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COMMUNICATION

Regioselective three-component synthesis of 1,2-diarylindoles from cyclohexanones, α-hydroxyketones and anilines under transition-metal-free conditions

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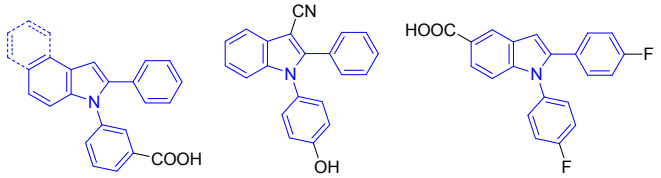
A facile method for the one-pot synthesis of 1,2-diarylindoles under transition-metal-free conditions is described. Cyclohexanones were used as the aryl sources via dehydrogenative aromatization process. One C-C and two C-N bonds were selectively formed via domino reaction. This protocol provides a convenient approach for the construction of valuable bioactive 1,2-diaryindoles from readily available cyclohexanones, α-hydroxyketones and anilines.

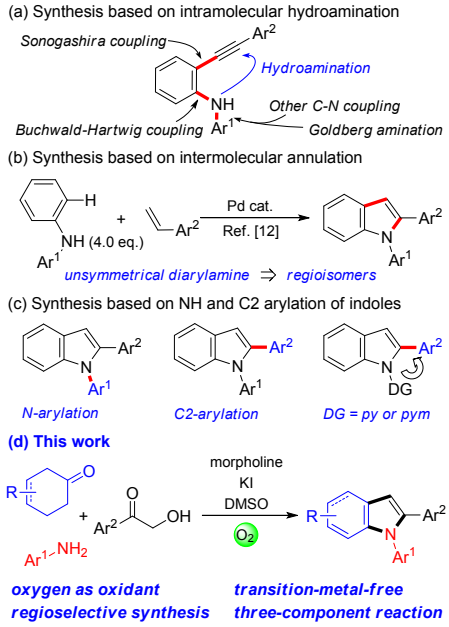
Indole is a nitrogen-containing heterocycle with a central position in organic chemistry and is considered to be a privileged structure in medicinal chemistry.[1] Furthermore, indole derivatives also serve as versatile precursors for the preparation of agricultural chemicals and functional materials.[2] Therefore, it is not surprising that enormous efforts have been devoted to the development of efficient synthetic protocols for the preparation and direct functionalization of this heteroaromatic compound. The classical indole ring synthesis mainly includes Fischer,[3] Bartoli,[4] Cadogan-Sundberg[5] and Larock[6] indole synthesis, among a multitude of other synthetic protocols. During the past several decades, transition-metal-catalyzed direct functionalization of indole N-H bond and C-H bond has proved to be very powerful protocol for the preparation of substituted indole derivatives since no prefunctionalization process is necessary.[7]



a, inhibitor of amyloid beta (Aβ42) secretion — **b**, estrogen receptor β-subtype (ERβ) cas: 1191387-63-9 — **c**, inhibitor of PASK activity cas: 1396341-02-8

Scheme 1 Selected bioactive 1,2-diarylindoles.

As a subclass of indole derivatives, 1,2-diarylindoles have a wide range of biological activities. As shown in Scheme 1, **a**[8] is an inhibitor of amyloid beta (Aβ42) secretion, **b**[9] is an estrogen receptor of β-subtype (ERβ) and **c**[10] shows inhibition towards PASK activity. Owing to the diverse significant biological properties of 1,2-diarylindoles, their synthesis has gained considerable interest.



Scheme 2 The development of 1,2-diarylindoles synthesis.

Traditionally, intramolecular hydroamination of highly functionalized 2-alkynylaniline substrates (usually need several steps to prepare) provides various substituted 1,2-diarylindoles in reasonable yields (Scheme 2a).[11] Furthermore, the Maiti group reported an excellent work on palladium-catalyzed annulation of diarylamines with olefins for the synthesis of 1,2-diarylindoles (Scheme 2b).[12] This method is more practical since both substrates are readily available. However, excess of diarylamines is required and regioisomers are formed when unsymmetrical diarylamines are employed, which limits application of this methodology. Arylation of the indole ring provides an alternative approach for construction of 1,2-diarylindoles. In recent years, transition-metal-catalyzed protocols have been developed via direct arylation of indoles at NH and C2 position using various aromatic reagents, i.e., aryl halides, aryl carbamates, aryl siloxanes and aryl boric acids (Scheme 2c).[13-15] However, multi-step procedure is usually required if substituents at

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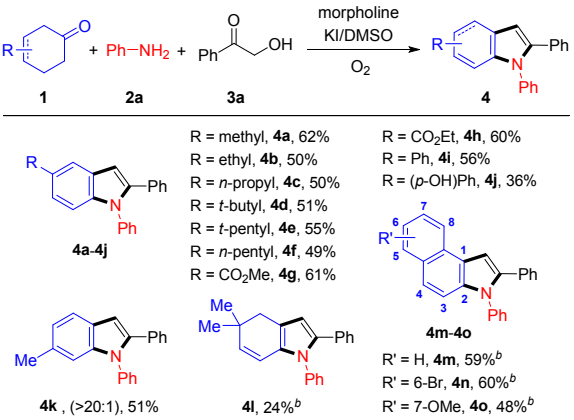
NH and C2 are different. At the same time, regioselectivity control is a key issue due to similar reactivity at C2 and C3 position in the indole ring. Moreover, despite the high efficiency and reasonably wide scope in the aforementioned strategies, transition-metal contamination remains an issue when certain transition-metals are used, especially when the products are destined for human consumption. Although few other methods are also available,[16] efficient one-pot methods for the facile construction of 1,2-diarylindoles from readily available substrates under transition-metal-free conditions are highly desirable. Inspired by the successful synthesis of heterocyclic compounds under transition-metal-free conditions in our group,[17] we herein report an one-pot regioselective synthesis of 1,2-diarylindoles from cyclohexanones, α-hydroxy-ketones and anilines under aerobic conditions (Scheme 2d). In this protocol, cyclohexanones were used as the aryl sources via dehydrogenative aromatization process and one C-C and two C-N bonds were selectively formed under transition-metal-free conditions.

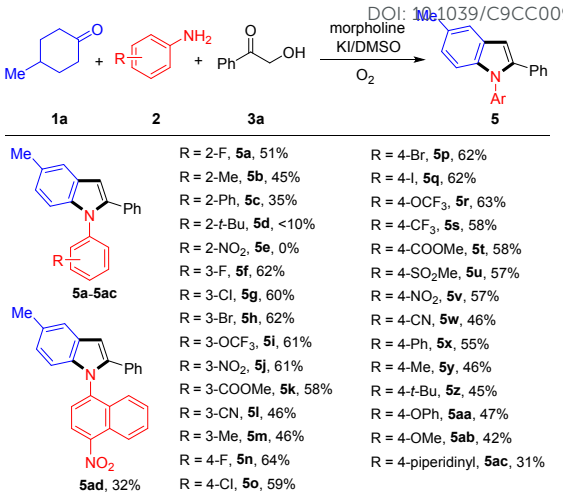
Table 1 Substrate scope of cyclohexanones[a]



[a] Conditions: **1** (0.3 mmol), **2a** (0.2 mmol), **3a** (0.25 mmol), KI (20 mol %), A2 (20 mol %), DMSO (2.0 equiv.), toluene (0.1 M), 150 °C, 12 h under oxygen. Isolated yields based on **2a**. [b] DMSO (1.0 equiv.).

After systematic investigation of the reaction conditions, we get the optimized conditions to realize this kind of transformation: 20 mol % of KI and 2 equiv. of DMSO as additives, 20 mol % morpholine as catalyst using toluene as the solvent (for details, see Table S1 in ESI). The scope and generality of the three-component reaction were explored with respect to cyclohexanones (Table 1). Moderate yields were obtained when alkyl substituents were presented at the *para*-position to the carbonyl group (**4b**-**4f**). Ester functional group was well tolerated under the given reaction conditions (**4g** and **4h**). When a phenyl group was employed, the corresponding product **4i** was obtained in 56% yield. However, lower yield was achieved when 4-phenylcyclohexanone bearing a free hydroxy group at the benzenoid moiety (**4j**). The reaction showed good regioselectivity for *meta*-substituted cyclohexanone to give **4k** as the dominated product. Interestingly, 4,4-dimethylcyclohexanone also could be involved in this kind of reaction to give partly dehydrogenated product **4l**, although the yield is not satisfactory. Notably, β-tetralone and its homologues were also suitable substrates to generate the target products (**4m**-**4o**). Unfortunately, α-tetralone and cyclohexanones with substituents at the *ortho*-position failed to provide the corresponding products, possibly due to steric hindrance effect.

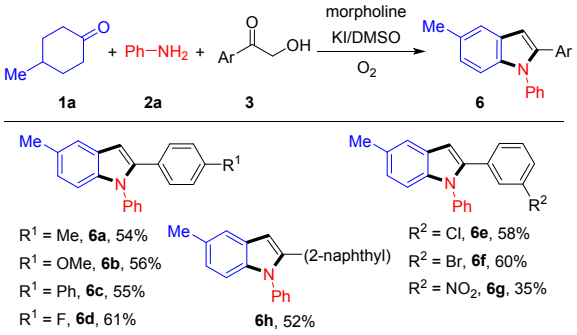
Table 2 Substrate scope of anilines[a]



[a] Conditions: **1a** (0.3 mmol), **2** (0.2 mmol), **3a** (0.25 mmol), KI (20 mol %), A2 (20 mol %), DMSO (2.0 equiv.), toluene (0.1 M), 150 °C, 12 h under oxygen. isolated yields based on **2**.

To further examine the scope and limitations of the reaction, we tested various anilines for this kind of reaction (Table 2). Obvious steric hindrance effect was observed when *ortho*-substituted anilines were used. When 2-fluoroaniline and 2-methylaniline were employed, the corresponding products **5a** and **5b** were obtained in moderate yields. The reaction yield decreased to 35% when a phenyl group was presented (**5c**). However, the reaction was almost completely prohibited when 2-(*tert*-butyl)aniline and 2-nitroaniline were used as the reactants (**5d** and **5e**). In general, better reaction yield could be obtained when substituents were located at the *meta* and *para* position in aniline substrates. Halogen substituents such as fluoro, chloro, bromo and even iodo were compatible to give the corresponding products in moderate to good yields (**5f**-**5h**, **5n**-**5q**). Furthermore, functional groups such as nitro, cyano and ester were all tolerated under the optimized reaction conditions. In most cases, electron-withdrawing substituents slightly improved the reaction yields whereas electron-donating groups decreased the reaction yields (**5r**-**5v** vs **5y**-**5ab**). 4-Nitro-1-naphthylamine was also reactive in this kind of transformation although lower yield was obtained (**5ad**).

Table 3 Substrate scope of α-hydroxyketones[a]

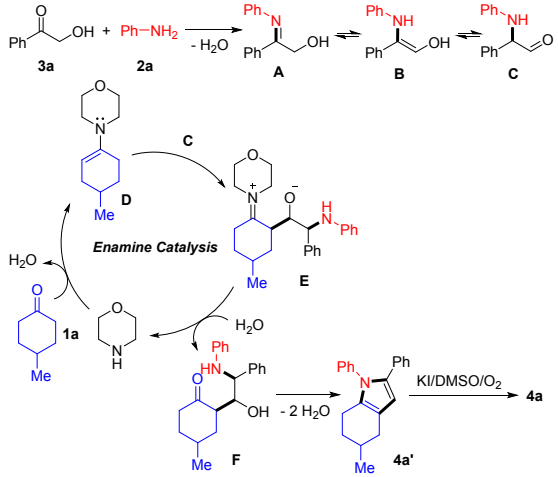


[a] Conditions: **1a** (0.3 mmol), **2a** (0.2 mmol), **3** (0.25 mmol), KI (20 mol %), A2 (20 mol %), DMSO (2.0 equiv.), toluene (0.1 M), 150 °C, 12 h under oxygen. Isolated yields based on **2a**.

After evaluating the scope with various cyclohexanones and anilines, different α-hydroxyketones were tested under the optimal

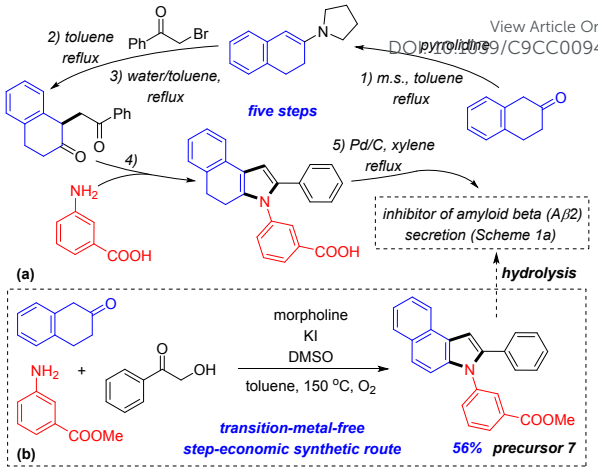
reaction conditions (Table 3). In general, moderate yields were obtained when halogens, methyl, methoxy and phenyl groups were presented. However, lower yield was obtained when a strong electron-withdrawing group was existed (**6g**). α-hydroxy-2-acetonaphthone was also suitable substrate to afford the target product **6h** in moderate yield.

To understand the reaction mechanism, a few control experiments were performed under different conditions (for details, see Scheme S1 in ESI). Conditions **A** were non-oxidizing conditions in the absence of KI, DMSO and molecular oxygen, and conditions **B** were equal to the standard conditions. Both **1a** and **1l** only gave a very small quantity of cyclized products that are difficult to be isolated (Scheme S1a and S1c). On the other hand, **1a** afforded dehydrogenative products **4a** in 62% yield (Scheme S1b), but **1l** which could not be aromatized only generated **4l** in a much lower yield of 24% under conditions **B** (Scheme S1d). These results revealed that the oxidative dehydrogenation might be a key step towards final target. The hydrated species **3a'**, which might be formed from **3a** under aerobic conditions, afforded **4a** in a much low yield under standard conditions (Scheme S1e). This kind of side reaction might decrease the yield of product and thus most of them gave moderate yields in this transformation.



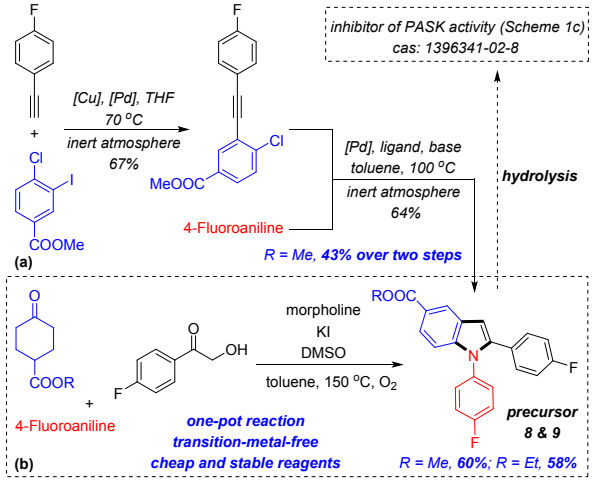
Scheme 3 Possible reaction mechanism.

On the basis of the control experiments and previous reports in the literature, we proposed a plausible mechanism for this kind of transformation (Scheme 3). Initially, condensation of **2a** and **3a** generates an imine intermediate **A** and subsequent tautomerization process yields enamine **B**. A crucial intermediate **C** is formed by enol-aldehyde tautomerization from **B**.[18] Meanwhile, condensation of morpholine and 4-methyl-cyclohexanone (**1a**) yield enamine **D** and subsequent nucleophilic attack of intermediate **C** yields an intermediate **E**.[19] Hydrolysis of **E** produces the alkylated intermediate **F** with the regeneration of morpholine catalyst for the next catalytic cycle. Cyclization of intermediate **F** forms **4a'**, which can lead to the final product **4a** under KI/DMSO/O_2 oxidative conditions.[17a] As an evidence, water formation can be observed in the reaction tube after completion of the reaction.



Scheme 4 Synthetic utilities of **7** using this protocol.

In order to further investigate the application of this method, we compared this protocol with other reported methods in the synthesis of bioactive indole-based functional molecules. As an inhibitor of amyloid beta (Aβ42) secretion (Scheme 1a), the literature reported method for the synthesis of 3-(2-phenyl-3*H*-benzo[*e*]indol-3-yl)benzoic acid need five steps from 3,4-dihydronaphthalen-2(1*H*)-one with the aid of precious palladium catalyst (Scheme 4a).[8] Interestingly, methyl 3-(2-phenyl-3*H*-benzo[*e*]indol-3-yl)benzoate (**7**) which is a precursor for the same target compound could be readily prepared in one pot from simple reagents with 56% yield by this protocol (Scheme 4b).



Scheme 5 Synthetic utilities of **8** and **9** using this protocol.

Furthermore, bioactive 1,2-bis(4-fluorophenyl)-1*H*-indole-5-carboxylic acid could inhibit the activity of PASK (Scheme 1c). The precursor (R = methyl, **8**) of this valuable molecule was synthesized by the traditional Pd/Cu-catalyzed Sonogashira crossing-coupling of methyl 4-chloro-3-iodobenzoate with 4-fluorophenylacetylene followed by the Pd-catalyzed/base-mediated amination/hydroamination reaction sequence with 4-fluoroaniline in 43% yield over two steps (Scheme 5a).[10] In contrast, the precursors (R = methyl, **8**, 60% yield; R = ethyl, **9**, 58% yield) could be prepared efficiently from cheap and stable alkyl 4-oxocyclohexane-carboxylate, α-hydroxy-4-fluoroacetophenone and 4-fluoroaniline using this method (Scheme 5b). Notably, the removal of transition-metal from the final bioactive products could be avoided by the current protocol.

In summary, we have developed a unique approach for the synthesis of various 1,2-diarylindoles from cyclohexanones, α-hydroxy ketones and anilines under transition-metal-free conditions. Cyclohexanones were employed as the aryl sources under aerobic conditions without the aid of transition-metal catalyst. Secondary amines acted as the efficient organic catalyst in this kind of transformation. The present method showed great advantages in the synthesis of two bioactive 1,2-diaryindole derivatives using readily available starting materials and less synthetic steps. This method can completely avoid transition-metal pollution which is very important factor for bioactive molecule synthesis. Further applications of this methodology for the synthesis of valuable indole-based compounds are in progress.

Acknowledgements

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Conflicts of interest

There are no conflicts to declare.

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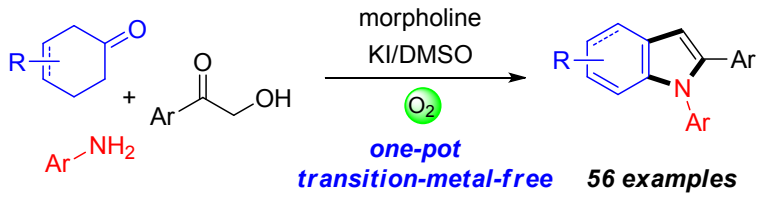
Regioselective Three-Component Synthesis of 1,2-Diarylindoles from Cyclohexanones, α-Hydroxyketones and Anilines under Transition-Metal-Free Conditions

Cheng Li, Yanjun Xie*, Fuhong Xiao, Huawen Huang, Guo-Jun Deng*



A facile method for the one-pot synthesis of 1,2-diarylindoles under transition-metal-free conditions is described.