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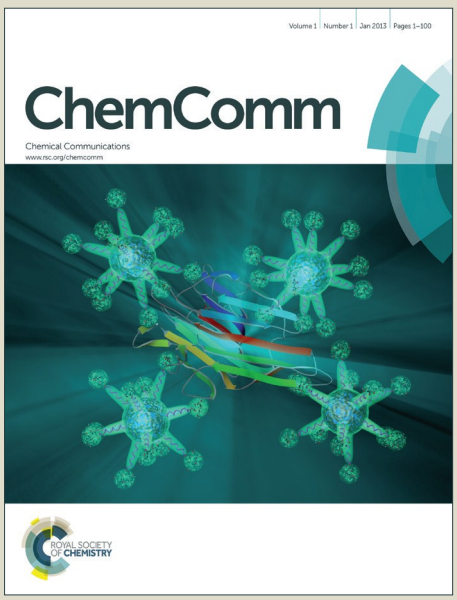

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Synchronous Double C-N Bond Formation via C-H Activation as a Novel Synthetic Route to Phenazine

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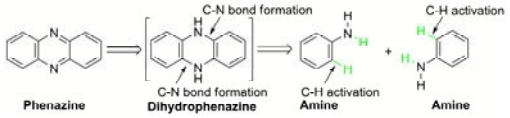
A novel synthetic strategy for phenazine formation is reported following self coupling of anilines by Pd-Ag binary nanocluster-catalysed synchronous double C-N bond formation via non-radical mode of *ortho*-aryl C-H activation.

The phenazine unit is a privileged heterocyclic scaffold widely present in various natural products and biologically active compounds and plays important role in several biochemical events such as behavioural and ecological fitness of bacteria, inhibits the angiotensin-converting enzyme and lipid peroxidation, and exhibits anticancer and antimalarial activities.[1] These make phenazines demanding synthetic targets.[1c]

While designing new synthetic strategy to construct the phenazine scaffold we realised that the use of transition metal-catalyst might present milder and better method. Efforts made towards this direction are based on the palladium-catalysed aryl-amination[2] that requires multistep synthetic sequence such as nitration, bromination, and reduction to generate the desired intermediate for the final cyclisation-oxidative transformations, high reaction temperature with special reaction set up, and pre-functionalized starting materials.[3]

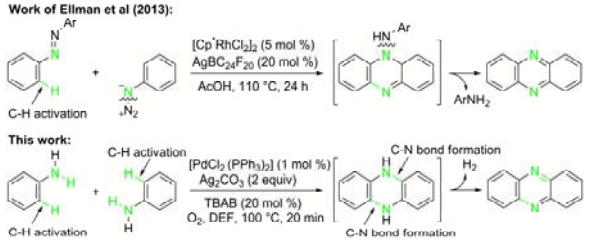
We hypothesised that a C-H activation route involving synchronous double C-N bond formation for the amination-cyclization-oxidation cascade (Scheme 1) would be a novel synthetic strategy for phenazine synthesis.



Scheme 1. New synthetic strategy for phenazines via C-H activation.

In recent years transition metals catalyzed oxidative C-H functionalization have emerged as new synthetic tool[4] and provides a straight forward method for direct heteroatom insertion to the aryl moiety.[5] Aryl C-N bond formation via C-H activation is also feasible with the help of transition metal catalysis[6] and the ruthenium-catalysed *ortho* C-H bond activation of aryl amines leads to heterocycle ring construction.[7]

The recent report on phenazine synthesis via Rh(III)-catalyzed C-H activation[8] requires azoarenes and aryl azides as starting materials and is not atom economical as it involves the elimination/loss of one equivalent of aryl amine (Scheme 2).



Scheme 2. Phenazine synthesis via C-H activation.

Initial attempts on the self coupling of aniline (**1a**) using various Pd compounds in the presence of stoichiometric amounts of Ag, Cu(II), or Fe(III) compounds as terminal oxidants in DMF at 100 °C did not produce any significant amount of phenazine (**2a**) (ESI: Table IA).† As metal nanoparticles (MNP) exhibit enhanced catalytic activity in comparison to the corresponding metal salts/complexes[9] MNPs are used as catalyst in various organic transformations.[10] Recently, the use of MNP has been gaining popularity as catalyst system for C-H functionalization.[11] Towards the endeavor of using MNP as catalyst for the desired C-H activation, we were delighted to observe that the use of tetrabutylammonium bromide (TBAB) (1 equiv) as stabilizer,[11d,e] to prevent aggregation of the MNP, that exerts action by electrostatic, steric, and electrosteric (combination of steric and electrostatic) means,[10] led to the formation of **2a** (> 60% yield) along with the azobenzene **3a** (ESI: Table IB).†

Further studies on the variation of the catalytic conditions included the use of varying amounts of different Pd compounds (as catalyst), various Ag compounds and other non-metallic agents as co-oxidant, different stabiliser and solvent, variation of reaction temperature and time etc. These led to the two best operating reaction conditions: (i) Method A

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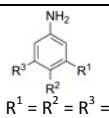
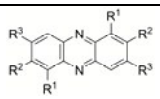
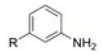
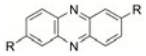
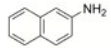
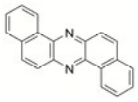
using $[Pd(PPh_3)_2Cl_2]$ (1 mol %), Ag_2CO_3 (2 equiv), TBAB (20 mol %) in diethylformamide (DEF) at 100 °C under O_2 bubbling for 20 min to afford **2a** (87%) along with **3a** (10%), and (ii) Method B using $[Pd(PPh_3)_2Cl_2]$ (1 mol %), TBAB (20 mol %), Ag_2CO_3 (1 equiv) and Cs_2CO_3 (1 equiv) in DEF at 100 °C under O_2 bubbling for 60 min to afford **2a** (79%) along with **3a** (13%) (ESI: Tables I-C - I-I).[†] The lack of formation of significant amount of **2a** in using only $[Pd(PPh_3)_2Cl_2]$ (1 mol %) or Ag_2CO_3 (2 equiv) as well as using other organic co-oxidant in place of Ag_2CO_3 revealed synergistic/co-operative role of the Pd-Ag binary nanocluster (NC).[12] The formation of the Pd-Ag binary NC was indicated by blackening of the reaction mixture in the initial phase (after 10 min) of mixing all components in DEF. The high resolution transmission electron microscopy (HRTEM) image and energy dispersive acquired X-ray (EDAX) spectra confirmed the presence of Pd (3-8 nm) and Ag (20-40 nm) particles (SI: Figure A and B).[†] The inferior results obtained with other Pd compounds such as $PdCl_2$ and Na_2PdCl_4 could be correlated with the larger size of the Pd NP (10-15 and 12-20 nm, respectively) formed from these Pd compounds (ESI: Figure C and D).[†] The binary Pd-Ag NC was recovered and reused for five consecutive times affording **2a** in 83, 80, 76, 71, and 63% yields. The decrease in catalytic activity of the recovered Pd-Ag binary NC after fifth cycle could be due to the increase in size to 20-25 and 50-60 nm for the Pd and Ag NP, respectively (ESI: Figure G).[†] The influence of the solvent can be rationalised due to their ability to offer conducive environment for the formation of the NP and aprotic polar solvents proved to be effective (ESI: Table I-I).[†] The best results obtained with DMF and DEF could be due to their reducing ability to assist the formation of the NP.[13] The comparable results obtained with *N,N*-dimethylacetamide (DMA) is due to its favourable physico-chemical properties[14] to enhance the reducing power of the base (CO_3^{2-}) to form the NP.[10d,15] From the different stabilisers used to prevent aggregation of the NP, TBAB was found to be the most effective (ESI: Table IH).[†]

The treatment of various anilines with the in situ formed Pd-Ag NC afforded the corresponding phenazines in moderate to good yields (Table 1).

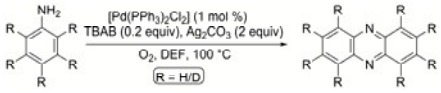
Anticipating that the phenazine formation during the self coupling of aniline proceeds through C-H activation, kinetic isotope effect studies were planned. Aniline and aniline-d_5 were separately subjected to self coupling (Table 2). Mass spectrometry-based ion-fishing has emerged as important tool in understanding mechanistic course of organic reactions.[16] A quantitative estimation of the formation of the corresponding phenazine from aniline and aniline-d_5 was made by determination of the ion current of the mass peak corresponding to the potassium adduct ($M+K^+$) of the respective phenazine by subjecting a measured volume of the individual reaction mixture, withdrawn after specified time interval to, ESI-MS analysis.[17] The ratio of the ion current provided the k_H/k_D values that reflected the kinetic isotope effect during the phenazine formation and provided evidence for C-H activation.

Table 1. Pd-Ag NC-catalyzed self coupling of anilines to form phenazines.[a]

Entry	Aniline	Phenazine	Method	Time (min)	Yield (%)[b,c]
					
1	$R^1 = R^2 = R^3 = H$		A	20	87(10)
			B	60	79(13)
2	$R^1 = R^3 = H$, $R^2 = Me$		A	20	87(10)
3	$R^1 = R^3 = H$, $R^2 = OBn$		A	20	86(10)
			B	60	78(12)
4	$R^1 = R^2 = R^3 = OMe$		A	40	66(29)
			B	60	60(23)
5	$R^1 = R^3 = H$, $R^2 = OMe$		A	20	61(31)
6	$R^1 = R^3 = H$, $R^2 = F$		A	20	56(40)
			B	60	49(31)
7	$R^1 = R^3 = H$, $R^2 = SMe$		A	30	31(66)
			B	60	25(53)
					
8	R = Me		A	20	59(30)
9	R = OMe		A	20	40(57)
10	R = F		A	20	43(54)
			B	60	37(41)
					
11			A	20	30(65)

[a]Method A: Anilines (2 mmol) were reacted in the presence of $[PdCl_2(PPh_3)_2]$ (1 mol %), TBAB (20 mol %) and Ag_2CO_3 (2 equiv) under O_2 bubbling (10 psi) in DEF/DMA (2 mL) at 100 °C; Method B: Anilines (2 mmol) were reacted in the presence of $[PdCl_2(PPh_3)_2]$ (1 mol %), TBAB (20 mol %), Ag_2CO_3 (1 equiv) and Cs_2CO_3 (1 equiv) under O_2 bubbling (10 psi) in DEF/DMA (2 mL) at 100 °C. [b]Isolated yield of the phenazine. [c]The data in the parenthesis is the isolated yield of the corresponding azoarene

Table 2. Determination of k_H/k_D during phenazine formation from aniline and aniline-d_5.[a]

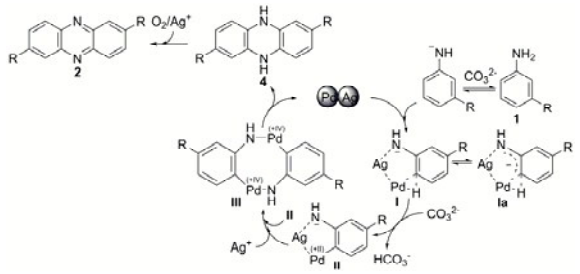


Entry	Time (min)	Ion current of the $(M+K^+)$ peak		k_H/k_D[c]
		X (R = H)[b]	Y (R = D)[b]	
1	5	1.45×10^5	3.30×10^4	4.39
2	10	2.03×10^5	4.69×10^4	4.33
3	15	2.36×10^5	4.75×10^4	4.98
4	20	2.50×10^5	4.84×10^4	5.18

[a]Aniline (1 mmol) and aniline-d_5 (1 mmol) were separately subjected to the reaction and after the specific time interval 10 µL of the respective reaction mixture was withdrawn and subjected to ESI-MS analysis. [b]The area of the ion peak of the potassium adduct of the corresponding phenazine. [c]The relative rate (k_H/k_D) is represented by the ratio X/Y.

In view of this, a plausible mechanism for the phenazine formation is depicted in Scheme 3. Some of the surface Ag atoms in Pd-Ag NC would be oxidized to Ag(I) under O_2[18] that would coordinate to N atom of the anilide anion, generated through the proton abstraction[14a] by the CO_3^{2-}, and would transfer electron density to the adjoining Pd center through metal-metal bond.[19] This would make the Pd centre electron rich and direct *ortho*-palladation to form **I/Ia** wherein the Pd centre is engaged in two electron three centred bond with the *ortho*-aryl C-H. Oxidative insertion of palladium,[20] under the influence of Ag_2CO_3, to the C-H bond followed by abstraction of the *ortho*-aryl proton in **I/Ia**, by the CO_3^{2-}, generates the

Pd(II) containing metallacycle **II**. Two molecules of **II** are converted to the Pd(IV) species[21] **III** through oxidation by O_2/Ag_2CO_3.[21e-g,22] Intramolecular mutual nucleophilic displacement of the Pd centres of **III** by the anilide nitrogen triggers the C-N bond formation to form the dihydrophenazine **4** which on dehydrogenation by the molecular oxygen (or the Ag_2CO_3 when used in 4 equiv in the absence of oxygen) is converted to **2**.

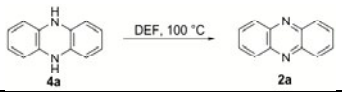


Scheme 3. Plausible mechanism for Pd-Ag NC-catalysed synchronous double C-N bond formation via C-H activation for phenazine formation from anilines.

Although silver salts used in stiochiometric amounts[23] or in catalytic quantities in the presence of stoichiometric amounts of other oxidants[24] are reported/known to promote oxidative C-H activation, the inability of Ag_2CO_3 used in stoichiometric or catalytic amount alone or along with O_2 bubbling in the absence of Pd salt to form the phenazine† indicate specific role of the Pd salt as the catalyst for C-H activation.

Control experiments with the preformed dihydrophenazine **4a** by separately treating (i) under O_2 bubbling, (ii) with Ag_2CO_3 (1 equiv), (iii) with Ag_2CO_3 (1 equiv) under O_2 bubbling, and (iv) with Ag_2CO_3 (10 mol%) under O_2 bubbling in DEF (2 mL) at 100 ^oC were carried out to further investigate the mechanistic course of the phenazine formation (Table 3). The experiment for case (i) gave **2a** in 96% yield after 20 min and treatment for case (ii) afforded **2a** in 94% yield after 30 min. However, the experiment for case (iii) afforded the **2a** in 96% yield after 5 min. However, the similar results obtained for case (i) and case (iv) revealed that the additional (1 equivalent) amount of Ag_2CO_3 present in Method A promotes the **4a** to **2a** conversion at a faster rate due to which the reactions under Method A require shorter time period. These clearly demonstrate the synergistic role of O_2 and Ag_2CO_3 for the oxidation of **4a** to **2a**. Although the conversion of **4a** to **2a** may occur in the presence of O_2 and is not dependent on the presence of Ag_2CO_3, the indispensable role of Ag_2CO_3 is to maintain the Pd(II)/Pd(IV) cycle.

Table 3. Treatment of **4a** under various conditions to form **2a**.[a]

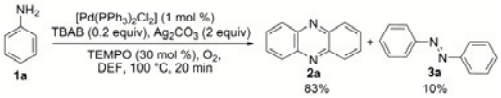


Entry	Condition	Time (min)	Yield (%)[b]
1	O_2 bubbling	20	96
2	Ag_2CO_3 (1 equiv)	30	94
3	O_2 bubbling + Ag_2CO_3 (1 equiv)	5	96
4	O_2 bubbling + Ag_2CO_3 (10 mol%)	20	96

[a]**4a** (1 mmol) was treated under the various conditions in DEF (2 mL) at 100 ^oC. [b]Isolated yield of **2a**.

It is essential to perform the reaction under oxygen as the yields decreased drastically when the reaction was performed under nitrogen even after prolonging the reaction time from 20 min to 5 h. It is necessary to pass (bubble) O_2 into the reaction mixture. As comparable yields were obtained with the cylinder outlet pressure of 10, 15 and 25 psi the reactions were performed by bubbling O_2 with 15 psi outlet pressure. However, the product yield drastically decreased when the reaction was performed under oxygen atmosphere using O_2 filled balloon.† In the absence of oxygen, large excess (4 equiv) of Ag_2CO_3, as the oxidant, was required to afford comparable yields indicating the essentiality of O_2 during the oxidative transformation of the transient species and the intermediate during the progress of the reaction (ESI, Table I-G).†

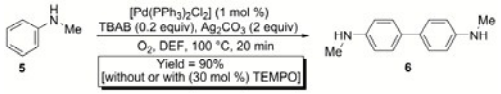
The involvement of free radical pathway is ruled out by the fact that no significant decrease in yield of **2a** was observed when the reaction of **1a** was performed in the presence of TEMPO as a radical scavenger (Scheme 4).



Scheme 4. Pd-Ag NC-Catalysed self coupling of **1a** in the presence of TEMPO.

The 4- and 3-substituted anilines lead to the same phenazine (entries 2 vs 8, 5 vs 9, and 6 vs 10; table 1). The 3-substituted anilines are expected to form regioisomeric phenazines. However, in each case a single regioisomer was formed. In case of the 3-substituted anilines (entries 8 - 10; table 1), the palladation (C-H activation) occurs at the less hindered *ortho* position of the amine group and accounts for the regioselectivity.

The self coupling of *N*-methylaniline (**5**) afforded exclusively the 4,4'-di-*N*-methylbiphenyl (**6**) (Scheme 5) and demonstrated the involvement of C-H activation. Due to the steric effect of the *N*-Me group, the *ortho* C-H activation is not feasible and the palladation takes place at the *para*-position. No decrease in the yield of **6** was observed in performing the reaction in the presence of TEMPO (30 mol %). This indicated non-radical mode *para* C-H.[25]



Scheme 5. Evidence for C-H activation and the influence of steric effect on its regioselectivity.

The lack of formation of phenazine from 2-aminodiphenyl amine under similar condition (ESI: Scheme IV-D)† indicates that a synergistic double C-N bond formation via C-H activation process involving two aniline molecules is operating rather than sequential C-H activation and C-N bond formation.

In conclusions, a novel strategy on synchronous mode double C-N bond formation via C-H activation has been achieved catalysed by Pd-Ag binary NC for the synthesis of phenazines from substituted anilines. The reaction proceeds through non-radical mode of *ortho* C-H activation as evidenced by mass spectrometry-based kinetic isotope effect studies and radical scavenging experiments.

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