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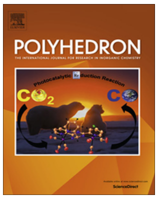

A novel route for large-scale synthesis of [Au(NHC)(OH)] complexes

Fady Nahra [a], Scott R. Patrick [a], Alba Collado [a], Steven P. Nolan [a,b,*]

[a] EaStCHEM School of Chemistry, University of St Andrews, St Andrews, KY16 9ST, UK
[b] Chemistry Department, College of Science, King Saud University, Riyadh 11451, Saudi Arabia

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ABSTRACT

A novel route for the large-scale synthesis of [Au(NHC)(OH)] complexes is reported. Using this new methodology, several [Au(NHC)(OH)] complexes were readily and efficiently accessed on multi-gram scale (up to 20 g).

1. Introduction

The use of gold in catalysis has witnessed an explosive growth over the past decade due to the broad reactivity it enables [1a–j]. In recent years, transition metal hydroxide complexes have emerged as simple and versatile reagents that forgo the need for external bases [1k,l]. Our group has leveraged the strong stabilizing power of *N*-heterocyclic carbene (NHC) ligands to isolate a number of reactive metal-hydroxide species, featuring gold [2], copper [3], rhodium [4], ruthenium [5], palladium [6] and iridium [7].

We have previously reported the synthesis of the first mononuclear NHC-gold hydroxide complex [Au(IPr)(OH)] (**2**) [IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene)] from [Au(IPr)Cl] (**1**) [2a]. The development of **2** has allowed access to a wide variety of novel Au(I) species whilst avoiding the use of inert atmosphere and additives. Complex **2** is remarkably stable while remaining highly basic (pKa 30.3 in DMSO) [2a,8]. It has been successfully employed in the synthesis of gold-acetylene complexes [9], carboxylation and decarboxylation reactions [8,10], silver-free gold catalysis [11] and many other transformations [12].

More recently, we reported a new synthetic method to access a wide range of [Au(NHC)(OH)] complexes in good yields, starting from [Au(NHC)Cl] (Scheme 1), without the use of silver salts [13]. However, attempts to perform this reaction on a larger scale led to irreproducibility issues and/or incomplete conversion.[1] For this reason, alternative synthetic protocols were explored, to access these valuable synthons in a more reliable and reproducible manner.

2. Results and discussion

[Au(IPr)Cl] (**1**) was chosen as the model substrate for initial optimisation principally because of its wide use in catalysis and the known stability of [Au(IPr)(OH)]. Preliminary results allowed the identification of a new way to access the desired complex **2**.

When **1** was reacted with KOH in the presence of 0.4 equiv. of *tert*-amyl alcohol, complete conversion to **2** was observed at room temperature. Although a low yield of **2** was obtained initially (Table 1, entry 2), the method proved to be more reliable than its predecessors. Optimisation of the amount of *tert*-amyl alcohol allowed us to obtain higher yields (Table 1, entries 2–4). There is clearly an effect exerted by the *tert*-amyl alcohol, thus strongly suggesting a completely new mechanism for this reaction leading to **2**. It should be noted that *tert*-butanol could also be used instead of *tert*-amyl alcohol (Table 1, entry 5); however, the latter was chosen for ease of handling. Gratifyingly, replacing potassium hydroxide with the less hygroscopic sodium hydroxide, which

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* Corresponding author at: EaStCHEM School of Chemistry, University of St Andrews, St Andrews, KY16 9ST, UK. Tel.: +44 1334463763; fax: +44 (0) 1334463 808.

E-mail address: snolan@st-andrews.ac.uk (S.P. Nolan).

[1] Previous methods required heat in order to achieve full conversion, which induced reproducibility problems at large scale (incomplete conversions were often observed on gram scale reactions). When CsOH was used, the gold(I) hydroxide complexes were obtained in lower purity as suggested by their failure to pass elemental analysis. This is due to the partial solubility of Cs salts (CsOH and CsCl) in organic solvents.

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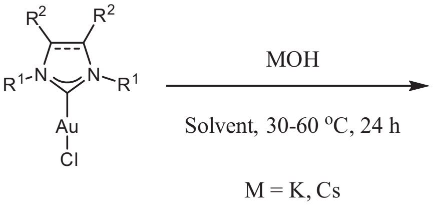
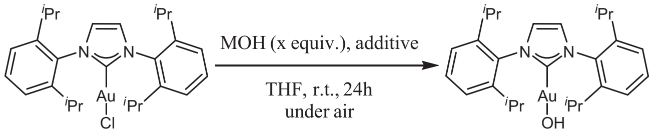


Scheme 1. Previous methods to prepare [Au(NHC)(OH)].

Table 1
Screening of reaction conditions.



1 2

Entry	MOH[a] (equiv.)	Additive (equiv.)	**1/2**[b]	Yield[c] (%)
1	KOH (8)	–	20/80	–
2	KOH (8)	^{t}AmOH (0.4)	0/100	56
3	KOH (8)	^{t}AmOH (0.2)	0/100	74
4	KOH (8)	^{t}AmOH (0.1)	37/63	–
5	KOH (8)	^{t}BuOH (0.2)	0/100	71
6	NaOH (8)	^{t}AmOH (0.2)	0/100	72
7	NaOH (6)	^{t}AmOH (0.2)	0/100	74

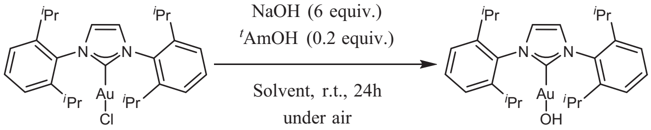
[a] Hydroxide salts were freshly grinded to fine powder before use.
[b] Ratio determined by ^{1}H NMR.
[c] Isolated yield.

was not possible with the previous conditions [2a], also gave good results (Table 1, entry 6). Furthermore, fewer equivalents of the hydroxide salt could now be used in this procedure with no detrimental effect on conversion (Table 1, entry 7).

Finally, optimisation of the reaction solvent and concentration allowed us to obtain full conversion to the hydroxide complex **2**, with 87% isolated yield (Table 2). It should be noted that these optimisation reactions were performed using freshly distilled THF, under air.[2] Furthermore, the workup was also optimised to obtain the final product in good purity using simple procedures; the final product was isolated by performing a filtration through Celite, followed by the addition of water and evaporation of the solvents under reduced pressure. Further addition of water permitted the removal of any remaining alcohol by filtration, affording **2** in high purity.[3]

This new methodology was extended to other IPr-type complexes and the corresponding [Au(NHC)(OH)] were obtained in good yields (Table 3). The method tolerates NHC ligands with a substituted backbone (IPr^{Cl}) and high steric bulk (IPr*, IPr^{*Tol}). Moreover, a saturated NHC (SIPr) was also tolerated under these novel reaction conditions. Unfortunately, this new methodology was unsuccessful when applied to *N*-alkyl substituted NHCs (e.g., ICy, IDD, IAd, I^{t}Bu) or smaller NHC ligands (e.g., IMes, SIMes), which yield highly moisture sensitive [Au(NHC)(OH)] complexes or a mixture of products.[4]

Table 2
Optimisation of the reaction solvent.

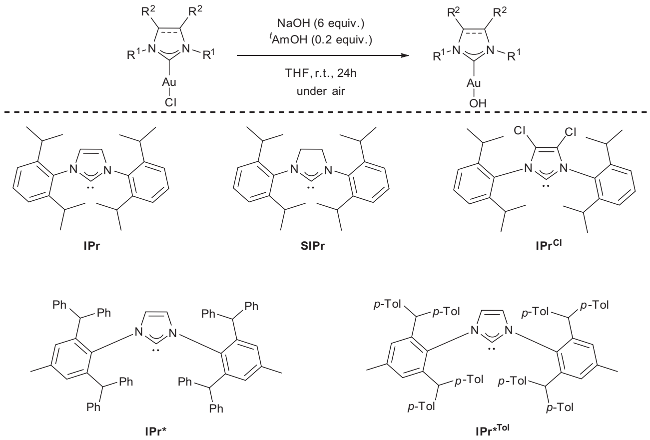


1 2

Entry	Solvent (M)	1/2[a]	Yield[b] (%)
1	THF (0.16)	0/100	74
2	THF/toluene (0.16)	58/42	–
3	THF (0.32)	0/100	87

[a] Ratio determined by ^{1}H NMR.
[b] Isolated yield.

Table 3
Scope of the reaction.



Entry	NHC	Yield[a] (%)
1	IPr	87
2	SIPr	72
3	IPr*	75
4	IPr^{*Tol}	83
5	IPr^{Cl}	76

[a] Isolated yield.

In order to further establish the robustness of the improved methodology, we sought to produce the [Au(NHC)(OH)] complexes on a larger scale (Table 4). Thus, **2** was successfully synthesised on 1, 5 and 20 g scales (Table 4, entries 1–3). Yields increased as the scale of the reaction was increased. This observation suggested that yield losses were intrinsically related to mechanical loss and work-up processes. Extending the large-scale methodology to other related NHC ligands also proved successful (Table 4, entries 4–7).

As previously mentioned, the new conditions dictate a different pathway from previous methodologies. A possible mechanism for this reaction is depicted in Scheme 2, in which the *tert*-amyl alcohol first reacts with NaOH to generate the alkoxide species [14]. Although the equilibrium position surely lies towards the hydroxide, the (small) amount of the alkoxide would react rapidly with [Au(NHC)Cl]. The intermediate thus formed, [Au(NHC)(O^{t}Am)], reacts quickly with water in the reaction mixture to form the [Au(NHC)(OH)] complex, and thus regenerating the *tert*-amyl alcohol. To support the proposed mechanism, we isolated and

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[2] Anhydrous THF was always used to ensure reproducibility of the procedure and product purity for large-scale reactions. Reagent grade THF was tested on normal scale reactions, affording similar results.

[3] IPr-based NHC gold(I) chlorides and hydroxides are insoluble in water. Traces of water were removed under high vacuum.

[4] Using N-alkyl substituted NHCs only resulted in decomposition. The use of IMes and SIMes as ligands did not result in full conversion and a mixture of starting material and final product was always obtained.

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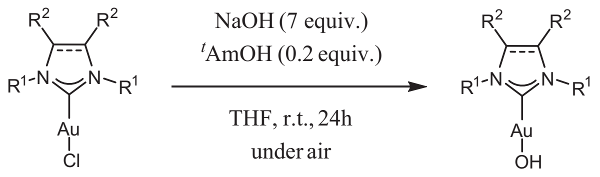
Table 4
Larger-scale reactions.



Entry	NHC	Scale (g)	Yield[a] (%)	Yield[a] (g)
1	IPr	1	95	0.9
2	IPr	5	97	4.7
3	IPr	20	99	19.2
4	SIPr	1	90	0.9
5	IPr*	1	91	0.9
6	IPr^{Cl}	1	70	0.7
7	IPr^{*Tol}	0.59	70	0.4

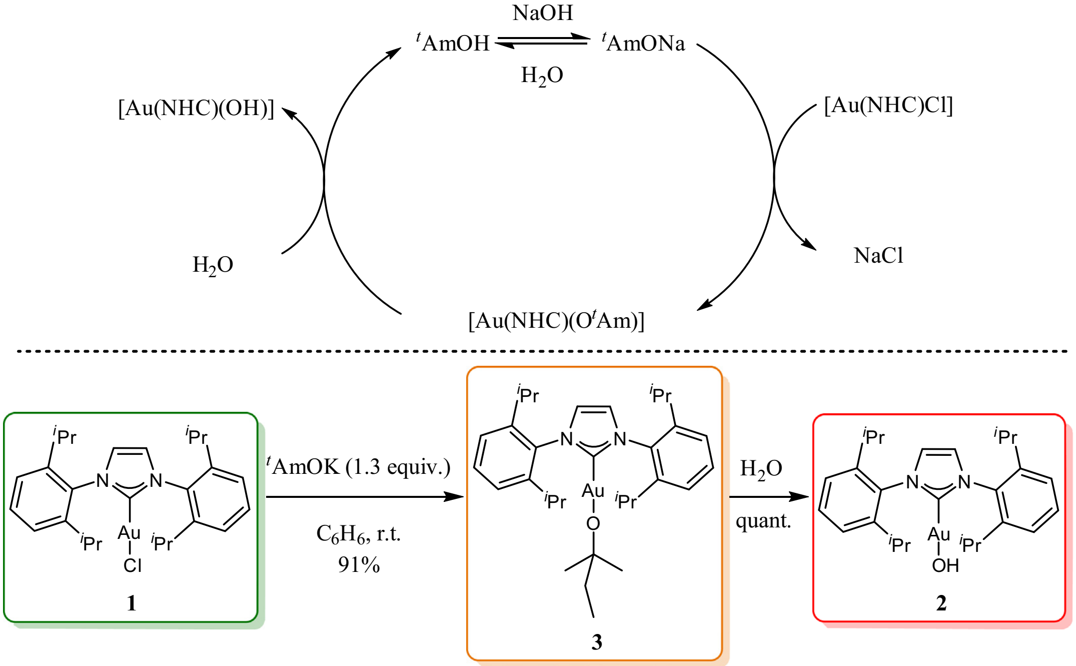
[a] Isolated yield.

characterised [Au(IPr)(O^{t}Am)] (**3**) starting from **1**. Excess water (7 equiv.) was added to **3**, and as expected full conversion to **2** occurred rapidly. Complex **3** is highly unstable in solution, and will react quickly with residual water to afford mixtures of alkoxide and hydroxide complexes.

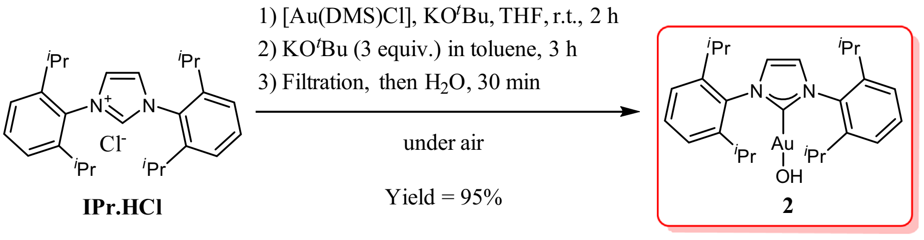
Finally, it was postulated that the ability of **3** to readily afford **2** could be exploited in a one-pot procedure starting from the NHC salt. When [Au(IPr)Cl] (**1**) was generated *in situ* from IPr.HCl and [Au(SMe$_2$)Cl] [15], then reacted with potassium *tert*-butoxide followed by filtration and water addition, **2** was obtained in 95% isolated yield (over two steps) (Scheme 3). This novel one-pot reaction is performed under air and affords **2** in excellent purity. Attempts to extend this new methodology to other NHC ligands are ongoing.

3. Conclusion

In conclusion, a new and reproducible procedure is disclosed for the synthesis of gold hydroxide complexes bearing NHC ligands. Experimental evidence supporting the mechanism is presented. Using this methodology, various [Au(NHC)(OH)] complexes were readily accessed in good to excellent yields on multigram-scale. A novel high-yielding one-pot procedure has been successfully developed for [Au(IPr)(OH)]. In view of its ease of synthesis, **2** has the potential to become a workhorse in gold-mediated transformations, as a pre-catalyst or as a useful mechanistic probe [16], without the use of silver at any stage of its preparation.



Scheme 2. Proposed mechanism under the new conditions.



Scheme 3. One-pot procedure from IPr·HCl and [Au(SMe$_2$)Cl].

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4. Experimental

4.1. General procedure for small-scale synthesis of [Au(NHC)(OH)]

A vial was charged with [Au(NHC)Cl] (1 equiv.), finely ground sodium hydroxide (6 equiv.) and THF (0.32 M) under air. *Tert*-amyl alcohol (0.2 equiv.) was then added under stirring. After 24 h at room temperature, the crude mixture was then filtered through Celite and washed with additional THF. Water (~1 mL/100 mg) was added to the solution and THF was removed under vacuum. More water was added to the white, cloudy suspension and the product was stirred vigorously for a few minutes. It was left to settle for 10 min, collected using a Buchner funnel and washed with hexane. It was then dried under vacuum for several days to produce a white microcrystalline solid (cf. Supporting information for analytical data).

4.2. General procedure for large-scale synthesis of [Au(NHC)(OH)]

A round-bottomed flask was charged with [Au(NHC)Cl] (1 equiv.), finely ground sodium hydroxide (7 equiv.) and THF (0.32 M). *Tert*-amyl alcohol (0.2 equiv.) was then added under stirring. After 24 h at room temperature, the crude mixture was then filtered through Celite and washed with additional THF. Water (~5 mL/1 g) was added to the solution and THF was removed under vacuum. More water was added to the white, cloudy suspension and the product was vigorously stirred until a fine suspension is achieved. If aggregation persists, break manually before filtration. It was left to settle for 10 min, collected using a Buchner funnel and washed with water. It was then dried under vacuum for several days to produce a white microcrystalline solid.

4.3. General procedure for the one-pot synthesis of [Au(NHC)(OH)]

A vial was charged with [Au(SMe_2)Cl] (53 mg, 190 μmol, 1.06 equiv.), IPr.HCl (76 mg, 179 μmol, 1 equiv.) and KO^{t}Bu (31 mg, 277 μmol, 1.5 equiv.) in THF (0.5 mL), under air. The mixture was stirred for 2 h at room temperature. KO^{t}Bu (62 mg, 553 μmol, 3 equiv.) was then added followed by toluene (0.5 mL). After 3 h at room temperature, the crude mixture was then filtered through Celite and washed with additional THF. Water (0.1 mL) was added to the solution and the solution was stirred for an additional 15 min. THF was then removed under vacuum. More water was added to the white, cloudy suspension and the product was vigorously stirred for a few minutes. It was left to settle for 10 min, collected using a Buchner funnel and washed with hexane. It was then dried under vacuum for several days to produce a white microcrystalline solid.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.poly.2014.06.017.

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