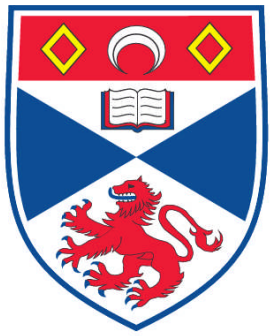
HOMOGENEOUS GOLD CATALYSIS
DEVELOPMENT OF APPLICATIONS GOR GOLD(I) CATALYSTS BEING N-HETEROCYCLIC CARBENE LIGANDS

Ruben S. Ramon Müller

A Thesis Submitted for the Degree of PhD
at the
University of St. Andrews



2011

HOMOGENEOUS GOLD CATALYSIS

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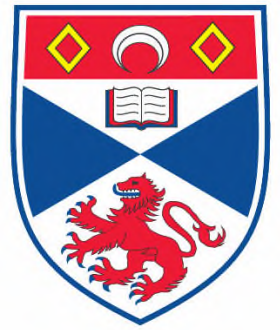

This thesis is submitted in partial fulfilment for the degree of PhD

at the

University of St Andrews

Tuesday, 08 November 2011

Declaration

I, Ruben S. Ramon Müller, hereby certify that this thesis, which is approximately 50000 words in length, has been written by me, that it is the record of work carried out by me and that it has not been submitted in any previous application for a higher degree.

I was admitted as a research student and as a candidate for the degree of PhD in September 2007; the higher study for which this is a record was carried out in the Institute of Chemical Research of Catalonia (ICIQ) between 2007 and 2009 and the University of St Andrews between 2009 and 2011.

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I hereby certify that the candidate has fulfilled the conditions of the Resolution and Regulations appropriate for the degree of PhD in the University of St Andrews and that the candidate is qualified to submit this thesis in application for that degree.

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Parts of this work have been already published:

Chapter **4** is partially based on:

R. S. Ramón, S. Gaillard, S. P. Nolan, *Strem Chemiker* **2009**, *14*, 11-20.

R. S. Ramón, S. P. Nolan, *e-EROS*, *N*,*N*′-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene Gold(I) Chloride, DOI: 10.1002/047084289X.rn01371.

Chapter **6** is based on:

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The experimental work in this chapter was carried out by the author. N. Marion contributed with helpful suggestions and proof reading of the manuscript.

Chapter **7** is based on:

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Large sections of the experimental work in this chapter were carried out by the author. The synthesis of $PGF_{2\alpha}$ and the additional optimization was provided by G. Zanoni and coworkers. S. Gaillard provided [(IPr)Au(OH)] and contributed with helpful suggestions and proof reading of the manuscript.

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The experimental work in this chapter was carried out by the author. N. Marion was first author of the manuscript. Chapter **8** was therefore largely rewritten.

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The experimental work in this chapter was carried out by the author. S. Gaillard provided [(IPr)Au(OH)] and contributed with helpful suggestions and proof reading of the manuscript. The computationial part was provided by A. Poater.

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  The experimental work in this chapter was carried out by the author. C. Pottier worked under the supervision of the author as an undergraduate student on the project and contributed with experimental work. A. Gómez-Suárez contributed by proof reading the manuscript.

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  The experimental work in this chapter was carried out mainly by the author. J. Bosson contributed almost equally to the experimental work. S. Díez-González provided numerous aldoximes and proofread the manuscript.

Some chapters were expanded by results of the author that were published in:

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1 Outline

2 Abbreviations

acac = Acetylacetonate

ADMET = Acyclic Diene Metathesis

BDE = Bond Dissociation Energy

CM = Cross Metathesis

DCE = 1,2-Dichloroethane

DFT = Density Functional Theory

DIBAL = Diisobutylaluminium hydride

DIP-Cl = Diisopinocampheyl chloroborane

dmba = Dimethylbenzylamine

DMF = Dimethyl formamide

DMS = Dimethylsulfide

DMSO = Dimethylsulfoxide

dvds = η^2,η^2-1,1,3,3-Tetramethyl-1,3-divinyl-disiloxane

EDA = Ethyl diazoacetate

ESI = Electron Spray Ionisation

FABA = *tetrakis*-(Pentafluorophenyl)borate

FT-IR = Fourier Transform Infrared Spectroscopy

GC = Gas Chromatography

HRMS = High Resolution Mass Spectrometry

HSAB = Hard and Soft Acids and Bases

HWE = Horner-Wadsworth-Emmons

IAd = 1,3-Diadamantylimidazol-2-ylidene

IMes = 1,3-Bis(2,4,6-trimethylphenyl)imidazol-2-ylidene

IPr = 1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene

IPr^{Cl} = 4,5-Dichloro-*1*,*3*-bis(2,6-diisopropylphenyl)imidazol-2-ylidene

IPr^{Me} = 4,5-Dimethyl-*1*,*3*-bis(2,6-diisopropylphenyl)imidazol-2-ylidene

I^tBu = 1,3-Di-*tert*-butylimidazol-2-ylidene

KHMDS = Potassium bis(trimethylsilyl)amide

KTC = Kumada-Tamao-Corriu

LTM = Late Transition Metal

MBO = Mayer Bond Order

MO = Molecular Orbital

NHC = N-Heterocyclic Carbene

NMR = Nuclear Magnetic Resonance

NOE = Nuclear Overhauser Effect

NPA = Natural Population Analysis

PCM = Polarizable Continuum Model

PEG = Polyethylene glycol

PEPPSI = Pyridine-Enhanced Precatalysts, Preparation, Stabilization, Initiation

$PGF_{2\alpha}$ = Prostaglandin $F_{2\alpha}$

Pyr = Pyridine

RCM = Ring-Closing Metathesis

ROCM = Ring-Opening Cross Metathesis

ROMP = Ring-Opening Metathesis Polymerization

RRM = Ring-Rearrangement Metathesis

rt = Room Temperature

SDD = Stuttgart/Dresden Dunning

SIMes = 1,3-Bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene

SIPr = 1,3-Bis(2,6-diisopropylphenyl)imidazolidin-2-ylidene

SVP = Split Valence + Polarization

TBAF = Tetrabutylammonium fluoride

TBDMS = *tert*-Butyldimethylsilyl

TBS = *tert*-Butyldimethylsilyl/silane

TEP = Tolman Electronic Parameter

Tf = Trifluoromethanesulfonate

THF = Tetrahydrofurane

TLC = Thin Layer Chromatography

TMS = Trimethylsilyl

TOF = Turnover Frequency

TON = Turnover Number

3 Abstract

Recently established as an excellent activator for π-systems, efforts made in gold chemistry have increased enormously, resulting in a new 'Gold Rush' in chemistry. This thesis is a small contribution to it.

There are two main aspects dominating the following chapters: gold catalysts bearing *N*-heterocyclic carbenes (NHCs) as supporting ligand, and H_2O assisted catalysis.

The initial motivation for the presented work was to specifically demonstrate the potential of [(NHC)AuCl] as suitable catalysts for both known and new organic transformations and to establish these commercially available catalysts in gold chemistry, a field currently dominated by phosphine bearing gold complexes. Water mediated catalysis became the next repeatingly occurring aspect of this thesis by pursuing this initial aim and finding water as a useful solvent or agent, respectively.

Various useful applications for gold-NHC complexes are presented, starting with the Meyer-Schuster rearrangement of propargylic alcohols as a continuation of the work realized with propargylic acetates by the Nolan group in early investigations on gold catalysts. Next, a study on alkyne hydration is presented with focus on low catalysts loadings to establish gold catalysts as a powerful choice for such a highly relevant reaction. The catalytic system is then advantageously adapted to a silver-free variation, still active at low catalyst loadings and with further mechanistic insight.

Inspired by gold activation of alkynes, a gap of reactivity in gold catalysis is closed by a successful demonstration of nitrile hydration, a functionality previously thought to be inert towards gold activation. In this context, formation and role of dinuclear hydroxy-bridged gold complexes is investigated highlighting these complexes as a possible resting state of gold complexes in the presence of water.

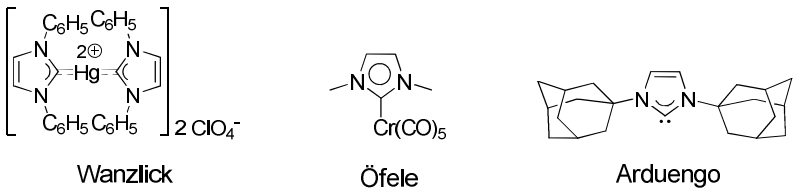
Next, the formation of furanones *via* alkoxylation/lactonization of propargylic propiolates is presented, an observation initially made when exploring the scope of the Meyer-Schuster rearrangement.

The dissertation finally closes with the gold-catalyzed formation of amides, this time however achieved from aldoximes reacting *via* dehydration/hydration mechanism.

4 Introduction

4.1 N-Heterocyclic Carbenes

Although the syntheses of *N*-heterocyclic carbene complexes were originally reported by Wanzlick[1] and Öfele[2] in 1968, it was not until 1991 and the isolation of a stable NHC by Arduengo[3] that the area burgeoned into the beehive of activity it is now (**Scheme 4.1**). The significant interest of the chemical community originates from the numerous carbenes and catalysts reported and the important catalytic applications making use of NHC and congeners. It is fair to say that after more than 20 years of intensive research NHCs have finally emerged from the shadow of the ubiquitous phosphines to a *primus inter pares.* The area is continuously growing and in the present chapter the NHC properties will be briefly summarized, as will synthetic approaches leading to NHCs and a brief overview of the most important catalytic applications will be highlighted, namely palladium cross-coupling, olefin metathesis and palladium-mediated telomerisation, and conclude with gold-NHC catalyzed reactions. Of note, a plethora of other applications are taking advantage of the stereoelectronic properties of NHCs but cannot be dealt with in this introduction.[4]



Scheme 4.1 Early reported NHC complexes by Wanzlick and Öfele and the Arduengo-carbene.

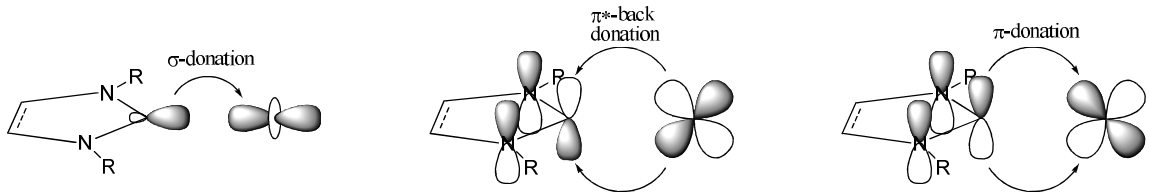
4.2 Steric and electronic properties

When discussing NHCs, two aspects are usually addressed: (a) their strong σ-donor ability and (b) their high steric demand. In his pioneering work, Tolman developed the concept of an electronic parameter (Tolman electronic parameter = TEP) establishing a uniform scale to evaluate donor capabilities of phosphine ligands by measurement of infrared carbonyl stretching frequencies.[5] Due to the higher electron density at the metal center induced by the coordination of strong donating ligands, CO as an intrinsically good π*-acceptor experiences increased back-donation by the metal resulting in a

weakened C-O bond and lower infrared ν_{CO} as an indicator for the ligand electronic donor ability. Of note, alternative concepts[6] are present in the literature but are not as widespread as the TEP.

In the numerous comparisons between NHCs and phosphines, the superior σ-donation of most NHCs is highlighted.[7] While the σ-donation ability of phosphines experiences significant variations depending on their substituents, most common NHCs are known for their very similar donor ability, which is typically intrinsically stronger than for tertiary phosphines.[8] Advanced ligand design has led however to various new NHCs with divergent electronic properties expanding the spectrum of NHC σ-donation.[7a]

Although σ-donation is undisputedly the most important ligand contribution to the M-L (L = ligand) bond, the π-interactions cannot be neglected.[9] π-Contributions have been widely accepted and the ongoing debate has moved forward to address their magnitude ranging from negligible to important. This deconvolution has proven difficult as this electronic interaction has to be distinguished between both the M-L π*-back-bonding as well as L-M π-donation (**Scheme 4.2**).

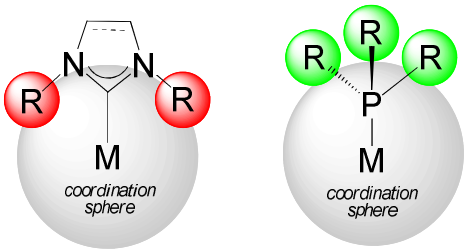


Scheme 4.2 Electronic contributions of the NHC to the M-NHC bond.

The struggle to identify and determine the value of π*-back-donation can be partially found in the standard use of the Tolman electronic parameter. The carbonyl ligands referred to, in order to determine the donating character of a NHC or phosphine, are intrinsic good π*-acceptors. As a consequence, the competition between a poor π*-acceptor such as NHC and CO would significantly affect investigations on the π-contributions. By specific complex design[10] and computational approaches[9a-c] it was however possible to shed light onto this aspect of the M-NHC bond. Typical approximated values for π*-back-bonding are nowadays 10 to 15% of the bonding contribution, with significant increase for electron rich metals such as those of Group 10

and 11. Electron-poor metals, in contrast, have illustrated the relevance of M-NHC π-donation.[11]

The other important and widely investigated aspect of NHCs is their bulk.[7a] To achieve an appropriate comparison of the steric demand between NHCs and phosphines, the well established Tolman cone angle[5] proved inadequate in the case of NHCs due to the very different structural design. Nolan, Cavallo and co-workers therefore developed the concept of the buried volume (%V_{Bur})[11b] which is suitable not only for NHCs but for any type of ligand and therefore privileged for comparison studies.[12] The steric demand of the NHC ligand is determined by calculating the occupied space of a well-defined sphere surrounding the metal center. As illustrated in **Scheme 4.3**, *N*-substituted NHCs are likely to occupy a significant amount of space in the sphere since they are directed towards the metal. This intuitive impression was confirmed by calculations of the %V_{Bur} for numerous complexes based on crystallographic or calculated data. The %V_{Bur} is however strongly dependant on the nature of the complex and the parameters used. As a consequence, significant variations for the same ligand in different complexes can be observed.[12] Additionally, the relevant steric flexibility of a ligand in solution is not strictly considered.[13] That is why care has to be taken when interpreting %V_{bur} results.



Scheme 4.3 Comparison of the %V_{Bur} for NHCs and phosphines.

While it has been demonstrated that stabilization of free NHCs is mainly accomplished through electronic properties and steric effects play only a minor role in this stabilization, the M-L bond is significantly dependent on the ligand's bulk.[8] Comparison of bond dissociation energies (BDE) clearly illustrated a prolongation of the M-L distance in correlation to %V_{Bur}.

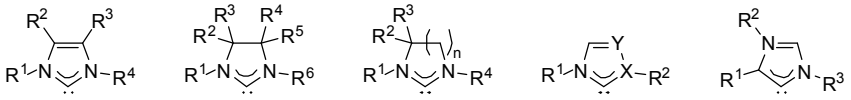
4.3 Stability and diversity

N-heterocyclic carbenes are neutral, nucleophilic 2e$^-$ donors. The specific architectural design has resulted in unprecedented stabilization of the NHCs. While

other carbenes are only stable if coordinated to complexes, numerous stable NHCs are known. The key to this unique stability is found in the two nitrogen atoms of the imidazole ring. The singlet state of NHCs is stabilized in a twofold manner: the amino groups are on the one hand pushing electron density into the empty *p*-orbital in the carbon and on the other hand withdraw electron density of the sp^2 orbitals bearing the free electrons, also referred to as a push-pull-stabilization. The stabilization of the singlet state results importantly in an increased singlet-triplet gap of the carbene, which is critical to avoid undesired dimerization and so a key to isolation of carbenes.[11b]

Coordinated to a metal center, the resulting complexes often show improved thermal stability allowing for catalytic performance at higher temperatures and turnovers in comparison to their phosphine analogues. Of note, the delicate modification of electronic and steric properties of a ligand in a metal complex has extensive and complex consequences on catalytic activity and minor changes can prove key in optimizing a specific reaction. Therefore, it is inevitable to separately consider ligand design for every reaction.

The NHC architecture facilitates the design of electronic and especially steric diversity. Even if one maintains the basic skeleton of imidazol-2-ylidene or imidazolin-ylidenes, 4 positions on the heterocycle are available for derivatization. The two positions available on the amino moiety are key for the introduction of steric bulk and chirality due to their proximity to the metal center. The electronic donor ability is also influenced by *N*-substitution. Substituents on the imidazol(in)-ylidene are distant to the catalytic center and hence are less interesting for steric considerations. Derivatization with electron-donating or accepting substituents or expansion of conjugation are valuable possibilities and have helped to clarify the electronic properties of NHCs.[10b]



Scheme 4.4 Generic examples for structural diversity of NHCs.

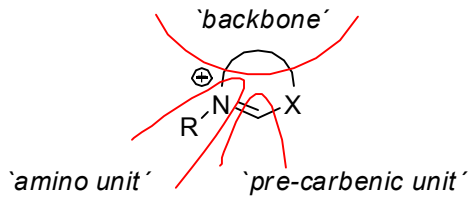
Apart from these obvious modifications, variation of the heterocycle was also evaluated. As illustrated in **Scheme 4.4**, NHCs with different ring sizes as well as replacement of a nitrogen atom by other heteroatom-types are possible. Moreover, so-called abnormal carbenes are known (**Scheme 4.4**, right), displaying alternative coordination connectivity to the metal center.[14]

4.4 Synthetic pathways to *N*-heterocyclic carbenes

The increasing number of NHCs, their high demand and the specific features of some members of this ligand family has led to the development of a variety of synthetic protocols leading to NHCs and their precursors. With most of the approaches to NHCs targeting the deprotonation of imidazolium salts as the most common route for NHC synthesis,[15] alternatives involve reductive desulfurization and α-elimination respectively.

4.4.1 N-heterocyclic carbenes via imidazolium salts

Several protocols for the synthesis of imidazolium salts have been established (**Scheme 4.5**). Numerous simple modifications lead to increased structural diversity. A frequently used approach is the ring closure with a C_1-building block and a diamine or 1,4-diaza-1,3-butadienes (DAB). Classic NHCs can be easily synthesized in a few steps starting from glyoxal and the desired amine to yield the DAB. Unsaturated symmetric imidazolium salts are typically cyclized with paraformaldehyde (**Scheme 4.6**, **a**) and, after reduction of the imines into amines, saturated imidazolium salts can be easily obtained by reaction with triethylorthoformate. Alternative synthetic protocols for the synthesis of asymmetric diamines, e.g. by changing from glyoxal to oxalylchloride, introduction of chiral motifs, and replacement of the C_1-source are diverse and allow for almost endless modifications of the NHC architecture.[15]



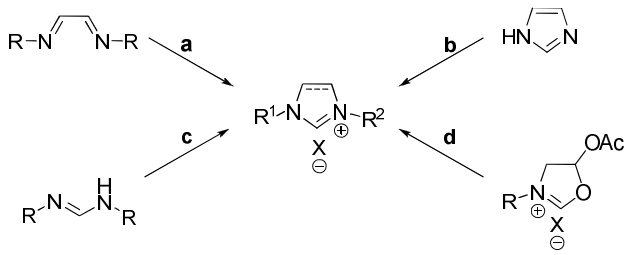
Scheme 4.5 Conceptual pathways to *N*-heterocyclic carbenes (X = NR', CR'R'', O, S) as shown in ref. 15.

Alternatively, an approach initially forming formamidine followed by introduction of the backbone has been successfully achieved (**Scheme 4.6**, **c**).[15] The formamidine formation is typically carried out by the acid catalyzed reaction of triethylorthoformate with 2 equiv. of the corresponding amine. While the synthesis of asymmetric formamidines for NHC synthesis is rare,[16] the concept of introducing the backbone in

the final step is an excellent approach for backbone functionalization. Various protocols based on the formamidines have been reported.[15]

Another approach leading to imidazolium salts is the insertion of an amino moiety at the final step. A key example for this synthetic route was presented by Fürstner and co-workers allowing for the formation of diverse, previously inaccessible unsymmetrical NHCs *via* oxazole precursors (**Scheme 4.6**, **d**).[17] A final condensation step limits the concept to unsaturated imidazolium salts.

Apart from synthesizing the imidazole skeleton, it appears promising to directly start the synthesis of N-functionalized imidazolium salts from 1*H*-imidazole (**Scheme 4.6**, **b**). Once the imidazolium salt is obtained, a deprotonation, e.g. with NaH/KO^{t}Bu in THF, is carried out under an inert atmosphere to afford the free NHC.



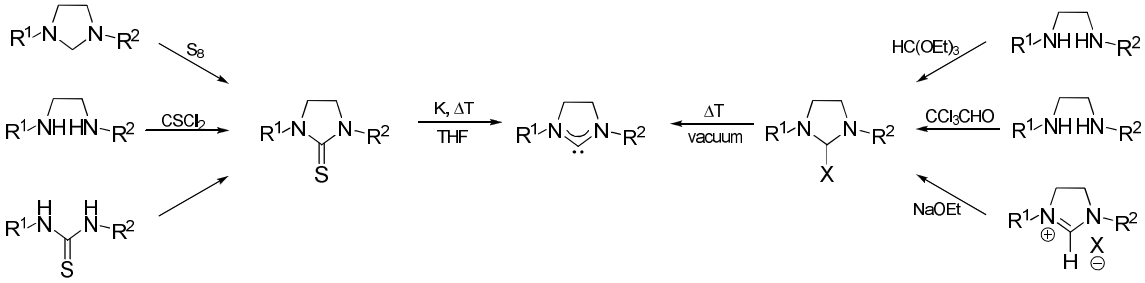
Scheme 4.6 Pathways to imidazolium salt precursors. Deprotonation with a base yields the *N*-heterocyclic carbene.

4.4.2 Reductive desulfurization and α-elimination

Apart from the synthesis and deprotonation of imidazolium salts, a limited number of synthetic alternatives have been used to access NHCs and their precursors. One such alternative is the reduction of imidazole-based thione derivatives (**Scheme 4.7**, left).[18]

These thiones can be synthesized e.g. reacting thiureas with α-hydroxy-ketones, diamines with thiophosgene, 1,1´-thiocarbonyl diimidazole[19] or CS_2 as well as oxidation of imidazolidenes with sulfur.[20] The imidazole-thione is then reduced with molten potassium in THF to yield the free carbene.

Vacuum pyrolysis has also been successfully used as a synthetic tool leading to NHCs (**Scheme 4.7**, right).[21] In this case, a volatile compound such as MeOH or $CHCl_3$ or CO_2[22] is eliminated through heating under vacuum affording the carbene. The α-elimination approach was used by Wanzlick and co-workers[23] to obtain their famous dimer and postulate the intermediate formation of NHCs as early as 1965.



Scheme 4.7 Example of the desulfurization and α-elimination and synthesis of the precursors.

4.5 Synthesis of NHC-metal complexes

Once the synthesis of NHCs or their precursors is achieved, the next challenge is to coordinate the ligand to the desired metal. Most complexes can easily be synthesized by one of various procedures.

Typically, metal complexes are accessible by ligand exchange.[24] A labile ligand coordinated to the metal center is therefore replaced by the better coordinating NHC. Alternatively, the NHC can break weakly bound dimer complexes in order to occupy the free coordination site and form stable monomeric complexes. Depending on other factors, the NHC can be either formed *in situ* with a base or added to the reaction as the isolated free carbene. Handling with free NHCs however requires conducting reactions under anhydrous conditions.

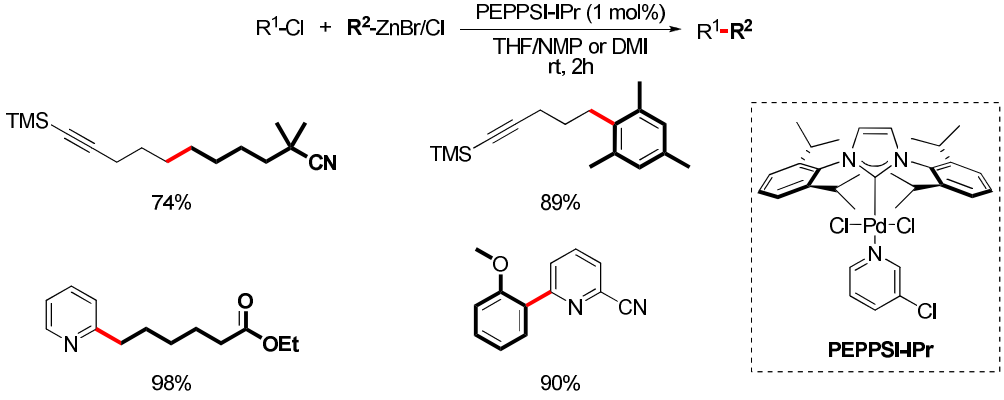
Another common approach involves transmetalation.[25] In this instance, the NHC first forms a complex with a M-NHC bond weaker than the desired complex that is then reacted with the target metal. A common example is the reaction of imidazolium salts with silver(I) oxide to yield complexes of type [(NHC)AgX]. The silver complexes, either isolated or formed *in situ,* can act as transmetalating agent and deliver their NHC payload to another metal. Depending on the metal precursor this is a very good method to obtain a variety of late transition metal NHC complexes. The reaction of [(NHC)AgX] with e.g. (L)AuX (with L = a weaker ligand) will then allow the isolation of the desired gold complex *via* transmetalation (see Chapter **5**). The stronger NHC-Au bond is key for the transmetalation to occur.

4.6 NHC complexes in cross coupling reactions.

Applications of NHC complexes in catalysis have led to improved reactivity for a large number of reactions[4a] but most particularly have proven essential in greatly improving cross-coupling reactions. Heck, Negishi and Suzuki were awarded the Nobel Prize in 2010 for their pioneering work in palladium catalyzed cross coupling reactions. These tools represent common and valuable catalytic methods for most synthetic chemists and have significantly benefited from the availability of Pd-NHC complexes.[26] In the following sections, the impact of NHCs in the area is illustrated.

4.6.1 Negishi coupling

Although the Negishi reaction is one of the most versatile cross coupling reactions due to its high functional group tolerance, only a limited number of Pd-NHC complexes catalyze the Negishi reaction, which originally employed a Pd-phosphine or Ni-catalyst and organozinc reagents.[27] Important contribution were made with the room temperature cross coupling of two alkyl bearing cross-coupling partners applying an *in situ* generated catalyst derived from IPr•HCl and $Pd_2(dba)_3$.[28] In contrast to other cross coupling reactions, well-defined complexes have proven superior catalytic activity to *in situ* generated species. PEPPSI-IPr[29] showed superior reactivity in Negishi coupling for a wide array of substrates under mild conditions (**Scheme 4.8**). Moreover, the use of a highly active catalyst with well-defined structure, which is easy to synthesize and air-stable, represents important advantages in terms of usability. To avoid stability issues when dealing with air-sensitive zinc substrates, an one-pot reaction with *in situ* generated zinc substrates using the most successful PEPPSI-IPr was developed.[30]



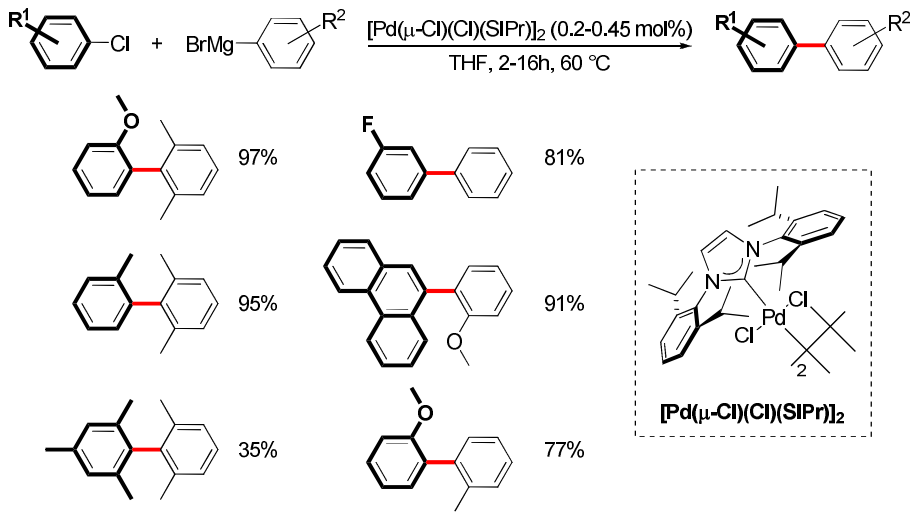
Scheme 4.8 PEPPSI-IPr catalyzing Negishi cross coupling of aryl- and alkylchlorides.[29]

Mechanistic considerations of PEPPSI-NHC catalyzed Negishi reactions have been reported by Organ and co-workers.[31]

In an expansion of the typical cross coupling reaction, a carbonylative variation of the Negishi cross coupling employing PEPPSI-IPr and alkynyl-zinc compounds in the presence of carbon monoxide allowed for the direct synthesis of alkynyl ketones from di-*ortho* substituted aryliodides.[32]

4.6.2 Kumada-Tamao-Corriu (KTC) reaction

The direct use of Grignard reagents for coupling reactions, which partially serve as starting materials for substrates used in alternative coupling reactions, e.g. arylboronic acids for Suzuki-Miyaura coupling,[33] appears desirable and was reported independently by Kumada and Tamao[34] as well as Corriu[35] (KTC) in 1972 using a nickel-based system. In addition to the saving of reaction steps, Grignard reagents are interesting substrates due to their ease of synthesis, low toxicity and costs. Murahashi was the first to report a Pd-catalyzed KTC coupling reaction in 1975 using $Pd(PPh_3)_4$.[36] In 1999, Nolan reported a Pd-NHC catalyst suitable for the involvement of aryl chlorides in the KTC reaction.[37] Using IPr•HCl and $Pd_2(dba)_3$ allowed for excellent yields and proved tolerant to aryl *ortho*-substitution as well as numerous functional groups. Further investigations on the Pd-NHC catalyzed KTC reaction resulted in protocols suitable for alkyl halides. The catalysis in this case was carried out at room temperature in reaction times as short as 1 hour.[38]

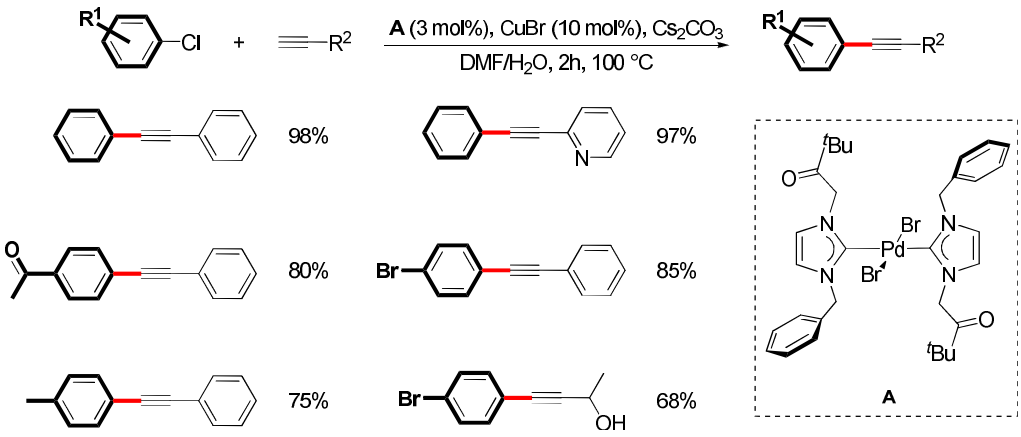


Scheme 4.9 Kumada-Tamao-Corriu coupling of *ortho*-substituted arylchlorides and Grignards.[39]

Cross couplings yielding tri- and tetra-*ortho*-substituted biaryls were reported by Cazin[39] using catalyst loadings ranging from 0.1 to 0.45 mol%. This was carried out at temperatures ranging from room temperature to 60 °C (**Scheme 4.9**). Using the PEPPSI-NHC catalyst allowed for a scope including bis-*ortho* substituted substrates. An example of a reaction conducted at -20 °C was given to emphasize the possibility of KTC reactions with sensitive Grignard reagents.[40] Later on, mechanistic aspects of the PEPPSI-NHC catalyst in various cross coupling reactions including the KTC reaction have been evaluated in more detail.[31] From an industrial and/or synthetic chemists point of view highly interesting, the synthesis of air stable Pd catalysts with good reactivity in KTC reactions was achieved recently, although the reported scope of the catalytic system was limited to examples with low steric hindrance.[41]

4.6.3 Sonogashira reaction

The coupling of terminal alkynes with aryl and alkylhalides is typically accomplished in the presence of copper and amines. This methodology allows the direct synthesis of interesting compounds and is well established and, one might say, routine in many laboratories. Inspite of significant efforts aimed at investigating the Pd-NHC catalyzed Sonogashira coupling, most catalysts reported to date struggle in dealing with arylchlorides and acceptable yields are limited to the use of arylbromides or iodides. Room temperature Sonogashira coupling of aryl iodides with an air stable *N*-carbamoyl-substituted heterocyclic carbene Pd-complex was one of the early successes demonstrating the potential of NHC complexes in this coupling reaction.[42]



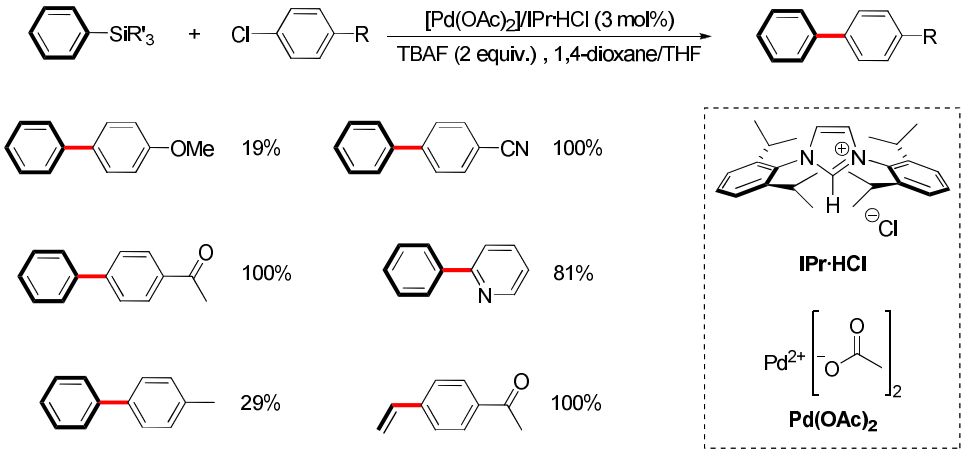
Scheme 4.10 Sonogashira reaction in air under amine free conditions.[43]

A catalyst formed *in situ* from $Pd(OAc)_2$ and IMes•HCl also showed good activity even under copper-free conditions for activated arylbromides. The first example for Pd-NHC Sonogashira coupling with alkyl bromides bearing β-hydrides followed shortly after and was performed by Fu and co-workers with $[Pd(\pi\text{-allyl})Cl]_2$ and the sterically demanding IAd•HCl at 45 °C.[44]

Another important contribution was made by Gosh who developed a NHC-based catalyst suitable for Sonogashira couplings under amine free conditions in air and in aqueous solvent mixtures (**Scheme 4.10**). The scope is, however, limited to aryl iodides,[43] but sulfonated NHCs coordinated to palladium permitted couplings with arylbromides in water/isopropanol.[45] PEPPSI catalysts successfully achieved the amine- and copper-free coupling of both aryliodides and –bromides in air.[46] Polymer supported systems have been published, e.g. dendritic polymers attached to paramagnetic nanoparticles, allowing for easy catalyst separation and recycling.[47]

4.6.4 Hiyama reactions

Although cross-coupling with organosilanes is of interest and has been widely investigated with phosphine complexes, reports on the Hiyama coupling with NHC ligands remain scarce (**Scheme 4.11**).[48] A main disadvantage of the Hiyama reaction is the need to polarize the Si-C bond in order to increase the nucleophilicity of the compound for catalysis. Usually a fluoride source such as TBAF is added to achieve this effect. The closely related Hiyama-Denmark reaction addresses this issue by modifying the original protocol.[49]

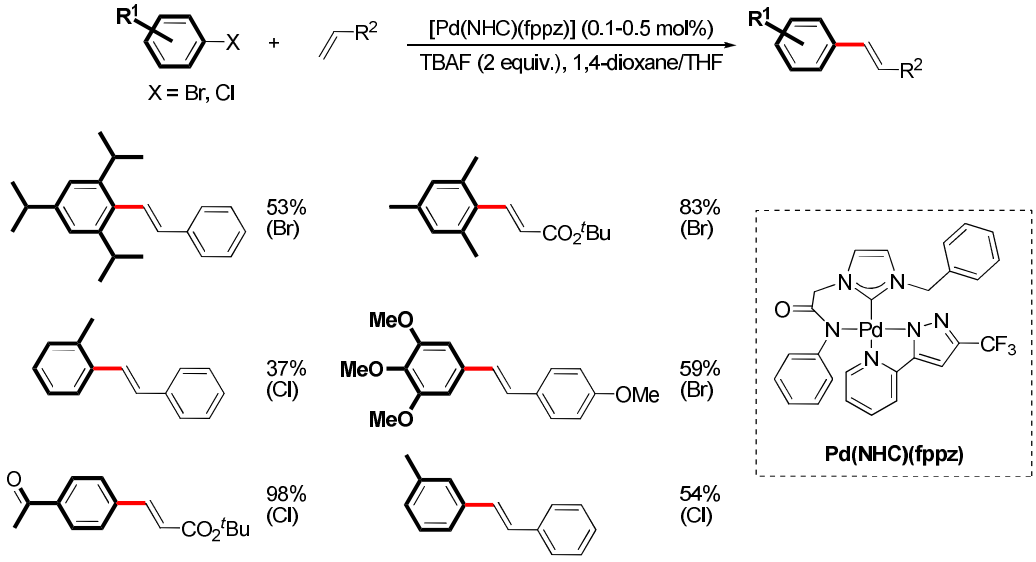


Scheme 4.11 Hiyama reaction with an *in situ* generated Pd-NHC complex.[48]

An example of fluoride-free Hiyama coupling was carried out with the PEPPSI-NHC complex and phenyl- or vinyltrimethoxysilanes in air in the presence of a base.[46b]

4.6.5 Heck-Mizoroki reaction

The coupling of aryl halides with alkenes had a significant impact in synthetic chemistry. Since these reactions are typically performed at high temperatures with long reaction times, application of NHC-based catalysts with their superior stability in comparison to phosphine analogues appears advantageous and has been thoroughly investigated. It is therefore not a coincidence, that the Heck-Mizoroki reaction was the first to be reported with Pd-NHC complexes by Herrmann in 1995. The reaction already performed well at 0.1 mol% catalyst loadings for the most challenging substrates and also most desired aryl chloride couplings.[7f] Early developments based on mixed NHC-phosphine complexes allowed for significant improvements in comparison to bis-NHC or bis-phosphine complexes. The steric demand of the NHC was once more crucial for the catalytic activity.[50] Despite enormous efforts, couplings of aryl chlorides remain difficult. Changing the reaction media to ionic liquids, more precisely tetrabutylammoniumbromide, was a successful modification achieving good yields with a variety of aryl chlorides and a well-defined monocarbenepalladium complex.[51]



Scheme 4.12 Heck reaction with heteroleptic Pd(II) complexes for fast catalyst activation.[52]

Lee and co-workers developed heteroleptic palladium(II) complexes bearing a bidentate carbene/amido ligand to perform this transformation. In an ionic liquid, this

catalyst performed exceedingly well even with unactivated aryl chlorides at catalyst loadings ranging 0.1-0.5 mol% (**Scheme 4.12**). Replacement of a second carbene/amido ligand by a weaker binding ligand was the key for an improved catalyst activation.[52]

With focus on an inexpensive and easily synthesized catalyst suitable for demanding aryl iodides and bromides, Ying *et al.* reported the one-pot synthesis of [Pd(IMes)(dmba)Cl] (dmba = dimethylbenzylamine) and its successful application with a series of interesting substrates.[53] Heck reactions conducted in air and in the presence of moisture have been achieved with SIMes-thiourea precursors and $Pd(dba)_2$[19] and various multidentate carbene palladium catalysts derived *in situ* from imidazolium salts and $Pd(OAc)_2$ even tolerated the presence of oxidants.[54] Turnover numbers (TONs) up to 2,000,000 with full conversion have been reported when testing a bis-NHC palladium(II) complex with 4-bromoacetophenone and butylacrylate.[55]

Catalytic systems that are supported on polymers have been constructed on a polystyrene support *via* ether linkages. The obtained system achieved excellent conversions at 0.2 mol% catalyst loadings even after 10 cycles and negligible Pd leaching. Catalyst recycling was crucially improved by the typically easy separation of the heterogenated catalyst.[56] An attractive alternative are immobilized Pd-catalysts on mesoporous structures such as SBA-16. The cage-like structures can be easily recycled and yield up to 87% coupling product after 8 cycles and low initial 0.01 mol% catalyst loading.[57]

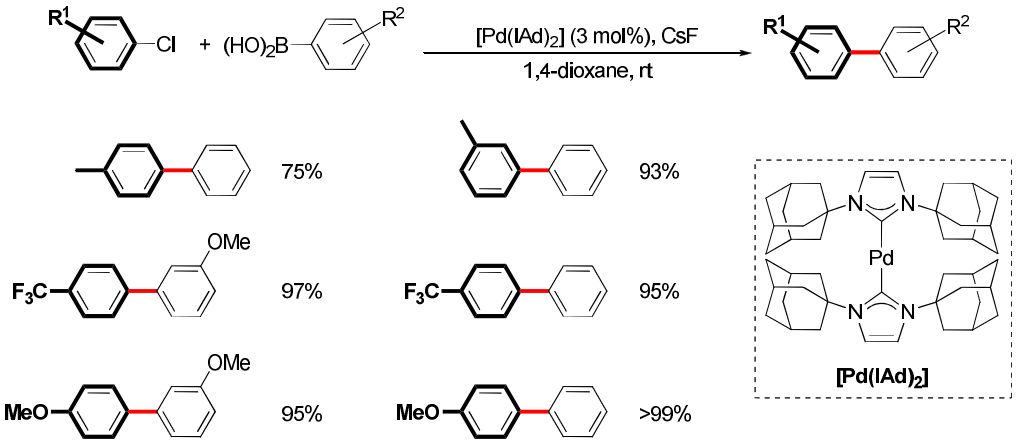
Hence, Pd-phosphine complexes remain the most active complexes in Heck-Mizoroki reactions.

4.6.6 Suzuki-Miyaura reaction

The coupling reaction of organoboron compounds with alkyl and arylhalides has and continues to enjoy great popularity. The exceptional status of this reaction is due, next to its excellent reactivity, to the wide availability of air and moisture-stable organoboron compounds and the non-toxic side products generated in the reaction. A disadvantage of the Suzuki-Miyaura coupling is the usually mandatory need of base in stoichiometric amounts. While boronic acids are the most commonly used reagents, boronic esters and other organoborons have been successfully used. Organotriflates, replacing halides, have also been involved in this reaction. Due to its popularity, numerous examples of Pd-NHC catalyzed reactions are known. The most challenging

substrates remain the inexpensive and widely available organochlorides. An early report successfully addressed the delicate coupling of arylchlorides with $Pd_2(dba)_3$/IMes•HCl in the presence of Cs_2CO_3.[58] A few years later, [Pd(IAd)$_2$] was reported to catalyze the Suzuki-Miyaura coupling of arylchlorides at room temperature, outperforming all catalysts known at this time under such mild reaction conditions (**Scheme 4.13**).[59]

Of note, *ortho* substitution on either the aryl chloride or the boronic acid prevented conversion. The lack of reactivity of *ortho*-substituted compounds was addressed with the very interesting IBiox ligand which has flexible sterics and can therefore adapt to the steric demand of the substrates.[60] Organ *et al.* employed PEPPSI-IPr catalyst in room temperature couplings allowing as well for the synthesis of bis-*ortho*-substituted biaryls. Moreover, a protocol for potassium trifluoroborates replacing boronic acids has been developed.[61]



Scheme 4.13 Suzuki-Miyaura reaction with [Pd(IAd)$_2$] at room temperature.[59]

Alternatively, the cinnamyl group proved to be a suitable ancillary ligand in [Pd(IPr)(cinnamyl)Cl] for Suzuki-Miyaura couplings at room temperature in technical grade isopropanol. Catalyst loadings of only 50 ppm with yields >90% were achieved when reaction temperatures were increased to 80 °C. These results highlight the importance of ancillary ligands for catalyst performance in addition to the nature of the NHC.[62] Modification of the NHC by sulfonation permitted reactions to be conducted in aqueous solutions for a broad spectrum of substrates including bis-*ortho*-substitution and heteroaromatic chlorides.[45] A solvent-free reaction was also carried out under microwave assisted heating.[63] Aryldiazonium salts have been used as a replacement for halides. This action superceded the use of stoichiometric amounts of base and partially enabled reactions even at 0 °C.[64] It was also demonstrated that sulfonyl chlorides are

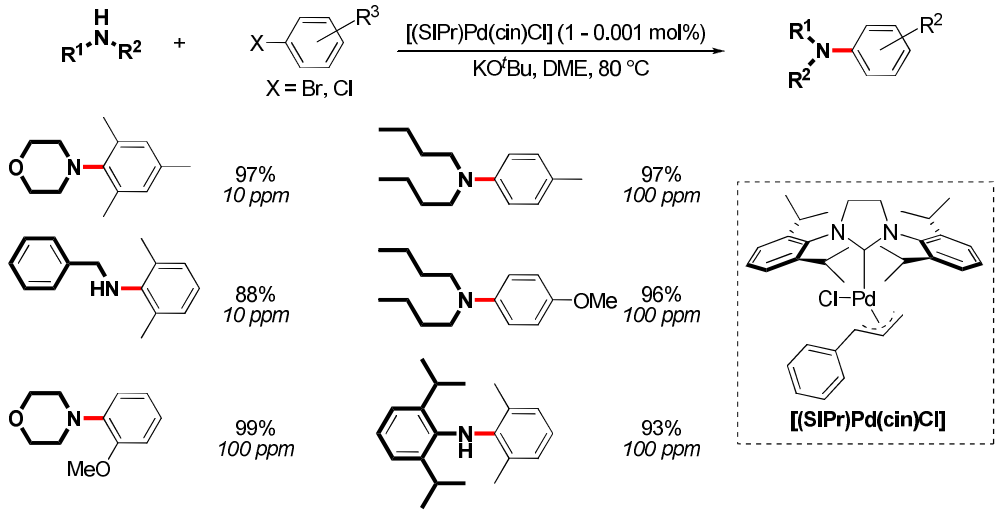
highly reactive in the Suzuki-Miyaura coupling and therefore suitable for stepwise coupling leading to asymmetric triaryl compounds.[65]

A first example for asymmetric coupling of aryl boronic acids with arylbromides involving a Pd-NHC complex was achieved with a chiral ferrocenyl phosphine-NHC ligand. The *ee*'s obtained are however moderate at this stage.[66]

Carbonylative Suzuki coupling of heteroarylhalides (including chlorides) and phenylboronic acid was achieved under carbon monoxide pressure of 5-50 bar yielding biarylketones.[67] In an extension of this concept, Andrus and co-workers added ammonia to a carbonylative Suzuki coupling of aryl diazonium salts and boronic acids. Catalyzed by $Pd(OAc)_2$/SIPr•HCl the authors obtained various aryl amides in this one-pot reaction.[68]

4.6.7 Buchwald-Hartwig amination

The Buchwald-Hartwig amination is probably the most important representative of the group of hetero cross coupling reactions. Interestingly, it has become a common reaction step in the synthesis of NHCs.[15] Employing NHC ligated complexes to synthesize a NHC ligand is a noteworthy observation. Initial reports on the use of NHCs in arylamination used an *in situ* generation of the catalyst. Arylchlorides required heating to allow for coupling products whereas other halides readily converted at room temperature. An initial report disclosed the amination of arylchlorides with acyclic primary and secondary alkyl amines.[69] A significant improvement of this first approach was the change from unsaturated IPr•HCl to its saturated analogue, SIPr•HCl.



Scheme 4.14 Buchwald-Hartwig-amination at low catalyst loadings.[62b]

Such a minor modification now also allowed for the room temperature conversion of arylchlorides in high turnover numbers.[70]

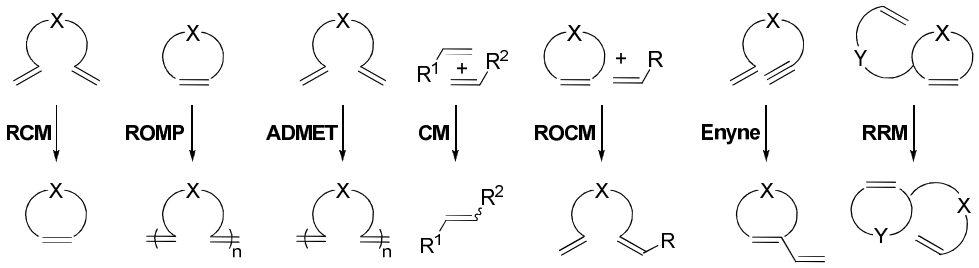
A major improvement in terms of ease of use was the utlilization of the air-stable $[Pd(IPr)Cl_2]_2$. Although moderate heating was necessary to convert arylchlorides, reactions were performed in air and using technical grade solvents.[71]

Similarly, the simple synthesis of [PdCl(acac)(IPr)] was highlighted when reporting it as a convenient catalyst for a broad substrate scope.[72] The cross coupling PEPPSI-NHC complex was also applied to the Buchwald-Hartwig amination. Interestingly, the authors report the successful replacement of KO^{t}Bu by the milder Cs_2CO_3, an important aspect when handling base sensitive substrates.[73] However, here reactions were, as for [PdCl(acac)(IPr)], perfomed under inert atmosphere.

[Pd(IPr)(cinnamyl)Cl], a most suitable catalyst for low catalyst loadings in Suzuki-Miyaura reactions, was found likewise extremely active in Buchwald-Hartwig aminations (**Scheme 4.14**). Reactions were either performed at room temperature with reaction times as short as 1 minute, or at elevated temperatures and prolonged reaction times with catalyst loadings as low as 10 ppm.[62]

4.7 Metathesis

The NHCs have also permitted a significant breakthrough in ruthenium-based olefin metathesis.[74] In this area, NHC complexes were rapidly demonstrated to exhibit higher thermal stability compared to their phosphine counterparts. This improved thermal stability has led to the opening of reactivity avenues in alkene metathesis.[75] As a consequence of these early breakthroughs, the development of new complexes for metathesis has been highly focused on NHCs. Considering the outstanding importance of metathesis in industrial terms and its impact in synthetic chemistry in general, it is fair to say that here *N*-heterocyclic carbenes have their most important application.



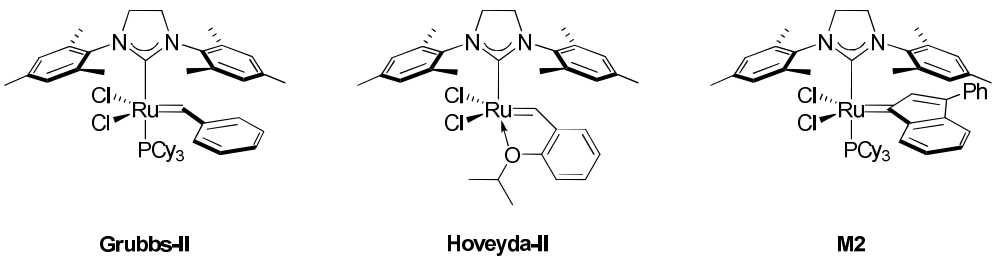
Scheme 4.15 Schematic illustration of common metathesis reactions catalyzed by ruthenium.

The importance of the area was recognized in 2005 with the Chemistry Nobel Prize to Chauvin, Schrock and Grubbs. If one were to wear NHC-coloured glasses, one might say that the last two organometallic Nobel prizes have a NHC tint to them.

As illustrated in **Scheme 4.15**, various types of olefin metathesis are known: Ring-closing metathesis (RCM), ring-rearrangement metathesis (RRM), ring-opening metathesis polymerization (ROMP), acyclic diene metathesis polymerization (ADMET), cross metathesis (CM), ring-opening cross metathesis (ROCM) and enyne metathesis.

Hundreds of ruthenium catalysts with NHC spectator ligands have been and still are regularly reported. This activity can be explained as a simple exercise to find the optimum catalyst and to gain deeper understanding of the various factors influencing activity and stability for particular substrates and metathesis reactions. As in other reactions, the easy access to a variety of NHCs resulted as well in examples for immobilized[76] or water-soluble[77] catalysts, important approaches for industry and pharmaceutical research since catalyst separation is a major issue possibly limiting their use.

A small selection of commercially available catalysts enables the user to cover a wide area of substrates and reactions in satisfying manner (**Scheme 4.16**). Next to the most prominent Grubbs-II,[78] Hoveyda disclosed a very successful alternative.[79] While Grubbs kept the typical benzylidene moiety and chose tricyclohexylphosphine as a labile throwaway ligand, Hoveyda appended an isopropoxy-moiety to the benzylidene. This way he achieved a chelating effect *via* an ether moiety and replaced the phosphine. Similarly, replacing the benzylidene moiety by a 3-phenylindenylidene resulted in improved stability and good catalytic activity (Scheme 4.16, **M2**).[80]



Scheme 4.16 Commercially available ruthenium complexes frequently used in metathesis.

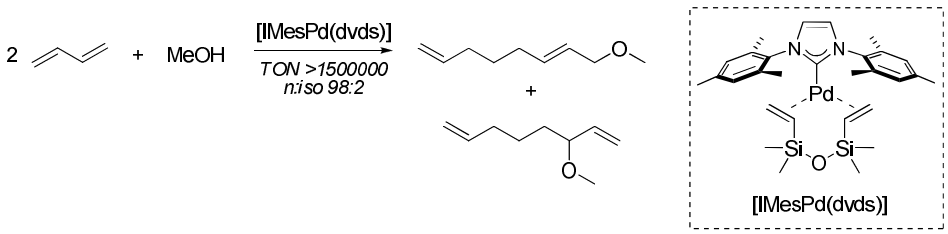
Nevertheless the NHC plays a key role in these three catalyst architectures. These "second generation" catalysts bear SIMes as the spectator ligand. In spite of the huge

progress made already, investigations on improved Ru-NHC complexes are still an important topic in academic and industrial research, not least due the high potential for the large-scale application of metathesis in industry.

4.8 Telomerization

The oligomerisation of 1,3-dienes with addition of a nucleophile was first described by Smutny[81] and Takahashi[82] in 1967. The reaction gained significant importance since it presents an easy protocol for the synthesis of industrial important substrates and precursors. 1-Octanol, obtained *via* telomerization of butadiene and water, is an important precursor for plasticizers such as dioctyl adipate. 1-Octene, similarly obtained from butadiene and methanol followed by subsequent hydrogenation/elimination, is an important co-monomer in the synthesis of linear low-density polyethylenes. Variation of the diene and nucleophile as well as reaction optimization leading to specific selectivity allows for numerous relevant substrates for pharmaceutical purposes and emulsifiers.[83]

Palladium was rapidly identified as a suitable catalyst for telomerization reactions and phosphine-ligated catalysts are dominant in this area. Although numerous parameters are of relevance for selectivity and yield, several examples of telomerisation also involving Pd-NHC are present in the literature,[84] mostly focusing on telomerization with alcohols. Important contributions on Pd-NHCs in telomerisation were made by Beller and co-workers. In the course of investigating the potential of monodentate Pd complexes, the slightly disappointing phosphine spectator ligands were replaced by IMes resulting in significantly higher conversions and chemoselectivity for the telomerisation of butadiene with various alcohols in comparison to e.g. $Pd(OAc)_2/3PPh_3$.[85]



Scheme 4.17 Pd-NHC catalyzed telomerisation of 1,3-butadiene with alcohols.[86]

In an extension of this work, the authors investigated the performance of *in situ* generated palladium complexes, expanding the ligand scope to ferrocenylated NHCs.[87]

A breakthrough in terms of efficiency was made when Beller *et al.* realized in an additional study the importance of adding IMes•HCl, the precursor for the carbene ligand to the reaction mixture. Extensive screenings resulted in an optimized method making use of catalyst loading as low as 0.5 ppm of [Pd(IMes)(dvds)] (dvds = η^2,η^2-1,1,3,3-tetramethyl-1,3-divinyl-disiloxane) and a TON of 1,540,000, which was the best turnover reported for telomerisation (**Scheme 4.17**).[86] Of note, high selectivity for butadiene dimerization instead of telomerization was achieved by a change of the NHC from IMes to the more bulky and, due to backbone substitution, less flexible IPr^{Me} and careful optimization of reaction conditions.[88] Alternatively, a variety of diols has been successfully used in telomerization of butadiene. The reaction could be carried out at catalyst loadings as low as 2 ppm and showed good selectivity for mono-octadienyl ethers.[89] The reactivity of bis-NHC- and mixed NHC-phosphine-Pd complexes has been investigated focusing on reactions involving butadiene and methanol in aqueous media. Interestingly, water-soluble complexes exhibit poor activity whereas *in situ* generated catalysts with IMes•HCl afforded very good yields under these conditions.[90]

In addition to 1,3-butadiene, the telomerization of isoprene has drawn significant attention. As, in this instance, we are dealing with a non-symmetric compound, an increased number of isomers is obtained and usually selectivity for a specific isomer is low. The research group of dos Santos reported unusual high selectivity for head-to-head coupling employing IMes•HX for *in situ* generation of the catalytic species.[91] Divergent reactivity was once more observed with the more bulky SIPr imidazolium salts. Here, increased amounts of trimerized product was observed. Shortly later, a similar study was published by Beller and co-workers.[92]

Scheme 4.18 Pd-NHC catalyzed telomerisation of 1,3-butadiene with primary and secondary amines.[93]

Using glycerol and PEG as nucleophiles in the reaction with isoprene further extended the scope of Pd-NHC catalyzed reactions. Interestingly, the authors observed high selectivity for linear monotelomer products.[94]

Conjugated C5 and C6 dienes were also tested for telomerization. [Pd(IMes)(dvds)] was found to be a superior catalyst. While chemoselectivity for telomerization was encouraging, maximum conversions of 48% and TONs <1000 leave room for further improvements.[95]

There are also some rare reports dealing with amines as nucleophiles. Nolan *et al.* initially reported the promising application of cationic Pd-NHC for the reaction of both secondary and primary amines with butadiene yielding the terminal C8 telomers in excellent selectivity.[96] Later, important improvement in terms of catalyst activity and TONs were made when Pd(0)(dvds) was found to be highly efficient in telomerization with *N*-nucleophiles (**Scheme 4.18**). Stunningly, reactions were performed in the presence of methanol as solvent without observing any side-products resulting from reaction with this potential nucleophile.[93]

4.9 Gold catalysts in organic synthesis

In 1976, Hubert Schmidbaur, a pioneer in the field of gold chemistry, provided a review with the headline *`Is Gold Chemistry a Topical Field of Study?´*.[97] In the course of his review, Schmidbaur answered this question with an *`emphatic yes´*. Fourteen years later, in 1990, it was again Schmidbaur stating that *`the number of scientists studying gold has increased rapidly to an unprecedented level´* and that it is *`impossible to overlook the avalanche (...) of the literature on gold research and development, and primarily in gold chemistry.´*[98] However, most people would date the beginning of the so-called `Gold Rush´ around the year 2000, when numerous applications in homogeneous gold catalysis started to appear in the literature.

Nevertheless, Schmidbaur's claim regarding gold chemistry can be considered adequate while the implications of these seminal reports did not obtained the necessary attention of wide parts of the chemical community to allow earlier breakthroughs. As a result, the `inertness of gold´ was taught to young academics till the millennium as experienced by the author of this doctoral thesis.

Considering that catalytic activity of gold had already been demonstrated and the potential of gold as a possible catalyst for olefin activation had been identified, it is actually surprising that the triumph of gold as a homogeneous catalyst took so long. Moreover, the successful synthesis of still ubiquitous [(L)AuX] (L = PR_3, X = Me, Cl) was achieved early, Purdie and coworkers reported the simple synthesis of [(PEt_3)AuCl] from chloroauric acid and its remarkable stability as early as 1937[99] and publications[100] partially refer for the synthesis of [(PPh_3)AuCl] to a procedure dated 1908.[101]

In the course of the past decade, the area of homogeneous gold catalysis has finally experienced a veritable explosion of activity as its relevance to organic catalysis has been demonstrated. This latest `Gold Rush´ has resulted in numerous publications on gold-mediated synthesis, frequent special journal issues and a number of reviews on the topic have appeared.[102] The still ongoing interest in gold catalysis is due to the metal's versatility and efficiency, covering a broad spectrum of transformations that is ever expanding. Having a retrospective look at gold-catalyzed chemistry, it is now clear that the mild Lewis acidic gold catalysts are excellent activators for various π-systems with an important emphasis on olefins.

Although trivial Au(I) and Au(III) salts such as AuCl, $AuCl_3$ and $NaAuCl_4$ are often sufficient to catalyze a number of organic reactions, the advantages of employing gold catalysts bearing an ancillary ligand, *e.g.* the most common being [(PPh_3)AuCl], are coming into focus. Supporting ligands not only improve the solubility of the metal but the nature of the ligand also affects reactivity and product selectivity. Although phosphines still represent the most important `players´ in organometallic chemistry, recently, *N*-heterocyclic carbenes (NHCs) have been demonstrated as valuable alternatives to the dominant tertiary phosphine ligands in homogeneous catalysis. Conceptually presented as a tertiary phosphine mimic at the onset of their use in catalysis, NHCs have proven to possess advantageous characteristics (see Chapter **4.1-4.3**).

In gold NHC-based catalysis, complexes have displayed significant thermal stability and are rarely moisture- or air-sensitive. Recently, there have been efforts aimed at developing stable cationic gold complexes, the postulated active catalysts in gold(I) systems.[103]

Additionally, Gagosz *et al.* reported the use of the weakly coordinating NTf_2 instead of chloride as a stabilizing and yet reactive ligand.[104] Both approaches eliminate the need for silver salt co-catalysts or activators to enable catalysis, rendering launching a reaction more straightforward and convenient. Some gold-NHC-based catalysts are even commercially available.

The following pages provide a glimpse into the benefits associated with this catalysis and some of its implications in organic synthesis.

4.9.1 Relativistic effects in gold chemistry

Elemental gold has been and still is of value in society due to its rarity, special color and its inertness to oxidation. These properties can be attributed to strong relativistic effects which are important in influencing gold chemistry.[102l, 105] Caused by the attraction of electrons due to the atomic nuclear charge Z, this attraction effects an acceleration of the electrons, resulting in an increased mass as a consequence of relativity.

The effect is strongest for electrons in proximity to the nucleus: *s*-orbitals and, to a minor extend, *p*-orbitals. In consequence, these orbitals experience a contraction, which at the same time decreases the effective nuclear charge for electrons in *d*- and *f*-orbitals

and results in orbital expansion. With the 6*s*-orbital energy lowered and the 5*d*-orbital destabilized, absorption is shifted into visible light inducing the characteristic color of gold (**Figure 4.1**).[106]

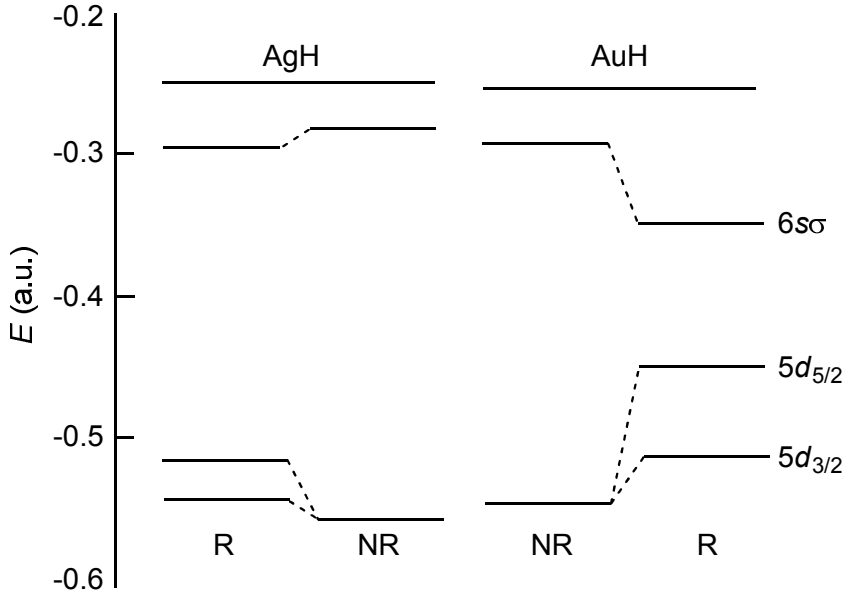


Figure 4.1 Relativistic (R) and non-relativistic (NR) orbitals for AgH and AuH.[102l]

With its position in the Periodic Table, gold experiences a local maximum of relativistic effects (**Figure 4.2**). Important from a catalytic point of view, the relativistic effect induces its high Lewis acidity, which is indicated by an electronegativity of 2.4. The stabilized 6*s*-orbital, which is also responsible for the high first ionization potential of gold and, in consequence, the inertness of gold towards oxidation, properly rationalize this behaviour.

In terms of the HSAB concept $(L)Au^{+}$, a diffuse and large cation, is a remarkably soft Lewis acid resulting in the excellent π-acidity it is known for.[102l] Moreover, relativistic effects also stabilize the Au(III) oxidation state, which is more common for gold in comparison to silver or copper and favored for non-ligated gold complexes.[107]

While the first ionization potential is higher for gold than for silver (*s*-orbital contraction), the second ionization potential is significantly lower as the electron is in a energetically higher 5*d*-orbital (**Figure 4.1**). Noteworthy, the lowest ionization potential for the oxidation state +II in group 11 is found with copper. The third ionization potential is however experiencing a minimum with gold in the group 11 metals. Apart from that, the preference for gold(III) is also explained by higher participation of the 6*p*

and 5*d* orbitals, forming more easily *spd* hybridized orbitals as a consequence of the smaller energy gap.

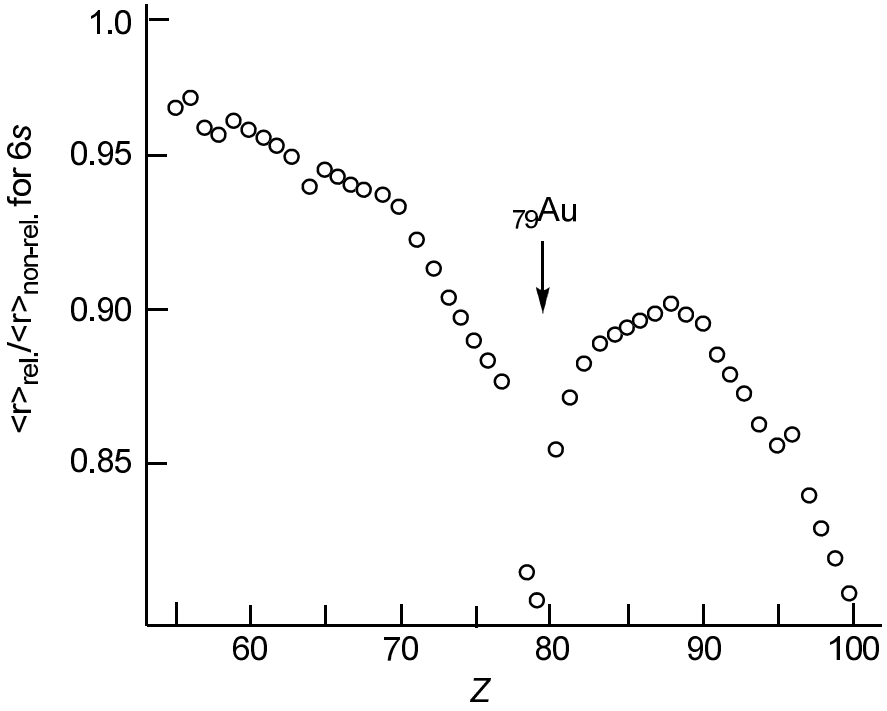


Figure 4.2 Relativistic contraction of the 6*s* orbital.[102l]

Nevertheless, gold, in contrast to other common transition metals, does not usually switch between oxidation states in catalysis and needs an additional oxidant to regenerate the gold(III) species for catalysis involving redox chemistry.[102a] Although gold(III) can still be considered mainly π-acidic, diverse reactivity has been demonstrated for Au(I) and Au(III) by Gevorgyan and coworkers.[108] In the higher oxidation state, Au(III) can be considered a harder Lewis acid and the observations made were rationalized with the increased oxophilicity of gold(III).

Another aspect in gold chemistry is its aurophilicity or aurophilic interactions, describing the tendency of gold to have Au-Au contacts in magnitudes close to the ones observed for hydrogen bonding. Again, stabilization and contraction of the 6s orbitals caused by relativistic effects are supposed to contribute to this effect which was summarized as *`another van der Waals interaction, but a particularly strong one occurring unexpectedly in systems which long have been taken as ''closed-shell'' $(nd^{10})(...)$'*.[109]

Taken as a whole, gold and its chemistry are widely dominated by relativistic effects resulting in its unique character taken advantage of by catalysis.

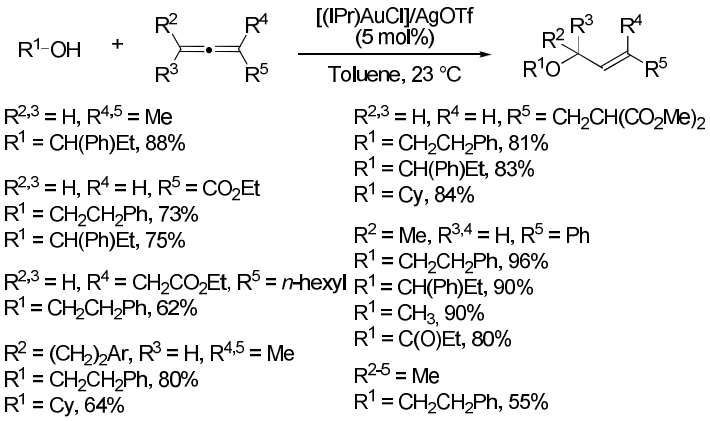
4.9.2 Applications of [(IPr)AuX] complexes in homogeneous catalysis

Due to the huge impact of gold catalysts in homogeneous catalysis in recent years, the amount of publications and applications is enormous and difficult to overview. Advantageously, the vast majority of gold catalysis is appropriately covered by frequent reviews, accounts or special issues highlighting gold, helping to keep track of new developments on the topic.[102] In consequence, the following pages have a focus different to most reviews, usually addressing recent developments or certain organic transformations like, e.g. cycloisomerization.

Paying tribute to the chemistry presented in this thesis, which is exclusively using IPr as a supporting ligand in the final reaction conditions, the focus here will be on the supporting ligand[110] instead and therefore on catalysis achieved with gold catalysts bearing NHCs. Of note, gold catalysis is still widely dominated by phosphine bearing complexes but in many cases NHCs, as well as phosphines, are suitable catalysts as partially seen in the optimization processes.

4.9.2.1 Hydration, hydroalkoxylation and hydroindolylation of allenes

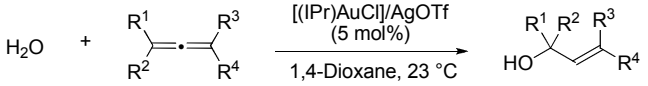
The regio- and stereoselective hydroalkoxylation of allenes was reported with numerous primary and secondary alcohols referring to a catalytic system of 5 mol% of [(IPr)AuCl]/AgOTf in toluene at room temperature (**Scheme 4.19**).[111] The authors highlight the importance of both ligand and counteranion on the yield. They succeeded in the alkoxylation of numerous allenes including mono-, di-, tri- and tetrasubstituted allenes in yields of 41-96%.



Scheme 4.19 Gold-catalyzed hydroalkoxylation of allenes.

The corresponding allyl ethers were formed in high stereospecificity. Loss of chiralty due to racemisation of enantiopure substrates was explained by formation of a gold σ-allyl cation.

In addition, Widenhoefer *et al.* reported the successful hydration of allenes (**Scheme 4.20**).[112] The choice of solvent was again crucial for good yields. While toluene resulted in moderate yields of 33% after 24 hours at room temperature, changes to water-miscible solvents increased the yield up to 77% after 4 hours at a catalyst loading of 5 mol% [(IPr)AuCl]/AgOTf. The hydration occurred selectively at the terminal allenyl carbons to furnish the corresponding (*E*)-allylic alcohols only.



R^{1-3} = H, R^4 = $(CH_2)_{17}Me$, 42%

$R^{1,2}$ = H, R^3 = H, R^4 = $CH_2CH(CO_2Me)_2$, 41%

$R^{1,4}$ = *n*-pentyl, $R^{2,3}$ = H, 54%

R^1 = Me, $R^{2,3}$ = H, R^4 = Ph, 64%

R^1 = Me, $R^{2,3}$ = H, R^4 = CH_2OBz, 73%
(2:1 mixture of 2 products)

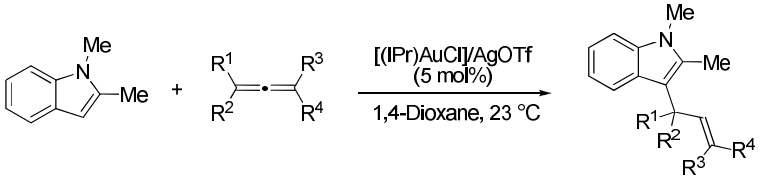
R^1 = $(CH_2)_2Ar$, R^2 = H, $R^{3,4}$ = Me, 73%
(2.5:1 mixture of 2 products)

R^1 = Me, $R^{2,3}$ = H, R^4 = *p*-$C_6H_4CF_3$, 62%

$R^{1,2}$ = H, R^3 = $(CH_2)_2OBn$, R^4 = *n*-hexyl, 36%

Scheme 4.20 Gold-catalyzed hydration of allenes.

The scope of allene activation with [(IPr)AuCl]/AgOTf was further extended to hydroarylation with indoles (**Scheme 4.21**).[113] Widenhoefer *et al.* demonstrated that such reactions can be efficiently realized with 1,2 dimethylindoles at a catalyst loading of 5 mol% in 1,4-dioxane at room temperature with an excess of allene in the reaction mixture. Increasing the catalyst loading to 10 mol% furnished good yields as well for indoles without *N*- or C2-substitution. Unsymmetric disubstituted allenes induce regioselective hydroarylation as a function of steric as well as electronic properties of the substituents. Interestingly, hydroarylation for 1,1-di- and trisubstituted allenes proved inefficient but tetramethylated allene furnished 56% of the target molecule.



R^1 = Cy, $R^{2,3}$ = H, R^4 = CH_2CO_2Et, 48%

$R^{1,4}$ = *n*-pentyl, $R^{2,3}$ = H, 64%

$R^{1,2}$ = H, R^3 = H, R^4 = $CH_2CH(CO_2Me)_2$, 82%

R^{1-4} = Me, 56%

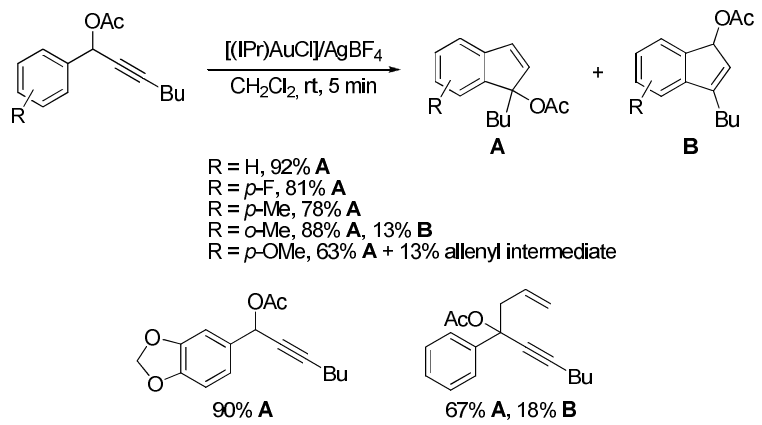
R^1 = Ph, $R^{2,3}$ = H, R^4 = *i*-Pr, 82%

R^1 = Ph, $R^{2,3}$ = H, R^4 = Me, 89%
(1.2:1 mixture of 2 products)

Scheme 4.21 Gold-catalyzed hydroindolylation of allenes.

4.9.2.2 Tandem [3,3] rearrangement/intramolecular hydroarylation.

The formation of substituted indenes can be accomplished with 2 mol% [(IPr)AuCl]/$AgBF_4$ at room temperature in reaction times as short as 5 minutes (**Scheme 4.22**).[114] Nolan *et al.* used propargylic acetates as starting compounds. While the initial [3,3]-sigmatropic rearrangement of the propargylic acetates into the corresponding allenyl acetate can be accomplished by silver only, the subsequent hydroarylation was catalyzed by cationic gold. The catalytic system furnished indenes in yields of 63-92%. Noteworthy, in a few cases the formation of another minor indene product was observed. Lately, it was demonstrated that these minor products resulted from a subsequent gold catalyzed rearrangement of the allyl acetate to yield the thermodynamically more favorable indene.[115]

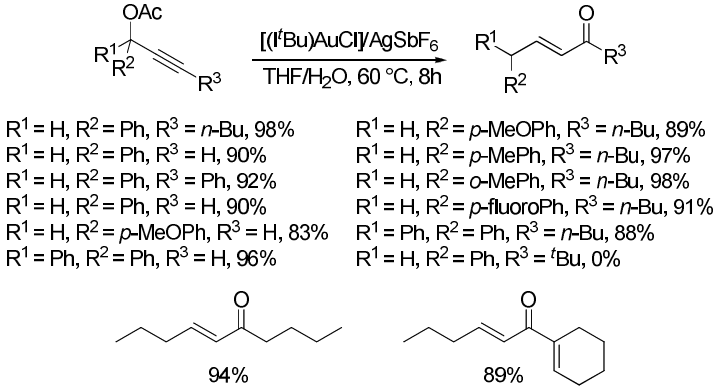


Scheme 4.22 Gold-catalyzed tandem [3,3] rearrangement/intramolecular hydroarylation.

4.9.2.3 Formation of α,β-unsaturated ketones and aldehydes from propargylic acetates

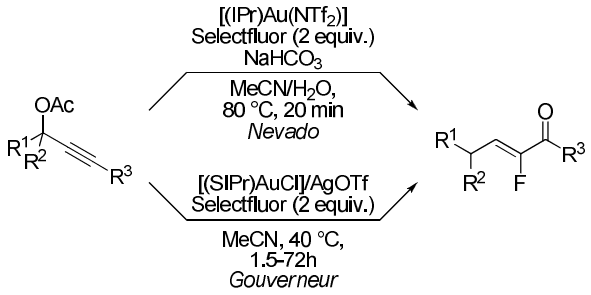
In an expansion of the work on tandem [3,3] rearrangement/intramolecular hydroarylation, the authors further investigated the formation of conjugated enones as a side product in the reaction above.[116] As it turned out, reactivity completely changed in the presence of H_2O (**Scheme 4.23**). Instead of a tandem rearrangement/hydroarylation the authors proposed the formation of [(IPr)Au(OH)] which would then react with the propargylic acetate. Of note, subsequent investigations refute this proposal.[117] As the authors demonstrated a lack of reactivity for allenoacetates as a potential intermediate, their initial hypothesis for enone formation *via* hydration appears more accurate. Subsequent elimination of the acetate as a leaving group yields an allenol which can

tautomerize into the unsaturated ketone. The catalytic system allows for a broad scope with substituents in both propargylic as well as acetylenic position.



Scheme 4.23 Gold-catalyzed formation of α,β-unsaturated ketones and aldehydes.

This methodology was recently expanded to the functionalization of the conjugated enones with selectfluor.[118] Nevado and coworker demonstrated that in the presence of selectfluor as an oxidant α-fluoroenones were obtained in good yields for numerous substrates. [(IPr)Au(NTf_2)] was found essential for a high selectivity for the product avoiding homocoupling. Mechanistically, the authors propose an oxidative addition/reductive elimination pathway. However, in a similar study by Gouverneur using [(SIPr)AuCl]/AgOTf, comparable yields for α-fluoroenones were obtained in the absence of base to trap acetic acid possibly formed. Moreover, formation of α-fluoroenones was realized in the absence of gold, starting from allenoacetates obtained by gold catalyzed [3,3] rearrangement of the propargylic acetate (**Scheme 4.24**).[119]

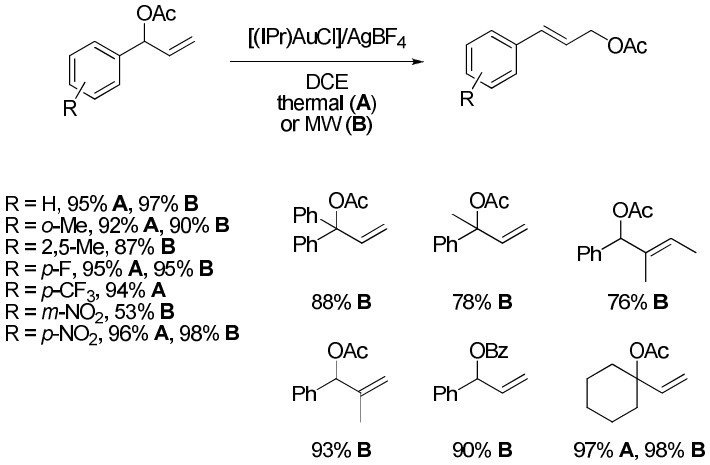


Scheme 4.24 Gold-catalyzed formation of α-fluoroenones.

4.9.2.4 Rearrangement of allylic acetates

Apart from the successful rearrangement of propargylic acetates, rearrangement of allylic esters has also been accomplished (**Scheme 4.25**).[120] It was, however, necessary to increase the temperature to trigger the reaction. To rule out catalysis by $AgBF_4$,

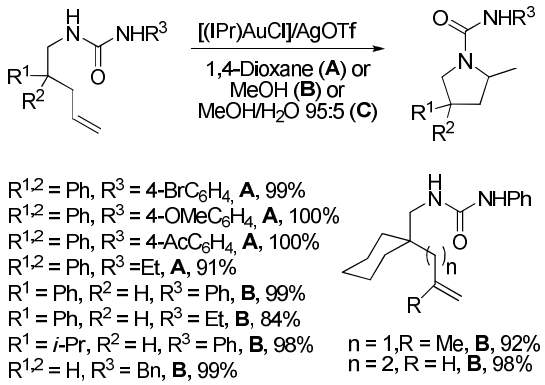
which showed inconclusive reactivity, [(IPr)AuCl] was applied in slight excess. For reasons of improved reaction times, microwave heating to 80 °C for 12 minutes was favoured over conventional heating. The scope consists of mostly aromatic substrates with a terminal allyl moiety. Successful conversion of aliphatic or internal allyl esters was reported, though. *p*-Cyanophenyl- , *o*-nitrophenyl as well as pyridine substituted allyl esters lacked reactivity. As a possible explanation, the formation of stable and inert gold complexes *via* the present heteroatoms was suggested.



Scheme 4.25 Gold-catalyzed rearrangement of allylic acetates.

4.9.2.5 Hydroamination of N-alkenyl ureas

[(IPr)AuCl]/$AgBF_4$ was found to be an excellent catalytic system for the hydroamination of *N*-alkenyl ureas (**Scheme 4.26**).[121] As reported, the excellent σ-donating character together with the steric bulk of IPr allowed the reaction to occur at room temperature with catalyst loadings as low as 1 mol% furnishing excellent yields

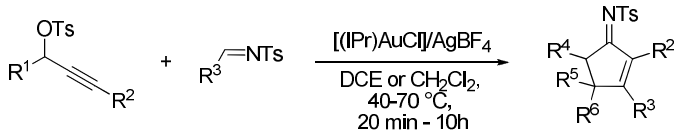


Scheme 4.26 Gold-catalyzed hydroamination of N-alkenyl ureas.

and clearly outperforming the initially tested [(P(^{t}Bu)$_2$(*o*-biphenyl))AuCl]/AgOTf which needed increased temperatures. The catalytic system was applied to hydroamination of a series of *N*-aryl and *N*-alkyl *N*-4-pentenyl ureas substituted in various positions. The isolated yields ranged from 84% up to 100% and it was pointed out that large amounts of both water and air were tolerated without hampering the catalysis.

4.9.2.6 Intermolecular reaction of propargyl tosylates and imines

The gold-catalyzed reaction of propargyl tosylates with imines to afford the synthesis of cyclopent-2-enimines *via* a formal [4+1] cyclization was reported by González and coworkers (**Scheme 4.27**).[122] It was reported that the functionalization of propargylic alcohols as well as tosylates was essential to allow for the formation of the product. A gold catalyzed 1,2-shift of the tosylate initialized the mechanistic cycle of a multistep rearrangement resulting in a Nazarov-like ring closure. Catalytic systems with weakly coordinating counteranions like [(IPr)AuCl]/$AgBF_4$ proved superior. Apart from the mandatory functionalization of both propargylic alcohols and imines, the authors succeeded in applying the catalytic system to various functionalized imines and propargyl tosylates. The yields for the corresponding cyclopent-2-enimines ranged from 34-88%.



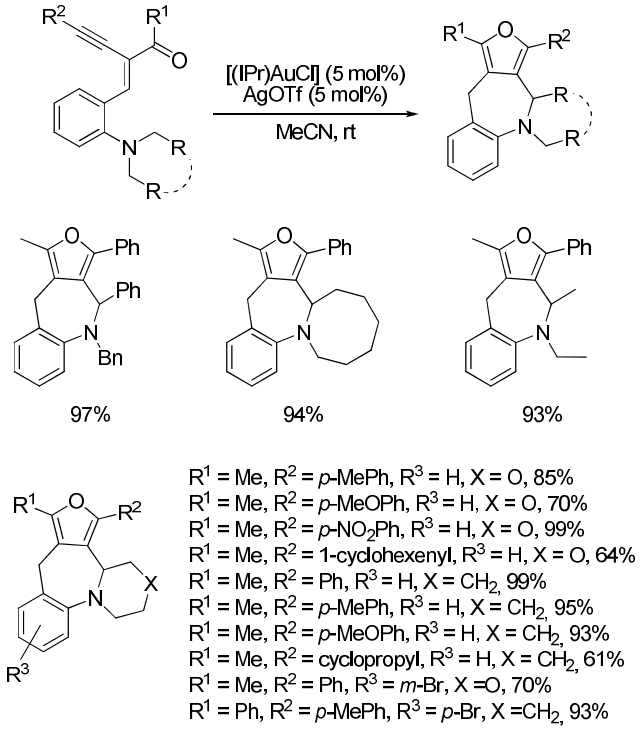
R^1 = *t*-Bu, R^2 = Bu, R^3 = Ph, $R^{4\text{-}6}$ = Me, 86%
R^1 = *t*-Bu, R^2 = Bu, R^3 = *p*-MePh, $R^{4\text{-}6}$ = Me, 82%
R^1 = *t*-Bu, R^2 = Bu, R^3 = *p*-ClPh, $R^{4\text{-}6}$ = Me, 64%
R^1 = *t*-Bu, R^2 = Bu, R^3 = *p*-MeOPh, $R^{4\text{-}6}$ = Me, 77%
R^1 = *t*-Bu, R^2 = Bu, R^3 = *p*-NO_2, $R^{4\text{-}6}$ = Me, 34%
R^1 = *t*-Bu, R^2 = Bu, R^3 = Cy, $R^{4\text{-}6}$ = Me, 70%
R^1 = *t*-Bu, R^2 = Bu, R^3 = *n*-C_7H_{15}, $R^{4\text{-}6}$ = Me, 82%
R^1 = *t*-Bu, R^2 = Bn, R^3 = Ph, $R^{4\text{-}6}$ = Me, 76%
R^1 = *t*-Bu, R^2 = Cy, R^3 = Ph, $R^{4\text{-}6}$ = Me, 75%
R^1 = *t*-Bu, R^2 = $(CH_2)_4OBn$, R^3 = Ph, $R^{4\text{-}6}$ = Me, 64%
R^1 = *t*-Bu, R^2 = *p*-NO_2Ph, R^3 = Ph, $R^{4\text{-}6}$ = Me, 59%
R^1 = *i*-Pr, R^2 = Bu, R^3 = Ph, R^4 = H, $R^{5\text{-}6}$ = Me, 76%

Scheme 4.27 Gold-catalyzed reaction of propargyl tosylates and imines.

4.9.2.7 Selective formation of ring-fused tetrahydroquinolines and tetrahydroazepines via intramolecular redox reaction

The characteristic carbophilicity of gold complexes was applied in the selective synthesis of tetrahydroazepines over tetrahydroquinolines (**Scheme 4.28**).[123] As Zhang and co-workers reported the choice of the Lewis acid is crucial for the further outcome of the reaction of the yne-enone tested. An oxophilic Lewis acid like $Sc(OTf)_3$ triggers an initial 1,5-H-shift by coordination to the ketone moiety resulting in the already

reported tetrahydroquinoline formation. In contrast, the carbophilic [(IPr)AuCl]/AgOTf used coordinates to the alkyne moiety triggering the cyclization into the gold-bearing furanyl intermediate.

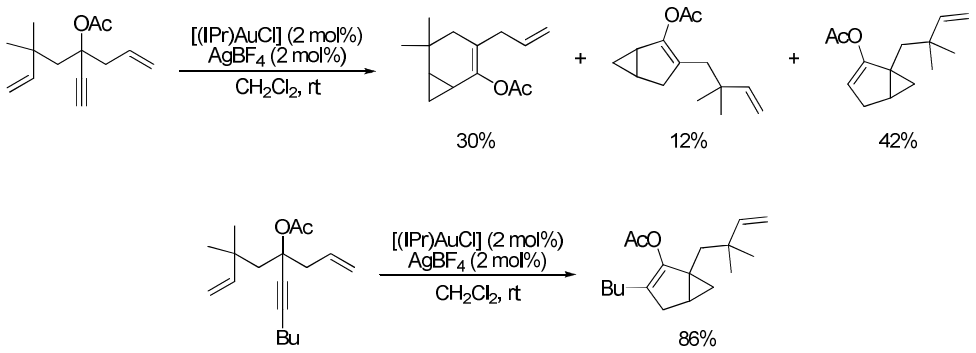


Scheme 4.28 Gold-catalyzed formation of ring-fused tetrahydroquinolines and tetrahydroazepines.

The subsequent 1,5-H-shift allows for a second cyclization to furnish the tetrahydroazepine product and release of the catalyst. Apart from the proof of concept, the authors applied the catalyst to a series of yne-enones furnishing yields as high as 99% with 5 mol% catalyst loading at room temperature.

4.9.2.8 Cycloisomerization of 1,5-enynes bearing a propargylic acetate

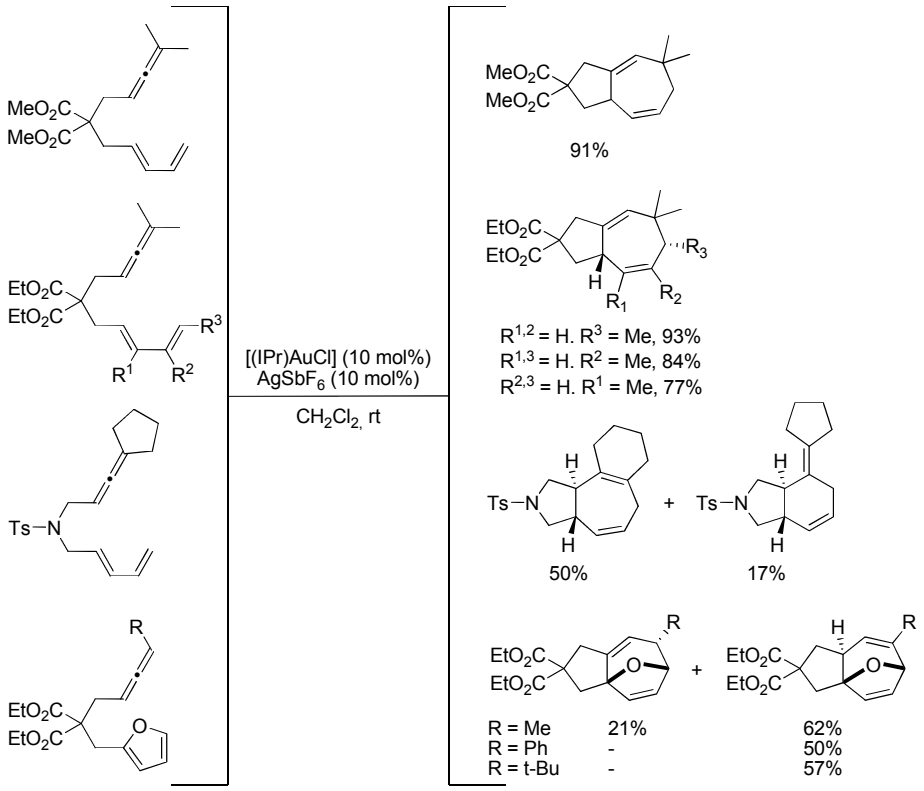
The unexpected formation of bicyclo[3.1.0]hexane *via* cycloisomerisation of propargylic acetate functionalized 1,5-enynes has been demonstrated (**Scheme 4.29**).[124] Au(I) complexes provided a new product in comparison to Pt(II). The choice of the ancillary ligand proved crucial for the product ratios. [(IPr)AuCl]/$AgBF_4$ provided the best ratios in favor of the product, exclusively formed by gold catalysis. A short test with substrates only modified in the acetylenic position revealed a huge impact on the product selectivity.



Scheme 4.29 Gold-catalyzed cycloisomerization of 1,5-enynes bearing a propargylic acetate.

4.9.2.9[4+3] Intramolecular cycloaddition of allenedienes and intermolecular [4+2] cycloaddition of allenamides and acyclic dienes

The excellent catalytic properties of [(IPr)AuCl]/$AgSbF_6$ were also demonstrated in the [4+3] intramolecular cycloaddion of allenedienes (**Scheme 4.30**).[125] The superior catalytic activity in comparison to former $PtCl_2$ catalysis as well as various Au^I- and Au^{III}-complexes allowed for a decrease of the reaction temperature from 110 °C, as for $PtCl_2$, to room temperature at a catalyst loading of 10 mol%.

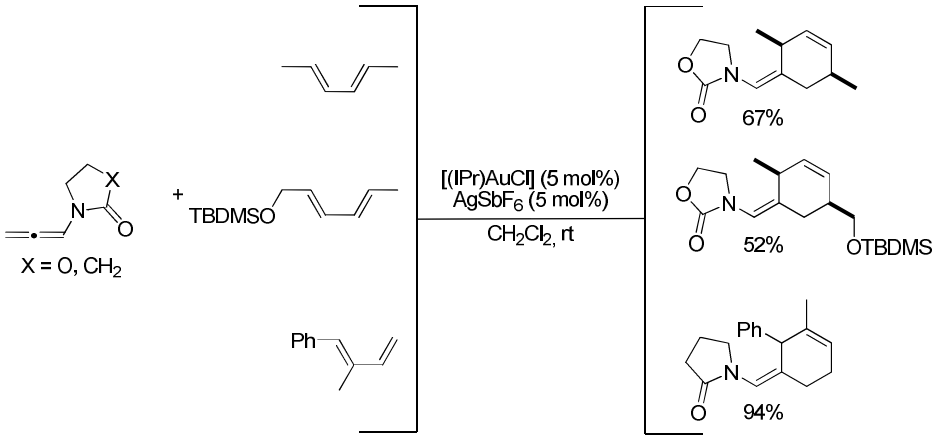


Scheme 4.30 Gold-catalyzed [4+3] intramolecular cycloaddition of allenedienes.

As a result, [(IPr)AuCl]/$AgSbF_6$ allowed for an extended substrate scope to furnish yields as high as 93%; a major improvement on other catalysts in this reaction type. The authors also provided DFT calculations on the cycloaddition with various catalysts indicating a decrease in the energy barrier of the 1,2-H shift in case of [(IPr)AuCl] as a potential explanation for the increased catalytic activity.

The same authors also mention in a recent report the application of [(IPr)AuCl]/$AgSbF_6$ in [4+2] cycloadditions of allenamides and acyclic dienes (**Scheme 4.31**).[126] Notably, [(IPr)AuCl]/$AgSbF_6$ was applied only to a small selection of substrates since in general, AuCl was the catalyst of choice.

Due to its diminished reactivity, AuCl provided a higher chemoselectivity for the desired [4+2] cycloaddition, whereas other Au-catalysts including [(IPr)AuCl]/$AgSbF_6$ also yielded minor amounts of side products resulting from a concurrent [2+2] cycloaddition.

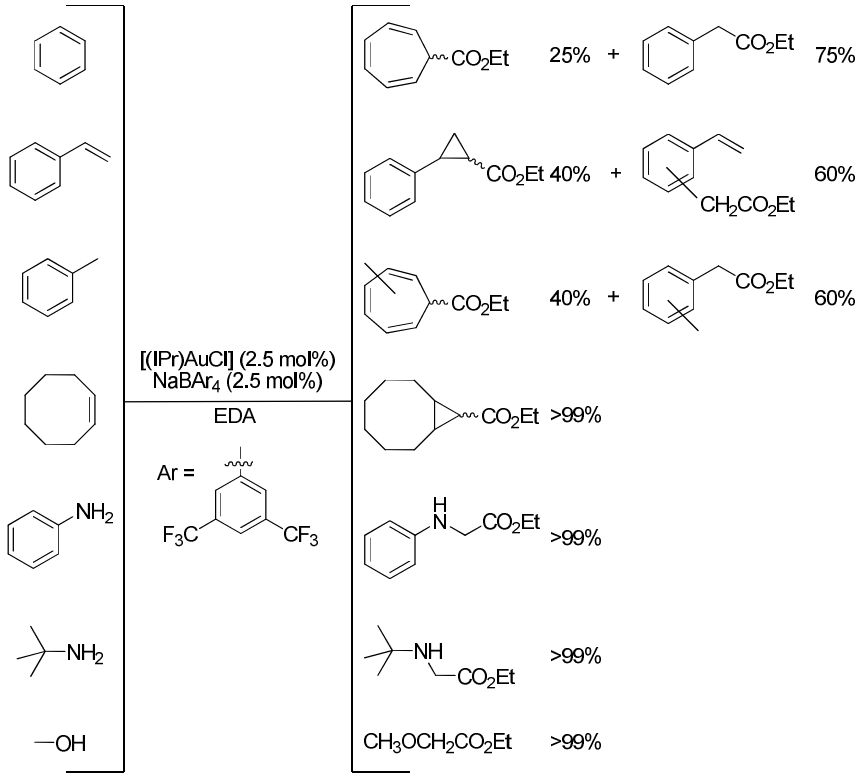


Scheme 4.31 Gold-catalyzed intermolecular (4+2) cycloaddition of allenamides and acyclic dienes.

4.9.2.10 Carbene-transfer reactions from ethyl diazoacetate

The gold-catalyzed carbene transfer resulting from Au-catalyzed decomposition of ethyl diazoacetate (EDA) was an early application of [(IPr)AuCl] (**Scheme 4.32**).[127] After activation with $NaBAr_F$, the gold catalyst furnished excellent results for cyclopropanation as well as insertion into N-H and O-H bonds. Moreover, the authors present an unprecedented reactivity for carbene transfer reactions with EDA: the C-H insertion into aromatic systems. As reported, gold provides mixtures of products in the cases of stilbene, benzene and toluene. While products well-known from other carbene transfer catalysts with EDA remained minor, in all three cases the C-H insertion product

was obtained in 60-75% yield. The authors highlight also the chemoselectivity of the catalyst demonstrated by the lack of diethylfumarate or maleate formation as a result of EDA coupling.

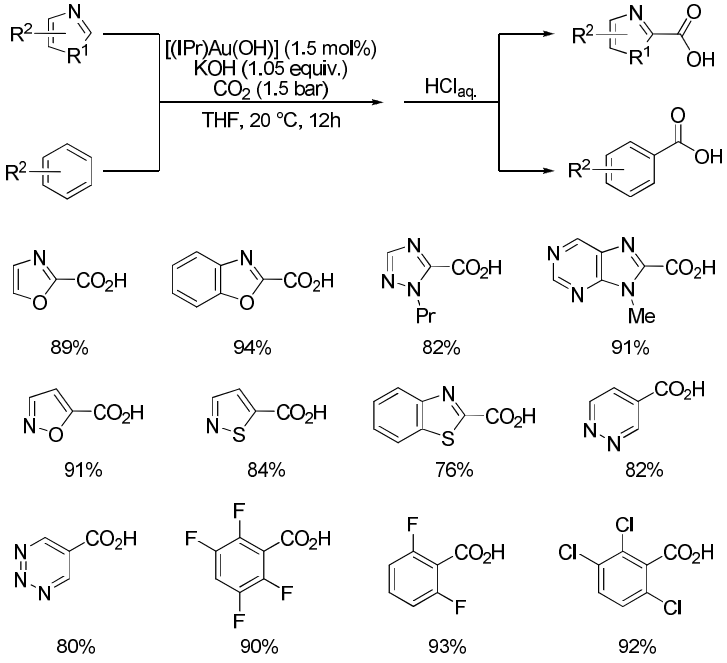


Scheme 4.32 Gold-catalyzed Carbene-transfer reactions from ethyl diazoacetate**.**

4.9.2.11 Carboxylation of C−H bonds and decarboxylation of carboxylic acids

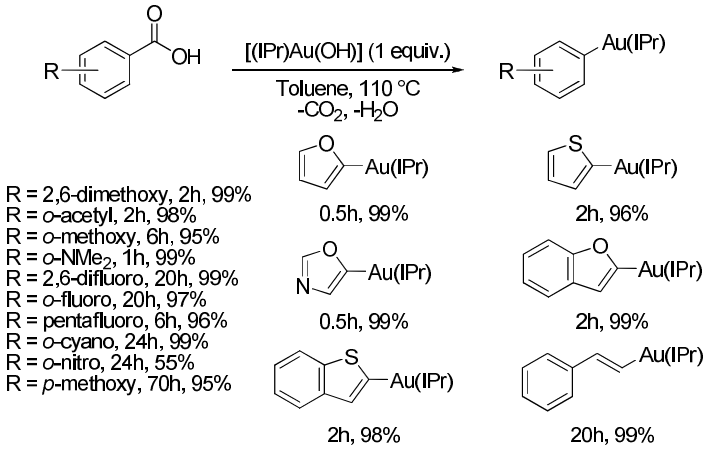
Recently, Nolan and co-workers succeeded in the highly regioselective carboxylation of aromatic heterocycles and activated arenes (**Scheme 4.33**).[128] In their widely acknowledged contribution [(IPr)Au(OH)] was employed, taking advantage of its remarkable basicity with a pk_{aDMSO} of 30.3. As reported, the activation of aromatic heterocycles *via* protonolysis of [(IPr)Au(OH)], under formation of H_2O works best at lower temperatures as a result of the improved solubility of CO_2 in such conditions. With a catalyst loading as low as 1.5 mol% and stoichiometric amounts of KOH for catalyst regeneration, a variety of substrates was carboxylated in high yields and more importantly, in high selectivity. As highlighted by the authors, the C2 selectivity is for a series of substrates in sharp contrast to the C4 selectivity typically observed employing other carboxylation procedures. Notably, it was necessary to change the ligand from IPr to the more donating I^{t}Bu in order to increase catalyst basicity and allow for

carboxylation of azoles and pyrimidines. Isolation of key intermediates supported the mechanistic proposal of the authors involving the protonolysis of [(IPr)Au(OH)] to



Scheme 4.33 Gold-catalyzed carboxylation of aromatic heterocycles and activated arenes.

afford the Au-oxazole intermediate followed by nucleophilic addition of the activated oxazole to CO_2. Catalyst regeneration with KOH and acidic workup furnish the desired carboxylic acid. The catalyst proved very stable and suitable for up to 6 cycles. Aqueous extraction allowed for easy product separation from the catalyst containing organic phase.



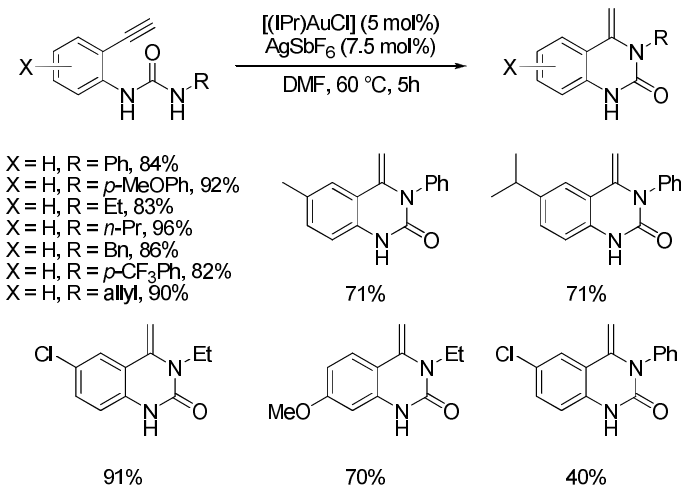
Scheme 4.34 Gold-catalyzed decarboxylation of aromatic and heteroaromatic carboxylic acids.

In a similar manner, gold was applied for the decarboxylation of aromatic carboxylic acids (**Scheme 4.34**).[129] Background for this study is the potential use of carboxylic acids as an attractive cross-coupling reagent.

As demonstrated, decarboxylation of *ortho*-substituted substrates was very efficient at elevated temperatures in toluene using [(IPr)Au(OH)] and could be conducted in air. Advantageously, with CO_2 and H_2O as the only side products, work-up was simple, evaporation of volatile compounds affording clean product without observation of any side products. Apart from a series of aromatic carboxylic acids, the scope was also expanded to a small series of heteroaromatic compounds furnishing excellent yields. Unfortunately, no application of these promising gold(I)-aryl in cross coupling reactions has been provided at this time.

4.9.2.12 6-exo-dig Heterocyclization of 1-(o-ethynylaryl)ureas

The selective 6-*exo*-dig cyclization catalyzed by [(IPr)AuCl]/$AgSbF_6$ was recently achieved by Asensio and co-workers (**Scheme 4.35**).[130] In their report, the authors highlight the importance of the ligand for the product selectivity. Analyzing the optimization process, [(IPr)AuCl] was crucial for the selective formation the 6-*exo*-dig product, which is usually disfavoured over the concurring 5-*endo*-dig. The latter cyclization products were observed for internal alkynes regardless of the catalyst.



Scheme 4.35 Gold-catalyzed 6-*exo*-dig heterocyclization of 1-(*o*-ethynylaryl)ureas.

At a catalyst loading of 5 mol%, a scope of various 1-(*o*-ethynylaryl)ureas was explored, revealing high tolerance for N3 substituents which apparently have negligible

influence on the reaction. In contrast, electron-withdrawing substituents on the aryl moiety showed significant decrease of product formation.

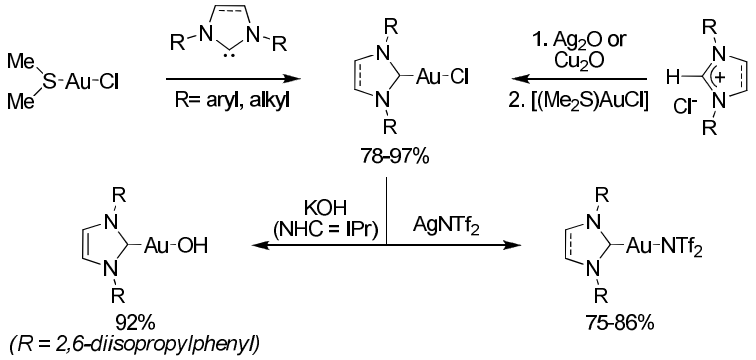
4.10 Outlook

Intensive research on the synthesis of *N*-heterocyclic carbenes and their application in catalysis allowed for countless reports within the last two decades. Very important progress was made on various fields of research like ligand design and theoretical background, as well as application in catalysis. NHCs proved to be very useful ligands in numerous important reactions. In here, only a few selected examples of NHC-metal catalyzed reactions were presented, but many more reports can be found in the literature. Nevertheless, great efforts are still undertaken to further broaden the already wide field of applications and new interesting and promising topics like e.g. organocatalysis with NHCs[4b] obtain rising interest. It is safe to say that more exciting findings on NHC related topics are yet to come.

5 Synthesis of [(NHC)AuX] Complexes

The following chapters systematically make use of a variety of [(NHC)AuX] complexes. For the convenience of the reader, syntheses of commonly used complexes are summarized in this chapter.

The synthesis of [(NHC)AuCl] complexes is most often achieved by one of two procedures: (a) ligand exchange or (b) transmetalation. Both methodologies take advantage of [(DMS)AuCl] as an intermediate gold species, which is obtained from commercially available $HAuCl_4$ as the preferred gold source and dimethylsulfide (DMS) (**Scheme 5.1**). Importantly, at least 2 equiv. of DMS are needed as it has dual functionality in this reaction, as both a supporting ligand and reductant.[131]



Scheme 5.1 Typical synthetic approaches to [(NHC)AuX] (X = Cl, OH, NTf_2).

Stable at reduced temperature, [(DMS)AuCl] is then reacted in anhydrous conditions *via* ligand exchange with carbenes in THF at room temperature. Due to the moisture sensitivity of carbenes it is necessary to work under inert atmosphere, increasing the amount of effort required for this procedure.

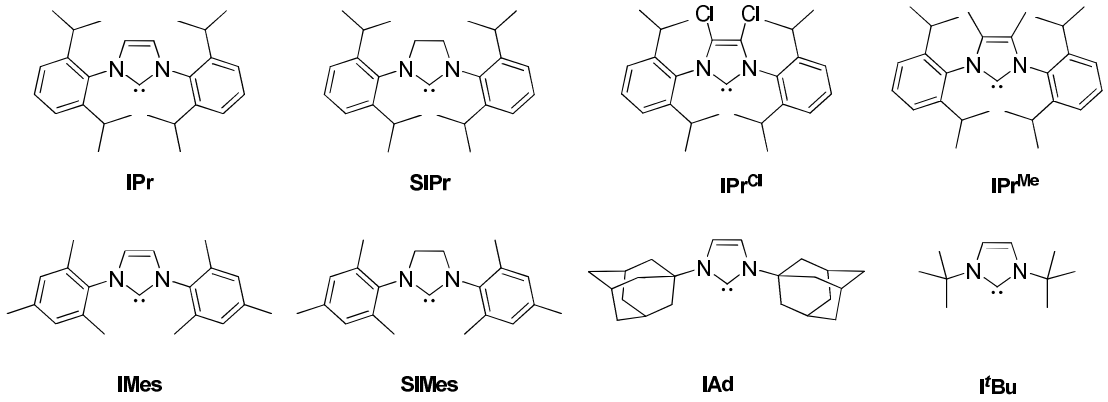
More commonly, [(NHC)AuCl] is synthesized from [(NHC)AgCl] and [(DMS)AuCl] *via* transmetalation in CH_2Cl_2 at room temperature.[132] Advantageously, Ag_2O can be reacted directly with NHC•HCl to afford fairly stable [(NHC)AgCl] complexes for further transmetalation.[133] The reaction can be performed in air without further precautions.

Moreover, it is possible to perform the synthesis in one-pot, starting with NHC•HCl and Ag_2O in CH_2Cl_2 and subsequent addition of [(DMS)AuCl].[134] This procedure was mostly used for the synthesis of the complexes used in this thesis. Recently, it was

shown that Ag_2O can be replaced by the less costly Cu_2O with a slightly modified procedure involving refluxing CH_2Cl_2.[135]

Gagosz and co-workers established the application of gold complexes bearing NTf_2 as the labile ligand. Fortunately, these air- and moisture-stable complexes do not need any additive for activation facilitating the catalysis process. The complexes are easily available in good yields from [(NHC)AuCl] and $AgNTf_2$ in CH_2Cl_2 after 5 minutes at room temperature. The latter is available *via* a straightforward reaction of Ag_2CO_3 and $HNTf_2$ in water at 65°C.

Recently, [(IPr)Au(OH)] was reported and received much attention.[136] The synthesis reacted [(NHC)AuCl] with excess KOH in a 1:1 solvent mixture of THF and toluene and heating at 60 °C for 24 hours. [(IPr)Au(NTf_2)] can be synthesized from [(IPr)Au(OH)] and $HNTf_2$.



Scheme 5.2 Illustration of NHCs used as supporting ligand for gold complexes in this thesis.

5.1 Experimental section

Synthesis of [(DMS)AuCl]:[131] $HAuCl_4 \cdot 3H_2O$ (30 g, 76 mmol) was dissolved in EtOH (300 mL) and dimethylsulfide (11.6 mL, 2.05 equiv.) was added slowly under stirring. Yellow precipitate was formed instantaneously. A 1:1 mixture of H_2SO_4/H_2O was added until the precipitate turned colourless. The precipitate was collected *via* filtration and washed subsequently with EtOH (2 x 5 mL), diethylether (2 x 10 mL) and pentane (2 x 20 mL). The colourless solid was dried in the dark at room temperature *in vacuo* for 30 min (20.4 g, 91%) and used directly . For storage, the compound has to be kept at -20 °C in the dark to avoid decomposition. ^1H NMR (400 MHz ,$CDCl_3$) δ 2.75 (s).

General procedure for the synthesis of [(NHC)AuCl] complexes

A mixture of silver(I) oxide (0.65 equiv.) and NHC•HCl (1 equiv.) in CH_2Cl_2 (0.25 M) was stirred for 4 hours. The mixture was filtered through Celite, and [(DMS)AuCl] (1.02 equiv.) was added. The resulting mixture was stirred for 12 hours, then activated carbon was added. After 30 min of stirring the mixture was filtered through Celite. The solvent was reduced to a minimum *in vacuo*. Pentane was added in large excess to the solution, resulting in an immediate precipitation of a colourless solid. The solid was filtered, further washed with pentane and dried *in vacuo*.

Alternative procedure: A mixture of silver(I) oxide (0.65 equiv.) and N,N'-bis(2,6-diisopropylphenyl)imidazolium chloride (1 equiv.) in CH_2Cl_2 (0.25 M) was stirred for 4 hours. The mixture was filtered through Celite and the solvent reduced to a minimum *in vacuo.* Pentane was added in large excess to the solution, resulting in an immediate precipitation of a colourless solid. The solid was filtered, further washed with pentane and dried *in vacuo*. The yield of [(NHC)AgCl] was determined and [(NHC)AgCl] was diluted in CH_2Cl_2 (0.25 M). [(DMS)AuCl] (1.02 equiv.) was added and the resulting mixture was stirred for 12 hours. Then activated carbon was added. After 30 min of stirring the mixture was filtered through Celite. The solvent was reduced to a minimum *in vacuo*. Pentane was added in large excess to the solution, resulting in an immediate precipitation of a colourless solid. The solid was filtered, further washed with pentane and dried *in vacuo*.

Synthesis of [(IPr)AuCl]: Following the general procedure (14.6 mmol), the compound was obtained as a colourless solid (6.4 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.9 Hz, 2H), 7.31 (d, *J* = 7.9 Hz, 4H), 7.28 (s, 2H), 2.48 (spt, *J* = 6.9 Hz, 4H), 1.31 (d, *J* = 6.9 Hz, 12H), 1.23 (d, *J* = 6.9 Hz, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9, 145.7, 133.6, 131.0, 124.4, 123.7, 29.0, 24.4, 24.0.

Synthesis of [(SIPr)AuCl]: Following the general procedure (2.34 mmol), the compound was obtained as a colourless solid (890 mg, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (t, *J* = 7.6 Hz, 2H), 7.24 (d, *J* = 7.6 Hz, 4H), 4.05 (s, 4H), 3.05 (spt, *J* = 6.8 Hz, 4H), 1.42 (d, *J* = 6.8 Hz, 12H), 1.34 (d, *J* = 6.8 Hz, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.3, 146.7, 134.2, 130.2, 124.8, 53.6, 29.1, 25.3, 24.3.

Synthesis of [(IMes)AuCl]: Following the general procedure (60 mmol), the compound was obtained as a colourless solid (24.8 g, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (s, 2H), 6.99 (s, 4H), 2.35 (s, 6H), 2.11 (s, 12H). ^{13}C NMR (75MHz, $CDCl_3$) δ 173.2, 139.8, 134.7, 129.5, 122.3, 21.2, 17.8.

Synthesis of [(SIMes)AuCl]: Following the general procedure (2.91 mmol), the compound was obtained as a colourless solid (1.12 g, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (s, 4H), 3.98 (s, 4H), 2.31 (s, 12H), 2.29 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.2, 139.1, 135.6, 134.7, 129.9, 50.8, 21.2, 18.1.

Synthesis of [(I^{t}Bu)AuCl]: Following the general procedure (4.59 mmol), the compound was obtained as a colourless solid (1.2 g, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (s, 2H), 1.88 (s, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 116.5, 59.1, 31.9.

Synthesis of [(IAd)AuCl]: Following the general procedure (2.68 mmol), the compound was obtained as a colourless solid (916 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (s, 2H), 2.57 (br. s, 12H), 2.27 (br. s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5, 115.6, 59.5, 44.3, 36.0, 30.1.

Synthesis of [(IPr^{Me})AuCl] (literature procedure):[137] Ag_2O (199.5 mg, 0.86 mmol) was added to a solution of IPr^{Me}·HCl (600 mg, 1.32 mmol) in CH_2Cl_2 (7 mL). The reaction mixture was stirred in the dark at room temperature for three hours and was then filtered through a pad of Celite. The solvent was removed *in vacuo* and hexane was added (10 mL). The resulting precipitate was collected by filtration, washed with hexane (3 × 5 mL) and dried under vacuum to afford [(IPr)AgCl] as a colourless powder. Yield: 563 mg (76%). [(IPr)AgCl] (200 mg, 0.36 mmol) was added to a solution of [(DMS)AuCl)] (116 mg, 0.40 mmol) in CH_2Cl_2 (4 mL). The resulting mixture was stirred for three days at room temperature. Activated carbon was then added and the reaction mixture was stirred an additional day under daylight. The suspension was filtered through a pad of silica. The solvent was reduced to 1 mL and hexane (10 mL) was added. The precipitate was filtered, washed with hexane (3 × 5 mL) and dried under vacuum to furnish a colourless solid (155 mg, 67%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.49 (t, J = 7.8 Hz, 2H); 7.28 (d, J = 7.8 Hz, 4H); 2.44 (spt, J = 6.9 Hz, 4H); 1.94 (s, 6H), 1.34 (d, J = 6.9 Hz,

12H); 1.22 (d, *J* = 6.9 Hz, 12H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.4, 145.8, 132.3, 130.1, 126.0, 124.3, 28.7, 25.1, 23.4, 9.7.

Synthesis of [(IPr^{Cl})AuCl] (literature procedure):[138] In a Schlenk tube, IPr·HBF_4 (953 mg, 2 mmol) was added to a suspension of NaH (96 mg, 4 mmol) in THF (10 mL). A spatula of KO^{t}Bu was added, and the reaction mixture was stirred at room temperature overnight. The solution was filtered and CCl_4 (386 μL, 4 mmol) was added to the filtrate. The reaction mixture was stirred an additional 3 h, and [(DMS)AuCl] (589 mg, 2 mmol) was added. The reaction mixture was stirred in darkness at room temperature during 14 hours. The reaction mixture was filtered on a pad of silica, and solvent was removed under vacuum. The crude mixture was dissolved in dichloromethane, and activated carbon was added. The resulting mixture was stirred at room temperature overnight. The solution was filtered on a pad of silica. Solvent was reduced to 2 mL under vacuum, and hexane (10 mL) was added. The resulting pale yellow precipitate was filtered, washed with hexane (3 × 5 mL), and dried under vacuum (771 mg, 56%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (t, *J* = 7.8 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 4H), 2.45 (spt, *J* = 6.8 Hz, 4H), 1.35 (d, *J* = 6.8 Hz, 12H), 1.26 (d, *J* = 6.8 Hz, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.1, 146.0, 131.6, 130.0, 124.6, 118.9, 29.1, 24.6, 23.4.

Synthesis of $AgNTf_2$:[139] Silver carbonate (398 mg, 1.44 mmol) was added to a solution of trifluoromethansulfonimide (809 mg, 2.88 mmol) in H_2O (15 ml) in a flask wrapped with alumina foil. The reaction mixture was heated to 65°C for 30 min and filtered over Celite. All volatile compounds were removed *in vacuo* and the colourless solid was dried in the dark at 80 ºC in *vacuo* for 6 hours. To remove remaining impurities the compound was dissolved in Et_2O, stirred for 2 hours at room temperature and filtered over Celite. After evaporation of the solvent, $AgNTf_2$ was obtained as a colourless solid (960 mg, 86%) and directly used. For storage, the compound has to be kept at -20 °C in the dark. ^{19}F NMR (376 MHz, $CDCl_3$) δ -80.12.

General procedure for the synthesis of [(NHC)Au(NTf_2)] complexes

To a solution of [(NHC)AuCl] (1 equiv.,) in CH_2Cl_2 (0.05 M) was added $AgNTf_2$ (1 equiv.). The solution was stirred for five minutes and passed through a filter of Celite. The solvent was reduced *in vacuo*. Pentane was added resulting in the immediate

precipitation of a colourless solid. This solid was filtered, washed with pentane and dried under reduced pressure to yield a colourless solid. If necessary, complexes were further purified: After dilution in CH_2Cl_2, a spatula of activated carbon was added and the mixture was stirred for 30 min. After filtration over Celite, the solvent was reduced under reduced pressure to a minimum and the complex precipitated by addition of excess pentane. ^{1}H-NMR data were in good agreement with the literature.[104a]

Synthesis of [(IPr)Au(NTf$_2$)]: Following the general procedure (1.26 mmol), the compound was obtained as a colourless solid (767 mg, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (t, *J* = 7.9 Hz, 2H), 7.31(d, *J* = 7.9 Hz, 4H), 7.28 (s, 2H), 2.48 (spt, *J* = 6.9 Hz, 4H), 1.31 (d, *J* = 6.9 Hz, 12H), 1.23 (d, *J* = 6.9 Hz, 12H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -76.49. ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9, 145.7, 133.6, 131.0, 124.4, 123.7, 119.0 (q, *J* = 323 Hz), 77.5, 76.8, 29.0, 24.4, 24.0.

Synthesis of [(SIPr)Au(NTf$_2$)]: Following the general procedure (0.5 mmol), the compound was obtained as a colourless solid (315 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (t, *J* = 7.9 Hz, 2H), 7.25 (d, *J* = 7.9 Hz, 4H), 4.17 (s, 4H), 3.00 (spt, *J* = 6.8 Hz, 4H), 1.38 (d, *J* = 6.8 Hz, 12H), 1.34 (d, *J* = 6.8 Hz, 12H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -76.49. ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.8, 146.7, 133.5, 130.3, 124.7, 119.0 (q, *J* = 324 Hz), 53.6, 29.2, 24.6.

Synthesis of [(IMes)Au(NTf$_2$)]: Following the general procedure (0.5 mmol), the compound was obtained as a colourless solid (356 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (s, 2H), 7.03 (s, 4H), 2.36 (s, 6H), 2.10 (s, 12H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -76.67. ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 140.3, 134.7, 134.2, 129.5, 122.8, 118.8 (q, *J* = 323 Hz), 21.2, 17.8.

Synthesis of [(SIMes)Au(NTf$_2$)]: Following the general procedure (186 μmol), the compound was obtained as a colourless solid (97 mg, 67%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.98 (s, 4H), 4.10 (s, 4H), 2.31 (s, 18H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -76.49. ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.5, 139.5, 135.6, 134.0, 129.7, 119.0 (q, *J* = 323 Hz), 77.6, 76.7, 51.0, 21.1, 18.0.

Synthesis of [(I^{t}Bu)Au(NTf$_2$)]: Following the general procedure (242 μmol), the compound was obtained as a colourless solid (141 mg, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (s, 2H), 1.85 (s, 18H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -75.55. ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.0, 119.6 (q, *J* = 323 Hz), 117.2, 59.5, 31.6.

Synthesis of [(IAd)Au(NTf$_2$)]: Following the general procedure (0.5 mmol), the compound was obtained as a colourless solid (234 mg, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (s, 2H), 2.55-2.45 (m, 12H), 2.28 (bs, 6H), 1.85-1.70 (m, 12H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -75.37. ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6, 119.7 (q, *J* = 323 Hz), 116.4, 60.0, 44.2, 35.7, 30.1.

Synthesis of [(IPr^{Me})Au(NTf$_2$)]: Following the general procedure (77 μmol), the compound was obtained as a colourless solid (68 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (t, *J* = 7.9 Hz, 2H), 7.31 (d, *J* = 7.9 Hz, 4H), 2.38 (spt, *J* = 6.8 Hz, 4H), 2.03 (s, 6H), 1.30 (d, *J* = 6.8 Hz, 12H), 1.23 (d, *J* = 6.8 Hz, 12H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -76.45. ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.5, 146.0, 132.1, 130.8, 127.0, 124.5, 119.0 (q, *J* = 323 Hz), 28.9, 24.6, 23.9, 9.8. Elemental analysis (calc): C 41.71 (41.66), H 4.42 (4.51), N 4.68 (4.70).

Synthesis of [(IPr^{Cl})Au(NTf$_2$)]: Following the general procedure (72 μmol), the compound was obtained as a colourless solid (59 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 - 7.53 (m, 2H), 7.35 (d, *J* = 7.9 Hz, 4H), 2.39 (spt, *J* = 6.9 Hz, 4H), 1.31 (d, *J* = 7.0 Hz, 12H), 1.27 (d, *J* = 6.8 Hz, 12H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -76.01. ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4, 146.2, 131.9, 130.9, 124.8, 119.8, 119.0 (q, *J* = 324 Hz), 29.4, 24.1, 23.9. Elemental analysis (calc): C 37.16 (37.27), H 3.57 (3.67), N 4.61 (4.50).

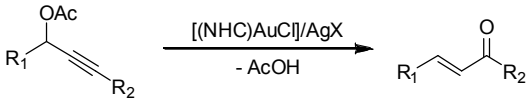
6 Gold(I)-Catalyzed Meyer-Schuster Rearrangement

6.1 Introduction

The interest in α,β-unsaturated carbonyl compounds is linked to their general importance in synthesis. Such compounds are useful chemical building blocks displaying biological activities[140] and are notably used as substrates in cyclopropanation,[141] Michael-Additions[142] and cycloadditions such as the Diels-Alder reaction.[143] Hence, it is worthwhile to develop efficient procedures to access these substrates. A typical approach to α,β-unsaturated ketones is aldol condensation,[144] including the Knoevenagel reaction,[145] and the Horner-Wadsworth-Emmons (HWE) reaction to produce unsaturated esters.[146] These classical reactions have proved to be very useful and are well-established as standard procedures. Nevertheless, for synthetic chemists there is still an interest in developing new routes to unsaturated carbonyl compounds as in some cases standard procedures fail to provide appropriate results. Furthermore, some of these methods generate considerable amounts of waste and do not meet the criteria of modern and environmentally-friendly chemistry. In this context, the isomerization of propargylic alcohols into α,β-unsaturated ketones and aldehydes allows total atom economy[147] and represents an attractive alternative. As the Rupe[148] and the Meyer-Schuster rearrangement,[149] this transformation can be catalyzed by several transition metals.[150]

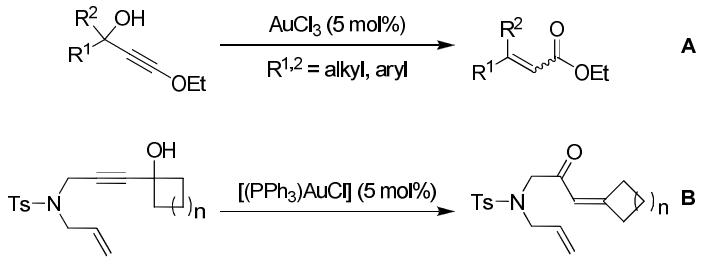
Gold catalysts appear useful in this type of catalysis. The activation of alkynes by Au(I,III), leading to many new structures and reactivities, highlights the use of gold as an excellent activator of π-systems.[102g, h, 110, 151] The Lewis-acidity of gold complexes and their ability to activate alkynes as well as allenes for inter- or intramolecular nucleophilic attack has prompted intense research, notably involving oxo-nucleophiles. Gold-catalyzed formation of conjugated enones can be performed using readily accessible propargylic acetates as substrates.[152]

Zhang and co-workers recently reported the formation of unsaturated ketones catalyzed by $[(PPh_3)Au(NTf_2)]$.[153] Concomitantly, the Nolan group reported the $[(NHC)Au^I]$-catalyzed formation of enones as well as enals from propargylic acetates (**Scheme 6.1**).[116]



Scheme 6.1 Formation of α,β-unsaturated enones from propargylic acetates.

Computational studies by Nolan and co-workers on the mechanism of the reaction led to the proposal of the unexpected activation of water by gold(I) instead of activation of the π-system. Formation of conjugated enones from propargylic alcohols in the presence of gold is also known. The Au^{III}-catalyzed rearrangement of propargylic alcohols was notably observed by Campagne, when using 5 mol% of $NaAuCl_4$ in the presence of ethanol.[154] Dudley reported the preparation of α,β-unsaturated esters, intending to find an alternative methodology to the HWE olefination of hindered ketones by using electron-rich ethoxyacetylene and tertiary propargylic alcohols (**Scheme 6.2**, A). While a tertiary alcohol should facilitate the proposed ionization of the C–O bond, the use of electron-rich alkynes enforces alkyne activation by a soft Lewis-acid catalyst such as $AuCl_3$.[155] An advantage of activating the alkyne instead of the alcohol function is the elimination of the concurring Rupe rearrangement.[148] Dudley later reported an improved catalytic system with expanded scope using Au^{I} instead of Au^{III}.[156] Au^{I}-catalyzed Meyer-Schuster rearrangement of propargylic alcohols was also reported by Chung in 2007 using [(PPh_3)AuCl] (**Scheme 6.2**, B),[157] but only moderate to good yields with specific substrates were obtained. Recently, Akai disclosed a promising catalytic system applicable to primary alcohols but requiring [$MoO_2(acac)_2$] in addition to [(PPh_3)AuCl] and AgOTf.[158]



Scheme 6.2 Meyer-Schuster rearrangements reported by Dudley and Chung.

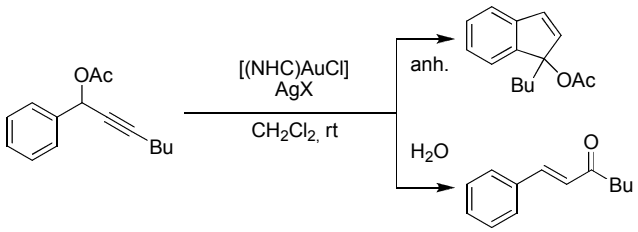
A general procedure to produce α,β-unsaturated ketones and esters in good yields and high stereocontrol with a [(NHC)AuCl]-catalyst under mild reaction conditions is

reported in this chapter. The scope and a proposed mechanism are discussed as well as the limitations of the present catalytic system.

6.2 Results and Discussion

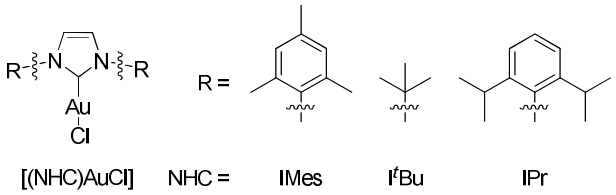
6.2.1 Optimization

Amongst others, the Nolan group reported the development of gold catalysts for the formation of indenes using propargylic acetates as substrates under anhydrous conditions[159] as well as the formation of enones in the presence of water (**Scheme 6.3**).[116]



Scheme 6.3 [(NHC)AuCl]-catalyzed formation of indenes and enones

The interest in propargylic alcohols lies in their availability, presenting a more straightforward synthesis, usually in one step from addition of an acetylide to a ketone or an aldehyde. As a starting point, compound **1a** with 2 mol% of [(IPr)AuCl] was used in the presence of $AgSbF_6$ in CH_2Cl_2. While there was no conversion under anhydrous conditions, the formation of remarkable amounts of the Meyer-Schuster product **2a** was observed when using technical grade CH_2Cl_2. After testing a broad spectrum of solvents, MeOH was chosen for further reactions. A brief screening of commonly used gold-NHC complexes (**Scheme 6.4**) was made. Notably, [(IPr)AuCl] was found to be by far the best catalyst in comparison to [(IMes)AuCl] and [(I^{t}Bu)AuCl] (**Table 6.1**, entries 1-6). [(IPr)AuCl] and silver tetrafluoroborate were independently tested as catalyst, in both cases the pure starting material was recovered. Concerning the nature of the counteranion, $AgBF_4$ gave similar results compared to $AgSbF_6$. Lowering the catalyst loading from 2 mol% to 0.1 mol% only led to minor conversion despite prolonged reaction times.

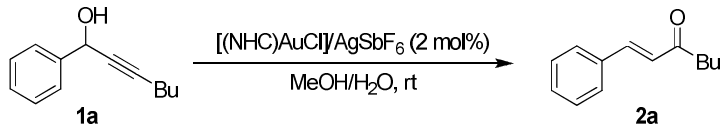


Scheme 6.4 Gold-NHC complexes used.

6.2.2 Substrate scope

Having an efficient catalytic system in hand, the scope of this transformation was explored. It should be noted that the reaction time and the temperature necessary to reach full conversion were found to be highly dependent on the specific substrate. In order to ensure complete conversion of all substrates, reactions were heated to 60 °C overnight. To examine the influence of substituents on the aryl moiety, different aryl derivatives with a *n*-butyl chain in the acetylenic position were screened. As illustrated in **Table 6.2**, good to excellent yields were obtained for a variety of substrates. Substitution of the aromatic ring with electron-withdrawing groups (entries 2 and 3) furnished slightly lower yields compared to **1a**. On the other hand, electron-donating substituents (entries 4 and 5) as well as the tertiary alcohol **1f** (entry 6) afforded excellent conversions. Of note, **1a**-**1e** were selectively converted into the (*E*)-isomers.

Table 6.1 Catalyst screening for Meyer-Schuster rearrangement.[a]



1a **2a**

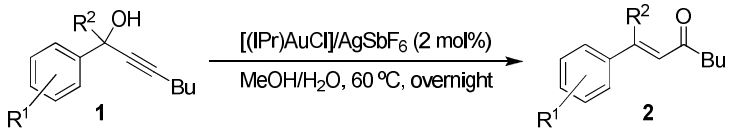
Entry	Catalyst	Time	Conv. (%)[b]
1	[(IPr)AuCl]	70 min	80
2	[(IMes)AuCl]	70 min	27
3	[(I^{t}Bu)AuCl]	70 min	37
4	[(IPr)AuCl]	4 h	99
5	[(IMes)AuCl]	4 h	42
6	[(I^{t}Bu)AuCl]	4 h	70

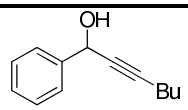
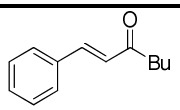
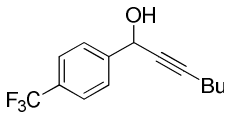
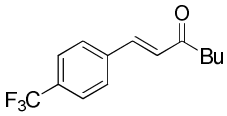
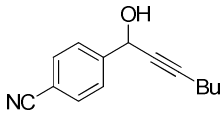
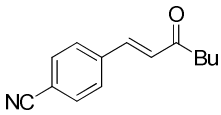
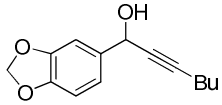
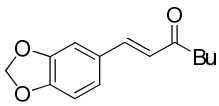
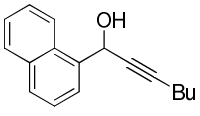
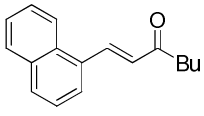
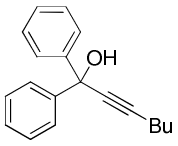
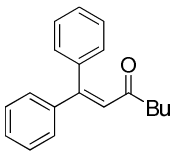
[a] Reaction conditions: **1a** (0.27 mmol) in MeOH (2 mL), water (0.3 mL), [(NHC)AuCl]/$AgSbF_6$ (2 mol%), room temperature. [b] Conversion determined by GC.

This result is in line with the stereoselective conversion of propargylic acetates as previously reported.[116] Furthermore, the present catalytic system equals or outperforms reported catalytic systems for the Meyer-Schuster rearrangement of propargylic alcohols.[160]

Next, the effect of the acetylenic substituent was examined in substrates containing a propargylic phenyl ring (**Table 6.3**). When the acetylenic substituent was modified from *n*-butyl to *tert*-butyl, a good conversion into the corresponding product was observed (**Table 6.3**, entry 1). This is remarkable since the corresponding propargylic acetate failed to react with the previous catalytic system.[116]

Table 6.2 Effect of aryl derivatives in propargylic position.



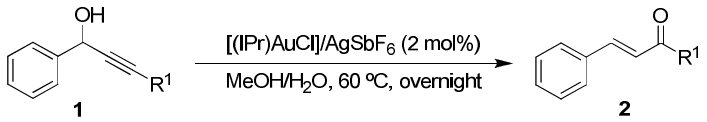
Entry	Propargylic alcohol	1	Enone	2	Yield (%)[a]
1		**1a**		**2a**	96
2		**1b**		**2b**	81[b]
3		**1c**		**2c**	74[b]
4		**1d**		**2d**	81[b]
5		**1e**		**2e**	92[b]
6		**1f**		**2f**	96

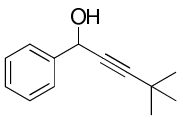
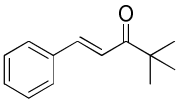
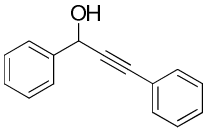
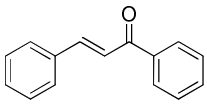
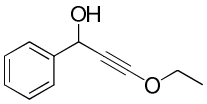
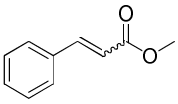
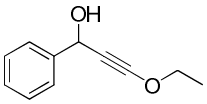
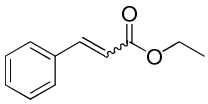
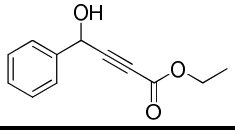
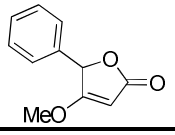
[a] NMR yields with respect of benzaldehyde as internal standard are average of two runs. [b] Isolated yield.

Using activating substituents such as a phenyl group (entry 2) provided excellent conversions. Interestingly, with **1i** the quantitative transesterificated methoxyester **2i$_a$** was obtained when using MeOH as solvent (entry 3). In order to avoid this transesterification, the same reaction was performed in 1,4-dioxane with yields of up to 97%, an *E*:*Z* ratio of 83:17. This represents a slightly better stereoselectivity for compound **2i$_b$** than reported previously by Dudley.[150b] Changing from ethoxy alkyne **1i** to the ethoxy propiolate **1j**, altered reactivity, leading to the unexpected product **2j** in 75% yield (entry 5).

Remarkably, when using 1,4-dioxane as solvent neither the Meyer-Schuster rearrangement nor the formation of a lactone was observed, but the hydration of the alkyne leading to the corresponding α-hydroxy ketone was obtained.

Table 6.3 Effect of aryl derivatives in propargylic position.



Entry	Propargylic alcohol	1	Enone	2	Yield (%)[a]
1		**1g**		**2g**	86
2		**1h**		**2h**	95
3		**1i**		**2i$_a$**	81 E/Z 3:2
4[b]		**1i**		**2i$_b$**	71 E/Z 5:1
5		**1j**		**2j**	69[c]

[a] NMR yields with respect of benzaldehyde as internal standard are average of two runs. [b] Reaction performed in 1,4-dioxane to avoid transesterification. [c] Isolated yield.

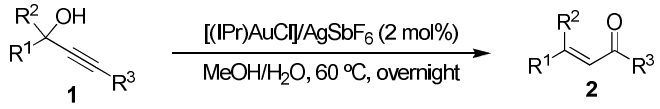
Finally, **Table 6.4** shows an extended scope of the reaction. As with the results in **Table 6.3**, when using the ethoxy alkyne **1k** good yields and stereoselectivity (**Table 6.4**, entry 1) were achieved. Entries 4 and 5 illustrate poor to moderate yields. The

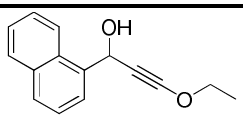
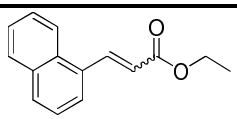
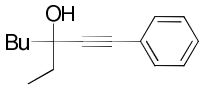
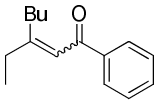
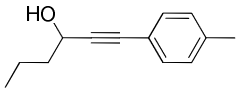
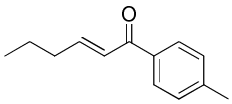
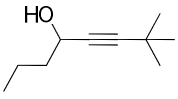
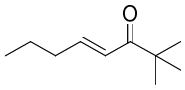
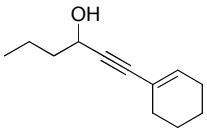
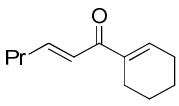
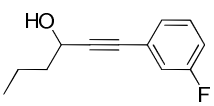
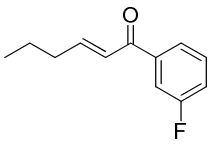
absence of an aryl substituent decreases the conversion of propargylic alcohols into the corresponding enones. Entries 3 and 6 present examples for "switched" substitution compared to **Table 6.2** and **Table 6.3**. Conversion of substrates having the aryl moiety in the acetylenic position while there is an alkyl substituent in propargylic position, was comparable to results for other substrates.

The conversion of the tertiary propargylic alcohol **1l** (**Table 6.4**, entry 2), gave as expected a 1:1 mixture of the two diastereomeres of **2l** as the *n*-butyl and the ethyl chain can hardly be differentiated structurally.

As shown in **Tables 6.2-4**, [(IPr)AuCl] in the presence of $AgSbF_6$ represents an adequate and fairly stereoselective catalytic system for the substrates tested, except for compound **1j** (**Table 6.3**, entry 5) with its interesting reactivity.

Table 6.4 Screening of substrates with varied substitution positions.



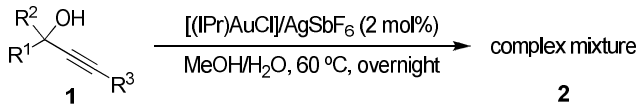
Entry	Propargylic alcohol	1	Enone	2	Yield (%)[a]
1[b]		**1k**		**2k**	E/Z 5:1 86
2		**1l**		**2l**	E/Z 1:1 86
3		**1m**		**2m**	96
4		**1n**		**2n**	28
5		**1o**		**2o**	58
6		**1p**		**2p**	89[c]

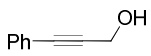
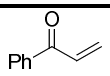
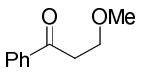
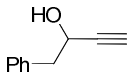
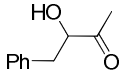
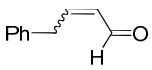
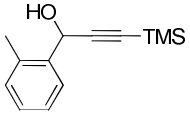
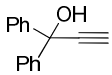
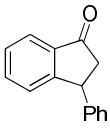
[a] NMR yields with respect of benzaldehyde as internal standard are average of two runs. [b] Reaction performed in 1,4-dioxane to avoid transesterification. [c] Isolated yield.

In spite of the remarkable scope of the catalytic system it is limited to substrates substituted in the acetylenic and propargylic positions. These reactions define the limits of the present catalytic system: Trials on either primary alcohols or terminal alkynes gave complex mixtures of products. Notably, the formation of the enone or enal was always observed, but yields were minor due to the significant formation of by-products. Similar results were achieved when using alkynes with TMS in the acetylenic position (**Table 6.5**, entry 3).

A compilation of substrates not suitable for the Meyer-Schuster rearrangement is presented in **Table 6.5**. Compound **1r** showed low reactivity towards the Meyer-Schuster rearrangement and Au^I-catalyzed hydration of the triple bond was observed instead.[161] Finally, the formation of 3-phenyl-indanone from alkynol **1t** should be pointed out, isolated with a poor yield of 9%. In the literature, the conversion of a propargylic alcohol into an indanone derivative has been achieved by rhodium-catalyzed isomerization,[162] whereas a Au^I-catalyzed process has not been reported so far.

Table 6.5 Substrates exhibiting low reactivity.



Entry	Propargylic alcohol	1	Products (Yield)			
1[b]		**1q**		**2q$_a$** (5%)		**2q$_b$** (35%)
2		**1r**		**2r$_a$** (32%)		**2r$_b$** (8%)
3		**1s**	Complex mixture			
4		**1t**		**2t** (9%)		

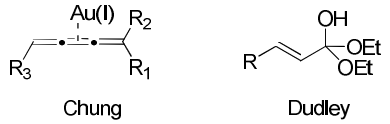
[a] NMR yields with respect of benzaldehyde as internal standard are average of two runs. [b] Reaction performed at room temperature.

A mechanism with the initial conversion of the propargylic alcohol into the enal, followed by a Au^{I}-activation of either the aryl or more likely the aldehyde moiety leading to an allyl alcohol that can isomerize into **2t** is proposed.[163] Both types of activation are unusual for gold(I) complexes.

6.2.3 Mechanistic considerations

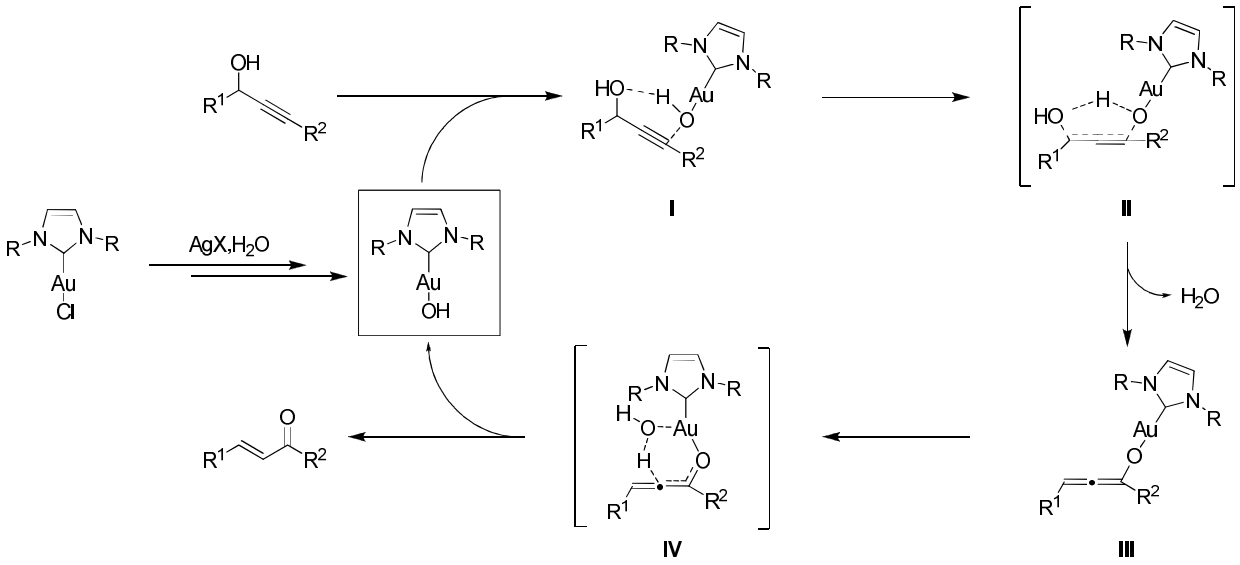
For the the Meyer-Schuster rearrangement, Dudley *et al.* postulated a mechanism catalyzed by gold(I)[156] as well as a revised one for scandium(III).[150b] Even if the mechanism proposed by Dudley was supported by experimental results with the substrates used in their scope, a different reaction pathway was supposed for the catalytic system in this chapter due to noteworthy differences between both systems. Dudley postulated the initial attack of the solvent, ethanol, followed by the attack of a water molecule to form an intermediate, shown in **Scheme 6.5**, that can convert into the conjugated ester. Using methanol instead of ethanol led to a 1:1 mixture of unsaturated ethoxy and methoxyester, supporting their mechanistic proposal. In contrast to Dudley, with **1i** (**Table 6.3**, entry 4) or with **1k** (**Table 6.4**, entry 1) quantitative transesterification to unsaturated methoxyester was observed when using MeOH as solvent. Notably, $\mathbf{2i_a}$ was recovered when subjected to standard reaction conditions in MeOH. This excludes the possibility of a Meyer-Schuster rearrangement followed by a gold-catalyzed transesterification and suggests another reaction pathway. On the other hand, $\mathbf{2i_a}$ (**Table 6.3**, entry 3) and **2k** (**Table 6.4**, entry 1) were formed in high yields in 1,4-dioxane as solvent.

Chung *et al.* proposed another mechanism going through a cumulene intermediate (**Scheme 6.5**).[157] As all compounds presented in **Table 6.4** do not bear the proton needed in the propargylic position to form such a cumulene intermediate, such a reaction pathway can be excluded in those cases. An alternate mechanism is proposed in **Scheme 6.6**.



Scheme 6.5 Key intermediates in the proposed mechanisms by Chung and Dudley.

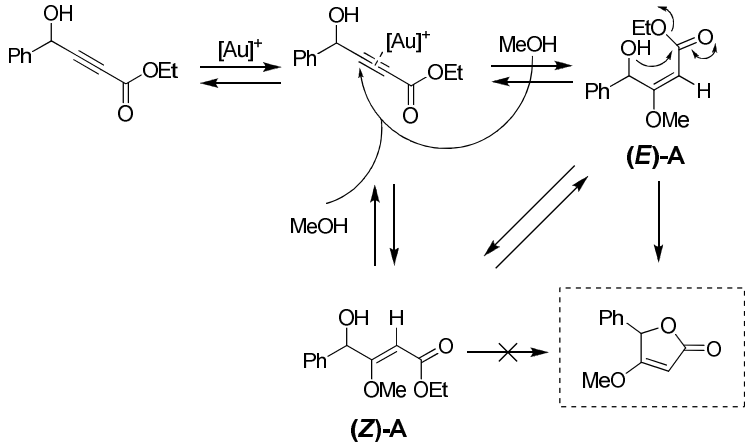
Instead of activating the triple bond the catalyst could "activate" a molecule of water to form a gold-hydroxo complex as previously postulated based on DFT calculations.[116] This [(NHC)Au(OH)] species could then attack the triple bond to give **I**. Transition state **II** should facilitate elimination of water leading to the activated allenolate **III**. The gold-hydroxo complex could finally be regenerated through interaction with another water molecule and release of product, as illustrated in **IV**. Nevertheless, a straightforward mechanism with the triple bond activated by gold towards a water (or methanol) attack to form an allenol (allenyl ether) that subsequently converts into the product was not excluded.



Scheme 6.6 Proposed mechanism for the [(NHC)AuCl] catalyzed Meyer–Schuster rearrangement.

As demonstrated in Chapter **7**, the initial proposal in **Scheme 6.6** has proven wrong, supporting a standard π-activation reaction pattern. Regarding the formation of the furanone **2j** a different pathway is suggested in which MeOH attacks the gold-activated triple bond leading to a vinylether **A**. If the (*E*)-isomer is formed, the hydroxy group is spacially close enough to attack the ester leading to the furanone derivative (**Scheme 6.7**).

In the case of the formation of the (*Z*)-isomer it was suggested that under these reaction conditions the (*Z*)-isomer could isomerize into the (*E*)-isomer. Further insights in the reactivity of α-hydroxy propiolates with [(NHC)AuX] were obtained in a detailed investigation presented in Chapter **12**, in which the alkoxylation was found to selectively yield the *syn*-addition product needed for lactonization.



Scheme 6.7 Proposed mechanism for the conversion of **1j** into **2j**.

6.3 Conclusion

A NHC-gold(I) based catalytic system for the conversion of propargylic alcohols into enones and α,β-unsaturated esters has been developed. Under optimized conditions, high conversion for a broad range of compounds was achieved. While being able to accommodate sterically demanding and deactivating substituents, the present catalytic system proved to be inactive towards primary alcohols or terminal alkynes. On the other hand, stereoselectivity was found to be good to excellent. A mechanism was proposed, suggesting activation of a water molecule instead of the C≡C triple bond. Furthermore, formation of a furanone and an indanone derivative was observed, raising interesting mechanistic issues in the context of gold(I) catalysis. Due to the ease of preparing propargylic alcohols, the gold(I)-catalyzed Meyer-Schuster rearrangement appears to be a promising tool accessing α,β-unsaturated ketones.

6.4 Experimental section

General information: All reagents were used as received. Reactions were performed under ambient atmosphere. Technical grade solvents were used. [(NHC)AuCl] complexes were synthesized as described in Chapter **5**. Propargylic alcohols **1i** and **1j** were synthesized as described in the literature[116] and purified by flash chromatography (silica 60 Å, Silicycle 230-400 mesh), **1a-h** and **1k-t** were available in the laboratory. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 ULTRASHIELD NMR spectrometer at ambient temperature in $CDCl_3$ containing 0.03 % TMS. Chemical shifts are given in parts per million (ppm) relative to $CDCl_3$ (^{1}H: 7.26 ppm, ^{13}C: 77.16

ppm). Coupling constants are given in Hertz (Hz). High resolution mass spectra (HRMS) were recorded by the HRMS unit of the ICIQ (Tarragona) using ESI (Electron Spray Ionisation). Gas chromatography (GC) was performed on an Agilent 6890 N Gas Chromatograph.

*3-Ethoxy-1-phenylprop-2-yn-1-ol (**1i**):* *n*-Butyllithium (1.53 ml, 2.45 mmol) was added to a solution of ethoxyethyne (0.68 ml, 2.83 mmol) in THF at -78 °C and the mixture was stirred for 25 min. Benzaldehyde (0.19 ml, 1.86 mmol) was added. The reaction mixture was allowed to warm up to room temperature while stirring over the course of 1 hour. The reaction was then quenched with NH_4Cl_{aq}, poured into brine and extracted with Et_2O. The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (gradient of EtOAc:pentane) to yield a yellow oil (313 mg, 94%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51-7.56 (m, 2H), 7.34-7.39 (m, 2H), 7.31 (d, *J* = 7.1 Hz, 1H), 5.51 (d, *J* = 6.1 Hz, 1H), 4.15 (q, *J* =7.1 Hz, 2H), 2.03 (d, *J* = 6.1 Hz, 1H), 1.39 (t, *J* = 7.2 Hz, 3H).[150b]

*Ethyl 4-hydroxy-4-phenylbut-2-ynoate (**1j**):* Ethyl propiolate (1.5 equiv., 3.1 mL, 30.6 mmol) was dissolved in THF (0.2 M, 100 mL) at -78°C. *n*-Butyl lithium (1.6 M, 1.3 equiv., 16.6 mL, 26.5 mmol) was added to the solution and the mixture was stirred for 25 min. Benzaldehyde (1 equiv., 2.1 mL, 20.4 mmol) was added dropwise and the resulting solution was stirred for 1 hour at -78°C. The reaction was first quenched with aq. NH_4Cl and then allowed to warm to room temperature. The reaction mixture was diluted with ethyl acetate and the layers were separated. The aqueous layer was extracted three times with ethyl acetate, and the combined organic phase was washed with brine, dried over magnesium sulfate, filtered and concentrated to under reduced pressure. The crude product was purified by column chromatography (gradient of EtOAc:pentane) to yield a pale yellow oil (3.8 g, 91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59-7.47 (m, 2H), 7.45-7.32 (m, 3H), 5.53 (s, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.46 (br. s, 1H), 1.29 (t, *J* = 7.1 Hz, 3H).[164]

General procedure: In a 4 mL vial equipped with a magnetic stirring bar [(IPr)AuCl] (3.1 mg, 5 μmol, 0.02 equiv.) was dissolved in MeOH (1.70 mL). $AgSbF_6$

(1.7 mg, 5 μmol, 0.02 equiv.) was added and the solution was stirred for 1 minute. The propargylic alcohol **1** (0.25 mmol, 1 equiv) was added, followed by distilled H_2O (300 μL). The reaction mixture was heated overnight to 60 ºC. Volatile components were then removed under reduced pressure and the residue was dissolved in a 1:1 mixture of pentane and Et_2O. The solution was filtered over a plug of silica (~1 cm) and solvents were removed under reduced pressure. NMR yields were determined as follow: A defined amount (~ 0.2 mmol) of benzaldehyde was added as internal standard to the crude product. Reported yields are average of two runs. New compounds were additionally prepared in 0.5 mmol scale and purified by flash chromatography for complete characterization and isolated yields.

Compounds **2a**,[116] **2f**,[116] **2h**,[116] **2l**,[116] **2n**,[116] **2o**[116] and **2r$_b$**[116], **2i$_a$**[165], **2i$_b$**,[165a, 166] **2g**,[167] **2k**,[168] **2m**,[169] **2q$_a$**,[170] **2q$_b$**,[171] **2r$_a$**,[172] and **2t**[173] were characterized by comparing their NMR spectra with literature data.

*(E)-1-(4-(Trifluoromethyl)phenyl)hept-1-en-3-one (**2b**):* The compound was prepared as described in the general procedure (81 % isolated yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (s, 4H), 7.55 (d, *J* = 16.2 Hz, 1H), 6.79 (d, *J* = 16.2 Hz, 1H), 2.68 (t, *J* = 7.4 Hz, 2H), 1.67 (m, 2H), 1.39 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.3, 140.4, 138.2, 131.9 (q, *J* = 32.52 Hz), 128.5, 128.4, 126.0 (q, *J* = 3.8 Hz), 123.9 (q, *J* = 272 Hz), 41.2, 26.4, 22.6, 14.0. HRMS calcd for $C_{14}H_{16}NO$: 214.1232. Found 214.1243.

*(E)-4-(3-Oxohept-1-enyl)benzonitrile (**2c**):* The compound was prepared as described in the general procedure (74 % isolated yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70-7.60 (m, 4H), 7.51 (d, *J* = 16.2 Hz, 1H), 6.79 (d, *J* = 16.2 Hz, 1H), 2.67 (t, *J* = 7.4 Hz, 2H), 1.66 (m, 2H), 1.39 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.0, 139.7, 139.1, 132.8, 129.1, 128.7, 118.5, 113.5, 41.3, 26.3, 22.5, 14.0. HRMS calcd for $C_{14}H_{16}F_3O$: 257.1153. Found 257.1166.

*(E)-1-(Benzo[d][1,3]dioxol-5-yl)hept-1-en-3-one (**2d**):* The compound was prepared as described in the general procedure (81 % isolated yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, *J* = 16.0 Hz, 1H), 7.05 (d, *J* = 1.4 Hz, 1H), 7.03 (dd, *J* = 7.9, 1.5 Hz, 1H), 6.82 (d, *J* = 8 Hz, 1H), 6.58 (d, *J*= 16.0 Hz, 1H), 6.01 (s, 2H), 2.63 (t, *J* = 7.5 Hz,

2H), 1.65 (m, 2H), 1.37 (m, 2H), 0.94 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.7, 149.9, 148.5, 142.2, 129.2, 124.9, 124.6, 108.8, 106.7, 101.7, 40.9, 26.7, 22.6, 14.1. HRMS calcd for $C_{14}H_{17}O_3$: 233.1178. Found 257.1166.

*(E)-1-(Naphthalen-1-yl)hept-1-en-3-one (**2e**):* The compound was prepared as described in the general procedure (92 % isolated yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41 (d, J = 15.9 Hz, 1H), 8.20 (d, J = 8.3 Hz, 1H), 7.90 (t, J = 5.3 Hz, 2H), 7.78 (d, J = 7.2 Hz, 1H), 7.62-7.46 (m, 3H), 6.85 (d, J = 15.9 Hz, 1H), 2.74 (t, J = 7.4 Hz, 2H), 1.78-1.66 (m, 2H), 1.50-1.37 (m, 2H), 0.98 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.6, 139.2, 133.8, 132.1, 131.7, 130.7, 128.9, 128.8, 127.0, 126.4, 125.6, 125.1, 123.4, 41.2, 26.6, 22.6, 14.1. HRMS calcd for $C_{17}H_{19}O$: 239.1436. Found 239.1443.

*4-Methoxy-5-phenylfuran-2(5H)-one (**2j**)*: The compound was prepared as described in the general procedure (69 % isolated yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.38 (m, 3H), 7.34-7.27 (m, 2H), 5.69 (s, 1H), 5.16 (s, 1H), 3.85 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.7, 172.3, 134.1, 129.5, 129.0, 126.8, 88.3, 80.4, 59.8. HRMS calcd for $C_{11}H_{11}O_3$: 191.0703. Found: 191.0702.

*(E)-1-(3-Fluorophenyl)hex-2-en-1-one (**2p**)*: The compound was prepared as described in the general procedure (89 % isolated yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75-7.70 (m, 1H), 7.65-7.55 (m, 1H), 7.50-7.40 (m, 1H), 7.30-7.20 (m, 1H), 7.09 (td, J = 15.4, 7.0 Hz, 1H), 6.83 (td, J = 15.4, 1.5 Hz, 1H), 2.40-2.30 (m, 2H), 1.65-1.50 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.6 (d, J = 2.2 Hz), 162.9 (d, J = 248 Hz), 150.8, 140.2 (d, J = 6.3 Hz), 130.2 (d, J = 7.8 Hz), 125.7, 124.3 (d, J = 2.9 Hz), 119.6 (d, J = 21.6 Hz), 115.4 (d, J = 22.3 Hz), 34.9, 21.5, 13.8. HRMS calcd for $C_{12}H_{14}FO$: 193.1029. Found 193.1039.

7 Synthesis of Prostaglandins *via* Meyer-Schuster Rearrangement

7.1 Introduction

In Chapter **6**, the gold-catalyzed Meyer-Schuster rearrangement was presented and proved to be highly efficient in the formation of conjugated enones.[160] In the course of developing a suitable gold-based catalyst for this reaction, [(IPr)AuCl]/$AgSbF_6$ was found to be the most active.[174] The proposed mechanism of the Meyer-Schuster reaction mediated by gold-NHC complexes was discussed and [(IPr)Au(OH)] **1** formed *in situ* was proposed as the active catalytic species (**Scheme 6.6**).

To investigate this mechanistic hypothesis, [(IPr)Au(OH)] **1** was targeted. Complex **1** was recently synthesized, isolated and fully characterised.[136] Further synthetic studies on this system permitted the isolation of a novel dinuclear complex [{(IPr)Au}$_2$(μ-OH)][BF_4] **2** in aqueous media. The synthesis and characterization of **2** is discussed in detail in Chapter **11**.[117, 175] Formation of **2** in aqueous media forced us to consider **2** as an active species in the Meyer-Schuster rearrangement when the reactions are performed in aqueous media.

The following chapter describes the application of both **1** and dinuclear gold complexes in the Meyer-Schuster rearrangement. The latter were found to be suitable catalysts, allowing for reactions at room temperature and afforded high turnover numbers (TONs). Additionally, the superior catalytic behaviour of **2** in the Meyer-Schuster rearrangement permits its use in the development of a molecular assembly strategy leading to the efficient synthesis of prostaglandins. Natural prostaglandins are unsaturated fatty acids derived from arachidonic acid. Many classes of prostaglandins are characterized by very high biological activity making them highly desirable targets for synthetic chemists.[176]

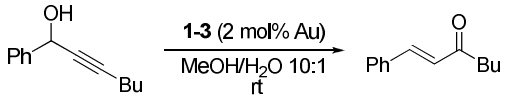
The modest reactivity of **1** without addition of excess acid results in a revision of the initially considered mechanism.

7.2 Results and Discussion

7.2.1 Optimization and catalyst synthesis

In order to optimize the Meyer-Schuster rearrangement using gold catalysts, reactivity studies were performed using the well-defined [(IPr)Au(OH)] **1** complex and a "protic acid activator". This strategy was also examined for numerous cationic gold(I) mediated transformations.[117] As shown in **Table 7.1**, without any addititive, **1** led to very low conversion even when prolonged reaction times and higher temperatures were applied (**Table 7.1**, entries 1-2). This initially surprising result excludes **1** as a reactive species in the Meyer-Schuster reaction and forces a revision of the catalytic proposal. Contrastingly, addition of HBF_4 to the reaction results in rapid conversion to product. In this instance, the *in situ* formation of [{(IPr)Au}$_2$(μ-OH)][BF_4] **2** (entry 3) or [{(IPr)Au}][BF_4] (entry 5) is observed.[117] Formation of each gold species formed is a function of the amount of acid used.

Table 7.1 Influence of HBF_4 on the catalytic activity of **1** and **2**.



Entry	Catalyst[a]	Acid (mol%)	Time (h)	Conv. (%)[b]
1	**1**	0	0.5	9
2	**1**	0	48	29[c]
3	**1**	HBF_4 (1)	0.5	73
4	**1**	HBF_4 (2)	0.5	98
5	**1**	HBF_4 (3)	0.5	99
6	none	HBF_4 (20)	1	0
7	**2**	0	0.5	61
8	**2**	0	1	99
9	**2**	HBF_4 (1)	0.5	99
10	**3**	0	3	99

[a] Catalysts: [(IPr)Au(OH)] **1**, [{[IPr)Au}$_2$(μ-OH)]BF_4 **2**. [b] Only the *E*-isomer was observed. [c] 60 °C.

As [{(IPr)Au}$_2$(μ-OH)][BF_4] **2** is easily formed in aqueous media, **2** was foreseen as a potentially highly active catalyst for the Meyer-Schuster rearrangement although a

comparison of entries 5 and 7-8 in **Table 7.1** indicates that slightly prolonged reaction times are required with **2**. As hoped, the well-defined **2** allowed for very good yields of product in short reactions times compared to the use of [(IPr)Au(NTf_2)] **3** (entry 8 vs. 10).

Complex **3** was previously reported to be an excellent and stable catalyst due to its inner sphere NTf_2 (NTf_2 = bis-(trifluoromethanesulfonyl)imidate) ligand and the apparent ease of this ligand to vacate the coordination sphere of gold(I) generating a vacant site.[104]

Using the synthetic strategy outlined above for the synthesis of **2**, the synthesis of [{(IPr)Au}$_2$(μ-OH)][NTf_2] (**4**) was attempted to validate the generality of our synthetic protocol and to possibly shed light on the fate of **3** in the course of catalytic reactions. Additionally, the isolation of such a dinuclear species would support a developing mechanistic hypothesis suggesting the initial formation of hydroxy-bridged dinuclear gold complexes in catalysis and would present an example where NTf_2 is an outer sphere ligand.[177]

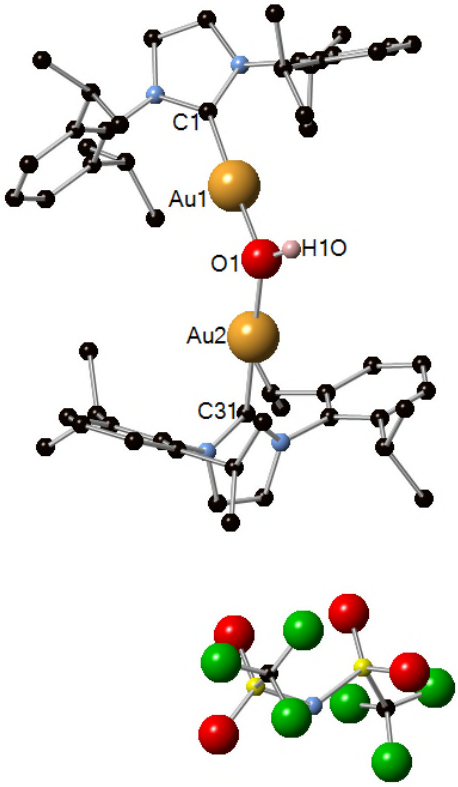


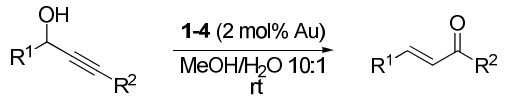
Figure 7.1 Molecular structure of [{[IPr)Au}$_2$(μ-OH)][NTf_2] **4**. Selected bond lengths [Å] and angles [deg]: Au1-Au2 3.6348(12); Au1-O1, 2.036(4); Au2-O1, 2.043(4); Au1-C1, 1.959(5); Au2-C31, 1.954(5); Au1-O1-Au2, 126.0(2); O1-H1O, 0.988(19) ; Au1-O1-H1O, 108(3); Au2-O1-H1O, 123(3); C1-Au1-O1, 175.26(19); C31-Au2-O1, 176.23(17).

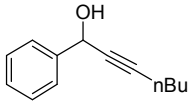
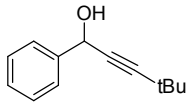
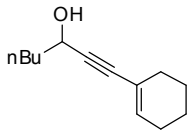
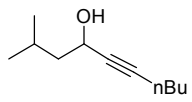
[{(IPr)Au}$_2$(μ-OH)][NTf$_2$] **4** was indeed synthesised in an analogous manner to that of **2** where **1** was added under nitrogen to a suspension of 0.5 equiv. HNTf$_2$ in anhydrous toluene at room temperature. Addition of pentane to the reaction mixture afforded precipitation of pure **4**. Complex **4** was isolated *via* filtration as a microcrystalline white solid in quantitative yield. The structure of **4** was confirmed by X-ray crystallography (**Figure 7.1**).

7.2.2 Substrate scope

To test the scope of the Meyer-Schuster methodology with the most interesting catalyst/pre-catalysts in hand, the reactivity of **1** (with 1.5 equiv. of HBF$_4$), **2**, [(IPr)Au(NTf$_2$)] (**3**) and [{[IPr)Au}$_2$(μ-OH)][NTf$_2$] (**4**) were tested for a small series of characteristic propargylic alcohols (**Table 7.2**).

Table 7.2 Screening of catalysts with representative propargylic alcohols.



Entry	Substrate	Catalyst[a]	Time (h)	Yield (*E/Z*)[b]
1		**2**	1	93% (*E*)
2		**3**	3	96% (*E*)
3		**4**	1	90% (*E*)
4		**1** + HBF$_4$[c]	0.5	97% (*E*)
5		**2**	24	73% (*E/Z* 72:28)[d]
6		**3**	24	73% (*E/Z* 77:23)[d]
7		**4**	24	56% (*E/Z* 68:32)[d]
8		**1** + HBF$_4$[c]	24	75% (*E/Z* 89:11)
9		**2**	3	nd[e]
10		**3**	2	27% (*E*)
11		**4**	3	nd[e]
12		**1** + HBF$_4$[c]	1	26% (*E*)
13		**2**	2	88% (*E*)
14		**3**	3	65% (*E*)
15		**4**	2	80% (*E*)
16		**1** + HBF$_4$[c]	1	80% (*E*)

[a] Catalysts: **1** [(IPr)Au(OH)], **2** [{[IPr)Au}$_2$(μ-OH)][BF$_4$], **3** [(IPr)Au(NTf$_2$)], **4** [{[IPr)Au}$_2$(μ-OH)][NTf$_2$]. [b] Isolated yields, reaction was monitored by TLC until no further conversion was observed. [c] 1.5 equiv. referring to Au.[d] The allenol tautomer was isolated as a side product: 26% (**2**), 6% (**3**), 21% (**4**). [e] nd = not determined. The target molecule was obtained in an inseparable mixture of products.

Catalysts **2**-**4** have the advantage of avoiding the use of air-, light- and moisture-sensitive silver salts (i.e. $AgBF_4$, $AgSbF_6$, AgOTf, $AgPF_6$) to abstract chloride from [(L)AuCl] (L = Ligand) complexes.

The use of well-defined complexes or of simple acid activation results in a simplified and more economically attractive catalytic protocol.[178] Results from reactions using some benchmark substrates revealed excellent reactivity and high isolated yields using the reaction conditions previously reported in Chapter **5** but now reactions are conducted at room temperature instead 60 °C (**Table 7.2**).

As shown in **Table 7.2**, the reactivity of all systems examined leads to very similar results for the corresponding substrates. Interestingly, [(IPr)Au(NTf_2)] **3** exhibited slightly reduced catalytic activity relative to other catalysts examined necessitating prolongation of reaction time for complete reaction**.** It should also be noted, in case of 1-cyclohexenylhept-1-yn-3-ol, catalysts **2** and **4** lead to a inseparable mixture of the desired Meyer-Schuster product and a second product resulting from the reaction with methanol (**Table 7.2**, entries 9,11). Changing the solvent to CH_2Cl_2 or THF resulted in a complete loss of reactivity.

In order to address the issues of catalyst stability and decomposition, the behaviour of [{[(IPr)Au}$_2$(μ-OH)][BF_4] **2** at low catalyst loadings was examined. To probe these important considerations, a reaction was conducted with multiple additions of starting material. Remarkably in this series of experiments, **2** proved extremely stable, resilient to decomposition and active under catalytic conditions (0.03 mol% of **2**, TON 3330) when the reaction was *continuously fed substrate for 3 weeks!*

7.2.3 Application in the synthesis of prostaglandin $F_{2\alpha}$

To finally demonstrate the use of the gold-catalyzed Meyer-Schuster rearrangement in synthesis, the catalytic system was applied to an assembly strategy leading to the straightforward synthesis of prostaglandins.

Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$, **Figure 7.2**) is known to be a very potent vasoconstrictor and oxytoxic agent and is therefore used with the pharmaceutical label `dinoprost´ for childbirth induction or abortion in mammals. Most of the synthetic procedures for prostaglandins synthesis employ one of the known variations of the Corey method, in which the side chains are sequentially attached in a specific order to a derivative of the commercially available (-)-Corey lactone aldehyde **5**.[179]

Thus, the Corey strategy involves the installation of the lower side chain (ω-chain) *via* an archetypal non atom-economical[147] approach: a HWE reaction of a suitable keto-phosphonate.

It was envisioned that a gold catalyzed Meyer-Schuster rearrangement could improve the atom-economy of the ω-chain installation through a catalytic rearrangement of propargylic alcohol **6** to the key enone **7** (**Figure 7.2**). Compound **6** was readily prepared from commercially available enantiopure **5** in 90% isolated yield. It was then treated with a catalytic amount of [(IPr)AuCl]/$AgSbF_6$ (2 mol%) as reported in Chapter **5**. Within the optimization process (**Table 7.3**), it was discovered that catalyst **2** (2 mol%) afforded **7** (*E*-isomer) in 85% isolated yield, using anhydrous CH_2Cl_2 as a solvent (entry 6). This was convenient for the following synthetic steps. Standard mixture of MeOH/Water 10:1 yielded **7** (*E*-isomer) in 86% with catalyst **2** (2 mol%, entry 7) and 84% with catalyst **4** (2 mol%, entry 8) respectively, while with the prior reported reaction conditions[174] a yield of 81% was obtained for **7** (entry 1).

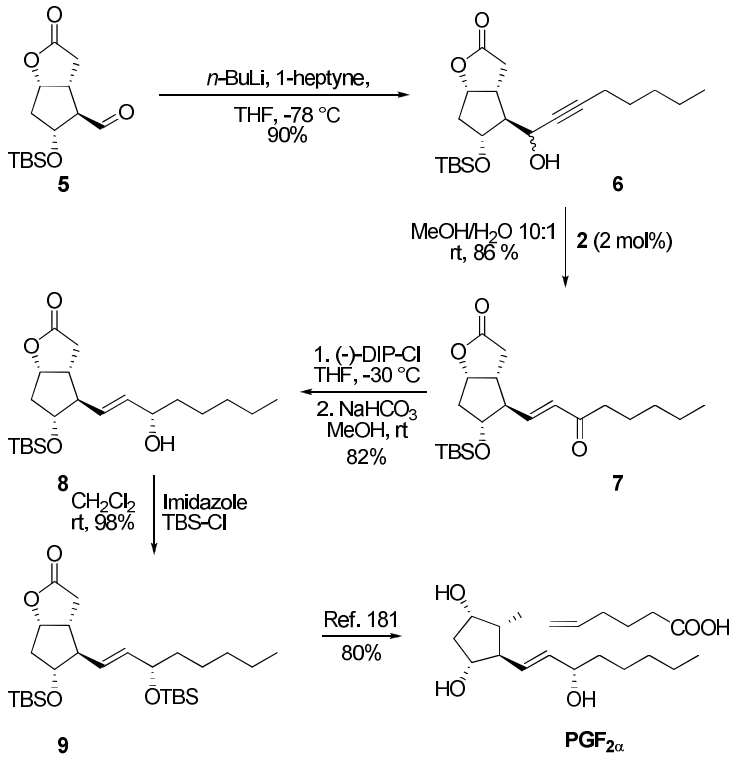
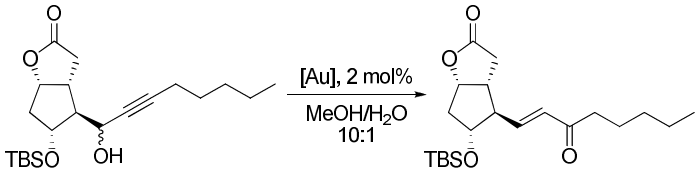


Figure 7.2 Synthetic route to prostaglandins *via* gold-catalyzed Meyer-Schuster rearrangement.

Compound **7** was then functionalized *via* **8** to bis-TBS-protected allyl alcohol **9**, involving the asymmetric diisopinocamphenyl chloroborane (DIP-Cl) mediated ketone reduction[180] followed by silylation of the corresponding alcohol. The latter has been

used by Mulzer *et al.*[181] for the asymmetric synthesis of $PGF_{2\alpha}$. It should be pointed out, with the Mulzer approach, **9** was obtained as a mixture of *E*:*Z* olefins in 17:1 ratio (*de* 88%), while the present protocol delivered only the desired *E* stereoisomer in *80% isolated yield.* With **9** in hand, the synthesis proceeded readily to the target prostaglandin $PGF_{2\alpha}$, *via* classical prostaglandin chemistry[181] in 80% isolated yield and as a single stereoisomer.

Table 7.3 Meyer-Schuster rearrangement in prostaglandin synthesis.



6 **7**

Entry	Catalyst	Time (h)	Temp (°C)	Yield (%)[a]
1	[(IPr)AuCl]/$AgSbF_6$	18	60	81
2	[(IPr)AuCl]/$AgBF_4$	18	60	71
3	[(IPr)Au(NTf_2)]	3	RT	83
4	[(IPr)Au(OH)]	18	60	70
5	[(IPr)Au(OH)]	18	RT	0[b]
6	[{(IPr)Au}$_2$(μ-OH)][BF_4]	3	RT	85[b]
7	[{(IPr)Au}$_2$(μ-OH)][BF_4]	2	RT	86
8	[{(IPr)Au}$_2$(μ-OH)][NTf_2]	2	RT	84
9	[(IPr)Au(OH)]/HBF_4 2:3	1	RT	75

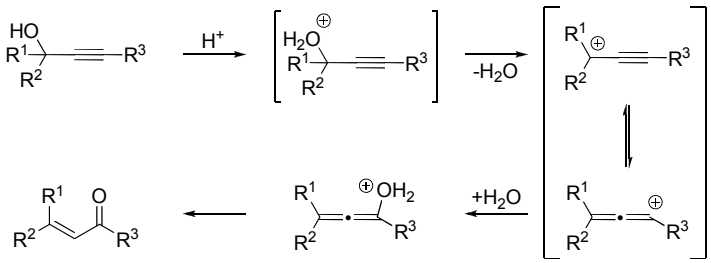
[a] Isolated yields. [b] Reaction in anhydrous CH_2Cl_2.

7.2.4 Mechanistic considerations

Mechanistically, the excellent conversion of **6** without added water strongly indicated a concerted mechanism. However, closer investigations with both mononuclear gold complexes and dinuclear gold complexes in anhydrous conditions revealed significantly longer reaction times with 1-phenylhept-2-yn-1-ol.

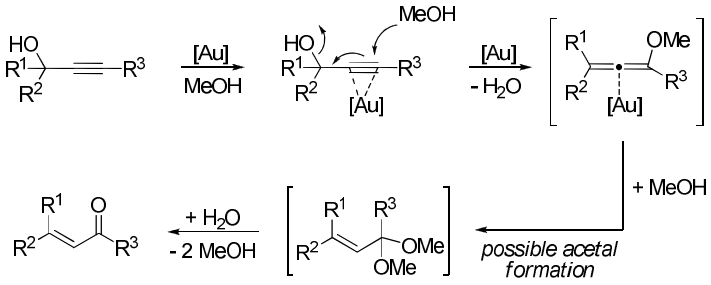
As a consequence, the involvement of water traces in catalysis cannot be excluded. A reasonable mechanism without water would be achieved considering $[Au]^+$ as a H^+ synthon and follow the classical dehydration/hydration mechanism of the Meyer-Schuster rearrangement. Initial coordination of the catalyst to the π-system and

subsequent elimination of water would result in an allenyl intermediate which could be then attacked by the water moiety liberated in the second step (**Scheme 7.1**).[160, 182]



Scheme 7.1 Mechanism of the classical acid-catalyzed Meyer-Schuster rearrangement.

Another mechanism in MeOH/water is the initial methoxylation of the triple bond as proposed by Dudley *et al*.[156] The hydroxyl moiety would then act as a leaving group to yield the allenylether which could then, analogously to gold mediated alkyne hydration (see Chapter **8** and **9**), quickly convert *via* acetal formation into the desired conjugated enone (**Scheme 7.2**). However, the results presented in Chapter **6** disfavour such a mechanism.



Scheme 7.2 Possible mechanism *via* allenyl ether under H_2O elimination.

Experimental results clearly exclude the initial proposal of the *in situ* formation of **1** initiating the catalytic cycle. Instead, a resting state of type **2** and **4** is more relevant, and may simply act as a reservoir of the active $[(IPr)Au]^+$ (see Chapter **11**).[183]

7.3 Conclusion

In conclusion, an improved protocol for the Meyer-Schuster rearrangement with dinuclear gold complexes allowing for low catalyst loadings was obtained. The new protocol has been successfully applied to the synthesis of prostaglandins. This study helps exclude earlier mechanistic proposals and highlights the relevance and possible more significant role of dinuclear gold complexes in gold catalysis.

7.4 Experimental section

Unless otherwise stated, manipulations were performed under ambient atmosphere. Solvents were of *puriss.* grade and used as received. NMR spectra were recorded on 400 MHz and 300 MHz spectrometers at ambient temperature in $CDCl_3$. Chemical shifts are given in parts per million (ppm) with respect to TMS. ^{19}F chemical shifts are given in parts per million (ppm) with respect to $CFCl_3$. The synthesis of $PGF_{2\alpha}$ and the optimization in **Table 7.3** were realized by G. Zanoni and co-workers. Crystallographic data of **4** were collected by A. M. S. Slawin.

*Synthesis of **2***: [(IPr)Au(OH)] (97 mg, 0.160 mmol) was disolved in benzene (2 ml) and tetrafluoroboric acid diethyl ether complex (11.0 μL, 0.080 mmol) was added. The reaction mixture was stirred for 4 hours at room temperature. Pentane was added to the reaction to precipitate a white solid. Recrystallization from CH_2Cl_2/pentane gives 92 mg (90%) of a white microcrystalline solid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.50 (t, J = 7.8 Hz, 4H), 7.26 (s, 4H), 7.24 (d, J = 7.8 Hz, 8H), 2.39 (sept, J = 6.9 Hz, 8H), 1.19 (d, J = 6.9 Hz, 24H), 1.11 (d, J = 6.9 Hz, 24H).^{13}C NMR (75 MHz, $CDCl_3$): δ 162.6 (q), 145.4 (q), 133.6 (q) , 130.7 (t), 124.4 (t), 124.2 (t), 124.1 (t), 28.6(t), 24.4 (p), 23.8 (p). ^{19}F NMR (185 Hz): δ -154.90, -154.85. Elemental Analysis (calc): C 51.06 (50.87), H 5.27 (5.77), N 4.36 (4.39).

*Synthesis of **4***: Trifluoromethanesulfonimide (73 mg, 0.260 mmol) was dissolved under N_2 in anhydrous toluene (2 mL) and [(IPr)Au(OH)] (313 mg, 0.519 mmol) was added. The reaction mixture was stirred overnight at room temperature. Pentane (10 mL) was added to the reaction to ensure complete precipitation of the product. The white solid was collected by filtration, washed with pentane (2x 5 mL) and dried *in vacuo* to give 381 mg (100%) of a white microcrystalline solid. ^1H NMR (300MHz , $CDCl_3$) δ 7.49 (t, J = 7.8 Hz, 4H), 7.24 (d, J = 7.8 Hz, 8H), 7.14 (s, 4H), 2.37 (spt, J = 6.8 Hz, 8H), 1.17 (d, J = 6.8 Hz, 24H), 1.11 (d, J = 6.8 Hz, 24H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.9, 145.6, 133.6, 133.7, 130.9, 124.3, 124.2, 120.1 (q, J = 321.7 Hz), 28.8, 24.6, 23.9. ^{19}F NMR (282 Hz, $CDCl_3$): δ -79.2. Elemental Analysis (calc): C 45.78 (45.81), H 4.92 (5.01), N 4.57 (4.77).

Meyer-Schuster rearrangement: In a typical reaction, 1-phenylhept-2-yn-1-ol (188 mg, 1 mmol) was charged in a vial and methanol (7.5 ml) was added. **2** (12.8 mg, 0.01 mmol) was added followed by water (750 μL). The reaction was stirred at room temperature until conversion reached completion. After evaporation of volatile compounds under reduced pressure, the residue was purified *via* flash chromatography (pentane/Et_2O 95:5) to obtain 176 mg (93%) of a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60-7-50 (m, 3H), 7.42-7.36 (m, 3H), 6.75 (d, J = 16.2 Hz, 1H), 2.67 (t, J = 7.5 Hz, 2H), 1.74-1.60 (m, 2H), 1.48-1.31 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H).

1-phenylhept-2-yn-1-ol: *n*-BuLi (1.6 M in hexane, 16.7 mL, 1.1 equiv) was added to a solution of 1-hexyne (3.34 mL, 29.1 mmol, 1.2 equiv) in dry THF (40 mL) at -78 °C. After stirring at -78°C for 30 min benzaldehyde (2.46 mL, 24.2 mmol, 1 equiv) was added. The reaction mixture was allowed to warm to room temperature and was stirred for 1h. The reaction was quenched with saturated aq. solution of NH_4Cl and the solution was diluted with Et_2O (40 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3x 25 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography to afford 1-phenylhept-2-yn-1-ol as a pale yellow oil (4.3 g, 94%). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.57-7.52 (m, 2H), 7.41-7.29 (m, 3H), 5.45 (s, 1H), 2.28 (td, J = 7.1; 2.0 Hz, 2H), 2.19 (br. s, 1H), 1.58-1.49 (m, 2H), 1.48-1.38 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H).[184]

4,4-dimethyl-1-phenylpent-2-yn-1-ol: n-BuLi (1.6 M in hexane, 3.94 mL, 1.05 equiv) was added to a solution of 3,3-dimethylbut-1-yne (0.780 mL, 6.6 mmol, 1.1 equiv) in dry THF (30 mL) at -78 °C. After stirring at -78°C for 30 min benzaldehyde (0.61 mL, 6.0 mmol, 1 equiv) was added. The reaction mixture was allowed to warm to room temperature and was stirred for 1h. The reaction was quenched with saturated aq. solution of NH_4Cl and the solution was diluted with Et_2O (10 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3x 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography to afford 4,4-dimethyl-1-phenylpent-2-yn-1-ol as a colourless oil (1.1 g, 90%). ^{1}H-NMR ($CDCl_3$, 400

MHz): δ 7.58-7.52 (m, 2H), 7.41-7.31 (m, 3H), 5.45 (s, 1H), 2.18 (br. s, 1H),1.27 (s, 9H).[185]

1-cyclohexenylhept-1-yn-3-ol: *n*-BuLi (1.6 M in hexane, 6.9 mL, 1.1 equiv) was added to a solution of 1-ethynylcyclohex-1-ene (1.29 mL, 11.0 mmol, 1.1 equiv) in dry THF (40 mL) at -78 °C. After stirring at -78°C for 30 min pentanal (1.06 mL, 10.0 mmol, 1 equiv) was added. The reaction mixture was allowed to warm to room temperature and was stirred for 1h. The reaction was quenched with saturated aq. solution of NH_4Cl and the solution was diluted with Et_2O (40 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3x 25 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography to afford 1-cyclohexenylhept-1-yn-3-ol as a colourless oil (2.05 g, 95%). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 6.06 (m, 1H), 4.44 (t, J = 6.6 Hz, 1H), 2.31 (br. s, 1H), 2.13-2.00 (m, 4H), 1.76-1.48 (m, 6H), 1.46-1.24 (m, 4H), 0.88 (t, J = 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 135.1, 120.3, 87.7, 86.6, 62.9, 37.8, 29.3, 27.5, 25.7, 22.5, 22.3, 21.5, 14.1. HRMS calc for $C_{13}H_{20}ONa$: 215.1412. Found: 215.1415.

2-methyldec-5-yn-4-ol: *n*-BuLi (1.6 M in hexane, 10.3 mL, 1.1 equiv) was added to a solution of 1-hexyne (1.9 mL, 16.5 mmol, 1.1 equiv) in dry THF (40 mL) at -78 °C. After stirring at -78°C for 30 min isovaleraldehyde (1.6 mL, 15.0 mmol, 1 equiv) was added. The reaction mixture was allowed to warm to room temperature and was stirred for 1h. The reaction was quenched with saturated aq. solution of NH_4Cl and the solution was diluted with Et_2O (30 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3x 20 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography to afford 2-methyldec-5-yn-4-ol as a colourless oil (2.5 g, 99%). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.36 (tt, J = 7.2; 1.9 Hz, 1H), 2.17 (td, J = 7.0; 1.9 Hz, 2H),1.98 (br. s, 1H), 1.81 (sept, J = 6.7 Hz, 1H), 1.62-1.31 (m, 6H), 0.93-0.85 (m, 9H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 85.4, 81.7, 61.3, 46.9, 30.9, 24.9, 22.7, 22.6, 22.0, 18.4, 13.7. HRMS calc for $C_{11}H_{20}ONa$: 191.1412. Found: 191.1412.

4,4-dimethyl-1-phenylpent-1-en-3-one: 4,4-dimethyl-1-phenylpent-2-yn-1-ol (154 mg, 0.82 mmol) was charged in a vial and methanol (6.2 ml) was added. **2** (10.4 mg, 0.01 mmol) was added followed by water (615 μL). The reaction was stirred at room temperature for 24 hours. After evaporation of volatile compounds under reduced pressure, the residue was purified *via* flash chromatography (pentane/Et_2O 95:5) to obtain 4,4-dimethyl-1-phenylpent-1-en-3-one of a colourless oil (116 mg, 75%, *E*/*Z* 72:28). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.69 (d, *J* = 15.6 Hz, 1H, *E*), 7.61-7.50 (m, 2H, *E*+*Z*), 7.41-7.35 (m, 3H, *E*), 7.34-7.27 (m, 3H, *Z*), 7.13 (d, *J* = 15.6 Hz, 1H, *E*), 6.78 (d, *J* = 13.0 Hz, 1H, *Z*), 6.45 (d, *J* = 13.0 Hz, 1H, *Z*), 1.23 (s, 9H, *E*), 1.20 (s, 9H, *Z*).[167]

(E)-1-cyclohexenylhept-2-en-1-one: 1-cyclohexenylhept-1-yn-3-ol (96 mg, 0.5 mmol) was charged in a vial and methanol (3.4 ml) was added. **3** (8.66 mg, 0.02 mmol) was added followed by water (340 μL). The reaction was stirred at room temperaturet until conversion reached completion. After evaporation of volatile compounds under reduced pressure, the residue was purified *via* flash chromatography (Pentane/Et_2O 95:5) to obtain (*E*)-1-cyclohexenylhept-2-en-1-one (27 mg, 28%) as a colourless oil. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 6.92-6.85 (m, 1H), 6.82 (t, *J* = 6.9 Hz, 1H), 6.62 (dt, *J* = 15.3; 1.3 Hz, 1H), 2.33-2.16 (m, 6H), 1.72-1.54 (m, 4H), 1.51-1.22 (m, 4H), 0.90 (t, J = 7.2 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 191.6, 147.2, 140.0, 139.9, 124.9, 32.4, 30.5, 26.2, 23.5, 22.4, 22.1, 21.7, 14.0. HRMS calc for $C_{13}H_{20}ONa$: 215.1412. Found: 215.1417.

(E)-9-methyldec-6-en-5-one: 2-methyldec-5-yn-4-ol (84 mg, 0.5 mmol) was charged in a vial and methanol (3.4 ml) was added. **5** (6.0 mg, 0.02 mmol [(IPr)Au(OH)] + 15 μL aq. HBF_4 1M) was added followed by water (340 μL). The reaction was stirred at room temperature until conversion reached completion. After evaporation of volatile compounds under reduced pressure, the residue was purified *via* flash chromatography (pentane/Et_2O 95:5) to obtain (*E*)-9-methyldec-6-en-5-one as a colourless oil (67 mg, 80%). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 6.80 (dt, *J* = 15.7; 7.4 Hz, 1H), 6.08 (dt, *J* = 15.8; 1.4 Hz, 1H), 2.53 (pseudo-t, *J* = 7.5 Hz, 2H), 2.10 (td, *J* = 7.2; 1.4 Hz, 2H), 1.77 (sept, *J* = 6.7 Hz, 1H), 1.63-1.54 (m, 3H), 1.39-1.29 (m, 2H), 0.94-0.89 (m, 9H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 201.0, 146.1, 131.5, 41.8, 40.0, 28.0, 26.6, 22.5, 22.4, 14.0. HRMS calc for $C_{11}H_{20}ONa$: 191.1412. Found: 191.1409.

Synthesis of propargylic alcohol ***6*****:** *n*-BuLi (1.6 M in hexane, 0.380 mL, 1.15 equiv) was added to a solution of 1-heptyne (0.063 mL, 0.66 mmol, 1.25 equiv) in anhydrous THF (3 mL) at -78 °C. After stirring at -78°C for 30 min aldehyde **5** (97 mg, 0.53 mmol, 1 equiv) in anhydrous THF (2 mL) was added. After 30 min the reaction was quenched with aq. solution of NH_4Cl (5 mL) and the solution was diluted with Et_2O (5 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3x 5 mL). The combined organic phases were dried on $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography. Elution with hexane/EtOAc (8:2) gave the diastereomeric mixture of **6** as a colourless oil (181 mg, 90%). ^{1}H-NMR (300 MHz; $CDCl_3$): δ 4.93 (td, *J* = 6.9; 2.8 Hz, 1H), 4.44-4.27 (m, 2H), 4.20* (q, *J* = 5.6 Hz, 0.2H), 2.97-2.59 (m, 3H), 2.41-2.15 (m, 4H), 2.07 (q, *J* = 5.6 Hz, 1H), 2.00-1.92 (m, 1H), 1.52 (quintet, *J* = 6.9 Hz, 2H), 1.41-1.30 (m, 4H), 0.94-0.89 (m, 12H), 0.10 (s, 3H), 0.08 (s, 3H). ^{13}C NMR (75 MHz, C*D*Cl_3): δ 177.13, 87.32, 83.62*, 83.37, 79.32, 75.12*, 74.33, 63.97*, 61.48, 59.96*, 59.86, 41.23*, 41.12, 38.88*, 37.30, 35.90*, 35.60, 31.07, 28.22, 25.65, 22.12, 18.58, 17.82, 13.92, -4.64, -4.99. (*) Minoritary diastereoisomer peaks. HRMS calc for $C_{21}H_{36}O_4Si$: 380.2383. Found 380.2401.

Synthesis of enone 7: **6** (57 mg, 0.15 mmol) was dissolved in MeOH (1 mL), then **2** (3.84 mg, 0.02 equiv.) was added followed by distilled H_2O (100 μL). The solution was stirred at room temperature until full conversion of **6** was indicated by TLC. Volatile compounds were removed under reduced pressure and the residue was purified by flash chromatography on silica gel. Elution with hexane/AcOEt (8:2) gave the enone **7** (49 mg, 86%) as pale yellow oil. $[\alpha]^{20}_D$ = -24.7 (*c* 1.0, CH_2Cl_2). ^{1}H-NMR (300 MHz; $CDCl_3$): δ 6.61 (dd, *J* = 15.8; 8.3 Hz, 1H), 6.19 (dd, *J* = 15.8; 1.1 Hz, 1H), 4.98 (td, *J* = 6.9; 2.8 Hz, 1H), 4.06 (q, *J* = 6.2 Hz, 1H), 2.85-2.70 (m, 2H), 2.61-2.49 (m, 3H), 2.44-2.34 (m, 2H), 2.03 (ddd, *J* = 14.7; 6.2; 2.8 Hz, 1H), 1.68-1.58 (m, 2H), 1.36-1.28 (m, 4H), 0.94-0.87 (m, 12H), 0.06 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.81, 176.23, 144.01, 131.15, 82.64, 77.25, 56.66, 41.74, 41.05, 40.87, 34.56, 31.39, 25.60, 23.71, 22.32, 17.91, 13.88, -4.76, -4.94. HRMS calc for $C_{21}H_{36}O_4Si$: 380.2383. Found 380.2381.

Diastereoselective reduction of enone 7 to ***8*****:** (-)-DIP-Cl (2.3 M in heptane, 0.97 mL, 2.23 mmol) was added dropwise to a stirred solution of **7** (170 mg, 0.447 mmol) at -30 °C in anhydrous THF (3 mL). After 4 hours $NaHCO_3$ (700 mg) and methanol (2 mL) were added and the reaction mixture was warmed to room temperature. The resulting suspension was stirred for 12 hours, the solid was removed by filtration with a paper filter and the volatile compounds were removed under reduced pressure; the crude colourless oil was dissolved in CH_2Cl_2 and 2% aq. solution of $NaHCO_3$ (5 mL) was added, the organic layer was collected and the water phase was extracted with CH_2Cl_2 (4x 10 mL). The combined organic phases were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel. Elution with hexane/AcOEt (6:4) gave the allylic alcohol **8** (141 mg, 82%) as a colourless oil. $[\alpha]^{20}_D$ = -19.43 (*c* 0.71, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.56 (dd, *J* = 15.5; 5.7 Hz, 1H), 5.45 (dd, *J* = 15.5; 7.5 Hz, 1H), 4.93 (td, *J* = 6.9; 2.3 Hz, 1H), 4.07 (q, *J* = 6.1 Hz, 1H), 3.97 (q, *J* = 5.8 Hz, 1H), 2.84-2.54 (m, 2H), 2.52-2.21 (m, 3H), 1.96 (ddd, *J* = 14.7; 5.4; 2.2 Hz, 1H), 1.67-1.20 (m, 8H), 0.88 (m, 12H), 0.04 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.89, 135.44, 129.63, 83.09, 77.75, 72.39, 56.57, 42.03, 40.56, 37.33, 34.76, 31.63, 25.64, 25.10, 22.52, 17.92, 13.96, -4.76, -4.90. HRMS calc for $C_{21}H_{38}O_4Si$: 382.2539. Found 382.2547.

Synthesis of silyl ether ***9*****: 8** (207 mg, 0.541 mmol) was dissolved in anhydrous CH_2Cl_2 (6 mL) and imidazole (110 mg, 1.62 mmol) was added followed by TBS-Cl (86 mg, 0.57 mmol). The mixture was stirred at room temperature for 12 hours, then water (6 mL) was added followed by CH_2Cl_2 (15 mL), the water phase was extracted with CH_2Cl_2 (3x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel. Elution with hexane/AcOEt (9:1) gave the allylic silyl ether **9** (263 mg, 98 %) as a colourless oil. $[\alpha]^{20}_D$ = -25.3 (*c* 1.5, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.52 (dd, *J* = 15.5; 5.5 Hz, 1H), 5.38 (dd, *J* = 15.5; 7.5 Hz, 1H), 4.97 (td, *J* = 7.0; 2.1 Hz, 1H), 4.13-3.92 (m, 2H), 2.85-2.58 (m, 2H), 2.56-2.36 (m, 2H), 2.34-2.17 (m, 1H), 2.06-1.92 (m, 1H), 1.58-1.13 (m, 8H), 0.89 (m, 21H), 0.14-0.11 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.05, 135.84, 128.37, 83.42, 78.10, 72.88, 56.70, 42.29, 40.64, 38.36, 35.04, 31.76, 25.86, 25.71, 25.02, 22.60, 18.23, 17.98, 14.02, -4.49, -4.72, -4.77, -4.91. HRMS calc for $C_{27}H_{52}O_4Si_2$: 496.3404. Found 496.3411.

*Synthesis of the lactol **10*:** DIBAL-H (1M in Hexane, 175 µL, 0.175 mmol) was added dropwise to a stirred solution of **9** (83 mg, 0.167 mmol) at -78°C in anhydrous CH_2Cl_2 (2 mL). After 30 min Rochelle's salt solution (8 mL) was added and the resulting two layers were vigorously stirred at room temperature for 4 hours. The organic layer was then separated and the aqueous phase was extracted with CH_2Cl_2 (3x 10 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude lactol was obtained in quantitative yield and used without further purification for the next step.

*Wittig olefination of lactol **10** into **11**:* KHMDS (8.9 equiv, 2.9 mL, 0.5 M in toluene) was added under an Ar atmosphere to a stirred suspension of 4-carboxybuthyl-triphenyl phosphonium bromide (4.5 equiv, 0.247 g) in anhydrous THF (1.5 mL). After 45 min the orange solution of the resulting ylide was cooled at -20 °C and anhydrous toluene (4 mL) was added followed by a toluene solution (1.5 mL) of crude lactol **10** (83 mg, 0.166 mmol). The resulting reaction mixture was warmed to -10 °C and stirred at this temperature for 4 hours. The reaction was quenched by adding a saturated aqueous solution of NH_4Cl (15 mL) and acetic acid (0.127 mL, 1.05 equiv); Et_2O (20 mL) was added to the mixture and the organic layer was separated. The aqueous phase was extracted with Et_2O (3x 20 mL) and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel. Elution with hexane/EtOAc (8:2) gave the hydroxyacid **11** (89 mg, 90 %) as pale yellow oil. $[\alpha]^{20}_D$= +21.36 (*c* 0.88, CH_2Cl_2).^{1}H NMR (300 MHz, $CDCl_3$): δ 5.61-5.23 (m, 4H), 4.13 (br. s, 1H), 4.05 (m, 2H), 2.42-2.05 (m, 6H), 1.93-1.81 (m, 2H), 1.72 (p, *J* = 7.5 Hz, 2H), 1.55-1.36 (m, 3H), 1.36-1.17 (m, 7H), 0.90 (m, 21H), 0.14-0.02 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.77, 134.37, 130.75, 129.69, 129.02, 80.03, 74.75, 73.25, 56.46, 51.85, 42.86, 38.48, 33.38, 31.81, 26.64, 26.47, 25.89, 25.78, 25.04, 24.62, 22.64, 18.27, 17.85, 14.03, -4.27, -4.62, -4.75, -4.89. HRMS calc for $C_{32}H_{62}O_5Si_2$: 582.4136. Found 582.4123.

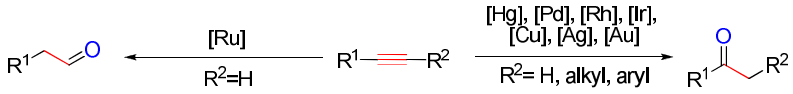
$PGF_{2\alpha}$: Aqueous HF (48%, 0.096 mL) was added to a stirred solution of bis-silyl ether **11** (30 mg, 0.051 mmol) in MeCN (2 mL) in a PE test tube. After 7 hours a phosphate buffer (pH 6.8, 6 mL) was added. The layers were separated and the aqueous

phase was extracted with EtOAc (6x 5mL). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel. Elution with EtOAc/MeOH (90:10) gave pure $PGF_{2\alpha}$ (16.3 mg, 90%) as a colourless oil. ^{1}H NMR (300 MHz, CD_3COCD_3): δ 5.60-5.46 (m, 3H), 5.41-5.28 (m, 1H), 4.12 (td, *J* = 5.2; 1.6 Hz, 1H), 4.04 (dd, *J* = 12.0; 5.7 Hz, 1H), 3.87 (ddd, *J* = 7.8; 6.0; 4.5 Hz, 1H), 2.42-1.99 (m, 8H), 1.74-1.58 (m, 3H), 1.57-1.18 (m, 9H), 0.90 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, CD_3COCD_3): δ 174.66, 136.12, 132.93, 130.53, 129.69, 78.06, 72.93, 72.16, 56.23, 51.18, 44.39, 38.46, 33.62, 32.61, 27.18, 26.07, 26.03, 25.64, 23.34, 14.32. HRMS calc for $C_{20}H_{34}O_5$: 354.2406. Found 354.2408.

8 Gold(I)-Catalyzed Alkyne Hydration

8.1 Introduction

Being excellent π-system activators, gold catalysts have mediated numerous organic reactions, including the gold-catalyzed hydration of alkynes. This transformation represents a convenient protocol to introduce a C-O bond into a molecule and is of high interest considering the broad commercial availability of alkynes and the relevance of the carbonyl motif in organic chemistry. Moreover, excellent atom economy[147] is achieved due to the use of water as hydrating agent. Depending on the amount and nature of the catalyst used, hydration of alkynes with water fulfills the criteria for environmentally friendly synthetic protocols. Therefore numerous reports on metal-based catalytic systems enabling this transformation can be found. Starting with Kucherov's finding of mercury-catalyzed alkyne hydration as early as 1881[186] numerous alternative catalytic systems emerged subsequently to master this type of reaction. Despite its high toxicity, mercury catalysts remained a common choice for this kind of reaction. However, acid catalyzed reactions as well as transition metal catalysts like palladium, rhodium, iridium, copper, silver and gold were found suitable for a variety of substrates. An interesting alternative has been found in ruthenium-based catalyst. Due to an alternative mechanistic pathway involving a vinylidene intermediate, terminal alkynes are converted selectively into the unusual anti-Markovnikov product yielding aldehydes instead of ketones (**Scheme 8.1**).[187]

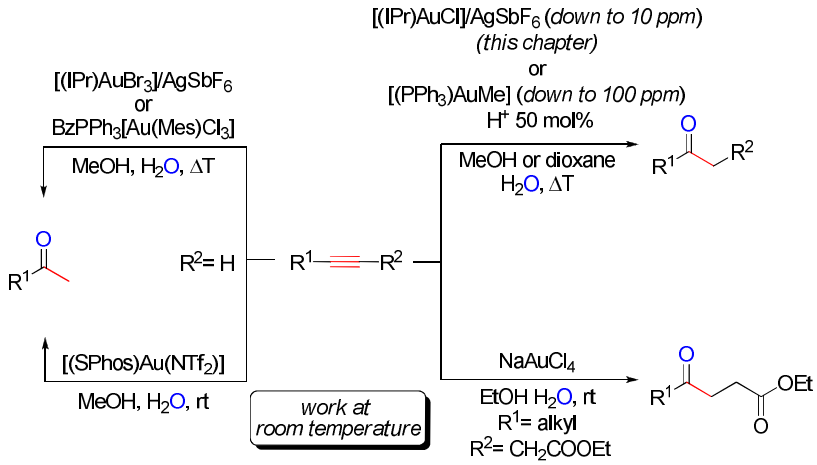


Scheme 8.1 Alkyne hydration with various catalysts.

Specifically gold(I) has attracted attention in view of the mild reaction conditions leading to product formation and has gradually taken a prominent place, replacing the toxic mercury(II) salts.[161, 188, 189] Au(III)-mediated alkyne hydration has also been reported, with emphasis on terminal alkynes. Catalysts facilitating this transformation include $NaAuCl_4$,[161] $BzPPh_3[Au(Mes)Cl_3]$[188b] and $[(IPr)AuBr_3]$.[190] In the latter case, the reaction is limited to phenylacetylene derivatives. Of note, Au(I) catalysts appear to exhibit a broader substrate scope and permit lower catalyst loadings. Hayashi and

Tanaka reported the use of a $[(Ph_3P)AuMe]/H^+$ catalytic system allowing for a high turnover frequency (TOF) in the hydration of 1-octyne.[178a] Despite its efficiency, this catalyst suffers from some drawbacks. While the low catalyst loading (100 ppm) and decreased acid promoter amount of 4% were exclusively reported for the hydration of 1-octyne, the vast majority of substrates were converted in the presence of 50 mol% of concentrated acid solutions (H_2SO_4, CF_3SO_3H) and increased catalyst loadings of typically 0.2 to 1 mol% leaving questions on the performance of the catalytic systems for alkynes other than 1-octyne. While $[(PPh_3)AuMe]/H^+$ demonstrated catalysis of alkyne hydration at 100 ppm for a single substrate only, the upcoming chapter describes how the alkyne hydration can be performed under acid-free conditions using 100 ppm catalyst loading for a wide series of alkynes and still works with catalyst loadings as low as 10 ppm of $[(IPr)AuCl]/AgSbF_6$ in case of 3-hexyne.

Alternatively, Corma *et al.* reported almost concomitantly with the present work the use of 0.5-5 mol% $[(SPhos)Au(NTf_2)]$ for the hydration of mostly terminal alkynes at room temperature.[191] At the same time, Hammond *et al.* succeeded in the $NaAuCl_4$-catalyzed hydration of β-keto esters at room temperature (selected examples are illustrated in **Scheme 8.2**).[192]



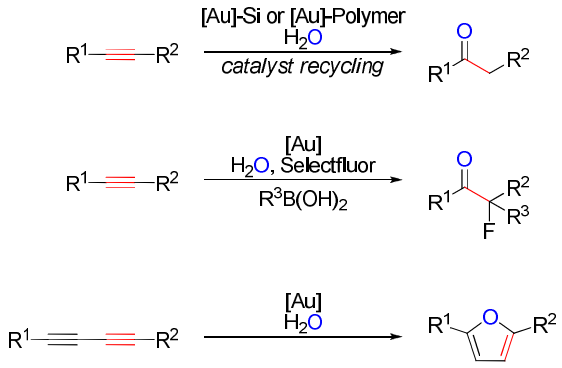
Scheme 8.2 Selection of exemplary gold-catalyzed hydrations.

8.1.1 Subsequent developments in gold catalyzed alkyne hydration

The enormous importance and the continuing interest in gold catalyzed hydration is impressively demonstrated by the amount of successive reports on this topic. Since submission of the work presented in this chapter, various new approaches with gold catalysts have been published. Computational work on the mechanism of the Au(III)

catalyzed reaction was reported indicating involvement of a second water moiety in the mechanism,[193] whereas the important influence of solvents was highlighted in a computational study on Au(I) catalyzed hydration.[194]

Functionalized alkyne hydration yielding α-fluorinated ketones was realized applying selectfluor and reported independently by both the research groups of Xu and Hammond[195] as well as Nevado and coworkers.[196] Sahoo and coworkers succeeded in the hydration of propargylic acetates.[197] Our own laboratory further contributed with the application of alkyne hydration for subsequent furan formation.[198] Similarly, Fiksdahl and coworkers applied a gold-catalyzed hydration step for the cyclization of 1,6-diynes.[199]



Scheme 8.3 Selected examples of gold-catalyzed alkyne hydration subsequent to this work.

Various contributions were made on the development of new catalysts or, ancillary ligands for this reaction type. This includes the application of water soluble Au(I) catalysts with functionalized NHCs.[200] Asymmetric NHCs for improved catalyst activity in alkyne alkoxylation have been reported to also yield ketones[201] while immobilization of gold catalysts on silica allowed for excellent activity but also for improvements in terms of the very important aspect of catalyst recycling.[202] Similarly, addressing catalyst recycling in alkyne hydration, polymer matrices involving covalently bound Au(I) have been presented suitable for reactions at elevated temperatures and have shown excellent reusability qualities (**Scheme 8.3**).[203] Finally, encapsulation of [(IPr)Au] in a self-assembling supramolecular capsule resulted not only in a severe drop in reactivity but more interestingly also in a diverse selectivity since partial formation of the unprecedented anti-Markovnikov product was observed in gold-catalyzed alkyne hydration.[204]

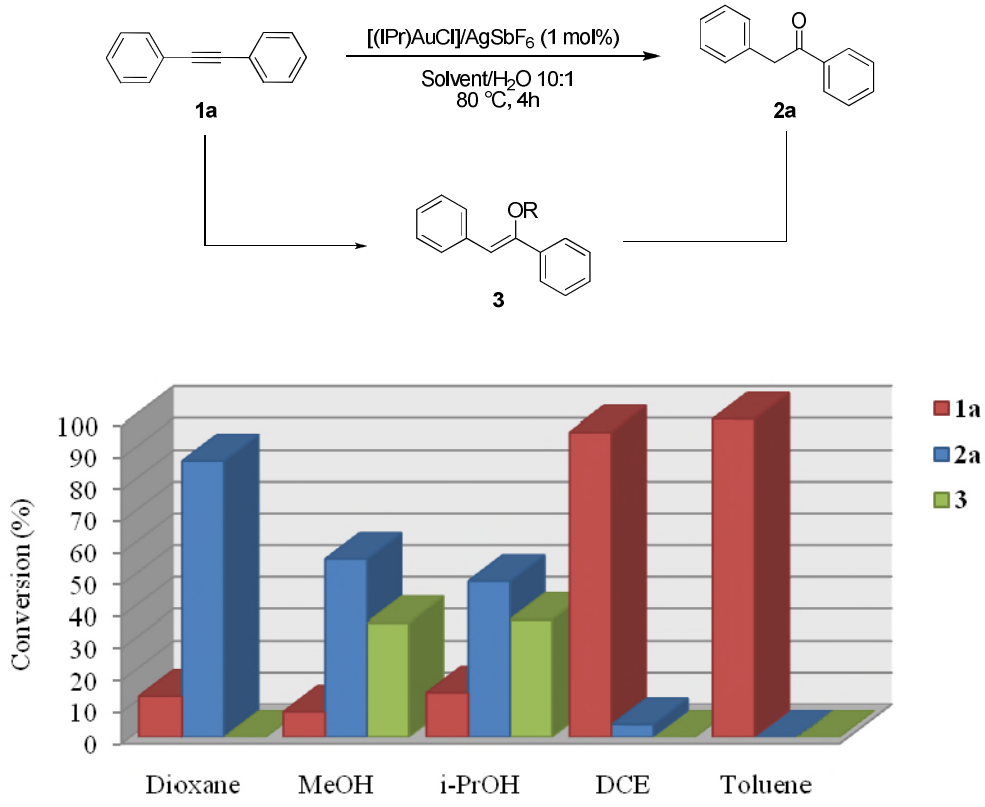
8.2 Results and Discussion

8.2.1 Optimization

In order to start optimizations for a highly efficient catalytic system at mild reaction conditions based on gold complexes, we focused on N-heterocyclic carbenes (NHCs) as supporting ligand for the gold catalysts since they have already proven successful in the rapidly developing field of homogeneous gold catalysis,[102h, 110a, 151] and they proved extraordinary efficient at low catalyst loading for various organometallic transformations.[205]

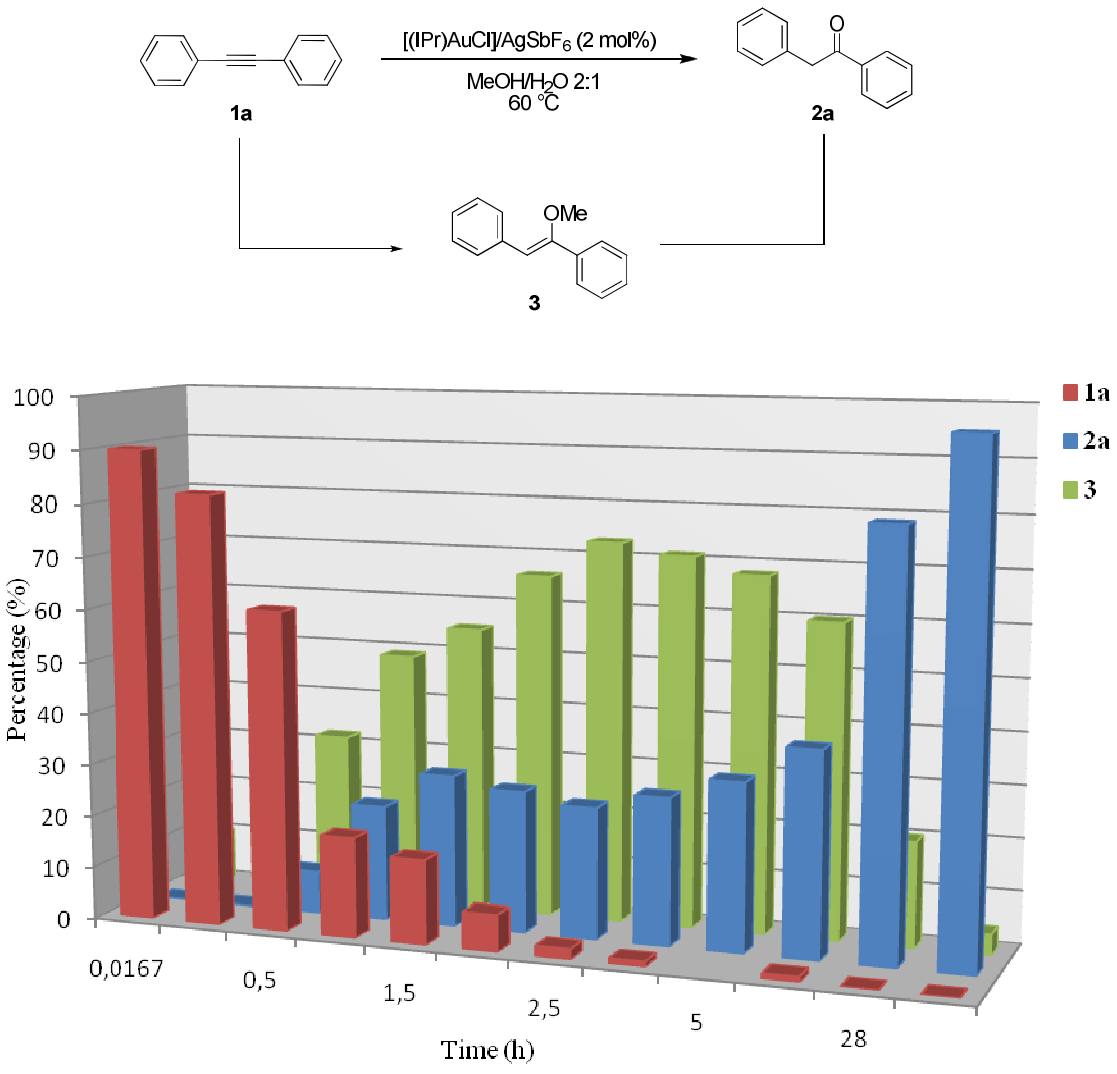
8.2.1.1 Solvent effects

We began the optimization studies on the hydration of diphenylacetylene **1a**, relying on our previous findings that [(NHC)AuCl] complexes promote water addition-type reactions.[116, 174] Several parameters were examined and important observations were made during the obligatory solvent screening (**Scheme 8.4**).



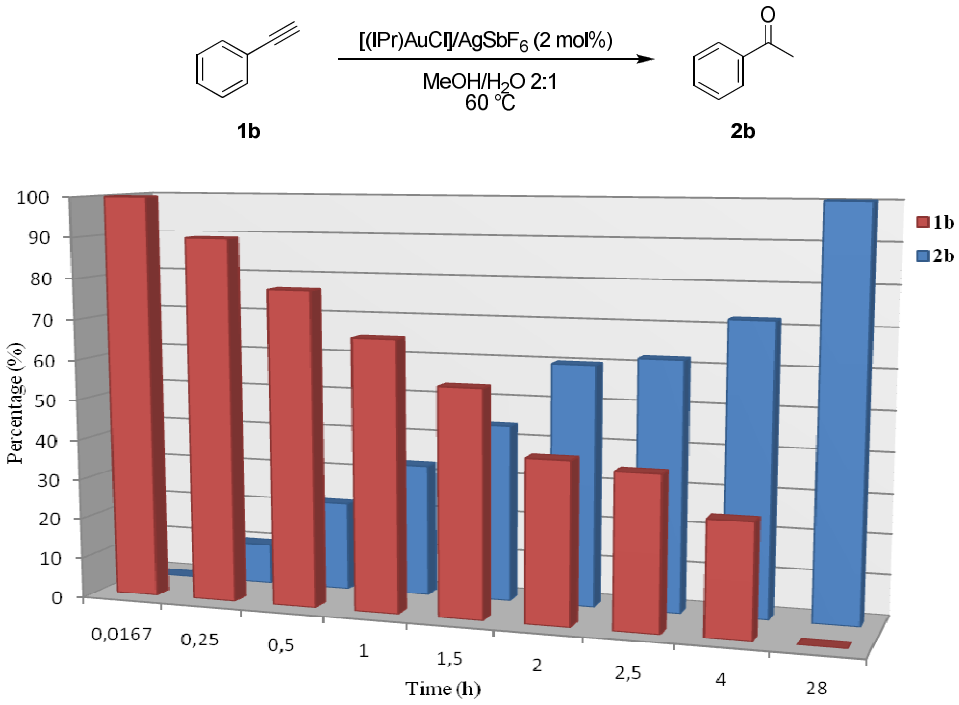
Scheme 8.4 GC conversion of diphenylacetylene **1a** in 1,2-diphenylethanone **2a** in various solvents. Reaction conditions: 0.28 mmol diphenylacetylene [(IPr)AuCl] 1 mol%, $AgSbF_6$ 1 mol%, 1 mL solvent, 100 µL H_2O, 80 °C, 4 hours.

While 1,4-dioxane was found to be most favourable for conversions into ketone **2a**, GC spectra revealed the formation of a second compound when performing the reaction in methanol or isopropanol. GC/MS analysis confirmed the suggested formation of the corresponding vinylether, which was thought to be an intermediate in the case of alkyne hydration performed in alcohols. This would of course implicate an alternative mechanism compared to 1,4-dioxane as solvent.



Scheme 8.5 Conversion of **1a** into **2a** *via* **3** in MeOH. Reaction conditions: diphenylacetylene (0.5 mmol), [(IPr)AuCl] 2 mol%, $AgSbF_6$ 2 mol%, MeOH:H_2O 2:1(0.3 M) , 60 °C.

To confirm the hypothesis that **3** is an intermediate in the alkyne hydration when using alcohol solvents, additional experiments were performed to record the reaction profile. As illustrated in **Scheme 8.5**, fast conversion of the alkyne **1a** into **3** was observed.



Scheme 8.6 Conversion of **1b** into **2b** in MeOH. Reaction conditions: phenylacetylene (1 mmol), [(IPr)AuCl] 2 mol%, $AgSbF_6$ 2 mol%, MeOH:H_2O 2:1(0,3 M) , 60 °C.

Prolonged reaction time however resulted in full conversion into target ketone **2a**, supporting initial assumptions. Interestingly, when the same reaction was performed with phenylacetylene **1b** instead of diphenylacetylene **1a**, GC analysis did not show any traces of intermediates. The resulting reaction profile (**Scheme 8.6**) therefore showed linear conversion.

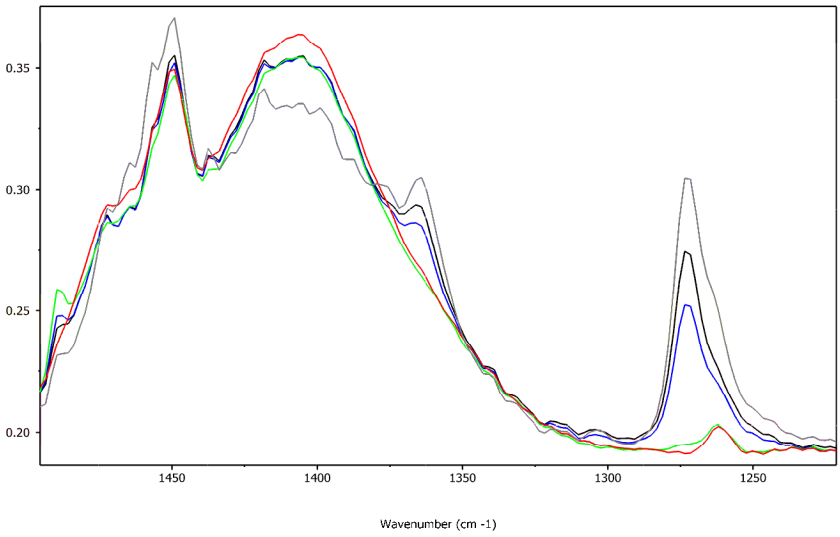
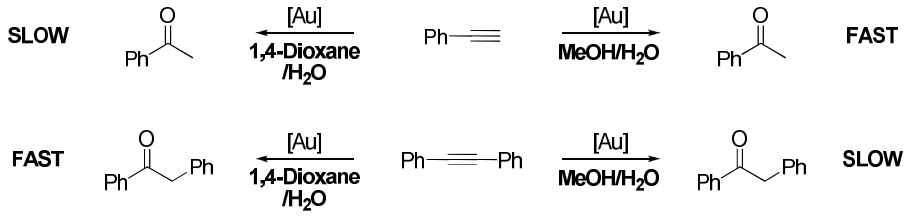


Figure 8.1 2-Dimensional *in situ* FT-IR of the phenylacetylene hydration in MeOH/H_2O. Enlargment of the region between 1200-1500 cm^{-1} showing a growing product peak at 1270 cm^{-1}.Reaction profile: red (start) → green → blue → black → grey (end).

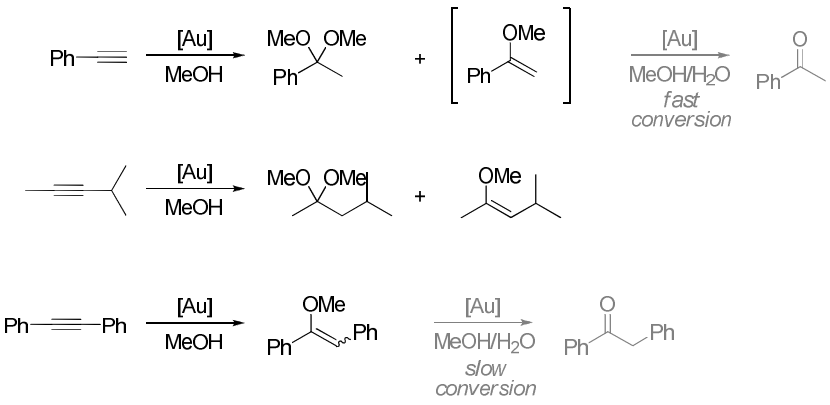
As an alternative, *in situ* FT-IR was considered as a suitable alternative to detect potential intermediates that might convert or decompose during GC. Although the 2D FTIR (**Figure 8.1**) nicely illustrates the reaction profile of the conversion of phenylacetylene **1b** into acetophenone **2b**, no IR-signals belonging to a vinylether or acetal were detected.

Surprisingly, in the case of terminal alkynes a divergent solvent preference was observed (**Scheme 8.7**). In strong contrast to internal alkynes methanol showed improved reaction rates in comparison to 1,4-dioxane. More precisely, while alkyne **1a** showed slower conversion to ketone **2a** in the presence of MeOH (20 h) when compared to 1,4-dioxane (1.5 h), this relation was reversed when using phenylacetylene. For reactions carried out at 65 °C for 18 hours, conversion of phenylacetylene **1b** into acetophenone **2b** was complete in MeOH, whereas in 1,4-dioxane conversion was only 29%. Nevertheless, the reaction performs well in both solvents at higher temperatures.



Scheme 8.7 Conversion of terminal and internal alkynes in MeOH and 1,4-dioxane.

The different solvent preference of terminal and internal alkynes was reasoned to be strongly related to the conversion rate of the intermediate vinylether into another, not detected acetal which then would almost instantly convert into the corresponding ketone with both substrates.

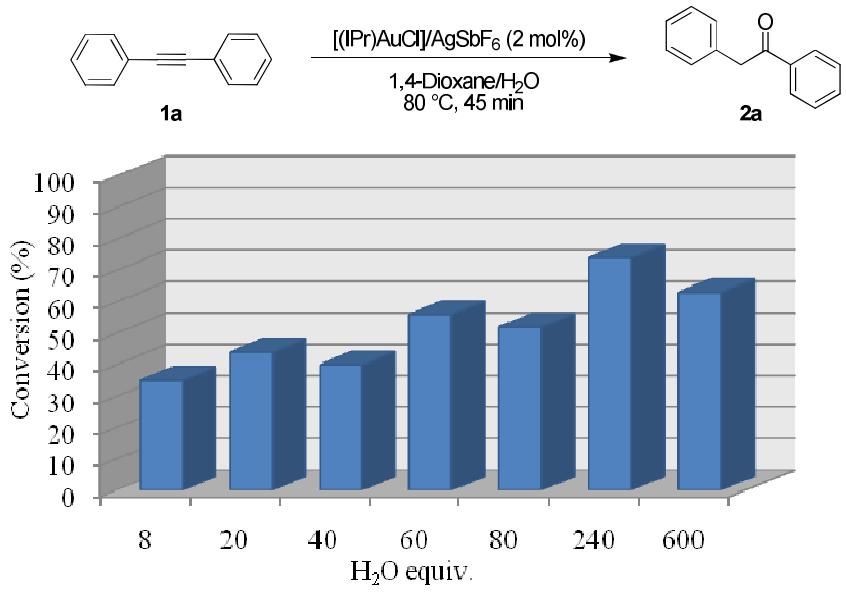


Scheme 8.8 Vinylether and acetal formation as observed by Teles. Conversions as observed in this chapter in dark grey.

This hypothesis is supported by findings of Teles and coworkers in their pioneering work on the highly efficient and closely related gold-catalyzed alkoxylation of alkynes.[178b] In there, the authors report formation of vinylethers or acetals depending of the bulk of the surrounding substituents matching the observations and conclusions made herein (**Scheme 8.8**). Further investigations addressing the aspect of interim acetal formation and conversion in the presence of gold catalysts are presented in Chapter **9**.

8.2.1.2 Water amount

Apart from the solvent screening and the resulting investigations the water amount was also found to be a surprisingly important reaction variable. As illustrated in **Scheme 8.9**, increasing the amount of water in the reaction mixture directly influenced the conversions achieved. Reaction in water alone however resulted in poor conversion. It appears reasonable to address this as a solubility issue of both substrate and catalyst in the absence of any organic solvent. A mixture of 2:1 solvent/water was finally found to be a suitable mixture to allow for promising conversions with both internal and external alkynes.



Scheme 8.9 Conversion into **2a** in relation to the H_2O amount. Reaction conditions: diphenylacetylene (0.28 mmol), [(IPr)AuCl] 2 mol%, $AgSbF_6$ 2 mol%, 1,4-dioxane (3 mL), 80 °C, 45 min.

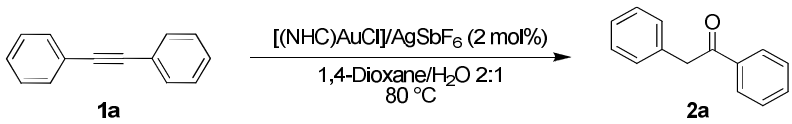
8.2.1.3 Miscellaneous

Next to the parameters discussed above, several more aspects of the catalytic systems were investigated including the reaction temperature, silver salt used for chloride abstraction and of course the NHC ancillary ligand of the gold catalyst. Most

relevant results are presented in **Table 8.1** showing the impact on conversions when changing various relevant parameters.

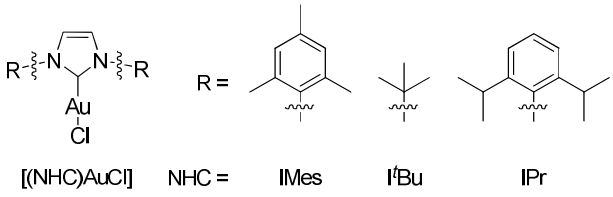
The equimolar combination of [(IPr)AuCl] and $AgSbF_6$ was found particularly active (entry 1). Other NHCs led to poor conversions or required extended reaction time (entries 2 and 3). Most silver(I) salts, including $AgPF_6$, AgOAc, AgOTs and AgTFA proved unsatisfactory, whereas $AgBF_4$ and $AgClO_4$ were found to be as active as $AgSbF_6$. Additionally, only trace conversion to the ketone was observed in the absence of gold. As mentioned above the composition of the reaction medium was critical, 1,4-dioxane being the best solvent (entries 1, 6-7) when employed in a 2:1 ratio with water (entries 1 and 8) while in pure water no conversion was observed (entry 9).

Table 8.1 Optimization of the hydration conditions.



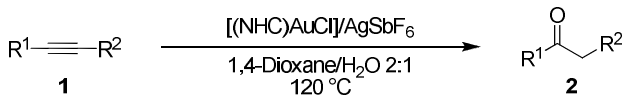
Entry	changes from standard conditions	time (h)	GC conv.
1	None	1.5	97%
2	IMes instead of IPr	20	nr
3	I^{t}Bu instead of IPr	20	93%
4	$AgBF_4$ instead of $AgSbF_6$	1.5	95%
5	AgOAc instead of $AgSbF_6$	20	nr
6	Toluene instead of 1,4-dioxane	5	< 5%
7	DCE instead of 1,4-dioxane	5	< 5%
8	1,4-Dioxane/H_2O (6:1) instead of (2:1)	1.5	67%
9	Neat water instead of 1,4-dioxane/H_2O (2:1)	20	nr
10	[Au] (0.1 mol%) instead of (2 mol%)	18	77%

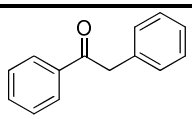
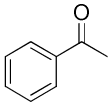
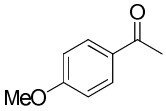
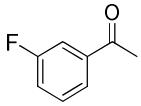
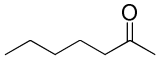
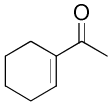
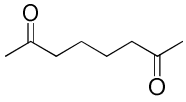
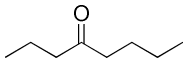
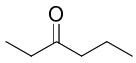
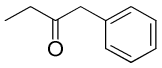
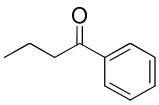
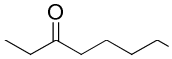
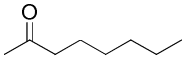
[a] GC conversions are average of at least two runs. nr = no reaction.



Keeping in mind the initial goal of developing a catalyst efficient at low loadings, the amount of [(IPr)AuCl] used was decreased to 0.1 mol% (i.e. 1000 ppm) for the

Table 2. Hydration of alkynes at low catalyst loadings.



Entry	Product	2	Yield[a]	Cat. Loading	TON
1		**2a**	77%	1000 ppm	770
2[b]		**2b**	85%	50 ppm	17000
3		**2c**	81%	100 ppm	8100
4[b]		**2d**	97%	100 ppm	9700
5[b]		**2e**	100%	50 ppm	20000
6		**2f**	72%	100 ppm	7200
7[b]		**2g**	91%	50 ppm	18200
8		**2h**	76%	100 ppm	7600
9		**2i**	95%	100 ppm	9500
10		**2j**	84%	10 ppm	84000
11	 **2k**$_a$	 **2k**$_b$	81% k_a/k_b 4.4:1	1000 ppm	810
12	 **2l$_a$**	 **2l$_b$**	74% l_a/l_b 2.2:1	100 ppm	7400

[a] 1H-NMR yields against benzaldehyde as internal standard. Yields are average of at least two runs. [b] Reaction performed with MeOH instead of 1,4-dioxane.

hydration of **1a** and a promising 77% yield (TON 770) of ketone **2a** (entry 10) was obtained. It should be noted that the hydration of diphenylacetylene **1a** has proven

difficult in the past, as for most internal alkynes. This result already constitutes a notable improvement in comparison to Tanaka and co-workers who reported a TON of 53 in the case of **1a**.[178a]

8.2.2 Substrate scope

With a fully optimized set of reaction conditions to hand, the scope of the catalytic system was examined. The reactivity of several terminal alkynes was investigated. As mentioned above, faster conversions with this type of alkyne was observed when the reactions were performed in methanol instead of 1,4-dioxane.

Of note, a blank reaction with silver salts in optimized reaction conditions revealed minor catalytic activity of silver salts in alkyne hydration with phenylacetylene in MeOH. Hence, phenylacetylene could be efficiently converted to acetophenone **2b** with only 50 ppm of the gold catalyst (85% yield, TON 17000). This result corresponds to a decrease in catalyst loading of nearly two orders of magnitude from previous studies. Similarly, *p*-OMe- and *m*-fluoro-acetophenones **2c** (81%) and **2d** (97%) were obtained in high yields at 100 ppm, although run in 1,4-dioxane, with TONs of 8100 and 9700, respectively. Alkyl-substituted terminal alkynes reacted equally well at 50 ppm (**2e**, 100%, TON 20000) and even the very sterically hindered *tert*-butylmethyl ketone **2f** was produced in good yield (72%, TON 7200) at low catalyst loading (100 ppm) in 1,4-dioxane.

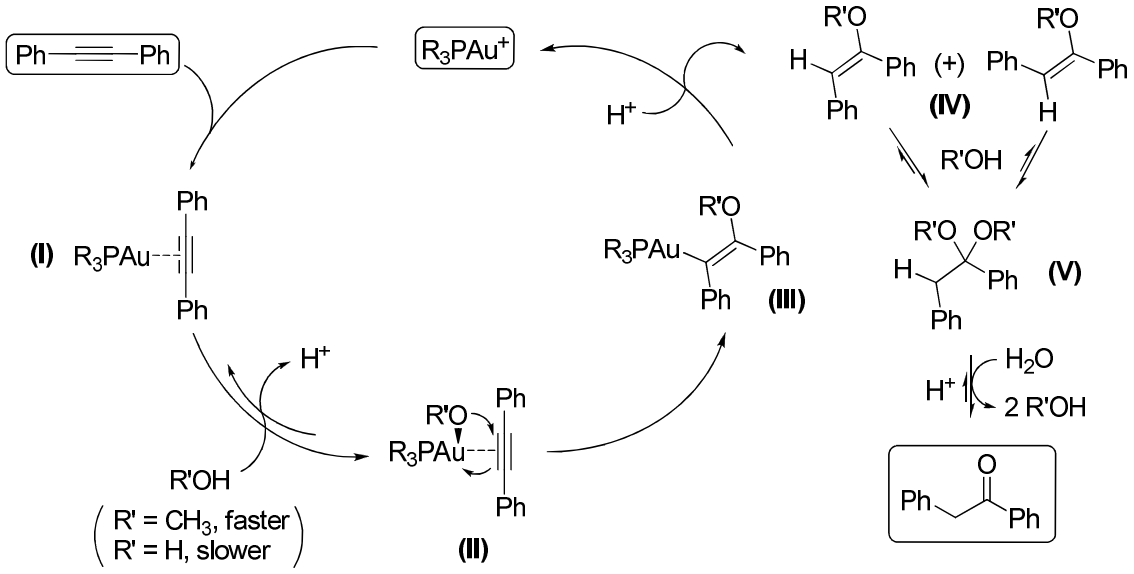
Remarkably, the presence of an alkene moiety was well tolerated and conjugated enone **2g** (50 ppm, 91%) was obtained with a high TON of 18200. Finally, a double hydration was efficiently performed in 1,4-dioxane at 100 ppm and yielded diketone **2h** in 76% (TON 7600).

Internal alkynes, as observed by Hayashi and Tanaka,[178a] are usually more reluctant participants than their terminal counterparts towards hydration reactions. Nevertheless, encouraged by the preliminary results with diphenylacetylene **1a**, the reactivity of both symmetrical and unsymmetrical disubstituted alkynes was examined. Delightfully, the high yield of 4-octyne into **2i** at 100 ppm (95%, TON 9500) was observed; a reaction that could be scaled up to 20 mmol without loss of activity. Similarly, 3-hexanone **2j** was obtained in high yield (84%). In this case, the reaction could be performed *with only 10 ppm* of [(IPr)AuCl] pre-catalyst, leading to an unprecedentedly high TON of 84000.

Finally, two unsymmetrical alkynes were efficiently hydrated, yielding **2k** (1000 ppm, 81%, TON 810) and **2l** (100 ppm, 74%, TON 7400), albeit with moderate selectivity, as previously reported with other catalytic systems. At this point, it should be noted that terminal and internal alkynes possessing any combination of alkyl and aryl substituents (alkyl/H, aryl/H, alkyl/alkyl, alkyl/aryl, and aryl/aryl) were found suitable substrates in the present catalytic system. This versatility at low catalyst loadings is unprecedented.

8.2.3 Mechanistic considerations

Mechanistically, findings made for the role of methanol in the alkyne hydration mechanism was extensively discussed by Corma *et al.* in a publication[191] published very shortly after the present work.[206] Delightfully, Corma's results, also obtained with diphenylacetylene, excellently match these observations and led him to the conclusion that methanol is competing with water for alkyne functionalization yielding the desired ketone *via* an intermediate vinylether and an unobserved acetal. Of note, isolation of the vinylether revealed an *E/Z* mixture which is in contrast to Corma's mechanistic proposal illustrated in **Scheme 8.10**.



Scheme 8.10 Mechanism for the alkyne hydration as proposed by Corma *et al.*[191]

8.3 Conclusion

To conclude, a highly efficient [(NHC)Au^{I}]-based catalytic system for the hydration of a wide array of alkynes that operates under acid-free conditions and at very low catalyst loadings (typically 50-100 ppm and as low as 10 ppm) was developed. An important influence of the water amount was found as well as divergent solvent preferences for internal and terminal alkynes. Mechanistically, the proposed mechanism for internal alkynes by Corma and co-workers widely matches the results presented here and is therefore considered accurate.

8.4 Experimental section

General information: All reagents were used as received. Reactions were performed under ambient atmosphere. Technical grade solvents were used. [(NHC)AuCl] complexes were synthesized as described in Chapter **5**. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 ULTRASHIELD NMR spectrometer at ambient temperature in $CDCl_3$ containing 0.03 % TMS. Chemical shifts are given in parts per million (ppm) relative to $CDCl_3$ (^{1}H: 7.26 ppm, ^{13}C: 77.16 ppm). Coupling constants are given in Hertz (Hz). High resolution mass spectra (HRMS) were recorded by the HRMS unit of the ICIQ (Tarragona) using ESI (Electron Spray Ionisation). Gas chromatography (GC) was performed on an Agilent 6890 N Gas Chromatograph. Anhydrous solvents were purified by passing through a purification column from Innovative Technology Inc. (SPS-400-6). Ketones **2** are commercially available (CAS #: **2a**, [451-40-1]; **2b**, [98-86-2]; **2c**, [100-06-1]; **2d**, [455-36-7]; **2e**, [110-43-0]; **2f**, [75-97-8]; **2g**, [932-66-1]; **2h**, [7029-06-3]; **2i**, [589-63-9]; **2j**, [589-38-8]; **2k$_a$**, [495-40-9]; **2k$_b$**, [1007-32-5]; **2l$_a$**, [111-13-7]; **2l$_b$**, [106-68-3]) and their spectroscopic data were found in good agreement with previously reported characterization data.

Gold catalyst optimization: In a sealed 4 mL reaction vial equipped with a magnetic stirring bar, the catalyst (2 mol%) was added to 1,4-dioxane (1 mL). A small amount of $AgSbF_6$ (covering the tip of a spatula) was added and the reaction mixture was stirred for 1 minute. Diphenylacetylene (100 mg, 561 μmol, 1 equiv.) was added, followed by distilled H_2O (100 μL). The reaction mixture was then heated at 80 ºC for the indicated time. Conversions were monitored by GC.

Silver salt optimization: In a sealed 4 mL reaction vial equipped with a magnetic stirring bar, [(IPr)AuCl] (7.0 mg, 11 μmol, 2 mol%) was added to 1,4-dioxane (1 mL). A small amount of silver salt (covering the tip of a spatula) was added and the reaction mixture was stirred for 1 minute. Diphenylacetylene (100 mg, 561 μmol, 1 equiv.) was added, followed by distilled H_2O (100 μL). The reaction mixture was then heated at 80 ºC for the indicated time. Conversions were monitored by GC.

Water amount optimization: In a sealed 4 mL reaction vial equipped with a magnetic stirring bar, [(IPr)AuCl] (3.5 mg, 5.61 μmol, 2 mol%) was added to 1,4-dioxane (3 mL). A small amount of $AgSbF_6$ (covering the tip of a spatula) was added and the reaction mixture was stirred for 1 minute. Diphenylacetylene (50 mg, 281 μmol, 1 equiv.) was added, followed by a defined amount of distilled H_2O. The reaction mixture was then heated for 2 hours at 80 ºC. Conversions were monitored by GC.

Solvent optimization: In a sealed 4 mL reaction vial equipped with a magnetic stirring bar, [(IPr)AuCl] (7.0 mg, 11 μmol, 2 mol%) was added to the solvent (1 mL). A small amount of $AgSbF_6$ (covering the tip of a spatula) was added and the reaction mixture was stirred for 1 minute. Diphenylacetylene (100 mg, 561 μmol, 1 equiv.) was added, followed by distilled H_2O (100 μL). The reaction mixture was then heated at 80 ºC for the indicated time. Conversions were monitored by GC.

Hydration of diphenylacetylene in methanol: In a sealed 4 mL reaction vial equipped with a magnetic stirring bar, [(IPr)AuCl] (7.0 mg, 11 μmol, 2 mol%) was added to MeOH (2 mL). A small amount of $AgSbF_6$ (covering the tip of a spatula) was added and the reaction mixture was stirred for 1 minute. Diphenylacetylene **1a** (100 mg, 561 μmol, 1 equiv.) was added, followed by addition of distilled H_2O (1 mL). The reaction mixture was heated at 60 ºC. Conversions were monitored by GC. Reported yields are average of two runs.

*Isolation of **3**:* In a 25 mL Schlenk tube equipped with a magnetic stirring bar, anhydrous MeOH (4 mL) was added to [(IPr)AuCl] (14 mg, 22 μmol, 2 mol%) under inert atmosphere. A small amount of $AgSbF_6$ (covering the tip of a spatula) was added and the reaction mixture was stirred for 1 minute. Diphenylacetylene (178 mg, 1 mmol,

1 equiv.) was added and the reaction mixture was then heated overnight at 65 ºC. Volatile components were then removed under reduced pressure and the residue was dissolved in CH_2Cl_2. The solution was filtered over a plug of silica (~1 cm, CH_2Cl_2) and the solvent removed under reduced pressure, affording 169 mg (804 μmol, *E*/*Z* 1:9, 80%) of compound **3**.

*Conversion of **3** into **2a**:* In a sealed 4 mL reaction vial equipped with a magnetic stirring bar the [(IPr)AuCl] (7.0 mg, 11 μmol, 2 mol%) was added to MeOH (2 mL). A small amount of $AgSbF_6$ (covering the tip of a spatula) was added and the reaction mixture was stirred for 1 minute. **3** (100 mg, 476 μmol, 1 equiv.) was then added, followed by addition of distilled H_2O (1 mL). The reaction mixture was heated for 6 days at 80 ºC. Full conversion into ketone **2a** was observed by GC.

General procedure at 1000 ppm catalyst loadings: In a sealed 4 mL reaction vial equipped with a magnetic stirring bar, [(IPr)AuCl] (62 μL of a 10 mg/mL solution in THF, 1 μmol, 1000 ppm) was added to 1,4-dioxane (660 μL). Then, the tip of a spatula of $AgSbF_6$ was added and the reaction mixture was stirred for 1 minute. Alkyne **1** (1 mmol, 1 equiv.) was added, followed by addition of distilled H_2O (330 μL). The reaction mixture was heated for 18 hours at 120 ºC and then allowed to cool to room temperature. ^{1}H NMR yields were determined by adding a known amount of benzaldehyde, as internal standard, to the crude product. Reported yields are average of two runs.

General procedure at 100 ppm catalyst loadings: In a sealed 4 mL reaction vial equipped with a magnetic stirring bar [(IPr)AuCl] (62 μL of a 1 mg/mL solution in THF, 0.1 μmol, 100 ppm) was added to 1,4-dioxane (660 μL). Then, the tip of a spatula of $AgSbF_6$ was added and the reaction mixture was stirred for 1 minute. Alkyne **1** (1 mmol, 1 equiv.) was added, followed by addition of distilled H_2O (330 μL). The reaction mixture was heated for 18 hours at 120 ºC and then allowed to cool to room temperature. ^{1}H NMR yields were determined by adding a known amount of benzaldehyde, as internal standard, to the crude product. Reported yields are average of two runs.

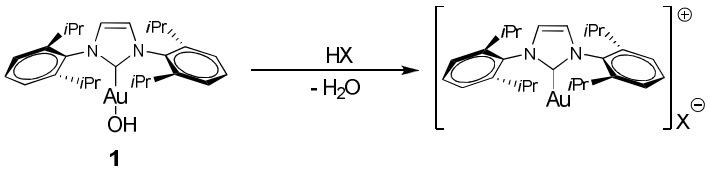
General procedure at 10 ppm catalyst loadings: In a sealed 50 mL reaction vial equipped with a magnetic stirring bar, [(IPr)AuCl] (62 μL of an 1 mg/mL solution in THF, 0.1 μmol, 10 ppm) was added to 1,4-dioxane (6.6 mL). Then, the tip of a spatula of $AgSbF_6$ was added and the reaction mixture was stirred for 1 minute. Alkyne **1** (10 mmol, 1 equiv.) was added, followed by addition of distilled H_2O (3.3 mL). The reaction mixture was heated for 72 hours at 120 ºC and then allowed to cool to room temperature. ^1H NMR yields were determined by adding a known amount of benzaldehyde, as internal standard, to the crude product. Reported yields are the average of two runs.

Large scale hydration reaction of 4-octyne: In a sealed 50 mL reaction vial equipped with a magnetic stirring bar, [(IPr)AuCl] (1.0 mg, 2 μmol, 100 ppm) was added to 1,4-dioxane (13 mL). $AgSbF_6$ (0.7 mg, 2 μmol, 100 ppm) was added and the solution was stirred for 1 minute. 4-Octyne **1i** (20 mmol, 2.2 g, 1 equiv.) was added, followed by addition of distilled H_2O (6.6 mL). The reaction mixture was then heated for 18 hours at 120 ºC. Volatile components were then removed under reduced pressure and the residue dissolved in CH_2Cl_2. The solution was filtered over a plug of silica (~1 cm) and the solvent was removed under reduced pressure, affording 2.15 g (16.8 mmol, 84%) of ketone **2i**. ^1H NMR (400 MHz, $CDCl_3$): δ 2.27-2.38 (m, 4H), 1.42-1.60 (m, 4H), 1.18-1.31 (m, 2H), 0.79-0.90 (m, 6H).[207]

9 Silver-Free Gold(I)-Catalyzed Alkyne Hydration

9.1 Introduction

Chapter **8** decribed the development of alkyne hydration at low catalyst loadings involving the [(IPr)AuCl]/$AgSbF_6$ catalytic system. This system's high efficiency even at part-per-million (ppm) catalyst loadings was demonstrated and proved to be a suitable alternative to the use of excess strong acid necessary to activate the gold center.[206] Nevertheless, pre-catalyst [(IPr)Au(OH)] (**1**)[136] was obtained and protonolysis in the presence of a Brønsted acid afforded $[(IPr)Au]^+$, the suggested catalytic active species in gold catalysis *via* a simple protocol (**Scheme 9.1**).[117] Therefore, the use of **1** as pre-catalyst in the hydration of various alkynes was investigated and the optimal amount of Brønsted acid necessary for activation of **1** was closely examined. In this procedure, silver additives are redundant resulting not only in a simplified procedure due to the lack of these air-, light- and moisture-sensitive reagents but also eliminates any questions on the catalytic activity of gold at low catalyst loadings due to the partial catalytic activity of silver salts in hydration of terminal alkynes in methanol.



Scheme 9.1 Generation of [(IPr)Au][X] *via* acid activation of complex **1.**

Additionally, acid activation of **1** results in the formation of water as a single side product which is not only the most ecologically friendly side product possible but also is the substrate and/or solvent in this methodology. Therefore, this very environmentally friendly and very atom-economical method to generate ketones from alkynes was further developed.

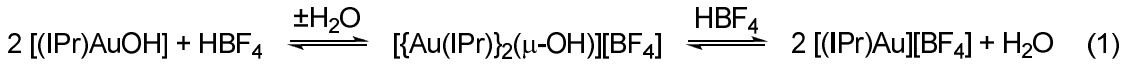
A remaining gap in the mechanistic understanding of the gold catalyzed alkyne hydration is also addressed *via* a small 'proof of concept'-experiment. While earlier findings described in Chapter **8** clearly revealed the formation of intermediate vinylethers, the subsequent formation of acetals with fast conversion into the corresponding ketones was only a proposal without actual experimental proof based on

findings by Teles[178b] in alkyne alkoxylation. Therefore, this gap is addressed in the present chapter.

9.2 Results and discussion

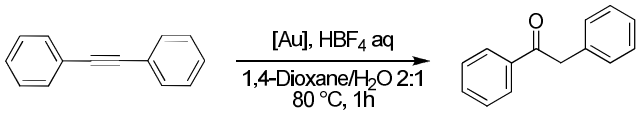
9.2.1 Optimization

An initial investigation focused on determining the catalytic capability of the two new catalysts obtained, [(IPr)Au(OH)] and [{(IPr)Au}$_2$(μ-OH)][BF_4]. As illustrated in **Table 9.1**, [(IPr)Au(OH)] (2 mol%) furnished only low conversions in the absence of any acid with demanding diphenylacetylene (entry 2). Addition of half an equivalent HBF_4 however dramatically increased conversion up to very good 90% (entry 3).



Of note, the addition of half an equivalent acid results in the *in situ* formation of [{(IPr)Au}$_2$(μ-OH)][BF_4] (see Chapter **11**). Further increase of the acid amount to generate [(IPr)Au][BF_4] allowed for full conversion into the ketone (entries 4-5).

Table 9.1 Initial comparison of gold complexes in alkyne hydration.[a]



2j **3j**

Entry	[Au] (mol%)	HBF_4 (mol%)	GC conversion (%)[b]
1	none	2	0
2	[(IPr)Au(OH)] (2)	0	12
3	[(IPr)Au(OH)] (2)	1	90
4	[(IPr)Au(OH)] (2)	2	>99
5	[(IPr)Au(OH)] (2)	3	>99
6	[{(IPr)Au}$_2$(μ-OH)][BF_4] (1)	0	88
7	[{(IPr)Au}$_2$(μ-OH)][BF_4] (1)	1	>99

[a] Gold complexes (based on gold) with different amounts of aqueous HBF_4 in a 2:1 mixture of 1,4-dioxane/water (1 mL) at 80 °C for 1 hour. [b] GC conversions are average of at least two runs.

Usage of excess acid was demonstrated necessary to guarantee exclusive formation of [(IPr)Au][BF_4] while with stoichiometric amounts [{(IPr)Au}$_2$(μ-OH)][BF_4] can still

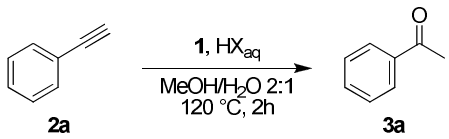
be present in the solution (eq. 1).[117] Similarly Toste and co-workers proposed a closely related equilibrium with (phosphine)gold hydroxonium based on calculations.[183]

Excess acid for [(IPr)Au][BF_4] formation is of importance, especially at low catalyst loadings, as entries 3 and 6 in **Table 9.1** clearly indicate a slightly diminished activity in catalysis for [{(IPr)Au}$_2$(μ-OH)][BF_4].

Once the general activity of [(IPr)Au(OH)] in the presence of acid was successfully demonstrated, various Brønsted acids and $HNTf_2$ in aqueous solutions were used to generate the active gold(I) species to evaluate a potential acid influence in the hydration of phenylacetylene. The optimized conditions as described in Chapter **8** were applied, a mixture of MeOH/water (2:1) at 120 °C during 24 hours (**Table 9.2**).

In order to develop a valuable alternative to the silver salt containing protocols, the amount of catalyst was decreased to 1000 ppm (i.e., 0.1 mol%) already at this stage of the study.

Table 9.2 Optimization of the reaction conditions.[a]



2a **3a**

Entry	1 (mol%)	HX (mol%)	GC conversion (%)[b]
1	0.1	$HSbF_6$ (0.15 mol%)	93
2	0.1	$HNTf_2$ (0.15 mol%)	93
3	0.1	HBF_4 (0.15 mol%)	nd[c]
4	0	$HSbF_6$ (0.15 mol%)	0
5	2	-	12

[a] Reaction conditions: phenylacetylene **2a** (2 mmol), complex **1** (solution 10mg/mL in MeOH) and acid (solution 0.05 M in MeOH) in 2 mL of a 2:1 MeOH/water mixture. [b] GC conversions are average of at least two runs. [c] nd = not determined due to irreproducibility issues.

Best results were obtained with $HSbF_6$ and $HNTf_2$ with average conversions of 93% (**Table 9.2**, entries 1 and 2), whereas the use of HBF_4 led to irreproducible results, with conversions from 0 to 51% under identical reaction conditions (entry 3). These experiments are in good agreement with the previously optimized reaction conditions where [(IPr)Au][SbF_6] generated by $AgSbF_6$ showed the highest activity. A slight excess of acid was necessary to ensure complete formation of the active species from **1** in the reaction medium.

Notably, alkyne **2a** did not lead to the corresponding ketone **3a** in the presence of the Brønsted acid alone; gold was necessary (entry 4), proving that the reaction does not proceed *via* simple acid catalysis. Without any acid and in the presence of a higher catalyst loading of **1** (entry 5), the conversion still only reached 12% for phenylacetylene. This low catalytic activity matches the results for diphenylacetylene and [(IPr)Au(OH)] in the absence of acid in **Table 9.1** (entry 2).

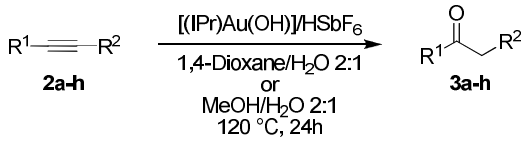
9.2.2 Substrate scope

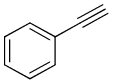
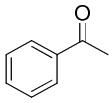
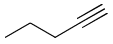
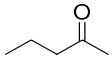
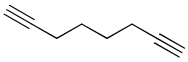
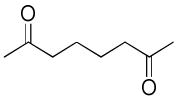
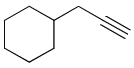
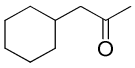
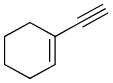
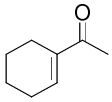
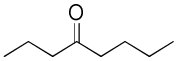
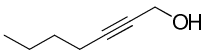
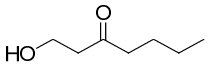
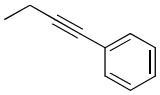
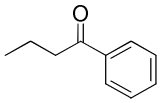
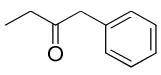
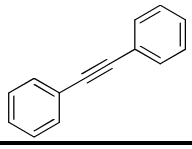
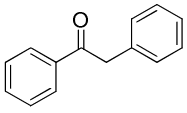
Using the optimized conditions with $HSbF_6$ as acid to activate complex **1**, a range of ketones was prepared from both terminal and internal alkynes (**Table 9.3**).

The procedure proved to be efficient, since the study of the reaction scope was performed using only 100 ppm of catalyst with all substrates except diphenylacetylene **2j**. Terminal alkynes **2a-f** were successfully converted in moderate to excellent yields (entries 1-6). Besides phenylacetylene **2a**, aliphatic alkynes **2b-e** were hydrated with high conversions but volatility of compounds **3b** and **3c** led to product isolation in moderate yields after work-up. The α,β-unsaturated ketone **3f** was also efficiently prepared (entry 6) demonstrating complete compatibility with conjugated double bonds. Internal alkynes, which have already been shown to be less reactive towards hydration, were also hydrated in the same conditions but in 1,4-dioxane with good yields (entries 7-10). Both aromatic and aliphatic alkynes could be converted under the given conditions.

Notably, the presence of a hydroxy group was tolerated with the quantitative hydration of **2h** in ketone **3h** (entry 8). Alkyne **2i** led to the two predicted ketones **3i** and **3i´** in 15 and 50% yield, respectively. The selectivity in this reaction might be improved by lowering the reaction temperature and a concomitant use of a higher catalyst loading. Diphenylacetylene **2j** showed the lowest reactivity of all substrates tested (entry 9), requiring a higher catalyst loading (1000 ppm) to enable the reaction and obtain product **3j** with a yield of 70%. The low reactivity of diphenylacetylene **2j** towards hydration has already been observed in the alkyne hydration with [(IPr)AuCl] in the presence of silver salts as chloride abstractors (Chapter **8**).[191, 206]

Table 9.3 Alkyne hydration with *in situ* generated cationic gold(I).[a]



Entry	Alkyne		Cat. Loading (ppm)	Product		Yield (%)[b]
1		**2a**	100		**3a**	81
2		**2b**	100		**3b**	40
3		**2c**	100		**3c**	41
4		**2d**	100		**3d**	90
5		**2e**	100		**3e**	94
6		**2f**	100		**3f**	76
7		**2g**	100		**3g**	56
8		**2h**	100		**3h**	99
9		**2i**	100		**3i**	15
					**3i´**	50
10		**2j**	1000		**3j**	70

[a] Reaction conditions: alkyne **2a** (2 mmol), complex **1** (0.02 mmol, 12μL of a 10 mg/mL solution in MeOH) and acid (0.06 mmol, 12 μL of a 0.05 M solution in MeOH) in 2 mL of a 2:1 MeOH/water or 1,4-dioxane/water mixture at 120 °C during 24 hours. [b] NMR yields determined with 4-nitrobenzaldehyde as internal standard.

9.2.3 Mechanistic considerations

As expected, the divergence between internal and terminal alkynes in terms of the optimum reaction medium is also observed with [(IPr)Au(OH)]/$HSbF_6$. By analogy, while the hydration of terminal alkynes led to the rapid product formation without observation of any intermediate species in MeOH, the same reaction with diphenylacetylene proceeds significantly slower and through an intermediate product identified as the vinyl ether, which then converts to the expected ketone. The kinetic profile of the reaction with application of the new catalyst is presented in **Figure 9.1**.

In order to obtain more rapid conversions, a higher catalyst loading of 4 mol% was applied. With such a high catalyst loading diphenylacetylene was completely consumed after 15 min and transformed into the corresponding vinylether and ketone in a 71:29 ratio. This ratio evolves within 30 min to 46:54, and the proportion of ketone rises continuously to obtain after 2 hours a complete conversion of vinylether into ketone.

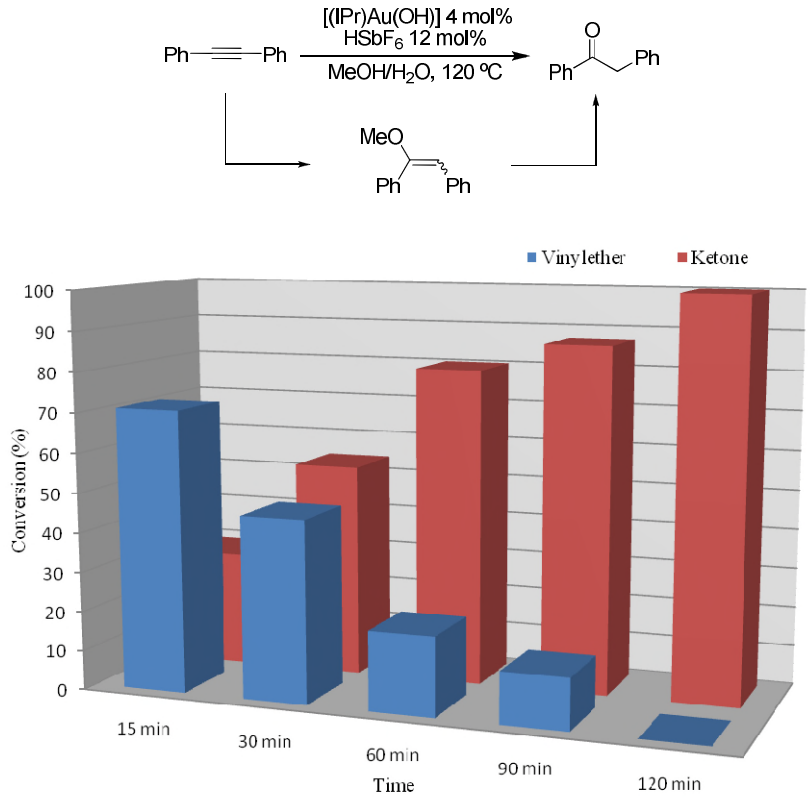
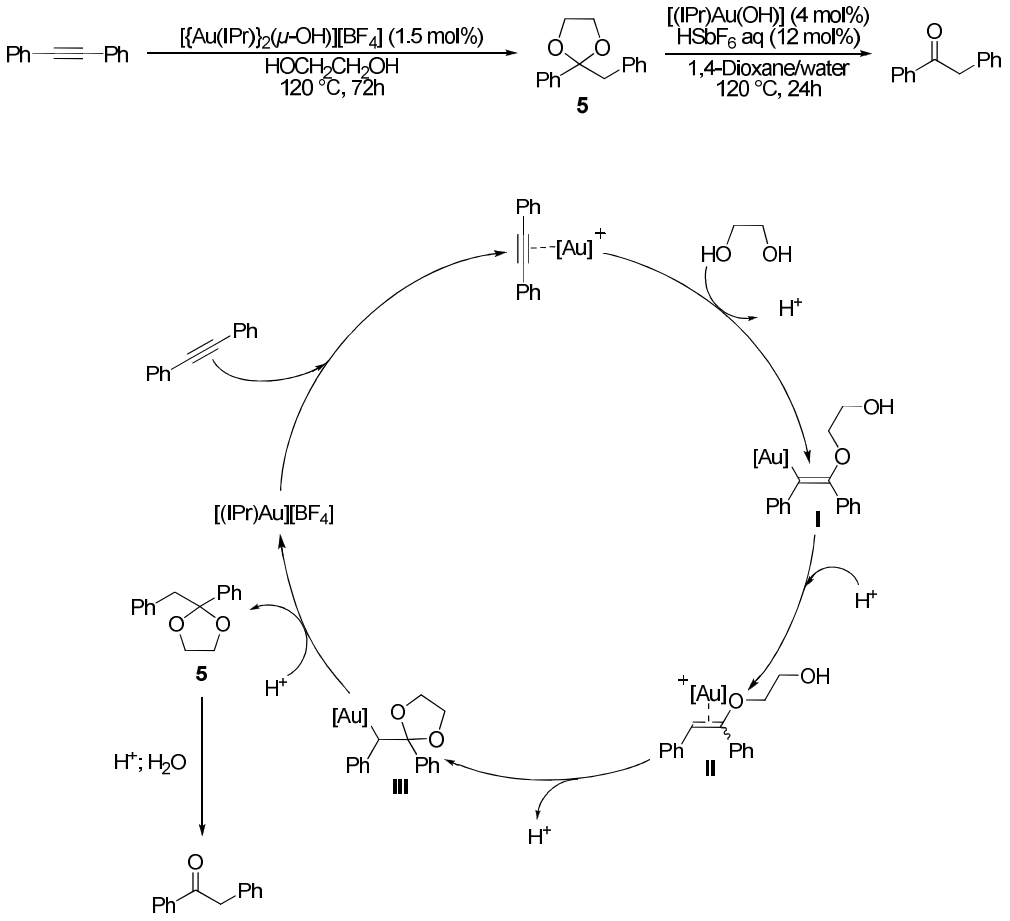


Figure 9.1 Kinetic follow of the hydration of diphenylacetylene in MeOH.

These results fit to both those obtained by Corma concerning the hydration of 1-octyne in alcohol solvents, showing that the attack of MeOH onto the alkyne is faster

compared to that of H_2O,[191] as well as the results on solvent effects in Chapter **8.** However, revision of experimental evidence and a new proposed mechanism demand for additional experiments.

Corma postulated that the vinyl ether could react with MeOH to give a diketal that quickly evolves into the corresponding ketone in the presence of water. Nevertheless, this diketal could not be observed either by Corma or in previous experiments. **Figure 9.1** clearly suggests that the conversion of vinylether into the desired ketone is the limiting step in the hydration of internal alkynes as the methoxylation appears to occur almost instantly while ketone formation needs 2 hours for completion. The vinylether formation is, of course, surpressed in a non-nucleophilic solvent like 1,4-dioxane, resulting in an increased reaction rate for internal alkynes directly reacting with water.



Scheme 9.2 Proposed mechanism for the hydration with ethylene glycol.

To clarify the mechanism proposed by Corma, attempts to isolate a more stable ketal resulting from a reaction of diphenylacetylene in ethylene glycol in the presence of gold were made. Michelet, Genêt and co-workers have already shown that cyclic

diketals could be prepared from bis-homopropargylic diols in the presence of gold.[208] Under inert atmosphere, the dinuclear complex [{(IPr)Au}$_2$(μ-OH)][BF_4] (**4**)[175] was used as catalyst in this reaction since no acid which would catalyze ketone formation is required for activation. As expected and under non-optimized conditions, the ketal **5** is obtained after 72 hours at 120 °C in the presence of 1.5 mol% of **4** (**Scheme 9.2**). This diketal was then reacted with **1** (4 mol%) and $HSbF_6$ (12 mol%) in a 1,4-dioxane/water (2:1) mixture and full conversion into the corresponding ketone was observed. These experimental data support the proposed mechanism, which can be written as illustrated in **Scheme 9.2**. After activation of the triple bond by the gold center, ketals **I** then **II** are formed. These react with the remaining hydroxyl moiety to give the isolated diketal **5**. In the presence of water, this diketal leads to the corresponding ketone **3j**.

9.3 Conclusion

To conclude, the additional experiments on alkyne hydration in this chapter successfully addressed two remaining aspects in gold catalyzed hydration: (a) a new protocol for the hydration of alkynes at a catalyst loading of only 100 ppm for most of the substrates and with TON up to 9900 was developed involving a Brønsted acid activation of the pre-catalyst [(IPr)Au(OH)] **1** instead of activation of a gold precatalysts *via* chloride abstraction with silver salts. These results importantly wipe away remaining concerns regarding the role of catalytically active silver salts in alkyne hydrations at low catalyst loadings. Apart from that it represents a more atom-economic and ecological protocol. (b) Moreover, the remaining gap in the catalytic cycle was closed when demonstrating the formation of a ketal species with gold catalysts and its conversion into the ketone under standard reaction conditions, a reaction which was earlier proposed by both Corma and coworkers as well as in Chapter **8**, but had not been experimentally confirmed yet.

9.4 Experimental

If not stated otherwise, reactions were carried out in air. [(IPr)Au(OH)] and [{(IPr)Au}$_2$(μ-OH)][BF_4] were prepared as described in Chapter **5** and **11**. Phenylacetylene was purified *via* Kugelrohr distillation before use. Solvents and other

reagents were purchased from commercial sources and used without any further purification.

General procedure for the alkyne hydration at 100 ppm catalyst loading. In a sealed reaction vial equipped with a magnetic stirring bar [(IPr)Au(OH)] (0.02 mmol, 12 μL of a 10 mg/mL solution in MeOH) is added to an aqueous solution of $HSbF_6$ (0.06 mmol, 12 μL of a 0.05 M solution in H_2O) in 2 mL of a 2:1 MeOH/water or 1,4-dioxane/water mixture. The alkyne (2 mmol) is added and the reaction mixture stirred for 24 hours at 120 °C. CH_2Cl_2 is added and the solution dried over $MgSO_4$, filtered and concentrated under reduced pressure. The yield was determined by ^1H NMR with 4-nitrobenzaldehyde as internal standard (76 mg, 0.5 mmol).

*Benzyl-2-phenyl-1,3-dioxolane **5***. In a sealed reaction vial equipped with a magnetic stirring bar [{(IPr)Au}$_2$(μ-OH)][BF_4] (0.03 mmol, 38 mg) is disolved in 2 mL of ethylene glycol. Diphenylacetylene (2 mmol) is added and the reaction mixture stirred for 72 hours at 120 °C, allowed to cool to room temperature and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (EtOAc/pentane, 2:98) to afford **5** (331 mg, 69%). ^1H NMR (300 MHz, CD_2Cl_2): δ 7.42-7.24 (m, 5H), 7.23-7.06 (m, 5H), 3.86-3.77 (m, 2H), 3.77-3.67 (m, 2H), 3.16 (s, 2H). ^{13}C NMR (126 MHz, CD_2Cl_2): δ 143.0, 136.6, 131.2, 128.2, 128.1, 128.0, 126.7, 126.3, 110.3, 65.1, 47.2. HRMS for $C_{16}H_{16}O_2Na$ (calc): 263.1055 (263.1048).

*1,2-Diphenylethanone **3j** from **5***. In a sealed reaction vial equipped with a magnetic stirring bar [(IPr)Au(OH)] (0.08 mmol, 48 mg) is added to an aqueous solution of $HSbF_6$ (0.24 mmol, 87.4 mg of a 65% solution in H_2O) in 2 mL of a 2:1 1,4-dioxane/water mixture. The ketal **5** (2 mmol) is added and the reaction mixture heated at 120 °C. In-process-control with GC showed full conversion into **3j** after 30 min.

10 Gold Activation of Nitriles: Catalytic Hydration to Amides

10.1 Introduction

The enormous interest in gold catalysis in recent years is due in part to the high versatility of gold(I/III) catalysts that can act both as σ- and π-Lewis acids, which has notably permitted the activation of a wide diversity of functional groups (**Figure 10.1**, top). Typically, carbon-based unsaturated systems (i.e. alkenes, allenes, and alkynes) are activated *via* π-coordination, whereas heteroatom-based systems (i.e. ethers, epoxides, carbonyls, aziridines, and imines) favor σ-coordination.[209]

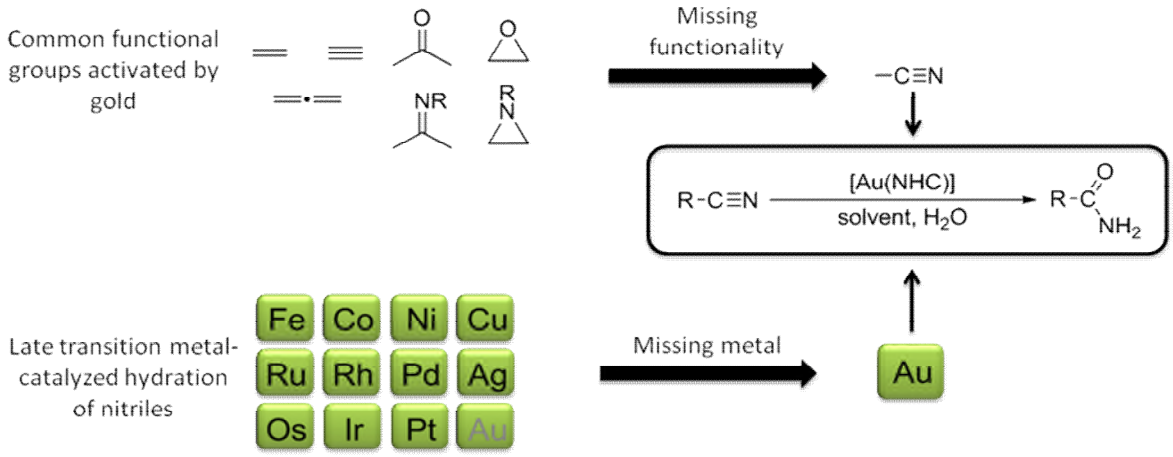


Figure 10.1 Gold-catalyzed nitrile hydration: two remaining challenges.

Despite this remarkable versatility in activating unsaturated C–X bonds (X = C, N, O), no report had appeared on the activation of nitriles by gold. Nitriles have been considered inert in the context of gold catalysis and have only been used as reaction solvent (e.g. acetonitrile)[210] or as throw-away ligands in well-defined cationic gold catalysts (**Figure 10.3**).[211]

The conversion of nitriles into their corresponding amides (i.e. the nitrile hydration reaction) is arguably one of the most important applications of nitriles as synthons in catalysis.[212] The hydration of nitriles has been achieved using enzymes[213] as well as a broad spectrum of Late Transition Metals (LTM).[212, 214] Strikingly, among the twelve LTMs of Groups 8 to 11, only gold has not proven active yet in this reaction (**Figure 10.1**, bottom).

Of note, two studies involving nitriles in gold homogeneous catalysis have been reported earlier than this study. Nevertheless, in both reports the nitrile moiety acts as a nucleophile and is, according to the authors, not activated by the gold center (**Figure 10.2**).[215]

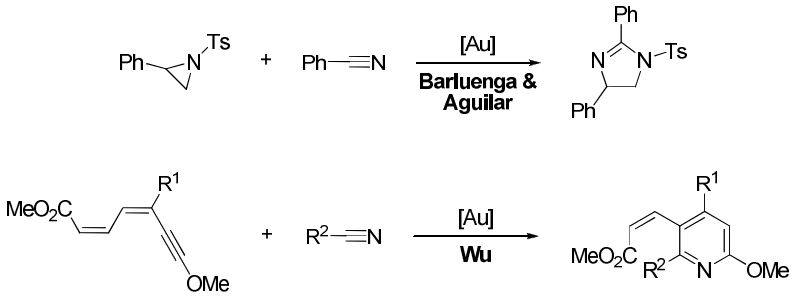


Figure 10.2 Gold catalyzed reactions involving nitriles acting as nucleophiles.

Apart from exploring this unusual and unlikely lack of reactivity for gold catalysts which already demands closer investigations, the activity of gold could have important implications. Cationic gold complexes bearing nitrile ligands would be widely influenced since the throw-away ligand would not be inert anymore and possibly hamper catalysis involving water.

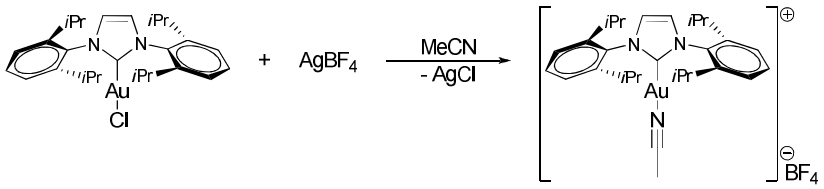


Figure 10.3 Typical synthesis of nitrile bearing cationic gold complexes.

This chapter describes how [(NHC)Au^{I}] complexes efficiently catalyze the hydration of a range of organonitriles. This study constitutes the first example of nitrile activation in gold homogeneous catalysis and fills the void left by gold in LTM-mediated nitrile hydration. Moreover, formation of amides from nitrile throw-away ligands of cationic gold catalysts have to be considered of relevance for high temperature catalysis in the presence of water.

Following the initial findings in gold catalyzed nitrile hydration, the concept of nitrile functionalization catalyzed by gold was further developed when Hashmi and coworkers recently reported the successful alkoxylation of nitriles with benzohydric alcohols.[216]

10.2 Results and Discussion

10.2.1 Optimization

Relying on previous results in [(NHC)Au]-catalyzed hydration-type chemistry (Chapter **8**), the optimization study was initiated with benzonitrile as a model substrate using a mixture of water/1,4-dioxane at 100 ºC and resulted in a promising 66% conversion using 2 mol% [(IPr)AuCl]/$AgSbF_6$ as a first positive result. Next, several parameters were examined beginning with a catalyst screening. As illustrated in **Figure 10.4**, [(IPr)Au(NTf_2)] afforded superior conversions in comparison to multiple catalysts. The screening included a series of typical gold complexes bearing different saturated and unsaturated NHCs like SIPr, IAd or IMes as well as some cationic complexes bearing IPr as spectator ligand like [(IPr)Au(NCMe)][PF_6]. Apart from [(IPr)Au(3-Br-Pyr)][PF_6], all complexes bearing IPr as ligand showed superior catalytic activity highlighting the crucial role of the ligand.

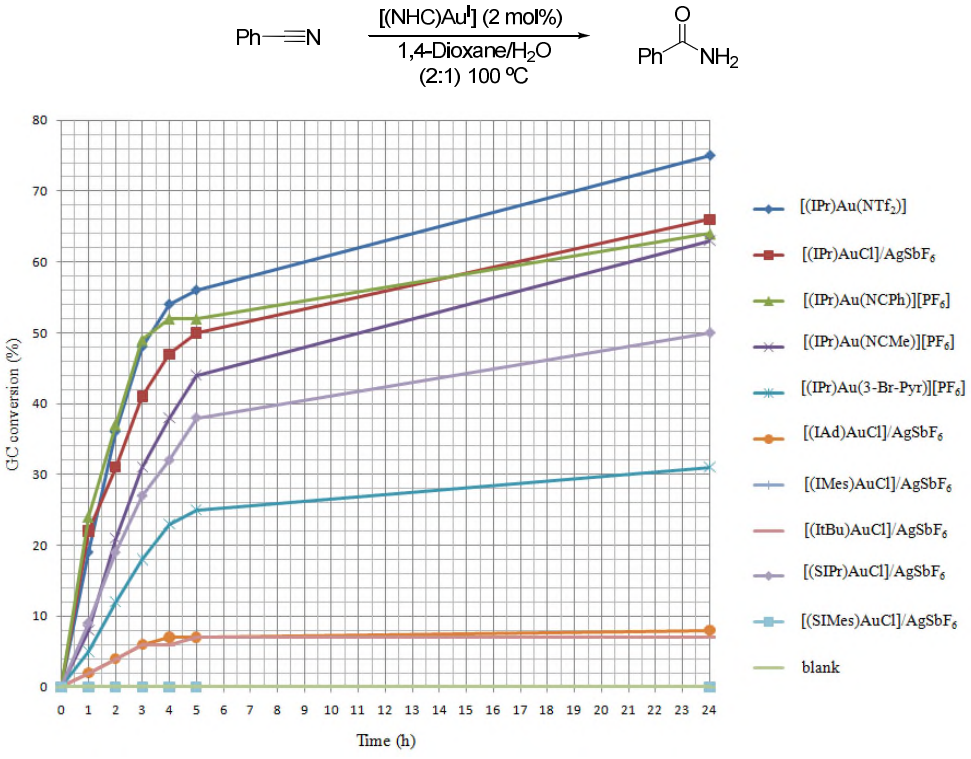


Figure 10.4 Catalyst screening for the gold mediated nitrile hydration.[(IMes)AuCl]/$AgSbF_6$, [(SIMes)AuCl]/$AgSbF_6$ and the blank reaction did not show conversion into benzamide and overlay in the graph.

Once the catalyst screening was completed with already satisfying conversions of 75% of benzonitrile into the corresponding benzamide, the role of the water amount and

the reaction molarity was investigated. Interestingly, a strong relationship between catalytic performance and both parameters was observed (**Figure 10.5**). While with low amounts of water (50 µL, 1:13 ratio water:1,4-dioxane) did not reach conversions above 25%, doubling the water amount already resulted in conversions above 50%. Finally, a 1:1 mixture allowed for conversions of 83%. At the same time, the reaction molarity proved also crucial. At a common dilution of 0.1 M, no conversion was detected in GC, whereas a concentration of 0.5 M already afforded decent conversions. A maximum was obtained at 1 M solutions which furnished identical results to 2 M trials.

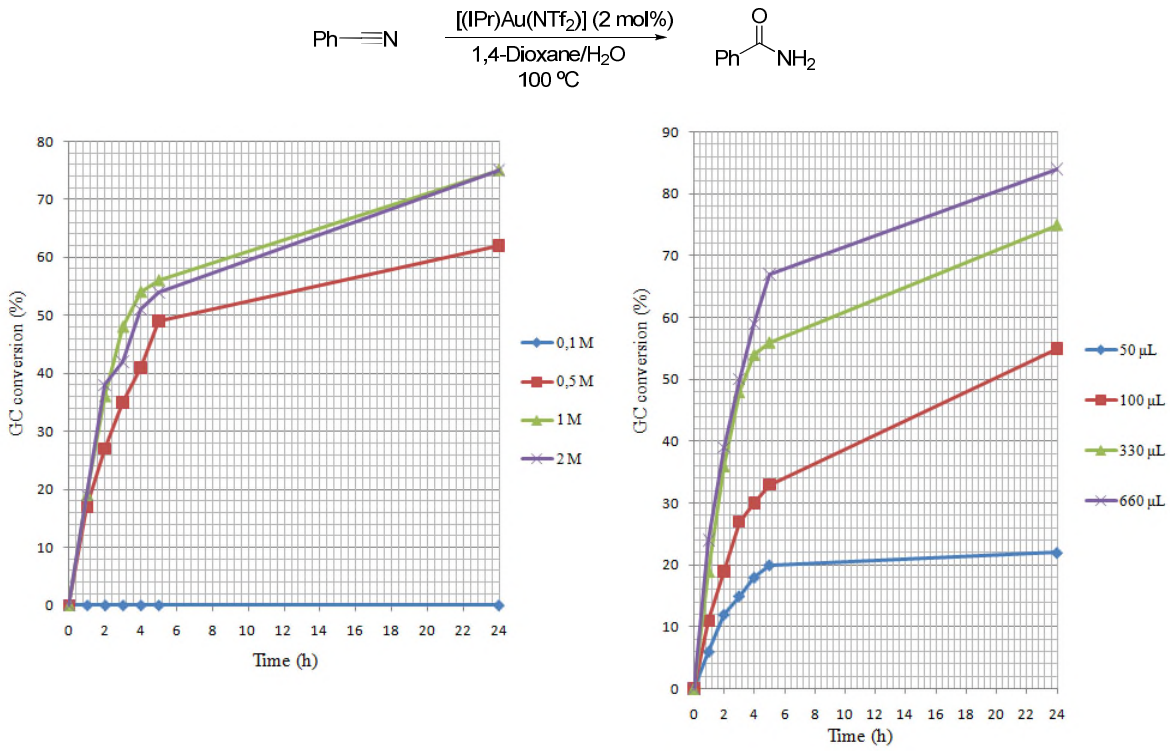


Figure 10.5 Molarity (left) and water amount (right) screening for the gold-mediated nitrile hydration.

To complete the optimization process, various solvents were tested under identical conditions as used for the catalyst screening. As shown in **Figure 10.6**, dramatic solvent effects exist. Very interestingly, the essential test of nitrile hydration in pure water furnished excellent conversions of 83%, listing pure water as the second best solvent in the screening. Although a mixture of THF/water was found superior in terms of conversions, water also bears the advantage of a very economical and ecological solvent in which the targeted amides would favourably precipitate at room temperature to facilitate their isolation. As a matter of fact, the high percentage of water in the THF/water mixture also resulted in precipitation of amides and in consideration of the

superior yield, this mixture was finally chosen for further studies. Of note, 1,4-dioxane as well as DMSO also proved to be suitable solvents for this reaction whereas all the other solvents including DCE and toluene furnished only disappointing conversions into benzamide.

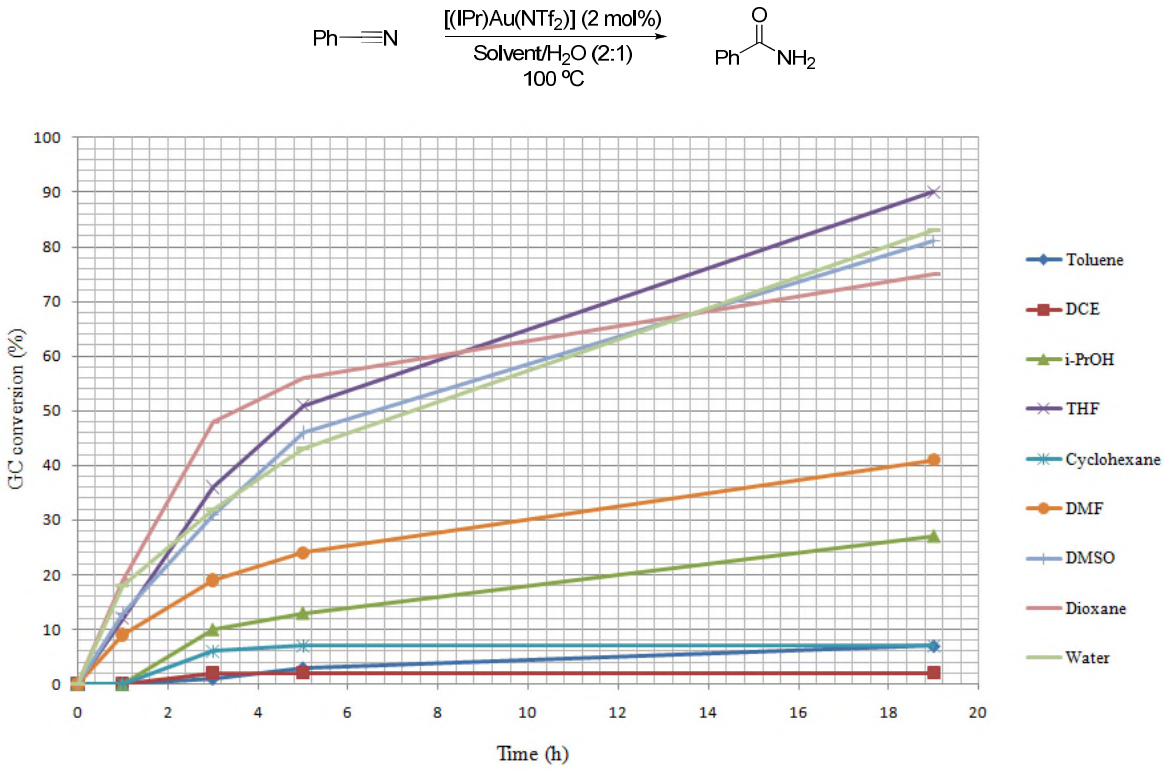


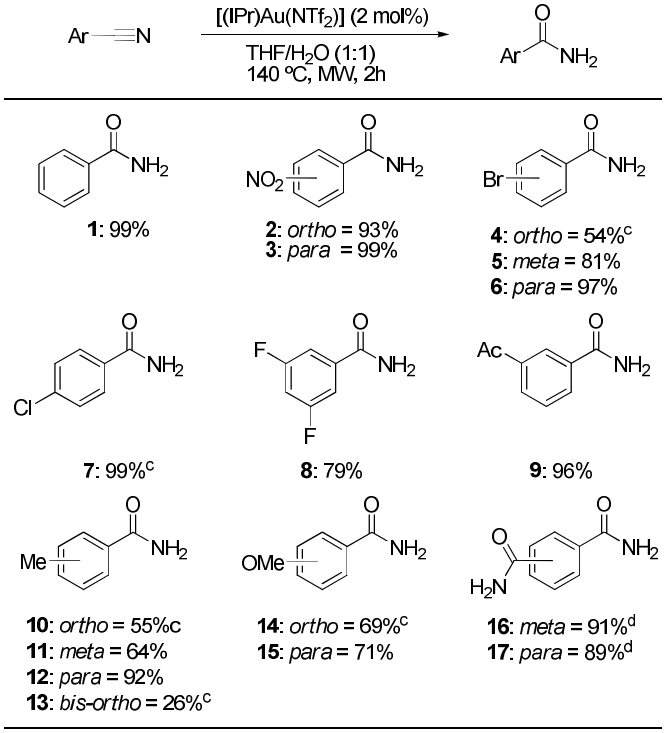
Figure 10.6 Solvent screening for the gold mediated nitrile hydration.

10.2.2 Substrate scope

The scope of this transformation was explored next. First, a wide array of functionalized benzonitriles (**Scheme 10.1**) was focused on. Overall, benzonitriles with electron-withdrawing substituents (**2-9**) afforded good to excellent yields, while substrates bearing electron-donating groups (**10-15**) exhibited slightly lower conversions. It should be noted that the present catalytic system is compatible with different functional groups such as aromatic nitro, bromo, chloro, and fluoro functionalities as well as methyl ketone and ethers. Aromatic substrates bearing two nitrile groups as in *m*-benzenedinitrile (**16**) and *p*-benzenedinitrile (**17**) underwent double nitrile hydration and afforded excellent yields in the corresponding diamides. Of note, *o*-substituted nitriles generally required 5 mol% catalyst loading and prolonged reaction time, regardless of the nature of the substituent. Taken together with the low

yield obtained for 2,6-dimethylbenzamide (**13**), steric hindrance was assumed responsible for the diminished catalytic activity.

Heteroaromatic nitriles were also found to participate in this reaction (**Scheme 10.2**). An excellent yield was obtained in the case of furan-2-carbonitrile (**18**). Moderate to good yields were observed with nitrogen-containing heteroaromatics (**19**-**22**), probably due to *N*-coordination to the gold center.

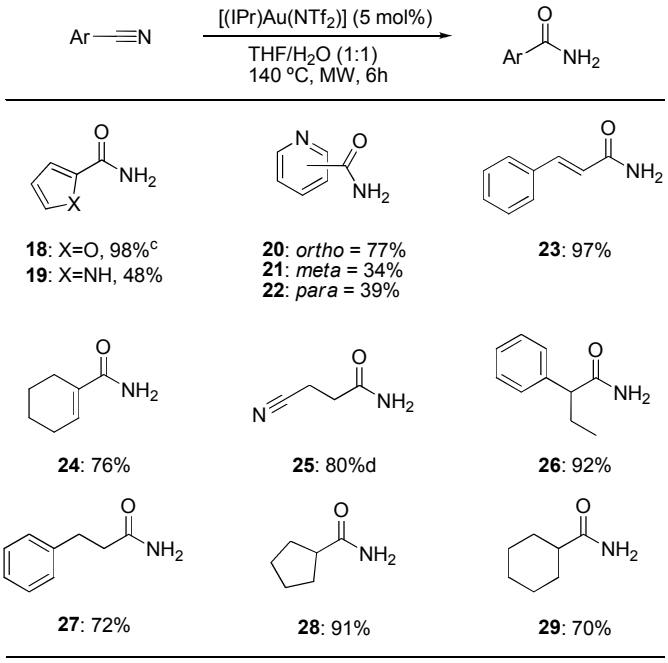


Scheme 10.1 Hydration of functionalized benzonitriles.[a,b] [a] [(IPr)Au(NTf$_2$)] (2 mol%), nitrile (1 mmol), water (0.5 mL), THF (0.5 mL), MW 140 ºC, 2 hours. [b] Isolated yield, average of two runs. [c] [(IPr)Au(NTf$_2$)] (5 mol%), 6 hours. [d] [(IPr)Au(NTf$_2$)] (4 mol%).

To extend the reaction scope, several non-aromatic substrates were also tested. Hence, cinnamamide (**23**) and cyclohexenecarboxamide (**24**) were obtained in good yields. Noteworthy, fumaronitrile (**25**) only afforded the monohydrated product, which is in sharp contrast with the double hydrations previously observed for dicyano aromatic substrates (**Scheme 10.1**, **16**-**17**). However, the selective hydration of only one nitrile group leads to the desymmetrization of fumaronitrile and is attractive for subsequent derivatization. Good to excellent yields were also obtained from benzylic and homobenzylic nitriles (**26**-**27**).

It should be noted that these examples can already be considered as "non-activated" since, in the amide product, the carbonyl bond is not conjugated with a π-system. To

fully determine the scope of the present catalytic system, we examined the reactivity of aliphatic nitriles (**28-29**). Satisfyingly, we observed the formation of cyclopentyl- and cyclohexylcarboxamide in 91% and 70% yield, respectively. However, a primary as well as a tertiary alkylnitrile, namely hexanenitrile and *tert*-butylnitrile, did not react under the reaction conditions developed. While steric hindrance can be assumed to prevent hydration in case of *tert*-butylnitrile, the reasons for the lack of reactivity for primary alkylnitriles remain unclear.



Scheme 10.2 Hydration of heteroaromatic and aliphatic nitriles.[a,b] [a] [(IPr)Au(NTf$_2$)] (5 mol%), nitrile (1 mmol), water (0.5 mL), THF (0.5 mL), MW 140 ºC, 6 hours. [b] Isolated yield, average of two runs. [c] [(IPr)Au(NTf$_2$)] (2 mol%), 2 hours. [d] [(IPr)Au(NTf$_2$)] (4 mol%).

10.2.3 Mechanistic considerations

In terms of mechanism, three hypotheses can be envisaged at this point. First, a σ-activation mechanism, based on the well-known coordination chemistry of cationic gold(I) complexes with nitriles, seems appealing. (**Figure 10.7**, **A**). σ-Coordination of the nitrile to the gold center would increase the cationic character of the carbon atom, which would undergo intermolecular nucleophilic attack by a water molecule. A related *inner-sphere* mechanism, where both the nitrile and water are coordinated to the gold center and would react in an intramolecular manner, could also be considered. Nevertheless, the propensity of gold(I) to form linear dicoordinated species seems to rule out this possibility.

Alternatively, π-coordination of the gold center to the C≡N bond, could also lead to intermolecular trapping by water of the nascent carbocation generated by slippage of the gold catalyst (**Figure 10.7**, **B**). Finally, in line with initial proposals for the conversion of propargylic alcohols into enones (Chapter **6**), an *in situ* formed hydroxo–gold species could "deliver" the OH moiety to the nitrile (**Figure 10.7**, **C**). A related *dinuclear* mechanism, involving the reaction of a [Au–OH] with a [Au--N≡C–R] species, was also considered at this stage. Further studies including mechanistic aspects on the gold catalyzed nitrile hydration are presented in the subsequent chapter.

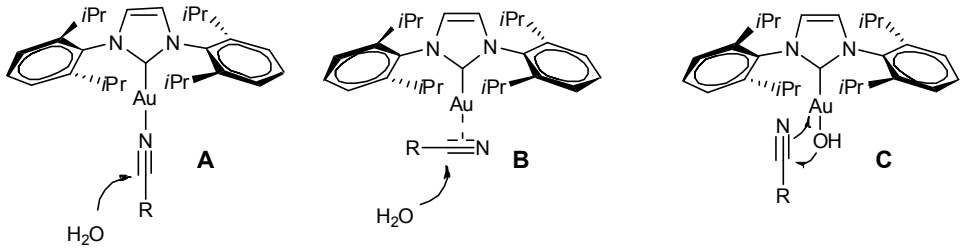


Figure 10.7 Possible intermediates for gold-mediated nitrile hydration.

10.3 Conclusion

In conclusion, a gold-based catalytic system that efficiently mediates the hydration of a broad spectrum of nitriles, including aromatic, heteroaromatic and aliphatic examples was developed. This study constitutes the first nitrile hydration catalyzed by gold, the only missing late transition metal of Groups 8 to 11 for this transformation. Most importantly, it represents the first nitrile activation in gold homogeneous catalysis. This possibility is of high relevance for the use of cationic gold complexes bearing such ligands and should have important implications in catalysis.

10.4 Experimental Section

General procedures:

Procedure A: [(IPr)Au(NTf_2)] (17 mg, 20 μmol, 2 mol%) was added to THF (500 μL) in a 2 mL microwave vial. The nitrile (1 mmol) was added, followed by destilled H_2O (500 μL). The vial was sealed and heated in the microwave for 2 hours at 140 ºC (7 bar). After the reaction mixture cooled down to room temperature, volatile compounds were evaporated under reduced pressure and the product was purified by flash chromatography using a gradient of pentane/ethylacetate (7:3 → 0:1).

Procedure B: [(IPr)Au(NTf_2)] (43 mg, 50 μmol, 5 mol%) was added to THF (500 μL) in a 2 mL microwave vial. The nitrile (1 mmol) was added, followed by destilled H_2O (500 μL). The vial was sealed and heated in the microwave for 6 hours at 140ºC (7 bar). After the reaction mixture cooled down to room temperature, volatile compounds were evaporated under reduced pressure and the product was purified by flash chromatography using a gradient of pentane/ethylacetate (7:3 → 0:1).

*Benzamide **1**:* According to the general procedure A, the title compound was isolated after purification by flash chromatography as a white solid (120 mg, 99%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.97 (br. s, 1H), 7.88 (d, J = 7.2 Hz, 2H), 7.52 (t, J = 7.3 Hz, 1H), 7.45 (m, 2H), 7.35 (br. s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.9, 134.3, 131.2, 128.2, 127.4. FT-IR (solid): 3362, 3161, 1657, 1622, 1577, 1448, 1397 cm^{-1}.

*o-Nitrobenzamide **2***: According to the general procedure A, the title compound was isolated after purification by flash chromatography as a white solid (155 mg, 93%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.13 (br. s, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.76 (dt, J = 7.6, 0.9 Hz, 1H), 7.74-7.60 (m, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.2, 147.2, 133.3, 132.6, 130.6, 128.8, 123.9. FT-IR (solid): 3353, 3164, 1654, 1622, 1574, 1518, 1487, 1444, 1406, 1354, 1193, 1122 cm^{-1}.

*p-Nitrobenzamide **3***: According to the general procedure A, the title compound was isolated after purification by flash chromatography as a white solid (165 mg, 99%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.37-8.21 (m, 3H), 8.10 (d, J = 8.8 Hz, 2H), 7.73 (br. s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.2, 149.1, 140.0, 128.9, 123.5. FT-IR (solid): 3473, 3413, 3303, 3178, 1663, 1592, 1511, 1407, 1339, 1320 cm^{-1}.

*o-Bromobenzamide **4**:* According to the general procedure B, the title compound was isolated after purification by flash chromatography as a white solid (108 mg, 54%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.85 (br. s, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.55 (br. s, 1H), 7.45-7.38 (m, 2H) 7.36-7.30 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.0, 139.4, 132.7, 130.6, 128.5, 127.5, 118.6. FT-IR (solid): 3352, 3174, 1621, 1561, 1473, 1398, 1134, 1026 cm^{-1}.

m-Bromobenzamide ***5***: According to the general procedure A, the title compound was isolated after purification by flash chromatography as a white solid (162 mg, 81%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.08 (br. s, 1H), 8.05 (t, J = 1.7 Hz, 1H), 7.87 (d, J = 7.9 Hz, 1H), 7.72 (d, J = 7.9 Hz, 1H), 7.51 (br. s, 1 H), 7.42 (t, J = 7.9 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.3, 136.5, 134.0, 130.5, 130.2, 126.6, 121.6. FT-IR (solid): 3342, 3160, 3068, 1656, 1619, 1564, 1421, 1382, 1148, 1124, 1066 cm^{-1}.

p-Bromobenzamide ***6***: According to the general procedure A, the title compound was isolated after purification by flash chromatography as a white solid (194 mg, 97%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.04 (br. s, 1H), 7.81 (d, J = 8.5 Hz, 2H), 7.67 (d, J = 8.5 Hz, 2H), 7.45 (br. s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.9, 133.4, 131.2, 129.6, 125.0. FT-IR (solid): 3351, 3167, 1705, 1655, 1617, 1586, 1383, 1181, 1146, 1065, 1006 cm^{-1}.

p-Chlorobenzamide ***7***: According to the general procedure B, the title compound was isolated after purification by flash chromatography as a white solid (148 mg, 95%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.04 (br. s, 1H), 7.89 (d, J = 8.5 Hz, 2H), 7.52 (d, J = 8.5 Hz, 2H), 7.45 (br. s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.8, 136.1, 133.0, 129.4, 128.3. FT-IR (solid): 3360, 3165, 1651, 1618, 1590, 1567, 1493, 1402, 1386, 1088, 1012 cm^{-1}.

3,5-Difluorobenzamide ***8****:* According to the general procedure A, the title compound was isolated after purification by flash chromatography as a white solid (124 mg, 79%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.13 (br. s, 1H), 7.67 (br. s, 1H), 7.61-7.52 (m, 2H), 7.45 (tt, J = 9.1, 2.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.2 (t, J= 2.9 Hz), 163.4 (d, J = 12.5 Hz), 161.0 (d, J = 12.5 Hz), 137.9 (t, J = 8.2 Hz), 110.9 (d, J = 7.2 Hz), 110.7 (d, J = 7.2 Hz), 106.7 (t, J = 26.0 Hz). FT-IR (solid): 3365, 3161, 1657, 1588, 1475, 1439, 1293, 1116, 985 cm^{-1}.

m-Acetylbenzamide ***9***: According to the general procedure A, the title compound was isolated after purification by flash chromatography as a white solid (157 mg, 96%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.44 (s, 1H), 8.18 (br. s, 1H), 8.12 (d, J = 7.8 Hz, 1H), 8.09 (d, J = 7.8 Hz, 1H) 7.62 (t, J = 7.8 Hz, 1H), 7.53 (br. s, 1H), 2.63 (s, 3H) . ^{13}C

NMR (100 MHz, DMSO-d_6): δ 197.6, 167.1, 136.8, 134.7, 132.0, 130.7, 128.8, 127.2, 26.9. FT-IR (solid): 3362, 3164, 1689, 1651, 1624, 1391, 1361, 1257, 1120 cm^{-1}.

o-Methylbenzamide ***10***: According to the general procedure B, the title compound was isolated after purification by flash chromatography as a white solid (74 mg, 55%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.69 (br. s, 1H), 7.40-7.25 (m, 3H), 7.25-7.15 (m, 2H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.0, 137.1, 135.1, 129.2, 127.0, 125.4, 19.6. FT-IR (solid): 3361, 3178, 2963, 2925, 1653, 1618, 1574, 1491, 1453, 1384, 1198, 1138, 1060 cm^{-1}.

m-Methylbenzamide ***11****:* According to the general procedure A, the title compound was isolated after purification by flash chromatography as a white solid (87 mg, 64%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.92 (br. s, 1H), 7.70 (s, 1H), 7.67 (m, 1H), 7.32 (m, 3H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.1, 137.4, 134.3, 131.8, 128.1, 124.6, 21.0. FT-IR (solid): 3371, 3189, 2917, 1648, 1614, 1580, 1428, 1384, 1112, 1039 cm^{-1}.

p-Methylbenzamide ***12****:* According to the general procedure A, the title compound was isolated after purification by flash chromatography as a white solid (124 mg, 92%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.88 (br. s, 1H), 7.78 (d, J = 8.0 Hz, 2H), 7.25 (m, 3H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.8, 141.0, 131.5, 128.7, 127.5, 20.9. FT-IR (solid): 3336, 3154, 2917, 1666, 1612, 1568, 1410, 1395, 1188, 1145, 1112, 1020 cm^{-1}.

2,6-Dimethylbenzamide ***13****:* According to the general procedure B, the title compound was isolated after purification by flash chromatography as a white solid (39 mg, 26%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.73 (br. s, 1H), 7.46 (br. s, 1H), 7.14 (t, J = 7.5 Hz, 1H), 7.03 (d, J = 7.5 Hz, 2H), 2.26 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.1, 138.9, 133.1, 127.7, 127.0, 18.9. FT-IR (solid): 3354, 3171, 2962, 2920, 1645, 1622, 1578, 1463, 1433, 1379, 1352, 1193, 1133, 1082, 1060, 1032 cm^{-1}.

o-Methoxybenzamide ***14***: According to the general procedure B, the title compound was isolated after purification by flash chromatography as a white solid (104 mg, 69%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.90-7.80 (m, 3H), 7.20 (br. s, 1H), 6.97 (d, J = 8.2 Hz, 2H), 3.80 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.3, 157.2, 132.4, 130.7, 122.7, 120.4, 112.0, 55.8. FT-IR (solid): 3409, 3190, 2947, 1621, 1596, 1573, 1487, 1461, 1433, 1393, 1273, 1239, 1178, 1147, 1105, 1047, 1020 cm^{-1}.

*p-Methoxybenzamide **15**:* According to the general procedure A, the title compound was isolated after purification by flash chromatography as a white solid (107 mg, 71%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.90-7.80 (m, 3H), 7.20 (br. s, 1H), 6.97 (d, J = 8.2 Hz, 2H), 3.80 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.5, 161.3, 129.4, 126.5, 113.4, 55.3. FT-IR (solid): 3388, 3158, 2970, 1643, 1615, 1572, 1515, 1456, 1421, 1392, 1309, 1249, 1179, 1145, 1114, 1022 cm^{-1}.

*Isophthalamide **16***: According to the general procedure A, the title compound was isolated after purification by flash chromatography as a white solid (146 mg, 89%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.38 (s, 1H), 8.04 (br. s, 2H), 8.00 (d, J = 7.7 Hz, 2H), 7.53 (t, J = 7.7 Hz, 1H), 7.47 (br. s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.6, 134.5, 130.1, 128.3, 126.9. FT-IR (solid): 3355, 3138, 2782, 1652, 1621, 1605, 1574, 1391, 1275, 1126, 921 cm^{-1}.

*Terephthalamide **17**:* According to the general procedure A, the title compound was isolated after purification by flash chromatography as a white solid (149 mg, 91%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.08 (br. s, 2H), 7.93 (s, 4H), 7.50 (br. s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.3, 136.6, 148.7, 127.4. FT-IR (solid): 3356, 3152, 2777, 1655, 1614, 1510, 1406, 1386, 1299, 1160, 1127, 1015 cm^{-1}.

*2-Furamide **18**:* According to the general procedure A, the title compound was isolated after purification by flash chromatography as a white solid (109 mg, 98%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.80 (br. s, 1H), 7.75 (br. s, 1H), 7.35 (br. s, 1H), 7.09 (d, J = 3.4 Hz, 1H) 6.60 (dd, $^{3}J_a$ = 3.4 Hz, 1.7 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.4, 148.1, 145.0, 113.6, 111.8. FT-IR (solid): 3341, 3158, 1660, 1621, 1479, 1410, 1371, 1233, 1196, 1137, 1099, 1012 cm^{-1}.

1H-pyrrole-2-carboxamide ***19****:* According to the general procedure B, the title compound was isolated after purification by flash chromatography as a white solid (53 mg, 48%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.46 (br. s, 1H), 6.90 (br. s, 1H), 6.84 (br. s, 1H), 6.76 (br. s, 1H) 6.07 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.4, 126.3, 121.4, 110.7, 108.6. FT-IR (solid): 3404, 3332, 3176, 1701, 1632, 1595, 1428, 1349, 1199, 1134, 1110, 1046 cm^{-1}.

Picolinamide ***20****:* According to the general procedure B, the title compound was isolated after purification by flash chromatography as a white solid (94 mg, 77%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.63 (d, J = 4.7 Hz, 1H), 8.11 (br. s, 1 H), 8.04 (d, J = 7.7 Hz, 1H), 7.98 (dt, ^{3}J = 7.7 Hz, 1.5 Hz, 1H), 7.64 (br. s, 1H), 7.59 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.0, 150.3, 148.4, 137.6, 126.4, 121.9. FT-IR (solid): 3431, 3213, 1671, 1585, 1566, 1468, 1442, 1387, 1285, 1249, 1154, 1089, 1046, 997 cm^{-1}.

Nicotinamide ***21***: According to the general procedure B, the title compound was isolated after purification by flash chromatography as a white solid (42 mg, 34%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.03 (br. s, 1H), 8.70 (d, J = 3.8 Hz, 1H), 8.20 (td, J = 7.9 Hz, 1.8 Hz, 1H), 8.16 (br. s, 1H), 7.59 (br. s, 1H), 7.49 (dd, J = 7.9 Hz, 4.8 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.5, 151.9, 148.7, 135.2, 129.7, 123.5. FT-IR (solid): 3356, 3152, 2851, 1674, 1615, 1593, 1574, 1486, 1421, 1394, 1340, 1201, 1153, 1124, 1028 cm^{-1}.

Isonicotinamide ***22****:* According to the general procedure B, the title compound was isolated after purification by flash chromatography as a white solid (48 mg, 39%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.72 (dd, J = 4.5 Hz, 1.5 Hz, 2H), 8.25 (br. s, 1H), 7.77 (dd, J = 4.5 Hz, 1.5 Hz, 2H), 7.72 (br. s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.3, 150.2, 141.3, 121.4. FT-IR (solid): 3327, 3057, 1678, 1624, 1599, 1554, 1491, 1397, 1225, 1150, 1129, 1062, 1002 cm^{-1}.

(E)-Cynnamamide ***23****:* According to the general procedure B, the title compound was isolated after purification by flash chromatography as a white solid (143 mg, 97%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.62-7.48 (m, 3H), 7.46-7.32 (m, 4H), 7.10 (br. s, 1H), 6.61 (d, J = 15.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 139.1, 134.9,

129.4, 128.9, 127.5, 122.3. FT-IR (solid): 3371, 3164, 1660, 1606, 1493, 1449, 1397, 1351, 1245, 1196, 1116, 1060, 967 cm^{-1}.

Cyclohex-1-enecarboxamide ***24****:* According to the general procedure B, the title compound was isolated after purification by flash chromatography as a white solid (95 mg, 76%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.19 (br. s, 1H), 6.80 (br. s, 1H), 6.55 (m, 1H), 2.15-2.05 (m, 4H), 1.65-1.40 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.4, 133.2, 132.3, 24.8, 24.0, 21.9, 21.3. FT-IR (solid): 3366, 3193, 2926, 2859, 1653, 1587, 1387, 1366, 1336, 1119, 927 cm^{-1}.

(*E)-3-Cyanoacrylamide* ***25***: According to the general procedure B, the title compound was isolated after purification by flash chromatography as a white solid (77 mg, 80%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.91 (br. s, 1H), 7.66 (br. s, 1H), 6.97 (d, J = 16.3 Hz, 1H), 6.50 (d, J = 16.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.2, 144.1, 117.1, 108.7. FT-IR (solid): 3441, 3160, 3067, 2224, 1697, 1611, 1401, 1282, 1113, 976, 960 cm^{-1}.

2-Phenylbutanamide ***26****:* According to the general procedure B, the title compound was isolated after purification by flash chromatography as a white solid (150 mg, 92%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.43 (br. s, 1H), 7.35-7.25 (m, 4H), 7.25-7.15 (m, 1H), 6.80 (br. s, 1H), 3.30 (t, J = 7.6 Hz, 1H), 2.0-1.85 (m, 1H), 1.59 (m, 1H), 0.81 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 174.6, 141.2, 128.1, 127.6, 126.5, 53.0, 26.1, 12.3. FT-IR (solid): 3376, 3173, 2962, 2929, 2874, 1651, 1630, 1496, 1459, 1413, 1297, 1242, 1187, 1127 cm^{-1}.

3-Phenylpropanamide ***27****:* According to the general procedure B, the title compound was isolated after purification by flash chromatography as a white solid (107 mg, 72%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.30-7.15 (m, 6H), 6.76 (br. s, 1H), 2.80 (t, J = 7.8 Hz, 2H), 2.35 (t, J = 7.8 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.4, 141.5, 128.2, 125.8, 36.7, 30.9. FT-IR (solid): 3390, 3178, 3026, 2960, 1626, 1602, 1497, 1449, 1415, 1279, 1242, 1159, 1118, 1079, 1030 cm^{-1}.

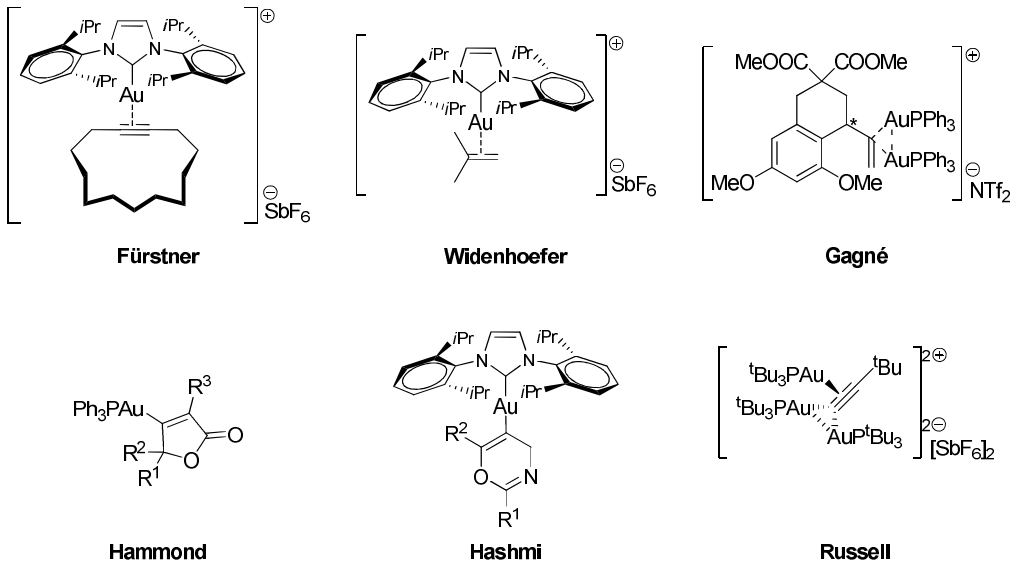
Cyclopentanecarboxamide ***28****:* According to the general procedure B, the title compound was isolated after purification by flash chromatography as a white solid (103 mg, 91%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.20 (br. s, 1H), 6.65 (br. s, 1H), 1.80-1.65 (m, 2H), 1.65-1.54 (m, 4H), 1.54-1.40 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.1, 45.2, 30.5, 26.0. FT-IR (solid): 3338, 3159, 2956, 2863, 1633, 1427, 1353, 1323, 1283, 1195, 1156, 1060 cm^{-1}.

Cyclohexanecarboxamide ***29****:* According to the general procedure B, the title compound was isolated after purification by flash chromatography as a white solid (89 mg, 70%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.13 (br. s, 1H), 6.61 (br. s, 1H), 2.10-2.05 (m, 1H), 1.69 (d, J = 10.4 Hz, 4H), 1.60 (d, J = 9.8 Hz, 1H), 1.40-1.05 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.4, 43.7, 29.2, 25.5, 25.3. FT-IR (solid): 3331, 3154, 2926, 2850, 1632, 1429, 1345, 1286, 1230, 1155 cm^{-1}.

11 [{(IPr)Au}$_2$(μ-OH)]X: Synthetic, Structural and Catalytic Studies

11.1 Introduction

Research into the mechanistic aspects of gold catalysis has gained increased attention. Isolating probable intermediates of catalytic cycles and resting states of the gold catalysts is highly relevant for the development and evaluation of accurate hypotheses.[177, 217] Numerous research groups active in the field of gold catalysis have recently contributed to this increasingly important topic. As illustrated in **Scheme 11.1**, a variety of gold structures has been obtained and help in the understanding of characteristics of the catalyst. Fürstner[217j], Widenhoefer[217a, 217i] and Russell[218] succeeded along with others in obtaining structures of cationic gold alkyne and alkene complexes, allowing for inferences on σ- and π-donating or accepting properties of the organogold complex. Addressing the exceptional role of η^2 coordination of gold to π centers, Hubert Schmitbauer as one of the early pioneers in gold chemistry, recently reviewed work in this field.[219]



Scheme 11.1 Structures of selected gold complexes as potential intermediates in catalytic cycles.

Additionally, Gagné reported unusual gold intermediates isolated during investigations on gold-catalyzed hydroarylation of allenes.[217h] The easy formation of a geminally diaurated complex and its unexpected stability are important reminders of the

true complexity of catalytic cycles. Fürstner subsequently reported formation of geminal diaurated complexes depending on the neighbouring heteroatoms and their importance as a stable intermediate in the catalytic cycle with possibly important implications for catalytic performance.[217d] Russell and co-workers moreover managed to contribute with the isolation of a dicationic triaurated gold complex involving geminal diauration and additionally π-coordination.[217e]

Hammond[217l] and Hashmi[217c, 217f] isolated vinylgold species which happen to present final stage intermediates before protodeauration. Apart from supporting catalytic proposals for product formation, isolation of such species allows according to the authors interesting opportunities for expansion of reactivity by careful choice of suitable additives reacting with the obtained gold species.

In the course of investigations on gold-mediated transformations, some of which involved water, computational results have suggested the viability of an [(IPr)Au(OH)] **1** "intermediate".[116, 174] Successes in catalysis such as the Meyer-Schuster rearrangement of propargylic alcohols to conjugated enones[174] and the hydration of nitriles to amides[220] resulted in increased efforts for the synthesis, isolation and application of **1**. This task was undertaken to hopefully permit these transformations in a more efficient and catalytically relevant manner, circumventing the need for silver co-catalysts and to support the hypothesis of **1** as an intermediate in aqueous catalysis.

The synthesis and complete characterization of [(IPr)Au(OH)] **1** was finally achieved.[136] Complex **1** proved to be an excellent precursor to a plethora of new gold species but exhibited only moderate catalytic efficacy in Meyer-Schuster rearrangement (Chapter **6** and **7**), alkyne hydration (Chapter **9**) as well as nitrile hydration (Chapter **10**).

In the course of NMR studies where acid activation of **1** was performed, the gold complex [{(IPr)Au}$_2$(μ-OH)][BF_4] **2** was isolated and its formation as a function of acid in solution was investigated.[117]

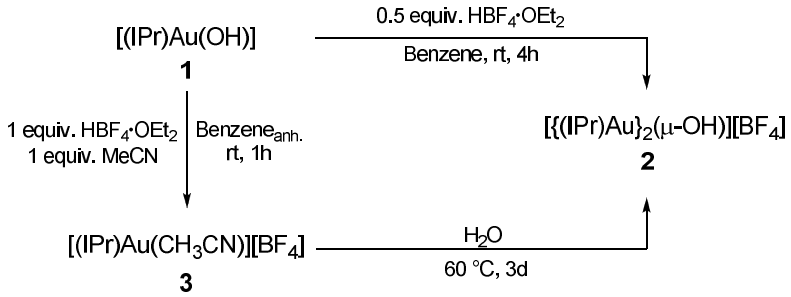
Encouraged by the reactivity of **2** in various gold catalyzed transformations and its stability, the series of [{(IPr)Au}$_2$(μ-OH)][X] (X= BF_4, NTf_2) complexes was extended by OTf^-, $FABA^-$ and SbF_6^- and applied in nitrile hydration to evaluate possible counteranion effects. The concept of [{(IPr)Au}$_2$(μ-OH)][X] formation and its behaviour has been further investigated by DFT calculations and deactivation patterns in the nitrile hydration have been identified.

11.2 Results and Discussion

11.2.1 Complex synthesis

The synthesis of [{(IPr)Au}$_2$(μ-OH)][BF_4] **2** can be realized *via* a number of approaches (**Scheme 11.2**) that were partially revealed by serendipity upon workup of the water-insoluble [(IPr)Au(CH_3CN)][BF_4] **3** synthesized from **1**. In the initial synthetic route, stirring **3** in water at 60 °C for 3 days in air led to the formation of **2** in high yield. Unfortunately, when the same reaction was done in THF in order to obtain the analogous THF complex, efforts to isolate the corresponding [{(IPr)Au}$_2$(μ-THF)][BF_4] remained unsuccessful.

Attempted extraction of **2** from the aqueous mother liquor with CH_2Cl_2 proved critical, as NMR analysis indicated partial conversion back to **3** possibly resulting from an equilibrium between [{(IPr)Au}$_2$(μ-OH)][BF_4] **2** and [(IPr)Au(CH_3CN)][BF_4] **3** due to the acetonitrile present in the organic layer. However, washing the organic phase with water three times led to the isolation of pure **2**. A more economic and practical synthetic route is to take advantage of the versatile synthon [(IPr)Au(OH)] (**1**) and its straightforward reaction with 0.5 equiv. HBF_4•OEt_2 in benzene at room temperature to produce **2** in 90% isolated yield after 4 hours. Advantageously, reactions conducted with easier to handle aqueous HBF_4 in less toxic toluene lead to identical isolated yields. In contrast to the standard procedure for the synthesis of cationic nitrile complexes, abstraction of chloride with silver salts and stirring using the nitrile as solvent or in stoichiometric amounts, the synthesis of [(IPr)Au(OH)] is favourably realized without the use of any silver salts.



Scheme 11.2 Synthetic routes to [(IPr)Au(CH_3CN)][BF_4] **3** and [{(IPr)Au}$_2$(μ-OH)][BF_4] **2**.

Interestingly, **1** can also function as a precursor to [(IPr)Au(CH_3CN)][BF_4] (**3**) under anhydrous conditions and avoiding the use of costly light- and moisture-sensitive

silver salts. Complex **1** was reacted with 1 equiv. HBF_4•OEt_2 in the presence of 1 equiv. acetonitrile to afford complete conversion into **3** (**Scheme 11.2**). Washing the organic phase with brine however resulted in full conversion into [(IPr)AuCl].

NMR studies on the acid activation of **1** are consistent with the sensitive equilibria between these gold complexes determined by acid and water concentration and the solvent used.[117]

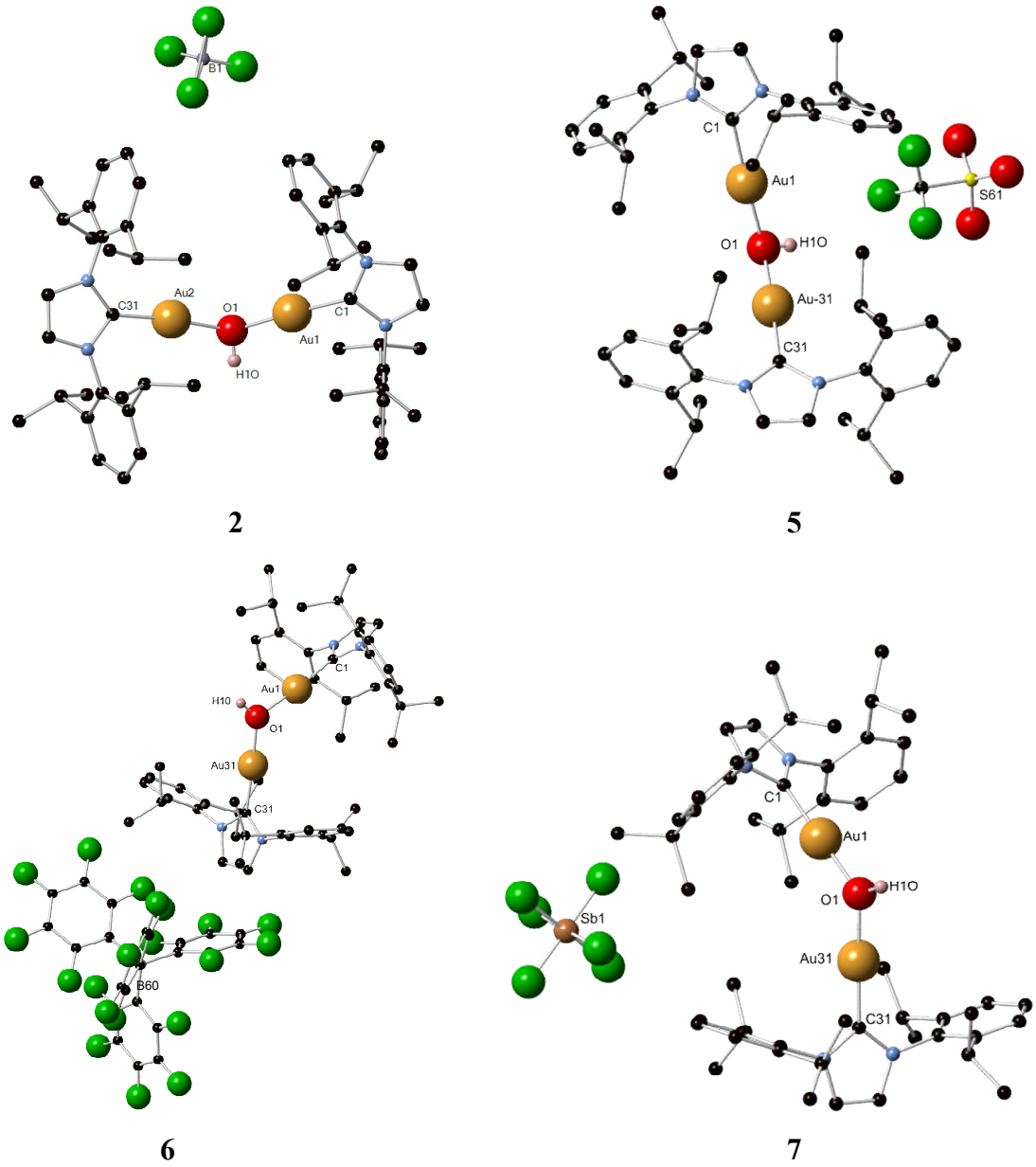
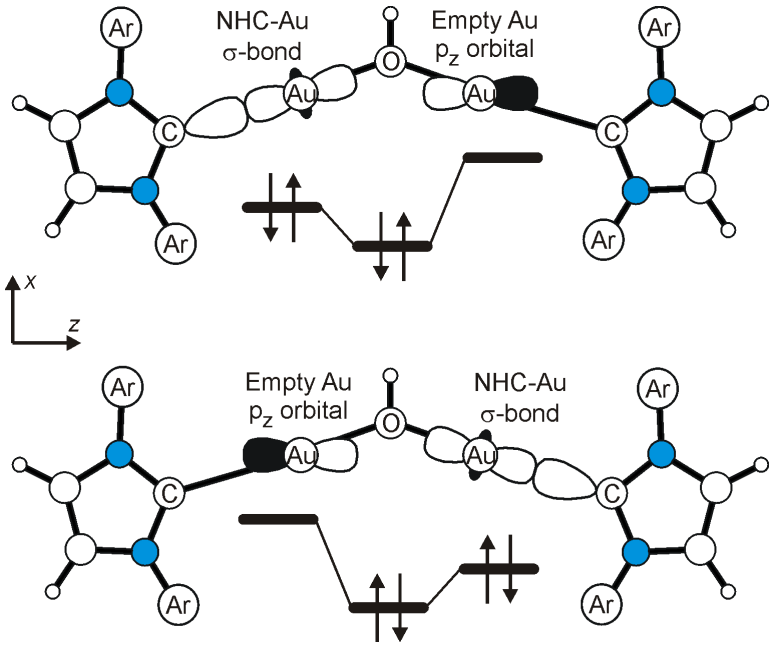


Figure 11.1 Molecular structures of new complexes [{(IPr)Au}$_2$(μ-OH)][X] (X= BF_4 (**2**), OTf (**5**), FABA (**6**), SbF_6 (**7**)). Selected bond lengths [Å] and angles [deg] for **2**: Au1-Au2 3.746(1); Au1-O1, 2.070(5); Au2-O1, 2.072(5); Au1-C1, 1.957(7); Au2-C31, 1.948(7); Au1-O1-Au2, 129.5(3); O1-H1O, 0.97(2) ; Au1-O1-H1O, 105(5); Au2-O1-H1O, 107(5); C1-Au1-O1, 174.2(2); C31-Au2-O1, 173.8(2). For **5**: Au(1)-O(1), 2.052(3); O(1)-Au(31), 2.042(4); Au(1)-C(1), 1.972(5); Au(31)-C(31), 1.961(5); Au(31)-O(1)-Au(1), 124.18(17); O(1)-H(1O), 0.95(2). For **6**: Au(1)-O(1), 2.040(4); O(1)-Au(31), 2.049(4); Au(1)-C(1), 1.961(6); Au(31)-C(31), 1.951(5); Au(31)-O(1)-Au(1), 118.5(2); O(1)-H(1O), 0.96(2). For **7**: Au(1)-O(1), 2.026(8); O(1)-Au(31), 2.055(8); Au(1)-C(1), 1.943(11); Au(31)-C(31), 1.957(11); Au(31)-O(1)-Au(1), 127.6(4); O(1)-H(1O), 0.9800.

In order to investigate the counteranion effects, a series of complexes (X = NTf_2 (**4**), OTf (**5**), FABA (**6**), SbF_6 (**7**)) was synthesized (for **5-7**, see **Figure 11.1**). Of note, **4** already has been successfully applied in the Meyer-Schuster rearrangement (Chapter **5**).[221] Satisfyingly, all the catalysts were obtained in good to excellent yields by applying the synthetic protocol of **2**. However, attempts to synthesize the PF_6 or succinimide analogues gave a mixture of products (X = PF_6) or a monogold complex (X = succinimide).

11.2.2 Computational studies

Additionally, DFT analysis was used to shed light on the energetics of these transformations. Firstly, the binding of nitriles and water to $[(IPr)Au]^+$ is highly competitive (the bond dissociation energies (BDE) of MeCN, PhCN and H_2O in CH_2Cl_2 are 31.0, 30.8 and 31.0 kcal/mol, respectively). This suggests that in aqueous solution the large excess of water present should completely displace the nitrile in **3**. Secondly, the **1** → **3** transformation in **Scheme 11.2** is favoured by 14.7 kcal/mol in benzene. Thirdly, the **1** → **2** transformation in **Scheme 11.2** is favoured by 16.7 kcal/mol in benzene.



Scheme 11.3 Schematic representation of the (IPr)Au···Au interactions and of the molecular orbitals involved.

DFT calculations were also done on the structure and nature of **2**. The optimized structure of **2** (DFT values for **2**: Au-Au 3.886; Au-O 2.081; Au-C 1.974; O-H 0.976;

Au-O-Au 137.9; Au-O-H 109.7) is in good agreement with its X-ray structure.[117] Focusing on a comparison between the DFT structures of **1** and **2**, the Au-O bond is slightly shorter in **1** (by 0.08 Å), whereas the O-H bond does not significantly vary (0.002 Å longer in **1**). These essentially unaltered distances suggest that a similar bonding scheme is present in **1** and **2**. However, the Mayer bond order (MBO)[222] within natural population analysis (NPA)[223] indicates remarkable changes. The MBO of the Au-O bonds in **2**, 0.60, is almost half that found in **1**, 1.16. Differently, the MBO of the O-H bond is slightly reduced, from 0.92 in **1** to 0.86 in **2**. This indicates that dimer formation principally affects the Au-O bond rather than the O-H bond. Furthermore, a non-negligible MBO of 0.14 is present between the Au centres, indicative of an interaction between the two [(IPr)Au] moieties. NPA decomposition indicates that donation occurs from each [(IPr)Au] σ-bond into an empty acceptor p_z AO on the other Au centre (**Scheme 11.3**). An estimate of this donor-acceptor interaction energy, in the framework of second order perturbation theory, $E(2)$, amounts to 8.7 kcal/mol. This bimetallic cooperativity, together with the short Au···Au distance derived from the X-ray structure, indicates an intriguing deviation from the classical isolobal analogy between Au^+ and H_3O^+.

The stability of **2** towards various dissociation pathways was examined next. Possible dissociation of **2** to **1** + [(IPr)Au][BF_4] is disfavoured by 11.5 kcal/mol in benzene. Key to the stability of **2** is the weak coordinating ability of $[BF_4]^-$ in benzene, the BDE of BF_4^- to $[(IPr)Au]^+$ is 81.5 kcal/mol lower than that of OH^-. Furthermore, the stability of **2** towards water was examined. Aqueous dissociation of a Au fragment in **2** to **1** + $[Au(IPr)(OH_2)]^+$ + $[BF_4]^-$ is favoured by 1.0 kcal/mol. In contrast, proton transfer from **2** to a water molecule to give [{(IPr)Au}$_2$(μ-O)] + H_3O^+, is disfavoured energetically by 47.0 kcal/mol, indicating that the weak links in **2** are the Au-O bonds.

The ease with which these transformations can be accomplished, and the calculated DFT energetic are suggestive of an equilibrium between [(IPr)Au(CH_3CN)][BF_4] and [{(IPr)Au}$_2$(μ-OH)][BF_4] in aqueous media.

Mechanistically, this implicates the direct involvement of a species such as **2** in catalysis involving water and cationic gold entities most likely acting as a reservoir for mononuclear gold.

11.2.3 Complex testing in nitrile hydration

With the series of catalysts in hand, activity was tested in the hydration of nitriles. Investigations reported in Chapter **10** have determined [(IPr)Au(NTf_2)][104a] (**8**) to be the most effective Au-catalyst under optimized conditions which took advantage of microwave heating.[220]

To adequately follow the reaction, the catalyst loading was lowered to 1 mol% of gold and conversion was monitored by GC. Results of other relevant gold catalysts as well as *in situ* activated catalysts have been added to complete the screening (**Figure 11.2**). No significant difference between the [{(IPr)Au}$_2$(μ-OH)][X] catalysts has been observed. With the exception of **8**, which showed slightly less performance, and **1,** which afforded poor yields overall, all catalysts showed comparable catalytic activity. Of note, closely related Bayler-Schmidbaur complexes already proven to be active in catalysis[224] as well as [R_3Au_3O][X] complexes have been used successfully.[225]

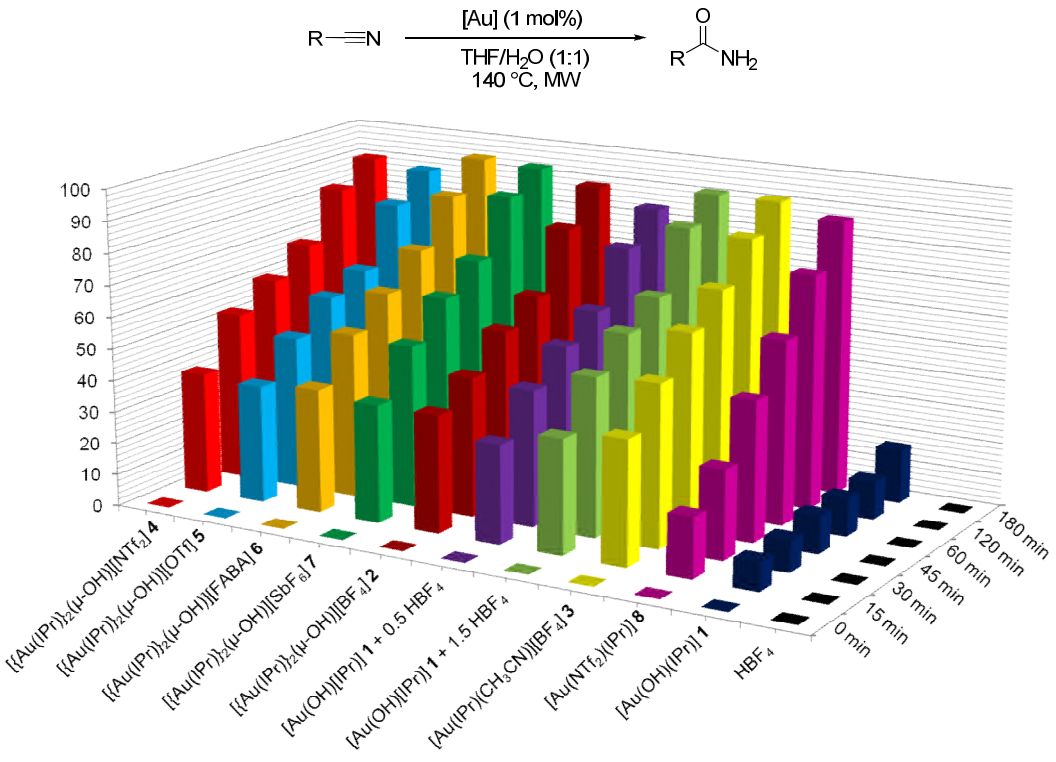


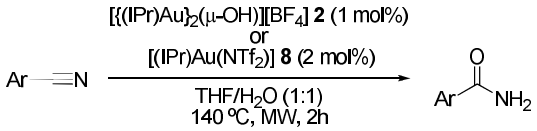
Figure 11.2 Comparison of various gold-based catalytic systems in nitrile hydration.

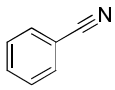
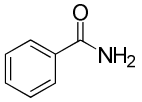
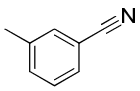
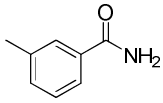
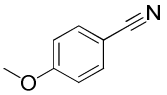
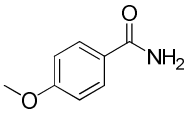
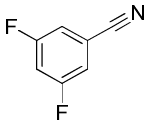
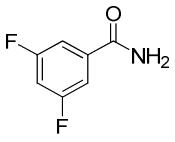
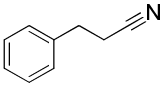
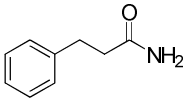
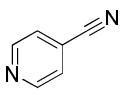
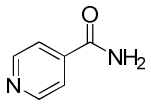
Using 10% HBF_4•OEt_2 in the absence of gold led to no conversion, even after 3 hours. It is of interest that [(IPr)Au(CH_3CN)][BF_4] **3** displays higher activity than [(IPr)Au(NTf_2)] **8**, as this is in contrast to the current results in nitrile hydration: The

initial catalyst screening was performed with 2 mol% catalyst in a 1 M solution of 1,4-dioxane/H_2O 2:1 at 100 °C and showed **8** to be the best catalyst. In order to compare **2** to all other catalysts tested, we subjected it to the same reaction conditions to seek the highest conversion rate among all catalysts.

Since the optimizations for nitrile hydration in Chapter **10** revealed the importance of the amount of water used, a lower conversion of [(IPr)AuCl]/$AgBF_4$ and [(IPr)Au(CH_3CN)]BF_4 into **2** occuring under these reaction conditions was suggested. This would result in lower conversions than when using **8** under the "unoptimised" conditions.

Table 11.1 Scope of nitrile hydration using [{(IPr)Au}$_2$(μ-OH)][BF_4] **2** and [(IPr)Au(NTf_2)] **8**.



Entry	Substrate	Product	Conv. with 2	Conv. with 8
1			98%	99%
2			97%	82%
3			94%	76%
4			100%	100%
5			90%[a]	30%[b]
6			75%[c]	31%[d]

[a] 2.5 mol% **2** [b] 5 mol% **8** [c] 2.5 mol% **2**, 6 hours [d] 5 mol% **8**, 6 hours.

However, under the new reaction conditions (THF/H_2O 1:1), [{(IPr)Au}$_2$(μ-OH)][BF_4] **2** easily formed *in situ* from **3** to outperforms **8**. The better coordinating NTf_2 ligand prevents **8** converting to the corresponding complex [{(IPr)Au}$_2$(μ-OH)][NTf_2] **4** at ambient temperature.

The excellent catalytic activity of **2** having been confirmed, a narrow reaction scope was examined with representative nitrile substrates. As shown in **Table 11.1**, good to excellent conversions were obtained for all substrates tested. Substrates that gave good conversions with **8** resulted in nearly quantitative conversion with **3** (entries 1-4).

Additionally, substrates that proved problematic in reactions mediated by **8** were tested in order to gauge the efficacy of **3**. Using 3-phenylpropanenitrile, the corresponding amide (entry 5) was obtained in excellent conversion (90%) compared to the previously obtained 30% when **8** was used. Moreover, with 2.5 mol% **2**, isonicotinonitrile (entry 6) afforded 75% yield of the desired amide after 6 hours, while using 5 mol% **8** only led to a low 31% conversion.

11.2.4 Mechanistic considerations

To support the hypothesis of easy formation of **2** in aqueous media, the proposed equilibrium between [(IPr)Au(CH_3CN)][BF_4] **3** and [{(IPr)Au}$_2$(μ-OH)][BF_4] **2** in aqueous reaction media was further examined.

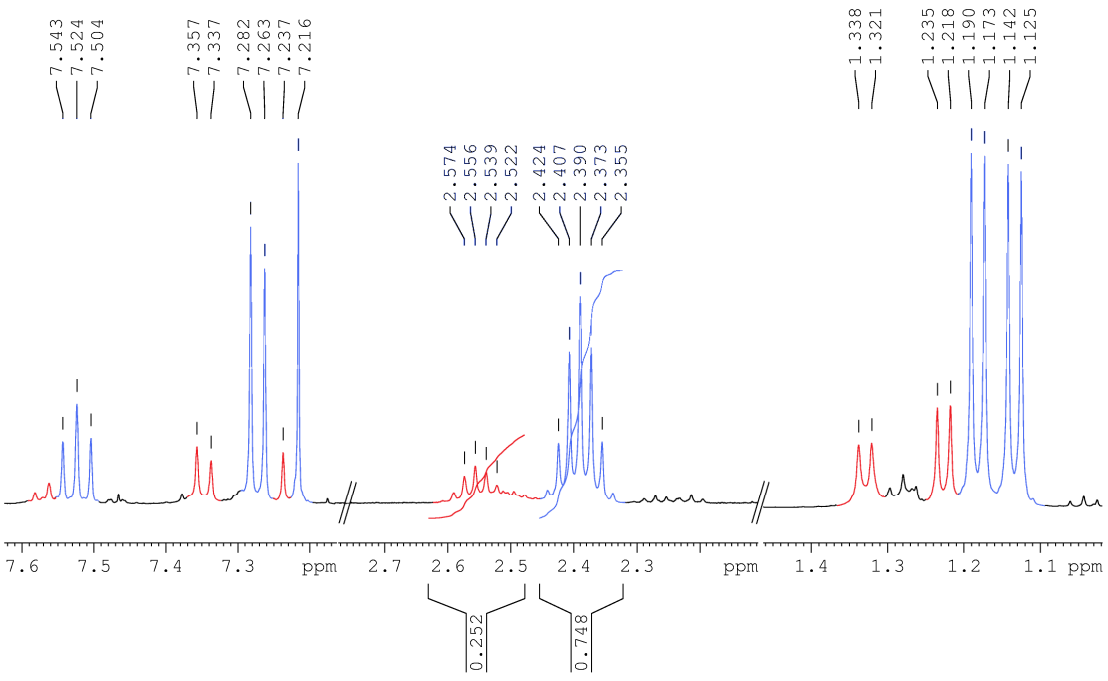


Figure 11.3 NMR spectrum of [(IPr)AuCl] activated by $AgBF_4$ in CD_2Cl_2/D_2O. [{(IPr)Au}$_2$(μ-OH)]BF_4 is presented in blue and [(IPr)Au]$^+BF_4^-$ in red.

When **3** is dissolved in CH_2Cl_2 and the resulting solution simply washed with water (3 times), **2** is formed in 96% yield. Since this reaction appears facile, the formation of **2** from [(IPr)AuCl] was also investigated. Chloride abstraction with $AgBF_4$ generates the putative $[(IPr)Au]^+[BF_4]^-$ species, and after removal of AgCl by filtration through Celite the organic phase was washed three times with water, in a similar manner as above. Recrystallisation from CH_2Cl_2/pentane afforded **2** in 81% yield. The rapid and straightforward formation of **2** in aqueous media and similar conversion rates in nitrile hydration strongly support the conclusion that **2** is an important gold species in reactions containing water.

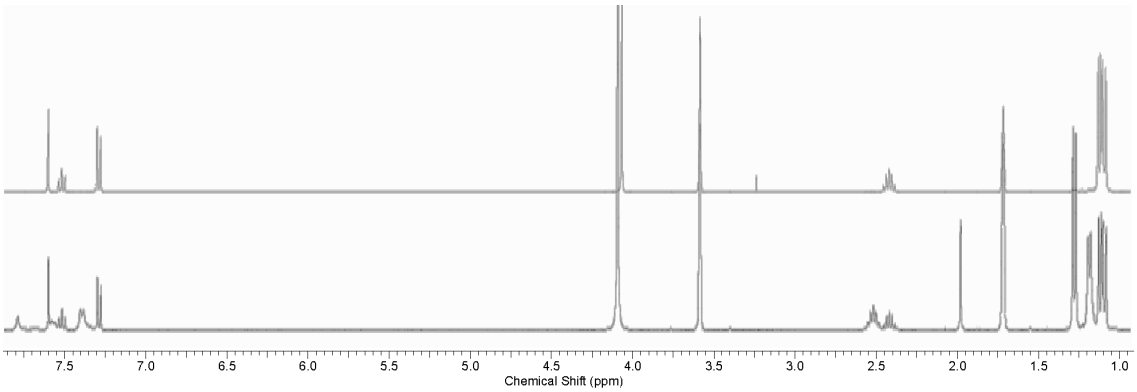
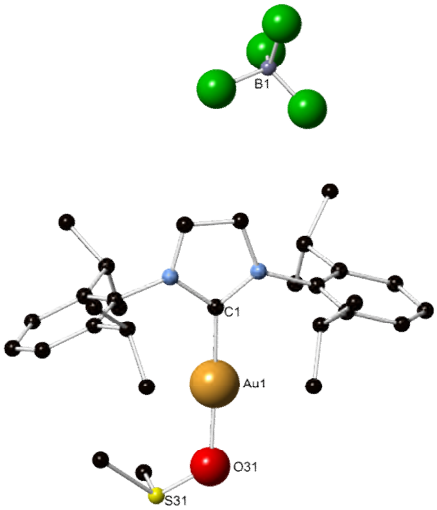


Figure 11.4 ^{1}H-NMR of **2** in THF-d_8 (top) and **3** in THF-d_8/D_2O (bottom) resulting in a mixture with **2**.

To support this hypothesis further, [(IPr)AuCl] was dissolved in CD_2Cl_2 and activated with $AgBF_4$. After separating the precipitated AgCl, 50 μL D_2O was added to the solution and a ^{1}H-NMR spectrum was recorded. $[\{(IPr)Au\}_2(\mu\text{-OD})][BF_4]$ was formed in 75% yield upon addition of D_2O. The remaining 25% appeared to be "naked" $[(IPr)Au]^+[BF_4]^-$ (**Figure 11.3**). Additionally, reaction conditions in a ^{1}H-NMR experiment using THF-d_8/D_2O, confirming the formation of significant amounts of $[\{(IPr)Au\}_2(\mu\text{-OH})][BF_4]$ **2**, were simulated (**Figure 11.4**). Interestingly, repeating the ^{1}H-NMR experiment in better coordinating DMSO-d_6 yielded the DMSO-d_6 complex quantitatively.

The structure of the analogue $[(IPr)Au(DMSO)][BF_4]$ **9** was verified by X-ray diffraction (see **Figure 11.5**) and the addition of water found to be redundant. While these observations are not direct evidence for the active involvement of **2** in the catalytic cycle, it proves the role of **2** as a relevant resting state in aqueous media. Furthermore, the excellent reactivity of $[\{(IPr)Au\}_2(\mu\text{-OH})][BF_4]$ **2** in catalysis excludes it as a deactivation intermediate, rather an active role appears more conclusive.

With formation of **2** excluded as a deactivation pattern, possible alternatives were conceived. Referring to the dramatically decreased reaction rate with increasing product formation, amido complexes have been considered responsible. In a first approach, a 1:1 reaction of **4** and acetonitrile was conducted at 100 °C for 5 hours in order to recover the catalyst at the end of the reaction. The corresponding ^{1}H-NMR spectrum showed the formation of acetic acid and signals for two different and unknown [(IPr)Au] species. X-ray diffraction revealed the formation of [{(IPr)Au}$_2$(MeCOO)][NTf$_2$] **10**.



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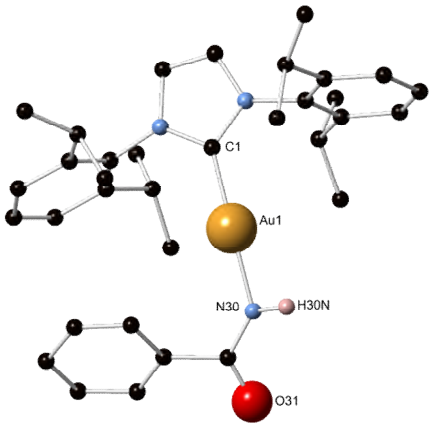

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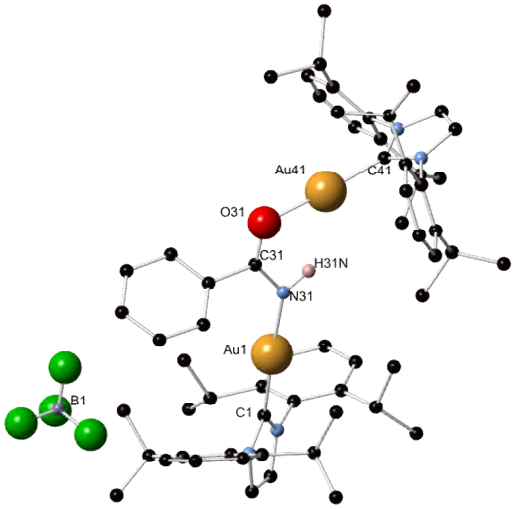


12

Figure 11.5 Molecular structures of [(IPr)Au(DMSO)][BF$_4$] **9**, [(IPr)Au(NHCOPh)] **11** and [{(IPr)Au}$_2$(PhCONH)][BF$_4$] **12**. Selected bond lengths [Å] and angles [deg] for **9**: Au(1)-C(1), 1.951(4); Au(1)-O(31), 2.057(3); O(31)-S(31), 1.536(3); C(1)-Au(1)-O(31), 174.66(15); S(31)-O(31)-Au(1), 122.56(17). For **11**: Au(1)-C(1), 1.973(11); Au(1)-N(30), 2.015(10); N(30)-H(30N), 0.97(2); C(1)-Au(1)-N(30), 174.4(4); C(31)-N(30)-Au(1), 132.8(9); C(31)-N(30)-H(30N), 130(6); Au(1)-N(30)-H(30N), 97(6); O(31)-C(31)-N(30), 125.1(12). For **12**: Au(1)-C(1), 1.983(7); Au(1)-N(31), 2.030(6); N(31)-H(31N), 0.97(2); Au(41)-C(41), 1.965(7); O(31)-Au(41), 2.023(5); C(1)-Au(1)-N(31), 176.7(2); C(31)-N(31)-Au(1), 130.7(5); C(31)-N(31)-H(31N), 91(6); Au(1)-N(31)-H(31N), 138(7); O(31)-C(31)-N(31), 125.0(6); C(41)-Au(41)-O(31), 176.1(2); C(31)-O(31)-Au(41), 125.0(4).

The unusual formation of carboxylic acid rationalized by the stoichiometric amounts of catalyst, the formation of **10** highlighted the need for synthesizing the amido complexes [(IPr)Au(NHCOPh)] **11** and [{(IPr)Au}$_2$(PhCONH)][BF_4] **12**. Using **1** and benzamide in stoichiometric amounts yielded **11** in 70% yield, as a 3:1 mixture of isomers. Under standard reaction conditions, **11** displayed very poor conversions in nitrile hydration, thus explaining the low reactivity of **1**. The most obvious synthetic approach of **12**, the analogous reaction of [{(IPr)Au}$_2$(μ-OH)][BF_4] with benzamide led to the desired complex **12** in 81% yield.

Interestingly, X-ray crystallography of **11** and **12** indicated that the spatial location of the amido-proton is significantly influenced by the gold centers (**Figure 11.5**). In **11** the C(31)-N(30)-H(30N) angle is 130° and Au(1)-N(30)-H(30N) is 97°, whereas in **12** a strong orientation of the proton to the oxo-coordinating gold center is observed (C(31)-N(31)-H(31N), 91°, Au(1)-N(31)-H(31N), 138°). Application of **12** in nitrile hydration as well as the addition of 1 equiv. *p*-chlorobenzamide to a standard reaction using catalyst **2** resulted in very poor conversion. It seems plausible that the amide product poisons the reaction by trapping the active catalysts resulting in a decreasing reaction rate with progressing conversion. This fact is of course limiting the catalyst loading to amounts above 1 mol% Au. Moreover, neither structure **11** or **12** can possibly act as a regular intermediate in the mechanistic cycle. If so, a drop of reactivity should be noted after the very first cycle, but this is not the case.

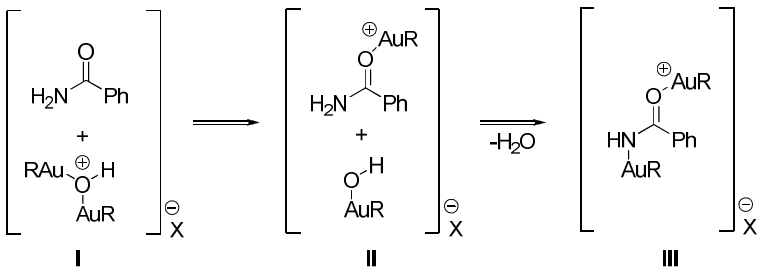


Figure 11.6 Analogy for Toste´s *et al.* proposal for an equilibrium of *tris*[phosphinegold(I)]oxonium in the presence of allenynes in cycloisomerization with complexes **2**, **4**-**7** with amides.

Apart from acting as a deactivation pathway, the formation of **12** from **2** presents another interesting aspect. While catalytic results do not correspond well with typical mechanistic approaches involving a metal hydroxide acting as a nucleophile, in fact mixing equimolar amounts of [(IPr)Au(CH_3CN)]BF_4 and [(IPr)Au(OH)] in CH_2Cl_2 results in full conversion into **2**, this represents a rare example of a catalyst with dual

reactivity. On the one hand, there is the [(IPr)Au(OH)] moiety acting as a base and deprotonating the amide, while the [(IPr)Au][BF_4] moiety coordinates *via* the oxygen. This is in fairly good agreement with a proposal by Toste *et al*. dealing with an equilibrium of *tris*[phosphinegold(I)]oxonium in the presence of allenynes in cycloisomerization.[183] Similarly, the dinuclear gold complexes would result in the observed complex **12** (**Figure 11.6**, I-III).

11.2.4.1 Synthesis and characterization of [Au(IPr)(RCN)]BF_4 complexes

It is of common knowledge that the nature of the substituents in a nitrile substrate, next to the nature of the metal center, influence the reactivity of the nitrile in hydrolysis.[212a] Electron acceptor groups improve the hydration on metal bound nitriles.[226] This trend was also recognized for the gold catalysts.[220] Since the synthesis of gold catalysts bearing nitrile ligands is well-known[103b] and these complexes have to be considered intermediates in the mechanistic cycle, a series of 10 representative [Au(IPr)(RCN)][X] complexes has been synthesized in order to possibly correlate the reactivity of the nitrile with relevant ^{1}H- and ^{13}C-NMR chemical shifts and bond distances gained by X-ray diffraction (Table **11.2**).

Table **11.2** Characteristic chemical shifts and bond distances of complexes **13**-**22**.

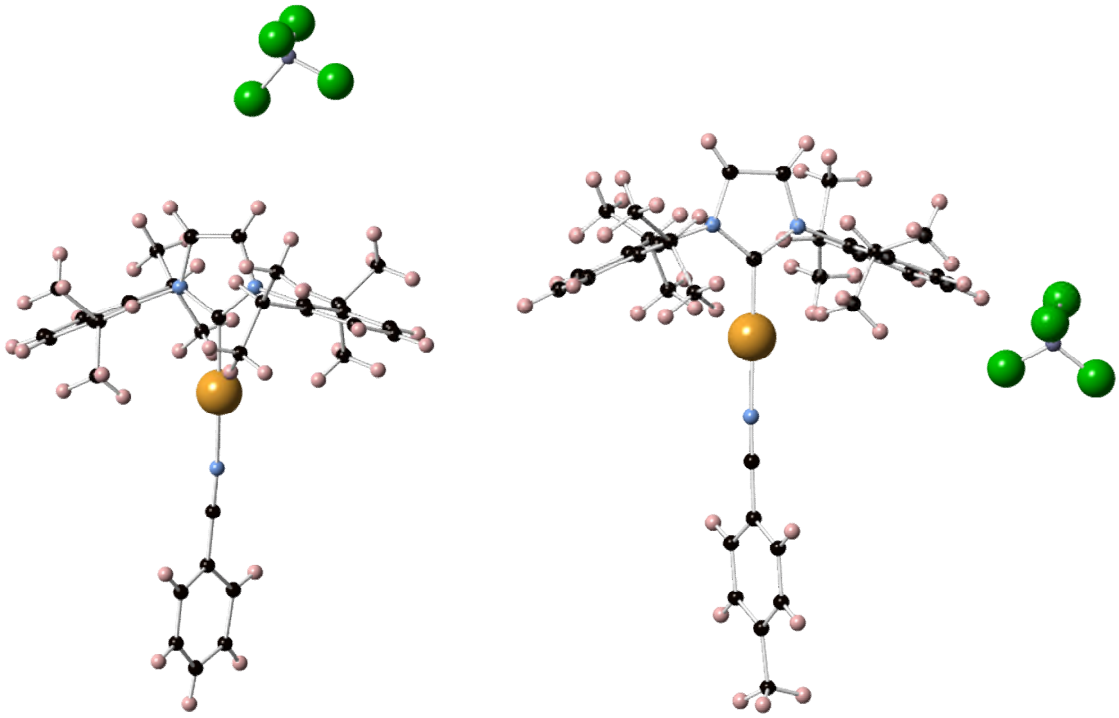
Entry	[Au(IPr)(R)][BF_4]		δ ($C_{carbene}$) in ppm	δ ($H_{backbone}$) in ppm	Å (Au-N)	Å (NΞC)
1	R = NCPh	**13**	165.5	7.48	2.018(7)[a]	1.141(10)[a]
2	R = $NCC_6H_4CH_3$	**14**	165.6	7.51	2.011(4)[a]	1.136(5)[a]
3	R = $NCC_6H_4N(CH_3)_2$	**15**	166.4	7.49	2.04(2)	1.15(3)
4	R = $NCC_6H_4OCH_3$	**16**	166.1	7.48	2.013(5)	1.146(7)
5	R = $NCC_6H_3(CH_3)_2$	**17**	165.4	7.57[b]	2.014(10)	1.147(14)
6	R = NCPhBr	**18**	165.6	7.46	2.015(3)	1.143(4)
7	R = $NCC_6H_4(COCH_3)$	**19**	165.3	7.46	nd[c]	nd[c]
8	R = $NCC(CH_3)_3$	**20**	165.3	7.47	2.023(7)	1.136(10)
9	R = 2-cyanopyridine	**21**	166.0	7.43	2.064(3)[d]	1.136(5)[d]
10	R = 4-cyanopyridine	**22**	166.2	7.42	2.056(5)[d]	1.142(8)[d]

[a] Bond length determined from one out two independent molecules. [b] Shift determined out of a multiplet. [c] Attempts to grow crystals were unsuccessful. [d] 2- and 4-cyanopyridine are coordinated to the gold center *via* the pyridine moiety.

Of note, several attempts to synthesize benzonitrile complexes bearing strong electron withdrawing substituents like NO_2 with the applied procedures were unsuccessful. As shown in Table **11.2**, benzonitrile ligands bearing electron donating substituents tend to effect a slight downfield shift of the carbenic carbon. The proton shift on the imidazolylidene backbone appears too minor for an adequate interpretation.

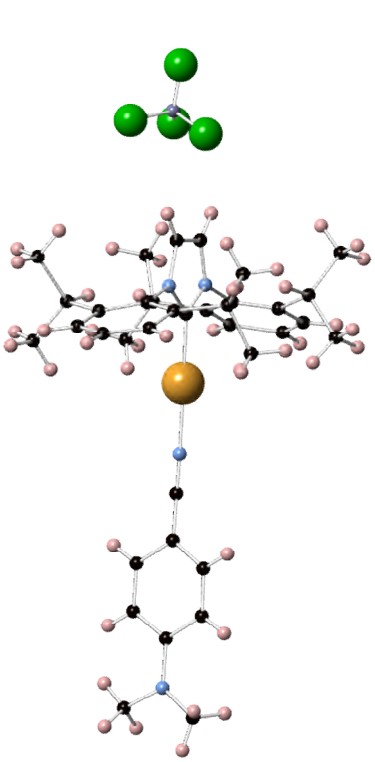
By analogy, a comparison of the Au-N and NΞC bond distances confirmed the lack of significant effects due to the nitrile moiety. In the case of complexes **21** and **22** X-ray diffraction revealed, as expected, a preferred coordination of the gold center *via* the pyridine[227] implicating the decreased reactivity of those heterocycles due to spatial distance of the gold center and the resulting lack of activation of the nitrile moiety.

Interestingly, here the Au-N distance is longer than in the complexes coordinating *via* a nitrile. The drop in reactivity is smaller for 2-cyanopyridine as the nitrile moiety is in the direct neighbourhood of the coordinated gold center while in case of 4-cyanopyridine the gold center is out of range.



13 **14**

Figure 11.7 Molecular structures of complexes **13-18** and **20-22**.



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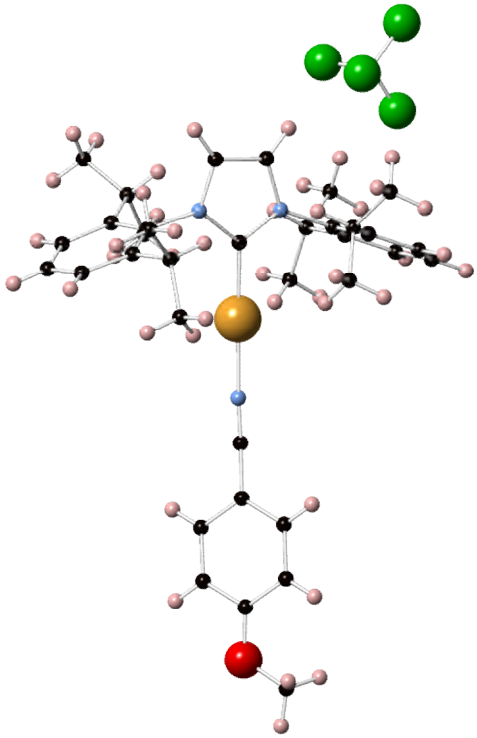

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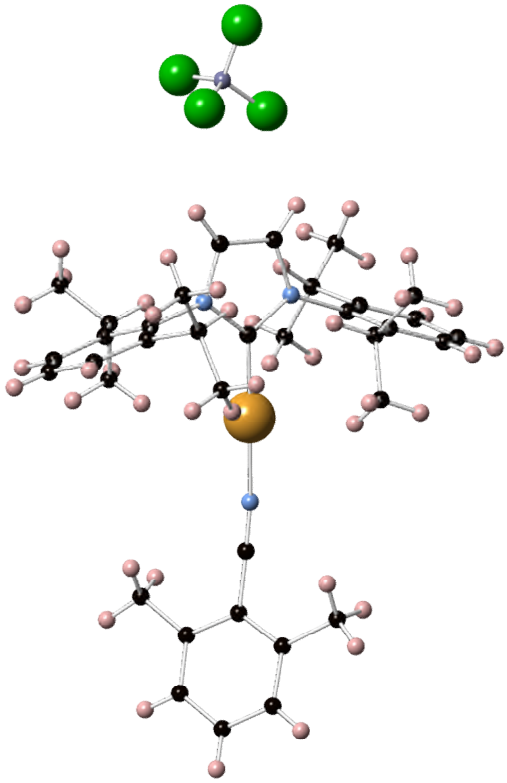

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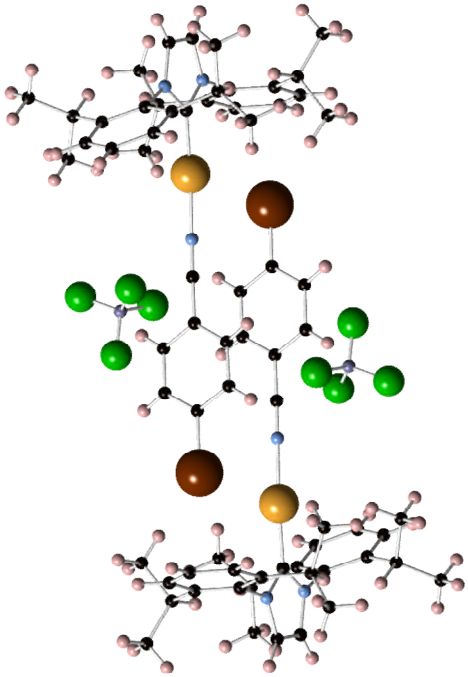

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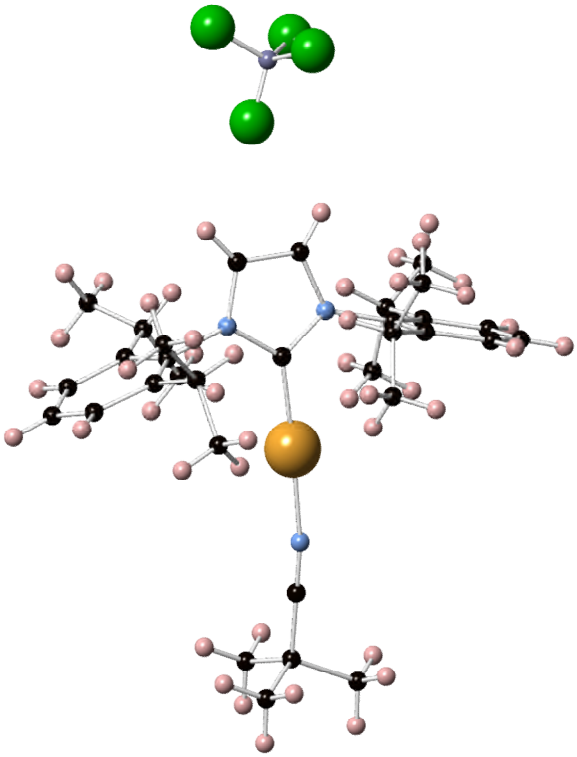
Figure 11.7 Molecular structures of complexes **13-18** and **20-22.** (continued)



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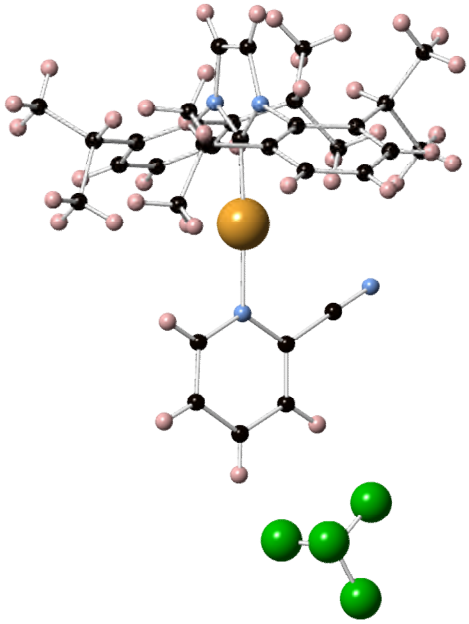

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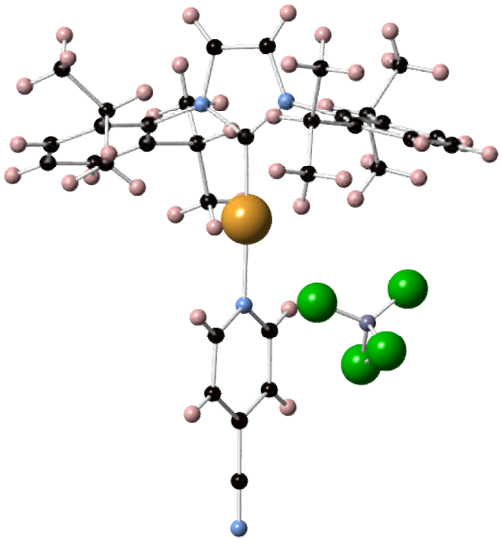


22

Figure 11.7 Molecular structures of complexes **13-18** and **20-22.** (continued)

From a catalytic point of view, the choice of the nitrile ligand is not significantly influencing the yields of the reaction: A comparison of e.g. [(IPr)Au(CH_3CN)]PF_6 and [(IPr)Au(PhCN)]PF_6 in nitrile hydration resulted in identical conversions. Therefore, other aspects like substrate costs, toxicity, ease of preparation and complex stability should be key considerations for the preparation of [Au(L)(RCN)][X] complexes.

11.3 Conclusion

The high-yield synthesis of a dinuclear gold complex **2** has been achieved and this species has demonstrated high catalyst efficiency in the hydration of nitriles and also permitted an expansion of the reaction scope. Advantageously, this simple synthetic protocol makes use of the readily available synthon **1**. Using the air- and moisture-stable **1**, a highly active catalytic species can be generated *in situ* and this methodology has proven exceedingly effective in the hydration of nitriles.

The facile formation of **2** and **3** from **1** suggest a broader potential role of **1** and **2** as "pre-catalytic" species in gold-mediated transformations. Formation of **2** from **3** and [(IPr)AuCl]/[$AgBF_4$] by simple addition of water strongly suggests **2** to be a reactive intermediate or relevant resting state in water-inclusive reactions. Mono- and dinuclear gold complexes of benzamide have been isolated and proved ineffective in nitrile hydration. In consequence, the reaction product must deactivate the active catalyst species in a side reaction.

A series of [(IPr)Au(RCN)][BF_4] complexes was synthesized for insights into the diverse reactivity of nitrile substrates. However, data as well as comparison of bond distances gained by X-ray diffraction hardly provide key information on the reactivity. Reactivity of heterocyclic nitriles like cyanopyridines is influenced due to the coordination of the gold center to the aromatic heteroatom.

The simple use of a gold complex in conjunction with an acidic protonic activator represents an attractive alternative to the use of gold halide complexes requiring a silver-based halide abstractor.

11.4 Experimental section

If not otherwise stated, manipulations were performed under ambient atmosphere. Solvents were of *puriss.* grade and used as received by the supplier. NMR spectra were collected on 400 MHz and 300 MHz spectrometers at ambient temperature in $CDCl_3$. Chemical shifts are given in parts per million (ppm) with respect to TMS. Chemical shifts of ^{19}F spectra are given in parts per million (ppm) with respect to $CFCl_3$. Crystallographic data were collected by A. M. S. Slawin.

Synthesis of [{(IPr)Au}$_2$(μ-OH)][BF$_4$] ***2***: *Route A*: [Au(IPr)(CH$_3$CN)[BF$_4$] (2 g, 2.80 mmol) was suspended in water (3 ml, 167 mmol) and stirred at 60 °C for 72 hours. The reaction mixture was extracted with CH_2Cl_2 and the organic phase was washed 4 times with a large excess of water and dried over $MgSO_4$. The mixture was filtered and the volatiles were evaporated under reduced pressure. The resulting white crude product was recrystallised from CH_2Cl_2/pentane to give 1.71 g (96%) of a white microcrystalline solid.

Route B: [(IPr)Au(OH)] (97 mg, 0.160 mmol) was dissolved in benzene (2 mL) and tetrafluoroboric acid-diethyl ether complex (11.0 μL, 0.080 mmol) was added by syringe. The reaction mixture was stirred 4 hours at room temperature. Pentane was added to the reaction to precipitate the product as a white solid. The crude white product was recrystallised from CH_2Cl_2/pentane to give 92 mg (90%) of a white microcrystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (t, *J* = 7.8 Hz, 4H), 7.26 (s, 4H), 7.24 (d, *J* = 7.8 Hz, 8H), 2.39 (spt, *J* = 6.9 Hz, 8H), 1.19 (d, *J* = 6.9 Hz, 24H), 1.11 (d, *J* = 6.9 Hz, 24H), 0.32 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.6, 145.4, 133.6, 130.7, 124.2, 124.1, 28.6, 24.4, 23.8. ^{19}F NMR (185 MHz, $CDCl_3$): δ -154.90, -154.85. Elemental Analysis (calc): C 51.06 (50.87), H 5.27 (5.77), N 4.36 (4.39).

Synthesis of [(Au(IPr)(CH$_3$CN)][BF$_4$] ***3*** *from* ***1***: [(IPr)Au(OH)] (100 mg, 0.166 mmol) was dissolved in toluene (2 mL) and tetrafluoroboric acid-diethyl ether complex (0.023 mL, 0.166 mmol) was added by syringe. Acetonitrile (8.67 μL, 0.166 mmol) was added and the heterogeneous reaction mixture was stirred 2 hours at room temperature. Pentane was added to precipitate 114 mg (96%) of a white microcrystalline solid whose NMR data confirms the synthesis of **3**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (t, *J* = 7.8 Hz, 2H), 7.38 (s, 2H), 7.34 (d, *J* = 7.8 Hz, 4H), 2.44 (spt, *J* = 6.9 Hz, 4H), 2.39 (s, 3H), 1.29 (d, *J* = 6.9 Hz, 12H), 1.24 (d, *J* = 6.9 Hz, 12H).^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3, 145.5, 133.0, 131.5, 124.8, 124.6, 121.0, 28.9, 24.7, 24.0, 2.7. ^{19}F NMR (185 MHz, $CDCl_3$): δ -154.98, -153.92.

Synthesis of [{(IPr)Au}$_2$(μ-OH)][NTf$_2$] ***4***: Trifluoromethanesulfonimide (73 mg, 0.260 mmol) was dissolved under N_2 in anhydrous toluene (2 mL) and [(IPr)Au(OH)] (313 mg, 0.519 mmol) was added. The reaction mixture was stirred overnight at room

temperature. Pentane (10 mL) was added to the reaction to ensure complete precipitation of the product. The white solid was collected by filtration, washed with pentane (2x 5 mL) and dried under vacuum to give 381 mg (100%) of a white microcrystalline solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (t, J = 7.8 Hz, 4H), 7.26-7.20 (m, 12H), 2.37 (spt, J = 6.8 Hz, 8H), 1.17 (d, J = 6.8 Hz, 24H), 1.11 (d, J = 6.8 Hz, 24H), 0.30 (s, 1H).. ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.9, 145.6, 133.7, 130.9, 124.3, 124.2, 120.1 (q, J = 322 Hz), 28.8, 24.6, 23.9. ^{19}F NMR (282 MHz, $CDCl_3$): δ -79.2. Elemental Analysis (calc): C 45.78 (45.81), H 4.92 (5.01), N 4.57 (4.77).

Synthesis of [{(IPr)Au}$_2$(μ-OH)][OTf] ***5***: Triflic acid (5.5 μL, 0.06 mmol) was added to anhydrous toluene (2 mL) and [(IPr)Au(OH)] (75 mg, 125 μmol) was added. The reaction mixture was stirred overnight at room temperature. Pentane (2 mL) was added to the reaction to ensure complete precipitation of the product. The white solid was collected by filtration, washed with pentane (2x 5 mL) and dried under vacuum to give 71 mg (85%) of a white microcrystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (t, J = 7.9 Hz, 4H), 7.25 (s, 4H), 7.24 (d, J = 7.9 Hz, 8H), 2.39 (spt, J = 6.9 Hz, 8H), 1.19 (d, J = 6.9 Hz, 24H), 1.12 (d, J = 6.9 Hz, 24H), 0.35 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.8, 145.4, 133.6, 130.7, 124.2, 124.1, 28.7, 24.5, 23.9. ^{19}F NMR (376 MHz, $CDCl_3$): δ -78.6. Elemental Analysis (calc): C 49.95 (49.40), H 5.88 (5.50), N 3.91 (4.19).

Synthesis of [{(IPr)Au}$_2$(μ-OH)][FABA] ***6***: N ,N –dimethylaniliniumtetrakis(penta-fluorophenyl)borate (DAN・FABA) (33 mg, 0.04 mmol) was dissolved in anhydrous toluene (2 mL) and [(IPr)Au(OH)] (50 mg, 0.08 mmol) was added. The reaction mixture was stirred overnight at room temperature. Pentane (2 mL) was added to the reaction to ensure complete precipitation of the product. The white solid was collected by filtration, washed with pentane (2x 5 mL) and dried under vacuum to give 73 mg (94%) of a white microcrystalline solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49 (t, J = 7.8 Hz, 4H), 7.24 (d, J = 7.8 Hz, 8H), 7.14 (s, 4H), 2.37 (spt, J = 6.8 Hz, 8H), 1.17 (d, J = 6.9 Hz, 24H), 1.11 (d, J = 6.9 Hz, 24H), 0.29 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.3, 145.4, 133.5, 130.9, 124.3, 123.8, 28.7, 24.4, 23.8. ^{19}F NMR (282 MHz, $CDCl_3$): δ -133.06, -163.95, -167.54. Elemental Analysis (calc): C 50.25 (50.17), H 4.10 (3.94), N 3.01 (3.00).

*Synthesis of [{(IPr)Au}$_2$(μ-OH)][SbF$_6$] **7***: 65 wt% aqueous $HSbF_6$ (31 mg, 85 μmol) was added to toluene (2 mL) and [(IPr)Au(OH)] (103 mg, 170 μmol) was added. The reaction mixture was stirred overnight at room temperature. Pentane (2 mL) was added to the reaction to ensure complete precipitation of the product. The white solid was collected by filtration, washed with pentane (2x 5 mL) and dried under vacuum to give 101 mg (83%) of a white microcrystalline solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 (t, J = 7.8 Hz, 4H), 7.24 (d, J = 7.8 Hz, 8H), 7.22 (s, 4H), 2.39 (spt, J = 6.8 Hz, 8H), 1.19 (d, J = 6.8 Hz, 24H), 1.11 (d, J = 6.8 Hz, 24H), 0.26 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.6, 145.5, 133.6, 130.7, 124.2, 124.1, 28.6, 24.4, 23.8. Elemental Analysis (calc): C 45.49 (45.55), H 5.18 (5.17), N 3.40 (3.93)

*Synthesis of [(IPr)Au(DMSO)][BF$_4$] **9***: In a NMR tube [(IPr)Au(CH_3CN)][BF_4] **3** (20 mg, 0.028 mmol) was diluted in DMSO (500 μL). NMR shows immediate full conversion. Volatile compounds were removed under low pressure to obtain colourless microcrystalline solid in quantitative yield (21 mg, 99%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.95 (s, 2H), 7.58 (t, J = 7.9 Hz, 2H), 7.41 (d, J = 7.9 Hz, 4H), 2.39 (spt, J = 6.8 Hz, 4H), 1.22 (d, J = 6.8 Hz, 12H), 1.17 (d, J = 6.8 Hz, 12H). ^{19}F NMR (376 MHz, DMSO-d_6): δ -148.63, -148.68. ^{13}C NMR (101 MHz, DMSO-d_6): δ 160.9, 145.3, 133.5, 130.9, 125.4, 124.3, 28.4, 24.0, 23.6. Elemental Analysis (calc): C 45.71 (46.04), H 5.50 (5.64), N 3.53 (3.70).

*Synthesis of [(IPr)Au(NHCOPh)] **11***: [(IPr)Au(OH)] **1** (50 mg, 0,083 mmol) was dispersed in toluene (2 ml) and benzamide (10 mg, 0,083 mmol) was added. The reaction mixture was stirred overnight at room temperature. Pentane (2 mL) was added and the precipitate was collected *via* filtration, washed with pentane (3 x 5 mL) and dried under reduced pressure to obtain a colourless solid (51%, 87 mg). ^{1}H and ^{13}C NMR data show a mixture of two isomers. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67-7.47 (m), 7.34-7.25 (m), 7.23-7.08 (m), 6.87 (t, J = 7.7 Hz), 5.35 (br. s), 4.98 (br. s), 2.62 (sept, J = 6.8 Hz), 2.50 (sept, J = 6.8 Hz), 1.42-1.12 (m). ^{13}C NMR (101 MHz, $CDCl_3$): δ 179.1, 177.3, 145.8, 145.7, 134.2, 130.8, 130.7, 129.2, 128.4, 127.6, 127.4, 124.3, 123.2, 123.1, 29.0, 28.9, 24.6, 24.3, 24.2, 24.1. Elemental Analysis (calc): C 56.84 (57.87), H 5.44 (6.00), N 5.45 (5.95).

Synthesis of [{(IPr)Au}$_2$(PhCONH)][BF$_4$] ***12***: [{(IPr)Au}$_2$(μ-OH)][BF$_4$] (25 mg, 0.02 mmol) was dispersed in toluene (3 mL) and benzamide (2.4 mg, 0.02 mmol) added. The reaction mixture was stirred overnight at room temperature. Pentane (2 mL) was added and the precipitate was collected *via* filtration, washed with pentane (3x 5 mL) and dried under reduced pressure to obtain a colourless solid (81%, 22 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (t, *J* = 7.9 Hz, 2H), 7.40 (s, 2H), 7.36 (t, *J* = 7.9 Hz, 2H), 7.31 (d, *J* = 7.9 Hz, 4H), 7.25 (s, 2H) 7.17 (d, *J* = 7.9 Hz, 4H), 6.78 (t, *J* = 7.9 Hz, 2H), 5.13 (s, 1H), 2.45 (m, 8H), 1.27-1.18 (m, *J* = 6.8 Hz, 24H), 1.17-1.11 (m, *J* = 7.5 Hz, 24H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -154.92, -154.98. ^{13}C NMR (101 MHz, $CDCl_3$): δ 180.2, 172.1, 163.9, 145.7, 135.9, 134.1, 133.8, 131.1, 131.0, 130.5, 128.1, 127.2, 124.6, 124.5, 124.3, 28.9, 24.7, 24.5, 24.1, 24.0. Elemental Analysis (calc): C 52.71 (53.17), H 5.60 (5.71), N 4.81 (5.08).

Synthesis of [(IPr)Au(PhCN)][BF$_4$] ***13***: 48 wt% aqueous HBF_4 (22 μL, 0.17 mmol) was added to a dispersion of [(IPr)Au(OH)] (100 mg, 0.17 mmol) and benzonitrile (24 μL, 0.18 mmol) in toluene (2 mL). The reaction mixture was stirred overnight at room temperature. Pentane (2 mL) was added to the reaction to ensure complete precipitation of the product. The white solid was collected by filtration, washed with pentane (2 x 5 mL) and dried under vacuum to give 123 mg (96%) of a white microcrystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86-7.74 (m, 3H), 7.66 - 7.55 (m, 4H), 7.48 (s, 2H), 7.37 (d, *J* = 7.7 Hz, 4H), 2.50 (spt, *J* = 6.9 Hz, 4H), 1.33 (d, *J* = 6.9 Hz, 12H), 1.27 (d, *J* = 6.9 Hz, 12H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -154.64, -154.69. ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.5, 145.8, 136.8, 133.8, 133.2, 131.4, 130.2, 125.4, 124.7, 119.8, 106.4, 29.0, 24.9, 24.1. Elemental Analysis (calc): C 51.77 (52.66), H 5.22 (5.33), N 5.32 (5.42).

Synthesis of [(IPr)Au(CH$_3$C$_6$H$_4$CN)][BF$_4$] ***14***: $AgBF_4$ (31 mg, 0.16 mmol) was placed under argon in a Schlenk tube wrapped with alumina foil. CH_2Cl_2 (4 mL) was added followed by 4-toluonitrile (19 mg, 0.16 mmol). Then, [(IPr)AuCl] (100 mg, 0.16 mmol) was added and the reaction mixture was stirred 30 min at room temperature. CH_2Cl_2 (5 mL) was added and the reaction mixture was filtered over a plug of silica. Volatile compounds were removed under reduced pressure to yield a colourless oil. Recrystallisation with CH_2Cl_2/pentane and addition of some ether yielded a colourless

solid (62 mg, 49%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, *J* = 8.2 Hz, 2H), 7.60 (t, *J* = 7.9 Hz, 2H), 7.51 (s, 2H), 7.43-7.33 (m, 6H), 2.51 (spt, *J* = 6.9 Hz, 4H), 2.45 (s, 3H), 1.33 (d, *J* = 6.8 Hz, 12H), 1.27 (d, *J* = 6.8 Hz, 12H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -154.66. -154.73. ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.6, 148.7, 145.7, 133.7, 133.3, 131.4, 130.9, 125.5, 124.6, 120.4, 103.0, 28.9, 24.9, 24.1, 22.4. Elemental Analysis (calc): C 52.63 (52.19), H 5.08 (5.38), N 6.12 (5.22).

Synthesis of [(IPr)Au($(CH_3)_2NC_6H_4CN$)][BF_4] ***15***: $AgBF_4$ (125 mg, 0.64 mmol) was placed under argon in a Schlenk tube wrapped with alumina foil. CH_2Cl_2 (14 mL) was added followed by 4-dimethylaminobenzonitrile (94 mg, 0.64 mmol). Then, [(IPr)AuCl] (400 mg, 0.64 mmol) was added and the reaction mixture was stirred 30 min at room tempaerature. CH_2Cl_2 (10 mL) was added and the reaction mixture was filtered over a plug of silica. Volatile compounds were removed under reduced pressure to yield a colourless oil. Recrystallisation with CH_2Cl_2/pentane and addition of some ether yielded a colourless solid (179 mg, 34%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (t, *J* = 7.9 Hz, 2H), 7.49 (s, 2H), 7.44 (d, *J* = 9.2 Hz, 2H), 7.34 (d, *J* = 7.9 Hz, 4H), 6.64 (d, *J* = 9.2 Hz, 2H), 3.06 (s, 6H), 2.49 (spt, *J* = 6.8 Hz, 4H), 1.30 (d, *J* = 6.8 Hz, 12H), 1.25 (d, *J* = 6.8 Hz, 12H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -154.67, 154.73. ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.4, 154.5, 145.7, 134.9, 133.4, 131.3, 125.3, 124.6, 123.9, 111.9, 88.2, 40.0, 28.9, 24.8, 24.0. Elemental Analysis (calc): C 53.65 (52.88), H 5.89 (5.66), N 6.28 (6.84).

Synthesis of [(IPr)Au($CH_3OC_6H_4CN$)][BF_4] ***16***: $AgBF_4$ (25 mg, 0.13 mmol) was placed under argon in a Schlenk tube wrapped with alumina foil. CH_2Cl_2 (4 mL) was added followed by anisonitrile (17 mg, 0.13 mmol). Then, [(IPr)AuCl] (79 mg, 0.13 mmol) was added and the reaction mixture was stirred 30 min at room temperature. CH_2Cl_2 (5 mL) was added and the reaction mixture was filtered over a plug of silica. Volatile compounds were removed under reduced pressure to yield a colourless oil. Recrystallisation with CH_2Cl_2/pentane and addition of some ether yielded a colourless solid (72 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 9.0 Hz, 2 H), 7.60 (t, *J* = 7.9 Hz, 2 H), 7.48 (s, 2 H), 7.37 (d, *J* = 7.9 Hz, 4 H), 7.08 (d, *J* = 9.0 Hz, 2 H), 3.90 (s, 3 H), 2.50 (spt, *J* = 6.8 Hz, 4 H), 1.33 (d, *J* = 6.8 Hz, 12 H), 1.27 (d, *J* = 6.8 Hz, 12 H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -154.57. -154.63. ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.1,

166.0, 145.7, 136.1, 133.3, 131.4, 125.4, 124.7, 121.2, 116.2, 96.7, 56.3, 29.0, 24.9, 24.1. Elemental Analysis (calc): C 53.35 (53.25) H 5.23 (5.49) N 6.13 (5.32).

Synthesis of [(IPr)Au((CH$_3$)$_2$)C$_6$H$_3$CN)][BF$_4$] ***17***: $AgBF_4$ (31 mg, 0.16 mmol) was placed under argon in a Schlenk tube wrapped with alumina foil. CH_2Cl_2 (4 mL) was added followed by 2,6-dimethylbenzonitrile (21 mg, 0.16 mmol). Then, [(IPr)AuCl] (100 mg, 0.16 mmol) was added and the reaction mixture was stirred 30 min at room temperature. CH_2Cl_2 (5 mL) was added and the reaction mixture was filtered over a plug of silica. Volatile compounds were removed under reduced pressure to yield a colourless oil. Recrystallisation with CH_2Cl_2/pentane and addition of some ether yielded a colourless solid (74 mg, 57%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66-7.48 (m, 5H), 7.36 (d, *J* = 7.7 Hz, 4H), 7.20 (d, *J* = 7.5 Hz, 2H), 2.52 (spt, *J* = 6.7 Hz, 4H), 2.36 (s, 6H), 1.31 (d, *J* = 6.7 Hz, 12H), 1.28 (d, *J* = 6.7 Hz, 12H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -154.58. -154.63. ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.4, 145.7, 144.6, 136.1, 133.3, 131.3, 128.5, 125.6, 124.6, 119.7, 107.6, 28.9, 24.8, 24.1, 20.6. Elemental Analysis (calc): C 53.3 (53.81), H 5.55 (5.64), N 5.82 (5.23).

Synthesis of [(IPr)Au(BrPhCN)][BF$_4$] ***18***: 48 wt% aqueous HBF_4 (11 μL, 0.08 mmol) was added to a dispersion of [(IPr)Au(OH)] (50 mg, 0.08 mmol) and *p*-bromobenzonitrile (17 μL, 0.09 mmol) in toluene (2 mL). The reaction mixture was stirred overnight at room temperature. Pentane (2 mL) was added to the reaction to ensure complete precipitation of the product. The white solid was collected by filtration, washed with pentane (2x 5 mL) and dried under vacuum to give 62 mg (87%) of a white microcrystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81-7.66 (m, 4H), 7.60 (t, *J* = 7.9 Hz, 2H), 7.46 (s, 2H), 7.37 (d, *J* = 7.9 Hz, 4H), 2.49 (spt, *J* = 6.8 Hz, 4H), 1.33 (d, *J* = 6.8 Hz, 12H), 1.27 (d, *J* = 6.8 Hz, 12H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -154.20, -154.25 . ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.6, 145.7, 135.1, 133.8, 133.2, 132.7, 131.5, 124.7, 119.3, 105.3, 29.0, 24.9, 24.1. Elemental Analysis (calc): C 48.06 (47.80), H 4.68 (4.72), N 4.64 (4.92).

Synthesis of [(IPr)Au((COCH$_3$)C$_6$H$_4$CN)][BF$_4$] ***19***: $AgBF_4$ (48 mg, 0.25 mmol) was placed under argon in a Schlenk tube wrapped with alumina foil. CH_2Cl_2 (6 mL) was added followed by 3-acetobenzonitrile (35 mg, 0.24 mmol). Then, [(IPr)AuCl] (150 mg,

0.24 mmol) was added and the reaction mixture was stirred 30 min at room temperature. CH_2Cl_2 (5 mL) was added and the reaction mixture was filtered over a plug of silica. Volatile compounds were removed under reduced pressure to yield a colourless oil. Recrystallisation with CH_2Cl_2/pentane and addition of some ether yielded a colourless solid (195 mg, 99%). ^{1}H NMR (400MHz, $CDCl_3$): δ 8.43-8.30 (m, 2H), 8.11-7.99 (m, 1H), 7.89-7.77 (m, 1H), 7.66-7.55 (m, 2H), 7.46 (s, 2H), 7.38 (d, *J* = 7.7 Hz, 4H), 2.64 (s, 3H), 2.50 (spt, *J* = 6.8 Hz, 4H), 1.35 (d, *J* = 6.8 Hz, 12H), 1.27 (d, *J* = 6.8 Hz, 12H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -154.08. -154.13. ^{13}C NMR (101 MHz, $CDCl_3$): δ 195.8, 165.3, 145.6, 137.8, 137.3, 136.1, 133.1, 131.4, 125.4, 124.6, 118.7, 107.3, 28.8, 26.7, 24.8, 24.0. Elemental Analysis (calc): C 52.99 (52.89), H 4.44 (5.30), N 4.81 (5.14).

Synthesis of [(IPr)Au((CH$_3$)$_3$CCN)][BF$_4$] ***20***: HBF_4•OEt_2 (11 μL, 0.08 mmol) was added to a dispersion of [(IPr)Au(OH)] (50 mg, 0.08 mmol) and pivalonitrile (18 μL, 0.08 mmol) in toluene (2 mL). The reaction mixture was stirred 3 hours at room temperature. Pentane (2 mL) was added to the reaction to ensure complete precipitation of the product. The white solid was collected by filtration, washed with pentane (2x 5 mL) and dried under vacuum to give 52 mg (83%) of a white microcrystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (t, *J* = 7.7 Hz, 2H), 7.47 (s, 2H), 7.36 (d, *J* = 7.7 Hz, 4H), 2.47 (spt, *J* = 6.8 Hz, 4H), 1.42 (s, 9H), 1.29 (d, *J* = 6.8 Hz, 12H), 1.26 (d, *J* = 6.8 Hz, 12H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -154.14, -154.19. ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.3, 145.7, 133.3, 131.3, 125.5, 124.7, 29.5, 28.9, 27.3, 24.8, 24.1. Elemental Analysis (calc): C 49.58 (50.87), H 5.79 (6.00), N 4.93 (5.56).

Synthesis of [(IPr)Au(2-cyanopyridine)][BF$_4$] ***21***: $AgBF_4$ (31 mg, 0.16 mmol) was placed under argon in a Schlenk tube wrapped with alumina foil. CH_2Cl_2 (5 mL) was added followed by 2-cyanopyridine (17 mg, 0.16 mmol). Then, [(IPr)AuCl] (100 mg, 0.16 mmol) was added and the reaction mixture was stirred 30 min at room temperature. CH_2Cl_2 (5 mL) was added and the reaction mixture was filtered over a plug of silica. Volatile compounds were removed under reduced pressure to yield a colourless oil. Recrystallisation with CH_2Cl_2/pentane yielded a colourless solid (122 mg, 98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.43-8.28 (m, 1H), 8.22-8.10 (m, 2H), 7.91 (d, *J* = 7.3 Hz, 1H), 7.58 (t, *J* = 7.9 Hz, 2H), 7.43 (s, 2H), 7.36 (d, *J* = 7.9 Hz, 4H), 2.54 (spt, *J* = 6.8

Hz, 4H), 1.36 (d, *J* = 6.8 Hz, 12H), 1.27 (d, *J* = 6.8 Hz, 12H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -153.40, -153.46. ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.0, 153.6, 145.6, 143.7, 133.3, 133.2, 132.2, 132.0, 131.6, 125.1, 124.7, 114.3, 29.1, 24.8, 24.2. Elemental Analysis (calc): C 49.12 (51.05), H 5.08 (5.19), N 6.67 (7.22).

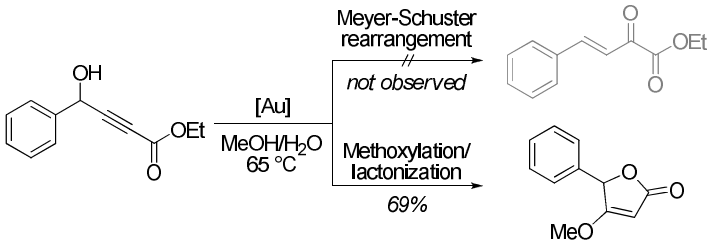
Synthesis of [(IPr)Au(4-cyanopyridine)][BF$_4$] ***22***: $AgBF_4$ (75 mg, 0.39 mmol) was placed under argon in a Schlenk tube wrapped with alumina foil. CH_2Cl_2 (10 mL) was added followed by 4-cyanopyridine (40 mg, 0.39 mmol). Then, [(IPr)AuCl] (240 mg, 0.39 mmol) was added and the reaction mixture was stirred 30 min at room temperature. CH_2Cl_2 (10 mL) was added and the reaction mixture was filtered over a plug of silica. Volatile compounds were removed under reduced pressure to yield a crude solid. Recrystallisation with CH_2Cl_2/pentane yielded a colourless solid (213 mg, 71%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.26 (d, *J* = 5.8 Hz, 2H), 7.92 (d, *J* = 5.8 Hz, 2H), 7.58 (t, *J* = 7.8 Hz, 2H), 7.42 (s, 2H), 7.36 (d, *J* = 7.8 Hz, 4H), 2.52 (spt, *J* = 6.8 Hz, 4H), 1.34 (d, *J* = 6.8 Hz, 12H), 1.27 (d, *J* = 6.8 Hz, 12H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -154.55. -154.60. ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.2, 152.3, 145.6, 133.2, 131.5, 129.6, 125.0, 125.0, 124.7, 114.5, 28.9, 24.9, 24.0. Elemental Analysis: C 51.55 (51.05), H 5.38 (5.19), N 7.15 (7.22).

General procedure for the nitrile hydration: In a typical reaction, [(IPr)Au(NTf_2)] (13 mg, 20 μmol, 2 mol%) or [{(IPr)Au}$_2$(μ-OH)][BF_4] (17 mg, 10 μmol, 1 mol%) was added to THF (0.5 mL) in a 2 mL microwave vial in ambient atmosphere. Benzonitrile (103 mg, 1 mmol) was added, followed by distilled H_2O (500 μL). The vial was sealed and heated in the microwave for 2 hours at 140 ºC (7 bar). The conversion was determined by gas chromatography.

Computational details: The computational studies are a contribution of L. Cavallo and co-workers. The BP86[228] calculations were performed with the Gaussian03 package. The SVP basis set was used for main group atoms,[229] while the relativistic SDD effective core potential in combination with a triple-ζ basis set was used for Au.[230] Solvent effects have been included through single-point calculations, on the gas-phase optimized geometries, with the PCM approach.[231]

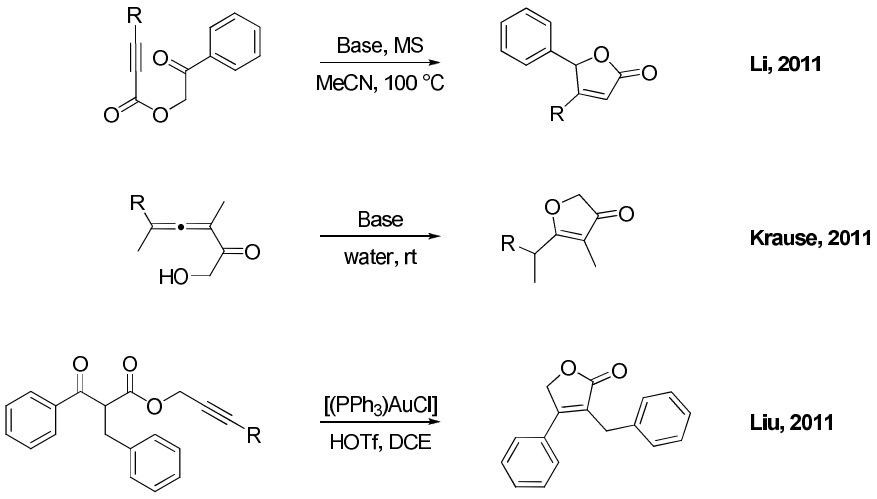
12 Au(I)-Catalyzed Tandem Alkoxylation/ Lactonization

In the course of exploratory studies, Nolan *et al.* contributed, amongst others, with the gold-catalyzed Meyer-Schuster rearrangement of propargylic alcohols as presented in Chapter **5**.[174] In the course of this study, an unexpected reactivity for progargylic alcohols bearing ethyl esters in the acetylenic position was observed and the novel products formed using this method were identified as 4-alkoxy-2(*5H*)-furanones (**Scheme 12.1**).



Scheme 12.1 2*(5H)*-Furanone formation as observed in an earlier contribution by Nolan *et al*.[174]

Since furanones or tetronic acids are common motifs in natural products and of potential relevance in pharmaceutical applications,[232] further investigations of this reaction were undertaken.

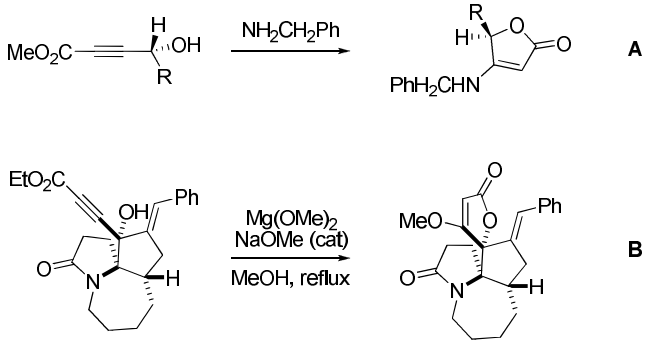


Scheme 12.2 Recent contribution addressing methodologies for furanone synthesis.

In the past, various approaches leading to furanones and tetronic acids have been devised[232c, 232e, f, 233] and are still a subject of intense research. This is emphasized by

recent publications addressing new synthetic strategies for various furanones,[233a, b] partially involving gold catalysis (**Scheme 12.2**).[234]

While 4-amino-2(*5H*)-furanones can be synthesized without use of a catalyst due to the basicity of the amine (**Scheme 12.3**, **A**),[235] alcohols remain unreactive upon alkyne addition without prior activation and only a few reports of methoxylated 2(*5H*)-furanones are in the literature (for a recent example, see **Scheme 12.3**, **B**).[236] These reported methods showcase the use of stoichiometric amounts of reagent or base and have limited scopes.[232f, 233e, 233i, 237]



Scheme 12.3 Uncatalyzed amination/lactonization (**A**) and recently applied alkoxylation/lactonization with a base (**B**).

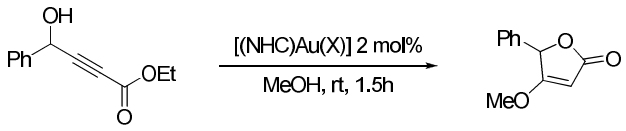
Teles and coworkers reported, in seminal work, the highly efficient gold-catalyzed alkoxylation of alkynes. This study together with the preliminary result in chapter **5** indicated the significant potential for gold catalysis in this arena.[178b] In this chapter, the base-free gold catalyzed formation of 4-alkoxy-2(*5H*)-furanones from a variety of propargylic alcohols using a simple and straightforward procedure is reported (**Scheme 12.1**). The scope includes secondary propargylic alcohols as well as tertiary propargylic alcohols yielding spiro compounds. Various alcohols have been tested to evaluate tolerance towards substitution at the nucleophile.

12.1 Results and Discussion

12.1.1 Optimization

For the present studies, IPr is the preferred ligand on gold for a number of reasons: [(IPr)AuCl] proved an excellent choice for both the Meyer-Schuster rearrangement[174] as well as for the related alkyne hydration reaction[206] and it is commercially available and therefore easily accessible to synthetic chemists.

Table 12.1 Initial catalyst screening with focus on the supporting ligand.



Entry	Catalyst	^{1}H-NMR-Conversion (%)
1	[(IPr)Au(NTf_2)]	67
2	[(SIPr)Au(NTf_2)]	45
3	[(IPr^{Me})Au(NTf_2)]	59
4	[(IPr^{Cl})Au(NTf_2)]	75
5	[(IMes)Au(NTf_2)]	nd[a]
6	[(SIMes)Au(NTf_2)]	nd[a]
7	[(IAd)Au(NTf_2)]	85
8	[(I^tBu)Au(NTf_2)]	83
9	[(IPr)Au(OH)]	traces
10	-	0

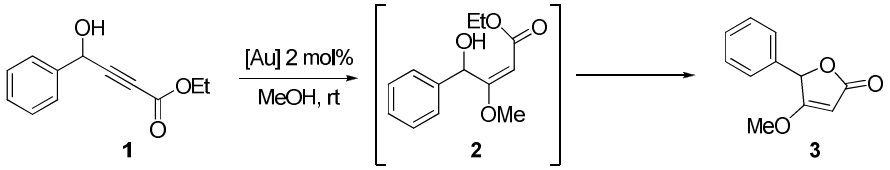
[a] nd= not determined. Next to the product the formation of various side products was observed.

It was decided however, to target the use of a well-defined catalyst and move from the two-component catalytic system [(IPr)AuCl]/$AgSbF_6$, already shown active in the present targeted transformation, to single component species. In order to obtain a proper overview of the catalytic capability of various [(NHC)Au(NTf_2)] complexes in this reaction, a catalyst screening is provided in **Table 12.1**. Of note, the sterically demanding ligands IAd and I^tBu as well as IPr^{Cl} furnished excellent conversions, superior to the common IPr ligand and can afford some increased yields.

Additionally, [(IPr)Au(NTf$_2$)] **C2**,[104a] was compared to some cationic [(IPr)Au] species like [(IPr)Au(CH$_3$CN)][BF$_4$] **C3**, [{(IPr)Au}$_2$(μ-OH)][BF$_4$] **C4** and [{(IPr)Au}$_2$(μ-OH)][NTf$_2$] **C5**,[175] which share the advantage of **C2** in avoiding the use of sensitive silver(I) salts (**Table 12.2**).[238] Interestingly, results of this narrow catalyst screening revealed superior conversions with [(IPr)Au(NTf$_2$)].

The methoxylation of the propargylic alcohol **1a** occurred rapidly for all catalysts tested. However, the conversion of the intermediate **2a** into the 2(*5H*)-furanone **3a** was accelerated in the case of **C2** allowing for full conversion to the corresponding furanone after 3 hours at room temperature. This was a rather unexpected result considering the assumption that all catalysts share the same catalytically active species. The nature of the labile ligands, $^-$NTf$_2$, CH$_3$CN or [Au](OH) is obviously key to this discrepancy. The increased conversion with **C5** in comparison to **C4** raises the possibility of a slight counteranion effect in the lactonization step.

Table 12.2 Additional catalyst screening.



Entry	Catalyst	$C_{Carbene}$ (ppm)	$H_{Imidazole}$ (ppm)	2[b]	3[b]
1	[(IPr)Au(NTf$_2$)] (**C2**)	168.9	7.33	45	55
2	[(IPr)Au(CH$_3$CN)][BF$_4$] (**C3**)	166.3	7.38	90	10
3	[{(IPr)Au}$_2$(μ-OH)][BF$_4$] (**C4**)	162.6	7.26	95	5
4	[{(IPr)Au}$_2$(μ-OH)][NTf$_2$] (**C5**)	162.9	7.25	83	17

[a] Reaction time was 3 hours and no sign of **1** remained. [b] Values are in %; Conversions were determined by ^{1}H NMR.

Apart from the catalyst screening, no further alterations to the catalytic systems were made since the reaction occurs at room temperature and *in situ*, since MeOH acts as a nucleophile in excess.

12.1.2 Substrate scope

12.1.2.1 Secondary propargylic alcohols

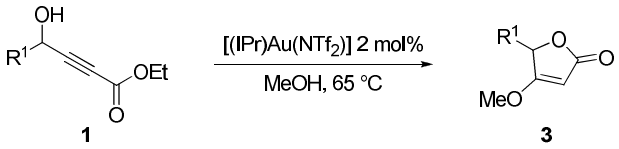
Next, **C2** was tested in a substrate screening in order to evaluate the scope of the catalytic system. In order to facilitate analysis and shorten reaction times, the operational reaction temperature was raised to 65 °C and a standard reaction time of 2 hours was used. As illustrated in **Table 12.3**, the catalytic system tolerated a broad spectrum of substrates and good to excellent yields were obtained. Both mesityl and napthyl substituents on the propargylic alcohol allowed for conversion into their corresponding furanones **3b** and **3c** (entries 2-3) as well as a series of substituted phenyls bearing either electronic-withdrawing or electron-donating functional groups in *para*-position (entries 4-7). It should be noted that in some cases the reaction time had to be prolonged to 12 hours in order to provide complete conversion of the methoxylated intermediates. In the case of the electron-donating *para*-phenoxy substituted propargylic alcohol a 57% yield of **3d** could be obtained after 2 hours reaction time. Its electron-withdrawing nitro substituted congener showed 55% NMR-conversion after 2 hours and the furanone **3e** was obtained in 68% yield after12 hours heating. In the same manner, the halogenated substrates required prolonged reaction times (entries 6-7). Encouraged by the initial results, both furan- and thiophene-derivatives were prepared and tested in catalysis. The yields of their corresponding furanones **3h** and **3i** after the standard 2 hours reaction time were 65 and 51%, respectively (entries 8-9).

The scope was then expanded to a series of aliphatic substituents. While *iso*-butyl and *tert*-butyl substituted propargylic alcohols converted in good yields into their corresponding furanones **3k** and **3l** (entries 11-12), surprisingly 4-cyclohexyl-4-hydroxybut-2-ynoate remained idle at the intermediate stage, even after heating for 12 hours (entry 13).

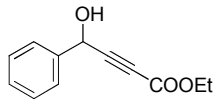
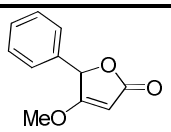
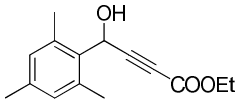
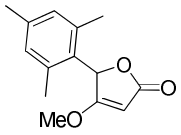
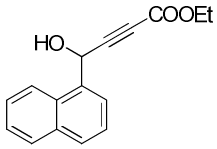
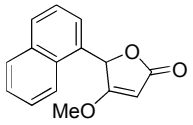
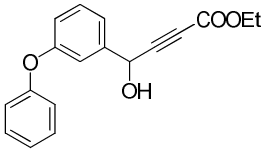
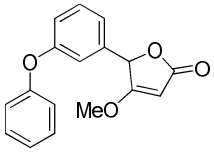
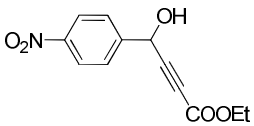
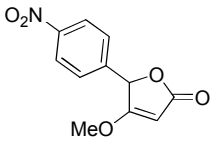
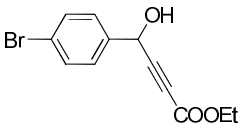
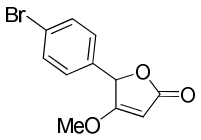
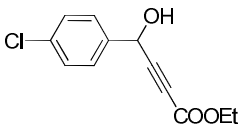
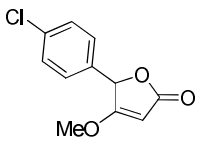
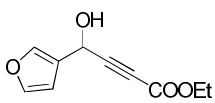
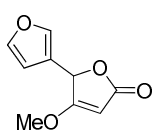
12.1.2.2 Tertiary propargylic alcohols

After evaluation of the scope for secondary alcohols, a series of tertiary alcohols was tested under similar reaction conditions (**Table 12.4**) with a 12 hours reaction time. In an initial attempt, the acyclic tertiary propargylic alcohol did convert (entry 1) and delightfully, 75% percent of the expected furanone **3n** was obtained.

Table 12.3 Scope of the Au(I)-catalyzed methoxylation/lactonization with secondary propargylic alcohols.[a]

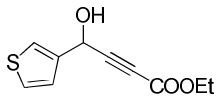
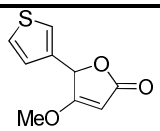
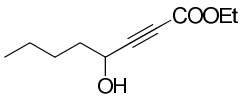
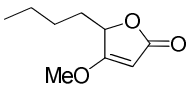
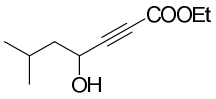
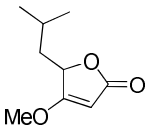
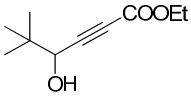
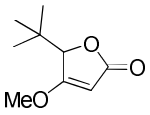
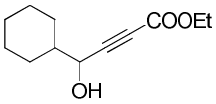
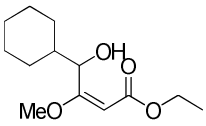


1 3

Entry	Propargylic Alcohol	1	Product	3	Yield (%)
1		**1a**		**3a**	71
2		**1b**		**3b**	43
3		**1c**		**3c**	95[b]
4		**1d**		**3d**	57
5		**1e**		**3e**	68[b]
6		**1f**		**3f**	68
7		**1g**		**3g**	87[b]
8		**1h**		**3h**	65

[a] 100 mg substrate, [(IPr)Au(NTf_2] (2 mol%), MeOH (2 mL), 12 hours at 65 °C. [b] Reaction time was prolonged to 12 hours.

Table 12.3 Scope of the Au(I)-catalyzed methoxylation/lactonization with secondary propargylic alcohols. (continued)

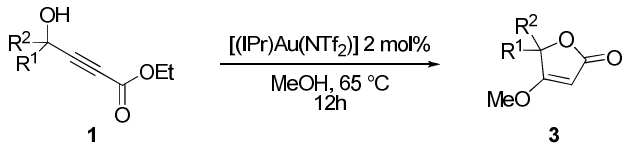
9		**1i**		**3i**	51
10		**1j**		**3j**	82
11		**1k**		**3k**	71
12		**1l**		**3l**	76
13		**1m**		**3m**	64[b]

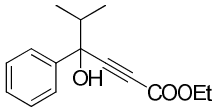
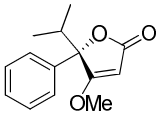
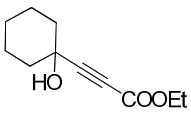
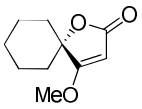
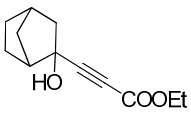
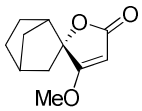
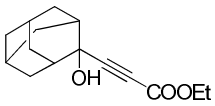
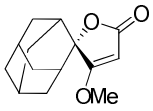
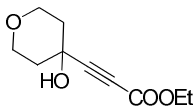
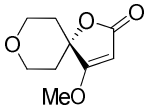
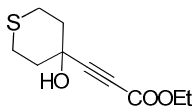
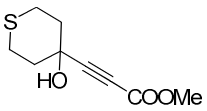
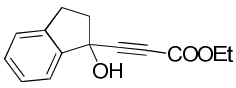
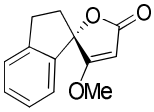
[a] 100 mg substrate, [(IPr)Au(NTf_2] (2 mol%), MeOH (2 mL), 2 hours at 65 °C. [b] Reaction time was prolonged to 12 hours.

Cyclic substrates were next considered as they would allow for rather interesting spiro compounds. As shown in **Table 12.4**, good to excellent yields were observed for these tertiary alcohols. Beginning with a cyclohexyl substituted propargylic alcohol (entry 2), which resulted in an pleasing 75% yield. This scope was extended to the bicyclic norbonane derivative yielding excellent 92% of **3p** followed by the adamantyl substituted which afforded 61% of **3q** (entries 3-4).

In a logical extension, heterocyclic substrates were tested and revealed an interesting and surprising anomaly. While the tetrahydropyran derivative converted, as expected, into the cyclized spiro-derivative in excellent 97% yield (entry 5), the tetrahydrothiopyran derivative reacted differently. While the propargylic alcohol did not react at all, a transesterification of the ester moiety was observed and the methoxyester was isolated in 69% yield (entry 6). It remains unclear how sulfur, which is most likely responsible, is interacting with the catalytic system to cause such a radical change in reactivity compared to its cyclohexyl and tetrahydropyran analogues.

Table 12.4 Scope of the Au(I)-catalyzed methoxylation/ lactonization of tertiary propargylic alcohols.[a]



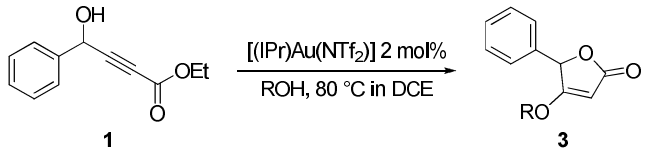
Entry	Propargylic Alcohol	1	Product	3	Yield (%)
1		**1n**		**3n**	75
2		**1o**		**3o**	82
3		**1p**		**3p**	92
4		**1q**		**3q**	61
5		**1r**		**3r**	97
6		**1s**		**3s**	69
7		**1t**		**3t**	53

[a] 100 mg substrate, [(IPr)Au(NTf$_2$] (2 mol%), MeOH (2 mL), 12 hours at 65 °C.

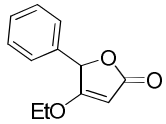
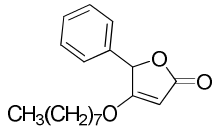
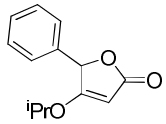
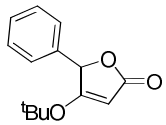
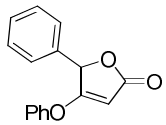
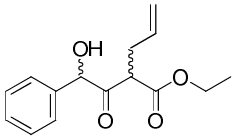
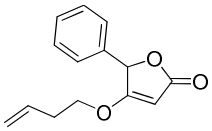
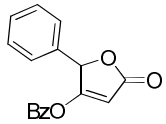
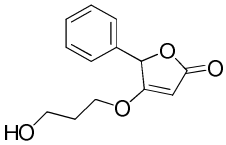
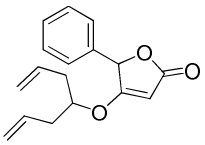
12.1.2.3 Alcohol variation

Apart from the study of substrate scope of the present catalytic system, the tolerance for different alcohols also appeared to be of major interest since earlier reports were limited to the addition of MeOH to the alkyne moiety. Therefore, a series of alcohols was tested (**Table 12.5**). Taking into account the higher steric demands of most alcohols investigated, the standard reaction temperature was increased to 80 °C.

Table 12.5 Reaction of **1a** with various alcohols.[a]



1 **3**

Entry	Alcohol	Product	3	Yield (%)
1[b]	EtOH		**3u**	67
2	Octanol		**3v**	54
3[b]	^{i}PrOH		**3w**	48
4	^{t}BuOH		**3x**	nr[c]
5	PhOH		**3y**	nr[c]
6	Allylalcohol		**3z**	33
7	3-Buten-1-ol		**3aa**	51
8	Benzylalcohol		**3ab**	58
9	Propandiol		**3ac**	65
10	1,6-Heptadien-4-ol		**3ad**	23

[a] **1** (100 mg, 0.5 mmol), ROH (1.1 equiv.), [(IPr)Au(NTf$_2$] (8.5 mg, 2 mol%), DCE (2 mL), 6 hours at 80 °C. [b] neat reaction [c] nr = no reaction

Moreover, in order to ensure an easy workup, the reactions were performed either in neat conditions for alcohols such as ethanol and isopropanol or in 1,2-dichloroethane for e.g. octanol, depending on the actual boiling point, availability and toxicity of the alcohol selected.

In comparison to methanol, primary alkyl alcohols like ethanol (entry 1) as well as octanol (entry 2) allowed for slightly diminished but still acceptable yields of 67% for **3u** and 54% for **3v**. Moreover, a moderate yield of 48% for **3w** was also obtained using isopropanol (entry 3) representing an example of a secondary alcohol being compatible with the methodology. As expected, reactions with *tert*-butanol and phenol (entries 4-5) failed due to their steric and electronic properties.[178b, 239]

Next, a reaction with allyl alcohol was envisioned (entry 6). The reasoning for this test was to allow for a Claisen rearrangement following the alkoxylation/lactonisation step yielding the interesting 5-phenyl-3-vinylfuran-2,4(*3H,5H*)-dione.[240] Unfortunately, under the given reaction conditions the Claisen rearrangement proceeded prior to lactonization yielding 33% of **3z** (entry 6). This reactivity pattern is attributed to a significant decrease of the activation barrier for the Claisen rearrangement by gold. The reaction usually requires heating to over 100 °C to proceed.

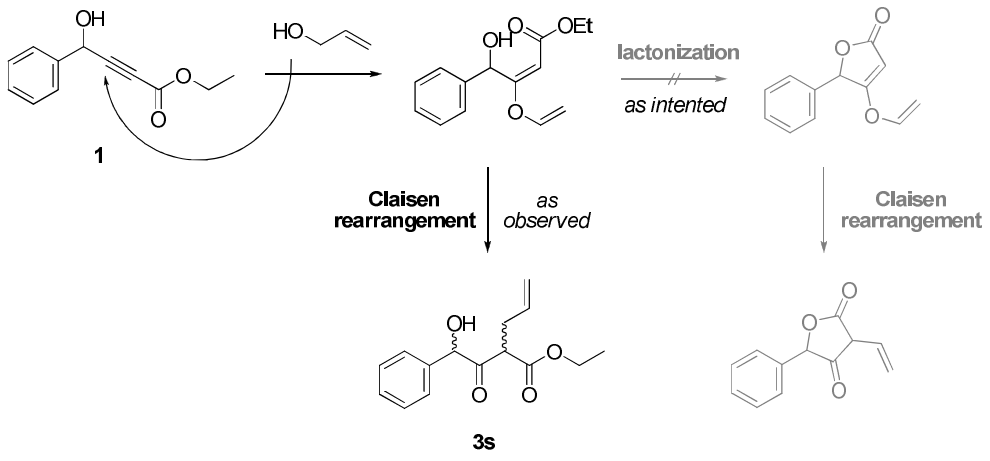


Figure 12.1 Reaction of **1** with allyl alcohol. The Claisen rearrangement occurs prior to the envisioned lactonization.

However, changing to homoallyl alcohol the regular alkoxylated furanone **3aa** was obtained in 51% (entry 7). Moving to benzylalcohol, 58% of **3ab** could be obtained (entry 8). Proceeding to a functionalized secondary alcohol was realized using 1,6-heptadien-4-ol. The yield of **3ad** was however notably diminished to 23% (entry 10) in comparison to **3aa**. To conclude, 1,3 propanediol was subjected to catalysis and 65% of the corresponding **3ac** was isolated (entry 9).

12.1.3 Mechanistic considerations

In terms of mechanism, the proposal is straightforward (**Scheme 12.4**). Due to the observation of the key intermediate **2**, evaluation of the *E/Z* configuration was most important in order to distinguish between an *E/Z* isomerization of **2** allowing for full conversions or alternatively an initial *E*-selectivity of the gold-catalyzed alkoxylation. Therefore, catalyst **C4** was used to obtain **2** selectively followed by analysis using a NOE (Nuclear Overhauser Effect) experiment.

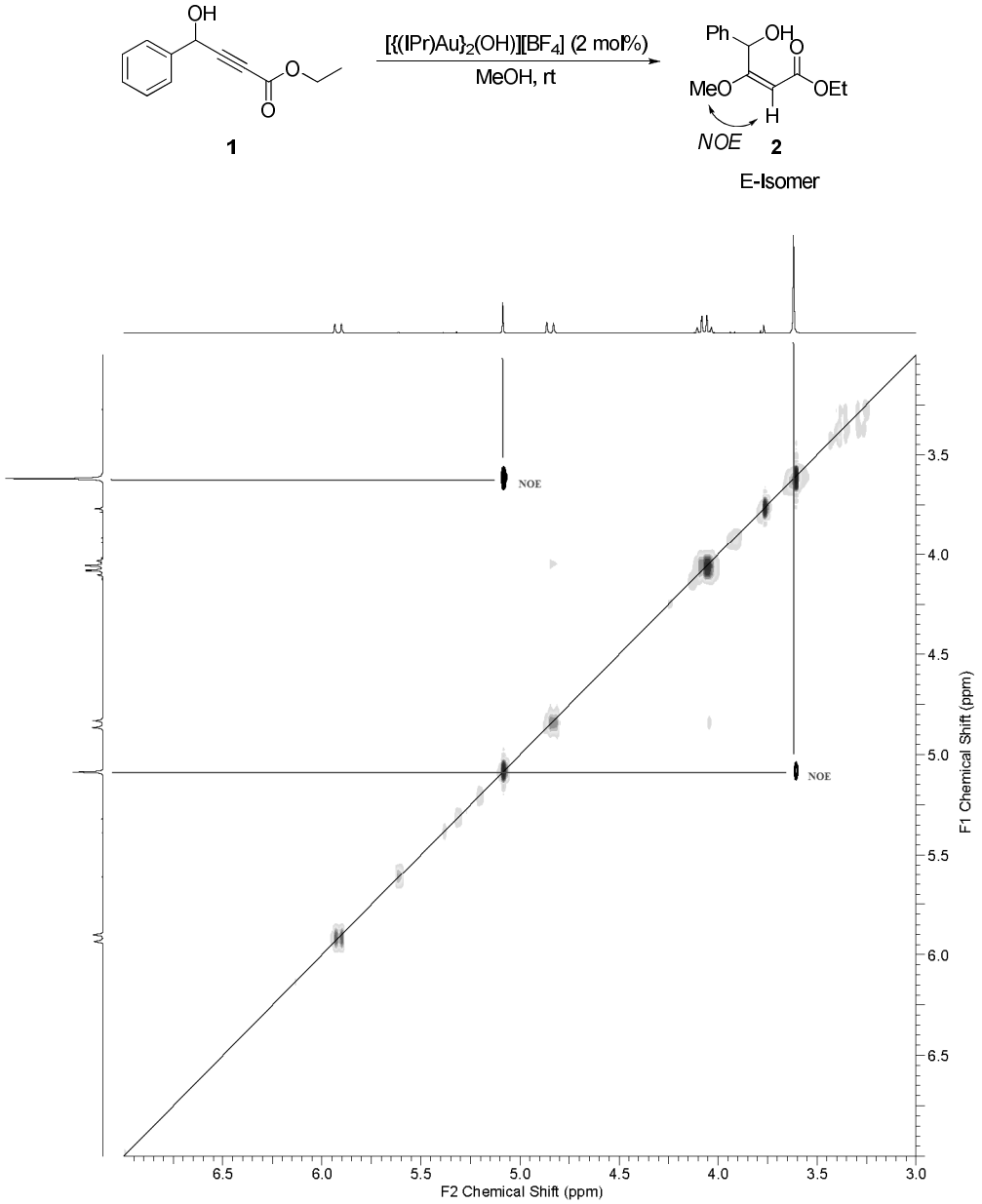
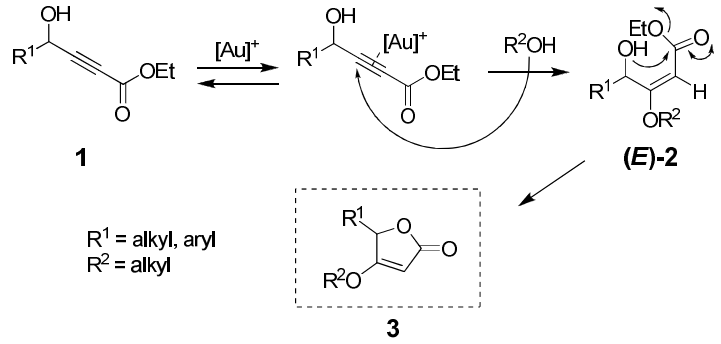


Figure 12.2 Illustration of the NOESY-NMR obtained for intermediate **3**.

The NOESY-NMR obtained (**Figure 12.2**) exclusively showed close contact between the methyl vinyl ether and the vinyl proton supporting a selective formation of the *E*-isomer which directly allows lactonization. As a consequence of these NOE experimental results, the initially envisioned isomerization of (possibly formed) *Z*-isomers has no need to be invoked.[174]



Scheme 12.4 Plausible mechanism for the gold catalyzed furanone formation.

12.2 Conclusion

In conclusion, an efficient catalytic system for the synthesis of alkoxylated furanones has been developed. With respect to the lactonization step, [(IPr)Au(NTf_2)] proved more efficient than dinuclear gold or gold-nitrile complexes. The catalyst and method permit, in some instances, for the potentially useful exclusive alkoxylation without following lactonization. The new catalytic system tolerates numerous propargylic alcohols, both secondary and tertiary with various primary and secondary alcohols allowing for the assembly of a significant variety of furanones.

12.3 Experimental Section

Unless otherwise stated, manipulations were performed under ambient atmosphere. Solvents were of *puriss.* grade and used as received. NMR spectra were recorded on 400 MHz and 300 MHz spectrometers at ambient temperature in $CDCl_3$. Chemical shifts are given in parts per million (ppm) with respect to TMS. Parts of the experimental work has been realized by C. Pottier under supervision of the author.

Synthesis of propargylic alcohols:

Procedure A: Ethyl propiolate (1.1 equiv., 0.56 mL, 5.5 mmol) was dissolved in THF (0.2 M, 25 mL) at -78°C. *n*-BuLi (1.6 M, 1.1 equiv., 3.4 mL, 5.5 mmol) was added slowly to the solution and the mixture was stirred for 25 min. Then the aldehyde/ketone (1 equiv., 5 mmol) was added dropwise, and the resulting solution was stirred for 1 hour at -78°C. The reaction was first quenched with aq. NH_4Cl and then allowed to warm to room temperature (with ketones the reaction mixture was allowed to warm to room temperature before quenching). The reaction mixture was diluted with ethyl acetate and the layers were separated. The aqueous layer was extracted three times with ethyl acetate, and the combined organic phase was washed with brine, dried over magnesium sulfate, filtered and concentrated to dryness. The crude product was purified by column chromatography (gradient of EtOAc:pentane).

Procedure B: $ZnBr_2$ (208 mg, 0.92 mmol) was dried by heating in a flask under vacuum for 30 min. The flask was then flushed with nitrogen and charged with anhydrous Et_2O (20 mL). Ethyl propiolate (1 equiv., 0.42 mL, 4 mmol), diisopropylethylamine (2 equiv., 1.4 mL, 8 mmol), aldehyde (2 equiv., 8 mmol) and TMSOTf (1.2 equiv., 0.9 mL, 4.78 mmol) were added sequentially. The solution was stirred for 1h and passed through a filter of Celite using ethyl acetate to wash afterwards. The mixture was concentrated *in vacuo*, and then dissolved in THF (15 mL). The solution was stirred with HCl_{aq} (6 mL) for 15 min, then diluted in Et_2O and washed with water and saturated $NaHCO_3$. The organic layer was diluted with pentane (1:2 pentane/Et_2O), dried over anhydrous magnesium sulphate, filtered and evaporated. If necessary, the crude product was purified by flash chromatography (gradient of EtOAc:pentane).

Procedure C: Preparation of silver acetylide**:** $AgNO_3$ (1 equiv., 3.4 g, 20 mmol) was dissolved in a solution of 40 mL of water and 80 mL of MeOH. NH_4OH was added until the initially formed brown precipitate dissolved to give a colourless solution, followed by an additional 5 mL. Ethyl propiolate in 5 mL of MeOH was added dropwise at room temperature. The mixture was stirred for 30 min and then extracted with CH_2Cl_2. The solution was reduced *in vacuo*. Pentane was added resulting in the

precipitation of a brown solid. The residue was then filtered and washed with pentane (3.57 g, 83%).

Silver acetylide (1.6 equiv., 0.96 mg, 3.2 mmol) and Cp_2ZrCl_2 (1.2 equiv., 0.70 g, 2.4 mmol) were added to a solution of an aldehyde (1equiv., 2 mmol) in anhydrous CH_2Cl_2 (7 mL) under a nitrogen atmosphere at room temperature. Silver trifluoromethanesulfonate (0.2 aq., 104 mg, 0.4 mmol) was added to the reaction mixture and stirred for 5 hours. The reaction mixture was quenched by addition of saturated $NaHCO_3$ (1 mL) and stirred for 5 min. The resulting reaction mixture was filtered through a pad of celite and concentrated in vacuo. The resulting residue was purified by column chromatography.

Synthesis of ethyl 4-hydroxy-4-phenylbut-2-ynoate ***1a***. Following procedure A, 64% of a pale yellow oil was obtained. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59-7.47 (m, 2H), 7.45-7.32 (m, 3H), 5.53 (s, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.46 (br. s, 1H), 1.29 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.6, 138.6, 128.9, 128.9, 126.8, 86.5, 77.8, 64.2, 62.4, 14.0.[164]

Synthesis of ethyl 4-hydroxy-4-mesitylbut-2-ynoate ***1b***. Following procedure A, 29% of a yellow oil was obtained. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.86 (s, 2H), 6.00 (d, *J* = 4.1 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 2.48 (s, 6H), 2.26 (s, 3H), 2.09 (d, *J* = 4.1 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.6, 138.2, 136.7, 131.7, 129.9, 86.9, 76.9, 62.1, 59.5, 20.8, 20.1, 13.9. HRMS for $C_{15}H_{18}O_3Na$ (calc): 269.1148 (269.1154).

Synthesis of ethyl 4-hydroxy-4-(naphthalen-1-yl)but-2-ynoate ***1c***. Following procedure B, 91% of a yellow oil was obtained. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, *J* = 8.4 Hz, 1H), 7.94-7.82 (m, 2H), 7.80 (d, *J* = 7.0 Hz, 1H), 7.63-7.43 (m, 3H), 6.22 (d, *J* = 5.0 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 2.68 (d, *J* = 5.9 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.6, 134.0, 133.8, 130.4, 129.9, 128.9, 126.8, 126.2, 125.3, 125.1, 123.7, 86.2, 78.5, 62.6, 62.4, 14.0. HRMS for $C_{16}H_{14}O_3Na$ (calc): 277.0842 (277.0841).

Synthesis of ethyl 4-hydroxy-4-(4-phenoxyphenyl)but-2-ynoate ***1d***. Following procedure A, 36% of a yellow oil was obtained. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.30 (m, 3H), 7.28-7.23 (m, 1H), 7.20-7.09 (m, 2H), 7.06-6.95 (m, 3H), 5.54 (d, *J* = 6.3 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 2.42 (d, *J* = 6.3 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.9, 156.8, 153.4, 140.6, 130.3, 130.0, 123.7, 121.4, 119.3, 119.0, 117.0, 85.9, 78.0, 64.0, 62.4, 14.1. HRMS for $C_{18}H_{16}O_4Na$ (calc): 319.0953 (319.0946).

Synthesis of ethyl 4-hydroxy-4-(4-nitrophenyl)but-2-ynoate ***1e***. Following procedure C, 67% of an orange oil was obtained. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.32-8.06 (m, 2H), 7.75-7.65 (m, 2H), 5.69 (s, 1H), 4.24 (q, *J* = 7.2 Hz, 2H), 3.68 (br. s., 1H), 1.29 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.3, 148.1, 145.4, 127.5, 124.1, 84.9, 78.5, 63.2, 62.8, 14.0. HRMS for $C_{12}H_{10}NO_5$ (calc): 248.0554 (248.0559).

Synthesis of ethyl 4-(4-bromophenyl)-4-hydroxybut-2-ynoate ***1f***. Following procedure B, 61% of an orange oil was obtained. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 5.53 (br. d, *J* = 3.2 Hz, 1H), 4.82 (br. d, *J* = 3.8 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.4, 137.4, 131.5, 128.2, 122.5, 86.1, 77.4, 62.9, 62.4, 13.7. HRMS for $C_{12}H_{11}O_3Na^{79}Br$ (calc): 304.9796 (304.9789).

Synthesis of ethyl 4-(4-chlorophenyl)-4-hydroxybut-2-ynoate ***1g***. Following procedure B, 38% of a yellow oil was obtained. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52-7.41 (m, 2H), 7.43-7.31 (m, 2H), 5.53 (s, 1H), 4.56 (s, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.5, 137.0, 134.4, 128.8, 128.0, 86.2, 77.6, 63.1, 62.5, 13.8. HRMS for $C_{12}H_{11}O_3NaCl$ (calc): 261.0300 (261.0294).

Synthesis of ethyl 4-(furan-3-yl)-4-hydroxybut-2-ynoate ***1h***. Following procedure A, 60% of a brown oil was obtained. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57 (td, *J* = 0.9, 1.6 Hz, 1H), 7.42 (t, *J* = 1.6 Hz, 1H), 6.52 (dd, *J* = 0.7, 1.9 Hz, 1H), 5.52 (d, *J* = 6.9 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 2.33 (d, *J* = 6.9 Hz, 1H), 1.32 (t, *J* = 7.1 Hz, 3H). ^{13}C

NMR (101 MHz, $CDCl_3$): δ 153.5, 143.9, 140.5, 124.6, 109.1, 85.9, 76.4, 62.4, 56.9, 14.0. HRMS for $C_{10}H_{10}O_4Na$ (calc): 217.0474 (217.0477).

Synthesis of ethyl 4-hydroxy-4-(thiophen-3-yl)but-2-ynoate ***1i***. Following procedure A, 26% of a brown oil was obtained. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48-7.41 (m, 1H), 7.35 (dd, *J* = 2.9, 5.0 Hz, 1H), 7.20 (dd, *J* = 1.2, 5.0 Hz, 1H), 5.62 (d, *J* = 6.8 Hz, 1H), 4.26 (q, *J* = 7.2 Hz, 2H), 2.40 (d, *J* = 6.8 Hz, 1H), 1.32 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.5, 139.8, 127.1, 126.2, 123.5, 85.9, 77.3, 62.5, 60.4, 14.1. HRMS for $C_{10}H_{14}O_3NS$ (calc): 228.0683 (228.0689)

Synthesis of ethyl 4-hydroxyoct-2-ynoate ***1j***. Following procedure A, 27% of a pale yellow oil was obtained. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.43 (t, *J* = 6.7 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.38 (br. s., 1H), 1.80-1.63 (m, 2H), 1.45-1.18 (m, 7H), 0.90-0.81 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.7, 88.5, 76.2, 62.2, 61.8, 36.5, 27.0, 22.2, 13.9, 13.8. HRMS for $C_{10}H_{20}O_3N$ (calc): 202.1436 (202.1438).

Synthesis of ethyl 4-hydroxy-6-methylhept-2-ynoate ***1k***. Following procedure B, 41% of a yellow oil was obtained. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.49-4.35 (m, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.93 (d, *J* = 5.2 Hz, 1H), 1.86-1.66 (m, 1H), 1.65-1.33 (m, 2H), 1.18 (t, *J* = 7.1 Hz, 3H), 0.83 (d, *J* = 2.5 Hz, 3H), 0.81 (d, *J* = 2.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.7, 88.6, 75.9, 62.0, 60.1, 45.5, 24.3, 22.3, 22.1, 13.8. HRMS for $C_{10}H_{16}O_3Na$ (calc): 207.0992 (207.0997).

Synthesis of ethyl 4-hydroxy-5,5-dimethylhex-2-ynoate ***1l***. Following procedure A, 7% of a pale yellow oil was obtained. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.23 (q, *J* = 7.1 Hz, 2H), 4.13 (d, *J* = 6.2 Hz, 1H), 2.03 (d, *J* = 6.2 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.01 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.6, 87.0, 77.7, 71.1, 62.3, 36.2, 25.4, 14.1.[164]

Synthesis of ethyl 4-cyclohexyl-4-hydroxybut-2-ynoate ***1m***. Following procedure A, 37% of a pale orange oil was obtained. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.29-4.19 (m, 3H), 1.96 (d, *J* = 5.6 Hz, 1H), 1.90-1.06 (m, 14H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.5, 87.1, 67.1, 62.3, 43.8, 28.5, 28.3, 26.3, 25.9, 14.2.[164]

Synthesis of ethyl 4-hydroxy-5-methyl-4-phenylhex-2-ynoate ***1n***. Following procedure A, 56% of a colourless oil was obtained. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63-7.49 (m, 2H), 7.45-7.28 (m, 3H), 4.26 (q, *J* = 7.2 Hz, 2H), 2.59 (s, 1H), 2.16 (spt, *J* = 6.8 Hz, 1H), 1.32 (t, *J* = 7.2 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.6, 142.2, 128.3, 128.2, 126.0, 88.2, 78.5, 62.3, 40.4, 17.9, 17.3, 14.2. HRMS for $C_{15}H_{18}O_3Na$ (calc): 269.1157 (269.1154).

Synthesis of ethyl 3-(1-hydroxycyclohexyl)propiolate ***1o***. Following procedure A, 43% of an orange oil was obtained. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.23 (q, *J* = 7.2 Hz, 2H), 2.17 (s, 1H), 1.94 (m., 2H), 1.80-1.46 (m, 8H), 1.31 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.8, 90.5, 76.2, 68.6, 62.2, 39.2, 25.0, 22.9, 14.1. HRMS for $C_{11}H_{16}NaO_3$ (calc): 219.0989 (219.0997).

Synthesis of ethyl 3-(2-hydroxybicyclo[2.2.1]heptan-2-yl)propiolate ***1p***. Following procedure A, 40% of a pale yellow oil was obtained. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.21 (q, *J* = 7.2 Hz, 2H), 2.45 (br. s., 2H), 2.29-2.10 (m, 2H), 2.04-1.89 (m, 1H), 1.85-1.71 (m, 1H), 1.65-1.49 (m, 1H), 1.46-1.33 (m, 4H), 1.29 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.0, 92.2, 75.2, 73.3, 62.2, 49.3, 47.2, 39.0, 36.9, 28.7, 21.0, 14.1. HRMS for $C_{12}H_{16}O_3Na$ (calc): 231.1003 (231.0997).

Synthesis of ethyl 3-(2-hydroxyadamantan-2-yl)prop-2-ynoate ***1q***. Following procedure A, 52% of a pale yellow oil was obtained. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.23 (q, *J* = 7.2 Hz, 2H), 2.27-1.96 (m, 7H), 1.91-1.65 (m, 6H), 1.62-1.51 (m, 2H), 1.31 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.9, 91.2, 76.9, 72.6, 62.2, 38.3, 37.4, 35.3, 31.4, 26.7, 26.7, 14.1. HRMS for $C_{15}H_{20}O_3Na$ (calc): 271.1299 (271.1310).

Synthesis of ethyl 3-(4-hydroxytetrahydro-2H-pyran-4-yl)propiolate ***1r***. Following procedure A, 52% of a colourless oil was obtained. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.22 (q, *J* = 7.1 Hz, 2H), 3.96-3.79 (m, 2H), 3.71-3.59 (m, 2H), 3.21 (br. d, *J* = 15.4 Hz, 1H), 2.10-1.94 (m, 2H), 1.89-1.63 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.5, 88.9, 76.5, 65.5, 64.3, 62.4, 39.0, 14.1. HRMS for $C_{10}H_{14}O_4Na$ (calc): 221.0789 (221.0790).

Synthesis of ethyl 3-(4-hydroxytetrahydro-2H-thiopyran-4-yl)propiolate ***1s***. Following procedure A, 55% of a pale yellow oil was obtained. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.20 (q, *J* = 7.2 Hz, 2H), 3.28 (br. s., 1H), 2.79-2.58 (m, 4H), 2.26-2.14 (m, 2H), 2.03-1.83 (m, 2H), 1.27 (t, *J* = 7.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.5, 88.8, 77.2, 67.3, 62.4, 39.6, 25.3, 14.0. HRMS for $C_{10}H_{14}O_3NaS$ (calc): 237.0570 (237.0561).

Synthesis of ethyl 3-(1-hydroxy-2,3-dihydro-1H-inden-1-yl)propiolate ***1t***. Following procedure A, 40% of a yellow oil was obtained. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60-7.53 (m, 1H), 7.40-7.27 (m, 3H), 4.27 (q, *J* = 7.2 Hz, 2H), 3.26-3.09 (m, 1H), 3.06-2.92 (m, 1H), 2.77 (s, 1H), 2.73-2.60 (m, 1H), 2.56-2.44 (m, 1H), 1.34 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.7, 144.1, 143.3, 129.6, 127.4, 125.3, 123.5, 88.4, 76.6, 76.1, 62.3, 42.7, 29.7, 14.1. HRMS for $C_{14}H_{14}O_3Na$ (calc): 253.0844 (253.0841).

General procedures for lactonization/alkoxylation:

Procedure A: In a vial, [(IPr)Au(NTf_2)] (2 mol%) was added to a solution of the corresponding propargylic alcohol (100 mg, 1 equiv.) in MeOH (2 ml). The solution was stirred for 2 hours at 65 °C and the resulting mixture was concentrated at reduced pressure. The crude product was purified by flash column chromatography using a gradient of pentane/ethyl acetate.

Procedure B: Analogue to procedure A, but with 12 hours heating.

Procedure C: In a vial, [(IPr)Au(NTf_2)] (8.5 mg, 2 mol%) was added to a solution of **1a** (100 mg, 0.5 mmol) and the corresponding alcohol (1.1 equiv.) in DCE (2 ml). The solution was stirred 6 hours at 80 °C and the resulting mixture was concentrated at reduced pressure. The crude product was purified by flash column chromatography using a gradient of pentane/ethyl acetate.

Synthesis of 4-methoxy-5-phenylfuran-2 (5H)-one **3a**. Following procedure A, 71% of a white solid was obtained. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.38 (m, 3H), 7.34-7.27 (m, 2H), 5.69 (s, 1H), 5.16 (s, 1H), 3.85 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ

181.7, 172.6, 134.1, 129.5, 129.0, 126.8, 88.3, 80.4, 59.8. HRMS for $C_{11}H_{11}O_3$ (calc): 191.0702 (191.0703).

Synthesis of 5-mesityl-4-methoxyfuran-2(5H)-one **3b**. Following procedure A, 43% of an off-white was obtained. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.85 (br. s., 2H), 6.20 (d, *J* = 1.2 Hz, 1H), 5.25 (d, *J* = 1.2 Hz, 1H), 3.86 (s, 3H), 2.50-2.10 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.7, 172.9, 139.2, 138.2, 131.2, 129.7, 125.8, 89.7, 77.8, 59.8, 21.0. HRMS for $C_{14}H_{17}O_3$ (calc): 233.1164 (233.1172).

Synthesis of 4-methoxy-5-(naphthalen-1-yl)furan-2(5H)-one **3c**. Following procedure B, 95% of a pale yellow oil was obtained. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.11 (d, *J* = 7.7 Hz, 1H), 8.01-7.89 (m, 2H), 7.70-7.45 (m, 4H), 6.57 (s, 1H), 5.33 (d, *J* = 1.0 Hz, 1H), 3.87 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 182.3, 172.8, 133.8, 131.4, 130.0, 129.8, 128.9, 126.8, 126.1, 125.3, 124.4, 123.0, 88.9, 77.2, 59.8. HRMS for $C_{15}H_{12}O_3Na$ (calc): 263.0682 (263.0684).

Synthesis of 4-methoxy-5-(3-phenoxyphenyl)furan-2(5H)-one **3d** Following procedure A, 57% of a colourless oil was obtained. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.30 (m, 3H), 7.13-6.95 (m, 6H), 5.63 (s, 1H), 5.13 (d, *J* = 0.8 Hz, 1H), 3.83 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.4, 172.4, 157.8, 156.8, 136.0, 130.3, 130.0, 123.8, 121.3, 119.5, 119.2, 117.2, 88.4, 79.9, 59.8. HRMS for $C_{17}H_{15}O_4$ (calc): 283.0958 (283.0965).

Synthesis of 5-(4-nitrophenyl)-4-methoxyfuran-2(5H)-one **3e**. Following procedure B, 68% of a pale orange solid was obtained. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.34-8.12 (m, 2H), 7.64-7.43 (m, 2H), 5.78 (s, 1H), 5.18 (d, *J* = 1.2 Hz, 1H), 3.87 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.7, 171.8, 148.5, 141.2, 127.4, 124.0, 88.3, 78.7, 60.1. HRMS for $C_{11}H_{10}O_5N$ (calc): 236.0546 (236.0553).

Synthesis of 5-(4-bromophenyl)-4-methoxyfuran-2(5H)-one **3f**. Following procedure B, 68% of a white solid was obtained. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52-7.49 (m, 2H), 7.20-7.17 (m, 2H), 5.63 (s, 1H), 5.15 (d, *J* = 1.0 Hz, 1H), 3.84 (s, 1H). ^{13}C NMR

(101 MHz, $CDCl_3$): δ 181.3, 172.3, 133.2, 132.1, 128.3, 123.6, 88.3, 79.5, 59.9. HRMS for $C_{11}H_9O_3Na^{79}Br$ (calc): 290.9632 (290.9633).

Synthesis of 5-(4-chlorophenyl)-4-methoxyfuran-2(5H)-one **3g**. Following procedure B, 87% of a white solid was obtained. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44-7.31 (m, 2H), 7.33-7.30 (m, 2H), 5.72 (s, 1H), 5.22 (d, *J* = 1.0 Hz, 1H), 3.91 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.3, 172.3, 135.3, 132.6, 129.1, 128.0, 88.2, 79.4, 59.9. HRMS for $C_{11}H_9O_3NaCl$ (calc): 247.0136 (247.0138).

Synthesis of 4-methoxy-5-(furan-3-yl)furan-2(5H)-one **3h**. Following procedure A, 65% of a yellow oil was obtained. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53-7.49 (m, 1H), 7.41 (t, *J* = 1.7 Hz, 1H), 6.34 (dd, *J* = 1.7, 0.6 Hz, 1H), 5.69 (s, 1H), 5.15 (d, *J* = 1.0 Hz, 1H), 3.89 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 181.0, 172.2, 144.0, 141.2, 119.6, 108.2, 88.6, 73.6, 59.8. HRMS for $C_9H_8O_4Na$ (calc): 203.0317 (203.0320).

Synthesis of 4-methoxy-5-(thiophen-3-yl)furan-2(5H)-one **3i**. Following the procedure A, 51% of an orange solid was obtained. ^{1}H NMR ($CDCl_3$, 300 MHz,): δ 7.36-7.31 (m, 2H), 7.02 (dd, *J* = 5.0, 1.4 Hz, 1H), 5.78 (s, 1H), 5.14 (d, *J* =1.0 Hz, 1H), 3.87 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz,): δ 181.2, 172.3, 134.8, 126.9, 125.3, 124.1, 88.4, 76.6, 59.8. HRMS for $C_9H_8O_3NaS$ (calc): 219.0086 (219.0092).

Synthesis of 5-butyl-4-methoxyfuran-2(5H)-one **3j**. Following procedure A, 82% of a white solid was obtained. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.10 (d, *J* = 0.8 Hz, 1H), 4.79 (qd, *J* = 3.7, 0.4 Hz, 1H), 3.93 (s, 3H), 1.96-1.89 (m, 1H), 1.67-1.60 (m, 1H), 1.44-1.29 (m, 4H), 0.94 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 182.6, 172.8, 88.6, 78.9, 59.4, 31.4, 26.3, 22.3, 13.8. HRMS for $C_9H_{14}O_3Na$ (calc): 193.0845 (193.0841).

Synthesis of 5-isobutyl-4-methoxyfuran-2(5H)-one **3k**. Following procedure A, 71% of a colourless oil was obtained. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.00 (d, *J* = 0.9 Hz, 1H), 4.73 (ddd, *J* = 9.8, 3.2, 0.7 Hz, 1H), 3.84 (s, 3H), 1.91-1.84 (m, 1H), 1.67-1.58 (m, 1H), 1.48-1.38 (m, 1H), 0.93 (d, *J* = 3.1 Hz, 3H), 0.91 (d, *J* = 3.1 Hz, 3H). ^{13}C NMR (75

MHz, $CDCl_3$): δ 183.2, 172.8, 88.2, 77.7, 59.4, 41.2, 24.9, 23.2, 21.8. HRMS for $C_9H_{14}O_3Na$ (calc): 193.0841 (193.0841).

Synthesis of 5-(tert-butyl)-4-methoxyfuran-2(5H)-one **3l**. Following procedure A, 76% of a white solid was obtained. ^1H NMR ($CDCl_3$, 300 MHz): δ 5.08 (d, J = 0.9 Hz, 1H), 4.42 (d, J = 0.9 Hz, 1H), 3.85 (s, 3H), 0.99 (s, 9H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 182.3, 172.8, 90.0, 86.1, 59.4, 34.9, 25.4. HRMS for $C_9H_{14}O_3Na$ (calc): 193.0847 (193.0841).

Synthesis of 5-(E)-ethyl 4-cyclohexyl-4-hydroxy-3-methoxybut-2-enoate **3m**. Following procedure B, 64% of a colourless oil was obtained. ^1H NMR (400 MHz, $CDCl_3$): δ 5.24 (s, 1H), 4.14 (q, J = 7.1 Hz, 2H), 3.99 (s, 3H), 3.75 (t, J = 6.2 Hz, 1H), 1.88-150 (m, 7H), 1.27 (t, J = 7.2 Hz, 3H), 1.24-0.96 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.3, 165.5, 96.0, 78.3, 61.7, 60.0, 42.1, 29.8, 27.9, 26.4, 26.3, 26.1, 14.4. HRMS for $C_{13}H_{24}O_4Na$ (calc): 265.1423 (265.1416).

Synthesis of 5-isopropyl-4-methoxy-5-phenylfuran-2(5H)-one **3n**. Following procedure B, 75% of an off-white solid was obtained. ^1H NMR (300 MHz, $CDCl_3$): δ 7.54-7.45 (m, 2H), 7.40-7.27 (m, 3H), 4.97 (s, 1H), 3.86 (s, 3H), 2.49 (spt, J = 6.8 Hz, 1H), 0.92 (d, J = 6.8 Hz, 3H), 0.81 (d, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 183.8, 172.4, 138.5, 128.5, 128.1, 125.2, 89.6, 87.8, 59.7, 34.5, 16.7, 16.2. HRMS for $C_{14}H_{17}O_3$ (calc): 233.1172 (233.1172).

Synthesis of 5-(4-methoxy-1-oxaspiro[4.5]dec-3-en-2-one **3o**. Following procedure B, 82% of a pale orange solid was obtained. ^1H NMR (400 MHz, $CDCl_3$): δ 4.95 (s, 1H), 3.86 (s, 3H), 1.83-1.54 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 186.4, 172.2, 87.1, 83.9, 59.4, 33.1, 24.5, 21.8. HRMS for $C_{10}H_{14}O_3Na$ (calc): 205.0835 (205.0841).

Synthesis of 3'-methoxy-5'H-spiro[bicyclo[2.2.1]heptane-2,2'-furan]-5'-one **3p**. Following procedure B, 92% of an off-white solid was obtained. ^1H NMR (300 MHz, $CDCl_3$): δ 4.89 (s, 1H), 3.85 (s, 3H), 2.35-2.28 (m, 2H), 2.16-1.81 (m, 3H), 1.70-1.28 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 185.5, 172.4, 89.4, 86.5, 59.6, 46.1, 40.8, 38.5, 36.5, 27.4, 23.8. HRMS for $C_{11}H_{15}O_3$ (calc): 195.1015 (195.1016).

Synthesis of 3-methoxy-5H-spiro[furan-2,2'-tricyclo[3.3.1.1^{3,7}]decan]-5-one **3q**. Following procedure B, 61% of a colourless solid was obtained. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.99 (s, 1H), 3.87 (s, 3H), 2.41-2.21 (m, 4H), 2.02-1.82 (m, 4H), 1.79-1.70 (m, 4H), 1.69-1.56 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.3, 171.6, 88.2, 88.0, 59.5, 37.9, 36.4, 34.6, 33.3, 26.7, 26.3. HRMS for $C_{14}H_{18}O_3Na$ (calc): 257.1155 (257.1154).

Synthesis of 3'-methoxy-5'H-spiro[bicyclo[2.2.1]heptane-2,2'-furan]-5'-one **3r**. Following procedure B, 97% of a white solid was obtained. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.02 (s, 1H), 3.99-3.86 (m, 5H), 3.79 (d, J = 2.1 Hz, 2H), 2.16-2.05 (m, 2H), 1.56-1.45 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 184.7, 171.5, 87.8, 81.1, 63.7, 59.7, 33.1. HRMS for $C_9H_{13}O_4$ (calc): 185.0803 (185.0808).

Synthesis of methyl 3-(4-hydroxytetrahydro-2H-thiopyran-4-yl)propiolate **3s**. Following procedure B, 69% of an off-white solid was obtained. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.77 (s, 3H), 2.90 (s, 1H), 2.81-2.681 (m, 4H), 2.27-2.17 (m, 2H), 2.03-1.92 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.9, 89.2, 77.0, 67.5, 53.1, 39.7, 25.4. HRMS for $C_9H_{13}O_3S$ (calc): 201.0581 (201.0580).

Synthesis of 3-methoxy-2',3'-dihydro-5H-spiro[furan-2,1'-inden]-5-one **3t**. Following procedure B, 53% of a pale orange solid was obtained. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48-7.35 (m, 2H), 7.35-7.28 (m, 1H), 7.24-7.10 (m, 1H), 5.27 (s, 1H), 3.93 (s, 3H), 3.35-3.20 (m, 1H), 3.18-3.04 (m, 1H), 2.77-2.61 (m, 1H), 2.59-2.47 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 182.9, 171.8, 145.1, 138.6, 130.1, 127.2, 125.2, 123.2, 92.9, 88.3, 59.7, 35.2, 30.2. HRMS for $C_{13}H_{13}O_3$ (calc): 217.0861 (217.0859).

Synthesis of 4-ethoxy-5-phenylfuran-2(5H)-one **3u**. Following procedure A but with 6 hours heating in ethanol, 67% of a pale yellow solid was obtained. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46-7.28 (m, 5H), 5.67 (s, 1H), 5.12 (d, J = 1.0 Hz, 1H), 4.27-3.86 (m, 2H), 1.35 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.7, 173.0, 134.3, 129.4, 128.9, 126.7, 88.2, 80.4, 69.0, 14.0. HRMS for $C_{12}H_{12}O_3$ (calc): 204.0783 (204.0781).

Synthesis of 4-(octyloxy)-5-phenylfuran-2(5H)-one **3v**. Following procedure C, 51% of a colourless oil was obtained. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.35 (m, 3H), 7.35-7.28 (m, 2H), 5.67 (s, 1H), 5.10 (d, *J* = 1.0 Hz, 1H), 4.03 (td, *J* = 6.5, 9.8 Hz, 1H), 3.92 (td, *J* = 6.5, 9.8 Hz, 1H), 1.78-1.62 (m, 2H), 1.40-1.12 (m, 10H), 0.87 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 180.9, 173.0, 134.4, 129.3, 128.8, 126.6, 88.1, 80.4, 73.3, 31.8, 29.1, 29.1, 28.3, 25.6, 22.7, 14.2. HRMS for $C_{18}H_{24}O_3$ (calc): 288.1718 (288.1720).

Synthesis of 4-isopropoxy-5-phenylfuran-2(5H)-one **3w**. Following procedure A but with 6 hours heating in isopropanol, 48% of a pale yellow solid was obtained. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44-7.26 (m, 5H), 5.63 (s, 1H), 5.08 (d, *J* = 0.9 Hz, 1H), 4.39 (spt, *J* = 6.1 Hz, 1H), 1.35 (d, *J* = 6.1 Hz, 3H), 1.21 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.7, 173.3, 134.4, 129.3, 128.8, 126.8, 88.1, 80.7, 76.9, 21.4, 21.0. HRMS for $C_{13}H_{14}O_3$ (calc): 218.0939 (218.0937).

Synthesis of 4-(benzyloxy)-5-phenylfuran-2(5H)-one **3x**. Following procedure C, 58% of a pale yellow solid was obtained. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47-7.28 (m, 8H), 7.25-7.13 (m, 2H), 5.73 (s, 1H), 5.20 (d, *J* = 0.9 Hz, 1H), 5.08 (d, *J* = 11.8 Hz, 1H), 5.01 (d, *J* = 11.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 180.2, 172.7, 134.1, 133.9, 129.4, 129.1, 128.9, 127.7, 126.7, 89.4, 80.5, 74.5. HRMS for $C_{17}H_{14}O_3$ (calc): 266.0938 (266.0937).

Synthesis of ethyl 2-(2-hydroxy-2-phenylacetyl)pent-4-enoate **3aa**. Following procedure C, 33% of a pale orange oil was obtained as a mixture of isomers. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45-7.12 (m), 5.65-5.50 (m), 5.30-5.20 (m), 5.10-4.89 (m), 4.82-4.64 (m), 4.27-3.92 (m), 3.78 (q, *J* = 7.1 Hz), 3.71-3.50 (m), 2.63-2.20 (m), 1.27-1.09 (m), 0.97 (t, *J* = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.4, 203.8, 168.2, 168.1, 136.7, 136.4, 133.6, 133.5, 129.1, 129.1, 129.0, 128.1, 127.9, 118.3, 117.7, 80.6, 79.8, 62.0, 61.5, 53.7, 53.3, 33.5, 31.9, 14.2, 13.9. HRMS for $C_{15}H_{18}O_4$ (calc): 285.1096 (285.1103).

Synthesis of 4-(but-3-enyloxy)-5-phenylfuran-2(5H)-one **3ab**. Following procedure C but with 12 hours heating, 54% of a pale yellow solid was obtained. ^{1}H NMR (300

MHz, $CDCl_3$): δ 7.46-7.27 (m, 5H), 5.77-5.58 (m, 2H), 5.12 (d, *J* = 1.3 Hz, 1H), 5.10-5.05 (m, 1H), 5.05-5.00 (m, 1H), 4.15-4.03 (m, 1H), 4.03-3.93 (m, 1H), 2.45 (tq, *J* = 1.3, 6.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.7, 172.8, 134.3, 132.6, 129.4, 128.9, 126.6, 118.3, 88.4, 80.4, 72.1, 32.7. HRMS for $C_{14}H_{14}O_3$ (calc): 230.0936 (230.0937).

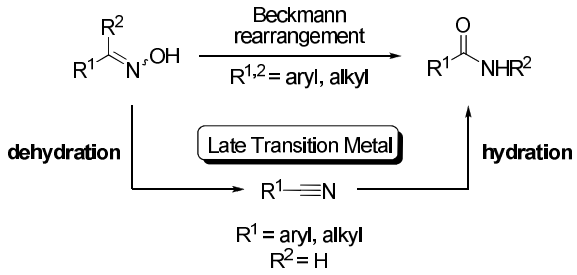
Synthesis of 4-(hepta-1,6-dien-4-yloxy)-5-phenylfuran-2(5H)-one **3ac**. Following procedure C but with 12 hours heating, 23% of a pale yellow oil was obtained. ^1H NMR (400 MHz, $CDCl_3$): δ 7.59-7.28 (m, 5H), 5.96-5.77 (m, 1H), 5.73 (s, 1H), 5.61-5.36 (m, 1H), 5.32-5.11 (m, 3H), 5.06-4.83 (m, 2H), 4.44-4.03 (m, 1H), 2.60-2.47 (m, 2H), 2.46-2.24 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 180.0, 173.1, 134.3, 132.3, 131.8, 129.4, 128.8, 126.8, 119.1, 119.0, 88.3, 82.8, 80.6, 37.5, 37.2. HRMS for $C_{17}H_{18}O_3Na$ (calc): 293.1164 (293.1154).

Synthesis of 4-(3-hydroxypropoxy)-5-phenylfuran-2(5H)-one **3ad**. Following procedure C but with 12 hours heating, 65% of a pale yellow solid was obtained. ^1H NMR (300 MHz, $CDCl_3$): δ 7.51-7.15 (m, 5H), 5.66 (s, 1H), 5.14 (d, *J* = 1.0 Hz, 1H), 4.30-3.97 (m, 2H), 3.76-3.43 (m, 2H), 2.17 (br. s., 1H), 1.90 (quin, *J* = 6.1 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.9, 173.2, 134.1, 129.4, 128.9, 126.6, 88.4, 80.5, 70.2, 58.5, 31.1. HRMS for $C_{13}H_{14}O_4$ (calc): 234.0884 (234.0887).

13 Au/Ag-Cocatalyzed Aldoximes to Amides Rearrangement

13.1 Introduction

The isomerization of oximes to amides, i.e. the Beckmann rearrangement (**Scheme 13.1**),[241] is arguably one of the most straightforward synthetic routes to obtain amides, next to nitrile hydration (Chapter **10**). Typically, this isomerization can be effected using strong acids, or other activating agents, usually in stoichiometric amounts and at high temperature. In addition to harsh reaction conditions, one of the main drawbacks of the Beckmann rearrangement is its poor efficiency towards aldoximes, often leading to the formation of nitriles.

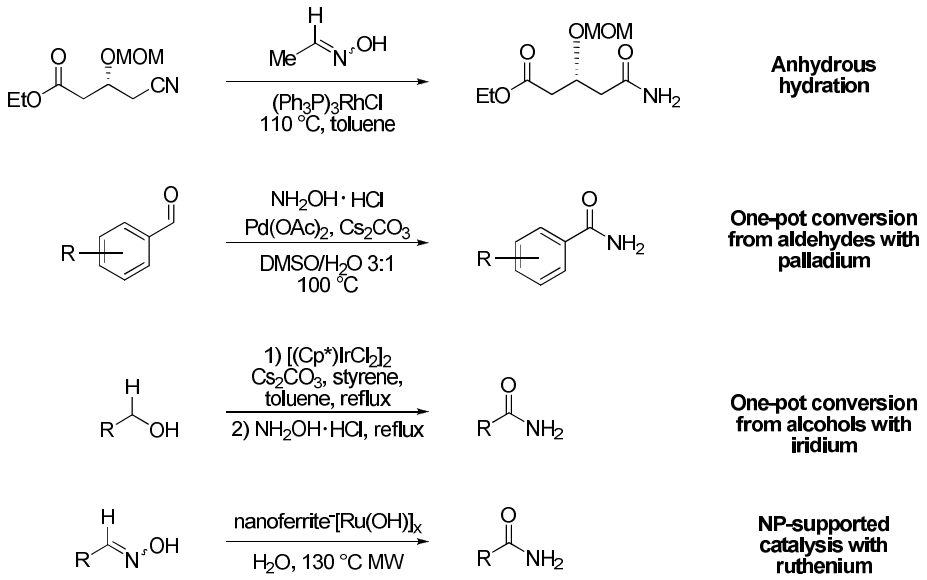


Scheme 13.1 LTM-catalyzed rearrangement of aldoximes.

In recent years, the use of Late Transition Metals (LTMs) has allowed for some improvements,[242] and systems based on Ru,[243] Rh,[244] Pd[245] and Ir[246] have shown interesting activities (**Scheme 13.2**).[247] The mechanistic hypothesis for these LTM-catalyzed rearrangements of aldoximes involves a dehydration/hydration sequence *via* the formation of a discrete nitrile intermediate (**Scheme 13.1**). A closely related report described using oximes as water source for anhydrous nitrile hydration.[248]

This particular aspect was the inspiration for the following investigations, especially in light of the discovery that cationic [(NHC)Au^{I}] complexes efficiently catalyze the hydration of nitriles (Chapter **10**),[220] and resulted in the examination of the potential of these gold(I) catalysts in the rearrangement of aldoximes.[249] The following chapter discusses this transformation, which is best achieved using an Au/Ag cocatalytic system, allowing for neat and acid-free conditions to form a variety of primary amides. In addition to expanding further the scope of homogeneous gold catalysis, this study

represents a rare example of cooperative catalysis involving gold,[250] and the first one, to the best of our knowledge, associating gold with silver.[177, 217h, 251]



Scheme 13.2 Selected examples for LTM-catalyzed amide formation *via* oximes.

Moreover, subsequent testing of new gold catalysts as [(IPr)Au(OH)] or [{(IPr)Au}$_2$(μ-OH)][BF_4] revealed reactivity also under silver-free conditions highlighting the ability of gold to also catalyze the dehydration step in decent rates and placing silver back to a supporting additive role in this reaction.

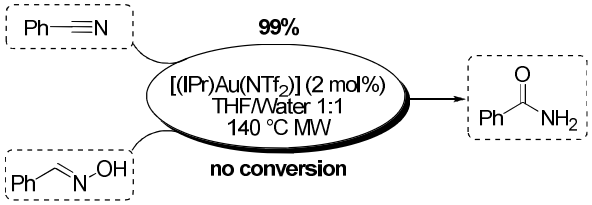
13.2 Results and Discussion

13.2.1 Optimization

The optimization studies were initiated with benzaldoxime as a model substrate using the conditions previously reported for the efficient hydration of nitriles (**Scheme 13.3**).[220] Disappointingly, no conversion was observed (**Table 13.2**, entry 1), as with other related catalytic systems for hydration-type reactivity.[174, 206]

Therefore an extensive screening of catalysts, solvents, and temperatures was quickly engaged. Changing the solvent to CH_2Cl_2, THF, toluene, 1,4-dioxane, DMSO or isopropanol did not improve conversion. The first "encouraging" results were obtained with 5 mol% of [(IPr)AuCl]/$AgBF_4$ instead of [(IPr)Au(NTf_2)] at 130 °C resulting in high conversions (**Table 13.1**), but with significant formation of side products such as benzoic acid and benzaldehyde. Nevertheless, reasonable conversions of up to 74% into

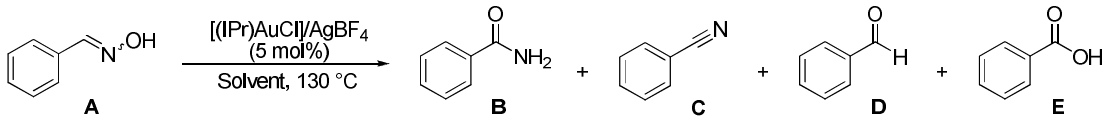
the desired benzamide were obtained when the reaction was performed in $CHCl_3$ which proved superior to all other solvents tested.



Scheme 13.3 Lack of reactivity for aldoximes under the nitrile hydration conditions.

Performing reactions at 130 °C in $CHCl_3$, however, caused not only significant side product formation but also was unfavorable in terms of reaction setup as high pressure apparatus would have been necessary to run such reactions in these conditions.

Table 13.1 Solvent screening for the oxime to amide rearrangement at 130 °C.



Entry	Time	Solvent	A	B	C	D	E	Other
1	2h	CH_2Cl_2	38%	45%	5%	7%	5%	<1%
2	2h	1,4-Dioxane	59%	16%	4%	19%	<1%	2%
3	19h	1,4-Dioxane	-	50%	1%	26%	7%	16%
4	2h	^{i}PrOH	87%	3%	2%	5%	-	3%
5	19h	^{i}PrOH	51%	29%	3%	12%	2%	3%
6	2h	THF	93%	2%	1%	4%	-	-
7	19h	THF	60%	26%	7%	7%	<1%	<1%
8	2h	Toluene	12%	32%	13%	33%	3%	7%
9	19h	Toluene	-	39%	12%	22%	16%	11%
10	2h	H_2O	70%	23%	1%	4%	2%	-
11	19h	H_2O	61%	15%	3%	8%	13%	-
12	2h	$CHCl_3$	40%	39%	8%	8%	3%	2%
13	4h	$CHCl_3$	-	**74%**	12%	10%	<1%	3%
14	6h	$CHCl_3$	-	**71%**	15%	14%	<1%	<1%

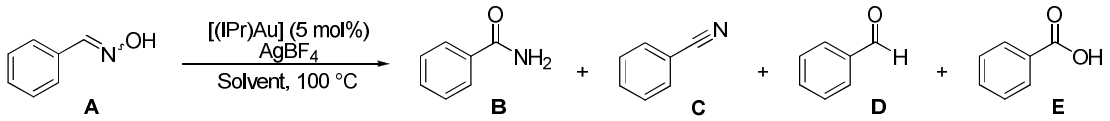
[a] GC conversions, average of two runs.

Therefore, decreasing the temperature to 100 °C was considered and a first attempt showed conversion of the oxime to the corresponding amide in a disappointing 6% along with formation of nitrile and aldehyde (**Table 13.2**, entry 2).

Interestingly, we soon realized, through a control reaction with only $AgBF_4$ in stoichiometric amount, that silver(I) salts were efficient catalysts for the conversion of benzaldoxime **A** into benzonitrile **C** and benzaldehyde **D** (**Table 13.2**, entry 3). As a consequence, we investigated the influence of the amount of silver salt on the aldoxime rearrangement with [(IPr)AuCl] and $AgBF_4$.

As shown in **Table 13.2** (entries 4-6) the use of more than 1 equiv. of silver tetrafluoroborate with respect to the gold catalyst increased the yield in benzamide **B** from 6 to 37% (entry 4). On the other hand, increasing the $AgBF_4$ loading from 10 (37%) to 15 mol% (41%) (entries 4-5) only has a minor effect on conversion into benzamide. Stoichiometric amounts of silver along with 5 mol% of [(IPr)AuCl] increased the formation of side products (entry 6).

Table 13.2 Optimization of the reaction conditions.[a]



Entry	Catalyst (5 mol%)	Solvent	Time	[$AgBF_4$] (mol%)	A	B	C	D	E
1	[(IPr)Au(NTf_2)]	$CHCl_3$	7 h	-	99%	<1%	<1%	<1%	<1%
2	[(IPr)AuCl]	$CHCl_3$	7 h	$AgBF_4$ (5)	80%	6%	6%	7%	-
3	-	$CHCl_3$	20 h	$AgBF_4$ (100)	-	-	58%	42%	-
4	[(IPr)AuCl]	$CHCl_3$	7 h	$AgBF_4$ (10)	29%	37%	17%	17%	-
5	[(IPr)AuCl]	$CHCl_3$	7 h	$AgBF_4$ (15)	28%	41%	15%	16%	-
6[b]	[(IPr)AuCl]	$CHCl_3$	7 h	$AgBF_4$ (100)	3%	46%	23%	3%	2%
7	[(IPr)AuCl]	neat	7 h	$AgBF_4$ (5)	93%	6%	<1%	<1%	-
8	[(IPr)AuCl]	neat	7 h	$AgBF_4$ (10)	51%	47%	1%	<1%	-
9	-	neat	7 h	$AgBF_4$ (10)	88%	8%	3%	1%	-
10	**[(IPr)AuCl]**	**neat**	**20 h**	**$AgBF_4$ (5)**	**44%**	**55%**	**1%**	**<1%**	**-**
11	**[(IPr)AuCl]**	**neat**	**20 h**	**$AgBF_4$ (10)**	**1%**	**95%**	**3%**	**<1%**	**-**

[a] GC conversions, average of two runs. [b] 22% of unidentified products.

Remarkably, it was next uncovered that neat reactions provided excellent yields of the rearranged amide **B,** suppressing the undesirable formation of benzaldehyde **D** and

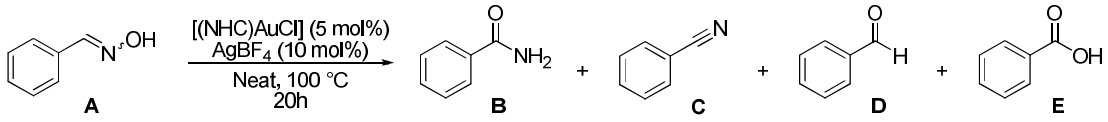
ensuring complete conversion of nitrile **C**. After a reaction time of 7 hours a conversion of 47% was observed with only minor amounts of side product detected in GC. A reaction time of 20 hours was found to be optimal with an excellent conversion of 95% (entry 11).

Notably, we observed amide formation with 10 mol% $AgBF_4$ as well (entry 9), but conversions of only 8% into benzamide were not competitive to the mixed Ag/Au system (entry 8).

With these conditions in hand, we screened various NHC-gold complexes, as well as several silver salts. As shown in **Table 13.3**, IPr was found to be remarkably superior compared to other NHCs tested (entry 1). However, bulky NHCs like I^{t}Bu and IAd provided moderate to good conversions as well as the saturated SIPr ligand (entries 3, 6-7). Slightly diminished conversions were obtained when using the smaller IMes and SIMes ligands (entries 11-15).

With the important improvements in neat conditions made for the Au/Ag catalytic systems, a control reaction was performed with [(IPr)Au(NTf_2)]. This time, the reaction afforded a decent conversion of 77% into benzamide illustrating the ability of gold catalyzing both the hydration *and* dehydration step in the anticipated reaction pattern. The conversion was however not competetive to the mixed system of Au/Ag.

Table 13.3 Catalyst screening for the oxime to amide rearrangement at 100 °C.[a]



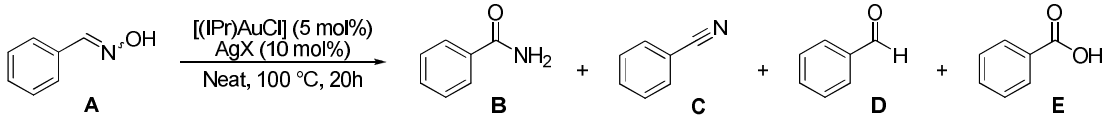
Entry	Catalyst	A	B	C	D	E
1	-	44%	34%	16%	3%	3%
2	**[(IPr)AuCl]**	**1%**	**95%**	**3%**	**<1%**	**-**
3	[(SIPr)AuCl]	3%	87%	2%	<1%	4%
4	[(IMes)AuCl]	21%	55%	8%	1%	12%
5	[(SIMes)AuCl]	12%	67%	7%	1%	9%
6	[(I^{t}Bu)AuCl]	4%	80%	6%	1%	6%
7	[(IAd)AuCl]	6%	78%	5%	<1%	6%
8[b]	[(IPr)Au(NTf_2)]	19%	77%	1%	2%	-

[a] GC conversions, average of two runs. [b] no silver salt added.

Considering that the reaction very likely involves a nitrile hydration step, the superiority of IPr is in excellent agreement with previous investigations as for this specific reaction [(IPr)Au(NTf_2)] was found more efficient than other [(NHC)Au(NTf_2)] complexes. The screening of silver salts in **Table 13.4** completed the investigations on the best reaction conditions for the gold-catalyzed oxime to amide rearrangement.

The screening of silver salts showcases silver tetrafluoroborate as the cocatalyst of choice (**Table 13.4**, entry 1). Nevertheless, the other silver salts tested (entries 2-5), with exception of AgOTs (entry 5), allowed for very competitive results indicating that the nature of the silver salt has low impact on the performance of the final catalytic system. Control experiments with [(IPr)AuCl] only (entry 6) as well as no catalyst at all did not show any conversion.

Table 13.4 Silver salt screening for the oxime to amide rearrangement at 100 °C.[a]



Entry	[AgX] (mol%)	A	B	C	D	E
1	**$AgBF_4$ (10)**	**1%**	**95%**	**3%**	**<1%**	**-**
2	$AgSbF_6$ (10)	4%	92%	2%	<1%	<1%
3	$AgPF_6$ (10)	1%	89%	5%	<1%	2%
4	AgOTf (10)	12%	84%	2%	<1%	1%
5	AgOTs (10)	37%	60%	2%	<1%	<1%
6	-	99%	<1%	<1%	<1%	<1%

[a] GC conversions, average of two runs.

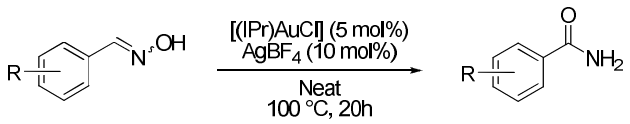
13.2.2 Substrate scope

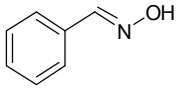
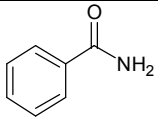
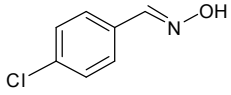
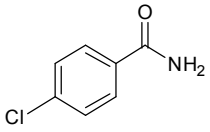
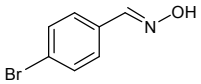
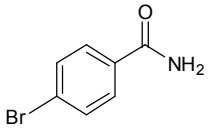
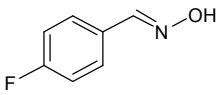
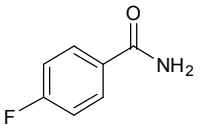
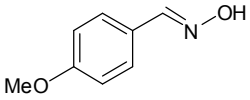
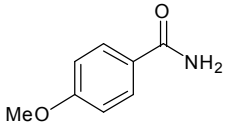
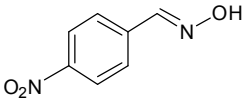
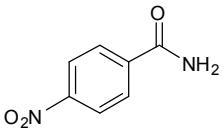
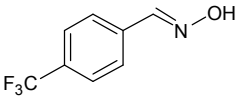
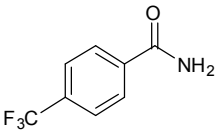
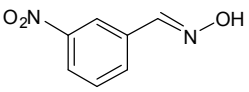
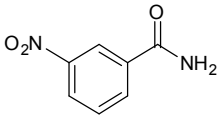
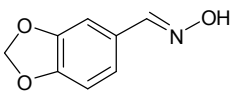
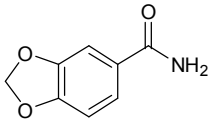
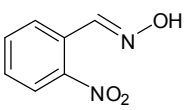
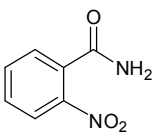
With optimized conditions to hand, the scope of this Au/Ag cocatalytic system was explored. Good to excellent yields were obtained for various aryl aldoximes regardless of the electronic properties of the aromatic substituents (**Table 13.5**).

Benzamide, as well as *p*-chloro-, *p*-bromo- and *p*-fluorobenzamide were all obtained in excellent yields of 85-92% (entries 1-4).

Electron-donating substituents, such as methoxy (entry 5), as well as the strongly electron-withdrawing nitro and trifluoromethyl groups (entries 6-7) afforded good to excellent yields.

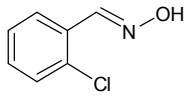
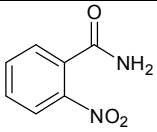
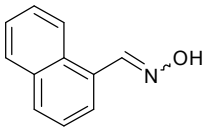
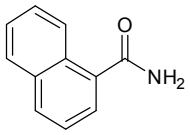
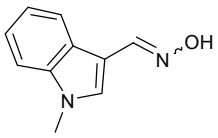
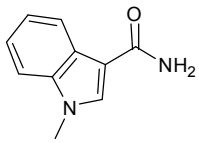
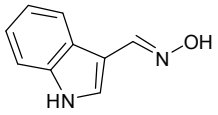
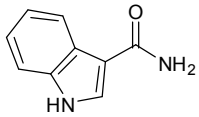
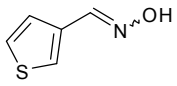
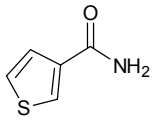
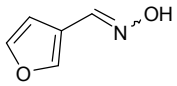
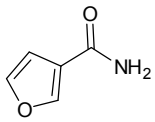
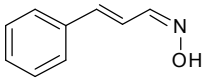
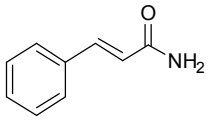
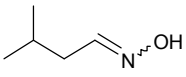
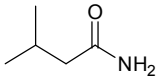
Table 13.5 Scope of the Au(I)-catalyzed aldoxime to amide rearrangement.[a]



Entry	Propargylic Alcohol	1	Product	2	Yield (%)[b]
1		**1a**		**2a**	92%
2		**1b**		**2b**	87%
3		**1c**		**2c**	90%
4		**1d**		**2d**	85%
5		**1e**		**2e**	95%
6		**1f**		**2f**	84%
7		**1g**		**2g**	77%
8		**1h**		**2h**	94%
9		**1i**		**2i**	98%
10		**1j**		**2j**	27%

[a] Aldoxime (1 mmol), [(IPr)AuCl] (5 mol%), $AgBF_4$ (10 mol%), 20 hours at 100 °C. [b] Isolated yields are average of 2 runs.

Table 13.5 Scope of the Au(I)-catalyzed aldoxime to amide rearrangement.(continued)

11		**1k**		**2k**	37%
12		**1l**		**2l**	25%
13		**1m**		**2m**	46%
14		**1n**		**2n**	53%
15		**1o**		**2o**	99%
16		**1p**		**2p**	68%
17		**1q**		**2q**	25%
18		**1r**		**2r**	24%

[a] Aldoxime (1 mmol), [(IPr)AuCl] (5 mol%), $AgBF_4$ (10 mol%), 20 hours at 100 °C. [b] Isolated yields are average of 2 runs.

Moving from *para*-substituted aryl aldoximes to *meta*-subtituted compounds, we obtained 94% yield in *m*-nitrobenzamide **2h** and 98% yield in benzo-1,3-dioxole-5-carboxamide **2i** (entries 8-9).

On the other hand, *ortho*-substituted substrates yielded only moderate amounts of the corresponding amides, regardless of the electronic nature of the substituent (entries 10-12). These observations clearly point to deleterious steric hindrance with the present catalytic system since there was hardly formation of any by-products either.

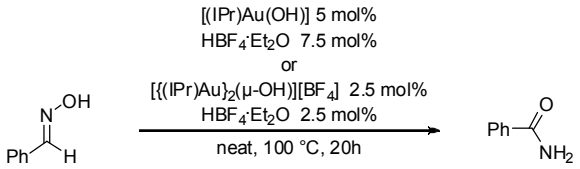
Next, the reaction scope was extended to heteroaromatic and aliphatic aldoximes. 1-Methylindole-3-carboxamide **2m** was formed in 46% yield (entry 13), while

unprotected indole-3-carboxamide **2n** was obtained in 53% yield (entry 14). Interestingly, this shows that the free *N*-indole does not lower the yield by complexation to either of the metal centers. In addition, thiophene-3-carbamide **2o** and furan-3-carbamide **2p** were obtained in good to excellent yields (entries 15-16).

Finally, in order to fully assess the limitations of the present catalytic system, more challenging substrates such as cinnamaldoxime **1q** and isobutyroxime **1r**, were tested (entries 17 and 18). While the low yields of amide obtained in both cases are not synthetically useful, these results are encouraging for future developments.

In the progress of exploring the scope of [(IPr)Au(OH)] and [{(IPr)Au}$_2$(μ-OH][BF_4], the complexes were also tested in the aldoxime to amide rearrangement. As illustrated in **Table 13.6**, the catalysts show significant activity. Acid activation to generate $[Au]^+$ resulted in excellent conversions (entries 4-5 and 7) eliminating the need of silver salt.

Table 13.6 [(IPr)Au(OH)] and [{(IPr)Au}$_2$(μ-OH][BF_4] in aldoxime to amide rearrangement.



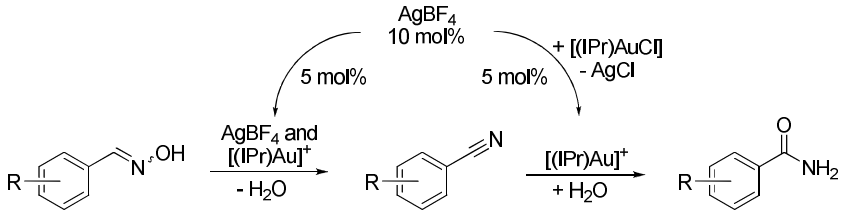
Entry	Catalyst (mol%)	Acid (mol%)	Conversion[a]
1	none	HBF_4 (20 mol%)	- (48)
2	[(IPr)Au(OH)] (5 mol%)	none	17 (5)
3	[(IPr)Au(OH)] (5 mol%)	HBF_4 (2.5 mol%)	46 (5)
4	[(IPr)Au(OH)] (5 mol%)	HBF_4 (5 mol%)	81 (4)
5	[(IPr)Au(OH)] (5 mol%)	HBF_4 (7.5 mol%)	92 (4)
6	[{(IPr)Au}$_2$(μ-OH][BF_4] (2.5 mol%)	none	25 (6)
7	[{(IPr)Au}$_2$(μ-OH][BF_4] (2.5 mol%)	HBF_4 (2,5 mol%)	90 (6)

[a] GC conversions, average of two runs. Percentage of side products is given in brackets.

13.2.3 Mechanistic considerations

Mechanistically, the present experimental results point towards a dehydration/hydration sequence (**Scheme 13.4**), as proposed in previous related studies. The initial dehydration of the oxime into a nitrile is notably supported by two aspects: (1) detection of the nitrile during the optimization studies, (2) the fact that both *E* and *Z*

isomers of the oxime, several oximes were used as *E/Z* mixtures, can be converted in the primary amide: In the case of a typical concerted Beckmann rearrangement, i.e. without intermediacy of a nitrile, only the substituent *anti* to the hydroxyl moiety would migrate. Furthermore, it was shown that $AgBF_4$ catalyzes the oxime dehydration (Table 13.2, entry 3) but performs poorly in the nitrile hydration. In summary, these observations strongly support a cocatalyzed dehydration/hydration mechanism (**Scheme 13.1**) for the catalytic system. However, amide formation with [(IPr)Au(NTf_2)] as well as [(IPr)Au(OH)] and [{(IPr)Au}$_2$(μ-OH][BF_4] in case of acid activation prove that gold is capable of catalyzing both steps of the reaction.



Scheme 13.4 Mechanistic proposal for the Au/Ag catalyzed rearrangement of aldoximes to amides.

Interestingly, water scavengers such as molecular sieves or $MgSO_4$ in reactions performed in chloroform to ensure scavenging did not inhibit amide formation by stopping the reaction at the nitrile stage as already observed by Chang and coworkers in the related rhodium-catalyzed oxime to amide rearrangement,[244d] suggesting a concerted mechanism (i.e. by interaction of water with the gold catalyst). The essential role of the silver salt, which serves as both activator of the [(NHC)AuCl] complex and as a catalyst for the oxime dehydration, also indicates potential for the development of well-defined silver catalysts for oxime dehydration which is also a reaction of interest.[252]

13.3 Conclusion

In summary, the first gold-based aldoxime to amide rearrangement was developed where a number of aldoximes could be converted into primary amides, regardless to their electronic properties, under neat and acid-free reaction conditions using an Au/Ag cocatalyst. This catalytic system represents a rare example of cocatalysis involving gold in homogeneous catalysis. The fact that it involves silver(I) is of particular interest in this context, since AgX species are traditionally used as gold precatalyst activators. Additionally, the *Entente Cordiale* between gold and silver opens new avenues for

cooperative catalysis combining the rich chemistry of both metals. Nevertheless, silver-free catalytic systems also proved to catalyze the reaction.

13.4 Experimental Section

J. Bosson contributed to the experimental work of this chapter. S. Díez-González provided several aldoximes.

General procedure for the synthesis of oximes from aldehydes: To a suspension of 20 mmol of aldehyde in a 1:1:2 mixture of H_2O/EtOH/ice (20 mL), 1.39 g (20 mmol) of hydroxylamine hydrochloride was added, followed by 4 mL of a 50% aqueous solution of NaOH (40 mmol), while keeping the temperature below 30 °C. After being stirred at room temperature for the indicated time, the solution was extracted with Et_2O. The aqueous phase was acidified to pH 6 by adding concentrated HCl while keeping the temperature below 30 °C and extracted with Et_2O. The combined organic phases were dried over $MgSO_4$, and the solvent was evaporated to give the oxime products.

*Benzaldehyde oxime (**1a**)* Following the general procedure, the title compound (2.27 g, 94%) was obtained after 1 hour of stirring as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (s, 1H), 7.64-7.55 (m, 2H), 7.43-7.36 (m, 3H).[253]

*p-Chlorobenzaldehyde oxime (**1b**)* Following the general procedure, the title compound (1.97 g, 64%) was obtained after 6 hours of stirring as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (s, 1H), 7.51 (d, J = 8.5 Hz, 2H), 7.37 (d, J = 8.5 Hz, 2H).[253]

*p-Bromobenzaldehyde oxime (**1c**)* Following the general procedure, the title compound (3.70 g, 95%) was obtained after 1.5 hours of stirring as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (s, 1H), 7.53 (d, J = 8.5 Hz, 2H), 7.45 (d, J = 8.5 Hz, 2H).[253]

*p-Fluorobenzaldehyde oxime (**1d**)* Following the general procedure, the title compound (2.37 g, 85%) was obtained after 6 hours of stirring as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (s, 1H), 7.60-7.53 (m, 2H), 7.12-7.04 (m, 2H). ^{19}F NMR (282 MHz, DMSO-d_6): δ -112.4 (s).[253]

*p-Methoxybenzaldehyde oxime (**1e**)* Following the general procedure from 0.2 mol of 4-methoxybenzaldehyde, the title compound (30.5 g, 100%) was obtained after 1.5 hours of stirring as a pale orange solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.52 (d, *J* = 8.5 Hz, 2H), 6.91 (d, *J* = 8.5 Hz, 2H), 3.84 (s, 3H).[253]

*p-Nitrobenzaldehyde oxime (**1f**)* Following the general procedure, the title compound (3.00 g, 83%) was obtained after 5 hours of stirring as a pale orange solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, *J* = 8.8 Hz, 2H), 8.22 (s, 1H), 7.75 (d, *J* = 8.8 Hz, 2H).[253]

*p-Trifluoromethylbenzaldehyde oxime (**1g**)* Following the general procedure, the title compound (1.65 g, 44%) was obtained after 5 hours of stirring as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (s, 1H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 2H). ^{19}F NMR (282 MHz, DMSO-d_6): δ -61.5 (s).[254]

*m-Nitrobenzaldehyde oxime (**1h**)* Following the general procedure, the title compound (2.04 g, 61%) was obtained after 6 hours of stirring as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.43 (t, *J* = 1.9 Hz, 1H), 8.26-8.20 (m, 2H), 7.91 (dt, *J* = 7.9; 1.2 Hz, 1H), 7.58 (t, *J* = 7.9 Hz, 1H).[255]

*Benzo[1,3]dioxole-5-carboxaldehyde oxime (**1i**)* Following the general procedure, the title compound (3.32 g, 100%) was obtained after 5 hours of stirring as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (s, 1H), 7.18 (s, 1H), 6.97 (d, *J* = 7.4 Hz, 1H), 6.81 (d, *J* = 7.4 Hz, 1H), 6.00 (s, 2H).[256]

*o-Nitrobenzaldehyde oxime (**1j**)* Following the general procedure, the title compound (2.58 g, 78%) was obtained after 18 hours of stirring as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69 (s, 1H), 8.07 (d, *J* = 8.2 Hz, 1H), 7.95 (d, *J* = 7.7 Hz, 1H), 7.66 (t, *J* = 7.7 Hz, 1H), 7.59 (t, *J* = 8.2 Hz, 1H).[257]

*o-Chlorobenzaldehyde oxime (**1k**)* Following the general procedure, the title compound (2.99 g, 96%) was obtained after 1.5 hours of stirring as a pale orange solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.58 (s, 1H), 7.86-7.78 (m, 1H), 7.42-7.36 (m, 1H), 7.36-7.23 (m, 2H).[258]

*Naphthalene-1-carboxaldehyde oxime (**1l**)* Following the general procedure, the title compound (3.10 g, 91%) was obtained after 18 hours of stirring as a white solid. mp = 96°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.82 (s, 1H), 8.48 (d, J = 8.3 Hz, 1H), 7.93-7.87 (m, 2H), 7.78 (d, J = 7.0 Hz, 1H), 7.62-7.46 (m, 3H). ^{13}C NMR (100 MHz, acetone-d_6): δ 149.7, 134.9, 131.5, 130.8, 129.9, 129.6, 128.1, 127.8, 127.0, 126.3, 125.8. HRMS calcd. for $C_{11}H_8NO$: 170.0606. Found: 170.0601.

*1-Methylindole-3-carboxaldehyde oxime (**1m**)* Following the general procedure from 10 mmol of 1-methylindole-3-carboxaldehyde, the title compound (1.49 g, 86%, 68:32 *E/Z*) was obtained after 18 hours of stirring as a white solid. Mixture of isomers: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (s, 1H, major), 8.28 (s, 1H, minor), 8.11 (td, J = 7.9; 0.9 Hz, 1H, major), 7.82 (td, J = 7.9; 0.9 Hz, 1H, minor), 7.44-7.22 (m, 4H), 3.89 (s, 3H, minor), 3.83 (s, 3H, major). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.2, 138.0 (minor), 137.3, 134.4 (minor), 132.0, 124.6, 122.3, 122.0 (minor), 121.5, 120.2, 120.1 (minor), 118.3 (minor), 110.0, 108.6, 105.3 (minor). HRMS calcd. for $C_{10}H_{11}N_2O$: 175.0871. Found: 175.0869.

*1-H-Indole-3-carboxaldehyde oxime (**1n**)* Following the general procedure, the title compound (1.98 g, 62%) was obtained after 18 hours of stirring and recrystallization in chloroform as a white solid. ^{1}H NMR (400 MHz, acetone-d_6): δ 10.76 (br. s, 1H), 10.45 (br. s, 1H), 8.42 (d, J = 2.6 Hz, 1H), 7.89 (d, J = 7.8 Hz, 1H), 7.82 (s, 1H), 7.51 (d, J = 7.6 Hz, 1H), 7.28-7.09 (m, 2H). ^{13}C NMR (100 MHz, acetone-d_6): δ 139.5, 136.3, 131.6, 127.6, 123.0, 121.1, 118.9, 112.5, 107.8. HRMS calcd. for $C_9H_9N_2O$: 161.0715. Found: 161.0714.

*3-Thiophenecarboxaldehyde oxime (**1o**)* Following the general procedure from 10 mmol of 3-thiophenecarboxaldehyde, the title compound (1.27 g, 100%, 64:36 mixture of isomers) was obtained after 18 hours of stirring as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (br. s, 1H), 8.19 (s, 1H, major), 8.18 (d, J = 1.1 Hz, 1H, minor), 7.51 (dd, J = 5.1; 1.1 Hz, 1H, minor), 7.48 (dd, J = 2.9; 1.1 Hz, 1H, major), 7.40 (d, J =

1.1 Hz, 1H, minor), 7.39 (d, *J* = 1.1 Hz, 1H, major), 7.35-7.30 (m, 1H, minor), 7.34 (d, *J* = 2.9 Hz, 1H, major). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.6, 134.2, 131.5, 129.4, 126.9, 126.8, 125.3, 124.7. HRMS calcd. for C_5H_6NOS: 128.0170. Found: 128.0170.

*3-Furancarboxaldehyde oxime (**1p**)* Following the general procedure from 10 mmol of 3-furancarboxaldehyde, the title compound (1.03 g, 93%, 68:32 mixture of isomers) was obtained after 18 hours of stirring as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (s, 1H, major), 8.07 (s, 1H, minor), 7.64 (broad s, 1H, minor), 7.45 (t, *J* = 1.7 Hz, 1H, major), 7.43 (t, *J* = 1.7 Hz, 1H, minor), 7.36 (broad s, 1H, major), 6.68 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.2 (major), 144.2 (minor), 143.7 (minor), 142.7 (major), 142.5 (minor), 139.7 (major), 119.6 (minor), 116.1 (major), 110.8 (major), 107.2 (minor). HRMS calcd. for $C_5H_5NO_2Na$: 134.0218. Found: 134.0223.

*Cinnamaldehyde oxime (**1q**)* Following the general procedure, the title compound (2.73 g, 93%, 55:45 E/Z) was obtained after 18 hours of stirring. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.02 (br. s, 1H), 7.98–7.94 (m, 1H, *E*), 7.56–7.51 (m, 1H, *Z*), 7.50–7.42 (m, 5H, *Z*+*E*), 7.41–7.27 (m, 7H, *Z*+*E*), 6.90–6.81 (m, 2H, *Z*+*E*).[259]

*3-Methylbutyraldehyde oxime (**1r**)* Following the general procedure, the title compound (1.76 g, 87%, 47:43 E/Z) was obtained after 18 hours of stirring. Mixture of isomers: ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.43 (br. s, 1H), 7.41 (t, *J* = 6.7 Hz, 1H, major), 6.45 (br. s, 1H, minor), 2.26 (t, *J* = 5.9 Hz, 1H), 2.07 (t, *J* = 6.7 Hz, 1H), 1.89-1.74 (m, 1H), 0.93 (t, *J* = 7.1 Hz, 6H).[260]

General procedure for the conversion of oximes into amides In a glovebox, the appropriate oxime (1.00 mmol), [(IPr)AuCl] (31 mg, 5 mol%) and $AgBF_4$ (19 mg, 10 mol%) were charged in a 4 mL vial equipped with a stirring bar. The vial was sealed and the reaction mixture was stirred outside the glovebox at 100 °C for 20 hours and purified by flash chromatography (gradient of EtOAc/pentane).

*Benzamide (**2a**)* Following the general procedure, the title compound was isolated after flash chromatography as a white solid (111 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (m, 2H), 7.54 (m, 1H), 7.46 (m, 2H), 6.08 (br. s, 1H), 5.86 (br. s, 1H).[220]

*p-Chlorobenzamide (**2b**)* Following the general procedure, the title compound was isolated after flash chromatography as a white solid (135 mg, 87%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.04 (br. s, 1H), 7.88 (d, J = 8.8 Hz, 2H), 7.52 (d, J = 8.8 Hz, 2H), 7.46 (br. s, 1H).[220]

*p-Bromobenzamide (**2c**)* Following the general procedure, the title compound was isolated after flash chromatography as a white solid (180 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, J = 8.5 Hz, 1H), 7.59 (d, J = 8.5 Hz, 1H), 6.02 (br. s, 1H), 5.81 (br. s, 1H).[220]

*p-Fluorobenzamide (**2d**)* Following the general procedure, the title compound was isolated after flash chromatography as a white solid (118 mg, 85%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.99 (br. s, 1H), 7.93 (dd, J = 8.9; 3.3 Hz, 2H), 7.39 (br. s, 1H), 7.28 (t, J = 8.9 Hz, 2H). ^{19}F NMR (282 MHz, DMSO-d_6): δ -110.1 (s).[246]

*p-Methoxybenzamide (**2e**)* Following the general procedure, the title compound was isolated after flash chromatography as a white solid (143 mg, 95%). ^{1}H NMR (400 MHz, acetone-d_6): δ 7.91 (d, J = 8.8 Hz, 2H), 7.32 (br. s, 1H), 6.97 (d, J = 8.8 Hz, 2H), 6.50 (br. s, 1 H), 3.85 (s, 3H).[220]

*p-Nitrobenzamide (**2f**)* Following the general procedure, the title compound was isolated after flash chromatography as a pale yellow solid (139 mg, 84%). ^{1}H NMR (400 MHz, acetone-d_6): δ 8.32 (d, J = 8.8 Hz, 2H), 8.17 (d, J = 8.8 Hz, 2H), 7.77 (br. s, 1H), 7.01 (br. s, 1H).[220]

*p-Trifluoromethylbenzamide (**2g**)* Following the general procedure, the title compound was isolated after flash chromatography as a off-white solid (145 mg, 77%). ^{1}H NMR (400 MHz, acetone-d_6): δ 8.14 (d, J = 8.2 Hz, 2H), 7.82 (d, J = 8.2 Hz, 2H), 7.69 (br. s, 1H), 6.95 (br. s, 1H). ^{19}F NMR (282 MHz, DMSO-d_6): δ -61.8 (s).[246]

*m-Nitrobenzamide (**2h**)* Following the general procedure, the title compound was isolated after flash chromatography as a white solid (156 mg, 94%). ^{1}H NMR (400

MHz, DMSO-d_6): δ = 8.69 (dd, J = 2.3; 1.1 Hz, 1H), 8.38 (ddd, J = 8.0; 2.3; 1.1 Hz, 1H), 8.35 (br. s, 1H), 8.31 (ddd, J = 8.0; 1.5; 1.1 Hz, 1H), 7.72 (br. s, 1H).[261]

Benzo[1,3]dioxole-5-carboxamide ***(2i)*** Following the general procedure, the title compound was isolated after flash chromatography as a white solid (162 mg, 98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, J = 8.1 Hz, 1H), 7.31 (s, 1H), 6.48 (d, J = 8.1 Hz, 1H), 6.04 (s, 2H), 5.82 (br. s, 2H).[243a]

o-Nitrobenzamide ***(2j)*** Following the general procedure, the title compound was isolated after flash chromatography as a pale yellow solid (44 mg, 27%). ^{1}H NMR (400 MHz, acetone-d_6): δ 8.05-7.95 (m, 1H), 7.85-7.75 (m, 1H), 7.72-7.65 (m, 2H), 7.74-7.60 (m, 3H), 7.52 (br. s, 1H), 6.99 (br. s, 1H).[246]

o-Chlorobenzamide ***(2k)*** Following the general procedure, the title compound was isolated after flash chromatography as a white solid (58 mg, 37%). ^{1}H NMR (400 MHz, acetone-d_6): δ 7.53 (dd, J = 7.2; 1.8 Hz, 1H), 7.50-7.32 (m, 3H), 7.21 (br. s, 1H), 6.92 (br. s, 1H).[262]

Naphthalene-1-carboxamide ***(2l)*** Following the general procedure, the title compound was isolated after flash chromatography as a white solid (43 mg, 25%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31-8.28 (m, 1H), 8.01-7.95 (m, 3H), 7.63 (dd, J = 7.0; 1.2 Hz, 1H), 7.59-7.51 (m, 4H).[263]

1-Methyl-indole-3-carboxamide ***(2m)*** Following the general procedure, the title compound was isolated after flash chromatography as a white solid (80 mg, 46%). ^{1}H NMR (400 MHz, CD_3OD): δ 8.10 (dd, J = 8.0; 1.2 Hz, 1H), 7.85 (s, 1H), 7.43 (dd, J = 8.2; 1.0 Hz, 1H), 7.26 (ddd, J = 8.2; 7.0; 1.2 Hz, 1H), 7.19 (ddd, J = 8.0; 7.0; 1.0 Hz, 1H), 3.85 (s, 3H).[264]

1-H-Indole-3-carboxamide ***(2n)*** Following the general procedure, the title compound was isolated after flash chromatography as a white solid (85 mg, 53%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.52 (br. s, 1H), 8.13 (d, J = 7.9 Hz, 1H), 8.01 (d, J =

2.9 Hz, 1H), 7.41 (d, *J* = 7.9 Hz, 1H), 7.40 (br. s, 1H), 7.15-7.06 (m, 2H), 6.78 (br. s, 1H).[265]

*3-Thiophenecarboxamide (**2o**)* Following the general procedure, the title compound was isolated after flash chromatography as a off-white solid (126 mg, 99%). ^{1}H NMR (400 MHz, acetone-d_6): δ 8.10 (dd, *J* = 2.9; 1.3 Hz, 1H), 7.54 (dd, *J* = 5.1; 1.3 Hz, 1H), 7.49 (dd, *J* = 5.1; 2.9 Hz, 1H), 7.27 (br. s, 1H), 6.52 (br. s, 1H). ^{13}C NMR (100 MHz, acetone-d_6): δ 164.9, 138.9, 129.5, 128.0, 127.0. HRMS calcd. for C_5H_5NONaS: 149.9990. Found: 149.9986.

*3-Furancarboxamide (**2p**)* Following the general procedure, the title compound was isolated after flash chromatography as a pale orange solid (75 mg, 68%). ^{1}H NMR (400 MHz, acetone-d_6): δ 8.10 (s, 1H), 7.60 (t, *J* = 1.6 Hz, 1H), 7.17 (br. s, 1H), 6.81 (s, 1H), 6.54 (br. s, 1H).[266]

*Cinnamamide (**2q**)* Following the general procedure, the title compound was isolated after flash chromatography as a white solid (37 mg, 25%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 15.6 Hz, 1H), 7.52-7.50 (m, 2H), 7.38-7.36 (m, 3H), 6.48 (d, *J* = 15.6 Hz, 1H), 5.67 (br. s, 2H).[220]

*3-Methylbutyramide (**2r**)* Following the general procedure, the title compound was isolated after flash chromatography as a white solid (24 mg, 24%) ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.34 (br. s, 2H), 2.10-2.08 (m, 3H), 0.98 (d, *J* = 6.4 Hz, 6H).[267]

14 Conclusion

In summary, searching for suitable applications for gold complexes bearing NHCs resulted in a series of interesting findings, increasing the array of gold-catalyzed organic reactions.

[(IPr)AuCl] was not only found to be a suitable catalyst for the Meyer-Schuster rearrangement but in a productive collaboration its use in organic synthesis was readily demonstrated with a new synthetic approach for prostaglandins.

Moreover, it was the starting point for the development of a new catalytic system to furanones *via* a tandem reaction pattern, allowing for an easy methodology to obtain this interesting heterocyclic compounds under very mild reaction conditions.

The potential of NHC gold complexes was further illustrated in the successful hydration of alkynes using unprecedented low catalyst loadings. With catalysts loadings as low as 10 ppm [(IPr)AuCl] proved superior in comparison to other catalysts. Important solvent effects were found with different preferences for internal or terminal alkynes and a good understanding of the mechanism was achieved in combination with additional studies on silver free alkyne hydration.

The concept of triple bond activation was further expanded to the first activation of nitriles by gold, formerly supposed not to be activated by gold and therefore used as a throw-away ligands in cationic complexes. It showed however, that nitrile hydration easily occurs under harsher reaction conditions and increased water amounts. [(IPr)AuCl] was also successfully applied in the oxime to amide rearrangement. The reaction proceeds *via* a mechanism involving dehydration into nitriles and subsequent hydration, which why it was envisioned as a possibly gold-catalyzed reaction once nitrile hydration was demonstrated.

Finally, as a result of the frequent presence of water in the organic transformations examined, the formation of new dinuclear gold complexes in the presence of water was observed and further investigated. Importantly, these complexes form easily in reactions conducted in aqueous reaction media and should be therefore considered common. Their significant catalytic activity exclude them as a deactivation pattern whereas a resting state of cationic gold species seems plausible. A series of cationic gold-nitrile was also synthesized to investigate the possibility of a structure-reactivity relationship. Based on NMR and X-ray data, such a relationship was not found.

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17 Appendix

Crystallographic data:

Compound	[{(IPr)Au}$_2$(μ-OH)][NTf$_2$]	[{(IPr)Au}$_2$(μ-OH)][BF$_4$]	[{(IPr)Au}$_2$(μ-OH)][OTf]
Formula	$C_{56}H_{73}Au_2F_6N_5O_5S_2$, CH_2Cl_2	$C_{54}H_{73}Au_2N_4OBF_4$, CH_2Cl_2	$C_{55}H_{73}Au_2N_4O_4F_3S$, 2 CH_2Cl_2
M/g.mol^{-1}	1553.17	1359.83	1507.02
Crystal system	Monoclinic	Monoclinic	Triclinic
Space group	P2(1)/n	P2(1)/c	P-1
a/ Å	19.482(7)	16.919(4)	10.546(2)
b/ Å	16.604(5)	14.891(3)	16.406(3)
c/ Å	21.564(7)	24.136(6)	19.027(3)
α/ °	90.00	90.00	77.772(13)
β/ °	115.751(5)	109.963(4)	84.954(15)
γ/ °	90.00	90.00	81.822(14)
V/ Å^3	6283(3)	5716(2)	3179.0(10)
Z	4	4	2
$\rho calcd$/ g.cm^{-3}	1.642	1.580	1.574
μ(Mo K$_\alpha$)/ mm^{-1}	4.883	5.274	4.864
T/ K	93(2)	93(2)	93(2)
No of reflections	62100	55668	20752
No of unique reflections	11503	10444	11278
R_{int}	0.0658	0.1431	0.0471
$R1$, wR_2 (I > 2σ(I))	0.0417, 0.1099	0.0608, 0.1464	0.0391, 0.0873
$R1$, wR_2 (all data)	0.0450, 0.1125	0.0663, 0.1504	0.0472, 0.0924
GOF	1.084	1.121	1.092

Crystallographic data (continued):

Compound	[{(IPr)Au}$_2$(μ-OH)][FABA]	[{(IPr)Au}$_2$(μ-OH)][SbF_6]	[(IPr)Au(DMSO)][BF_4]
Formula	$C_{78}H_{73}Au_2BF_{20}N_4O$, 2 CH_2Cl_2	$C_{54}H_{73}Au_2F_6N_4OSb$, C_7H_{16}, H_2O, CH_2Cl_2	$C_{29}H_{42}AuBF_4N_2OS$
M/g.mol^{-1}	2037.00	1626.99	750.48
Crystal system	Monoclinic	Triclinic	Monoclinic
Space group	P2(1)/n	P-1	P2(1)/n
a/ Å	20.220(9)	11.5222(19)	8.7189(6)
b/ Å	19.041(8)	15.981(3)	20.6444(14)
c/ Å	21.521(10)	19.203(4)	17.9706(13)
α/ °	90.00	80.120(18)	90.00
β/ °	96.130(7)	74.111(15)	100.341(7)
γ/ °	90.00	79.654(19)	90.00
V/ Å^3	8238(6)	3317.4(10)	3182.1(4)
Z	4	2	4
$\rho calcd$/ g.cm^{-3}	1.642	1.629	1.567
μ(Mo K_α)/ mm^{-1}	3.779	4.956	4.736
T/ K	93(2)	93(2)	125(2)
No of reflections	78850	21552	30938
No of unique reflections	14917	11716	7284
R_{int}	0.0815	0.0570	0.0572
$R1$, wR_2 (I > 2σ(I))	0.0472, 0.1237	0.0716, 0.1900	0.0364, 0.0782
$R1$, wR_2 (all data)	0.0493, 0.1250	0.0838, 0.2031	0.0501, 0.0828
GOF	1.084	1.082	1.155

Crystallographic data (continued):

Compound	[(IPr)Au(NHCOPh)]	[{(IPr)Au}$_2$(PhCONH)][BF_4]	[(IPr)Au(NCPh)][BF_4]
Formula	$C_{34}H_{42}AuN_3O$, 0.5 CH_2Cl_2	$C_{61}H_{78}Au_2BF_4N_5O$, CH_2Cl_2	$C_{34}H_{41}AuN_3BF_4$, CH_2Cl_2
M/g.mol^{-1}	748.14	1462.95	860.40
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	P2(1)/n	P2(1)/c	P2(1)/c
a/ Å	16.719(4)	11.267(2)	25.961(4)
b/ Å	19.348(4)	35.272(5)	19.013(3)
c/ Å	21.476(4)	16.746(3)	16.077(3)
α/ °	90.00	90.00	90.00
β/ °	105.808(5)	102.756(3)	101.407(5)
γ/ °	90.00	90.00	90.00
V/ Å^3	6684(2)	6490.8(19)	7779(2)
Z	8	4	8
$\rho calcd$/ g.cm^{-3}	1.487	1.497	1.469
μ(Mo K_α)/ mm^{-1}	4.511	4.650	3.965
T/ K	93(2)	93(2)	93(2)
No of reflections	42416	63245	48335
No of unique reflections	12182	11864	14076
R_{int}	0.1413	0.0691	0.0503
$R1$, wR_2 (I > 2σ(I))	0.0695, 0.1495	0.0533, 0.1427	0.0527, 0.1333
$R1$, wR_2 (all data)	0.1087, 0.1673	0.0597, 0.1508	0.0727, 0.1439
GOF	1.044	1.091	1.079

Crystallographic data (continued):

Compound	[(IPr)Au(NCC$_6$H$_4$CH$_3$)][BF$_4$]	[(IPr)Au(NCC$_6$H$_4$N(CH$_3$)$_2$)][BF$_4$]
Formula	C$_{35}$H$_{43}$AuN$_3$BF$_4$, 2 CH$_2$Cl$_2$	C$_{36}$H$_{46}$AuN$_4$BF$_4$, 3 CH$_2$Cl$_2$
M/g.mol^{-1}	959.35	1073.32
Crystal system	Monoclinic	Monoclinic
Space group	P2(1)/c	P2(1)/n
a/ Å	24.341(4)	15.861(4)
b/ Å	18.759(3)	18.534(5)
c/ Å	18.782(3)	15.771(4)
α/ °	90.00	90.00
β/ °	106.489(5)	92.336(8)
γ/ °	90.00	90.00
V/ Å^3	8223(2)	4632(2)
Z	8	4
$\rho calcd$/ g.cm^{-3}	1.550	1.539
μ(Mo K$_\alpha$)/ mm^{-1}	3.885	3.570
T/ K	93(2)	93(2)
No of reflections	50954	28800
No of unique reflections	14965	8472
R_{int}	0.0459	0.1316
$R1$, wR_2 (I > 2σ(I))	0.0356, 0.0863	0.2159, 0.4861
$R1$, wR_2 (all data)	0.0426, 0.0906	0.2290, 0.4917
GOF	1.090	1.211

Crystallographic data (continued):

Compound	[(IPr)Au(NCC$_6$H$_4$OCH$_3$)][BF$_4$]	[(IPr)Au(NCC$_6$H$_3$(CH$_3$)$_2$)][BF$_4$]
Formula	C$_{35}$H$_{43}$AuN$_3$OBF$_4$	C$_{36}$H$_{45}$AuN$_3$BF$_4$, 3 CH$_2$Cl$_2$
M/g.mol^{-1}	805.50	1058.30
Crystal system	Triclinic	Monoclinic
Space group	P-1	P2(1)/c
a/ Å	9.397(4)	11.948(3)
b/ Å	13.351(5)	21.257(5)
c/ Å	15.415(5)	18.797(5)
α/ °	103.852(8)	90.00
β/ °	105.809(5)	107.970(7)
γ/ °	103.537(3)	90.00
V/ Å^3	1711.6(11)	4541(2)
Z	2	4
$\rho calcd$/ g.cm^{-3}	1.563	1.548
μ(Mo K$_\alpha$)/ mm^{-1}	4.351	3.639
T/ K	93(2)	93(2)
No of reflections	10598	28961
No of unique reflections	5983	8223
R_{int}	0.0343	0.0933
$R1$, wR_2 (I > 2σ(I))	0.0397, 0.0857	0.0799, 0.1901
$R1$, wR_2 (all data)	0.0440, 0.0900	0.1041, 0.2037
GOF	1.085	1.109

Crystallographic data (continued):

Compound	[(IPr)Au(NCPhBr)][BF_4]	[(IPr)Au(NCC(CH_3)$_3$)][BF_4]
Formula	$C_{34}H_{40}AuBrN_3BF_4$, CH_2Cl_2	$C_{32}H_{45}AuN_3BF_4$, CH_2Cl_2
M/g.mol^{-1}	939.30	840.41
Crystal system	Monoclinic	Monoclinic
Space group	P2(1)/c	P2(1)
a/ Å	10.271(2)	8.554(3)
b/ Å	19.166(4)	18.544(5)
c/ Å	19.988(4)	11.737(3)
α/ °	90.00	90.00
β/ °	103.999(6)	101.568(8)
γ/ °	90.00	90.00
V/ Å^3	3818.0(13)	1823.9(9)
Z	4	2
$\rho calcd$/ g.cm^{-3}	1.634	1.530
μ(Mo K_α)/ mm^{-1}	5.087	4.226
T/ K	93(2)	93(2)
No of reflections	23643	10937
No of unique reflections	6948	5865
R_{int}	0.0548	0.0467
$R1$, wR_2 (I > 2σ(I))	0.0317, 0.0648	0.0401, 0.0975
$R1$, wR_2 (all data)	0.0370, 0.0676	0.0415, 0.0996
GOF	1.033	1.086

Crystallographic data (continued):

Compound	[(IPr)Au(2-cyanopyridine)][BF_4]	[(IPr)Au(4-cyanopyridine)][BF_4]
Formula	$C_{33}H_{40}AuN_4BF_4$	$C_{33}H_{40}AuN_4BF_4$
M/g.mol^{-1}	776.47	776.47
Crystal system	Monoclinic	Monoclinic
Space group	P2(1)/m	P2(1)/c
a/ Å	8.8652(6)	10.230(5)
b/ Å	15.9689(11)	17.221(7)
c/ Å	11.9739(8)	20.039(9)
α/ °	90.00	90.00
β/ °	97.997(7)	96.835(5)
γ/ °	90.00	90.00
V/ Å^3	1678.6(2)	3505(3)
Z	2	4
$\rho calcd$/ g.cm^{-3}	1.536	1.471
μ(Mo K_α)/ mm^{-1}	4.432	4.245
T/ K	125(2)	93(2)
No of reflections	14355	26102
No of unique reflections	3185	5639
R_{int}	0.0316	0.0386
$R1$, wR_2 (I > 2σ(I))	0.0183, 0.0433	0.0552, 0.1644
$R1$, wR_2 (all data)	0.0205, 0.0442	0.0715, 0.2316
GOF	0.986	1.112