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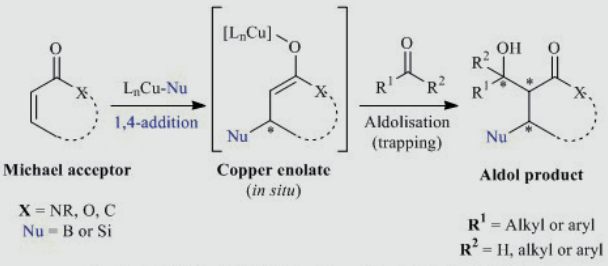
Development of New Reactions Catalyzed by Copper(I) Complexes using Silylboranes and Bisboronates as Pronucleophiles

This thesis has been done under the supervision of Professor Olivier Riant.
In this thesis, we attempted applying the 1,4-addition/aldolisation domino reaction, which was previously developed in our group [1], to new Michael acceptors bearing a fluorine substituent on the double bond and to new silylboranes. Several interesting adducts were obtained. We also tried to develop an enantioselective version of the borylation reaction. We also developed a strategy for the synthesis of new cationic copper(I) complexes bearing a bifluoride (HF_2^-) counteranion. These complexes were then used in the borylation reaction and have shown a good reactivity.

In a later point, we also developed new methodologies for the copper-catalyzed 1,2-addition of silyl nucleophiles to several electrophiles. Our method enables efficient, simple and general synthesis of acylsilanes and enantiomerically enriched α-hydroxysilanes in high yields.

1. Domino Reaction: Introduction and Objectives

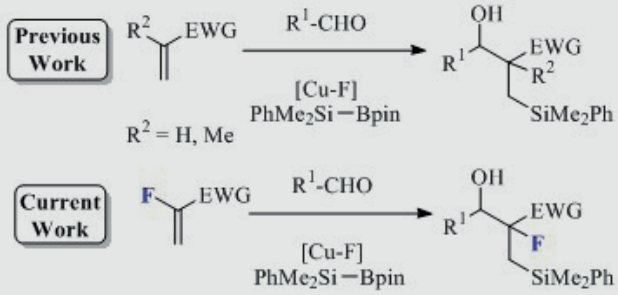
The development of new catalytic methods has been an area of intense research in recent years and particular efforts are currently devoted to transition-metal-catalyzed reactions. We are thus interested in developing new reactions catalyzed by copper(I) complexes. Our group has a history in the development of new methodologies for the copper catalyzed 1,4-addition/aldolisation with several nucleophiles [1]. 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 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 1).



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

The first objective 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 this strategy 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 2).

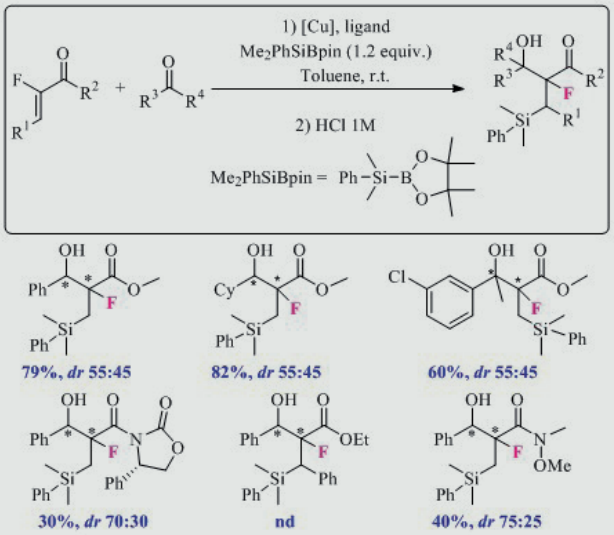


Scheme 2. Extension of the silylation reaction.

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 [2]. These new catalysts allowed us to avoid some of the drawbacks encountered in some reactions, such as the use of additives (NaO^{t}Bu, silver salts, etc…) or reproducibility of reactions. The use of hydrogen bifluoride as counteranion was also envisaged due to its interesting characteristics to activate our system [2]. Our aim was thus to use these new chiral cationic complexes in various catalytic processes and develop a non racemic version of the borylation domino reaction.

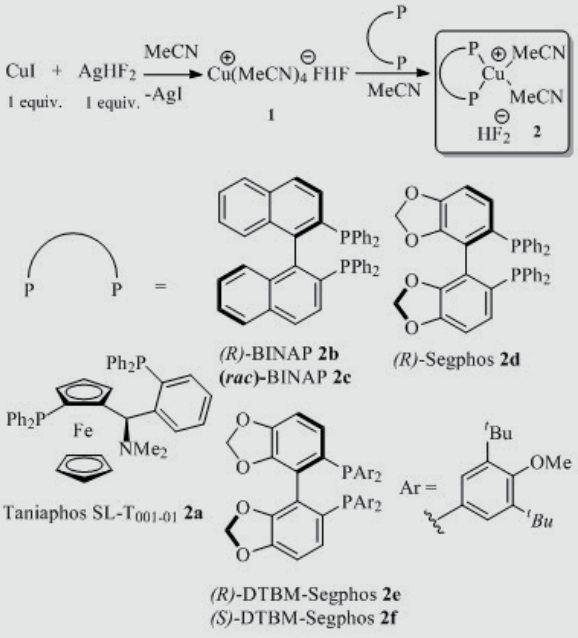
2. Domino Reaction: Results

The desired substrates bearing a fluorine substituent were thus synthesized. We were able to isolate several interesting adducts with moderate to good yields but with low diastereoselectivity in almost all cases (Scheme 3). A good diastereoselectivity was only achieved when we used acryloyl oxazolidinones or Weinreb acrylamides as substrates (*dr* up to 75:25). Syntheses of other silylboranes were also performed and we found that they had almost the same reactivity as Suginome's reagent ($Me_2PhSiBPin$).



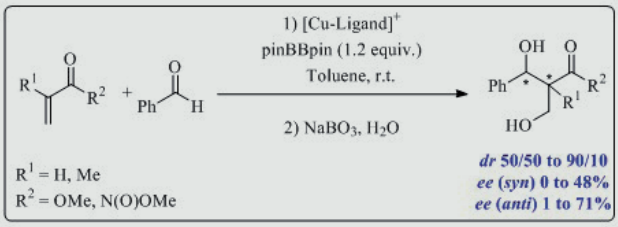
Scheme 3. Silylation reaction with fluorine substrates.

Concerning the development of new air and moisture stable cationic copper(I) complexes, a strategy was developed. We found that the reaction of copper(I) iodide with silver(I) hydrogenfluoride in acetonitrile gave, after filtration, the tetrakis(acetonitrile) copper(I) hydrogen(bifluoride) intermediate **1** *in situ.* The addition of various diphosphine ligands afforded, after removal of the solvent, the new cationic complexes **2a-f** in excellent yields (Scheme 4). It is important to mention that these complexes are also air and moisture stable both in the solid state and in solution.



Scheme 4. Development of new cationic copper(I) complexes.

These complexes were consequently used in our borylation reaction and a good reactivity towards our domino process was shown. Good diastereoselectivities with these copper complexes were observed, however enantioselectivities were always low. Moderate to good enantiomeric excesses were only achieved when a low diastereoisomeric ratio was obtained (Scheme 5).

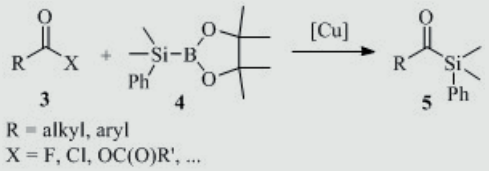


Scheme 5. Enantioselective version of the borylation reaction.

In conclusion, we were able to synthetize some interesting adducts with quaternary centres bearing a fluorine substituent with moderate diastereoselectivities. We have shown that the use of other silylboranes in our domino reaction was possible. A strategy for the synthesis of new cationic copper(I) complexes was also developed and these complexes were quite active in our process. Unfortunately, we were not able to obtain the desired products with good diastereoselectivity and enantioselectivity.

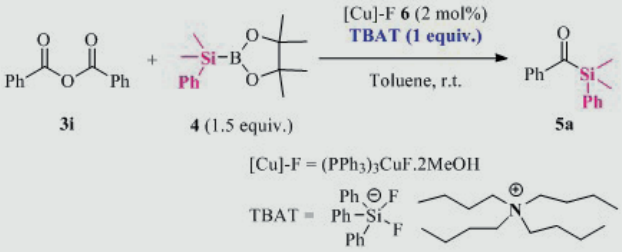
3. Copper-Catalyzed 1,2-Addition

Another important goal was to develop new reactions for the synthesis of interesting building blocks in organic synthesis. Acylsilanes [$RCOSi(R')_3$] are compounds in which a silane fragment is directly attached to a carbonyl group resulting in unique chemical properties. 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 [3]. Such compounds are versatile intermediates in organic synthesis [4, 5, 6]. We thus envisaged a new strategy for the preparation of acylsilanes through acylation of a copper(I)-silyl intermediate (Scheme 6).



Scheme 6. Synthesis of acylsilanes.

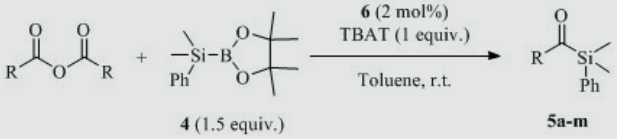
Our investigation started with a screening of different acid derivatives and the best yield was obtained using benzoic anhydride. To establish suitable reaction conditions, we then optimized the solvent, the reaction temperature, the copper source and the addition of different additives. Afterwards, we concluded that running the reaction in strictly dry toluene at room temperature with 2 mol% of catalyst **6** and a fluoride source was the optimal result. Indeed, acylsilane **5a** was obtained in 93% isolated yield after 6 hours with addition of 1 equivalent of tetrabutylammonium triphenyldifluorosilicate (TBAT) and a slow addition of **4** (Scheme 7).



Scheme 7. Optimal conditions for the synthesis of **5a**.

With the new optimal conditions in hand, it was then possible to study the scope of this reaction. First of all, the desired anhydrides have been prepared starting from the corresponding acyl chlorides with moderate to good yields [7]. Our methodology was then applied to these substrates and results are shown in table 1. Under the previously defined conditions, the reaction gave satisfactory results for all types of substituents. The reaction tolerated quite well both electron-deficient (Table 1, entries 3-4, 6-7 and 9) and electron-rich (Table 1, entries 2, 5 and 8) aromatic systems. The *para*- or *meta*-position of the substituent does not influence the desired reactivity. Satisfyingly, aliphatic substituents also underwent the desired reaction and the corresponding acylsilane was isolated in high yield (Table 1, entry 11).

Table 1. Scope of the reaction.

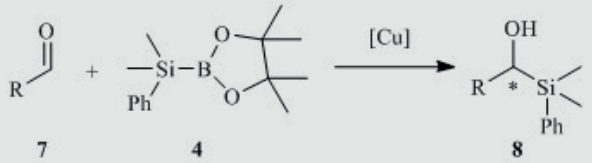


Entry	R	Product	Yield[a] (%)
1	Ph	5a	93
2	4-(MeO)C_6H_4	5b	52
3	4-(Cl)C_6H_4	5c	76
4	4-(Br)C_6H_4	5d	82
5	4-(Me)C_6H_4	5e	98
6	4-(F)C_6H_4	5f	89
7	3-(F)C_6H_4	5g	85
8	3-(Me)C_6H_4	5h	>99
9	3-(Br)C_6H_4	5i	67
10	2-naphtyl	5j	68
11	Cy	5k	82
12	2-thiophene	5l	46
13	2-furoyl	5m	47

[a] Isolated yield.

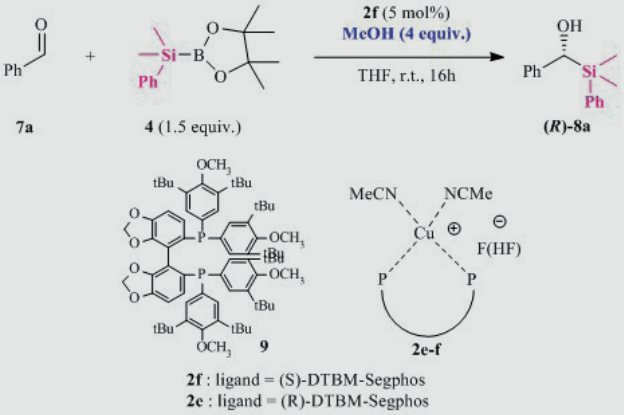
In conclusion, we have developed a new strategy for the synthesis of acylsilanes by using symmetrical carboxylic anhydrides that can be accessed from commercially available acyl chlorides. Good to excellent yields were obtained with various substrates. This methodology is mild, practical and does not require strongly basic precursors [8].

Afterwards, our interest turned to the addition of the copper(I)-silyl intermediates to aldehydes, thus generating α-hydroxysilanes in a catalytic one-step reaction. 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 resulted in a wide variety of chiral organic compounds [9, 10, 11, 12, 13]. The majority of literature-known methods for the preparation of α-hydroxysilanes are based on the asymmetric reduction of acylsilanes [14]. Starting from commercially available aldehydes in the presence of Suginome's reagent **4** and a copper catalyst, the process should lead to the corresponding α-hydroxysilanes. And by using chiral ligands, high enantioselectivities could be achieved (Scheme 8).



Scheme 8. Synthesis of α-hydroxysilanes.

Our investigation started with benzaldehyde which was selected as a model substrate for initial screening. Reaction of **7a** with $Me_2PhSiBpin$ reagent **4** and $CuF(PPh_3)_3.2MeOH$ **6** as the copper catalyst, at room temperature was completed in 2h to afford the racemic α-hydroxysilane in 39% isolated yield. To establish suitable reaction conditions, we optimized the reaction temperature, the solvent and we screened different catalysts and additives thus concluding that running the reaction in THF at room temperature with CuCl/NaO^{t}Bu as catalyst and a sterically hindered ligand (*(S)*-DTBM-Segphos **9**) was the optimal result. We also found that the addition of methanol led to significant improvement of both yield and enantioselectivity. However, we found that those conditions gave fairly irreproducible results for both yields and enantioselectivities with significant drops regarding the enantioselection. Thus, we decided to use our new cationic complexes in the copper-catalyzed 1,2-addition of a silicon nucleophile to aldehydes. Reaction of **7a**, reagent **4** and 5 mol% of copper complex **2f** under the previously established optimal conditions, was completed in 16h to afford the (*R*)-α-hydroxysilane ***(R)*-8a** in >99% *e.e.* and 87% isolated yield (Scheme 9). The absolute configuration of compound **8a** was determined according to the literature data's [14].

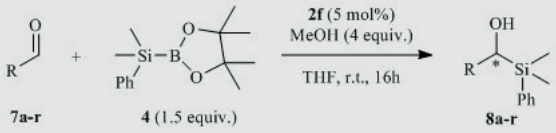


Scheme 9. Optimal conditions for the synthesis of ***(R)*-8a**.

Optimal reaction conditions were then applied to various aromatic and aliphatic aldehydes (Table 2). Regarding aromatic aldehydes, both electron-donating as well as electron-withdrawing groups were well tolerated. 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 2, entries 3 and 16) as a consequence of the steric hindrance at the *ortho* position. To our delight, we found that aliphatic aldehydes were also well tolerated (Table 2, entries 9, 12 and 13).

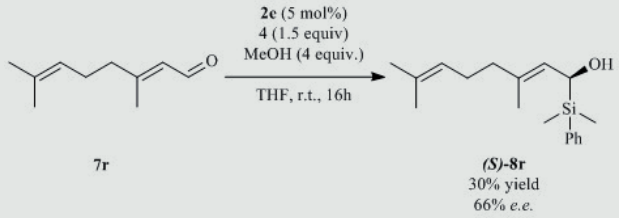
Table 2. Copper-catalyzed 1,2-addition to aldehydes: Substrate scope.



Entry	R	Product	Yield (%)[a]	*ee* (%)[b]
1	Ph	(*R*)-8a	87	>99
2[c]	Ph	(*S*)-8a	82	>99
3	2-MeC_6H_4	8b	51	99
4	2-thiophene	8c	99	>99
5	4-MeC_6H_4	8d	78	96
6	4-(MeO)C_6H_4	8e	53	96
7	3,4-(MeO)C_6H_4	8f	80	95
8	4-PhC_6H_4	8g	95	95
9	Cy	8h	67	>99
10	1-naphtyl	8i	60	96
11	3-(MeO)C_6H_4	8j	99	96
12	CH_3CH_2	8k	60	87
13	$Ph(CH_2)_2$	8l	88	>99
14	4-(CN)C_6H_4	8m	98	95
15	3-ClC_6H_4	8n	99	94
16	2-BrC_6H_4	8o	66	93
17	4-FC_6H_4	8p	98	98
18	4-$CF_3C_6H_4$	8q	65	>99

[a] Isolated product yield after flash chromatography on silica gel. [b] Data determined by chiral HPLC analysis. [c] Reaction with catalyst **2e**.

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. Aldehyde **7r** reacted with $Me_2PhSiBpin$ in the presence of copper complex **2e** under optimal conditions to afford the (*S*)-α-hydroxysilane **8r** in 66% *e.e.* and 30% isolated yield (Scheme 10). Such structures are particularly attractive as they could be employed in various useful transformations such as the Ireland-Claisen rearrangement [15].



Scheme 10. Copper-catalyzed 1,2-addition to citral **7r**.

In conclusion, 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 *e.e.* and good to high yields. Thus, this method provides a new, efficient and practical route to form chiral silane compounds from readily available aldehydes [16].

Acknowledgments

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