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A gold-catalysed imine–propargylamine cascade sequence: synthesis of 3-substituted-2,5-dimethylpyrazines and the reaction mechanism†

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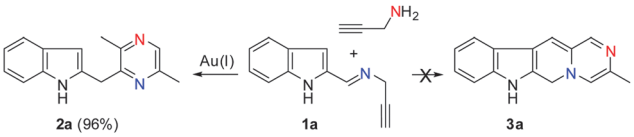
The gold-catalysed coupling reaction between propargylamine-derived imines and propargylamine exclusively afforded pyrazines. Besides, in order to understand the mechanism of this sequence, deuterium labeling and computational studies have been performed.

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 exhibit antitumoral, antiviral, and enzyme inhibitory activities, among others.[1] Besides, the fragrance and agricultural industries take advantage of the pyrazine core.[2] On the other hand, gold complexes continue to attract considerable interest of 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 alkynes with imines derived from indole-2-carbaldehyde and propargylamine. Interestingly, it was found that the gold-catalysed reaction between imine **1a** and propargylamine exclusively afforded the indole-linked pyrazine **2a**,[3] instead of the expected fused carboline **3a** (Scheme 1).[4] Remarkably, the rearranged product **2a** bears the nitrogen atom in the 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 Gagosz' catalyst [$(Ph_3P)AuNTf_2$] as the most suitable promoter.[5] Change in the nature of the phosphine in the gold pre-catalyst has little effect on the reaction, because replacing [$(Ph_3P)AuNTf_2$] by [$P(tBu)_2$(*o*-biphenyl)$AuNTf_2$] did not show any appreciable difference. Consequently, the much cheaper Ph_3P 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 yield of 96% (Scheme 1). The addition of 3 Å molecular sieves (MS) to the reaction mixture considerably decreased the yield, but did not affect regio- or chemoselectivity. The gold-catalysed reaction between imine **1a** and propargylamine in the presence of 3 Å MS did not go to completion, thus highlighting the importance of adventitious water for the success of pyrazine formation. The addition of 5 equiv. of H_2O to the gold-catalysed reaction under otherwise identical conditions accelerated the conversion and retained the excellent yield. This reaction could also be catalysed by $AuCl_3$, but with diminished effectiveness because pyrazine **2a** was isolated in just 12% yield after 4 days. Different Lewis acid catalysts such as $PtCl_2$, $InCl_3$, $Bi(OTf)_3$, $ZnCl_2$, and $AgNTf_2$ were found to be completely ineffective in carrying out any transformation of the imine.



Scheme 1 Cyclization reaction of [(indol-2-yl)methylene]prop-2-yn-1-amine **1a** and propargylamine *via* gold catalysis.

The scope of the optimized reaction was demonstrated by utilizing varied propargylamine-derived imines **1b–p**. By examining the influence of the substituent, we found that aromatic and α,β-unsaturated aldehydes were smoothly transformed into pyrazines **2b–p** in good yields (Scheme S1, see ESI†). The electronic nature of the aromatic rings did not have a strong influence on the above reaction. In fact, different heterocycles were well tolerated.

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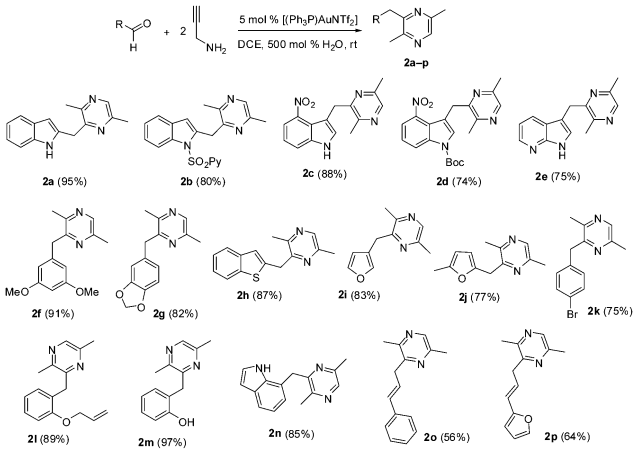
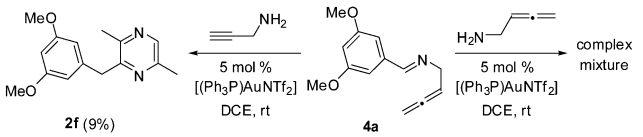


Scheme 2 Gold-catalysed one-pot protocol for the synthesis of pyrazines **2** from aldehydes and propargylamine.

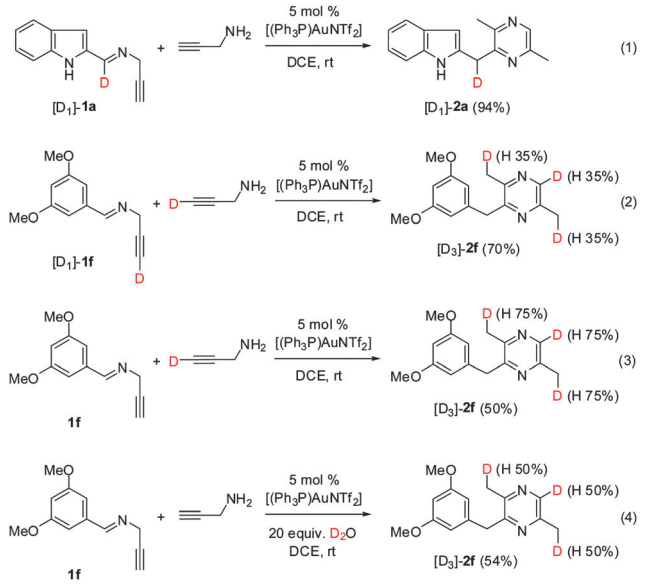
Starting from the corresponding aldehyde and using two equivalents of propargylamine, the gold-catalysed one-pot protocol can also be accomplished in similar yields (Scheme 2), which in terms of efficiency and simplicity would be more attractive. To evaluate the practicability of our method, it was desirable to scale-up the procedure to obtain gram quantities of pyrazine derivatives. It is worth noting that no obvious loss of yield was observed for adduct **2g** (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 propargylamine and aliphatic aldehydes were not as rewarding as their aromatic counterparts. The single crystal XRD structure of nitroderivative **2c** 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 propargylamines nor *C*-substituted propargylamines were suitable coupling partners in the above gold-catalysed transformation. On the other hand, when the allenyl-derived imine **4a** was employed, an intractable complex reaction mixture was formed using buta-2,3-dien-1-amine (Scheme 3). The reaction of allenyl imine **4a** with propargylamine was sluggish and pyrazine **2a** was isolated in very low yield (Scheme 3).

We monitored the tandem reaction by ^{1}H NMR spectroscopy (an NMR tube with an equimolecular mixture of imine **1f** and propargylamine and 5 mol% [$(Ph_3P)AuNTf_2$]) in order to track the reaction intermediates (Fig. S2, see ESI†). Even at the early stage of the reaction the only species that could be clearly detected were imines **1** and final adducts **2**. Unfortunately, we could not observe, in appreciable amounts, the formation of



Scheme 3 Treatment of allenyl imine **4a** with propargylamine as well as buta-2,3-dien-1-amine *via* gold catalysis.



Scheme 4 Deuterium labeling experiments leading to deuterated pyrazines [D]-**2** *via* gold catalysis.

any intermediate. ^{31}P NMR spectra were also recorded. The rapid disappearance of the peak at δ = 29.47 ppm (^{31}P NMR signal of the Gagosz' catalyst) with concomitant appearance of a new peak at δ = 45.77 ppm may point to the formation of the propargylamine gold complex. The reaction progress shows several detectable ^{31}P NMR signals, with an important peak at δ = 39.53 ppm, which appeared quickly (Fig. S3, see ESI†). After completion of the reaction, the ^{31}P NMR signal of Gagosz' catalyst reappeared.

To gain mechanistic insights into this transformation, a deuterium-labeled imine [D_1]-**1a** was prepared. Reaction of [D_1]-**1a** with propargylamine in the presence of [$(Ph_3P)AuNTf_2$] produced [D_1]-pyrazine **2a** with total deuterium incorporation at the methylenic carbon [Scheme 4, eqn (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_1]-**1f** and [D_1]-propargylamine [Scheme 4, eqn (2)]. This triple deuteration caused both the modification of the peaks at 3.39 and 2.46 ppm, which are the signals of the C*HHH* 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 C*H* pyrazine proton, in adduct **2f**. NMR calculations showed, for both cases, a deuteration of 65%. An intermolecular competition experiment involving equimolar amounts of non-deuterated imine **1f** and [D_1]-propargylamine afforded triply deuterated pyrazine [D_3]-**2f** with 25% of D-isotope abundance [Scheme 4, eqn (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_2O, the reaction between

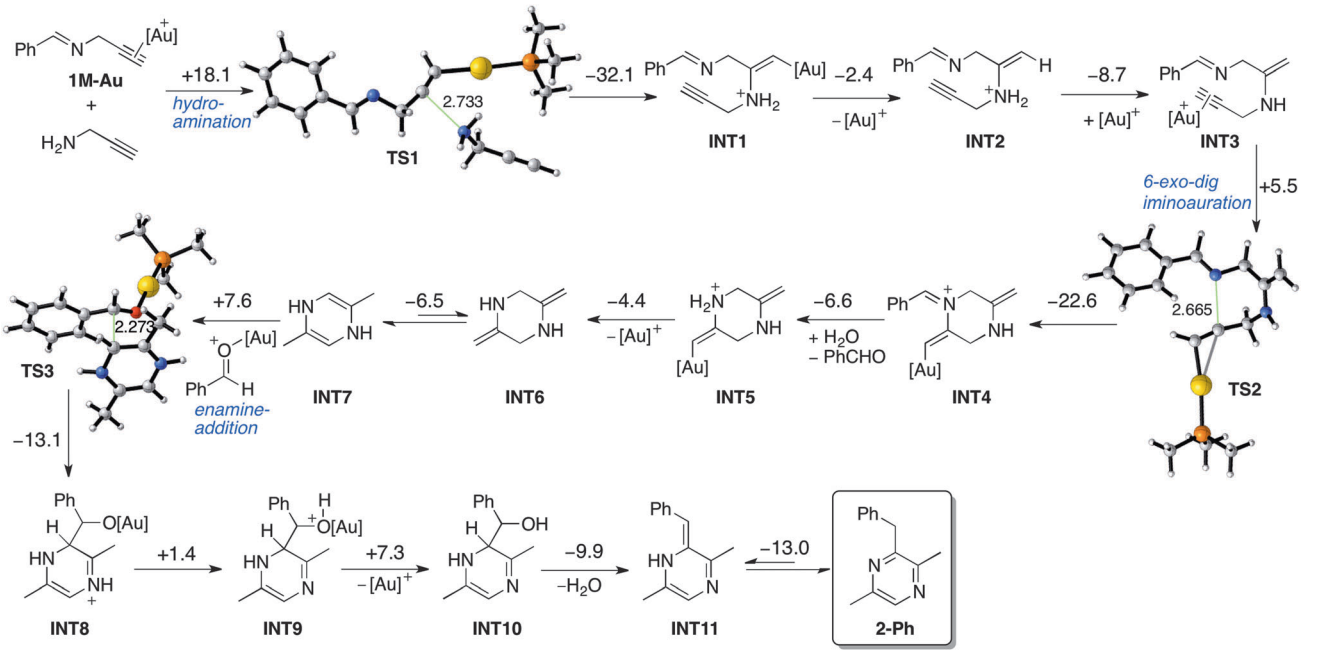


Fig. 1 Computed reaction profile for the gold(I)-catalysed reaction between **1M-Au** and propargylamine. Free energies (ΔG, at 298 K) and bond distances are given in kcal mol^{-1} and angstroms, respectively. $[Au]^+$ denotes $[(PMe_3)Au]^+$. All data have been computed at the PCM(dichloroethane)M06/def2-SVP//B3LYP/def2-SVP level.

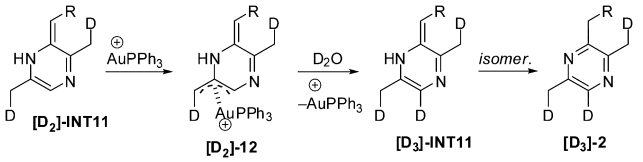
imine **1f** and propargylamine catalysed by $[(Ph_3P)AuNTf_2]$ in 1,2-dichloroethane afforded pyrazine $[D_3]$-**2f** with a 50% deuterium content [Scheme 4, eqn (4)].

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.[7] The potential species of this double activation by gold are shown in Fig. S4 (see ESI†). However, this double activation pathway is not in accordance with some of the labeling studies shown in Scheme 4 because pentadeuterated $[D_5]$-**2** pyrazines should be obtained instead of triply deuterated pyrazines $[D_3]$-**2**.[8]

Density functional theory (DFT) calculations have been carried out at the PCM-M06/def2-SVP//B3LYP/def2-SVP level[9] 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 the aromatic ring) and propargylamine in the presence of the model catalyst $[(PMe_3)AuNTf_2]$ is depicted in Fig. 1, which shows the corresponding computed free energies (ΔG_{298}, at 298.15 K) using DCE as the 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 propargylamine to produce intermediate **INT1**. This exergonic process ($\Delta G_R = -14.0$ kcal mol^{-1}) 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^{-1}. **INT1** then evolves to **INT2** *via* a 1,3-proton shift. This reaction proceeds very likely with the assistance of NTf_2^- following a similar protonolysis of the Au–C bond to that reported by us in related $[(PPh_3)AuNTf_2]$-catalysed processes.[11] Exergonic coordination ($\Delta G_R = -8.7$ kcal mol^{-1}) 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^{-1}) and high exergonicity ($\Delta G_R = -17.1$ kcal mol^{-1}) 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 isomer **INT7** ($\Delta\Delta G_{298} = -6.5$ kcal mol^{-1}).[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^{-1}) in an exergonic transformation ($\Delta G_R = -5.5$ kcal mol^{-1}), 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**.

The above reaction mechanism is fully compatible with the deuterium labeling experiments depicted in Scheme 4. Despite that, one should expect the formation of doubly deuterated pyrazines $[D_2]$-**2** (Scheme S2, see ESI†) instead of the observed triple incorporation of deuterium in pyrazine $[D_3]$-**2f**. This inconsistency may be explained from the fact that intermediate $[D_2]$-**INT11** is in equilibrium with the π-allyl complex $[D_2]$-**12**.[13] Deuterolysis of the carbon–gold bond in species $[D_2]$-**12** generates triply deuterated intermediate $[D_3]$-**INT11**, which finally isomerizes[14] to form pyrazines $[D_3]$-**2** (Scheme 5).



Scheme 5 Explanation for the formation of deuterated pyrazines [D_3]-**2**.

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

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