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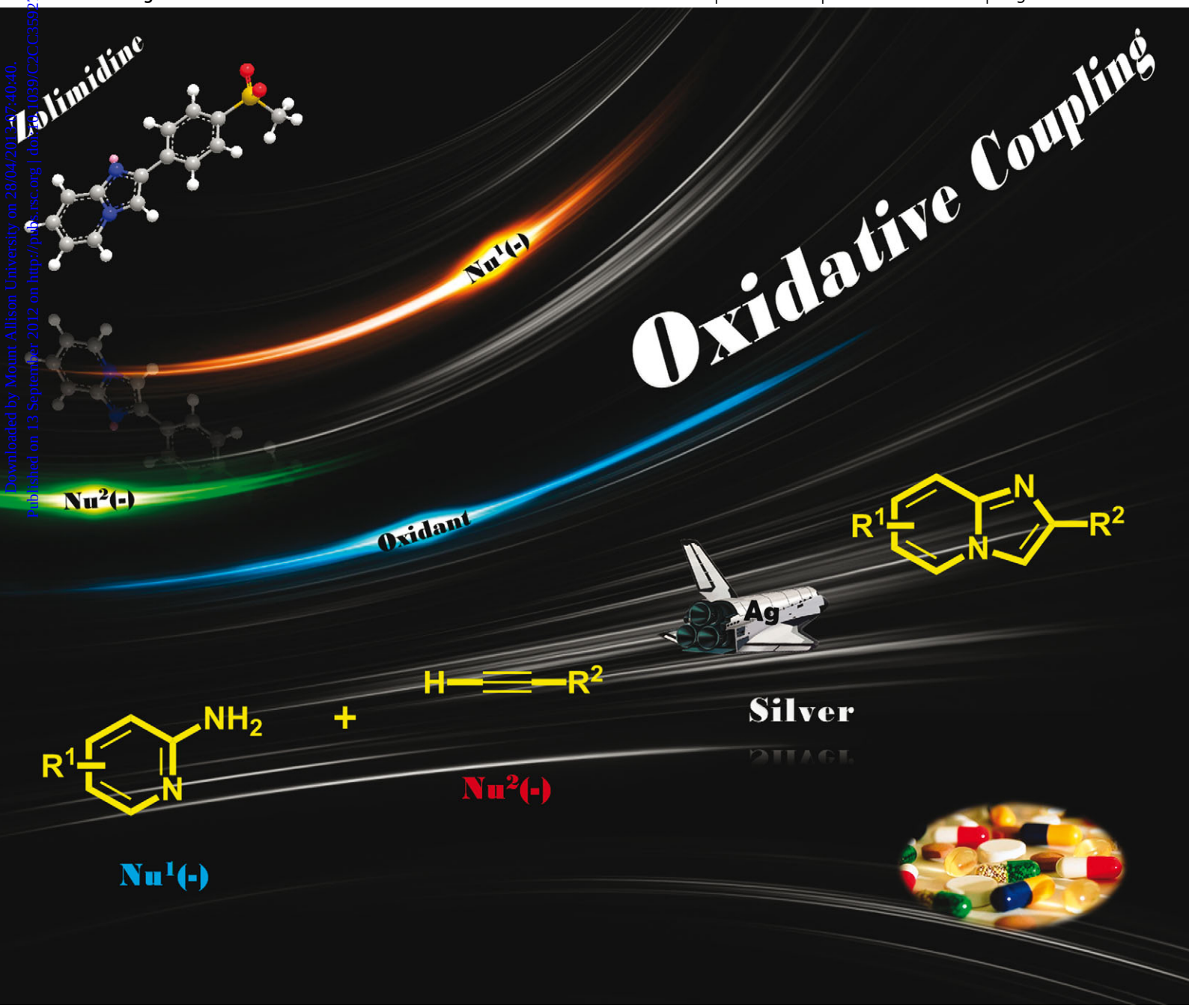


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# Heteroaromatic imidazo[1,2-*a*]pyridines synthesis from C–H/N–H oxidative cross-coupling/cyclization†

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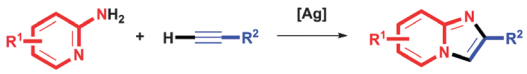
**A novel silver-mediated highly selective C–H/N–H oxidative cross-coupling/cyclization between 2-aminopyridines and terminal alkynes has been demonstrated. This approach provided a simple way to construct heteroaromatic imidazo[1,2-*a*]pyridines. By using this protocol, the marketed drug zolimidine (antiulcer) could be synthesized easily.**

Direct C–H functionalization towards the formation of C–C and C–heteroatom (N, O and S, *etc.*) bonds is of great significance and a challenge, and application of these strategies to construct heterocycles is especially attractive.

Compared to the classical transition-metal-catalyzed coupling reactions, the direct oxidative coupling between two different C–H or heteroatom-H bonds has an inherent advantage such as avoiding pre-functionalization of the substrates, and represents an ideal chemical synthesis.[1] In this emerging field, the highly efficient and selective cross-coupling reactions involving terminal alkynes are still challenging. Under the oxidative conditions, the reactions usually suffer from the inevitable homocoupling of terminal alkynes (Glaser–Hay coupling).[2] Recently, some insights into the direct oxidative C–H functionalization/alkynylation have been realized.[3] However, the challenge of selectivity still remains in such reactions. Only few examples could avoid the homocoupling of terminal alkynes. Very recently, silver salts have shown great potential in the highly selective chemical syntheses involving terminal alkynes.[3f,i,j]

Imidazoheterocycles represent an important class of heterocycles prevalent in a myriad of natural products and biologically active compounds.[4] In particular, imidazo[1,2-*a*]pyridine with important therapeutic properties is the key structural moiety in several pharmaceutical drugs, such as the hugely successful and valuable molecules zolpidem, alpidem and zolimidine, *etc.*[5] In addition, some abnormal *N*-heterocyclic carbenes are also prepared based on imidazo[1,2-*a*]pyridines.[6] Although some methods are available for the synthesis of this important scaffold,[5a,7] the straightforward and region-defined routes for constructing 2-arylimidazo-[1,2-*a*]pyridines from basic chemical materials, such as pyridine derivatives and terminal alkynes, are highly attractive. Herein, we communicate our effort in silver-mediated synthesis of hetero-aromatic imidazo[1,2-*a*]pyridines through C–H/N–H oxidative cross-coupling/cyclization between 2-aminopyridines and terminal alkynes (Scheme 1).




**Scheme 1** Silver-mediated C–H/N–H oxidative cross-coupling/cyclization.

We reasoned that the imidazo[1,2-*a*]pyridine frameworks could be assembled by a direct C–H/N–H oxidative cross-coupling/cyclization between 2-aminopyridines and terminal alkynes in the presence of suitable transition metal catalysts and oxidants. Our initial efforts focused on the reaction of 2-aminopyridine **1a** and phenylacetylene **2a** by using copper(II), iron(III), and silver(I) salts, *etc.* After some attempts, when silver(I) salts were employed, the corresponding target 2-phenylimidazo-[1,2-*a*]pyridine **3aa** was obtained with perfect selectivity and in good yield (Scheme 1 and Table 1). This interesting one-step transformation to the imidazoheterocycles encouraged us to further examine the feasibility of this efficient C–H/N–H oxidative cross-coupling/cyclization.

The simplest was the best. Only employing $Ag_2CO_3$ (2.0 equiv.) in dioxane at 110 °C, the C–H/N–H oxidative cross-coupling/cyclization could proceed smoothly in good yield (Table 1, entry 8). To enhance the conversion of terminal alkyne, 2 equiv. of 2-aminopyridine was employed in the reaction. Even if the two substrates were added in one-pot, no terminal alkyne homo-coupling and other byproducts were observed under these oxidative reaction conditions. Neither base nor acid additives could improve the yields, such as KOAc, NaOAc, $K_2CO_3$, $Cs_2CO_3$, DBU, HOAc, and HOPiv (Table 1, entries 1–7). $Ag_2O$ could also produce the desired product in 63% yield, while $AgNO_3$ was totally ineffective (Table 1, entries 9 and 10). The reaction could proceed in other solvents, such as polar solvents DMF, DMSO and NMP, albeit in lower yields (Table 1, entries 11–13). When DCE was used, only 15% yield was obtained (Table 1, entry 14). When 1.0 equiv. of $Ag_2CO_3$ was employed, only 41% yield was afforded (Table 1, entry 15). An attempt to utilize $O_2$ as the oxidant in the reaction was also unsuccessful (Table 1, entry 16).

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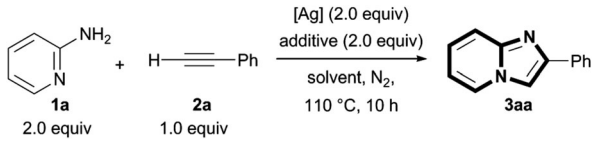
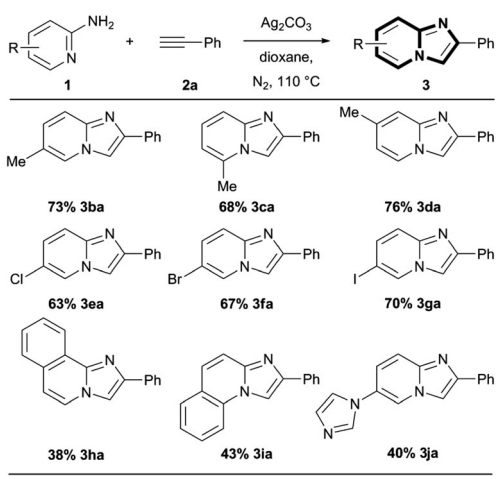
**Table 1** Optimization conditions for the reaction of 2-aminopyridine **1a** and phenylacetylene **2a**




| Entry | [Ag] | Additive | Solvent | Yield[a] (%) |
|---|---|---|---|---|
| 1[b] | $Ag_2CO_3$ | KOAc | Dioxane | 71 |
| 2 | $Ag_2CO_3$ | NaOAc | Dioxane | 63 |
| 3 | $Ag_2CO_3$ | $K_2CO_3$ | Dioxane | 62 |
| 4 | $Ag_2CO_3$ | $Cs_2CO_3$ | Dioxane | 53 |
| 5 | $Ag_2CO_3$ | DBU | Dioxane | 43 |
| 6 | $Ag_2CO_3$ | HOAc | Dioxane | 51 |
| 7 | $Ag_2CO_3$ | HOPiv | Dioxane | Trace |
| **8**[c] | **$Ag_2CO_3$** | | **Dioxane** | **71** |
| 9 | $Ag_2O$ | | Dioxane | 63 |
| 10 | $AgNO_3$ | | Dioxane | 0 |
| 11 | $Ag_2CO_3$ | | DMF | 45 |
| 12 | $Ag_2CO_3$ | **None** | DMSO | 31 |
| 13 | $Ag_2CO_3$ | | NMP | 43 |
| 14 | $Ag_2CO_3$ | | DCE | 15 |
| 15[d] | $Ag_2CO_3$ | | Dioxane | 41 |
| 16[e] | $Ag_2CO_3$ | | Dioxane | 13 |

[a] Isolated yields. [b] Reactions were carried out on the scale of 0.25 mmol of **2a** in the presence of 2.0 equiv. of $Ag_2CO_3$ and 2.0 equiv. of additives in 6 mL of solvent at 110 °C for 10 h, $N_2$ atmosphere (entries 1–7). [c] Reactions were carried out on the scale of 0.5 mmol of **2a** in the presence of 2.0 equiv. of [Ag] in 6 mL of solvent at 110 °C for 10 h, $N_2$ atmosphere (entries 8–16). [d] 1.0 equiv. of $Ag_2CO_3$. [e] 0.5 equiv. of $Ag_2CO_3$, $O_2$ atmosphere.

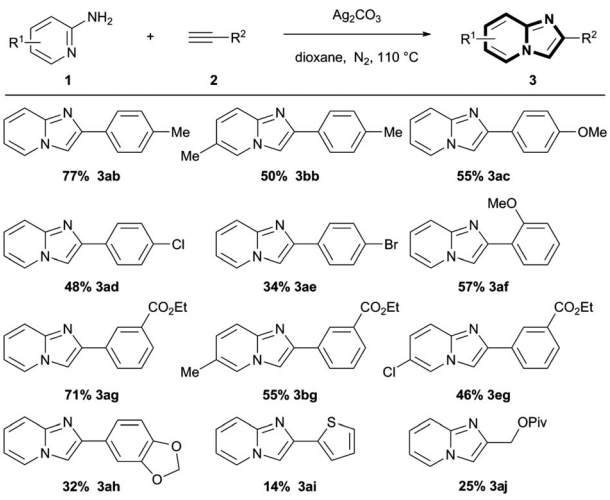
Under the optimized reaction conditions, various 2-aminopyridines **1** were found to be suitable reaction partners with phenylacetylene **2a** to provide the corresponding imidazopyridine derivatives **3** (Scheme 2). 2-Aminopyridines substituted at different positions with methyl group could react with phenylacetylene **2a** in good yields. The position of substituents almost had no influence on the chemical yields (Scheme 2, **3ba–3da**). Halogen groups substituted at the aromatic ring of 2-aminopyridine, such as chloro, bromo and even iodo, were all well tolerated, which provided the possibility for further functionalization (Scheme 2, **3ea–3ga**). Moreover, 1-aminoisoquinoline **1h** and 2-aminoquinoline **1i** could also be readily introduced in the transformation, affording imidazoisoquinoline and imidazoquinoline, respectively, albeit in lower yields (Scheme 2, **3ha** and **3ia**). Interestingly, 2-aminopyridine with imidazole moieties could also be employed to afford the imidazo[1,2-*a*]pyridine scaffold in 40% yield (Scheme 2, **3ja**).



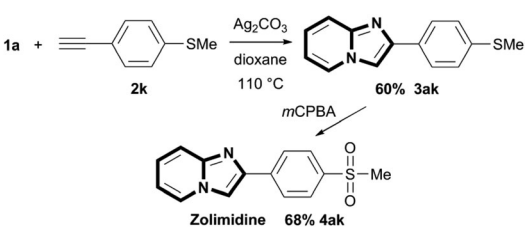

**Scheme 2** Substrate scope for the reaction of 2-aminopyridines **1** and phenylacetylene **2a**. Reactions conditions: 1.0 mmol of **1** and 0.5 mmol of **2a** in the presence of 1.0 mmol of $Ag_2CO_3$ in 6 mL of dioxane at 110 °C for 10 h, $N_2$ atmosphere. Isolated yields.

Varied terminal alkynes **2** were also tested to access the imidazo[1,2-*a*]pyridines (Scheme 3). Either electron-withdrawing and -donating substituted groups or halogen groups at the aromatic ring of aryl alkynes were well tolerated in the reactions, such as Me, OMe, Cl, Br, and $CO_2Et$ (Scheme 3, **3ab**–**3ac**, **3ad**–**3ag**, **3bb**, **3bg** and **3eg**). Meanwhile, aryl alkynes with substituents at the *ortho*, *meta*, or *para* position of the aromatic ring could react satisfactorily to afford the desired products in moderate to good yields. Terminal alkynes containing benzodioxole and thiophene moieties could also be transformed into the imidazo[1,2-*a*]pyridines scaffold in 32% and 14% yields respectively (Scheme 3, **3ah** and **3ai**). Moreover, alkyl terminal alkyne prop-2-ynyl pivalate **2j** could react with **1a** producing the target product **3aj** in 25% yield.

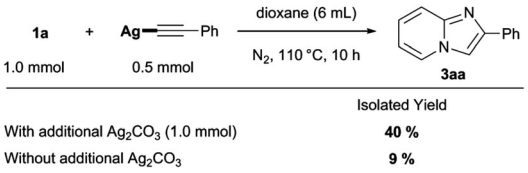
Zolimidine (antiulcer) could be synthesized in a concise route. As shown in Scheme 4, by utilizing 2-aminopyridine **1a** and 4-ethynylphenylmethylsulfane **2k**, the cyclization product **3ak** could be generated smoothly in 60% yield under the Ag-mediated conditions. The SMe functional group could be well tolerated in the reaction. Further oxidation of **3ak** using



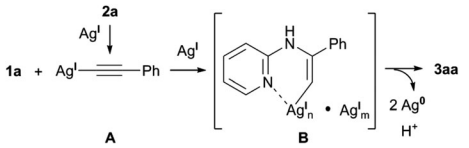

**Scheme 3** Substrate scope for the reaction of 2-aminopyridines **1** and terminal alkynes **2**. Reactions conditions: 1.0 mmol of **1** and 0.5 mmol of **2** in the presence of 1.0 mmol of $Ag_2CO_3$ in 6 mL of dioxane at 110 °C for 10 h, $N_2$ atmosphere. Isolated yields.




**Scheme 4** Preparation of zolimidine.




**Scheme 5** Reaction of **1a** and silver phenylacetylide.




**Scheme 6** Proposed mechanism.

*m*CPBA as the oxidant could simply produce the target product zolimidine **4ak** in 68% yield. Actually, a one-pot reaction sequence enables convenient access to zolimidine in about 40% overall yield.

Moreover, we have also tested some internal alkynes such as prop-1-ynylbenzene, 1,2-diphenylethyne and dimethyl but-2-ynedioate instead of terminal alkynes. However, no corresponding imidazo[1,2-*a*]pyridine products could be observed under the current conditions. Accordingly, we envisioned that silver acetylide might be the key intermediate in the reaction. As shown in Scheme 5, the prepared silver acetylide was allowed to react with **1a** under the standard conditions. In the presence of additional $Ag_2CO_3$, silver phenylacetylide could indeed react with **1a** giving 40% yield of **3aa**. Without additional $Ag_2CO_3$, only 9% yield was obtained.

A putative mechanism for this Ag-mediated C–H/N–H oxidative cross-coupling/cyclization is outlined in Scheme 6. Initially, silver acetylide complex **A** is formed by the reaction of terminal alkyne **2a** with Ag(I). Then, through the silver-promoted nucleophilic attack of 2-aminopyridine **1a** on complex **A**, the crucial intermediate **B** is obtained,[8] possibly aggregated with additional Ag(I).[9] Finally, silver-induced oxidative cyclization of **B** affords the product **3aa** *via* two single-electron oxidation. Although 2.0 equiv. of $Ag_2CO_3$ was employed in the reaction, actually, the silver species after the reaction could be recycled conveniently by filtration and treating with nitric acid and $Na_2CO_3$.[3*i*]

In summary, we have developed a novel silver-mediated highly selective C–H/N–H oxidative cross-coupling/cyclization between 2-aminopyridines and terminal alkynes. This approach provides a simple way to construct heteroaromatic imidazo[1,2-*a*]pyridines from basic chemical materials. Only promoted by silver species, various 2-aminopyridines could react smoothly with terminal alkynes in perfect selectivity and in moderate to good yields. In this oxidative transformation, no terminal alkyne homocoupling byproduct was observed. By using this protocol, the marketed drug zolimidine (antiulcer) could be easily synthesized in a concise route. Further mechanistic studies on this oxidative transformation are currently ongoing in our laboratory.

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