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Development of New Reactions Catalyzed by Copper(I) Complexes using Silylboranes and Bisboronates as Pronucleophiles.

Dissertation présentée en vue de l'obtention

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Abstract

The development of new catalytic methods has been an area of intense research in recent years and particular efforts are currently devoted to transition-metal-catalyzed reactions. We are thus interested in developing new reactions catalyzed by copper(I) complexes.

In the chapter 1, the objective was the extension of 1,4-addition/aldolisation reactions developed earlier in our group. Concerning the silylation reaction, we were able to isolate several interesting adducts with moderate to good yields but with low diastereoselectivities in almost all cases. About the borylation reaction, two strategies for the synthesis of new cationic copper(I) complexes bearing a bifluoride counteranion were described. These complexes were therefore used in our reaction and have shown a good reactivity. However, the selectivities were low in most cases.

In the chapter 2, our interest lies in the addition of silicon nucleophile to acid derivatives, thus generating acylsilanes. They are versatile intermediates in organic synthesis and are used mainly as umpolung reagents for the preparation of carbonyl derivatives. An efficient method to synthesize these compounds, starting from easy-to-form anhydrides, was described here with good to excellent yields.

In the chapter 3, the first example of enantioselective addition of a silicon nucleophile to aldehydes catalyzed by our newly developed copper(I) complexes are reported. A series of aromatic and aliphatic aldehydes were converted to the corresponding α-hydroxysilanes in excellent *ee* and very good yields.

Résumé

Le développement de nouvelles réactions catalysées par des métaux de transition est un domaine en pleine expansion depuis quelques années. C'est pourquoi nous nous sommes intéressés à l'étude de nouvelles méthodologies catalysées par des complexes de cuivre(I).

Dans le chapitre 1, l'objectif était d'étendre les réactions d'addition-1,4/aldolisation développées précédemment dans notre laboratoire. En ce qui concerne la réaction de silylation, certains adduits intéressants ont pu être isolés avec de bons rendements mais avec de faibles diastéréosélectivités dans la plupart des cas. Concernant la réaction de borylation, deux stratégies de synthèse de nouveaux complexes cationiques de cuivre(I) avec un contre-anion bifluorure ont été développées. Ces complexes ont ensuite été testés dans notre réaction et ont montré une très bonne réactivité. Malheureusement, jusqu'à maintenant, les sélectivités obtenues ne sont pas très bonnes.

Dans le chapitre 2, notre intérêt s'est porté sur l'addition de nucléophiles silylés sur des dérivés d'acide dans le but de former des acylsilanes. Ces composés sont très intéressants comme blocs de construction en chimie organique. Une méthode très pratique et efficace a donc été développée à partir d'anhydrides facilement synthétisables. De nombreux acylsilanes ont été obtenus avec de très bons rendements.

Dans le chapitre 3, le premier exemple d'addition énantiosélective de nucléophiles silylés sur des aldéhydes catalysée par des complexes cationiques de cuivre(I) a été reporté. Une large gamme d'aldéhydes aromatiques et aliphatiques a été transformée en α–hydroxysilanes avec de très bons rendements et d'excellentes énantioséléctivités.

Abreviations

Å	:	Angström
AcOEt	:	Ethyl acetate
AcOH	:	Acetic acid
AIBN	:	Azobisisobutyronitrile
Alk	:	Alkyl
APCI	:	Atmospheric Pressure Chemical Ionization
Aq.	:	Aqueous
Ar	:	Aryl
atm.	:	Atmosphere
BINAP	:	2,2'-(diphenylphosphino)-1,1'-binaphtalene
Bn	:	Benzyl
Boc	:	Di-*tert*-butyl dicarbonate
Bt	:	Benzotriazole
^{n}Bu	:	Butyl
^{t}Bu	:	*Tert*-butyl
Cat.	:	catalytic
Cp	:	Cyclopentadienyl
Cy	:	Cyclohexyl
d	:	Days
DBM	:	dibenzoylmethane
DBU	:	1,8-diazabicyclo[5.4.0]undec-7-ene

DCC	:	Dicyclohexylcarbodiimide
DCE	:	Dichloroethane
DCI	:	Diisopropylcarbodiimide
DCM	:	Dichloromethane
DMAP	:	4-dimethylaminopyridine
DME	:	Dimethylether
DMF	:	*N,N*-dimethylformamide
DMP	:	2,2-dimethoxypropane
DMPU	:	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	:	Dimethylsulfoxyde
DPEPhos	:	Bis(2-diphenylphosphinophenyl)ether
DPPE	:	Diphenylphosphinoethane
DPPF	:	Diphenylphosphinoferrocene
dtbpy	:	4,4'-Di-tert-butyl-2,2'-dipyridyl
E	:	Electrophile
de	:	Diastereomeric excess
dr	:	Diastereoisomeric ratio
EDC	:	1-Ethyl-3-(3-dimethylaminopropyl)-carbodiimide
ee	:	Enantiomeric excess
equiv.	:	Equivalent
er	:	Enantioselective ratio
ESI	:	Electrospray ionization

Et	:	Ethyl
EWG	:	Electronwithdrawing group
GC	:	Gas chromatography
h	:	Hour
HMPA	:	Hexamethylphosphoramide
HMPT	:	Hexamethylphosphorictriamide
HPLC	:	High Pressure Liquid Chromatography
HRMS	:	High resolution mass spectroscopy
Hz	:	Hertz
^{i}Pr	:	Isopropyl
IR	:	Infra-red
L	:	Ligand
LDA	:	Lithium diisopropylamide
nd	:	Not determined
Me	:	Methyl
$MePh_2SiH$	:	Methyldiphenylsilane
$Me(EtO)_2SiH$	:	Methyldiethoxysilane
mmol	:	Millimole
M.W.	:	Molecular weight
NBS	:	N-bromosuccinimide
NHS	:	N-hydroxysuccinimide
NHC	:	*N*-heterocyclic carbene
NMP	:	1-methyl-2-pyrrolidinone

NMR	:	Nuclear magnetic resonance
Nu	:	Nucleophile
PE	:	Petroleum ether
Ph	:	Phenyl
$PhSiH_3$	:	Phenylsilane
PMHS	:	Polyméthylhydrosilyloxane
^{n}Pr	:	*n*-Propyl
Ppm	:	Part par million
Py	:	pyridine
rt	:	Room temperature
TBAF	:	Tetrabutylammonium fluoride
TBAT	:	Tetrabutylammonium triphenyldifluorosilicate
TBME	:	*Tert*-butylmethylether
Tf	:	Triflate
TFA	:	Trifluoroacetate
THF	:	Tetrahydrofuran
TLC	:	Thin layer chromatography
TMDS	:	1,1,3,3-tétraméthylhydrosiloxane
TMS	:	Trimethylsilyl
Ts	:	Tosyl
Tol.	:	Toluene
XantPhos	:	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

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GENERAL INTRODUCTION

I. Introduction

The development of new catalytic methods has been an area of intense research in recent years. Particular efforts are currently devoted to transition-metal-catalyzed reactions, which often lead to the synthesis of new derivatives that were otherwise inaccessible, with remarkable control of chemo-, regio-, diastereo- and even enantioselectivities. Copper(I) has proven to be an excellent metal to develop catalytic reactions. This is the reason why we were interested in the development of new methodologies using neutral copper(I)-nucleophiles complexes. As shown in figure 1, the reaction of copper complexes bearing a hard ligand and a pronucleophile (silane, silylborane, bisboronate …) can lead to the formation of "Cu-Nu" species.

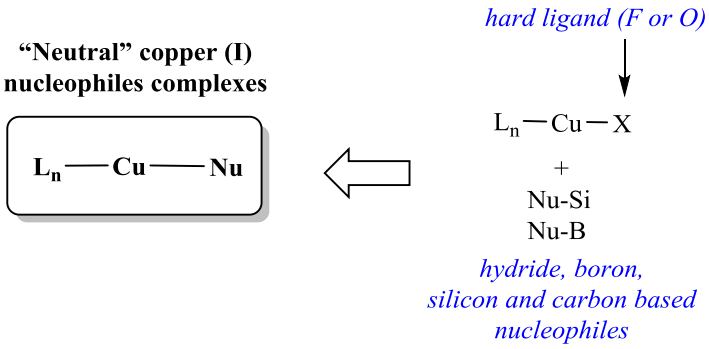


Figure 1. Neutral copper(I) nucleophiles complexes.

These intermediates are very interesting because they can be involved in various reactions such as 1,2-additions, 1,4-additions, hydrocuprations, silylcuprations, etc… (Figure 2).

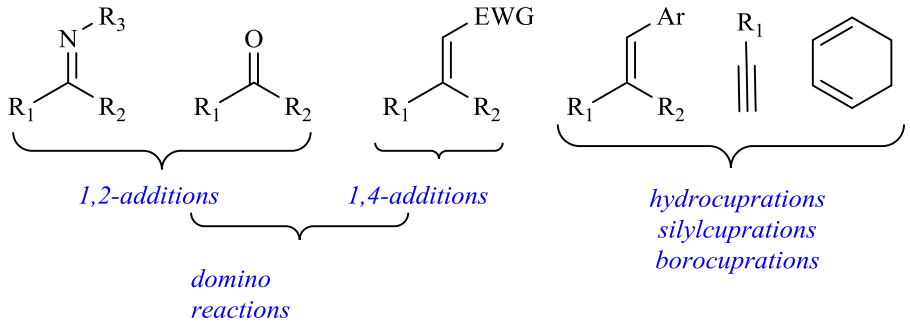
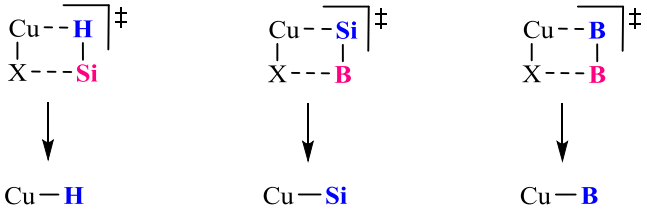


Figure 2. Reactions catalyzed by copper(I) complexes.

As mentioned earlier, cooperative transmetalation of interelement linkages with copper catalysts provides a facile entry into nucleophilic main group element/copper(I) compounds. An intriguing σ-bond metathesis is believed to be the activating step, thus building a conceptual bridge between the emerging areas of Cu–H, Cu–B, and Cu–Si chemistry (Scheme 1).



Scheme 1. Neutral copper(I) nucleophiles complexes.

The aim of this general introduction is to illustrate methods for the preparation of such reagents and catalytic systems and their use in organic chemistry. Activation of these interelement bonds (Si-Si, Si-B and B-B) is also discussed in this section. We will see that copper(I) complexes are very efficient for the addition of a large number of nucleophiles to various electrophiles.

II. Copper(I) hydride reagents[1]

Since the first report on the synthesis and characterization of a copper(I) hydride complex in 1971 by the group of Churchill and Osborn,[2] the use of such soft hydride in organic synthesis has known a growing success due to the work of Stryker. Indeed, modern usage of Cu-H in synthesis is well recognized to have begun with the "Stryker's reagent" in 1988. The mildness of reaction conditions, functional group compatibility and excellent overall efficiencies were so impressive that this crystalline red solid was propelled to the status of "Reagent of the Year" in 1991 by a well known chemical supplier. In addition to the reduction of electrophilic double bonds, it was also shown that these mild complexes could be used in catalytic reduction reactions using various sources of hydrides (molecular hydrogen, silanes and boranes). Moreover, copper(I) hydride complexes have exhibited excellent ability to reduce harder electrophiles such as aldehydes and ketones. More recent development in this field showed that the addition of copper(I) hydride to electrophilic

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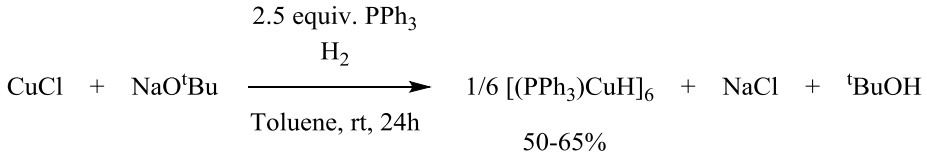
[1] (a) Lipshutz, B. H., In *Modern Organocopper Chemistry*; Ed., N. Krause; Wiley-VCH: Weinheim, **2002**, 167-187 and references cited therein. (b) Riant, O., *Copper(I) Hydride Reagents and Catalysts in The Chemistry of Organocopper Compounds* (Ed.: Z. Rappoport, I. Marek), Wiley, New York, **2009**, 731 –774. (c) Rendler, S.; Oestreich, M., *Angew. Chem. Int. Ed.* **2007**, *46*, 498-504. (d) Deutsch, C.; Krause, N.; Lipshutz, B. H., *Chem. Rev.* **2008**, *108*, 2916-2927. (e) Fátima, A., *Synlett* **2005**, 1805-1806.

[2] Churchill, M. R.; Bezman, S. A.; Osborn, J. A.; Wormald, J., *J. Am. Chem. Soc.* **1971**, *93*, 2063-2065.

double bond leads to the formation of copper enolates that can be used in domino processes and therefore allows the formation of C-C bonds.

II.1. Generating Stryker's reagent and alternatives

The most common and frequently used copper hydride species is the phosphine-stabilized hexamer, $[(Ph_3P)CuH]_6$, the so-called "Stryker's reagent".[3] The structure of this complex was proven by X-ray crystallography by Bau and co-workers.[4] It was used from 1988 as an efficient chemoselective reducing agent of electrophilic double bonds and later as a precatalyst for various hydrogenation and hydrosilylation reactions. Stryker reported a convenient procedure for the multi-gram scale preparation of this complex (Scheme 2).[3a]



Scheme 2. Preparation of Stryker's reagent.

Copper alkoxide can be generated *in situ* from copper(I) chloride and sodium *tert*-butoxide. Reduction to the copper hydride occurs then under pressure (1 atm) of hydrogen. This procedure was later improved to

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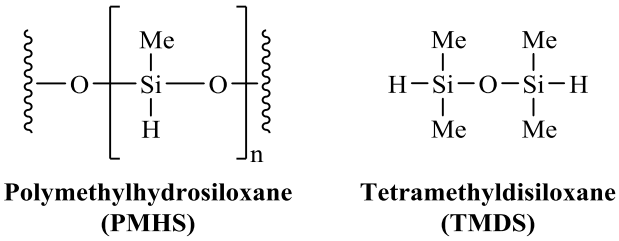
[3] (a) Brestensky, D. M.; Huseland, D. E.; McGettigan, C.; Stryker, J. M., *Tet. Lett.* **1988**, *29*, 3749-3752. (b) Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M., *J. Am. Chem. Soc.* **1988**, *110*, 291-293. (c) Brestensky, D. M.; Stryker, J. M., *Tet. Lett.* **1989**, *30*, 5677-5680. (d) Koenig, T. M.; Daeuble, J. F.; Brestensky, D. M.; Stryker, J. M., *Tet. Lett.* **1990**, *31*, 3237-3240.

[4] Stevens, R. C.; McLean, M. R.; Bau, R.; Koetzle, T. F., *J. Am. Chem. Soc.* **1989**, *111*, 3472-3473.

avoid the use of this air-sensitive system. For example, Chiu and co-workers reported the use of dimethylphenylsilane as a reducing agent.[5] Yun and Lee also showed that copper(II) salts allowed to obtain the Stryker's reagent in high purity and yield thus avoiding the preparation of the sensitive copper(I) alkoxide.[6]

Silanes, which are in general inexpensive and environmentally friendly, are the most common source of stoichiometric hydride:[7] polymethylhydrosiloxane (PMHS), tetramethyldisiloxane (TMDS), Fleming's silane ($PhMe_2SiH$) and phenylsilane ($PhSiH_3$) for example (Scheme 3).



Polymethylhydrosiloxane (PMHS) **Tetramethyldisiloxane (TMDS)**

Scheme 3. Structures of PMHS and TMDS.

Use of nonracemic bis-phosphines as ligands led to the generation of chiral copper hydride species that allowed to perform reactions in a diastereo- and enantioselective fashion. All success realized to date has

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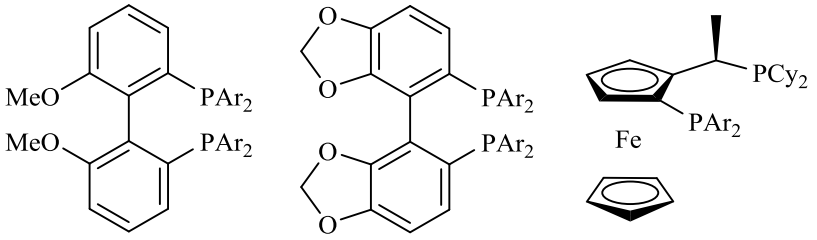
[5] Chiu, P.; Li, Z.; Fung, K. C. M., *Tet. Lett.* **2003**, *44*, 455-457.

[6] Lee, D.-w.; Yun, J., *Tet. Lett.* **2005**, *46*, 2037-2039.

[7] (a) Llamas, T.; Arrayás, R. G.; Carretero, J. C., *Angew. Chem. Int. Ed.* **2007**, *46*, 3329-3332. (b) Lipshutz, B. H.; Servesko, J. M.; Petersen, T. B.; Papa, P. P.; Lover, A. A., *Org. Lett.* **2004**, *6*, 1273-1275. (c) Lipshutz, B. H.; Chrisman, W.; Noson, K.; Papa, P.; Sclafani, J. A.; Vivian, R. W.; Keith, J. M., *Tetrahedron* **2000**, *56*, 2779-2788.

come from the use of certain atropo-diphosphines of the Biphep, Segphos series and Solvias Josiphos series (Scheme 4).[8] These ligands deserve special merit not only for their remarkable structural features but also for the high turnover numbers (TONs) achieved.



Biphep series **Segphos series** **Josiphos series**

Scheme 4. Ligands frequently used for asymmetrical Cu-H reductions.

Nowadays, N-heterocyclic carbenes (NHCs) are becoming very popular as an alternative to phosphorus based ligands because they are quite distinct both electronically and structurally.[9] Usually, (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 5).

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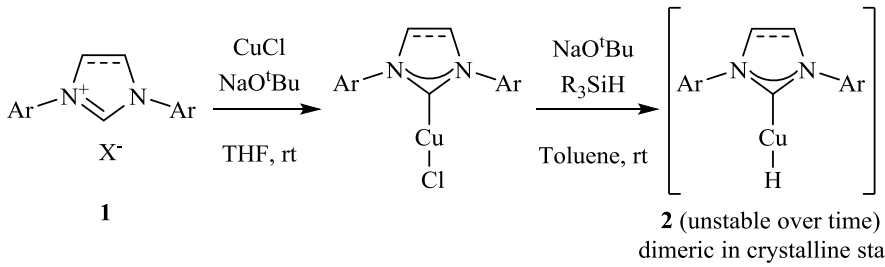
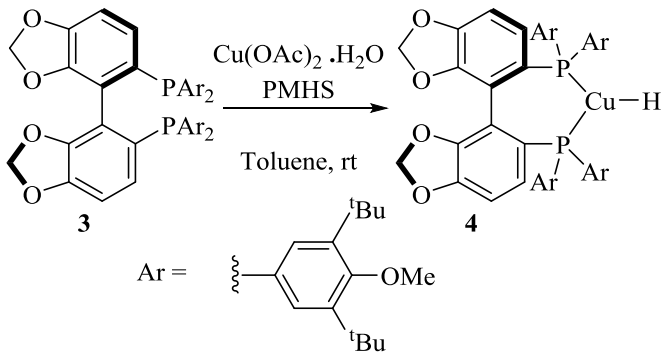
[8] (a) Schmid, R., Broger, E. A., Cereghetti, M., Crameri, Y., Foricher, J., Lalonde, M., Müller, R. K., Scalone, M., Schoettel, G., Zutter, U., *Pure Appl. Chem.* **1996**, *68*, 131-138. (b) Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H., *Adv. Synth. Catal.* **2001**, *343*, 264-267. (c) Blaser, H.-U.; Brieden, W.; Pugin, B.; Spindler, F.; Studer, M.; Togni, A., *Top. Catal.* **2002**, *19*, 3-16.

[9] (a) Díez-González, S.; Nolan, S. P., *Synlett* **2007**, 2158-2167. (b) Díez-González, S.; Scott, N. M.; Nolan, S. P., *Organometallics* **2006**, *25*, 2355-2358. (c) Yun, J.; Kim, D.; Yun, H., *Chem. Commun.* **2005**, 5181-5183.



Scheme 5. Preparation of (NHC)Cu-H.

However, each one of these reactive species described here (except the Stryker's reagent) must be generated *in situ*. This drawback was later solved by Lipshutz and Frieman in 2005.[10] They described a chiral copper hydride species bearing the *(R)*-DTBM-Segphos ligand **3** (Scheme 6). This complex is claimed to be exceptionally stable and can be stored in solution if kept under argon.

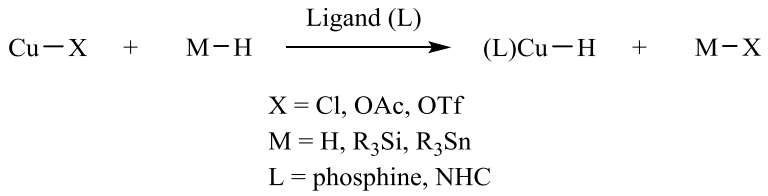


Scheme 6. « Cu-H-in-a-bottle ».

To summarize, we have seen that there are many different ways to generate Cu-H species (Scheme 7). With several sources of copper(I) hydride now available, current Cu-H chemistry is still focused on

[10] Lipshutz, B. H.; Frieman, B. A., *Angew. Chem. Int. Ed.* **2005**, *44,* 6345-6348.

catalytic enantioselective processes. Applications of theses catalysts are described in the following sections.



Scheme 7. Catalytic generation of copper hydrides.

II.2. 1,4-Reductions

1,4-additions of copper(I) hydride to a variety of electrophilic groups such as unsaturated carbonyl compounds have been largely developed during the past few years.[11] These reactions take advantage of the carbophilic nature of copper, usually affording the 1,4-addition product. The first example of enantioselective conjugate reduction using *in situ* generation of a bis-phosphine chiral Cu-H species was decribed by Buchwald and co-workers.[12] They used CuCl as copper source, NaO^{t}Bu as base and *(S)-p*-tol-Binap **5** as chiral ligand (Scheme 8). With this system, enones as well as unsaturated esters, lactones and lactams can be smoothly reduced affording the corresponding saturated systems in very good yields and high enantiomeric excesses.

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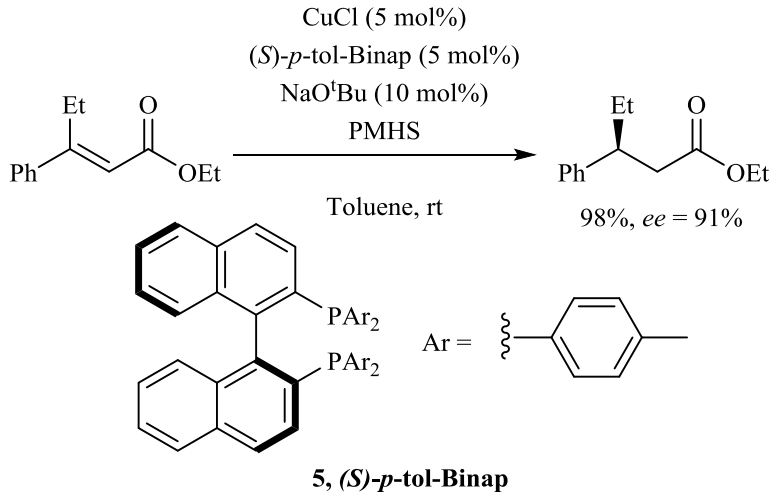
[11] Christoffers, J.; Koripelly, G.; Rosiak, A.; Rössle, M., *Synthesis* **2007**, 1279-1300.

[12] (a) Appella, D. H.; Moritani, Y.; Shintani, R.; Ferreira, E. M.; Buchwald, S. L., *J. Am. Chem. Soc.* **1999**, *121*, 9473-9474. (b) Moritani, Y.; Appella, D. H.; Jurkauskas, V.; Buchwald, S. L., *J. Am. Chem. Soc.* **2000**, *122*, 6797-6798. (c) Hughes, G.; Buchwald, S. L., *J. Am. Chem. Soc.* **2003**, *125*, 11253-11258.



5, *(S)*-*p*-tol-Binap

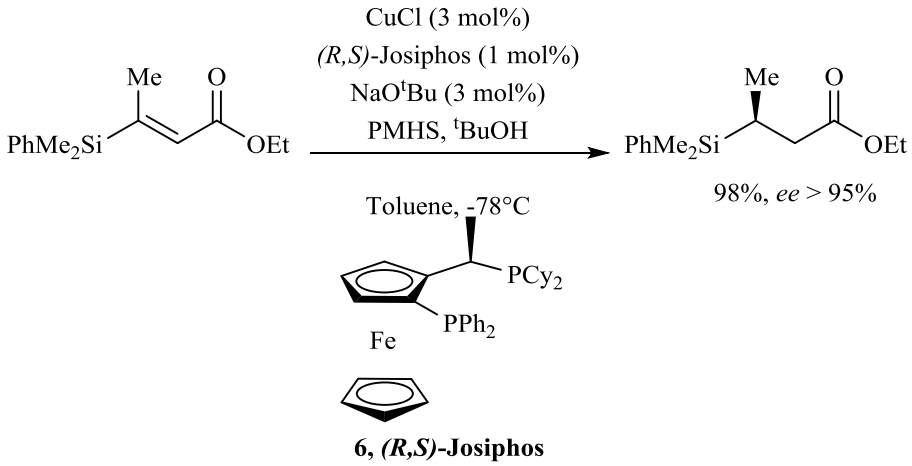
Scheme 8. Catalytic enantioselective 1,4-reduction.

Following the first developments of the group of Buchwald, Lipshutz and co-workers found that Josiphos- and Segphos-chiral Cu-H species led to higher levels of chiral induction than those obtained with the corresponding Binap Cu-H derivatives. They reported in 2003 the conjugated reduction of acyclic enones (Scheme 9).[13] Various enones were successfully reduced with Josiphos ligand **6** and high enantioselectivities were obtained in most cases. The use of Segphos ligand was later applied to the conjugated reduction of other family of substrates including α,β-unsaturated esters, lactones, ...[7b,14] However, DTBM-Segphos **3** gave the best enantioselection for cyclic substrates (Scheme 10).

---

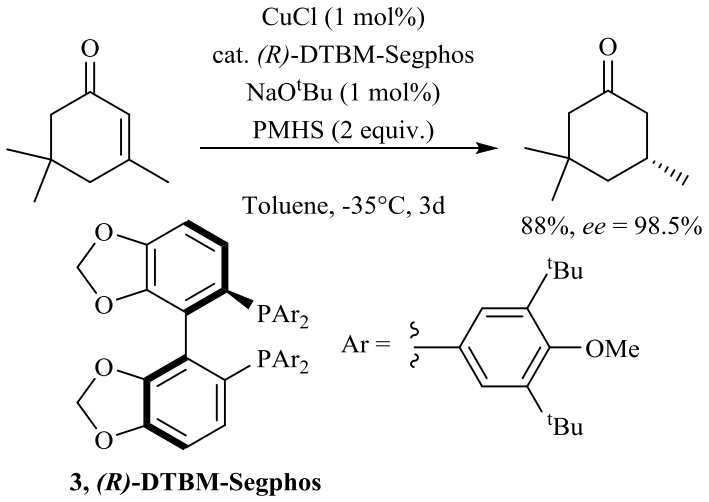
[13] Lipshutz, B. H.; Servesko, J. M., *Angew. Chem. Int. Ed.* **2003**, *42*, 4789-4792.

[14] (a) Lipshutz, B. H.; Tanaka, N.; Taft, B. R.; Lee, C.-T., *Org. Lett.* **2006**, *8*, 1963-1966. (b) Lipshutz, B. H.; Lee, C.-T.; Taft, B. R., *Synthesis* **2007**, 3257-3260.



6, *(R,S)*-Josiphos

Scheme 9. Catalytic enantioselective 1,4-reduction with Josiphos.

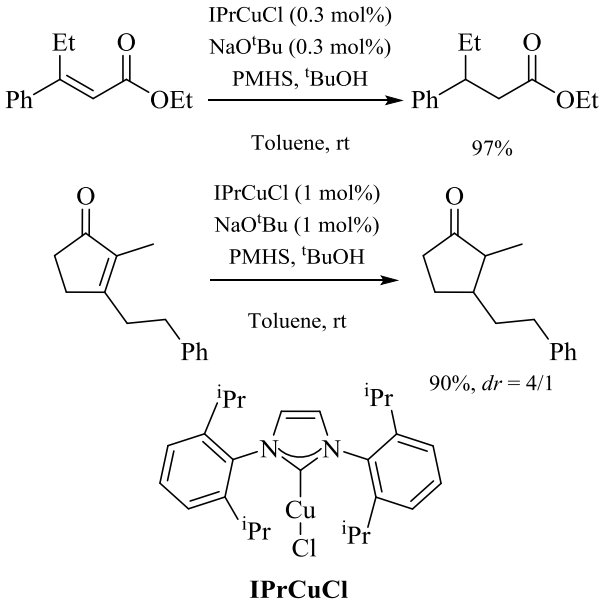


3, *(R)*-DTBM-Segphos

Scheme 10. Catalytic enantioselective 1,4-reduction with *(R)*-DTBM-Segphos.

The pioneer work of Buchwald in the asymmetric conjugated addition of copper hydrides led other groups to investigate this methodology on various types of electrophilic double bonds bearing electron-withdrawing

groups such as nitro, cyano and sulfonyl groups.[15] Use of N-heterocyclic carbenes as ligands instead of phosphines can be interesting achiral alternative for the generation of catalytic reducing hydride species. For example, Buchwald and co-workers reported in 2003 the use of IPrCuCl to reduce various cyclic and acyclic enones (Scheme 11).[16]



Scheme 11. 1,4-reduction with NHC-Cu complex.

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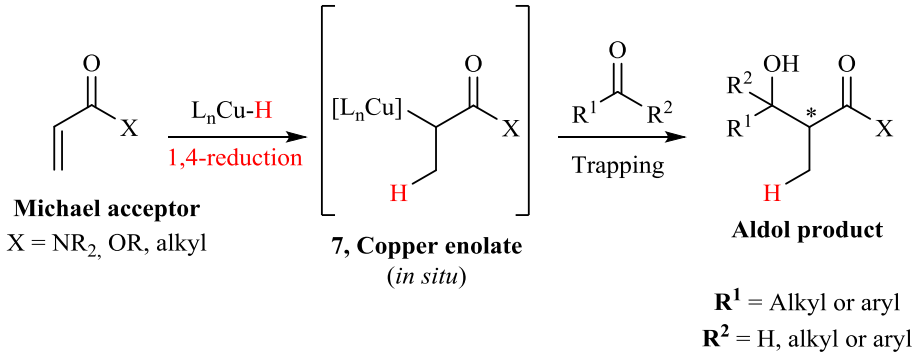
[15] Selected examples : (a) Czekelius, C.; Carreira, E. M., *Angew. Chem. Int. Ed.* **2003**, *42*, 4793-4795. (b) Lee, D.; Yang, Y.; Yun, J., *Org. Lett.* **2007**, *9*, 2749-2751. (c) Llamas, T.; Arrayás, R. G.; Carretero, J. C., *Angew. Chem. Int. Ed.* **2007**, *46*, 3329-3332.

[16] Jurkauskas, V.; Sadighi, J. P.; Buchwald, S. L., *Org. Lett.* **2003**, *5*, 2417-2420.

II.3. Tandem reactions

II.3.1. Catalytic tandem process with non-chiral ligands

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 intramolecular trapping of the generated intermediate. If the resulting copper enolate **7** reacts with an aldehyde or a ketone, this reaction can generate the desired aldolisation product in a *one-pot* domino process (Scheme 12).

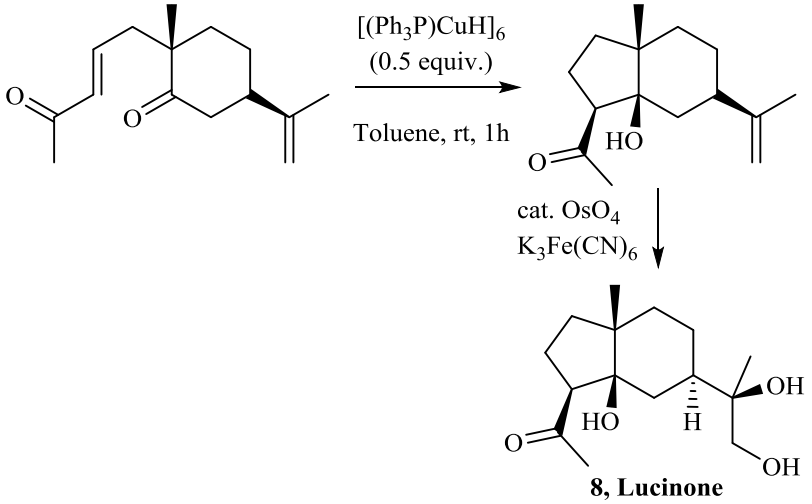


Scheme 12. 1,4-reduction/aldolisation process.

The pioneer work was reported in 1998 by Chiu and co-workers. They described elegant variations of intramolecular versions of reductive aldol reactions using the Stryker reagent in stoichiometric and catalytic amounts.[17] A few years later, the same group developed an

[17] (a) Chiu, P.; Chen, B.; Cheng, K. F., *Tet. Lett.* **1998**, *39*, 9229-9232. (b) Chiu, P.; Szeto, C.-P.; Geng, Z.; Cheng, K.-F., *Org. Lett.* **2001**, *3*, 1901-1903. (c) Chiu, P.; Leung, S. K., *Chem. Commun.* **2004**, 2308-2309.

intramolecular reduction-aldol reaction as a key step in the total synthesis of lucinone **8**, an antispasmodic drug (Scheme 13).[18]



Scheme 13. Synthesis of Lucinone **8**.

One of the first examples of an intermolecular version of the reductive aldol reaction between Michael acceptors and aldehydes was reported by Riant and co-workers.[19] It was shown earlier that NHC copper(I) chloride complexes could be used as precatalysts for the reduction of various types of electrophilic double bonds. Therefore, they found that (NHC)Cu^{I} catalysts bearing a DBM counterion such as **9** are extremely reactive in the intermolecular reaction of methyl acrylate and aldehydes (Scheme 14). High chemoselectivities, good yields and good diastereoselectivities were observed for various Michael acceptors and aromatic and aliphatic aldehydes.

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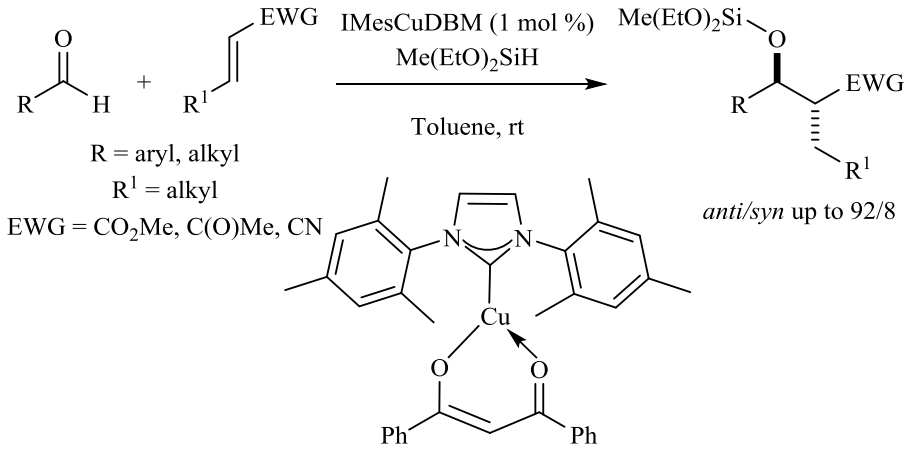
[18] Chiu, P.; Szeto, C. P.; Geng, Z.; Cheng, K. F., *Tet. Lett.* **2001**, *42*, 4091-4093.

[19] Welle, A.; Díez-González, S.; Tinant, B.; Nolan, S. P.; Riant, O., *Org. Lett.* **2006**, *8*, 6059-6062.



9, IMesCuDBM

Scheme 14. 1,4-reduction/aldolisation using (NHC)Cu-complex.

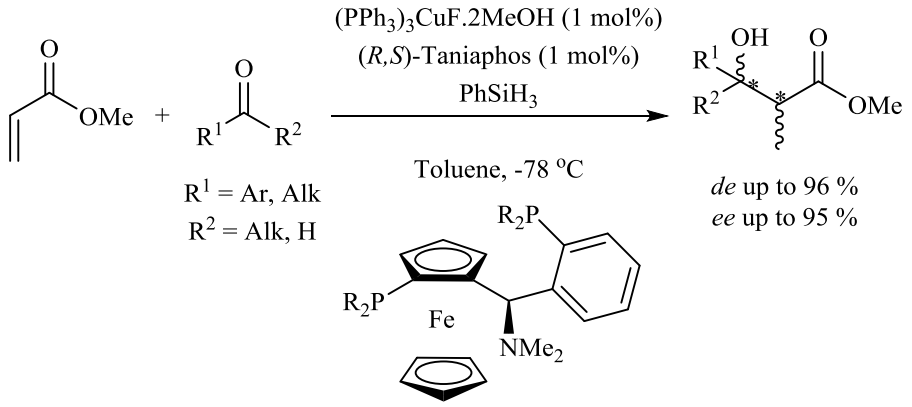
II.3.2. Catalytic tandem processes with chiral ligands

The first enantioselective version of an intermolecular reductive aldol reaction between methyl acrylates and electrophiles was reported by the group of Riant in 2006.[20] Aromatic and aliphatic aldehydes and ketones readily react with the copper enolate intermediate to afford the desired aldol product with high *syn*-selectivity and good to excellent *ee's* (Scheme 15). The chiral ligand of choice for this transformation is Taniaphos **10**. Since the chirality transfer must derive from an asymmetrically ligated copper enolate, reactions are best carried out in toluene at low temperature. Related reactions with dialkyl ketones have also been reported with modest success.[21]

---

[20] (a) Deschamp, J.; Chuzel, O.; Hannedouche, J.; Riant, O., *Angew. Chem. Int. Ed.* **2006**, *45*, 1292-1297. (b) Chuzel, O.; Deschamp, J.; Chausteur, C.; Riant, O., *Org. Lett.* **2006**, *8*, 5943-5946.

[21] Zhao, D.; Oisaki, K.; Kanai, M.; Shibasaki, M., *Tet. Lett.* **2006**, *47*, 1403-1407.

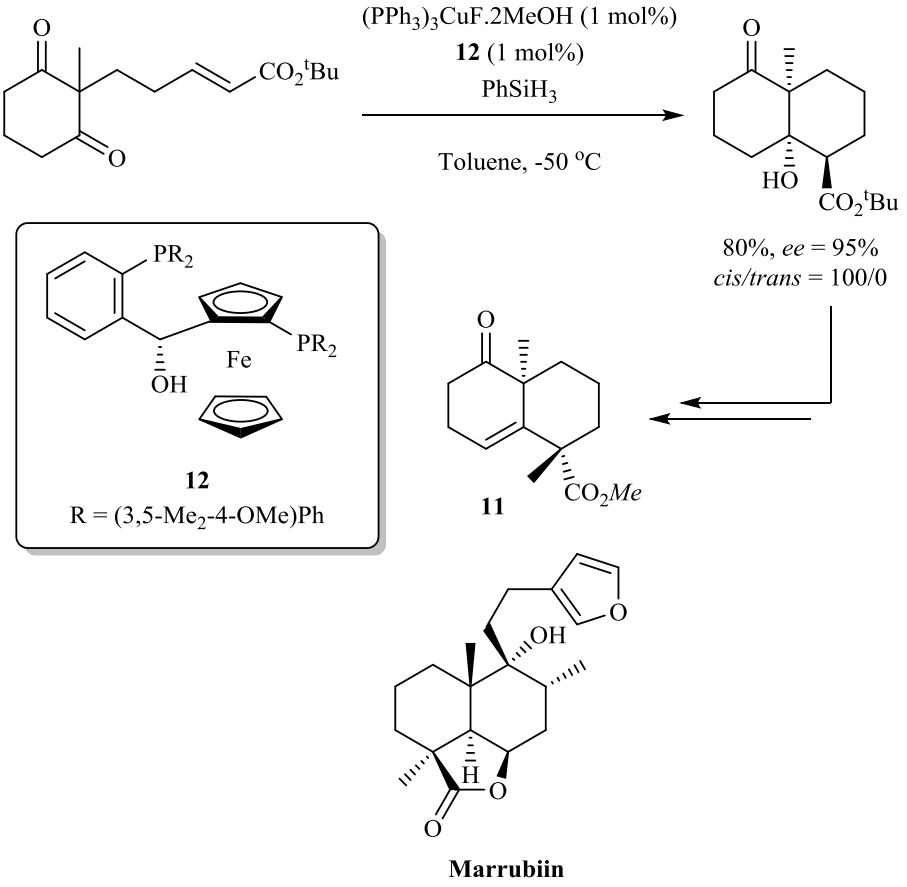


10, (*R*,*S*)-Taniaphos
R = Ph or Cy

Scheme 15. Enantioselective 1,4-reduction/aldolisation of acrylates.

An intramolecular version was also developed by the same group to form various bicyclic products.[22] This strategy was later applied to the synthesis of **11** which is a key intermediate in the synthesis of Marrubiin, a natural diterpene (Scheme 16).

[22] (a) Deschamp, J.; Riant, O., *Org. Lett.* **2009**, *11*, 1217-1220. (b) Deschamp, J.; Hermant, T.; Riant, O., *Tetrahedron* **2012**, *68*, 3457-3467.



Scheme 16. Synthesis of key intermediate **11**.

III. Cu^{I}-Si and Cu^{I}-B reagents

Organoboranes and organosilanes are versatile reagents for organic synthesis due, in part, to a combination of accessibility, stability and reactivity. Among the electropositive elements, silicon and boron are highly characteristic in that they form highly stable, covalent bonds to carbon. The chart below show bond energies of these elements.[1]

	E (kJ/mol)
B-B	293
C-B	356
B-F	613
Si-Si	222
C-Si	318
Si-F	565

These functional groups serve as exceptionnally versatile linchpins in synthesis selectively transforming into an enormous breadth of C-C and C-Het bonds. Recent uses of organosilicon and organoboron compounds in a wide variety of chemical transformations have greatly enhanced their utility in synthetic organic chemistry. Therefore it is essential to explore new efficient methodologies for their synthesis. We will summarize here the different modes of B-B, Si-Si and Si-B

[1] Barton D.; Ollis, W. D.; in "Comprehensive Organic Chemistry", ed. Jones, D. N., Pergamon, Oxford, 1979, vol. 3.

activation. The major portion of this section provides a comprehensive survey of applications, including some tentative reaction mechanisms.

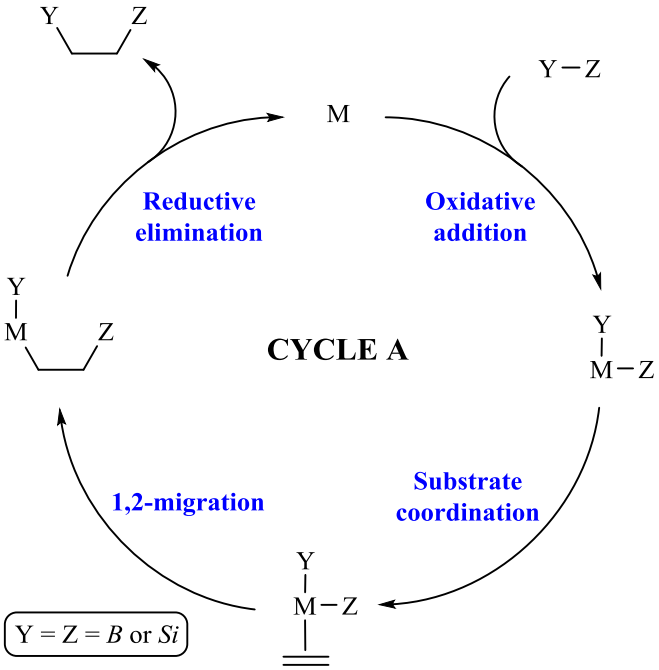
III.1. Mechanisms of B-B, Si-Si and Si-B interelement bond activation

Interelement compounds are compounds containing a bond linking two heteroatoms. They are attractive because they provide the opportunity to transfer both bonding partners to an unsaturated substrate. Two generalized reaction mechanisms account for the majority of catalytic dimetalation reactions and can be used for selecting appropriate catalytic metal-ligand combinations.[2] The most common mechanism is depicted in scheme 17.[3] It involves oxidative addition of the interelement compound to the transition-metal catalyst. The first step is the oxidative insertion of the metal catalyst followed by substrate coordination. Finally, 1,2-migration followed by reductive elimination releases the product and returns the catalyst to the original oxidation state.

---

[2] Burks, H. E.; Morken, J. P., *Chem. Commun.* **2007**, 4717-4725.

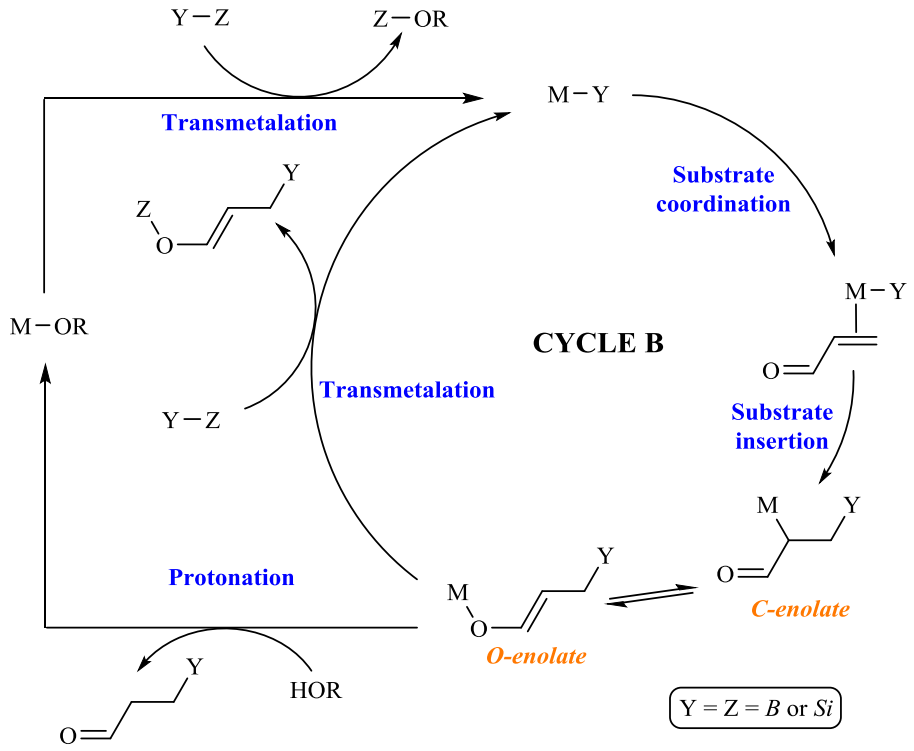
[3] Oxidative addition of diboron reagents to d^8 metals : (a) Iverson, C. N.; Smith, M. R., *J. Am. Chem. Soc.* **1995**, *117*, 4403-4404. (b) Ishiyama, T.; Matsuda, N.; Murata, M.; Ozawa, F.; Suzuki, A.; Miyaura, N., *Organometallics* **1996**, *15*, 713-720. (c) Clegg, W.; Lawlor, F. J.; Lesley, G.; Marder, T. B.; Norman, N. C.; Orpen, A. G.; Quayle, M. J.; Rice, C. R.; Scott, A. J.; Souza, F. E. S., *J. Organomet. Chem.* **1998**, *550*, 183-192.



Scheme 17. Cycle A.

Lastly, a catalytic cycle that employs interelement reagents but one that avoids any type of oxidative addition may operate with activated alkene substrates (Scheme 18, Cycle B).[4]

[4] Ito, H.; Ishizuka, T.; Tateiwa, J.-I.; Sonoda, M.; Hosomi, A., *J. Am. Chem. Soc.* **1998**, *120*, 11196-11197. Clark, C. T.; Lake, J. F.; Scheidt, K. A., *J. Am. Chem. Soc.* **2003**, *126*, 84-85.



Scheme 18. Cycle B.

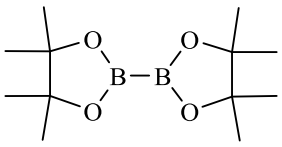
The mechanism involves substrate insertion into an M-Si or M-B bond which affords C-enolate. It should be noticed that there is an equilibrium between C-enolate and O-enolate as explained later in this chapter. The process is then followed by either transmetalation (dimetalation process) or protonation-transmetalation (hydrometalation process). The last steps are the release of the product and regeneration of the M-Si or M-B catalyst.

In considering the above-described cycles, it becomes clear that the nature of the dimetalation reagent is of critical consideration. Another important issue in reagent selection is availability. We will see in the

following sections selected examples which illustrate these considerations.

III.2. Reactions of Cu^{I}-B reagents

Bis(pinacolato)diboron ($B_2(pin)_2$) **13** is the most commonly used diboron reagent in organic chemistry, due in most part to its commercial availability (Figure 3). In this section, we are going to report selected examples of reactions using this diboron reagent.



13, $B_2(pin)_2$

Figure 3. Structure of $B_2(pin)_2$.

As can be see in the chart below, there are a lot of possible reactions which use $B_2(pin)_2$. Indeed, this species in a presence of a copper catalyst can react with various substrates.[5]

---

[5] For selected examples of reactions with Cu^{I}-B reagents see: (a) Hata, T.; Kitagawa, H.; Masai, H.; Kurahashi, T.; Shimizu, M.; Hiyama, T., *Angew. Chem. Int. Ed.* **2001**, *40*, 790-792 (Gem-dimetalation). (b) Lee, Y.; Hoveyda, A. H., *J. Am. Chem. Soc.* **2009**, *131*, 3160-3161. (Hydroboration) (c) Lillo, V.; Fructos, M. R.; Ramírez, J.; Braga, A. A. C.; Maseras, F.; Díaz-Requejo, M. M.; Pérez, P. J.; Fernández, E., *Chem. Eur. J.* **2007**, *13*, 2614-2621 (Diboration of alkenes and alkynes). (d) Alfaro, R.; Parra, A.; Alemán, J.; García Ruano, J. L.; Tortosa, M., *J. Am. Chem. Soc.* **2012**, *134*, 15165-15168 (Carboboration). (e) Ibrahem, I.; Breistein, P.; Córdova, A., *Angew. Chem. Int. Ed.* **2011**, *50*, 12036-12041 (1,6-addition). (f) Semba, K.; Fujihara, T.; Terao, J.; Tsuji, Y., *Angew. Chem. Int. Ed.*

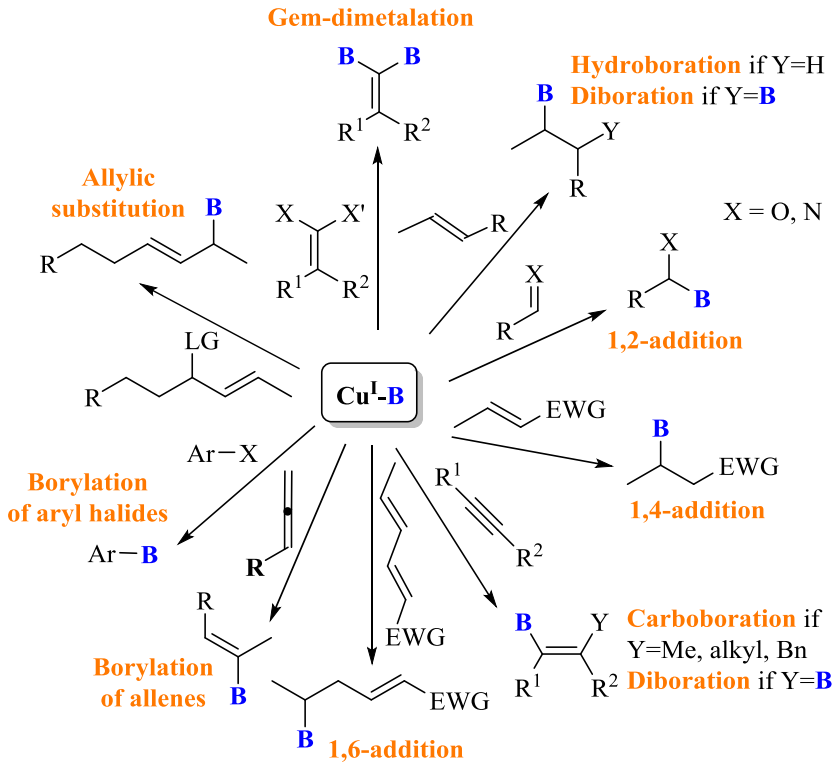


Figure 4. Reactions with Cu^{I}-B reagents.

Because we don't have time to describe all of these reactions, we will focus our attention to 1,4- and 1,2-addition of this Cu^{I}-B species.

2013, *52*, 12400-12403 (Borylation of allenes). (g) Kleeberg, C.; Dang, L.; Lin, Z.; Marder, T. B., *Angew. Chem. Int. Ed.* **2009**, *48*, 5350-5354 (Borylation of aryl halides). (h) Ito, H.; Kawakami, C.; Sawamura, M., *J. Am. Chem. Soc.* **2005**, *127*, 16034-16035 (Allylic substitution).

III.2.1. Enantioselective conjugate borylation[6]

Catalytic diboration of unsaturated ketones, nitriles, esters and phosphonates generally provides the 1,4-addition product. First example of Cu^{I}-catalyzed conjugate borylation was reported independently by Hosomi and Miyaura in racemic systems.[7] They showed that the combination of copper(I) sources with Bu_3P activates the B-B bond in $B_2(pin)_2$ and promotes the conjugate addition of the "B(Pin)" moiety to electron-deficient acceptors. More recently, quantum-chemical calculations by Marder and co-workers provided necessary mechanistic understanding to further extend the development of this type of catalysis.[8] Their investigation rationalized the role of the addition of methanol and the difference in reactivity between α,β–unsaturated carbonyl and carboxyl compounds. The catalytic cycle begins with the formation of the active species Cu(I)-Bpin **II** by a σ-bond metathesis between copper(I)-complex **I** and **13** (Scheme 19). Coordination of **II** to the C=C bond of **III** followed by insertion into the Cu-B bond afforded C-enolate **IV**. As indicated by calculated barriers, the σ-bond metathesis of **IV** with **13** is energetically unlikely compared to the reaction of copper(I)-oxygen bond of **V** in the related σ-bond metathesis. Therefore equilibrium between **IV** and **V** fundamentally affects the turnover and its

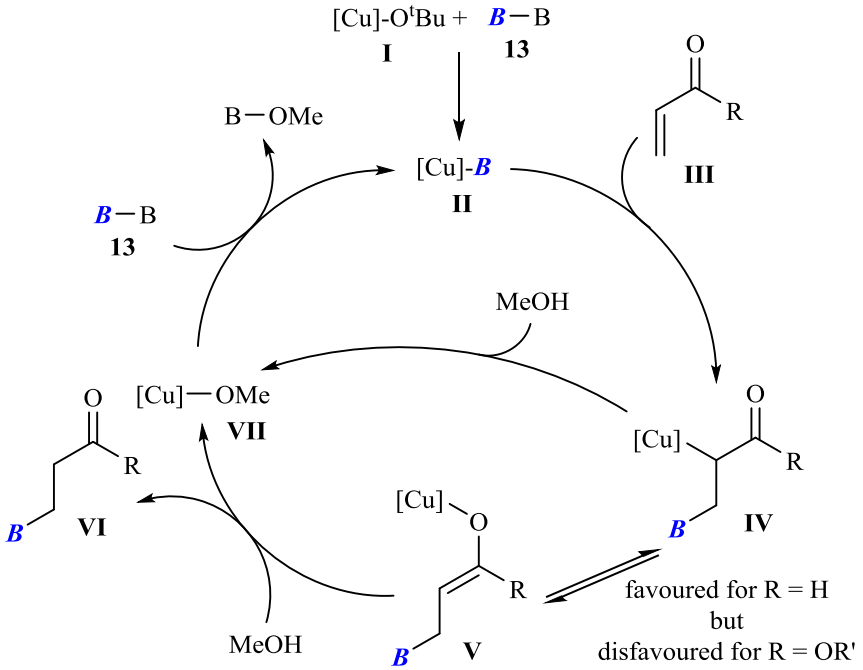
---

[6] Schiffner, J. A.; Müther, K.; Oestreich, M., *Angew. Chem. Int. Ed.* **2010**, *49*, 1194-1196.

[7] (a) Ito, H.; Yamanaka, H.; Tateiwa, J.-I.; Hosomi, A., *Tet. Lett.* **2000**, *41*, 6821-6825. (b) Takahashi, K.; Ishiyama, T.; Miyaura, N., *J. Organomet. Chem.* **2001**, *625*, 47-53.

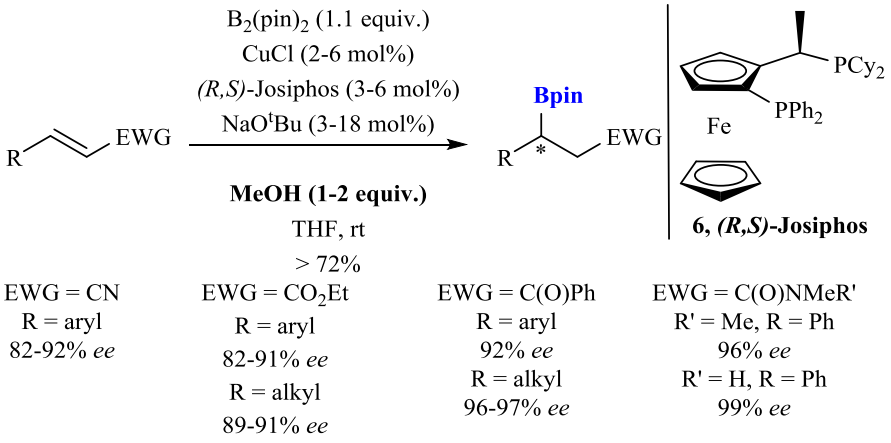
[8] Dang, L.; Lin, Z.; Marder, T. B., *Organometallics* **2008**, *27*, 4443-4454.

interconversion barrier is pivotal. Moreover, quantum chemical data indicated that both kinetic and thermodynamic stabilities are low for carbonyls ($\Delta G^{\#}$ = 12.7 kcal.mol^{-1} and ΔG = 3.7 kcal.mol^{-1}) but high for carboxyl compounds ($\Delta G^{\#}$ = 19.5 kcal.mol^{-1} and ΔG = 13.7 kcal.mol^{-1}) and thus clearly disfavour **V** in the latter case. As a consequence, the turnover is only secured for α,β–unsaturated carbonyls. For carboxyls, methanol must be added affording the borylated compound **VI** and copper(I)-methoxide complex **VII**. Finally, active catalyst **II** is regenerated by σ-bond metathesis of **VII** with **13**.



Scheme 19. Catalytic cycle of the Cu^{I}-catalyzed conjugate borylation.

Yun and co-workers described the catalytic enantioselective conjugated addition of boryl groups to acyclic acceptors using CuCl/NaO^{t}Bu/Josiphos ligand **6** and MeOH (Scheme 20).[9]



Scheme 20. Enantioselective borylation of acyclic acceptors.

They also developed an efficient copper-catalyzed addition reaction of bis(pinacolato)diboron to α,β-acetylenicesters which produces the corresponding β-borylated-α,β-ethylenicesters in high yields under mild reaction conditions.[10] N-heterocyclic carbene instead of phosphorus ligands was also employed in this transformation by Fernandez and McQuade.[11] The scope of this reaction was further extended by the

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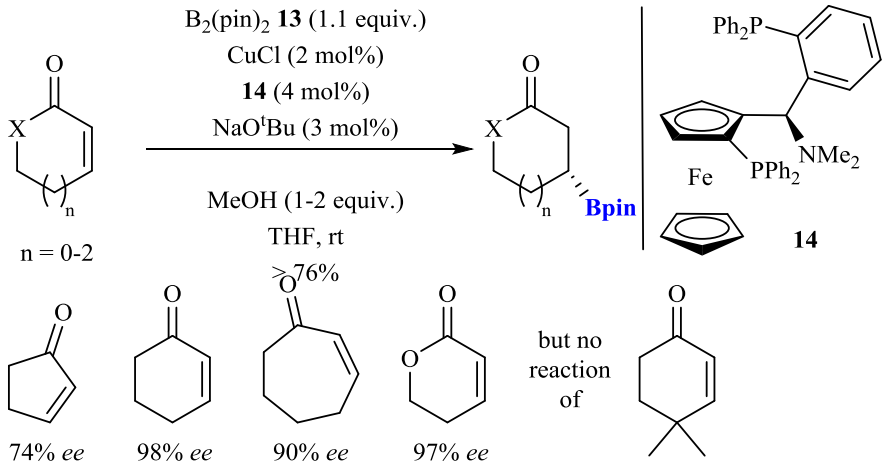
[9] (a) Mun, S.; Lee, J.-E.; Yun, J., *Org. Lett.* **2006**, *8*, 4887-4889. (b) Lee, J.-E.; Yun, J., *Angew. Chem. Int. Ed.* **2008**, *47*, 145-147. (c) Sim, H.-S.; Feng, X.; Yun, J., *Chem. Eur. J.* **2009**, *15*, 1939-1943. (d) Chea, H.; Sim, H.-S.; Yun, J., *Adv. Synth. Catal.* **2009**, *351*, 855-858.

[10] Lee, J.-E.; Kwon, J.; Yun, J., *Chem. Commun.* **2008**, 733-734.

[11] (a) Lillo, V.; Prieto, A.; Bonet, A.; Díaz-Requejo, M. M.; Ramírez, J.; Pérez, P. J.; Fernández, E., *Organometallics* **2009**, *28*, 659-662. (b) Park, J. K.; Lackey, H.

replacement of **6** by Taniaphos ligand **14**. This minor modification allowed for the asymmetric conjugated boryl addition onto cyclic substrates (Scheme 21).[12] However no reaction was observed with γ,γ-disubstituted and β-substituted cyclic acceptors.



Scheme 21. Enantioselective conjugate borylation of cyclic α,β-unsaturated acceptors.

Simultaneously, this issue was solved by Shibasaki and co-workers who accessed tertiary organoborate compounds with excellent enantioselectivities (Scheme 22).[13] In this system, they use $CuPF_6$ and LiO^tBu to allow the formation of $LiPF_6$, a Lewis acid which might enhance the reactivity of $B_2(pin)_2$. They almost used the same system

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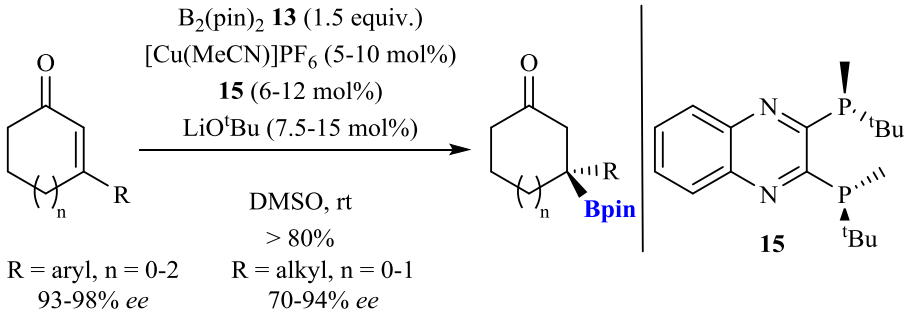
H.; Rexford, M. D.; Kovnir, K.; Shatruk, M.; McQuade, D. T., *Org. Lett.* **2010**, *12*, 5008-5011.

[12] Feng, X.; Yun, J., *Chem. Commun.* **2009**, 6577-6579.

[13] Chen, I. H.; Yin, L.; Itano, W.; Kanai, M.; Shibasaki, M., *J. Am. Chem. Soc.* **2009**, *131*, 11664-11665.

with linear β,β-disubstituted enones.[14] A copper(I)-chiral secondary diamine complex catalyzes the reaction in a presence of 2-propanol and chiral tertiary organoboronates are obtained in high yields and up to 99% *ee*.



Scheme 22. Enantioselective conjugate boryl transfer onto cyclic acceptors.

It is also important to mention the work of Hoveyda and co-workers who described the catalytic enantioselective conjugate boronate additions to trisubstituted alkenes of acyclic α,β-unsaturated carboxylic esters, ketones, and alkylthioesters, resulting in the formation of β-substituted quaternary carbon stereogenic centres. This transformation is promoted by a chiral C_1-symmetric Cu-based N-heterocyclic carbene (NHC) complex (Scheme 23).[15]

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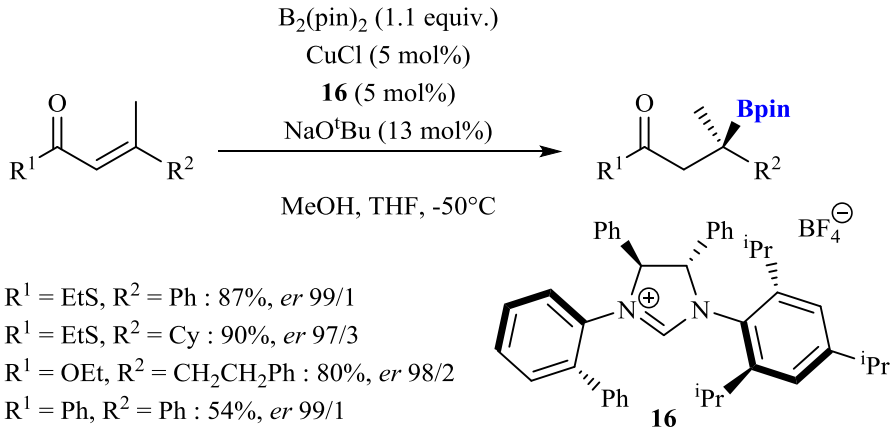
[14] Chen, I. H.; Kanai, M.; Shibasaki, M., *Org. Lett.* **2010**, *12*, 4098-4101.

[15] O'Brien, J. M.; Lee, K.-S.; Hoveyda, A. H., *J. Am. Chem. Soc.* **2010**, *132*, 10630-10633. For metal-free catalytic protocol see: (a) Lee, K.-S.; Zhugralin, A. R.; Hoveyda, A. H., *J. Am. Chem. Soc.* **2009**, *131*, 7253-7255. (b) Wu, H.; Radomkit, S.; O'Brien, J. M.; Hoveyda, A. H., *J. Am. Chem. Soc.* **2012**, *134*, 8277-8285.



Scheme 23. Borylation of acyclic α,β-unsaturated carboxylic esters, ketones and alkylthioesters.

III.2.2. Diboration of carbonyl substrates

1,2-addition products derived from carbonyl substrates were first described by Sadighi and co-workers.[16] They found that a copper complex [(ICy)CuO^{t}Bu; ICy = *N*,*N*-dicyclohexylimidazolyl] efficiently catalyzed the diboration of aldehydes at ambient temperature. A few years later, Ellman and co-workers demonstrated that Sadighi's catalyst could be used to form α-amino boronate esters starting from *N*-*tert*-butanesulfinyl aldimines (Scheme 24).[17] This transformation proceeds in good yields and very high diastereoselectivities for both hindered and unhindered *N*-sulfinyl imine substrates. Moreover, they also demonstrated the synthetic utility of this transformation in the efficient

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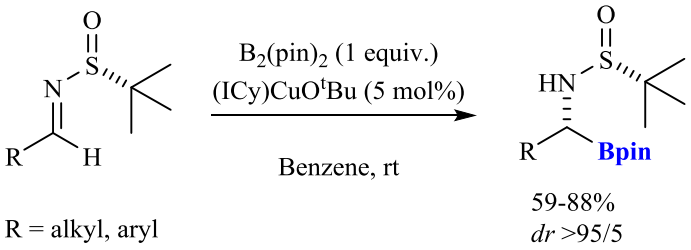
[16] Laitar, D. S.; Tsui, E. Y.; Sadighi, J. P., *J. Am. Chem. Soc.* **2006**, *128*, 11036-11037.

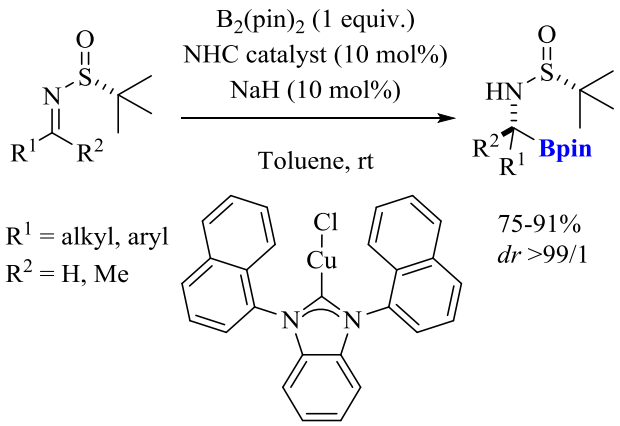
[17] Beenen, M. A.; An, C.; Ellman, J. A., *J. Am. Chem. Soc.* **2008**, *130*, 6910-6911.

synthesis of bortezomib, a potent proteasome inhibitor approved for cancer treatment.



Scheme 24. Diboration of *N*-tert-butanesulfinyl aldimines.

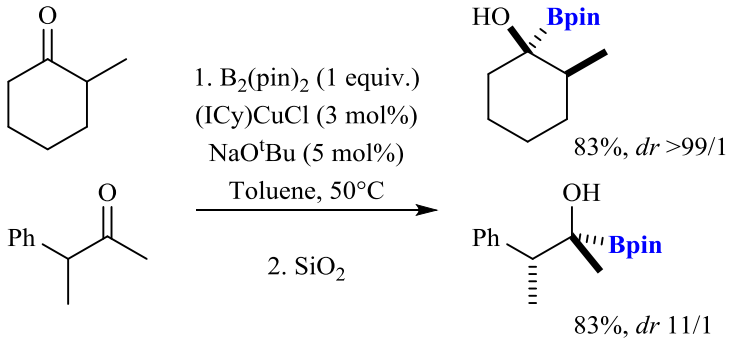
Although the Ellman method had a great advantage in using widely available aldehydes and had excellent stereocontrol, its drawbacks were that it had to be carried out in a glovebox due to the preparation, storage and handling of Sadighi's catalyst. More recently, Sun reported an improved protocol for asymmetric synthesis of α-aminoboronic esters by tuning the properties of NHC catalysts (Scheme 25).[18]



Scheme 25. Asymmetric synthesis of α-aminoboronic esters.

[18] Wen, K.; Wang, H.; Chen, J.; Zhang, H.; Cui, X.; Wei, C.; Fan, E.; Sun, Z., *J. Org. Chem.* **2013**, *78*, 3405-3409.

The starting materials for the transformation could also be extended from aldehydes to ketones. Finally, Clark and co-workers reported the diboration of ketones in 2010 (Scheme 26).[19] *In situ* formation of (ICy)CuO^{t}Bu provided convenient reaction conditions to achieve high catalyst efficiency. High diastereoselectivities were also observed in the diboration of chiral ketones.



Scheme 26. Diboration of ketones.

III.3. Reactions of Cu^I-Si reagents

Reactions using Cu^I-Si reagents have largely been studied during the past few years. Figure 5 shows various methods which use this silicon nucleophile.[20]

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[19] McIntosh, M. L.; Moore, C. M.; Clark, T. B., *Org. Lett.* **2010**, *12*, 1996-1999.

[20] For selected examples of reactions which used Cu^I-Si reagents see: (a) Kurahashi, T.; Hata, T.; Masai, H.; Kitagawa, H.; Shimizu, M.; Hiyama, T., *Tetrahedron* **2002**, *58*, 6381-6395 (Gem-dimetalation). (b) Wang, P.; Yeo, X.-L.; Loh, T.-P., *J. Am. Chem. Soc.* **2011**, *133*, 1254-1256 (Silylcupration of alkynes). (c) Lee, K.-S.; Hoveyda, A. H., *J. Am. Chem. Soc.* **2010**, *132*, 2898-2900 (1,6-addition). (d) Vyas, D. J.; Hazra, C. K.; Oestreich, M., *Org. Lett.* **2011**, *13*, 4462-

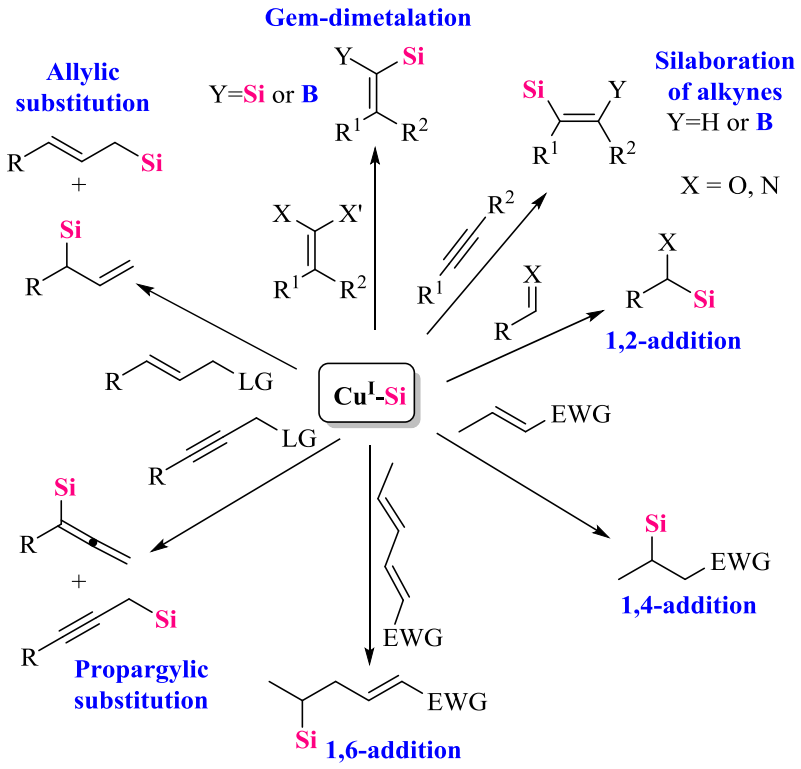

Figure 5. Reactions with Cu^{I}-Si reagents.

As explained earlier for $B_2(pin)_2$ reagent, we don't have the possibility to report all the reactions here so we decided to focus on selected examples of synthesis which use copper silicon nucleophile such as 1,2- and 1,4-addition reactions.

III.3.1. Reactions of disilanes: activation of Si-Si bond

The generation of nucleophilic silicon by activation of a Si-Si bond from disilanes is particularly attractive because disilanes are commercially

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4465 (Propargylic substitution). (e) Vyas, D. J.; Oestreich, M., *Angew. Chem. Int. Ed.* **2010**, *49*, 8513-8515 (Allylic substitution).

available. Compounds **17** and **18** are commonly used in metal-mediated conjugate addition (Figure 6).

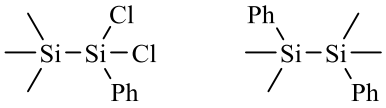
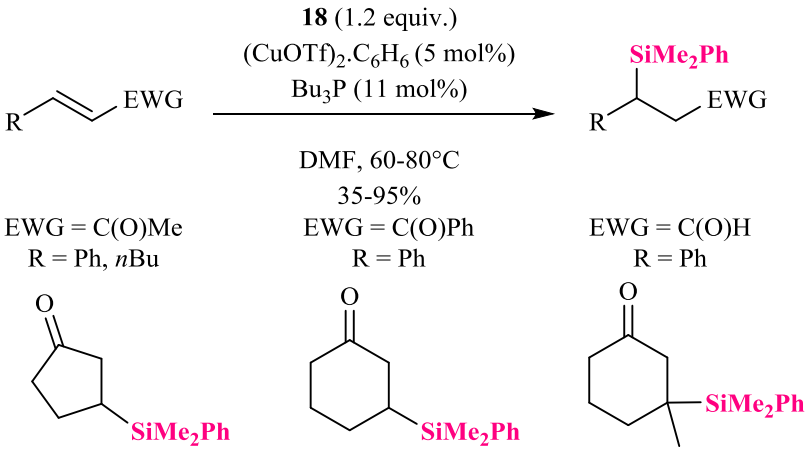


Figure 6. Representative silicon-based interelement compounds.

The first example of copper-catalyzed conjugate silylation of enones and enals was reported by Hosomi (Scheme 27).[21] They used disilane **18** and copper triflate to generate the silicon nucleophile. Although this reaction only generated racemic products, the use of catalytic amounts of copper was a real breakthrough.



Scheme 27. Copper(I)-catalyzed racemic conjugate silylation of cyclic and acyclic α,β-unsaturated carbonyls.

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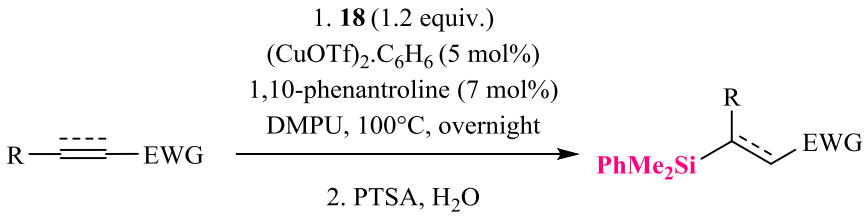
[21] Ito, H.; Ishizuka, T.; Tateiwa, J.-I.; Sonoda, M.; Hosomi, A., *J. Am. Chem. Soc.* **1998**, *120*, 11196-11197.

A few years later, Sheidt reported an extension of this method to α,β-unsaturated esters.[22] However, the system was restricted to highly electrophilic alkylidene malonates. More recently, Molander described a general method for the conjugate silylation of various α,β-unsaturated compounds using disilanes.[23] Diphenyltetramethyldisilane **18** was used with copper(I) triflate and phenantroline in DMPU at 100°C to generate nucleophilic silicon species which were then trapped by several Michael acceptors. Optimal conditions could also extend to the use of alkynes, leading to vinylsilanes with moderate to excellent stereoselectivity (Scheme 28).



Scheme 28. Copper(I)-catalyzed conjugate silylation.

Last but not least, we should mention that Ito and Sawamura recently reported the first example of copper(I)-catalyzed allylic substitution of silyl nucleophiles through Si-Si bond activation.[24] Although they are commercially available, reactions with disilanes use very harsh conditions

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[22] Clark, C. T.; Lake, J. F.; Scheidt, K. A., *J. Am. Chem. Soc.* **2004**, *126*, 84-85.

[23] Iannazzo, L.; Molander, G. A., *Eur. J. Org. Chem.* **2012**, 4923-4926.

[24] Ito, H.; Horita, Y.; Sawamura, M., *Adv. Synth. Catal.* **2012**, *354*, 813-817.

such as high temperature. This explains that there were only a few examples in the literature which used these compounds. An interesting question was therefore why disilanes were not reactive enough compared to silylborane species which have been largely used during the past few years. We will try to answer this question later in this manuscript.

III.3.2. Activation of Si-B bond[25]

Si-B bond displays several attractive features. First it is sufficiently stable with appropriate substitution at the boron atom and secondly the difference in affinity between boron and silicon allows for chemoselective activation of the Si-B bond. Also, distinct reactivities of the boryl and silyl groups are likely to enable their sequential introduction into a carbon skeleton with high levels of regiocontrol. The transition metal-catalyzed transfer of silicon nucleophiles onto various electrophiles has recently gained considerable attention, due to the now readily available silicon pro-nucleophiles. In particularly, the Suginome reagent[26] **19** involving a Si-B linkage has become one of the major sources of nucleophilic silicon (Figure 7). Compound **19** is commercially available but it is usually more practical to synthesize it using the procedure reported by Ito, Suginome and co-workers.[26]

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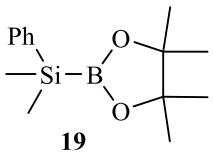
[25] For reviews on Si-B bond see: (a) Oestreich, M.; Hartmann, E.; Mewald, M., *Chem. Rev.* **2013**, *113*, 402-441. (b) Hartmann, E.; Vyas, D. J.; Oestreich, M., *Chem. Commun.* **2011**, *47*, 7917-7932. (c) Ohmura, T.; Suginome, M., *Bull. Chem. Soc. Jpn.* **2009**, *82*, 29-49. (d) Burks, H. E.; Morken, J. P., *Chem. Commun.* **2007**, 4717-4725.

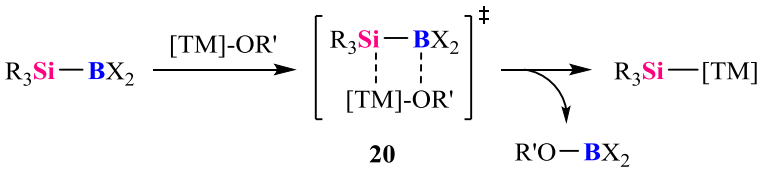
[26] Suginome, M.; Matsuda, T.; Ito, Y., *Organometallics* **2000**, *19*, 4647-4649.



19

Figure 7. Suginome's reagent.

The mechanisms of Si-B bond activation are diverse (oxidative addtition/reductive elimination transition metal catalyses, stoichiometric and catalytic transmetalation processes, photochemical homolytic cleavage, etc…). The discovery by Ito and Tanaka that Si-B bond oxidatively adds to various low-valent transition metals (Pt^0, Pd^0, Ni^0) more than a decade ago marked the beginning of the rich synthetic chemistry of silylborane reagents (see Scheme 17, cycle A). Another mode of activation is the cleavage of Si-B bond by addition of a strong nucleophile (M^+OR^- where M = K or M^+R^- where M = Li, MgX) that would attack at the more Lewis acidic boron atom. However, we were more interested by the generation of catalytic transition metal-based silicon nucleophiles (TM = Rh^I, Cu^I ou Ni^{II}). The catalysis is believed to involve a σ-bond metathesis-type transition state such as **20** (Scheme 29). However, in this case, only the silicon group is transferred to an electrophile, the boryl group is sacrificed.



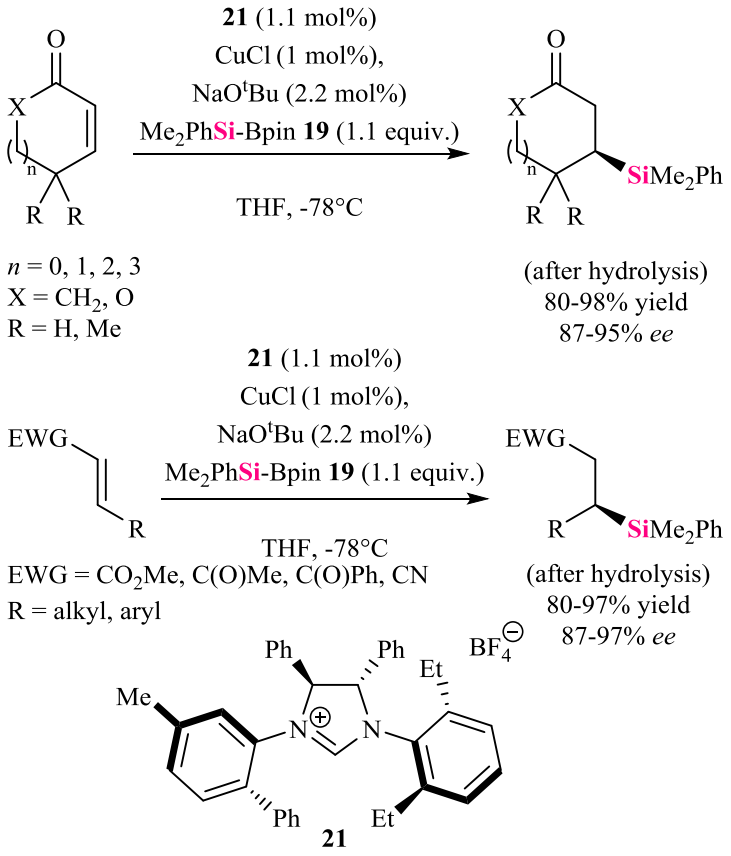
20

Scheme 29. Si-B bond activation by transmetalation.

III.3.3. Conjugate addition of Si-B

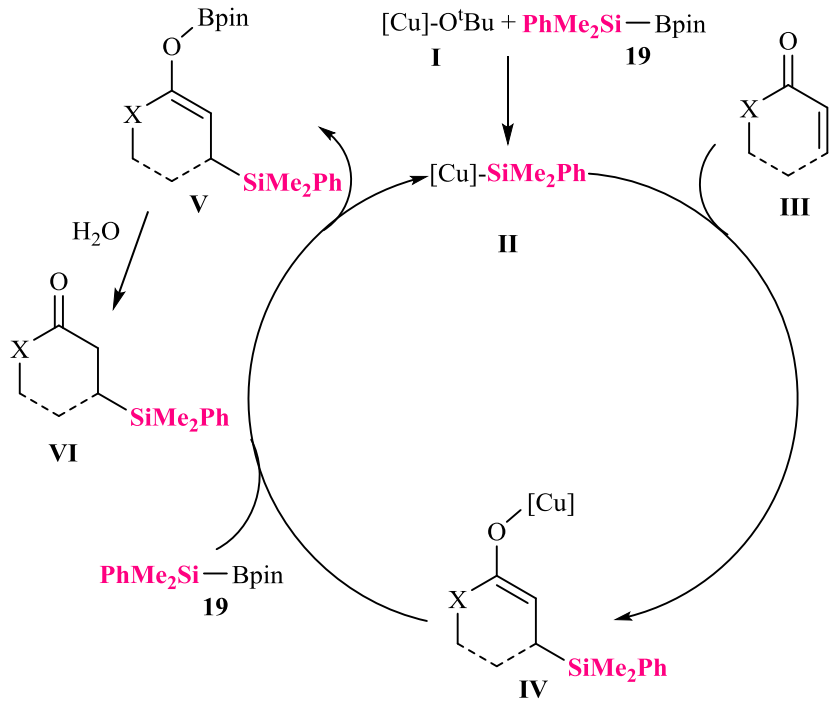
Conjugate silylation was largely reported in the literature but rhodium(I) catalysts are usually used. There are only a few examples of copper(I)-catalyzed conjugate silylation. Lee and Hoveyda succeeded in developing a generally applicable enantioselective conjugate silyl transfer that relies on the copper(I)-catalyzed activation of Me_2PhSi-Bpin **19**.[27] Cyclic enones and δ-lactones reacted with CuCl, NaO^tBu and the chiral carbene precursor **21** in THF at -78°C to afford the desired product in high yields and good *ee's* (Scheme 30, upper). Moreover, same conditions were applied to acyclic α,β-unsaturated carbonyls and carboxyls substituted with different aryl or alkyl groups at the β-carbon atom and again high yields and excellent *ee's* were obtained (Scheme 30, lower).

[27] Lee, K.-S.; Hoveyda, A. H., *J. Am. Chem. Soc.* **2010**, *132*, 2898-2900.



Scheme 30. Copper(I)-catalyzed conjugate silylation.

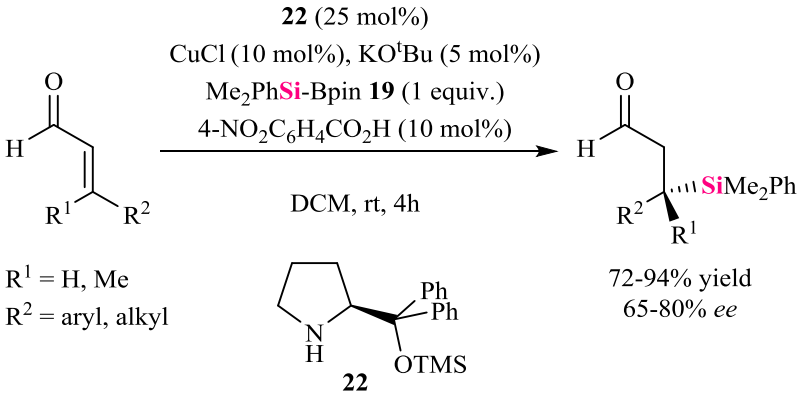
Concerning the mechanism, the main features of the copper(I)-catalyzed conjugate borylations were applied, however no alcohol additive is required in this case. A σ-bond metathesis of copper(I)-alkoxide **I** with **19** is assumed to initiate the catalytic cycle generating Cu(I)-SiMe$_2$Ph nucleophile species **II** (Scheme 31). Subsequent 1,4-addition of **II** onto α,β-unsaturated compound **III** affords the copper enolate **IV**. Another σ-bond metathesis of **19** with **IV** allows to regenerate the catalytically active Cu(I)-SiMe$_2$Ph **II** and boron enolate **V**. Final hydrolysis furnishes the desired β–silylated compound **VI**.



Scheme 31. Mechanism of the copper(I)-catalyzed conjugate silylation.

In 2011, Ibrahem, Cordova and co-workers reported a protocol that enables the enantioselective conjugate silylation of challenging α,β-unsaturated aldehydes.[28] They described the copper(I)-catalyzed activation of **19** with chiral amine catalysis. 1,4-products were obtained with good yields and excellent levels of enantioselectivity thanks to the presence of proline derivative **22** and CuCl/KO^{t}Bu (Scheme 32).

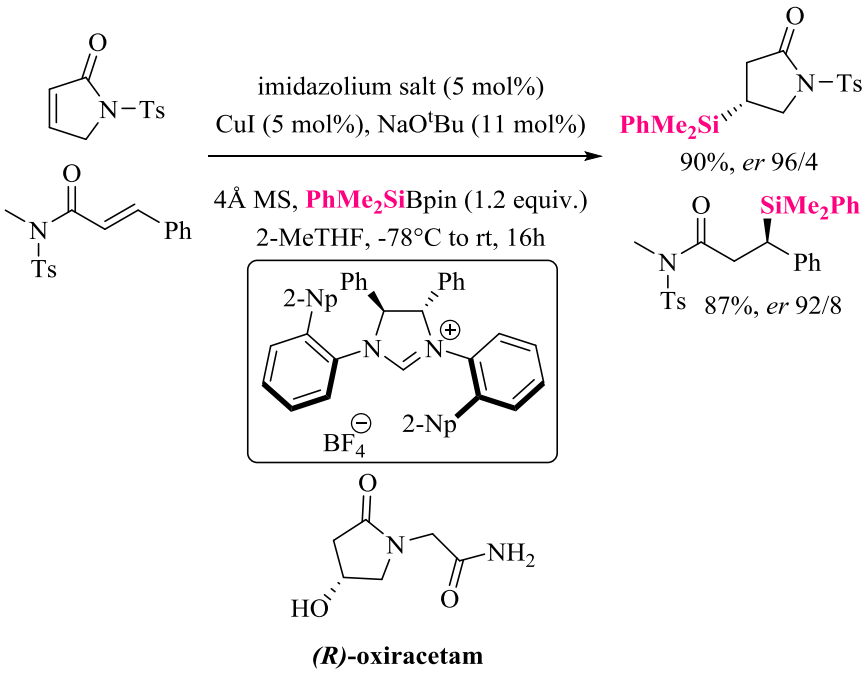
[28] Ibrahem, I.; Santoro, S.; Himo, F.; Córdova, A., *Adv. Synth. Catal.* **2011**, *353*, 245-252.



Scheme 32. Copper(I)/iminium ion-catalyzed conjugate silylation.

Finally, the first asymmetric silylation of unsaturated lactams and amides using Cu(I)−NHC catalysts and **19** has been accomplished by Procter and co-workers in 2014. The method has been exploited in an expedient asymmetric synthesis of the *(R)*-enantiomer of the nootropic drug oxiracetam (Scheme 33).[29]

[29] Pace, V.; Rae, J. P.; Procter, D. J., *Org. Lett.* **2014**, *16*, 476-479.



Scheme 33. Asymmetric silylation of unsaturated lactams and amides.

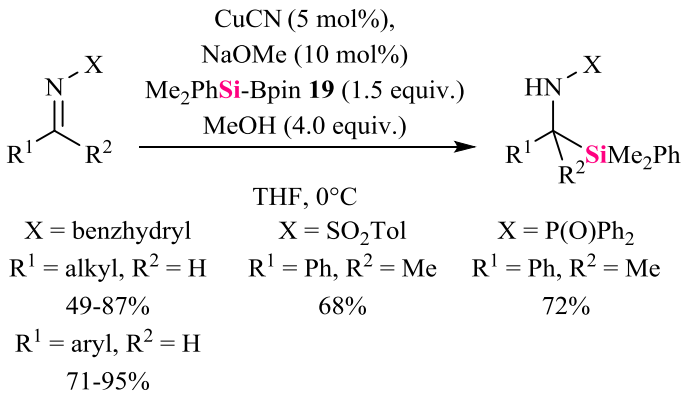
It should also be mentioned that beyond metal-catalyzed protocols, O'Brien and Hoveyda introduced the first metal-free enantioselective conjugate silylation of α,β-unsaturated compounds. They used *N*-heterocyclic carbenes (NHCs) to activate the Si-B bond.[30]

III.3.4. 1,2-addition of Si-B to C-Het double bonds

The catalytic generation of nucleophilic Cu-Si species through transmetalation of copper(I) alkoxide complexes with **19** attracted considerable interests. Among others, 1,2-addition of silicon nucleophiles to electrophiles represents a potential field of application. In 2011, Oestreich and co-workers described the copper(I)-catalyzed

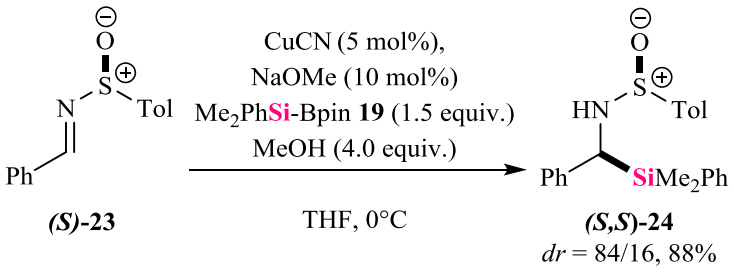
[30] O'Brien, J. M.; Hoveyda, A. H., *J. Am. Chem. Soc.* **2011**, *133*, 7712-7715.

addition of silicon to imines to form α–silylated amines.[31] A range of substituents at the nitrogen atom are tolerated under the reaction conditions. Good yields were obtained for aryl as well as alkyl compounds. Moreover, challenging ketimines proved to be suitable substrates for this transformation but electron-withdrawing groups at the nitrogen atom were necessary (Scheme 34).



Scheme 34. Copper(I)-catalyzed 1,2-silylation of imines.

Enantiopure sulfinylimine ***(S)*-23** was also tested in these conditions and the chiral α–silylated amine ***(S,S)*-24** was obtained with good yield and reasonable diastereoselectivity (Scheme 35).



Scheme 35. Copper(I)-catalyzed 1,2-silylation of enantiopure imines.

[31] Vyas, D. J.; Fröhlich, R.; Oestreich, M., *Org. Lett.* **2011**, *13*, 2094-2097.

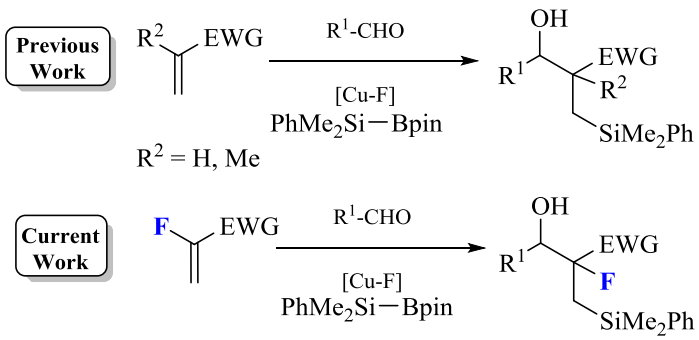
Copper-catalyzed 1,2-addition of silicon nucleophile to aldehydes was also reported. We will describe this range of reaction later in this manuscript (see bibliographic introduction of chapter 3).

This section concludes the general introduction to copper(I) catalysis. This manuscript is then divided into three parts. Chapter 1 focuses on the development of the copper-catalyzed 1,4-addition/aldolisation domino reaction. The use of silylborane and *bis*-boronate in tandem reactions are widely illustrated in this section. Following chapters describe new methodologies for the copper-catalyzed 1,2-addition of silicon nucleophiles to various electrophiles. Indeed, chapter 2 depicts the development of a new synthesis of acylsilanes, a versatile compound in organic synthesis. And finally chapter 3 reports a novel synthesis of chiral α-hydroxysilanes starting from readily available aldehydes using new cationic copper(I) complexes.

GENERAL OBJECTIVES

The development of new catalytic methods has been an area of intense research in recent years and particular efforts are currently devoted to transition-metal-catalyzed reactions. In our group, we are thus interested in developing and studying new reactions catalyzed by copper(I) complexes.

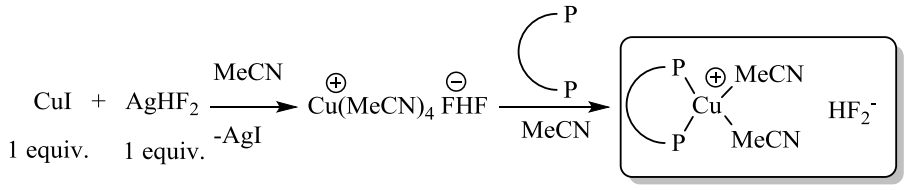
As described in the introduction, our group has a history in the development of new methodologies for the copper catalyzed 1,4-addition/aldolisation with bisboronates and silylboranes. The first objective of chapter 1 was therefore to try to extend the silylation reaction to new substrates. Using the copper(I) nucleophilic species developed in our group, we endeavoured to apply it to Michael acceptors bearing a fluorine substituent on the double bond. The ultimate goal was the formation of chiral quaternary centres bearing a fluorine substituent.



Scheme 1. Extension of the silylation reaction.

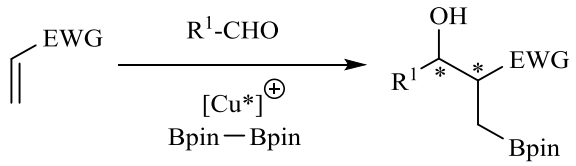
Another objective of this chapter was to extend these domino reactions from several points of view. We are therefore interested in using other silyboranes in the copper catalyzed 1,4-addition/aldolisation domino reaction. We wanted to work on the valorization of the domino adducts in various useful transformations. The development of new air and

moisture stable cationic copper(I) complexes which could be used in various catalytic reactions was also envisaged during this project. These new catalysts could allow avoiding some of the drawbacks encountered in some reactions, such as the use of additives (NaO^{t}Bu, …) or reproducibility of reactions.



Scheme 2. Development of new cationic copper(I) complexes.

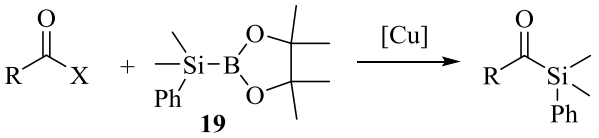
And finally, concerning the borylation reaction, our aim was to develop a non racemic version for these molecules. Asymmetric induction could be aroused by a chiral ligand and we envisaged to use our new cationic copper(I) complexes. This is the last objective of chapter 1.



Scheme 3. Enantioselective version of the borylation reaction.

Another important goal of this thesis, as mentioned before, was to develop new reactions for the synthesis of interesting building blocks in organic synthesis. We are thus interested in using our background in copper catalysis and silylboranes chemistry in this purpose. Initially, we wished to report in chapter 2 our own contribution leading to a useful and straightforward method to access acylsilanes. Indeed, we envisaged a new strategy for the preparation of acylsilanes through acylation of a

copper(I)-silyl intermediate. Starting from acid derivatives in the presence of Suginome's reagent **19** and a copper catalyst, the process should lead to the corresponding acylsilanes.

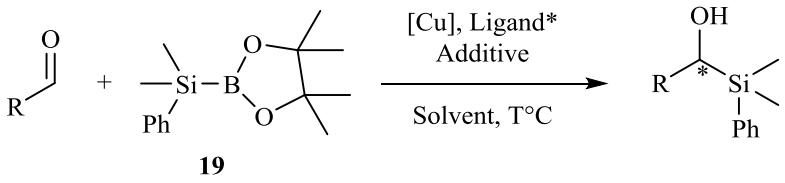


19

R = alkyl, aryl
X = F, Cl, OC(O)R', ...

Scheme 4. Synthesis of acylsilanes.

Secondly, in chapter 3, our interest turned to the addition of the copper(I)-silyl intermediates to aldehydes, thus generating α-hydroxysilanes in a catalytic one-step reaction. Starting from commercially available aldehydes in the presence of Suginome's reagent **19** and a copper catalyst, the process should lead to the corresponding α-hydroxysilanes. And by using chiral ligands, high enantioselectivities should be achieved.



19

Scheme 5. Synthesis of α-hydroxysilanes.

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

I. Bibliographic Introduction

I.1. Multistep reactions

Synthetic organic chemistry has developed in a fascinating way over the past decades. Several highly selective procedures have been developed which allow the preparation of complex molecules with excellent regio-, chemo-, diastereo-, and enantioselectivity. The usual procedure for the synthesis of organic compounds is the stepwise formation of the individual bonds in the target molecule. However, it would be much more efficient if one reaction could form several bonds in one sequence without isolating the intermediates, changing the conditions, or adding reagents. These types of transformation are called "multistep reactions". They are divided into two major groups, tandem reactions and *in situ* or one-pot reactions.[1] Tandem reactions have two sub-classes, simple tandem reactions and domino reactions (cascade reactions are a special case of domino reaction). With the intention of clarifying the current state of the field, Tietze and dos Santos proposed a brief taxonomy, or classification scheme, in a attempt to codify this increasingly important area (Figure 1).

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[1] (a) Tietze, L. F., *Chem. Rev.* **1996**, *96*, 115-136. (b) Fogg, D. E.; dos Santos, E. N., *Coord. Chem. Rev.* **2004***, 248*, 2365-2379. (c) Shindoh, N.; Takemoto, Y.; Takasu, K., *Chem. Eur. J.* **2009**, *15*, 12168-12179.

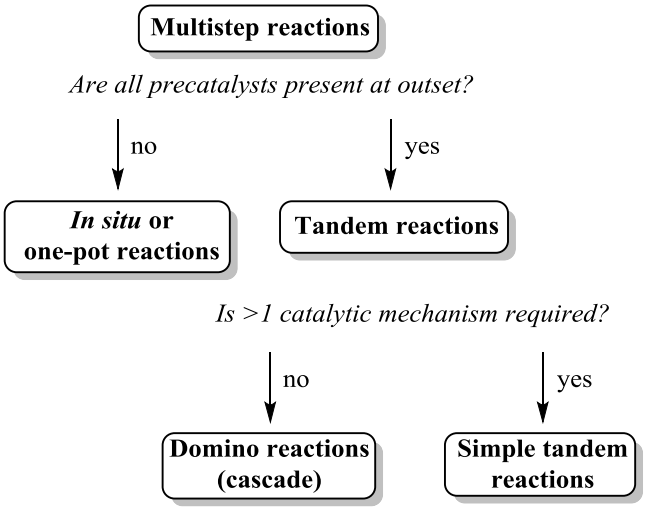


Figure 1. Classification of catalyzed multistep reactions.

The modification of an organic moiety via two catalytic elaborations, with addition of the second catalyst only after the first catalytic transformation is complete, is not a tandem catalysis, but a one-pot sequential reaction. *In situ* or one-pot reactions are independent of each other in that they can be conducted separately with isolation of the products. These types of reactions are quite common. For example, Grignard reagents, enolate complexes or transition metal species are usually generated *in situ*. This technique is often applied where the intermediate species are not stable or difficult to handle. They define domino and tandem catalyses, in contrast, as having all catalytic species present from the outset. A domino process describes a reaction where one single catalytic mechanism is required. This term is then used for a process where two or more chemical transformations occurring under identical conditions and the subsequent transformation takes place at the functionalities obtained in the former transformation (Figure 2).

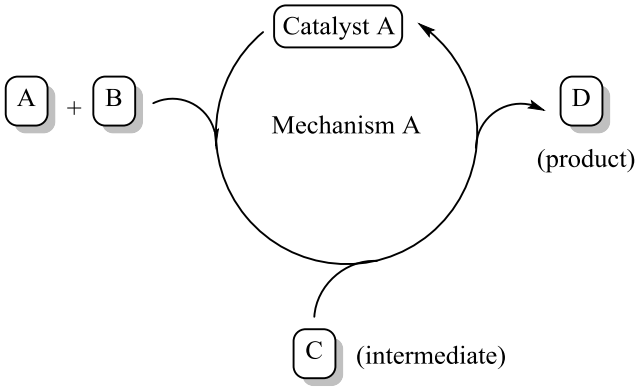
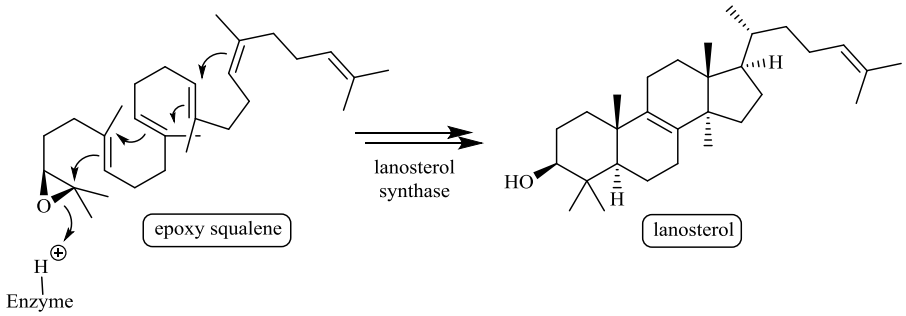


Figure 2. Domino reaction.

Cascade catalysis is a virtually synonymous term of domino reaction, reserved for multiple domino sequences (≥3). A beautiful example of cascade reaction is the polycyclization of epoxy squalene in lanosterol (Scheme 1).[2]



Scheme 1. Cascade reaction.

They employed the term "tandem catalysis" to describe coupled catalyses in which sequential transformation of the substrate occurs via two (or more) mechanistically distinct processes. Two categories may be distinguished: orthogonal and auto-tandem catalysis. Orthogonal tandem

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[2] Yoder, R. A.; Johnston, J. N., *Chem. Rev.* **2005**, *105,* 4730-4756.

catalysis involves two or more functionally distinct and (in principle) noninterfering catalysts or precatalysts, all of which are present from the outset of reaction (Figure 3). The two catalytic cycles operate simultaneously once substrate B is generated.

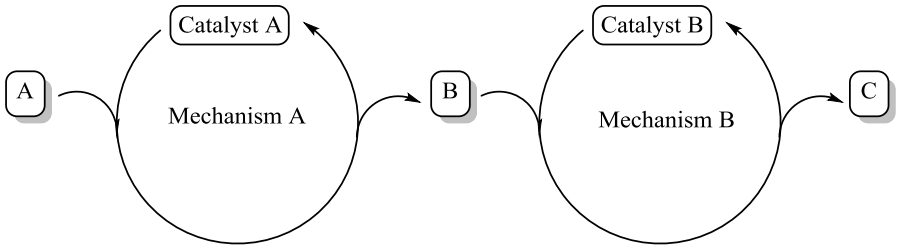
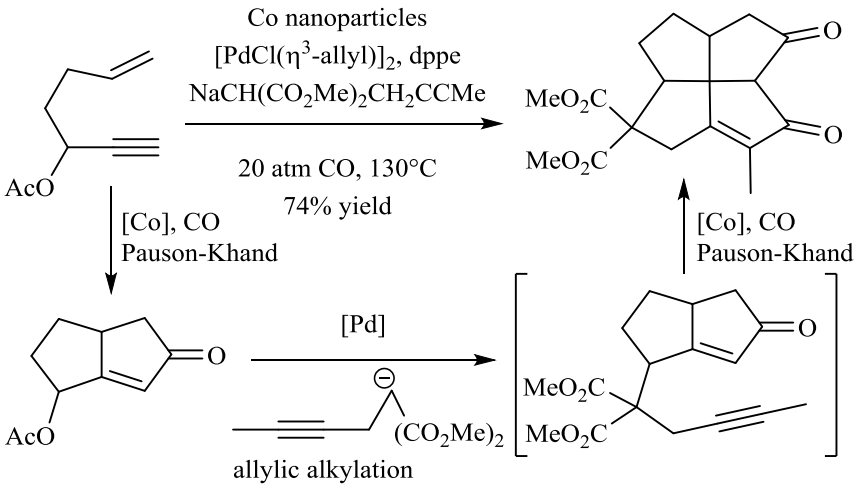


Figure 3. Orthogonal tandem catalysis.

Scheme 2 shows an example of orthogonal tandem catalysis in ene–yne elaboration to yield fenestranes: the first Pauson–Khand reaction is not part of the tandem catalysis, as the Pd catalyst is added only once this step is complete.[3]



Scheme 2. Example of orthogonal catalysis.

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[3] Son, S. U.; Park, K. H.; Chung, Y. K., *J. Am. Chem. Soc.* **2002**, *124*, 6838-6839.

On the other hand, auto-tandem catalysis involves two or more mechanistically distinct catalyses promoted by a single catalyst precursor: both cycles occur spontaneously by cooperative interaction of the various species present at the outset of the reaction (Figure 4).

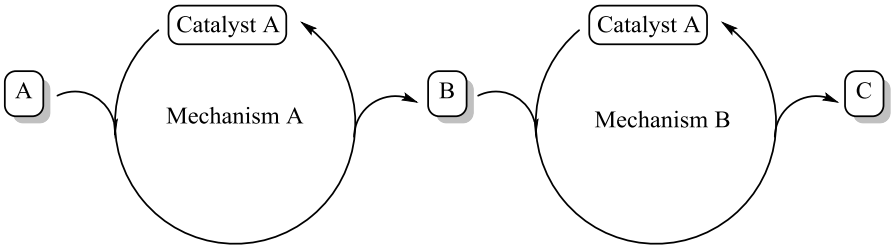
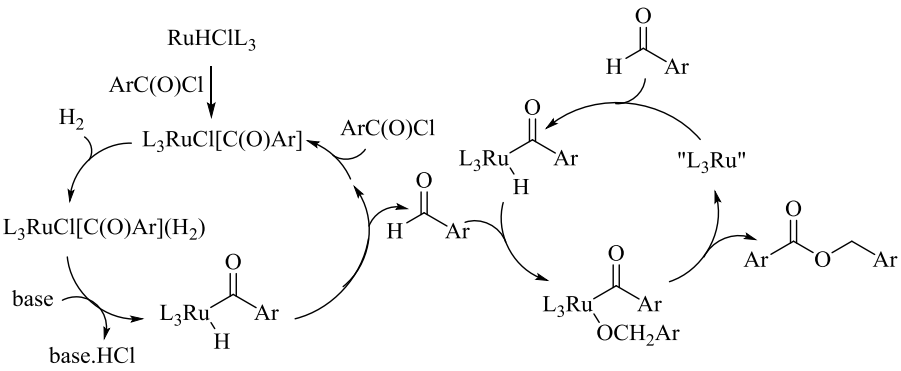


Figure 4. Auto-tandem catalysis.

An example of auto-tandem catalysis is reported by Grushin and Alper. They described the synthesis of esters from acid chlorides via sequential (homogeneous) Rosenmund-Tishchenko catalysis (L = PPh_3).[4]

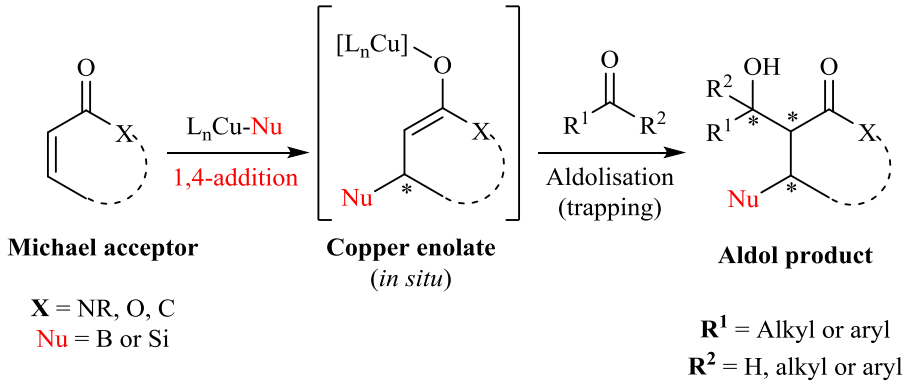


Scheme 3. Example of auto-tandem catalysis.

[4] Grushin, V. V.; Alper, H., *J. Org. Chem.* **1991**, *56*, 5159-5161.

I.2. Previous work

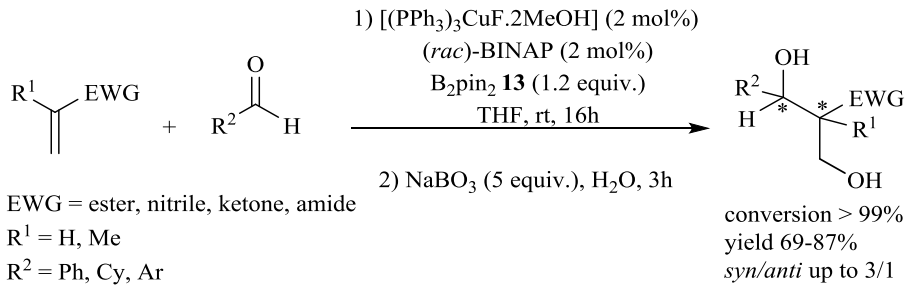
The 1,4-addition/aldolisation reaction is classified as a domino type reaction. This means that these two reactions are occurring successively and in our case catalyzed by copper(I) complexes. Indeed 1,4-addition reactions using *in situ* formed Cu-B or Cu-Si (see general introduction) can be further exploited when ran in the presence of an electrophile, inducing an inter- or intramolecular trapping of the addition product. In our case, the aldolisation process involves trapping the copper intermediates with aldehydes or ketones to furnish aldol products in one step (Scheme 4). This type of domino process was already developed in our group with Cu-H species as described earlier in the general introduction. The idea here is to use other nucleophiles such as silylboranes or bisboronates.



Scheme 4. 1,4-addition/aldolisation domino reaction.

I.2.1. Borylation reaction

During his PhD thesis, Alexandre Welle developed a diastereoselective domino borylative aldol reaction using B_2pin_2 **13** as pronucleophile.[5] A copper(I) catalyst generated from [(Ph_3P)CuF].2MeOH **25** and *(rac)*-BINAP **26** promoted the conjugate boryl transfer onto various acyclic Michael acceptors and the resulting enolate was trapped with various aldehydes (Scheme 5). Aldols adducts were obtained with good yields and moderate diastereoselectivities (up to 3 to 1 in favour of *syn* isomer). It is important to mention that because boronate compounds are unstable on silica gel, products were isolated after oxidation of the boronic moiety under mild conditions to the corresponding alcohol.[6]



Scheme 5. Copper(I)-catalyzed domino borylative aldol reaction.

Relative configuration was determined after treatment of compound **27** with DMP in the presence of a catalytic amount of PTSA (Scheme 6). Dioxolane **28** was obtained in quantative yield and NMR analysis

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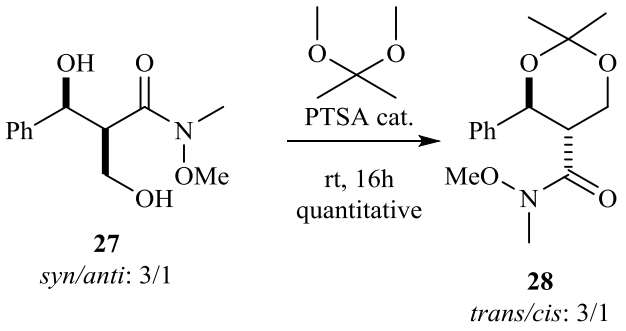
[5] Welle, A.; Cirriez, V.; Riant, O., *Tetrahedron* **2012**, *68*, 3435-3443.

[6] Mun, S.; Lee, J.-E.; Yun, J., *Org. Lett.* **2006**, *8*, 4887-4889.

showed unambiguously a *trans* relationship between the amide and the phenyl for the major product.



27
syn/anti: 3/1

28
trans/cis: 3/1

Scheme 6. Determination of the relative configuration of **27**.

While modest diastereoselectivities were observed with acyclic Michael acceptors, they decided to check the reactivity of simple cyclic enones as models. Geometry of the enolate is blocked in cyclic compounds thus the diastereocontrol would be better. As the true nature of the enolate intermediate that will react with the aldehyde has still not been established as well as the transition state involved in the aldol process between the metal enolate and the aldehyde, previsions on the stereochemical outcome of cyclic substrates are not straightforward. However, a recent study by Hoveyda group gave one example of a highly diastereoselective tandem conjugated addition/aldol reaction on cyclohexenone using NHC complex (Scheme 7).[7]

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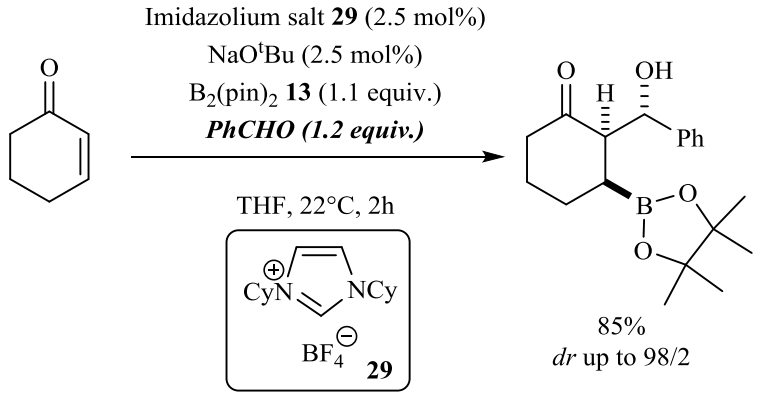
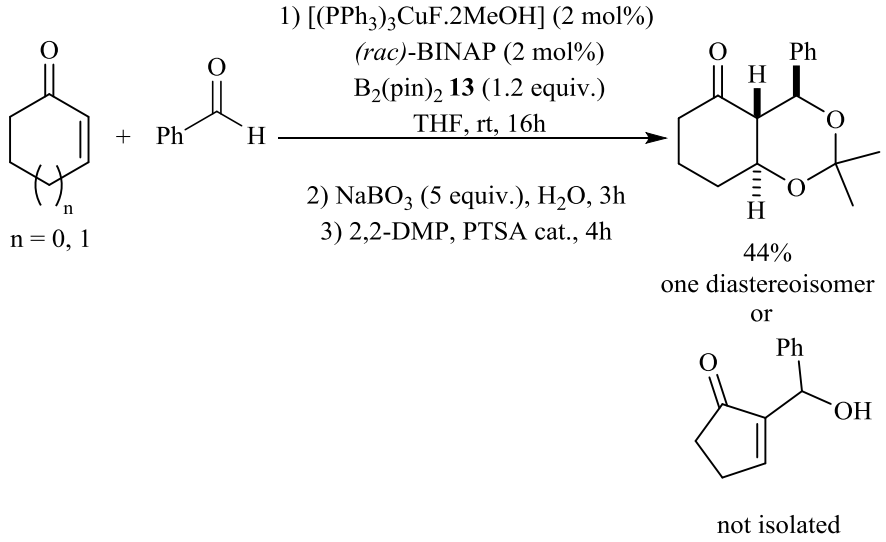
[7] Lee, K.-S.; Zhugralin, A. R.; Hoveyda, A. H., *J. Am. Chem. Soc.* **2009**, *131*, 7253-7255. For the first metal-free enantioselective conjugate borylation of α,β-unsaturated compounds with phosphorus ligands, see: Bonet, A.; Gulyás, H.; Fernández, E., *Angew. Chem. Int. Ed.* **2010**, *49*, 5130-5134.



Scheme 7. Tandem conjugated addition/aldol reaction using NHC complex by Hoveyda's group.

Likewise, we tested cyclohexenone and cyclopentenone as model substrates and found different behaviour depending on the ring size of the Michael acceptor. In all cases, the boron ester arising from the tandem process was identified in the crude reaction mixture but was not isolated and was directly oxidized to the corresponding diol, which was then protected as a dioxolane in a one pot sequence for relative configuration determination (Scheme 8). Although the unoptimised yield with cyclohexenone is modest, only one diastereoisomer was detected in the crude reaction mixture prior to oxidation. In contrast, the spontaneous dehydration after boronic ester oxidation when using cyclopentenone was observed, although diastereocontrol was very good. Unfortunately, every attempt to prevent water elimination failed.



Scheme 8. Domino reaction using cyclic enones.

The use of a functionalised chiral Michael acceptor was also investigated and focussed on the enantiopure enone **30**, which was easily prepared from D-ribose using a protocol from the literature.[8] After reacting **30** in the standard catalytic conditions, the desired adduct was obtained as the major product and only one diastereoisomer was detected in the crude reaction mixture, meaning that the absolute configuration of three new centres was controlled (Scheme 9). As the oxidation of the boronate ester was not possible for cyclopentenone, the pure adduct was not isolated and stereochemistry of the newly formed chiral carbon centres was not confirmed.

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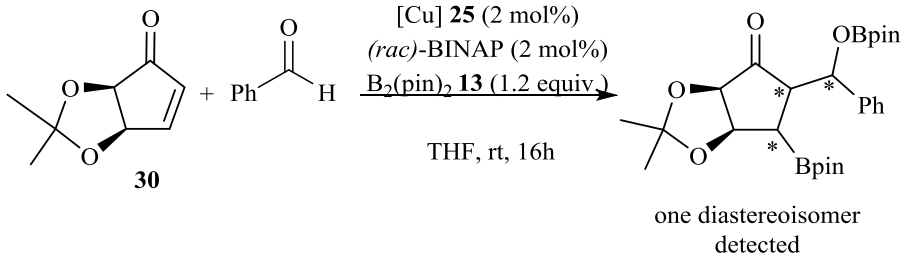
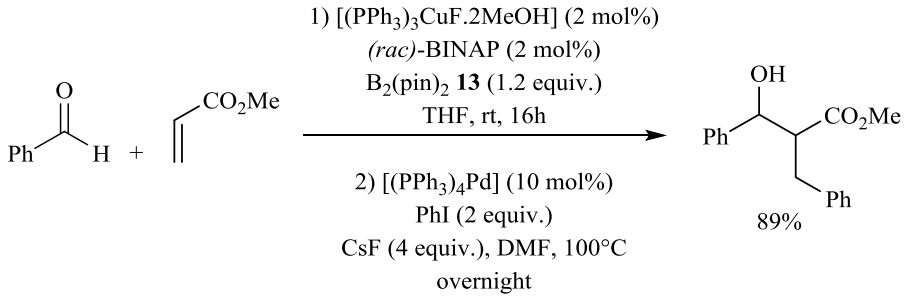
[8] Choi, W. J.; Park, J. G.; Yoo, S. J.; Kim, H. O.; Moon, H. R.; Chun, M. W.; Jung, Y. H.; Jeong, L. S., *J. Org. Chem.* **2001**, *66*, 6490-6494.



Scheme 9. Domino reaction using enantiopure cyclic enone.

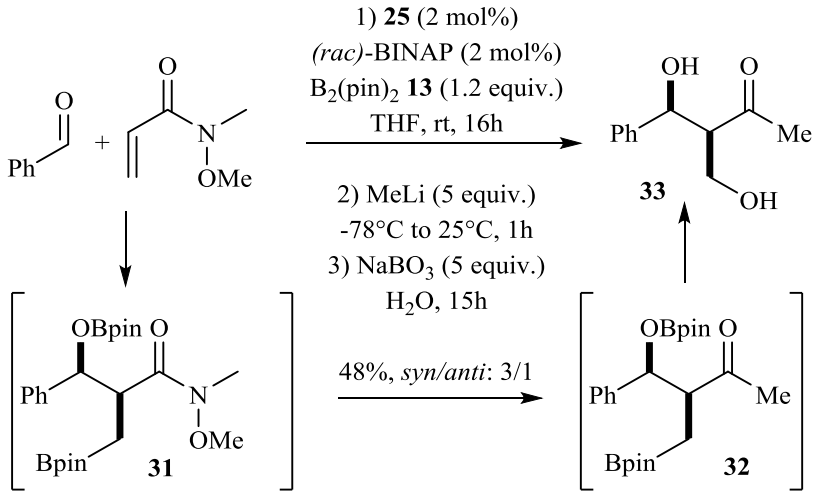
However, organoboranes derivatives are quite unstable in some cases although they are versatile intermediates in organic synthesis. Indeed their main application is found in the Suzuki cross-coupling reaction. Thus, valorization of these adducts with palladium catalysis might be interesting. After condensation of benzaldehyde, methyl acrylate and **13** using the standard catalytic conditions, the solvent was evaporated from the crude reaction mixture without any work-up and replaced by DMF. The Suzuki reaction was then directly carried out with iodobenzene using $Pd(PPh_3)_4$ as a catalyst and cesium carbonate as a base using an optimised protocol from the literature.[9] The corresponding adduct could be isolated as a separable mixture of *syn*/*anti* diastereoisomers in an excellent 89% yield after two steps (Scheme 10).

[9] Lawrence, J. D.; Takahashi, M.; Bae, C.; Hartwig, J. F., *J. Am. Chem. Soc.* **2004**, *126*, 15334-15335.



Scheme 10. Domino borylation/aldol/Suzuki coupling.

This preliminary result shows that it is possible to have access to structural diversity on this family of adducts by simple variation of the aldehyde and the aryl iodide. In order to go further in the synthetic versatility of the three component adducts, they finally checked the transformation of a model adduct bearing a Weinreb amide group. The borate ester intermediate **31** was not isolated and directly reacted with a large excess of methyl lithium to carry out the transformation of the amide group into the corresponding methyl ketone **32** (Scheme 11).



Scheme 11. One-pot transformation of a Weinreb amide.

Final oxidation of the boronic ester by sodium perborate delivered the desired keto-diol **33** in a 48% overall yield for the three steps and a 3/1 *syn*/*anti* ratio.

In summary, an efficient procedure for the tandem borylation/aldol reaction based on copper catalysis was developed. A wide variety of aldehydes were used and the desired adducts were obtained in good to excellent yields. Regarding the Michael acceptor, the catalytic system tolerates α substitution. Different types of electronwithdrawing groups on the Michael acceptor may be employed and low level of diastereoselectivity is observed with linear substrates. However, the use of cyclic substrates increases dramatically the diastereoselectivity and enantiopure substrates lead to the control of the absolute configuration of three new contiguous centres. It is also possible to combine this protocol with a Suzuki coupling.

I.2.2. Silylation reaction

Our group wanted also to develop a tandem process using silylboranes as pronucleophiles. Although the use of silyl-metal species is not suitable for silylative aldol because of potential direct addition of the silyl group to the aldehyde (this problem of chemoselectivity is well known in copper hydride chemistry),[10] they described a diastereoselective domino

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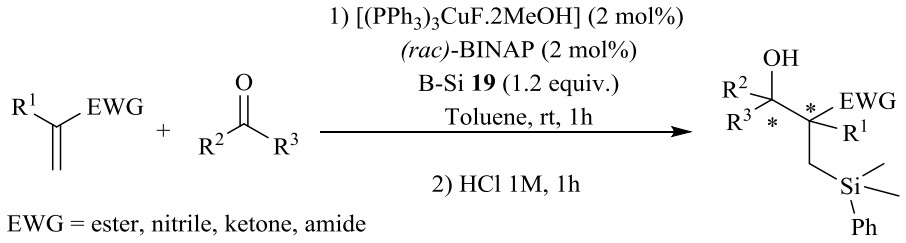
[10] (a) Lipshutz, B. H.; Amorelli, B.; Unger, J. B., *J. Am. Chem. Soc.* **2008**, *130*, 14378-14379. (b) Chuzel, O.; Deschamp, J.; Chausteur, C.; Riant, O., *Org. Lett.* **2006**, *8,* 5943-5946.

silylative aldol reaction using silylborane **19**.[11] At the same time, an asymmetric conjugated addition of silylborane on electrophilic double bonds with high enantioselectivities was reported by Hoveyda using chiral copper-diaminocarbene complexes with an example of a tandem aldol reaction.[12]

Initial experiments performed by our group showed that reaction between various carbonyl compounds (aldehydes and ketones), various Michael acceptors and a stoichiometric amount of silylborane **19** in toluene at room temperature in the presence of $[CuF(PPh_3)_3]\cdot 2MeOH$ **25**, and (*rac*)-BINAP **26** readily afforded the desired aldol adduct in good yield (Scheme 12).



EWG = ester, nitrile, ketone, amide
R^1 = H, Me
R^2 = alkyl, aryl
R^3 = H, alkyl

conversion > 99%
yield 73-89%
syn/anti up to 7/1

Scheme 12. Copper(I)-catalyzed domino silylative aldol reaction.

They observed an excellent reactivity of their catalytic system and excellent yields of the three components adducts were obtained in each case with low catalyst loading and short reaction time. However, no or very low diastereoselectivity was achieved except for the intramolecular

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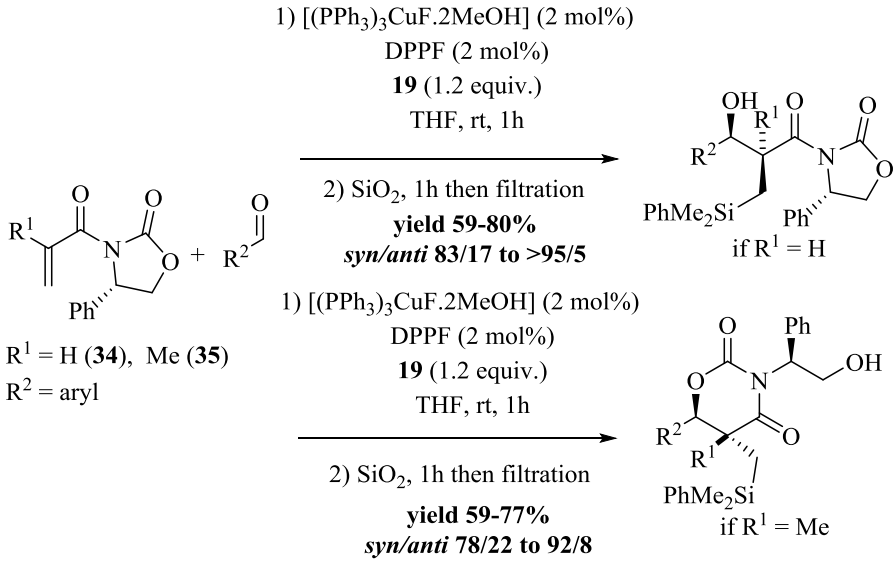
[11] Welle, A.; Petrignet, J.; Tinant, B.; Wouters, J.; Riant, O., *Chem. Eur. J.* **2010**, *16*, 10980-10983.

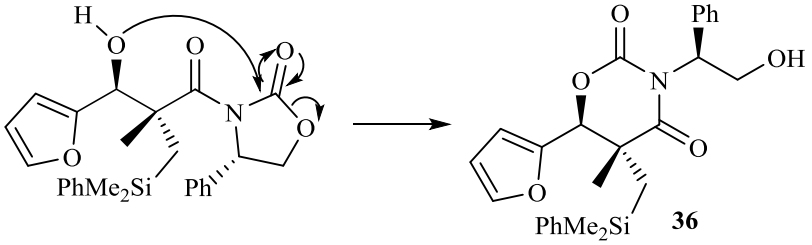
[12] Lee, K.-S.; Hoveyda, A. H., *J. Am. Chem. Soc.* **2010**, *132*, 2898-2900.

version, cyclic enones or Weinreb amides. They therefore decided to use other substrates. Their hypothesis was that the stereochemistry could be controlled by using chiral auxiliaries such as oxazolidinones on the Michael acceptors. After optimization of the catalytic system and a survey of various achiral diphosphine ligands, they found that a better reproducibility could be achieved by replacing (*rac*)-BINAP **26** by DPPF (1,1'-bis(diphenylphosphino) ferrocene) and toluene by THF. Under these optimised catalytic conditions, the reaction between various aromatic aldehydes and acryloyloxazolidinones **34** gave the corresponding *syn*-aldol adducts in good yields (59-80%) and with almost complete control of the stereochemistry in most cases (Scheme 13). The absolute configuration of these compounds was determined by X-ray diffraction.



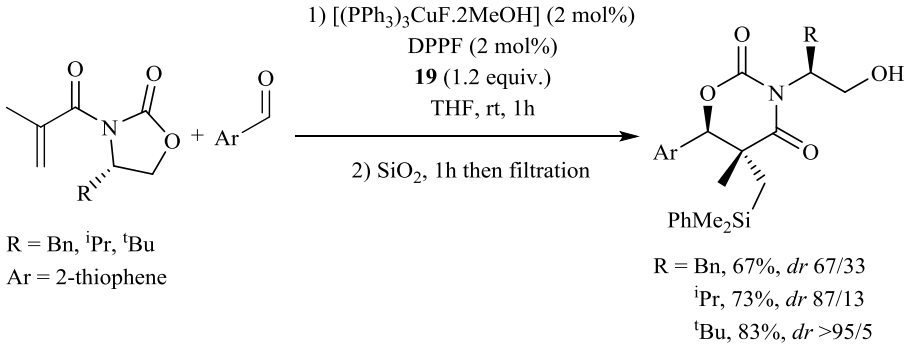
Scheme 13. Copper-catalyzed silylative–aldol reaction between enoyloxazolidinones and various aldehydes.

They next investigated the use of methacryloyloxazolidinones **35** with various aromatic and heteroaromatic aldehydes. Moderate to good isolated yields were obtained (59-77%) and diastereoselectivities in the range of 78/22 to 92/8 were achieved (Scheme 13). This means that the absolute stereochemistry of the chiral quaternary carbon chiral centres was controlled. The structure of the aldol adduct was first attributed to a simple open structure but a rearranged structure was later attributed when an X-ray crystal-structure analysis of the 2-furyl carboxaldehyde adduct was carried out to analyze the absolute configuration of the newly formed asymmetric carbon centres. The rearranged adduct **36** is assumed to arise from an intramolecular ring opening of the oxazolidinone moiety by the hydroxyl group of the aldol adduct (Scheme 14).



Scheme 14. Formation of rearranged adduct **36**.

They finally investigated the effect of the structure of the chiral auxiliary (Scheme 15). The optimization was carried out with thiophene-2-carboxaldehyde because it gave the lowest diastereomeric ratio. The selectivity is dependent on the steric hindrance because the benzyl-substituted substrate led to a lower selectivity. The isopropyl-substituted oxazolidinone led to an improved *dr* and the *tert*-butyl derivative restored the full control of the selectivity.



Scheme 15. Effect of the structure of the chiral auxiliary.

In summary, they have developed a domino silylation–aldol reaction between enoyloxazolidinones and various aldehydes. The process catalyzed by a copper–diphosphine complex in the presence of silylborane led to high diastereoselectivities. Yields ranging from 59 to 90% and diastereoisomeric ratios up to 95/5 were obtained. When α methyl-substituted acryloyloxazolidinones were used, a controlled chiral quaternary carbon was generated.

I.3. Cationic complexes

Earlier in this manuscript, we introduced the generation of neutral copper(I) nucleophiles catalysts and their efficiency in organic chemistry. However, this system can have several disadvantages such as a weak chirality induction and addition of a base to continue the catalytic cycle. Therefore the use of cationic complexes as a new class of catalysts for metal catalysis has emerged as a great alternative to solve this problem. In this part, we are going to describe the important characteristics of such complexes as well as their synthesis and development in our laboratory.

Weakly or non-coordinating anions (WCAs) are of considerable interest as counterions for the synthesis of novel ionic compounds as well as counterions for cationic catalysts, due to their potential in enhancing reactivity of metal complexes.[13] Moreover, little attention has been paid to the development of Cu(I) complexes with WCAs and to their potential catalytic applications. The $[Cu(MeCN)_4]^+$ cation coordinated with some couterions such as BF_4^-, ClO_4^- and PF_6^- is well known both

[13] For reviews on WCAs see: (a) Strauss, S. H., *Chem. Rev.* **1993**, *93*, 927-942. (b) Liang, H.-C.; Kim, E.; Incarvito, C. D.; Rheingold, A. L.; Karlin, K. D., *Inorg. Chem.* **2002**, *41*, 2209-2212. (c) Krossing, I.; Raabe, I., *Angew. Chem. Int. Ed.* **2004**, *43*, 2066-2090. (d) Zhang, Y.; Sun, W.; Freund, C.; Santos, A. M.; Herdtweck, E.; Mink, J.; Kühn, F. E., *Inorganica Chimica Acta* **2006**, *359*, 4723-4729.

with respect to its properties, structure and catalytic activity.[14] Salts of tetrakis(acetonitrile)copper(I), $[Cu(MeCN)_4]^+$, are exceedingly useful starting materials for the synthesis of copper(I) complexes possessing polydentate ligands. To extend the utility of such chemistry from the generally used solvents dichloromethane, acetonitrile… to relatively low-dielectric solvents, the group of Karlin have employed fluorinated tetraarylborate anions such as tetrakis(3,5-bis-trifluoromethylphenyl)borate.[15] They also used $B(C_6F_5)_4^-$ as the counteranion since it affords excellent solubility. Another advantage is that these cationic complexes are easily crystallized and characterized by X-ray crystallography.[16] However, our group was interested in using hydrogen bifluoride as counteranion. In that manner, a new pathway to unprecedented (NHC)copper(I) bifluoride complexes was developed, which proved to be excellent catalysts for nucleophilic transfer onto

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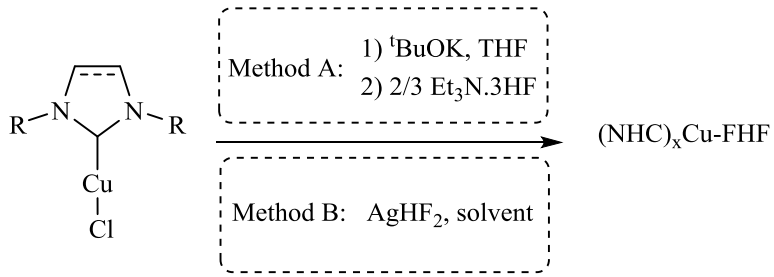
[14] (a) Knaust, J.; Knight, D.; Keller, S., *J. Chem. Cryst.* **2003**, *33*, 813-823. (b) Díaz-Requejo, M., M.; Pérez, P. J., *J. Organomet. Chem.* **2001**, *617*, 110-118. (c) Borriello, C.; Cucciolito, M. E.; Panunzi, A.; Ruffo, F., *Tetrahedron Asymmetry* **2001**, *12*, 2467-2471. (d) Storhoff, B., N.; Lewis, C., H., *Coord. Chem. Rev.* **1977**, *23*, 1-29.

[15] Kopf, M.-A.; Neuhold, Y.-M.; Zuberbühler, A. D.; Karlin, K. D., *Inorg. Chem.* **1999**, *38*, 3093-3102.

[16] Liang, H.-C.; Kim, E.; Incarvito, C. D.; Rheingold, A. L.; Karlin, K. D., *Inorg. Chem.* **2002**, *41*, 2209-2212.

electrophilic double bonds, such as aldehydes and chiral imines (Scheme 16).[17]



Scheme 16. Synthesis of (NHC)CuFHF.

These small and nucleophilic fluorinated anions have several attractive features. Hydrogen fluoride anions are of significant structural and theoretical interest as classical examples of the strongest hydrogen bonds.[18] In addition the structures with bulky cations represent special cases of weak cation-anion interactions, thus contributing to the study of "isolated" hydrogen fluoride anions.[19] This prompted us to design a new family of well defined diphosphine copper(I) complexes bearing a bifluoride counteranion. First experiments were performed by Dr. Julien Petrignet and Dr. Alexandre Welle (Scheme 17). It should be mentioned that ligandless copper(I) fluoride is not isolable. Preparation of the *in situ* LCuCl was carried out in THF with copper(I) chloride and a diphosphine ligand. Addition of sodium *tert*-butoxide allowed the

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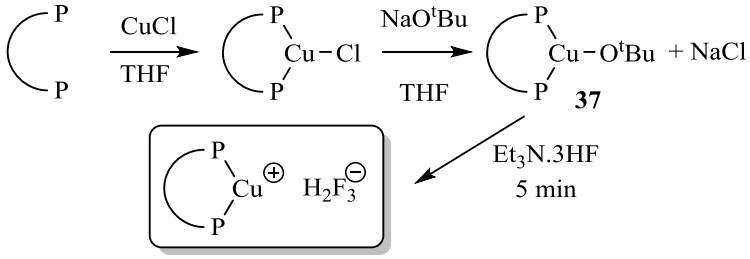
[17] Vergote, T.; Nahra, F.; Welle, A.; Luhmer, M.; Wouters, J.; Mager, N.; Riant, O.; Leyssens, T., *Chem. Eur. J.* **2012**, *18*, 793-798.

[18] Hibbert, F.; Emsley, J., *Adv. Phys. Org. Chem.* **1991**, *26*, 255-379.

[19] Troyanov, S. I.; Morozov, I. V.; Kemnitz, E., *Z. Anorg. Allg. Chem.* **2005**, *631,* 1651-1654.

formation of the copper-alkoxide intermediate **37**. Removal of NaCl by filtration under argon and then reaction of **37** with $Et_3N.3HF$ yielded the new copper complex. However, they found that the counteranion was $H_2F_3^-$ instead of HF_2^-.



Scheme 17. First generation of cationic complexes.

This complex was purified by crystallization in acetonitrile to afford white, air stable crystals in 65% yield when MeOBiphep **38** was used as ligand. ^{19}F NMR analysis showed the presence of fluoride ions and X-ray analysis revealed a copper(I) cationic complex bearing the diphosphine ligand and two molecules of acetonitrile. Counterion was well identified as $H_2F_3^-$ (Figure 5).

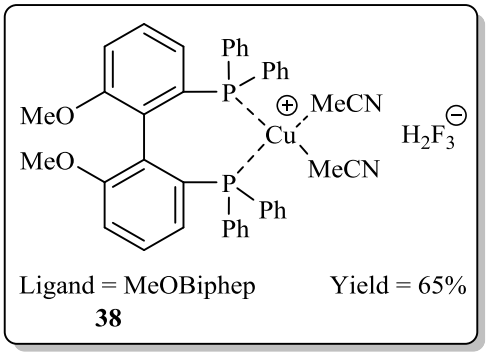
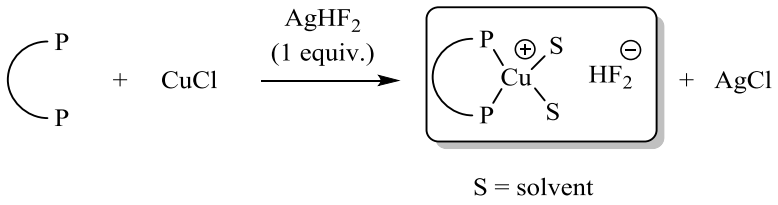


Figure 5. Cationic complex with MeOBiphep.

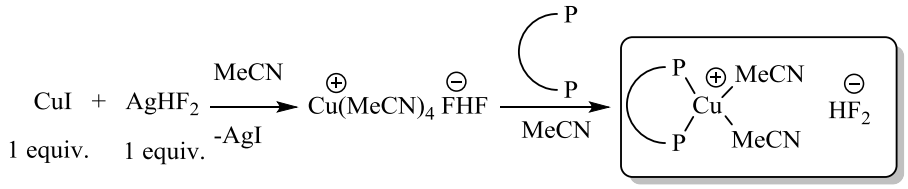
With this complex readily prepared, they wanted to know if interesting catalytic activity can be achieved. Despite encouraging results, problems of reproducibility were observed. This is due to the presence of several species. In addition, in some cases, the nature of the conteranion was very difficult to confirm in spite of X-ray analysis ($H_2F_3^-$ versus HF_2^-). To avoid these problems Dr. Thomas Hermant decided to improve this methodology and developed another strategy for the synthesis of new cationic complexes (Scheme 18).



Scheme 18. Second generation of cationic complexes.

Copper(I) chloride and a diphosphine ligand were stirred in THF for 30 minutes then the commercially available source of bifluoride, $AgHF_2$, was added to the reaction mixture. Filtration under inert atmosphere allowed the elimination of salts and after removal of the solvent, a white powder was obtained. A large number of ligands and differents solvents were tested. These complexes have several advantages: they are air stable, highly active in catalysis and easily prepared. Nevertheless a rapid degradation was observed in solution and some silver impurities seemed to be always present. Moreover, no crystals were obtained with any of the ligands attempted. Therefore they were not able to confirm the structure of both cationic complex and counteranion. Finally a solution was found to avoid some of these drawbacks. A novel strategy was

developed and applied by our group as reported in scheme 19. This methodology will be described in more details later on in this chapter.

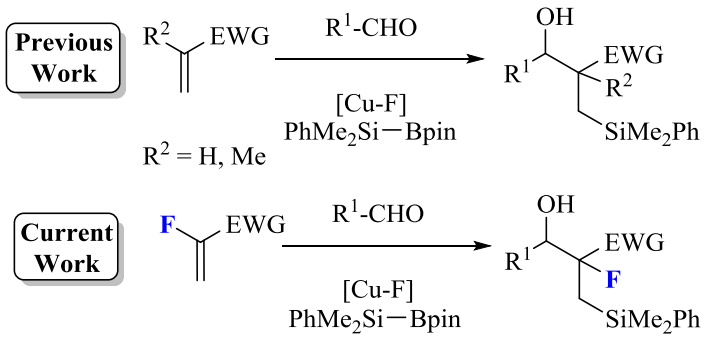


Scheme 19. Third generation of cationic complexes.

II. Objectives

As described in the introduction, our group has a history of developing new methodologies for the copper catalyzed 1,4-addition/aldolisation with bisboronate **13** and silylborane **19**.

First of all, we found it interesting to try to extend the silylation reaction to new substrates. Using the copper(I) nucleophilic species developed in our group, we endeavoured to apply it to Michael acceptors bearing a fluorine substituent on the double bond. Various substrates could be envisaged, as well as different electrophiles (Scheme 20). The ultimate goal is the formation of chiral quaternary centres bearing a fluorine substituent. Indeed fluorine chemistry has become highly attractive during the past few years, mostly for the synthesis of biologically active compounds.[1]



Scheme 20. Previous and current work on our methodology.

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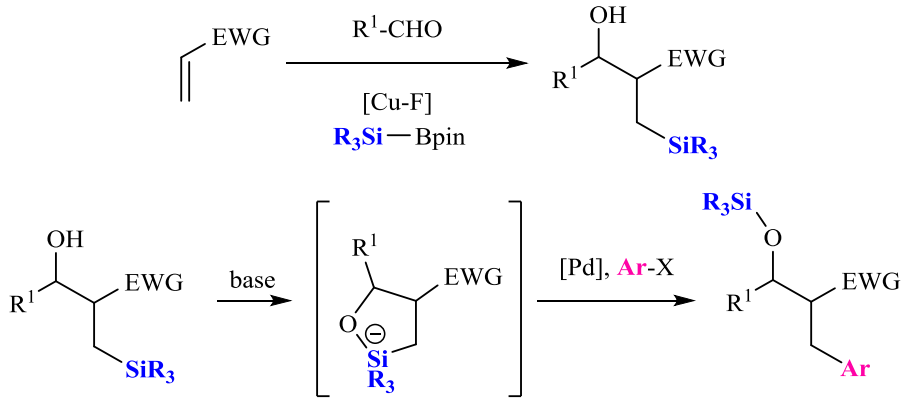
[1] For review see: Filler, R.; Saha, R., *Future Med. Chem.* **2009**, *1*, 777-791. For selected examples of biological actif compounds bearing a fluorine substituent see: (a) Murphy, C. D.; Schaffrath, C.; O'Hagan, D., *Chemosphere* **2003**, 455-461. (b) Isanbor, C.; O'Hagan, D., *J. Fluor. Chem.* **2006**, *127*, 303-319.

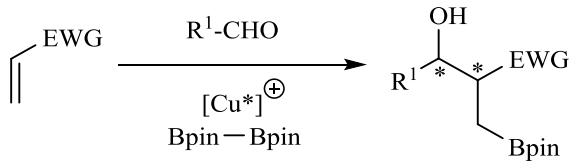
Organosilane derivatives are versatile intermediates in organic synthesis and one of their main applications is found in the Hiyama cross-coupling reaction. Therefore another objective was to use different silylboranes in the copper catalyzed 1,4-addition/aldolisation domino reaction. We hoped that the aldol adduct, in a presence of a base, could undergo the formation of a cyclic intermediate which could subsequently react with a palladium catalyst and a halo-benzene to yield the desired cross-coupling product (Scheme 21). If successful, this experiment will show that it could be possible to access various products with different structural diversity by simple variation of the aldehyde and the Hiyama coupling electrophilic partner.



Scheme 21. Hiyama coupling.

Concerning the borylation reaction, our aim was to develop a non racemic version for these molecules. Asymmetric induction could be induced by a chiral ligand and we envisaged to use our new cationic copper(I) complexes (Scheme 22). However, finding the right ligand is not an easy task. The variables in play are quite extensive and this system

should be chemoselective, regioselective, diastereoselective and ultimately enantioselective.



Scheme 22. Enantioselective version of borylation reaction.

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.

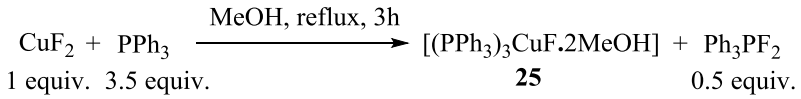
III. Results and discussion

III.1. Silylation reaction

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

The catalytic system frequently used in our group 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. The system involves the use of a phosphine-based copper fluoride complex. Complex **25** is readily obtained, using a modified literature procedure,[2] by reacting copper(II) fluoride with triphenylphosphine in refluxing methanol (Scheme 23).



Scheme 23. Synthesis of complex **25** used in our group.

This complex has generally been used in the presence of a diphosphine ligand. The BINAP ligand is frequently used in model reactions due to its commercial availability both in racemic and enantiopure forms. The

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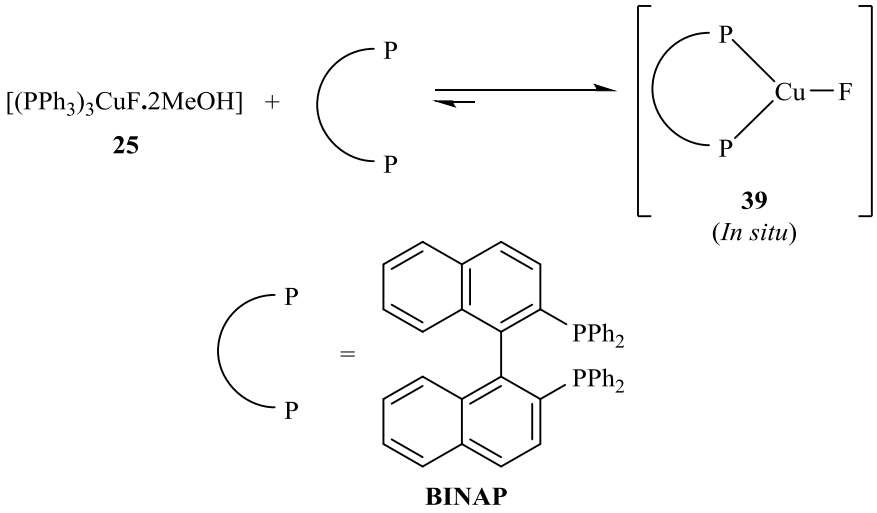
[1] S. Sirol, J. Courmarcel, N. Mostefai, O. Riant, *Org. lett.* **2001**, *3*, 4111.

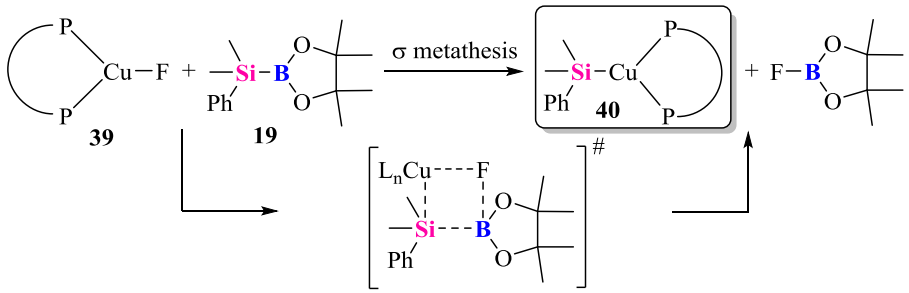
[2] D. J. Gulliver, W. Levason, M. Webster, *Inorganica Chimica Acta Articles* **1981,** *52*, 153.

diphosphine displaces quasi irreversibly the monophosphine ligands, rendering the newly formed complex **39** more stable and less susceptible to the decomplexation/complexation phenomenon, usually observed with monophosphines (Scheme 24).



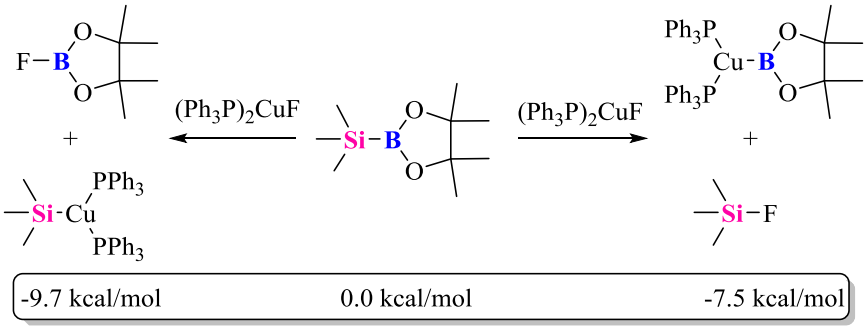
Scheme 24. *In situ* generation of diphosphine copper(I) complex.

The diphosphine copper(I) complex **39** obtained *in situ* has shown to react easily with silylborane **19** to form the desired copper silane complex **40** (Scheme 25). This complex will then undergo the conjugated addition/aldolisation domino process successfully.



Scheme 25. *In situ* generation of the copper(I)-Si complex **40**.

It is important to mention that at the beginning of this project, we thought that the boryl group would be transferred to the copper, not the silyl group, due to their electronegativity (2.04 for boron and 1.8 for silicon). However, calculations were carried out by Professor Raphael Robiette and these results showed that it is thermodynamically favoured to form Cu^{I}-Si instead of Cu^{I}-B species (Scheme 26).[3]



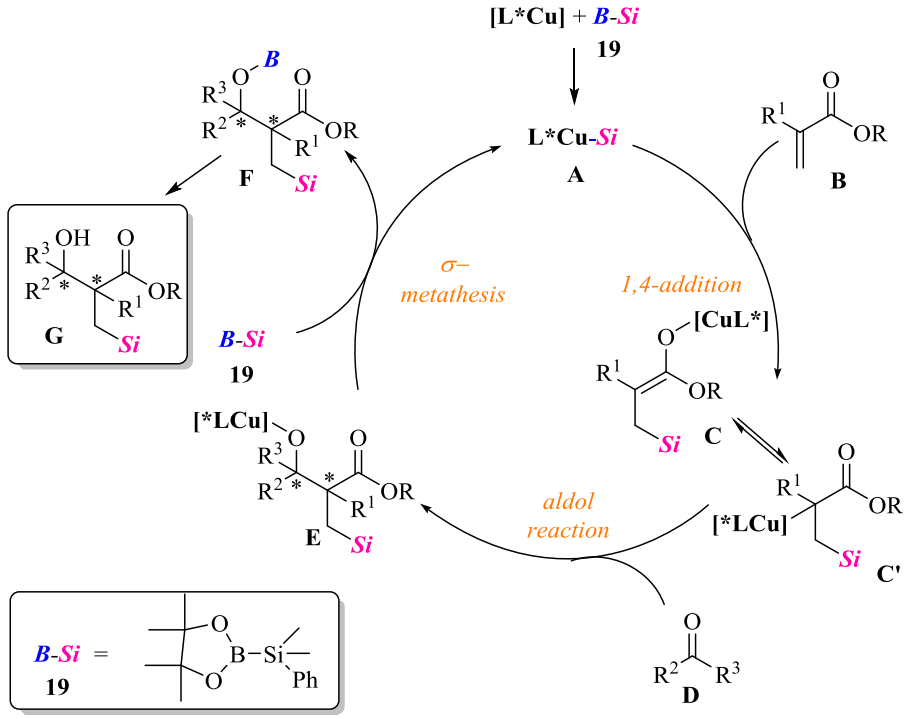
Scheme 26. Formation of Cu-Si *versus* Cu-B species.

III.1.2. Proposed mechanism

The proposed mechanism for the model reaction is illustrated in scheme 27. The copper silane 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 silylborane **19** will simultaneously form the silylated aldol adduct **F** and regenerate the copper silane complex to close the catalytic cycle. The silylated aldol adduct is transformed afterwards by hydrolysis to the desired aldol

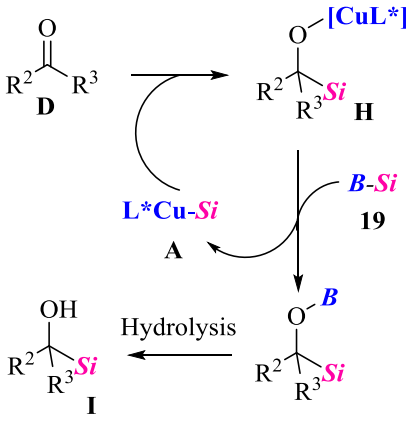
[3] Methods used for the calculations are described in the experimental part.

adduct **G**. This is generally achieved by an acidic work-up of the reaction mixture.



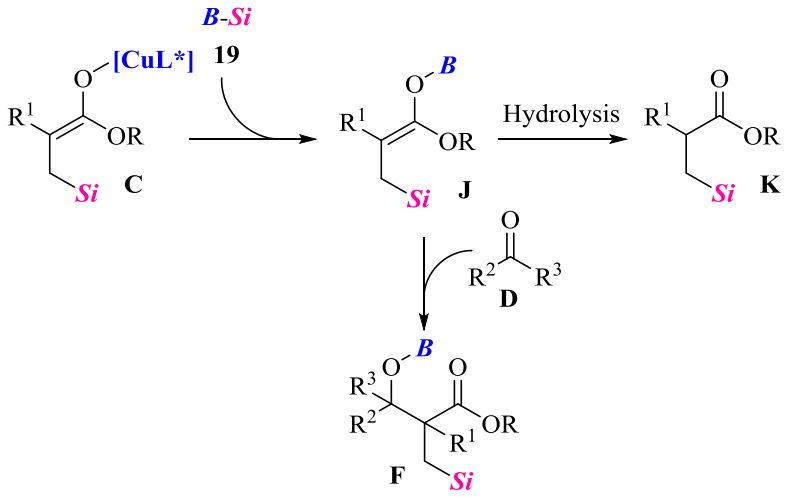
Scheme 27. Proposed catalytic cycle for the silylation reaction.

However, there are a few secondary reactions that could influence the outcome. For example, if the system is not chemoselective, the copper silane **A** could react directly with the electrophile **D** to form the corresponding copper alkoxide **H** (Scheme 28). Exchange of the copper with silylborane **19** would generate, after hydrolysis, α–silyl–alcohols **I**. This secondary reaction completely consumes the electrophile, if it is faster than the 1,4-addition reaction.



Scheme 28. Secondary reaction: formation of α–silyl–alcohols **I.**

Another secondary reaction could occur when the reaction of the copper enolate **C** with the electrophile is not favoured. In this case, **C** reacts with silylborane **19** to form boryl enol ether **J** (Scheme 29). Two additional pathways could then evolve. The boryl enol ether **J** could after hydrolysis generate the 1,4-addition product **K**. But **J** could also react with the electrophile **D**, as in Mukaiyama-aldol reactions to form product **F**. This pathway is highly undesirable because it does not allow for asymmetric catalysis.



Scheme 29. Secondary reactions.

However, where does the idea to use silylborane species in our domino reaction come from? As mentioned in the general introduction, silylborane species are largely used in the literature compared to disilanes which are commercially available and less sensitive and we were interested in understanding why. This is actually due to the low reactivity of Si-Si compounds. The problem may come from the slow regeneration of the active species with this nucleophile (regeneration of **A** from **E** in the proposed catalytic cycle). Calculations were thus performed by Professor Raphael Robiette to prove this hypothesis. The figure 6 shows that it was more thermodynamically favoured to regenerate Cu-Si species from silylboranes than disilanes.[4] These results explain that it is easier to continue the catalytic cycle in the case of Si-B compound and harsh conditions are not necessary. That is why chemists decided to use Si-B bond although this kind of reagent is expensive and difficult to handle.

[4] Methods used for the calculations are described in the experimental part.

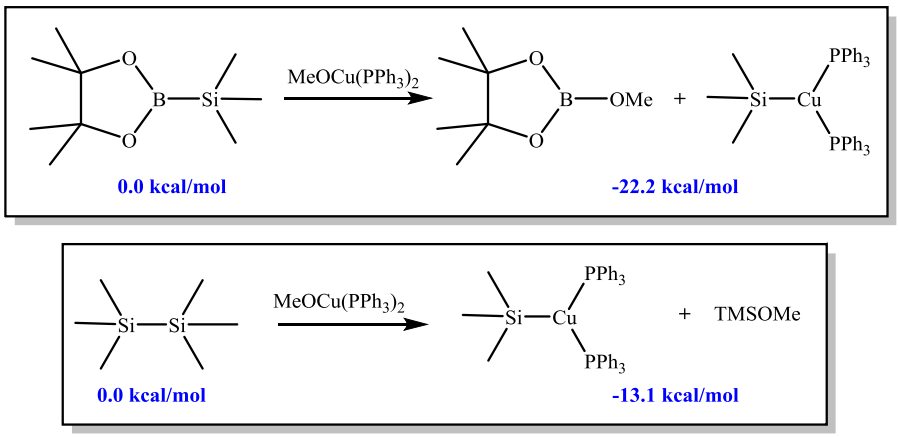
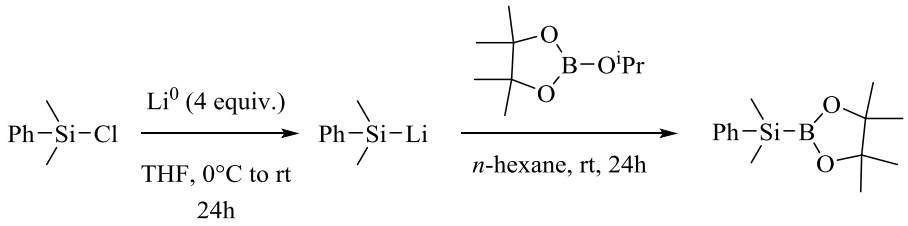


Figure 6. Reactivity of disilanes *versus* silylboranes species.

III.1.3. Synthesis of silylboranes

The project started with the synthesis of Suginome's reagent **19** (Scheme 30). A procedure from the literature was used.[5]



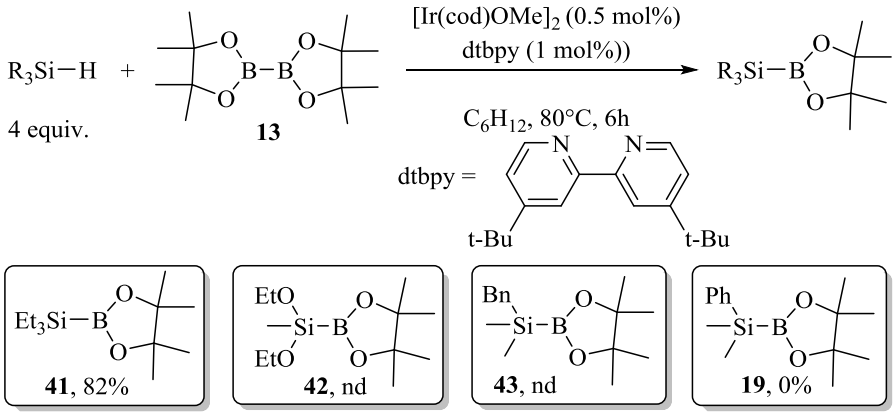
Scheme 30. Synthesis of Suginome's reagent **19**.

Under inert atmosphere, an excess of metallic lithium reacts with dimethylphenylchlorosilane in THF at 0°C to form the dimethylphenyllithiumsilane. A vigorous stirring is necessary to have a complete conversion. The latter was then reacted with 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane in *n*-hexane to afford the

[5] Suginome, M.; Matsuda, T.; Ito, Y., *Organometallics* **2000**, *19*, 4647-4649.

silylborane product and lithium salts. The desired product **19** is obtained as a colorless liquid in 80% yield. The final product is sensitive to air, so it was kept in a Schlenk tube under inert atmosphere and was usually used within one month.

Another useful procedure reported by the group of Hartwig to synthesize silylboranes has been used during this project.[6] Reaction of 4 equivalents of triethylsilane directly with $B_2(pin)_2$ **13** in a presence of an iridium catalyst and 4,4'-di-*tert*-butylpyridine as ligand afforded the corresponding silylborane **41** with good yield after distillation of the crude product (Scheme 31).



Scheme 31. Synthesis of silylboranes.

Several other silanes also reacted to form silylborane products but in low yield and we were not able to isolate the desired product in a pure form. Concerning the silylborane **42**, we observed a degradation of the desired product during the filtration on silica. Purification by distillation did not

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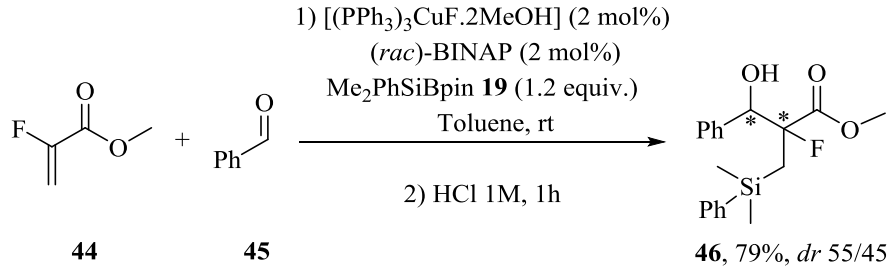
[6] Boebel, T. A.; Hartwig, J. F., *Organometallics* **2008**, *27*, 6013-6019.

allow the isolation of the desired product either. In the case of silylborane **43**, the silane is recovered at the end of the reaction. Finally, attempts to form silylborane **19** using this procedure were not successful, due to the lability of the Ar-Si bond under the reaction conditions.[7]

III.1.4. First optimization

As described in the objectives of this chapter, we endeavoured to apply our methodology to Michael acceptors bearing a fluorine substituent on the double bond. It is noteworthy to mention here that the presence of fluorine atom could decrease the reactivity of the aldol process due to its electronic properties (inductive effect but also mesomeric effect). However, various substrates could be envisaged and the ultimate goal is the formation of chiral quaternary carbons bearing a fluorine substituent. The project started with substrate **44** as a model substrate for the desired domino reaction. This substrate is commercially available and the previously described copper system was used. Thus, initial tests were conducted with **44** in the presence of benzaldehyde **45** in toluene at room temperature (Scheme 32).

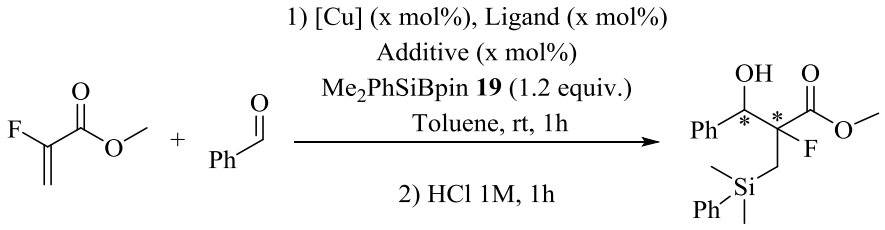


Scheme 32. Domino reaction with substrate **44**.

[7] Boebel, T. A.; Hartwig, J. F., *J. Am. Chem. Soc.* **2008**, *130*, 7534-7535.

The reaction was highly chemoselective as no 1,2-addition product was observed. Conversion was complete after 1h of reaction and the desired aldol adduct **46** was obtained in 79% yield after purification. However, low diastereoselectivity was achieved. This ratio was determined on the crude mixture by ^{19}F NMR. Although this ratio was very low, this result remained encouraging because diastereoselectivity of 50/50 was always obtained with simple acrylate as mentioned in the introduction. We then decided to improve this result and a screening of different conditions was applied as shown in table 1.

Table 1. Screening of different reaction conditions.



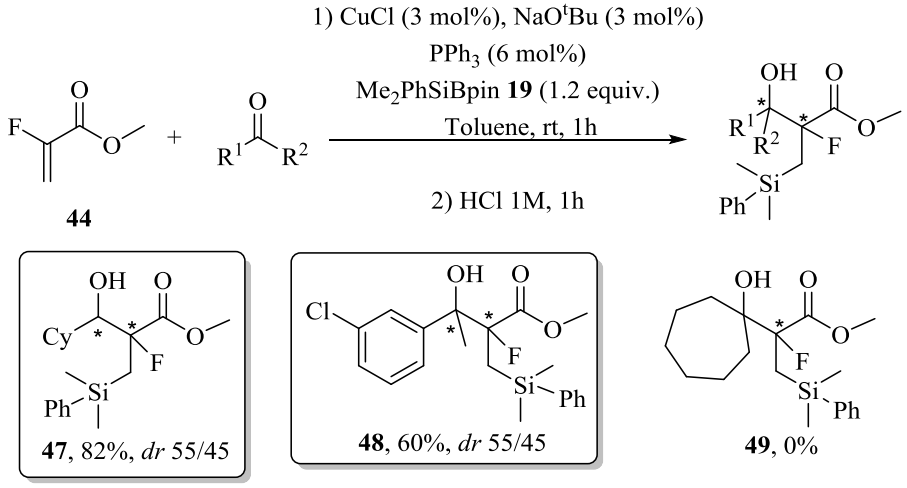
44 **45** **46**

Entry	[Cu] (mol%)	Ligand (mol%)	Additive (mol%)	dr[c]
1	$(Ph_3P)_3CuF$ (2)	(*rac*)-BINAP (2)	-	55/45
2	$(Ph_3P)_3CuF$ (2)	-	-	52/48
3	CuCl (3)	Ph_3P (3)	NaO^tBu (3)	55/45
4	CuCl (3)	Ph_3P (3)	NaO^tBu (4.5)	55/45
5	**CuCl (3)**	**Ph_3P (6)**	**NaO^tBu (3)**	**60/40**
6	CuCl (3)	(*rac*)-BINAP (3)	NaO^tBu (3)	-
7	CuCl (3)	DPPF[a] (3)	NaO^tBu (3)	58/42[b]

[a] dppf = 1,1'-Bis(diphenylphosphino)ferrocene. [b] Complete conversion after 16h of reaction. [c] Determined on the crude mixture by ^{19}F NMR.

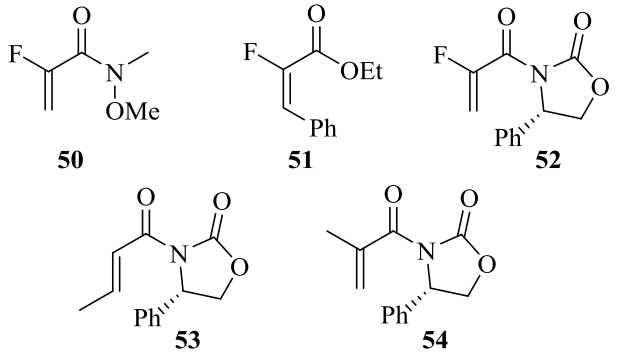
Reactions were first carried out with $CuF(PPh_3)_3$ **25** and *(rac)*-BINAP, and the same result was obtained indicating that the reaction was reproducible. Conducting the reaction without the BINAP ligand gave almost the same outcome (entry 2). Our hypothesis was that the reaction was faster with monophosphine ligands and thus another catalyst system was used. A combination of copper(I) chloride and sodium *tert*-butoxide allowed the *in situ* generation of copper(I)-*tert*-butoxide. This copper source was then used with triphenylphosphine as ligand. Although the reaction was faster with this system, the ratio Cu/base did not influence the diastereoselectivity. The best result was obtained with a ratio Cu/ligand of 1/2 (entry 5). Diphosphine ligands were also tested with this system. However, no product was obtained after 1h of reaction with (*rac*)-BINAP and the conversion was complete after only 16h when DPPF was used as ligand. These results demonstrated once again that the reaction was very slow with diphosphines. Unfortunately, no improvement of the diastereoselectivity was achieved.

At the same time, other electrophiles were tested to extend the scope of this reaction (Scheme 33). Aliphatic aldehydes allowed to afford the desired aldol adduct **47** with good yield but with the same diastereoisomeric ratio. The use of aromatic ketones was also possible. Reaction of *m*-chloroacetophenone furnished the desired product **48** in 60% yield. Nevertheless, cyclic ketone seemed to be less reactive and therefore failed to react under our conditions. No conversion was observed with cycloheptanone as electrophile.



Scheme 33. Scope of the reaction.

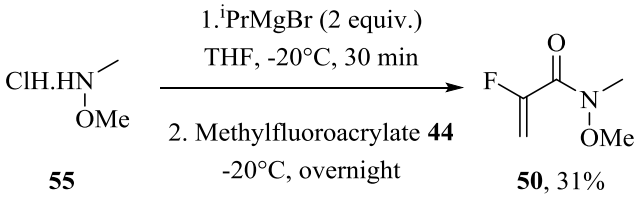
After these disappointing results, we thought that maybe other Michael acceptors could be more susceptible to improve the selectivity of the reaction. Scheme 34 shows an overview of the different substrates that we attempted to synthesize. Indeed these substrates are not commercially available so we will describe their synthesis in the following sections.



Scheme 34. Overview of the different substrates synthesized.

III.1.5. Synthesis of substrates

We decided to synthesize substrate **50** because Weinreb acrylamide has shown very interesting results in the silylation reaction as reported by Dr Alexandre Welle (see point I.2).[8] The first step of the synthesis was the addition of isopropylmagnesium bromide at -20°C to N,O-dimethyl hydroxylamine hydrochloride **55**. Then the reaction of the anionic intermediate with methylfluoroacrylate **44** yielded the desired product **50**. A low yield of 31% was obtained. This is probably due to the volatility of the final product. Moreover, conversion was not complete and starting material was recovered. Unfortunately, further optimization of this reaction-(e.g., the use of $AlMe_3$ or butyllithium as activating agents) did not improve this result.[9]



Scheme 35. Synthesis of substrate **50**.

To avoid volatility problems, we attempted to synthesize α–fluoroacrylate **51** according to the literature procedure.[10] This substrate is synthesized in two steps starting from commercially available

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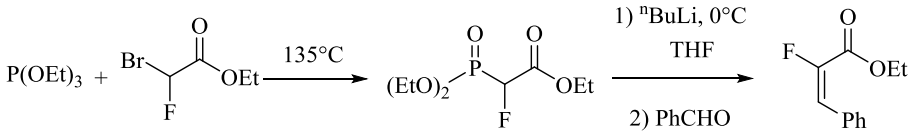
[8] Welle, A.; Petrignet, J.; Tinant, B.; Wouters, J.; Riant, O., *Chem. Eur. J.* **2010**, *16*, 10980-10983.

[9] Fuwa, H.; Sasaki, M., *Org. Lett.* **2010**, *12*, 584-587.

[10] Engman, M.; Diesen, J. S.; Paptchikhine, A.; Andersson, P. G., *J. Am. Chem. Soc.* **2007**, *129*, 4536-4537.

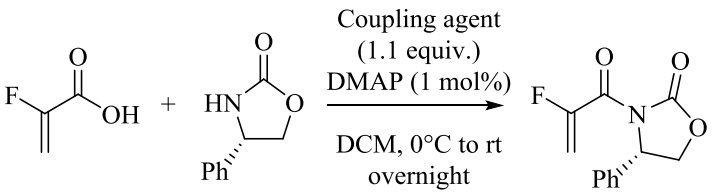
triethylphosphite and substrate **56**. At first the two latter substrates were reacted *via* an Arbuzov reaction to form the desired product **57** in a 69% yield. Triethyl phosphonoacetate **57** was then transformed into the desired α–fluoroacrylate **51** *via* an Horner-Wadsworth-Emmons olefination in good yields and stereoselectivities (E/Z ratio of 4/1).



56 **57**, 69% **51,** 53%

Scheme 36. Synthesis of **51.**

Chiral auxiliaries were also used in the first development of this reaction in our laboratory. These substrates have the potential to improve the diastereoselectivity of the reaction.



58 **59** **52**, 0%

Coupling agent = DCC or DCI

Scheme 37. First attempts for the synthesis of **52**.

First attempts to synthesize these substrates started with the activation of acid **58** with a coupling agent (DCC or DCI) followed by the addition of oxazolidinone **59** (also known as Evans auxiliary).[11] However, under

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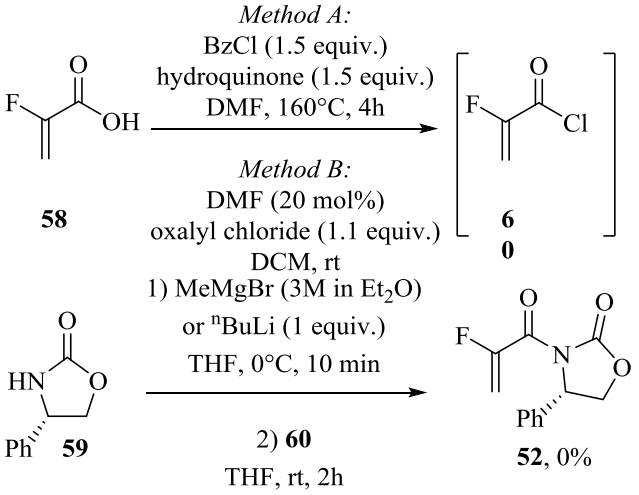
[11] (a) Van der Veken, P.; Senten, K.; Kertèsz, I.; De Meester, I.; Lambeir, A.-M.; Maes, M.-B.; Scharpé, S.; Haemers, A.; Augustyns, K., *J. Med. Chem.* **2005**, *48*, 1768-1780. (b) Andrade, C. K. Z.; Rocha, R. O.; Vercillo, O. E.; Silva, W. A.; Matos, R. A. F., *Synlett* **2003**, 2351-2352.

these conditions, no reaction occurred and only the starting material was recovered (Scheme 37). Another alternative was to form the acyl chloride **60** *in situ* starting from the corresponding acid **58**. Then reaction of **60** with oxazolidinone **59** in the presence of a base could afford the desired adduct. Different reaction conditions were used to form the acyl chloride as shown in scheme 38. Unfortunately, no product was obtained. Only degradation of the starting material was observed. Intermediate **60** was again volatile which was a problem for this synthesis. The use of $AlMe_3$ as activating agent with methylfluoroacrylate **44** also did not give the desired product. [12]

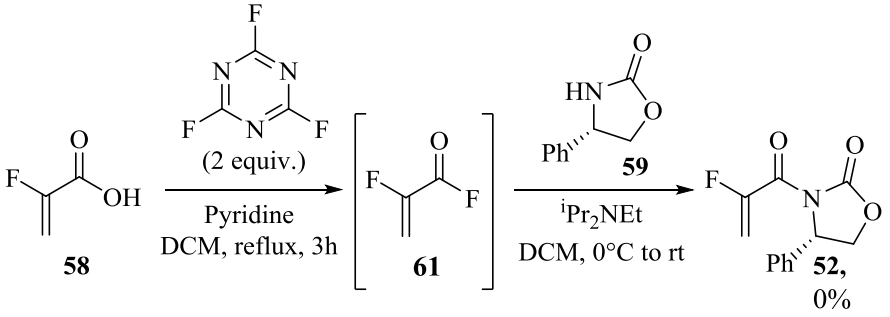


Scheme 38. First attempts for the synthesis of **52**.

Furthermore, formation of acyl fluoride **61** *in situ* from the corresponding acid in the presence of 2,4,6-trifluoro-1,3,5-triazine

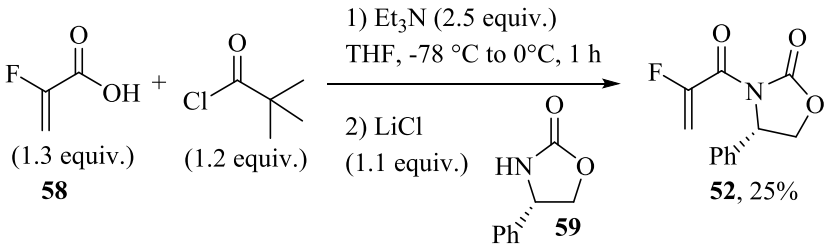
[12] Karaffa, J.; Lindsay, K. B.; Skrydstrup, T., *J. Org. Chem.* **2006**, *71*, 8219-8226.

followed by reaction with oxazolidinone **59** did not yield the desired product (Scheme 39).[13]



Scheme 39. Synthesis of **52** starting from the corresponding acid.

Finally, the reaction of **58** with pivaloyl chloride afforded the corresponding asymmetric anhydride **62** *in situ*. This intermediate was then transformed into the desired product by reaction with oxazolidinone **59** in the presence of triethylamine (Scheme 40).



Scheme 40. Synthesis of **52**.

The yield of the reaction is quite low but it is easily explained by the poor selectivity of the reaction (Scheme 41). Indeed, oxazolidinone **59** preferred the addition to the tertiobutyl side than the other side in a 2/1

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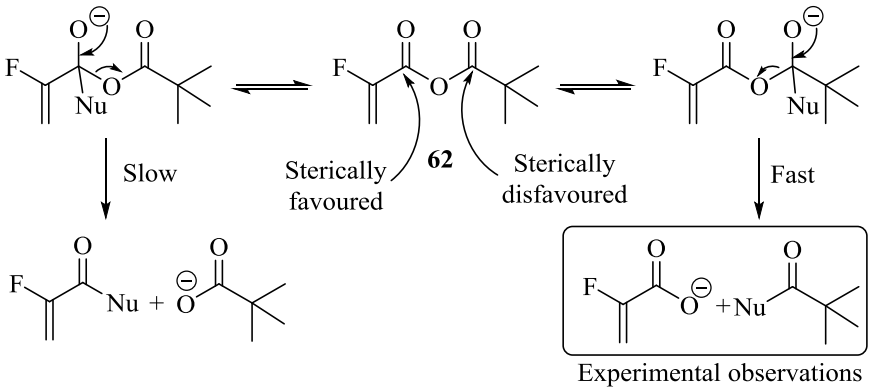
[13] (a) Schindler, C. S.; Forster, P. M.; Carreira, E. M., *Org. Lett.* **2010**, *12*, 4102-4105. (b) Evans, D. A.; Chapman, K. T.; Bisaha, J., *J. Am. Chem. Soc.* **1988**, *110*, 1238-1256.

ratio. This is probably influenced by electronic effects rather than steric ones, since fluoroacryloyl group was a better leaving group than the pivaloyl group.



Scheme 41. Explanation of the selectivity in the synthesis of **52**.

We also decided to synthesize other model substrates such as **53** and **54**. Syntheses are described in scheme 42 and scheme 43 according to a modified procedure.[14] Theses substrates are interesting because they have substituents on the double bond position α or β to the carbonyl group. We also wanted to check if the fluorine atom is influencing the oxazolidinone coupling. Substrate **53** is easily synthesized by reacting the corresponding acid and acyl chloride to form the symmetric anhydride. Reaction of this anhydride with oxazolidinone **59** furnished product **53** in 54% yield (Scheme 42).

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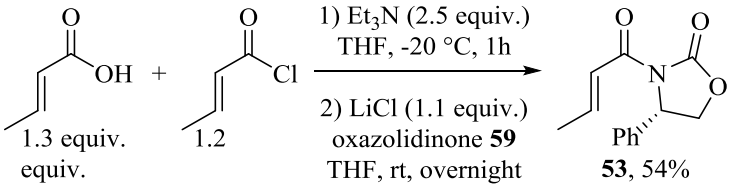
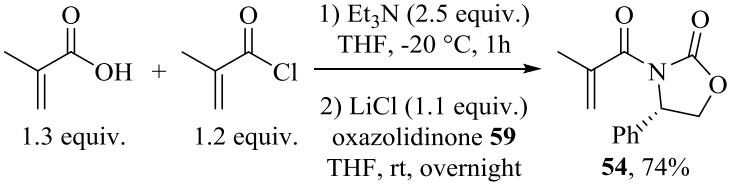
[14] Cannizzaro, C. E.; Ashley, J. A.; Janda, K. D.; Houk, K. N., *J. Am. Chem. Soc.* **2003**, *125*, 2489-2506.



Scheme 42. Synthesis of substrate **53**.

Same procedure was used to synthesize substrate **54**. This reaction furnished product **54** in 74% yield (Scheme 43).

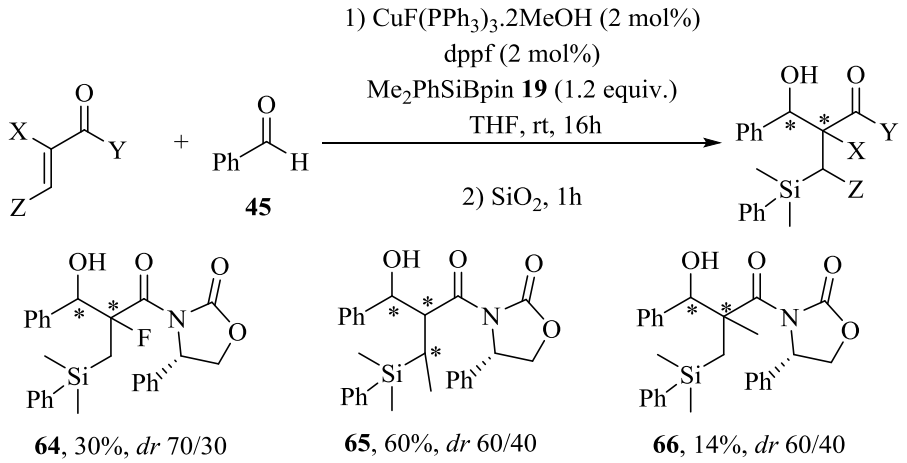


Scheme 43. Synthesis of substrate **54**.

In conclusion, the syntheses of substrates bearing a fluorine substituent were very difficult as the fluorine atom alters the reactivity of the intermediate in the subsequent reactions. This is probably due to the electronic effects of this atom. The yields obtained were very low and substrates were quite sensitive. In the following part, we will discuss the reactivity of these compounds in our domino process.

III.1.6. Catalytic tests

The different Michael acceptors previously synthesized were then tested in the domino process. Initial results are shown in scheme 44. We used the conditions previously reported by Alexandre Welle when oxazolidinones were employed as substrates.

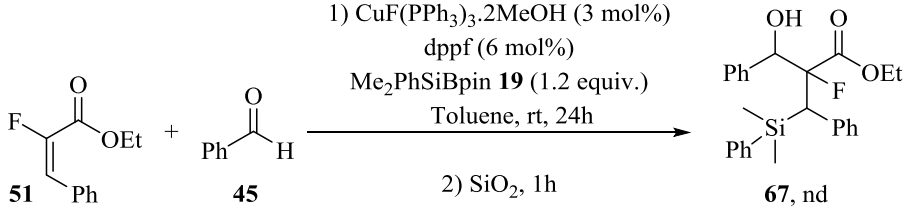


Scheme 44. Reactivity of enoyloxazolidinones in silylation reaction.

These results showed that these substrates were less reactive than the previous ones. Conversion was complete after 16 hours instead of 1 hour. Product **64** was obtained in 30% yield after purification indicating the presence of byproducts. Indeed, the major product was the oxazolidinone **59**. Moreover, diastereoisomeric ratio was very difficult to determine because ^{1}H NMR spectrum was unclear. However, an improvement of the selectivity compared to the previous results (see point III.1.4.) was detected, as the final product was obtained with diastereomeric ratio of 70/30. When the reaction was carried out with substrate **53**, three chiral centres were formed in one step. Although the yield of this reaction was good, the selectivity was very poor. It is not very surprising because the same result was obtained previously by Dr Alexandre Welle when he used substrate with substituent in β position. Substrate **54** gave a more surprising result because we did not obtain the same result as the one previously reported in our group. The yield and the selectivity were very low in our case. We thought that maybe it was a

problem of reproducibility because the purity of reagents in this reaction was always crucial.

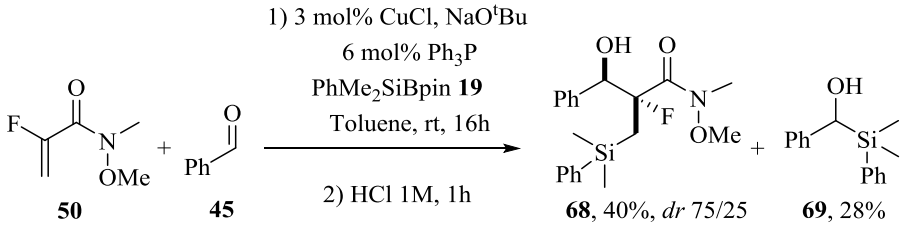
Concerning substrate **51**, we were quite disappointed in its reactivity in the domino process (Scheme 45). Conversion was incomplete after 24h even when we increased the catalyst loading. However, we observed small traces of the product but we were not able to determine a diastereoisomeric ratio on the crude ^{1}H NMR spectrum. Moreover, isolation of the product was impossible.



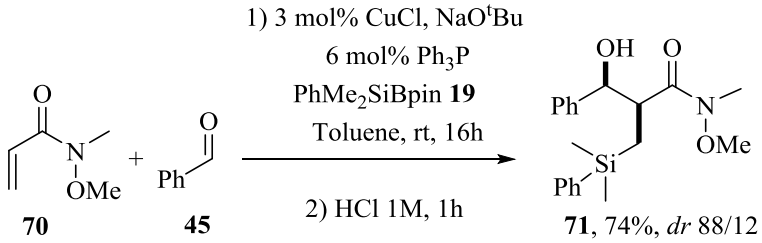
Scheme 45. Reactivity of substrate **51**.

When we carried out the reaction with substrate **50**, we observed several products on the crude ^{1}H NMR spectrum. The first product identified was the desired aldol adduct. Indeed compound **68** was isolated in 40% yield and with a diastereoisomeric ratio of 75/25. This result was the best one obtained so far. A second product was also isolated and, after analysis, it was identified as the 1,2-addition product **69**. As explained earlier in this chapter, if the Michael acceptor was not reactive enough, this type of secondary reactions could occur. In this case, the reaction of the active species (Cu-Si) is faster directly with the aldehyde than with Weinreb fluoroacrylamide. This secondary product **69** was obtained in 28% yield (Scheme 46). This result was very surprising because when we carried out the same reaction with the substrate **70**, no 1,2-addition product was observed. Desired product **71** was isolated in 74% yield and

a good diastereoselective ratio of 88/12 (Scheme 47). This indicating that the fluorine substituent plays a significant role in the reactivity of these kinds of substrates. Relative stereochemistry was determined as previously described.[15]



Scheme 46. Reactivity of substrate **50**.



Scheme 47. Reactivity difference between substrate **50** and **70**.

After some reflexion, we thought that this secondary product could be interesting in itself due to the lack of reliable procedures in the literature to prepare such compounds. We therefore started the development of this secondary reaction to form chiral α–hydroxysilanes in one step as well as the synthesis of acylsilanes and it will be explained in more details in chapters 2 and 3 of this manuscript.

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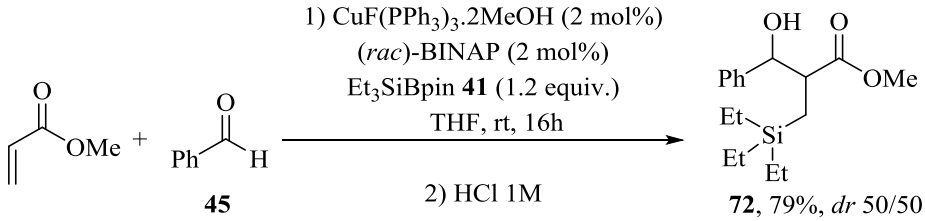
[15] Welle, A.; Petrignet, J.; Tinant, B.; Wouters, J.; Riant, O., *Chem. Eur. J.* **2010**, *16*, 10980-10983.

Finally, we decided to check the reactivity of other silylboranes in our domino process. The reaction was carried out with methyl acrylate and benzaldehyde **45** with silylborane **41** as pronucleophile.



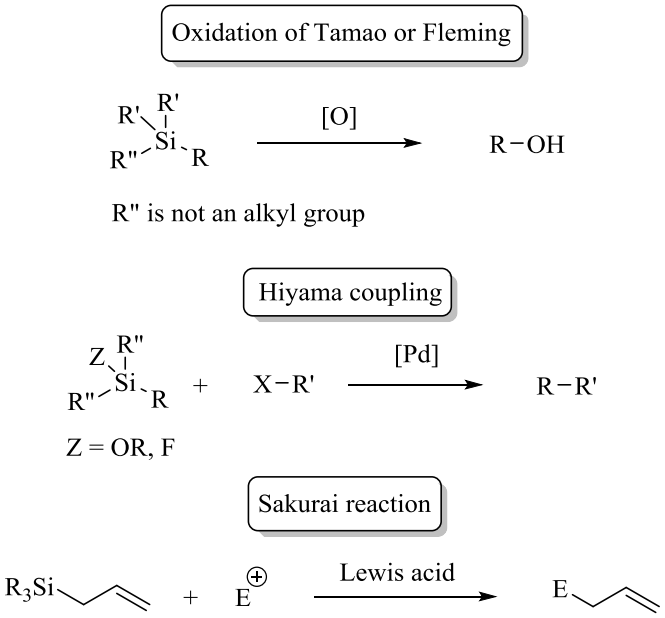
Scheme 48. Domino process with other silylboranes.

To our delight, the desired aldol adduct was obtained in 79% yield after purification. Nevertheless, a diastereoselectivity ratio of 50/50 was determined by ^{1}H NMR. The reaction was also performed with silylborane **43**. Unfortunately, only traces of the desired product were observed and we were not able to isolate the desired product. At this time, we can say that substrates bearing a fluorine substituent seem to be less reactive in our domino process. Although the yields are often encouraging, only substrates **50** and **52** afforded moderate to good diastereoselectivities. However, we have shown that the use of other silylboranes was also possible.

III.1.7. Palladium catalysis

Organosilanes derivatives are versatile intermediates in organic synthesis (Scheme 49). Although they are less reactive than organoboranes, they are more stable and purification of these compounds is easier. Indeed, organosilanes are easily oxidized when Tamao or Fleming conditions are applied. Furthermore, they have been used in palladium-catalyzed cross-

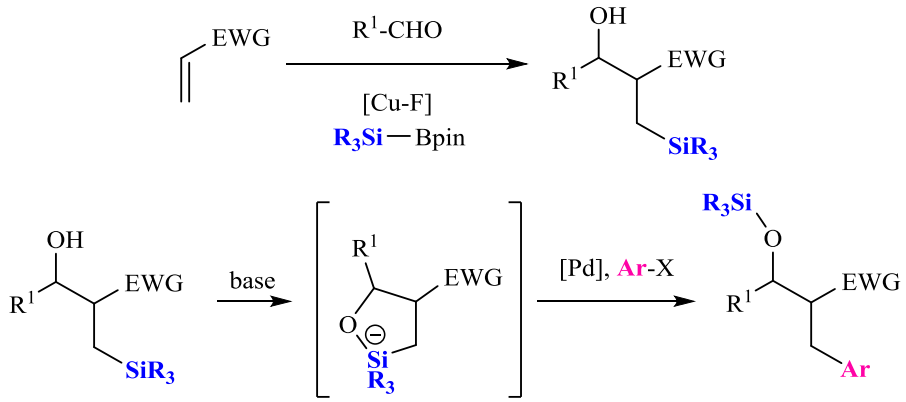
coupling reactions. Allylsilanes can also react with various electrophiles *via* a Sakurai reaction.



Scheme 49. Versatility of organosilanes.

One of the main applications of organosilanes is therefore found in the Hiyama cross-coupling reaction, a variant of the Suzuki coupling. We hoped that the aldol adduct, in a presence of a base, could undergo the formation of a cyclic intermediate (*via* a Brook rearrangement) which could subsequently react with a palladium catalyst and a halo-benzene to yield the desired cross-coupling product (Scheme 50). We decided to use silylborane **41** instead of **19** to avoid the transfer of the phenyl group. The challenge in this reaction was to avoid the retro-aldol reaction. We hoped also that our silicon atom was activated enough to do the desired transformation. Indeed the silicon-based methods had relied on the use of polyfluorinated alkylsilane reagents, which are moisture-, acid-, and

base-sensitive and usually required the use of a highly nucleophilic and expensive fluoride activator.[16]



Scheme 50. Strategy to perform Hiyama coupling.

After condensation of benzaldehyde, methyl acrylate and **41** using the standard catalytic conditions, the solvent was evaporated from the crude reaction mixture without any work-up and replaced by DME. The Hiyama reaction was then directly carried out with iodobenzene using $Pd(OAc)_2$ and RuPHOS as catalysts and cesium carbonate as a base (Scheme 51).

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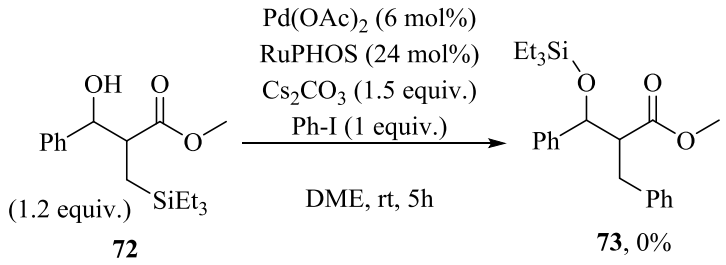
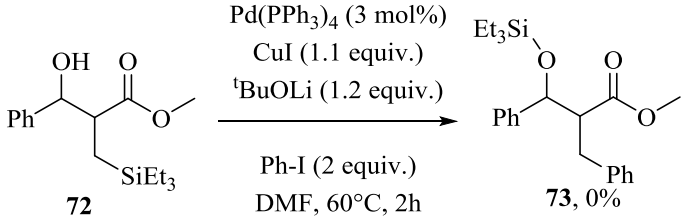
[16] Selected examples: (a) Denmark, S. E.; Sweis, R. F., *Chem. Pharm. Bull.* **2002**, *50*, 1531-1541. (b) Hatanaka, Y.; Hiyama, T., *Tet. Lett.* **1988**, *29*, 97-98. (c) Matsuhashi, H.; Kuroboshi, M.; Hatanaka, Y.; Hiyama, T., *Tet. Lett.* **1994**, *35*, 6507-6510.



Scheme 51. First test of Hiyama coupling.

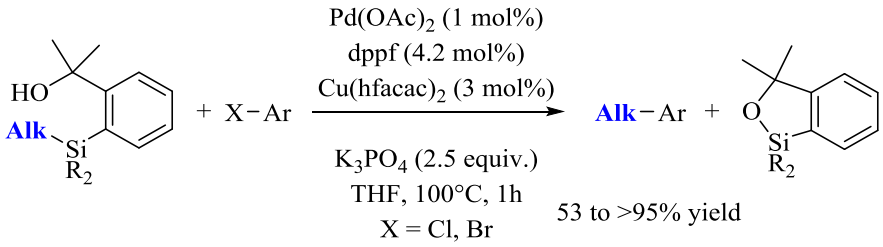
Unfortunately, product **73** was not obtained. Only the retroaldol product and the starting material were recovered. We also tested the same strategy after purification of **72** and similar results were achieved. We thought that maybe the use of a more polar solvent and a stronger base could afford the desired cross-coupled product. Product **72** was therefore reacted with $Pd(PPh_3)_4$ as catalyst, copper(I) iodide and lithium *tert*-butoxide as a base in DMF. The reaction was also carried out at 60°C instead of room temperature to activate the system (Scheme 52).



Scheme 52. Test of Hiyama coupling.

Nevertheless, analysis of the ^1H NMR spectrum of the crude mixture revealed that only retro-aldol reaction has occurred. In 2010, Hiyama and co-workers reported a palladium/copper-catalyzed alkyl-cross coupling reaction using 2-(2-hydroxyprop-2-yl)phenyl-substituted alkylsilanes which are highly stable tetraorganosilicon reagents that transfer both primary and secondary alkyl groups with the aid of K_3PO_4 as a mild base

(Scheme 53).[17] It was one of the first examples of alkyl transfer in Hiyama cross-coupling reaction. Indeed, the majority of literature known-methods described the transfer of aryl or alkenyl groups.[18]



Scheme 53. Selective C(sp^3)-Si activation.

Conditions used by Hiyama were then tested with our substrate. Silylborane **19** was used because Hiyama noticed that the very strong Si-alkyl bond of the tetraorganosilicon reagent is activated exclusively over the Si-Ar bond with the aid of the metal catalysts and the mild base. Moreover, no coupling of the phenyl group was observed under their reaction conditions.

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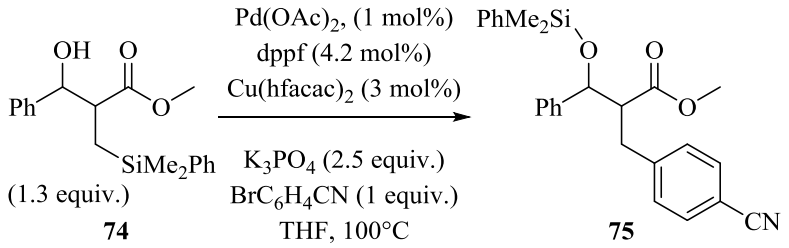
[17] Nakao, Y.; Takeda, M.; Matsumoto, T.; Hiyama, T., *Angew. Chem. Int. Ed.* **2010**, *49*, 4447-4450.

[18] Selected exemples: (a) Nakao, Y.; Imanaka, H.; Sahoo, A. K.; Yada, A.; Hiyama, T., *J. Am. Chem. Soc.* **2005**, *127*, 6952-6953. (b) Alacid, E.; Nájera, C., *J. Org. Chem.* **2008**, *73*, 2315-2322. (c) So, C. M.; Lee, H. W.; Lau, C. P.; Kwong, F. Y., *Org. Lett.* **2008**, *11*, 317-320.



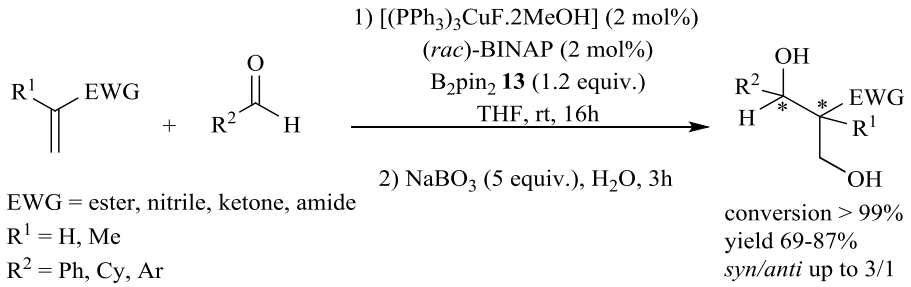
Scheme 54. Test of Hiyama coupling.

However, we were not able to observe the desired product with these conditions and only decomposition of the starting material was detected. After these disappointing results, this route was eventually abandoned.

III.2. Borylation reaction

III.2.1. Previous work

As described earlier, the borylation reaction was initially developed in our laboratory by Dr. Alexandre Welle during his thesis. Very good results were obtained with various Michael acceptors and electrophiles in a diastereoselective version of this process (Scheme 55).

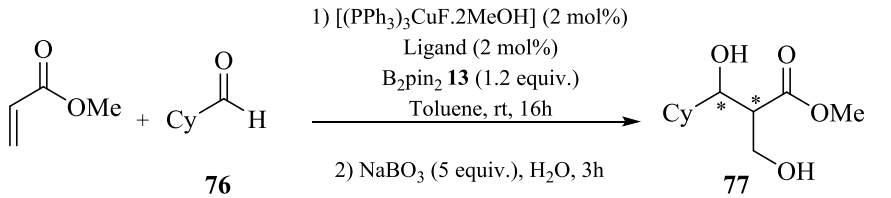


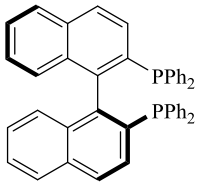
Scheme 55. Previous work.

First experiments for the development of an enantioselective version were also performed in our group and the results are reported in table 2. They used cyclohexane carboxaldehyde and methyl acrylate as model

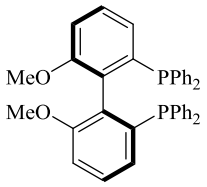
substrates and a screening of several chiral ligands was performed. Relative stereochemistry of the products was determined by NMR on the cyclization adducts (see the introduction, point II.2). It should be noted that the conversion was always complete.

Table 2. Screening of chiral ligands in the borylation reaction.

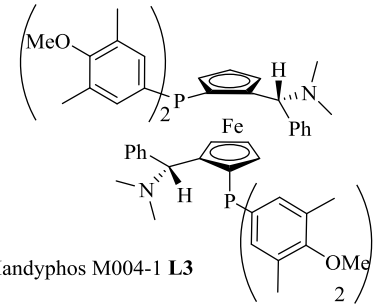




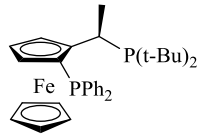
(*S*)-BINAP (S)-**L1**



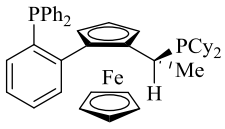
(*S*)-MeOBiphep (S)-**L2**



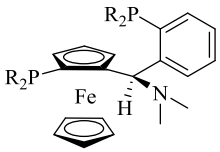
Mandyphos M004-1 **L3**



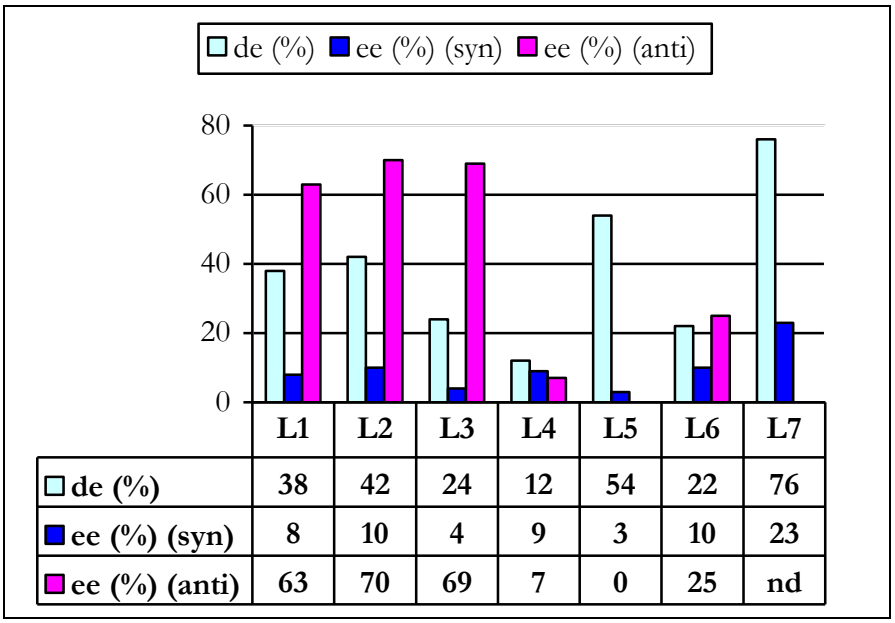
Josiphos J002-1 **L4**



Walphos W003-1 **L5**



R = Ph
Taniaphos T001-1 **L6**
R = Cy
Taniaphos T002-1 **L7**



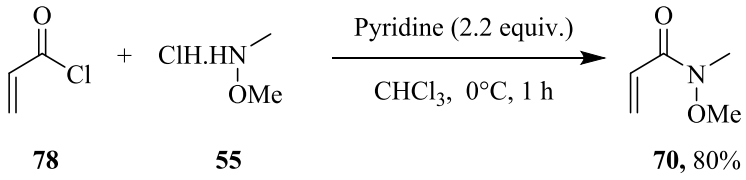
	L1	L2	L3	L4	L5	L6	L7
de (%)	38	42	24	12	54	22	76
ee (%) (syn)	8	10	4	9	3	10	23
ee (%) (anti)	63	70	69	7	0	25	nd

The first ligand, *(S)*-BINAP **L1**, allowed to obtain a diastereoisomeric excess (*de*) of 38% and enantiomeric excesses of only 8% for the major isomer and 63% for the minor one. *(S)*-MeOBiphep **L2** showed a slight improvement, with a diastereoisomeric excess of 42%. Enantiomeric excess of the *syn* isomer was only 10% and that of the *anti* 70%. The diphosphine ligand Mandyphos **L3** led to inferior results in terms of diastereo- and enantioselectivities. The Josiphos ligand **L4** also gave bad results: diastereoisomeric excess of 12% was achieved and enantiomeric excesses didn't exceed 9%. The Walphos ligand **L5** generated a good diasteroselectivity with an excess of 54%. However, adducts were obtained in almost racemic form. Better enantiomeric excesses were acquired with Taniaphos ligand **L6** but the diastereoselectivity was lower (22%). Finally, the Tanaphios ligand **L7** gave the best result. Diastereoisomeric excess of 76% was detected indicating a ratio *syn*/*anti* of 88/12. Enantiomeric excess of the *anti* isomer could not be

determined and that of the *syn* isomer was 23%. In conclusion, when a ligand allowed the obtention of a good diastereoselectivity, enantiomeric excesses were very low. In addition, it was only for the minor isomer that good enantioselectivities were achieved. We therefore decided to use other substrates such as Weinreb acrylamides for further development of the enantioselective version of the borylation reaction. The use of other copper complexes such as our new cationic complexes developed in our laboratory was also envisaged and these points are explained in the following sections.

III.2.2. Synthesis of substrates

We chose Weinreb acrylamides as model substrates for the further development of this process because this class of compounds has shown good selectivity in previous work. They were synthesized using a modified procedure of the literature.[19] Substrate **78** reacted with *N,O*-dimethylhydroxylamine hydrochloride in the presence of pyridine to afford the desired product **70** in 80% yield (Scheme 56).



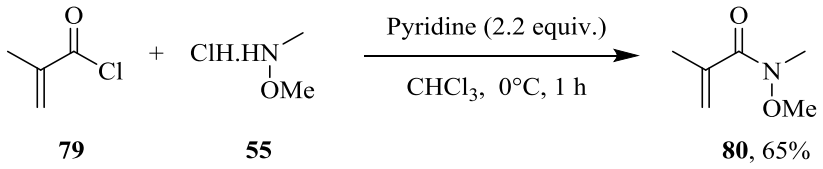
78 **55** **70,** 80%

Scheme 56. Synthesis of susbstrate **70**.

The same procedure was used with methacryloyl chloride **79** in order to give the product **80**. The desired product was obtained after distillation

[19] Yoshitomi, Y.; Makino, K.; Hamada, Y., *Org. Lett.* **2007**, *9*, 2457-2460.

in 65% yield. Although final products were volatile, the desired substrates were obtained in good yields and could be used later on.



79 **55** **80**, 65%

Scheme 57. Synthesis of susbstrate **80**.

III.2.3. Synthesis of cationic complexes

Note: the work presented in this section was optimized over several years by various members of our group **and includes my own contribution** during the past four years. This is the reason why this part is presented as a whole work, quoting all the contributors, as it is still under optimization and development with new improved synthetic methodologies.

As explained earlier in this introduction, our group developed a new pathway to unprecedented diphosphine copper(I) bifluoride complexes and we wanted to see if our catalysts could be used in our domino process.[20] We found that the reaction of copper(I) iodide with silver(I) hydrogenfluoride in acetonitrile gave after elimination of silver iodide by filtration the tetrakis(acetonitrile) copper(I) hydrogen(bifluoride) intermediate *in situ*. The complex was identified by a sharp singlet at δ =

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[20] Hermant, T ; *Catalyse de réactions conjuguées par les complexes de cuivre(I) : méthodologies et applications*, Université catholique de Louvain, Louvain-la-Neuve, **2012**.

-166 ppm by ^{19}F NMR (in CD_3CN) and an acidic proton at δ = 14.1 ppm by ^{1}H NMR but could not be isolated by crystallization (Figure 7).

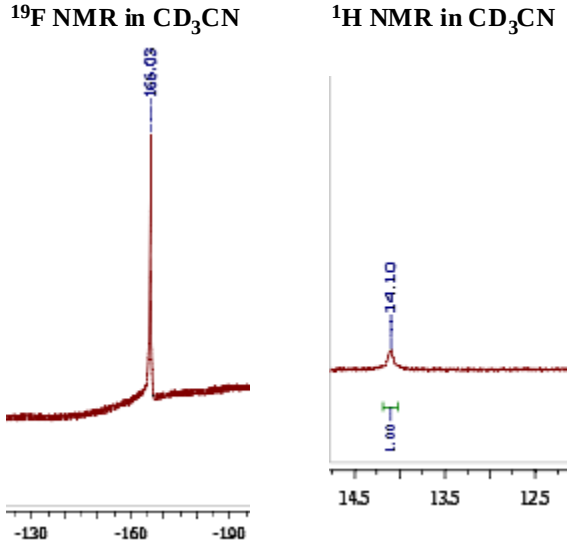
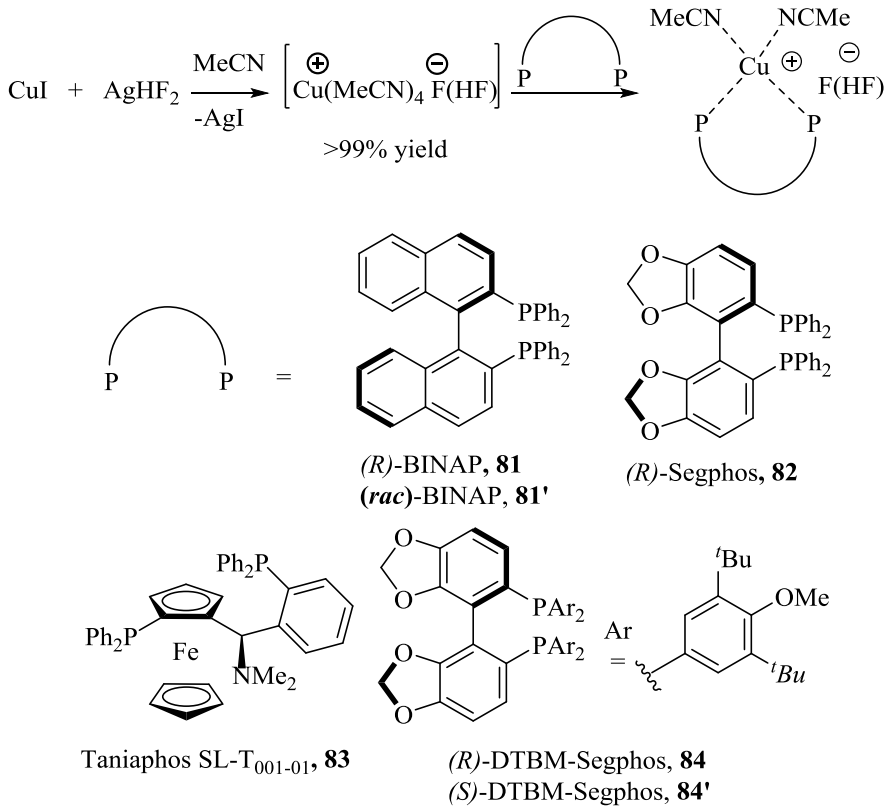


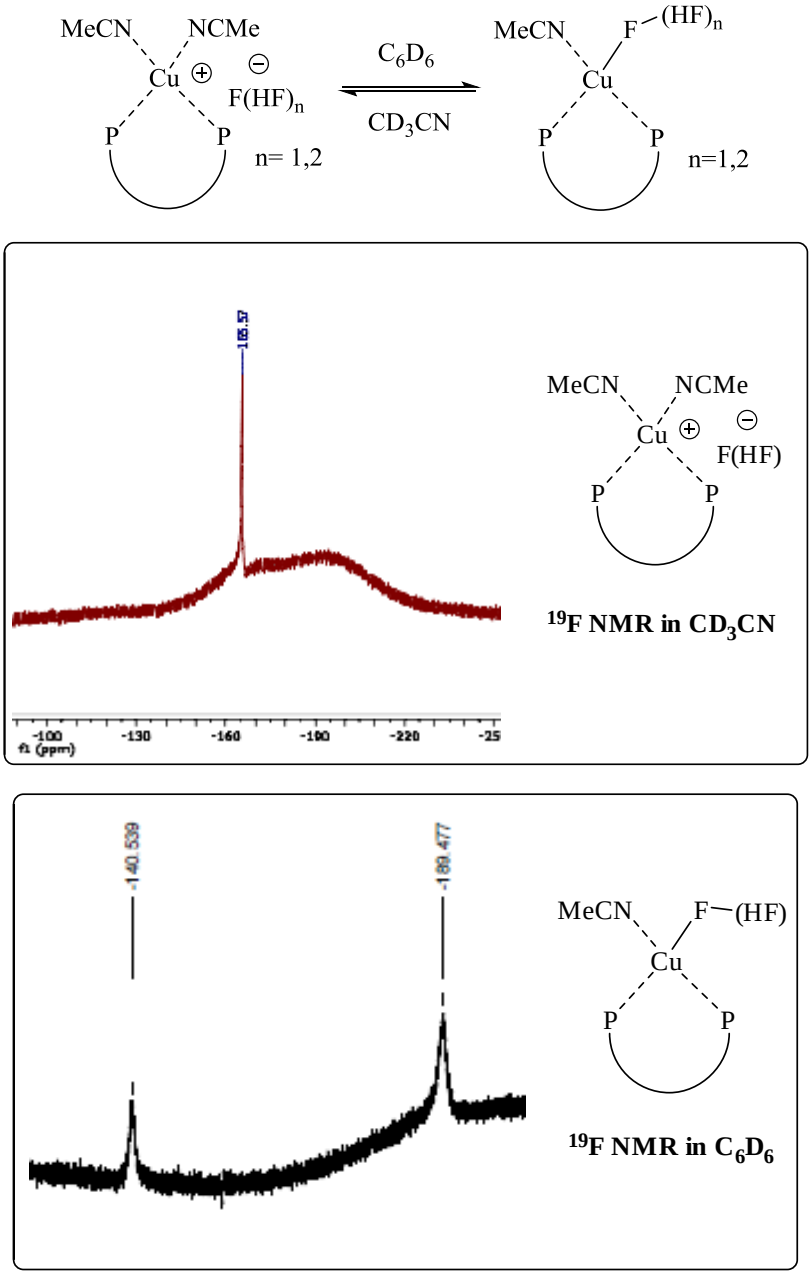
Figure 7. Characteristic peaks of $Cu(MeCN)_4^+HF_2^-$.

However, the addition of various diphosphine ligands gave, after removal of the solvent, the new cationic complexes in excellent yield (Scheme 58). Indeed we performed ^{19}F NMR experiments with an internal standard (TFE = trifluoroethanol) to determine the yield of the first step. This analysis showed that the desired intermediate was obtained in quantitative yield. It should also be noticed that the reactions were carried out in disposable polyethylene plastic vial to avoid the reaction of the bifluoride with the glassware that would give contamination of the samples by SiF_6^- counteranion.



Scheme 58. Synthesis of the third generation cationic complexes.

We found that, depending on the quality of the commercially available silver bifluoride, the bifluoride anion could be contaminated with dihydrogen trifluoride anion ($H_2F_3^-$). Furthermore, ^{19}F NMR suggested that those complexes could exist in either cationic or neutral form when coordinating solvents such as acetonitrile (one sharp peak around δ = -165.5 ppm) or non coordinating solvents such as benzene (δ = -140.5 ppm for Cu-F-H-*F* and δ = -189.5 ppm for Cu-*F*-H-F) were employed, respectively (Scheme 59).



Scheme 59. ^{19}F NMR of cationic complexes in CD_3CN and C_6D_6.

This was confirmed by a successful crystallization in toluene-hexane at -20°C (with DTBM-segphos as ligand) which afforded X-ray quality crystals of **84** for analysis. The structure confirmed the formation of a neutral complex bearing a σ-bounded $H_2F_3^-$ anion (Figure 8). Moreover we were delighted to find that those complexes are very air and moisture stable both in the solid state and in solution.

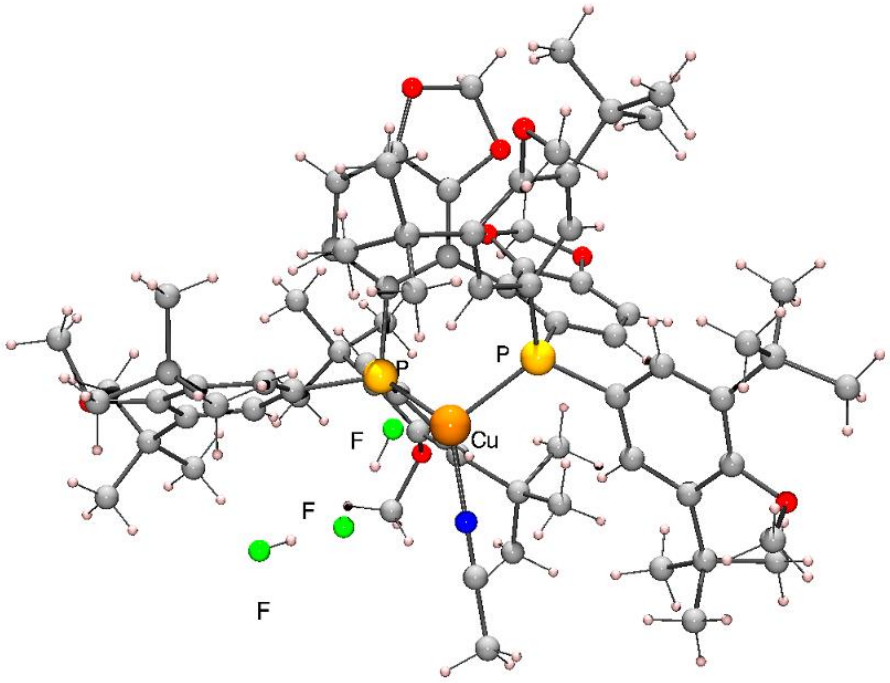


Figure 8. X-ray structure of complex **84**.

We also found that a mixture of copper complexes bearing one or two ligands could be obtained in some cases, when using this methodology. Several experiments were thus performed to crystallize the complexes and confirm our hypothesis. We found that addition of diethyl ether to complex **82** bearing the Segphos allowed to afford only the copper complex bearing two ligands.[20] This was confirmed by NMR and X-ray

analysis (Figure 9). A molecule of acetonitrile was always present but there is no bond between the copper and the nitrogen atom as previously reported.

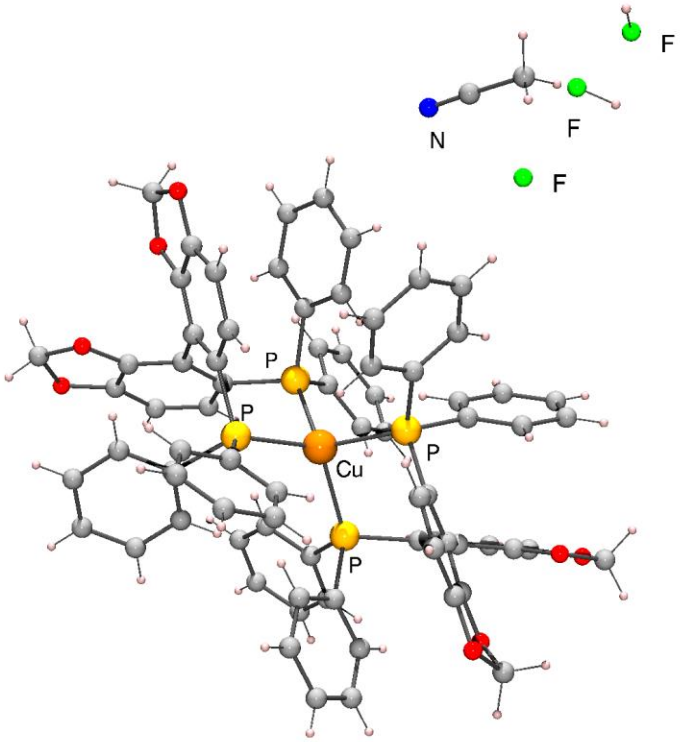
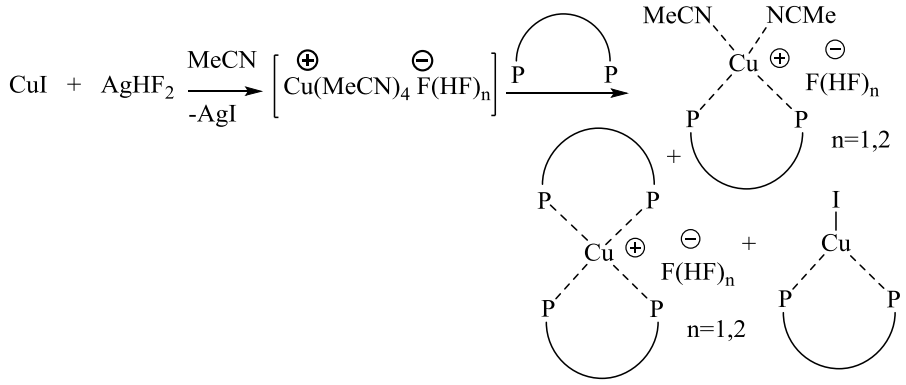


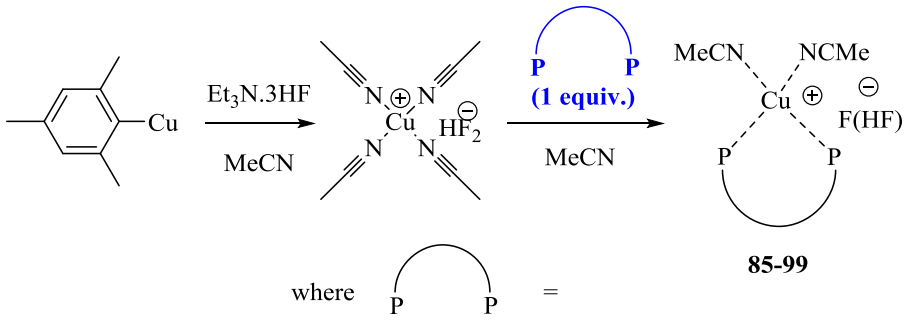
Figure 9. X-ray structure of copper complex bearing two Segphos ligand, **82**.

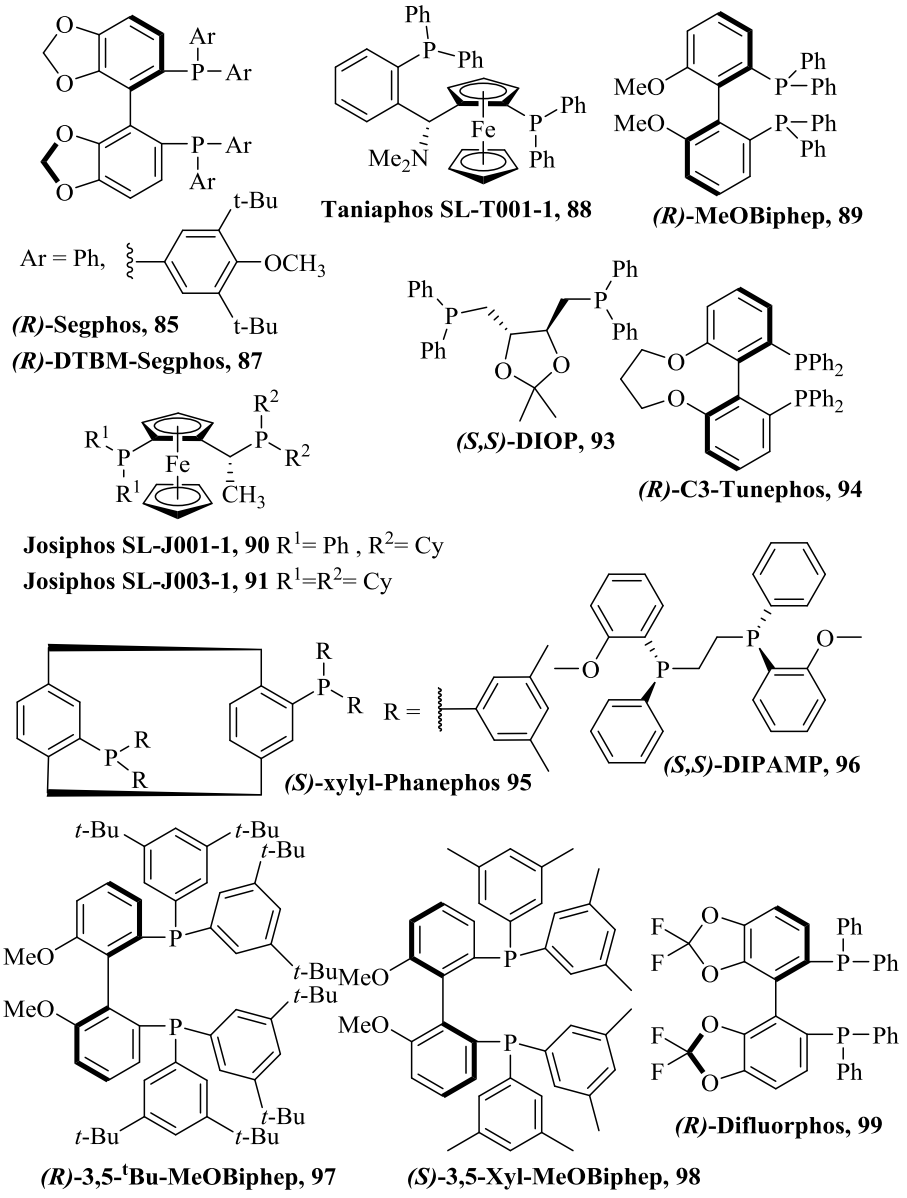
Another drawback of this methodology was the contamination by a copper complex bearing an iodide atom instead of the bifluoride anion (Cu-I species). Characterictic peaks were observed in ^{1}H NMR with some ligands.[20] To conclude, although these complexes are very promising and air stable, a mixture of three products was observed in some cases when we used this synthesis (Scheme 60).



Scheme 60. Synthesis of cationic copper(I) complexes.

These problems prompted us to design a new strategy for the synthesis of these complexes. This work was initated by Corentin Rasson during his PhD thesis (undergoing work). To avoid silver contamination of our complexes, the use of $Et_3N.3HF$ was considered as a more reliable source of HF. Replacement of copper(I) iodide as the copper source by mesityl copper seemed to be also a good alternative to avoid the contamination with halides.

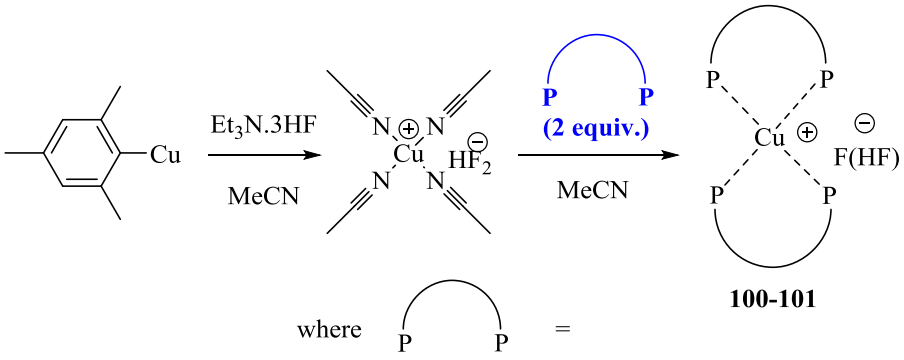


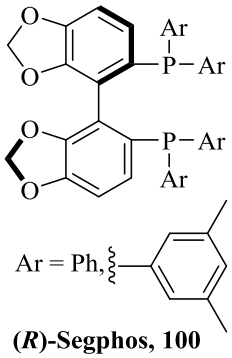


Scheme 61. Copper complexes bearing one ligand.

After optimization of the reaction conditions, we found that the reaction of mesityl copper with one equivalent of $Et_3N.3HF$ in acetonitrile gave *in*

situ the intermediate $Cu(MeCN)_4^+HF_2^-$. Then addition of one equivalent of various phosphine ligands allowed the formation of the desired copper complexes in excellent purity (Scheme 61). To our delight, only the copper complexes bearing one ligand were detected. These complexes are also air and moisture stable both in the solid state and in solution. Moreover, the presence of the bifluoride counter anion was further confirmed by thermogravimetric analysis (TGA). TGA is commonly used to determine selected characteristics of materials that exhibit either mass loss or gain due to decomposition, oxidation, … In our case, this analysis have shown a loss of HF. However, at that time, no crystals were obtained for any ligand but this work is still in progress. Another advantage of this new strategy was the control of the stoichiometry of the resulting complexes. Indeed addition of two equivalents of a ligand to the intermediate afforded the desired ML_2 complexes in good yield (Scheme 62). No presence of the ML complexes was observed.





(*R*)-Segphos, 100

(*R*)-DM-Segphos, 101

Scheme 62. Copper complexes bearing two ligands.

These complexes are also air and moisture stable both in the solid state and in solution but no crystals were obtained so far. We were also interested in comparing the reactivity of the two families of copper complexes. The difference in reactivity between the complex synthesized from copper(I) iodide and from mesityl copper was also investigated.

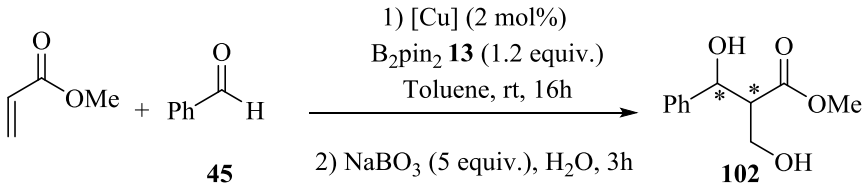
III.2.4. Development of an enantioselective version using cationic copper(I) complexes

With these complexes readily prepared and characterized, they were expected to show interesting catalytic activity due to the unique nature of the bifluoride counterion. The first substrate to be investigated in the borylation reaction was methyl acrylate and the results are shown in table 3. Benzaldehyde **45** was used as an electrophile to allow a better separation of the stereoisomers by chiral HPLC. The *syn* isomer was

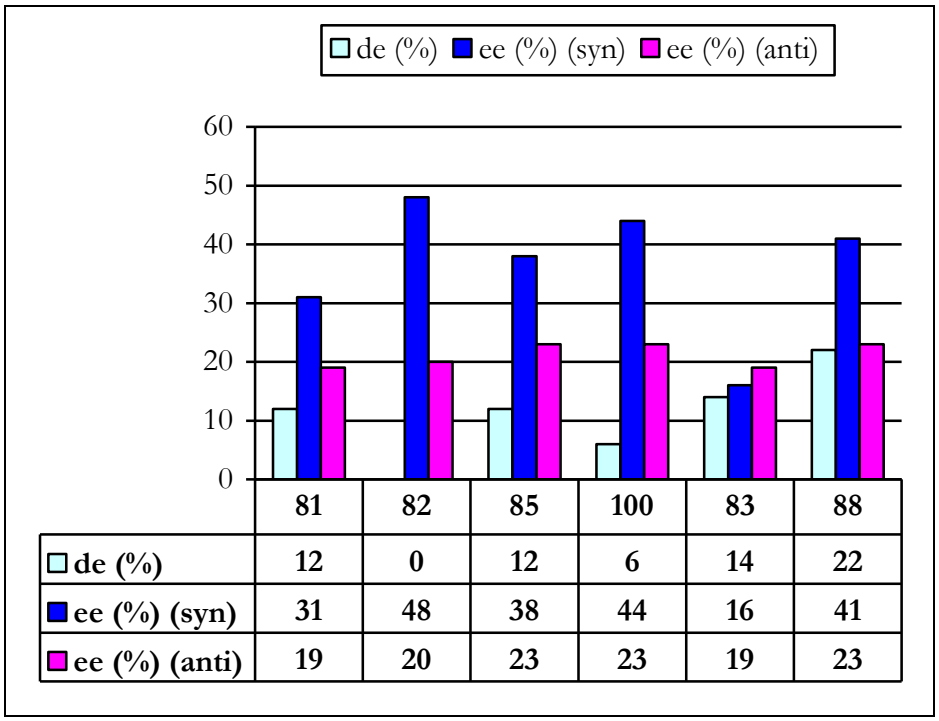
always the major diastereoisomer as determined previously.[21] Conversion was determined by ^{1}H NMR and was always complete.

Note: It is important to point out here that we did not routinely carried out control experiments with the $CuF(PPh_3)_3$/diphosphine combinations as it was shown in our group that this system consistently gave lower enantioselectivities. In this case, this can be attributed to the fact that this "catalytic cocktail" will give different species in solution (and usually in fast equilibrium as it is well known in the chemistry of copper(I)-phosphine complexes), with various catalytic activities that can result in a loss of the overall measured enantioselectivity.

Table 3. Enantioselective version with methyl acrylate.



[21] Welle, A ; *« Catalyse stéréoselective de nouvelles réactions tandems basées sur des complexes de cuivre(I) »*. Université catholique de Louvain, Louvain-la-Neuve, **2010**.



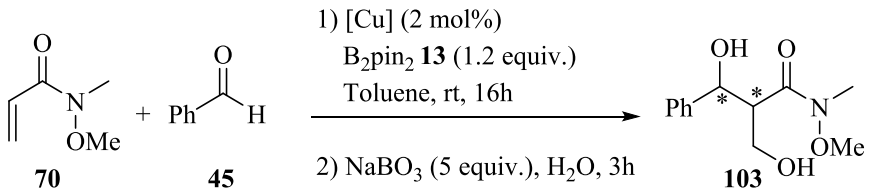
	81	82	85	100	83	88
de (%)	**12**	**0**	**12**	**6**	**14**	**22**
ee (%) (syn)	**31**	**48**	**38**	**44**	**16**	**41**
ee (%) (anti)	**19**	**20**	**23**	**23**	**19**	**23**

First the use of complex **81** with *(R)*-BINAP afforded product **102** with 12% of diastereoisomeric excess and low enantiomeric excesses of 31% and 19% for the *syn* isomer and the *anti* isomer respectively. No diastereoselectivity was obtained with complex **82** bearing the Segphos ligand. However the *syn* isomer was achieved with 48% *ee* and the *anti* with 20% *ee,* which was the best result so far. An increase of the diastereoselectivity was observed for the complex **85**. An excess of 12% was obtained. However enantioselectivity was a bit lower. When the dimer ligand **100** was used, almost the same results were achieved. These considerations indicating that in the case of this ligand, the different method for the synthesis of these complexes did not influence the results. The use of Taniaphos complex **83** gave lower enantiomeric

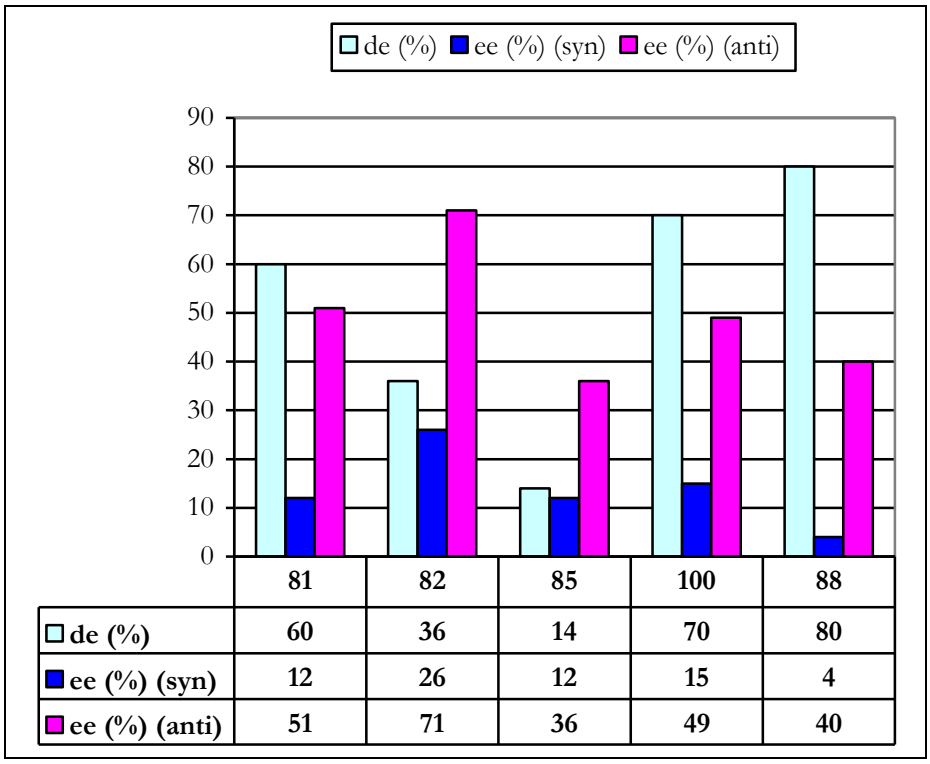
excesses compared to the Segphos ligand and a diasteroisomeric excess of 14%. Concerning the complex **88**, it gave the best result in term of diastereoselectivity. In this case, we could say that the complex **88** seemed to be more efficient than the complex **83.** Nevertheless, there is only a small difference between all these complexes. Reactivity difference between the complex synthesized from copper(I) iodide and from mesityl copper was not clear. However, compared to the results obtained previously in our group, enantiomeric excess of the *syn* isomer was higher in almost all the cases although the diastereoselectivity was lower.

Borylation reaction was then carried out with Weinreb acrylamide to try to improve the diastereoselectivity. Results obtained with substrate **70** are reported in table 4.

Table 4. Enantioselective version with substrate **77**.



70 **45** **103**

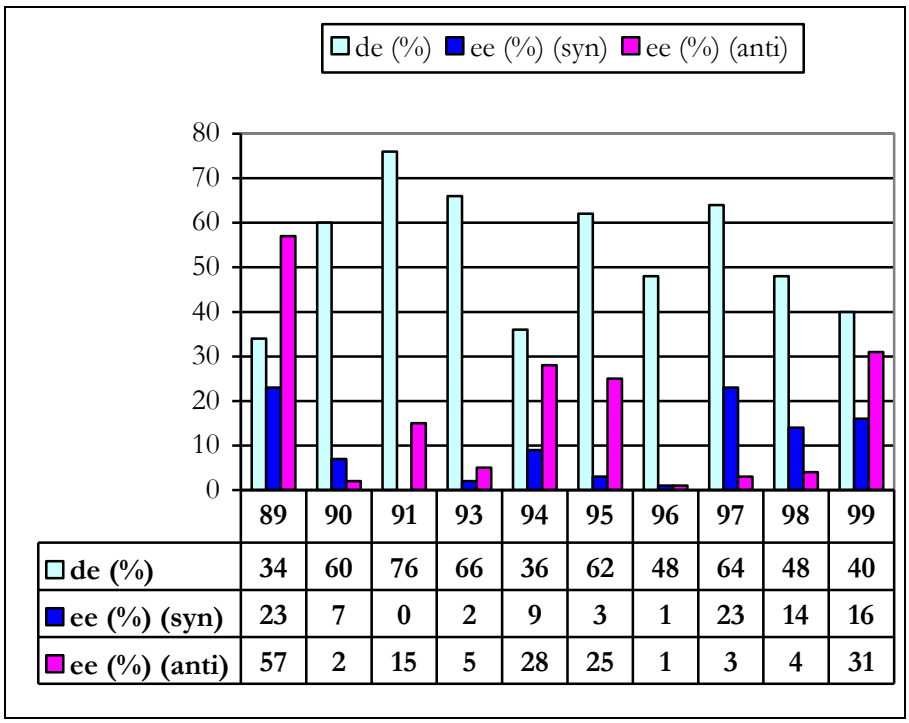


	81	82	85	100	88
de (%)	60	36	14	70	80
ee (%) (syn)	12	26	12	15	4
ee (%) (anti)	51	71	36	49	40

We started by employing the same complexes we used with methyl acrylate. These results showed that the diastereoisomeric excesses were effectively better. Moderate to very good diastereoselectivity (up to 90/10 for **88**) were achieved in almost all the cases except with complexes bearing the *(R)*-Segphos ligand (**82** and **85**). Surprisingly, we observed a large increase of the diasteroselectivity with complex **100** compared to **82** and **85**. Nevertheless, the best *ee's* of both isomers were obtained with complex **82** indicating that when a good diastereoselectivity was induced, lower enantiomeric excess was achieved and *vice versa*. It is important to notice that enantiomeric excess of the *syn* isomer was lower compared to results in table 3 but the *ee* of the *anti* isomer was higher. Several other complexes were tested in our reaction

in collaboration with Florence Josse during her master thesis and the results are reported in table 5. It should be noticed that all these complexes were synthesized using the procedure with mesityl copper.

Table 5. Screening of other complexes.



	89	90	91	93	94	95	96	97	98	99
de (%)	34	60	76	66	36	62	48	64	48	40
ee (%) (syn)	23	7	0	2	9	3	1	23	14	16
ee (%) (anti)	57	2	15	5	28	25	1	3	4	31

These results revealed the same tendancy as before. Indeed good diastereoselectivities were obtained with various complexes. However enantioselectivities did not exceed 30% except when the *(R)*-MeO-Biphep complex **89** was used. This complex gave the best result in term of enantioselectivity but only 34% of diastereoisomeric excess was observed. We decided therefore to use derivatives of this complex such as **97** and **98**, we observed an increase of the diastereoselectivity but unfortunately, no improvement of the enantioselectivity was accomplished. It is important to state that the Josiphos complex **91** gave

the best result in term of diastereoselectivity with 76% of diastereoisomeric excess. To summarize this part, there is only a small difference between all these complexes. Reactivity difference between the complex synthesized from copper(I) iodide and from mesityl copper was not clear. Actually, we must be careful when we compare these results because if we look at the activation energy to form the enantiomer *(R)* or *(S)* when the enantiomeric excesses are below 50%, the difference is very small. For example, the difference in energy to have 70% instead of 40% of enantiomeric excess is only 0.53 kcal/mol following the kinetic formula reported in figure 10.[22] However, if we calculate the difference in energy to obtain 99% instead of 95% of enantiomeric excess, we find 0.97 kcal/mol. This example indicates that the difference observed with all these complexes is not significant. Nevertheless, screening of other complexes is still in progress to find the ligand which would induce high diastereo- AND enantioselectivity.

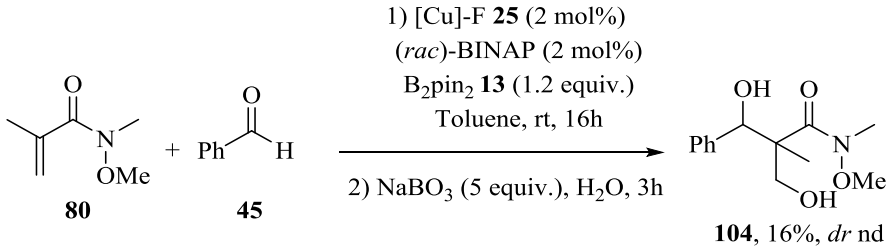
$$\Delta E_A = RT * \ln (ee\text{-}1/\text{-}1\text{-}ee)$$

Entry	ee	R (cal/mol.K)	T (K)	ΔE_A (kcal/mol)
1	0.4	1.988	298	-0.50
2	0.7	1.988	298	-1.03
3	0.95	1.988	298	-2.17
4	0.99	1.988	298	-3.14

Figure 10. Activation energies according to the enantioselectivity.

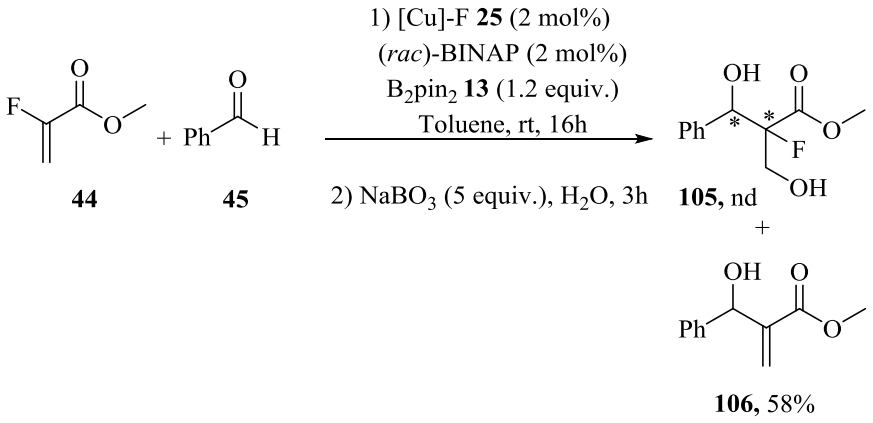
[22] Leyssens, T.; Peeters, D.; Harvey, J. N., *Organometallics* **2008**, *27*, 1514-1523.

We also wanted to test substrate **80** in our reaction (Scheme 63). In order to synthesize first the racemic product, the reaction was carried out with [Cu]-F **25** and (*rac*)-BINAP. However, the conversion was very low and difficult to determine (due to the volatility of the starting material) as well as the diastereoisomeric ratio. Product **104** was isolated in 16% yield and only one diastereoisomer was detected. An optimization of the reaction conditions (temperature, solvent, etc…) is therefore in progress. Unfortunately no improvement of these results was achieved so far.



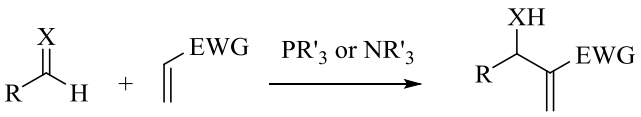
Scheme 63. Use of substrate **80** in the borylation reaction.

α-fluoroacrylate **44** was also tested in the borylation reaction to investigate the effect of the fluorine atom on the selectivity of the reaction (Scheme 64). The result obtained was quite surprising. After analysis of the crude reaction mixture, only traces of the desired product **105** were observed. We were not able to isolate the desired product. Nevertheless, a non-identified product was detected. This unknown product was then isolated in 58% yield and found to be product **106**. This product mimics a Baylis-Hillman adduct.



Scheme 64. Borylation reaction with substrate **44**.

The Baylis–Hillman reaction is a carbon-carbon bond forming reaction between the α-position of an activated alkene and an aldehyde, or generally a carbon electrophile. Employing a nucleophilic catalyst, such as a tertiary amine or a phosphine, this reaction provides a highly functionalized product (Scheme 65).[23]

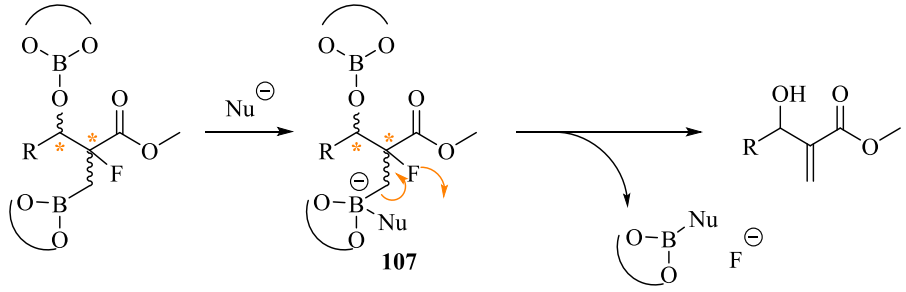


Scheme 65. Baylis-Hillman reaction.

We were intrigued by the formation of this unexpected product. The postulated mechanism is described in scheme 66. We thought that the driving force of this secondary reaction was the formation of a boron-

[23] For review on Baylis-Hillman reaction see : (a) Morita, K.-i.; Suzuki, Z.; Hirose, H., *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815-2815. (b) Ciganek, E., In *Organic Reactions*, John Wiley & Sons, Inc.: **2004**. (c) Basavaiah, D.; Rao, A. J.; Satyanarayana, T., *Chem. Rev.* **2003**, *103*, 811-892. (d) Masson, G.; Housseman, C.; Zhu, J., *Angew. Chem. Int. Ed.* **2007**, *46*, 4614-4628.

fluorine species due to the high affinity of these atoms. Therefore a [B-F] elimination afforded product **106**.

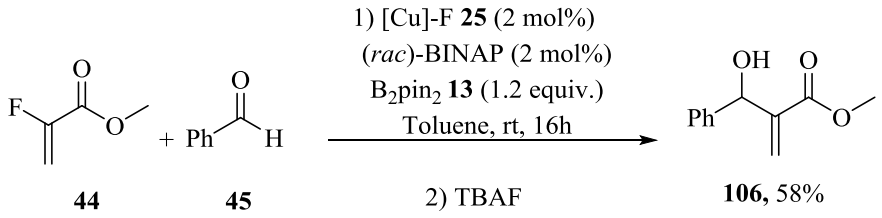


Scheme 66. Postulated mechanism for the formation of product **106**.

However, activation of the boron atom by a nucleophile to form the intermediate **107** seems to be necessary to obtain the desired product. Indeed, we carried out the reaction without the work-up with sodium perborate and no traces of the product **106** were observed in the crude reaction mixture. We thought that the hydrogen peroxide generated *in situ* during the oxidation step plays the role of the nucleophile in this transformation.[24] If there is no nucleophile in the reaction, formation of product **106** does not occur. To confirm our hypothesis the reaction was performed using TBAF instead of sodium perborate (Scheme 67). To our delight, the desired product was detected in the crude reaction

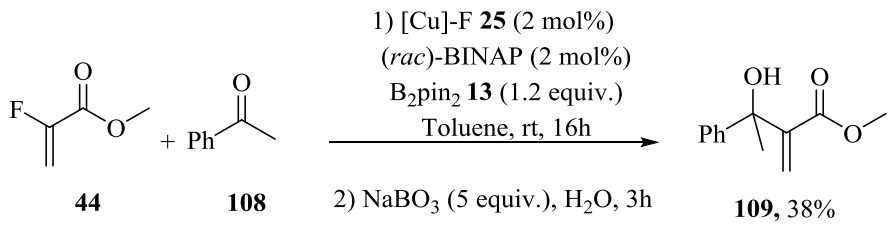
[24] It is known that sodium perborate is soluble in water and releases hydrogen peroxide, but it is not merely a mixture of hydrogen peroxide and sodium borate. NMR and Raman spectroscopy indicate that in dilute solution, equilibrium exists that still contains peroxoborate anions. These peroxoborate species are able to deliver the hydroperoxide anion at a lower pH than when H_2O_2 is used. See: A. McKillop, W. R. Sanderson, *Tetrahedron*, **1995**, *51*, 6145-6166.

mixture indicating that the fluoride plays the role of the nucleophile in this case.



Scheme 67. Same reaction using TBAF as work-up.

This secondary product could be interesting because a chiral centre was formed during the transformation. In addition, Baylis-Hillman reaction with ketones as electrophile is not easy. Thus, application of this strategy to ketones would be a highly interesting strategy. In order to confirm our hypothesis, reaction was carried out with acetophenone as substrate (Scheme 68).

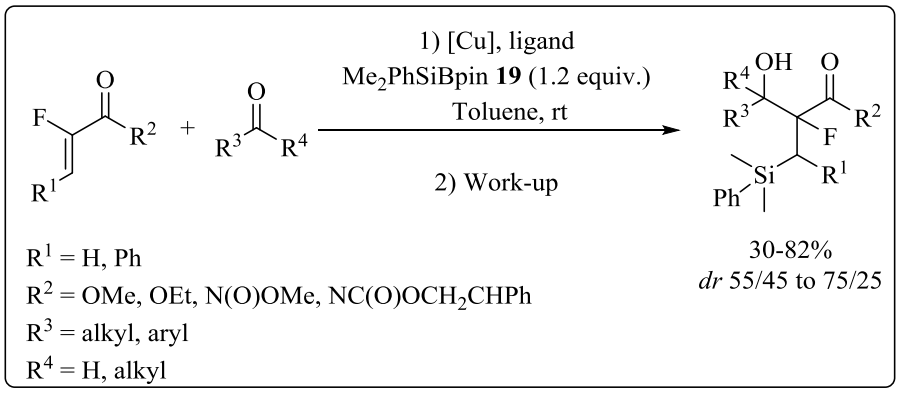


Scheme 68. Reaction with ketone.

We were very pleased to isolate the desired product in 38% yield. Only traces of the domino product were observed. This is a very promising result for further development of this unexpected reaction.

IV. Conclusions and perspectives

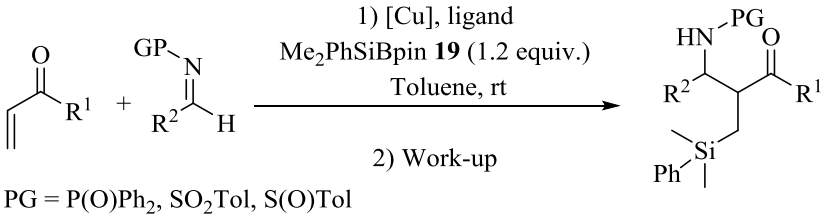
As a conclusion, we tried to extend the domino reaction developed earlier in our laboratory using new substrates, new silylboranes and new catalysts. Concerning the silylation reaction, we have shown that synthesis of substrates bearing a fluorine substituent turned out to be tedious. It is not very surprising due to the electronic properties of fluorine atom. However, we were able to isolate several interesting adducts with moderate to good yields but with low diastereoselectivity in almost all the cases. A good diastereoselectivity was only achieved when we used acryloyl oxazolidinones or Weinreb acrylamides as substrates (*dr* up to 75/25).



Scheme 69. Silylation reaction with fluorine substrates.

Syntheses of other silylboranes were also performed and we found that silylborane **41** had almost the same reactivity than the Suginome's reagent **19**. Unfortunately, attempts to promote our silyl adducts in a Hiyama coupling were unsuccessful.

In the future we are interested in using aldimines as electrophiles (Scheme 70). Actually, the motif of silylated amines is particularly relevant to the area of silicon-containing peptide isosteres.[25] Moreover, the use of either Ellman's or Davis' sulfinyl group as a chiral auxiliary could be interesting in our case to increase the diastereoselective ratio of the transformation.



Scheme 70. Use of aldimines as electrophiles.

Concerning the borylation reaction, we first described two strategies for the synthesis of new cationic copper(I) complexes bearing a bifluoride counteranion. These complexes were therefore engaged in our reaction and they have shown a good reactivity towards our domino process. However, although we obtained good diastereoselectivities with various copper complexes, enantioselectivities were low in these cases. Moderate to good enantiomeric excesses were only achieved when a low diastereoisomeric ratio was obtained. It is difficult to rationalize these results due to the high number of parameters in play (for example the conformation of the starting materials and intermediates) and because the difference between each complexes was not significant. Ligand

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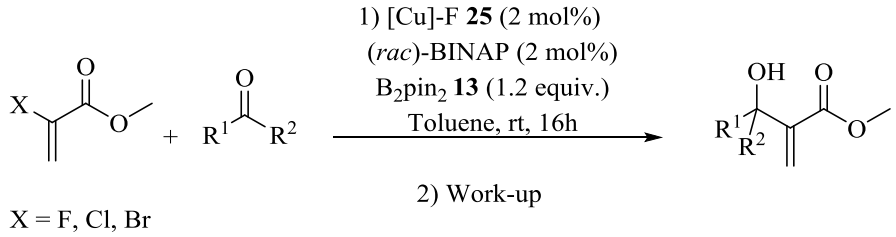
[25] Mortensen, M.; Husmann, R.; Veri, E.; Bolm, C., *Chem. Soc. Rev.* **2009**, *38*, 1002-1010.

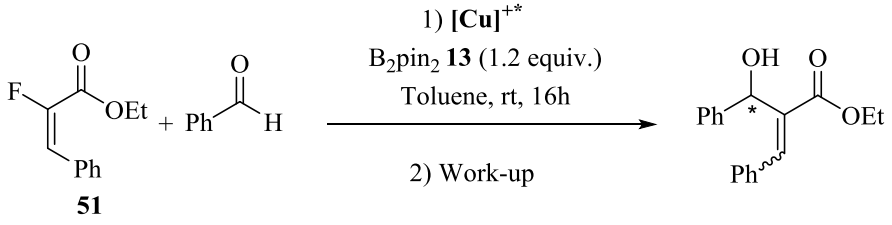
effects were also too complicated to permit extrapolation of any useful data.

In the future, we are interested in screening different complexes to find the best ligand for this enantioselective borylation reaction. We are also interested in further exploring our Baylis-Hillman adducts. This work was developed in collaboration with a master student, Florence Josse, and involves applying our methodology to other substrates such as chloro- and bromoacrylate (Scheme 71).



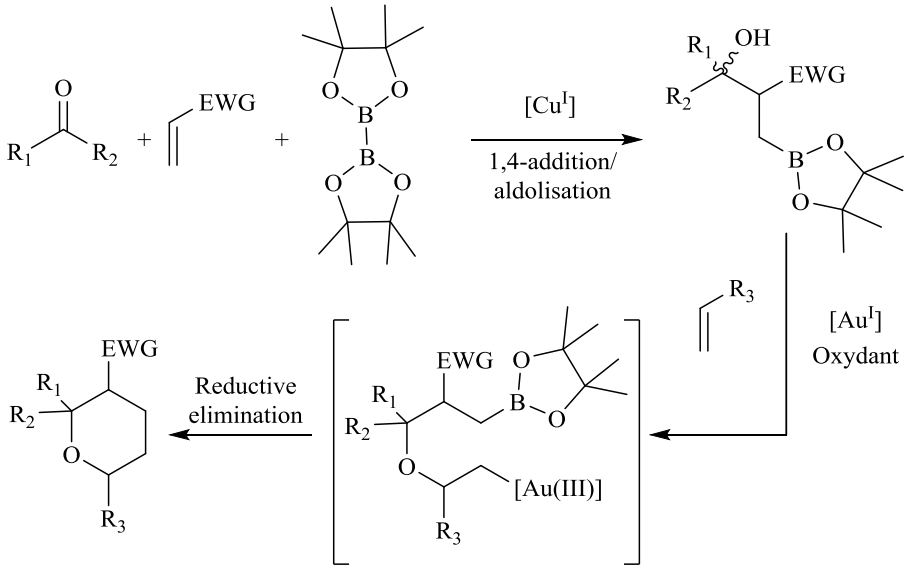
Scheme 71. Development of a secondary reaction.

The use of different ketones was also envisaged as well as the development of an enantioselective version of this reaction with our new cationic copper(I) complexes. Indeed acyclic substrates did not react well in the Baylis Hillman reaction. An interesting idea was thus to use substrate such as **51** in our reaction to form chiral compounds (Scheme 72).



Scheme 72. Enantioselective version.

Valorization of our borylated adducts are also envisaged. We are interested in using our methodology to form cyclic products *via* a cooperative dual process. This extension of the methodology will be developed by another PhD student, Arnaud Boreux. After our domino reaction, our compound is put together with gold(I) catalyst, an oxidant and an alkene. Addition of the alkene followed by reductive elimination should afford tetrahydropyran compound. We will hope that this cooperative dual process will show promising results.



Scheme 73. Valorization of our borylated adducts.

Chapter 2: Synthesis of Acylsilanes

I. Bibliographic Introduction

Acylsilanes ($RCOSiR'_3$) can be considered as unusual carbonyl compounds for which a silane fragment is directly attached to a carbonyl group resulting in unique chemical properties. Since the first report of their synthesis in 1957,[1] acylsilanes have attracted considerable interest and much effort has been devoted to investigate both their preparation and synthetic utility in organic chemistry. The steric and the electronic effects of bulky trisubstituted silyl groups in acylsilanes have proven pivotal for achieving excellent regio- and diastereoselectivities in several of their synthetic applications. The use of acylsilanes in organic synthesis has increased significantly over the last few years due to the discovery of valuable new transformations and some improvements in the synthetic methods leading to acylsilanes.[2]

I.1. Properties of acylsilanes

The spectral data of acylsilanes are well described in the reviews by Brook and Page *and co-workers*.[3] The early studies of acylsilanes focused

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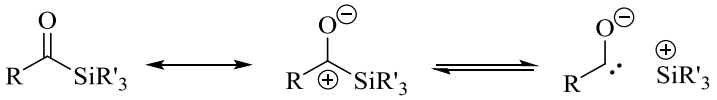
[1] Brook, A. G., *J. Am. Chem. Soc.* **1957**, *79*, 4373-4375.

[2] For reviews on acylsilanes, their preparation and applications in organic chemistry: (a) Patrocínio, A. F.; Moran, P. J. S., *J. Braz. Chem. Soc.* **2001,** *12*, 07-31. (b) Zhang, H.-J.; Priebbenow, D. L.; Bolm, C. *Chem. Soc. Rev.* **2013,** *42*, 8540-8571. (c) Bonini, B. F.; Comes-Franchini, M.; Fochi, M.; Mazzanti, G.; Ricci, A., *J. Organomet. Chem.* **1998**, *567*, 181-189. (d) Ricci, A.; Degl'Innocenti, A., *Synthesis* **1989**, 647-660.

[3] Page, P. C. B.; Klair, S. S. ; Rosenthal, S. *Chem. Soc. Rev.* **1990**, *19*, 147-195.

on their unusual spectroscopic properties such as their significantly longer wavelength absorption in infrared and ultraviolet regions compared with their carbon analogues. This is due to the inductive effect of the silicon which favours the polarization of the carbonyl group (Si: X = 1.90; C: X = 2.55). In ^{13}C NMR spectroscopy, the signals for the carbonyl atom are quite different from the corresponding ketones, appearing at higher δ values. The anisotropy effect and electronegativity differences also lead to higher δ values in ^{1}H NMR spectra for hydrogens attached to the α–carbon of acylsilanes.[4] Another interesting characteristic of acylsilanes is the abnormally long Si-CO bond (1.926 Å); first observed by Trotter based on X-ray analysis, which can be compared to the analogous bond length in C-CO (1.51 Å) compounds.[5]



Scheme 1. Resonance structures of acylsilanes.

The plausible resonance structures of acylsilanes are depicted in scheme 1. Notably, the large bathochromic shift of n-π* transitions of conjugated acylsilanes such as aroyl-silanes or α,β-unsaturated acylsilanes gives them a bright yellow color and also results in them being very sensitive to light.[6] These observations have provided insight into the

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[4] Brook, A. G.; Quigley, M. A.; Peddle, G. J. D.; Schwartz, N. V.; Warner, C. M., *J. Am. Chem. Soc.* **1960,** *82*, 5102-5106.

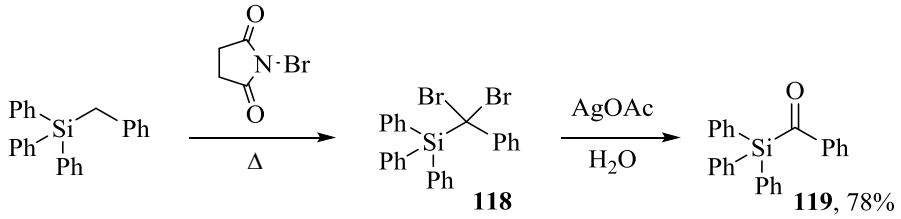
[5] Chieh, P. C.; Trotter, J. *J. Chem. Soc. A: Inorganic, Physical, Theoretical* **1969**, 1778-1783.

[6] Bock, H.; Alt, H.; Seidl, H., *J. Am. Chem. Soc.* **1969**, *91*, 355-361.

chemical properties of acylsilanes, including the inherent reactivity of the carbonyl group, the activation of the C-Si bond and the photochemical features of silyl ketones.

I.2. Literature-known methods for their synthesis

The first synthesis of acylsilanes was reported by Brook in 1957.[7] He obtained benzoyltriphenylsilane **119** in 6% yield from potassium triphenylsilane and benzoyl chloride. The same compound was obtained in a much better yield by hydrolysis of the bromine intermediate **118** (Scheme 2).



Scheme 2. First synthesis decribed by Brook.

After that, many synthetic routes have been designed for the preparation of acylsilanes. A useful summary is presented in figure 1, showing that some of the common organic functional groups may be used for the preparation of these compounds. Some of the most widely used methods will be described in this section.

[7] Brook, A. G., *J. Am. Chem. Soc.* **1957**, *79*, 4373-4375.

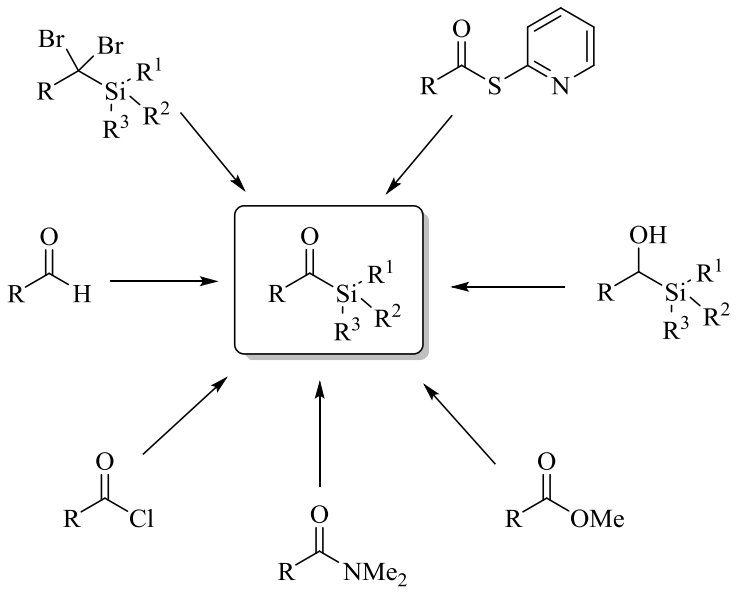


Figure 1. Different synthetic routes for acylsilanes preparation.[8]

I.2.1. Use of benzotriazoles or dithianes

The most general procedure for the formation of acylsilane is the Brook-Corey strategy, also called the "dithiane route", involving the formation of 1,3-dithiane from an aldehyde, lithiation and subsequent silylation. Finally, hydrolytic deprotection of silyl 1,3-dithiane leads to the desired acylsilane (Scheme 3).[9] The great advantage of this method is the variety of compounds that can be prepared, including aroylsilanes, alkanoylsilanes and functionalized acylsilanes. The first two steps generally afford the desired products in high yields. However, the third

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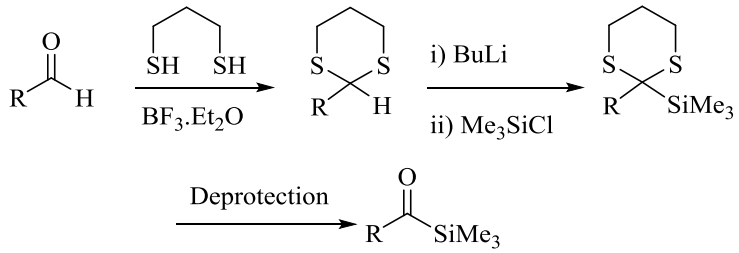
[8] Patrocínio, A. F.; Moran, P. J. S., *J. Braz. Chem. Soc.* **2001,** *12*, 07-31.

[9] (a) Brook, A. G.; Duff, J. M.; Jones, P. F.; Davis, N. R., *J. Am. Chem. Soc.* **1967**, *89*, 431-434. (b) Corey, E. J.; Seebach, D.; Freedman, R., *J. Am. Chem. Soc.* **1967**, *89*, 434-436.

step can be problematic. In early research, mercuric chloride was predominantly used to remove the thioketal protecting group of the silyl 1,3-dithiane. But there were several drawbacks to this approach, in particular the toxicity of mercury salts and potential over-hydrolysis of the relatively weak Si-C(O) bond.



Scheme 3. Brook-Corey strategy.

In this context, other methods have been applied for the regeneration of the masked carbonyl group such as chloramine-T/methanol, ceric ammonium nitrate, anodic oxidation, [bis(trifluoroacetoxy)-iodo]benzene, $CuCl_2$-CuO and MeI or $I_2/CaCO_3$.[10] More recently, Moran and co-workers found that *N*-bromosuccinimide could be used as a mild oxidizing reagent. Nevertheless, for aromatic acylsilanes, over-oxidation to the carboxylic acid was observed.[11] Therefore, the

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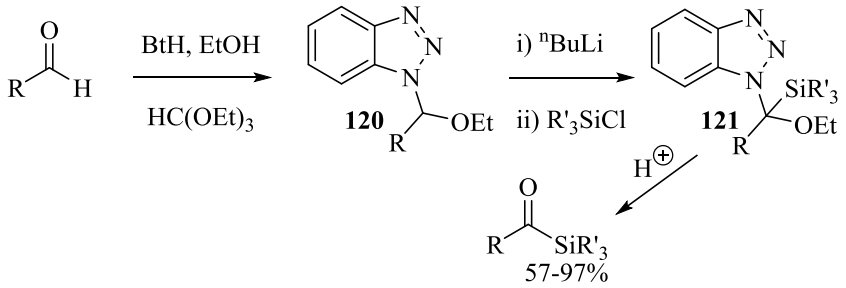
[10] For selected examples see: (a) Reich, H. J.; Eisenhart, E. K.; Olson, R. E.; Kelly, M. J., *J. Am. Chem. Soc.* **1986,** *108*, 7791-7800. (b) Reich, H. J.; Holtan, R. C.; Bolm, C., *J. Am. Chem. Soc.* **1990**, *112*, 5609-5617. (c) Chuang, T.-H.; Fang, J.-M.; Jiaang, W.-T.; Tsai, Y.-M., *J. Org. Chem.* **1996**, *61*, 1794-1805. (d) Bouillon, J.-P.; Portella, C., *Tet. Lett.* **1997**, *38*, 6595-6598. (e) Suda, K.; Watanabe, J.-I.; Takanami, T., *Tet. Lett.* **1992**, *33*, 1355-1356.

[11] Patrocínio, A. F.; Moran, P. J. S., *J. Org. Chem.* **2000**, *603*, 220-224.

identification of milder and selective hydrolytic conditions is still necessary.

Besides silyl 1,3-dithianes, several other α-silyl acyl anion equivalents were also adopted for the synthesis of acylsilanes.[12] In 1996, Katritsky developed the use of benzotriazole derivatives as a similar approach to the dithiane methodology. This strategy involves lithiation and silylation of **120** to form the acylsilane precursor **121** which is subsequently hydrolyzed under acidic conditions to form various aroyl-, heteroaroyl-, α,β-unsaturated alkenoyl- and alkynoylsilanes (Scheme 4).



Scheme 4. Synthesis of acylsilanes from *N,O*-acetals.

However, as in the case of the Brook-Corey strategy, the Katritzky method is indirect and requires protection-deprotection steps to access the desired products.

I.2.2. Oxidation of α-hydroxysilanes

A more efficient method is perhaps the direct oxidation of α-hydroxysilanes which can be prepared by several methods, such as the

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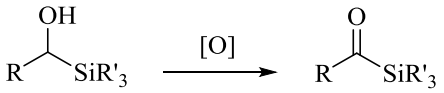
[12] (a) Katritzky, A. R.; Lang, H.; Wang, Z.; Lie, Z., *J. Org. Chem.* **1996**, *61*, 7551-7557. (b) Katritzky, A. R.; Wang, Z.; Lang, H., *Organometallics* **1996**, *15*, 486-490. (c) Katritzky, A. R.; Lang, H., *J. Org. Chem.* **1995**, *60*, 7612-7618.

condensation of trialkylsilyl anions with aldehydes.[13] The subsequent oxidation of α-hydroxysilanes with ordinary oxidizing reagents like potassium permanganate or chromic acid leads to acylsilanes (Scheme 5). Nevertheless, this route has several limitations because the Si-C bond may be easily cleaved and the products may suffer over-oxidation to carboxylic acids.



Scheme 5. Oxidation of α-hydroxysilanes to acylsilanes.

Lipshutz and co-workers described another approach in 1994. They reported that the attack of a series of nucleophiles on the α-epoxytriisopropylsilane afforded the corresponding α-hydroxysilanes in good yields.[14] These compounds can then be readily oxidized with CrO_3/H_2SO_4, DCC/DMSO, CrO_3/pyridine, oxalyl chloride/DMSO (Swern oxidation) or $KMnO_4/Al_2O_3$ (Scheme 6).[15]

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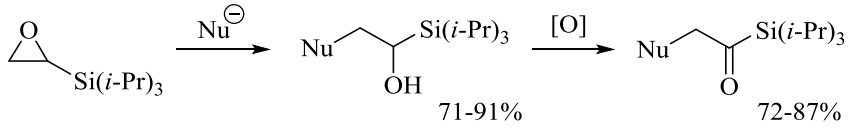
[13] (a) Mori, A.; Fujita, A.; Ikegashira, K.; Nishihara, Y.; Hiyama, T., *Synlett* **1997**, 693-694. (b) Wilson, S. R.; Haque, M. S.; Misra, R. N., *J. Org. Chem.* **1982**, *47*, 747-748; (c) Barrett, A. G. M.; Hill, J. M.; Wallace, E. M.; Flygare, J. A., *Synlett* **1991**, 764-770.

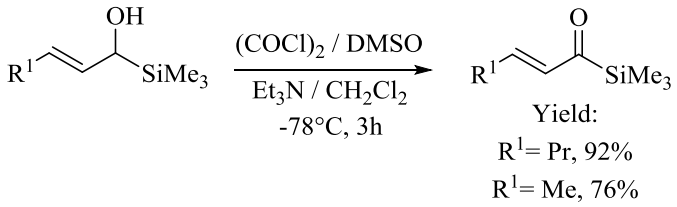
[14] Lipshutz, B. H.; Lindsley, C.; Susfalk, R.; Gross, T., *Tet. Lett.* **1994**, *35*, 8999-9002.

[15] (a) Patrocínio, A. F.; Moran, P. J. S., *Synth. Commun* **2001**, *31*, 2457-2461. (b) Brook, A. G.; Pierce, J. B., *J. Org. Chem.* **1965**, *30*, 2566-2571.



Scheme 6. Synthesis of acylsilanes from α-epoxytriisopropylsilane.

In this context, Swern oxidation seems to be the most accessible and general oxidizing system commonly employed (Scheme 7). The major drawback of these procedures remains the synthesis of α-hydroxysilanes as we will see later on.

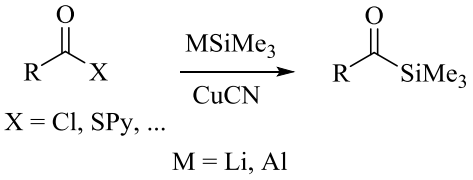


Scheme 7. Swern oxidation of α-hydroxysilanes.

I.2.3. Silylation of carboxylic derivatives

Nucleophilic silylation of carboxylic acid derivatives facilitates the direct formation of the corresponding acylsilanes. Various silicon nucleophiles and pro-nucleophiles have been adopted in these strategies. For example, the reaction of esters or acyl chlorides with silyl-Grignard derivatives ($SiMe_3Cl$/Mg/HMPT) reported by Picard in 1979 allowed access to aroyltrimethylsilanes and α,β-unsaturated acylsilanes with relatively good

yields.[16] This method was further optimized through the use of $Mg/I_2/SiMe_3Cl/NMP$ in the preparation of aroylsilanes.[17]



Scheme 8. Copper-mediated synthesis of acylsilanes.

Compounds containing lithium attached to silicon are extremely important reagents in organic chemistry. Direct reaction of acid chlorides with Ph_3SiLi in the presence of a stoichiometric amount of CuI provided rapid access to acylsilanes.[18] In 1987, Kang reported that $LiAl(SiMe_3)_4$ or $LiMeAl(SiMe_3)_3$ reacted with acid chlorides and anhydrides in the presence of a catalytic amount of CuCN, affording the desired acylsilanes in good yields (Scheme 8).[19] At the same time, the use of (trimethylsilyl)cuprate were also reported by Degl'Innocenti and allowed access to acylsilanes in good yields.[20] Furthemore, *(S)*-2-pyridyl esters reacted very smoothly with $Al(SiMe_3)_3$ in the presence of CuCN to

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[16] Picard, J. P.; Calas, R.; Dunogues, J.; Duffaut, N.; Gerval, J.; Lapouyade, P., *J. Org. Chem.* **1979**, *44*, 420-424.

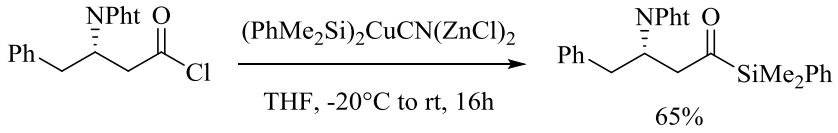
[17] Tongco, E. C.; Wang, Q.; Surya Prakash, G. K., *Synth. Commun.* **1997**, *27*, 2117-2123.

[18] Wittenberg, D.; Gilman, H., *J. Am. Chem. Soc.* **1958**, *80*, 4529-4531.

[19] Kang, J.; Lee, J. H.; Kim, K. S.; Jeong, J. U.; Piun, C., *Tet. Lett.* **1987**, *28*, 3261-3262.

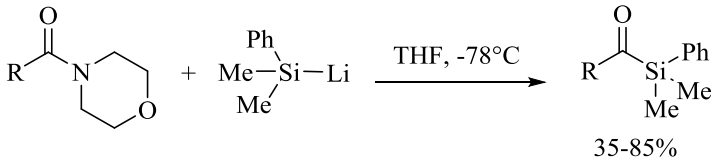
[20] Capperucci, A.; Degl'Innocenti, A.; Faggi, C.; Ricci, A.; Dembech, P.; Seconi, G., *J. Org. Chem.* **1988**, *53*, 3612-3614.

afford α-chiral acylsilanes in good yields (Scheme 8).[21] In 1995, a much more readily applicable silyl-zinc cyanocuprate $(Me_2PhSi)_2Cu(CN)(ZnCl_2)$ was developed by Ricci and co-workers. This reagent was then reacted with acyl chlorides to form acylsilanes (Scheme 9).[22] A large number of functional groups were well tolerated in this procedure.



Scheme 9. Preparation of acylsilanes using organocuprates.

In 1994, Fleming and co-workers first reported the reaction of (dimethyl)phenylsilyllithium with amides or esters.[23] A competitive method has also been reported by Scheidt in 2004. He described the general synthesis of acylsilanes from the corresponding morpholinamides and silyllithium species (Scheme 10).[24]



Scheme 10. Synthesis of acylsilanes from morpholinamides.

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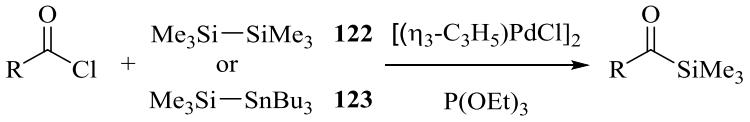
[21] Nakada, M.; Nakamura, S.-i.; Kobayashi, S.; Ohno, M., *Tet. Lett.* **1991**, *32*, 4929-4932.

[22] Bonini, B. F.; Comes-Franchini, M.; Mazzanti, G.; Passamonti, U.; Ricci, A.; Zani, P., *Synthesis* **1995**, 92-96.

[23] Fleming, I.; Ghosh, U., *J. Chem. Soc., Perkin Trans. 1* **1994**, 257-262.

[24] Clark, C. T.; Milgram, B. C.; Scheidt, K. A., *Org. Lett.* **2004**, *6*, 3977-3980.

In addition to metal-silicon reagents described above, readily available di-silicon or tin-silicon compounds can also be employed in acylsilane synthesis through transmetalation following activation by transition metal complexes. Yamamoto and co-workers prepared aroylsilanes by reaction of disilanes **122** with benzoyl chloride under palladium catalysis.[25] However this procedure was not suitable for aliphatic group. A good alternative was the use of trimethyl(tributylstannyl)silane **123** providing both aroyl and alkanoylsilanes by reaction with acid chlorides.[26]



Scheme 11. Palladium-catalyzed synthesis of acylsilanes.

I.2.4. Synthesis of acylsilanes from alkynes

Several functionalized acylsilanes have also been prepared from alkynes. Zweifel and Miller highly contributed to this field. They reported the synthesis of acylsilanes by hydroboration-oxidation of silylacetylenes (Scheme 12).[27]

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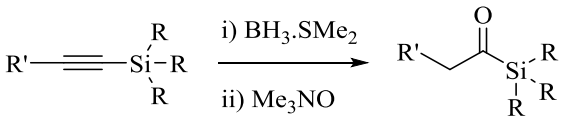
[25] (a) Yamamoto, K.; Suzuki, S.; Tsuji, J., *Tet. Lett.* **1980**, *21*, 1653-1656. (b) Ricci, A.; Degl'Innocenti, A.; Chimichi, S.; Fiorenza, M.; Rossini, G., *J. Org. Chem.* **1985**, *50*, 130-133.

[26] Geng, F.; Maleczka Jr, R. E., *Tet. Lett.* **1999**, *40*, 3113-3114.

[27] (a) Miller, J. A.; Zweifel, G., *J. Am. Chem. Soc.* **1981**, *103*, 6217-6219; (b) Miller, J. A.; Zweifel, G., *Synthesis* **1981**, 288-289.

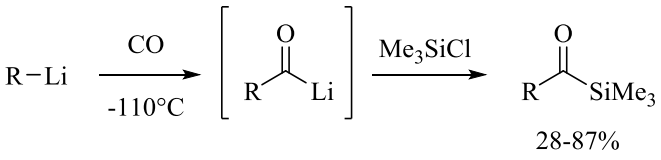


Scheme 12. Hydrolysis of silyl-alkynes to form acylsilanes.

In 1995, Oshima and Utimoto found that α-haloacylsilanes could be formed from the reaction of 2-halo-2-trimethylsilyloxiranes with metal salts such as $ZnCl_2$, $ZnBr_2$, NaI and $AgBF_4$.[28]

I.2.5. Alternative methods for acylsilane synthesis

In 1982, Seyferth and Weinstein reported the most direct procedure to access aliphatic acylsilanes: through the carbonylation of organolithium reagents to form acyllithium reagent followed by reaction with trimethylchlorosilane (Scheme 13).[29] But this approach remained unsatisfactory due to the limited substrate scope and rigorous reaction conditions required.



Scheme 13. Carbonylative synthesis of acylsilanes from organolithium reagents.

More recently, a nickel-catalyzed protocol has been reported by Grée and co-workers for the preparation of aliphatic-substituted acylsilanes

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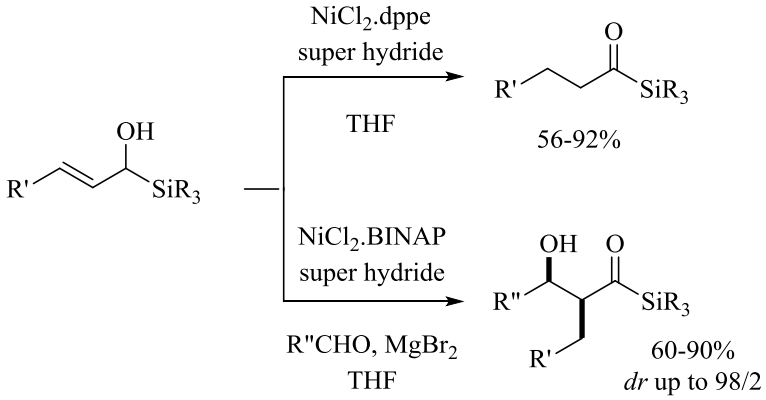
[28] Horiuchi, Y.; Taniguchi, M.; Oshima, K.; Utimoto, K., *Tet. Lett.* **1995**, *36*, 5353-5356.

[29] Seyferth, D.; Weinstein, R. M., *J. Am. chem. Soc.* **1982**, *104*, 5534-5535.

from α–hydroxyallylsilanes.[30] An isomerization-aldolisation process using a catalytic amount of $NiCl_2$.BINAP, super hydride (lithium triethylborohydride) and $MgBr_2$ facilitated the reaction between the hydroxyallylsilane and an aldehyde to form highly substituted acylsilanes (Scheme 14).



Scheme 14. Nickel-mediated synthesis of acylsilanes.

Finally, Oshima and co-workers reported a simple method for the preparation of various acylsilanes starting from dichlorobis(methyldiphenylsilyl)methanes or boryldichloromethylsilane (Scheme 15).[31]

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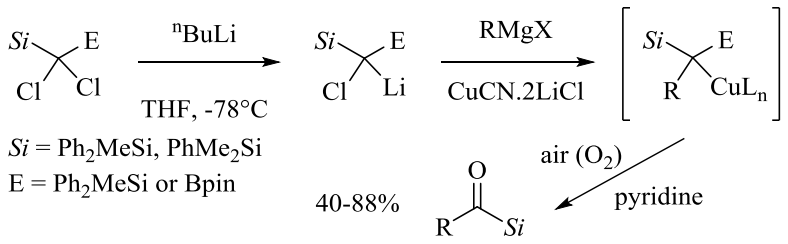
[30] Reddy, G. P.; Reddy, J. S.; Das, S.; Roisnel, T.; Yadav, J. S.; Chandrasekhar, S.; Grée, R., *Org. Lett.* **2013**, *15*, 1524-1527.

[31] Kondo, J.; Shinokubo, H.; Oshima, K., *Org. Lett.* **2006**, *8*, 1185-1187.



Scheme 15. Synthesis of acylsilanes from *gem*-dichlorosilanes.

In conclusion, most of these standard procedures for accessing such compounds have some limitations such as low overall efficiency, a reliance on stoichiometric amount of a transition metal or even more inconveniently needs to be prepared in several steps. Thus, there is still a need for designing new straightforward and versatile methods for the synthesis of acylsilanes.

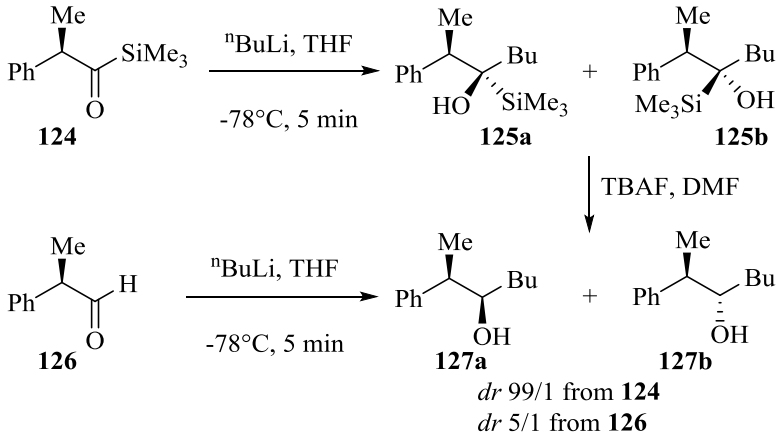
I.3. Synthetic applications of acylsilanes

Interestingly, in the majority of the reports on acylsilanes, the word *versatility* has been frequently used to describe their various reaction modes in processes. In some of these transformations, acylsilanes were employed as sterically hindered aldehydes. In other processes, the umpolung reactivities of acylsilanes (i.e. the reversible rearrangement of silyl groups from the carbon to the oxygen, also called "Brook rearrangement") were considered to be the driving force. Herein some of the most important synthetic applications of acylsilanes will be presented.

I.3.1. Nucleophilic additions with organometallic reagents

Acylsilanes can be considered as carbonyl derivatives. Therefore, they typically react in a same manner as aldehydes or ketones in nucleophilic

addition reactions with organometallic reagents. However, due to the presence of bulky silicon groups, they show higher selectivities in these reactions.[32] For example, the reaction of acylsilane **124** with *n*-butyllithium affords *syn*- and *anti*-α-hydroxysilanes **125a** and **125b** with high diastereoselectivity (>99/1, Scheme 16). After treatment with *n*-tetrabutylammonium fluoride (TBAF), stereospecifically desilylated products **127a** and **127b** are obtained with retention of the configuration.[33] In contrast, the reaction of the corresponding aldehyde **126** with *n*-BuLi gave **127a** and **127b** in a diastereomeric ratio of only 5/1 (Scheme 16). Both steric and electronic effects of the silyl group are considered to contribute to the high level of stereoselectivity achieved.



Scheme 16. High diastereofacial selectivity in nucleophilic additions to chiral acylsilanes.

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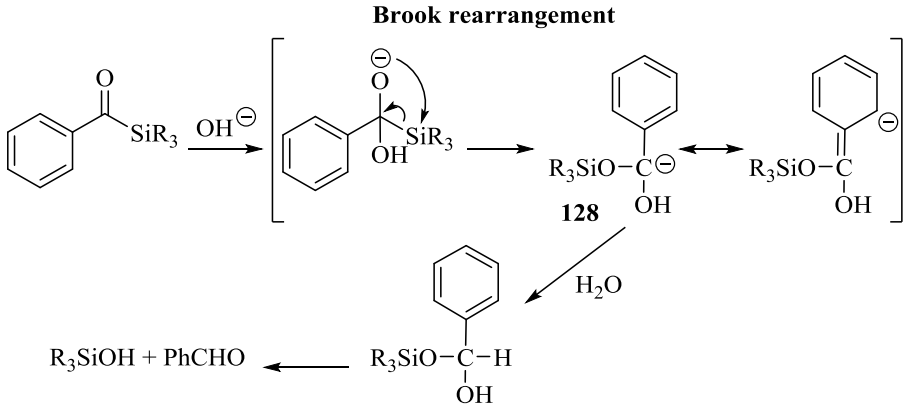
[32] Fleming, I.; Barbero, A.; Walter, D., *Chem. Rev.* **1997**, *97*, 2063-2192.

[33] Nakada, M.; Urano, Y.; Kobayashi, S.; Ohno, M., *J. Am. Chem. Soc.* **1988**, *110*, 4826-4827.

In the case of aroylsilanes reacting with nucleophiles, the Brook rearrangement[34] is very common. An example is the known hydrolysis of aroylsilanes to the corresponding aldehydes, promoted by traces of OH^- (Scheme 17). This rearrangement is commonly observed due to the relative stabilization of the carbanion intermediate **128** by the aromatic ring.



Scheme 17. Hydrolysis of aroylsilanes and Brook rearrangement.

The Brook rearrangement is the intramolecular 1,2-anionic migration of a silyl group from a carbon atom to an oxygen atom. It was originally recognized and studied by A.G. Brook in the late 1950s and early 1960s.[35] The migratory aptitude of silyl groups in this context has since been observed to be more general, comprising a family of [1,*n*]-carbon to oxygen silyl migrations. The reverse process, intramolecular migration of

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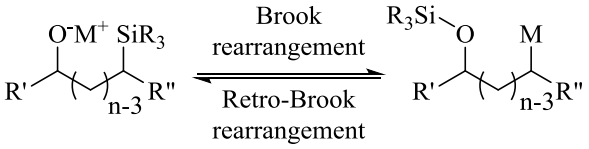
[34] Brook, A. G.; Warner, C. M.; McGriskin, M. E., *J. Am. Chem. Soc.* **1959**, *81*, 981-983.

[35] (a) Brook, A. G.; Warner, C. M.; McGriskin, M. E., *J. Am. Chem. Soc.* **1959**, *81*, 981-983; (b) Brook, A. G., *J. Am. Chem. Soc.* **1958**, *80*, 1886-1889. (c) Brook, A. G.; Schwartz, N. V., *J. Am. Chem. Soc.* **1960**, *82*, 2435-2439.

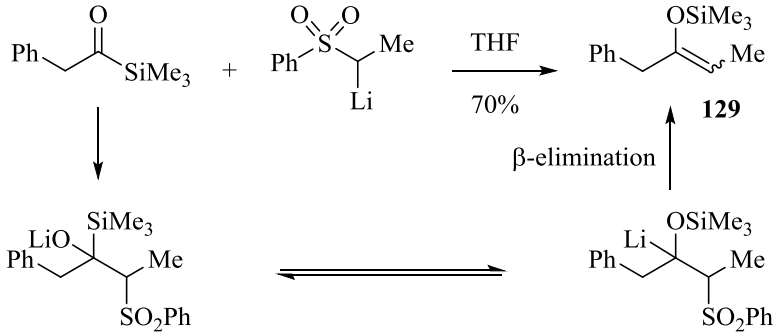
a silyl group from oxygen to carbon, was also observed in some cases (Scheme 18).

[1,*n*]-Silyl Migrations



Scheme 18. Anionic silyl migrations.

It has been noticed that α-silyl alkoxides could undergo Brook rearrangement to form useful carbanionic species.[36] In 1979, Reich reported that when a leaving group was present at the α-position, β-elimination of α-silyl alkoxides led to formation of silyl enol ethers **129** (Scheme 19).[37] This chemistry has been applied to the synthesis of allenyl and dienyl silyl ethers.



Scheme 19. Synthesis of allenyl and dienyl silyl ethers by Brook rearrangement.

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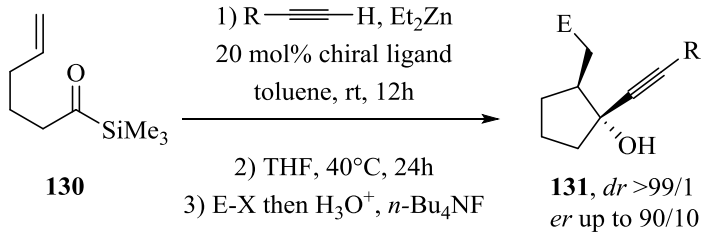
[36] Moser, W. H., *Tetrahedron* **2001**, *57*, 2065-2084.

[37] Reich, H. J.; Rusek, J. J.; Olson, R. E., *J. Am. Chem. Soc.* **1979**, *101*, 2225-2227.

Scheme 20 shows a recent example of acylsilane reactions involving the Brook rearrangement.[38] Marek and co-workers described the zinc-catalyzed addition of various alkynes to acylsilanes **130** followed by a Zn-Brook rearrangement and either the Zn-ene-allene or Zn-yne-allene cyclization that led to the enantio- and diastereoselective formation of carbocycles **131** in a single-pot operation.



130 **131**, *dr* >99/1
er up to 90/10

Scheme 20. Synthesis of cyclopentanes from acylsilanes.

Since 1993, Takeda and co-workers have investigated the reaction of acylsilanes with ketone enolates and designed several tandem reactions which have been used in total synthesis.[39]

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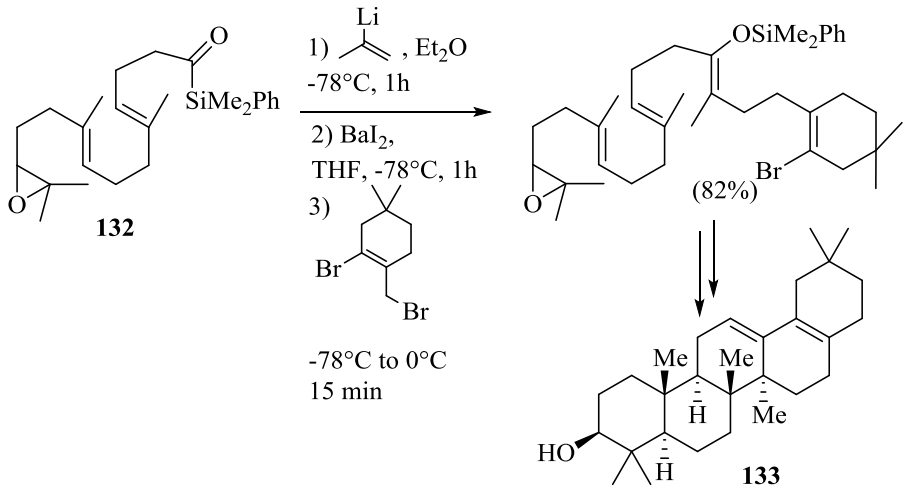
[38] Unger, R.; Weisser, F.; Chinkov, N.; Stanger, A.; Cohen, T.; Marek, I., *Org. Lett.* **2009**, *11*, 1853-1856.

[39] For selected examples see : (a) Takeda, K.; Fujisawa, M.; Makino, T.; Yoshii, E.; Yamaguchi, K., *J. Am. Chem. Soc.* **1993**, *115*, 9351-9352. (b) Takeda, K.; Nakajima, A.; Yoshii, E., *Synlett* **1996**, 752-754. (c) Takeda, K.; Ohtani, Y., *Org. Lett.* **1999**, *1*, 677-680. (d) Sasaki, M.; Oyamada, K.; Takeda, K., *J. Org. Chem.* **2010**, *75*, 3941-3943. (e) Sasaki, M.; Hashimoto, A.; Tanaka, K.; Kawahata, M.; Yamaguchi, K.; Takeda, K., *Org. Lett.* **2008**, *10*, 1803-1806. (f) Lettan, R. B.; Galliford, C. V.; Woodward, C. C.; Scheidt, K. A., *J. Am. Chem. Soc.* **2009**, *131*, 8805-8814.

Scheme 21 illustrates a key step of Corey's total synthesis of pentacyclic triterpene **133** of the β–Amyrin family.[40] The addition of 2-propenyl-lithium to acylsilane **132**, followed by a Brook rearrangement and coupling with allylic bromide, resulted in the *Z*-olefin in an overall yield of 82% with excellent stereoselectivity (>95%).



Scheme 21. Key step of Corey's total synthesis of pentacyclic triterpene.

I.3.2. Acylsilanes as acyl anions

The cyanide anion promoted Brook rearrangement of acylsilanes to form silyloxy nitrile anions and has been utilized as an efficient way to form acyl anion equivalents from acylsilanes.[41] The reaction of these compounds with a cyanide anion was first reported by the group of

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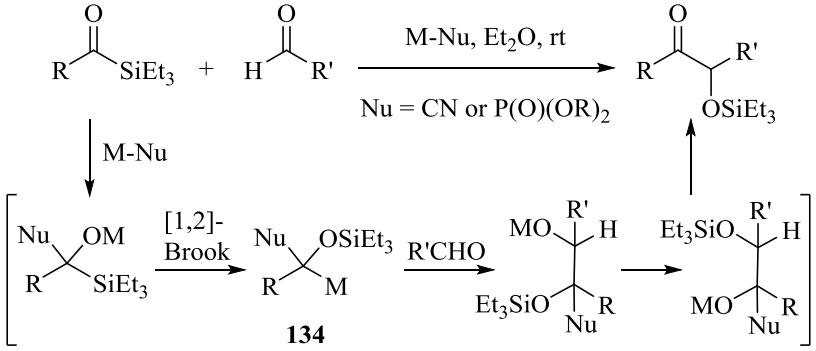
[40] Huang, A. X.; Xiong, Z.; Corey, E. J., *J. Am. Chem. Soc.* **1999**, *121*, 9999-10003.

[41] (a) Reich, H. J.; Holtan, R. C.; Bolm, C., *J. Am. Chem. Soc.* **1990**, *112*, 5609-5617. (b) Takeda, K.; Ohnishi, Y., *Tet. Lett.* **2000**, *41*, 4169-4172.

Degl'Innocenti and Ricci in 1987.[42] A few years later, Johnson and co-workers investigated the cyanide-catalyzed reaction of acylsilanes with a series of electrophiles. For example, a regiospecific cross silyl benzoin reaction of an acylsilane with an aldehyde was reported using KCN as a catalyst, which resolved the poor selectivity of the benzoin reaction of two different aldehydes (Scheme 22).[43] Chiral metallophosphites are also ideal catalysts for the asymmetric cross silyl benzoin reaction and umpolung intermediates **134** are proposed to be involved in the reaction pathway (Scheme 22).[44] The 1,4-addition of acylsilanes to α,β-unsaturated amides was also achieved using a metallophosphite catalyst.[45]



Scheme 22. A cyanide or phosphite catalyzed cross silyl benzoin reaction.

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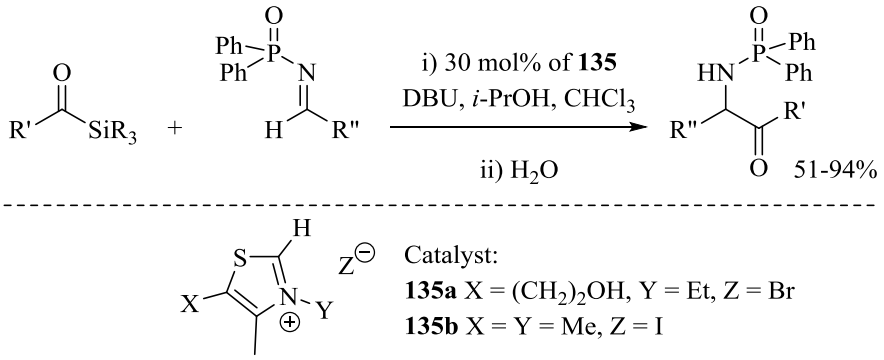
[42] Degl'Innocenti, A., Ricci, A., Mordini, A., Reginato, G., Colotta, V., *Gazz. Chim. Ital.* **1987**, *117*, 645.

[43] Linghu, X.; Johnson, J. S., *Angew. Chem. Int. Ed.* **2003**, *42*, 2534-2536.

[44] (a) Linghu, X.; Bausch, C. C.; Johnson, J. S., *J. Am. Chem. Soc.* **2005**, *127*, 1833-1840. (b) Takeda, K.; Tanaka, T., *Synlett* **1999**, *6*, 705-708.

[45] Nahm, M. R.; Linghu, X.; Potnick, J. R.; Yates, C. M.; White, P. S.; Johnson, J. S., *Angew. Chem. Int. Ed.* **2005**, *44*, 2377-2379.

Through the addition of a neutral Lewis base catalyst, acyl anion precursors could be formed from acylsilanes in the presence of a thiazolium catalyst, which underwent conjugate addition with α,β-unsaturated ketones.[46] Scheidt and co-workers reported the thiazolium-catalyzed sila-Stetter reaction of acylsilanes with α,β-unsaturated compounds.[47] They also investigated the reaction of acylsilanes with *N*-phosphinoylimines catalyzed by thiazolium salts (**135a** and **135b**) to provide an efficient route to α–aminoketone derivatives (Scheme 23).[48]



Scheme 23. Thiazolium-catalyzed addition reactions of acylsilanes with *N*-phosphinoylimines.

I.3.3. Radical reactions involving acylsilanes

Traditionally, kinetic studies have suggested that the intramolecular addition of radicals to carbonyl species is reversible and fragmentation

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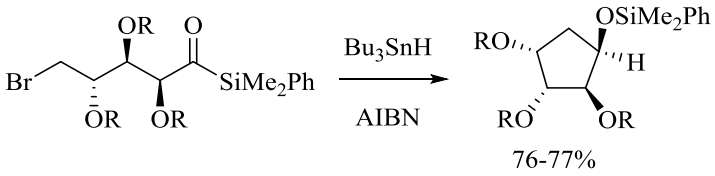
[46] Mattson, A. E.; Bharadwaj, A. R.; Zuhl, A. M.; Scheidt, K. A., *J. Org. Chem.* **2006**, *71*, 5715-5724.

[47] Mattson, A. E.; Bharadwaj, A. R.; Scheidt, K. A., *J. Am. Chem. Soc.* **2004**, *126*, 2314-2315.

[48] Mattson, A. E.; Scheidt, K. A., *Org. Lett.* **2004**, *6*, 4363-4366.

rates are typically faster than the rate of addition. In the case of acylsilanes, however, the irreversible radical-Brook rearrangements of β–silyl alkoxy radical intermediates make acylsilanes excellent substrates for radical addition processes.[49]

Tsai and co-workers have investigated the intramolecular radical cyclization of carbohydrate-based acylsilanes to afford polyoxygenated carbocycles (Scheme 24).[50] To demonstrate the importance of intramolecular radical cyclizations of acylsilanes in organic synthesis, this approach was recently employed in the total synthesis of polyhydroxylated alkaloids such as (+)-swainsonine and (-)-epiquinamide to access the core skeleton structure.[51]



Scheme 24. Radical cyclizations using acylsilanes to access the polyoxygenated core structure in total synthesis.

I.3.4. Transition metal-catalyzed reactions with acylsilanes

The first example of a transition metal-catalyzed reaction with acylsilanes was reported by Kang and co-workers in 1990, who described the metal-

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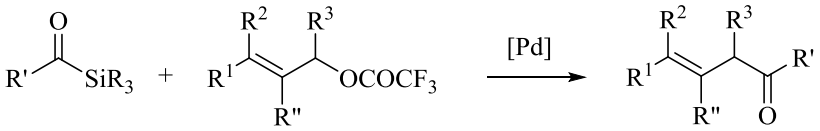
[49] (a) Chuang, T.-H.; Fang, J.-M.; Jiaang, W.-T.; Tsai, Y.-M., *J. Org. Chem.* **1996**, *61*, 1794-1805. (b) Tang, K.-H.; Liao, F.-Y.; Tsai, Y.-M., *Tetrahedron* **2005**, *61*, 2037-2045.

[50] Chang, C.-C.; Kuo, Y.-H.; Tsai, Y.-M., *Tet. Lett.* **2009**, *50*, 3805-3808.

[51] Chen, M.-J.; Tsai, Y.-M., *Tet. Lett.* **2007**, *48*, 6271-6274.

carbonyl complex-catalyzed reaction of *o*-(α-phenylthio)alkylbenzoyltrimethylsilanes for the formation of benzocyclobutenones.[52] Narasaka and co-workers developed rhodium-catalyzed intramolecular acylation of an acylsilane containing a tethered alkynyl group.[53] Around the same time, Tsuji and co-workers reported the acylation of allylic trifluoroacetates with acylsilanes catalyzed by palladium complexes (Scheme 25).[54]



[Pd] = [Pd(η_3-PhCH=CHCH$_2$)(CF$_3$CO$_2$)]$_2$

Scheme 25. Palladium-catalyzed allylic acylation of acylsilanes.

I.3.5. Other applications

Another interesting application of acylsilanes is the highly stereoselective synthesis of substituted γ–lactams described by Scheidt in 2008.[55] They developed a modular strategy for the stereoselective synthesis of β-silyloxy homoenolates that can be accessed from amide enolates and acylsilanes. These nucleophilic species underwent addition to imines to

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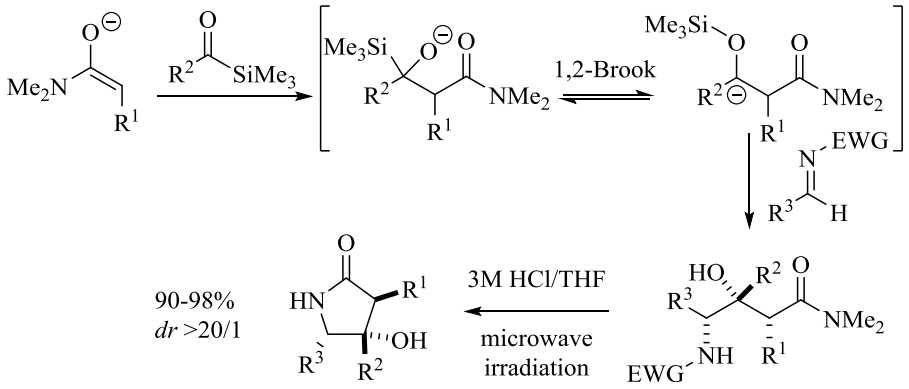
[52] Kang, J.; Choi, Y. R.; Kim, B. J.; Jeong, J. U.; Lee, S.; Lee, J. H.; Pyun, C., *Tet. Lett.* **1990**, *31*, 2713-2716.

[53] Yamane, M.; Amemiya, T.; Narasaka, K., *Chem. Lett.* **2001**, *30*, 1210-1211.

[54] Obora, Y.; Ogawa, Y.; Imai, Y.; Kawamura, T.; Tsuji, Y., *J. Am. Chem. Soc.* **2001**, *123*, 10489-10493.

[55] Lettan, R. B.; Woodward, C. C.; Scheidt, K. A., *Angew. Chem. Int. Ed.* **2008**, *47*, 2294-2297.

provide the γ-amino-β-hydroxy amides with good yields and excellent diastereoselectivity (Scheme 26). Exposure of the linear amide products to microwave irradiation and acidic conditions promoted a cyclization to form the corresponding γ-lactams in excellent yields and retention of the diastereoselectivity.



Scheme 26. Highly stereoselective synthesis of substituted γ–lactams.

Synthesis of fluoro-substituted products from acylsilanes has also gained considerable attention during the last few years. Recently, Portella reported the reaction of difluoroenol silyl ethers with amines, affording difluoroamines (Scheme 27).[56]

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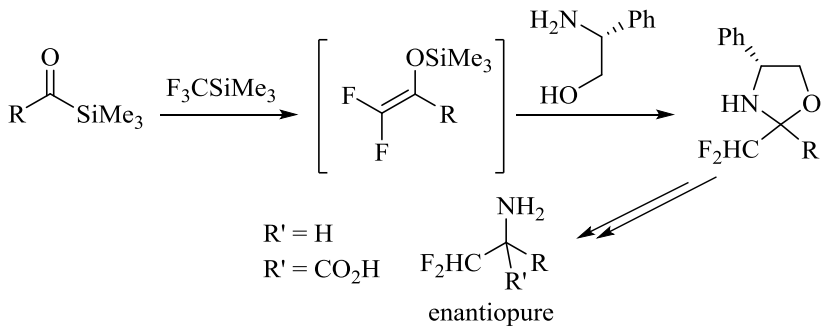
[56] Huguenot, F.; Billac, A.; Brigaud, T.; Portella, C., *J. Org. Chem.* **2008**, *73*, 2564-2569.



Scheme 27. Synthesis of 2-difluoromethyl oxazolidines.

The use of *(R)*-phenylglycinol allowed to prepare diastereomerically pure 2-difluoromethyl oxazolidines which proved to be good precursors towards enantiopure *(R)*-difluoromethyl amines (by $LiAlH_4$ reduction) or *(R)*-difluoromethyl alanine (*via* a Strecker reaction).

In addition to the aforementioned applications of acylsilanes, various others have been reported, involving photochemical transformations,[57] oxidation reactions,[58] reactivity of carbamoylsilanes,[59] etc…

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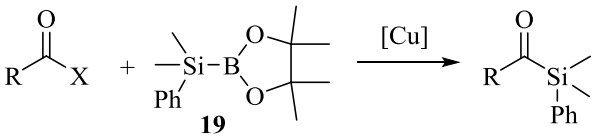
[57] For recent examples see : (a) Becker, P.; Priebbenow, D. L.; Zhang, H.-J.; Pirwerdjan, R.; Bolm, C., *J. Org. Chem.* **2014**, *79*, 814-817. (b) Becker, P.; Priebbenow, D. L.; Pirwerdjan, R.; Bolm, C., *Angew. Chem. Int. Ed.* **2013**, *1*, 269-271. (c) Zhang, H.-J.; Becker, P.; Huang, H.; Pirwerdjan, R.; Pan, F.-F.; Bolm, C., *Adv. Synth. Catal.* **2012**, *354*, 2157-2161.

[58] (a) Yoshida, J.-I.; Matsunaga, S.-i.; Isoe, S., *Tet. Lett.* **1989**, *30*, 5293-5296. (b) Yoshida, J.; Itoh, M.; Matsunaga, S.; Isoe, S., *J. Org. Chem.* **1992**, *57*, 4877-4882.

[59] Chen, J.; Cunico, R. F., *J. Org. Chem.* **2004**, *69*, 5509-5511.

II. Objectives

As it was shown in the introduction, acylsilanes have attracted considerable interest and much effort has been devoted to investigating both their preparation and synthetic utility in organic chemistry. To our knowledge, there are only few examples of acylation reaction with nucleophilic copper(I) species. Indeed, Ball and co-workers described the addition of well identified arylcopper compounds (NHCCuAryl) to acetyl chloride.[1] **However, there are still no example of catalytic acylation reaction of copper(I)-nucleophile species in the literature** and we wish to report here our own contribution leading to a useful and straightforward method to access acylsilanes. Indeed, based on our previous work in the area of transition metal-catalyzed transfer of silicon nucleophiles, we envisaged a new strategy for the preparation of acylsilanes through acylation of a copper(I)-silyl intermediate (Scheme 28). Starting from acid derivatives in the presence of Suginome's reagent **19** and a copper catalyst, the process should lead to the corresponding acylsilanes.



19

R = alkyl, aryl
X = F, Cl, OC(O)R', ...

Scheme 28. New synthetic strategy towards acylsilanes.

[1] Herron, J. R.; Ball, Z. T., *J. Am. Chem. Soc.* **2008**, *130*, 16486-16487.

III. Results and Discussion

III.1. First model reaction

The first strategy was to use an acid derivative in the presence of the Suginome's reagent and a copper catalyst to afford acylsilane in one step. The choice of an adequate substrate that would allow us to do the desired transformation was therefore crucial. That is why our investigation started with a screening of different acid derivatives. Some of these substrates were commercially available but the others had to be synthesized and we will describe the different syntheses in the following part.

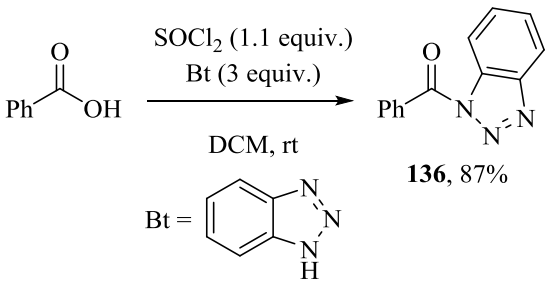
Note: This work was initiated during the Master thesis project of Corentin Rasson under my supervision.[1]

III.1.1. Synthesis of the substrates

The project started with the synthesis of different benzoyl derivatives bearing various leaving groups for initial trials. Some substrates were commercially available (benzoyl fluoride **143,** benzoyl chloride **144** and benzoyl cyanide **145**) but we had to prepare several substrates in order to assess the influence of the leaving group on our model acylation reaction (Scheme 28). The first substrate **136** was easily obtained in one step by reaction between benzoic acid and 3 equivalents of benzotriazole (Bt) in

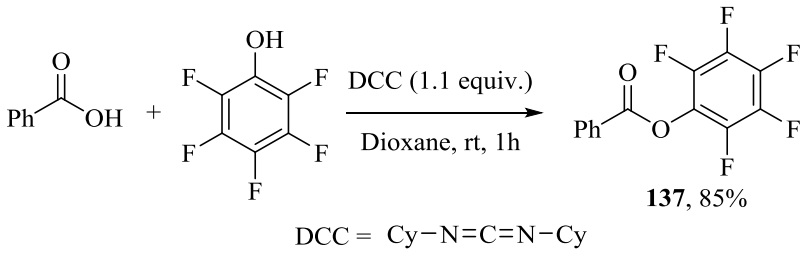
[1] Rasson, C ; Master thesis: *« Nouvelle méthodologie pour la synthèse énantiosélective d'a-hydroxysilanes et la synthèse d'acylsilanes »* **2011,** UCL, Louvain-la-Neuve.

the presence of thionyl chloride (Scheme 29).[2] The desired product was obtained in 87% yield.



Scheme 29. Synthesis of **136**.

Perfluorophenyl benzoate **137** was obtained by reaction between benzoic acid and pentafluorophenol according to the literature procedure.[3] A good yield of 85% was achieved after purification (Scheme 30).



Scheme 30. Synthesis of substrate **137.**

Substrate **138** was also prepared according to a modified literature procedure.[4] Benzoic acid reacted with DCC and *N*-hydroxysuccinimide

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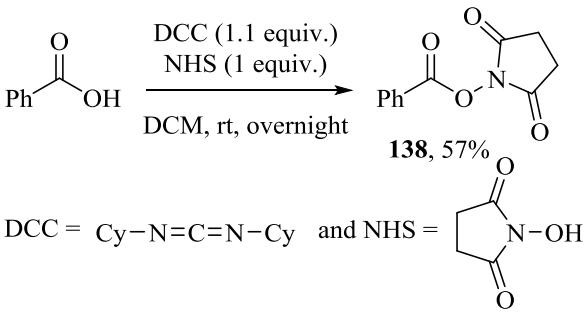
[2] Katritzky, A. R.; Cai, C.; Singh, S. K., *J. Org. Chem.* **2006**, *71*, 3375-3380.

[3] Babadzhanova, L. A.; Kirij, N. V.; Yagupolskii, Y. L.; Tyrra, W.; Naumann, D., *Tetrahedron* **2005**, *61*, 1813-1819.

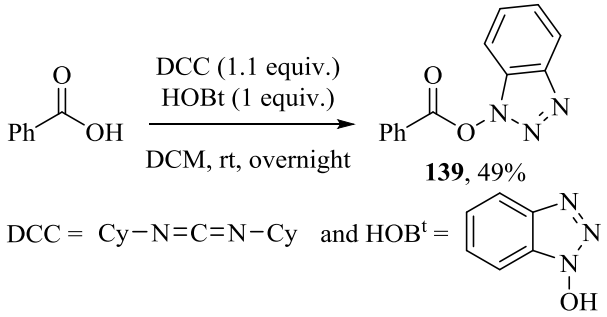
[4] Brink, B. D.; DeFrancisco, J. R.; Hillner, J. A.; Linton, B. R., *J. Org. Chem.* **2011**, *76*, 5258-5263.

(NHS) to afford in one step the acid derivative in 57% yield (Scheme 31).



Scheme 31. Synthesis of substrate **138**.

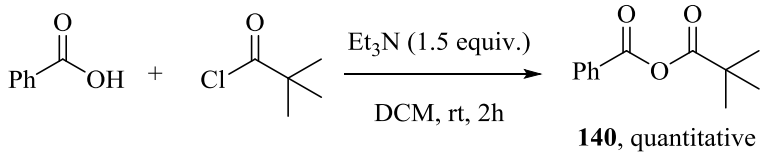
The same strategy was employed to synthesize substrate **139**. The desired product was obtained with 49% yield after recrystallization (Scheme 32).



Scheme 32. Synthesis of substrate **139**.

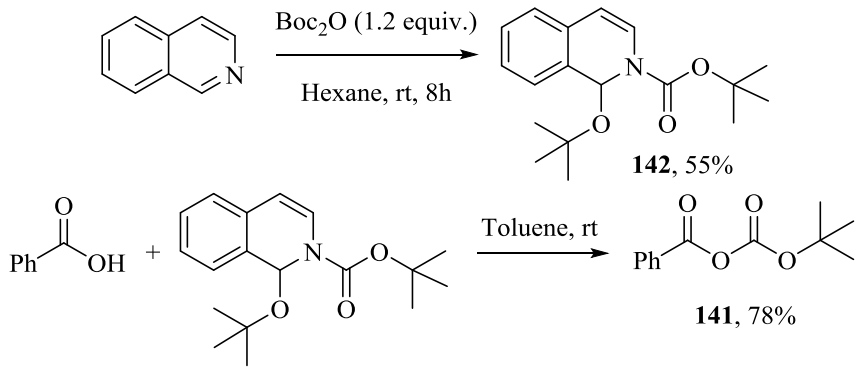
A procedure from the literature was used to synthesize the substrate **140**.[5] Actually, reaction of benzoic acid and one equivalent of pivaloyl chloride in the presence of triethylamine allowed us to isolate the desired mixed anhydride in a quantitative yield (Scheme 33).

[5] Lai, L.-L.; Wang, E.; Luh, B.-J., *Synthesis* **2001**, 361-363.



Scheme 33. Synthesis of substrate **140.**

Finally, the mixed anhydride **141** was synthesized in two steps according to the literature procedure.[6] The first step was the synthesis of *tert*-butyl 1-*tert*-butoxyisoquinoline-2(1H)-carboxylate **142** (BBDI) starting from isoquinoline and Boc_2O. The intermediate was isolated in 55% yield. The reaction between BBDI and benzoic acid gave the desired product **141** in 78% yield (Scheme 34).



Scheme 34. Synthesis of substrate **141**.

III.1.2. Catalytic tests

With these products in hand, we started the first catalytic testing. Reactions were carried out with 5 mol% of the copper catalyst $CuF(PPh_3)_3.2MeOH$ **25** in THF at room temperature and with 1.2

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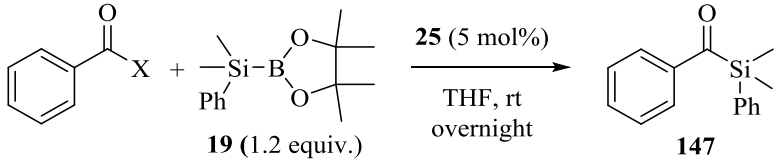
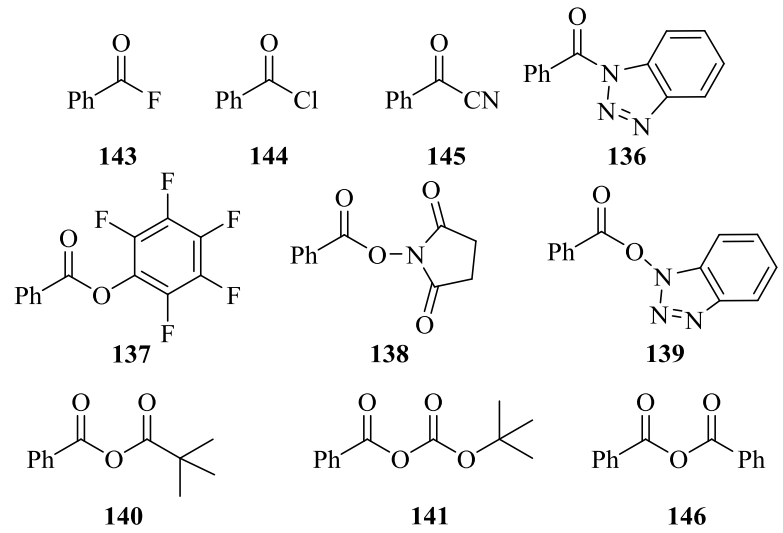
[6] (a) Ouchi, H.; Saito, Y.; Yamamoto, Y.; Takahata, H., *Org. Lett.* **2002**, *4*, 585-587. (b) Saito, Y.; Ouchi, H.; Takahata, H., *Tetrahedron* **2006**, *62*, 11599-11607.

equivalents of silylborane **19**. The results are reported in table 1. Yields were estimated by ^{1}H NMR on the crude reaction mixture with hexamethylbenzene as internal standard after 1 night of reaction.

Table 1. Screening of various acid derivatives.





Entry	Acid derivatives	Yield (%)[a]
1	**143**	5
2	**144**	5
3	**145**	0
4	**136**	0
5	**137**	6

6	**138**	1
7	**139**	1
8	**140**	11
9	**141**	27
10	**146**	**30**

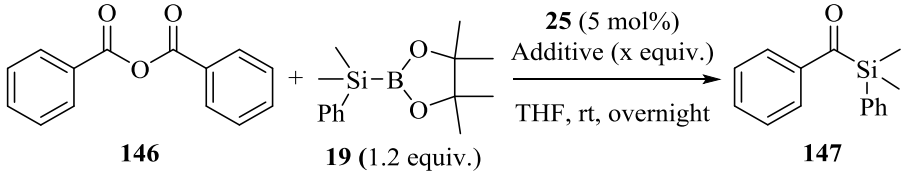
[a] Yield was determined by ^{1}H NMR using hexamethylbenzene as internal standard.

Acyl fluoride **143** and acyl chloride **144** gave only traces (about 5% by ^{1}H NMR) of the desired product **147** (Table 1, entries 1 and 2). Substrate **145** did not allow to improve this result (Table 1, entry 3). Other commonly known activated acid derivatives **136-139** gave similar results (Table 1, entries 4-7). The best yields were obtained using benzoic anhydride **146** and the mixed anhydride **141** which gave respectively the desired acylsilane **147** in 30% and 27% yield (Table 1, entries 10 and 9). Surprisingly, unsymmetrical anhydride **140** gave a lower yield (Table 1, entry 8). These results prompted us to start an optimization of the reaction conditions with benzoic anhydride **146** especially as this substrate is commercially available and not expensive.

III.2. Optimization with benzoic anhydride

To establish suitable reaction conditions, we decided first to improve the yield by addition of an activating agent. A screening of various additives was therefore performed and the results are reported in table 2. These experiments were carried out using anhydride **146** as model substrate and **19** as pronucleophile with catalyst **25** in THF at room temperature.

Table 2. Screening of various additives.



Entry	Additives (x equiv.)	Yield (%)[a]
1	-	30
2	(*rac*)-BINAP (0.2)	26
3	MeOH (1)	8
4	MeOH (4)	0
5	^{t}BuOK (1)	2
6	CsF (1)	52
7	**TBAT (1)**	**54**

[a] Yield was determined by ^{1}H NMR using hexamethylbenzene as internal standard.

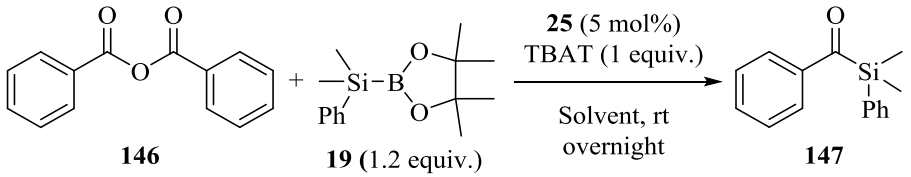
These results showed that the use of a diphosphine ligand, (*rac*)-BINAP, to stabilize the copper catalyst did not improve the yield (Table 2, entry 2). The desired product was obtained with 26% yield compared to 30% yield without ligand (Table 2, entry 1). We thought that addition of an alcohol could regenerate the active species to continue the catalytic cycle as shown previously in the introduction. However, addition of methanol or potassium *tert*-butoxide had a negative effect on this reaction (Table 2, entries 3-5). The reaction between the alcohol and the anhydride might be much faster than the desired transformation rendering our substrate totally inactive. Interestingly, addition of a fluoride source proved to be

much more rewarding. Indeed, acylsilane was obtained in 54% yield with addition of 1 equivalent of tetrabutylammonium triphenyldifluorosilicate (TBAT) (Table 2, entry 7). We obtained almost the same result when we used cesium fluoride as activating agent (Table 2, entry 6). Nevertheless, the latter was difficult to handle and very moisture sensitive. An optimization of the reaction conditions were then carried out with our model substrate, benzoic anhydride, and TBAT as additive.

III.2.1. Solvent and temperature

Various solvents were tested in the reaction and the results are reported in table 3. These experiments were carried out using anhydride **146** and **19** as pronucleophile with catalyst **25** and 1 equivalent of TBAT at room temperature. It is noteworthy to mention that the starting materials are soluble in all solvents.

Table 3. Screening of various solvents.



146 **19** (1.2 equiv.) **147**

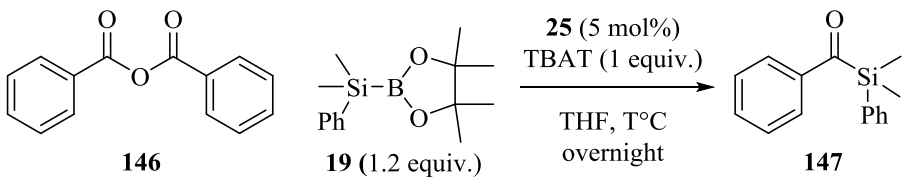
Entry	Solvent	Yield (%)[a]
1	THF	50
2	Et_2O	67
3	MeCN	27
4	**Toluene**	**70**
5	Hexane	72

6	DCM	50
7	DMF	43
8	DMSO	14

[a] Yield was determined by ^{1}H NMR using hexamethylbenzene as internal standard.

Variation of the solvent was accompanied by significant variations on the yield of the desired product. As seen in table 3, the use of polar solvents such as acetonitrile, dimethylformamide and dimethylsulfoxide (entries 3, 7 and 8) led to a decrease in the yield. However, Et_2O, hexane and toluene improved considerably the yield of the reaction (entries 2, 4 and 5). It should be noted that although hexane gave the best yield, this solvent is very toxic and its low polarity might cause solubility problems with some substrates. Therefore it was not chosen. Then, several reaction temperatures were screened as reported in table 4. Optimization of the temperature revealed that there was no significant variation of the yield when a lower temperature was used (entries 1 and 2). When the reaction was running at 40°C, the yield was similar to the previous one (entry 5). Nevertheless, when an even higher temperature was used a decrease in the yield was observed (entry 6).

Table 4. Optimization of reaction temperature.



146 **19** (1.2 equiv.) **147**

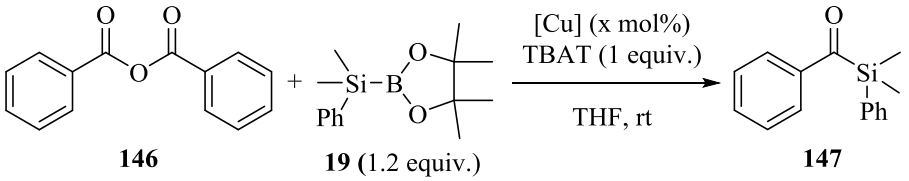
Entry	T (°C)	Yield (%)[a]
1	0	48
2	20	49
3	**25**	**54**
4	30	52
5	40	50
6	65	24

[a] Yield was determined by ^{1}H NMR using hexamethylbenzene as internal standard.

III.2.2. Influence of the copper source

Furthemore, we wanted to check if the copper source could have an effect on the reaction yield.

Table 5. Effect of the copper source on the reaction.

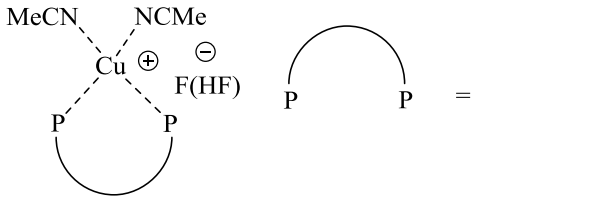


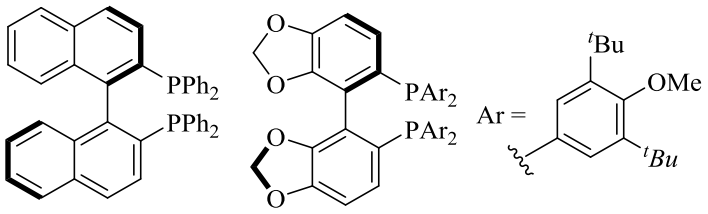
146 **19** (1.2 equiv.) **147**

Entry	[Cu]	(x mol%)	Yield (%)[a]
1	$CuF(PPh_3)_3.2MeOH$ **25**	5	50
2	**$CuF(PPh_3)_3.2MeOH$ 25**	**2**	**57**
3	$CuF(PPh_3)_3.2MeOH$ **25**	1	43
4	Cu^+(*rac*)-BINAP HF_2^- **81'**	2	52

5	Cu^{+}*(R)*-DTBM-Segphos HF_2^- **84**	2	9
6	IMesCuCl	2	46

[a] Yield was determined by ^1H NMR using hexamethylbenzene as internal standard.





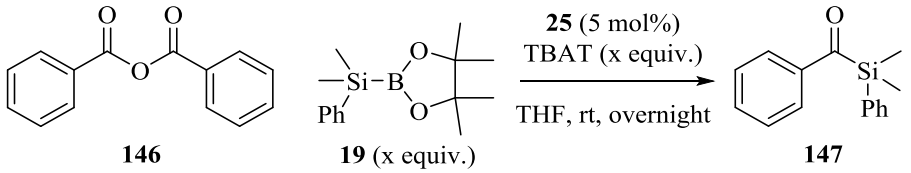
(*rac*)-BINAP, **81'** *(R)*-DTBM-Segphos, **84**

Interestingly, when we used 2 mol% of copper catalyst **25** instead of 5 mol%, an increase of the yield was observed. This was probably due to the presence of methanol in this catalyst. As shown in table 2, the use of methanol led to a degradation of the product. We thought that it was also interesting to test the new cationic copper(I) complexes developed in our group (see Chapter 1, point III.2.3.). No change was detected in the case of complex **81'** indicating that our complexes are active in catalysis. However, we only obtained 9% yield when we used complex **84**. This is probably due to the increased steric hindrance of this ligand compared to BINAP. Finally, the use of a copper diaminocarbene complex did not improve the yield of the acylsilane.

III.2.3. Other parameters

Optimization of various parameters is reported in table 6. First, we thought that it was interesting to decrease the amount of the additive because TBAT is quite expensive. Unfortunately, we showed after several trials that 1 equivalent of TBAT is necessary to obtain the desired product. When we carried out the reaction with 0.5 or 0.2 equivalents, a decrease in the yield was detected (Table 6, entries 2 and 3). The concentration seemed important too. As seen in entry 4, a higher concentration had a negative effect on this reaction. We also found that a slow addition of silylborane **19** played a significant role in the reaction. Indeed, addition of **19** over 10 minutes allowed to increase the yield up to 68% (Table 6, entry 6). In a last series of experiments, we showed that increasing the amount of **19** to 1.5 equivalents gave better yields (Table 6, entry 8).

Table 6. Influence of various parameters.



146 **19** (x equiv.) **147**

Entry	TBAT (x equiv.)	"B-Si" (x equiv.)	Yield (%)[a]
1	1	1.2[b]	50
2	0.5	1.2	37

3	0.2	1.2	21
4	1	1.2[c]	36
5	1	1.2[d]	48
6	**1**	**1.2[e]**	**68**
7	1	1.2[f]	54
8	**1**	**1.5[b]**	**59**

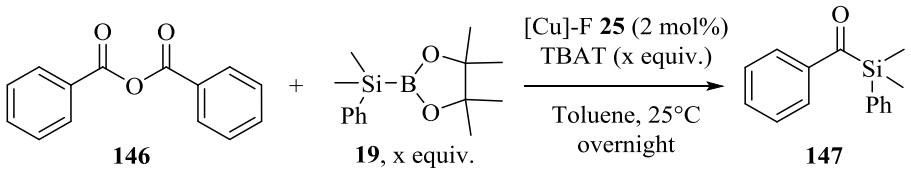
[a] Yield was determined by ^{1}H NMR using hexamethylbenzene as internal standard. [b] C=0.125 M and **19** was added dropwise. [c] C=0.25 M. [d] C=0.0625M. [e] Slow addition of **19** (over 10 min). [f] Fast addition of **19**.

After these interesting results, we decided to carry out the reaction with our best conditions found during our optimization and the results are reported in table 7. We found that in these optimal conditions, the desired acylsilane was obtained with 81% isolated yield (Table 7, entry 1). It should be noticed that it is necessary to add silylborane **19** slowly over 10 minutes and after all the other reagents to obtain a complete conversion. On the other part, increasing the amount of TBAT or silylborane did not change the outcome (entries 2 and 3). Moreover, the reaction was complete after 6 hours instead of overnight as seen in entry 4. Finally, the use of strictly dry toluene[7] gave the acylsilane **147** in 93% isolated yield (entry 5). Our hypothesis was that the reaction is very sensitive to water. Indeed, the presence of a small quantity of water in our solvent explained the difference between entries 1 and 5. Therefore,

[7] Bottle of anhydrous toluene 99.8% with molecular sieves was purchased from Sigma-Aldrich.

further experiments were performed with the same bottle of commercially available dry toluene to avoid solvent reproducibility problems. It should also be noted that a good reproducibility was obtained when freshly prepared silylborane **19** was used.[8]

Table 7. Final optimization.

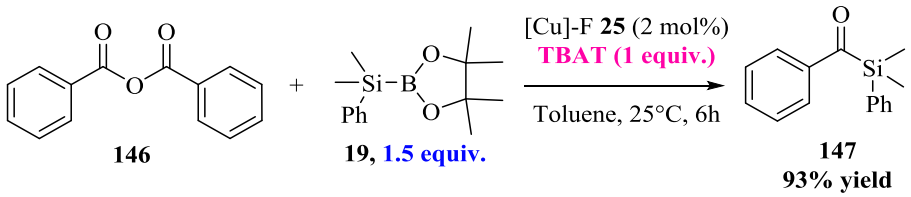


Entry	TBAT (x equiv.)	"B-Si" (x equiv.)	Yield (%)[a]
1	1	1.5	81[b]
2	1.3	1.5	78
3	1	1.8	65
4	1	1.5	83[b,c]
5	**1**	**1.5**	**93**[b,d]

[a] Yield was determined by ^{1}H NMR using hexamethylbenzene as internal standard. [b] Isolated yield. [c] Stop the reaction after 6 hours. [d] Use of strictly dry toluene.

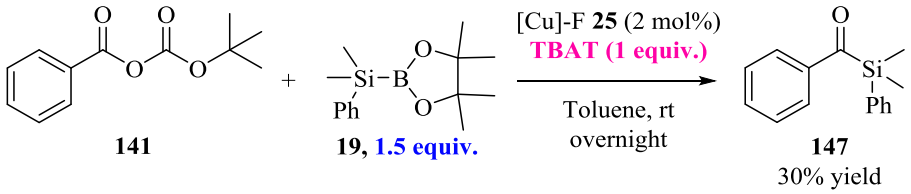
[8] If we use silylborane which has been synthesized for more than 1 month, we observe a decrease of the yield due to the transformation of the silylborane to his corresponding oxide.

After these results, we can conclude that running the reaction with benzoic anhydride, 1.5 equivalents of silylborane **19** in the presence of 1 equivalent of TBAT, 2 mol% of copper catalyst **25** in strictly dry toluene at 25°C for 6 hours are the optimal conditions (Scheme 35). It is noteworthy to mention here that the reaction does not work without copper catalyst indicating that the metal is necessary to obtain the desired product.



Scheme 35. Best conditions to afford acylsilanes in one step.

Several tests were also performed on substrate **141** using our previously optimized conditions. This substrate is much more interesting first in term of atom economy mostly in the case of further exemplification of this reaction with complex substrates. Secondly, the synthesis of this coumpound is very easy. Unfortunately, yields obtained did not exceed 30% (Scheme 36).



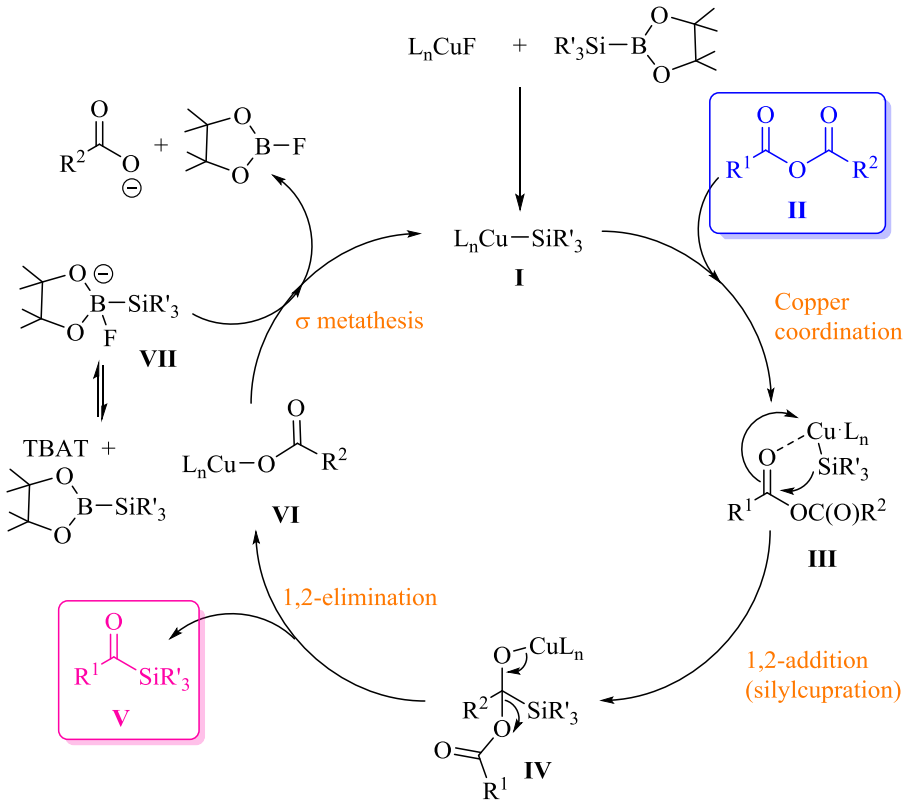
Scheme 36. Best conditions with substrate **141.**

We were intrigued by this result because we do not understand why the reaction works well with symmetric anhydrides and does not work as

well with mixed anhydrides. Therefore, we thought that it was interesting to investigate the mechanism of this reaction.

III.3. Proposed Mechanism

After the development of a new strategy to synthesize acylsilanes in one step, we were interested in postulating a mechanism. We propose a catalytic cycle in scheme 37. It starts with the formation of the active species Cu-Si (**I**) by activation of the silylborane with the copper fluoride complex as previously described in chapter 1 and general introduction. Coordination of **I** to **II** followed by the 1,2-addition allows the formation of intermediate **IV**. Elimination of the leaving group gives the desired acylsilane **V** and Cu-O carboxylate species **VI**. The role of the fluoride is most likely to activate the silylborane by coordination to the boron atom to form the active intermediate **VII** which will facilitate the transfer of the silyl group onto the copper atom by reaction with **VI,** and thus regenerate the active species **I**.



Scheme 37. Postulated mechanism.

This hypothesis could be supported by the results obtained by Dr. Thomas Vergote during his thesis.[9] Indeed mechanism of the copper hydride catalyzed ketone hydrosilylation was studied through kinetic investigations and DFT calculations on realistic systems. They showed

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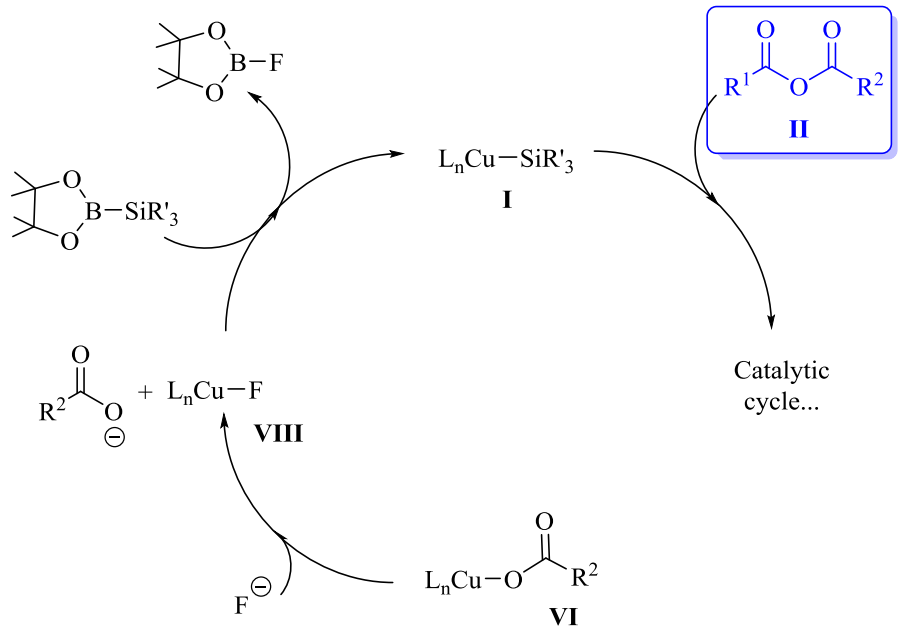
[9] (a) Vergote, T.; Nahra, F.; Merschaert, A.; Riant, O.; Peeters, D.; Leyssens, T., *Organometallics* **2014**, *33*, 1953-1963. (b) Vergote, T ; *Mechanistic study of catalytic copper-diaminocarbene (NHC) systems through computational ab initio, as well as experimental chemical studies*, Université catholique de Louvain, Louvain-la-Neuve, **2014**.

that when a Lewis base (OR^- or F^-) is present in the reaction, a modified mechanistic scheme had to be taken into account. This base intervenes actively in the catalytic cycle, rendering the first step rate limiting, whereas the two steps are governed by similar rate constants in its absence. This change in behavior is due to an activation of the silane reactant. Nevertheless, another hypothesis for the role of the fluoride in this reaction could be the regeneration of the active species **I** by the formation of intermediate **VIII.** This species is maybe more reactive than **VI** for the transmetalation (Scheme 38). This is supported by the work of Amatore and co-workers.[10]



Scheme 38. Another hypothesis for the role of the TBAT.

[10] (a) Amatore, C.; Grimaud, L.; Le Duc, G.; Jutand, A., *Angew. Chem. Int. Ed.* **2014**, *53*, 6982-6985. (b) Amatore, C.; Le Duc, G.; Jutand, A., *Chem. Eur. J.* **2013**, *19*, 10082-10093.

But how can we explain why the reaction is less efficient when we used another substrate? The nature of the R^2 group in intermediate **VI** may play a significant role. When we used mixed anhydride, we expected a decarboxylation of the species **VI** to yield tert-butanolate copper species. Maybe the decarboxylation did not work or if it did, when R^2 is a methoxy or an O^{t}Bu group, the copper complex was not reactive enough to transmetallate. Regeneration of the active species (even in the presence of fluoride anion) is therefore difficult and the direct acylation of this copper species to the acid derivative is faster. This hypothesis could also explain why the addition of methanol or potassium *tert*-butoxide has a negative effect on this reaction. It is not impossible also that both sides of the symmetric anhydride are involved in the formation of the acylsilane. This would explain the poor yield obtained with substrate **141**.

III.4. Copper-catalyzed 1,2-addition of silicon nucleophiles to anhydrides: examplification

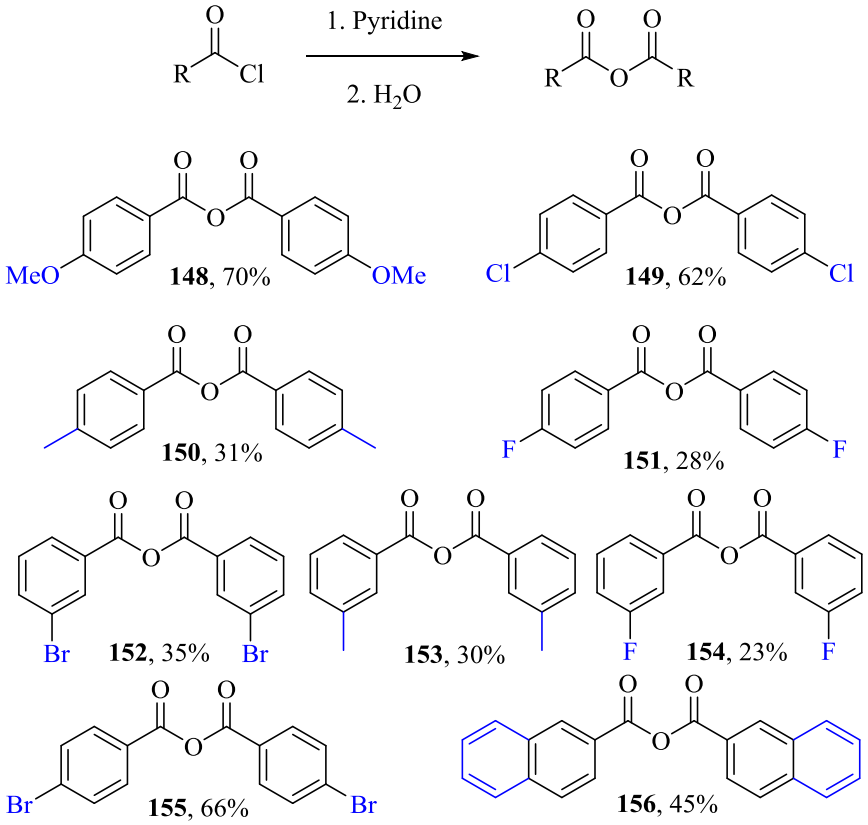
With the new optimal conditions in hand, it was then possible to study the scope of this reaction.

III.4.1. Synthesis of substrates

First of all, the desired anhydrides have been prepared using a procedure from the literature.[11] Reaction between the corresponding acyl chlorides and pyridine followed by addition of water afforded the desired

[11] Dhimitruka, I.; SantaLucia, J., *Org. Lett.* **2006**, *8*, 47-50.

symmetric anhydrides with moderate to good yields after recrystallization (Scheme 39).

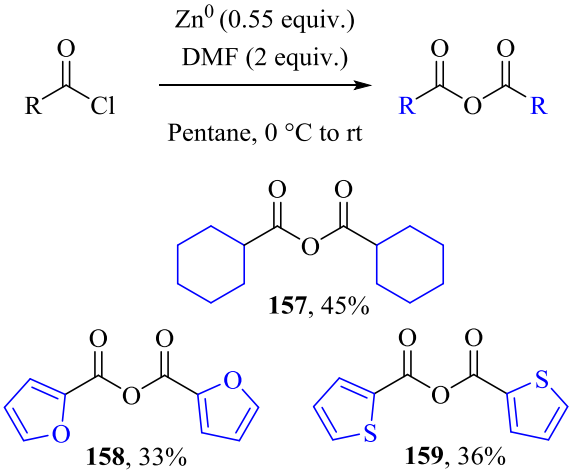


Scheme 39. Synthesis of substrates **148-156.**

Unfortunately, we were not able to obtain aliphatic anhydrides with this strategy. Therefore, another method described in the literature was used.[12] Symmetrical carboxylic anhydrides were synthesized from the corresponding acid chlorides mediated by zinc dust in the presence of

[12] Serieys, A.; Botuha, C.; Chemla, F.; Ferreira, F.; Pérez-Luna, A., *Tet. Lett.* **2008**, *49*, 5322-5323.

dimethylformamide. A mechanism involving the reductive insertion of zinc(0) into the C–Cl bond of a Vilsmeier-type iminium intermediate as the crucial step was proposed by the authors. The desired products **157-159** were obtained with moderate yields after purification (Scheme 40).

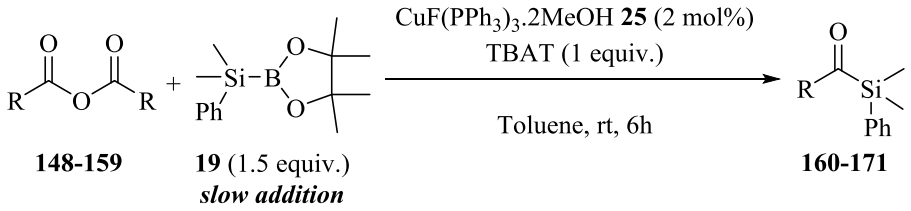


Scheme 40. Synthesis of substrates **157-159.**

III.4.2. Catalytic tests

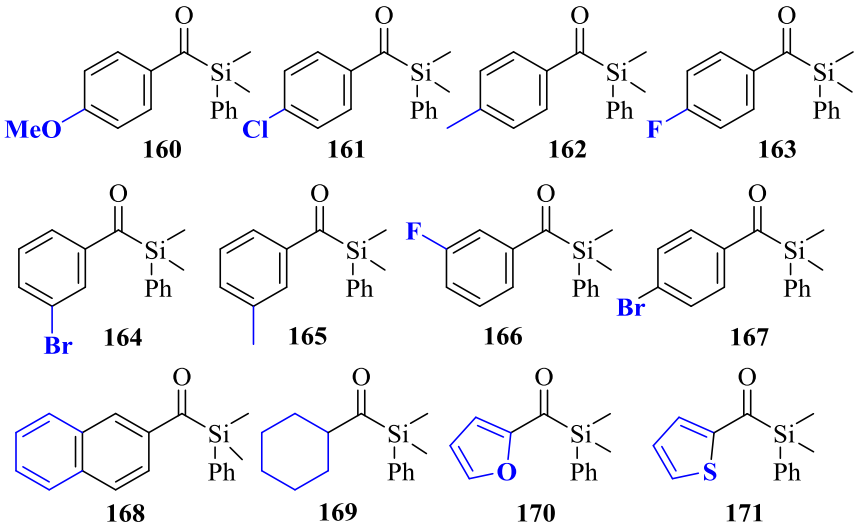
Our methodology was then applied to these substrates and results are shown in table 8. Under the previously optimized conditions, the reaction gave satisfactory results for all types of substituents. The reaction tolerated quite well both electron-deficient (Table 8, entries 2, 4, 5, 7 and 8) and electron-rich (Table 8, entries 3 and 6) aromatic systems. Nevertheless, we observed a lower reactivity for anhydride with a methoxy substituent (Table 8, entry 1).

Table 8. Exemplification.



Entry	Anhydrides	Product	Yield (%)[a]
1	**148**	**160**	52
2	**149**	**161**	76
3	**150**	**162**	98
4	**151**	**163**	89
5	**152**	**164**	67
6	**153**	**165**	>99
7	**154**	**166**	85
8	**155**	**167**	82
9	**156**	**168**	68
10	**157**	**169**	82
11	**158**	**170**	47
12	**159**	**171**	46

[a] Isolated yield.

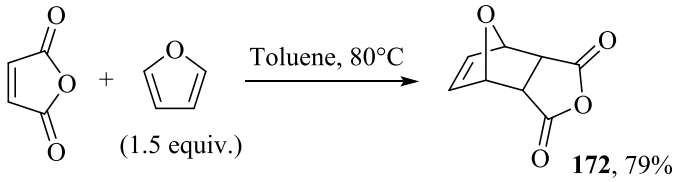


This could be explained by the electron rich substituent that might reduce the electrophilic character of the anhydride. Interestingly, the *para*- or *meta*- position of the substituent did not influence the desired reactivity. Satisfyingly, the substrate bearing aliphatic substituents afforded the corresponding acylsilane in high yield (Table 8, entry 10). However, the reaction was less efficient with electron rich heteroaromatic rings such as furane and thiophene (Table 8, entries 11 and 12). The system seemed to be less reactive with electron rich aromating rings as observed earlier in the case of substrate **148**. Despite this consideration, most studied substrates afforded the desired acylsilanes in excellent yields after purification.

III.4.3. Reaction's limitations

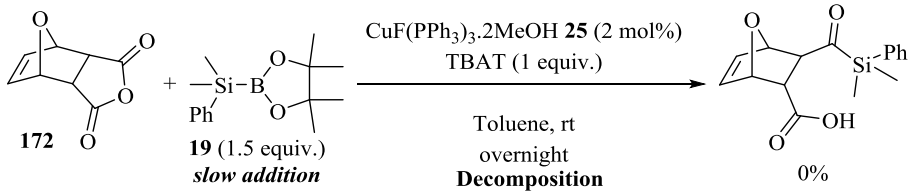
Even though we were very happy with the above results, additional attempts were made to extend this methodology to other substrates, most notably cyclic anhydrides.

Substrate **172** was thus synthesized in one step starting from commercially available maleic anhydride and furan following a procedure from the literature (Scheme 41).[13] These reagents reacted *via* a Diels-Alder reaction to form the desired bicyclic adduct **172** in 79% yield.



Scheme 41. Synthesis of substrate **172.**

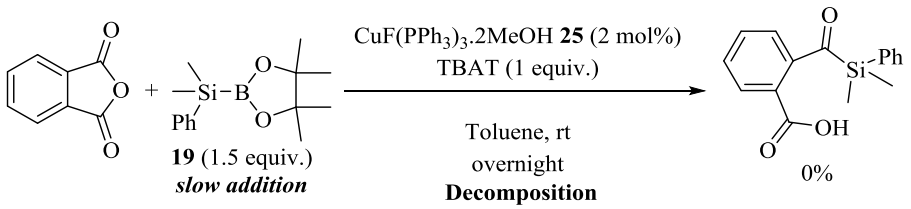
This compound was subsequently engaged in our reaction conditions (Scheme 42). Unfortunately, no reaction occurred and only decomposition of the starting material was observed each time. We suspected that the main problem came from the carboxylic acid generated during the transformation. Consequently, we decided to quench the reaction *in situ* with a methylating agent such as $TMSCHN_2$ to afford directly the ester. But again no desired product was detected.



Scheme 42. Catalytic tests on substrate **172.**

[13] Daskalaki, E.; Le Droumaguet, B.; Gerard, D.; Velonia, K., *Chem. Comm.* **2012**, *48*, 1586-1588.

At the same time, we attempted to apply our methodology onto phtalic anhydride which was commercially available. As seen in scheme 43, no desired transformation occurred with this substrate. Phtalic anhydride failed to generate any identifiable product and only decomposition of the starting material was observed.

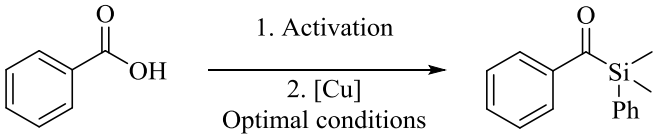


Scheme 43. Catalytic tests on phtalic anhydride.

Several tests were also performed using disilanes instead of silylborane **19**. Our optimal conditions were employed. Unfortunately, no desired acylsilane was observed. The low reactivity of these pronucleophiles was certainly the problem in this case as discussed in the general introduction and chapter 1.

III.5. Development of a "one-pot" procedure

Finally we decided to carry out preliminary tests that might lead to the development of a "one-pot" procedure of the aforementioned reaction starting directly from the corresponding acid (Scheme 44). This strategy requires the activation of the carboxylic acid before applying our previously optimized methodology.

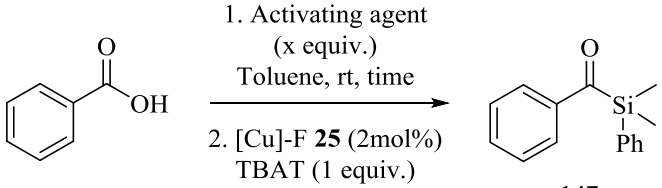


147

Scheme 44. Development of a « one-pot » procedure.

We therefore started an optimization of various reaction conditions. First, we tried to find the best activating agent to form *in situ* an activated acid which would be able to react in our catalytic process. The results are reported in table 9.

Table 9. Screening of various coupling agents.



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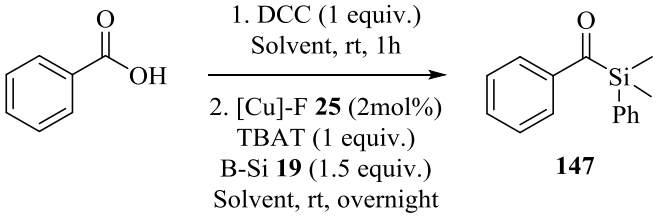
Entry	Coupling agent (x equiv.)	Time (min)	Yield (%)[a]
1	DCC (1)	60	32
2	DIC (1)	60	27
3	EDC (1)	60	0
4	PPh_3 (1) + NBS (1.2)	30	0

[a] Yield was determined by ^1H NMR using hexamethylbenzene as internal standard.

Several known coupling agents were employed and the best result was obtained with dicyclohexylcarbodiimide (DCC). The desired acylsilane was afforded in 32% yield (Table 9, entry 1). A slight decrease in yield was observed when we used DIC (Table 9, entry 2). However, activation by EDC or triphenylphosphine did not afford the desired adduct (Table 9, entries 3-5). DCC as coupling agent was therefore chosen to continue the optimization.

Various solvents were then engaged in our reaction. We were quite disappointed by the results obtained when DCM or THF were used as solvent (Table 10, entries 2 and 3). More surprisingly, a good yield of 49% was detected with diethylether (Table 10, entry 4). The use of hexane or *tert*-butylmethylether gave the same result as toluene. Finally, no satisfactory result was obtained when the reaction was carried out in acetonitrile (Table 10, entries 5-7).

Table 10. Optimization of the solvent.



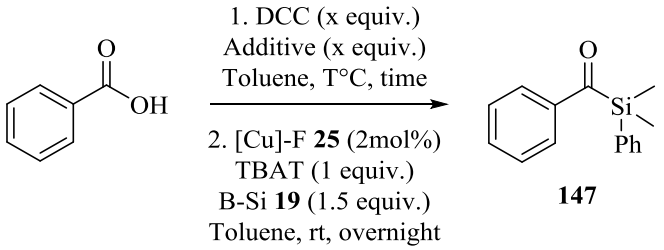
147

Entry	Solvent	Yield (%)[a]
1	Toluene	32
2	THF	4
3	DCM	8
4	**Et_2O**	**49**
5	Hexane	30
6	TBME	28
7	MeCN	11

[a] Yield was determined by ^1H NMR using hexamethylbenzene as internal standard.

Several other experiments showed that an activation of the acid during 1 hour was necessary (Table 11, entries 1-4). We also found that the reaction temperature was important. A better yield of 38% was obtained when the first step of the reaction was carried out at 0°C instead of room temperature (Table 11, entry 5). The addition of an additive such as DMAP did not improve the yield of the transformation. However, a variation of the amount of the coupling agent influenced the outcome of the reaction (Table 11, entries 7 and 8). Indeed, the desired acylsilane was obtained in 36% yield with 1.2 equivalents of DCC.

Table 11. Optimization of various parameters.



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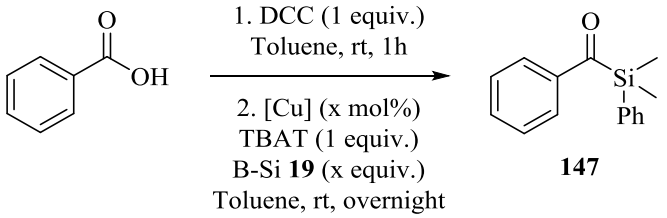
Entry	Additive (x equiv.)	T (°C)	DCC (x equiv.)	Time (min)	Yield (%)[a]
1	-	rt	1	30	17
2	-	rt	1	60	32
3	-	rt	1	90	25
4	-	rt	1	240	24
5	**-**	**0**	**1**	**60**	**38**
6	DMAP (1)	rt	1	60	22
7	-	rt	0.2	60	5
8	**-**	**rt**	**1.2**	**60**	**36**

[a] Yield was determined by ^{1}H NMR using hexamethylbenzene as internal standard.

We thought that it might be interesting to see the effect of the copper source on this "one-pot" process. As reported earlier, a decrease of the yield was observed when we used a larger amount of catalyst **25** due to the presence of methanol (Table 12, entries 1-3). Increasing the amount of silylborane did not affect the reaction. (Table 12, entry 4). Finally, the

use of copper-NHC complexes did not improve the yield as well (Table 12, entries 5-7).

Table 12. Optimization of copper source and silylborane.



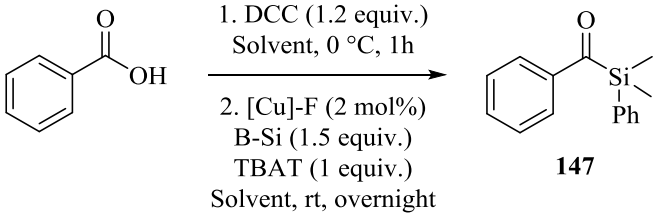
Entry	Copper source (x mol%)	B-Si (x equiv.)	Yield (%)[a]
1	[Cu]-F 25 (2)	1.5	32
2	[Cu]-F **25** (5)	1.5	30
3	[Cu]-F **25** (20)	1.5	18
4	[Cu]-F **25** (2)	2	29
5	IMesCuCl (2)	1.5	30
6	IMesCuCl (20)	1.5	24
7	IMesCuDBM (2)	1.5	29

[a] Yield was determined by ^{1}H NMR using hexamethylbenzene as internal standard.

We therefore decided to test our optimal conditions. Reaction was carried out with 1.2 equivalents of DCC in Et_2O at 0°C during one hour followed by the optimal conditions previously described. We were quite

surprised to obtain only 18% yield with these conditions (Table 13, entry 1). After several trials, we were not able to improve this result. Lack of reproducibility due to the purity of diethylether seemed to be the problem. We thus decided to move to the use of toluene with the previously described conditions. To our delight, the desired acylsilane was isolated in 51% yield under these conditions (Table 13, entry 2).

Table 13. Final optimization.



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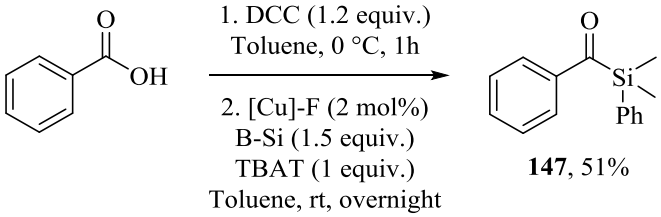
Entry	Solvent	Yield (%)[a]
1	Et_2O	18
2	**Toluene**	**51**

[a] Yield was determined by ^1H NMR using hexamethylbenzene as internal standard.

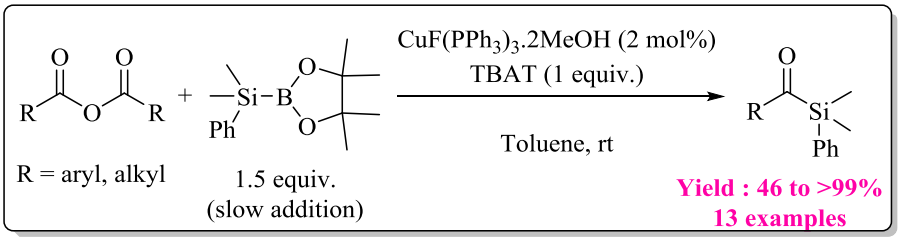
After this optimization, we found that activation of the carboxylic acid with dicyclohexylcarbodiimide in toluene at 0°C for 1 hour gave the best result. The intermediate was directly engaged in the second reaction and we obtained the desired product in 51% yield after purification. This result is very interesting as it provides an easy access to acylsilanes directly from carboxylic acids under mild conditions.



Scheme 45. Develoment of a "one-pot" procedure.

IV. Conclusions and Perspectives

In conclusion, we have developed a new strategy for the synthesis of acylsilanes by using symmetric carboxylic anhydrides that can be accessed from commercially available acyl chlorides. Good to excellent yields were obtained with various substrates. Concerning aromatic substrates, both electron-withdrawing groups as well as electron-donating groups are well tolerated. To our delight, aliphatic groups were also tolerated. This mild and practical methodology does not require strongly basic precursors.[1] However, the use of an activating agent, TBAT, is necessary to obtain complete conversion of the starting material.



Scheme 46. One-step synthesis of various acylsilanes.

Moreover, we also started to develop a "one-pot" reaction procedure which allowed us to access acylsilanes directly from commercially available carboxylic acids. So far, a moderate yield of 51% was obtained. However, it is noteworthy to mention that the major drawback of this procedure was the impossibility to apply this strategy as an industrial process (lack of atom economy).

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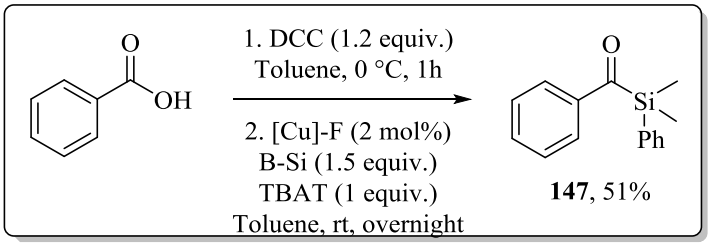
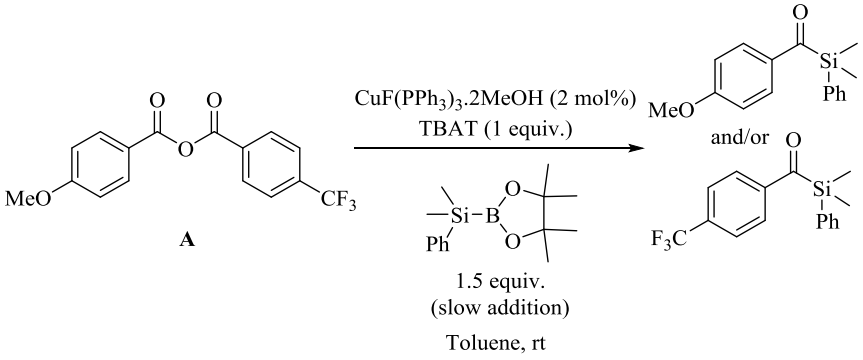
[1] Cirriez, V.; Rasson, C.; Riant, O., *Adv. Synth. Catal.* **2013**, *355*, 3137-3140.



Scheme 47. « One-pot » procedure.

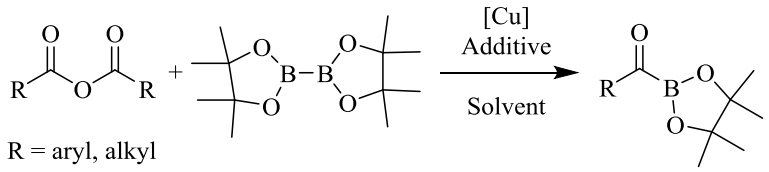
In the future, we are interested in better understanding the mechanism of this reaction. Additional experiments could be envisaged to confirm or deny our hypothesis. For example, it will be interesting to carry out the reaction with only 0.5 equivalents of benzoic anhydride. If the yield is over 50%, we could say that the two parts of the symmetric anhydride are involved in the mechanism. Reaction of a compound such as **A** in our best conditions could also provide valuable informations on the mechanism of this process (Scheme 48).



Scheme 48. Additional experiments.

This would help us develop a more efficient strategy for the synthesis of these compounds. The use of more complex substrates can thus be

envisaged as well as the promotion of this adduct in various reactions.[2] Further development of the "one-pot" procedure is also ongoing. Finally, an interesting perspective would be the application of our methodology to synthesize acylboranes. Indeed, only a few groups are interested in the synthesis of this family of compounds because they are currently considered as esoteric compounds that are difficult to prepare. Moreover the lack of acess has impeded a thorough investigation of their chemistry.[3] Therefore, the development of a practical method starting from easy-to-form anhydrides might be an interesting idea (Scheme 49).



Scheme 49. Synthesis of acylboranes.

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[2] For example: Dumas, A. M.; Molander, G. A.; Bode, J. W., *Angew. Chem. Int. Ed.* **2012**, *51*, 5683-5686.

[3] (a) Erős, G.; Kushida, Y.; Bode, J. W., *Angew. Chem. Int. Ed.* **2014**, *53*, 7604-7607. (b) Dumas, A. M.; Bode, J. W., *Org. Lett.* **2012**, *14*, 2138-2141.

Chapter 3: Synthesis of α-hydroxysilanes

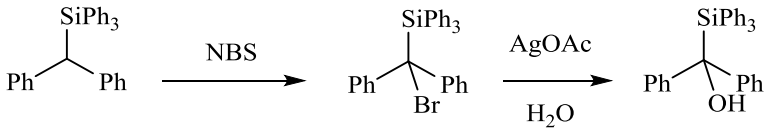
I. Bibliographic Introduction

α-hydroxysilanes ($RC(OH)R''SiR'_3$) are compounds for which a silane fragment is directly attached to the α–carbon of a hydroxyl group. As acylsilanes, they are building blocks of great interest in organic chemistry. This type of C-Si bond formation as well as the hydroxyl group are of crucial importance in organic synthesis. In addition, a stereogenic centre is formed in this process generating possible opportunities for asymmetric catalysis. Moreover, optically active α-hydroxysilanes are regarded as a class of chiral organometallic compounds containing a functional group. These molecules and their derivatives have been used for stereocontrolled C-C bond formation and rearrangements, which result in a wide variety of chiral organic compounds. As their oxidized homologues, α-hydroxysilanes have different spectral properties. It is also important to notice that degradation of those compounds bearing a trimethylsilylgroup occurs rapidly in acidic conditions. In this introduction, we are going to present first the literature-known methods for the preparation of this kind of compounds and then we will develop their different applications in organic synthesis.

I.1. Literature: synthesis of α-hydroxysilanes

The first synthesis of α-hydroxysilanes was reported by Brook in 1958.[1] The use of benzhydryltriphenylsilane with NBS afforded α-bromobenzhydryltriphenylsilane which was then treated with aqueous silver acetate. The desired product was obtained in high yield (Scheme 1).

[1] Brook, A. G., *J. Am. Chem. Soc.* **1958**, *80*, 1886-1889.

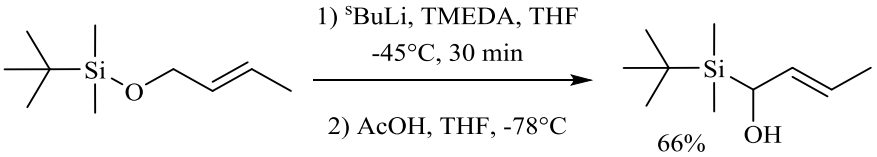


Scheme 1. First synthesis of α-hydroxysilane.

As mentioned earlier, a stereogenic centre is formed in this process and although we are interested in asymmetric synthesis of these compounds, we are going to describe first the non-asymmetric methods.

I.1.1. Non-asymmetric synthesis of α-hydroxysilanes

As described in chapter 2, the Brook rearrangement is a reversible process and some groups decided to use this unique property for the preparation of α-hydroxysilanes. For example, Ireland and co-workers described the synthesis of α-hydroxysilanes starting from silyl ethers.[2] Indeed the retro-Brook rearrangement of *tert*-butyldimethylsilyl crotyl ether under the conditions of Still[3] afforded racemic α-silyl alcohol in 66% yield (Scheme 2).



Scheme 2. Synthesis of α-hydroxysilanes starting from silyl ethers.

The same strategy was later applied starting directly from the corresponding alcohol (Scheme 3). The goal is to carry out the synthesis in a "one-pot" process to improve the yield. Ohfune and co-workers

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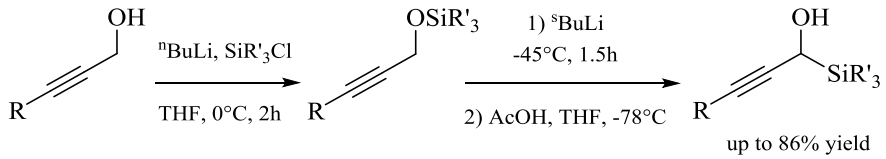
[2] Ireland, R. E.; Varney, M. D., *J. Am. Chem. Soc.* **1984,** *106*, 3668-3670.

[3] Still, W. C.; Macdonald, T. L., *J. Am. Chem. Soc.* **1974**, *96*, 5561-5563.

reported the synthesis of racemic α-hydroxysilanes in good yields starting from propargylic alcohols.[4] They obtained up to 86% yield after two steps.



Scheme 3. Synthesis of α-hydroxysilanes starting from alcohols.

An alternative approach is the addition of a silicon nucleophile to a carbonyl compound.[5] In 1983, Hiyama and co-workers introduced a fluoride-catalyzed Si-Si bond cleavage followed by the addition of the nucleophilic silicon *in situ* to aldehydes.[6] However, yields were partially diminished by [1,2]-Brook rearrangement. Indeed, with aromatic aldehydes and ketones, the initial adduct rapidly rearranges and silyl ethers are isolated. Barrett and Hill elaborated a practical procedure based on the addition of easy-to-form $Me_2PhSiLi$ to aliphatic and

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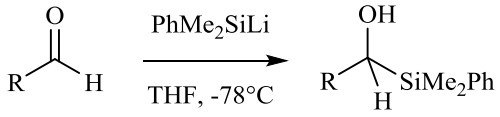
[4] (a) Sakaguchi, K.; Fujita, M.; Suzuki, H.; Higashino, M.; Ohfune, Y., *Tet. Lett.* **2000**, *41*, 6589-6592. (b) Sakaguchi, K.; Higashino, M.; Ohfune, Y., *Tetrahedron* **2003**, *59*, 6647-6658.

[5] (a) Chénedé, A.; Abd.Rahman, N.; Fleming, I., *Tet. Lett.* **1997**, *38*, 2381-2382 ($Me_2PhSiLi$). (b) Chang, C.-C.; Kuo, Y.-H.; Tsai, Y.-M., *Tet. Lett.* **2009**, *50*, 3805-3808 [$(Me_2PhSi)_2CuLi$]. (c) Paredes, M. D.; Alonso, R., *J. Org. Chem.* **2000**, *65,* 2292-2304 ($Me_2PhSiLi$). (d) For an usual 1,2-addition using a tantalum reagent, see: Arnold, J.; Tilley, T. D., *J. Am. Chem. Soc.* **1987**, *109*, 3318-3322.

[6] Hiyama, T.; Obayashi, M.; Mori, I.; Nozaki, H., *J. Org. Chem.* **1983**, *48*, 912-914.

aromatic aldehydes (Scheme 4).[7] Neither α-deprotonation (high chemoselectivity for enolizable aldehydes) nor Brook rearrangement were competing with the 1,2-addition.



Scheme 4. 1,2-addition of silyl anions.

However, the use of such strongly basic nucleophiles is not without problems for functionalized aldehydes. Recently, Oestreich and co-workers described a racemic 1,2-addition of a silicon nucleophile to imines and aldehydes and proposed a mechanism involving a Cu-Si intermediate as the silyl transfer species.[8] They reported two independent protocols. They first turned toward the elaboration of a general procedure employing a well-defined (IPr)-CuO^{t}Bu complex as a catalyst precursor (Scheme 5). 5.5 mol% of this catalyst in toluene at 60°C were found to be the optimal conditions. This reaction was applied to various aromatic and aliphatic aldehydes and the desired products were obtained in good yields.

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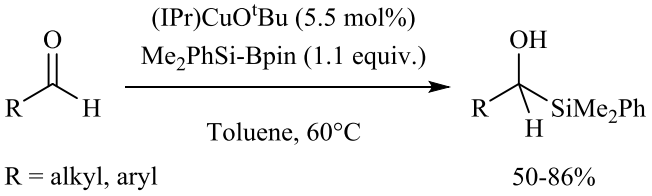
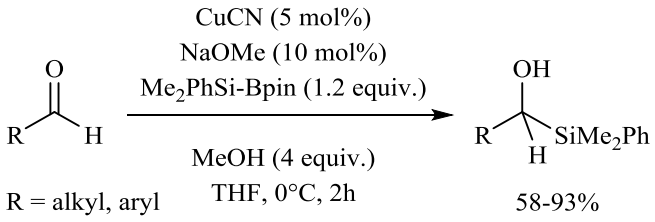
[7] (a) Barrett, A. G. M.; Hill, J. M., *Tet. Lett.* **1991**, *32*, 3285-3288. (b) Barrett, A. G. M.; Hill, J. M.; Wallace, E. M.; Flygare, J. A., *Synlett* **1991**, 764-770.

[8] (a) Vyas, D. J.; Fröhlich, R.; Oestreich, M., *Org. Lett.* **2011**, *13*, 2094-2097. (b) Kleeberg, C.; Feldmann, E.; Hartmann, E.; Vyas, D. J.; Oestreich, M., *Chem. Eur. J.* **2011**, *17*, 13538-13543.



Scheme 5. Copper-catalyzed 1,2-addition to aldehydes employing (IPr)CuO^{t}Bu.

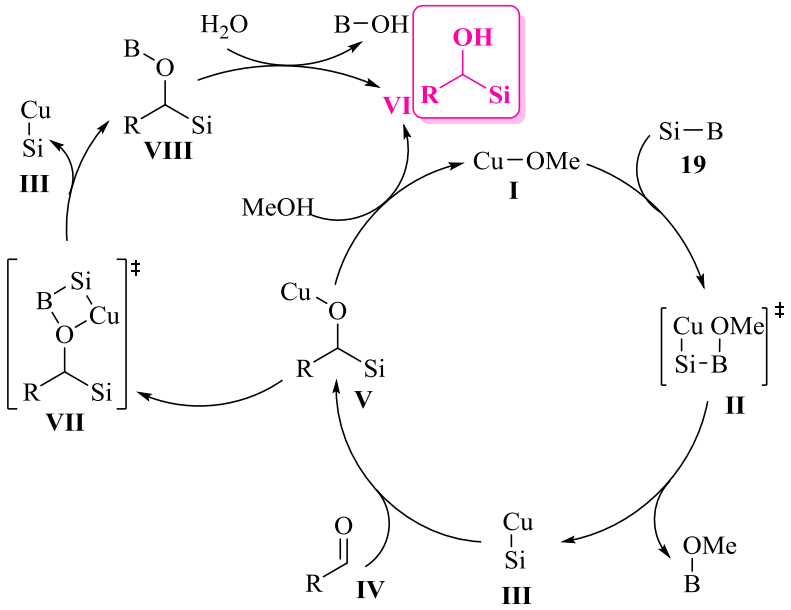
Another protocol for the α-silylation of aldehydes, employing a not yet characterized catalyst, prepared *in situ* from CuCN and NaOMe, showed comparable performance at a significantly lower temperature. They anticipated that this catalytic system might be more reactive (Scheme 6). Aromatic and aliphatic aldehydes were efficiently transformed into α-silyl alcohols under these reaction conditions (MeOH–THF). Compared with the NHC-based system, the second setup was superior in terms of practicability and reactivity, as no pre-prepared copper complex and no heating were required. The latter aspect might be beneficial for sensitive substrates.



Scheme 6. Copper-catalyzed 1,2-addition to aldehydes employing CuCN–NaOMe without added ligand.

The proposed catalyic cycle begins with the transmetalation of *in situ* formed Cu-OMe and **19** (**I** → **III**), through the formal σ-bond metathesis (**II)**. Thus Cu-Si reagent **III** adds to aldehyde **IV** to generate intermediate **V**. Because of the addition of MeOH in the mixture, **V** is

likely to be immediately protonated (**V** → **VI**). The catalysis also works without MeOH, presumably through another σ-bond metathesis of intermediate **V** with **19** resulting in the formation of **VIII** and Cu-Si reagent **III**. Final hydrolysis during the aqueous work-up affords the α-silyl alcohol **VI**.

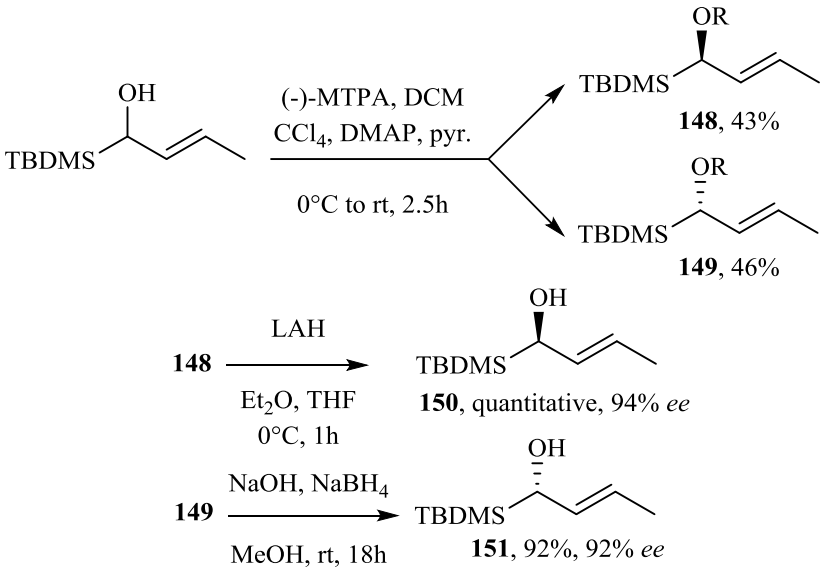


Scheme 7. General catalytic cycle of the 1,2-addition of nucleophilic silicon using a CuCN–NaOMe as the pre-catalyst.

To summarize, various methods were reported for the synthesis of these compounds. However, it was much more attractive for chemists to develop asymmetric synthesis to afford enantiopure α-hydroxysilanes.

I.1.2. Asymmetric synthesis of α-hydroxysilanes

One of the first reports for the preparation of non-racemic compounds was reported by Ireland and co-workers in 1984.[9] They developed the synthesis of the racemic substrates starting from silyl ethers as decribed earlier. Then the resolution of this racemic mixture was accomplished through formation of the diastereoisomeric MTPA esters[10]. The esters **148** and **149**, separable by medium-pressure liquid chromatography, were obtained in 43% and 46% yields respectively (Scheme 8).



Scheme 8. Resolution with (-)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA).

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[9] Ireland, R. E.; Varney, M. D., *J. Am. Chem. Soc.* **1984**, *106*, 3668-3670.

[10] (a) Dale, J. A.; Dull, D. L.; Mosher, H. S., *J. Org. Chem.* **1969**, *34*, 2543-2549. (b) Mosher, H. S.; Biernbaum, M. S., *J. Org. Chem.* **1971**, *36*, 3168-3177.

The conditions necessary for removal of the MTPA group were found to be different for each diastereoisomer. For ester **148**, simple LAH reduction afforded the *(R)*-α-silyl alcohol **150** in quantitative yield with 94% *ee*. In the case of ester **149**, treatment with NaOH and $NaBH_4$ in methanol at room temperature for 18h was required to remove completely the MTPA group. The *(S)*-α-silyl alcohol **151** was obtained in 92% yield and 92% *ee*. The major drawback of this method was the poor yield obtained in the first step.

A literature search revealed asymmetric reduction of acylsilanes as the most common approach for the synthesis of such non racemic compounds (Scheme 9). Specifically, hydroboration with B-chlorodiisopinocampheylborane (IPC_2BCl) was the most widely used method for this important transformation.[11] An example was reported by Soderquist and co-workers in 1990. Aliphatic acylsilanes were reduced in the presence of IPC_2BCl in THF. Removal of the borane group afforded the desired product in high yield and excellent *ee*. Buynak and Ohfune

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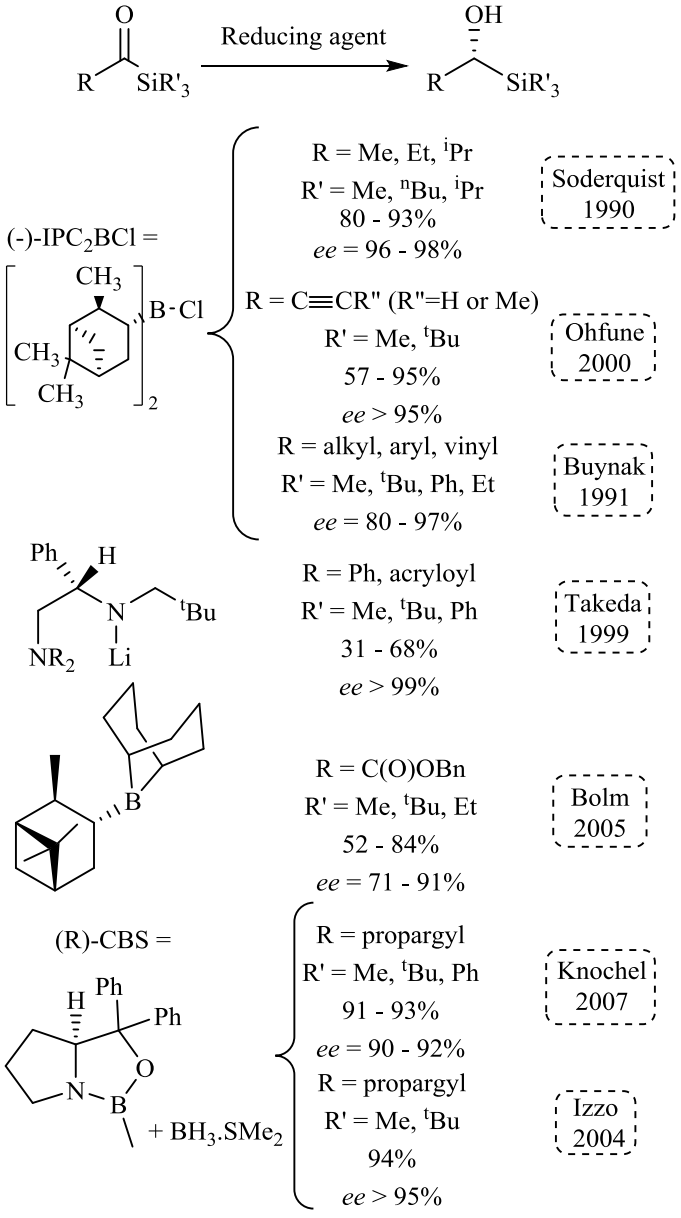
[11] (a) Sakaguchi, K.; Mano, H.; Ohfune, Y., *Tet. Lett.* **1998**, *39*, 4311-4312. (b) Buynak, J. D.; Strickland, J. B.; Lamb, G. W.; Khasnis, D.; Modi, S.; Williams, D.; Zhang, H., *J. Org. Chem.* **1991**, *56*, 7076-7083. (c) Jacobi, P. A.; Tassa, C., *Org. Lett.* **2003**, *5*, 4879-4882. (d) Sakaguchi, K.; Higashino, M.; Ohfune, Y., *Tetrahedron* **2003**, *59*, 6647-6658. (e) Soderquist, J. A.; Anderson, C. L.; Miranda, E. I.; Rivera, I.; Kabalka, G. W., *Tet. Lett.* **1990**, *31*, 4677-4680. (f) Sakaguchi, K.; Fujita, M.; Suzuki, H.; Higashino, M.; Ohfune , Y., *Tet. Lett.* **2000**, *41*, 6589-6592.

also described the use of this reducing agent. They obtained very good yields and *ee's* with various compounds.



Scheme 9. Asymmetric reduction of acylsilanes.

Other chiral organoborane reagents were effective for the asymmetric reduction of acylsilanes as reported by Knochel, Bolm and Izzo.[12] In 1999, Takeda also reported that a chiral lithium amide could reduce α,β-unsaturated acylsilanes with excellent enantioselectivities (Scheme 9).[13] However, these procedures require more than one equivalent of the chiral reagent to the substrate.

A catalytic alternative of this method was found by Rychnovsky. A reported transfer hydrogenation catalyzed by an arene/*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine (Ts-dpen) Ru^{II} complex using 2-propanol as a reducing agent was effective for aromatic acylsilanes.[14] Although this was the first catalytic chemical process for this reaction, the substrate-to-catalyst molar ratio (S/C) of 33/200 was not satisfactory for practical use. More recently, Ohkuma and co-workers developed the highly enantioselective hydrogenation of acylsilanes catalyzed by Tolbinap/pica Ru^{II} complexes.[15] The reaction was carried out with a S/C value as high as 10000 under 10 atm of H_2. A series of

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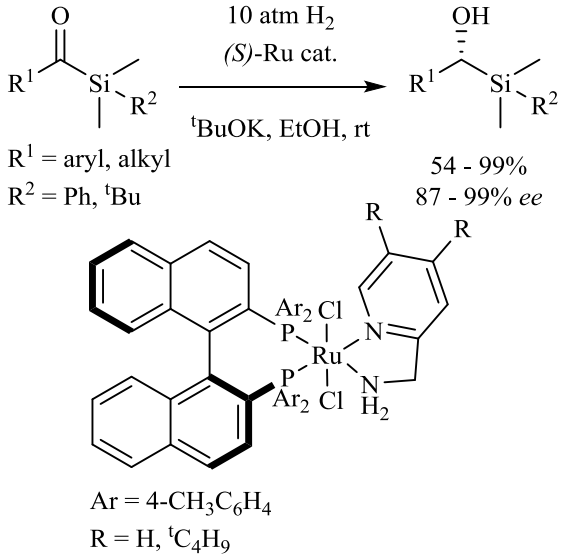
[12] (a) Izzo, I.; Avallone, E.; Corte, L. D.; Maulucci, N.; De Riccardis, F., *Tetrahedron: Asymmetry* **2004**, *15*, 1181-1186. (b) Perrone, S.; Knochel, P., *Org. Lett.* **2007**, *9*, 1041-1044. (c) Guintchin, B. K.; Bienz, S., *Organometallics* **2004**, *23*, 4944-4951. (d) Bolm, C.; Saladin, S.; Claßen, A.; Kasyan, A.; Veri, E.; Raabe, G., *Synlett* **2005**, 461-464.

[13] (a) Takeda, K.; Ohnishi, Y.; Koizumi, T., *Org. Lett.* **1999**, *1*, 237-240. (b) Mosher, H. S.; Biernbaum, M. S., *J. Org. Chem.* **1971**, *36*, 3168-3177.

[14] Huckins, J. R.; Rychnovsky, S. D., *J. Org. Chem.* **2003**, *68*, 10135-10145.

[15] Arai, N.; Suzuki, K.; Sugizaki, S.; Sorimachi, H.; Ohkuma, T., *Angew. Chem. Int. Ed.* **2008**, *47*, 1770-1773.

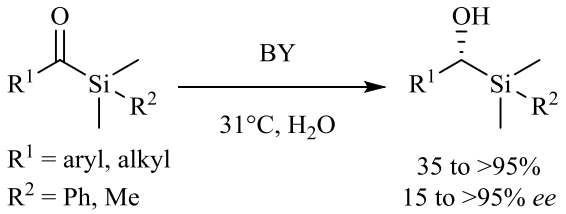
benzylic, aliphatic, and allylic α-hydroxysilanes were obtained in good to excellent yields and up to 99% *ee* (Scheme 10).



Scheme 10. Enantioselective hydrogenation of acylsilanes catalyzed by Ru^{II} complexes.

Asymmetric microbial reductions have also shown to exhibit high stereoselectivity merely for specific acylsilane substrates. Indeed, the enantioselective reduction of acylsilanes has been performed employing baker's yeast (BY)[16]. In fermenting conditions a series of substrates of different structure was investigated, showing that the reactivity as well as the level of enantioselectivity depends on the steric bulk of the substituents on the acylsilane. The α-hydroxysilanes were obtained with chemical and optical yields over 90% in the most favorable cases (Scheme 11).

[16] Zani, P., *J. Mol. Cat. B: Enzymatic* **2001**, *11*, 279-285.



Scheme 11. Biocatalytic transformation of acylsilane.

To sum up, organoborane hydride additions, asymmetric hydrogenations, chiral lithium amide reactions, and biocatalytic transformations of acylsilanes have afforded a variety of α-hydroxysilanes with high levels of enantioselectivity. However, the synthesis of acylsilanes usually requires several steps as reported in chapter 2. Moreover, in many of these examples, the starting acylsilanes are generated by the oxidation of racemic α-hydroxysilanes, which themselves are produced *via* Brook rearrangement-based processes. An alternative to avoid this oxidation step was reported by Maleczka and co-workers.[17] They were interested in the enzymatic kinetic resolution of α-hydroxysilanes in combination with different enzymes, solvents, temperatures and acetylation reagents. The reactions were sensitive to the structure of both the silyl group and the organic side chain. (±)-1-Hydroxyallyltrimethylsilane and its DMPS analogue responded well to Novozym 435 (Scheme 12). The optically active acetates so formed could be converted to their enantioenriched α-hydroxysilanes with DIBAL. Unfortunately, the use of other α-hydroxysilanes afforded substrates that do not resolve under the conditions described.

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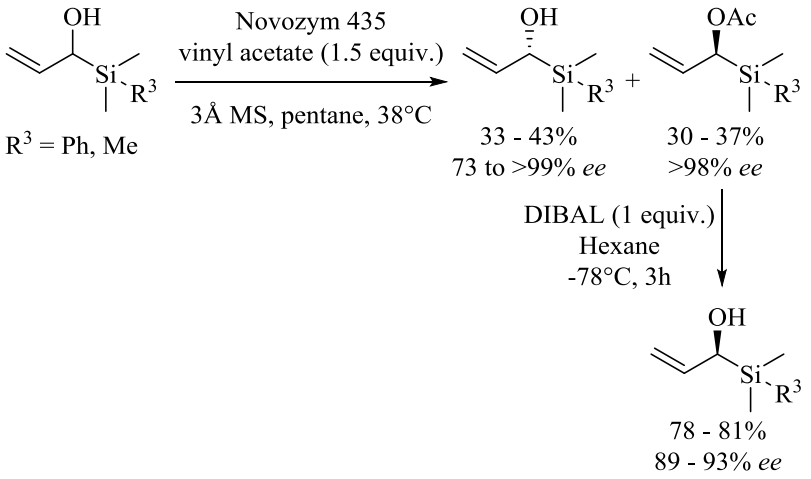
[17] An, I.; Onyeozili, E. N.; Maleczka Jr, R. E., *Tetrahedron: Asymmetry* **2010**, *21*, 527-534.



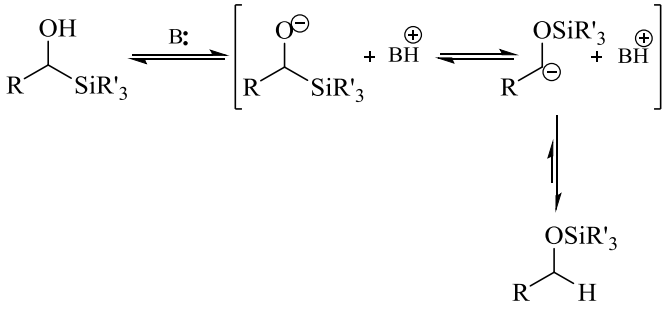
Scheme 12. Enzymatic kinetic resolution.

I.2. Applications of α-hydroxysilanes

As for acylsilanes, the word *versatility* has been frequently used to describe their various reaction modes in processes. Optically active α-hydroxysilanes are regarded as a class of chiral organometallic compounds containing a functional group and these molecules and their derivatives have been used for stereocontrolled C-C bond formation and rearrangements, which resulted in a wide variety of enantiomerically enriched chiral organic compounds. In some of these transformations, the umpolung reactivities of α-hydroxysilanes (i.e. the reversible rearrangement of silyl groups from the carbon to the oxygen, also called "Brook rearrangement") were considered to be the driving force. Herein some of the most important synthetic applications of α-hydroxysilanes will be presented.

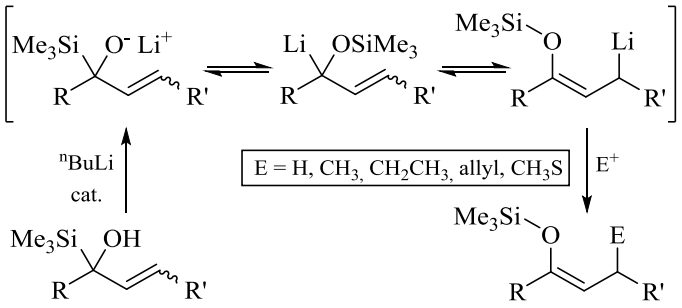
I.2.1. The Brook rearrangement of α-hydroxysilanes

The Brook rearrangement, as reported in Chapter 2, can occur with acylsilanes in the presence of a nucleophile. α-hydroxysilanes can undergo the same transformation in the presence of a base (Scheme 13).



Scheme 13. Brook rearrangement.

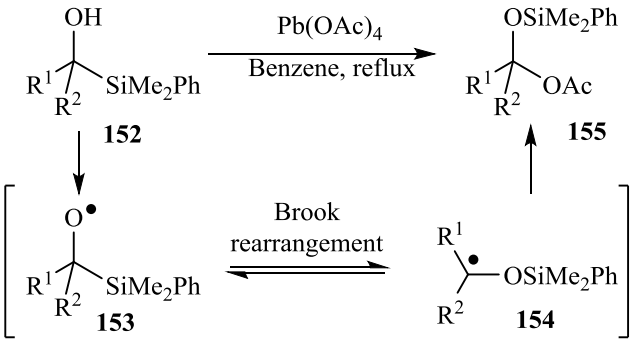
This process is reversible and can be used to synthesize various compounds. Indeed, Kuwajima described in 1980 a direct stereo- and regioselective conversion of α-hydroxysilanes into the corresponding *(Z)*-silyl-enolethers catalyzed by butyllithium.[18] The rearrangement was followed by γ–protonation, alkylation or sulfenylation (Scheme 14).



Scheme 14. Synthesis of *(Z)*-silyl-enolethers.

[18] Kuwajima, I.; Kato, M.; Mori, A., *Tet. Lett.* **1980**, *21*, 2745-2748.

Alonso investigated a method to generate α-silyl alkoxyl radicals **153** from α-silyl alcohols by treatment with lead tetraacetate (LTA). They then studied the radical Brook rearrangement of **153** to α-silyloxy carbon radicals **154** (Scheme 15). LTA treatment of **152** led to their quick and efficient conversion into mixed acetyl-silyl acetals **155** under very mild conditions.[19]



Scheme 15. Radical Brook rearrangement.

I.2.2. Reactions using chiral aliphatic and benzylic α-hydroxysilanes

Linderman and co-workers reported the highly regioselective 1,4-addition of several [α-(methoxymethoxy)benzyl]trimethylsilanes to cyclic enones.[20] The aryl-substituted cyclic homoaldol products were obtained as mixtures of diastereomers in 42-85% yield. Optimized reaction conditions involved *in situ* reaction of the silane and enones with CsF (catalytic or stoichiometric) in DMF (Scheme 16).

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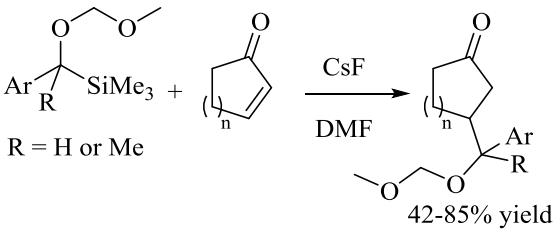
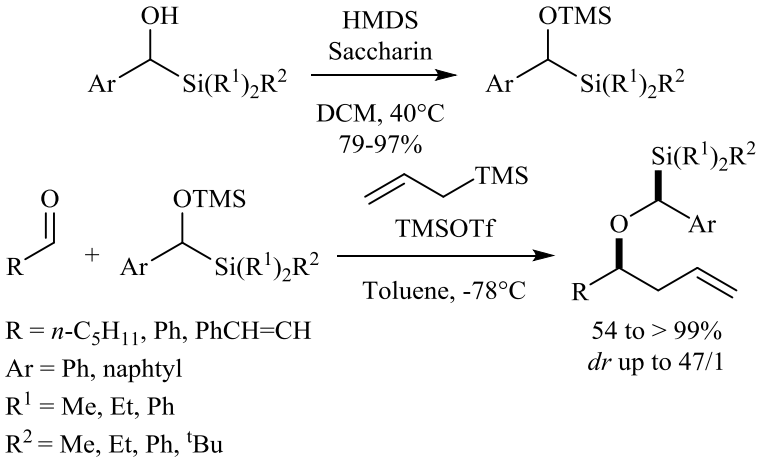
[19] Paredes, M. D.; Alonso, R., *J. Org. Chem.* **2000**, *65*, 2292-2304.

[20] Linderman, R. J.; Ghannam, A.; Badejo, I., *J. Org. Chem.* **1991**, *56*, 5213-5216.



Scheme 16. Conjugated addition of silanes to enones.

The same year, another application was described by Buynak and co-workers.[21] They explored the thermal rearrangement of chiral α-acetoxysilanes into silyl acetates. This methodology was then used to prepare chiral non-silicon-containing secondary alcohols with reasonably high *ee's*. Finally, Rychnovsky decided to use arylsilylcarbinols as chiral auxiliaries for oxacarbenium ion reactions (Scheme 17).[22]



Scheme 17. Arylsilylcarbinols as chiral auxiliaries.

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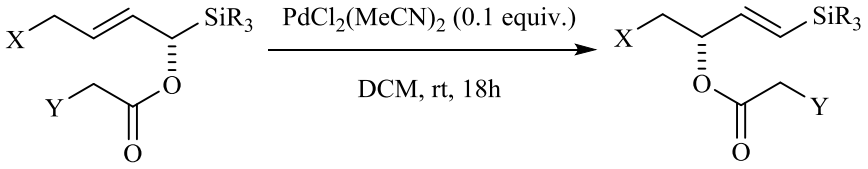
[21] Buynak, J. D.; Strickland, J. B.; Lamb, G. W.; Khasnis, D.; Modi, S.; Williams, D.; Zhang, H., *J. Org. Chem.* **1991**, *56*, 7076-7083.

[22] Huckins, J. R.; Rychnovsky, S. D., *J. Org. Chem.* **2003**, *68*, 10135-10145.

The diastereoselective addition of allyltrimethylsilane to an *in situ* generated oxacarbenium cation was explored using TMSOTf in toluene at -78°C. The selectivity for a representative aliphatic aldehyde was very good (up to 47/1), but the selectivity was significantly reduced with unsaturated and aromatic aldehydes (up to 10/1).

I.2.3. Reactions using chiral allylic α-hydroxysilanes

Many applications using chiral allylic α-hydroxysilanes were reported in the literature.[23] For example, Panek and co-workers investigated the stereospecific transpositions of crotylsilanes.[24] The palladium dichloride catalyzed allylic transpositions of homochiral C1-oxygenated allylic silanes *(R)* and *(S)* provided a new and effective method for the synthesis of *(E)*-vinylsilanes bearing an alkoxy group at the allylic position in optically active form (Scheme 18).



X = H, OBn
Y = H, OCH_3, N_3, Cl
R = Me, Ph

Scheme 18. Stereospecific transpositions of crotylsilanes to vinylsilanes.

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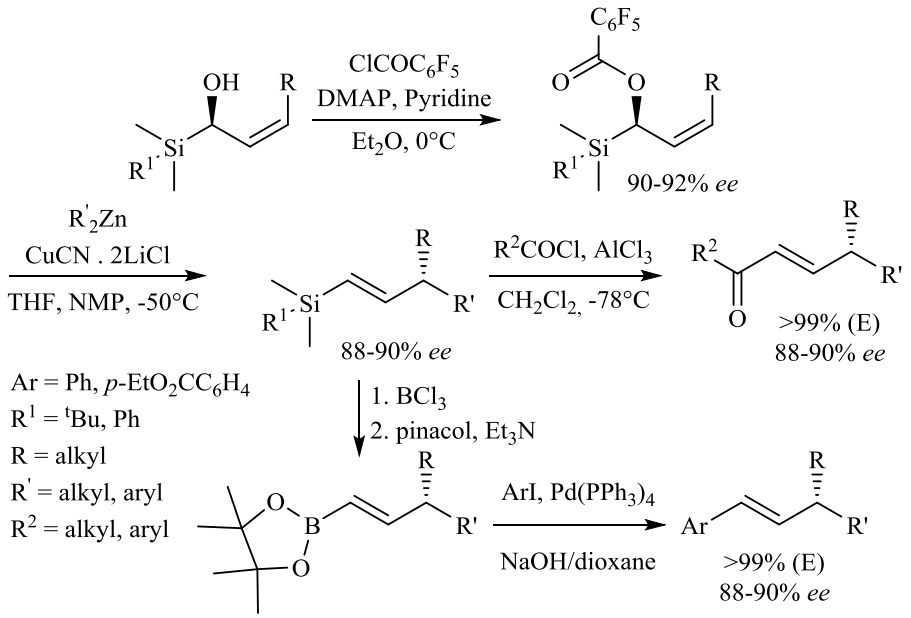
[23] (a) Ireland, R. E.; Varney, M. D., *J. Am. Chem. Soc.* **1984**, *106*, 3668-3670. (b) Kamimura, A.; Kaneko, Y.; Ohta, A.; Matsuura, K.; Fujimoto, Y.; Kakehi, A.; Kanemasa, S., *Tetrahedron* **2002***, 58*, 9613-9620.

[24] Panek, J. S.; Sparks, M. A., *J. Org. Chem.* **1990**, *55*, 5564-5566.

An elegant application was also reported by the group of Knochel.[25] The copper(I)-mediated anti-SN_2' allylic substitution allowed a highly stereoselective preparation of alkenylsilanes bearing a chiral centre in the α-position with high transfer of chirality. These compounds are versatile intermediates and could be readily converted into α,*β*-unsaturated ketones by a Friedel-Crafts-type acylation reaction or into the corresponding alkenylboronates by an *ipso*-borodesilylation followed by cross-coupling reactions. Moreover, the desired products were obtained without loss of the chiral information (Scheme 19).

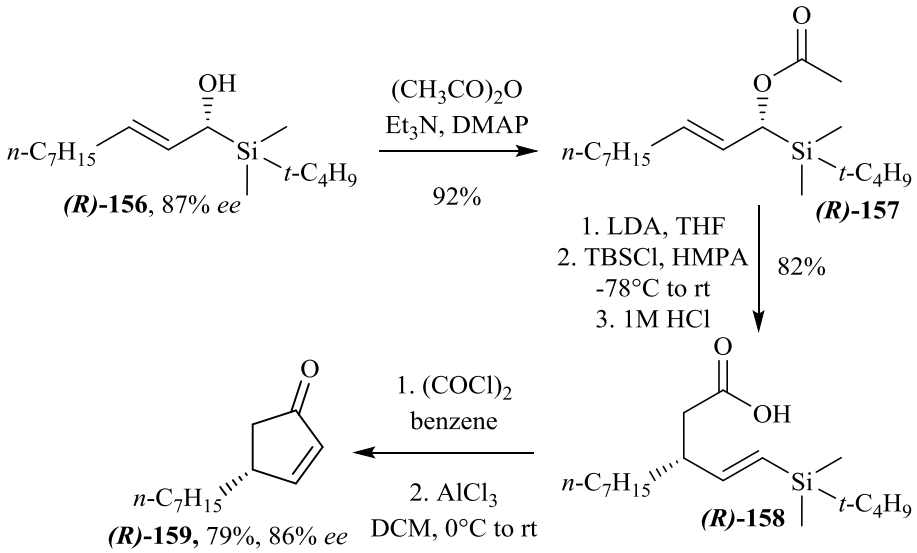


Scheme 19. Diastereoselective preparation of *(E)*-alkenylsilanes.

The Ireland-Claisen rearrangement was used by Ohkuma in 2008 to convert α–hydroxysilanes into non racemic substituted pentenone

[25] Perrone, S.; Knochel, P., *Org. Lett.* **2007**, *9*, 1041-1044.

derivatives without loss of enantioselectivity.[26] Acetylation of ***(R)*-156** under standard conditions gave ***(R)*-157** in 92% yield. Then deprotonation with LDA followed by treatment with TBSCl in the presence of HMPA at -78°C and hydrolysis with an acid afforded the chiral 5-silyl-4-pentenonic acid ***(R)*-158** in 82% yield. Finally, intramolecular vinylation of the acid anhydride mediated by $AlCl_3$ gave the chiral enone ***(R)*-159** in 86% *ee* and 79% yield (Scheme 20).



Scheme 20. Ireland-Claisen rearrangement of α–hydroxysilanes.

I.2.4. Reactions using chiral propargylic α-hydroxysilanes

Chiral propargylic α–hydroxysilanes are also largely used to synthesize interesting building blocks in organic synthesis. Ohfune reported in 1998

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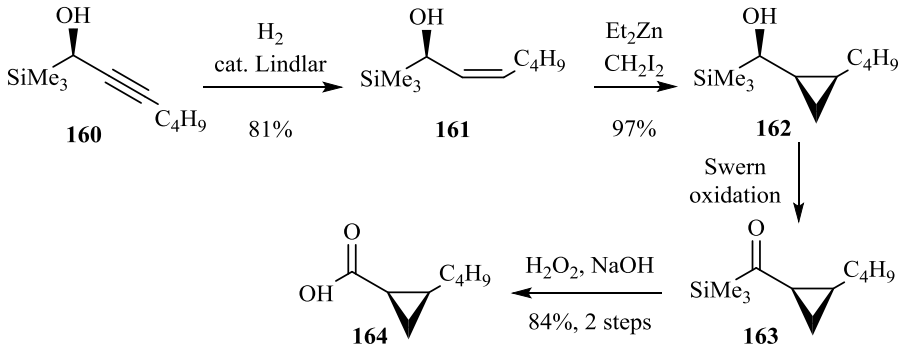
[26] Arai, N.; Suzuki, K.; Sugizaki, S.; Sorimachi, H.; Ohkuma, T., *Angew. Chem. Int. Ed.* **2008**, *47*, 1770-1773.

an elegant synthesis of optically active substituted cyclopropanecarboxylic acids (Scheme 21).[27] Reduction of propargylic silane **160** with the Lindlar catalyst afforded the desired (1*R*,2*Z*)-allyl alcohol **161** (81%, Z/E = 18/1). The key cyclopropanation was performed using **161** with Et_2Zn-CH_2I_2. The reaction proceeded in a highly stereoselective manner to give (1*R*, 1'*R*, 2'*S*)-**162** as the exclusive diastereoisomer (97%). Swern oxidation of **162** and subsequent oxidation of the resulting α-ketocyclopropylsilane **163** with H_2O_2-NaOH gave (1*R*,2*S*)-*cis*-2-butylcyclopropanecarboxylic acid **164** (84%).



Scheme 21. Synthesis of optically active substituted cyclopropane.

Bienz described another application of propargylic silanes.[28] A number of differently substituted allenylsilanes were prepared by cuprate substitution of α-acetoxy- and α-mesyloxypropargylic silanes. The reactions were shown to proceed stereospecifically *via* attack of the nucleophile *anti* to the leaving group (Scheme 22).

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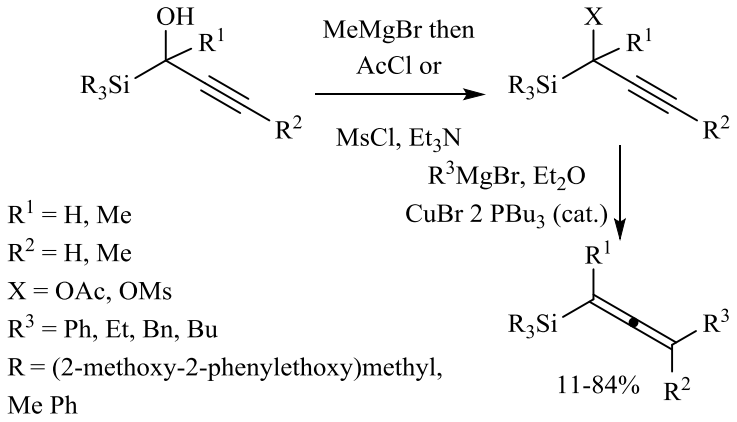
[27] Sakaguchi, K.; Mano, H.; Ohfune, Y., *Tet. Lett.* **1998**, *39*, 4311-4312.

[28] Guintchin, B. K.; Bienz, S., *Organometallics* **2004**, *23*, 4944-4951.



Scheme 22. Synthesis of allenylsilanes.

The desired products were obtained with high enantiomeric purities and they were ready to be used for subsequent stereoselective transformations.

I.2.5. α-hydroxysilanes in total synthesis

There are a few reports in the literature which used α–hydroxysilanes in total synthesis.[29] We will describe in this section some examples. Indeed, Panek and co-workers used α–hydroxysilane to synthesize cycles A and B of (+)-Sesbanimide A, a potent cytotoxic agent (Scheme 23).[30]

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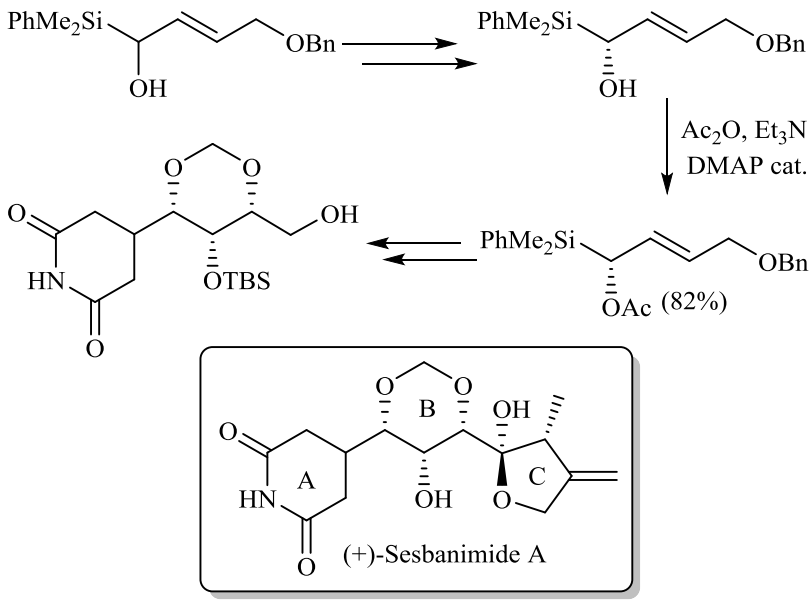
[29] (a) Avery, M. A.; Jennings-White, C.; Chong, W. K. M., *J. Org. Chem.* **1989**, *54*, 1789-1792. (b) Jacobi, P. A.; Tassa, C., *Org. Lett.* **2003**, *5*, 4879-4882.

[30] Cirillo, P. F.; Panek, J. S., *J. Org. Chem.* **1994**, *59*, 3055-3063.



Scheme 23. Use of α-hydroxysilanes in the total synthesis of (+)-Sesbanimide A.

Key features of the synthesis included the stereoselective introduction of the C8 and C9 hydroxyl groups through the use of a diastereoselective catalytic osmylation of enantiomerically enriched α-alkoxy allylsilanes. A chelation-controlled nucleophilic addition of a vinyl Grignard reagent to a *syn* α-alkoxy/β-(silyloxy) aldehyde allowed the introduction of the C7 stereocentre required for assembly of the B-ring.

Izzo and De Riccardis reported the first enantioselective synthesis of *N,O*-deprotected (2*S*,3*S*)-*N*-methyl-δ-hydroxyisoleucine **166**, starting from readily available (*tert*-butyldimethylsilyl)-2-butyn-1-ol **165**.[31]

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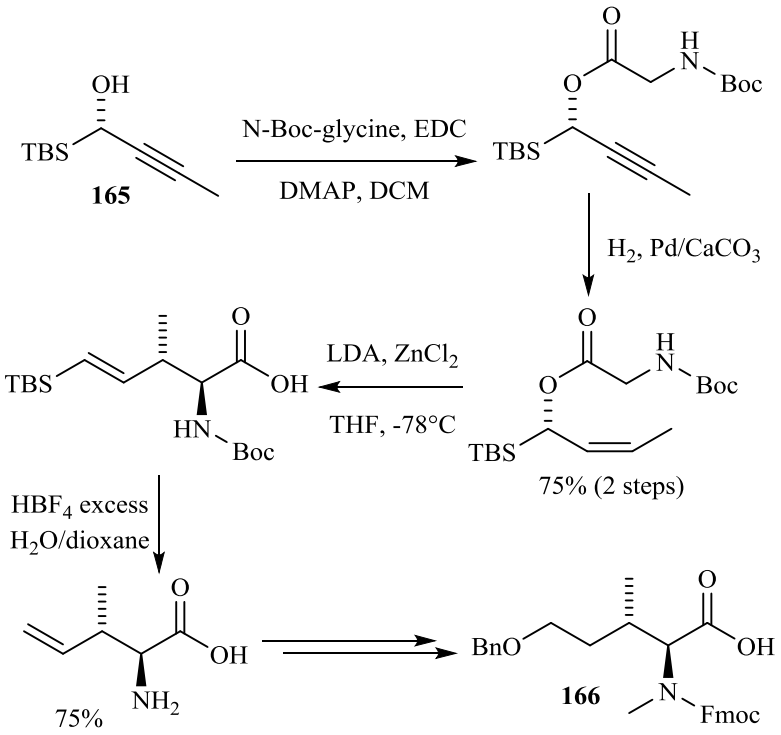
[31] Izzo, I.; Avallone, E.; Corte, L. D.; Maulucci, N.; De Riccardis, F., *Tet. Asymmetry* **2004**, *15*, 1181-1186.



Scheme 24. Enantioselective synthesis of *N,O*-deprotected (2*S*,3*S*)-*N*-methyl-δ-hydroxyisoleucine **166**.

The key steps of this stereochemical flexible synthetic route involve a silyl-assisted [3,3]-sigmatropic rearrangement, for the establishment of the correct stereoisomeric pattern, and a triethylsilane–TFA induced reduction of an oxazolidinone intermediate, to yield the requested *N*-methylation (Scheme 24). This *N*-alkyl amino acid **166** is quite common in bioactive natural peptides such as Halipeptin A (Figure 1).

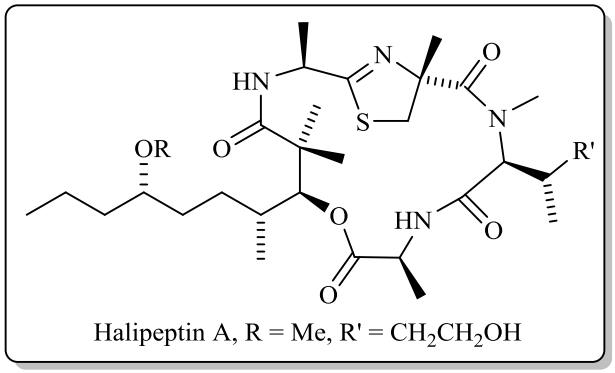
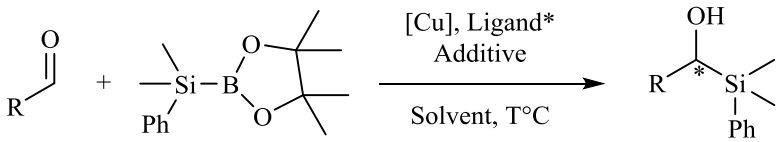


Figure 1. Structure of Halipeptin A.

To conclude, although there are a lot of existing methods to synthesize α–hydroxysilanes, there is still a need for new and efficient synthesis to form these versatile compounds as we have seen in this introduction.

II. Objectives

The transition metal-catalyzed transfer of silicon nucleophiles onto various electrophiles has recently gained considerable attention, due to the now readily available silicon pro-nucleophiles. In particularly, the Suginome's reagent **19** involving a Si-B linkage has become one of the major sources of nucleophilic silicon. This new methodology is particularly attractive as it provides a facile access to metal-silicon reagents rendering the use of any activating agents unnecessary. These metal-silicon intermediates allow the catalytic transfer of a silicon nucleophile onto various electrophiles and our interest lies here in the addition of such species to aldehydes, thus generating α-hydroxysilanes in a catalytic one-step reaction (Scheme 25). Starting from commercially available aldehydes in the presence of Suginome's reagent **19** and a copper catalyst, the process should lead to the corresponding α-hydroxysilanes. Moreover, if we use chiral ligands, high enantioselectivities should be achieved.



19

Scheme 25. Synthesis of α–hydroxysilanes.

Herein, we report the first enantioselective version of the 1,2-addition of a silicon nucleophile to aromatic and aliphatic aldehydes catalyzed by copper(I) complexes.

III. Results and Discussion

III.1. First Model Reaction

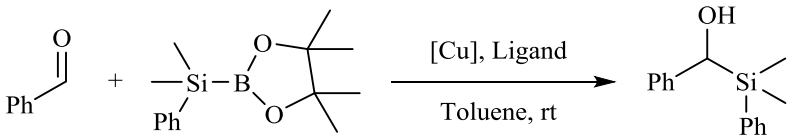
The initial strategy was to use an aldehyde in the presence of the Suginome's reagent and a copper catalyst to afford the α-hydroxysilane in one step. The choice of an adequate substrate that would allow us to do the desired transformation was therefore crucial. Our choice fell on benzaldehyde as model substrate because it is commercially available and not expensive. Reactions were carried out with 5 mol% of the copper catalyst $CuF(PPh_3)_3.2MeOH$ **25** in toluene at room temperature and with 1.2 equivalents of silylborane **19**. The yield was determined after purification of the product by silicagel chromatography.
Note: This work was initiated during the Master thesis project of Corentin Rasson under my supervision.[1]

The desired α-hydroxysilane **167** was obtained in 37% yield after 2 hours of reaction (Table 1, entry 1). The reaction was very fast and we wanted to check if the reaction would also work with a diphosphine ligand. If it was not the case, induction of enantioselectivity with a chiral ligand would therefore be impossible. Reaction was thus performed with (*rac*)-BINAP and we obtained almost the same result (Table 1, entry 2). Thus, we decided to change the copper source to see the effect of the ligand. The use of copper(I) chloride in combination with sodium *tert*-butoxide

[1] Rasson, C ; Master thesis: *« Nouvelle méthodologie pour la synthèse énantiosélective d'a-hydroxysilanes et la synthèse d'acylsilanes »* **2011,** UCL, Louvain-la-Neuve.

was thus chosen. As seen in entry 3, the reaction was less efficient but we still obtained the desired product. A short screening of non chiral ligands to evaluate the bite angle effect of various diphosphines showed that the best result was achieved with DPPB (Table 1, entries 4-6). A small bite angle gave the best activity for the resulting copper catalyst. This result will help us in further optimization.

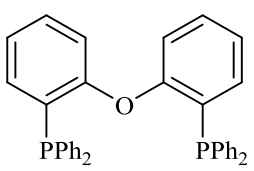
Table 1. First tests.



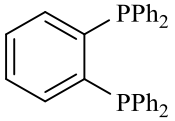
19 (1.2 equiv.) **167**

Entry	[Cu] (x mol%)	Ligand (x mol%)	Yield (%)[a]
1	[Cu]-F **25** (5)	-	37
2	[Cu]-F **25** (5)	(*rac*)-BINAP (5)	39
3	CuCl/NaO^{t}Bu (6/6)	PPh_3 (6)	11
4	CuCl/NaO^{t}Bu (6/6)	dPEPhos (6)	0
5	CuCl/NaO^{t}Bu (6/6)	XantPhos (6)	0
6	CuCl/NaO^{t}Bu (6/6)	DPPB (6)	45

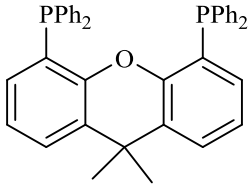
[a] Isolated product yield after hydrolysis and flash chromatography on silica gel.



dPEPHOS



DPPB



XantPhos

We have shown that the reaction works with bidentate non chiral ligands but our goal was to develop an enantioselective version of this reaction. Before describing further results, it should be noticed that the two enantiomers of the product **167** could be separated by chiral HPLC using a chiralcel OD-H column and isohexane/EtOH (90/10) as eluent. Retention times of ***(S)*-167** and ***(R)*-167** are respectively 6 and 7.2 minutes.[2]

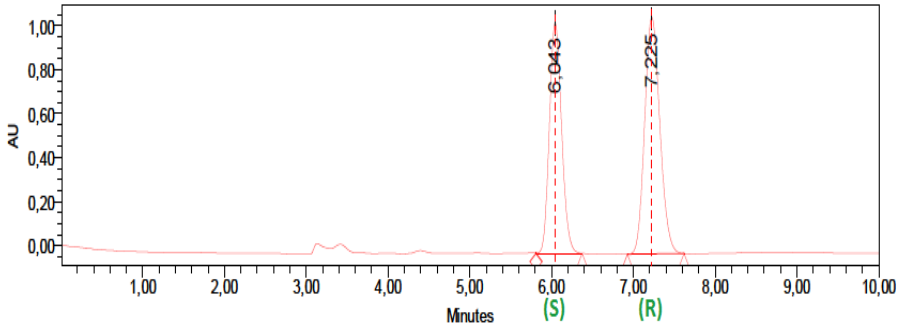


Figure 2. Chromatogram of racemic-**167**.

A preliminary short screening of chiral ligands was performed as reported in table 2. We found that diphosphine ligands, Taniaphos and MeO-Biphep, when used with $CuF(PPh_3)_3.2MeOH$ **25** also promoted the 1,2-addition, but a prolonged reaction time was required (Table 2, entries 1 and 2).

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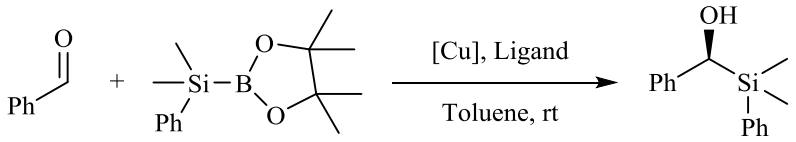
[2] The absolute configuration of compound **167** was determined according to the literature data's: (a) Huckins, J. R.; Rychnovsky, S. D., *J. Org. Chem.* **2003**, *68*, 10135-10145. (b) Arai, N.; Suzuki, K.; Sugizaki, S.; Sorimachi, H.; Ohkuma, T., *Angew. Chem. Int. Ed.* **2008**, *47*, 1770-1773.

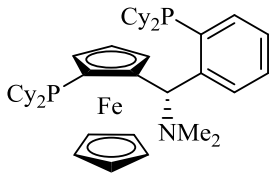
Table 2. Screening of chiral ligands.



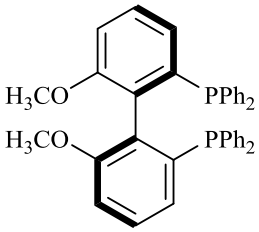
19 (1.2 equiv.) ***(S)*-167**

Entry	[Cu] (6 mol%)	Ligand (6 mol%)	Yield (%)[a]	ee (%)[b]
1	[Cu]-F **25**	Taniaphos	28	2
2	[Cu]-F **25**	*(R)*-MeOBiphep	49	5
3	CuCl/NaO^{t}Bu	Taniaphos	0	-
4	CuCl/NaO^{t}Bu	*(R)*-MeOBiphep	0	-
5[c]	**CuCl/NaO^{t}Bu**	***(R)*-Monophos**	**12**	**20**

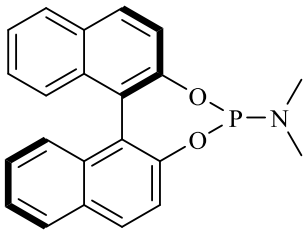
[a] Isolated product yield after hydrolysis and flash chromatography on silica gel. [b] Determined by chiral HPLC analysis. [c] Reaction was carried out with 12 mol% of ligand.



Taniaphos



(R)-MeOBiphep



(R)-Monophos

Conversion was complete after 1 night. Moreover, no significant enantioselectivity was observed with chiral ligands because the reaction was much faster with PPh_3 as ligand as seen previously. Therefore we decided to change the catalytic system. When the same ligands were used in combination with the CuCl/NaO^{t}Bu system, the reaction did not give

the desired product **167** (Table 2, entries 3 and 4). However, when we used the phosphoramidite ligand, *(R)*-Monophos, we observed an enantioselectivity up to 20% although the yield did not exceed 12%. This was the best result obtained so far. Further optimization was thus performed using *(R)*-Monophos as ligand.

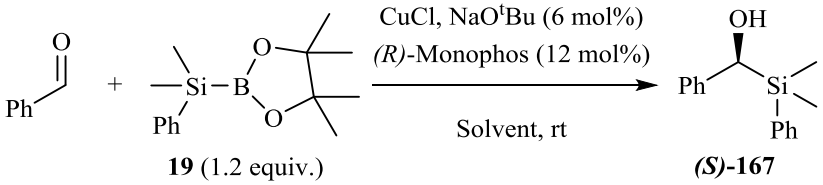
III.2. Copper-catalyzed 1,2-addition: optimization

To establish suitable reaction conditions, we optimized various parameters and the results are reported in the following sections.

III.2.1. Optimization of solvent and reaction temperature

We first optimized the solvent of the reaction. When we used THF as solvent, we detected an increase of both yield and enantioselectivity compared to the use of toluene (Table 3, entries 1 and 2). The desired product was obtained with 25% isolated yield and 37% of enantiomeric excess. Although the best yield was achieved with acetonitrile as solvent, the selectivity was very low (Table 3, entry 4). The use of dichloromethane or dioxane did not improve these results (Table 3, entries 3 and 5).

Table 3. Screening of solvents.



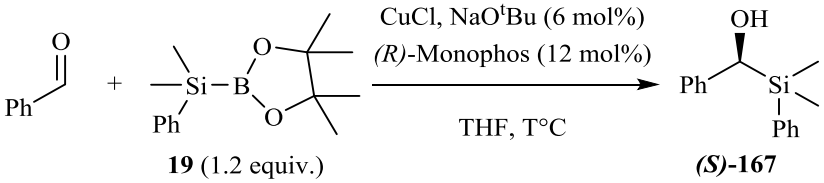
Entry	Solvent	Yield (%)[a]	ee (%)[b]
1	Toluene	12	20
2	**THF**	**25**	**37**
3	DCM	9	16
4	MeCN	36	4
5	Dioxane	18	6

[a] Isolated product yield after hydrolysis and flash chromatography on silica gel.

[b] Determined by chiral HPLC analysis.

Reaction temperature was also optimized as shown in table 4. These results indicate that the best result was achieved when the reaction was performed at room temperature (Table 4, entry 3). An important decrease of the conversion was observed at a lower temperature (Table 4, entry 1). Surprisingly, at 35°C the desired product was obtained in 30% yield but no enantioselectivity was detected (Table 4, entry 4). The reaction might be too fast to induce high selectivity. Finally, the decomposition of the product was observed at a higher temperature (Table 4, entry 5).

Table 4. Effect of the reaction temperature.



19 (1.2 equiv.) ***(S)*-167**

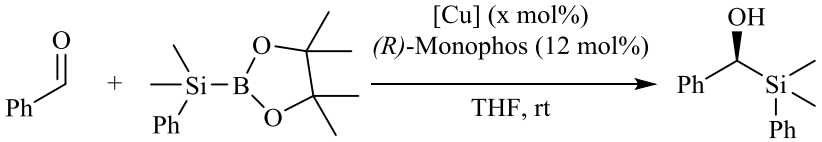
Entry	T (°C)	Yield (%)[a]	ee (%)[b]
1	0	nd[c]	-
2	5	21	14
3	**rt**	**25**	**37**
4	35	30	1
5	40	16	nd[c]

[a] Isolated product yield after hydrolysis and flash chromatography on silica gel. [b] Determined by chiral HPLC analysis. [c] Not determined, conversion <30%.

III.2.2. Effect of the copper source

The effect of the copper source was then evaluated. We decided to use another copper precursor, $Cu(CH_3CN)_4PF_6$. Nevertheless, the results were disappointing. A decrease of both yield and enantioselectivity was observed. Interestingly we found that an increase of the yield was achieved when we used a larger amount of base (Table 5, entries 3 and 4).

Table 5. Effect of the copper source.



19 (1.2 equiv.) ***(S)*-167**

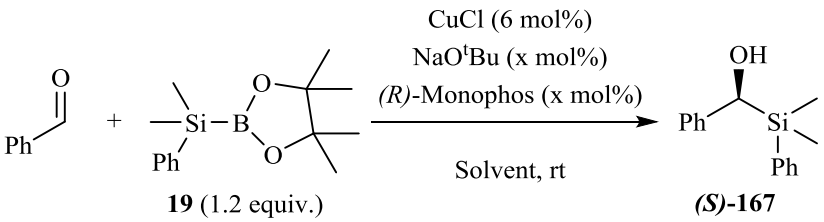
Entry	[Cu] (x mol%)	Yield (%)[a]	ee (%)[b]
1	**CuCl/NaO^{t}Bu (6/6)**	**25**	**37**
2	$Cu(CH_3CN)_4PF_6$ (6)	14	1
3	$Cu(CH_3CN)_4PF_6$/NaO^{t}Bu (6/6)	nd[c]	-
4	$Cu(CH_3CN)_4PF_6$/NaO^{t}Bu (6/18)	20	2

[a] Isolated product yield after hydrolysis and flash chromatography on silica gel.

[b] Determined by chiral HPLC analysis. [c] Not determined.

This prompted us to test the influence of the ratio copper/base/ligand on this process. First, several experiments were performed in THF. These results showed that a higher yield was obtained when we increased the amount of NaO^{t}Bu (Table 6, entry 2). However, no enantioselectivity was detected. Moreover, the use of 30 or 50 mol% of base did not improve the yield and the enantioselectivity was very poor (Table 6, entries 3 and 4). Exchanging NaO^{t}Bu by KO^{t}Bu had a surprising effect. A good yield of 55% was achieved when 6 mol% of base was used. On the other hand, no product was detected when 18 mol% was used (Table 6, entries 5 and 6). **This suggested a lack of reproducibility of the reaction depending on the purity of the reagents.**

Table 6. Influence of the ratio Cu/base/ligand.



19 (1.2 equiv.) ***(S)*-167**

Entry	Solvent	NaO^{t}Bu (x mol%)	Ligand (x mol%)	Yield (%)[a]	ee (%)[b]
1	**THF**	**6**	**12**	**25**	**37**
2	THF	18	12	45	1
3	THF	30	12	20	2
4	THF	50	12	27	7
5	THF	KO^{t}Bu (6)	12	55	1
6	THF	KO^{t}Bu (18)	12	0	-
7	Toluene	6	12	12	20
8	Toluene	6	18	80	17
9	Toluene	12	6	46	14
10	Toluene	18	6	59	4
11	Toluene	18	12	43	24

[a] Isolated product yield after hydrolysis and flash chromatography on silica gel.

[b] Determined by chiral HPLC analysis.

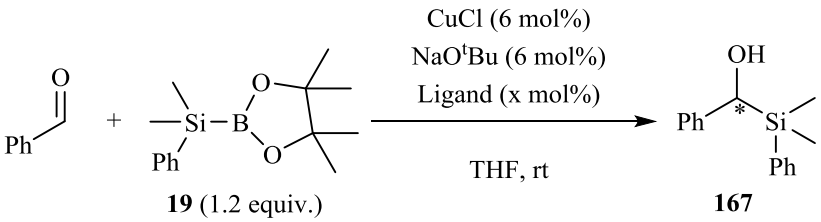
We were also interested in checking the effect of a larger amount of ligand. However, when we carried out the reaction in toluene instead of THF, the desired product was obtained in 80% yield and 17% of

enantiomeric excess (Table 6, entry 8). We thus decided to use toluene in future experiments. The same observation as previously was noticed when we increased the amount of base. The best enantiomeric excess in toluene was obtained when a ratio 1/3/2 was used (Table 6, entry 11). However, enantioselectivity did not exceed 37% in all of these experiments.

III.2.3. Screening of various ligands

At this point, it seemed important to accomplish a new screening of various ligands. The reaction conditions found previously were used. First, a library of several phosphoramidites was engaged in the reaction. The *(R)*-Phosphoramidite **1** gave the best result. The desired α-hydroxysilane was obtained in 29% yield and 38% *ee* (Table 7, entry 1).

Table 7. Screening of other phosphoramidites.

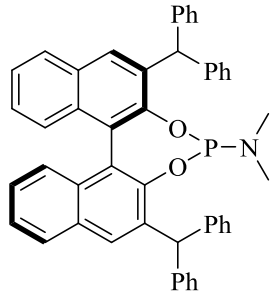


Entry	Ligand (x mol%)	Yield (%)[a]	ee (%)[b]
1	***(R)*-Phosphoramidite 1 (6)**	**29**	**38**
2	*(S)*-Phosphoramidite 2 (12)	17	6
3	*(R,R)*-Phosphoramidite 3 (6)	0	-
4	***(R)*-Monophos (12)**	**25**	**37**

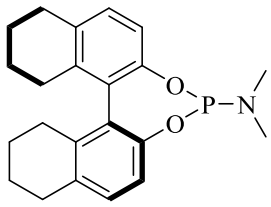
5	*(R)*-Phosphoramidite 5 (6)	8	8
6	*(S)*-Phosphoramidite 6 (12)	15	12
7	*(S)*-Phosphoramidite 7 (12)	10	10
8	*(S)*-Phosphoramidite 8 (12)	13	5

[a] Isolated product yield after hydrolysis and flash chromatography on silica gel.

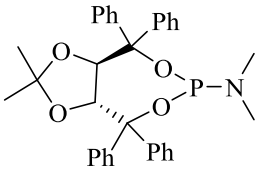
[b] Determined by chiral HPLC analysis.



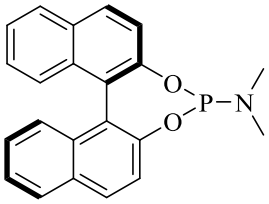
(*R*)-Phosphoramidite 1



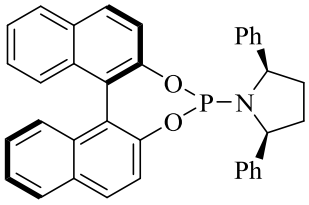
(S)-Phosphoramidite 2



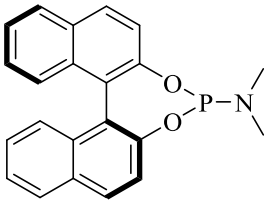
(R,R)-Phosphoramidite 3



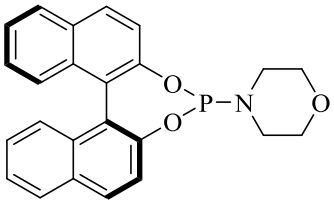
(*R*)-Monophos



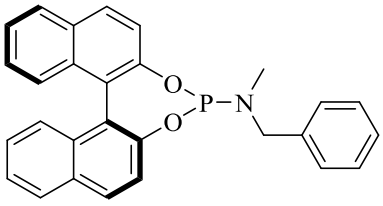
(R)-Phosphoramidite 5



(S)-Phosphoramidite 6



(S)-Phosphoramidite 7

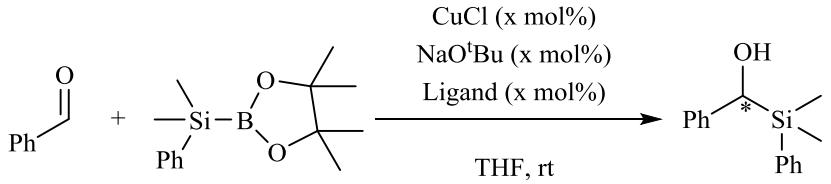


(S)-Phosphoramidite 8

This result is similar to the one obtained previously with *(R)*-Monophos (Table 7, entry 4). Unfortunately, for all the other ligands tested, no satisfactory results were obtained (Table 7, entries 2-3 and 5-8). It was very difficult to explain this ligand effect mostly if we compared entries 4

and 6. The only change is the absolute configuration of the ligand. However, a decrease of the yield and the enantioselectivity was observed. We suspected that sometimes the reaction was not reproducible due to the purity of copper(I) chloride and sodium *tert*-butoxide, two reagents which are air sensitive.[3] A last screening of ligands was performed and the results are reported in table 8.

Table 8. Influence of the ligand.



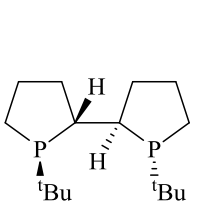
19 (1.2 equiv.) **167**

Entry	CuCl/NaO^{t}Bu (x mol%)	Ligand (x mol%)	Yield (%)[a]	ee (%)[b]
1	3.5/3.5	*(S,R)*-Tangphos (3.5)	< 5	20
2	5/5	*(R,S_p)*-Josiphos (1.5)[c]	65	8
3	5/5	*(R,S)*-Duanphos (5)	20	13
4	5/5	*(R_p,R)*-Taniaphos (5)	10	2
5	6/6	*(R)*-Segphos (6)	26	4

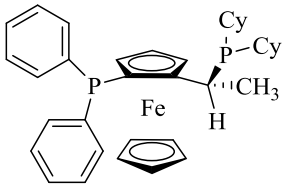
[3] Copper(I) chloride and metal alkoxyde were stored in a glove box when received from the chemical supplier. Small amounts of both reagents were regularly taken from the glove box in a closed gall vial and used for a short amount of time (2-3 days).

6	6/6	*(R)*-Segphos (12)	44	24
7	6/6	*(R)*-DTBM-Segphos (6)	3	64
8	**6/6**	***(R)*-DTBM-Segphos (12)**	**23**	**84**
9	6/6	*(R)*-DTBM-Segphos (12)	18	65
10	6/6	*(R)*-DTBM-Segphos (12)	26	76

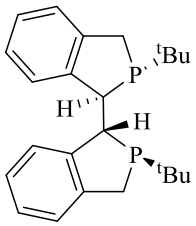
[a] Isolated product yield after hydrolysis and flash chromatography on silica gel. [b] Determined by chiral HPLC analysis. [c] We had very small quantities of this ligand this is why we only used 1.5 mol%.



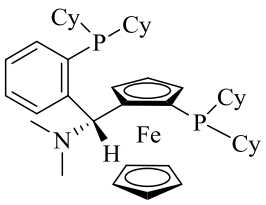
*(S,S',R,R')*Tangphos



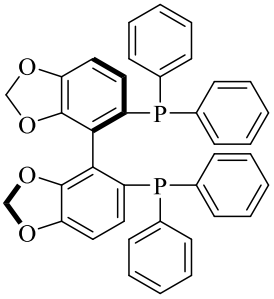
(R,S$_p$)-Josiphos



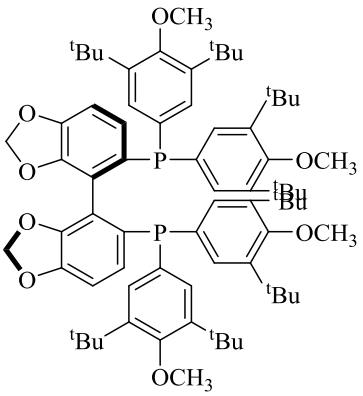
(1R,1'R,2S,2'S)-Duanphos



(R$_p$,R)-Taniaphos



(R)-Segphos



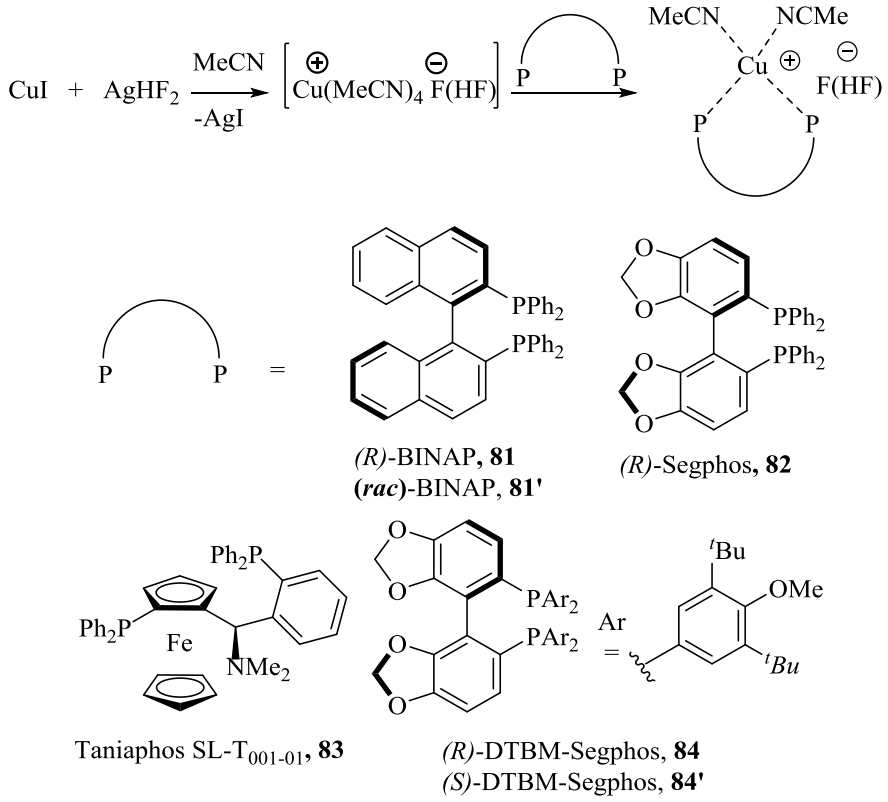
***(R)*-DTBM-Segphos**

We noticed at the beginning of this optimization that ligands with a small bite angle seemed to be favourable in this process. We were thus interested in engaging Tangphos and Duanphos ligands in this reaction. Nevertheless, the results were very disappointing (Table 8, entries 1 and 3). Ferrocenic based ligands did not improve the yield nor the selectivity

of the reaction (Table 8, entries 2 and 4). At the same time, the Tagasako society, gave two interesting ligands to our laboratory which belong to the Segphos family. We thus decided to carry out our reaction with these ligands. The *(R)*-Segphos ligand gave the same result as previously although we observed an increase of both yield and enantioselectivity when a larger amount of ligand per copper atom was used (Table 8, entries 5 and 6). Furthemore, the use of a sterically hindered ligand, the *(R)*-DTBM-Segphos improved considerably the enantioselectivity. The desired product was obtained with 84% of enantiomeric excess (Table 8, entry 8). Unfortunately, the yield of the reaction was quite low. **Moreover, we found that those conditions gave fairly irreproducible results for both yields and enantioselectivities with significant drops (down to 65% vs 84%, Table 8, entries 8-10) regarding the enantioselection.**

III.2.4. Development of the reaction with the new cationic copper(I) complexes

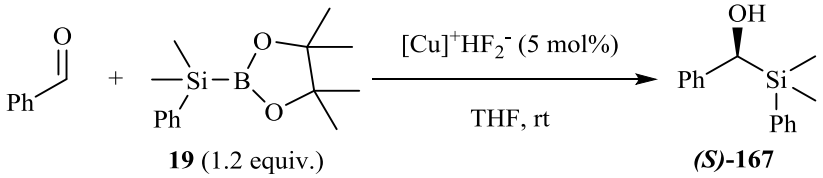
As described earlier in chapter 1, our group developed a new pathway to unprecedented diphosphine copper(I) bifluoride complexes which proved to be excellent catalysts for nucleophilic transfer onto electrophilic double bonds (Scheme 26). The counterion, HF_2^-, is an anhydrous source of fluoride that can activate the Si-B reagent **19** and thus does not need the addition of co-catalysts such as alkoxides. Furthemore, these complexes might lead to a better control of the formation of the copper-nucleophile active species. This should lead to more reproducible experiments as they are isolated as well-defined catalysts.



Scheme 26. Synthesis of the new cationic complexes.

Reactions were carried out with these complexes and the results are reported in table 9.

Table 9. Tests with our cationic complexes.



Entry	$[Cu]^+HF_2^-$	Yield (%)[a]	ee (%)[b]
1	**81'**	19	-
2	84	15	98
3	**82**	11	20
4	**83**	10	22

[a] Isolated product yield after hydrolysis and flash chromatography on silica gel.

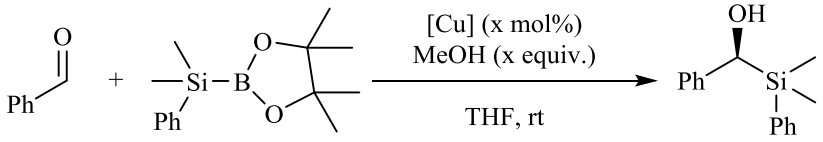
[b] Determined by chiral HPLC analysis.

We were very happy to discover that the reaction worked with our new cationic copper(I) complexes. Furthemore, with complex **84** bearing the *(R)*-DTBM-Segphos, we were able to obtain almost one single enantiomer. Product **167** was isolated with 98% *ee*. However, the yield of the reaction was still low in all cases.

In 2011, Oestreich and co-workers described a racemic 1,2-addition of a silicon nucleophile to imines and aldehydes and proposed a mechanism involving a Cu-Si intermediate as the silyl transfer species.[4] They showed that it was necessary to add methanol as an additive to obtain a good conversion. We thought that addition of methanol to our system might solve the problem.

[4] (a) Kleeberg, C.; Feldmann, E.; Hartmann, E.; Vyas, D. J.; Oestreich, M., *Chem. Eur. J.* **2011**, *17*, 13538-13543. (b) Vyas, D. J.; Fröhlich, R.; Oestreich, M., *Org. Lett.* **2011**, *13*, 2094-2097.

Table 10. Addition of methanol.



19 (1.2 equiv.) ***(S)*-167**

Entry	[Cu] (x mol%)	MeOH (x equiv.)	Yield (%)[a]	ee (%)[b]
1	84 (5)	0	15	98
2	**84 (5)**	**4**	**59**	**>99**
3	CuCl/NaO^{t}Bu/*(R)*-DTBM-Segphos (6/6/12)	4	46	97
4	CuCl/NaO^{t}Bu/*(R)*-DTBM-Segphos (6/6/12)	4	28	88
5	CuCl/KO^{t}Bu/*(R)*-DTBM-Segphos (6/6/12)	4	10	94

[a] Isolated product yield after hydrolysis and flash chromatography on silica gel.

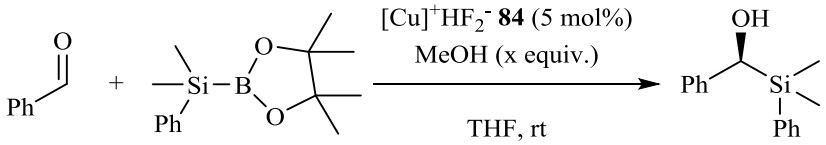
[b] Determined by chiral HPLC analysis.

Several tests were performed with cationic complexes and also with our previous system, CuCl/base/ligand. Addition of MeOH led to significant improvement of both yield and enantioselectivity which suggests that methanol plays a significant role in regenerating the catalyst (Table 10, entries 1 and 2). In the best case, the product was isolated with 59% yield and more than 99% *ee*. As seen in entry 3, we could conclude that the effect of methanol was the same when we used

NaO^{t}Bu as a base. An increase of the yield and enantioselectivity was observed. Unfortunately, irreproducible results were again obtained with this system (Table 10, entry 3 versus entry 4).

A short optimization of the amount of methanol was also achieved as shown in table 11. Smaller amount of MeOH had a negative effect on the outcome of the reaction. Conversion did not exceed 20% (Table 11, entries 1-3). When a larger amount of methanol was used, the product could be isolated but with a low yield and a lower enantioselectivity (Table 11, entries 5 and 6).

Table 11. Variation of the amount of MeOH.



19 (1.2 equiv.) **(S)-167**

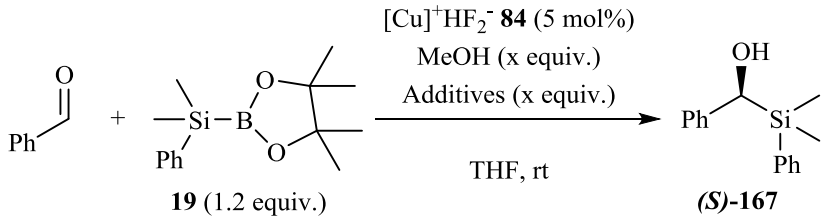
Entry	MeOH (x equiv.)	Yield (%)[a]	ee (%)[b]
1	0.5	nd	-
2	1	nd	-
3	2	nd	-
4	**4**	**59**	**>99**
5	6	10	94
6	10	20	72

[a] Isolated product yield after hydrolysis and flash chromatography on silica gel.

[b] Determined by chiral HPLC analysis.

We were also interested in studying the effect of additives on the reaction to improve the yield.

Table 12. Screening of various additives.

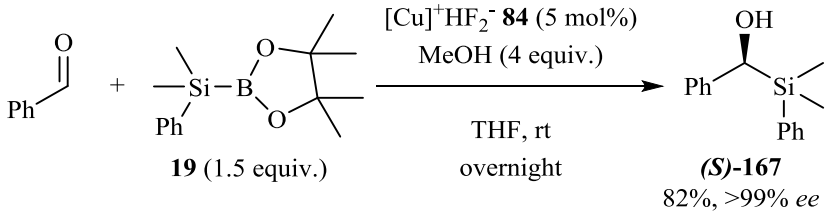


Entry	MeOH (x equiv.)	Additives (x equiv.)	Conversion (%)[a]	ee (%)[b]
1	1	$(EtO)_3SiF$ (1)	0	-
2	1	TBAF (1)	100	0
3	4	TBAT (1)	100	0
4	1	TBAT (0.1)	100	10
5	4	TBAT (0.02)[c]	100	42
6	**0**	**TBAT (0.02)[c]**	**100**	**86**

[a] Determined by ^1H NMR with hexamethylbenzene as internal standard. [b] Determined by chiral HPLC analysis. [c] In solution in THF.

No product was detected when we used a fluorosilane (Table 12, entry 1). Addition of 1 equivalent of a fluoride source (TBAF or TBAT) allowed to reach a complete conversion but no enantioselectivity was achieved (Table 12, entries 2 and 3). We think that TBAT can directly activate the Si-B reagent leading to a direct transfer to the aldehyde, and consequently forming the racemic adducts. Indeed, decreasing the

amount of TBAT enabled us to achieve more selectivity (Table 12, entries 4 and 5). Surprisingly a good enantiomeric excess of 86% was obtained with 2 mol% of TBAT and no addition of methanol (Table 12, entry 6). However we were not able to improve this result and furthermore TBAT is more expensive as additive than methanol. We therefore concluded that addition of 4 equivalents of methanol remained the best choice. Finally, we found that recrystallization of the cationic copper(I) complexes[5] before its use in our process was necessary to obtain a good yield. Indeed, reaction of benzaldehyde, 1.5 equivalents of Si-B reagent **19**, 5 mol% of copper complex **84** and 4 equivalents of MeOH at room temperature in THF was completed in 16h to afford the *(S)*-α-hydroxysilane ***(S)*-167** in more than 99% *ee* and 82% isolated yield (Scheme 27).

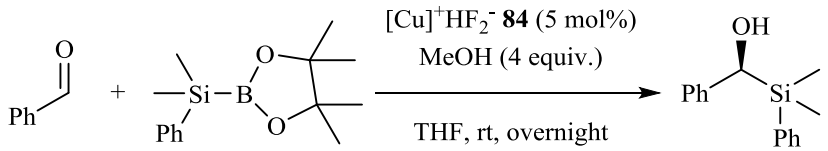


Scheme 27. Synthesis of chiral α–hydroxysilane with complex **84**.

It should be noticed that methanol was added after all the other reagents and no problem of reproducibility was observed with these optimal conditions as shown in table 13.

[5] Recrystallization was performed in toluene as solvent.

Table 13. Test of reproducibility.



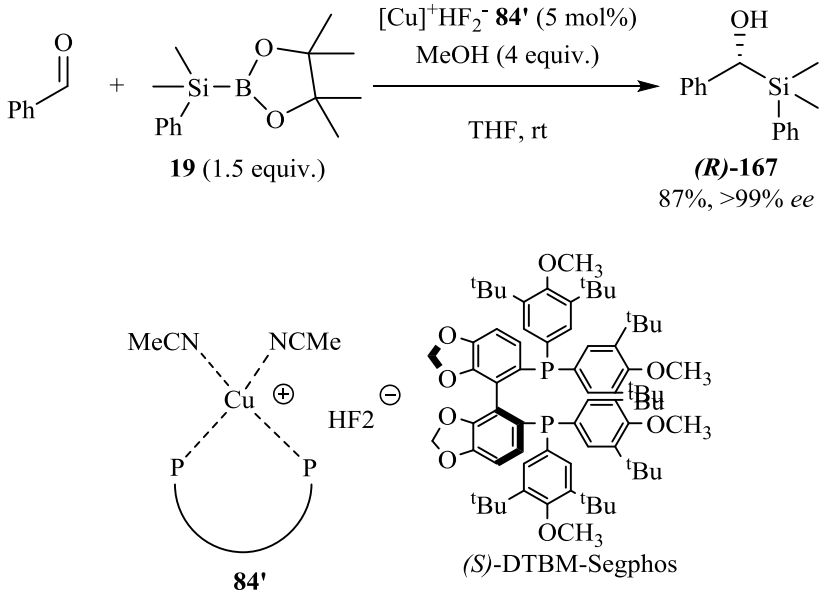
19 (1.5 equiv.) ***(S)*-167**

Entry	Yield (%)[a]	ee (%)[b]
1	82	>99
2	80	>99
3	84	>99
4	79	>99

[a] Isolated yield after flash chromatography on silica gel. [b] Determined by chiral HPLC analysis.

As a control experiment, the use of copper complex **84'** (same copper complex but with the other enantiomer of DTBM-Segphos) afforded the *(R)*-α-hydroxysilane ***(R)*-167** in more than 99% *ee* and 87% isolated yield (Scheme 28). The absolute configuration of compound **167** was determined according to the literature data.[6]

[6] (a) Huckins, J. R.; Rychnovsky, S. D., *J. Org. Chem.* **2003**, *68*, 10135-10145. (b) Arai, N.; Suzuki, K.; Sugizaki, S.; Sorimachi, H.; Ohkuma, T., *Angew. Chem. Int. Ed.* **2008**, *47*, 1770-1773.



Scheme 28. Synthesis of chiral α–hydroxysilane with complex **84'**.

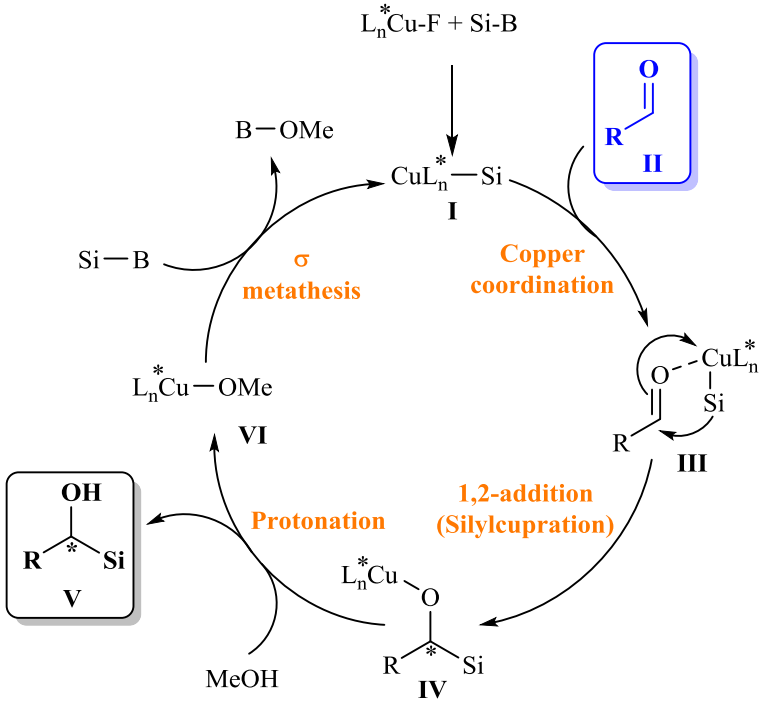
To conlude, we developed a new and efficient method to synthesize chiral α-hydroxysilane in one step starting from readily available benzaldehyde. The desired product was obtained with excellent yield and enantioselectivity. Moreover, we were able to synthesize each single enantiomer simply by changing the ligand on the copper(I) complexes.

III.3. Proposed mechanism

After the optimization of this new methodology, we turned our attention to the mechanism. A first attempt can be proposed in scheme 29. It starts with the formation of the active species Cu-Si (**I**) by activation of the silylborane with the copper fluoride complex as previously described in chapter 1 and general introduction. Coordination of **I** to **II** allows the formation of intermediate **III**. The following 1,2-addition affords the copper alkoxide **IV**. Reaction with methanol gives the desired α-

hydroxysilane **V** and Cu-OMe species **VI**. We postulate that with added MeOH, **IV** is likely to be immediately protonated to form the desired product **V**. Moreover this reaction forms the Cu-OMe species **VI** which will facilitate the transfer of the silyl group onto the copper atom and regenerate the active species **I**. This step explains why the addition of methanol is necessary to obtain a good conversion. Until now there is no proof for this catalytic system. However, Oestreich and co-workers investigated the mechanism of NHC-Cu addition of Si-B reagent to aldehydes in detail by stoichiometric and catalytic experiments as well as NMR spectroscopic measurements.[7] They concluded that the insertion of the aldehyde into the Cu-Si bond was the rate-determining step. They also concluded that the transmetalation reaction was significantly faster than the competing [1,2]-Brook rearrangement.

[7] Kleeberg, C.; Feldmann, E.; Hartmann, E.; Vyas, D. J.; Oestreich, M., *Chem. Eur. J.* **2011**, *17*, 13538-13543.



Scheme 29. Proposed catalytic cycle.

It must be also emphasized that the outlined catalytic cycle is remarkably similar to the catalytic cycle proposed for the copper-catalyzed 1,2-bisboration of aldehydes on basis of DFT calculations, indicating a closely related mechanism of the 1,2-bisboration and C-silyl-O-boration of aldehydes.[8]

III.4. Copper-catalyzed 1,2-addition: examplification

With this new methodology in hand, we were interested in extending it to other substrates. In order to characterize all the new products and to

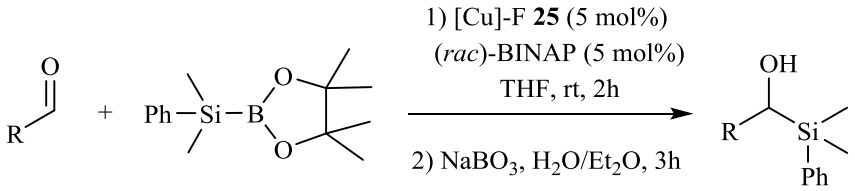
[8] Zhao, H.; Dang, L.; Marder, T. B.; Lin, Z., *J. Am. Chem. Soc.* **2008**, *130*, 5586-5594.

be able to separate the enantiomers by HPLC, the reaction was first performed in a racemic version.

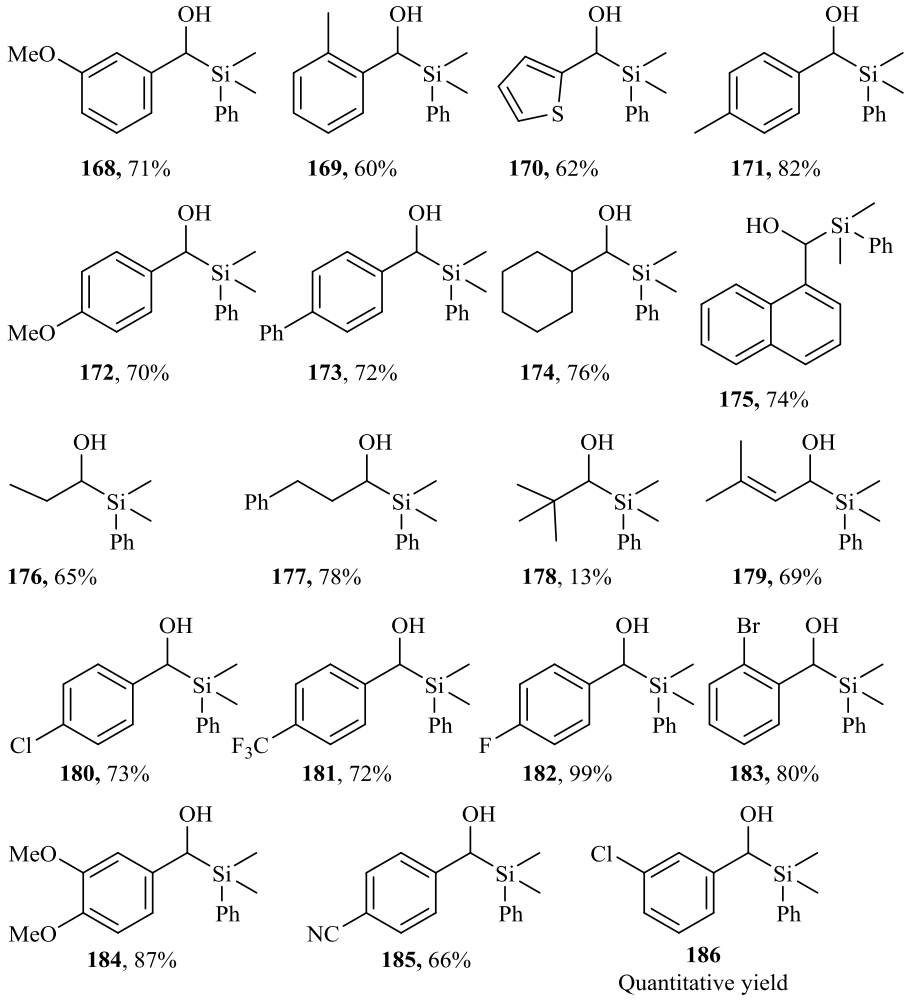
III.4.1. Racemic version

Reactions of various aldehydes with 1.5 equivalents of silylborane **19**, 5 mol% of copper catalyst **25** and 5 mol% of (*rac*)-BINAP in THF at room temperature were carried out. Conversion was complete after 2 hours. Yields were determined after hydrolysis and purification by chromatography on silicagel. Very good to excellent yields were obtained for all the substrates tested except for pivalaldehyde. In that latter case, the desired α-hydroxysilane was only obtained in 13% isolated yield. This is probably due to the steric hindrance of this substrate. However we were happy to see that the reaction worked well with 3-methyl butenal. The desired product **179** was obtained in 69% yield.

Table 14. Racemic version.



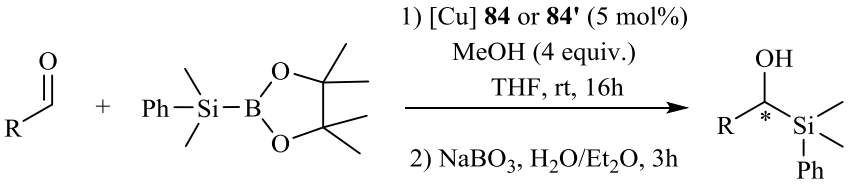
19 (1.5 equiv.) **168-186**



III.4.2. Enantioselective version

After separation of the enantiomers of all these products by HPLC on chiral stationary phases, we were ready to develop the enantioselective version of our process. We carried out the reaction with silylborane **19**, 5 mol% of copper catalyst **84** or **84'** and 4 equivalents of methanol in THF at room temperature. Reaction was slower than the racemic version. The conversion was complete after one night of reaction.

Table 15. Enantioselective version.



19 (1.5 equiv.)

168-177
81-186

Entry	R	Product	Yield (%)[a]	ee (%)[b]
1	3-(MeO)C_6H_4	**168**	99	96
2	2-MeC_6H_4	**169**	51	99
3	2-thiophene	**170**	99	>99
4	4-MeC_6H_4	**171**	78	96
5	4-(MeO)C_6H_4	**172**	53	96
6	4-PhC_6H_4	**173**	95	95
7	Cy	**174**	67	>99
8	1-naphtyl	**175**	60	96
9	Pr	**176**	60	87
10	Ph$(CH_2)_2$	**177**	88	>99
11	4-$CF_3C_6H_4$	**181**	65	>99
12	4-FC_6H_4	**182**	98	98
13	2-BrC_6H_4	**183**	66	93
14	3,4-(MeO)C_6H_4	**184**	80	95
15	4-CNC_6H_4	**185**	98	95
16	3-ClC_6H_4	**186**	99	94

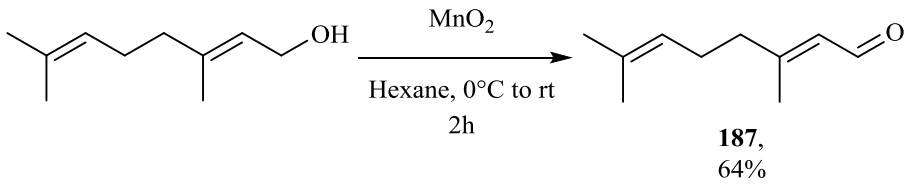
[a] Isolated product yield after flash chromatography on silica gel. [b] Data determined by chiral HPLC analysis.

Unfortunately, in a first try, all the substrates bearing a halogen substituent did not give the desired product. We were quite disappointed

with these results. Nevertheless, after several tests and reflexion, we found that the purity of the aldehyde was crucial. It was necessary to use freshly distilled aldehydes to obtain a good conversion. We thus started again all the reactions and each aldehyde was purified by distillation immediately before use. As seen in table 15, we obtained using this procedure good to excellent yields with almost all the substrates previously engaged in the racemic version of the reaction. Moreover, excellent enantioselectivities were achieved. Regarding aromatic aldehydes, both electron-donating as well as electron-withdrawing groups were well tolerated. Isolated yields were good to high and the corresponding α-hydroxysilanes were obtained with excellent enantioselectivity. The electronic substitutions on the aromatic ring did not affect the enantioselectivity. However, aromatic aldehydes with functional groups at the *ortho*-position proved to be less reactive and gave the product in moderate yields (Table 15, entries 2 and 13) probably as a consequence of the steric hindrance at the *ortho* position. To our delight, we found that aliphatic aldehydes reacted well (Table 15, entries 7, 9 and 10). However, propionaldehyde gave the desired product in only 87% *ee* (Table 15, entry 9). This result suggested that the aldehyde was not bulky enough to obtain good selectivity. It should be mentioned that no product was observed in our optimal conditions with pivalaldehyde although this substrate allowed the preparation of the desired product in the racemic version.

Finally, we decided to check the reactivity of more challenging substrates such as α,β-unsaturated aldehydes for which competition between 1,2- and 1,4-addition could be expected. As seen in table 14, the reaction with

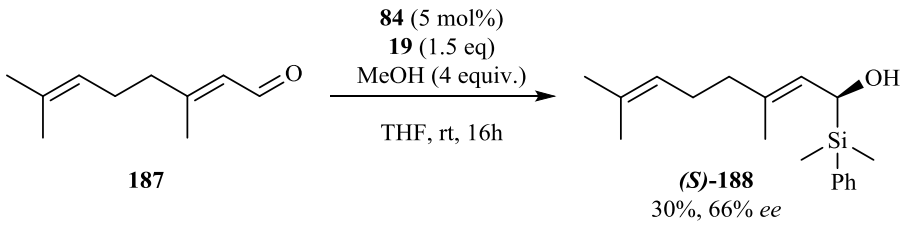
3-methylcrotonaldehyde in the racemic version afforded the desired product **179** in 69% yield. Unfortunately, after several experiments, we were not able to obtain the desired product with our chiral cationic copper(I) complexes. Starting material was recovered at the end of the reaction. However, we decided to test another substrate, citral **187**. Citral **187** was easily synthesized starting from geraniol. Oxidation with MnO_2 in hexane during 2 hours gave the desired product in 64% yield after purification (scheme 30).



Scheme 30. Synthesis of citral.

Citral **187** was thus reacted with $Me_2PhSiBpin$ **19** in the presence of copper complex **84** under our optimal conditions to afford the *(S)*-α-hydroxysilane ***(S)*-188** in 66% *ee* and 30% isolated yield (Scheme 31). Such structures are particularly attractive as they can be employed in various useful transformations such as the Ireland-Claisen rearrangement.[9] The low yield can be explained by the presence of a large amount of unreacted starting material in the crude reaction mixture, the conversion of the reaction was very low.

[9] Ireland, R. E.; Varney, M. D., *J. Am. Chem. Soc.* **1984**, *106*, 3668-3670.



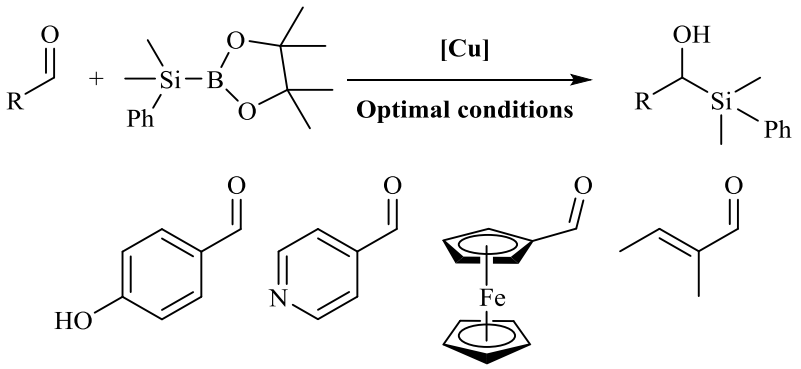
Scheme 31. Copper catalyzed silyl 1,2-addition to citral.

To conclude this part, a series of aromatic and aliphatic aldehydes was converted to the corresponding α-hydroxysilanes in excellent *ee's* and good to high yields.

III.4.3. Reaction's limitations

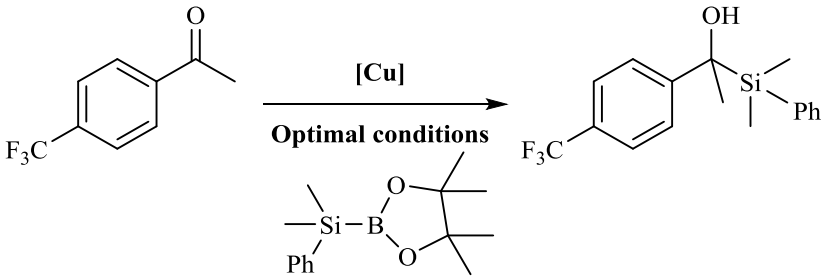
Even though we were quite happy with these results, additional attempts were made to extend this methodology to other substrates, most notably other functionalized aldehydes, ketones and imines.

First of all, it is important to notice that the reaction does not work with functionalized aromatic aldehydes bearing reactive functional groups in the *para*-position (-NO_2 and -OH groups). Decomposition of the starting material was observed in the crude reaction mixture. Pyridine-4-carboxaldehyde did not afford the corresponding α-hydroxysilane in our reaction conditions. Coordination between the nitrogen and the copper atom may be the problem in this case. The reaction does not work with the electron-rich ferrocene carboxaldehyde nor with tiglic aldehyde. Concerning the tiglic aldehyde, only the 1,4-addition product was observed in the crude reaction mixture.



Scheme 32. Reaction's limitations.

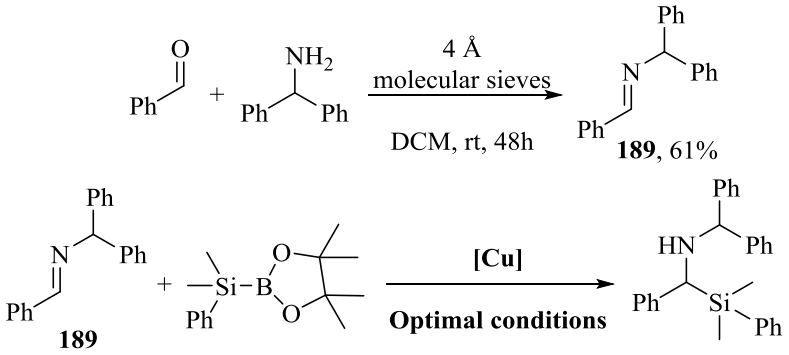
We were also interested in applying our methodology to ketones. *Para*-CF_3-acetophenone was engaged in our optimal conditions (Scheme 33). Unfortunately, this substrate did not furnish the desired α-hydroxysilane. Ketones were not reactive enough to undergo the desired transformation. Only the starting material was recovered.



Scheme 33. Use of ketone as electrophile.

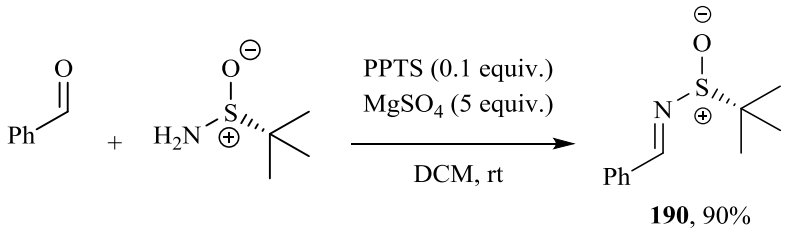
Finally, we turned our attention to the use of imines (Scheme 34). The substrate was first synthesized starting from the corresponding aldehyde. Imine **189** was obtained with 61% yield. However, no desired product was observed in the crude reaction mixture when the reaction was carried out with this substrate. Only the starting material was recovered. We thought that this substrate presents a completely different reactivity

due to the presence of the nitrogen atom. A new optimization of the reaction conditions would be therefore necessary.



Scheme 34. Use of imine as electrophile.

However, we decided to use imine **190** in our reaction because promising results was obtained with this substrate in other groups.[10] This substrate was first synthesized starting from the corresponding aldehyde with good yield (Scheme 35).[11]



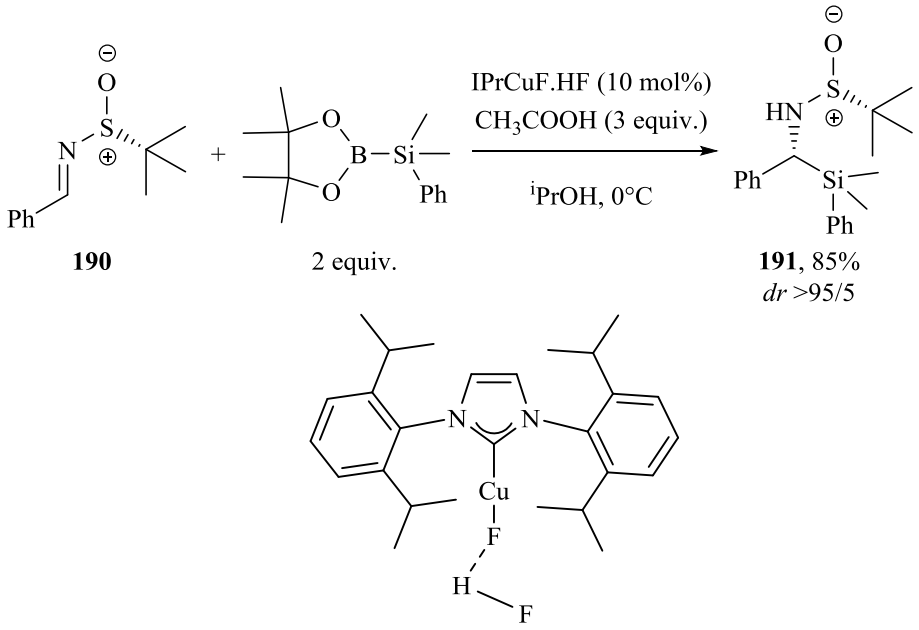
Scheme 35. Synthesis of substrate **190**.

Reaction was therefore carried out with this imine and after a short optimization of the reaction conditions, the desired product was

[10] (a) Hensel, A.; Nagura, K.; Delvos, L. B.; Oestreich, M., *Angew. Chem. Int. Ed.* **2014**, *53*, 4964-4967. (b) Mita, T.; Sugawara, M.; Saito, K.; Sato, Y., *Org. Lett.* **2014**, *16*, 3028-3031.

[11] Liu, G.; Cogan, D. A.; Ellman, J. A.; *J. Am. Chem. Soc.* **1997,** *119*, 9913-9914.

obtained with 85% yield and a diastereoselective ratio up to 95/5 (Scheme 36). Further improvement of this preliminary result and exemplification of this reaction are ongoing.



190 2 equiv. **191**, 85% *dr* >95/5

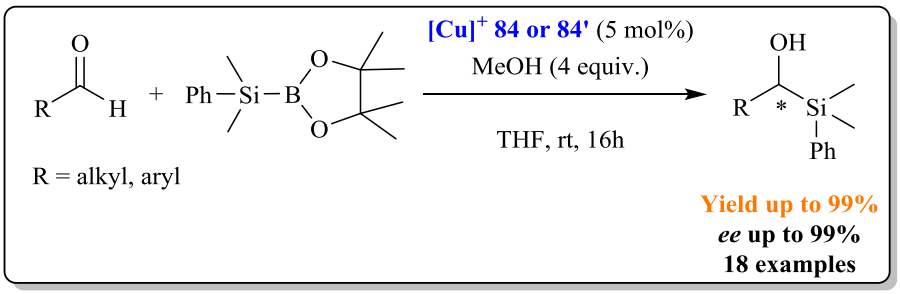
IPrCuF.HF

Scheme 36. Extension of the methodology to imines.

IV. Conclusions and perspectives

In conclusion, we have successfully developed a new method to access α-hydroxysilanes in one step.[1] We report here the first example of the highly reactive and enantioselective addition of a silicon nucleophile to aldehydes catalyzed by newly developed copper(I) complexes.

A series of aromatic and aliphatic aldehydes were converted to the corresponding α-hydroxysilanes in excellent enantiomeric excesses and good to high yields. We even checked the reactivity of more complex substrates such as α,β-unsaturated aldehydes. Although they were less reactive, the desired products were obtained when a disubstitution is present at the β-position of the double bond, consequently blocking the 1,4-conjugated addition. Thus, this method provides a new, efficient and practical route to producing chiral silane compounds from readily available aldehydes.

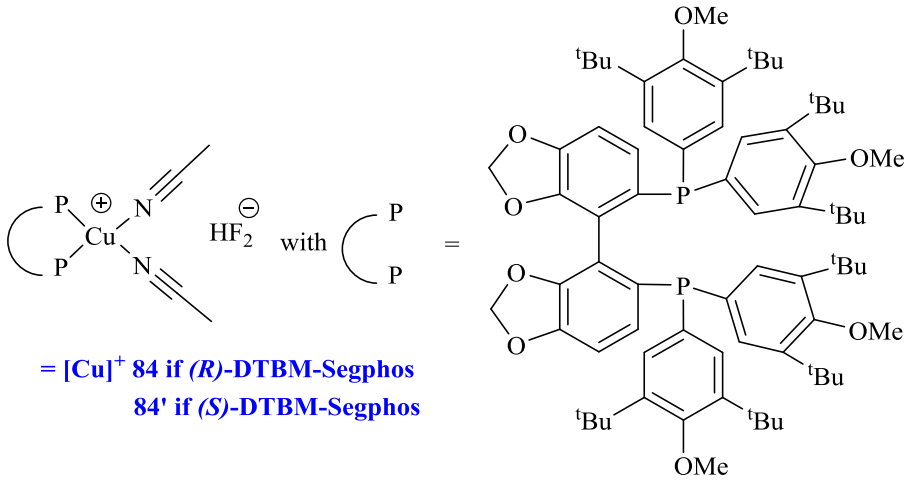


Scheme 37. Synthesis of chiral α-hydroxysilanes.

These results were achieved due to the use of our new cationic copper(I) complexes (Scheme 38). No problems of reproducibility were obtained

[1] Cirriez, V.; Rasson, C.; Hermant, T.; Petrignet, J.; Díaz Álvarez, J.; Robeyns, K.; Riant, O., *Angew. Chem. Int. Ed.* **2013**, *52*, 1785-1788.

with this system compared to the previous one. The great advantage of these catalysts was their air and moisture stability rendering them highly bench stable species. Moreover, we have shown during this thesis the high reactivity of these complexes in various reactions.



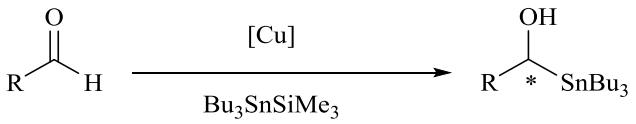
= [Cu]$^+$ 84 if *(R)*-DTBM-Segphos
84' if *(S)*-DTBM-Segphos

Scheme 38. Cationic copper(I) complexes with DTBM-Segphos.

In the future, we are interested in investigating in more details the mechanism of this reaction. The use of other silylboranes is also envisaged.

An interesting extension of this methodology would be the use of alkylstannanes as pronucleophiles. Actually, α-(Hydroxyalkyl) triorganostannanes are versatile synthetic intermediates that have found wide applicability in the total synthesis of natural products. Numerous synthetic strategies to enantioenriched α-(hydroxyalkyl) triorganostannanes exist but the goal of a widely applicable and simple

synthesis from readily available starting materials remains elusive.[2] Therefore applying our methodology for the synthesis of these compounds might be useful (Scheme 39).



Scheme 39. Extension to the use of other nucleophiles.

We also hope to extend these studies to other electrophiles such as imines or phosphorus derivatives. Oestreich and co-workers reported recently the enantioselective addition of silicon nucleophiles to aldimines using a preformed NHC-copper(I) complex as the catalyst.[3] We are interested in using our new cationic copper(I) complexes to form in one step chiral α-silylated amines. As seen earlier, the reactivity of such substrates is quite different compared to aldehydes. Thus a new optimization might be performed to find the best conditions for this transformation. Several experiments were already carried out as reported in page 281 and promising results were obtained.

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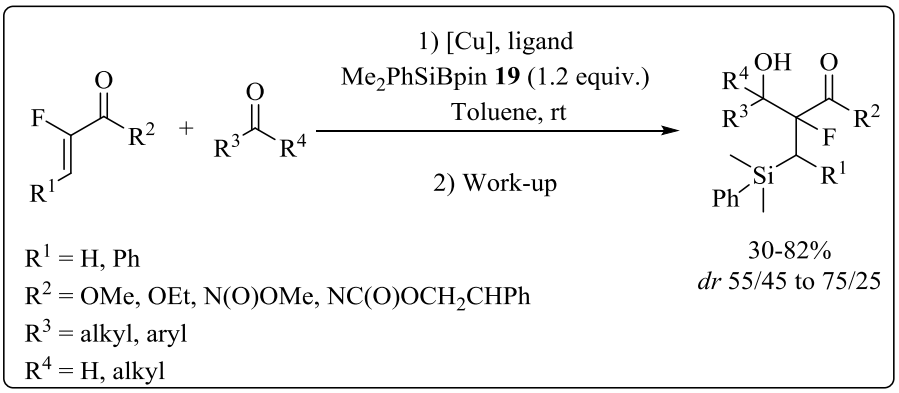
[2] (a) He, A.; Falck, J. R., *Angew. Chem. Int. Ed.* **2008**, *47*, 6586-6589. (b) Kells, K. W.; Chong, J. M., *J. Am. Chem. Soc.* **2004**, *126*, 15666-15667.

[3] Hensel, A.; Nagura, K.; Delvos, L. B.; Oestreich, M., *Angew. Chem. Int. Ed.* **2014**, *53*, 4964-4967. For another recent examples see: Mita, T.; Sugawara, M.; Saito, K.; Sato, Y., *Org. Lett.* **2014**, *16*, 3028-3031.

CONCLUSIONS

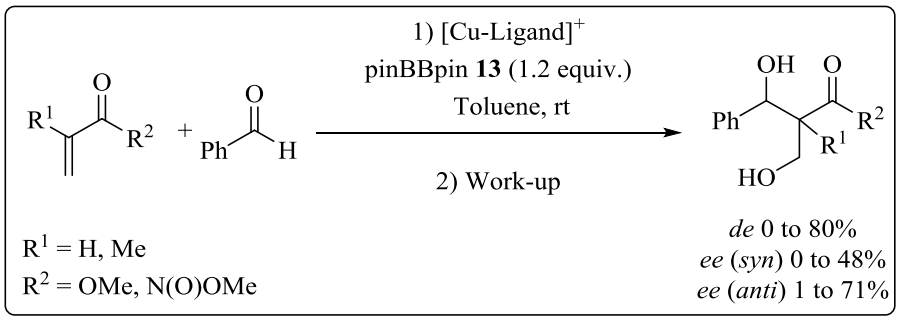
As a general summary of this thesis, we can say that almost all the objectives announced were achieved. First, we tried to extend the domino reaction developed earlier in our group using new substrates, new silylboranes and new catalysts. Concerning the silylation reaction, we have shown that synthesis of substrates bearing a fluorine substituent turned out to be tedious. However, we were able to isolate several interesting adducts with moderate to good yields but with low diastereoselectivities in almost all cases. A good diastereoselectivity was only achieved when we used acryloyl oxazolidinones or Weinreb acrylamides as substrates (*dr* up to 75/25).



Scheme 1. Extension of the silylation reaction.

Syntheses of other silylboranes were also performed and we found that they had almost the same reactivity as the Suginome's reagent. Unfortunately, attempts to promote our silyl adducts in a Hiyama coupling reaction were unsuccessful. About the borylation reaction, we first described two strategies for the synthesis of new cationic copper(I) complexes bearing a bifluoride counteranion. These complexes were therefore used in our reaction and they have shown a good reactivity

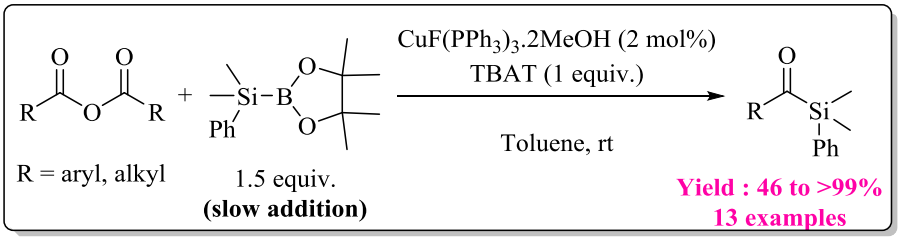
towards our domino process. However, although we obtained good diastereoselectivities with various copper complexes, enantioselectivities were low in these cases. Moderate to good enantiomeric excesses were only achieved when a low diastereoisomeric ratio was obtained.



Scheme 2. Enantioselective version of the borylation reaction.

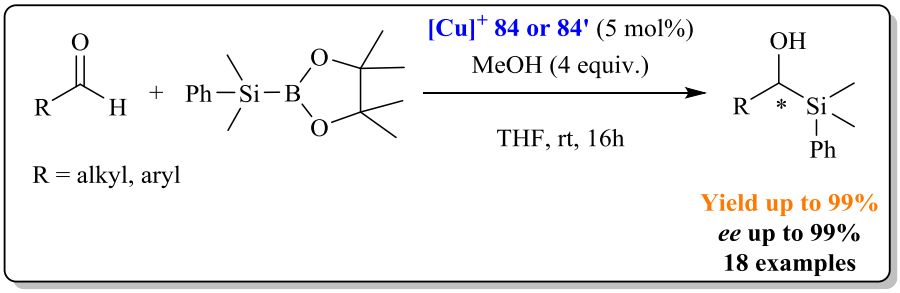
We also want to point out the formation of interesting secondary products in our reactions during these projects. The unexpected product which mimics Baylis-Hillman adduct is very attractive and this reaction has already shown promising results. Moreover, the discovery of the 1,2-addition product during the extension of the silylation reaction allowed us to develop new methodologies as reported in chapters 2 and 3 of this thesis. First, we have developed a new strategy for the synthesis of acylsilanes by using symmetric carboxylic anhydrides that can be accessed from commercially available acyl chlorides. Good to excellent yields were obtained with various substrates. This methodology is mild, practical and does not require strongly basic precursors.[1]

[1] Cirriez, V.; Rasson, C.; Riant, O., *Adv. Synth. Catal.* **2013**, *355*, 3137-3140.



Scheme 3. Synthesis of acylsilanes.

Secondly, we have successfully developed a new method to access α-hydroxysilanes in one step.[2] We report here the first example of the highly reactive and enantioselective addition of a silicon nucleophile to aldehydes catalyzed by newly developed copper(I) complexes. A series of aromatic and aliphatic aldehydes were converted to the corresponding α-hydroxysilanes in excellent enantiomeric excesses and good to high yields. Thus, this method provides a new, efficient and practical route to producing chiral silane compounds from readily available aldehydes.



Scheme 4. Synthesis of α-hydroxysilanes.

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[2] Cirriez, V.; Rasson, C.; Hermant, T.; Petrignet, J.; Díaz Álvarez, J.; Robeyns, K.; Riant, O., *Angew. Chem. Int. Ed.* **2013**, *52*, 1785-1788.

These results were achieved due to the use of our new cationic copper(I) complexes. No problems of reproducibility were encountered with this system compared to the previous one. Their great advantages are their stablility to air and moisture, and their storage does not require particular conditions. Moreover, we have shown during this thesis the high reactivity of these complexes in various reactions.

EXPERIMENTAL PART

Instrumentation and Chemicals

Unless otherwise noted, all manipulations were performed under an argon atmosphere using standard Schlenk-type glassware. Solvents are of analytical grade or distilled before use. Toluene was distilled on sodium under an argon atmosphere. Diethyl ether and THF were distilled on sodium/benzophenone under an argon atmosphere. Dichloromethane and acetonitrile were distilled on CaH_2. Chloroform was distilled on P_2O_5. Solvents used for work-up were of technical grade. Commercial reagents were purchased from Acros, Sigma-Adrich, ABCR, TCI, Strem or Apollo scientific and used as received unless stated otherwise. Segphos families ligands were gracefully provided by Tagasako society. 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 and ^{31}P 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) and CD_3CN (1.94 ppm). Hexamethylbenzene was used as internal standard for ^{1}H NMR. 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. Coupling constant J is given in Hertz (Hz). High resolution Mass Spectra were obtained from a Thermo Scientific QExactive, with accurate mass reported for the molecular ion $[M+H]^+$ or suitable fragment ions. HPLC analyses were recorded on a Waters 600 apparatus with PDA 996 detector and 717 autosampler injector. Products were diluted in ethanol. Flash column chromatography was

carried out on silica gel (ROCC 60, 40-63 μm). TLC analyses were performed on commercial aluminum plates bearing a 0.25 mm layer of Merck Silica gel 60F254 and revealed under UV at 254 nm and with a solution of para-anisaldehyde in ethanol (10% w/v) or an acid solution of $KMnO_4$. $[\alpha]_D^{21}$ were recorded on a Perkin-Elmer 343 polarimeter and concentrations are given in g/mL.

I. Chapter I: Copper-Catalyzed 1,4-Addition/Aldolisation domino reaction

I.1. Synthesis of substrates

I.1.1. Synthesis of copper complex (25)

$$CuF_2 + 3.5\ PPh_3 \xrightarrow[2h30,\ reflux]{MeOH} CuF(PPh_3)_3.2MeOH$$

A modified procedure from the literature was used.[1] A 200 mL round-bottom flask was loaded with triphenylphosphine (9.18 g, 35.0 mmol, 3.5 equiv.), copper(II) fluoride (1.03 g, 10.0 mmol, 1 equiv.) and wet methanol (100 mL). The mixture was heated to reflux during 2 h 30. The solution was filtered and half of the solvent was removed under reduced pressure and then stored at 4 °C overnight. The white crystals formed were then filtered and a second harvest of complex was obtained after concentration of the filtrate to obtain 20 mL. The final product **25** was obtained as a white solid with 70% yield (6.53 g).

❖ **[$(Ph_3P)_3$CuF.2MeOH] (25)**

[$(Ph_3P)_3$CuF.2MeOH]

25 (70%)

Chemical Formula: $C_{56}H_{53}CuFO_2P_3$
Molecular Weight: 933,48

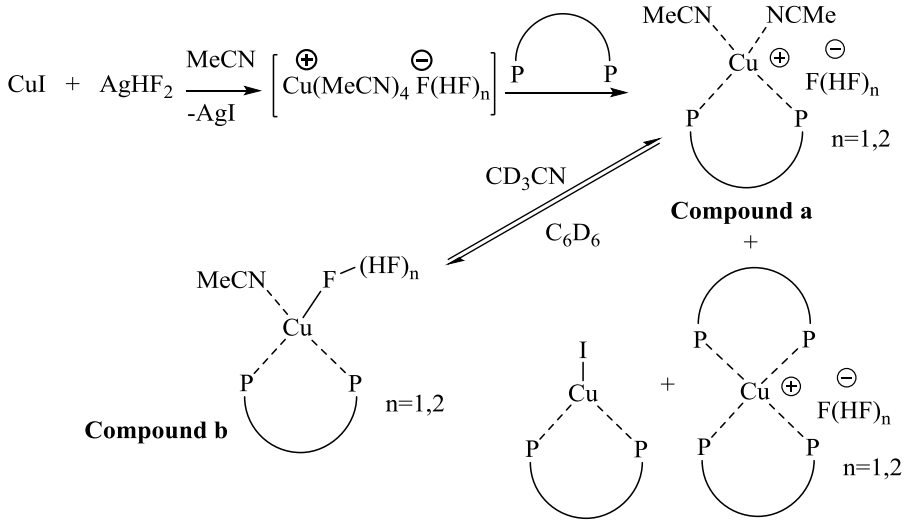
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 45 H, ***Ph***), 3.44 (s, 6 H, C***H***$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.2 (d, *J* = 5.8 Hz, ***C***ar), 134.1 (d,

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

J = 18.7 Hz, ***C***Har), 129.5 (s, ***C***Har), 128.6 (d, *J* = 10.5 Hz, ***C***Har), 50.8 (s, ***C***H_3). ^{19}F NMR (282 MHz, $CDCl_3$) δ -204.8. ^{31}P NMR (202 MHz, $CDCl_3$) δ -3.55.

I.1.2. General procedure for the syntheses of cationic copper(I) complexes: method A

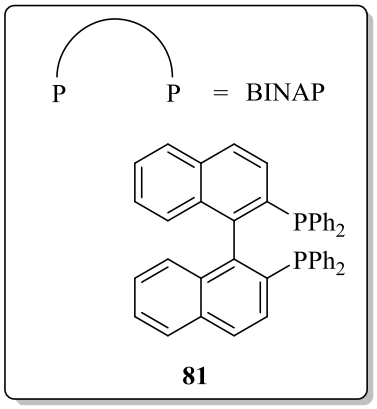
Note: Silver bifluoride was purchased from Acros and ABCR and was kept and manipulated in a glove box. Plastic bottles containing silver bifluoride were kept covered with aluminum foil during storage to avoid decomposition of the silver salt. Standard glassware should be avoided for the manipulations involving silver bifluoride to avoid reaction of the bifluoride anion with glass (formation of SiF_6^- anion was often observed in some experiments in glassware). Initial experiments were carried out in teflon vessels but we found that reproducible results were obtained by using disposable polyethylene tubes.



A plastic vial was charged with silver (I) hydrogenfluoride (46.5mg, 0.31 mmol, 1.2 equiv.). Dry acetonitrile (3~4 mL) was added and the mixture

was stirred for 30 seconds. Copper(I) iodide (50mg, 0.26 mmol, 1.0 equiv.) was added and the mixture was stirred for 2 minutes. The suspension was then filtered on a milliport in a disposable plastic syringe into a clean plastic vial. Ligand (0.26 mmol, 1.0 equiv.) was added in small portion and the solution was stirred for an additional 2 minutes. The resulting solution was filtered on a milliport to remove any remaining solids and concentrated *in vacuo*.

❖ **From 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (81)**

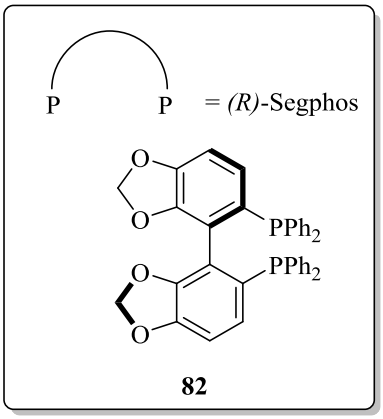


81

Chemical Formula: $C_{88}H_{65}CuF_2P_4$
Molecular Weight: 1347.89

Complex was obtained as a pale yellow solid. Major product is the copper complex bearing two ligands. ^{1}H NMR (300 MHz, CD_3CN) δ 13.73 (brs, 1H, ***H***F_2), 7.87 – 6.59 (m, 64H, ***H***ar). ^{19}F NMR (282 MHz, CD_3CN) δ -166.3. ^{31}P NMR (202 MHz, CD_3CN) δ -1.58. MS (ESI): $[L_2M]^+$ = 1307.33, 100 %.

❖ **From 4,4'-Bi-1,3-benzodioxole-5,5'-diylbis (82)**



82

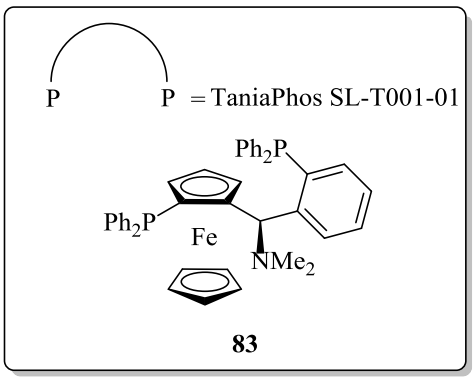
Chemical Formula: $C_{76}H_{57}CuF_2O_8P_4$
Molecular Weight: 1323,69

Complex was obtained as a white solid. Major product is the copper complex bearing two ligands but the copper iodide complex was well identified. ^{1}H NMR (300 MHz, CD_3CN) δ 13.62 (brs, 1H, ***H***F_2), 7.71 - 7.63 (m, 40H, ***H***ar), 6.71 - 6.63 (m, 8H, ***H***ar), 5.97 (s, 4H, ***H***$_2CO_2$), 5.82 (s, 4H, ***H***$_2CO_2$). ^{19}F NMR (282 MHz, CD_3CN) δ -165.88. ^{31}P NMR (202 MHz, CD_3CN) δ 5.50.

❖ Characteristic peaks of iodide complex :

^{1}H NMR (300 MHz, CD_3CN) δ 7.86 (s, ***H***ar), 5.85 (s, 2H, ***H***$_2CO_2$), 5.60 (s, 2H, ***H***$_2CO_2$). ^{31}P NMR (202 MHz, CD_3CN) δ -8.42.

❖ **From (Dimethylamino)[2-(diphenylphosphino) phenyl]methyl]-2-(diphenylphosphino)ferrocene (83)**



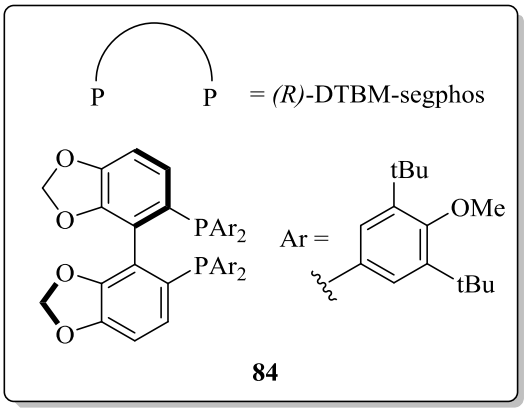
83

Chemical Formula: $C_{86}H_{79}CuF_2Fe_2N_2P_4$
Molecular Weight: 1477,69

Complex was obtained as an orange solid. Major product is the copper complex bearing two ligands. ^{1}H NMR (300 MHz, CD_3CN) δ 13.67 (brs,

1H, ***H***F_2), 7.92 – 6.80 (m, 48H, ***H***$_{Ar}$), 6.66 - 6.61 (t, *J* = 7.6 Hz 2H, C_5***H***$_5$), 6.29 - 6.24 (t, *J* = 8.5 Hz, 4H, C_5***H***$_5$), 6.19 - 6.14 (t, *J* = 8.4 Hz, 4H, C_5***H***$_5$), 5.58 (s, 2H, Ar_2C***H***NMe_2), 4.96 (s, 2H, R_2C_5***H***$_3$), 4.70 (s, 2H, R_2C_5***H***$_3$), 4.24 (s, 2H, R_2C_5***H***$_3$), 3.92 (s, 12H, RN***Me***$_2$). ^{19}F NMR (282 MHz, CD_3CN) *δ* -166.38. ^{31}P NMR (121 MHz, CD_3CN) *δ* -13.83.

❖ **From (R)-5,5'-Bis[di(3,5-di-t-butyl-4-methoxyphenyl)phosphino]-4,4'-bi-1,3-benzodioxole (84)**



Chemical Formula: $C_{78}H_{107}CuF_2N_2O_8P_2$
Molecular Weight: 1364,18

Complex was obtained with crystallization in toluene-hexane as a white crystals. Major product is the copper complex bearing one ligand due to the steric hindrance. ^{1}H NMR (300 MHz, CD_3CN) *δ* 13.76 (brs, 1H, ***H***F_2), 7.71 – 6.64 (s, 12H, ***H***$_{ar}$), 5.59 (s, 2H, ***H***$_2CO_2$), 5.48 (s, 2H, ***H***$_2CO_2$), 3.74 (s, 6H, ***Me***OAr), 3.65 (s, 6H, ***Me***OAr), 1.44 (s, 36H, ***^{t}Bu***Ar), 1.30 (s, 36H, ***^{t}Bu***Ar). ^{19}F NMR (282 MHz, CD_3CN) δ -165.65 (compound a). ^{19}F NMR (282 MHz, C_6D_6) δ -139.6 (s), -192.4 (brs) (compound b). ^{31}P NMR (202 MHz, CD_3CN) *δ* -3.11. MS (ESI): $[LMHF_2+H]^+$ = 1283.20, 100 %.

The X-ray intensity data were collected at 150K with a MAR345 image plate using MoKα (λ = 0.71073Å) radiation (Rigaku UltraX18). A crystal that was crystallized from toluene-hexane at -20°C having approximate

dimensions of 0.27x0.16x0.14 mm was chosen, mounted and transferred to the cold gas stream for flash cooling. The unit cell parameters were refined using all the collected spots after the integration process. Molecular formula = $C_{76}H_{103}CuNO_8P_2$, F H, F, F H Mr = 1343.09, trigonal, P_1, $a = b = 14.3896(3)$ Å, $c = 30.8063(8)$ Å, $V = 5524.2(2)$ Å^3, Z = 3, $\varrho_{calc} = 1.211$ gcm^{-3}, $\varrho = 0.400$ mm^{-1}, F(000) = 2154, T = 150K. The data (150 images (Θ=1.2°) were integrated by Crysalis and a multi-scan absorption correction was applied. There are 37436 reflections of which 13222 independent ($R_{int} = 0.0683$).

The structure was solved by direct methods SHELXS97 (1) and refined by full-matrix block least-squares on F^2 using SHELXL97 (1). All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were placed at calculated positions and refined isotropically with temperature factors fixed at 1.2 $U_{(eq)}$ of the parent atom (1.5 $U_{(eq)}$ for methyl groups). Except for the $H_2F_3^-$ hydrogens where the HF distances, as well as the FH...F$^-$ distances, were refined with a free variable and a linear restraint so that the sum of both amounts to 2.340(20)Å (i.e. F - - - F distance). Final R-values are: $R_1 = 0.0482$ for 10756 observed reflections (>2sigma(I)); R_1 (all data) = 0.0697, wR_2 (>2sigma(I)) = 0.1031 , wR_2 (all) = 0.1180, S = 1.029. Refined flack parameter -0.004(11).

Compound **84** crystallizes in the trigonal space group $P3_1$, and shows (pseudo)-2-fold symmetry with respect to the phosphine ligand. The tetragonal coordination of the central Cu(I) atom is formed by the bulky bidentate coordinating biphosphine and completed by a neutral acetonitrile molecule and a F atom which is part of a $H_2F_3^-$ anion. The

$H_2F_3^-$ anion resides in a 156.7Å^3 pocket flanked by the CH_3CN molecule and surrounded by neighbouring *tert*-butyl groups. The absence of stabilizing interactions makes the $H_2F_3^-$ anion to be disordered over two discrete sites, as to occupy all the available space of the apolar pocket. No hydrogen bond interactions are present except within the $H_2F_3^-$ anion (Figure 1) for details on the hydrogen bonds and the observed disorder). An ORTEP representation is given in Figure 1.

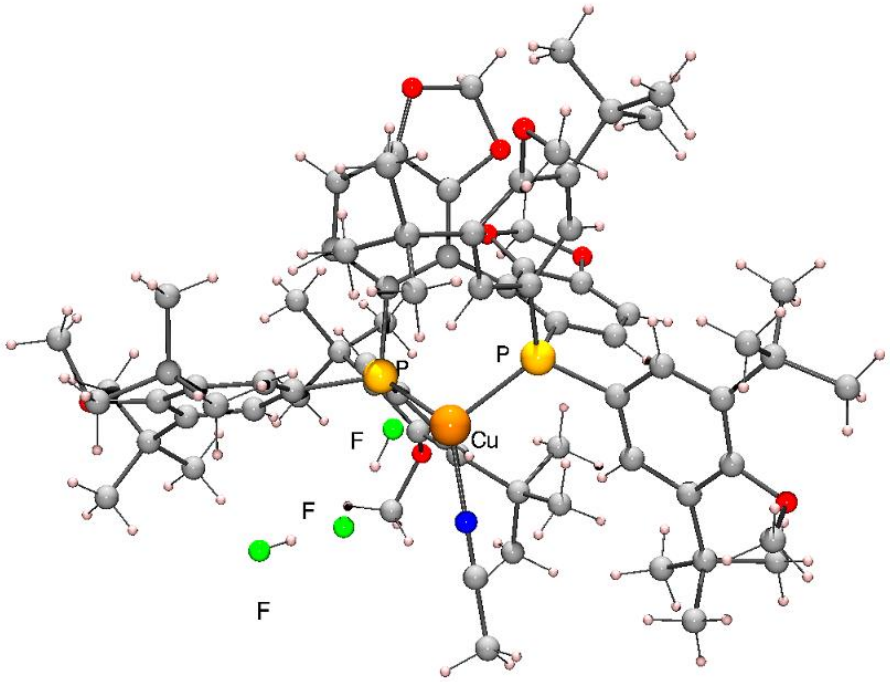
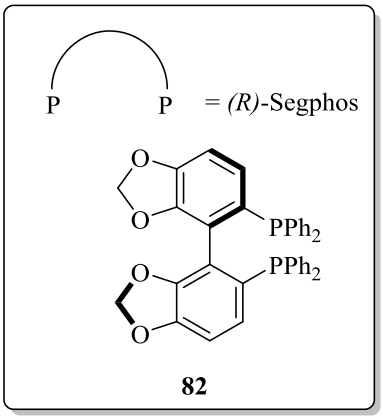


Figure 1. Ortep representation of the complex showing displacement ellipsoids drawn at the 30% probability level. Disorder (both in some tert-butyl groups as well as in the $H_2F_3^-$ anion) are omitted for clarity.

I.1.3. Synthesis of complex L_2CuHF_2

A plastic vial was charged with silver (I) hydrogenfluoride (46.5mg, 0.31 mmol, 1.2 equiv.). Dry acetonitrile (3~4 mL) was added and the mixture was stirred for 30 seconds. Copper(I) iodide (50mg, 0.26 mmol, 1.0 equiv.) was added and the mixture was stirred for 5 minutes. The suspension was then filtered on a milliport in a disposable plastic syringe into a clean plastic vial. Ligand was added in small portion until a precipitate appeared and the solution was stirred for an additional 5 minutes. The resulting solution was filtered on a milliport to remove any remaining solids and half of the solvent was removed under reduced pressure. Diethyl ether was then added to crystallize and afford the desired complex.

❖ **From 4,4'-Bi-1,3-benzodioxole-5,5'-diylbis (82)**

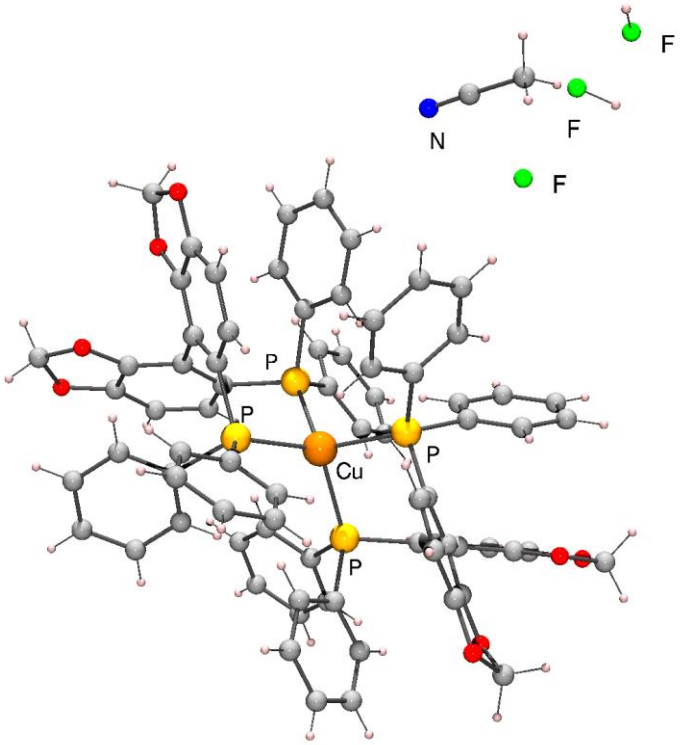


82

Chemical Formula: $C_{76}H_{57}CuF_2O_8P_4$
Molecular Weight: 1323.69

Complex was obtained with crystallization in diethyl ether as a white crystals. ^{1}H NMR (300 MHz, CD_3CN) δ 13.62 (brs, 1H, $\boldsymbol{H}F_2$), 7.71 - 7.63 (m, 40H, $\boldsymbol{H}_{ar}$), 6.71 - 6.63 (m, 8H, $\boldsymbol{H}_{ar}$), 5.97 (s, 4H, $\boldsymbol{H}_2CO_2$), 5.82 (s, 4H, $\boldsymbol{H}_2CO_2$). ^{1}H NMR (500 MHz, CD_2Cl_2, -80°C) δ 16.00-16.50 (t, J = 124 Hz, $\boldsymbol{H}F_2$). ^{19}F NMR (282

MHz, CD_3CN) δ -165.88. ^{31}P NMR (121 MHz, CD_3CN) δ 5.50. MS (ESI): $[LM]^+$ = 673.08, 10 % ; $[L_2M]^+$ = 1283.22, 100 %, $[L_2Ag]^+$ = 1329.20, 20 %. IR (KBr, cm^{-1}): 1791, 1593, 1456, 1434, 1261, 1056.



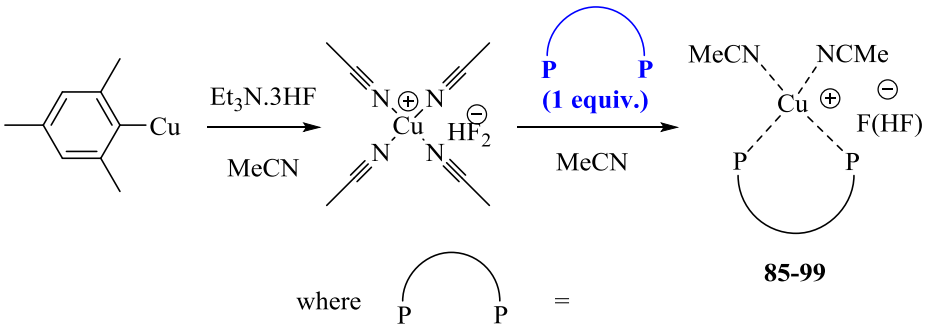
RX $C_{76}H_{56}CuO_8P_4$, C_2H_3N, HF, F Mr = 1364.69, Monoclinic, $P2_1$, a = 12.6358(7)Å, b = 20.2322(9)Å, c = 13.3298(9)Å, β = 93.39(3)°, V = 3230.9(3)$Å^3$, Z = 2, ϱ_x = 1.403gcm^{-3}. A total of 16295 reflections were collected using a MAR345 image plate detector and Mo Kα radiation (λ=0.71073 Å). T = 120K. 5823 (4480>2sigma(I)) independent reflections (R_{int} = 0.119), 2Θmax = 39.56°.

The structure was solved by direct methods SHELXS97[1] and refined by full-matrix block least-squares on F^2 using SHELXL97[1]. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were placed at calculated positions and refined isotropically with temperature factors fixed at 1.2 $U_{(eq)}$ of the parent atom (1.5 $U_{(eq)}$ for methyl groups). Final R-values are: R_1 = 0. 0766 for 5823 observed reflections (>2sigma(I)); R_1 (all data) = 0. 1034, wR_2 = 0.1646 S = 1.058.

Refined flack parameter 0.01(3).

The diffraction limit for the crystals was about 1.05Å and clearly allows observing the F^- anion presence in the crystal structure. Also the absolute configuration is unambiguously determined. The presence of the additional HF is less pronounced. Currently the HF molecule is refined over two positions with a 56/44% ratio.

I.1.4. General procedure for the syntheses of cationic copper(I) complexes: method B

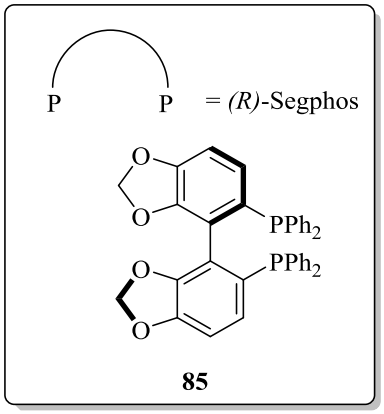


To a plastic vial equipped with a magnetic stirring bar was added mesityl copper (18.3 mg, 0.1 mmol, 1 equiv.) under inert atmosphere. Dry acetonitrile (0.5 mL) was then added and the solution is stirred for 5 min after which $Et_3N.3HF$ (16.3 µL, 0.1 mmol, 1 equiv.) in solution in

acetonitrile (0.2 M) is added and the solution is stirred for 30 min. The diphosphine ligand (0.1 mmol, 1 equiv.) is then added and the solution stirred for 2 hours. The solvent is then evaporated under reduced pressure.

Note: Standard glassware and syringes should be avoided for all the manipulations involving $Et_3N.3HF$.

❖ **From 4,4'-Bi-1,3-benzodioxole-5,5'-diylbis (85)**

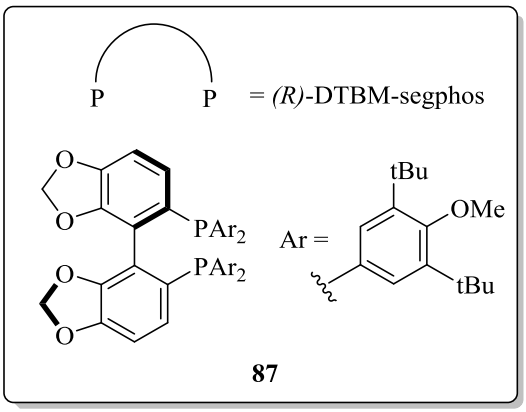


85

Chemical Formula: $C_{42}H_{35}CuF_2N_2O_4P_2$
Molecular Weight: 795.22

Complex was obtained as a white solid. ^1H NMR (300 MHz, CD_3CN) δ 13.79 (brs, 1H, ***H***F_2), 7.72 (d, *J* = 3.5 Hz, 4H, C***H***ar), 7.59 – 7.42 (m, 10H, C***H***ar), 7.42 – 7.32 (m, 2H, C***H***ar), 7.28 (t, *J* = 7.2 Hz, 4H, C***H***ar), 6.48 (d, *J* = 8.1 Hz, 2H, C***H***ar), 6.41 – 6.31 (m, 2H, C***H***ar), 5.84 (s, 2H, C***H***$_2$O), 5.57 (s, 2H, C***H***$_2$O). ^{19}F NMR (282 MHz, CD_3CN) δ -166.6. ^{31}P NMR (121 MHz, CD_3CN) δ -4.40.

❖ **From *(R)*-5,5'-Bis[di(3,5-di-t-butyl-4-methoxyphenyl)phosphino]-4,4'-bi-1,3-benzodioxole (87)**

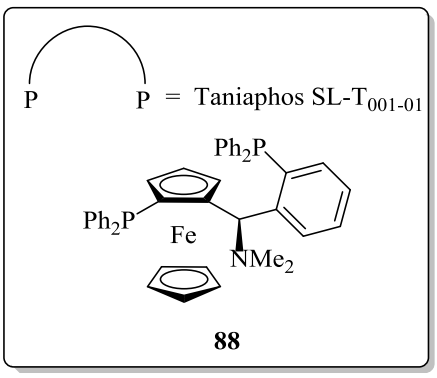


87

Chemical Formula: $C_{78}H_{107}CuF_2N_2O_8P_2$
Molecular Weight: 1364,18

Complex was obtained as a white solid. ^{1}H NMR (300 MHz, CD_3CN) δ 13.77 (brs, 1H, ***H***F_2), 7.65 (s, 4H, C***H***ar), 7.30 (s, 4H, C***H***ar), 6.61 (s, 4H, C***H***ar), 5.57 (s, 2H, C***H***$_2$O), 5.46 (s, 2H, C***H***$_2$O), 3.72 (s, 6H, OC***H***$_3$), 3.63 (s, 6H, OC***H***$_3$), 1.42 (s, 36H, ^{t}Bu), 1.28 (s, 36H, ^{t}Bu). ^{19}F NMR (282 MHz, CD_3CN) δ -166.92. ^{31}P NMR (121 MHz, CD_3CN) δ -2.79.

❖ **From (Dimethylamino)[2-(diphenylphosphino)phenyl]methyl]-2-(diphenylphosphino)ferrocene (88)**



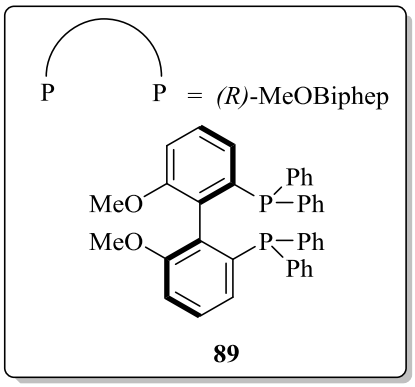
88

Chemical Formula: $C_{47}H_{46}CuF_2FeN_3P_2$
Molecular Weight: 872.22

Complex was obtained as an orange solid. ^{1}H NMR (300 MHz, CD_3CN) δ 13.76 (brs, 1H, ***H***F_2), 7.92 – 7.80 (m, 3H, C***H***ar), 7.74 – 7.51 (m, 10H, C***H***ar), 7.38 (t, *J* = 5.9 Hz, 3H, C***H***ar), 7.25 (t, *J* = 7.3 Hz, 1H, C***H***ar), 7.17 (t, *J* = 7.1 Hz, 1H, C***H***ar), 7.11 – 7.04 (m, 3H, C***H***ar), 6.99 (dd, *J* = 13.6 & 7.2 Hz, 3H, C***H***ar), 6.63 (t, *J* = 7.5 Hz, 1H, Cp), 6.25 (t, *J* = 8.4 Hz, 2H, Cp), 6.14 (t, *J* = 8.4 Hz, 2H, Cp), 5.54 (d, *J*

= 5.1 Hz, 1H, C***H***NMe_2), 4.95 (s, 1H, R_2C_5***H***$_3$), 4.69 (t, *J* = 2.6 Hz, 1H, R_2C_5***H***$_3$), 4.25 (s, 1H, R_2C_5***H***$_3$), 3.90 (s, 6H, NC***H***$_3$). ^{31}P NMR (121 MHz, CD_3CN) δ -11.57. ^{19}F NMR (282 MHz, CD_3CN) δ -166.89.

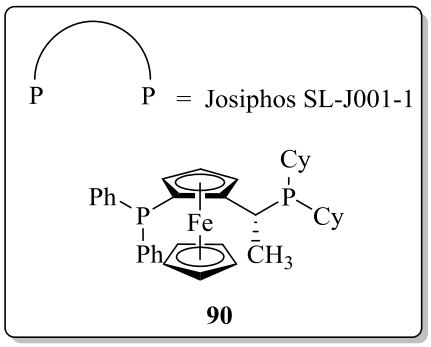
❖ **From *(R)*-MeO-Biphep (89)**



Chemical Formula: $C_{42}H_{39}CuF_2N_2O_2P_2$
Molecular Weight: 767.26

Complex was obtained as a white solid. ^{1}H NMR (300 MHz, CD_3CN) δ 7.73 (d, *J* = 2.9 Hz, 4H, C***H***ar), 7.52 (s, 6H, C***H***ar), 7.37 (d, *J* = 5.2 Hz, 4H, C***H***ar), 7.27 (d, *J* = 7.3 Hz, 2H, C***H***ar), 7.16 (t, *J* = 7.1 Hz, 4H, C***H***ar), 6.96 (t, *J* = 8.1 Hz, 2H, C***H***ar), 6.51 (s, 2H, C***H***ar), 6.37 (d, *J* = 8.2 Hz, 2H, C***H***ar), 3.37 (s, 6H, OC***H***$_3$). ^{31}P NMR (121 MHz, CD_3CN) δ -3.40. ^{19}F NMR (282 MHz, CD_3CN) δ -157.91.

❖ **From Josiphos (90)**

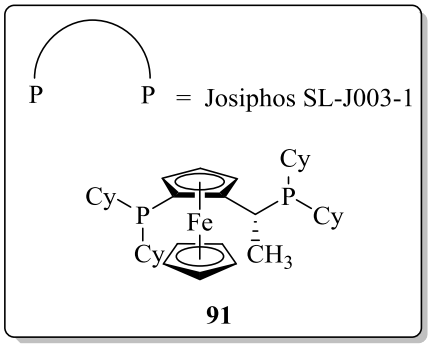


Chemical Formula: $C_{40}H_{51}CuF_2FeN_2P_2$
Molecular Weight: 779.18

Complex was obtained as an orange solid. ^{1}H NMR (300 MHz, CD_3CN) δ 13.87 (brs, 1H, ***H***F_2), 8.01 – 7.88 (m, 2H, C***H***ar), 7.59 (dd, *J* = 4.4, 2.3 Hz, 3H, C***H***ar), 7.40 – 7.27 (m, 3H, C***H***ar), 7.20 – 7.08 (m, 2H, C***H***ar), 4.65 (s, 1H, C_5***H***$_3$), 4.46

(t, *J* = 2.6 Hz, 1H, $C_5\boldsymbol{H}_3$), 4.39 – 4.33 (m, 1H, $C_5\boldsymbol{H}_3$), 3.71 (s, 5H, Cp), 3.39 (d, *J* = 5.8 Hz, 1H, C***H***PCy_2), 1.90 – 0.95 (m, 25H, C$\boldsymbol{H}_3$ & ***Cy***). ^{19}F NMR (282 MHz, CD_3CN) δ -166.16. ^{31}P NMR (121 MHz, CD_3CN) δ 8.55, -16.72.

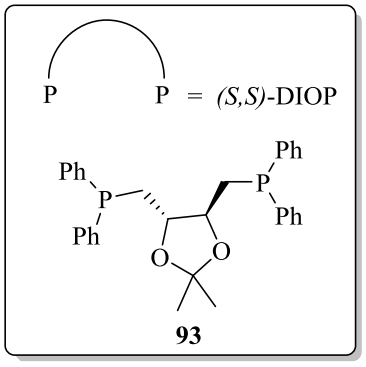
❖ **From Josiphos (91)**



91

Chemical Formula: $C_{40}H_{63}CuF_2FeN_2P_2$
Molecular Weight: 791.27

Complex was obtained as an orange solid. ^{1}H NMR (300 MHz, CD_3CN) δ 13.57 (brs, 1H, ***H***F_2), 4.63 - 4.35 (m, 4H, $C_5\boldsymbol{H}_3$ & C***H***PCy_2), 4.30 (bs, 3H, Cp) 4.24 (s, 2H, Cp), 2.25 – 0.83 (m, 47H, C$\boldsymbol{H}_3$ & ***Cy***). ^{19}F NMR (282 MHz, CD_3CN) δ -166.92. ^{31}P NMR (121 MHz, CD_3CN) δ 2.89, -10.07.



93

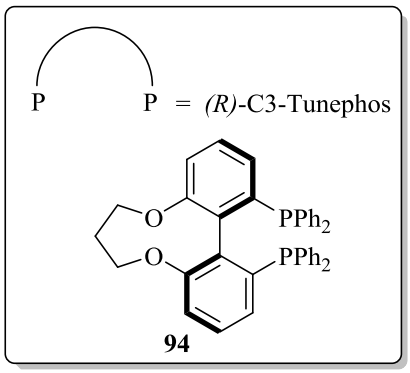
Chemical Formula: $C_{35}H_{39}CuF_2N_2O_2P_2$
Molecular Weight: 683.18

❖ **From 2,2-Dimethyl-4,5-((diphenylphosphino) dimethyl)dioxolane (93)**

Complex was obtained as a white solid. ^{1}H NMR (300 MHz, CD_3CN) δ 13.86 (brs, 1H, ***H***F_2), 7.51 – 7.12 (m, 20H, C***H***ar),

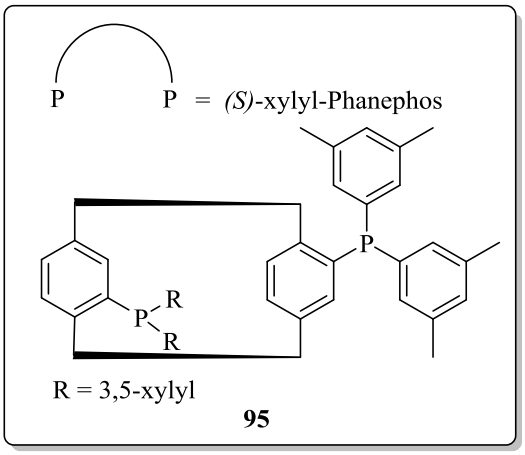
3.48 (m, 2H, OC***H***), 2.63 (m, 4H, PC$\boldsymbol{H}_2$), 1.14 (s, 6H, C$\boldsymbol{H}_3$). ^{19}F NMR (282 MHz, CD_3CN) δ -165.96. ^{31}P NMR (121 MHz, CD_3CN) δ -15.71.

❖ **From Tunephos (94)**



Chemical Formula: $C_{43}H_{39}CuF_2N_2O_2P_2$
Molecular Weight: 779.27

Complex was obtained as a white solid. ^{1}H NMR (300 MHz, CD_3CN) δ 13.67 (brs, 1H, ***H***F_2), 7.61 (dd, *J* = 4.9, 2.6 Hz, 4H, C***H***ar), 7.50 (d, *J* = 5.7 Hz, 6H, C***H***ar), 7.44 – 7.31 (m, 4H, C***H***ar), 7.20 (dt, *J* = 14.1, 7.0 Hz, 6H, C***H***ar), 6.95 (t, *J* = 7.9 Hz, 2H, C***H***ar), 6.73 (d, *J* = 8.0 Hz, 2H, C***H***ar), 6.46 – 6.34 (m, 2H, C***H***ar), 4.25 – 4.11 (m, 4H, OC$\boldsymbol{H}_2$), 1.77 – 1.67 (m, 2H, C$\boldsymbol{H}_2$). ^{19}F NMR (282 MHz, CD_3CN) δ -166.78. ^{31}P NMR (121 MHz, CD_3CN) δ -3.12.



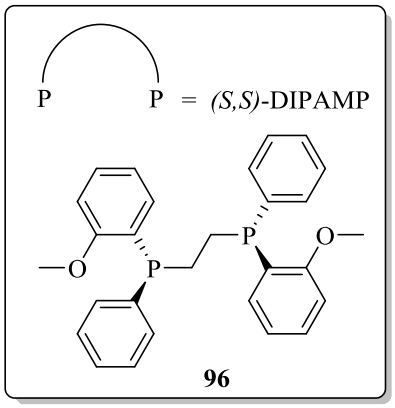
Chemical Formula: $C_{52}H_{57}CuF_2N_2P_2$
Molecular Weight: 873.51

❖ **From Phanephos (95)**

Complex was obtained as a white solid. ^{1}H NMR (300 MHz, CD_3CN) δ 7.51 – 7.01 (m, 16H, C***H***ar), 6.72 – 6.59 (m, 2H, C***H***ar), 2.82 (q, *J* = 7.2 Hz, 8H, C$\boldsymbol{H}_2$), 2.21 (s, 24H, C$\boldsymbol{H}_3$). ^{19}F

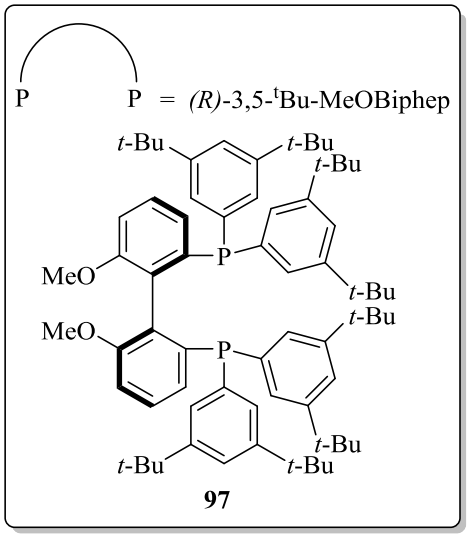
NMR (282 MHz, CD_3CN) δ -161.54. ^{31}P NMR (121 MHz, CD_3CN) δ 0.91.

❖ **From Dipamp (96)**



Chemical Formula: $C_{32}H_{35}CuF_2N_2O_2P_2$
Molecular Weight: 643.12

Complex was obtained as a white solid. ^1H NMR (300 MHz, CD_3CN) δ 7.50 (d, *J* = 5.6 Hz, 2H, C***H***ar), 7.41 – 7.33 (m, 2H, C***H***ar), 7.32 – 7.17 (m, 6H, C***H***ar), 7.09 (t, *J* = 7.4 Hz, 2H, C***H***ar), 7.01 (t, *J* = 7.5 Hz, 4H, C***H***ar), 6.45 (d, *J* = 8.3 Hz, 2H, C***H***ar), 3.21 (s, 6H, OC$\boldsymbol{H}_3$), 2.22 (s, 4H, C$\boldsymbol{H}_2$). ^{19}F NMR (282 MHz, CD_3CN) δ -163.66. ^{31}P NMR (121 MHz, CD_3CN) δ -7.50.



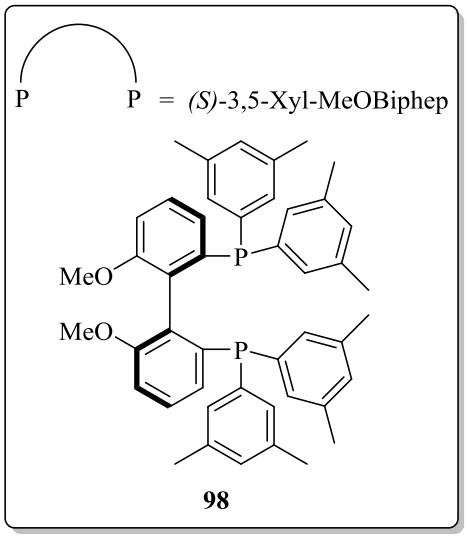
Chemical Formula: $C_{74}H_{103}CuF_2N_2O_2P_2$
Molecular Weight: 1216.11

❖ **From 3.5 tBu MeO Biphep (97)**

Complex was obtained as a white solid. ^1H NMR (300 MHz, CD_3CN) δ 7.73 (s, 3H, C***H***ar), 7.64 (s, 2H, C***H***ar), 7.39 (s, 3H, C***H***ar), 7.20 (s, 3H, C***H***ar), 7.02 (s, 2H, C***H***ar), 6.81 (s, 1H, C***H***ar), 6.74 (s, 2H, C***H***ar), 6.39 (d, *J* = 8.2 Hz, 2H,

C***H***ar), 3.39 (s, 6H, OC***H***$_3$), 1.34 (s, 72H, ^{t}Bu). NMR (282 MHz, CD_3CN) δ -152.19.^{31}P NMR (121 MHz, CD_3CN) δ 0.71.

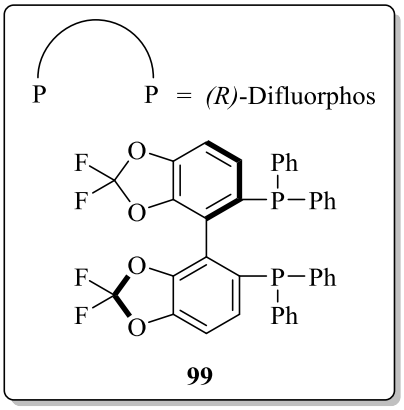
❖ **From 3.5 xyl MeOBiphep (98)**



98

Chemical Formula: $C_{50}H_{55}CuF_2N_2O_2P_2$
Molecular Weight: 879.47

Complex was obtained as a yellow solid. ^{1}H NMR (300 MHz, CD_3CN) δ 7.40 (s, 4H, C***H***ar), 7.18 (s, 3H, C***H***ar), 7.01 (t, *J* = 8.1 Hz, 3H, C***H***ar), 6.92 (dd, *J* = 10.9 & 5.0 Hz, 3H, C***H***ar), 6.81 (s, 1H, C***H***ar), 6.65 (m, 2H, C***H***ar), 6.38 (d, *J* = 8.2 Hz, 2H, C***H***ar), 3.34 (s, 6H, OC***H***$_3$), 2.44 – 2.17 (m, 24H, C***H***$_3$). ^{19}F NMR (282 MHz, CD_3CN) δ -164.28. ^{31}P NMR (121 MHz, CD_3CN) δ -3.51.



99

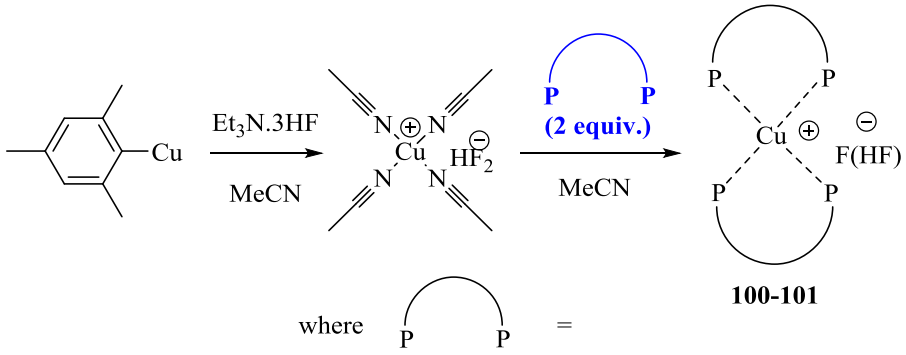
Chemical Formula: $C_{42}H_{31}CuF_6N_2O_4P_2$
Molecular Weight: 867.19

❖ **From Difluorphos (99)**

Complex was obtained as a white solid. ^{1}H NMR (300 MHz, CD_3CN) δ 7.92 (dd, *J* = 11.7, 5.8 Hz, 4H, C***H***ar), 7.64 (d, *J* = 5.7 Hz, 4H, C***H***ar), 7.42 – 7.18 (m, 12H, C***H***ar), 6.88 (d, *J* = 8.4 Hz, 2H, C***H***ar), 6.68 (dt, *J* = 8.5,

4.3 Hz, 2H, C***H***ar). ^{19}F NMR (282 MHz, CD_3CN) δ -48.33 (C***F***), -48.67 (C***F***), -53.45 (C***F***), -53.80 (C***F***), -128.69 (brs, H***F***$_2$). ^{31}P NMR (121 MHz, CD_3CN) δ -8.74.

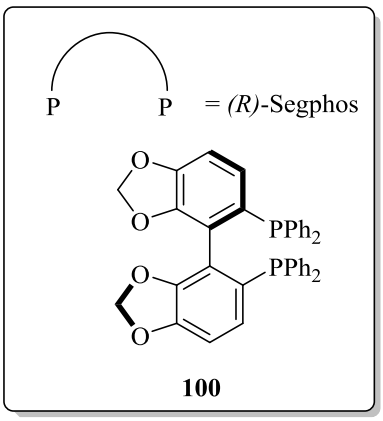
I.1.5. Modified procedure for the synthesis of L_2CuFHF



To a plastic vial equipped with a magnetic stirring bar was added mesityl copper (18.3 mg, 0.1 mmol, 1 equiv.) under inert atmosphere. Dry acetonitrile (0.5 mL) was then added and the solution is stirred for 5 min after which $Et_3N.3HF$ (16.3 µL, 0.1 mmol, 1 equiv.) in solution in acetonitrile (0.2 M) is added and the solution is stirred for 30 min. The diphosphine ligand (0.2 mmol, 2 equiv.) is then added and the solution stirred for 2 hours. The solvent is then evaporated under reduced pressure.

❖ **From 4,4'-Bi-1,3-benzodioxole-5,5'-diylbis (100)**

Complex was obtained as a white solid. ^{1}H NMR (300 MHz, CD_3CN) δ 13.40 (brs, 1H, ***H***F$_2$), 7.69 (s, 8H, C***H***ar), 7.49 (t, *J* = 7.4 Hz, 6H, C***H***ar), 7.28 (d, *J* = 7.9 Hz, 18H, C***H***ar), 7.10 (t, *J* = 7.4 Hz, 4H, C***H***ar), 6.71 (s, 6H, C***H***ar), 6.64 (t, *J* = 7.6 Hz, 6H, C***H***ar), 5.95 (s, 4H, OC***H***$_2$), 5.80 (s,

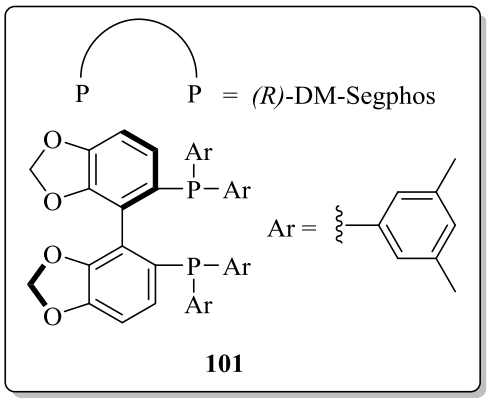


100

Chemical Formula: $C_{76}H_{57}CuF_2O_8P_4$
Molecular Weight: 1323,69

4H, OC***H***$_2$). ^{19}F NMR (282 MHz, CD_3CN) δ -168.27. ^{31}P NMR (121 MHz, CD_3CN) δ -13.70.

❖ **From *(R)*-DM-Segphos (101)**



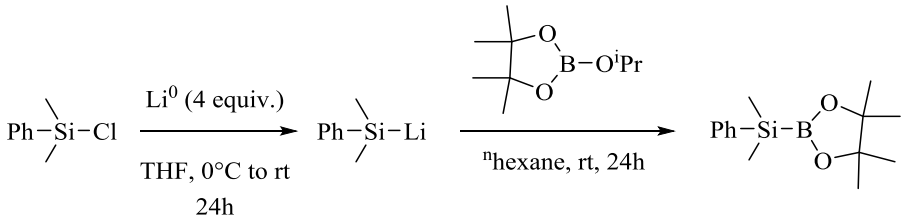
101

Chemical Formula: $C_{92}H_{89}O_8P_4CuF_2$
Molecular Weight: 1548.12

Complex was obtained as a white solid. ^{1}H NMR (300 MHz, CD_3CN) δ 14.41 (brs, 1H, ***H***F_2), 7.36 (m, 4H, C***H***ar), 7.19 (m, 2H, C***H***ar), 7.15 – 7.01 (m, 10H, C***H***ar), 6.97 (s, 2H, C***H***ar), 6.90 (s, 2H, C***H***ar), 6.78 (m, 4H, C***H***ar), 6.70 – 6.43 (m, 8H, C***H***ar), 5.81 (s, 4H, OC***H***$_2$), 5.68 (s, 4H, OC***H***$_2$), 2.17 (s, 48H, C***H***$_3$). ^{19}F NMR (282 MHz, CD_3CN) δ -161.71. ^{31}P NMR (121 MHz, CD_3CN) δ 3.17.

I.1.6. Syntheses of silylboranes

I.1.6.1. Synthesis of 19

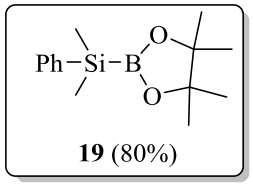


A modified procedure from the literature was used.[2] Metallic lithium in mineral oil (826 mg, 120 mmol, 4 equiv.) was washed with *n*-hexane and added in small portion to THF (30 mL) under an argon flow. The flask was placed in an ice bath and dimethylphenylchlorosilane (5 mL, 30 mmol, 1 equiv.) was added dropwise. The red mixture was vigorously stirred overnight at room temperature and added dropwise *via* syringe to a solution of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (12.2 mL, 60 mmol, 2 equiv.) in *n*-hexane (30 mL). The mixture was stirred overnight at room temperature, and the volatile materials were removed *in vacuo*. The residue was taken in *n*-hexane (30 mL) and filtered through celite under argon (celite was dried *in vacuo* before use). The solvent was removed under reduced pressure and the product was purified by fractioned distillation (bp = 120 °C at 0.1 mbar) to give **19** as a colorless liquid (6.29 g, 80%).

- **Dimethyl(phenyl)(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)silane (19)**

---

[2] Suginome, M.; Matsuda, T.; Ito, Y., *Organometallics* **2000**, *19*, 4647-4649.

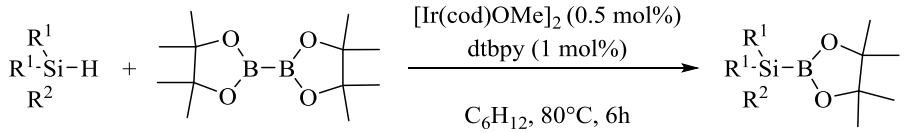


19 (80%)

Chemical Formula: $C_{14}H_{23}BO_2Si$
Molecular Weight: 262,23

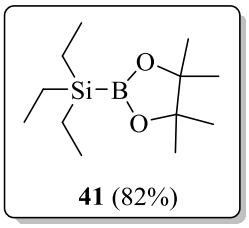
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60-7.50 (m, 2H, C***H***ar.), 7.35-7.30 (m, 3H, C***H***ar.), 1.22 (s, 12H, C***H***$_3$C), 0.32 (s, 6H, C***H***$_3$Si). Spectral data are identical to those reported in the publication.[2]

I.1.6.2. Synthesis of other silylboranes



4 equiv.

A procedure of the literature was used.[3] A dried flask was charged with $[Ir(cod)OMe]_2$ (3.3 mg, 0.005 mmol, 0.005 equiv.), 4,4'-di-tert-butyl-2,2'-dipyridyl (2.7 mg, 0.01 mmol, 0.01 equiv.), B_2pin_2 (0.254 g, 1 mmol, 1 equiv.), cyclohexane (10 mL) and silane (4 mmol, 4 equiv.). The resulting dark brown solution was heated at 80°C. After 6 h, the reaction was cooled to room temperature. The crude reaction mixture was concentrated under high vacuum.



41 (82%)

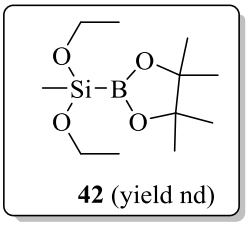
Chemical Formula: $C_{12}H_{27}BO_2Si$
Molecular Weight: 242,24

❖ **Triethyl(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)silane (41)**

[3] Boebel, T. A.; Hartwig, J. F., *Organometallics* **2008**, *27*, 6013-6019.

Purified product was obtained by distillation to give **41** as a colorless oil (0.199 g, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (s, 12H, C***H***$_3$C), 0.96 (t, *J* = 8.0 Hz, 9H, SiCH$_2$C***H***$_3$), 0.58 (q, *J* = 7.3 Hz, 6H, SiC***H***$_2$CH$_3$),. Spectral data are identical to those reported in the publication.[3]

❖ **Diethyl(methoxy)(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)silane (42)**

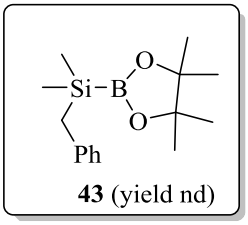


42 (yield nd)

Chemical Formula: $C_{11}H_{25}BO_4Si$
Molecular Weight: 260.21

We were not able to isolate the desired product. Decomposition of the starting material and the product **42** on silica was observed. Characteristic peaks of the product: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.84 - 3.76 (m, 4H, OC***H***$_2$), 1.26 – 1.24 (m, 6H, OCH$_2$C***H***$_3$), 1.23 (s, 12H, OC(C***H***$_3$)$_2$), 0.13 (s, 3H, C***H***$_2$Si).

❖ **Benzyldimethyl(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)silane (43)**

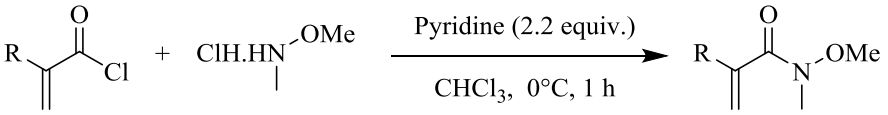


43 (yield nd)

Chemical Formula: $C_{15}H_{25}BO_2Si$
Molecular Weight: 276.25

We were not able to isolate the desired product. A mixture of starting material and product **43** was always obtained. Characteristic peaks of the product: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 – 7.25 (m, 2H, C***H***ar), 7.10 – 7.02 (m, 3H, C***H***ar), 2.60 (d, J = 3.2 Hz, 2H, C***H***$_2$Ph), 1.35 (s, 12H, OC(C***H***$_3$)$_2$), 0.15 (s, 6H, C***H***$_2$Si).

I.1.7. Synthesis of Weinreb acrylamide



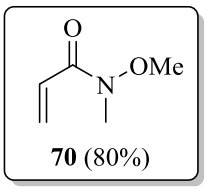
R = H, CH_3

These compounds were synthesized using a modified procedure of the literature.[4] The hydroxylamine hydrochloride was dried on P_2O_5 prior use. A flame-dried flask was loaded with *N,O*-dimethylhydroxylamine hydrochloride (1.95 g, 20 mmol, 1 equiv.). The flask was placed in an ice bath, and dry chloroform (45 mL) was added, followed by the corresponding acryloyl chloride (1.6 mL, 20 mmol, 1 equiv.). A solution of dry pyridine (3.5 mL, 44 mmol, 2.2 equiv.) in $CHCl_3$ (16.5 mL) was then added dropwise. The mixture is removed from the bath, and the solution was stirred at room temperature during one hour. The reaction was quenched with brine (170 mL), and phases were separated. Aqueous phase was extracted with a DCM/ether mixture (1/1, 3 x 50 mL). Combined organic phases were dried over Na_2SO_4 and the product was isolated as a transparent liquid by fractioned distillation under reduced pressure.

❖ **N-methoxy-N-methylacrylamide (70)**

Purified product was obtained by distillation to give **70** as a colorless oil (2.30 g, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.73 (dd, *J* = 17.0, 10.3 Hz, 1H, =C***H***), 6.43 (dd, *J* = 17.0, 2.0 Hz, 1H, *Cis* =C***H***$_2$), 5.75 (dd, *J* = 10.3,

[4] Yoshitomi, Y.; Makino, K.; Hamada, Y., *Org. Lett.* **2007**, *9*, 2457-2460.

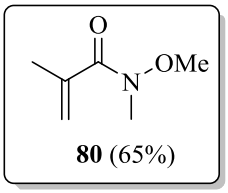


70 (80%)

Chemical Formula: $C_5H_9NO_2$
Molecular Weight: 115,13

2.0 Hz, 1H, *trans* =C***H***$_2$), 3.71 (s, 3H, OC***H***$_3$), 3.25 (s, 3H, NC***H***$_3$). Spectral data are identical to those reported in the publication.[4]

❖ **N-methoxy-N-methylmethacrylamide (80)**

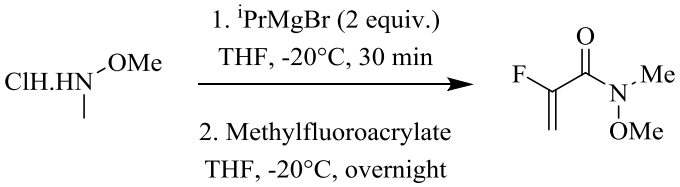


80 (65%)

Chemical Formula: $C_6H_{11}NO_2$
Molecular Weight: 129,16

Purified product was obtained by distillation to give **80** as a colorless oil (2.58 g, 65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.19 (d, *J* = 0.9 Hz, 1H, *Cis* =C***H***$_2$), 5.13 (d, *J* = 0.9 Hz, 1H, *trans* =C***H***$_2$), 3.55 (s, 3H, OC***H***$_3$), 3.13 (s, 3H, NC***H***$_3$), 1.87 (s, 3H, =C***H***$_3$). Spectral data are identical to those reported in the publication.[4]

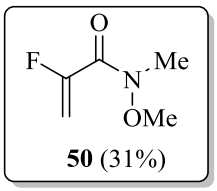
I.1.7.1. Modified procedure for the synthesis of 50



To a solution of N,O-dimethyl hydroxylamine hydrochloride (0.975 g, 10 mmol, 1 equiv.) in anhydrous THF (30 mL) at -20°C is added ^{i}PrMgBr (12.9 mL, 1.5M in Et_2O, 20 mmol, 2 equiv.). After 30 min, methylfluoroacrylate (0.93 mL, 10 mmol, 1 equiv.) is added. The mixture is stirred at -20°C overnight. The reaction is quenched with excess saturated aqueous ammonium chloride. The mixture is diluted with ether and washed successively with saturated aqueous sodium bicarbonate and

brine. The organic layer is dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel using P.E./Et_2O (80/20) as eluent to give the desired product **50** as a colorless oil (1.33 g, 31%).

❖ **2-fluoro-N-methoxy-N-methylacrylamide (50)**

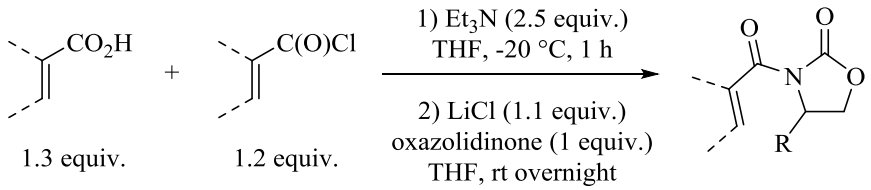


50 (31%)

Chemical Formula: $C_5H_8FNO_2$
Molecular Weight: 133,12

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.32 (dd, *J* = 3.3, 46.5 Hz, 1H, *Trans* =C***H***$_2$), 5.09 (dd, *J* = 3.3, 16.4 Hz, 1 H, *Cis* =C***H***$_2$), 3.66 (s, 3H, OC***H***$_3$), 3.17 (s, 3H, NC***H***$_3$),. Spectral data are identical to those reported in the publication.[5]

I.1.8. Synthesis of enoyloxazolidinones



1.3 equiv. 1.2 equiv.

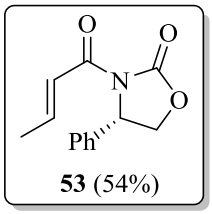
A modified procedure from the literature was used.[6] Under an argon atmosphere, the acid (5.2 mmol, 1.3 equiv.) was dissolved in dry THF (20 mL) with Et_3N (1.4 mL, 10 mmol, 2.5 equiv.). Acyl chloride (4.8 mmol, 1.2 equiv.) was added dropwise at -20 °C and the mixture was stirred 1 h. Dry lithium chloride (186 mg, 4.4 mmol, 1.1 equiv.) was

[5] Mandal, S. K.; Ghosh, A. K.; Kumar, R.; Zajc, B., *Org. Biomol. Chem.* **2012**, *10,* 3164-3167.

[6] Cannizzaro, C. E.; Ashley, J. A.; Janda, K. D.; Houk, K. N., *J. Am. Chem. Soc.* **2003,** *125*, 2489-2506.

added followed by (S)-4-phenyloxazolidin-2-one (0.653 g, 4 mmol, 1 equiv.) and the mixture was stirred overnight. HCl (0.2 M in water, 40 mL) was added. The aqueous phase was saturated with NaCl and extracted with AcOEt (5 x 20 mL). Combined organic phases were washed with $NaHCO_3$ (saturated water solution, 10 mL), brine (10 mL) and dried over Na_2SO_4. The solution was filtered and the solvent was removed under reduced pressure.

❖ ***(S,E)*-3-but-2-enoyl-4-phenyloxazolidin-2-one (53)**



53 (54%)

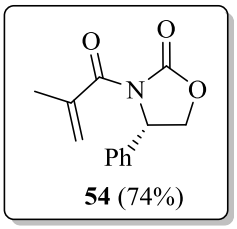
Chemical Formula: $C_{13}H_{13}NO_3$
Molecular Weight: 231,25

The product was purified by flash chromatography on silica gel using P.E./AcOEt (75/25) as eluent to give **53** as a white solid (0.50 g, 54%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 -7.28 (m, 6H, C***H***ar. Et CHC=O), 7.18-7.00 (m, 1H, $CH_3C\boldsymbol{H}$), 5.48 (dd, *J* = 8.7*,* 3.9 Hz, 1H, C***H***N), 4.70 (t, *J* = 8.7 Hz, 1H, $C\boldsymbol{H}_2O$), 4.28 (dd, *J* = 8.7, 3.9 Hz, 1H, $C\boldsymbol{H}_2O$), 1.93 (d, J = 6.3 Hz, 3H, $C\boldsymbol{H}_3$). Spectral data are identical to those reported in the publication.[7]

❖ ***(S)*-3-acryloyl-4-phenyloxazolidin-2-one (54)**

The product was purified by flash chromatography on silica gel using P.E./AcOEt (70/30) as eluent to give **54** as a white solid (0.68 g, 74%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.28 (m, 5H, C***H***ar.), 5.54 - 5.44 (m,

[7] Nakamura, T.; Oshida, M.; Nomura, T.; Nakazaki, A.; Kobayashi, S., *Org. Lett.* **2007**, *9*, 5533-5536.

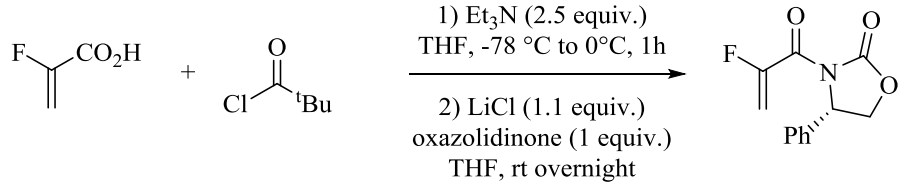


54 (74%)

Chemical Formula: $C_{13}H_{13}NO_3$
Molecular Weight: 231,25

3H, C***H***$_2$=CH & C***H***N), 4.73 (t, *J* = 8.7 Hz, 1H, C***H***$_2$O), 4.26 (dd, *J* = 8.7 & 6.8 Hz, 1H, C***H***$_2$O), 2.00 (s, 3H, C***H***$_3$). Spectral data are identical to those reported in the literature.[5,8]

I.1.8.1 Modified procedure for the synthesis of 52

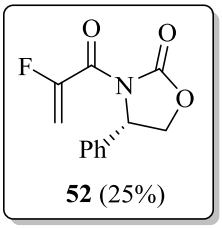


Under an argon atmosphere, the acid (468 mg, 5.2 mmol, 1.3 equiv.) was dissolved in dry THF (15 mL) with Et_3N (1.4 mL, 10 mmol, 2.5 equiv.). Pivaloyl chloride (590 µL, 4.8 mmol, and 1.2 equiv.) was added dropwise at -78 °C and the mixture was stirred 1 h at 0°C. Dry lithium chloride (186 mg, 4.4 mmol, 1.1 equiv.) was added followed by (S)-4-phenyloxazolidin-2-one (0.653 g, 4 mmol, 1 equiv.) and the mixture was stirred overnight. HCl (0.2 M in water, 40 mL) was added and THF was removed under reduced pressure. The aqueous phase was saturated with NaCl and extracted with AcOEt (5 x 20 mL). Combined organic phases were washed with $NaHCO_3$ (saturated water solution, 10 mL), brine (10 mL) and dried over Na_2SO_4. The solution was filtered and the solvent was removed under reduced pressure. The product was finally purified

[8] Welle, A.; Petrignet, J.; Tinant, B.; Wouters, J.; Riant, O., *Chem. Eur. J.* **2010**, *16*, 10980-10983.

by chromatography using P.E./AcOEt (70/30) as eluent to give **52** as a white solid (0.24 g, 25%).

❖ ***(S)*-3-(2-fluoroacryloyl)-4-phenyloxazolidin-2-one (52)**

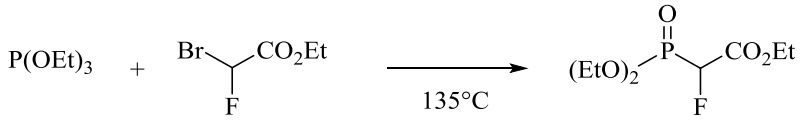


Chemical Formula: $C_{12}H_{10}FNO_3$
Molecular Weight: 235,21

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.30 (m, 5H, C***H***ar.), 5.4 (dd, *J* = 64.5, 3.8 Hz, 1H, =C***H***$_2$), 5.44 (dd, *J* = 8.4, 6.9 Hz, 1H, C***H***N), 5.35 (dd, 6.0, 3.8 Hz, 1H, =C***H***$_2$), 4.76 (t, *J* = 8.8 Hz, 1H, C***H***$_2$O), 4.30 (dd, *J* = 8.8, 6.9 Hz, 1H, C***H***$_2$O). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.3 (d, *J* = 36.6 Hz, ***C***OCF), 155.5 (d, *J* = 267.7 Hz, ***C***F=), 152.4 (N***C***O$_2$), 136.9 (***C***ar.), 129.5 (***C***Har.), 129.3 (***C***Har.), 126.4 (***C***Har.), 102.5 (d, *J* = 14.4 Hz, =***C***H$_2$), 70.7 (***C***H$_2$O), 58.5 (***C***HN). ^{19}F NMR (282 MHz, $CDCl_3$) δ -109.9. HRMS (EI) calculated for $C_{12}H_{10}O_3NF$ $[M]^{+\cdot}$: 235.06392, found: 235.06340 (2.21 ppm). I.R. (cm^{-1}): 3245, 1799, 1737, 1693, 1654, 1380, 1330, 1236, 1037, 694. $[\alpha]_D^{21}$ = +95.8° (c = 0.014, $CHCl_3$).

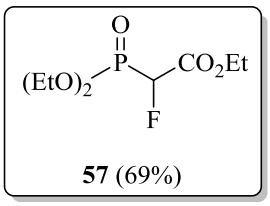
I.1.9. Synthesis of 51

I.1.9.1. Synthesis of intermediate 57



A procedure from the literature was used.[9] Under an argon atmosphere, the flask was loaded with triethylphosphite (1.43 mL, 8.2 mmol, 1 equiv.) and bromofluoroacetate (0.95 mL, 8 mmol, 0.98 equiv.). The mixture was stirred at 135°C during 23h. The product was purified by distillation (1.4 mbar, 100-110°C) during 1h (for removing starting materials) to give the product **57** as yellow oil in 69% yield (1.37 g).

❖ **Ethyl 2-(diethoxyphosphoryl)-2-fluoroacetate (57)**

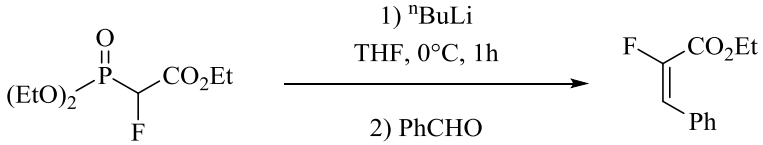


57 (69%)

Chemical Formula: $C_8H_{16}FO_5P$
Molecular Weight: 242.18

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.20 (dd, *J* = 46.9, 12.5 Hz, 1H, C***H***F), 4.38-4.21 (m, 6H, OC***H***$_2$CH$_3$), 1.39-1.31 (m, 9H, OCH$_2$C***H***$_3$). ^{31}P NMR (202 MHz, $CDCl_3$) δ 10.10. Spectral data are identical to those reported in the publication.[6]

I.1.9.2. Synthesis of 51



A dried flask under argon atmosphere was loaded with fluoroacetate (0.484 g, 2 mmol, 1 equiv.) in 2 mL of THF at 0°C (ice bath). Then ^{n}BuLi (1.4 mL, 1.6 M in THF, 2.2 mmol, 1.1 equiv.) was added dropwise

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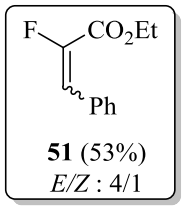
[9] Engman, M.; Diesen, J. S.; Paptchikhine, A.; Andersson, P. G., *J. Am. Chem. Soc.* **2007**, *129*, 4536-4537.

and the mixture was stirred at 0°C during 1h. Benzaldehyde (244 µL, 2.4 mmol, 1.2 equiv.) was added and the mixture was stirred overnight at room temperature. The reaction was quenched with saturated NH_4Cl and then extracted with AcOEt. Organic phases was washed with saturated NaCl and dried over $MgSO_4$. The solution was filtered and solvent was removed under reduced pressure. The product was then purified by flash chromatography on silica gel using P.E./Et_2O (99/1) as eluent to give **51** in 53% yield (0.21 g).

❖ ***(E)*-ethyl 2-fluoro-3-phenylacrylate (51)**



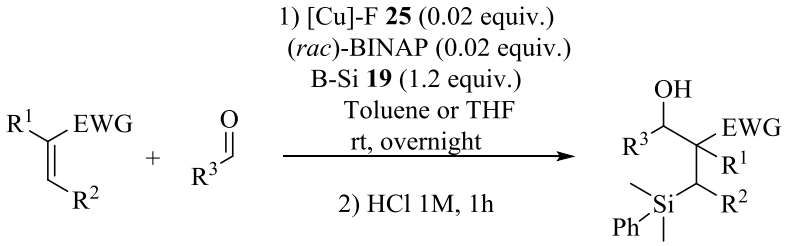
51 (53%)
E/Z : 4/1

Chemical Formula: $C_{11}H_{11}FO_2$
Molecular Weight: 194,20

^{1}H NMR (300 MHz, $CDCl_3$): *(E)*-isomer δ 7.47-7.25 (m, 5H, C***H***ar.), 6.92 (d, J = 22.6 Hz, 1H, C***H***=F), 4.25 (q, *J* = 6.2 Hz, 2H, OC***H***$_2$$CH_3$), 1.24 (t, *J* = 6.0 Hz, 3H, OCH_2C***H***$_3$) and *(Z)*-isomer δ 7.25-7.47 (m, 5H, C***H***ar.), 6.95 (m, 1H, C***H***=F), 4.36 (q, *J* = 7.1 Hz, 2H, OC***H***$_2$$CH_3$), 1.39 (t, *J* = 2.7 Hz, 3H, OCH_2C***H***$_3$). Spectral data are identical to those reported in the publication.[6]

I.2. Catalytic Tests

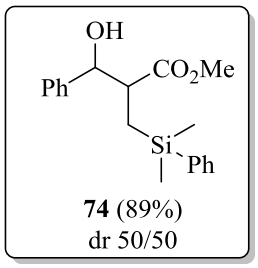
I.2.1. General procedure for domino 1,4-addition/aldolisation reaction with B-Si



R^1 = H, Me, F
R^2 = H, Ph
EWG = CO_2Me, CO_2Et, N(Me)OMe, oxazolidinone
R^3 = Ph, Cy

A dried flask was loaded with $[(Ph_3P)_3CuF.2MeOH]$ (9.3 mg, 0.01 mmol, 0.02 equiv.) and (*rac*)-BINAP (6.2 mg, 0.01 mmol, 0.02 equiv.). The system is closed and after 3 vacuum/argon cycles, solvent (THF or toluene) is added (2.5 mL). After dissolution of solids, Michael acceptor (0.5 mmol, 1 equiv.) and electrophile (0.5 mmol, 1 equiv.) are added. Borosilane **19** (0.17 mL, 0.6 mmol, 1.2 equiv.) is added and the mixture is stirred overnight. The reaction is followed by TLC. HCl (1M, 2.5 mL) is added and the mixture is stirred 1h. Et_2O (5 mL) is added and the phases are separated. The aqueous phase is extracted with Et_2O (3 x 5 mL) and the combined organic phases are dried with Na_2SO_4 and concentrated under reduced pressure. The product is finally purified by flash chromatography on silica gel.

- **Methyl 2-((dimethyl(phenyl)silyl)methyl)-3-hydroxy-3-phenylpropanoate (74)**

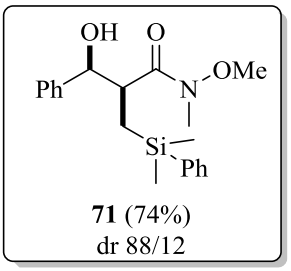


74 (89%)
dr 50/50

Chemical Formula: $C_{19}H_{24}O_3Si$
Molecular Weight: 328,48

The product was purified by flash chromatography on silica gel using P.E./AcOEt as eluent (85/15) to give **74** as a light yellow oil (0.15 g, 89%). ^{1}H NMR (300 MHz, $CDCl_3$) First fraction : δ 7.27-7.60 (m, 10H, C***H***ar.), 4.91 (d, *J* = 4.7 Hz, 1H, C***H***OH), 3.38 (s, 3H, OC***H***$_3$), 2.80 (bs, 1H, O***H***), 2.71-2.78 (m, 1H, C***H***CO_2Me), 1.25 (dd, *J* = 14.8, 7.3 Hz, 1H, C***H***$_2$Si), 1.03 (dd, *J* = 14.8, 2.8 Hz, 1H, C***H***$_2$Si), 0.21 (s, 3H, C***H***$_3$Si), 0.19 (s, 3H, C***H***$_3$Si). Second fraction : δ 7.35-7.23 (m, 10H, C***H***ar.), 4.68 (dd, *J* = 7.8, 5.3 Hz, 1H, C***H***OH), 3.45 (s, 3H, OC***H***$_3$), 2.79 (ddd, *J* = 7.8, 4.7 Hz, 3.5 Hz, 1H, C***H***CO_2Me), 2.71 (d, *J* = 5.3 Hz, 1H, O***H***), 1.17 (dd, *J* = 14.8, 11.6 Hz, 1H, C***H***$_2$Si), 0.73 (dd, *J* = 14.8, 3.5 Hz, 1H, C***H***$_2$Si), 0.24 (s, 3H, C***H***$_3$Si), 0.21 (s, 3H, C***H***$_3$Si). ^{13}C NMR (75 MHz, $CDCl_3$) First fraction δ 175.8 (***C***O_2Me), 141.4 (***C***ar.), 138.3 (***C***ar.), 133.8 (***C***Har.), 129.1 (***C***Har.), 128.4 (***C***Har.), 128.0 (***C***Har.), 127.8 (***C***Har.), 127.7 (***C***Har.), 126.2 (***C***Har.), 75.4 (***C***HOH), 51.6 (O***C***H_3), 48.5 (***C***HCO_2Me), 12.2 (***C***H_2Si), -2.7 (***C***H_3Si), -2.9 (***C***H_3Si). Second fraction δ 176.0 (***C***O_2Me), 141.9 (***C***ar.), 138.0 (***C***ar.), 133.7 (***C***Har.), 129.2 (***C***Har.), 128.7 (***C***Har.), 128.2 (***C***Har.), 127.9 (***C***Har.), 126.8 (***C***Har.), 78.0 (***C***HOH), 51.7 (O***C***H_3), 48.6 (***C***HCO_2Me), 16.0 (***C***H_2Si), -2.8 (***C***H_3Si), -2.9 (***C***H_3Si). LRMS (CI) *M/Z*: 313.0 (35 %), 311.4 (100 %), 251.2 (25 %), 145.3 (35 %), 144.2 (65 %), 137.1 (55 %), 135.2 (35 %), 107.0 (20 %), 105.2 (15 %). IR (cm^{-1}): 3446, 2923, 2850, 1731, 1716, 1247, 1197, 1170, 1112, 1035, 831, 730, 700.

❖ **2-((dimethyl(phenyl)silyl)methyl)-3-hydroxy-N-methoxy-N-methyl-3-phenylpropanamide (71)**



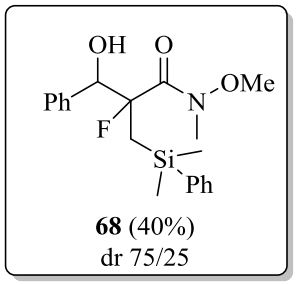
71 (74%)
dr 88/12

Chemical Formula: $C_{20}H_{27}NO_3Si$
Molecular Weight: 357,52

The product was purified by flash chromatography on silica gel using P.E./AcOEt as eluent (75/25) to give **71** as a light yellow oil (0.13 g, 74%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.20 (m, 10H, C***H***Ar.), 4.94 (d, *J* = 3 Hz, 1H, C***H***OH), 3.42 (s, 3H, C***H***$_3$O), 3.20-3.16 (m, 1H, C***H***C(O)), 2.95 (s, 3H, , C***H***$_3$N), 1.30 (dd, *J* = 14.7, 11.8 Hz, 1H, C***H***$_2$Si), 0.96 (dd, *J* = 14.7, 2.3 Hz, 1H, C***H***$_2$Si), 0.18 (s, 3H, C***H***$_3$Si), 0.15 (s, 3H, C***H***$_3$Si). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0 (***C***=O), 141.8 (***C***ar.), 138.5 (***C***ar.), 133.8 (***C***Har.), 128.9 (***C***Har.), 128.3 (***C***Har.), 127.7 (***C***Har.), 127.3 (***C***Har.), 126.1 (***C***Har.), 74.8 (***C***HOH), 61.2 (***C***H$_3$O), 42.7 (***C***HC(O)), 32.0 (***C***H$_3$N), 10.8 (***C***H$_2$Si), -2.5(***C***H$_3$Si), -2.8 (***C***H$_3$Si). LRMS (CI) *M/Z*: 358.6 (20 %), 342.4 (40 %), 340.5 (35 %), 280.5 (100 %), 278.4 (15 %). IR (cm^{-1}): 3398, 2954, 1633, 1427, 1247, 1112, 842, 732, 700.

❖ **2-((dimethyl(phenyl)silyl)methyl)-2-fluoro-3-hydroxy-N-methoxy-N-methyl-3-phenylpropanamide (68)**

The product was purified by flash chromatography on silica gel using P.E./AcOEt as eluent (90/10) to give **68** as a light yellow oil (0.075 g, 40%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.26 (m, 10H, C***H***Ar), 5.03 (d, *J* = 12.7 Hz, 1H, C***H***OH), 3.48 (s, 3H, C***H***$_3$O), 2.89 (s, 3H, , C***H***$_3$N), 1.81 (m, 1H, C***H***$_2$Si), 1.68 (m, 1H, C***H***$_2$Si), 0.30 (s, 3H, C***H***$_3$Si), 0.28 (s, 3H, C***H***$_3$Si). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0 (***C***=O), 138.8 (***C***ar.),

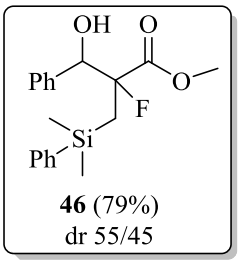


68 (40%)
dr 75/25

Chemical Formula: $C_{20}H_{26}FNO_3Si$
Molecular Weight: 375,51

138.7 (***C***ar.), 129.1 (***C***Har.), 128.5 (***C***Har.), 128.1 (***C***Har.), 128.0 (***C***Har.), 127.9 (***C***Har.), 127.8 (***C***Har.), 101.5 (F***C***), 77.8 (***C***HOH), 61.8 (***C***H_3O), 33.5 (***C***H_3N), 21.8 (***C***H_2Si), -1.5(***C***H_3Si), -1.9 (***C***H_3Si). ^{19}F NMR (282 MHz, $CDCl_3$) δ -157.0. HRMS (APCI): Mass Calculated for $C_{20}H_{25}O_2NFSi$ $[M+H-H_2O]^+$, theoretical Mass: 358.16331, measured Mass: 358.16336. IR (cm^{-1}): 3419, 2955, 1635, 1454, 1427, 1386, 1226, 1112, 1059, 955, 845, 824, 735, 700.

❖ **Methyl 2-((dimethyl(phenyl)silyl)methyl)-2-fluoro-3-hydroxy-3-phenylpropanoate (46)**



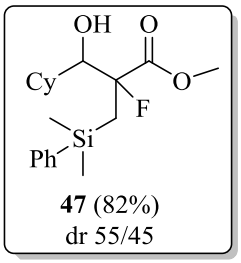
46 (79%)
dr 55/45

Chemical Formula: $C_{19}H_{23}FO_3Si$
Molecular Weight: 346,47

The product was purified by flash chromatography on silica gel using P.E./Et_2O as eluent (80/20) to give **46** as a light yellow oil (0.14 g, 79%). ^{1}H NMR (300 MHz, $CDCl_3$) First fraction δ 7.48-7.28 (m, 10H, C***H***Ar.), 4.81 (d, *J* = 17.4 Hz, 1H, C***H***OH), 3.27 (s, 3H, OC***H***$_3$), 2.83 (bs, 1H, O***H***), 1.78 (dd, *J* = 14.9, 5.5 Hz, 1H, C***H***$_2$Si), 0.85 (m, 1H, C***H***$_2$Si), 0.31 (s, 3H, C***H***$_3$Si), 0.29 (s, 3H, C***H***$_3$Si). Second fraction δ 7.48-7.28 (m, 10H, C***H***Ar.), 4.86 (s, 1H, C***H***OH), 3.47 (s, 3H, OC***H***$_3$), 1.81 (m, 2H, C***H***$_2$Si), 0.36 (s, 3H, C***H***$_3$Si), 0.34 (s, 3H, C***H***$_3$Si). ^{13}C NMR (75 MHz, $CDCl_3$) First fraction δ 170.8 (***C***O_2Me), 137.7 (***C***ar.), 133.8 (***C***ar.), 129.7 (***C***Har.), 128.6 (***C***Har.), 128.2 (***C***Har.), 128.0 (***C***Har.), 127.8 (***C***Har.), 127.6 (***C***Har.), 127.1 (***C***Har.), 100.3 (F***C***CO_2Me), 78.2

(***C***HOH), 52.1 (O***C***H_3), 21.6 (***C***H_2Si), -1.8 (***C***H_3Si), -2.6 (***C***H_3Si). Second fraction δ 171.6 (***C***O_2Me), 137.8 (***C***ar.), 133.8 (***C***ar.), 129.7 (***C***Har.), 128.6 (***C***Har.), 128.2 (***C***Har.), 128.0 (***C***Har.), 127.8 (***C***Har.), 127.6 (***C***Har.), 127.1 (***C***Har.), 100.5 (F***C***CO_2Me), 79.1 (***C***HOH), 52.3 (O***C***H_3), 22.3 (***C***H_2Si), -1.7 (***C***H_3Si), -2.5 (***C***H_3Si). ^{19}F NMR (282 MHz, $CDCl_3$) δ -168.2 (Second fraction), -163.1 (First fraction). HRMS (APCI): Mass Calculated for $C_{19}H_{22}O_2FSi$ $[M+H-H_2O]^+$, theoretical Mass: 329.13676, measured Mass: 329.13677. IR (cm^{-1}): 3475, 3069, 2953, 1738, 1427, 1315, 1250, 1226, 1198, 1112, 1061, 827, 798, 729, 692.

❖ **Methyl 3-cyclohexyl-2-((dimethyl(phenyl)silyl)methyl)-2-fluoro-3-hydroxypropanoate (47)**

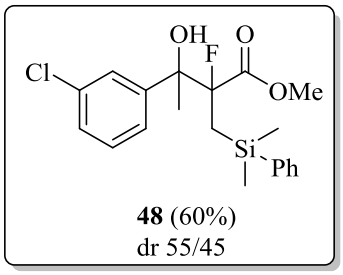


Chemical Formula: $C_{19}H_{29}FO_3Si$
Molecular Weight: 352,52

The product was purified by flash chromatography on silica gel using DCM/Et_2O as eluent (90/10) to give **47** as a light yellow oil (0.14 g, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 – 7.45 (m, 2H, C***H***ar), 7.35 (dd, J = 6.1, 2.7 Hz, 3H, C***H***ar), 3.55 (s, 0.5H, C***H***OH), 3.47 (s, 3H, OC***H***$_3$), 3.44 (s, 0.5H, C***H***OH), 1.82 – 1.57 (m, 6H, Cy), 1.51 (d, J = 14.5 Hz, 2H, C***H***$_2$Si), 1.39 – 0.99 (m, 5H, Cy), 0.36 (s, 3H, C***H***$_3$Si), 0.33 (s, 3H, C***H***$_3$Si). ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.9 (***C***O_2Me), 133.9 (***C***ar.), 129.4 (***C***Har.), 127.9 (***C***Har.), 100.4 (F***C***CO_2Me), 79.9 (***C***HOH), 52.4 (O***C***H_3), 38.7 (***C***H), 31.3 (***C***H_2), 26.4 (***C***H_2), 22.8 (***C***H_2Si), -1.8 (***C***H_3Si), -2.4 (***C***H_3Si). ^{19}F NMR (282 MHz, $CDCl_3$) δ -163.3. HRMS (APCI): Mass Calculated for $C_{19}H_{29}O_3Si$ $[M+H-HF]^+$,

theoretical Mass: 333.18805, measured Mass: 333.18804. IR (cm^{-1}): 3508, 2926, 2853, 1742, 1437, 1312, 1274, 1249, 1199, 1113, 1007, 835, 700.

❖ **Methyl 3-(3-chlorophenyl)-2-((dimethyl(phenyl)silyl)methyl)-2-fluoro-3-hydroxybutanoate (48)**



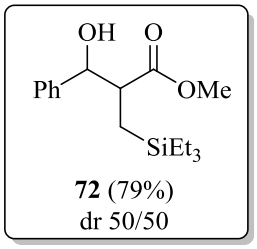
48 (60%)
dr 55/45

Chemical Formula: $C_{20}H_{24}ClFO_3Si$
Molecular Weight: 394,94

The product was purified by flash chromatography on silica gel using DCM/Et_2O as eluent (90/10) to give **48** as a light yellow oil (0.12 g, 60%). ^{1}H NMR (300 MHz, $CDCl_3$) First fraction δ 7.94 (s, 1H, C***H***ar), 7.62 – 7.16 (m, 8H, C***H***ar), 3.55 (s, 3H, OC***H***$_3$), 1.80 (d, *J* = 12.1 Hz, 2H, C***H***$_2$Si), 1.59 (s, 3H, C***H***$_3$), 0.36 (s, 3H, C***H***$_3$Si), 0.33 (s, 3H, C***H***$_3$Si). Second fraction δ 7.84 (d, *J* = 7.7 Hz, 1H, C***H***ar), 7.62 – 7.16 (m, 8H, C***H***ar), 3.41 (s, 3H, OC***H***$_3$), 1.72 (d, *J* = 17.5 Hz, 2H, C***H***$_2$Si), 1.56 (s, 3H, C***H***$_3$), 0.25 (s, 3H, C***H***$_3$Si), 0.19 (s, 3H, C***H***$_3$Si). ^{13}C NMR (75 MHz, $CDCl_3$) First fraction δ 172.7 (d, *J* = 16.2 Hz, ***C***O_2Me), 145.5 (***C***ar), 137.6 (***C***ar), 133.8 (***C***Har), 129.3 (***C***Har), 129.1 (***C***Har), 129.0 (***C***Har), 127.8 (***C***Har), 127.8 (***C***Har), 127.5 (***C***Har), 126.5 (***C***Har), 125.3 (***C***Har), 124.4 (***C***OH), 101.5 (***C***F), 52.2 (O***C***H_3), 26.8 (C***C***H_3), 20.9 (d, *J* = 8.1 Hz, ***C***H_2Si), -1.6 (***C***H_3Si), -2.1 (***C***H_3Si). Second fraction δ 172.0 (d, *J* = 23.1 Hz, ***C***O_2Me), 143.6 (***C***ar), 133.9 (***C***ar), 133.3 (***C***Har), 129.2 (***C***Har), 127.8 (***C***Har), 127.7 (***C***Har), 127.4 (***C***Har), 126.5 (***C***Har), 125.3 (***C***Har), 124.4 (***C***OH), 98.9 (***C***F), 52.2 (O***C***H_3), 25.4 (C***C***H_3), 20.5 (d, *J* = 8.5 Hz, ***C***H_2Si), -1.7 (***C***H_3Si), -2.6 (***C***H_3Si). ^{19}F NMR (282 MHz, $CDCl_3$) δ -159.2. HRMS (APCI): Mass Calculated for

$C_{20}H_{23}O_2ClFSi$ $[M+H-H_2O]^+$, theoretical Mass: 377.11344, measured Mass: 377.11318. IR (cm^{-1}): 3504, 3070, 2953, 1738, 1689, 1570, 1425, 1313, 1249, 1177, 1112, 1009, 825, 757, 673.

❖ **Methyl 2-(triethylsilyl)methyl)-3-hydroxy-3-phenylpropanoate (72)**



Chemical Formula: $C_{17}H_{28}O_3Si$
Molecular Weight: 308,49

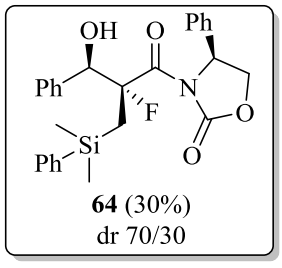
The product was purified by flash chromatography on silica gel using P.E./AcOEt as eluent (80/20) to give **72** as a light yellow oil (0.12 g, 79%). ^{1}H NMR (300 MHz, $CDCl_3$) First fraction δ 7.89 – 7.86 (m, 2H, C***H***ar.), 7.47-7.43 (m, 3H, C***H***ar.), 4.67 (d, *J* = 8.0 Hz, 1H, C***H***OH), 3.68 (s, 3H, OC***H***$_3$), 2.81 – 2.74 (m, 1H, C***H***C(O)OMe), 2.33 (bs, 1H, O***H***), 1.23 (m, 2H, C***H***$_2$Si), 0.81 (td, *J* = 7.8, 2.1 Hz, 9H, SiCH$_2$C***H***$_3$), 0.42 (dd, *J* = 8.0, 3.0 Hz, 6H, SiC***H***$_2$CH$_3$). Second fraction δ 7.63 – 7.53 (m, 2H, C***H***ar.), 7.42 – 7.33 (m, 3H, C***H***ar.), 4.89 (d, *J* = 5.0 Hz, 1H, C***H***OH), 3.57 (s, 3H, OC***H***$_3$), 2.86 – 2.81 (m, 1H, C***H***C(O)OMe), 1.25 (m, 2H, C***H***$_2$Si), 0.91 (td, *J* = 7.9, 2.8 Hz, 9H, SiCH$_2$C***H***$_3$), 0.58 (dd, *J* = 8.0, 3.0 Hz, 6H, SiC***H***$_2$CH$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) First fraction δ 176.3 (***C***O$_2$Me), 142.0 (***C***ar), 128.7 (***C***Har), 126.7 (***C***Har), 75.6 (***C***HOH), 51.9 (O***C***H$_3$), 48.7 (***C***HCO$_2$Me), 30.7 (Si***C***H$_2$), 7.4 (Si***C***H$_2$CH$_3$), 3.2 (SiCH$_2$***C***H$_3$). Second fraction δ 175.4 (***C***O$_2$Me), 141.0 (***C***ar), 128.3 (***C***Har), 127.8 (***C***Har), 126.1 (***C***Har), 74.8 (***C***HOH), 50.7 (O***C***H$_3$), 46.5 (***C***HCO$_2$Me), 29.1 (Si***C***H$_2$), 7.2 (Si***C***H$_2$CH$_3$), 3.0 (SiCH$_2$***C***H$_3$). HRMS (APCI): Mass Calculated for $C_{17}H_{27}O_2Si$ $[M+H-H_2O]^+$, theoretical Mass: 291.17748, measured Mass:

291.17717. IR (cm^{-1}): 2951, 2933, 2910, 2873, 1735, 1454, 1436, 1261, 1166, 1118, 1014, 796, 757, 700.

I.2.2. Modified procedure for tandem reaction with enoyloxazolidinones

A dried round bottom flask was loaded with [$CuF(PPh_3)_3$.2MeOH] (9.1 mg, 0.01 mmol, 0.02 equiv.), DPPF (5.5 mg, 0.01 mmol, 0.02 equiv.) and the enoyloxazolidinone (0,5 mmol, 1 equiv.). After 3 vacuum-argon cycles, THF (2.5 mL) and the aldehyde (0.5 mmol, 1 equiv.) were added by syringe, followed by the borosilane (170 μL, 0.6 mmol, 1.2 equiv.). The medium became warm and after stirring 1 h, SiO_2 (1 g) was added, and the mixture was stirred 30 min. EtOAc (20 mL) was added and the solution was filtered, the silica was washed with EtOAc and solvent was removed under reduced pressure. The product was purified by flash chromatography on silica gel.

❖ ***(4S)*-3-(2-((dimethyl(phenyl)silyl)methyl)-2-fluoro-3-hydroxy-3-phenylpropanoyl)-4 phenyloxazolidin-2-one (64)**



64 (30%)
dr 70/30

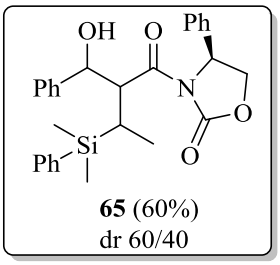
Chemical Formula: $C_{27}H_{28}FNO_4Si$
Molecular Weight: 477,60

The product was purified by flash chromatography on silica gel using P.E./AcOEt as eluent (80/20) to give **64** as a light yellow oil (0.072 g, 30%). ^{1}H NMR (300 MHz, $CDCl_3$) δ *major isomer* 7.60-7.08 (m, 13H, C***H***ar), 6.67 (d, *J* = 7.2 Hz, 2H, C***H***ar), 5.50 (d, *J* = 21.7 Hz, 1H, C***H***OH), 4.34 (dd, *J* = 8.6 & 4.5 Hz, 1H, C***H***N), 4.02 – 3.87 (m, 2H, C$\boldsymbol{H_2}$O), 2.20 (d, *J* = 15.5 Hz, 0.5H,

SiC***H***$_2$), 2.08 – 2.01 (m, 1.5H, SiC***H***$_2$), 0.40 (d, *J* = 1.5 Hz, 3H, SiC***H***$_3$), 0.27 (s, 3H, SiC***H***$_3$). *Minor isomer* 7.50-7.20 (m, 15H, C***H***ar), 5.05 (d, *J* = 25.2 Hz, 1H, C***H***OH), 4.64 (bs, 1H, OH), 4.50 – 4.14 (m, 2H, C***H***N, C***H***$_2$O), 4.13 – 4.09 (m, 1H, C***H***$_2$O), 1.75 (dd, *J* = 39.2 & 14.8 Hz, 1H, SiC***H***$_2$), 1.54 (dd, *J* = 14.8 & 7.2 Hz, 1H, SiC***H***$_2$), 0.20 (s, 3H, SiC***H***$_3$), 0.17 (s, 3H, SiC***H***$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ *major isomer* 168.5 (d, *J* = 25.0 Hz, **C**(O)N), 152.3 (***C***(O)O), 138.6 (***C***ar), 138.5 (***C***ar), 137.9 (***C***ar), 134.2 (***C***Har), 129.2 (***C***Har), 129.0 (***C***Har), 128.5 (***C***Har), 127.9 (***C***Har), 127.8 (***C***Har), 127.7 (***C***Har), 126.0 (***C***Har), 101.9 (d, *J* = 187.8 Hz, ***C***FCH$_2$Si), 75.6 (d, *J* = 20.7 Hz, ***C***HOH), 70.1 (***C***H$_2$O), 59.0 (***C***HN), 20.7 (d, *J* = 29.8 Hz, ***C***H$_2$Si), -1.0 (Si***C***H$_3$), -2.9 (Si***C***H$_3$). *Minor isomer* 171.7 (d, *J* = 24.6 Hz, **C**(O)N), 152.9 (***C***(O)O), 138.4 (***C***ar), 138.0 (***C***ar), 137.6 (***C***ar), 134.4 (***C***Har), 129.2 (***C***Har), 129.1 (***C***Har), 128.7 (***C***Har), 128.5 (***C***Har), 128.2 (***C***Har), 127.7 (***C***Har), 125.6 (***C***Har), 103.2 (d, *J* = 195.0 Hz, ***C***FCH$_2$Si), 78.5 (d, *J* = 22.0 Hz, ***C***HOH), 70.7 (***C***H$_2$O), 59.9 (***C***HN), 22.8 (d, *J* = 30.3 Hz, ***C***H$_2$Si), -1.9 (Si***C***H$_3$). ^{19}F NMR (282 MHz, $CDCl_3$) δ *major* -154.2, *minor* -161.2. HRMS (ESI) calculated for $C_{27}H_{28}FNaNO_4Si$ $[M+Na]^+$: 500.1669, found 500.1673. IR (film, cm^{-1}): 3485, 2920, 1780, 1704, 1384, 1323, 1197, 1112, 1045, 838, 698.

- ***(4S)*-3-(3-(dimethyl(phenyl)silyl)-2-(hydroxy(phenyl)methyl)butanoyl)-4-phenyloxazolidin-2-one (65)**

The product was purified by flash chromatography on silica gel using P.E./AcOEt as eluent (85/15) to give **65** as a light yellow oil (0.16 g, 60%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70-7.10 (m, 15H, C***H***ar.), 5.01 (d, *J* = 4 Hz, 1H, C***H***OH), 4.96 (dd, *J* = 8.3 & 3.0 Hz, 1H, C***H***N), 4.42 (dd,

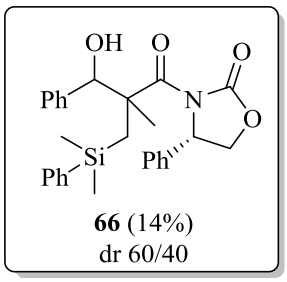


65 (60%)
dr 60/40

Chemical Formula: $C_{28}H_{31}NO_4Si$
Molecular Weight: 473,64

J = 8.2 & 4.0 Hz, 1H, C***H***CON), 4.10 (dd, *J* = 8.6 & 2.8 Hz, 1H, C***H***$_2$O), 4.01 (t, *J* = 8.2 Hz, 1H, C***H***$_2$O), 1.64 (d, *J* = 7.6 Hz, 1H, SiC***H***CH$_3$), 1.01 (d, *J* = 7.6 Hz, 3H, SiCHC***H***$_3$), 0.21 (s, 3H, C***H***$_3$Si), 0.09 (s, 3H, C***H***$_3$Si). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.6 (***C***(O)N), 153.1 (***C***(O)O), 143.0 (***C***ar), 138.6 (***C***ar), 138.1 (***C***ar), 134.1 (***C***Har), 129.1 (***C***Har), 128.9 (***C***Har), 128.3 (***C***Har), 127.8 (***C***Har), 127.3 (***C***Har), 126.6 (***C***Har), 125.3 (***C***Har), 73.0 (***C***HOH), 69.7 (***C***H$_2$O), 57.7 (***C***HN), 50.3 (***C***HCHSi), 20.2 (***C***H$_3$CH), 12.5 (***C***HSi), -3.1 (***C***H$_3$Si), -4.8 (***C***H$_3$Si). HRMS (ESI) calculated for $C_{28}H_{31}NO_4NaSi$ $[M+Na]^+$: 496.1920, found 496.1898. IR (film, cm^{-1}): 3954, 3504, 1778, 1379, 1321, 1249, 1188, 1105, 813, 769, 734.

❖ 3-(2-((dimethyl(phenyl)silyl)methyl)-3-hydroxy-2-methyl-3-phenylpropanoyl)oxazolidin-2-one (66)



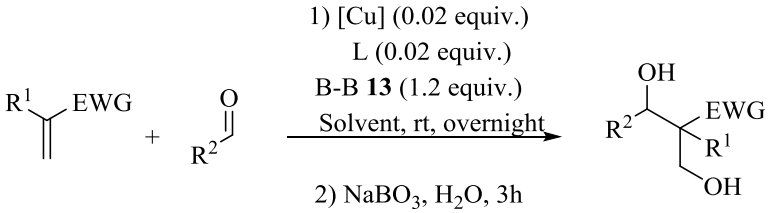
66 (14%)
dr 60/40

Chemical Formula: $C_{28}H_{31}NO_4Si$
Molecular Weight: 473,64

The product was purified by flash chromatography on silica gel using P.E./DCM as eluent (50/50) to give **66** as a light yellow oil (0.033 g, 14%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10-7.60 (m, 15H, C***H***ar.), 5.96 (dd, *J* = 8.8 & 5.4 Hz, 1H, C***H***N), 5.12 (s, 1H, C***H***OH), 4.61 (t, *J* = 10.2 Hz, 1H, C***H***$_2$O), 4.26 (dd, *J* = 11.3 & 5.4 Hz, 1H, C***H***$_2$O), 2.69 (bs, 1H, O***H***), 1.23 (d, *J* = 14.5 Hz, 1H, SiC***H***$_2$), 1.05-1.12 (m, 4H, C***H***$_3$ & Si***H***$_2$),

0.40 (s, 3H, SiC***H***$_3$), 0.38 (s, 3H, SiC***H***$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.4 (***C***(O)N), 151.4 (***C***(O)O), 139.2 (***C***ar.), 136.5 (***C***ar.), 133.8 (***C***Har.), 133.7 (***C***ar.), 129.3 (***C***Har.), 129.2 (***C***Har.), 128.6 (***C***Har.), 128.4 (***C***Har.), 128.3 (***C***Har.), 128.1 (***C***Har.), 128.0 (***C***Har.), 127.9 (***C***Har.), 83.7 (***C***HOH), 62.0 (***C***H$_2$O), 58.9 (***C***HN), 45.3 (***C***CH$_2$Si), 24.5 (***C***H$_2$Si), 20.3 (C***C***H$_3$), -0.4 (***C***H$_3$Si), -0.6 (***C***H$_3$Si). HRMS (ESI) calculated for $C_{28}H_{31}NO_4NaSi$ $[M+Na]^+$: 496.1920, found : 496.1910. I.R. (film, cm^{-1}): 3496, 2975, 1753, 1695, 1379, 1353, 1311, 1247, 835, 698.

I.2.3. General procedure for domino 1,4-addition/aldolisation reaction with B-B



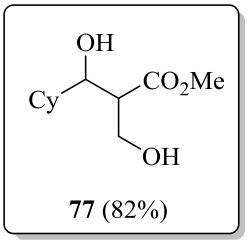
R^1 = H, Me, F
EWG = CO_2Me, CO_2Et, N(Me)OMe, oxazolidinone
R^2 = Ph, Cy

A dried flask was loaded with [Cu] (0.01 mmol, 0.02 equiv.) and ligand (0.01 mmol, 0.02 equiv.). The system is closed and after 3 vacuum/argon cycles, the solvent (2.5 mL) was added by syringe. After dissolution of the solids, the Michael acceptor (0.5 mmol, 1 equiv.) and the electrophile (0.5 mmol, 1 equiv.) are added. Bis(pinacolato)diboron (152 mg, 0.6 mmol, 1.2 equiv.) is added in solution in THF or toluene (0.5 mL), and the mixture is stirred overnight. Water (2.5 mL) and $NaBO_3$ (249 mg, 2.5 mmol, 5 equiv.) are added and the solution is stirred for 3 h. AcOEt (5 mL) is added, the aqueous phase is saturated with NaCl and the phases

are separated. The aqueous phase is extracted with AcOEt (3 x 5 mL) and the combined organic phases are dried over Na_2SO_4 and concentrated under reduced pressure. The product is finally purified by flash chromatography on silica gel. Pinacol is often a by product found in analytical samples. A simple distillation under vacuum leads to the pure aldol adducts.

N.B. When toluene is used as solvent, Et_2O (2.5 mL) must be added to the mixture during the oxidation.

❖ **Methyl 3-cyclohexyl-3-hydroxy-2-(hydroxymethyl)propanoate (77)**



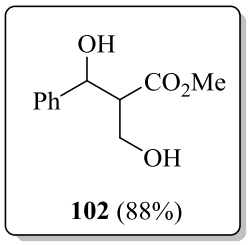
77 (82%)

Chemical Formula: $C_{11}H_{20}O_4$
Molecular Weight: 216,27

The product was purified by flash chromatography on silica gel using P.E./AcOEt as eluent (65/35) to give **77** as a light yellow oil (0.0887 g, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) Major isomer: δ 4.03 (d, *J* = 3.6 Hz, 2H, C***H***$_2$OH & C***H***OH), 3.84 (dd, J = 7.5 Hz & 4.2 Hz, 1H, C***H***$_2$OH), 3.77 (s, 3H, C***H***$_3$O), 2.73 (q, *J* = 4.2 Hz, 1H, ***H***CO_2Me), 0.8-2.1 (m, 11H, C***H***cy). Minor isomer: δ 3.97 (t, *J* = 5.5 Hz, 2H, C***H***$_2$OH & C***H***OH), 3.76 (s, 3H, C***H***$_3$O), 3.56 (dd, J = 7.7 Hz & 3.5 Hz, 1H, C***H***$_2$OH), 2.83 (q, *J* = 5 Hz, 1H, ***H***CO_2Me), 0.8-2.1 (m, 11H, C***H***cy). ^{13}C NMR (75 MHz, $CDCl_3$) Major isomer: δ 174.9 (***C***O_2Me), 76.7 (***C***HOH), 61.0 (O***C***H_2), 52.2 (O***C***H_3), 48.3 (***C***HCO_2Me), 41.2 (***C***Hcy), 29.4 (***C***H_2cy), 26.4 (***C***H_2cy.), 25.9 (***C***H_2cy). Minor isomer: δ 174.5 (***C***O_2Me), 76.5 (***C***HOH), 63.6 (O***C***H_2), 52.0 (O***C***H_3), 48.7 (***C***HCO_2Me), 42.0 (***C***Hcy), 29.6 (***C***H_2cy), 26.1 (***C***H_2cy), 25.9 (***C***H_2cy). LRMS (APCI) *M/Z* : 216.8 (100 %), 198.5 (75 %), 100.8 (25 %). HRMS

(CI) calculated for $C_{11}H_{20}O_4Na$ ($[M+Na]^+$) 239.1259, found 239.1256. IR (film, cm^{-1}): 3419, 2925, 2852, 1731, 1436, 1259, 1172, 1118, 723, 696.

❖ **Methyl 3-hydroxy-2-(hydroxymethyl)-3-phenylpropanoate (102)**

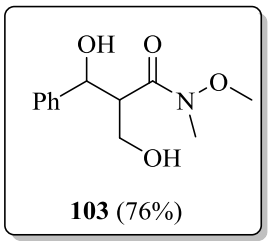


102 (88%)

Chemical Formula: $C_{11}H_{14}O_4$
Molecular Weight: 210,23

The product was purified by flash chromatography on silica gel using P.E./AcOEt as eluent (65/35) to give **102** as a light yellow oil (0.0925 g, 88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.35 (m, 5H, C***H***ar.), 5.27 (t, *J* = 4.5 Hz, 0.5H, C***H***OH), 5.04 (dd, *J* = 7.2 & 4.5 Hz, 0.5H, C***H***OH), 3.95 (d, *J* = 2.1 Hz, 1H, C***H***$_2$OH), 3.75 (bs, 0.5H, O***H***), 3.66 and 3.71 (s, 3H, C***H***$_3$O), 3.63 (d, *J* = 5.7 Hz, 1H, C***H***$_2$OH), 3.34 (d, *J* = 4.5 Hz, 0.5H, C***H***$_2$OH), 3.01 (bs, 0.5H, O***H***), 2.91-2.97 (dt, *J* = 7.2 & 2.1 Hz, 0.5H, ***H***CO_2Me), 2.80-2.91 (dd, *J* = 5.7 & 4.5 Hz, 0.5H, ***H***CO_2Me), 2.48 (bs, 0.5H, O***H***). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3 (***C***O_2Me), 173.6 (***C***O_2Me), 141.4 (***C***ar.), 141.4 (***C***ar.), 128.7 (***C***Har.), 128.6 (***C***Har.), 128.2 (***C***Har.), 127.9 (***C***Har.), 126.3 (***C***Har.), 125.9 (***C***Har.), 74.1 (***C***HOH), 73.1 (***C***HOH), 61.6 (O***C***H_2), 60.9 (O***C***H_2), 54.6 (O***C***H_3), 53.4 (O***C***H_3), 52.2 (***C***HCO_2Me). LRMS (APCI) *M/Z* : 103.1 (35 %), 131.1 (100 %), 163.1 (45 %). IR (film, cm^{-1}): 3419, 2952, 1720, 1436, 1197, 1026, 702. HRMS (CI) calculated for $C_{11}H_{14}O_4Na$ ($[M+Na]^+$) 233.0790, found 233.0800.

❖ **3-hydroxy-2-(hydroxymethyl)-N-methoxy-N-methyl-3-phenylpropanamide (103)**

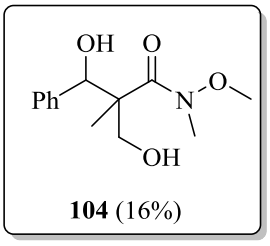


103 (76%)

Chemical Formula: $C_{12}H_{17}NO_4$
Molecular Weight: 239,27

The product was purified by flash chromatography on silica gel using P.E./^{i}PrOH as eluent (85/15) to give **103** as a light yellow oil (0.0909 g, 76%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.45 (m, 5H, C***H***ar), 5.07 (d, *J* = 5.2 Hz, 1H, C***H***OH), 4.60-4.80 (m, 3H, C***H***$_2$OH & O***H***), 3.68-3.75 (m, 1H, C***H***C(O)), 3.57 (s, 3H, C***H***$_3$O), 3.20 (bs, 1H, O***H***), 3.14 (s, 3H, C***H***$_3$N). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.5 (***C***(O)), 140.5 (***C***ar), 128.7 (***C***Har), 128.3 (***C***Har), 126.0 (***C***Har), 72.6 (***C***HOH), 65.9 (O***C***H$_3$), 61.7 (***C***H$_2$OH), 46.4 (H***C***C(O)), 32.2 (N***C***H$_3$). LRMS (CI) *M/Z* : 240.3 (100 %), 229.2 (15 %), 101.1 (15 %), 100.2 (45 %). HRMS (CI) calculated for $C_{12}H_{17}NO_4Na$ ([M+Na]$^+$) 262.1055, found 262.1047. IR (film, cm^{-1}): 3350, 2923, 2850, 1633, 1448, 1419, 1384, 1178, 1110, 989.

❖ **3-hydroxy-2-(hydroxymethyl)-N-methoxy-N,2-dimethyl-3-phenylpropanamide (104)**



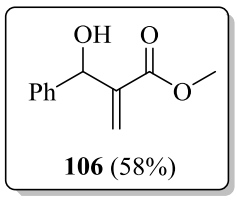
104 (16%)

Chemical Formula: $C_{13}H_{19}NO_4$
Molecular Weight: 253,29

The product was purified by flash chromatography on silica gel using P.E./^{i}PrOH as eluent (85/15) to give **104** as a light yellow oil (0.020 g, 16%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.29 (m, 5H, C***H***ar), 5.33 (d, *J* = 8.5 Hz, 1H, C***H***OH), 4.67 (d, *J* = 8.5 Hz, 1H, O***H***), 4.01 (dd, *J* = 7.8, 6.1 Hz, 1H, C***H***$_2$OH), 3.82 (s, 3H, C***H***$_3$O), 3.57 (d, J = 7.8 Hz, 1H, C***H***$_2$OH), 3.33 (s, 3H, C***H***$_3$N), 0.94 (s, 3H, C***H***$_3$C).

^{13}C NMR (75 MHz, $CDCl_3$) δ 176.4 (***C***(O)), 139.7 (***C***ar), 128.1 (***C***Har), 127.9 (***C***Har), 127.8 (***C***Har), 79.1 (***C***HOH), 66.7 (***C***H_2OH), 60.9 (O***C***H_3), 52.2 (H_3C***C***C(O)), 33.7 (N***C***H_3), 17.0 (***C***H_3). HRMS (ESI) calculated for $C_{13}H_{19}NO_4Na$ ([M+Na]$^+$) 276.12063, found 276.12070. IR (film, cm^{-1}): 3340, 3057, 2926, 1643, 1483, 1437, 1366, 1178, 1119, 1028, 721, 694, 658.

❖ **Methyl 2-(hydroxy(phenyl)methyl)acrylate (106)**

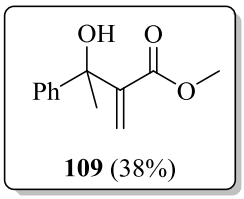


106 (58%)

Chemical Formula: $C_{11}H_{12}O_3$
Molecular Weight: 192,21

The product was purified by flash chromatography on silica gel using P.E./AcOEt as eluent (80/20) to give **106** as a light yellow oil (0.0557 g, 58%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 5H, C***H***ar), 6.36 – 6.30 (t, *J* = 1.1 Hz, 1H, =C***H***$_2$), 5.84 (t, *J* = 1.1 Hz, 1H, =C***H***$_2$), 5.57 (s, 1H, C***H***OH), 3.78 – 3.68 (m, 3H, OC***H***$_3$), 2.78 (bs, 1H, O***H***). Spectral data are identical to those reported in the literature.[10]

❖ **Methyl 3-hydroxy-2-methylene-3-phenylbutanoate (109)**



109 (38%)

Chemical Formula: $C_{12}H_{14}O_3$
Molecular Weight: 206,24

The product was purified by flash chromatography on silica gel using P.E./AcOEt as eluent (90/10) to give **109** as a light yellow oil (0.0389 g, 38%). ^{1}H

[10] Zhu, B.; Yan, L.; Pan, Y.; Lee, R.; Liu, H.; Han, Z.; Huang, K.-W.; Tan, C.-H.; Jiang, Z. *J. Org. Chem.* **2011**, *76*, 6894-6900.

NMR (300 MHz, $CDCl_3$) δ 7.47 – 7.41 (m, 2H, C***H***ar), 7.38 – 7.30 (m, 2H, C***H***ar), 7.29 – 7.26 (m, 1H, C***H***ar), 6.43 (s, 1H, =C***H***$_2$), 6.00 (s, 1H, =C***H***$_2$), 4.60 (d, *J* = 1.0 Hz, 1H, O***H***), 3.73 – 3.64 (m, 3H, OC***H***$_3$), 1.68 (d, *J* = 0.9 Hz, 3H, C***H***$_3$COH). Spectral data are identical to those reported in the literature.[11]

I.3. Computational methods

Computations have been carried out using the Jaguar 8.0 pseudospectral program package. All species have been fully geometry optimized using the **BP86** density functional as implemented in Jaguar. The standard split valence polarized **6-31G*** basis set was used for all atoms except Cu for which the **LACV3P** effective core potential was used. Single point calculations were carried out at the BP86/6-311+G**(LACV3P) using the polarizable continuum–Poisson method as incorporated in Jaguar with a dielectric constant of 2.38, and a solvent probe radius of 2.76 Å, which are suitable for **toluene**.

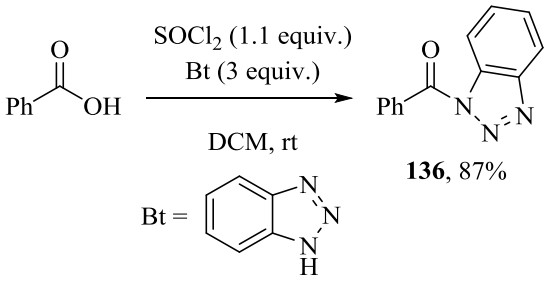
Reported relative energies are electronic energies (in kcal/mol).

[11] Aoki, M.; Izumi, S.; Kaneko, M.; Ukai, K.; Takaya, J.; Iwasawa, N., *Org. Lett.* **2007**, *9*, 1251-1253.

II. Chapter II: Synthesis of Acylsilanes

II.1. Synthesis of substrates

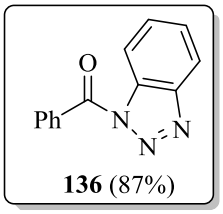
II.1.1. Synthesis of 136



A procedure of the literature was used.[1] Thionyl chloride (0.79 mL, 11 mmol, 1.1 equiv.) and benzotriazole (3.57 g, 30 mmol, 3 equiv.) in methylene chloride (20 mL) were added dropwise to benzoic acid (1.22 g, 10 mmol, 1 equiv.) in methylene chloride (20 mL). A white solid precipitated within 5 min. The reaction mixture was stirred for 1 h. The precipitated white solid was filtered off, and the solvent was removed in vacuo to obtain the crude product, which was purified by recrystallization from chloroform/hexane to obtain colorless needles **136** in 87% yield (1.942 g).

[1] Katritzky, A. R.; Cai, C.; Singh, S. K., *J. Org. Chem.* **2006**, *71*, 3375-3380.

❖ **(1H-benzo[d][1,2,3]triazol-1-yl)(phenyl)methanone (136)**

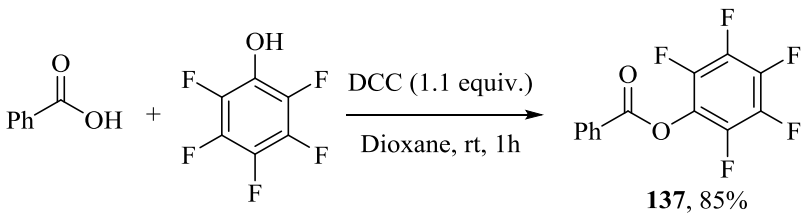


136 (87%)

Chemical Formula: $C_{13}H_9N_3O$
Molecular Weight: 223,23

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (d, *J* = 8.3 Hz, 1H, C***H***ar), 8.23–8.15 (m, 3H, C***H***ar), 7.70–7.72 (m, 2H, C***H***ar), 7.67–7.52 (m, 3H, C***H***ar). Spectral data are identical to those reported in the literature.[12]

II.1.2. Synthesis of 137



137, 85%

DCC = Cy−N=C=N−Cy

A procedure of the literature was used.[2] To a mixture of benzoic acid (0.6106 g, 5 mmol, 1 equiv.) and pentafluorophenol (1.00 g, 5.5 mmol, 1.1 equiv.) in dioxane (15 mL), 1,3-dicyclohexylcarbodiimide (DCC) (1.14 g, 5.5 mmol, 1.1 equiv.) was added. The mixture was stirred for 1 h at room temperature. The formed dicyclohexylurea was filtered off, the solvent was evaporated under reduced pressure and the residue was purified by crystallisation from hexane. The desired product **137** was obtained as a white solid in 85% yield (1.229 g).

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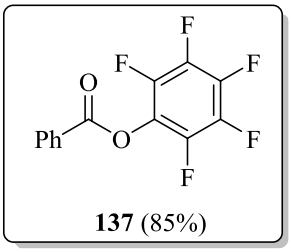
[2] Babadzhanova, L. A.; Kirij, N. V.; Yagupolskii, Y. L.; Tyrra, W.; Naumann, D., *Tetrahedron* **2005**, *61*, 1813-1819.

❖ **Perfluorophenyl benzoate (137)**

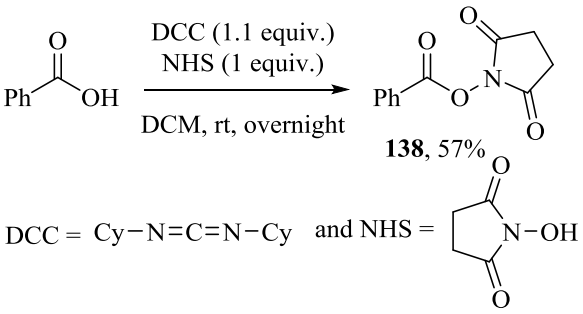


137 (85%)

Chemical Formula: $C_{13}H_5F_5O_2$
Molecular Weight: 288,17

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (ddd, *J* = 4.8, 2.8, 1.6 Hz, 2H, ***H***-ortho), 7.71 (ddd, *J* = 6.9, 4.1, 1.3 Hz, 1H, ***H***-para), 7.62 – 7.49 (m, 2H, ***H***-meta). Spectral data are identical to those reported in the literature.[13]

II.1.3. Synthesis of 138

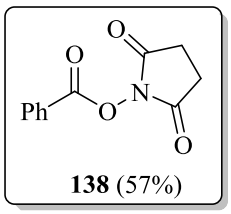


A modified procedure of the literature was used.[3] Benzoic acid (0.2442 g, 2 mmol, 1 equiv.) was dissolved in dry CH_2Cl_2 (10 ml), DCC (0.4539 g, 2.2 mmol, 1.1 equiv.) and NHS (0.2302 g, 2 mmol, 1 equiv.) were added. The mixture was stirred at room temperature overnight and the solvent was evaporated under reduced pressure. After purification by flash chromatography on silica gel using P.E./Et_2O (95/5) as eluent, the succinimide ester **138** (0.251 g, 57%) was obtained as a white solid.

---

[3] Brink, B. D.; DeFrancisco, J. R.; Hillner, J. A.; Linton, B. R., *J. Org. Chem.* **2011**, *76*, 5258-5263.

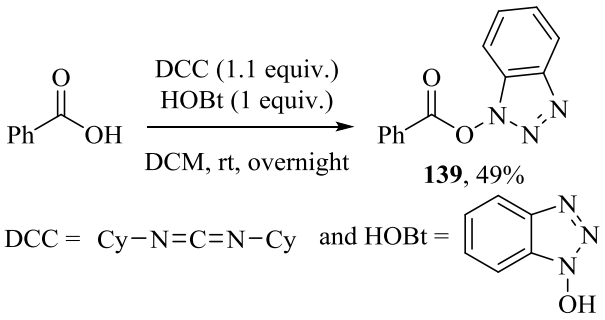
❖ **2,5-dioxopyrrolidin-1-yl benzoate (138)**



Chemical Formula: $C_{11}H_9NO_4$
Molecular Weight: 219,19

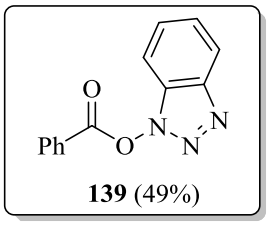
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 – 8.12 (m, 2H, ***H***-ortho), 7.75 – 7.65 (m, 1H, ***H***-para), 7.58 – 7.47 (m, 2H, ***H***-meta), 2.91 (s, 4H, C***H***$_2$). Spectral data are identical to those reported in the literature.[14]

II.1.4. Synthesis of 139



A modified procedure of the literature was used.[14] Benzoic acid (0.2442 g, 2 mmol, 1 equiv.) was dissolved in dry CH_2Cl_2 (10 ml), DCC (0.4539 g, 2.2 mmol, 1.1 equiv.) and HOBt (0.2703 g, 2 mmol, 1 equiv.) were added. The mixture was stirred at room temperature overnight. The resulting mixture was filtered off and the solvent was evaporated under reduced pressure. After purification by recrystallization in AcOEt the ester **139** (0.236 g, 49%) was obtained as a white solid.

❖ **1H-benzo[d][1,2,3]triazol-1-yl benzoate (139)**

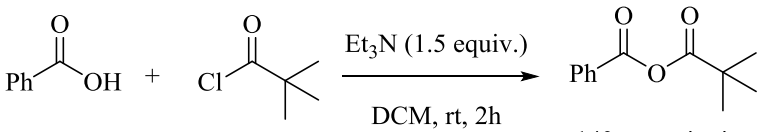


139 (49%)

Chemical Formula: $C_{13}H_9N_3O_2$
Molecular Weight: 239,23

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 – 8.26 (m, 2H, C***H***ar), 8.11 (dt, *J* = 8.5, 0.8 Hz, 1H, C***H***ar), 7.85 – 7.73 (m, 1H, C***H***ar), 7.71 – 7.40 (m, 5H, C***H***ar). Spectral data are identical to those reported in the literature.[14]

II.1.5. Synthesis of 140

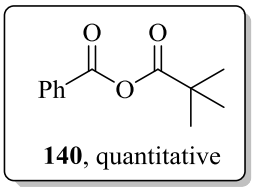


140, quantitative

A procedure of the literature was used.[4] Et_3N (1.01 mL, 7.5 mmol, 1.5 equiv.) was added to a mixture of benzoic acid (0.6106 g, 5 mmol, 1 equiv.) in dry CH_2Cl_2 (25 mL). Trimethylacetyl chloride (0.615 mL, 5 mmol, 1 equiv.) was then added dropwise. The resulting mixture was stirred at room temperature during 2 hours. The reaction mixture was washed with HCl 1M (10 mL) then extracted with DCM (3 x 5 mL). Organic phase was washed with $NaHCO_3$ (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Desired product **139** was obtained in quantitative yield without purification (1.03 g).

[4] Lai, L.-L.; Wang, E.; Luh, B.-J., *Synthesis* **2001**, 361-363.

❖ **Benzoic pivalic anhydride (140)**



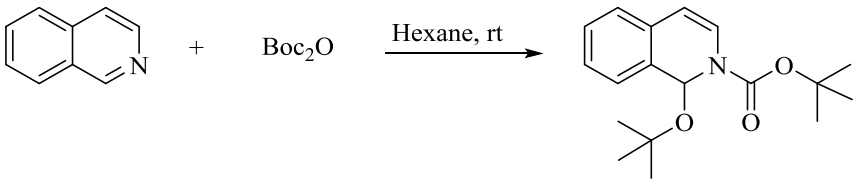
140, quantitative

Chemical Formula: $C_{12}H_{14}O_3$
Molecular Weight: 206,24

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 – 8.03 (m, 2H, ***H***-ortho), 7.65 (d, *J* = 7.5 Hz, 1H, ***H***-para), 7.51 (t, *J* = 7.7 Hz, 2H, ***H***-meta), 1.39 (d, *J* = 1.2 Hz, 9H, $C(C\boldsymbol{H}_3)_3$). Spectral data are identical to those found in the literature.[15]

II.1.6. Synthesis of 141

II.1.6.1. Synthesis of intermediate 142



A procedure from the literature was used.[5] A mixture of isoquinoline (1.17 mL, 10 mmol, 1 equiv.) and di-tert-butyl dicarbonate (2.62 g, 12 mmol, 1.2 equiv.) in hexane (10 mL) was stirred at room temperature for 8h. After concentration in vacuo, the residue was purified by recrystallization from Et_2O-hexane to give **142** (1.67 g, 55%) as colorless prisms.

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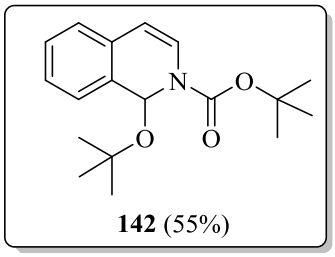
[5] (a) Ouchi, H.; Saito, Y.; Yamamoto, Y.; Takahata, H., *Org. Lett.* **2002**, *4*, 585-587. (b) Saito, Y.; Ouchi, H.; Takahata, H., *Tetrahedron* **2006**, *62*, 11599-11607.

❖ **1-tert-Butoxy-2-tert-butoxycarbonyl-1,2-dihydroisoquinoline (142, BBDI)**

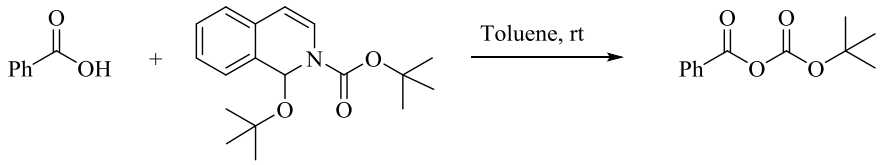


142 (55%)

Chemical Formula: $C_{18}H_{25}NO_3$
Molecular Weight: 303,40

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 – 7.18 (m, 4H, C***H***ar), 6.88 (d, *J* = 7.6 Hz, 1H, NC***H***=), 6.66 (s, 1H, NC***H***O), 6.10 (d, *J* = 7.6 Hz, 1H, NCH=C***H***), 1.52 (s, 9H, C(O)OC(C***H***$_3$)$_3$), 1.30 (s, 9H, OC(C***H***$_3$)$_3$). Spectral data are identical to those reported in the literature.[13]

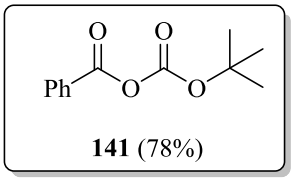
II.1.6.2. Synthesis of 141



A modified procedure from the literature was used.[13] A mixture of BBDI (303.4 mg, 1 mmol, 1 equiv.) and benzoic acid (122.1 mg, 1 mmol, 1 equiv.) in toluene (3 mL) was stirred at room temperature for 2h. The reaction mixture was washed with 5% HCl solution (2 mL) then extracted with Et_2O (3 x 5 mL). Organic phase was washed with brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purifed by flash column chromatography on silica gel with P.E./Et_2O (80/20) as eluent to give **141** in 78% yield (0.173 g).

❖ **Benzoic (tert-butyl carbonic) anhydride (141)**

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (dd, *J* = 8.3, 1.3 Hz, 2H, C***H***ar), 7.63 (d, *J* = 7.5 Hz, 1H, C***H***ar), 7.48 (dd, *J* = 8.2, 7.5 Hz, 2H, C***H***ar), 1.60 (s,

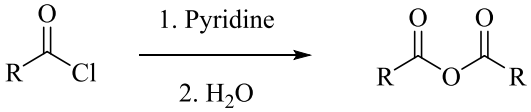


141 (78%)

Chemical Formula: $C_{12}H_{14}O_4$
Molecular Weight: 222,24

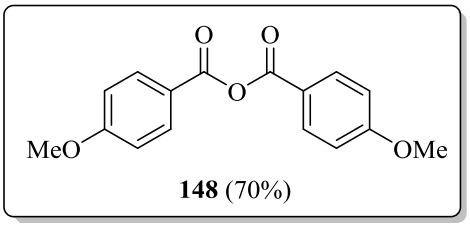
9H, OC(C***H***$_3$)$_3$). Spectral data are identical to those reported in the literature.[13]

II.1.7. General procedure for the synthesis of anhydrides (Method A)



A modified procedure from the literature was used.[6] Acid chloride (5 mmol, 1 equiv.) was dissolved in 3-5 ml of dry pyridine, depending on the solubility of the starting material. The solution was stirred for about 30 min and then quenched with 10 ml of ice-cold water. The solid that precipitated was filtered off, washed with 5 ml of ice-cold water and dried *in vacuo*. The crude product was then recrystallized with ethyl acetate.

❖ **4-methoxybenzoic anhydride (148)**



148 (70%)

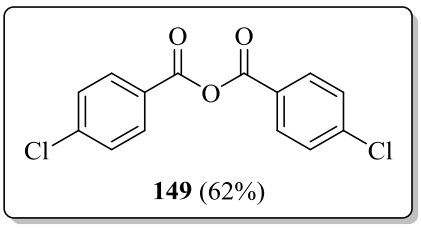
Chemical Formula: $C_{16}H_{14}O_5$
Molecular Weight: 286,28

The product was purified to give **148** as a white crystals (1.002 g, 70%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.9 Hz, 4H, ***H***-ortho), 6.98 (d, *J* = 8.9 Hz, 4H, ***H***-meta), 3.90 (s,

[6] Dhimitruka, I.; SantaLucia, J., *Org. Lett.* **2005**, *8*, 47-50.

6H, OC***H***$_3$). Spectral data are identical to those reported in the literature.[17]

❖ **4-chlorobenzoic anhydride (149)**

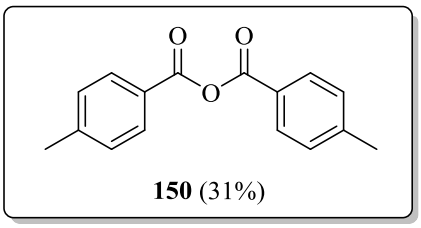


149 (62%)

Chemical Formula: $C_{14}H_8Cl_2O_3$
Molecular Weight: 295,12

The product was purified to give **149** as a white solid (0.915 g, 62%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.7 Hz, 4H, ***H***-ortho), 7.51 (d, *J* = 8.6 Hz, 4H, ***H***-meta). Spectral data are identical to those reported in the literature.[7]

❖ **4-methylbenzoic anhydride (150)**



150 (31%)

Chemical Formula: $C_{16}H_{14}O_3$
Molecular Weight: 254,28

The product was purified to give **150** as a white solid (0.394 g, 31%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.2 Hz, 4H, ***H***-ortho), 7.32 (d, *J* = 8.1 Hz, 4H, ***H***-meta), 2.46 (s, 6H, C***H***$_3$). Spectral data are identical to those reported in the literature.[17]

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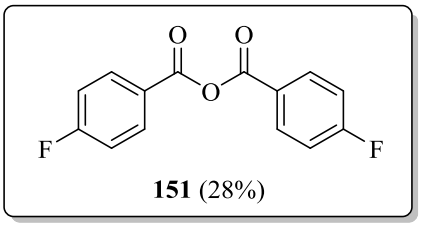
[7] Serieys, A.; Botuha, C.; Chemla, F.; Ferreira, F.; Pérez-Luna, A., *Tet. Lett.* **2008**, *49*, 5322-5323.

❖ **4-fluorobenzoic anhydride (151)**

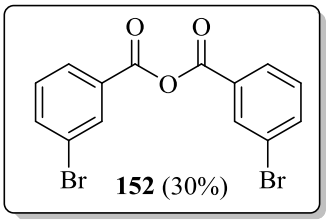


151 (28%)

Chemical Formula: $C_{14}H_8F_2O_3$
Molecular Weight: 262,21

The product was purified to give **151** as a white solid (0.367 g, 28%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 – 8.12 (m, 4H, ***H***-ortho), 7.22 (dd, *J* = 16.0, 7.5 Hz, 4H, ***H***-meta). Spectral data are identical to those reported in the literature.[8]

❖ **3-bromobenzoic anhydride (152)**



152 (30%)

Chemical Formula: $C_{14}H_8Br_2O_3$
Molecular Weight: 384,02

The product was purified to give **152** as a white solid (0.576 g, 30%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (t, *J* = 1.8 Hz, 2H, ***H***-ortho), 8.13 – 8.03 (m, 2H, BrC=C***H***-ortho), 7.82 (ddd, *J* = 8.0, 1.9, 1.1 Hz, 2H, ***H***-para), 7.43 (t, *J* = 7.9 Hz, 2H, ***H***-meta). Spectral data are identical to those reported in the literature.[9]

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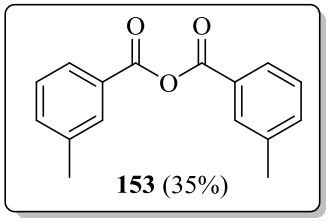
[8] Li, Y.; Xue, D.; Wang, C.; Liu, Z.-T.; Xiao, J., *Chem. Comm.* **2012**, *48*, 1320-1322.

[9] Greene, F. D.; Adam, W., *J. Org. Chem.* **1964**, *29*, 136-139.

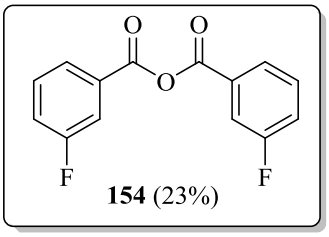
❖ **3-methylbenzoic anhydride (153)**



Chemical Formula: $C_{16}H_{14}O_3$
Molecular Weight: 254,28

The product was purified to give **153** as a white solid (0.445 g, 35%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (m, 2H, ***H***-ortho), 7.96 (m, 2H, CH_3C=C***H***-ortho), 7.51 (d, *J* = 7.8 Hz, 2H, ***H***-para), 7.44 (dd, *J* = 10.9, 4.9 Hz, 2H, ***H***-meta). Spectral data are identical to those reported in the literature.[10]

❖ **3-fluorobenzoic anhydride (154)**



Chemical Formula: $C_{14}H_8F_2O_3$
Molecular Weight: 262,21

The product was purified to give **154** as a white solid (0.302 g, 23%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 – 7.91 (m, 2H, ***H***-ortho), 7.82 (ddd, *J* = 9.0, 2.5, 1.7 Hz, 2H, FC=C***H***-ortho), 7.53 (td, *J* = 8.0, 5.5 Hz, 2H, ***H***-para), 7.40 (tdd, *J* = 8.3, 2.6, 1.0 Hz, 2H, ***H***-meta). Spectral data are identical to those reported in the literature.[11]

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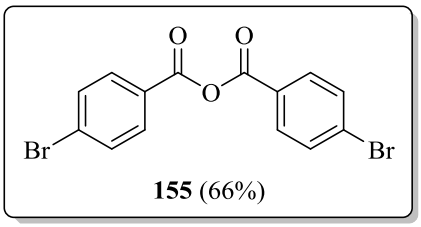
[10] Hajipour, A. R.; Mazloumi, G., *Synthetic Comm.* **2002**, *32*, 23-30.

[11] Wood, W. J. L.; Patterson, A. W.; Tsuruoka, H.; Jain, R. K.; Ellman, J. A., *J. Am. Chem. Soc.* **2005**, *127*, 15521-15527.

❖ **4-bromobenzoic anhydride (155)**

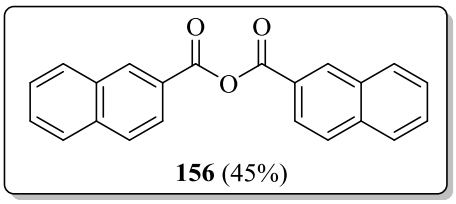


155 (66%)

Chemical Formula: $C_{14}H_8Br_2O_3$
Molecular Weight: 384,02

The product was purified to give **155** as a white solid (1.267 g, 66%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.6 Hz, 4H, ***H***-ortho), 7.68 (d, *J* = 8.6 Hz, 4H, ***H***-meta). Spectral data are identical to those reported in the literature.[12]

❖ **2-naphtoic anhydride (156)**



156 (45%)

Chemical Formula: $C_{22}H_{14}O_3$
Molecular Weight: 326,34

The product was purified to give **156** as a white solid (0.734 g, 45%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (s, 2H, C***H***ar), 8.20 (dd, *J* = 8.6, 1.7 Hz, 2H, C***H***ar), 8.09 – 7.89 (m, 6H, C***H***ar), 7.64 (dtd, *J* = 14.8, 7.0, 1.2 Hz, 4H, C***H***ar). Spectral data are identical to those reported in the literature.[13]

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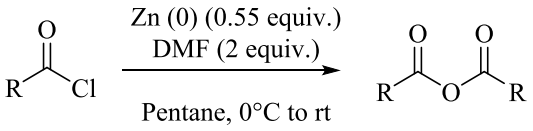
[12] H. Yulai, W. Jin-Xian and L. Shihua, *Synthetic Comm.* **1997**, *27*, 243 – 248.

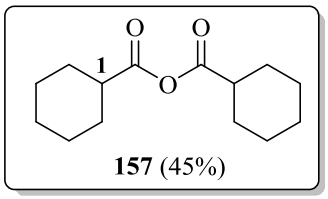
[13] White, E. H.; McGirk, R. H.; Aufdermarsh, C. A.; Tiwari, H. P.; Todd, M. J., *J. Am. Chem. Soc.* **1973**, *95*, 8107-8113.

II.1.8. General procedure for the synthesis of anhydrides (Method B)



A procedure from the literature was used.[14] Under argon, to a suspension of zinc dust (72 mg, 1.1 mmol, 0.55 equiv.) in pentane (2 mL) and anhydrous DMF (0.3 mL, 4 mmol, 2 equiv.) was added dropwise at 0 °C the acid chloride (2 mmol, 1 equiv.). The resulting mixture was warmed to room temperature and stirred during 20 h. The mixture was then filtered over a pad of flash silica gel eluting with 3% Et_2O in pentane (100 mL). Removal of the solvents *in vacuo* furnished the corresponding anhydrides.

❖ **Cyclohexanecarboxylic anhydride (157)**



Chemical Formula: $C_{14}H_{22}O_3$
Molecular Weight: 238,32

The product was purified by fractioned distillation (bp = 190 °C at 1 mbar) to give **157** as a colorless oil (0.536 g, 45%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.46 – 2.29 (m, 2H, ***H*$_1$**), 2.01 – 1.84 (m, 4H, C***H*$_2$**), 1.84 – 1.56 (m, 6H, C***H*$_2$**), 1.45 (d, *J* = 10.8 Hz, 4H, C***H*$_2$**), 1.25 (t, *J* = 10.7 Hz, 6H, C***H*$_2$**). Spectral data are identical to those reported in the literature.[25]

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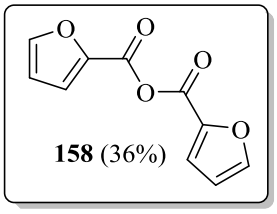
[14] Serieys, A.; Botuha, C.; Chemla, F.; Ferreira, F.; Pérez-Luna, A., *Tet. Lett.* **2008**, *49*, 5322-5323.

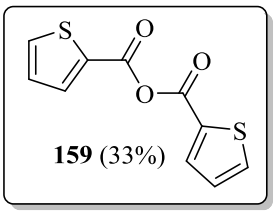
❖ **Furan-2-carboxylic anhydride (158)**



Chemical Formula: $C_{10}H_6O_5$
Molecular Weight: 206,15

The product was purified by recrystallization with AcOEt and E.P. to give **158** as a white solid (0.371 g, 36%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 1.5, 0.7 Hz, 2H, OC***H***), 7.42 (dd, *J* = 3.6, 0.7 Hz, 2H, C(O)C=C***H***), 6.62 (dd, *J* = 3.6, 1.6 Hz, 2H, HC=C***H***-CH). Spectral data are identical to those reported in the literature.[17]

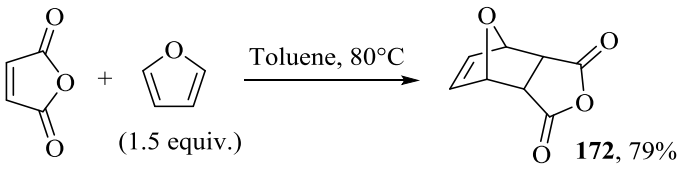
❖ **Thiophene-2-carboxylic anhydride (159)**



Chemical Formula: $C_{10}H_6O_3S_2$
Molecular Weight: 238,28

The product was purified by recrystallization with AcOEt and E.P. to give **159** as a white solid (0.393 g, 33%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 3.8, 1.0 Hz, 2H, SC***H***), 7.75 (dd, *J* = 4.9, 1.0 Hz, 2H, C(O)C=C***H***), 7.20 (dd, *J* = 4.8, 3.9 Hz, 2H, HC=C***H***-CH). Spectral data are identical to those reported in the literature.[15]

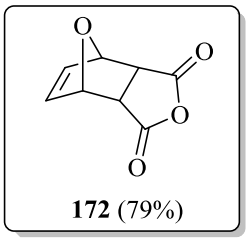
II.1.9. Synthesis of substrate 172



[15] S. Funasaka, T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **2008**, *81*, 148 – 159.

A procedure of the literature was used.[16] Maleic anhydride (0.980 g, 10 mmol, 1 equiv.) was suspended in 5 mL of toluene and the mixture warmed to 80°C. Furan (1.1 mL, 15 mmol, 1.5 equiv.) was added via syringe and the turbid solution stirred for 6 h. The mixture was then cooled to ambient temperature and the stirring stopped. After 1 h, the resulting white crystals were collected by filtration and washed with 2×5 mL of petroleum ether to obtain 1.312 g (79% yield) of the product **172** as small white needles.

❖ **(172)**



172 (79%)

Chemical Formula: $C_8H_6O_4$
Molecular Weight: 166,13

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.58 (t, J = 1.0 Hz, 2H, C***H***$_{vinyl}$), 5.46 (t, J = 1.0 Hz, 2H, C***H***O), 3.18 (s, 2H, C***H***). Spectral data are identical to those reported in the literature.[27]

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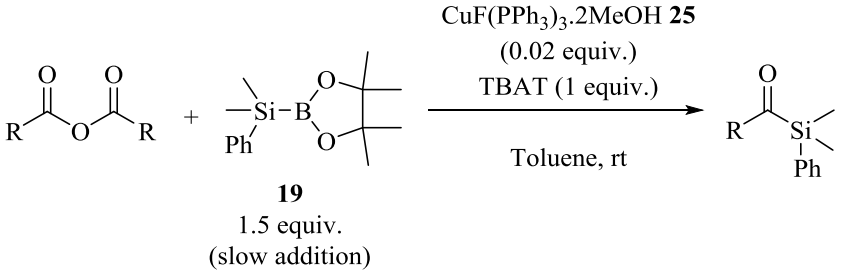
[16] Daskalaki, E.; Le Droumaguet, B.; Gerard, D.; Velonia, K., *Chem. Comm.* **2012**, *48*, 1586-1588.

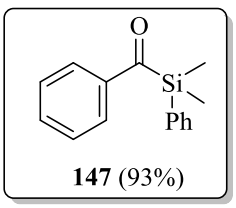
II.2. Catalytic Tests

II.2.1. General procedure for the synthesis of acylsilanes



A flame-dried schlenk was loaded with $CuF(PPh_3)_3.2MeOH$ **25** (4.7 mg, 0.005 mmol, 0.02 equiv.), TBAT (0.1349 g, 0.25 mmol, 1 equiv.) and anhydride (0.25 mmol, 1 equiv.). The vessel was then sealed and after 3 vacuum/argon cycles, toluene was added (2 mL). After dissolution of solids, borosilane **19** (0.1 mL, 0.325 mmol, 1.5 equiv.) was added dropwise over 10 minutes and the mixture was stirred at room temperature for 6 h. The solution was filtered over a pad of flash silica gel eluting with Et_2O and then concentrated under reduced pressure. Hexamethylbenzene was added to the crude product to determine the yield by ^1H NMR. The product was finally purified by flash chromatography on silica gel.

❖ **(Dimethyl(phenyl)silyl)(phenyl)methanone (147)**

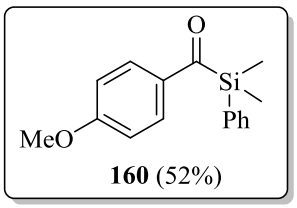


Chemical Formula: $C_{15}H_{16}OSi$
Molecular Weight: 240,37

Commercially available benzoic anhydride was used as substrate. The product was purified by flash chromatography on silica gel using P.E./Et_2O (95/5) as eluent to give **147** as

a bright yellow oil (0.0559 g, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 – 7.70 (m, 2H, C***H***ar), 7.65 – 7.56 (m, 2H, C***H***ar), 7.46 (d, *J* = 7.3 Hz, 1H, C***H***ar), 7.43 – 7.32 (m, 5H, C***H***ar), 0.63 (s, 6H, Si(C***H***$_3$)$_2$). Spectral data are identical to those reported in the literature.[17]

❖ **(Dimethyl(phenyl)silyl)(4-methoxyphenyl)methanone (160)**



160 (52%)

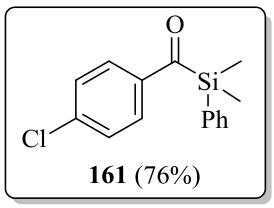
Chemical Formula: $C_{16}H_{18}O_2Si$
Molecular Weight: 270,40

Anhydride **148** was used as substrate. The product was purified by flash chromatography on silica gel using P.E./Et_2O (95/5) as eluent to give **160** as a bright yellow oil (0.0351 g, 52%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.9 Hz, 2H, C***H***ar), 7.59 (d, *J* = 7.6 Hz, 2H, C***H***ar), 7.39 (m, 3H, C***H***ar), 6.85 (d, *J* = 8.9 Hz, 2H, C***H***ar), 3.81 (s, 3H, OC***H***$_3$), 0.61 (s, 6H, Si(C***H***$_3$)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 231.0 (***C***(O)), 163.4 (***C***OMe), 136.3 (***C***ar), 136.1 (***C***Har), 135.4 (***C***Har), 134.6 (***C***Har), 134.1 (***C***Har), 130.4 (***C***Har), 129.9 (***C***ar), 128.4 (***C***Har), 113.9 (***C***Har), 55.6 (O***C***H$_3$), -2.6 (Si(***C***H$_3$)$_2$). HRMS (ESI): Mass Calculated for $C_{16}H_{19}O_2Si$, theoretical Mass: 271.11488, measured Mass: 271.11489. IR (cm^{-1}): 2964, 2839, 1610, 1566, 1506, 1427, 1305, 1257, 1226, 1163, 1109, 839.

❖ **(4-chlorophenyl)(Dimethyl(phenyl)silyl)methanone (161)**

Anhydride **149** was used. The product was purified by flash chromatography on silica gel using P.E./Et_2O (95/5) as eluent to give **161** as a bright yellow oil (0.0522 g, 76%). ^{1}H NMR (300 MHz, $CDCl_3$) δ

[17] Kondo, J.; Shinokubo, H.; Oshima, K., *Org. Lett.* **2006**, *8*, 1185-1187.

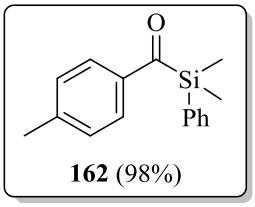


161 (76%)

Chemical Formula: $C_{15}H_{15}ClOSi$
Molecular Weight: 274,82

7.67 (d, *J* = 8.6 Hz, 2H, C***H***ar), 7.57 (dd, *J* = 7.4, 2.1 Hz, 2H, C***H***ar), 7.38 (ddd, *J* = 17.7, 10.3, 5.2 Hz, 5H, C***H***ar), 0.61 (s, 6H, Si(C***H***$_3$)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 232.5 (***C***(O)), 139.6 (***C***Cl), 139.2 (***C***ar), 135.4 (***C***Har), 135.1 (***C***Har), 134.1 (***C***Har), 130.9 (***C***Har), 130.1 (***C***Har), 129.3 (***C***Har), 129.0 (***C***Har), 128.5 (***C***Har), 128.2 (***C***Har), -2.9 (Si(***C***H$_3$)$_2$). HRMS (ESI): Mass Calculated for $C_{15}H_{15}OClNaSi$, theoretical Mass: 297.04229, Measured Mass: 297.04744. IR (cm^{-1}): 3068, 2964, 1612, 1568, 1427, 1250, 1205, 1085, 1012, 837.

❖ **(Dimethyl(phenyl)silyl)(p-tolyl)methanone (162)**

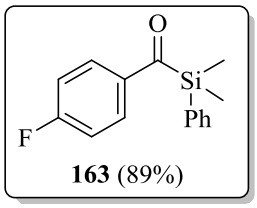


162 (98%)

Chemical Formula: $C_{16}H_{18}OSi$
Molecular Weight: 254,40

Anhydride **150** was used. The product was purified by flash chromatography on silica gel using P.E./Et_2O (95/5) as eluent to give **162** as a bright yellow oil (0.0623 g, 98%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.2 Hz, 2H, C***H***ar), 7.63 – 7.55 (m, 2H, C***H***ar), 7.43 – 7.32 (m, 3H, C***H***ar), 7.17 (d, *J* = 7.9 Hz, 2H, C***H***ar), 2.35 (s, 3H, C***H***$_3$), 0.61 (s, 6H, Si(C***H***$_3$)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 233.0 (***C***(O)), 143.7 (***C***CH$_3$), 139.3 (***C***ar), 136.1 (***C***Har), 134.1 (***C***Har), 129.9 (***C***Har), 129.4 (***C***Har), 128.4 (***C***Har), 128.2 (***C***Har), 21.8 (C***C***H$_3$), -2.7 (Si(***C***H$_3$)$_2$). HRMS (ESI): Mass Calculated for $C_{16}H_{18}ONaSi$, theoretical Mass: 277.10191, measured Mass: 277.10187. IR (cm^{-1}): 3049, 2962, 1614, 1593, 1427, 1220, 1172, 1108, 825, 781.

❖ **(Dimethyl(phenyl)silyl)(4-fluorophenyl)methanone (163)**

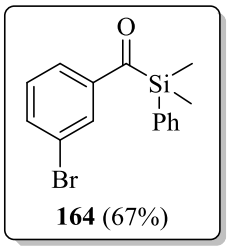


163 (89%)

Chemical Formula: $C_{15}H_{15}FOSi$
Molecular Weight: 258,36

Anhydride **151** was used. The product was purified by flash chromatography on silica gel using P.E./Et_2O (95/5) as eluent to give **163** as a bright yellow oil (0.0575 g, 89%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 – 7.72 (m, 2H, C***H***ar), 7.63 – 7.54 (m, 2H, C***H***ar), 7.46 – 7.34 (m, 3H, C***H***ar), 7.04 (t, *J* = 8.7 Hz, 2H, C***H***ar), 0.62 (s, 6H, Si(C***H***$_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 231.8 (***C***(O)), 167.2 (***C***F), 163.8 (***C***ar), 138.0 (***C***Har), 135.6 (***C***Har), 134.1 (***C***Har), 130.6 (***C***Har), 130.5 (***C***Har), 130.1 (***C***Har), 128.5 (***C***Har), 115.9 (***C***Har), 115.7 (***C***Har), -2.8 (Si(***C***$H_3)_2$). ^{19}F NMR (282 MHz, $CDCl_3$) δ -106.7. HRMS (ESI): Mass Calculated for $C_{15}H_{15}OFNaSi$, theoretical Mass: 281.07684, measured Mass: 281.07676. IR (cm^{-1}): 3070, 2964, 1614, 1583, 1500, 1429, 1230, 1108, 820, 781.

❖ **(Dimethyl(phenyl)silyl)(3-bromophenyl)methanone (164)**



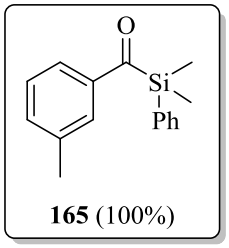
164 (67%)

Chemical Formula: $C_{15}H_{15}BrOSi$
Molecular Weight: 319,27

Anhydride **152** was used. The product was purified by flash chromatography on silica gel using P.E./Et_2O (95/5) as eluent to give **164** as a bright yellow oil (0.0535 g, 67%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (t, *J* = 1.7 Hz, 1H, C***H***ar), 7.67 – 7.54 (m, 4H, C***H***ar), 7.40 (dd, *J* = 5.0, 2.0 Hz, 3H, C***H***ar), 7.27 – 7.22 (m, 1H, C***H***ar), 0.62 (s, 6H, Si(C***H***$_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 232.6 (***C***(O)), 142.9 (***C***Br), 140.1 (***C***ar), 135.6 (***C***Har), 134.1 (***C***Har), 130.3 (***C***Har), 130.2 (***C***Har),

128.5 (***C***Har), 127.1 (***C***Har), 123.3 (***C***Har), -3.0 (Si(***C***H_3)$_2$). HRMS (ESI): Mass Calculated for $C_{15}H_{15}OBrNaSi$, theoretical Mass: 340.99678, measured Mass: 340.99702. IR (cm^{-1}): 3068, 2964, 1614, 1560, 1427, 1249, 1191, 1108, 816, 792.

❖ **(Dimethyl(phenyl)silyl)(m-tolyl)methanone (165)**



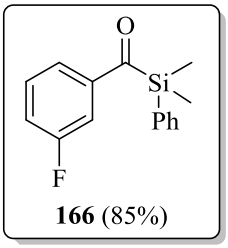
165 (100%)

Chemical Formula: $C_{16}H_{18}OSi$
Molecular Weight: 254,40

Anhydride **153** was used. The product was purified by flash chromatography on silica gel using P.E./Et_2O (95/5) as eluent to give **165** as a bright yellow oil (0.0636 g, quantitative yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (ddd, *J* = 11.2, 3.7, 1.9 Hz, 4H, C***H***ar), 7.45 – 7.33 (m, 3H, C***H***ar), 7.33 – 7.20 (m, 2H, C***H***ar), 2.32 (s, 3H, C***H***$_3$), 0.62 (s, 6H, Si(C***H***$_3$)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 234.1 (***C***(O)), 141.6 (***C***CH_3), 138.5 (***C***ar), 136.0 (***C***Har), 134.1 (***C***Har), 133.7 (***C***Har), 129.9 (***C***Har), 128.5 (***C***Har), 128.4 (***C***Har), 128.0 (***C***Har), 125.8 (***C***Har), 21.5 (***C***H_3), -2.7 (Si(***C***H_3)$_2$). HRMS (ESI): Mass Calculated for $C_{16}H_{19}OSi$, theoretical Mass: 255.11997, measured Mass: 255.11998. IR (cm^{-1}): 3068, 2964, 1614, 1587, 1427, 1246, 1149, 1108, 829, 791.

❖ **(Dimethyl(phenyl)silyl)(3-fluorophenyl)methanone (166)**

Anhydride **154** was used. The product was purified by flash chromatography on silica gel using P.E./Et_2O (95/5) as eluent to give **166** as a bright yellow oil (0.0549 g, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 – 7.56 (m, 2H, C***H***ar), 7.55 – 7.50 (m, 1H, C***H***ar), 7.44 – 7.37 (m, 4H, C***H***ar), 7.34 (d, *J* = 5.4 Hz, 1H, C***H***ar), 7.18 (ddd, *J* = 8.2, 2.6, 1.0

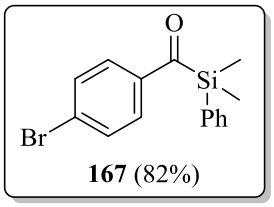


166 (85%)

Chemical Formula: $C_{15}H_{15}FOSi$
Molecular Weight: 258,36

Hz, 1H, C***H***ar), 0.63 (s, 6H, Si(C***H***$_3$)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 232.6 (***C***(O)), 164.7 (***C***F), 161.4 (***C***ar), 143.4 (***C***Har), 143.3 (***C***Har), 135.3 (***C***Har), 134.1 (***C***Har), 130.4 (***C***Har), 130.3 (***C***Har), 130.2 (***C***Har), 128.5 (***C***Har), 124.4 (***C***Har), 124.4 (***C***Har), 120.0 (***C***Har), 119.7 (***C***Har), 113.8 (***C***Har), 113.5 (***C***Har), -2.9 (Si(***C***H$_3$)$_2$). ^{19}F NMR (282 MHz, $CDCl_3$) δ -113.0. HRMS (ESI): Mass Calculated for $C_{15}H_{16}OFSi$, theoretical Mass: 259.09490, measured Mass: 259.09498. IR (cm^{-1}): 3070, 2962, 1618, 1583, 1479, 1429, 1244, 1110, 831, 793.

❖ (4-bromophenyl)(Dimethyl(phenyl)silyl)methanone (167)

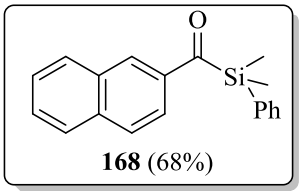


167 (82%)

Chemical Formula: $C_{15}H_{15}BrOSi$
Molecular Weight: 319,27

Anhydride **155** was used. The product was purified by flash chromatography on silica gel using P.E./Et_2O (95/5) as eluent to give **167** as a bright yellow oil (0.0655 g, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 – 7.46 (m, 6H, C***H***ar), 7.46 – 7.33 (m, 3H, C***H***ar), 0.61 (s, 6H, Si(C***H***$_3$)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 232.8 (***C***(O)), 144.0 (***C***Br), 139.9 (***C***ar), 138.8 (***C***Har), 134.1 (***C***Har), 132.3 (***C***Har), 132.0 (***C***Har), 130.2 (***C***Har), 129.9 (***C***Har), 129.4 (***C***Har), 128.5 (***C***Har), 128.1 (***C***Har), -2.9 (Si(***C***H$_3$)$_2$). HRMS (ESI): Mass Calculated for $C_{15}H_{15}OBrNaSi$, theoretical Mass: 340.99678, measured Mass: 340.99699. IR (cm^{-1}): 3068, 2962, 1612, 1566, 1427, 1205, 1108, 1009, 835, 781.

❖ **(Dimethyl(phenyl)silyl)(naphtalen-2-yl)methanone (168)**

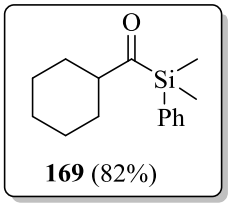


168 (68%)

Chemical Formula: $C_{19}H_{18}OSi$
Molecular Weight: 290,43

Anhydride **156** was used. The product was purified by flash chromatography on silica gel using P.E./Et_2O (98/2) as eluent to give **168** as a bright yellow oil (0.0494 g, 68%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (s, 1H, C***H***ar), 7.90 – 7.72 (m, 4H, C***H***ar), 7.67 (d, *J* = 7.6 Hz, 2H, C***H***ar), 7.61 – 7.46 (m, 2H, C***H***ar), 7.42 (dd, *J* = 5.3, 1.8 Hz, 3H, C***H***ar), 0.69 (s, 6H, Si(C***H***$_3$)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 233.6 (***C***(O)), 138.9 (***C***ar), 136.1 (***C***Har), 135.6 (***C***Har), 134.2 (***C***Har), 132.7 (***C***Har), 131.8 (***C***Har), 130.0 (***C***Har), 129.8 (***C***Har), 128.6 (***C***Har), 128.5 (***C***Har), 127.9 (***C***Har), 126.7 (***C***Har), 122.6 (***C***Har), -2.7 (Si(***C***H$_3$)$_2$). HRMS (ESI): Mass Calculated for $C_{19}H_{19}OSi$, theoretical Mass: 291.11997, measured Mass: 291.12015. IR (cm^{-1}): 3055, 2962, 1593, 1427, 1350, 1247, 1174, 1109, 825, 744.

❖ **(Dimethyl(phenyl)silyl)(cyclohexyl)methanone (169)**



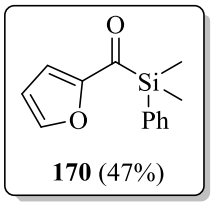
169 (82%)

Chemical Formula: $C_{15}H_{22}OSi$
Molecular Weight: 246,42

Anhydride **157** was used. The product was purified by flash chromatography on silica gel using P.E./Et_2O (98/2) as eluent to give **169** as a colorless oil (0.0505 g, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 7.1, 2.4 Hz, 2H, C***H***ar), 7.42 – 7.37 (m, 3H, C***H***ar), 2.67 (d, *J* = 6.4 Hz, 1H, C***H***), 1.69 (d, *J* = 5.7 Hz, 5H, C***H***$_2$), 1.17 (d, *J* = 9.3 Hz, 5H, C***H***$_2$), 0.49 (s, 6H, Si(C***H***$_3$)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 248.7 (***C***(O)), 135.2 (***C***ar), 135.1 (***C***Har), 134.1 (***C***Har), 131.0 (***C***Har), 129.8 (***C***Har), 128.2 (***C***Har), 55.8

(***C***H), 26.9 (***C***H_2), 26.0 (***C***H_2), 25.7 (***C***H_2), -4.0 (Si(***C***H_3)$_2$). HRMS (APCI): Mass Calculated for $C_{15}H_{23}OSi$, theoretical Mass: 247.15127, measured Mass: 247.15116. IR (cm^{-1}): 2927, 2852, 1636, 1448, 1427, 1247, 1108, 835, 820, 779.

❖ **(Dimethyl(phenyl)silyl)(furan-2-yl)methanone (170)**

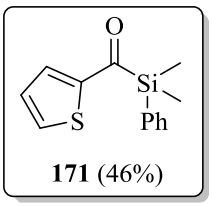


170 (47%)

Chemical Formula: $C_{13}H_{14}O_2Si$
Molecular Weight: 230,33

Anhydride **158** was used. The product was purified by flash chromatography on silica gel using P.E./Et_2O (95/5) as eluent to give **170** as a bright yellow oil (0.0271 g, 47%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 – 7.56 (m, 2H, C***H***ar), 7.56 – 7.49 (m, 1H, C***H***ar), 7.39 (dd, *J* = 5.6, 2.8 Hz, 3H, C***H***ar), 6.91 – 6.84 (m, 1H, C***H***ar), 6.43 (dd, *J* = 3.6, 1.7 Hz, 1H, C***H***ar), 0.62 (s, 6H, Si(C***H***$_3$)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.1 (***C***(O)), 146.2 (***C***ar), 134.4 (***C***Har), 130.1 (***C***Har), 128.3 (***C***Har), 117.0 (***C***Har), 112.2 (***C***Har), -3.7 (Si(***C***H_3)$_2$). HRMS (ESI): Mass Calculated for $C_{13}H_{15}O_2Si$, theoretical Mass: 231.08358, measured Mass: 231.08366. IR (cm^{-1}): 3047, 2962, 1772, 1556, 1456, 1248, 1111, 1013, 835, 783.

❖ **(Dimethyl(phenyl)silyl)(thiophen-2-yl)methanone (171)**



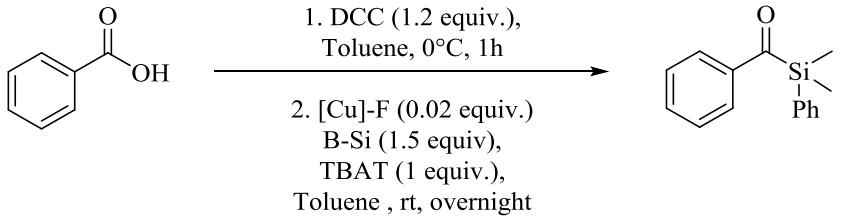
171 (46%)

Chemical Formula: $C_{13}H_{14}OSSi$
Molecular Weight: 246,40

Anhydride **159** was used. The product was purified by flash chromatography on silica gel using P.E./Et_2O (95/5) as eluent to give **171** as a bright yellow oil (0.0283 g, 46%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 – 7.54 (m, 3H, C***H***ar),

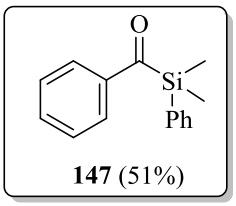
7.47 – 7.35 (m, 4H, C***H***ar), 7.01 (dd, *J* = 4.9, 3.8 Hz, 1H, C***H***ar), 0.63 (s, 6H, Si(C$\boldsymbol{H}_3$)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 222.7 (***C***(O)), 135.3 (***C***ar), 134.3 (***C***Har), 133.9 (***C***Har), 133.7 (***C***Har), 133.4 (***C***Har), 130.2 (***C***Har), 129.7 (***C***Har), 128.4 (***C***Har), 128.3 (***C***Har), 127.9 (***C***Har), -3.2 (Si(***C***H$_3$)$_2$). HRMS (APCI): Mass Calculated for $C_{13}H_{15}OSSi$, theoretical Mass: 247.06074, measured Mass: 247.06055. IR (cm^{-1}): 3069, 2962, 1575, 1410, 1230, 1108, 1051, 844, 797, 727.

II.2.2. General procedure for "one-pot" reaction



A flame-dried schlenk was loaded with benzoic acid (0.0305 g, 0.25 mmol, 1 equiv.) and dicyclohexylcarbodiimide (0.0619 g, 0.3 mmol, 1.2 equiv.). The vessel was then sealed and after 3 vacuum/argon cycles, toluene was added (2 mL) and the mixture was stirred at 0°C during 1 hour. Then CuF(PPh$_3$)$_3$.2MeOH **25** (4.7 mg, 0.005 mmol, 0.02 equiv.) and TBAT (0.1349 g, 0.25 mmol, 1 equiv.) was added to the reaction mixture followed by borosilane **19** (0.1 mL, 0.325 mmol, 1.5 equiv.) which was added dropwise over 10 minutes. The mixture was stirred at room temperature for 6 h. The solution was filtered over a pad of flash silica gel eluting with Et_2O and then concentrated under reduced pressure. Hexamethylbenzene was added to the crude product to determine the yield by ^{1}H NMR. The product was finally purified by flash chromatography on silica gel.

❖ **(Dimethyl(phenyl)silyl)(phenyl)methanone (147)**



147 (51%)

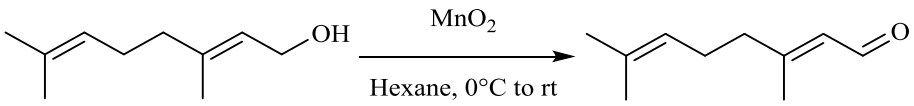
Chemical Formula: $C_{15}H_{16}OSi$
Molecular Weight: 240,37

The product was purified by flash chromatography on silica gel using P.E./Et_2O (95/5) as eluent to give **147** as a bright yellow oil (0.0306 g, 51%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 – 7.70 (m, 2H, C***H***ar), 7.65 – 7.56 (m, 2H, C***H***ar), 7.46 (d, *J* = 7.3 Hz, 1H, C***H***ar), 7.43 – 7.32 (m, 5H, C***H***ar), 0.63 (s, 6H, Si(C***H***$_3$)$_2$). Spectral data are identical to those reported in the literature.[28]

III. Chapter III : Synthesis of α-hydroxysilanes

III.1. Synthesis of substrates

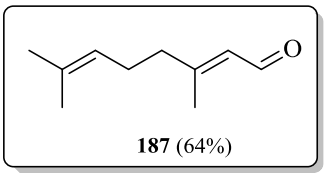
III.1.1. Synthesis of substrate 187



187, 64%

A procedure of the literature was used.[18] MnO_2 (1.3 g, 15 mmol, 15 equiv.) was added to a solution of geraniol (0.17 mL, 1 mmol, 1 equiv.) in 20 mL of hexane at 0°C. The mixture was stirred at room temperature and followed by TLC. After 2 hours, the solution was filtered and concentrated under reduced pressure. The desired product was obtained as a colorless oil in 64% yield (0.0974 g).

❖ ***(E)*-3,7-dimethylocta-2,6-dienal (187)**



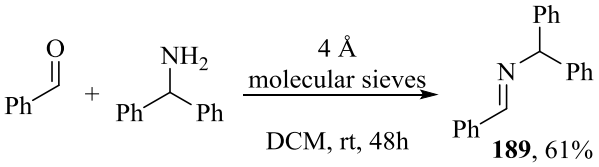
Chemical Formula: $C_{10}H_{16}O$
Molecular Weight: 152,23

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.99 (d, *J* = 8.1 Hz, 1H, C***H***O), 5.88 (d, *J* = 8.1 Hz, 1H, C$\boldsymbol{H}_{vinyl}$), 5.07 (dd, *J* = 4.1, 2.8 Hz, 1H, C$\boldsymbol{H}_{vinyl}$), 2.22 (s, 4H, C$\boldsymbol{H}_2$), 2.17 (d, *J* = 1.1 Hz, 3H, C$\boldsymbol{H}_3$), 1.69 (s, 3H, C$\boldsymbol{H}_3$), 1.61 (s,

[18] Bobbitt, J. M., *J. Org. Chem.* **1998**, *63*, 9367-9374. (b) Tsuboi, S., Ishii, N., Sakai, T., Tari, I., Utaka, M., *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1888-1893.

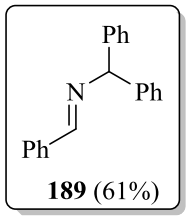
3H, C***H***$_3$). Spectral data are identical to those reported in the literature.[29]

III.1.2. Synthesis of substrate 189



A procedure of the literature was used.[19] A flame-dried schlenk was charged with 4Å molecular sieves (0.2 g), benzaldehyde (0.1 mL, 1 mmol, 1 equiv.) and benzhydrylamine (0.172 mL, 1 mmol, 1 equiv.) under an inert atmosphere. This mixture was then stirred in dry DCM (10 mL) for 48 hours at room temperature. After completion of reaction (TLC monitoring), the reaction mixture was filtered over celite and washed with DCM (5 mL). Evaporation of the solvent under reduced pressure afforded the crude aldimine which was purified by crystallization using n-pentane/DCM (9/1). Desired product **189** was obtained with 61% yield as a white solid (0.166 g, E/Z ratio: >99/1).

❖ ***(E)-N*-benzylidene-1,1-diphenylmethanamine (189)**



Chemical Formula: $C_{20}H_{17}N$
Molecular Weight: 271,36

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (s, 1H, C***H***N), 7.86 (d, *J* = 3.8 Hz, 2H, C***H***ar), 7.49 – 7.14 (m, 14H, C***H***ar), 5.62 (s, 1H, Ph_2C***H***). Spectral data are identical to those reported in the literature.[30]

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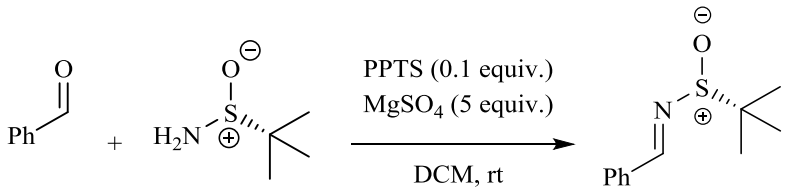
[19] Vyas, D. J.; Fröhlich, R.; Oestreich, M., *Org. Lett.* **2011**, *13*, 2094-2097.

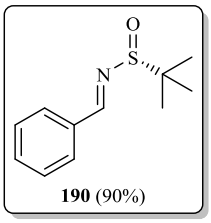
III.1.3. Synthesis of substrate 190



190

A flame-dried Schlenk was charged sequentially with (*R*)-t-butanesulfinamide (1.0 equiv.) in DCM (0.75 M). PPTS (0.1 equiv.) was added followed by $MgSO_4$ (5 equiv.) and the corresponding aldehyde (2.0 equiv.). 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 to afford the desired product.

❖ ***(R_S)-N-benzylidene-2-methylpropane-2-sulfinamide (190)***



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). ^1H NMR (300 MHz, $CDCl_3$) δ 8.59 (s, 1H, N=C***H***), 7.87 – 7.84 (m, 2H, C***H***ar), 7.52 – 7.47 (m, 3H, C***H***ar), 1.27 (s, 9H, CC***H***$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.9, 134.2, 132.5, 129.5, 129.0, 57.9, 22.7.

Spectral data are identical to those reported in the literature (CAS: 186249-76-3).[20]

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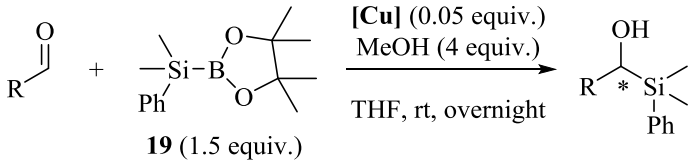
[20] Liu, G.; Cogan, D. A.; Ellman, J. A.; *J. Am. Chem. Soc.* **1997,** *119*, 9913-9914.

III.2. Catalytic Tests

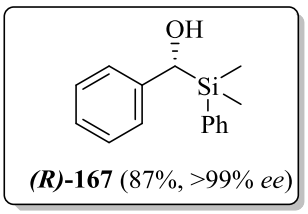
III.2.1. General procedure for the synthesis of α-hydroxysilanes



A flame-dried schlenk is loaded with copper (I) complexes **84** or **84'** (16 mg, 0.0125 mmol, 0.05 equiv.). The vessel is then sealed and after 3 vacuum/argon cycles, THF is added (2 mL). After dissolution of solids, freshly distilled aldehyde (0.25 mmol, 1 equiv.) is added. Borosilane **19** (0.1 mL, 0.375 mmol, 1.5 equiv.) is then added dropwise. Finally, MeOH (0.04 mL, 1 mmol, 4 equiv.) is added and the mixture is stirred at room temperature overnight. $NaBO_3$ (125 mg, 1 mmol, 4 equiv.), 1 mL of Et_2O and 3 mL of water is added and the mixture is stirred for 3 hours. Et_2O (5 mL) is added and the phases are separated. The aqueous phase is then extracted with Et_2O (3 x 5 mL). The combined organic phases are washed with NH_4Cl sat. (15 mL), $NaHCO_3$ sat. (15 mL) and brine (15 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The product is finally purified by flash chromatography on silica gel.

❖ ***(R)*-(Dimethyl(phenyl)silyl)(phenyl)methanol [*(R)*-167]**

Copper complex **84'** was used. The product was purified by flash chromatography on silica gel using P.E./Et_2O (80/20) as eluent to give ***(R)*-167** as a colorless oil (0.105 g, 87%). Enantioselectivity: >99% e.e. The enantiomeric ratio was determined by HPLC using CHIRALPAK

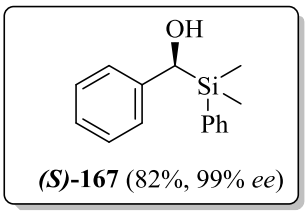


***(R)*-167** (87%, >99% *ee*)

Chemical Formula: $C_{15}H_{18}OSi$
Molecular Weight: 242,39

IA column (isohexane/EtOH: 90/10, 1 mL/min, 220 nm, t_R of (S) = 5.7 min (minor), t_R of (R) = 6.9 min (major)). ^1H NMR (300 MHz, $CDCl_3$) δ 7.53 – 7.45 (m, 2H, C***H***ar), 7.45 – 7.34 (m, 3H, C***H***ar), 7.26 (dd, *J* = 6.5, 1.1 Hz, 2H, C***H***ar), 7.18 (d, *J* = 7.2 Hz, 1H, C***H***ar), 7.15 – 7.06 (m, 2H, C***H***ar), 4.71 (s, 1H, C***H***OH), 1.76 (s, 1H, O***H***), 0.32 (s, 3H, Si(C***H***$_3$)$_2$), 0.28 (s, 3H, Si(C***H***$_3$)$_2$). Spectral data are identical to those reported in the literature.[21]

❖ ***(S)*-(Dimethyl(phenyl)silyl)(phenyl)methanol [*(S)*-167]**



***(S)*-167** (82%, 99% *ee*)

Chemical Formula: $C_{15}H_{18}OSi$
Molecular Weight: 242,39

Copper complex **84** was used. The product was purified by flash chromatography on silica gel using P.E./Et_2O (80/20) as eluent to give ***(S)*-167** as a colorless oil (0.099 g, 82%). Enantioselectivity: 99% e.e. The enantiomeric ratio was determined by HPLC using CHIRALPAK IA column (isohexane/EtOH: 90/10, 1 mL/min, 220 nm, t_R of (S) = 5.7 min (major), t_R of (R) = 6.9 min (minor)). $[\alpha]_D^{20}$ = -63.0 (c = 0.0125,

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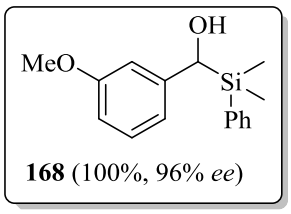
[21] N. Arai, K. Suzuki, S. Sugizaki, H. Sorimachi and T. Ohkuma, *Angew. Chem. Int. Ed.* **2008**, *47*, 1770-1773 ; C. Kleeberg, E. Feldmann, E. Hartmann, D. J. Vyas and M. Oestreich, *Chem. Eur. J.* **2011**, *17*, 13538-13543 ; X-F. Bai, G. Gao, Z-J. Zheng, F. Li, G-Q. Lai, K. Jiang, F. Li, L-W. Xu, *Synlett*, **2011**, *20*, 3031-3035.

CH_2Cl_2) (lit.[22] : $[\alpha]_D^{24}$ = -66.1 (c = 1.06, CH_2Cl_2), 95% ee (S)). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 – 7.45 (m, 2H, C***H***ar), 7.45 – 7.34 (m, 3H, C***H***ar), 7.26 (dd, *J* = 6.5, 1.1 Hz, 2H, C***H***ar), 7.18 (d, *J* = 7.2 Hz, 1H, C***H***ar), 7.15 – 7.06 (m, 2H, C***H***ar), 4.71 (s, 1H, C***H***OH), 1.76 (s, 1H, O***H***), 0.32 (s, 3H, Si(C***H***$_3$)$_2$), 0.28 (s, 3H, Si(C***H***$_3$)$_2$). Spectral data are identical to those reported in the literature.[31]

❖ **(Dimethyl(phenyl)silyl)(3-methoxyphenyl)methanol (168)**



168 (100%, 96% *ee*)

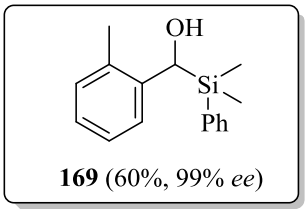
Chemical Formula: $C_{16}H_{20}O_2Si$
Molecular Weight: 272,41

Copper complex **84** was used. The product was purified by flash chromatography on silica gel using P.E./Et_2O (80/20) as eluent to give **168** as a colorless oil (0.136 g, quantitative yield). Enantioselectivity: 96% e.e. The enantiomeric ratio was determined by HPLC using CHIRALPAK IB column (isohexane/EtOH: 98/2, 1 mL/min, 220 nm, t_R = 10.3 min (major), t_R = 14.3 min (minor)). $[\alpha]_D^{20}$ = -46.6 (c = 0.0134, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 – 7.45 (m, 2H, C***H***ar), 7.38 (td, *J* = 6.8, 3.6 Hz, 3H, C***H***ar), 7.17 (t, *J* = 7.9 Hz, 1H, C***H***ar), 6.77 – 6.64 (m, 2H, C***H***ar), 6.61 (s, 1H, C***H***ar), 4.69 (s, 1H, C***H***OH), 3.69 (s, 3H, OC***H***$_3$), 1.75 (s, 1H, O***H***), 0.32 (s, 3H, Si(C***H***$_3$)$_2$), 0.29 (s, 3H, Si(C***H***$_3$)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6 (***C***OCH$_3$), 145.4 (***C***ar), 136.1 (Si***C***ar), 134.5 (***C***Har), 129.6 (***C***Har), 129.1 (***C***Har), 127.9 (***C***Har), 117.6 (***C***Har), 111.9 (***C***Har), 110.4 (***C***Har), 70.1 (***C***HOH), 55.2 (O***C***H$_3$), -5.3 (Si(***C***H$_3$)$_2$),

[22] J. R. Huckins, S. D. Rychnovsky, *J. Org. Chem.* **2003**, *68*, 10135–10145.

-6.0 (Si(***C***H_3)$_2$). HRMS (ESI): Mass Calculated for $C_{16}H_{21}O_2Si$, theoretical Mass: 273.13053, Measured Mass: 273.13062.

❖ **(Dimethyl(phenyl)silyl)(o-tolyl)methanol (169)**



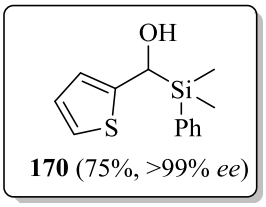
169 (60%, 99% *ee*)

Chemical Formula: $C_{16}H_{20}OSi$
Molecular Weight: 256,41

Copper complex **84** was used. The product was purified by flash chromatography on silica gel using P.E./Et_2O (80/20) as eluent to give **169** as a colorless oil (0.077 g, 60%). Enantioselectivity: 99% e.e. The enantiomeric ratio was determined by HPLC using CHIRALPAK IB column (isohexane/EtOH: 95/5, 1 mL/min, 220 nm, t_R = 5.4 min (minor), t_R = 6.0 min (major)). $[\alpha]_D^{20}$ = -56.3 (c = 0.0075, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 – 7.29 (m, 6H, C***H***ar), 7.22 (dd, *J* = 14.5, 7.6 Hz, 1H, C***H***ar), 7.09 (dt, *J* = 10.9, 4.1 Hz, 2H, C***H***ar), 4.96 (s, 1H, C***H***OH), 2.00 (s, 3H, C***H***$_3$), 1.65 (s, 1H, O***H***), 0.40 (s, 3H, Si(C***H***$_3$)$_2$), 0.29 (s, 3H, Si(C***H***$_3$)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.0 (***C***ar), 136.4 (CH_3***C***ar), 134.4 (Si***C***ar), 133.5 (***C***Har), 130.1 (***C***Har), 129.6 (***C***Har), 127.9 (***C***Har), 126.0 (***C***Har), 65.8 (***C***HOH), 19.6 (***C***H_3), -5.1 (Si(***C***H_3)$_2$), -5.9 (Si(***C***H_3)$_2$). HRMS (EI): Mass Calculated for $C_{16}H_{20}OSi$, theoretical Mass: 256.12779, measured Mass: 256.12823.

❖ **(Dimethyl(phenyl)silyl)(thiophen-2-yl)methanol (170)**

Copper complex **84'** was used. The product was purified by flash chromatography on silica gel using P.E./Et_2O (80/20) as eluent to give **170** as a colorless oil (0.093 g, 75%). Enantioselectivity: >99% e.e. The enantiomeric ratio was determined by HPLC using CHIRALPAK IB

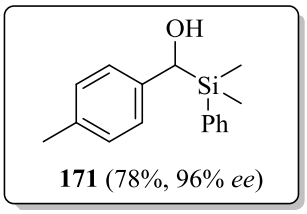


170 (75%, >99% *ee*)

Chemical Formula: $C_{13}H_{16}OSSi$
Molecular Weight: 248,42

column (isohexane/EtOH: 98/2, 1 mL/min, 220 nm, t_R = 13.0 min). $[\alpha]_D^{20}$ = -45.6 (c = 0.01005, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 7.4, 1.7 Hz, 2H, C***H***ar), 7.39 (t, *J* = 7.0 Hz, 3H, C***H***ar), 7.15 (d, *J* = 5.0 Hz, 1H, C***H***ar), 7.00 – 6.84 (m, 1H, C***H***ar), 6.70 (d, *J* = 3.4 Hz, 1H, C***H***ar), 4.94 (s, 1H, C***H***OH), 1.90 (s, 1H, O***H***), 0.40 (s, 3H, Si(C***H***$_3$)$_2$), 0.34 (s, 3H, Si(C***H***$_3$)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.6 (S***C***ar), 135.9 (Si***C***ar), 134.5 (***C***Har), 129.7 (***C***Har), 128.0 (***C***Har), 126.9 (***C***Har), 123.4 (***C***Har), 122.4 (***C***Har), 66.3 (***C***HOH), -5.2 (Si(***C***H$_3$)$_2$), -5.9 (Si(***C***H$_3$)$_2$). HRMS (EI): Mass Calculated for $C_{13}H_{16}OSSi$, theoretical Mass: 248.06856, Measured Mass: 248.06892.

❖ **(Dimethyl(phenyl)silyl)(p-tolyl)methanol (171)**



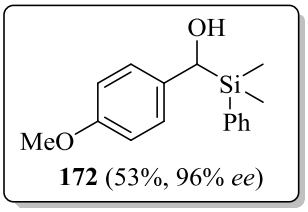
171 (78%, 96% *ee*)

Chemical Formula: $C_{16}H_{20}OSi$
Molecular Weight: 256,41

Copper complex **84** was used. The product was purified by flash chromatography on silica gel using P.E./Et_2O (80/20) as eluent to give **171** as a colorless oil (0.099 g, 78%). Enantioselectivity: 96% e.e. The enantiomeric ratio was determined by HPLC using CHIRALPAK IB column (isohexane/EtOH: 98/2, 1 mL/min, 220 nm, t_R = 10.2 min (major), t_R = 11.4 min (minor)). $[\alpha]_D^{20}$ = -77.3 (c = 0.01095, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 7.5, 1.8 Hz, 2H, C***H***ar), 7.37 (d, *J* = 7.7 Hz, 3H, C***H***ar), 7.08 (d, *J* = 8.0 Hz, 2H, C***H***ar), 6.99 (d, *J* = 8.1 Hz, 2H, C***H***ar), 4.67 (s, 1H, C***H***OH), 2.33 (s, 3H, CC***H***$_3$), 1.64 (d, *J* =

2.4 Hz, 1H, O***H***), 0.30 (s, 3H, Si(C***H***$_3$)$_2$), 0.26 (s, 3H, Si(C***H***$_3$)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.5 (***C***ar), 134.5 (***C***ar), 129.6 (***C***ar), 128.9 (***C***Har), 127.9 (***C***Har), 125.3 (***C***Har), 70.0 (***C***HOH), 21.2 (C***C***H$_3$), -5.2 (Si(***C***H$_3$)$_2$), -6.2 (Si(***C***H$_3$)$_2$). HRMS (ESI): Mass Calculated for $C_{16}H_{20}ONaSi$, theoretical Mass: 279.11756, measured Mass: 279.11778.

❖ **(Dimethyl(phenyl)silyl)(4-methoxyphenyl)methanol (172)**

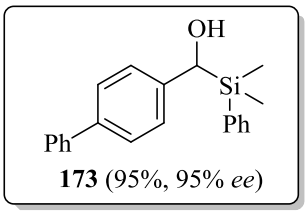


172 (53%, 96% *ee*)

Chemical Formula: $C_{16}H_{20}O_2Si$
Molecular Weight: 272,41

Copper complex **84** was used. The product was purified by flash chromatography on silica gel using P.E./Et_2O (80/20) as eluent to give **172** as a colorless oil (0.072 g, 53%). Enantioselectivity: 96% e.e. The enantiomeric ratio was determined by HPLC using CHIRALPAK IB column (isohexane/EtOH: 98/2, 1 mL/min, 220 nm, t_R = 14.6 min (major), t_R = 15.2 min (minor)). $[\alpha]_D^{20}$ = -48.3 (c = 0.00605, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 – 7.46 (m, 2H, C***H***ar), 7.46 – 7.32 (m, 3H, C***H***ar), 7.02 (d, *J* = 8.7 Hz, 2H, C***H***ar), 6.82 (d, *J* = 8.7 Hz, 2H, C***H***ar), 4.65 (s, 1H, C***H***OH), 3.80 (s, 3H, OC***H***$_3$), 1.76 (s, 1H, O***H***), 0.32 (s, 3H, Si(C***H***$_3$)$_2$), 0.27 (s, 3H, Si(C***H***$_3$)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0 (Ar***C***OMe), 135.6 (***C***ar), 134.5 (***C***ar), 129.5 (***C***Har), 127.8 (***C***Har), 126.5 (***C***Har), 113.6 (***C***Har), 69.6 (***C***HOH), 55.3 (CO***C***H$_3$), -5.3 (Si(***C***H$_3$)$_2$), -6.1 (Si(***C***H$_3$)$_2$). HRMS (EI): Mass Calculated for $C_{16}H_{19}O_2Si$ (M-H), theoretical Mass: 271.11543, Measured Mass: 271.11579.

❖ **Biphenyl-4-yl(dimethyl(phenyl)silyl)methanol (173)**

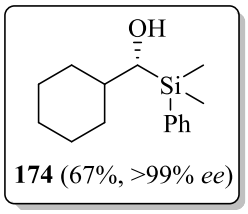


173 (95%, 95% *ee*)

Chemical Formula: $C_{21}H_{22}OSi$
Molecular Weight: 318,48

Copper complex **84** was used. The product was purified by flash chromatography on silica gel using P.E./Et_2O (80/20) as eluent to give **173** as a colorless oil (0.151 g, 95%). Enantioselectivity: 95% e.e. The enantiomeric ratio was determined by HPLC using CHIRALPAK IB column (isohexane/iPrOH: 95/5, 1 mL/min, 220 nm, t_R = 6.0 min (major), t_R = 6.9 min (minor)). $[\alpha]_D^{20}$ = -85.8 (c = 0.011525, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 – 7.32 (m, 12H, C***H***ar), 7.17 (d, *J* = 8.0 Hz, 2H, C***H***ar), 4.77 (s, 1H, C***H***OH), 1.73 (s, 1H, O***H***), 0.35 (s, 3H, Si(C***H***$_3$)$_2$), 0.32 (s, 3H, Si(C***H***$_3$)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.7 (***C***ar), 141.0 (***C***ar), 138.8 (***C***ar), 135.9 (***C***Har), 134.4 (***C***Har), 129.6 (***C***Har), 128.8 (***C***Har), 127.9 (***C***Har), 127.1 (***C***Har), 126.9 (***C***Har), 126.8 (***C***Har), 125.6 (***C***Har), 69.9 (***C***HOH), -5.3 (Si(***C***H$_3$)$_2$), -6.2 (Si(***C***H$_3$)$_2$). HRMS (EI): Mass Calculated for $C_{21}H_{22}OSi$, theoretical Mass: 318.14343, Measured Mass: 318.14393.

❖ ***(R)*-Cyclohexyl(dimethyl(phenyl)silyl)methanol [*(R)*-174]**



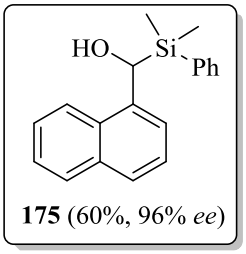
174 (67%, >99% *ee*)

Chemical Formula: $C_{15}H_{24}OSi$
Molecular Weight: 248,44

General procedure was used. Copper complex **84'** was used. The product was purified by flash chromatography on silica gel using P.E./Et_2O (80/20) as eluent to give ***(R)*-174** as a colorless oil (0.083 g, 67%). Enantioselectivity: >99% e.e. The enantiomeric ratio was determined by HPLC using

CHIRALCEL OJ-H column (isohexane/EtOH: 99.5/0.5, 1 mL/min, 220 nm, t_R of (S) = 15.1 min (minor), t_R of (R) = 19.0 min (major)). $[\alpha]_D^{20}$ = -14.4 (c = 0.0118, CH_2Cl_2) (lit.[31]: $[\alpha]_D^{22}$ +14.2 (c = 1.02, $CHCl_3$), 99% ee (S)). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 – 7.52 (m, 2H, C***H***ar), 7.38 (dd, *J* = 4.1, 2.3 Hz, 3H, C***H***ar), 3.36 (d, *J* = 5.9 Hz, 1H, C***H***OH), 1.84 (d, *J* = 5.9 Hz, 1H, C***H***), 1.81 – 1.48 (m, 5H, C$\boldsymbol{H}_2$), 1.31 – 0.98 (m, 6H, C$\boldsymbol{H}_2$), 0.40 (s, 3H, Si(C$\boldsymbol{H}_3$)$_2$), 0.39 (s, 3H, Si(C$\boldsymbol{H}_3$)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.9 (Si***C***ar), 134.2 (***C***Har), 129.3 (***C***Har), 128.0 (***C***Har), 71.1 (***C***HOH), 42.1 (***C***H), 30.9 (***C***H_2), 29.7 (***C***H_2), 26.6 (***C***H_2), 26.5 (***C***H_2), 26.4 (***C***H_2), -3.7 (Si(***C***H_3)$_2$), -4.2 (Si(***C***H_3)$_2$). HRMS (ESI): Mass Calculated for $C_{15}H_{24}ONaSi$, theoretical Mass: 271.14886, Measured Mass: 271.14897.

❖ **(Dimethyl(phenyl)silyl)(naphthalen-1-yl)methanol (175)**



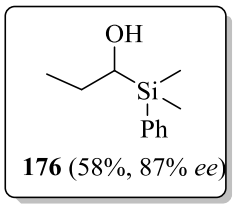
175 (60%, 96% *ee*)

Chemical Formula: $C_{19}H_{20}OSi$
Molecular Weight: 292,45

Copper complex **84** was used. The product was purified by flash chromatography on silica gel using P.E./Et_2O (80/20) as eluent to give **175** as a colorless oil (0.088 g, 60%). Enantioselectivity: 96% e.e. The enantiomeric ratio was determined by HPLC using CHIRALPAK IB column (isohexane/iPrOH: 95/5, 1 mL/min, 220 nm, t_R = 5.9 min (major), t_R = 6.7 min (minor)). $[\alpha]_D^{20}$ = -82 (c = 0.00935, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 11.6, 8.3 Hz, 2H, C***H***ar), 7.69 (dd, *J* = 6.2, 3.3 Hz, 1H, C***H***ar), 7.57 – 7.29 (m, 9H, C***H***ar), 5.60 (s, 1H, C***H***OH), 1.70 (s, 1H, O***H***), 0.34 – 0.26 (m, 3H, Si(C$\boldsymbol{H}_3$)$_2$), 0.26 – 0.13 (m, 3H, Si(C$\boldsymbol{H}_3$)$_2$). ^{13}C NMR (75 MHz,

$CDCl_3$) δ 140.0 (***C***ar), 136.3 (***C***ar), 134.7 (***C***ar), 133.6 (***C***ar), 129.6 (***C***Har), 129.2 (***C***Har), 128.8 (***C***Har), 127.7 (***C***Har), 127.3 (***C***Har), 127.1 (***C***Har), 126.5 (***C***Har), 125.6 (***C***Har), 125.3 (***C***Har), 125.0 (***C***Har), 123.6 (***C***Har), 122.9 (***C***Har), 66.0 (***C***HOH), -4.3 (Si(***C***$H_3)_2$), -5.8 (Si(***C***$H_3)_2$). HRMS (EI): Mass Calculated for: $C_{19}H_{20}OSi$, theoretical Mass: 292.12779, Measured Mass: 292.12719.

❖ **1-(Dimethyl(phenyl)silyl)propan-1-ol (176)**

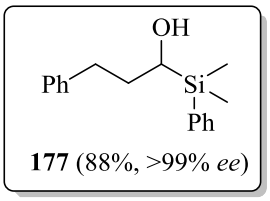


176 (58%, 87% *ee*)

Chemical Formula: $C_{11}H_{18}OSi$
Molecular Weight: 194,35

Copper complex **84** was used. The product was purified by flash chromatography on silica gel using P.E./Et_2O (80/20) as eluent to give **176** as a colorless oil (58%). Enantioselectivity: 87% e.e. The enantiomeric ratio was determined by HPLC using CHIRALCEL OJ-H column (isohexane/EtOH: 95/5, 1 mL/min, 220 nm, t_R = 7.2 min (minor), t_R = 9.0 min (major)). $[\alpha]_D^{20}$ = -3.4 (c = 0.00865, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 – 7.48 (m, 2H, C***H***ar), 7.45 – 7.29 (m, 3H, C***H***ar), 3.41 (dd, *J* = 10.1, 4.1 Hz, 1H, C***H***OH), 1.56 (ddd, *J* = 10.0, 7.3, 3.6 Hz, 2H, C***H***$_2$), 1.26 (s, 1H, O***H***), 0.98 (t, *J* = 7.3 Hz, 3H, C***H***$_3$), 0.34 (s, 3H, Si(C***H***$_3)_2$), 0.33 (s, 3H, Si(C***H***$_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.2 (Si***C***ar), 129.4 (***C***Har), 128.0 (***C***Har), 67.5 (***C***HOH), 26.6 (***C***H_2), 11.6 (***C***H_3), -5.2 (Si(***C***$H_3)_2$), -5.5 (Si(***C***$H_3)_2$). HRMS (EI): Mass Calculated for $C_{11}H_{17}OSi$ (M-H), theoretical Mass: 193.10486, Measured Mass: 193.10435.

❖ **1-(Dimethyl(phenyl)silyl)-3-phenylpropan-1-ol (177)**



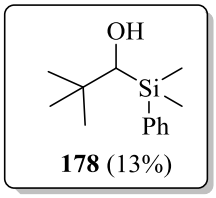
177 (88%, >99% *ee*)

Chemical Formula: $C_{17}H_{22}OSi$
Molecular Weight: 270,44

Copper complex **84** was used. The product was purified by flash chromatography on silica gel using P.E./Et_2O (80/20) as eluent to give **177** as a colorless oil (0.119 g, 88%). Enantioselectivity: >99% e.e. The enantiomeric ratio was determined by HPLC using CHIRALPAK IB column (isohexane/iPrOH: 95/5, 1 mL/min, 220 nm, t_R = 4.4 min (minor), t_R = 5.0 min (major)). $[\alpha]_D^{20}$ = +14.5 (c = 0.01225, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 – 7.51 (m, 2H, C***H***ar), 7.46 – 7.35 (m, 3H, C***H***ar), 7.29 (dd, *J* = 13.2, 6.0 Hz, 2H, C***H***ar), 7.20 (t, *J* = 7.0 Hz, 3H, C***H***ar), 3.64 – 3.48 (m, 1H, C***H***OH), 2.91 (dd, *J* = 13.8, 7.2 Hz, 1H, C***H***$_2$), 2.73 – 2.53 (m, 1H, C***H***$_2$), 1.86 (dd, *J* = 14.7, 7.8 Hz, 2H, C***H***$_2$), 1.14 (s, 1H, O***H***), 0.36 (s, 3H, Si(C***H***$_3$)$_2$), 0.35 (s, 3H, Si(C***H***$_3$)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.3 (***C***ar), 136.6 (***C***ar), 134.3 (***C***Har), 134.3 (***C***Har), 133.1 (***C***Har), 129.6 (***C***Har), 128.7 (***C***Har), 128.6 (***C***Har), 128.5 (***C***Har), 128.1 (***C***Har), 127.8 (***C***Har), 125.9 (***C***Har), 65.0 (***C***HOH), 35.4 (***C***H$_2$), 33.4 (***C***H$_2$), -5.3 (Si(***C***H$_3$)$_2$), -5.6 (Si(***C***H$_3$)$_2$). HRMS (CI): Mass Calculated for $C_{17}H_{23}OSi$, theoretical Mass: 271.15181, Measured Mass: 271.15126.

❖ **(Dimethyl(phenyl)silyl)-2,2-dimethylpropan-1-ol (178)**

Copper complex **25** and (*rac*)-BINAP was used. The product was purified by flash chromatography on silica gel using P.E./Et_2O (80/20) as eluent to give **178** as a colorless oil (7.2 mg, 13%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, J = 3.4 Hz, 2H, C***H***ar), 7.36 (dd, J = 4.1, 2.2 Hz,

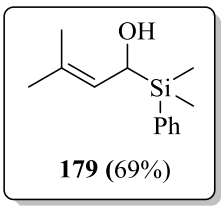


178 (13%)

Chemical Formula: $C_{13}H_{22}OSi$
Molecular Weight: 222,40

3H, C***H***ar), 3.22 (d, J = 5.5 Hz, 1H, C***H***OH), 0.91 (d, J = 1.6 Hz, 9H, C(C***H***$_3$)$_3$), 0.42 (s, 6H, Si(C***H***$_3$)$_2$). Spectral data are identical to those reported in the literature.[23]

❖ **(Dimethyl(phenyl)silyl)-3-methylbut-2-en-1-ol (179)**



179 (69%)

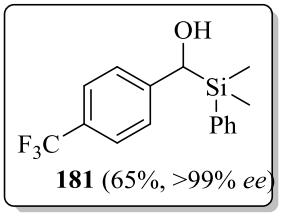
Chemical Formula: $C_{13}H_{20}OSi$
Molecular Weight: 220,38

Copper complex **25** and (*rac*)-BINAP was used. The product was purified by flash chromatography on silica gel using P.E./Et_2O (80/20) as eluent to give **179** as a colorless oil (0.0378 g, 69%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 – 7.51 (m, 2H, C***H***ar), 7.46 – 7.29 (m, 3H, C***H***ar), 5.26 (dd, J = 10.2, 1.3 Hz, 1H, C***H***$_{vinyl}$), 4.35 (d, J = 10.2 Hz, 1H, C***H***OH), 1.72 (s, 3H, C***H***$_3$), 1.49 (s, 3H, C***H***$_3$), 0.33 (dd, J = 10.7, 3.1 Hz, 6H, Si(C***H***$_3$)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.71 (Si***C***ar), 134.34 ((CH$_3$)$_2$***C***), 132.69 (***C***Har), 129.44 (***C***Har), 127.92 (***C***Har), 125.44 (H***C***=), 64.22 (***C***HOH), 26.08 (***C***H$_3$), 18.48 (***C***H$_3$), -5.27 (Si(***C***H$_3$)$_2$), -5.91 (Si(***C***H$_3$)$_2$).

❖ **(Dimethyl(phenyl)silyl)(4-(trifluoromethyl)phenyl)methanol (181)**

Copper complex **84** was used. The product was purified by flash chromatography on silica gel using P.E./Et_2O (80/20) as eluent to give **181** as a colorless oil (0.101 g, 65%). Enantioselectivity: >99% e.e. The

[23] Paredes, M. D.; Alonso, R., *J. Org. Chem.* **2000**, *65*, 2292-2304.

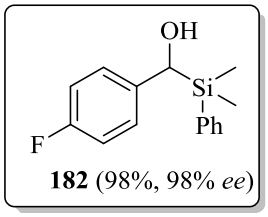


181 (65%, >99% *ee*)

Chemical Formula: $C_{16}H_{17}F_3OSi$
Molecular Weight: 310,39

enantiomeric ratio was determined by HPLC using CHIRALPAK IB column (isohexane/EtOH: 98/2, 1 mL/min, 220 nm, t_R = 7.2 min). $[\alpha]_D^{20}$ = -55.9 (c = 0.01125, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 – 7.32 (m, 7H, C***H***ar), 7.17 (d, *J* = 8.1 Hz, 2H, C***H***ar), 4.77 (s, 1H, C***H***OH), 1.75 (s, 1H, O***H***), 0.31 (s, 3H, Si(C***H***$_3$)$_2$), 0.30 (d, *J* = 3.2 Hz, 3H, Si(C***H***$_3$)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.8 (***C***ar), 135.2 (***C***ar), 134.4 (***C***ar), 129.9 (***C***Har), 128.1 (***C***Har), 125.2 (***C***Har), 125.1 (***C***Har), 69.8 (***C***HOH), -5.6 (Si(***C***H$_3$)$_2$), -6.2 (Si(***C***H$_3$)$_2$). ^{19}F NMR (282 MHz, $CDCl_3$) δ -63.54. HRMS (ESI): Mass Calculated for $C_{16}H_{17}OF_3NaSi$, theoretical Mass: 333.08930, Measured Mass: 333.08975.

❖ (4-Fluorophenyl)(dimethyl(phenyl)silyl)methanol (182)



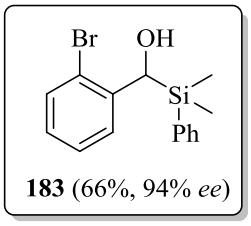
182 (98%, 98% *ee*)

Chemical Formula: $C_{15}H_{17}BrOSi$
Molecular Weight: 321,28

Copper complex **84** was used. The product was purified by flash chromatography on silica gel using P.E./Et_2O (80/20) as eluent to give **182** as a colorless oil (0.157 g, 98%). Enantioselectivity: 98% e.e. The enantiomeric ratio was determined by HPLC using CHIRALPAK IB column (isohexane/EtOH: 98/2, 1 mL/min, 220 nm, t_R = 6.6 min (major), t_R = 7.1 min (minor)). $[\alpha]_D^{20}$ = -57.9 (c = 0.01275, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 – 7.31 (m, 5H, C***H***ar), 7.07 – 6.88 (m, 4H, C***H***ar), 4.68 (s, 1H, C***H***OH), 1.67 (s, 1H, O***H***), 0.30 (s, 3H, Si(C***H***$_3$)$_2$), 0.27 (s, 3H, Si(C***H***$_3$)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7

(***C***ar), 139.2 (***C***ar), 135.7 (***C***ar), 134.4 (***C***Har), 129.7 (***C***Har), 127.9 (***C***Har), 126.7 (***C***Har), 126.6 (***C***Har), 115.1 (***C***Har), 114.8 (***C***Har), 69.5 (***C***HOH), -5.5 (Si(***C***H_3)$_2$), -6.2 (Si(***C***H_3)$_2$). ^{19}F NMR (282 MHz, $CDCl_3$) δ -118.72. HRMS (ESI): Mass Calculated for $C_{15}H_{17}OFNaSi$, theoretical Mass: 283.09249, Measured Mass: 283.09274.

❖ **(2-Bromophenyl)(dimethyl(phenyl)silyl)methanol (183)**

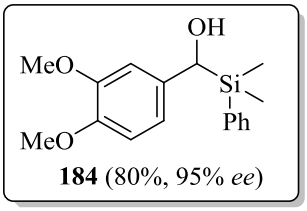


183 (66%, 94% *ee*)

Chemical Formula: $C_{15}H_{17}BrOSi$
Molecular Weight: 321,28

Copper complex **84** was used. The product was purified by flash chromatography on silica gel using P.E./Et_2O (80/20) as eluent to give **183** as a colorless oil (0.106 g, 66%). Enantioselectivity: 94% e.e. The enantiomeric ratio was determined by HPLC using CHIRALPAK IB column (isohexane/EtOH: 98/2, 1 mL/min, 220 nm, t_R = 6.1 min (major), t_R = 6.3 min (minor)). $[\alpha]_D^{20}$ -= -85.8 (c = 0.01475, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 – 7.22 (m, 8H, C***H***ar), 7.11 – 6.99 (m, 1H, C***H***ar), 5.20 (s, 1H, C***H***OH), 0.37 (s, 3H, Si(C***H***$_3$)$_2$), 0.36 (d, *J* = 2.0 Hz, 3H, Si(C***H***$_3$)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.2 (***C***ar), 135.9 (***C***ar), 134.5 (***C***ar), 132.5 (***C***Har), 129.7 (***C***Har), 128.0 (***C***Har), 127.9 (***C***Har), 127.5 (***C***Har), 127.4 (***C***Har), 121.3 (***C***Har), 68.2 (C***H***OH), -4.2 (Si(***C***H_3)$_2$), -6.1 (Si(***C***H_3)$_2$). HRMS (ESI): Mass Calculated for $C_{15}H_{17}OBrNaSi$, theoretical Mass: 343.01243, Measured Mass: 343.01273.

❖ **(3,4-Dimethoxyphenyl)(dimethyl(phenyl)silyl)methanol (184)**



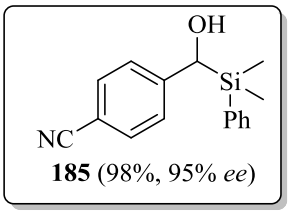
184 (80%, 95% *ee*)

Chemical Formula: $C_{17}H_{22}O_3Si$
Molecular Weight: 302,44

Copper complex **84** was used. The product was purified by flash chromatography on silica gel using P.E./Et_2O (60/40) as eluent to give **184** as a colorless oil (0.121 g, 80%). Enantioselectivity: 95% e.e. The enantiomeric ratio was determined by HPLC using CHIRALPAK IB column (isohexane/EtOH: 98/2, 1 mL/min, 220 nm, t_R = 19.9 min (major), t_R = 21.3 min (minor)). $[\alpha]_D^{20}$ = -56 (c = 0.01015, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 – 7.44 (m, 2H, C***H***ar), 7.36 (dd, *J* = 8.9, 5.9 Hz, 3H, C***H***ar), 6.78 (d, *J* = 8.2 Hz, 1H, C***H***ar), 6.64 (dd, *J* = 8.2, 1.8 Hz, 1H, C***H***ar), 6.48 (d, *J* = 1.9 Hz, 1H, C***H***ar), 4.63 (s, 1H, C***H***OH), 3.86 (s, 3H, OC***H***$_3$), 3.66 (s, 3H, OC***H***$_3$), 1.70 (s, 1H, O***H***), 0.30 (s, 3H, Si(C***H***$_3$)$_2$), 0.29 (s, 3H, Si(C***H***$_3$)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.7 (***C***ar), 147.3 (***C***ar), 136.2 (***C***ar), 134.6 (***C***ar), 129.5 (***C***Har), 127.9 (***C***Har), 117.2 (***C***Har), 110.9 (***C***Har), 108.9 (***C***Har), 69.9 (***C***HOH), 56.0 (O***C***H$_3$), 55.7 (O***C***H$_3$), -5.4 (Si(***C***H$_3$)$_2$), -5.8 (Si(***C***H$_3$)$_2$). HRMS (ESI): Mass Calculated for $C_{17}H_{23}O_3Si$, theoretical Mass: 303.14110, Measured Mass: 303.14168.

❖ **4-((Dimethyl(phenyl)silyl)(hydroxy)methyl)benzonitrile (185)**

Copper complex **84** was used. The product was purified by flash chromatography on silica gel using P.E./Et_2O (80/20) as eluent to give **185** as a colorless oil (0.131 g, 98%). Enantioselectivity: 95% e.e. The

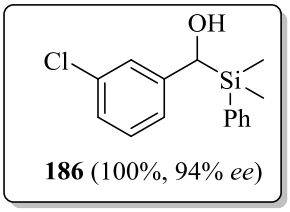


185 (98%, 95% *ee*)

Chemical Formula: $C_{16}H_{17}NOSi$
Molecular Weight: 267,40

enantiomeric ratio was determined by HPLC using CHIRALPAK IB column (isohexane/EtOH: 98/2, 1 mL/min, 220 nm, t_R = 14.1 min (major), t_R = 15.3 min (minor)). $[\alpha]_D^{20}$ = -76 (c = 0.01125, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.3 Hz, 2H, C***H***ar), 7.47 – 7.30 (m, 5H, C***H***ar), 7.13 (d, *J* = 8.1 Hz, 2H, C***H***ar), 4.76 (d, *J* = 2.9 Hz, 1H, C***H***OH), 1.86 (d, *J* = 3.3 Hz, 1H, O***H***), 0.31 (s, 3H, Si(C***H***$_3$)$_2$), 0.29 (s, 3H, Si(C***H***$_3$)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.5 (***C***ar), 134.8 (Si***C***ar), 134.4 (***C***Har), 131.9 (***C***Har), 130.0 (***C***Har), 128.1 (***C***Har), 125.5 (***C***Har), 119.4 (C***C***N), 109.3 (***C***CN), 70.0 (***C***HOH), -5.7 (Si(***C***H$_3$)$_2$), -6.1 (Si(***C***H$_3$)$_2$). HRMS (ESI): Mass Calculated for $C_{16}H_{18}ONSi$, theoretical Mass: 268.11522, Measured Mass: 268.11545.

❖ **(3-Chlorophenyl)(dimethyl(phenyl)silyl)methanol (186)**



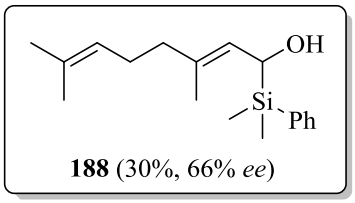
186 (100%, 94% *ee*)

Chemical Formula: $C_{15}H_{17}ClOSi$
Molecular Weight: 276,83

Copper complex **84** was used. The product was purified by flash chromatography on silica gel using P.E./Et_2O (80/20) as eluent to give **186** as a colorless oil (0.138 g, quantitative yield). Enantioselectivity: 94% e.e. The enantiomeric ratio was determined by HPLC using CHIRALPAK IB column (isohexane/EtOH: 90/10, 1 mL/min, 220 nm, t_R = 5.0 min (major), t_R = 5.4 min (minor)). $[\alpha]_D^{20}$ = -53.3 (c = 0.0097, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 – 7.34 (m, 5H, C***H***ar), 7.24 – 7.08 (m, 3H, C***H***ar), 6.94 (d, *J* = 7.0 Hz, 1H, C***H***ar), 4.69

(s, 1H, C***H***OH), 1.76 (s, 1H, O***H***), 0.34 (s, 3H, Si(C***H***$_3$)$_2$), 0.31 (s, 3H, Si(C***H***$_3$)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.1 (***C***Cl), 145.9 (***C***ar), 136.1 (***C***ar), 135.5 (***C***Har), 134.5 (***C***Har), 134.2 (***C***Har), 129.8 (***C***Har), 129.3 (***C***Har), 128.0 (***C***Har), 126.1 (***C***Har), 125.3 (***C***Har), 123.3 (***C***Har), 69.6 (***C***HOH), -5.5 (Si(***C***H$_3$)$_2$), -6.2 (Si(***C***H$_3$)$_2$). HRMS (ESI): Mass Calculated for $C_{15}H_{17}OClNaSi$, theoretical Mass: 299.06294, Measured Mass: 299.06352.

- ***(E)*-1-(dimethyl(phenyl)silyl)-3,7-dimethylocta-2,6-dien-1-ol (188)**



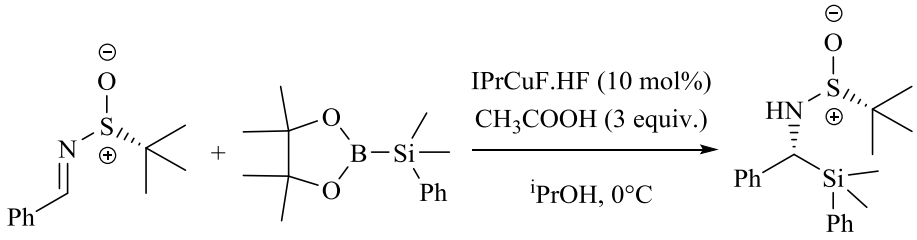
188 (30%, 66% *ee*)

Chemical Formula: $C_{18}H_{28}OSi$
Molecular Weight: 288,50

Copper complex **84** was used. The product was purified by flash chromatography on silica gel using P.E./Et_2O (70/30) as eluent to give **188** as a colorless oil (0.043 g, 30%). Enantioselectivity: 66% e.e. The enantiomeric ratio was determined by HPLC using CHIRALCEL OJ-H column (isohexane/EtOH: 95/5, 1 mL/min, 220 nm, t_R = 6.0 min (minor), t_R = 7.3 min (major)). $[\alpha]_D^{20}$ = -4.4 (c = 0.0064, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 – 7.53 (m, 2H, C***H***ar), 7.45 – 7.31 (m, 3H, C***H***ar), 5.26 (dd, *J* = 10.1, 0.9 Hz, 1H, C***H***$_{vinyl}$), 5.09 (d, *J* = 1.1 Hz, 1H, C***H***$_{vinyl}$), 4.37 (d, *J* = 10.1 Hz, 1H, C***H***OH), 2.17 – 1.97 (m, 4H, C***H***$_2$), 1.70 (s, 3H, C***H***$_3$), 1.62 (s, 3H, C***H***$_3$), 1.49 (d, *J* = 1.0 Hz, 3H, C***H***$_3$), 1.17 (s, 1H, O***H***), 0.35 (s, 3H, Si(C***H***$_3$)$_2$), 0.32 (s, 3H, Si(C***H***$_3$)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.7 (Si***C***ar), 135.8 ((CH$_3$)$_2$***C***=), 134.4 (CH$_3$***C***=), 131.7 (***C***Har), 129.5 (***C***Har), 127.9 (***C***Har), 125.6 (H***C***=), 124.3 (H***C***=), 64.2 (C***H***OH), 40.1 (***C***H$_2$), 26.8 (***C***H$_2$), 25.8 (***C***H$_3$), 17.9

($\boldsymbol{C}H_3$), 16.9 ($\boldsymbol{C}H_3$), -5.3 (Si($\boldsymbol{C}H_3$)$_2$), -5.9 (Si($\boldsymbol{C}H_3$)$_2$). HRMS (ESI): Mass Calculated for $C_{18}H_{28}ONaSi$, theoretical Mass: 311.18016, Measured Mass: 311.1853.

III.2.2. General procedure for the synthesis of α-silylated amines

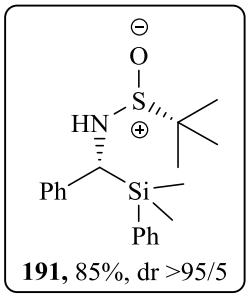


190 2 equiv. **191**

A flame-dried schlenk is loaded with IPrCuF.HF (12.2 mg, 0.025 mmol, 0.1 equiv.) and imine **190** (52.3 mg, 0.25 mmol, 1 equiv.). The vessel is then sealed and after 3 vacuum/argon cycles, isopropanol is added (2 mL). After dissolution of solids, borosilane **19** (0.16 mL, 0.5 mmol, 2 equiv.) is added dropwise and the mixture is stirred at 0°C overnight. CH_3COOH (0.045 mL, 0.75 mmol, 3 equiv.) is added and the mixture is filtered over a pad of silica gel with AcOEt as eluent. The resulting solution is concentrated under reduced pressure and the product is finally purified by flash chromatography on silica gel.

- **(*S*)-N-((*R*)-(dimethyl(phenyl)silyl)(phenyl)methyl)-2-methylpropane-2-sulfinamide (191)**

The product is purified by flash chromatography on silica gel using E.P/AcOEt (60/40) as eluent to give **191** as a colorless oil (0.0734 g, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 – 7.31 (m, 5H, C$\boldsymbol{H}$ar), 7.24 (dd, J = 6.7, 5.3 Hz, 2H, C$\boldsymbol{H}$ar), 7.15 (s, 1H, C$\boldsymbol{H}$ar), 7.07 – 7.00 (m, 2H,



191, 85%, dr >95/5

Chemical Formula: $C_{19}H_{27}NOSSi$
Molecular Weight: 345,58

C***H***ar), 4.06 (d, *J* = 8.4 Hz, 1H, C***H***), 3.46 (d, *J* = 8.4 Hz, 1H, N***H***), 1.08 (s, 9H, CC$\boldsymbol{H}_3$), 0.37 (s, 3H, Si(C$\boldsymbol{H}_3$)$_2$), 0.24 (s, 3H, Si(C$\boldsymbol{H}_3$)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.32 (***C***ar), 134.85 (***C***Har), 134.55 (***C***Har), 130.01 (***C***Har), 128.26 (***C***Har), 128.05 (***C***Har), 126.82 (***C***Har), 126.20 (***C***Har), 56.66 (***C***(CH$_3$)$_3$), 52.93 (N***C***H), 22.49 (C(***C***H$_3$)$_3$), -4.26 (Si(***C***H$_3$)$_2$), -5.07 (Si(***C***H$_3$)$_2$). HRMS (ESI): Mass Calculated for $C_{19}H_{28}NOSSi$, theoretical Mass: 346.16554, Measured Mass: 346.16531. IR (film, cm^{-1}): 3430, 3245, 3063, 2956, 1250, 1114, 1062, 833, 814, 700.

ANNEXE

My papers

- Cornelissen, L.; Cirriez, V.; Vercruysse, S.; Riant, O.; *Chem. Comm.* **2014**, *50*, 8018-8020.

- Cirriez, V.; Rasson, C.; Riant, O.; *Adv. Synth. Catal.* **2013**, *355*, 3137-3140.

- Cirriez, V.; Rasson, C.; Hermant, T.; Petrignet, J.; Diaz Alvarez, J.; Robeyns, K.; Riant, O.; *Angew. Chem. Int. Ed.* **2013**, *52*, 1785-1788.

- Cirriez, V.; Welle, A.; Riant, O.; *Tetrahedron* **2011**, *68*, 3435-3443.

- Hawner, C.; Li, K.; Cirriez, V.; Alexakis, A.; *Angew. Chem. Int. Ed.* **2008**, *47*, 8211-8214.