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Palladium-catalyzed tandem reaction of *o*-aminophenols, bromoalkynes and isocyanides to give 4-amine-benzo[*b*][1,4]oxazepines†

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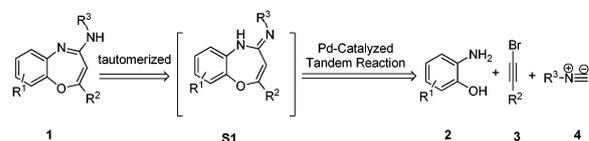
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A robust route to 4-amine-benzo[*b*][1,4]oxazepines relying upon a palladium-catalyzed tandem reaction of *o*-aminophenols, bromoalkynes and isocyanides has been developed. This chemistry presumably proceeds through the migratory insertion of isocyanides into the vinyl-palladium intermediate as a key step.

N-Heterocycles represent a long sought after target because a number of biological activities have been conferred to them and they are common components of many natural products, pharmaceuticals and agrochemical products.¹ Among them, significant interest has been increased in seven-membered heterocyclic rings, as these structural units widely exist in numerous natural products² and various biologically interesting molecules.³ Benzooxazepine derivatives are very important kinds of the seven-membered rings and the core scaffolds in medicinal chemistry with remarkable biological activities and pharmaceutical interest.⁴ The fascinating biological profiles of this group of compounds stimulated researchers to explore efficient methods for the synthesis of benzooxazepines and their structural analogues.⁵ Unfortunately, the major drawback of the reported methods is their multistep synthesis, which usually hinder them from constructing a large number of structural derivatives of these heterocycles.^{5a} Thus, the development of new methodologies for the efficient synthesis of this type of skeleton is highly desired.

Haloalkynes are attractive starting materials and important intermediates in organic synthesis because they are highly reactive and easily prepared from terminal alkynes.⁶ Recently, we and other groups have revealed that certain nucleophiles,⁷ such as halide ions (F⁻, I⁻),^{7a,b} acetate anions (OAc⁻),^{7c} isocyanides,^{7d} phenols,^{7e} thiols,^{7f} imidazoles,^{7g,h} and sulfonamides^{7i,j} could easily undergo nucleophilic addition to haloalkynes, which generated corresponding (*Z*)-2-bromoalkenes. More importantly, the (*Z*)-2-bromoalkenes obtained by these reactions are important precursors and have been explored in the synthesis of useful heterocycles.^{7c-e,i,j} Isocyanides have been recognized as powerful



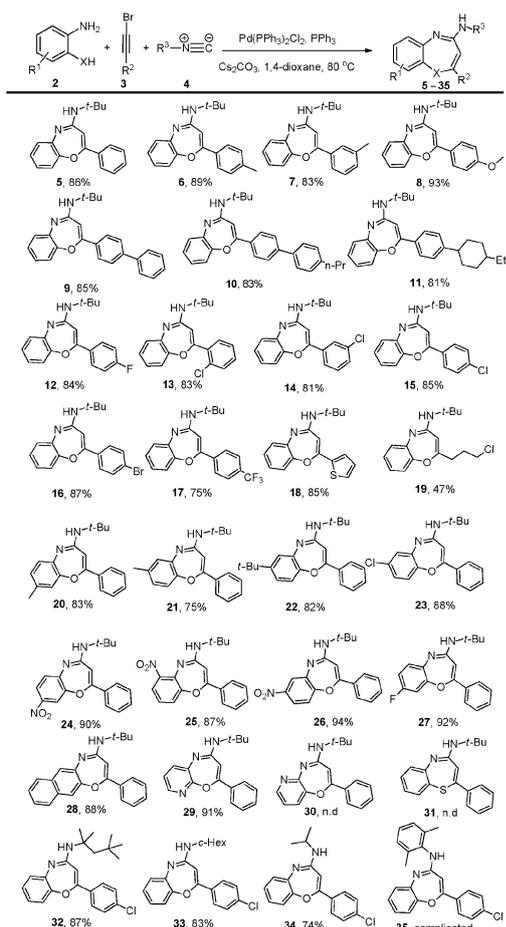
Scheme 1 Initial retrosynthetic analysis of 4-amine-benzo[*b*]-[1,4]oxazepines **1**.

building blocks in the construction of structurally appealing *N*-containing heterocycles,⁸ however, transition metal-catalyzed multicomponent tandem reactions involving isocyanides are relatively undervalued.⁹ Based on our previous studies in bromoalkynes^{7a-d,10} and isocyanides,^{7d,11} we envisaged that a palladium-catalyzed tandem reaction of *o*-aminophenols **2**, bromoalkynes **3**, and isocyanides **4** would allow an efficient access to 4-amine-benzo[*b*][1,4]-oxazepines **1** by selective C–O and C–N bond-forming events (Scheme 1). To the best of our knowledge, this catalytic version has not yet been reported. Herein, we disclose a robust route to construct a series of 4-amine-benzo[*b*][1,4]oxazepines in a rapid and convenient manner *via* a palladium-catalyzed tandem reaction of *o*-aminophenols, bromoalkynes and isocyanides.

To our delight, the palladium-catalyzed tandem reaction of *o*-aminophenols, bromoalkynes and isocyanides afforded good to excellent yields of functionalized 4-amine-benzo[*b*]-[1,4]oxazepines (Scheme 2). For instance, 2-aminophenol (**2a**), phenylethynyl bromide (**3a**) and *tert*-butylisocyanide (**4a**) were allowed to react in the presence of Cs₂CO₃ (2.0 equiv.) in 1, 4-dioxane at 80 °C for 2 h, affording 86% yield of the desired product **5** (Scheme 2, **5**).¹² With this result in hand, we next investigated the scope of the reaction using different kinds of bromoalkynes, *o*-aminophenols and isocyanides (Scheme 2). Gratifyingly, aromatic alkynylbromides with either an electron-donating (**6–11**) or electron-withdrawing (**12–17**) group on the benzene ring could be smoothly transformed into the desired products in good to excellent yields. Interestingly, halogen atoms (–Cl, –Br) on the aromatic ring were inert in this reaction, allowing them to be used for further transformation (**13–16**). It is noteworthy that heteroaromatic alkynylbromide such as 2-(bromoethynyl)thiophene was also compatible with the reaction conditions and generated the corresponding product **18** in 85% yield. Alkynyl bromide such as 5-chloropentynyl bromide could also undergo the same transformation but gave the desired product

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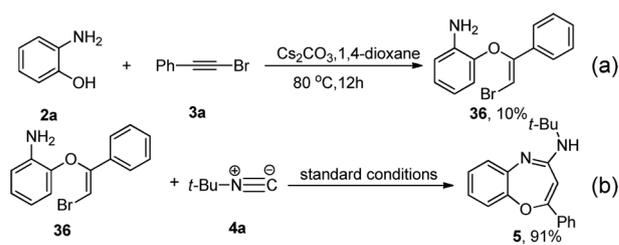
† Electronic supplementary information (ESI) available: Experimental section, characterization of all compounds, copies of ¹H and ¹³C NMR spectra for isolated compounds. See DOI: 10.1039/c2cc35802f



Scheme 2 Palladium-catalyzed tandem reaction of *o*-aminophenols **2**, bromoalkynes **3**, and isocyanides **4**.^a

19 in 47% yield. Next, various substituted *o*-aminophenols were also applied to this process under the optimized reaction conditions (**20–27**). As can be seen from Scheme 2, the reactivity of phenols with an electron-withdrawing group (**23–27**), such as $-F$, $-Cl$, or $-NO_2$, was much higher than that of the phenols without a substituent or with an electron-donating group (**20–22**). Additionally, 3-amino-2-naphthol (**28**) and 3-amino-2-pyridinol (**29**) could be also employed in this transformation affording the expected products in 88% and 91% yields, respectively. Unfortunately, no reaction occurred when 2-amino-3-pyridinol (**30**) or 2-aminothiophenol (**31**) was employed in this transformation. Finally, various alkyl, cycloalkyl, and aryl isocyanides were also applied to probe the scope of the reaction substrates (**32–35**). Generally, when alkyl and cycloalkyl isocyanides, even if sterically bulky isocyanides such as 1,1,3,3-tetramethylbutyl isonitrile (**32**) were used, the reaction gave the corresponding products in good yields. However, when 2,6-dimethylphenyl isocyanide was applied in this process under the optimized reaction conditions, the desired product was detected by GC-MS, but was complicated and failed to obtain the pure product (**35**).

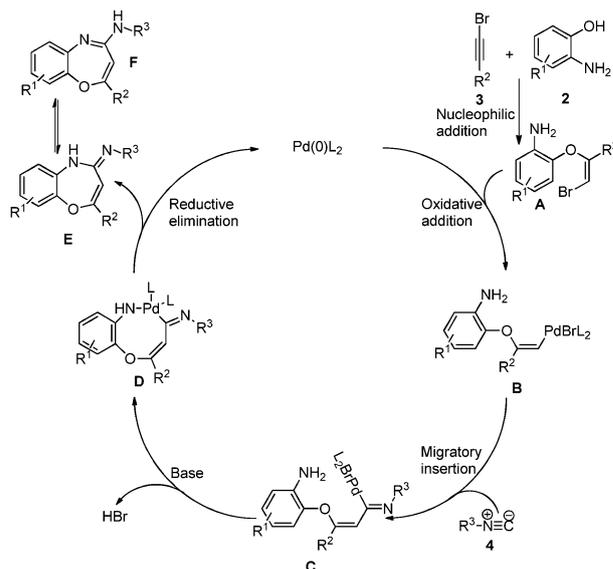
To gain insight into the mechanism of the reaction, several control experiments were conducted as shown in Scheme 3.



Scheme 3 Investigation of the reaction mechanism.

When **2a** and **3a** were treated in 1,4-dioxane using Cs_2CO_3 (2.0 equiv.) as base, only 10% of the desired nucleophilic addition product (*Z*)-2-((2-bromo-1-phenylvinyl)oxy)aniline (**36**) was obtained even the reaction time was prolonged to 12 h (Scheme 3, eqn (a)).¹³ However, when **36** and **4a** were carried out under the optimized reaction conditions, 91% of the desired product **5** was obtained (Scheme 3, eqn (b)). These experimental results revealed that this reaction proceeded through the *cis*-nucleophilic addition of *o*-aminophenols to bromoalkynes, and then the migratory insertion of isocyanides into the vinyl-palladium intermediate. We presumed that, for the palladium-catalyzed tandem reaction, the consumption of **36** in the second step obviously promoted the generation of the **36** in the first step.

On the basis of these preliminary results and the control experiments conducted, a possible catalytic cycle involved in the present process was outlined in Scheme 4. Initial nucleophilic addition of *o*-aminophenols (**2**) to bromoalkynes (**3**) gave the intermediate **A**, which underwent oxidative addition to $Pd(0)$ species to generate a vinyl palladium species **B**. Subsequent migratory insertion of isocyanide (**4**) would result in the formation of intermediate **C**.¹⁴ With the aid of the base, hydrogen bromide was extruded out of **C** to generate the eight-membered azapalladacyclic intermediate **D**. Finally, reductive elimination afforded **E**, regenerating the $Pd(0)$ catalyst. Immediately, the unstable product **E** isomerized to give the final product **F**.



Scheme 4 A plausible reaction mechanism.

In conclusion, we have demonstrated a novel and straightforward procedure for the synthesis of a new class of substituted 4-amine-benzo[*b*][1,4]oxazepines via palladium-catalyzed three-component tandem reaction of bromoalkynes, *o*-aminophenols and isocyanides. The reaction was successful with a variety of bromoalkynes, *o*-aminophenols and smoothly converted to the desired product in good to excellent yields. Most importantly, this reaction may be applied to the construction of some important benzo[*b*][1,4]oxazepine derivatives as effective pharmaceutical compounds with various biological activities.

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