

# Hydration Reactions Catalyzed by Transition Metal– NHC (NHC = N-Heterocyclic Carbene) Complexes

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## Contents

|                                                                                          |    |
|------------------------------------------------------------------------------------------|----|
| 1. Introduction .....                                                                    | 4  |
| 2. NHC–metal catalyzed hydration of alkynes.....                                         | 7  |
| 2.1 NHC–Au catalyzed hydration of alkynes.....                                           | 7  |
| 2.1.1 Overview.....                                                                      | 7  |
| 2.1.2 2003-2010.....                                                                     | 8  |
| 2.1.3 2011-2022.....                                                                     | 14 |
| 2.2 NHC–Au catalyzed hydration of alkynes by encapsulated and immobilized catalysts..... | 35 |
| 2.3 NHC–Pt catalyzed hydration of alkynes.....                                           | 41 |
| 3. NHC–metal catalyzed hydration of allenes.....                                         | 42 |
| 3.1 NHC–Au catalyzed hydration of allenes.....                                           | 42 |
| 4. NHC–metal catalyzed hydration of nitriles.....                                        | 43 |
| 4.1 NHC–Au catalyzed hydration of nitriles.....                                          | 43 |
| 4.2 NHC–Ag catalyzed hydration of nitriles.....                                          | 47 |

|                                                 |    |
|-------------------------------------------------|----|
| 4.3 NHC–Ru catalyzed hydration of nitriles..... | 47 |
| 4.4 NHC–Os catalyzed hydration of nitriles..... | 48 |
| 4.5 NHC–Rh catalyzed hydration of nitriles..... | 50 |
| 4.6 NHC–Ni catalyzed hydration of nitriles..... | 52 |
| 5. Conclusions and Outlook .....                | 53 |
| 6. Author Information.....                      | 55 |
| 7. Acknowledgements .....                       | 55 |
| 8. References .....                             | 56 |

The catalytic addition of water to unsaturated C–C or C–N  $\pi$  bonds represent one of the most important and environmentally sustainable methods to form C–O bonds for the production of synthetic intermediates, medicinal agents and natural products. The traditional acid-catalyzed hydration of unsaturated compounds typically requires strong acids or toxic mercury salts, which limits practical applications and presents safety and environmental concerns. Today, transition-metal-catalyzed hydration supported by NHC (NHC = N-heterocyclic carbene) ligands has attracted major attention. By rational design of ligands, choice of metals and counterions as well as mechanistic studies and the development of heterogeneous systems, major progress has been achieved for a broad range of hydration processes. In particular, the combination of NHC ligands with gold shows excellent reactivity compared with other catalytic systems; however, other systems based on silver, ruthenium, osmium, platinum, rhodium and nickel have also been discovered. Ancillary NHC ligands provide stabilization of transition metals and ensure high catalytic activity in hydration owing to their unique electronic and steric properties. NHC–Au(I) complexes are particularly favored for hydration of unsaturated hydrocarbons due to soft and carbophilic properties of gold. In this review, we present a comprehensive overview of hydration reactions catalyzed by transition metal–NHC complexes and their applications in catalytic hydration of different classes of  $\pi$ -substrates with a focus on the role of NHC ligands, types of metals and counterions.

Keywords: N-heterocyclic carbenes; hydration; ligands; transition-metal-catalysis; alkynes; allenes; nitriles

## 1. Introduction

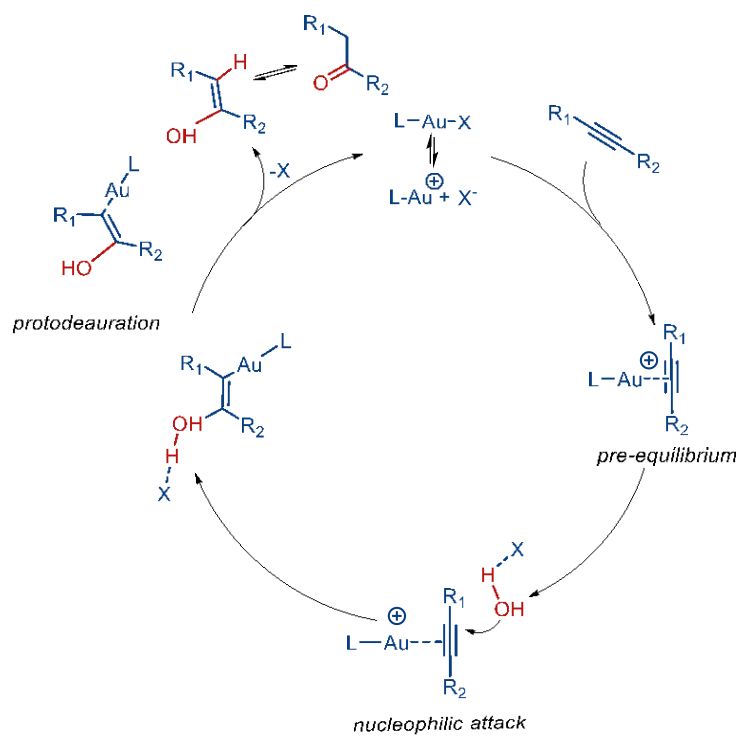
The addition of a water molecule to C–C and C–N  $\pi$ -bonds to produce carbonyl compounds is a classic transformation in industrial and academic research [1]. Hydration reactions of alkynes, nitriles and allenes are regarded as an atom-economical and environmentally-friendly method of converting feedstock materials into high value carbonyl, amide and alcohol products with broad utility in the synthesis of fine chemicals, pharmaceutical agents and complex natural products [1].

The first alkyne hydration reaction was reported by Kutscheroff in 1881 using Hg as a catalyst [2]. Since then, major efforts have been devoted to developing more benign catalysts, and among them, transition metals have emerged as a particularly attractive alternative [3]. After Herrmann reported the first NHC–gold complex in alkyne hydration in 2003 [4], the Nolan group reported a breakthrough in NHC–Au-catalyzed hydration reactions in 2009 by developing highly active [(IPr)AuCl] for alkyne hydrations [5]. Although after this discovery various NHC-ligated transition metals, such as Au, Pt, Ag, Ru, Os, Rh, Ni, have been developed for hydration reactions, the most reactive are gold(I)–NHC complexes [6].

NHC (NHC = N-heterocyclic carbene) ligands are widely used in catalysis as ancillary ligands stabilizing transition metals [7]. Their strong  $\sigma$ -donating and  $\pi$ -accepting ability, combined with variable steric hindrance permit for strong metal–ligand bonds and prevent complex decomposition [8]. A general class of NHC–metal complexes used in hydration reaction is [NHC–M–X] (M = transition metal; X = counterion). Mechanistically, the active species is considered as a cationic [ $L_nM^+$ ] obtained by counterion abstraction from a well-defined [NHC–M–X] complex (Scheme 1). There are three main steps in hydration reactions: (i) coordination and activation alkyne, (ii) nucleophilic attack, and (iii) proton transfer and protodeauration [9]. The major factors that affect hydration reactions are (i) ligands, (ii) metals, (iii) counterions, and (iv) reaction conditions. NHC ligands provide strong metal–NHC bond, preventing catalyst decomposition and the formation of a resting state, by increasing the stability and lifetime of the active species [10]. The bulkiness and strong  $\sigma$ -donation of NHCs provide steric shielding and strong NHC–Au bonds, enabling high activity in hydration reactions [10a, 11]. Gold as a

soft and carbophilic metal is favored for the activation of unsaturated hydrocarbons [12]. Recently, the counterion effect in hydration reactions was systematically investigated by the Zuccaccia group [9b, 13]. It was found that the basicity of the counter anion played a significant role in each step of the mechanism, while counter anions with moderate basicity and coordination have generally been favored. The study highlighted that the appropriate matching of NHC ligand and counter anion is required to achieve high activity.

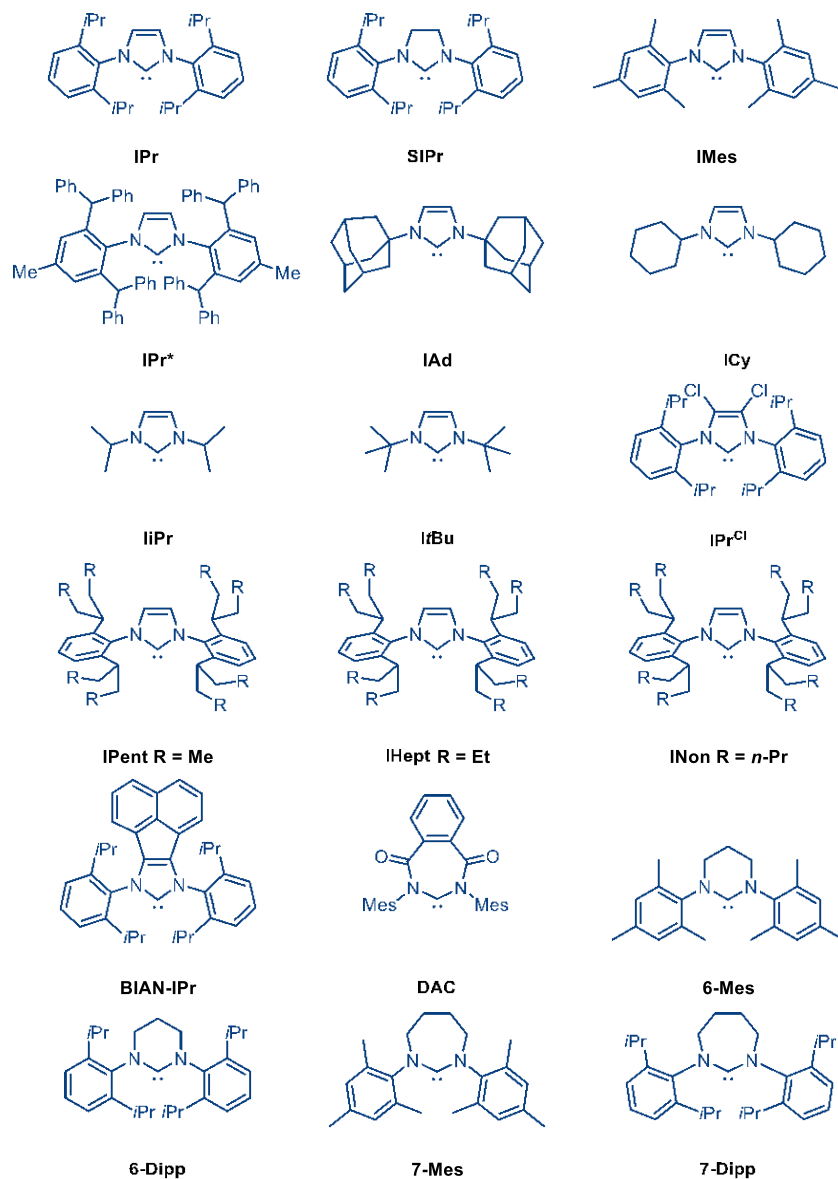
**Scheme 1.** General mechanism for gold-catalyzed hydration.



In this review, we present a comprehensive overview of hydration reactions catalyzed by NHC-transition metal complexes. The review covers the literatures since 2003 through 2022 focusing on NHC ligands, their structure and activity in hydration reactions. With regard to  $\pi$ -systems, hydration reactions of alkynes, nitriles and allenes are discussed. Heterogeneous catalysts based on NHCs, such as encapsulated and immobilized NHC-metal complexes are also covered.

This review is organized by the type of  $\pi$ -substrates (alkyne, allene and nitrile) and further divided by the type of metals used in hydration reactions catalyzed by NHC-metal complexes. Gold(I)-NHCs are the most common and the most reactive class of metal-NHC complexes in catalysis. The structures of the most common used NHC ligands in hydration reactions are shown in Figure 1.

We hope that by discussing the relationship between the structure of NHC ligands and the catalytic efficiency, the readers will gain a complete overview and better understanding of the role of NHC ligands in this important area. We further hope that this review will stimulate the development of more efficient, more environmentally-friendly and scalable protocols by designing new reaction strategies and more efficient NHC–metal catalysts.



**Figure 1.** Structures of the most common NHC ligands used in the transition metal-catalyzed hydration reactions.

## 2. NHC–metal catalyzed hydration of alkynes

In 2003, Herrmann and coworkers reported the first example of NHC–transition metal catalyzed alkyne hydration [4]. In 2009, Nolan pioneered the highly efficient [(IPr)AuCl] catalytic system which showed superior reactivity in hydration reactions [5]. Notably, very low catalyst loading (10-1000 ppm) was sufficient to achieve high conversions. After this seminal report, the use of Au(I)–NHCs in alkyne hydrations has rapidly increased during the last decade. In particular, new NHC ligands have been developed and applied in gold(I)-catalyzed homogeneous alkyne hydration. Furthermore, water-soluble NHC–Au complexes were developed and showed high efficiency. In addition, new applications of encapsulated and immobilized NHC–Au complexes have been demonstrated.

### 2.1. NHC–Au catalyzed hydration of alkynes

#### 2.1.1 Overview

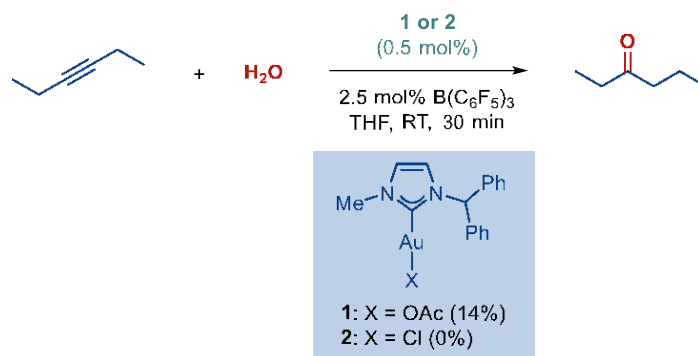
Among NHC–M-catalyzed hydration of alkynes, NHC–Au–X is the most reactive catalytic system due to excellent carbophilic  $\pi$ -acidity of gold(I) and good stability. In contrast, much less studies have been reported on NHC–Au(III) complexes due to their relatively lower stability and reactivity to activate  $\pi$ -systems (see, Schemes 3, 25, 37). Although the stability of Au(III)–NHC is lower than that of Au(I)–NHCs, it should be noted that NHC–Au(III) complexes are still considerably more stable and more resistant to decomposition than phosphine–Au(III). In terms of NHC ligand structure-reactivity relationship for alkyne hydration reactions, it is worth mentioning that to date IPr is by far the most reactive and most general NHC ligand. In general, reactive NHC ligands for this class of reactions should feature the most balanced steric hindrance of N-wingtip substituents and strong  $\sigma$ -donor electronic properties. Based on the reported studies, the catalytic reactivity of NHC ligands generally decreases when there is too much bulk or too little bulk compared to IPr (see, Schemes 11, 15, 19, 23). Furthermore, in addition to the classical five-membered NHCs, the expanded ring NHCs, such as six-membered and seven-membered NHCs have been screened and showed promising but lower reactivity in the hydration reactions (see, Schemes 7, 11, 40). In addition, it is worth noting that the more electron

donating abnormal NHCs (see, Schemes 12, 17) have been shown to be less reactive than IPr, which indicated that the balance between electronic properties of NHC ligands is favored. Overall, thus far, the imidazol-2-ylidene IPr ligand is the most popular and reactive NHC ligand for alkyne hydration. In terms of the anion effects, anions with moderate coordinating ability and basicity, such as  $\text{SbF}_6^-$ ,  $\text{OTf}^-$ ,  $\text{NTf}_2^-$  are favored (see, Scheme 27). In addition, to the direct alkyne hydration reactions, the NHC–Au-catalyzed tandem hydration-reduction transformation are also reviewed (see, Scheme 13, 21, 42). The following sections outline the applications of Au–NHC complexes in hydration of alkynes. The section has been arranged in chronological order due to overlap between classes of Au–NHC complexes used.

### 2.1.2. 2003-2010

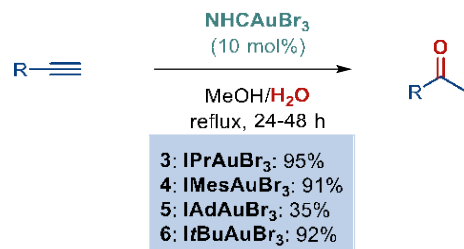
In 2003, the first example of Au–NHC catalyzed hydration of alkyne was reported by Herrmann and co-workers (Scheme 2) [4]. They prepared  $[\text{Au}(\text{R}_2\text{-imy})\text{X}]$  ( $\text{R}_2\text{-imy}$  = 1-diphenylmethyl-3-methyl-imidazol-2-ylidene;  $\text{X} = \text{Cl}, \text{OC}(\text{O})\text{CH}_3$ ) via transmetallation of the corresponding silver precursor. Complex **1** or the in situ formed **1** was successfully applied as a catalyst in the hydration of 3-hexyne in the presence of Lewis acid co-catalyst,  $\text{B}(\text{C}_6\text{F}_5)_3$ . The analogous Lewis acid,  $\text{BF}_3 \cdot \text{OEt}_2$ , was shown to be unreactive due to the formation of carbene borane adducts by the less bulky  $\text{BF}_3 \cdot \text{OEt}_2$ . THF was shown to be a better solvent than MeOH, which was proposed to act as a competing nucleophile hampering the addition of water. Importantly, in this early study, Herrmann found complex **2** was unreactive which indicated that a weakly coordinating anion is required to form the active  $[\text{LAu}^+]$  cation. However, at that point, the catalytic efficiency of complex **1** was inferior to the previously reported phosphine–gold(I) complexes [3e].

**Scheme 2.** Hydration of 3-hexyne with complexes **1-2**.



In 2007, the Nolan group reported the first use of a (NHC)–Au(III) complex to catalyze the hydration reaction of alkynes (Scheme 3) [14]. A series of [NHC–Au<sup>III</sup>Br<sub>3</sub>] complexes **3–6** was prepared. Catalytic studies showed [IPrAuBr<sub>3</sub>] to have the best catalytic activity in MeOH as a solvent at 10 mol% catalyst loading for the hydration of terminal alkynes. However, these complexes were inefficient with internal alkynes. Importantly, the authors found that when 1 equiv silver salt was added (cf. complex), the catalytic efficiency was dramatically improved, and this allowed reduce the catalyst loading to 2 mol%.

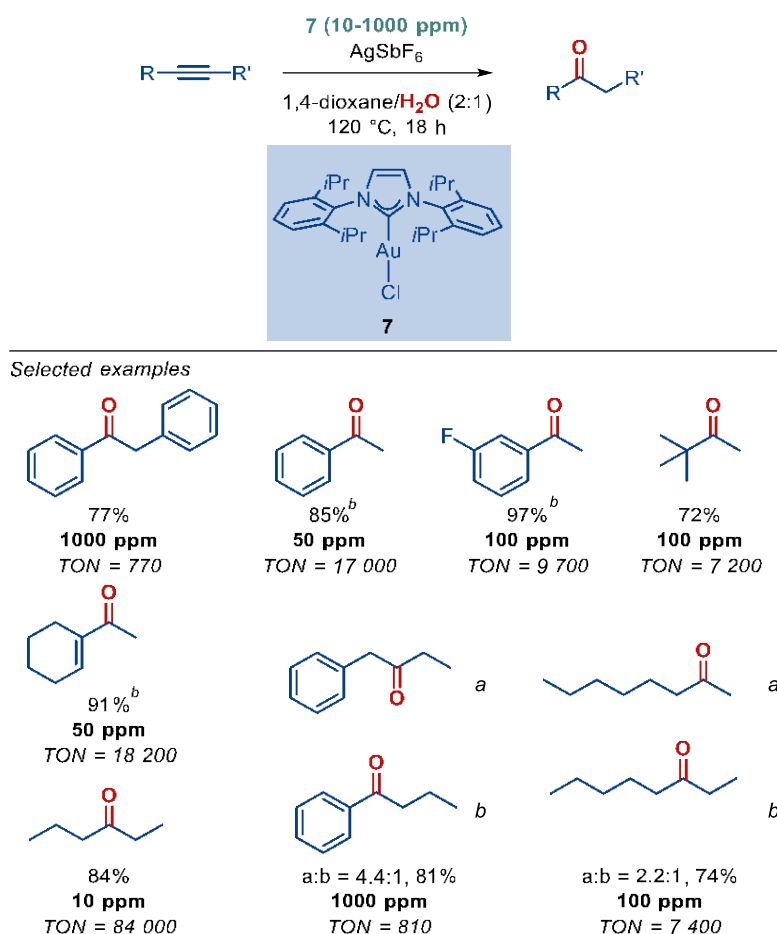
**Scheme 3.** Hydration of terminal alkynes with complexes **3-6**.



In 2009, a highly efficient Au(I)–NHC catalytic system was reported by Nolan and co-workers (Scheme 4) [5]. The catalytic system **7** [(IPr)AuCl]/AgSbF<sub>6</sub> featured very low catalyst loadings, (typically, 10-100 ppm), very wide scope of different alkynes and acid-free conditions for alkyne hydration. Crucially, during the optimization studies, the authors showed that NHC ligand played an important role; interestingly, less bulky IMes showed no reactivity, while ItBu was less reactive than IPr. Different solvent systems of dioxane/water and methanol/water were developed for hydration reactions at 120 °C. High yields and TON were achieved for wide substrate scope, including terminal and internal alkynes, alkyl-substituted and aryl-substituted alkynes, symmetrical and unsymmetrical disubstituted alkynes. Specifically, hexan-3-one product was formed at TON of 84,000.

In this system, NHCs as strong  $\sigma$ -donors, [(IPr)AuCl]/AgSbF<sub>6</sub>, showed high efficiency, which had been discussed by Teles in terms of hydration reactions facilitated by electron-poor ligands [15]. The study by the Nolan group indicated that protodeauration and catalyst stability as well as coordination with alkyne are important factors in gold(I)-catalyzed hydrations. The [(IPr)AuCl]/AgSbF<sub>6</sub> system was later investigated by the Corma group in 2013. In kinetic studies of the hydration of diphenylacetylene catalyzed by [(IPr)AuCl]/AgSbF<sub>6</sub>, they discovered an induction time at the beginning of the reaction. They suggested that small gold clusters containing 3-6 atoms might be the catalytically active species [16].

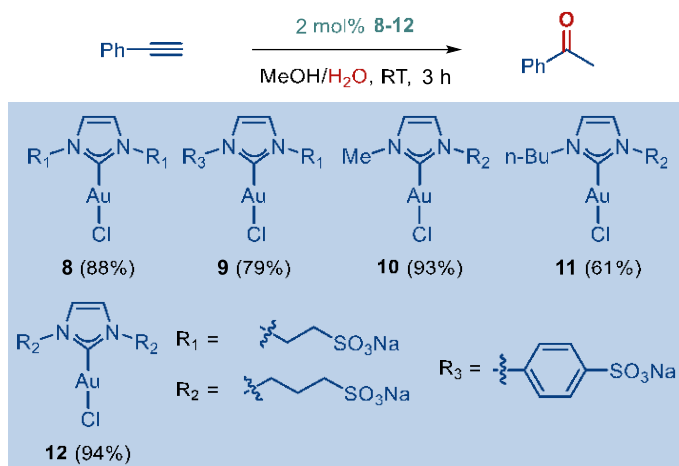
**Scheme 4.** Hydration of alkyne with complex **7**.



In 2010, the Joó group synthesized a series of novel water-soluble gold(I) sulfonated imidazol-2-ylidene complexes (Scheme 5) [17]. Complexes **8–12** showed good activity in the hydration of terminal alkynes in refluxing MeOH/H<sub>2</sub>O solutions. Among them, complex **8** was used to further explore the effect of additives. They found that adding 10 mol% H<sub>2</sub>SO<sub>4</sub> increased the reaction rate. Surprisingly, the

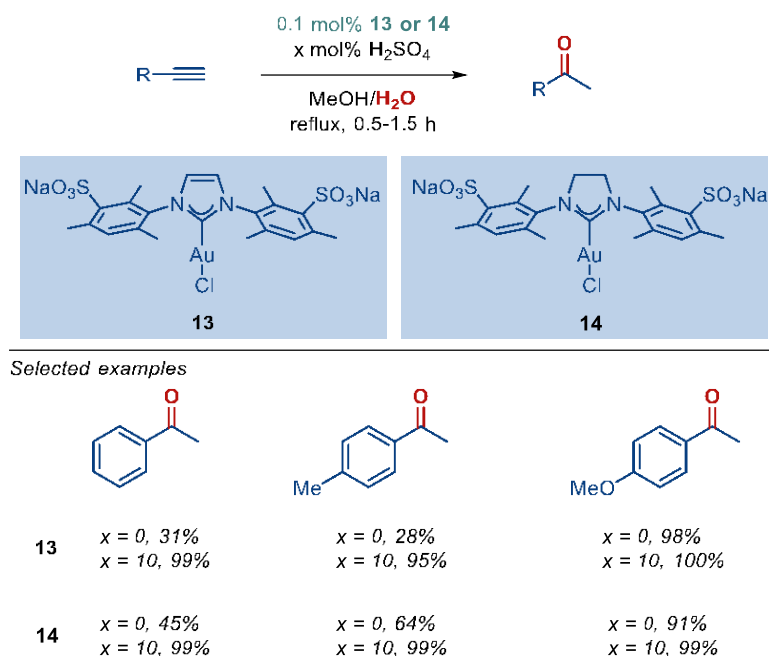
silver additive AgOTf, a common co-catalyst in hydration reactions, decreased the activity of this catalyst, which was explained by the decomposition of the catalyst by the resulting AgCl precipitate. Solvent effects were also considered; in general, hydration of phenylacetylene catalyzed by complex **8** in refluxing neat methanol gave 2.7 % ketone product. On the other hand, the low conversion of 17% in refluxing neat water was attributed to the low solubility of alkyne substrates.

**Scheme 5.** Hydration of phenylacetylene with complexes **8-12**.



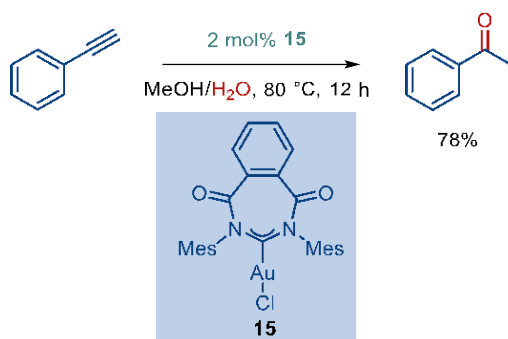
Subsequently, the Joó group reported another class of water-soluble, sulfonated IMes and SIMes gold(I)-NHC complexes (Scheme 6) [18]. Both complexes **13** and **14** displayed good catalytic activity in hydration of terminal aromatic and aliphatic alkynes. The turnover frequency (TOF) was determined up to 1,990  $\text{h}^{-1}$  in the hydration of ethynyltoluene with 0.1 mol% catalyst. The reaction rate could be increased by using a combination of 10%  $\text{H}_2\text{SO}_4$  in refluxing  $\text{MeOH/H}_2\text{O}$ . For electron-rich 4-ethynylanisole as a substrate, the reaction proceeded in high efficiency without any added acid using catalysts **13** or **14** at 0.1 mol% loading. However, complexes **13** and **14** were less reactive for internal alkynes.

**Scheme 6.** Hydration of alkynes with complexes **13-14**.



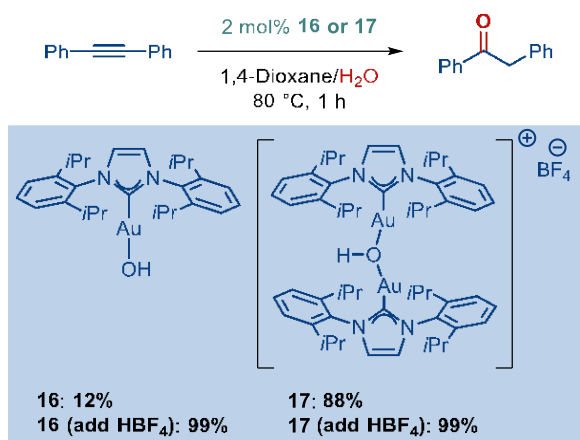
In 2010, Bielawski and co-workers developed a seven-membered *N,N'*-diamidocarbene (DAC) and applied DAC–Au(I) complex **15** in hydration of phenylacetylene (Scheme 7) [19]. The Tolman electronic parameter (TEP) of **15** was calculated to be 2047 cm<sup>-1</sup> from its [NHCRh(CO)<sub>2</sub>Cl] complex, which indicated that **15** is a stronger  $\sigma$ -donor than IMes (TEP = 2050.7 cm<sup>-1</sup>) and six-membered DACs (TEP = 2055 cm<sup>-1</sup>). This TEP result was unexpected because electron-withdrawing amide carbonyl groups should lower carbene donicity. The authors proposed that the strong donicities of seven-membered DACs are attributed to an increased N–C–N angle and sp-character of the carbenic carbon. The catalytic ability of complex **15** was tested in hydration of phenylacetylene. Although only 78% conversion was obtained at 2 mol% catalyst loading, the reaction worked under silver and additive-free conditions.

**Scheme 7.** Hydration of phenylacetylene with complex **15**.



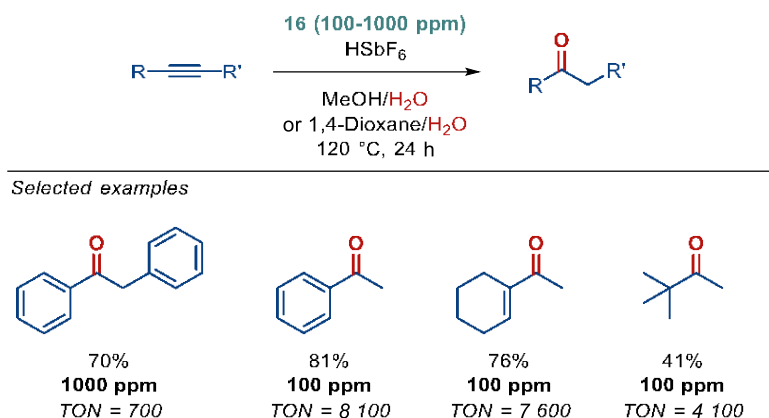
In 2010, the Nolan group developed a versatile, silver-free protocol for Au(I)–NHC-catalyzed hydration of alkynes (Scheme 8) [20]. In this design, the hydroxide NHC–Au complex **16** acts as a precatalyst, which is activated in the presence of HBF<sub>4</sub>. The di-carbene complex [Au(IPr)<sub>2</sub>](BF<sub>4</sub>) is unreactive in hydration reaction due to decomposition. The hydroxide-bridged complex **17** was prepared from **16** using half an equivalent of aqueous HBF<sub>4</sub>. The best result was obtained by using complex **16** or **17** in the presence of one equivalent of HBF<sub>4</sub>. Interestingly, di-nuclear gold hydroxide complex **17** showed good efficiency (88%) without the activation with HBF<sub>4</sub>.

**Scheme 8.** Hydration of diphenylacetylene with complexes **16-17**.



At the same time, the Nolan group further optimized different acids, HBF<sub>4</sub>, HSbF<sub>6</sub>, HNTf<sub>2</sub>, to activate the gold-hydroxide complex **16** (Scheme 9) [20]. They identified that HSbF<sub>6</sub> and HNTf<sub>2</sub> showed better efficiency than HBF<sub>4</sub>. A series of alkyne substrates were tested at 100–1,000 ppm catalyst loading using complex **16** and HSbF<sub>6</sub>. Although the efficiency was slightly lower than the original [IPrAuCl]/AgSbF<sub>6</sub> system, this protocol obviates the need for using silver salt as halide abstractor.

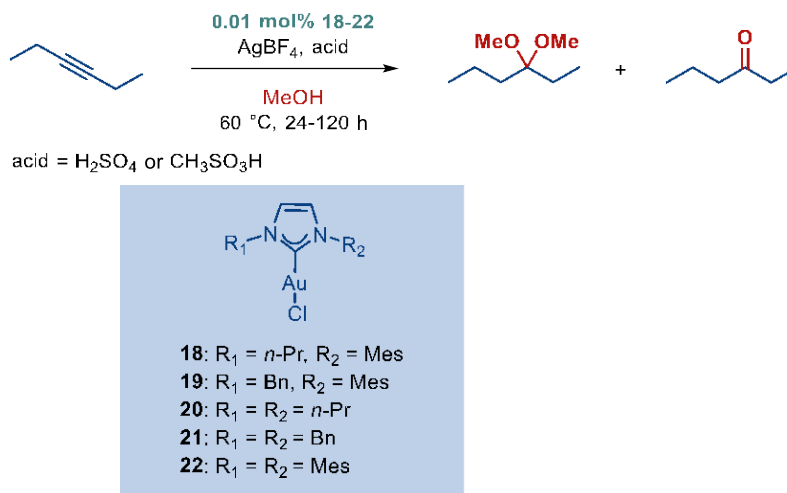
### Scheme 9. Hydration of alkynes with complex **16**.



#### 2.1.3. 2011-2022

In 2011, the Thieuleux group reported a series of symmetrical and unsymmetrical Au(I)–NHC complexes for the addition of alcohols and water to 3-hexyne (Scheme 10) [21]. This reaction was catalyzed by catalysts **18–22** in the presence of acid H<sub>2</sub>SO<sub>4</sub> or CH<sub>3</sub>SO<sub>3</sub>H. High conversions (from 70% to 100%) were achieved at 0.01-0.0001 mol% catalyst loading. Interestingly, the authors found that symmetrical complexes **20–22** were inactive. However, unsymmetrical complexes **18–19** were highly reactive at low catalyst loading and with high TON.

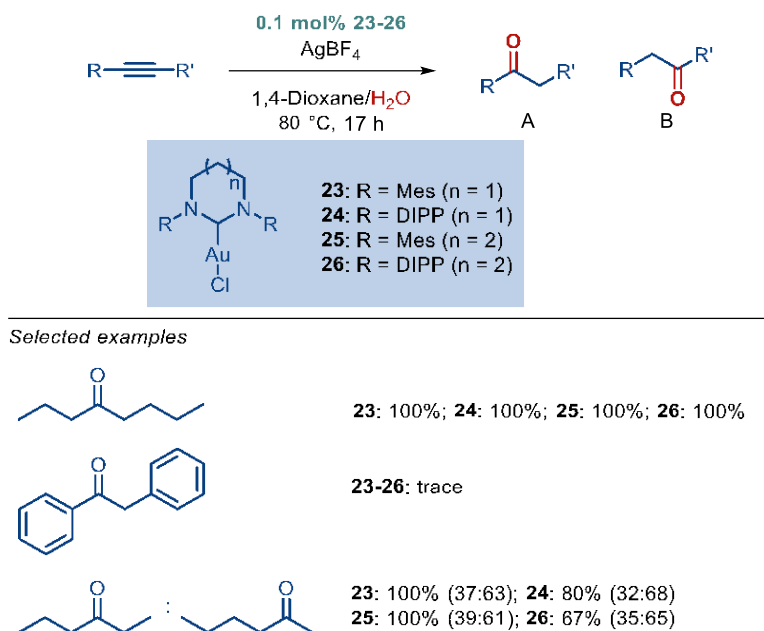
### Scheme 10. Hydration of alkynes with complexes **18–22**.



In 2012, the Cavell group reported ring-expanded six- and seven-membered NHC–Au(I) complexes in alkyne hydration (Scheme 11) [22]. The key feature of these NHC ligands is increased steric demand. The percent buried volume (%V<sub>bur</sub>) is in the following order: seven-membered ring > six-membered ring > five-membered ring, IPr > IMes. In particular, seven-membered ring-expanded carbenes are more

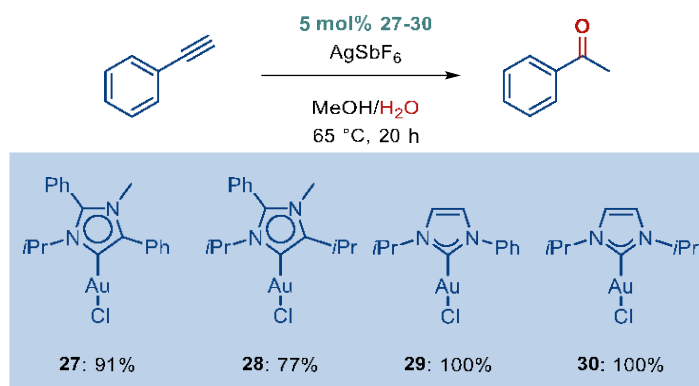
basic and more sterically-hindered due to decreased  $C_{(\text{carbene})}\text{--N--C}_{(\text{Ar})}$  angle [23]. The corresponding Au(I)–NHC complexes **23–26** showed similar levels of efficiency in hydration of aliphatic alkynes, where the more sterically-hindered complexes **24** and **26** showed lower reactivity than complexes **23** and **25**. Unexpectedly, all complexes **23–26** were found to be inactive in the hydration of aromatic alkynes, such as phenylacetylene and diphenylacetylene.

**Scheme 11.** Hydration of alkynes with complexes **23–26**.



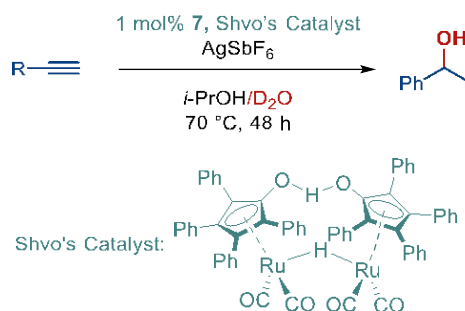
In 2012, the Hong group conducted a comparative study between abnormal N-heterocyclic carbenes (*a*NHC) and imidazol-2-ylidene NHCs in alkyne hydration (Scheme 12) [24]. The authors proposed that *a*NHCs could offer new opportunities in hydration catalysis due to their stronger  $\sigma$ -donor properties than imidazol-2-ylidenes [25].  $[(a\text{NHC})\text{AuCl}]$  **27–28** were prepared via transmetalation of the corresponding  $[(a\text{NHC})\text{AgI}]$ . Interestingly, X-ray studies and DFT calculations revealed that *a*NHC complexes **27–28** have longer Au– $C_{(\text{carbene})}$  bonds and stronger binding energies than the sterically-similar imidazol-2-ylidene complexes **29–30**. In comparison with imidazol-2-ylidenes **29–30**,  $[(a\text{NHC})\text{AuCl}]$  **27–28** showed decreased efficiency in the hydration of phenylacetylene. This study showed that *a*NHC gold complexes are less reactive than imidazol-2-ylidenes in alkyne hydration reactions.

**Scheme 12.** Hydration of alkynes with complexes **27–30**.



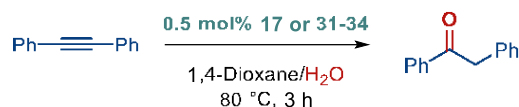
In 2012, the Herzon group reported regioselective reductive hydration of alkynes using a combination of  $[(\text{IPr})\text{AuCl}]/\text{AgSbF}_6$  and Shvo's Catalyst (Scheme 13) [26]. This protocol allows for the formation of secondary alcohols with branched selectivity in one step from alkynes.

**Scheme 13.** Reductive hydration with complex **7** and Shvo's Catalyst.



In 2013, Nolan and co-workers prepared new di-gold hydroxide complexes **32–34** and compared their reactivity in the hydration of alkynes with the known complexes **17** and **31** (Scheme 14) [27, 20]. This class of di-nuclear organogold complexes have attracted increased attention due to the potential for a dual  $\sigma,\pi$ -activation of terminal alkynes [28]. In their study, the Nolan group selected hydration of the challenging diphenylacetylene as a model reaction. Their results showed that di-gold complexes bearing **17** and **32** bearing  $\text{IPr}$  and  $\text{IPr}^{\text{Cl}}$  have the highest efficiency and can catalyze the reaction even at 0.1 mol% to 0.05 mol% loading. Importantly, these catalysts are highly active without any additives.

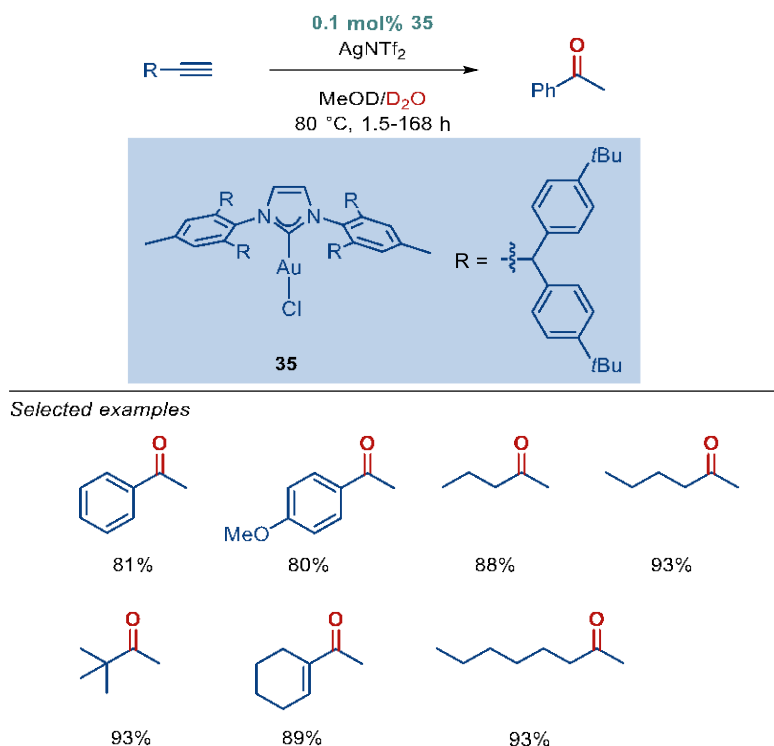
**Scheme 14.** Hydration of diphenylacetylene with complexes **17** and **31–34**.



**17:**  $[\{\text{Au}(\text{IPr})\}_2(\mu\text{-OH})][\text{BF}_4]$  92%  
**31:**  $[\{\text{Au}(\text{SIPr})\}_2(\mu\text{-OH})][\text{BF}_4]$  83%  
**32:**  $[\{\text{Au}(\text{IPr}^{\text{Cl}})\}_2(\mu\text{-OH})][\text{BF}_4]$  91%  
**33:**  $[\{\text{Au}(\text{IPr}^*)\}_2(\mu\text{-OH})][\text{BF}_4]$  55%  
**34:**  $[\{\text{Au}(\text{IPent})\}_2(\mu\text{-OH})][\text{BF}_4]$  74%

In 2013, the Straub group synthesized and characterized highly sterically-hindered NHC–Au gold complex, IPr\*\*AuCl (**35**), which is based on IPr\* class of N-heterocyclic carbenes (Scheme 15) [29]. They suggested that sterically demanding ancillary ligands could be more effective in hydration reactions due to the formation of higher concentrations of the active cationic  $[\text{LAu}^+]$  as well as steric inhibition of catalyst decomposition and formation of inactive di-nuclear resting states. The authors found that the addition of  $\text{HNTf}_2$  facilitated the hydration rate. Furthermore, they identified a primary kinetic isotope effect in the reaction, which indicated the protonolysis of the gold-carbon bond might be the rate-limiting step. Complex **35** was active in the hydration of terminal alkynes at 0.1 mol% loading.

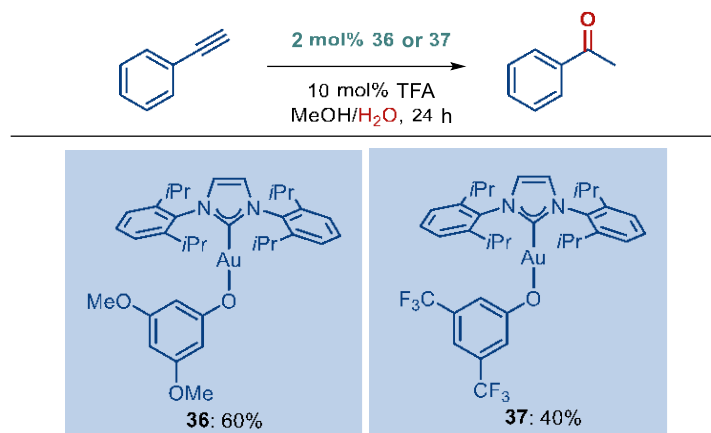
**Scheme 15.** Hydration of alkyne with complex **35**.



In 2013, Hashmi and co-workers investigated a series of NHC–gold(I) phenolate complexes (Scheme 16) [30]. Computational natural bond order analysis revealed three-center/four-electron hyperbonds of

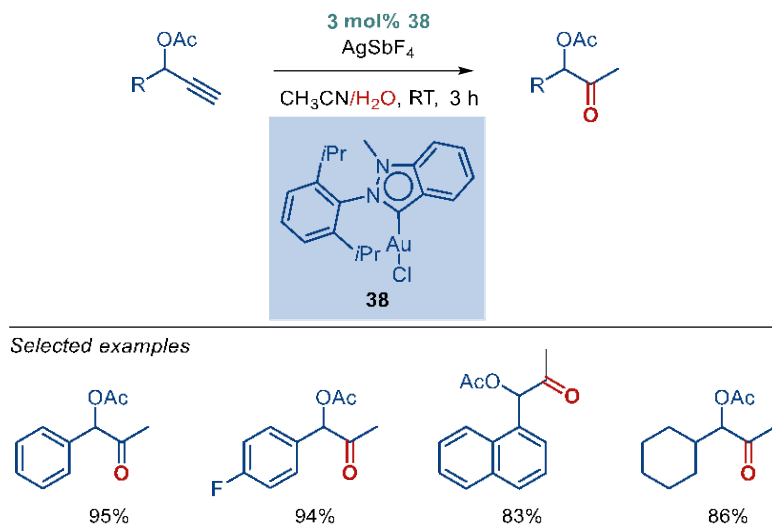
carbene–Au–O bond with an approximate 60:40 distribution in favor of the C<sub>(carbene)</sub>–gold bond. Complexes **36** and **37** were tested in alkyne hydration, showing moderate activity in the presence of 10 mol% TFA (Scheme 16). The authors proposed that incomplete conversions were due to the reductive properties of the phenolate counterions, which shortened the catalyst lifetime [30].

**Scheme 16.** Hydration of phenylacetylene with complexes **36–37**.



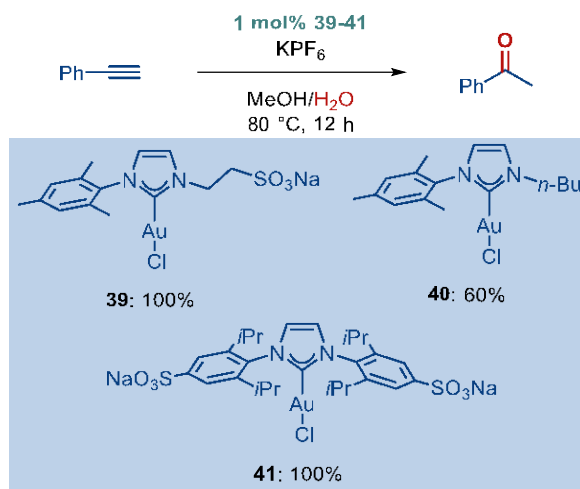
In 2013, Zhao and co-workers developed a series of indy–NHC ligands (indy = indazolin-*s*-ylidene) for Au(I)-catalyzed hydration of terminal alkynes (Scheme 17) [31]. These indy–NHCs belong to non-classical N-heterocyclic carbenes with strong  $\sigma$ -donating ability. Gold(I) complex **38** was used in hydration of terminal alkynes at 3 mol% loading. Although the catalyst loading is relatively high, the obtained yields are generally excellent, and the reaction proceeded at room temperature.

**Scheme 17.** Hydration of alkyne with complex **38**.



In 2013, the Silbestri group synthesized and characterized sulfonated gold(I)–NHC complexes **39** and **41** and compared their reactivity with non-sulfonated analogues in alkyne hydration (Scheme 18) [32]. Interestingly, complexes **39** and **41** bearing N-alkyl vs. N-Ar wingtips showed similar activity in the hydration of phenylacetylene, giving quantitative conversions at 80 °C after 12 h. In contrast, non-sulfonated analogous complexes **40** and **7** showed lower activity and longer reaction time was required to give higher yield. Furthermore, compared with complexes **7** and **40**, sulfonated complexes **39** and **41** featured high levels of recyclability (up to 5 times with >80% yield). The high recyclability was explained by the fact that sulfonated NHC–gold(I) could be efficiently trapped in the aqueous phase, while **40** and **7** decayed faster in aqueous phase after extraction with organic solvents.

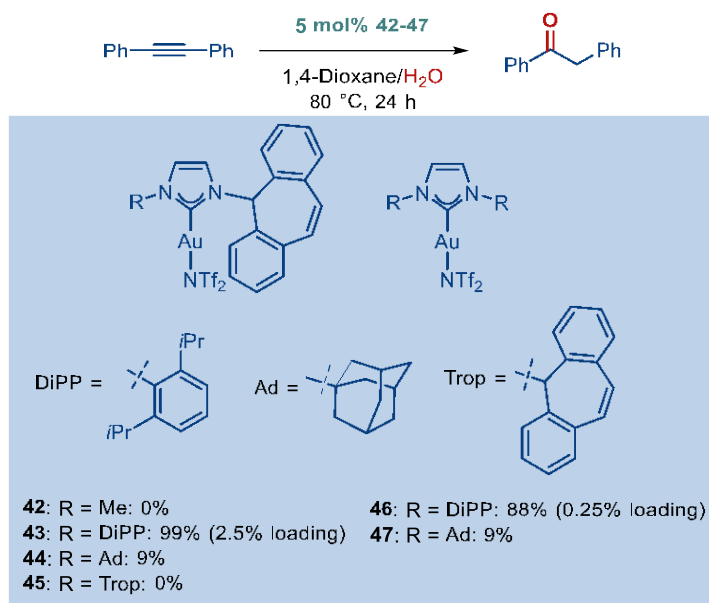
**Scheme 18.** Hydration of phenylacetylene with complexes **39**–**41**.



In 2014, the Nolan group synthesized and characterized gold(I) complexes of dibenzotropyliene NHC ligands (Trop-NHCs) (Scheme 19) [33]. The X-ray structures of gold complexes revealed that the Trop group is a flexible-yet-bulky substituent, which can adopt less and more bulky conformations (*endo* and *exo* of the Trop unit) in the solid state. The authors hypothesized on a possible interaction of the olefin unit with the gold center in this class of catalysts. The authors found that N-aryl-substituted catalysts **43** and **46** were active in the hydration of diphenylacetylene. On the contrary, N-alkyl-substituted Trop-NHCs were inactive in the same hydration reaction. Complexes **42** and **45** gave no conversion, while complexes **44** and **47** afforded ca. 10% conversion. The authors attributed this

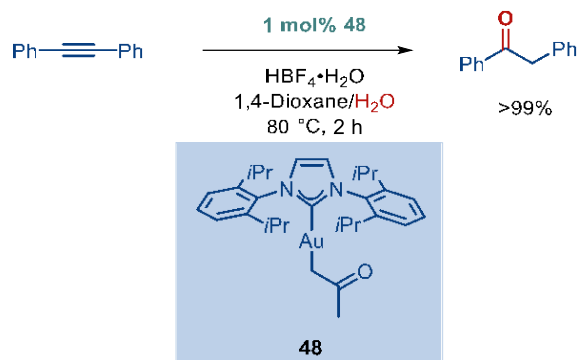
difference in reactivity to the increased sensitivity of N-alkyl-substituted NHCs to hydrolysis under aqueous conditions.

**Scheme 19.** Hydration of diphenylacetylene with complexes **42-47**.



In 2015, NHC–gold–acetyl complex **48** was synthesized by the Nolan group from NHC·HCl in the presence of acetone and a large excess of  $\text{K}_2\text{CO}_3$  (Scheme 20) [34]. This intriguing complex was tested in the hydration of diphenylacetylene. The authors found that the best reaction conditions were achieved by using 1 mol% **48** and 2 mol%  $\text{HBF}_4 \cdot \text{H}_2\text{O}$ , while **48** or  $\text{HBF}_4 \cdot \text{H}_2\text{O}$  alone were ineffective. In this case, using a slight excess of  $\text{HBF}_4 \cdot \text{H}_2\text{O}$  facilitated the formation of the active  $[\text{LAu}^+]$  species.

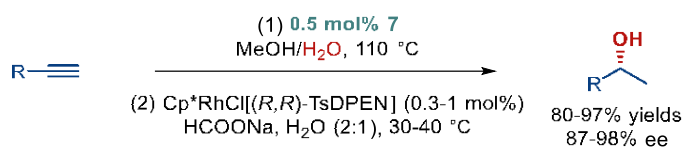
**Scheme 20.** Hydration of diphenylacetylene with complex **48**.



In 2015, the Li group found that the well-defined complex **7**  $[(\text{IPr})\text{AuCl}]$  can catalyze the hydration of terminal alkynes without silver additives to abstract the halide (Scheme 21) [35]. However, in the

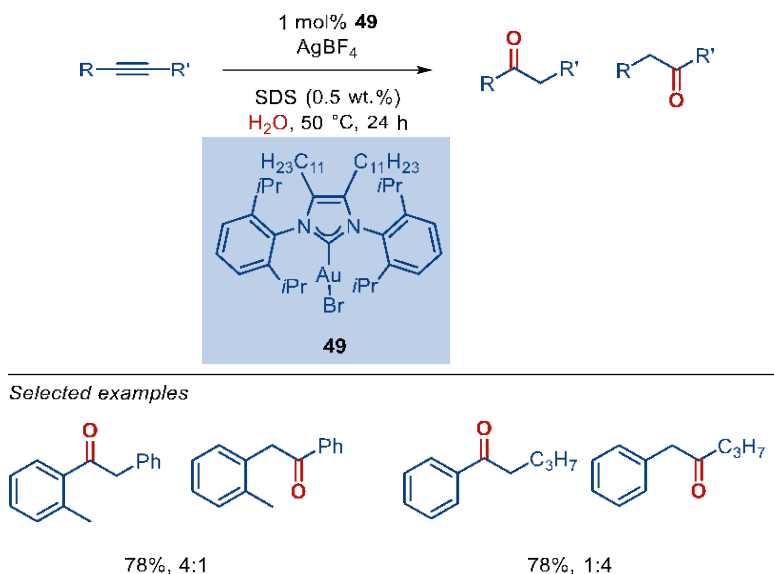
absence of silver salts, internal alkynes cannot be transformed to ketone products. Furthermore, they developed a sequential protocol to afford chiral secondary alcohols from terminal alkynes using the combination of [(IPr)AuCl] and Cp<sup>\*</sup>RhCl[(*R,R*)-TsDPEN] (TsDPEN = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine, Cp<sup>\*</sup> = pentamethylcyclopentadienyl). Overall, this method provided a new pathway to prepare optically active secondary alcohols with high enantioselectivity (89%-99% ee) from terminal alkynes.

**Scheme 21.** Hydration of diphenylacetylene with complex **7**.



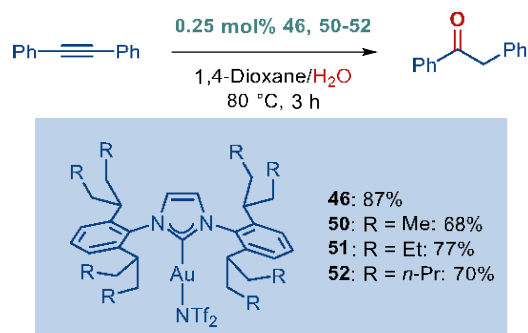
In 2015, the Glorius group synthesized a hybrid surfactant/NHC ligand and its gold complex **49** (Scheme 22) [36]. This hybrid gold complex was applied in the alkyne hydration catalysis in micellar arrays, such as 0.5 wt% sodium dodecyl sulfate (SDS) of water solution. A series of terminal and internal alkynes could be hydrated to ketones in the presence of 1 mol% **49** and 1 mol% AgBF<sub>4</sub>. Notably, good yields (78%–92%) could be obtained for internal alkynes. However, this catalyst system is only moderately effective for the hydration of terminal alkynes (30%–59% yields). The functional group tolerance is broad, including esters, bromides, protected amines, and alcohols. Based on dynamic-light scattering and film balance studies, the authors suggested that the gold atom should be placed in the boundary layer position of micelle to achieve high reaction rate.

**Scheme 22.** Hydration of alkynes with complex **49**.



In 2015, the Nolan group synthesized the complexes **50–52** based on the flexible-yet-bulky ITent (Tent = tentacular) class of NHCs and compared their catalytic activity in hydration of diphenylacetylene with complex **46** (Scheme 23) [37]. These ITent NHCs include IPent, IHept and INon ligands, featuring an increase of the donating ability and the steric hindrance is in the following order: INon = IHept > IPent >> IPr. All complexes gave full conversion at 0.5 mol% catalyst loading. In order to differentiate the catalytic activity, 0.25 mol% loading was used, with complex **46** showing the best efficiency. These results suggested that increasing alkyl chain length in ITent ligands had a detrimental effect in gold-catalyzed hydration.

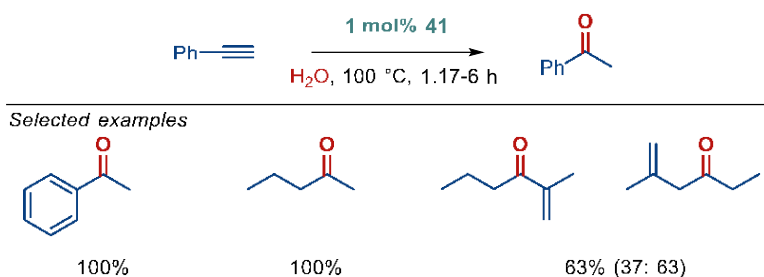
**Scheme 23.** Hydration of diphenylacetylene with complexes **46** and **50–52**.



In 2015, the Silbestri group further investigated their sulfonated gold(I)–NHC complexes (Scheme 24) [38]. A comparative study showed that complex **41** has the highest activity in neat water under acid and

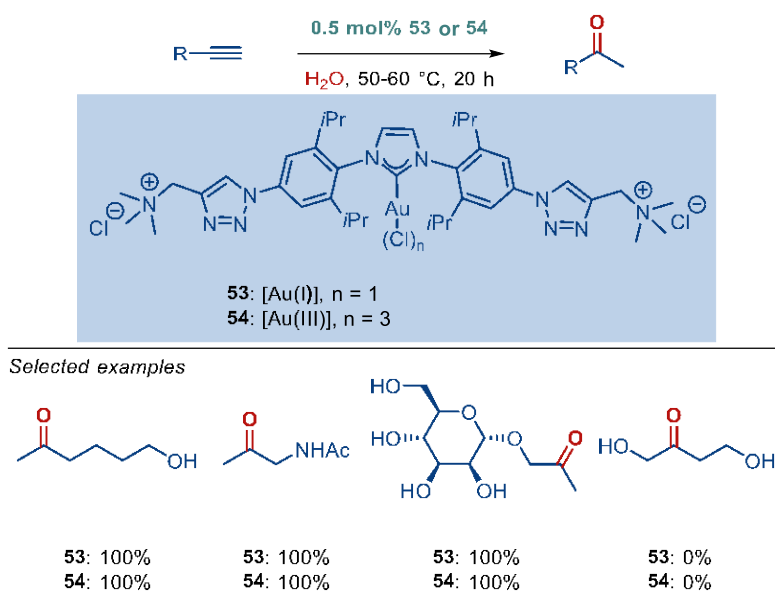
silver-free conditions. This reaction could achieve full conversion with terminal alkynes and moderate conversion with internal alkynes (63%). The protocol showed good recyclability of complex **41** (10 recycles with >80% yield). Furthermore, DFT studies suggested that the sulfonated alkyl chain of analogue [(3-sulfonatepropyl)imidazol-2-ylidene]AuCl folds to generate steric hindrance around the gold center. Later, in 2020, the same group showed microwave and ultrasound facilitated hydration of alkynes in pure water or aqueous methanol using the same sulfonated gold(I)–NHC complex **41** [39]. These irradiation conditions resulted in shorter reaction time and higher yields compared to standard conditions.

**Scheme 24.** Hydration of diphenylacetylene with complex **41**.



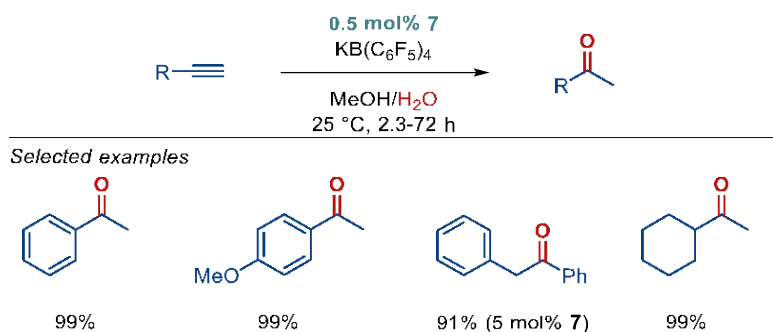
In 2015, Gautier's group reported a water-soluble gold(I/III)-NHC complexes **53–54** using ammonium tagging (Scheme 25) [40]. Water-soluble complexes **53–54** serve as efficient catalysts in the acid and silver-free hydration of hydrophilic alkynes. In presence of 0.5 mol% **53** or **54**, water-soluble terminal alkynes could be fully converted to the corresponding ketones in pure water at 50–60 °C. Remarkably, a ketopropyl mannoside can be synthesized without the need for hydroxyl protection. However, **53–54** are ineffective in catalyzing the hydration of internal alkynes. Furthermore, the Gautier group proposed a possible mechanism of NHC–Au(III) catalyzed alkyne hydration by DFT calculations (not shown). The Au(III) complex **54** could coordinate with alkyne, leading to a displacement of the chloride ligand. Addition of water and proton release produces a gold-bonded enol. Enol-ketone tautomerization and reductive elimination give  $\alpha$ -chloro-ketone and a catalytically active NHC–Au(I)–Cl. This active NHC–Au(I)–Cl could be involved in the general mechanism of alkyne hydration.

**Scheme 25.** Hydration of alkynes with complex **53-54**.



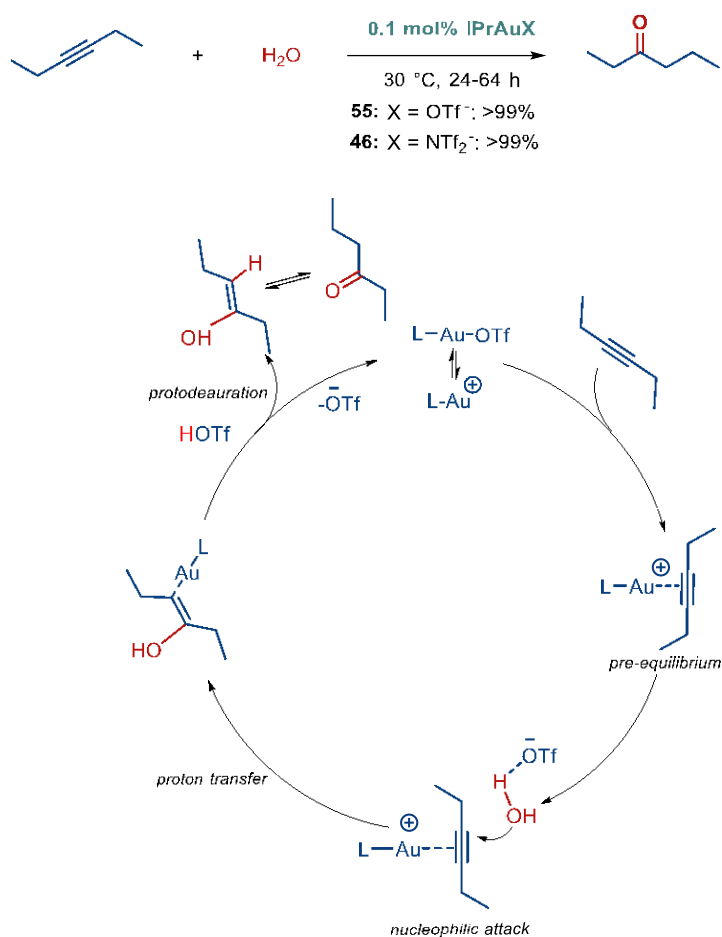
In 2016, Wu and co-workers developed new catalytic system based on the well-defined [(IPr)AuCl] **7** complex and  $\text{KB}(\text{C}_6\text{F}_5)_4$  (Scheme 26) [41]. This combination was found to be the most active catalyst for alkyne hydration at room temperature. Potassium tetrakis(pentafluorophenyl)borate  $\text{KB}(\text{C}_6\text{F}_5)_4$ , is a popular noncoordinating anion that has been applied as a chloride scavenger in various Au(I)-catalyzed reactions [42]. [(IMes)AuX] was inactive irrespective of a counterion used. This method showed high efficiency for the hydration of terminal alkynes at 0.5 mol% catalyst loading. However, lower reactivity was observed for internal alkynes, requiring 5 mol% catalyst loading and prolonged reaction time. Since this catalyst system operated at mild room temperature conditions, decomposition of catalyst could be avoided allowing for catalyst recycling up to 6 times without a noticeable loss of activity. The study by Wu demonstrated that the counterion played a significant role in Au(I) hydration catalysis.

**Scheme 26.** Hydration of alkynes with complex **7**/  $\text{KB}(\text{C}_6\text{F}_5)_4$ .



In 2016, Zuccaccia's group conducted a comprehensive study on the role of counterion in Au(I)–NHC catalyzed hydration of alkynes under solvent-, silver-, and acid-free condition (Scheme 27) [13b]. After screening a series of counterions, such as  $\text{BAr}^{\text{F}}_4^-$ ,  $\text{BF}_4^-$ ,  $\text{SbF}_6^-$ ,  $\text{OTf}^-$ ,  $\text{NTf}_2^-$ ,  $\text{ClO}_4^-$ ,  $\text{OTs}^-$ ,  $\text{TFA}^-$ , they discovered that only two complexes **55** and **46** bearing  $\text{OTf}^-$  and  $\text{NTf}_2^-$  showed full conversion of the starting alkyne substrates. By kinetic isotopic effect and DFT studies, the authors proposed that this effect originates from the intermediate coordination ability and basicity of  $\text{OTf}^-$  and  $\text{NTf}_2^-$ . For other anions, their lower efficiency was ascribed to an excessively strong coordination and basicity ( $\text{OTs}^-$ ,  $\text{TFA}^-$ ) or too weak basicity and coordinating ability ( $\text{BAr}^{\text{F}}_4^-$ ,  $\text{BF}_4^-$ ,  $\text{SbF}_6^-$ ,  $\text{ClO}_4^-$ ). This study by Zuccaccia allowed to use mild temperature and catalyst recycling up to 4 times without loss of efficiency.

**Scheme 27.** Hydration of alkynes with  $[(\text{IPr})\text{AuX}]$ .

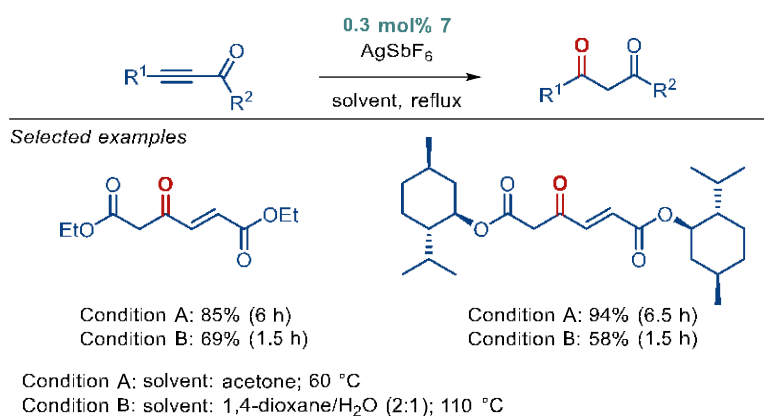


Based on this mechanistic study [13b], the authors proposed a specific role of anion in each step (Scheme 1). (1) In the nucleophilic attack step, the anion can lock the reactive water molecule in a close

proximity to the alkyne and increase nucleophilicity of the water oxygen atom through hydrogen bonding  $\text{HOH}\cdots\text{OTf}$ . (2) In the first proton transfer step,  $\text{OTf}^-$  can act as a proton shuttle to facilitate the formation of the gold–enol complex. (3) In the protodeauration step, a concerted Au/anion-mediated proton transfer to the unsaturated carbon atom can take place under acid-free conditions. Interestingly, they found that KIE is close to 1 (no exact KIE value was reported) when 5 mol% HOTf was added, which suggested that the nucleophilic attack becomes the rate-determining step under acidic conditions.

In 2016, substrate-controlled regioselective hydration of alkynyl esters and alkynyl ketones was reported by Balamurugan's group using  $[(\text{IPr})\text{AuCl}]/\text{AgSbF}_6$  catalyst system (Scheme 28) [43]. They discovered that the reaction conditions using acetone as a solvent showed superior activity for the hydration of 2-alkynoates. In contrast, they found that 1,4-dioxane/ $\text{H}_2\text{O}$  was more effective for the hydration of alkynones. By conducting KIE experiments, they proposed that water produced in the aldol self-condensation under Lewis-acidic conditions participates in this alkyne hydration reaction.

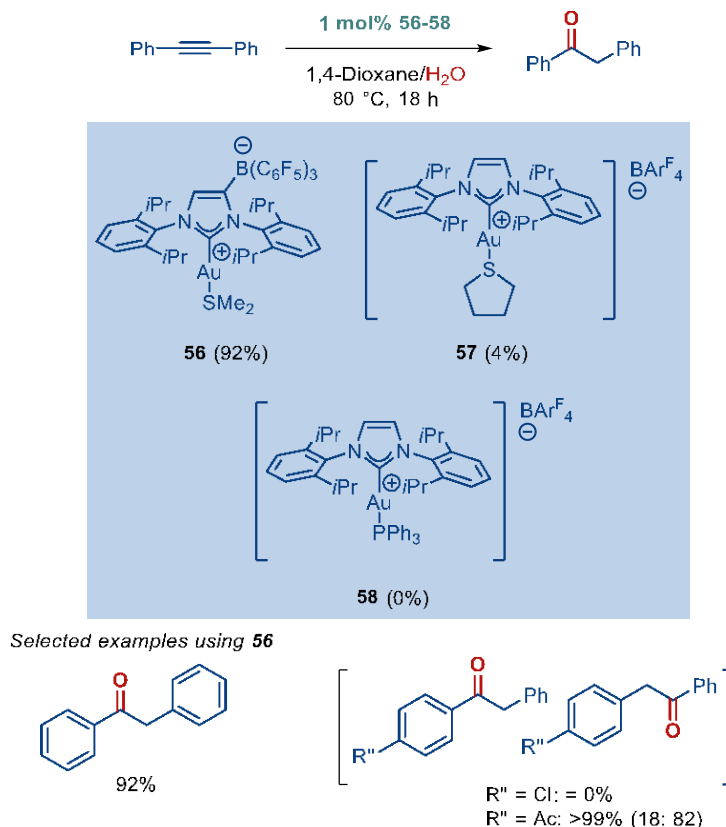
**Scheme 28.** Regioselective hydration of alkyne with complex **7**.



In 2016, Dobereiner's group used an anionic N-heterocyclic carbene ligand B–NHC bearing  $\text{B}(\text{C}_6\text{F}_5)_3$  anion at the imidazole backbone in alkyne hydration (Scheme 29) [44]. This class of anionic carbenes was first reported by Tamm and co-workers [45]. The authors found that the complex **56** was more reactive than cationic complexes **57–58**, which suggested that the anionic B–NHC ligand could play a crucial role in hydration of alkynes. Interestingly, they found that complex **56** is more reactive for the hydration of internal alkynes than terminal alkynes, which is quite unusual with other  $\text{Au}(\text{I})$ –NHC catalytic systems. The reaction showed high regio- and chemoselectivity in the hydration of

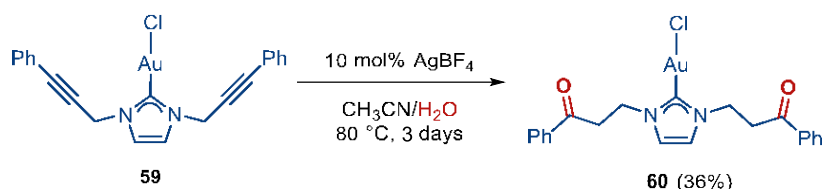
unsymmetrical internal alkynes. Complex **56** is a halide-free catalyst, however, the addition of AgSbF<sub>6</sub> increased the hydration rate.

**Scheme 29.** Regioselective hydration of alkyne with complexes **56-58**.



In 2017, Roesky's group used the alkyne hydration reaction to functionalize *N,N*-bis-phenylpropynyl-substituted NHC–gold complexes (Scheme 30) [46]. Gold(I)–NHC complex **59** was post-functionalized by autocatalytic hydration of the alkynyl side chain. As expected, the reaction required catalyst activation with AgSbF<sub>6</sub>.

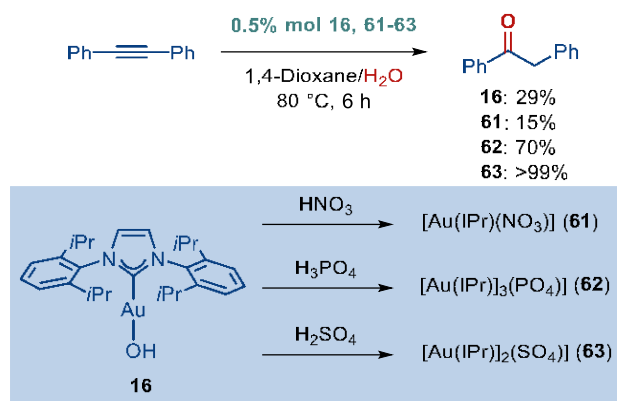
**Scheme 30.** Autocatalytic hydration with complexes **59-60**.



In 2017, Nolan's group synthesized and characterized a new class of  $[(\text{IPr})\text{Au}^{\text{I}}]$  complexes **61-63** derived from nitric, sulfuric, phosphoric acids (Scheme 31) [47]. These Au(I) complexes are derived from mineral acids and could potentially serve as active catalysts in alkyne hydration due to the low

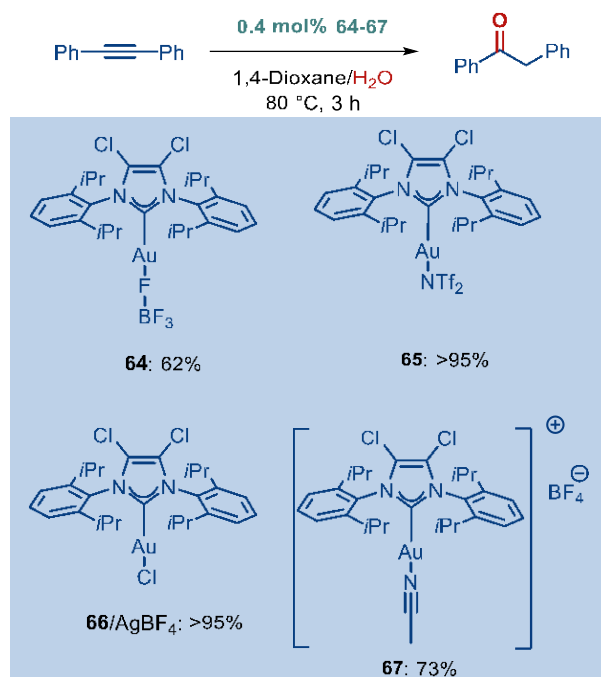
oxophilicity of Au<sup>I</sup>. The hydration of diphenylacetylene suggested that sulfuric acid derived complex **63** is more reactive than di-gold hydroxide complex **16** and complexes **61–62**. The reaction proceeded quite well under silver- and acid-free conditions at 0.5 mol% gold loading. The higher activity of multinuclear complexes **62–63** cf. mononuclear **61** is possibly a result of a dual activation mode of water and  $\pi$ -system [28].

**Scheme 31.** Hydration of diphenylacetylene with complexes **16** and **61–63**.



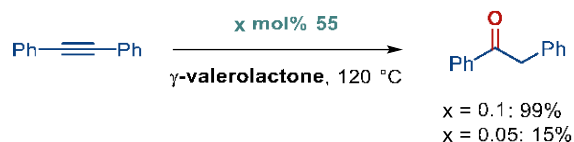
In 2017, the Nolan group disclosed an equilibrium between inner and outer-sphere conformations of  $[(\text{IPr}^{\text{Cl}})\text{AuBF}_4]$  complex (Scheme 32) [48]. The counterion  $\text{BF}_4^-$  can occupy inner-sphere or outer-sphere of gold complex. The inner sphere coordination form, complex **64**, was tested in the hydration of diphenylacetylene. The results showed that **65** and **66**/ $\text{AgSbF}_6$  are more reactive catalysts. The authors proposed that the efficient conversion by **66**/ $\text{AgSbF}_6$  could be attributed to the traces of acid generated from residual silver. On the other hand, since **64** and **67** can be converted to the less active hydroxide complex **16** under the reaction conditions, complexes **64** and **67** are comparatively less efficient in the hydration of alkynes.

**Scheme 32.** Hydration of diphenylacetylene with complexes **64–67**.



In 2018, Zuccaccia's group published a green protocol for Au(I)–NHC-catalyzed alkoxylation and hydration of alkynes in polar solvents, such as ethyl lactate, glycerol, D-limonene and  $\gamma$ -valerolactone (Scheme 33) [49]. Based on experimental and DFT studies of alkoxylation of alkynes, they concluded that the more polar  $\gamma$ -valerolactone as a solvent featured stronger ability to separate the counter anion and activate the  $[\text{LAu}^+]$  species. This in turn stabilized the transition state and increased the electrophilic character of the  $[\text{LAu}^+\text{--alkyne}]$  complex. This hypothesis was tested in alkyne hydration, where they found that  $[(\text{IPr})\text{AuOTf}]$  complex **55** gave the highest efficiency using  $\gamma$ -valerolactone as a solvent. Moreover, they found that proton-acceptor/donor groups and coordinating groups on solvents also played an important role in the hydration of alkynes.

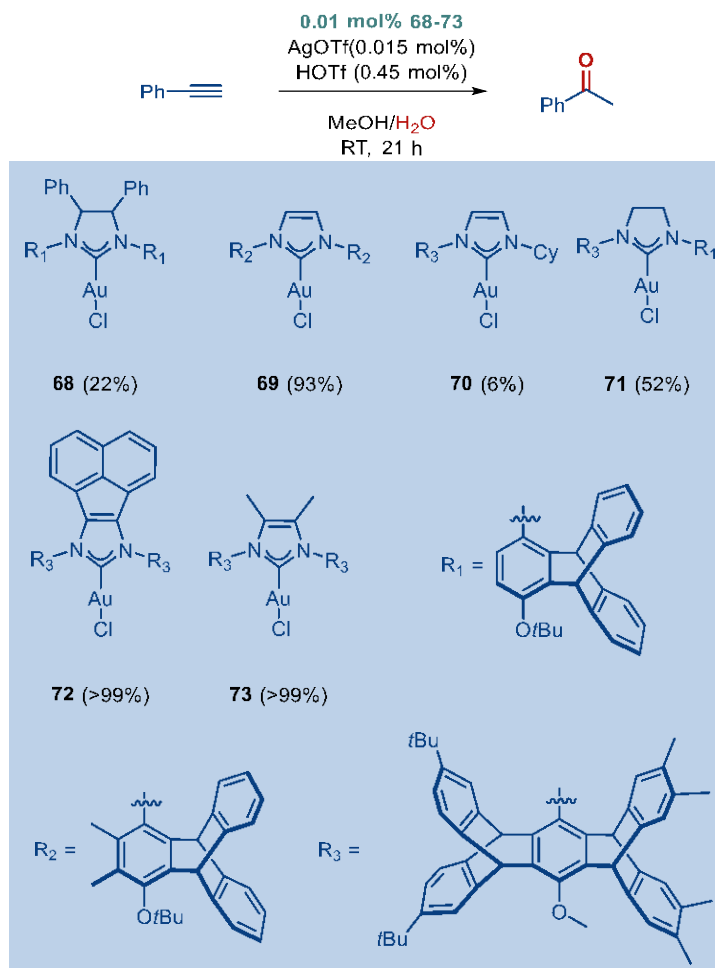
**Scheme 33.** Hydration of diphenylacetylene with complex **55**.



In 2018, the Plenio group reported bis-pentiptycenyl-NHC gold complexes **68–73** in alkyne hydration (Scheme 34) [50a]. These complexes are based on sterically-demanding N-IPtycenyl-substituted NHC ligands [50b]. Using 0.01 mol% gold complexes, 0.015 mol%  $\text{AgOTf}$  and 0.45 mol%  $\text{HOTf}$ , complexes

**72–73** showed the highest efficiency, indicating that the steric bulk of ligands is essential for catalytic activity. Interestingly, the hydration results of unsymmetrical complexes **70–71** showed that evenly distributed steric bulk is required for high catalytic activity. Using the most reactive complex **73**, various alkynes were tested under standard reaction condition. In general, these conditions favored terminal and electron-rich alkynes cf. internal and electron-deficient alkynes. Furthermore, these conditions tolerated steric hindrance on alkyne substrates. Although 3-furanyl-acetylene could be transformed into the corresponding ketone, *S*-containing and *N*-containing heterocyclic alkynes were not compatible with the reaction conditions.

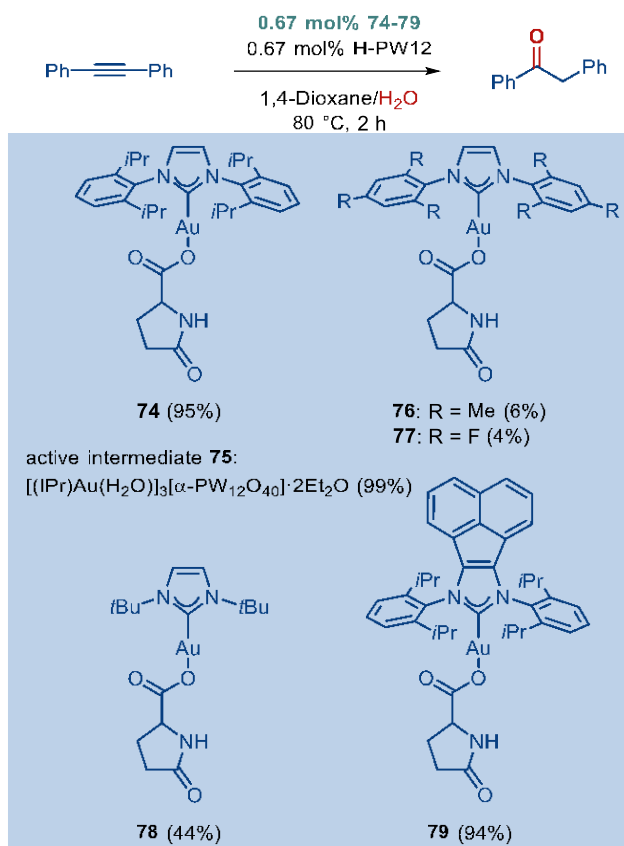
**Scheme 34.** Hydration of phenylacetylene with complexes **68–73**.



In 2019, Matsubara, Nomiya and co-workers developed [(NHC)Au(RS-pyrrolid)] (RS-pyrrolid = RS-2-pyrrolidone-5-carboxylic acid) catalyzed alkyne hydration in the presence of polyoxometalates (POMs) (Scheme 35) [51]. In this system, polyoxometalates are anionic, molecular transition metal-oxygen

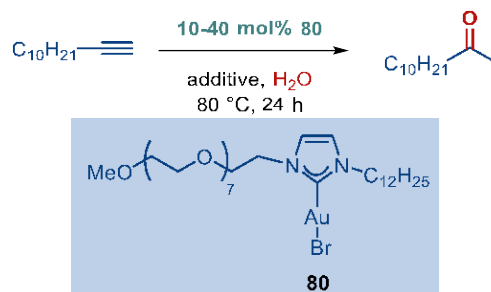
bonding clusters. The active catalyst is generated from NHC–Au(I) precatalyst and the protonic acid form of POMs. In the presence of protonic acid,  $\text{H}_3[\alpha\text{-PW}_{12}\text{O}_{40}] \cdot 9\text{H}_2\text{O}$  (H-PW<sub>12</sub>), less steric hindered complexes **76–78** were less reactive than complexes **74** and **79**. The authors isolated a stable complex **75**  $[\text{Au}(\text{H}_2\text{O})(\text{IPr})]_3[\alpha\text{-PW}_{12}\text{O}_{40}]$ , which showed comparable efficiency to complex **74** in the presence of H-PW<sub>12</sub>. This indicated that complex **75** or ion-pair species  $\{[\text{Au}(\text{IPr})(\text{H}_2\text{O})][\alpha\text{-PW}_{12}\text{O}_{40}]\}^{2-}$  could be the active catalyst in alkyne hydration. The authors proposed that H-PW<sub>12</sub> serves as both a protonic acid and an anion to stabilize the ion-pair active species in alkyne hydration.

**Scheme 35.** Hydration of diphenylacetylene with complexes **74–79**.



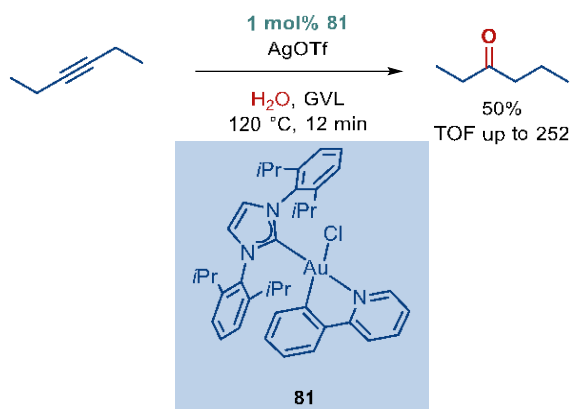
In 2020, Taira and coworkers reported the synthesis of NHC–Au(I)-coordinated surfactants and application in hydration of 1-dodecyne in water (Scheme 36) [52]. Mechanistic study revealed that NHC–Au(I)-coordinate surfactants are transformed to Au nanoparticles (AuNPs), which are the active catalyst species. However, high catalyst loading was required to achieve full conversion.

**Scheme 36.** Hydration of 1-dodecyne with complex **80**.



In 2020, the Zuccaccia group reported  $[AuCl(IPr)(ppy)]Cl$  for hydration of alkynes in  $\gamma$ -valerolactone (GVL) as a green solvent under acid-free conditions (Scheme 37) [53]. The authors investigated the mechanism of NHC–Au(III)-catalyzed hydration of alkynes by spectroscopic and computational methods. Interestingly, NMR monitoring during the catalysis indicated high stability of complex **81**  $[AuCl(IPr)(ppy)]Cl$  with the reduction to Au(I) or Au(0) species not observed. In comparison,  $[AuCl(PPh_3)(ppy)]OTf$  was readily reduced and deactivated to Au(I) species under these conditions, which showcased higher stability of NHC–Au(III) complexes. Experimental and DFT studies indicated pre-equilibrium and coordination between alkyne and Au(III) as the rate-limiting step. Thus, weakly and moderately coordinating anions, such as  $BF_4^-$ ,  $SbF_6^-$  and  $OTf^-$ , are favored for this hydration process.

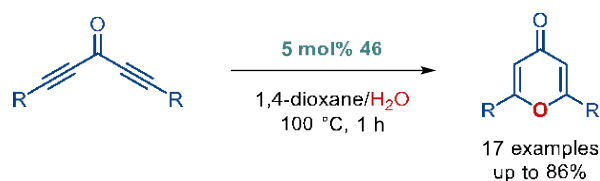
**Scheme 37.** Hydration of hex-3-yne with complex **81**.



In 2020, the Sanz group reported  $[NHC-Au(I)]$ -catalyzed divergent, tandem hydration/oxa-cyclization of skipped diyones (Scheme 38) [54]. NHC ligand, silver salt and counterion are crucial for the divergent regioselectivity. With  $[(IPr)AuNTf_2]$  **46** as a catalyst, this tandem reaction provided oxygenated six-membered heterocycles in good yields. Broad substrate scope was well-tolerated,

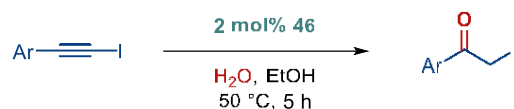
including alkenyl substituents. Furthermore, this methodology was successfully applied to the total synthesis of naturally occurring 2-substituted  $\gamma$ -pyrones, such as polyporapyranone B.

**Scheme 38.** Hydration-cyclization of diynones with complex **46**.



In 2020, the Cazin group reported a catalytic protocol for [(IPr)AuNTf<sub>2</sub>]-catalyzed hydration of 1-iodoalkynes (Scheme 39) [55]. This catalytic protocol enabled a straightforward synthesis of a series of valuable  $\alpha$ -iodo acetophenones. The methodology was compatible with sequential iodination/hydration and hydration/functionalization. Owing to the well-behaved Au(I)–NHC catalyst system, the protocol provided good selectivity and yields for a variety of aromatic  $\alpha$ -iodoketones under mild conditions.

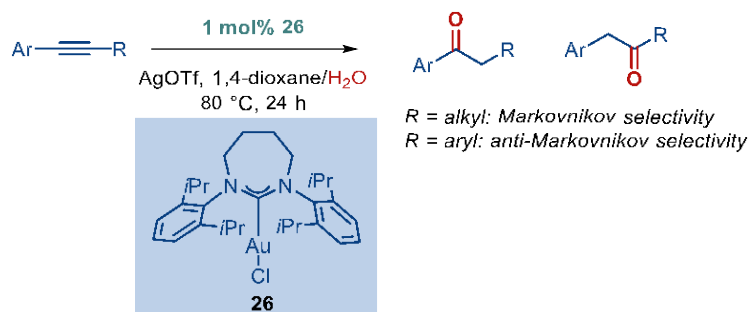
**Scheme 39.** Hydration of 1-iodoalkynes with complex **46**.



In 2021, Asachenko and co-workers conducted a comprehensive study on the regioselectivity of hydration of unsymmetrical diarylacetylenes and arylalkylacetylenes by NHC–Au(I) complexes (Scheme 40) [56]. Interestingly, they found that the hydration of diarylacetylenes proceeded with Markovnikov selectivity. However, the reaction of arylalkylacetylenes gave anti-Markovnikov products. By screening a series of Au(I) complexes with various NHC ligands, they found that [(6-Dipp)AuCl] and in particular [(7-Dipp)AuCl] **26** gave the highest anti-Markovnikov regioselectivity in the hydration of *n*-hexylphenylacetylene. This outcome was rationalized based on transition state of [NHC–Au(I)–alkyne] complexes by DFT computation. Importantly, aryl substituents of arylalkylacetylenes are subject to steric repulsion of Dipp-substituents of the NHC ligand in the case of Markovnikov addition process, which leads to the selectivity reversal and anti-Markovnikov products. In contrast, there is no preference for the hydration of diarylacetylenes in terms of steric repulsion. In these substrates, the

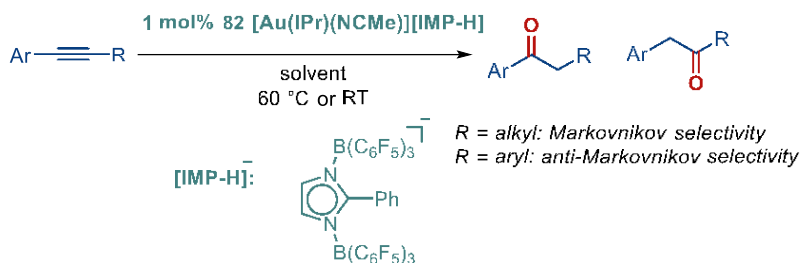
regioselectivity is guided by electronic properties of the aromatic rings, which results in Markovnikov selectivity.

**Scheme 40.** Regioselective hydration of alkyne with complex **26**.



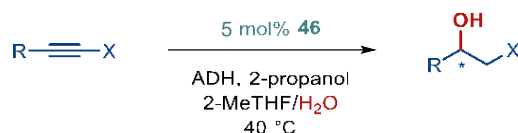
In 2022, the Dobereiner group reported a study to explore factors controlling the regioselectivity of Au(I)-catalyzed hydration of unsymmetrical internal alkynes using [IPrAu<sup>+</sup>] paired with a weakly-coordinating phenylimidazole-based anion [IMP-H] (Scheme 41) [57]. Under these catalytic conditions, the hydration could proceed at ambient temperature with a similar regioselectivity to high temperatures. In addition, the basicity of the solvents was found to be relevant to the hydration regioselectivity. KIE studies suggested that nucleophilic attack or proton transfer might be a turnover limiting step.

**Scheme 41.** Regioselective hydration of alkyne with complex **82**.



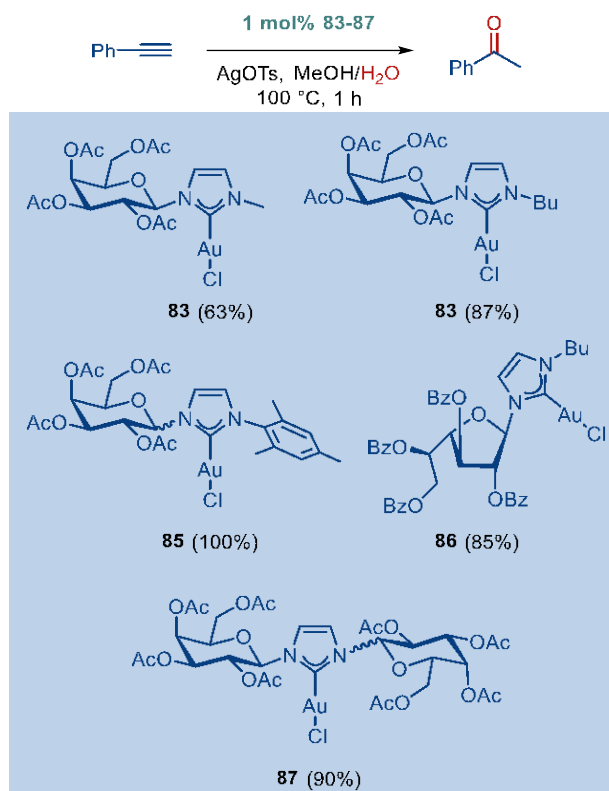
In 2022, Gotor-Fernández and co-workers reported a one-pot, sequential method for [IPrAuNTf<sub>2</sub>]-catalyzed hydration of 1-haloalkynes and ketone bioreduction by alcohol dehydrogenase (Scheme 42) [58]. By using H<sub>2</sub>O/2-MeTHF as medium for Au(I)-NHC system and adding 2-propanol for the enzymatic system, the NHC-Au catalyst and enzyme are fully compatible in this one-pot cascade process. Most impressively, the methodology provided a series of chiral chloro- and bromohydrins in good to high yields (65-86%) with excellent enantioselectivity (98-99% ee). In addition, hydration/bioreduction/epoxidation sequence was developed to produce chiral styrene oxides.

**Scheme 42.** Hydration-bioreduction of alkyne with complex **46** and **ADH** (alcohol dehydrogenase).



In 2022, the Silbestri group reported the synthesis and characterization of five galactopyranoside-functionalized NHC–Au(I) complexes (Scheme 43) [59]. Interestingly, in these systems, the gold complexes are not stable after the deprotection of hydroxyl group. Catalytic studies in alkyne hydration showed that the galactopyranoside complexes with *O*-acyl-protection can serve as active and reusable hydration catalysts under H<sub>2</sub>O/MeOH conditions.

**Scheme 43.** Hydration of phenylacetylene with complexes **83-87**.



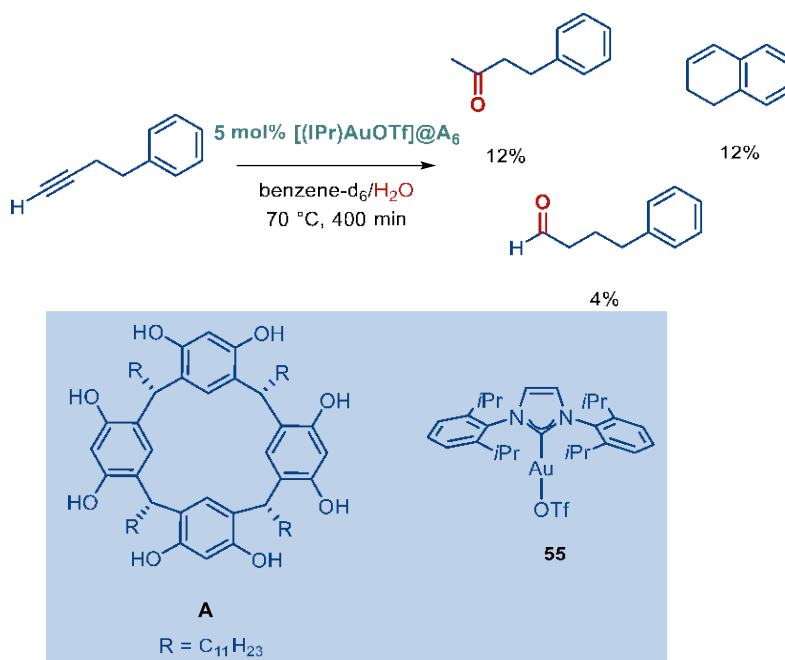
## 2.2. NHC–Au catalyzed hydration of alkynes by encapsulated and immobilized catalysts

In 2011, the Reek group reported the first encapsulation of complex **55** [(IPr)AuOTf] within a self-assembled, hydrogen bonded, hexameric host for alkyne hydration (Scheme 44) [60]. The authors showed that chemo and regioselectivity of alkyne hydration could be controlled by both capsule and

substrate size. The encapsulated catalyst **[(IPr)AuOTf]@A6** was quantitatively obtained by mixing complex **[(IPr)AuOTf]** **55** with resorcin[4]arene **A** (1:7 ratio) in water saturated chloroform. The encapsulated complex **[(IPr)AuOTf]** **55** occupies 30% of the volume of the cavity, which allows the substrate to react with water inside cavity of the capsule.

Using 4-phenyl-1-butyne as a model substrate, the authors demonstrated that compared with complex **[(IPr)AuOTf]** **55** in solution, the encapsulated catalyst **[(IPr)AuOTf]@A6** gave 12% 1,2-dihydronaphthalene and 5 % linear aldehyde in addition to the standard hydration product. This different product distribution demonstrated that intramolecular cyclization is favored when **[(IPr)AuOTf]@A6** was used because of the limited space of the cavity. The reaction with encapsulated **[(IPr)AuOTf]@A6** is also much slower due to the barrier provided by the capsule to entry of the alkyne to access the catalyst.

**Scheme 44.** Regioselective hydration of alkynes with **[(IPr)AuOTf]@A6**.



In 2013, the Strukul group observed significant variations in the selectivity of alkyne hydration with the encapsulated catalyst **[(IPr)AuOTf]@A6** (not shown) [61]. In this encapsulated design, the alkyne substrate requires to break several hydrogen bonds and disassemble one resorcin[4]arene unit to access the encapsulated catalyst. Thus, the reaction rate is much slower compared with free catalyst **[(IPr)AuOTf]** **55** in solution. The authors found that encapsulated **[(IPr)AuOTf]@A6** catalyst favors the

reaction of aliphatic cyclic alkynes and disfavors terminal aromatic alkynes, especially substituted aromatic alkynes.

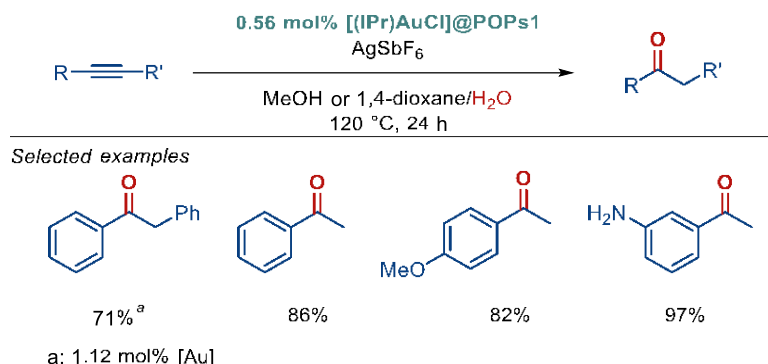
In 2016, the Reek group designed a switchable gold catalytic system by mixing di-nuclear gold complex  $[\{\text{Au}(\text{IPr})\}_2(\mu\text{-OH})][\text{BF}_4]$  **17** and hexameric capsule **A6** (Scheme 45) [62]. In the presence of **A6** capsule, the di-nuclear gold complex breaks into mononuclear units that are encapsulated. This is explained by the complex  $[\{\text{Au}(\text{IPr})\}_2(\mu\text{-OH})][\text{BF}_4]$  **17** being too large to fit inside the cage. As a result, the dual-activation mode of complex  $[\{\text{Au}(\text{IPr})\}_2(\mu\text{-OH})][\text{BF}_4]$  **17** in solution is blocked. In the presence of complex  $[\{\text{Au}(\text{IPr})\}_2(\mu\text{-OH})][\text{BF}_4]$  **17** and capsule **A6**, the dimer of 4-phenyl-1-butyne is not formed compared with the free complex  $[\{\text{Au}(\text{IPr})\}_2(\mu\text{-OH})][\text{BF}_4]$  **17** in solution.

**Scheme 45.** Regioselective hydration of alkynes with  $[\{\text{Au}(\text{IPr})\}_2(\mu\text{-OH})][\text{BF}_4]@A_6$ .



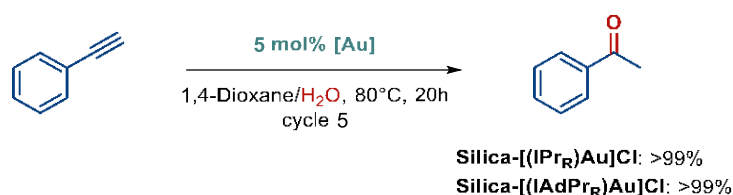
In 2014, Li's group reported Au-NHC@porous organic polymers (POPs) as recoverable catalysts for alkyne hydration (Scheme 46) [63]. These Au-IPr@POPs were synthesized via the Pd-catalyzed Sonogashira cross-coupling between iodine-functionalized  $[(\text{IPr})\text{AuCl}]$  and alkyne functionalized monomer. In the presence of  $\text{AgSbF}_6$ , Au-IPr@POPs displayed high reactivity for the hydration of terminal alkynes with good functional group tolerance. Recycling of the catalyst Au-IPr@POPs up to 5 times was feasible without a significant loss in activity.

**Scheme 46.** Hydration of alkyne with  $[(\text{IPr})\text{AuCl}]@POPs1$ .



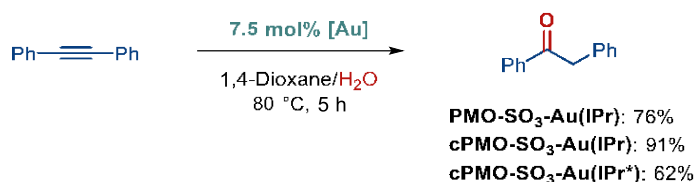
In 2017, Asensio, Varea and co-workers reported silica-immobilized [NHC–Au(I)] complexes, Silica-[(IPr<sub>R</sub>)Au]Cl and Silica-[(IAdPr<sub>R</sub>)Au]Cl, by anchoring NHC ligands on silica by hydrosilylation (Scheme 47) [64]. The immobilized complexes showed excellent activity in alkyne hydration even after 5 recycles. The complexes could be recycled by simple filtration. Furthermore, these immobilized catalysts are especially suitable under continuous flow conditions, which obviates catalyst degradation caused by magnetic stirring.

**Scheme 47.** Hydration of phenylacetylene with Silica-[(IPr<sub>R</sub>)Au]Cl and Silica-[(IAdPr<sub>R</sub>)Au]Cl.



In 2018, Voort, Nolan and co-workers reported a series of [NHC–Au(I)] complexes immobilized on sulfonic-acid-functionalized periodic mesoporous organosilica (PMO) (Scheme 48) [65]. These sulfonic-acid-functionalized PMO–SO<sub>3</sub>H were prepared by using two bis-silanes, 1,2-bis(triethoxysilyl)ethane and 1-thiol-1,2-bis(triethoxysilyl)ethane, and easily converted to a capped form, cPMO–SO<sub>3</sub>H, with hexamethyldisilazane. The PMO material was anchored with complex **16** [(IPr)AuOH] by simple acid-base esterification. The authors showed that in the hydration of diphenylacetylene complex cPMO–SO<sub>3</sub>–Au(IPr) had the highest activity. However, cPMO–SO<sub>3</sub>–Au(IPr) was prone to decomposition after one run. Instead, the authors found that the more sterically hindered cPMO–SO<sub>3</sub>–Au(IPr\*) is more effective in recycling after acidic work-up between the cycles.

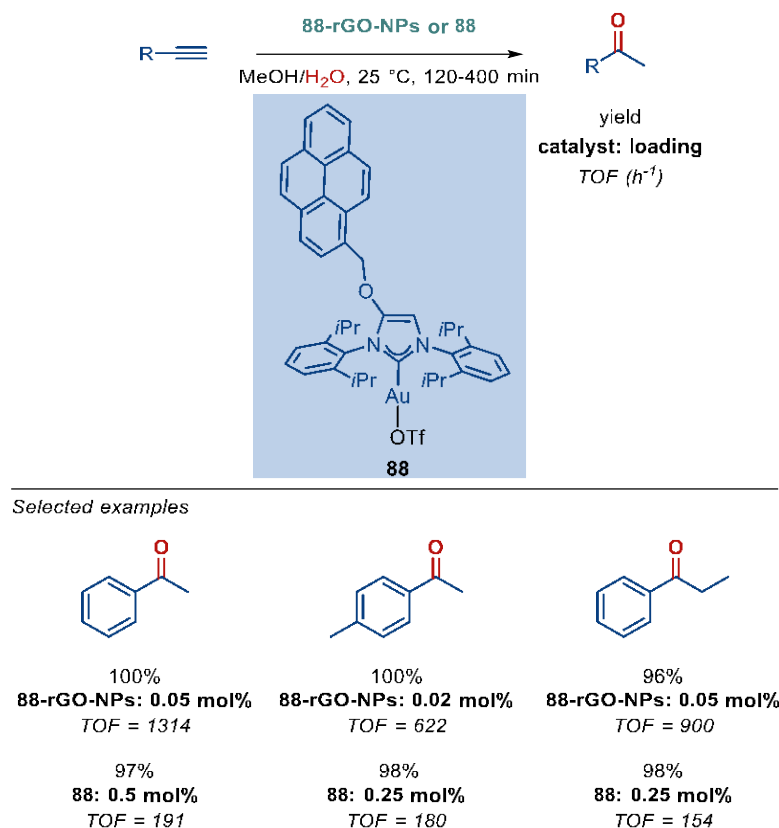
**Scheme 48.** Hydration of diphenylacetylene with PMO–NHC–Au(I).



In 2019, Mata's group reported graphene-supported ultra-small gold nanoparticles (AuNPs) that were functionalized with N-heterocyclic carbene ligands (Scheme 49) [66]. The graphene-immobilized catalyst **88-rGO-NPs** showed higher efficiency than the free complex **88** in alkyne hydration. The

authors found that graphene plays an important role in stabilizing AuNPs during catalysis. The immobilized catalyst **88-rGO-NPs** could be recycled up to 10 times without a significant loss of activity.

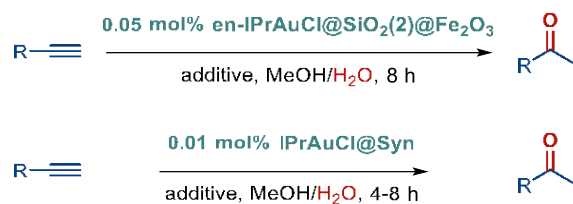
**Scheme 49.** Hydration of alkynes with complex **88** and **88-rGO-NPs**.



In 2020, the Öztürk group successfully encapsulated  $[(\text{IPr})\text{AuCl}]$  complex **7** with magnetic core/shell silica gel ( $\gamma\text{-Fe}_2\text{O}_3@\text{SiO}_2$ ) by silylation (Scheme 50) [67]. The post-pore size reduction minimizes gold leaching during alkyne hydration. Thus, the resulting catalyst is robust and can be used at low catalyst loading. Furthermore, catalyst recycling is easily performed using a magnet. The catalyst could be reused up to 6 times without leaching.

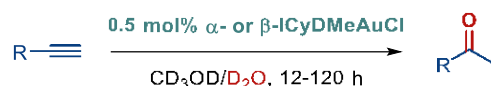
Subsequently, the same group reported another encapsulation strategy for alkyne hydration using  $[\text{NHC-Au-Cl}]$  complexes with polymeric surfactant Synperonic®F108 (Syn) (Scheme 50) [68]. This catalytic system was highly reactive at low catalyst loading due to homogenous dispersion and high stability. The catalyst could be recycled up to 7 times without a significant loss in activity.

**Scheme 50.** Hydration of alkynes with **en-IPrAuCl@SiO<sub>2</sub>(2)@Fe<sub>2</sub>O<sub>3</sub>** and **IPrAuCl@Syn**.



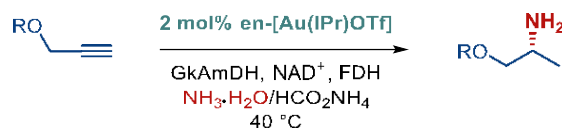
In 2020, Sollogoub and co-workers developed encapsulated gold, silver and copper complexes based on permethylated NHC-capped  $\alpha$ - and  $\beta$ -cyclodextrins (ICyD<sup>Me</sup>) for alkyne hydration (Scheme 51) [69]. Interestingly, although less reactive than gold complexes, ( $\alpha$ -ICyD<sup>Me</sup>)AgCl were also found to be catalytically-active for alkyne hydration. In contrast, the corresponding Cu complexes were inactive in alkyne hydration.

**Scheme 51.** Hydration of alkynes with  $\alpha$ - or  $\beta$ -ICyDMeAuCl.



In 2021, the Liu group developed a cascade hydration/reductive amination process by combining the hollow-shell-structured mesoporous silica encapsulated [(IPr)AuOTf] with a chemoenzymatic approach using amine dehydrogenase (Scheme 52) [70]. This study addressed an inherent challenge of incompatibility between enzymes and transition metals by [(IPr)AuOTf] encapsulation. The transformation included [NHC–Au(I)]-catalyzed hydration of propargyl ethers, followed by in situ reductive amination. The process is characterized by a broad substrate scope, affording chiral amines in high yields (82-97%) with excellent enantioselectivity (96-98% ee). Furthermore, the encapsulated Au catalyst could be recycled up to 5 times.

**Scheme 52.** Hydration of alkynes with **en-[Au(IPr)OTf]**.

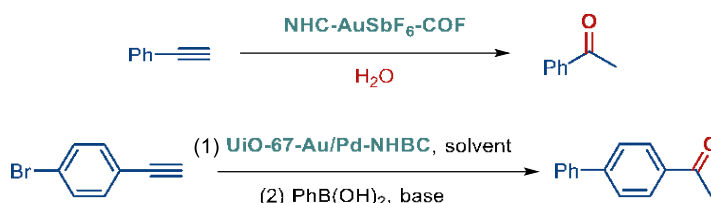


In 2020, the Dong group reported NHC–AuX covalent organic framework (COF) by direct condensation under solvothermal conditions (Scheme 53) [71]. In this approach, solid-state anion

exchange could be used to replace the Cl anion with SbF<sub>6</sub><sup>-</sup>. The prepared NHC–AuSbF<sub>6</sub>–COF was applied in alkyne hydration and showed comparable catalytic activity to the reported metal-loaded solid heterogeneous catalytic system [71].

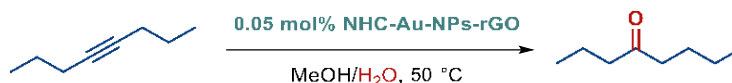
Subsequently, the same group reported UiO-67-Au/Pd–NHBC (UiO-67: a zirconium-based metal-organic frameworks, NHBC: N-heterocyclic bis-carbene) metal organic framework (MOF) by incorporating NHC–Au and NHC–Pd into MOFs (Scheme 53) [72]. The potential utility of this bimetallic catalyst was demonstrated in sequential alkyne hydration/Suzuki cross-coupling.

**Scheme 53.** Hydration of alkynes with NHC-AuSbF<sub>6</sub>-COF and UiO-67-Au/Pd-NHBC.



In 2021, the Mata group investigated NHC ligand effects on the stabilization of gold nanoparticles immobilized on graphene (Scheme 54) [73]. The authors found that polyaromatic groups, such as pyrenyl, on NHC ligands increased the stability of gold nanoparticles by  $\pi$ -stacking interactions, thus affording high efficiency in alkyne hydration even after recycling.

**Scheme 54.** Hydration of alkynes with NHC-Au-NPs-rGO.

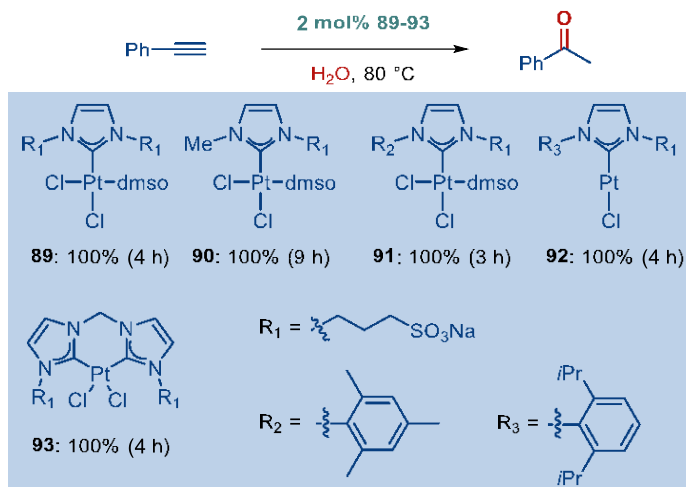


### 2.3. NHC–Pt catalyzed hydration of alkynes

In 2013, Flores, Jesús and co-workers reported the first example of NHC–Pt complexes for the hydration of alkynes (Scheme 55) [6c]. In the synthesized series of sulfonated, water-soluble NHC–platinum(II) complexes **89–93**, all complexes showed moderate activity in the hydration of phenylacetylene in neat water at 2 mol% catalyst loading at 80 °C. Complex **91** showed the highest efficiency and was tested in the reaction scope with different alkyne substrates. The activity of **91** in the reactions with substituted phenylacetylenes decreased in the following order: H > OMe > CF<sub>3</sub> > NO<sub>2</sub>.

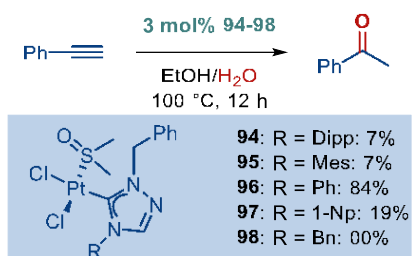
However, the low reactivity of nitrophenylacetylene and diphenylacetylene was attributed to the low solubility of alkynes [6c].

**Scheme 55.** Hydration of phenylacetylene with complexes **89-93**.



In 2020, Nguyen and coworkers reported five NHC–Pt(II) complexes bearing 1,2,4-triazolin-5-ylidene ligand and different N-wingtips, such as Dipp, Mes, Ph, 1-Np and Bn (Scheme 56) [74]. However, these complexes showed low to moderate efficiency in the hydration of phenylacetylene. Interestingly, all five NHC ligands showed lower efficiency than the analogous [(NHC)PtCl<sub>2</sub>(DMSO)] complexes bearing functionalized imidazolin-2-ylidenes.

**Scheme 56.** Hydration of phenylacetylene with complexes **94-98**.



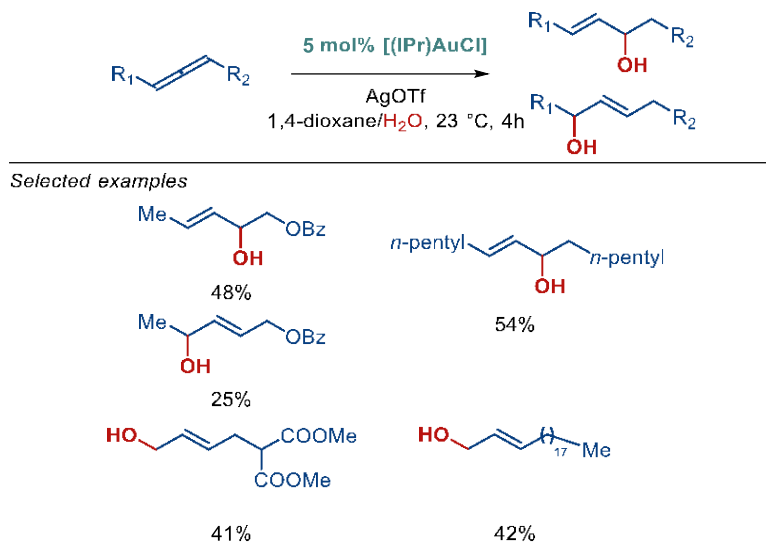
### 3. NHC–metal catalyzed hydration of allenes

#### 3.1. NHC–Au catalyzed hydration of allenes

Hydration of allenes catalyzed by NHC–metals is rare compared to the hydration of alkynes despite the high synthetic value of allylic alcohol products obtained in this process. In 2009, Widenhoefer's group reported the first example of hydration of allenes using [(IPr)AuCl] complex **7** in the presence of

AgOTf at 23 °C (Scheme 57) [75]. Their results showed modest yields (41-73%) to form (*E*)-allylic alcohols via selective addition of water at the terminal allenyl carbon atom for unsubstituted allenes.

**Scheme 57.** Hydration of allenes with complex **7** [(IPr)AuCl].



#### 4. NHC–metal catalyzed hydration of nitriles

Hydration of nitriles is one of the most important and atom economical methods to synthesize amides with broad applications in organic synthesis, drug discovery and materials science. In the last few decades, nitrile hydration has been extensively studied with a broad range of late transition metals, such as Rh, Ru, Ni, Os and Au as catalysts [6b, 6e, 27a, 76]. Compared with alkyne hydration, nitrile hydration by metal–NHC complexes is significantly less developed. NHC–metal-catalyzed nitrile hydration was pioneered by Nolan’s group in 2009 using NHC–gold [77]. Since then, NHC complexes of Os, Ru, Ag, Rh and Ni have been reported for the hydration of nitriles.

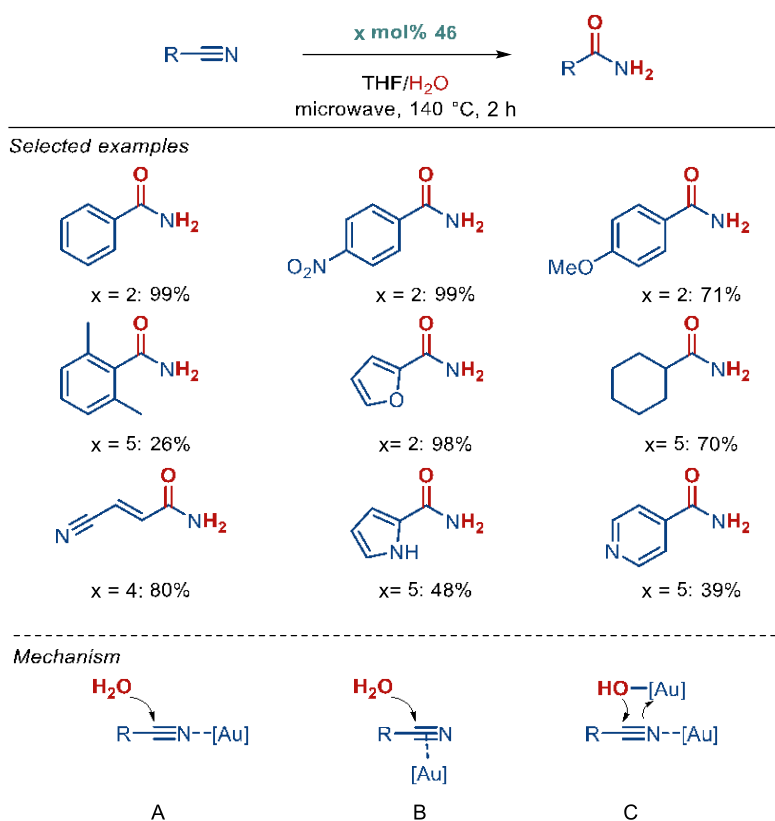
##### 4.1. NHC–Au catalyzed hydration of nitriles

In 2009, the Nolan group reported the first example of [NHC–Au]-catalyzed hydration of nitriles (Scheme 58) [77]. The catalyst [Au(IPr)(NTf<sub>2</sub>)] **46** showed good to excellent activity in the hydration of a broad range of nitriles. Benzonitriles bearing electron-deficient groups exhibited slightly higher yield than electron-rich benzonitriles. *Ortho*-di-substituted 2,6-dimethylbenzonitrile gave lower yield, which was proposed to result from steric inhabitation of the catalytic activity. Compared with benzonitriles, *N*-containing heteroaromatic nitriles showed lower reactivity due to possible coordination between gold

and the nitrogen atom. Interestingly, mono-selective hydration of fumaronitrile was achieved, which was in contrast to exhaustive hydration of di-cyano aromatic substrates.

In terms of mechanism, three possible pathways were proposed (Scheme 58). The nitrile group can be activated by  $\sigma$ - or  $\pi$ -coordination of the gold center to the triple bond, which could be followed by the addition of water. Alternatively, the in situ generated [NHC–Au–OH] species could mediate concerted addition to the nitrile group [77]. This seminal study by the Nolan group clearly identified the challenges and new opportunities in the hydration of nitriles by metal–NHC complexes.

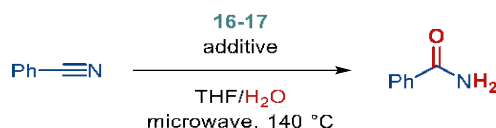
**Scheme 58.** Hydration of nitriles with complex **46**.



In 2010, the Nolan group tested [NHC–Au] complexes **16**–**17** in nitrile hydration (Scheme 59) [20]. Interestingly, complex **16** showed no activity without the presence HBF<sub>4</sub> as acidic additive; however, full conversion of benzonitrile to benzamide was achieved by a combination of **16** with HBF<sub>4</sub>, which is consistent with the activity shown in alkyne hydration. Furthermore, the di-nuclear gold hydroxide complex **17** showed full conversion without any acid and silver additives. These results suggested that both alkyne and nitrile hydration may involve the same [NHC–Au] active species in catalysis.

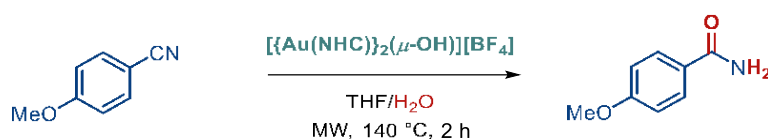
In order to further evaluate counter anion effects, Nolan's group synthesized a series of  $[\{\text{Au}(\text{IPr})\}_2(\mu\text{-OH})][\text{X}]$  complexes,  $\text{X} = \text{BF}_4$ ,  $\text{NTf}_2$ ,  $\text{OTf}$ , FABA (tetrakis(pentafluorophenyl)borate) and  $\text{SbF}_6$ . No significant activity difference among different  $[\{\text{Au}(\text{IPr})\}_2(\mu\text{-OH})][\text{X}]$  complexes was observed. However, these di-nuclear gold complexes showed slightly better performance than complex **46**. Amido complexes  $[\text{Au}(\text{IPr})(\text{NHCOPh})]$  and  $[\{\text{Au}(\text{IPr})\}_2(\text{NHCOPh})]$  were also synthesized and showed to be inactive in nitrile hydration.

**Scheme 59.** Hydration of nitriles with complexes **16–17**.



Later, Nolan's group tested different NHC ligands in  $[\{\text{Au}(\text{NHC})\}_2(\mu\text{-OH})][\text{BF}_4]$  complexes **17**, **31–34** in nitrile hydration (Scheme 60) [27]. In this study, they compared the effect of NHC ligands, such as IPr, SIPr,  $\text{IPr}^{\text{Cl}}$ ,  $\text{IPr}^*$  and IPent. The authors found that imidazolin-2-ylidene complexes, such as **31**  $[\{\text{Au}(\text{SIPr})\}_2(\mu\text{-OH})][\text{BF}_4]$  showed slightly better activity than imidazol-2-ylidene complexes, such as **32**  $[\{\text{Au}(\text{IPrCl})\}_2(\mu\text{-OH})][\text{BF}_4]$  and **34**  $[\{\text{Au}(\text{IPent})\}_2(\mu\text{-OH})][\text{BF}_4]$  in hydrations at 0.5 mol% and 0.25 mol% loading. In contrast, the sterically-hindered complex **33**  $[\{\text{Au}(\text{IPr}^*)\}_2(\mu\text{-OH})][\text{BF}_4]$  showed lower reactivity at 0.5 mol% catalyst loading.

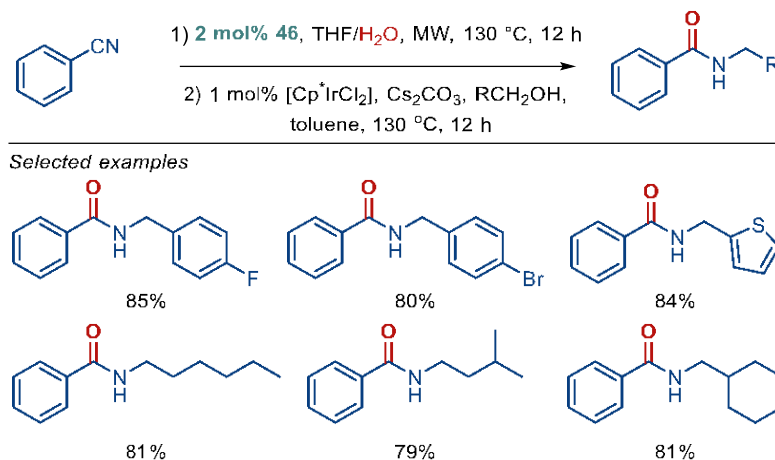
**Scheme 60.** Hydration of nitriles with complexes **17**, **31–34**.



In 2015, Li's group developed a sequential approach to the synthesis of *N*-alkylated amides in good to excellent yields by a one-pot combination of  $[(\text{IPr})\text{Au}(\text{NTf}_2)]$ -catalyzed nitrile hydration and  $[\text{Cp}^*\text{IrCl}_2]$ -catalyzed *N*-alkylation with alcohols (Scheme 61) [78]. In this synthetically valuable method, benzonitriles were first hydrated to primary amides, catalyzed by complex **46**, followed by alkylation with alcohols in presence of  $[\text{Cp}^*\text{IrCl}_2]$  under borrowing hydrogen conditions to afford secondary *N*-alkylated amides. A broad range of nitriles and alcohols can be tolerated in this reaction, affording the

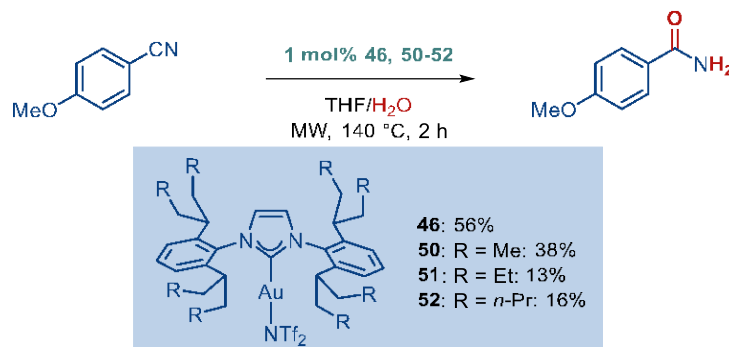
products in 79-85% overall yields. This protocol is noteworthy for its high atom economy compared with previous methods for the synthesis of *N*-alkylated amides.

**Scheme 61.** Hydration-alkynylation of nitriles with complex **46**.



In 2015, Nolan's group applied complexes **50–52** based on the bulky-yet-flexible 'ITent' ligands in the hydration of nitriles (Scheme 62) [37]. This 'ITent' family of ligands has been very successfully used in challenging Pd-catalyzed cross-coupling reactions, where the flexible sterics of the N-Ar wingtips facilitate oxidative addition and reductive elimination steps [79]. In this study, the authors found that bulky-yet-flexible ITent complexes **50–52** were less active than the parent IPr analogue **46** in the hydration of 4-methoxybenzonitrile at 1 mol% catalyst loading. However, it is worth noting that [ $\{\text{Au}(\text{NHC})\}_2(\mu\text{-OH})$ ][BF<sub>4</sub>] complex bearing IPent was more effective than the IPr analogue in the hydration of alkynes [27].

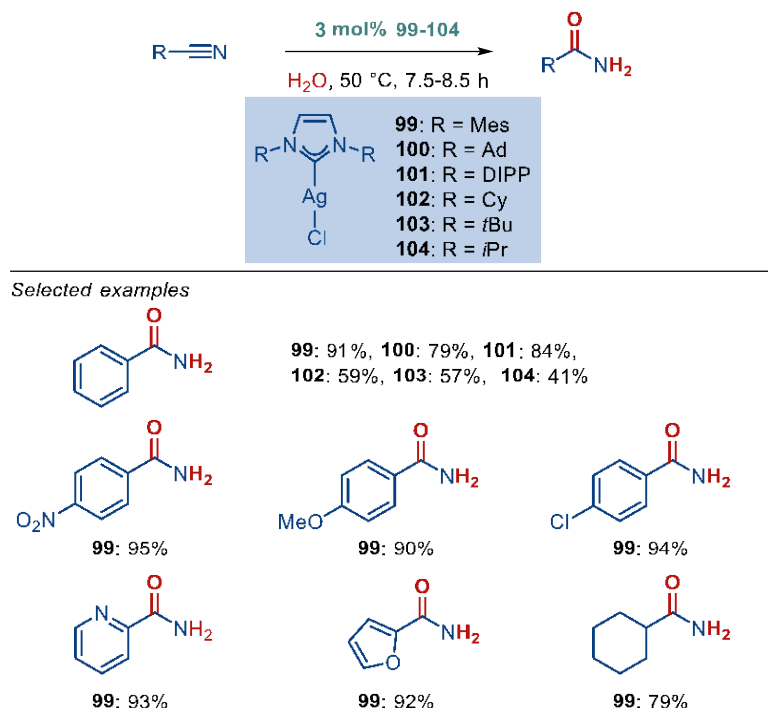
**Scheme 62.** Hydration of nitriles with complex **46**.



## 4.2. NHC–Ag catalyzed hydration of nitriles

In 2019, the first example of [NHC–Ag]-catalyzed hydration of nitriles to primary amides was reported by Vasam and co-workers (Scheme 63) [6f]. They screened a series of NHC ligands, including IPr, IMes, IAd, ICy, I*t*Bu and I*i*Pr. Their results showed the following order of ligand reactivity: IMes > IPr > IAd > ICy > I*t*Bu > I*i*Pr. Interestingly, IMes showed higher activity than IPr in this NHC–silver(I)-catalyzed hydration, which is the opposite trend to NHC–gold(I)-catalyzed hydration. Using neat water as a solvent gave better results than with water/organic solvents. This reaction works with a broad substrate scope, including aromatic, aliphatic and the challenging *N*-heterocyclic nitriles.

**Scheme 63.** Hydration of nitriles with complexes **99–104**.

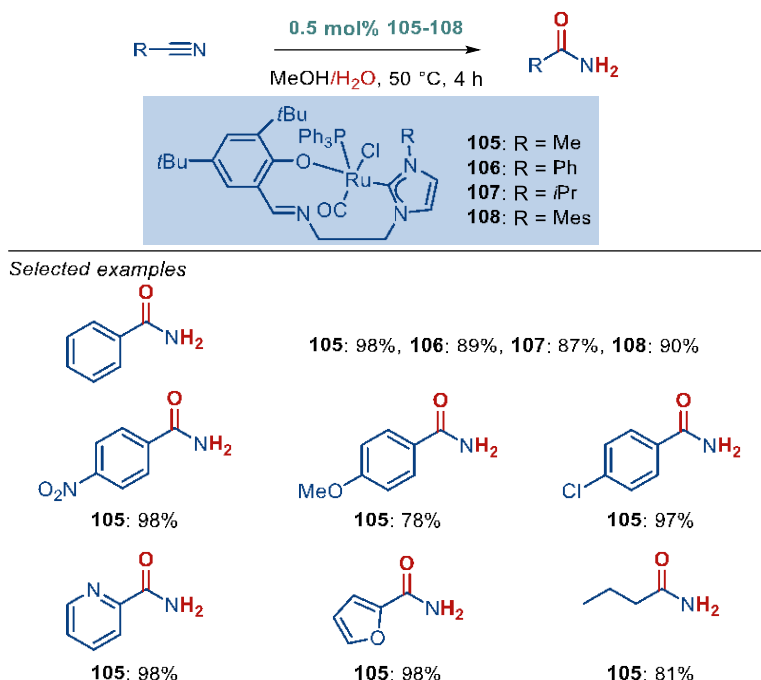


## 4.3. NHC–Ru catalyzed hydration of nitriles

In 2015, Viswanathamurthi's group synthesized and characterized a series of novel NHC–Ru(II) complexes bearing salicylaldiminato-functionalized hybrid NHC/phosphine ligands (Scheme 64) [6d]. These salicylaldiminato-functionalized imidazolium salts and the corresponding [NHC–Ru] complexes **105–108** were tested in hydration of benzonitrile. Unexpectedly, the imidazolium salts were found to be catalytically active, affording the hydration products in 21–33% yields. The Ru(II) complexes **105–108**

were significantly more active, affording the hydration products in 87-98% yields. Using the most active complex **105**, excellent yields were obtained with a broad range of nitriles at low catalyst loading (0.5 mol%) under mild reaction conditions (H<sub>2</sub>O/MeOH, 50 °C). Furthermore, these NHC–Ru catalysts were found to be stable under the reactions conditions and could be recycled up to 6 times with similar efficiency.

**Scheme 64.** Hydration of nitriles with complexes **105**–**108**.



#### 4.4. NHC–Os catalyzed hydration of nitriles

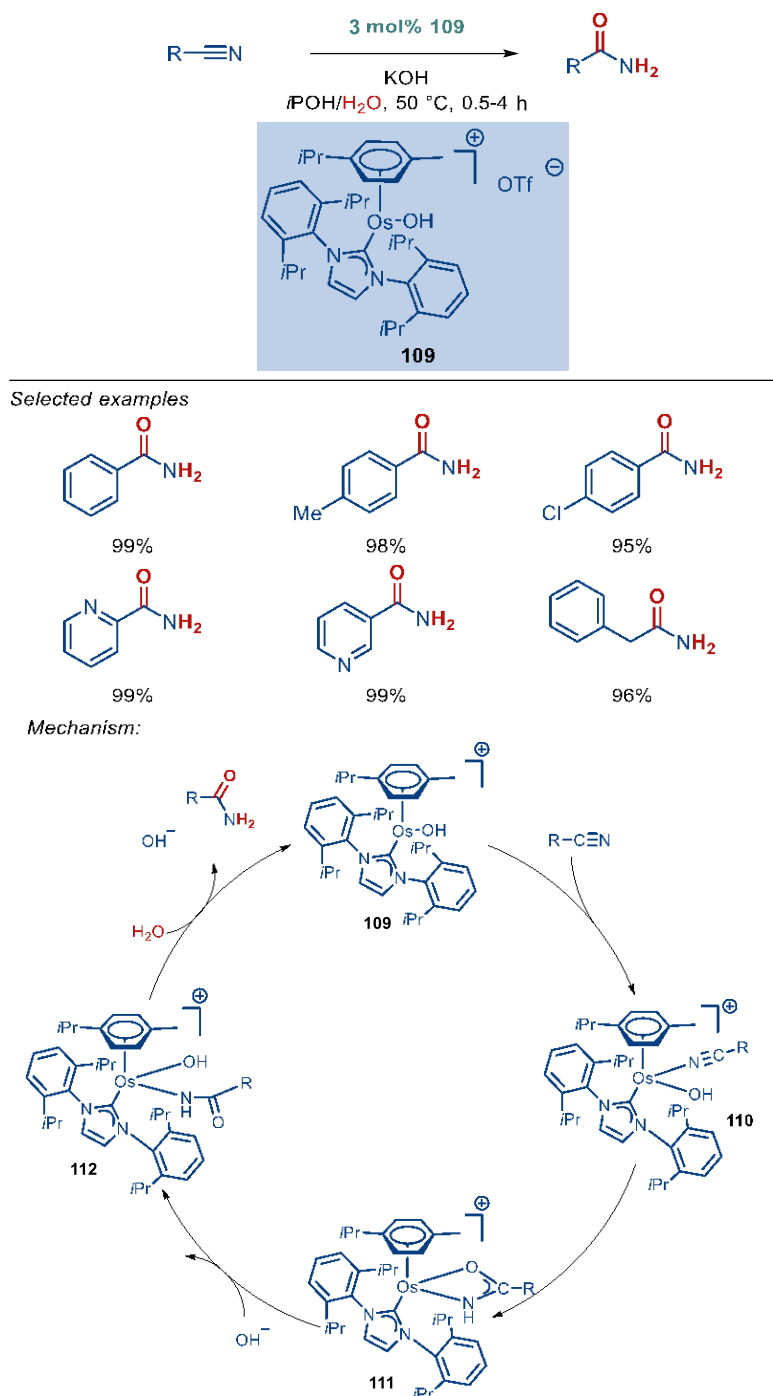
In 2012, the first [NHC–Os]-catalyzed hydration of nitriles to amides was established by Esteruelas, Gimeno and co-workers (Scheme 65) [6b]. The cationic complex [Os( $\eta^6$ -*p*-cymene)(OH)IPr]OTf **109** could be converted to the  $\kappa^2$ -amidate derivative **111**, which was characterized by X-ray crystallography. Both **109** and **111** were found catalytically active in the hydration of nitriles.

This [NHC–Os]-based complex **109** is applicable to a wide range of nitrile substrates. A general order of reactivity is as follows: aromatic nitriles > aliphatic nitriles and substituted benzonitriles: para > meta > ortho. Interestingly, high conversions were obtained for the hydration of cyanopyridines, which represent very challenging substrates for other catalytic systems. This indicated that competing catalyst

inhibition by the pyridine nitrogen atom is non-existent in the [NHC–Os] system. Moreover, the hydration rate of 2-cyanopyridine was faster than that of 3-cyanopyridine, which was explained by a possible hydrogen bonding between the pyridine nitrogen atom and the osmium hydroxide group [6b].

Based on the isolated active intermediates, the authors proposed a mechanism involving the following steps: (1) coordination of CN triple bond via  $\sigma$ -activation; (2) addition of the OH ligand on Os to the sp carbon of CN triple bond, followed by the hydrogen migration from the oxygen to the nitrogen atom to form **111**; (3) addition of external OH<sup>-</sup> to the complex **111** to give **112**; and (4) amide release with the concomitant regeneration of the active catalyst **109**.

**Scheme 65.** Hydration of nitriles with complex **109**.

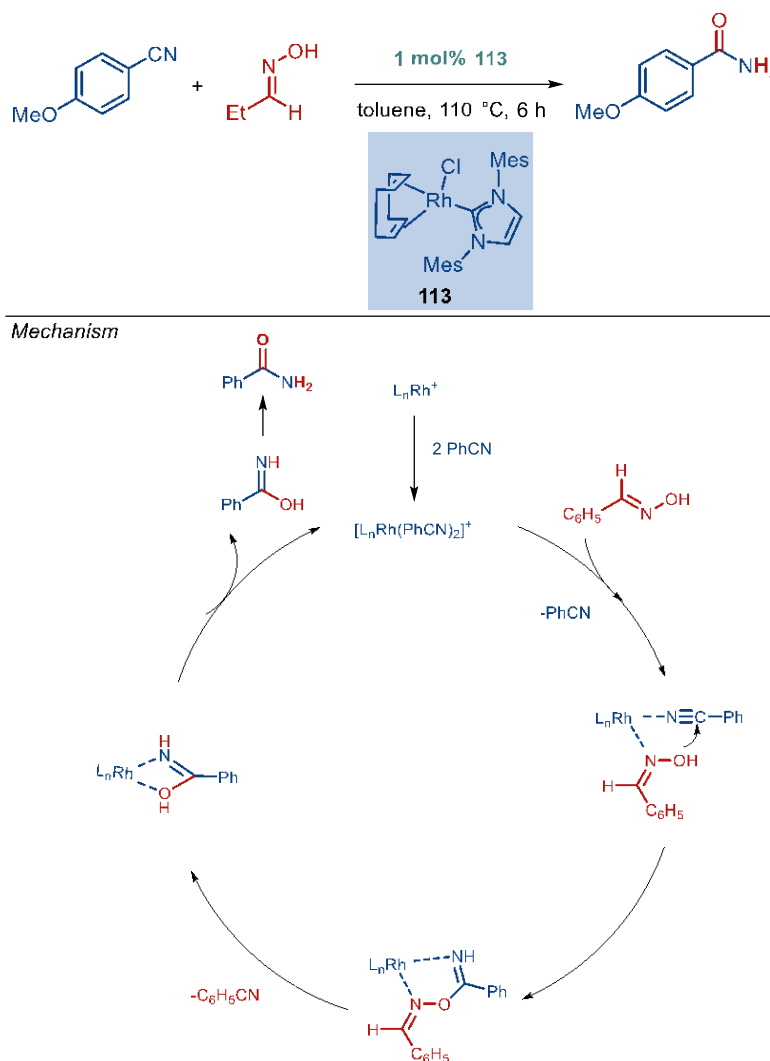


#### 4.5. NHC–Rh catalyzed hydration of nitriles

In 2009, Lee and co-workers reported hydration of nitriles using NHC–Rh(I) complex **113** under anhydrous conditions using propionaldoxime as the water source (Scheme 66) [80]. This methodology was achieved with 1 mol% of complex **113** in toluene at 110 °C. Interestingly, in the proposed

mechanism, the resulting propionitrile from propionaldoxime is inert to hydration due to its lower binding affinity compared with aromatic nitriles, such as 4-methoxybenzonitrile; thus, aromatic nitriles can be selectively hydrated to the corresponding 1° amides using this system. In this study, the authors also demonstrated that  $[\text{RhCl}(\text{PPh}_3)_3]$  shows comparable efficiency to  $[\text{RhCl}(\text{cod})\text{IMes}]$  **113**.

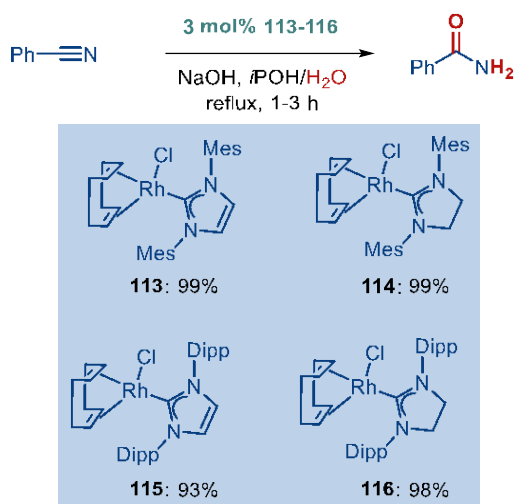
**Scheme 66.** Hydration of nitriles with complex **113**.



In 2020, Joó and co-workers established a new method for nitrile hydration using  $[(\text{NHC})\text{Rh}(\text{cod})\text{Cl}]$  complexes **113–116** (Scheme 67) [81]. Their results showed that all tested complexes gave full conversion of benzonitrile in water/2-propanol. Complex **113** was tested with different nitrile substrates and the TOF value of up to  $276 \text{ h}^{-1}$  was determined. Interestingly, the hydration reactions of 3- and 4-cyanopyridine proceeded efficiently even in the absence of base, NaOH. However, 2-cyanopyridine afforded low conversions (<10%), which was attributed to the bidentate coordination of the amino and

pyridyl group to the metal center. The authors established that this NHC–Rh(I) system is highly efficient, promoting hydration of benzonitrile to benzamide with 1 mol% of **113** at 25 °C, which represents very mild conditions compared with other methods.

**Scheme 67.** Hydration of nitriles with complexes **113-116**.



#### 4.6. NHC–Ni catalyzed hydration of nitriles

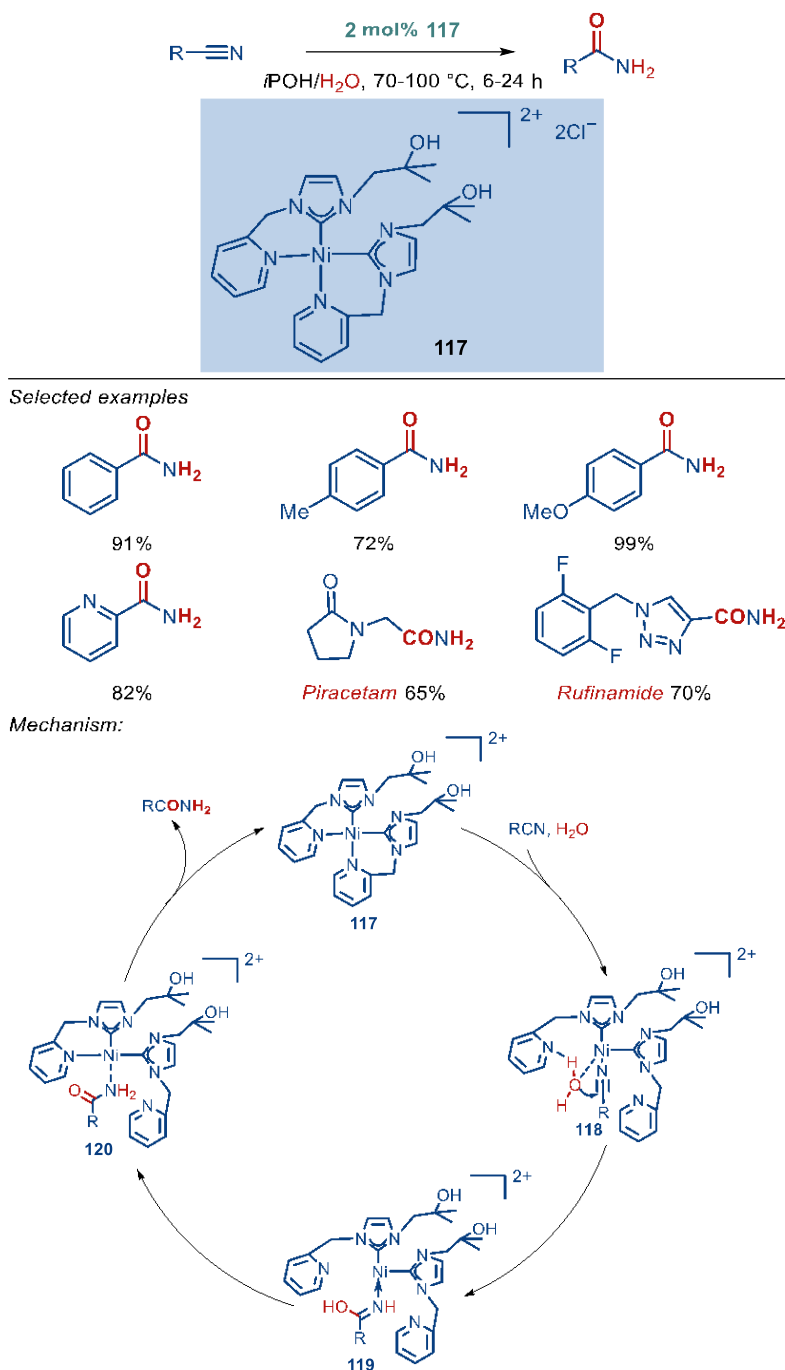
In 2017, the Bera group reported a new strategy for the hydration of nitriles by using [NHC–Ni] complexes under aqueous base-free conditions (Scheme 68) [6e].

The developed dicationic complex **117** exploits a hemilabile pyridyl unit in the N-Ar wingtip to activate water through hydrogen bonding and facilitate the nucleophilic attack on nitrile. Control experiments and kinetic studies supported a hemilabile ligand-promoted water addition. In the presence of 2 mol% of complex **117**, a wide scope of nitriles could be hydrated to the corresponding amides in  $\text{H}_2\text{O}/i\text{PrOH}$  at 70 °C. Importantly, pharmaceuticals, such as *Rufinamide* and *Piracetam* could be directly obtained at 10 mol% catalyst loading.

The authors proposed a hemilability-driven hydration mechanism involving the following steps: (1) formation of complex **118** by ligand exchange and nitrile coordination to the metal center; (2) the detached pyridyl unit activates water by hydrogen-bonding and places the water molecule close to the metal center; (3) complex **119** is generated by ligand-promoted nucleophilic water addition; (4) the

amide product is released and catalyst **117** is regenerated after rapid tautomerization to complete the cycle.

**Scheme 68.** Hydration of nitriles with complex **117**.



## 5. Conclusions and Outlook

In conclusion, since 2009, tremendous progress has been made in using [NHC–M–X] complexes as catalysts in hydration reactions. The unique steric and electronic properties of NHC ligands, different

transition metals as well as counterions with varying coordinating affinity and basicity have enabled the development of new highly active catalytic systems for hydration reactions.

Specifically, NHC ligands form stronger bonds with transition metal centers than the vast majority of other ligands, including phosphines. Thus, NHC–metal complexes are generally more resistant to decomposition and can be used at low catalyst loading to achieve high TON. Among the reported NHC–M systems, [IPrAuX] (X = SbF<sub>6</sub><sup>−</sup>, OTf, NTf<sub>2</sub><sup>−</sup>) became the most popular choice for its high reactivity and commercial availability. Based on the well-defined homogenous NHC–Au–X complexes, recent advances have seen the development of encapsulated and immobilized NHC–Au–X. These encapsulated catalysts show orthogonal regio and chemoselectivity, while the protocols using immobilized catalysts permit for the development of sustainable and recyclable organometallic catalysis.

Despite major progress made in the field, there are numerous challenges and directions that need to be considered: (1) There is still a very small subset of NHC ligands that have been tested in hydration reactions. Well-characterized and structurally-diverse classical NHC scaffolds as well as more recently developed NHC ligands, such as CAACs, should be tested in hydration reactions to provide a better understanding of structure-activity relationship in this area. (2) There are few transition metals that have been tested in NHC–M complexes for hydration reactions. Gold is by far the most explored transition metal in this field. The most desirable will be the development of less expensive and sustainable transition metals as NHC–M–X catalysts for hydration reactions. This challenge is likely to be addressed by using appropriate combination of NHC ligands and counterions. (3) The development of improved acid-, silver- and additive-free catalytic protocols at low catalyst loading is needed for the future advancement of this field. For example, nitrile hydrations still require a relative high catalyst loading compared with alkyne substrates. In order to address this challenge, mechanistic studies determining catalyst decay pathways should be further investigated. In particular, the mechanistic investigations should address the possibility of the formation of off-cycle species, such as azolones NHC=O, from active catalytic NHC–M in the presence of oxygen bases and oxygen nucleophiles for NHC–M catalyzed hydration reactions [82]. The formation of such intermediates can be hindered by providing appropriate steric protection of the metal center by N-wingtips. (4) Compared with other

classes of ligands, there are still very few NHC ligands and complexes that are commercially available, which hinders broad adoption of this class of catalysts by the synthetic community. Importantly, in order to gain valuable insights into the NHC ligand structure-reactivity-relationship, systematic comparisons between NHC ligands under same hydration catalysis conditions are required. In addition, the specific design of new NHC ligands based on steric and electronic tuning for hydration reactions is in high demand, especially to enhance the regioselectivity of the hydration reactions of unsymmetrical alkynes. Based on the reported results, it is important to consider that a subtle balance between the steric and electronic properties is often required, which necessitates a systematic variation of NHC ligands. Furthermore, the introduction of hemilabile groups improves the catalytic activity. (5) Owing to the excellent catalytic activity, superior stability and broad availability, the industrial applications of hydration reactions using NHC–M complexes should be considered for larger scale chemical production. Au(I)–NHC complexes are particularly well-suited for transformations of biomolecules and bioactive intermediate synthesis due to their mild operating conditions and broad functional group tolerance [12a, 54, 83, 84]. The beneficial impact of available NHC ligands will facilitate fundamental comparative studies and deeper mechanistic insights.

It is clear that the use of transition-metal–NHC complexes has led to major advances in the synthetically-critical hydration reactions. The future progress will be achieved by designing more efficient NHC ligands and new strategies, which will spearhead the increasingly powerful application of NHC ligands in challenging organic transformations.

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