PÉCSI TUDOMÁNYEGYETEM
UNIVERSITY OF PÉCS

Doctoral School of Chemistry

PhD thesis

Synthesis and application of gold-carbene complexes in asymmetric synthesis

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1. Introduction

Nucleophilic heterocyclic carbenes have only been dealt with since the end of the last century and have now become an extensive field of research, thanks to their diverse transition metal-carbene-complexes. At the *Servier Research Institute*, we have long been engaged in the mapping of this research area, looking for the answer to how transition metal-carbene-complexes can be used as efficient and selective catalysts.

I got to know *NHC* complexes for the first time in 2017, as a final-year MSc student, during which I had the opportunity to investigate the catalytic properties of silver-carbene-complexes. Silver-*NHC*-complexes are known to be used on their own in various synthetic transformations. However, they are mostly used for transmetalation, to incorporate other metal centers. Thus, we set out to explore the further possibilities of this research area. We have planned the production of transition metal complexes that can be easily synthesized from existing silver complexes in a simple step. Nowadays, gold-catalyzed transformations are gaining more and more popularity, so we were looking for a reaction that could be catalyzed by a gold-carbene-complex, which already had a literature background, but was not yet nearly mature. We focused our attention on the study of an enantioselective cyclopropanation reaction, for which we needed sterically crowded gold-carbene-complexes.

In the following, it will be presented how the synthetic process of the carbene precursors was developed, followed by the determination of their stereocenters using several measurement and calculation methods. We can thank the research groups of the *University of Debrecen* for the latter results. After perfecting the synthesis route, we show how it was possible to produce various cyclopropyl derivatives with good enantioselectivity by optimizing the catalytic process.

In the thesis, we can also read about some interesting phenomena regarding metal complexes, which unusual results are explained with NMR measurements. These results in themselves contain a lot of added value, since a publication was also born from it.

2. Research objectives

The goal of my doctoral work was to produce chirality-carrying gold-*NHC*-complexes with the general structure shown in *Figure 1*, which behave advantageously in enantioselective reactions due to their crowded steric structure. I prepared the gold complexes from the appropriate carbene precursors directly or through silver complexes by transmetalation. During the synthesis of carbene precursors, yield and atomic efficiency were important considerations. The procedures we developed earlier provided a good basis, but several of their reaction steps also needed optimization. In addition to these innovations, another important aspect was the avoidance of chiral preparative chromatographic separations, since this method is unfavorable from the point of view of scale up and is inaccessible to many research groups. The primary requirement for the synthesis routes was the easy variability of the ligands. This required the development of advanced intermediate(s) from which carbene precursors bearing diverse side chains can be produced. The number of commercially available enantiomerically pure building blocks is small, which limited direct access to variable side chains, so my goal was to bridge this shortcoming with the synthetic procedure we developed.

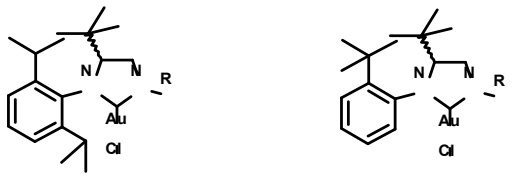


Figure 1: General structure of target molecules

Another area of my doctoral research was the investigation of the cyclopropanation reaction shown in *Figure 2*. The cyclopropyl ring is a popular and important motif in medicinal chemistry, so its enantioselective synthesis is of great interest to many. My task was to optimize the chosen model reaction, investigate the role of individual parameters and use the produced gold-*NHC*-complexes under the optimized conditions. My other goals included investigating the extendability of the reaction, incorporating different acetylene and olefin derivatives into the molecule.

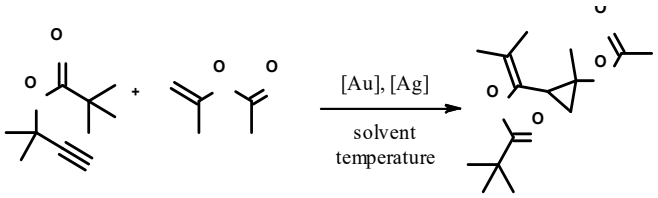


Figure 2: The investigated reaction

3. Thesis statements and new scientific results

3.1 Synthesis of carbene precursors

In this chapter, our synthesis route, by which enantiomerically pure carbene precursors can be produced, is presented. The formation of the pure chirality center in the dihydroimidazole ring did not require a chiral chromatography method, since the desired quality was achieved by taking advantage of the beneficial effect of the naturally occurring menthol in this regard. In the course of the synthesis, we obtained two important key intermediates, which can be easily produced in larger quantities, and starting from these intermediates, we can obtain carbene precursors with diverse steric and electronic properties. Another chirality center of our carbene precursors is found in the side chain, for which we used different primary amines or oxo compounds. The resulting diastereomer pair of diamine derivatives were separated by normal phase chromatography, if necessary. After a simple cyclization, we achieved at the carbene precursors in one step.

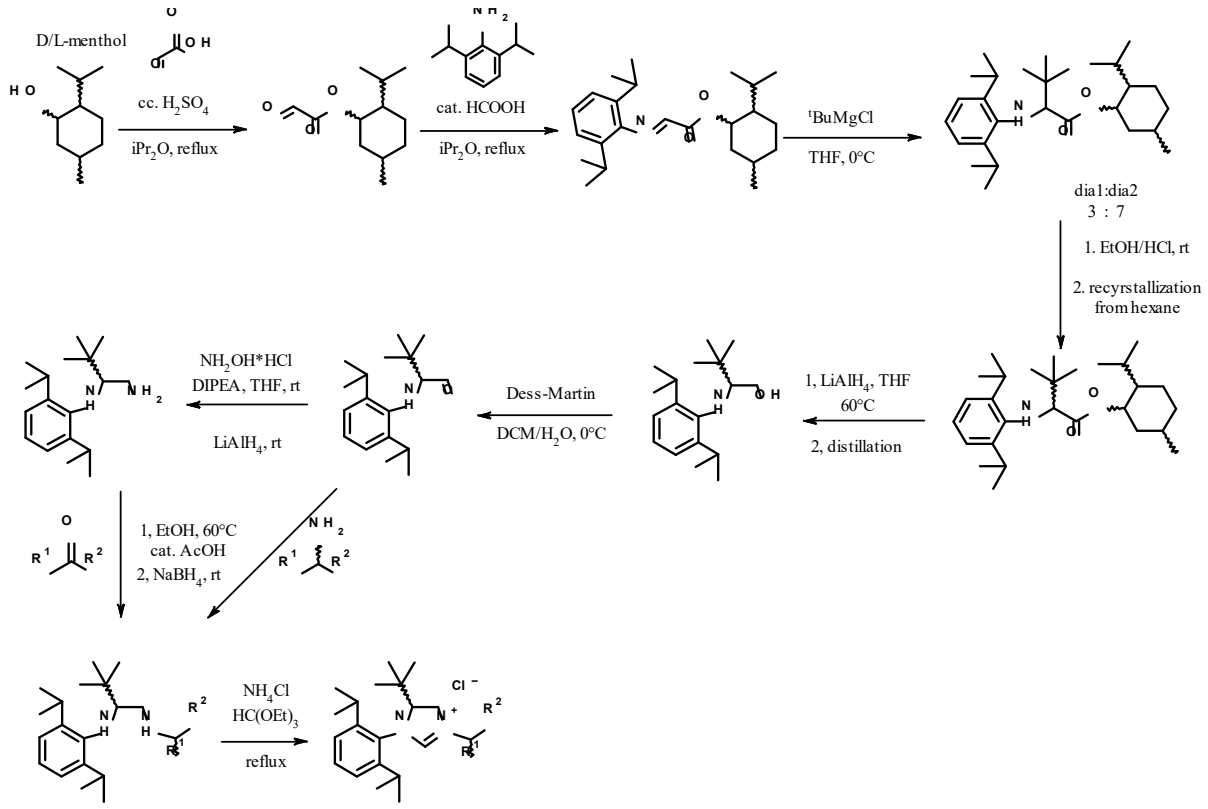
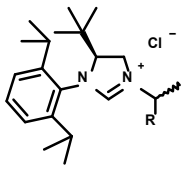
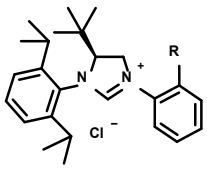


Figure 3: Presentation of the synthesis route

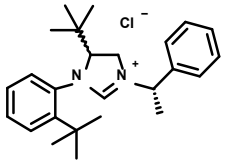
Using the process we developed, we successfully produced several carbene precursor derivatives, which are summarized in *Figure 4*.



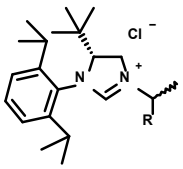
25a: R=Ph (***SS***), **25b**: R=Ph (***SR***)
25c: R=1-naftil (***SS***), **25d**: R=1-naftil (***SR***)
25e: R=2-naftil (***SS***), **25f**: R=2-naftil (***SR***)
25g: R=*t*-Bu (***SS***), **25h**: R=*t*-Bu (***SR***)



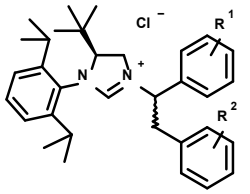
25i: R=*i*-Pr (***S***)
25j: R=*t*-Bu (***S***)



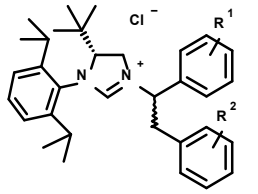
25k: R=Ph (***SS***), **25l**: R=Ph (***RS***)



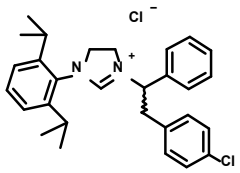
25m: R=Ph (***RS***)
25n: R=1-naftil (***RS***)
25o: R=adamantil (***RS***), **25p**: R=adamantil (***RR***)



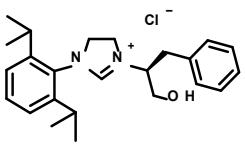
25s: R^1=*p*-CF_3, R^2=H (***SR***), **25t**: R^1=*p*-CF_3, R^2=H (***SS***)
25u: R^1=*p*-OCH_3, R^2=H (***SR***), **25v**: R^1=*p*-OCH_3, R^2=H (***SS***)
25w: R^1=*p*-CH_3, R^2=H (***SR***), **25x**: R^1=*p*-CH_3, R^2=H (***SS***)
25y: R^1=*o*-OCH_3, R^2=H (***SS***), **25z**: R^1=*o*-OCH_3, R^2=H (***SR***)
25aa: R^1=*o*-CH_3, R^2=H (***SS***), **25ab**: R^1=*o*-CH_3, R^2=H (***SR***)
25ac: R^1=*m*-OCH_3, R^2=H (***SS***), **25ad**: R^1=*m*-OCH_3, R^2=H (***SR***)
25ag: R^1=H, R^2=*p*-CH_3 (***SS***), **25ag**: R^1=H, R^2=*p*-CH_3 (***SR***)
25ai: R^1=H, R^2=*p*-Cl (***SS***), **25aj**: R^1=H, R^2=*p*-Cl (***SR***)
25am: R^1=H, R^2=*o*-Cl (***SS***), **25an**: R^1=H, R^2=*o*-Cl (***SR***)



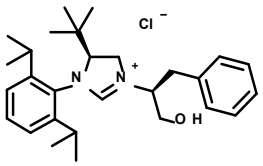
25q: R^1=H, R^2=H (***RR***), **25r**: R^1=H, R^2=H (***RS***)
25ak: R^1=H, R^2=*m*-Cl (***RR***), **25al**: R^1=H, R^2=*m*-Cl (***RS***)
25ae: R^1=*m*-CF_3, R^2=H (***RR***), **25af**: R^1=*m*-CF_3, R^2=H (***RS***)



25ao: (***S***), **25ap**: (***R***)



25aq: (***S***)



25ar: (***S***)

Figure 4: The NHC precursors produced by our synthesis

3.2. Determination of the absolute configuration of carbene precursors by circular dichroism

A number of diastereomeric carbene precursors were produced, in case of which the chirality in the side chain was unknown . For this, in case of a smaller number of compounds, X-ray crystallography is a reliable test method. But in our case, due to the large number of unknown derivatives, a different method was needed. To this end, a collaboration was established with the research group led by Tibor Kurtán of the *University of Debrecen*, who determined the absolute configuration of our molecules with VCD and ECD measurements and

calculations. The results obtained in this way were supported not only by the optical rotation results, but also in some cases by an X-ray measurement.

3.3. Synthesis of silver-*NHC*-complexes and their structural features

The silver-*NHC*-complexes were formed from the corresponding carbene precursors in the presence of silver oxide. This intermediate was necessary because in many cases other transition metals are incorporated into the molecule by means of transmetalation, for which silver is most often used.

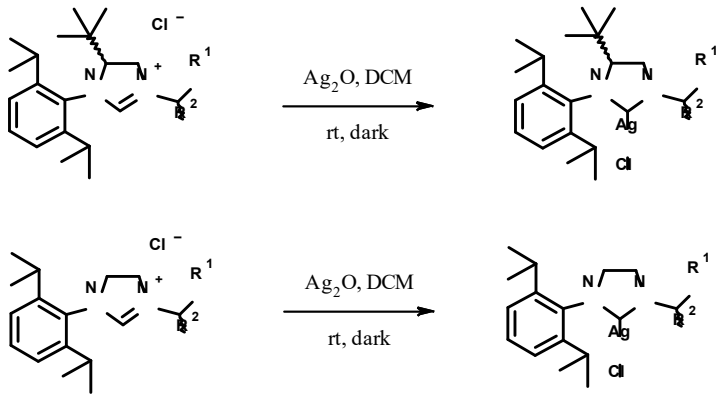


Figure 5: Preparation of silver-carbene-complexes in the presence of silver oxide

In the case of successfully produced silver-carbene-complexes, we observed interesting phenomena in their ^{1}H and ^{13}C NMR spectra. The first observation is that the incorporation of the metal center limits the conformational freedom in the case of the diisopropylphenyl ring connected to the *N3* atom. Another interesting phenomenon can be observed in the ^{13}C NMR spectrum of silver-*NHC*-complexes, where the silver-carbon coupling appears and the carbene carbon signal appears as a 2-2 doublet.

3.4. Synthesis of gold-*NHC*-complexes

The gold complexes were prepared in two ways, by transmetalation via a silver complex, and by direct metalation from the corresponding carbene precursor. The latter was necessary because some compounds in the silver carbene form showed instability during recrystallization. In both cases, goldchloride-dimethylsulfide reagent was used with short, 30 minutes reaction time.

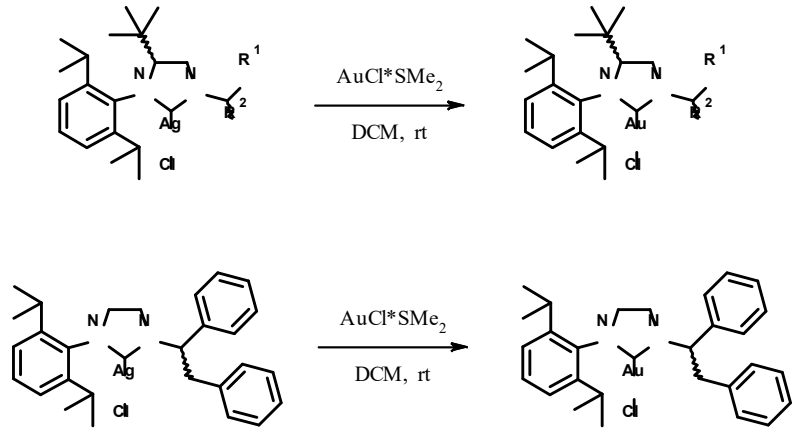


Figure 6: Synthesis of gold complexes by transmetalation

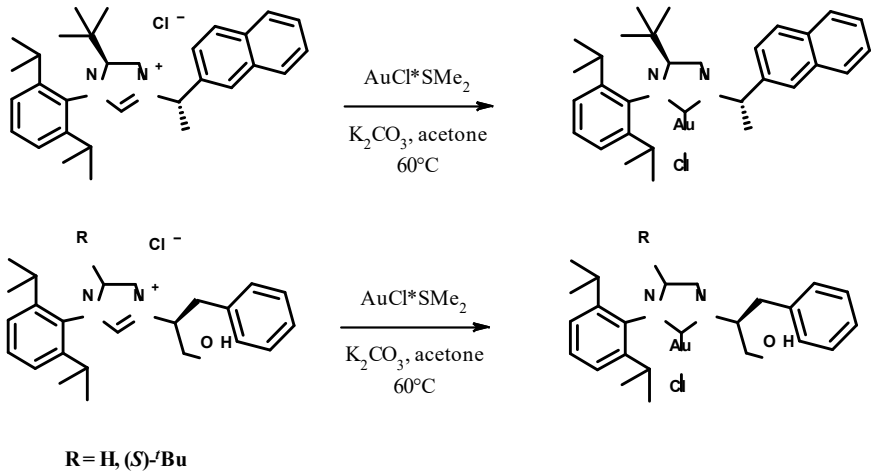


Figure 7: Direct synthesis of gold complexes from carbene precursors

3.5. Application of gold-*NHC*-complexes in asymmetric cyclopropanation reaction

Although the literature of gold-catalyzed stereoselective reactions shows a growing trend in the last decade, it is still limited to only a few types of reactions. In this chapter of my research work, I present the use of the gold-*NHC*-complexes we have produced as catalysts in a cyclopropanation reaction. In the reaction, also examined in the literature, we tested all our catalysts, and then successfully optimized all its parameters with the gold complexes considered to be the best. Thanks to this, we were able to reach 92% instead of the literary 28% enantiomer excess. In addition to changing the quality of the solvent, we slightly increased the reaction temperature and reduced the amount of the required catalyst.

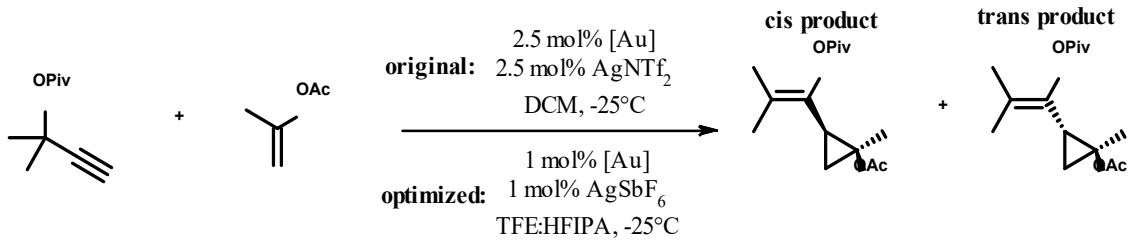


Figure 8: Comparison of optimized reaction conditions with the original parameters

After optimizing the reaction conditions, the variability of the reactants in the cyclopropanation reaction was investigated. The selected substituted acetylenes were reacted with various olefins under the best chosen reaction parameters, in a TFE:HFIPA 1:1 solvent mixture, at -25°C in the presence of 1 mol% **45al** gold-*NHC*-complex and $AgSbF_6$ cocatalyst. In the series of experiments, cyclopropyl rings with different substitution patterns were obtained with varied production values and enantiomeric excess, which were summarized in the dissertation.

4. Publications related to the thesis

- Szabo, Z.; Timari, M.; Kassai, R.; Szokol, B.; Benyei, A. C.; Gáti, T.; Paczal, A.; Kotschy, A. Modular Synthesis of Chiral NHC Precursors and Their Silver and Gold Complexes. *Organometallics* **2020**, *39*, 3572.

- Szabo, Z.; Paczal, A.; Kovács, T.; Mándi, A.; Kotschy, A.; Kurtán, T. Synthesis and Vibrational Circular Dichroism Analysis of N-Heterocyclic Carbene Precursors Containing Remote Chirality Centers. *Int. J. Mol. Sci.* **2022**, *23*, 3471.

- Szabo, Z.; Ben Ahmed, S.; Nagy, Z.; Paczal, A.; Kotschy, A. Enantioselective cyclopropanation catalyzed by gold(I)-carbene complexes. *Molecules* **2022**, *27*, 5805.