University of Helsinki
Dissertationes Universitatis Helsingiensis 244/2024

SILVER-FREE HOMOGENEOUS GOLD CATALYSIS USING ISOLATED CATIONIC COMPLEXES, FUNCTIONALIZED LIGANDS AND ACID ADDITIVES

Otto Seppänen

Department of Chemistry
Faculty of Science
Doctoral School in Chemistry and Molecular Sciences
University of Helsinki
Finland

DOCTORAL DISSERTATION

To be presented, with the permission of the Faculty of Science of the University of Helsinki, for public examination in lecture room CK112, Exactum, Pietari Kalmin katu 5, on the 4th of October 2024, at 13 o’clock.

Helsinki 2024

Supervisor
Senior University Lecturer Juho Helaja
Department of Chemistry
University of Helsinki
Finland

Reviewers
Professor Ola Wendt
Department of Chemistry
University of Lund
Sweden

Professor Daniela Bezuidenhout
Faculty of Technology
University of Oulu
Finland

Opponent
Professor Marco Bandini
Department of Chemistry
University of Bologna
Italy

Publisher: Helsingin yliopisto
Series: Dissertationes Universitatis Helsingiensis 244/2024

ISBN 978-952-84-0225-1 (print)
ISBN 978-952-84-0224-4 (online)
ISSN 2954-2898 (print)
ISSN 2954-2952 (online)
PunaMusta, Joensuu 2024

Vapaus on sitä, että itseään saa toteuttaa
Vihdoinkin on aikaa kenttätutkimukseen panostaa
Sieniveitsi, mikroskooppi, harja, petrimalja laukussa
Väitöskirja kaiken muuttaa, Darwin huutaa haudassa

- Opi tuntemaan sienet, Kuha. (san. J. Kuha)

ABSTRACT

Activation of π-bonds towards a nucleophilic attack is an atom economic way of making new bonds, thus creating new molecules. The application of transition metal catalysts enables us to perform these reactions faster and in milder conditions. Amongst the metals, gold has the ability to act as a strong Lewis acid and activate alkenes, allenes and alkynes to react with a variety of nucleophiles. Hence, gold catalysis has become a widespread tool in the laboratories for crafting molecular complexity in mild conditions.

The Lewis acidity of gold can be increased by using cationic complexes. The majority of homogeneous gold catalysis involves silver, which abstracts the halide counteranion and creates the cationic complex. In many cases this leads to successful catalysis, but there are numerous reports where silver interferes or completely inhibits the desired reaction. To overcome this obstacle chemists have developed various silver-free activation methods for homogeneous cationic gold catalysis, which are explored in the literature review of this thesis. The experimental results have been published in three peer-reviewed journals and consist of alkyne activation in synthesis of essential organic molecules and catalyst development using silver-free conditions.

The first publication of this thesis is a study of a gold catalyzed hydroamination of alkynes. A comparison of different catalysts was performed in the synthesis of 4-quinolones, where a preformed commercial cationic gold complex was the most efficient. The catalyst screening was done partly in the presence of silver, but no specific effects stemming from the other metal could be observed. Non-cationic gold salts were screened for their reactivity, but inferior results were obtained compared to the cationic complexes.

The second publication describes a self-activating Au(I) complex which contains a functionalized NHC-ligand. The self-activation is based on the interaction of H-bond donors in the ligand and substrate with the chloride counteranion. The effect of moisture on catalysis was investigated and optimal level of moisture was recognized. The scope of reactivity could be expanded by using acid additives, which led to effective cyclization of 1,6-enynes.

Finally, the third publication presents the synthesis of cyclometallated NHC-Au(III) compounds, which act as stable precatalysts. These complexes can be activated by an equimolar amount of a Brønsted acid, which enables the utilization of the desired counteranions without expensive additives. The activated catalyst is effective in alkyne activation towards hydrophenoxylation. The nature of the catalyst was examined by ^{1}H-NMR spectroscopic measurements, which suggest that the NHC-Au(III) is the principal catalytic species in the studied reaction.

ACKNOWLEDGEMENTS

This work was done in and outside the Chemistry Department of the University of Helsinki, where my instructor Juho gave me much appreciated guidance and support through the years. I'm quite sure we made almost every possible mistake, so this has been an educational experience to say the least. Those mishaps and some successes could not have been possible without the funding received from the University of Helsinki, the Emil Aaltonen Foundation, and the Magnus Ehrnrooth Foundation.

I can't take the credit for completing the work by myself, since I've had talented scientists as co-authors and their contribution has been crucial for our publications. I would also like to thank Professor Ola Wendt and Professor Daniela Bezuidenhout for pre-examing my thesis and giving critical comments to improve it. The final stage would not be set without an opponent, so I'm deeply honored that Professor Marco Bandini accepted our invitation.

This work would not have been possible without the helpful experts in the department: Petri helped with mass spectrometry related issues, Sami took care of all my needs regarding NMR, and Gudrun took care of everything and everyone. Thank you.

My first day in the group was quite some time ago, which means I've had the chance to meet a great deal of brilliant people. In the early days Erika's, Taru's and Aleksandar's presence made the impression that PhD students were adults or at least could act like one. If I had to boil down the memories of our time in the lab to one word, it would be kindness.

Some different word would be chosen to describe the years spent with Mikko (or should I say Whisky Mike…) and Tom but choosing just one is impossible. Aside from the much-needed chemistry conversations (or lectures) I'm equally grateful for the moments spent outside the lab. When the forementioned elderly people left, Juulia has been the victim of my babbling on any random topic, scientific or less so. Thank you for listening, but also thank you for translating young people words to me when needed.

Aside from gold, other metals such as death and black metal have been a key factor in the daily laboratory work. Thank you, Anna and Lukas, for the chats, recommendations and gigs! A big shout-out in the group goes also to Santeri, Iida, Mikko, David, Vladimir and Jesus.

Along with the research I've had many opportunities to teach the basic skills in laboratory and in the lecture room. This was mainly done with two experienced teachers, whose example I tried to copy and hopefully sometimes succeeded in it. Kjell taught me when to show interest and excitement in teaching, whereas Leena demonstrated when to show patience with the students.

Completing this thesis took a small detour during the Covid years and I had the opportunity to work in the group of Professor Petri Pihko in Jyväskylä. I

highly value this eye-opening experience and when leaving I packed more warm memories than furniture into my moving van. I feel indebted to the people who made me feel welcomed from day one: Sami, Teppo, Rajanish, Big Anton, Small Anton, Anniina, Roope, Jussi, Sini, Prachi, and Maxime.

On more personal side of life, my parents and sister have been a source of never-ending support. Very likely this thesis would not have been finished without it. Even more importantly I've been lucky to receive encouragement and aid from the people living with me: Salla, without you this thesis would be pretty much the same as it is now. But everything else would be worse. Toivo, thank you for reminding me constantly of what is actually important.

The following people, organizations and entities have influenced this thesis, positively or negatively, but influenced nonetheless: Friends, University of Helsinki Kendo Club, Finnish Kendo Association and the national team, Yksivaihde.net (nod at Bikes'n'Burgers & Ompelukerho), Surly Steamroller 2010, Radio Helsinki, Tuska Festival, Laajavuori Bike Park, Pihlajarinteet, International Chemistry Olympiads, and particularly the hedgehogs, bats and woodpeckers in my neighbourhood.

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I O. Seppänen, M. Muuronen, J. Helaja, Gold-Catalyzed Conversion of Aryl- and Alkyl-Substituted 1-(o-Aminophenyl)-2-propyn-1-ones to the Corresponding 2-Substituted 4-Quinolones, *European Journal of Organic Chemistry,* **2014**, *19*, 4044-4052.

II O. Seppänen, S. Aikonen, M. Muuronen, C. Alamillo-Ferrer, J. Burés, J. Helaja, Dual H-bond Activation of NHC–Au(I)–Cl Complexes with Amide Functionalized Side-arms Assisted by H-bond Donor Substrates or Acid Additives, *Chemical Communications,* **2020**, *56*, 14697-14700.

III O. Seppänen, A. Lenarda, M. Nieger, J. Helaja, In Situ Brønsted Acid Activated Cyclometalated N-Heterocyclic Carbene-Au(III)-Sulfonamide Complexes as Precatalysts for Alkyne Activation in Benzofuran Synthesis, *Organometallics*, **2024**, *5*, 605-610.

The publications are referred to in the text by their roman numerals.

AUTHOR CONTRIBUTIONS

I The author performed all experimental work. M.M. provided computational results. J.H. supervised the work. The manuscript was written with contributions from all authors.

II The work was divided equally between the author and S.A. for experimental and computational work, respectively. C.A.-F. and J.B. supervised the kinetic measurements. M.M. and J.H. supervised the work. The manuscript was written with contributions from all authors.

III The author performed all experimental work. M.N. performed X-ray diffractometry analysis. A.L. and J.H. supervised the work. The manuscript was written with contributions from all authors.

ABBREVIATIONS

Ac	acetyl
Ar	aryl
BArF	tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
BINOL	1,1'-binaphthalene-2,2'-diol
Bn	benzyl
Boc	*t*-butyloxycarbonyl
box	bisoxazoline
bpy	bipyridine
Bu	butyl
Bz	benzoyl
CAAC	cyclic(alkyl)(amino)carbene
Cbz	benzyloxycarbonyl
CSA	camphorsulfonic acid
^{Cl}IPr	4,5-dichloro-1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene
DBFPhos	bis(diphenylphosphino)dibenzofuran
DCE	1,2-dichloroethane
DCM	dichloromethane
DES	deep eutectic solvent
DFT	density functional theory
Dipp	2,6-diisopropylphenyl
DPCB	3,4-diphosphinidenecyclobutene
DPEPhos	bis[(2-diphenylphosphino)phenyl] ether
DTBM	3,5-di-*tert*-butyl-4-methoxyphenyl
d.r.	diastereomeric excess
ee	enantiomeric excess
eq	equivalent
Fc	ferrocene
Et	ethyl
Flu	fluorenyl
HEH	Hantzsch ester
i	*iso*
IMes	1,3-bis(2,4,6-trimethylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene
IPr	1,3-bis(2,6-diisopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene
L	ligand
LUMO	lowest unoccupied molecular orbital
Me	methyl
Mes	2,4,6-trimethylphenyl
*Mes	2,4,6-tri-*tert*-butylphenyl
MOM	methoxymethyl

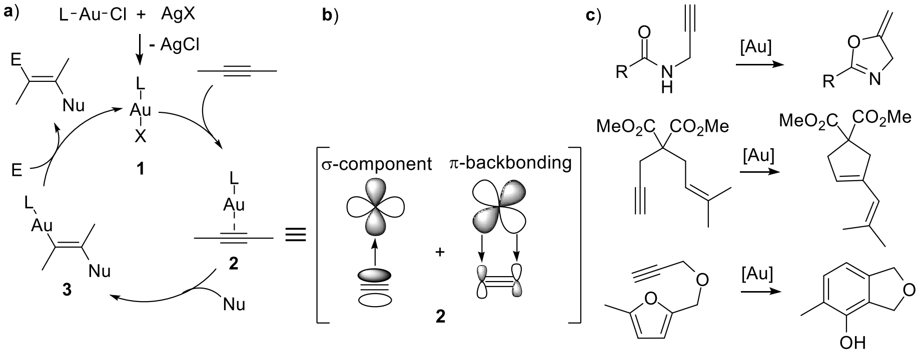
Ms	methylsulfonyl
MS	molecular sieves
mw	microwave
NHC	N-heterocyclic carbene
NMR	nuclear magnetic resonance
Nu	nucleophile
n.r.	no reaction
Ph	phenyl
Piv	pivaloyl
PMP	polymethylpentene
PNB	*p*-nitrobenzyl
ppm	parts per million
py	pyridine
rt	room temperature
SIMes	1,3-Bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene
SIPr	1,3-Bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene
t	*tert-*
TA	1,2,3-triazole anion
TA-Me	N-methyl-1,2,3-triazole
TBA	tetrabutylammonium
TEA	triethylamine
Tf	triflate
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
tht	tetrahydrothiophene
TMS	trimethylsilyl
TOF	turnover frequency
Tol	toluene
TON	turnover number
Ts	*p*-toluenesulfonyl

1 INTRODUCTION

For decades gold was perceived as a noble material and unreactive compared to other transition metals.[1] During the 1900s only few glimpses of catalytic abilities were reported, but the true gold rush started in the beginning of the current millennium making the field of gold catalysis rather young. Gold catalysts come in many forms such as gold salts, nanoparticles or bound to heterogeneous carrier materials.[2] During the last decades, the salts have evolved to ligand-stabilized single gold atom containing cationic complexes, which have become an effective tool in the laboratory to perform organic reactions.[3]

1.1 HOMOGENEOUS GOLD CATALYSIS

Gold is a soft Lewis acid that can activate π-systems for a nucleophilic attack.[2] The unique properties of gold can be traced to relativistic effects: the velocity of electrons near a heavy nucleus approaches the speed of light, which makes their mass increase compared to the electrons further from the nucleus.[4] This leads to contraction of the *s* and *p* orbitals, which then is responsible for a LUMO orbital relatively low in energy, thus strengthening the Lewis acidity. When the *s* and *p* orbitals contract, the *d* and *f* orbitals expand and electrons on these orbitals have weaker nuclear attraction and electronic repulsion. These effects are exceptionally strong in gold and enable the beneficial characteristics required for the typical catalytic cycle (Scheme 1a).[5] When it comes to cationic gold, the effects are stronger for Au(I) than Au(III).



Scheme 1 a) Typical catalytic cycle of homogeneous Au(I) catalyst, b) the interaction between gold and π-system described using the Dewar-Chatt-Duncanson model and c) common gold catalyzed reactions

In the catalytic cycle, the cationic gold coordinates to a π-system (**2**, Scheme 1a). According to the Dewar-Chatt-Duncanson model, the coordination is divided into two components: substrate-to-metal σ-donation and metal-to-substrate π-backdonation (Scheme 1b).[6,7] The former results from the interaction of the low-lying LUMO of the metal and the alkyne. The latter is possible due to the expanded 5*d* orbital, which partially overlaps with the empty *p* orbital of the carbon. Computational results indicate that this backbonding is highly tunable and can be even comparable to the σ-bond component in L-Au(I)-substrate catalytic intermediates, whilst in the corresponding Au(III) complexes the π-backdonation seems to be generally smaller than the σ-donation.[8,9] In the case of carbon-carbon π-bonds, the nonbonding orbitals are higher in energy, and gold is unable to form a bond with its electrons in the 5*d* orbital. When the bond is not formed, the coordination of gold withdraws electron density from the π-bond, thus weakening and activating it towards a nucleophilic attack. Predominantly the nucleophile approaches from the *anti* side creating a *trans* alkenyl (**3**, Scheme 1a). Finally, the product and the catalyst are released by an electrophile such as a proton. Common gold catalyzed reactions that follow this cycle are cyclization of propargylamides into oxazolines, cyclization of 1,6-enynes and the phenol synthesis (Scheme 1c). The higher energy of 5*d* orbital separates gold from metals like palladium: it makes the metal center less nucleophilic, which is why the common steps for palladium cycle such as β-hydride elimination or oxidative addition are not part of the typical gold catalytic cycle. With the right oxidant Au(III) is obtainable, which is another difference between gold and silver.

Relativistic effects are responsible also for the shape of gold complexes: due to the expansion and contraction of the orbitals, their energies are closer to each other, which allows the formation of *sd* and *sp* hybridization.[10] This accounts for the linear geometry of the Au(I) complexes, but also for the shortened L-Au(I) bond compared to the L-Ag(I) bond. In squareplanar Au(III) and Ag(III) the difference in bond lengths is less profound.[11] The common ligands in gold chemistry are phosphites, phosphines and N-heterocyclic carbenes (NHC) (Figure 1). As in all transition metal chemistry, the primary function of the ligand is to stabilize the gold centre. The nature of the ligand affects the electrophilicity of the gold complex, which can be tuned to match a specific reaction or substrate, but also the structure of the ligand can play different roles when it comes to manipulation of the counterion.[12,13] With Au(I), it is more demanding to have an interaction between the ligand and the counteranion due to the 180° angle surrounding the gold centre. The squareplanar geometry of the Au(III) complexes brings counteranions closer to the ligand for easier interaction.

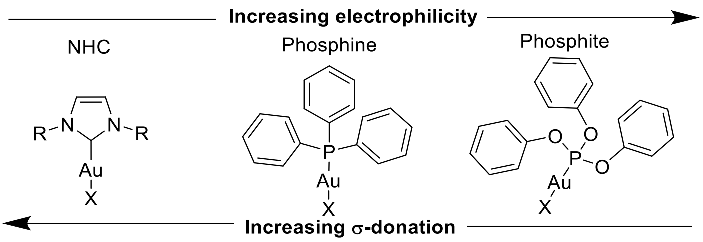


Figure 1 Relative differences of gold(I) complexes using typical classes of ligands[14]

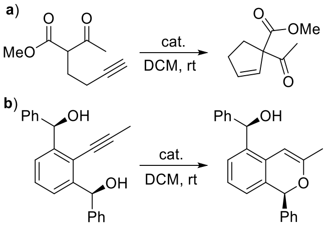
The majority of the precatalysts are ligated gold chlorides. The strong coordination of chloride in L-Au-Cl_n complexes makes them benchstable and easy to handle. This comes at the expense of reactivity, as the required site for substrate coordination is occupied by the chloride, which is usually removed by a halide scavenger, such as a silver salt (AgX, Scheme 1a). In an optimal scenario the chloride is replaced by a weakly coordinating counteranion (X^-), which presents another method for optimization of the reaction conditions, and silver chloride is eliminated from the solution as an insoluble precipitate.[15] Yet, silver plays a more complex role than a mere precipitant.

1.2 THE PROBLEMS WITH SILVER IN HOMOGENEOUS GOLD CATALYSIS

To understand the value of alternative activation methods, it's worthwhile to consider the factors that support silver-free conditions. Handling of silver salts may cause issues due to their hygroscopicity, light-sensitivity and toxicity, but even after all precautions, silver can cause recognized distortions in reactions due to its catalytic properties that can be labelled as “the silver effect”. This term was cemented to the area of homogeneous gold catalysis by Shi *et al.* in their comprehensive study, where they compared the activity of gold catalyzed reactions in the presence and absence of silver along with NMR studies of the catalytic species.[16] The authors divided silver activated gold catalysis into genuine gold catalysis, Au/Ag bimetallic catalysis and silver-assisted gold catalysis based on the effect of silver. However, other researchers have reported cases where silver produces more diverse or negative effects.

1.2.1 BIMETALLIC AND SILVER-ASSISTED CATALYSIS

Shi and coworkers found that many reactions that were considered gold catalytic, such as alkyne hydroalkylation, in fact did not proceed without silver (Scheme 2a). A similar observation was made by Sota *et al.* in alkyne hydroalkoxylation, when their catalyst lost all activity after a filtration, but regained it by a second addition of a silver salt (Scheme 2b).[17]

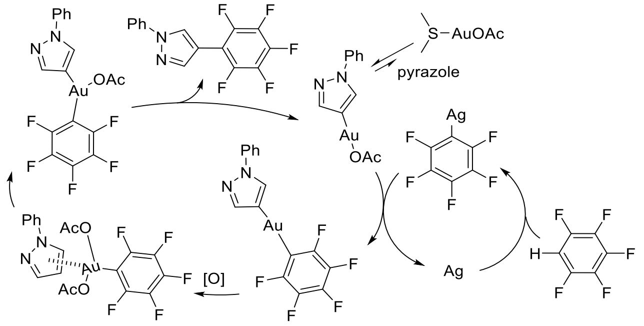


cat.	yield
$Ph_3PAuSbF_6$ (1 mol%)	0%
$AgSbF_6$ (5 mol%)	0%
Ph_3PAuCl (1 mol%) + $AgSbF_6$ (1 mol%)	88%
$Ph_3PAuSbF_6$ (1 mol%) + $AgSbF_6$ (1 mol%)	73%

cat.	yield
a) (*R*)-xylylbinap$(AuCl)_2$ (5 mol%) + $AgNTf_2$ (10 mol%)	92%, 88% *ee*
b) catalyst from a) filtered throught Celite	<5%, - *ee*
c) $AgNTf_2$ added to the filtrate (10 mol%)	76%, 98% *ee*

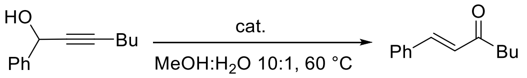
Scheme 2 Reactions catalyzed by a bimetallic catalytic system

The actual mechanism was not investigated at that time, but in 2015 Larrosa's group speculated on the possibility of silver catalysed C-H activation.[18] These speculations were confirmed by NMR experiments and DFT calculations which revealed that silver had a catalytic cycle of its own, which could be utilized in coupling reactions (Scheme 3).[19]



Scheme 3 Example of a Au/Ag-catalyzed C-H activation

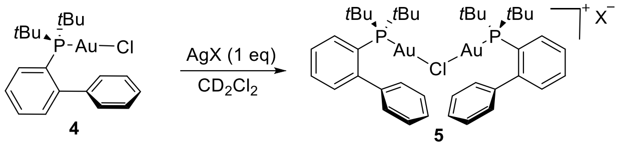
Although silver is a potent alkyne activator, many reactions are out of its league and require the more active gold catalyst.[20] Yet, in some of these cases, the reactivity can be improved by addition of silver. This phenomenon can be seen for example in the Meyer-Schuster rearrangement (Scheme 4).



cat.	yield
$IPrAuSbF_6$ (2 mol%)	26%
$AgSbF_6$ (10 mol%)	0%
IPrAuCl + $AgSbF_6$ (2 mol%)	90%
$IPrAuSbF_6$ + $AgSbF_6$ (2 mol%)	94%

Scheme 4 Silver-assisted Meyer-Schuster rearrangement

Despite the catalytic properties of silver, the positive effect could be reasoned by a complete counteranion exchange, which is finalized with the addition of silver salt. Echavarren has shown that activating JohnPhosAuCl **4** with 1 equivalent of silver additive leads to a bridged complex **5**, which is a far inferior catalyst compared to the cationic monogold complex (Scheme 5).[21] The formation of the bridged complex could be circumvented by executing the halide abstraction in the presence of the alkyne substrate. Similar findings were reported by Fensterbank, when the studied 1,6-enyne cycloisomerization reached higher yields with excess silver additive in the reaction.[22]



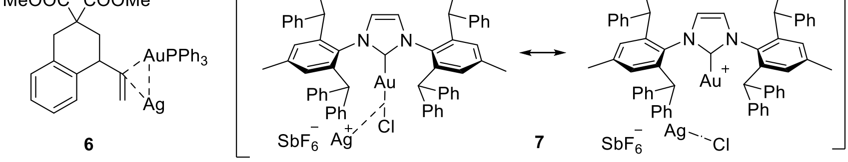
Scheme 5 Synthesis of chloride-bridged digold complex

The activation by silver can go beyond formation of the cationic complex, as silver has been reported to dissociate carbene ligand from gold.[23] This leads to formation of highly catalytic nanoparticles, which can once again hinder the identification of the catalytic species and complicate the whole process of catalyst design.

1.2.2 INHIBITION AND UNWANTED REACTIVITY

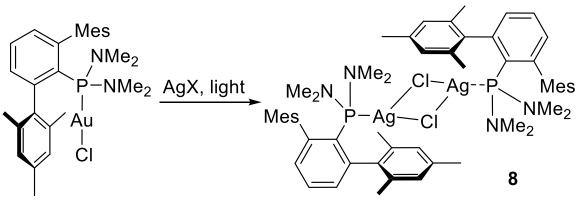
In the previous paragraph the effect of silver can be seen as positive from the perspective of general activity, but several examples of inhibition by silver have been published that were outside the scope of Shi's original study. Experimental data mainly from NMR measurements and computational analysis have granted insight to the mechanisms of how silver operates in various reactions.

A major breakthrough for discovering the mechanism of inhibition by silver was the bimetallic complex **6** characterized by Gagne while studying allene hydroarylation.[24] This off-cycle species formed after the nucleophilic attack and was resistant towards the protodeauration step thus stopping the catalytic cycle. Acetic acid had little effect on this resting state, but notably stronger $HNTf_2$ was able to release the product from metals. The formation of such species has been suggested as the reason for lower activity in several other reactions, such as alkyne hydration, hydroalkoxylation, hydroamination and propargylamide cyclization.[25] Maier followed Gagne's results and conducted a thorough mechanistic study regarding alkyne hydroalkoxylation with a conclusion that silver only affects the catalysis by inducing variation to the concentration of the in-cycle organogold intermediates.[26] Straub characterized a different intermediate **7**, where silver was interacting with the gold center, but supposedly these species have lesser effect on the catalysis due to their lower stability.[27]



Scheme 6 Isolated silver-containing intermediates by Gagne and Straub

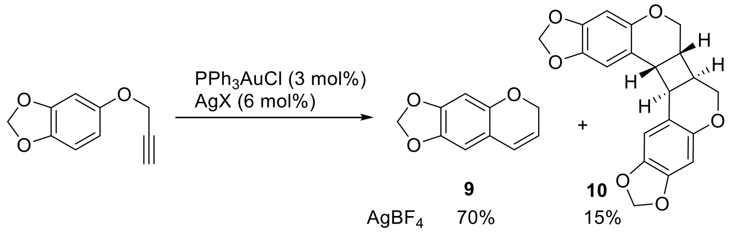
Not all interactions are reversible, as was detected by Siewert *et al.* when studying terphenyl(bisamino)phosphines as ligands for gold: the intended cationic gold complex decomposed in the presence of silver salt and light to inactive metallic gold and a dimeric silver complex **8** (Scheme 7).[28]



8

Scheme 7 Decomposition of cationic gold complex in the presence of silver

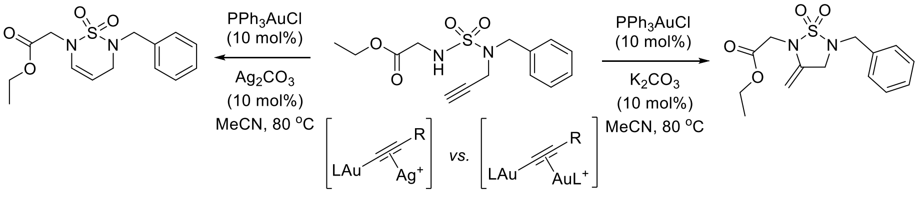
The previous examples present silver as the cause for inactivity, but on the other hand the silver species can generate unwanted reactivity or lead to an unexpected product. Such a case was reported by Nevado and Echavarren in 2010, when they noticed that a hydroarylation product **9** formed a dimer **10** in the presence of excess silver additive (Scheme 8).[29]



	9	**10**
$AgBF_4$	70%	15%
$AgSbF_6$	30%	32%

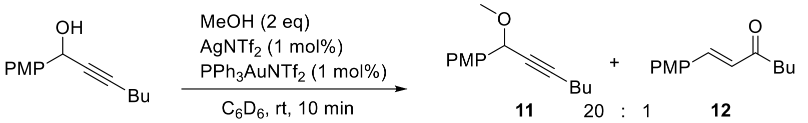
Scheme 8 An unwanted silver catalyzed dimerization of chromenes

Silver has dire effects on reactions proceeding via gold acetylides. Computational results show that silver can coordinate to such a π-system making it less reactive towards a nucleophilic attack.[30] Experimental data demonstrates that this coordination can lead to a completely different stereoselectivity in hydroamination reaction (Scheme 9).[31] Gold prefers a 5-*exo-dig* cyclization whereas silver affected reaction proceeds through a 6-*endo-dig* cyclization. Later, these results were backed up by DFT calculations, where it was found that steric factors did not affect the outcome, but the involvement of silver was crucial for the 6-*endo-dig* cyclization.[32]



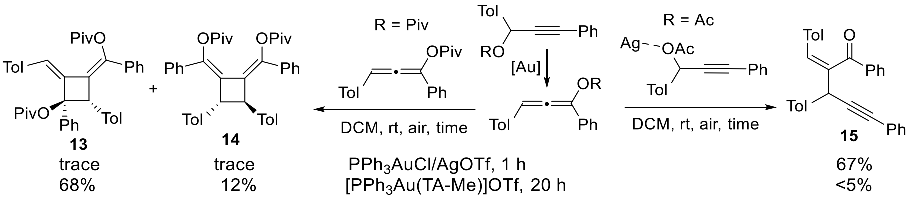
Scheme 9 Different products obtained via 5-*exo-dig* (Au) and 6-*endo-dig* (Ag) cyclizations

Diverse reactivity was reported by Pennell *et al.*, when an intended Meyer-Schuster rearrangement curiously yielded a substitution product.[33] The reason for this activity was residual $AgNTf_2$ in the preformed catalyst batch. In a competition experiment the substitution product **11** was obtained in large excess over the gold catalyzed rearrangement product **12** (Scheme 10).



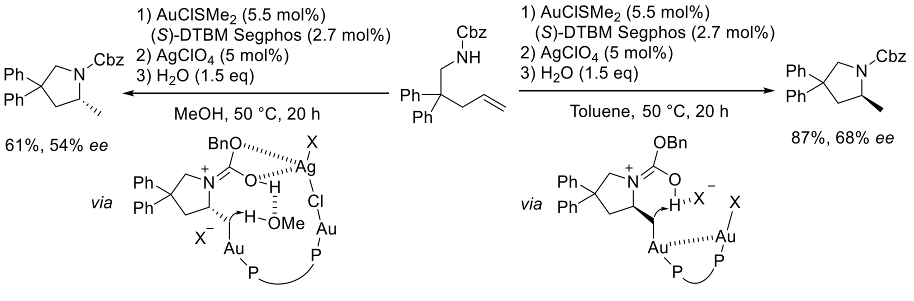
Scheme 10 Silver-catalyzed substitution proceeds over the gold-catalyzed rearrangement

A similar outcome was noticed in a cyclobutene formation which formed an unwanted dimer when silver was added in the reaction mixture (Scheme 11).[34] The desired cyclobutanes **13** and **14** formed from two allenes when using a preformed cationic complex with gold-coordinating *N*-methyl triazole (TA-Me), but dimer **15** was formed if silver coordinated to the propargylic acetate starting material activating it for a nucleophilic attack.



Scheme 11 The effect of silver on propargyl ester activation

Finally, the choice of solvent can stir the pot further. Abadie *et al.* showed that a protic solvent enables the formation of Au-Ag-complexes (Scheme 12). These complexes lead to an *R*-enantiomer in alkene hydroamination reaction, whereas the same reaction in toluene led to a *S*-product, although the enantiomeric excess in both cases remains modest.[35]



Scheme 12 Solvent-dependent configuration of alkene hydroamination products

Due to these problems caused by silver, the search for alternative activation methods has been on the rise ever since the “silver effect” was realized. The following chapters describe the some of these methods for silver-free homogeneous L-Au(I) and L-Au(III) catalysis.

2 REVIEW OF THE LITERATURE

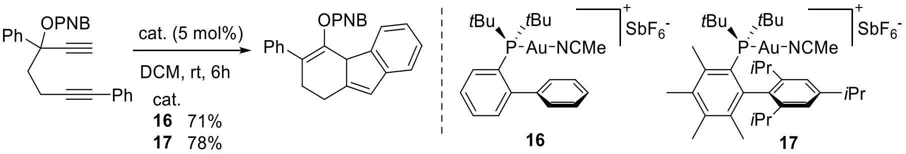
A myriad of alternative activators has been reported during the past decades, for example other metal salts can replace silver or activating additives can be made unnecessary by polar solvents. The following chapters concentrate on the methods concerning publications I-III, which are isolated cationic gold complexes, functionalized ligands, chloride replacement by basic treatment and acid activation.

2.1 ISOLATED COMPLEXES AND THE REMOVAL OF SILVER

2.1.1 ISOLABLE CATIONIC COMPLEXES

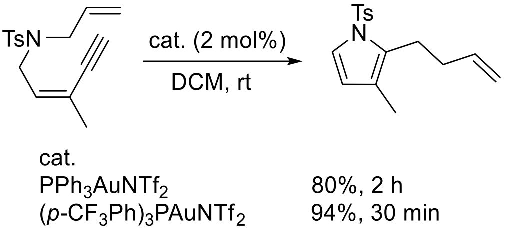
The straightforward way of performing silver-free gold catalysis is synthesizing the cationic complexes and removing the precipitated AgCl from the mixture. The isolation of gold compounds that can act as a source of cationic gold predates the cationic catalysis boom. Schmidbaur-Bayler salt $[(Mes_3PAu)_2Cl]BF_4$ was reported in 1997[36], and the first report of Uson-Laguna salt $[(Ph_3PAu)_2Cl]BF_4$ goes back to 1979[37], but the catalytic properties of these binuclear complexes in alkyne hydroarylation and phenol synthesis were reported by Hashmi and coworkers in 2006.[38] The isolation of trinuclear salt $[(Ph_3PAu)_3O]BF_4$ was published in 1980[39], and decades later it was used in many studies concerning enyne rearrangements and alkene activation by Toste.[40,41] As mentioned, common for these salts is that they can act as reservoir of the catalytically active gold species. Since the cationic species is formed in equilibrium with the salt, they are in most cases less reactive than "monoauric" cationic complexes. In some cases this helps to prevent catalyst and substrate decomposition[42] or promote reactions which proceed via dual gold catalysis[43], but the overall lack of reactivity compared to mononuclear cationic complexes might be the reason why these salts are typically ignored in catalyst screenings.

Two isolated complexes from 2005 have become the workhorses of homogeneous gold catalysis. First is the Echavarren catalyst **16**, which uses JohnPhos as a ligand.[44] The efficiency of these Buchwald ligands in gold catalysis was known, but the remarkable fact was that the catalyst could be isolated as a stable cationic complex with a solvent molecule coordinated to gold just by using $AgSbF_6$ in MeCN followed by filtration and evaporation. The activity was showcased in 1,6-enyne cyclizations, which is widely used as a benchmark reaction in catalyst development. The versatility of the complex was noticed, and it was used for a myriad of alkyne activations. The cationic complex has become a standard catalyst in the screening tables, but it also has inspired many modifications such as the bulky biphenylphosphine complex **17**, which can reach higher yields in cyclization of 1,6-diynes (Scheme 13).[45]



Scheme 13 Cyclization of 1,6-diyne using biphenyl Au(I) complexes

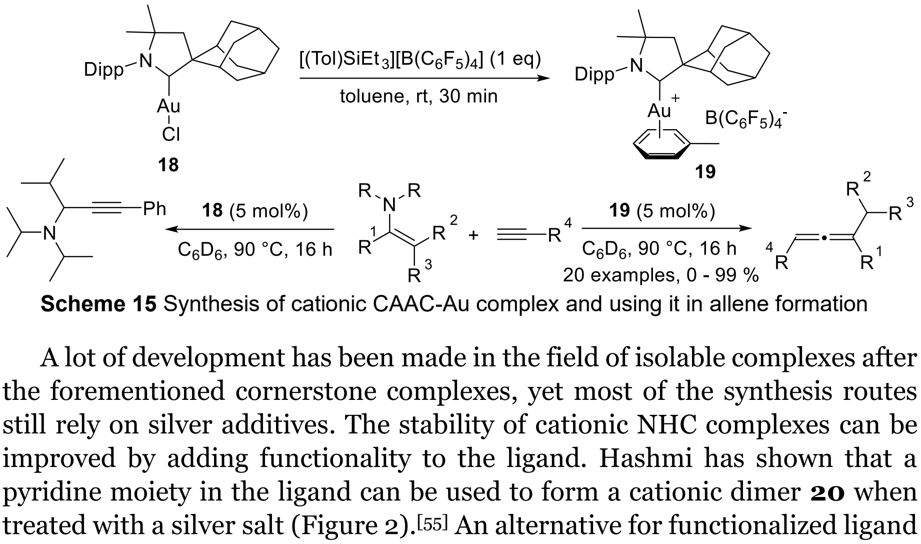
A month after the publication of isolated complex **16**, Gagosz followed with his catalyst PPh_3AuNTf_2.[46] Using bis(trifluoromethanesulfonyl)imidate enabled the isolation of air-stable complexes, which was not possible with other counteranions. Already in the original publication Gagosz presented the activity of the complex in various alkyne activations, including enyne cyclizations, Claisen rearrangement, and hydroarylation. In addition to easier handling, the catalyst was more efficient than complexes formed *in situ* with AgOTf or $AgSbF_6$. The catalyst could be tuned more electrophilic by using (p-$CF_3Ph)_3P$ as the ligand, and higher yields were recorded in rearrangements like aza-Claisen[47] (Scheme 14) and cyclization of *tert*-butylcarbonates[48]. Gagosz expanded the ligand scope quickly to NHCs, which also produced isolable compounds, but the original complex has remained as one of the most used catalysts.[49]



Scheme 14 An Aza-Claisen-type rearrangement using Gagosz catalysts

Shortly after these phospine ligands, Nolan followed with the isolation of cationic NHC complexes, where an acetonitrile molecule was coordinated to the gold atom.[50] These complexes were isolated with PF_6^- and BF_4^- counteranions, which led to unstable complexes in the case of Gagosz's phosphines. The most stable complex was [$IPrAu(NCMe)PF_6$], but the stability was questionable: the complex decomposed partially when solvent was evaporated and it was stable for longer periods only in THF, which slowly polymerized to a gel in the presence of the cationic complex. As could be expected, these complexes were also catalytically active, and the first example of catalysis was the reaction of ethyl diazoacetate with alcohols, amines and alkenes.

The use of silver is not mandatory in the synthesis of cationic complexes. In 2007 Bertrand's group published the synthesis for an isolable cationic complex **19**, which was formed after treatment of gold chloride **18** with $[Et_3Si(Tol)]^+[B(C_6F_5)_4]^-$ in toluene (Scheme 15).[51] The ligand is a cyclic (alkyl)(amino)carbene (CAAC) with only one nitrogen atom which makes the ligand more π-accepting than a classical NHC. In addition to the structural information, the compound had profound catalytic value in coupling enamines and alkynes to allenes, whereas other studied gold catalysts formed propargylamines. In the following studies the expensive silyl salt was replaced with $K[B(C_6F_5)_4]$, but these results were used as a base for broadening the catalytic scope to alkyne and allene hydroamination with ammonia or hydrazine, and interestingly the Markovnikov hydroamination of allenes was also possible.[52–54] Common for all reactions were long reaction times in high temperatures: an extreme example for an allene hydroamination was heating at 175 °C for 44 hours.



Scheme 15 Synthesis of cationic CAAC-Au complex and using it in allene formation

A lot of development has been made in the field of isolable complexes after the forementioned cornerstone complexes, yet most of the synthesis routes still rely on silver additives. The stability of cationic NHC complexes can be improved by adding functionality to the ligand. Hashmi has shown that a pyridine moiety in the ligand can be used to form a cationic dimer **20** when treated with a silver salt (Figure 2).[55] An alternative for functionalized ligand is to use an external bridging ligand, such as an electron poor thiol to obtain a digold complex **21**.[56] In addition to the better stability, these bimetallic complexes are actual precatalysts that are able to temporarily release a cationic species that can catalyze the phenol synthesis or alkyne hydroalkoxylation.

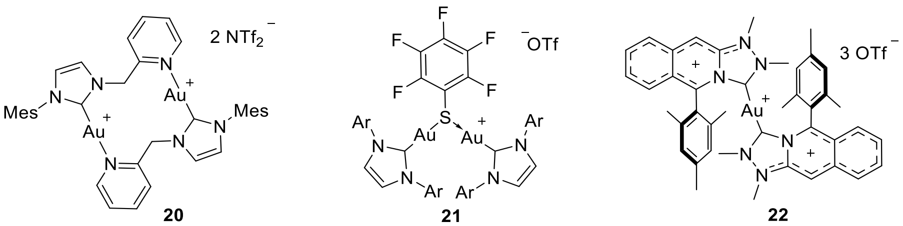


Figure 2 Isolated stable cationic gold complexes

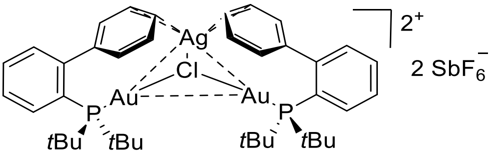
Two NHC ligands can also coordinate to the same gold atom leading to stable cationic complexes. A recent example is using a cationic NHC ligand.

The tricationic complex **22** is formed through a transmetallation reaction when the corresponding silver complex is treated with AuI. Like the forementioned bimetallic species, complex **20** can catalyze a hydroarylation reaction without any additional halide scavenger present.

2.1.2 PROBLEMS WITH REMOVAL OF SILVER

Utilizing silver to create a cationic complex and subsequently removing it may appear as a straightforward method in gold catalysis. Unfortunately, there are certain challenges in it, especially when working in small scale. The standard method for the removal of the precipitated silver chloride from the catalyst solution is a Celite filtration. Hammond *et al.* showed that the material might not be as innocent as it is generally perceived.[57] They filtered an active catalyst solution through Celite, which led to complete deactivation of the catalysis. Alkali base impurities in Celite explain the observed phenomenon, as the activity could be restored with acid additives. This could lead to mislabeling genuine gold catalysis as ”silver-assisted” catalysis if no further investigation of the catalytic species is conducted.

The fundamental issue with Celite is that it does not guarantee the complete removal of silver. Celite is unable to remove species which do not precipitate, and the precipitation of AgCl might be incomplete due to insufficient reaction time or the silver reagent can take part in the formation of unexpected complexes. A prime example would be the trimetallic complex **23** which was obtained by Jones *et al.* from a Celite filtered solution.[58]



23

Figure 3 A silver-containing species isolated from a Celite filtered solution

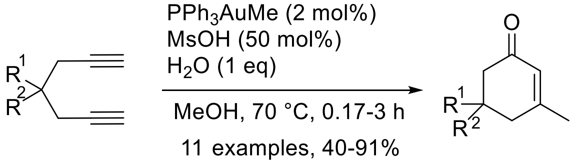
Despite these problems, commercial complexes exist and offer a fast way to expand catalyst screening most likely without any silver present. A commercial Gagosz catalyst was used in Publication I for this reason. To avoid the risk of contamination or the presence of silver residues, the synthesis of the gold complexes should be done in total absence of silver. While this is not (yet) an option for all gold precatalysts, an innovative silver-free route was published for Echavarren’s catalyst starting from gold powder (Scheme 16).[59] The method avoids also the use of aqua regia, but the notable downside is the high price of the required oxidant $[NO][BF]_4$.

$$\mathrm{Au}\xrightarrow[\mathrm{MeCN}]{[\mathrm{NO}]\mathrm{BF_4}}\left[\mathrm{MeCN{-}Au{-}NCMe}\right]^{+}\mathrm{BF_4^{-}}\xrightarrow{\mathrm{JohnPhos}}\left[\mathrm{JohnPhos{-}Au{-}NCMe}\right]^{+}\mathrm{BF_4^{-}}$$

Scheme 16 Silver-free route for the synthesis of Echavarren's catalyst

2.2 ACTIVATION BY BRØNSTED ACIDS

In 1998 the seminal work by Teles and coworkers was published.[60] Motivated by finding a substitute for mercury in the alkyne hydroalkoxylation, they found out that activating methyl gold complexes such as PPh_3AuMe with Lewis or Brønsted acid created a highly active catalyst. The TON values were increased to 10 000 for this new system, whereas the earlier reported values were 100 for mercury and 50 for $NaAuCl_4$. The turnover frequency could be improved by electron deficient ligands, but the overall turnovers were lower despite the faster initial reaction rate. This groundbreaking work had also NMR evidence on the nature of the gold species formed by acids and DFT calculations of the catalytic cycle, although their proposed mechanism contained a *syn*-addition of methanol based on coordination of methanol to gold-alkyne complex prior the nucleophilic attack. Later studies have found this unlikely providing experimental and computational evidence to support the *anti*-addition.[61] This catalytic system was also utilized in a less common 1,6-diyne cyclization by Hayashi and Zhang (Scheme 17).[62] The reaction starts with a hydration of an alkyne, which is followed by the cyclization producing 2-cyclohexenone derivatives.



Scheme 17 Cyclization of 1,6-diynes

The original work used quite harsh conditions due to the large amount of concentrated sulfuric acid. Tanaka, Hayashi and Mizushima used the same gold complex but succeeded in the activation reaching nearly quantitative yields with lower acid loading using phosphotungstic, molybdotungstic and silicotungstic acid in alkyne hydroamination (50 mol% vs 1 mol%).[63] Slightly lower yield was obtained with TfOH, but using MsOH lowered the yield of the desired ketimine dramatically probably due to stronger coordination to gold (26% vs 88%). Later, Echavarren and coworkers adopted these catalytic systems for 1,6-enyne cyclizations which further established the possibilities in cationic Au(I) catalysis.[64]

A few years after Teles's work, Laguna, Mohr, Sanz and Jones published their version of the acid activated gold complexes (Figure 4).[65] They created a robust catalytic system for alkyne hydration replacing the methyl with a variety of alkynes and using a water-soluble triarylphosphine ligand. Complexes **24-30** were able to hydrate alkynes with a low 0.05 mol% catalyst loading when they were activated with an acid. Acetic acid was too weak to produce the active catalyst, and sulfuric acid was detected as the most effective. Interesting difference in activity was seen when varying the alkyne in the complexes: complexes **25** and **26** were far more reactive than other alkynes. Authors speculated that η^2-coordinated alkyne stabilized cations would be the source of the different activities. Unfortunately, no further experiments were made to authenticate this claim. Thanks to the water-soluble ligand, this complex was one of the first recyclable Au(I) catalysts for alkyne hydration.

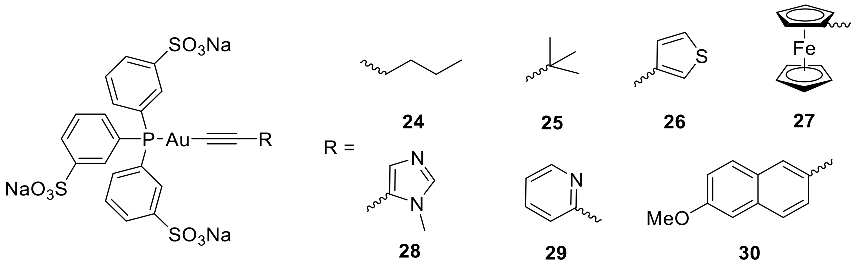
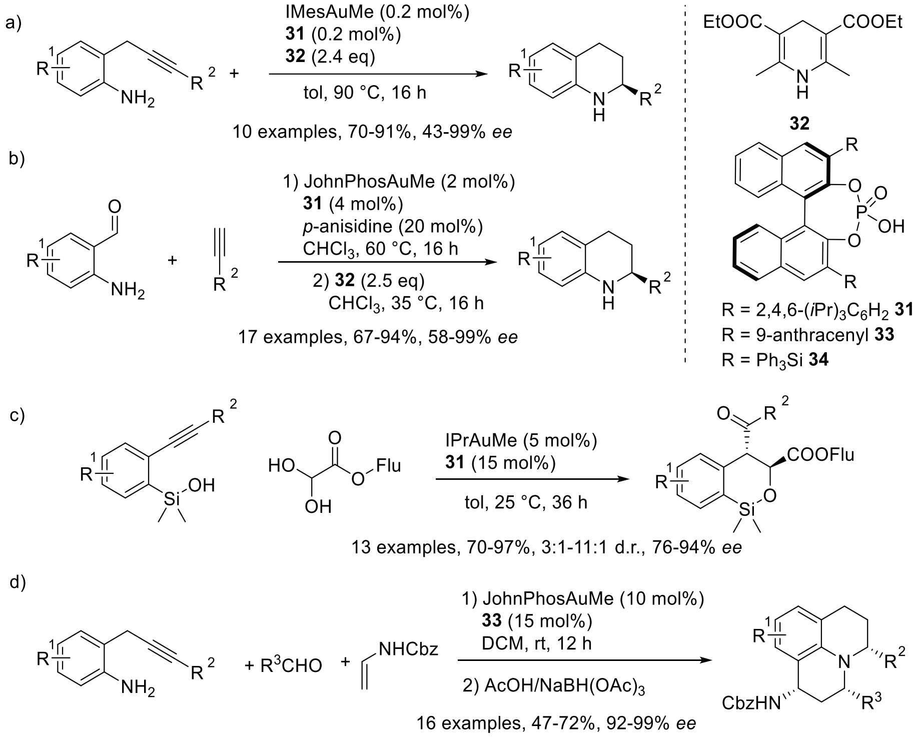


Figure 4 Water-soluble acid-activated Au-alkyne complexes

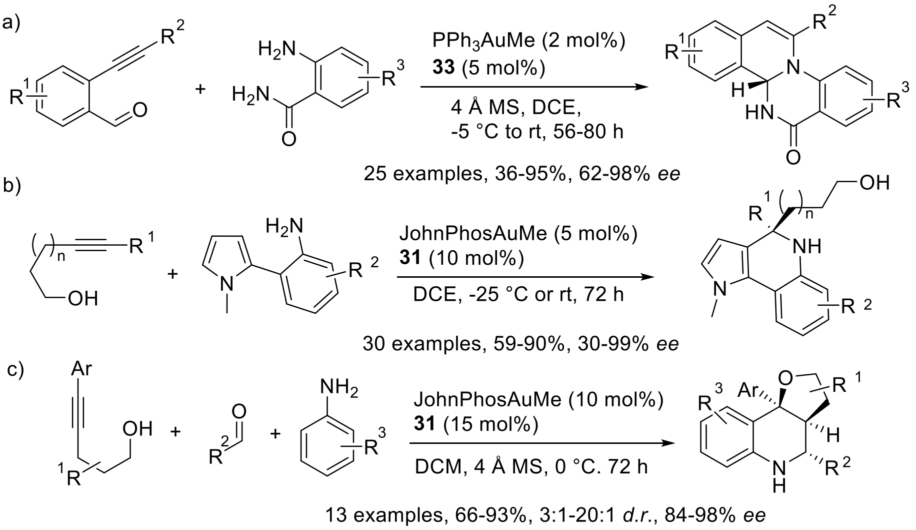
2.2.1 CHIRAL ACIDS

Remarkable synthetic value comes from utilizing chiral phosphoric acids. In addition to creating the active catalyst, these chiral anions can induce enantioselectivity in the reactions catalyzed by gold. The pioneering work was published by Gong *et al.* in 2009, where they applied gold catalysis to hydroamination followed by chiral acid **31** controlled asymmetric transfer hydrogenation by Hantzsch ester (HEH, **32**) producing tetrahydroquinolines with excellent enantioselectivity.[66] The catalytic loading was relatively high and acid had to be used in excess, but in a follow up study they found out, that using IMes as a ligand and raising the temperature allowed them to reduce the gold loading from 5 to 0.2 mol% reaching high yields without any excess acid (Scheme 18a).[67] If the latter transfer hydrogenation step was performed for quinolines, catalyst loading could be as low as 0.01 mol% with using a preformed IMes-Au(I) phosphate complex.[68] Fast reactions still required heating, but quantitative conversion with up to 98% *ee* was reached in 6-48 hours. The absence of the excess acid reveals that the anion can be the sole source of enantioselectivity. Patil took the tetrahydroquinoline cascade reaction a step further by reporting an intermolecular reaction yielding the same heterocycles (Scheme 18b).[69] The cascade reaction used three different catalysts: amine for the A3 coupling, gold for the hydroamination and phosphoric acid for the transfer hydrogenation. This complex mixture led to high enantioselectivity with a broad substrate scope. In addition to tetrahydroquinolines, chiral phosphoric acids **31** and **33** have been used to create silicon and nitrogen heterocycles in cascade reactions combining hydrosiloxylation and Mukaiyama aldol reaction (Scheme 18c) or imine formation and activation of imines (Scheme 18d).[70,71]



Scheme 18 Stereoselective gold catalysis enabled by chiral phosphoric acids

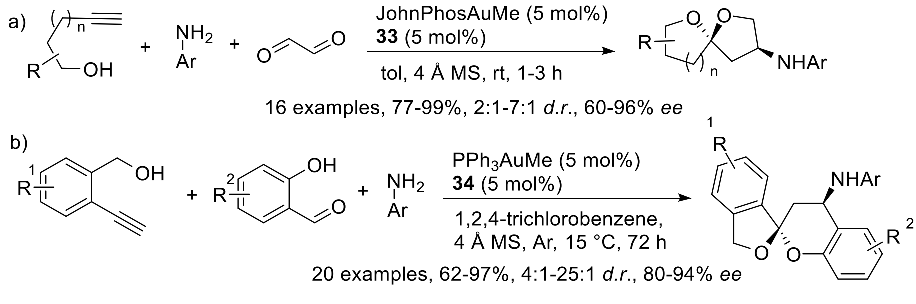
Patil used a similar approach but with less moving parts in the synthesis of fused 1,2-dihydroquinolines, which consists of enantioselective condensation forming an aminal followed by hydroamination (Scheme 19a).[72] The reaction time was 56 hours in most cases, but apparently no major racemization of the intermediate aminal took place in the reaction conditions since stereoselectivity of the reaction was excellent with most substrates. The same group synthesized also tetrahydroquinolines and other N-heterocycles with a fused pyrrole by a hydroamination-hydroarylation cascade (Scheme 19b).[73] Alkynes with a hydroxyl group were crucial for the enantioselectivity and DFT calculations backed the authors explanation, in which the hydroxyl group is coordinated to the excess phosphoric acid before the hydroarylation step.



Scheme 19 Enantioselective syntheses of N-heterocycles

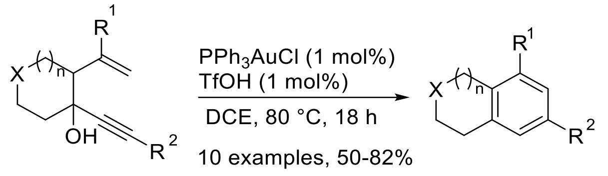
Finally, Álvarez *et al.* published their version of the quinolone synthesis in 2013 (Scheme 19c).[74] Their route consisted of alkyne hydroalkoxylation and imine formation followed by a Povarov reaction between the formed alkene and imine producing hexahydrofuro[3,2]quinolines. The three-component reaction required a 10 mol% gold loading, excess phosphoric acid and 72-hour reaction time, but the yields were good and enantiomeric ratio up to 99:1. Interestingly, the reaction required an aromatic group present in the alkyne. This offered crucial π-stacking during the reaction and led to the desired product.

Stereocontrol provided by chiral phosphoric acids has been used to synthesize spiroacetals. Within two months two three-component routes were published with very similar yields and enantioselectivity (Scheme 20).[75,76] A remarkable difference lies in the reaction time: saturated spiroacetals with 5-membered rings form in 1-3 hours, but fused aromatic spiroacetals with 5- and 6-membered rings take 3 days to finish.



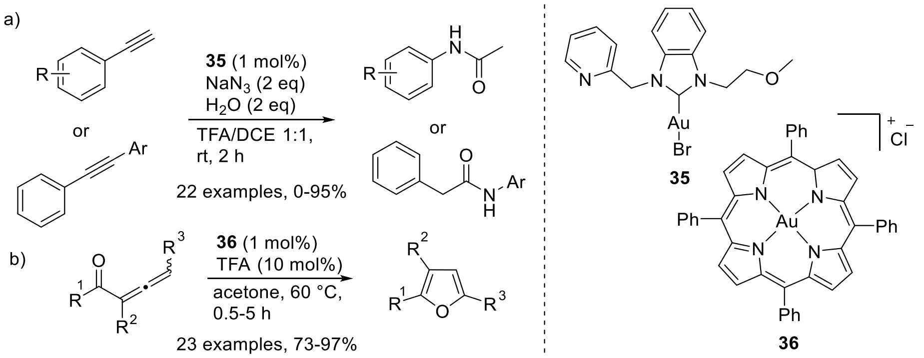
Scheme 20 Enantioselective syntheses of spiroacetals

Synthesis of the precatalysts becomes more straightforward when the common chloride complexes are used instead of alkyl gold complexes, although the catalysis then demands harsher conditions. In 2008 Barriault and coworkers published a study on benzannulation of 3-hydroxy-1,5-enynes, where a wide substrate scope had been studied using PPh_3AuCl with triflic acid (Scheme 21).[77] Carboxylic or mineral acids could not activate the catalyst. The authors tried to observe the catalytic species formed with ^{31}P-NMR spectroscopy: a different shift was detected for PPh_3AuOTf formed with AgOTf, but treating PPh_3AuCl with triflic acid in the presence of the substrate did not change the original shift of PPh_3AuCl. The authors proposed that the active species was formed, but the concentration was below the limit of detection.



Scheme 21 Acid activated benzannulation of 3-hydroxy-1,5-enynes

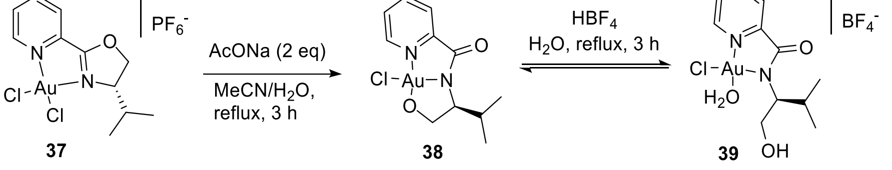
In DCE/TFA solvent mixture strongly coordinating bromide can be solvated. Bera *et al.* turned alkynes into amides with a hydration/Schmidt reaction cascade utilizing an interesting NHC-Au complex **35**, which contained a pyridine and an ether moiety (Scheme 22a).[78] Unfortunately the role of the latter group was not discussed, but changing the pyridinium group to an aryl group reduced the yield drastically. Still, the pyridine group was not enough to start the reaction through coordination to gold: TFA was required for the reaction to happen, as no product was seen without the acid or in the presence of acetic acid.



Scheme 22 a) Amine synthesis through hydration of alkynes and a Schmidt reaction; b) furan formation from allenones

Au(III) is less utilized in acid activation studies, although some examples exist. Already in 2006 Chen and coworkers studied Au(III)-porphyrin complex **36** for allene activation (Scheme 22b).[79] They applied the complexes for cyclization of allenones to furans. High yields required mild heating and trifluoroacetic acid as an additive. The authors speculated that the acid facilitated the protodeauration step, indicating that the formed Au-furan complex is relatively stable as weaker acids could not produce similar activity. The possibility of the acid taking part in the activation of the catalyst was not discussed.

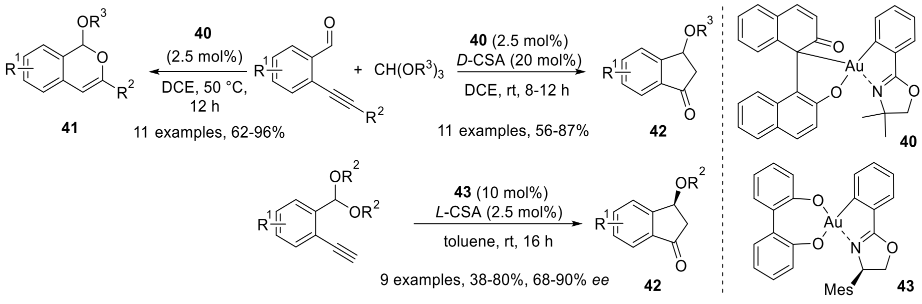
Cinellu, Manassero and coworkers reported a pyridine-oxazoline Au(III) complex **37** (Scheme 23).[80] The oxazoline ring opens in aqueous conditions which leads to the formation of the Au-O bond in complex **38**. This could be used to form a cationic complex by treating it with a Brønsted acid. HBF_4 activated complex **39** was able to polymerize 4-methoxystyrene, but for plain styrene no activity was detected and $AgPF_6$ activated **37** was required for successful catalysis. The function of the acid resembles the catalyst system presented in Publication III.



Scheme 23 Synthesis of a cationic gold(III) complex using a Brønsted acid

Wong and coworkers have synthesized a series of BINOL-Au(III) complexes, which consisted of different *C,N*-coordinating ligands.[81] The bidendate BINOL ligands tautomerized and bonded to the gold through *C,O*-chelation. The racemic complex **40** was able to cyclize *ortho*-alkynylbenzaldehydes in the presence of trialkyl orthoformate into acetals **41** under mild heating (Scheme 24). Curiously, this changed in acidic conditions: only the racemic carboalkoxylation product **42** was formed when *D*-camphorsulfonic acid

(CSA) was added to the reaction mixture. Other Au(III) complexes or cationic Au(I) complexes failed to form the carboalkoxylation product.



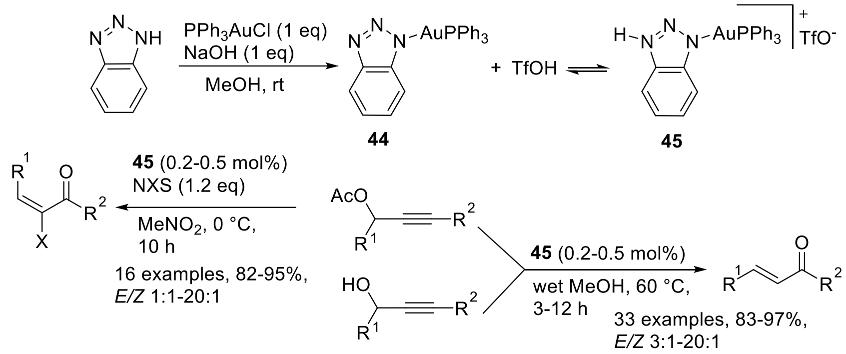
Scheme 24 The effect of an acid additive to cyclization of alkynylbenzaldehydes

Finally, the same group used a chiral oxazoline moiety in combination with 4,4'-biphenol to form the *O,O'*-chelated compound **43**.[82] No activity without an acid additive was reported, but with *L*-CSA these compounds could catalyze the carboalkoxylation at room temperature. High enantioselectivity could be reached when a bulky aryl substituent was placed in the oxazoline ring, but curiously both yield and enantiopurity dropped when the amount of acid was increased. The optimal acid:catalyst ratio was 1:4. The authors proposed that the active species is formed when one of the Au-O bonds breaks in protodeauration creating a vacant coordination site. These results demonstrate that high selectivity can be reached with Au(III), however the reactions are slower than with silver activated Au(I) catalysis.[83]

2.2.2 REPLACING THE CHLORIDE ANION BY A BASE TREATMENT

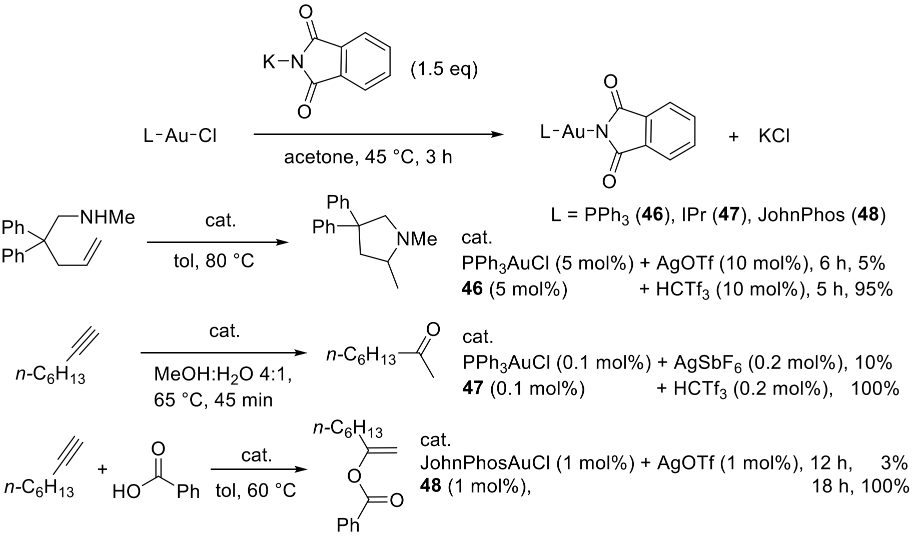
2.2.2.1 N-Heterocycles

The need for silver can be circumvented by replacing the halide with a better leaving group in basic conditions. The chloride can be simply replaced in PPh_3AuCl by a triazole group using a facile NaOH treatment (Scheme 25).[84] When the triazole gold complex **44** was published in 2009, the absence of silver was not the emphasized feature, but rather the improved thermal stability was pursued for the hydroamination of more demanding internal alkynes. Efficient catalysis required a cocatalyst such as $H_3PO_4{\cdot}12WO_3$. This observation could be the reason for the isolation of cationic triazole complexes synthesized by addition of TfOH. Complex **45** was an excellent catalyst for rearranging propargylic esters into enones and α-haloenones with a strong *E*-selectivity, although any effect arising from traces of TfOH was not ruled out.[85,86] When the α-haloenones were synthesized using PPh_3AuNTf_2 as the catalyst, the Z-isomer was the major product. The selectivity difference was explained by complex **45** forming the intermediate allene without activating it for a nucleophilic attack, whereas PPh_3AuNTf_2 is coordinated to the allene leading to the *Z*-isomer. Apart from the unique selectivity, the major upside of the triazole precatalyst is the cheap price of triazoles compared to other additives.



Scheme 25 Synthesis of benzotriazole-Au complexes and their use in catalysis

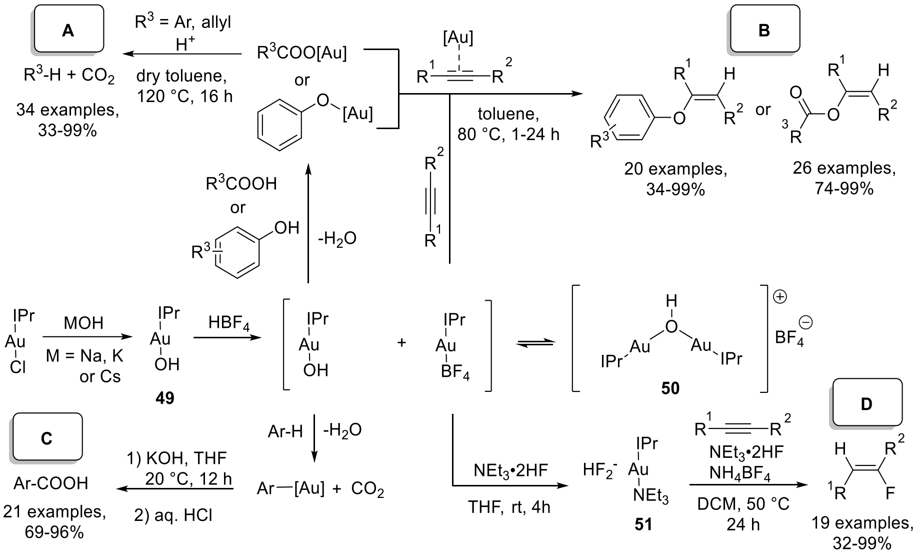
Hammond, Xu and coworkers have replaced the chloride with phthalimide in various phosphine and NHC complexes (Scheme 26).[87] These complexes can be activated with Lewis and Brønsted acids and in reactions such as alkene hydroamination or alkyne hydration this method produces a more active catalyst than corresponding chloride complexes with silver salts. In the case of acid-labile substrates and products milder Brønsted acids such as carboxylic acids can be used. This is highly beneficial for example in the addition of carboxylic acid to alkynes, where the silver activated catalyst produced a complex mixture with only traces of the desired vinyl acetate.



Scheme 26 Synthesis and application of phthalimide-gold complexes

2.2.2.2 Gold Hydroxides

In 2010 Nolan and coworkers published the synthesis of NHC gold hydroxide **49**, which was formed by simply treating IPrAuCl with sodium, potassium or cesium hydroxide (Scheme 27).[88] The gold hydroxides are air-stable compounds which can act as a Brønsted base. Using this ability, the hydroxide could be replaced by a plethora of reagents containing an acidic proton.



Scheme 27 Synthesis of gold hydroxides and their diverse use in synthesis

The basicity was studied in more detail with HBF_4, and it was noticed that depending on solvent conditions the forming species was in an equilibrium between μ-OH-Au_2-species **50** and monometallic $IPrAuBF_4$.[89] The catalytic activity of the hydroxide complex was studied in alkyne and nitrile hydrations, enyne cyclization and other rearrangements, where little activity was seen without the acid, but high yields were reached with equimolar amount of acid with gold.[90,91] Numerous Brønsted acids had the similar effect, and other counteranions such as OTf^- or NTf_2^- could be introduced to the system.[92] The original catalytic activity of the hydroxide complex was presented with the IPr-ligand, but later a variety of NHC ligands have been screened increasing the structural diversity of NHC-Au hydroxides.[93–95] In addition to strong acids, also milder carboxylic acids were used as activators, and the catalytic scope of reactivity could be broadened to decarboxylation of allylic and aromatic carboxylic acids (Scheme 27, A).[96]

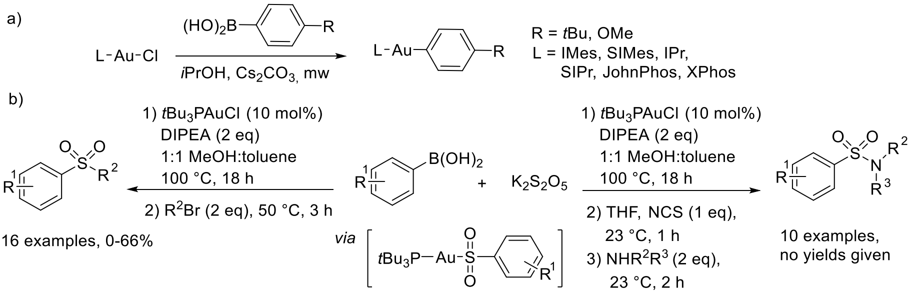
The combined ability to act as a Brønsted base and as a Lewis acid has been utilized for phenoxylation of alkynes, where the dual catalytic nature consists of Brønsted base activation of phenol nucleophile and Lewis acid activation of alkyne leading to a highly efficient catalytic system (Scheme 27, B).[97] Thorough computational analysis has been made in order to verify this dual catalytic effect.[98,99] After the hydrophenoxylation, the possibility of activating acidic nucleophiles was used in the addition of carboxylic acids to alkynes.[100] Especially intramolecular reactions of alkynoic acids were well suited for this catalytic system: high turnovers were reached with very low gold loading of 25 ppm and depending on the substrate full conversion could be reached in minutes.[101]

Without any additives, the hydroxide complex could be used for carboxylation of different aromatic compounds, including several heterocycles (Scheme 27, C).[102] The mechanism of the reaction is based on the hydroxide abstracting the most acidic proton in the substrate followed by nucleophilic addition of the deprotonated substrate to CO_2. The reaction was performed in the presence of KOH, and many L-AuCl complexes could catalyze the reaction in these conditions, although with higher catalyst loadings and lower yields than the gold hydroxides.

The hydroxide complex could be activated with a pyridinium or ammonium BF_4^- salt in formation of allenes from propargylic acetates.[103] Remarkably, allenes could be isolated as the presence of gold-coordinating pyridine or TEA hindered the formation of an indene from the allene, which commonly follows the allene formation. Similar use of triethylamine was seen in synthesis of gold bifluoride species **51**, which was synthesized from **49** using $NEt_3{\bullet}2HF$.[104] This species could be used to hydrofluorinate alkynes with $NEt_3{\bullet}2HF$ and NH_4BF_4 (Scheme 27, D). This method led to more effective fluorination than using ^{Cl}IPrAuCl/$AgBF_4$ and SIPrAuO*t*Bu in similar conditions.[105]

2.2.2.3 Aryl Boronic Acids

Stockland and coworkers synthezised gold-aryl complexes from L-AuCl complexes and boronic acids with cesium carbonate and microwave irradiation (Scheme 28a).[106] Like the gold hydroxides, these aryl complexes were potent catalysts for inactivated internal alkyne hydrophenoxylation. The reactions proceeded efficiently in minutes without any additives or solvent, although temperatures above 100 °C were used. IMes and SIMes complexes turned out to be less stable than the IPr and SIPr complexes; the reaction led to lower yield and noticeable decomposition of the catalyst to metallic gold. The substituent in the aryl group did not have a notable effect on the reaction.



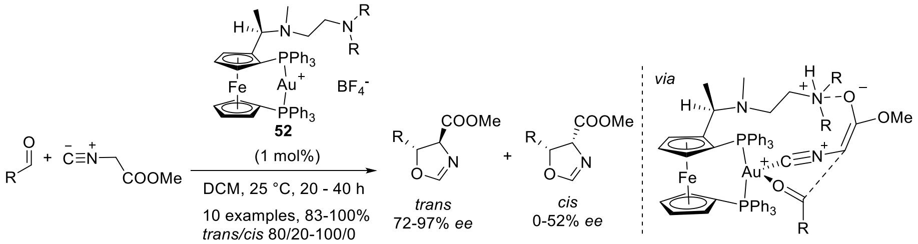
Scheme 28 The synthesis of L-Au-Ar complexes from aryl boronic acids and their applications in synthesis

In 2014 Mascitti, Toste and coworkers used a very similar approach in synthesis of sulfinates (Scheme 28b).[107] In this synthesis, SO_2 inserts into gold-carbon bond, and an electrophile is used to react with the formed sulfinate intermediate. Benzyl or alkyl bromides could be used as the electrophile to form sulfonates. Alternatively, amines could be used to trap the sulfinate to form sulfonamides. The reaction did not tolerate electron poor boronic acids such as 4-cyanophenylboronic acid: the aryl complex could be formed, but no insertion of SO_2 took place with this electron poor aryl.

2.3 FUNCTIONALIZED LIGANDS IN AU(I) CATALYSIS

2.3.1 METAL CONTAINING LIGANDS

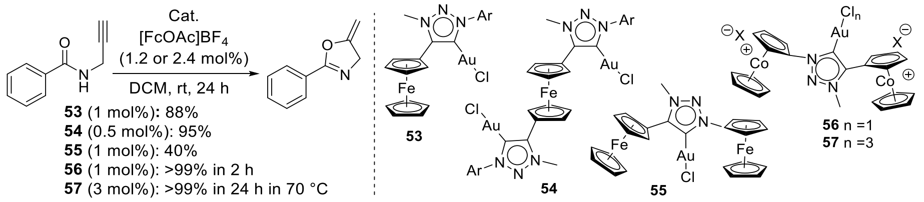
Given that the popularity of gold catalysis rose in the early 2000's, the first example of homogeneous enantioselective Au(I) catalysis is surprisingly old: in 1986 Ito, Sawamura and Hayashi published a chiral cationic ferrocenylphosphine-gold(I) complex **52**, which they applied for asymmetric aldol reaction of isocyanoacetates with aldehydes (Scheme 29).[108] The complex was synthesized by mixing the phosphine ligand with bis(cyclohexylisocyanide)gold(I) tetrafluoroborate in dry DCM. Immediately after this step the aldol reaction starting materials could be added and oxazolines were obtained with high enantio- and diastereoselectivity. The length of the carbon chain between the nitrogens in the ligand was crucial: with a propyl chain the *ee* dropped to 26%, and without the chain a near racemic mixture was obtained.



Scheme 29 Enantioselective oxazoline synthesis

The high selectivity of the system was explained with the dialkylamino group creating an enolate and coordinating to the oxygen. The pivotal role of the amino group in the side chain was confirmed, when the researchers replaced the dialkyl amino group with different cyclic amines and noticed a rise in the selectivity.[109] Acyclic amines could deliver only modest enantioselectivity with acetaldehyde as a substrate, but pyrrolidino or piperidino group in the chain improved the *ee* above 80%, and finally morpholino group affording 89% *ee* for the trans product. The selectivity could be improved further by using bulkier α-isosyanoacetamides as a starting material instead of isocyanoacetates.[110] Curiously, in the case of formaldehyde this trend did not apply anymore, and dimethyl amino group afforded higher selectivity than pyrrolidino side chain.[111] Later spectroscopic evidence was collected with NOE measurements from a corresponding silver complex, where an interaction between the pendant amine group and the methoxy from the isocyanoacetate was observed.[112] Togni and coworkers showed that a catalytically active neutral complex could be formed from the same ligand and Me_2SAuCl, but the enantioselectivity was not as high as with the cationic complex.[113] They studied thoroughly the chiral nature of the ferrocene ligand, and by switching the conformation of the chiral carbon atom and the ferrocene, they could improve the enantioselectivity in the minor *cis*-product.[114]

More recently the use of ferrocenes has concentrated on using them as an attached redox-handle. Sarkar and his group synthesized a ferrocene containing mesoionic carbene complex **53** and evaluated the catalytic activity of the complex (Scheme 30).[115] Only 10% conversion was recorded after 24 hours, but oxidizing the ferrocene afforded 88% conversion in the same time. The reasoning behind this change is that the oxidized ferrocene increases the Lewis acidity of the gold center. Similar behaviour was seen with digold complex **54**, which was slightly better catalyst than the monogold complex.[116] The complex **55** could also be activated through oxidation, and while the dicationic complex was more active than monocationic or neutral form, the overall yield remained low. Instead of electronic or steric factors, this was explained by poor solubility of the complex.



Scheme 30 Catalysts activated by oxidated ferrocene in oxazoline synthesis

The ligand could be tuned even more electron poor by replacing the ferrocenes of **55** with a cobaltoceniumyls in complex **56**.[117] This led to the most active catalyst, but in turn the redox stability suffered, thus the complex could not be reactivated by oxidation. The group made an interesting discovery in synthesis of the corresponding Au(III) complex: more common oxidizing agents such $PhICl_2$ afforded impure reactions and Br_2 or $CsBr_2$ failed to oxidize the gold center. Aqua regia was found to oxidize the complex in clean reactions, but the obtained complex **57** was far inferior compared to the Au(I) counterpart.[118]

Heinze and her group created complex **58**, where the ferrocene was in α-position to the gold (Figure 5).[119] The complex was highly active after the oxidation, but there was an incubation time of 2.5 hours. The authors explained that first the ferrocene is oxidized and the Fe(III)Au(I) complex is formed. During the incubation time this complex turns into Fe(II)Au(II) which is the active catalytic species.

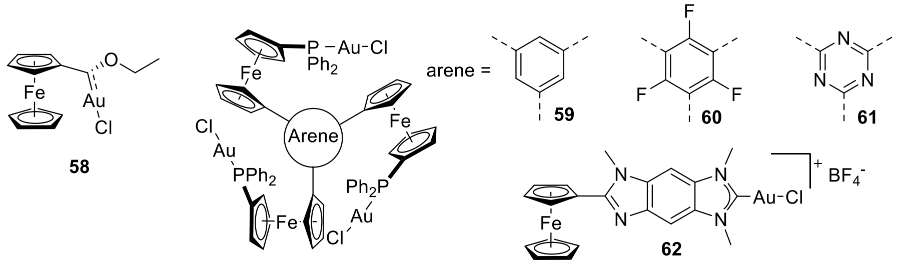
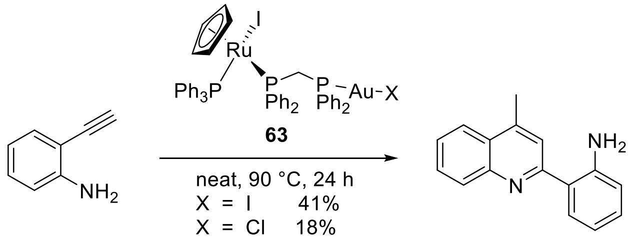


Figure 5 Redox-activated ferrocene-containing gold complexes

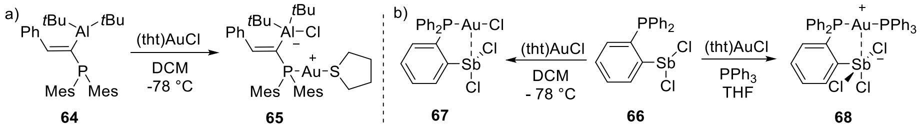
Hey-Hawkins and her group synthesized trigold complexes **59-61**.[120] All four possible ferrocene redox states could be detected, and the complexes were stable for redox switchable catalysis. The complexes were not so effective in catalysis, but in addition to the interesting redox chemistry they offered structural information on C_3-symmetric gold complexes.[121]

Peris and coworkers used a NHC-ligand instead of mesoionic carbene: complex **62** was found to be suitable for redox-induced catalysis, and even though the cyclizations of 2,5-dimethylfuran with different alkynes were made with NaBArF present, the reaction did not proceed at all without the oxidation of the ferrocene.[122]



Scheme 31 Dimerization of 2-alkynylanilie catalyzed by a heterobimetallic complex

McElwee-White and her group synthesized heterobimetallic Au/Ru complexes **63** (Scheme 31).[123] The complexes dimerized 2-alkynylanilines into quinolines in modest yield, but it is notable that no product was observed with monometallic Au or Ru complexes separately or together. Unfortunately, the specific role of the two metals was not deciphered.



Scheme 32 Gold complexes with chloride abstracting metal containing ligands

Bourissou and his group used a organoaluminum ligand **64** to form a zwitterionic complex **65** (Scheme 32a).[124] Aluminum readily abstracted the chloride when a labile co-ligand such as tetrahydrothiophene or PMe_3 was present. This complex was briefly studied in catalysis, and it could effectively cyclize propargylamides into oxazolines.

Gabbaï and Jones studied the same function with stibine ligand **66** (Scheme 32b).[125] In complex **67** a weak interaction between gold and antimony was detected, and based on this structural evidence they rationalized that antimony could abstract chloride anion from gold. Indeed, the charged complex **68** was formed when the synthesis was made in the presence of PPh_3. Alkyne substrates presumably had the same effect, as complex **67** could cyclize propargylamide into oxazoline in high yields. The reaction was retarded by addition of TBACl, which suggests that addition of extra stibine-coordinating chlorides prevents the displacement of the gold-coordinated chloride.

2.3.2 COMPLEXES WITH PHOSPHININES, PHOSPHAALKENES, AND RELATED LIGANDS

Sarkar, Müller, and coworkers compared the properties of mesoionic carbenes and phosphinines (Figure 6).[126] The compounds have differing electronic properties, as the former are stronger σ-donors and weaker π-acceptors than the latter. Indeed, complex **69** was more effective than **70** in 1,6-enyne cyclization, but still the catalytic activity was on the same level as Me_2SAuCl. In cyclization of propargylamides into oxazolines both **69** and **70** outperformed Me_2SAuCl, which failed to deliver any product.

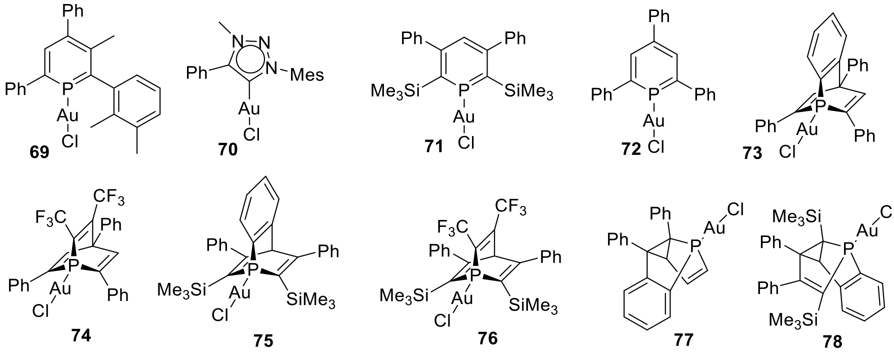


Figure 6 Phosphinine, phosphabarrelene and phosphasemibullvalene gold complexes

Müller and his group studied the effect of different substituents by synthesizing complex **71**.[127] This ligand is a stronger σ-donor compared to **72**, which could help stabilizing the cationic species as the yield of oxazoline synthesis was higher than with **72**. Still, complex **71** could not match the activity of **69**. They extended the ligand scope to phosphabarrelenes **73-76** and 5-phosphasemibullvalenes **77-78**. Since the order in activity did not follow the order in net donation properties, the activity of these complexes was rationalized to consist of electronic and steric properties. **73** and **74** gave moderate yields in the oxazoline synthesis, but **75** and **76** were completely inactive without silver additives. Similarly, 5-phosphasemibullvalene **77** was able to provide moderate yield, but the bulkier ligand **78** did not cyclize the substrate.

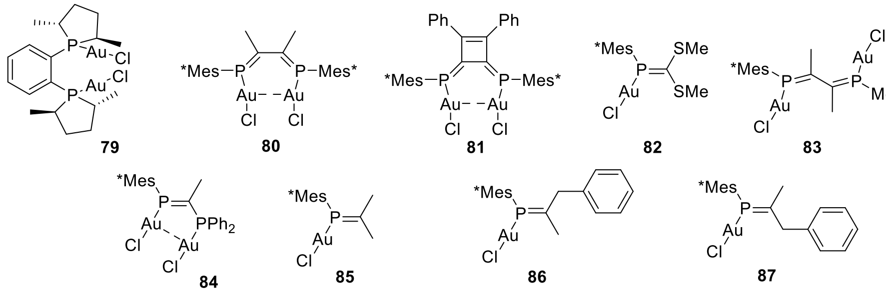


Figure 7 Phosphaalkene gold complexes

In 2005 Corma and coworkers published a neutral dimeric gold(I) complex **79** (Figure 7).[128] The complex was detected to have an aurophilic interaction between the gold centers, which could be a factor in the complex's ability to induce the postulated heterolytic hydrogen splitting and catalyze the hydrogenation of alkenes and imines. In addition to high yields, enantiomeric excess of over 90% could be reached with bulky substituents. Taking advantage of the aurophilic interaction motivated Ito, Yoshifuji and Freytag to prepare Au(I) complexes with phospaalkene ligands.[129] In structural studies they could detect intramolecular aurophilic interaction in complexes **80** and **81**, while complex **82** had an interaction between one of the sulfur atoms and gold. The complexes were used in cyclization of 1,6-enynes and they could catalyze the reaction without any additives, while **83** and **84** showed only minimal product formation. The activity was explained by different factors: the energetically low LUMO of phosphorus-carbon double bond could raise the Lewis acidity of the gold complex and the Au-Au interaction might make the catalysis possible with **80** and **81**, while the presence of sulfur in **82** could lower the Au-Cl interaction and ease the generation of cationic gold center. Following the theory of the π-accepting orbital as possible activating moiety, Ito and his group prepared complexes **85**-**87** which matched the activity of **80**-**82** in 1,6-enyne cyclization, but they were also used for lactonization of 4-pentynoic acids in basic conditions.[130]

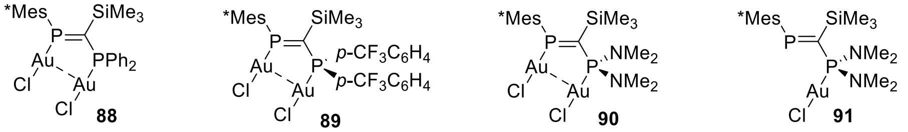


Figure 8 Silylated phosphaalkene gold complexes

In a following study a silyl moiety was incorporated to the phosphapropene ligand (Figure 8).[131] Complex **88** had a shorter Au-Au distance compared to non-silylated complex **84**, which was explained by the silyl group acting as a π-withdrawing group. Indeed, complexes **88** and **89** were active catalysts in the absence of additives, whereas **84** was not an efficient catalyst. The mesomeric effect of the nitrogen lone pairs in **90** could be the reason for the observed low activity and complex **91** was completely inactive.

The effect of conjugation in ligands was studied in more detail when Ito and coworkers prepared a series of DPCB-ligands with varying the substituents in the cyclobutene backbone (Figure 9).[132] All complexes enabled silver-free catalysis, but there were notable differences between the ligands. Phenyl substituted **92** turned out to be the least effective catalyst with 45% yield in the cycloalkoxylation of 1,6-enynes, whereas was the most active 1-naphthyl substituted **93** gave a 99% yield. Electronic properties were not the only factor to affect the yield, because 2-naphthyl substituted **94** provided a considerably lower 67% yield. In DFT calculations cyclopropyl substituents in complex **95** were shown to have a large contribution to the LUMO of the complex, and the complex afforded a 75% yield. Being the most active complex, **93** was also used for hydration of terminal alkyne and cyclization of propargylamine into an oxazoline, but the yields were moderate in these reactions.

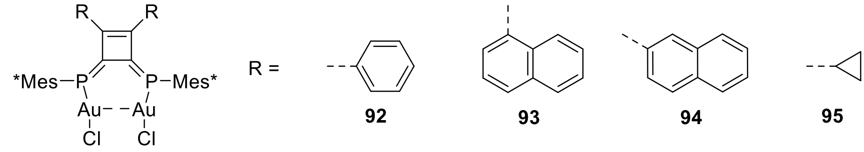


Figure 9 Phosphaalkene gold complexes with conjugated ligands

Next, the effect of conjugation was studied in monogold complexes (Figure 10).[133] Silylated alkyne complex **96** was far more active than aryl complex **97** not only in cyclization and cycloalkoxylation of 1,6-enynes, but also in hydration of terminal alkyne where they outperformed the digold complex **93**. Interestingly, the isomer **98** had considerably lower catalytic performance. No definitive reason for the difference was given, but steric hindrance could arise from the smaller P-C-C_{sp} angle in **98** (113.6(4)°) than the corresponding P-C-C_{sp2} angle in **96** (122.7(4)°). Comparing the type of conjugating group, the diaryl complex **99** was more active than the dialkynyl complex **100** in all reactions.

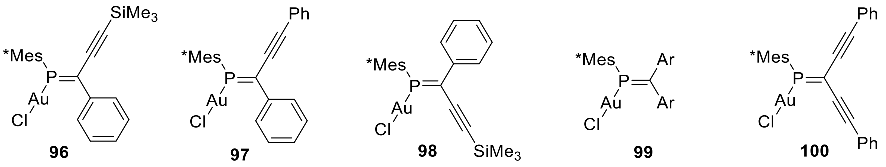
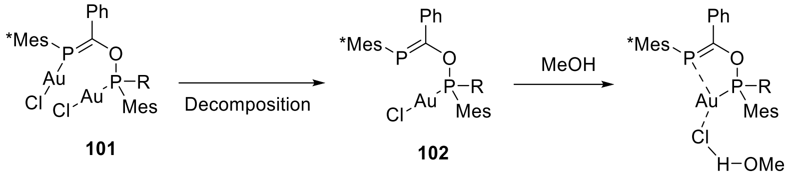


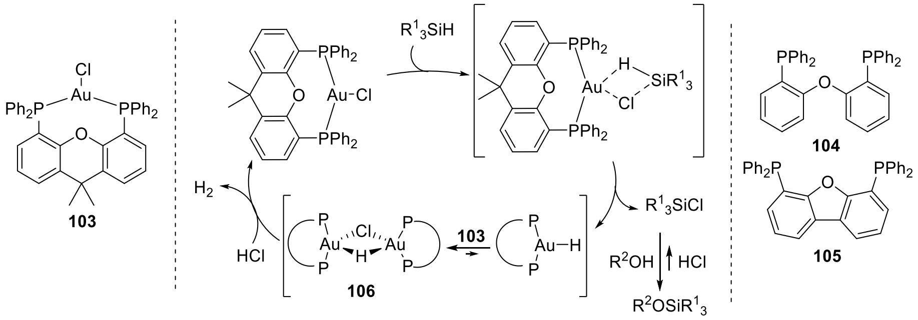
Figure 10 Phosphaalkene complexes using ligands with π-conjugation

Most recently, Ito and coworkers have prepared phosphanoxy-substituted phosphaalkenes (Scheme 33).[134] No aurophilic interaction was detected in the complex **101**, which might partly explain the worse performance compared to DPCB complexes **92-95**. During the cycloalkoxylation of 1,6-enyne, **101** partially decomposed into monogold complex **102**. The activity of this was also screened, but the yields were low even after days. The activation of **102** was attributed to the P=C-O skeleton, which was thought to increase the Lewis acidity of the gold centre and strengthen the coordination of methanol to the chloride anion. To test the latter hypothesis 1,6-enyne cyclization with **102** was performed in the presence of trifluoroethanol and the activity was as high as with the digold complex **101**.



Scheme 33 Phosphanoxy-phosphaalkene complexes for cycloalkoxylation of enynes

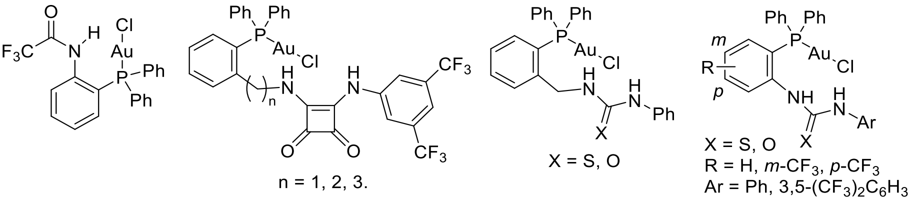
In 2005 phosphine complex **103** was reported as a robust catalyst for hydrosilylation of alcohols (Scheme 34).[135] The catalytic system was highly selective: alcohols were hydrosilylated in the presence of halides, aldehydes, alkenes or alkynes, and primary alcohols could be reacted while tertiary alcohol remained unreacted. Phenol and tertiary alcohols could be hydrosilylated by raising the temperature. Activation of the catalyst was explained by large P-Au-P bite angles, which could activate the Au-Cl bond. Only very little activity was seen with DPEPhos complex **104** and DBFPhos **105** failed to catalyze the reaction completely, indicating that the tricoordinated Au-center was essential for the catalysis.[136] Originally the proposed mechanism was based on monometallic Au(I) hydride, but in thorough spectroscopic investigation a digold Au(I) hydride **106** was identified as the probable catalytic species. The hydride is formed in a α-bond metathesis between the complex **103** and hydrosilane, which generates the chlorosilane required for the silylation.



Scheme 34 Additive-free silylation of alcohols

2.3.3 H-BOND DONOR CONTAINING LIGANDS

Several groups have studied ligands with a hydrogen bond donor creating a vacant coordination site and the work from our research group is presented in Publication II. Before that in 2017 Sen and Gabbaï studied an ambiphilic phosphine complex **107** for catalysis (Figure 11).[137] Using NMR spectroscopy they found out that the complex was in a concentration dependant monomer-dimer equilibrium. They applied the complex for cyclization of propargylamine and were able to detect some oxazoline product. Even though the catalytic activity of the complex was low, the result demonstrated that ligand bound H-bond donor could activate the gold center by interacting with the chloride anion.



107 **108** **109** **110**

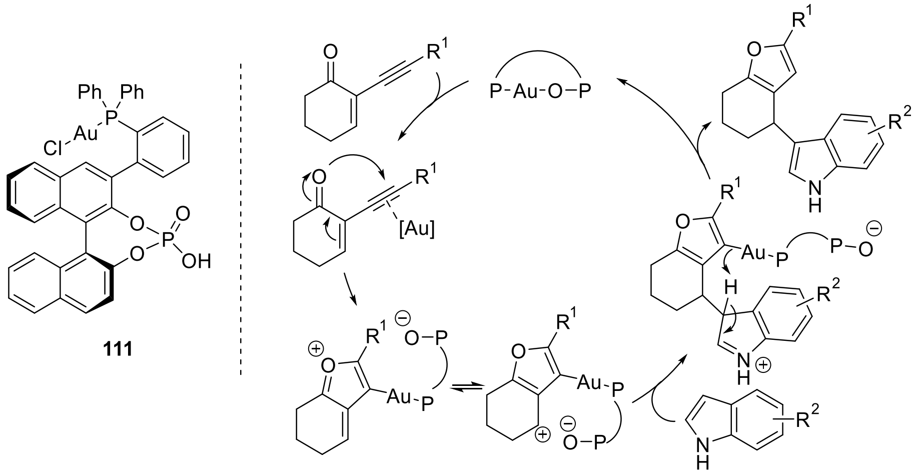
Figure 11 Au(I) complexes with H-bond donor containing ligands

Recently Echavarren, Franchino and coworkers developed this concept towards ligands containing bidentate H-bond donors, such as ureas and squaramides with increased catalytic activity in the oxazoline synthesis.[138] Clear trends in activity were seen in different complexes. In squaramide complexes **108** the shortest linker between the squaramide and the aromatic ring was favored: with 5 mol% catalytic loading and 24 hours 98% of oxazoline formed with the shortest linker. The conversion dropped to 57% with one added CH_2-group and the longest linker gave only a trace of the product. In complexes **109** the urea created a bit more effective catalyst than thiourea, but both of these complexes were less active than complex **107** indicating that also the type of the H-bond donor played a crucial role in addition to the length of the linker. Since both studied thiourea complexes failed to perform the catalysis, the authors stated that the thiourea moiety likely coordinates strongly to the metal center preventing the desired coordination of the substrate. Finally, the H-bond donor strength was assessed with different electron withdrawing groups in complexes **110**. Electron withdrawing groups were beneficial to the catalysis, which was speculated to derive from two effects; greater stabilization of the abstracted chloride by stronger H-bond donors and assisting in protodeauration step by increased acidity of the protons in the ligand. A thorough kinetic analysis combined with DFT calculations demonstrated that the turnover-limiting steps of the oxazoline cyclization consisted of chloride abstraction and cyclization steps.

After using squaramides as a part of the ligand, it was discovered that they can be used as separate additives to activate common precatalysts PPh_3AuCl

and IPrAuCl.[139] Extra steps of the ligand design and synthesis could be avoided and no excess additive relative to the gold catalyst was needed. Oxazoline synthesis and other alkyne activations proceeded smoothly with 5 mol% catalytic loading when the temperature was slightly raised to 35 °C, which was needed for the disaggregation of the squaramides.

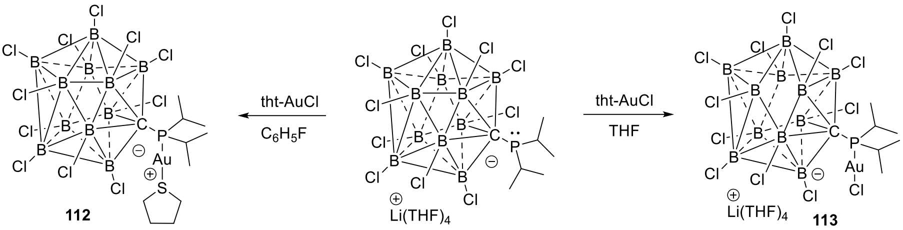
Finally, Marinetti, Guinchard and coworkers attached a chiral phosphoric acid to a phosphine ligand creating complex **111**.[140] Even though the majority of catalytic experiments were made with a silver additive, the pure chloride complex also displayed remarkable catalytic activity. With a low catalytic loading of 0.2 mol% the complex catalyzed a tandem cycloisomerization/nucleophilic addition at room temperature reaching as high *ee* as 94%. The precatalyst **111** was thought to react with a basic nucleophile, which results in creating the active catalyst via HCl elimination. The high enantioselectivity was explained by an intermediate in the catalytic cycle, where the chiral phosphate interacts with the prochiral carbon leading to nucleophilic attack and formation of the chiral center.



Scheme 35 Cycloisomerization followed by an enantioselective nucleophilic addition

2.3.4 ANIONIC LIGANDS

Lavallo and coworkers utilized perhalogenated carba-*closo*-dodecaborate anions as ligands (Scheme 36).[141] Depending on the metalation solvent either the thiophene-coordinated complex **112** or the chloride complex **113** could be isolated, both of which were able to catalyze intermolecular alkyne hydroamination without additives. Using **112** the catalyst loading could be lowered to 0.001 mol% and still achieve yields over 90%. The exceptional activity was explained by two factors: the proximity of the anionic moiety to the metal center, where it could stabilize electrostatically the reaction intermediates and the carborane preventing the phosphine dissociation elongating the lifetime of the catalyst.



Scheme 36 Synthesis of gold complexes with an anionic carborane ligand

Anionic NHC-complexes **114** derived from malonates were studied by Bastin, César and coworkers (Figure 12).[142] They were able to cyclize 1,6-enynes, but the reaction required elevated temperature and reaction time of 18 hours. Notably, the complexes were active in toluene, whereas typical cationic Au(I) complexes benefit from a more polar solvent. The cation in the complex played an important role and differences were significant. Lithium was the least active which was explained by stronger interaction between lithium and the oxygen atoms of the malonate. The difference between tetraethylammonium and potassium was justified by the lower solubility of forming KCl than Et_4NCl, which leads to more efficient formation of the active cationic complex.

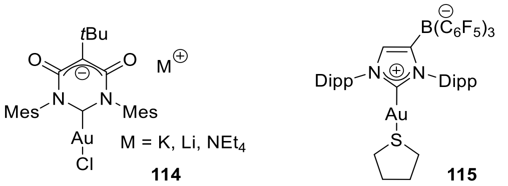
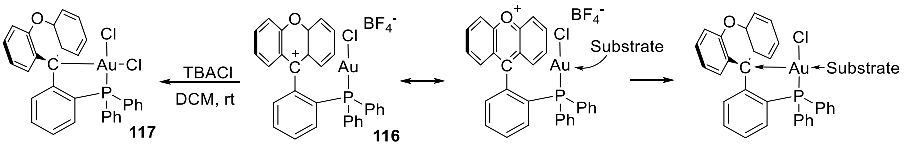


Figure 12 Gold complexes formed with anionic ligands

Tamm incorporated the weakly coordinating boron anion to the backbone of the NHC-complex **115**.[143] As with complex **114**, this neutral complex did not require a polar solvent to catalyze the cyclization of 1,6-enynes into completion in 5 minutes in toluene or diethyl ether. This type of complex was also suitable catalyst for alkyne hydration, whereas [IPrAu(tht)][BArF] or IPrAuCl activated with NaBArF showed only very little activity.[144]

2.3.5 Z-TYPE LIGANDS



Scheme 37 Oxidation and substrate activation of Z-type ligand-Au complex

Gabbaï and his group developed the idea of additive free catalysis by a Z-type ligand for gold.[145] They reasoned that the accepting orbitals of a carbenium ion are low in energy, which would lead to enhanced Lewis acidity and contribute to oxidizing properties. This was confirmed by treating the complex **116** with chlorides leading to an oxidized complex **117** because of the chloride push-carbenium pull effect (Scheme 37). Complex **116** was an efficient catalyst for cyclization of propargylamide into oxazoline, and it was proposed that the substrate could induce similar push effect as a chloride. PPh_3AuCl could not be activated with separate carbenium ion additives, so the proximity of carbenium ion was vital to the activation of the gold center.

This system was enhanced by using an acenaphthene backbone for the ligand.[146] The position of gold was more optimal in complex **118**: it resides on the π-hole which was computed to be in the middle of the xanthylium unit (Figure 13). This Au-π^+ interaction was reported as the source of catalytic activity. The oxidation of the complex could not be verified this time, since **118** decomposed when treated with chloride anions. The complex was far more active in several reactions than the previous **116**. For example, a quantitative yield in oxazoline synthesis was reached in 20 minutes with 2 mol% catalyst *vs.* the 21% yield with **116**. In the cyclization of 1,6-enynes the difference was even more evident: **118** afforded a yield of 69% whereas **116** could only produce 2% of the desired product. An *N*-methylacridone derivative **119** was also studied, but this turned out to be inferior in catalysis. The reasoning was that the interaction between the chloride anion and a hydrogen from the methyl group, which stabilized the complex.

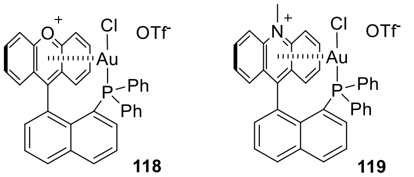


Figure 13 Ligands utilizing a π-hole for activation

2.4 FUNCTIONALIZED LIGANDS IN GOLD(III) CATALYSIS

2.4.1 DICHLORO(2-PYRIDINECARBOXYLATO)GOLD(III)

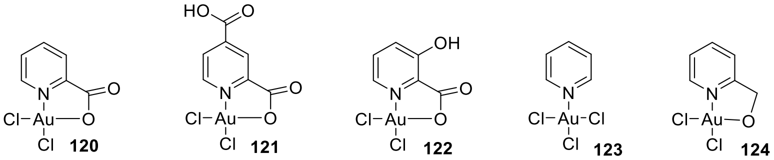
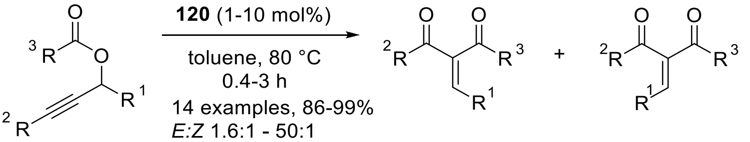


Figure 14 Au(III) complexes with N-coordinated pyridine ligands

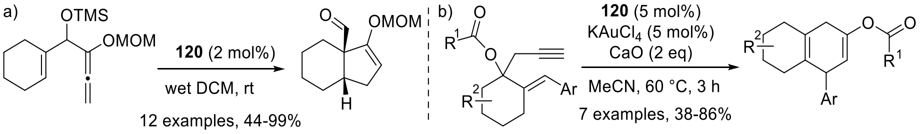
In 2004 Hashmi and coworkers published Au(III) complexes **120-124** with N-coordinated pyridine ligands (Figure 14).[147] Using these complexes, the catalysis of phenol synthesis had an induction time and the reactions were initially slower, but overall yields were higher than with gold salts, since no catalyst deactivation occurred. These complexes were extensively studied in different variations of the phenol synthesis, but it was dichloro(2-pyridinecarboxylato)gold(III) (**120**), also known as $PicAuCl_2$, that became one of the most widely utilized Au(III) precatalysts.

Wang and Zhang used $PicAuCl_2$ in converting propargyl esters into *α*-ylidene-*β*-diketones (Scheme 38).[148,149] The reactions were warmed to 80 °C, where $PicAuCl_2$ had better selectivity between *E* and *Z* isomers than gold salts. Cationic Au(I) complexes could not catalyze the reaction efficiently.



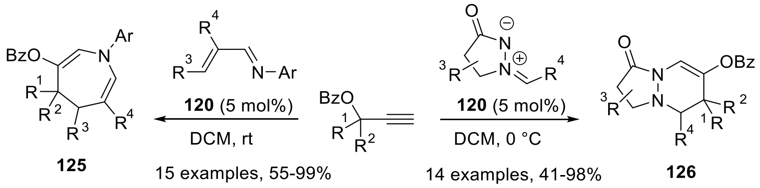
Scheme 38 Isomerization of propargyl esters into α-ylidene-β-diketones

Shortly after the same authors used $PicAuCl_2$ in a [3+2] cycloaddition between enones and allenes, which produced a quaternary center with excellent stereocontrol (Scheme 39a).[150] Zhang also used $PicAuCl_2$ to synthesize 1-carboxycyclohexa-1,4-dienes from 1,5-enynes (Scheme 39b).[151] The stability of $PicAuCl_2$ was not enough to produce high yields with all substrates, so $KAuCl_4$ was added to scavenge any pyridine-2-carboxylate originating from the decomposing catalyst.



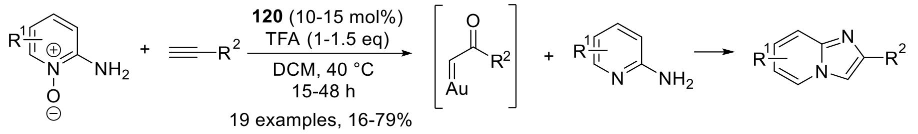
Scheme 39 $PicAuCl_2$ catalyzed cyclizations

Toste and coworkers used $PicAuCl_2$ first in the synthesis of azepines **125** in 2008 (Scheme 40). In this [4+3] annulation the Au(III) complex gave considerably higher yields than cationic Au(I) complexes.[152] Shortly after their original finding, they fused propargyl esters with azomethine imines to form cycloadducts **126**.[153]



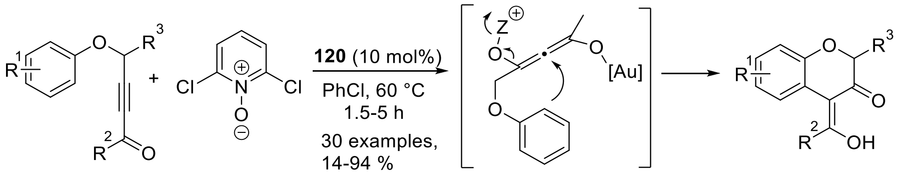
Scheme 40 Cycloadditions using propargyl esters

$PicAuCl_2$ has been a suitable catalyst for tandem reactions starting with oxidation by *N*-oxides. Toste utilized this method of creating a metal carbene in the synthesis of imidazo[1,2-*a*]pyridines (Scheme 41).[154] $PicAuCl_2$ and 2-aminopyridine *N*-oxide first converted the alkyne into the metal carbene, which then reacted with the formed 2-aminopyridine. Again, $PicAuCl_2$ was more efficient than cationic Au(I) complexes or gold salts in this reaction.



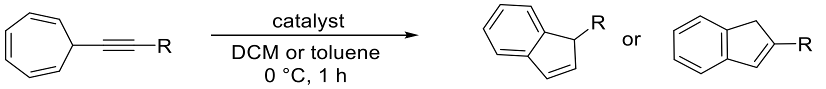
Scheme 41 Synthesis of imidazo[1,2-a]pyridines

Ji and coworkers discovered an oxidation-cyclization cascade of ynones, which led to 4-substituted chroman-3-ones (Scheme 42).[155] The narrow catalyst screen indicated that cationic Au(I) complexes were not able to catalyze the reaction.[155]



Scheme 42 Synthesis of chroman-3-ones

In many instances $PicAuCl_2$ has been used to demonstrate the different products forming between Au(III) and cationic Au(I) catalysts. Echavarren and coworkers noticed that the formed product depended on the catalyst used in a rearrangement of 1,3,5-cycloheptatriene-alkynes into indenes (Scheme 43).[156] When comparing Au(III) catalysts, $PicAuCl_2$ afforded cleaner reaction than $AuCl_3$.

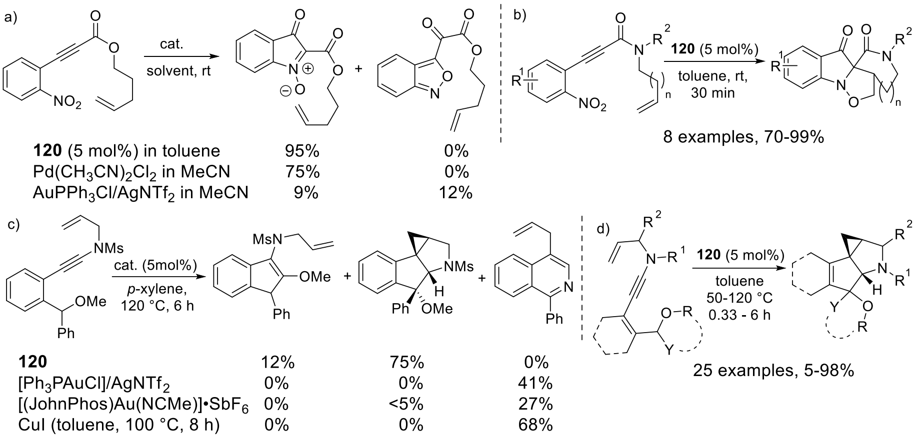


120 (1 mol%) 15 examples, 55-88 %

Tris(2,4-di-*tert*-butylphenyl)phosphite-Au-SbF_6 (5 mol%) 21 examples, 23-76 %

Scheme 43 Isomerization of 1,3,5-cycloheptatriene-alkynes

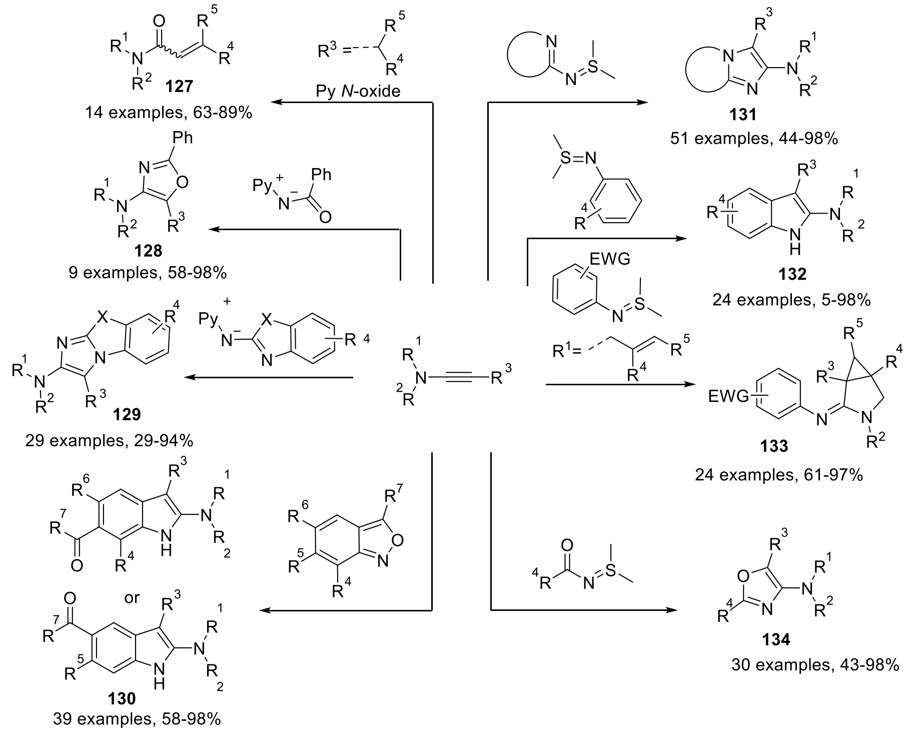
Verniest's group investigated gold catalysts in cycloisomerization of nitroalkynes and found that $PicAuCl_2$ was highly selective towards the 5-*exo*-dig cyclization which formed isatogens (Scheme 44a).[157] When using a substrate with an amide moiety, the reaction continued to form 2-spiropseudoindoxyls, which were speculated to be potential scaffolds for drug research (Scheme 44b). Similar phenomenon was noticed by Davies when *N*-allyl ynamides were attempted to cyclize into fused N-heterocycle scaffolds (Scheme 44c).[158] Cationic Au(I) complexes formed an indene and CuI an isoquinoline as the major product from the same substrate, but with the Au(III) catalyzed reaction four sp^3-carbon centers could be formed and a diverse product library was synthesized (Scheme 44d).



Scheme 44 a) Synthesis of isatogens, b) synthesis of 2-spiropseudoindoxyls, c) a successful synthesis of a indole with a fused N-heterocycle and d) general reaction scheme for the isomerization of *N*-allyl ynamides

When discussing the use of PicAuCl$_2$ in the past decade, the various ynamide activations must be mentioned (Scheme 45). Davies noticed that many of these reactions with PicAuCl$_2$ required elevated temperature, but still in the case of α,β-unsaturated amides **127** the reaction was cleaner than with AuBr$_3$ room temperature.[159] Similar observation was made in the synthesis of trisubstituted oxazoles **128** from pyridine-*N*-aminides and ynamides where PicAuCl$_2$ provided better yields than Au(III) salts, but more importantly it offered a cleaner reaction compared to cationic Au(I) catalyst.[160] The scope of products could be broadened to larger fused products **129** by using *N*-heteroaryl-pyridinium-*N*-aminides instead of pyridine-*N*-aminidines.[161] Finally, after the phenol synthesis PicAuCl2 was the catalyst of choice for Hashmi and coworkers in ynamide activations. They reacted ynamides with anthranils at room temperature to form substituted indoles **130**, when Au(I) catalysts yielded only quinoline scaffolds.[162] Reactions with sulfilimines required elevated temperature, but they successfully produced fused imidazoles **131**, substituted indoles **132**, or 3-azabicyclo[3.1.0]hexan-2-imines **133**.[163–165] Lastly, the reaction with *N*-acyl sulfilimines formed 4-aminooxazoles **134** in similar conditions as the reaction with pyridine-*N*-aminides (**128**).[166]

The strengths of PicAuCl$_2$ are the ease of handling and good selectivity, but the reactions are often sluggish at room temperature. In some cases an induction period has been detected, so especially in harsh conditions PicAuCl$_2$ might act just as a precatalyst and the actual catalytic species is unknown.



Scheme 45 A variety of ynamide activations using $PicAuCl_2$

2.4.2 OTHER *N*-COORDINATED PYRIDINE LIGANDS

Che, Wong and coworkers studied a group of cyclometallated Au(III) complexes **135-140** which contained a bidentate *C,N*-ligand (Figure 15).[167] All complexes were able to catalyze the A3-reaction in water, but six-membered ring cyclometallated complexes were strikingly more efficient than the five-membered ring complexes. The synthesized propargylic amines could be reacted further into chiral allenes by just changing the reaction solvent from water to MeCN. Lastly, the PEG-linked catalyst **141** enabled catalyst recycling and it could catalyze the A3-reaction efficiently for up to 12 cycles.

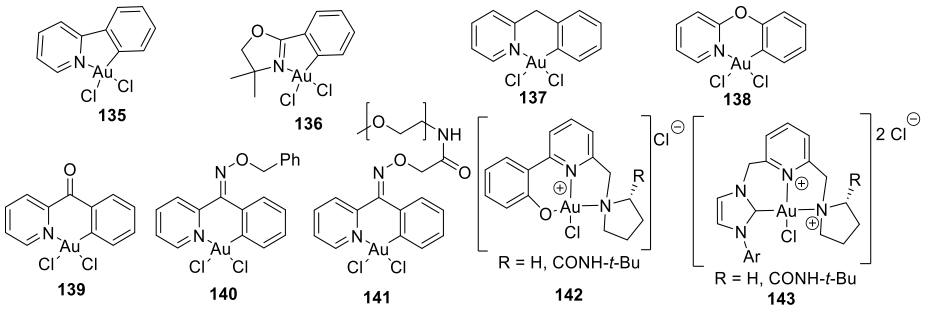
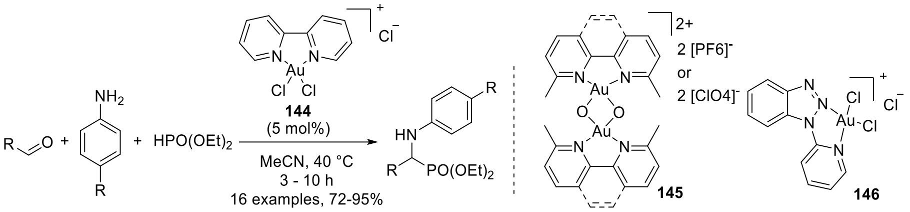


Figure 15 Au(III) complexes with N-coordinated pyridine ligands

Sánchez, Iglesias and Debono published cationic *O,N,N*-pincer Au(III) complexes **142**, which were used for hydrogenation of diethyl benzylidenesuccinate and hydrosilylation of styrene, benzaldehydes and acetophenone.[168] The amide moiety in the pyrrolidine ring was crucial for high enantiomeric excess in the hydrogenation reaction, but the unsubstituted pyrrolidine ligand led to higher yields in hydrosilylation of benzaldehyde, acetophenone and styrene. Later they published an improved C,N,N-pincer **143** which increased the enantioselectivity in asymmetric hydrogenation.[169]

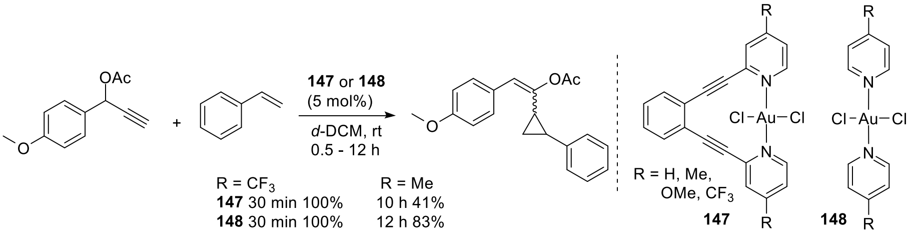
Zhang and Zhu studied the catalytic activity of **144** in Kabachnik-Fields reaction (Scheme 46).[170] The bipyridine complex turned out to be more efficient for the C-P bond formation than other Au(III) catalysts including PicAuCl₂.



Scheme 46 Cationic Au(III) complexes with *N*-coordinated pyridine ligands

Lee and coworkers synthesized Au(III)-oxo complexes **145** with bipyridine and phenanthroline ligands.[171] The former were better catalysts for hydroamination of alkynes than the latter, but they also outperformed Au(III) salts and **144**. Bipyridine could be replaced with a pyridyltriazole ligand in complex **146**.[172] This stable cationic complex was a suitable catalyst for Meyer-Schuster rearrangement and by addition of NCS the sequential allene halogenation took place, which offered a synthesis route towards α-chloroenones in good yields.

The synthesis of these cationic Au(III) complexes is very straightforward: the complexes can be obtained by mixing the ligands with KAuCl4. The alternative anions can be introduced as potassium and sodium salts without the need for silver, which circumvents the problematic removal of silver presented in chapter 2.1.2.



Scheme 47 Au(III) complexes with *trans*-coordinated pyridine moieties

Trans-coordination of the two pyridine moieties has also been studied (Scheme 47).[173] For the first time a *trans*-chelating bidentate ligand in **147** could be used in Au(III) catalysis, although the analogous bis(pyridine) complexes **148** were slightly more efficient catalysts for the cyclopropanation of styrene with propargyl ester. The difference was explained by stronger coordination of Au(III) to the bidentate ligand, which was observed in ^{15}N NMR measurements and DFT calculations. The catalytic efficiency could be modulated by the electron density of the pyridines: CF_3-substituted ligands delivered clearly faster reactions than Me-substituted and OMe-substituted. The results were consistent for both complex types, which indicates that they react with the same mechanism.

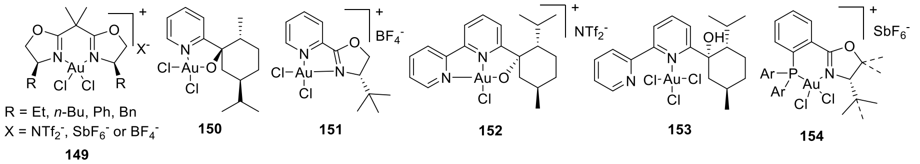


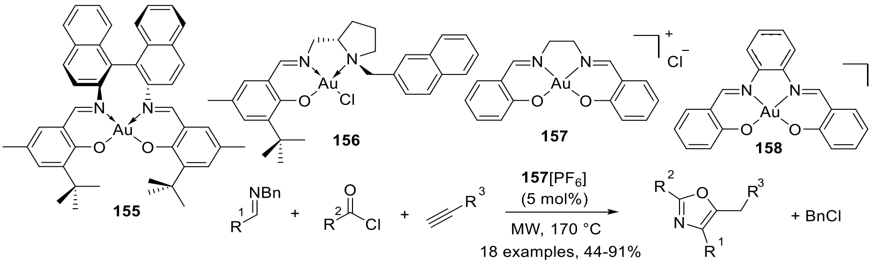
Figure 16 Au(III) complexes with *N*-coordinated pyridine and axazoline ligands

Kato and Akita synthesized bisoxazoline (box) complexes **149** which cyclized 1,5-allenynes notably faster than gold or platinum chlorides, but in hydroalkoxylation of alkynes higher turnovers could be reached with Au(III) salts (Figure 16).[174,175] Fiksdahl and coworkers used these complexes for the cyclopropanation reactions and detected that they also strongly activate the *cis*-to-*trans* isomerization of the cyclopropyl products.[176] The (−)mentholate-Au(III) complex **150** was far less active compared to the cationic complexes. The Au(III)-box complexes were studied in the synthesis of spiroketals where the cationic pyridine-oxazoline complex **151** exhibited outstanding activity without any additives.[177] An acid additive improved the activity only slightly, although the opening of the oxazoline ring was not studied as was done with similar complex **37**. Despite the chiral ligand, only minor enantioselectivity was reached and **151** could not be regarded as a universal catalyst as low conversions were detected in cyclization of 1,6-enynes.[178]

Similar reactivity in the cyclopropanation was observed with the cationic *N,N,O*-Au(III) complex **152**, although the *cis-trans* selectivity was lower than with Au(III)-box complexes.[179] The neutral complex **153** was unstable, which did not lead to greater catalytic activity. Recently, Fiksdahl, Erdélyi and coworkers have studied *P,N*-Au(III) complexes **154** in the cyclization of 1,6-enynes and the cyclopropanation.[180] These Au(III) complexes exhibited low catalytic activity with the enyne, whereas corresponding Au(I) complexes with SbF_6^- counteranion reached moderate conversions. Contrarily, the cationic Au(III) showed its advantage in the cyclopropanation and they afforded higher conversions in minutes than the Au(I) complexes in several hours.

2.4.3 SCHIFF BASES

After the first complete characterization of the Au(III) salen complexes in 2001 several groups studied Au(III) complexes with Schiff base ligands for catalysis.[181] Corma and coworkers applied complexes **155** and **156** successfully in homocoupling of boronic acids and hydrosilylation of carbonyls and olefins (Scheme 48).[182,183] Hydroamination of alkynes with the same complexes required NH_4PF_6 as an acidic promoter, but in these conditions higher yields were obtained than with cationic Au(I) catalyst.[184]



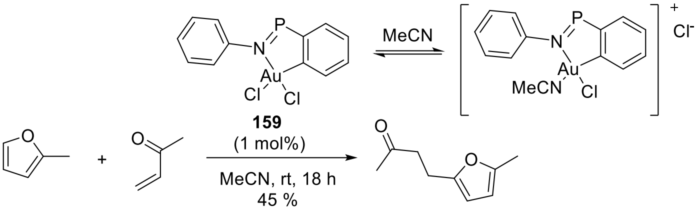
Scheme 48 Salen-Au(III) complexes and a multicomponent oxazole synthesis

Wong, Che, Lo and Liu synthesized salen-Au(III) complex **157** and studied its catalytic abilities in A3-coupling in water.[185] With mild heating and catalyst loading of 0.05 mol% a TON of 820 could be reached. The group also reported high diastereoselectivity in the case of chiral amines. The salen complexes were slightly more effective catalysts in these conditions than the *C,N*-complex **135**. Cai and Chen have studied the similar salen complex **158** in alkyne hydration, but the reaction did not occur without an acid additive.[186] Notably, acids were more effective additives than silver salts for the hydration.

Strand and coworkers used **157**[PF_6] to catalyze a multicomponent reaction between imines, acid chlorides and alkynes affording oxazoles as a product.[187] The reactions were conducted in high temperatures and 1 mol% of the salen complex afforded near quantitative yields, whereas $AuCl_3$ was needed in 30 mol% loading for efficient catalysis. In this study, the rearrangement of oxazolines into oxazoles was also investigated. Commonly, oxazoline has been regarded as the Au(I) product of gold catalyzed cyclizations, while Au(III) is responsible for the formation of oxazole.[188] The research group found out that the rearrangement can happen rapidly with acid catalysis in elevated temperatures offering an alternative route for the rearrangement in this common gold catalyzed reaction.

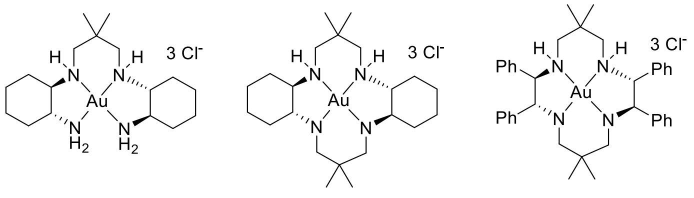
2.4.4 OTHER *N*-COORDINATED LIGANDS

Urriolabeitia, Contel and coworkers studied iminophosphorane *C,N*-pincer ligands for Au(III) (Scheme 49).[189] They found out that the complex **159** could catalyze the addition of methyl vinyl ketone to methyl furan without any additives, although the activity could be considerably boosted with AgOTf. The activity of the complex was speculated to arise from the combination of a polar solvent, trans effect from the arylic carbon and the zwitteranionic nature of the complex. The stabilizing effect of the C,N-backbone was noticed, when a similar complex with only the nitrogen coordinated to gold decomposed during catalysis.



Scheme 49 Gold catalyzed addition of methyl vinyl ketone to a furan

Fiksdahl's group synthesized tetradentate-cyclam ligands and evaluated their suitability for alkyne carboalkoxylation and cyclopropanation reactions (Figure 17).[190] The less sterically hindered complex **160** was the fastest catalyst for both reactions, but unfortunately none of the complexes showed any enantioselectivity in the reactions. Complex **162** was found highly unstable in the catalysis studies, which led to very fast conversion of the starting materials, but low yields of the wanted products.

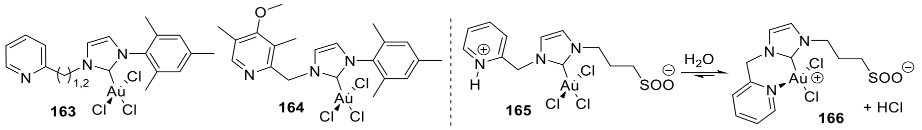


160 **161** **162**

Figure 17 Au(III) complexes with tetra N-coordinated ligands

2.4.5 PENDANT *N*-HETEROCYCLE CONTAINING LIGANDS

Limbach and coworkers studied NHC complexes **163** with a pendant pyridine arm (Scheme 50).[55] The synthesized Au(I) complexes suffered from instability but the corresponding Au(III) complexes were more stable, however there was very little catalytic activity in the phenol synthesis even with a silver additive. Helaja's group confirmed the low activity of **163** in the same reaction without the silver additive. Still, the concept of creating temporarily a free coordination site to the gold center with pyridine coordination seemed viable. The conversion could be improved by lengthening the reaction time and with mild heating. More interesting results were gained from designing a electron rich pyridine arm for **164**, which made the catalyst notably without any additives compared to **163**.[191] This complex was also moderately active in hydroamination of alkynylanilines into indoles. Michelet and coworkers studied water-soluble derivatives of similar complexes. The complex **165** turned out to be a very effective catalyst for lactonization of alkynoic acids in toluene/H_2O-mixtures.[192] Remarkably, no hydration product was observed in these conditions and the catalyst could be recycled simply by separating the NHC-Au-complex containing aqueous phase. Mechanistic evidence on the chelation of the ligand was gained by ^{1}H NMR spectroscopy, where it was detected that the methylenic protons of the arm become diasterotopic due to the conformational rigidity of the metallocycle **166**.[193] Using terminal alkynes the catalyst loading could be lowered to 0.1 mol% and TOF of 1000 h^{-1} was reached. Corresponding Au(I) complexes were initially more active in these reactions, but a clear difference was seen in the catalyst recycling, when the TOF started to decrease after the 4th cycle, where the Au(III) complexes reached ten cycles with constant TOF values.



Scheme 50 NHC-Au(III) complexes of ligands with a pendant pyridine moiety

Recently, Fiksdahl and Reiersølmoen synthesized a group of Au(III) complexes **167-171** with a pendant pyridine or quinoline group (Figure 18).[194] Silver salts and heat were explored to create N-coordinated species, but these efforts failed. Electron density of the N-heterocycle in **168** was increased with methoxy group in the same manner as in **164**, but even these complexes did not lead to *N*-coordination. A clear trend in stability was detected with the complexes, when quinoline complexes in MeCN started to decompose in a day while pyridine complexes remained intact. The catalytic activity of the neutral complexes was assessed in the cyclopropanation reaction, and the level of activity was similar between the pyridine and quinoline complexes. It was noted that the increased electron density of the complex **168** was beneficial for the catalysis. All complexes were able to catalyze the cyclopropanation reaction, but in the catalyst screening it was reported that the cationic complex **151** was remarkably more active once again.

In addition to pyridine and quinoline, pyrazole has also been found as a suitable coordinating moiety. Messerle used NHC-ligands containing two pyrazole arms with both Au(I) and Au(III) catalysis.[195] Even though the majority of the hydroalkoxylation reactions were reported with NaBArF present, it is of worth noting that the complex **172** was quite active on its own. The reaction went into completion without additives in 68 minutes vs. the 10 minutes with NaBArF. The activity of the corresponding Au(I) complex was reported only with NaBArF present, but in these conditions the Au(III) complex was far more active.

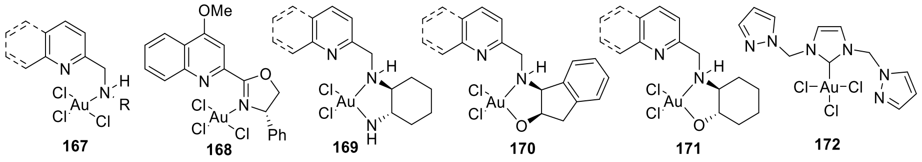


Figure 18 Au(III) complexes with pendant *N*-heterocycles

3 RESULTS AND DISCUSSION

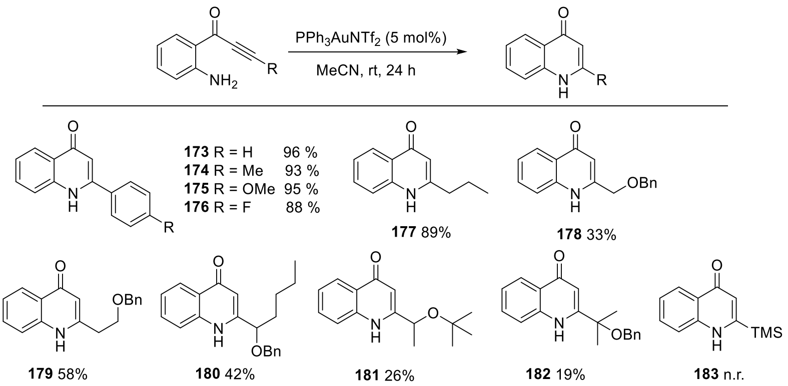
3.1 PUBLICATION I: GOLD CATALYZED ALKYNE HYDROAMINATION

4-Quinolones are a class of compounds with diverse antibacterial, antiviral and antitumor properties.[196–198] Traditionally, the synthesis of these compounds has required harsh conditions.[199] Modern organic synthesis can avert the use of strong bases or greatly elevated temperature, and especially transition metal catalysis has enabled more diverse synthetic routes with milder conditions towards quinolone structures.[200] In our first publication, we investigated the synthesis of 2-substituted 4-quinolones through a gold catalyzed alkyne hydroamination.

In the study, multiple different gold species were tested for their suitability for the cyclization. We began the screen from a heterogeneous catalyst where gold nanoparticles were bound to a carbon carrier material, but even prolonged heating did not yield any product. We quickly moved on to homogeneous catalysis with simple Au(III) sources $HAuCl_4$ and $KAuCl_4$, but the reaction did not proceed at room temperature even with 10 mol% catalyst loading. The highest yield of 61% was achieved with $KAuCl_4$ in EtOH in 70 °C after 24 hours. Also, $PtCl_2$ was used as a catalyst, but the yields remained low in the tested conditions. Finally, heating the reaction to 90 °C in toluene and 5 mol% catalyst loading yielded 17% of the desired product.

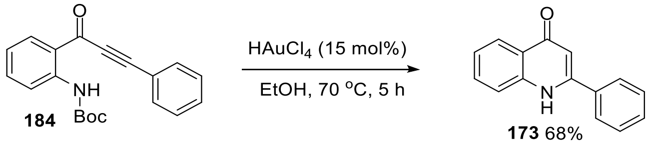
We decided to move on from gold salts to cationic gold(I) complexes and immediately a rise in activity was noticed. IMes-$AuNTf_2$ afforded 40% of the desired product at room temperature with 5 mol% catalyst loading in DCM. The outcome was improved by changing the solvent to MeCN and the 51% yield was recorded. PPh_3AuNTf_2 was not as active in DCM, but MeCN was a suitable solvent choice and 96% of the desired product was isolated after 24 hours at room temperature with 5 mol% catalyst loading. Catalyst decomposition was observed with both cationic Au(I) complexes in DCM, so while the initial rate of the reaction was higher in DCM than in MeCN, the σ-donating ability of MeCN presumably enhanced the stability of the complexes and eventually led to almost quantitative yields.

With these conditions we investigated the substrate scope with varying alkyne part (Scheme 51). Neutral and electron rich aryl alkynes **173-175** provided excellent yields and the quinolone yields from electron poor aromatic alkyne **176** or linear aliphatic alkyne **177** were not significantly lower. Lower yields were recorded with different alkyne substrates with branched aliphatic chain and benzyl ether **178-182**. This indicates that the reaction was affected by the bulkiness of the substrate and the vicinity of the alkoxy group. A TMS-protected alkyne was unable to go through the cyclization and no quinolone product **183** was detected.



Scheme 51 Synthesis of 2-substituted 4-quinolones from 1-(o-aminophenyl)-2-propyn-1-ones. Yields presented are isolated yields.

In addition to nucleophilic attack of a free amine nucleophile, some catalytic tests were made with a *N*-Boc-protected substrate **184**. To our surprise, the cationic Au(I) complexes failed to catalyse the cyclization and no quinoline product could be isolated with either PPh_3AuNTF_2 or $IMesAuNTf_2$ in MeCN. The highest yield was recorded with 15 mol% loading of $HAuCl_4$ in EtOH and the Boc group was cleaved during the reaction (68%). As the free aniline did not react under these conditions, it could be hypothesized that prior its cleaving the Boc group chelates the gold(III) chloride and this way leads to a successful catalysis.

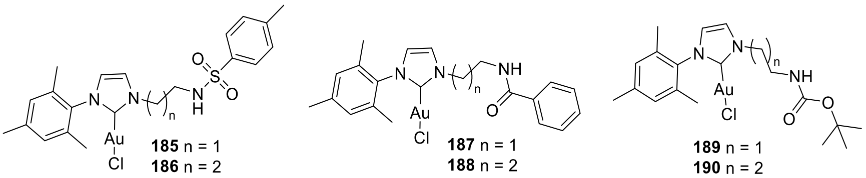


Scheme 52 Quinolone synthesis using a *N*-Boc protected substrate

3.2 PUBLICATION II: FUNCTIONALIZED LIGAND ACTIVATION IN AU(I) CATALYSIS

In our second publication we designed a hemilabile ligand for Au(I) catalysis based on amide-tethered NHC-ligands. In addition to the H-bond donor in the ligand, the catalytic system requires another H-bond donor either from a substrate or an acid additive to create a vacant coordination site to the gold center.

We started the study by synthesizing imidazolium salts with a sidearm of two or three methylene groups and an amide or sulfonamide group attached to the imidazole ring. The salts were reacted with Ag_2O to form an NHC-Ag complex, which were treated with Me_2SAuCl and the gold complexes **185-190** were formed through transmetallation.

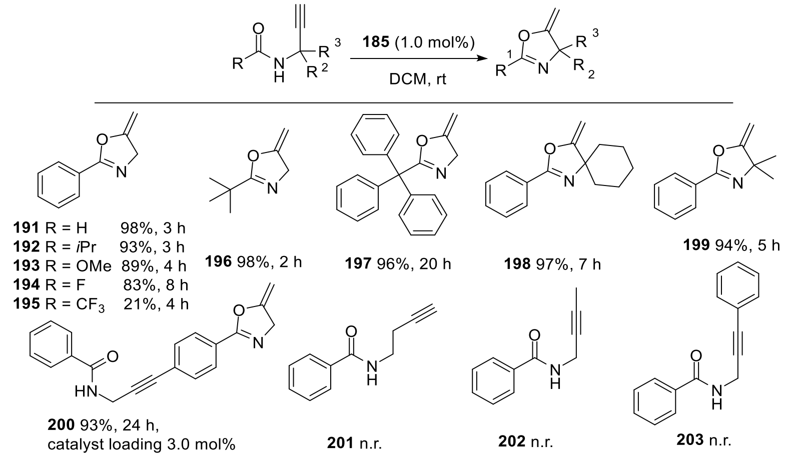


185 n = 1
186 n = 2
187 n = 1
188 n = 2
189 n = 1
190 n = 2

Figure 19 NHC-Au(I) complexes with functionalized sidearms

The activity of these complexes was determined in cycloisomerization of *N*-(prop-2-yn-1-yl)benzamide to 2-phenyl-5-methyleneoxazoline **191**. Shorter sidearmed complexes turned out to be more effective catalysts. The sulfonamide functionalized complex **185** was the most effective catalyst with 95% yield after 3 hours in DCM at room temperature, whereas the longer sidearmed counterpart **186** could only reach a 67% conversion. The benzoyl amide functionalized complex **187** could catalyze a 73% conversion in the same conditions, and the longer sidearmed **188** gave a poor 58% yield. The Boc-functionalized complexes **189** and **190** showed little activity and great instability: they decomposed quickly to dark nanoparticles and the catalytic activity was not studied further.

While investigating the substrate scope for the oxazoline synthesis, it was noticed that products **191**, **192** and **196** with neutral substituents were formed in excellent yields with our catalyst system (Scheme 53). Both electron donating or withdrawing groups in the aromatic ring slowed down the reaction and lowered the overall yield of oxazolines **193-195**. Notably, the CF_3-substituted substrate **195** led to catalyst decomposition during the first hours of the reaction. Bulky substrates were tolerated, but the formation of oxazolines **197-199** was slower. Unlike some other gold species, our catalyst was selective towards terminal alkynes as oxazoline **200** was isolated in an excellent yield, whereas no product was obtained from substrates **202** and **203**.[201] After a series of 5-*exo*-dig cyclizations, we attempted a 6-*exo*-dig cyclization with substrate **201** but could not detect any reactivity.



191 R = H 98%, 3 h
192 R = *i*Pr 93%, 3 h
193 R = OMe 89%, 4 h
194 R = F 83%, 8 h
195 R = CF_3 21%, 4 h
196 98%, 2 h
197 96%, 20 h
198 97%, 7 h
199 94%, 5 h
200 93%, 24 h,
catalyst loading 3.0 mol%
201 n.r.
202 n.r.
203 n.r.

Scheme 53 Oxazoline synthesis using functionalized NHC-Au(I) complexes

Since the activation is based on hydrogen bonds, the effect of ambient moisture was investigated in the oxazoline synthesis (Figure 20). We found out that the catalysis could be done in dry conditions, but the reaction did not proceed after a certain point. The rate of the reaction was increased when the amount of water was increased gradually from 0 ppm to 200 ppm. After this point, the excess water started to hinder the reaction. We reasoned that low water content could ease the anion solvation or the proton transfer, whereas a higher water content interferes with the H-bond interactions between the sidearm's functional group and chloride anion making the activation more difficult.

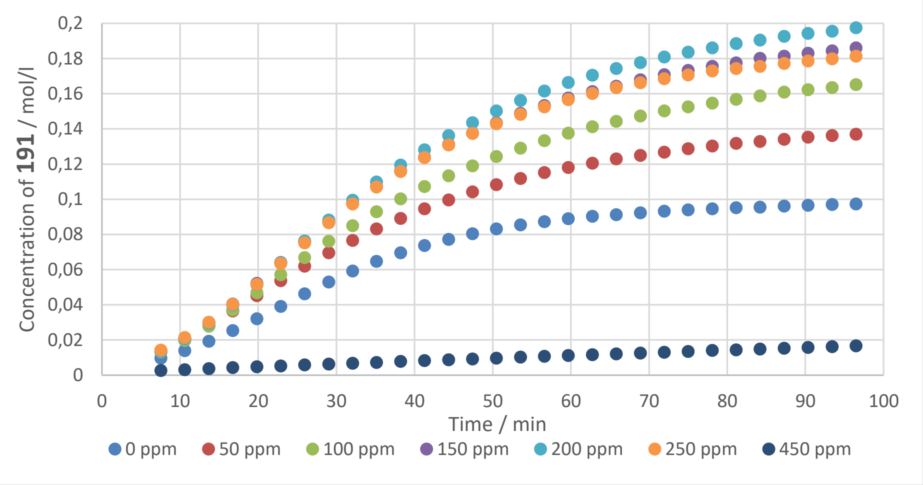
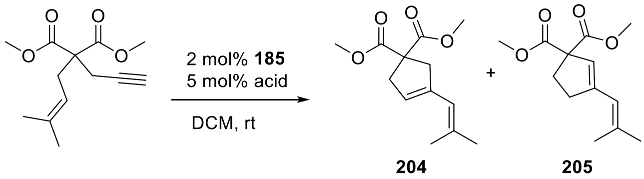


Figure 20 The effect of water on the oxazoline synthesis. Concentration of the substrate was 0.226 M and catalyst **185** 0.0023 M. The desired water content in the samples was reached by mixing dry and wet CD_2Cl_2 when loading the samples to NMR tubes in a glove box.

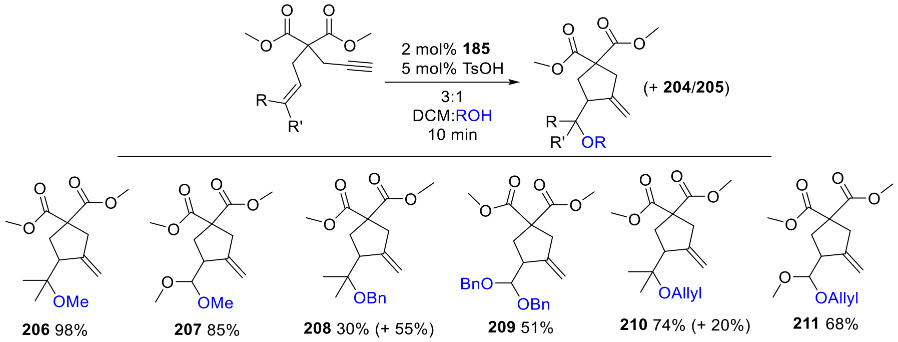
In addition to the oxazoline cyclization, we also studied the cycloisomerization of enynes. As the catalysis did not proceed in the initial conditions, we decided to use acid additives as additional H-bond donors for the activation (Table 1, entry 1). Trifluoroethanol or acetic acid could not initiate the catalysis (entries 2 and 3). The catalysis required a stronger acid; chloroacetic acid afforded 50% yield after one hour and with full conversion was reached with dichloroacetic acid in the same conditions (entries 4 and 5). Full conversion with TFA as an additive was reached in 15 minutes (entry 7). Also, using MsOH and *p*-TsOH led to full conversion, but these acids produced a mixture of two isomers (entries 8 and 9).

The optimized conditions were then used to extend the enyne cyclization with a nucleophilic attack of different alcohols (Scheme 54). The reactions reached full conversion and the highest isolated yield of the desired product was isolated with MeOH (**206** and **207**). In the case of benzylic alcohol, the methoxy group was replaced by benzylic alcohol in a transetherification reaction (**209**). This reaction did not take place when using allylic alcohol, but with these two latter alcohols a mixture of **204** and **205** was isolated from the reaction mixture (**208** and **210**).

Table 1 Screening of acid additives for cyclization of 1,6-enynes



Entry	Acid	Time	Yield (%) **204**:**205**
1	-	1 h	Trace : 0
2	TFE	1 h	Trace : 0
3	AcOH	1 h	Trace : 0
4	$ClCH_2COOH$	1 h	50 : 0
5	$Cl_2CHCOOH$	1 h	99 : 0
6	Cl_3CCOOH	40 min	99 : 0
7	TFA	15 min	99 : 0
8	MsOH	15 min	45 : 54
9	*p*-TsOH	10 min	66 : 33

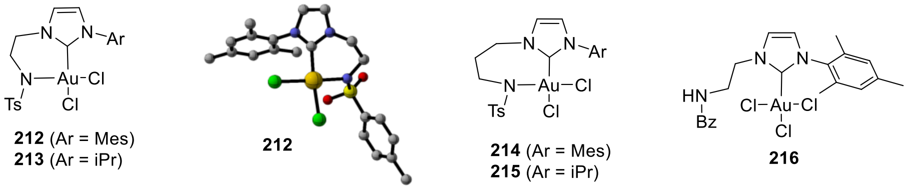


Scheme 54 Enyne cyclization followed by a nucleophilic attack of different alcohols

3.3 PUBLICATION III: ACID ACTIVATION IN AU(III) CATALYSIS

In our third publication we used our functionalized ligands for Au(III) catalysis. During the synthesis of NHC-Au(III) complexes we observed the formation of a cyclometallated species, which inspired us to study counteranion addition by addition of Brønsted acids. We applied these complexes to hydroalkoxylation of alkynes where they showed high catalytic activity in ambient conditions.

We synthesized NHC-Au complexes by varying the length of the “sidearm”, the functional group in the sidearm and the aryl group attached to the carbene ring (Figure 21). This time, the Au(I) complexes were synthesized via the silver-free mild base route developed independently by Gimeno[202] and Nolan[203], after which they were oxidized by $PhICl_2$. The obtained Au(III) complexes were treated with K_2CO_3 to eliminate one molecule of HCl from the complex and closing the ring. Cyclometallated complexes **212-215** were isolated as benchstable solids. The cyclic structure of **212** could be verified by X-ray analysis. Complex **216** remained unreactive when treated with excess K_2CO_3 or NaH in elevated temperatures.



212 (Ar = Mes)
213 (Ar = iPr)

212

214 (Ar = Mes)
215 (Ar = iPr)

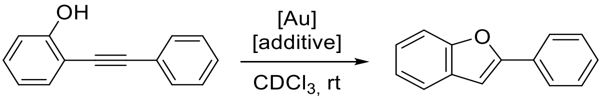
216

Figure 21 NHC-Au(III) complexes with amide functionalized sidearms

We tested the catalytic activity of our complexes in 2-phenylbenzofuran **218** formation through alkyne hydrophenoxylation (Table 2). Many transition metals have been used for studying this cyclization, but as far as we know, no examples of NHC-Au(III) catalyzed benzofuran syntheses have been reported. The acid and complex **214** were inactive on their own (entries 1 and 2). This implies that the bond between gold and nitrogen is stable, and the coordination site is not vacant. We were pleased to see that our activation hypothesis was correct, as **214** with a MsOH additive produced a near quantitative yield in 30 minutes with 2 mol% loading (entry 3). A smaller loading of 1 mol% could then be used, and the same 99% yield was recorded after 2 hours (entry 4). Replacing the mesityl group with a 2,6-diisopropylphenyl (**215**) did not affect the yield, but the shorter carbon chain in **212** and **213** led to slower reactions (entries 5-7). Our catalytic system did not fall behind in comparison to silver activation, and we were content when the acid activated **214** produced slightly faster catalysis than AgOMs treated $IMesAuCl_3$ (99% vs 54%) in similar conditions (entry 8).

After establishing complex **214** as the precatalyst of choice, different acid additives were screened for the activation. We started from weaker Brønsted acids, but to our disappointment AcOH did not yield even a trace of the desired product (entry 10). Small increase in the acidity provided small increase in the activity: Cl_2AcOH yielded 7% and Cl_3AcOH 33% of **218** (entries 11 and 12). Surprisingly, TFA afforded only a trace of product which could be explained by the high affinity of the anion towards gold (entry 13).[204] Excluding this result, generally the activity in the reaction rose hand in hand with the pKa of the Brønsted acid and fast reactions were observed using $HNTf_2$ and TfOH (entries 16 and 17).

Table 2 Screening of reaction conditions for alkyne hydrophenoxylation

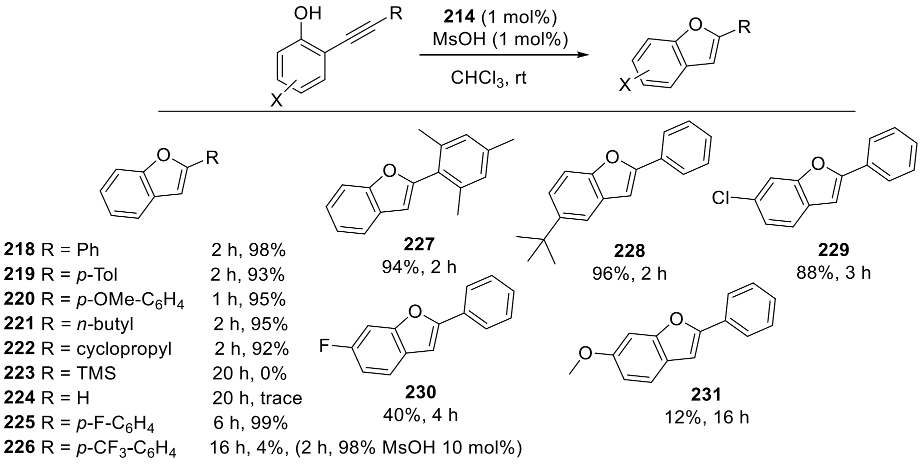


217 **218**

Entry	Gold complex	Additive	Loading of catalyst and additive (mol%)	Yield after 0.5 h (%)	Yield after 1 h (%)
1	-	MsOH	2	0	-
2	**214**	-	2	0	0
3	**214**	MsOH	2	99	-
4	**214**	MsOH	1	49	88 (99 in 2 h)
5	**212**	MsOH	1	34	64
6	**213**	MsOH	1	36	65
7	**215**	MsOH	1	47	87
8	$IMesAuCl_3$	AgOMs	2	54	99
9	**214**	AgOMs	2	5	18
10	**214**	AcOH	2	0	0
11	**214**	Cl_2AcOH	2	-	7
12	**214**	Cl_3AcOH	2	-	33
13	**214**	TFA	2	-	trace
14	**214**	HBF_4	2	-	47
15	**214**	*p*-TsOH	1	48	-
16	**214**	$HNTf_2$	1	95	-
17	**214**	TfOH	1	99	-

The scope of the reaction was studied with *o*-alkynylphenols (Scheme 55). MsOH was chosen as the activating acid since it is a milder acid than TfOH or $HNTf_2$, thus unable to activate $IMesAuCl_3$ so we can assume the detected activity stems from the opened cyclometallated species rather than gold chlorides generally. The chosen conditions lead to excellent yields in most cases (**218-222**, **227-228**), but electron poor substrates required longer reaction time possibly due to slower protodeauration step (**225-226**, **229-230**). Surprisingly, electron rich phenol (**231**) accelerated the reaction but formed a complex mixture which contained only a fraction of the benzofuran product. Our catalytic system could not turn terminal or TMS-protected alkynes into the corresponding benzofuran products (**223-224**).

The nature of the active species was studied with ^1H NMR spectroscopic measurements since Au(III) is prone to reduction. We monitored the progress of the hydrophenoxylation reaction with **214** and MsOH (0.9 mol%) and noticed no induction period or acceleration of the reaction after the initial state (Figure 22a). Still, the gold catalyst partially reduced during the reaction (Figure 22b). The reduction decelerated together with the reaction, so we suggest that the reduction is a side reaction and the initial catalytic species would be Au(III) and Au(I) could contribute to the activity in the later stages of the reaction.



218 R = Ph	2 h, 98%
219 R = *p*-Tol	2 h, 93%
220 R = *p*-OMe-C_6H_4	1 h, 95%
221 R = *n*-butyl	2 h, 95%
222 R = cyclopropyl	2 h, 92%
223 R = TMS	20 h, 0%
224 R = H	20 h, trace
225 R = *p*-F-C_6H_4	6 h, 99%
226 R = *p*-CF_3-C_6H_4	16 h, 4%, (2 h, 98% MsOH 10 mol%)

Scheme 55 Hydrophenoxylation of 2-alkynylphenols. Yields presented are isolated yields.

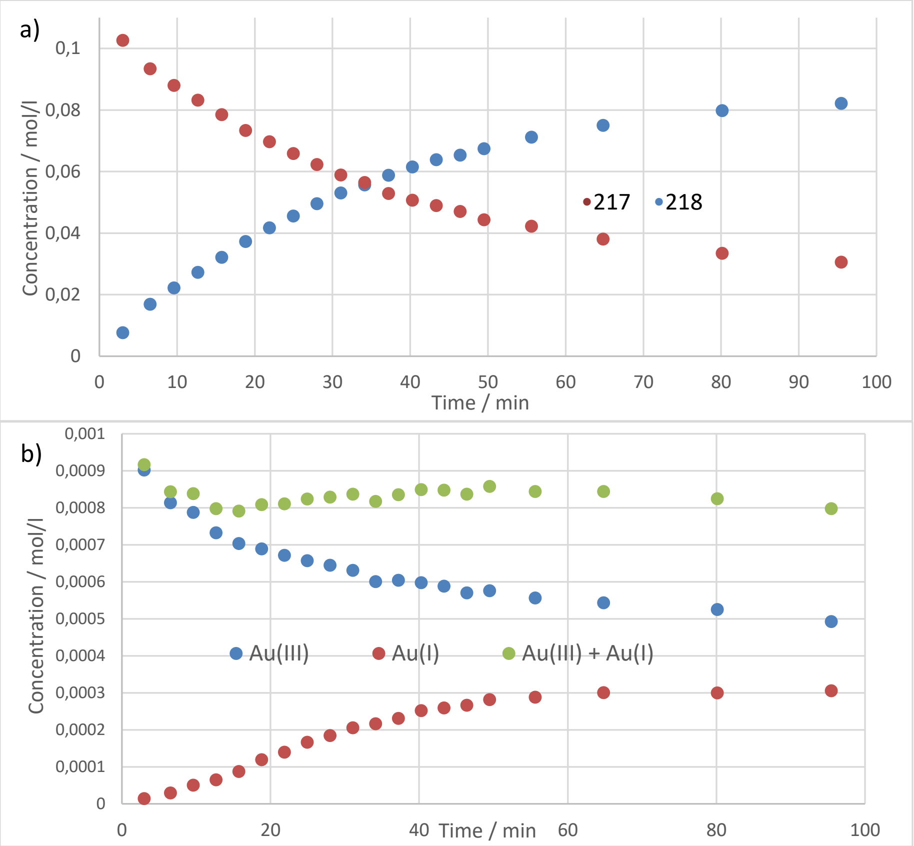


Figure 22 a) Progress of alkyne hydrophenoxylation using **214** and MsOH. b) Reduction of **214** during the hydrophenoxylation reaction. Concentration of **217** was 0.112 M and **214** and MsOH 0.009 M. Temperature was 298 K.

4 CONCLUSIONS

The development of silver-free activation methods is a diverse field of organometallic and catalysis chemistry, which has yielded chemists a vast knowledge on the functions of different metals in catalysis. Avoiding the negative effects of silver has led to substantial chemical findings and streamlined catalytic processes. This work discusses three different approaches to eliminating silver from the catalytic reactions.

In publication I, we investigated a gold-catalyzed alkyne hydroamination to produce 4-quinolones. The reaction proceeded smoothly in ambient conditions using a commercial Gagosz type catalyst. Using a preformed cationic complex enabled efficient catalysis in silver-free conditions and suited for research concentrated on reaction development and synthesis of organic core structures. The availability of commercial complexes is still limited and purchasing the ones available is impractical for any laboratory, which encouraged us to pursue other activation methods through catalyst design.

In publication II, functionalized NHC ligands were synthesized and used in Au(I) catalysis. The displacement of the chloride was enabled by hydrogen bonding, which could be influenced by the water content in the reaction mixture. In addition to the H-bond donor in the ligand, the propargylamide substrate also contributed to the displacement of the chloride. The lack of H-bond donor in the substrate could be solved by a Brønsted acid additive, which enabled rapid cyclizations of 1,6-enynes.

In publication III, NHC ligands were used to replace the chloride with a non-coordinating counteranion in Au(III) catalysis. The stereochemistry of Au(III) permitted the formation of a bond between the sulfonamide and the gold center, which led to cyclometallated compounds. Counteranions could be introduced in the form of Brønsted acids, which protonates the sulfonamide and leaves the anion coordinated to gold. The method enables facile access to different counteranions, as they can be used as widely available acids in stoichiometric amounts. The observed reduction of the catalyst is a challenge, which requires more research on the ligand structure and oxidation methods of Au(I) to Au(III) in the synthesis of the catalysts.

Numerous alternatives for silver exist. Some settle for matching its activity, while others surpass it. However, silver is still widely used in gold catalysis so the search for alternative activation methods is far from finished. On one hand, a general method of activation would be highly useful to benchmark the catalytic properties of gold complexes. The activation should be viable without expensive or harmful additives, which complicate the workup of the reactions. On the other hand, new opportunities in more demanding reactions could be seized by tuning the existing activation methods, e.g. developing enantioselective reactions using functionalized ligands in Au(III) chemistry.

REFERENCES

[1] A. S. K. Hashmi, *Gold Bull.* **2004**, *37*, 51–65.

[2] A. S. K. Hashmi, G. J. Hutchings, *Angew. Chem. Int. Ed.* **2006**, *45*, 7896–7936.

[3] R. Dorel, A. M. Echavarren, *Chem. Rev.* **2015**, *115*, 9028–9072.

[4] J. P. Desclaux, P. Pyykkö, *Chem. Phys. Lett.* **1976**, *39*, 300–303.

[5] D. J. Gorin, F. D. Toste, *Nature* **2007**, *446*, 395–403.

[6] M. J. S. Dewar, *M. Bull. Soc. Chim. Fr.* **1951**, *1*, 79–79.

[7] J. Chatt, L. A. Duncanson, *J. Chem. Soc.* **1953**, 2939–2947.

[8] N. Salvi, L. Belpassi, F. Tarantelli, *Chem. Eur. J.* **2010**, *16*, 7231–7240.

[9] L. Gregori, D. Sorbelli, L. Belpassi, F. Tarantelli, P. Belanzoni, *Inorg. Chem.* **2019**, *58*, 3115–3129.

[10] H. Schmidbaur, *Gold Bull.* **1990**, *23*, 11–21.

[11] N. Bartlett, *Gold Bull.* **1998**, *31*, 22–25.

[12] A. Collado, D. J. Nelson, S. P. Nolan, *Chem. Rev.* **2021**, *121*, 8559–8612.

[13] D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev.* **2008**, *108*, 3351–3378.

[14] Y. C. Lee, K. Kumar, H. Waldmann, *Angew. Chem. Int. Ed.* **2018**, *57*, 5212–5226.

[15] M. Jia, M. Bandini, *ACS Catal.* **2015**, *5*, 1638–1652.

[16] D. Wang, R. Cai, S. Sharma, J. Jirak, S. K. Thummanapelli, N. G. Akhmedov, H. Zhang, X. Liu, J. L. Petersen, X. Shi, *J. Am. Chem. Soc.* **2012**, *134*, 9012–9019.

[17] Y. Sota, M. Yamamoto, M. Murai, J. Uenishi, M. Uemura, *Chem. Eur. J.* **2015**, *21*, 4398–4404.

[18] X. C. Cambeiro, N. Ahlsten, I. Larrosa, *J. Am. Chem. Soc.* **2015**, *137*, 15636–15639.

[19] W. Li, D. Yuan, G. Wang, Y. Zhao, J. Xie, S. Li, C. Zhu, *J. Am. Chem. Soc.* **2019**, *141*, 3187–3197.

[20] G. Fang, X. Bi, *Chem. Soc. Rev.* **2015**, *44*, 8124–8173.

[21] A. Homs, I. Escofet, A. M. Echavarren, *Org. Lett.* **2013**, *15*, 5782–5785.

[22] F. Schröder, C. Tugny, E. Salanouve, H. Clavier, L. Giordano, D. Moraleda, Y. Gimbert, V. Mouriès-Mansuy, J.-P. Goddard, L. Fensterbank, *Organometallics* **2014**, *33*, 4051–4056.

[23] D. Canseco-Gonzalez, A. Petronilho, H. Mueller-Bunz, K. Ohmatsu, T. Ooi, M. Albrecht, *J. Am. Chem. Soc.* **2013**, *135*, 13193–13203.

[24] D. Weber, M. R. Gagné, *Org. Lett.* **2009**, *11*, 4962–4965.

[25] Z. Lu, J. Han, G. B. Hammond, B. Xu, *Org. Lett.* **2015**, *17*, 4534–4537.

[26] A. Zhdanko, M. E. Maier, *ACS Catal.* **2015**, *5*, 5994–6004.

[27] S. G. Weber, F. Rominger, B. F. Straub, *Eur. J. Inorg. Chem.* **2012**, *2012*, 2863–2867.

[28] J.-E. Siewert, A. Schumann, M. Fischer, C. Schmidt, T. Taeufer, C. Hering-Junghans, *Dalton Trans.* **2020**, *49*, 12354–12364.

[29] C. Nevado, A. M. Echavarren, *Chem. Eur. J.* **2005**, *11*, 3155–3164.

[30] L. Jašíková, J. Roithová, *Organometallics* **2013**, *32*, 7025–7033.

[31] M. Veguillas, G. M. Rosair, M. W. P. Bebbington, A.-L. Lee, *ACS Catal.* **2019**, *9*, 2552–2557.

[32] R. Fang, A. M. Kirillov, L. Yang, *Mol. Catal.* **2020**, *486*, 110847.

[33] M. N. Pennell, P. G. Turner, T. D. Sheppard, *Chem. Eur. J.* **2012**, *18*, 4748–4758.

[34] Y. Su, Y. Zhang, N. G. Akhmedov, J. L. Petersen, X. Shi, *Org. Lett.* **2014**, *16*, 2478–2481.

[35] M.-A. Abadie, X. Trivelli, F. Medina, N. Duhal, M. Kouach, B. Linden, E. Génin, M. Vandewalle, F. Capet, P. Roussel, I. Del Rosal, L. Maron, F. Agbossou-Niedercorn, C. Michon, *Chem. Eur. J.* **2017**, *23*, 10777–10788.

[36] A. Bayler, A. Bauer, H. Schmidbaur, *Chem. Ber.* **1997**, *130*, 115–118.

[37] R. Uson, A. Laguna, M. V. Castrillo, *Synth. React. Inorg. Met. Chem.* **1979**, *9*, 317–324.

[38] A. S. K. Hashmi, M. C. Blanco, E. Kurpejović, W. Frey, J. W. Bats, *Adv. Synth. Catal.* **2006**, *348*, 709–713.

[39] A. N. Nesmeyanov, E. G. Perevalova, Y. T. Struchkov, M. Y. Antipin, K. I. Grandberg, V. P. Dyadhenko, *J. Organomet. Chem.* **1980**, *201*, 343–349.

[40] B. D. Sherry, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 15978–15979.

[41] R. L. Lalonde, W. E. Brenzovich, D. Benitez, E. Tkatchouk, K. Kelley, W. A. Goddard, F. D. Toste, *Chem. Sci.* **2010**, *1*, 226–233.

[42] J. T. Binder, B. Crone, T. T. Haug, H. Menz, S. F. Kirsch, *Org. Lett.* **2008**, *10*, 1025–1028.

[43] F. Zamani, R. Babaahmadi, B. F. Yates, M. G. Gardiner, A. Ariafard, S. G. Pyne, C. J. T. Hyland, *Angew. Chem. Int. Ed.* **2019**, *58*, 2114–2119.

[44] C. Nieto-Oberhuber, S. López, M. P. Muñoz, D. J. Cárdenas, E. Buñuel, C. Nevado, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2005**, *44*, 6146–6148.

[45] W. Rao, M. J. Koh, D. Li, H. Hirao, P. W. H. Chan, *J. Am. Chem. Soc.* **2013**, *135*, 7926–7932.

[46] N. Mézailles, L. Ricard, F. Gagosz, *Org. Lett.* **2005**, *7*, 4133–4136.

[47] F. M. Istrate, F. Gagosz, *Org. Lett.* **2007**, *9*, 3181–3184.

[48] A. Buzas, F. Gagosz, *Org. Lett.* **2006**, *8*, 515–518.

[49] L. Ricard, F. Gagosz, *Organometallics* **2007**, *26*, 4704–4707.

[50] P. De Frémont, E. D. Stevens, M. R. Fructos, M. Mar Díaz-Requejo, P. J. Pérez, S. P. Nolan, *Chem. Commun.* **2006**, 2045–2047.

[51] V. Lavallo, G. D. Frey, S. Kousar, B. Donnadieu, G. Bertrand, *Proc. Natl. Acad. Sci. U. S. A.* **2007**, *104*, 13569–13573.

[52] V. Lavallo, G. D. Frey, B. Donnadieu, M. Soleilhavoup, G. Bertrand, *Angew. Chem. Int. Ed.* **2008**, *47*, 5224–5228.

[53] R. Kinjo, B. Donnadieu, G. Bertrand, *Angew. Chem. Int. Ed.* **2011**, *50*, 5560–5563.

[54] Z. Xiaoming, M. Soleilhavoup, G. Bertrand, *Org. Lett.* **2009**, *11*, 3166–3169.

[55] M. Pažický, A. Loos, M. J. Ferreira, D. Serra, N. Vinokurov, F. Rominger, C. Jäkel, A. S. K. Hashmi, M. Limbach, *Organometallics* **2010**, *29*, 4448–4458.

[56] R. Visbal, R. P. Herrera, M. C. Gimeno, *Chem. Eur. J.* **2019**, *25*, 15837–15845.

[57] M. Kumar, G. B. Hammond, B. Xu, *Org. Lett.* **2014**, *16*, 3452–3455.
[58] Y. Zhu, C. S. Day, L. Zhang, K. J. Hauser, A. C. Jones, *Chem. Eur. J.* **2013**, *19*, 12264–12271.
[59] M. Albayer, R. Corbo, A. F. Hill, J. L. Dutton, *Dalton Trans.* **2018**, *47*, 1321–1324.
[60] J. H. Teles, S. Brode, M. Chabanas, *Angew. Chem. Int. Ed.* **1998**, *37*, 1415–1418.
[61] A. Zhdanko, M. E. Maier, *Chem. Eur. J.* **2014**, *20*, 1918–1930.
[62] C. Zhang, D. M. Cui, L. Y. Yao, B. S. Wang, Y. Z. Hu, T. Hayashi, *J. Org. Chem.* **2008**, *73*, 7811–7813.
[63] E. Mizushima, T. Hayashi, M. Tanaka, *Org. Lett.* **2003**, *5*, 3349–3352.
[64] C. Nieto-Oberhuber, M. Paz Muñoz, E. Buñuel, C. Nevado, D. J. Cárdenas, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2004**, *43*, 2402–2406.
[65] S. Sanz, L. A. Jones, F. Mohr, M. Laguna, *Organometallics* **2007**, *26*, 952–957.
[66] Z. Y. Han, H. Xiao, X. H. Chen, L. Z. Gong, *J. Am. Chem. Soc.* **2009**, *131*, 9182–9183.
[67] Y. L. Du, Y. Hu, Y. F. Zhu, X. F. Tu, Z. Y. Han, L. Z. Gong, *J. Org. Chem.* **2015**, *80*, 4754–4759.
[68] X. F. Tu, L. Z. Gong, *Angew. Chem. Int. Ed.* **2012**, *51*, 11346–11349.
[69] N. T. Patil, V. S. Raut, R. B. Tella, *Chem. Commun.* **2012**, *49*, 570–572.
[70] P.-S. Wang, K.-N. Li, X.-L. Zhou, X. Wu, Z.-Y. Han, R. Guo, L.-Z. Gong, *Chem. Eur. J.* **2013**, *19*, 6234–6238.
[71] C. Wang, Z. Y. Han, H. W. Luo, L. Z. Gong, *Org. Lett.* **2010**, *12*, 2266–2269.
[72] N. T. Patil, A. K. Mutyala, A. Konala, R. B. Tella, *Chem. Commun.* **2012**, *48*, 3094–3096.
[73] V. S. Shinde, M. V. Mane, K. Vanka, A. Mallick, N. T. Patil, *Chem. Eur. J.* **2015**, *21*, 975–979.
[74] J. Calleja, A. B. González-Pérez, Á. R. De Lera, R. Álvarez, F. J. Fañanás, F. Rodríguez, *Chem. Sci.* **2014**, *5*, 996–1007.
[75] H. Wu, Y. P. He, L. Z. Gong, *Org. Lett.* **2013**, *15*, 460–463.
[76] L. Cala, A. Mendoza, F. J. Fañanás, F. Rodríguez, *Chem. Commun.* **2013**, *49*, 2715–2717.
[77] C. M. Grisé, E. M. Rodrigue, L. Barriault, *Tetrahedron* **2008**, *64*, 797–808.
[78] K. Singh, N. K. Pal, C. Guha, J. K. Bera, *J. Organomet. Chem.* **2019**, *886*, 1–8.
[79] C. Y. Zhou, P. W. H. Chan, C. M. Che, *Org. Lett.* **2006**, *8*, 325–328.
[80] M. A. Cinellu, L. Maiore, G. Minghetti, F. Cocco, S. Stoccoro, A. Zucca, M. Manassero, C. Manassero, *Organometallics* **2009**, *28*, 7015–7024.
[81] J.-F. Cui, H.-M. Ko, K.-P. Shing, J.-R. Deng, N. C.-H. Lai, M.-K. Wong, *Angew. Chem. Int. Ed.* **2017**, *56*, 3074–3079.
[82] J.-J. Jiang, J.-F. Cui, B. Yang, Y. Ning, N. C.-H. Lai, M.-K. Wong, *Org. Lett.* **2019**, *21*, 6289–6294.
[83] W. Zi, F. D. Toste, *J. Am. Chem. Soc.* **2013**, *135*, 12600–12603.
[84] H. Duan, S. Sengupta, J. L. Petersen, N. G. Akhmedov, X. Shi, *J. Am. Chem. Soc.* **2009**, *131*, 12100–12102.

[85] D. Wang, Y. Zhang, A. Harris, L. N. S. Gautam, Y. Chen, X. Shi, *Adv. Synth. Catal.* **2011**, *353*, 2584–2588.

[86] D. Wang, X. Ye, X. Shi, *Org. Lett.* **2010**, *12*, 2088–2091.

[87] J. Han, N. Shimizu, Z. Lu, H. Amii, G. B. Hammond, B. Xu, *Org. Lett.* **2014**, *16*, 3500–3503.

[88] S. Gaillard, A. M. Z. Slawin, S. P. Nolan, *Chem. Commun.* **2010**, *46*, 2742–2744.

[89] S. Gaillard, J. Bosson, R. S. Ramón, P. Nun, A. M. Z. Slawin, S. P. Nolan, *Chem. Eur. J.* **2010**, *16*, 13729–13740.

[90] P. Nun, R. S. Ramón, S. Gaillard, S. P. Nolan, *J. Organomet. Chem.* **2011**, *696*, 7–11.

[91] R. S. Ramón, S. Gaillard, A. M. Z. Slawin, A. Porta, A. D'Alfonso, G. Zanoni, S. P. Nolan, *Organometallics* **2010**, *29*, 3665–3668.

[92] R. S. Ramón, S. Gaillard, A. Poater, L. Cavallo, A. M. Z. Slawin, S. P. Nolan, *Chem. Eur. J.* **2011**, *17*, 1238–1246.

[93] A. Gómez-Suárez, Y. Oonishi, S. Meiries, S. P. Nolan, *Organometallics* **2013**, *32*, 1106–1111.

[94] A. Collado, S. R. Patrick, D. Gasperini, S. Meiries, S. P. Nolan, *Beilstein J. Org. Chem.* **2015**, *11*, 1809–1814.

[95] S. R. Patrick, A. Gómez-Suárez, A. M. Z. Slawin, S. P. Nolan, *Organometallics* **2014**, *33*, 421–424.

[96] S. Dupuy, S. P. Nolan, *Chem. Eur. J.* **2013**, *19*, 14034–14038.

[97] Y. Oonishi, A. Gómez-Suárez, A. R. Martin, S. Nolan, *Angew. Chem. Int. Ed.* **2013**, *52*, 9767–9771.

[98] A. Gõmez-Suárez, Y. Oonishi, A. R. Martin, S. V. C. Vummaleti, D. J. Nelson, D. B. Cordes, A. M. Z. Slawin, L. Cavallo, S. P. Nolan, A. Poater, *Chem. Eur. J.* **2016**, *22*, 1125–1132.

[99] M. Ramos, J. Poater, N. Villegas-Escobar, M. Gimferrer, A. Toro-Labbé, L. Cavallo, A. Poater, *Eur. J. Inorg. Chem.* **2020**, *2020*, 1123–1134.

[100] S. Dupuy, D. Gasperini, S. P. Nolan, *ACS Catal.* **2015**, *5*, 6918–6921.

[101] D. Gasperini, L. Maggi, S. Dupuy, R. M. P. Veenboer, D. B. Cordes, A. M. Z. Slawin, S. P. Nolan, *Adv. Synth. Catal.* **2016**, *358*, 3857–3862.

[102] I. I. F. Boogaerts, S. P. Nolan, *J. Am. Chem. Soc.* **2010**, *132*, 8858–8859.

[103] P. Nun, S. Gaillard, A. M. Z. Slawin, S. P. Nolan, *Chem. Commun.* **2010**, *46*, 9113–9115.

[104] F. Nahra, S. R. Patrick, D. Bello, M. Brill, A. Obled, D. B. Cordes, A. M. Z. Slawin, D. O'Hagan, S. P. Nolan, *ChemCatChem* **2015**, *7*, 240–244.

[105] J. A. Akana, K. X. Bhattacharyya, P. Müller, J. P. Sadighi, *J. Am. Chem. Soc.* **2007**, *129*, 7736–7737.

[106] M. E. Richard, D. V. Fraccica, K. J. Garcia, E. J. Miller, R. M. Ciccarelli, E. C. Holahan, V. L. Resh, A. Shah, P. M. Findeis, R. A. Stockland, *Beilstein J. Org. Chem.* **2013**, *9*, 2002–2008.

[107] M. W. Johnson, S. W. Bagley, N. P. Mankad, R. G. Bergman, V. Mascitti, F. D. Toste, *Angew. Chem. Int. Ed.* **2014**, *53*, 4404–4407.

[108] Y. Ito, M. Sawamura, T. Hayashi, *J. Am. Chem. Soc.* **1986**, *108*, 6405–6406.

[109] Y. Ito, M. Sawamura, T. Hayashi, *Tetrahedron Lett.* **1987**, *28*, 6215–6218.

[110] Y. Ito, M. Sawamura, M. Kobayashi, T. Hayashi, *Tetrahedron Lett.* **1988**, *29*, 6321–6324.

[111] Y. Ito, M. Sawamura, E. Shirakawa, K. Hayashizaki, T. Hayashi, *Tetrahedron Lett.* **1988**, *29*, 235–238.

[112] M. Sawamura, Y. Ito, T. Hayashi, *Tetrahedron Lett.* **1990**, *31*, 2723–2726.

[113] A. Togni, S. D. Pastor, G. Rihs, *J. Organomet. Chem.* **1990**, *381*, C21–C25.

[114] A. Togni, S. D. Pastor, *J. Org. Chem.* **1990**, *55*, 1649–1664.

[115] L. Hettmanczyk, S. Manck, C. Hoyer, S. Hohloch, B. Sarkar, *Chem. Commun.* **2015**, *51*, 10949–10952.

[116] L. Hettmanczyk, L. Suntrup, S. Klenk, C. Hoyer, B. Sarkar, *Chem. Eur. J.* **2017**, *23*, 576–585.

[117] S. Vanicek, M. Podewitz, J. Stubbe, D. Schulze, H. Kopacka, K. Wurst, T. Müller, P. Lippmann, S. Haslinger, H. Schottenberger, K. R. Liedl, I. Ott, B. Sarkar, B. Bildstein, *Chem. Eur. J.* **2018**, *24*, 3742–3753.

[118] S. Vanicek, J. Beerhues, T. Bens, V. Levchenko, K. Wurst, B. Bildstein, M. Tilset, B. Sarkar, *Organometallics* **2019**, *38*, 4383–4386.

[119] P. Veit, C. Volkert, C. Förster, V. Ksenofontov, S. Schlicher, M. Bauer, K. Heinze, *Chem. Commun.* **2019**, *55*, 4615–4618.

[120] A. Straube, P. Coburger, L. Dütsch, E. Hey-Hawkins, *Chem. Sci.* **2020**, *11*, 10657–10668.

[121] A. Straube, P. Coburger, M. Michak, M. R. Ringenberg, E. Hey-Hawkins, *Dalton Trans.* **2020**, *49*, 16667–16682.

[122] S. Ibáñez, M. Poyatos, L. N. Dawe, D. Gusev, E. Peris, *Organometallics* **2016**, *35*, 2747–2758.

[123] P. A. Shelton, C. R. Hilliard, M. Swindling, L. McElwee-White, *Arkivoc* **2010**, *2010*, 160–166.

[124] M. Devillard, E. Nicolas, C. Appelt, J. Backs, S. Mallet-Ladeira, G. Bouhadir, J. C. Slootweg, W. Uhl, D. Bourissou, *Chem. Commun.* **2014**, *50*, 14805–14808.

[125] J. S. Jones, F. P. Gabbai, *Chem. Eur. J.* **2017**, *23*, 1136–1144.

[126] M. Rigo, L. Hettmanczyk, F. J. L. Heutz, S. Hohloch, M. Lutz, B. Sarkar, C. Müller, *Dalton Trans.* **2016**, *46*, 86–95.

[127] M. Rigo, E. R. M. Habraken, K. Bhattacharyya, M. Weber, A. W. Ehlers, N. Mézailles, J. C. Slootweg, C. Müller, *Chem. Eur. J.* **2019**, *25*, 8769–8779.

[128] C. González-Arellano, A. Corma, M. Iglesias, F. Sánchez, *Chem. Commun.* **2005**, 3451–3453.

[129] M. Freytag, S. Ito, M. Yoshifuji, *Chem. Asian J.* **2006**, *1*, 693–700.

[130] S. Ito, S. Kusano, N. Morita, K. Mikami, M. Yoshifuji, *J. Organomet. Chem.* **2010**, *695*, 291–296.

[131] S. Ito, L. Zhai, K. Mikami, *Chem. Asian J.* **2011**, *6*, 3077–3083.

[132] S. Ito, M. Nanko, K. Mikami, *ChemCatChem* **2014**, *6*, 2292–2297.

[133] S. Ito, T. Shinozaki, K. Mikami, *Eur. J. Org. Chem.* **2017**, *2017*, 6889–6900.

[134] M. Kato, Y. Ueta, S. Ito, *Chem. Eur. J.* **2021**, *27*, 2469–2475.

[135] H. Ito, K. Takagi, T. Miyahara, M. Sawamura, *Org. Lett.* **2005**, *7*, 3001–3004.

[136] H. Ito, T. Saito, T. Miyahara, C. Zhong, M. Sawamura, *Organometallics* **2009**, *28*, 4829–4840.

[137] S. Sen, F. P. Gabbaï, *Chem. Commun.* **2017**, *53*, 13356–13358.

[138] A. Franchino, À. Martí, S. Nejrotti, A. M. Echavarren, *Chem. Eur. J.* **2021**, *27*, 11989–11996.

[139] P. Elías-Rodríguez, E. Matador, M. Benítez, T. Tejero, E. Díez, R. Fernández, P. Merino, D. Monge, J. M. Lassaletta, *J. Org. Chem.* **2023**, *88*, 2487–2492.

[140] Z. Zhang, V. Smal, P. Retailleau, A. Voituriez, G. Frison, A. Marinetti, X. Guinchard, *J. Am. Chem. Soc.* **2020**, *142*, 3797–3805.

[141] V. Lavallo, J. H. W. Ii, F. S. Tham, S. Quinlivan, *Angew. Chem. Int. Ed.* **2013**, *52*, 3172–3176.

[142] S. Bastin, C. Barthes, N. Lugan, G. Lavigne, V. César, *Eur. J. Inorg. Chem.* **2015**, *2015*, 2216–2221.

[143] S. Kronig, E. Theuergarten, C. G. Daniliuc, P. G. Jones, M. Tamm, *Angew. Chem. Int. Ed.* **2012**, *51*, 3240–3244.

[144] K. C. Weerasiri, D. Chen, D. I. Wozniak, G. E. Dobereiner, *Adv. Synth. Catal.* **2016**, *358*, 4106–4113.

[145] L. C. Wilkins, Y. Kim, E. D. Litle, F. P. Gabbaï, *Angew. Chem. Int. Ed.* **2019**, *131*, 18266–18270.

[146] W. C. Liu, F. P. Gabbaï, *Chem. Sci.* **2023**, *14*, 277–283.

[147] A. S. K. Hashmi, J. P. Weyrauch, M. Rudolph, E. Kurpejović, *Angew. Chem. Int. Ed.* **2004**, *43*, 6545–6547.

[148] S. Wang, L. Zhang, *J. Am. Chem. Soc.* **2006**, *128*, 8414–8415.

[149] S. Wang, L. Zhang, *J. Am. Chem. Soc.* **2006**, *128*, 9979.

[150] X. Huang, L. Zhang, *J. Am. Chem. Soc.* **2007**, *129*, 6398–6399.

[151] S. Wang, L. Zhang, *J. Am. Chem. Soc.* **2006**, *128*, 14274–14275.

[152] N. D. Shapiro, F. D. Toste, *J. Am. Chem. Soc.* **2008**, *130*, 9244–9245.

[153] N. D. Shapiro, Y. Shi, F. D. Toste, *J. Am. Chem. Soc.* **2009**, *131*, 11654–11655.

[154] E. P. A. Talbot, M. Richardson, J. M. McKenna, F. D. Toste, *Adv. Synth. Catal.* **2014**, *356*, 687–691.

[155] J. Li, F. Yang, Y.-T. Ma, K. Ji, *Adv. Synth. Catal.* **2019**, *361*, 2148–2153.

[156] P. R. McGonigal, C. de León, Y. Wang, A. Homs, C. R. Solorio-Alvarado, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2012**, *51*, 13093–13096.

[157] N. Marien, B. Brigou, B. Pinter, F. De Proft, G. Verniest, *Org. Lett.* **2014**, *17*, 270–273.

[158] H. V. Adcock, E. Chatzopoulou, P. W. Davies, *Angew. Chem. Int. Ed.* **2015**, *54*, 15525–15529.

[159] P. W. Davies, A. Cremonesi, N. Martin, *Chem. Commun.* **2010**, *47*, 379–381.

[160] P. W. Davies, A. Cremonesi, L. Dumitrescu, *Angew. Chem. Int. Ed.* **2011**, *50*, 8931–8935.

[161] M. Garzón, E. M. Arce, R. J. Reddy, P. W. Davies, *Adv. Synth. Catal.* **2017**, *359*, 1837–1843.

[162] X. Tian, L. Song, K. Farshadfar, M. Rudolph, F. Rominger, T. Oeser, A. Ariafard, A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2020**, *59*, 471–478.

[163] X. Tian, L. Song, M. Rudolph, Q. Wang, X. Song, F. Rominger, A. S. K. Hashmi, *Org. Lett.* **2019**, *21*, 1598–1601.

[164] X. Tian, L. Song, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Org. Lett.* **2019**, *21*, 4327–4330.

[165] X. Tian, L. Song, M. Rudolph, F. Rominger, T. Oeser, A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2019**, *58*, 3589–3593.

[166] X. Tian, L. Song, C. Han, C. Zhang, Y. Wu, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Org. Lett.* **2019**, *21*, 2937–2940.

[167] K. K.-Y. Kung, V. K.-Y. Lo, H.-M. Ko, G.-L. Li, P.-Y. Chan, K.-C. Leung, Z. Zhou, M.-Z. Wang, C.-M. Che, M.-K. Wong, *Adv. Synth. Catal.* **2013**, *355*, 2055–2070.

[168] N. Debono, M. Iglesias, F. Sánchez, *Adv. Synth. Catal.* **2007**, *349*, 2470–2476.

[169] M. Boronat, A. Corma, C. González-Arellano, M. Iglesias, F. Sánchez, *Organometallics* **2009**, *29*, 134–141.

[170] Y. Zhang, C. Zhu, *Catal. Commun.* **2012**, *28*, 134–137.

[171] J. A. T. O'Neill, G. M. Rosair, A.-L. Lee, *Catal. Sci. Technol.* **2012**, *2*, 1818–1821.

[172] Y. Yang, W. Hu, X. Ye, D. Wang, X. Shi, *Adv. Synth. Catal.* **2016**, *358*, 2583–2588.

[173] A. C. Reiersølmoen, D. Csókás, S. Øien-Ødegaard, A. Vanderkooy, A. K. Gupta, A.-C. C. Carlsson, A. Orthaber, A. Fiksdahl, I. Pápai, M. Erdélyi, *J. Am. Chem. Soc.* **2020**, *142*, 6439–6446.

[174] K. Kato, T. Kobayashi, T. Fujinami, S. Motodate, T. Kusakabe, T. Mochida, H. Akita, *Synlett* **2008**, *2008*, 1081–1085.

[175] Y. Miura, T. Mochida, S. Motodate, K. Kato, *Polyhedron* **2016**, *113*, 1–4.

[176] A. C. Reiersølmoen, E. Østrem, A. Fiksdahl, *Eur. J. Org. Chem.* **2018**, *2018*, 3317–3325.

[177] H. F. Jónsson, A. Fiksdahl, *Arkivoc* **2021**, *2020*, 338–352.

[178] A. C. Reiersølmoen, D. Csókás, I. Pápai, A. Fiksdahl, M. Erdélyi, *J. Am. Chem. Soc.* **2019**, *141*, 18221–18229.

[179] T. N. Solvi, A. C. Reiersølmoen, A. Orthaber, A. Fiksdahl, *Eur. J. Org. Chem.* **2020**, *2020*, 7062–7068.

[180] A. C. Reiersølmoen, S. Battaglia, A. Orthaber, R. Lindh, M. Erdélyi, A. Fiksdahl, *Inorg. Chem.* **2020**, *60*, 2847–2855.

[181] S. L. Barnholtz, J. D. Lydon, G. Huang, M. Venkatesh, C. L. Barnes, A. R. Ketring, S. S. Jurisson, *Inorg. Chem.* **2001**, *40*, 972–976.

[182] C. González-Arellano, A. Corma, M. Iglesias, F. Sánchez, *Chem. Commun.* **2005**, 1990–1992.

[183] A. Corma, C. González-Arellano, M. Iglesias, F. Sánchez, *Angew. Chem. Int. Ed.* **2007**, *46*, 7820–7822.

[184] A. Corma, C. González-Arellano, M. Iglesias, M. T. Navarro, F. Sánchez, *Chem. Commun.* **2008**, 6218–6220.

[185] V. K. Y. Lo, Y. Liu, M. K. Wong, C. M. Che, *Org. Lett.* **2006**, *8*, 1529–1532.

[186] T. Chen, C. Cai, *Catal. Commun.* **2015**, *65*, 102–104.

[187] H. V. Wachenfeldt, P. Röse, F. Paulsen, N. Loganathan, D. Strand, *Chem. Eur. J.* **2013**, *19*, 7982–7988.

[188] A. S. K. Hashmi, M. Rudolph, S. Schymura, J. Visus, W. Frey, *Eur. J. Org. Chem.* **2006**, *2006*, 4905–4909.

[189] D. Aguilar, M. Contel, R. Navarro, E. P. Urriolabeitia, *Organometallics* **2007**, *26*, 4604–4611.

[190] A. C. Reiersølmoen, T. N. Solvi, A. Fiksdahl, *Beilstein J. Org. Chem.* **2021**, *17*, 186–192.

[191] M. Muuronen, J. E. Perea-Buceta, M. Nieger, M. Patzschke, J. Helaja, *Organometallics* **2012**, *31*, 4320–4330.

[192] E. Tomás-Mendivil, P. Y. Toullec, J. Díez, S. Conejero, V. Michelet, V. Cadierno, *Org. Lett.* **2012**, *14*, 2520–2523.

[193] E. Tomás-Mendivil, P. Y. Toullec, J. Borge, S. Conejero, V. Michelet, V. Cadierno, *ACS Catal.* **2013**, *3*, 3086–3098.

[194] A. C. Reiersølmoen, A. Fiksdahl, *Eur. J. Org. Chem.* **2020**, *2020*, 2867–2877.

[195] A. G. Nair, R. T. McBurney, M. R. D. Gatus, S. C. Binding, B. A. Messerle, *Inorg. Chem.* **2017**, *56*, 12067–12075.

[196] L. A. Mitscher, *Chem. Rev.* **2005**, *105*, 559–592.

[197] B. D. A. Lucero, C. R. B. Gomes, I. C. D. P. P. Frugulhetti, L. V. Faro, L. Alvarenga, M. C. B. V. De Souza, T. M. L. De Souza, V. F. Ferreira, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1010–1013.

[198] S. Nakamura, M. Kozuka, K. F. Bastow, H. Tokuda, H. Nishino, M. Suzuki, J. Tatsuzaki, S. L. Morris Natschke, S. C. Kuo, K. H. Lee, *Bioorg. Med. Chem.* **2005**, *13*, 4396–4401.

[199] R. H. Reitsema, *Chem. Rev.* **1948**, *43*, 43–68.

[200] C. Shen, A. Wang, J. Xu, Z. An, K. Y. Loh, P. Zhang, X. Liu, *Chem* **2019**, *5*, 1059–1107.

[201] A. S. K. Hashmi, A. M. Schuster, M. Schmuck, F. Rominger, *Eur. J. Org. Chem.* **2011**, *2011*, 4595–4602.

[202] R. Visbal, A. Laguna, M. Concepción Gimeno, *Chem. Commun.* **2013**, *49*, 5642–5644.

[203] A. Collado, A. Gómez-Suárez, A. R. Martin, A. M. Z. Slawin, S. P. Nolan, *Chem. Commun.* **2013**, *49*, 5541–5543.

[204] A. Zhdanko, M. E. Maier, *ACS Catal.* **2014**, *4*, 2770–2775.