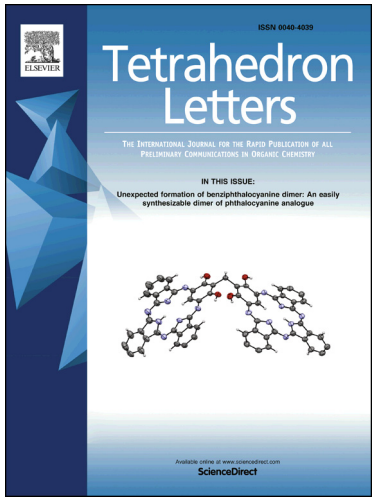


# One-Pot Synthesis of 6H-2,2a[1],3-triazaaceanthrylen-6-ones and 6H-2,2a[1],4-triazaaceanthrylen-6-ones via Tandem Cyclization Strategies

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## *Graphical Abstract*

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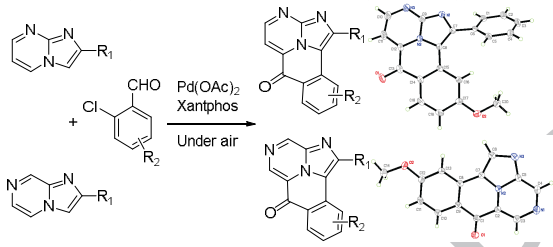

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# One-Pot Synthesis of 6H-2,2a[1],3-triazaaceanthrylen-6-ones and 6H-2,2a[1],4-triazaaceanthrylen-6-ones via Tandem Cyclization Strategies

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ABSTRACT

Two operationally simple one-pot protocols have been developed for the synthesis of 6H-2,2a[1],3-triazaaceanthrylen-6-ones and 6H-2,2a[1],4-triazaaceanthrylen-6-ones. The first Pd-catalyzed tandem cyclization of imidazo[1,2-a]pyrimidines/imidazo[1,2-a]pyrazines with 2-chlorobenzaldehydes could proceed in aqueous medium under air, affording the desired products in moderate to good yields. The molecular structures of products **3i** and **5b** were confirmed by X-ray crystallographic analysis.

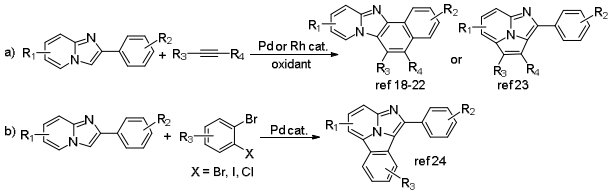


## Introduction

Fused heterocyclic compounds with a bridgehead nitrogen atom usually not only possess biological activity but also serve as a backbone for marketed drugs and functional materials.[1-3] Accordingly, the highly efficient construction of structurally diverse *N*-heteropolycyclic scaffolds from readily available chemical feedstocks is an important and ongoing research area in the development of potent bioactive molecules and efficient electronic materials.[4-6] In recent years, transition-metal-catalyzed tandem cyclization has emerged as a powerful tool for the assembly of highly functionalized polycyclic systems.[7-10] The cyclization not only enables the creation of molecular complexity and diversity but also reduces the reaction steps and waste production. In particular, palladium-catalyzed cascade annulation reaction has proven to be much efficient method to construct polycyclic products due to its ability to form multiple carbon-carbon/carbon-heteroatom bonds in one step, high chemo-, regio- and stereoselectivity, and great functional-group tolerance.[11-13]

Imidazole rings[14] and diaryl ketones[15-17] are also versatile building blocks in organic synthesis with numerous applications in natural products, pharmaceuticals, agrochemicals, and functional materials. Therefore, the synthesis of imidazo fused heterocycles containing aryl ketone structural motif for potential applications of pharmaceuticals and optoelectronic materials is highly desirable. Recently, the synthesis of imidazo[1,2-a]pyridine fused heterocycles have been extensively investigated by the palladium- and rhodium-catalyzed dehydrogenative annulation of imidazo[1,2-a]pyridines with alkynes[18-23] or *o*-dihaloarenes[24] (Scheme 1). Moreover, the direct acylation of unsaturated hydrocarbons with aldehydes by means of transition-metal-mediated aldehyde C-H activation is an atom-efficient synthetic approach to ketones.[25-27] Building on these strategies, we speculated that the Pd-catalyzed dehydrogenative annulation of imidazo fused heterocycles with 2-chlorobenzaldehydes would provide *N*-heteropolycyclic scaffolds containing aryl ketone structural motif.

**Scheme 1.** Dehydrogenative annulation strategies for imidazo[1,2-a]pyridine fused heterocycles




Very recently, we disclosed Pd-catalyzed tandem cyclization of imidazo[1,2-a]pyridines with 2-chlorobenzaldehydes through C-H arylation and acylation for the preparation of 6H-benzo[b]imidazo[5,1,2-de]quinolizin-6-ones (Scheme 2a).[28] Meanwhile, the Pd-catalyzed acylation of unsaturated hydrocarbons with aldehydes by C-H bond activation without the

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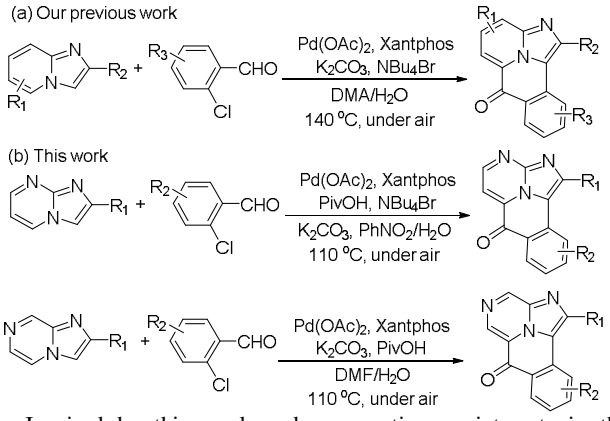
aid of directing groups in the presence of air as the terminal oxidant was developed by us. Furthermore, we inferred that bridgehead nitrogen atom of imidazo[1,2-a]pyridines was necessary for the intramolecular C-H acylation/cyclization. To test our hypothesis, we investigated the Pd-catalyzed tandem annulation of imidazo[1,2-a]pyrimidine/imidazo[1,2-a]pyrazine containing bridgehead nitrogen atom with 2-chlorobenzaldehyde under the known dehydrogenative annulation conditions.[28] Contrary to this initial intention, the corresponding products were not detected by LC-MS analysis.

**Scheme 2.** Dehydrogenative annulation strategies for imidazole fused heterocycles containing aryl ketone structural motif.

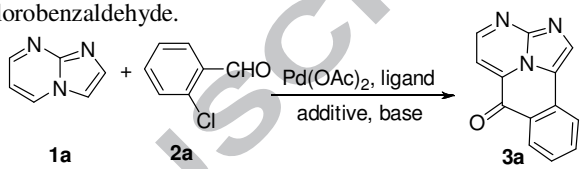



Inspired by this work and our continuous interests in the construction of diverse polycyclic scaffolds, herein we attempt to develop practical methods for the synthesis of 6H-2,2a[1],3-triazaaceanthrylen-6-ones and 6H-2,2a[1],4-triazaaceanthrylen-6-ones via the Pd-catalyzed tandem annulation reactions of imidazo[1,2-a]pyrimidines/imidazo[1,2-a]pyrazines with 2-chlorobenzaldehydes in aqueous medium under air (Scheme 2b). To the best of our knowledge, this work represents the first reported example of the synthesis of 6H-2,2a[1],3-triazaaceanthrylen-6-ones and 6H-2,2a[1],4-triazaaceanthrylen-6-ones via tandem cyclizations in one step.

## Results and Discussion

We began our study by exploring the reaction of imidazo[1,2-a]pyrimidine **1a** with 2-chlorobenzaldehyde **2a** to screen the reaction conditions, and the results are summarized in Table 1. First, the model reaction was performed in the presence of 5 mol % of $Pd(OAc)_2$, 10 mol % of Xantphos, 0.3 mmol of $NBu_4Br$ and 0.9 mmol of $K_2CO_3$ in 3 mL of DMA/$H_2O$ under air at 110 °C for 24 h, and only 9% LC yield was observed (entry 1). To our delight, the yield significantly changed with the addition of PivOH to the catalytic system, and the desired product was obtained in 45% yield (entry 2). However, lower yields were obtained by increasing the amount of $H_2O$ to 60 uL or decreasing the amount of 2-chlorobenzaldehyde to 2.0 equiv (entries 3 and 4). Then, the effects of different solvents were tested, and $PhNO_2$ (3 mL) with $H_2O$ (30 uL) as the solvent was shown to be the most effective for this reaction (entries 5-9). When the reaction was carried out in the absence of $NBu_4Br$ or PivOH, the yield drastically decreased to 8% and 31%, respectively (entries 10 and 11). Moreover, the amounts of 2-chlorobenzaldehyde and $K_2CO_3$ were also essential to the reaction (entries 12 and 13). Subsequently, other bases such as $Na_2CO_3$, $K_3PO_4$ and $Cs_2CO_3$ were also investigated, but they could only give lower yields (entries 14-16). Finally, the replacement of Xantphos with S-Phos, $PBu_3{\cdot}HBF_4$ and $BuAd_2P$ led to a drop in yields (entries 17-19). When the reaction was carried out under an Ar atmosphere without the addition of oxidant to the catalytic system, the product was obtained in the relatively lower yield of 72% (entry 20). Although the detailed reaction mechanism is not definite at this stage, on the basis of previous literature reports,[28, 29] we inferred that under an Ar atmosphere the cyclization reaction of imidazo[1,2-a]pyrimidine with 2-chlorobenzaldehyde could proceed via Pd-catalyzed C-H arylation, followed by a Friedel-Crafts type reaction, and final cyclization.

**Table 1.** Effect of reaction conditions on the tandem annulation of imidazo[1,2-a]pyrimidine with 2-chlorobenzaldehyde.




**1a** **2a** **3a**

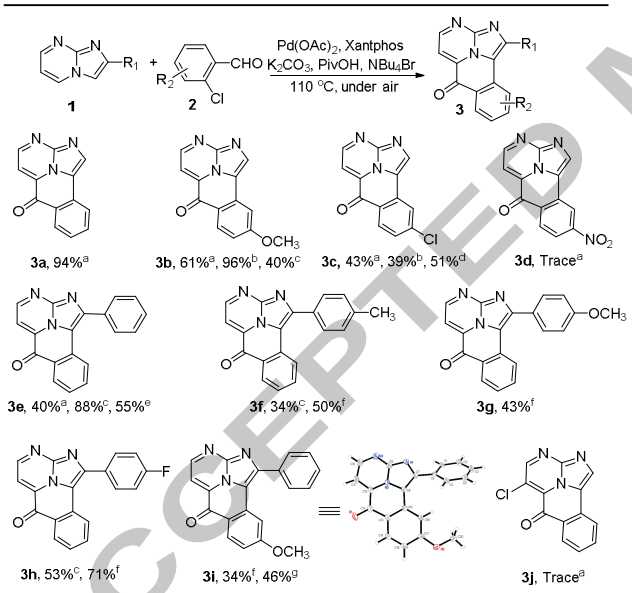
| Entry[a] | Ligand | Additive | Base | Solvent | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | Xantphos | $NBu_4Br$ | $K_2CO_3$ | DMA/$H_2O$ | 9 |
| 2 | Xantphos | $NBu_4Br$/PivOH | $K_2CO_3$ | DMA/$H_2O$ | 45 |
| 3[c] | Xantphos | $NBu_4Br$/PivOH | $K_2CO_3$ | DMA/$H_2O$ | 28 |
| 4[d] | Xantphos | $NBu_4Br$/PivOH | $K_2CO_3$ | DMA/$H_2O$ | 21 |
| 5 | Xantphos | $NBu_4Br$/PivOH | $K_2CO_3$ | $PhCOCH_3/H_2O$ | NR |
| 6 | Xantphos | $NBu_4Br$/PivOH | $K_2CO_3$ | DMF/$H_2O$ | 77 |
| 7 | Xantphos | $NBu_4Br$/PivOH | $K_2CO_3$ | $PhNO_2/H_2O$ | 99 |
| 8 | Xantphos | $NBu_4Br$/PivOH | $K_2CO_3$ | $PhNO_2$ | 18 |
| 9[e] | Xantphos | $NBu_4Br$/PivOH | $K_2CO_3$ | $PhNO_2/H_2O$ | 75 |
| 10 | Xantphos | PivOH | $K_2CO_3$ | $PhNO_2/H_2O$ | 8 |
| 11 | Xantphos | $NBu_4Br$ | $K_2CO_3$ | $PhNO_2/H_2O$ | 31 |
| 12[e] | Xantphos | $NBu_4Br$/PivOH | $K_2CO_3$ | $PhNO_2/H_2O$ | 67 |
| 13[f] | Xantphos | $NBu_4Br$/PivOH | $K_2CO_3$ | $PhNO_2/H_2O$ | 15 |
| 14 | Xantphos | $NBu_4Br$/PivOH | $Na_2CO_3$ | $PhNO_2/H_2O$ | NR |
| 15 | Xantphos | $NBu_4Br$/PivOH | $K_3PO_4$ | $PhNO_2/H_2O$ | 27 |
| 16 | Xantphos | $NBu_4Br$/PivOH | $Cs_2CO_3$ | $PhNO_2/H_2O$ | 46 |
| 17 | S-Phos | $NBu_4Br$/PivOH | $K_2CO_3$ | $PhNO_2/H_2O$ | 37 |
| 18 | $PBu_3{\cdot}HBF_4$ | $NBu_4Br$/PivOH | $K_2CO_3$ | $PhNO_2/H_2O$ | NR |
| 19 | $BuAd_2P$ | $NBu_4Br$/PivOH | $K_2CO_3$ | $PhNO_2/H_2O$ | 48 |
| 20[g] | Xantphos | $NBu_4Br$/PivOH | $K_2CO_3$ | $PhNO_2/H_2O$ | 72 |

[a] Reaction conditions: 0.3 mmol of imidazo[1,2-a]pyrimidine, 0.9 mmol of 2-chlorobenzaldehyde, 5 mol % of $Pd(OAc)_2$, 10 mol % of ligand, 0.9 mmol of base, 0.3 mmol of $NBu_4Br$, 30 mol% of PivOH, 3 mL of organic solvent and 30 uL of $H_2O$ under air at 110 °C for 24 h. [b] HPLC yields.
[c] 60 uL of $H_2O$. [d] 0.6 mmol of 2-chlorobenzaldehyde. [e] 0.45 mmol of 2-chlorobenzaldehyde. [f] 0.6 mmol of $K_2CO_3$. [g] under an Ar atmosphere.

With the optimized catalytic system in hand, we next investigated the generality of this reaction (Scheme 3). The scope of 2-chlorobenzaldehydes **2** was first studied using imidazo[1,2-a]pyrimidine **1a** as the reaction partner. For 2-chlorobenzaldehyde, product **3a** was isolated in 94% yield under the standard conditions. When 2-chloro-4-methoxybenzaldehyde was employed in the annulation reaction, the product **3b** was obtained in 96% yield by prolonging the reaction time to 48 h. When the annulation of 2,4-dichlorobenzaldehyde with imidazo[1,2-a]pyrimidine was performed at a higher temperature of 130 °C, the yield increased to 51% (product **3c**). In addition, 2-chloro-4-nitrobenzaldehyde was also checked, but only a trace

amount of the product **3d** was detected by LC-MS analysis. The results reveal that 2-chlorobenzaldehydes bearing strong electron-withdrawing groups display lower reactivity for this transformation. We next investigated the scope of imidazo[1,2-a]pyrimidines **1** using 2-chlorobenzaldehyde **2a** as the reaction partner. When the annulation of 2-phenylimidazo[1,2-a]pyrimidine with **2a** was performed in the presence of 4 equiv of $K_2CO_3$ for 24 h, the yield could be improved to 88% (product **3e**). But for 5 equiv of $K_2CO_3$, the product **3e** was obtained in 55% yield. In the presence of 4 equiv of $K_2CO_3$ for 48 h, 2-aryl group substituted imidazo[1,2-a]pyrimidines such as 2-(*p*-tolyl)imidazo[1,2-a]pyrimidine, 2-(4-methoxyphenyl)imidazo[1,2-a]pyrimidine and 2-(4-fluorophenyl)imidazo[1,2-a]pyrimidine were also found to be suitable coupling partners, and the corresponding products **3f-h** were isolated in 50%, 43%, and 71% yields, respectively. The annulation of 2-phenylimidazo[1,2-a]pyrimidine with 2-chloro-4-methoxybenzaldehyde could afford the desired product in 46% yield by the extra addition of 0.3 mmol of 2-chloro-4-methoxybenzaldehyde after 24 h (product **3i**). Furthermore, the structure of product **3i** was unambiguously determined by X-ray crystallographic analysis (see Supporting Information). However, the reaction using 6-chloroimidazo[1,2-a]pyrimidine only gave a trace amount of product **3j** by LC-MS analysis.

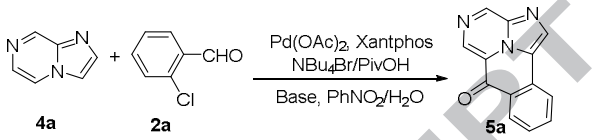
**Scheme 3.** Dehydrogenative annulation of imidazo[1,2-a]pyrimidines with 2-chlorobenzaldehydes.




[a] Reaction conditions: 0.3 mmol of imidazo[1,2-a]pyrimidines, 0.9 mmol of 2-chlorobenzaldehydes, 5 mol % of $Pd(OAc)_2$, 10 mol % of Xantphos, 0.9 mmol of $K_2CO_3$, 0.3 mmol of $NBu_4Br$, 30 mol% of PivOH, 3 mL of $PhNO_2$ and 30 uL of $H_2O$ under air at 110 °C for 24 h. Isolated yields. [b] 48 h. [c] 1.2 mmol of $K_2CO_3$. [d] at 130 °C. [e] 1.5 mmol of $K_2CO_3$. [f] 1.2 mmol of $K_2CO_3$, 48 h. [g] 1.2 mmol of $K_2CO_3$, 48 h. After 24 h, an additional 0.3 mmol of 2-chloro-4-methoxybenzaldehyde was added to the reaction system.

After investigating the scope of imidazo[1,2-a]pyrimidines, we turned our attention to the applicability of imidazo[1,2-a]pyrazines for this transformation. Under the standard conditions, imidazo[1,2-a]pyrazine with 2-chlorobenzaldehyde were also employed in the annulation reaction to give the product **5a** in 36% yield (Table 2, entry 1). To improve the yield, we explored the effect of different reaction parameters on the annulation which included temperature, bases, the amount of $Pd(OAc)_2$ and $K_2CO_3$, and oxidant. The results are summarized in Table 2. Unfortunately, the transformations did not result in dramatically improved tandem annulations in $PhNO_2/H_2O$.

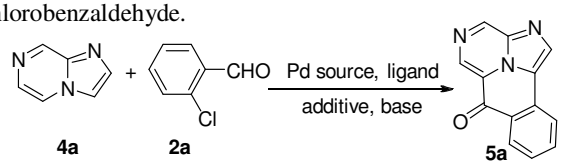
**Table 2.** Optimization of the reaction conditions.




| Entry[a] | $Pd(OAc)_2$ (mol %) | Xantphos (mol %) | Base (mmol) | Temp (°C) | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | 5 | 10 | $K_2CO_3$(0.9) | 110 | 36 |
| 2 | 5 | 10 | $K_2CO_3$(0.9) | 140 | 37 |
| 3 | 5 | 10 | $K_2CO_3$(1.2) | 110 | 34 |
| 4 | 5 | 10 | $Cs_2CO_3$(0.9) | 110 | Trace |
| 5 | 5 | 10 | $Na_2CO_3$(0.9) | 110 | Trace |
| 6[c] | 5 | 10 | $K_2CO_3$(0.9) | 110 | NR |
| 7 | 7.5 | 15 | $K_2CO_3$(0.9) | 110 | 40 |
| 8 | 7.5 | 15 | $K_2CO_3$(0.6) | 110 | 40 |

[a] Reaction conditions: imidazo[1,2-a]pyrazine (0.3 mmol), 2-chlorobenzaldehyde (0.9 mmol), $Pd(OAc)_2$ (quantity noted), Xantphos (quantity noted), base (quantity noted), $NBu_4Br$ (0.3 mmol), PivOH (30 mol%), $PhNO_2$ (3 mL) and $H_2O$ (30 uL) under air at 110 °C for 24 h.
[b] HPLC yields.
[c] under an $O_2$ atmosphere.

**Table 3.** Optimization for the palladium-catalyzed tandem annulation of imidazo[1,2-a]pyrazine with 2-chlorobenzaldehyde.




| Entry[a] | Pd catalyst (mol %) | Ligand (mol %) | Base (mmol) | Yield (%)[b] |
|---|---|---|---|---|
| 1 | $Pd(OAc)_2$(5) | Xantphos(10) | $K_2CO_3$(0.6) | 41 |
| 2[c] | $Pd(OAc)_2$(5) | Xantphos(10) | $K_2CO_3$(0.6) | 28 |
| 3 | $Pd(OAc)_2$(5) | Xantphos(10) | $Cs_2CO_3$(0.6) | Trace |
| 4 | $Pd(OAc)_2$(5) | Xantphos(10) | $K_3PO_4$(0.6) | 6 |
| 5 | $Pd(OAc)_2$(5) | Xantphos(10) | $K_2CO_3$(0.45) | 9 |
| 6 | $PdCl_2$(5) | Xantphos(10) | $K_2CO_3$(0.6) | 11 |
| 7 | $Pd(acac)_2$(5) | Xantphos(10) | $K_2CO_3$(0.6) | NR |
| 8 | $Pd(TFA)_2$(5) | Xantphos(10) | $K_2CO_3$(0.6) | 9 |
| 9 | $PdCl_2(COD)_2$(5) | Xantphos(10) | $K_2CO_3$(0.6) | Trace |
| 10 | $Pd(dba)_2$(5) | Xantphos(10) | $K_2CO_3$(0.6) | NR |
| 11[d] | $Pd(OAc)_2$(5) | Xantphos(10) | $K_2CO_3$(0.6) | 33 |
| 12 | $Pd(OAc)_2$(7.5) | Xantphos(15) | $K_2CO_3$(0.6) | 67 |
| 13[e] | $Pd(OAc)_2$(7.5) | Xantphos(15) | $K_2CO_3$(0.6) | 21 |
| 14[f] | $Pd(OAc)_2$(7.5) | Xantphos(15) | $K_2CO_3$(0.6) | 60 |
| 15[g] | $Pd(OAc)_2$(7.5) | Xantphos(15) | $K_2CO_3$(0.6) | 7 |
| 16[h] | $Pd(OAc)_2$(7.5) | Xantphos(15) | $K_2CO_3$(0.6) | 42 |
| 17 | $Pd(OAc)_2$(10) | Xantphos(20) | $K_2CO_3$(0.6) | 59 |
| 18[i] | $Pd(OAc)_2$(7.5) | Xantphos(15) | $K_2CO_3$(0.6) | Trace |
| 19 | $Pd(OAc)_2$(7.5) | Xantphos(15) | $K_2CO_3$(0.9) | 77 |

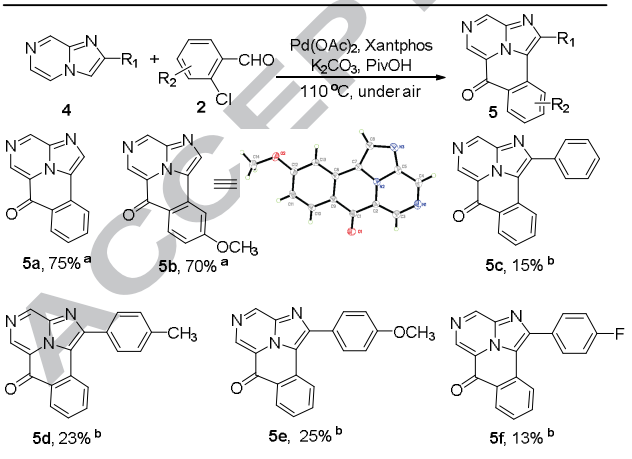
[a] Reaction conditions: imidazo[1,2-a]pyrazine (0.3 mmol), 2-chlorobenzaldehyde (0.33 mmol), Pd catalyst (quantity noted), Xantphos (quantity noted), base (quantity noted), PivOH (30 mol%), DMF (3 mL) and $H_2O$ (30 uL) under air at 110 °C for 24 h.
[b] HPLC yields. [c] 0.6 mmol of 2-chlorobenzaldehyde.

[d] at 100 °C. [e] 0.1 mL of $H_2O$. [f] $H_2O$ was excluded.
[g] PivOH was excluded. [h] 0.15 mmol of $NBu_4Br$. [i] under an Ar atmosphere.

Subsequently, the reaction conditions were further optimized in DMF/$H_2O$ (Table 3). Other bases and palladium sources were also checked, but they did not afford the desired product in higher yields (entries 1-10). When the reaction was conducted at 100 °C, the desired coupling product was obtained in a lower yield of 33% (entry 11). The suitable amount of $H_2O$ and PivOH were found to be particularly beneficial for this reaction (entries 13-15). However, when the traditional surfactant $NBu_4Br$ was added, the relatively lower yield of 42% was obtained (entry 16). To our delight, changing the amount of $Pd(OAc)_2$ to 7.5 mol% and $K_2CO_3$ to 3 equiv could afford the corresponding product in a yield of up to 77% (entry 19). In addition, only a trace amount of product **5a** was observed under an argon atmosphere (entry 18), thus suggesting that air as the oxidant is essential for Pd-catalyzed C-H acylation/cyclization of imidazo[1,2-a]pyrazines with 2-chlorobenzaldehydes, as proposed by us.[28]

With the optimized catalytic system in hand, we next explored the scope of imidazo[1,2-a]pyrazines and 2-chlorobenzaldehydes (Scheme 4). As expected, 2-chlorobenzaldehyde or 2-chloro-4-methoxybenzaldehyde could be efficiently coupled with imidazo[1,2-a]pyrazine, and the corresponding products **5a** and **5b** were isolated in 75% and 70%, respectively. The molecular structure of **5b** was confirmed by single-crystal X-ray diffraction analysis (see Supporting Information). However, when phenyl, *p*-tolyl, 4-methoxyphenyl and 4-fluorophenyl substituted imidazo[1,2-a]pyrazines at position C2 were checked, the corresponding products **5c-f** were obtained in low isolated yields of 13-25% along with large amounts of imidazo[1,2-a]pyrazines, small amounts of the arylation product and the homocoupling product of imidazo[1,2-a]pyrazines detected by LC-MS analysis. However, when an additional 0.3 mmol of 2-chlorobenzaldehyde was added to the reaction system after 24 h, and the yields were not improved. So we deduced that the steric effect of C2 substituted group could have influence on the annulations.

**Scheme 4.** Dehydrogenative annulation of imidazo[1,2-a]pyrazines with 2-chlorobenzaldehydes.




[a] Reaction conditions: imidazo[1,2-a]pyrazines (0.3 mmol), 2-chlorobenzaldehydes (0.33 mmol), $Pd(OAc)_2$ (7.5 mol %), Xantphos (15 mol %), $K_2CO_3$ (0.9 mmol), PivOH (30 mol%), DMF (3 mL) and $H_2O$ (30 uL) under air at 110 °C for 24 h. Isolated yields.
[b] 1.2 mmol of $K_2CO_3$, 48 h.

## Conclusion

In summary, we first demonstrated the Pd-catalyzed tandem dehydrogenative annulation of imidazo[1,2-a]pyrimidines/imidazo[1,2-a]pyrazines with 2-chlorobenzaldehydes in aqueous medium under air for the synthesis of novel polycyclic 6H-2,2a[1],3-triazaaceanthrylen-6-ones and 6H-2,2a[1],4-triazaaceanthrylen-6-ones. This reaction represents a convenient methodology for the one-pot synthesis of imidazo fused heterocycles containing aryl ketone structural motif from simple and readily available starting materials under mild conditions. Furthermore, the molecular structures of products **3i** and **5b** were confirmed by single-crystal X-ray diffraction analysis. Studies are ongoing to gain further insights into the mechanism of this reaction, and to expand the scope and application of the present methodology.

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## Highlights

1. The synthesis of 6H-2,2a$^1$,3-triazaaceanthrylen-6-ones and 6H-2,2a$^1$,4-triazaaceanthrylen-6-ones.

2. Pd-catalyzed tandem cyclization of imidazo[1,2-a]pyrimidines/imidazo[1,2-a]pyrazines with 2-chlorobenzaldehydes.

3. Two operationally simple one-pot protocols in aqueous medium under air.