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Study of New Reactions Catalysed by Copper(I) Complexes: Investigation of Domino Catalysis- and Dual Catalysis-Type Reactions

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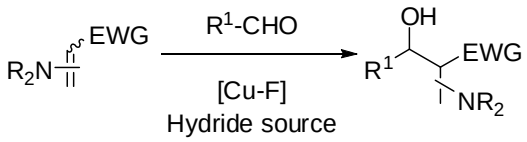
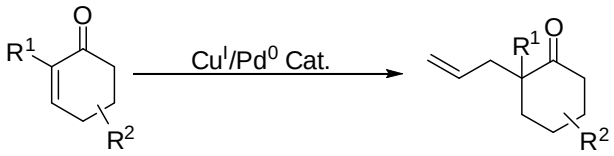
A final thanks to all the students I had over the past 5 years. I hope to see you one of these days and wish you all the success in the world.

ABSTRACT

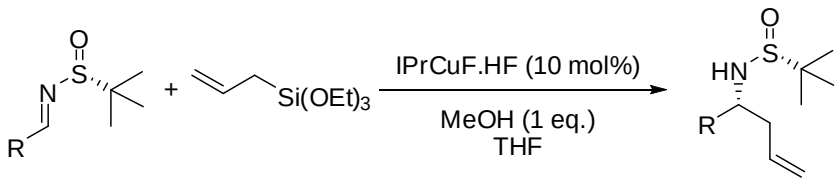
At first, we are going to discuss the application of a copper hydride system, which was previously developed in our lab, to new Michael acceptors bearing a nitrogen group on the double bond.



We are equally going to illustrate the development of a new cooperative dual catalysis strategy based on a Cu^{I}/Pd^{0} system. This strategy allowed us to successfully access α-allylated ketones diastereoselectively as well as enantioselectively.

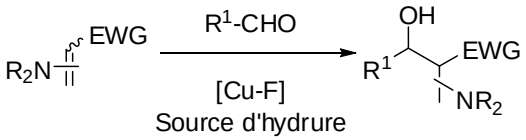


We also developed two synthetic pathways to generate unprecedented (NHC)Cu^{I} bifluoride complexes. We later tested the activity of these complexes in several known Cu^{I}-catalyzed reactions, and consequently established the first Cu^{I}-catalyzed diastereoselective allylation of (*R*)-*N*-*tert*-butanesulfinyl aldimines. The method enables efficient, simple and general synthesis of enantiomerically enriched homoallylic amines at room temperature in high yields.

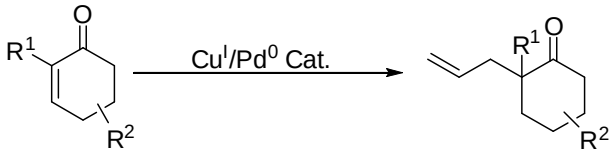


RÉSUMÉ

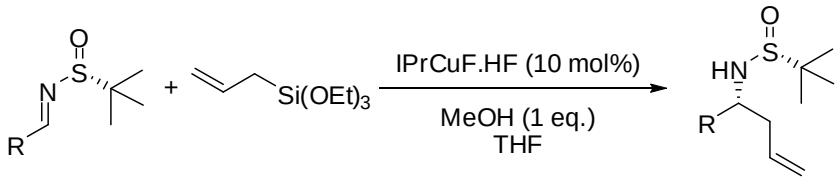
Dans un premier temps, nous allons discuter de l'application d'un système hydrure de cuivre, qui a déjà été développé dans notre laboratoire, à de nouveaux accepteurs de Michael portant un motif azoté sur la double liaison.



Nous allons également illustrer le développement d'une nouvelle stratégie de « cooperative dual catalysis » basée sur un système Cu^{I}/Pd^{0}. Cette stratégie nous a permis d'accéder avec succès, aux cétones α-allylées diastéréosélectivement ainsi qu'énantiosélectivement.



Nous avons encore développé deux voies de synthèse pour produire les premiers complexes de bifluorure de $(NHC)Cu^{I}$. Nous avons ensuite testé l'activité de ces complexes dans plusieurs réactions connues pour être catalysées par le cuivre. Et par conséquence, nous avons établi la première allylation diastéréosélective de la (*R*)-*N*-*tert*-butanesulfinyl aldimines catalysée par ces complexes de Cu^{I}. Cette méthode permet de synthétiser, d'une manière efficace et simple, des amines homoallyliques énantiomériquement enrichis, à température ambiante avec de très bons rendements.



ABREVIATIONS

Å	:	Angström
AcOEt	:	Ethyl acetate
AcOH	:	Acetic acid
Aq.	:	Aqueous
Ar	:	Aryl
atm.	:	Atmosphere
BINAP	:	2,2'-(diphenylphosphino)-1,1'-binaphtalene
Bn	:	Benzyl
Boc	:	*Di-tert-butyl dicarbonate*
n-Bu	:	Butyl
t-Bu	:	Tert-butyl
Cat.	:	catalytic
Cp	:	Cyclopentadienyl
Cy	:	cyclohexyl
DBU	:	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	:	Dichloroethane
DCM	:	Dichloromethane
DIBAL-H	:	Diisobutylaluminium hydride
DME	:	Dimethylether
DMF	:	*N*,*N*-dimethylformamide
DMPU	:	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	:	Dimethylsulfoxide
DPPBz	:	Diphenylphosphinobenzene

DPPE	:	Diphenylphosphinoethane
DPPF	:	Diphenylphosphinoferrocene
DPPM	:	Diphenylphosphinomethane
DPPP	:	Diphenylphosphinopropane
E	:	Electrophile
d.e.	:	Diastereomeric excess
d.r.	:	Enantiomeric ratio
e.e.	:	Enantiomeric excess
Eq.	:	Equivalent
Et	:	Ethyl
EWG	:	Electrowithdrawing group
GC	:	Gas chromatography
h	:	Hour
HMPA	:	Hexamethylphosphoramide
HRMS	:	High resolution mass spectroscopy
Hz	:	Hertz
i-Pr	:	Isopropyl
IR	:	Infra-red
L	:	Ligand
LDA	:	Lithium diisopropylamide
n.d.	:	Non detyermined
Me	:	Methyl
$MePh_2SiH$	:	Methyldiphenylsilane
$Me(EtO)_2SiH$	:	Methyldiethoxysilane

mmol	:	Millimole
n-BuLi	:	*n*-butyllithium
NHC	:	*N*-heterocyclic carbene
Nu	:	Nucleophile
Ph	:	Phenyl
$PhSiH_3$	:	Phenylsilane
PMHS	:	Polyméthylhydrosilyloxane
n-Pr	:	*n*-Propyl
ppm	:	Part par million
NMR	:	Nuclear magnetic resonance
r.t.	:	Room temperature
TASF	:	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF	:	Tetrabutylammonium fluoride
TBAT	:	Tetrabutylammonium triphenyldifluorosilicate
Tf	:	Triflate
TFA	:	Trifluoroacetate
THF	:	Tetrahydrofuran
TLC	:	Thin layer chromatography
TMDS	:	1,1,3,3-tétraméthylhydrosiloxane
TMS	:	Trimethylsilyl
Ts	:	Tosyl
Tol.	:	Toluene

“Never doubt that a small group of committed people can
CHANGE THE WORLD
Indeed, it’s the only thing that ever has”
Margaret Mead

“Victory needs no explanation, defeat allows none”

“If you tell the truth you don’t have to remember anything”
Mark Twain

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GENERAL INTRODUCTION

I. Multistep Reactions

The ultimate goal of synthetic organic chemistry today is to find an elegant synthesis for modern target molecules. The elegance in chemical terms is normally associated with a synthesis that affords the product in a very low number of synthetic transformations, in high yield and selectivity and, last but not least, one that requires simple, readily available and easy to handle reagents. In short, chemists are trying to replicate the task that nature has done for many years. And as nature evolved over the years, synthetic methodologies and transformations are in constant evolution in sync with economic and synthetic needs.

For a synthesis to be considered elegant, it needs to be highly convergent and requires incorporating very efficient transformations. Frequently, such syntheses employ multistep reactions such as one-pot, tandem and cascade reactions. In the recent literature, a large number of publications are concerned either with the application of these multistep sequences or with the development of new methodologies of this type.

Multistep sequences are divided into three major groups: concurrent, tandem and *in situ* or one-pot reactions.[1] Tandem reactions have three sub-classes, the simple tandem reaction, the domino reaction and the cascade reaction, of which the cascade reaction can be further divided into zipper and crochet mode reactions (Figure 1).

---

[1] a) Ed. T.-L. Ho, *Tandem Organic Reactions*; John Wiley & Sons, Inc.: New York, 1992; b) L. F. Tietze *Chem. Rev.* **1996**, *96*, 115; c) D. E. Fogg, E. N. dos Santos, *Coord. Chem. Rev.* **2004**, *248*, 2365.

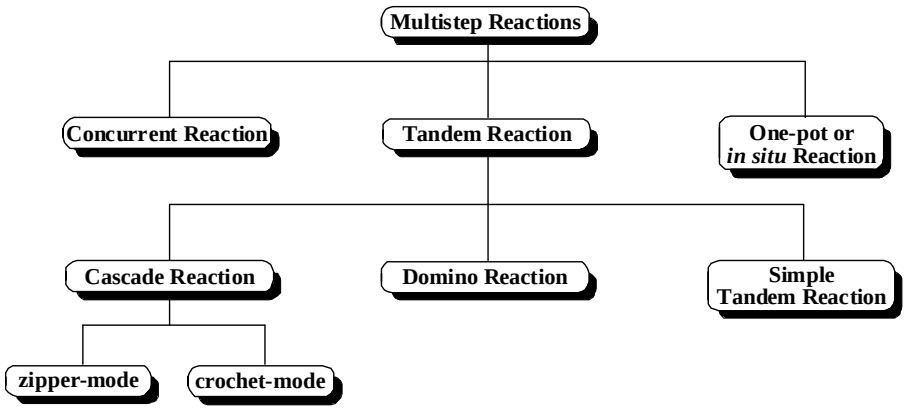


Figure 1. Multistep reactions: Classification tree

The classification of multistep reactions is not always straightforward. Since by definition multistep reactions consist of several reactions, they might not all be classified specifically into one type but rather as a combination of several of them. In addition, some of the reactions cannot be classified unambiguously as one or another type, but instead fall into a grey area between two of the classifications. Despite such exceptions, the vast majority of the multistep reactions are classifiable.

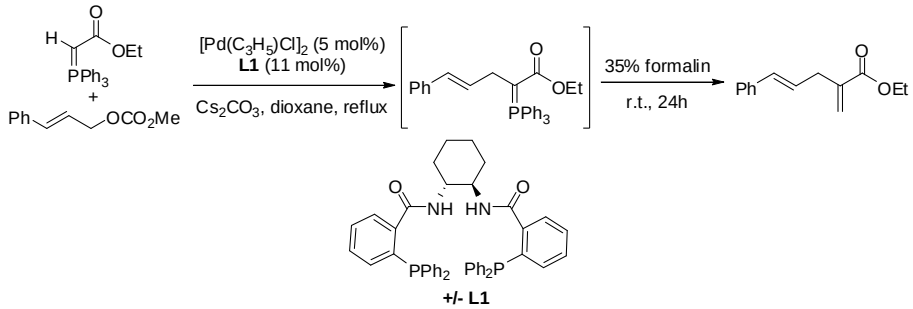
Since subsequent chapters will evoke some of these terminologies and classifications, especially one-pot, domino and simple tandem reactions, it was felt that an attempt should be made to assign proper definitions to these types of multistep reactions.

I.1. One-pot or *In situ* Reactions

One-pot or *in situ* reactions are a combination of two or more reactions that are conducted in the same vessel, without isolation of the intermediate(s). The occurrence of these reactions is in a specific order, and involves the sequential change in reaction conditions and the introduction of additional reagents (Scheme 1). I*n situ* or one-pot reactions are independent of each

other in that they can be conducted separately with isolation of the products, and without the need for additional reagents if conducted separately.

In situ reactions are quite common nowadays. Many reagents are usually generated *in situ*, for example Grignard reagents[2], enolate complexes[3], transition metal species; such as palladium complexes[4], organoboranes[5] and many more. The *in situ* technique is preferentially applied where the intermediate species, albeit stable, are difficult to handle or are heterogeneous in nature.



Scheme 1. The one-pot allylic alkylation of P-ylides/Wittig reaction[6]

I.2. Tandem Reactions

The tandem reaction sequence is one of the larger groups of multistep reactions, which is likely the reason why there are several reviews on this

---

[2] D. Seebach, B. Weber, *Angew. Chern., Int. Ed.* **1992**, *31*, 84.

[3] Ed. M. Nógrádi, *Stereoselective Synthesis*; VCH: Weinheim, **1995**.

[4] C. Amatore, G. Broeker, F. Khalil, *J. Am. Chern. Soc.* **1997**, *119*, 5176.

[5] R. Soundararajan, D. S. Matteson, *J. Org. Chern.* **1990**, *55*, 2274.

[6] W. B. Liu, H. He, L. X. Dai, S. L. You, *Chem. Euro. J.* **2010**, *16*, 7376.

topic.[1a,7] The application of tandem reactions is a growing area of organic synthesis and the tandem methodology has been applied to an impressive variety of organic reactions.

Tandem Reactions are a combination of two or more different reactions that occur in a specific order, but of which the subsequent reaction(s) is (are) directly dependent on the previous. The intermediates in tandem reactions are either not stable by normal standards (25°C, normal pressure) or can only be obtained as a mixture of products and intermediates.

I.2.1. Cascade Reactions

The term cascade reaction was coined in 1955 by Eschenmoser[8] when he proposed that lanosterol[9] could be synthesized in nature through a polyene cyclisation from squalene epoxide. Through time, the definition has expanded to include other reactions, and the expression is associated nowadays with any repeated sequence of the same reaction. A cascade reaction can be defined as follows:

Cascade reactions are a repetition of the same reaction occurring intramolecularly two or more times in a specific order, under similar conditions and without the addition of additional reagents. The preceding

---

[7] a) R. A. Bunce, *Tetrahedron* **1995**, *51*, 13103; b) P. J. Parsons, C. S. Penkett, A. J. Shell, *Chern. Rev.* **1996**, *96*, 195; c) S. E. Denmark, A. Thorarensen, *Chem. Rev.* **1996**, *96*, 137; d) N. Shindoh, Y. Takemoto, K. Takasu, *Chem. Euro. J.* **2009**, *15*, 12168.

[8] A. Eschenmoser, L. Ruzicka, O. Jeger, D. Arigoni, *Helv. Chim. Acta.* **1955**, *38*, 1890.

[9] Ed. P. M. Dewick, *Medicinal Natural Products*; John Wiley & Sons: Chichester, **1997**.

reaction in the sequence has to be completed in order for the following reaction to proceed (Figure 2).

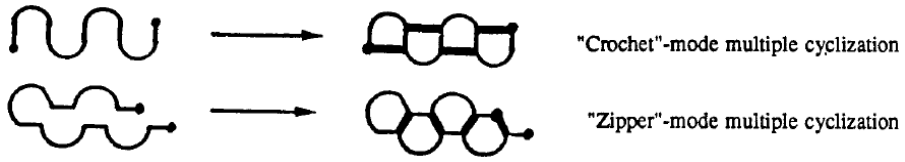


Figure 2. Zipper and crochet mode cyclisation

Cascade reactions involving multiple cyclisations are sometimes referred to as zipper reactions since they involve the "zipping-up" of a linear molecule to yield a cyclic structure. Therefore, Negishi[10] has further divided cascade reactions into two types: a) crochet mode cascade reaction; and b) zipper mode cascade reactions as shown in Figure 2.

I.2.2. Domino Reactions

The domino effect, as defined by Tietze,[1] means that once the first reaction has taken place, all the subsequent ones will follow under the same reaction conditions. This condition separates domino reactions from simple tandem reactions. Energetically, this necessitates that the subsequent reactions have approximately the same activation energy as the preceding reactions. Kinetically, this means that the subsequent reactions take place even though the preceding reaction(s) have not gone to completion. These considerations can be summarised as follows:

Domino Reactions are tandem reactions in which several different reactions take place under the same reaction conditions, in a well defined order with no additional reagents being required.

---

[10] a) E.-I. Negishi, T. Sugihara, C. Coperet, Z. Owezarczyk, L. S. Harring, *J. Am. Chern. Soc.* **1994**, *116*, 7923; b) E. Negishi, *Pure Appl. Chern.* **1992**, *64*, 323.

By definition this means that domino reactions as a class are a subset of the tandem reaction. If a tandem reaction couldn't be classified as a cascade reaction or a domino reaction, then it could only be classified as a simple tandem reaction.

In recent years, the domino sequence has been further divided into two sub-classes; Pure-domino and pseudo-domino (type I and II). While the aforementioned pure-domino sequences involve a single catalytic cycle, pseudo-domino ones involve the succession of two or more catalytic cycles.[11] In this latter case, a simple multitasking catalytic system may drive the cycles (type I)[12] or different and mutually compatible catalysts may be responsible for different cycles (type II).[13] Although according to the above notation, most of the known multistep transition metal-catalyzed reactions are pure-domino processes, only a few examples of pseudo-domino type I and type II have been so far reported.

---

[11] G. Poli, G. Giambastiani, *J. Org. Chem.* **2002**, *67*, 9456.

[12] a) G. Poli, G. Giambastiani, B. Pacini, *Tetrahedron Lett.* **2001**, *42*, 5179; b) S. Lemaire, G. Prestat, G. Giambastiani, D. Madec, B. Pacini, G. Poli, *J. Organomet. Chem.* **2003**, *687*, 291; c) G. Maitro, S. Vogel, G. Prestat, D. Madec, G. Poli, *Org. Lett.* **2006**, *8*, 5951.

[13] a) J.-C. Walsike, J. O. Obrey, R. T. Baker, G. C. Bazan, *Chem. Rev.* **2005**, *105*, 1001; b) D. E. Fogg, E. N. dos Santos, *Coord. Chem. Rev.* **2004**, *248*, 2365; c) J. M. Lee, Y.Na, H. Han, S. Chang, *Chem. Soc. Rev.* **2004**, *33*, 302; d) C. Kammerer, G. Prestat, T. Gaillard, D.Madec, G. Poli, *Org. Lett.* **2008**, *10*, 405; e) G. Prestat, G. Poli, *Chemtracts-Org. Chem.* **2004**, *17*, 104.

II. Multicatalysis Reactions

Various attempts were undertaken to minimize the adverse environmental impact and maximize the efficiency of chemical reactions. As one of numerous advances, "multicatalysis", defined as the modular combination of distinct catalysts for consecutive transformations in a single flask, emerged as a highly valuable tool for the construction of complex molecular frameworks from simple and readily available starting materials.[1]

Multicatalysis may condense the operational simplicity and synthetic efficiency provided by the numerous single catalysts concepts, which exists in the literature nowadays, to allow the rapid synthesis of even complex molecules in one pot syntheses.[2] The main challenge in the development of multicatalytic reactions is to ensure compatibility of reactants, intermediates and catalysts throughout the whole reaction sequence. In order to circumvent compatibility problems, the following strategies have been adopted: the use of obviously compatible catalysts, sequential addition of catalysts, and the site isolation or phase separation of catalysts.

Different types of multicatalysis mechanisms exist in the literature but our main interest lies only in the cooperative dual catalysis concept. As this is the only multicatalysis concept mentioned in this thesis, it will be the only one depicted in this introduction. Cooperative dual catalysis exists today under many names and definitions that make it quite hard and confusing to classify or even spot any given reaction of this type. In order to understand

---

[1] A) J. Zhou, *Chem Asian J* **2010**, *5*, 422; b) L. M. Ambrosini, T. H. Lambert, *ChemCatChem* **2010**, *2*, 1373.

[2] C. Vaxelaire, P. Winter, M. Christmann, *Angew. Chem. Int. Ed.* **2011**, *50*, 3605.

some of the concepts put forward in this thesis we felt it is important to define them herein.

II.1. Cooperative Dual Catalysis

Cooperative dual catalysis is a process where two catalysts separately and selectively activate two different substrates, catalytically generating two active intermediates that could subsequently react to form the desired product (Figure 3).[3] The formation of the final product is generally coupled with simultaneous regeneration of the catalysts.

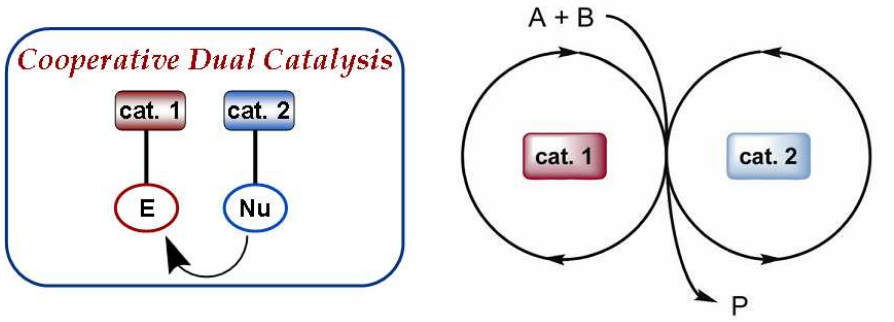


Figure 3. The concept of cooperative dual catalysis

This type of dual catalysis is still underdeveloped and only a few examples have been reported, mainly due to the difficulties encountered in finding compatible as well as selective catalysts.[3] Another contributor factor is that the catalytic intermediates, that would be formed, could react with the

[3] a) A. E. Allen, D. W. Macmillan, *Chem. Sci.* **2012**, *2012*, 633; b) N. T. Patil, V. S. Shinde, B. Gajula, *Org. Biomol. Chem.* **2012**, *10*, 211; c) J. M. Lee, Y. Na, H. Han, S. Chang, *Chem. Soc. Rev.* **2004**, *33*, 302; d) R. C. Wende, P. R. Schreiner, *Green Chem.* **2012**, *14*, 1821.

reagents present in stoechiometric amounts, thus generating side reactions and undesired products, rendering the reaction very difficult to control.[4]

II.1.1. Comparison to Other Dual Processes

It is important to mention that this process should be differentiated from other processes involving two catalysts.[3a] First, if both the nucleophile and electrophile are activated separately by discrete functional groups on the same catalyst, this has been classified as "bifunctional catalysis".[5] When both catalysts work in concert to activate only one of the reacting partners, it's called "double activation catalysis".[6] If one catalyst is used to conduct the desired reaction and the other is only present to regenerate the first catalyst, it's considered as "restorative catalysis".[3b] Finally, when two catalysts perform sequential organic transformations, in which the first step

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[4] a) B. M. Trost, X. Luan, *J. Am. Chem. Soc.* **2011**, *133*, 1706; b) B. M. Trost, X. Luan, Y. Miller, *J. Am. Chem. Soc.* **2011**, *133*, 12824.

[5] For reviews on bifunctional catalysis, see: a) M. Shibasaki, M. Kanai, S. Matsunaga and N. Kumagai, *Acc. Chem. Res.* **2009**, *42*, 1117; b) R. Breslow, *J. Mol. Catal.* **1994**, *91*, 161; c) M. Shibasaki and N. Yoshikawa, *Chem. Rev.* **2002**, *102*, 2187; d) Y. Wang and L. Deng in *Catalytic Asymmetric Synthesis*, 3rd Ed, ed. I. Ojima, John Wiley & Sons, New Jersey, **2010**, p 59; e) M. Shibasaki and M. Kanai in *New Frontiers in Asymmetric Catalysis*, ed. K. Mikami and M. Lautens, John Wiley & Sons, New Jersey, **2007**, p 383.

[6] For examples of double activation catalysis, see: a) H. Xu, S. J. Zuend, M. G. Woll, Y. Tao and E. N. Jacobsen, *Science* **2010**, *327*, 986; b) M. Rubina, M. Conley and V. Gevorgyan, *J. Am. Chem. Soc.* **2006**, *128*, 5818; c) S. Mukherjee and B. List, *J. Am. Chem. Soc.* **2007**, *129*, 11336; d) Y. Shi, S. M. Peterson, W. W. Haberaecker III and S. A. Blum, *J. Am. Chem. Soc.*, **2008**, *130*, 2168; e) Y. J. Park, J.-W. Park and C.-H. Jun, *Acc. Chem. Res.* **2008**, *41*, 222.

is carried out by one catalyst to afford certain intermediates to be subjected to the second catalyst for the next reaction, it's classified as "sequential catalysis" (Figure 4).[7]

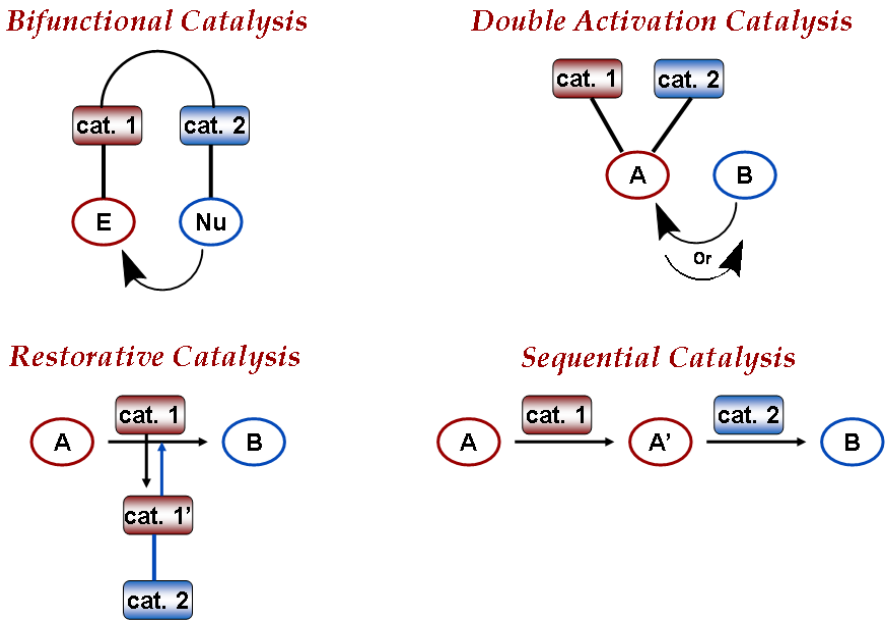


Figure 4. Classification of catalytic systems involving two catalysts[3a]

[7] For examples of sequential catalysis, see: a) S. Belot, K. A. Vogt, C. Besnard, N. Krause and A. Alexakis, *Angew. Chem., Int. Ed.* **2009**, *48*, 8923; b) Z.-Y. Han, H. Xiao, X.-H. Chen and L.-Z. Gong, *J. Am. Chem. Soc.* **2009**, *131*, 9182; c) K. Sorimachi and M. Terada, *J. Am. Chem. Soc.* **2008**, *130*, 14452; d) Q. Cai, Z.-A. Zhao and S.-L. You, *Angew. Chem., Int. Ed.* **2009**, *48*, 7428; e) B. Simmons, A. M. Walji and D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *48*, 4349; f) S. P. Lathrop and T. Rovis, *J. Am. Chem. Soc.* **2009**, *131*, 13628.

II.1.2. Concept and Mechanism

Within the realm of chemical synthesis, traditional catalytic pathways generally rely on the interaction of a unique catalyst with a single substrate, thereby lowering the energetic barrier to bond formation with a second, unactivated substrate (Figure 5). While this mono-catalysis strategy has successfully delivered vast numbers of new reactions over many decades, emerging multicatalysis concepts have the potential to allow access to new and difficult or even unattainable transformations. In particular, cooperative dual catalysis, wherein two catalysts and two catalytic cycles work in concert to create a single new bond, has emerged as a powerful new mechanistic approach to reaction engineering. In its simplest form, cooperative dual catalysis involves the concurrent activation of both a nucleophile and an electrophile using distinct catalysts. This simultaneously creates two reactive species, one with a higher HOMO and the other with a lower LUMO, in comparison to the respective ground state of the starting materials (Figure 5). If selected wisely, these activated catalytic species can rapidly couple, in many cases enabling chemical reactions that are impossible or inefficient using traditional mono-catalysis methods.

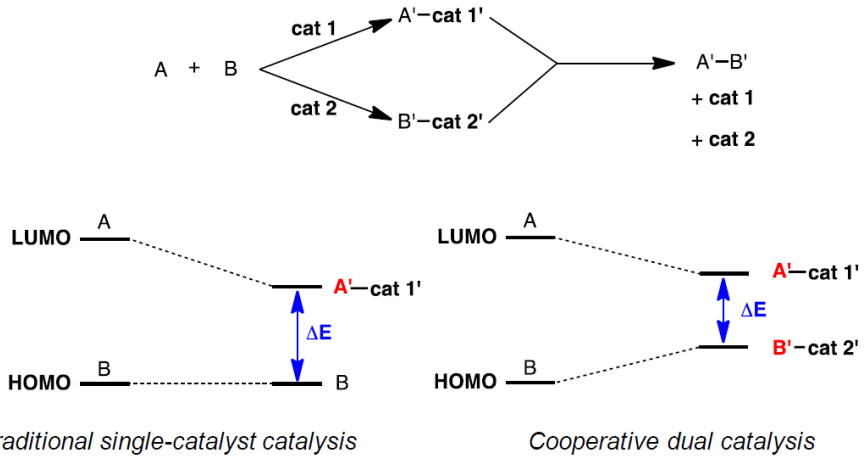
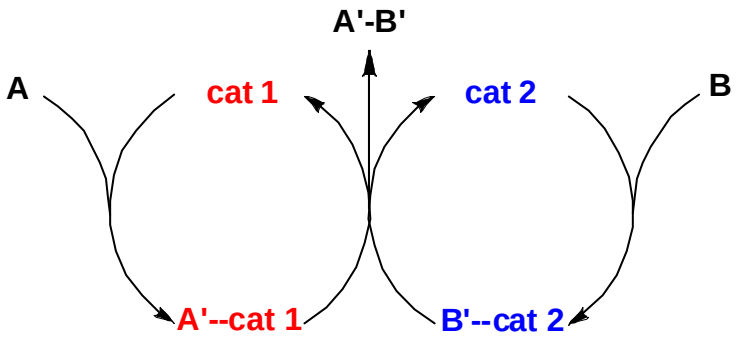


Figure 5. Cooperative *vs* mono catalysis in orbital-controlled reactions

The literature is struggling to classify this type of catalysis. Each publication seems to be a race to classify the cooperative dual catalysis and to attribute a suitable different name. As a result, many names are given to the same reaction rendering it extremely confusing and hard to identify. As seen in Scheme 2, different names are attributed to different reactions in the literature but all of these reactions exhibit a similar mechanism to the cooperative dual catalysis.[4,8]

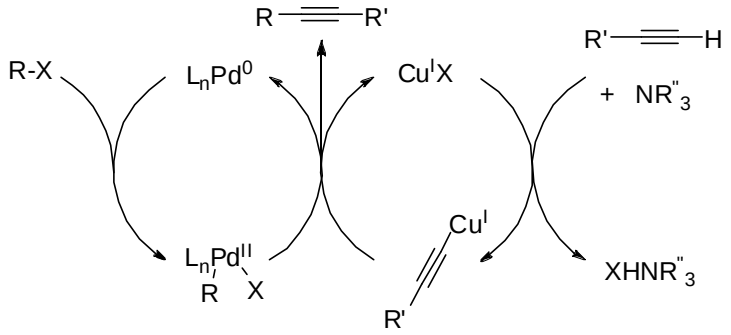
[8] a) M. Sawamura , M. Sudoh, Y. Ito, *J. Am. Chem. Soc.* **1996**, 118, 3309-3310; b) J. Panteleev, L. Zhang, M. Lautens, *Angew. Chem. Int. ed.* **2011**, *50*, 9089-9092; c) E. Shirakawa, D. Ikeda, S. Masui, M. Yoshida, T. Hayashi, *J. Am. Chem. Soc.* **2012**, *134*, 272-279; d) Z. Gu, A. T. Herrmann, A. Zakarian, *Angew. Chem. Int. Ed.* **2011**, *50*, 7136-7139; e) K. Motoyama, M. Ikeda, Y. Miyake, Y. Nishibayashi, *Organometallics* **2012**, *31*, 3426-3430.



Cooperative dual catalysis
=
Catalyzed catalysis
=
Synergistic catalysis
=
Contemporaneous dual catalysis

Scheme 2. Different names, similar mechanism

Although it has many new names nowadays, this strategy is far from being a new one. If we take a good look at the mechanism shown in Scheme 2, we could notice that this mechanism bares a quite interesting resemblance to the Sonogashira mechanism described as early as 1975 (Scheme 3). But unfortunately since then, the development of similar methodologies has been at best scarce, mainly due to the difficulties encountered in catalyst pairing and limiting secondary undesired reactions.



Scheme 3. The Sonogashira reaction and mechanism

II.1.3. Catalyst Pairing

The main problem that everyone has to face in these reactions is to find the proper catalyst which should not only be compatible with other catalysts but also tolerates all reagents and intermediates generated during the course of the reaction. Unlike biological processes, where nature takes advantage of enzyme architecture to facilitate a multiple reaction manifold, it is very difficult to exploit on such process in a flask. The most important challenge of the cooperative dual catalysis, that has yet to be fully developed, is enantioselectivity. In the recent literature, quite a few examples of different catalyst pairing have emerged. As shown in Figure 6, different types of catalyst have been paired in an attempt to solve the difficulties encountered in cooperative processes.[9,10,11]

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[9] For organocatalysis / metallocatalysis catalyst pairing see: a) Y. J. Park, J.-W. Park, C.-H. Jun, *Acc. Chem. Res.* **2008**, *41*, 222; b) Z. Shao, H. Zhang, *Chem. Soc. Rev.* **2009**, *38*, 2745; c) M. Rueping, R. M. Koenigs, I. Atodiresei, *Chem. Eur. J.* **2010**, *16*, 9350; d) D. DiRocco, T. Rovis, *J. Am. Chem. Soc.* **2012**, *134*, 8094; e) Z. Chai, T. Rainey, *J. Am. Chem. Soc.* **2012**, *134*, 3615; f) Y. Ye, M. Sanford, *J. Am. Chem. Soc.* **2012**, *134*, 9034.

[10] For biocatalysis / metallocatalysis catalyst pairing see: a) O. Pamies, J.-E. Baeckvall, *Chem. Rev.* **2003**, *103*, 3247; b) C. Zhong, X. Shi, Euro. *J. Org. Chem.* **2010**, *16*, 2999; c) J. H. Lee, K. Han, M.-J. Kim, J. Park, Euro. *J. Org. Chem.* **2010**, *6*, 999; d) B. L. Conley, M. K. Pennington-Boggio, E. Boz, T. J. Williams, *Chem. Rev.* **2010**, *110*, 2294; e) A. C. Marr, S. Liu, *Trends Biotechnol.* **2011**, *29*, 199.

[11] For metallocatalysis / metallocatalysis catalyst pairing see:a) J. Cossy, F. Bargiggia, S. BouzBouz, *Org. Lett.* **2003**, *5*, 459; b) Y. Nishibayashi, M. Yoshikawa, Y. Inada, M. Hidai, S. Uemura, *J. Am. Chem. Soc.* **2004**, *126*, 16066; c) A. S. Goldman, A. H. Roy, Z. Huang, R. Ahuja, W. Schinski, M. Brookhart, *Science* **2006**, *312*, 257; d) T. A. Cernak, T. H. Lambert, *J. Am. Chem. Soc.* **2009**, *131*, 3124; e) K. Takahashi, M. Yama- shita, T. Ichihara, K. Nakano, K. Nozaki, *Angew. Chem.* **2010**, *122*, 4590; *Angew. Chem. Int. Ed.* **2010**, *49*, 4488; f) M. Kuriyama, T. Takeichi, M. Ito, N. Yamasaki, R. Yamamura, Y. Demizu, O. Onomura, *Chem. Eur. J.* **2012**, *18*, 2477; g) K. Motoyama, M. Ikeda, Y. Miyake, Y. Nishibayashi, *Organometallics* **2012**, *31*, 3426; h) E. Skucas, D. Macmillan, *J. Am. Chem. Soc.* **2012**, *134*, 9090; i) J. Park, S. Hong, *Chem. Soc. Rev.* **2012**, *41*, 6931.

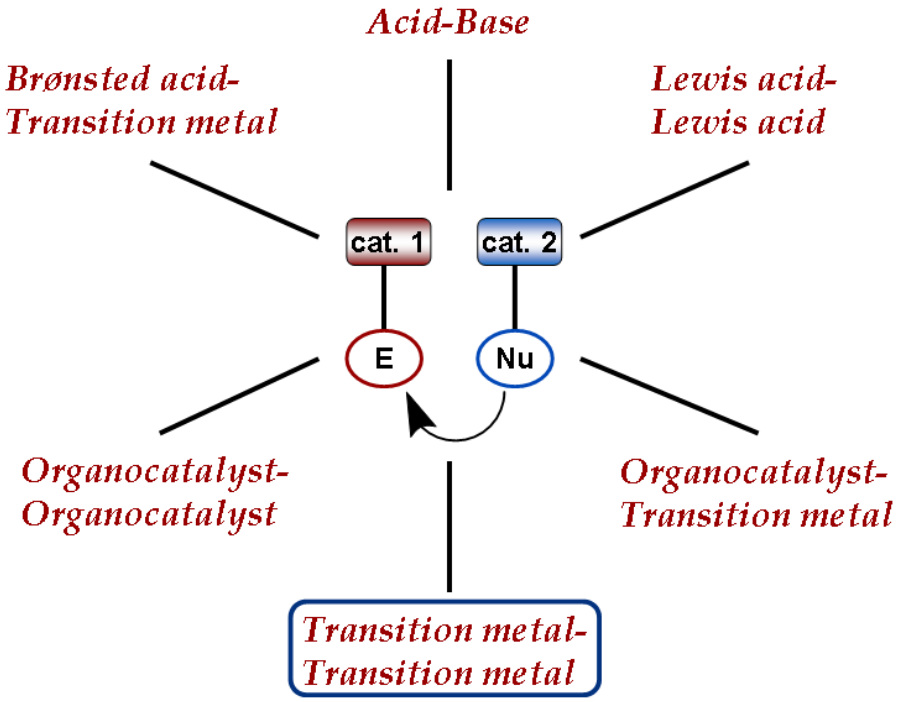


Figure 6. Different types of catalyst pairing

However, in this thesis, we aim to focus on the most significant reactions catalyzed by metal-metal binary catalytic systems, as it is the only system emphasized hereafter.[11]

III. *N*-Heterocyclic Carbene (NHC) Chemistry

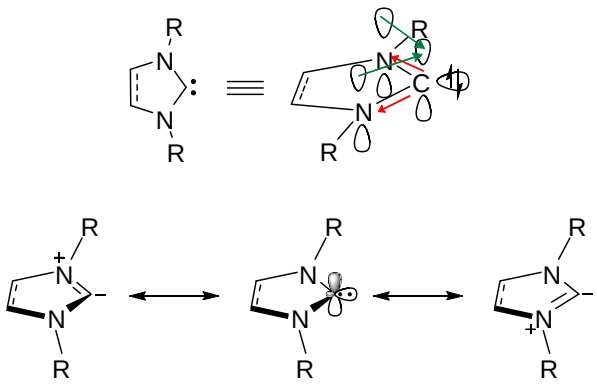
NHC chemistry is a new and rapidly emerging field in organometallic chemistry. As such, some of the chemistry discussed in later chapters will involve at some degree (NHC)metal complexes. Thus to better understand some of the terms and strategies employed later on, an attempt is made herein to describe this new and exciting chemistry.

N-Heterocyclic carbenes (NHCs) are defined as singlet carbenes, in which the divalent carbenic center is connected directly to at least one nitrogen atom within the heterocycle.[1,2] Contrary to other Fischer carbenes, which are generally found to be electrophilic, *N*-heterocyclic carbenes are electron-rich nucleophilic species in which the carbene center benefits from the stabilization associated with both the σ-electron-withdrawing and π-electron-donating character of the nitrogen centers (Scheme 4).

---

[1] For reviews on carbenes in general, see: a) D. Bourissou, O. Guerret, F. P. Gabbai, G. Bertrand, *Chem. Rev.* **2000**, *100*, 39; b) P. de Fremont, N. Marion, S. P. Nolan, *Coord. Chem. Rev.* **2009**, *25*3, 862; c) Y. Canac, M. Soleilhavoup, S. Conejero, G. J. Bertrand, *Organomet. Chem.* **2004**, *689*, 3857

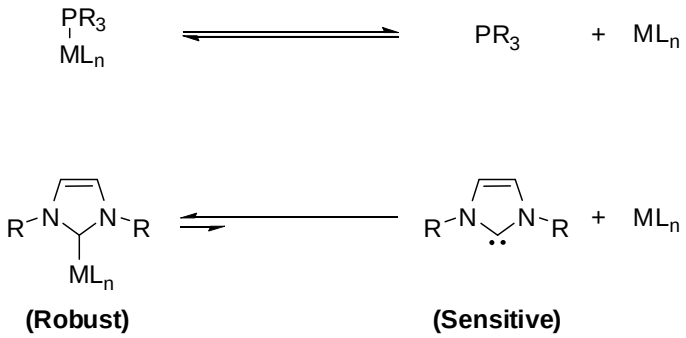
[2] For cyclic carbenes other than diaminocarbenes, see the following reviews: a) M. Melaimi, M. Soleilhavoup, G. Bertrand, *Angew. Chem., Int. Ed.* **2010**, *49*, 8810; b) O. Schuster, L. Yang, H. G. Raubenheimer, M. Albrecht, *Chem. Rev.* **2009**, *109*, 3445; c) K. Öfele, E. Tosch, C. Taubmann, W. A. Herrmann, *Chem. Rev.* **2009**, *109*, 3408



Scheme 4. Stabilization of NHC as shown by resonance and orbital overlap

Due to their strong σ-electron-donating properties, NHC ligands form stronger bonds with metal centers than most classical ligands, such as phosphines, thus giving transition metal complexes that are generally resistant to decomposition and can therefore be used as precatalysts without an excess of ligand (Scheme 5).[3]

[3] Reviews on stereoelectronic parameters of NHCs: a) T. Dröge, F. Glorius, *Angew. Chem., Int. Ed.* **2010**, *49*, 6940; b) H. Clavier, S. P. Nolan, *Chem. Commun.* **2010**, *46*, 841; c) O. Kühl, *Coord. Chem. Rev.* **2009**, *253*, 2481; d) S. Díez-González, S. P. Nolan, *Coord. Chem. Rev.* **2007**, *251*, 874; e) L. Cavallo, A. Correa, C. Costabile, H. J. Jacobsen, *Organomet. Chem.* **2005**, *690*, 5407; f) T. Strassner, *Top. Organomet. Chem.* **2004**, *13*, 1.



Scheme 5. Stability of NHC-metal vs phosphine-metal complexes

Wanzlick[4] originally suggested their existence in the early 1960s and proposed a practical way to generate them *in situ*. This early finding paved the way to their use as ligands in organometallic chemistry, as originally described in the seminal reports by Wanzlick[5] and Ofele[6] in 1968 and in the extensive work of Lappert[7] in the 1970s and 1980s.

Nevertheless, the breakthrough of this chemistry came in 1988 with the benchmark report by Bertrand[8] *et al* of the first stable (phosphino)(silyl)carbene and in 1991 with the isolation and full characterization by Arduengo[9] *et al* of the stable free NHC 1,3-di(adamantyl)imidazol-2-ylidene (IAd), obtained by deprotonation of its imidazolium precursor (IAd.HCl) (Scheme 6).

---

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

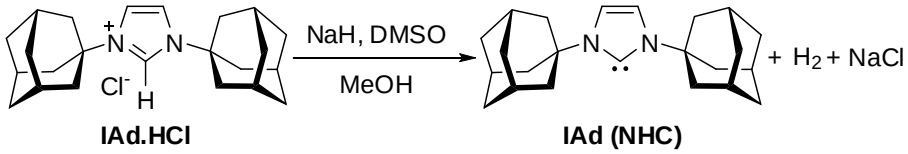
[5] a) H.-W. Wanzlick, H. J. Schönherr, *Angew. Chem., Int. Ed.* **1968**, *7*, 141.

[6] K. J. Öfele, *Organomet. Chem.* **1968**, *12*, 42.

[7] M. F. J. Lappert, *Organomet. Chem.* **1988**, *358*, 185; b) D. J. Cardin, B. Cetinkaya, M. F. J. Lappert, *Chem. Rev.* **1972**, *72*, 545.

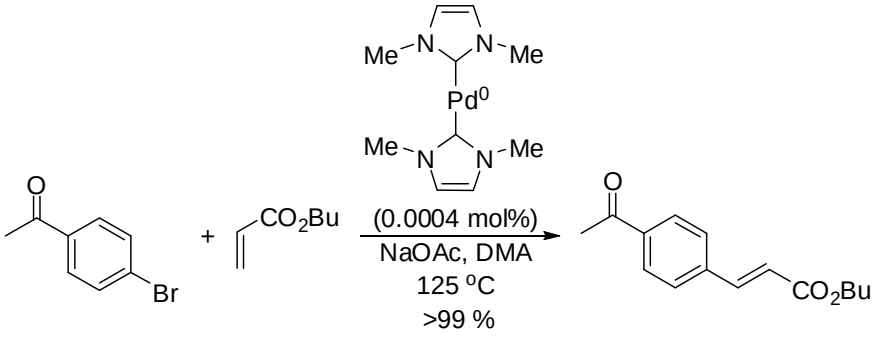
[8] A. Igau, H. Grützmacher, A. Baceiredo, G. Bertrand, *J. Am. Chem. Soc.* **1988**, *110*, 6463.

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



Scheme 6. Isolation of the free NHC (IAd) by Arduengo *et al*[9]

The potential of this class of compounds to serve as ligands was recognized in 1995 by Herrmann[10] *et al* and soon thereafter, the exploitation of the potential of NHC ligands in catalysis began (Scheme 7).[11]



Scheme 7. First application of NHC in transition metal catalysis

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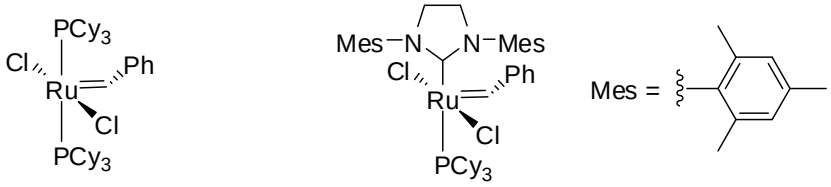
[10] W. A. Herrmann, M. Elison, J. Fischer, C. Köcher, G. R. J. Artus, *Angew. Chem., Int. Ed.* **1995**, *34*, 2371.

[11] a) W. A. Herrmann, C.-P. Reisinger, M. *J.* Spiegler, *Organomet. Chem.* **1998**, *557*, 93; b) C. Zhang, J. Huang, M. L. Trudell, S. P. Nolan, *J. Org. Chem.* **1999**, *64*, 3804; c) J. Huang, S. P. Nolan, *J. Am. Chem. Soc.* **1999,** *121*, 9889; d) V. P. W. Böhm, T. Weskamp, C. W. K. Gstöttmayr, W. A. Herrmann, *Angew. Chem., Int. Ed.* **2000**, *39*, 1602; e) M. Eckhardt, G. C. Fu, *J. Am. Chem. Soc.* **2003**, *125*, 13642; f) G. A. Grasa, S. P. Nolan, *Org. Lett.* **2001**, *3*, 119; g) N. Hadei, E. A. B. Kantchev, C. J. O'Brien, M. G. Organ, *J. Org. Chem.* **2005**, *70*, 8503; h) L. Liu, J. Montgomery, *J. Am. Chem. Soc.* **2006**, *128*, 5348; i) J. Huang, G. Grasa, S. P. Nolan, *Org. Lett.* **1999**, *1*, 1307; j) N. Marion, O. Navarro, J. Mei, E. D. Stevens, N. M. Scott, S. P. Nolan, *J. Am. Chem. Soc.* **2006**, *128*, 4101.

The significant advancement occurred in the development of a variety of NHC ligands and their transition-metal complexes were utilized in several catalytic reactions.[11] However, only NHCs derived from imidazolium or, 4,5-dihydroimidazolium salts found wide-spread application in homogeneous catalysis. The most important example was the ruthenium metathesis catalyst developed by Grubbs and co-workers, for which the Nobel Prize was awarded in 2005.[12] The replacement of one of the tricyclohexyl phosphine, in the Grubbs 1st generation catalyst, by *N*-heterocyclic carbene of the type imidazole-2-ylidene led to significant improvements in catalytic activity as well as stability. This is known nowadays as the Grubbs 2nd generation catalyst (Scheme 8).



Grubbs 1st generation catalyst **Grubbs 2nd generation catalyst**

Scheme 8. Grubbs 1st and 2nd generation catalysts

The NHC ligand is frequently compared to phosphines.[13] As both are strong σ-donor ligands, with the majority of NHCs displaying stronger electron-donating properties than the strongest phosphine donors. The π-acceptor character of phosphine ligands varies over a broad range, while NHCs tend

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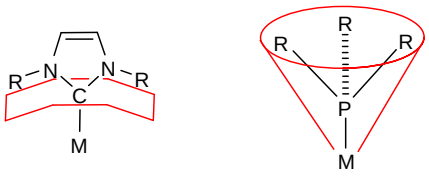
[12] a) M. Scholl, T. M. Trnka, J. P. Morgan, R. H. Grubbs, *Tetrahedron Lett.* **1999**, *40*, 2247; b) M. Scholl, S. Ding, C. W. Lee, R. H. Grubbs, *Org. Lett.* **1999**, *1*, 953; c) T. M. Trnka, R. H. Grubbs, *Acc. Chem. Res.* **2001**, *34*, 18; d) R. H. Grubbs. *Angew. Chem. Int. Ed.* **2006**, *45*, 3760.

[13] a) W. A. Herrmann, C. Kicher, *Angew. Chem. Int. Ed.* **1997**, *36*, 2162; b) D. Bourissou, O. Gerret, F. P. Gabbaï, G. Bertrand, *Chem. Rev.* **2000**, *100*, 39.

to be poor π-acceptors. A further advantage of the NHC ligands rests on a better steric protection of the active site within the inner metal's coordination sphere; because the exocyclic nitrogen substituents of the NHC shield the metal center more efficiently than a tertiary phosphine can do, with its cone angle pointing away from the metal center (Scheme 9). These beneficial features have contributed to the recognition of NHCs, first as an important class of ligands in organometallic chemistry,[14] as demonstrated by numerous applications ranging from homogeneous catalysis to material and medicinal sciences, and second as excellent nucleophilic organocatalysts.[15]



Scheme 9. The steric shape of phosphines and NHCs

A wide variety of NHCs can be prepared.[16] Substituents on the nitrogen sites of the NHC can be alkyl or aryl, and can be further functionalized to have

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[14] a) Ed. S. P. Nolan, *N-Heterocyclic Carbenes in Synthesis*; Wiley-VCH: New York, **2006**; b) Ed. F. Glorius, *N-Heterocyclic Carbenes in Transition Metal Catalysis*; Topics in Organometallic Chemistry, Vol. 21; Spinger-Verlag: Berlin/Heidelberg, **2007**.

[15] a) D. Enders, T. Balensiefer, *Acc. Chem. Res.* **2004**, *37*, 534; b) N. Marion, S. Díez-González, S. P. Nolan, *Angew. Chem., Int. Ed.* **2007**, *46*, 2988; c) D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606; d) V. Nair, S. Vellalath, B. P. Babu, *Chem. Soc. Rev.* **2008**, *37*, 2691.

[16] a) W. A. Herrmann, M. Elison, J. Fischer, C. Köcher, G. R. J. Artus, *Chem. Eur. J.* **1996**, *2*, 772; b) W. A. Hermann, C. Köcher, L. J. Goossen, G. R. J. Artus, *Chem. Eur. J.* **1996**, *2*, 1627.

ethers, phosphines or amines. *N*-Heterocyclic carbenes with chiral *N*-substituents and backbones have also been prepared.[17]

NHCs played an important role in all our projects and allowed a vital evaluation of our work. All along this manuscript, NHCs will be mentioned gradually and a more detailed report of the current research interests in the literature will be developed later on in the final chapter.

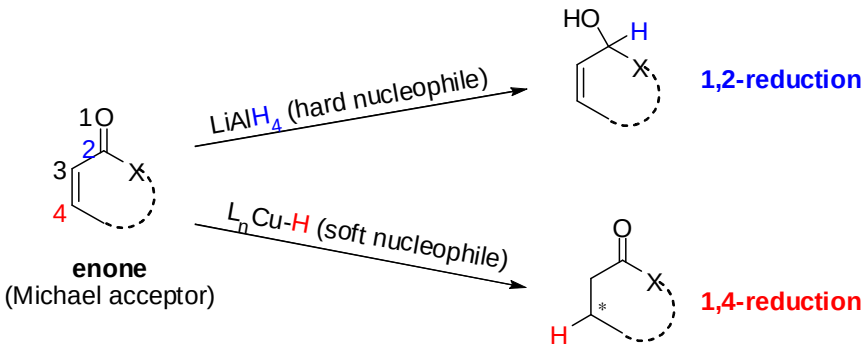
[17] a) T. W. Funk, J. M. Berlin, R. H. Grubbs, *J. Am. Chem. Soc.* **2006**, *128*, 1840; b) D. Baskakov, W. A. Herrmann, E. Herdtweck, S. D. Hoffmann, *Organometallics* **2007**, *26*, 6260.

Chapter 1: Copper Catalyzed-1,4-Reduction/Aldolisation Domino Reaction

I. Bibliographic Introduction

The 1,4-reduction/aldolisation reaction is classified as a domino type reaction. As explained earlier in this thesis, this means that these two reactions are occurring successively and in our case catalyzed by copper(I) complexes.

1,4-reduction reactions have a long and rich history due to the emergence of new stable and highly selective copper hydrides (Cu-H). These reactions take advantage of the carbophilic nature of copper, usually affording the 1,4-addition product exclusively (Scheme 10). This can be accomplished using phosphine or NHC-stabilized copper hydrides.[1]



Scheme 10. 1,4- reduction vs 1,2-reduction of enones

1,4-reduction reactions using *in situ* formed Cu-H can be further exploited when run in the presence of an electrophile, inducing an inter- or

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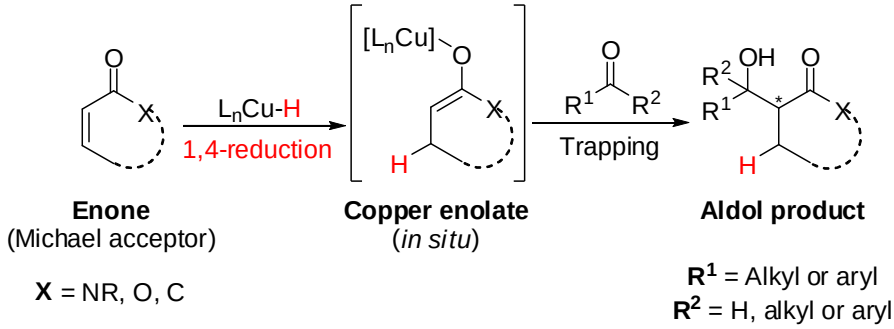
[1] a) B. H. Lipshutz, In *Modern Organocopper Chemistry*; Ed., N. Krause; Wiley-VCH: Weinheim, **2002**, pp 167-187, and references cited therein ; b) S. Rendler, M. Oestreich, *Angew. Chem., Int. Ed.* **2007**, *46*, 498; c) C. Deutsch, N. Krause, *Chem Rev* **2008**, *108*, 2916.

intramolecular trapping of the reduction product. In our case, the aldolisation process involves trapping the copper intermediates with aldehydes or ketones to furnish aldol products (Scheme 11).[2]



Scheme 11. The 1,4-reduction/aldolisation domino reaction

This type of domino processes is nowadays well-known in the literature and it owes its fast growing popularity to the extensive development of Cu-H complexes, which became more selective and more reactive over time. But in order to understand this milestone in history, we have to look back at the beginnings.

Modern usage of Cu-H in synthesis is well recognized to have begun with "Stryker's reagent" in 1988.[3] Stryker *et al* described the remarkable

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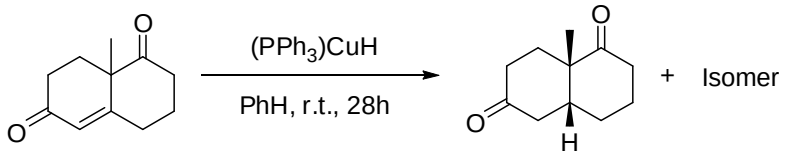
[2] a) J. Deschamp, O. Chuzel, J. Hannedopuche, O. Riant, *Angew. Chem., Int. Ed.* **2006**, *45*, 1292; b) O. Chuzel, J. Deschamp, C. Chausteur, O. Riant, *Org. Lett.* **2006**, *8*, 5943; c) A. Welle, S. Díez-González, B. Tinant, S. P. Nolan, O. Riant, *Org. Lett.* **2006**, *8*, 6059; d) D. Zhao, K. Oisaki, M. Kanai, M. Shibasaki, *Tetrahedron Lett.* **2006**, *47*, 1403; e) H. Nishiyama, T. Shiomi, In *Topics in Current Chemistry*; Ed., M. J.Krische; Springer: New York, **2007**; Vol. 279.

[3] a) D. M. Brestensky, D. E. Huseland, C. McGettigan, J. M. Stryker, *Tetrahedron Lett.* **1988**, *29*, 3749; b) W. S. Mahoney, D. M. Brestensky, J. M. Stryker, *J. Am. Chem. Soc.* **1988**, *110*, 291; c) D. M. Brestensky, J. M. Stryker, *Tetrahedron Lett.*

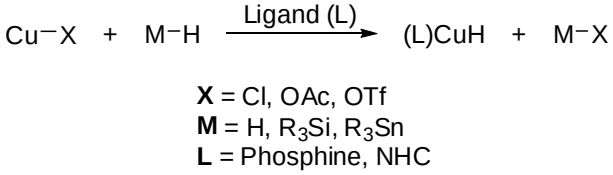
tendency of the phosphine stabilized hexamer, $[(PPh_3)Cu\text{-}H]_6$ (or $(PPh_3)Cu\text{-}H$ for simplicity), to effect highly regioselective conjugate reductions of various carbonyl derivatives, including α,β-unsaturated ketones, esters and aldehydes (Scheme 12).[3b]



85%, d.r. = 17:1

Scheme 12. Reduction of Wieland–Miescher ketone by "Strycker's reagent"

The mildness of the reaction conditions, functional group compatibility, and excellent overall efficiencies were considered highly impressive at the time.[4] Furthermore, the catalytic use of this mild hydride source (Scheme 13), in particular with inexpensive and environmentally benign silanes, has shifted the spotlight toward asymmetric uses of now-labelled hydrosilylation reactions.[1]



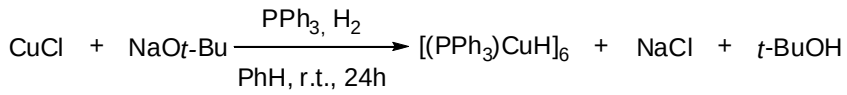
Scheme 13. Catalytic generation of copper hydrides

1989, *30*, 5677; d) T. M. Koenig, J. F. Daeuble, D. M. Brestensky, J. M. Stryker, *Tetrahedron Lett.* **1990**, *31*, 3237; e) For the first application of Cu-H in synthesis, see: Brunner, H.; Miehling, W. *J. Organomet. Chem.* **1984**, *275*, C17–C21.

[4] A. Fátima, *Synlett* **2005**, 1805.

I.1. Generating Stryker's Reagent and Alternatives

The "Stryker's reagent" is the most common and frequently used copper hydride species.[4] The early recipe leading to this commercially available complex that called for CuCl and NaO*t*-Bu to generate CuO*t*-Bu is still used (Scheme 14).[5]



Scheme 14. Preparation of "Strycker's reagent"

Nevertheless, quite a few advances have been made to avoid using this extremely air-sensitive system (cf. Scheme 13). For example, $Cu(OAc)_2 \cdot H_2O$ has been found to be an attractive replacement which streamlines the procedure to generate Cu-H.[6] Yun *et al* showed that, if the latter is used as a copper source, in contrast to the CuO*t*-Bu's *in situ* generation, the Stryker's reagent is more easily obtained in high purity and yields. For generating copper hydride, silanes, which in general are inexpensive and environmentally friendly, are the most common source of stoichiometric hydride. A brief summary of several combinations that produce Cu-H is shown in Table 1.[5,6,7]

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[5] P. Chiu, Z. Li, K. C. M. Fung, *Tetrahedron Lett.* **2003**, *44*, 455.

[6] D.-w. Lee, J. Yun, *Tetrahedron Lett.* **2005**, *46*, 2037.

[7] a) J.-X Chen,. J. F. Daeuble, J. M. Stryker, *Tetrahedron* **2000**, *56*, 2789 ; b) L. T. Leung, S. K. Leung, P.Chiu, *Org. Lett.* **2005**, *7*, 5249; c) T. Llamas, R. G. Arrayás, J. C. Carretero, *Angew. Chem., Int. Ed.* **2007**, *46*, 3329; d) B. H. Lipshutz, J. M. Servesko, T. B. Petersen, P. P. Papa, A. A. Lover, *Org. Lett.* **2004**, *6*, 1273; e) B. H. Lipshutz, W. Chrisman, K. Noson, P. Papa, J. A. Scalfani, R. W. Vivian, J. M. Keith, *Tetrahedron* **2000**, *56*, 2779; f) A. Mori, A. Fujita, H. Kajiro, Y. Nishihara, T.

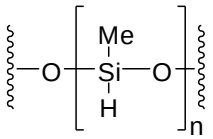
Table 1. Reagent combinations to generate copper hydride

Copper source	Additive	Hydride source
CuCl	NaO*t*-Bu	H_2
CuCl	NaO*t*-Bu	Bu_3SnH
CuCl	NaO*t*-Bu	$PhSiH_3$
CuCl	NaO*t*-Bu	PMHS
CuCl	NaO*t*-Bu	TMDS
$(PPh_3)_3CuF \cdot 2EtOH$	-	$PhMe_2SiH$
$Cu(OAc)_2 \cdot H_2O$	-	PMHS
$CuCl_2 \cdot H_2O$	-	PMHS
$[P(3,5\text{-xylyl})_3]_2CuNO_3$	-	H_2
CuOt-Bu		PMHS
CuF_2		$PhSiH_3$/PMHS

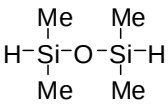
Polymethylhydrosiloxane[8] (PMHS) is a very cheap silane which explains why it's quite often used as a stoichiometric source of hydride. Tetramethyldisiloxane (TMDS) is another inexpensive silane that, on occasion, is a superior source of hydride (Scheme 15). Also Fleming's silane ($PhMe_2SiH$) and phenylsilane ($PhSiH_3$) are occasionally used.

Hiyama, *Tetrahedron* **1999**, *55*, 4573; g) M. P. Rainka, J. E. Milne, S. L. Buchwald, *Angew. Chem., Int. Ed.* **2005**, *44*, 6177; h) H. Shimizu, D. Igarashi, W. Kuriyama, Y. Yusa, N. Sayo, T. Saito, *Org. Lett.* **2007**, *9*, 1655; i) C. Czekelius, E. M. Carreira, *Org. Process Res. Dev.* **2007**, *11*, 633; j) C. Czekelius, E. M. Carreira, *Org. Lett.* **2004**, *6*, 4575.

[8] N. J. Lawrence, M. D. Drew, S. M. Bushell, *J. Chem. Soc., Perkin Trans. 1* **1999**, 3381.



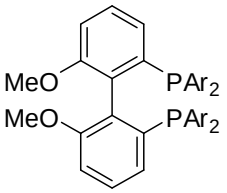
Polymethylhydrosiloxane (PMHS)



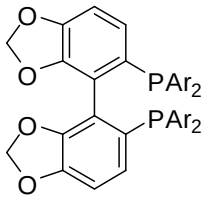
Tetramethyldisiloxane (TMDS)

Scheme 15. Structures of PMHS and TMDS

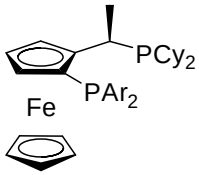
The substitution of triphenylphosphine with chiral bis-phosphines as ligands leads to a chiral copper hydride species that performs reactions in a diastereo- and enantioselective manner. Almost all success realized to date with chiral Cu-H complexes has come from a relatively small subset of either biaryl or ferrocenyl bis-phosphines. Most notably, certain biaryls of the BIPHEP,[9] SEGPHOS[10] and JOSIPHOS[11] series deserve special merit not only for their remarkable selectivity but also for the turnover numbers (TONs) achieved with these types of ligands (Scheme 16).



BIPHEP series



SEGPHOS series



JOSIPHOS series

Scheme 16. Ligands frequently used for asymmetrical Cu-H reductions

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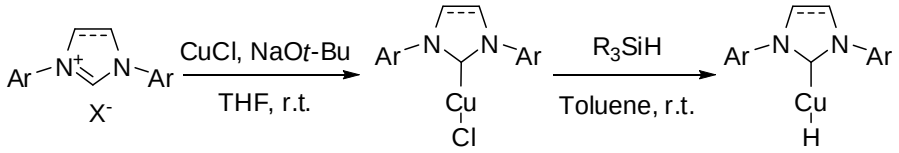
[9] R. Schmid, E. A. Broger, M. Cereghetti, Y. Crameri, J. Foricher, M. Lalonde, R. K. Muller, M. Scalone, G. Schoettel, U. Zutter, *Pure Appl. Chem.* **1996**, *68*, 131.

[10] T. Saito, T. Yokozawa, T. Ishizaki, T. Moroi, N. Sayo, T. Miura, T. Kumbayashi, *Adv. Synth. Catal.* **2001**, *343*, 264.

[11] H.-U. Blaser, W. Brieden, B. Pugin, F. Spindler, M. Studer, A. Togni, *Top. Catal.* **2002**, *19*, 3.

Nowadays, *N*-heterocyclic carbenes[12] (NHCs) are becoming very popular as an alternative to phosphine ligands. Use of isolated, air stable copper-carbene complexes, in particular, has become an attractive alternative.[13] NHCs are quite distinct from tertiary phosphines both electronically and structurally (cf. general introduction). Usually, the (NHC)Cu-H catalyst **2** is prepared from the starting imidazolium salt **1** by treatment with a base and CuCl, followed by *in situ* conversion in the presence of a silane (Scheme 17).



1 **2**

Scheme 17. Generation of (NHC)Cu-H complexes

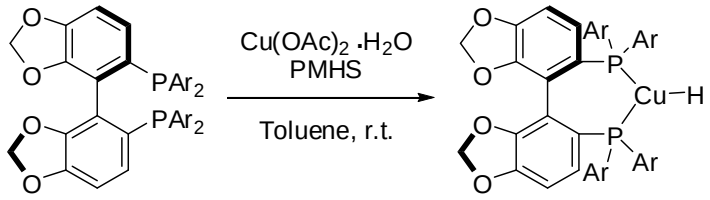
A drawback of the systems described so far is the fact that, except for Stryker's reagent itself, each of these reactive species must be generated *in situ*. This was recently addressed by Lipshutz[14] *et al* who described a chiral copper hydride species **4** bearing the SEGPHOS ligand **3**, a complex which is stable and can be easily stored in solution if kept under argon (Scheme 18).

---

[12] a) W. A. Herrmann, *Angew. Chem., Int. Ed.* **2002**, *41*, 1290; b) *Topics in Organometallic Chemistry*; Ed., F. Glorius,; Springer: Berlin, Heidelberg, NY, **2007**; Vol. 21; c) S. P. Nolan, *N-Heterocyclic Carbenes in Synthesis*; Wiley-VCH: Weinheim, **2006**.

[13] S. Díez-González, S. P. Nolan, *Synlett* **2007**, 2158; b) S. Díez-González, N. M. Scott, S. P. Nolan, *Organometallics* **2006**,*25*, 2355; c) J. Yun, D. Kim, H. Yun, *Chem. Commun.* **2005**, 5181.

[14] B. H. Lipshutz, B. A. Frieman, *Angew. Chem., Int. Ed.* **2005**, *44*, 6345.



3 **4**

Scheme 18. Lipshutz *et al*'s stable chiral copper hydride **4**

With several sources of copper hydride now available, the focus of current Cu-H chemistry continues to be on catalytic asymmetric processes. Thus, 1,4-additions of hydrides onto a variety of electrophilic centers have been developed, where the level of chiral induction derives from the innate bias of the ligand-metal complex.

I.2. 1,4-Reductions and Tandem Reactions

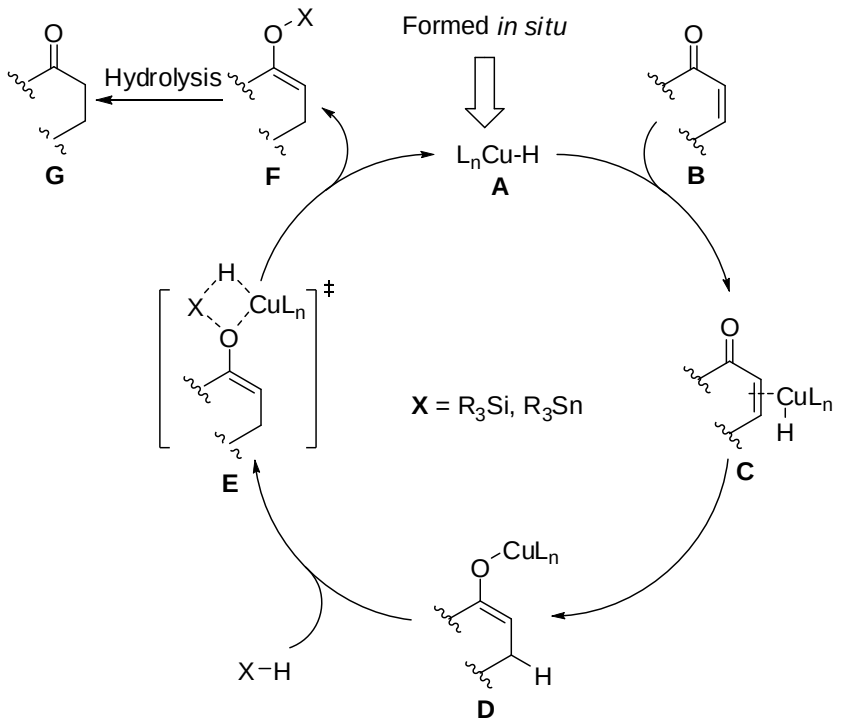
I.2.1. Copper Hydride Catalyzed- 1,4-Reduction of Enones and Enoates

The use of copper(I) hydride complexes to perform 1,4-reduction of α,β-unsaturated Michael acceptors is a very reliable method.[15] Not long after Stryker's initial report on stoichiometric uses of $[(PPh_3)Cu\text{-}H]_6$, it was discovered that a catalytic cycle could be established.[16] As Shown in Scheme 19, the carbophilic copper hydride species **A** reacts with the Michael acceptor **B** to form a π-complex **C**. Delivery of the hydride to the β-carbon atom affords the enolate **D**, which undergoes a σ-bond metathesis with the

[15] a) N. Krause, A. Hoffmann-Röder, *Synthesis* **2001**, 171; b) J. Christoffers, G. Koripelly, A. Rosiak, M. Rössle, *Synthesis* **2007**, 1279.

[16] W. S. Mahoney, J. M. Stryker, *J. Am. Chem. Soc.* **1989**, *111*, 8818.

stoichiometric hydride source via transition state **E**, thus closing the cycle by regaining the catalytically active copper hydride species **A** and releasing species **F** which, after hydrolysis, will give product **G**.



Scheme 19. Proposed mechanism for the 1,4-reduction reaction

Although this catalytic use of copper hydride is the most used method nowadays to perform 1,4-reductions of α,β-unsaturated Michael acceptors, stoichiometric uses of Stryker's reagent are still used successfully. Such a copper-mediated conjugate reduction was recently used by Hirama *et al* in their total synthesis of the shellfish poison (+)-pinnatoxin A (Scheme 20).[17]

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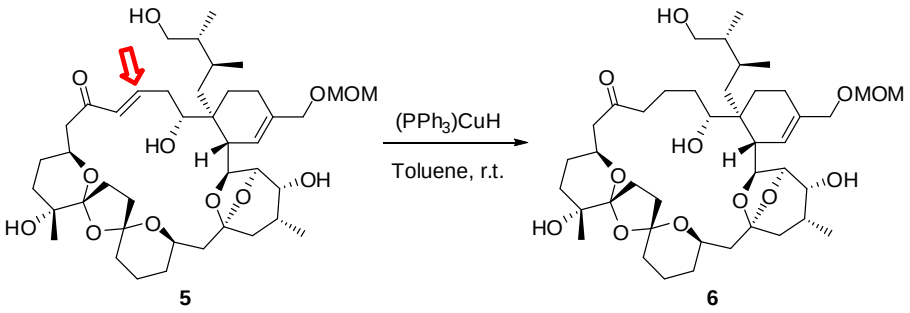
[17] a) S. Sakamoto, H. Sazaki, K. Hagiwara, K. Kamada, K. Ishii, T. Noda, M. Inoue, M. Hirama, *Angew. Chem., Int. Ed.* **2004**, *43*, 6505; b) C. Gaul, J. T. Njardarson, D. Shan, D. C. Dorn, K.-D. Wu, W. P. Tong, X.-Y. Huang, M. A. S. Moore, S. J. Danishefsky, *J. Am. Chem.*

A key step in this synthesis was the chemoselective reduction of an α,β-unsaturated ketone. This was accomplished with an excess of Stryker's reagent, thus forming the macrocyclic intermediate **6** starting from enone **5**. Although only a moderate yield was obtained, this reaction showcases the benefits of copper hydride chemistry in an impressive way: high chemoselectivity, and considerable tolerance to a second double bond as well as a variety of functional groups (alcohols, acetals, ethers) and stereogenic centers. These advantages were a driving force for further improvements.



5 **6**

Scheme 20. Hirama *et al*'s key step in the total synthesis of (+)-pinnatoxin A

The basis for these new developments lies in an appreciation for the facility with which various silyl hydrides undergo transmetalation with copper enolates.[18] These hydride sources not only are easy to handle but also are quite inexpensive. Furthermore, their use in this chemistry didn't affect the high tolerance toward functional groups, the mildness of the reaction conditions, and especially the chemoselectivity that this methodology entails. TMDS and PMHS, which were mentioned earlier, are the most

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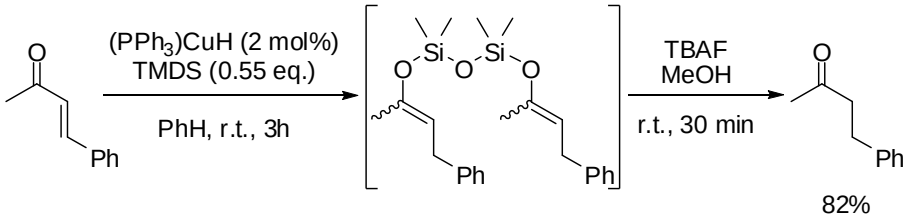
Soc. **2004**, *126*, 11326; c) M. P. Coogan, L.-l. Ooi, D. S. Wilkins, *J. Organomet. Chem.* **2005**, *690*, 1861; d) B. Moon, S. Han, Y. Yoon, H. Kwon, *Org. Lett.* **2005**, *7*, 1031; e) B. Wakefield, R. J. Halter, P. Wipf, *Org. Lett.* **2007**, *9*, 3121.

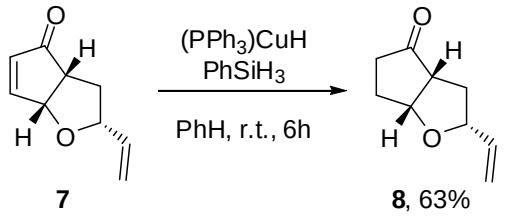
[18] P. Chiu, *Synthesis* **2004**, 2210.

frequently used silanes, allowing for reduction of α,β-unsaturated ketones with catalytic amounts of Stryker's reagent (Scheme 21).[7e]



Scheme 21. Catalytic 1,4-reduction of α,β-unsaturated ketones

Chandler *et al* used stoichiometric amounts of Stryker's reagent and phenylsilane for the synthesis of the ketone **8**, a precursor of the marine natural product (±)-trans-kumausyne (Scheme 22).[19]



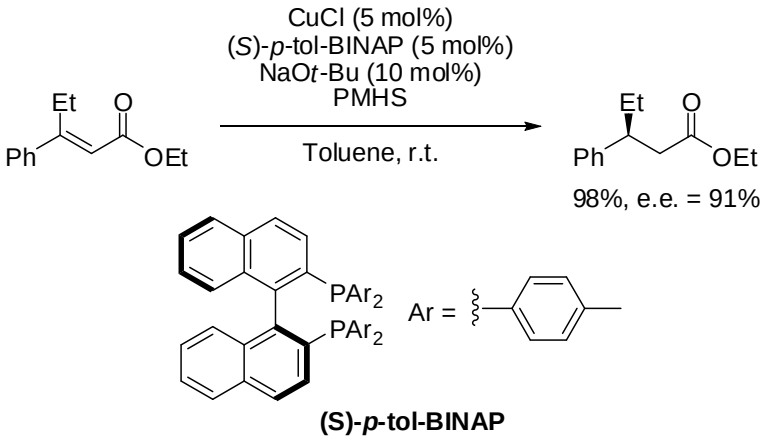
Scheme 22. Chandler *et al*'s synthesis of the precursor **23**

Inspired by early work on Cu-H, Buchwald[20] *et al* developed the first enantioselective conjugate reduction using *in situ* generation of a bis-phosphine-stabilized chiral Cu-H species from CuCl as the copper source, NaO*t*-Bu as the base, and (*S*)-*p*-tol-BINAP as the chiral ligand (Scheme 23).

---

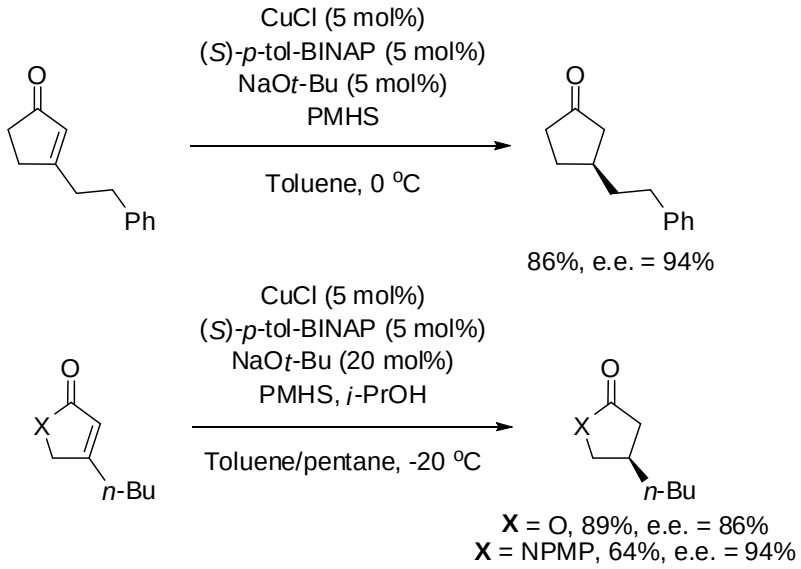
[19] C. L. Chandler, A. J. Phillips, *Org. Lett.* **2005**, *7*, 3493.

[20] a) D. H. Apella, Y. Moritani, R. Shintani, E. M. Ferreira, S. L. Buchwald, *J. Am. Chem. Soc.* **1999**, *121*, 9473; b) Y. Moritani, D. H. Apella, V. Jurkauskas, S. L. Buchwald, *J. Am. Chem. Soc.* **2000**, *122*, 6797; c) G. Hughes, M. Kimura, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 11253; d) M. P. Rainka, Y. Aye, S. L. Buchwald, *Proc. Natl. Acad. Sci.* **2004**, *101*, 5821.



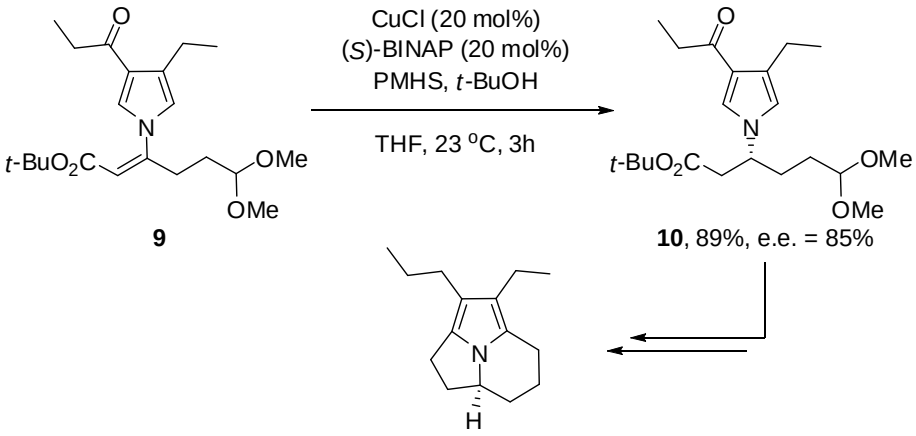
Scheme 23. Buchwald *et al*'s catalytic enantioselective 1,4-reduction

With this system, enones as well as unsaturated esters, lactones, and lactams undergo smooth 1,4-reduction furnishing the corresponding saturated systems in very good yields and high e.e.'s (Scheme 23 and 24).



Scheme 24. Enantioselective 1,4-reduction of cyclic Michael acceptors

This method was later applied successfully to the synthesis of Myrmicarin 217 **11** (a tricyclic myrmicarin alkaloid) (Scheme 25).[21] Because of the high steric hindrance at the β-site in Michael acceptor **9**, somewhat higher catalyst loadings of the *in situ* formed chiral Cu-H complex were needed to form the intermediate **10**.

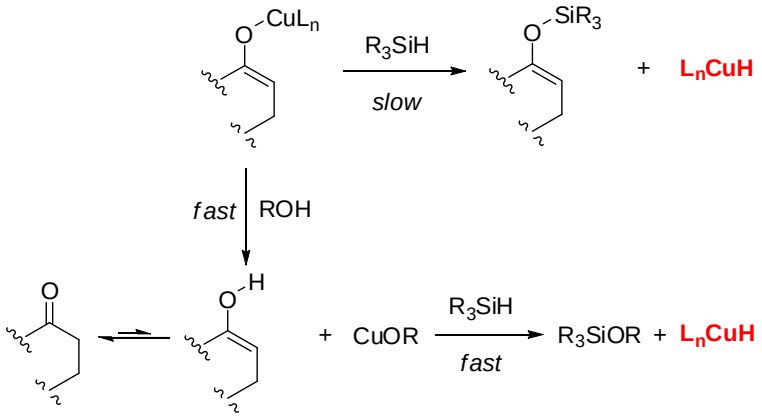


Scheme 25. Synthesis of Myrmicarin 217

Remarkably this methodology takes advantage of the tolerance of Cu-H complexes to various alcohols and water. In fact, several methods rely on the presence of a bulky alcohol to enhance reaction rates. The role of this additive is usually credited to the more rapid quenching of the copper enolate intermediate, thus generating a copper alkoxide which is an ideal precursor to the rapid restoration of Cu-H in the presence of excess silane (Scheme 26). Thus, the rate increase is presumably due to the bypass of the slow metathesis step between Cu-O (from the copper enolate) and Si-H

[21] M. Movassaghi, A. E. Ondrus, *Org. Lett.* **2005**, *7*, 4423.

bonds that is otherwise essential for regenerating Cu-H in the catalytic cycle (cf. Scheme 19).[22]



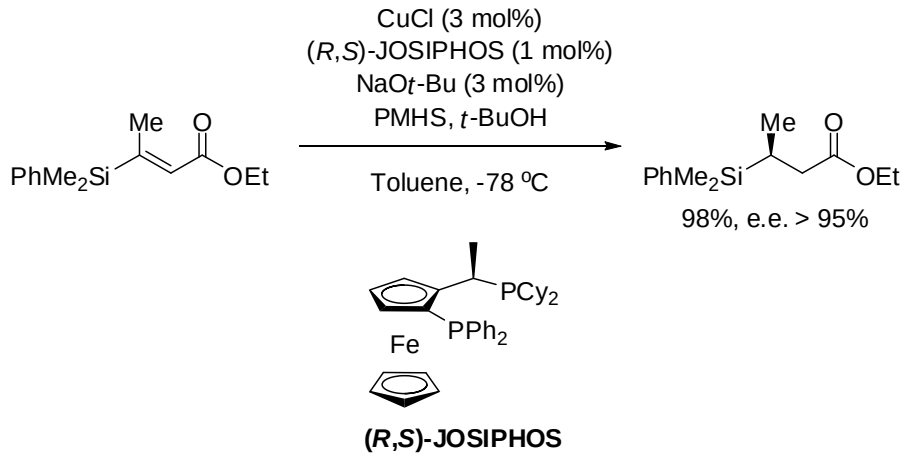
Scheme 26. Cu-H catalyzed 1,4-reduction in the presence of alcohols

Improvements in both enantioselectivity and reactivity toward sterically hindered systems followed these reports based on BINAP ligands. In a series of publications, Lipshutz and co-workers found that JOSIPHOS and SEGPHOS derived chiral Cu-H species lead to higher levels of chiral induction than those obtained with the corresponding BINAP-(Cu-H) derivatives (Scheme 27).[7d,23]

---

[22] B. H. Lipshutz, J. M. Servesko, B. R. Taft, *J. Am. Chem. Soc.* **2004**, *126*, 8352.

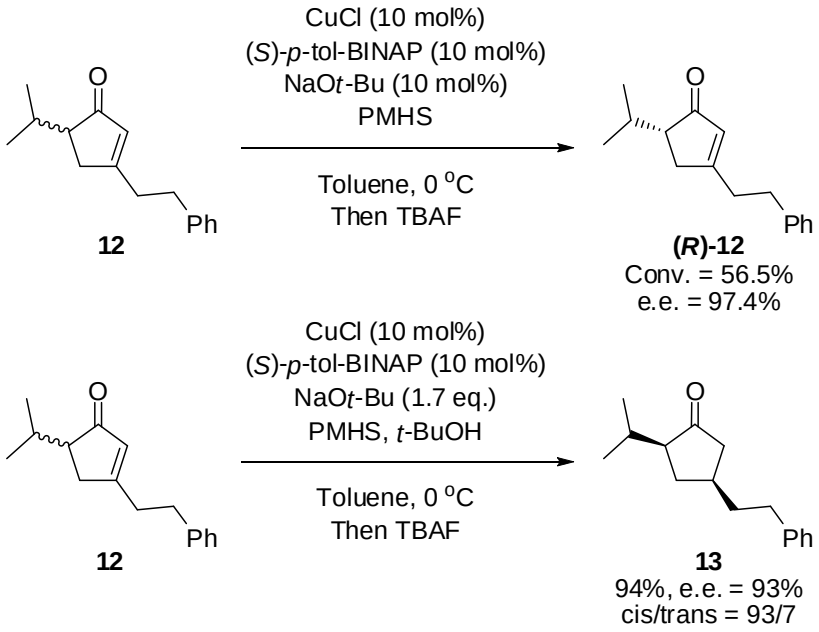
[23] a) B. H. Lipshutz, J. M. Servesko, *Angew. Chem., Int. Ed.* **2003**, *42*, 4789; b) B. H. Lipshutz, N. Tanaka, B. R. Taft, C.-T. Lee, *Org. Lett.* **2006**, *8*, 1963; c) B. H. Lipshutz, C.-T. Lee, B. R. Taft, *Synlett* **2007**, *20*, 3257.



Scheme 27. Lipshutz *et al*'s catalytic system

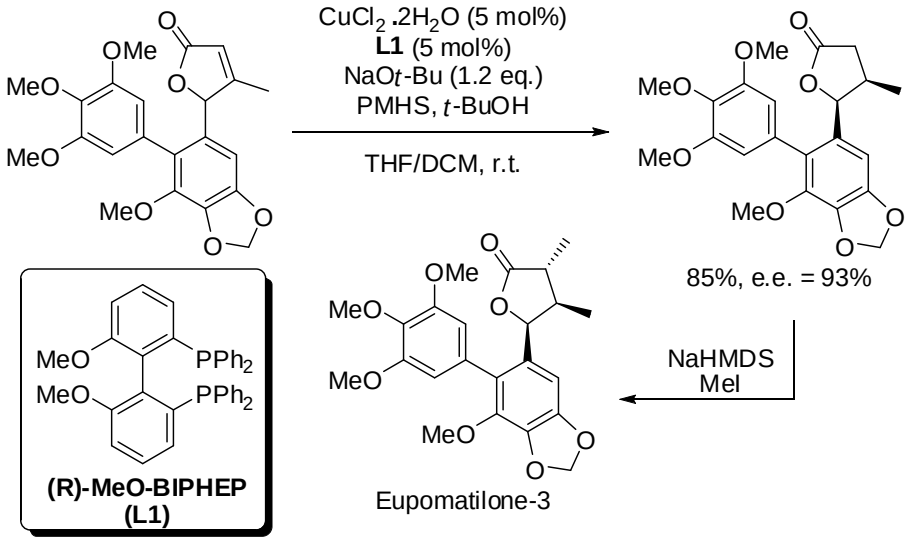
A remarkable extension for the generation of two stereogenic centers was reported by Buchwald and co-workers.[7g,24] This group used their chiral Cu-H system (cf. Scheme 23) for the kinetic resolution of α,β-unsaturated lactones,[20c] as well as the kinetic and dynamic kinetic resolution of 2,4-dialkylcyclopent- 2-enones **12** (Scheme 28).[24]

[24] V. Jurkauskas, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 2892.



Scheme 28. Kinetic and dynamic kinetic resolution using catalytic Cu-H

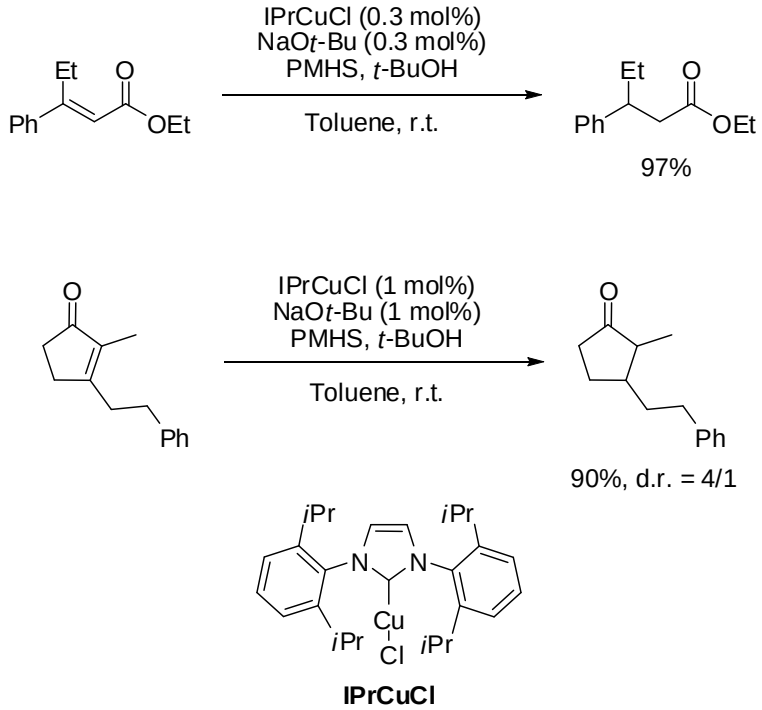
In the presence of catalytic amounts of NaO*t*-Bu as base, an efficient kinetic resolution of racemic enone **12** takes place to afford the less reactive (*R*)-enantiomer with high e.e.. However, for the dynamic kinetic resolution, an excess of NaO*t*-Bu and *t*-BuOH serves to accelerate racemization of the substrate **12** to such an extent that the reduction product **13** can be isolated in high yield and enantiomeric excess. The usefulness of this method was illustrated in a short synthesis of the lignan Eupomatilone-3 (Scheme 29).[7g]



Scheme 29. Synthesis of Eupomatilone-3 by dynamic kinetic resolution

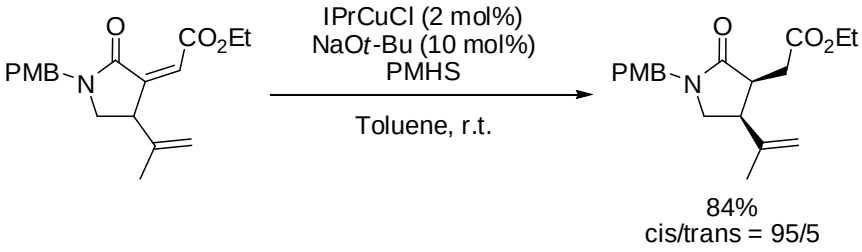
An interesting achiral alternative for Stryker's reagent can be generated by exchanging the phosphine with an *N*-heterocyclic carbene (NHC).[25] The isolable and highly stable (IPr)CuCl complex was treated with a base to generate the corresponding (IPr)CuO*t*-Bu complex *in situ*; this ultimately forms a reactive copper hydride complex in the presence of PMHS. This system reacts smoothly with cyclic and acyclic enones furnishing the saturated products in excellent yields (Scheme 30).

[25] V. Jurkauskas, J. P. Sadighi, S. L Buchwald,. *Org. Lett.* **2003**, *5*, 2417.



Scheme 30. 1,4-Reduction with an (NHC)Cu complex

With its application to the synthesis of the precursor of kainic acid (Scheme 31), a natural non-proteinogenic amino acid, IPrCuCl has clearly emerged as a useful alternative to Stryker's reagent.[26]



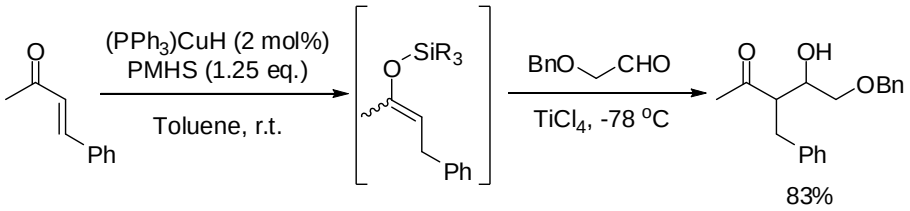
Scheme 31. Synthesis of a precursor for Kainic Acid using IPrCuCl

[26] M. B. T. Thuong, S. Sottocornola, G. Prestat, G. Broggini, D. Madec, G. Poli, *Synlett* **2007**, 1521, and references cited therein.

I.2.2. Tandem Variation: Aldolisation

1,4-reductions of α,β-unsaturated Michael acceptors with catalytic *in situ* formed Cu-H can be further trapped either inter- or intramolecularly with an aldehyde or a ketone, generating the desired aldolisation product (cf. Scheme 11).

In initial studies, Lipshutz *et al* treated several enones with catalytic amounts of Stryker's reagent and a silane forming the silyl enol ether which, in the presence of a Lewis acid ($TiCl_4$), reacted with aldehydes to form the corresponding aldol products (Scheme 32).[7e]

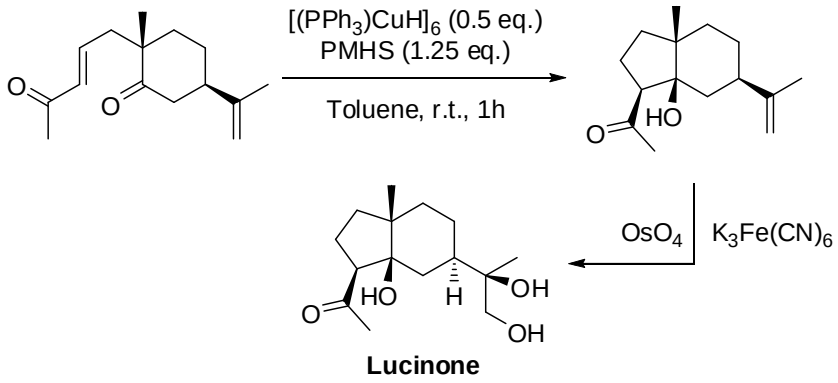


Scheme 32. Tandem 1,4-reduction/aldolisation reaction

Not long after this report, Chiu[27] *et al* reported an intramolecular 1,4-reduction/aldolisation reaction as a key step in their total synthesis of Lucinone, an antispasmodic drug (Scheme 33).[27b]

---

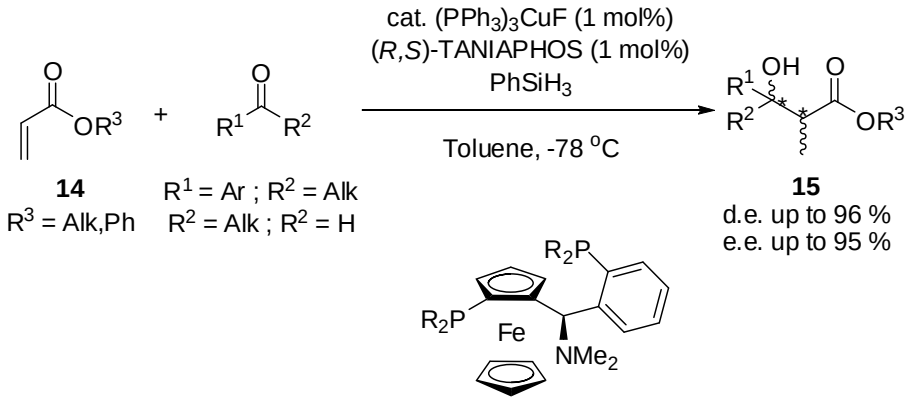
[27] a) P. Chiu, C.-P. Szeto, Z. Geng, K.-F. Cheng, *Org. Lett.* **2001**, *3*, 1901; b) P. Chiu, C. P. Szeto, Z. Geng, K. F. Cheng, *Tetrahedron Lett.* **2001**, *42*, 4091; c) P. Chiu, S. K. Leung, *Chem. Comm.* **2004**, 2308; d) W. K. Chung, P. Chiu, *Synlett* **2005**, 55.



Lucinone

Scheme 33. Synthesis of Lucinone

It is not surprising that enantioselective conjugate 1,4-reductions with L*Cu-H (with L* as chiral ligands) have also been used in tandem reactions. Chiral Cu-H catalysts have been successfully applied to the domino 1,4-reduction/aldolisation reaction as demonstrated by Riant *et al.*[2a,b] Thus, aromatic aldehydes and ketones readily react with the copper enolate intermediate generated by the copper catalyzed 1,4-reduction of methyl acrylate **14** to afford the desired aldol adduct **15** with high syn-selectivity and good to excellent e.e.'s (Scheme 34).



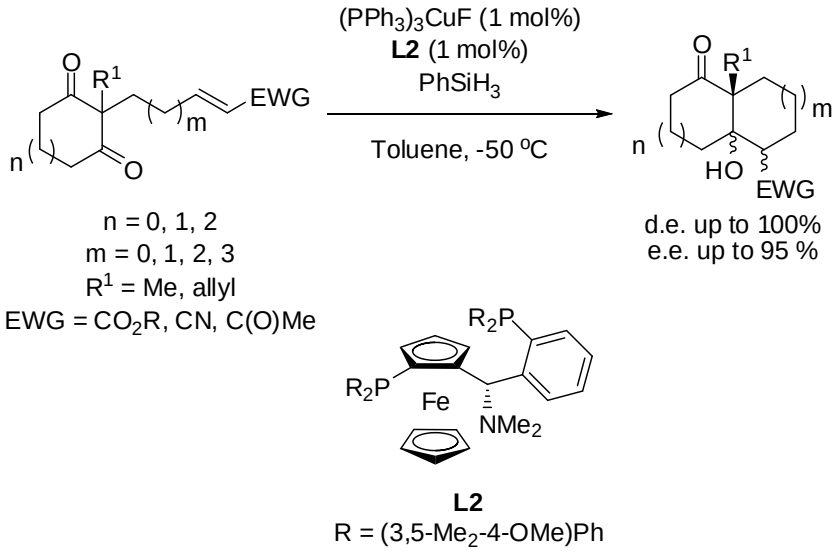
Scheme 34. Enantioselective domino 1,4-reduction/aldolisation of acrylates

The chiral ligand of choice for this transformation is TANIAPHOS. Since the chirality transfer must derive from the chiral copper enolate intermediate, reactions are best carried out in toluene at low temperature to minimize ligand decomplexation; under these conditions, the aldolisation reaction occurs faster than the metathesis with $PhSiH_3$ and ergo formation of the reduction product or silyl enolate is avoided. Related trapping reactions with dialkyl ketones have also been reported with modest success.[2d]

An intramolecular version of this reaction was also developed by the same group starting from diketo-esters to form various bicyclic products (Scheme 35).[28]

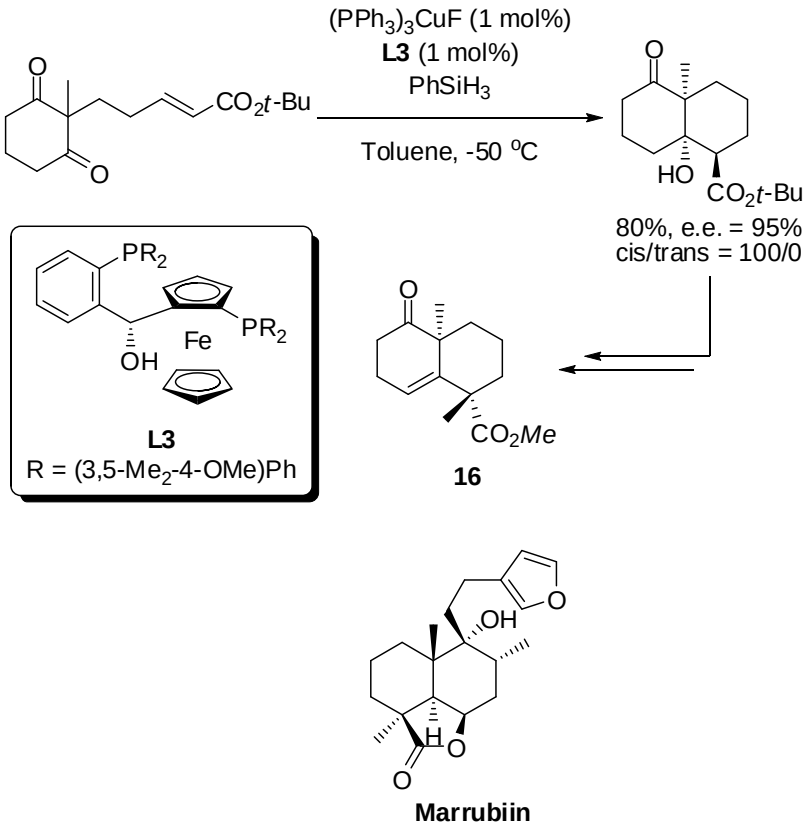
---

[28] a) J. Deschamp, O. Riant, *Org. Lett.* **2009,** *11*, 1217; b) J. Deschamp, T. Hermant, O. Riant, *Tetrahedron* **2012**, *68*, 3457.



Scheme 35. Enantioselective intramolecular 1,4-reduction/aldolisation

The usefulness of this strategy was demonstrated in the synthesis of **16**; a key intermediate in the synthesis of Marrubiine, a natural diterpene, in fewer steps compared to the original synthesis (Scheme 36).[28b]

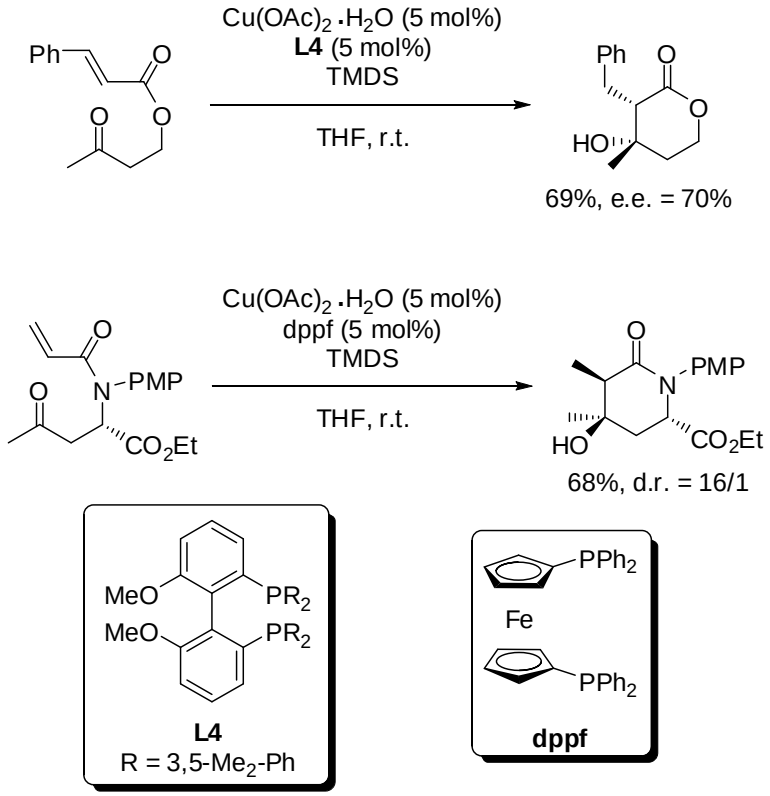


Scheme 36. Synthesis of Marrubiin

Other intramolecular versions leading to newly formed 5- and 6-membered ring lactones are smoothly catalyzed by chiral Cu-H formed *in situ*.[29] Good yields and e.e.'s are obtained (Scheme 37). Related reactions with unsaturated amides, using dppf also showed some promising results (Scheme 37).[29a] Thus, allowing access to the desired lactames in a diastereoselective fashion.

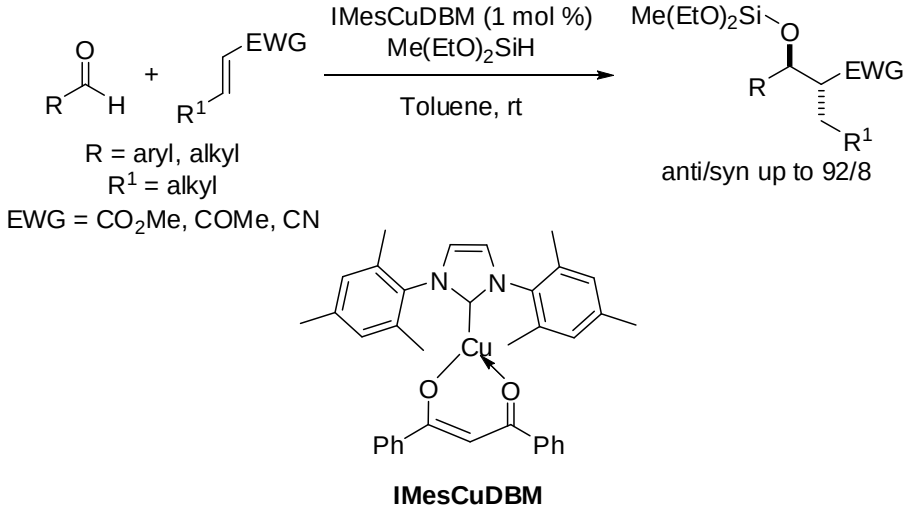
---

[29] a) H. W. Lam, G. J. Murray, J. D. Firth, *Org. Lett.* **2005**, *7*, 5743; b) H. W. Lam, P. M. Joensuu, *Org. Lett.* **2005**, *7*, 4225.



Scheme 37. Intramolecular cyclisations via 1,4-reduction/aldolisation

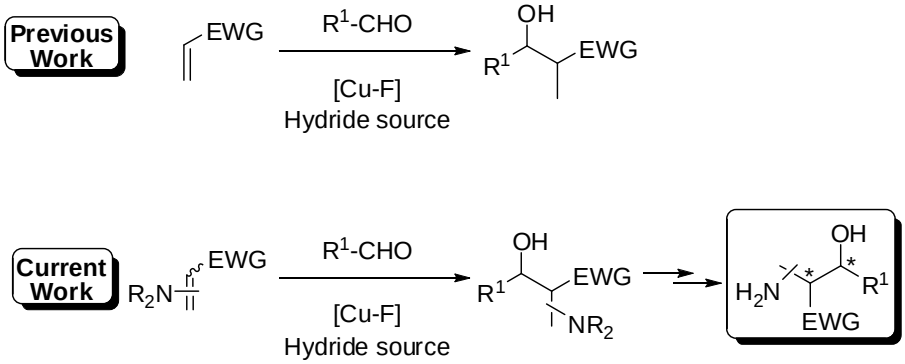
An NHC alternative was also investigated for this type of tandem reactions.[2c] Using an (NHC)copper complex developed "in house"; the IMesCuDBM, various aldehydes and α,β-unsaturated Michael acceptors were reacted to furnish aldol type products in high chemoselectivity, good yields and good diastereoselectivity (Scheme 38).



Scheme 38. Domino 1,4-reduction/aldolisation using an (NHC)Cu complex

II. Objectives

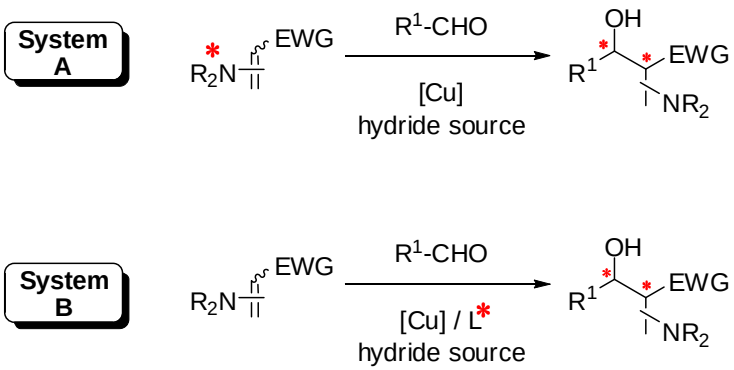
Our group has a history of developing new methodologies for the copper catalyzed 1,4-reduction/aldolisation. As shown earlier (cf. Scheme 34-36 and 38), several copper hydride systems have been developed to tackle this problem.[2a-c,28] We found it interesting to try to extend this methodology to new substrates. Using the copper hydride systems developed in our lab, we endeavoured to apply it to Michael acceptors bearing a nitrogen group on the double bond. Acyclic and cyclic nitrogen motifs could be envisaged, as well as different electrophiles. This new class of substrates could ultimately give us access to hydroxy- α- or β-amino carbonyls or carboxyls, bearing several chiral centres (Scheme 39).



Scheme 39. Previous and current work on our methodology

Although our primary goal is to find a suitable class of substrate that will readily undergo the desired reaction using our previously developed catalytic systems, our ultimate aim is to develop a chiral system for these molecules. Chiral induction could be induced *via* two systems (Scheme 40). System A, involves the use of a chiral nitrogen motif, thus the chirality will be conveyed by the substrate itself. The advantage of this method is that the substrate could be easily prepared and is quite inexpensive. Nevertheless,

this system renders the methodology fairly dependant on one class of substrates, ergo limiting the general scope of the system and hindering its extension to different types of substrates. In system B, the chirality induction is derived from the innate bias of the ligand-metal complex. This system is usually more general, and allows further extension to other derived substrates, but it is not without its problems. Finding the right combination of ligand and metal complexes is no easy task. The variables in play are quite extensive; this system should be chemoselective, regioselective, diastereoselective and ultimately enantioselective. These two systems are equally interesting to us, as we hoped that they would be complementary.



Scheme 40. Systems used for chiral induction

The subsequent parts of this chapter will mostly depict the synthesis of different types of substrates. After which, we will be using these substrates in our catalytic system in an attempt to find one class that gives us some promising results to build on.

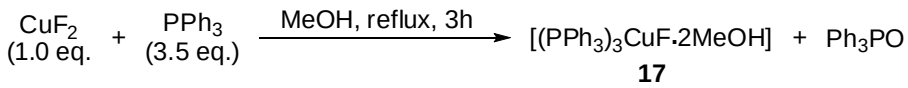
III. Results and Discussion

III.1. Previous Work

As stated before, this project is an extension of previous work. In order to better understand some of the choices made in this work we felt it was important to describe the catalytic system used in our laboratory so far.

III.1.1. The Copper Catalytic System

Until now, the catalytic system frequently used in our laboratory is the one that was first developed for the 1,2-reduction of ketones.[1] Later on, this system was successfully applied to the 1,4-reduction/aldolisation domino reaction of Michael acceptors.[2a-b,28] The system involves the use of a phosphine-based copper fluoride complex **17**. Complex **17** is readily obtained, using a modified literature procedure,[2] by reacting copper(II) fluoride with triphenylphosphine in refluxing methanol (Scheme 41).



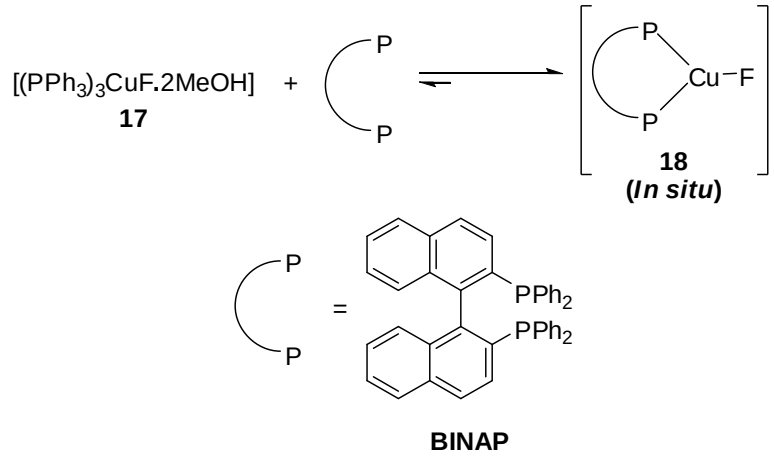
Scheme 41. Synthesis of complex **17** used in our group

This complex has generally been used in the presence of a *bis*-phosphine. BINAP is frequently used in model reactions due to its commercial availability both in racemic and enantiopure forms. The *bis*-phosphine displaces quasi irreversibly the phosphine ligands, rendering the newly formed complex **18** more stable and less susceptible to the

[1] S. Sirol, J. Courmarcel, N. Mostefai, O. Riant, *Org. lett.* **2001**, *3*, 4111.

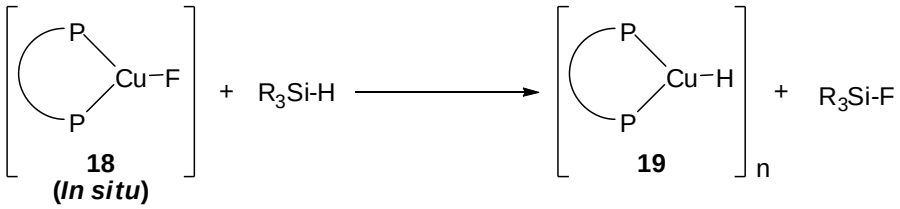
[2] D. J. Gulliver, W. Levason, M. Webster, *Inorganica Chimica Acta Articles* **1981,** *52*, 153.

decomplexation/complexation phenomenon, usually observed with mono-phosphines (Scheme 42).



Scheme 42. *In situ* generation of the *bis*-phosphine copper(I) complex **18**

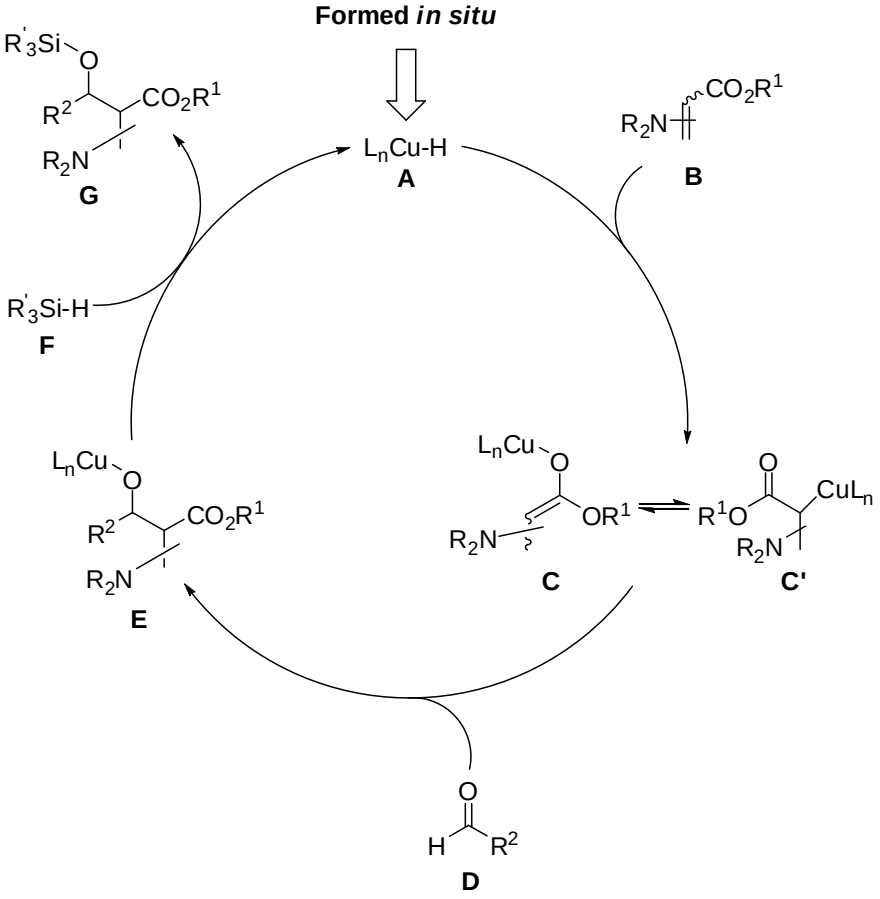
The *bis*-phosphine copper(I) complex **18** obtained *in situ* has shown to react easily with silanes to form the desired copper hydride complex **19** (Scheme 43). This complex will then undergo the conjugated reduction/aldolisation domino process successfully. It has also been shown that this *bis*-phosphine copper system is far superior to the mono-phosphine one in the aforementioned reaction.[2a]



Scheme 43. *In situ* generation of the copper(I) hydride complex **19**

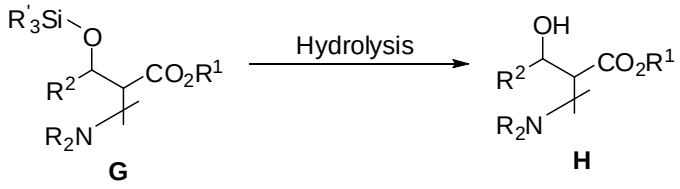
III.2. Proposed Mechanism

The proposed mechanism for the model reaction is illustrated in Scheme 44. The copper hydride complex **A** is formed *in situ* as mentioned above. Complex **A** will then react with the Michael acceptor **B** to form the copper enolate intermediate **C**, which is in equilibrium with **C'**. The copper enolate will subsequently attack aldehyde **D** to form the copper alkoxide **E**. σ-bond metathesis of the copper alkoxide with silane **F** will simultaneously form the silylated aldol adduct **G** and regenerate the copper hydride complex to close the catalytic cycle.



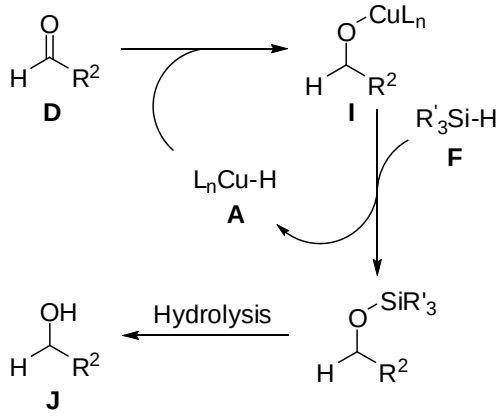
Scheme 44. Proposed mechanism for the 1,4-reduction/aldolisation reaction

The silylated aldol adduct is transformed afterwards by hydrolysis to the desired aldol product **H** (Scheme 45). This is generally achieved by an acidic work-up of the reaction mixture.



Scheme 45. Formation of the aldol adduct *via* hydrolysis

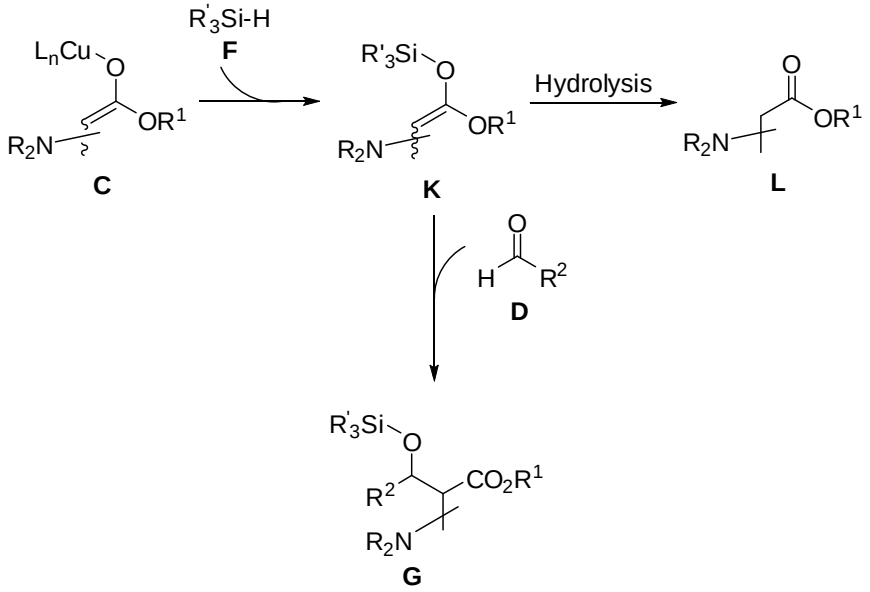
This mechanism is the same described in the literature for acrylates. And as for acrylates, there are a few secondary reactions that could influence the outcome. For example, if the system turns out not to be chemoselective, the copper hydride **A** could react directly with aldehyde **D** to form the corresponding copper alkoxide **I** (Scheme 46). Exchange of the copper with silane **F** would then generate, after hydrolysis alcohol **J**. This secondary reaction, if it's faster than the 1,4-reduction reaction completely consumes the aldehyde. Although the copper hydride is regenerated at the end, it still won't be available to perform the desired reaction until total consumption of the aldehyde (Scheme 46).



Scheme 46. Secondary reactions: reduction of the aldehyde

Another secondary reaction could occur, when the reaction of the copper enolate **C** with the aldehyde is not favoured (Scheme 47). In this case, **C** will prefer exchanging with silane **F** to form the silyl enol ether **K**. From there, two additional pathways could evolve. The silyl enolate **K** could just accumulate till the reaction is stopped and therefore, after hydrolysis, generate the 1,4-reduction product **L**. Secondary product **L** (or the reduction product) is actually the most common by-product of this type of reactions.

But **K** could also react with aldehyde **D**, as in Mukaiyama reactions,[3] to equally form the aldol adduct **G** (Scheme 47). Although the same desired product **G** could be obtained, this pathway is actually highly undesirable as it reduces the copper complex's role in the reaction and more importantly, doesn't allow for asymmetric catalysis later on.



Scheme 47. Secondary reactions: the silyl enolate's formation and reactivity

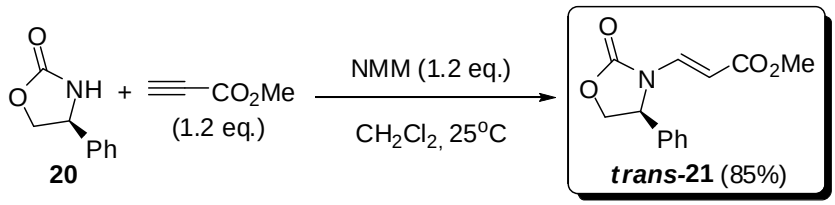
III.3. Synthesis and Catalytic Testing

III.3.1. Preliminary Model Reaction

III.3.1.1. Synthesis of Model Substrates

[3] a) T. Mukaiyama, *et al. Chem. Lett.* **1973**, 1011.; b) T. Mukaiyama, *et al. J. Am. Chem. Soc*. **1974**, *96*, 7503.; c) T. Mukaiyama, *et al. Chem. Lett*. **1975**, 741.

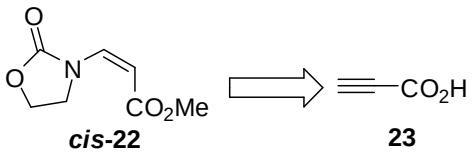
The project started with the synthesis of substrate ***trans*-21** as a model substrate for the desired domino reaction (Scheme 48). We thought, as mentioned earlier, that this type of substrates could easily induce chirality in the construction of new sterogenic centres. ***Trans*-21** is easily obtained in one step, by reacting oxazolidinone **20** (also called Evans auxiliary) with methyl propiolate in the presence on *N*-methylmorpholine (NMM).[4] The desired product is obtained in 85% yield.



Scheme 48. Synthesis of model substrate ***trans*-21**

Although this method gives us high yields, it could only form *trans* substrates. We felt that the *cis* substrate should also be synthesized to study the difference in reactivity. Furthermore, *cis* compounds are known to undergo the copper catalyzed 1,4-reduction more easily than their *trans* counterparts. This is due to the less steric hindrance generated by the former, around the double bond. To this end, an attempt to synthesize substrate ***cis*-22** from propionic acid **23** was undertaken (Scheme 49).

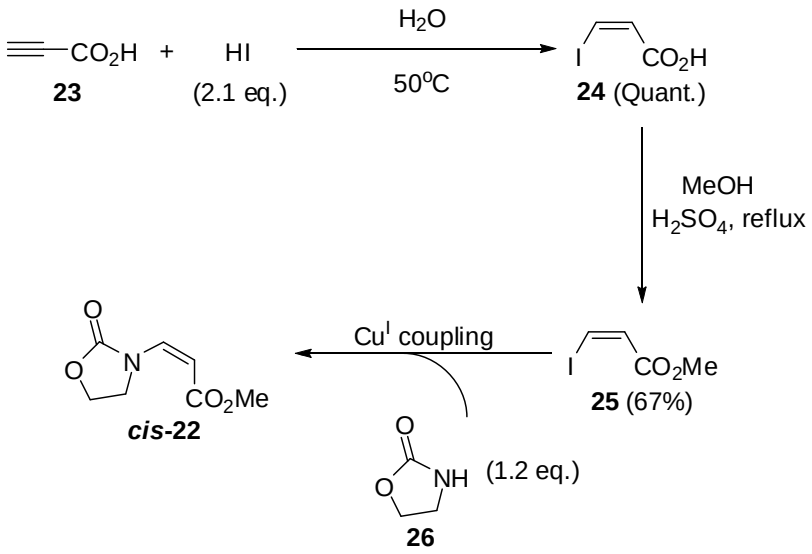
[4] M. Barbazanges, C. Meyer, J. Cossy, *Org. Lett.* **2007**, *9*, 3245.



***cis*-22** **23**

Scheme 49. Retrosynthesis of model substrate ***cis*-22**

Propionic acid **23** was thus reacted with hydriodic acid (HI) in water to form the desired *cis*-iodovinylic acid **24** in a quantitative yield.[5] Subsequent acid-catalyzed esterification of **24** in methanol gave the desired ester **25** in a 67% yield. The next step is a Cu^{I}-catalyzed amidation reaction of *cis*-iodovinylic ester **25** with oxazolidinone **26** to form the desired product ***cis*-22** (Scheme 50). This coupling reaction is well described in the literature.[6]



Scheme 50. Synthesis of model substrate ***cis*-22**

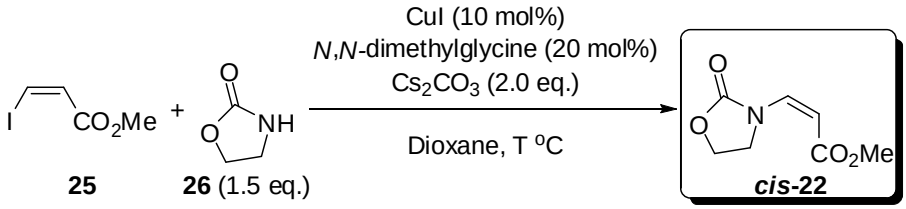
---

[5] R. Takeuchi, K. Tanabe, S. Tanaka, *J. Org. Chem.* **2000**, *65*, 1558.

[6] L. Jiang, G. E. Job, A. Klapars, S. L. Buchwald, *Org. Lett.* **2003**, *5*, 3667.

First attempts at the coupling reaction didn't quite turn out as we hoped (Table 2). Although total consumption of the starting material was always observed, the *trans*/*cis* ratio was in favour of the *trans* product (94/6, Table 2, entry 1). After optimisation, we managed to increase the ratio up to 54/46, but it was still in favour of the *trans* product. Furthermore separation of the two stereoisomers was no easy task.

Table 2. Optimisation of the Cu^{I} catalyzed coupling reaction



25 **26** (1.5 eq.) ***cis*-22**

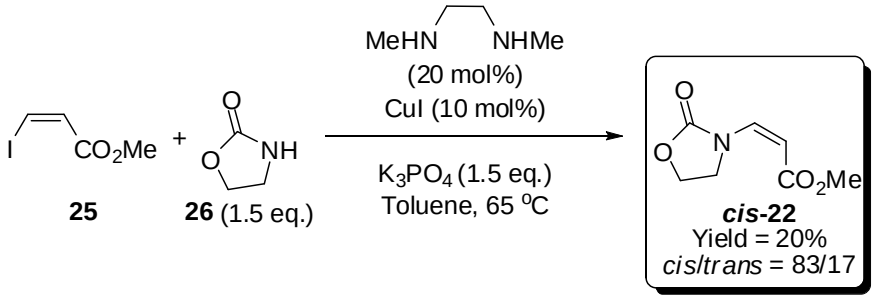
Entry	Temp. (°C)	Time (hours)	Conversion[a] (%)	*trans*/*cis* Ratio[b]
1	60	24	>99	94/6
2	60	8	>99	63/37
3	60	1	>99	72/28
4	45	2	>99	54/46

[a] Conversion to ***cis*-22** is determined on the crude mixture by ^{1}H NMR relative to the starting material **25** [b] Determined by ^{1}H NMR, the stereochemistry was assigned by comparison with literature data.

For that reason, other coupling conditions were employed in an effort to avoid forming the *trans* product. After a few attempts, we managed to find the best conditions to suppress the formation of the *trans* product (Scheme 51).[7] Although ***cis*-22** was obtained in a low yield (20%), the selectivity for

[7] M. P. Rainka, Y. Aye, S. L. Buchwald, *Proc. Natl. Acad. Sci.* **2004**, *101*, 5821.

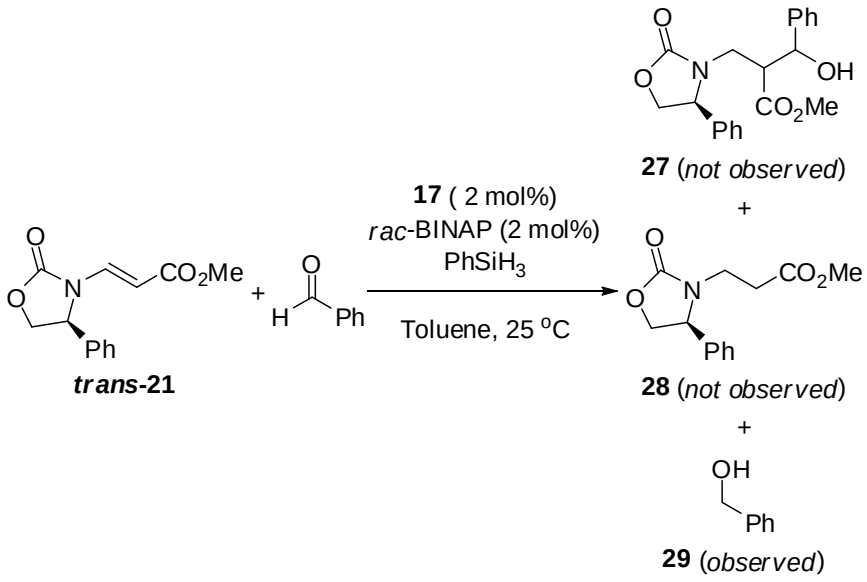
the *cis* product was high enough to allow us to obtain satisfactory quantities for further testing.



Scheme 51. Optimised reaction conditions for the synthesis of ***cis*-22**

III.3.1.2. Catalytic Tests

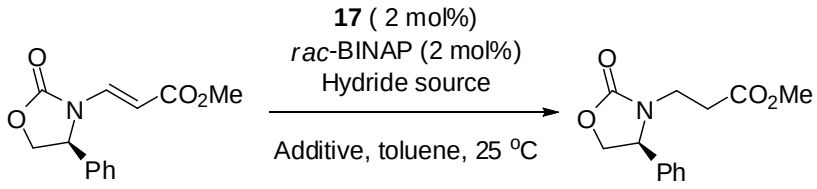
With these two products in hand, we started catalytic testing with our previously described copper system (cf. the copper catalytic system section). First tests were conducted with ***trans*-21** in the presence of benzaldehyde, and they turned out to be quite disappointing (Scheme 52). The copper hydride formed *in situ* reacted with the benzaldehyde directly, thus forming benzyl alcohol **29** exclusively. No traces of the desired aldol product **27** or even the reduction product **28** were observed.



Scheme 52. Testing ***trans*-21** in our reaction conditions

These results suggest that the reaction of the copper hydride is faster with benzaldehyde than with ***trans*-21**, or that ***trans*-21** is not a suitable Michael acceptor for the copper hydride, ergo no reduction is occurring. In order to examine this chemoselectivity problem, further tests were conducted in the absence of benzaldehyde (Table 3). ***Trans*-21** was subjected to our copper hydride system in order to form the reduction product **28**. Using phenylsilane or the more reactive pinacolborane as the hydride source did not change the outcome, as only the starting material was recovered (Table 3, entries 1 and 2). We added $ZnCl_2$ as a Lewis acid in an attempt to increase the electrophilic character of the Michael acceptor ***trans*-21** (Table 3, entries 3 and 4). Unfortunately, still no reaction occurred.

Table 3. Attempting the 1,4-reduction of ***trans*-21**

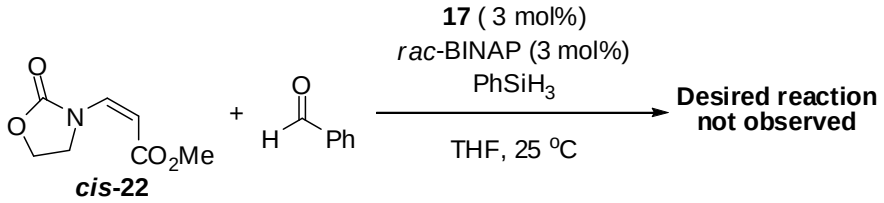


***trans*-21** **28**

Entry[a]	Additive (eq.)	Hydride source	28[b] (%)
1	-	$PhSiH_3$	0
2	-	Pinacolborane	0
3	$ZnCl_2$ (2.8)	Pinacolborane	0
4	$ZnCl_2$ (2.2)	$PhSiH_3$	0

[a] All reactions were run under argon [b] Determined on the crude mixture by ^1H NMR relative to the starting material ***trans*-21**.

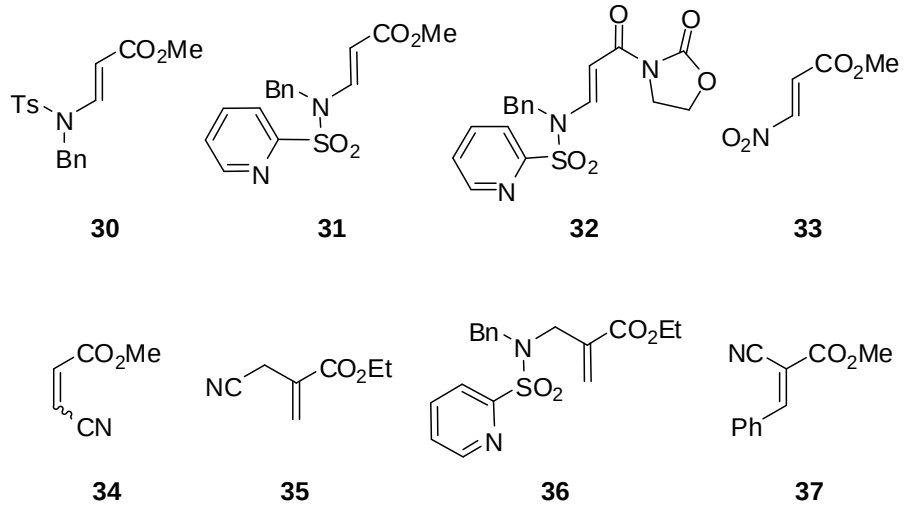
After these disappointing results, we thought that maybe substrate ***cis*-22** could be more susceptible to the 1,4-reduction reaction, as it is less sterically hindered than the ***trans*-21**. Therefore, ***cis*-22** was engaged in the same reaction conditions in the presence of benzaldehyde and as with ***trans*-21**, no reaction was observed (Scheme 53). Only the starting material and benzyl alcohol **29** are recovered.



Scheme 53. Testing ***cis*-22** in our reaction conditions

III.3.2. Extension to Other Substrates

After the previous unsatisfactory results, we decided to screen other substrates in our reaction conditions. We only needed to find one suitable class of substrates that would allow us to perform the desired domino reaction. We can see, in Scheme 54, an overview of the different substrates that we attempted to synthesize. The logical trail of synthesis of these substrates is herein explained.

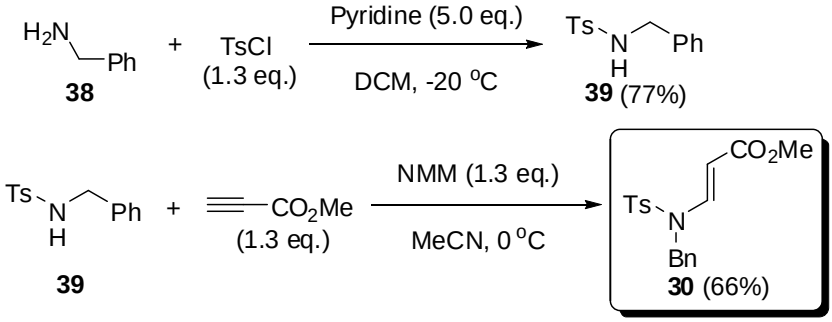


Scheme 54. Overview of the different substrates synthesized

III.3.2.1. Synthesis and Reactivity of 30

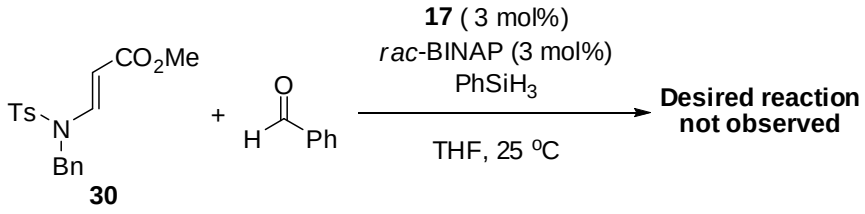
Our hypothesis for the earlier disappointment is that the lone pair of the nitrogen atom is not conjugated enough with the carbonyl of the oxazolidinone, which means that this lone pair is still contributing important electronic density to the double bond. This could significantly reduce the electrophilic character of the β-position. Therefore, we argued that a tosyl (Ts) and a benzyl (Bn) group on the nitrogen moiety should significantly reduce the electron density on the nitrogen and consequently on the double bond (Scheme 55).

Substrate **30** was synthesized starting from benzylamine **38**. The latter reacts with tosyl chloride (TsCl) in the presence of pyridine to form the tosylated amine **39** in a 77% yield. Afterwards, amine **39** reacts with methyl propiolate and NMM to give **30** in a 66% yield (Scheme 55).[4]



Scheme 55. Synthesis of substrate **30**

We engaged substrate **30** in our reaction conditions in the presence of benzaldehyde (Scheme 56). Same as earlier, the chemoselectivity of the copper hydride was still in favour of the benzaldehyde and no 1,4-reduction/aldolisation product was observed. Starting materiel **30** was recovered along with the benzyl alcohol **29**.



Scheme 56. Testing substrate **30** in our reaction conditions

III.3.2.2. Synthesis and Reactivity of 31

Afterwards, we amended our strategy by replacing the tosyl group on the nitrogen with the 2-pyridylsulfonyl group (Scheme 57). This group has been employed by Carretero[8] *et al* in copper catalyzed conjugate reductions and has produced a dramatic increase in reactivity compared to the usual tosyl group. They argued that the pyridine group might coordinate the copper complex and thus result in a strong acceleration of the conjugate reduction.[8,9] For that reason, we began the synthesis of substrate **31** by using the pyridine-2-thiol as a starting point (Scheme 57). The latter is therefore oxidized with bleach in concentrated sulfuric acid to furnish the sulfonyl chloride **40** in 84% yield. Reaction of **40** with benzylamine yields 88% of the corresponding sulfonamide **41**. Addition of **41** to methyl propiolate in typical conditions generates the desired product **31** in 85% yield.

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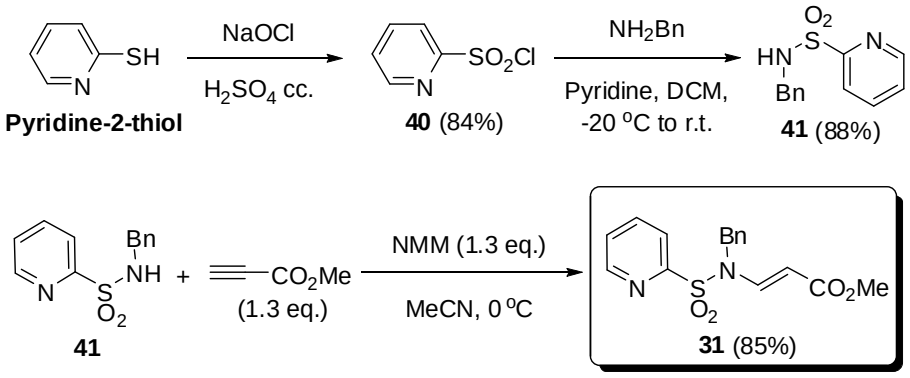
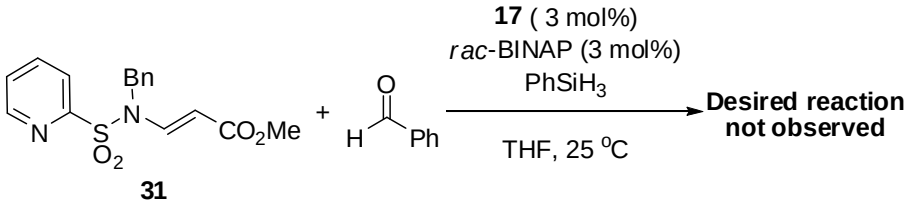
[8] a) A. García-Rubia, R. G. Arrayás, J. C. Carretero, *Angew. Chem.* **2009**, *121*, 6633; b) A. Garcia-Rubia, B. Urones, R. Gomez Arrayas, J. C. Carretero, *Angew. Chem. Int. Ed.* **2011**, *50*, 10927; c) J. Esquivias, R. Gómez Arrayás, J. C. Carretero, *Angew. Chem.* **2006**, *118*, 645.

[9] G. Rousseau, B. Breit, *Angew. Chem. Int. Ed.* **2011**, *50*, 2450.



Scheme 57. Synthesis of substrate **31**

With the starting material **31** now in hand, we conducted the typical reaction with benzaldehyde using our conditions (Scheme 58). No reaction occurred and as before, starting materiel **31** and benzyl alcohol **29** were recovered.



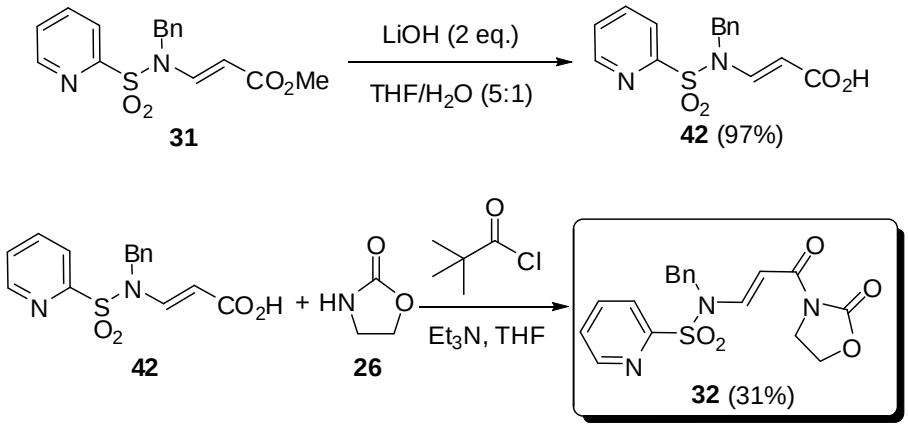
Scheme 58. Testing substrate **31** in our reaction conditions

III.3.2.3. Synthesis and Reactivity of 32

Much to our disappointment, the chemoselectivity is still causing a huge problem. However we didn't give up that easily on this type of substrates. We thought that if we replaced the methyl ester function in **31** with a chelating group, we could stabilize the second step in our catalytic cycle (the attack of the copper enolate **C**, see Scheme 44), and thus drive forward the desired domino reaction. Indeed, if the copper enolate intermediate is stabilized, it could pull the equilibrium towards the formation of this enolate and its subsequent addition to the aldehyde, despite the low affinity of the

copper hydride for the conjugate reduction of the Michael acceptor. As a result, we chose oxazolidinone **26** to replace the OMe group of the ester (Scheme 59). Furthermore, acyl oxazolidinone groups are considered equivalents of ketones in terms of their electron withdrawing capacity, which will consequently increase the elecetrophilic character of the conjugated double bond.

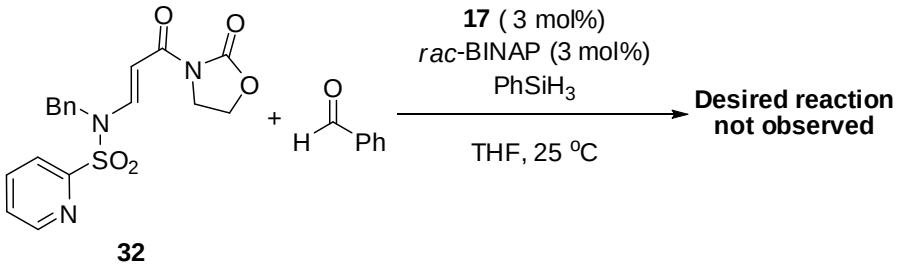
Consequently, substrate **31** was hydrolyzed in typical basic conditions to form the corresponding acid **42** in a 97% yield. Acid **42** was later coupled with oxazolidinone **26** using a modified literature procedure *via* an *in situ* mixed anhydride to generate the desired product **32** in a 31% yield (Scheme 59).[10]



Scheme 59. Synthesis of substrate **32**

Substrate **32** was then put in the presence of benzaldehyde and our copper hydride complex (Scheme 60). Unfortunately, no reaction was observed and again **32** and benzyl alcohol **29** were recovered at the end of the reaction.

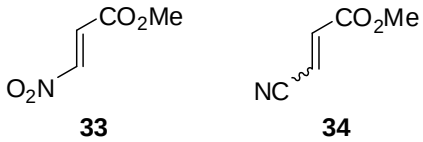
[10] S. Nakamura, F. Kikuchi, S. Hashimoto, *Tetrahedron: Asym.* **2008**, *19*, 1059.



Scheme 60. Testing substrate **32** in our reaction conditions

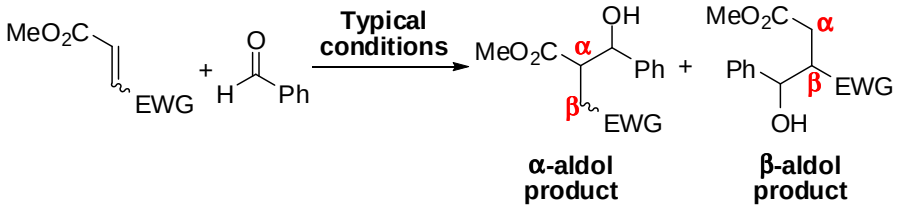
III.3.2.4. Synthesis and Reactivity of 33 and 34

After all these unsatisfactory results, we needed a radical change in our strategy. As a result, we started thinking that an electron withdrawing nitrogen group could solve our problem regarding the poor electrophilic character of the nitrogen substituted double bonds. Two groups emerged as likely candidates; a nitro group (NO_2) and a nitrile group (CN) (Scheme 61).



Scheme 61. The two new substrates that were envisioned

These groups are well known as strong electron withdrawing groups (EWGs). Nonetheless, putting a strong EWG at that position will most likely change the reactivity of the domino reaction, more specifically the regioselectivity of the copper hydride could be altered (Scheme 62).

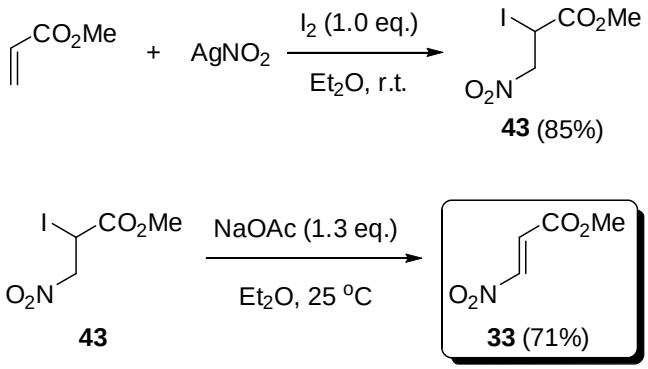


Scheme 62. Possible regioselectivity for the new substrates

As shown in Scheme 62, the aldolisation reaction could occur α to the ester as originally planned (α-aldol product) and/or β to the ester (β-aldol product). It all depends on the regioselectivity of the copper hydride as it will add to the β-position of the strongest of the two EWGs (CO_2Me is also considered an EWG). Reduction of nitro and nitrile acrylates with copper hydride complexes is documented in the literature. This regioselectivity isn't really that inconvenient as both products could be of interest to us (as long as only one of the two could be obtained selectively).

III.3.2.4.1. Synthesis of 33

Substrate **33** was prepared according to a modified literature procedure starting from methyl acrylate (Scheme 63).[11] The latter is added to a solution of silver nitrite and iodine in diethyl ether to generate intermediate **43** in an 85% yield. This product is poorly stable and has to be used in the next step immediately. Reaction of **43** with sodium acetate yields 71% of the desired olefin **33** *via* elimination.

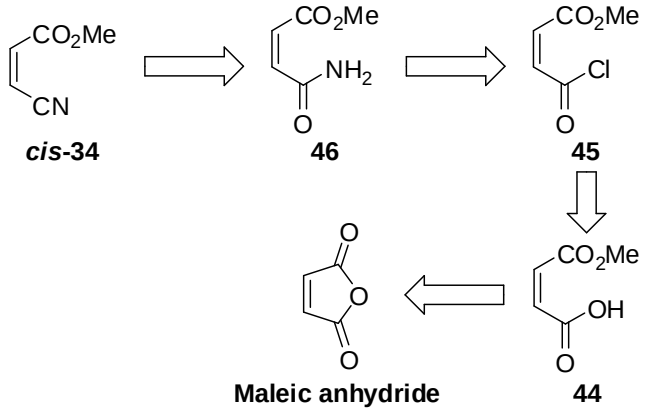


Scheme 63. Synthesis of substrate **33**

[11] K. Itoh, K. Kitoh, S. Kishimoto, *Can. J. Chem.* **2006**, *84*, 392.

III.3.2.4.2. Synthesis of 34

Substrate **34** is different from the other substrates synthesized up to now. It is the first substrate that doesn't have the nitrogen atom directly linked to the double bond. In fact, the nitrogen is separated from the double bond by the carbon atom of the nitrile group. However, this class of substrates remains quite interesting to our plans. The literature on the synthesis of such substrates is quite old and scarce. The first route that we investigated employs commercially available maleic anhydride as the starting material (Scheme 64). This method only allows access to the *cis* substrate (***cis*-34**).[12]



Scheme 64. Retrosynthesis of substrate ***cis*-34**

Maleic anhydride was thus heated at 50 °C in methanol to form product **44** in a quantitative yield. Only the *cis* isomer of **44** was observed. Several attempts were subsequently made to isolate the corresponding acyl chloride **45** which all turned out to be unfruitful (Scheme 65). The *in situ* generation of **45** and subsequent trapping with ammonia was also unsuccessful.

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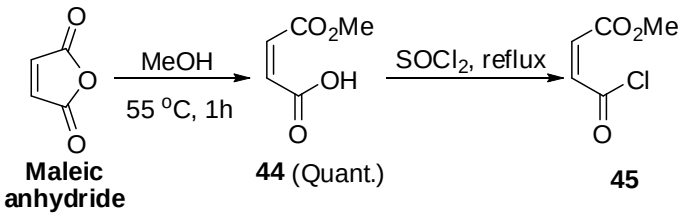
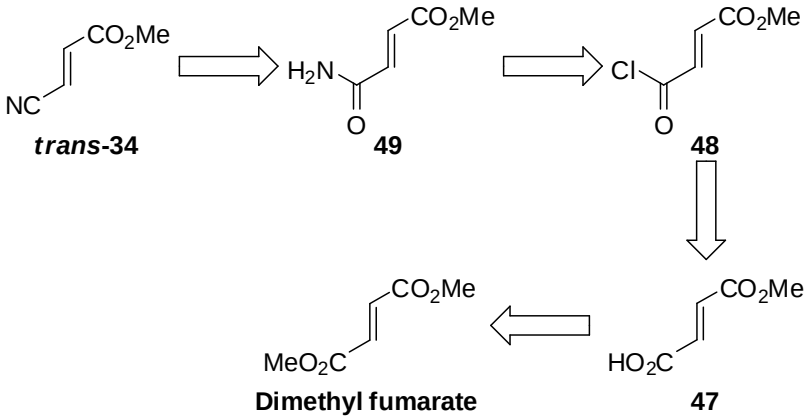
[12] M. Drescher, F. Hammerschmidt, *Monatshefte für Chemie* **1997**, *128*, 713, and references cited therein.



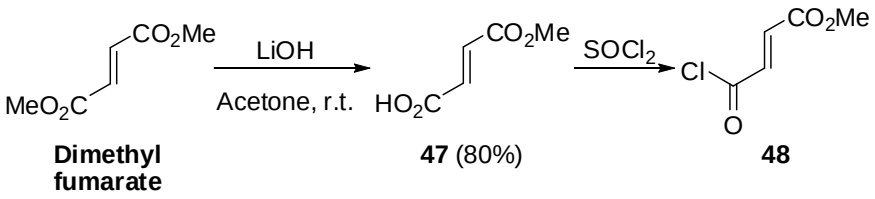
Scheme 65. Attempt to synthesis substrate ***cis*-34**

The second approach that we tested uses commercially available dimethyl fumarate as a starting material for substrate **34** (Scheme 66). This pathway resembles the first one we describe above but only allows access to the *trans* substrate (***trans*-34**).



Scheme 66. Retrosynthesis of substrate ***trans*-34**

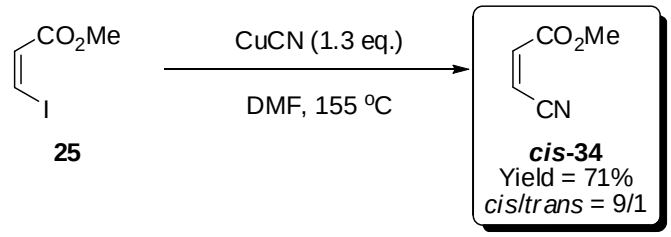
Hydrolysis of dimethyl fumarate in typical basic conditions furnishes the corresponding acid **47** in an 80% yield. Only the *trans* isomer of **47** is observed. As earlier, attempts to isolate the corresponding acyl chloride **48** were all futile (Scheme 67).



Dimethyl fumarate **47** (80%) **48**

Scheme 67. Attempt to synthesis substrate ***trans*-34**

Undeterred by these poor results we decided to design our own pathway for the synthesis of **34**. The *cis*-iodovinylic ester **25** was prepared as previously described (see Scheme 50) and then refluxed with copper cyanide in dimethylformamide (DMF) to afford the desired product ***cis*-34** in a 71% yield (Scheme 68). Interestingly, the *cis* geometry is conserved and a very good *cis*/*trans* ratio was obtained (9/1).



25

Scheme 68. New synthesis of substrate ***cis*-34**

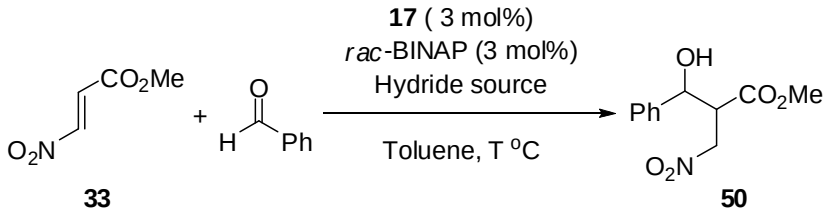
The *trans* isomer of substrate **34** was not synthesized but we were confident that the same methodology could also be applied starting from the *trans* isomer of **25**. We wanted to see the reactivity of such substrates before committing to this endeavour.

III.3.2.4.3. Catalytic Tests

Substrate **33** was put in the presence of benzaldehyde and our copper hydride complex (Table 4). Phenylsilane as well as pinacolborane were used as hydride sources. Despite our efforts, the desired product **50** was not observed. Nevertheless, a new observation was noted as the starting material

was not recovered. We concluded that substrate **33** must have been too reactive and most likely very unstable which resulted in its degradation or even its auto condensation.

Table 4. Testing substrate **33** in our reaction conditions



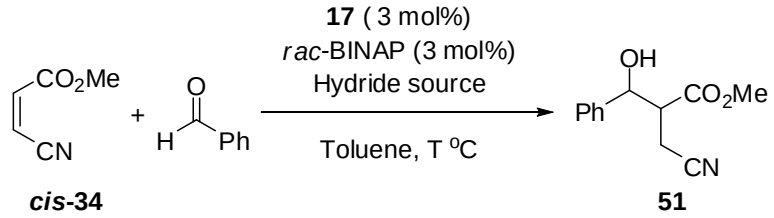
33 **50**

Entry[a]	T (°C)	Hydride source	50[b] (%)
1	r.t.	$PhSiH_3$	0
2	r.t.	Pinacolborane	0

[a] All reactions were run under argon [b] Determined on the crude mixture by ^1H NMR relative to the starting material **33**.

Afterwards we tested substrate ***cis*-34** in the same conditions using phenylsilane as a hydride source (Table 5). At room temperature, no reaction was observed along with degradation of the starting material (Table 5, entry 1). We tried to slow down the degradation side reactions by decreasing the temperature of the reaction (Table 5, entry 2). Unfortunately, even at -78 °C degradation of the starting material was still observed.

Table 5. Testing substrate ***cis*-34** in our reaction conditions



***cis*-34** **51**

Entry[a]	T (°C)	Hydride source	51[b] (%)
1	r.t.	$PhSiH_3$	0
2	-70	$PhSiH_3$	0

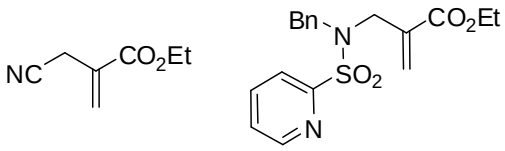
[a] All reactions were run under argon [b] Determined on the crude mixture by ^1H NMR relative to the starting material ***cis*-34**.

In conclusion we noticed that these substrates are clearly too unstable in our reaction conditions. Although, the chemoselectivity seems to be on the right track, the stability of the intermediates is quite low.

III.3.2.5. Synthesis and Reactivity of 35 and 36

After the previous results, we were convinced that placing the nitrogen moiety on the β-position of the ester is probably not the best approach. As observed earlier, the nitrogen moiety is either too sterically hindered to react or too electronically unstable resulting in degradation. For that reason, we altered our strategy and moved the nitrogen moiety to the other side of the double bond (onto the α-position of the ester). Thus, the β-position of the ester is now free from substitution and electronic interference.

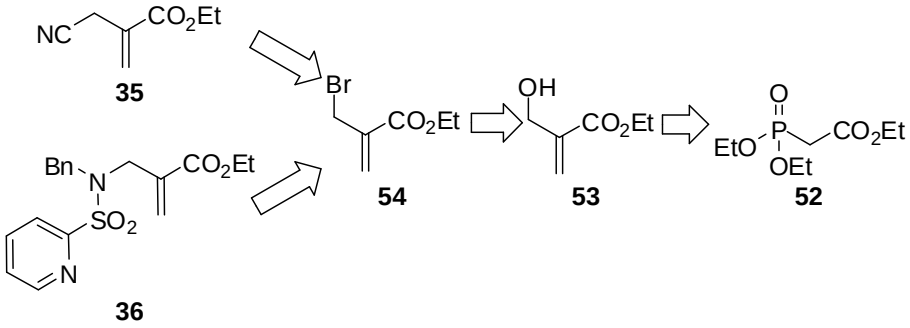
As a result, our new aim was to synthesize substrate **35** and **36** and later test these substrates in our reaction conditions. As seen in Scheme 69, these two substrates are not directly connected to the double bond as we wanted to avoid any electronic interference from the nitrogen motif.



35 **36**

Scheme 69. Substrates **35** and **36**

Substrates **35** and **36** were thought to be synthesized from the same synthon **54**, using a modified literature procedure.[13] In order to accomplish that, synthon **54** is to be prepared in two steps from the commercially available starting material **52** (Scheme 70).

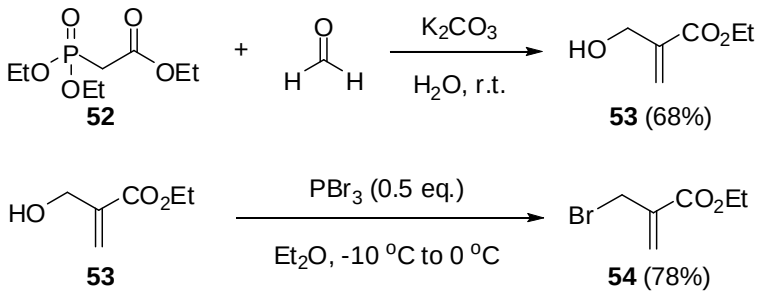


Scheme 70. Common retrosynthesis of substrates **35** and **36**

Following this strategy, substrate **52** is transformed to product **53** by a Horner-Wadsworth-Emmons reaction (or HWE reaction) in the presence of paraformaldehyde. Product **53** is thus isolated in a 68% yield and then used in a substitution reaction using phosphorus tribromide in ether. The hydroxy function is replaced by bromide to yield the desired synthon **54** in a 78% yield (Scheme 71).

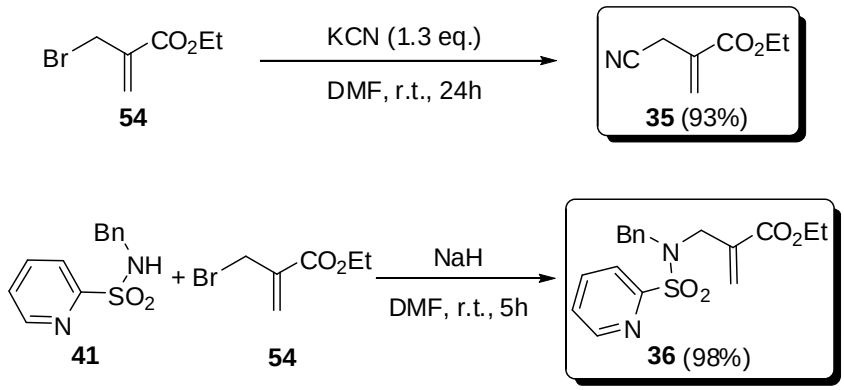
---

[13] a) W. R. Robert, H. S. Louis, P. G. Nicholas, P. Reuben *J. Org. Chem.*, **1963**, *28*, 2835; b) A. F. Ferris, *J. Org. Chem.*, **1955**, *20*, 780.



Scheme 71. Synthesis of synthon **54**

With substrate **54** in hand, we endeavoured on the synthesis of **35** and **36**. Substrate **35** was obtained in a 93% yield by reacting **54** with potassium cyanide in DMF (Scheme 72). This substitution reaction worked very well and a slightly modified procedure was consequently applied to the synthesis of **36**. Previously prepared substrate **41** was deprotonated with sodium hydride, and then engaged with **54** in a substitution reaction to furnish the desired product **36** in a 98% yield (Scheme 72).



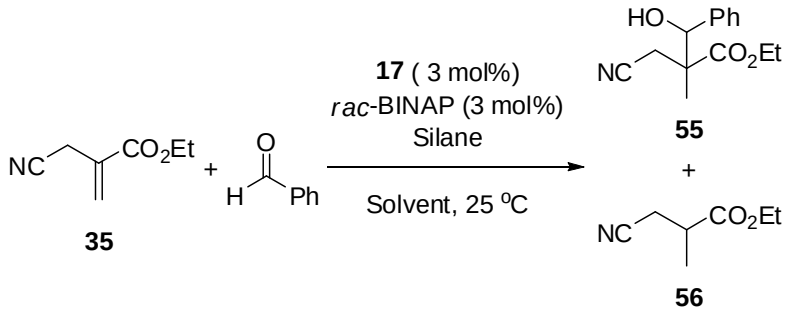
Scheme 72. Synthesis of substrates **35** and **36**

Now that the two substrates have been synthesized successfully, we started testing them in our reaction conditions.

The first to be engaged with our copper hydride complex and in the presence of benzaldehyde was substrate **35** (Table 6). Standard conditions using

toluene as solvent didn't lead to the formation of the desired product but nevertheless no starting material was observed (Table 6, entry 1). Varying the silane as well as changing the solvent to tetrahydrofuran (THF) didn't work either (Table 6, entries 2-4). In all these cases, starting material **35** was not observed and only traces of benzyl alcohol **29** and the reduced product **56** were found (derived from the reduction of benzaldehyde and substrate **35**, respectively). However, in entry 2 (Table 6), the reduction product was observed along with an unidentified product (U.P.). Despite our best efforts, we weren't able to cleanly isolate these two products for a clear identification.

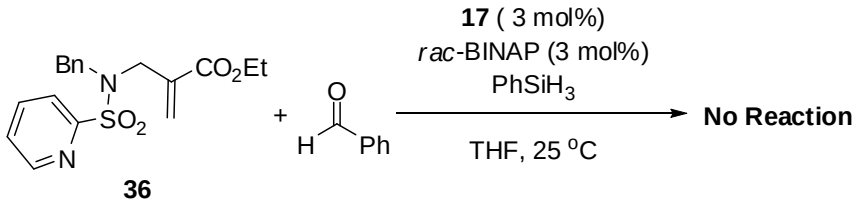
Table 6. Testing substrate **35** in our reaction conditions



Entry[a]	Solvent	Silane	55[b] (%)	56[b] (%)
1	Toluene	$PhSiH_3$	0	0
2	THF	$PhSiH_3$	U.P.[c]	n.d.[d]
3	THF	Me_2PhSiH	0	n.d.[d]
4	THF	$Me(EtO)_2SiH$	0	n.d.[d]

[a] All reactions were run under argon [b] Determined on the crude mixture by ^1H NMR [c] U.P. = unidentified product [d] n.d. = not determined.

Substrate **36** was later used in the same reaction conditions (Scheme 73). Unfortunately, no reaction was observed and again **36** and benzyl alcohol **29** were recovered at the end of the reaction.

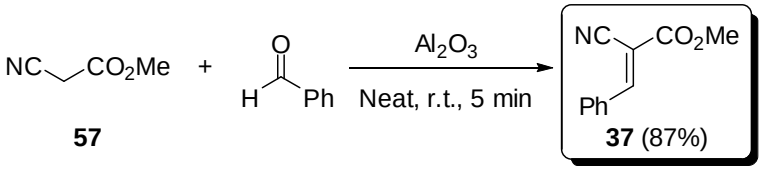


Scheme 73. Testing substrate **36** in our reaction conditions

III.3.2.6. Synthesis and Reactivity of 37

Faced with the disappointing fail of all our previous strategies, we turned to more activated Michael acceptors; the α,β-unsaturated malonates. This class of substrates are well known in the literature as powerful Michael acceptors and has been successfully used in an intramolecular version of the copper catalyzed domino 1,4-reduction/aldolisation.

As a result, we set out to synthesize substrate **37** starting from the commercially available methyl cyanoacetate **57** (Scheme 74).[14] The latter was added to benzaldehyde at room temperature, followed by alumina powder. After subsequent workup and purification, the desired product is isolated in 87% yield.

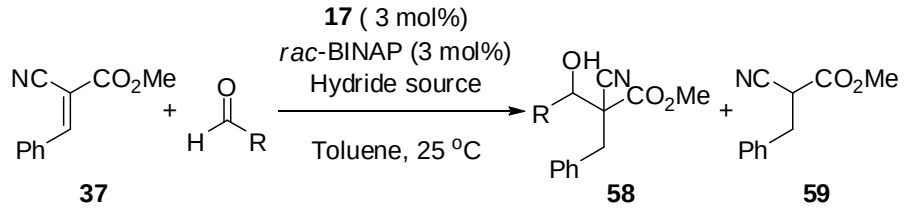


Scheme 74. Synthesis of substrate **37**

[14] F. Texier-Boullet, A. Foucaud, *Tetrahedron Lett.* **1982**, *23*, 4927.

Afterwards, we started testing substrate **37** in our typical conditions (Table 7). For the first time, we clearly observed the reduction product **59** and were able to isolate it in a 92% yield using pinacolborane as the hydride source (Table 7, entry 2). But still the desired product **58** was not observed. We argued that the copper enolate is now highly stabilized by the two EWGs (CN and CO_2Me) and thus less reactive towards benzaldehyde. For that reason, benzaldehyde was replaced with ethyl glyoxalate, a more reactive aldehyde. As seen in entry 3 (Table 7), this alteration did not solve the problem as no aldolisation product was observed. The starting material **37** was recovered along with traces of the reduction product **59**.

Table 7. Testing substrate **37** in our reaction conditions



37 **58** **59**

Entry[a]	R	Hydride source	58[b] (%)	59[c] (%)
1	Ph	$PhSiH_3$	0	52
2	Ph	Pinacolborane	0	92
3	CO_2Et	Pinacolborane	0	n.d.[d]

[a] All reactions were run under argon [b] Determined on the crude mixture by ^1H NMR [c] Isolated yields [d] n.d. = not determined.

IV. Conclusions and Perspectives

Unfortunately, all the substrates that we tested did not provide any substantial results. The problem with this reaction seems to be the choice of the starting material rather than the catalytic conditions. Several factors must be taken into account:

• If the copper enolate formed *in situ* is very stable, it may not react with the aldehyde.

• If the enolate is very unstable, the starting material may decompose or even polymerize.

• The presence of the nitrogen in the β-position of the Michael acceptor can disable the electrophilic character of the double bond vis-à-vis the attack of the copper hydride.

• The reactivity of the copper hydride seems intimately related to the steric hindrance, thus we can postulate that substrates with the *cis* stereochemistry will react better than those with the *trans* one.

Untill now, only one study by Buchwald[7] *et al* on the conjugated reduction of acrylate derivatives, bearing a nitrogen atom in the β-position, is known. The nitrogen motifs in this paper are lactams and aromatic heterocycles (pyrroles and indoles). The lone pair of the nitrogen is thus well dispersed so that it won't interfere with the electrophilic character of the double bond (Figure 7). Furthermore, the substrates employed are all of a *cis* stereochemistry, which clearly states that steric hindrance plays an important role in the approach of the copper hydride complex.

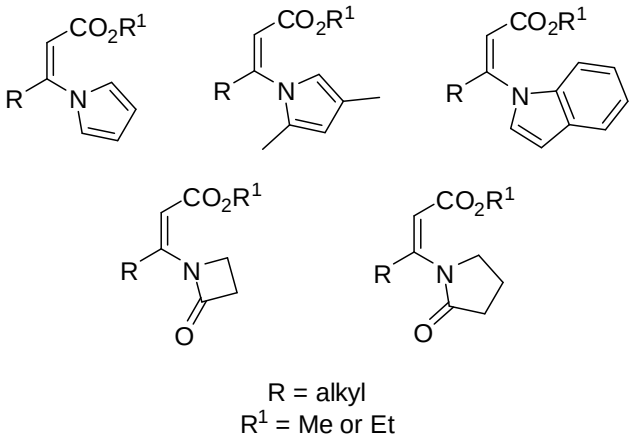


Figure 7. Substrates employed by Buchwald[7] *et al*

In the future, it will be interesting to repeat these tests on substrates possessing a *cis* stereochemistry such as ***cis*-22** but with more dispersed electronic density (most likely aromatic nitrogen motifs). Another interesting approach could be replacing the ester moiety on substrates such as substrates ***cis*-22** or **30** with a more powerful EWG such as nitrile or a nitro group. This way we could have a more balanced class of substrates somewhere in between the non reactive **30** and the highly reactive **33** and **34**.

Another practical approach to this dilemma could be changing our current copper hydride complex. As seen in Scheme 38 (see bibliographic introduction), we have already developed another catalytic system for this type of domino reaction using IMesCuDBM (an NHC copper complex). Although in most cases this new copper system has proven to be more selective, chiral induction with this type of catalysts is more complicated. Indeed only a few chiral NHCs have been described to date due to the complicated synthesis of such ligands. Commercial unavailability of these ligands compared to phosphines plays an important role as well.

Chapter 2: Cu^{I}/Pd^{0} Cooperative Dual Catalysis

I. Bibliographic Introduction

The development of new catalytic methods has been an area of intense research in recent years. It is becoming more and more vital to develop new forms of catalysis that enable easy and reproducible access to otherwise difficult to obtain products. The most recent idea to emerge is the combination of two or more different catalysts in a single vessel to promote domino reactions.[1]

In most domino reactions, a single catalyst is used to promote two or more reactions in a specific order.[2] The significant drawback of this approach is the limited type of reactions that a particular catalyst could undergo. By combining two catalysts, the range of transformations, that could be achieved, is thus expanded.[3] Different types of dual catalysis have been recently reported in the literature; Organocatalysis/metallocatalysis,[4]

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[1] a) For a review on cooperative multicatalyst systems for one-pot organic transformations, see: J. M. Lee, Y. Na, H. Han, S. Chang, *Chem. Soc. Rev*. **2004**, *33*, 302-312. b) For a review on current tandem catalysis, see: J.-C. Wasilke, S. J. Obrey, R. T. Baker, G. C. Bazan, *Chem. Rev.* **2005**, *105*, 1001-1020.

[2] a) A. Bruggink, R. Schoevaart, T. Kieboom, *Org. Process Res. Dev.* **2003**, *7*, 622-640; b) L. M. Ambrosini, T. H. Lambert, *ChemCatChem* **2010**, *2*, 1373-1380; c) D. B. Ramach- ary, S. Jain, *Org. Biomol. Chem.* **2011**, *9*, 1277-1300.

[3] a) S. Kamijo, Y. Yamamoto, in *Multimetallic Catalysis in Organic Synthesis* (Eds.: M. Shibasaki, Y. Yamamoto), WILEY-VCH, Weinheim, **2004**, pp. 1-52; b) M. H. Pérez-Temprano, J. Casares, P. Espinet, *Chem. Eur. J.* **2012**, *18*, 1864-1884; c) J. J. Hirner, Y. Shi, S. A. Blum, *Acc. Chem. Res.* **2011**, *44*, 603-613.

[4] a) Y. J. Park, J.-W. Park, C.-H. Jun, *Acc. Chem. Res.* **2008**, *41*, 222-234; b) Z. Shao, H. Zhang, *Chem. Soc. Rev.* **2009**, *38*, 2745-2755; c) M. Rueping, R. M. Koenigs, I. Atodiresei, *Chem. Eur. J.* **2010**, *16*, 9350-9365; d) D. DiRocco, T.

biocatalysis/metallocatalysis[5] and metallocatalysis/metallocatalysis.[6] As stated before in the general introduction, we are only interested in the transition metal/metal catalysis as this is the only type of catalysis undertaken in this project.

In the majority of examples in which two metals are used, the first metal generates the active species which undergoes the reaction and affords the desired product. Whereas the second metal is present either to regenerate the first metal's active species or to transmetallate as is the case of the majority

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Rovis, *J. Am. Chem. Soc.* **2012**, *134*, 8094-8097; e) Z. Chai, T. Rainey, *J. Am. Chem. Soc.* **2012**, *134*, 3615-3618; f) Y. Ye, M. Sanford, *J. Am. Chem. Soc.* **2012**, *ASAP*, dx.doi.org/10.1021/ja301553c.

[5] a) O. Pamies, J.-E. Baeckvall, *Chem. Rev.* **2003**, *103*, 3247-3261; b) C. Zhong, X. Shi, Euro. *J. Org. Chem.* **2010**, *16*, 2999-3025; c) J. H. Lee, K. Han, M.-J. Kim, J. Park, Euro. *J. Org. Chem.* **2010**, *6*, 999-1015; d) B. L. Conley, M. K. Pennington-Boggio, E. Boz, T. J. Williams, *Chem. Rev.* **2010**, *110*, 2294-2312; e) A. C. Marr, S. Liu, *Trends Biotechnol.* **2011**, *29*, 199-204.

[6] a) J. Cossy, F. Bargiggia, S. BouzBouz, *Org. Lett.* **2003**, *5*, 459-462; b) Y. Nishibayashi, M. Yoshikawa, Y. Inada, M. Hidai, S. Uemura, *J. Am. Chem. Soc.* **2004**, *126*, 16066-16072; c) A. S. Goldman, A. H. Roy, Z. Huang, R. Ahuja, W. Schinski, M. Brookhart, *Science* **2006**, *312*, 257- 261; d) T. A. Cernak, T. H. Lambert, *J. Am. Chem. Soc.* **2009**, *131*, 3124-3125; e) K. Takahashi, M. Yamashita, T. Ichihara, K. Nakano, K. Nozaki, *Angew. Chem.* **2010**, *122*, 4590-4592; *Angew. Chem. Int. Ed.* **2010**, *49*, 4488-4490; f) M. Kuriyama, T. Takeichi, M. Ito, N. Yamasaki, R. Yamamura, Y. Demizu, O. Onomura, *Chem. Eur. J.* **2012**, *18*, 2477-2480; g) K. Motoyama, M. Ikeda, Y. Miyake, Y. Nishibayashi, *Organometallics* **2012**, *31*, 3426-3430; h) E. Skucas, D. Macmillan, *J. Am. Chem. Soc.* **2012**, *ASAP*, dx.doi.org/10.1021/ja303116v; i) J. Park, S. Hong, *Chem. Soc. Rev.* **2012**, *ASAP*, 10.1039/c2cs35129c.

of C-C couplings. The most interesting approach to this type of metal/metal catalysis is the cooperative dual catalysis.[6g,7] In this case, the two catalysts separately and selectively activate two different substrates, catalytically generating two active intermediates that could subsequently react to form the desired product. The formation of the final product is generally coupled with simultaneous regeneration of the catalysts. This type of dual catalysis is still underdeveloped and only a few examples have been reported.[7] A major contributing factor is that the catalytic intermediates, that would be formed, could react with the reagents present in stoichiometric amounts, thus generating side reactions and undesired products, rendering the reaction very difficult to control.

This type of catalysts has only a few examples in the literature due to the known difficulties encountered with various metal couplings. And even fewer examples exist where enantioselectivity is induced by this methodology.[8] Herein, we describe some of the most noticeable work done in this field in order to give some idea of the current research's spectrum of interest.

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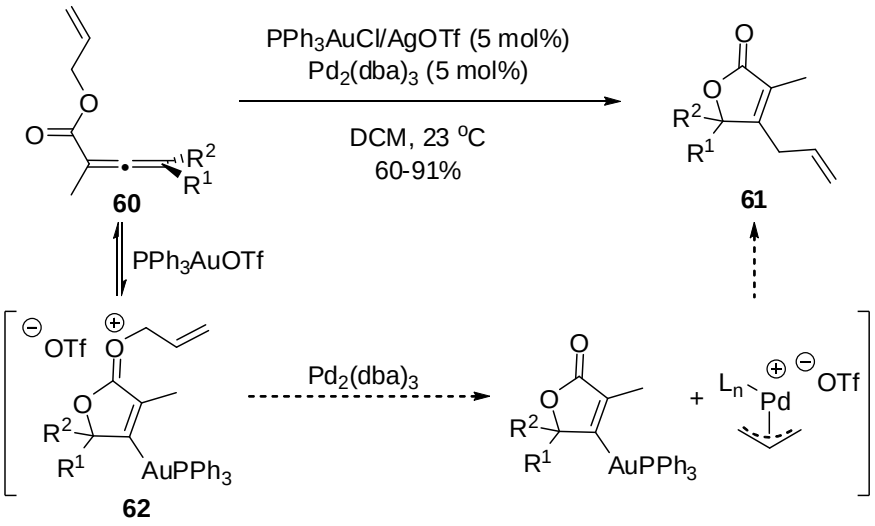
[7] a) M. Sawamura , M. Sudoh, Y. Ito, *J. Am. Chem. Soc.* **1996**, 118, 3309-3310; b) B. Trost, X. Luan, *J. Am. Chem. Soc.* **2011**, *133*, 1706-1709; c)B. Trost, X. Luan, Y. Miller, *J. Am. Chem. Soc.* **2011**, *133*, 12824-12833; d) J. Panteleev, L. Zhang, M. Lautens, *Angew. Chem. Int. ed.* **2011**, *50*, 9089-9092; e) E. Shirakawa, D. Ikeda, S. Masui, M. Yoshida, T. Hayashi, *J. Am. Chem. Soc.* **2012**, *134*, 272-279; f) Z. Gu, A. T. Herrmann, A. Zakarian, *Angew. Chem. Int. Ed.* **2011**, *50*, 7136-7139.

[8] a) A. E. Allen, D. W. Macmillan, *Chem. Sci.* **2012**, *2012*, 633; b) N. T. Patil, V. S. Shinde, B. Gajula, *Org. Biomol. Chem.* **2012**, *10*, 211; c) J. M. Lee, Y. Na, H. Han, S. Chang, *Chem. Soc. Rev.* **2004**, *33*, 302; d) R. C. Wende, P. R. Schreiner, *Green Chem.* **2012**, *14*, 1821.

I.1. Transition Metal/Metal Catalysts in the Literature

I.1.1. Application to Achiral Reactions

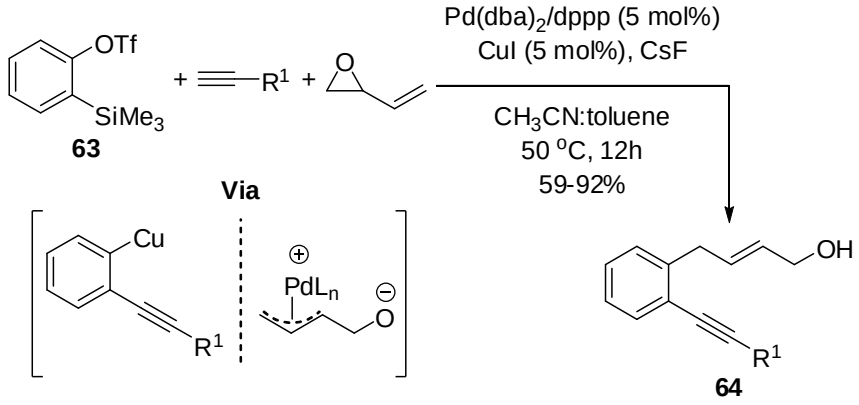
In 2009, Blum and co-workers[9] investigated the cooperative catalytic process consisting of carbophilic Lewis acidic Au-catalyst and Lewis basic Pd-catalyst that afforded substituted butenolides **61** from allenoate **60** (Scheme 75). The proposed mechanism involves Au^{I}-catalyzed intramolecular oxy-auration in allenoate that produces the allyl oxonium ion intermediate **62**. Deallylation of **62** by Pd^{0} affords two catalytic species and subsequent coupling of these species affords the desired product **61**. Several examples underwent the reaction successfully generating high yields; thus establishing a fundamental pattern of a cooperative dual catalytic cross-coupling reaction with a Au/Pd binary system.



Scheme 75. Blum *et al*'s binary catalytic system

[9] Y. Shi, K. E. Roth, S. D. Ramgren, S. A. Blum, *J. Am. Chem. Soc.* **2009**, *131*, 18022.

In yet another example, Cheng[10] *et al* reported a cooperative Pd^0 and Cu^I catalyzed highly regio and chemoselective three-component coupling reaction of benzyne, generated from **63**, terminal alkynes and 2-vinyloxirane to afford products **64** in moderate to good yields (Scheme 76). Although the three-component reaction also proceeds in the presence of the palladium complex alone without CuI, the dual metal catalytic system greatly enhances the regioselectivity of the reaction.



Scheme 76. Cheng *et al*'s Pd/Cu binary catalytic system

Later on, Hu and co-workers[11] reported a three component coupling reaction of α-diazoester **65** with 2-alkynylarylaldimines **66** and alcohols to afford 1,2-dihydroisoquinolines **67** using $Rh_2(OAc)_4$ and AgOTf (Scheme 77). Although the diastereoselectivity is still quite low, this powerful dual process allows access to highly functionalized 1,2-dihydroisoquinolines bearing an α-hydroxy-β-amino carboxylate skeleton in one step.

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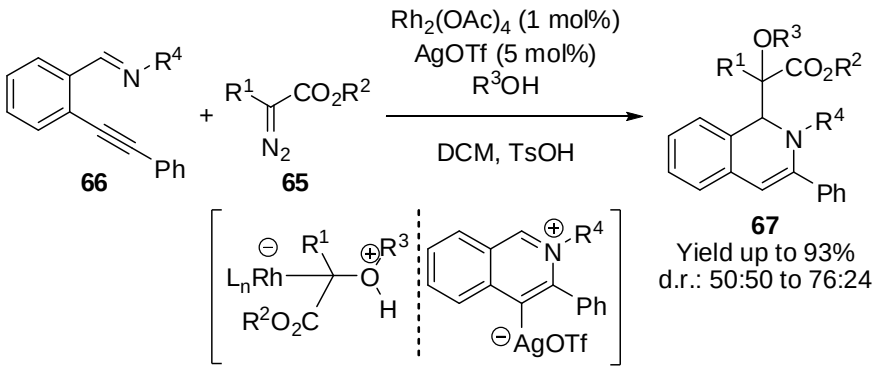
[10] M. Jeganmohan, S. Bhuvaneswari, C. H. Cheng, *Angew. Chem. Int. Ed.* **2009**, *48*, 391.

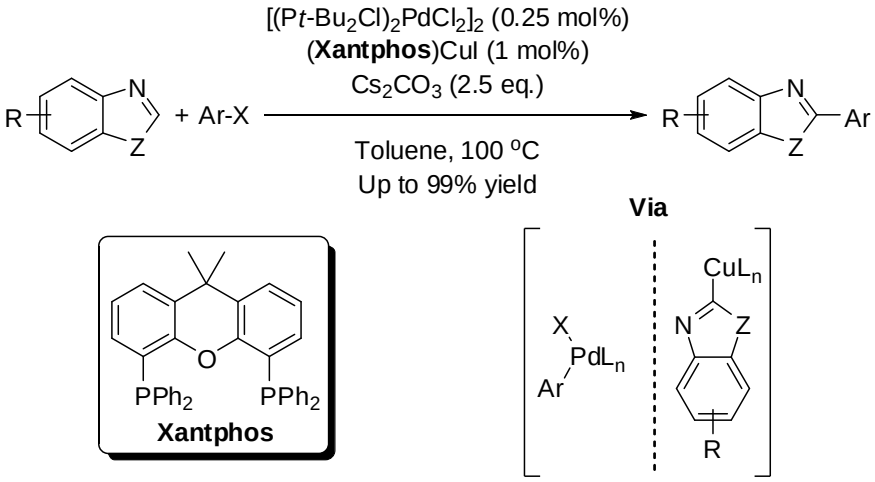
[11] Z. Guo, M. Cai, J. Jiang, L. Yang, W. Hu, *Org. Lett.* **2010**, *12*, 652.



Scheme 77. Hu *et al*'s Rh/Ag binary catalytic system

In 2010, Huang[12] *et al* reported a mild and efficient catalytic system for direct C-H activation/arylation of heteroarenes (Scheme 78). This new catalytic system has been demonstrated to be suitable for the couplings of a broad range of substrates. Notable features of this system include the unprecedented high efficiency achieved by very low metal loadings, which is attributed to the cooperation of the Cu/Pd dual metal system.

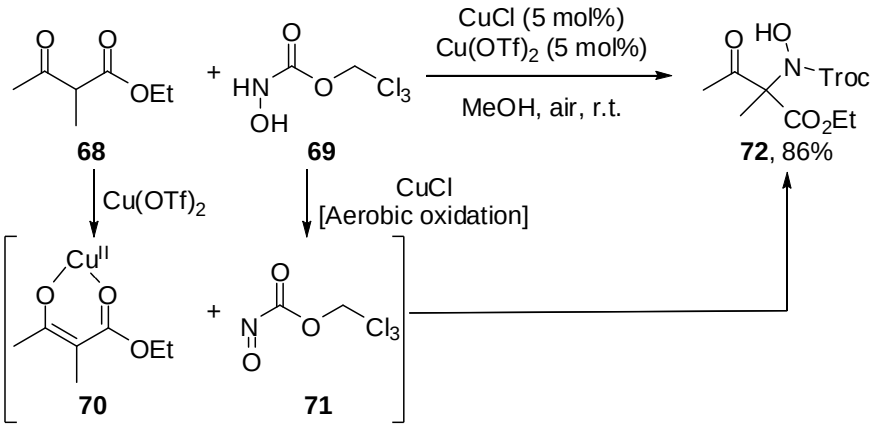
[12] J. Huang, J. Chan, Y. Chen, C. J. Borths, K. D. Baucom, R. D. Larsen, M. M. Faul, *J. Am. Chem. Soc.* **2010**, *132*, 3674.



Scheme 78. Huang *et al*'s Pd/Cu dual metal system

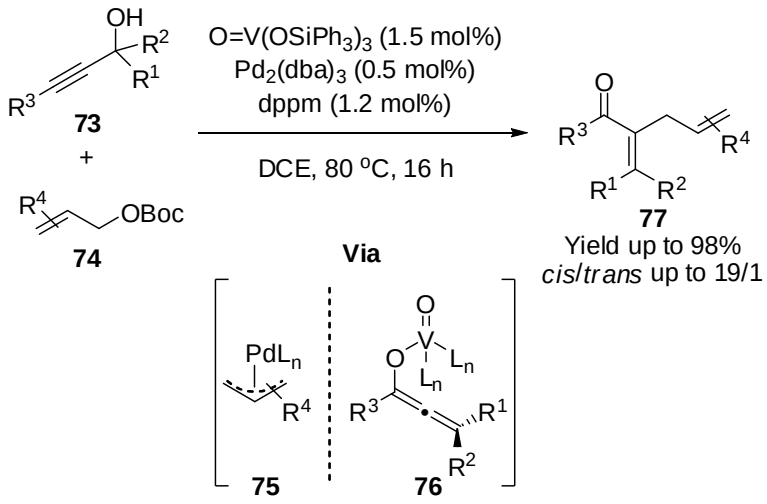
In a beautiful example of the synthetic utility of such a methodology, Read de Alaniz[13] *et al* developed a binary Cu^{I}/Cu^{II} catalytic system, whereas two oxidation states of the same metal catalyze the α-amination of a wide range of carbonyl compounds. The mechanism proposed by the authors involves the concurrent activation of β-ketoester **68** and hydroxylamine **69**. The former is activated by the Cu^{II} complex to form the nucleophilic enolate **70** and the latter generates the electrophilic nitrosoformate **71** via a Cu^{I}-catalyzed aerobic oxidation. The subsequent coupling of these two species furnishes the desired product **72** in 86% (Scheme 79).

[13] D. Sandoval, C. P. Frazier, A. Bugarin, J. Read de Alaniz, *J. Am. Chem. Soc.* **2012**, *134*, 18948.



Scheme 79. Read de Alaniz *et al*'s dual copper system

Very recently, Trost and Luan established a novel catalytic cooperative system by combining vanadium-catalyzed 1,3-transposition of propargyl alcohols **73** (Meyer–Shuster rearrangement) and a palladium-catalyzed alkylation of allylic carbonates **74** (Scheme 80).[7b,c] The authors reported the formation of products **77** from two highly reactive catalytic intermediates **75** and **76** by overcoming the other possible competing side reactions. The success of such a reaction shows the power of cooperative dual catalysis.

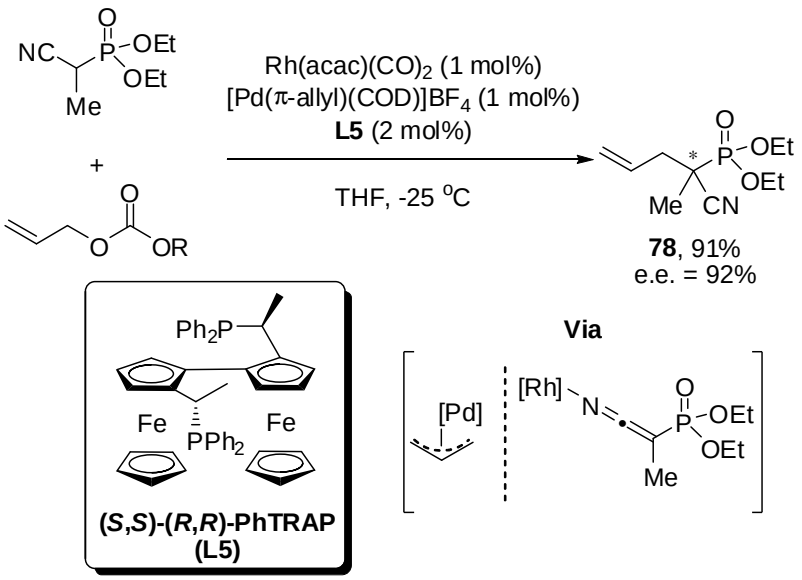


Scheme 80. Trost *et al*'s V/Pd binary catalytic system

I.1.2. Application to Enantioselective Reactions

Asymmetric processes using this methodology are highly scarce, and only a handful of examples exist in the literature nowadays. One of the early examples was reported in 1996 by Sawamura and Ito.[14] They developed the enantioselective allylation of α-cyano esters by a Rh/Pd dual metal system (Scheme 81). The reaction proceeds via a rhodium enolate addition onto a palladium π-allyl species generating the desired allylated α-cyano ester **78** in a 91% yield and 92% e.e..

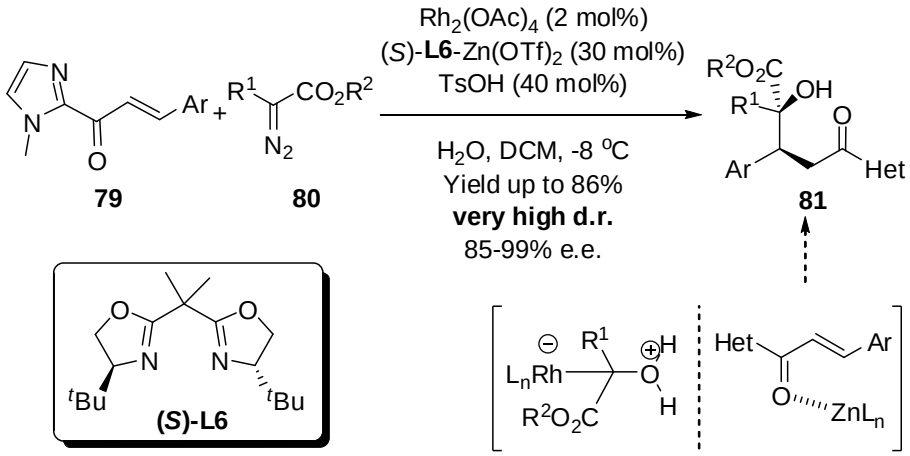
[14] M. Sawamura, M.Sudoh, Y. Ito, *J. Am. Chem. Soc.* **1996**, *118*, 3309.



Scheme 81. Sawamura and Ito's work on allylated α-cyano esters

Later on, Hu and co-workers[15] reported an enantioselective three component coupling reaction of conjugated enone **79**, water and α-diazoester **80** using the cooperative catalytic system consisting of $Rh_2(OAc)_4$ and (*S*)-**L6**-$Zn(OTf)_2$ to give γ-hydroxyketones **81** in good yields and with excellent enantioselectivities 85–99% (Scheme 82). This novel reaction provides an efficient route to γ-hydroxyketone derivatives containing a stereogenic quaternary carbon centre.

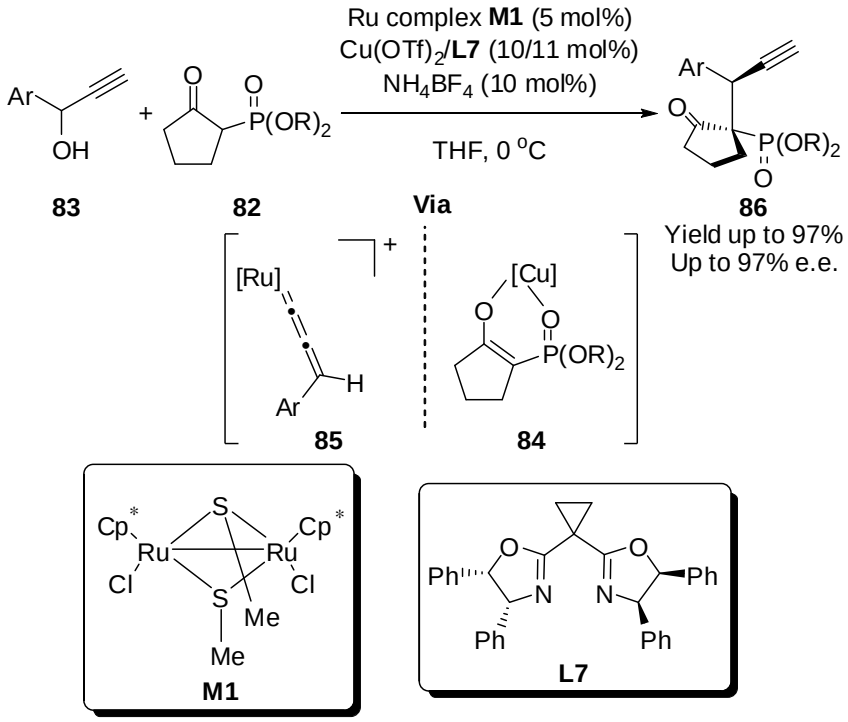
[15] X. Y. Guan, L. P. Yang, W. Hu, *Angew. Chem. Int. Ed.* **2010**, *49*, 2190.



Scheme 82. Hu *et al*'s Rh/Zn binary catalytic system

More recently, Nishibayashi[16] *et al* established an enantioselective propargylic alkylation of β-keto phosphonates **82** with propargylic alcohols **83**. The reaction is catalyzed by a Ru/Cu dual metal system to generate propargylic alkylated products **86** in excellent yields with high diastereo- and enantioselectivities. In this cooperative dual catalysis process, both the ruthenium complex and the copper complex activate propargylic alcohols and β-keto phosphonates, respectively. Consequently, copper enolate **84** and ruthenium-allenylidene **85** will cooperatively and simultaneously work to promote the propargylic alkylation enantioselectively. It should be noted that the propargylic alkylated products have a chiral tetrasubstituted carbon at the homopropargylic position.

[16] K. Motoyama, M. Ikeda, Y. Miyake, Y. Nishibayashi, *Organometallics* **2012**, *31*, 3426.



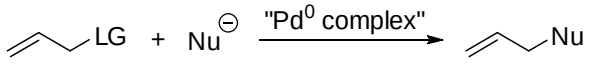
Scheme 83. Nishibayashi *et al*'s enantioselective propargylic alkylation

If we take a good look at all the examples illustrated above, we clearly see a pattern emerging. Seven of the nine examples mentioned contain a copper catalyst or a palladium catalyst or both. This observation actually propagates all over the literature, and it is not by coincidence. These two metals are highly versatile, compatible and tolerant towards a wide range of substrates and chemical transformations. These qualities make them a perfect match for cooperative catalysis. For that reason, we thought we could use this dual metal system to our advantage and thus apply it to a new catalytic process.

I.2. Pd^0-Catalyzed Asymmetric Allylic Alkylation

The catalytic dual process that we had in mind is the 1,4-reduction/allylation reaction. To our knowledge, this cooperative dual reaction has no precedent in the literature. However the two reactions separately have been intensively developed and studied in recent decades. As we already illustrated the history of the 1,4-reduction reaction in the previous chapter, we thought that an attempt to depict the Pd^0-catalyzed asymmetric allylic alkylation reaction (or AAA) should be made. This reaction has been mentioned numerous times in the recent literature, as it is one of the most used coupling reactions to form C-C, C-N and C-O bonds.[17]

The reagents involved in the AAA reaction are mostly stabilised nucleophiles such as dialkylmalonate reacting with electrophiles bearing an allylic leaving group such as carbonates, acetates and halogens (Scheme 84).



LG = OCO_2R, OAc, Br, I,

Scheme 84.

Due to the immensely rich background of this type of reactions, we won't be able to mention all of its developments. Instead, we wish to illustrate some of the key reactions that have influenced our work on this project as well as have marked the rise of this powerful strategy.

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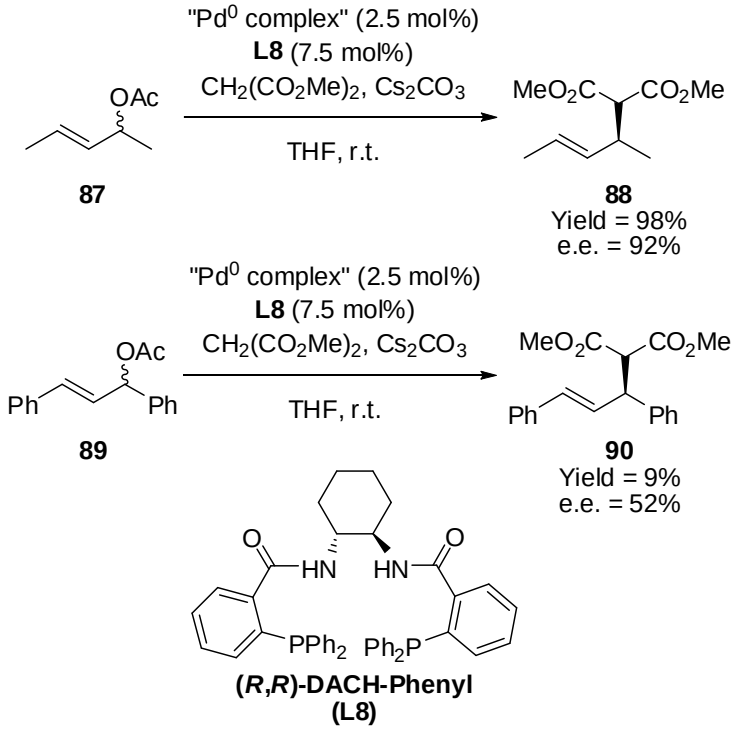
[17] a) B. Trost, G. Schroeder, *Chem. Eur. J.* **2004**, *11*, 174; b) B. M. Trost, *Chem. Pharm. Bull.* **2002**, *50*, 1; c) B. M. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395; d) B. M. Trost, *Acc. Chem. Res.* **1996**, *29*, 355; e) D. C. Behenna, Y. Liu, T. Yurino, J. Kim, D. E. White, S. C. Virgil, B. M. Stoltz, *Nature Chem.* **2012**, *4*, 130; f) F. R. Busch, G. A. Berchtold *J. Am. Chem. Soc.* **1983**, *105*, 3346.

I.2.1. Key Examples in the Literature

In early examples of this methodology, the main difficulty was to successfully convey the chiral information on the other side of the allylic system. Ligands such as diphosphines, which were successful in asymmetric hydrogenation reactions, failed in the AAA reaction because they couldn't influence the nucleophilic attack efficiently.

An effective class of diphosphines, which are able to overcome this problem, were later developed by Trost and co-workers (Scheme 85).[17c,d] They successfully demonstrated that malonates are competent nucleophiles for the deracemization of cyclic allylic acetates, to afford chiral malonate derivatives. This new kind of ligands (**L8**) afforded good levels of enantioselectivity for substrates such as 1,3-dimethylallyl acetate **87**, generating the desired allylated malonate **88** in 92% e.e.. However, 1,3-diarylallyl derivatives still afforded products with low enantioselectivity which affected this methodology's general application (e.g., 52% e.e. for **90**).



Scheme 85. The AAA reaction pioneered by Trost *et al*

To overcome this problem, another class of ligands was developed independently by Helmchen,[18] Pfalz[19] and Williams[20] and later on by Stoltz.[17e,21] This new type of ligands (**L9**) turned out to be somewhat

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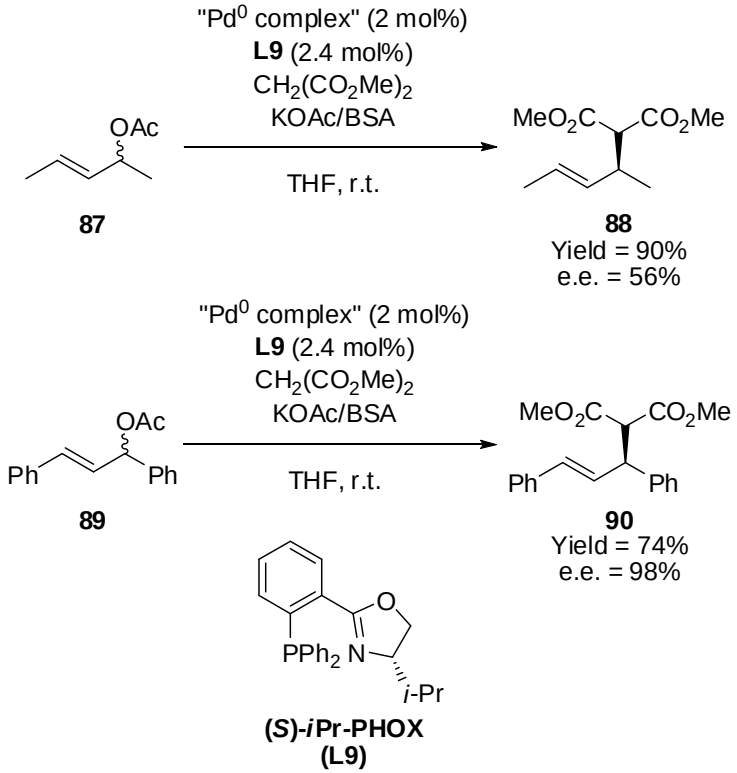
[18] J. Sprinz, G. Helmchen, *Tetrahedron Lett.* **1993**, *34*, 1769.

[19] P. Vonmatt, A. Pfaltz, *Angew. Chem. Int. Ed.* **1993**, *32*, 566.

[20] a) S. J. Coote, G. J. Dawson, C. G. Frost, J. M. J. Williams, *Synlett* **1993,** 509; b) G. J. Dawson, C. G. Frost, J. M. J. Williams, *Tetrahedron Lett.* **1993**, *34*, 3149.

[21] a) K. Tani, D. C. Behenna, R. M. McFadden, B. M. Stoltz, *Org. Lett.* **2007**, *9*, 2529; b) D. C. Behenna, B. M. Stoltz, *J. Am. Chem. Soc.* **2004**, *126*, 15044; c) D. C. Behenna, B. M. Stoltz, J. T. Mohr, A. M. Harned, US Patent, 0,084,820, **2006**; d) A. Y. Hong, M. R. Krout, T. Jensen, N. B. Bennett, A. M. Harned, B. M. Stoltz,

complementary to the Trost-type ligands (**L8**). For example, the 1,3-dimethylallyl acetate **87** engaged with ligand **L9** afforded product **88** with a rather modest enantioselectivity (56% ee) in comparison to the Trost ligand **L8** (92% e.e.). Whereas the 1,3-diphenylallyl acetate **89** gave a higher enantioselectivity with **L9** (98% e.e.) than that obtained with **L8** (52% e.e.).



Scheme 86. Application of the PHOX ligand to the AAA reaction

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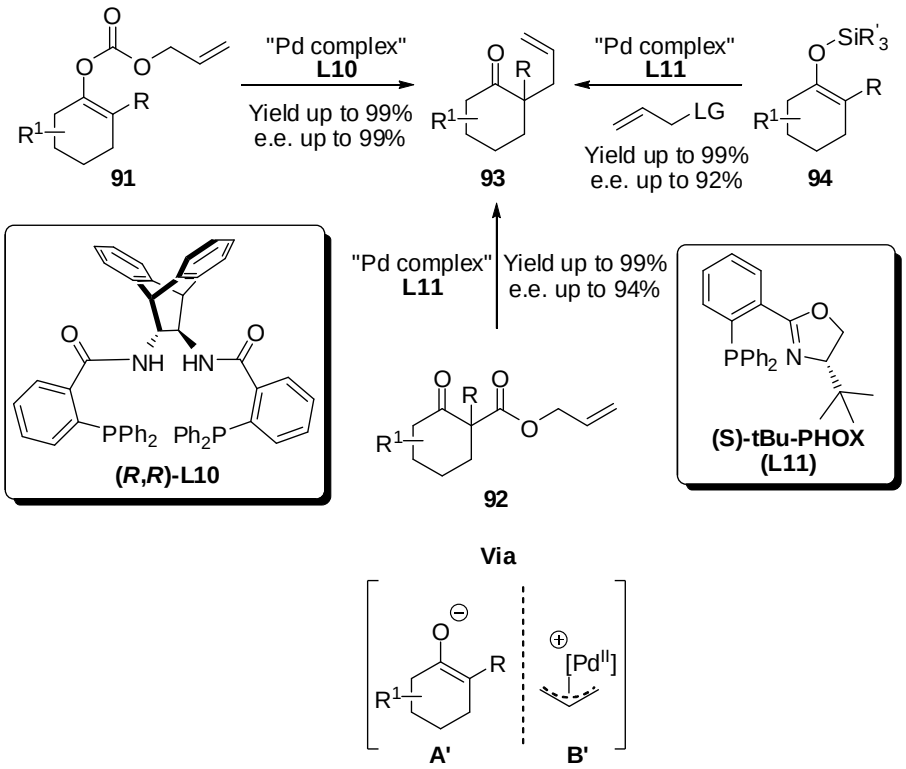
Angew. Chem. Int. Ed. **2011**, *50*, 2756; e) H. Mukherjee, N. T. McDougal, S. C. Virgil, B. M. Stoltz, *Org. Lett.* **2011**, *13*, 825; f) N. B. Bennett , A. Y. Hong , A. M. Harned, B. M. Stoltz, *Org. Biomol. Chem.* **2012**, *10*, 56; g) B. Stoltz *et al*, *Chem. Eur. J.* **2011**, *17*, 14199.

More recently, Trost[17a-d,22] and Stoltz[21] independently pioneered the Pd^{0}-catalyzed decarboxylative asymmetric allylic alkylation reaction (or DAAA). This methodology is an even more interesting approach to the α-allylation of carboxyl groups as it incorporates the nucleophilic and electrophilic moieties on the same substrate. As seen in Scheme 87, these substrates could be approached in two ways; the first is by placing the allyl acetate on the carbon α to the carbonyl generating α-keto allyl esters such as substrate **91**. The second is by placing the same allyl acetate on the oxygen of the carbonyl thus forming allyl enol carbonates such as substrate **92**. Although these are two different substrates, once in the presence of Pd^{0} complexes they proceed via the same intermediates; oxidative addition of the palladium complex onto the C-OAc bond and subsequent decarboxylation generates simultaneously the nucleophilic enolate **A'** and the electrophilic π-allyl palladium species **B'**. These two intermediates will then react to form the desired α-allylated product **93**.

[22] a) B. Trost, J. Xu, T. Schmidt, *J. Am. Chem. Soc.* **2009**, *131*, 18343; b) B. Trost, B. Schäffner, M. Osipov, D. A. Wilton, *Angew. Chem. Int. Ed.* **2011**, *50*, 3548.



Scheme 87. Different approaches for the α-allylation of ketones

Another approach originally pioneered by Tsuji[23] and recently developed by Stoltz[21g] *et al*, employs silyl enolates **94** as starting material for the AAA reaction (Scheme 87). This reaction still proceeds via the same intermediates mentioned earlier. The enolate **A'** is formed by removing the silyl group usually in the presence of a fluorine source, and the π-allyl palladium species **B'** is generated from the oxidative addition of Pd^{0} onto a distinct allylic substrate.

[23] a) J. Tsuji, I. Minami, I. Shimizu, *Chem. Lett.* **1983**, 1325; b) J. Tsuji, I. Minami, I. Shimizu, H. Kataoka, *Chem. Lett.* **1984**, 1133.

The two types of ligands mentioned above influence the approach of the nucleophile towards the π-allyl species in two different ways. The selectivity of the PHOX ligand could be rationalized by a combination of steric and electronic effects.[24] The preference of nucleophilic attack at the allylic carbon atom *trans* to the phosphino group is a key factor, resulting in effective electronic discrimination of the allylic termini. Moreover, Stoltz[21c,25] *et al* recently submitted evidence in support of the inner-sphere mechanism for the DAAA reaction of ketones using Pd-PHOX complexes (Figure 8). X-ray structures of key intermediates as well as DFT calculations were crucial elements in this mechanistic investigation.

[24] a) A. Pfaltz, *Comp. Asymm. Catalysis*; Springer-Verlag: Berlin, **1999**, Vol. 2, p 834; b) A. Pfaltz, W. J. Drury, 3rd, *Proc. Natl. Acad. Sci.* **2004**, *101*, 5723.

[25] a) J. A. Keith, D. C. Behenna, N. Sherden, J. T. Mohr, S. Ma, S. C. Marinescu, R. J. Nielsen, J. Oxgaard, B. M. Stoltz, W. A. Goddard, 3rd, *J. Am. Chem. Soc.* **2012**, *134*, 19050; b) N. H. Sherden, D. C. Behenna, S. C. Virgil, B. M. Stoltz, *Angew. Chem. Int. Ed.* **2009**, *48*, 6840.

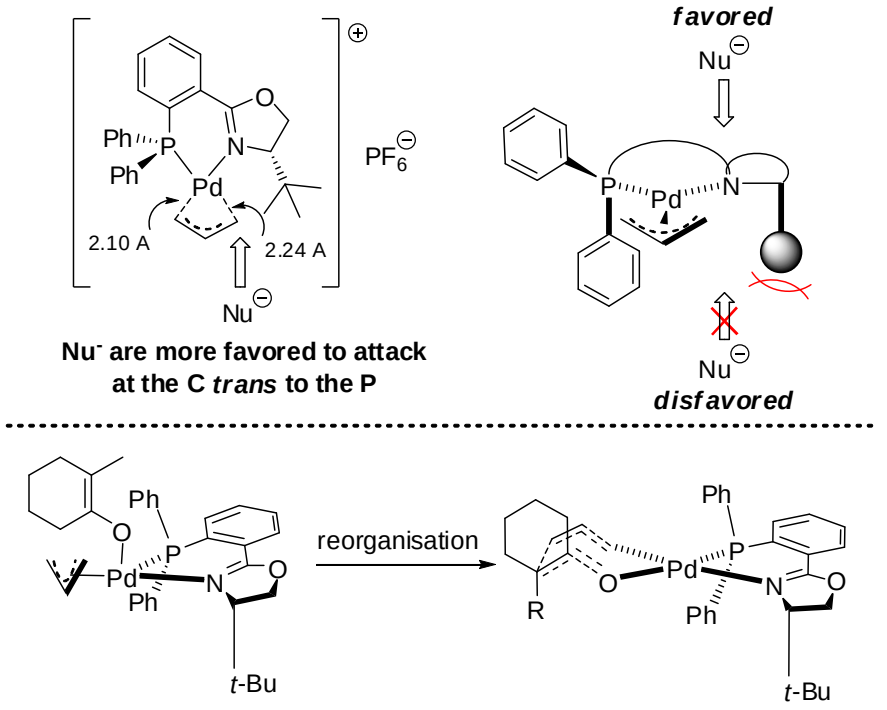


Figure 8. Electronic and steric discrimination by the PHOX ligand series

In the case of the Trost ligands, the *bis*-phosphine ligand creates a kind of chiral pocket around the π-allyl palladium species.[17c-d] The approach of the nucleophile is therefore driven by the need to minimize the steric hindrance between the latter and the complex (Figure 9). This chiral pocket could also explain the results obtained in Scheme 85. Indeed, as seen above, Trost ligands gave higher enantioselectivity with smaller π-allyl species such as **87** and that's probably due to the size of this chiral pocket. If the π-allyl species is small enough to fit in the pocket, high enantioselectivity could be obtained, otherwise the steric discrimination won't be as effective.

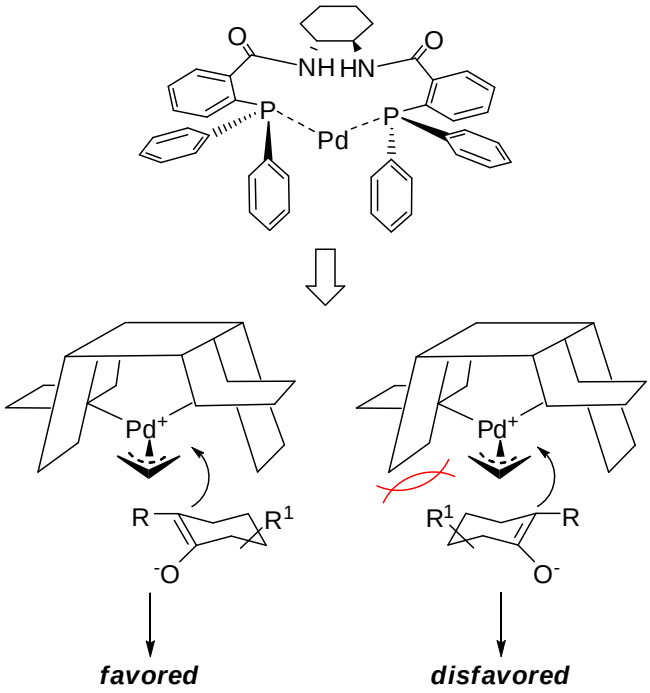


Figure 9. Steric discrimination by the Trost ligand series

These different but intrinsically related approaches have redefined the asymmetric allylic alkylation of ketones and allowed access to α-allylated carbonyls in high yields and excellent enantioselectivities. Furthermore, these landmarks in palladium catalysis have helped us understand and develop our catalytic system as we are going to see later on.

II. Objectives

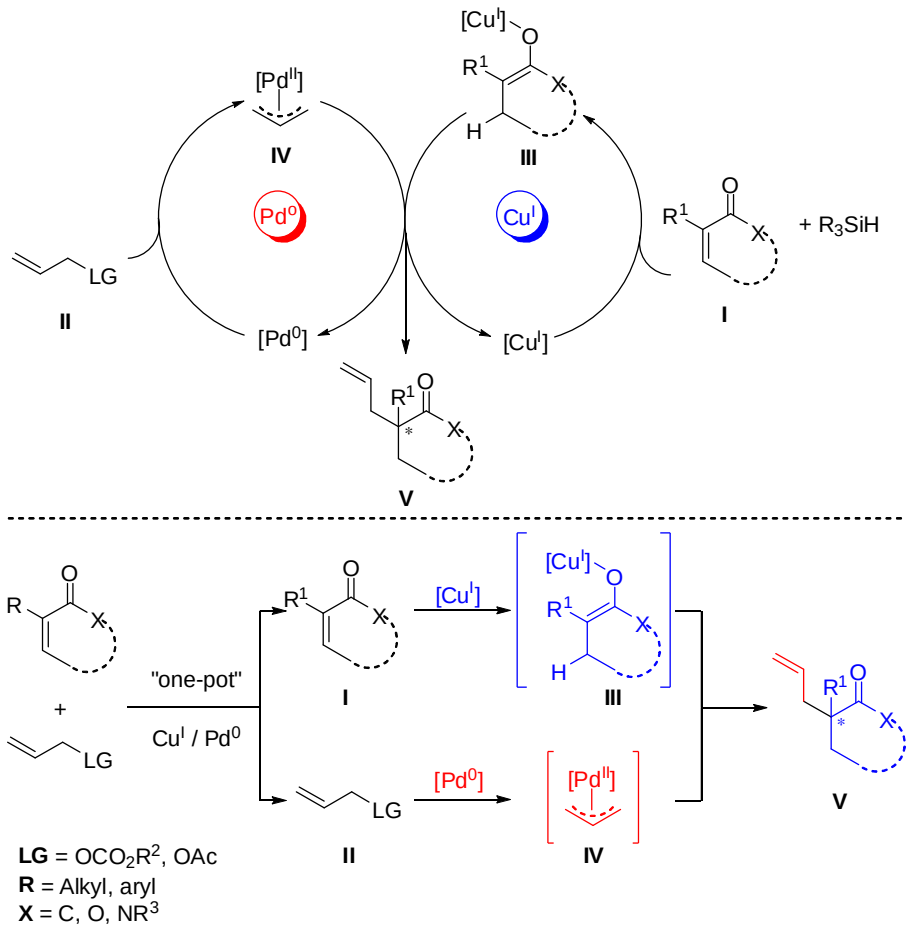
As stated earlier, we wanted to use the Pd^0 and Cu^I cooperative catalysis to develop a new synthetic transformation. The cooperativity of such system is well documented. The compatibility and selectivity of these two metals have been repeatedly proven in the two famous examples; the Wacker-Tsuji[1] process and the Sonagashira[2] coupling.

As shown in chapter 1, we have a long history of developing copper catalyzed conjugated 1,4-reduction reactions. As a result, we decided to combine our experience in this field with the Pd^0-catalyzed asymmetric allylic alkylation reaction (Scheme 88). The reaction that we envisioned involved a Cu^I-catalyzed 1,4-reduction reaction of Michael acceptors **I** to form the copper enolate intermediate **III**. Simultaneously, oxidative addition of Pd^0 to the allyl leaving group moiety **II** generates the π-allyl palladium species **IV**. The two catalytic species will subsequently react to form the desired product **V** (Scheme 88).

---

[1] J. Keith, P. Henry, *Angew. Chem. Inter. ed.* **2009**, *48*, 9038, and references cited there.

[2] a) K. Sonogashira, In *Metal-Catalyzed Reactions*; (Eds; F. Diederich,; P. J. Stang), WILEY-VCH: New York, **1998**, 203-229; b) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem. Int. Ed.* **2005**, *44*, 4442; c) R. Chinchilla, C. Nájera, *Chem. Rev.* **2007**, *107*, 874; d) H. Doucet, J.-C. Hierso, *Angew. Chem. Int. Ed.* **2007**, *46*, 834.

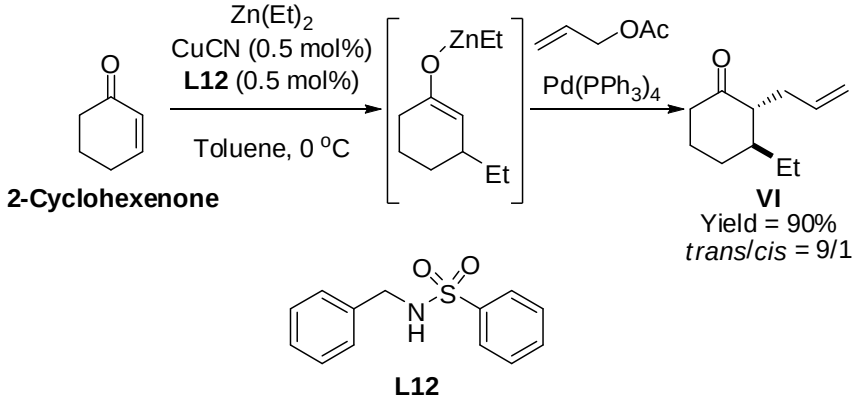


Scheme 88. The proposed reaction and its mechanism

To the best of our knowledge, this cooperative dual process has no precedent in the literature but a couple of reactions came close. In 1996, Noyori[3] reported a one pot sequential reaction involving a Cu^I/Pd^0 system (Scheme 89). The first reaction is a Cu^I-catalyzed 1,4-addition of an ethyl group onto 2-cyclohexenone. The zinc enolate thus formed *in situ*, is subsequently trapped with allyl acetate and a Pd^0 complex to form the desired product **VI**.

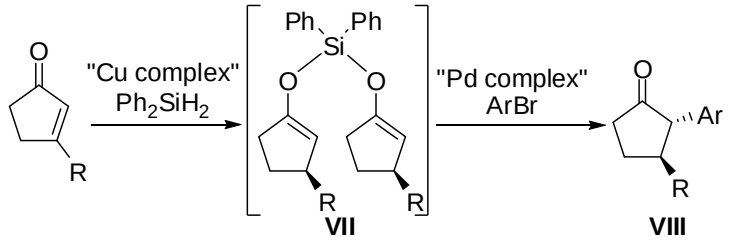
[3] M. Kitamura, T. Miki, K. Nakano, R. Noyori, *Tetrahedron Lett.* **1996**, *37*, 5141.

The reaction proceeds with a high yield (90%) and good selectivity, but it was the only substrate engaged in this reaction.



Scheme 89. Noyori *et al*'s one pot sequential reaction

More recently, Buchwald[4] *et al* developed another Cu^{I}/Pd^{0} one pot sequential reaction, whereas the copper hydride adds to different enones to form *in situ* the silyl enolate **VII** (Scheme 90). Intermediate **VII** is then directly engaged with arylbromides and a palladium complex to form the desired product **VIII**. This novel reaction sets up two new chiral centres in good yields and high diastereomeric excess (Scheme 90).



Scheme 90. Buchwald *et al*'s one pot sequential reaction

[4] J. Chae, J. Yun, S. L. Buchwald, *Org. Lett.* **2004**, *6*, 4809.

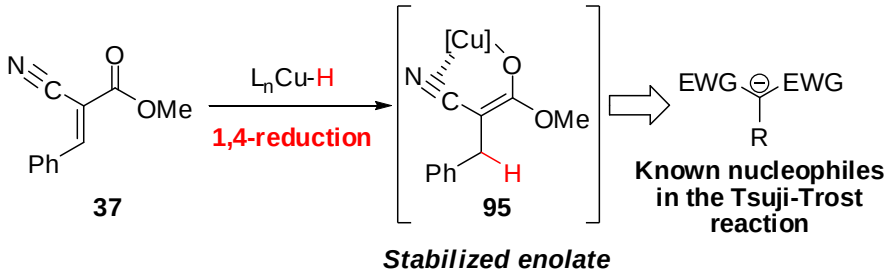
Although these reactions are not cooperative dual processes, they do give us a good idea on the behaviour of the two targeted systems (1,4-reduction and allylation). They bear some similarities to the idea we laid out at the beginning of this chapter, but instead of engaging these reagents sequentially, we wanted to engage them at the same time in a one pot reaction.

Now that we've established the viability of such methodology, we started working on determining a compatible system to perform the desired transformation. Ultimately, our goal is also to induce chirality in order to obtain enantiopure adducts.

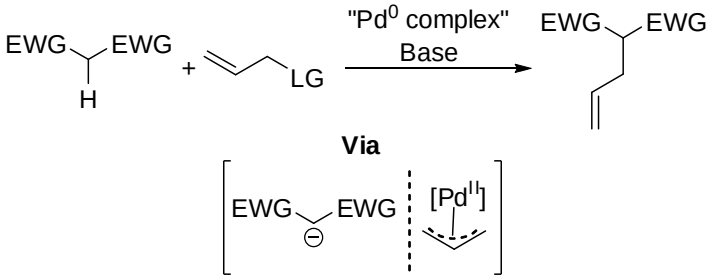
III. Results and Discussion

III.1. First Model Reaction: Benzylidene Malonate

As stated above, we wanted to apply the cooperative dual catalysis reaction using the Cu^{I}/Pd^{0} dual metal system on the 1,4-reduction/allylation of Michael acceptors. The key to this strategy is to choose adequate substrates that will allow us to do the desired transformation. The first substrate that we selected was substrate **37** (Scheme 91). Although this substrate had closed the door on the previous project, it did open a window to this one as it is the only substrate to be readily reduced by our copper system (see Table 7, Chapter 1). Furthermore, if we look closely at the likely enolate intermediate **95**, this choice becomes self-evident. Indeed, enolate **95** belongs to a class of known nucleophiles in the AAA reaction (more specifically the Tsuji-Trost reaction) which is basically the allylic alkylation reaction that we wish to perform on intermediate **95**.



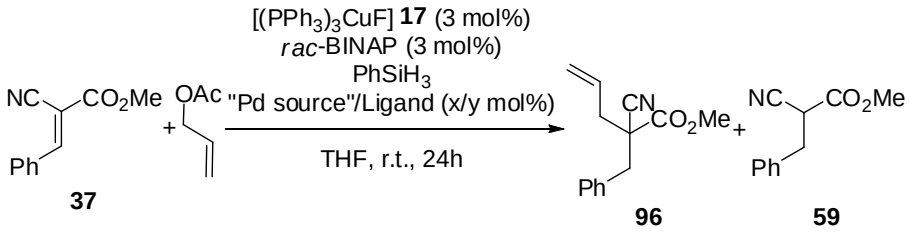
Tsuji-Trost reaction:



Scheme 91. Initial strategy and possible intermediates

With this in mind, we started exploring this methodology on substrate **37**. The same copper system used earlier was chosen as it readily reduced substrate **37** (see Table 7). The next step was to vary the palladium complex hoping to obtain or at least observe the desired product (Table 8). Gratifyingly, after a couple of tests we were able to find the right combination of conditions and the desired product **96** was isolated in a 73% yield (Table 8, entry 2). It should be noted that total consumption of the starting material **37** was observed as well as the formation of the reduction product **59**. It should also be mentioned that these reaction conditions consisted in adding all the catalysts, followed by the two starting materials and finally the silane was added to initiate the reaction.

Table 8. Dual catalysis tests on substrate **37**



37 **96** **59**

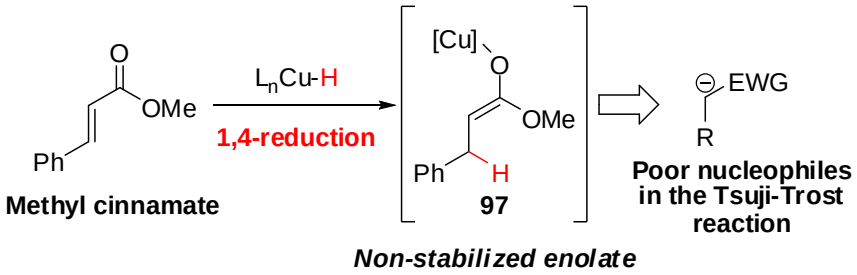
Entry[a]	«Pd source» (mol%)	Ligand (mol%)	96[b] (%)
1	$[(\eta^3\text{allyl})PdCl]_2$ (3)	Phenantroline (5)	0
2	**$Pd(PPh_3)_4$ (3)**	**-**	**73**

[a] All reactions were run under argon [b] Isolated yield.

We were excited to see that the suggested approach was successful in generating the desired product. However, we soon realized that there was no synthetic value in generating these types of allylated products. Indeed, these products are easily obtained *via* the Tsuji-Trost reaction and present no synthetic challenge. Furthermore, if we had continued the optimisation and exemplification of such substrates, the importance of our methodology would have been significantly compromised. For that reason, we set out to find another class of substrates to engage in the newly developed conditions.

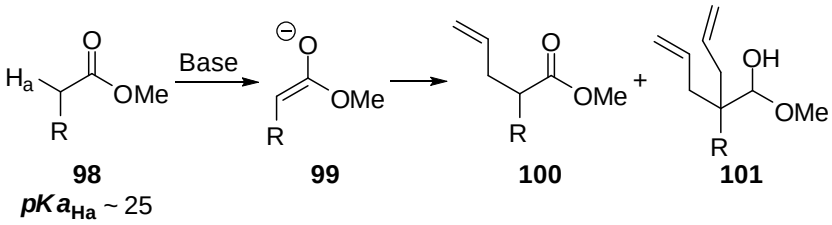
III.2. Second Model Reaction: α,β-unsaturated Esters

After some reflexion, we decided to use an α,β-unsaturated ester; methyl cinnamate. This way, we have a substrate that greatly resembles substrate **37** but without the stabilisation effect on the corresponding enolate (Scheme 92). Consequently, the ester enolate **97** thus generated is far less stabilized than the previous one and constitutes a poor nucleophile for the Tsuji-Trost reaction.



Scheme 92. Methyl cinnamate as the new model substrate

Furthermore, α-allylation of esters is underdeveloped in the literature and only a few examples exist to date. The major route to this type of products is by a deprotonation/allylation reaction of esters **98** (Scheme 93). The high *pKa* value of the designated proton $\mathbf{H_a}$ causes the corresponding enolate **99** to be classified as a hard nucleophile (hard nucleophiles = pka>20) which in turn makes it not quite suitable for the Tsuji-Trost reaction (although some hard nucleophiles undergo this reaction, soft nucleophiles are the most preferred). Another contributing factor is the fact that more than one product could be obtained; the desired mono-allylated product **100** as well as the di-allylated product **101**.

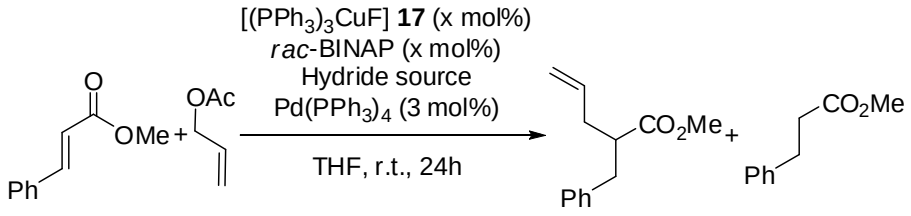


Scheme 93. Typical allylation strategy and its disadvantages

Testing on the methyl cinnamate started with the previously determined conditions (see Table 8, entry 2). Under these conditions, the desired product **102** was not observed and only the reduction product **103** was recovered (Table 9, entry 1). It should be noted that the starting material was

completely consumed at the end of the reaction. Afterwards, we started varying the hydride source in order to determine its effect on the reaction. Dimethylphenylsilane and pinacolborane failed to deliver a better result as we observed mainly the starting material and small amounts of the reduction product **103** (Table 9, entries 2-3). Finally, when we increased the catalytic loading of the copper system to 10 mol% and 20 mol%, we gratifyingly obtained a 13% yield and 49% yield respectively of **102** (Table 9, entries 4-5).

Table 9. Dual catalysis tests on methyl cinnamate



Methyl cinnamate **102** **103**

Entry[a]	17 (mol%)	*rac*-BINAP (mol%)	Hydride source	102[b] (%)	103[b] (%)
1	3	3	$PhSiH_3$	0	>99
2	3	3	Me_2PhSiH	0	10
3	3	3	Pinacolborane	0	traces
4	10	10	$PhSiH_3$	13	87
5	**20**	**20**	**$PhSiH_3$**	**49[c]**	**50**

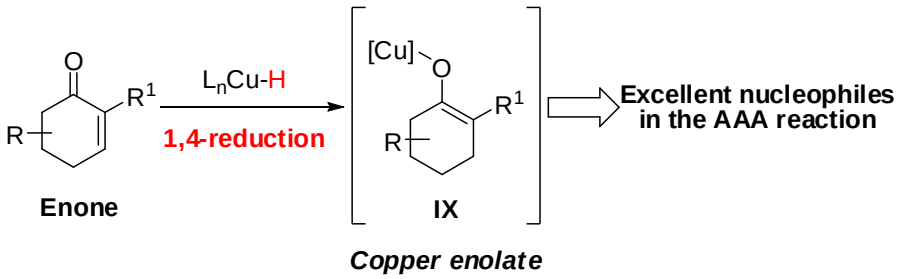
[a] All reactions were run under argon [b] Yield determined on the crude mixture by ^1H NMR [c] Isolated yield.

Despite our best effort, we couldn't optimize the reaction further. Although these results are quite promising, a 49% maximum yield is still low. Furthermore, the catalytic loadings of **17** and *rac*-BINAP used in the optimal

conditions are very high (20 mol%). In order to establish a more reliable and general process, we decided to search for another type of substrates to employ in our reaction conditions.

III.3. Third Model Reaction: α,β-unsaturated Ketones

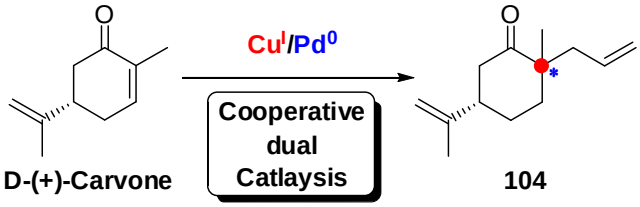
Due to the huge success of substrates such as cyclic ketones in the AAA reaction (See Scheme 87), we thought that enones would be an excellent choice to undergo the present reaction. Indeed, after the 1,4-reduction reaction occurs, the newly formed intermediate **IX** is a copper enolate (Scheme 94). And as seen in Scheme 87, such enolates react smoothly with the π-allyl palladium species and excellent enantioselectivities could thus be obtained with the same ligands used by Trost and Stoltz.



Scheme 94. Extending the strategy to ketones as model susbtrates

For that reason, D-(+)-carvone was chosen as a third model substrate for initial optimisations (Scheme 95). Carvone was primarily selected for two reasons; its commercial availability and the fact that it could generate products with a quaternary centre in an enantioselective manner. Accessing

stereoselectively these centres remains an important challenge in organic synthesis.[1]

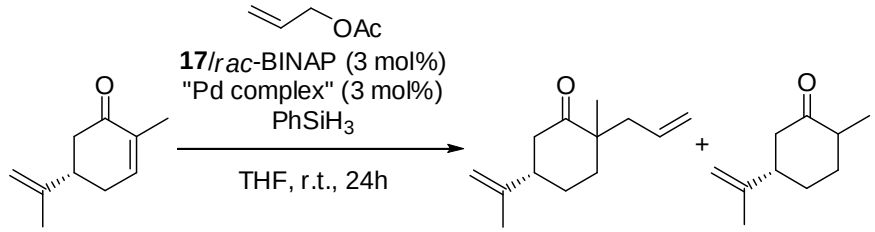


Scheme 95. D-(+)-carvone as model substrate for the dual process

Initial tests on the selected carvone started with the previously determined conditions for substrates **37** (Table 10, entry 1). Under these conditions, total conversion of the starting material to the reduction product **105** was observed. The desired alkylation product **104** was not obtained. Varying the palladium complex didn't improve the result, and this time only the starting material was recovered (Table 10, entry 2).

[1] a) M. Shimizu, *Angew. Chem.* **2011**, *123*, 6122-6124; *Angew. Chem. Int. Ed.* **2011**, *50*, 5998-6000; b) B. M. Wang, Y. Q. Tu, *Acc. Chem. Res.* **2011**, *44*, 1207-1222; c) J. Christoffers, A. Baro, *Quaternary Stereocenters-Challenges and Solutions for Organic Synthesis*, Wiley-VCH, Weinheim, **2005**.

Table 10. Dual catalysis tests on D-(+)-carvone



D-(+)-Carvone **104** **105**

Entry[a]	[Pd]	104[b] (%)	105[b] (%)
1	$Pd(PPh_3)_4$	0	>99
2	$Cl_2Pd(PPh_3)_2$	0	0

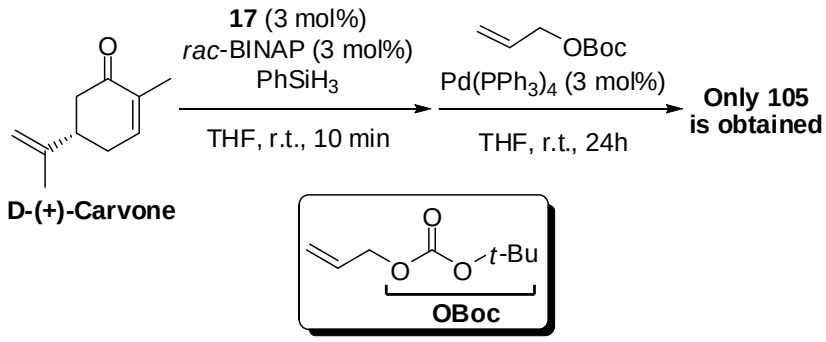
[a] All reactions were run under argon [b] Yield determined on the crude mixture by ^{1}H NMR.

Afterwards, we tried numerous conditions in an attempt to obtain the desired alkylated product, but all our efforts were unfruitful.

III.3.1. Sequential Reactivity and Optimisation

After the previous disappointing results, we were convinced that the problem initiated from the alkylation reaction. This hypothesis was reinforced by the fact that in the majority of the reactions attempted, the reduction product **105** was almost always observed. Therefore we decided to take a different approach to the problem at hand and thus perform the above reaction in a sequential manner; carvone was added to a solution of the copper complex followed by the silane (1,4-reduction reaction), and after 10 minutes, a solution of the palladium complex and the allylic substrate was added to the first reaction mixture (alkylation reaction) (Scheme 96). Under these conditions, we used copper complex **17**, $Pd(PPh_3)_4$ and phenylsilane.

Furthermore, we replaced the OAc with OBoc,[2] a better leaving group, in an attempt to further activate the alkylation reaction. Unfortunately, only the reduction product **105** was observed (Scheme 96).



Scheme 96. Sequential strategy and conditions

After several attempts, we came to realize that complex **17** was a poor choice to undertake this reaction and that was for two reasons. First and foremost, the results obtained, using complex **17**, were most of the time irreproducible. Second, we realized that if we wanted to develop an enantioselective version of this reaction later on, a chiral phosphine would be needed. Therefore, this chiral phosphine could exchange with the triphenylphosphine present as ligand on complex **17**. Consequently we would be forced to use an excess of chiral ligand in a hope to suppress the interference of the triphenylphosphine. Furthermore, this future solution could reasonably inhibit the 1,4-reduction reaction, as the resulting copper hydride could turn out to be less reactive. For those reasons, we started searching for a copper complex that, unlike phosphine-based complex **17**, won't undergo this exchange reaction. Thus the NHC copper complex (IMesCuDBM) emerged as an excellent alternative (Table 11). This copper

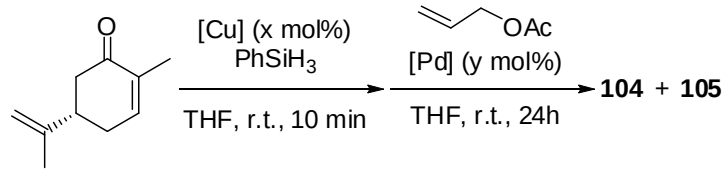
[2] F. Houlihan, F. Bouchard, J. M. J. Frechet *Can. J. Chem.* **1985**, *63*, 153.

complex was developed in our group and was successfully used to perform the 1,4-reduction/aldolisation reaction of acrylates and α,β-unsaturated ketones.[3]

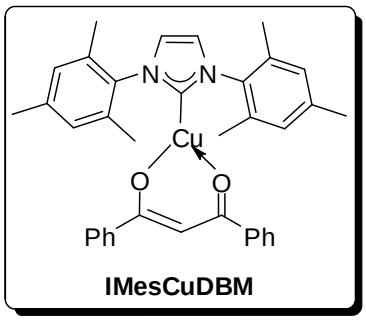
Once again, under these new conditions, we started exploring the sequential process (Table 11). First we varied the palladium source (Table 11, entries 1-2), then we increased the catalytic loadings of both catalysts (Table 11, entries 3-4). In all these cases, we only observed the total conversion of the starting material into the reduction product **105**. These observations lead us to believe that the phenylsilane is probably too reactive and probably not compatible with the π-allyl palladium species. Therefore methyldiethoxysilane ($Me(EtO)_2SiH$), a less reactive silane, was used but unfortunately no alkylation product was observed as well (Table 11, entry 5). Only 14% of the reduction product **105** was recovered along with the rest of the starting material.

[3] A. Welle, S. Díez-González, B. Tinant, S. P. Nolan, O. Riant, *Org. Lett.* **2006**, *8*, 6059.

Table 11. Sequential optimisation



D-(+)-Carvone



IMesCuDBM

Entry[a]	[Pd] (mol%)	[Cu] (mol%)	104[b] (%)	105[b] (%)
1	$Pd(PPh_3)_4$ (3)	IMesCuDBM (3)	0	>99
2	$Pd(OAc)_2$ (3)	IMesCuDBM (3)	0	>99
3	$Pd(OAc)_2$ (5)	IMesCuDBM (5)	0	>99
4	$Pd(OAc)_2$ (10)	IMesCuDBM (10)	0	>99
5[c]	$Pd(OAc)_2$ (5)	IMesCuDBM (5)	0	14

[a] All reactions were run under argon [b] Yield determined on the crude mixture by ^{1}H NMR [c] $Me(EtO)_2SiH$ was used instead of phenylsilane.

Undiscouraged by these results, we attempted one last sequential strategy. We decided to follow the evolution of the first reaction by TLC, and once all the starting material is consumed, the reaction mixture is added to a solution of the palladium complex and the allyl carbonate. Key changes to the reaction conditions were also made (Table 12). After the failure of previous attempts, we were convinced that the phenylsilane was too reactive in these conditions. Therefore we decided to use less reactive silanes such as

diphenylsilane and methyldiethoxysilane. Furthermore, based on our previous experience in this field, acceleration of the copper hydride addition could be accomplished by adding *t*-BuOK especially when using less reactive silanes. Another key modification was the addition of dppe (diphenylphosphinoethane, a bis-phosphine ligand) to the palladium solution in an attempt to further stabilize the π-allyl palladium species.[4] Although the first reaction could be done at room temperature, it's well known that the 1,4-reduction reaction is optimally performed at lower temperatures, thus 0 ^{o}C was chosen for this reaction. Another crucial step was taken by increasing the temperature of the alkylation reaction from room temperature to 65 ^{o}C. In the literature, Pd^{0}-catalyzed AAA reactions often require higher temperatures (>40 ^{o}C). All these changes didn't come about by coincidence. Indeed, after a careful screening of the literature, we found these conditions to be the most used in each reaction separately hence it should be a better starting point for our optimisation.

When diphenylsilane and $Pd_2(dba)_3$ were used, we were able, for the first time, to observe some allylic signals indicating some traces of the desired product **104** (Table 12, entry 1). Nevertheless, the reduction product **105** was the major product under these conditions. Gratifyingly, replacing the diphenylsilane with the methyldiethoxysilane allowed us to isolate product **104** in a 30% yield (Table 12, entry 2). Unfortunately, variation of the palladium source didn't improve the desired yield (Table 12, entry 3). However, we were still pleased to have finally observed and isolated the desired product.

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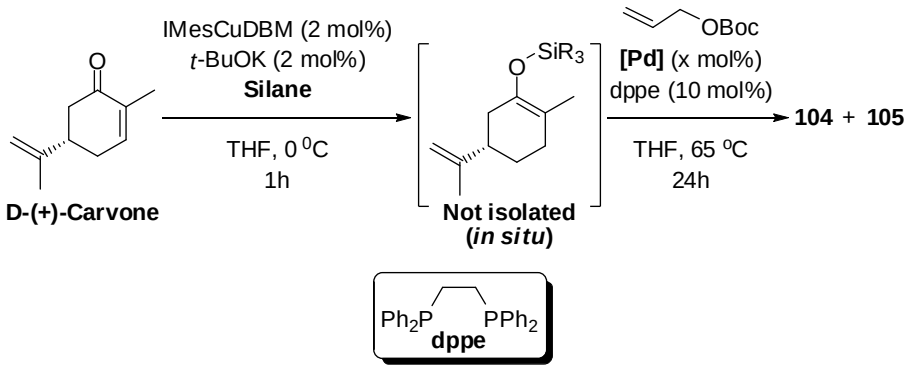
[4] M. Elliott, A. Dhimane, M. Malacria, *Tetrahedron Lett.* **1998**, 39, 8849.

Table 12. Optimisation of the sequential process under new conditions



Entry[a]	Silane	[Pd] (mol%)	104[b] (%)	d.r.[c] (104)	105[b] (%)
1	Ph_2SiH_2	$Pd_2(dba)_3$ (3.5)	Traces	-	99
2	**$Me(EtO)_2SiH$**	**$Pd_2(dba)_3$ (3.5)**	**30**	**73/27**	**-**
3	$Me(EtO)_2SiH$	$Pd(OAc)_2$ (7)	17	78/22	Traces

[a] All reactions were run under argon [b] Isolated yield [c] Diastereomeric ratio determined by ^{1}H NMR.

At that time, we stumbled upon an interesting report on the asymmetric allylation of silyl enolates (generated from ketones) which had many similarities to our system (Scheme 97).[5] The conditions used in this publication seemed very interesting and we thought we could take advantage of these conditions in our allylic alkylation reaction. Most notably, using TBAT,[6] a fluoride source, as an additive to activate the silyl group and toluene as a solvent seemed like a very attractive approach.

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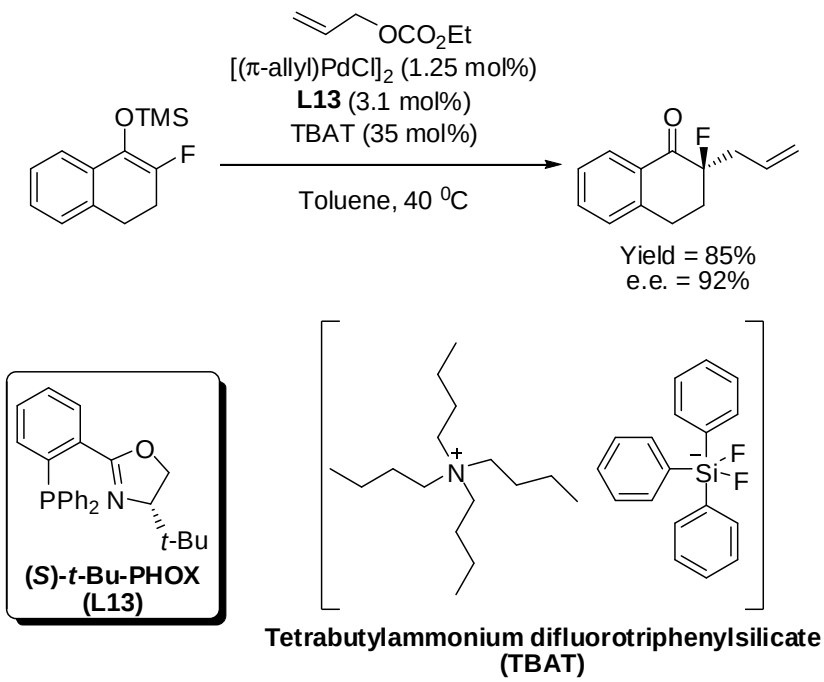
[5] E. Belanger, K. Cantin, O. Messe, M. Tremblay, J. F. Paquin, *J. Am. Chem. Soc.* **2007**, *129*, 1034.

[6] A. S. Pilcher, H. L. Ammon, P. DeShong, *J. Am. Chem. Soc.* **1995**, *117*, 5166.

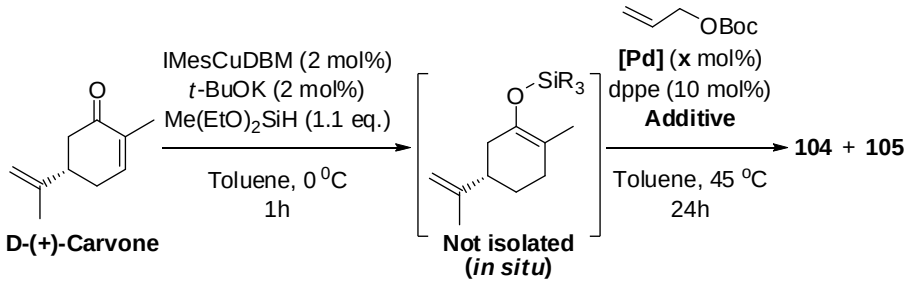


Scheme 97. Paquin *et al*'s conditions for the allylation of silyl enol ethers

The previous results indicated that methyldiethoxysilane was the better hydride source (see Table 12). Thus we fixed the copper system as previously determined and started to vary the conditions for the allylation reaction. As stated above, we felt that changing the solvent to toluene and adding TBAT to the allylation reaction might increase the yield of the desired product. As a result, we conducted the reduction reaction in toluene and the resulting silyl enolate was reacted *in situ* with a solution of the palladium complex, TBAT and the allyl carbonate at 45 °C (Table 13). As expected, the desired product **104** was isolated in a very good yield (77%). This yield was later increased to 90% by using palladium acetate as a palladium source (Table 13, entries 1-2). It should be noted that using TBAF instead of TBAT, a cheaper fluorine source, gave us a lower yield (40%),

probably because TBAT is a more anhydrous source of fluorine than TBAF (Table 13, entry 3).

Table 13. Sequential catalysis tests on D-(+)-carvone



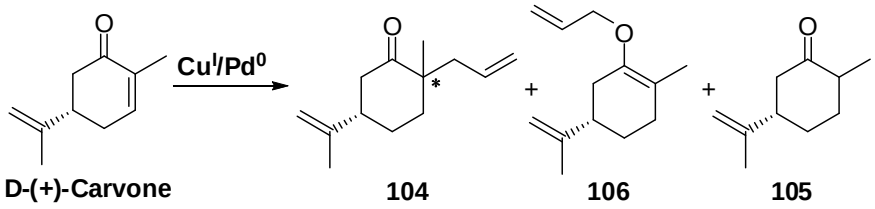
Entry[a]	[Pd] (mol%)	Additive (eq.)	104[b] (%)	d.r.[c] (104)	105[b] (%)
1	$Pd_2(dba)_3$ (3.5)	TBAT (0.35)	77	73/27	20
2	**$Pd(OAc)_2$ (7)**	**TBAT (0.35)**	**90**	**75/25**	**Traces**
3	$Pd(OAc)_2$ (7)	TBAF (1.0)	40	78/22	Traces

[a] All reactions were run under argon [b] Isolated yield [c] Diastereomeric ratio determined by ^{1}H NMR [d] Yield determined on the crude mixture by ^{1}H NMR.

III.3.2. Cooperative Dual Catalysis Investigation

We were very excited with these results, as we now possess two compatible catalytic systems that provide the desired product in a high yield. With these two systems at hand, several attempts at the dual catalysis reaction were conducted. Early trials were conducted using the two basic systems of catalysts which meant that reagents such as TBAT and *t*-BuOK were not added. These preliminary tests gratifyingly allowed the observation of the desired *C*-alkylation product **104** and the reduction product **105**. However, a new product was observed for the first time, the *O*-alkylation product **106** (Scheme 98). Although this product is sometimes mentioned in the literature as a by-product of such reactions,[22a] it is still not known to be formed

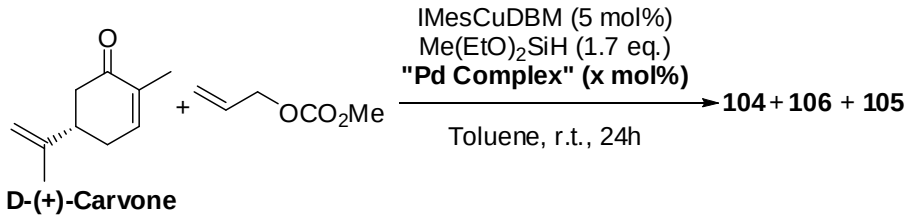
selectively in Pd^{0}-catalyzed AAA reactions with nucleophiles such as metal enolates.



Scheme 98. Observed products in our dual process using D-(+)-carvone

Preliminary tests started with a pre-fixed copper system for the 1,4-reduction reaction. Indeed, as shown in previous results, IMesCuDBM and $Me(EtO)_2SiH$ gave the most promising results and therefore were kept for the dual catalysis conditions. We also kept toluene as the reaction solvent and begun investigating the optimal palladium source (Table 14). Variation of the palladium source was accompanied by significant variations on the ratio of the three products. As seen in entry 4 (Table 14), $Pd(OAc)_2$/dppe acts as the best catalyst in terms of overall conversion and yield of combined alkylated products **104** and **106** which correlates quite well with our sequential results (see Table 13). Although $Pd(PPh_3)_4$ gives the best yield of *C*-alkylated product **104**, a lower overall conversion from D-(+)-carvone was observed (Table 14, entry 2). Nevertheless, when comparing entries 1 and 2 (Table 14), we see that a higher palladium loading results in lower yields of **104** which suggests that tuning the Cu/Pd ratio could be essential to minimize secondary reactions. No significant changes in diastereoselectivity of **104** were observed.

Table 14. Effect of the Pd source on the dual catalysis reaction's yield

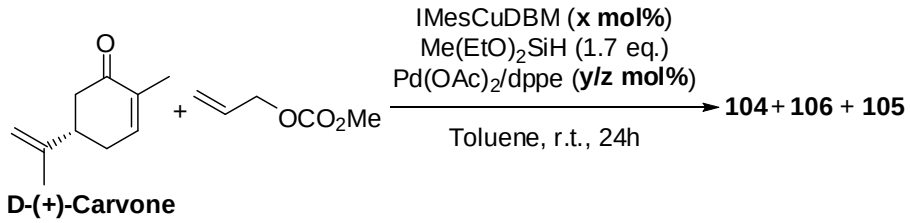


Entry[a]	[Pd] (mol%)	104[b] (%)	d.r.[c] (104)	106[b] (%)	105[b] (%)
1	$Pd(PPh_3)_4$ (5mol%)	29	69/31	0	71
2	$Pd(PPh_3)_4$ (1mol%)	44	69/31	12	17
3	$Pd_2(dba)_3$/dppe (0.5/2.5 mol%)	31	73/27	30	21
4	**$Pd(OAc)_2$/dppe (1/2.5 mol %)**	**20**	**67/33**	**51**	**29**

[a] All reactions were run under argon [b] Yield determined on the crude mixture by ^{1}H NMR [c] Diastereomeric ratio determined by ^{1}H NMR.

As predicted, the [Cu]/[Pd] ratio had a significant effect on the yield of alkylated products. A "5/1/2.5" ratio of [Cu]/[Pd]/dppe is necessary to obtain a maximum combined yield of **104** and **106** (Table 15, entry 3). It's suspected that higher Pd loadings could accelerate the consumption of the allyl methyl carbonate in secondary reactions.

Table 15. Variation of the "[Cu]/[Pd] ratio"



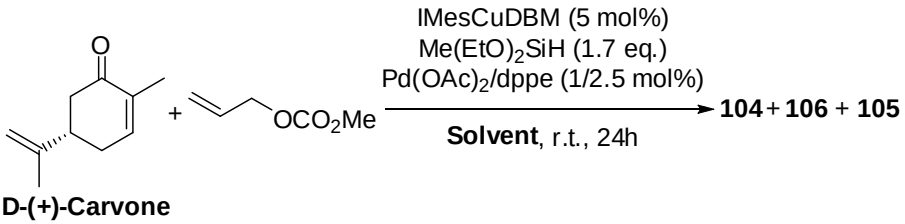
D-(+)-Carvone

Entry[a]	[Cu]/[Pd]/dppe ratio (x/y/z mol%)	104[b] (%)	d.r.[c] (104)	106[b] (%)	105[b] (%)
1	5 / 5 / 12.5	0	0	0	33
2	5 / 2 / 5	9	56/44	47	44
3	**5 / 1 / 2.5**	**20**	**67/33**	**51**	**29**
4	1 / 5 / 12.5	0	0	0	16

[a] All reactions were run under argon [b] Yield determined on the crude mixture by ^{1}H NMR [c] Diastereomeric ratio determined by ^{1}H NMR.

Optimisation of the solvent revealed that both toluene and THF gave total conversion of the starting material (Table 16, entries 1-2). But when using THF, the formation of **105** could be almost suppressed and it was thus chosen as the optimal solvent.

Table 16. Optimisation of the solvent

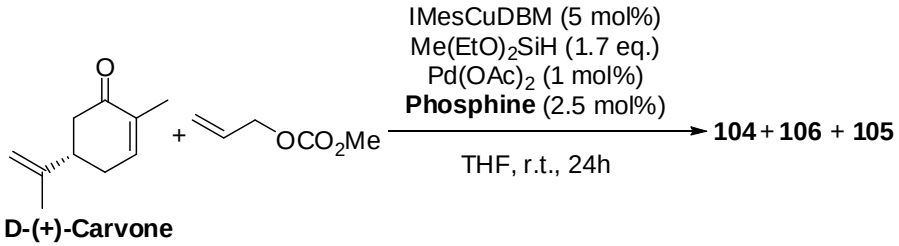


Entry[a]	Solvent	104[b] (%)	d.r.[c] (104)	106[b] (%)	105[b] (%)
1	Toluene	20	67/33	51	29
2	**THF**	**12**	**61/39**	**80**	**8**
3	CH_2Cl_2	Traces	-	0	12
4	CH_3CN	0	-	0	11

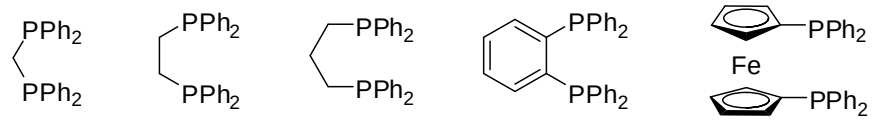
[a] All reactions were run under argon [b] Yield determined on the crude mixture by ^{1}H NMR [c] Diastereomeric ratio determined by ^{1}H NMR.

Furthermore, several phosphines were screened in our reaction conditions (Table 17). Subsequent results showed that dppe gave the best yield of combined alkylated products (Table 17, entry 3). It should be noted that although dppf gave the highest conversion to the *C*-alkylated product **104**, the overall conversion from D-(+)-carvone was not complete and therefore was not chosen (Table 17, entry 6).

Table 17. Screening of different phosphines



D-(+)-Carvone



dppm **dppe** **dppp** **dppBz** **dppf**

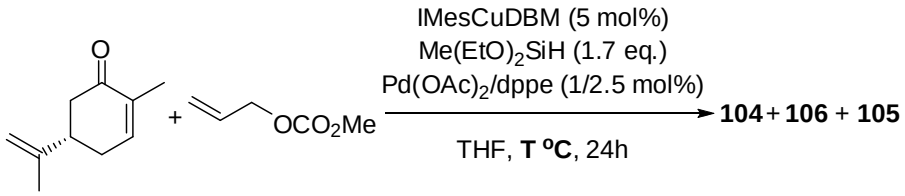
Entry[a]	Phosphine	104[b] (%)	d.r.[c] (104)	106[b] (%)	105[b] (%)
1	PPh_3	27	70/30	54	19
2	dppm	28	71/29	54	18
3	**dppe**	**12**	**61/39**	**80**	**8**
4	dppp	8	53/47	32	30
5	dppBz	36	73/23	43	21
6	dppf	58	68/32	1	0

[a] All reactions were run under argon [b] Yield determined on the crude mixture by ^{1}H NMR [c] Diastereomeric ratio determined by ^{1}H NMR.

Interestingly, when the reaction was carried out at room temperature, it was found that the *O*-alkylation product **106** was favoured with an 80% yield and when a higher temperature is used; the desired *C*-alkylation product **104** became the only alkylated product with 79% yield (Table 18, entries 3-4). In the latter case, no *O*-alkylation was observed. It should be noted that when the same experiment was stopped after three hours, a 38/43 ratio of **104**/**106** is observed (Table 18, entry 5), which indicates that under these conditions, **106** is formed then rearranged into the Claisen-type product **104** probably

catalyzed by palladium.[7] Despite our efforts, we couldn't determine if it was the only pathway to form product **104** or a mixture of both direct *C*-alkylation and rearrangement of **106**. Nevertheless, we found it highly interesting to be able to switch between the two alkylated substrates simply by changing the temperature of the reaction.

Table 18. Variation of the temperature



Entry [a]	T °C	104 [b] (%)	d.r. [c] (104)	106 [b] (%)	105 [b] (%)
1	0	3	n.d.	6	91
2	10	8	61/39	23	69
3	**r.t.**	**12**	**61/39**	**80**	**8**
4	**45**	**79**	**67/33**	**0**	**21**
5[x]	45	38	60/30	43	19

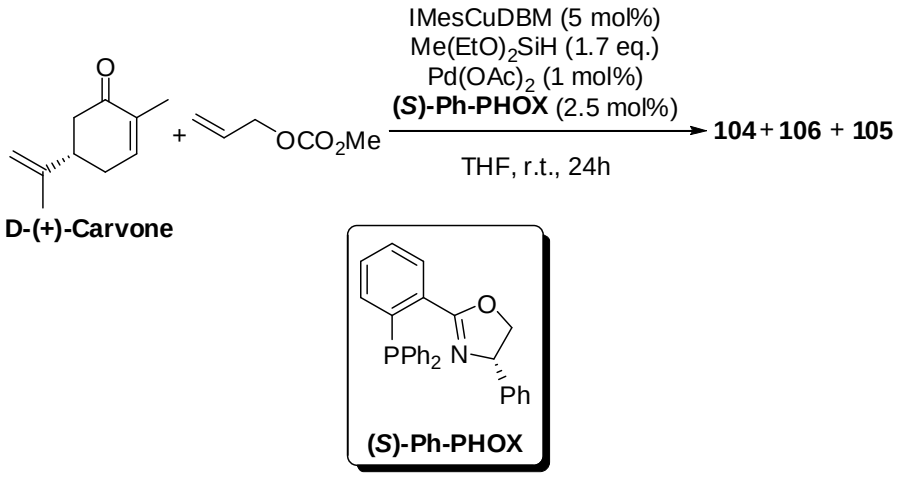
[a] All reactions were run under argon [b] Yield determined on the crude mixture by ^{1}H NMR [c] Diastereomeric ratio determined by ^{1}H NMR [d] Reaction was run for 3 hours.

However, replacing the dppe with (*S*)-Ph-PHOX, a chiral P-N type ligand widely used in the Pd^0-catalyzed AAA reaction (see bibliographic introduction), increased the diastereoselectivity of **104** up to 90% d.e. (or 95/5 d.r.) along with a slight increase in the overall conversion to product **104** (82%). The most interesting observation is that the reaction now provides selectively the *C*-alkylation product **104** at room temperature

[7] J. L. van der Baan, F. Bieckelhaupt, *Tetrahedron Lett.* **1986**, *27*, 6267.

(Table 19). Under these conditions, the desired product was isolated in 75% yield.

Table 19. The use of a chiral phosphine as ligand



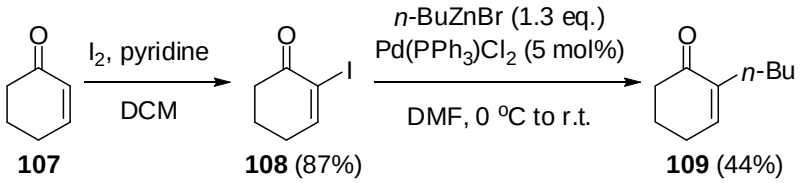
Entry [a]	104 [b] (%)	d.r. [c] (104)	106 [b] (%)	105 [b] (%)
1	82 (75%)[d]	95/5	5	13

[a] All reactions were run under argon [b] Yield determined on the crude mixture by ^{1}H NMR [c] Diastereomeric ratio determined by ^{1}H NMR [d] Isolated yield in parentheses.

III.3.3. Development of an Enantioselective Version

After these satisfying results, efforts were concentrated on developing an enantioselective version of this reaction starting from the prochiral substrate **109** (Scheme 99). Substrate **109** was easily synthesized in two steps starting from 2-cyclohexenone **107**.[8] Substrate **107** was transformed to product **108** in an 87% yield and subsequent Negishi coupling with *n*-BuZnBr afforded the desired product **109** in a 44% yield.

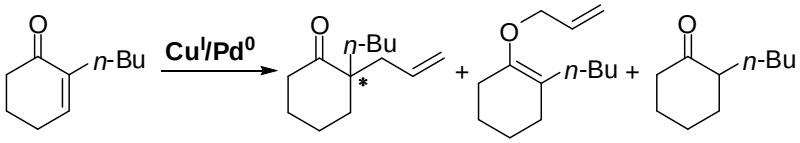
[8] E. Negishi, Z. Tan, S.-Y. Liou, B. Liao *Tetrahedron* **2000**, *56*, 10197.



107 **108** (87%) **109** (44%)

Scheme 99. Synthesis of substrate **109**

With this new substrate at hand, we engaged it in our optimised conditions. Preliminary tests showed that substrate **109** proceeded in the same fashion as D-(+)-carvone and thus affording three products; the desired *C*-alkylation product **110**, the *O*-alkylation product **111** and the reduction product **112** (Scheme 100).

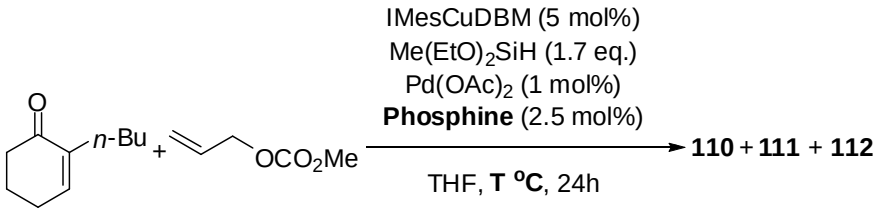


109 **110** **111** **112**

Scheme 100. Observed products in our dual process using substrate **109**

At first, we applied the previously determined racemic conditions using dppe as the designated ligand for palladium (Table 20). Initial tests demonstrated that although we were able to observe and isolate the alkylated products, yields obtained for **110** and **111** were much lower than those obtained for **104** and **106** at room temperature as well as 45 °C (Table 20, entries 1-2). Lower yields were also observed when (*S*)-Ph-PHOX was used. Nevertheless, the reaction seems to be more selective at 45 °C, providing product **110** in a 58% yield and 34% e.e. (Table 20, entry 4). Contrary to previous results, toluene turned out to be the best solvent, thus increasing the yield of **110** up to 67% with no significant change in the enantioselectivity (Table 20, entry 5).

Table 20. Preliminary tests on substrate **109**



109

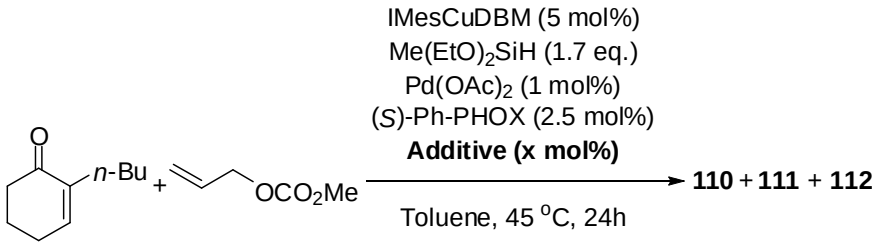
Entry[a]	Phosphine	T (°C)	110[b] (%) (e.e.%)	111[b] (%)	112[b] (%)
1	dppe	r.t.	19	38	37
2	dppe	45	41	5	52
3	(*S*)-Ph-PHOX	r.t.	33 (35%) [c]	14	52
4	(*S*)-Ph-PHOX	45	58 (34%) [c]	-	41
5[d]	**(*S*)-Ph-PHOX**	**45**	**67 (32%)** [c]	**-**	**32**

[a] All reactions were run under argon [b] Yield determined on the crude mixture by ^{1}H NMR and GC analysis [c] Enantiomeric excess in parentheses is determined by GC analysis [d] Toluene was used instead of THF.

Using the above optimised conditions, we endeavoured to further optimise the yield of this reaction. We hoped that adding catalytic amounts of *tert*-butoxide salts would further activate the copper active species and therefore accelerate the copper's catalytic cycle. This acceleration would therefore have a domino effect on the second catalytic cycle involving palladium and subsequently accelerate the latter thus reducing secondary reactions. However, upon introduction of lithium, sodium and potassium *tert*-butoxide salts, some unexpected observations were recorded (Table 21). Although the yield of **110** was not significantly influenced, the most interesting observation was the unexpected fluctuation of enantioselectivity. For example, on one hand lithium *tert*-butoxide significantly reduced the e.e.

down to 5% and on the other hand, potassium *tert*-butoxide increased the e.e. up to 48%. No significant changes were observed with sodium *tert*-butoxide (Table 21, entries 2-4). In addition, increasing the catalytic loadings of potassium *tert*-butoxide decreased the yield and e.e. of the reaction (Table 21, entry 5). Even though we were happy with these results, we were driven later on to investigate the role of these salts and their influence on the enantioselectivity (see mechanistic investigation, Section III.3.4).

Table 21. The effect of *tert*-butoxide salts



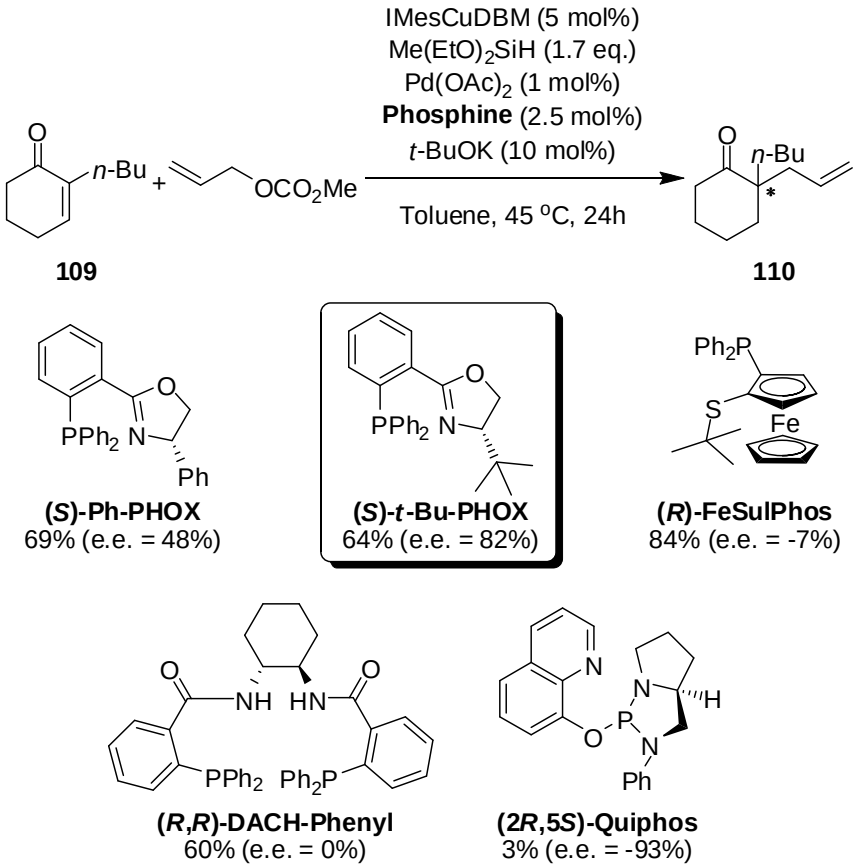
109

Entry[a]	Additive (mol%)	110[b] (%) (e.e. %)[c]	111[b] (%)	112[b] (%)
1	-	67 (32%)	-	32
2	*t*-BuOLi (10)	50 (5%)	-	20
3	*t*-BuONa (10)	68 (29%)	-	27
4	***t*-BuOK (10)**	**69 (48%)**	**5**	**25**
5	*t*-BuOK (30)	32 (25%)	-	67

[a] All reactions were run under argon [b] Yield determined on the crude mixture by ^{1}H NMR and GC analysis [c] Enantiomeric excess in parentheses is determined by GC analysis.

Further optimisation of the enantioselectivity was realized by a quick screening of known chiral ligands in the literature for Pd^{0}-catalyzed AAA reactions. Some of the ligands screened gave similar or even higher yields compared to the (*S*)-Ph-PHOX but lower enantioselectivities and others, on

the contrary, gave similar enantioselectivities but lower yields (Scheme 101). The PHOX ligand series seem to be the best suited to induce chirality under these conditions with (*S*)-*t*-Bu-PHOX giving the best e.e. for **110** (82%) with no significant change in the overall reaction yield (64%).

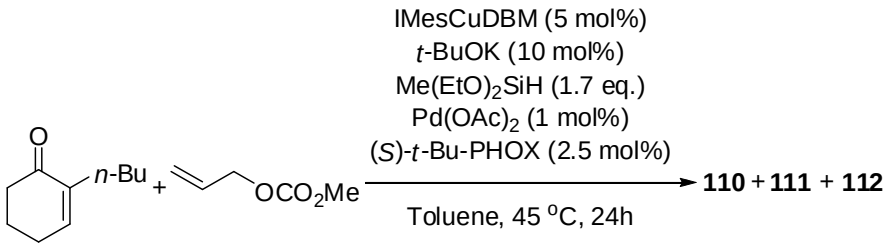


Scheme 101. Variation of the chiral phosphine ligand

Until now, 1.5 equivalent of allyl methyl carbonate was always used. Later on, we varied the number of equivalent of the allyl carbonate and thus realised that two equivalents were essential to increase the yield of the

desired product (Table 22). Under these conditions, **110** was obtained with an 83% yield and 81% e.e. (Table 22, entry 2).

Table 22. Optimising the number of equivalents of the allyl carbonate



109 **Allyl carbonate (x eq.)**

Entry[a]	x (eq.)	110[b] (%)	e.e. 110[c] (%)	111[b] (%)	112[b] (%)
1	1.5	64	82%	8	36
2	**2.0**	**83**	**81%**	**-**	**17**
3	2.5	80	79%	-	20

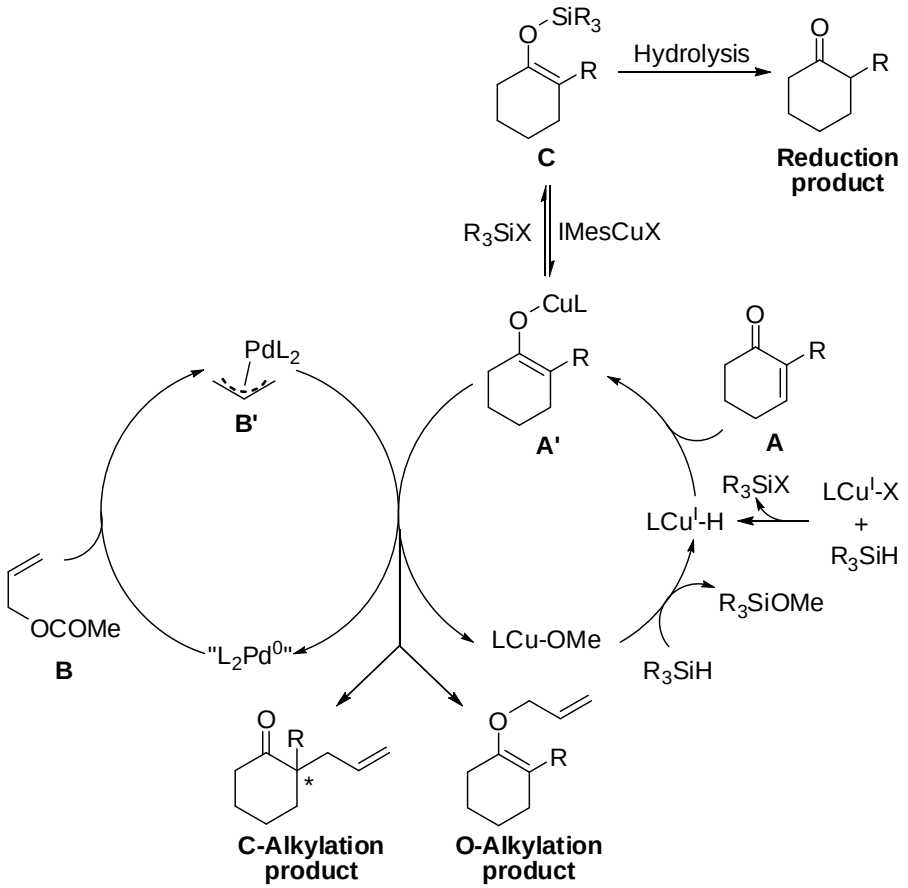
[a] All reactions were run under argon [b] Yield determined on the crude mixture by ^{1}H NMR and GC analysis [c] Enantiomeric excess determined by GC analysis.

III.3.4. Mechanistic Investigation

The optimisation reactions described above gave us valuable information on the mechanism of the reaction. Nevertheless, there are a still some unanswered questions that we felt were necessary to investigate. In order to do so, we have to carefully depict the reaction's mechanism and identify all the intermediates that afford the observed products.

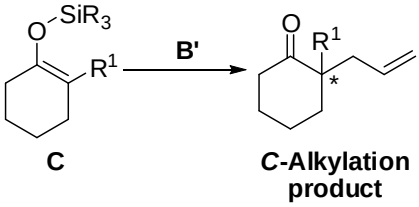
The detailed mechanism that we proposed involves the formation of an *in situ* copper hydride complex that will subsequently add to enone **A** to form copper enolate **A'** (Scheme 102). Simultaneously, the palladium active species will undergo an oxidative addition onto the allyl carbonate to form the π-allyl Pd complex **B'**. Consequently the two intermediates **A'** and **B'**

will readily react to form the alkylated products, thus freeing the copper complex which will regenerate the copper hydride upon reaction with the silane. Due to the sequential reactions that we performed, we know that the silyl enolate **C** is a possible intermediate of the reaction and is also responsible for affording the reduction product after hydrolysis. Although this proposed mechanism gives some answers to the origins of some observed products, it also raises quite a few questions.



Scheme 102. Preliminary mechanism proposed

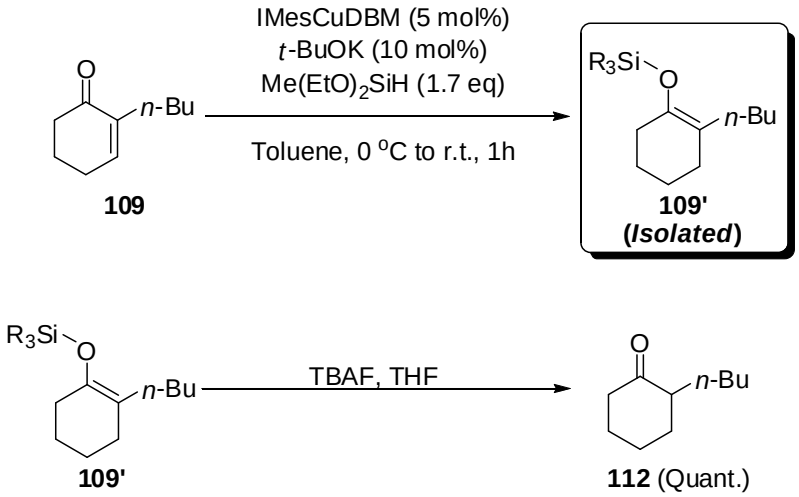
The most important question arises from the reactivity of the silyl enolate **C**. This intermediate could potentially react with the π-allyl Pd species **B'** to generate the desired product, as silyl enolates are known nucleophiles in the Pd^{0}-catalyzed AAA reaction (Scheme 103).[23] This possible secondary reaction is highly unwanted since it reduces the role of the copper and decreases the importance of such a reaction. Indeed, if this reaction is actually occurring, the reaction at hand is no longer a coupling between two catalytic species and therefore could not be classified as a cooperative dual process.



Scheme 103. Possible secondary reaction

III.3.4.1. Silyl Enol Ether's Synthesis and Reactivity

For that reason, we needed to investigate the reactivity of this silyl enolate and determine if, in our reaction conditions, it will add to intermediate **B'** and form the *C*-alkylated product. Thus we conducted the 1,4-reduction reaction in our standard optimized conditions, and isolated the silyl enolate by simple filtration over a plug silica gel followed by evaporation of the solvent (Scheme 104). The obtained residue was a mixture of two inseparable silyl enols. Therefore this residue was not purified any further and was later hydrolysed to make sure that the reaction was complete and to confirm the observation of the reduction product. As predicted, hydrolysis of enolate **109'** in the presence of TBAF gave a quantitative yield of the reduction product **112**.



Scheme 104. Isolation of the silyl enol ether **109'**

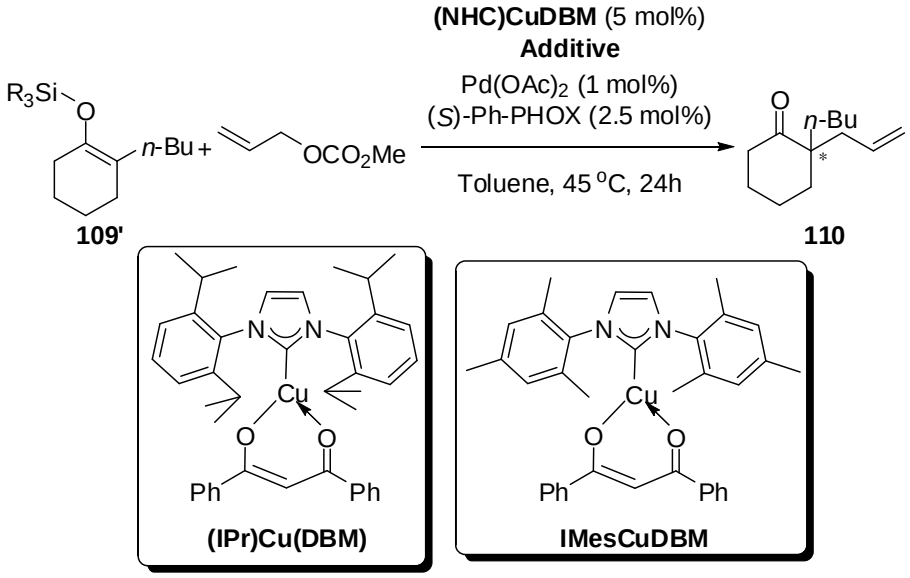
We then started engaging **109'** in a series of tests under our above optimised conditions (see Table 22, entry 2) in order to determine its role in the reaction as well as the influence of other reagents on the reaction yield and enantioselectivity.

III.3.4.1.1. Role of the Copper Complex

At first we wanted to investigate the role of copper in our reaction conditions (Table 23). As seen in entry 1, when **109'** was put in our standard reaction conditions (using (*S*)-Ph-PHOX as ligand for palladium), it afforded **110** with a yield similar to the dual process, however a noticeable increase in the e.e. was observed (59% e.e. compared to the 48% e.e. obtained in the dual process under the same conditions). This increase is probably due to the absence of silane which could compromise the palladium active species over time. We were quite relieved to see that only 7% of **110** were obtained when the same reaction was conducted in the absence of the copper complex (Table 23, entry 3). This result unambiguously suggests that the reaction

duly proceeds *via* a copper enolate and not a silyl enolate to furnish the desired alkylated product **110**. Furthermore, replacing the (IMes) ligand on the copper complex with another slightly more hindered NHC ligand (IPr), significantly decreased the yield as well as the enantioselectivity of the reaction (Table 23, entry 2). Interestingly enough, this observation suggests that copper not only is essential for the reaction to occur but it also influences the enantioselectivity of the final product. It should be noted that using TBAT could equally allow the reaction to occur in similar yields. However, the obtained e.e. is lower than that obtained with our copper complex (48% in entry 4, compared to 59% in entry 1) and the catalytic loadings of TBAT are far higher as well (35 mol% of TBAT compared to 5 mol% of our copper complex).

Table 23. Investigation of the copper's influence on the AAA reaction



Entry[a]	(NHC)CuDBM	Additive (mol%)	110[b] (%)	e.e. 110[c] (%)
1	IMesCuDBM	*t*-BuOK (10)	74	59
2	IPrCuDBM	*t*-BuOK (10)	48	27
3	-	*t*-BuOK (10)	7	34
4	-	TBAT (35)	74	48

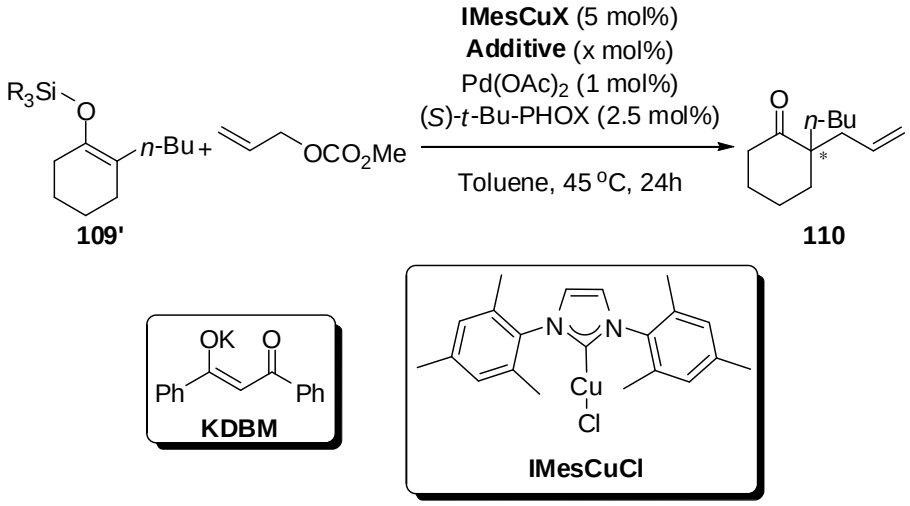
[a] All reactions were run under argon [b] Yield determined on the crude mixture by ^{1}H NMR and GC analysis [c] Enantiomeric excess determined by GC analysis.

III.3.4.1.2. Influence of the Residual Salts

Next, we wanted to investigate the role of the salts in our reaction and more notably, the influence of *tert*-butoxide salts on the reaction's enantioselectivity (Table 24). Thus, when **109'** was again put in our standard reaction conditions but this time using (*S*)-*t*-Bu-PHOX as ligand, it afforded **110** with a similar yield to the dual process, and once more a noticeable increase in the e.e. was observed (91% e.e. compared to the 81% e.e.

obtained in the dual process under the same conditions) (Table 24, entry 1). The active copper complex that undergoes the reaction is believed to be IMesCuO*t*-Bu that results from the reaction of IMesCuDBM with *t*-BuOK. The residual salt of this reaction is KDBM. Thus by removing this salt and applying only the active copper complex in our reaction conditions, we should be able to observe its influence. Consequently, IMesCuO*t*-Bu was synthesised *in situ* by reacting IMesCuCl with *t*-BuOK followed by a quick filtration using a microfilter to remove the residual salt (IMesCuCl was used because KCl is easier removed than KDBM). This copper complex is not very stable and was subsequently engaged with **109'** in typical reaction conditions (Table 24, entry 2). Under these conditions, product **110** was obtained with a high yield but more interestingly, a significant decrease in the e.e. was observed which indicates that the salt in case (KDBM) is probably responsible for increasing the e.e. of the final product. Furthermore, the use of KDBM in the absence of copper affords **110** in only a 9% yield which yet again indicates that the copper complex is essential to the reaction (Table 24, entry 3). Moreover, in entry 4, we changed the nature of the residual salt by changing the counter-anion of the copper complex in an attempt to reinforce our previous conclusions. And as predicted, when IMesCuCl is used a significant decrease in the enantioselectivity is observed (80% e.e. compared to 91%, Table 24, entries 4 and 1 respectively) but more interestingly, a notable increase in the reaction yield was obtained (98%).

Table 24. Investigation of the salt's influence on the AAA reaction



Entry[a]	IMesCuX	Additive (mol%)	110[b] (%)	e.e. 110[c] (%)
1	IMesCuDBM	*t*-BuOK (10)	81	91
2	IMesCuO*t*-Bu[d]	-	92	65
3	-	KDBM (5)	9	59
4	IMesCuCl	*t*-BuOK (10)	98	80

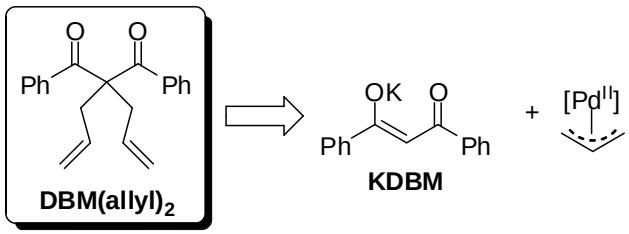
[a] All reactions were run under argon [b] Yield determined on the crude mixture by ^{1}H NMR and GC analysis [c] Enantiomeric excess determined by GC analysis [d] Formed *in situ* from IMesCuCl and *t*-BuOK then filtered using a microfilter to remove the salt.

These previous results were found to be highly interesting. If we compare the two optimal copper/salt systems to the copper/no-salt system, we find that:

- KDBM decreases the yield by 11% and increases the e.e. by 26% (Table 24, comparing entries 1 and 2).
- KCl gives a similar yield and increases the e.e. by 15% (Table 24, comparing entries 2 and 4).

These observations suggest that KCl only influences the enantioselectivity of the reaction, whereas KDBM influences both the yield and the enantioselectivity of the reaction.

At that time, we accidently isolated a new by-product of the reaction at hand; the $DBM(allyl)_2$ (Scheme 105). This product is most likely generated from the reaction of KDBM with the π-allyl Pd species. Afterwards, we revisited all the reactions where we used IMesCuDBM as the copper catalyst and re-analyzed the corresponding spectra. To our surprise, we observed the signals for the $DBM(allyl)_2$ in almost all of the NMR spectra that we analyzed.



Scheme 105. The newly observed by-product

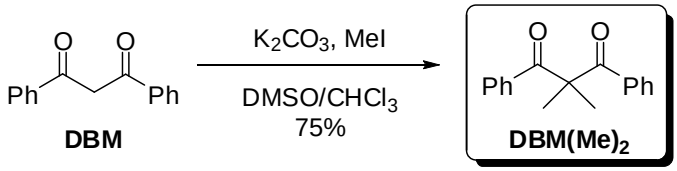
We then argued that this by-product could be the missing link that we were looking for, as it's highly probable that the above side reaction is the main reason why we observe an 11% decrease in the reaction's yield (when IMesCuDBM is used as a copper source, see Table 24). However, we still couldn't explain the dramatic increase observed in the enantioselectivity (26%).

In an attempt to investigate the role of this new product, we suggested the following hypothesis:

- If the $DBM(allyl)_2$ is actually responsible for the influence on enantioselectivity observed with the copper/KDBM system, then upon combining this reagent or one of its derivatives with the

copper/KCl system, we should obtain a high yield similar to that obtained with the latter but also a high enantioselectivity.

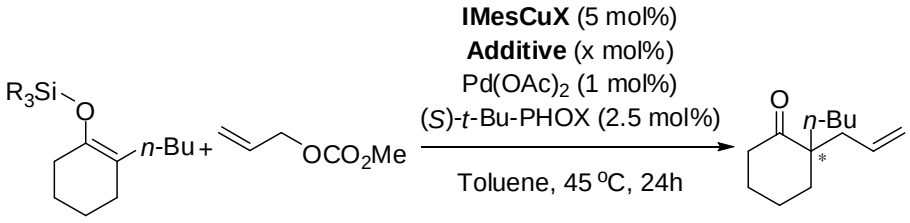
At first we wanted to synthesise a less sterically hindered and much easily accessible di-alkylated DBM. This was accomplished by replacing the allyl groups with two methyl groups. This substrate is thus easily obtained in one step starting from DBM and methyl iodide in a 75% yield (Scheme 106).



Scheme 106. Synthesis of $DBM(Me)_2$

As stated earlier, the copper/KDBM system affords a 91% e.e. and the copper/KCl system affords a 98% yield. And therefore, by using the copper/KCl system in conjunction with the $DBM(Me)_2$ we should obtain a similar yield to the latter and a similar enantioselectivity to the former. Gratifyingly, that is exactly what we obtained when we added 5 mol% of the $DBM(Me)_2$ to the copper/KCl reaction conditions (Table 25). Product **110** was obtained with 88% yield and 87% e.e. (Table 25, entry 4). These yield and e.e. values are situated exactly in between those obtained with the copper/KDBM and the copper/KCl systems (Table 25, entry 3 compared to entries 1-2). Furthermore, when we added the $DBM(Me)_2$ to the IMesCuO*t*-Bu complex with no salts, we obtained 84% yield and 88% e.e.. The obvious increase of e.e. from 65% (no salt system/without $DBM(Me)_2$) to 88% e.e. (no salt system/with $DBM(Me)_2$) clearly indicates that the $DBM(Me)_2$, and not KDBM, is actually responsible for the increase in enantioselectivity observed in the copper/KDBM system.

Table 25. Evaluating the role of the $DBM(alk)_2$



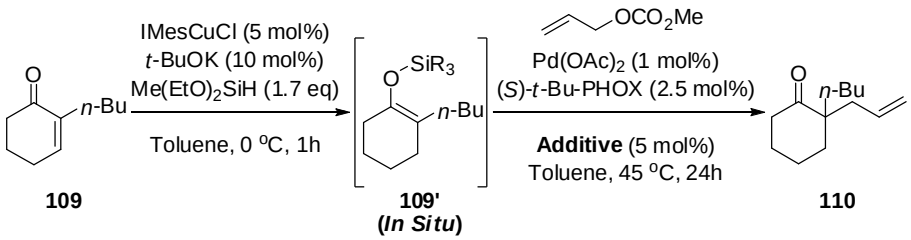
109' **110**

Entry[a]	IMesCuX	Additive (mol%)	110 [b] (%)	e.e. 110 [c] (%)
1	IMesCuDBM	*t*-BuOK (10)	81	91
2	IMesCuCl	*t*-BuOK (10)	98	80
3	IMesCuO*t*-Bu	$DBM(Me)_2$ (5) [d]	84	88
3	IMesCuCl	*t*-BuOK (10) / $DBM(Me)_2$ (5) [d]	88	87

[a] All reactions were run under argon [b]Yield determined on the crude mixture by ^1H NMR and GC analysis [c] Enantiomeric excess is determined by GC analysis [d] $DBM(Me)_2$ is added to the copper mixture.

Similarly, when we repeated the same experiment, but this time using our sequential test (without any isolation of the silyl enolate **109'**), we obtained comparable e.e. and yield values to those observed above (Table 26). In the absence of the $DBM(Me)_2$, the copper/KCl system gives a 96% yield and 80% e.e. (Table 26, entry 1). When $DBM(Me)_2$ is used in combination with the copper/KCl system, no significant change in the yield is observed, however just like before, an increase in the enantioselectivity is duly noted (Table 26, entry 2).

Table 26. Sequential test with $DBM(Me)_2$



109 **109'** (***In Situ***) **110**

Entry [a]	Additive	110 [b] (%)	e.e. 110 [c] (%)
1	-	95	80
2	$DBM(Me)_2$	96	85

[a] All reactions were run under argon [b] Yield determined on the crude mixture by ^{1}H NMR and GC analysis [c] Enantiomeric excess determined by GC analysis.

All of the reactions depicted in this section are highly reproducible and we did our best to insure maximum accuracy in order to compare such close data, especially in the case of the e.e. variation for the different systems. In that manner, all the best results obtained in each table were systemically repeated two times with less than a 2% difference always observed; the result with the highest e.e. of the two was always chosen as the representing data for the selected reaction.

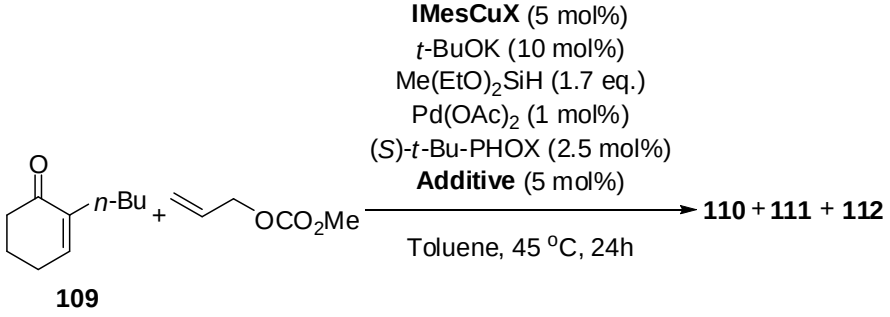
In conclusion, these experiments allowed us to conclude the following:

- The copper/KCl system gives high yields for this reaction and thus should be tested in our dual process.
- KDBM is responsible for slightly lowering the yield due to the secondary reaction with the π-allyl Pd species to afford the $DBM(allyl)_2$.
- The di-alkylated DBM is most likely responsible for the increase in enantioselectivity, usually observed when the copper/KDBM is used.

III.3.4.2. Final Optimisation of the Dual Process

In an effort to apply the above acquired information onto the dual process, we engaged 5 mol% of IMesCuCl and $DBM(Me)_2$ in our optimised cooperative dual catalysis reaction conditions (Table 27). As expected we observe an increase in the yield (91%) compared to IMesCuDBM (83%), but unfortunately we obtained a significantly lower enantioselectivity (60%) (Table 27, entry 2). Fortunately, when IMesCuCl is used, without the $DBM(Me)_2$, an increase in the enantioselectivity is observed (Table 27, entry 3). We were quite happy with this last result, even though we weren't able to directly correlate results from the mechanistic tests to the dual process's optimisation.

Table 27. Final testing on the dual process



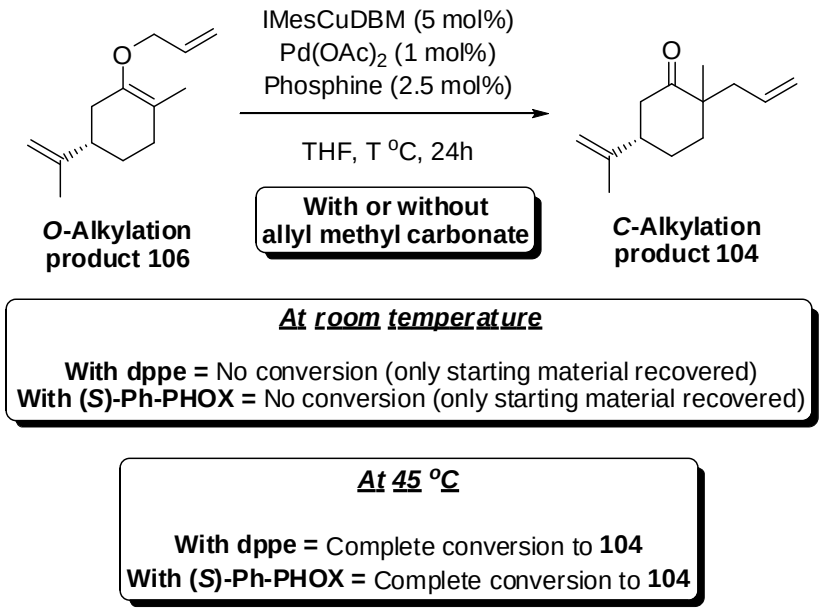
Entry [a]	(NHC)CuX	Additive	110 [b] (%)	e.e. 110 [c] (%)
1	IMesCuDBM	-	83	81
2	IMesCuCl	$DBM(Me)_2$	91	60
3	IMesCuCl	-	83	87

[a] All reactions were run under argon [b] Yield determined on the crude mixture by ^{1}H NMR and GC analysis [c] Enantiomeric excess is determined by GC analysis [d] $DBM(Me)_2$ is added to the copper mixture.

III.3.4.3. *C*-alkylation vs *O*-alkylation

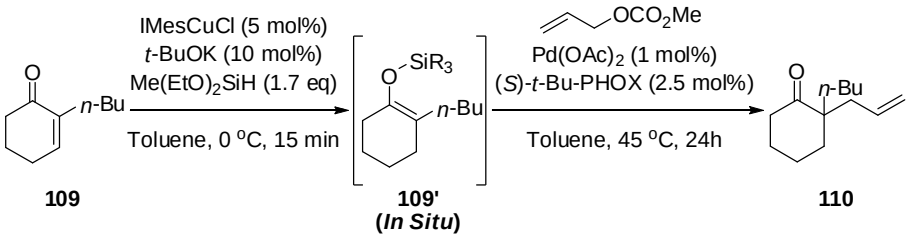
Finally, we decided to investigate a bit further the transformation, which we observed in Table 18, of **106** into **104** using dppe as ligand. We postulated earlier that this transformation probably proceeds *via* a palladium-catalyzed Claisen rearrangement of **106** which is described in the literature.[7] However, when the PHOX ligand series is used at room temperature, only the *C*-alkylation is observed, and the *O*-alkylation is almost suppressed. Therefore, we wanted to see if this observed transformation with the dppe ligand is also occurring with the PHOX ligand, this time at room temperature.

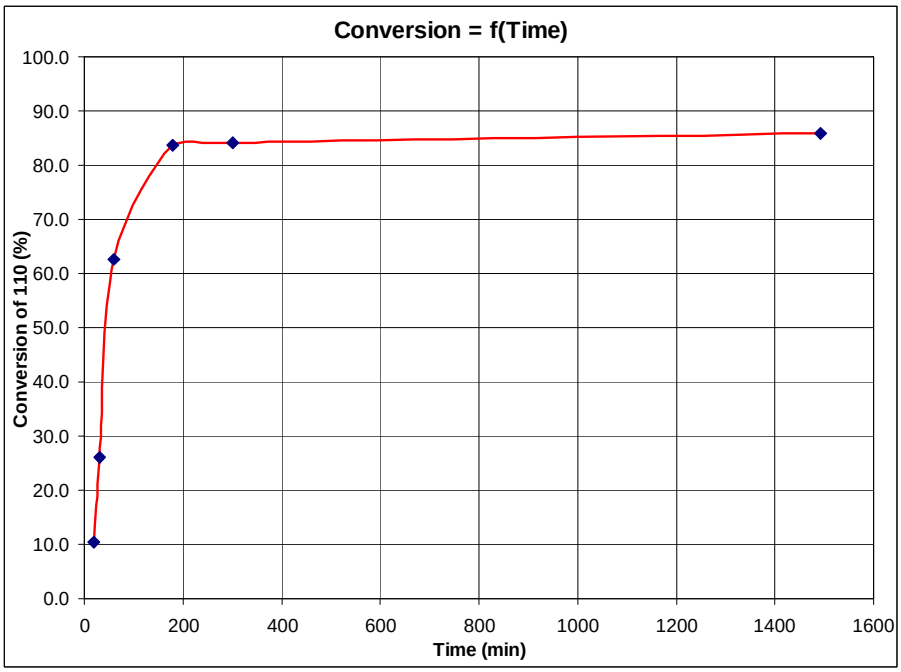
The *O*-alkylation product **106** was isolated and then put in the reaction conditions used for the dual process while varying the temperature, the ligand and the palladium species (Pd^{II} (with the allyl carbonate) or Pd^{0} (without the allyl carbonate) (Scheme 107). At room temperature, no *C*-alkylation product is observed in all cases and only the starting material is recovered. At 45 ^{o}C, total conversion to the *C*-alkylated product is observed with both ligands, and surprisingly both Pd^{0} and Pd^{II} complexes readily catalyse the reaction. As one could expect, it seems that this rearrangement is temperature-dependant and only occurs at 45 ^{o}C. In conclusion, we could safely say that no rearrangement is occurring at room temperature, which means that at least for the carvone's version of the dual catalysis (performed at room temperature), the PHOX ligand directly and selectively forms the *C*-alkylation product.



Scheme 107. Mechanistic tests on substrate **106**

As for the optimised dual process for substrate **109**, the reaction proceeds somewhat differently. The addition of *t*-BuOK dramatically increases the first reaction's rate which is generally finished after 10 minutes generating quantitatively the silyl enolate **109'** (as observed by GC and NMR analysis). But because this silyl enolate doesn't afford product **110** without the copper catalyst, we suspect that the silyl enolate transforms back to the copper enolate which then proceeds to form selectively the desired product **110**. We therefore decided to follow only the second reaction (AAA reaction) by GC and NMR analysis to see its *in situ* behaviour (Scheme 108). As seen in Scheme 108, product **110** is formed at 10% after 20 min and reaches maximum conversion after 3 hours. No *O*-alkylation was observed all along this follow-up.



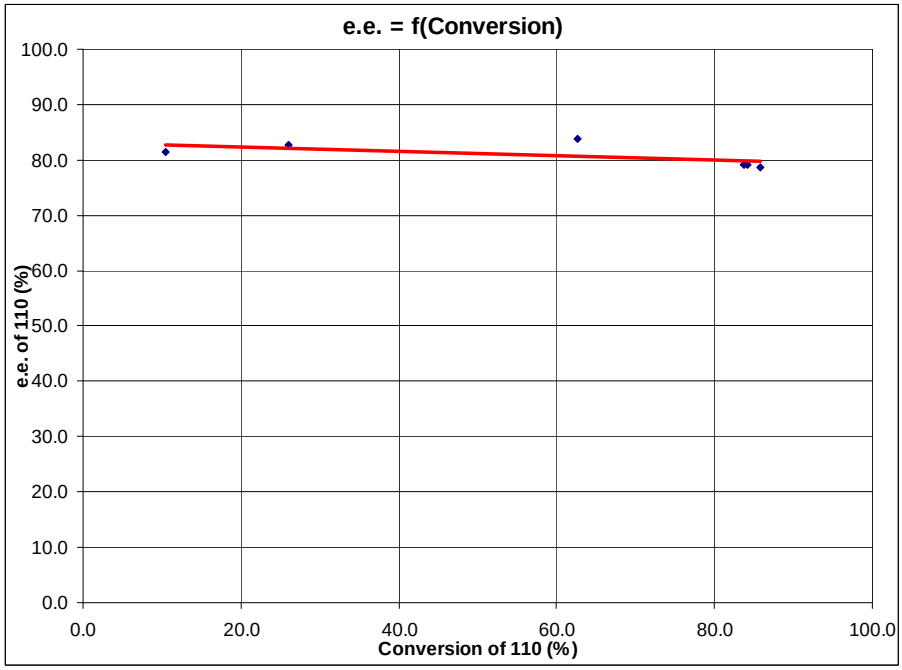


Scheme 108. Plot of the conversion rate of **110** over time

We were also able to draw another plot using the information recorded above. Indeed, we could also observe the progress of the enantioselectivity of **110** all along the reaction, and therefore wanted to see if the advancement of the reaction had any influence on the e.e.. This phenomenon[9] has been reported in the literature and we wanted to make sure it wasn't occurring in our reaction; otherwise the salts' influence reported above could be

[9] D. P. Heller, D. R. Goldberg, W. D. Wulff, *J. Am. Chem. Soc.* **1997**, *119*, 10551.

irrelevant. We were pleased to see that the e.e. rate of **110** was independent of the conversion and thus was stable at ~ 80% all along the reaction.



Scheme 109. Plot of the e.e. rate as a function of the conversion rate of **110**

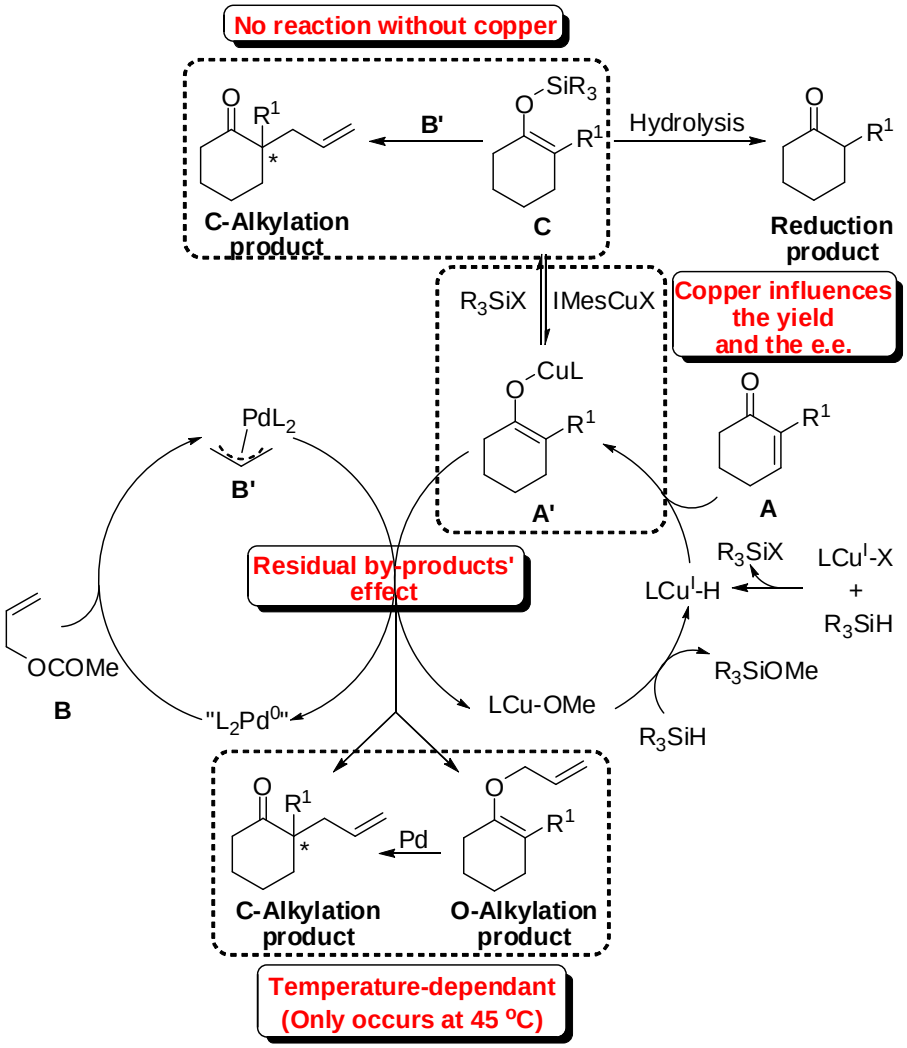
Although the tests above are only qualitative attempts to investigate the reaction's mechanism, they gave us valuable information that allowed us to move forward and optimise even further the reaction at hand.

III.3.4.4. The Final Proposed Mechanism

After all these mechanistic tests, we were able to paint a more detailed picture of the reaction mechanism. As shown in Scheme 110, we now know that:

- The rearrangement of **106** to **104** is temperature-dependant and only occurs at 45 ^{o}C in the presence of both Pd^{0} and Pd^{II} species.

- The PHOX ligand selectively forms the *C*-alkylation product at room temperature.
- Copper is essential to the reaction and the copper enolate intermediate **A'** is most likely the active nucleophilic species, thus validating our reaction as a cooperative dual catalysis process.
- The nature of the copper complex as well as the residual by-products (salts and diallylated DBM) have a significant influence on the reaction yield and enantioselectivity, however their specific role is still unknown.

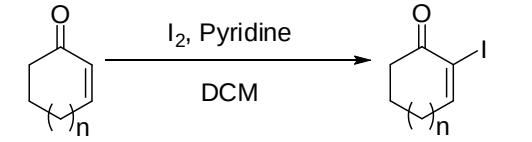


Scheme 110. Final mechanism scheme

III.4. Extension of the Reaction's Scope

In order to extend the reaction's scope, we planed to replace the *n*-butyl group on substrate **109** with different alkyl, benzyl and aryl groups. We also thought of using 5-membered ring ketones as well as 6-membered ring

ketones. Similarly to substrate **109**, we had to synthesise the corresponding 2-iodo substituted enones (5-membered and 6-membered iodoenones). Substrates **108** and **114** were obtained in 87% and 61% yields, respectively starting from the commercially available cyclic enones **107** and **113** (Scheme 111).

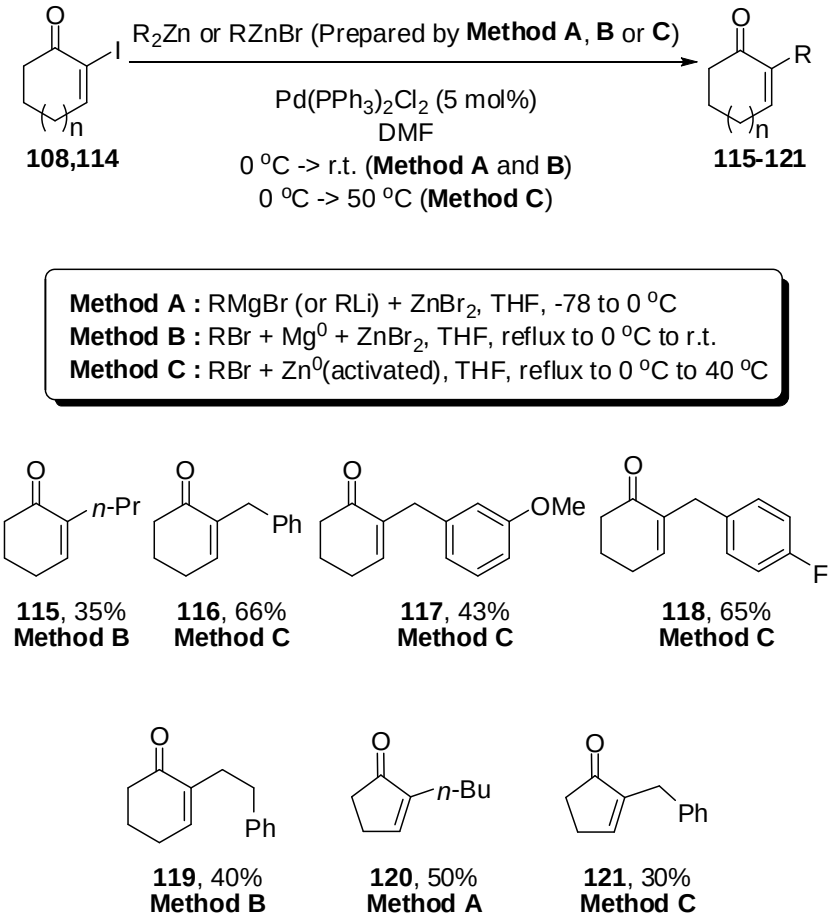


113, n = 0
107, n = 1

114, n = 0, 61%
108, n = 1, 87%

Scheme 111. Synthesis of iodoenones **108** and **114**

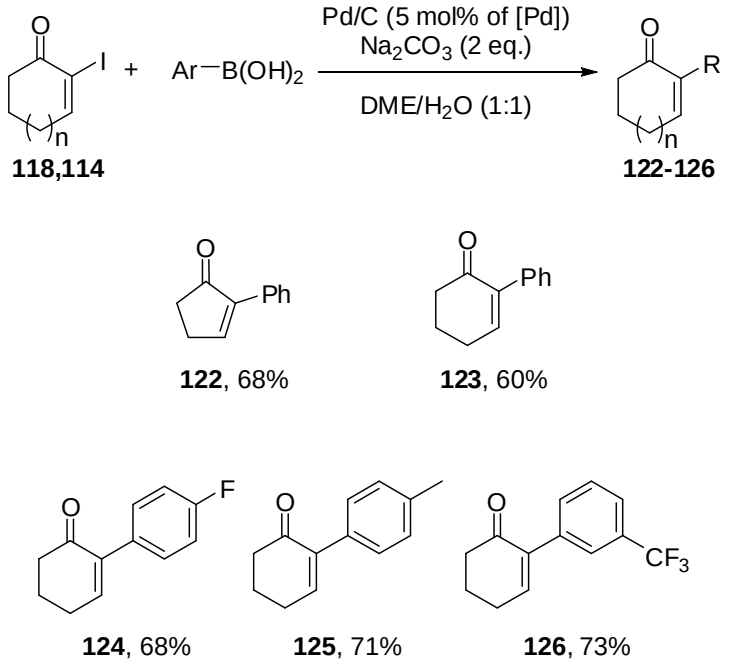
We then engaged these iodoenones in typical Negishi coupling conditions in an effort to obtain different groups substitution at that position (Scheme 112). After a few optimisation reactions, it was obvious that different types of substitution require different coupling conditions. Alkyl groups were found to favour methods **A** or **B** depending on the commercial availability of the Grignard or organolithium reagents. Alternatively, benzyl groups gave higher yields by the use of method **C**. With these three methods at hand, seven new substrates were readily synthesised with acceptable yields.



Scheme 112. Optimised conditions for the Negishi coupling reaction

However, aryl groups needed to be coupled by the way of a Suzuki reaction (Scheme 113). Typical Suzuki conditions found in the literature were sufficient to generate five new substrates in good yields.[10]

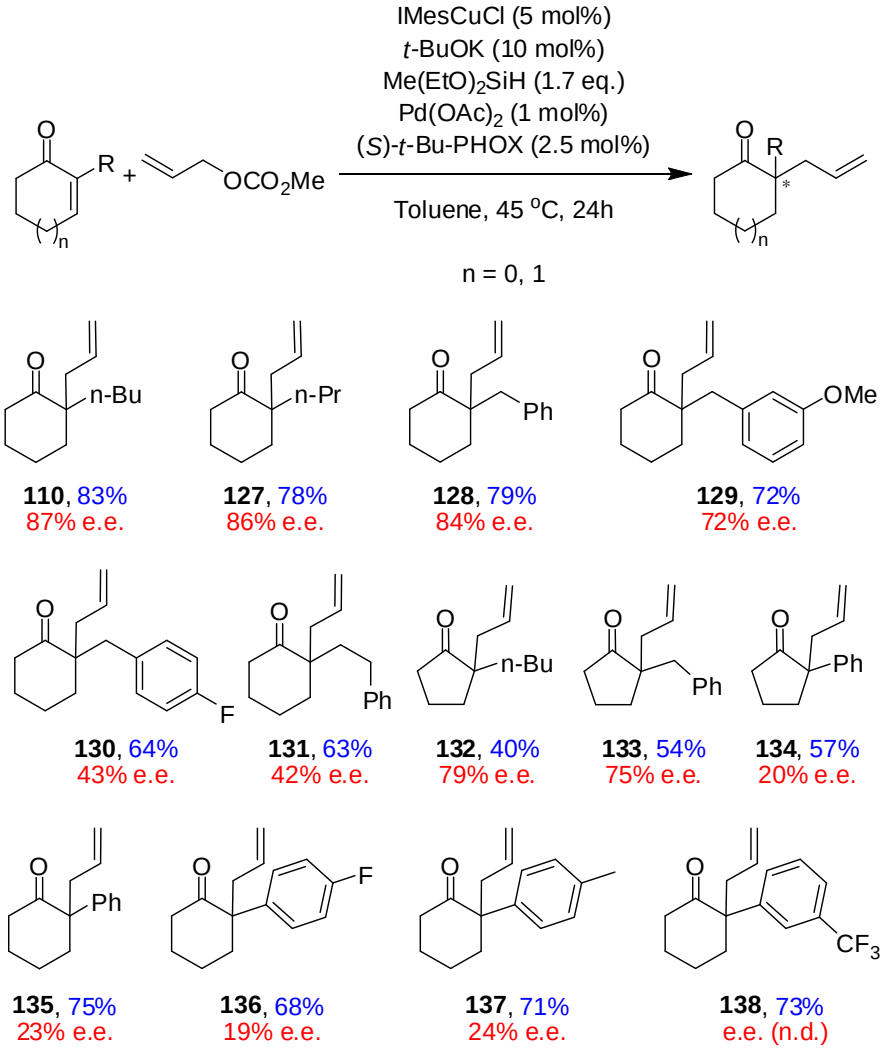
[10] F.-X. Felpin, *J. Org. Chem.* **2005**, *70*, 8575.



Scheme 113. Synthesis of aryl substituted ketones *via* a Suzuki coupling

Finally, we applied our optimised enantioselective version of the dual process onto these twelve new substrates using IMesCuCl as the copper source (Scheme 114). The reaction showed a tolerance toward alkyl and benzyl groups, and the corresponding products were obtained with comparable yields and enantioselectivities. Although aryl groups are also tolerated under these conditions, and **134**-**138** were obtained in good yields, unfortunately low enantioselectivities were observed. This is probably due to the planar structure of the corresponding enolate. Indeed, once the corresponding copper enolate is formed the aryl group will consequently be conjugated to the former rendering this nucleophilic intermediate less sterically hindered which could be responsible for the decrease in enantioselectivity. Furthermore, Michael acceptors with 6-membered rings as well as 5-membered rings readily undergo the reaction using our

optimized conditions. However, 5-membered rings gave a slightly lower enantioselectivity than their 6-membered counterparts, and that's probably due to the difference in conformation between these two types of substrates.[21g]



Scheme 114. Extension of the reaction's scope

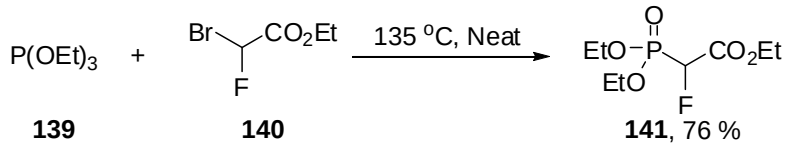
III.5. Reaction's Limitation

Even though we were quite happy with the above results, additional attempts were made to extend this methodology to other substrates, most notably α-fluoroacrylates and other types of ketones.

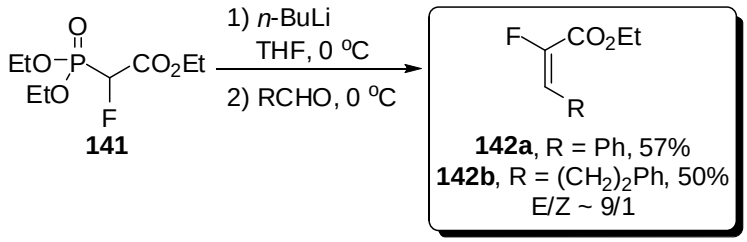
III.5.1.1. α-fluoroacrylates

α-fluoroacrylates are an important class of substrates, and if we were able to apply our methodology to these substrates, we could then obtain enantioselective α-fluoro esters which could be very useful building blocks. α-fluoroacrylates **142a-b** were thus synthesised in two steps starting from commercially available triethylphosphite **139** and substrate **140** (Scheme 115).[11] At first these two latter substrates were reacted *via* an Arbuzov reaction to form the desired product **141** in a 76% yield. Triethyl phosphonoacetate **141** was then transformed into the desired α-fluoroacrylates **142a-b** *via* a Wittig olefination in good yields and stereoselectivities.

[11] M. Engman, J. S. Diesen, A. Paptchikhine, P. G. Andersson, *J. Am. Chem. Soc.* **2007**, *129*, 4536.



139 **140** **141**, 76 %

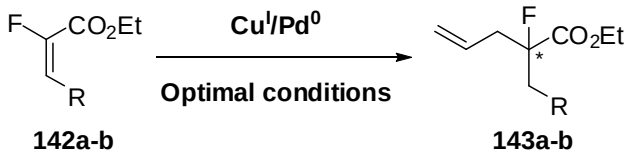


141

142a, R = Ph, 57%
142b, R = $(CH_2)_2$Ph, 50%
E/Z ~ 9/1

Scheme 115. Synthesis of α-fluoroacrylates **142a-b**

Substrates **142a** and **142b** were subsequently engaged in our reaction conditions (Scheme 116). Unfortunately, no reaction occurred and only the starting material was observed each time. After several attempts, we suspected that the main problem came from the reluctance of such substrates to undergo the copper catalyzed 1,4-reduction reaction. Consequently, these substrates weren't suitable for our reaction conditions.



142a-b **143a-b**

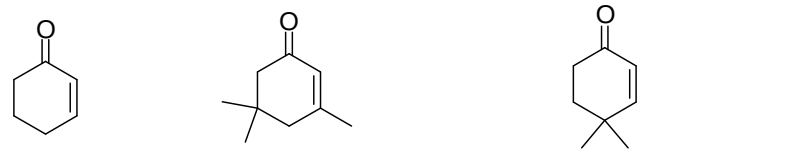
No reaction
(only starting material is recovered)

Scheme 116. Dual catalysis tests on substrates **142a-b**

III.5.1.2. Other Types of Ketones

Afterwards, we turned our attention to an easier task by attempting to apply our methodology to other types of ketones, particularly some commercially available ketones. As seen in Scheme 117, the three ketones that we chose

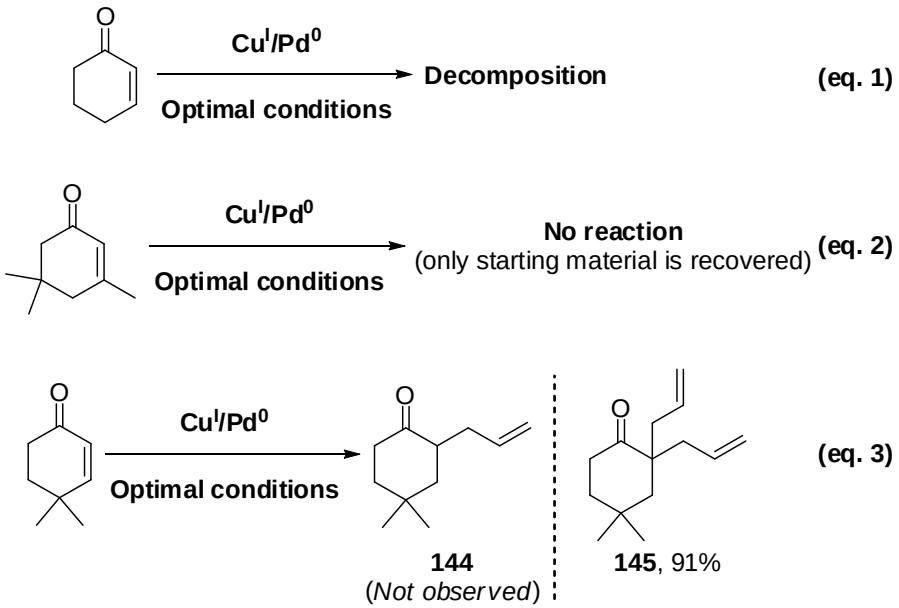
are all commercially available and are particularly interesting, as they all have no substituent on the double bond position α to the carbonyl group.



2-Cyclohexenone **Isophorone** **4,4-dimethyl-2-cyclohexenone**

Scheme 117. Commercially available ketones

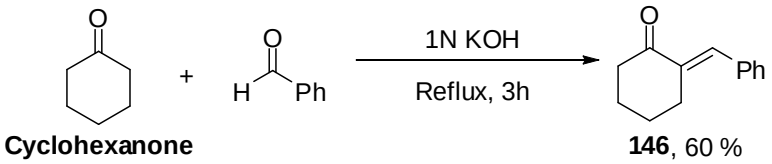
These enones were engaged in our reaction conditions (Scheme 118). Unfortunately, none of the selected enones furnished the desired *C*-alkylated product. However several interesting observations were duly noted. 2-cyclohexanone failed to generate any identifiable product and only decomposition of the starting material was observed probably resulting from its auto-condensation or dimerisation (eq. 1). Moreover, no reaction was also observed with isophorone as it was the only product recovered at the end of the reaction (eq. 2). Further tests showed that isophorone is reluctant to be reduced by our copper hydride complex. Interestingly enough, 4,4-dimethyl-2-cyclohexenone also failed to deliver the desired allylated product **144**, however a 91% conversion to the di-allylated product **145** was observed (eq. 3). Finally, we decided not to pursue this route any further. Though products such as **145** could be interesting, no asymmetric catalysis could be applied in this case rendering the methodology less attractive.



Scheme 118. Dual catalysis tests on the selected ketones

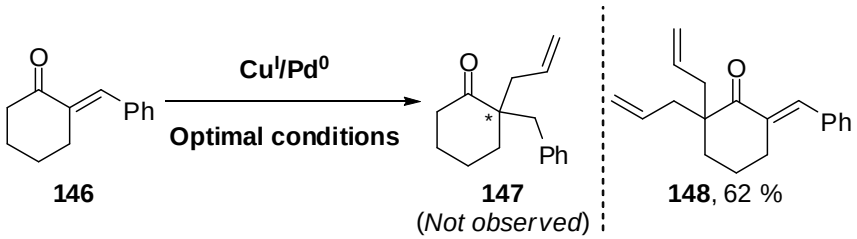
One last type of enones was also attempted as we synthesised substrate **146**, an enone with an exocyclic double bond (Scheme 119). Substrate **146**, if it undergoes our optimised reaction procedure, will give the same product **128**. This will offer a new way to access the previously described products **110** and **127** to **138** (see Schem 114). Moreover, these starting material are very easily accessible starting from the corresponding cyclic ketone.[12] In that manner, substrate **146** was prepared *via* condensation of cyclohexanone onto benzaldehyde in basic conditions (Scheme 119).

[12] S. M. Lu, C. Bolm, *Angew. Chem. Int. Ed.* **2008**, *47*, 8920.



Scheme 119. Synthesis of substrate **146**

We then engaged this newly obtained substrate in our optimised reaction conditions, but failed to observe the desired alkylated product **147** (Scheme 120). Instead we isolated product **148** in a 62% yield. We investigated the problem and found that this type of double bonds was also reluctant to react with the copper hydride complex. Interesting as it may seems, the di-allylated product **148** offers no opportunities to do asymmetric catalysis and therefore was not further pursued.



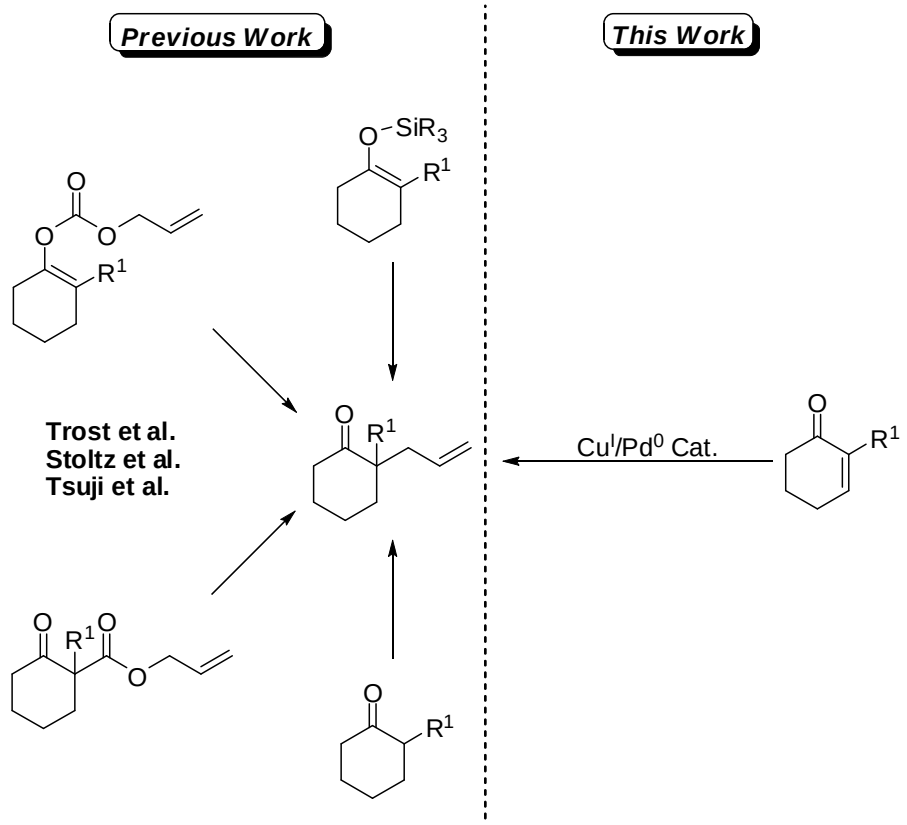
Scheme 120. Dual catalysis tests on substrate **146**

However, this last bad news could be no bad news at all, depending on how you look at it. It seems that our reaction is quite selective and if given a choice between exocyclic enones and endocyclic enones, it will solely react with the latter. This selectivity underlines even further the importance of our method and thus giving a new meaning to the phrase “looking at the glass half full”.

IV. Conclusions

In conclusion we have successfully developed a new method to access α-allylated ketones.[1] This new Cu^I/Pd^0 cooperative dual catalysis reaction is based on the catalytic coupling of the two organometallic intermediates. Thus, the Cu^I catalytic cycle generates the starting material for the Pd^0 catalytic cycle. Although the reagents are present in stoichiometric amounts in the reaction mixture and are in principal able to trap both active species (four different possible pathways), the reaction proceeds as desired. The reaction mechanism has also been investigated. Its details and implicated intermediates, along with their influence on the desired reactivity, have also been explored.

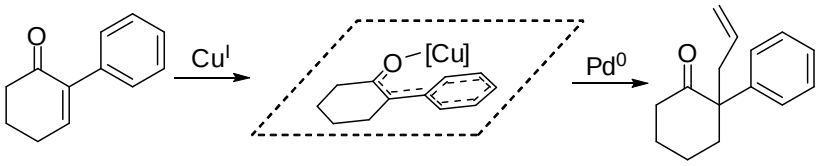
[1] F. Nahra, Y. Mace, D. Lambin, O. Riant, *Angew. Chem. Int. Ed.* **2013**, *52*, 3208.



Scheme 121. Previous *vs* current work to access α-allylated ketones

A diastereoselective version of this dual process has been developed on D-(+)-carvone which allowed us to develop an enantioselective version later on. Thirteen substrates successfully underwent this enantioselective dual process, thus generating comparable yields and enantioselectivities. The method seems to tolerate alkyl and benzyl groups substitutions α to the carbonyl, allowing the enantioselective construction of various quaternary centres. Even though aryl groups gave low enantioselectivities, good yields were obtained. We suspected that enolate intermediates of these types of substrates such as **123'** have a planar structure due to the conjugation of the enolate system with the substituted aryl (Scheme 122). The newly formed

system renders this nucleophilic intermediate less sterically hindered, which could be responsible for the decrease in enantioselectivity.



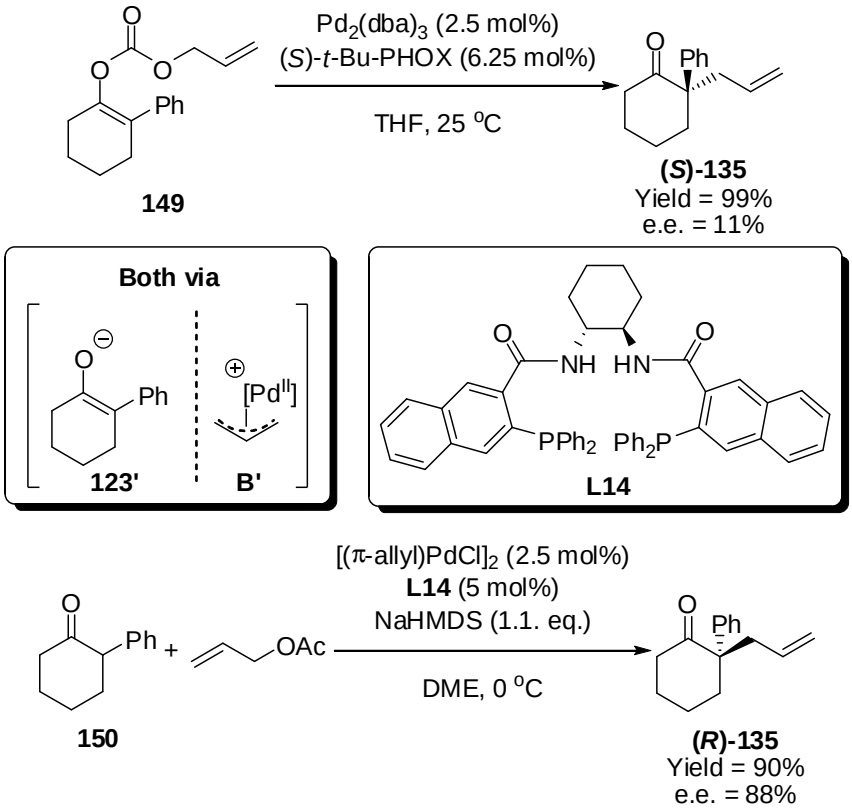
123 **123'** **135**

Scheme 122. The planar structure of enolate intermediate **123'**

To remedy this problem, two solutions could be undertaken:

- The easy solution could be to use *ortho*-substituted aryls which could eventually break this planary system and thus hinder the approach of the electrophile. However this solution is not a general one and will therefore be dependant on the substrate.
- The other solution is to optimise the palladium complex and most notably the chiral phosphine, in an attempt to better differentiate the two sides of the enolate.

The latter solution is the most attractive approach to us. As we showed earlier in the bibliographic introduction, the PHOX ligand series and the Trost ligand series are highly complementary. Where the first fails, the other succeeds. A more tangible example of this hypothesis could be found in the literature, where the same intermediates are involved (Scheme 123).[21g] When substrate **149** and **150** are put in the two reaction conditions described below, they generate the same intermediates **123'** and **B'**. Those two intermediates are exactly the same intermediates implicated in our reaction. As we can see, when (*S*)-*t*-Bu-PHOX is used, a low enantioselectivity is obtained which is in accordance with our previous observations. However, when Trost's ligand (**L14**) is used, high enantioselectivity is achieved with the same intermediates.

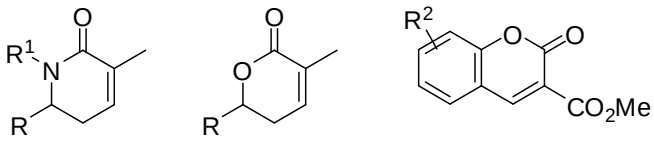


Scheme 123. Comparing Stoltz and Trost's work on product **135**

However, no effort has yet been made to optimise the reaction for the aryl-substituted ketones (**122** to **126**) based on the hypothesis laid above. But future plans are drawn and will be implemented in the near future.

V. Perspectives

The success of the herein described cooperative dual catalysis reaction encouraged us to extend this methodology even further. The first extension of this methodology is currently being done in collaboration with a Masters student Arnaud Boreux. This work involves applying our optimised procedure onto new types of substrates, more particularly lactones and lactames. Coumarines could also be suitable substrates for this dual process and were therefore selected as well. Current tests are showing promising results and full disclosure of their reactivity will be described in more details in Arnaud's Master thesis later on.

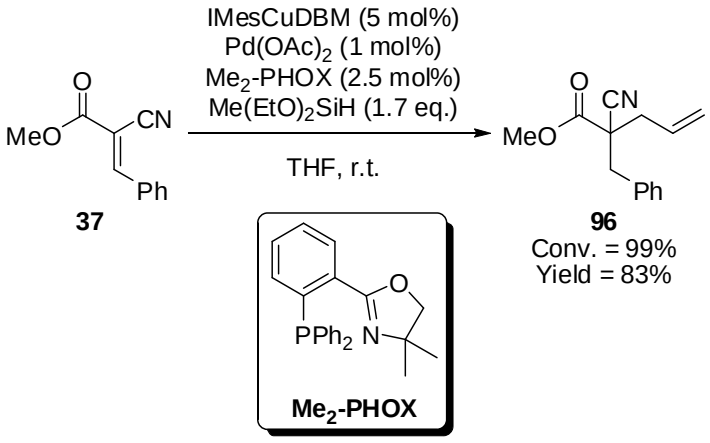


R = Aryl
R^1 = Ts, Bn, CO_2Me
R^2 = H, OMe

Scheme 124. Selected substrates to be engaged in our dual process

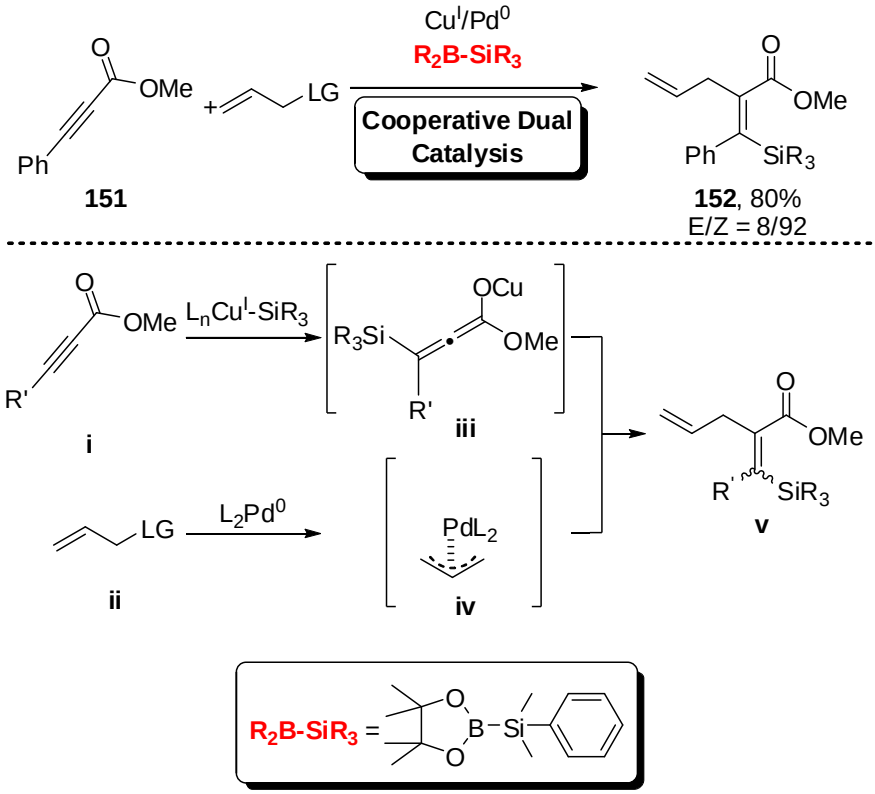
However, one old substrate was picked up once again in this study and engaged in our racemic conditions. Under these conditions, substrate **37** gave a high yield of the desired allylated product **96**. This promising result encouraged us to start the development of an enantioselective version along with the extension of the reaction's scope. For that reason, we are in the process of synthesising various α,β-unsaturated malonates similar to **37** in an effort to engage them in our optimised conditions later on.[1]

[1] See Arnaud Boreux's Master thesis **2013**.



Scheme 125. Dual process re-applied on substrate **37**

An additional extension of this methodology was further developed in collaboration with another PhD student (Sébastien Vercruysse). This collaboration involved applying the newly developed dual process onto Michael acceptors bearing a triple bond. We also replaced the hydride source with a silane source, thus the first reaction became a copper-catalyzed 1,4-silylation reaction instead of a 1,4-reduction reaction. This cooperative dual process is now more suitably called 1,4-silylation/alkylation reaction. Similarly to our process, this new strategy involves a copper-catalyzed 1,4-silylation of Michael acceptor **i** to form the copper allenoate intermediate **iii**. Oxidative addition of Pd^{0} onto **ii** generates the π-allyl palladium species **iv**, and the subsequent coupling of the two catalytic species (**iii** and **iv**) affords the desired product **v**. Optimisation of this reaction has been completed on substrate **151** allowing us to obtain a high yield and a good stereoselectivity of product **152**. We are now in the final stages of this study. Various substrates, similar to **151**, are being synthesised, characterised and then engaged in the optimised procedure.



Scheme 126. The Cu^{I}/Pd^{0} catalyzed 1,4-silylation/alkylation reaction

All of the above extended methodologies are showing very promising results. Unfortunately, we weren't able to include them in the main body of this chapter due to the fact that they are still incomplete. Nevertheless, the success of these different variations of our Cu^{I}/Pd^{0} dual process emphasises quite clearly the huge potential of such a strategy.

Chapter 3: Synthesis, Characterisation and Reactivity of (Carbene)CuX Complexes

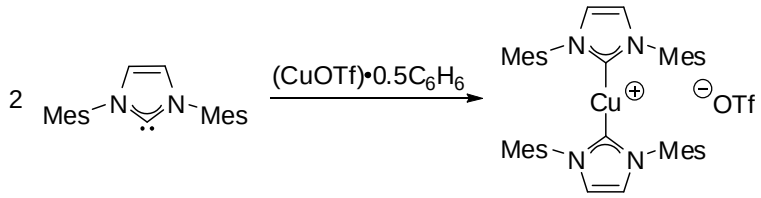
I. Bibliographic Introduction

Earlier in this manuscript (see general introduction), we introduced the emerging role of NHCs in organometallic synthesis and their important characteristics as a new class of ligand for metal catalysis. In this introduction, we're going to focus more specifically on the development of (NHC)Cu^{I} complexes and their use in catalysis. Herein we describe in more details the synthesis of such complexes, as well as their use in important reactions that are of interest to this work. Furthermore, some attention is also given to the ADC (acyclic diaminocarbene) type ligand, a new type of carbene ligands that has found a growing success in recent years.

I.1. *N*-Heterocyclic Carbenes (NHCs)

I.1.1. Synthesis of (NHC)Cu^{I} Complexes

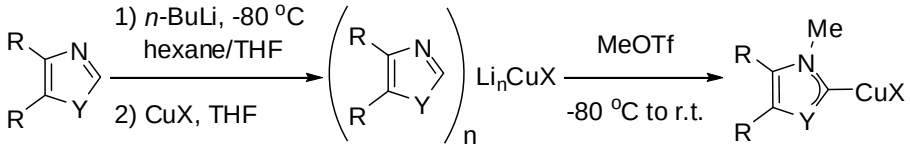
The first reported (NHC)Cu^{I} species was a bis(NHC) cationic complex of copper(I) prepared by Arduengo *et al* from a triflate salt and two equivalents of an imidazol-2-ylidene (Scheme 127).[1]



Scheme 127. Arduengo *et al*'s first reported (NHC)$_2$$Cu^{I}$ complex

[1] A. J. Arduengo III, H. V. R. Dias, J. C. Calabrese, F. Davidson, *Organometallics* **1993**, *12*, 3405.

A year later, Raubenheimer and co-workers[2] synthesized neutral mono(carbene) copper(I) complexes by alkylation of thiazolyl or imidazolyl cuprates (Scheme 128).



Scheme 128. Raubenheimer *et al*'s synthesis of (NHC)Cu^{I} complexes

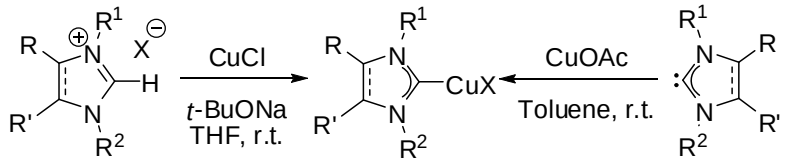
Later on, monomeric (NHC)CuX complexes were obtained by deprotonation of the starting salt with copper(I) oxide.[3] This preparation avoids the use of strong bases and generates only water as by-product. However, this kind of complexes are now more generally prepared by reacting a copper(I) salt (CuCl, CuBr, CuI, or CuOAc) with a free carbene, either isolated or generated *in situ* (Scheme 129).[4]

---

[2] a) H. G. Raubenheimer, S. Cronje, P. H. van Rooyen, P. J. Olivier, J. G. Toerien, *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 672; b) H. G. Raubenheimer, S. Cronje, P. J. Olivier, *J. Chem. Soc., Dalton Trans.* **1995**, 313.

[3] a) A. A. D. Tulloch, A. A. Danopoulos, S. Kleinhenz, M. E. Light, M. B Hursthouse,. G. Eastham, *Organometallics* **2001**, *20*, 2027; b) R. McKie, J. A. Murphy, S. R. Park, M. D. Spicer, S.-z. Zhou, *Angew. Chem., Int. Ed.* **2007**, *46*, 6525.

[4] a) N. P. Mankad, T. G. Gray, D. S. Laitar, J. P. Sadighi, *Organometallics* **2004**, *23*, 1191; b) N. Schneider, V. César, S. Bellemin-Laponnaz, L. H. Gade, *J. Organomet. Chem.* **2005**, *690*, 5556; c) C. Michon, A. Ellern, R. J. Angelici, *Inorg. Chim. Acta* **2006**, *359*, 4549.



X = Cl, BF_4, PF_6

Scheme 129. Preferred methods for the generation of (NHC)Cu^I complexes

These (NHC)CuX complexes are air- and moisture-stable and have been used as convenient precursors of usually more unstable related compounds. Thus, alkoxide,[5] boryl,[6] dibenzoylmethanoate (DBM),[7] cyclopentadienyl,[8] and alkyl[9] derivatives have been prepared from the halogenated complexes. Similarly, the acetate-containing complexes have been transformed into their corresponding alkyl,[4a,10] anilido, alkoxide, acetylide,[9a,11] or thiolate[12] analogues (Scheme 130).

---

[5] N. P. Mankad, D. S. Laitar, Sadighi, J. P. *Organometallics* **2004**, *23*, 3369.

[6] D. S. Laitar, P. Müller, J. P. Sadighi, *J. Am. Chem. Soc.* **2005**, *127*, 17196.

[7] A. Welle, S. Díez-González, B. Tinant, S. P. Nolan, O. Riant, *Org. Lett.* **2006**, *8*, 6059.

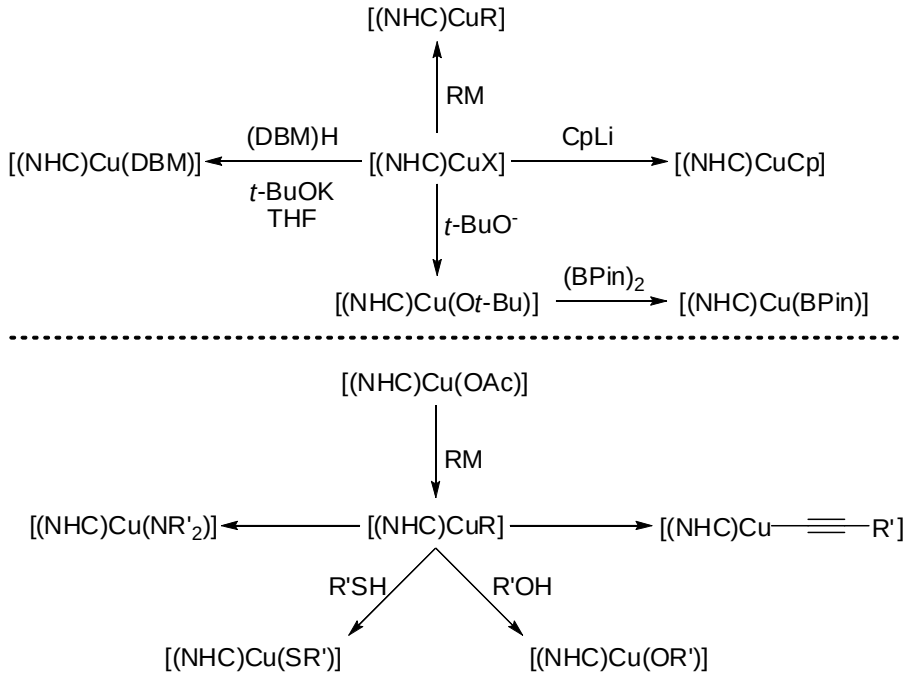
[8] H. Ren, X. Zhao, S. Xu, H. Song, B. Wang, *J. Organomet. Chem*. **2006**, *691*, 4109.

[9] a) L. A. Goj, E. D. Blue, S. A. Delp, T. B. Gunnoe, T. R. Cundari, A. W. Pierpont, J. L. Petersen, P. D. Boyle, *Inorg. Chem.* **2006**, *45*, 9032; b) M. Niemeyer, *Z. Anorg. Allg. Chem.* **2003**, *629*, 1535.

[10] L. A. Goj, E. D. Blue, S. A. Delp, T. B. Gunnoe, T. R. Cundari, J. L. Petersen, *Organometallics* **2006**, *25*, 4097.

[11] L. A. Goj, E. D. Blue, C. Munro-Leighton, T. B. Gunnoe, J. L. Petersen, *Inorg. Chem*. **2005**, *44*, 8647.

[12] S. A. Delp, C. Munro-Leighton, L. A. Goj, M. A. Ramírez, T. B. Gunnoe, J. L. Petersen, P. D. Boyle, *Inorg. Chem.* **2007**, *46*, 2365.



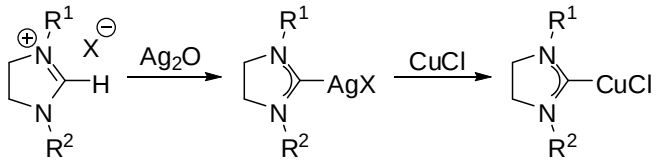
Scheme 130. The use of (NHC)CuX complexes as precursors

Alternatively, (NHC)Cu^{I} complexes can be prepared by carbene transfer from the corresponding (NHC)Ag^{I} reagents,[13] a frequent approach for the preparation of NHC complexes of late transition metals (Scheme 131).[14]

---

[13] a) P. L. Arnold, A. C. Scarisbrick, A. J. Blake, C. Wilson, *Chem. Commun.* **2001**, 2340; b) X.-J. Wan, F.-B. Xu, Q.-S. Li, H.-B. Song, Z.-Z. Zhang, *Inorg. Chem. Commun.* **2005**, *8*, 1053; c) O. Winkelmann, C. Näther, U. Lüning, *J. Organomet. Chem*. **2008**, *693*, 923.

[14] I. J. B. Lin, C. S. Vasam, *Coord. Chem. Rev.* **2007**, *251*, 642, and references cited therein.



Scheme 131. Carbene transfer from silver(I) to copper(I)

It should be noted that all the above syntheses that involve copper halogene species, always use Cl^-, Br^- or I^- as counter-ions with no or little mention of F^--containing complexes. Late transition metal complexes containing a fluoro ligand are of considerable interest due to their high reactivity,[15] relevance to metal-mediated C-F bond cleavage,[16] formation[17] and potential use in catalysis.[18] However, their rare abundance compared to their analogous chloro, bromo, and iodo complexes, is due to two main reasons.

---

[15] a) J. Vicente, J. Gil-Rubio, D. Bautista, *Inorg. Chem.* **2001**, *40*, 2636; b) J. E. Veltheer, P. Burger, R. G. Bergman, *J. Am. Chem. Soc.* **1995**, *117*, 12478.

[16] : a) J. L. Kiplinger, T. G. Richmond, C. E. Osterberg, *Chem. Rev.* **1994**, *94*, 373; b) G. Ferrando-Miguel, H. Gérard, O. Eisenstein, K. G. Caulton, *Inorg. Chem.* **2002**, *41*, 6440; c) N. A. Jasim, R. N. Perutz, A. C. Whitwood, T. Braun, J. Izundu, B. Neumann, S. Rothfeld, H.-G. Stammler, *Organometallics* **2004**, *23*, 6140.

[17] a) S.L. Fraser, M. Y. Antipin, V. N. Khroustalyov, V. V. Grushin, *J. Am. Chem. Soc.* **1997**, *119*, 4769; b) P. Barthazy, A. Togni, A. Mezzetti, *Organometallics* **2001**, *20*, 3472.

[18] a) A. Mezzetti, C. Becker, *Helv. Chim. Acta* **2002**, *85*, 2686-2703; b) N. M. Doherty, N. W. Hoffmann, *Chem. Rev.*, **1991**, *91*, 553; c) E. F. Murphy, R. Murugavel, H. W. Roesky, *Chem. Rev.* **1997**, *97*, 3425; d) V. V. Grushin, *Acc. Chem. Res.* **2010**, *43*, 160; e) V. V. Grushin, W. J. Marshall, *J. Am. Chem. Soc.* **2004**, *126*, 3068; f) V. V. Grushin, *Chem. Eur. J.* **2002**, *8*, 1006.

First, according to the hard-soft acid-base theory,[19] the "hard" fluoride ion is mismatched with the "soft" cations of late transition metals in low oxidation states. Second, the π-donating ability of the fluoro ligand can lead to destabilizing interactions with filled d-orbitals.[20] The resulting metal-fluorine bond tends to be labile and reactive.[21] Thus, despite the attention paid to late transition metal fluoride complexes, group 11 metals have long been neglected, with only a small number of examples found in the literature.[22,23,24] NHC ligands, particularly of the type developed by Arduengo[25] and co-workers, appeared ideally suited to overcome the difficulties associated with copper(I) fluoride complexes, to stabilize

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[19] a) I. Leden, J. Chatt, *J. Chem. Soc.* **1955**, 2936; b) R. G. Pearson, *J. Am. Chem. Soc.* **1963**, *85*, 3533.

[20] K. Fagnou, M. Lautens, *Angew. Chem. Int. Ed.* **2002**, *41*, 26.

[21] a) M. C. Pilon, V. V. Grushin, *Organometallics* **1998**, *17*, 1774; b) A. Yahav, I. Goldberg, A. Vigalok, *J. Am. Chem. Soc.* **2003**, *125*, 13634; c) P. Nilsson, F. Pampler, O. F. Wendt, *Organometallics* **2003**, *22*, 5235.

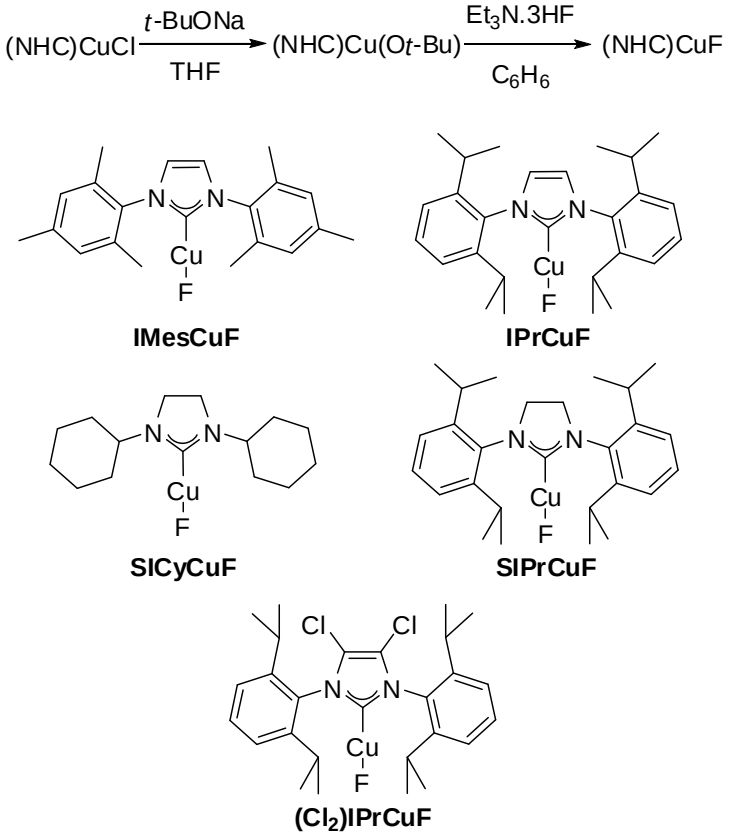
[22] a) D. J. Gulliver, W. Levason, M. Webster, *Inorg. Chim. Acta.* **1981,** *52*, 153; b) M. K. Chaudhuri, S. S. Dhar, N. Vijayashree, *Trans. Met. Chem.* **2000**, *25*, 559; c) B. F. Straub, F. Rominger, P. Hofmann, *Inorg. Chem.* **2000**, *39*, 2113.

[23] a) Q. Wang, G. Guo, T. C. W. Mak, *Polyhedron* **2003**, *22*, 217; b) P. J. Steel, C. J. Sumby, *Chem. Commun.* **2002**, 322; c) Q. Wang, T. C. W. Mak, *Chem. Commun.* **2000**, 1435.

[24] a) J. R. Herron, Z. T. Ball, *J. Am. Chem. Soc.* **2008**, *130*, 16486; b) J. R. Herron, V. Russo, E.J. Valente, Z. T. Ball, *Chem. Eur. J.* **2009**, *15*, 87136; c) V. Russo, J. R. Herron, Z. T. Ball, *Org. Lett.* **2010**, *12*, 220; d) D. S. Laitar, Ph.D. thesis, Massachusetts Institute of Technology (Cambridge), **2006**; e) T. Fujihara, T. Xu, K. Semba, J. Terao, Y. Tsuji, *Angew. Chem. Int. Ed.* **2011**, *50*, 523.

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

copper(I) fluoride and to afford solubility in aprotic organic solvents. To our knowledge, only five NHC copper(I) fluoride complexes have been reported in the literature, IPrCuF, SIPrCuF, SICyCuF, IMesCuF and (Cl_2)IPrCuF, available upon treatment of [(NHC)Cu(O*t*-Bu)] with Et_3N•3HF (Scheme 132).[24]



Scheme 132. Procedure for the preparation of (NHC)Cu^{I} fluorides

Uniquely, these (NHC)CuF complexes are soluble in a wide range of organic solvents and demonstrate a high catalytic activity towards some catalytic transformations.

Even if efforts have focused mainly on Cu^{I} species, some (NHC)Cu^{II} complexes are also known in the literature. The first example, a divalent copper complex with a chelating tris(NHC) ligand, was prepared by Meyer and co-workers[26] by oxidation of its Cu^{I} analogue. Other Cu^{II} complexes have been synthesized by reactions with (NHC)lithium adducts[27] or free carbenes,[26,28] and by carbene transfer from silver species.[29]

I.1.2. The Use of (NHC)Cu^{I} Complexes in Catalysis

I.1.2.1. Reduction of Carbonyl Compounds

The reduction of carbonyl and pseudo-carbonyl functions is a fundamental reaction in organic synthesis.[30] Transition-metal catalysis has been successfully applied to the reduction of olefins, alkynes, and many carbonyl compounds *via* hydrogenation or hydrosilylation.[31] "Cu–H" is among the earliest metal hydrides reported in the literature[32] but, for a long time, it was

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[26] X. Hu, I. Castro-Rodriguez, K. Meyer, *J. Am. Chem. Soc.* **2003**, *125*, 12237.

[27] P. L. Arnold, M. Rodden, K. M. Davis, A. C. Scarisbrick, A. J. Blake, C. Wilson, *Chem. Commun*. **2004**, 1612.

[28] J. Yun, D. Kim, H. Yun, *Chem. Commun.* **2005**, 5181.

[29] A. O. Larsen, W. Leu, C. Nieto Oberhuber, J. E. Campbell, A. H. Hoveyda, *J. Am. Chem. Soc*. **2004**, *126*, 11130.

[30] M. B. Smith, J. March, *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 5th ed.; Wiley-Interscience: New York, **2001**; pp 1544–1604.

[31] a) I. Ojima, Z. Li, J. Zhu, In *The Chemistry of Organic Silicon Compounds*; Eds., Z. Rappoport, Y. Apeloig; Wiley: New York, **1998**; Vol. 2, Part 1, pp 1687–1792; b) O. Riant, N. Mostefaï, J. Courmarcel, *Synthesis* **2004**, 2943.

[32] A. Wurtz, *Ann. Chim*. **1844**, *11*, 250.

considered too unstable to be used in organic chemistry.[33] As seen in the first chapter of this manuscript, pioneering work by Stryker and Lipshutz showed that a stabilized form of copper hydride, $[(Ph_3P)CuH]_6$, is a convenient reagent for the reduction of carbonyl derivatives. Since then, copper catalysis has become a well-established method for a number of reductions.[34] (NHC)Cu^I complexes, and IPrCuCl in particular, were first reported as catalysts in the conjugate reduction of α,β-unsaturated esters and cyclic enones (Scheme 133).[35] High yields were obtained in both instances at room temperature using a silane as a hydride source. Nolan[36] *et al*'s concomitant work showed that the same complex could be used in the hydrosilylation of simple ketones to afford the corresponding silyl ethers in excellent yields (Scheme 133).

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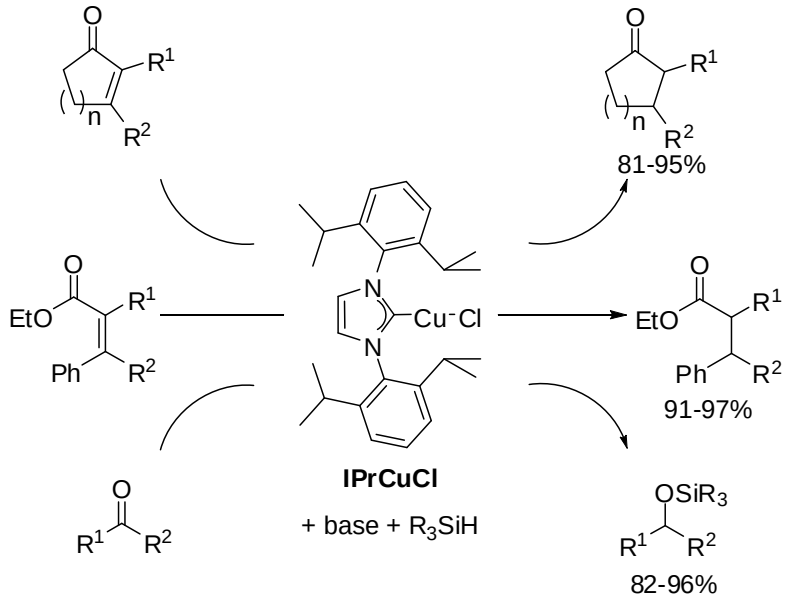
[33] a) R. K. Boeckman Jr., R. Michalak, *J. Am. Chem. Soc*. **1974**, *96*, 1623; b) M. F. Semmelhack, R. D. Stauffer, *J. Org. Chem.* **1975**, *40*, 3619; c) H. Brunner, W. Miehling, *J. Organomet. Chem.* **1984**, *275* (Issue 2), C17.

[34] a) S. Rendler, M. Oestreich, *Angew. Chem., Int. Ed*. **2007**, *46*, 498; b) S. Díez-González, S. P. Nolan, *Acc. Chem. Res.* **2008**, *41*, 349.

[35] V. Jurkauskas, J. P. Sadighi, S. L. Buchwald, *Org. Lett*. **2003**, *5*, 2417.

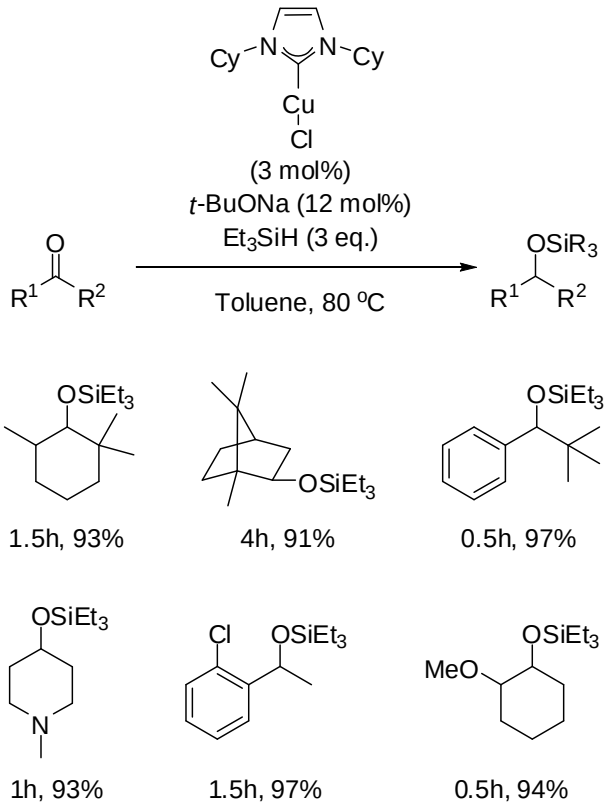
[36]) a) H. Kaur, F. K. Zinn, E. D. Stevens, S. P. Nolan, *Organometallics* **2004**, *23*, 1157; b) B. Bantu, D. Wang, K. Wurst, M. R. Buchmeiser, *Tetrahedron* **2005**, *61*, 12145.



Scheme 133. (IPr)CuCl-catalyzed reduction and hydrosilylation reactions

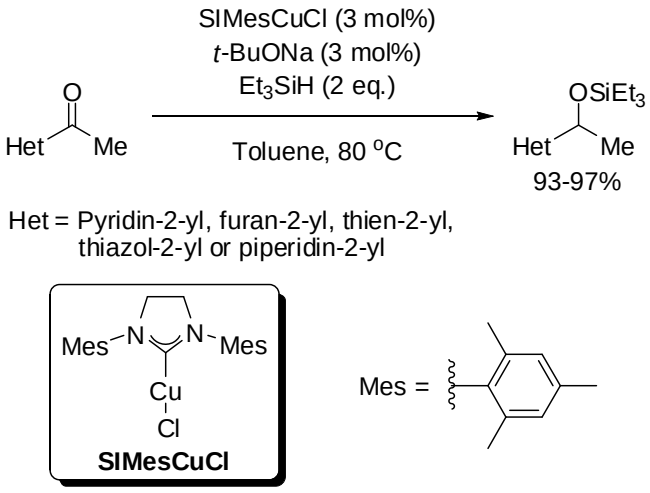
For more challenging ketones, ICy turned out to be a more effective ligand. Thus, in the presence of ICyCuCl, a number of ketones with varying congestion around the carbonyl function alkyl, aromatic, aliphatic, cyclic, and bicyclic ketones are efficiently reduced (Scheme 134).[37] Even highly congested starting materials yield the corresponding silyl ethers in high yields and acceptable reaction times. This catalytic system was also successfully applied to ketones incorporating a diversity of functional groups such as amine, ether, or halogen.

[37] S. Díez-González, H. Kaur, F. K. Zinn, E. D. Stevens, S. P. Nolan, *J. Org. Chem.* **2005**, *70*, 4784.



Scheme 134. Hydrosilylation of hindered and functionalized ketones

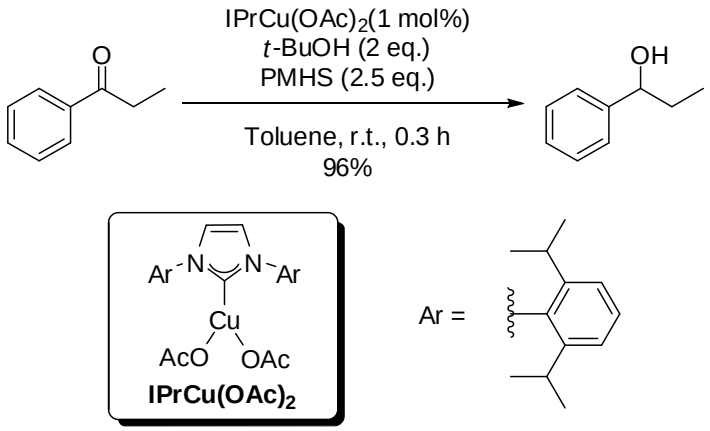
However, despite its broad scope, ICyCuCl was inefficient in the hydrosilylation of heteroaromatic ketones. In this case, the best results were obtained with SIMes as ligand (Scheme 135).



Scheme 135. Hydrosilylation of heteroaromatic ketones

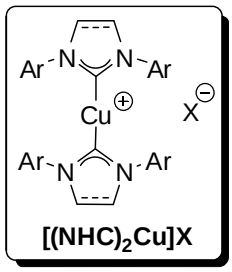
Interestingly, Yun[28] *et al* reported that Cu^{II} salts, in combination with an NHC ligand, can be employed for the hydrosilylation of ketones, as they had previously shown with a chiral phosphine[38] (Scheme 136). However, no evidence is currently available to unequivocally determine whether the active species is a Cu^{I} or a Cu^{II} hydride.

[38] D.-w. Lee, J. Yun, *Tetrahedron Lett.* **2004**, *45*, 5415.



Scheme 136. Yun *et al*'s system for the hydrosilylation of ketones

Another family of NHC-containing complexes of general formula $[(NHC)_2Cu]X$ (X = PF_6^- or BF_4^-), has recently been the subject of a thorough study (Scheme 137).[39]

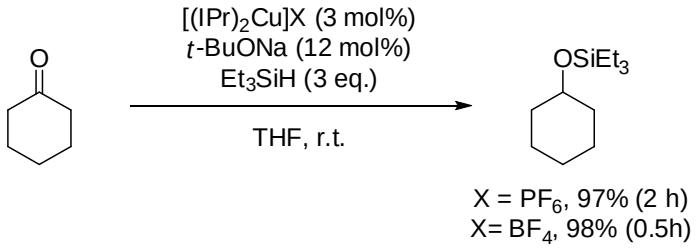


Scheme 137. *Bis*-(NHC) copper(I) complexes

The activity of these cationic bis-(NHC) complexes in the hydrosilylation of ketones was examined, and both the ligand and the counter-ion had a significant influence on the catalytic performance. Whereas the ligand

[39] a) S. Díez-González, N. M. Scott, S. P. Nolan, *Organometallics* **2006**, *25*, 2355; b) S. Díez-González, E. D. Stevens, N. M. Scott, J. L. Petersen, S. P. Nolan, *Chem. Eur. J.* **2008**, *14*, 158.

influence could not be rationalized by using pure steric or electronic arguments,[40] complexes with BF_4^- as counterion were consistently superior to their PF_6^- analogues. For instance, under the same reaction conditions, cyclohexanone was quantitatively transformed into the corresponding silyl ether in 2 hours in the presence of $[(IPr)_2Cu]PF_6$, whereas only 0.5 hours was required in the presence of the BF_4^- counterpart (Scheme 138).



Scheme 138. Hydrosilylation of ketones with $[(NHC)_2Cu]X$ complexes

When compared to their neutral analogues, e.g. (NHC)CuCl, these cationic complexes offer the advantages of requiring lower reaction temperatures and smaller excesses of hydrosilane (Table 28). Moreover, when submitted to comparable reaction conditions, the cationic species were generally more efficient than their neutral analogues (Table 28, comparing entries 1 and 2).[36a,37,39] It is worth noting that for hindered ketones, such as dicyclohexyl ketone, a faster reaction is observed with ICyCuCl than with $[(ICy)_2Cu]BF_4$, but under harsher conditions (Table 28, comparing entries 3 and 5). However, when comparable reaction conditions were used, the cationic complex was the best catalyst (Table 28, comparing entries 4 and 5).

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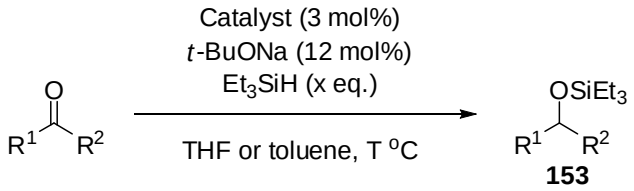
[40] a) T. Strassner, *Top. Organomet. Chem.* **2004**, *13*, 1; b) L. Cavallo, A. Correa, C. Costabile, H. Jacobsen, *J. Organomet. Chem.* **2005**, *690*, 5407; c) S. Díez-González, S. P. Nolan, *Coord. Chem. Rev*. **2007**, *251*, 874.

Table 28. Comparing the reactivity of *bis*- and *mono*-(NHC)Cu^{I} complexes



153

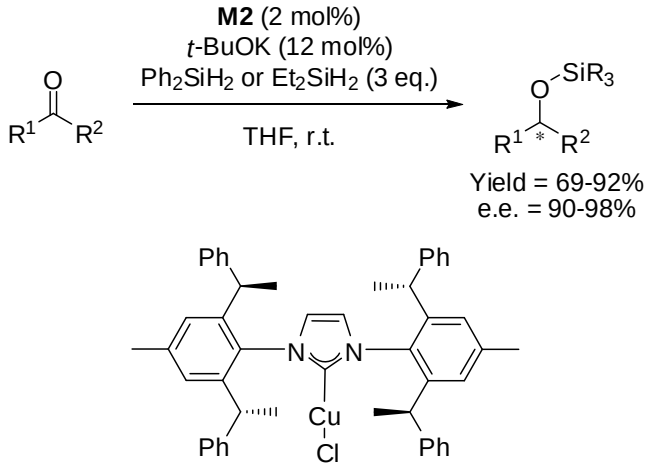
Entry[a]	R^1, R^2	X (eq.)	Catalyst	T (^{o}C)	Time (h)	153[b] (%)
1	$(CH_2)_5$	3	IPrCuCl	r.t.	3	83
2	$(CH_2)_5$	2	$[(IPr)_2Cu]BF_4$	r.t.	0.5	98
3	Cy, Cy	3	ICyCuCl	80	0.5	99
4	Cy, Cy	2	ICuCuCl	55	1.5	50
5	Cy, Cy	3	$[(ICy)_2Cu]BF_4$	55	3	98

[a] All reactions were run under argon [b] Yield determined by GC analysis.

Although the application of NHCs as ligands in the hydrosilylation of carbonyl compounds was quite successful, their chiral analogues were much less explored. Only a handful of chiral NHC catalysts have been employed with some success in the enantioselective hydrosilylation of prochiral ketones most notably with rhodium or ruthenium metals.[41] While some aryl-alkyl ketones can be reduced with excellent enantioselectivity using these NHC hydrosilylation catalysts, the asymmetric hydrosilylation of dialkyl

[41] a) W.-L. Duan, M. Shi, G.-B. Rong, *Chem. Commun.* **2003**, 2916; b) L. Liu, F. Wang, M. Shi, *Organometallics* **2009**, *28*, 4416; c) C. Song, C. Ma, Y. Ma, W. Feng, S. Ma, Q. Chai, M. B. Andrus, *Tetrahedron Lett.* **2005**, *46*, 3241; d) V. César, S. Bellemin-Laponnaz, H. Wadepohl, L. H. Gade, *Chem. Eur. J.* **2005**, *11*, 2862; e) L. H. Gade, V. César, S. Bellemin-Laponnaz, *Angew. Chem., Int. Ed.* **2004**, *43*, 1014.

ketones remained an elusive goal.[41d-e,42] Recently, Gawley[43] *et al* reported one of the most effective asymmetric hydrosilylation of prochiral ketones using a chiral (NHC)Cu^{I} complex (Scheme 139). They managed to synthesize the C_2-symmetric (NHC)Cu^{I} complex; (PhEt)CuCl, and then successfully apply it to the enantioselective hydrosilylation of a wide range of hindered ketones to form the desired silyl ethers in high yields and excellent enantioselectivities.



(*R*,*R*,*R*,*R*)-(PhEt)CuCl (M2)

Scheme 139. Asymmetric hydrosilylation of ketones by Gawley *et al*

The first step of the proposed mechanism for the (NHC)CuCl-catalyzed hydrosilylation of carbonyls is the formation of (NHC)Cu(O*t*-Bu) from the

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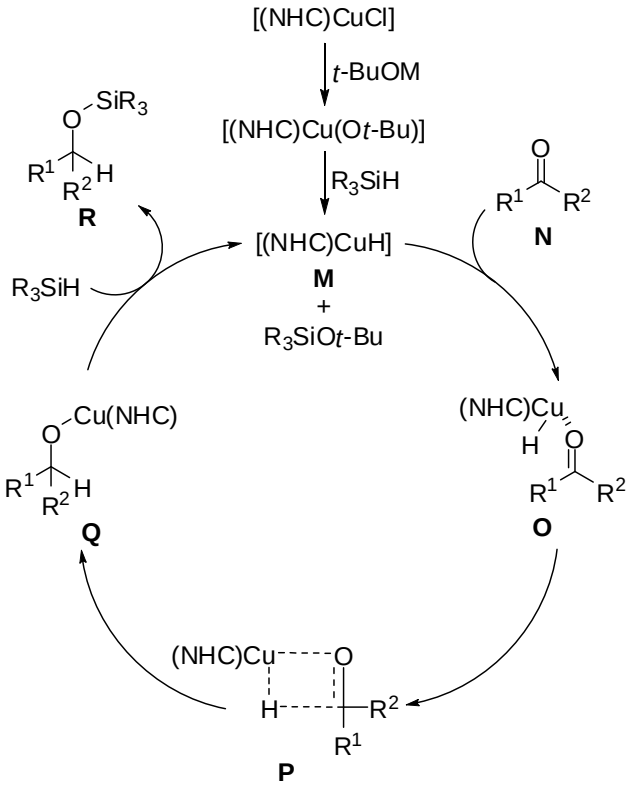
[42] D. K. Heldmann, D. Seebach, *Helv. Chim. Acta* **1999**, *82*, 1096.

[43] a) A. Albright, D. Eddings, R. Black, C. J. Welch, N. N. Gerasimchuk, R. E. Gawley, *J. Org. Chem.* **2011**, *76*, 7341; b) A. Albright, R. E. Gawley, *J. Am. Chem. Soc.* **2011**, *133*, 19680; c) E. Spahn, A. Albright, M. Shevlin, L. Pauli, A. Pfaltz, R. E. Gawley, *J. Org. Chem.* **2013**, *78*, 2731.

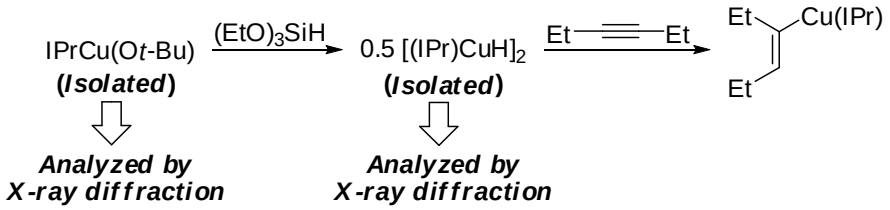
starting chloride complex and the base (Scheme 140). Then, the active catalyst, an (NHC)CuH species (**M**), would be formed by σ-bond metathesis between the copper alkoxide and the hydrosilane. Addition of the copper hydride species to the carbonyl **N** results in a copper alkoxide **Q** that would undergo another σ-bond metathesis with the hydrosilane to form the expected silyl ether **R** and regenerate the active catalyst **M** (Scheme 140).



Scheme 140. Proposed mechanism for the hydrosilylation of carbonyls

These steps are supported by the isolation and characterization of both complexes (the (NHC)Cu^{I} *tert*-butoxide and hydride complexes, Scheme 141).[5] For example, [(IPr)CuH] was isolated as an unstable dimeric complex

that readily reacts with a terminal alkyne to provide the corresponding hydrocupration product (Scheme 141).



Scheme 141. Laitar and Sadighi's hydrocupration of alkynes

This mechanism is in agreement with experimental evidence for the phosphine copper catalytic systems,[44] but it does not explain why an excess of base is generally required in order to complete the reaction with NHC-based catalytic systems. As it is well known that hydrosilanes are prone to nucleophilic attack, recently Nolan *et al* proposed that the excess base that is generally required could be interacting with the hydrosilane to facilitate the second σ-bond metathesis (**Q** to **R**).[37,45]

I.1.2.2. Reduction of Other Compounds

As described earlier (see first chapter), copper hydrides can also be used as a reducing agent in tandem reactions. Thus, the copper intermediate obtained after hydride addition can be quenched to form the corresponding reduced product, or it could be directly engaged in further reactions. To date, there are only a few examples involving NHC ligands in this type of reactions. For example, Nolan, Riant *et al* developed a domino reaction using an (NHC)Cu^{I} complex developed "in house"; the IMesCuDBM. Various aldehydes and

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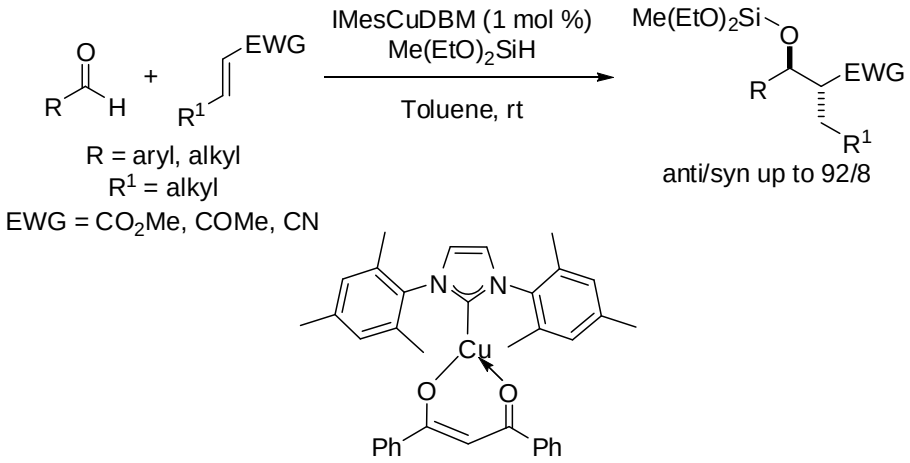
[44] a) Y. Moritani, D. H. Appella, V. Jurkauskas, S. L. Buchwald, *J. Am. Chem. Soc*. **2000**, *122*, 6797; b) J. Yun, S. L. Buchwald, *Org. Lett*. **2001**, *3*, 1129.

[45] C. Lorenz, U. Schubert, *Chem. Ber*. **1995**, *128*, 1267.

α,β-unsaturated Michael acceptors were reacted to furnish aldol type products in high chemoselectivities, good yields and good diastereoselectivities (Scheme 142).[7]

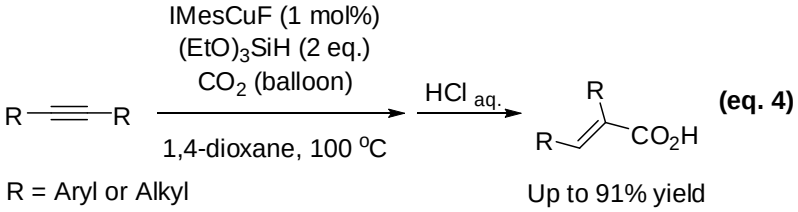


IMesCuDBM

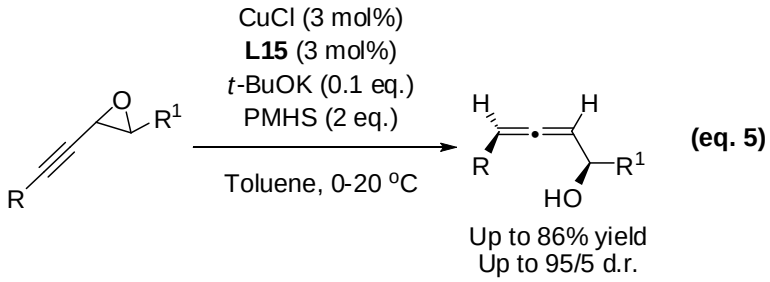
Scheme 142. Domino 1,4-reduction/aldolisation using IMesCuDBM

The activity of (NHC)Cu^{I} hydride complexes towards alkynes or alkenes remains greatly unexplored. However a few examples have recently been reported. Sadighi and co-workers,[5] as shown in Scheme 141, reported the hydrocupration of 3-hexyne by an isolated, dimeric $[(NHC)CuH]_2$ complex. Recently, other reactions involving di-substituted acetylenes and propargyl oxiranes have also been examined (Scheme 143). Various acetylenes were engaged in a hydrocarboxylation reaction catalyzed by (NHC)Cu^{I} fluoride complexes in the presence of carbon dioxide and an hydrosilane, affording α,β-unsaturated acids in good yields (Scheme 143, eq. 4).[24e] Krause *et al* used (NHC)Cu^{I} hydride complexes to reduce various propargylic oxiranes,

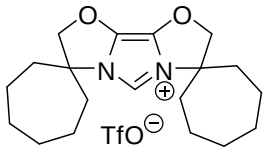
thus yielding diastereoselectively α-hydroxyallenes that were diversely functionalized (Scheme 143, eq. 5).[46]



(eq. 4)



(eq. 5)



IBiox7.HOTf
(L15)

Scheme 143. Hydrosilylation and hydrocarboxylation of alkynes

I.1.2.3. Carbon-Carbon Bond Formation

In recent years, the (NHC)Cu^{I} systems had a significant impact on various C-C coupling reactions. It has promoted conjugated addition reactions as well as allylic alkylation reactions in high enantioselectivity; in all such processes, metal-based nucleophiles, such as Grignard, organozinc or

[46] C. Deutsch, B. H. Lipshutz, N. Krause, *Angew. Chem. Int. Ed.* **2007**, *46*, 1650.

organoaluminum reagents are used.[47] In this part, we are going to describe only the systems that were of key interest to us and that allowed us to move forward in our current project.

I.1.2.3.1. Arylation and Alkenylation Reactions

One of the most elegant examples of such reactions is the enantioselective conjugate addition reaction of aryl- and alkenyl-silyl fluoride reagents that was recently developed by Hoveyda and co-workers (Scheme 144).[48] They have recently reported the synthesis of a new class of chiral NHC salts and their subsequent application to the copper-catalyzed 1,4-addition reaction of various alkenyl and aryl groups onto α,β-unsaturated cyclic ketones. Reactions proceed in the presence of the aryl- or alkenyl-silane reagents and a fluorine source (TASF) to activate the silane. Desired products are isolated in 63-97% yield and 47%-97% enantiomeric excess.

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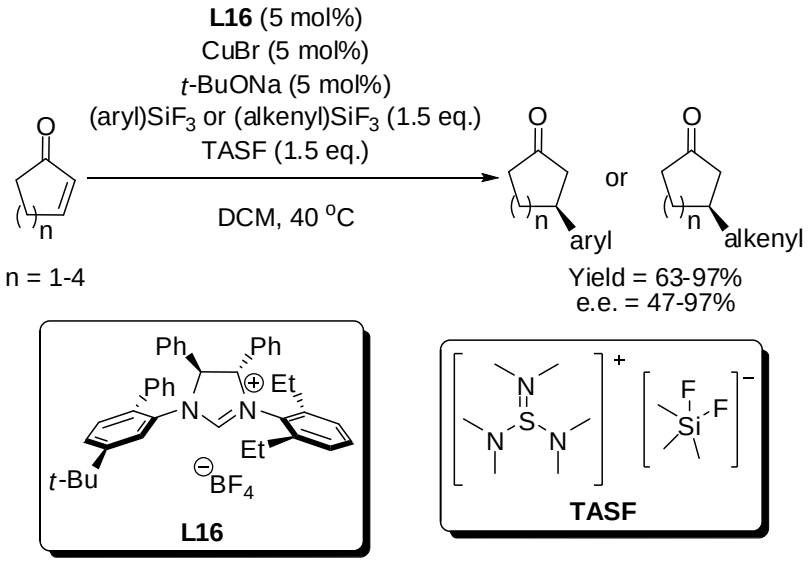
[47] a) A. O. Larsen, W. Leu, C. Nieto-Oberhuber, J. E. Campbell, A. H. Hoveyda, *J. Am. Chem. Soc.* **2004**, *126*, 11130; b) K-s. Lee, M. K. Brown, A. W. Hird, A. H. Hoveyda, *J. Am. Chem. Soc.* **2006**, *128*, 7182; d) M. K. Brown, T. L. May, C. A. Baxter, A. H. Hoveyda, *Angew. Chem., Int. Ed.* **2007**, *46*, 1097; e) M. A. Kacprzynski, T. L. May, S. A. Kazane, A. H. Hoveyda, *Angew. Chem., Int. Ed.* **2007**, *46*, 4554; f) Y. Lee, K. Akiyama, D. G. Gillingham, M. K. Brown, A. H. Hoveyda, *J. Am. Chem. Soc.* **2008**, *130*, 446; g) T. L. May M. K., Brown, A. H. Hoveyda, *Angew. Chem., Int. Ed.* **2008**, *47*, 7468; h) M. K. Brown, A. H. Hoveyda, *J. Am. Chem. Soc.* **2008**, *130*, 12904; i) P. Arnold, M. Rodden, K. M. Davis, A. C. Scarisbrick, A. J. Blake, C. Wilson, *Chem. Commun.* **2004**, 1612; j) H. Clavier, L. Coutable, L. Toupet, J.-C. Guillemin, M. Mauduit, *J. Organomet. Chem.* **2005**, *690*, 5237; k) D. Martin, S. Kehrli, M. d'Augustin, H. Clavier, M. Mauduit, A. Alexakis, *J. Am. Chem. Soc.* **2006**, *128*, 8416.

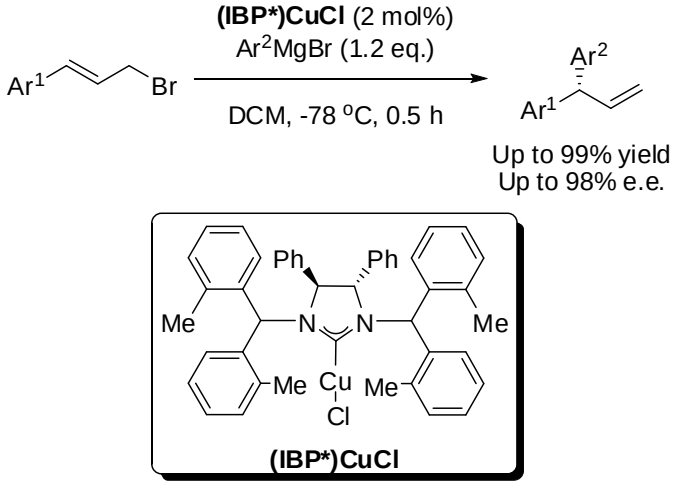
[48] K. S. Lee, A. H. Hoveyda, *J. Org. Chem.* **2009**, *74*, 4455.



Scheme 144. Hoveyda *et al*'s alkenylation and arylation of cyclic ketones

Although addition of Grignard reagents to conjugated systems such as allylic halides is not of much interest to this work, this next example uses a particularly remarkable and easily accessible chiral (NHC)Cu^{I} complex that performs the aforementioned reaction. Indeed, Tomioka[49] *et al* developed a new class of chiral NHC salts that are easily synthesised in contrast to other chiral NHCs (Scheme 145). This newly formed NHC ligand was successfully applied to the Cu^{I}-catalyzed asymmetric allylic arylation using aryl Grignard reagents and allylic bromide, thus affording high regioselectivities, excellent yields and enantioselectivities of the branched product.

[49] K. B. Selim, Y. Matsumoto, K. Yamada, K. Tomioka, *Angew. Chem. Int. Ed.* **2009**, *48*, 8733.

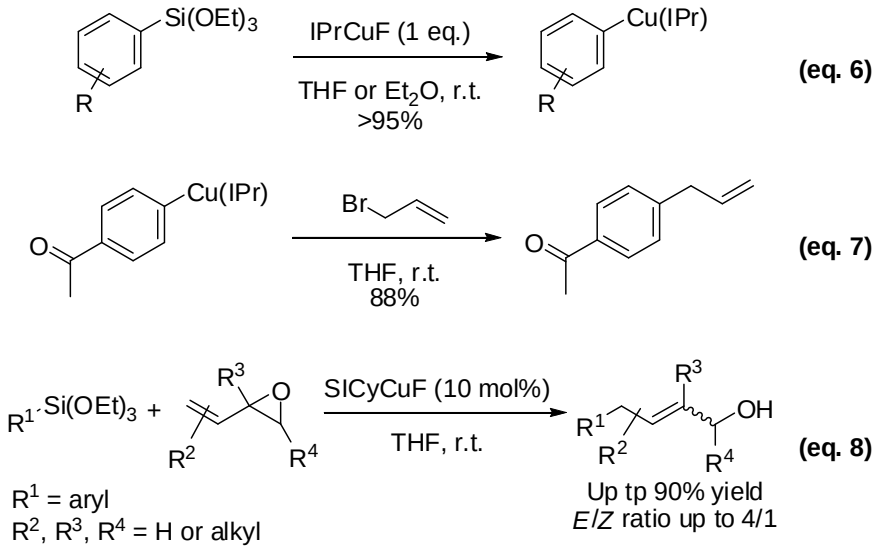


Scheme 145. Asymmetric allylic arylation using a chiral (NHC)Cu^{I} complex

One more important addition to the (NHC)Cu^{I}-catalyzed arylation type reaction was the contribution made by Ball[50] *et al*. They established a general preparative method for functionalized (NHC)Cu-aryl compounds by a silicon-to-copper transmetallation (Scheme 146, eq. 6). These complexes were successfully isolated, characterised and later engaged with various electrophiles, stoichiometrically at first then catalytically. Also in these reports, Ball *et al* successfully implemented for the first time the NHC copper fluoride complexes in catalysis. Thus all of the (NHC)Cu-aryl compounds were generated from their (NHC)CuF counterparts, interestingly with no base or any other additives. IPrCuF was used to form all the arylcopper complexes in very high yields. In order to demonstrate the high tolerance of such intermediates to functional groups, an example of an arylcopper species bearing a ketone group was thus reacted with allyl bromide to form the desired allylated product in 88% yield (Scheme 146, eq.

[50] J. R. Herron, Z. T. Ball, *J. Am. Chem. Soc.* **2008**, *130*, 16486.

7). This methodology was later applied to the arylation of vinylepoxides using arylsiloxanes and catalytic amounts of SICyCuF, to form the desired allylic alcohols in good yields and moderate stereoselectivities (Scheme 146, eq. 8).[51]



Scheme 146. Ball e*t al*'s work on aryl transfer from silicon to copper

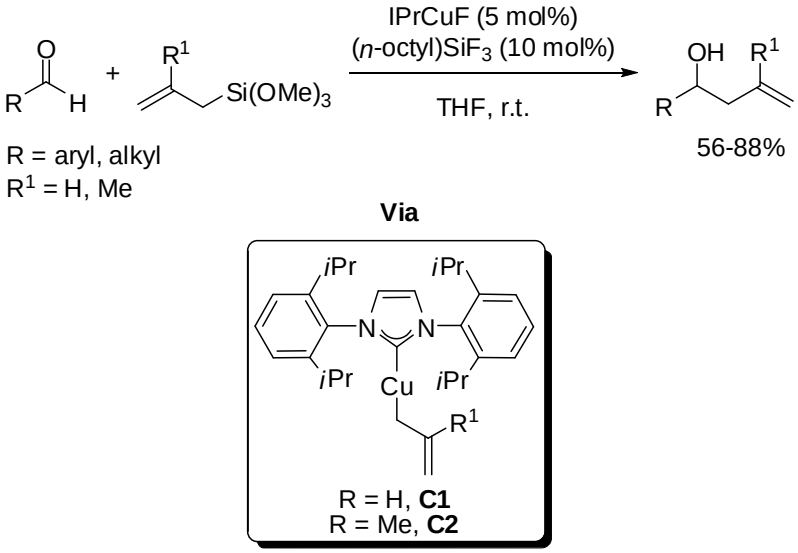
I.1.2.3.2. Allylation of Carbonyl and Related Compounds

The above strategy was further extended, by the same group, to the allylation of aldehydes using once again (NHC)CuF complexes and allylsiloxanes.[52] In that manner, various aldehydes were engaged with allylsiloxanes, in the presence of 5 mol% of IPrCuF to form the desired homoallylic alcohols in good yields (Scheme 147). The report included some mechanistic investigation of this reaction. Complexes **C1** and **C2**, which are thought to

[51] J. R. Herron, V. Russo, E. J. Valente, Z. T. Ball, *Chem. Euro. J.* **2009**, *15*, 8713.

[52] V. Russo, J. R. Herron, Z. T. Ball, *Org Lett* **2010**, *12*, 220.

be the nucleophilic intermediates of this reaction, were isolated and characterised by X-ray structure. Subsequent NMR experiments on these complexes showed that they smoothly react with the aldehyde to form the desired product. However, when used in catalytic amounts, a trifluorosilane additive is needed to achieve high catalytic activity. The exact role of this additive remains unclear, but it has been argued that it could be responsible for increasing the turnover rate, by increasing the fluoride concentration or in allowing an inactive catalyst form to be reintroduced into the catalytic cycle.

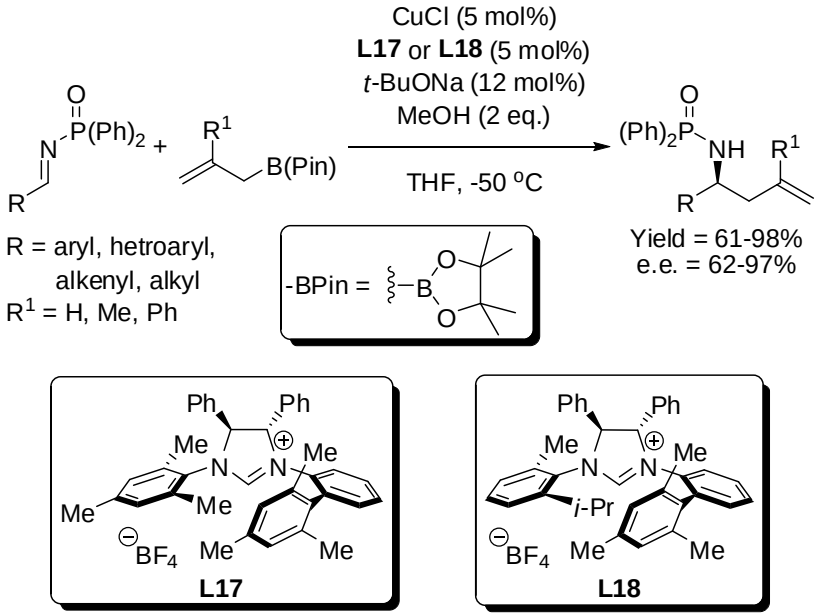


Scheme 147. (NHC)Cu^{I}-catalyzed allylation of aldehydes

A more recent variation of this allylation reaction was developed by Hoveyda[53] *et al*. They reported the asymmetric allylation of aldimines using allylborons and chiral (NHC)Cu^{I} complexes (Scheme 148). They were able

[53] E. M. Vieira, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.* **2011**, *133*, 3332.

to achieve high yields and high enantioselectivities of various homoallylic amines, using their designed chiral NHC ligands **L17** or **L18**.



Scheme 148. (NHC)Cu^{I}-catalyzed allylation of aldimines

I.1.2.4. β-Borylation and β-Silylation Reactions

The conjugate addition of boron and silicon moieties to electron-poor alkenes (β-borylation[54] and β-silylation[55] respectively) provides access to

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[54] a) J.-E. Lee, J. Yun, *Angew. Chem., Int. Ed.* **2008**, *47*, 145; b) V. Lillo, A. Prieto, A. Bonet, M. M. Díaz-Requejo, J. Ramírez, P. J. Pérez, E. Fernández, *Organometallics* **2009**, *28*, 659; c) H.-S. Sim, X. Feng, J. Yun, *Chem. Eur. J.* **2009**, *15*, 1939.

[55] a) B. H.Lipshutz, J. A.Sclafani, T.Takanami, *J. Am. Chem. Soc.* **1998**, *120*, 4021; b) G. Auer, B. Weiner, M. Oestreich, *Synthesis* **2006**, 2113; c) K. Tamao, S. Okazaki, M. Kumada, *J. Organomet. Chem.* **1978**, *146*, 87; d) H. Ito, T. Ishizuka, J.-

highly useful building blocks in the construction of more complex products. Recent advances in this field revealed that copper(I) catalysts are particularly suited for this type of reactions generating greater selectivity than other transition metals,[54-56] presumably via a "Cu-B"[57] and "Cu-Si"[58] species. Though both chiral phosphines and NHCs are competent ligands for the aforementioned reactions, phosphine catalysts generally have exhibited a higher enantioselectivity. Hoveyda's group, however, used their designed chiral NHC salts in combination with a copper(I) precursor to catalyze both reactions in high yields and excellent enantioselectivities.

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i. Tateiwa, M. Sonoda, A. Hosomi, *J. Am. Chem. Soc.* **1998**, *120*, 11196; e) S. Ogoshi, S. Tomiyasu, M. Morita, H. Kurosawa, *J. Am. Chem. Soc.* **2002**, *124*, 11598; f) C. T. Clark, J. F. Lake, K. A. Scheidt, *J. Am. Chem. Soc.* **2004**, *126*, 84.

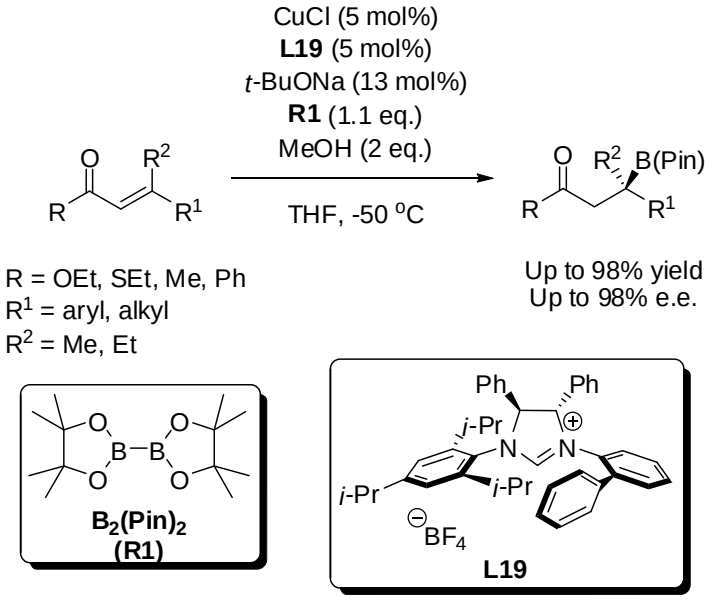
[56] a) H. Ito, H. Yamanaka, J. Tateiwa, A. Hosomi, *Tetrahedron Lett.* **2000**, *41*, 6821; b) K. Takahashi, T. Ishiyama, N. Miyaura, *J. Organomet. Chem.* **2001**, *625*, 47; c) S. Mun, J.-E. Lee, J. Yun, *Org. Lett.* **2006**, *8*, 4887; d) J.-E. Lee, J. Kwon, J. Yun, *Chem. Commun.* **2008**, 733; e) J. A. Schiffner, K. Müther, M. Oestreich, *Angew. Chem., Int. Ed.* **2010**, *49*, 1194; f) X. Feng, J. Yun, *Chem. Commun.* **2009**, 6577; g) W. J. Fleming, H. Müller-Bunz, V. Lillo, Fernández, E. P. J. Guiry, *Org. Biomol. Chem.* **2009**, *7*, 2520; h) J.-E. Lee, J. Yun, *Angew. Chem., Int. Ed.* **2008**, *47*, 145.

[57] a) D. S. Laitar, E. Y. Tsui, J. P. Sadighi, *J. Am. Chem. Soc.* **2006**, *128*, 11036; b) D. S. Laitar, P. Müller, J. P. Sadighi, *J. Am. Chem. Soc.* **2005**, *127*, 17196; c) H. Zhao, L. Dang, T. B. Marder, Z. Lin, *J. Am. Chem. Soc.* **2008**, *130*, 5586; d) L. Dang, Z. Lin, T. B. Marder, *Chem. Commun.* **2009**, 3987; e) V. Lillo, A. Bonet, E. Fernández, *Dalton Trans.* **2009**, 2899; f) L. Dang, Z. Lin, T. B. Marder, *Organometallics* **2008**, *27*, 4443.

[58] a) E. Hartmann, D. J. Vyas, M. Oestreich, *Chem. Commun.* **2011**, *47*, 7917, and references cited therein; b) K. S. Lee, A. H. Hoveyda, *J. Am. Chem. Soc.* **2010**, *132*, 2898.

I.1.2.4.1. The β-Borylation Reaction

In a recent report, the Cu^{I}-catalyzed enantioselective β-borylation reaction onto trisubstituted alkenes of acyclic α,β-unsaturated carboxylic esters, ketones, and thioesters is disclosed (Scheme 149).[59] All transformations were catalyzed by 5 mol% of a chiral monodentate (NHC)Cu^{I} complex, derived from a readily available C1-symmetric imidazolinium salt (**L19**), and in the presence of commercially available bis(pinacolato)diboron (**R1**). Reactions are highly efficient (up to 98% isolated yield) and deliver the desired β-boryl carbonyl compounds in up to 98% enantiomeric excess.



Scheme 149. (NHC)Cu^{I}-catalyzed enantioselective β-borylation of enones

I.1.2.4.2. The β-Silylation Reaction

[59] J. M. O'Brien, K. S. Lee, A. H. Hoveyda, *J. Am. Chem. Soc.* **2010**, *132*, 10630.

Silylmetalation of enone systems can be used to put in place a β-silyl carbonyl compound. This approach was, until recently, restricted to the unstable mixed silylzincate[60] and silylcuprate[61] reagents, thus the development of transition metal-catalyzed conjugate addition of silicon nucleophiles onto α,β-unsaturated carbonyl compounds was limited. In the last 10 years, this approach became particularly attractive, due to the now readily available silicon pro-nucleophiles such as the widely used Suginome reagent,[62] i.e., dimethyl(phenyl)(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)silane (**R2**). Since then, a number of catalytic enantioselective silyl conjugate additions to α,β-unsaturated carbonyls have been disclosed.[63] Such protocols, promoted by Pd- and Rh-based phosphine complexes, are

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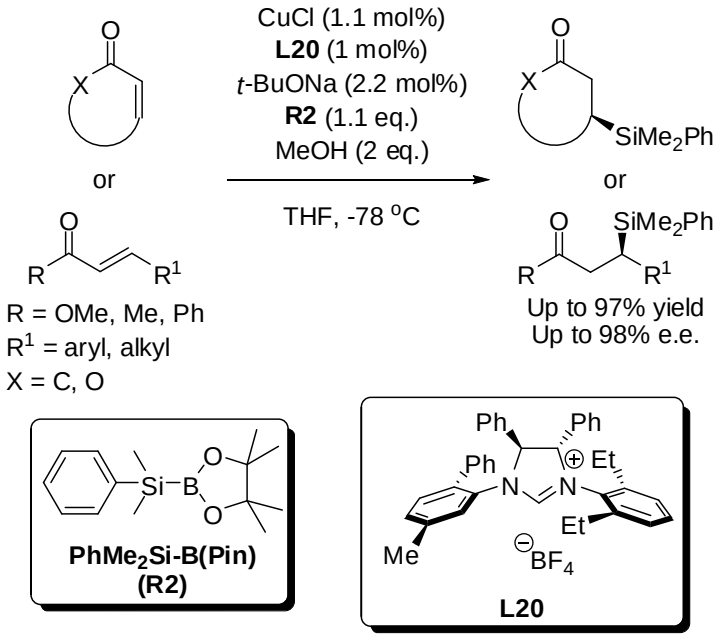
[60] a) W. Tückmantel, K. Oshima, H. Nozaki, *Chem. Ber*. **1986**, *119*, 1581; b) R. A. N. C. Crump, I. Fleming, C. J. Urch, *J. Chem. Soc. Perkin Trans. 1* **1994**, 701; c) A. Vaughan, R. D. Singer, *Tetrahedron Lett.* **1995**, *36*, 5683; d) B. H. Lipshutz, J. A. Sclafani, T. Takanami, *J. Am. Chem. Soc.* **1998**, *120*, 4021.

[61] a) D. J. Ager, I. Fleming, *J. Chem. Soc. Chem. Commun.* **1978**, *177*; b) D. J. Ager, I. Fleming, S. K. Patel, *J. Chem. Soc. Perkin Trans. 1* **1981**, 2520; c) S. Sharma, A. C. Oehlschlager, *J. Org. Chem.* **1991**, *56*, 770; d) M. R. Hale, A. H. Hoveyda, *J. Org. Chem.* **1994**, *59*, 4370; e) C. J. Palomo, M. Aizpurua, M. Iturburu, R. Urchegui, *J. Org. Chem.* **1994**, *59*, 240; f) J. Dambacher, M. Bergdahl, *J. Org. Chem.* **2005**, *70*, 580.

[62] a) M. Suginome, T. Matsuda, Y. Ito, *Organometallics* **2000**, *19*, 4647; b) M. Suginome, Y. Ohmori, Y. Ito, *J. Organomet. Chem.* **2000**, *611*, 403.

[63] a) T. Hayashi, Y. Matsumoto, Y. Ito, *J. Am. Chem. Soc.* **1988**, *110*, 5579; b) Y. Matsumoto, T. Hayashi, Y. Ito, *Tetrahedron* **1994**, *50*, 335; c) C. Walter, G. Auer, M. Oestreich, *Angew. Chem., Int. Ed.* **2006**, *45*, 5675; d) C. Walter, M. Oestreich, *Angew. Chem., Int. Ed.* **2008**, *47*, 3818; e) C. Walter, R. Fröhlich, M. Oestreich, *Tetrahedron* **2009**, *65*, 5513.

noteworthy but operate within a relatively narrow substrate range (e.g., require *cis*-alkenes) and at times proceed with low to moderate enantioselectivity or moderate efficiency. More recently, Hoveyda *et al* disclosed a new and highly efficient Cu-based system involving chiral NHC ligands (Scheme 150).[58b] Cyclic and acyclic enone systems undergo the desired reaction using 1 mol% of the chiral copper catalyst to form the β-silylated compounds in high yields (up to 97%) and excellent enantioselectivities (up to 98%).

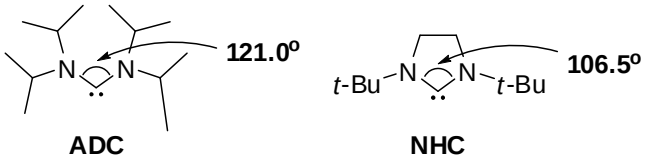


Scheme 150. (NHC)Cu^{I}-catalyzed enantioselective β-silylation of enones

I.2. Acyclic Diaminocarbenes (ADCs)

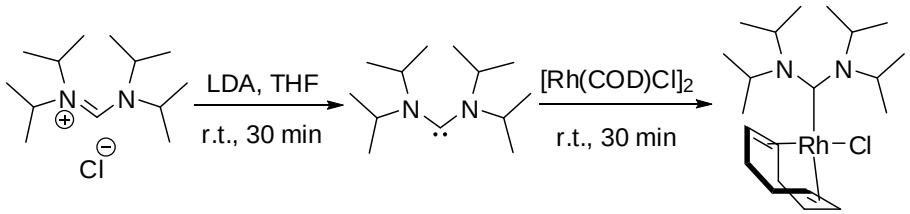
Acyclic diaminocarbenes (ADCs) are of particular interest, as they possess different electronic and steric parameters from NHCs. This difference stems

from ADCs' larger N-C-N carbene bond angle, which generates a more strongly donating and sterically demanding ligand (Scheme 151).[64]



Scheme 151. N-C-N bond angles of ADCs and NHCs

The first isolable ADC was discovered by Alder[65] *et al* in 1996, and following this report, Herrmann and co-workers[64c-g] prepared ADC complexes with a variety of metals (Scheme 152).



Scheme 152. Alder and Herrmann's work on ADCs

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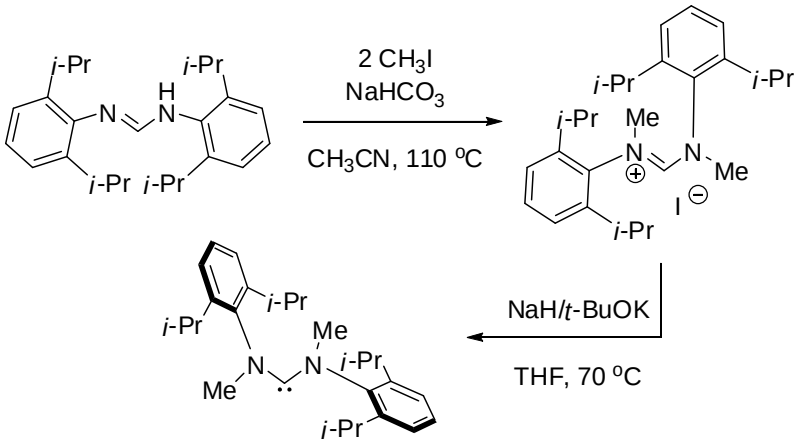
[64] a) R. W. Alder, M. E. Blake, L. Chaker, J. N. Harvey, F. Paolini, J. Schlitz, *Angew. Chem., Int. Ed.* **2004**, *43*, 5896; b) R. W. Alder, P. R. Allen, M. Murray, A. G. Orpen, *Angew. Chem., Int. Ed.* **1996**, *35*, 1121; c) G. D. Frey, C. F. Rentzsch, D. von Preysing, T. Scherg, M. Mlihlhofer, E. Herdtweck, W. A. Herrmann, *J. Organomet. Chem.* **2006**, *691*, 5725; d) G. D. Frey, E. Herdtweck, W. A. Herrmann, *J. Organomet. Chem.* **2006**, *691*, 2465; e) G. D. Frey, W. A. Herrmann, *J. Organomet. Chem.* **2005**, *690*, 5876; f) W. A. Herrmann, K. Ofele, D. von Preysing, E. Herdtweck, *J. Organomet. Chem.* **2003**, *684*, 235; g) K. Denk, P. Sirsch, W. A. Herrmann, *J. Organomet. Chem.* **2002**, *649*, 219.

[65] R. W. Alder, P. R. Allen, M. Murray, A. G. Orpen, *Angew. Chem., Int. Ed.* 1996, *35*, 1121.

Bielawski and co-workers[66] have also demonstrated that the rotamers of ADCs can be controlled to some extent by using two different substituents on each nitrogen atom, whereas one of them is a bulky group (Scheme 153). Thus the outcome could be controlled by favouring one configuration over the others.



Scheme 153. Bielawski *et al*'s work on ADCs

While many examples of chiral NHCs exist, the first chiral ADC complex was recently prepared by Slaughter and co-workers, featuring a bidentate Chugaev-type carbene bound to palladium (Scheme 154).[67]

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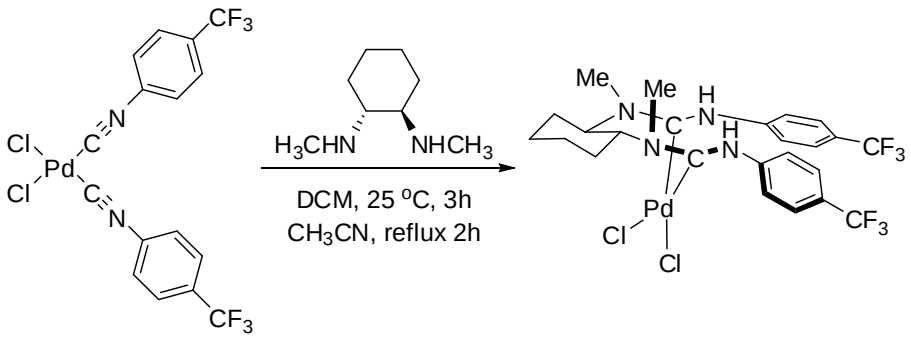
[66] a) E. L. Rosen, D. H. Sung, Z. Chen, V. M. Lynch, C. W. Bielawski, *Organometallics* **2010**, *29*, 250; b) M. S. Collins, E. L. Rosen, V. M. Lynch, C. W. Bielawski, *Organometallics* **2010**, *29*, 3047.

[67] a) Y. A. Wanniarachchi, Y. Kogiso, L. M. Slaughter, *Organometallics* **2008**, *27*, 21; b) Y. A. Wanniarachchi, L. M. Slaughter, *Chem. Commun.* **2007**, 3294.



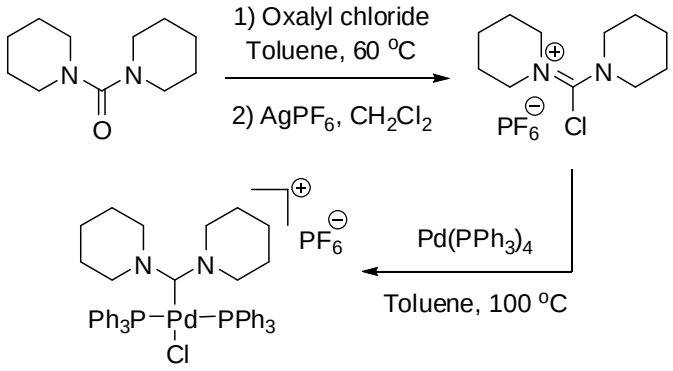
Scheme 154. Slaughter *et al*'s work on ADCs

The proliferation of ADCs has lagged behind that of NHCs partially due to challenges associated with synthesis of amidinium precursors and ADC metal complexes, and this has inspired alternative routes of accessing ADC compounds. For example, while imidazolium (NHC) and amidinium (ADC) salts are the most common precursors to free carbene, ureas or thioureas can also be used as carbene synthons (Scheme 155). Early research by Lappert[68] and Stone[69] laid the groundwork for the methods of Cavell *et al*, Fürstner *et al* (Scheme 155) and Arduengo *et al* in the conversion of ureas to

[68] a) A. J. Hartshorn, M. F. Lappert, K. Turner, *J. Chem. Soc., Dalton Trans.* **1978**, 348; b) A. J. Hartshorn, M. F. Lappert, K. Turner, *J. Chem. Soc., Chem. Commun.* **1975**, 929; c) M. F. Lappert, *J. Organomet. Chem.* **1975**, *100*, 139; d) M. F. Lappert, A. J. Oliver, *J. Chem. Soc., Dalton Trans.* **1974**, 65 ; e) M. Cetinkaya, M. F. Lappert, K. Turner, *J. Chern. Soc., Chem. Commun.* **1972**, 851.

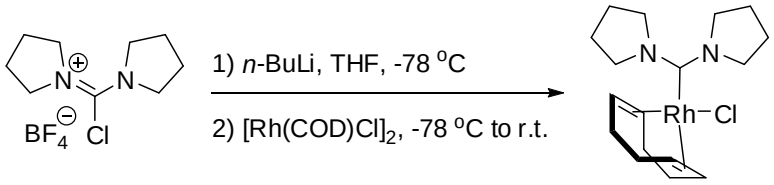
[69] a) Green, M. Stone, F. G. A. Underbill, M. *J. Chem. Soc., Dalton Trans.* **1975**, 939; b) P. J. Fraser, W. R. Roper, F. G. A. Stone, *J. Chem. Soc., Dalton Trans.* **1974**, 760; c) Fraser, P. J. Roper, W. R. Stone, F. G. A. *J. Chem. Soc., Dalton Trans.* **1974**, 102.

chloroimidazoliums and subsequent oxidative addition by an electron-rich metal center (Ni, Pd, or Pt) to make carbenoid species.[70]



Scheme 155. Fürstner *et al*'s work on ADCs

Specifically, Fürstner used this methodology to generate acyclic diaminocarbenes (Scheme 155),[70a,c] and following that report, Hong *et al* used lithium-halogen exchange to convert chloroamidiniums into carbenes and then bind the corresponding ADC to a transition metal (Scheme 156).[71]



Scheme 156. Hong *et al*'s work on ADCs

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[70] a) D. Kremzow, G. Seidel, C. W. A. Lehmann, Fürstner, *Chem. Eur. J.* **2005,** 11, 1833; b) A. J. Arduengo III, D. Tapu, W. J. Marshall, *J. Am. Chem. Soc.* **2005**, *127*, 16400; c) A. Fürstner, G. Seidel, D. Kremzow, C. W. Lehmann, *Organometallics* **2003**, *22*, 907; d) D. S. McGuinness, K. J. Cavell, B. F. Yates, B. W. Skelton, A. H. White, *J. Am. Chem. Soc.* **2001**, *123*, 8317.

[71] D. R. Snead, I. Ghiviriga, K. A. Abboud, S. Hong, *Org. Lett.* **2009**, *11*, 3274.

Results detailing ADC-promoted catalytic activity have recently surfaced with efforts exploring the Suzuki cross coupling,[72] olefin metathesis,[66] and allylic alkylation[73] among other reactions.

However, an account by Hong *et al* caught our attention.[73] They recently reported a highly S_N2'-selective allylic alkylation catalyzed by a mixture of a chloroamidinium salt and Cu^I-thiophenecarboxylate in the presence of a Grignard reagent (Scheme 157). More interestingly, they performed a ^{13}C NMR study on the generation of the active catalyst, and results were found to be in accordance with generation of an acyclic diaminocarbene-copper species (Scheme 157). Nevertheless the observed (ADC)copper complex was not isolated nor fully characterised.

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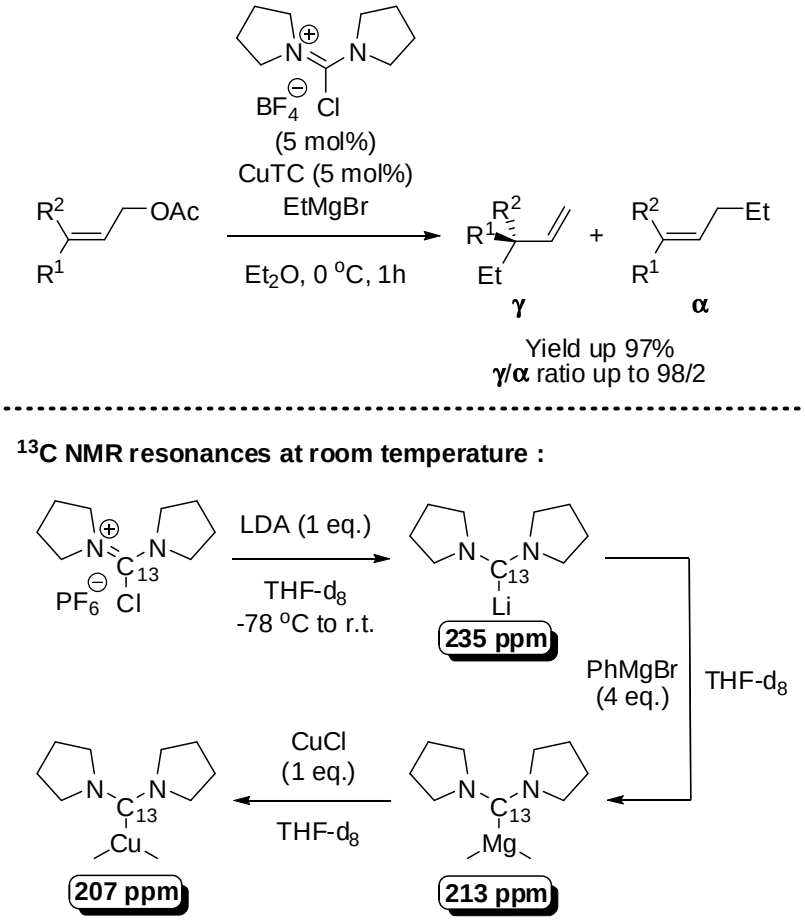
[72] a) A. L. Moncada, S. Manne, J. M. Tanski, L. M. Slaughter, *Organometallics* **2006**, *25*, 491; b) A. L. Moncada, M. A. Khan, L. M. Slaughter, *Tetrahedron Lett.* **2005,** *46*, 1399; c) B. Dhudshia, A. N. Thadani, *Chem. Commun.* **2006**, 668.

[73] D. Hirsch-Weil, D. R. Snead, S. Inagaki, H. Seo, K. A. Abboud, S. Hong, *Chem. Commun.* **2009**, 2475.



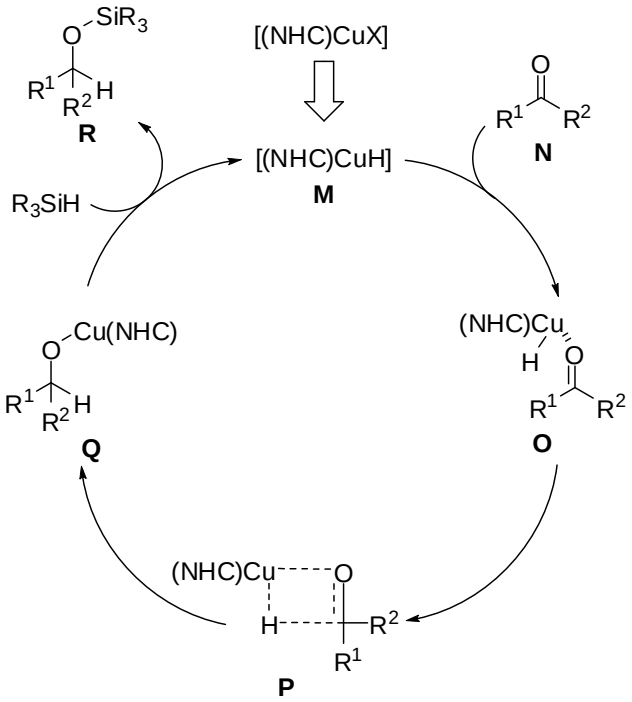
Scheme 157. (ADC)Cu^{I}-catalyzed allylic alkylation reaction

This is one of the first observations in the literature of such a copper complex and its subsequent highly selective reactivity. For that reason, we were greatly motivated to fill in the blanks and try to further investigate or even isolate these (ADC)Cu^{I} type complexes.

II. Objectives

As shown previously, NHC ligand-based copper catalysis is a growing field, and the need to study in more details the mechanism of reactions such as hydrosilylation and 1,4-addition of nucleophiles is becoming more and more important. Mechanistic studies involving catalyst activation, detailed reactivity and consequent regeneration of the active species are particularly important to this field. Indeed this type of study could allow future development of new (NHC)Cu^{I} catalytic systems with improved properties and better activation capacity which could eventually match or even surpass that of phosphine-based catalysis.

The goal of this research project is to elaborate the full mechanism of the (NHC)Cu^{I}-catalyzed hydrosilylation reaction of carbonyls by experimental methods, kinetic studies and DFT calculations (Scheme 158). Thus, to cover all three fields, this project is conducted as a collaborated effort between three distinct chemistry groups; the theoretical chemistry group (headed by Pr. D. Peeters), the physical chemistry group (headed by Pr. T. Leyssens), and the organic chemistry group (headed by Pr. O. Riant). Furthermore, this collaboration was practically implemented by two PhD students; Thomas Vergote (theoretical and physical chemistry) and I (organic chemistry).

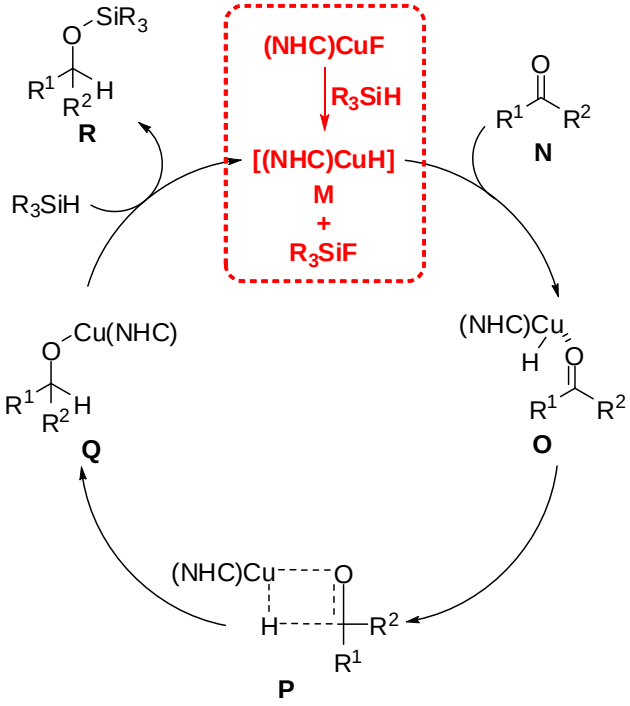


Scheme 158. Hydrosilylation reaction of carbonyls by (NHC)Cu^{I} complexes

Our part in this project was to supply the starting (NHC)Cu^{I} complexes as well as establishing a quick and reliable method for their preparation. We were also involved in the NMR experimental studies of the mechanism in an attempt to identify some of the active species in this reaction (Scheme 159).

In this thesis, we are going to describe only the experimental part of this project, most notably catalysts preparation and activation procedures. The (NHC)Cu^{I} complexes selected for this work were the (NHC)CuF. As seen in Scheme 146, these complexes readily react with siloxanes and require no previous activation (e.g., base or other additives) to form the copper active species. We argued that this reactivity could be duplicated with silanes to form the copper hydride species (Scheme 159). In that manner, we could

avoid the use of sensitive and unstable complexes such as the (NHC)Cu(O-*t*-Bu), usually used in this reaction.

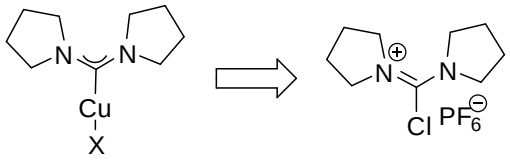


Scheme 159. Aim of the current project

Although catalysts preparation and activation was our primary goal in this project, events soon took a turn in a completely different direction, due to a discovery made in the catalyst preparation stage. As we are going to see later on, we managed to synthesise a new class of $(NHC)Cu^{I}$ complexes that opened the door to a whole new range of possibilities.

Also described in this chapter, are attempts made to isolate $(ADC)Cu^{I}$ complexes. As shown before, ADCs have started to emerge as a new ligand class for metal catalysis, and like NHCs they could offer a new type of reactivity. Following the report made by Hong *et al*, we thought that it could be interesting to try and isolate an $(ADC)Cu^{I}$ complex, especially since no

such complex has ever been isolated to this day. Our strategy involved forming these complexes starting from the commercially available chloroamidinium salt **154** (Scheme 160).

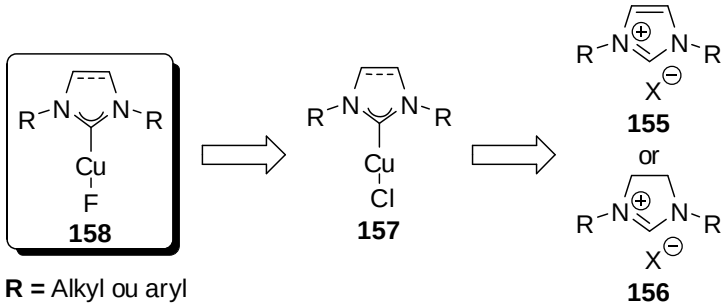


154

Scheme 160. (ADC)Cu^{I} complex's attempted synthesis

III. Results and Discussion

The first stage of this project was to establish a reliable method for the preparation of (NHC)CuF complexes **158** starting from their corresponding salt precursors (**155** and **156**). These salt precursors are transformed to the (NHC)CuF complexes *via* the formation of (NHC)CuCl complexes **157** (Scheme 161).



Scheme 161. Methodology used for the synthesis of (NHC)Cu^{I} complexes

Thus the first step in our methodology was to synthesise a small library of imidazolium and imidazolidinium salts (**155** and **156**, respectively) to be readily transformed later on to their corresponding (NHC)Cu^{I} complexes.

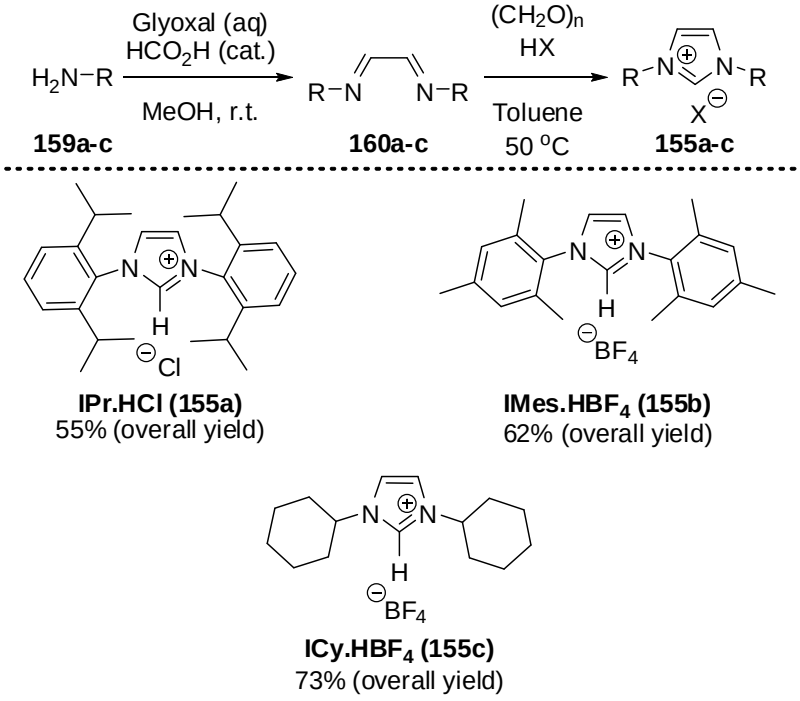
III.1. Synthesis of the Salt Precursors

III.1.1. Synthesis of Imidazolium Salts

Synthesis of imidazolium salts **155** are well described in the literature. They are usually prepared starting from the corresponding primary amines **159** (Scheme 162).[1] Amines **159** are condensed with an aqueous solution of

[1] a) J. Huang, S. P. Nolan, *J. Am. Chem. Soc.* **1999**, *121*, 9889; b) W. A. Herrmann, *Angew. Chem. Int. Ed.* **2000**, 39, 1602.

glyoxal to form the desired diimine **160**. The diimine is later reacted with paraformaldehyde and a selected acid (HBF_4 or HCl), depending on the desired counter-ion needed, to form the 5-membered cyclic imidazolium salt **155**. Using this procedure, three salts were prepared starting from the corresponding aniline (for IPr and IMes) or cyclohexylamine (for ICy) in acceptable yields (Scheme 162). We have noticed that using HCl always gives low yields of the chloride salt, and when HBF_4 is used high yields are obtained. However, in the case of the IPr salt, using HBF_4 was unfruitful and therefore we were forced to use HCl as the selected acid.



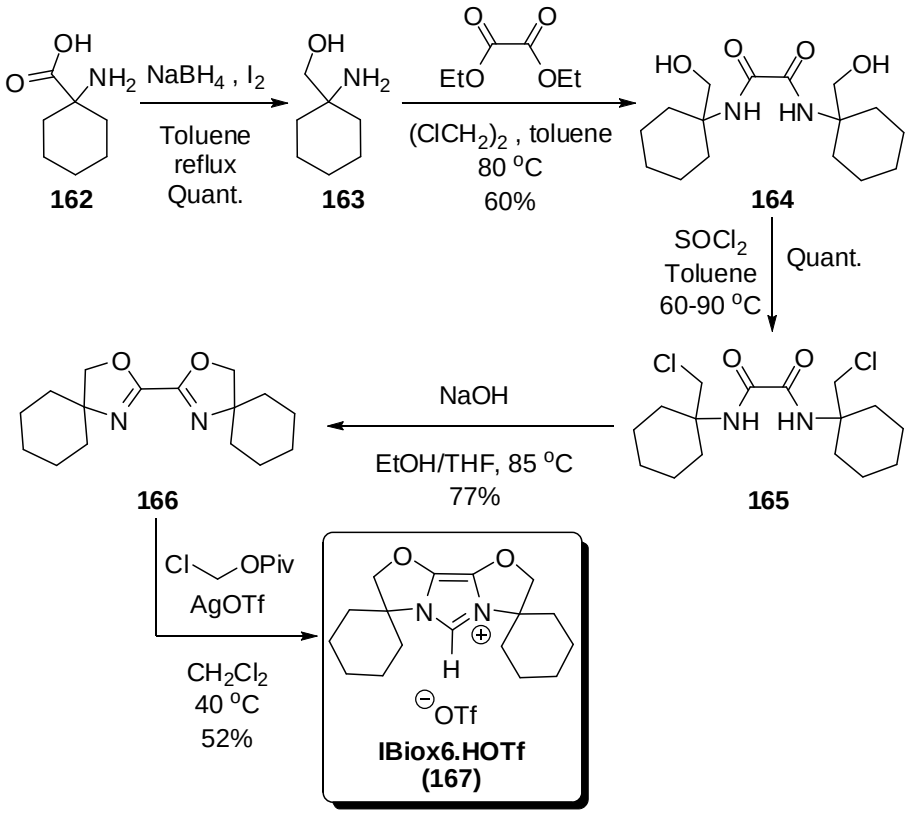
Scheme 162. Synthesis of imidazolium salts[2]

[2] This work was done in collaboration with an IPL student, Jonathan Thill, **2011**.

Another imidazolium salt type precursor was also envisioned; the *bis*-oxazoline-derived NHC, IBiox6.HOTf (**167**) (Scheme 163). This type of NHC precursor was quite intensively developed in the last decade by Glorius *et al* as a more sterically demanding ligand for catalysis. Its rigid structure, especially at the nitrogen substituent, uniquely directs the steric hindrance towards the metal centre, consequently affording more steric interference than usual NHC ligands. This NHC salt was synthesized in five steps, following a described literature procedure (Scheme 163).[3] Commercially available α-amino acid **162** was reduced in typical conditions to afford amino alcohol **163** in a 73% yield. Two equivalents of **163** were subsequently engaged with diethyl oxalate to form the desired di-amide **164** in a 60% yield. Substitution of the hydroxy group on substrate **164** with a chloride was performed with thionyl chloride ($SOCl_2$) in a quantitative manner to afford product **165**. Treatment of **165** with sodium hydroxide allowed for the cyclization reaction, thus forming the desired *bis*-oxazoline **166** in a 77% yield. The final step of our reaction sequence consisted in the cyclization to the desired imidazolium salt **167**, using the Glorius procedure, with an acceptable yield of 52%.

---

[3] a) G. Altenhoff, R. Goddard, C. W. Lehmann, F. Glorius, *J. Am. Chem. Soc.* **2004**, *126*, 15195; b) S. Wurtz, C. Lohre, R. Frohlich, K. Bergander, F. Glorius, *J. Am. Chem. Soc.* **2009**, *131*, 8344.



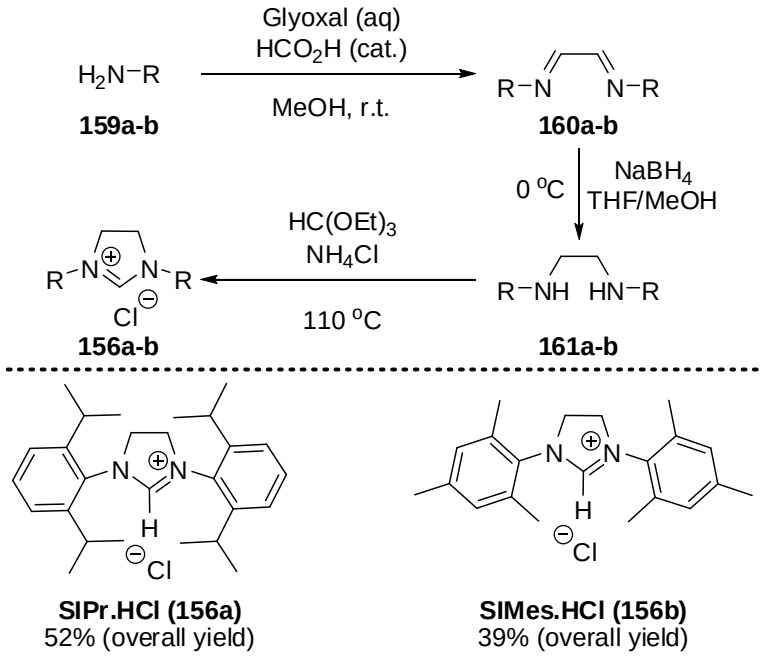
Scheme 163. Synthesis of the IBiox6.HOTf salt[2]

III.1.2. Synthesis of Imidazolidinium Salts

Synthesis of imidazolidinium salts **156** are also well described in the literature. They are prepared in the same manner as the imidazolium salts starting from the corresponding primary amines **159** (Scheme 164).[4] Amines **159** are condensed with an aqueous solution of glyoxal to form the desired

[4] a) A. J. Arduengo III, R. Krafczyk, R. Schmutzler, *Tetrahedron* **1999**, *55*, 14523, b) A. J., Arduengo III, U.S. Patent 5 077 414, **1991**; c) a) A. Aidouni, S. Bendahou, A. Demonceau, L. Delaude, *J. Comb. Chem.* **2008**, *10*, 886.

diimine **160**. However, for this synthesis the diimine is readily reduced with sodium borohydride to form the desired diamine **161** in good yields. The later is then reacted with triethyl orthoformate and ammonium chloride to form the desired 5-membered cyclic imidazolidinium salt **156**. Using this procedure, two salts were prepared starting from the corresponding aniline in acceptable yields (Scheme 164).

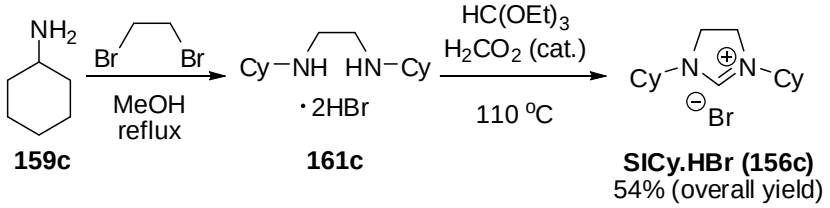


Scheme 164. Synthesis of imidazolidinium salts[2]

As for the SICy imidazolidinium salt, it was prepared using a modified procedure (Scheme 165).[5] Cyclohexylamine **159c** was reacted with 1,2-dibromoethane to form the diamine **161c** in its salt form as its bis-hydrobromide. The diamine **161c** was later put in presence of diethyl

[5] S. P. Roche, M.-L. Teyssot, A. Gautier, *Tetrahedron Lett.* **2010**, *51*, 1265.

orthoformate and a catalytic amount of formic acid to form the desired imidazolidinium salt **156c** (Scheme 165).



Scheme 165. Alternative method for preparing the SICy.HBr salt

III.1.3. Synthesis of Chiral NHC Salts

As shown earlier in this chapter, chiral NHCs' use as ligands in catalysis is rapidly growing, therefore as this project later unfolded, we were compelled to synthesize some chiral NHC salts and then isolate and characterize the copper complexes of these salts. We argued that these complexes could later allow us to study the chirality induction of such ligands, thus eventually leading to the development of new asymmetric processes involving chiral NHCs. For that reason, we chose to synthesize chiral NHC salts **171a-b** starting from commercially available chiral diamine **168** (Scheme 166).[49,6] This class of NHC precursors was first described by Tomioka *et al* and used successfully in copper-catalyzed 1,4-addition reactions as well as allylation reactions.

Diamine **168** was di-alkylated using reagent **169** in basic conditions to afford the desired product **170** in good yields (Scheme 166). The later is then reacted with triethyl orthoformate and ammonium tetrafluoroborate to form the desired chiral imidazolidinium salt **171** in a quantitative yield. In that manner, two chiral NHC salts were prepared in good yields; **171a** and **171b**.

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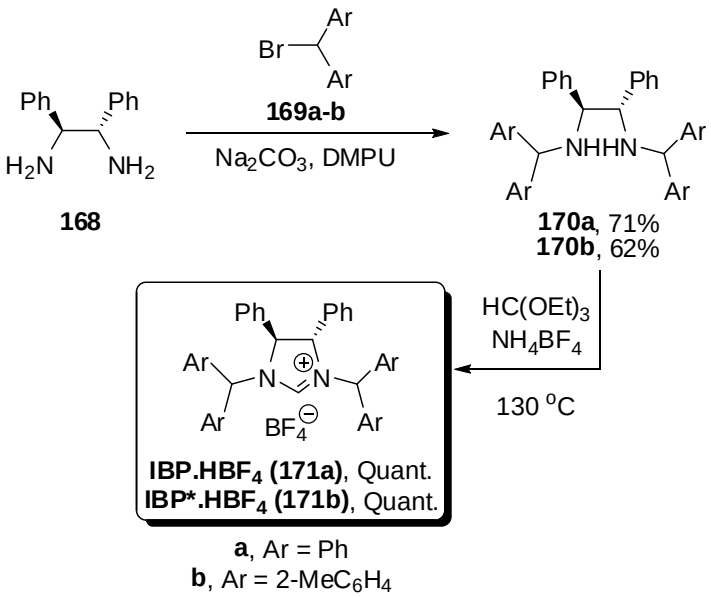
[6] Y. Matsumoto, K. Yamada, K. Tomioka, *J. Org. Chem.* **2008**, *73*, 4578.



Scheme 166. Synthesis of the chiral NHC precursors[7]

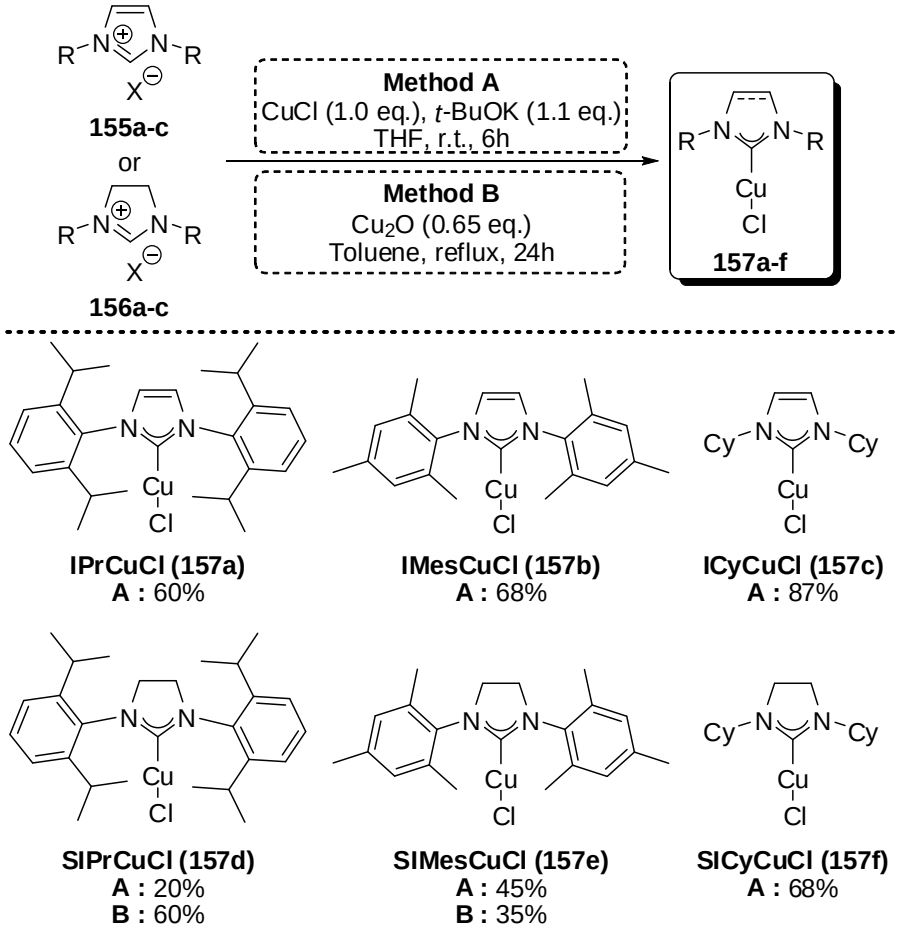
III.2. Synthesis of the (NHC)CuCl Complexes

With all the NHC salts now in hand, we started synthesizing the copper chloride complexes (Scheme 167). The most used method to access these complexes is by a deprotonation/complexation procedure using potassium *tert*-butoxide and copper chloride (method A).[36a,8] Using this method, we managed to synthesize the copper chloride complexes of the six imidazolium and imidazolidinium salts (**155a-c** and **156a-c**) that we prepared earlier in moderate to acceptable yields. We also tested another method described in

[7] This work has been done in collaboration with a Master 1 trainee, Nathalie Mager, **2011**.

[8] S. P. Nolan, *J. of Organometallic Chem.* **2000**, *606*, 49.

the literature on two of the six salts using copper(I) oxide (method B).[9] This method gave acceptable yields for complexes **157d** and **157e**, and in the case of **157d** it gave a substantially higher yield than method A (60% for method B, compared to 20% for method A).

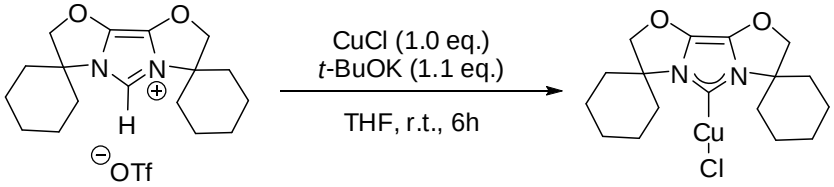


Scheme 167. Synthesis of (NHC)CuCl complexes

We engaged IBiox6.HOTf (**167**) in method A's conditions and managed to isolate complex **172** in only traces amount (Scheme 168). The amount

[9] S. J. Cazin, *Dalton Trans.* **2010**, *39*, 4489.

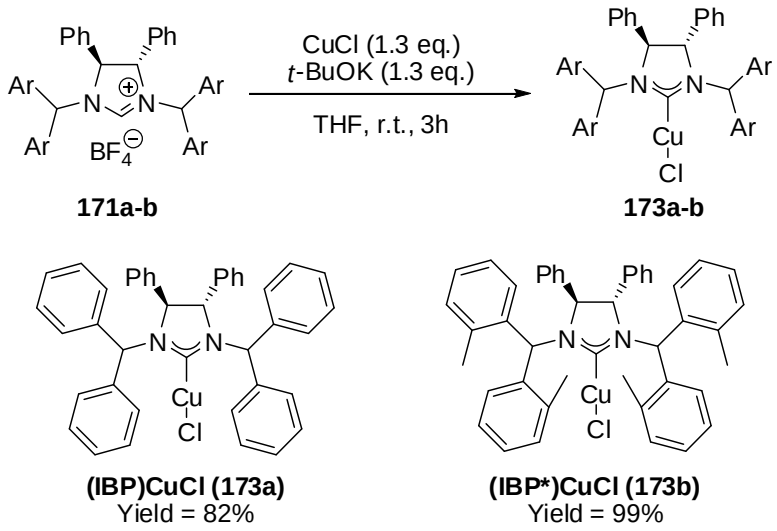
obtained was sufficient to obtain adequate analytical data, however the method was never optimized because the NHC salt was too difficult to synthesize. This route was later abandoned and no further use of this NHC salt was made.



IBiox6.HOTf (167) **(IBiox6)CuCl (172)**

Scheme 168. Synthesis of the (IBiox6)CuCl complex

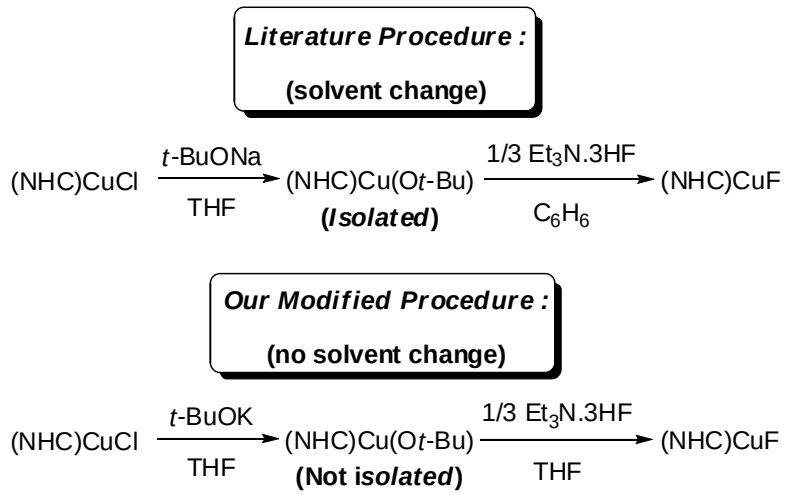
The synthesis of the chiral (NHC)CuCl complexes were also accomplished using method A (Scheme 169).[6] Complexes **173a** and **173b** were formed in 82% and 99%, respectively. The most interesting approach to this synthesis is the purification process. We were able to successfully purify these complexes by silica gel column chromatography, with no degradation or decomposition observed.



Scheme 169. Synthesis of the chiral (NHC)CuCl complexes[7]

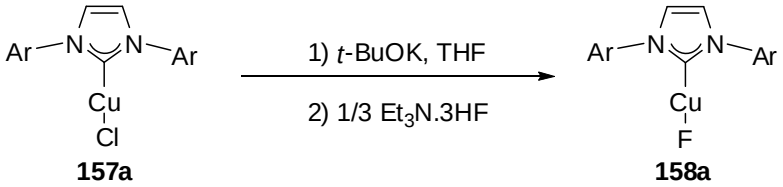
III.3. Synthesis of the (NHC)CuF Complexes

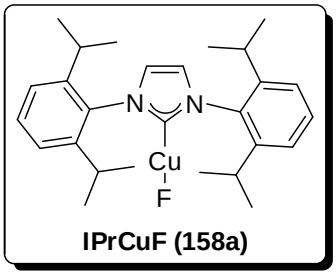
The next step in our strategy was to transform all the newly formed (NHC)CuCl complexes to their fluoride analogues. To that end, we exploited the procedure developed by Laitar *et al*,[24d] but with some modifications (Scheme 170). As seen in Scheme 170, the literature procedure involves isolating the very unstable (NHC)Cu(O*t*-Bu) complexes, followed by treatment with triethylamine trihydrofluoride (Et_3N•3HF) in benzene. However, upon examining this procedure, we saw no reason to change the solvent from THF to benzene. We argued that the high sensitivity of (NHC)Cu(O*t*-Bu) complexes should be avoided and therefore, it was better to generate and react these intermediates without prior isolation.



Scheme 170. Method used for the preparation of (NHC)CuF complexes

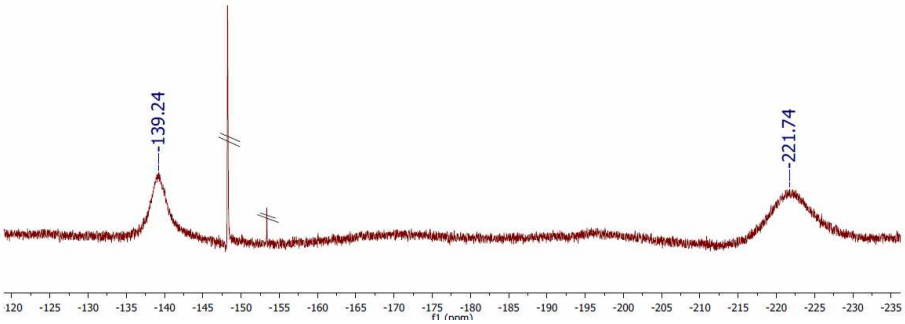
Upon reacting IPrCuCl with *t*-BuOK followed by filtration under an inert atmosphere to remove KCl and addition of Et_3N•3HF without removal of THF, a complex was isolated in good quantities (Scheme 171). However, after careful analysis, the NMR data for this newly formed complex did not completely match those described in the literature for the same complex.[24d] Although, the ^1H and ^{13}C NMR data (in CD_2Cl_2) for this complex were almost identical to the IPrCuF complex reported in the literature, the ^{19}F NMR was completely different. It showed two peaks (at -221 ppm and -139 ppm) instead of one (at -240 ppm). Furthermore, ^1H NMR in CD_3CN at room temperature showed an additional broad singlet at 14.1 ppm.





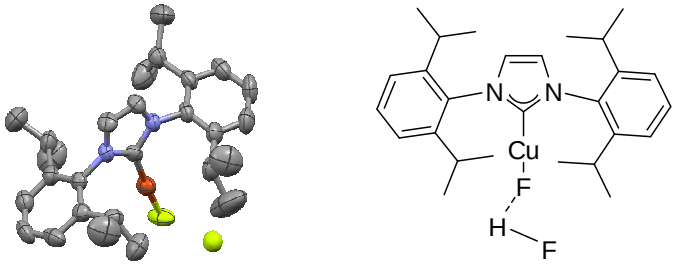
^{1}H NMR spectra was in complete accordance with the literature
^{19}F NMR spectra showed two peaks instead of one

^{19}F NMR spectrum



Scheme 171. Attempted synthesis of the IPrCuF complex

To understand this unusual result, single crystals were grown and X-ray analysis revealed an unprecedented (NHC)Cu^{I} bifluoride complex; IPrCuF.HF **174a** (Figure 10). We redid the reaction exactly as described in the literature, and successfully obtained the desired IPrCuF complex (see Scheme 170). Crystals of IPrCuF were also grown, and the structure of both compounds was unambiguously shown to be different.



IPrCuF.HF (174a)

Figure 10. X-Ray structure of the new IPrCuF.HF complex

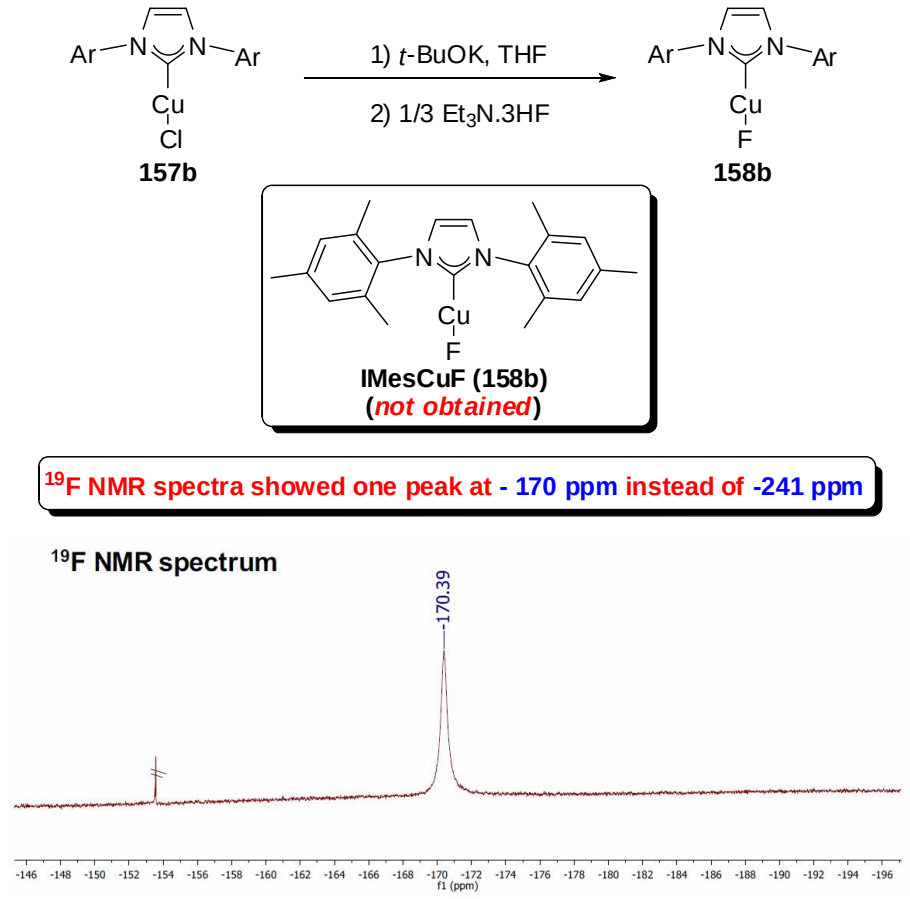
Complex **174a** was fully characterized and unlike the corresponding IPrCuF complex, proved to be highly air stable in the solid state and moderately stable in solution, with degradation occurring after two days. As mentioned above, the ^{19}F NMR spectrum exhibits two different peaks, one at -138 ppm, corresponding to the distal fluorine atom (Cu-F-H-***F***) and one at -220 ppm referring to the proximal fluorine (Cu-***F***-H-F). The broad singlet on the ^{1}H NMR spectrum (in CD_3CN) refers to the acidic proton (Cu-F-***H***-F). These results are in agreement with those found for other transition metal bifluorides described in the literature.[10]

---

[10] a) T. Braun, S. P. Foxon, R. N. Perutz, P. H. Walton, *Angew. Chem. Int. Ed.* **1999**, *38*, 3326; b) S. J. Archibald, T. Braun, J. A. Gaunt, J. E. Hobson, R. N. Perutz, *J. Chem. Soc., Dalton Trans.* **2000**, 2013; c) M. C. Pilon, V. V. Grushin, *Organometallics* **1998**, *17*, 1774; d) D.C. Roe, W. J. Marshall, F. Davidson, P.D. Soper, V. V. Grushin, *Organometallics* **2000**, *19*, 4575; e) N. D. Ball, M. S. Sanford, *J. Am. Chem. Soc.* **2009**, *131*, 3796; f) N. A. Jasim, R. N. Perutz, *J. Am. Chem. Soc.* **2000**, *122*, 8685; g) D. R. Coulson, *J. Am. Chem. Soc.* **1976**, *98*, 3111; h) D. Noveski, T. Braun, S. Kruckemeier, *J. Fluor. Chem.* **2004**, *125*, 959; i) J. Vicente, J. Gil-Rubio, D. Bautista, A. Sironi, N. Masciocchi, *Inorg. Chem.* **2004**, *43*, 5665; j) S. A. MacGregor, D. C. Roe, W. J. Marshall, K. M. Bloch, V. I. Bakhmutov, V. V. Grushin, *J. Am. Chem. Soc.*, **2005**, *127*, 15304; k) M. K. Whittlesey, R. N. Perutz, B.

Simultaneously, the same modified procedure was attempted on the (NHC)Cu^{I} chloride complex **157b** (Scheme 172). This time, the NMR data of the obtained complex was considerably different than that described in the literature.[24e] Furthermore, the ^{19}F NMR spectrum exhibits one peak at -170 ppm instead of the described -241 ppm. This last observation also distinguishes the newly obtained complex from complex **174a**.

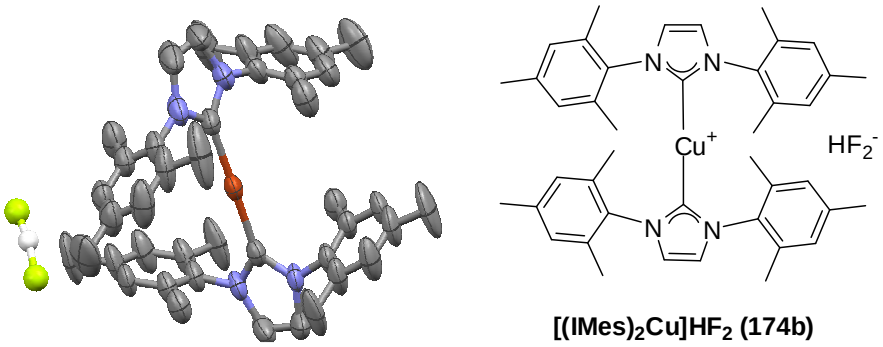
Greener, M. H. Moore, *Chem. Comm.* **1997**, 187; l) M. S. Kirkham, M. F. Mahon, M. K. Whittlesey, *Chem. Comm.* **2001**, 813; m) N. A. Jasim, R. N. Perutz, S. P. Foxon, P. H. Walton, *J. Chem. Soc. Dalton Trans.* **2001**, 1676; n) V. J. Murphy, D. Rabinovich, T. Hascall, W. T. Klooster, T. F. Koetzle, G. Parkin, *J. Am. Chem. Soc.* **1988**, *120*, 4372; o) V. J. Murphy, T. Hascall, J. Y. Chen, G. Parkin, *J. Am. Chem. Soc.* **1996**, *118*, 7428; p) U. Bentrup, K. Harms, W. Massa, J. Pebler, *Solid State Sci.* **2000**, *2*, 373.



Scheme 172. Attempted synthesis of the IMesCuF complex

In an attempt to unravel this new mystery, single crystals were also grown. Remarkably, X-ray analysis revealed a *bis*-(NHC) copper(I) bifluoride complex; $[(IMes)_2Cu]HF_2$ **174b** (Figure 11). *Bis*-(NHC) copper(I) complexes are well known with classical non-coordinating counter-ions such as PF_6^-

and BF_4^-,[13b,26,37,39b,11] but to our knowledge no such complex has ever been described containing a HF_2^- counter-ion. Complex **174b** showed a *bis*-coordinated copper(I) atom in a linear environment with a C-Cu-C angle of 180°. The aryl groups are twisted almost perpendicularly with respect to the imidazole plane, resulting in a favourable steric arrangement. The Cu-C bond length of 2.182 Å is comparable, even slightly longer, to reported Cu-C bond lengths in *bis*-NHC complexes. The torsion angle between the two NHC ligands of 60.04° is also in agreement with those found in other $[(IMes)_2Cu]X$ complexes. The acidic proton resonance is observed at 13.6 ppm (in CD_2Cl_2), while the ^{19}F NMR exhibits a singlet at -170 ppm, characteristic of a symmetric HF_2^- anion.



$[(IMes)_2Cu]HF_2$ (174b)

Figure 11. X-Ray structure of the new $[(IMes)_2Cu]HF_2$ complex

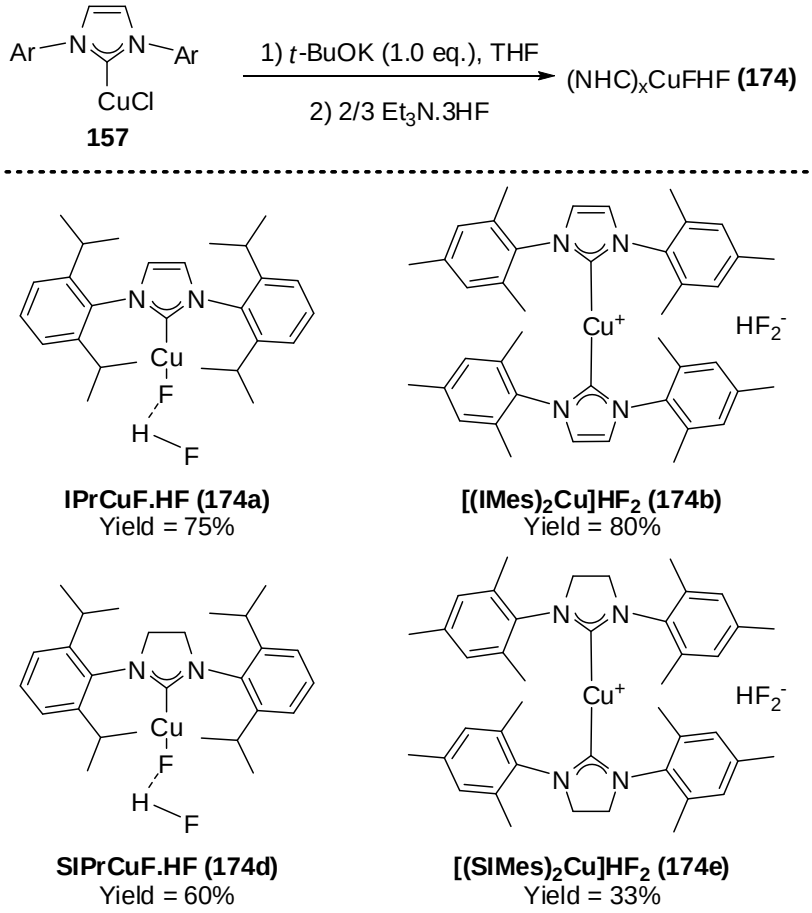
^{19}F NMR thus emerged as a direct and practical method to determine whether the obtained complex is either of the (NHC)CuF.HF or the $[(NHC)_2Cu]HF_2$ type.

---

[11] a) G. Venkatachalam, M. Heckenroth, A. Neels, M. Albrecht, *Helv. Chim. Acta* **2009**, *92*, 1034; b) X. Hu, I. Castro-Rodriguez, K. Olsen, K. Meyer, *Organometallics* **2004**, *23*, 755.

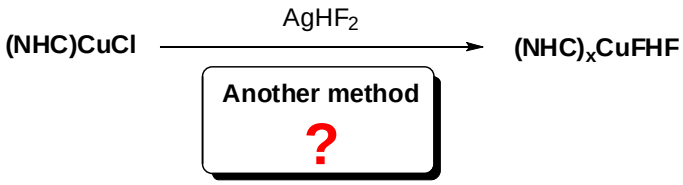
III.4. Synthesis of the $(NHC)_xCu^I$ Bifluoride Complexes

Intrigued by these unexpected results, we sought to apply this modified procedure to all previously synthesized (NHC)CuCl complexes. In light of the newly available data, we adjusted the number of equivalents of NEt_3•3HF from 0.33 to 0.66, thus reacting two equivalents of HF instead of one. In that manner, we applied the aforementioned procedure on complexes **157a-f**, and managed to obtain moderate to good yields of their bifluoride analogues (Scheme 173). However, complexes **174c** and **174f** were never obtained, and only degradation of the starting material was observed. This last result is probably due to the highly basic character of the corresponding NHCs (ICy and SICy). Furthermore, chiral (NHC)CuCl complexes **173a-b** failed to undergo the desired reaction, and thus no chiral $(NHC)Cu^I$ bifluoride complexes were obtained.



Scheme 173. Synthesis of new $(NHC)_xCuFHF$ complexes

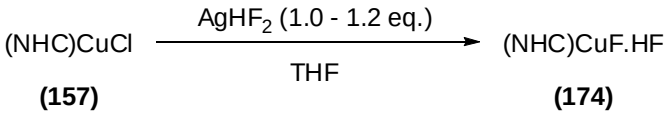
Encouraged by these results, we wanted to develop a more practical and convenient way of synthesizing these new $(NHC)Cu^I$ bifluoride complexes. We argued that these new complexes could be accessed directly from their chloride analogues by engaging the latter with the commercially available silver bifluoride salt ($AgHF_2$) (Scheme 174). This method gives us an easy access from easily prepared and air stable copper chloride complexes, thus completely avoiding the need to generate the highly air sensitive *tert*-butoxide complexes.



Scheme 174. Possible alternative method to generate the bifluoride complexes

We started by testing the designated reaction on the *mono*-(NHC) complexes and after a couple of attempts, we observed that the reaction indeed works quite well (Table 29). IPrCuCl and SIPrCuCl reacted directly with $AgHF_2$ in THF to form the desired bifluoride complexes **174a** and **174d** in 83% and 50% yield, respectively.

Table 29. Synthesis of *mono*-(NHC)Cu^I bifluoride complexes



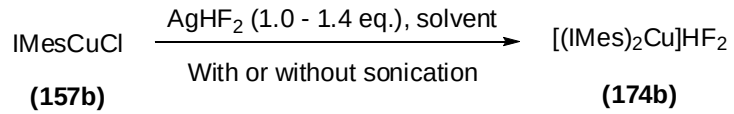
Entry[a]	(NHC)CuCl	(NHC)CuF.HF	Yield[b] (%)
1	IPrCuCl (**157a**)	IPrCuF.HF(**174a**)	83
2	SIPrCuCl (**157d**)	SIPrCuF.HF (**174d**)	50

[a] All reactions were run under argon and in the dark [b] Isolated yield.

However, when we engaged IMesCuCl in the same optimal conditions described above, a mixture of IMesCuCl and $[(IMes)_2Cu]HF_2$ was obtained in a 70/30 ratio (Table 30, entry 1). We managed to optimize the reaction a bit further by sonicating the reaction mixture for 90 minutes (Table 30, entry 2). A final optimisation of the solvent showed that DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone) was the solvent of choice, affording

full conversion to the desired *bis*-(NHC) complex **174b** (Table 30, entry 5). This solvent is well-known for its ability to solvate cationic metallic species, which made it a perfect candidate for our reaction.[12]

Table 30. Optimisation of the new methodology on complex **157b**



Entry [a]	Solvent	Sonication [b]	Product [c]
1	THF	Without	Mixture Cl/HF_2 (70/30)
2	THF	With	Mixture Cl/HF_2 (60/40)
3	CH_2Cl_2	With	Mixture Cl/HF_2 (19/81)
4	Et_2O	With	No product isolated
5	DMPU	With	Complete conversion

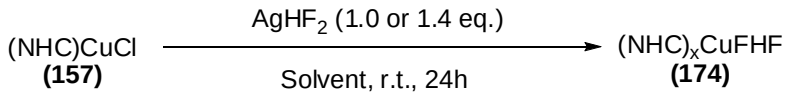
[a] All reactions were run under argon and in the dark [b] Sonication at room temperature for 90 minutes, then stirring overnight at room temperature without sonication [c] Mixture ratio determined on the crude solid by ^{1}H NMR.

With this new method in hand, we re-synthesized the previously described four NHCs in good yields (Table 31). Interestingly, the formation of either a $[(NHC)_2Cu]HF_2$ or a (NHC)CuF.HF bifluoride complex depends entirely on the nature of the nitrogen's substituent in the corresponding NHC, independent of the method used. Steric congestion around the metal centre is presumed to be the predominant factor. It should be noted that sonication is

[12] D. Lundberg, Ph.D. thesis, Swedish University of Agricultural Sciences, Uppsala, **2006**.

only needed when the expected bifluoride complex is a *bis*-(NHC) copper(I) bifluoride, nevertheless all reactions are performed in the dark for 24 hours.

Table 31. Synthesis of *mono*- and *bis*-(NHC)Cu^{I} bifluoride complexes

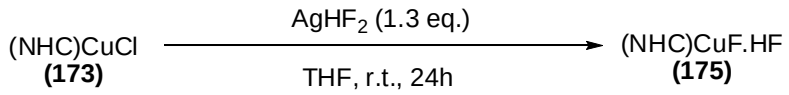


Entry[a]	(NHC)CuCl	Solvent	$(NHC)_xCuFHF$	Yield[c] (%)
1	IPrCuCl	THF	IPrCuF.HF (**174a**)	83
2[b]	IMesCuCl	DMPU	$[(IMes)_2Cu]HF_2$ (**174b**)	60
3	SIPrCuCl	THF	SIPrCuF.HF (**174d**)	50
4[b]	SIMesCuCl	DMPU	$[(SIMes)_2Cu]HF_2$ (**174e**)	85

[a] All reactions were run under argon and in the dark [b] Sonication at room temperature for 90 minutes, then stirring overnight at room temperature without sonication [c] Isolated yield.

As stated earlier, chiral (NHC)CuCl complexes failed to afford the corresponding bifluoride complexes using the first method. However, when these complexes were engaged with silver bifluoride, they readily afforded the desired bifluoride complexes in good to excellent yields (Table 32). It should be mentioned that these chiral complexes only furnished *mono*-(NHC) copper(I) bifluoride complexes (**175a** and **175b**).

Table 32. Synthesis of the chiral (NHC)Cu^{I} bifluoride complexes



Entry[a]	(NHC)CuCl	(NHC)CuF.HF	Yield[b] (%)
1	(IBP)CuCl	(IBP)CuF.HF (**175a**)	64
2	(IBP*)CuCl	(IBP*)CuF.HF (**175b**)	>99

[a] All reactions were run under argon and in the dark [b] Isolated yield.

III.5. Catalytic Activity of the $(NHC)_xCuFHF$ Complexes

With these complexes readily prepared and characterized, they were expected to show interesting catalytic activity due to the unique nature of the bifluoride counter-ion and the recent advances in (NHC)Cu^{I} catalyzed reactions. For these reasons, the reactivity of these complexes was investigated in previously described Cu^{I}-catalyzed reactions.[4a,24,35,36a,37a,13]

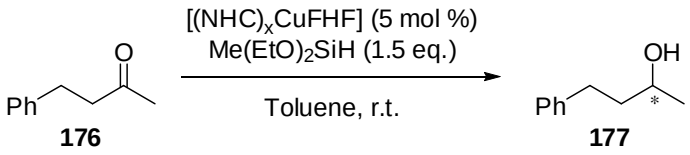
III.5.1. Cu^{I}-Catalyzed Reduction Reactions

The first reaction to be investigated was the reduction of ketones to the corresponding alcohols. As shown earlier in this chapter, Nolan *et al* established both (NHC)Cu^{I}, as well as $(NHC)_2Cu^{I}$ complexes to be successful in reducing a variety of ketones. However, the copper(I) complexes used required activation by a base (*t*-BuONa). When investigating this reaction using the bifluoride complexes described here, the

[13] a) W. A. Herrmann, *Angew. Chem., Int. Ed.* **2002**, *41*, 1290-1309; b) S. Diez-Gonzalez, S. P. Nolan, *Synlett* **2007**, 2158; c)

reaction was shown to occur instantaneously without the requirement of any activating substances (Table 33). Reduction of benzylacetone proceeded smoothly under very mild conditions to generate the desired alcohol **177**, upon hydrolysis. *Mono*- and *bis*-(NHC) copper bifluorides successfully catalyzed the desired reaction in quantitative yields (Table 33, entries 1-3). Although all three complexes afford complete conversion in an hour or less, *bis*-(NHC)Cu^{I} bifluorides were more efficient, achieving complete conversion in 0.25 hours (Table 33, entry 2). We also tested our chiral bifluoride complexes (**175a** and **175b**) in an attempt to reduce the selected ketone in an enantioselective manner (Table 33, entries 4 and 5); however no significant enantiomeric excess was obtained (only 15% with **175b**).

Table 33. Hydrosilylation of benzylacetone



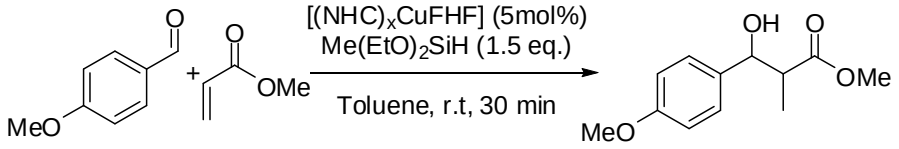
176 **177**

Entry[a]	$(NHC)_xCuFHF$	Time (hour)	Yield[b] (%) (e.e.)[c]
1	**174a**	1	>99
2	**174b**	0.25	>99
3	**174d**	0.5	>99
4[d]	**175a**	24	27 (0%)
5[d]	**175b**	24	26 (15%)

[a] All reactions were run under argon [b] Yield determined on the crude mixture by ^{1}H NMR and GC analysis [c] Enantiomeric ratio in parentheses is determined by GC analysis [d] Reaction was run at 0 ^{o}C.

Next, we extended the testing to the 1,4-reduction/aldolisation of Michael acceptors, which was also previously described by Riant and Nolan, using a $(NHC)Cu^{I}$ complex (see Scheme 142). In the same manner, methyl acrylate was reacted with *para*-anisaldehyde in the presence of $Me(EtO)_2SiH$ and a copper bifluoride catalyst (Table 34). Complexes **174a** and **174b** readily catalyze the desired reaction and afford complete conversion to the aldol product **180** (Table 34, entries 1 and 2). However, low diastereoselectivities were observed in both cases. Nevertheless, when we used the chiral bifluoride **175a** at 0 °C, a significant increase in the diastereomeric ratio of **180** was observed (up to 84/16) (Table 34, entry 3). Furthermore, a modest enantiomeric excess was duly noted (30%).

Table 34. 1,4-reduction/aldolisation reaction



178 **179** **180**

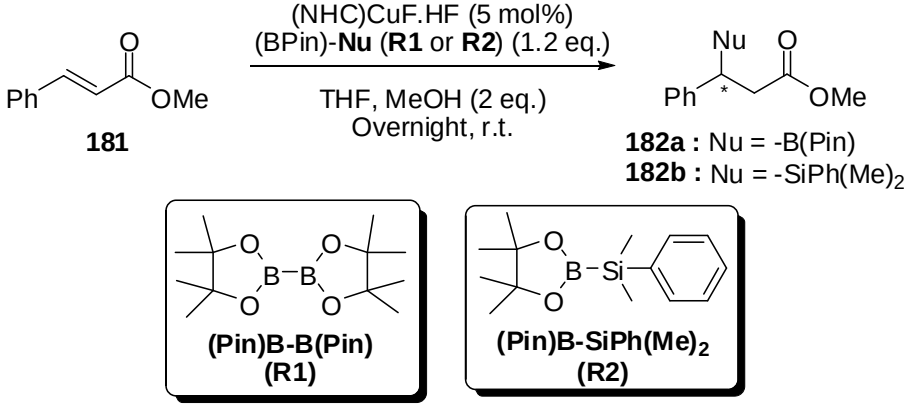
Entry[a]	$(NHC)_xCuFHF$	Yield[b] (%)	d.r.[c] (e.e.)[d]
1	**174a**	>99	53/47
2	**174b**	>99	60/40
3[e]	**175a**	>99	84/16 (30%)

[a] All reactions were run under argon [b] Yield determined on the crude mixture by ^{1}H NMR [c] Diasteromeric ratio determined by ^{1}H NMR [d] Enantiomeric ratio in parentheses is determined by HPLC analysis [d] Reaction was run at 0 °C overnight.

III.5.2. β-Borylation and β-Silylation Reactions

After these encouraging results, the 1,4-conjugate β-borylation and β-silylation reactions were subsequently investigated (Table 35). As seen earlier, recent studies have shown that (NHC)Cu^{I} complexes can successfully catalyze these reactions with high yields and selectivities (see Section I.1.2.4, Chapter 3). However, an activating agent is required in almost all cases. Bifluoride complexes, once again were shown to be active in both reactions, generating good yields of **182a** and **182b**, and did not require an activating agent. Unfortunately, the chiral complexes studied here did not lead to a high enantioselectivity (only 31% for **182a**, using chiral complex **175b**) (Table 35, entry 2).

Table 35. β-borylation and β-silylation reactions of methyl cinnamate



Entry[a]	(NHC)CuF.HF	Product	Yield[b] (%)	e.e. (%)
1	**174d**	**182a**	99	-
2[d]	**175b**	**182a**	58	31[c]
3	**174d**	**182b**	83	-

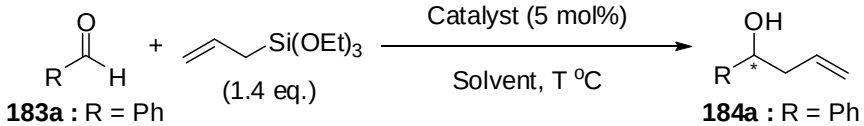
[a] All reactions were run under argon [b] Isolated yield [c] Enantiomeric ratio is determined by HPLC after oxidation to the alcohol by $NaBO_3/H_2O$, B(Pin) = pinacolborane [d] Toluene was used instead of THF.

III.5.3. Cu^I-Catalyzed Allylation Reactions

To further investigate the possibility of inducing enantioselectivity with these chiral (NHC)CuF.HF complexes, the Cu^I-catalyzed allylation reaction of aldehydes was consequently investigated (Table 36). The work of Ball *et al* that we described previously,[24] showed that (NHC)CuF complexes are good catalysts for this reaction but require the addition of fluorosilanes to achieve efficient yields and reproducible results (see Scheme 147). The bifluoride complexes described here do not require any additives and readily catalyze the allylation reaction of aldehydes **183a** and **183b** (Table 36). High

yields of both **184a** and **184b** are achieved under mild conditions and remarkably, a moderate enantioselectivity (46%) has been obtained for product **184a**, using our chiral complex **175b** (Table 36, entry 6).

Table 36. Allylation of aldehydes using an allyl siloxane



183a : R = Ph
183b : R = Cy

184a : R = Ph
184b : R = Cy

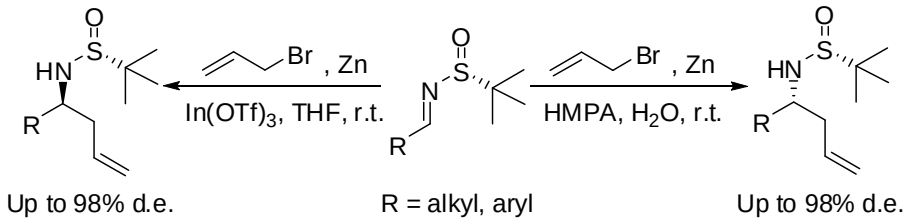
Entry[a]	Catalyst	R	T (°C)	Solvent	Yield[b] (%)	e.e.[d] (%)
1	**174a**	Ph	25	THF	>99(83%)[c]	-
2	**174d**	Ph	25	THF	>99	-
3	**174d**	Cy	25	THF	>99 (69%)[c]	-
4	**175a**	Ph	25	THF	>99	28
5[e]	**175a**	Ph	0	Toluene	>99	42
6[e]	**175b**	Ph	0	Toluene	>99	46

[a] All reactions were run under argon until total conversion was indicated by TLC [b] Yield determined on the crude mixture by ^{1}H NMR [c] Isolated yield indicated in parentheses [d] Enantiomeric ratio determined by HPLC analysis [e] Reaction is run overnight.

Recently, another allylation-type reaction became a subject of high interest in the literature: the allylation of aldimines. Lin[14] *et al* reported a practical synthesis of chiral homoallylic amines based on a Zn-mediated allylation of chiral (*R*)-*N*-*tert*-butanesulfinyl imines (Scheme 175). By varying the

[14] a) M.-H. Xu, G.-Q. Lin, *O*rg. Lett. **2006**, *8*, 4979; b) M.-H. Xu, G.-Q. Lin, *O*rg. Lett. **2008**, *10*, 1259.

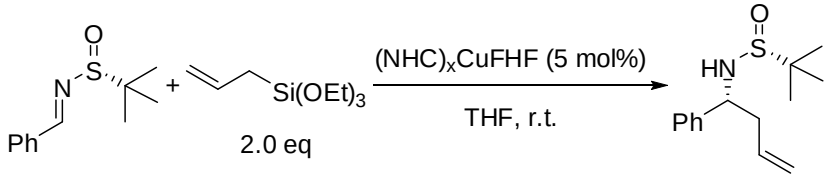
reaction conditions, their method allowed the achievement of opposite stereocontrol by giving access to the two diastereoisomers.



Scheme 175. Lin *et al*'s allylation of aldimines

Intrigued by these results and the remarkable reactivity that these copper(I) bifluoride complexes have shown towards silane activation, we hoped to achieve similar results by reacting an allyl siloxane with chiral (*R*)-*N*-*tert*-butanesulfinyl imines. To this end, different copper(I) bifluoride complexes were screened (Table 37). Results showed that both IPrCuF.HF (**174a**) and SIPrCuF.HF (**174d**) successfully catalyzed the desired reaction with good diastereoselectivities (Table 37, entries 1 and 2). However, total conversion of the starting material **185** was not achieved under these conditions. It should be noted that our reaction conditions lead to the difficult to obtain (*R*)-amine diastereoisomer (**186a**), whereas the reaction conditions described by Lin *et al* to obtain this diastereoisomer require the use of HMPA, a human carcinogen, rendering the method somewhat impractical on a larger scale (see Scheme 175). To our knowledge, this is the first Cu^{I}-catalyzed allylation reaction of chiral aldimines.

Table 37. Allylation of aldimine **185a**: variation of the bifluoride complex



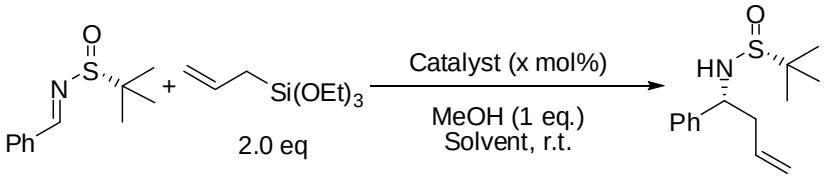
185a **186a**

Entry[a]	$(NHC)_xCuFHF$	Yield[b] (%)	d.r.[c]
1	**174a**	59	91/9
2	**174b**	51	84/16
3	**174d**	19	100/0

[a] All reactions were run under argon until total conversion was indicated by TLC [b] Yield determined on the crude mixture by ^{1}H NMR [c] Diasteromeric ratio is determined by ^{1}H NMR, the configuration was assigned by comparison with literature data.

In light of the above encouraging results, we sought to further optimise the designated reaction. Addition of one equivalent of methanol as an additive gave us a higher conversion to the desired product (Table 38). IPrCuF.HF (**174a**) and SIPrCuF.HF (**174b**) were equally tested and results showed that IPrCuF.HF (**174a**) was the best catalyst for this reaction affording **186a** in a 90% yield and a 94/6 diastereomeric ratio (Table 38, entry 1). Full conversion was achieved by using 10 mol% of **174a** instead of 6 mol% in THF (Table 38, entry 3). Under these conditions, product **186a** was isolated in 81% yield and a 95/5 diastereomeric ratio. Varying the reaction's solvent did not improve the diastereomeric ratio, however full conversion was also achieved in DCM and diethyl ether.

Table 38. Allylation of aldimine **185a**: Optimisation



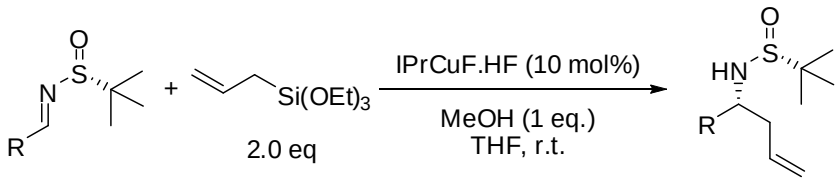
185a **186a**

Entry[a]	Catalyst (mol%)	Solvent	Yield[b] (%)	d.r.[c]
1	**174a** (6)	THF	90	94/6
2	**174d** (6)	THF	85	89/11
3	**174a (10)**	**THF**	**>99 (81%)[d]**	**95/5**
4	**174a** (10)	DCM	>99	89/11
5	**174a** (10)	Et_2O	>99	93/7
6	**174a** (10)	Toluene	90	92/8

[a] All reactions were run under argon until total conversion was indicated by TLC [b] Yield determined on the crude mixture by ^{1}H NMR [c] Diasteromeric ratio is determined by ^{1}H NMR, the configuration was assigned by comparison with literature data [d] Isolated yield in parentheses.

Under the new optimized conditions, several aldimines were successfully screened to afford good yields of the corresponding amines along with comparable diastereomeric ratio (Table 39). *Ortho*- as well as *para*-substituted aryls effectively underwent the desired reaction to afford good yields and excellent diastereoselectivities of the corresponding amines (Table 39, entries 2-4). Furthermore, aliphatic aldimines were also tolerated; cyclohexyl aldimine **185e** afforded the desired product **186e** in a good yield and a good diastereoselectivity (Table 39, entry 5).

Table 39. Allylation of aldimine **185a**: the reaction's scope



185a-e **186a-e**

Entry[a]	R[b]	Product	Yield[c] (%)	d.r.[d]
1	C_6H_5	**186a**	81	95/5
2	4-$MeOC_6H_4$	**186b**	90	92/8
3	2-$MeOC_6H_4$	**186c**	91	95/5
4	2-MeC_6H_4	**186d**	83	96/4
5	cyclohexyl	**186e**	69	93/7

[a] All reactions were run under argon until total conversion was indicated by TLC [b] Starting material prepared according to literature procedures (see Experimental part, Chapter 3) [c] Isolated yield [d] Diasteromeric ratio is determined by ^{1}H NMR, the configuration was assigned by comparison with literature data.

We were extremely happy with all these results, however no further reactions were explored, and to our satisfaction, all the above data was recently published giving a more than decent closure to this part of the project.[15]

[15] F. Nahra, T. Vergote, A. Welle, M. Luhmer, J. Wouters, N. Mager, O. Riant, T. Leyssens, *Chem. Euro. J.* **2012**, *18*, 793.

III.6. NMR Studies

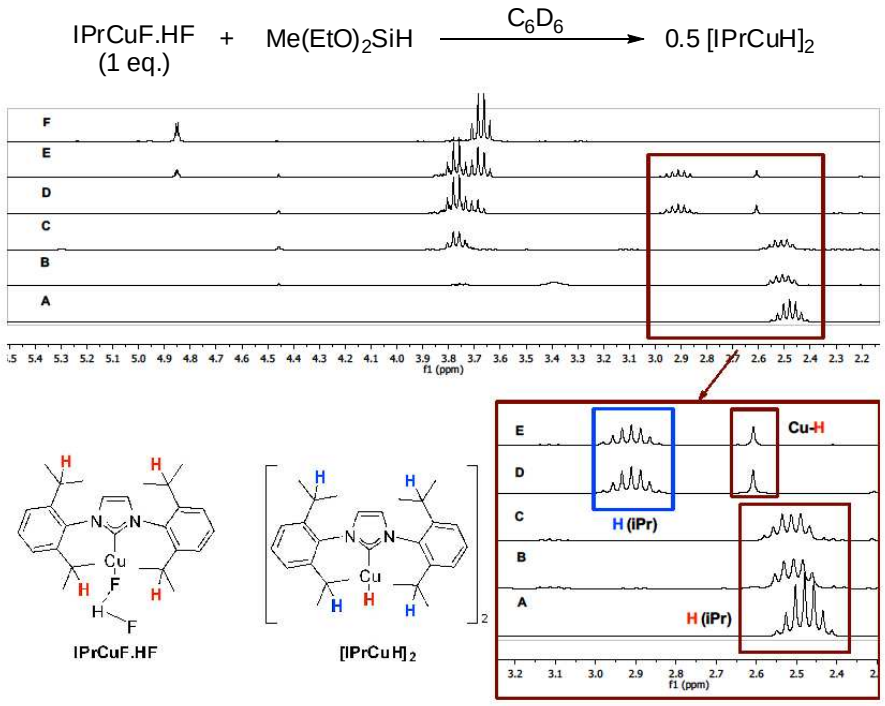
The next step in this project was to identify some of the formed intermediates as a result of the reaction of our new bifluoride complexes with silanes. We wanted to identify this new reactivity exhibited by our complexes towards silane activation. We were also highly intrigued by the fact that our bifluoride complexes were quite active without any need for additional reagents, contrary to all other (NHC)Cu^{I} complexes including (NHC)CuF complexes. To that end, a detailed study of the reaction's mechanism, as well as the activation mechanism and intermediates involved within, was intensively pursued. However, we are going to describe hereafter only some aspects of this study. Indeed, we are going to illustrate only the part that involves silane activation by our copper(I) bifluorides, and the difference in reactivity compared to their fluoride analogues.

III.6.1. Titration of IPrCuF.HF

The titration method involved adding the silane to a copper(I) bifluoride complex in a deuterated solvent until all the copper(I) bifluoride is consumed and the corresponding peak of the hydride complex has appeared. As seen in Scheme 141, Sadighi *et al* generated and isolated IPrCuH as a dimeric complex by reacting IPrCu(O*t*-Bu) with $(EtO)_3SiH$. This copper hydride species was consequently fully characterized.[5] We argued that if we engaged our IPrCuF.HF in the same type of reaction, we could follow the formation of the same $[IPrCuH]_2$ species without any attempts to isolate this very unstable intermediate. However, due to high toxicity, $(EtO)_3SiH$ was abandoned in favour of $Me(EtO)_2SiH$. The latter silane is much less toxic than the former but still equally reactive.

In that manner, one equivalent of IPrCuF.HF in C_6D_6 was titrated by $Me(EtO)_2SiH$ at room temperature (Figure 12). After each addition of $Me(EtO)_2SiH$, a ^1H NMR spectrum was immediately recorded. After the addition of the first equivalent of silane, no visible shifts in NMR were observed and the hydride peak at 2.63 was not recorded. However, upon the addition of the second equivalent total conversion to the dimeric IPrCuH species was observed *via* three main observations (Figure 12):

- The septuplet at 2.48 ppm, belonging to the hydrogen of the isopropyl group, which normally indicates the presence of the copper(I) bifluoride has disappeared.
- Apparition of the hydride peak at 2.63 ppm which corresponds to the $[IPrCuH]_2$ complex recorded by *Sadighi et al*.
- Apparition of a new septuplet at 2.91 ppm, belonging to the hydrogen of the isopropyl group, which also corresponds to the $[IPrCuH]_2$ complex recorded by *Sadighi et al*.



A) ^{1}H NMR of IPrCuF.HF; B) ^{1}H NMR of IPrCuF.HF (1 eq.) + MeEtO)$_2$SiH (0.5 eq.) ; C) ^{1}H NMR of IPrCuF.HF (1 eq.) + MeEtO)$_2$SiH (1 eq.) ; D) ^{1}H NMR of IPrCuF.HF (1 eq.) + MeEtO)$_2$SiH (2 eq.) ; E) ^{1}H NMR of IPrCuF.HF (1 eq.) + MeEtO)$_2$SiH (3 eq.) ; F) ^{1}H NMR of MeEtO)$_2$SiH. All ^{1}H NMR spectra were recorded in C_6D_6

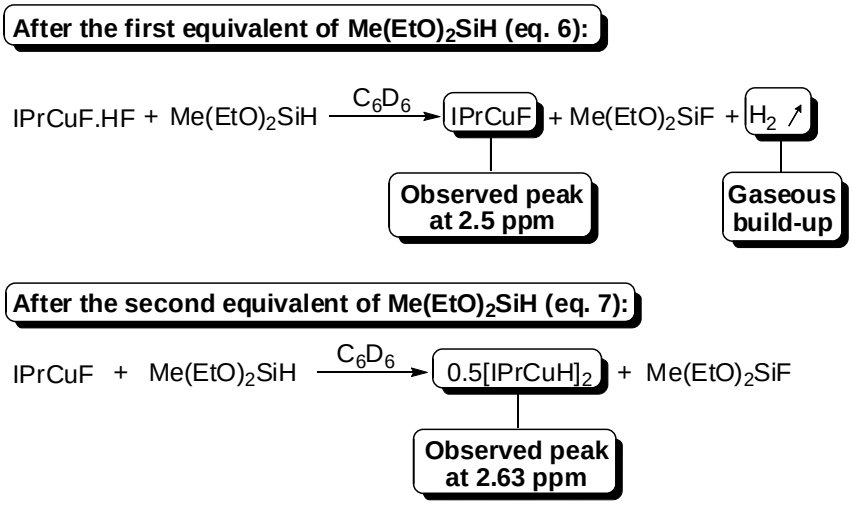
Figure 12. Titration of IPrCuF.HF with Me(EtO)SiH in C_6D_6

All this data unambiguously indicated that after two equivalents of silane, total conversion to the dimeric copper(I) hydride complex was achieved. Moreover, if we look closely at the first three spectra (**A**, **B** and **C**), we could notice a slight shift of the septuplet signal from 2.48 ppm in spectrum **A** to 2.5 ppm in spectra **B** and **C** (Figure 12). Usually, this small shift in signals is not quite significant, however in this case 2.5 ppm corresponds quite conveniently to the proton signal of the same isopropyl group of the IPrCuF complex (also known as Laitar's catalyst). Thus the above results strongly

suggest that after the first equivalent of silane, IPrCuF.HF is converted to IPrCuF which in turn is transformed to the $[IPrCuH]_2$ after the second equivalent of silane. It should also be noted that the addition of silane was accompanied, in the early stages, by a gaseous build-up in the NMR tube. We were forced to relieve the pressure before each next addition of silane. In light of these results, the following hypothesis concerning the silane activation step by our bifluoride complexes was put forward (Scheme 176):

- The first equivalent of silane reacts with IPrCuF.HF to form the IPrCuF complex (characterized by the septuplet shift to 2.5 ppm), the fluorosilane ($Me(EtO)_2SiF$) and hydrogen gas (illustrated by the gaseous build-up) (Scheme 176, eq. 6).
- The second equivalent of silane reacts with the newly formed IPrCuF complex to generate the dimeric IPrCuH species (depicted by the apparition of the hydride signal at 2.63 ppm and the septuplet shift to 2.91 ppm), and another equivalent of the fluorosilane (Scheme 176, eq. 7).

The above hypothesis allowed us to paint a good enough picture of the activation mechanism involving our bifluoride complexes and $Me(EtO)_2SiH$.



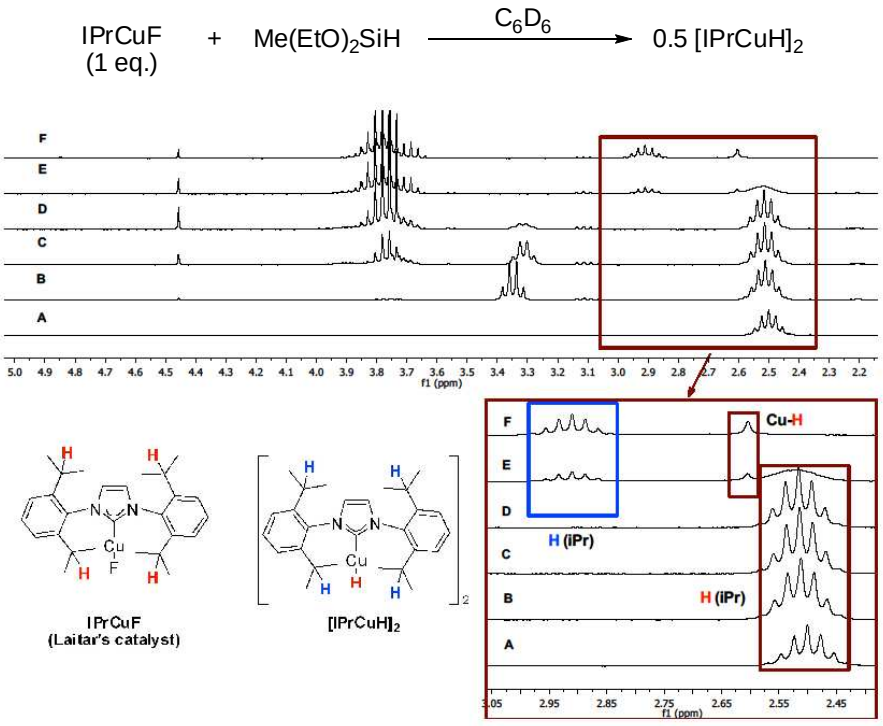
Scheme 176. Proposed mechanism for the formation of $[IPrCuH]_2$

However, as mentioned earlier in the works of Ball *et al*, IPrCuF was not very active and required the addition of a catalytic amount of a fluorosilane (*n*-octylSiF_3).[24] Moreover, in the mechanism scheme that we illustrated earlier, we can see that one equivalent of the fluorosilane is formed after the first addition of the silane. We suspected that this fluorosilane is not an innocent bystander in the mechanistic scheme.

III.6.2. Titration of IPrCuF

In an attempt to verify the conformity of the laid out activation scheme, we sought to react $Me(EtO)_2SiH$ directly with IPrCuF (Laitar's catalyst) in the absence of a fluorosilane at first, then in the presence of the latter. In the absence of a fluorosilane, IPrCuF was titrated with an increasing amount of $Me(EtO)_2SiH$, in the same manner as we performed the previous titration of IPrCuF.HF (Figure 13). Interestingly, ^1H NMR analysis showed that four equivalents of the silane were needed in order to achieve full conversion to the $[IPrCuH]_2$ complex. This observation was in accordance with the fact

that IPrCuF is indeed less reactive in the activation of the silane than our bifluoride complex.

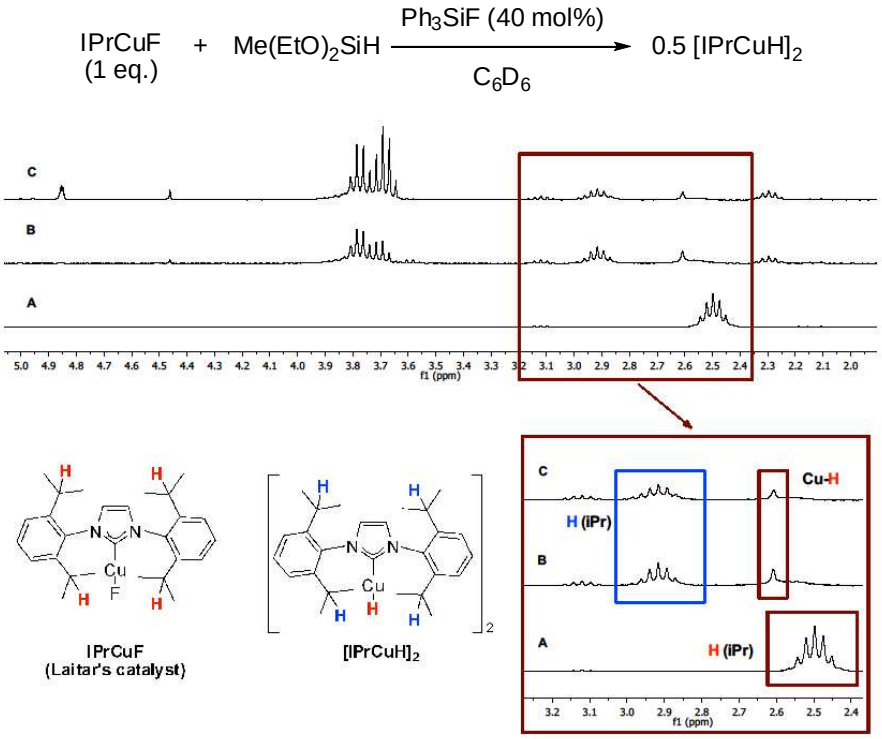


A) ^{1}H NMR of IPrCuF (Laitar's catalyst); B) ^{1}H NMR of IPrCuF (1 eq.) + MeEtO)$_2$SiH (0.5 eq.) ; C) ^{1}H NMR of IPrCuF (1 eq.) + MeEtO)$_2$SiH (1 eq.) ; D) ^{1}H NMR of IPrCuF (1 eq.) + MeEtO)$_2$SiH (2 eq.) ; E) ^{1}H NMR of IPrCuF (1 eq.) + MeEtO)$_2$SiH (3 eq.) ; F) ^{1}H NMR of IPrCuF (1 eq.) + MeEtO)$_2$SiH (4 eq.). All ^{1}H NMR spectra were recorded in C_6D_6

Figure 13. Titration of IPrCuF with $Me(EtO)_2SiH$ in C_6D_6

The above titration was repeated on the Laitar catalyst, but this time in the presence of a catalytic amount of a fluorosilane (Figure 14). However, we didn't use $Me(EtO)_2SiF$ or any other ethoxy fluorosilane ($R_{3-n}(EtO)_nSiF$) due to their difficult synthesis as well as their non-commercial availability. For those reasons, we used the more stable and commercially available triphenyl fluorosilane (Ph_3SiF) in catalytic amounts (40 mol%). At first, one

equivalent of IPrCuF was mixed with the fluorosilane in C_6D_6 and a ^1H NMR was recorded (Figure 14, spectrum A). The NMR analysis showed no interaction between the fluorosilane and the fluoride complex. However, upon addition of the first equivalent of silane to the mix, complete conversion to the $[IPrCuH]_2$ is observed (Figure 14).



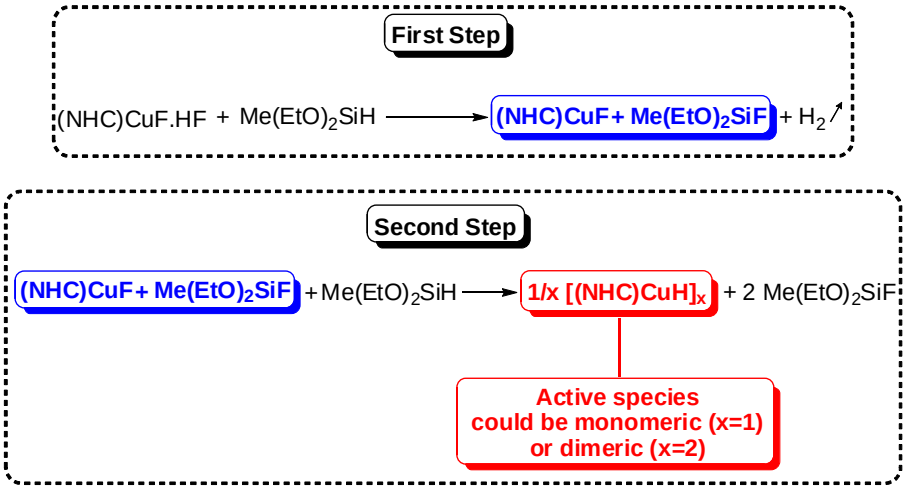
A) ^1H NMR of IPrCuF (Laitar's catalyst) + Ph_3SiF (40 mol%); B) ^1H NMR of IPrCuF (1 eq.) + $MeEtO)_2SiH$ (1 eq.) ; C) ^1H NMR of IPrCuF (1 eq.) + $MeEtO)_2SiH$ (2 eq.). All ^1H NMR spectra were recorded in C_6D_6

Figure 14. Titration of IPrCuF and Ph_3SiF with $Me(EtO)_2SiH$ in C_6D_6

These results strongly suggest that indeed the fluorosilane, generated after the first addition of silane to the bifluoride complex (IPrCuF.HF), has an activating role in the second step of the mechanistic scheme. This two-steps

activation of silane by our bifluoride complexes could thus label these complexes as "auto-activating catalysts" (Scheme 177).[16] They generate the copper(I) fluoride complexes, along with the fluorosilane which acts like a catalyst for the next step, thus forming the copper(I) hydride species more efficiently (Scheme 177). However the exact role of the fluorosilane is still unknown, but steps were taken to investigate this part of the mechanism in more details, *via* DFT calculations and other methods. More detailed results will eventually be depicted in the thesis of Thomas Vergote, sometime in the near future. Moreover, even though the copper(I) hydride isolated by Sadighi *et al* has been unambiguously shown to be a dimeric species in the solid state, we are not quite convinced that it exhibits the same behaviour in solution (Scheme 177, second step). Thus steps were also taken to investigate if the active species is a monomeric or a dimeric complex; results will be fully illustrated later on, in the thesis of Thomas Vergote.

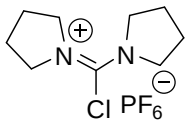
[16] T. Vergote, F. Nahra, D. Peeters, O. Riant, T. Leyssens, *J. Organomet. Chem.* **2013**, *ASAP*, 10.1016/j.jorganchem.2012.10.011.



Scheme 177. Final mechanistic scheme for the activation of silane by our copper(I) bifluoride complexes

III.7. Exploring the Synthesis of (ADC)Cu^{I} Complexes

We mentioned at the beginning that attempts to isolate a (ADC)Cu^{I} complex would be undertaken. In this part, we are going to describe the attempts made to generate the (ADC)Cu^{I} complex starting from the chloroamidinium salt **154** (Figure 15).

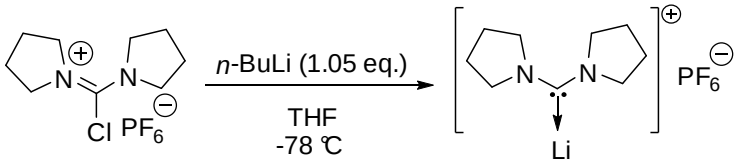


154

Figure 15. Structure of the chloroamidinium salt **154**

In order to generate an (ADC)Cu^{I} complex, we needed to first generate the carbene species. The most practical method used for that purpose is the lithium-halogen exchange method, which generates the carbene ligand bound to lithium. In that manner, chloroamidinium **154** was reacted with *n*-

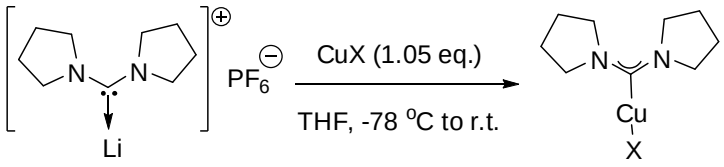
butyllithium in THF at -78 °C to form the desired lithiated species **187** *in situ* (Scheme 178).[71,73]



Scheme 178. *In situ* generation of the Li-carbene species

Once the Li-carbene complex **187** was generated *in situ*, several attempts were made to directly transmetallate this species to copper (Table 40). Formation of the (ADC)Cu^{I} complex could be verified by ^{13}C NMR, given that the carbene bound to copper has a very distinctive signal at ~200 ppm. Unfortunately, we weren't able to isolate any desired product.

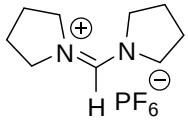
Table 40. Attempted synthesis of (ADC)Cu^{I} complexes



Entry[a]	CuX	Product[b]
1	CuCl	/
2	CuI	/
3	$[Cu(CH_3CN)_4]PF_6$	/
4	$Me_2S.CuBr$	/

[a] All reactions were run under argon [b] The obtained solids were directly analyzed by ^{13}C NMR.

When simple complexation was attempted in entries 1 and 2 (Table 40), the only product isolated was the protonated salt **189** (Figure 16). On the other hand, when ligand displacement by the Li-carbene was tried (Table 40, entries 3 and 4), no identifiable product was isolated.

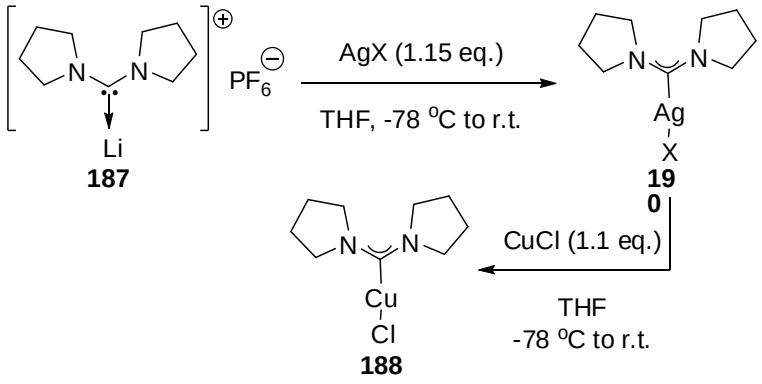


189

Figure 16. Structure of the protonated salt **189**

In light of these discouraging results, we tried another approach which is usually used in the synthesis of (NHC)Cu^{I} complexes (Table 41). We engaged the Li-carbene species with a silver salt at -78 ^{o}C, and then after stirring overnight in the dark, the mixture was filtered over celite and concentrated *in vacuo*. Without any purification or attempted identification, we directly engaged the obtained residue with CuCl also in the dark. However, no desired complex was obtained, and the only product isolated was once again the protonated salt **189**.

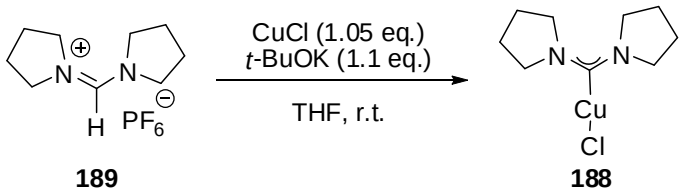
Table 41. Synthesis of (ADC)Cu[I] complexes *via* silver intermediates



Entry[a]	AgX	Product[b]
1	AgOTf	/
2	AgCl	/

[a] All reactions were run under argon [b]The obtained solids were directly analyzed by ^{13}C NMR.

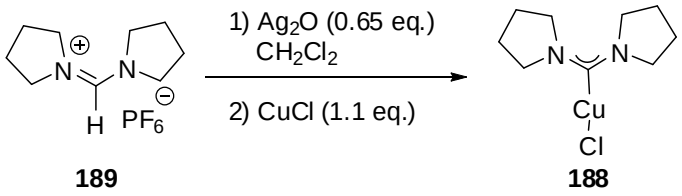
All attempts made till now seem to systemically generate the protonated salt **189**. For that reason, we decided to start from this salt to generate the carbene species, *via* a deprotonation/complexation method instead of the usual lithium-halogene exchange. Thus salt **189** was taken up in THF and reacted directly with copper(I) chloride and potassium *tert*-butoxide in the same manner used to generate the (NHC)CuCl complexes (Scheme 180). Unfortunately, no identifiable product was isolated using this methodology.



189 **188**

Scheme 180. Deprotonation/complexation method

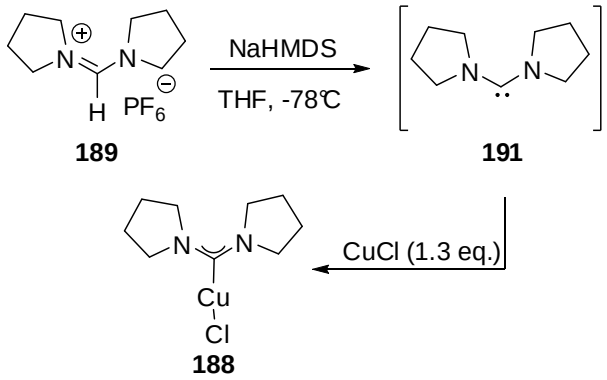
We also tried to generate the silver complex using silver oxide, and then engaged the obtained residue directly with copper(I) chloride (Scheme 181). Yet again, no desired complex was isolated and only the starting material **189** was recovered.



189 **188**

Scheme 181. Deprotonation/complexation/transmetallation strategy

In light of the previous results, we argued that the bases used so far to deprotonate salt **189** were not basic enough. Therefore, one last attempt was made, starting from the protonated salt **189**. We tried to directly deprotonate using a strong base (NaHMDS) to generate the free carbene species *in situ* (Scheme 184). CuCl was then added to the mixture and stirred for three hours. After filtration and consequent concentration, the NMR analysis of the crude mixture showed only the starting material **189**. No desired complex was thus identified or isolated.



189 **191** **188**

Scheme 184. Deprotonation/complexation method *via* a strong base

We were quite disappointed with these results, however we now understand this chemistry a little bit better. ADC generation seems to be far more complicated than that of NHC, but recent advances in this field made us alter our strategy and start planning for new ways to generate these elusive (ADC)Cu^{I} species.[17]

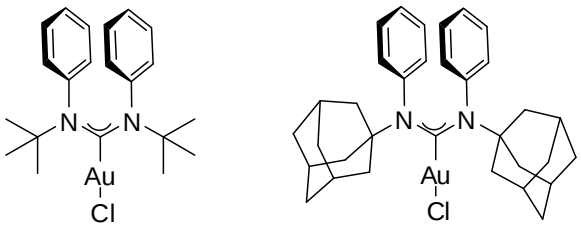
[17] H. Seo, B. P. Roberts, K. A. Abboud, K. M. Merz, Jr., S. Hong, *Org. lett.* **2010**, *12*, 4860.

IV. Conclusions and Perspectives

In conclusion, we have developed a mini library of NHC precursors and (NHC)CuCl complexes. Two synthetic pathways were also established to generate unprecedented (NHC)Cu^{I} bifluoride complexes. These complexes were fully characterized. Catalytic tests demonstrated the copper(I) bifluorides to be very efficient catalysts that do not require any additional activating agent. The more detailed NMR studies on the activation mechanism of silanes by our complexes gave a more intricate picture. These bifluoride complexes could now be considered as "auto-activating catalysts", generating the active hydride species in two steps.[16]

We also established the first Cu^{I}-catalyzed diastereoselective allylation of (*R*)-*N*-*tert*-butanesulfinyl aldimines. The method enables efficient, simple and general synthesis of enantiomerically enriched homoallylic amines at room temperature in high yields.[15]

Unfortunately, no ADC-based copper(I) complex was isolated despite all our efforts. However, we suspect that the problem seems to be the starting chloroamidinium salt. Indeed, this ligand is too small to be stable, and as Arduengo *et al* demonstrated in their isolation of the first free NHC, the steric hindrance around the copper moiety is crucial for shielding it from spontaneous decomposition. The problem could be resolved by increasing the steric hindrance on the nitrogen. Recently, Hong *et al* synthesized stable (ADC)AuCl complexes using very hindered substituents on the nitrogen atoms. In the same manner, we could use these types of ADCs to generate their copper(I) analogues (Scheme 185).[17]



Scheme 185. Hong *et al*'s synthesis and isolation of (ADC)AuCl complexes

EXPERIMENTAL PART

Instrumentation and Chemicals

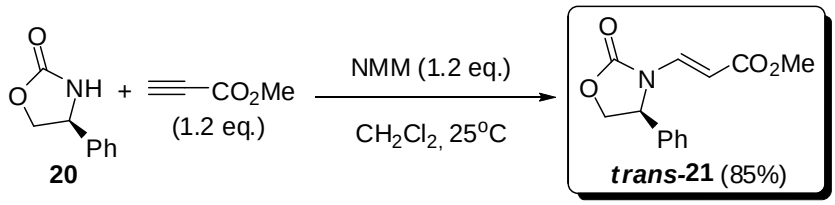
Unless otherwise noted, all manipulations were performed under an argon atmosphere using standard Schlenk-type glassware. Toluene was distilled on sodium under an argon atmosphere then degassed. Diethyl ether and THF were distilled on sodium/benzophenone under an argon atmosphere. Dichloromethane was distilled on CaH_2. Solvents used for work-up were of technical grade. Commercial reagents were purchased from Acros, Sigma-Adrich, ABCR, TCI or Apollo scientific and used as received unless stated otherwise. Infrared spectra (IR) were recorded on a Shimadzu FTIR-8400S spectrometer. Wave numbers are given in cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded on Bruker-300 and Bruker-500 spectrometers. ^{19}F NMR spectra were recorded on a Bruker-300 spectrometer. ^{1}H and ^{13}C NMR chemical shifts are reported relative to $CDCl_3$ (7.26, 77.16 ppm), C_6D_6 (7.15 ppm, 128.06 ppm), CD_3CN (1.94 ppm, 118.26 ppm) and CD_2Cl_2 (5.32, 53.8 ppm). Trichlorofluoromethane ($CFCl_3$) was used as internal standard for ^{19}F NMR. Multiplicity is given as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad. High resolution Mass Spectra were obtained from a Thermo Scientific QExactive, with accurate mass reported for the molecular ion $[M+H]^+$ or suitable fragment ions. Elementary analyses were performed by Dr. Richard Morris at MEDAC LTD, London. GC analyses were recorded on a ThermoFinningan Trace GC apparatus with a CHIRALSIL-DEX CB (25m, 0.25 mm, 25 µm) column. Ultrasonic manipulation was carried out in an Aquasonic 50HT ultrasound bath. Column chromatography was carried out on silica gel (ROCC 60, 40-63 µm). TLC analyses were performed on commercial aluminum plates bearing

a 0.25 mm layer of Merck Silica gel 60F254. $(PPh_3)_3CuF.2MeOH$, [1] IMesCuCl[2] and IMesCuDBM[3] were prepared by literature methods.

I. Chapter 1: Copper Catalyzed- 1,4-Reduction / Aldolisation Domino Reaction

I.1. Synthesis of Substrates 21, 22, 30-37

I.1.1. Synthesis of trans-21[4]



A flame-dried round bottom flask was charged with substrate **20** (821 mg, 5 mmol, 1.0 eq.) and *N*-methylmorpholine (NMM) (0.67 mL, 6 mmol, 1.2 eq.) and 15 mL of DCM. Methyl propiolate (0.54 mL, 6 mmol, 1.2 eq.) was then added at room temperature. The reaction mixture was stirred overnight and then concentrated *in vacuo*. The obtained residue was purified by column chromatography (eluting with petroleum ether/AcOEt, 7/3 to 6/4) to give the desired product ***trans*-21** (1.06 g, 85%).

❖ ***(S,E)-methyl 3-(2-oxo-4-phenyloxazolidin-3-yl)acrylate (trans-21)***

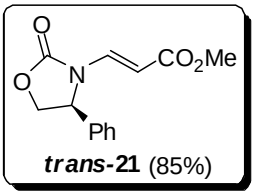
---

[1] A. Welle, Ph.D thesis, « Université catholique de Louvain », **2009**.

[2] a) Cazin. S. J., *Dalton Trans.* **2010**, *39*, 4489, b) Nolan S. P., *Organometallics* **2004,** *23*, 1157-1160 , c) Nolan S. P., *J. of Organometallic Chem.* **2000**, *606*, 49.

[3] A. Welle, S. Diez-Gonzalez, B. Tinant, S. P. Nolan, O. Riant *Org. Lett.* **2006**, *8*, 6059.

[4] M. Barbazanges, C. Meyer, J. Cossy, *Org. Lett.* **2007**, *9*, 3245.



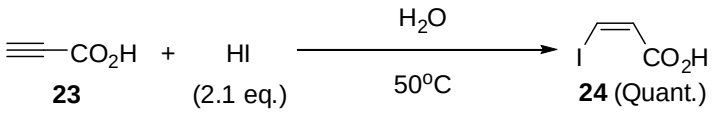
***trans*-21** (85%)

Chemical Formula: $C_{13}H_{13}NO_4$
Molecular Weight: 247,25

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.94 (d, J = 14.4 Hz, 1H), 7.47 – 7.36 (m, 3H), 7.25 – 7.23 (m, 2H), 5.04 (dd, *J* = 9.0, 5.1 Hz, 1H), 4.95 (d, *J* = 14.4 Hz, 1H), 4.79 (t, *J* = 8.9 Hz, 1H), 4.22 (dd, *J* = 8.8, 5.1 Hz, 1H), 3.65 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.99, 155.05, 137.63, 136.80, 129.88, 129.53, 125.92, 101.95, 71.07, 58.47, 51.58. HRMS m/z calcd. for $C_{13}H_{14}N_1O_4$ $[M + H]^+$ 248.09174; found 248.09173.

I.1.2. Synthesis of cis-22

I.1.2.1. Synthesis of Intermediate 24[5]

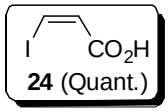


23 (2.1 eq.) **24** (Quant.)

A round bottom flask, equipped with a reflux condenser, was charged with substrate **23** (0.62 mL, 10 mmol, 1.0 eq.) and hydriodic acid (57%wt., 2.8 mL, 21.2 mmol, 2.1 eq.) and 6 mL of H_2O. The reaction mixture was then heated to 50 °C. After 48 hours, the reaction mixture was allowed to cool down to room temperature and then water was added followed by Et_2O. The two phases were then separated and the aqueous layer was extracted three times with Et_2O. The combined organic layers were washed with a 0.1M aqueous solution of $Na_2S_2O_3$, dried over $MgSO_4$, filtered and concentrated *in vacuo*. ^{1}H NMR of the yellow-brown solid obtained, showed that it was indeed the desired product **24** (2.09 g, quantitative yield).

❖ ***(Z)-3-iodoacrylic acid (24)***

[5] R. Takeuchi, K. Tanabe, S. Tanaka, *J. Org. Chem.* **2000**, *65*, 1558.



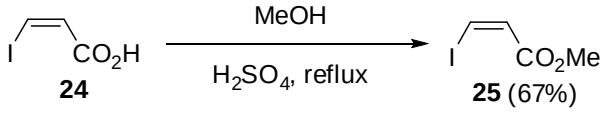
24 (Quant.)

Chemical Formula: $C_3H_3IO_2$
Molecular Weight: 197,96

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.68 (d, *J* = 9.0 Hz, 1H), 6.99 (d, *J* = 9.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 98.20, 129.40, 169.70.

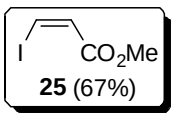
Spectral data are identical to those reported in the literature (CAS: 6214-35-3).[5]

I.1.2.2. Synthesis of Intermediate 25



A round bottom flask, equipped with a reflux condenser, was charged with substrate **24** (1.97 g, 9.95 mmol, 1.0 eq.) and 6 mL of methanol. A catalytic amount of sulfuric acid (0.2 mL) was added dropwise to the mixture. The reaction mixture was refluxed for 4 hours, and then concentrated *in vacuo*. Water was added followed by Et_2O. The two phases were then separated and the aqueous layer was extracted three times with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The obtained oil was purified by fractional distillation under reduced pressure (bp = 78-79 ^oC / 10 mmHg) to give the desired product **25** (1.42 g, 67%).

❖ ***(Z)-methyl 3-iodoacrylate (25)***



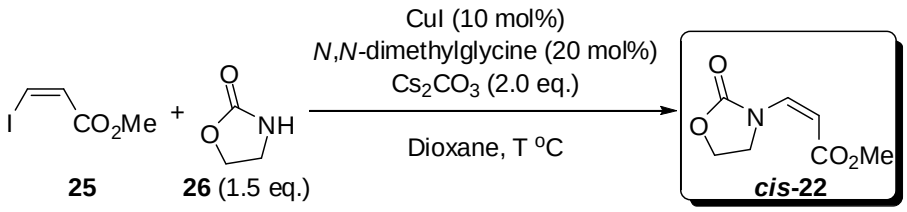
25 (67%)

Chemical Formula: $C_4H_5IO_2$
Molecular Weight: 211,99

^{1}H NMR (300 MHz, CDCl3) δ = 7.45 (d, *J* = 8.9 Hz, 1H), 6.89 (d, *J* = 8.9 Hz, 1H), 3.76 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ = 165.00, 129.50, 95.34, 51.73.

Spectral data are identical to those reported in the literature (CAS: 6214-23-9).[6]

I.1.2.3. Attempted Synthesis of *cis*-22[7]



25 **26** (1.5 eq.) ***cis*-22**

A flame-dried Schlenk tube was charged with substrate **26** (1.5 eq.), *cis*-iodovinylic ester **25** (1 eq.), CuI (0.1 eq.), *N*,*N*-dimethylglycine (0.2 eq.) and cesium carbonate (2 eq.). 3 mL of dioxane was added under argon. The Schlenk tube was immersed in a preheated oil bath, and the reaction mixture was stirred at the indicated temperature until the corresponding reaction time in the table. The reaction mixture was cooled to room temperature, and the resulting suspension was diluted with 10 mL ethyl acetate, then, it was filtrated through a plug silica gel eluting with ethyl acetate. The filtrate was concentrated and the residue was analysed by ^{1}H NMR to determine the overall conversion of the reaction as well as the *trans*/*cis* ratio. Under these conditions the undesired *trans* product was always obtained majoritarily.

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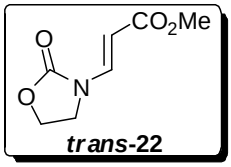
[6] G. Bartoli, R. Cipolletti, G. Di Antonio, R. Giovannini, S. Lanari, M. Marcolini, E. Marcantoni, *Org. Biomol. Chem.* **2010**, *8*, 3509.

[7] L. Jiang, G. E. Job, A. Klapars, S. L. Buchwald, *Org. Lett.* **2003**, *5*, 3667.

❖ ***(E)-methyl 3-(2-oxooxazolidin-3-yl)acrylate (trans-22)***

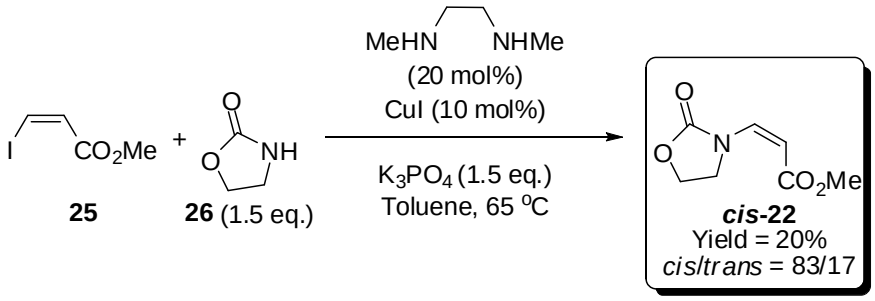


Chemical Formula: $C_7H_9NO_4$
Molecular Weight: 171,15

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.96 (d, *J* = 14.1 Hz, 1H), 5.16 (d, *J* = 14.1 Hz, 1H), 4.59 – 4.40 (m, 2H), 3.84 – 3.59 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.52, 154.22, 139.32, 101.16, 62.93, 51.12, 42.40.

Spectral data are identical to those reported in the literature (CAS: 145294-83-3).[8]

I.1.2.4. Successful Synthesis of *cis*-22[9]



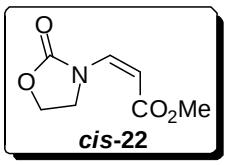
A flame-dried Schlenk tube was charged with substrate **26** (132 mg, 1.52 mmol, 1.5 eq.), CuI (20.1 mg, 0.11 mmol, 0.1 eq.) and potassium phosphate (318.8 mg, 1.5 mmol, 1.5 eq.) in 0.5 ml of toluene. *N*,*N'*-dimethylethylenediamine (22mg, 0.2 mmol, 0.2 eq.) was subsequently added followed by a solution of *cis*-iodovinylic ester **25** (217 mg, 1 mmol, 1 eq.) in 0.5 mL of toluene. The Schlenk tube was immersed in a preheated oil bath, and the reaction mixture was stirred at 65 °C for 48 hours. The reaction mixture was cooled to room temperature, and water was added to the resulting suspension followed by ethyl acetate. The two phases were then

[8] Y. Liu, D. Li, C. M. Park, *Angew. Chem. Int. Ed.* **2011**, *50*, 7333.

[9] M. P. Rainka, Y. Aye, S. L. Buchwald, *Proc. Natl. Acad. Sci.* **2004**, *101*, 5821.

separated and the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The obtained residue was purified by column chromatography (eluting with petroleum ether/AcOEt, 7/3 to 6/4) to give the desired product ***cis*-22** (34 mg, 20%).

❖ ***(Z)-methyl 3-(2-oxooxazolidin-3-yl)acrylate (cis-22)***



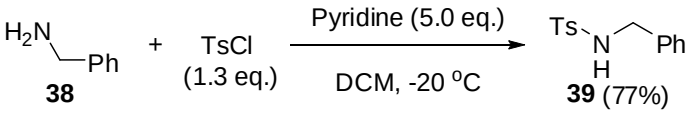
***cis*-22**

Chemical Formula: $C_7H_9NO_4$
Molecular Weight: 171,15

^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.97 (d, *J* = 10.6 Hz, 1H), 5.16 (d, *J* = 10.6 Hz, 1H), 4.52 – 4.39 (m, 2H), 4.34 – 4.26 (m, 2H), 3.69 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 165.73, 156.62, 135.24, 98.29, 63.07, 51.48, 45.48. HRMS m/z calcd. for $C_7H_{10}N_1O_4$ $[M + H]^+$ 172.06047; found 172.06043.

I.1.3. Synthesis of 30

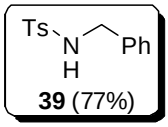
I.1.3.1. Synthesis of Intermediate 39



A flame-dried round bottom flask was charged with substrate **38** (1.1 mL, 10 mmol, 1.0 eq.) and pyridine (4.1 mL, 50 mmol, 5 eq.) in 10 mL of DCM. The mixture was cooled down to -20 °C and TsCl (2.44 g, 12.8 mmol, 1.3 eq.) was then added. The reaction was allowed to stir for 3 hours at room temperature. 30 mL of a 1M solution of HCl was added. The two phases were then separated and the aqueous layer was extracted three times with DCM. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was left overnight to crystallise. The obtained solid was dissolved in hot ethanol, and then was allowed to cool

down to room temperature. A mixture of hexane/Et_2O (2/1) was subsequently added (~ 30 mL). After one night at 4 °C, the desired product **39** recrystallised and was isolated as an off-white solid (2.01 g, 77%).

❖ ***N-benzyl-4-methylbenzenesulfonamide (39)***

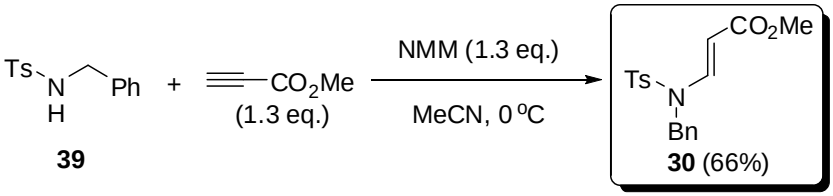


Chemical Formula: $C_{14}H_{15}NO_2S$
Molecular Weight: 261,34

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.77 (d, *J* = 8.2 Hz, 2H), 7.35 – 7.27 (m, 5H), 7.23 – 7.17 (m, 2H), 4.57 (br. s, 1H), 4.13 (s, 2H), 2.44 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 143.70, 136.97, 136.37, 129.90, 128.86, 128.09, 128.02, 127.35, 47.44, 21.69.

Spectral data are identical to those reported in the literature (CAS: 1576-37-0).[10]

I.1.3.2. Synthesis of 30

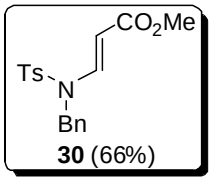


To a solution of substrate **39** (1.99 g, 7.6 mmol, 1 eq.) and methyl propiolate (0.9 mL, 10.1 mmol, 1.3 eq.) in MeCN (35 mL) at 0 °C, was added dropwise *N*-methylmorpholine (1.1 mL, 9.97 mmol, 1.3 eq.). After 2 h at 0 °C, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc and the resulting solution was washed sequentially with a 0.1M solution of HCl (until the aqueous layer remained slightly acidic) and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure.

[10] M. Zhu, K. Fujita, R. Yamaguchi, *Org. lett.* **2010**, *12*, 1336.

The obtained residue was purified by column chromatography (eluting with petroleum ether/AcOEt, 95/5 to 70/30) to give the desired product **30** as a yellow solid, with some impurities. The solid was recrystallised in hot isopropanol to obtain pure **30** as a white solid (1.73 g, 66%).

❖ ***(E)-methyl 3-(N-benzyl-4-methylphenylsulfonamido)acrylate (30)***



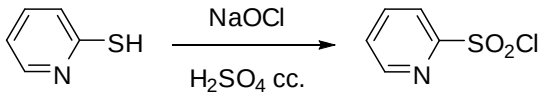
Chemical Formula: $C_{18}H_{19}NO_4S$
Molecular Weight: 345,41

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.17 (d, *J* = 14.0 Hz, 1H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.38 – 7.29 (m, 5H), 7.23 – 7.16 (m, 2H), 4.97 (d, *J* = 14.0 Hz, 1H), 4.60 (s, 2H), 3.66 (s, 3H), 2.44 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.29, 144.93, 141.79, 135.32, 133.90, 130.22, 128.83, 127.87, 127.24, 126.71, 99.39, 51.39, 49.81, 21.65.

Spectral data are identical to those reported in the literature (CAS: 950777-48-7).[4]

I.1.4. Synthesis of 31

I.1.4.1. Synthesis of Intermediate 40

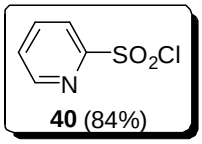


Pyridine-2-thiol **40** (84%)

A solution of pyridine-2-thiol (2.03 g, 18.29 mmol., 1 eq.) in conc. H_2SO_4 (50 mL) was cooled to 0°C and treated dropwise with 200 mL of commercially available bleach (ca. 5% NaOCl soln). The resulting mixture was stirred at 0°C for 30 min before it was extracted with DCM (2 x 50 mL). The combined organic phases were dried on $MgSO_4$ and concentrated *in vacuo* to afford the 2-pyridylsulfonyl chloride **40** as a colourless oil (2.72 g,

84%). This compound is relatively unstable at room temperature and was immediately used in the next step without further purification.

❖ ***Pyridine-2-sulfonyl chloride (40)***



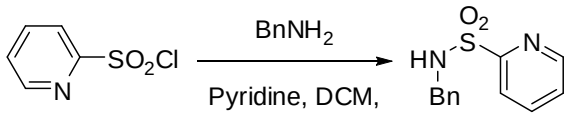
40 (84%)

Chemical Formula: $C_5H_4ClNO_2S$
Molecular Weight: 177,61

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.30 (d, *J* = 4.2 Hz, 1H), 8.19 – 8.01 (m, 2H), 7.69 (ddd, *J* = 7.3, 4.7, 1.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 158.83, 150.65, 139.19, 129.33, 121.86.

Spectral data are identical to those reported in the literature (CAS: 66715-65-9).[11]

I.1.4.2. Synthesis of Intermediate 41



40 **41** (88%)

To a solution of benzylamine (1.3 mL, 11.82 mmol, 1 eq.) and pyridine (4.85 mL, 59.1 mmol, 5 eq.) in 15 mL of DCM at -20 °C, was slowly added a solution of the 2-pyridylsulfonyl chloride **40** (2.72 g, 15.34 mmol, 1.3 eq.) in 1 mL of DCM. The mixture was stirred at -20 °C for 1h30 then left overnight at room temperature. 30 mL of a 1M solution of HCl was added. The two phases were then separated and the aqueous layer was extracted three times with DCM. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was recrystallised in hot isopropanol to obtain pure **41** as an off-white solid (2.58 g, 88%).

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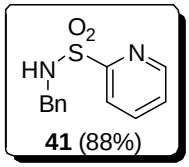
[11] C. Taillier, T. Hameury, V. Bellosta, J. Cossy, *Tetrahedron* **2007**, *63*, 4472.

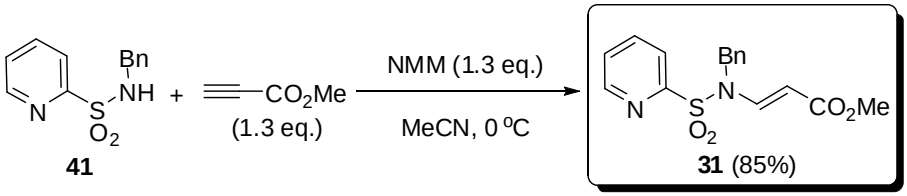
❖ ***N-benzylpyridine-2-sulfonamide (41)***



Chemical Formula: $C_{12}H_{12}N_2O_2S$
Molecular Weight: 248,30

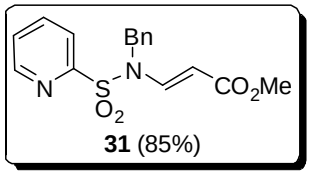
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.73 – 8.59 (m, 1H), 7.98 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.88 (td, *J* = 7.7, 1.7 Hz, 1H), 7.47 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.29 – 7.21 (m, 5H), 5.32 (br. t, *J* = 5.9 Hz, 1H), 4.25 (d, *J* = 6.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 157.52, 150.04, 138.00, 136.24, 128.66, 127.96, 127.92, 126.63, 122.23, 47.80. HRMS m/z calcd. for $C_{12}H_{13}N_2O_2S_1$ $[M + H]^+$ 249.06919; found 249.06922.

I.1.4.3. Synthesis of 31



To a solution of substrate **41** (1.95 g, 7.84 mmol, 1 eq.) and methyl propiolate (0.91 mL, 10.23 mmol, 1.3 eq.) in MeCN (35 mL) at 0 °C, was added dropwise *N*-methylmorpholine (1.12 mL, 10.15 mmol, 1.3 eq.). After 19 h at 0 °C, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc and the resulting solution was washed sequentially with a 0.1M solution of HCl (until the aqueous layer remained slightly acidic) and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The obtained residue was recrystallised in hot isopropanol to obtain pure **31** as a brown solid (2.21 g, 85%).

❖ ***(Z)-methyl 3-(N-benzylpyridine-2-sulfonamido)acrylate (31)***



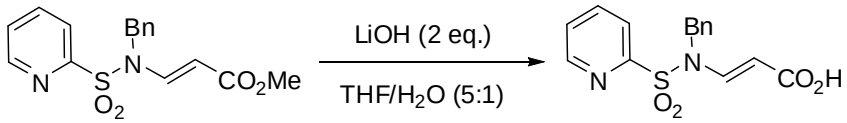
31 (85%)

Chemical Formula: $C_{16}H_{16}N_2O_4S$
Molecular Weight: 332,37

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.72 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.13 (d, *J* = 14.0 Hz, 1H), 7.99 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.91 (td, *J* = 7.8, 1.7 Hz, 1H), 7.53 (ddd, *J* = 7.6, 4.7, 1.2 Hz, 1H), 7.36 – 7.17 (m, 5H), 5.08 (d, *J* = 14.0 Hz, 1H), 4.84 (s, 2H), 3.65 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 167.28, 156.41, 150.66, 142.48, 138.38, 134.30, 128.91, 127.94, 127.58, 126.85, 122.60, 100.17, 51.49, 51.07. HRMS m/z calcd. for $C_{16}H_{17}N_2O_4S_1$ $[M + H]^+$ 333.09042; found 333.09035.

I.1.5. Synthesis of 32[12]

I.1.5.1. Synthesis of Intermediate 42



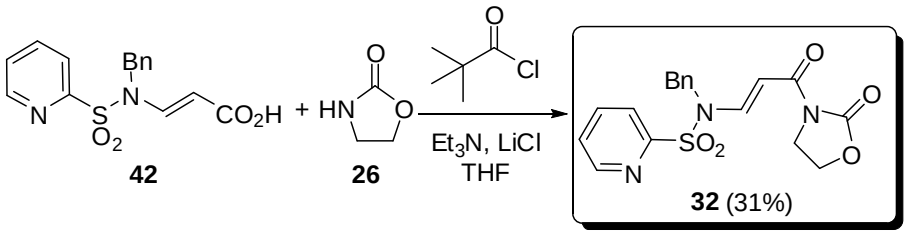
31 **42** (97%)

A round bottom flask, equipped with a reflux condenser, was charged with substrate **31** (665.1 mg, 2 mmol, 1.0 eq.) in 9 mL of a THF/H_2O (5/1) mixture. LiOH (168.5 mg, 2.6 mmol, 1.3 eq.) was then added to the mixture at room temperature. The reaction mixture was allowed to stir overnight at room temperature before it was refluxed for 4 hours, and then concentrated *in vacuo*. The residue is portioned between Et_2O and a 5% aqueous solution of $NaHCO_3$. The two phases were then separated and the aqueous layer was acidified with a 1M solution of HCl (until a white suspension persisted). The aqueous phase was extracted two times with AcOEt. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The

[12] S. Nakamura, F. Kikuchi, S. Hashimoto, *Tetrahedron: Asym.* **2008**, *19*, 1059.

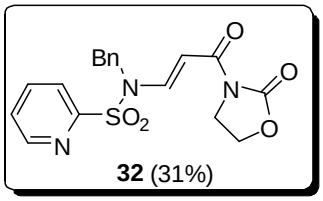
desired product **42** was obtained as a white solid (623 mg, 97%). This product was directly engaged in the next step without any further purification.

I.1.5.2. Synthesis of 32



Under an argon atmosphere, substrate **42** (623 mg, 1.96 mmol, 1 eq.) was dissolved in dry THF (7 mL) with Et_3N (0.9 mL, 6.26 mmol, 3.1 eq.). The acyl chloride (0.32 mL, 2.6 mmol, 1.3 eq.) was added dropwise at -20 °C and the mixture was stirred 2 h. Dry LiCl (126.3 mg, 2.98 mmol, 1.5 eq.) was added followed by the oxazolidinone **26** (395.1 mg, 4.54 mmol, 2.3 eq.) and the mixture was stirred overnight at room temperature. The reaction mixture was poured onto a mixture of Et_2O and a saturated solution of $NaHCO_3$ at 0 ^oC. The two phases were then separated and the aqueous layer was extracted two times with AcOEt. The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The obtained residue was recrystallised in hot isopropanol to obtain the desired product **32** as a white solid (233.8 mg, 31%).

❖ ***(E)-N-benzyl-N-(3-oxo-3-(2-oxooxazolidin-3-yl)prop-1-enyl)pyridine-2-sulfonamide (32)***



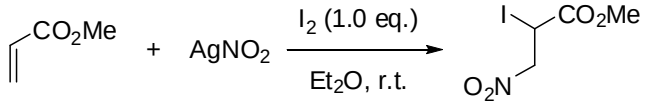
32 (31%)

Chemical Formula: $C_{18}H_{17}N_3O_5S$
Molecular Weight: 387,41

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.72 (d, *J* = 4.6 Hz, 1H), 8.29 (d, *J* = 13.8 Hz, 1H), 8.04 – 7.99 (m, 1H), 7.96 – 7.86 (m, 1H), 7.56 – 7.50 (m, 1H), 7.42 – 7.27 (m, 5H), 6.73 (d, *J* = 13.7 Hz, 1H), 4.89 (s, 2H), 4.33 (t, *J* = 8.1 Hz, 2H), 4.00 (t, *J* = 8.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 164.81, 150.56, 143.87, 142.37, 138.25, 134.05, 128.79, 128.67, 127.70, 127.46, 126.74, 122.49, 99.21, 61.83, 51.38, 42.68. HRMS m/z calcd. for $C_{18}H_{18}N_3O_5S_1$ $[M + H]^+$ 388.09626; found 388.09617.

I.1.6. Synthesis of 33

I.1.6.1. Synthesis of Intermediate 43

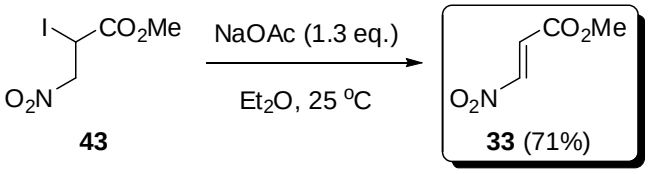


43 (85%)

A round bottom flask was charged with $AgNO_2$ (1 g, 6.5 mmol, 1.0 eq.) in 13 mL of Et_2O. Iodine (1.66 g, 6.53 mmol, 1 eq.) was then added to the mixture, followed by methyl acrylate (1.17 mL, 13 mmol, 2 eq.) at room temperature. The reaction mixture was allowed to stir for 5 days then filtered to remove the yellow solid. A 0.1M solution of $Na_2S_2O_3$ was added to the filtrate. The two phases were separated and the aqueous layer was extracted two times with Et_2O. The combined organic phases were washed sequentially with a saturated solution of Na_2CO_3 and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The desired product **43** was

obtained as a yellow oil (1.44 g, 85%). This compound is relatively unstable at room temperature and was immediately used in the next step without further purification.

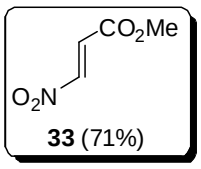
I.1.6.2. Synthesis of 33



43 **33** (71%)

A flame-dried round bottom flask was charged with substrate **43** (2.74 g, 10.58 mmol, 1.0 eq.) in 25 mL of Et_2O, under argon. NaOAc (1.094 g, 13.34 mmol, 1.26 eq.) was then added and the reaction mixture was allowed to stir overnight at room temperature. Afterwards 20 mL of Et_2O is added and the reaction mixture was filtered to remove all solids. A saturated aqueous solution of Na_2CO_3 was added to the filtrate and the 2 phases were shaken vigorously until a colour change occurred. The two phases were separated (no extraction of the aqueous phase). The organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The desired product **33** was obtained as a yellow solid (985.6 mg, 71%). This compound was pure enough to engage in the next step, however it should be noted that it is not very stable for a long period of time at room temperature, therefore should be stored in the freezer if longer shelf life is needed.

❖ ***(E)-methyl 3-nitroacrylate (33)***



33 (71%)

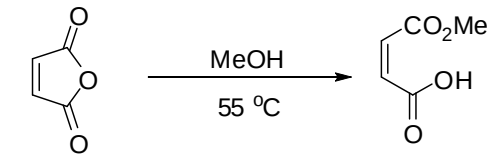
Chemical Formula: $C_4H_5NO_4$
Molecular Weight: 131,09

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.68 (d, *J* = 13.5 Hz, 1H), 7.09 (d, *J* = 13.5 Hz, 1H), 3.87 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 163.10, 149.16, 127.25, 53.13.

Spectral data are identical to those reported in the literature (CAS: 52745-92-3).[13]

I.1.7. Attempted Synthesis of cis-34

I.1.7.1. Synthesis of Intermediate 44

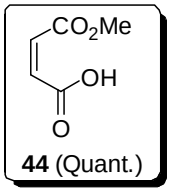


Maleic anhydride **44** (Quant.)

A flame-dried round bottom flask, equipped with a reflux condenser, was charged with maleic anhydride (982.2 mg, 10 mmol, 1.0 eq.) in 3 mL of methanol, under argon. The reaction mixture was stirred for 1 hour at 55 °C. The reaction mixture was then allowed to cool down to room temperature. The solution was concentrated *in vacuo*. The obtained residue was dissolved in DCM, and then concentrated one more time *in vacuo*. The desired product **44** was obtained as a solid (1.29 g, quantitative yield). No purification was needed; the desired product was obtained with enough purity to be engaged in the next step.

[13] K. Itoh, K. Kitoh, S. Kishimoto, *Can. J. Chem.* **2006**, *84*, 392.

❖ ***(Z)-4-methoxy-4-oxobut-2-enoic acid (44)***



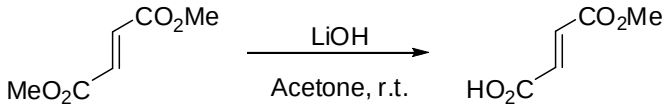
44 (Quant.)

Chemical Formula: $C_5H_6O_4$
Molecular Weight: 130,10

^{1}H NMR (300 MHz, $CDCl_3$) δ = 11.02 (s, 1H), 6.47 (d, *J* = 12.6 Hz, 1H), 6.40 (d, *J* = 12.7 Hz, 1H), 3.91 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.97, 165.04, 135.79, 129.25, 53.49.

Spectral data are identical to those reported in the literature (CAS: 3052-50-4).[14]

I.1.8. Attempted Synthesis of trans-34



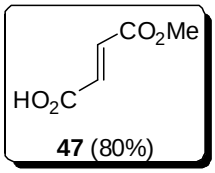
Dimethyl fumarate

47 (80%)

A round bottom flask was charged with dimethyl fumarate (1.44 g, 10 mmol, 1.0 eq.) in 70 mL of acetone. 1N aqueous LiOH (20 mL, 20 mmol) was slowly added over 15 min to the stirred solution at room temperature. The reaction was stirred overnight, diluted with 2N HCl (200 mL), saturated with NaCl and then extracted with EtOAc (3 x 200 mL). The EtOAc layer was concentrated *in vacuo* to yield pure (*E*)-but-2-enedioic acid monomethyl ester **47** (1.05 g, 80%) as a white solid.

[14] A. Goti, M. Cacciarini, F. Cardona, F. M. Cordero, A. Brandi, *Org. lett.* **2001**, *3*, 1367.

❖ ***(E)-4-methoxy-4-oxobut-2-enoic acid (47)***

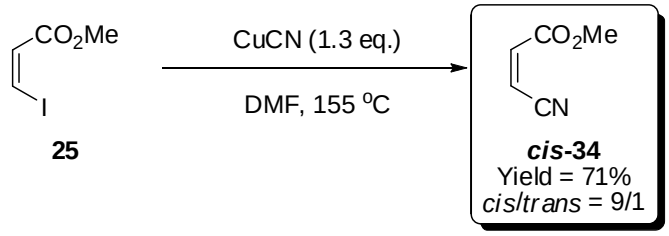


Chemical Formula: $C_5H_6O_4$
Molecular Weight: 130,10

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95 (d, *J* = 15.7 Hz, 1H), 6.86 (d, *J* = 15.7 Hz, 1H), 3.83 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.14, 166.3, 134.65, 133.88, 52.64.

Spectral data are identical to those reported in the literature (CAS: 2756-87-8).[15]

I.1.9. Successful Synthesis of cis-34

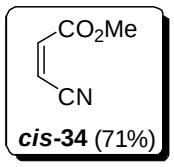


A flame-dried Schlenk tube, equipped with a reflux condenser, was charged with CuCN (497.6 mg, 5.56 mmol, 1.3 eq.) in 2.6 ml of DMF. *cis*-iodovinylic ester **25** (933.6 mg, 4.4 mmol, 1 eq.) was subsequently added, and the Schlenk tube was immersed in a preheated oil bath, and the reaction mixture was stirred at 155 °C for 5 hours. The reaction mixture was cooled to room temperature, and water (100 mL) was added to the resulting suspension followed by DCM (20 mL). The two phases were then separated and the aqueous layer was extracted three times with DCM. The combined organic layers were washed with a 10% aqueous solution of LiCl (2 x 15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The obtained

[15] S. Niwayama, *J. Org. Chem.* **2000**, *65*, 5834.

residue was purified by column chromatography (eluting with petroleum ether/AcOEt, 85/15 to 75/25) to give the desired product ***cis*-34** (348.4 mg, 71%).

❖ ***(Z)-methyl 3-cyanoacrylate (cis-34)***



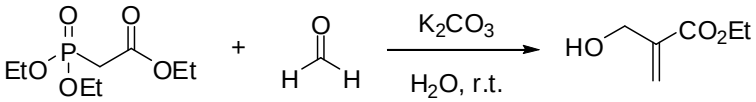
Chemical Formula: $C_5H_5NO_2$
Molecular Weight: 111,10

^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.60 (d, *J* = 11.5 Hz, 1H), 5.98 (d, *J* = 11.5 Hz, 1H), 3.87 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 162.91, 137.95, 114.28, 110.92, 52.64.

Spectral data are identical to those reported in the literature (CAS: 925-55-3).[16]

I.1.10. Synthesis of 35 and 36

I.1.10.1. Synthesis of Intermediate 53

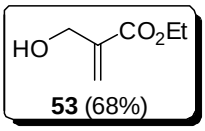


A round bottom flask was charged with paraformaldehyde (45.6 g, 0.52 mol, 4 eq.) and H_3PO_4 (0.4 mL, 1M aq. sol.) in 40 mL of water. The mixture was stirred for 5 hours at 90 °C to form a clear solution. The reaction mixture was cooled to room temperature and triethylphosphonoacetate (25.6 mL, 0.13 mol, 1 eq.) was added in one portion. A solution of K_2CO_3 (19.8 g, 0.14 mol, 1.1 eq.) in water (40 mL) was then slowly added over 1.5 hours. After the addition was completed, the reaction mixture was cooled rapidly to -5 °C

[16] C.-X. Bai, W.-Z. Zhang, R. He, X.-B. Lu, Z.-Q. Zhang, *Tetrahedron Lett.* **2005**, *46*, 7225.

and Et_2O was added followed by brine. The two phases were then separated and the aqueous layer was extracted three times with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The obtained oil was purified by fractional distillation under reduced pressure (bp = 93-97 °C / 18 mmHg) to give the desired product **53** (11.46 g, 68%).

❖ ***Ethyl 2-(hydroxymethyl)acrylate (53)***



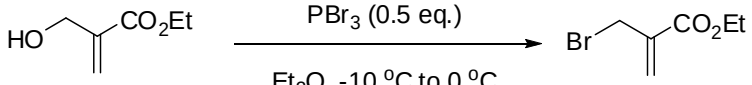
53 (68%)

Chemical Formula: $C_6H_{10}O_3$
Molecular Weight: 130,14

^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.21 (s, 1H), 5.80 (s, 1H), 4.28 (s, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.11, 139.36, 125.24, 62.10, 60.77, 14.08.

Spectral data are identical to those reported in the literature (CAS: 10029-04-6).[17]

I.1.10.2. Synthesis of Intermediate 54



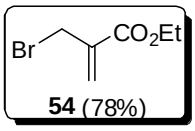
53 **54** (78%)

A flame-dried round bottom flask was charged with substrate **53** (15.68 g, 0.12 mol, 1.0 eq.) in 126 mL of Et_2O, under argon. The reaction mixture was cooled to -10 °C, and then PBr_3 (16.31 g, 0.06 mol, 0.5 eq.) was slowly added over 30 minutes. After the addition was completed, the solution was stirred for additional 4 hours at room temperature. The solution was cooled to -10 °C and water (20 mL) was slowly added (very exothermic!!). The two

[17] W. R. Robert, H. S. Louis, P. G. Nicholas, P. Reuben *J. Org. Chem.*, **1963**, *28*, 2835.

phases were then separated and the aqueous layer was extracted three times with Et_2O. The combined organic layers were washed two times with a saturated solution of NH_4Cl, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The obtained oil was purified by fractional distillation under reduced pressure (bp = 85-87 °C / 18 mmHg) to give the desired product **54** (18.09 g, 78%).

❖ ***Ethyl 2-(bromomethyl)acrylate (54)***

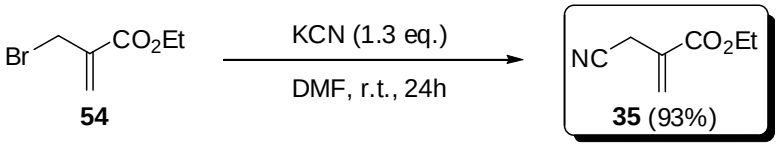


Chemical Formula: $C_6H_9BrO_2$
Molecular Weight: 193,04

^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.33 (d, *J* = 0.7 Hz, 1H), 5.94 (d, *J* = 0.7 Hz, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 4.18 (d, *J* = 0.8 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 164.71, 137.36, 128.80, 61.14, 29.44, 14.15.

Spectral data are identical to those reported in the literature (CAS: 17435-72-2).[18]

I.1.10.3. Synthesis of 35

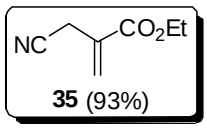


A flame-dried round bottom flask was charged with KCN (83.6 mg, 1.28 mmol, 1.4 eq.) in 3 mL of DMF, under argon. A solution of substrate **54** (180 mg, 0.93 mmol, 1.0 eq.) in 3 mL of DMF was added, and the reaction mixture was stirred for 24 hours at room temperature. The solution was cooled to -10 °C and Et_2O was slowly added. Water was then added to the mixture very slowly (very exothermic!!). The mixture is stirred for 5

[18] A. F. Ferris, *J. Org. Chem.*, **1955**, *20*, 780.

minutes, and then slowly added to a saturated solution of NaCl. The two phases were then separated. The organic layer was washed three times with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The obtained residue was purified by column chromatography (eluting with petroleum ether/AcOEt, 8/2) to give the desired product **35** (131.4 mg, 93%).

❖ ***Ethyl 2-(cyanomethyl)acrylate (35)***

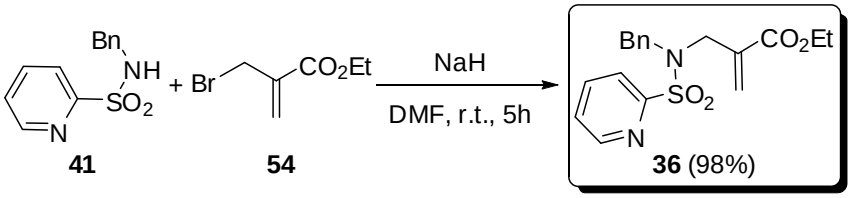


Chemical Formula: $C_7H_9NO_2$
Molecular Weight: 139,15

^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.48 (t, *J* = 1.2 Hz, 1H), 6.08 (t, *J* = 1.7 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.43 (t, *J* = 1.4 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 164.64, 130.42, 128.31, 116.71, 61.74, 20.75, 14.14.

Spectral data are identical to those reported in the literature (CAS: 99488-48-9).[19]

I.1.10.4. Synthesis of 36

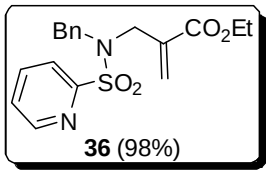


A flame-dried round bottom flask was charged with NaH (133 mg, 3.32 mmol, 2.2 eq., 60% dispersion in oil) in 10 mL of DMF, under argon. A solution of substrate **41** (632.4 mg, 2.55 mmol, 1.7 eq.) in 10 mL of DMF was added, and the reaction mixture was stirred for 15 minutes at room temperature. Substrate **54** (259 mg, 1.5 mmol, 1.0 eq.) was then added, and

[19] A. Arfaoui, H. Amri, *Tetrahedron* **2009**, *65*, 4904.

the reaction mixture was stirred for an additional 5 hours at room temperature. A saturated solution of NH_4Cl was then added to the mixture very slowly, followed by Et_2O. The two phases were then separated and the aqueous layer was extracted three times with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The obtained residue was purified by column chromatography (silica gel, eluting with petroleum ether/AcOEt, 6/4) to give the desired product **36** (531.1 g, 98%).

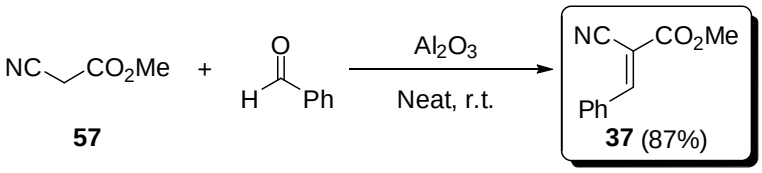
❖ ***Ethyl 2-((N-benzylpyridine-2-sulfonamido)methyl)acrylate (36)***



Chemical Formula: $C_{18}H_{20}N_2O_4S$
Molecular Weight: 360,43

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.67 (ddd, *J* = 4.7, 1.6, 0.9 Hz, 1H), 8.06 – 7.76 (m, 2H), 7.45 (ddd, *J* = 7.4, 4.7, 1.3 Hz, 1H), 7.28 – 7.22 (m, 5H), 6.18 (d, *J* = 1.0 Hz, 1H), 5.73 (d, *J* = 1.1 Hz, 1H), 4.62 (s, 2H), 4.20 (s, 2H), 4.06 (q, *J* = 7.1 Hz, 2H), 1.22 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 165.79, 158.58, 149.87, 137.77, 135.87, 135.31, 128.67, 128.47, 127.84, 127.77, 126.38, 122.33, 60.80, 53.06, 48.32, 14.11. HRMS m/z calcd. for $C_{18}H_{21}N_2O_4S_1$ $[M + H]^+$ 361.12160; found 361.12165.

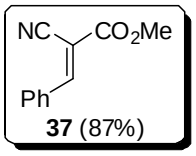
I.1.11. Synthesis of 37[20]



[20] F. Texier-Boullet, A. Foucaud, *Tetrahedron Lett.* **1982**, *23*, 4927.

To a stirred solution of substrate **57** (995.4 mg, 10 mmol, 1.0 eq.) and benzaldehyde(1.1 mL, 10.8 mmol, 1.1 eq.) was added 3 g of neutral Al_2O_3. The reaction was very exothermic. After 5 min, DCM was added and the solution was filtered. Water was added to the filtrate and the two phases were then separated. The aqueous layer was extracted three times with DCM. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The solid was recrystallised in hot isopropanol to obtain pure **37** as a white solid (1.64 g, 87%).

❖ ***(E)-methyl 2-cyano-3-phenylacrylate (37)***



37 (87%)

Chemical Formula: $C_{11}H_9NO_2$
Molecular Weight: 187,19

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.27 (s, 1H), 8.15 – 7.86 (m, 2H), 7.71 – 7.39 (m, 3H), 3.94 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 163.05, 155.40, 133.47, 131.41, 131.16, 129.34, 115.50, 102.54, 53.46.

Spectral data are identical to those reported in the literature (CAS: 14533-86-9).[21]

I.2. Catalytic Tests

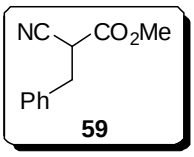
I.2.1. General Procedure for the Tandem 1,4-Reduction-Aldolisation Reaction of 21, 22, 30-37

A flame-dried Schlenk tube under argon was charged with the copper complex **17** (0.02 – 0.03 eq.) and *rac*-BINAP (0.02 – 0.03 eq.). 3 mL of the

[21] D. Blanco-Ania, C. Valderas-Cortina, P. H. Hermkens, L. A. Sliedregt, H. W. Scheeren, F. P. Rutjes, *Molecules* **2010**, *15*, 2269.

indicated solvent (THF or toluene, freshly distilled) were introduced, followed by sequential addition of the olefin (0.5 mmol, 1.0 eq.), the aldehyde (0.6 mmol, 1.2 eq.). The hydride source (1.5 eq.) was subsequently added. After 2 hours at the indicated temperature, Et_2O was added, followed by a 1M solution of HCl. The mixture is stirred for an additional 30 minutes. The two phases were then separated and the aqueous layer was extracted three times with Et_2O. The combined organic layers were washed with a saturated solution of $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. A sample of the residue was analysed by ^1H NMR to determine the composition of the crude mixture as well as the overall conversion.

❖ ***methyl 2-cyano-3-phenylpropanoate (59)***



Chemical Formula: $C_{11}H_{11}NO_2$
Molecular Weight: 189,21

Purified by column chromatography (silica gel, eluting with petroleum ether/AcOEt, 9/1 to 8/2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.21 (m, 5H), 3.80 (s, 3H), 3.74 (dd, *J* = 8.4, 5.8 Hz, 1H), 3.35 – 3.14 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.01, 135.22, 128.17, 128.87, 127.93, 116.11, 53.62, 38.97, 35.84.

Spectral data are identical to those reported in the literature (CAS: 57519-78-5).[22]

[22] S. Nakamura, H. Sugimoto, T. Ohwada, *J. Org. Chem.* **2008**, *73*, 4219.

I.2.2. General Procedure for the 1,4-Reduction Reaction of trans-21

A flame-dried Schlenk tube under argon was charged with the copper complex **17** (5.9 mg, 0.006 mmol, 0.02 eq.) and *rac*-BINAP (4.3 mg, 0.006 mmol, 0.02 eq.). 4 mL of the indicated solvent (THF or toluene, freshly distilled) were introduced, followed by sequential addition of the olefin ***trans*-21** (76.4 mg, 0.3 mmol, 1.0 eq.) and, if indicated, $ZnCl_2$ (2.2 – 2.8 eq.). The hydride source (1.4 eq.) was subsequently added. After 24 hours at room temperature, DCM was added, followed by water. The two phases were then separated and the aqueous layer was extracted three times with DCM. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. A sample of the residue was analysed by ^1H NMR to determine the composition of the crude mixture as well as the overall conversion.

II. Chapter 2: Pd^0/Cu^I Cooperative Dual Catalysis

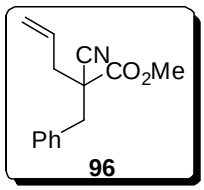
II.1. First Model Reaction: Benzylidene malonate

Synthesis of substrate **37** was performed using the procedure described in the previous chapter (see Experimental part, Chapter 1, Synthesis of **37**).

II.1.1. General Procedure A for the Cooperative Dual Catalysis Testing on Substrate 37

A flame-dried Schlenk **A** was charged sequentially with the palladium complex (0.015 mmol, 0.03 eq.) and, if indicated, 1,10-phenanthroline (0.024 mmol, 0.05 eq.) in 1.5 mL of THF. The reaction mixture was stirred at room temperature. Afterwards, the allyl acetate (0.6 mmol, 1.2 eq.) was added and the mixture was stirred for an additional 5 minutes. Simultaneously another flame-dried Schlenk **B** was charged with the copper complex **17** (0.016 mmol, 0.03 eq.) and *rac*-BINAP (0.016 mmol, 0.03 eq.) in 2 mL of THF. After 30 minutes, phenylsilane (0.28 mL, 1.7 mmol, 1.7 eq.) was added to Schlenk **B** and the mixture was stirred for an additional 5 minutes. The palladium mixture in Schlenk **A** was transferred, via cannula, into Schlenk **B** containing the copper catalyst, followed immediately by substrate **37** (0.5 mmol, 1 eq.). After 24 hours, a saturated solution of NH_4Cl and AcOEt were added, and the two phases were then separated and the aqueous layer was extracted three times with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. A sample of the residue was analysed by ^1H NMR to determine the composition of the crude mixture as well as the overall conversion.

❖ ***Methyl 2-benzyl-2-cyanopent-4-enoate (96)***



Chemical Formula: $C_{14}H_{15}NO_2$
Molecular Weight: 229,27

The crude product was purified by column chromatography (silica gel, petroleum ether/EtOAc, 85/15 to 8/2) to afford the desired product **96**. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.35 – 7.27 (m, 5H), 5.85 (ddt, *J* = 17.1, 9.8, 7.3 Hz, 1H), 5.30 – 5.25 (m, 2H), 3.69 (s, 3H), 3.22 (d, *J* = 13.5 Hz, 1H), 3.08 (d, *J* = 13.5 Hz, 1H), 2.76 (dd, *J* = 13.7, 7.4 Hz, 1H), 2.59 (dd, *J* = 13.7, 7.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 168.63, 134.02, 133.30, 130.52, 129.89, 128.65, 127.96, 121.17, 118.44, 53.24, 51.41, 42.58, 41.36. HRMS m/z calcd. for $C_{14}H_{16}N_1Na_1O_2$ $[M + Na]^+$ 252.09941; found 252.09950.

II.2. Second Model Reaction: α,β-unsaturated esters

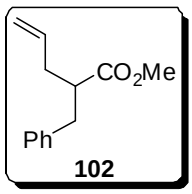
Commercially available methyl cinnamate was used as received.

II.2.1. General Procedure B for the Cooperative Dual Catalysis Testing on Methyl Cinnamate

A flame-dried Schlenk **A** was charged with $Pd(PPh_3)_4$ (0.03 eq.) in 1.5 mL of THF. The reaction mixture was stirred at room temperature. Afterwards, the allyl acetate (2.0 eq.) was added and the mixture was stirred for an additional 5 minutes. Simultaneously another flame-dried Schlenk **B** was charged with the indicated amount of the copper complex **17** and *rac*-BINAP in 2 mL of THF. After 30 minutes at room temperature, a solution of the hydride source (1.5 eq. for silanes and 2.8 eq. for pinacolborane) in 3 mL of THF was added to Schlenk **B** and the mixture was stirred for an additional 5 minutes. The palladium mixture in Schlenk **A** was transferred, via cannula, into Schlenk **B**

containing the copper catalyst, followed immediately by substrate **37** (0.5 mmol, 1 eq.). After 24 hours, a saturated solution of NH_4Cl and Et_2O were added, and the two phases were then separated and the aqueous layer was extracted three times with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. A sample of the residue was analysed by ^1H NMR to determine the composition of the crude mixture as well as the overall conversion.

❖ ***Methyl 2-benzylpent-4-enoate (102)***



102

Chemical Formula: $C_{13}H_{16}O_2$
Molecular Weight: 204,26

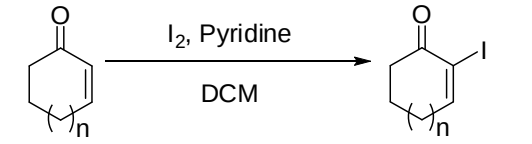
The crude product was purified by column chromatography (silica gel, petroleum ether/ Et_2O, 9/1 to 85/15) to afford the desired product **102**. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.32 – 7.15 (m, 5H), 5.76 (ddt, *J* = 17.1, 10.2, 7.0 Hz, 1H), 5.20 – 4.93 (m, 2H), 3.60 (s, 3H), 3.03 – 2.86 (m, 1H), 2.87 – 2.67 (m, 2H), 2.48 – 2.19 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 175.36, 139.16, 135.14, 128.91, 128.42, 126.40, 117.15, 51.46, 47.28, 37.79, 36.04.

Spectral data are identical to those reported in the literature (CAS: 29805-49-0).[1]

[1] K. Kamikawa, A. Tachibana, Y. Shimizu, K. Uchida, M. Furusyo, M. Uemura, *Tetrahedron* **2006**, *62*, 922.

II.3. Third Model Reaction: α,β-unsaturated Ketones

II.3.1. Synthesis of α-Iodoenones 108 and 114

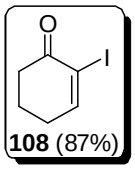


113, n = 0
107, n = 1

114, n = 0, 61%
108, n = 1, 87%

In a 500 mL round-bottomed three necked flask immersed in a water bath and equipped with an addition funnel were placed the cyclic enone (25.5 mmol, 1 eq.) and 1/5 pyridine-CH_2Cl_2 (43 mL). To this were added dropwise a solution of I_2 (7.8 g, 31 mmol, 1.2 eq.) in 43 mL of 1/5 pyridine-CH_2Cl_2 over 1 hour. The mixture was stirred for an additional 4h, quenched with 50 mL of citric acid (6% aqueous solution), and extracted 3 times with CH_2Cl_2. The combined organic layers were washed with an aqueous 10% solution of $Na_2S_2O_3$, 1M HCl and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel, petroleum ether/EtOAc, 29/1) to afford the desired product.

❖ ***2-iodocyclohex-2-enone (108)***



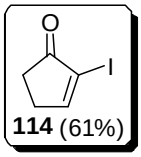
108 (87%)

Chemical Formula: C_6H_7IO
Molecular Weight: 222,02

Prepared according to the general procedure described above, using 2-cyclohexenone, to afford the desired product **108** in 87% yield (4.95 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.77 (t, *J* = 4.4 Hz, 1H), 2.72 – 2.59 (m, 2H), 2.44 (td, *J* = 6.0, 4.6 Hz, 2H), 2.09 (dt, *J* = 12.2, 6.1 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 192.35, 159.56, 104.02, 37.39, 30.07, 22.98.

Spectral data are identical to those reported in the literature (CAS: 33948-36-6).[2]

❖ ***2-iodocyclopent-2-enone (114)***

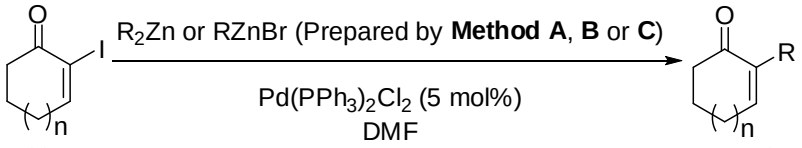


114 (61%)

Chemical Formula: C_5H_5IO
Molecular Weight: 208,00

Prepared according to the general procedure described above, using 2-cyclopentenone, to afford the desired product **114** in 61% yield (3.33 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.01 (t, *J* = 2.9 Hz, 1H), 2.84 – 2.69 (m, 2H), 2.60 – 2.37 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 204.11, 169.76, 102.98, 31.25, 30.84. Spectral data are identical to those reported in the literature (CAS: 33948-35-5).[2]

II.3.2. Synthesis of Starting Materials 110, 115-121[2]



108,114 **115-121**

Method A : RMgBr (or RLi) + $ZnBr_2$, THF, -78 to 0 °C
Method B : RBr + Mg^0 + $ZnBr_2$, THF, reflux to 0 °C to r.t.
Method C : RBr + Zn^0(activated), THF, reflux to 0 °C to 40 °C

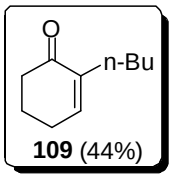
II.3.2.1.Method A

A flame-dried Schlenk was charged with $ZnBr_2$ (1.3 eq.) which was then flame-dried and flushed with Ar. To this were added THF (1.1 mL per mmol

[2] E. Negishi, Z. Tan, S.-Y. Liou, B. Liao *Tetrahedron* **2000**, *56*, 10197.

of $ZnBr_2$) and *n*-BuLi (1.3 eq., 2.5 M in hexane) at -78 °C. The mixture was allowed to reach 0 °C. Then was cannulated into a solution of the corresponding α-iodoenone (1 eq.), $Pd(PPh_3)_2Cl_2$ (0.05 equiv. to enone) in DMF (3.7 mL per mmol of enone) at 0 °C. The reaction mixture was stirred for 3 h at room temperature, quenched with aqueous NH_4Cl and c.c. NH_4OH, and extracted 3 times with Et_2O. The organic layers were washed with water, 1M HCl, 5% aq. $NaHCO_3$, 10% aq. LiCl (2 times) and brine, dried over $MgSO_4$, and concentrated. Fractional distillation afforded the desired product.

❖ ***2-butylcyclohex-2-enone (109)***



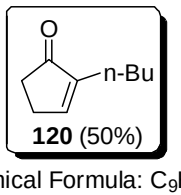
109 (44%)

Chemical Formula: $C_{10}H_{16}O$
Molecular Weight: 152,23

Prepared according to the general procedure described above, using α-iodoenone **108**, to afford the desired product **109** in 44% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.69 (t, *J* = 4.2 Hz, 1H), 2.46 – 2.38 (m, 2H), 2.38 – 2.29 (m, 2H), 2.22 – 2.12 (m, 2H), 1.97 (dt, *J* = 12.3, 6.1 Hz, 2H), 1.44 – 1.21 (m, 4H), 0.89 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 199.78, 144.94, 140.12, 38.78, 30.92, 29.37, 26.21, 23.33, 22.64, 14.09.

Spectral data are identical to those reported in the literature (CAS: 34737-39-8).[2]

❖ ***2-butylcyclopent-2-enone (120)***



120 (50%)

Chemical Formula: $C_9H_{14}O$
Molecular Weight: 138,21

Prepared according to the general procedure described above, using α-iodoenone **114**, to afford the desired product **120** in 50% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.33 – 7.27 (m, 1H), 2.60 – 2.49 (m, 2H), 2.44 – 2.34 (m, 2H),

2.22 – 2.08 (m, 2H), 1.53 – 1.40 (m, 2H), 1.40 – 1.23 (m, 2H), 0.91 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 210.15, 157.35, 146.59, 34.69, 29.98, 26.51, 24.56, 22.56, 13.92.

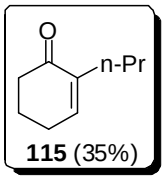
Spectral data are identical to those reported in the literature (CAS: 5561-05-7).[2]

II.3.2.2.Method B

A flame-dried round-bottomed three necked flask, equipped with a reflux condenser, was charged with Mg turnings (1.7 eq.) and a catalytic amount of iodine in THF (0.7 mL per mmol of Mg). The mixture was refluxed for 30 minutes under argon. The mixture was then allowed to cool down to 65 ^oC, and the alkyl bromide (1.3 eq) was added at that temperature over 20 minutes. At the end of the addition, the mixture was again refluxed for 1 hour. Afterwards, the mixture was cooled to room temperature. The supernatant was collected and used as the Grignard reagent later on in the procedure.

A flame-dried Schlenk was charged with $ZnBr_2$ (0.65 eq.) which was then flame-dried and flushed with Ar. To this were added THF (1 mL per mmol of $ZnBr_2$) and the above prepared Grignard reagent (1.3 eq.) at -78 ^oC. The mixture was allowed to reach 0 ^oC (R_2Zn is formed in this procedure). Then was cannulated into a solution of α-iodoenone **108** (1 eq.), $Pd(PPh_3)_2Cl_2$ (0.05 equiv. to enone) in DMF (3.7 mL per mmol of enone) at 0 ^oC. The reaction mixture was stirred for 3 h at room temperature, quenched with aqueous NH_4Cl and c.c. NH_4OH, and extracted 3 times with Et_2O. The organic layers were washed with water, 1M HCl, 5% aq. $NaHCO_3$, 10% aq. LiCl (2 times) and brine, dried over $MgSO_4$, and concentrated. Fractional distillation afforded the desired product.

❖ ***2-propylcyclohex-2-enone (115)***

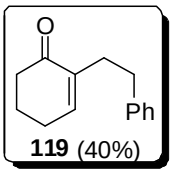


Chemical Formula: $C_9H_{14}O$
Molecular Weight: 138,21

Prepared according to the general procedure described above, using 1-bromopropane, to afford the desired product **115** in 35% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.70 (t, *J* = 4.2 Hz, 1H), 2.50 – 2.30 (m, 4H), 2.15 (td, *J* = 7.7, 1.3 Hz, 2H), 1.97 (dt, *J* = 12.3, 6.2 Hz, 2H), 1.48 – 1.33 (m, 2H), 0.89 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 199.84, 145.13, 139.81, 38.77, 31.74, 26.21, 23.34, 21.87, 14.01.

Spectral data are identical to those reported in the literature (CAS: 59034-18-3).[3]

❖ ***2-phenethylcyclohex-2-enone (119)***



Chemical Formula: $C_{14}H_{16}O$
Molecular Weight: 200,28

Prepared according to the general procedure described above, using (2-bromoethyl)benzene, to afford the desired product **119** in 40% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.33 – 7.10 (m, 5H), 6.61 (t, *J* = 4.1 Hz, 1H), 2.81 – 2.65 (m, 2H), 2.55 – 2.38 (m, 4H), 2.34 – 2.23 (m, 2H), 2.05 – 1.88 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 199.50, 145.96, 142.01, 139.00, 128.67, 128.33, 125.89, 38.72, 35.02, 31.88, 26.17, 23.24. HRMS m/z calcd. for $C_{14}H_{17}O_1$ $[M + H]^+$ 201.12753; found 201.12739.

II.3.2.3.Method C

A flame-dried three-necked flask equipped with a septum inlet, magnetic stirring bar and a reflux condenser was charged with Zn dust (2.0 eq.) and

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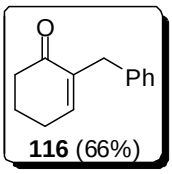
[3] G. Chelucci, S. Gladiali, *J. Heterocyclic Chem.* **1986**, *23*, 1761.

then flushed with Ar. To this were added THF (0.5 mL per mmol of Zn) and and 1,2-dibromoethane (0.03 eq. to Zn). This suspension was heated to reflux for 20 min and then cooled to room temperature. A solution of I_2 (0.0025 eq. to Zn) in THF (1 ml per 0.1 mmol of I_2) and 1,2-dibromoethane (0.01 eq. to Zn) were added. This suspension was again heated to reflux for 20 min and then cooled to 0 °C. Benzyl bromide derivatives (1.0 eq) were added dropwise, and the mixture was stirred at room temperature for 3 h. The mixture was then cannulated into a solution of the corresponding α-iodoenone (0.8 eq.), $Pd(PPh_3)_2Cl_2$ (0.05 equiv. to enone) in DMF (3.7 mL per mmol of enone) at 0 °C. The reaction mixture was stirred for 3 h at room temperature then overnight at 50 °C, quenched with aqueous NH_4Cl and c.c. NH_4OH, and extracted 3 times with Et_2O. The organic layers were washed with water, 1M HCl, 5% aq. $NaHCO_3$, 10% aq. LiCl (2 times) and brine, dried over $MgSO_4$, and concentrated. Flash chromatography (silica gel, petroleum ether/EtOAc, 29/1) provided the desired product.

❖ ***2-benzylcyclohex-2-enone (116)***

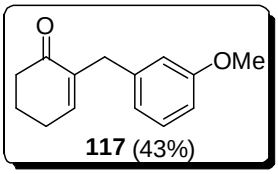


Chemical Formula: $C_{13}H_{14}O$
Molecular Weight: 186,25

Prepared according to the general procedure described above, using benzyl bromide and α-iodoenone **108**, to afford the desired product **116** in 66% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.33 – 7.24 (m, 2H), 7.23 – 7.13 (m, 3H), 6.56 (t, *J* = 4.1 Hz, 1H), 3.52 (s, 2H), 2.51 – 2.40 (m, 2H), 2.38 – 2.27 (m, 2H), 2.06 – 1.91 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 199.16, 146.54, 139.80, 139.65, 129.32, 128.49, 126.19, 38.62, 35.55, 26.22, 23.18.

Spectral data are identical to those reported in the literature (CAS: 13694-36-5).[2]

❖ ***2-(3-methoxybenzyl)cyclohex-2-enone (117)***

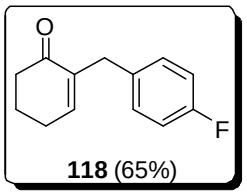


117 (43%)

Chemical Formula: $C_{14}H_{16}O_2$
Molecular Weight: 216,28

Prepared according to the general procedure described above, using 1-(bromomethyl)-3-methoxybenzene and α-iodoenone **108**, to afford the desired product **117** in 43% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.20 (t, *J* = 7.8 Hz, 1H), 6.80 – 6.68 (m, 3H), 6.57 (t, *J* = 4.2 Hz, 1H), 3.79 (s, 3H), 3.49 (s, 2H), 2.52 – 2.39 (m, 2H), 2.39 – 2.25 (m, 2H), 2.07 – 1.89 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 199.14, 159.74, 146.65, 141.42, 139.43, 129.44, 121.73, 115.08, 111.46, 55.30, 38.62, 35.55, 26.23, 23.18. HRMS m/z calcd. for $C_{14}H_{17}O_2$ $[M + H]^+$ 217.12231; found 217.12245.

❖ ***2-(4-fluorobenzyl)cyclohex-2-enone (118)***

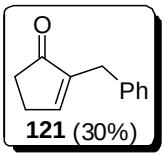


118 (65%)

Chemical Formula: $C_{13}H_{13}FO$
Molecular Weight: 204,24

Prepared according to the general procedure described above, using 1-(bromomethyl)-4-fluorobenzene and α-iodoenone **108**, to afford the desired product **118** in 65% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.18 – 7.04 (m, 2H), 7.03 – 6.88 (m, 2H), 6.57 (t, *J* = 4.2 Hz, 1H), 3.48 (s, 2H), 2.53 – 2.40 (m, 2H), 2.40 – 2.27 (m, 2H), 2.12 – 1.88 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 198.93, 146.41, 139.42, 135.29, 130.53, 130.42, 115.24, 114.96, 38.46, 34.77, 26.08, 23.02. ^{19}F NMR (282 MHz, $CDCl_3$) δ = -117.42. HRMS m/z calcd. for $C_{13}H_{14}F_1O_1$ $[M + H]^+$ 205.10232; found 205.10252.

❖ ***2-benzylcyclopent-2-enone (121)***



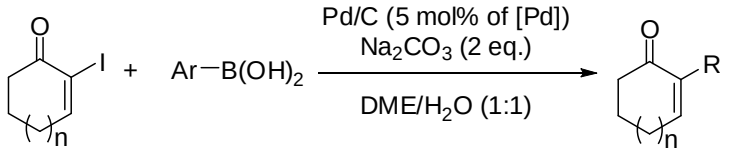
121 (30%)

Chemical Formula: $C_{12}H_{12}O$
Molecular Weight: 172,22

Prepared according to the general procedure described above, using benzyl bromide and α-iodoenone **114**, to afford the desired product **121** in 30% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.34 – 7.25 (m, 2H), 7.25 – 7.17 (m, 3H), 7.17 – 7.11 (m, 1H), 3.49 (br. s, 2H), 2.54 (td, *J* = 4.6, 2.2 Hz, 2H), 2.49 – 2.37 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 209.26, 158.91, 146.18, 139.01, 129.04, 128.63, 126.40, 34.73, 31.47, 26.60.

Spectral data are identical to those reported in the literature (CAS: 22354-39-8).[2]

II.3.3. Synthesis of Starting Materials 122-126[4]



118,114 **122-126**

To a solution of α-iodoenone (1.5 mmol, 1 eq.) in DME (4.5 mL) and H_2O (4.5 mL) were added Na_2CO_3 (318 mg, 3 mmol, 2 eq.), Ar- $B(OH)_2$ (3 mmol, 2 eq.), and 10% Pd/C (79.5 mg, 5 mol% of Pd). The mixture was stirred for 80 °C for 5 hours. Pd/C was filtered, and the filtrate was diluted with H_2O (4.5 mL) and extracted with Et_2O (3 times). The collected organic extracts were dried on $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (silica gel, petroleum ether/EtOAc, 29/1) provided the desired product.

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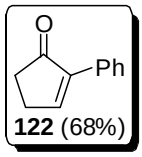
[4] F.-X. Felpin, *J. Org. Chem.* **2005**, *70*, 8575.

❖ ***2-phenylcyclopent-2-enone (122)***

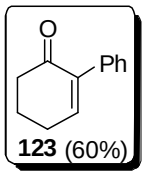


Chemical Formula: $C_{11}H_{10}O$
Molecular Weight: 158,20

Prepared according to the general procedure described above, using phenylboronic acid and α-iodoenone **114**, to afford the desired product **122** in 68% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.83 (t, *J* = 2.9 Hz, 1H), 7.68 (dt, *J* = 3.7, 2.1 Hz, 2H), 7.50 – 7.28 (m, 3H), 2.79 – 2.66 (m, 2H), 2.66 – 2.51 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 207.58, 158.92, 143.50, 131.68, 128.42, 128.35, 127.05, 35.80, 26.22.

Spectral data are identical to those reported in the literature (CAS: 39545-99-8).[4]

❖ ***2-phenylcyclohex-2-enone (123)***

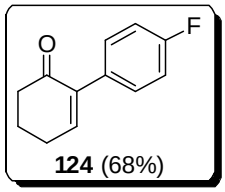


Chemical Formula: $C_{12}H_{12}O$
Molecular Weight: 172,22

Prepared according to the general procedure described above, using phenylboronic acid and α-iodoenone **108**, to afford the desired product **123** in 60% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.42 – 7.23 (m, 5H), 7.03 (t, *J* = 4.3 Hz, 1H), 2.67 – 2.46 (m, 4H), 2.22 – 2.00 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 198.06, 148.07, 140.57, 136.70, 128.76, 128.13, 127.69, 39.22, 26.76, 23.08.

Spectral data are identical to those reported in the literature (CAS: 4556-09-6).[4]

❖ ***2-(4-fluorophenyl)cyclohex-2-enone (124)***

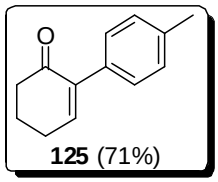


Chemical Formula: $C_{12}H_{11}FO$
Molecular Weight: 190,21

Prepared according to the general procedure described above, using 4-fluorophenylboronic acid and α-iodoenone **108**, to afford the desired product **124** in 68% yield. ^{1}H NMR (300 MHz,

$CDCl_3$) δ = 7.42 – 7.16 (m, 2H), 7.14 – 6.95 (m, 3H), 2.70 – 2.47 (m, 4H), 2.17 – 2.04 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 197.93, 147.95, 139.45, 132.48, 130.35, 130.24, 115.02, 114.74, 39.00, 26.60, 22.90. ^{19}F NMR (282 MHz, $CDCl_3$) δ = -114.89. HRMS m/z calcd. for $C_{12}H_{12}F_1O_1$ $[M + H]^+$ 191.08681; found 191.08667.

❖ ***2-p-tolylcyclohex-2-enone (125)***

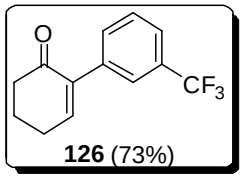


125 (71%)

Chemical Formula: $C_{13}H_{14}O$
Molecular Weight: 186,25

Prepared according to the general procedure described above, using *p*-tolylboronic acid and α-iodoenone **108**, to afford the desired product **125** in 71% yield. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.24 – 7.11 (m, 4H), 7.00 (t, *J* = 4.3 Hz, 1H), 2.67 – 2.47 (m, 4H), 2.35 (s, 3H), 2.17 – 2.05 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 198.10, 147.32, 140.33, 137.32, 133.68, 128.73, 128.50, 39.11, 26.61, 22.99, 21.17. HRMS m/z calcd. for $C_{13}H_{15}O_1$ $[M + H]^+$ 187.11199; found 187.11174.

❖ ***2-(3-(trifluoromethyl)phenyl)cyclohex-2-enone (126)***



126 (73%)

Chemical Formula: $C_{13}H_{11}F_3O$
Molecular Weight: 240,22

Prepared according to the general procedure described above, using 3-(trifluoromethyl)phenylboronic acid and α-iodoenone **108**, to afford the desired product **122** in 73% yield. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.67 – 7.36 (m, 4H), 7.10 (t, *J* = 4.3 Hz, 1H), 2.75 – 2.45 (m, 4H), 2.29 – 2.03 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 197.39, 149.00, 139.37, 137.19, 132.74, 132.11, 130.65, 128.34, 125.44, 124.29, 38.89, 26.62, 22.82. ^{19}F NMR (282 MHz, $CDCl_3$) δ = -

62.57. HRMS m/z calcd. for $C_{13}H_{12}F_3O_1$ $[M + H]^+$ 241.08354; found 241.08348.

II.3.4. General Procedure C for the Preliminary Cooperative Dual Catalysis Testing on D-(+)-Carvone (Table 10)

A flame-dried Schlenk **A** was charged sequentially with the palladium complex (0.03 mmol, 0.03 eq.) in 1.5 mL of THF. The reaction mixture was stirred at room temperature. Simultaneously another flame-dried Schlenk **B** was charged with the copper complex **17** (0.031 mmol, 0.03 eq.) and *rac*-BINAP (0.031 mmol, 0.03 eq.) in 1.5 mL of THF. After 20 minutes, the palladium mixture in Schlenk **A** was transferred, via cannula, into Schlenk **B** containing the copper catalyst, followed immediately by D-(+)-carvone (1.0 mmol, 1 eq.) and the allyl acetate (1.5 mmol, 1.5 eq.). Phenylsilane (1.5 mmol, 1.5 eq.) was added and the mixture was stirred at room temperature. After 24 hours, a saturated solution of NH_4Cl and Et_2O were added, and the two phases were then separated and the aqueous layer was extracted three times with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. A sample of the residue was analysed by ^1H NMR to determine the composition of the crude mixture as well as the overall conversion.

II.3.5. General Procedure D for the First Sequential Catalysis Testing on D-(+)-Carvone (Table 11)

A flame-dried Schlenk **A** was charged with the indicated amount of the palladium complex and the allyl acetate (1.5 mmol, 1.5 eq.) in 1.5 mL of

THF. Simultaneously another flame-dried Schlenk **B** was charged sequentially with the indicated amount of IMesCuDBM in 1 mL of THF. After 15 minutes, the silane (1.2 eq.) was added, followed by D-(+)-carvone (1 eq.). The reaction mixture was stirred at room temperature and after 5 minutes, the palladium mixture in Schlenk **A** was transferred, via cannula, into Schlenk **B** containing the copper catalyst. After 24 hours, a saturated solution of NH_4Cl and Et_2O were added, and the two phases were then separated and the aqueous layer was extracted three times with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. A sample of the residue was analysed by ^1H NMR to determine the composition of the crude mixture as well as the overall conversion.

II.3.6. General Procedure E for the Second Sequential Catalysis Testing on D-(+)-Carvone (Table 12 and 13)

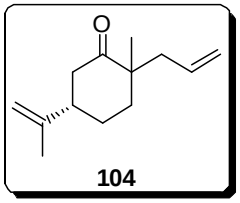
II.3.6.1.Preparation of the Silyl Enolate (*in situ*)

A flame-dried Schlenk was charged sequentially with the copper catalyst (10.2 mg, 0.02 mmol, 0.02 eq.), *t*-BuOK (2.4 mg, 0.02 mmol, 0.02 eq.) and 1 mL of the designated solvent (THF or toluene). Carvone was then added (153.3 mg, 1 mmol, 1 eq.) at 0 ^oC, followed by the silane (1.7 mmol, 1.7 eq.). The reaction is monitored by TLC and after total consumption of the starting materiel (1hour), the reaction mixture was used in the next step without any further purification.

II.3.6.2.Sequential Allylation Reaction

A flame-dried Schlenk was charged sequentially with the indicated amount of the palladium complex, dppe (0.1 mmol, 0.1 eq.) and 0.5 mL of the indicated solvent. The reaction mixture was stirred at room temperature. After 5 minutes the *tert*-butyl allylcarbonate (1.5 mmol, 1.5 eq.) was added, followed by the additive (if indicated) and the mixture was stirred for an additional 5 minutes. The silyl enolate solution obtained above was then transferred to the palladium solution at the indicated temperature (65 ^{o}C or 45 ^{o}C). After 24 hours, 1.4 mL of TBAF (1M in THF) was added to the reaction mixture followed by a saturated aqueous solution of NH_4Cl and Et_2O. The two phases were then seperated and the aqueous layer was extracted three times with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (petroleum ether/ Et_2O, 96/4) to give the two diastereoisomers of the desired product **104**.

❖ ***(5S)-2-allyl-2-methyl-5-(prop-1-en-2-yl)cyclohexanone (104)***



Chemical Formula: $C_{13}H_{20}O$
Molecular Weight: 192,30

<u>*Diastereoisomer **104a** (Major):*</u> ^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.70 – 5.53 (m, 1H), 5.10 – 4.98 (m, 2H), 4.79 – 4.64 (m, 2H), 2.53 – 2.27 (m, 4H), 2.21 – 2.14 (m, 1H), 1.93 – 1.83 (m, 1H), 1.82 – 1.65 (m, 5H), 1.56 – 1.42 (m, 1H), 1.02 (s, 3H). ^{13}C NMR (75 MHz, CDCl3) δ = 214.76, 147.60, 133.01, 118.31, 109.97, 48.13, 46.24, 43.62, 41.57, 37.59, 26.11, 22.27, 20.80. HRMS m/z calcd. for $C_{13}H_{21}O_1$ $[M + H]^+$ 193.15869; found 193.15885.

<u>*Diastereoisomer **104b** (Minor):*</u> ^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.87 – 5.63 (m, 1H), 5.04 (dd, *J* = 13.7, 4.1 Hz, 2H), 4.83 – 4.63 (m, 2H), 2.59 – 2.16 (m, 4H), 1.88 – 1.56 (m, 6H), 1.30 – 1.18 (m, 2H), 1.13 (s, 3H). ^{13}C NMR

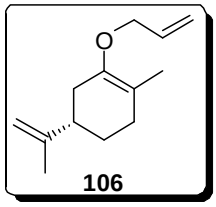
(75 MHz, $CDCl_3$) δ = 215.04, 147.67, 134.77, 117.95, 110.06, 47.41, 45.95, 43.50, 42.52, 36.40, 26.25, 23.21, 20.83. HRMS m/z calcd. for $C_{13}H_{21}O_1$ $[M + H]^+$ 193.15869; found 193.15881.

II.3.7. General Procedure F for the Optimisation of the Cooperative Dual Catalysis Reaction on D-(+)-Carvone (Table 14 – 19)

II.3.7.1.Optimisation Procedure (Table 14 – 18)

A flame-dried Schlenk was charged sequentially with the indicated amount of the palladium complex, the indicated amount of the corresponding phosphine and 0.5 mL of the desired solvent. The reaction mixture was stirred at room temperature. After 5 minutes the indicated amount of the methyl allylcarbonate was added and the mixture was stirred for an additional 5 minutes. Simultaneously, another flame-dried Schlenk was charged with the indicated amount of IMesCuDBM in 0.5 mL of the same solvent as above. Once the palladium complex was totally dissolved, the palladium mixture was transferred into the Schlenk containing the copper catalyst followed immediately by the Carvone (1 mmol, 1 eq.). $Me(EtO)_2SiH$ (1.7 mmol, 1.7 eq.) was diluted in 0.5 mL of the above solvent and quickly added. The reaction mixture was then stirred at the indicated temperature. After 24 hours, 1.4 mL of TBAF (1M in THF) was added to the reaction mixture at room temperature. The latter was then filtered on a plug silica gel (eluting with petroleum ether/Et_2O, 4/1). The filtrate was concentrated *in vacuo* to obtain a colorless residue. The residue was purified by column chromatography (petroleum ether/Et_2O, 96/4) to give the desired alkylated products **104** and **106**.

❖ ***(S)-2-(allyloxy)-1-methyl-4-(prop-1-en-2-yl)cyclohex-1-ene (106)***



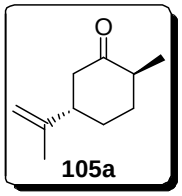
106

Chemical Formula: $C_{13}H_{20}O$
Molecular Weight: 192,30

^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.88 (ddd, *J* = 22.7, 11.0, 5.8 Hz, 1H), 5.42 – 5.19 (m, 2H), 4.79 – 4.68 (m, 2H), 4.68 – 4.58 (m, 2H), 2.65 – 2.42 (m, 3H), 2.39 – 2.26 (m, 1H), 1.92 – 1.76 (m, 1H), 1.70 (s, 3H), 1.67 – 1.59 (m, 1H), 1.52 – 1.37 (m, 1H), 1.30 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 207.28, 172.58, 147.13, 131.39, 119.12, 109.99, 65.84, 56.39, 46.63, 45.74, 37.01, 28.09, 21.11, 20.37. HRMS m/z calcd. for $C_{13}H_{21}O_1$ $[M + H]^+$ 193.15869; found 193.15891.

The reduction product **105** was always observed as a mixture of two diastereoisomers with a ratio ranging from 7/3 to 8/2. The major diastereoisomer **105a** was successfully isolated and was determined to be the *trans* isomer of **105**.

❖ ***(2S,5S)-2-methyl-5-(prop-1-en-2-yl)cyclohexanone (105a)***



105a

Chemical Formula: $C_{10}H_{16}O$
Molecular Weight: 152,23

^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.78 – 4.74 (m, 1H), 4.73 (s, 1H), 2.53 – 2.26 (m, 4H), 2.20 – 2.07 (m, 1H), 2.00 – 1.89 (m, 1H), 1.74 (s, 3H), 1.72 – 1.61 (m, 1H), 1.37 (ddd, *J* = 26.0, 13.0, 3.6 Hz, 1H), 1.03 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 211.92, 147.35, 109.27, 46.88, 46.52, 44.40, 34.67, 30.48, 20.11, 14.09.

Spectral data are identical to those reported in the literature (CAS: 5524-05-0).[5]

[5] C. H. Jiang, A. Bhattacharyya, C. K. Sha, *Org. lett.* **2007**, *9*, 3241.

Unfortunately, we weren't able to cleanly isolate the minor diastreoisomer of **105**, however, we were able to compare some of the proton shifts (δ = 4.82 (s, 1H), 4.68 (s, 1H), which corresponds to the two ethylenic protons C***H₂***=C) in ^{1}H NMR to the literature, which confirmed the product to be the *cis* isomer **105b**.

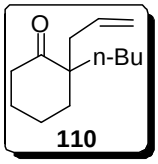
II.3.7.2.Final Optimised Procedure (Table 19)

A flame-dried Schlenk was charged sequentially with the palladium acetate (2.3 mg, 0.01 mmol, 0.01 eq.), (*S*)-Ph-PHOX (10.2 mg, 0.025 mmol, 0.025 eq.) and 0.5 mL of toluene. The reaction mixture was stirred at room temperature. After 5 minutes, methyl allylcarbonate (0.18 mL, 1.5 mmol, 1.5 eq.) was added and the mixture was stirred for an additional 5 minutes. Simultaneously, another flame-dried Schlenk was charged with IMesCuDBM (30 mg, 0.05 mmol, 0.05 eq.) in 0.5 mL of toluene. Once the palladium acetate was totally dissolved, the palladium mixture was transferred into the Schlenk containing the copper catalyst followed immediately by the Carvone (153.3 mg, 1 mmol, 1 eq.). $Me(EtO)_2SiH$ (0.28 mL, 1.7 mmol, 1.7 eq.) was diluted in 0.5 mL of toluene and quickly added. After 24 hours at room temperature, 1.4 mL of TBAF (1M in THF) was added to the reaction mixture. The latter was then filtered on a plug silica gel (eluting with petroleum ether/Et_2O, 4/1). The filtrate was concentrated *in vacuo* to obtain a colourless residue. The residue was purified by column chromatography (petroleum ether/Et_2O, 96/4) to give the desired product **104** (145 mg, 75%, d.r. = 95/5).

II.3.8. General Procedure G for the Enantioselective Cooperative Dual Catalysis Testing on Substrate 109 (Table 20 – 22)

A flame-dried Schlenk was charged sequentially with the palladium acetate (0.005 mmol, 0.01 eq.), the indicated phosphine (0.0125 mmol, 0.025 eq.) and 0.4 mL of the indicated solvent. The reaction mixture was stirred at room temperature. After 5 minutes the indicated amount of methyl allylcarbonate was added and the mixture was stirred for an additional 5 minutes. Simultaneously, another flame-dried Schlenk was charged with IMesCuDBM (0.025 mmol, 0.05 eq.) and the additive (if indicated, 0.05 mmol, 0.1 eq.) in 0.4 mL of the same solvent as above and stirred for 1 minute. Once the palladium acetate was totally dissolved, the palladium mixture was transferred into the Schlenk containing the copper catalyst followed immediately by the Substrate **109** (0.5 mmol, 1. eq., diluted in 0.2 mL of the indicated solvent). The mixture was then immediately put at the desired temperature and $Me(EtO)_2SiH$ (0.85 mmol, 1.7 eq.) was quickly added (without dilution). After 24 hours, 0.7 mL of TBAF (1M in THF) was added to the reaction mixture. The latter was then filtered on a plug silica gel (eluting with petroleum ether/Et_2O, 4/1). The filtrate was concentrated *in vacuo* to obtain a colourless residue. A sample of this residue was taken for GC and NMR analysis. The residue was purified by column chromatography (petroleum ether/Et_2O, 29/1) to give the alkylated products **110** and **111**.

❖ ***2-allyl-2-butylcyclohexanone (110)***



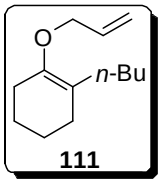
110

Chemical Formula: $C_{13}H_{22}O$
Molecular Weight: 194,31

^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.68 (ddt, *J* = 15.1, 11.4, 7.4 Hz, 1H), 5.10 – 4.91 (m, 2H), 2.49 – 2.13 (m, 4H), 1.97 – 1.80 (m, 1H), 1.81 – 1.56 (m, 6H), 1.48 – 1.34 (m, 1H), 1.32 – 1.16 (m, 3H), 1.04 – 0.92 (m, 1H), 0.88 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 215.26, 134.43, 117.77, 51.56, 39.39, 39.18, 36.68, 34.62, 27.34, 25.67, 23.45, 20.95, 14.13. HRMS m/z calcd. for $C_{13}H_{23}O_1$ $[M + H]^+$ 195.17434; found 195.17446.

The enantiomeric ratio was determined by chiral GC (T = 118 °C (27 min), t_R = 20.4 min (minor), t_R = 20.8 min (major)).

❖ ***1-(allyloxy)-2-butylcyclohex-1-ene (111)***



111

Chemical Formula: $C_{13}H_{22}O$
Molecular Weight: 194,31

^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.90 (ddt, *J* = 16.2, 10.4, 5.8 Hz, 1H), 5.41 – 5.17 (m, 2H), 4.63 (d, *J* = 5.8 Hz, 2H), 2.65 – 2.35 (m, 3H), 2.13 – 1.81 (m, 2H), 1.81 – 1.39 (m, 5H), 1.39 – 1.05 (m, 4H), 0.88 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 207.96, 171.83, 131.60, 118.96, 65.63, 41.15, 35.94, 34.39, 27.62, 26.36, 23.10, 22.55, 13.90. HRMS m/z calcd. for $C_{13}H_{23}O_1$ $[M + H]^+$ 195.17434; found 195.17458.

II.3.9. General Procedure H for the Mechanistic Investigation

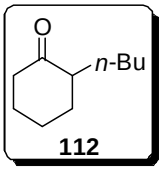
II.3.9.1.Formation of the Silyl Enol Ether 109'

A flame-dried Schlenk was charged sequentially with IMesCuDBM (15 mg, 0.025 mmol, 0.05 eq.), *t*-BuOK (5.8 mg, 0.05 mmol, 0.1 eq.) and 1 mL of toluene. Substrate **109** (75 mg, 0.5 mmol, 1 eq.) was then added at 0 °C, followed by $Me(EtO)_2SiH$ (0.14 mL, 0.85 mmol, 1.7 eq.). The reaction is monitored by TLC and after total consumption of the starting materiel (1hour), the mixture was filtered on a plug silica gel (eluting with petroleum ether/Et_2O, 4/1). The filtrate was concentrated *in vacuo* to obtain a colourless residue.

The obtained residue was a mixture of two inseparable silyl enols. Therefore this residue was not purified any further and was later hydrolysed to make sure that the reaction was complete and to confirm the observation of the reduction product. This residue (**109'**) was used directly in the subsequent allylation tests, and this procedure was repeated for each sequential test.

Hydrolysis of enolate **109'** in the presence of TBAF (0.8 mL, 0.8 mmol, 1.6 eq., 1M soln. in THF) gave a quantitative yield of the reduction product **112**.

❖ ***2-butylcyclohexanone (112)***



112

Chemical Formula: $C_{10}H_{18}O$
Molecular Weight: 154,25

^1H NMR (300 MHz, $CDCl_3$) δ = 2.44 – 2.18 (m, 3H), 2.17 – 1.94 (m, 2H), 1.91 – 1.54 (m, 4H), 1.48 – 1.10 (m, 6H), 0.88 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 213.67, 50.77, 41.96, 33.83, 29.41, 29.12, 28.05, 24.81, 22.84, 14.02.

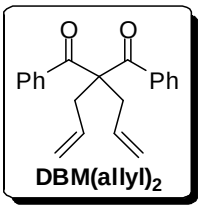
Spectral data are identical to those reported in the literature (CAS: 1126-18-7).[6]

[6] C. F. Malosh, J. M. Ready, *J. Am. Chem. Soc.* **2004**, *126*, 10240.

II.3.9.2.Allylation Tests on Substrate 109' (Table 23 – 25)

A flame-dried Schlenk was charged sequentially with the palladium acetate (0.005 mmol, 0.01 eq.), the indicated phosphine (0.0125 mmol, 0.025 eq.) and 0.4 mL of toluene. The reaction mixture was stirred at room temperature. After 5 minutes, methyl allylcarbonate (1 mmol, 1 eq.) was added and the mixture was stirred for an additional 5 minutes. Simultaneously, another flame-dried Schlenk was charged with the copper catalyst (if indicated, 0.025 mmol, 0.05 eq.) and the appropriate amount of additives (if indicated) in 0.4 mL of toluene and stirred for 1 minute. Once the palladium acetate was totally dissolved, the palladium mixture was transferred into the Schlenk containing the copper catalyst followed immediately by the above obtained residue **109'** (0.5 mmol, 1. eq., diluted in 0.2 mL of toluene). The mixture was then immediately put at 45 ^{o}C. After 24 hours, 0.7 mL of TBAF (1M in THF) was added to the reaction mixture. The latter was then filtered on a plug silica gel (eluting with petroleum ether/Et_2O, 4/1). The filtrate was concentrated *in vacuo* to obtain a colorless residue. A sample of this residue was taken for GC and NMR analysis.

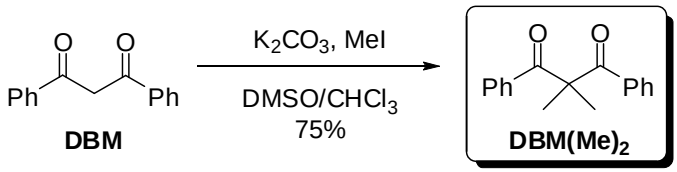
❖ ***DBM(allyl)$_2$***



Chemical Formula: $C_{21}H_{20}O_2$
Molecular Weight: 304,38

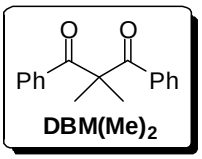
^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.94 – 7.73 (m, 4H), 7.49 – 7.39 (m, 2H), 7.39 – 7.29 (m, 4H), 5.48 (ddt, *J* = 17.5, 10.1, 7.5 Hz, 2H), 5.10 – 4.98 (m, 2H), 4.90 (dd, *J* = 16.9, 1.8 Hz, 2H), 2.97 (d, *J* = 7.5 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 198.61, 136.33, 133.14, 131.60, 128.97, 128.72, 119.67, 66.44, 37.53.

Spectral data are identical to those reported in the literature (CAS: 53316-02-2).[7]



A flame-dried round-bottomed flask was charged with DBM (1.121 g, 5 mmol, 1 eq.) in 70 mL of a mixture of DMSO/$CHCl_3$ (53/17). K_2CO_3 (4.146 g, 30 mmol, 6 eq.) was added to the mixture, followed by MeI (1.25 mL, 20 mmol, 4 eq.). The reaction mixture was stirred at room temperature for 3 days, after which MTBE (50 mL) was added, and the solution was stirred for an additional 30 minutes. The mixture was filtered over celite, and the two phases were separated. The organic layer was washed three times with water, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the desired product **DBM(Me)$_2$** (0.95 g, 75%).

❖ ***DBM(Me)$_2$***



Chemical Formula: $C_{17}H_{16}O_2$
Molecular Weight: 252,31

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.28 – 8.05 (m, 4H), 7.82 – 7.72 (m, 2H), 7.65 (dd, *J* = 8.2, 6.9 Hz, 4H), 2.00 (s, 6H).

Spectral data are identical to those reported in the literature (CAS: 41169-42-0).[8]

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[7] R. Grigg, J. F. Malone, T. R. B. Mitchell, A. Ramasubbu, R. M. Scott, *Journal of the Chemical Society, Perkin Transactions 1* **1984**, 1745.

II.3.9.3. Sequential and Cooperative Dual Testing on Substrate 109 (Table 26 and 27)

Sequential testing on substrate **109** (Table 26) was done using general procedure E, and the cooperative dual catalysis testing (Table 27) was done using general procedure G.

II.3.9.4. C-alkylation vs O-alkylation Testing (Scheme 107)

II.3.9.4.1. Preparation of the O-alkylated product 106

A flame-dried Schlenk was charged sequentially with palladium acetate (0.005 mmol, 0.01 eq.), dppe (0.0125 mmol, 0.025 eq.) and 0.5 mL of THF. The reaction mixture was stirred at room temperature. After 5 minutes, methyl allylcarbonate (1 mmol, 2 eq.) was added and the mixture was stirred for an additional 5 minutes. Simultaneously, another flame-dried Schlenk was charged with IMesCuDBM (0.025 mmol, 0.05 eq.) in 0.5 mL of THF. Once the palladium acetate was totally dissolved, the palladium mixture was transferred into the Schlenk containing the copper catalyst followed immediately by the Carvone (0.5 mmol, 1 eq.). $Me(EtO)_2SiH$ (0.85 mmol, 1.7 eq.) was then quickly added. The reaction mixture was then stirred at room temperature. After 24 hours, 1.4 mL of TBAF (1M in THF) was added to the reaction mixture. The latter was then filtered on a plug silica gel (eluting with petroleum ether/Et_2O, 4/1). The filtrate was concentrated *in vacuo* to obtain a colourless residue. The residue was purified by column

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[8] E. Volker Dehmlow, M. Kaiser, J. Bollhöfer, *New J. Chem.* **2001**, *25*, 588.

chromatography (petroleum ether/Et_2O, 96/4) to give the desired product **106** in 63% yield.

II.3.9.4.2. Rearrangement Tests on Substrate 106

A flame-dried Schlenk was charged sequentially with the palladium acetate (0.005 mmol, 0.01 eq.), the indicated phosphine (0.0125 mmol, 0.025 eq.) and 0.4 mL of toluene. The reaction mixture was stirred at room temperature. After 5 minutes, methyl allylcarbonate (if indicated, 1 mmol, 1 eq.) was added and the mixture was stirred for an additional 5 minutes. Simultaneously, another flame-dried Schlenk was charged with IMesCuDBM (0.025 mmol, 0.05 eq.) in 0.4 mL of toluene. Once the palladium acetate was totally dissolved, the palladium mixture was transferred into the Schlenk containing the copper catalyst followed immediately by substrate **106** (0.5 mmol, 1. eq., diluted in 0.2 mL of toluene). The mixture was then immediately put at the indicated temperature. After 24 hours, 0.7 mL of TBAF (1M in THF) was added to the reaction mixture. The latter was then filtered on a plug silica gel (eluting with petroleum ether/Et_2O, 4/1). The filtrate was concentrated *in vacuo* to obtain a colourless residue. A sample of this residue was taken for GC and NMR analysis.

II.3.9.5.NMR and GC Follow-up for the Formation of Product 110

- ***First Step: Silyl enol ether formation***

A flame-dried Schlenk was charged sequentially with IMesCuCl (10.1 mg, 0.025 mmol, 0.05 eq.), *t*-BuOK (5.8 mg, 0.05 mmol, 0.1 eq.) and 1 mL of toluene. Substrate **109** (75 mg, 0.5 mmol, 1 eq.) was then added at 0 ^oC,

followed by $Me(EtO)_2SiH$ (0.85 mmol, 1.7 eq.). The reaction is monitored by TLC and after total consumption of the starting materiel (15 minutes), the reaction mixture was used in the next step without any further purification.

- ***Second Step: Allylation reaction***

A flame-dried Schlenk was charged sequentially with the palladium acetate (0.005 mmol, 0.01 eq.), (*S*)-*t*-Bu-PHOX (0.0125 mmol, 0.025 eq.) and 0.4 mL of toluene. The reaction mixture was stirred at room temperature. After 5 minutes, methyl allylcarbonate (1 mmol, 2.0 eq.) was added and the mixture was stirred for an additional 5 minutes. The silyl enol ether solution obtained above was then transferred to the palladium solution at 45 ^{o}C.

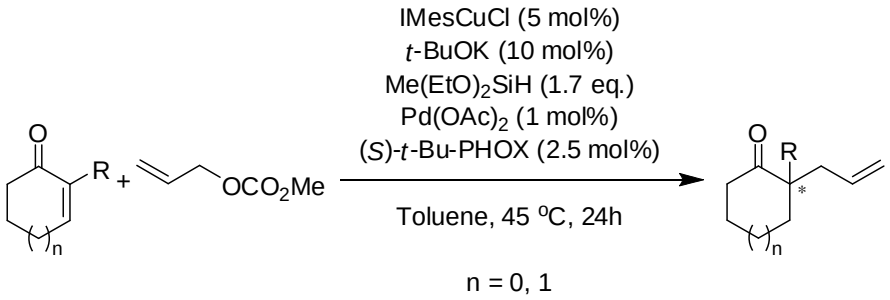
- ***Sampling and analysis***

A 0.05 mL sample of the above mentioned reaction was taken at the indicated times (20, 30, 60, 180, 300 and 1492 minutes) and directly quenched with 0.1 mL of TBAF (1M soln in THF). This hydrolyzed sample was passed through a plug mixture of silica gel and celite (eluting with 1 ml of Et_2O). 1 mL of the obtained solution was taken up for GC analysis. Each sample was, later on, evaporated in order to record a ^{1}H NMR spectrum.

Time (min.)	Conversion 110 (%)	e.e. 110 (%)
20	10.5	81.4
30	26.0	82.8
60	62.7	83.7
180	83.7	79.2
300	84.2	79.1
1492	85.8	78.8

II.4. Extension of the Reaction's Scope

II.4.1. General Procedure for the Optimized Enantioselective Cooperative Dual Catalysis Reaction

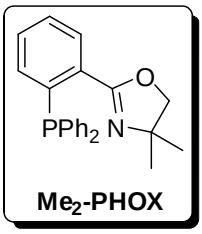


A flame-dried Schlenk was charged sequentially with the palladium acetate (1.2 mg, 0.005 mmol, 0.01 eq.), (*S*)-*t*Bu-PHOX (10.2 mg, 0.0125 mmol, 0.025 eq.) and 0.4 mL of toluene.[9] The reaction mixture was stirred at room temperature. After 5 minutes the allylcarbonate (0.12 mL, 1 mmol, 2.0 eq.) was added and the mixture was stirred for an additional 5 minutes. Simultaneously, another flame-dried Schlenk was charged with IMesCuCl (10.1 mg, 0.025 mmol, 0.05 eq.) and *t*-BuOK (5.8 mg, 0.05 mmol, 0.1 eq.) in 0.4 mL of toluene and stirred for 1 min. Once the palladium acetate was totally dissolved, the palladium mixture was transferred into the Schlenk containing the copper catalyst followed immediately by the Michael

[9] Preparation of the toluene distillation is crucial to obtain reproducible results. It should be carried out as follows: Toluene should be distilled in a 1 L distillation flask on < 6 g of sodium. The solvent is taken from the distillation, then degassed for 1 hr under argon before use. It could be stored and used for no more than one week. The older the distillation, the more reproducible are the results.

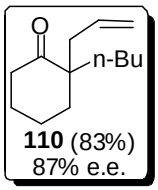
acceptors **109**, **115-126** (0.5 mmol, diluted in 0.2 mL of toluene). The mixture was then immediately heated to 45 °C and the silane (0.14 mL, 0.85 mmol, 1.7 eq.) was quickly added (without dilution). After 24 hours, 0.7 mL of TBAF (1M in THF) was added to the reaction mixture. The latter was then filtered on a plug silica gel (eluting with petroleum ether/ Et_2O, 2/1). The filtrate was concentrated *in vacuo* to obtain a colourless residue. A sample of this residue is taken for GC and NMR analysis. The residue was purified by column chromatography (silica gel, petroleum ether/Et_2O, 29/1) to give the desired products **110**, **127-138**.

Separation of the two enantiomers was performed on the racemic products. The corresponding racemic products were obtained using the same above described procedure, however an achiral ligand was used instead of (*S*)-*t*-Bu-PHOX; the Me_2-PHOX shown below.



Me_2-PHOX

❖ ***2-allyl-2-butylcyclohexanone (110)***



110 (83%)
87% e.e.

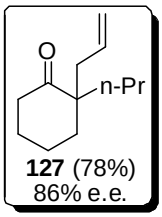
Chemical Formula: $C_{13}H_{22}O$
Molecular Weight: 194,31

Prepared according to the general procedure described above in 83% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.68 (ddt, *J* = 15.1, 11.4, 7.4 Hz, 1H), 5.10 – 4.91 (m, 2H), 2.49 – 2.13 (m, 4H), 1.97 – 1.80 (m, 1H), 1.81 – 1.56 (m, 6H), 1.48 – 1.34 (m, 1H), 1.32 – 1.16 (m, 3H), 1.04 – 0.92 (m, 1H), 0.88 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 215.26, 134.43, 117.77, 51.56, 39.39, 39.18, 36.68, 34.62, 27.34, 25.67,

23.45, 20.95, 14.13. HRMS m/z calcd. for $C_{13}H_{23}O_1$ $[M + H]^+$ 195.17434; found 195.17446.

The enantiomeric ratio was determined by chiral GC (T = 118 °C (27 min), t_R = 20.4 min (6.38 %), t_R = 20.8 min (93.62 %)).

❖ ***2-allyl-2-propylcyclohexanone (127)***



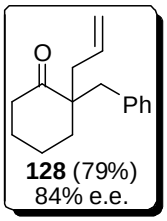
127 (78%)
86% e.e.

Chemical Formula: $C_{12}H_{20}O$
Molecular Weight: 180,29

Prepared according to the general procedure described above in 78% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.80 – 5.57 (m, 1H), 5.12 – 4.90 (m, 2H), 2.47 – 2.17 (m, 4H), 1.93 – 1.83 (m, 1H), 1.74 – 1.58 (m, 5H), 1.46 – 1.23 (m, 4H), 0.88 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 215.13, 134.42, 117.75, 51.70, 39.38, 39.27, 37.32, 36.66, 27.34, 20.96, 16.82, 14.86. HRMS m/z calcd. for $C_{12}H_{21}O_1$ $[M + H]^+$ 181.15869; found 181.15895.

The enantiomeric ratio was determined by chiral GC (T = 115 °C (30 min), t_R = 16.1 min (7.1 %), t_R = 16.5 min (92.9 %)).

❖ ***2-allyl-2-benzylcyclohexanone (128)***



128 (79%)
84% e.e.

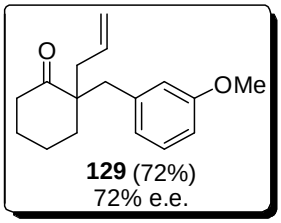
Chemical Formula: $C_{16}H_{20}O$
Molecular Weight: 228,33

Prepared according to the general procedure described above in 79% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.32 – 7.17 (m, 3H), 7.16 – 7.08 (m, 2H), 5.74 (ddt, *J* = 17.4, 10.3, 7.2, 1H), 5.08 (m, 2H), 2.91 (s, 2H), 2.53 – 2.37 (m, 2H), 2.29 (d, *J* = 7.2 Hz, 2H), 1.77 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 214.25, 137.69, 133.89,

130.72, 128.08, 126.42, 118.31, 52.69, 40.96, 39.72, 39.35, 35.65, 26.89, 20.93. HRMS m/z calcd. for $C_{16}H_{21}O_1$ $[M + H]^+$ 229.15869; found 229.15882.

The enantiomeric ratio was determined by chiral GC (T = 110-170 °C (1 °C/min), t_R = 52 min (91.8 %), t_R = 52.4 min (8.2 %)).

❖ ***2-allyl-2-(3-methoxybenzyl)cyclohexanone (129)***



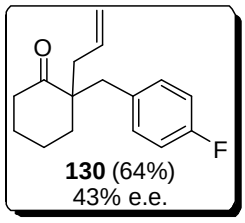
129 (72%)
72% e.e.

Chemical Formula: $C_{17}H_{22}O_2$
Molecular Weight: 258,36

Prepared according to the general procedure described above in 72% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.16 (t, *J* = 7.8 Hz, 1H), 6.80 – 6.63 (m, 3H), 5.73 (ddt, *J* = 17.5, 10.4, 7.2 Hz, 1H), 5.16 – 5.00 (m, 2H), 3.77 (s, 3H), 2.88 (s, 2H), 2.53 – 2.38 (m, 2H), 2.30 (d, *J* = 7.2 Hz, 2H), 1.90 – 1.61 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 214.19, 159.33, 139.32, 133.89, 128.96, 123.19, 118.31, 116.72, 111.56, 55.22, 52.68, 40.97, 39.70, 39.43, 35.74, 26.90, 20.95. HRMS m/z calcd. for $C_{17}H_{23}O_2$ $[M + H]^+$ 259.16926; found 259.16940.

The enantiomeric ratio was determined by chiral GC (T = 150 °C (40 min) to 170 °C (1 °C/min), t_R = 60.3 min (86.2 %), t_R = 60.6 min (13.8 %)).

❖ ***2-allyl-2-(4-fluorobenzyl)cyclohexanone (130)***



130 (64%)
43% e.e.

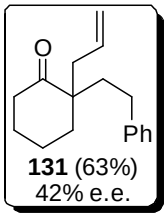
Chemical Formula: $C_{16}H_{19}FO$
Molecular Weight: 246,32

Prepared according to the general procedure described above in 64% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.16 – 7.01 (m, 2H), 7.01 – 6.85 (m, 2H), 5.70 (ddt, *J* = 17.3, 10.3, 7.2 Hz, 1H), 5.21 – 4.96 (m, 2H), 2.91 (d, *J* = 13.9 Hz, 1H), 2.82 (d, *J* = 13.9 Hz, 1H), 2.50 – 2.37 (m, 2H), 2.33 – 2.20 (m, 2H), 1.92 – 1.56 (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 213.87, 161.61 (d, *J* = 244.4 Hz), 133.50, 133.26 (d, *J* = 3.2 Hz), 131.98 (d, *J* = 7.7 Hz), 118.35, 114.75 (d, *J* = 21.0 Hz), 52.56, 40.01, 39.56, 39.40, 35.41, 26.69, 20.78. ^{19}F NMR (282 MHz, $CDCl_3$) δ = -116.95. HRMS m/z calcd. for $C_{16}H_{20}F_1O_1$ $[M + H]^+$ 247.14927; found 247.14935.

The enantiomeric ratio was determined by chiral GC (T 110-170 °C (1 °C/min), t_R = 53.8 min (71.6 %), t_R = 54.4 min (28.4 %)).

❖ ***2-allyl-2-phenethylcyclohexanone (131)***



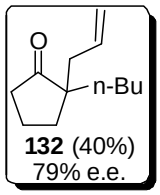
131 (63%)
42% e.e.

Chemical Formula: $C_{17}H_{22}O$
Molecular Weight: 242,36

Prepared according to the general procedure described above in 63% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.37 – 7.23 (m, 2H), 7.23 – 7.13 (m, 3H), 5.90 – 5.65 (m, 1H), 5.24 – 4.97 (m, 2H), 2.71 – 2.23 (m, 6H), 2.09 – 1.64 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 214.53, 142.37, 133.89, 128.42, 128.29, 125.86, 118.04, 51.52, 39.27, 39.08, 37.10, 36.53, 29.99, 27.19, 20.79. HRMS m/z calcd. for $C_{17}H_{23}O_1$ $[M + H]^+$ 243.17445; found 243.17434.

The enantiomeric ratio was determined by HPLC using Chiralcel OD-H column (Heptane/IPA : 99.9/0.1, 0.8 mL/min, 210 nm, t_R = 20.251 min (29.1 %), t_R = 20.527 min (70.9 %)).

❖ ***2-allyl-2-butylcyclopentanone (132)***



132 (40%)
79% e.e.

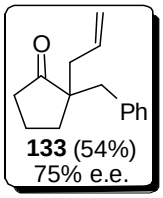
Chemical Formula: $C_{12}H_{20}O$
Molecular Weight: 180,29

Prepared according to the general procedure described above in 40% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.68 (ddt, *J* = 16.6, 10.5, 7.4 Hz, 1H), 5.09 – 4.99 (m, 2H), 2.25 – 2.09 (m, 4H), 1.96 – 1.77 (m, 4H), 1.42 – 1.36 (m, 2H),

1.34 – 1.19 (m, 4H), 0.87 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 223.1, 134.21, 118.18, 51.81, 39.96, 38.63, 35.29, 32.82, 26.43, 23.45, 18.90, 14.13. HRMS m/z calcd. for $C_{12}H_{21}O_1$ $[M + H]^+$ 181.15869; found 181.15901.

The enantiomeric ratio was determined by chiral GC (T = 100-140°C (1 ^oC/min), t_R = 19.6 min (10.5 %), t_R = 19.9 min (89.5 %)).

❖ ***2-allyl-2-benzylcyclopentanone (133)***



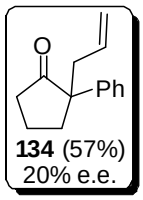
133 (54%)
75% e.e.

Chemical Formula: $C_{15}H_{18}O$
Molecular Weight: 214,30

Prepared according to the general procedure described above in 54% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.29 – 7.19 (m, 3H), 7.15 – 7.00 (m, 2H), 5.83 – 5.61 (m, 1H), 5.21 – 4.93 (m, 2H), 2.92 (d, *J* = 13.3 Hz, 1H), 2.60 (d, *J* = 13.3 Hz, 1H), 2.36 – 2.22 (m, 1H), 2.22 – 2.08 (m, 2H), 2.03 – 1.80 (m, 3H), 1.83 – 1.66 (m, 1H), 1.54 – 1.40 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 223.00, 137.92, 133.81, 130.42, 128.33, 126.59, 118.82, 53.36, 41.89, 41.08, 39.02, 31.18, 18.80. HRMS m/z calcd. for $C_{15}H_{19}O_1$ $[M + H]^+$ 215.14304; found 215.14324.

The enantiomeric ratio was determined by chiral GC (T = 121 ^oC (60 min) to 160 °C (1 ^oC/min), t_R = 71.1 min (87.4 %), t_R = 71.6 min (12.6 %)).

❖ ***2-allyl-2-phenylcyclopentanone (134)***



134 (57%)
20% e.e.

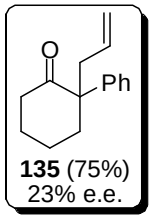
Chemical Formula: $C_{14}H_{16}O$
Molecular Weight: 200,28

Prepared according to the general procedure described above in 57% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.46 – 7.37 (m, 2H), 7.37 – 7.27 (m, 2H), 7.28 – 7.17 (m, 1H), 5.50 (ddt, *J* = 19.7, 9.5, 7.3 Hz, 1H), 5.11 – 4.84 (m, 2H), 2.66 – 2.49 (m, 2H), 2.49 – 2.42 (m, 1H), 2.35 – 2.23

(m, 2H), 2.16 – 2.05 (m, 1H), 2.00 – 1.74 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 219.11, 139.57, 133.98, 128.50, 126.80, 118.00, 56.48, 43.29, 37.66, 33.25, 18.55. HRMS m/z calcd. for $C_{14}H_{17}O_1$ $[M + H]^+$ 201.12744; found 201.12739.

The enantiomeric ratio was determined by HPLC using Chiralcel OJ-H column (Heptane/EtOH : 98/2, 0.8 mL/min, 210 nm, t_R = 10.433 min (40.37 %), t_R = 12.622 min (59.63 %)).

❖ ***2-allyl-2-phenylcyclohexanone (135)***



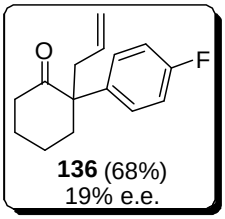
135 (75%)
23% e.e.

Chemical Formula: $C_{15}H_{18}O$
Molecular Weight: 214,30

Prepared according to the general procedure described above in 75% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.39 – 7.28 (m, 2H), 7.28 – 7.19 (m, 1H), 7.18 – 7.10 (m, 2H), 5.44 (dddd, *J* = 17.0, 10.3, 7.8, 6.9 Hz, 1H), 5.00 – 4.78 (m, 2H), 2.72 – 2.60 (m, 1H), 2.57 – 2.39 (m, 2H), 2.36 – 2.21 (m, 2H), 2.00 – 1.87 (m, 1H), 1.79 – 1.61 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 213.14, 140.66, 134.41, 128.89, 126.95, 126.82, 117.74, 56.95, 45.12, 40.23, 34.81, 28.35, 21.65. HRMS m/z calcd. for $C_{15}H_{19}O_1$ $[M + H]^+$ 215.14304; found 215.14308.

The enantiomeric ratio was determined by HPLC using Chiralcel OD-H column (Heptane/IPA : 99.9/0.1, 0.8 mL/min, 210 nm, t_R = 9.9 min (61.24 %), t_R = 10.7 min (38.76 %)).

❖ ***2-allyl-2-(4-fluorophenyl)cyclohexanone (136)***



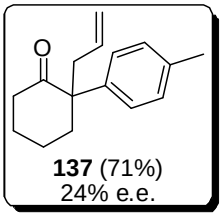
136 (68%)
19% e.e.

Chemical Formula: $C_{15}H_{17}FO$
Molecular Weight: 232,29

Prepared according to the general procedure described above in 68% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.19 – 6.92 (m, 4H), 5.41 (ddt, *J* = 10.2, 7.8, 7.4 Hz, 1H), 5.05 – 4.75 (m, 2H), 2.65 – 2.54 (m, 1H), 2.53 – 2.34 (m, 2H), 2.35 – 2.19 (m, 2H), 2.04 – 1.84 (m, 1H), 1.79 – 1.54 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 212.71, 161.56 (d, *J* = 246.0 Hz), 136.21 (d, *J* = 3.2 Hz), 133.94, 128.48 (d, *J* = 7.8 Hz), 117.93, 115.62 (d, *J* = 21.2 Hz), 56.29, 44.95, 39.97, 34.88, 28.14, 21.45. ^{19}F NMR (282 MHz, $CDCl_3$) δ = -116.00. HRMS m/z calcd. for $C_{15}H_{18}F_1O_1$ $[M + H]^+$ 233.13378; found 233.13362.

The enantiomeric ratio was determined by HPLC using Chiralcel OD-H column (Heptane/IPA : 99.9/0.1, 0.8 mL/min, 210 nm, t_R = 9.141 min (59.42 %), t_R = 9.697 min (40.58 %)).

❖ ***2-allyl-2-p-tolylcyclohexanone (137)***



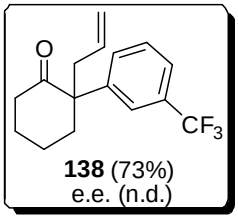
137 (71%)
24% e.e.

Chemical Formula: $C_{16}H_{20}O$
Molecular Weight: 228,33

Prepared according to the general procedure described above in 71% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.15 (d, *J* = 8.3 Hz, 2H), 7.03 (d, *J* = 8.3 Hz, 2H), 5.59 – 5.27 (m, 1H), 5.08 – 4.75 (m, 2H), 2.63 (dd, *J* = 14.0, 2.7 Hz, 1H), 2.54 – 2.37 (m, 2H), 2.37 – 2.20 (m, 5H), 1.95 – 1.87 (m, 1H), 1.82 – 1.54 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 213.22, 137.54, 136.30, 134.47, 129.49, 126.72, 117.50, 56.44, 45.01, 40.03, 34.72, 28.22, 21.54, 20.94. HRMS m/z calcd. for $C_{16}H_{20}O_1$ $[M + H]^+$ 229.15885; found 229.15869.

The enantiomeric ratio was determined by HPLC using Chiralcel OD-H column (Heptane/IPA : 99.9/0.1, 0.8 mL/min, 210 nm, t_R = 8.26 min (62.12 %), t_R = 8.93 min (37.88 %)).

❖ ***2-allyl-2-(3-(trifluoromethyl)phenyl)cyclohexanone (138)***



138 (73%)
e.e. (n.d.)

Chemical Formula: $C_{16}H_{17}F_3O$
Molecular Weight: 282,30

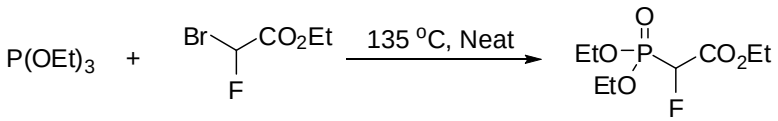
Prepared according to the general procedure described above in 73% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.63 – 7.27 (m, 4H), 5.42 (ddt, *J* = 17.2, 10.2, 7.4 Hz, 1H), 5.04 – 4.75 (m, 2H), 2.77 – 2.58 (m, 1H), 2.58 – 2.44 (m, 2H), 2.38 – 2.16 (m, 2H), 2.05 – 1.88 (m, 1H), 1.87 – 1.54 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 212.08, 131.18 (d, J = 32.1 Hz), 124.04 (d, J = 272.4 Hz), 123.71 (q, J = 15.0 Hz), 123.51 (q, J = 15.0 Hz), 141.75, 133.42, 130.47, 129.29, 118.38, 56.91, 44.80, 40.12, 34.62, 28.06, 21.43. ^{19}F NMR (282 MHz, $CDCl_3$) δ = -62.58. HRMS m/z calcd. for $C_{16}H_{18}F_3O_1$ $[M + H]^+$ 283.13078; found 283.13043.

We weren't able to successfully separate the two enantiomers by any HPLC or GC method.

II.5. Reaction's Limitations

II.5.1. α-Fluoroacrylates

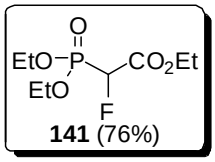
II.5.1.1.Synthesis of Substrate 141



139 **140** **141**, 76 %

Ethyl 2-bromo 2-fluoroacetate **140** (0.94 mL, 8.03 mmol, 0.98 eq.) was added to triethylphosphite **139** (1.43 mL, 8.2 mmol, 1 eq.) and heated at 130 °C for 24 h in a fractional distillation apparatus set-up. The resulting mixture was distilled under low pressure (1.4 mbar, 75-110 °C for 1h, using a bulb-to-bulb distillation apparatus), in order to remove any excess of the volatile starting material. The remaining yellowish oil yielded 1.48 g of the desired product **141** (76%).

❖ ***Ethyl 2-(diethoxyphosphoryl)-2-fluoroacetate (141)***



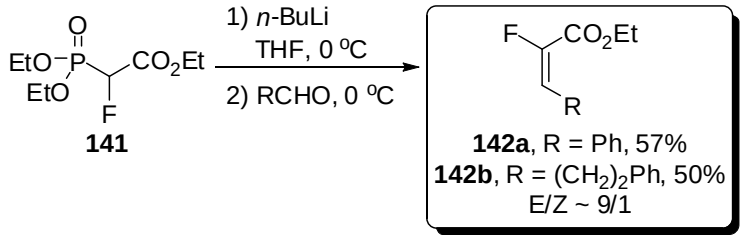
141 (76%)

Chemical Formula: $C_8H_{16}FO_5P$
Molecular Weight: 242,18

^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.20 (dd, *J* = 47.0, 12.5 Hz, 1H), 4.45 – 4.19 (m, 6H), 1.49 – 1.32 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 164.72 (d, *J* = 22 Hz), 84.94 (dd, *J* = 197, 159 Hz), 64.96 (t, *J* = 6.4 Hz), 62.11, 16.21 (d, *J* = 5.9 Hz), 14.01. ^{31}P NMR (121 MHz, $CDCl_3$) δ 10.10 (d, *J* = 71.8 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ -210.45 (d, *J* = 71.9 Hz).

Spectral data are identical to those reported in the literature (CAS: 2356-16-3).[10]

II.5.1.2.Synthesis of α-Fluoroacrylates 142a-b



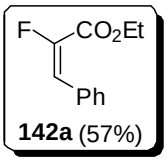
141

142a, R = Ph, 57%
142b, R = $(CH_2)_2$Ph, 50%
E/Z ~ 9/1

[10] M. Engman, J. S. Diesen, A. Paptchikhine, P. G. Andersson, *J. Am. Chem. Soc.* **2007**, *129*, 4536.

Ethyl 2-(diethoxyphosphoryl)-2-fluoroacetate **141** (2 mmol, 1 eq.) was dissolved in dry THF (2 mL) under argon. The solution was cooled to 0 °C and *n*-BuLi (1.6 M, 2.2 mmol, 1.1 eq.) was added. The solution was stirred for 1 h at 0 °C. The corresponding aldehyde (2.4 mmol, 1.2 eq.) was added and the solution was left overnight at room temperature. The reaction was quenched with a saturated aqueous solution of NH_4Cl and extracted three times with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. A sample of the obtained residue was analysed by ^1H NMR, and we determined an *E*/*Z* ratio of 9/1. The (*E*)-isomers of **142a-b** were successfully separated by column chromatography (petroleum ether/Et_2O, 99/1).

❖ ***(E)-ethyl 2-fluoro-3-phenylacrylate (142a)***



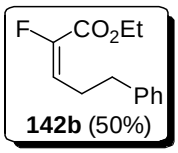
142a (57%)

Chemical Formula: $C_{11}H_{11}FO_2$
Molecular Weight: 194,20

^1H NMR (300 MHz, $CDCl_3$) δ = 7.54 – 7.30 (m, 5H), 6.92 (d, *J* = 22.2 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 1.24 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 160.52 (d, *J* = 36.1 Hz), 147.02 (d, *J* = 255.0 Hz), 131.03 (d, *J* = 9.4 Hz), 130.33 (d, *J* = 8.2 Hz), 129.65 (d, *J* = 2.7 Hz), 128.84, 128.72, 128.07, 121.49 (d, *J* = 25.8 Hz), 61.65, 13.89. ^{19}F NMR (282 MHz, $CDCl_3$) δ = -117.24.

Spectral data are identical to those reported in the literature (CAS: 20397-58-4).[10]

❖ ***(E)-ethyl 2-fluoro-5-phenylpent-2-enoate (142b)***



142b (50%)

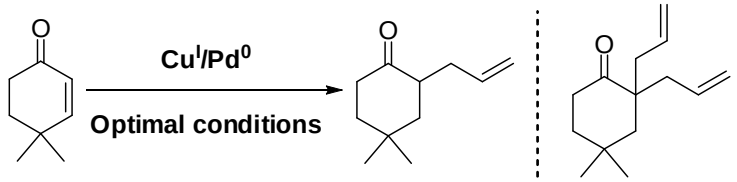
Chemical Formula: $C_{13}H_{15}FO_2$
Molecular Weight: 222,26

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.34 – 7.27 (m, 2H), 7.24 – 7.17 (m, 3H), 5.93 (dt, *J* = 21.3, 7.9 Hz, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 2.92 – 2.70 (m, 4H), 1.34 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 160.91 (d, *J* = 35.8 Hz), 160.67, 149.01, 145.67, 140.70, 128.45, 126.19, 122.37 (d, *J* = 18.5 Hz), 61.36, 35.28, 35.25, 27.15 (d, *J* = 5.0 Hz), 14.13. ^{19}F NMR (282 MHz, $CDCl_3$) δ = -121.74.

Spectral data are identical to those reported in the literature (CAS: 147410-72-8).[11]

II.5.2. Other Types of Ketones

II.5.2.1. Dual Catalysis Testing on 4,4-dimethyl-2-cyclohexenone



144
(*Not observed*)

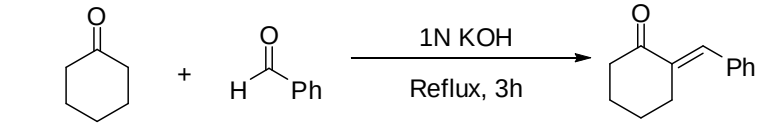
145, 91%

Testing was done using general procedure F. Optimal conversion (91%) to product **145** was obtained using IMesCuDBM (15 mg, 0.025 mmol, 0.05 eq.), $Pd(PPh_3)_4$ (5.8 mg, 0.005 mmol, 0.01 eq.), methyl allylcarbonate (0.14 mL, 1.15 mmol, 2.3 eq.), $Me(EtO)_2SiH$ (0.12 mL, 0.75 mmol, 1.5 eq.) and 1 mL of THF at 45 °C. Product **145** was always isolated along with the

[11] S. Sano, Y. Kuroda, K. Saito, Y. Ose, Y. Nagao, *Tetrahedron* **2006**, *62*, 11881.

diallylated DBM. No further attempts to ameliorate the purity of this product were performed as it wasn't the desired product. However, we were able to obtain a proper NMR analysis of the product. **2,2-diallyl-4,4-dimethylcyclohexanone (145) :** ^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.67 (ddt, *J* = 17.5, 10.3, 7.3 Hz, 2H), 5.11 – 4.96 (m, 4H), 2.40 (t, *J* = 6.9 Hz, 2H), 2.29 (d, *J* = 7.3 Hz, 4H), 1.68 (t, *J* = 7.1 Hz, 2H), 1.61 (s, 2H), 1.07 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 215.41, 133.94, 118.31, 50.38, 46.79, 41.66, 37.45, 35.94, 30.39, 30.29. HRMS m/z calcd. for $C_{14}H_{23}O_1$ $[M + H]^+$ 207.17456; found 207.17434.

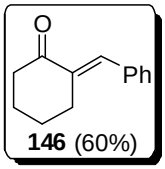
II.5.2.2.Synthesis of Substrate 146



Cyclohexanone **146**, 60 %

A mixture of benzaldehyde (2 mL, 20 mmol, 1 eq.), cyclohexanone (3.1 mL, 30 mmol, 1.5 eq.), and 1N KOH solution (33 mL) was refluxed for 3 h. After cooling, diethyl ether was added and the aqueous layer was separated and extracted three times with ether. The combined ethereal solution was washed to neutrality with water and dried over $MgSO_4$. The solvent was evaporated, and the product was purified by silica gel column chromatography (eluting with petroleum ether/AcOEt, 96/4) to obtain the desired product **146** as yellow solid (2.2309 g, 60%).

❖ ***(E)-2-benzylidenecyclohexanone (146)***



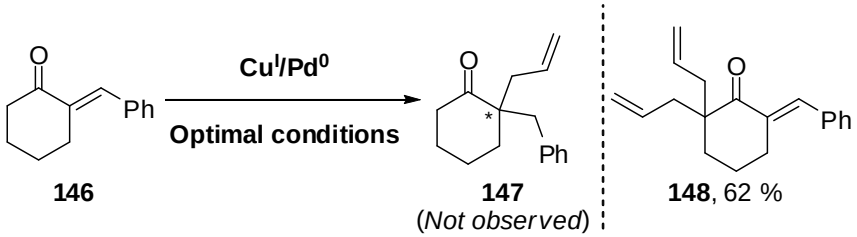
146 (60%)

Chemical Formula: $C_{13}H_{14}O$
Molecular Weight: 186,25

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.50 (t, *J* = 2.1 Hz, 1H), 7.43 – 7.28 (m, 5H), 2.84 (td, *J* = 6.5, 2.2 Hz, 2H), 2.54 (t, *J* = 6.7 Hz, 2H), 2.00 – 1.87 (m, 2H), 1.82 – 1.70 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 201.81, 136.71, 135.64, 135.59, 130.31, 128.53, 128.34, 40.35, 28.95, 23.90, 23.40.

Spectral data are identical to those reported in the literature (CAS: 5682-83-7).[12]

II.5.2.3.Dual Catalysis Testing on Substrate 146



146 **147** (*Not observed*) **148**, 62 %

Testing was done using general procedure F. Optimal conversion (62%) to product **148** was obtained using IMesCuDBM (15 mg, 0.025 mmol, 0.05 eq.), $Pd(OAc)_2$ (1.2 mg, 0.005 mmol, 0.01 eq.), dppe (5 mg, 0.0125 mmol, 0.025 eq.), methyl allylcarbonate (0.12 mL, 1 mmol, 2 eq.), $Me(EtO)_2SiH$ (0.12 mL, 0.75 mmol, 1.5 eq.) and 1 mL of THF at 45 °C. **(*E*)-2,2-diallyl-6-benzylidenecyclohexanone (148) :** ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.50 – 7.29 (m, 6H), 5.87 – 5.65 (m, 2H), 5.15 – 4.96 (m, 4H), 2.81 (td, *J* = 6.4, 1.8 Hz, 2H), 2.58 – 2.39 (m, 2H), 2.23 (dd, *J* = 13.8, 7.8 Hz, 2H), 1.92 – 1.69 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 205.60, 137.35, 135.91, 135.52,

[12] S. M. Lu, C. Bolm, *Angew. Chem. Int. Ed.* **2008**, *47*, 8920.

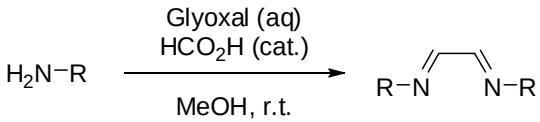
133.94, 130.14, 128.35, 128.30, 118.18, 50.35, 41.13, 32.12, 29.24, 19.66. HRMS m/z calcd. for $C_{19}H_{23}O_1$ $[M + H]^+$ 267.17489; found 267.17495.

III. Chapter 3: Synthesis, Characterisation and Reactivity of (Carbene)CuX Complexes

III.1. Synthesis of the Salt Precursors

III.1.1. Synthesis of Imidazolium Salts 155a-c

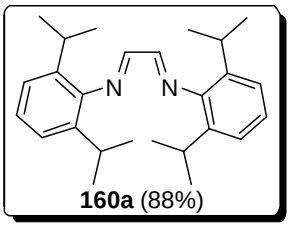
III.1.1.1. Synthesis of diimine 160a-b



159a-b **160a-b**

A round-bottomed flask was charged with the corresponding aniline **159a-b** (2 eq.) in MeOH. An aqueous solution of 40% glyoxal (1 eq.) was then introduced. After a minute, H_2CO_2 (0.1 eq.) was added dropwise. The solution was stirred overnight at room temperature, after which a yellow precipitate appeared. The solid was recovered by filtration and washed with MeOH to afford the desired diimine **160a-b** as a yellow solid.

❖ ***Glyoxal-bis-(2,6-diisopropylphenyl)imine (160a)***



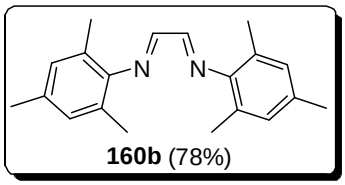
160a (88%)

Chemical Formula: $C_{26}H_{36}N_2$
Molecular Weight: 376,58

Prepared according to the general procedure described above in 88% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.11 (s, 2H), 7.21 – 7.03 (m, 6H), 2.93 (dd, *J* = 13.6, 6.8 Hz, 4H), 1.21 (d, *J* = 6.9 Hz, 24H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 163.05, 148.18, 136.64, 125.12, 123.09, 28.33, 22.43.

Spectral data are identical to those reported in the literature (CAS: 74663-75-5).[1]

❖ ***Glyoxal-bis-(2,4,6-trimethylphenyl)imine (160b)***



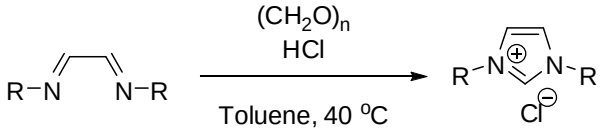
160b (78%)

Chemical Formula: $C_{20}H_{24}N_2$
Molecular Weight: 292,42

Prepared according to the general procedure described above in 78% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.12 (s, 2H), 6.93 (s, 4H), 2.31 (s, 6H), 2.18 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 163.61, 147.57, 134.38, 129.11, 126.68, 20.90, 18.35.

Spectral data are identical to those reported in the literature (CAS: 56222-36-7).[2]

III.1.1.2. Synthesis of 155a



160a **155a**

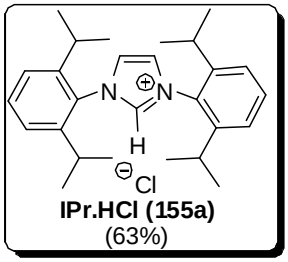
A three-necked flask, equipped with a reflux condenser, was charged with the diimine **160a** (2.825 g, 7.458 mmol, 1 eq.) in 56 mL of toluene, Paraformaldehyde 96% (0.226 g, 7.46 mmol, 1 eq.) was added in one portion to the mixture. The solution was stirred at 100 °C until maximum dissolution of the suspension was achieved (~ 1 hour). Afterwards, the mixture was cooled to 40 °C, and a solution of HCl (4M in dioxane, 1.9 mL, 7.46 mmol, 1 eq.) was slowly added dropwise. The solution was allowed to stir for 3

[1] T. Chivers, J. Konu, *Angew. Chem. Int. Ed.* **2009**, *48*, 3025.

[2] S. Shahane, L. Toupet, C. Fischmeister, C. Bruneau, *Euro. J. Inorg. Chem.* **2013**, *2013*, 54.

hours at 40 °C and then at room temperature overnight, after which a precipitate appeared. The solid was recovered by filtration and washed with THF to afford the desired product **155a** as a white solid (2.00 g, 63%).

❖ ***1,3-bis(2,6-diisopropylphenyl)-1H-imidazol-3-ium chloride (155a)***



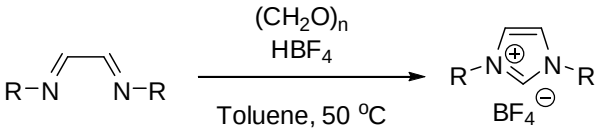
IPr.HCl (155a)
(63%)

Chemical Formula: $C_{27}H_{37}ClN_2$
Molecular Weight: 425,05

^{1}H NMR (300 MHz, $CDCl_3$) δ = 10.01 (s, 1H), 8.16 (s, 2H), 7.58 (t, *J* = 7.9 Hz, 2H), 7.35 (d, *J* = 7.8 Hz, 4H), 2.45 (dt, *J* = 13.6, 6.8 Hz, 4H), 1.30 (d, *J* = 6.8 Hz, 12H), 1.25 (d, *J* = 6.8 Hz, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 145.03, 132.22, 129.87, 126.86, 124.77, 29.18, 24.83, 23.79.

Spectral data are identical to those reported in the literature (CAS: 250285-32-6).[3]

III.1.1.3. Synthesis of 155b



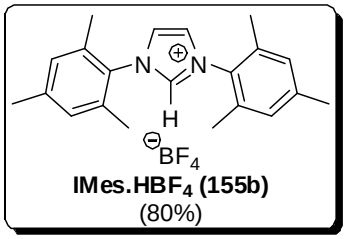
160b **155b**

A three-necked flask, equipped with a reflux condenser, was charged with the diimine **160b** (15 g, 51.3 mmol, 1 eq.) and paraformaldehyde 96% (1.621 g, 51.3 mmol, 1 eq.) in 300 mL of toluene. The solution was stirred at room temperature until a suspension was achieved. Afterwards, a solution of HBF_4 (50% in water, 6.4 mL, 51.3 mmol, 1 eq.) was slowly added dropwise, and

[3] a) J. Huang, S. P. Nolan, *J. Am. Chem. Soc.* **1999**, *121*, 9889; b) W. A. Herrmann, *Angew. Chem. Int. Ed.* **2000**, 39, 1602.

the mixture was stirred at 50 °C overnight, after which a precipitate appeared. The solid was recovered by filtration and washed with THF to afford the desired product **155b** as a white solid (16.05 g, 80%).

❖ ***1,3-dimesityl-1H-imidazol-3-ium tetrafluoroborate (155b)***



IMes.HBF$_4$ (155b)
(80%)

Chemical Formula: $C_{21}H_{25}BF_4N_2$
Molecular Weight: 392,24

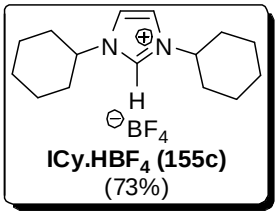
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.89 (s, 1H), 7.56 (s, 2H), 7.05 (s, 4H), 2.36 (s, 6H), 2.12 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 141.21, 137.06, 134.11, 130.45, 129.69, 125.25, 21.10, 17.89.

Spectral data are identical to those reported in the literature.[3]

III.1.1.4. Synthesis of 155c

A three-necked flask, equipped with a reflux condenser, was charged with paraformaldehyde 96% (0.975 g, 31.2 mmol, 1 eq.) in 30 mL of toluene. The solution was stirred and when a suspension was formed, the first equivalent of the cyclohexylamine **159c** (3.58 mL, 31.2 mmol, 1 eq.) was added. The flask was then placed in an ice bath and after 10 minutes, the second equivalent of cyclohexylamine **159c** (3.58 mL, 31.2 mmol, 1 eq.) was added. A solution of HBF_4 (50% in water, 3.88 mL, 31.2 mmol, 1 eq.) was added and the solution was allowed to stir at room temperature. Afterwards, a solution of 40% aqueous glyoxal (3.58 mL, 31.2 mmol, 1 eq.) was added, and the reaction was stirred at 50 °C for 20 hours, after which a precipitate appeared. The solution is cooled to room temperature, and the solid was recovered by filtration and washed with isopropanol to afford the desired product **155c** as a white solid (7.3 g, 73%).

❖ ***1,3-dicyclohexyl-1H-imidazol-3-ium tetrafluoroborate (155c)***

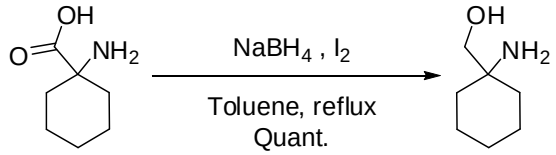


ICy.HBF$_4$ (155c)
(73%)

Chemical Formula: $C_{15}H_{25}BF_4N_2$
Molecular Weight: 320,18

IR (neat, cm^{-1}): 3147, 2958, 2937, 2860, 2356, 1554, 1446, 1423, 1365, 1269, 1191, 1161, 1145, 1118, 1053, 1024. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.92 (s, 1H), 7.45 (dd, *J* = 19.66, 1.67 Hz, 2H), 4.30 (tt, *J* = 11.89, 3.76 Hz, 2H), 2.26 – 1.12 (m, 20H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 133.4, 120.4, 60.2, 33.4, 25.1, 24.7. LRMS (APCI) (m/z): 233.21 (100%), 234.23 (16%), 151.06 (4%), 68.95 (3%). Spectral data are identical to those reported in the literature.[3]

III.1.1.5. Synthesis of IBiox6.HOTf[4]



162 **163**

A three-necked flask, equipped with a reflux condenser, was charged with amino acid **162** (5 g, 34.92 mmol, 1 eq.), $NaBH_4$ (3.17 g, 83.81 mmol, 2.4 eq.) and 92 mL of dry THF, under argon. Iodine (8.86 g, 34.92 mmol, 1 eq.) was then dissolved in 23 mL of dry THF and added dropwise at 0 °C to the above solution over 30 minutes, via an addition funnel. After the evolution of H_2 is complete, the solution was refluxed for 18 hours. The solution was then allowed to return to room temperature, and 25 mL of MeOH were

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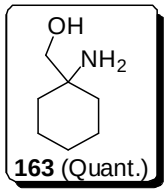
[4] a) G. Altenhoff, R. Goddard, C. W. Lehmann, F. Glorius, *J. Am. Chem. Soc*. **2004**, *126*, 15195, and references cited therein; b) S. Wurtz, C. Lohre, R. Frohlich, K. Bergander, F. Glorius, *J. Am. Chem. Soc.* **2009**, *131*, 8344, and references cited therein.

added to hydrolyze the reaction and dissolve the formed solid. Both solvents were then evaporated, and a 20% aqueous solution of KOH (75 mL) was added. This solution was stirred at room temperature for 4 hours, after which the aqueous solution was extracted with CH_2Cl_2 (3 x 75mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the desired amino alcohol **163** as a colourless oil (5 g, quantitative yield).

❖ ***(1-aminocyclohexyl)methanol (163)***

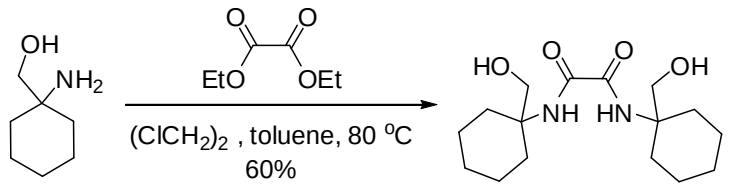


Chemical Formula: $C_7H_{15}NO$
Molecular Weight: 129,20

^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.32 (s, 2H), 2.00 (br. s, 3H), 1.51 – 1.34 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 70.1, 52.1, 35.5, 26.0, 21.9.

Spectral data are identical to those reported in the literature (CAS: 4313-56-8).[5]

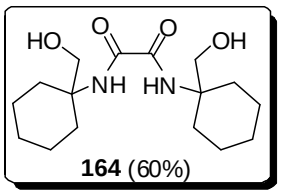
[5] US. Patent, WO2010/45166 A1, **2010**



163 **164**

A three-necked flask, equipped with a reflux condenser, was charged with amino alcohol **163** (5 g, 38.7 mmol, 2 eq.) in 145 mL of dichloroethane and 97 mL of toluene, under argon. The reaction mixture was stirred at room temperature and then diethyl oxalate (2.64 mL, 19.35 mmol, 1 eq.) was added. After the addition, the reaction mixture was stirred overnight at 80 °C. The solution was allowed to reach room temperature and then the solvent was concentrated *in vacuo*. The obtained residue was purified by column chromatography (silica gel, eluting with AcOEt, then AcOEt/*i*-PrOH, 9/1 to 8/2) to afford the desired product **164** as a white powder (3.61 g, 60%).

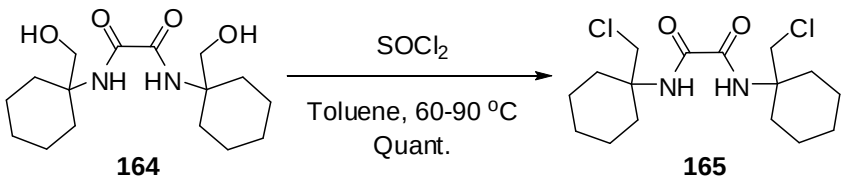
❖ ***N^1,N^2-bis(1-(hydroxymethyl)cyclohexyl)oxalamide (164)***



Chemical Formula: $C_{16}H_{28}N_2O_4$
Molecular Weight: 312,40

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.54 (s, 2H), 3.99 – 3.80 (m, 2H), 3.73 – 3.64 (m, 4H), 1.90 (d, *J* = 6.49 Hz, 2H), 1.61 – 1.29 (m, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.8, 68.2, 58.5, 31.8, 25.4, 21.4.

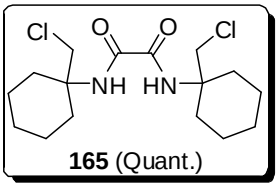
Spectral data are identical to those reported in the literature (CAS: 101725-44-4).[4]



164 **165**

A three-necked flask, equipped with a reflux condenser, was charged with substrate **164** (3.61 g, 11.55 mmol, 1 eq.) in 115 mL of toluene, under argon. The clear solution was stirred at 60 °C, and then $SOCl_2$ was added (2.43 mL, 33.51 mmol, 2.9 eq.). The solution was stirred for 1 hour at this temperature, and then at 90 °C for 3 hours. The brown solution was allowed to cool down to room temperature, after which it was separated into 2 portions (~ 60ml each). To each portion, it was added a 20% aqueous solution of KOH (100 mL for each portion). Each portion was extracted two times with a 100 mL of DCM. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the desired product **165** as a brown solid (4.04 g, quantitative yield).

❖ ***N^1,N^2-bis(1-(chloromethyl)cyclohexyl)oxalamide (165)***

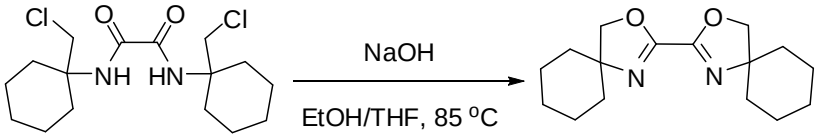


165 (Quant.)

Chemical Formula: $C_{16}H_{26}Cl_2N_2O_2$
Molecular Weight: 349,30

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.28 (s, 2H), 3.95 – 3.77 (m, 4H), 2.17 (dd, *J* = 16.0, 9.4 Hz, 4H), 1.71 – 1.20 (m, 16H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.2, 56.6, 49.3, 32.3, 25.3, 21.4.

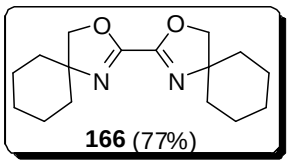
Spectral data are identical to those reported in the literature (CAS: 606970-66-5).[4]



165 **166**

A three-necked flask, equipped with a reflux condenser, was charged with substrate **165** (4.04 g, 11.56 mmol, 1 eq.) in 231 mL of THF, under argon. A solution of NaOH (0.97 g, 24.29 mmol, 2.1 eq.) in 64 mL of ethanol was then added at room temperature. Afterwards, the solution was stirred at 85 °C for 2 hours. After total consumption of the starting materiel (as indicated by TLC, eluting with petroleum ether/AcOEt, 50/50), the solution was allowed to cool down to room temperature and the solvent was then evaporated. MTBE (~650 mL) was added, and the organic phase was washed two times with a saturated solution of Na_2CO_3 (2 x 100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the desired product **166** as a yellow solid (2.14 g, 77%).

❖ ***Bis-oxazoline (166)***

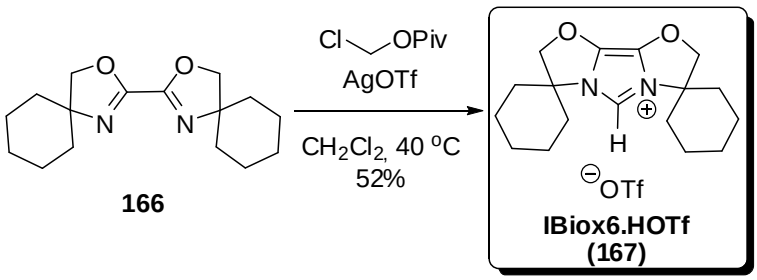


166 (77%)

Chemical Formula: $C_{16}H_{24}N_2O_2$
Molecular Weight: 276,37

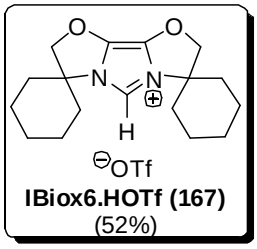
^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.17 (d, *J* = 20.26 Hz, 4H), 1.85-1.16 (m, 20H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 153.2, 78.1, 72.1, 37.2, 25.0, 22.7.

Spectral data are identical to those reported in the literature (CAS: 606970-67-6).[4]



A flame-dried Schlenk was charged with AgOTf (1.34 g, 5.24 mmol, 1.45 eq.) and chloromethylpivalate (0.76 mL, 5.24 mmol, 1.45 eq.) in 18 mL of DCM, under argon. The solution was stirred in the dark at room temperature for 1 hour. The supernatant solution was then cannulated to another Schlenk containing the *bis*-oxazoline **166** (1 g, 3.61 mmol, 1 eq.) in 1 mL of DCM. The reaction mixture was stirred overnight in the dark at 40 °C. The solvent was then concentrated *in vacuo*. The resulting yellow oil was first purified by column chromatography (silica gel, eluting with DCM/MeOH, 15/1) to afford an orange oil. The resulting oil was dissolved in the minimum amount of an ether/DCM (3/1) mixture (a clear homogenous solution should be obtained), and then a pentane/ether (9/1, cooled to -10 °C) mixture was added to precipitate the desired product. The solution was allowed to stand at 4 °C (refrigerator) for a few hours. The solid was recovered by filtration and washed with cold pentane to provide the desired product **167** as a brown solid (653,5 mg, 52%).

❖ ***IBiox6.HOTf (167)***



IBiox6.HOTf (167)
(52%)

Chemical Formula: $C_{18}H_{25}F_3N_2O_5S$
Molecular Weight: 438,46

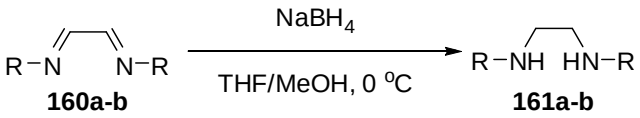
IR (neat, cm^{-1}): 3091, 2939, 2929, 2910, 2864, 1723, 1514, 1454, 1355, 1257, 1238, 1222, 1182, 1151, 1112, 1099, 1076, 1029. ^1H NMR (300 MHz, $CDCl_3$) δ = 9.08 (s, 1H), 4.78 (s, 4H), 2.27 – 2.13 (m, 4H), 2.01 – 1.86 (m, 8H), 1.67 – 1.43 (m, 4H), 1.39 –1.22 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 124.5, 113.7, 85.6, 67.5, 34.7, 23.6, 23.2. LRMS (APCI) (m/z): 289.12 (100%), 290.12 (22%).

Spectral data are identical to those reported in the literature (CAS: 606970-69-8).[4]

III.1.2. Synthesis of Imidazolidinium Salts 156a-c

Synthesis of diimine **160a-b** was performed using the same procedure described earlier (see Section III.1.1.1).

III.1.2.1. Synthesis of diamine 161a-b

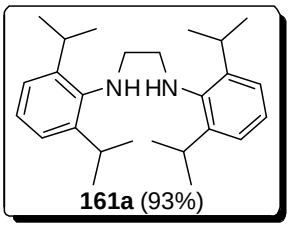


160a-b **161a-b**

A flame-dried round-bottomed flask was charged with diimine **160a-b** (1 eq.) in a mixture of MeOH/THF (40/60, 2.5 mL per mmol). $NaBH_4$ (10 eq.) was added in portions at 0 °C. After 3 h at room temperature, the solution turns white thus indicating the end of the reaction. A saturated solution of NH_4Cl (2.5 mL per mmol) was added, and the resulting mixture was extracted three times with ether. The combined organic phases were washed

with water, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the desired diamine **161a-b**.

❖ ***N^1,N^2-bis(2,6-diisopropylphenyl)ethane-1,2-diamine (161a)***



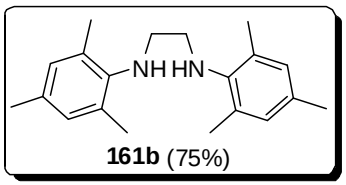
161a (93%)

Chemical Formula: $C_{26}H_{40}N_2$
Molecular Weight: 380,61

Prepared according to the general procedure described above in 93% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.33 – 7.11 (m, 6H), 3.53 – 3.46 (m, 6H), 3.18 (s, 4H), 1.27 (d, *J* = 6.8 Hz, 24H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 143.4, 142.5, 123.9, 123.6, 52.3, 27.8, 24.3.

Spectral data are identical to those reported in the literature (134030-22-1).[6]

❖ ***N^1,N^2-dimesitylethane-1,2-diamine (161b)***



161b (75%)

Chemical Formula: $C_{20}H_{28}N_2$
Molecular Weight: 296,45

Prepared according to the general procedure described above in 75% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.84 (s, 4H), 3.16 (s, 4H), 2.29 (s, 6H), 2.24 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 143.3, 131.5, 129.8, 129.5, 49.2, 20.6, 18.5.

Spectral data are identical to those reported in the literature (CAS: 134030-21-0).[6]

III.1.2.2. Synthesis of diamine 161c

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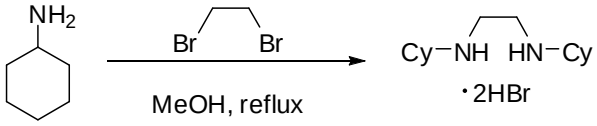
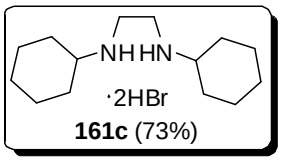
[6] a) A. J. Arduengo III, R. Krafczyk, R. Schmutzler, *Tetrahedron* **1999**, *55*, 14523, b) A. J., Arduengo III, U.S. Patent 5 077 414, **1991**; c) a) A. Aidouni, S. Bendahou, A. Demonceau, L. Delaude, *J. Comb. Chem.* **2008**, *10*, 886.



159c **161c**

A round-bottomed flask was charged with cyclohexylamine **159c** (23.08 mL, 201.66 mmol, 3 eq.) and 1,2-dibromoethane (5.81 mL, 67.22 mmol, 1 eq.) in 50 mL of methanol. The solution was refluxed and vigorously stirred overnight. The solvent was then concentrated *in vacuo* to provide a brown solid. The solid was triturated in 40 mL of acetone, filtered and washed with acetone to afford the desired product **161c** as a white solid (19.02 g, 73%).

❖ ***N^1,N^2-bis-(cyclohexylamino)ethane dihydrobromide (161c)***



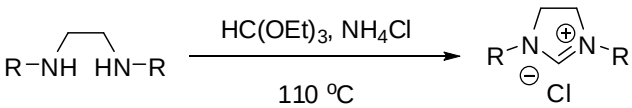
161c (73%)

Chemical Formula: $C_{14}H_{30}Br_2N_2$
Molecular Weight: 386,21

Prepared according to the general procedure described above in 73% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.25 (s, 4H), 3.07 – 3.05 (m, 2H), 2.03 – 1.09 (m, 22H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 56.5, 30.8, 29.2, 25.2, 24.3.

Spectral data are identical to those reported in the literature.[7]

III.1.2.3. Synthesis of 156a-b



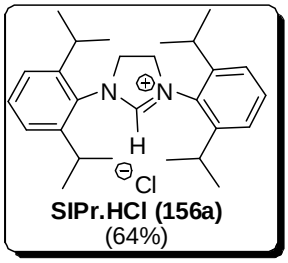
161a-b **156a-b**

A three-necked flask, equipped with a reflux condenser, was charged sequentially with diamine **161a-b** (1 eq.), triethylorthoformate (2.5 eq.) and pulverised $NH_4Cl_{(s)}$ (1.1 eq.). The reaction mixture was stirred at 110 °C for

[7] S. P. Roche, M.-L. Teyssot, A. Gautier, *Tetrahedron Lett.* **2010**, *51*, 1265.

2 hours, after which the excess of triethylorthoformate was evaporated under high vacuum to afford a solid residue. The resulting solid was dissolved in $CHCl_3$, and re-precipitated by adding ether. The solid was recovered by filtration and washed with cold ether to provide the desired salt **156a-b**.

❖ ***1,3-bis(2,6-diisopropylphenyl)-4,5-dihydro-1H-imidazol-3-ium chloride (156a)***



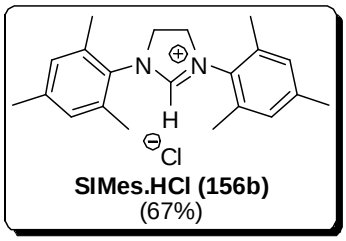
SIPr.HCl (156a)
(64%)

Chemical Formula: $C_{27}H_{39}ClN_2$
Molecular Weight: 427,06

Prepared according to the general procedure described above in 64% yield. IR (neat, cm^{-1}): 3188, 2964, 2933, 2918, 2858, 2736, 2364, 1614, 1583, 1490, 1456, 1442, 1388, 1365, 1325, 1311, 1284, 1255, 1242, 1230, 1182, 1012. ^1H NMR (300 MHz, $CDCl_3$) δ = 8.37 (s, 1H), 7.50 – 7.26 (m, 6H), 4.84 (s, 4H), 3.01 (Sept, *J* = 6.9 Hz, 4H), 1.39 (d, *J* = 6.8 Hz, 12H), 1.25 (d, *J* = 6.8 Hz, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 158.2, 131.6, 129.2, 125.0, 55.4, 29.2, 25.5, 23.8. LRMS (APCI) (m/z): 391.35 (100%), 363.19 (89%), 186.20 (59%), 392.35 (28%), 364.21 (23%), 427.34 (18%).

Spectral data are identical to those reported in the literature.[6]

❖ ***1,3-dimesityl-4,5-dihydro-1H-imidazol-3-ium chloride (156b)***



SIMes.HCl (156b)
(67%)

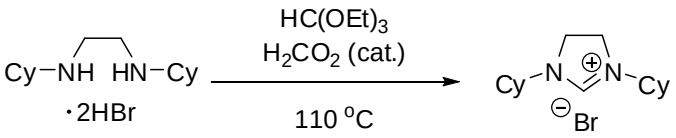
Chemical Formula: $C_{21}H_{27}ClN_2$
Molecular Weight: 342,91

Prepared according to the general procedure described above in 67% yield. IR (neat, cm^{-1}): 3338, 3249, 2956, 2939, 2920, 2904, 2852, 2358, 2322, 1625, 1483, 1461, 1380, 1309, 1265, 1220, 1199, 1151, 1035, 1014. ^1H NMR (300 MHz, $CDCl_3$) δ = 9.39 (s, 1H), 6.87 (s, 4H), 4.50 (s, 4H), 2.39 – 2.27

(m, 12H), 2.23 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.8, 135.0, 130.1, 51.9, 21.1, 18.0. LRMS (APCI) (m/z): 279.16 (100%), 307.30 (40%), 134.15 (38%), 280.19 (19%), 343.20 (17%).

Spectral data are identical to those reported in the literature.[6]

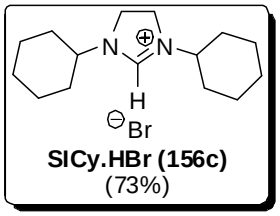
III.1.2.4. Synthesis of 156c



161c **SICy.HBr (156c)**

A three-necked flask, equipped with a distillation apparatus, was charged with substrate **161c** (5 g, 12.95 mmol, 1 eq.), a few drops of H_2CO_2 and triethylorthoformate (5.4 mL, 32.38 mmol, 2.5 eq.). The solution was stirred at 110 °C until no more ethanol distilled (~1.5 hour). The flask was then placed in an ice bath, and after 45 minutes, the mixture was filtered to recover the desired product **156c** as a white solid. Ether was added to the filtrate to further precipitate the desired product. The latter was also filtered and recovered. This operation was repeated two times and all the collected solids were combined to give the desired product **156c** in a 73% yield (2.56 g).

❖ ***1,3-dicyclohexyl-4,5-dihydro-1H-imidazol-3-ium bromide (156c)***



SICy.HBr (156c)
(73%)

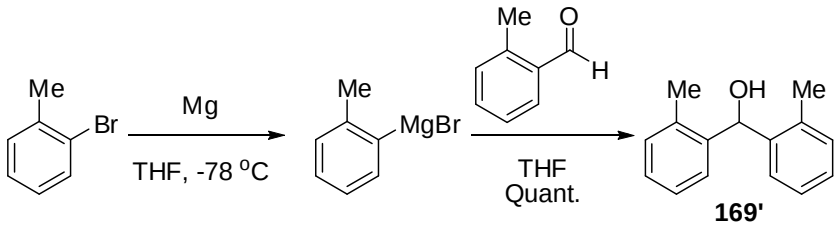
Chemical Formula: $C_{15}H_{27}BrN_2$
Molecular Weight: 315,29

IR (neat, cm^{-1}): 3022, 2937, 2925, 2918, 2902, 2875, 2850, 2360, 1639, 1514, 1448, 1402, 1377, 1348, 1336, 1307, 1276, 1238, 1190, 1151, 1114, 1089, 1049, 1031, 1004. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.37 (s, 1H), 3.97 (s, 4H), 3.80 (tt, *J* = 11.5, 3.6 Hz, 2H),

2.06 – 1.04 (m, 20H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 155.5, 57.5, 45.6, 31.1, 24.8. LRMS (APCI) (m/z): 235.28 (100%), 236.30 (13%).
Spectral data are identical to those reported in the literature.[6]

III.1.3. Synthesis of Chiral NHC Salts

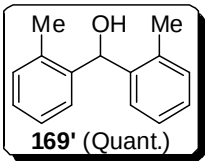
III.1.3.1. Synthesis of 169b



169'

A three-necked flask, equipped by a reflux condenser, was charged sequentially with solid magnesium (1.31 g, 54 mmol, 1.8 eq.), 2 or 3 iodine granules and distilled THF (50 mL), under argon. The mixture was refluxed for 30 minutes until the coloration disappeared. The temperature was cooled to 60 °C and *o*-bromotoluene (5.4 mL, 45 mmol, 1.5 eq.), diluted in THF (5 mL), was added at a rate of 1ml every 6 minutes. The mixture was then refluxed for one hour. In another flask, was prepared a solution of *o*-tolualdehyde (3.5 mL, 30 mmol, 1.0 eq.) in THF (30 mL) which was cooled down to -78°C. The first mixture solution was cooled down to 0°C and the supernatant was added dropwise to the second one at -78°C. The solution was then stirred for 1h30 at room temperature. The reaction progress was followed by TLC. The mixture was quenched with saturated NH_4Cl at 0°C. The aqueous layer was extracted two times with AcOEt. The combined organic layers were washed once with water and twice with brine. They were then dried over $MgSO_4$ and concentrated *in vacuo*. This procedure provided **169'** as a white solid with a quantitative yield (6.84 g).

❖ ***Di-o-tolylmethanol (169')***

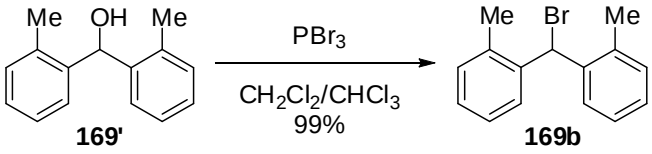


169' (Quant.)

Chemical Formula: $C_{15}H_{16}O$
Molecular Weight: 212,29

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.33 – 7.27 (m, 2H), 7.24 – 7.13 (m, 6H), 6.15 (s, 1H), 2.29 (s, 6H), 1.95 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 140.81, 135.86, 130.49, 127.62, 126.49, 126.11, 70.28, 19.09.

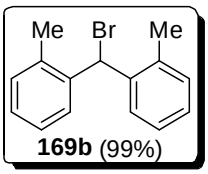
Spectral data are identical to those reported in the literature (CAS: 2845-91-2).



169' **169b**

A round-bottomed three-necked flask was charged sequentially with alcohol **169'** (3.80 g, 18 mmol, 1.0 eq.), chloroform (20 mL) and dichloromethane (20 mL). Phosphorus tribromide (3.9 mL, 21.4 mmol, 1.2 eq.) was slowly added at a rate of 1 mL every 10 minutes, at 0 °C. The reaction mixture was then stirred at room temperature and followed by TLC. After 5 hours, the mixture was hydrolyzed with water at 0 °C. The aqueous layer was extracted two times with CH_2Cl_2. The combined organic layers were washed with saturated $NaHCO_3$ and brine. They were then dried over $MgSO_4$ and concentrated *in vacuo*. This procedure provided **169b** as a white solid with a yield of 99% (4.88 g).

❖ ***2,2'-(bromomethylene)bis(methylbenzene) (169b)***



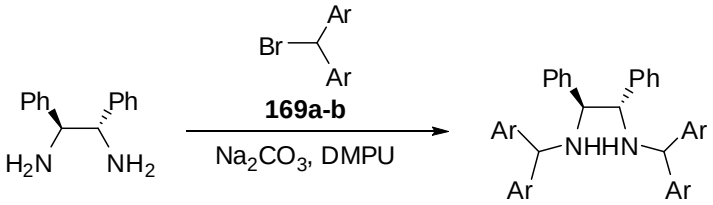
169b (99%)

Chemical Formula: $C_{15}H_{15}Br$
Molecular Weight: 275,18

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.56 – 7.46 (m, 2H), 7.24 – 7.10 (m, 6H), 6.58 (s, 1H), 2.32 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 138.48, 135.14, 130.51, 129.62, 128.12, 126.46, 50.82, 19.18.

Spectral data are identical to those reported in the literature (CAS: 60973-62-8).[8]

III.1.3.2. Synthesis of diamine 170a-b



168

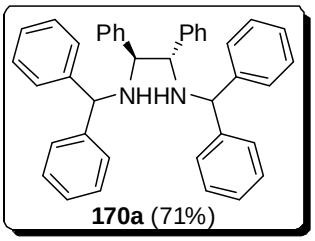
170a, 71%
170b, 62%

A round-bottomed three-necked flask, equipped by a reflux condenser, was charged sequentially with (1*S*,2*S*)-1,2-diphenylethane-1,2-diamine **168** (1.0 eq.), sodium carbonate (4.0 eq.), the corresponding bromide **169a-b** (2.4 eq.) and DMPU. The mixture was stirred for 4 hours at 120 °C. It was then slowly hydrolyzed. The aqueous layer was extracted three times with AcOEt. The combined organic layers were washed with water and brine. They were then dried over $MgSO_4$ and concentrated *in vacuo*. Purification

[8] a) Y. Matsumoto, K. Yamada, K. Tomioka, *J. Org. Chem.* **2008**, *73*, 4578; b) K. B. Selim, Y. Matsumoto, K. Yamada, K. Tomioka, *Angew. Chem. Int. Ed.* **2009**, *48*, 8733.

by column chromatography (hexane/AcOEt, 95/5) provided the desired product **170a-b.**

❖ ***(1S,2S)-N^1,N^2-dibenzhydryl-1,2-diphenylethane-1,2-diamine (170a)***



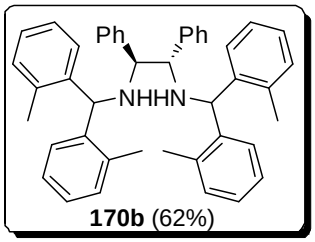
170a (71%)

Chemical Formula: $C_{40}H_{36}N_2$
Molecular Weight: 544,73

Prepared according to the general procedure described above in 71% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.31 – 7.18 (m, 20H), 7.16 – 7.12 (m, 6H), 6.98 – 6.96 (m, 4H), 4.53 (s, 2H), 3.64 (s, 2H), 2.72 (br. s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 142.7, 138.3, 129.2, 128.5, 128.2, 127.9, 127.5, 126.2, 61.6, 58.5.

Spectral data are identical to those reported in the literature.[8]

❖ ***(1S,2S)-N^1,N^2-bis(dio-tolylmethyl)-1,2-diphenylethane-1,2-diamine (170b)***



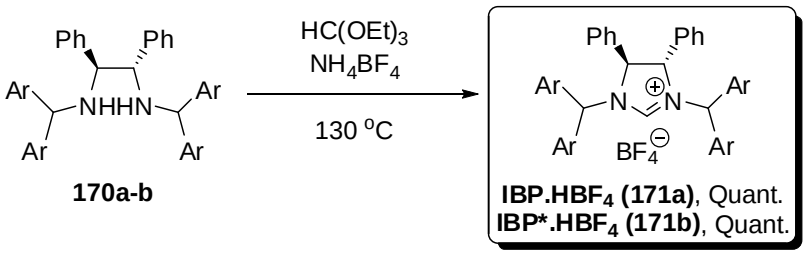
170b (62%)

Chemical Formula: $C_{44}H_{44}N_2$
Molecular Weight: 600,83

Prepared according to the general procedure described above in 62% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.74 (d, *J* = 7.2 Hz, 2H), 7.21 – 7.04 (m, 20H), 6.92 (dd, *J* = 6.4, 2.9 Hz, 4H), 4.85 (s, 2H), 3.78 (s, 2H), 2.55 (br. s, 2H), 1.99 (s, 6H), 1.82 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 141.3, 140.2, 136.4, 136.3, 130.5, 130.3, 128.5, 128.4, 127.8, 127.7, 127.0, 126.7, 126.4, 125.9, 125.8, 65.9, 55.80, 19.1, 19.0.

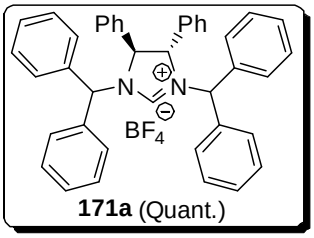
Spectral data are identical to those reported in the literature.[8]

III.1.3.3. Synthesis of 171a-b



A round-bottomed three-necked flask, equipped by a reflux condenser, was charged sequentially with the diamine **170a-b** (1.0 eq.), NH_4BF_4 (1.1 eq.), and triethylorthoformate. The mixture was stirred for 4 hours at 130 °C. The yellow solution was filtered and washed with a small amount of CH_2Cl_2. The filtrate was concentrated, and azeotropic evaporation with toluene provided a light yellow solid. The solid was washed with cold diethyl ether and dried *in vacuo* to afford the desired salt **171a-b**.

❖ ***IBP.HBF$_4$ (171a)***

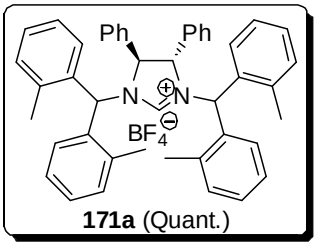


Chemical Formula: $C_{41}H_{35}BF_4N_2$
Molecular Weight: 642,53

Prepared according to the general procedure described above in a quantitative yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.48 – 7.38 (m, 10H), 7.37 – 7.23 (m, 15H), 7.17 (d, *J* = 7.6 Hz, 6H), 5.66 (s, 2H), 5.05 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 156.0, 134.7, 134.2, 133.9, 130.3, 130.0, 129.6, 129.5, 129.4, 129.3, 128.9, 128.0, 127.7, 74.1, 65.6.

Spectral data are identical to those reported in the literature.[8]

❖ ***IBP*.HBF$_4$ (171b)***



171a (Quant.)

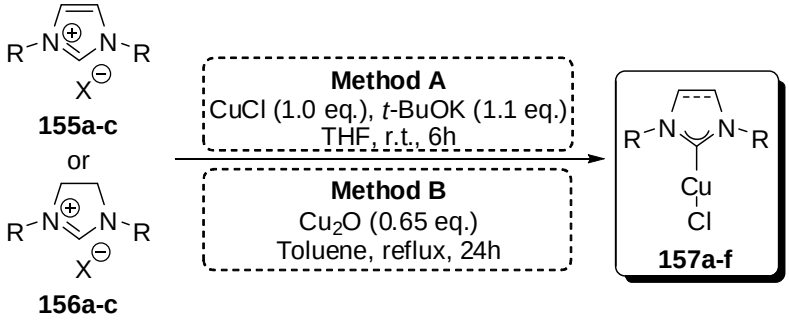
Chemical Formula: $C_{45}H_{43}BF_4N_2$
Molecular Weight: 698,64

Prepared according to the general procedure described above in a quantitative yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.59 (t, *J* = 7.5 Hz, 2H), 7.48 – 7.40 (m, 8H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.24 – 7.08 (m, 10H), 7.02 (t, *J* = 7.2 Hz, 2H), 6.89 (d, *J* = 7.7 Hz, 2H), 6.78 (s, 1H), 5.77 (s, 2H), 5.32 (s, 2H), 2.27 (s, 6H), 1.75 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 154.6, 136.8, 136.4, 132.6, 131.8, 131.75, 131.7, 131.5, 130.9, 130.0, 129.7, 129.2, 128.8, 128.4, 127.2, 127.0, 126.8, 73.32, 58.13, 18.9, 18.6.

Spectral data are identical to those reported in the literature.[8]

III.2. Synthesis of the (NHC)CuCl Complexes

III.2.1. Synthesis of Complexes 157a-f and 172



❖ ***Method A***[9a,b]

A flame-dried Schlenk was charged with *t*-BuOK (1.1 eq.), the NHC salt (1.0 eq.) and CuCl (1.0 eq.) under argon. Anhydrous THF was added. The mixture was stirred for 3 hours at room temperature. It was then filtered over a bed of celite (eluting with THF), concentrated *in vacuo* until a suspension appeared (should not evaporate all the solvent). Hexane was then added to precipitate the complex, and the mixture was allowed to stand at room temperature for 1 hour. The solid was recovered by filtration and washed with cold hexane to provide the desired complex **157a-f**.

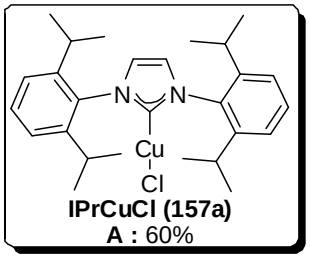
❖ ***Method B***[9c]

A round-bottomed flask, equipped with a reflux condenser, was charged with copper oxide (0.65 eq.) and the NHC salt (1 eq.). The flask was purged with argon prior to addition of toluene (2 mL per mmol). The reaction mixture was stirred at reflux for 24 hours. The solvent was then evaporated *in vacuo*, and the crude solid was dissolved in DCM and filtered over a bed of celite (eluting with DCM). The obtained filtrate was concentrated *in vacuo* until a suspension appeared (should not evaporate all the solvent). Hexane was then added to precipitate the complex, and the mixture was allowed to stand at room temperature for 1 hour. The solid was recovered by filtration and washed with cold hexane to provide the desired complex **157d-e**.

---

[9] a) S. P. Nolan, *J. of Organometallic Chem.* **2000**, *606*, 49; b) a) H. Kaur, F. K. Zinn, E. D. Stevens, S. P. Nolan, *Organometallics* **2004**, *23*, 1157; c) S. J. Cazin, *Dalton Trans.* **2010**, *39*, 4489.

❖ ***IPrCuCl (157a)***



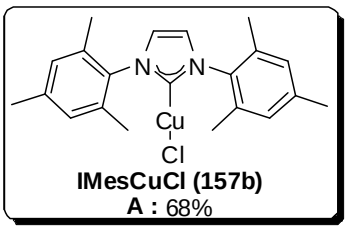
IPrCuCl (157a)
A : 60%

Chemical Formula: $C_{27}H_{36}ClCuN_2$
Molecular Weight: 487,60

Prepared according to method **A** in 60% yield. ^{1}H NMR (300 MHz, C_6D_6) δ = 7.20 (d, *J* = 8.3 Hz, 2H), 7.04 (d, *J* = 7.6 Hz, 4H), 6.21 (s, 2H), 2.53 (dt, *J* = 13.8, 6.9 Hz, 4H), 1.34 (d, *J* = 6.9 Hz, 12H), 1.05 (d, *J* = 6.9 Hz, 12H). ^{13}C NMR (75 MHz, CD_2Cl_2) δ = 180.6, 145.6, 134.4, 130.6, 124.2, 123.2, 28.8, 24.9, 23.9.

Spectral data are identical to those reported in the literature.[9]

❖ ***IMesCuCl (157b)***



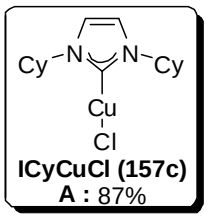
IMesCuCl (157b)
A : 68%

Chemical Formula: $C_{21}H_{24}ClCuN_2$
Molecular Weight: 403,44

Prepared according to method **A** in 68% yield. IR (neat, cm^{-1}): 3494, 3448, 3265, 3136, 3026, 2977, 2964, 2341, 2329, 1608, 1595, 1487, 1436, 1400, 1377, 1338, 1282, 1265, 1234, 1201. ^{1}H NMR (300 MHz, CD_2Cl_2) δ = 7.05 (s, 2H), 7.00 (s, 4H), 2.35 (s, 6H), 2.10 (s, 12H). ^{13}C NMR (75 MHz, CD_2Cl_2) δ = 178.81, 139.52, 135.21, 134.51, 129.50, 122.33, 21.13, 17.74. LRMS (APCI) (m/z): 385.17 (100%), 453.14 (32%), 451.17 (26%), 321.19 (23%), 303.21 (13%), 89.11 (13%).

Spectral data are identical to those reported in the literature.[9]

❖ ***ICyCuCl (157c)***



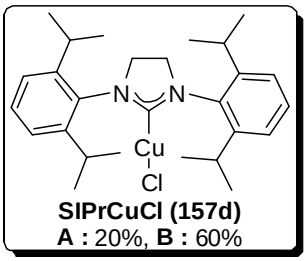
ICyCuCl (157c)
A : 87%

Chemical Formula: $C_{15}H_{24}ClCuN_2$
Molecular Weight: 331,37

Prepared according to method **A** in 87% yield. IR (neat, cm^{-1}): 2923, 2904, 2889, 2854, 1668, 1558, 1448, 1425, 1409, 1382, 1348, 1280, 1265, 1238, 1199, 1029. ^{1}H NMR (300 MHz, CD_2Cl_2) δ = 6.96 (s, 2H), 4.25 (t, *J* = 11.81 Hz, 2H), 2.08-1.19 (m, 20H). ^{13}C NMR (75 MHz, CD_2Cl_2) δ = 173.5, 117.6, 61.3, 34.7, 25.5, 25.1. LRMS (APCI) (m/z): 380.92 (100%), 379.04 (81%), 327.17 (73%), 382.95 (50%), 328.96 (48%), 233.06 (42%), 313.06 (36%), 267.07 (34%), 150.99 (27%).

Spectral data are identical to those reported in the literature.[9]

❖ ***SIPrCuCl (157d)***



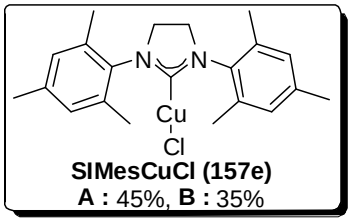
SIPrCuCl (157d)
A : 20%, **B :** 60%

Chemical Formula: $C_{27}H_{38}ClCuN_2$
Molecular Weight: 489,61

Prepared according to method **A** in 20% yield and method **B** in 60% yield. ^{1}H NMR (300 MHz, CD_2Cl_2) δ = 7.41 (t, *J* = 8 Hz, 2H), 7.25 – 7.23 (m, 4H), 4.02 (s, 4H), 3.07 (sept, *J* = 7 Hz, 4H), 1.37 (d, *J* = 7 Hz, 12H), 1.35 (d, *J* = 7 Hz, 12H). ^{13}C NMR (75 MHz, CD_2Cl_2) δ = 204.3, 163.3, 146.8, 130.1, 124.7, 112.1, 29.2, 25.7.

Spectral data are identical to those reported in the literature.[9]

❖ ***SMesCuCl (157e)***



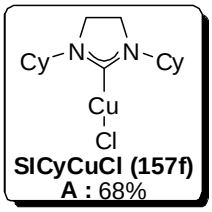
SIMesCuCl (157e)
A : 45%, **B :** 35%

Chemical Formula: $C_{21}H_{26}ClCuN_2$
Molecular Weight: 405,45

Prepared according to method **A** in 45% yield and method **B** in 35% yield. ^{1}H NMR (300 MHz, CD_2Cl_2) δ = 6.99 (s, 4H), 3.95 (s, 4H), 2.31 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 201.8, 138.9, 136.3, 135.5, 129.9, 51.9, 21.3, 18.5.

Spectral data are identical to those reported in the literature.[9]

❖ ***SICyCuCl (157f)***

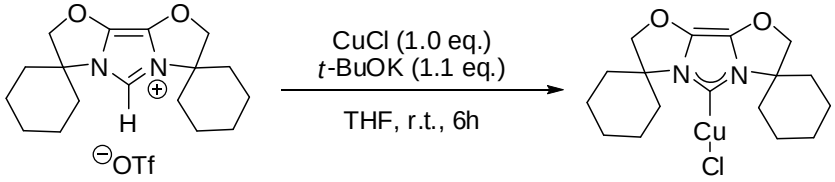


SICyCuCl (157f)
A : 68%

Chemical Formula: $C_{15}H_{26}ClCuN_2$
Molecular Weight: 333,39

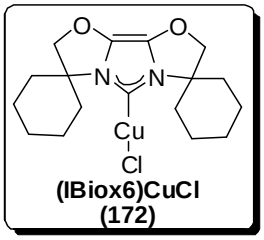
Prepared according to method **A** in 68% yield. IR (neat, cm^{-1}): 3134, 3043, 2987, 2894, 2883, 1666, 1643, 1573, 1554, 1487, 1373, 1346, 1332, 1271, 1245, 1188. ^{1}H NMR (300 MHz, CD_2Cl_2) δ = 3.79 (tt, *J* = 11.78, 3.60 Hz, 2H), 3.47 (s, 4H), 1.81-1.07 (m, 20H). ^{13}C NMR (75 MHz, CD_2Cl_2) δ = 191.9, 59.7, 51.4, 32.1, 25.7, 25.3.

Spectral data are identical to those reported in the literature.[9]



IBiox6.HOTf (167) → **(IBiox6)CuCl (172)**

❖ ***(IBiox6)CuCl (172)***



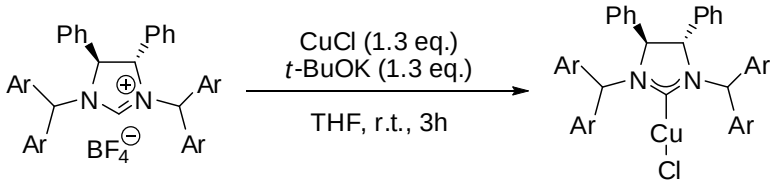
(IBiox6)CuCl (172)

Chemical Formula: $C_{17}H_{24}ClCuN_2O_2$
Molecular Weight: 387,39

Prepared according to method **A**. IR (neat, cm^{-1}): 2916, 2898, 2852, 2356, 2337, 1737, 1469, 1452, 1429, 1353, 1340, 1215, 1097, 1068. ^{1}H NMR (300 MHz, CD_2Cl_2) δ 4.66 (s, 4H), 2.26-2.07 (m, 4H), 1.99-1.86 (m, 8H), 1.28 (td, *J* = 16.0, 7.0 Hz, 8H). ^{13}C NMR (75 MHz, CD_2Cl_2) δ = 205.9, 123.7, 84.8, 63.3, 36.4, 24.4, 23.6.

Spectral data are identical to those reported in the literature.[10]

III.2.2. Synthesis of the Chiral (NHC)CuCl Complexes

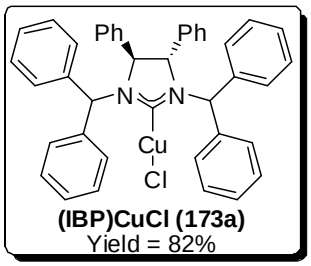


171a-b **173a-b**

A flame-dried Schlenk was charged sequentially with *t*-BuOK (1.3 eq.), the NHC salt (1.0 eq.), CuCl (1.3 eq.) and distilled THF. The mixture was stirred for 3 hours at room temperature. It was then filtered over a bed of celite, concentrated *in vacuo* and purified by column chromatography (DCM/ethanol, 99/1).

❖ ***Synthesis of [(4S,5S)-1,3-Dibenzylhydryl-4,5-diphenylimidazolidin-2-ylidene]copper(I) chloride [(IBP)CuCl] (173a)***

[10] K. Vehlow, M. Porta, S. Blechert, *ChemCatChem* **2010**, *2*, 803.



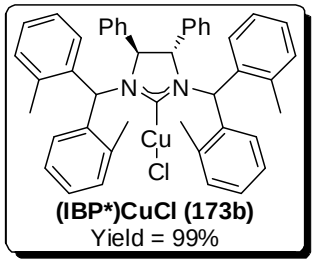
(IBP)CuCl (173a)
Yield = 82%

Chemical Formula: $C_{41}H_{34}ClCuN_2$
Molecular Weight: 653,73

Prepared according to the general procedure described above from (IBP).HBF_4 (1.00 g, 1.60 mmol), *t*-BuOK (229 mg, 2.05 mmol), CuCl (202 mg, 2.04 mmol) and THF (18 mL). Purification by column chromatography (CH_2Cl_2/ethanol, 99/1) afforded the desired product as a white solid (0.84 mg, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.50 – 7.42 (m, 6H), 7.38 – 7.36 (m, 10H), 7.32 – 7.30 (m, 6H), 7.11 – 7.05 (m, 8H), 5.41 (s, 2H), 4.56 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 198.5, 138.3, 138.0, 136.8, 129.5 129.3, 129.2, 128.8, 128.6, 127.7, 74.5, 65.1.

Spectral data are identical to those reported in the literature.[8]

❖ ***Synthesis of [(4S,5S)-1,3-Bis(bis(2-methylphenyl)methyl)-4,5-diphenylimidazolidin-2-ylidene]copper(I) chloride [(IBP*)CuCl] (173b)***



(IBP*)CuCl (173b)
Yield = 99%

Chemical Formula: $C_{45}H_{42}ClCuN_2$
Molecular Weight: 709,84

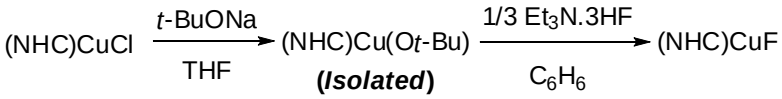
Prepared according to the general procedure described above from (IBP*).HBF_4 (1.03 g, 1.43 mmol), *t*-BuOK (0.21 g, 1.87 mmol), CuCl (0.18 g 1.85 mmol) and THF (14 mL). Purification by column chromatography (CH_2Cl_2/ethanol, 99/1) afforded the desired product as a white solid (1.04 g, 99%). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.55 (d, *J* = 7.4 Hz, 2H), 7.47 (t, *J* = 7.4 Hz, 2H), 7.34 – 7.30 (m, 8H), 7.16 (dt, *J* = 16.8, 6.7 Hz, 10H), 7.03 (t, *J* = 7.5 Hz, 2H), 6.72 (d, *J* = 7.7 Hz, 2H), 5.55 (s, 2H), 4.84 (s, 2H), 2.19 (s, 6H), 1.73 (s, 6H). ^{13}C

NMR (75 MHz, $CDCl_3$) δ = 197.2, 136.7, 136.6, 135.7, 135.4, 134.7, 131.4, 131.1, 130.4, 129.6, 129.1, 128.9, 128.9, 128.1, 127.6, 127.2, 126.5, 73.9, 59.3, 19.9, 18.5.

Spectral data are identical to those reported in the literature.[8]

III.3. Synthesis of the (NHC)CuF Complexes

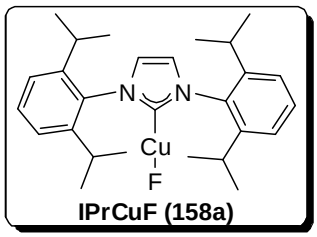
III.3.1. Literature Procedure (also known as Laitar's procedure)



A flame-dried Schlenk was charged with IPrCuCl (1.0 g, 2 mmol, 1 eq.) and *t*-BuONa (0.2 g, 2 mmol, 1 eq.). Dry and degassed THF (9 mL) was added. The resulting suspension was stirred for 2 hours, filtered through celite, and concentrated *in vacuo* to give the IPrCu(O*t*-Bu) complex as a red solid (675.4 mg, 63%). The solid was directly stored in a glovebox (the complex is highly sensitive to light and air).

In a glovebox, a flame-dried Schlenk was charged with IPrCu(O*t*-Bu) (101.2 mg, 0.194 mmol, 1 eq.). The Schlenk was sealed with a septum, taken out of the glovebox and benzene (2 mL) was added. Triethylamine tris(hydrofluoride) (0.01 mL, 0.064 mmol, 0.33 eq.) was added via syringe. The resulting white suspension was stirred for 2 hours. The white solid was collected by filtration under argon, washed with benzene and dried to afford IPrCuF (81 mg, 90%).

❖ ***IPrCuF (158a)***



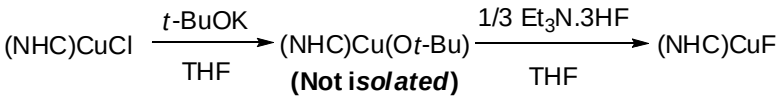
IPrCuF (158a)

Chemical Formula: $C_{27}H_{36}CuFN_2$
Molecular Weight: 471,14

^{1}H NMR (300 MHz, CD_2Cl_2) δ = 7.52 (t, *J* = 7.7 Hz, 2H), 7.33 (d, *J* = 7.0 Hz, 4H), 7.17 (s, 2H), 2.55 (dt, *J* = 13.6, 6.8 Hz, 4H), 1.27 (d, *J* = 6.8 Hz, 12H), 1.22 (d, *J* = 6.8 Hz, 12H). ^{13}C NMR (75 MHz, CD_2Cl_2) δ = 180.30, 145.76, 134.52, 130.42, 128.28, 124.14, 123.33, 28.69, 24.49, 23.57. ^{19}F NMR (282 MHz, CD_2Cl_2) δ = -239.67.

Spectral data are identical to those reported in the literature.[11]

III.3.2. Modified Procedure



A flame-dried Schlenk was charged with (NHC)CuCl (1.0 eq.) and *t*-BuOK (1.0 eq.). Dry and degassed THF (4 mL per mmol) was added and the mixture was stirred for 1.5 hours, under argon. The solution was then filtered under argon over celite (eluting with THF), and triethylamine tris(hydrofluoride) (0.33 eq.) was added to the filtrate, and the solution was stirred for an additional 3 hours. The resulting solution was half-concentrated *in vacuo* (until a suspension appeared). Hexane was added and the resulting precipitate was filtered and washed with cold hexane to afford a white solid.

---

[11] D. S. Laitar, Ph.D thesis, Massachusetts Institute of Technology (Cambridge), **2006**.

As stated in the text, the white solid obtained with this procedure was not the fluoride complex but the bifluoride complex of the corresponding NHC (IPr and IMes). These complexes will be depicted in more details afterwards.

III.4. Synthesis of the $(NHC)_xCu^I$ Bifluoride Complexes

III.4.1. Procedure A

A flame-dried Schlenk was charged with (NHC)CuCl (1.0 eq.) and *t*-BuOK (1.0 eq.). Dry and degassed THF (3~4 mL per mmol) was added and the mixture was stirred for 1.5 hours, under argon. The solution was then filtered under argon over celite (eluting with THF), and triethylamine trihydrofluoride (0.66 eq.) was added to the filtrate, and the solution was stirred for an additional 2 hours. The resulting solution was half-concentrated *in vacuo*. Hexane was added and the resulting precipitate was filtered and washed with hexane to afford the desired bifluoride complex.

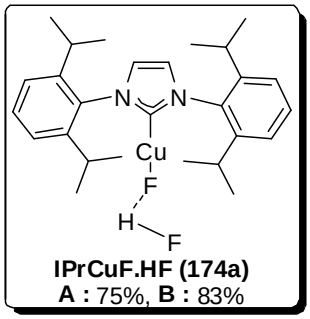
III.4.2. Procedure B

A flame-dried Schlenk was charged with the (NHC)CuCl (1.0 eq.) and $AgHF_2$ (1.0 to 1.4 eq.) freshly taken out from the glovebox in a plastic vial. Dry and degassed THF or DMPU was added and the mixture was stirred in the dark for 15 min, under argon.

Procedure B1 (in case of [NHC)CuF.HF]): The solution was stirred at room temperature for 24 hours in the dark. The resulting mixture was filtered through an HPLC millipore (13 mm, 0.2 µm) under argon. Hexane was then added and the resulting precipitate was filtered after 1 hour and washed with hexane to afford the desired product as a white crystalline solid.

Procedure B2 (in case of [NHC)$_2$CuHF$_2$]: After stirring for 15 min the solution was placed in an ultrasound bath for 90 min in the dark. The Schlenk was then taken out of the bath and stirred at room temperature for 24 hours in the dark. The resulting mixture was filtered through an HPLC millipore (13 mm, 0.2 µm) under argon. Hexane and THF (4/1) were added and the resulting precipitate was filtered after 1 hour and washed with hexane to afford the desired product as a white crystalline solid.

❖ ***IPrCuF.HF (174a)***



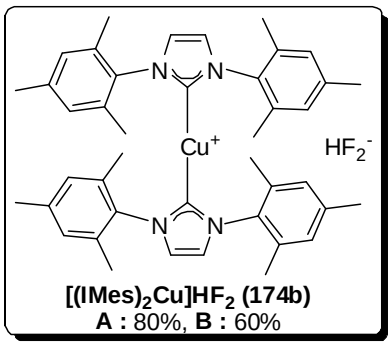
IPrCuF.HF (174a)
A : 75%, **B :** 83%

Chemical Formula: $C_{27}H_{37}CuF_2N_2$
Molecular Weight: 491,15

Procedure B1: Prepared from IPrCuCl (0.5 g, 1.025 mmol), $AgHF_2$ (0.151 g, 1.025 mmol) and THF (20 mL) to afford the desired product in 83% yield (0.419 g).
Procedure A: Prepared from IPrCuCl (0.893 g, 1.832 mmol), *t*-BuOK (0.23 g, 2.015 mmol), triethylamine trihydrofluoride (0.21 mL, 1.264 mmol) and THF (10 mL) to afford the desired product in 75% yield (0.673 g). IR (neat, cm^{-1}): 2959, 2742, 2360, 1469, 1407, 1366, 1330, 1215, 1061, 945, 806, 760, 698. ^{1}H NMR (300 MHz, CD_2Cl_2) δ = 7.54 (t, *J* = 7.8 Hz, 2H), 7.35 (d, *J* = 7.8 Hz, 4H), 7.18 (s, 2H), 2.64 – 2.47 (m, 4H), 1.29 (d, *J* = 6.8 Hz, 12H), 1.23 (d, *J* = 6.9 Hz, 12H). ^{1}H NMR (300 MHz, CD_3CN) δ = 14.03 (br. s, 1H, F-***H***-F). ^{13}C NMR (125 MHz, CD_2Cl_2) δ = 180.1 (N***C***Cu), 146.2, 135.0, 131.0, 124.7, 124.2, 29.2, 25.0, 24.1. ^{19}F NMR (282 MHz, CD_2Cl_2) δ = -219.5 (br. s, Cu-***F***-HF), -139.1 (br. s, Cu-F-H***F***). Anal. Calcd. for $C_{27}H_{37}CuF_2N_2$: C, 65.89; H, 7.78; N, 5.69; F, 7.72 %. Found: C, 65.09; H, 7.70; N, 5.72; F, 5.65 %.

Single crystals of the complex were obtained by recrystallization from THF/hexane. The structure was confirmed by X-ray crystallography (see data at the end of this thesis).

❖ ***[(IMes)$_2$Cu]HF$_2$ (174b)***

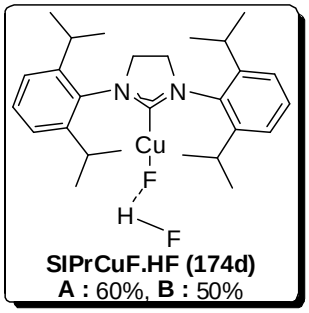


Chemical Formula: $C_{42}H_{49}CuF_2N_4$
Molecular Weight: 712,42

Procedure B2: Prepared from IMesCuCl (0.1 g, 0.247 mmol), $AgHF_2$ (51 mg, 0.347 mmol) and DMPU (2 mL) to afford the desired product in 60% yield (0.03 g). ***Procedure A:*** Prepared from IMesCuCl (315.7 mg, 0.785 mmol), *t*-BuOK (90.8 mg, 0.79 mmol), triethylamine trihydrofluoride (0.084 mL, 0.518 mmol) and THF (5 mL) to afford the desired product in 80% yield (224 mg). IR (neat, cm^{-1}): 3167, 3120, 2920, 2858, 2326, 1809, 1666, 1485, 1407, 1288, 1234, 1076, 929, 856, 733. ^{1}H NMR (300 MHz, CD_2Cl_2) δ = 13.62 (br. s, 1H, F-***H***-F), 7.02 (s, 4H), 6.92 (s, 8H), 2.42 (s, 12H), 1.68 (s, 24H). ^{13}C NMR (125 MHz, CD_2Cl_2) δ = 178.1 (N***C***Cu), 140.0, 135.1, 135.0, 129.7, 123.2, 21.5. ^{19}F NMR (282 MHz, CD_2Cl_2) δ = -169.6 (br. s, H***F$_2$***). Anal. Calcd. for $C_{42}H_{50}CuF_2N_4$: C, 70.71; H, 7.20; N, 7.85; F, 5.33 %. Found: C, 66.59; H, 6.67; N, 7.57; F, 6.58 %.

Single crystals of the complex were obtained by recrystallization from DCM/hexane. The structure was confirmed by X-ray crystallography (see data at the end of this thesis).

❖ ***SIPrCuF.HF (174d)***

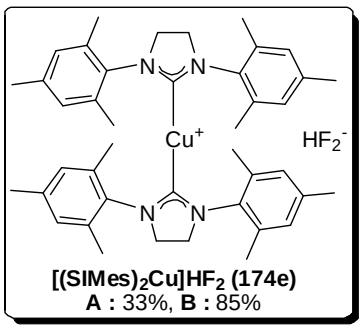


SIPrCuF.HF (174d)
A : 60%, **B :** 50%

Chemical Formula: $C_{27}H_{39}CuF_2N_2$
Molecular Weight: 493,16

Procedure B1: Prepared from SIPrCuCl (0.1 g, 0.204 mmol), $AgHF_2$ (0.036 g, 0.245 mmol) and THF (2 mL) to afford the desired product in 50% yield (0.051 g). ***Procedure A:*** Prepared from SIPrCuCl (0.5 g, 1.021 mmol), *t*-BuOK (0.13 g, 1.123 mmol), triethylamine trihydrofluoride (0.11 mL, 0.68 mmol) and THF (5 mL) to afford the desired product in 60% yield (0.303 g). IR (neat, cm^{-1}): 2958, 2870, 2754, 2360, 1801, 1485, 1458, 1326, 1269, 1056, 933, 806, 760. ^1H NMR (300 MHz, CD_2Cl_2) δ = 7.45 (t, *J* = 7.7 Hz, 2H), 7.29 (d, *J* = 7.6 Hz, 4H), 4.02 (s, 4H), 3.23 – 2.92 (m, 4H), 1.35 (d, *J* = 6.7 Hz, 24H). ^1H NMR (300 MHz, CD_3CN) δ = 14.20 (br. s, 1H, F-***H***-F). ^{13}C NMR (125 MHz, CD_2Cl_2) δ = 203.1 (N***C***Cu), 147.3, 135.0, 130.4, 125.1, 54.2, 29.4, 25.6, 24.2. ^{19}F NMR (282 MHz, CD_2Cl_2) δ = -216.2 (br. s, Cu-***F***-HF), -139.4 (br. s, Cu-F-H***F***). Anal. Calcd. for $C_{27}H_{39}CuF_2N_2$: C, 65.62; H, 8.16; N, 5.67; F, 7.69 %. Found: C, 66.79; H, 8.19; N, 4.20; F, 3.12 %.

❖ ***[(SIMes)$_2$CuHF$_2$] (174e)***



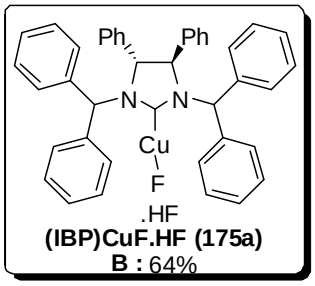
[(SIMes)$_2$Cu]HF$_2$ (174e)
A : 33%, **B :** 85%

Chemical Formula: $C_{42}H_{53}CuF_2N_4$
Molecular Weight: 716,46

Procedure B2: Prepared from SIMesCuCl (0.1 g, 0.248 mmol), $AgHF_2$ (0.044 g, 0.297 mmol) and DMPU (1.5 mL) to afford the desired product in 85% yield (0.044 g). ***Procedure A:*** Prepared from SIMesCuCl (0.412 g, 1.02 mmol), *t*-BuOK (0.14 g, 1.22

mmol), triethylamine trihydrofluoride (0.11 mL, 0.68 mmol) and THF (4 mL) to afford the desired product in 33% yield (0.12 g). IR (neat, cm^{-1}): 3005, 2912, 2314, 2005, 1739, 1496, 1454, 1377, 1273, 1219, 1091, 848, 732. ^{1}H NMR (300 MHz, CD_2Cl_2) δ = 6.87 (s, 8H), 3.83 (s, 8H), 2.39 (s, 12H), 1.85 (s, 24H). ^{1}H NMR (300 MHz, CD_3CN) δ = 14.26 (br. s, 1H, F-***H***-F). ^{13}C NMR (125 MHz, CD_2Cl_2) δ = 201.8 (N***C***Cu), 139.3, 136.1, 134.9, 129.9, 51.5, 21.4, 17.7. ^{19}F NMR (282 MHz, CD_2Cl_2) δ = -169.5 (br. s, H***F***$_2$). Anal. Calcd. for $C_{42}H_{54}CuF_2N_4$: C, 70.31; H, 7.73; N, 7.81; F, 5.30 %. Found: C, 65.05; H, 7.18; N, 7.45; F, 7.33 %.

❖ ***(IBP)CuF.HF (175a)***

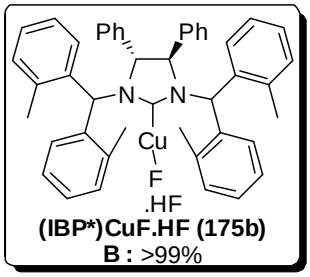


(IBP)CuF.HF (175a)
B : 64%

Chemical Formula: $C_{41}H_{35}CuF_2N_2$
Molecular Weight: 657,28

Prepared according to general ***procedure B1*** from (IBP)CuCl (0.450 g, 0.69 mmol), $AgHF_2$ (0.131 g, 0.89 mmol) and THF (5.5 mL) to afford the desired product in 64% yield (0.29 g). IR (neat, cm^{-1}): 3062, 2354, 1967, 1816, 1706, 1627, 1494, 1452, 1263, 1201, 1029, 916, 875. ^{1}H NMR (300 MHz, CD_2Cl_2) δ = 7.53 – 7.03 (m, 30H), 5.41 (s, 2H), 4.59 (s, 2H). ^{13}C NMR (125 MHz, CD_2Cl_2) δ = 199.0, 139.4, 138.6, 137.5, 130.2, 129.7, 129.5, 129.3, 129.1, 128.8, 128.3, 75.5, 65.6. ^{19}F NMR (282 MHz, CD_2Cl_2) δ = -205.6 (br. s, Cu-***F***-HF), -138.8 (br. s, Cu-F-H***F***). Anal. Calcd. for $C_{41}H_{35}CuF_2N_2$: C, 74.81; H, 5.51; N, 4.25; F, 5.77 %. Found: C, 73.06; H, 5.43; N, 4.29; F, 4.20 %.

❖ ***(IBP*)CuF.HF (175b)***



(IBP*)CuF.HF (175b)
B : >99%

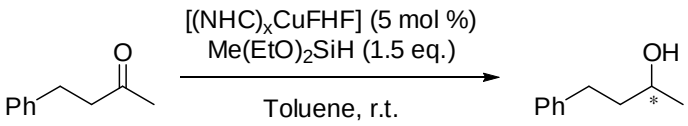
Chemical Formula: $C_{45}H_{43}CuF_2N_2$
Molecular Weight: 713,39

Prepared according to the general ***procedure B1*** with some modification. A flame-dried Schlenk equipped with a Teflon-coated stirbar was charged with the (IBP*)CuCl (0.208 g, 0.292 mmol) and $AgHF_2$ (0.056 g, 0.38 mmol) freshly taken out from the glovebox in a plastic vial. Dry and degassed THF (3 mL) was added and the mixture was stirred in the dark for 24h. The resulting mixture was filtered through an HPLC millipore (13 mm, 0.2 µm) under argon. Hexane was then added and a white solid precipitated. The product was not filtered but concentrated in vacuo instead (the desired complex is partially soluble in hexane/THF). Hexane was added and the solution was evaporated once again. This process was repeated until a white powder was obtained in quantitative yield (0.217 g). IR (neat, cm^{-1}): 3074, 2972, 2923, 2343, 1828, 1704, 1602, 1487, 1454, 1340, 1265, 1213, 1029, 941, 808. ^{1}H NMR (500 MHz, CD_2Cl_2) δ = 7.52 (d, *J* = 2.6 Hz, 4H), 7.38 – 7.33 (m, 8H), 7.21 – 7.11 (m, 10H), 7.00 – 6.97 (m, 2H), 6.75 (d, *J* = 7.7 Hz, 2H), 5.55 (s, 2H), 4.88 (s, 2H), 2.19 (s, 6H), 1.73 (s, 6H). ^{13}C NMR (125 MHz, CD_2Cl_2) δ = 197.8, 153.8, 137.5, 137.2, 135.9, 135.6, 131.9, 131.4, 130.7, 130.6, 130.2, 129.6, 129.5, 129.3, 128.6, 127.6, 127.1, 74.4, 59.7, 20.0, 18.6. ^{19}F NMR (282 MHz, CD_2Cl_2) δ = -205.2 (br. s, Cu-***F***-HF), -139.1 (br. s, Cu-F-H-***F***). Anal. Calcd. for $C_{45}H_{43}CuF_2N_2$: C, 75.76; H, 6.08; N, 3.93; F, 5.33 %. Found: C, 75.32; H, 6.05; N, 3.90; F, 2.99 %.

III.5. Catalytic Activity of the $(NHC)_xCuFHF$ Complexes

III.5.1. Cu^I-Catalyzed Reduction Reactions

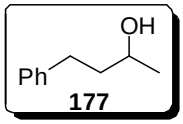
III.5.1.1. Procedure for the Hydrosilylation of Benzylacetone



176 **177**

A flame-dried Schlenk was sequentially charged with the NHC copper complex (0.05 eq.) and freshly distilled toluene (4 mL per mmol). Methyldiethoxysilane (1.5 eq.) was added. After 5 min, benzylacetone **176** (1.0 eq.) was slowly added and the mixture was allowed to stir at room temperature. After total consumption of the starting material as indicated by TLC, TBAF (1 M in THF, 1.5 mL per mmol) was added and the solution was allowed to stir for 15 min. The light grey mixture was filtered on a plug silica gel (eluting with petroleum ether/AcOEt, 7/3). The filtrate was concentrated *in vacuo*. A sample of the crude mixture thus obtained was taken for analysis. Overall conversion **177** was determined by ^1H NMR and enantioselectivity was determined by chiral GC analysis.

❖ ***4-phenylbutan-2-ol (177)***



177

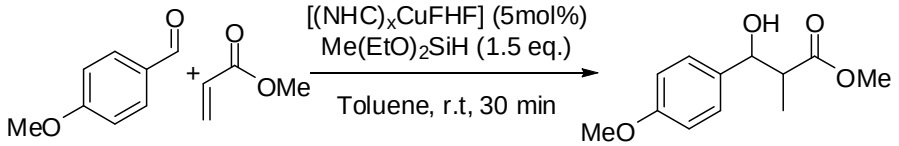
Chemical Formula: $C_{10}H_{14}O$
Molecular Weight: 150,22

^1H NMR (300 MHz, $CDCl_3$) δ = 7.32 – 7.19 (m, 5H), 3.83 (q, *J* = 5.0 Hz, 1H), 2.76 (m, 2H), 1.79 (dt, *J* = 9.0, 5.9 Hz, 2H), 1.33 (br. s, 1H), 1.23 (d, *J* = 6.2 Hz, 3H).

The enantiomeric ratio was determined by chiral GC (T = 120°C (25 min), t_R = 19.1 min (major), t_R = 20.2 min (minor)).

Spectral data are identical to those reported in the literature (CAS: 2344-70-9).[12]

III.5.1.2. Procedure for the 1,4-Reduction/Aldolisation Reaction



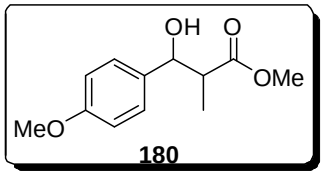
178 **179** **180**

A flame-dried Schlenk was charged with the indicated copper complex (0.05 mmol, 0.05 eq.) in 2 mL of THF. Methyl acrylate **179** (0.09 mL, 1 mmol, 1 eq.), *p*-anisaldehyde **178** (0.097 mL, 0.8 mmol, 0.8 eq.) and methyldiethoxysilane (0.24 mL, 1.5 mmol, 1.5 eq.) were added successively, and the solution was then stirred for 30 minutes at room temperature (reaction was performed at 0 °C and overnight when complex **175a** was used). When all the starting material was consumed (as indicated by TLC, eluting with petroleum ether/AcOEt, 9/1) a 1M solution of TBAF in THF (1.5 mL) was added to the reaction mixture. The solution was then filtered through a plug silica gel (eluting with petroleum ether/AcOEt, 8/2). The filtrate was concentrated *in vacuo*. A sample of the crude mixture thus obtained was taken for ^{1}H NMR analysis to determine the conversion rate and diastereomeric ratio of **180**.

---

[12] R. J. Rahaim Jr., R. E. Maleczka Jr., *Org. Lett.* **2011**,*13*, 584.

❖ ***Methyl 3-hydroxy-3-(4-methoxyphenyl)-2-methylpropanoate (180)***



180

Chemical Formula: $C_{12}H_{16}O_4$
Molecular Weight: 224,25

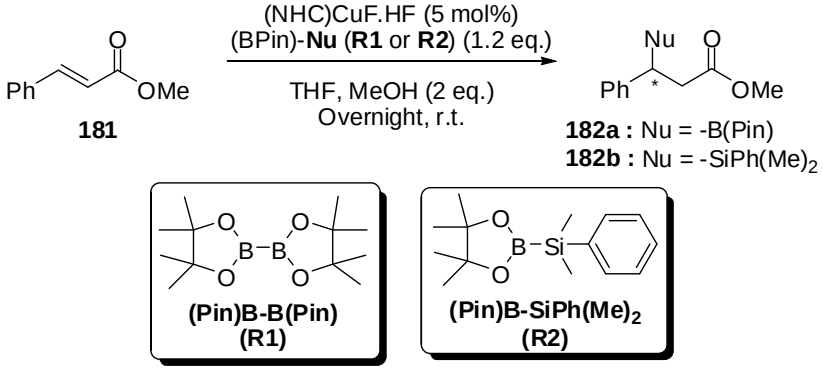
Purified by column chromatography (petroleum ether/AcOEt, 80/20). ***Syn*-180:** ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.55 – 6.82 (m, 4H), 5.03 (m, 1H), 3.80 (s, 3H), 3.49 (s, 3H), 2.75 (m, 1H), 1.21 (d, *J* = 7.2 Hz, 3H). ***Anti*-180:** ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.55 – 6.82 (m, 4H), 4.71 (m, 1H), 3.80 (s, 3H), 3.66 (s, 3H), 2.85 (m, 1H), 0.87 (d, *J* = 7.2 Hz, 3H).

^{1}H NMR analysis showed the major diastereoisomer to be the ***syn*-180**. The enantiomeric ratio was determined by HPLC using Chiralpak IA column (isohexane/EtOH : 90/10, 1 mL/min, 225 nm, t_R = 9.3 min (minor), t_R = 10.2 min (major)).

Spectral data are identical to those reported in the literature (CAS: 17226-85-6).[13]

[13] a) J. Deschamp, O. Chuzel, J. Hannedopuche, O. Riant, *Angew. Chem., Int. Ed.* **2006**, *45*, 1292; b) O. Chuzel, J. Deschamp, C. Chausteur, O. Riant, *Org. Lett.* **2006**, *8*, 5943.

III.5.2. β-Borylation and β-Silylation Reactions

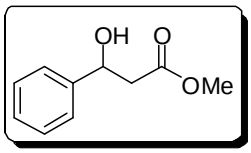


III.5.2.1. β-Borylation Procedure

A flame-dried Schlenk was sequentially charged with the NHC copper complex (0.05 eq.) and THF or toluene (2 mL). Bis(pinacolato)diboron **R1** (165 mg, 0.65 mmol, 1.3 eq.) was subsequently added. After 5 minutes, *trans*-methylcinnamate **181** (81 mg, 0.5 mmol, 1.0 eq.) diluted in the solvent was slowly added followed by 2~3 drops of MeOH and the mixture was allowed to stir overnight at room temperature. Water (3 mL) was added to the resulting mixture followed by Et_2O (2 mL) and $NaBO_3$ (260 mg, 2.6 mmol, 5.2 eq) and left to stir for 3 hours. The two layers were separated and the aqueous layer was extracted two times with ether. The combined organic layers were washed with HCl (1M) then brine. They were dried on $MgSO_4$ and concentrated *in vacuo*.

Overall conversion of **182a** was determined, after oxidation to the corresponding alcohol, by ^1H NMR on a sample of the crude mixture. Enantioselectivity of **182a** was determined, after oxidation to the corresponding alcohol, by chiral HPLC analysis.

❖ ***Methyl 3-(dimethyl(phenyl)silyl)-3-phenylpropanoate***



Chemical Formula: $C_{10}H_{12}O_3$
Molecular Weight: 180,20

Purified by column chromatography (petroleum ether/AcOEt, 90/10). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.41 – 7.27 (m, 5H), 5.15 (dd, *J* = 8.4, 4.3 Hz, 1H), 3.73 (s, 3H), 3.18 (br. s, 1H), 2.79 – 2.71 (m, 2H).

The enantiomeric ratio was determined by HPLC using CHIRALPAK IA column (isohexane/EtOH : 90/10, 1 mL/min, 205 nm, t_R = 10.0 min (major), t_R = 10.9 min (minor)).

Spectral data are identical to those reported in the literature (CAS: 7497-61-2).[14]

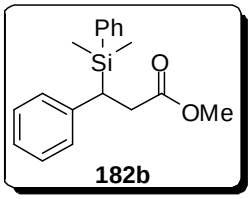
III.5.2.2. β-Silylation Procedure

A flame-dried Schlenk was sequentially charged with SIPrCuF.HF (12.3 mg, 0.025 mmol, 0.05 eq.) and THF (2 mL). Borosilane **R2** (0.18 mL, 0.6 mmol, 1.2 eq.) was subsequently added. After 5 minutes, *trans*-methylcinnamate **181** (81.1 mg, 0.5 mmol, 1.0 eq.) diluted in toluene was slowly added followed by 2~3 drops of MeOH, and the mixture was allowed to stir overnight at room temperature. HCl (1M) was then added to the resulting mixture and left to stir for 1 hour. Ether was then added. The two layers were separated and the aqueous layer was extracted two times with ether. The combined organic layers were washed with water then brine. They were then dried on $MgSO_4$ and concentrated *in vacuo*.

Overall conversion of **182b** was determined by ^{1}H NMR on a sample of the crude mixture.

❖ ***Methyl 3-(dimethyl(phenyl)silyl)-3-phenylpropanoate (182b)***

[14] D. T. McQuade, *Org. Lett.* **2010**, *12*, 5008.



182b

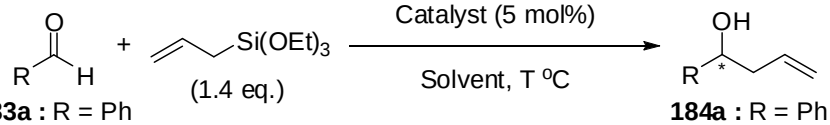
Chemical Formula: $C_{18}H_{22}O_2Si$
Molecular Weight: 298,45

Purified by column chromatography (petroleum ether/AcOEt, 90/10) to afford 83 % (124 mg) yield of a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.44 – 7.31 (m, 5H), 7.22 – 7.17 (m, 2H), 7.11 – 7.06 (m, 1H), 6.96 – 6.93 (m, 2H), 3.46 (s, 3H), 2.87 – 2.60 (m, 3H), 0.25 (s, 3H), 0.21 (s, 3H).

Spectral data are identical to those reported in the literature (CAS: 94286-28-9).[15]

III.5.3. Cu^I-Catalyzed Allylation Reactions

III.5.3.1. General Procedure for the Allylation of Aldehydes



183a : R = Ph
183b : R = Cy

184a : R = Ph
184b : R = Cy

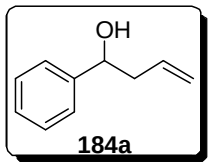
A flame-dried Schlenk was charged sequentially with the NHC copper complex (0.05 eq.) and THF or toluene (4 mL per mmol). The solution was put at the indicated temperature. Allyltriethoxysilane (1.4 eq.) was added. After 5 minutes, aldehyde **183a-b** (1.0 eq.) was slowly added and the mixture was allowed to stir overnight. After total consumption of the aldehyde as indicated by TLC, TBAF (1M in THF, 1.5 mL per mmol) was added. The solution was allowed to stir for 15 minutes at room temperature. The mixture was filtered on a plug silica gel (eluting with petroleum ether

[15] A. H. Hoveyda, *J. Am. Chem. Soc.* **2010**, *132*, 2898.

/AcOEt, 7/3). The filtrate was then concentrated *in vacuo*. A sample of the crude mixture thus obtained was taken for analysis.

Overall conversion of **184a-b** was determined by ^{1}H NMR. Enantioselectivity of **184a-b** was determined by chiral HPLC analysis.

❖ ***1-phenylbut-3en-1-ol (184a)***



184a

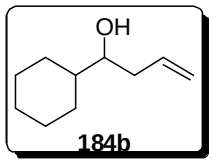
Chemical Formula: $C_{10}H_{12}O$
Molecular Weight: 148,20

Purified by fractional distillation (100 ^{o}C, 15 torr). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.37 – 7.28 (m, 5H), 5.82 (ddt, *J* = 17.1, 10.2, 7.2 Hz, 1H), 5.21 – 5.10 (m, 2H), 4.74 (dd, *J* = 7.2, 5.7 Hz, 1H), 2.59 – 2.44 (m, 2H), 2.14 (br. s, 1H).

The enantiomeric ratio was determined by HPLC using CHIRALPAK IB column (isohexane/EtOH : 95/5, 0.7 mL/min, 205 nm, t_R = 8.6 min (major), t_R = 9.2 min (minor)).

Spectral data are identical to those reported in the literature (CAS: 80735-94-0).[16]

❖ ***1-cyclohexyllbut-3en-1-ol (184b)***



184b

Chemical Formula: $C_{10}H_{18}O$
Molecular Weight: 154,25

Purified by fractional distillation (100 ^{o}C, 0.1 torr). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.96 – 5.73 (m, 1H), 5.22 – 5.04 (m, 2H), 3.39 (ddd, *J* = 9.0, 5.8, 3.5 Hz, 1H), 2.39 – 2.25 (m, 1H), 2.12 (dt, *J* = 14.1, 8.4 Hz, 1H), 1.93 – 0.8 (m, 11H).

Spectral data are identical to those reported in the literature (CAS: 69036-26-6).[17]

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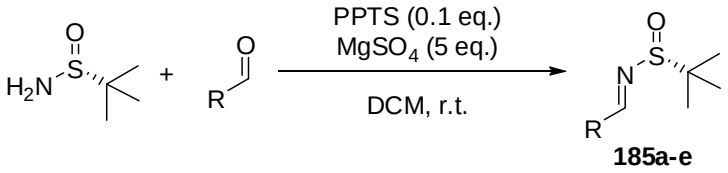
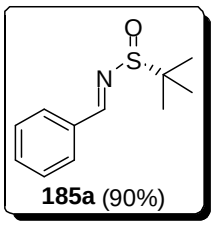
[16] Z. T. Ball, *Org. Lett.* **2010**, *12*, 220.

III.5.3.2. General Procedure for the synthesis of enantiomerically pure *N*-sulfinyl aldimines 185a-e



A flame-dried Schlenk was charged sequentially with (*R*)-t-butanesulfinamide (1.0 eq.) in DCM (0.75 M). PPTS (0.1 eq.) was added followed by $MgSO_4$ (5 eq.) and the corresponding aldehyde (2.0 eq.). The mixture was stirred at room temperature overnight, then filtered over celite (eluting with DCM). The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography on flash silica gel (eluting with petroleum ether/Et_2O or petroleum ether/AcOEt) to afford the desired product **185a-e**.

❖ ***(R_S)-N-benzylidene-2-methylpropane-2-sulfinamide (185a)***



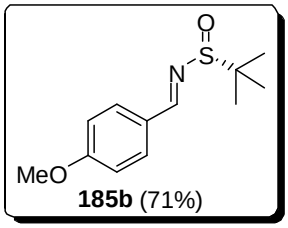
Chemical Formula: $C_{11}H_{15}NOS$
Molecular Weight: 209,31

Purification by column chromatography (petroleum ether/Et_2O, 90/10 to 60/40) afforded the desired product in 90% yield (1.875 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.59 (s, 1H), 7.87 – 7.84 (m, 2H), 7.52 – 7.47 (m, 3H), 1.27 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 162.9, 134.2, 132.5, 129.5, 129.0, 57.9, 22.7.

[17] V. P. Srivastava, R. Patel, L. D. Yadav, *Adv. Synth. Catal.* **2011**, 353, 6950.

Spectral data are identical to those reported in the literature (CAS: 186249-76-3).[18]

❖ ***(R_S)-N-(4-methoxybenzylidene)-2-methylpropane-2-sulfinamide (185b)***



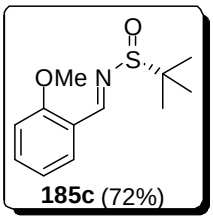
185b (71%)

Chemical Formula: $C_{12}H_{17}NO_2S$
Molecular Weight: 239,33

Purification by column chromatography (petroleum ether/AcOEt, 85/15 to 60/40) afforded the desired product in 71% yield (510 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.51 (s, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 6.97 (d, *J* = 8.4 Hz, 2H), 3.87 (s, 3H), 1.25 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 163.1, 161.9, 131.4, 127.4, 114.5, 57.7, 55.6, 22.7.

Spectral data are identical to those reported in the literature (CAS: 244092-54-4).[19]

❖ ***(R_S)-N-(2-methoxybenzylidene)-2-methylpropane-2-sulfinamide (185c)***



185c (72%)

Chemical Formula: $C_{12}H_{17}NO_2S$
Molecular Weight: 239,33

Purification by column chromatography (petroleum ether/AcOEt, 85/15 to 70/30) afforded the desired product in 72% yield (518.1 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.06 (s, 1H), 7.98 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.54 – 7.38 (m, 1H), 7.07 – 6.90 (m, 2H), 3.89 (s, 3H), 1.25 (s, 9H). ^{13}C NMR (75

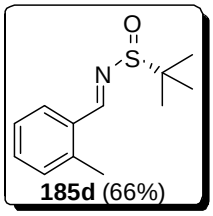
[18] J. A. Ellman, *J. Am. Chem. Soc.* **1997,** *119*, 9913.

[19] K. W. Kells, J. M. Chong, *J. Am. Chem. Soc.* **2004**, *126*, 15666.

MHz, $CDCl_3$) δ = 159.8, 158.9, 134.0, 128.3, 122.9, 120.8, 111.5, 57.8, 55.7, 22.8.

Spectral data are identical to those reported in the literature (CAS: 1015198-49-8).[20]

- ***(R_S)-2-methyl-N-(2-methylbenzylidene)propane-2-sulfinamide (185d)***

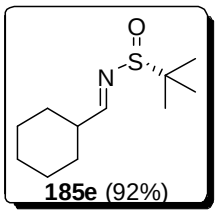


Chemical Formula: $C_{12}H_{17}NOS$
Molecular Weight: 223,33

Purification by column chromatography (petroleum ether/AcOEt, 90/10 to 70/30) afforded the desired product in 66% yield (438.3 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.86 (s, 1H), 7.91 (d, *J* = 7.6 Hz, 1H), 7.46 – 7.18 (m, 3H), 2.61 (s, 3H), 1.27 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 161.8, 139.6, 132.3, 132.1, 131.5, 129.6, 126.4, 22.7, 20.1.

Spectral data are identical to those reported in the literature.[20]

- ***(R_S)-N-(cyclohexylmethylene)-2-methylpropane-2-sulfinamide (185e)***



Chemical Formula: $C_{11}H_{21}NOS$
Molecular Weight: 215,36

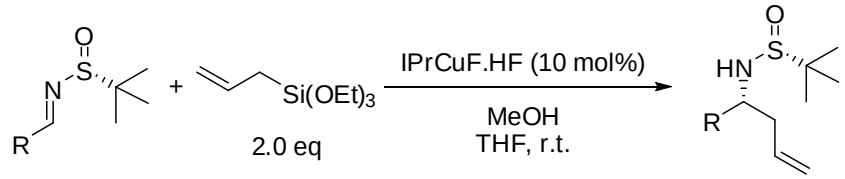
Purification by column chromatography (petroleum ether/AcOEt, 95/5 to 80/20) afforded the desired product in 92% yield (593 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.96 (d, *J* = 4.4 Hz, 1H), 2.46 (m, 1H), 2.00 – 1.52 (m, 6H), 1.18 (s, 9H), 1.45 – 1.04 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.8,

[20] A. Studer, *Org. Lett.* **2008**, *10*, 1847.

56.5, 44.1, 29.4, 26.0, 25.4, 22.4.

Spectral data are identical to those reported in the literature (CAS: 336105-28-3).[20]

III.5.3.3. General Procedure for the Allylation of *N*-sulfinyl aldimines 185a-e

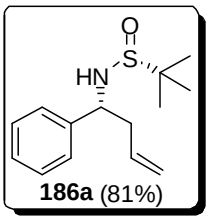


185a-e **186a-e**

A flame-dried Schlenk was charged sequentially with IPrCuF.HF (14.8 mg, 0.03 mmol, 0.1 eq.), THF (1.2 mL), 3 drops of MeOH and the corresponding *N*-sulfinyl aldimine **185a-e** (0.3 mmol, 1.0 eq). Allyltriethoxysilane (0.15 mL, 0.6 mmol, 2.0 eq.) was added and the mixture was allowed to stir at room temperature for 3 hours. After total consumption of the aldimine as indicated by TLC, TBAF (1M in THF, 0.6 mL) was added. The solution was allowed to stir for 30 minutes and then filtered on a plug silica gel (eluting with petroleum ether/AcOEt, 2/8). The filtrate was then concentrated *in vacuo*. A sample of the crude mixture thus obtained was taken for analysis and the residue was purified by column chromatography on flash silica gel (eluting with petroleum ether/EtOAc) to afford the desired product **186a-e**.

Overall conversion and diastereoselectivity of **186a-e** were determined by ^{1}H NMR.

- ***(R)-2-methyl-N-((R)-1-phenylbut-3-enyl)propane-2-sulfinamide (186a)***



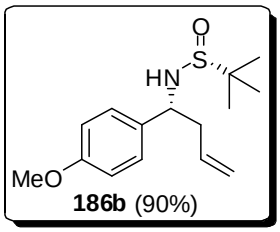
186a (81%)

Chemical Formula: $C_{14}H_{21}NOS$
Molecular Weight: 251,39

Purification by column chromatography (petroleum ether/AcOEt, 60/40 to 50/50) afforded the desired product in 81% yield (61 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.46 – 7.22 (m, 5H), 5.61 (ddt, *J* = 17.3, 10.2, 7.0 Hz, 1H), 5.09 – 4.97 (m, 2H), 4.45 (ddd, *J* = 7.6, 5.8, 3.9 Hz, 1H), 3.50 (br. d, *J* = 3.3 Hz, 1H), 2.82 – 2.67 (m, 1H), 2.62 – 2.47 (m, 1H), 1.22 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 141.9, 133.9, 128.7, 127.9, 127.3, 118.3, 58.5, 56.1, 41.3, 22.7.

Spectral data are identical to those reported in the literature (CAS: 915089-09-7).[21]

- ***(R)-N-((R)-1-(4-methoxyphenyl)but-3-enyl)-2-methylpropane-2-sulfinamide (186b)***



186b (90%)

Chemical Formula: $C_{15}H_{23}NO_2S$
Molecular Weight: 281,41

Purification by column chromatography (petroleum ether/AcOEt, 50/50) afforded the desired product in 90% yield (76.2 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.26 – 7.23 (m, 2H), 6.89 – 6.86 (m, 2H), 5.61 (ddt, *J* = 17.2, 10.1, 7.0 Hz, 1H), 5.08 – 4.97 (m, 2H), 4.49 – 4.33 (m, 1H), 3.80 (s, 3H), 3.43 (br. s, 1H), 2.83 – 2.66 (m, 1H), 2.56 – 2.47 (m, 1H), 1.22 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.2, 134.1, 128.5, 118.2, 114.1, 58.1, 55.4, 41.2, 22.8.

Spectral data are identical to those reported in the literature.[21]

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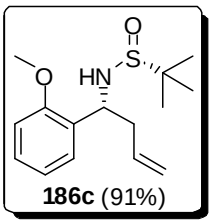
[21] a) M.-H. Xu, G.-Q. Lin, *O*rg. Lett. **2006**, *8*, 4979; b) M.-H. Xu, G.-Q. Lin, *O*rg. Lett. **2008**, *10*, 1259.

❖ ***(R)-N-((R)-1-(2-methoxyphenyl)but-3-enyl)-2-methylpropane-2-sulfinamide (186c)***



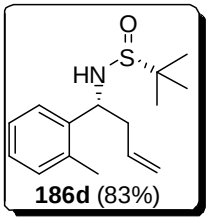
186c (91%)

Chemical Formula: $C_{15}H_{23}NO_2S$
Molecular Weight: 281,41

Purification by column chromatography (petroleum ether/AcOEt, 50/50) afforded the desired product in 91% yield (76.7 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.32 – 7.17 (m, 2H), 7.01 – 6.80 (m, 2H), 5.69 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H), 5.09 – 4.96 (m, 2H), 4.64 (q, *J* = 6.9 Hz, 1H), 3.98 (br. d, *J* = 7.1 Hz, 1H), 3.85 (s, 3H), 2.75 – 2.45 (m, 2H), 1.20 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 156.8, 134.9, 130.5, 128.6, 128.0, 120.8, 117.5, 111.0, 56.1, 55.9, 55.4, 40.6, 22.8.

Spectral data are identical to those reported in the literature.[21]

❖ ***(R)-2-methyl-N-((R)-1-o-tolylbut-3-enyl)propane-2-sulfinamide (186d)***



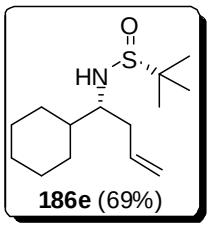
186d (83%)

Chemical Formula: $C_{15}H_{23}NOS$
Molecular Weight: 265,41

Purification by column chromatography (petroleum ether/AcOEt, 60/40) afforded the desired product in 83% yield (65.9 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.35 (d, *J* = 7.4 Hz, 1H), 7.24 – 7.13 (m, 3H), 5.62 (ddt, *J* = 17.2, 10.1, 7.1 Hz, 1H), 5.12 – 4.96 (m, 2H), 4.76 – 4.64 (m, 1H), 3.43 (br. s, 1H), 2.71 (ddd, *J* = 13.5, 7.1, 6.2 Hz, 1H), 2.61 – 2.55 (m, 1H), 2.37 (s, 3H), 1.21 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 139.9, 135.8, 133.9, 130.8, 127.6, 126.4, 118.3, 56.0, 53.7, 40.7, 22.8, 19.6.

Spectral data are identical to those reported in the literature.[21]

❖ ***(R)-N-((R)-1-cyclohexylbut-3-enyl)-2-methylpropane-2-sulfinamide (186e)***



Chemical Formula: $C_{14}H_{27}NOS$
Molecular Weight: 257,44

Purification by column chromatography (petroleum ether/AcOEt, 70/30 to 60/40) afforded the desired product in 69% yield (53 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.89 – 5.69 (m, 1H), 5.15 – 5.02 (m, 2H), 3.16 (br. s, 2H), 2.39 – 2.13 (m, 2H), 1.91 – 1.45 (m, 5H), 1.41 – 0.85 (m, 15H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 135.5, 117.3, 61.1, 42.1, 37.3, 29.1, 29.0, 26.5, 26.3, 22.9. Spectral data are identical to those reported in the literature.[21]

III.5.4. NMR Studies

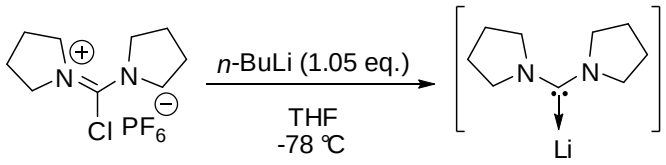
III.5.4.1. General Procedure for the Titration Method

A flame-dried Schlenk was charged with (NHC)CuX (X = F or FHF) (0.010607 mmol, 1 eq.), Ph_3SiF (if indicated, 1.2 mg, 0.004242 mmol, 0.4 eq.) and 0.6 mL of C_6D_6. Another flame-dried Schlenk was charged with $Me(EtO)_2SiH$ (18 µL, 0.10607 mmol) in 0.5 mL of C_6D_6 to form a solution with a C = 0.21212 M. The solution containing the complex was transferred to a NMR tube under argon (using a home made apparatus for continuous handling under argon). The NMR tube was then sealed with a septum under argon. A ^{1}H NMR spectrum was taken of the initial complex solution, and again after each addition of the silane (0.5 eq. of silane = 25 µL, 1 eq. of silane = 50 µL).

It should be noted that all the glassware and apparatus used, were firstly dried under reduced pressure and placed under an argon atmosphere.

III.6. Exploring the Synthesis of (ADC)Cu^{I} Complexes

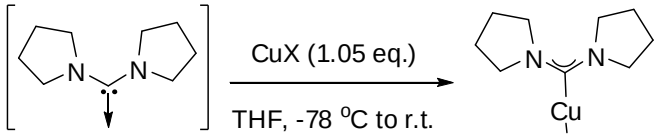
III.6.1. Lithium-Halogen Exchange Procedure[22]



154 **187**

A flame-dried Schlenk was charged sequentially with a magnetic stirrer and chlorodipyrrolidinocarbenium hexofluorophosphate **154** (1 eq.). After three cycles of vacuum/argon, THF is added (6 mL per mmol). The solution was stirred until complete dissolution of the solid. The suspension was cooled to -78°C. After cooling, *n*-BuLi (2.5 M in hexane, 1.05 eq.) was added. After 5 minutes, the suspension turned to a clear and slightly yellowish solution. The solution proceeded to stir at -78 °C for a total of 1 hour. [N.B.: reactions were usually done with 300 mg of reactant]. This carbene solution of **187** was used directly in the next step.

III.6.2. Complexation and/or Transmetallation Procedure



187 **188**

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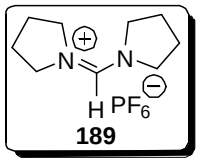
[22] a) D. R. Snead, I. Ghiviriga, K. A. Abboud, S. Hong, *Org. Lett.* **2009**, *11*, 3274; b) D. Hirsch-Weil, D. R. Snead, S. Inagaki, H. Seo, K. A. Abboud, S. Hong, *Chem. Commun.* **2009**, 2475.

III.6.2.1. Procedure for the Reaction with CuCl

To the carbene solution of **187** (generated as decribed above by lithium-halogen exchange), CuCl (1.05 eq.) was added, followed by a small amount of THF. The mixture was stirred for 30 minutes at -78 °C then allowed to slowly warm to room temperature. The suspension was stirred for 3 hours to become dark green. It was then filtered over a bed of celite and washed with THF. The filtrate was half concentrated and hexane was added. The formed green precipitate was filtered and dried under vacuum. ^{1}H NMR of the crude product showed that it was dipyrrolidinocarbenium hexafluorophosphate **189** along with some unidentifiable by-products. No ^{13}C signal characteristic of the desired carbene **188** was observed by ^{13}C NMR analysis.

❖ ***Dipyrrolidinocarbenium hexafluorophosphate (189)***



189

Chemical Formula: $C_9H_{17}F_6N_2P$
Molecular Weight: 298,21

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.80 (s, 1H), 3.88 (t, *J* = 6.9 Hz, 4H), 3.74 (t, *J* = 6.8 Hz, 4H), 2.05 (t, *J* = 6.8 Hz, 4H), 1.94 (t, *J* = 6.8 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 151.41, 54.69, 48.70, 26.27, 24.21. ^{31}P NMR (121 MHz, $CDCl_3$) δ = -143.70 (hept, *J* = 712.3 Hz).

Spectral data are identical to those reported in the literature.[22b]

III.6.2.2. Procedure for the Reaction with CuI

To the carbene solution of **187** (generated as decribed above by lithium-halogen exchange), CuI (1.05 eq.) was added, followed by a small amount of THF. The mixture was stirred for 30 minutes at -78 °C then allowed to slowly warm to room temperature. The suspension was stirred for 3 hours to become dark green. It was then filtered over a bed of celite with CH_2Cl_2. The

filtrate was concentrated *in vacuo*, giving a blue-yellow oil. ^{1}H NMR of the crude product showed that it was dipyrrolidinocarbenium hexafluorophosphate **189** along with some unidentifiable impurities. No ^{13}C signal characteristic of the desired carbene **188** was observed by ^{13}C NMR analysis.

III.6.2.3. Procedure for the Reaction with $[Cu(CH_3CN)_4]PF_6$

To the carbene solution of **187** (generated as decribed above by lithium-halogen exchange), tetrakis(acetonitrile)copper(I) hexafluorophosphate (0.55 eq.) was added at -78 °C. The mixture was stirred for 30 minutes at -78 °C then allowed to slowly warm to room temperature. The suspension was stirred for 4 hours and become light green. It was then filtered over a bed of celite and washed with THF. The filtrate was a half concentrated and hexane was added. The solution became opaque but no solid was formed. The solution was concentrated, diluted with CH_2Cl_2 and hexane was added. This time a dark green solid was formed and was then filtered. The filtrate was concentrated to give another light brown solid. Analysis of both solids showed none of them to be the desired product. The actual products could not be identified.

III.6.2.4. Procedure for the Reaction with $Me_2S.CuBr$

To the carbene solution of **187** (generated as decribed above by lithium-halogen exchange), but the mixture was only stirred for 15 minutes after the addition of *n*-BuLi. Copper(I) bromide dimethyl sulfide complex (1.0 eq.) was then added at -78 °C. The mixture was allowed to slowly warm to room temperature and stirred for 2 hours. The yellow solution was filtered over a

bed of celite and washed with THF. The filtrate was concentrated *in vacuo*. The analysis of the crude product did not afford any desired product.

III.6.2.5. Procedure for the Reaction with AgOTf

To the carbene solution of **187** (generated as decribed above by lithium-halogen exchange), AgOTf (1.15 eq.) was added. The mixture was stirred for 30 minutes in the dark at -78 °C, then allowed to slowly warm to room temperature. The mixture was stirred overnight. The next day, the black mixture was filtered over a bed of celite under argon and the yellow filtrate half concentrated. CuCl was added (1.1 eq.) with some THF. The mixture was stirred overnight in the dark. The black solution was filtered over celite, the filtrate half concentrated and hexane was then added. A light green solid was formed and filtered. The filtrate was concentrated again and washed with hexane. A dark green solid appeared this time and was filtered as well. The first product could not be identified, but it is not the desired product. ^{1}H NMR of the second product showed that it was dipyrrolidinocarbenium hexafluorophosphate **189** along with some unidentifiable impurities.

III.6.2.6. Procedure for the Reaction with AgCl

To the carbene solution of **187** (generated as decribed above by lithium-halogen exchange), AgCl (1.15 eq.) was added. The mixture was stirred for 30 minutes in the dark at -78 °C, then allowed to slowly warm to room temperature. The mixture was stirred overnight. The next day, the dark grey mixture was filtered over a bed of celite and the opaque yellow filtrate concentrated to afford a black-grey solid. The solid was diluted in THF and CuCl was added (1.1 eq.). The mixture was stirred overnight in the dark. The light brown solution was filtered over celite and the yellow filtrate

concentrated to obtain a light brown solid. The solid was dried *in vacuo*. The solid was identified as the dipyrrolidinocarbenium hexafluorophosphate **189**.

III.6.3. Deprotonation / Complexation Procedures

III.6.3.1. First Procedure

A flame-dried Schlenk was charged with dipyrrolidinocarbenium hexafluorophosphate **189** (1 eq.) in THF. *t*-BuOK (1.1 eq.) and CuCl (1.05 eq.) were then added. The mixture was stirred overnight at room temperature. The brown solution was filtered over celite and washed with THF. The opaque yellow filtrate was half concentrated and hexane was then added. A light green solid was formed and filtered. The analysis of the crude product did not afford any desired product.

III.6.3.2. Second Procedure (Strong Base)

A flame-dried Schlenk was charged sequentially with the dipyrrolidinocarbenium hexafluorophosphate **189** (1 eq.) and THF (20 mL per mmol). The brown solution was cooled down to -78 °C and NaHMDS (2M in THF, 1.2 eq.) was slowly added. After 10 minutes, the solution became light green. The mixture was stirred for 30 minutes at -78 °C, then 30 minutes at room temperature. The brown mixture was cooled down again to -78 °C and CuCl (1.3 eq.) was added. The solution was stirred for 30 minutes at -78 °C then allowed to slowly warm to room temperature. The suspension was stirred for 3 hours to become green-black, and then was filtered over a bed of celite. The filtrate was half concentrated and hexane was added. A dark green solid was formed and filtered. ^{1}H NMR analysis showed only the starting material **189**.

III.6.4. Deprotonation / Complexation / Transmetallation Procedure

A flame-dried Schlenk was charged sequentially with the dipyrrolidinocarbenium hexafluorophosphate **189** (1 eq.) and DCM (12 mL per mmol). Silver(I) oxide (0.65 eq.) was then added. The brown solution was stirred overnight at room temperature and in the dark. The dark brown mixture was filtered over a bed of celite, and washed with THF. The yellow filtrate was concentrated to obtain a light yellow solid. CuCl (1.1 eq.) was added followed by a small amount of DCM. The mixture was stirred overnight in the dark. The opaque yellow solution was filtered over celite and the yellow filtrate concentrated *in vacuo*. A white yellowish solid was formed, which was washed several times with pentane. ^{1}H NMR analysis showed only the starting material **189**.

IV. Crystallographic data for IPrCu-FHF and $(IMes)_2Cu\text{-}HF_2$:

Single crystal X-ray diffraction was performed on a Gemini Ultra R system (4-circle kappa platform, Ruby CCD detector) using Cu Kα radiation (λ = 1.54056 Å). Cell parameters were estimated from a pre-experiment run and full data sets collected at room temperature. The structure was solved by direct methods with SHELXS-97 program and then refined on F^2 using SHELXL-97 software[a]. Non-hydrogen atoms were anisotropically refined and the hydrogen atoms (not implicated in H-bonds) in the riding mode with isotropic temperature factors fixed at 1.2 times U(eq) of the parent atoms (1.5 times for methyl groups). Hydrogen atoms implicated in H-bonds were

localized by Fourier difference maps (DF).

[a] Sheldrick, M.G., SHELX-97: Program for the Solution of Crystal Structures, University of Göttingen, Göttingen (Germany), 1998.

	IPrCu-FHF	**$[(IMes)_2Cu]FHF$**
formula	$C_{27}H_{36}CuF_2N_2$	$C_{42}H_{48}CuF_2N_4$
M [g mol^{-1}]	489.84	710.00
crystalline system	monoclinic	orthorhombic
space group	$P2_1/c$	P b c n
a [Å]	12.5235(6)	14.5041(7)
b [Å]	9.3236(7)	16.7537(11)
c [Å]	22.7815(15)	16.6909(9)
α [°]	90.00	90.00
β [°]	97.961(6)	90.00
γ [°]	90.00	90.00
V [Å^3]	2634.43	4055.84
Z	4	4
ρ_{clacd} [g cm^{-3}]	1.235	1.163