Chinese Journal of Chemistry
中国化学 - An International Journal

Accepted Article

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This work may now be cited as: *Chin. J. Chem.* **2021**, *39,* 10.1002/cjoc.202100094.

The final Version of Record (VoR) of it with formal page numbers will soon be published online in Early View: http://dx.doi.org/10.1002/cjoc.202100094.

WILEY-VCH SIOC CCS

ISSN 1001-604X • CN 31-1547/O6
mc.manuscriptcentral.com/cjoc
www.cjc.wiley-vch.de

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Cite this paper: *Chin. J. Chem.* **2021**, *39*, XXX—XXX. **DOI: 10.1002/cjoc.202100XXX**

Divergent Syntheses of Pyridoacridine Alkaloids via Palladium-Catalyzed Reductive Cyclization with Nitro-Biarenes

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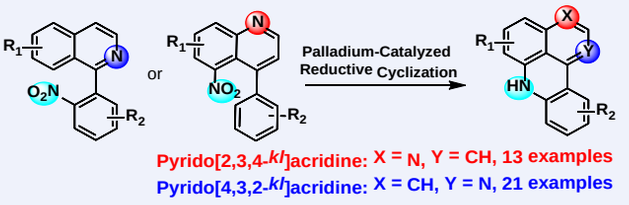
Keywords

Polycyclic Heteroaromatics | Palladium-Catalyzed Reductive Cyclization | Marine Nature Alkaloids | Divergent Syntheses | Pyridoacridine

Main observation and conclusion

A divergent and novel protocol for the preparation of both pyrido[2,3,4-kl]acridine and pyrido[4,3,2-kl]acridine alkaloids was developed. This method featured the remote palladium-catalyzed reductive cyclization with Mo(CO)6 as reductant. A wide range including three types of nitro arenes were tolerated and afforded corresponding products in good to excellent yields. This method has been successfully applied to the total synthesis of norsegoline, styelsamine C and the skeleton of necatorone.

Comprehensive Graphic Content



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Background and Originality Content

Pyridoacridine alkaloids are a series of structurally fascinating tetracyclic aromatic compounds sharing the pyridine ring fused acridine framework. There are total 15 isomers according to the different ring systems distributed in a broad range of functional products, but only two isomers sharing two common bonds are well-known owing to their existence in natural alkaloids (Figure. 1).[1] Pyrido[2,3,4-*kl*]acridine is a large family and more than 100 of these polycyclic heteroaromatics have been isolated from sessile marine invertebrates.[2] Correspondingly, pyrido[4,3,2-*kl*]acridine is a quite small family and only discovered in nature as the necatorone and its dimer from fungi *Lactarius necator*.[3]

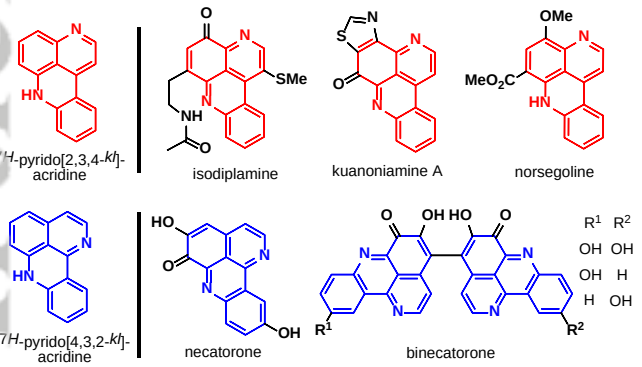
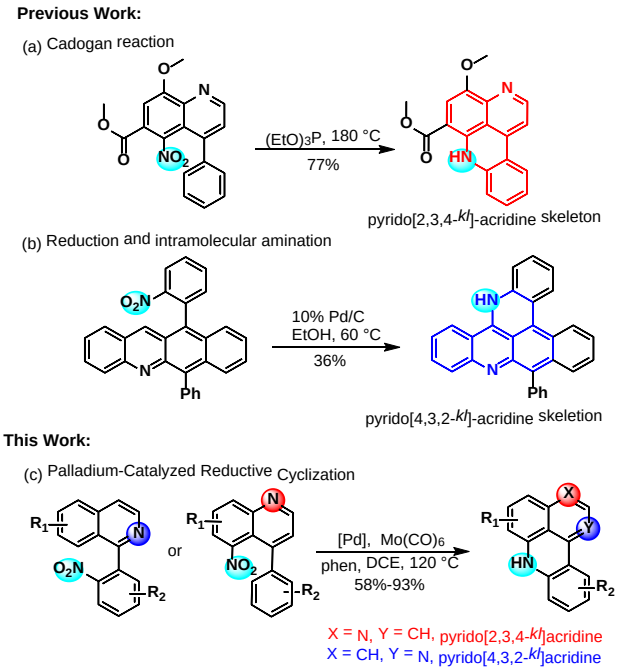


Figure. 1 Selective natural products containing pyrido[2,3,4-*kl*]acridine or pyrido[4,3,2-*kl*]acridine skeleton.

Both two types of pyridoacridine alkaloids have received enormous attentions due to the unique biological properties and many efforts have been devoted to construct these pyridoacridine frameworks, involving condensation of amino-ketone substrates,[4] cyclization of anionic nucleophilic addition,[5] electrocyclic ring closure,[6] Cadogan reaction[7] and biomimetic cascade reaction.[8] However, these methods suffered from the drawbacks such as use of harsh conditions, prolonged reaction times and especially the narrow substrate scopes and could not be applied in different ring systems. Accordingly, for further screening biological evaluation, the development of a divergent and efficient access for both pyrido[2,3,4-*kl*]acridine and pyrido[4,3,2-*kl*]acridine analogues is still of great interest.

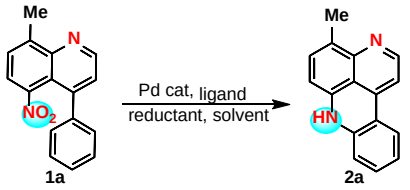
In past decades, the use of nitroarenes or nitroalkenes to synthesize *N*-heterocycles *via* transition-metal catalyzed reductive cyclization have progressed rapidly, which lead to directly generate the final products and save several synthetic steps.[9] Carbon monoxide is the most frequently employed reductant due to the good selectivity and atomic economy.[10] Recently, CO-surrogates were developed to overcome the limitation of hazardous pressurized gas manipulation,[11] but most cases focus on the construction of 5-membered ring containing heterocycles. As part of our efforts to develop *N*-heterocycles synthesis, we have demonstrated that palladium-catalyzed reductive cyclization with $Mo(CO)_6$ can successfully applied in nitroalkene system to afford indole alkaloids.[11a] Inspired by the pioneered reports and our previous work, we proposed that the tetracyclic pyridoacridine skeleton could be achieved by reductive cyclization of nitro biarenes. To the best of our knowledge, a relative remote reductive cyclization of nitro biarenes to construct new pyridine ring of polycyclic heteroaromatic has never been developed. Furthermore, this method provides a useful synthetic tool to access diverse types of pyridoacridines (Scheme. 1).



Scheme 1 Reported and current work on construction of pyridoacridine from nitro-biarenes.

Results and Discussion

Table 1 Optimization of palladium-catalyzed reductive cyclization of 1a.[a]



Entry	Reductant	Catalyst/Ligand	Solvent	Yield[d] %
1	HCOOPh	$Pd(OAc)_2$/phen	CH_3CN	38
2	$Cr(CO)_6$	$Pd(OAc)_2$/phen	CH_3CN	36
3	$W(CO)_6$	$Pd(OAc)_2$/phen	CH_3CN	42
4	$Mo(CO)_6$	$Pd(OAc)_2$/phen	CH_3CN	56
5	$Mo(CO)_6$	$Pd(CH_3CN)_2Cl_2$/phen	CH_3CN	70
6	$Mo(CO)_6$	$[Pd(Phen)_2][BF_4]_2$/ phen	CH_3CN	62
7	$Mo(CO)_6$	$Pd(dppf)Cl_2$/phen	CH_3CN	63
8	$Mo(CO)_6$	$Pd(CH_3CN)_2Cl_2$/tmphen	CH_3CN	68
9	$Mo(CO)_6$	$Pd(CH_3CN)_2Cl_2$/phen	DMF	62
10	$Mo(CO)_6$	$Pd(CH_3CN)_2Cl_2$/ phen	DCE	72
11[b]	$Mo(CO)_6$	$Pd(CH_3CN)_2Cl_2$/ phen	DCE	65
12[c]	$Mo(CO)_6$	$Pd(CH_3CN)_2Cl_2$/ phen	DCE	54

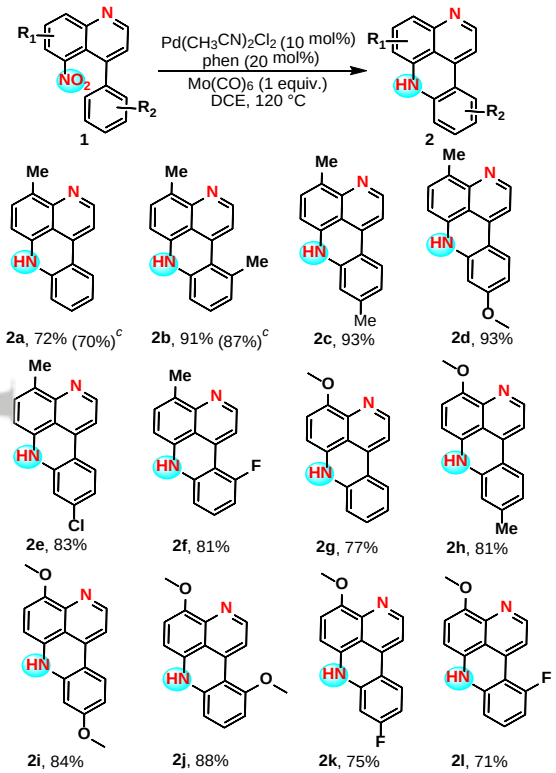
[a] Reaction conditions: 1a (0.1 mmol), Reductant (0.1 mmol), Pd catalyst (10 mol %), Ligand (20 mol %), solvent (2 mL), 120 °C, 3h; [b] The reaction was carried out at 140 °C; [c] 5 mol % $Pd(CH_3CN)_2Cl_2$, 10 mol % phen used; [d] isolated yield. phen = 1,10-phenanthroline, tmphen = 3,4,7,8-tetramethyl-1,10-phenanthroline, DCE = 1,2-dichloroethane, DMF = dimethyformamide.

In initial studies, the reductive cyclization of nitro phene-quinoline biarene **1a** was carried out in the presence of a catalytic amount of $Pd(OAc)_2$ and phenanthroline with phenyl formate as reductant in acetonitrile at 120°C for 3h. To our delight, the desired

pyrido[2,3,4-*kl*]acridine **2a** was furnished in 38% yield (Table 1, entry 1). To improve the yields, different reductants, palladium catalysts and ligands were tested as summarized in Table 1. It was found that $Mo(CO)_6$ was most suitable for this reaction and other CO-surrogates gave lower yields (Table 1, entries 2-4). All the commercially available palladium catalysts were active for this reaction and $Pd(CH_3CN)_2Cl_2$ afforded the best result (Table 1, entries 5-7). The ligand with bulky substituent was less detrimental than phenanthroline (Table 1, entry 8). Solvent screening was also conducted and DCE was optimal to other solvents. (Table 1, entries 9, 10). Increasing the reaction temperature to 140 °C or reducing the catalysts loading (5% mol palladium, 10% mol ligand) were proved to be negative for the conversion (Table 1, entries 11, 12).

This result motivated us to further investigate the substrate scope of this transformation. Gratifyingly, the desired pyrido[2,3,4-*kl*]acridine **2** were obtained in medium to good yields and the results are summarized in Table 2. A comparison of the substituents on phenyl ring showed that those substrates with electron donating substituents produced higher yields than electron withdrawing substituents, which could be ascribed to that electron deficient substrates were disfavored for this electrophilic reductive cyclization. To demonstrate the utility of this method, reactions of **1a** and **1b** on gram scale (4 mmol) were carried out and the products were afforded in reliable yield (Table 2, **2a** and **2b**).

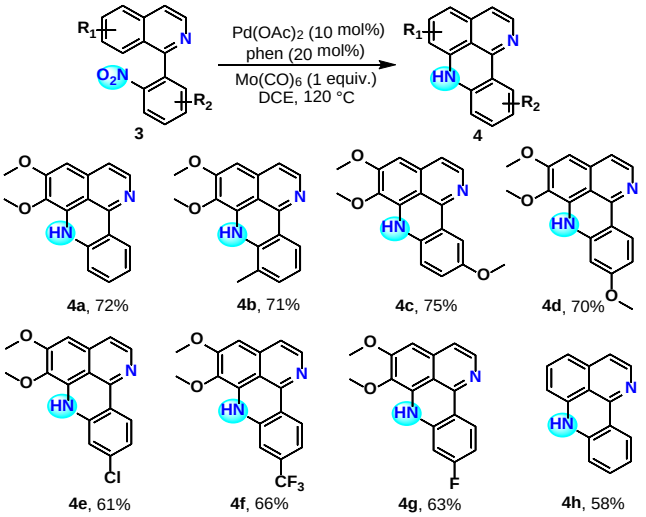
Table 2 Substrate scope of reductive cyclization with phene-quinoline *N*-biarene **1**[a, b]



[a] Reaction conditions: 1 (0.1 mmol), $Mo(CO)_6$ (0.1 mmol), $Pd(CH_3CN)_2Cl_2$, (10 mol %), Phen (20 mol %), DCE (2 mL), 120 °C, 3h. [b] isolated yield. [c] Reaction was carried out on scale of 4 M.

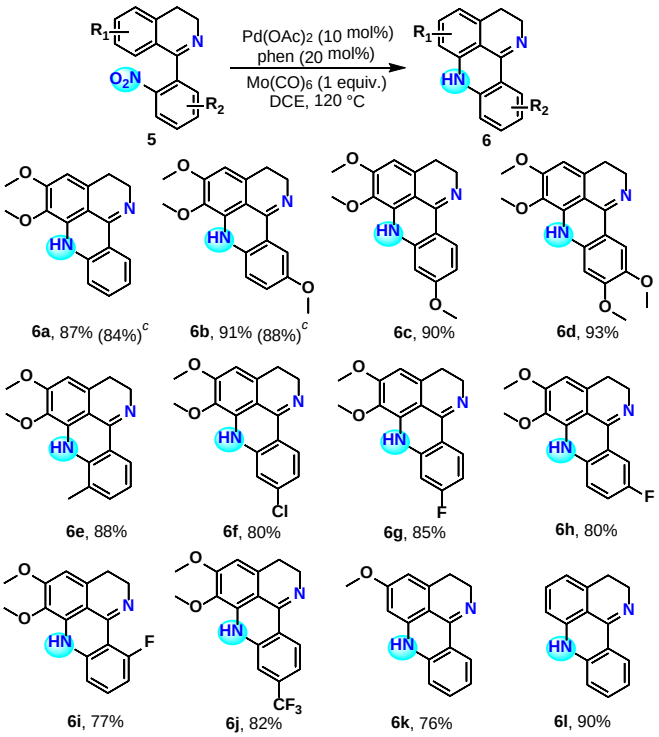
Next, the transformation from isoquinoline-derived *N*-biarene **3** to pyrido[4,3,2-*kl*]acridine **4** was further investigated. Different palladium sources, ligands and solvents were also screened and the combination of $Pd(OAc)_2$ and phenanthroline in DCE was proved to the optimal for this substrate (see Supporting information). The substrate scope investigation was also conducted and the results suggest that the substituents on phenyl ring has similar impact on the reaction efficiency as quinoline-derived substrates (Table 3). Moreover, it should be noted that the carbon-halogen bonds were tolerated under the optimal condition, which assures further functionalization through transition-metal catalyzed cross-coupling reactions.

Table 3 Substrate scope of reductive cyclization with phene-isoquinoline *N*-biarene **3**.[a, b]



[a] Reaction conditions: **3** (0.1 mmol), $Mo(CO)_6$ (0.1 mmol), $Pd(OAc)_2$ (10 mol %), Phen (20 mol %), DCE (2 mL), 120 °C, 3h; [b] isolated yield.

Table 4 Substrate scope of reductive cyclization with phene-dihydroisoquinoline *N*-biarene **5**.[a, b]



[a] Reaction conditions: **3** (0.1 mmol), $Mo(CO)_6$ (0.1 mmol), $Pd(OAc)_2$ (10 mol %), Phen (20 mol %), DCE (2 mL), 120 °C, 3h; [b] isolated yield. [c] Reaction was carried out on scale of 4 M.

To our surprise, when the nitro phene-dihydroisoquinoline *N*-biarene **5** was tested for this reaction, the desired tetracyclic aro-

matic product **6** was obtained (Table 4), and the yields were significantly higher than the products from isoquinoline derived *N*-biarene **3**. Reactions of **5a** and **5b** on large scale were also tested and the corresponding products were obtained in excellent yields. The different reactive activity for the two substrates was rationalized by density functional theory (DFT) calculations[12], and the distribution of Mulliken atomic charge[13] on carbon 8 of **5l** (-0.657) showed higher electronic density than on the corresponding carbon of **3h** (-0.488) (Figure. 2), which is favored for electrophilic cyclization process to form hydroxyl intermediate (**D** in Scheme 2). By analogy with the previously reported mechanism[10b, 11a] and our experimental observation, a tentative mechanism was proposed with compound **5l**: First, in the presenc of $Mo(CO)_6$ and phenanthroline, $Pd(OAc)_2$ converts to palladium CO complex **A**. Afterward, complex **A** reacts with the nitro-biarene **5l** through single-electron transfer and afforded radical anion **B**. Third, reduction of **B** provides the nitroso intermediate **C**, which plays the role of aminating species and affords the *N*-hydroxy tetracyclic heterocycle **D**. Finally, intermediate **D** was transformed into desired product **6l** in this reductive system (Scheme 2). To confirm this mechanism, nitroso *N*-biarene **5l'** was synthesized and subjected to the optimized conditions, and the expected product **6a** was obtained in 91 % yield (Scheme 3).

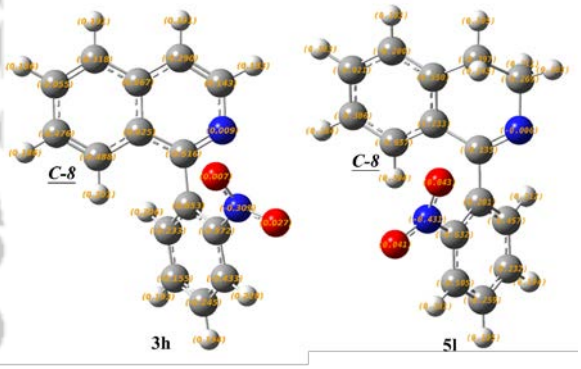
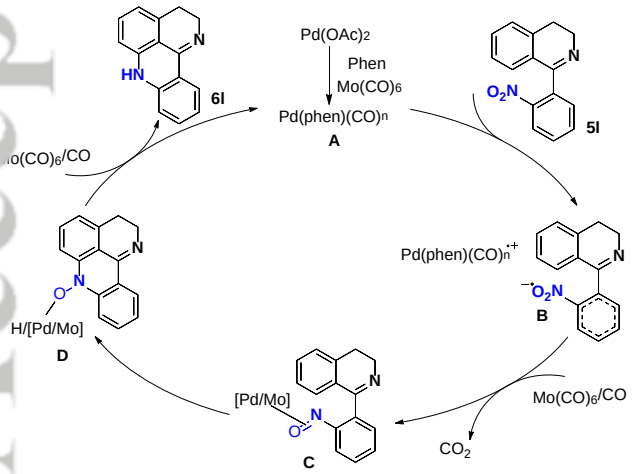
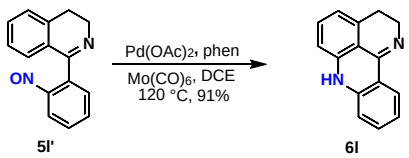


Figure. 2 Mulliken atomic charge distribution for **3h** and **5l.**

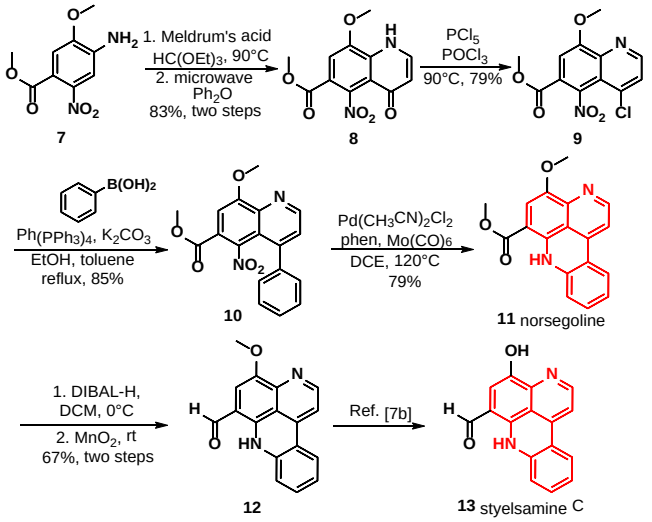


Scheme 2 Proposed reaction mechanism.

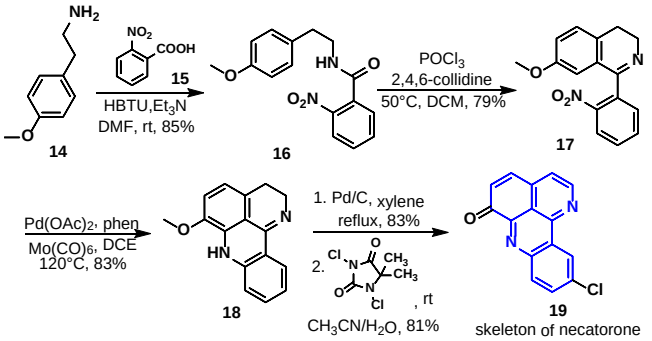


Scheme 3 Reductive cyclization of nitroso *N*-biarene **5l'**.

To further demonstrate the synthetic utility of this transformation, total synthesis of three natural products containing the two types of skeleton were investigated. Synthesis of natural alkaloid with pyrido[2,3,4-*kl*]acridine starting from nitrobenzoate **7**. The chloroquinoline **9** was prepared in a three-step procedure *via* Meldrum derivative and quinolinone **8** in 65% overall yield according to the literature.[14] Next, the cross-coupling reaction of **9** with phenylboronic acid gave the targeted phene-quinoline *N*-biarene **10** in 85% yield. Fortunately, the carboxyl group kept intact when **10** was subjected to the optimal condition and norsegoline **11** was successfully afforded in 79% yield. Moreover, after reduction of the ester group and the following oxidation, the known compound **12**[7b] was produced (Scheme 4). Thus, starting from commercially available nitrobenzoate **7**, we accomplished the total synthesis of norsegoline and formal synthesis of styelsamine C in five steps and seven steps, the overall yields were 44% and 29% respectively. Following the literature procedures, aldehyde **12** could be demethylated to give the styelsamine C in one step.[7b]



Scheme 4 Total synthesis of norsegoline and formal synthesis of styelsamine C



Scheme 5. Synthesis of necatorone skeleton.

The synthesis of natural product with pyrido[4,3,2-*kl*]acridine skeleton was also investigated. The amide **16** was first obtained from commercially available phenylethylamine derivative **14** and 2-nitrobenzoic acid **15** in 85% yield. Subsequent Bischler- Napieralski reaction afforded the dihydroisoquinoline *N*-biarene **17** in 79% yield. Next, the catalytic reductive cyclization of **17** successfully formed the new pyridine ring and the pyrido[4,3,2-*kl*]acridine product **18** was obtained in 83% yield. Finally, after aromatization and oxidation, the skeleton of necatorone[15] was acquired in five steps and 15% overall yield (Scheme 5).

Conclusions

In summary, we have developed a divergent and novel method to synthesize two types of pyridoacridine alkaloids through palladium-catalyzed reductive cyclization with $Mo(CO)_6$ as reductant. This transformation has a wide scope demonstrated by the preparation of total 34 analogues of both pyrido[2,3,4-*kl*]acridine and pyrido[4,3,2-*kl*]acridine skeletons. The potential of employing this method as a valuable synthetic tool to access polycyclic *N*-heterocycles is attractive and intriguing due to the versatility of *N*-heterocycle family in marine natural products, and we have demonstrated it by the accomplishment of total synthesis of norsegoline, styelsamine C and the necatorone skeleton.

Experimental

In a 10 mL Schlenk tube, *N*-biarene (1 mmol, 1 equiv), Pd catalyst (0.1 mmol, 10 mol%), 1,10-phenanthroline (0.2 mmol, 20 mol%) and $Mo(CO)_6$ (1 mmol, 1 equiv) was dissolved in DCE (2 ml) under nitrogen atmosphere. The solution was allowed to be heated at 120 °C for 3-12 hours. After complete conversion of starting material, the solvent was removed. Purification was achieved by column chromatography on silica gel using PE/EA as the eluent to give the corresponding pyridoacridine.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2021xxxxx.

Acknowledgement

This project is financially supported by National Key Research and Development Program of China (No. 2018YFC0310900), National Natural Science Foundation of China (No. 81903499, 21729002), Innovative Research Team of High-Level Local Universities in Shanghai (No. SSMU-ZLCX20180702).

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(The following will be filled in by the editorial staff)
Manuscript received: XXXX, 2021
Manuscript revised: XXXX, 2021
Manuscript accepted: XXXX, 2021
Accepted manuscript online: XXXX, 2021
Version of record online: XXXX, 2021

Entry for the Table of Contents

Divergent Syntheses of Pyridoacridine Alkaloids via Palladium-Catalyzed Reductive Cyclization with Nitro-Biarenes

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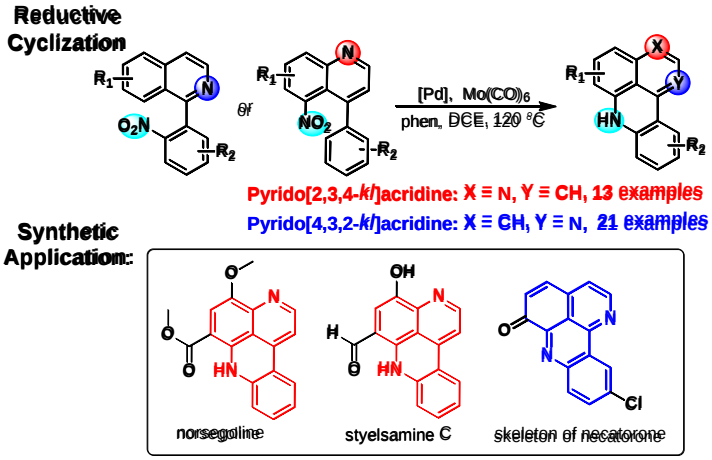
Chin. J. Chem. **2021**, *39*, XXX—XXX. **DOI: 10.1002/cjoc.202100XXX**



A divergent and efficient method for preparing pyrido[2,3,4-*kl*]acridine and pyrido[4,3,2-*kl*]acridine alkaloid is reported. This method featured a novel remote palladium-catalyzed reductive cyclization with $Mo(CO)_6$ as reductant by nitro biarenes, and a wide scope of substrates were tolerated and total 34 analogues containing the two types of polycyclic heteroaromatic skeleton were prepared. Furthermore, the potential synthetic application of this method was demonstrated by the accomplishment of synthesis of norsegoline, styelsamine C and the necatorone skeleton.