A facile transition-metal-free regioselective halogenation of imidazo[1,2-a]pyridines using sodium chlorite/bromite as the halogen source has been developed, employing Pd, Rh or Cu as the catalysts and carboxylic acid, amide, nitrile, or pyridine as the directing groups (Scheme 1a). Recently, NH₄X, NaX and HX have been employed as the halogen sources in transition-metal-free conditions for the halogenation of several arenes and heteroarenes (Scheme 1b). Nevertheless, directing groups and additional oxidants were usually needed in these transformations and the halogen sources were very limited.

In order to expand the richness of green synthetic methods, we tried to hunt for other atom-economical and easy-to-obtain halogen sources. As we know, sodium chlorite or bromite are commodity chemicals that are widely used as main efficient systems of bleaches or desizing agents. Herein, our current interest is focused on developing novel strategies for the construction of imidazo[1,2-a]pyridines without direct group, in which sodium chlorite or bromite were used as both halogen sources and oxidants (Scheme 2c).

Our initial investigation focused on the halogenation of imidazo[1,2-a]pyridine 1a. The results of the optimized reaction conditions are summarized in Table 1. The reaction was conducted in the presence of NaClO₂ (1 equiv.), AcOH (2 mmol), in toluene at 60 °C for 10 h (Table 1, entry 1). To our delight, the desired product 2a was formed in 64% yield. No regioisomeric formations and the halogen sources were very limited.

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obtained after increasing the amount of NaClO₂ to 3 equiv., while a decreased yield was observed after decreasing the amount from 2 to 1 equiv. Among the set of additives examined, AcOH gave the desired product 2a in good yield, while CF₃COOH, PivOH and TsOH were found to be less effective in affording the corresponding product 2a in 29–40% yield (Table 1, entries 4–6). It was worth noting that if acid was not added, only trace amount of target product was generated (Table 1, entry 7). The effect of solvents was further tested. It was found that DMF was the best choice in comparison to toluene, 1,4-dioxane, NMP, CH₃CN, DMSO and DCE (Table 1, entries 8–13). We then screened the reaction temperature and found the reaction performed at 40 °C or 80 °C gave a lower yield of the product 2a (Table 1, entries 14–15). The control experiment indicated that product 2a was not generated in the absence of NaClO₂ (Table 1, entry 16).

With the establishment of the optimal conditions, the scope of this transition-metal-free chlorination reaction was next investigated. And the results have been described in Scheme 3. A variety of 2-unsubstituted imidazo[1,2-a]pyridines were first employed under the optimized conditions. Different position substituted groups on the pyridine ring of imidazo[1,2-a]pyridine, having 6-CH₃, 6-Cl, 6-I, 7-CH₃, 8-CH₃ substitution, were well-tolerated under the optimized conditions. The results indicated that selective C-3 chlorination products 2a–2f were formed in good to excellent yields. This catalytic system was further found to be successfully applied to catalyze the chlorination of 2-CH₃, 2-C(CH₃)₃, and 2-Ph substituted imidazo[1,2-a]pyridines, generating the desired products in moderate to good yields (2g–2p). It was worth noting that when imidazo[1,2-a]pyridines substituted with sterically hindered 2-C(CH₃)₃ were employed as substrates, the transformation worked well and led to a beneficial effect on the reaction outcome.

We next examined the bromination of imidazo[1,2-a]pyridines derivatives in the presence of NaBrO₂ and AcOH in DMF at 60 °C for 10 h. The results were summarized in Scheme 4. As we expected, the optimal conditions could also be applied to bromination of imidazo[1,2-a]pyridines and afforded the brominated products 3a–3f in 70–88% yields. It was found that the reaction was also with great regioselective in the case of 2-unsubstituted imidazo[1,2-a]pyridines.

The reactions of 2a or 3d with phenylboronic acid were conducted in the presence of Pd-catalyst (Scheme 5). The Suzuki–Miyaura reactions were performed very well, affording the product 5a or 6a in 74% or 79% yields, respectively.

In order to test whether this method is compatible with other aromatic species or not, we have tried to use indoles, 1-methyl-

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**Table 1** Optimization of the reaction conditions

| Entry | NaClO₂ [equiv.] | Additive | Solvent | Temp (°C) | Yield (%) |
|-------|-----------------|----------|---------|-----------|-----------|
| 1     | 2               | AcOH     | Toluene | 60        | 64        |
| 2     | 3               | AcOH     | Toluene | 60        | 62        |
| 3     | 1               | AcOH     | Toluene | 60        | 43        |
| 4     | 2               | CF₃COOH  | Toluene | 60        | 40        |
| 5     | 2               | PivOH    | Toluene | 60        | 29        |
| 6     | 2               | TsOH     | Toluene | 60        | 31        |
| 7     | 2               | —        | Toluene | 60        | Trace     |
| 8     | 2               | AcOH     | Dioxane | 60        | 69        |
| 9     | 2               | AcOH     | NMP     | 60        | 45        |
| 10    | 2               | AcOH     | CH₃CN   | 60        | 37        |
| 11    | 2               | AcOH     | DMSO    | 60        | 63        |
| 12    | 2               | AcOH     | DMF     | 60        | 87        |
| 13    | 2               | AcOH     | DCE     | 60        | 14        |
| 14    | 2               | AcOH     | DMF     | 40        | 74        |
| 15    | 2               | AcOH     | DMF     | 80        | 85        |
| 16*   | 2               | AcOH     | DMF     | 60        | n.r.      |

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*Reaction conditions: 1a (0.5 mmol), NaClO₂ (1–3 mmol), AcOH (2 mmol), solvent (2 mL), 40–80 °C for 10 h. Determined by GC analysis. Without NaClO₂.

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**Scheme 3** Chlorination of imidazo[1,2-a]pyridines.
H-indoles, benzofurans, \(N,N\)-dimethylaniline, \(N\)-phenylacetamide and 1,3,5-trimethoxybenzene to perform under the present reaction conditions, while no target products were obtained. We supposed that the specificity of this reported method is because of the rich electronic ethene-1,2-diamine moiety of imidazo[1,2-\(a\)]pyridine (Scheme 6).

Gaining insight into the mechanism, control experiments were carried out for this transition-metal-free halogenation reaction. To prove a radical species involved in transformation, the reactions were conducted by adding radical-trapping reagent (TEMPO) or radical inhibitor (BHT) (Scheme 7, eqn (1)) in the reaction, and only trace amount of product 2a was observed. The result clearly showed that this reaction had been inhibited and a radical process was involved for this transformation, which was consistent with previous reported.\(^\text{17}\) To further investigated the chlorine source, NaClO and NaClO\(_3\) were employed to react with imidazo[1,2-\(a\)]pyridine 2a under the standard conditions. The results showed that the chlorination products were obtained in yields of 47% or 63% respectively, which means chlorine ions having a charge of 1+ or 5+ can also proceed this transformation, albeit with low yields (Scheme 7, eqn (2)).

Base on the above results and previous works,\(^\text{19}\) a possible mechanism was proposed to account for this transition-metal-free regioselective halogenation reaction (Scheme 8). Firstly, oxidation–reduction reaction of sodium chlorite happened in the presence of AcOH to produce chlorine, NaOAc and H\(_2\)O. Subsequently, the chlorine radical was easily formed \(\text{via}\) homolysis of chlorine, which then attack the double bond between C2 and C3 of imidazo[1,2-\(a\)]pyridine, resulting in free radical intermediate I (more stable than II because of the p–\(\pi\) conjugation). Finally, the free radical intermediate I underwent an aromatization with chlorine free radical to give the target product 2a.

Conclusions

In conclusion, we have developed an efficient transition-metal-free regioselective C–H functionalization approach. The
reaction provides a new selective route to synthesize 3-Cl or 3-Br-imidazo[1,2-a]pyridines without directing groups. The use of cheap sodium chlorite or bromite as both halogenic sources and oxidants is a major advantage. The 3-Cl or 3-Br-imidazo[1,2-a]pyridines as the substrates can successful apply to Suzuki–Miyaura reactions.

Conflicts of interest
There are no conflicts to declare.

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