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Iridium/Acid Cocatalyzed Direct Access to Fused Indoles via Transfer Hydrogenative Annulation of Quinolines and 1,2-Diketones

Guangpeng Lu, Feng Xie, Rong Xie, Huanfeng Jiang, and Min Zhang*

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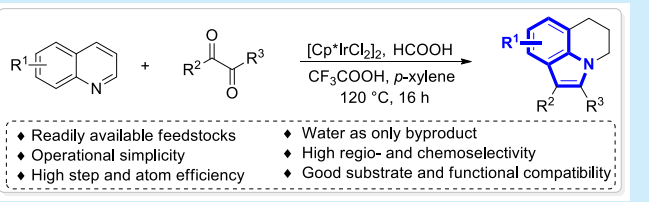
ABSTRACT: Herein, we present an unprecedented iridium/acid cocatalyzed construction of fused indoles via transfer hydrogenative annulation of nonactivated quinolines and 1,2-diketones. The products are assembled via initial reduction followed by selective coupling of 1,2-diketones with the N and C8 sites of the quinolyl skeleton. The developed synthetic method features operational simplicity, readily available feedstocks, applicability for streamline synthesis of functional molecules, high step and atom efficiency, and generation of water as the byproduct.

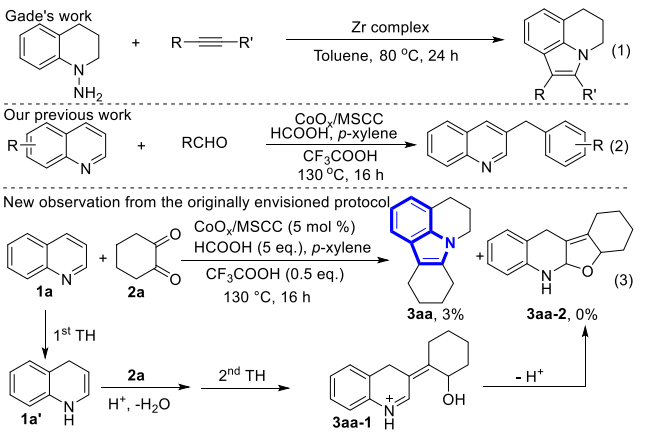


The indole core is ubiquitous in natural alkaloids (e.g., reserpine and strychnine),[1] marketing drugs (e.g., indomethacin and pravadoline are used as analgesic and nonsteroidal anti-inflammatory drugs (NSAID), respectively),[2] dyes and functional materials.[3] Consequently, the construction of indole derivatives has long been an attractive subject in the scientific community. Except for the well-established name reactions (e.g., Fischer, Bartoli, Bischler, Nenitzescu, Larock et al.),[4] a range of alternative approaches via inter-[5] or intramolecular[6] cyclization have also been developed to access various indoles.

In comparison, less attention has been focused on the construction of fused indoles. Generally, the functionalization of two indolyl carbo sites is considered as a useful tool to achieve the related end in this regard. For instance, the [3 + 2] cycloaddition reactions of indoles with 2-aryl-*N*-tosylaziridines or *N*-sulfonyl-1,2,3-triazoles were successively developed by the Davies and Yang groups.[7] Lei et al. demonstrated an electrooxidative [3 + 2] cyclization reaction of phenols and indole derivatives.[8] Recently, we reported a synthesis of indole-fused N-heterocycles through the annulation of diarylamines and indoles.[9] Via deaminative annulation of tetrahydroquinoline-based hydrazines and internal alkynes, the Gade group reported an interesting zirconium-catalyzed synthesis of fused indoles by functionalization of both N and carbo sites (Scheme 1, eq 1).[10] Despite the significant utility, many of the existing synthetic approaches suffer from one or more limitations such as the need for preinstallation of requisite reactants, the use of less environmentally benign reagents, and low step and atom efficiency. As such, the search for new methods, enabling direct access to new fused indoles from readily available feedstocks, would be highly desirable.

In recent years, transfer hydrogenation has emerged as an appealing tool in the reduction of unsaturated chemical bonds, since it does not require high pressure H_2 gas with operational simplicity.[11] In addition, such a tool has also been elegantly employed to generate functional products via new bond formations.[12] For instance, the Li and Zeng groups have successfully transformed phenol derivatives into cyclic amines with HCOONa.[13] Bruneau et al. reported the C(sp^3)−H bond alkylation of cyclic amines with formic acid.[14] However, the strategy, utilizing transfer hydrogened N-heteroarenes as the coupling partners for the subsequent step of a given sequence, remains a new subject to be explored, which would pave new

Scheme 1. Previous Work and the New Finding



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avenues to access novel functional products with structural diversity.

From our sustained effort toward direct functionalization of N-heterocycles,[15] we have recently reported a direct reductive quinolyl β-C−H alkylation by multispherical cavity carbon-supported cobalt oxide nanocatalysts (Scheme 1, eq 2).[15d] Inspired by this work, we envisioned a new reaction for the synthesis of polycyclic N-heterocycle. As shown in eq 3 of Scheme 1 employing the same catalyst system of eq 2, the first transfer hydrogenation (1st TH) of quinoline **1a** is expected to generate enamine **1a′** *in situ*, which would be able to trap cyclohexane-1,2-dione **2a** at the β-site and generate iminium **3aa-1** under the assistance of acid. Then, the second transfer hydrogenation (2nd TH) of the unreacted carbonyl group followed by intramolecular nucleophilic addition (**3aa-1**) and deprotonation gives rise to a fused tetrahydroquinoline **3aa-2**. However, after performing such a reaction, we observed that, instead of the anticipated product **3aa-2**, a structurally novel fused indole **3aa** was obtained in 3% yield. Based on this finding, we wish herein to report, for the first time, a hydrogen-transfer mediated access to fused indoles from nonactivated quinolines and 1,2-diketones.

To formulate an efficient reaction system, we chose the synthesis of product **3aa** from quinoline **1a** and 1,2-cyclohexanedione **2a** as a model system to evaluate different reaction parameters (Table 1 and Table S1 in Supporting Information (SI) for details). Initially, several catalysts employed frequently for transfer hydrogenation reactions were evaluated (Table 1, entries 1−4); only $[Cp^*IrCl_2]_2$ exhibited the best catalytic performance and afforded the desired product **3aa** in 80% yield. However, the absence of additives, hydrogen donor, or catalyst failed to yield compound **3aa** (entries 5−7), showing that these three elements are indispensable for product formation. Thus, we then used $[Cp^*IrCl_2]_2$ as the preferred catalyst and examined several additives (entries 8−10), hydrogen donors (entries 11−13), and solvents (entry 14), but the results showed that all of them were inferior to CF_3COOH, HCOOH, and *p*-xylene, respectively. Further, the increase or decrease of reaction temperature and catalyst loading diminished the yields (entries 15−16). Changing the loading amount of the hydrogen donor, reactant **2a**, and additive was unable to further improve the product yields (entries 16−18). Hence, the optimal conditions are as shown in entry 4.

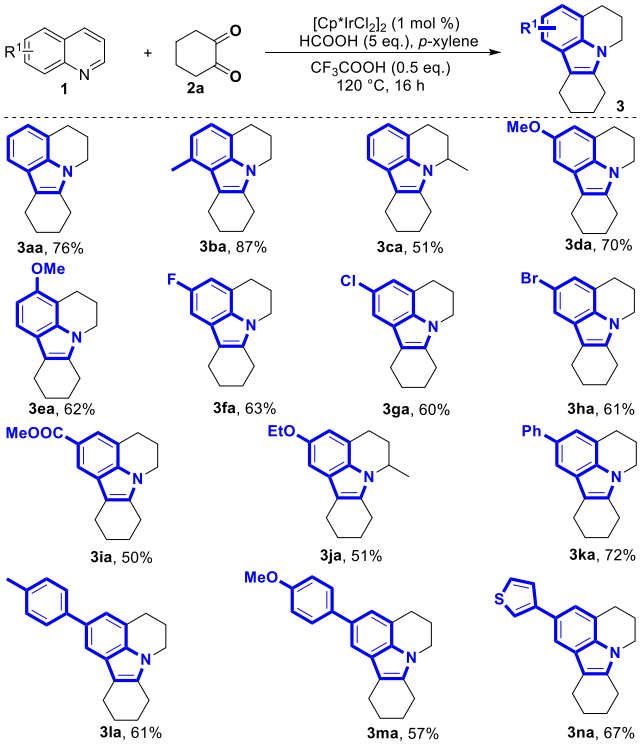
Table 1. Optimization of the Reaction Conditions[a]

Entry	Catalyst	Hydrogen donor	Additive	Yield of **3aa** (%)[b]
1	$IrCl_3$	HCOOH	CF_3COOH	<5
2	$Ru_3(CO)_{12}$	HCOOH	CF_3COOH	0
3	$Pd(OAc)_2$	HCOOH	CF_3COOH	0
4	$[Cp^*IrCl_2]_2$	HCOOH	CF_3COOH	80
5	$[Cp^*IrCl_2]_2$	HCOOH	–	0
6	–	HCOOH	CF_3COOH	0
7	$[Cp^*IrCl_2]_2$	–	CF_3COOH	0
8	$[Cp^*IrCl_2]_2$	HCOOH	*P*-TSA	<5
9	$[Cp^*IrCl_2]_2$	HCOOH	$Hf(OTf)_3$	38
10	$[Cp^*IrCl_2]_2$	HCOOH	Benzoic acid	0
11	$[Cp^*IrCl_2]_2$	isopropanol	CF_3COOH	0
12	$[Cp^*IrCl_2]_2$	HCOONa	CF_3COOH	0
13	$[Cp^*IrCl_2]_2$	H_2	CF_3COOH	<5[c]
14	$[Cp^*IrCl_2]_2$	HCOOH	CF_3COOH	(0, 32, 35, 0)[d]
15	$[Cp^*IrCl_2]_2$	HCOOH	CF_3COOH	(61, 68)[e]
16	$[Cp^*IrCl_2]_2$	HCOOH	CF_3COOH	(66, 80)[f]
17	$[Cp^*IrCl_2]_2$	HCOOH	CF_3COOH	(70, 76)[g]
18	$[Cp^*IrCl_2]_2$	HCOOH	CF_3COOH	(48, 76)[h]
19	$[Cp^*IrCl_2]_2$	HCOOH	CF_3COOH	79[i]

[a]Conditions: unless otherwise stated, all the reactions were performed with **1a** (0.20 mmol), **2a** (0.30 mmol), catalyst (1 mol %), hydrogen donor (5.0 equiv), additive (0.5 equiv), *p*-xylene (1.5 mL) at 120 °C for 16 h. [b]GC yield using hexadecane as an internal standard. [c]H_2 balloon. [d]Yields obtained with H_2O, *tert*-amyl alcohol, 1,4-dioxane, and DMF as the solvents, respectively. [e]Yields obtained at 110 and 130 °C, respectively. [f]Yields obtained with catalyst loading of 0.8 mol % and 1.2 mol %, respectively. [g]Yields obtained with 4 and 6 equiv of HCOOH, respectively. [h]Yields obtained with 0.2 and 0.4 mmol of **2a**, respectively. [i]CF_3COOH: 1 equiv.

With the optimal reaction conditions in hand, we then examined the substrate scope of the synthetic protocol. First, 1,2-diketone **2a** in combination with various quinolines **1** (for the structures of **1a−1q**; see Scheme S2 in SI) was tested. As illustrated in Scheme 2, all the reactions proceeded smoothly

Scheme 2. Variation of Quinolines



and furnished the desired products in moderate to good yield upon isolation. Various functionalities (−Me, −OMe, −F, −Cl, −Br, $-CO_2Me$, −Ph) were well tolerated in the transformation, which offers the potential for molecular complexity via further chemical transformations. The electronic property of the substituents on the quinolyl benzene ring affected the product yields to some extent. In general, quinolines with a strong electron-donating group (**3ba**, **3da**) afforded the products in relatively higher yields than those of electron-deficient ones (**3fa−3ia**), presumably because electron-rich quinolines result in more reactive intermediates arising from the transfer hydrogenation process and favor the coupling process. However, quinolines (**1p** and **1q**) containing a strong electron-withdrawing group (e.g., $-NO_2$, −CN) failed to

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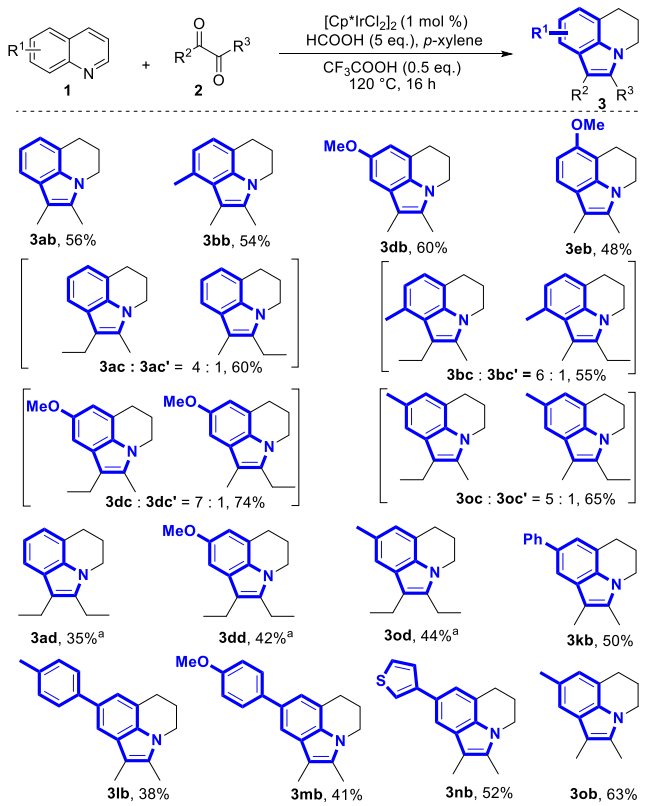
Org. Lett. XXXX, XXX, XXX−XXX

afford the desired products, indicating that a relatively electron-rich quinoline is essential in affording the desired annulation product. Of note, the methyl group on the pyridyl ring (**3ca**) gave a lower yield than that of quinoline with a methyl group on the benzene ring (**3ba**), which is assigned to the pyridyl methyl group disfavoring the transfer hydrogenation process.

Subsequently, we turned our attention to the variation of both coupling partners. Thus, various quinolines and 1,2-diketones (for the structures of **2a**−**2d**; see Scheme S2 in SI) were tested for the transformation. As shown in Scheme 3, all

Scheme 3. Variation of Both Coupling Agents

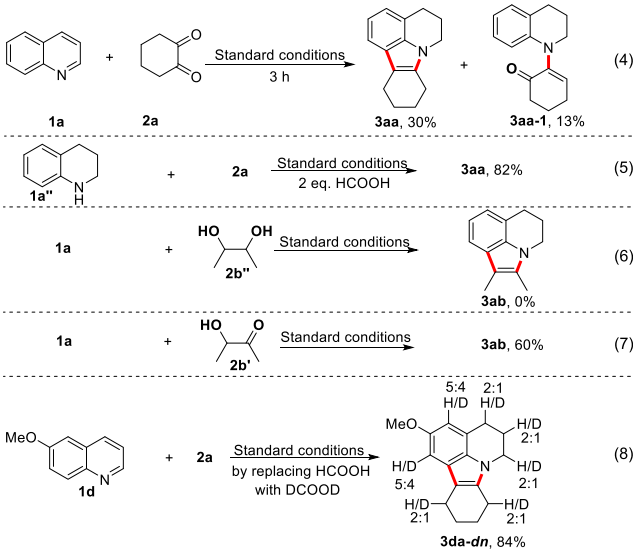


[a]Temperature: 130 °C.

of the substrates underwent efficient transfer hydrogenative annulation reaction, delivering the desired products in moderate to good isolated yields. Noteworthy, the reactions employing unsymmetrical 1,2-diketone **2c** exhibited unique regioselectivity (**3ac** vs **3ac′**, **3bc** vs **3bc′**, **3dc** vs **3dc′**, and **3oc** vs **3oc′**), and the major products were obtained by reacting the sterically less-hindered carbonyl group with the quinolyl N-site, which suggests that the N-site of the transfer hydrogenated intermediate is initially involved in the annulation process. However, employing greatly hindered compound phenylglyoxal **2e** failed to form the desired product.

In an effort to gain mechanistic insights into the reaction, we conducted several control experiments (Scheme 4). Interruption of the model reaction after 3 h generated product **3aa** and enamino ketone **3aa-1** in 30% and 13% GC yields, respectively (eq 4). Prolonging the reaction time to 16 h led to full consumption of **3aa-1** to product **3aa**, showing that **3aa-1** is a reaction intermediate. Then, tetrahydroquinoline **1a′′** was able to react with **2a** and afforded **3aa** in 82% GC yield (eq 5).

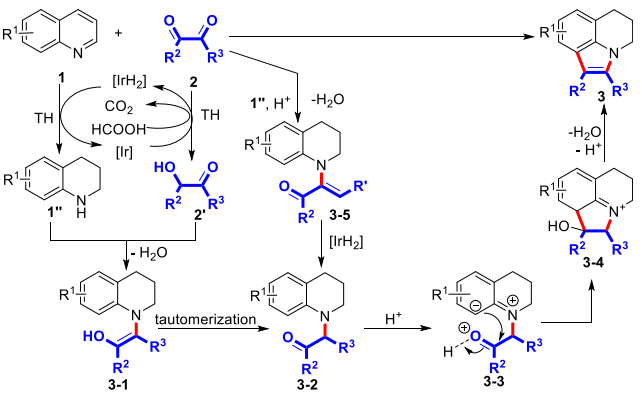
Scheme 4. Control Experiments



Subjection of quinoline **1a** and butane-2,3-diol **2b′′** under the standard conditions failed to yield product **3ab** (eq 6), whereas the reaction of quinoline **1a** with 3-hydroxybutan-2-one **2b′** afforded product **3ab** in 60% GC yield (eq 7). These results indicate that tetrahydroquinoline **1a′′** and α-hydroxylketone, instead of vicinal diol, are involved in the reaction process. Further, the reaction of 6-methoxyquinoline **1d** and cyclohexane-1,2-dione **2a** by replacing HCOOH with DCOOD gave product **3da-*dn*** in 84% yield with different deuterium ratios on the product, supporting that the reaction undergoes a transfer hydrogenative annulation pathway (eq 8).

Based on the above findings, a plausible reaction pathway is depicted in Scheme 5. The presence of an iridium catalyst and

Scheme 5. Plausible Reaction Pathway



hydrogen donor HCOOH initially forms the metal hydride species [IrH_2] with liberation of CO_2.[14] Upon two rounds of transfer hydrogenation (TH) by [IrH_2], quinoline **1** is transformed to tetrahydroquinoline **1′′**.[16] Meanwhile, the TH of diketone **2** gives hydroxylketone **2′**. Then, **1′′** condenses with the carbonyl group of **2′** and affords α-amino ketone **3-2** via tautomerization of the coupling adduct **3-1**. Alternatively, **3-2** can also be afforded via the condensation of tetrahydroquinoline **1′′** and diketone **2** followed by a TH process. Then, the acid-catalyzed intramolecular cyclization between the electron-rich aryl ring and carbonyl group gives intermediate **3-4**. Finally, dehydration-

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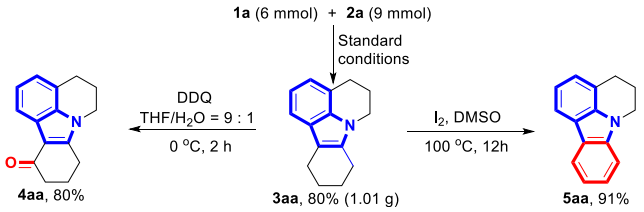
Org. Lett. XXXX, XXX, XXX−XXX

induced aromatization and deprotonation give rise to product **3**. In addition, TH of the carbonyl group of **3-2** followed by an acid-catalyzed intramolecular Fridel-Crafts type cyclization also rationalizes the product formation. It is important to note that, with the present catalyst system, TH of quinoline to tetrahydroquinoline is faster than the reduction of 1,2-diketone to 1,2-diol, thus offering high chemoselectivity.

To demonstrate the synthetic utility of the developed chemistry, a gram scale synthesis of compound **3aa** was achieved by scaling the quinoline amount to 6 mmol, which still afforded high product yield upon isolation (Scheme 6, 80%, 1.01 g). Then, the treatment of **3aa** with DDQ resulted in product **4aa**,[17a] a key intermediate applied for the preparation of drug molecules such as 5-HT3 receptor antagonist[17b] and serotonin agents.[17c] Such a synthesis is far superior to the reported protocol that requires 4 steps to give only 42% of overall product yield.[17b] Further, subjection of **3aa** in DMSO with molecular I_2 generated a carbazole derivative **5aa** via dehydroaromatization of **3aa**.[18] Noteworthy, the obtained product constitutes the core structure of many kinds of oxime ester photoinitiators with high activity and high thermostability.[19]

Scheme 6. Synthetic Utility



In summary, we have developed an unprecedented iridium/acid cocatalyzed transfer hydrogenative annulation reaction of nonactivated quinolines with 1,2-diketones, which allows direct access to a wide array of fused indoles, a class of valuable compounds with the potential for further discovery and creation of functional molecules. The products are furnished via initial reduction followed by selective coupling of 1,2-diketones with the N and C8 sites of the quinolyl skeleton. The developed chemistry proceeds with the merits of operation simplicity, high step and atom efficiency, broad substrate scope, liberation of water as the byproduct, and applicability for streamline synthesis of functional molecules. In consideration of the significant importance of indole-fused N-heterocycles in biological, medicinal, and synthetic organic chemistry, the present work has the potential to be applied for various purposes, and the hydrogen transfer-mediated coupling strategy will pave new avenues for the transformation of inert organic systems into functional frameworks.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00500.

Experimental details, NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Min Zhang − *Key Lab of Functional Molecular Engineering of Guangdong Province, School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou 510641, P. R. China; School of Biotechnology and Health Sciences, Wuyi University, Jiangmen 529020, China;* orcid.org/0000-0002-7023-8781; Email: minzhang@scut.edu.cn

Authors

Guangpeng Lu − *Key Lab of Functional Molecular Engineering of Guangdong Province, School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou 510641, P. R. China*

Feng Xie − *School of Biotechnology and Health Sciences, Wuyi University, Jiangmen 529020, China*

Rong Xie − *Key Lab of Functional Molecular Engineering of Guangdong Province, School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou 510641, P. R. China*

Huanfeng Jiang − *Key Lab of Functional Molecular Engineering of Guangdong Province, School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou 510641, P. R. China;* orcid.org/0000-0002-4355-0294

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c00500

Notes

The authors declare no competing financial interest.

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