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

This thesis has been done under the supervision of Professor Olivier Riant.

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

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

Dual Catalysis: Introduction and Objectives

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

For a synthesis to be considered elegant, it needs to be highly convergent and requires incorporating very efficient transformations. Frequently, such syntheses employ multistep reactions such as one-pot, tandem and cascade reactions. In the recent literature, a large number of publications are concerned either with the application of these multistep sequences or with the development of new methodologies of this type.
Various attempts were also undertaken to minimize the adverse environmental impact and maximize the efficiency of chemical reactions. As one of numerous advances, "multicatalysis", defined as the modular combination of distinct catalysts for consecutive transformations in a single flask, emerged as a highly valuable tool for the construction of complex molecular frameworks from simple and readily available starting materials.[1]

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

Cooperative dual catalysis is a process where two catalysts separately and selectively activate two different substrates, catalytically generating two active intermediates that could subsequently react to form the desired product (Figure 1).[3] The formation of the final product is generally coupled with simultaneous regeneration of the catalysts.

In this study, we wanted to use the Pd^{0} and Cu^{I} cooperative dual catalysis to develop a new synthetic transformation. The cooperativity of such a system is well documented. The compatibility and selectivity of these two metals have been repeatedly proven in the two famous examples; the Wacker-Tsuji[4] process and the Sonagashira[5] coupling.

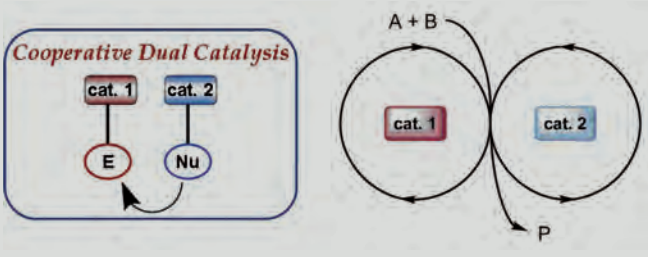
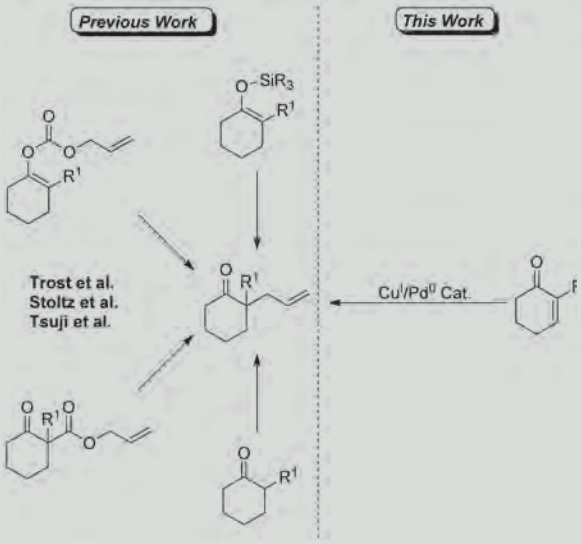
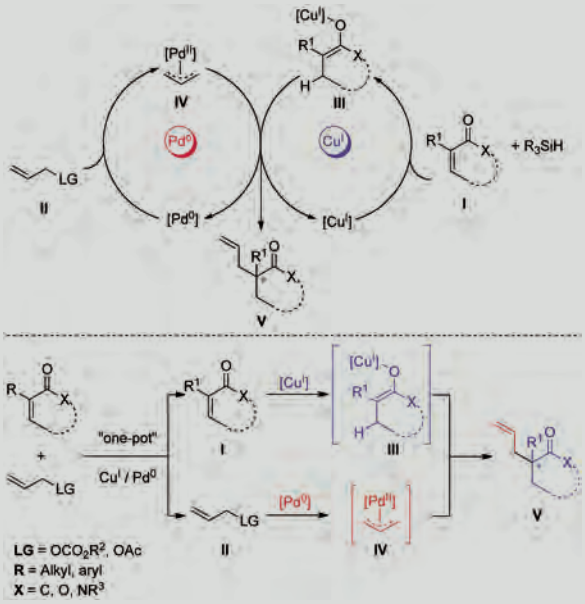


Figure 1. The concept of cooperative dual catalysis



Scheme 1. Previous[6-7] *vs* current work to access α-allylated ketones



Scheme 2. The proposed reaction and its mechanism

Using this methodology and the above mentioned dual system, we wanted to develop a new way to access α-allylated ketones, starting from easily available α,β-unsaturated ketones (Scheme 1).

The reaction that we envisioned involved a Cu^{I}-catalyzed 1,4-reduction reaction of Michael acceptors **I** to form the copper enolate intermediate **III**. Simultaneously, oxidative addition of Pd^{0} to the allyl leaving group moiety **II** generates the π-allyl palladium species **IV**. The two catalytic species will subsequently react to form the desired product **V** (Scheme 2).

We started working on determining a compatible system to perform the desired transformation. Ultimately, our goal is also to induce chirality in order to obtain enantiopure adducts.

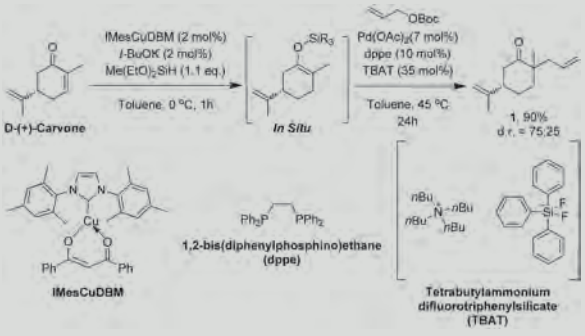
Dual Catalysis: Results

Commercially available D-(+)-carvone was chosen as a model substrate for initial optimisations, thus allowing us to access final products containing a quaternary center. Accessing stereoselectively these centers remains an important challenge in organic synthesis.[8] At first, the two reactions were conducted separately in order to determine the best compatible conditions. Preliminary results were successful and allowed us to determine two compatible systems (Scheme 3). The desired product **1** was obtained in 90% yield and 75:25 diastereomeric ratio (d.r.).

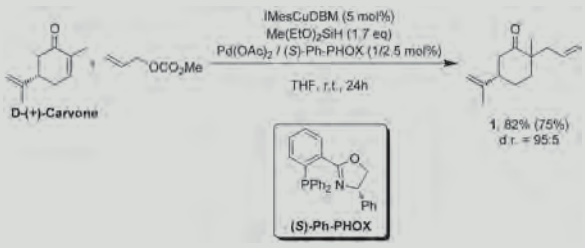
With these two systems at hand, several attempts at the dual catalysis reaction were conducted. Early trials allowed the observation of the desired product along with two secondary products. After careful optimization, we successfully established an efficient diasteroselective version and the desired product **1** was obtained in 75% isolated yield (82% overall conversion) and a 95:5 d.r. (Scheme 4).

After these satisfying results, efforts were concentrated on developing an enantioselective version of this reaction starting from the prochiral substrate **2a** (Scheme 5). Some modifications of the previous conditions were necessary to obtain high yields and high enantioselectivities. Final optimisation of the reaction conditions yielded 83% of the desired product **3a** with 87% enantiomeric excess (e.e.).

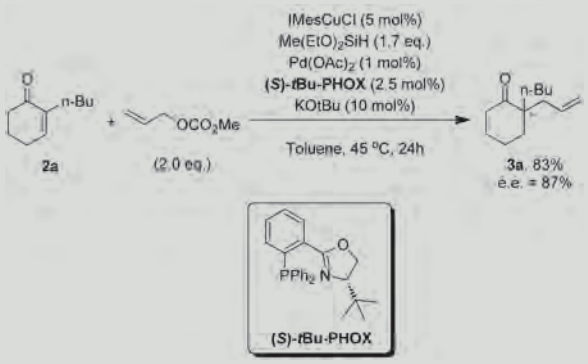
The optimal conditions thus obtained were then applied to other cyclic enones. The reaction showed a tolerance toward alkyl and benzyl groups, and the corresponding products **3a-3h** were obtained with comparable yields and enantioselectivities (Scheme 6). Although aryl groups are also tolerated under these conditions and products **3i-3m** were obtained in good yields, unfortunately low enantioselectivities were observed. Furthermore, Michael



Scheme 3. Preliminary results



Scheme 4. Optimised diasteroselective version



Scheme 5. Optimal conditions for the enantioselective version

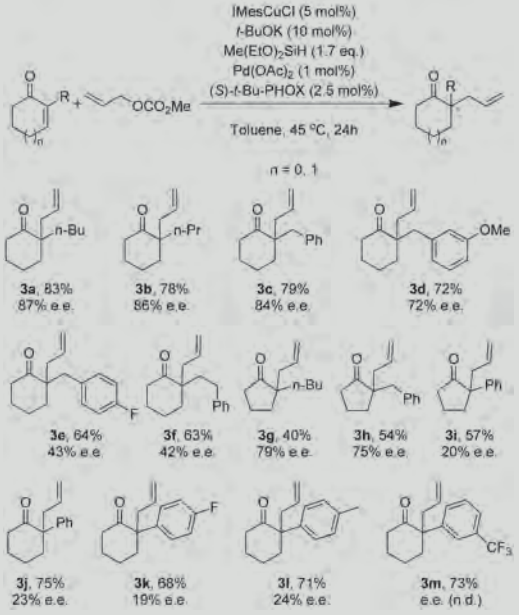
acceptors with 6-membered rings as well as 5-membered rings readily undergo the reaction using our optimized conditions. However, 5-membered rings gave a slightly lower enantioselectivity than their 6-membered counterparts, and that's probably due to the difference in conformation between these two types of substrates.[9]

In conclusion we have successfully developed a new method to access α-allylated ketones.[10] This new Cu^{I}/Pd^{0} cooperative dual catalysis reaction is based on the catalytic coupling of the two organometallic intermediates. Thus, the Cu^{I} catalytic cycle generates the starting material for the Pd^{0} catalytic cycle. Although the reagents are present in stoichiometric amounts in the reaction mixture and are in principal able to trap both active species (four different possible pathways), the reaction proceeds as desired. The reaction mechanism has also been investigated; its details and implicated intermediates, along with their influence on the desired reactivity, have also been explored but won't be developed any further.

Unprecedented (NHC)Cu^{I} Bifluorides

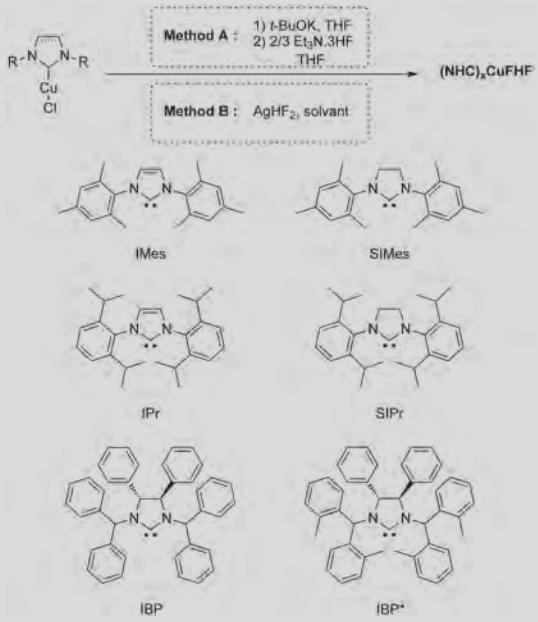
This project was done in collaboration with Thomas Vergote under the supervision of Professors Tom Leyssens and Olivier Riant.
In another project during this thesis, unprecedented (NHC)Cu^{I} bifluoride complexes were discovered and fully characterized by NMR, elemental and X-ray analysis to unambiguously unveil their molecular structures. Afterwards, two new methodologies were devised to access six of these new complexes (Table 1).[11]

Catalytic tests demonstrated the copper(I) bifluorides to be very efficient catalysts that do not require any additional activating



Scheme 6. Extension of the reaction's scope

Table 1. Preparation of $(NHC)_xCu$-FHF complexes



NHC	Method[a]	Solvent[b]	$(NHC)_xCuFHF$[c]	Yield(%)[d]
IPr	A (or B)	THF	IPrCu-FHF(**4**)	75 (83)[e]
IMes	B	DMPU	$[(IMes)_2Cu]HF_2$ (**5**)	60
SIPr	A (or B)	THF	SIPrCu-FHF (**6**)	60 (50)[e]
SIMes	A (or B)	DMPU	$[(SIMes)_2Cu]HF_2$ (**7**)	32 (85)[e]
(IBP)	B	THF	(IBP)Cu-FHF (**8**)	64
(IBP*)	B	THF	(IBP*)Cu-FHF (**9**)	Quant.

[a] Method **A** was run in THF, method **B** was run in THF or in DMPU depending on the type of copper(I) bifluoride formed [b] Solvent used in method **B** : THF for (NHC)Cu-FHF complexes and DMPU for $(NHC)_2Cu$-FHF complexes [c] The type of $(NHC)_xCuFHF$ was determined by ^{19}F NMR [d] Isolated yields [e] Isolated yields for method **B**.

agent. These tests allowed us to establish later on, the first Cu-catalyzed diastereoselective allylation of (*R*)-*N*-*tert*-butanesulfinyl aldimines. The method enables efficient, simple and general synthesis of enantiomerically enriched homoallylic amines at room temperature in high yields (Table 2).[11]

In conclusion, we have developed a mini library of (NHC)Cu^{I} complexes. Two synthetic pathways were established to generate unprecedented (NHC)Cu^{I} bifluoride complexes. These complexes were fully characterized. These copper(I) bifluorides efficiently undergo several previously described Cu-catalyzed reactions without the need for any additional activating agent. The more detailed NMR studies on the activation mechanism of silanes by our complexes gave a more intricate picture. These bifluoride complexes could now be considered as "auto-activating catalysts", generating the active hydride species in two steps.[12]

We also established the first Cu^{I}-catalyzed diastereoselective allylation of (*R*)-*N*-*tert*-butanesulfinyl aldimines to easily access enantiomerically enriched homoallylic amines at room temperature in high yields.

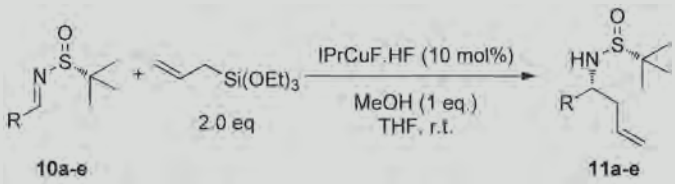


Table 2. Allylation of aldimines: the reaction's scope

Entry[a]	R[b]	Product	Yield[c] (%)	d.r.[d]
1	C_6H_5	**11a**	81	95:5
2	4-$MeOC_6H_4$	**11b**	90	92:8
3	2-$MeOC_6H_4$	**11c**	91	95:5
4	2-MeC_6H_4	**11d**	83	96:4
5	cyclohexyl	**11e**	69	93:7

[a] All reactions were run under argon until total conversion was indicated by TLC [b] Starting material prepared according to literature procedures [c] Isolated yield [d] Diasteromeric ratio is determined by 1H NMR, the configuration was assigned by comparison with literature data.

ACKNOWLEDGMENTS

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