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Thomas Scattolin, Nikolaos V. Tzouras, Laura Falivene, Luigi Cavallo ...+1 more authors

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Using sodium acetate for the synthesis of [Au(NHC)X] complexes†‡

Thomas Scattolin,a Nikolaos V. Tzouras,a Laura Falivene,b Luigi Cavallo a,b* and Steven P. Nolan a,‡

The role of sodium acetate in the synthesis of [Au(NHC)Cl] complexes was examined. The use of this base was also investigated for the activation of C–H and S–H bonds by experimental and computational methods. The synthetic use of NaOAc to assemble these complexes is applicable to a wide range of NHCs and proceeds under air, under mild conditions and using technical grade green solvent.

Introduction

N-heterocyclic carbenes (NHCs), first isolated by Arduengo in 1991, have become of paramount importance in the last two decades as efficient organocatalysts1 and above all, have become a privileged ligand class supporting numerous transition metal,2 main group3 and f-block complexes.4 A number of these compounds have become standards in homogeneous and heterogeneous catalysis5,6 and, by virtue of the strength of the metal-carbenic carbon bond, these have also most recently been studied in the field of material science7 and medicinal chemistry.8 The latter area especially studied for the design of potent and selective anticancer8a,8b and antimicrobial8c,d agents.

In this context, several research groups have focused on the synthesis and applications of well-defined organogold compounds. Among these distinct complexes, a position of special importance is occupied by the [Au(NHC)Cl] motif8 as it can be elaborated into catalytic species in situ10 but more importantly, we feel, into powerful synthons, such as [Au(NHC)OH],11 [Au(NHC)(aryl)]12 and [Au(NHC)(acetonyl)]13 complexes. The versatility of these well-defined synthons is clear as they can be transformed into a plethora of gold-NHC derivatives and catalysts.11–14

The importance of such well-defined compounds and their emerging uses in numerous areas of synthesis are clear drivers to develop operationally simpler assembly methods.

† Dedicated to the memory of our friend and colleague Professor Edwin D. Stevens.
‡ Electronic supplementary information (ESI) available: Synthetic procedure, characterisation and computational data. See DOI: 10.1039/d0dt02240c

Scheme 1 Most common synthetic routes to [Au(NHC)Cl].
that has thus far not been deployed in the “weak base approach” to M-NHC complex synthesis is NaOAc. This base is inexpensive and significantly weaker ($p_{K_a \text{ water}} = 9.25$) than $K_2CO_3$ or $\text{NET}_3$ ($p_{K_a \text{ water}} = 3.67$ and 3.25, respectively).\textsuperscript{18} We hypothesised that such a base might also productively be used in the weak base approach and at the same time be a litmus test of the limitations of this synthetic route.

It should be noted that past reports on M-NHC complex synthesis have disclosed the use of this weak base but under fairly harsh reaction conditions (80–120 °C for several hours) and above all using environmentally deleterious solvents such as dimethyl sulfoxide\textsuperscript{19a} or dimethyl formamide.\textsuperscript{19b}

In 2017, Tunik and co-workers reported on the reaction between bisbenzimidazolium salts and [Au(tht)Cl] in the presence of NaOAc in methanol at room temperature.\textsuperscript{20} Unfortunately, the final complexes, because of reported poor solubility, in this study were not fully characterised and therefore the usefulness of the method was not recognised. We felt NaOAc worthy of further investigation with a series of common NHC ligand precursors.

**Results and discussion**

**Synthesis of Au(NHC)Cl complexes**

The reaction between six different unsaturated and saturated imidazolium salts (1a–f) with [Au(DMS)Cl] in the presence of NaOAc (1.2 equiv.) stirring in technical grade acetone (or green acetone) at 60 °C afforded the final complexes 2a–f in high purity and in yields comparable to reactions conducted using $K_2CO_3$ (Table 1).\textsuperscript{17a}

**Table 1** Synthesis of [Au(NHC)Cl] using NaOAc

<table>
<thead>
<tr>
<th>Entry\textsuperscript{a}</th>
<th>NHC-HCl</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IPr-HCl (1a)</td>
<td>1</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>IAd-HCl (1b)</td>
<td>3</td>
<td>71</td>
</tr>
<tr>
<td>3</td>
<td>IMes-HCl (1c)</td>
<td>4</td>
<td>81</td>
</tr>
<tr>
<td>4</td>
<td>tBu-HCl (1d)</td>
<td>4</td>
<td>52</td>
</tr>
<tr>
<td>5</td>
<td>SIPr-HCl (1e)</td>
<td>4</td>
<td>71</td>
</tr>
<tr>
<td>6</td>
<td>SIMes-HCl (1f)</td>
<td>24</td>
<td>77</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Reaction conditions: NHC-HCl (100 mg), [Au(DMS)Cl] (1.0 equiv.), NaOAc (1.2 equiv.) and 1.0 mL of acetone at 60 °C.

DTF calculations support the thermodynamic feasibility of the CMD-like reaction mechanism, a pathway similar to that recently proposed when NEt\textsubscript{3} as base.\textsuperscript{17b}

It is interesting to note that the activation barrier between the well-known aurate intermediate and the final species is considerably lower in the case of NaOAc to that found for KOH, KO[Bu] and NaOMe to generate Au-OR (R = H or hydro- carbonyl) bonds \textit{in situ} or by action of magnesium, tin and silicon alkynyls as transmetallating agents.\textsuperscript{21}

Gratifyingly, the reaction between complexes 2a–f and phenylacetylene in the presence of NaOAc (3 equiv.) using ethanol as a sustainable solvent afforded the desired alkynyl species 3a–f in excellent yields and under very mild conditions (6 h at r.t.), see Table 2.

This category of compound has been described in the patent literature, by Fujimura, for their luminescent properties but their synthesis is reported using a strong base.\textsuperscript{22c}

**Table 2** Synthesis of Au(alkynyl) (3) complexes with NaOAc

<table>
<thead>
<tr>
<th>Entry\textsuperscript{a}</th>
<th>NHC</th>
<th>Yield (%)</th>
<th>Entry\textsuperscript{a}</th>
<th>NHC</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IPr (a)</td>
<td>94</td>
<td>4</td>
<td>IAd (b)</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td>IAd (b)</td>
<td>90</td>
<td>5</td>
<td>SIPr (c)</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td>IMes (e)</td>
<td>85</td>
<td>6</td>
<td>SIMes (f)</td>
<td>92</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Reaction conditions: [Au(NHC)Cl] (100 mg), phenylacetylene (2 equiv.), NaOAc (3 equiv.) and 1.0 mL of EtOH at 25 °C.
Computational studies also permit support of a mechanism involving base-assisted concerted mechanism for alkyne delivery onto gold (Fig. S16 in ESI).\(^2\) We have considered the existence of a [Au(IPr)(OAc)]\(^{4a}\) intermediary in these reactions but have dismissed it as it is never observed in the synthesis of 1a.

Supporting this conclusion, reacting [Au(IPr)Cl]\(^2a\) in various solvents (acetone, ethanol or methanol) at 60 °C for prolonged reaction times (24 h) in the presence of a large excess of NaOAc (3 or 10 equiv.) never leads to the formation of [Au(IPr)(OAc)]\(^{4a}\).\(^2\) The latter is currently obtained by reaction between acetic acid and either of the two synthons, [Au(NHC)(OH)]\(^{11}\) or [Au(NHC)(acetonyl)].\(^1\)

To be thorough in this reactivity study, it should be stated that 4a can be used to access 3a and represents another example of the built-in base approach yet requires the prior installation of the Au-OAc bond (Scheme 2). If the endgame is the synthesis of complexes of type 3 (e.g. [Au(IPr)(C≡CPh)]), then the use of a weak base such as NaOAc in the presence of the alkyne and 2 represents the simplest synthetic route.

In order to extend the weak base approach to the activation of other C–H bonds, we examined the reaction between [Au(IPr)Cl]\(^2a\) and pentafluorobenzene in the presence of NaOAc or K\(_2\)CO\(_3\). Pentafluorobenzene is slightly more acidic than phenylacetylene (\(pK_a\) \(\text{DMSO} = 24.25\)\(^a\) and 28.7,\(^2\)\(^b\) respectively) and we have previously isolated the corresponding [Au(IPr)(C\(_6\)F\(_5\))\] complex using [Au(IPr)(OH)]\(^2\) as a gold synthon in the absence of external bases under mild conditions (toluene, 60 °C, 14 h).\(^1\)

Disappointingly, no product was formed when 2a was reacted with pentafluorobenzene in the presence of NaOAc or K\(_2\)CO\(_3\) (3 equiv.) in both ethanol and toluene at rt or 60 °C for prolonged reaction times (24 h). The desired product was also not formed when [Au(IPr)(OAc)]\(^{4a}\) was used as the gold precursor (Scheme 3).

It appears that more than simple acid/base concepts are at play here and we suspect the sterically encumbered transition state in the CMD-like mechanism is a key element hindering formation of Au–R bonds with more sterically demanding substrates (see Fig. S17 in ESI\(^\dagger\) for computational analysis).

Reactivity of Au(IPr)Cl towards thiophenol (S–H activation)

To explore how far the weak base approach could be extended, we explored the reactivity of the S–H bond of thiophenol.

Mononuclear NHC-gold-thiolato complexes are normally obtained by treating the thiol with a strong base (i.e. NaH or KOH) and subsequent addition of the gold precursor.\(^2\)\(^6\)\(^,\)\(^2\)\(^7\) The seminal paper of Baker and co-workers\(^2\)\(^6\)\(^,\)\(^2\)\(^7\) and Corrigan and Workentin\(^2\)\(^8\) for the preparation of NHC analogues of Auranofin and gold(i) complexes bearing azide-modified arylthiylates, respectively, are noteworthy as are the potential of such compounds in biology and medicine.

The weak base approach would clearly represent a significant advance. Indeed, [Au(IPr)Cl]\(^2a\) and thiophenol react cleanly in the presence of NaOAc. Under very mild conditions already deployed for Au-alkynyl complexes (EtOH, r.t., 6 h) complete conversion into the thiolato complex 5a is obtained in an excellent 95% yield. Spectroscopic data confirm the clean formation of the complex first reported by Sadighi and Gray, whose procedure leads to a lower yield (46%) and makes use of a much more laborious protocol (Scheme 4).\(^2\)\(^8\)

Computational analysis also suggests this synthetic route is thermodynamically very feasible and proceeds through a different mechanism first involving base-assisted thiol deprotonation followed by salt elimination. This mechanism is presented in Fig. S18 in the ESI\(^\dagger\).

Conclusions

In summary, we have shown that a very weak base, NaOAc, can be used to enable the formation of [Au(NHC)Cl] complexes under mild conditions and in high yields. The protocol using NaOAc proves highly efficient in processes involving C–H and S–H bond auration but is substrate specific for C–H bond activation. We suspect steric factors dictate the feasibility of the reaction in this case. Studies aimed at extending this simple weak base...
Experimental

Materials and methods

All complex syntheses were performed in air. Solvents and all other reagents were purchased and used as received without further purification unless otherwise stated. $^1$H and $^{13}$C($^1$H) Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker Advance 400 Ultrashield spectrometer at 298 K. Chemical shifts (expressed by parts per million) are referenced to residual solvent peaks.

Synthesis of [Au(IPr)Cl] (2a). A vial was charged, under air, with 101.4 mg of IPr·HCl (1a, 0.2386 mmol), 70.3 mg of [Au(DMS)Cl] (0.239 mmol) and suspended in acetone (1 mL).

The mixture was stirred at 60 °C for 10 min and then 23.5 mg of NaOAc (0.287 mmol, 1.2 equiv.) was added. The reaction mixture was stirred at 60 °C for 50 min.

After this time the solvent was removed in vacuo and dichloromethane was added (2 mL).

The mixture was filtered through silica (the pad of silica was washed with dichloromethane $3 \times 1$ mL). The solvent was concentrated and pentane (3 mL) was added, affording a white solid which was washed with further portions of pentane ($3 \times 1$ mL) and dried under vacuum.

Yield: 142.0 mg (96%).$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) = 7.50 (t, $J$ = 7.8 Hz, 2H), 7.29 (d, $J$ = 7.8 Hz, 4H), 7.16 (s, 2H), 2.56 (sept, $J$ = 6.9 Hz, 4H), 1.34 (d, $J$ = 6.9 Hz, 12H), 1.22 (d, $J$ = 6.9 Hz, 12H).

The data are in agreement with the reported values.$^{17a}$

Synthesis of [Au(IMes)Cl] (2c). Complex 2c was prepared in an analogous manner to that described for 2a starting from 107.0 mg of IMes·HCl, 101.2 mg of [Au(DMS)Cl] and 33.8 mg of NaOAc.

Reaction time: 4 hours. Yield: 108.3 mg (52%).$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) = 7.09 (s, 2H), 1.87 (s, 18H).

The data are in agreement with the reported values.$^{17a}$

Synthesis of [Au(SIPr)Cl] (2e). Complex 2e was prepared in an analogous manner to that described for 2a starting from 99.3 mg of SIPr-HCl, 68.5 mg of [Au(DMS)Cl] and 22.9 mg of NaOAc.

Reaction time: 24 hours. Yield: 102.4 mg (71%).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) = 7.42 (t, $J$ = 7.7 Hz, 2H), 7.25 (d, $J$ = 7.7 Hz, 4H), 4.05 (s, 4H), 3.06 (sept, $J$ = 6.9 Hz, 4H), 1.42 (d, $J$ = 6.9 Hz, 12H), 1.33 (d, $J$ = 6.9 Hz, 12H).

The data are in agreement with the reported values.$^{17a}$
Reaction time: 6 hours. Yield: 109.1 mg (88%).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) = 7.53–7.49 (m, 2H), 7.24–7.11 (m, 3H), 7.06 (s, 2H), 1.89 (s, 18H).

The data are in agreement with the reported values.\textsuperscript{22c}

**Synthesis of [Au(SIPr)CCPh]** (3e). Complex 3e was prepared in an analogous manner to that described for 3a starting from 138.5 mg of 2e, 45.4 mg of phenylacetylene and 54.7 mg of NaOAc.

Reaction time: 6 hours. Yield: 154.4 mg (92%).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) = 7.41 (t, $J$ = 7.7 Hz, 2H), 7.27–7.24 (m, 2H), 7.24 (d, $J$ = 7.7 Hz, 4H), 7.11–7.02 (m, 3H), 3.99 (s, 4H), 3.09 (sept, $J$ = 6.9 Hz, 4H), 1.46 (d, $J$ = 6.9 Hz, 12H), 1.34 (d, $J$ = 6.9 Hz, 12H).

The data are in agreement with the reported values.\textsuperscript{22c}

**Synthesis of [Au(SIMes)CCPh]** (3f). Complex 3f was prepared in an analogous manner to that described for 3a starting from 149.5 mg of 2f, 56.7 mg of phenylacetylene and 68.3 mg of NaOAc.

Reaction time: 6 hours. Yield: 149.9 mg (98%).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) = 7.28–7.24 (m, 2H), 7.17–7.02 (m, 3H), 6.80 (s, 4H), 3.94 (s, 4H), 2.37 (s, 6H), 1.84 (s, 12H).

The data are in agreement with the reported values.\textsuperscript{22c}

**Synthesis of [Au(IPr)(CCPh)]** (3a) starting from [Au(IPr)(OAc)] (4a). A vial was charged, under air, with 27.6 mg of [Au(IPr)(OAc)] (4a, 0.0428 mmol), 8.7 mg of phenylacetylene (9.4 $\mu$L, 0.0856 mmol, 2 equiv.) and suspended in ethanol (0.5 mL). The reaction mixture was stirred at room temperature for 6 hours. After this time the solvent was removed in vacuo and dichloromethane was added (1 mL).

Addition of pentane (2 mL) to the concentrated solution yields the final complex 3a as a white solid which was filtered and dried under vacuum.

Yield: 27.2 mg (93%).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) = 7.49 (t, $J$ = 7.8 Hz, 2H), 7.32–7.28 (m, 6H), 7.12 (s, 2H), 7.11–7.01 (m, 3H), 2.70–2.51 (hept, $J$ = 6.9 Hz, 4H), 1.38 (d, $J$ = 6.9 Hz, 12H), 1.21 (d, $J$ = 6.9 Hz, 12H).

The data are in agreement with the reported values.\textsuperscript{22c}

**Reaction of [Au(IPr)(Cl)]** (2a) with pentafluorobenzene. A vial was charged, under air with 85.2 mg of [Au(IPr)(Cl)] (2a, 0.1372 mmol), 0.412 mmol (3 equiv.) of NaOAc or K$_2$CO$_3$, 46.1 mg of pentafluorobenzene (30.5 $\mu$L, 0.274 mmol, 2 equiv.) and suspended in ethanol or toluene (1 mL). The reaction mixture was stirred at 60 °C for 24 hours. After this time no conversion to the desired product was observed.

**Reaction of [Au(IPr)(OAc)]** (4a) with pentafluorobenzene. A vial was charged, under air, with 32.4 mg of [Au(IPr)(OAc)] (4a, 0.0503 mmol), 16.9 mg of pentafluorobenzene (11.2 $\mu$L, 0.100 mmol, 2 equiv.) and suspended in ethanol or toluene (0.5 mL). The reaction mixture was stirred at 60 °C for 24 hours. After this time no conversion to the desired product was observed.

**Synthesis of [Au(IPr)(SPh)]** (5a). A vial was charged, under air, with 50.9 mg of [Au(IPr)(Cl)] (2a, 0.0820 mmol), 20.2 mg of NaOAc (0.246 mmol, 3 equiv.), 18.1 mg of thiophenol (16.7 $\mu$L,

0.164 mmol, 2 equiv.) and suspended in ethanol (0.5 mL). The reaction mixture was stirred at room temperature for 6 hours. After this time the solvent was removed in vacuo and dichloromethane was added (1 mL).

The mixture was filtered on a millipore membrane filter and addition of pentane (2 mL) to the concentrated solution yields the final complex 5a as a white solid which was filtered and dried under vacuum.

Yield: 54.1 mg (95%).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) = 7.54 (t, $J$ = 7.8 Hz, 2H), 7.31 (d, $J$ = 7.8 Hz, 4H), 7.19 (s, 2H), 6.86–6.83 (m, 2H), 6.78–6.74 (m, 3H), 2.67–2.58 (hept, $J$ = 6.9 Hz, 4H), 1.34 (d, $J$ = 6.9 Hz, 12H), 1.23 (d, $J$ = 6.9 Hz, 12H).

The data are in agreement with the reported values.\textsuperscript{28}

**Computational details**

Geometries were optimized with the Gaussian09 package\textsuperscript{30} at the PBE0-D3 level of theory.\textsuperscript{31} The standard split-valence basis set with a polarization function of Ahlrichs and coworkers was used for H, C, N, O, F, S and Cl atoms (SVP keyword in Gaussian)\textsuperscript{32} while the quasi relativistic small-core Stuttgart effective core potential (ECP) was used for Au (SDD keyword in Gaussian09).\textsuperscript{33} Solvent effects, acetone and ethanol, were included using the PCM method.\textsuperscript{34} To this PBE0-D3/TZVP electronic energy in solvent, zero point and thermal corrections were added from the gas-phase frequency calculations at the PBE0-D3/SVP level.

**Conflicts of interest**

There are no conflicts to declare.

**Acknowledgements**

We gratefully acknowledge VLAIO (SBO project CO2PERATE), the Special Research Fund (BOF) of Ghent University for starting and project grants to SPN, and project grant (01N03217) to KVH and MS. KVH thanks the Hercules Foundation (project AUGE/11/029). Umicore AG is gratefully acknowledged for generous gifts of materials.

**Notes and references**


2 (a) M. N. Hopkinson, C. Richter, M. Schedler and F. Glorius, Nature, 2014, 510, 485–496; (b) P. de Frémont,


The high $pK_a$ water value of phenylacetylene (23.2$^{21a}$) excludes its deprotonation by sodium acetate ($pK_a$ water HOAc = 4.78$^{18}$) before interaction with the NHC-gold(i) precursor.


