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# Selective synthesis of nitrogen bi-heteroarenes by a hydrogen transfer-mediated direct $\alpha$ , $\beta$ -coupling reaction<sup>+</sup>

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By an external hydrogen transfer-mediated activation mode, we herein demonstrate a new palladium-catalyzed direct  $\alpha,\beta$ -coupling of different types of N-heteroarenes. Such a selective coupling reaction proceeds with the advantages of operational simplicity, high atom-economical efficiency, and use of safe and abundant i-propanol as the activating agent, offering a practical way to access nitrogen bi-heteroarenes. Preliminary exploration has revealed that the obtained bis-1,10-phenanthroline 2qq' as a ligand is capable of improving a copper catalyst for C–C bond formation. The work reported in this paper has built an important basis for the creation of extended  $\pi$ -conjugated systems that are of high significance in biological, medicinal, materials and synthetic organic chemistry as well as catalysis.

#### Introduction

Transfer hydrogenation (TH) constitutes a fundamental tool in organic chemistry, which has been considered as a promising alternative to conventional hydrogenation methods since it does not need special equipment such as autoclave and flammable  $H_2$  gas. As a result, a series of hydrogen donors<sup>1–3</sup> have been explored for various synthesis purposes. For example in recent years, Li and co-workers reported the synthesis of amine derivatives directly from phenol derivatives and amines (ammonia) by using HCO<sub>2</sub>Na as a TH reagent.<sup>4</sup> In the presence of Hantzsch esters, the Zhou group realized the enantioselective TH of various N-heteroarenes.<sup>5</sup> Moreover, the Bruneau group successfully developed the non-directed  $C(sp^3)$ –H bond alkylation by using HCO<sub>2</sub>H as the hydrogen source.<sup>6</sup> More recently, the abundant and sustainable alcohols

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serving as alternative hydrogen suppliers have also been elegantly utilized for the reduction of various unsaturated chemical bonds,<sup>7</sup> hydrogen-borrowing reactions<sup>8</sup> and transfer hydrogenative coupling reactions.<sup>9</sup> Despite these significant achievements, the application of the TH strategy in the activation of N-heteroarenes to generate bi-N-heteroaryl motifs, the core structures of numerous bioactive molecules, functional materials, dyes, agrochemicals, pharmaceuticals and natural products,<sup>10</sup> still remains an unexplored goal.

Upon a thorough literature investigation, the early metallic sodium-mediated  $\alpha$ , $\beta$ -coupling of quinolines was reported in 1980 by Carlier and Einhorn.<sup>11*a*</sup> Then, the Aksenov group observed that NaH also could be employed to achieve the same reaction.<sup>11*b*</sup> Despite the utility of these two precedents, they suffer from limited substrate scope, use of air- and moisture-sensitive reagents (Na and NaH), the need for stringent protections, and harsh reaction temperatures (160–190 °C). Hence, there is a demand for new protocols that enable synthesis diversity from stable raw materials and with easy manipulations.

Prompted by our recent efforts in the creation of functionalized N-heterocycles by a hydrogen transfer strategy,<sup>12</sup> we wished herein to report a new palladium-catalysed synthesis of nitrogen bi-heteroarenes (2) by a hydrogen transfer-mediated direct  $\alpha,\beta$ -coupling of different types of N-heteroarenes (1), in which, the abundant and safe i-propanol was employed as the activating agent (eqn (1)).



#### **Results and discussion**

To test the feasibility of the above idea, the reaction of 2-phenyl-1,8-naphthyridine (1a) in toluene was performed at 125 °C by using NaOH as a base and i-propanol as the external hydrogen donor (HD). Among four catalysts tested (Table 1, entries 1–4), both Pd catalysts were able to afford the

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Table 1 Screening of optimal reaction conditions<sup>a</sup>



<sup>*a*</sup> Reaction conditions: Unless otherwise stated, all reactions were carried out by using **1a** (0.2 mmol), HD (0.6 mmol), catalyst (3 mol%), NaOH (0.2 mmol), and solvent (1.0 mL) at 125 °C for 16 h under a N<sub>2</sub> atmosphere. <sup>*b*</sup> Yield of isolation. <sup>*c*</sup> Yields are listed with respect to using Na<sub>2</sub>CO<sub>3</sub>, MeONa and *t*-BuOK as the bases, respectively. <sup>*d*</sup> Yields are listed with respect to the temperatures 120 °C and 140 °C, respectively. <sup>*e*</sup> i-propanol: 0.4 mmol. <sup>*f*</sup> i-propanol: 3 mol% or 10 mol%.

 $\alpha$ , $\beta$ -coupling product 2aa' in 50% and 42% yields along with a small portion of tetrahydro-1,8-naphthyridine 1a' (<15%), respectively. However, the absence of i-propanol or Pd catalyst failed to yield any desired product (entries 5 and 6), showing that both are essential for product formation. Then, several conventional bases (entry 7) and solvents (entries 8-10) were tested by using  $Pd(OAc)_2$  as the catalyst. 1,4-Dioxane appeared to be a better choice and gave 2aa' in 63% yield (entry 10). However, the change of the reaction temperature was not fruitful since no increase in yields was found (entry 11). Furthermore, several hydrogen donors were screened (entries 12-15), but they proved to be less effective as compared to i-propanol. Finally, using the same loading of the NaH catalyst as reported by the Aksenov group<sup>11b</sup> led to no product formation in our reaction system (entry 16), decreasing the amount of i-propanol diminished the product yield (entry 17), and the presence of a catalytic amount of i-propanol (3 mol% or 10 mol%) gave only a trace of product 2aa', suggesting that the metal hydride species is unable to regenerate. Thus, the optimal conditions are as described in entry 10 of Table 1.

With the optimal reaction conditions established, we then examined the generality and the limitation of the synthesis protocol. First, different 2-aryl(heteroaryl)- and 2,3-diaryl-1,8naphthyridines were employed for the transformation. As illustrated in Scheme 1, all the reactions proceeded smoothly to furnish the  $\alpha$ , $\beta$ -coupling products in reasonable to good isolated yields (**2aa'-2ff**), and the electron properties of the substituents



Scheme 1 The  $\alpha,\beta$ -coupling of 1,8-naphthyridyl derivatives. Conditions: 1 (0.2 mmol), Pd(OAc)<sub>2</sub> (3 mol%), NaOH (0.2 mmol), i-propanol (0.6 mmol), 125 °C.

on the aryl ring of the reactants (1) have little influence on the product formation. Gratifyingly, the less reactive non-substituted 1,8-naphthyridine (1g) and 2-alkyl-1,8-naphthyridine (1h) were also applicable for the transformation to give the products (2gg', 2hh') in reasonable yields. Similarly, the alkyl and aryl disubstituted 1,8-naphthyridines (1i-1l) underwent effective α,β-coupling to generate the *tetra*-substituted products (2ii'-2ll'). In comparison, the diaryl-substituted 1,8-naphthyridines were able to afford the corresponding products (2ee', 2ff') in much higher yields than those arising from the coupling of mono-arylor non-aryl-substituted 1,8-naphthyridines (2aa'-2dd', 2gg'-2ll'), which might be ascribed to the fact that diaryl-substituted substrates have low-LUMO regarding the ease of transfer hydrogenation. It is noteworthy that, performing the reaction of two different 1,8-naphthyridines (1a, 1g) led to two homo-coupling (2aa', 2gg') and two cross-coupling (2ag', 2ga') products in similar yields (eqn (2)), supporting the fact that the reaction intermediates possess the reactive  $\alpha$ - and  $\beta$ -sites. However, the reactions of 2- and 3-substituted 1,8-naphthyridines were unable to give the corresponding products, presumably because of the influence of steric hindrance.





Subsequently, we turned our attention to the application of other N-heteroarenes. First, the more challenging quinoline derivatives were tested. As shown in Scheme 2, all the substrates were amenable to the synthesis protocol, furnishing the 2,3-biquinolines (**2mm'-20o'**) in acceptable yields. 2,3-Diphenylpyrido[2,3-*b*]pyrazine (**1p**), a representative polynitrogen heteroarene, was successfully converted into the desired product **2pp'** in 48% yield. Interestingly, the catalytic system was also compatible with the transformation of 1,10-phenanthroline (**1q**), affording the new bis-1,10-phenanthroline **2qq'** in 32% yield, which has the potential to be applied as a *tetra*dentate ligand in organometallic chemistry and catalysis as 1,10-phenanthroline–metal catalysts were shown to be crucial.<sup>13</sup>

To gain insight into the reaction information, we performed several verification experiments (Scheme 3). The coupling of **1c** was surveyed by employing deuterium-labeled i-propanol as the activating agent (eqn (3)). The H-NMR analysis showed no H/D exchange on the *m*-tolyl unit, whereas different H/D ratios was observed on the naphthyridyl skeleton ( $2\mathbf{cc'}\cdot\mathbf{d_n}$ ), which shows that the reaction undergoes a hydrogen transfer pathway, rather than a nitrogen atom-directed *otho*-C-H bond activation. And the coupling occurred selectively at the steri-



**Scheme 4** Plausible pathway of the  $\alpha$ , $\beta$ -coupling of N-heteroarenes.

cally less-hindered pyridyl ring. Then, the model reaction was interrupted after 5 h to observe the reaction intermediates.

By means of GC-MS analyses, product 2aa', tetrahedron naphthyridine 1a', enamine (1a-B) or imine (1a-C) were detected in 9%, 2% and 1% yields, respectively (eqn (4), and ESI Scheme S3†). Furthermore, the treatment of the mixture of 1a-B and 1a-C in 1,4-dioxane gave product 2aa' in 76% yield (eqn (5)), suggesting that the coupling of these two intermediates and the formation of product 2aa' do not need a catalyst. The reaction of 1a' under standard conditions failed to afford 2aa' (eqn (6)). These results clearly indicate that 1a-B and 1a-C are the key reaction intermediates, and the conversion of tetrahedron naphthyridine 1a' into product 2aa' is difficult, which rationalizes the product yields being somewhat low in some cases (see Schemes 1 and 2).

Based on the above observations, a plausible reaction pathway is depicted in Scheme 4. The N-heteroarene **1** is initially activated by the hydrogen transfer of  $[MH_2]$  arising from the metal catalyst and hydrogen donor (i-propanol), affording allylic amine **A** and its tautomer enamine **B**, and imine **C**. Then, the  $\beta$ -site of **B** would be able to undergo nucleophilic addition to the  $\alpha$ -carbon of **C**, thereby releasing the coupling adduct **D**. Finally, the auto-dehydroaromatization of **D** would give rise to product **2**.

Finally, we were interested in demonstrating the application of the obtained compounds. In consideration of the extensive applications of 1,10-phenanthroline (L1) as a ligand in



Scheme 3 Verification experiments.



Fig. 1 Comparison of the catalytic performance of L1 and L2 (2qq').

catalysis, both L1 and the new product 2qq' (L2) were employed as the ligands for the copper-catalysed  $\alpha$ -arylation of deoxybenzoin 4a with 1-iodo-4-methoxybenzene 3a.<sup>13d</sup> As shown in Fig. 1, by using 10 mol% of CuI, 5 mol% of L2 exhibited a much better catalytic performance than that of 10 mol% of L1, and the desired  $\alpha$ -arylation product 5aa was afforded in a higher yield within a shorter reaction time while using L2 as the ligand.

### Conclusions

In summary, by an external hydrogen transfer-mediated activation mode, we herein demonstrate a new palladium-catalyzed direct  $\alpha,\beta$ -coupling of different types of N-heteroarenes. Such a homo-coupling reaction proceeds with the advantages of operational simplicity, high atom-economical efficiency, and the use of safe and abundant i-propanol as the activating agent, offering a practical way to access bi-N-heteroarenes. Preliminary exploration has revealed that the obtained bis1,10-phenanthroline **2qq'** as a ligand is capable of improving the copper catalyst for C–C bond formation. The work reported in this paper has built an important basis for the creation of extended  $\pi$ -conjugated systems that are of high significance in biological, medicinal, materials and synthetic organic chemistry as well as catalysis.

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