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COMMUNICATION

$FeCl_3$-promoted ring size-dictating diversity-oriented synthesis (DOS) of *N*-heterocycles using *in situ*-generated cyclic imines and enamines

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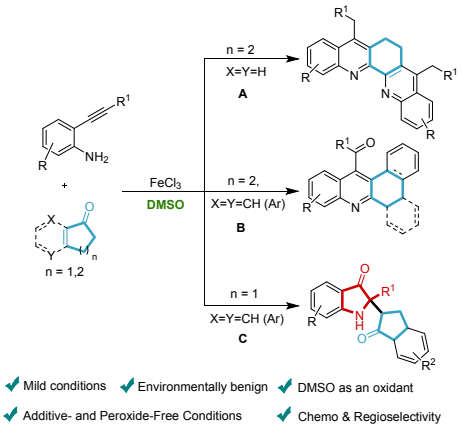
The $FeCl_3$-promoted ring size-controlled oxidative activation of *o*-alkynylanilines open a complementary appealing protocol for poly-*N*-heterocycle synthesis. When electron-poor π-alkyne iron species meet cyclic enamines endowed from cyclohexanone and β-tetralone, they undergo a regioselective 6-*exo*-dig cyclization to afford the corresponding dibenzo[*b,j*][1,10]phenanthrolines and 12-benzoylated dihydrobenzo[*a*]acridine skeletons. Later, these acridine motifs become completely unsaturated by exercising dehydrogenative aromatization *via* the *aza*-allyl oxidation intermediate. We realized all quaternary carbon centre pseudoindoxyls through the Mannich-type alkylation of 2,3-dihydro-1*H*-inden-1-one with cyclic ketimines generated from the *in situ* intramolecular nucleophilic cyclization of *o*-alkynylanilines.

1,10-Phenanthrolines are crescent-shaped polyheterocyclic compounds embedded with two nitrogens in a distinctive position that play a pivotal role in its ligand family.[1] Its specific characteristics, such as planarity, extended aromaticity, and strong metal binding affinity give this molecule a wide range of applications in catalysis, materials applications and pharmacology.[2] In particular, dibenzo[1,10]phenanthrolines functionalized at the para position to the nitrogen atoms act as a murine leukaemia cell therapeutic agent,[3a] an emerging photosensitizer in the reduction of water to generate hydrogen,[3b] an improved chemosensor in environmental and biological systems[3c] and a key building block in electron transport and OLED materials synthesis.[3d,e] Although dibenzo[1,10]phenanthroline has predominant usage in science, the synthetic method to achieve this core molecule is often limited due to the reduced availability of the substrate and complicated reaction procedure.[4] Thus, developing a general and conventional method to construct these core molecules has a tangible impact in both academia and industry. The selective oxidative dehydrogenation of



Scheme 1. Chemodivergent synthesis of aza-heterocycles

cyclohexanones is an evolving research area to manifold heterocyclic synthesis.[5] Applying this method, Jiao's group reported an elegant method to achieve synthetically robust substituted catechols using DMSO as a solvent and an oxidant.[6a] Inspired by this work, Pan et al disclosed an iodine-catalysed synthesis of *N,N'*-diaryl-*o*-phenylenediamines using cross-dehydrogenative aromatization between cyclohexanone and anilines.[6b] In the same year, Deng et al developed a complementary approach to synthesize *o*-diarylamines exploiting elemental sulfur-promoted aerobic oxidative dehydrogenation/cross-coupling reactions.[6c] All of the above-mentioned methods demonstrate cascade inter-/intra-molecular coupling and complete aromatization of cyclohexanone (6π electrons). However, the development of regioselective controlled oxidation (only 4π electrons) and annulation reaction sequences to synthesize polyheterocylcles is an unattained challenge. In continuation of our research work on sustainable synthetic method development,[7] herein, we developed the first selective 4-carbon oxidation of the

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cyclohexanone reaction cascade to synthesize the synthetically valuable dibenzo[*b,j*][1,10]phenanthroline scaffold (Scheme 1A). In advance, these two unoxidized methylene carbons present in the phenanthroline ring act as chemical handles for further product diversification.

Pseudo-indoxyl derivatives are privileged nuclei encountered in a myriad of natural products and pharmaceutically active small molecule drugs, such as duocarmycins, (-)-isatisine A, hinckdentine A and Lipid Green.[8] These core molecules are expedient precursors in the area of semiconductor design[9] and fluorescence probe assembly.[10] The common method for the synthesis of C2 quaternary 3-oxyindolines is the direct functionalization of 3*H*-indol-3-ones, indolin-3-ones and indoles involving alkylation, allylation, and arylation reactions by using both metal and metal-free conditions.[11] However, the indole's preferred pathway to undergo homo dimerization reactions enormously hampers these direct transformation strategies.[11c] An alternative predominant approach involves the *in situ* generation of 3*H*-indol-3-ones or indolin-3-ones using the intramolecular cyclization of an alkyne, followed by the tandem addition of a nucleophile or radical source at the C2 position of the indole motif.[12] This direct synthetic system is a more efficient and sustainable method to synthesize indoxyl motif compared with formyl methods. Thus, we developed a method that generated *in situ* the α-aryl cyclic ketimines explored in a Mannich-type alkylation reaction with five-membered cyclic ketones to afford the 2-(inden-2-yl)-3-oxo-indoline derivatives (Scheme 1C). To the best of our knowledge, this is the first report of an intermolecular enol nucleophilic attack upon the *in situ*-generated 3*H*-indol-3-ones from *o*-alkynylanilines.

After careful optimization studies (see supporting information Table S1), we realize that our standard reaction conditions for the intermolecular oxidative cyclization have proved successfully by synthesizing a variety of different dibenzo[*b,j*][1,10]phenanthroline frameworks containing a broad range of functional groups (Table 1). Initially, the electron deficient and electron rich *o*-alkynylanilines (**1a-1c**) were tested under our title reaction conditions, which yielded the desired products with moderate to good yields (55-90%) (Table 1, **3aa-3ca**). The substrates bearing an R^1-group, such as *m*-F (**1d**), *m*-CF_3 (**1e**), *m*-Me (**1f**), *p*-Cl (**1g**), *p*-CF_3 (**1h**), *p*-COMe (**1i**) and *p*-Me (**1j**), were invariably transformed to the corresponding dibenzo[*b,j*][1,10]phenanthroline scaffold in 48-84% yields (Table 1, **3da-3ja**). Remarkably, the electron-poor alkyne motif **1k** resulted in a higher yield (90%) than the electron-rich *o*-alkynylanilines.

When we introduced benzo-fused cyclohexanone in our regular reaction conditions, we did not observe any dibenzo phenanthroline scaffold. To our pleasure, we isolated a carbonyl group decorated with a benzoacridine system (Scheme 1B). These carbonylated/acylated acridine scaffolds are ubiquitous to the *N*-heterocyclic rings present in valuable natural products and bioactive molecules.[13] This kind of acridine scaffold synthesis generally requires a multi-step operation.[14] Therefore, we developed a single step protocol, employing Lewis acid-promoted aerobic dehydrogenative aromatization of *o*-alkynylanilines with β-tetralones to synthesize the benzoyl group tethered to the benzo[*a*]acridines. Next, we explored the efficiency of our aerobic dehydrogenative aromatization reaction with a variety of electronically different anilines (Table 2). Both electron-rich and electron-deficient *o*-alkynylanilines underwent a smooth

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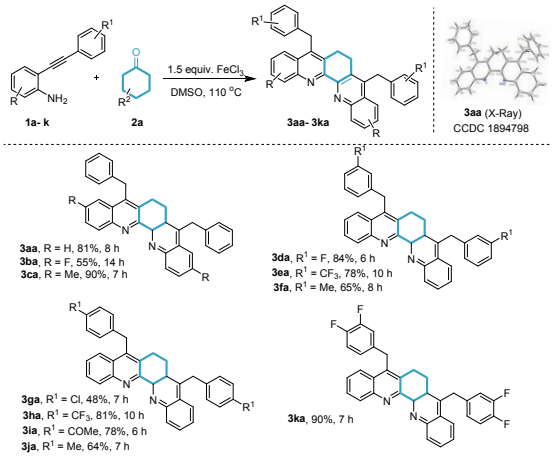
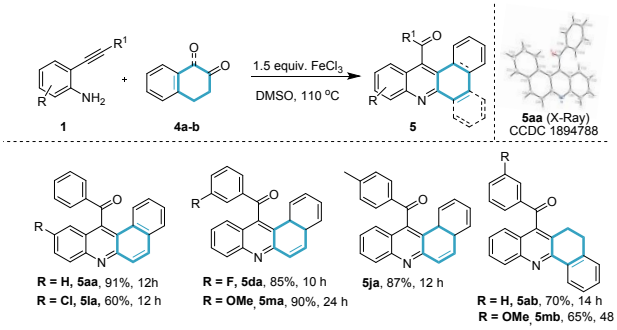
Table 1. Reaction scope for the formation of dibenzo[*b,j*][1,10]phenanthrolines [a,b]



[a] Reaction conditions: Compound **1a-1k** (1.05 mmol), **2a** (0.5 mmol), $FeCl_3$ (0.75 mmol) and DMSO (1 mL) at 110 °C for the indicated time unless otherwise noted. [b] Isolated yields.

dehydrogenative annulation reaction to afford the corresponding benzoylated acridines (Table 2, **5aa**, **5la 5da**, **5ma, 5ja**) in 60–91% yield. When we examined the reaction with α-tetralone, we concluded that our reaction conditions were not compatible with this discrete reaction. However, we isolated the benzylic carbon oxidized products **5ab** and **5mb** with moderate yield (65-70%). These results confirmed the participation of the *aza*-allyl oxidation intermediate (Scheme 3) in the dehydrogenative aromatization of the cyclohexanone ring residue. Because the cyclized intermediate (**5ab'**) of α-tetralone has restricted isomerization and cannot produce an *exo*-methylene double bond that would eventually undergo aza-allyl oxidation, the ring was not aromatized.

Table 2. Reaction scope for the formation of benzoylated acridines [a,b]

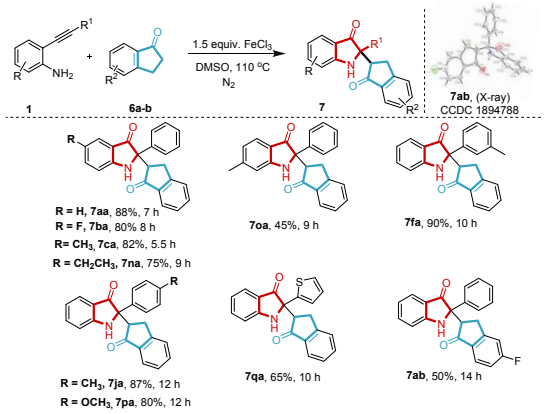


[a] Reaction conditions: Compound **1** (0.5 mmol), **4a-b** (0.75 mmol), $FeCl_3$ (0.75 mmol) and DMSO (1.0 mL) at 110 °C for the indicated time unless otherwise noted. [b] Isolated yields.

After realizing the optimal reaction conditions to synthesize the 2(-inden-2-yl)-3-oxo-indoline derivatives (see supporting

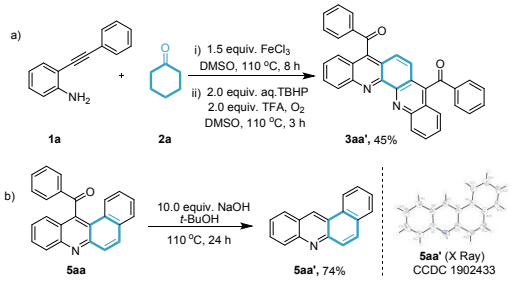
information Table S2), the generality of our protocol was tested with an array of *o*-alkynylanilines (Table 3). Initially, different R-group embedded *o*-alkynylanilines were subjected to our optimized reaction conditions, and all of these *o*-alkynylanilines were successfully transformed to C2-tetrasubstituted indolin-3-ones with moderate to good yields (Table 3, **7aa**-**7oa**, 45-88%). Next, the R^1-group containing *m*-Me-Ph (**1f**), *p*-Me-Ph (**1j**), and *p*-OMe-Ph (**1p**) gave the products **7fa, 7ja and 7pa** (yields 80-90%). The thiophene substituent was compatible under our title reaction conditions and provided the corresponding product in 65% yield (**7qa**). The fluoro-substituted dihydro-1*H*-indenone was an effective coupling partner, affording the product **7ab** in a moderate yield of 50%.

Table 3. Reaction scope for the formation of 2(-inden-2-yl)-3-oxo-indoline derivatives [a,b]



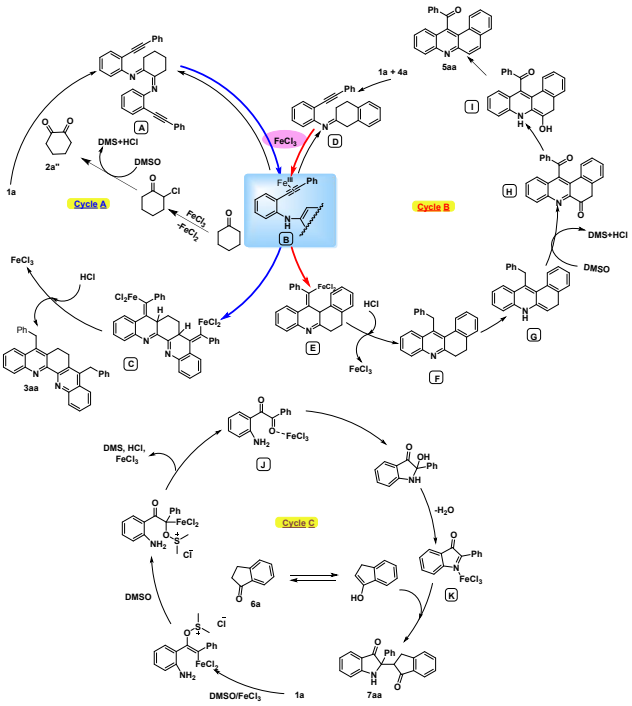
[a] Reaction conditions: Compound **1** (0.5 mmol), **6a-b** (0.75 mmol), $FeCl_3$ (0.75 mmol) and DMSO (1.0 mL) at 110 °C for the indicated time unless otherwise noted. [b] Isolated yields.

To highlight the efficiency of our synthetic protocol, we developed a sequential one-pot oxidation reaction using our lab's metal-free oxidative dehydrogenation conditions[7a] with aq. TBHP/O_2 (Scheme 2a) to synthesize the benzoyl analogue of the well-known diimine ligand **3aa'**.[15] The delicate decarbonylation of aldehydes and ketones has widened the spectrum of synthetic manipulations in medicinal chemistry.[16] Therefore, we disclose the first base-promoted debenzoylation of the benzo[*a*]acridine skeleton **5aa** (Scheme 2b). The structure of the debenzoylated product, benzo[*a*]acridine (**5aa'**), was confirmed by X-ray crystallography.[21]



Scheme 2. Late-stage modifications of *N*-heterocycles

Based on the literature reports and control experiments (see supporting information), a plausible mechanism was proposed in Scheme 3. In cycle A, the β-chlorinated cyclohexanone initially underwent an *in situ* Kornblum oxidation to generate 1,2-cyclohexadione **2a'**.[17] This was reacted with 2-(phenylethynyl)aniline to facilitate the imine intermediate **A**. Consequently, intermediate **A** isomerized to the reactive enamine and underwent regioselective 6-*exo*-dig annulation with the active π Fe(III) species to produce the vinyl iron complex **C**. Acid-promoted protolysis of **C** afforded the desired product **3aa**.[18,6a,b] The similar π alkyne-iron species **B** was yielded by the reaction between β-tetralone and **2a** *via* a 6-*exo*-dig annulation (Cycle B), furnishing the cyclized intermediate **F**.[7b] Under high temperature/acidic conditions, compound **F** isomerized to form *exo*-methylene compound **G**. Presumably, **G** underwent *aza*-allyl-oxidation initiated by DMSO to afford compound **H**, and compound **I** was generated from the enolization of **H**, followed by dehydration and isomerization to provide the final product **5aa**.[19,7a,b] In cycle C, compound **1a** was transformed to 1,2-di-carbonyl (compound **J**) using Fe(III)/DMSO as an oxidizing system.[17] Next, the Fe(III)-induced anionic cyclization facilitates the *in situ* generation of 3*H*-indol-3-one **K**.[12] Finally, a Mannich-type alkylation reaction of compound **K** with the enol generated from 1*H*-inden-1-one delivered our desired product **7aa.**[20,14]



Scheme 3. Plausible reaction mechanism

In summary, we have developed a diversity-oriented synthesis of different *N*-heterocyclic molecules, such as dibenzo[*b,j*][1,10]phenanthrolines, 12-benzoylacridines and 2-(inden-2-yl)-3-oxo-indolines via functionalization of the *in situ*-generated cyclic enamine and imine intermediates. The mechanistic studies revealed that the *in situ*-oxidized product 1,2-cyclohexadione undergoes double imination and hydro-enamination reaction cascade with *o*-alkynylaniline to furnish the dibenzo[*b,j*][1,10]phenanthrolines. In the case of 12-benzoylated acridines, the reactions proceed *via* an

imination/annulation/aza-allyl oxidation cascade sequence. For inden-1-one tethered 3-oxyindole construction, the intramolecular cyclization of *o*-alkynylaniline furnished the cyclic C-acylimines. Then, these cyclic ketimines were subjected to an alkylation reaction with the enol derived from the dihydro-1*H*-inden-1-one derivative. The major features of our methods are the external oxidant-free, additive-free and distinguished ligand-free conditions, as well as the potential of the greener oxidizing system $FeCl_3$/DMSO.

Conflicts of interest

"Author claim no conflicts of interest".

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21 CCDC numbers: **3aa** (1894798), **5aa** (1894788), **7ab** (1902337), **5aa**' (1902433).