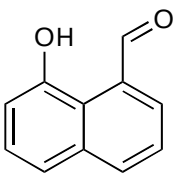
1,8-naphtalic anhydride (198.18 g/mol, 65.5 mmol, 13 g) was put in a flame-dried two-neck round-bottomed 250 mL flask, followed by the hydroxylamine hydrochloride (69.5 g/mol, 66.8 mmol, 4.64 g) and previously CaH_2-dried pyridine (90 mL) The suspension was heated to reflux for 1.5 hours to give a dark brown solution. *p*-TsCl (190.65 g/mol, 144.1 mmol, 27.4 g) was then added in portions (exothermic) The dark solution was heated again to reflux for 2 hours. The suspension was poured in water (300 mL) and the precipitate was filtrated and washed with NaOH 0.5 M and water to remove hydroxynaphtalimide.

The crystals were stirred in refluxing water (150 mL), NaOH (10g) and EtOH (50 mL) for 2 hours. The refrigerant was exchanged by a Claisen bridge and the EtOH was then removed by distillation. The hot suspension was then acidified with concentrated HCl. The suspension was allowed to come back to RT and the obtained yellow precipitate was filtered and washed with water. The precipitate was dried on rotavapor at 80 °C 30 mbar for 1 hour. The dry pale brown solid was then recrystallized in toluene (70 mL) and acetone (10 mL) (warm filtration) to give a yellow crystalline precipitate. This was filtered and dried to give the pure product as a yellow solid. MM = 169.18 g/mol (7.63 g, 68%) ^{1}H NMR (400 MHz, $CDCl_3$) 8.25 (br s, 1 H), 8.12 (d, 1 H, *J* = 7.1 Hz), 8.08 (d, 1 H, *J* = 8.3 Hz), 7.77 (t, 1 H, *J* = 7.6 Hz), 7.59 (d, 1 H, *J* = 8.4 Hz), 7.49 (t, 1 H, *J* = 7.1 Hz), 7.01 (d, 1 H, *J* = 7.1 Hz).



2*H*-naphtho[1,8-*bc*]furan-2-one (17):[150]

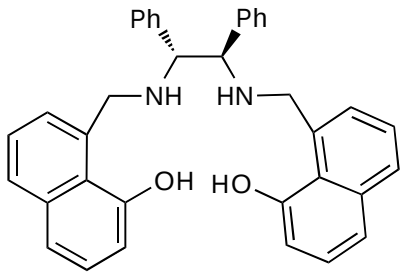
Naphtolactam 16 (169.18 g/mol, 45 mmol, 7.63 g) was added to an aqueous solution of NaOH 0.5M (360 mL). The suspension was heated to reflux to achieve complet homogeneity (30 minutes). The brown solution was cooled to 0 °C and sodium nitrite (69.00 g/mol, 45 mmol, 3.10 g) was added. The solution was then added on a mixture of H_2SO_4 (50 mL) in ice water (1'000 mL) The acidified solution was put in a 2L flask and was heated to 80 °C for 1 hour. The system was then cold down to 0 °C and the obtained precipitate was filtered off, dissolved in toluene (45 mL), dried on Na_2SO_4 and passed trough a silica column (30 mm x 70 mm dia) and eluated with toluene (150 mL). The solvent was evaporated to give the pure product as a pale yellow solid. MM = 170.16 g/mol (5.57 g, 73%) ^{1}H NMR (400 MHz, $CDCl_3$) 8.88 (d, 1 H, J = 7.2 Hz), 8.42 (d, 1 H, *J* = 7.1 Hz), 7.93 (d, 1 H, *J* = 8.0 Hz), 7.79 (t, 1 H, *J* = 8.0 Hz), 7.61 (t, 1 H, *J* = 7.8 Hz), 7.03 (d, 1 H, *J* = 7.2 Hz).



8-hydroxy-1-naphthaldehyde (18):[150,187]

Naphtolactone 17 (170.16 g/mol, 32.3 mmol, 5.50 g) in THF (75 mL) was cooled to 0 °C under N_2. A solution of LiAlH(O*t*-Bu)$_3$ (254.27 g/mol, 35.5 mmol, 9.0 g) in THF (75 mL) was added dropwise over 10 minutes. The reaction mixture was then allowed to warm up to RT and it was stirred under N_2 overnight. The yellow solution turned orange. HCl 1M (75 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 75 mL) The

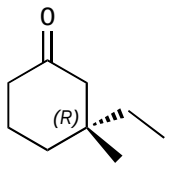
combined organic layers were then extracted with NaOH 1M (3 x 75 mL) The aqueous phase was washed with Et_2O (75 mL), then acidified with conc. HCl and extracted with Et_2O (3 x 80 mL) The combined organic layers were dried on Na_2SO_4, filtered and concentrated to give an orange-brown semi-solid. This was dissolved in $CHCl_3$ (30 mL) and passed trough a column of silica. Additional $CHCl_3$ (400 mL) was added and the obtained crude product was recristallized in hexane (200 mL) to give the pure product as an orange solid. MM = 172.18 g/mol (2.51 g, 45%) ^1H NMR (400 MHz, $CDCl_3$) 12.09 (s, 1 H), 11.75 (s, 1 H), 8.20 (dd, 1 H, *J* = 1.3 Hz, 8.1 Hz), 8.10 (dd, 1 H, *J* = 1.3 Hz, 7.1 Hz), 7.65-7.56 (m, 2 H), 7.50-7.47 (m, 1 H), 7.25 (dd, 1 H, *J* = 1.3 Hz, 7.6 Hz).



8,8'-((1*R*,2*R*)-1,2-diphenylethane-1,2-diyl)bis (azanediyl)bis(methylene)dinaphthalen-1-ol (19):
A round-bottomed flask was charged with the DPEDA 5 (212.29 g/mol, 2.35 mmol, 500 mg), dry acetonitrile (10 mL) and cooled to 0 °C. A solution of 8-hydroxynaphthaldehyde 18 (172.18 g/mol, 4.7 mmol, 809 mg) in dry acetonitrile (4 mL) was added dropwise over 2 minutes in the cool solution. The system was allowed to come back to RT and was stirred for 1.5 hours. $NaBH_3CN$ (62.84 g/mol, 5.17 mmol, 325 mg) was then added and the solution was stirred for 15 additional minutes at RT. AcOH (1 mL) was finally added and the mixture was stirred overnight. The solids were removed by filtration and the filtrate evaporated to give a yellow solid. This was purified by chromatography on silica with EtOAc : c-hexane 1:2 to give the pure product as a pale yellow solid. MM = 524.65 g/mol (1.00 g, 81%) MS-ESI pos.: 525.5.

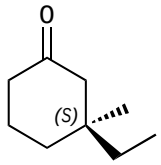
Typical procedure for 1,4-addtions :
A flame-dried Schlenk tube was charged with copper salt (3.0 mol%) and the chiral ImH^+ salt (4.0 mol%) The system was flushed under N_2 and dry Et_2O (2.5 mL) was added. The mixture was cooled to the desired reaction temperature in an ethanol cold bath. The Grignard reagent (1.2 eq.) in Et_2O was added dropwise to the solution for 5 minutes. A solution of the substituted cyclohexenone (1 eq.) in Et_2O (8 mL) was then added dropwise to the solution at the desired low reaction temperature for 15 minutes and the solution was stirred for 30 more minutes. The reaction was quenched at reaction temperature by addition of HCl 1M (30 mL) (or

MeOH if the reaction temperature lies under -20 °C) and the aqueous layer was separated and extracted further with diethyl ether (3 x 10mL). The combined organic layers were dried on $MgSO_4$, filtrated and concentrated in vacuo to give an oily residue. That crude was purified by flash chromatography on a silica column with pentane : Et_2O 10:1 to give the pure product.



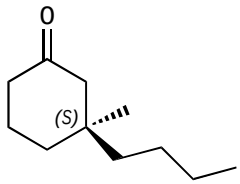
(R)-3,3-ethyl-methyl-cyclohexanone (20):[16]

^1H NMR (400 MHz, $CDCl_3$) : 2.26 (t, 2 H, *J* = 6.6 Hz), 2.16 (d of AB sys., 1 H, *J* = 13.6 Hz), 2.08 (d of AB sys., 1 H, *J* = 13.6 Hz), 1.88-1.81 (m, 2 H), 1.64-1.48 (2 m, 2 H), 1.33 (q, 2 H, *J* = 7.3 Hz), 0.88 (s, 3 H), 0.83 (t, 3 H, *J* = 7.6 Hz) ^{13}C NMR (100 MHz, $CDCl_3$) : 212.8, 53.7, 41.4, 39.0, 35.7, 34.3, 24.7, 22.5, 8.1 $[\alpha]_D$: +4.74 ($CHCl_3$, c = 1.64, *ee* = 80% *R.* Absolute configuration was assigned in analogy with the literature).[16] Enantiomeric excess was measured by chiral GC (lipodex E, 75-23-20-170-5 v=40cm/s), Rt_1 = 15.5 (*R*), Rt_2 = 19.9 (*S*)).



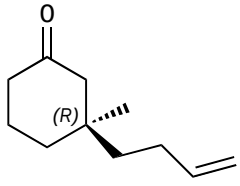
(S)-3,3-ethyl-methylcyclohexanone (21):[16]

^1H NMR (400 MHz, $CDCl_3$) : see 20 $[\alpha]_D$: -4.50 ($CHCl_3$, c = 1.70, *ee* = 68% *S.* Absolute configuration was assigned in analogy with the literature).[16] Enantiomeric excess was measured by chiral GC (lipodex E, isotherm 75 °C v=40cm/s), Rt_1 = 16.3 (*R*), Rt_2 = 19.5 (*S*)).



(S)-3,3-butyl-methyl-cyclohexanone (22):[188]

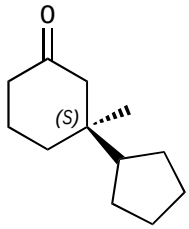
^1H NMR (400 MHz, $CDCl_3$) : 2.19 (t, 2 H), 2.11 (q, 2 H), 1.78 (quint., 2 H), 1.55-1.41 (m, 2 H), 1.18 (m, 6 H), 0.83 (m, 6 H) ^{13}C NMR (100 MHz, $CDCl_3$) : 212.2, 53.8, 41.3, 41.0, 38.5, 35.8, 25.5, 25.1, 23.4, 22.1, 14.0 $[\alpha]_D$: -12.3 ($CHCl_3$, c = 15.4, *ee* = 72% *S.* Absolute configuration was assigned in analogy with the literature).[16] Enantiomeric excess was measured by chiral GC (lipodex E, 80-0-1-170-5 v=30cm/s), Rt_1 = 25.7 (*R*), Rt_2 = 27.4 (*S*)).



(R)-3-(3-butenyl)-3-methylcyclohexanone (23):[16]

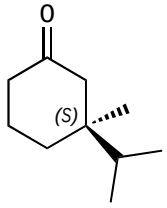
^1H NMR (400 MHz, $CDCl_3$) : 5.82-5.72 (m, 1 H), 5.01-4.97 (d, 1 H, *J* = 16.9 Hz), 4.93-4.91 (d, 1 H, *J* = 10.1 Hz), 2.28-2.24 (t, 2 H, *J* = 6.8 Hz), 2.20-2.08 (q, 2 H, *J* = 13.6 Hz), 2.03-1.97 (m, 2 H), 1.88-1.82 (m, 2 H), 1.66-1.51 (m, 2 H), 1.36-1.32 (t, 2 H, *J* = 8.6 Hz), 0.92 (s, 3 H) ^{13}C NMR (125 MHz, $CDCl_3$) :

212.2, 138.9, 114.5, 53.8, 41.1, 41.0, 38.6, 35.9, 27.9, 25.0, 22.2 $[\alpha]_D$: +1.9 ($CHCl_3$, c = 1.9, *ee* = 73% *R.* Absolute configuration was assigned in analogy with the literature).[16] Enantiomeric excess was measured by chiral GC (Hydrodex B-3P, isotherm 140 °C, Rt_1 = 10.6 (*S*), Rt_2 = 10.9 (*R*)).



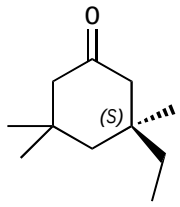
(S)-3,3-*c*-pentyl-methylcyclohexanone (24):[132]

^{1}H NMR (400 MHz, $CDCl_3$) : 2.23-2.17 (m, 3 H), 2.06-2.02 (d, 1 H), 1.85-1.69 (m, 3 H), 1.61-1.50 (m, 8 H), 1.17-1.13 (m, 2 H), 0.79 (s, 3 H) ^{13}C NMR (100 MHz, $CDCl_3$) : 212.7, 52.4, 49.6, 41.2, 40.6, 35.1, 26.4, 25.6, 22.1, 20.9 *ee* = 56% *S.* Absolute configuration was assigned in analogy with the literature).[16] Enantiomeric excess was measured by chiral GC (Lipodex E, 120-1-20-170-5 40cm/s, Rt_1 = 13.1 (*R*), Rt_2 = 14.3 (*S*)).



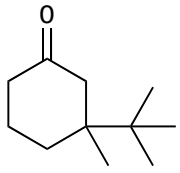
(S)-3,3-*i*-propyl-methylcyclohexanone (25):[41]

^{1}H NMR (400 MHz, $CDCl_3$) : 2.32-2.22 (m, 3 H), 2.11 (dt, 1 H), 1.98-1.77 (m, 2 H), 1.64 (m, 2 H), 1.51 (sept., 1 H), 0.85-0.86 (d, 6 H, *J* = 1.7 Hz), 0.80 (s, 3 H) ^{13}C NMR (100 MHz, $CDCl_3$) : 212.9, 52.0, 41.2, 36.4, 34.2, 22.1, 19.9, 17.1, 16.9 *ee* = 70% *S.* Absolute configuration was assigned in analogy with the literature).[16] Enantiomeric excess was measured by chiral GC (Lipodex E (60-0-1-110-20-170-5 45cm/s) Rt_1 = 21.4 (*R*), Rt_2 = 24.6 (*S*)).



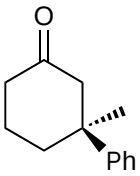
(S)-3,3-ethyl-methylisophorone (27):[189]

^{1}H NMR (400 MHz, $CDCl_3$) : 2.19-2.06 (m, 4 H), 1.61-1.45 (dd, 2 H, *J* = 14.2 Hz, 46.2 Hz), 1.43-1.24 (m, 2 H), 1.02(m, 6 H), 0.96 (s, 3 H), 0.85-0.82 (t, 3 H, *J* = 7.6 Hz) ^{13}C NMR (100 MHz, $CDCl_3$) : 212.9, 54.5, 53.0, 48.8, 39.0, 37.3, 36.3, 32.5, 30.9, 27.0, 8.4 $[\alpha]_D$: -1.89 ($CHCl_3$, c = 1.70, *ee* = 71% *S.* Absolute configuration was assigned in analogy with the literature).[16] Enantiomeric excess was measured by chiral GC (Chirasil DEX-CB, 60-110-2-170-5, Rt_1 = 133.7 (*R*), Rt_2 = 134.0 (*S*)).



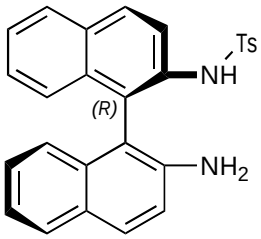
3-*tert*-butyl-3-methylcyclohexanone (28): [190]

^{1}H NMR (300 MHz, $CDCl_3$) : 2.35-2.31 (m, 2 H), 2.15-2.11 (m, 2 H), 2.0-1.74 (m, 4 H), 0.92 (s, 9 H), 0.86 (s, 3 H) MS (EI): 168, 112, 97*,83, 69, 55. *ee* = 0%. Enantiomeric excess was measured by chiral GC (Hydrodex B6 TBDMS, 80-0-1-95-0- v=45 cm/s), Rt_1 = 10.3 (*S*), Rt_2 = 10.7 (*R*)).



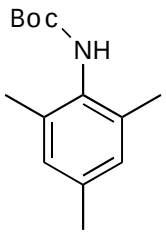
(S)-3,3-phenyl-methylcyclohexanone (29):[163,191]

^{1}H NMR (400 MHz, $CDCl_3$) : 7.33-7.32 (m, 4 H), 7.22-7.19 (m, 1 H), 2.90-2.42 (q, 2 H), 2.33-2.30 (t, 2 H), 2.22-2.16 (m, 1 H), 1.96-1.84 (m, 2 H), 1.71-1.63 (m, 1 H), 1.33 (s, 3 H) ^{13}C NMR (100 MHz, $CDCl_3$) : 211.5, 147.5, 128.6, 126.3, 125.6, 53.2, 42.9, 40.9, 38.0, 29.9, 22.1 $[\alpha]_D$: +28.2 ($CHCl_3$, c = 1.7, *ee* = 70% *S*). Absolute configuration was assigned in analogy with the literature).[16] Enantiomeric excess was measured by chiral GC (Hydrodex-B-3P, isotherm 140 °C v=48 cm/s, Rt_1 = 23.1 (*R*), Rt_2 = 23.8 (*S*)).



(*R*)-*N*-(2'-amino-1,1'-binaphthyl-2-yl)-4-methylbenzene sulfonamide (30):[192]

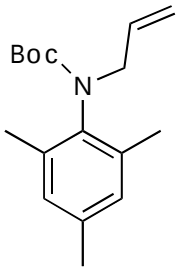
A flame-dried 20 mL microwave reactor was charged with S-2,2-diaminobinaphtyl (284.35 g/mol, 3.52 mmol, 1.01 g) and DCM (15 mL). Freshly distilled triethylamine (101.19 g/mol, 7.74 mmol, 1.1 mL) and DMAP (122.17 g/mol, 0.35 mmol, 45 mg) were added followed by toluensulfonyl chloride (190.65 g/mol, 6.34 mmol, 1.21 g) at RT. The reactor was put in a microwave reactor and it was warmed up to 100 °C for 35 minutes. Water (20 mL) was added and the organic layer was extracted with DCM (2 x 30 mL). The combined organic layers were washed with brine and water, dried on $MgSO_4$ and concentrated in *vacuo* to give an off-white foam. An NMR showed that the product was pure at >99%. No purification was needed. $Rf_{basic\ alumina}$ = 0.09; MM = 438.54 g/mol (1.51 g, 97%) ^{1}H NMR (400 MHz, $CDCl_3$) 8.11 (m, 1 H), 7.96 (m, 1 H), 7.83 (m, 2 H), 7.76 (m, 1 H), 7.40 (m, 3 H), 7.21 (m, 2 H), 7.06 (m, 2 H), 7.00 (m, 3 H), 6.68 (br s, 1 H), 6.39 (m, 1 H), 3.40 (s, 2 H), 2.31 (s, 3 H).



tert-butyl mesitylcarbamate (31):[193]

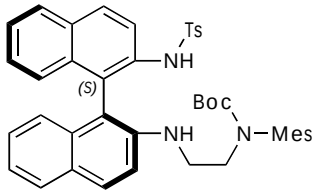
A 20 mL flame dried microwave reactor was charged with 2,4,6-trimethylaniline (135.21 g/mol, 29.6 mmol, 3.74 mL) and dry THF (6 mL) $(Boc)_2O$ (218.25 g/mol, 29.9 mmol, 6.53 g) was weighted in a flask and dissolved in dry THF (7 mL) The solution was added at RT to the amine by a cannula. The pale brown solution was then heated first 180 °C for 2 minutes. The microwave oven was stopped because of high pressure (up to 22 bar near to 165 °C). The reactor was cooled to 25 °C, but there was still a 7 bar pressure in the reactor. The formed gas was discarded by foring the septum with a needle. The

reactor was placed again in the microwave and was warmed at 140 °C for 35 minutes. The solvent was discarded in *vacuo* to give a pale brown solid. MM = 235.32 g/mol (6.32 g, 91%) ^{1}H NMR (400 MHz, $CDCl_3$) 6.87 (s, 2 H), 5.80 (br s, 1 H), 2.25 (s, 3 H), 2.22 (s, 6 H), 1.50 (br s, 9 H).



tert-butyl allyl(mesityl)carbamate (32):

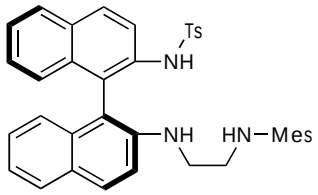
KH 20% in oil (40.11 g/mol, 31.2 mmol, 2.25 g) was put in a flame dried two-necked flask with dry DMF (10 mL). The solution was cooled to 0 °C and *tert*-butyl mesitylcarbamate 31 (235.32 g/mol, 26.0 mmol, 6.11 g) in DMF (18 mL) was added dropwise by cannula. The mixture was then allowed to rise up to RT and stirred for 1.5 hours. Bromoallyl (120.98 g/mol, 31.2 mmol, 2.64 mL) was then added dropwise at RT. After 10 drops, the KBr salt fells out as white solid. $NaHCO_3$ aq. (30 mL), H_2O (30 mL) and Et_2O (70 mL) were added and the organic layer was separated. The aqueous layer was extracted twice with Et_2O (50 mL) The combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and concentrated to give a yellow oil. There was still starting material. DMF (5 mL) was added to the yellow oil, followed by KH (2.82 g; 39 mmol, 1.5 eq) in DMF (5 mL) Bromoallyl (2.64 mL) was then added dropwise. $NaHCO_3$ aq. (30 mL), H_2O (30 mL) and Et_2O (70 mL) was added and the organic layer was separated. The aqueous layer was extracted twice with Et_2O (50 mL) The combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and concentrated to give a yellow oil. A chromatography on silica was done with Hexane:Et_2O 10:1 to give the pure product as a transparent oil. Two rotamers on NMR, ratio: 0.3:1. Rf = 0.37 (0.18 = st. mat); MM = 275.39 g/mol (5.57 g, 82%) ^{1}H NMR (400 MHz, $CDCl_3$) 6.86 (s, 2 H), 6.83 (s, 2 H), 5.94 (m, 1 H), 5.93 (m, 1 H), 5.07 (s, 1 H), 5.05 (s, 1 H), 5.04 (s, 1 H), 5.00 (s, 1 H), 4.03 (d, 2 H, *J* = 6.8 Hz), 3.95 (d, 2 H, *J* = 6.8 Hz), 2.26 (s, 6 H), 2.24 (s, 3 H), 2.16 (s, 3 H), 2.14 (s, 6 H), 1.51 (s, 9 H), 1.32 (s, 9 H).



(*S*)-*tert*-butyl mesityl(2-(2'-(4-methylphenylsulfonamido)-1,1'-binaphthyl-2-ylamino)ethyl)carbamate (33):

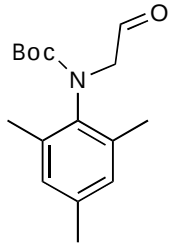
(*R*)-*N*-(2'-amino-1,1'-binaphthyl-2-yl)-4-methylbenzenesulfonamide 30 (424.51 g/mol, 1.65 mmol, 700 mg) and $NaHB(OAc)_3$ (211.94 g/mol, 3.30 mmol, 700 mg) were put in a two-necked flame-dried round flask and suspended in freshly $MgSO_4$ dried 1,2-dichloroethane (15 mL). A

solution of *tert*-butyl mesityl(2-oxoethyl)carbamate 35 (277.36 g/mol, 2.15 mmol, 596 mg) in 1,2-dichloroethane (8 mL) was added dropwise (45 min.) at RT under stirring. The suspension was stirred at RT overnight. The obtained solution was dissolved with $NaHCO_3$ aq. (30 mL) and DCM (15 mL) The aqueous layer was extracted twice with DCM (2x10 mL) The combined organic layers were dried over $MgSO_4$, filtered and concentrated to give a yellow-white solid foam. This was purified by chromatography on silica with hexane:EtOAc 5:1 to give a white solid foam. Two rotamers on NMR. Rf = 0.26 (0.12=30; 0.41=35); MM = 699.90 g/mol (483 mg, 49%) Rotamers on ^{1}H NMR (400 MHz, $CDCl_3$) 8.13-8.12 (m, 2 H), 7.95-7.92 (m, 4 H), 7.85-7.83 (m, 2 H), 7.75-7.73 (m, 2 H), 7.37-6.78 (m, 6 H), 6.67 (s, 2 H), 3.55-3.49 (m, 2 H), 3.42-3.39 (m, 2 H), 3.39-3.35 (m, 2 H), 2.28 (s, 6 H), 2.21 (s, 3 H), 2.12 (s, 3 H), 2.06 (s, 9 H).



(*S*)-*N*-(2'-(2-(mesitylamino)ethylamino)-1,1'-binaphthyl-2-yl)-4-methylbenzenesulfonamide (34):

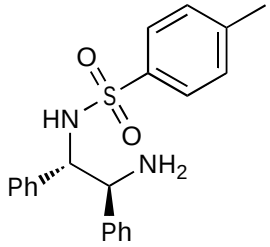
A solution of (*S*)-*tert*-butyl mesityl(2-(2'-(4-methylphenyl sulfonamido)-1,1'-binaphthyl-2-ylamino)ethyl)carbamate 33 (699.90 g/mol, 2.1 mmol, 1.45 g) in chloroform (10 mL) was introduced in a flame-dried microwave reactor. Trifluoroacetic acid (114.02 g/mol, 8.4 mmol, 0.62 mL) was added dropwise and the solution was placed in the microwave and warmed at 100 °C for 10 minutes. The solution became black. Solvents were evaporated under high *vacuo*. The residue was dissolved in DCM (10 mL), washed with $NaHCO_3$ (3 x 10 mL), brine (10 mL) and dried on Na_2SO_4. The solvent was then discarded in *vacuo*. The black crude solid was passed on a plug of basic alumina with pure DCM to obtain the pure product as an yellow foamy solid. Rf = 0.32 Pent.:DCM 1:1; MM = 599.78 g/mol (1.01 g, 83%) Rotamers on ^{1}H NMR (400 MHz, $CDCl_3$) 8.13-8.12 (m, 2 H), 7.95-7.92 (m, 4 H), 7.85-7.83 (m, 2 H), 7.75-7.73 (m, 2 H), 7.37-6.78 (m, 6 H), 6.67 (s, 2 H), 3.88-3.86 (m, 1 H), 3.55-3.49 (m, 2 H), 3.42-3.39 (m, 2 H), 3.39-3.35 (m, 2 H), 2.28 (s, 6 H), 2.21 (s, 3 H), 2.12 (s, 3 H).



tert-butyl mesityl(2-oxoethyl)carbamate (35):[193]

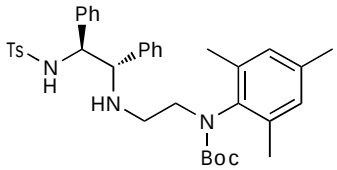
A flame-dried two necked round bottom flask was charged with *tert*-butyl allyl(mesityl)carbamate 32 (275.39 g/mol, 20 mmol, 5.57 g) in DCM (65 mL) and methanol (22 mL). A spatula of solid $NaHCO_3$ was then added. The flask was cooled to -78 °C and ozone was bubbled in

the suspension until completion of the reaction (6 hours). O_2 was bubbled for 15 minutes, followed by N_2. The suspension was allowed to come back to RT with stirring and Me_2S (62.13 g/mol, 40 mmol, 2.9 mL) was added. After 40 hours, the solvent and excess of Me_2S was discarded by high *vacuum* pump. A chromatography on silica was done with Hexane : EtOAc 5:1 to give the pure product as a transparent oil. Two rotamers on NMR, ratio 0.7:1. Rf = 0.39; MM = 277.36 g/mol (3.05 g, 62%) ^{1}H NMR (400 MHz, $CDCl_3$) 9.81 (m, 1 H), 6.90 (s, 1 H), 6.87 (s, 1 H), 3.97 (m, 1 H), 3.94 (m, 1 H), 2.27 (m, 3 H), 2.22 (m, 6 H), 1.48 (s, 3 H), 1.36 (6 H).



N-((1*S*,2*S*)-2-amino-1,2-diphenylethyl)-4-methylbenzene sulfonamide (36): , commercially available

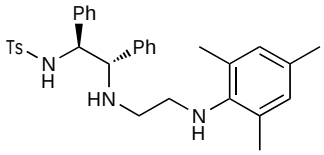
A flame-dried 5 mL microwave reactor was charged with the S,S-DPEDA 5 (212.29 g/mol, 0.47 mmol, 100 mg) and DCM (3 mL) Freshly distilled triethylamine (101.19 g/mol, 1.03 mmol, 0.14 mL) and DMAP (122.17 g/mol, 0.05 mmol, 6.1 mg) were added followed by toluensulfonyl chloride (190.65 g/mol, 0.49 mmol, 94.0 mg) at RT. The reactor was put in the microwave and was warmed at 100 °C for 50 minutes. Water (20 mL) was added and the organic layer was extracted. The water phase was extracted twice with DCM. The combined organic phases were washed with brine and water, dried on $MgSO_4$ and concentrated in *vacuo* to give pale yellow creamy oil. NMR spectra showed that the product was pure at >95%. No further purification was needed. MM = 366.48 g/mol (141 mg, 82%) ^{1}H NMR (400 MHz, $CDCl_3$) 7.32-7.30 (m, 3 H), 7.27-7.23 (m, 2 H), 7.16-7.13 (m, 6 H), 7.12-7.11 (m, 4 H), 6.98-6.96 (m, 2 H), 4.36 (d, 1 H, *J* = 5.3 Hz), 4.12 (d, 1 H, *J* = 5.3 Hz), 2.32 (s, 3 H).



tert-butyl mesityl(2-((1*S*,2*S*)-2-(4-methylphenylsulfonamido)-1,2-diphenylethylamino)ethyl)carbamate (37):

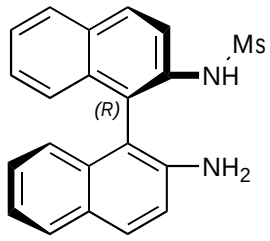
The protected diamine *N*-((1*S*,2*S*)-2-amino-1,2-diphenylethyl)-4-methylbenzenesulfonamide 36 (366.48 g/mol, 2.34 mmol, 860 mg) and $NaHB(OAc)_3$ (211.94 g/mol, 7.02 mmol, 1.49 g) were put in a 20 mL flame dried microwave reactor. Dry DCM (10 mL) was added and the suspension was stirred for 30 minutes at RT. A solution of *tert*-butyl mesityl(2-oxoethyl)carbamate 35 (277.36 g/mol, 2.57 mmol, 714 mg) in DCM (5 mL) was added dropwise over 1 minute at RT under stirring. The suspension was put in the

microwave reactor and heated at 100 °C for 50 minutes. The obtained solution was dissolved with $NaHCO_3$ aq. (2 x 30 mL) and DCM (15 mL) The aqueous layer was extracted twice with DCM (2 x 10 mL) The combined organic layers were dried over $MgSO_4$, filtered and concentrated to give a yellow-white oily residue. This was purified by chromatography on silica with hexane : EtOAc 5:1 to give a white solid foam. Rf = 0.12 (0.41 = 35); MM = 627.84 g/mol (989 mg, 67%) ^1H NMR (400 MHz, $CDCl_3$) 7.38-7.36 (m, 2 H), 7.12-7.08 (m, 4 H), 7.03-6.97 (m, 6 H), 6.87-6.84 (m, 4 H), 6.31 (br s, 1 H), 4.23-4.21 (m, 1 H), 3.74-3.72 (m, 1 H), 3.30-3.24 (m, 1 H), 2.60-2.56 (m, 2 H), 2.43-2.39 (m, 2 H), 2.33 (s, 3 H), 2.26 (s, 3 H), 2.07 (s, 6 H), 1.34 (s, 9 H).



N-((1*S*,2*S*)-2-(2-(mesitylamino)ethylamino)-1,2-diphenylethyl) -4-methylbenzenesulfonamide (38):

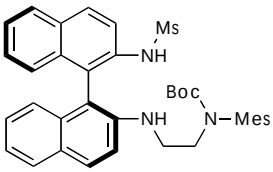
A solution of *tert*-butyl mesityl(2-((1*S*,2*S*)-2-(4-methylphenyl sulfonamido)-1,2-diphenylethylamino)ethyl)carbamate 37 (627.84 g/mol, 0.43 mmol, 270 mg) in DCM (10 mL) was introduced in a flame-dried microwave reactor. Trifluoroacetic acid (114.02 g/mol, 1.7 mmol, 0.13 mL) was added dropwise and the sealed reactor was warmed with the microwave for 10 minutes at 100 °C. The solution became pale brown. Solvents were evaporated at the high *vacuum* pump. The residue was dissolved in DCM (10 mL), washed with $NaHCO_3$ (3 x 10 mL), brine (10 mL) and dried on Na_2SO_4. The solvent was then discarded in *vacuo*. The dark crude solid was passed on a plug of basic alumina with pure DCM to discard the black polymers of TFA and obtain the crude as a brown foamy solid. Rf = 0.32 Pent.:DCM 1:1; MM = 527.72 g/mol (220 mg, 97%) MS-(ESI) : 528.3.



(*R*)-*N*-(2'-amino-1,1'-binaphthyl-2-yl)methanesulfonamide (39) :

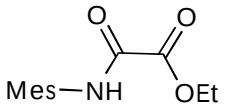
A flame-dried 50 mL round-bottomed two-neck flask was charged with *R*-2,2-diaminobinaphtyl (284.35 g/mol, 2.11 mmol, 600 mg), dry pyridine (79.1 g/mol, 25.3 mmol, 2.0 mL) and DCM (15 mL). A solution of methylsulfonyl chloride (114.55 g/mol, 2.15 mmol, 0.17 mL) in DCM (5 mL) was then added dropwise at RT under stirring and N_2. When the addition was completed, the solution was stirred overnight at RT. The solution was washed with HCl 5% (3 x 30 mL), dried on $MgSO_4$, filtered and concentrated to give a pale red solid. This was purified on silica with *c*-hexane : EtOAc 2:1 to give the pure product as an yellow solid. Rf = 0.13; MM = 362.44 g/mol (566 mg, 74%) ^1H NMR (400 MHz, $CDCl_3$)

8.07-8.01 (m, 2 H), 7.93 (d, 1 H, *J* = 8.1 Hz), 7.87 (d, 1 H, *J* = 8.6 Hz), 7.82 (d, 1 H, *J* = 8.1 Hz), 7.46 (t, 1 H, *J* = 7.3 Hz), 7.33-7.28 (m, 2 H), 7.25-7.18 (m, 4 H), 7.13 (d, 1 H, *J* = 8.8 Hz), 6.86 (d, 1 H, *J* = 8.4 Hz), 6.37 (s, 1 H), 2.75 (s, 3 H) MS (ESI) : 363.0.



(*S*)-*tert*-butyl mesityl(2-(2'-(methylsulfonamido)-1,1'-binaphthyl -2-ylamino)ethyl)carbamate (40):

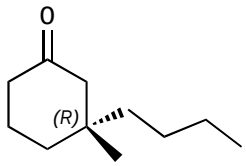
The protected diamine (*R*)-*N*-(2'-amino-1,1'-binaphthyl-2-yl) methanesulfonamide 39 (362.44 g/mol, 1.38 mmol, 500 mg) and $NaHB(OAc)_3$ (211.94 g/mol, 4.14 mmol, 877 mg) were put in a two-necked flame-dried round flask and suspended in freshly distilled 1,2-dichloroethane (15 mL). The suspension was stirred for 30 minutes at RT. A solution of *tert*-butyl mesityl(2-oxoethyl)carbamate 35 (277.36 g/mol, 1.44 mmol, 398 mg) in 1,2-dichloroethane (10 mL) was added dropwise (30 min.) at RT under stirring. The suspension was stirred at RT overnight. The obtained solution was dissolved with $NaHCO_3$ aq. (2 x 30 mL) and DCM (15 mL) The aqueous layer was extracted twice with DCM (2 x 10 mL) The combined organic layers were dried over $MgSO_4$, filtered and concentrated to give a yellow-white solid foam. This was purified by chromatography on silica with c-hexane : EtOAc 2:1 to give a white solid foam. Rf = 0.29 (0.57 = 35); MM = 623.80 g/mol (331 mg, 52%) ^{1}H NMR (400 MHz, $CDCl_3$) 8.10-8.04 (m, 2 H), 7.96 (d, 1 H, *J* = 8.3 Hz), 7.89 (d, 1 H, *J* = 6.4 Hz), 7.85 (d, 1 H, *J* = 8.1 Hz), 7.49 (t, 1 H, *J* = 6.8 Hz), 7.36-7.27 (m, 3 H), 7.25-7.22 (m, 2 H), 7.18-7.16 (d, 1 H, *J* = 8.6 Hz), 6.89 (br s, 2 H), 6.42 (br s, 1 H), 3.81-3.80 (m, 2 H), 3.65-3.63 (m, 2 H), 3.03 (s, 1 H), 2.77 (s, 3 H), 2.30 (s, 2 H), 2.22 (s, 4 H), 1.46 (s, 6 H), 1.36 (s, 6 H) ^{13}C NMR (100 MHz, $CDCl_3$) : 135.2, 134.0, 133.6, 132.8, 131.7, 131.0, 130.3, 129.1, 128.7, 128.5, 127.6, 127.6, 125.9, 125.7, 123.3, 123.2, 122.5, 120.2, 118.4, 80.4, 62.9, 53.0, 40.3, 28.3, 27.0, 21.0, 18.1, 15.2.



ethyl 2-(mesitylamino)-2-oxoacetate (41):[194]

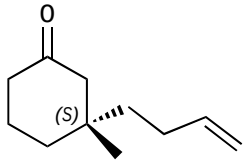
A round-bottomed flask was charged with trimethylaniline (135.21 g/mol, 6.7 mmol, 906 mg) and pyridine (79.10 g/mol, 8.0 mmol, 0.65 mL) in dry DCM (10 mL) The solution was cooled to 0 °C and ethyloxalylchloride (136.53 g/mol, 8.0 mmol, 0.9 mL) was added. The solution was then allowed to come back to RT and was stirred overnight. EtOAc (20 mL) was added and the solution was washed with HCl 1M (2 x 30 mL), $NaHCO_3$ (30 mL), brine (30 mL), dried on $MgSO_4$, filtered and concentrated to give the pure product as a white solid. MM = 235.28

g/mol (1.51 g, 96%) ^{1}H NMR (400 MHz, $CDCl_3$) 8.38 (br s, 1 H), 6.93 (s, 2 H), 4.44 (q, 2 H,J = 7.3 Hz, 7.1 Hz), 2.29 (s, 3 H), 2.22 (s, 6 H), 1.46 (t, 3 H,J = 7.3 Hz) ^{13}C NMR (100 MHz, $CDCl_3$) : 161.4, 155.2, 138.2, 135.1, 129.9, 129.5, 64.0, 21.4, 18.8, 14.4.



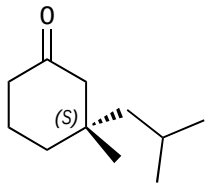
(R)-3,3-butyl-methyl-cyclohexanone (42):[188]

^{1}H NMR (400 MHz, $CDCl_3$) : see 22 $[\alpha]_D$: +4.74 ($CHCl_3$, c = 1.64, *ee* = 78% *R.* Absolute configuration was assigned in analogy with the literature).[16] Enantiomeric excess was measured by chiral GC (lipodex E, 80-0-1-170-5 v=40cm/s), Rt_1 = 26.5 (*R*), Rt_2 = 27.2 (*S*)).



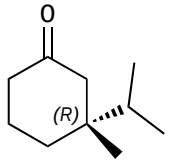
(S)-3-(3-butenyl)-3-methylcyclohexanone (43):[16]

^{1}H NMR (400 MHz, $CDCl_3$) : see 23 $[\alpha]_D$: -2.45 ($CHCl_3$, c = 1.71, *ee* = 90% *S.* Absolute configuration was assigned in analogy with the literature).[16] Enantiomeric excess was measured by chiral GC (Hydrodex B-3P, isotherm 135 °C, Rt_1 = 6.5 (*S*), Rt_2 = 6.7 (*R*)).



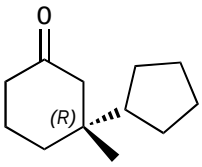
(S)-3,3-*i*-butyl-methylcyclohexanone (44):[16]

^{1}H NMR (400 MHz, $CDCl_3$) : 2.29-2.26 (m, 2 H), 2.24-2.10 (q, 2 H, *J* = 13.4 Hz, 42.5 Hz), 1.92-1.83 (m, 2 H), 1.74-1.64 (m, 2 H), 1.60-1.56 (m, 1 H), 1.26-1.17 (m, 2 H), 0.95 (s, 3 H), 0.93 (m, 6 H)^{13}C NMR (100 MHz, $CDCl_3$) : 212.7, 54.6, 51.2, 41.3, 39.7, 36.8, 25.8, 25.7, 25.6, 24.2, 22.5 IR (neat, cm^{-1}) : 2956, 1716, 1467 MS (EI) : 153(2), 125 (9), 112 (9), 111 (100), 110 (3), 107 (2), 98 (2), 97 (9), 95 (7), 93 (2), 85 (1), 84 (2), 83 (22), 82 (4), 81 (2), 79 (2), 77 (1), 71 (2), 70 (6), 69 (25), 68 (3), 67 (6), 65 (1), 58 (1), 57 (5), 56 (15), 55 (98), 54 (2), 53 (5) HRMS (ESI-MS) : $[M+Na]^+$ found 191.1408390, calculated for $C_{11}H_{20}ONa$: 191.1406364. $[\alpha]_D$: +2.19 ($CHCl_3$, c = 1.73, *ee* = 96% *S*. Absolute configuration was assigned in analogy with the literature).[16] Enantiomeric excess was measured by chiral GC (lipodex E, isotherm 80 °C, Rt_1 = 12.9 (*S*), Rt_2 = 15.8 (*R*)).



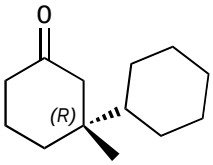
(R)-3,3-*i*-propyl-methylcyclohexanone (45):[41]

^{1}H NMR (400 MHz, $CDCl_3$) : see 25 $[\alpha]_D$: +12.2 ($CHCl_3$, c = 1.70, *ee* = 77% *R.* Absolute configuration was assigned in analogy with the literature).[16] Enantiomeric excess was measured by chiral GC (Lipodex E 60-1-130 v=49 cm/s, Rt_1 = 24.3 (*R*), Rt_2 = 26.3 (*S*)).



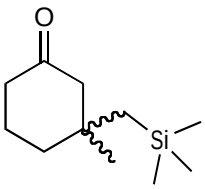
(R)-3,3-*c*-pentyl-methylcyclohexanone (46):

^{1}H NMR (400 MHz, $CDCl_3$) : see 24 MS (EI) : 180 (2), 122 (14), 112 (10), 111 (77), 110 (18), 97 (18), 83 (14), 82 (13), 69 (25), 67 (17), 55 (100) HRMS (EI-MS) : $[M]^+$ found 180.151440, calculated for $C_{12}H_{20}O$: 180.151415. $[\alpha]_D$: +7.11 ($CHCl_3$, c = 1.70, *ee* = 86% *R.* Absolute configuration was assigned in analogy with the literature).[16] Enantiomeric excess was measured by chiral GC (Lipodex E, isotherm 125 °C, Rt_1 = 6.9 (*R*), Rt_2 = 7.4 (*S*)).



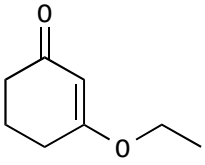
(R)-3,3-*c*-hexyl-methylcyclohexanone (47):

^{1}H NMR (400 MHz, $CDCl_3$) : 2.31-2.12 (m, 3 H), 2.02-1.99 (m, 1 H), 1.85-1.78 (m, 1 H), 1.77-1.62 (m, 5 H), 1.60-1.56 (m, 2 H), 1.52-1.46 (m, 1 H), 1.17-1.00 (m, 4 H), 0.93-0.83 (m, 2 H), 0.75 (s, 3 H) ^{13}C NMR (100 MHz, $CDCl_3$) : 212.8, 51.9, 46.6, 41.1, 41.0, 34.1, 27.0, 27.0, 26.8, 26.6, 26.6, 21.9, 21.0 MS (EI) : 194 (<1), 112 (12), 111 (90), 110 (17), 97 (39), 83 (20), 82 (17), 69 (17), 67 (14), 55 (100) HRMS (EI-MS) : $[M]^+$ found 194.166980, calculated for $C_{13}H_{22}O$: 194.167066. $[\alpha]_D$: +4.55 ($CHCl_3$, c = 1.70, *ee* = 79% *R.* Absolute configuration was assigned in analogy with the literature).[16] Enantiomeric excess was measured by chiral GC (Lipodex E, isotherm 125 °C, Rt_1 = 10.9 (*R*), Rt_2 = 11.2 (*S*)).



3,3-methyl-(trimethylsilyl)methyl)cyclohexanone (48):

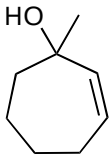
^{1}H NMR (400 MHz, $CDCl_3$) : 2.22-2.09 (m, 4 H), 1.83-1.77 (m, 2 H), 1.61-1.56 (m, 2 H), 0.95 (s, 3 H), 0.68 (s, 2 H), 0.00 (s, 9 H) ^{13}C NMR (100 MHz, $CDCl_3$) : 212.5, 57.3, 41.2, 39.6, 32.3, 29.1, 28.4, 22.8, 1.26 MS-EI 197, 183, 170, 155, 130, 115, 75, 73*, 55 *ee* = 0%. Enantiomeric excess was measured by chiral GC (Lipodex E, isotherm 100 °C v = 45cm/s), Rt_1 = 7.0, Rt_2 = 7.3).



3-ethoxycyclohex-2-enone (49): commercially available

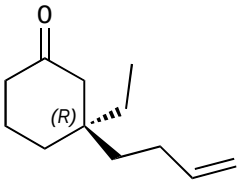
c-hexanedione (112.13 g/mol, 535 mmol, 59.99 g) and EtOH (500 mL) were introduced in a 1L round flask and stirred under N_2. I_2 (253.81 g/mol, 16.05 mmol, 4.07 g) was then added and the solution was stirred over for 50 hours. The solvent was removed by rotavapor, the residue was solubilized in Et_2O (300 mL) and washed with a sodium thiosulfate solution (3 x 100 mL). The organic layer was then washed with brine (2 x 100 mL) and water (100 mL). It was then dried on $MgSO_4$ filtered and concentrated on rotavapor to give the crude

product. This was purified by distillation at 90 °C/5mmHg to give a pale yellow liquid. (46.54 g, 62%) ^{1}H NMR (400 MHz, $CDCl_3$) 5.17 (s, 1 H), 3.74 (m, 2 H), 2.23 (m, 2 H), 2.16 (m, 2 H), 1.81 (m, 2 H), 1.19 (m, 3 H) MS (EI) : 140, 112, 84*, 69, 68, 55.



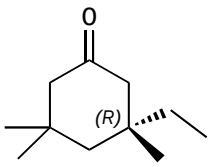
1-methylcyclohept-2-enol (50):[195]

A solution of *c*-heptenone (3.58 g, 32.49 mmol) in dry Et_2O (40 mL) was stirred and cooled to -30 °C. Methyllithium in Et_2O (40 mmol, 25 mL) was added dropwise and the solution was then allowed to come back to RT and stirred for 3 hours. H_2O (20 mL) was added and the organic layer was separated. The aqueous layer was extracted with Et_2O (3x20 mL) The combined organic fractions were washed with H_2O, dried over $MgSO_4$, filtered and concentrated to give the title product. No further purification was needed. MM = 126.20 g/mol (3.70 g, 92%) ^{13}C NMR (100 MHz, $CDCl_3$) : 139.6, 129.6, 74.1, 40.9, 28.9, 27.6, 27.4, 24.4.



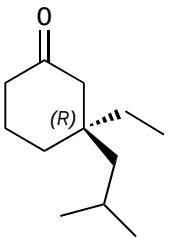
(R)-3,3-butenyl-ethylcyclohexanone (51):

^{1}H NMR (400 MHz, $CDCl_3$) : 5.82-5.72 (ddt, 1 H, *J* = 6.6 Hz, 10.1 Hz, 13.1 Hz), 5.02-4.91 (m, 2 H), 2.28-2.25 (m, 2 H), 2.15 (s, 2 H), 1.97-1.90 (m, 2 H), 1.86-1.80 (m, 2 H), 1.60-1.57 (m, 2 H), 1.34-1.28 (m, 4 H), 0.81-0.77 (t, 3 H, *J* = 7.3 Hz) ^{13}C NMR (100 MHz, $CDCl_3$) : 212.6, 139.0, 114.6, 52.0, 41.3, 41.1, 36.1, 33.6, 29.5, 27.5, 21.8, 7.5 $[\alpha]_D$: +7.58 ($CHCl_3$, c = 1.70, *ee* = 69% *R.* Absolute configuration was assigned in analogy with the literature).[16] Enantiomeric excess was measured by chiral GC (Hydrodex-B-3P isotherm 135 °C v = 40 cm/s, Rt_1 = 13.1 (*S*), Rt_2 = 13.3 (*R*)).



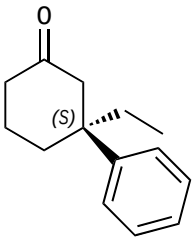
(R)-3,3-ethyl-methylisophorone (52):[189]

^{1}H NMR (400 MHz, $CDCl_3$) : see 27 $[\alpha]_D$: +8.52 ($CHCl_3$, c = 1.70, *ee* = 82% *R.* Absolute configuration was assigned in analogy with the literature).[16] Enantiomeric excess was measured by chiral GC (Chirasil DEX-CB, 60-110-2-170-5, Rt_1 = 133.8 (*R*), Rt_2 = 134.5 (*S*)).



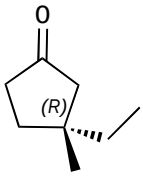
(R)-3,3-ethyl-*i*-butylcyclohexanone (53):

^{1}H NMR (400 MHz, $CDCl_3$) : 2.28-2.24 (t, 2 H, *J* = 6.8 Hz), 2.20-2.12 (dd, 2 H, *J* = 13.7, 19.0 Hz), 1.91-1.75 (m, 2 H), 1.70-1.63 (m, 1 H), 1.61-1.58 (t, 2 H, *J* = 12.4 Hz), 1.37-1.36 (d, 1 H, *J* = 7.6 Hz), 1.35-1.33 (d, 1 H, *J* = 7.3 Hz), 1.19-1.15 (m, 2 H), 0.92-0.85 (m, 6 H), 0.81-0.77 (t, 3 H, *J* = 7.3 Hz) ^{13}C NMR (100 MHz, $CDCl_3$) : 212.9, 52.7, 46.0, 42.0, 41.3, 34.0, 29.8, 25.6, 25.6, 23.7, 21.9, 7.8 MS (EI) : 182 (<1), 153 (32), 125 (66), 97 (69), 95 (11), 83 (22), 70 (10), 69 (28), 67 (11), 55 (100) HRMS (EI-MS) : $[M]^+$ found 182.167160, calculated for $C_{12}H_{22}O$: 182.167066. $[\alpha]_D$: +4.43 ($CHCl_3$, c = 1.70, *ee* = 81% *R.* Absolute configuration was assigned in analogy with the literature).[16] Enantiomeric excess was measured by chiral GC (lipodex E, isotherm 87 °C v = 40 cm/s), Rt_1 = 25.8 (*R*), Rt_2 = 27.9 (*S*)).



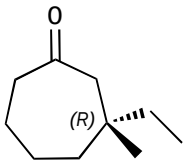
(S)-3,3-ethyl-phenylcyclohexanone (54):[133]

^{1}H NMR (400 MHz, $CDCl_3$) : 7.33-7.29 (m, 2 H), 7.27-7.24 (m, 2 H), 7.21-7.17 (m, 1 H), 2.94-2.39 (dd, 2 H, *J* = 14.4 Hz, 201.4 Hz), 2.31-2.27 (m, 2 H), 2.20-1.95 (m, 2 H), 1.87-1.53 (m, 4 H), 0.62-0.58 (t, 3 H, *J* = 7.3 Hz) ^{13}C NMR (100 MHz, $CDCl_3$) : 211.8, 146.0, 128.6, 126.7, 126.3, 50.8, 46.7, 41.3, 36.5, 35.9, 21.8, 8.2 IR (neat, cm^{-1}) : 2993, 2961, 2873, 1710, 1444, 1227 MS (EI) : 202 (12), 174 (11), 173 (72), 145 (13), 131 (13), 117 (15), 115 (12), 103 (10), 91 (28), 69 (13), 55 (100) $[\alpha]_D$: +58.3 ($CHCl_3$, c = 1.70, *ee* = 72% *S.* Absolute configuration was assigned in analogy with the literature).[16] Enantiomeric excess was measured by chiral GC (Chirasil DEX-CB 135-0-1-160 v = 40 cm/s, Rt_1 = 18.5 (*S*), Rt_2 = 19.0 (*R*)).



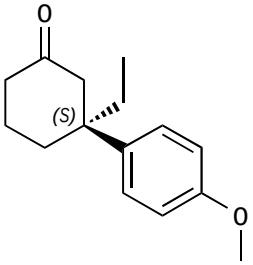
(R)-3,3-ethyl-methylcyclopentanone (55):[44,196]

^{1}H NMR (400 MHz, $CDCl_3$) : 2.30-2.26 (m, 2 H), 2.09-1.97 (dd, 2 H, *J* = 17.9 Hz, 29.8 Hz), 1.83-1.70 (m, 2 H), 1.47-1.41 (q, 2 H, *J* = 7.6 Hz), 1.03 (s, 3 H), 0.91-0.87 (t, 3 H, *J* = 7.3 Hz) ^{13}C NMR (100 MHz, $CDCl_3$) : 220.4, 52.0, 39.9, 37.0, 34.9, 34.1, 24.7, 9.2 $[\alpha]_D$: +22.59 ($CHCl_3$, c = 1.70, *ee* = 46% *R.* Absolute configuration was assigned in analogy with the literature).[16] Enantiomeric excess was measured by chiral GC (Lipodex E isotherm 60 °C v = 40 cm/s, Rt_1 = 15.2 (*R*), Rt_2 = 18.0 (*S*)).



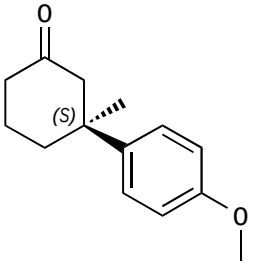
(R)-3,3-ethyl-methylcycloheptanone (57):[133]

^{1}H NMR (400 M Hz, $CDCl_3$) : 2.58-2.39 (q, 2 H, *J* = 12.2 Hz, 62.9 Hz), 2.46-2.42 (m, 2 H), 1.83-1.51 (m, 6 H), 1.41-1.23 (m, 2 H), 0.91 (s, 3 H), 0.90-0.87 (m, 3 H) ^{13}C NMR (100 MHz, $CDCl_3$) : 214.4, 54.4, 44.0, 42.1, 35.3, 34.9, 25.4, 24.7, 24.2, 8.0 IR (neat, cm^{-1}) : 2966, 2932, 1736, 1797, 1457 MS (EI) :154 (2), 125 (23), 112 (10), 97 (40), 96 (50), 86 (47), 84m (19), 84 (74), 83 (18), 81 (15), 70 (17), 69 (21), 56 (15), 55 (100), 49 (16), 47 (20) HRMS (ESI-MS) : $[M+H]^+$ found, 155.1436 calculated for $C_{10}H_{19}O$: 155.1439. $[\alpha]_D$: +10.33 ($CHCl_3$, c = 1.41, *ee* = 82% *R.* Absolute configuration was assigned in analogy the literature).[133] Enantiomeric excess was measured by chiral GC (Lipodex E isotherm 60 °C v = 50cm/s, Rt_1 = 24.3 (*R*), Rt_2 = 25.7 (*S*)).



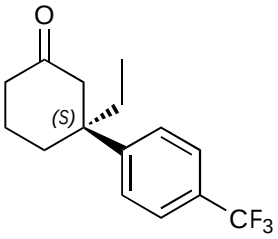
(S)-3-ethyl-3-(4-methoxyphenyl)cyclohexanone (59):[197]

^{1}H NMR (400 MHz, $CDCl_3$) : 7.17-7.15 (m, 2 H), 6.86-6.84 (2 H, m), 3.79 (s, 3 H), 2.63 (q, 2 H, *J* = 14.2 Hz, 20.3 Hz), 2.30-2.26 (m, 2 H), 2.16-1.91 (m, 2 H), 1.86-1.78 (m, 2 H), 1.76-1.52 (m, 2 H), 0.59 (t, 3 H, *J* = 7.6 Hz) ^{13}C NMR (100 MHz, $CDCl_3$) : 211.9, 157.8, 136.9, 127.7, 113.8, 55.3, 50.9, 46.1, 41.2, 36.5, 36.1, 21.7, 8.1 $[\alpha]_D$: +92.7 ($CHCl_3$, c = 1.9, *ee* = 78% *S.* Absolute configuration was assigned in analogy with the literature).[16] Enantiomeric excess was measured by chiral SFC (S2-AS (5%-2-1-15%) Rt_1 = 4.3 (*R*), Rt_2 = 4.7 (*S*)).

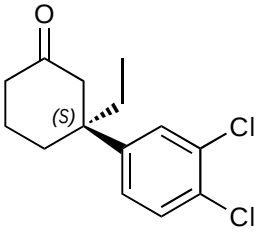


(S)-3-(4-methoxyphenyl)-3-methylcyclohexanone (60):[133]

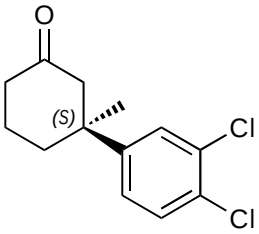
^{1}H NMR (400 MHz, $CDCl_3$) : 7.24-7.22 (m, 2 H), 6.87-84 (m, 2 H), 3.79 (s, 3 H), 2.88-2.83 (d, 1 H), 2.44-2.39 (d, 1 H), 2.20-2.11 (m, 2 H), 1.92-1.82 (m, 2 H), 1.71-1.61 (m, 2 H), 1.30 (s, 3 H) ^{13}C NMR (75 MHz, $CDCl_3$) : 126.8, 116.2, 115.0, 113.9, 55.4, 53.4, 42.5, 40.9, 38.2, 30.2, 22.2 $[\alpha]_D$: +63.6 ($CHCl_3$, c = 1.3, *ee* = 15% *S.* Absolute configuration was assigned in analogy with the literature).[16,133] Enantiomeric excess was measured by chiral SFC (S2-OD (2%-2-1-15%-0 2mL/min) Rt_1 = 5.4 (*R*), Rt_2 = 6.0 (*S*)).



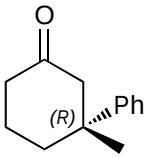
(S)-3-ethyl-3-(4-(trifluoromethyl)phenyl)cyclohexanone (61):[197] ^{1}H NMR (400 MHz, $CDCl_3$) : 7.58-7.56 (m, 2 H), 7.39-7.36 (m, 2 H), 2.69 (q, 2 H, *J* = 14.3 Hz, 142.7 Hz), 2.34-2.28 (m, 2 H), 2.22-2.16 (m, 1 H), 2.06-1.97 (m, 1 H), 1.92-1.73 (m, 1 H), 1.72-1.64 (m, 2 H), 1.62-1.47 (m, 1 H), 0.60 (t, 3 H, *J* = 7.4 Hz) ^{13}C NMR (100 MHz, $CDCl_3$) : 210.9, 149.3, 127.1, 125.6, 125.6, 125.5, 50.5, 46.9, 41.1, 36.6, 35.9, 21.6, 8.0 $[\alpha]_D$: +41.2 ($CHCl_3$, c = 2.1, *ee* = 80% *S.* Absolute configuration was assigned in analogy with the literature).[16] Enantiomeric excess was measured by chiral GC (Chirasil-Dex-CB (100-0-1-170-10 v = 40 cm/s Rt_1 = 50.7 (*S*), Rt_2 = 53.2 (*R*)).



(S)-3-(3,4-dichlorophenyl)-3-ethylcyclohexanone (62): ^{1}H NMR (400 MHz, $CDCl_3$) : 7.43-7.38 (m, 2 H), 7.15-7.11 (m, 1 H), 2.91-2.45 (q, 2 H, *J* = 14.2 Hz), 2.39-2.32 (m, 2 H), 2.21-1.85 (m, 3 H), 1.80-1.61 (m, 3 H), 0.68-0.63 (t, 3 H, *J* = 7.4 Hz) ^{13}C NMR (100 MHz, $CDCl_3$) : 211.5, 145.5, 132.8, 130.9, 130.5, 128.8, 126.3, 50.5, 46.6, 41.0, 36.1, 35.7, 21.6, 8.0 GC-MS (80-1-20-270-6 v = 45 cm/s) : 11.68 (272, 270, 241, 173, 159, 149, 136, 128, 115, 89, 69, 55*) *ee* = 80% *S.* Absolute configuration was assigned in analogy with the literature).[16] Enantiomeric excess was measured by chiral SFC (S2-AS (2%-2-1-15%) Rt_1 = 5.07 (*R*), Rt_2 = 5.46 (*S*)).

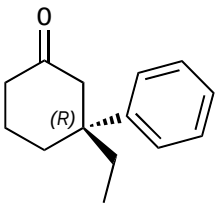


(S)-3-(3,4-dichlorophenyl)-3-methylcyclohexanone (63): ^{1}H NMR (400 MHz, $CDCl_3$) : 7.39-7.37 (m, 2 H), 7.16-7.13 (m, 1 H), 2.83-2.78 (d, 1 H, *J* = 14.1 Hz), 2.47-2.42 (d, 1 H, *J* = 14.2 Hz), 2.36-2.31 (m, 2 H), 2.17-2.10 (m, 1 H), 1.96-1.87 (m, 2 H), 1.73-1.64 (m, 1 H), 1.30 (s, 3 H) ^{13}C NMR (100 MHz, $CDCl_3$) : 211.3, 147.9, 130.6, 128.1, 125.4, 117.7, 115.4, 52.9, 42.9, 40.8, 37.8, 29.7, 22.1 $[\alpha]_D$: +76.0 ($CHCl_3$, c = 1.0, *ee* = 23% *S.* Absolute configuration was assigned in analogy with the literature).[16] Enantiomeric excess was measured by chiral SFC (S2-AS (2%-2-1-15%) Rt_1 = 7.0 (*R*), Rt_2 = 7.6 (*S*)).



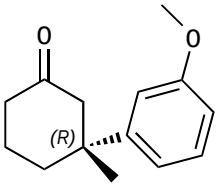
(R)-3,3-phenyl-methylcyclohexanone (64):[191]

^{1}H NMR (400 MHz, $CDCl_3$) : see 29 $[\alpha]_D$: -26.3 ($CHCl_3$, c = 1.70, *ee* = 66% *R.* Absolute configuration was assigned in analogy with the literature).[16] Enantiomeric excess was measured by chiral GC (Hydrodex-B-3P, isotherm 140 °C v = 38 cm/s, Rt_1 = 31.7 (*R*), Rt_2 = 32.7 (*S*)).



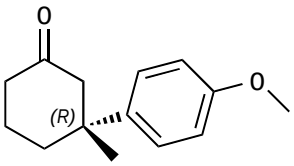
(R)-3,3-ethyl-phenylcyclohexanone (65):[133]

^{1}H NMR (400 MHz, $CDCl_3$) : see 54 $[\alpha]_D$: -22.2 ($CHCl_3$, c = 1.69, *ee* = 34% *R.* Absolute configuration was assigned in analogy with the literature).[16,133] Enantiomeric excess was measured by chiral GC (Chirasil DEX-CB (135-0-160-20-170-5 v = 40 cm/s), Rt_1 = 18.2 (*S*), Rt_2 = 18.6 (*R*)).



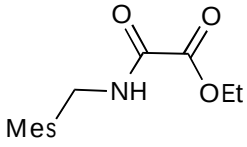
(*R*)-3-(3-methoxyphenyl)-3-methylcyclohexanone (66):[163]

^{1}H NMR (300 MHz, $CDCl_3$) : 7.27-7.22 (m, 1 H), 7.62-6.86 (m, 2 H), 6.77-6.73 (dd, 1 H, *J* = 8.2 Hz, 2.4 Hz), 3.80 (s, 3 H), 2.86 (d, 1 H, *J* = 14.1 Hz), 2.42 (d, 1 H, *J* = 14.2 Hz), 2.31 (t, 2 H, *J* = 6.7 Hz), 2.21-2.13 (m, 1 H), 1.94-1.81 (m, 2 H), 1.74-1.63 (m, 1 H), 1.31 (s, 3 H) $[\alpha]_D$: -55.3 ($CHCl_3$, c = 0.8, *ee* = 90% *R.* Absolute configuration was assigned in analogy with the literature).[16] Enantiomeric excess was measured by chiral SFC (S5-AD (5%-2-1-15% 2mL/min) Rt_1 = 4.7 (*R*), Rt_2 = 7.1 (*S*)).



(R)-3-(4-methoxyphenyl)-3-methylcyclohexanone (67):[133]

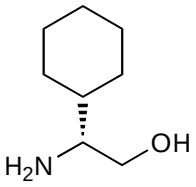
^{1}H NMR (400 MHz, $CDCl_3$) : see 60 $[\alpha]_D$: -72.5 ($CHCl_3$, c = 1.5, *ee* = 70% *R.* Absolute configuration was assigned in analogy with the literature).[16,133] Enantiomeric excess was measured by chiral SFC (S2-OD (2%-2-1-15%-0 2 mL/min) Rt_1 = 5.8 (*R*), Rt_2 = 6.3 (*S*)).



ethyl 2-oxo-2-(2,4,6-trimethylbenzylamino)acetate (68):

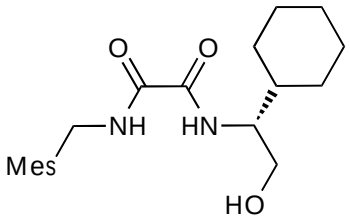
A round-bottomed flask was charged with trimethylbenzylamine (149.24 g/mol, 6.7 mmol, 1.00 g) and pyridine (79.10 g/mol, 8.0 mmol, 0.65 mL) in dry DCM (10 mL) The solution was cooled to 0 °C and ethyloxalyl chloride (136.53 g/mol, 8.0 mmol, 0.9 mL) was added. The solution was then allowed to come back to RT and was stirred overnight. EtOAc (20 mL) was added and the solution was washed with HCl 1M (2 x 30 mL), $NaHCO_3$ (30 mL), brine (30 mL), dried on

$MgSO_4$, filtered and concentrated to give the pure product as a white solid. MM = 249.31 g/mol (1.52 g, 91%) ^{1}H NMR (400 MHz, $CDCl_3$) 6.91 (br s, 1H), 6.89 (s, 2 H), 4.52 (d, 2 H, *J* = 5.1 Hz), 4.33 (q, 2 H, *J* = 7.1 Hz, 14.2 Hz); 2.32 (s, 6 H), 2.28 (s, 3 H), 1.38 (t, 3 H, *J* = 7.3 Hz).



(*R*)-2-amino-2-cyclohexylethanol (69):[198]

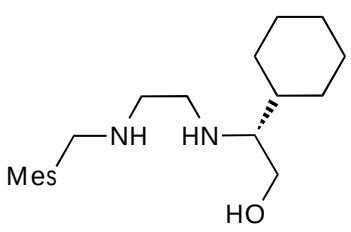
A flame-dried round-bottomed flask fitted with a condenser and an addition funnel was charged with $NaBH_4$ (37.82 g/mol, 15.1 mmol, 571 mg) and dry THF (20 mL). D-cyclohexylglycine (157.21 g/mol, 6.3 mmol, 1.0 g) was then added and the suspension was cooled to 0 °C. A solution of I_2 (253.81 g/mol, 6.3 mmol, 1.59 g) in THF (10 mL) was added dropwise. The mixture was then heated to reflux overnight (73 °C oil bath). MeOH (50 mL) was added and the solution was stirred for 30 minutes. The solvents were then removed by rotavapor and the obtained white paste was dissolved in KOH aq. 20% (100 mL) and stirred for 3.5 hours at RT. The solution was then extracted with DCM (3 x 40 mL). The combined organic layer were dried on Na_2SO_4, filtered and concentrated to give a pale brown solid. This was purified by Kugelrohr distillation at 140 °C under high *vacuo* to obtain the pure product as a white crystalline solid. Some solid went directly in the nitrogen trap. MM = 143.23 g/mol (603 mg, 67%) ^{1}H NMR (300 MHz, $CDCl_3$) : 3.69-3.64 (m, 1 H), 3.33-3.27 (m, 1 H), 2.61-2.54 (m, 1 H), 1.77-1.66 (m, 8 H), 1.27-1.17 (m, 4 H), 1.03-0.95 (m, 2 H).



(*R*)-*N*^{1}-(1-cyclohexyl-2-hydroxyethyl)-*N*^{2}-(2,4,6-trimethyl benzyl) oxalamide (70):

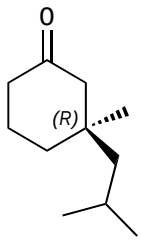
A round-bottomed flask was charged with ethyl 2-oxo-2-(2,4,6-trimethylbenzylamino)acetate 68 (249.31 g/mol, 3.4 mmol, 850 mg) and (*R*)-2-amino-2-cyclohexylethanol 69 (143.23 g/mol, 4.2 mmol, 600 mg) in dry DCM (10 mL) The solution was refluxed over the weekend. A white suspension was obtained. This was allowed to come back to RT and was diluted with EtOAc (20 mL), but was not completely soluble. The solution was washed with HCl 1M (2x30 mL) but the obtained precipitate was neither soluble in water nor in EtOAc or DCM. The organic phase was then washed with brine (30 mL), dried on $MgSO_4$, filtered and concentrated to give the pure product as a white solid. MM = 346.46 g/mol (930 mg, 79%) ^{1}H NMR (400 MHz, $CDCl_3$) 7.72-7.70 (m, 1 H),

7.37-7.36 (m, 1 H), 6.87 (s, 2 H), 4.46 (d, 2 H, *J* = 5.3 Hz), 3.72 (br s, 3 H), 2.32 (s, 6 H), 2.26 (s, 3 H), 1.75-1.72 (m, 4 H), 1.67-1.63 (m, 2 H), 1.26-1.11 (m, 4 H), 1.08-0.95 (m, 2 H) ^{13}C NMR (100 MHz, $CDCl_3$) : 160.2, 159.7, 138.0, 137.5, 129.6, 129.4, 63.0, 57.2, 38.5, 38.4, 29.8, 29.3, 26.3, 26.1, 26.1, 21.1, 19.8.



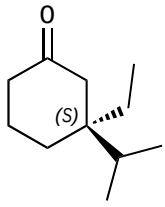
(*R*)-2-cyclohexyl-2-(2-(2,4,6-trimethylbenzylamino) ethylamino) ethanol (71):

A flame-dried round-bottomed flask was charged with $LiAlH_4$ and dry THF (10 mL) The suspension was cooled to 0 °C and (*R*)-*N*^{1}-(1-cyclohexyl-2-hydroxyethyl)-*N*^{2}-(2,4,6-trimethyl benzyl) oxalamide 70 was added. The suspension was then heated to reflux overnight. After cooling to 0 °C, H_2O followed by NaOH 15% were added dropwise. The suspension was stirred for 15 minutes, then it was filtered on Celite®. The mother liquor was concentrated in *vacuo* (bath: 60 °C, then high *vacuum* pump) to give a pale yellow oily solid. This was dried in a P_2O_5 containing dessicator over the weekend but there was still an oily residue. MM = 318.50 g/mol (758 mg, 91%) ^{1}H NMR (400 MHz, $CDCl_3$) 6.85 (s, 2 H), 3.80 (d, 2 H), 3.78 (s, 1 H), 3.73-3.69 (m, 2 H), 2.65- 2.60 (m, 5 H), 2.30 (s, 6 H), 2.24 (s, 3 H), 2.11-2.09 (br s, 2 H), 1.75-1.72 (m, 4 H), 1.66-1.62 (m, 1 H), 1.25-1.12 (m, 4 H), 1.07-0.97 (m, 2 H).



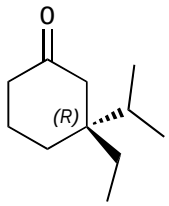
(R)-3,3-*i*-butyl-methylcyclohexanone (72):[16]

^{1}H NMR (400 MHz, $CDCl_3$) : see 44 *ee* = 18% *R*. Absolute configuration was assigned in analogy with the literature).[16] Enantiomeric excess was measured by chiral GC (lipodex E, isotherm 80 °C, Rt_1 = 10.1 (*S*), Rt_2 = 11.1 (*R*)).



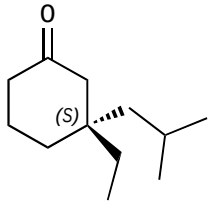
(*S*)-3-ethyl-3-isopropylcyclohexanone (73):

^{1}H NMR (300 MHz, $CDCl_3$) : 2.35-2.05 (m, 4 H), 2.00-1.79 (m, 3 H), 1.68-1.61 (m, 2 H), 1.26 (q, 2 H), 0.85 (d, 6 H), 0.78 (s, 3 H) *ee* = 83% *S*. Absolute configuration was assigned in analogy with the literature).[16] Enantiomeric excess was measured by chiral GC (lipodex E, 100-35-40-170 v = 40 cm/s, Rt_1 = 6.8 (*R*), Rt_2 = 7.4 (*S*)).



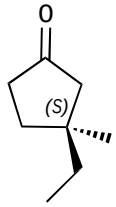
(*R*)-3-ethyl-3-isopropylcyclohexanone (74):

^{1}H NMR (300 MHz, $CDCl_3$) : see 73 *ee* = 72% *R*. Absolute configuration was assigned in analogy with the literature).[16] Enantiomeric excess was measured by chiral GC (lipodex E, 100-35-40-170 v = 40 cm/s, Rt_1 = 6.8 (*R*), Rt_2 = 7.6 (*S*)).



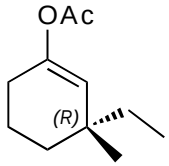
(S)-3,3-ethyl-*i*-butylcyclohexanone (75) :

^{1}H NMR (400 MHz, $CDCl_3$) : see 53 *ee* = 67% *S.* Absolute configuration was assigned in analogy with the literature).[16] Enantiomeric excess was measured by chiral GC (lipodex E, isotherm 87 °C v = 40 cm/s), Rt_1 = 25.8 (*R*), Rt_2 = 27.9 (*S*)).



(S)-3,3-ethyl-methylcyclopentanone (76):[44,196]

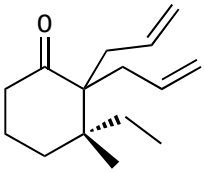
^{1}H NMR (400 MHz, $CDCl_3$) : see 55 *ee* = 66% *S.* Absolute configuration was assigned in analogy with the literature).[16] Enantiomeric excess was measured by chiral GC (Lipodex E isotherm 60 °C v = 40 cm/s, Rt_1 = 9.2 (*R*), Rt_2 = 10.3 (*S*)).



(R)-3,3-ethyl-methylcyclohex-1-enyl acetate (77):[44]

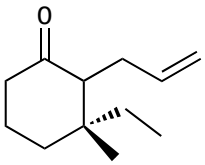
A schlenk tube was dried at the high *vacuum* pump. $Cu(OTf)_2$ (361.69 g/mol, 0.03 mmol, 10.8 mg) and the ImH^+ 3d (434.39 g/mol, 0.04 mmol, 17.4 mg) were put in the Schlenk tube and dried in *vacuo* for 15 minutes. Et_2O (1.5 mL) was added and the solution was cooled to 0 °C under stirring and N_2. EtMgBr (3.2 mol/L, 1.2 mmol, 0.38 mL) in Et_2O was added dropwise to the solution (2 min.) The solution turned dark brown, then blue. A solution of methylcyclohexenone (110.15 g/mol, 1.0 mmol, 110 mg) in Et_2O (8 mL) was added dropwise to the solution at 0 °C over 45 minutes. Ac_2O (102.09 g/mol, 3.0 mmol, 0.28 mL) was then added with formation of a white suspension and the system was stirred at RT for 4 hours. NH_4Cl 1M was added and the organic layer was separated. The aqueous layer was extracted with DCM (2x10 mL) The combined organic phases were washed with $NaHCO_3$, dried on Na_2SO_4, filtered and concentrated to give a yellow oil. This was purified by chromatography on silica with pentane : Et_2O 10:1 to give the pure product as a transparent oil. Rf = 0.55; MM = 182.26 g/mol (148 mg, 81%)

^{1}H NMR (300 MHz, $CDCl_3$) : 5.12 (s, 1 H), 2.15–2.03 (m, 5 H), 1.78–1.69 (m, 2 H), 1.51–1.42 (m, 1 H), 1.39–1.31 (m, 3 H), 0.98 (s, 3 H), 0.84 (t, 3 H, *J* = 7.5 Hz) ^{13}C NMR (100 MHz, $CDCl_3$) : 169.4, 147.4, 123.0, 35.1, 33.8, 27.0, 26.7, 21.2, 19.5, 8.5 $[\alpha]_D$: -11.5 ($CHCl_3$, c = 0.01, *ee* = 76% *R.* Absolute configuration was assigned in analogy with the literature).[44] Enantiomeric excess was measured by chiral GC (Hydrodex B3P, isotherm 70 °C v = 45 cm/s), Rt_1 = 42.8 (*R*), Rt_2 = 47.2 (S)).



(*R*)-2,2-diallyl-3-ethyl-3-methylcyclohexanone (78):[44]

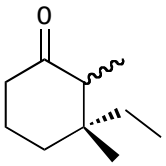
^{1}H NMR (400 MHz, $CDCl_3$) : 5.75-5.61 (m, 2 H), 5.08 (s, 2 H), 5.05 (s, 2 H), 2.40-2.09 (m, 6 H), 1.77-1.66 (m, 3 H), 1.57-1.47 (m, 1 H), 1.28 (q, 2 H, *J* = 7.6 Hz), 0.88 (s, 3 H), 0.84 (t, 3 H, *J* = 7.6 Hz) ^{13}C NMR (100 MHz, $CDCl_3$) : 214.2, 133.9, 133.5, 118.1, 118.0, 50.6, 50.4, 39.3, 39.2, 38.7, 34.0, 31.4, 31.3, 24.4 *ee* = 76% *R.* Absolute configuration was assigned in analogy with the literature.[16] Enantiomeric excess of the ethylmethylcyclohexanone was measured by chiral GC (lipodex E, 75-23-20-170-5 v = 40 cm/s), Rt_1 = 15.5 (*R*), Rt_2 = 19.9 (*S*)).



(3*R*)-2-allyl-3,3-ethyl-methylcyclohexanone (79):

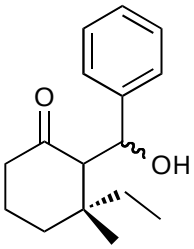
A Schlenk tube was dried at the high *vacuum* pump. $Cu(OTf)_2$ (361.69 g/mol, 0.03 mmol, 10.8 mg) and the ImH^+ 3d (434.39 g/mol, 0.04 mmol, 17.4 mg) were put in the schlenk and dried in *vacuo* for 15 minutes. Et_2O (1.5 mL) was added and the solution was cooled to 0 °C under stirring and N_2. EtMgBr (3.2 mol/L, 1.2 mmol, 0.38 mL) in Et_2O was added dropwise to the solution (2 min.) The solution turned dark brown, then blue. A solution of methylcyclohexenone (110.15 g/mol, 1.0 mmol, 110 mg) in Et_2O (8 mL) was added dropwise to the solution at 0 °C over 15 minutes. When the addition was finished, the solution was stirred for 5 minutes at 0 °C. Allyl iodide (167.98 g/mol, 2.0 mmol, 0.18 mL) was then added, followed by CaH_2-dried HMPA (2 mL) and THF (2 mL) The solution became white and was warmed to 40 °C for 25 hours (after: 12 hours, 87% allylated product; 19 hours, 93% allylated product; 25 hours, >98% allylated product) The mixture was quenched with HCl 1M, extracted with Et_2O, dried on MgSO4, filtered and concentrated to give a yellow oil. This was purified by chromatography with pentane Et_2O 10:1 to give the pure product as a mixture of diastereoisomeres (70:30). MM = 180.29 g/mol (175 mg, 97%) ^{13}C NMR (100 MHz, $CDCl_3$) : 213.2, 212.9, 137.9,

137.7, 115.4, 115.3, 61.5, 58.3, 42.2, 41.7, 41.4, 40.9, 34.7, 34.4, 33.4, 28.8, 28.2, 27.0, 24.8, 22.9, 22.6, 20.9, 7.9, 7.4 *ee* 76% *R* Absolute configuration was assigned in analogy with the literature.[16] Enantiomeric excess was measured by chiral GC on the ethyl addition (Lipodex E, iso 75 °C v = 45 cm/s, Rt_1 = 11.0 (*R*), Rt_2 = 13.8 (S)). GC-MS (80-1-20-270-6 v = 45 cm/s) : 6.91 maj. (180,151,109,96,81,67,55*) ; 6.95 (180,151,109,96,81,67,55*) HRMS (EI-MS) : found 180.1514, expected : 180.1512 Accuracy = -0.2.

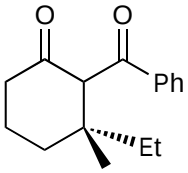


3-ethyl-2,3-dimethylcyclohexanone (80):[199]

$Cu(OTf)_2$ (361.69 g/mol, 0.03 mmol, 11 mg) and ImH^+ 3d (434.40 g/mol, 0.04 mmol, 17.4 mg) were put in a flame-dried Schlenk tube and dried in *vacuo*. Et_2O (2 mL) was added and the solution was cooled to 0 °C under stirring and N_2. EtMgBr (2.9 mol/L, 1.2 mmol, 0.41 mL) in Et_2O was then added dropwise to the solution over 1 minute. A solution of methylcyclohexenone (110.15 g/mol, 1.0 mmol, 110 mg) in Et_2O (8 mL) was added dropwise to the solution at 0 °C over 25 minutes. When the addition was finished, the solution was stirred for 30 minutes at 0 °C. Methyliodide (167.98 g/mol, 2.0 mmol, 0.18 mL) was then added, followed by HMPA (2 mL) and THF (2 mL) The solution became white and was warmed to RT for 12 hours. The white suspension was quenched with HCl 1M, extracted with Et_2O, dried on $MgSO_4$, filtered and concentrated to give an yellow oil. This was purified by chromatography on silica with pentane : Et_2O 10:1 to give the pure product as a mixture of diastereoisomeres (59:41). MM = 154.25 g/mol (122 mg, 79%) ^1H NMR (400 MHz, $CDCl_3$) : 2.41-2.32 (m, 2.8 H), 2.31-2.22 (m, 2.1 H), 1.97-1.69 (m, 5.5 H), 1.52-1.45 (m, 1.6 H), 1.43-1.35 (m, 2.1 H), 1.31-1.21 (m, 1 H), 1.19-1.15 (m, 1 H), 0.98-0.96 (m, 4.1 H), 0.93-0.92 (m, 2.9 H), 0.90-0.86 (m, 3.1 H), 0.79-0.75 (m, 2.2 H), 0.73 (s, 3 H) ^{13}C NMR (100 MHz, $CDCl_3$) : 214.7, 214.4, 55.6, 52.1, 41.6, 41.1, 41.0, 40.7, 35.0, 34.4, 33.7, 25.5, 25.1, 22.5, 22.2, 20.0, 8.8, 8.3, 7.9, 7.4 *ee* 76% *R (*Absolute configuration was assigned in analogy with the literature).[16] Enantiomeric excess was measured by chiral GC on the ethyl addition (Lipodex E, iso 75 °C v = 45 cm/s, Rt_1 = 11.5 (*R*), Rt_2 = 14.4 (S)).

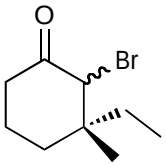


(3*R*)-3-ethyl-2-(hydroxy(phenyl)methyl)-3-methylcyclohexanone (81): $Cu(OTf)_2$ (361.69 g/mol, 0.03 mmol, 11.3 mg) and ImH^+ 3d (434.40 g/mol, 0.04 mmol, 18.0 mg) were put in a flame-dried Schlenk tube and dried in *vacuo*. Et_2O (2.6 mL) was added and the solution was cooled to 0 °C under stirring and N_2. EtMgBr (2.95 mol/L, 1.2 mmol, 0.41 mL) in Et_2O was added dropwise to the solution over 4 minutes. The solution turned dark brown, then blue. A solution of methylcyclohexenone (110.15 g/mol, 1.0 mmol, 110 mg) in Et_2O (10 mL) was added dropwise to the solution at 0 °C over 15 minutes. When the addition was finished, the solution was stirred for 30 minutes at 0 °C. Benzaldehyde (106.12 g/mol, 2 mmol, 0.20 mL) was added and the formed suspension was stirred overnight. The obtained dark suspension was quenched with saturated NH_4Cl (25 mL) The organic layer was separated and washed with water (50 mL). The organic layer was then concentrated in high *vacuo* at RT to remove benzaldehyde and give an unanalyzable mixture of diastereoisomers. MM = 246.34 g/mol (185 mg, 75%).



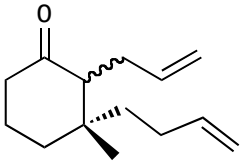
(3*R*)-2-benzoyl-3,3-ethyl-methylcyclohexanone (82):

PCC (215.56 g/mol, 1.5 mmol, 323.3 mg), NaOAc (82.04 g/mol, 1.5 mmol, 123.1 mg), dried molecular sieves (4 A, 60 mg) and Celite® (80 mg) were put in a dried bottom flask. A solution of (3*R*)-3-ethyl-2-(hydroxy(phenyl)methyl)-3-methylcyclohexanone 81 (246.34 g/mol, 0.75 mmol, 185 mg) in DCM (20 mL) was added to the mixture and it was stirred overnight. Et_2O (50 mL) was added and the mixture was flushed through a big plug of Celite®. There were still some chromium salts in it. The crude was then filtrated on a silica column eluted with Et_2O. The solvent was removed in high *vacuo* to obtain the pure product as a dark yellow oil in a 32:68 mixture of 2 diastereoisomers. MM = 244.33 g/mol (132 mg, 72%) ^1H NMR (400 MHz, $CDCl_3$) : 8.00-7.94 (m, 2 H), 7.58-7.54 (m, 1 H), 7.47-7.43 (m, 2 H), 4.39 (m, 1 H), 2.40-2.19 (m, 2 H), 2.07-1.95 (m, 1 H), 1.92-1.76 (m, 1 H), 1.56-1.31 (m, 4 H), 0.98 (s, 3 H), 0.86 (t, 3 H, *J* = 7.3 Hz) ^{13}C NMR (100 MHz, $CDCl_3$) : 208.6, 208.3, 197.0, 197.0, 138.7, 138.4, 133.4, 133.4, 128.8, 128.8, 128.7, 128.7, 69.1, 68.0, 43.5, 42.6, 39.3, 38.9, 32.4, 31.9, 31.9, 31.1, 23.6, 23.2, 22.3, 21.7, 7.9, 7.6 *ee* 1st dia = 77% *R. ee* 2nd dia = 68% *R (*Absolute configuration was assigned in analogy with the literature).[16] Enantiomeric excess was measured by chiral GC (Chirasil Dex-CB, 110-0-1-170-5 v = 40 cm/s, 1st dia: Rt_1 = 50.7 (*R*), Rt_2 = 51.1 (S); 2nd dia: Rt_1 = 53.2, Rt_2 = 53.6).



(3*R*)-2-bromo-3,3-ethyl-methylcyclohexanone (83):

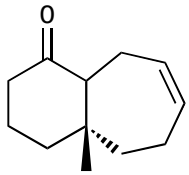
$Cu(OTf)_2$ (361.69 g/mol, 0.03 mmol, 11.4 mg) and ImH^+ 3d (434.40 g/mol, 0.04 mmol, 18.1 mg) were put in a flame-dried Schlenk tube and dried in *vacuo*. Et_2O (2.6 mL) was added and the solution was cooled to 0 °C under stirring and N_2. EtMgBr (2.8 mol/L, 1.2 mmol, 0.45 mL) in Et_2O was added dropwise to the solution over 4 minutes. The solution turned dark brown, then blue. A solution of methylcyclohexenone (110.15 g/mol, 1.0 mmol, 109 mg) in Et_2O (10 mL) was added dropwise to the solution at 0 °C over 15 minutes. When the addition was finished, the solution was stirred for 30 minutes at 0 °C. Br_2 (159.81 g/mol, 1.1 mol, 0.06 mL) was added and the formed suspension was stirred for 1 hour at 0 °C. The obtained suspension was quenched with saturated $Na_2S_2O_3$ (15 mL) The organic layer was separated and washed with brine (20 mL) The organic layer was then dried on Na_2SO_4, filtered and concentrated to give the crude product as an yellow oil. This crude was purified by chromatography on a silica column using pentane : Et_2O 9:1 as eluent to give the pure product as a 32:67 mixture of 2 diastereoisomers. Rf = 1st dia=0.3; 2nddia=0.17; MM = 219.12 g/mol (171 mg, 78%) ^1H NMR (400 MHz, $CDCl_3$) : 4.23 (s, 1 H), 4.05 (s, 1 H), 3.11-3.03 (m, 1 H), 2.95-2.88 (m, 1 H), 2.30-2.23 (m, 1.5 H), 1.87-1.80 (m, 4 H), 1.68-1.55 (m, 1.5 H), 1.50-1.43 (m, 3.2 H), 1.42-1.32 (m, 2.2 H), 1.02 (s, 3 H), 0.99 (s, 3 H), 0.92-0.82 (m, 4.5 H) ^{13}C NMR (100 MHz, $CDCl_3$) : 204.7, 204.0, 65.5, 63.7, 42.3, 41.2, 37.1, 36.1, 31.9, 31.4, 31.2, 28.0, 22.9, 21.4, 21.3, 21.1, 8.0, 7.1 *ee* 1st dia = 76% *R. ee* 2nd dia = 78% *R* (Absolute configuration was assigned in analogy with the literature).[16] Enantiomeric excess was measured by chiral GC (Lipodex E, 80-60-1-120-80-170-3 v = 40 cm/s, 1st dia: Rt_1 = 68.8 (*R*), Rt_2 = 74.0 (S); 2nd dia: Rt_1 = 88.0, Rt_2 = 88.9).



(3*R*)-2-allyl-3-(but-3-enyl)-3-methylcyclohexanone (84):

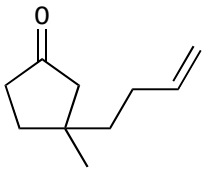
$Cu(OTf)_2$ (361.69 g/mol, 0.03 mmol, 10.9 mg) and ImH^+ 3d (434.40 g/mol, 0.04 mmol, 17.4 mg) were put in a flame-dried Schlenk tube and dried in *vacuo*. Et_2O (1.5 mL) was added and the solution was cooled to -30 °C under stirring and N_2. ButenylMgBr (1.7 mol/L, 1.2 mmol, 0.71 mL) in Et_2O was added dropwise to the solution over 2 minutes. A solution of methylcyclohexenone (110.15 g/mol, 1.0 mmol, 109 mg) in Et_2O (8 mL) was added dropwise to the solution at -30 °C over 25 minutes. Allyl iodide (167.98 g/mol, 2.0 mmol, 0.18 mL) was then added, followed by CaH_2-dried HMPA (3 mL) and THF (3 mL) The yellow white suspension was warmed at 40 °C for 25 hours. The mixture was

quenched with HCl 1M, extracted with Et_2O, dried on $MgSO_4$, filtered and concentrated to give a yellow oil. This was purified by chromatography with pentane Et_2O 20:1 to give the pure product as a 94:6 mixture of 2 diastereoisomers. Rf = 0.38 1st dia; 0.21 2nd dia; MM = 206.32 g/mol (148 mg, 72%) ^1H NMR (400 MHz, $CDCl_3$) : ^{13}C NMR (100 MHz, $CDCl_3$) : 212.8, 212.4, 137.8, 137.5, 136.7, 136.5, 116.4, 116.3, 115.6, 115.4, 53.9, 53.5, 49.6, 49.3, 41.6, 41.4, 35.5, 35.4, 33.8, 33.7, 28.9, 28.8, 28.0, 27.9, 27.7, 27.5, 22.9, 22.8 GC-MS (80-1-20-270-6 v = 45 cm/s) : 8.0 (206, 191, 162, 151, 109, 95, 81*, 67, 55) ; 8.1 (206, 191, 162, 151, 109, 95, 81*, 67, 55) *ee* 91% *S* (Absolute configuration was assigned in analogy with the literature).[16] Enantiomeric excess was measured by chiral GC on the butenyl addition (Hydrodex B3P, iso 130 °C v = 43 cm/s, Rt_1 = 8.7 (*S*), Rt_2 = 9.0 (*R*)).



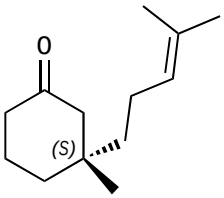
4a-methyl-2,3,4,4a,5,6,9,9a-octahydro-1*H*-benzo[7]annulen-1-one (85):

A flame-dried two-necked round-bottomed flask was charged with (3*R*)-2-allyl-3-(but-3-enyl)-3-methylcyclohexanone 84 (206.32 g/mol, 0.3 mmol, 63 mg) followed by dry DCM (3 mL). Grubbs II catalyst (849.98 g/mol, 0.006 mmol, 5.1 mg) was added and the solution was stirred at RT for 1 hour. The solution was then quenched with HCl 1M. The organic layer was separated and the aqueous layer was extracted with DCM (3 x 15 mL). The combined organic layers were washed with brine, dried on $MgSO_4$, filtered and concentrated to give a dark brown oil. This was purified by chromatography on silica with pentane : Et_2O 20:1 to give the pure product as a 58:42 mixture of 2 diastereoisomers as a transparent oil. Rf: 1st dia = 0.38, 2nd dia = 0.21; MM = 178.27 g/mol (62%) ^1H NMR (400 MHz, $CDCl_3$) : 1st dia : 5.81-5.75 (m, 1 H), 5.74-5.69 (m, 1 H), 2.54-2.51 (m, 1 H), 2.43-2.29 (m, 3 H), 2.19-2.14 (m, 3 H), 2.01-1.82 (m, 3 H), 1.63-1.57 (m, 1 H), 1.55-1.45 (m, 2 H), 0.87 (s, 3 H) 2nd dia : 5.70-5.68 (m, 2 H), 2.59-2.52 (m, 1 H), 2.48-2.45 (m.1 H), 2.36-2.20 (m, 3 H), 2.07-2.00 (m, 1 H), 1.97-1.92 (m, 2 H), 1.87-1.74 (m, 3 H), 1.52-1.48 (m, 1 H), 1.45-1.39 (m, 1 H), 1.02 (s, 3 H) ^{13}C NMR (100 MHz, $CDCl_3$) : 1st dia : 213.5, 132.3, 130.4, 57.5, 43.0, 41.9, 41.3, 40.0, 23.6, 23.3, 22.9, 18.6 2nd dia : 214.4, 131.6, 129.0, 59.4, 40.1, 39.8, 39.1, 35.9, 27.4, 25.5, 23.3, 22.0 (MS-EI) 178, 163, 150, 145, 135, 117, 107, 91, 79*, 67, 55.



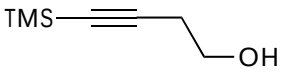
3-(but-3-enyl)-3-methylcyclopentanone (86):[136]

^{1}H NMR (400 MHz, $CDCl_3$) : 5.89-5.79 (m, 1 H), 5.07-4.96 (m, 2 H), 2.34-2.29 (m, 2 H), 2.14-2.03 (m, 4 H), 1.85-1.79 (m, 2 H), 1.55-1.50 (m, 2 H), 1.09 (s, 3 H) ^{13}C NMR (100 MHz, $CDCl_3$) : 220.1, 138.8, 114.6, 52.4, 41.1, 39.6, 36.9, 35.4, 29.3, 25.0 MS-(EI): 152, 137, 109, 97, 81, 69, 55* *ee* = 0%. Enantiomeric excess of the ethylmethylcyclohexanone was measured by chiral GC (lipodex E, 50-0-1-110-40- v = 40 cm/s), Rt_1 = 56.7, Rt_2 = 58.1).



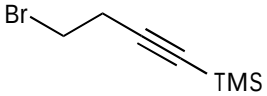
(3*S*)-3-methyl-3-(4-methylpent-3-enyl)cyclohexanone (87):[172]

^{1}H NMR (400 MHz, $CDCl_3$) : 5.08 (t, 1 H, *J* = 5.9 Hz), 2.31-2.26 (m, 2 H), 2.23-2.10 (m, 2 H), 1.98-1.85 (m, 4 H), 1.68 (s, 3 H), 1.67-1.60 (m, 2 H), 1.60 (s, 3 H), 1.31-1.26 (m, 2 H), 0.94 (s, 3 H) ^{13}C NMR (100 MHz, $CDCl_3$) : 212.4, 131.7, 124.4, 53.8, 41.8, 41.2, 38.7, 36.0, 25.8, 25.0, 22.3, 22.2, 17.7 $[\alpha]_D$: -6.8 ($CHCl_3$, c = 1.17, *ee* = 86% *S. (*Absolute configuration was assigned in analogy with the literature).[16] Enantiomeric excess was measured by chiral GC (lipodex E, 80-0-1-120 v = 45 cm/s), Rt_1 = 28.1 (S), Rt_2 = 29.5 (R)).



4-(trimethylsilyl)but-3-yn-1-ol (88):[174]

A flame-dried two-necked round-bottomed flask, surmounted by an addition funnel, was charged with butynol (70.09 g/mol, 43 mmol, 3.2 mL) and dry THF (80 mL). The solution was cooled to -78 °C and *n*-BuLi (1.6 mol/L, 95 mmol, 59 mL) was added dropwise under stirring and N_2. TMSCl (108.64 g/mol, 129 mmol, 16.5 mL) was then added, the solution was allowed to warm to RT and was stirred 2 hours. HCl 2M was added and the biphasic suspension was stirred for 30 minutes at RT. The mixture was extracted with EtOAc (3 x 40 mL). The combined organic phases were washed with NH_4Cl, NaCl aq, dried on $MgSO_4$, filtered and concentrated to give the crude product as a transparent oil. MM = 142.27 g/mol (4.58 g , 74%) ^{1}H NMR (300 MHz, $CDCl_3$) : 3.73 (t, 2 H, *J* = 5.3 Hz), 2.51 (t, 2 H, *J* = 7.4 Hz), 0.17 (s, 9 H).



(4-bromobut-1-ynyl)trimethylsilane (89):[175]

A flame-dried round-bottomed flask was charged with TMS-butynol 88 (142.28 g/mol, 32.2 mmol, 4.58 g) in dry DCM (60 mL). The solution was cooled to -30 °C and CBr_4 (331.65 g/mol, 38.6 mmol, 12.8 g) was added. The solution was stirred for 10 minutes and PPh_3 (262.30 g/mol, 32.2 mmol, 8.45 g) in DCM (20 mL)

was added. The solution was stirred 2 hours at -30 °C, warmed to 0 °C and stirred 1.5 hour more. The reaction mixture was filtered on a plug of silica and washed off with petroleum ether. The solvent was discarded in *vacuo* to give the crude product as an yellow oil. The product was purified by chromatography on silica with pure petroleum ether (boiling range 60-80 °C) to give the pure product as a colorless oil. Volatile product, was eliminated in *vacuo*!!! Rf : 0.5; MM = 205.17 g/mol (5.44 g, 82%) ^{1}H NMR (400 MHz, $CDCl_3$) : 3.44 (t, 2 H, *J* = 7.6 Hz), 2.79 (t, 2 H, *J* = 7.6 Hz), 0.18 (s, 9 H) MS (EI) : 206, 191*, 189*, 163, 161, 139, 137, 109.

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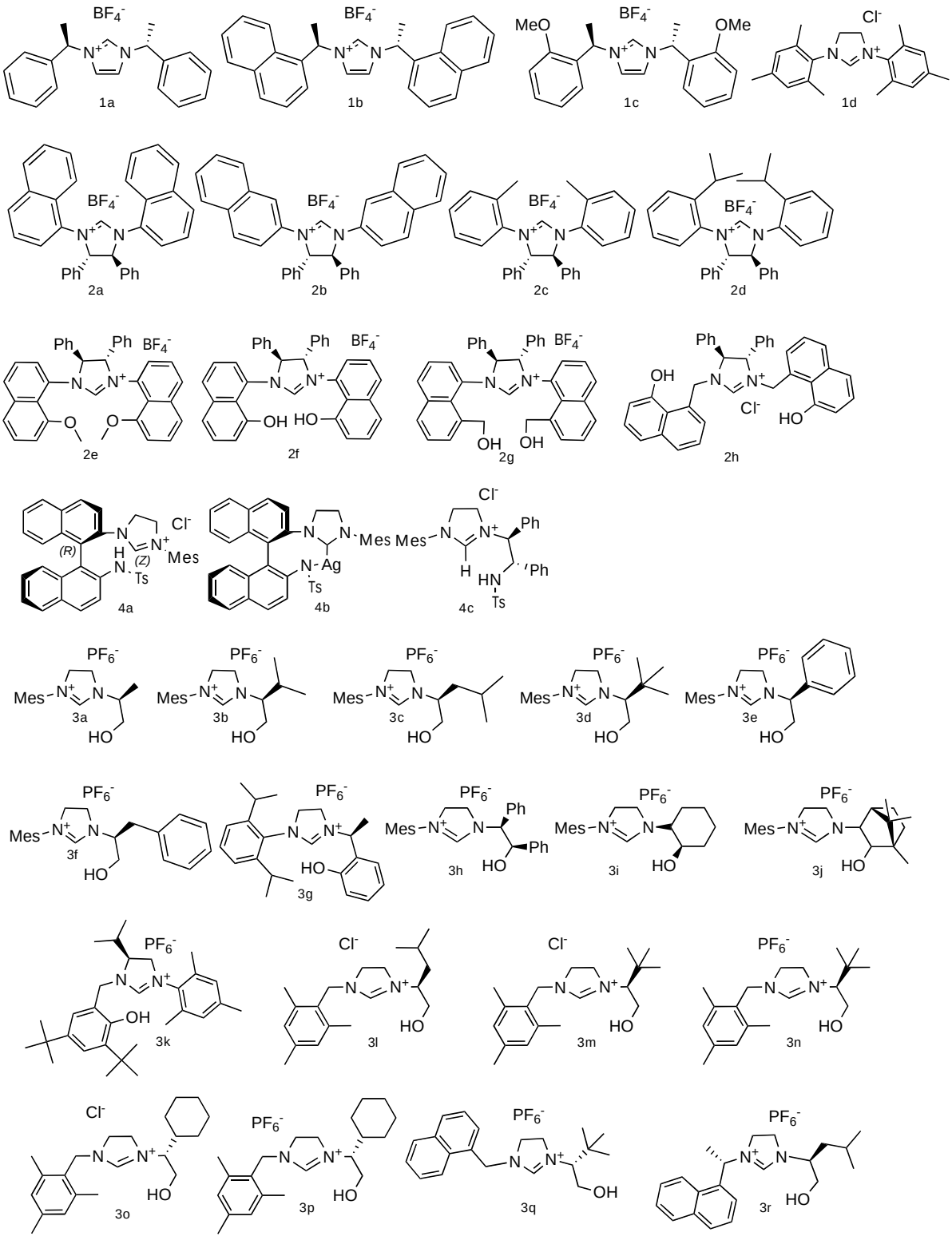
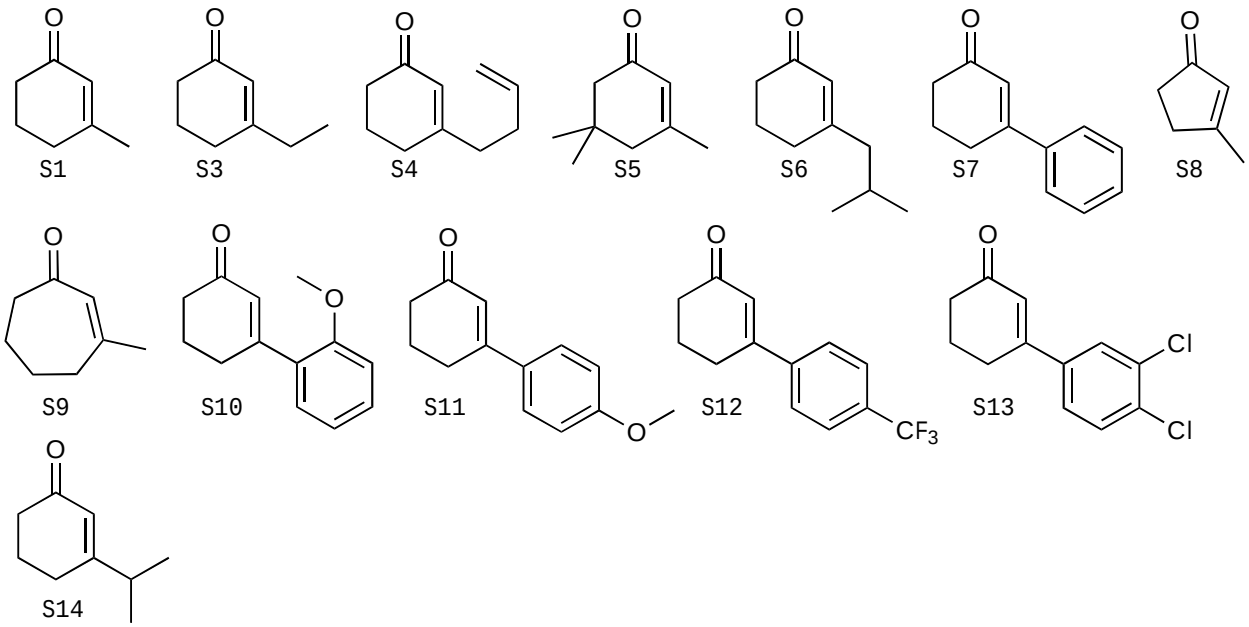
11. *Appendix*

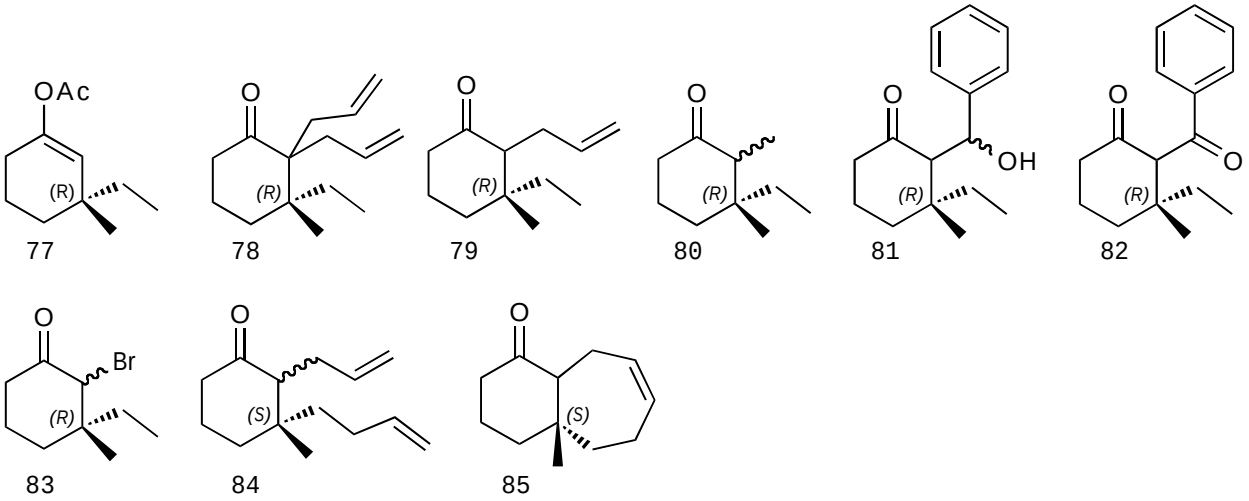
11.1 List of ligands



11.2 List of substrates



11.3 List of enolate trapping products



11.4 List of 1,4-addition products