Gold-catalysed imine-propargylamine cascade sequence: Synthesis of 3-substituted-2,5-dimethylpyrazines and reaction mechanism

Benito Alcaide, Pedro Almendros, José M. Alonso, Israel Fernández, Gonzalo Gómez-Campillos, and M. Rosario Torres

The gold-catalysed coupling reaction between propargyl amine-derived imines and propargyl amine exclusively afforded pyrazines. Besides, in order to understand the mechanism of this sequence, deuterium labeling and computational studies have been performed.

Aromatic azaheterocycles are key components in a large number of bioactive molecules. In particular, the electron-deficient pyrazine nucleus is present in small molecule drugs which exhibited antitumoral, antiviral, and enzyme inhibitory activities, among others. Besides, the fragrance and agricultural industries take advantage of the pyrazine core. On the other hand, gold complexes continue to attract considerable interest in the synthetic community due to their powerful soft Lewis acidic nature. We decided to analyse the possibility of synthesizing carbolines through metal-catalysed cyclization reactions of alkenes with imines derived from indole-2-carbaldehyde and propargyl amine. Interestingly, it was found that the gold-catalysed reaction between imine 1a and propargyl amine exclusively afforded indole-linked pyrazine 2a instead the expected fused carbone 3a (Scheme 1).

Remarkably, rearranged product 2a bears the nitrogen atom in β-position, while in the starting imine the nitrogen atom is in the α-position. Our catalyst screening employing indole-imine 1a led to the identification of the Gagosz’ catalyst [(Ph₃P)AuNTf₂] as the most suitable promoter. Change on the nature of the phosphine in the gold pre-catalyst has little effect in the reaction, because replacing [(Ph₃P)AuNTf₂] by [P(o-Bu)₂(o-biphenyl)AuNTf₂] did not show any appreciable difference. Consequently, much cheaper Ph₃P complex was used in the following reactions. The gold-catalysed reaction was facile at room temperature in toluene or dimethyl sulfoxide (DMSO) and provided the pyrazine product in good yield. Among all the solvents examined, 1,2-dichloroethane (DCE) proved to be the best choice, affording product 2a in an excellent 96% yield (Scheme 1). The addition of 3 Å molecular sieves (MS) to the reaction mixture considerably decreased the yield, but did not affect neither regio- nor chemoselectivity. The gold-catalysed reaction between imine 1a and propargyl amine in presence of 3 Å MS did not go to completion, thus highlighting the importance of adventitious water for the success of the pyrazine formation. The addition of 5 equiv. of H₂O to the gold-catalysed reaction under otherwise identical conditions accelerated the conversion and retained the excellent yield. This reaction could also be catalysed by AuCl₃, but with diminished effectiveness because pyrazine 2a was isolated in just 12% yield after 4 days. Different Lewis acid catalysts such as PtCl₂, InCl₃, Bi(OTf)₃, ZnCl₂, and AgNTf₂ were found to be completely ineffective in carrying out any transformation of the imine.
would be more attractive. To evaluate the practicability of our method, it was desirable to scale-up the procedure to obtain gram quantities of pyrazine derivatives. Worthy of note, not obvious loss of yield was observed for adduct 2f (isolated yield: 90%) when the reaction was carried out on a 1-gram scale and the catalyst loading was reduced from 5 mol% to 1 mol%.

Unfortunately, imines derived from propargyl amine and aliphatic aldehydes were not as rewarding as their aromatic counterparts. Single crystal XRD structure of nitroderivative 2e unambiguously confirmed the 1,4-relationship of the two nitrogen atoms of the heterocycle. (6)

Surprisingly, the reaction is very selective to the assembly of the amine precursor involved during construction of the diazacycle. For example, neither secondary propargyl amines nor C-substituted propargyl amines were suitable coupling partners in the above gold-catalysed transformation. On the other hand, with the allenyl-derived imine 4a employed, an intractable complex reaction mixture was formed using buta-2,3-dien-1-amine (Scheme 3). The reaction of allenyl imine 4a with propargyl amine was sluggish and pyrazine 2a was isolated in very low yield (Scheme 3).

\[
\text{Scheme 3: Treatment of allenyl imine 4a with propargyl amine as well as buta-2,3-dien-1-amine under gold catalysis.}
\]

We monitored the tandem reaction by \( ^1 \text{H} \) NMR spectroscopy (NMR tube with an equimolecular mixture of imine 1f and propargyl amine and 5 mol\% [(Ph\( _3 \text{P} \))AuNTf\(_2\)]) in order to track the reaction intermediates (Figure S2, see ESI). Even at the early stage of the reaction the only species that can be clearly detected are imines 1 and final adducts 2. Unfortunately, we could not observe in appreciable amounts the formation of any intermediate. \(^{31} \text{P} \) NMR spectra were also recorded. The rapid disappearance of the peak at \( \delta = 29.47 \) ppm (\(^{31} \text{P} \) NMR signal of the Gagos’ catalyst) with concomitant appearance of a new peak at \( \delta = 45.77 \) ppm may point to the formation of propargyl amine gold complex. The reaction progress shows several detectable \(^{31} \text{P} \) NMR signals, with an important peak at \( \delta = 39.53 \) ppm, which appeared quickly (Figure S3, see ESI). After completion of the reaction, the \(^{31} \text{P} \) NMR signal of the Gagos’ catalyst reappeared.

To gain mechanistic insights on this transformation, deuterium-labeled imine [D\(_2\)]-1a was prepared. Reaction of [D\(_2\)]-1a with propargyl amine in the presence of [(Ph\( _3 \text{P} \))AuNTf\(_2\)] produced [D\(_2\)]-pyrazine 2a with total deuteration incorporation at the methylenic carbon [Scheme 4, Eq. (1)]. No doubly deuterated pyrazine was detected by mass spectrometry, thus indicating that the rearrangement process occurred exclusively in an intramolecular fashion. By contrast, triply deuterated pyrazine [D\(_3\)]-2f was obtained by an experiment involving mixing equimolar amounts of deuterium-labeled imine [D\(_3\)]-1f and [D\(_3\)]-propargyl amine [Scheme 4, Eq. (2)]. This triple deuteration caused both the modification of the peaks at 3.39 and 2.46 ppm, which are the signals of the CHHHH protons corresponding to the methyl groups attached to the pyrazine ring, and the decrease of the signal at 8.25 ppm, which is the signal of the aromatic CH pyrazine proton, on the adduct 2f. NMR calculations showed for both cases a deuteration of a 65%. An intermolecular competition experiment involving equimolar amounts of non-deuterated imine 1f and [D\(_3\)]-propargyl amine afforded triply deuterated pyrazine [D\(_3\)]-2f with 25% of D-isotope abundance [Scheme 4, Eq. (3)].

With the aim of trapping a possible organometallic intermediate in order to understand the mechanism of this reaction, we performed deuterium labeling studies with deuterium oxide as well. Under the same above conditions but with the addition of 20 equiv of D\(_2\)O, the reaction between imine 1f and propargyl amine was catalysed by [(Ph\( _3 \text{P} \))AuNTf\(_2\)] in 1,2-dichloroethane afforded pyrazine [D\(_3\)]-2f with 50% deuterium content [Scheme 4, Eq. (4)].

\[
\text{Scheme 4: Deuterium labeling experiments leading to deuterated pyrazines [D]-2 under gold catalysis.}
\]

Taking into consideration that the reaction is limited to terminal alkynes, a reaction mechanism involving dual gold activation of the alkyne substrates may be contemplated. (13) The potential species of this double activation by gold are shown in Figure S4 (see ESI). However, this double activation pathway is not in accordance with some of the labeling studies of Scheme 4 because pentadeuterated [D\(_5\)]-2 pyrazines should be obtained instead of triply deuterated pyrazines [D\(_3\)]-2.

Density functional theory (DFT) calculations have been carried out at the PCM-M06/def2-SVP/B3LYP/def2-SVP level(10) to gain more insight into the reaction mechanism(10) of the above discussed gold-catalysed pyrazine formation. The corresponding computed reaction profile of the reaction of imine 1M (bearing a phenyl group as aromatic ring) and propargyl amine in the presence of the model catalyst [(PM\( _3 \))AuNTf\(_2\)] is shown in Figure 1, which gathers the corresponding computed free energies (\( \Delta G_{298}^\circ \)) at 298.15 K in DCE as solvent.

The process begins with the coordination of the gold(I) catalyst to the triple bond of imine 1M to form 1M-Au. This species then undergoes a chemo- and regioselective hydroamination reaction with propargyl amine to produce intermediate INT1. This exergonic process (\( \Delta G_r = -14.0 \) kcal/mol) occurs through transition state TS1, which is associated...
with the formation of the first N–C bond, with an activation barrier of $\Delta G_a = 18.1$ kcal/mol. INT1 then evolves to INT2 via a 1,3-proton shift. This reaction proceeds very likely with assistance of NTf$_2^-$ following a similar protonolysis of the Au–C bond to that reported by us in related [(P Ph$_3$)AuNTf$_2$]-catalysed processes.$^{[11]}$ Exergonic coordination ($\Delta G_k = -8.7$ kcal/mol) of the cationic gold in complex INT2 produces INT3, which experiences an intramolecular nucleophilic addition of the imine to the activated-alkyne moiety through TS2. The ease of this process becomes evident from the low barrier ($\Delta G_a = 5.5$ kcal/mol) and high exergonicity ($\Delta G_k = -17.1$ kcal/mol) computed for this step. The new cationic intermediate INT4 readily releases benzaldehyde by hydrolysis therefore producing INT5. Similar NTf$_2^-$-mediated protonolysis of the Au–C bond leads to the formation of 2,5-dimethylenepiperazine INT6 with concurrent regeneration of the gold catalyst. The latter intermediate readily isomerizes to its more stable 2,5-dimethyl-1,4-dihydropyrazine INT7 isomer ($\Delta G_{298} = -6.5$ kcal/mol).$^{[12]}$ Then, an intermolecular enamine addition from INT7 towards the gold-activated benzaldehyde occurs to produce INT8 via TS3, a saddle point associated with the formation of the new C–C bond. This reaction step also proceeds with a low activation barrier ($\Delta G_a = 7.6$ kcal/mol) in an exergonic transformation ($\Delta G_k = -5.5$ kcal/mol), compatible with a reaction at room temperature. Subsequent proton-migration forming INT9 and release of the catalyst produces INT10, which after dehydration leads to the 2-alkylidene-3,6-dimethyl-1,2-dihydropyrazine INT11. The last step of the transformation involves the isomerization by aromatization of INT11 to the final pyrazine 2-Ph.

**In conclusion,** it has been observed that the gold-catalyzed coupling reaction between propargyl amine-derived imines and propargyl amine exclusively afforded pyrazines. Besides, in order to understand the mechanism of this sequence, both deuterium labeling experiments and a computational study have been performed.

**Support for this work by the MINECO** [Projects CTQ2012-33664-C02-01, CTQ2012-33664-C02-02, CTQ2010-20714-C02-01] and CAM (Projects S2009/PPQ-1752 and S2009/PPQ-1634) are gratefully acknowledged. J. M. A. thanks Comunidad Autónoma de Madrid and Fondo Social Europeo for a postdoctoral contract. G. G. C. thanks the MEC for a predoctoral grant.

**Notes and references**

*Grupo de Lactamas y Heterociclos Bioactivos, Departamento de Química Orgánica, Unidad asociada al CSIC, Facultad de Química, Universidad Complutense de Madrid, 28040-Madrid, Spain. Fax: +34 91-3944103; E-mail: alcaideb@quim.ucm.es*

CCDC-953438. The intermolecular contact N(pyrazine)···H(indole) in compound 2c may indicate hydrogen bonding; these contacts link the molecules into dimers (Figure S1, see ESI).

This reaction mechanism is supported by the isolation of 2,5-dimethylpyrazine during the gold-catalysed dimerization reaction of propargylamine in the absence of aldehyde.