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Stereo- and regioselective gold(I)-catalyzed hydroamination of 2-(arylethynyl)pyridines with anilines†

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The gold-catalyzed hydroamination of 2-(arylethynyl)pyridines with anilines affords stereoselectively *Z*-enamine products with excellent regioselectivity. The reaction proceeds with moderate to excellent yields and accommodates a diverse range of functional groups on alkynes (ether, bromo, trifluoromethyl, acetyl, and carbomethoxy) and anilines (ether, bromo, chloro, and carbethoxy). The stereochemistry of the obtained enamines is complementary to that reported in previous studies. A plausible explanation for the observed selectivity was attained by means of NMR experiments.

Introduction

Enamines are versatile nucleophiles and because of their relevance as synthetic intermediates they have attracted considerable interest of chemists who developed many distinct methodologies for their preparation.[1] One of the most appealing, atom-efficient approaches to this class of compounds is represented by the intermolecular hydroamination of non-activated alkynes with secondary amines in the presence of suitable catalysts. In such a reaction, involving the addition of a N–H bond to a C–C triple bond, no side products are formed and this, as well as the utilization of readily available and usually inexpensive starting materials, makes it a very attractive transformation, particularly from an industrial point of view. Consequently, extensive studies have been made on this subject. Initially, they focused on the use of mercury[2] and thallium[3] catalysts but their toxicity and poor handling made them unsuitable for broad utilization in organic synthesis. In the last fifteen years or so, remarkable progress has been made and a number of convenient and general procedures based on zirconium,[4] rhodium,[5] ruthenium,[6] silver,[7] copper,[8] and gold[9] catalysts have been developed. Clearly, it would be highly desirable to extend the reaction to primary amines, which instead tend to produce preferentially imines.[10] The formation of enamines as the main products has been observed only in a few, particular cases.[11] The development of a regio- and stereoselective addition of primary amines to internal alkynes is still a challenge in the transition metal-catalyzed hydroamination route to enamines.

In this context, as part of our interest in gold-catalyzed C–N bond-forming reactions[12] and given the ubiquity of the pyridine core in biologically active compounds[13] as well as the importance of pyridine-containing enamines as ligands in coordination chemistry,[14] it appeared of interest to us to study a new synthesis of enamines through a hydroamination process of 2-(arylethynyl)pyridine **1** and aniline **2** partners: in fact, this kind of chemistry may be in part related to the regio- and stereoselective hydroamination of α-β-inones to *Z* enamines, a research topic that has been studied by our group.[15a–f] Therefore, hypothesizing a similar behaviour of 2-(arylethynyl) pyridines compared to α-β-inones, our reaction could therefore offer a useful way to obtain enamines (Scheme 1). It is interesting that according to our hypothesis, *Z* enamines should be obtained while, as reported by Stradiotto,[9c] the hydroamination of 2-(pent-1-yn-1-yl)pyridine with a secondary amine, morpholine, is reported to give the *E* stereoisomer.

Herein we report the results of our study.

Results and discussion

The reaction of 2-(phenylethynyl)pyridine **1a** with aniline **2a** was used as the model system. A brief screening study revealed that the corresponding *Z*-hydroamination product **3a** could be isolated in excellent yield when employing JohnPhos(MeCN) $AuSbF_6$ in dichloromethane at 80 °C (Table 1, entry 1). The regiochemistry of **3a** was assigned on the basis of the ^{1}H- and

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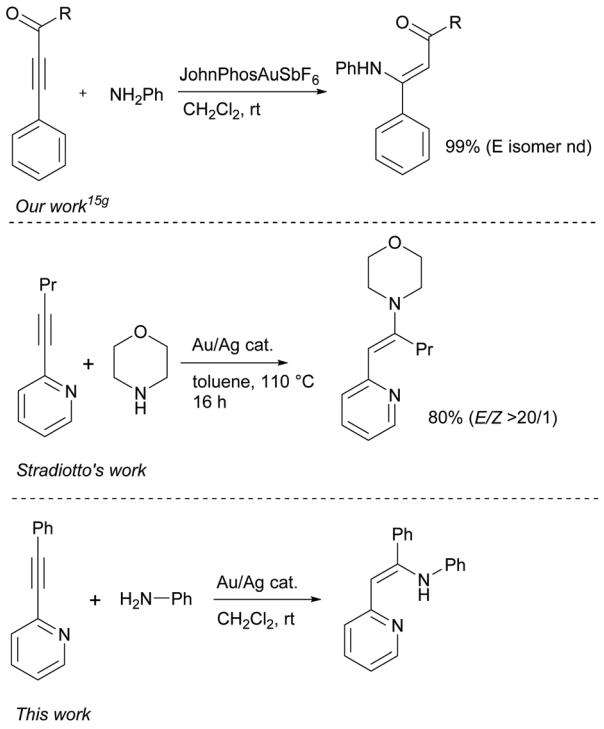
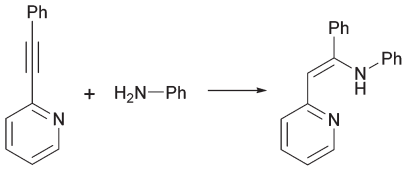
†Electronic supplementary information (ESI) available: Experimental details, characterization data of all compounds, and copies of ^{1}H and ^{13}C NMR spectra (PDF). See DOI: 10.1039/c8ob02356e



Scheme 1

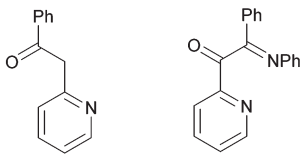
Table 1 Synthesis of **3a** from 2-(phenylethynyl)pyridine **1a** and aniline **2a**: optimization studies[a]



1a **2a** **3a**

Entry	Catalyst (mol%)	Solvent	T (°C)	Time (h)	Yield % of **3a**[b]
1	L(MeCN)AuSbF$_6$[c] (4)	CH_2Cl_2	80	20	93
2	L(MeCN)AuSbF$_6$[c] (4)	DMSO	80	24	19[d]
3	L(MeCN)AuSbF$_6$[c] (4)	Toluene	80	24	92
4	—	CH_2Cl_2	80	24	—[e]
5	$NaAuCl_4$ (10)	EtOH	100	8	—[e]
6	$AlCl_3$ (10)	MeOH	60	24	—[e]
7[f]	CuI (5)/PPh_3 (5)	DMF	100	24	—[e]
8	$(CF_3CO_2)2Pd$ (5)	CH_2Cl_2	100	48	31
9	$(CF_3SO_3)Ag$ (5)	CH_2Cl_2	80	48	19

[a] Unless otherwise stated, reactions were carried out on a 0.5 mmol scale using 1 equiv. of **1a**, 1.1 equiv. of **2a**, and 1.5 mL of solvent. [b] Yields refer to isolated products. [c] L = JohnPhos. [d] Compounds **4a** and **5a** were isolated in 27 and 9% yield, respectively, along with an 18% yield of the recovered **1a**. [e] The starting alkyne was recovered in almost quantitative yield. [f] The reaction was carried out in the presence of 2.0 equiv. of K_3PO_4.



4a **5a**

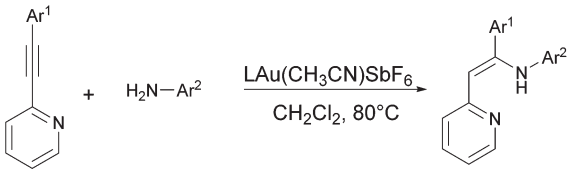
^{13}C-NMR spectra of the ketonic derivative **4a** (prepared *via* acid-catalyzed hydrolysis of **3a**), which resulted to be identical to those of an authentic specimen. Its (*Z*)-stereochemistry has been assigned by NOESY experiments, which showed also the presence of an intra-molecular hydrogen bond (N–H$\cdots$N$_{py}$). Switching to DMSO as the solvent led to the isolation of **3a** in low yield (Table 1, entry 2) along with significant amounts of **4a** (27%) and **5a** (9%), and the recovery of **1a** in 18% yield (Table 1, entry 2). No hydroamination product was formed, omitting the gold catalyst (Table 1, entry 3), in the presence of $NaAuCl_4$ (Table 1, entry 4), or $AlCl_3$ (Table 1, entry 5), or CuI/PPh_3 (Table 1, entry 6). Unsatisfactory results were also obtained with $(CF_3CO_2)_2Pd$ (Table 1, entry 7) or $(CF_3SO_3)Ag$ (Table 1, entry 8).

The conditions shown in Table 1, entry 1 have been then used when the reaction was extended to other substrates to probe its synthetic scope. Our preparative results are summarized in Tables 2 and 3. Usually, the reaction of 2-(arylethynyl) pyridines **1** and 2-(alkylethynyl)pyridines **6** with anilines afforded the corresponding enamines in moderate-to-excellent yields with excellent regio- and stereoselectivities. The nitrogen nucleophile was always found to be bound to the carbon far from the pyridine ring and the stereochemistry of the enamine was invariably found to be *Z*. A variety of important functional groups are tolerated both in anilines (ether, bromo, chloro, and carbethoxy) and alkynes (ether, bromo, trifluorome-thyl, acetyl, and carbomethoxy). Only with 2-[(3-methoxyphenyl) ethynyl]pyridine and 4-cyanoaniline compound **3o** was isolated in poor yield (Table 2, entry 15), possibly because of the low nucleophilicity of the latter. Our attempts to extend the reaction to primary and secondary aliphatic amines met with failure. No evidence of enamine products was attained when **1a** was subjected to benzylamine or morpholine under standard conditions. In both cases, the starting alkyne was recovered in almost quantitative yields.

The presence of two strong coordinating centers in the starting alkyne, the C–C triple bond and the pyridine nitrogen atom, required careful analysis to identify the correct role of each of them towards the outcome of this highly regio- and stereoselective reaction. In fact, two complexes could be formed through the reaction between an alkyne and catalyst (Fig. 1, **I** and **II**).

To this purpose, NMR complexation experiments between JohnPhos(MeCN)AuSbF$_6$ catalyst, **1c** and **1h** in $CDCl_3$ have been performed. In both cases, we observed a remarkable polarization of the carbon–carbon triple bond. The chemical shifts of C2 and C1 moved from 89.5 and 87.6 ppm ($\delta_{C2} - \delta_{C1}$ = 1.9 ppm) in the uncoordinated **1c** to 94.9 and 82.8 ppm ($\delta_{C2} - \delta_{C1}$ = 12.1 ppm) in the coordinated **1c** and from 88.1 and 91.5 ppm ($\delta_{C2} - \delta_{C1}$ = −2.4 ppm) in the uncoordinated **1h** to 92.8 and 86.0 ppm ($\delta_{C2} - \delta_{C1}$ = 6.8 ppm) in the coordinated

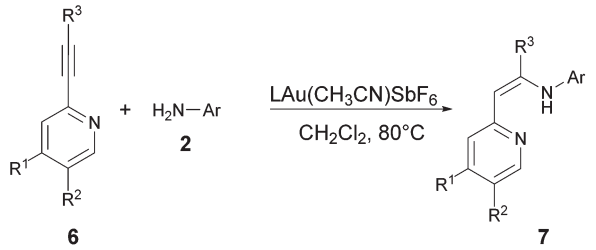
Table 2 Gold-catalyzed hydroamination of 2-(arylethynyl)pyridines **1** with anilines **2** [a]



Entry	1 Ar^1		2 Ar^2	Time (h)	Yield % of 3 [b,c]	
1	Ph	**a**	Ph	20	93	**a**
2	Ph	**a**	4-$MeOC_6H_4$	48	83	**b**
3	Ph	**a**	2-BrC_6H_4	48	35 (63)	**c**
4	Ph	**a**	4-BrC_6H_4	72	75	**d**
5	Ph	**a**	4-ClC_6H_4	96	49 (27)	**e**
6	Ph	**a**	3-$EtOCOC_6H_4$	120	73 (8)	**f**
7	4-MeC_6H_4	**b**	Ph	48	85	**g**
8	4-MeC_6H_4	**b**	4-$MeOC_6H_4$	24	78	**h**
9	4-Me C_6H_4	**b**	3-$MeOC_6H_4$	32	94	**i**
10	4-$MeOC_6H_4$	**c**	Ph	20	83	**j**
11	4-$MeOC_6H_4$	**c**	4-MeC_6H_4	48	67 (16)	**k**
12	4-$MeOC_6H_4$	**c**	3-$MeOC_6H_4$	24	98	**l**
13	3-$MeOC_6H_4$	**d**	Ph	24	90	**m**
14	3-$MeOC_6H_4$	**d**	4-$MeOC_6H_4$	24	75	**n**
15	3-$MeOC_6H_4$	**d**	4-CNC_6H_4	72	19 (67)	**o**
16	2-BrC_6H_4	**e**	Ph	48	75	**p**
17	3-$CF_3C_6H_4$	**f**	4-$MeOC_6H_4$	52	79	**q**
18	2-$MeOCOC_6H_4$	**g**	Ph	72	79	**r**
19	4-$COMeC_6H_4$	**h**	Ph	48	46 (49)	**s**

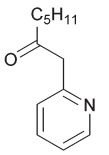
[a] Unless otherwise stated, reactions were carried out on a 0.5 mmol scale using 1.1 equiv. of aniline **2**, 0.04 equiv. of catalyst and 1.5 mL of CH_2Cl_2. [b] Yields are given for isolated products. [c] Numbers in parentheses refer to the recovered **1**.

Table 3 Gold-catalyzed hydroamination of 2-(phenylethynyl)pyridines and 2-(pentylethynyl)pyridine **6** with anilines **2** [a]



Entry	R^1	6 R^2	R^3		2 Ar	Time (h)	Yield % of 7 [b]	
1	CF_3	H	Ph	**a**	Ph	20	97	**a**
2	CF_3	H	Ph	**a**	4-ClC_6H_4	24	99	**b**
3	H	F	Ph	**b**	Ph	24	86	**c**
4	H	F	Ph	**b**	3-$MeOC_6H_4$	24	96	**d**
5	H	F	Ph	**b**	4-MeC_6H_4	24	89	**e**
6[c]	H	H	C_5H_{11}	**c**	4-$MeOC_6H_4$	48	89[d]	**f**
7[c]	H	H	C_5H_{11}	**c**	Ph	48	48[d,e]	**g**

[a] Unless otherwise stated, reactions were carried out on a 0.5 mmol scale using 1.1 equiv. of aniline **2**, 0.04 equiv. of catalyst and 1.5 mL of CH_2Cl_2. [b] Yields are given for isolated products. [c] Reaction carried out at 120 °C. [d] Yields determined by NMR. [e] Along with **7f**, compound **4b** and its tautomer were detected in 41% yield (89/11).



4b

1h. As it is known that unfunctionalized alkynes coordinate symmetrically at gold,[16] these data are more consistent with the trend observed when we treated 2-(arylethynyl)pyridines **1** with DCl in DMSO/D_2O in an NMR probe. Indeed, under these conditions, a large downfield shift of C2 was observed in all cases with a strong polarization of the carbon–carbon triple bond as compared to the polarization of the uncoordinated alkynes. For example, the chemical shifts of C2 and C1 in **1c** moved to 101.8 and 80.3 ppm ($\delta_{C2} - \delta_{C1}$ = 21.5 ppm) and those in **1h** moved to 98.7 and 83.4 ppm ($\delta_{C2} - \delta_{C1}$ = 15.3 ppm). This effect was ascribed to the protonation of the pyridine nitrogen. Consequently, the related downfield shift of C2 and the polarization of the carbon–carbon triple bond following the addition of JohnPhos(MeCN)AuSbF$_6$ to 2-(arylethynyl)pyridines were ascribed to the coordination of the pyridine nitrogen at gold.

The complex **I** could undergo a regioselective intermolecular nucleophilic attack of the aniline nitrogen on the C2 of the acetylenic fragment, the point of lower electron density. This was found to be the general trend of all of the 2-(arylethynyl)pyridines listed in Tables 2 and 3, independent of the nature of the aromatic rings. However, no reaction was observed when **1a** was reacted in the presence of a Brønsted catalyst. Therefore, the polarization of the C–C triple bond

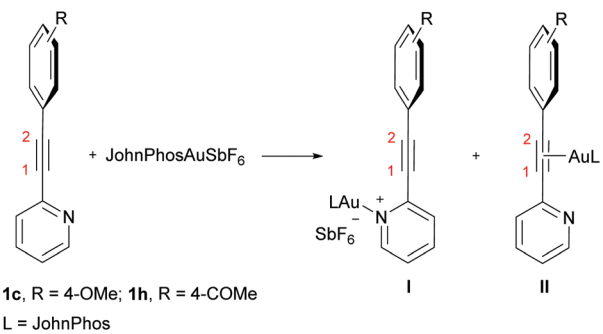
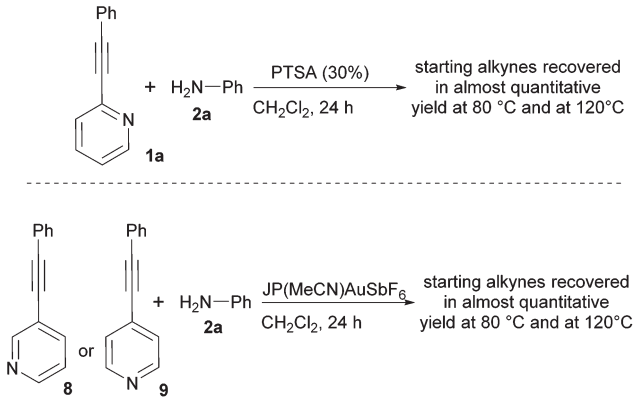


Fig. 1 Nitrogen- and C≡C- gold(I) complexes.

derived from the coordination catalyst pyridine nitrogen is not enough for nucleophilic addition of **2a**. Furthermore, no reaction was observed when 3-(phenylethynyl)pyridine **8** and, more importantly, 4-(phenylethynyl)pyridine **9** were treated with aniline **2a** under standard conditions, even when increasing the reaction temperature up to 110 °C.[17] The starting alkyne was recovered in almost quantitative yield in all of the reported cases (Scheme 2).

These experiments suggest that the catalyst is involved in multiple equilibria,[18] with complex **I** predominant on complex **II**

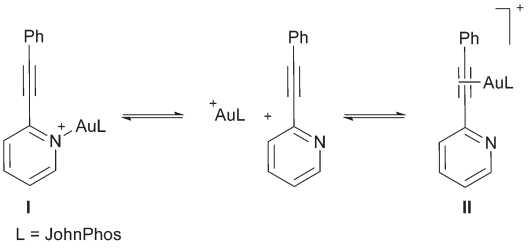


Scheme 2

(Scheme 3); most probably, the nitrogen–gold coordination in **I** is not adequate to promote the amine nucleophilic attack on the acetylenic moiety that requires the activation of gold present in complex **II**.

As an explanation for the observed regiochemistry which is always the same regardless of the electronic effects of the substituents on the aryl group, the main factor could be the formation of an intramolecular hydrogen bond between the amine and pyridine nitrogen atom during the *anti* nucleophilic attack, according to the classical *outer sphere* mechanism. A similar behaviour was found by Nolan and colleagues in their cooperative gold-catalyzed hydrophenoxylation of unsymmetrical alkynes,[19] where the observed regioselectivity was ascribed to the chelating property of nitrogen towards the gold–phenoxide complex.[20] In fact, since the hydrogen bond between pyridine nitrogen and amine should involve the C–C triple bond polarization (*vide supra*), this factor could account for the observed regioselectivity as a result of the nucleophilic attack on the C2 of the acetylenic fragment, the point of lower electron density. Furthermore, in this scenario the hydroamination could proceed through an *endo-dig*-like TS **10** instead of the *exo-dig*-like **11** (Fig. 2), with the former often preferred in gold-catalyzed cycloisomerization.[10]

Due to the stereoselectivity of the reaction, even if the *Z* isomer should be the one formed according to this pathway, HF calculations on both the **3a** isomers (at 6-31** basis set level) showed that the *Z* isomer is more stable over the *E* isomer of about 7.66 kcal mol^{-1} by the presence of a strong



Scheme 3

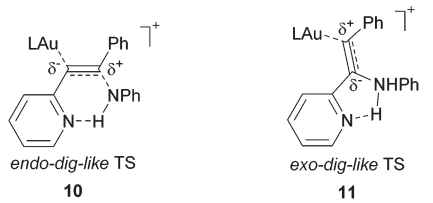
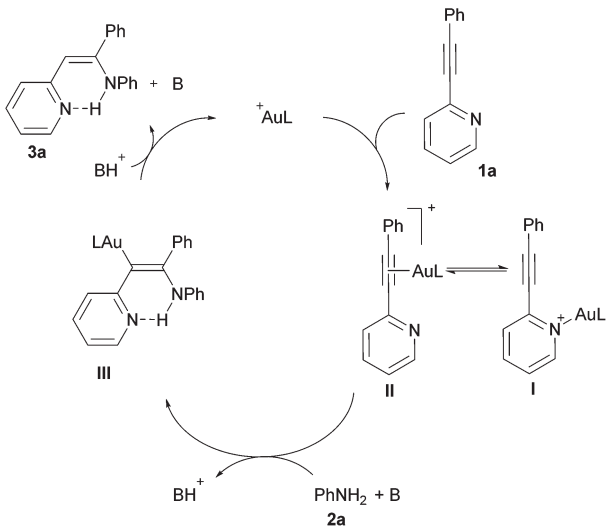


Fig. 2 Possible TS of the aminoauration step.



Scheme 4

intramolecular hydrogen bond, confirmed by ^{1}H NMR in all of the reported cases. Therefore, whatever the stereoisomer ratio was after the aminoauration step, an equilibration during protodeauration or on final enamine[21] catalyzed by gold[22] cannot be excluded.

Based on the above, a possible catalytic cycle for the gold-catalyzed hydroamination of 2-(arylethynyl)pyridines may be the following (Scheme 4). The gold catalyst in the presence of **1a** forms two complexes **I** and **II** in rapid equilibrium at the reaction temperature. The complex **II** then undergoes a regioselective nucleophilic *anti* attack from **2a** due to the formation of a hydrogen bond between pyridine nitrogen and amine. The resulting vinyl-gold intermediate **III** after protodeauration gives the final *Z* enamine **3a** together with the active catalyst.

Conclusions

In conclusion, we have developed a new and versatile method for the stereo- and regioselective conversion of 2-(arylethynyl) pyridines into the corresponding enamines in the presence of a gold catalyst and anilines. The reaction, which proceeds with moderate-to-excellent yields, significantly extends the scope of the hydroamination of unsymmetrical internal alkynes and tolerates a range of functional groups on alkynes (ether, bromo,

trifluoromethyl, acetyl, and carbomethoxy) and anilines (ether, bromo, chloro, and carbethoxy).

Experimental

A list of chemicals and instruments are provided in the ESI.†

Typical procedure for the preparation of 2-(arylethynyl) pyridines (1): synthesis of 2-(phenylethynyl)pyridine (1a)

A flask equipped with a magnetic stirring bar was charged with $PdCl_2(PPh3)_2$ (49 mg, 0.07 mmol, 0.02 equiv.) and CuI (26.5 mg, 0.14 mmol, 0.04 equiv.) dissolved in diisopropylamine (7 mL) and *N*,*N*-dimethylformamide (5 mL). The resultant solution was stirred under nitrogen at room temperature for 10 minutes before adding 2-bromopyridine (553 mg, 3.5 mmol, 1.0 equiv.) in diisopropylamine (3 mL) and phenylacetylene (428.5 mg, 461 μl, 4.2 mmol, 1.2 equiv.). Then, stirring was continued at room temperature for an additional hour. After this time, the reaction mixture was diluted with Et_2O and washed with a saturated NH_4Cl solution and with brine. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (25–40 μm) eluting with an 85/15 (v/v) *n*-hexane/AcOEt mixture (R_f = 0.25) to obtain 608.5 mg (97% yield) of 2-(phenylethynyl)pyridine **1a**. Brown oil; IR (neat): 3054, 2919, 2222, 1580, 1490 cm^{-1}; ^1H NMR (400.13 MHz) (DMSO d_6): δ = 8.62 (ddd, J_1 = 4.8 Hz, J_2 = 1.8 Hz, J_3 = 1.0, 1 H), 7.86 (td, J_1 = 7.7 Hz, J_2 = 1.8 Hz, 1 H), 7.66–7.60 (m, 3 H), 7.48–7.45 (m, 3 H), 7.42 (ddd, J_1 = 7.7 Hz, J_2 = 4.8 Hz, J_3 = 1.0 Hz, 1 H);^{13}C NMR (100.6 MHz) (DMSO d_6): δ = 150.6, 142.7, 137.2, 132.1, 129.0, 129.3, 127.8, 124.0, 121.9, 89.4, 88.8; MS (EI ion source): *m*/*z* (%) = 179 (100, [M^+]), 151 (14), 126 (12); HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{10}N$: 180.0808; found: 180.0808.

Typical procedure for the preparation of (*Z*)-*N*-(1-aryl-2-(pyridin-2-yl)vinyl)anilines (3): (*Z*)-*N*-(1-phenyl-2-(pyridin-2-yl) vinyl)aniline (3a)

A Carousel Tube Reactor (Radley Discovery Technology) containing a stirring bar was charged with 2-(phenylethynyl)pyridine **1a** (89.6 mg, 0.5 mmol, 1.0 equiv.) dissolved in CH_2Cl_2 (1.5 mL) and (acetonitrile)[(2-biphenyl)di-*tert*-butylphosphine] gold(I) hexafluoroantimonate (15.4 mg, 0.02 mmol, 0.04 equiv.). Then, aniline **2a** was added (51 mg, 50 μl, 0.55 mmol, 1.1 equiv.). The resultant solution was warmed at 80 °C and stirred for 20 hours. After cooling, the volatile materials were evaporated at reduced pressure and the residue was purified by flash chromatography on neutral Al_2O_3 (Brockmann activity 1) eluting with *n*-hexane (R_f = 0.21) to obtain 126.5 mg of (*Z*)-*N*-(1-phenyl-2-(pyridin-2-yl)vinyl)aniline **3a** (93% yield). Yellow solid; mp: 83–85 °C; IR (KBr): 3357, 3050, 2923, 1626, 1587, 1374 cm^{-1}; ^1H NMR (400.13 MHz) ($CDCl_3$): δ = 11.61 (br s 1 H), 8.40 (br d, J = 4.5 Hz, 1 H), 7.47 (td, J_1 = 7.7 Hz, J_2 = 1.6 Hz, 1 H), 7.43–7.40 (m, 2 H), 7.24–7.22 (m, 3 H), 7.01–6.97 (m, 3 H), 6.87–6.84 (m, 1 H), 6.73 (t, J = 7.2 Hz, 1 H), 6.61 (d, J = 7.7 Hz, 2 H), 5.52 (s, 1 H); ^{13}C NMR (100.6 MHz) ($CDCl_3$): δ = 158.8, 148.5, 147.5, 142.6, 138.3, 136.1, 128.6, 128.5, 128.4, 128.1, 123.1, 121.1, 121.0, 118.4, 103.7; MS (EI ion source): *m*/*z* (%) = 272 (76 [M^+]), 256 (16), 207 (13), 194 (26), 180 (55), 92 (18), 77 (100), 51 (23); HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{17}N_2$: 273.1386; found: 273.1393.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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18 DOSY experiment on **1c** and JohnPhos(MeCN)AuSbF$_6$ shows two traces corresponding to the alkyne and the catalyst and are clearly present at $D = 0.096$ m^2 s^{-1} and 0.1049 m^2 s^{-1}, respectively.

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